BAKER & MCKENZIE

Baker & McKenzie S.A.S
NIT: 900.532.339-9

Av. 82 No. 10-62 Piso 6
Bogotá
Colombia

SUPERINTENDENCIA DE INDUSTRIA Y COMERCIO

No. 10-011972- -00011-0000
Fecha: 2013-08-09 16:17:56 Dep. 2020 DIR.NUEVASCR
Tra. 11 PATENTEIYII Eve: 378 FASENACIONALI
Act. 412 REPOSPRESRECU Folios: 10

Señor

Superintendente de Industria y Comercio

SUPERINTENDENCIA DE INDUSTRIA Y COMERCIO

E. S. D.

Referencia: Expediente No. 10.011.972
Solicitud de Patente de Invención titulada: "Forma cristalina de la sal diclorhidrato de ((1S)-1-(((2S)-2-(5-(4'-(2-((2S)-1-((Metoxicarbonil)Amino)-3-Metilbutanol)-2-Pirrolidinil)-1H-Imidazol-5-IL)-4-Bifenilil)-1H-Imidazol-2-il)-1-Pirrolidinil)Carbonil)-2-Metilpropil)Carbamato de metilo"

Solicitante: Bristol-Myers Squibb Company

RECURSO DE REPOSICIÓN

ÁLVARO CORREA ORDÓÑEZ, mayor de edad y vecino de Bogotá D.C., identificado según aparece al pie de mi firma, en mi condición de apoderado de la sociedad Bristol-Myers Squibb Company, domiciliada en Route 206 and Province Line Road Princeton, New Jersey 08543-4000, Estados Unidos, presento oportunamente el siguiente recurso de reposición en contra de la Resolución 37021 de fecha 20 de junio de 2013 notificado por listado único de notificación de propiedad industrial fijado el 2 de agosto de 2013.

1. OBJETO DEL RECURSO

Que se revoque la Resolución 37021 de fecha 20 de junio de 2013, y en su lugar, se conceda el privilegio de patente de invención para la totalidad de las reivindicaciones (1 a 8) de la presente solicitud de patente.

2. ANTECEDENTES

2.1. El 31 de julio de 2008 la sociedad Bristol-Myers Squibb Company presentó en fase internacional la solicitud de patente para la invención titulada:

"*Forma cristalina de la sal diclorhidrato de ((1S)-1-(((2S)-2-(5-(4'-(2-((2S)-1-((Metoxicarbonil)Amino)-3-Metilbutanol)-2-Pirrolidinil)-1H-Imidazol-5-IL)-4-Bifenilil)-1H-Imidazol-2-il)-1-Pirrolidinil)Carbonil)-2-Metilpropil)Carbamato de metilo*"

Esto, bajo el Tratado de Cooperación en Materia de Patentes (PCT), con el número de solicitud internacional núm. PCT/US2008/071734, en cuyo capítulo reivindicatorio reclamaba 25 reivindicaciones.

2.2. El 12 de febrero de 2009, bajo Publicación Internacional núm. WO 2009/020828 A1, se publicó la Solicitud Internacional de Patente núm. PCT/US2008/071734, arriba mencionada.

2.3. El 4 de febrero de 2010, dentro del término establecido en el artículo 22.1. del Tratado de Cooperación en Materia de Patentes, incorporado al ordenamiento colombiano mediante Ley 463 de 1998, la sociedad Bristol-Myers Squibb Company inició ante la Dirección de Nuevas Creaciones de la Superintendencia de Industria y Comercio, la fase nacional en Colombia de la solicitud de patente para la invención titulada:

"*Forma cristalina de la sal diclorhidrato de ((1S)-1-(((2S)-2-(5-(4'-(2-((2S)-1-((Metoxicarbonil)Amino)-3-Metilbutanol)-2-Pirrolidinil)-1H-Imidazol-5-IL)-4-Bifenilil)-1H-Imidazol-2-il)-1-Pirrolidinil)Carbonil)-2-Metilpropil)Carbamato de metilo*"

A esta solicitud correspondió el expediente administrativo núm. PCT/10.011.972, donde reivindicó prioridad de fecha 8 de agosto de 2007, con fundamento en la solicitud de patente núm. 60/954,592 de los Estados Unidos de América.

2.4. Habiendo superado los requisitos de forma, la solicitud núm. PCT/10.011.972, fue publicada el día 20 de mayo de 2010 en la Gaceta de la Propiedad Industrial No. 616. Se solicitó el examen de patentabilidad el día 12 de noviembre de 2010.

2.5. Mediante Oficio 00331 del 7 de enero de 2011, la sociedad Lafrancol S.A. se opuso a la solicitud contenida en este expediente, con fundamento en la falta de novedad y nivel inventivo. Dicha oposición fue oportunamente respondida por la solicitante el día 5 de Abril de 2011, en el cual se allegó un nuevo capítulo reivindicatorio conformado por 20 reivindicaciones.

2.6. La Dirección de Nuevas Creaciones de la Superintendencia de Industria y Comercio emitió un único examen de fondo el día 23 de octubre de 2012, en el cual objetó la claridad del pliego reivindicatorio y la novedad de las reivindicaciones 1 a 20, con fundamento en las enseñanzas contenidas en el documento CO 0913323.

2.7. Por medio del memorial radicado el 17 de enero de 2013, mi representada respondió al examen de fondo, en el cual se allegó un nuevo capítulo reivindicatorio conformado por 8 reivindicaciones y en el cual se argumentó que la solicitud Colombiana 0913323 no puede ser anterioridad de la presente solicitud de patente, por cuanto su divulgación fue posterior a la fecha de prioridad reivindicada en el presente trámite.

2.8. Por medio de la Resolución 37021 de fecha 20 de junio de 2013, notificada por edicto desfijado el día 2 de agosto de 2013, el Despacho niega las reivindicaciones 1 a 8 por cuanto considera que carecen de novedad a pesar de los argumentos presentados por la solicitante en la respuesta al examen de fondo.

2.9. Ese Despacho menciona que la falta de novedad se debe a las enseñanzas contenidas en el documento CO 0913323. Particularmente, el Examinador establece que:

> *"(...) las características esenciales de la forma N-2 de la reivindicación 1 habían sido divulgadas previamente en el documento D1, por lo tanto, la materia reivindicada no es nueva.*
>
> *En consecuencia, la reivindicación 1 no es nueva, según lo divulgado en el documento D1. Por su parte, las reivindicaciones dependientes 2 a 8 no mencionan alguna característica que haga nuevo el compuesto de la*

reivindicación 1, por lo tanto, tampoco cumplen con lo establecido en el mencionado artículo 16 de la Decisión 486.

Con respecto a la afectación por falta de novedad de la presente solicitud, la solicitante argumenta que el polimorfo descrito en la referencia D1 no era parte del documento de prioridad y se agregó en la fecha de presentación de la solicitud PCT que ocurrió en agosto 9 de 2007. La materia objeto de la presente solicitud ahora bajo examen, tiene fecha de prioridad de Agosto 8, 2007 y por lo tanto es anterior a la fecha de presentación del documento D1 (con la información del polimorfo) lo que hace que la referencia D1 no pueda afectar de manera alguna la presente invención, es decir, no constituye anterioridad de la presente solicitud de patente. Concluye la solicitante que la presente solicitud es nueva y posee nivel inventivo.

Es oportuno aclarar que, contrario a lo afirmado por la solicitante, la presente solicitud no es nueva frente a lo divulgado en el documento de acuerdo con lo expuesto arriba.
Por otra parte, según lo establecido en el Artículo 16 de la Decisión 486: "Sólo para el efecto de la determinación de la novedad, también se considerará dentro del estado de la técnica, el contenido de una solicitud de patente en trámite ante la oficina nacional competente, cuya fecha de presentación o de prioridad fuese anterior a la fecha de presentación o de prioridad de la solicitud de patente que se estuviese examinando, siempre que dicho contenido esté incluido en la solicitud de fecha anterior cuando ella se publique o hubiese transcurrido el plazo previsto en el artículo 40.

En el presente caso la fecha de presentación del documento D1 corresponde al 11 de febrero de 2009, y la fecha de presentación de la actual solicitud fue el 4 de febrero de 2010 siendo la fecha de presentación de D1 anterior a la fecha de presentación de esta solicitud. Por lo tanto, el documento D1 si es una anterioridad válida para afectar la novedad de esta solicitud".

3. FUNDAMENTO DEL RECURSO

3.1. Para analizar adecuadamente este asunto, lo primero que debe establecerse es la fecha efectiva y reconocida como fecha de presentación de la presente solicitud:

El artículo 11 del tratado del PCT establece:

*1. La Oficina receptora otorgará como **fecha de presentación internacional la fecha de recepción de la solicitud internacional**, siempre que compruebe en el momento de la recepción que:*

i) El solicitante no está manifiestamente desprovisto, por motivos de residencia o nacionalidad, del derecho a presentar una solicitud internacional en la Oficina receptora;
ii) La solicitud internacional está redactada en el idioma prescrito;
iii) La solicitud internacional contiene por lo menos los elementos siguientes:
a) Una indicación según la cual ha sido presentada a título de solicitud internacional;
b) La designación de un Estado contratante por lo menos;
c) El nombre del solicitante, indicado en la forma prescrita;
d) Una parte que, a primera vista, parezca constituir una descripción;
e) Una parte que, a primera vista, parezca constituir una o varias reivindicaciones.
2. a) Si, en el momento de su recepción, la Oficina receptora comprueba que la solicitud internacional no cumple los requisitos enumerados en el párrafo 1, invitará al solicitante a efectuar la corrección necesaria, de conformidad con lo previsto en el Reglamento;
b) Si el solicitante da cumplimiento a esta invitación en la forma establecida en el Reglamento, la Oficina receptora otorgará como fecha de presentación internacional la de recepción de la corrección exigida.
*3. Sin perjuicio de lo dispuesto en el artículo 64.4), **cualquier solicitud internacional que cumpla las condiciones señaladas en los puntos i) a iii) del párrafo 1 y a la cual le haya sido otorgada una fecha de presentación internacional, tendrá los efectos de una presentación nacional, regular en cada Estado designado desde dicha fecha; esta fecha se considerará como la de presentación efectiva en cada Estado designado**.*
4. Toda solicitud internacional que cumpla los requisitos enumerados en los puntos i) a iii) del párrafo 1, tendrá igual valor que una presentación nacional regular en el sentido del Convenio de París para la Protección de la Propiedad Industrial.

Para este caso, las fechas relevantes son:

- 8 de agosto de 2007: Fecha de la prioridad reivindicada.

- 31 de julio de 2008: Fecha de presentación de la solicitud ante la Oficina Internacional

- 12 de febrero de 2009: Fecha de publicación de la Solicitud Internacional.

- 4 de febrero de 2010: Fecha de inicio de la fase nacional en Colombia.

En aplicación del artículo 11 del PCT, a la presente solicitud, que cumplió con todos los requisitos exigidos en la norma, se le debe reconocer como fecha de presentación aquella fecha de la solicitud internacional, es decir, el 31 de julio de 2008, y se beneficia del derecho

de prioridad invocado, que data del **8 de agosto de 2007**, como se reivindicó en la fase internacional y en la fase nacional.

En la resolución impugnada, el Despacho manifestó:*"(...) En el presente caso la fecha de presentación del documento D1 corresponde al 11 de febrero de 2009, y **la fecha de presentación de la actual solicitud fue el 4 de febrero de 2010 siendo la fecha de presentación de D1 anterior a la fecha de presentación de esta solicitud**. Por lo tanto, el documento D1 si es una anterioridad válida para afectar la novedad de esta solicitud".*

Es evidente el error en el que incurrió el Despacho al considerar que la presente solicitud fue presentada el 4 de febrero de 2010, cuando en aplicación del artículo 11 del PCT, se cumplieron todas las exigencia para que la fase nacional se beneficiara de la fecha de la solicitud internacional, y por lo tanto, para todos los efectos, debía considerarse que esta solicitud **fue presentada el 31 de julio de 2008, con una reivindicación de prioridad que data del 8 de agosto de 2007**.

Este solo argumento es suficiente para demostrar el error en que incurrió el Depacho y suficiente para superar la objeción elevada a la novedad de la presente solicitud, pues la fecha de prioridad reivindicada (8 de agosto de 2007) es claramente anterior a la fecha de presentación de D1 (9 de agosto de 2007).

3.2. Aparte de lo anterior, también es pertinente citar como fundamento de este recurso el artículo 16 de la Decisión 486 que establece:

> *"Una invención se considerará nueva cuando no está comprendida en el estado de la técnica.*
> *El estado de la técnica comprenderá todo lo que haya sido accesible al público por una descripción escrita u oral, utilización, o comercialización o cualquier otro medio antes de la fecha de presentación de la solicitud de patente o, en su caso de la prioridad reconocida.*
> *Sólo para el efecto de la determinación de la novedad, **también se considerará dentro del estado de la técnica**, el contenido de una solicitud de patente en trámite ante la oficina nacional competente, cuya fecha de presentación o de prioridad **fuese anterior** a la fecha de presentación o de prioridad de la solicitud de patente que se estuviese examinando, siempre que dicho contenido esté incluido en la solicitud de fecha anterior cuando ella se publique o hubiese transcurrido el plazo previsto en el artículo 40"*

Se demostrará en este recurso que las características relevantes de la presente solicitud no fueron divulgadas con anterioridad a la fecha de la presente solicitud (8 de agosto de 2007).

3.3. En aplicación del artículo 16 citado, una solicitud en trámite solo podría haber sido considerada como parte del estado de la técnica si su **fecha de presentación** era anterior a la fecha de la solicitud analizada.

En este caso, la fecha de presentación de D1 es 9 de agosto de 2007, y por lo tanto, es posterior a la presente solicitud, cuya fecha de prioridad es 8 de agosto de 2007

3.4. En un segundo escenario, el artículo 16 citado, establece que una solicitud en trámite solo podría haber sido considerada como parte del estado de la técnica si su **fecha de prioridad** era anterior a la fecha de la solicitud analizada.

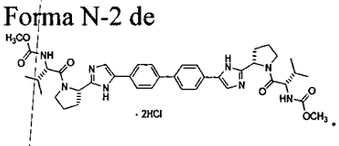
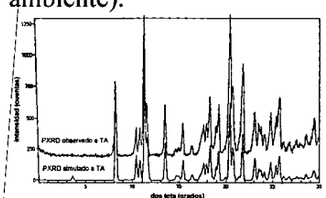
En este caso, para tener en cuenta la divulgación de la prioridad reivindicada en D1, se hace necesario aclarar el contenido de la prioridad, pues cada una de la fecha de la prioridad y de la solicitud internacional, solo podía tenerse como parte de estado del arte, el contenido particular de cada uno de tales documentos:

Es importante aclarar que la información del polimorfo revelada en el documento D1 no hacía parte del documento de prioridad US 60,836,996 de D1. Para sustentar lo anterior, presento con este recurso copia electrónica del documento de prioridad US 60/836,996 del 11 de agosto de 2006 donde el polimorfo en cuestión no se encuentra revelado.

Es fundamental que el Despacho tenga claro que la información del polimorfo revelada en el documento D1 fue adicionada en la presentación de la solicitud internacional cuya fecha es el **9 de Agosto de 2007.**

Teniendo en cuenta que la información del polimorfo en cuestión del documento D1 se efectuó posteriormente a la prioridad de la solicitud en estudio, dicha divulgación no puede ser anterioridad de la presente solicitud, por consiguiente, la presente solicitud de patente es novedosa con relación a D1.

3.5. Para mayor ilustración del Despacho, a continuación presento una línea de tiempo sobre las divulgaciones relevantes:

Fecha	Hecho	Documento	Contenido
11 de agosto de 2006	Fecha Presentación de la Prioridad reivindicada en D1.	US 60/836,996	**NO contiene:** Forma N-2 de  · 2HCl No contiene: los siguientes patrones de difracción de rayos X en polvo experimentales y simulados (CuKα λ=1,54178 A a T = temperatura ambiente):  FIG. 1 NO contiene: La composición farmacéutica que contiene que comprende la forma N-2
9 de agosto de 2007	Fecha Presentación ante la Oficina Internacional de la solicitud correspondiente a D1.	PCT/US2007/075544	**SI contiene:** *La forma cristalina de diclorhidrato de ((1S)-1-(((2S)-2-(5-(4'-(2-((2S)-1-((2S)-2-((Metoxicarbonil)Amino)-3-Metilbutanol)-2-Pirrolidinil)-1H-Imidazol-5-IL)-4-Bifenilil)-1H-Imidazol-2-il)-1-Pirrolidinil)Carbonil)-2-Metilpropil)Carbamato de metilo.* Posiciones de picos de

			difracción característicos: (2 theta+ 0.1) son: 10.3, 12.4, 12.8, 13.3, 13.6, 15.5, 20.3, 21.2, 22.4, 22.7, 23.7 Una composición que comprende un compuesto de la reivindicación 1 o una sal del mismo y un portador farmacéuticamente aceptable.

Demuestra esta tabla que solo hasta el 9 de agosto de 2007, con la solicitud internacional PCT/US2007/075544 fue divulgado y podía considerarse como parte del estado del arte, lo referente a las siguientes características de D1:

- La forma cristalina de diclorhidrato de ((1S)-1-(((2S)-2-(5-(4'-(2-((2S)-1-((2S)-2-((Metoxicarbonil)Amino)-3-Metilbutanol)-2-Pirrolidinil)-1H-Imidazol-5-IL)-4-Bifenilil)-1H-Imidazol-2-il)-1-Pirrolidinil)Carbonil)-2-Metilpropil)Carbamato de metilo.

- Posiciones de picos de difracción característicos: (2 theta+ 0.1) son: 10.3, 12.4, 12.8, 13.3, 13.6, 15.5, 20.3, 21.2, 22.4, 22.7, 23.7

- Una composición que comprende un compuesto de la reivindicación 1 o una sal del mismo y un portador farmacéuticamente aceptable.

En conclusión, la fecha de divulgación de las características citadas por el Despacho fue el 9 de agosto de 2007, y por lo tanto, **es posterior a la presente solicitud**, cuya fecha de prioridad es 8 de agosto de 2007.

BAKER & McKENZIE

3.6. Por lo anteriormente expuesto, queda demostrado que la Resolución impugnada vulnera la establecido en el artículo 11 del PCT y el artículo 16 de la Decisión 486, y po esto, respetuosamente solicito que se revoque la Resolución núm. 37021 de fecha 20 de junio de 2013, y en su lugar, se conceda el privilegio de patente de invención para la totalidad de las reivindicaciones (1 a 8) de la presente solicitud de patente.

4. NOTIFICACIONES

Recibiré notificaciones en mis oficinas ubicadas en la Avenida 82 No. 10-62 Piso 6 de la ciudad de Bogotá, D.C.

Atentamente,

ÁLVARO CORREA ORDÓÑEZ
C.C. No. 79.143.366 de Usaquén
T.P. 20.281

Anexos:
- Copia electrónica de la prioridad US 60/836,996 del 11 de Agosto de 2006.
- Copia electrónica de la prioridad US 11/835,462 del 8 de Agosto de 2007.

BOGMGT/BOGDMS-#1620722-V1-P2010_000002-RECURSO_DE_REPOSICIÓN.DOC

Industria y Comercio SUPERINTENDENCIA	PLANILLA DE RADICACIÓN - DIGITALIZACIÓN DIARIA ***RELACIÓN DE ANEXOS***	
Dependencia: 2020	Fecha: 2013 / 08 / 09 AAAA MM DD	Recorrido:
Tipo de Radicación: Entrada: ☐ Salida: ☐ Traslado: ☐ Convenio: ☐		
Radicador:		Planilla:

ID	*No. Radicación*	*Consecutivo*	*Item*
1	10- 011972	11	
2			
3			
4			
5			
6			
7			
8			
9			
10			
11			
12			
13			
14			
15			
16			
17			

Item	*Unidad de Conservación*
1	Bolsa
2	Caja
3	Libro
4	Sobre
5	Tomo
6	**Otro**
Item	***Soporte Documental***
7	CD
8	Disquete
9	DVD
10	Folleto
11	Foto
12	Periódico
13	Plano
14	Publicación Periódica
15	USB
16	**Otro**

Observaciones:

Se anexa e-D

Document made available under the Patent Cooperation Treaty (PCT)

International application number: PCT/US2007/075544

International filing date: 09 August 2007 (09.08.2007)

Document type: Certified copy of priority document

Document details: Country/Office: US
Number: 60/836,996
Filing date: 11 August 2006 (11.08.2006)

Date of receipt at the International Bureau: 14 September 2007 (14.09.2007)

Remark: Priority document submitted or transmitted to the International Bureau in compliance with Rule 17.1(a) or (b)

World Intellectual Property Organization (WIPO) - Geneva, Switzerland
Organisation Mondiale de la Propriété Intellectuelle (OMPI) - Genève, Suisse

4408

THE UNITED STATES OF AMERICA

TO ALL TO WHOM THESE PRESENTS SHALL COME:

UNITED STATES DEPARTMENT OF COMMERCE

United States Patent and Trademark Office

September 14, 2007

THIS IS TO CERTIFY THAT ANNEXED HERETO IS A TRUE COPY FROM THE RECORDS OF THE UNITED STATES PATENT AND TRADEMARK OFFICE OF THOSE PAPERS OF THE BELOW IDENTIFIED PATENT APPLICATION THAT MET THE REQUIREMENTS TO BE GRANTED A FILING DATE.

APPLICATION NUMBER: *60/836,996*
FILING DATE: *August 11, 2006*
RELATED PCT APPLICATION NUMBER: *PCT/US07/75544*

THE COUNTRY CODE AND NUMBER OF YOUR PRIORITY APPLICATION, TO BE USED FOR FILING ABROAD UNDER THE PARIS CONVENTION, IS *US60/836,996*

Certified by

Under Secretary of Commerce
for Intellectual Property
and Director of the United States
Patent and Trademark Office

17581 U.S. PTO
081106

112919 U.S.PTO
60/836996
081106

Docket Number	10889PSP

FILING BY "EXPRESS MAIL" UNDER 37 CFR 1.10

EV272263996US	August 11, 2006
Express Mail Label Number	Date of Deposit

Address to: Commissioner for Patents
P.O. Box 1450
Alexandria, VA 22313-1450

PROVISIONAL APPLICATION FOR PATENT COVER SHEET

Transmitted herewith for filing under 37 CFR §1.53(c) is the PROVISIONAL APPLICATION for patent of

INVENTOR(S)

Given Name (first and middle [if any])	Family Name or Surname	Residence (City and either State or Foreign Country)
Carol	Bachand	Quebec, Canada
Makonen	Belema	North Haven, Connecticut
Daniel H.	Deon	Quebec, Canada
Andrew C.	Good	Wallingford, Connecticut
Jason	Goodrich	Meriden, Connecticut
Clint A.	James	Quebec, Canada
Rico	Lavoie	Quebec, Canada
Omar D.	Lopez	Wallingford, Connecticut
Alain	Martel	Quebec, Canada
Nicholas A.	Meanwell	East Hampton, Connecticut
Van N.	Nguyen	New Britain, Connecticut
Jeffrey Lee	Romine	Meriden, Connecticut
Edward H.	Ruediger	Quebec, Canada
Lawrence B.	Snyder	Killingworth, Connecticut
Denis R.	St. Laurent	Newington, Connecticut
Fukang	Yang	Madison, Connecticut

TITLE OF THE INVENTION (280 characters max)

Hepatitis C Virus Inhibitors

CORRESPONDENCE ADDRESS

Direct all correspondence to the address associated with Customer No. 23914, which is currently:
Louis Wille
Bristol-Myers Squibb Company
Patent Department
P.O. Box 4000
Princeton, NJ 08543-4000

ENCLOSED APPLICATION PARTS *(check all that apply)*

- ☒ Specification (Including Any Claims and Abstract) - 263 pages
- ☐ Drawings - sheets
- ☒ Other (specify): Title page (1 page)

METHOD OF PAYMENT

The Commissioner is hereby authorized to charge filing fee and any additional fees required to Deposit Account Number: 19-3880 in the name of Bristol-Myers Squibb Company.

PROVISIONAL FILING FEE AMOUNT: $ 200

Application Size Fee: If the specification and drawings exceed 100 sheets, the application size fee due is $250 for each additional 50 sheets or fraction thereof.

TOTAL FEE AMOUNT : $1200

☐ U.S. Government agency and contract number: (if the invention was made by an agency of the United States Government or under a contract with an agency of the United States Government.)

Respectfully submitted,

Bristol-Myers Squibb Company
Patent Department
P.O. Box 4000
Princeton, NJ 08543-4000

Pamela A. Mingo, Ph.D.
Agent for Applicant
Reg. No. 48,256
Phone: 203-677-7669
Date: 8/11/06

10889PSP

UNITED STATES PROVISIONAL PATENT APPLICATION OF\

Carol Bachand
119 Place Mercure
J5R181 Candiac
Quebec, Canada

Alain Martel
29 Rue Monette
J5B1G8, Delson
Quebec, Canada

Makonen Belema
108 Sugar Hill Road
North Haven, CT 06473
United States of America

Nicholas A. Meanwell
15 Valli Drive
East Hampton, CT 06424
United States of America

Daniel H. Deon
#401-4905 Colomb
J4Z3T2 Brossard
Quebec, Canada

Van N. Nguyen
1317 East Street, Apt. 413
New Britain, CT 06053
United States of America

Andrew C. Good
52 High Hill Road
Wallingford, CT 06492
United States of America

Jeffrey Lee Romine
187 Royal Oak Circle
Meriden, CT 06450
United States of America

Jason Goodrich
71 Scott Street, Apt. 215
Meriden, CT 06450
United States of America

Edward H. Ruediger
133 St. Charles
J4V2K3, Greenfield Park
Quebec, Canada

Clint A. James
500 Boulevard Quinn
J4H2N4, Longueuil
Quebec, Canada

Lawrence B. Snyder
85 Laurel Ridge Trail
Killingworth, CT 06419
United States of America

Rico Lavoie
4 Place de Chambord
J5R4P9, Candiac
Quebec, Canada

Denis R. St. Laurent
7 Fox Run Court
Newington, CT 06111
United States of America

Omar D. Lopez
108 Staffordshire Commons
Wallingford, CT 06492
United States of America

Fukang Yang
282 County Road
Madison, CT 06443
United States of America

FOR

HEPATITIS C VIRUS INHIBITORS

EXPRESS MAILING LABEL NO. EV272263996US

DATE OF DEPOSIT August 11, 2006

I HEREBY CERTIFY THAT THE ATTACHED CORRESPONDENCE AND DOCUMENTS ARE BEING DEPOSITED WITH THE U.S. POSTAL SERVICE "EXPRESS MAIL POST OFFICE TO ADDRESSEE" SERVICE UNDER 37 CFR 1.10 ON THE DATE INDICATED ABOVE AND IS ADDRESSED TO THE COMMISSIONER FOR PATENTS, P.O. BOX 1450, ALEXANDRIA, VA 22313-1450.

Pamela A. Mingo 8/11/06

(Signature) Pamela A. Mingo (Date)

23914
PATENT TRADEMARK OFFICE

HEPATITIS C VIRUS INHIBITORS

The present disclosure is generally directed to antiviral compounds, and more specifically directed to compounds which can inhibit the function of the NS5A protein encoded by Hepatitis C virus (HCV), compositions comprising such compounds, and methods for inhibiting the function of the NS5A protein.

HCV is a major human pathogen, infecting an estimated 170 million persons worldwide - roughly five times the number infected by human immunodeficiency virus type 1. A substantial fraction of these HCV infected individuals develop serious progressive liver disease, including cirrhosis and hepatocellular carcinoma.

Presently, the most effective HCV therapy employs a combination of alpha-interferon and ribavirin, leading to sustained efficacy in 40% of patients. Recent clinical results demonstrate that pegylated alpha-interferon is superior to unmodified alpha-interferon as monotherapy. However, even with experimental therapeutic regimens involving combinations of pegylated alpha-interferon and ribavirin, a substantial fraction of patients do not have a sustained reduction in viral load. Thus, there is a clear and long-felt need to develop effective therapeutics for treatment of HCV infection.

HCV is a positive-stranded RNA virus. Based on a comparison of the deduced amino acid sequence and the extensive similarity in the 5' untranslated region, HCV has been classified as a separate genus in the Flaviviridae family. All members of the Flaviviridae family have enveloped virions that contain a positive stranded RNA genome encoding all known virus-specific proteins via translation of a single, uninterrupted, open reading frame.

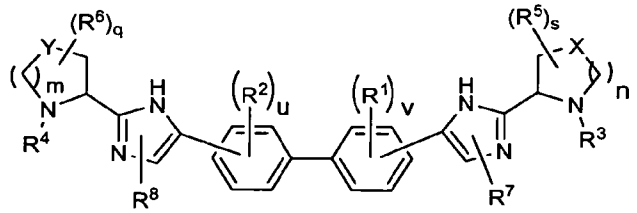
Considerable heterogeneity is found within the nucleotide and encoded amino acid sequence throughout the HCV genome. At least six major genotypes have been characterized, and more than 50 subtypes have been described. The major genotypes of HCV differ in their distribution worldwide, and the clinical significance of the genetic heterogeneity of HCV remains elusive despite numerous studies of the possible effect of genotypes on pathogenesis and therapy.

The single strand HCV RNA genome is approximately 9500 nucleotides in length and has a single open reading frame (ORF) encoding a single large polyprotein of about 3000 amino acids. In infected cells, this polyprotein is cleaved at multiple sites by cellular and viral proteases to produce the structural and non-structural (NS)

proteins. In the case of HCV, the generation of mature non-structural proteins (NS2, NS3, NS4A, NS4B, NS5A, and NS5B) is effected by two viral proteases. The first one is believed to be a metalloprotease and cleaves at the NS2-NS3 junction; the second one is a serine protease contained within the N-terminal region of NS3 (also referred to herein as NS3 protease) and mediates all the subsequent cleavages downstream of NS3, both in cis, at the NS3-NS4A cleavage site, and in trans, for the remaining NS4A-NS4B, NS4B-NS5A, NS5A-NS5B sites. The NS4A protein appears to serve multiple functions, acting as a cofactor for the NS3 protease and possibly assisting in the membrane localization of NS3 and other viral replicase components. The complex formation of the NS3 protein with NS4A seems necessary to the processing events, enhancing the proteolytic efficiency at all of the sites. The NS3 protein also exhibits nucleoside triphosphatase and RNA helicase activities. NS5B (also referred to herein as HCV polymerase) is a RNA-dependent RNA polymerase that is involved in the replication of HCV.

Compounds useful for treating HCV-infected patients are desired which selectively inhibit HCV viral replication. In particular, compounds which are effective to inhibit the function of the NS5A protein are desired. The HCV NS5A protein is described, for example, in Tan, S.-L., Katzel, M.G. *Virology* **2001**, *284*, 1-12; and in Park, K.-J.; Choi, S.-H, *J. Biological Chemistry* **2003**.

In one embodiment the present disclosure provides a compound of Formula (I)



(I),

or a pharmaceutically acceptable salt thereof, wherein

m and n are independently 0, 1, or 2;

q and s are independently 0, 1, 2, 3, or 4;

u and v are independently 0, 1, 2, or 3;

X is selected from O, S, S(O), SO_2, CH_2, CHR^5, and $C(R^5)_2$;

provided that when m is 0, X is selected from CH_2, CHR^5, and $C(R^5)_2$;

Y is selected from O, S, S(O), SO_2, CH_2, CHR^6, and $C(R^6)_2$;

provided that when n is 0, Y is selected from CH_2, CHR^6, and $C(R^6)_2$;

each R^1 and R^2 are each independently selected from alkoxy, alkoxycarbonyl, alkyl, carboxy, halo, haloalkyl, hydroxy, $-NR^aR^b$, (NR^aR^b)alkyl, and (NR^aR^b)carbonyl;

R^3 and R^4 are each independently selected from hydrogen and R^9-C(O)-;

each R^5 and R^6 is independently selected from alkoxy, alkyl, halo, haloalkyl, hydroxy, and $-NR^aR^b$, wherein the alkyl can optionally form a fused cyclopropyl ring with an adjacent carbon atom;

R^7 and R^8 are each independently selected from hydrogen, alkoxycarbonyl, alkyl, carboxy, haloalkyl, (NR^aR^b)carbonyl, and trialkylsilylalkoxyalkyl; and

each R^9 is independently selected from alkoxy, alkoxyalkyl, alkoxycarbonyl, alkoxycarbonylalkyl, alkyl, alkylcarbonylalkyl, aryl, arylalkenyl, arylalkoxy, arylalkyl, aryloxyalkyl, cycloalkyl, (cycloalkyl)alkenyl, (cycloalkyl)alkyl, cycloalkyloxyalkyl, haloalkyl, heterocyclyl, heterocyclylalkenyl, heterocyclylalkoxy, heterocyclylalkyl, heterocyclyloxyalkyl, hydroxyalkyl, $-NR^cR^d$, (NR^cR^d)alkyl, and (NR^cR^d)carbonyl.

In a first aspect of the first embodiment the present disclosure provides a compound of Formula (I), or a pharmaceutically acceptable salt thereof, wherein m and n are each 1.

In a second aspect of the first embodiment the present disclosure provides a compound of Formula (I), or a pharmaceutically acceptable salt thereof, wherein m and n are each 1 and at least one of X and Y is S.

In a third aspect of the first embodiment the present disclosure provides a compound of Formula (I), or a pharmaceutically acceptable salt thereof, wherein m and n are each 1 and X and Y are each S.

In a fourth aspect of the first embodiment the present disclosure provides a compound of Formula (I), or a pharmaceutically acceptable salt thereof, wherein m and n are each 1; X and Y are each S, q and s are each 0; and u and v are each 0.

In a fifth aspect of the first embodiment the present disclosure provides a compound of Formula (I), or a pharmaceutically acceptable salt thereof, wherein m and n are each 1; X and Y are each S; q and s are each 0; u and v are each 0; and at least one of R^3 and R^4 is hydrogen.

In a sixth aspect of the first embodiment the present disclosure provides a compound of Formula (I), or a pharmaceutically acceptable salt thereof, wherein m and n are each 1; X and Y are each S; q and s are each 0; u and v are each 0; and R^3 and R^4 are each -C(O)-R^9.

In a seventh aspect of the first embodiment the present disclosure provides a compound of Formula (I), or a pharmaceutically acceptable salt thereof, wherein m and n are each 1; X and Y are each S; q and s are each 0; u and v are each 0; R^3 and R^4 are each -C(O)-R^9; and each R^9 is independently selected from arylalkyl and heterocyclylalkyl.

In an eighth aspect of the first embodiment the present disclosure provides a compound of Formula (I), or a pharmaceutically acceptable salt thereof, wherein m and n are each 1; X is selected from CHR^5 and $C(R^5)_2$; and Y is selected from CH_2, CHR^6, and $C(R^6)_2$.

In a ninth aspect of the first embodiment the present disclosure provides a compound of Formula (I), or a pharmaceutically acceptable salt thereof, wherein m and n are each 1; X is selected from CHR^5 and $C(R^5)_2$; Y is selected from CH_2, CHR^6, and $C(R^6)_2$; and each R^5 and R^6 is independently selected from halo and hydroxy.

In a tenth aspect of the first embodiment the present disclosure provides a compound of Formula (I) wherein m and n are each 1; X is selected from CHR^5 and $C(R^5)_2$; Y is selected from CH_2, CHR^6, and $C(R^6)_2$; each R^5 and R^6 is independently selected from halo and hydroxy; and each R^1 and R^2 is independently selected from hydrogen, C_1 alkyl, and halo.

In an eleventh aspect of the first embodiment the present disclosure provides a compound of Formula (I), or a pharmaceutically acceptable salt thereof, wherein m and n are each 1; X is selected from CHR^5 and $C(R^5)_2$; Y is selected from CH_2, CHR^6, and $C(R^6)_2$; each R^5 and R^6 is independently selected from halo and hydroxy; and R^1 and R^2 are hydrogen.

In a twelfth aspect of the first embodiment the present disclosure provides a compound of Formula (I), or a pharmaceutically acceptable salt thereof, wherein m and n are each 1; X is selected from CHR^5 and $C(R^5)_2$; Y is selected from CH_2, CHR^6, and $C(R^6)_2$; each R^5 and R^6 is independently selected from halo and hydroxy; and R^1 and R^2 are hydrogen.

In a thirteenth aspect of the first embodiment the present disclosure provides a compound of Formula (I), or a pharmaceutically acceptable salt thereof, wherein m and n are each 1; X is selected from CHR^5 and $C(R^5)_2$; Y is selected from CH_2, CHR^6, and $C(R^6)_2$; each R^5 and R^6 is independently selected from halo and hydroxy; R^1 and R^2 are hydrogen; and at least one of R^3 and R^4 is hydrogen.

In a fourteenth aspect of the first embodiment the present disclosure provides a compound of Formula (I), or a pharmaceutically acceptable salt thereof, wherein m and n are each 1; X is selected from CHR^5 and $C(R^5)_2$; Y is selected from CH_2, CHR^6, and $C(R^6)_2$; each R^5 and R^6 is independently selected from halo and hydroxy; R^1 and R^2 are hydrogen, and R^3 and R^4 are each -C(O)-R^9.

In a fifteenth aspect of the first embodiment the present disclosure provides a compound of Formula (I), or a pharmaceutically acceptable salt thereof, wherein m and n are each 1; X is selected from CHR^5 and $C(R^5)_2$; Y is selected from CH_2, CHR^6, and $C(R^6)_2$; each R^5 and R^6 is independently selected from halo and hydroxy; R^1 and R^2 are hydrogen; R^3 and R^4 are each -C(O)-R^9; and each R^9 is independently selected from alkoxy and arylalkyl.

In a sixteenth aspect of the first embodiment the present disclosure provides a compound of Formula (I), or a pharmaceutically acceptable salt thereof, wherein m and n are each 1 and X and Y are each CH_2.

In a seventeenth aspect of the first embodiment the present disclosure provides a compound of Formula (I), or a pharmaceutically acceptable salt thereof, wherein m and n are each 1; X and Y are each CH_2; and at least one of q and s is 0.

In an eighteenth aspect of the first embodiment the present disclosure provides a compound of Formula (I), or a pharmaceutically acceptable salt thereof, wherein m and n are each 1; X and Y are each CH_2; and q and s are each 0.

In a nineteenth aspect of the first embodiment the present disclosure provides a compound of Formula (I), or a pharmaceutically acceptable salt thereof, wherein m and n are each 1; X and Y are each CH_2; q and s are each 0; and R^1 and R^2 are independently selected from hydrogen, alkyl, halo, and haloalkyl.

In a twentieth aspect of the first embodiment the present disclosure provides a compound of Formula (I), or a pharmaceutically acceptable salt thereof, wherein m and n are each 1; X and Y are each CH_2; q and s are each 0; R^1 and R^2 are independently selected from hydrogen, alkyl, halo, and haloalkyl; and at least one of

R^3 and R^4 is hydrogen.

In a twenty first aspect of the first embodiment the present disclosure provides a compound of Formula (I), or a pharmaceutically acceptable salt thereof, wherein m and n are each 1; X and Y are each CH_2; q and s are each 0; R^1 and R^2 are independently selected from hydrogen, alkyl, halo, and haloalkyl; and R^3 and R^4 are each -C(O)-R^9.

In a twenty second aspect of the first embodiment the present disclosure provides a compound of Formula (I), or a pharmaceutically acceptable salt thereof, wherein m and n are each 1; X and Y are each CH_2; q and s are each 0; R^1 and R^2 are independently selected from hydrogen, alkyl, halo, and haloalkyl; R^3 and R^4 are each -C(O)-R^9; and each R^9 is independently selected from alkoxy, alkoxyalkyl, alkyl, alkylcarbonylalkyl, aryl, arylalkenyl, arylalkoxy, arylalkyl, aryloxyalkyl, cycloalkyl, (cycloalkyl)alkyl, cycloalkyloxyalkyl, heterocyclyl, heterocyclylalkyl, hydroxyalkyl, (NR^cR^d)alkyl, and (NR^cR^d)carbonyl.

In a twenty third aspect of the first embodiment the present disclosure provides a compound of Formula (I), or a pharmaceutically acceptable salt thereof, wherein m and n are each 1; X and Y are each CH_2; q and s are each 0; R^1 and R^2 are independently selected from hydrogen, alkyl, halo, and haloalkyl; R^3 and R^4 are each -C(O)-R^9; and each R^9 is arylalkyl.

In a twenty fourth aspect of the first embodiment the present disclosure provides a compound of Formula (I), or a pharmaceutically acceptable salt thereof, wherein m and n are each 1; X and Y are each CH_2; q and s are each 0; R^1 and R^2 are independently selected from hydrogen, alkyl, halo, and haloalkyl; R^3 and R^4 are each -C(O)-R^9; one R^9 is heterocyclyl, and the other is arylalkyl.

In a twenty fifth aspect of the first embodiment the present disclosure provides a compound of Formula (I), or a pharmaceutically acceptable salt thereof, wherein m and n are each 1; X and Y are each CH_2; q and s are each 0; R^1 and R^2 are independently selected from hydrogen, alkyl, halo, and haloalkyl; R^3 and R^4 are each -C(O)-R^9; one R^9 is heterocyclylalkyl, and the other is arylalkyl.

In a twenty sixth aspect of the first embodiment the present disclosure provides a compound of Formula (I), or a pharmaceutically acceptable salt thereof, wherein m and n are each 1; X and Y are each CH_2; q and s are each 0; R^1 and R^2 are independently selected from hydrogen, alkyl, halo, and haloalkyl; R^3 and R^4 are each

-C(O)-R^9, and each R^9 is (NR^cR^d)alkyl.

In a twenty seventh aspect of the first embodiment the present disclosure provides a compound of Formula (I), or a pharmaceutically acceptable salt thereof, wherein m and n are each 1; X and Y are each CH_2; q and s are each 0; R^1 and R^2 are independently selected from hydrogen, alkyl, halo, and haloalkyl; R^3 and R^4 are each -C(O)-R^9; one R^9 is (NR^cR^d)alkyl, and the other is arylalkyl.

In a twenty eighth aspect of the first embodiment the present disclosure provides a compound of Formula (I), or a pharmaceutically acceptable salt thereof, wherein m and n are each 1; X and Y are each CH_2; q and s are each 0; R^1 and R^2 are independently selected from hydrogen, alkyl, halo, and haloalkyl; R^3 and R^4 are each -C(O)-R^9; one R^9 is selected from alkoxy, alkyl, aryl, arylalkoxy, arylalkyl, cycloalkyl, (cycloalkyl)alkyl, heterocyclyl, and hydroxyalkyl; and the other is selected from alkoxy, alkoxyalkyl, alkyl, alkylcarbonylalkyl, arylalkenyl, aryl, arylalkoxy, aryloxyalkyl, cycloalkyl, (cycloalkyl)alkyl, cycloalkyloxyalkyl, heterocyclyl, hydroxyalkyl, -NR^cR^d, and (NR^cR^d)carbonyl.

In a second embodiment the present disclosure provides a composition comprising a compound of Formula (I), or a pharmaceutically acceptable salt thereof, and a pharmaceutically acceptable carrier.

In a first aspect of the second embodiment the present disclosure provides a composition comprising a compound of Formula (I), or a pharmaceutically acceptable salt thereof, a pharmaceutically acceptable carrier, an interferon and ribavirin.

In a second aspect of the second embodiment the present disclosure provides a composition comprising a compound of Formula (I), or a pharmaceutically acceptable salt thereof, a pharmaceutically acceptable carrier, and a second compound having anti-HCV activity.

In a third aspect of the second embodiment the present disclosure provides a composition comprising a compound of Formula (I), or a pharmaceutically acceptable salt thereof, a pharmaceutically acceptable carrier, and a second compound having anti-HCV activity wherein the second compound having anti-HCV activity is an interferon.

In a fourth aspect of the second embodiment the present disclosure provides a composition comprising a compound of Formula (I), or a pharmaceutically

acceptable salt thereof, a pharmaceutically acceptable carrier, and a second compound having anti-HCV activity wherein the second compound having anti-HCV activity is an interferon, wherein the interferon is selected from interferon alpha 2B, pegylated interferon alpha, consensus interferon, interferon alpha 2A, and lymphoblastiod interferon tau.

In a fifth aspect of the second embodiment the present disclosure provides a composition comprising a compound of Formula (I), or a pharmaceutically acceptable salt thereof, a pharmaceutically acceptable carrier, and a second compound having anti-HCV activity wherein the second compound having anti-HCV activity is selected from interleukin 2, interleukin 6, interleukin 12, a compound that enhances the development of a type 1 helper T cell response, interfering RNA, anti-sense RNA, Imiqimod, ribavirin, an inosine 5'-monophospate dehydrogenase inhibitor, amantadine, and rimantadine.

In a third embodiment the present disclosure provides a method of inhibiting the function of HCV NS5A protein comprising contacting the HCV NS5A protein with a compound of Formula (I), or a pharmaceutically acceptable salt thereof.

In a fourth embodiment the present disclosure provides a method of treating an HCV infection in a patient, comprising administering to the patient a therapeutically effective amount of a compound of Formula (I), or a pharmaceutically acceptable salt thereof.

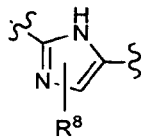
In a first aspect of the fourth embodiment the present disclosure provides a method of treating an HCV infection in a patient, comprising administering to the patient a therapeutically effective amount of a compound of Formula (I), or a pharmaceutically acceptable salt thereof, and further comprising administering a second compound having anti-HCV activity prior to, after, or simultaneously with the compound of Formula (I) or a pharmaceutically acceptable salt thereof.

In a second aspect of the fourth embodiment the present disclosure provides a method of treating an HCV infection in a patient, comprising administering to the patient a therapeutically effective amount of a compound of Formula (I), or a pharmaceutically acceptable salt thereof, and further comprising administering a second compound having anti-HCV activity prior to, after, or simultaneously with the compound of Formula (I) or a pharmaceutically acceptable salt thereof, wherein the second compound having anti-HCV activity is an interferon.

In a third aspect of the fourth embodiment the present disclosure provides a method of treating an HCV infection in a patient, comprising administering to the patient a therapeutically effective amount of a compound of Formula (I), or a pharmaceutically acceptable salt thereof, and further comprising administering a second compound having anti-HCV activity prior to, after, or simultaneously with the compound of Formula (I) or a pharmaceutically acceptable salt thereof, wherein the second compound having anti-HCV activity is an interferon, wherein the interferon is selected from interferon alpha 2B, pegylated interferon alpha, consensus interferon, interferon alpha 2A, and lymphoblastiod interferon tau.

In a fourth aspect of the fourth embodiment the present disclosure provides a method of treating an HCV infection in a patient, comprising administering to the patient a therapeutically effective amount of a compound of Formula (I), or a pharmaceutically acceptable salt thereof, and further comprising administering a second compound having anti-HCV activity prior to, after, or simultaneously with the compound of Formula (I) or a pharmaceutically acceptable salt thereof, wherein the second compound having anti-HCV activity is selected from interleukin 2, interleukin 6, interleukin 12, a compound that enhances the development of a type 1 helper T cell response, interfering RNA, anti-sense RNA, Imiqimod, ribavirin, an inosine 5'-monophospate dehydrogenase inhibitor, amantadine, and rimantadine.

The description of the present disclosure herein should be construed in congruity with the laws and principals of chemical bonding. In some instances it may be necessary to remove a hydrogen atom in order accommodate a substitutent at any given location. For example, in the structure shown below



R^8 may be attached to either the carbon atom in the imidazole ring or, alternatively, R^8 may take the place of the hydrogen atom on the nitrogen ring to form an N-substituted imidazole.

It should be understood that the compounds encompassed by the present disclosure are those that are chemically stable.

It is intended that the definition of any substituent or variable (e.g., R^1, R^2, R^5, R^6, etc.) at a particular location in a molecule be independent of its definitions

elsewhere in that molecule. For example, when u is 2, each of the two R^1 groups may be the same or different.

All patents, patent applications, and literature references cited in the specification are herein incorporated by reference in their entirety. In the case of inconsistencies, the present disclosure, including definitions, will prevail.

As used in the present specification, the following terms have the meanings indicated:

As used herein, the singular forms "a", "an", and "the" include plural reference unless the context clearly dictates otherwise.

Unless stated otherwise, all aryl, cycloalkyl, and heterocyclyl groups of the present disclosure may be substituted as described in each of their respective definitions. For example, the aryl part of an arylalkyl group may be substituted as described in the definition of the term 'aryl'.

The term "alkenyl," as used herein, refers to a straight or branched chain group of two to six carbon atoms containing at least one carbon-carbon double bond.

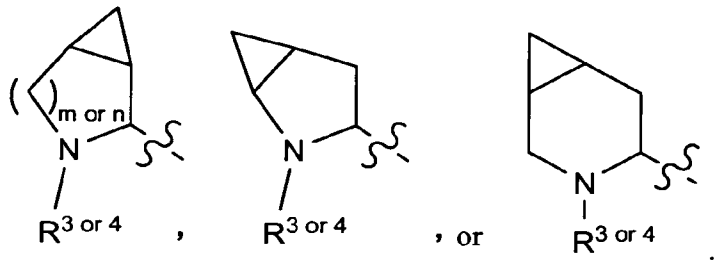
The term "alkoxy," as used herein, refers to an alkyl group attached to the parent molecular moiety through an oxygen atom.

The term "alkoxyalkyl," as used herein, refers to an alkyl group substituted with one, two, or three alkoxy groups.

The term "alkoxycarbonyl," as used herein, refers to an alkoxy group attached to the parent molecular moiety through a carbonyl group.

The term "alkoxycarbonylalkyl," as used herein, refers to an alkyl group substituted with one, two, or three alkoxycarbonyl groups.

The term "alkyl," as used herein, refers to a group derived from a straight or branched chain saturated hydrocarbon containing from one to six carbon atoms. In the compounds of the present disclosure, when R^5 and/or R^6 is alkyl, the alkyl can optionally form a fused cyclopropyl ring with an adjacent carbon atom to provide one of the structures shown below:



The term "alkylcarbonyl," as used herein, refers to an alkyl group attached to the parent molecular moiety through a carbonyl group.

The term "alkylcarbonylalkyl," as used herein, refers to an alkyl group substituted with one, two, or three alkylcarbonyl groups.

The term "alkylcarbonyloxy," as used herein, refers to an alkylcarbonyl group attached to the parent molecular moiety through an oxygen atom.

The term "alkylsulfonyl," as used herein, refers to an alkyl group attached to the parent molecular moiety through a sulfonyl group.

The term "aryl," as used herein, refers to a phenyl group, or a bicyclic fused ring system wherein one or both of the rings is a phenyl group. Bicyclic fused ring systems consist of a phenyl group fused to a four- to six-membered aromatic or non-aromatic carbocyclic ring. The aryl groups of the present disclosure can be attached to the parent molecular moiety through any substitutable carbon atom in the group. Representative examples of aryl groups include, but are not limited to, indanyl, indenyl, naphthyl, phenyl, and tetrahydronaphthyl. The aryl groups of the present disclosure are optionally substituted with one, two, three, four, or five substituents independently selected from alkoxy, alkoxyalkyl, alkoxycarbonyl, alkyl, alkylcarbonyl, a second aryl group, arylalkyl, arylcarbonyl, cyano, halo, haloalkoxy, haloalkyl, heterocyclyl, heterocyclylalkyl, heterocyclylcarbonyl, hydroxy, hydroxyalkyl, nitro, $-NR^xR^y$, (NR^xR^y)alkyl, and oxo, wherein the alkyl part of the arylalkyl and the heterocyclylalkyl are unsubstituted and wherein the second aryl group, the aryl part of the arylalkyl, the aryl part of the arylcarbonyl, the heterocyclyl, and the heterocyclyl part of the heterocyclylalkyl and the heterocyclylcarbonyl are further optionally substituted with one, two, or three substituents independently selected from alkoxy, alkyl, cyano, halo, haloalkoxy, haloalkyl, and nitro.

The term "arylalkenyl," as used herein, refers to an alkenyl group substituted with one, two, or three aryl groups.

The term "arylalkoxy," as used herein, refers to an aryl group attached to the parent molecular moiety through an alkoxy group.

The term "arylalkoxycarbonyl," as used herein, refers to an arylalkoxy group attached to the parent molecular moiety through a carbonyl group.

The term "arylalkyl," as used herein, refers to an alkyl group substituted with one, two, or three aryl groups. The alkyl part of the arylalkyl is further optionally substituted with one or two additional groups independently selected from alkoxy, alkylcarbonyloxy, halo, haloalkoxy, haloalkyl, heterocyclyl, hydroxy, and $-NR^cR^d$, wherein the heterocyclyl is further optionally substituted with one or two substituents independently selected from alkoxy, alkyl, unsubstituted aryl, unsubstitued arylalkoxy, unsubstituted arylalkoxycarbonyl, halo, haloalkoxy, haloalkyl, hydroxy, and $-NR^xR^y$.

The term "arylalkylcarbonyl," as used herein, refers to an arylalkyl group attached to the parent molecular moiety through a carbonyl group.

The term "arylcarbonyl," as used herein, refers to an aryl group attached to the parent molecular moiety through a carbonyl group.

The term "aryloxy," as used herein, refers to an aryl group attached to the parent molecular moiety through an oxygen atom.

The term "aryloxyalkyl," as used herein, refers to an alkyl group substituted with one, two, or three aryloxy groups.

The term "arylsulfonyl," as used herein, refers to an aryl group attached to the parent molecular moiety through a sulfonyl group.

The term "carbonyl," as used herein, refers to -C(O)-.

The term "carboxy," as used herein, refers to $-CO_2H$.

The term "cyano," as used herein, refers to -CN.

The term "cycloalkenyl," as used herein, refers to a non-aromatic, partially unsaturated monocyclic, bicyclic, or tricyclic ring system having three to fourteen carbon atoms and zero heteroatoms. Representative examples of cycloalkenyl groups include, but are not limited to, cyclohexenyl, octahydronaphthalenyl, and norbornylenyl.

The term "cycloalkyl," as used herein, refers to a saturated monocyclic, hydrocarbon ring system having three to seven carbon atoms and zero heteroatoms. Representative examples of cycloalkyl groups include, but are not limited to,

cyclopropyl, cyclopentyl, and cyclohexyl. The cycloalkyl groups of the present disclosure are optionally substituted with one, two, three, four, or five substituents independently selected from alkoxy, alkyl, aryl, cyano, halo, haloalkoxy, haloalkyl, heterocyclyl, hydroxy, hydroxyalkyl, nitro, and $-NR^xR^y$, wherein the aryl and the heterocyclyl are futher optionally substituted with one, two, or three substituents independently selected from alkoxy, alkyl, cyano, halo, haloalkoxy, haloalkyl, hydroxy, and nitro.

The term "(cycloalkyl)alkenyl," as used herein, refers to an alkenyl group substituted with one, two, or three cycloalkyl groups.

The term "(cycloalkyl)alkyl," as used herein, refers to an alkyl group substituted with one, two, or three cycloalkyl groups.

The term "cycloalkyloxy," as used herein, refers to a cycloalkyl group attached to the parent molecular moiety through an oxygen atom.

The term "cycloalkyloxyalkyl," as used herein, refers to an alkyl group substituted with one, two, or three cycloalkyloxy groups.

The term "formyl," as used herein, refers to -CHO.

The terms "halo" and "halogen," as used herein, refer to F, Cl, Br, or I.

The term "haloalkoxy," as used herein, refers to a haloalkyl group attached to the parent molecular moiety through an oxygen atom.

The term "haloalkyl," as used herein, refers to an alkyl group substituted by one, two, three, or four halogen atoms.

The term "heterocyclyl," as used herein, refers to a four-, five-, six-, or seven-membered ring containing one, two, three, or four heteroatoms independently selected from nitrogen, oxygen, and sulfur. The four-membered ring has zero double bonds, the five-membered ring has zero to two double bonds, and the six- and seven-membered rings have zero to three double bonds. The term "heterocyclyl" also includes bicyclic groups in which the heterocyclyl ring is fused to a phenyl group, a monocyclic cycloalkenyl group, a monocyclic cycloalkyl group, or another monocyclic heterocyclyl group. The heterocyclyl groups of the present disclosure can be attached to the parent molecular moiety through a carbon atom or a nitrogen atom in the group. Examples of heterocyclyl groups include, but are not limited to, benzothienyl, furyl, imidazolyl, indolinyl, indolyl, isothiazolyl, isoxazolyl, morpholinyl, oxazolyl, piperazinyl, piperidinyl, pyrazolyl, pyridinyl, pyrrolidinyl,

pyrrolopyridinyl, pyrrolyl, thiazolyl, thienyl, and thiomorpholinyl. The heterocyclyl groups of the present disclosure are optionally substituted with one, two, three, four, or five substituents independently selected from alkoxy, alkoxyalkyl, alkoxycarbonyl, alkyl, alkylcarbonyl, aryl, arylalkyl, arylcarbonyl, cyano, halo, haloalkoxy, haloalkyl, a second heterocyclyl group, heterocyclylalkyl, heterocyclylcarbonyl, hydroxy, hydroxyalkyl, nitro, $-NR^xR^y$, (NR^xR^y)alkyl, and oxo, wherein the alkyl part of the arylalkyl and the heterocyclylalkyl are unsubstituted and wherein the aryl, the aryl part of the arylalkyl, the aryl part of the arylcarbonyl, the second heterocyclyl group, and the heterocyclyl part of the heterocyclylalkyl and the heterocyclylcarbonyl are further optionally substituted with one, two, or three substituents independently selected from alkoxy, alkyl, cyano, halo, haloalkoxy, haloalkyl, and nitro.

The term "heterocyclylalkenyl," as used herein, refers to an alkenyl group substituted with one, two, or three heterocyclyl groups.

The term "heterocyclylalkoxy," as used herein, refers to a heterocyclyl group attached to the parent molecular moiety through an alkoxy group.

The term "heterocyclylalkyl," as used herein, refers to an alkyl group substituted with one, two, or three heterocyclyl groups. The alkyl part of the heterocyclylalkyl is further optionally substituted with one or two additional groups independently selected from alkoxy, alkylcarbonyloxy, halo, haloalkoxy, haloalkyl, heterocyclyl, hydroxy, and $-NR^cR^d$, wherein the aryl is further optionally substitued with one or two substituents independently selected from alkoxy, alkyl, unsubstituted aryl, unsubstitued arylalkoxy, unsubstituted arylalkoxycarbonyl, halo, haloalkoxy, haloalkyl, hydroxy, and $-NR^xR^y$.

The term "heterocyclylalkylcarbonyl," as used herein, refers to a heterocyclylalkyl group attached to the parent molecular moiety through a carbonyl group.

The term "heterocyclylcarbonyl," as used herein, refers to a heterocyclyl group attached to the parent molecular moiety through a carbonyl group.

The term "heterocyclyloxy," as used herein, refers to a heterocyclyl group attached to the parent molecular moiety through an oxygen atom.

The term "heterocyclyloxyalkyl," as used herein, refers to an alkyl group substituted with one, two, or three heterocyclyloxy groups.

The term "hydroxy," as used herein, refers to -OH.

The term "hydroxyalkyl," as used herein, refers to an alkyl group substituted with one, two, or three hydroxy groups.

The term "nitro," as used herein, refers to $-NO_2$.

The term "$-NR^aR^b$," as used herein, refers to two groups, R^a and R^b, which are attached to the parent molecular moiety through a nitrogen atom. R^a and R^b are independently selected from hydrogen, alkenyl, and alkyl.

The term "(NR^aR^b)alkyl," as used herein, refers to an alkyl group substituted with one, two, or three $-NR^aR^b$ groups.

The term "(NR^aR^b)carbonyl," as used herein, refers to an $-NR^aR^b$ group attached to the parent molecular moiety through a carbonyl group.

The term "$-NR^cR^d$," as used herein, refers to two groups, R^c and R^d, which are attached to the parent molecular moiety through a nitrogen atom. R^c and R^d are independently selected from hydrogen, alkoxycarbonyl, alkyl, alkylcarbonyl, alkylsulfonyl, arylalkoxycarbonyl, arylalkyl, arylalkylcarbonyl, arylcarbonyl, arylsulfonyl, formyl, heterocyclylalkyl, heterocyclylalkylcarbonyl, heterocyclylcarbonyl, (NR^eR^f)alkyl, (NR^eR^f)alkylcarbonyl, and (NR^eR^f)carbonyl, wherein the alkyl part of the arylalkyl, the arylalkylcarbonyl, the heterocyclylalkyl, and the heterocyclylalkylcarbonyl are further optionally substituted with one $-NR^eR^f$ group; and wherein the aryl part of the arylalkyl, the arylalkylcarbonyl, the arylcarbonyl, and the arylsulfonyl, and the heterocyclyl part of the heterocyclylalkyl, the heterocyclylalkylcarbonyl, and the heterocyclylcarbonyl are further optionally substituted with one, two, or three substituents independently selected from alkoxy, alkyl, cyano, halo, haloalkoxy, haloalkyl, and nitro.

The term "(NR^cR^d)alkyl," as used herein, refers to an alkyl group substituted with one, two, or three $-NR^cR^d$ groups.

The term "(NR^cR^d)carbonyl," as used herein, refers to an $-NR^cR^d$ group attached to the parent molecular moiety through a carbonyl group.

The term "$-NR^eR^f$," as used herein, refers to two groups, R^e and R^f, which are attached to the parent molecular moiety through a nitrogen atom. R^e and R^f are independently selected from hydrogen, alkyl, unsubstituted aryl, unsubstituted arylalkyl, unsubstituted cycloalkyl, unsubstituted (cyclolalkyl)alkyl, unsubstituted heterocyclyl, unsubstituted heterocyclylalkyl, (NR^xR^y)alkyl, and (NR^xR^y)carbonyl.

The term "(NR^eR^f)alkyl," as used herein, refers to an alkyl group substituted with one, two, or three -NR^eR^f groups.

The term "(NR^eR^f)alkylcarbonyl," as used herein, refers to an (NR^eR^f)alkyl group attached to the parent molecular moiety through a carbonyl group.

The term "(NR^eR^f)carbonyl," as used herein, refers to an -NR^eR^f group attached to the parent molecular moiety through a carbonyl group.

The term "-NR^xR^y," as used herein, refers to two groups, R^x and R^y, which are attached to the parent molecular moiety through a nitrogen atom. R^x and R^y are independently selected from hydrogen, alkoxycarbonyl, alkyl, alkylcarbonyl, unsubstituted aryl, unsubstituted arylalkyl, unsubstituted cycloalkyl, and unsubstituted heterocyclyl.

The term "(NR^xR^y)alkyl," as used herein, refers to an alkyl group substituted with one, two, or three -NR^xR^y groups.

The term "oxo," as used herein, refers to =O.

The term "sulfonyl," as used herein, refers to -SO_2-.

The term "trialkylsilyl," as used herein, refers to -SiR_3, wherein R is alkyl. The R groups may be the same or different.

The term "trialkylsilylalkyl," as used herein, refers to an alkyl group substituted with one, two, or three trialkylsilyl groups.

The term "trialkylsilylalkoxy," as used herein, refers to a trialkylsilylalkyl group attached to the parent molecular moiety through an oxygen atom.

The term "trialkylsilylalkoxyalkyl," as used herein, refers to an alkyl group substituted with one, two, or three trialkylsilylalkoxy groups.

Asymmetric centers exist in the compounds of the present disclosure. These centers are designated by the symbols "R" or "S", depending on the configuration of substituents around the chiral carbon atom. It should be understood that the disclosure encompasses all stereochemical isomeric forms, or mixtures thereof, which possess the ability to inhibit NS5A. Individual stereoisomers of compounds can be prepared synthetically from commercially available starting materials which contain chiral centers or by preparation of mixtures of enantiomeric products followed by separation such as conversion to a mixture of diastereomers followed by separation or recrystallization, chromatographic techniques, or direct separation of enantiomers on chiral chromatographic columns. Starting compounds of particular

stereochemistry are either commercially available or can be made and resolved by techniques known in the art.

Certain compounds of the present disclosure may also exist in different stable conformational forms which may be separable. Torsional asymmetry due to restricted rotation about an asymmetric single bond, for example because of steric hindrance or ring strain, may permit separation of different conformers. The present disclosure includes each conformational isomer of these compounds and mixtures thereof.

The term "compounds of the present disclosure", and equivalent expressions, are meant to embrace compounds of Formula (I), and pharmaceutically acceptable enantiomers, diastereomers, and salts thereof. Similarly, references to intermediates are meant to embrace their salts where the context so permits.

The compounds of the present disclosure can exist as pharmaceutically acceptable salts. The term "pharmaceutically acceptable salt," as used herein, represents salts or zwitterionic forms of the compounds of the present disclosure which are water or oil-soluble or dispersible, which are, within the scope of sound medical judgment, suitable for use in contact with the tissues of patients without excessive toxicity, irritation, allergic response, or other problem or complication commensurate with a reasonable benefit/risk ratio, and are effective for their intended use The salts can be prepared during the final isolation and purification of the compounds or separately by reacting a suitable nitrogen atom with a suitable acid. Representative acid addition salts include acetate, adipate, alginate, citrate, aspartate, benzoate, benzenesulfonate, bisulfate, butyrate, camphorate, camphorsulfonate; digluconate, glycerophosphate, hemisulfate, heptanoate, hexanoate, formate, fumarate, hydrochloride, hydrobromide, hydroiodide, 2-hydroxyethanesulfonate, lactate, maleate, mesitylenesulfonate, methanesulfonate, naphthylenesulfonate, nicotinate, 2-naphthalenesulfonate, oxalate, palmoate, pectinate, persulfate, 3-phenylproprionate, picrate, pivalate, propionate, succinate, tartrate, trichloroacetate, trifluoroacetate, phosphate, glutamate, bicarbonate, para-toluenesulfonate, and undecanoate. Examples of acids which can be employed to form pharmaceutically acceptable addition salts include inorganic acids such as hydrochloric, hydrobromic, sulfuric, and phosphoric, and organic acids such as oxalic, maleic, succinic, and citric.

Basic addition salts can be prepared during the final isolation and purification of the compounds by reacting a carboxy group with a suitable base such as the hydroxide, carbonate, or bicarbonate of a metal cation or with ammonia or an organic primary, secondary, or tertiary amine. The cations of pharmaceutically acceptable salts include lithium, sodium, potassium, calcium, magnesium, and aluminum, as well as nontoxic quaternary amine cations such as ammonium, tetramethylammonium, tetraethylammonium, methylamine, dimethylamine, trimethylamine, triethylamine, diethylamine, ethylamine, tributylamine, pyridine, N,N-dimethylaniline, N-methylpiperidine, N-methylmorpholine, dicyclohexylamine, procaine, dibenzylamine, N,N-dibenzylphenethylamine, and N,N'-dibenzylethylenediamine. Other representative organic amines useful for the formation of base addition salts include ethylenediamine, ethanolamine, diethanolamine, piperidine, and piperazine.

When it is possible that, for use in therapy, therapeutically effective amounts of a compound of formula (I), as well as pharmaceutically acceptable salts thereof, may be administered as the raw chemical, it is possible to present the active ingredient as a pharmaceutical composition. Accordingly, the disclosure further provides pharmaceutical compositions, which include therapeutically effective amounts of compounds of formula (I) or pharmaceutically acceptable salts thereof, and one or more pharmaceutically acceptable carriers, diluents, or excipients. The term "therapeutically effective amount," as used herein, refers to the total amount of each active component that is sufficient to show a meaningful patient benefit, e.g., a sustained reduction in viral load. When applied to an individual active ingredient, administered alone, the term refers to that ingredient alone. When applied to a combination, the term refers to combined amounts of the active ingredients that result in the therapeutic effect, whether administered in combination, serially, or simultaneously. The compounds of formula (I) and pharmaceutically acceptable salts thereof, are as described above. The carrier(s), diluent(s), or excipient(s) must be acceptable in the sense of being compatible with the other ingredients of the formulation and not deleterious to the recipient thereof. In accordance with another aspect of the present disclosure there is also provided a process for the preparation of a pharmaceutical formulation including admixing a compound of formula (I), or a pharmaceutically acceptable salt thereof, with one or more pharmaceutically

acceptable carriers, diluents, or excipients. The term "pharmaceutically acceptable," as used herein, refers to those compounds, materials, compositions, and/or dosage forms which are, within the scope of sound medical judgment, suitable for use in contact with the tissues of patients without excessive toxicity, irritation, allergic response, or other problem or complication commensurate with a reasonable benefit/risk ratio, and are effective for their intended use.

Pharmaceutical formulations may be presented in unit dose forms containing a predetermined amount of active ingredient per unit dose. Dosage levels of between about 0.01 and about 250 milligram per kilogram ("mg/kg") body weight per day, preferably between about 0.05 and about 100 mg/kg body weight per day of the compounds of the present disclosure are typical in a monotherapy for the prevention and treatment of HCV mediated disease. Typically, the pharmaceutical compositions of this disclosure will be administered from about 1 to about 5 times per day or alternatively, as a continuous infusion. Such administration can be used as a chronic or acute therapy. The amount of active ingredient that may be combined with the carrier materials to produce a single dosage form will vary depending on the condition being treated, the severity of the condition, the time of administration, the route of administration, the rate of excretion of the compound employed, the duration of treatment, and the age, gender, weight, and condition of the patient. Preferred unit dosage formulations are those containing a daily dose or sub-dose, as herein above recited, or an appropriate fraction thereof, of an active ingredient. Generally, treatment is initiated with small dosages substantially less than the optimum dose of the compound. Thereafter, the dosage is increased by small increments until the optimum effect under the circumstances is reached. In general, the compound is most desirably administered at a concentration level that will generally afford antivirally effective results without causing any harmful or deleterious side effects.

When the compositions of this disclosure comprise a combination of a compound of the present disclosure and one or more additional therapeutic or prophylactic agent, both the compound and the additional agent are usually present at dosage levels of between about 10 to 150%, and more preferably between about 10 and 80% of the dosage normally administered in a monotherapy regimen.

Pharmaceutical formulations may be adapted for administration by any appropriate route, for example by the oral (including buccal or sublingual), rectal,

nasal, topical (including buccal, sublingual, or transdermal), vaginal, or parenteral (including subcutaneous, intracutaneous, intramuscular, intra-articular, intrasynovial, intrasternal, intrathecal, intralesional, intravenous, or intradermal injections or infusions) route. Such formulations may be prepared by any method known in the art of pharmacy, for example by bringing into association the active ingredient with the carrier(s) or excipient(s). Oral administration or administration by injection are preferred.

Pharmaceutical formulations adapted for oral administration may be presented as discrete units such as capsules or tablets; powders or granules; solutions or suspensions in aqueous or non-aqueous liquids; edible foams or whips; or oil-in-water liquid emulsions or water-in-oil emulsions.

For instance, for oral administration in the form of a tablet or capsule, the active drug component can be combined with an oral, non-toxic pharmaceutically acceptable inert carrier such as ethanol, glycerol, water, and the like. Powders are prepared by comminuting the compound to a suitable fine size and mixing with a similarly comminuted pharmaceutical carrier such as an edible carbohydrate, as, for example, starch or mannitol. Flavoring, preservative, dispersing, and coloring agent can also be present.

Capsules are made by preparing a powder mixture, as described above, and filling formed gelatin sheaths. Glidants and lubricants such as colloidal silica, talc, magnesium stearate, calcium stearate, or solid polyethylene glycol can be added to the powder mixture before the filling operation. A disintegrating or solubilizing agent such as agar-agar, calcium carbonate, or sodium carbonate can also be added to improve the availability of the medicament when the capsule is ingested.

Moreover, when desired or necessary, suitable binders, lubricants, disintegrating agents, and coloring agents can also be incorporated into the mixture. Suitable binders include starch, gelatin, natural sugars such as glucose or beta-lactose, corn sweeteners, natural and synthetic gums such as acacia, tragacanth or sodium alginate, carboxymethylcellulose, polyethylene glycol, and the like. Lubricants used in these dosage forms include sodium oleate, sodium chloride, and the like. Disintegrators include, without limitation, starch, methyl cellulose, agar, betonite, xanthan gum, and the like. Tablets are formulated, for example, by preparing a powder mixture, granulating or slugging, adding a lubricant and

disintegrant, and pressing into tablets. A powder mixture is prepared by mixing the compound, suitable comminuted, with a diluent or base as described above, and optionally, with a binder such as carboxymethylcellulose, an aliginate, gelating, or polyvinyl pyrrolidone, a solution retardant such as paraffin, a resorption accelerator such as a quaternary salt and/or and absorption agent such as betonite, kaolin, or dicalcium phosphate. The powder mixture can be granulated by wetting with a binder such as syrup, starch paste, acadia mucilage, or solutions of cellulosic or polymeric materials and forcing through a screen. As an alternative to granulating, the powder mixture can be run through the tablet machine and the result is imperfectly formed slugs broken into granules. The granules can be lubricated to prevent sticking to the tablet forming dies by means of the addition of stearic acid, a stearate salt, talc, or mineral oil. The lubricated mixture is then compressed into tablets. The compounds of the present disclosure can also be combined with a free flowing inert carrier and compressed into tablets directly without going through the granulating or slugging steps. A clear or opaque protective coating consisting of a sealing coat of shellac, a coating of sugar or polymeric material, and a polish coating of wax can be provided. Dyestuffs can be added to these coatings to distinguish different unit dosages.

Oral fluids such as solution, syrups, and elixirs can be prepared in dosage unit form so that a given quantity contains a predetermined amount of the compound. Syrups can be prepared by dissolving the compound in a suitably flavored aqueous solution, while elixirs are prepared through the use of a non-toxic vehicle. Solubilizers and emulsifiers such as ethoxylated isostearyl alcohols and polyoxyethylene sorbitol ethers, preservatives, flavor additive such as peppermint oil or natural sweeteners, or saccharin or other artificial sweeteners, and the like can also be added.

Where appropriate, dosage unit formulations for oral administration can be microencapsulated. The formulation can also be prepared to prolong or sustain the release as for example by coating or embedding particulate material in polymers, wax, or the like.

The compounds of formula (I), and pharmaceutically acceptable salts thereof, can also be administered in the form of liposome delivery systems, such as small unilamellar vesicles, large unilamellar vesicles, and multilamellar vesicles.

Liposomes can be formed from a variety of phopholipids, such as cholesterol, stearylamine, or phophatidylcholines.

The compounds of formula (I) and pharmaceutically acceptable salts thereof may also be delivered by the use of monoclonal antibodies as individual carriers to which the compound molecules are coupled. The compounds may also be coupled with soluble polymers as targetable drug carriers. Such polymers can include polyvinylpyrrolidone, pyran copolymer, polyhydroxypropylmethacrylamidephenol, polyhydroxyethylaspartamidephenol, or polyethyleneoxidepolylysine substituted with palitoyl residues. Furthermore, the compounds may be coupled to a class of biodegradable polymers useful in achieving controlled release of a drug, for example, polylactic acid, polepsilon caprolactone, polyhydroxy butyric acid, polyorthoesters, polyacetals, polydihydropyrans, polycyanoacrylates, and cross-linked or amphipathic block copolymers of hydrogels.

Pharmaceutical formulations adapted for transdermal administration may be presented as discrete patches intended to remain in intimate contact with the epidermis of the recipient for a prolonged period of time. For example, the active ingredient may be delivered from the patch by iontophoresis as generally described in *Pharmaceutical Research* **1986**, *3*(6), 318.

Pharmaceutical formulations adapted for topical administration may be formulated as ointments, creams, suspensions, lotions, powders, solutions, pastes, gels, sprays, aerosols, or oils.

For treatments of the eye or other external tissues, for example mouth and skin, the formulations are preferably applied as a topical ointment or cream. When formulated in an ointment, the active ingredient may be employed with either a paraffinic or a water-miscible ointment base. Alternatively, the active ingredient may be formulated in a cream with an oil-in-water cream base or a water-in oil base.

Pharmaceutical formulations adapted for topical administrations to the eye include eye drops wherein the active ingredient is dissolved or suspended in a suitable carrier, especially an aqueous solvent.

Pharmaceutical formulations adapted for topical administration in the mouth include lozenges, pastilles, and mouth washes.

Pharmaceutical formulations adapted for rectal administration may be presented as suppositories or as enemas.

Pharmaceutical formulations adapted for nasal administration wherein the carrier is a solid include a course powder having a particle size for example in the range 20 to 500 microns which is administered in the manner in which snuff is taken, *i.e.*, by rapid inhalation through the nasal passage from a container of the powder held close up to the nose. Suitable formulations wherein the carrier is a liquid, for administration as a nasal spray or nasal drops, include aqueous or oil solutions of the active ingredient.

Pharmaceutical formulations adapted for administration by inhalation include fine particle dusts or mists, which may be generated by means of various types of metered, dose pressurized aerosols, nebulizers, or insufflators.

Pharmaceutical formulations adapted for vaginal administration may be presented as pessaries, tampons, creams, gels, pastes, foams, or spray formulations.

Pharmaceutical formulations adapted for parenteral administration include aqueous and non-aqueous sterile injection solutions which may contain anti-oxidants, buffers, bacteriostats, and soutes which render the formulation isotonic with the blood of the intended recipient; and aqueous and non-aqueous sterile suspensions which may include suspending agents and thickening agents. The formulations may be presented in unit-dose or multi-dose containers, for example sealed ampoules and vials, and may be stored in a freeze-dried (lyophilized) condition requiring only the addition of the sterile liquid carrier, for example water for injections, immediately prior to use. Extemporaneous injection solutions and suspensions may be prepared from sterile powders, granules, and tablets.

It should be understood that in addition to the ingredients particularly mentioned above, the formulations may include other agents conventional in the art having regard to the type of formulation in question, for example those suitable for oral administration may include flavoring agents.

The term "patient" includes both human and other mammals.

The term "treating" refers to: (i) preventing a disease, disorder or condition from occurring in a patient that may be predisposed to the disease, disorder, and/or condition but has not yet been diagnosed as having it; (ii) inhibiting the disease, disorder, or condition, i.e., arresting its development; and (iii) relieving the disease, disorder, or condition, i.e., causing regression of the disease, disorder, and/or condition.

Certain illustrative HCV inhibitor compounds which can be administered with the compounds of the present disclosure include those disclosed in the following publications: WO 02/04425 A2 published January 17, 2002, WO 03/007945 A1 published January 30, 2003, WO 03/010141 A2 published February 6, 2003, WO 03/010142 A2 published February 6, 2003, WO 03/010143 A1 published February 6, 2003, WO 03/000254 A1 published January 3, 2003, WO 01/32153 A2 published May 10, 2001, WO 00/06529 published February 10, 2000, WO 00/18231 published April 6, 2000, WO 00/10573 published March 2, 2000, WO 00/13708 published March 16, 2000, WO 01/85172 A1 published November 15, 2001, WO 03/037893 A1 published May 8, 2003, WO 03/037894 A1 published May 8, 2003, WO 03/037895 A1 published May 8, 2003, WO 02/100851 A2 published December 19, 2002, WO 02/100846 A1 published December 19, 2002, EP 1256628 A2 published November 13, 2002, WO 99/01582 published January 14, 1999, WO 00/09543 published February 24, 2000.

The compounds of the present disclosure can also be administered with a cyclosporin, for example, cyclosporin A. Cyclosporin A has been shown to be active against HCV in clinical trials (*Hepatology* **2003**, *38*, 1282; *Biochem. Biophys. Res. Commun.* **2004**, *313*, 42; *J. Gastroenterol.* **2003**, *38*, 567).

Table 1 below lists some illustrative examples of compounds that can be administered with the compounds of this disclosure. The compounds of the present disclosure can be administered with other anti-HCV activity compounds in combination therapy, either jointly or separately, or by combining the compounds into a composition.

Table 1

Brand Name	Type of Inhibitor or Target	Source Company
Omega IFN	IFN-ω	BioMedicines Inc., Emeryville, CA
BILN-2061	serine protease inhibitor	Boehringer Ingelheim Pharma KG, Ingelheim, Germany
Summetrel	antiviral	Endo Pharmaceuticals

Brand Name	Type of Inhibitor or Target	Source Company
		Holdings Inc., Chadds Ford, PA
Roferon A	IFN-α2a	F. Hoffmann-La Roche LTD, Basel, Switzerland
Pegasys	PEGylated IFN-α2a	F. Hoffmann-La Roche LTD, Basel, Switzerland
Pegasys and Ribavirin	PEGylated IFN-α2a/ribavirin	F. Hoffmann-La Roche LTD, Basel, Switzerland
CellCept	HCV IgG immunosuppressant	F. Hoffmann-La Roche LTD, Basel, Switzerland
Wellferon	lymphoblastoid IFN-αn1	GlaxoSmithKline plc, Uxbridge, UK
Albuferon - α	albumin IFN-α2b	Human Genome Sciences Inc., Rockville, MD
Levovirin	ribavirin	ICN Pharmaceuticals, Costa Mesa, CA
IDN-6556	caspase inhibitor	Idun Pharmaceuticals Inc., San Diego, CA
IP-501	antifibrotic	Indevus Pharmaceuticals Inc., Lexington, MA
Actimmune	INF-γ	InterMune Inc., Brisbane, CA
Infergen A	IFN alfacon-1	InterMune Pharmaceuticals Inc., Brisbane, CA
ISIS 14803	antisense	ISIS Pharmaceuticals Inc, Carlsbad, CA/Elan Phamaceuticals Inc., New York, NY

Brand Name	Type of Inhibitor or Target	Source Company
JTK-003	RdRp inhibitor	Japan Tobacco Inc., Tokyo, Japan
Pegasys and Ceplene	PEGylated IFN-α2a/ immune modulator	Maxim Pharmaceuticals Inc., San Diego, CA
Ceplene	immune modulator	Maxim Pharmaceuticals Inc., San Diego, CA
Civacir	HCV IgG immunosuppressant	Nabi Biopharmaceuticals Inc., Boca Raton, FL
Intron A and Zadaxin	IFN-α2b/α1-thymosin	RegeneRx Biopharmiceuticals Inc., Bethesda, MD/ SciClone Pharmaceuticals Inc, San Mateo, CA
Levovirin	IMPDH inhibitor	Ribapharm Inc., Costa Mesa, CA
Viramidine	IMPDH inhibitor	Ribapharm Inc., Costa Mesa, CA
Heptazyme	ribozyme	Ribozyme Pharmaceuticals Inc., Boulder, CO
Intron A	IFN-α2b	Schering-Plough Corporation, Kenilworth, NJ
PEG-Intron	PEGylated IFN-α2b	Schering-Plough Corporation, Kenilworth, NJ
Rebetron	IFN-α2b/ribavirin	Schering-Plough Corporation,

Brand Name	Type of Inhibitor or Target	Source Company
		Kenilworth, NJ
Ribavirin	ribavirin	Schering-Plough Corporation, Kenilworth, NJ
PEG-Intron / Ribavirin	PEGylated IFN-α2b/ribavirin	Schering-Plough Corporation, Kenilworth, NJ
Zadazim	immune modulator	SciClone Pharmaceuticals Inc., San Mateo, CA
Rebif	IFN-β1a	Serono, Geneva, Switzerland
IFN-β and EMZ701	IFN-β and EMZ701	Transition Therapeutics Inc., Ontario, Canada
T67	β-tubulin inhibitor	Tularik Inc., South San Francisco, CA
VX-497	IMPDH inhibitor	Vertex Pharmaceuticals Inc., Cambridge, MA
VX-950/LY-570310	serine protease inhibitor	Vertex Pharmaceuticals Inc., Cambridge, MA/ Eli Lilly and Co. Inc., Indianapolis, IN
Omniferon	natural IFN-α	Viragen Inc., Plantation, FL
XTL-002	monoclonal antibody	XTL Biopharmaceuticals Ltd., Rehovot, Isreal

The compounds of the present disclosure may also be used as laboratory reagents. Compounds may be instrumental in providing research tools for designing

of viral replication assays, validation of animal assay systems and structural biology studies to further enhance knowledge of the HCV disease mechanisms. Further, the compounds of the present disclosure are useful in establishing or determining the binding site of other antiviral compounds, for example, by competitive inhibition.

The compounds of this disclosure may also be used to treat or prevent viral contamination of materials and therefore reduce the risk of viral infection of laboratory or medical personnel or patients who come in contact with such materials, e.g., blood, tissue, surgical instruments and garments, laboratory instruments and garments, and blood collection or transfusion apparatuses and materials.

This disclosure is intended to encompass compounds having formula (I) when prepared by synthetic processes or by metabolic processes including those occurring in the human or animal body (in vivo) or processes occurring in vitro.

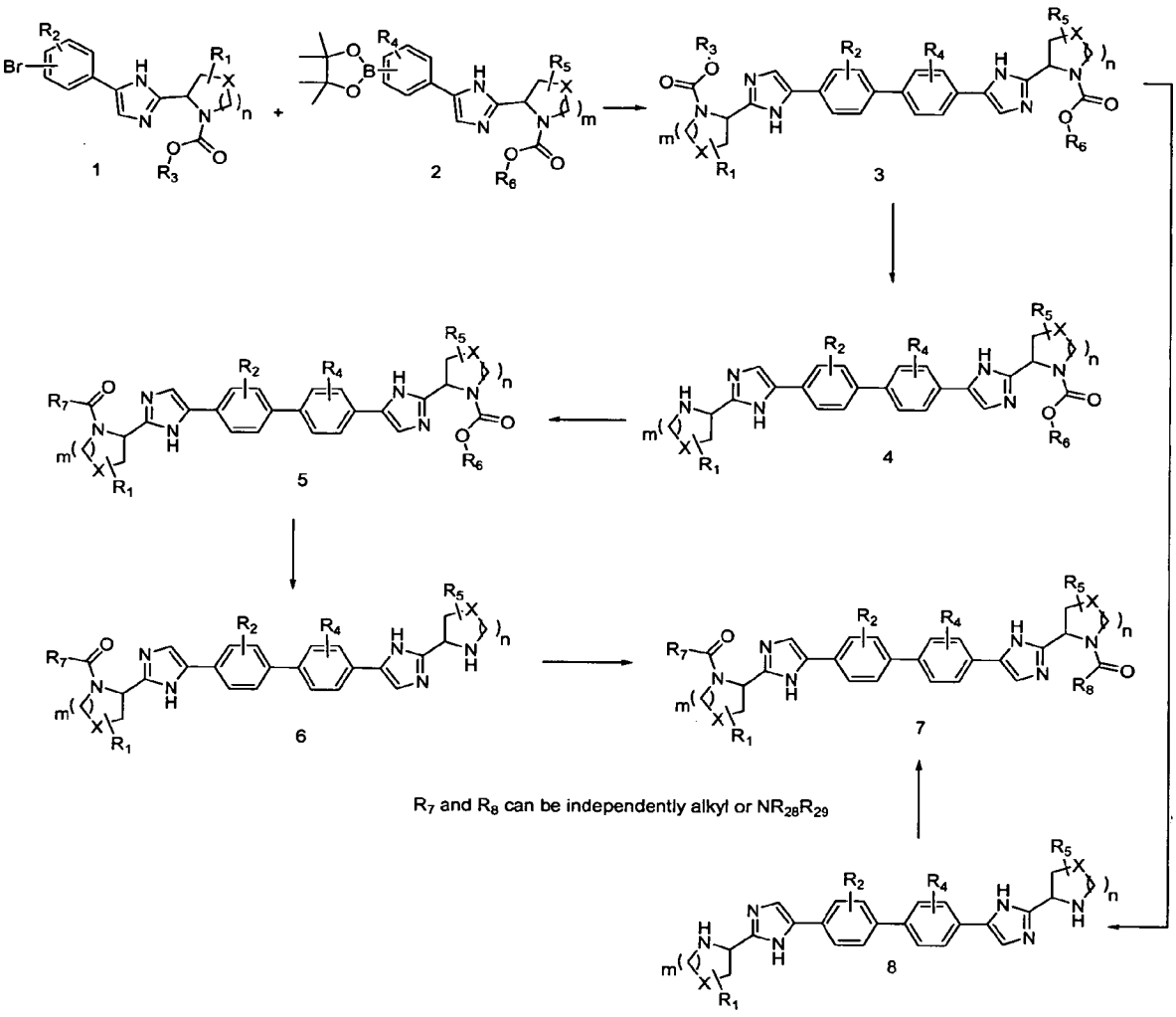
The abbreviations used in the present application, including particularly in the illustrative schemes and examples which follow, are well-known to those skilled in the art. Some of the abbreviations used are as follows: HATU for O-(7-azabenzotriazol-1-yl)-N,N,N',N'-tetramethyluronium hexafluorophosphate; Boc or BOC for tert-butoxycarbonyl; NBS for N-bromosuccinimide; SEM for -(trimethylsilyl)ethoxymethyl; DMSO for dimethylsulfoxide; MeOH for methanol; TFA for trifluoroacetic acid; RT and t_R for retention time; EDCI for 1-(3-dimethylaminopropyl)-3-ethylcarbodiimide hydrochloride; DMAP for 4-dimethylaminopyridine; THF for tetrahydrofuran; DBU for 1,8-diazabicyclo[5.4.0]undec-7-ene; *t*-Bu; HMDS for hexamethyldisilazide; DMF for N,N-dimethylformamide; Ph for phenyl; OAc for acetate; EtOAc for ethyl acetate; dppf for 1,1'-bis(diphenylphosphino)ferrocene; iPr_2EtN for diisopropylethylamine; Cbz for carbobenzyloxy; n-BuLi for n-butyllithium; ACN for acetonitrile; h for hours; and m for minutes.

The compounds and processes of the present disclosure will be better understood in connection with the following synthetic schemes which illustrate the methods by which the compounds of the present disclosure may be prepared. Starting materials can be obtained from commercial sources or prepared by well-established literature methods known to those of ordinary skill in the art. It will be readily apparent to one of ordinary skill in the art that the compounds defined above can be synthesized by substitution of the appropriate reactants and agents in the

syntheses shown below. It will also be readily apparent to one skilled in the art that the selective protection and deprotection steps, as well as the order of the steps themselves, can be carried out in varying order, depending on the nature of the variables to successfully complete the syntheses below. The variables are as defined above unless otherwise noted below.

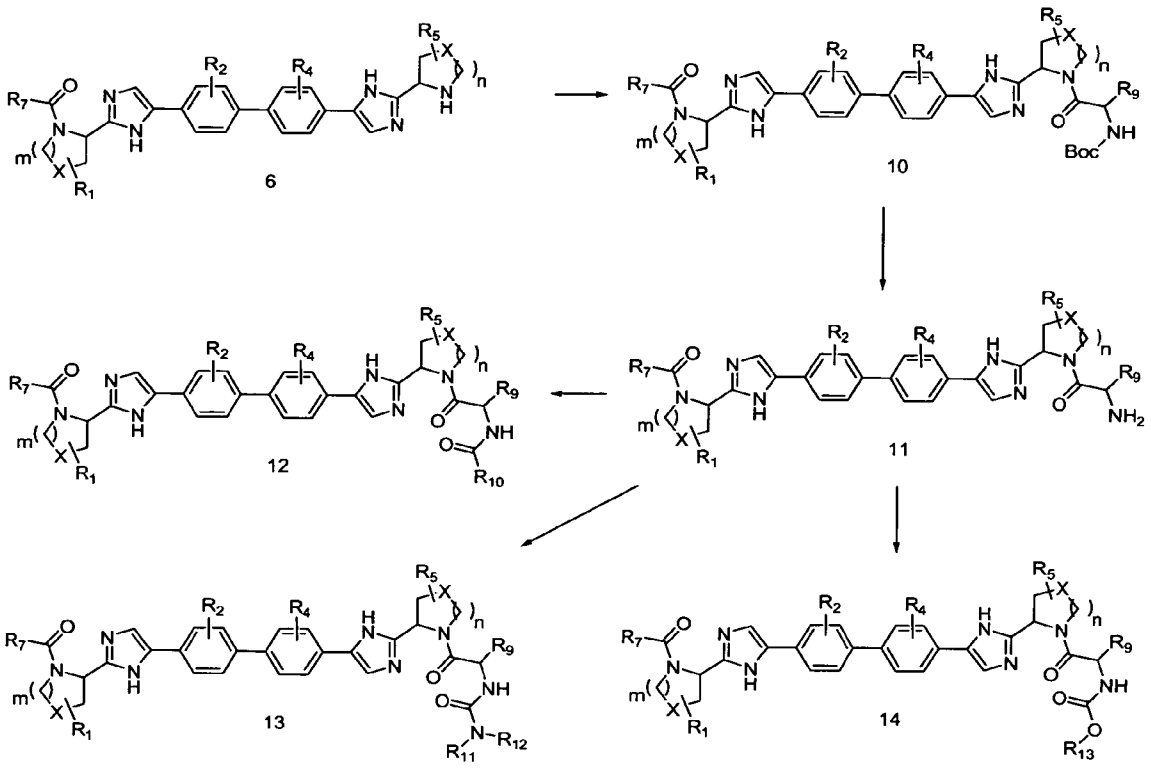
Scheme 1: Symmetric or Asymmetric Biphenyls

Aryl halide **1** and boronic ester **2** can be coupled to produce biaryl **3** using standard Suzuki-Miayura coupling conditions (*Angew Chem. Int. Ed. Engl* **2001**, 40, 4544). It should be noted that the boronic acid analog of **2** may be used in place of the ester. Mono-deprotection of the pyrrolidine moiety may be accomplished when R_3 and R_6 are different. When R_3 = benzyl, and R_6 = t-butyl treatment to hydrogenolytic conditions produces **4**. For example, Pd / C catalyst in the presence of a base such as potassium carbonate can be used. Acylation of **4** can be accomplished under standard acylation conditions. A coupling reagent such as HATU in combination with an amine base such as Hunig's base can be used in this regard. Alternatively, **4** may be reacted with an isocyanate ($R_{28}NCO$) or carbamoyl chloride ($R_{28}R_{29}COCl$) to provide **5**. Further deprotection of **5** can be accomplished by treatment with strong acid such as HCl or trifluoroacetic acid. Standard conditions analogous to those used to convert **4** to **5** can be used to prepare **7** from **6**. In another embodiment where $R_3 = R_6$ = t-Bu, direct conversion to **8** can be accomplished by treatment of **3** with strong acid such as HCl or trifluoroacetic acid. Conversion of **8** to **7** is accomplished in analogous fashion to the methods used to prepare **5** from **4** or **7** from **6**. In this instance however, **7** will be symmetrical in nature.



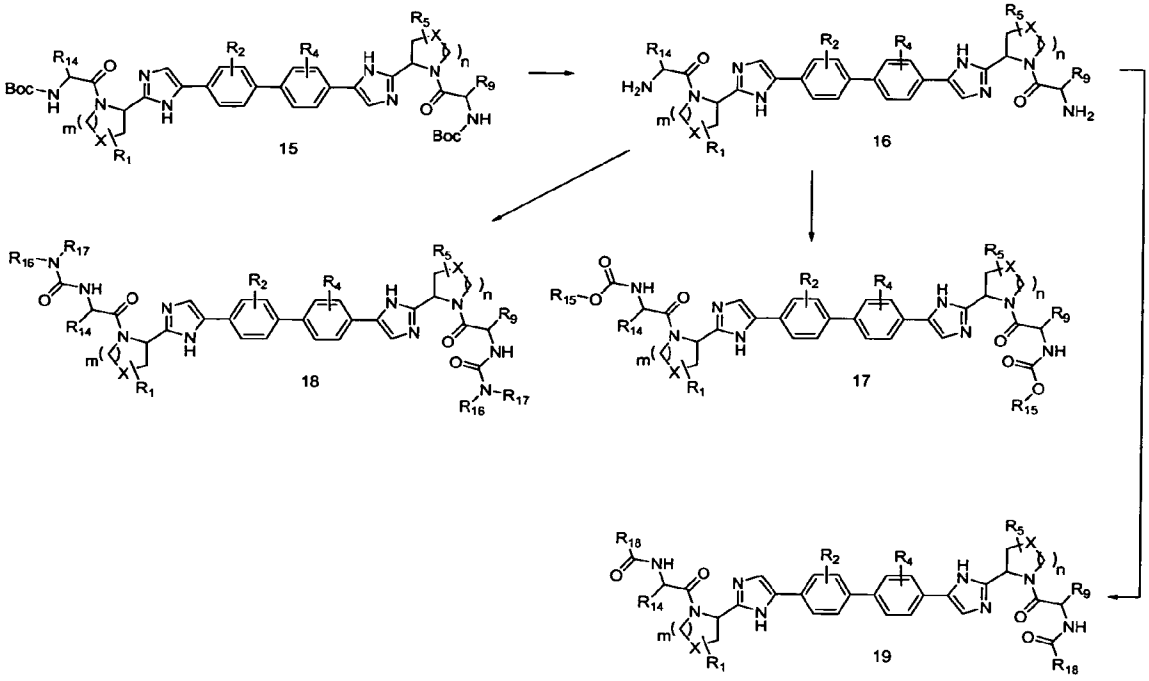
Scheme 2: Asymmetric Cap Elaborated Biphenyls

Conversion of **6** (from Scheme 1) to **10** can be done using standard amide coupling conditions such as HATU with an amine base, such as Hunig's base. Deprotection can be accomplished with strong acid such as HCl or trifluoroacetic acid affording **11**. Compound **11** can then be converted to **12**, **13**, or **14** using an acid chloride, an isocyanate or carbamoyl chloride, or a chloroformate respectively.



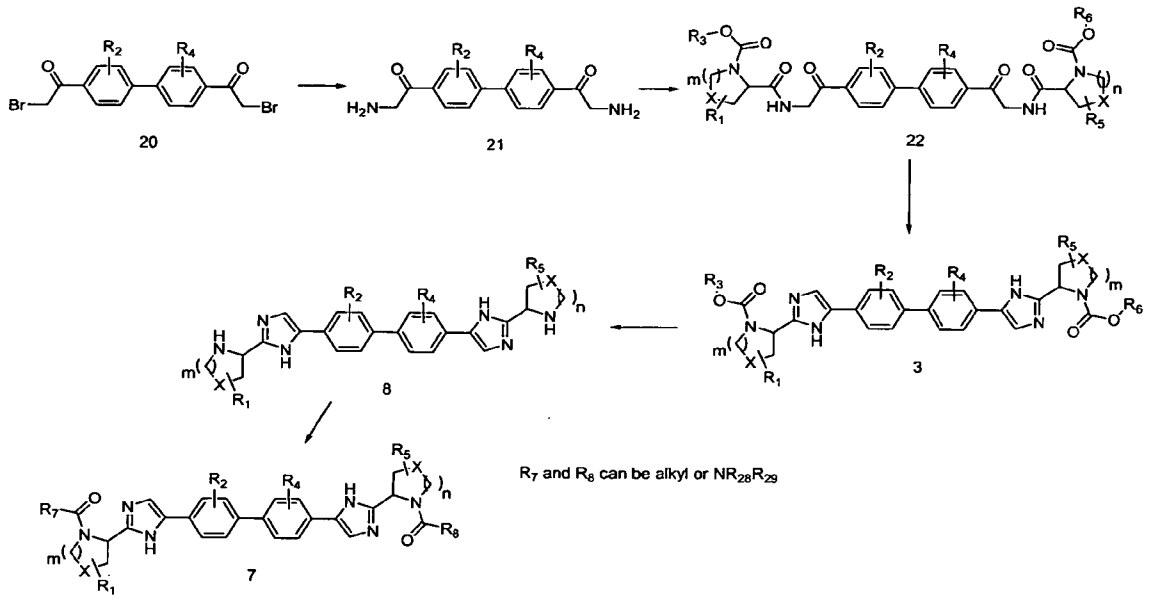
Scheme 3: Symmetric Cap Elaborated Biphenyls

Compound **15** (**15** = **7** (Scheme 1) wherein $R_7 = R_8 = -CH(NHBoc)R_{14}$)can be converted to **16** via treatment with strong acid such as HCl or trifluoroacetic acid. Compounds **17**, **18**, and **19** can be prepared from **16** by treating **16** with an appropriate chloroformate, isocyanate or carbamoyl chloride, or an acid chloride respectively.



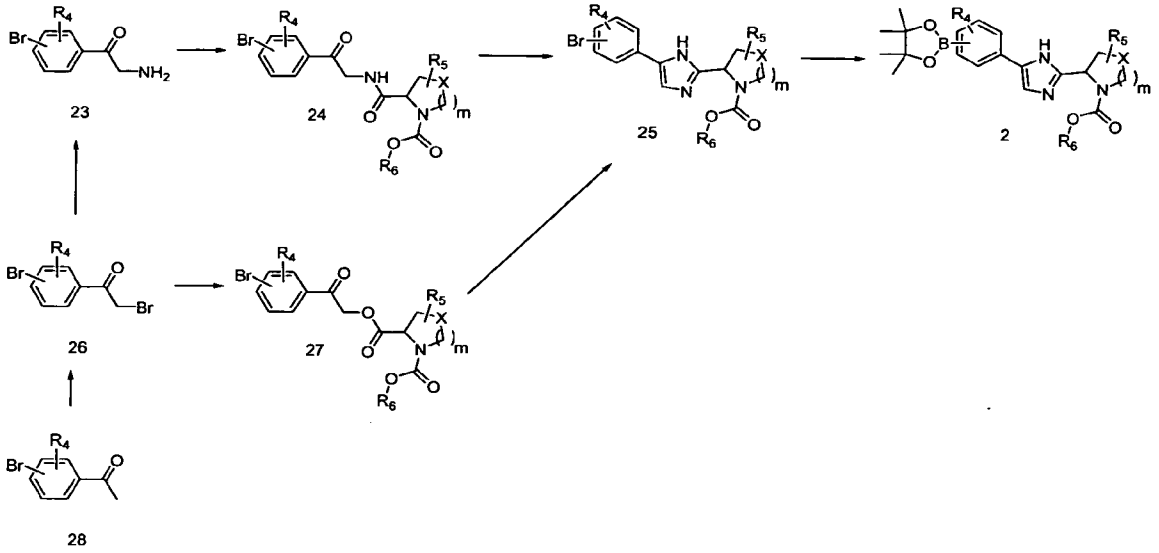
Scheme 4: Symmetric Biphenyls

Symmetric biphenyl analogs **7** ($R_1 = R_5$; $R_7 = R_8$; m = n) can be synthesized starting from bromoketone **20**. Amination by displacement with a nucleophile such as azide, phthalimide or preferably sodium diformylamide (Yinglin and Hongwen, Synthesis, (1990), page 122) followed by deprotection affords **21**. Condensation under standard amination conditions such as HATU and Hunig's base with an appropriately protected amino acid provides **22**. Heating with ammonium acetate under thermal or microwave conditions results in the formation of **3** which can be deprotected with strong acid such as HCl or trifluoroacetic acid ($R_3 = R_6$ = t-Bu) or by hydrogenolysis with hydrogen gas and a transition metal catalyst such as Pd / C ($R_3 = R_6$ = benzyl). Acylation can be affected with a carboxylic acid ($R_7CO_2H = R_8CO_2H$) in a similar manner to the conversion of **21** to **22**. Urea formation can be accomplished by treatment with an appropriate isocycante ($R_7 = R_8 = R_{28}R_{29}N$; R_{29} =H) or carbamoyl chloride ($R_7 = R_8 = R_{28}R_{29}N$; R_{29} is notH).



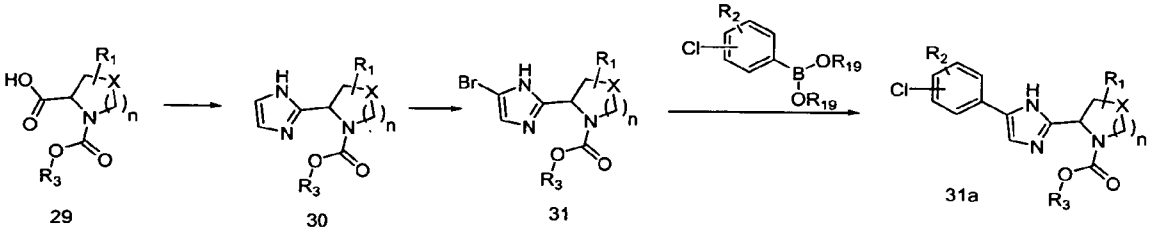
Scheme 5: Starting Materials 25 and 2

Scheme 5 describes the preparation of some of the starting materials required for the synthetic sequences depicted in Schemes 1-4. Key intermediate **25** (analogous to **1** in Scheme 1) is prepared from keto-amide **24** or keto-ester **27** via heating with ammonium acetate under thermal or microwave conditions. Keto-amide **24** can be prepared from **23** via condensation with an appropriate cyclic or acyclic amino acid under standard amide formation conditions. Bromide **26** can give rise to **23** by treatment with a nucleophile such as azide, phthalimide or sodium diformylamide (Synthesis **1990**, 122) followed by deprotection. Bromide **26** can also be converted to **27** by reacting with an appropriate cyclic or acyclic N-protected amino acid in the presence of base such as potassium carbonate or sodium bicarbonate. Bromination of **28** with a source of bromonium ion such as bromine, NBS, or CBr_4 results in the formation of **26**. Bromide **25** can be converted to boronic ester **2** via treatment with bis-pinacalotodiboron under palladium catalysis according to the method described in Journal of Organic Chemistry **1995**, 60, 7508, or variations thereof.



Scheme 6: Starting Material 31a

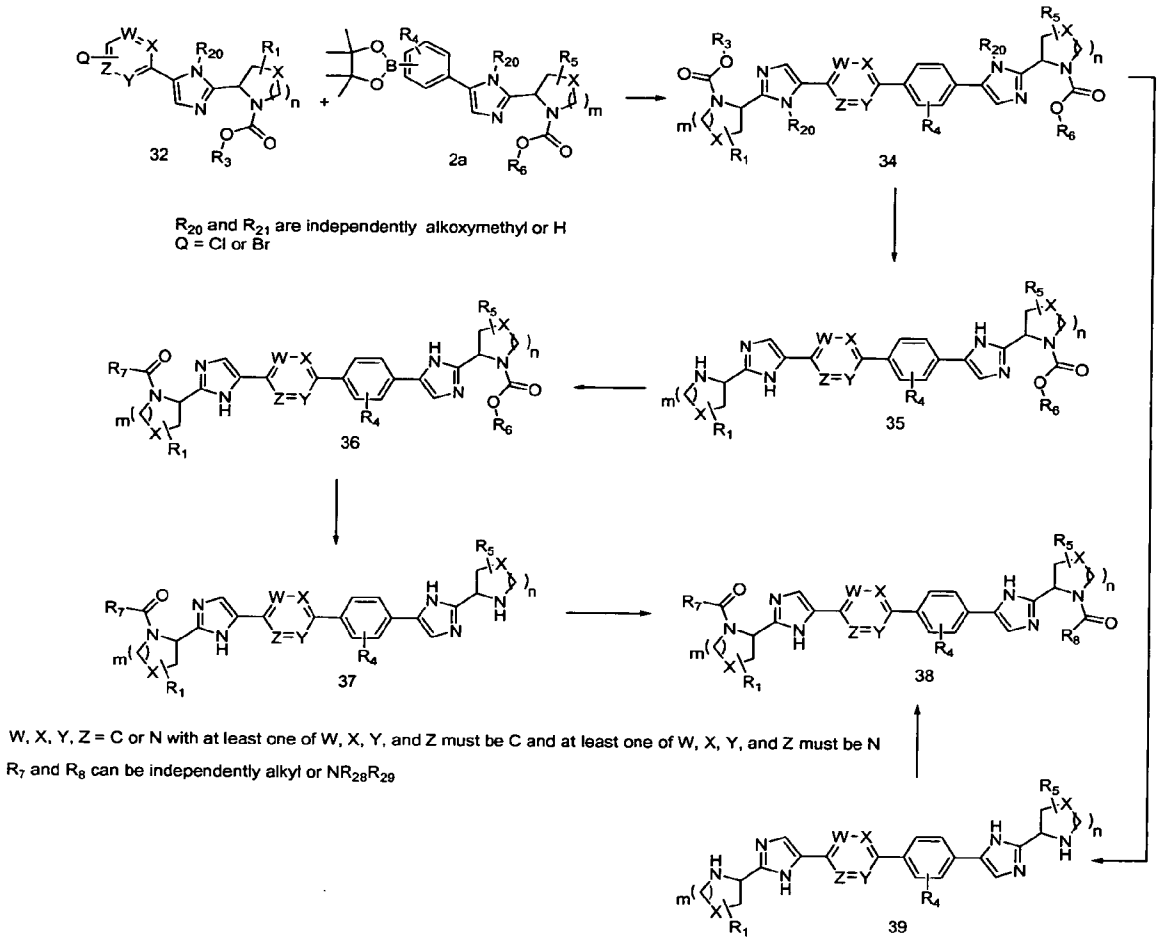
In another embodiment, starting materials such as **31a** (analogous to **25** in Scheme 5 and **1** in Scheme 1) may be prepared by reacting bromoimidazole derivatives **31** under Suzuki-type coupling conditions with a variety of chloro-substituted aryl boronic acids which can either be prepared by standard methodologies (see, for example, Organic Letters **2006**, 8, 305 and references cited therein) or purchased from commercial suppliers. Bromoimidazole **31** can be obtained by brominating imidazole **30** with a source of bromonium ion such as bromine, CBr_4, or N-bromosuccinimide. Imidazole **30** can be prepared from N-protected amino acids which are appropriately substituted by reacting with glyoxal in a methanolic solution of ammonium hydroxide.



Scheme 7: Heteroaryls

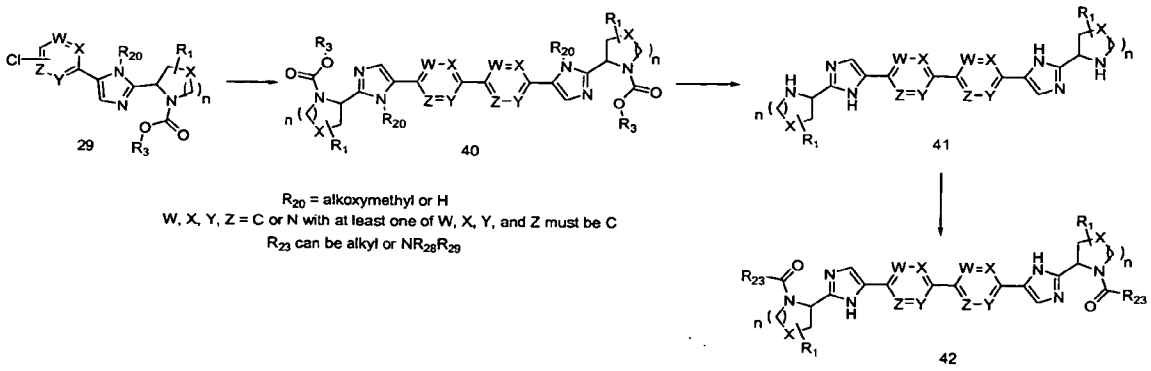
In yet another embodiment of the current disclosure, aryl halide **32** can be coupled under Suzuki-Miyaura palladium catalyzed conditions to form the heteroaryl derivative **34**. Compound **34** can be elaborated to **35** by treatment to hydrogenolytic

conditions with hydrogen and a transition metal catalyst such as palladium on carbon (R_3 = benzyl). Acylation of **35** can be accomplished with an appropriate acid chloride (R_7COCl) in the presence of a base such as triethylamine, with an appropriately substituted carboxylic acid (R_7CO_2H) in the presence of a standard coupling reagent such as HATU, or with an isoscyanate ($R_{28}NCO$ wherein R_7 = $R_{28}R_{29}N$-; R_{29} =H)or carbamoyl chloride ($R_{28}R_{29}NCOCl$ wherein $R_7 = R_{28}R_{29}N$-). Compound **37** can be prepared from **36** (R_6 = t-Bu) via treatment with strong acid such as HCl or trifluoroacetic acid. Acylation of the resultant amine in **37** to give **38** can be accomplished as in the transformation of **35** to **36**. In cases where $R_3 = R_6$, **34** can be directly transformed into **39** by treatment with strong acid such as HCl or trifluoroacetic acid ($R_3 = R_6$ = t-Bu) or by employing hydrogenolytic conditions with hydrogen and a transition metal catalyst such as palladium on carbon ($R_3 = R_6$ = benzyl). Acylation of **39** can be accomplished in analogous fashion to that described for the transformation of **35** to **36**.



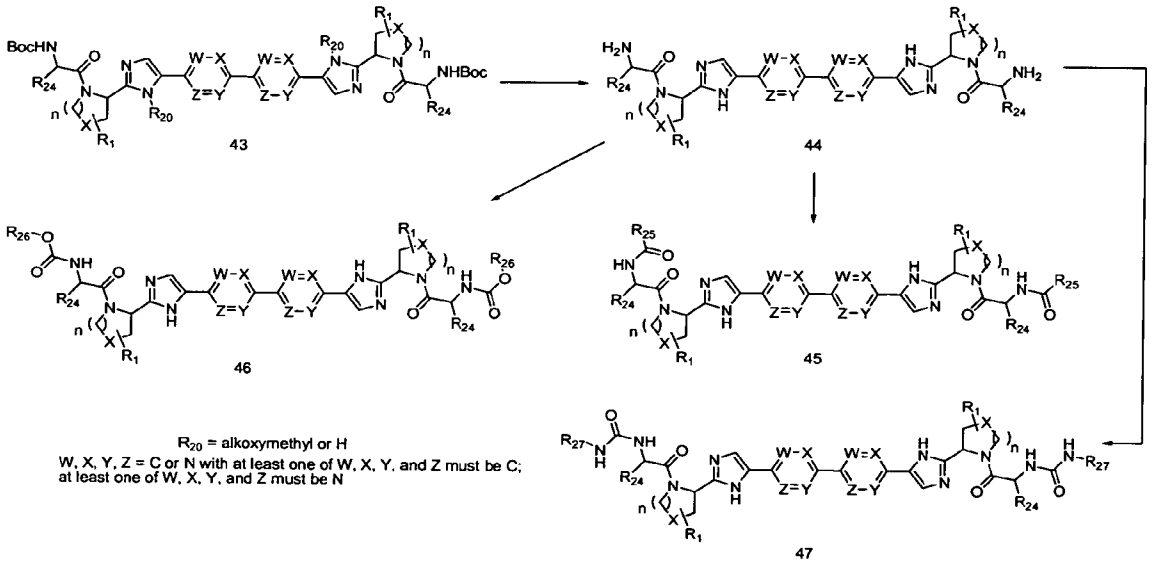
Scheme 8

Heteroaryl chloride **29** can be converted to symmetrical analog **40** via treatment with a source of palladium such as dichlorobis(benzonitrile) palladium in the presence of tetrakis(dimethylamino)ethylene at elevated temperature. Removal of the SEM ether and Boc carbamates found in **40** can be accomplished in one step by treatment with a strong acid such as HCl or trifluoroacetic acid providing **41**. Conversion to **42** can be accomplished in similar fashion to the conditions used to convert **38** to **39** in Scheme 7.



Scheme 9: Symmetric Cap Substituted Heteroaryls

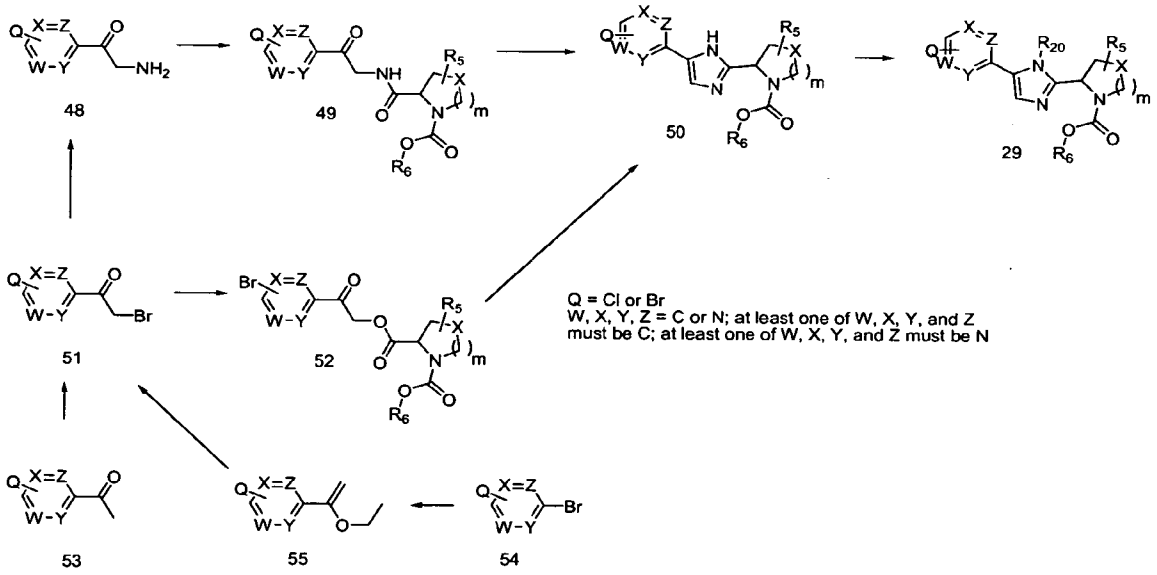
Compound **43** (analogous to **42** wherein R_{23} = -CH(NHBoc)R_{24}) may be elaborated to **45**, **46**, and **47** via similar methodologies to those described in Scheme 3. In cases where R_{20} = alkoxymethyl (ie; SEM), removal can be accomplished simultaneously with removal of the Boc carbamate (cf; **43** to **44**) using strong acid such as HCl or trifluoroacetic acid.



Scheme 10: Starting Material 29

Heteroaryl bromides **54** may be reacted with a vinyl stannane such as tributyl(1-ethoxyvinyl)tin in the presence of a source of palladium such as dichlorobis(triphenylphosphine)palladium (II) to provide **55** which can be subsequently transformed into bromoketone **51** via treatment with a source of bromonium ion such as N-bormosuccinimide, CBr_4, or bromine. Alternatively, keto-

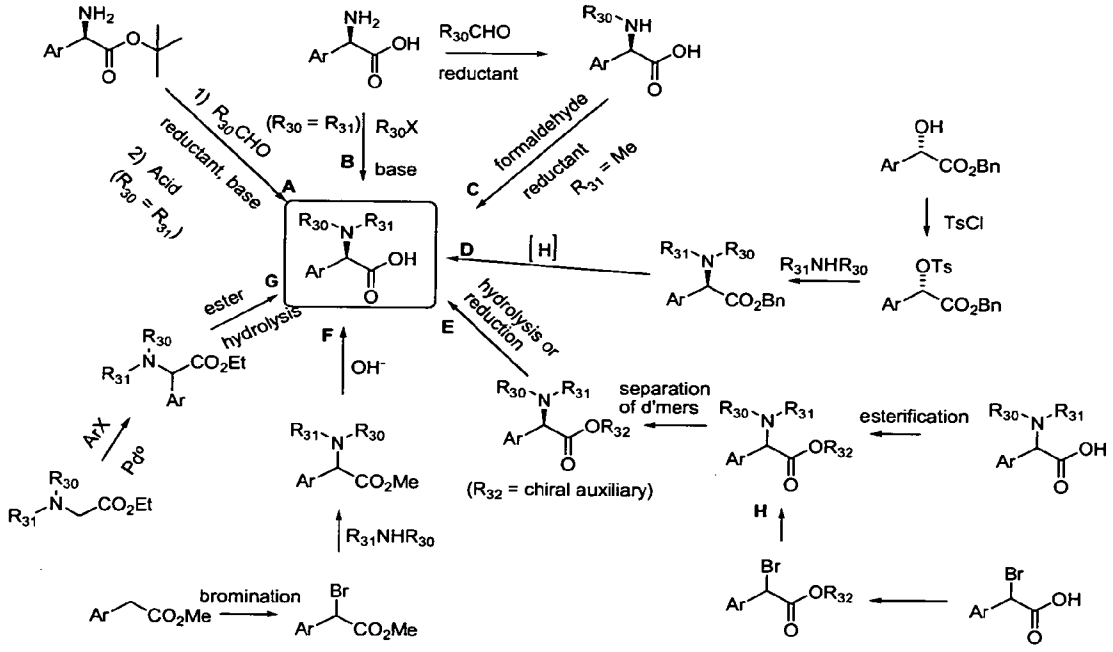
substituted heteroaryl bromides **53** may be directly converted to **51** via treatment with a source of bromonium ion such as bromine, CBr_4, or N-bromosuccinimide. Bromide **51** can be converted to aminoketone **48** via addition of sodium azide, potassium phthalimide or sodium diformylamide (Synthesis **1990**, 122) followed by deprotection. Aminoketone **48** can then be coupled with an appropriately substituted amino acid under standard amide formation conditions (ie; a coupling reagent such as HATU in the presence of a mild base such as Hunig's base) to provide **49**. Compound **49** can then be further transformed into imidazole **50** via reacting with ammonium acetate under thermal or microwave conditions. Alternatively, **51** can be directly reacted with an appropriately substituted amino acid in the presence of a base such as sodium bicarbonate or potassium carbonate providing **52** which can in turn be reacted with ammonium acetate under thermal or microwave conditions to provide **50**. Imidazole **50** can be protected with an alkoxylmethyl group by treatment with the appropriate alkoxymethyl halide such as 2-(trimethylsilyl)ethoxymethyl chloride after first being deprotonated with a strong base such as sodium hydride.



Scheme 11: Substituted Phenylglycine Derivatives

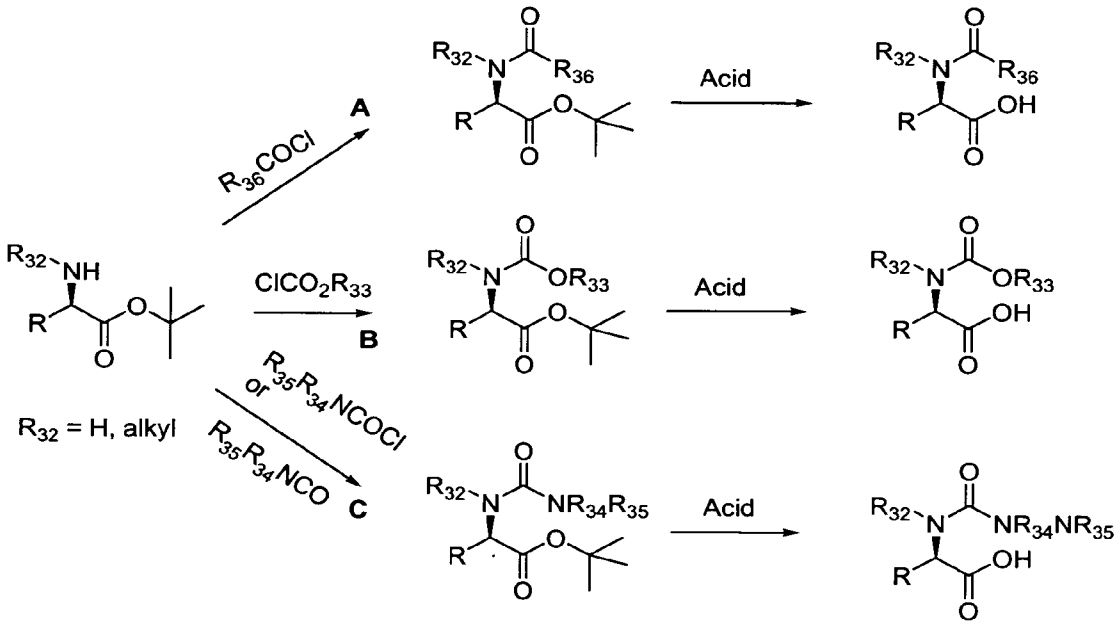
Substituted phenylglycine derivatives can be prepared by a number of methods shown below. Phenylglycine t-butyl ester can be reductively alkylated (pathyway A) with an appropriate aldehyde and a reductant such as sodium

cyanoborohydride in acidic medium. Hydrolysis of the t-butyl ester can be accomplished with strong acid such as HCl or trifluoroacetic acid. Alternatively, phenylglycine can be alkylated with an alkyl halide such as ethyl iodide and a base such as sodium bicarbonate or potassium carbonate (pathway B). Pathway C illustrates reductive alkylation of phenylglycine as in pathway A followed by a second reductive alkylation with an alternate aldehyde such as formaldehyde in the presence of a reducing agent and acid. Pathway D illustrates the synthesis of substituted phenylglycines via the corresponding mandelic acid analogs. Conversion of the secondary alcohol to a competent leaving group can be accomplished with p-toluensulfonyl chloride. Displacement of the tosylate group with an appropriate amine followed by reductive removal of the benzyl ester can provide substituted phenylglycine derivatives. In pathway E a racemic substituted phenylglycine derivative is resolved by esterification with an enantiomerically pure chiral auxiliary such as but not limited to (+)-1-phenylethanol, (-)-1-phenylethanol, an Evan's oxazolidinone, or enantiomerically pure pantolactone. Separation of the diastereomers is accomplished via chromatography (silica gel, HPLC, crystallization, etc) followed by removal of the chiral auxiliary providing enantiomerically pure phenylglycine derivatives. Pathway H illustrates a synthetic sequence which intersects with pathway E wherein the aforementioned chiral auxiliary is installed prior to amine addition. Alternatively, an ester of an arylacetic acid can be brominated with a source of bromonium ion such as bromine, N-bromosuccinimide, or CBr_4. The resultant benzylic bromide can be displaced with a variety of mono- or disubstituted amines in the presence of a tertiary amine base such as triethylamine or Hunig's base. Hydrolysis of the methyl ester via treatment with lithium hydroxide at low temperature or 6N HCl at elevated temperature provides the substituted phenylglycine derivatives. Another method is shown in pathway G. Glycine analogs can be derivatized with a variety of aryl halides in the presence of a source of palladium (0) such as palladium bis(tributylphosphine) and base such as potassium phosphate. The resultant ester can then be hydrolyzed by treatment with base or acid. It should be understood that other well known methods to prepare phenylglycine derivatives exist in the art and can be amended to provide the desired compounds in this description. It should also be understood that the final phenylglycine derivatives can be purified to enantiomeric purity greater than 98%ee via preparative HPLC.



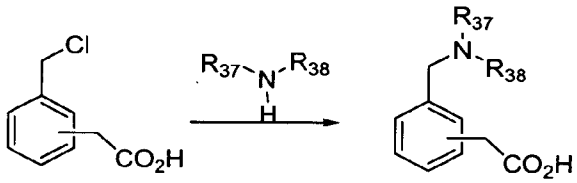
Scheme 12: Acylated Amino Acid Derivatives

In another embodiment of the present disclosure, acylated phenylglycine derivatives may be prepared as illustrated below. Phenylglycine derivatives wherein the carboxylic acid is protected as an easily removed ester, may be acylated with an acid chloride in the presence of a base such as triethylamine to provide the corresponding amides (pathway A). Pathway B illustrates the acylation of the starting phenylglycine derivative with an appropriate chloroformate while pathway C shows reaction with an appropriate isocyanate or carbamoyl chloride. Each of the three intermediates shown in pathways A – C may be deprotected by methods known by those skilled in the art (ie; treatment of the t-butyl ester with strong base such as HCl or trifluoroacetic acid).



Scheme 13

Amino-substituted phenylacetic acids may be prepared by treatment of a chloromethylphenylacetic acid with an excess of an amine.



Compound analysis conditions

Purity assessment and low resolution mass analysis were conducted on a Shimadzu LC system coupled with Waters Micromass ZQ MS system. It should be noted that retention times may vary slightly between machines. The LC conditions employed in determining the retention time (RT) were:

Condition I

Column = Phenomenex-Luna 3.0X 50 mm S10

Start %B = 0

Final %B = 100

Gradient time = 2 min

Stop time = 3 min
Flow Rate = 4 mL/min
Wavelength = 220 nm
Slovent A = 0.1% TFA in 10% methanol/90%H_2O
Solvent B = 0.1% TFA in 90% methanol/10% H_2O

Condition II

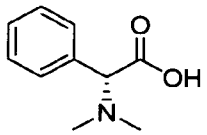
Column = Phenomenex-Luna 4.6X50 mm S10
Start %B = 0
Final %B = 100
Gradient time = 2 min
Stop time = 3 min
Flow Rate = 5 mL/min
Wavelength = 220 nm
Slovent A = 0.1% TFA in 10% methanol/90%H_2O
Solvent B = 0.1% TFA in 90% methanol/10% H_2O

Condition III

Column = HPLC XTERRA C18 3.0 x 50mm S7
Start %B = 0
Final %B = 100
Gradient time = 3 min
Stop time = 4 min
Flow Rate = 4 mL/min
Wavelength = 220 nm
Slovent A = 0.1% TFA in 10% methanol/90%H_2O
Solvent B = 0.1% TFA in 90% methanol/10% H_2O

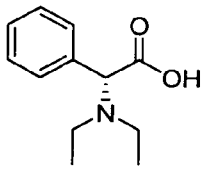
Synthesis of common pyrrolidine caps

Cap-1



A suspension of 10% Pd/C (2.0g) in methanol (10 mL) was added to a mixture of (R)-2-phenylglycine (10g, 66.2 mmol), formaldehyde (33 mL of 37% wt. in water), 1N HCl (30 mL) and methanol (30 mL), and exposed to H_2 (60 psi) for 3 hours. The reaction mixture was filtered through diatomaceous earth (Celite®), and the filtrate was concentrated in vacuo. The resulting crude material was recrystallized from isopropanol to provide the HCl salt of **Cap-1** as a white needle (4.0 g). Optical rotation: -117.1° [c = 9.95 mg/mL in H_2O; λ = 589 nm]. ^{1}H NMR (DMSO-d_6, δ = 2.5 ppm, 500 MHz): δ 7.43-7.34 (m, 5H), 4.14 (s, 1H), 2.43 (s, 6H); LC (Cond. I): RT = 0.25; LC/MS: Anal. Calcd. for $[M+H]^+$ $C_{10}H_{14}NO_2$ 180.10; found 180.17; HRMS: Anal. Calcd. for $[M+H]^+$ $C_{10}H_{14}NO_2$ 180.1025; found 180.1017.

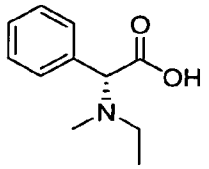
Cap-2



$NaBH_3CN$ (6.22g, 94 mmol) was added in portions over a few minutes to a cooled (ice/water) mixture of (R)-2-Phenylglycine (6.02 g, 39.8 mmol) and MeOH (100 mL), and stirred for 5 min. Acetaldehyde (10 mL) was added drop-wise over 10 min and stirring was continued at the same cooled temperature for 45 min and at ambient temperature for ~6.5 hr. The reaction mixture was cooled back with ice-water bath, treated with water (3 mL) and then quenched with a drop-wise addition of concentrated HCl over ~ 45 min until the pH of the mixture is ~ 1.5 – 2.0. The cooling bath was removed and the stirring was continued while adding concentrated HCl in order to maintain the pH of the mixture around 1.5-2.0. The reaction mixture was stirred over night, filtered to remove the white suspension, and the filtrate was concentrated in vacuo. The crude material was recrystallized from ethanol to afford the HCl salt of **Cap-2** as a shining white solid in two crops (crop-1: 4.16 g; crop-2: 2.19 g). ^{1}H NMR (DMSO-d_6, δ= 2.5 ppm, 400 MHz): 10.44 (1.00, br s, 1H), 7.66

(m, 2H), 7.51 (m, 3H), 5.30 (s, 1H), 3.15 (br m, 2H), 2.98 (br m, 2H), 1.20 (app br s, 6H). Crop-1: $[\alpha]^{25}$ -102.21° (c = 0.357, H_2O); crop-2: $[\alpha]^{25}$ -99.7° (c = 0.357, H_2O). LC (Cond. I): RT = 0.43 min; LC/MS: Anal. Calcd. for $[M+H]^+$ $C_{12}H_{18}NO_2$: 208.13; found 208.26

Cap-3

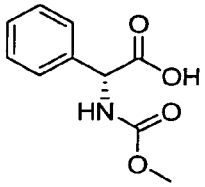


Acetaldehyde (5.0 mL, 89.1 mmol) and a suspension of 10% Pd/C (720 mg) in methanol/H_2O (4mL/1 mL) was sequentially added to a cooled (~ 15 °C) mixture of (R)-2-phenylglycine (3.096g, 20.48 mmol), 1N HCl (30 mL) and methanol (40 mL). The cooling bath was removed and the reaction mixture was stirred under a balloon of H_2 for 17 hours. An additional acetaldehyde (10 mL, 178.2 mmol) was added and stirring continued under H_2 atmosphere for 24 hours [Note: the supply of H_2 was replenished as needed throughout the reaction]. The reaction mixture was filtered through diatomaceous earth (Celite®), and the filtrate was concentrated in vacuo. The resulting crude material was recrystallized from isopropanol to provide the HCl salt of (R)-2-(ethylamino)-2-phenylacetic acid as a shining white solid (2.846g). ^1H NMR (DMSO-d_6, δ = 2.5 ppm, 400 MHz): δ 14.15 (br s, 1H), 9.55 (br s, 2H), 7.55-7.48 (m, 5H), 2.88 (br m, 1H), 2.73 (br m, 1H), 1.20 (app t, J = 7.2, 3H). LC (Cond. I): RT = 0.39 min; >95 % homogeneity index; LC/MS: Anal. Calcd. for $[M+H]^+$ $C_{10}H_{14}NO_2$: 180.10; found 180.18.

A suspension of 10% Pd/C (536 mg) in methanol/H_2O (3 mL/1 mL) was added to a mixture of (R)-2-(ethylamino)-2-phenylacetic acid/HCl (1.492g, 6.918 mmol), formaldehyde (20 mL of 37% wt. in water), 1N HCl (20 mL) and methanol (23 mL). The reaction mixture was stirred under a balloon of H_2 for ~72 hours, where the H_2 supply was replenished as needed. The reaction mixture was filtered through diatomaceous earth (Celite®) and the filtrate was concentrated in vacuo. The resulting crude material was recrystallized from isopropanol (50 mL) to provide the HCl salt of **Cap-3** as a white solid (985 mg). ^1H NMR (DMSO-d_6, δ = 2.5 ppm, 400 MHz): δ 10.48 (br s, 1H), 7.59-7.51 (m, 5H), 5.26 (s, 1H), 3.08 (app br s, 2H), 2.65

(br s, 3H), 1.24 (br m, 3H). LC (Cond. I): RT = 0.39 min; >95 % homogeneity index; LC/MS: Anal. Calcd. for $[M+H]^+$ $C_{11}H_{16}NO_2$: 194.12; found 194.18; HRMS: Anal. Calcd. for $[M+H]^+$ $C_{11}H_{16}NO_2$: 194.1180; found 194.1181.

Cap-4

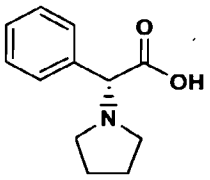


$ClCO_2Me$ (3.2 mL, 41.4 mmol) was added dropwise to a cooled (ice/water) THF (410 mL) semi-solution of (R)-tert-butyl 2-amino-2-phenylacetate/HCl (9.877 g, 40.52 mmol) and diisopropylethylamine (14.2 mL, 81.52 mmol) over 6 min, and stirred at similar temperature for 5.5 hours. The volatile component was removed in vacuo, and the residue was partitioned between water (100 mL) and ethyl acetate (200 mL). The organic layer was washed with 1N HCl (25 mL) and saturated $NaHCO_3$ solution (30 mL), dried ($MgSO_4$), filtered, and concentrated in vacuo. The resultant colorless oil was triturated from hexanes, filtered and washed with hexanes (100 mL) to provide (R)-tert-butyl 2-(methoxycarbonylamino)-2-phenylacetate as a white solid (7.7 g). ^1H NMR (DMSO-d_6, δ = 2.5 ppm, 400 MHz): 7.98 (d, J = 8.0, 1H), 7.37-7.29 (m, 5H), 5.09 (d, J = 8, 1H), 3.56 (s, 3H), 1.33 (s, 9H). LC (Cond. I): RT = 1.53 min; ~90 % homogeneity index; LC/MS: Anal. Calcd. for $[M+Na]^+$ $C_{14}H_{19}NNaO_4$: 288.12; found 288.15.

TFA (16 mL) was added dropwise to a cooled (ice/water) CH_2Cl_2 (160 mL) solution of the above product over 7 minutes, and the cooling bath was removed and the reaction mixture was stirred for 20 hours. Since the deprotection was still not complete, an additional TFA (1.0 mL) was added and stirring continued for an additional 2 hours. The volatile component was removed in vacuo, and the resulting oil residue was treated with diethyl ether (15 mL) and hexanes (12 mL) to provide a precipitate. The precipitate was filtered and washed with diethyl ether/hexanes (~1:3 ratio; 30 mL) and dried in vacuo to provide **Cap-4** as a fluffy white solid (5.57 g). Optical rotation: -176.9° [c = 3.7 mg/mL in H_2O; λ = 589 nm]. ^1H NMR (DMSO-d_6, δ = 2.5 ppm, 400 MHz): δ 12.84 (br s, 1H), 7.96 (d, J = 8.3, 1H), 7.41-7.29 (m, 5H),

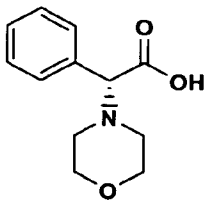
5.14 (d, J = 8.3, 1H), 3.55 (s, 3H). LC (Cond. I): RT = 1.01 min; >95 % homogeneity index; LC/MS: Anal. Calcd. for $[M+H]^+$ $C_{10}H_{12}NO_4$ 210.08; found 210.17; HRMS: Anal. Calcd. for $[M+H]^+$ $C_{10}H_{12}NO_4$ 210.0766; found 210.0756.

Cap-5



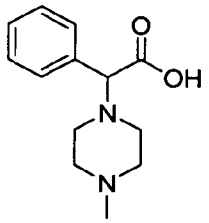
A mixture of (R)- 2-phenylglycine (1.0 g, 6.62 mmol), 1,4-dibromobutane (1.57 g, 7.27 mmol) and Na_2CO_3 (2.10 g, 19.8 mmol) in ethanol (40 mL) was heated at 100 °C for 21 hours. The reaction mixture was cooled to ambient temperature and filtered, and the filtrate was concentrated in vacuo. The residue was dissolved in ethanol and acidified with 1N HCl to pH 3-4, and the volatile component was removed in vacuo. The resulting crude material was purified by a reverse phase HPLC (water/methanol/TFA) to provide the TFA salt of **Cap-5** as a semi-viscous white foam (1.0 g). ^{1}H NMR (DMSO-d_6, δ = 2.5, 500 MHz) δ 10.68 (br s, 1H), 7.51 (m, 5H), 5.23 (s, 1H), 3.34 (app br s, 2H), 3.05 (app br s, 2H), 1.95 (app br s, 4H); RT = 0.30 min (Cond. I); >98% homogeneity index; LC/MS: Anal. Calcd. for $[M+H]^+$ $C_{12}H_{16}NO_2$: 206.12; found 206.25.

Cap-6



The TFA salt of **Cap-6** was synthesized from (R)-2-phenylglycine and 1-bromo-2-(2-bromoethoxy)ethane by using the method of preparation of **Cap-5**. ^{1}H NMR (DMSO-d_6, δ = 2.5, 500 MHz) δ 12.20 (br s, 1H), 7.50 (m, 5H), 4.92 (s, 1H), 3.78 (app br s, 4H), 3.08 (app br s, 2H), 2.81 (app br s, 2H); RT = 0.32 min (Cond. I); >98%; LC/MS: Anal. Calcd. for $[M+H]^+$ $C_{12}H_{16}NO_3$: 222.11; found 222.20; HRMS: Anal. Calcd. for $[M+H]^+$ $C_{12}H_{16}NO_3$: 222.1130; found 222.1121.

Cap-7



Cap-7a: enantiomer-1
Cap-7b: enantiomer-2

A CH_2Cl_2 (200 mL) solution of p-toluenesulfonyl chloride (8.65 g, 45.4 mmol) was added dropwise to a cooled (-5 °C) CH_2Cl_2 (200 mL) solution of (S)-benzyl 2-hydroxy-2-phenylacetate (10.0 g, 41.3 mmol), triethylamine (5.75 mL, 41.3 mmol) and 4-dimethylaminopyridine (0.504 g, 4.13 mmol), while maintaining the temperature between -5 °C and 0 °C. The reaction was stirred at 0 °C for 9 hours, and then stored in a freezer (-25 °C) for 14 hours. It was allowed to thaw to ambient temperature and washed with water (200 mL), 1N HCl (100 mL) and brine (100 mL), dried ($MgSO_4$), filtered, and concentrated in vacuo to provide benzyl 2-phenyl-2-(tosyloxy)acetate as a viscous oil which solidified upon standing (16.5 g). The chiral integrity of the product was not checked and that product was used for the next step without further purification. ^1H NMR (DMSO-d_6, $\delta = 2.5$, 500 MHz) δ 7.78 (d, J = 8.6, 2H), 7.43-7.29 (m, 10H), 7.20 (m, 2H), 6.12 (s, 1H), 5.16 (d, J = 12.5, 1H), 5.10 (d, J = 12.5, 1H), 2.39 (s, 3H). RT = 3.00 (Cond. III); >90% homogeneity index; LC/MS: Anal. Calcd. for $[M+H]^+$ $C_{22}H_{20}NaO_5S$: 419.09; found 419.04.

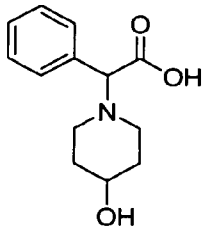
A THF (75 mL) solution of benzyl 2-phenyl-2-(tosyloxy)acetate (6.0 g, 15.1 mmol), 1-methylpiperazine (3.36 mL, 30.3 mmol) and N,N-diisopropylethylamine (13.2 mL, 75.8 mmol) was heated at 65 °C for 7 hours. The reaction was allowed to cool to ambient temperature and the volatile component was removed in vacuo. The residue was partitioned between ethylacetate and water, and the organic layer was washed with water and brine, dried ($MgSO_4$), filtered, and concentrated in vacuo. The resulting crude material was purified by flash chromatography (silica gel, ethyl acetate) to provide benzyl 2-(4-methylpiperazin-1-yl)-2-phenylacetate as an orangish-brown viscous oil (4.56 g). Chiral HPLC analysis (Chiralcel OD-H) indicated that the sample is a mixture of enantiomers in a 38.2 to 58.7 ratio. The separation of the enantiomers were effected as follow: the product was dissolved in 120 mL of ethanol/heptane (1:1) and injected (5 mL/injection) on chiral HPLC column (Chiracel

OJ, 5 cm ID x 50 cm L, 20 μm) eluting with 85:15 Heptane/ethanol at 75 mL/min, and monitored at 220 nm. Enantiomer-1 (1.474 g) and enantiomer-2 (2.2149 g) were retrieved as viscous oil. ^{1}H NMR ($CDCl_3$, δ = 7.26, 500 MHz) 7.44-7.40 (m, 2H), 7.33-7.24 (m, 6H), 7.21-7.16 (m, 2H), 5.13 (d, *J* = 12.5, 1H), 5.08 (d, *J* = 12.5, 1H), 4.02 (s, 1H), 2.65-2.38 (app br s, 8H), 2.25 (s, 3H). RT = 2.10 (Cond. III); >98% homogeneity index; LC/MS: Anal. Calcd. for $[M+H]^+$ $C_{20}H_{25}N_2O_2$: 325.19; found 325.20.

A methanol (10 mL) solution of either enantiomer of benzyl 2-(4-methylpiperazin-1-yl)-2-phenylacetate (1.0 g, 3.1 mmol) was added to a suspension of 10% Pd/C (120 mg) in methanol (5.0 mL). The reaction mixture was exposed to a balloon of hydrogen, under a careful monitoring, for <50 min. Immediately after the completion of the reaction, the catalyst was filtered through diatomaceous earth (Celite®) and the filtrate was concentrated in vacuo to provide **Cap-7**, contaminated with phenylacetic acid as a tan foam (867.6 mg; mass is above the theoretical yield). The product was used for the next step without further purification. ^{1}H NMR (DMSO-d_6, δ = 2.5, 500 MHz) δ 7.44-7.37 (m, 2H), 7.37-7.24 (m, 3H), 3.92 (s, 1H), 2.63-2.48 (app. bs, 2H), 2.48-2.32 (m, 6H), 2.19 (s, 3H); RT = 0.31 (Cond. II); >90% homogeneity index; LC/MS: Anal. Calcd. for $[M+H]^+$ $C_{13}H_{19}N_2O_2$: 235.14; found 235.15; HRMS: Anal. Calcd. for $[M+H]^+$ $C_{13}H_{19}N_2O_2$: 235.1447; found 235.1440.

The synthesis of **Cap-8** and **Cap-9** was conducted according to the synthesis of **Cap-7** by using appropriate amines for the SN_2 displacement step (i.e., 4-hydroxypiperidine for **Cap-8** and (S)-3-fluoropyrrolidine for **Cap-9**) and modified conditions for the separation of the respective stereoisomeric intermedites, as described below.

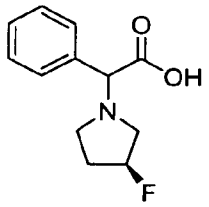
Cap-8



8a: enantiomer-1
8b: enantiomer-2

The enantiomeric separation of the intermediate benzyl 2-(4-hydroxypiperidin-1-yl)-2-phenyl acetate was effected by employing the following conditions: the compound (500 mg) was dissolved in ethanol/heptane (5 mL/45 mL). The resulting solution was injected (5 mL/injection) on a chiral HPLC column (Chiracel OJ, 2 cm ID x 25 cm L, 10 μm) eluting with 80:20 heptane/ethanol at 10 mL/min, monitored at 220 nm, to provide 186.3 mg of enantiomer-1 and 209.1 mg of enantiomer-2 as light-yellow viscous oils. These benzyl ester was hydrogenolysed according to the preparation of **Cap-7** to provide **Cap-8**: ^{1}H NMR (DMSO-d_6, δ = 2.5, 500 MHz) 7.40 (d, J = 7, 2H), 7.28-7.20 (m, 3H), 3.78 (s 1H), 3.46 (m, 1H), 2.93 (m, 1H), 2.62 (m, 1H), 2.20 (m, 2H), 1.70 (m, 2H), 1.42 (m, 2H). RT = 0.28 (Cond. II); >98% homogeneity index; LC/MS: Anal. Calcd. for $[M+H]^+$ $C_{13}H_{18}NO_3$: 236.13; found 236.07; HRMS: Calcd. for $[M+H]^+$ $C_{13}H_{18}NO_3$: 236.1287; found 236.1283.

Cap-9

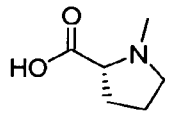


9a: diastereomer-1
9b: diastereomer-2

The diastereomeric separation of the intermediate benzyl 2-((S)-3-fluoropyrrolidin-1-yl)-2-phenylacetate was effected by employing the following conditions: the ester (220 mg) was separated on a chiral HPLC column (Chiracel OJ-H, 0.46 cm ID x 25 cm L, 5 μm) eluting with 95% CO_2 / 5% methanol with 0.1% TFA, at 10 bar pressure, 70 mL/min flow rate, and a temperature of 35 °C. The HPLC elute for the respective stereiosmers was concentrated, and the residue was dissolved in CH_2Cl_2 (20 mL) and washed with an aqueous medium (10 mL water + 1 mL saturated $NaHCO_3$ solution). The organic phase was dried ($MgSO_4$), filtered, and concentrated in vacuo to provide 92.5 mg of fraction-1 and 59.6 mg of fraction-2.

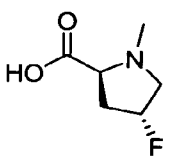
These benzyl esters were hydrogenolysed according to the preparation of **Cap-7** to prepare **Caps 9a and 9b**. **Cap-9a** (diastereomer-1; the sample is a TFA salt as a result of purification on a reverse phase HPLC using H_2O/methanol/TFA solvent): ^1H NMR (DMSO-d_6, $\delta = 2.5$, 400 MHz) 7.55-7.48 (m, 5H), 5.38 (d of m, $J = 53.7$, 1H), 5.09 (br s, 1H), 3.84-2.82 (br m, 4H), 2.31-2.09 (m, 2H). RT = 0.42 (Cond. I); >95% homogeneity index; LC/MS: Anal. Calcd. for $[M+H]^+$ $C_{12}H_{15}FNO_2$: 224.11; found 224.14; **Cap-9b** (diastereomer-2): ^1H NMR (DMSO-d_6, $\delta = 2.5$, 400 MHz) 7.43-7.21 (m, 5H), 5.19 (d of m, $J = 55.9$, 1H), 3.97 (s, 1H), 2.95-2.43 (m, 4H), 2.19-1.78 (m, 2H). RT = 0.44 (Cond. I); LC/MS: Anal. Calcd. for $[M+H]^+$ $C_{12}H_{15}FNO_2$: 224.11; found 224.14.

Cap-10



To a solution of D-proline (2.0 g, 17 mmol) and formaldehyde (2.0 mL of 37% wt. in H_2O) in methanol (15 mL) was added a suspension of 10% Pd/C (500 mg) in methanol (5 mL). The mixture was stirred under a balloon of hydrogen for 23 hours. The reaction mixture was filtered through diatomaceous earth (Celite®) and concentrated in vacuo to provide **Cap-10** as an off-white solid (2.15 g). ^1H NMR (DMSO-d_6, $\delta = 2.5$, 500 MHz) 3.42 (m, 1H), 3.37 (dd, $J = 9.4$, 6.1, 1H), 2.85-2.78 (m, 1H), 2.66 (s, 3H), 2.21-2.13 (m, 1H), 1.93-1.84 (m, 2H), 1.75-1.66 (m, 1H). RT = 0.28 (Cond. II); >98% homogeneity index; LC/MS: Anal. Calcd. for $[M+H]^+$ $C_6H_{12}NO_2$: 130.09; found 129.96.

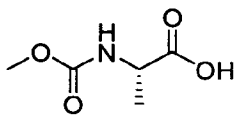
Cap-11



A mixture of (2S,4R)-4-fluoropyrrolidine-2-carboxylic acid (0.50 g, 3.8 mmol), formaldehyde (0.5 mL of 37% wt. in H_2O), 12 N HCl (0.25 mL) and 10% Pd/C (50 mg) in methanol (20 mL) was stirred under a balloon of hydrogen for 19

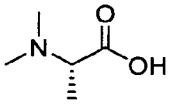
hours. The reaction mixture was filtered through diatomaceous earth (Celite®) and the filtrate was concentrated in vacuo. The residue was recrystallized from isopropanol to provide the HCl salt of **Cap-11** as a white solid (337.7 mg). ^{1}H NMR (DMSO-d_6, δ = 2.5, 500 MHz) 5.39 (d m, J = 53.7, 1H), 4.30 (m, 1H), 3.90 (ddd, J = 31.5, 13.5, 4.5, 1H), 3.33 (dd, J = 25.6, 13.4, 1H), 2.85 (s, 3H), 2.60-2.51 (m, 1H), 2.39-2.26 (m, 1H). RT = 0.28 (Cond. II); >98% homogeneity index; LC/MS: Anal. Calcd. for $[M+H]^+$ $C_6H_{11}FNO_2$: 148.08; found 148.06.

Cap-12



L-Alanine (2.0 g, 22.5 mmol) was dissolved in 10% aqueous sodium carbonate solution (50 mL), and a THF (50 mL) solution of methyl chloroformate (4.0 mL) was added to it. The reaction mixture was stirred under ambient conditions for 4.5 hours and concentrated in vacuo. The resulting white solid was dissolved in water and acidified with 1N HCl to a pH ~ 2-3. The resulting solutions was extracted with ethyl acetate (3 x 100 mL), and the combined organic phase was dried (Na_2SO_4), filtered, and concentrated in vacuo to provide a colorless oil (2.58 g). 500 mg of this material was purified by a reverse phase HPLC (H_2O/methanol/TFA) to provide 150 mg of **Cap-12** as a colorless oil . ^{1}H NMR (DMSO-d_6, δ = 2.5, 500 MHz) 7.44 (d, J = 7.3, 0.8H), 7.10 (br s, 0.2H), 3.97 (m, 1H), 3.53 (s, 3H), 1.25 (d, J = 7.3, 3H).

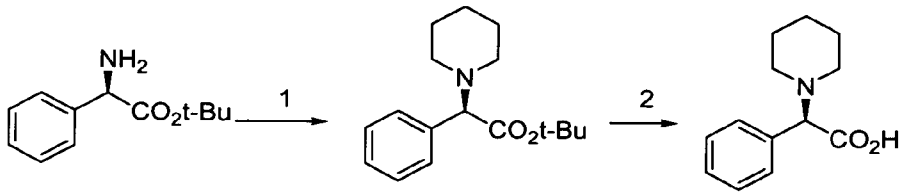
Cap-13



A mixture of L-alanine (2.5 g, 28 mmol), formaldehyde (8.4 g, 37 wt. %), 1N HCl (30 mL) and 10% Pd/C (500 mg) in methanol (30 mL) was stirred under a hydrogen atmosphere (50 psi) for 5 hours. The reaction mixture was filtered through diatomaceous earth (Celite®) and the filtrate was concentrated in vacuo to provide the HCl salt of **Cap-13** as an oil which solidified upon standing under vacuum (4.4 g; the mass is above theoretical yield). The product was used without further purification.

^{1}H NMR (DMSO-d_6, δ = 2.5, 500 MHz) δ 12.1 (br s, 1H), 4.06 (q, J = 7.4, 1H), 2.76 (s, 6H), 1.46 (d, J = 7.3, 3H).

Cap-14



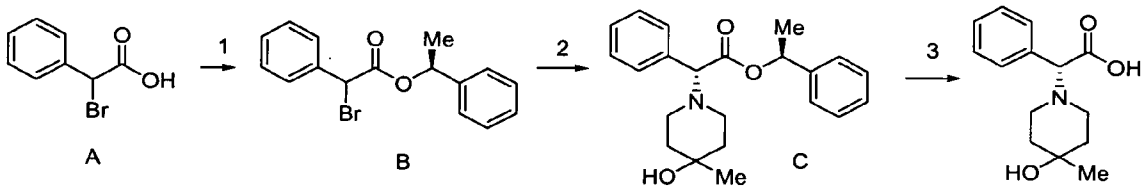
Cap-14

Step 1: A mixture of (R)-(-)-D-phenylglycine tert-butyl ester (3.00 g, 12.3 mmol), $NaBH_3CN$ (0.773 g, 12.3 mmol), KOH (0.690 g, 12.3 mmol) and acetic acid (0.352 mL, 6.15 mmol) were stirred in methanol at 0 °C. To this mixture was added glutaric dialdehyde (2.23 mL, 12.3 mmol) dropwise over 5 minutes. The reaction mixture was stirred as it was allowed to warm to ambient temperature and stirring was continued at the same temperature for 16 hours. The solvent was subsequently removed and the residue was partitioned with 10% aqueous NaOH and ethyl acetate. The organic phase was separated, dried ($MgSO_4$), filtered and concentrated to dryness to provide a clear oil. This material was purified by reverse-phase preparative HPLC (Primesphere C-18, 30 x 100mm; CH_3CN-H_2O-0.1% TFA) to give the intermediate ester (2.70 g, 56%) as a clear oil. ^{1}HNMR (400 MHz, $CDCl_3$) δ 7.53-7.44 (m, 3H), 7.40-7.37 (m, 2H), 3.87 (d, J = 10.9 Hz, 1H), 3.59 (d, J = 10.9 Hz, 1H), 2.99 (t, J = 11.2 Hz, 1H), 2.59 (t, J = 11.4 Hz, 1H), 2.07-2.02 (m, 2H), 1.82 (d, J = 1.82 Hz, 3H), 1.40 (s, 9H). LC/MS: Anal. Calcd. for $C_{17}H_{25}NO_2$: 275; found: 276 $(M+H)^+$.

Step 2: To a stirred solution of the intermediate ester (1.12g, 2.88mmol) in dichloromethane (10 mL) was added TFA (3 mL). The reaction mixture was stirred at ambient temperature for 4 hours and then it was concentrated to dryness to give a light yellow oil. The oil was purified using reverse-phase preparative HPLC (Primesphere C-18, 30 x 100mm; CH_3CN-H_2O-0.1% TFA). The appropriate fractions were combined and concentrated to dryness in vacuo. The residue was then dissolved in a minimum amount of methanol and applied to applied to MCX LP extraction cartridges (2 x 6 g). The cartridges were rinsed with methanol (40 mL)

and then the desired compound was eluted using 2M ammonia in methanol (50 mL). Product-containing fractions were combined and concentrated and the residue was taken up in water. Lyophilization of this solution provided the title compound (0.492 g, 78%) as a light yellow solid. ^{1}HNMR (DMSO-d_6) δ 7.50 (s, 5H), 5.13 (s, 1H), 3.09 (br s, 2H), 2.92-2.89 (m, 2H), 1.74 (m, 4H), 1.48 (br s, 2H). LC/MS: Anal. Calcd. for $C_{13}H_{17}NO_2$: 219; found: 220 $(M+H)^+$.

Cap-15



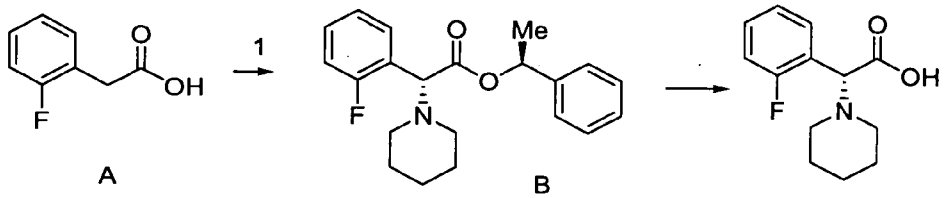
Step 1; (S)-1-Phenylethyl 2-bromo-2-phenylacetate: To a mixture of α-bromophenylacetic acid (10.75 g, 0.050 mol), (S)-(-)-1-phenylethanol (7.94 g, 0.065 mol) and DMAP (0.61 g, 5.0 mmol) in dry dichloromethane (100 mL) was added solid EDCI (12.46 g, 0.065 mol) all at once. The resulting solution was stirred at room temperature under Ar for 18 hours and then it was diluted with ethyl acetate, washed (H_2O x 2, brine), dried (Na_2SO_4), filtered, and concentrated to give a pale yellow oil. Flash chromatography (SiO_2/ hexane-ethyl acetate, 4:1) of this oil provided the title compound (11.64 g, 73%) as a white solid. ^{1}HNMR (400 MHz, $CDCl_3$) δ 7.53-7.17 (m, 10H), 5.95 (q, J = 6.6 Hz, 0.5H), 5.94 (q, J = 6.6 Hz, 0.5H), 5.41 (s, 0.5H), 5.39 (s, 0.5H), 1.58 (d, J = 6.6 Hz, 1.5H), 1.51 (d, J = 6.6 Hz, 1.5H).

Step 2; (S)-1-Phenylethyl (R)-2-(4-hydroxy-4-methylpiperidin-1-yl)- 2-phenylacetate: To a solution of (S)-1-phenylethyl 2-bromo-2-phenylacetate (0.464 g, 1.45 mmol) in THF (8 mL) was added triethylamine (0.61 mL, 4.35 mmol), followed by tetrabutylammonium iodide (0.215 g, 0.58 mmol). The reaction mixture was stirred at room temperature for 5 minutes and then a solution of 4-methyl-4-hydroxypiperidine (0.251 g, 2.18 mmol) in THF (2 mL) was added. The mixture was stirred for 1 hour at room temperature and then it was heated at 55-60 °C (oil bath temperature) for 4 hours. The cooled reaction mixture was then diluted with ethyl acetate (30 mL), washed (H_2O x2, brine), dried ($MgSO_4$), filtered and concentrated.

The residue was purified by silica gel chromatography (0-60% ethyl acetate-hexane) to provide first the (S,R)-isomer of the title compound (0.306 g, 60%) as a white solid and then the corresponding (S,S)-isomer (0.120 g, 23%), also as a white solid. **(S,R)-isomer**: ^{1}HNMR (CD_3OD) δ 7.51-7.45 (m, 2H), 7.41-7.25 (m, 8H), 5.85 (q, J = 6.6 Hz, 1H), 4.05 (s, 1H), 2.56-2.45 (m, 2H), 2.41-2.29 (m, 2H), 1.71-1.49 (m, 4H), 1.38 (d, J = 6.6 Hz, 3H), 1.18 (s, 3H). LCMS: Anal. Calcd. for $C_{22}H_{27}NO_3$: 353; found: 354 $(M+H)^+$. **(S,S)-isomer**: ^{1}HNMR (CD_3OD) δ 7.41-7.30 (m, 5H), 7.20-7.14 (m, 3H), 7.06-7.00 (m, 2H), 5.85 (q, J = 6.6 Hz, 1H), 4.06 (s, 1H), 2.70-2.60 (m, 1H), 2.51 (dt, J = 6.6, 3.3 Hz, 1H), 2.44-2.31 (m, 2H), 1.75-1.65 (m, 1H), 1.65-1.54 (m, 3H), 1.50 (d, J = 6.8 Hz, 3H), 1.20 (s, 3H). LCMS: Anal. Calcd. for $C_{22}H_{27}NO_3$: 353; found: 354 $(M+H)^+$.

Step 3; (R)-2-(4-Hydroxy-4-methylpiperidin-1-yl)-2-phenylacetic acid: To a solution of (S)-1-phenylethyl (R)-2-(4-hydroxy-4-methylpiperidin-1-yl)-2-phenylacetate (0.185 g, 0.52 mmol) in dichloromethane (3 mL) was added trifluoroacetic acid (1 mL) and the mixture was stirred at room temperature for 2 hours. The volatiles were subsequently removed in vacuo and the residue was purified by reverse-phase preparative HPLC (Primesphere C-18, 20 x 100mm; CH_3CN-H_2O-0.1% TFA) to give the title compound (as TFA salt) as a pale bluish solid (0,128 g, 98%). LCMS: Anal. Calcd. for $C_{14}H_{19}NO_3$: 249; found: 250 $(M+H)^+$.

Cap-16



***(R)*-Cap-16**

Step 1; (S)-1-Phenylethyl 2-(2-fluorophenyl)acetate: A mixture of 2-fluorophenylacetic acid (5.45 g, 35.4 mmol), (S)-1-phenylethanol (5.62 g, 46.0 mmol), EDCI (8.82 g, 46.0 mmol) and DMAP (0.561 g, 4.60 mmol) in CH_2Cl_2 (100 mL) was stirred at room temperature for 12 hours. The solvent was then concentrated and the residue partitioned with H_2O-ethyl acetate. The phases were separated and the aqueous layer back-extracted with ethyl acetate (2x). The

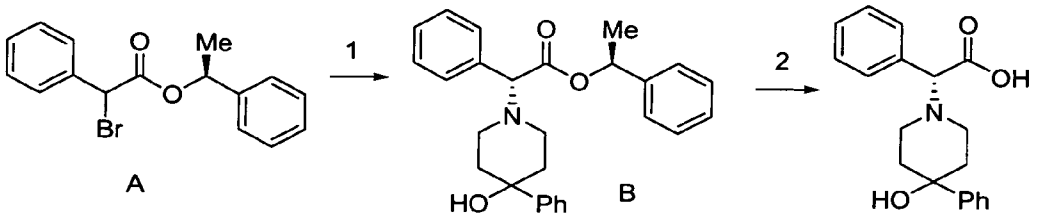
combined organic phases were washed (H_2O, brine), dried (Na_2SO_4), filtered, and concentrated in vacuo. The residue was purified by silica gel chromatography (Biotage/ 0-20% ethyl acetate-hexane) to provide the title compound as a colorless oil (8.38 g, 92%). ^{1}HNMR (400 MHz, CD_3OD) δ 7.32 - 7.23 (m, 7H), 7.10-7.04 (m, 2), 5.85 (q, J = 6.5 Hz, 1H), 3.71 (s, 2H), 1.48 (d, J = 6.5 Hz, 3H).

Step 2; (R)-((S)-1-Phenylethyl) 2-(2-fluorophenyl)-2-(piperidin-1-yl)acetate: To a solution of (S)-1-phenylethyl 2-(2-fluorophenyl)acetate (5.00 g, 19.4 mmol) in THF (1200 mL) at 0°C was added DBU (6.19 g, 40.7 mmol) and the solution was allowed to warm to room temperature while stirring for 30 minutes. The solution was then cooled to -78 °C and a solution of CBr_4 (13.5 g, 40.7 mmol) in THF (100 mL) was added and the mixture was allowed to warm to -10 °C and stirred at this temperature for 2 hours. The reaction mixture was quenched with saturated aq. NH_4Cl and the layers were separated. The aqueous layer was back-extracted with ethyl acetate (2x) and the combined organic phases were washed (H_2O, brine), dried (Na_2SO_4), filtered, and concentrated in vacuo. To the residue was added piperidine (5.73 mL, 58.1 mmol) and the solution was stirred at room temperature for 24 hours. The volatiles were then concentrated in vacuo and the residue was purified by silica gel chromatography (Biotage/ 0-30% diethyl ether-hexane) to provide a pure mixture of diastereomers (2:1 ratio by ^{1}HNMR) as a yellow oil (2.07 g, 31%), along with unreacted starting material (2.53 g, 51%). Further chromatography of the diastereomeric mixture (Biotage/ 0-10% diethyl ether-toluene) provided the title compound as a colorless oil (0.737 g, 11%). ^{1}HNMR (400 MHz, CD_3OD) δ 7.52 (ddd, J = 9.4, 7.6, 1.8 Hz, 1H), 7.33 – 7.40 (m, 1), 7.23 – 7.23 (m, 4H), 7.02 – 7.23 (m, 4H), 5.86 (q, J = 6.6 Hz, 1H), 4.45 (s, 1H), 2.39 – 2.45 (m, 4H), 1.52 – 1.58 (m, 4H), 1.40 – 1.42 (m, 1H), 1.38 (d, J = 6.6 Hz, 3H). LCMS: Anal. Calcd. for $C_{21}H_{24}FNO_2$: 341; found: 342 $(M+H)^+$.

Step 3; (R)-2-(2-fluorophenyl)-2-(piperidin-1-yl)acetic acid: A mixture of (R)-((S)-1-phenylethyl) 2-(2-fluorophenyl)-2-(piperidin-1-yl)acetate (0.737 g, 2.16 mmol) and 20% $Pd(OH)_2/C$ (0.070 g) in ethanol (30 mL) was hydrogenated at room temperature and atmospheric pressure (H_2 balloon) for 2 hours. The solution was then purged with Ar, filtered through diatomaceous earth (Celite®), and concentrated in vacuo. This provided the title compound as a colorless solid (0.503 g, 98%).

^{1}HNMR (400 MHz, CD_3OD) δ 7.65 (ddd, J = 9.1, 7.6, 1.5 Hz, 1H), 7.47-7.53 (m, 1H), 7.21-7.30 (m, 2H), 3.07-3.13 (m, 4H), 1.84 (br s, 4H), 1.62 (br s, 2H). LCMS: Anal. Calcd. for $C_{13}H_{16}FNO_2$: 237; found: 238 $(M+H)^+$.

Cap-17



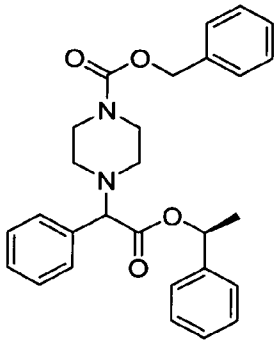
A B ***(R)*-Cap-17**

Step 1; (S)-1-Phenylethyl (R)-2-(4-hydroxy-4-phenylpiperidin-1-yl)- 2-phenylacetate: To a solution of (S)-1-phenylethyl 2-bromo-2-phenylacetate (1.50 g, 4.70 mmol) in THF (25 mL) was added triethylamine (1.31 mL, 9.42 mmol), followed by tetrabutylammonium iodide (0.347 g, 0.94 mmol). The reaction mixture was stirred at room temperature for 5 minutes and then a solution of 4-phenyl-4-hydroxypiperidine (1.00 g, 5.64 mmol) in THF (5 mL) was added. The mixture was stirred for 16 hours and then it was diluted with ethyl acetate (100 mL), washed (H_2O x2, brine), dried ($MgSO_4$), filtered and concentrated. The residue was purified on a silica gel column (0-60% ethyl acetate-hexane) to provide an approximately 2:1 mixture of diastereomers, as judged by ^{1}HNMR. Separation of these isomers was performed using supercritical fluid chromatography (Chiralcel OJ-H, 30 x 250mm; 20% ethanol in CO_2 at 35 °C), to give first the (R)-isomer of the title compound (0.534 g, 27%) as a yellow oil and then the corresponding (S)-isomer (0.271 g, 14%), also as a yellow oil. **(S,R)-isomer**: ^{1}HNMR (400 MHz, CD_3OD) δ 7.55-7.47 (m, 4H), 7.44-7.25 (m, 10H), 7.25-7.17 (m, 1H), 5.88 (q, J = 6.6 Hz, 1H), 4.12 (s, 1H), 2.82-2.72 (m, 1H), 2.64 (dt, J = 11.1, 2.5 Hz, 1H), 2.58-2.52 (m, 1H), 2.40 (dt, J = 11.1, 2.5 Hz, 1H), 2.20 (dt, J = 12.1, 4.6 Hz, 1H), 2.10 (dt, J = 12.1, 4.6 Hz, 1H), 1.72-1.57 (m, 2H), 1.53 (d, J = 6.5 Hz, 3H). LCMS: Anal. Calcd. for $C_{27}H_{29}NO_3$: 415; found: 416 $(M+H)^+$; **(S,S)-isomer**: H^{1}NMR (400 MHz, CD_3OD) δ 7.55-7.48 (m, 2H), 7.45-7.39 (m, 2H), 7.38-7.30 (m, 5H), 7.25-7.13 (m, 4H), 7.08-7.00 (m, 2H), 5.88 (q, J = 6.6 Hz, 1H), 4.12 (s, 1H), 2.95-2.85 (m, 1H), 2.68 (dt, J = 11.1, 2.5 Hz, 1H), 2.57-2.52 (m, 1H), 2.42 (dt, J = 11.1, 2.5 Hz, 1H), 2.25 (dt, J = 12.1, 4.6

Hz, 1H), 2.12 (dt, J = 12.1, 4.6 Hz, 1H), 1.73 (dd, J = 13.6, 3.0 Hz, 1H), 1.64 (dd, J = 13.6, 3.0 Hz, 1H), 1.40 (d, J = 6.6 Hz, 3H). LCMS: Anal. Calcd. for $C_{27}H_{29}NO_3$: 415; found: 416 $(M+H)^+$.

The following esters were prepared in similar fashion:

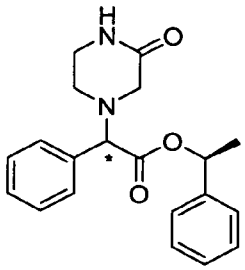
Intermediate-17a



Diastereomer 1: ^{1}H NMR (500 MHz, DMSO-d_6) δ ppm 1.36 (d, J=6.41 Hz, 3H) 2.23 - 2.51 (m, 4H) 3.35 (s, 4H) 4.25 (s, 1H) 5.05 (s, 2H) 5.82 (d, J=6.71 Hz, 1H) 7.15 - 7.52 (m, 15H).
LCMS: Anal. Calcd. for: $C_{28}H_{30}N_2O_4$ 458.55; Found: 459.44 $(M+H)^+$.

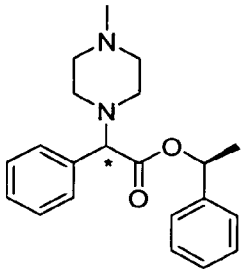
Diastereomer 2: ^{1}H NMR (500 MHz, DMSO-d_6) δ ppm 1.45 (d, J=6.71 Hz, 3H) 2.27 - 2.44 (m, 4H) 3.39 (s, 4H) 4.23 (s, 1H) 5.06 (s, 2H) 5.83 (d, J=6.71 Hz, 1H) 7.12 (dd, J=6.41, 3.05 Hz, 2H) 7.19 - 7.27 (m, 3H) 7.27 - 7.44 (m, 10H).
LCMS: Anal. Calcd. for: $C_{28}H_{30}N_2O_4$ 458.55; Found: 459.44 $(M+H)^+$.

Intermediate -17b



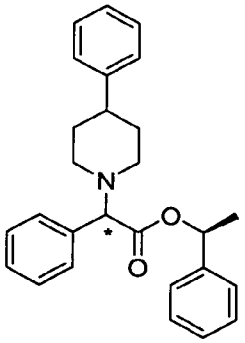
Diasteromer 1: RT = 11.76 min (Cond'n II); LCMS: Anal. Calcd. for: $C_{20}H_{22}N_2O_3$ 338.4 Found: 339.39 $(M+H)^+$; Diastereomer 2: RT = 10.05 min (Cond'n II); LCMS: Anal. Calcd. for: $C_{20}H_{22}N_2O_3$ 338.4; Found: 339.39 $(M+H)^+$.

Intermediate -17c



Diastereomer 1: T_R = 4.55 min (Cond'n I); LCMS: Anal. Calcd. for: $C_{21}H_{26}N_2O_2$ 338.44 Found: 339.45 $(M+H)^+$; Diastereomer 2: T_R = 6.00 min (Cond'n I); LCMS: Anal. Calcd. for: $C_{21}H_{26}N_2O_2$ 338.44 Found: 339.45 $(M+H)^+$.

Intermediate -17d



Diastereomer 1: RT = 7.19 min (Cond'n I); LCMS: Anal. Calcd. for: $C_{27}H_{29}NO_2$ 399.52 Found: 400.48 $(M+H)^+$; Diastereomer 2: RT = 9.76 min (Cond'n I); LCMS: Anal. Calcd. for: $C_{27}H_{29}NO_2$ 399.52 Found: 400.48 $(M+H)^+$.

Chiral SFC Conditions for determining retention time

Condition I

Column: Chiralpak AD-H Column, 4.6X250 mm, 5μm

Solvents: 90% CO2 - 10% methanol with 0.1%DEA

Temp: 35 °C

Pressure: 150 bar

Flow rate: 2.0 mL/min.

UV monitored @ 220 nm

Injection: 1.0 mg/3mL methanol

Condition II

Column: Chiralcel OD-H Column, 4.6X250 mm, 5μm

Solvents: 90% CO2 - 10% methanol with 0.1%DEA

Temp: 35 °C

Pressure: 150 bar

Flow rate: 2.0 mL/min.

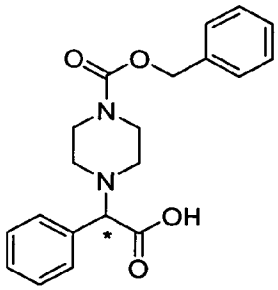
UV monitored @ 220 nm

Injection: 1.0 mg/mL methanol

Cap 17, Step 2; (R)-2-(4-Hydroxy-4-phenylpiperidin-1-yl)-2-phenylacetic acid: To a solution of (S)-1-phenylethyl (R)-2-(4-hydroxy-4-phenylpiperidin-1-yl)-2-phenylacetate (0.350 g, 0.84 mmol) in dichloromethane (5 mL) was added trifluoroacetic acid (1 mL) and the mixture was stirred at room temperature for 2 hours. The volatiles were subsequently removed in vacuo and the residue was purified by reverse-phase preparative HPLC (Primesphere C-18, 20 x 100mm; CH_3CN-H_2O-0.1% TFA) to give the title compound (as TFA salt) as a white solid (0.230 g, 88%). LCMS: Anal. Calcd. for $C_{19}H_{21}NO_3$: 311; found: 312 $(M+H)^+$.

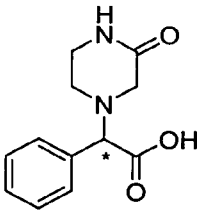
The following carboxylic acids were prepared in a similar fashion:

Cap-17a



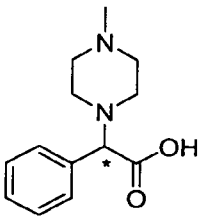
RT = 2.21 (Cond'n II); ^{1}H NMR (500 MHz, DMSO-d_6) δ ppm 2.20 - 2.35 (m, 2H) 2.34 - 2.47 (m, 2H) 3.37 (s, 4H) 3.71 (s, 1H) 5.06 (s, 2H) 7.06 - 7.53 (m, 10H). LCMS: Anal. Calcd. for: $C_{20}H_{22}N_2O_4$ 354.40; Found: 355.38 $(M+H)^+$.

Cap-17b



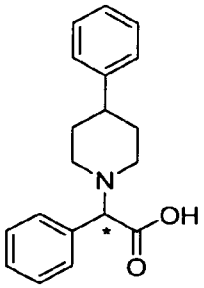
RT = 0.27 (Cond'n III); LCMS: Anal. Calcd. for: $C_{12}H_{14}N_2O_3$ 234.25; Found: 235.22 $(M+H)^+$.

Cap-17c



RT = 0.48 (Cond'n II); LCMS: Anal. Calcd. for: $C_{13}H_{18}N_2O_2$ 234.29; Found: 235.31 $(M+H)^+$.

Cap-17d



RT = 2.21 (Cond'n I); LCMS: Anal. Calcd. for: $C_{19}H_{21}NO_2$ 295.38; Found: 296.33 $(M+H)^+$.

LCMS Conditions for determining retention time

Condition I

Column: Phenomenex-Luna 4.6 X 50 mm S10

Start % B = 0

Fianl % B = 100

Gradient Time = 4 min

Flow Rate = 4 mL/min

Wavelength = 220

Solvent A = 10% methanol – 90% H_2O – 0.1% TFA

Solvent B = 90% methanol – 10% H_2O – 0.1% TFA

Condition II

Column: Waters-Sunfire 4.6 X 50 mm S5

Start % B = 0

Fianl % B = 100

Gradient Time = 2 min

Flow Rate = 4 mL/min

Wavelength = 220

Solvent A = 10% methanol – 90% H_2O – 0.1% TFA

Solvent B = 90% methanol – 10% H_2O – 0.1% TFA

Condition III

Column: Phenomenex 10µ 3.0 X 50 mm

Start % B = 0

Fianl % B = 100

Gradient Time = 2 min

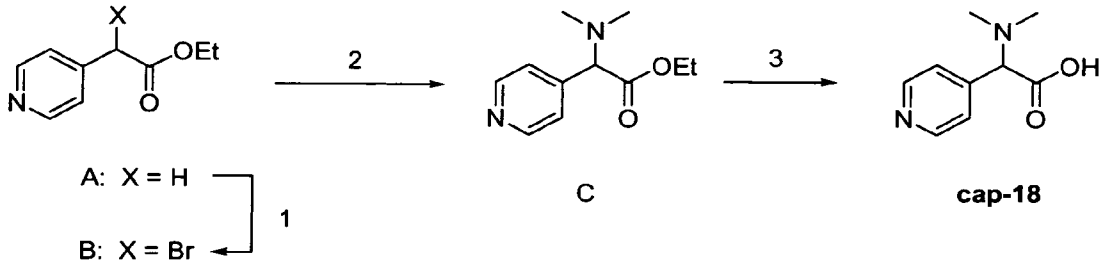
Flow Rate = 4 mL/min

Wavelength = 220

Solvent A = 10% methanol – 90% H_2O – 0.1% TFA

Solvent B = 90% methanol – 10% H_2O – 0.1% TFA

Cap-18



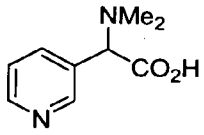
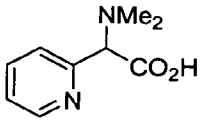
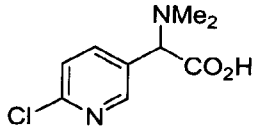
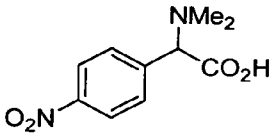
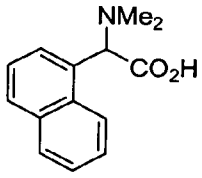
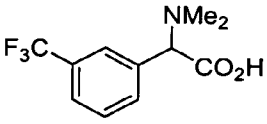
Step 1; (R,S)-Ethyl 2-(4-pyridyl)-2-bromoacetate: To a solution of ethyl 4-pyridylacetate (1.00 g, 6.05 mmol) in dry THF (150 mL) at 0 °C under argon was added DBU (0.99 mL, 6.66 mmol). The reaction mixture was allowed to warm to room temperature over 30 minutes and then it was cooled to -78 °C. To this mixture was added CBr_4 (2.21 g, 6.66 mmol) and stirring was continued at -78 °C for 2 hours. The reaction mixture was then quenched with sat. aq. NH_4Cl and the phases were separated. The organic phase was washed (brine), dried (Na_2SO_4), filtered, and concentrated in vacuo. The resulting yellow oil was immediately purified by flash chromatography (SiO_2/ hexane-ethyl acetate, 1:1) to provide the title compound (1.40 g, 95%) as a somewhat unstable yellow oil. ^{1}HNMR (400 MHz, $CDCl_3$) δ 8.62 (dd, J = 4.6, 1.8 Hz, 2H), 7.45 (dd, J = 4.6, 1.8 Hz, 2H), 5.24 (s, 1H), 4.21-4.29 (m, 2H), 1.28 (t, J = 7.1 Hz, 3H). LCMS: Anal. Calcd. for $C_9H_{10}BrNO_2$: 242, 244; found: 243, 245 $(M+H)^+$.

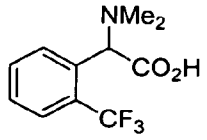
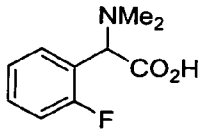
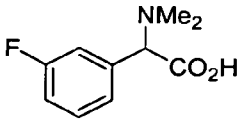
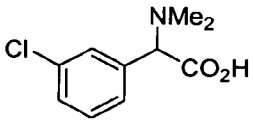
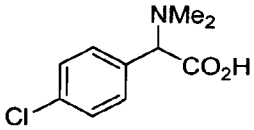
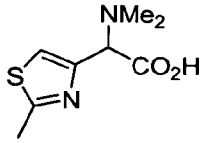
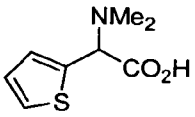
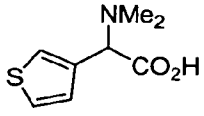
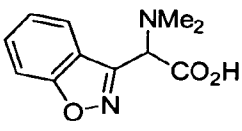
Step 2; (R,S)-Ethyl 2-(4-pyridyl)-2-(N,N-dimethylamino)acetate: To a solution of (R,S)-ethyl 2-(4-pyridyl)-2-bromoacetate (1.40 g, 8.48 mmol) in DMF (10 mL) at room temperature was added dimethylamine (2M in THF, 8.5 mL, 17.0 mmol). After completion of the reaction (as judged by tlc) the volatiles were removed in vacuo and the residue was purified by flash chromatography (Biotage, 40+M SiO_2 column; 50%-100% ethyl acetate-hexane) to provide the title compound (0.539 g, 31%) as a light yellow oil. ^{1}HNMR (400 MHz, $CDCl_3$) δ 8.58 (d, J = 6.0 Hz, 2H), 7.36 (d, J = 6.0 Hz, 2H), 4.17 (m, 2H), 3.92 (s, 1H), 2.27 (s, 6H), 1.22 (t, J = 7.0 Hz). LCMS: Anal. Calcd. for $C_{11}H_{16}N_2O_2$: 208; found: 209 $(M+H)^+$.

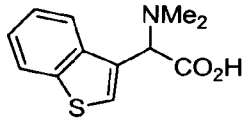
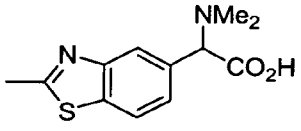
Step 3; (R,S)-2-(4-Pyridyl)-2-(N,N-dimethylamino)acetic acid: To a solution of (R,S)-ethyl 2-(4-pyridyl)-2-(N,N-dimethylamino)acetate (0.200 g, 0.960 mmol) in a mixture of THF-methanol-H_2O (1:1:1, 6 mL) was added powdered LiOH (0.120 g, 4.99 mmol) at room temperature. The solution was stirred for 3 hours and then it was

acidified to pH 6 using 1N HCl. The aqueous phase was washed with ethyl acetate and then it was lyophilized to give the dihydrochloride of the title compound as a yellow solid (containing LiCl). The product was used as such in subsequent steps. ^{1}HNMR (400 MHz, DMSO-d_6) δ 8.49 (d, J = 5.7 Hz, 2H), 7.34 (d, J = 5.7 Hz, 2H), 3.56 (s, 1H), 2.21 (s, 6H).

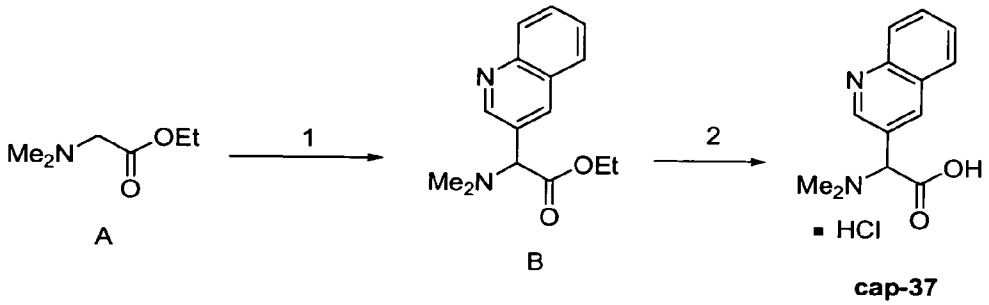
The following examples were prepared in similar fashion using the method described in Example 4;

Cap-19		LCMS: Anal. Calcd. for $C_9H_{12}N_2O_2$: 180; found: 181 $(M+H)^+$.
Cap-20		LCMS: no ionization. ^{1}HNMR (400 MHz, CD_3OD) δ 8.55 (d, J = 4.3 Hz, 1H), 7.84 (app t, J = 5.3 Hz, 1H), 7.61 (d, J = 7.8 Hz, 1H), 7.37 (app t, J = 5.3 Hz, 1H), 4.35 (s, 1H), 2.60 (s, 6H).
Cap-21		LCMS: Anal. Calcd. for $C_9H_{11}ClN_2O_2$: 214, 216; found: 215, 217 $(M+H)^+$.
Cap-22		LCMS: Anal. Calcd. for $C_{10}H_{12}N_2O_4$: 224; found: 225 $(M+H)^+$.
Cap-23		LCMS: Anal. Calcd. for $C_{14}H_{15}NO_2$: 247; found: 248 $(M+H)^+$.
Cap-24		LCMS: Anal. Calcd. for $C_{11}H_{12}F_3NO_2$: 247; found: 248 $(M+H)^+$.

Cap-25		LCMS: Anal. Calcd. for $C_{11}H_{12}F_3NO_2$: 247; found: 248 $(M+H)^+$.
Cap-26		LCMS: Anal. Calcd. for $C_{10}H_{12}FNO_2$: 247; found: 248 $(M+H)^+$.
Cap-27		LCMS: Anal. Calcd. for $C_{10}H_{12}FNO_2$: 247; found: 248 $(M+H)^+$.
Cap-28		LCMS: Anal. Calcd. for $C_{10}H_{12}ClNO_2$: 213, 215; found: 214, 217 $(M+H)^+$.
Cap-29		LCMS: Anal. Calcd. for $C_{10}H_{12}ClNO_2$: 213, 215; found: 214, 217 $(M+H)^+$.
Cap-30		LCMS: Anal. Calcd. for $C_{10}H_{12}ClNO_2$: 213, 215; found: 214, 217 $(M+H)^+$.
Cap-31		LCMS: Anal. Calcd. for $C_8H_{11}N_2O_2S$: 200; found: 201 $(M+H)^+$.
Cap-32		LCMS: Anal. Calcd. for $C_8H_{11}NO_2S$: 185; found: 186 $(M+H)^+$.
Cap-33		LCMS: Anal. Calcd. for $C_8H_{11}NO_2S$: 185; found: 186 $(M+H)^+$.
Cap-34		LCMS: Anal. Calcd. for $C_{11}H_{12}N_2O_3$: 220; found: 221 $(M+H)^+$.

Cap-35		LCMS: Anal. Calcd. for $C_{12}H_{13}NO_2S$: 235; found: 236 $(M+H)^+$.
Cap-36		LCMS: Anal. Calcd. for $C_{12}H_{14}N_2O_2S$: 250; found: 251 $(M+H)^+$.

Cap-37



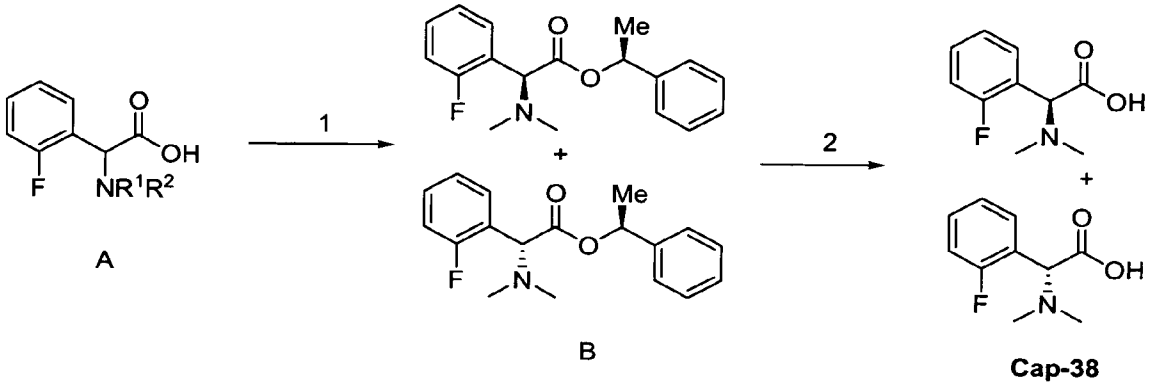
A B **cap-37**

Step 1; (R,S)-Ethyl 2-(quinolin-3-yl)-2-(N,N-dimethylamino)-acetate: A mixture of ethyl N,N-dimethylaminoacetate (0.462 g, 3.54 mmol), K_3PO_4 (1.90 g, 8.95 mmol), $Pd(t\text{-}Bu_3P)_2$ (0.090 g, 0.176 mmol) and toluene (10 mL) was degassed with a stream of Ar bubbles for 15 minutes. The reaction mixture was then heated at 100 °C for 12 hours, after which it was cooled to room temperature and poured into H_2O. The mixture was extracted with ethyl acetate (2x) and the combined organic phases were washed (H_2O, brine), dried (Na_2SO_4), filtered, and concentrated in vacuo. The residue was purified first by reverse-phase preparative HPLC (Primesphere C-18, 30 x 100mm; CH_3CN-H_2O-5 mM NH_4OAc) and then by flash chromatography (SiO_2/ hexane-ethyl acetate, 1:1) to provide the title compound (0.128 g, 17%) as an orange oil. ^{1}HNMR (400 MHz, $CDCl_3$) δ 8.90 (d, J = 2.0 Hz, 1H), 8.32 (d, J = 2.0 Hz, 1H), 8.03-8.01 (m, 2H), 7.77 (ddd, J = 8.3, 6.8, 1.5 Hz, 1H), 7.62 (ddd, J = 8.3, 6.8, 1.5 Hz, 1H), 4.35 (s, 1H), 4.13 (m, 2H), 2.22 (s, 6H), 1.15 (t, J = 7.0 Hz, 3H). LCMS: Anal. Calcd. for $C_{15}H_{18}N_2O_2$: 258; found: 259 $(M+H)^+$.

Step 2; (R,S) 2-(Quinolin-3-yl)-2-(N,N-dimethylamino)acetic acid: A mixture of (R,S)-ethyl 2-(quinolin-3-yl)-2-(N,N-dimethylamino)acetate (0.122 g, 0.472 mmol) and 6M HCl (3 mL) was heated at 100 °C for 12 hours. The solvent

was removed in vacuo to provide the dihydrochloride of the title compound (0.169 g, >100%) as a light yellow foam. The unpurified material was used in subsequent steps without further purification. LCMS: Anal. Calcd. for $C_{13}H_{14}N_2O_2$: 230; found: 231 $(M+H)^+$.

Cap-38



Cap-38

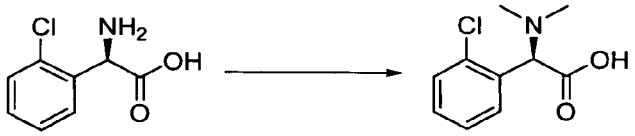
Step 1; (R)-((S)-1-phenylethyl) 2-(dimethylamino)-2-(2-fluorophenyl)acetate and (S)-((S)-1-phenylethyl) 2-(dimethylamino)-2-(2-fluorophenyl)acetate: To a mixture of (RS)-2-(dimethylamino)-2-(2-fluorophenyl)acetic acid (2.60 g, 13.19 mmol), DMAP (0.209 g, 1.71 mmol) and (S)-1-phenylethanol (2.09 g, 17.15 mmol) in CH_2Cl_2 (40 mL) was added EDCI (3.29 g, 17.15 mmol) and the mixture was allowed to stir at room temperature for 12 hours. The solvent was then removed in vacuo and the residue partitioned with ethyl acetate-H_2O. The layers were separated, the aqueous layer was back-extracted with ethyl acetate (2x) and the combined organic phases were washed (H_2O, brine), dried (Na_2SO_4), filtered, and concentrated in vacuo. The residue was purified by silica gel chromatography (Biotage/ 0-50% diethyl ether-hexane). The resulting pure diastereomeric mixture was then separated by reverse-phase preparative HPLC (Primesphere C-18, 30 x 100mm; CH_3CN-H_2O-0.1% TFA) to give first (S)-1-phenethyl (R)-2-(dimethylamino)-2-(2-fluorophenyl)acetate (0.501 g, 13%) and then (S)-1-phenethyl (S)-2-(dimethylamino)-2-(2-fluorophenyl)-acetate (0.727 g. 18%), both as their TFA salts. **(S,R)-isomer**: ^{1}HNMR (400 MHz, CD_3OD) δ 7.65 - 7.70 (m, 1H), 7.55-7.60 (ddd, J = 9.4, 8.1, 1.5 Hz, 1H), 7.36-7.41 (m, 2H), 7.28-7.34 (m, 5H), 6.04 (q, J = 6.5 Hz, 1H), 5.60 (s, 1H), 2.84 (s, 6H), 1.43 (d, J = 6.5 Hz, 3H). LCMS: Anal. Calcd. for $C_{18}H_{20}FNO_2$: 301; found: 302 $(M+H)^+$; **(S,S)-isomer**: ^{1}HNMR (400 MHz, CD_3OD) δ

7.58-7.63 (m, 1H), 7.18-7.31 (m, 6H), 7.00 (dd, J = 8.5, 1.5 Hz, 2H), 6.02 (q, J = 6.5 Hz, 1H), 5.60 (s, 1H), 2.88 (s, 6H), 1.54 (d, J = 6.5 Hz, 3H). LCMS: Anal. Calcd. for $C_{18}H_{20}FNO_2$: 301; found: 302 $(M+H)^+$.

Step 2; (R)-2-(dimethylamino)-2-(2-fluorophenyl)acetic acid: A mixture of (R)-((S)-1-phenylethyl) 2-(dimethylamino)-2-(2-fluorophenyl)acetate TFA salt (1.25 g, 3.01 mmol) and 20% $Pd(OH)_2/C$ (0.125 g) in ethanol (30 mL) was hydrogenated at room temperature and atmospheric pressure (H_2 balloon) for 4 hours. The solution was then purged with Ar, filtered through diatomaceous earth (Celite®), and concentrated in vacuo. This gave the title compound as a colorless solid (0.503 g, 98%). ^{1}HNMR (400 MHz, CD_3OD) δ 7.53-7.63 (m, 2H), 7.33-7.38 (m, 2H), 5.36 (s, 1H), 2.86 (s, 6H). LCMS: Anal. Calcd. for $C_{10}H_{12}FNO_2$: 197; found: 198 $(M+H)^+$.

The S-isomer could be obtained from (S)-((S)-1-phenylethyl) 2-(dimethylamino)-2-(2-fluorophenyl)acetate TFA salt in similar fashion.

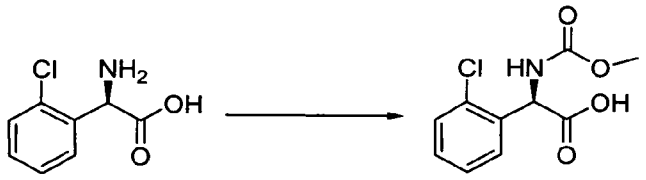
Cap-39



cap-39

A mixture of (R)-(2-chlorophenyl)glycine (0.300 g, 1.62 mmol), formaldehyde (35% aqueous solution, 0.80 mL, 3.23 mmol) and 20% $Pd(OH)_2/C$ (0.050 g) was hydrogenated at room temperature and atmospheric pressure (H_2 balloon) for 4 hours. The solution was then purged with Ar, filtered through diatomaceous earth (Celite®) and concentrated in vacuo. The residue was purified by reverse-phase preparative HPLC (Primesphere C-18, 30 x 100mm; CH_3CN-H_2O-0.1% TFA) to give theTFA salt of the title compound (R)-2-(dimethylamino)-2-(2-chlorophenyl)acetic acid as a colorless oil (0.290 g, 55%). ^{1}H NMR (400 MHz, CD_3OD) δ 7.59-7.65 (m, 2H), 7.45-7.53 (m, 2H), 5.40 (s, 1H), 2.87 (s, 6H). LCMS: Anal. Calcd. for $C_{10}H_{12}ClNO_2$: 213, 215; found: 214, 216 $(M+H)^+$.

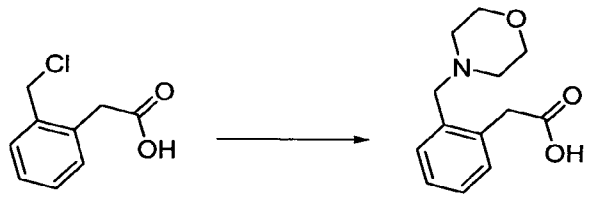
Cap-40



cap-40

To an ice-cold solution of (R)-(2-chlorophenyl)glycine (1.00 g, 5.38 mmol) and NaOH (0.862 g, 21.6 mmol) in H_2O (5.5 mL) was added methyl chloroformate (1.00 mL, 13.5 mmol) dropwise. The mixture was allowed to stir at 0 °C for 1 hour and then it was acidified by the addition of conc. HCl (2.5 mL). The mixture was extracted with ethyl acetate (2x) and the combined organic phase was washed (H_2O, brine), dried (Na_2SO_4), filtered, and concentrated in vacuo to give the title compound (R)-2-(methoxycarbonylamino)-2-(2-chlorophenyl)acetic acid as a yellow-orange foam (1.31 g, 96%). ^{1}H NMR (400 MHz, CD_3OD) δ 7.39 – 7.43 (m, 2H), 7.29 – 7.31 (m, 2H), 5.69 (s, 1H), 3.65 (s, 3H). LCMS: Anal. Calcd. for $C_{10}H_{10}ClNO_4$: 243, 245; found: 244, 246 $(M+H)^+$.

Cap-41

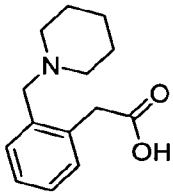


cap-41

To a suspension of 2-(2-(chloromethyl)phenyl)acetic acid (2.00 g, 10.8 mmol) in THF (20 mL) was added morpholine (1.89 g, 21.7 mmol) and the solution was stirred at room temperature for 3 hours. The reaction mixture was then diluted with ethyl acetate and extracted with H_2O (2x). The aqueous phase was lyophilized and the residue was purified by silica gel chromatography (Biotage/ 0-10% methanol-CH_2Cl_2) to give the title compound 2-(2-(Morpholinomethyl)phenyl)acetic acid as a colorless solid (2.22 g, 87%). ^{1}HNMR (400 MHz, CD_3OD) δ 7.37-7.44 (m, 3H), 7.29-7.33 (m, 1H), 4.24 (s, 2H), 3.83 (br s, 4H), 3.68 (s, 2H), 3.14 (br s, 4H). LCMS: Anal. Calcd. for $C_{13}H_{17}NO_3$: 235; found: 236 $(M+H)^+$.

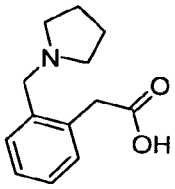
The following examples were similarly prepared using the method described for Cap-41:

Cap-42



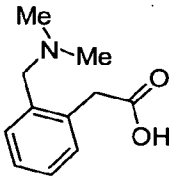
LCMS: Anal. Calcd. for $C_{14}H_{19}NO_2$: 233; found: 234 $(M+H)^+$.

Cap-43



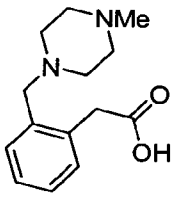
LCMS: Anal. Calcd. for $C_{13}H_{17}NO_2$: 219; found: 220 $(M+H)^+$.

Cap-44



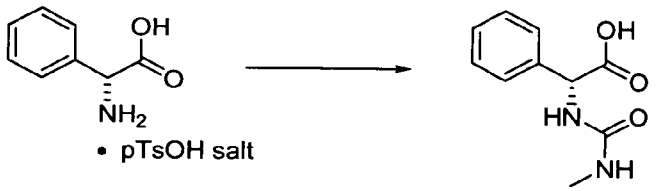
LCMS: Anal. Calcd. for $C_{11}H_{15}NO_2$: 193; found: 194 $(M+H)^+$.

Cap-45



LCMS: Anal. Calcd. for $C_{14}H_{20}N_2O_2$: 248; found: 249 $(M+H)^+$.

Cap-45

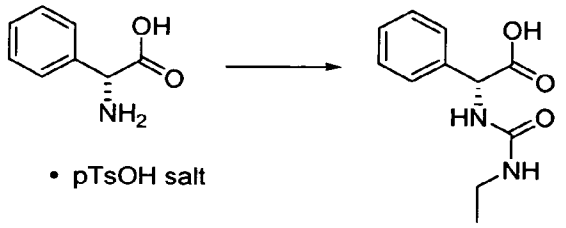


Cap-45

HMDS (1.85 mL, 8.77 mmol) was added to a suspension of (R)-2-amino-2-phenylacetic acid p-toluenesulfonate (2.83 g, 8.77 mmol) in CH_2Cl_2 (10 mL) and the mixture was stirred at room temperature for 30 minutes. Methyl isocyanate (0.5 g, 8.77 mmol) was added in one portion stirring continued for 30 minutes. The reaction was quenched by addition of H_2O (5 mL) and the resulting precipitate was filtered, washed with H_2O and n-hexanes, and dried under vacuum. (R)-2-(3-methylureido)-

2-phenylacetic acid (1.5 g; 82 %).was recovered as a white solid and it was used without further purification. ^{1}H NMR (500 MHz, DMSO-d_6) δ ppm 2.54 (d, J=4.88 Hz, 3H) 5.17 (d, J=7.93 Hz, 1H) 5.95 (q, J=4.48 Hz, 1H) 6.66 (d, J=7.93 Hz, 1H) 7.26 - 7.38 (m, 5H) 12.67 (s, 1H). LCMS: Anal. Calcd. for $C_{10}H_{12}N_2O_3$ 208.08 found 209.121 $(M+H)^+$; HPLC Phenomenex C-18 3.0 × 46 mm, 0 to 100% B over 2 minutes, 1 minute hold time, A = 90% water, 10% methanol, 0.1% TFA, B = 10% water, 90% methanol, 0.1% TFA, RT = 1.38 min, 90% homogeneity index.

Cap-46

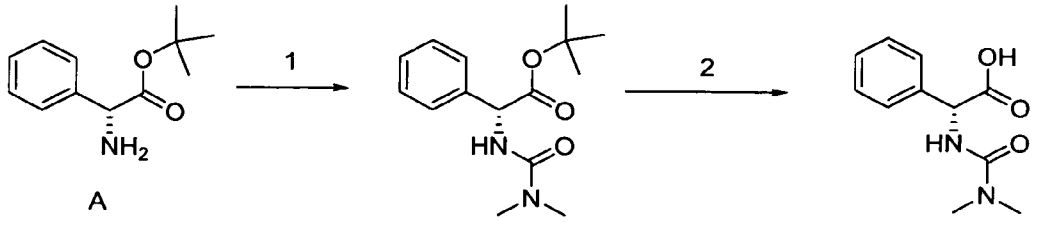


cap-46

The desired product was prepared according to the method described for Cap-45. ^{1}H NMR (500 MHz, DMSO-d_6) δ ppm 0.96 (t, J=7.17 Hz, 3H) 2.94 - 3.05 (m, 2H) 5.17 (d, J=7.93 Hz, 1H) 6.05 (t, J=5.19 Hz, 1H) 6.60 (d, J=7.63 Hz, 1H) 7.26 - 7.38 (m, 5H) 12.68 (s, 1H). LCMS: Anal. Calcd. for $C_{11}H_{14}N_2O_3$ 222.10 found 209.121 $(M+H)^+$.

HPLC XTERRA C-18 3.0 × 506 mm, 0 to 100% B over 2 minutes, 1 minutes hold time, A = 90% water, 10% methanol, 0.2% H_3PO_4, B = 10% water, 90% methanol, 0.2% H_3PO_4, RT = 0.87 min, 90% homogeneity index.

Cap-47



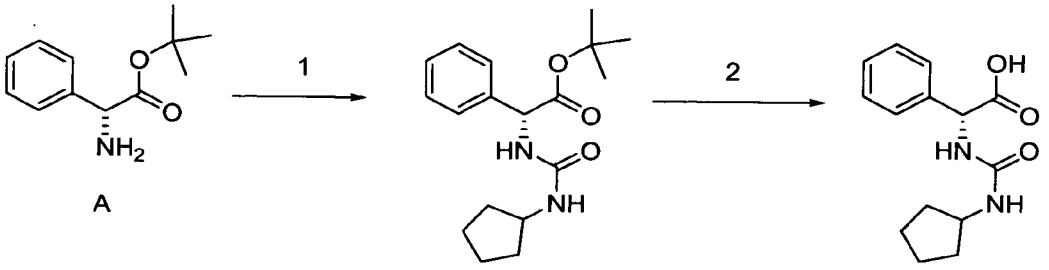
Cap-47

Step 1; (R)-tert-butyl 2-(3,3-dimethylureido)-2-phenylacetate: To a stirred solution of (R)-tert–butyl-2-amino-2-phenylacetate (1.0 g, 4.10 mmol) and Hunig's

base (1.79 mL, 10.25 mmol) in DMF (40 mL) was added dimethylcarbamoyl chloride (0.38 mL, 4.18 mmol) dropwise over 10 minutes. After stirring at room temperature for 3 hours, the reaction was concentrated under reduced pressure and the resulting residue was dissolved in ethyl acetate. The organic layer was washed with H_2O, 1N aq. HCl and brine, dried ($MgSO_4$), filtered and concentrated under reduced pressure. (R)-tert-butyl 2-(3,3-dimethylureido)-2-phenylacetate was obtained as a white solid (0.86 g; 75%) and used without further purification. ^1H NMR (500 MHz, DMSO-d_6) δ ppm 1.33 (s, 9H) 2.82 (s, 6H) 5.17 (d, J=7.63 Hz, 1H) 6.55 (d, J=7.32 Hz, 1H) 7.24 - 7.41 (m, 5H). LCMS: Anal. Calcd. for $C_{15}H_{22}N_2O_3$ 278.16 found 279.23 $(M+H)^+$; HPLC Phenomenex LUNA C-18 4.6 × 50 mm, 0 to 100% B over 4 minutes, 1 minutes hold time, A = 90% water, 10% methanol, 0.1% TFA, B = 10% water, 90% methanol, 0.1% TFA, RT = 2.26 min, 97% homogeneity index.

Step 2; (R)-2-(3,3-dimethylureido)-2-phenylacetic acid: To a stirred solution of ((R)-tert-butyl 2-(3,3-dimethylureido)-2-phenylacetate (0.86 g, 3.10 mmol) in CH_2Cl_2 (250 mL) was added TFA (15 mL) dropwise and the resulting solution was stirred at rt for 3 h. The desired compound was then precipitated out of solution with a mixture of EtOAC:Hexanes (5:20), filtered off and dried under reduced pressure. (R)-2-(3,3-dimethylureido)-2-phenylacetic acid was isolated as a white solid (0.59g, 86%) and used without further purification. ^1H NMR (500 MHz, DMSO-d_6) δ ppm 2.82 (s, 6H) 5.22 (d, J=7.32 Hz, 1H) 6.58 (d, J=7.32 Hz, 1H) 7.28 (t, J=7.17 Hz, 1H) 7.33 (t, J=7.32 Hz, 2H) 7.38 - 7.43 (m, 2H) 12.65 (s, 1H). LCMS: Anal. Calcd. for $C_{11}H_{14}N_2O_3$: 222.24; found: 223.21 $(M+H)^+$. HPLC XTERRA C-18 3.0 × 50 mm, 0 to 100% B over 2 minutes, 1 minutes hold time, A = 90% water, 10% methanol, 0.2% H_3PO_4, B = 10% water, 90% methanol, 0.2% H_3PO_4, RT = 0.75 min, 93% homogeneity index.

Cap-48



Step 1; (R)-tert-butyl 2-(3-cyclopentylureido)-2-phenylacetate: To a stirred solution of (R)-2-amino-2-phenylacetic acid hydrochloride (1.0 g, 4.10 mmol) and Hunig's base (1.0 mL, 6.15 mmol) in DMF (15 mL) was added cyclopentyl isocyanate (0.46 mL, 4.10 mmol) dropwise and over 10 minutes. After stirring at room temperature for 3 hours, the reaction was concentrated under reduced pressure and the resulting residue was traken up in ethyl acetate. The organic layer was washed with H_2O and brine, dried ($MgSO_4$), filtered, and concentrated under reduced pressure. (R)-tert-butyl 2-(3-cyclopentylureido)-2-phenylacetate was obtained as an opaque oil (1.32 g; 100 %) and used without further purification. ^{1}H NMR (500 MHz, CD_3Cl-D) δ ppm 1.50 - 1.57 (m, 2H) 1.58 - 1.66 (m, 2H) 1.87 - 1.97 (m, 2H) 3.89 - 3.98 (m, 1H) 5.37 (s, 1H) 7.26 - 7.38 (m, 5H). LCMS: Anal. Calcd. for $C_{18}H_{26}N_2O_3$ 318.19 found 319.21 $(M+H)^+$; HPLC XTERRA C-18 3.0 × 50 mm, 0 to 100% B over 4 minutes, 1 minutes hold time, A = 90% water, 10% methanol, 0.1% TFA, B = 10% water, 90% methanol, 0.1% TFA, RT = 2.82 min, 96% homogeneity index.

Step 2; (R)-2-(3-cyclopentylureido)-2-phenylacetic acid: To a stirred solution of (R)-tert-butyl 2-(3-cyclopentylureido)-2-phenylacetate (1.31 g, 4.10 mmol) in CH_2Cl_2 (25 mL) was added TFA (4 mL) and trietheylsilane (1.64 mL; 10.3 mmol) dropwise, and the resulting solution was stirred at room temperature for 6 hours. The volatile components were removed under reduced pressure and the crude product was recrystallized in ethyl acetate/pentanes to yield (R)-2-(3-cyclopentylureido)-2-phenylacetic acid as a white solid (0.69 g, 64%). ^{1}H NMR (500 MHz, DMSO-d_6) δ ppm 1.17 - 1.35 (m, 2H) 1.42 - 1.52 (m, 2H) 1.53 - 1.64 (m, 2H) 1.67 - 1.80 (m, 2H) 3.75 - 3.89 (m, 1H) 5.17 (d, *J*=7.93 Hz, 1H) 6.12 (d, *J*=7.32 Hz, 1H) 6.48 (d, *J*=7.93 Hz, 1H) 7.24 - 7.40 (m, 5H) 12.73 (s, 1H). LCMS: Anal. Calcd. for $C_{14}H_{18}N_2O_3$: 262.31; found: 263.15 $(M+H)^+$. HPLC XTERRA C-18 3.0 × 50 mm, 0 to 100% B

over 2 minutes, 1 minutes hold time, A = 90% water, 10% methanol, 0.2% H_3PO_4, B = 10% water, 90% methanol, 0.2% H_3PO_4, RT = 1.24 min, 100% homogeneity index.

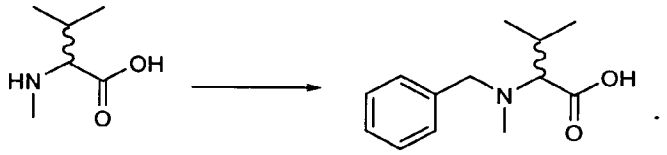
Cap-49



cap-49

To a stirred solution of 2-(benzylamino)acetic acid (2.0 g, 12.1 mmol) in formic acid (91 mL) was added formaldehyde (6.94 mL, 93.2 mmol). After five hours at 70 °C, the reaction mixture was concentrated under reduced pressure to 20 mL and a white solid precipitated. Following filtration, the mother liquors were collected and further concentrated under reduced pressure providing the crude product. Purification by reverse-phase preparative HPLC (Xterra 30 X 100 mm, detection at 220 nm, flow rate 35 mL/min, 0 to 35% B over 8 min; A = 90% water, 10 % methanol, 0.1% TFA, B = 10% water, 90 % methanol, 0.1% TFA) provided the title compound 2-(benzyl(methyl)-amino)acetic acid as its TFA salt (723 mg, 33%) as a colorless wax. ^{1}H NMR (300 MHz, DMSO-d_6) δ ppm 2.75 (s, 3H) 4.04 (s, 2H) 4.34 (s, 2H) 7.29 - 7.68 (m, 5H). LCMS: Anal. Calcd. for: $C_{10}H_{13}NO_2$ 179.22; Found: 180.20 $(M+H)^+$.

Cap-50

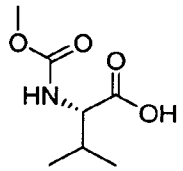


Cap-50

To a stirred solution of 3-methyl-2-(methylamino)butanoic acid (0.50 g, 3.81 mmol) in water (30 mL) was added K_2CO_3 (2.63 g, 19.1 mmol) and benzyl chloride (1.32 g, 11.4 mmol). The reaction mixture was stirred at ambient temperature for 18 hours. The reaction mixture was extracted with ethyl acetate (30 mL x 2) and the aqueous layer was concentrated under reduced pressure providing the crude product which was purified by reverse-phase preparative HPLC (Xterra 30 x 100mm, detection at 220 nm, flow rate 40 mL/min, 20 to 80% B over 6 min; A = 90% water,

10 % methanol, 0.1% TFA, B = 10% water, 90 % methanol, 0.1% TFA) to provide 2-(benzyl(methyl)amino)-3-methylbutanoic acid, TFA salt (126 mg, 19%) as a colorless wax. ^{1}H NMR (500 MHz, DMSO-d_6) δ ppm 0.98 (d, 3H) 1.07 (d, 3H) 2.33 - 2.48 (m, 1H) 2.54 - 2.78 (m, 3H) 3.69 (s, 1H) 4.24 (s, 2H) 7.29 - 7.65 (m, 5H). LCMS: Anal. Calcd. for: $C_{13}H_{19}NO_2$ 221.30; Found: 222.28 $(M+H)^+$.

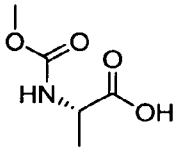
Cap-51



Na_2CO_3 (1.83g, 17.2 mmol) was added to NaOH (33 mL of 1M/H_2O, 33 mmol) solution of L-valine (3.9 g, 33.29 mmol) and the resulting solution was cooled with ice-water bath. Methyl chloroformate (2.8 mL, 36.1 mmol) was added drop-wise over 15 min, the cooling bath was removed and the reaction mixture was stirred at ambient temperature for 3.25 hr. The reaction mixture was washed with ether (50 mL, 3x), and the aqueous phase was cooled with ice-water bath and acidified with concentrated HCl to a pH region of 1-2, and extracted with CH_2Cl_2 (50 mL, 3x). The organic phase was dried ($MgSO_4$) and evaporated in vacuo to afford **Cap-51** as a white solid (6 g). ^{1}H NMR for the dominant rotamer (DMSO-D_6, δ= 2.5 ppm, 500 MHz): 12.54 (s, 1H), 7.33 (d, J = 8.6, 1H), 3.84 (dd, J = 8.4, 6.0, 1H), 3.54 (s, 3H), 2.03 (m, 1H), 0.87 (m, 6H).

HRMS: Anal. Calcd. for $[M+H]^+$ $C_7H_{14}NO_4$: 176.0923; found 176.0922

Cap-52



Cap-52 was synthesized from L-alanine according to the procedure described for the synthesis of **Cap-51**. For characterization purposes, a portion of the crude material was purified by a reverse phase HPLC (H_2O/MeOH/TFA) to afford **Cap-52** as a colorless viscous oil. ^1H NMR (DMSO-D_6, δ= 2.5 ppm, 500 MHz): 12.49 (br s, 1H), 7.43 (d, J = 7.3, 0.88H), 7.09 (app br s, 0.12H), 3.97 (m, 1H), 3.53 (s, 3H), 1.25 (d, J = 7.3, 3H).

EXAMPLES

The present disclosure will now be described in connection with certain embodiments which are not intended to limit its scope. On the contrary, the present disclosure covers all alternatives, modifications, and equivalents as can be included within the scope of the claims. Thus, the following examples, which include specific embodiments, will illustrate one practice of the present disclosure, it being understood that the examples are for the purposes of illustration of certain embodiments and are presented to provide what is believed to be the most useful and readily understood description of its procedures and conceptual aspects.

Solution percentages express a weight to volume relationship, and solution ratios express a volume to volume relationship, unless stated otherwise. Nuclear magnetic resonance (NMR) spectra were recorded either on a Bruker 300, 400, or 500 MHz spectrometer; the chemical shifts (δ) are reported in parts per million. Flash chromatography was carried out on silica gel (SiO_2) according to Still's flash chromatography technique (*J. Org. Chem.* **1978**, *43*, 2923).

Purity assessment and low resolution mass analysis were conducted on a Shimadzu LC system coupled with Waters Micromass ZQ MS system. It should be noted that retention times may vary slightly between machines. The LC conditions employed in determining the retention time (RT) were:

Condition I

Column = Phenomenex-Luna 3.0X 50 mm S10
Start %B = 0
Final %B = 100
Gradient time = 2 min
Stop time = 3 min

Flow Rate = 4 mL/min

Wavelength = 220 nm

Solvent A = 0.1% TFA in 10% methanol/90%H_2O

Solvent B = 0.1% TFA in 90% methanol/10% H_2O

Condition II

Column = Phenomenex-Luna 4.6X50 mm S10

Start %B = 0

Final %B = 100

Gradient time = 2 min

Stop time = 3 min

Flow Rate = 5 mL/min

Wavelength = 220 nm

Solvent A = 0.1% TFA in 10% methanol/90%H_2O

Solvent B = 0.1% TFA in 90% methanol/10% H_2O

Condition III

Column = HPLC XTERRA C18 3.0 x 50mm S7

Start %B = 0

Final %B = 100

Gradient time = 3 min

Stop time = 4 min

Flow Rate = 4 mL/min

Wavelength = 220 nm

Solvent A = 0.1% TFA in 10% methanol/90%H_2O

Solvent B = 0.1% TFA in 90% methanol/10% H_2O

Method A: LCMS – Xterra MS C-18 3.0 x 50mm, 0 to 100% B over 30.0 minute gradient, 1 minute hold time, A = 5% acetonitrile, 95% water, 10mm ammonium acetate, B = 95% acetonitrile, 5% water, 10mm ammonium acetate.

Method B: HPLC – X-Terra C-18 4.6 x 50mm, 0 to 100% B over 10.0 minute gradient, 1 minute hold time, A = 10% methanol 90% water 0.1% TFA, B = 90% methanol 10% water 0.1% TFA

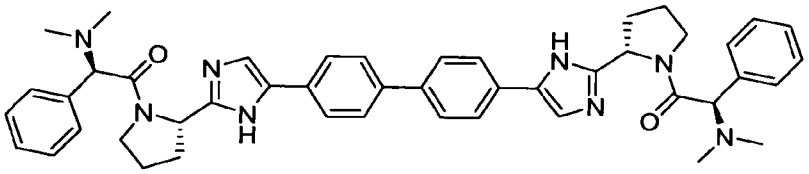
Method C: HPLC – YMC C-18 4.6 x 50mm, 0 to 100% B over 10.0 minute gradient, 1 minute hold time, A = 10% methanol 90% water 0.2% H_3PO_4, B = 90% methanol 10% water 0.2% H_3PO_4.

Method D: HPLC – Phenomenex C-18 4.6 x 150mm, 0 to 100% B over 10.0 minute gradient, 1 minute hold time, A = 10% methanol 90% water 0.2% H_3PO_4, B = 90% methanol 10% water 0.2% H_3PO_4

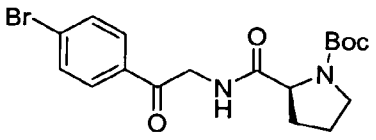
Method E: LCMS – Gemini C-18 4.6 x 50mm, 0 to 100% B over 10.0 minute gradient, 1 minute hold time, A = 5% acetonitrile, 95% water, 10mm ammonium acetate, B = 95% acetonitrile, 5% water, 10mm ammonium acetate.

Method F: LCMS-Luna C-18 3.0 x 50mm, 0 to 100% B over 7.0 minute gradient, 1 minute hold time, A = 5% acetonitrile, 95% water, 10mm ammonium acetate, B = 95% acetonitrile, 5% water, 10mm ammonium acetate.

Example 1



Example 1, Step a

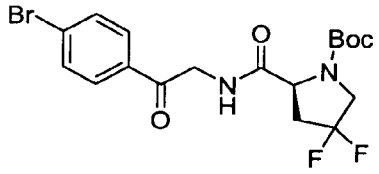


1a

N,N-Diisopropylethylamine (18 mL, 103.3 mmol) was added dropwise, over 15 minutes, to a heterogeneous mixture of *N*-Boc-L-proline (7.139 g, 33.17 mmol),

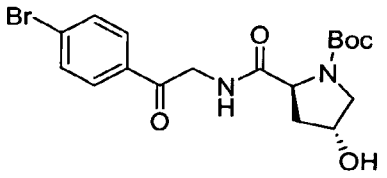
HATU (13.324 g, 35.04 mmol), the HCl salt of 2-amino-1-(4-bromophenyl)ethanone (8.127 g, 32.44 mmol), and DMF (105 mL), and stirred at ambient condition for 55 minutes. Most of the volatile component was removed *in vacuo*, and the resulting residue was partitioned between ethyl acetate (300 mL) and water (200 mL). The organic layer was washed with water (200 mL) and brine, dried ($MgSO_4$), filtered, and concentrated *in vacuo*. A silica gel mesh was prepared from the residue and submitted to flash chromatography (silica gel; 50-60 % ethyl acetate/hexanes) to provide ketoamide **1a** as a white solid (12.8 g). ^{1}H NMR (DMSO-d_6, δ = 2.5 ppm, 400 MHz): δ 8.25-8.14 (m, 1H), 7.92 (br d, J = 8.0, 2H), 7.75 (br d, J = 8.6, 2H), 4.61 (dd, J = 18.3, 5.7, 1H), 4.53 (dd, J = 18.1, 5.6, 1H), 4.22-4.12 (m, 1H), 3.43-3.35 (m, 1H), 3.30-3.23 (m, 1H), 2.18-2.20 (m, 1H), 1.90-1.70 (m, 3H), 1.40/1.34 (two app br s, 9H). LC (Cond. I): RT = 1.70 min; LC/MS: Anal. Calcd. for $[M+Na]^+$ $C_{18}H_{23}BrN_2NaO_4$: 433.07; found 433.09.

Analogous compounds such as intermediate **1-1a to 1-5a** can be prepared by incorporating the appropriately substituted amino acid and aryl bromide isomer.



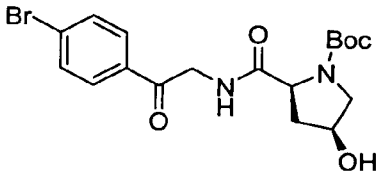
1-1a

^{1}H NMR (500 MHz, DMSO-d_6) δ ppm 1.35/1.40 (two br s, 9H), 2.27-2.42 (m, 1H), 2.73-2.95 (m, 1H), 3.62-3.89 (m, 2H), 4.36-4.50 (m, 1H), 4.51-4.60 (m, 1H), 4.62-4.73 (m, 1H), 7.75 (d, J=8.24 Hz, 2H), 7.92 (d, J=7.63 Hz, 2H), 8.31-8.49 (m, 1H). HPLC XTERRA C-18 4.6 × 30 mm, 0 to 100% B over 4 minutes, 1 minute hold time, A = 90% water, 10% methanol, 0.2% H_3PO_4, B = 10% water, 90% methanol, 0.2% H_3PO_4, RT = 1.59 minutes, 99% homogeneity index. LCMS: Anal. Calcd. for $C_{18}H_{21}BrF_2N_2O_4$: 446.06; found: 445.43 $(M-H)^+$.



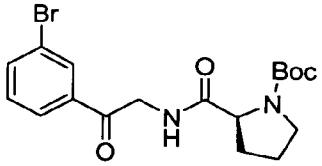
1-2a

^{1}H NMR (500 MHz, DMSO-d_6) δ ppm (8.25 1H, s), 7.91 (2H, d, *J*=8.24Hz), 7.75 (2H, d, *J*=8.24 Hz), 4.98 (1H, s), 4.59-4.63 (1H, m), 4.46-4.52 (1H, m), 4.23 (1H, m), 3.37 (1H, s), 3.23-3.28 (1H, m), 2.06 (1H, m), 1.88 (1H, s), 1.38 (3H, s), 1.33 (6H, s). LCMS – Phenomenex C-18 3.0 x 50mm, 0 to 100% B over 4.0 minute gradient, 1 minute hold time, A = 10% methanol 90% water 0.1% TFA, B = 90% methanol 10% water 0.1% TFA mobile phase, RT = 3.34 minutes, Anal Calcd. for $C_{18}H_{23}BrN_2O_5$ 427.30; found 428.08 $(M+H)^+$.



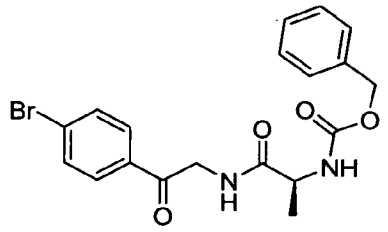
1-3a

^{1}H NMR (500 MHz, DMSO-d_6) δ ppm 8.30 (1H, s) 7.93-7.96 (2H, m) 7.76 (2H d, *J*=8.24 Hz) 5.13 (1H, s) 4.66-4.71 (1H, m) 4.52-4.55 (1H, m) 4.17 (1H, m) 3.51 (1H, s) 3.16-3.19 (1H, m) 2.36 (1H, m) 1.78 (1H, s) 1.40 (s, 3H), 1.34 (s, 6H). LCMS – Phenomenex C-18 3.0 x 50mm, 0 to 100% B over 4.0 minute gradient, 1 minute hold time, A = 10% methanol 90% water 0.1% TFA, B = 90% methanol 10% water 0.1% TFA, RT= 3.69 minutes, Anal Calcd. for $C_{18}H_{23}BrN_2O_5$ 427.30; found 428.16 $(M+H)^+$.



1-4a

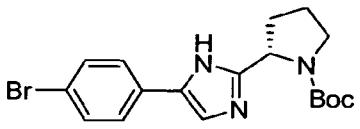
^{1}H NMR (500 MHz, DMSO-d_6) δ ppm 1.29-1.47 (m, 9H), 1.67-1.90 (m, 3H), 2.00-2.20 (m, 1H), 3.23-3.30 (m, 1H), 3.34-3.44 (m, 1H), 4.16 (dd, 1H), 4.57 (q, 2H), 7.51 (t, *J*=7.78 Hz, 1H), 7.86 (dd, *J*=7.93, 1.22 Hz, 1H), 7.98 (d, *J*=7.63 Hz, 1H), 8.11 (s, 1H), 8.15-8.29 (m, 1H). LC/MS $(M+Na)^+$ = 433.12/435.12.



1-5a

LCMS conditions: Phenomenex LUNA C-18 4.6 × 50 mm, 0 to 100% B over 2 minutes, 1 minute hold time, A = 90% water, 10% methanol, 0.1% TFA, B = 10% water, 90% methanol, 0.1% TFA, 220nm, 5 µL injection volume. RT = 1.93 min; LRMS: Anal. Calcd. for $C_{19}H_{18}BrN_2O_4$ 418.05; found: 419.07 $(M+H)^+$.

Example 1, Step b



1b

A mixture of ketoamide **1a** (12.8 g, 31.12 mmol) and NH_4OAc (12.0 g, 155.7 mmol) in xylenes (155 mL) was heated in a sealed tube at 140 °C for 2 hours. The volatile component was removed *in vacuo*, and the residue was partitioned carefully between ethyl acetate and water, whereby enough saturated $NaHCO_3$ solution was added so as to make the pH of the aqueous phase slightly basic after the shaking of the biphasic system. The layers were separated, and the aqueous layer was extracted with an additional ethyl acetate. The combined organic phase was washed with brine, dried ($MgSO_4$), filtered, and concentrated *in vacuo*. The resulting material was recrystallized from ethyl acetate/hexanes to provide two crops of imidazole **1b** as a light-yellow dense solid, weighing 5.85 g. The mother liquor was concentrated *in vacuo* and submitted to a flash chromatography (silica gel; 30% ethyl acetate/hexanes) to provide an additional 2.23 g of imidazole **1b**. ^1H NMR (DMSO-d_6, δ = 2.5 ppm, 400 MHz): δ 12.17/11.92/11.86 (m, 1H), 7.72-7.46/7.28 (m, 5H), 4.86-4.70 (m, 1H), 3.52 (app br s, 1H), 3.36 (m, 1H), 2.30-1.75 (m, 4H), 1.40/1.15 (app br s, 9H). LC (Cond. Ib): RT = 1.71 min; >98% homogeneity index; LC/MS: Anal. Calcd. for $[M+H]^+$ $C_{18}H_{23}BrN_3O_2$: 392.10; found 391.96; HRMS: Anal. Calcd. for $[M+H]^+$ $C_{18}H_{23}BrN_3O_2$: 392.0974; found 392.0959

The optical purity of the two samples of **1b** were assessed using the chiral HPLC conditions noted below (ee > 99% for the combined crops; ee = 96.7% for the sample from flash chromatography):

Column: Chiralpak AD, 10 um, 4.6 x 50 mm

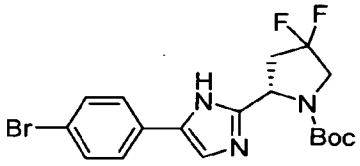
Solvent: 2% ethanol/heptane (isocratic)

Flow rate: 1 mL/min

Wavelength: either 220 or 254 nm

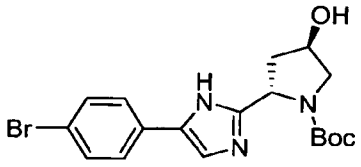
Relative retention time: 2.83 minutes (*R*), 5.34 minutes (*S*)

Analogous compounds such as intermediate **1-1b to 1-4b** can be prepared by incorporating the appropriate ketoamide.



1-1b

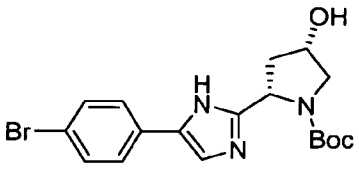
^{1}H NMR (500 MHz, DMSO-d_6) δ ppm 1.17/1.40 (two br s, 9H), 2.50-2.74 (m, *J*=25.64 Hz, 1H), 2.84-3.07 (m, 1H), 3.88 (d, *J*=10.07 Hz, 2H), 5.03 (s, 1H), 7.50 (d, *J*=8.55 Hz, 2H), 7.60 (s, 1H), 7.70 (d, *J*=8.55 Hz, 2H), 12.10 (s, 1H). HPLC XTERRA C-18 4.6 × 30 mm, 0 to 100% B over 4 minutes, 1 minute hold time, A = 90% water, 10% methanol, 0.2% H_3PO_4, B = 10% water, 90% methanol, 0.2% H_3PO_4, RT = 1.59 minutes, 99% homogeneity index; LCMS: Anal. Calcd. for $C_{18}H_{20}BrF_2N_3O_2$: 428.27; found: 428.02 $(M)^+$.



1-2b

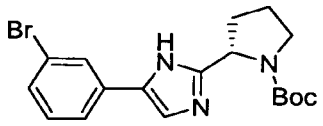
^{1}H NMR (500 MHz, DMSO-d_6) δ ppm 11.89-11.99 (1H, m), 7.68 (2H, d, *J*=8.54 Hz), 7.52-7.59 (1H, m), 7.48 (2H, d, *J*=8.54 Hz), 4.80 (1H, m), 4.33 (1H, s), 3.51-3.60 (1H, m), 3.34 (1H, d, *J*=10.99 Hz), 2.14 (1H, s), 1.97-2.05 (1H, m), 1.37 (3H, s), 1.10 (6H, s); LCMS – Phenomenex C-18 3.0 x 50mm, 0 to 100% B over 4.0

minute gradient, 1 minute hold time, A = 10% methanol 90% water 0.1% TFA, B = 90% methanol 10% water 0.1% TFA, (RT= 3.23 min) Anal Calcd. for $C_{18}H_{22}BrN_3O_3$ 408.30; found 409.12 $(M+H)^+$.



1-3b

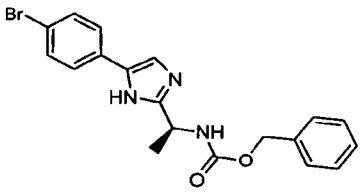
^{1}H NMR (500 MHz, DMSO-d_6) δ ppm 12.06-12.24 (1H, m), 7.58-7.69 (5H, m), 4.84-4.95 (1H, m), 4.34 (1H, s), 3.61 (1H, s), 3.34-3.40 (1H, m), 2.52 (1H, s), 1.92-2.20 (1H, m), 1.43 (3H, s), 1.22 (6H, s); LCMS – Phenomenex C-18 3.0 x 50mm, 0 to 100% B over 4.0 minute gradient, 1 minute hold time, A = 10% methanol 90% water 0.1% TFA, B = 90% methanol 10% water 0.1% TFA, (RT= 3.41 min) Anal Calcd. for $C_{18}H_{22}BrN_3O_3$ 408.30; found 409.15 $(M+H)^+$.



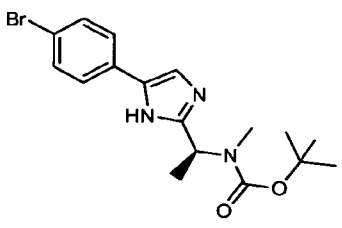
1-4b

^{1}H NMR (500 MHz, DMSO-d_6) δ ppm 0.98-1.51 (m, 9H), 1.82-2.12 (m, 3H), 2.31-2.48 (m, 1H), 3.30-3.51 (m, 1H), 3.52-3.66 (m, 1H), 4.88-5.16 (m, 1H), 7.47 (t, *J*=7.93 Hz, 1H), 7.61 (d, *J*=7.93 Hz, 1H), 7.81 (d, *J*=7.93 Hz, 1H), 8.04 (s, 1H), 8.12 (d, *J*=28.38 Hz, 1H), 14.65 (s, 1H). LC/MS $(M+H)^+$ = 391.96/393.96.

Additional imidazole analogs made following procedures similar to those described above.

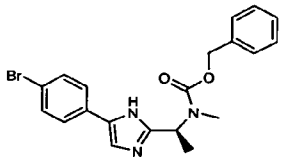
Example	Structure	Data
1-5b		RT = 1.70 minutes (condition 2, 98%); LRMS: Anal. Calcd. for $C_{19}H_{18}BrN_3O_2$ 399.05; found: 400.08 $(M+H)^+$.

1-6b



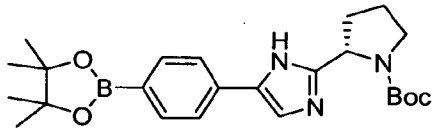
RT = 1.64 minutes (condtion 2, 98%); LRMS: Anal. Calcd. for $C_{17}H_{22}N_3O_2$ 379.09; found: 380.06 $(M+H)^+$.

1-7b



RT = 2.28 minutes (95%); LCMS: Anal. Calcd. for $C_{20}H_{21}BrN_3O_2$ 414.08; found: 414.08 $(M+H)^+$; HRMS: Anal. Calcd. for $C_{20}H_{21}BrN_3O_2$ 414.0817; found: 414.0798 $(M+H)^+$.

Example 1, Step c

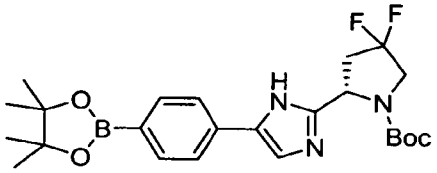


1c

$Pd(Ph_3P)_4$ (469 mg, 0.406 mmol) was added to a pressure tube containing a mixture of bromide **1b** (4.008 g, 10.22 mmol), bis(pinacolato)diboron (5.422 g, 21.35 mmol), potassium acetate (2.573g, 26.21 mmol) and 1,4-dioxane (80 mL). The reaction flask was purged with nitrogen, capped and heated with an oil bath at 80 °C for 16.5 hours. The reaction mixture was filtered and the filtrate was concentrated *in vacuo*. The crude material was partitioned carefully between CH_2Cl_2 (150 mL) and an aqueous medium (50 mL water + 10 mL saturated $NaHCO_3$ solution). The aqueous layer was extracted with CH_2Cl_2, and the combined organic phase was dried ($MgSO_4$), filtered, and concentrated *in vacuo*. The resulting material was purified with flash chromatography (sample was loaded with eluting solvent; 20-35% ethyl acetate/CH_2Cl_2) to provide boronate **1c,** contaminated with pinacol, as an off-white dense solid; the relative mole ratio of **1c** to pinacol was about 10:1 (^{1}H NMR). The sample weighed 3.925 g after ~2.5 days exposure to high vacuum. ^{1}H NMR (DMSO-d_6, δ= 2.5 ppm, 400 MHz): 12.22/11.94/ 11.87 (m, 1H), 7.79-7.50/ 7.34-7.27 (m, 5H), 4.86-4.70 (m, 1H), 3.52 (app br s, 1H), 3.36 (m, 1H), 2.27-1.77 (m,

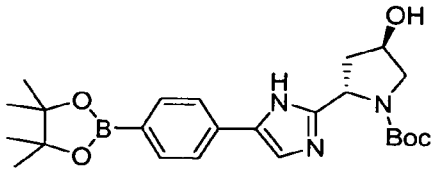
4H), 1.45-1.10 (m, 21H). LC (Cond. I): RT = 1.64 min; LC/MS: Anal. Calcd. for $[M+H]^+$ $C_{24}H_{35}BN_3O_4$: 440.27; found 440.23.

Analogous compounds such as intermediate **1-1c to 1-4c** can be prepared by incorporating the appropriate aryl bromide.



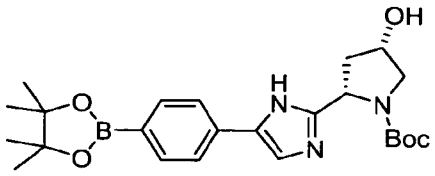
1-1c

^{1}H NMR (500 MHz, DMSO-d_6) δ ppm 1.16 (s, 8H), 1.29 (s, 13H), 2.51-2.72 (m, 1H), 2.84-3.03 (m, 1H), 3.79-4.00 (m, 2H), 4.88-5.21 (m, 1H), 7.62 (d, *J*=7.93 Hz, 2H), 7.67 (s, 1H), 7.76 (d, *J*=7.93 Hz, 2H), 12.11/12.40 (two br s, 1H). HPLC GEMINI C-18 4.6 × 50 mm, 0 to 100% B over 4 minutes, 1 minute hold time, A = 95% water, 5% acetonitrile, 0.1% NH_4OAc, B = 5% water, 95% acetonitrile, 0.1% NH_4OAc, RT = 1.62 minutes, 99% homogeneity index. LCMS: Anal. Calcd. for $C_{34}H_{32}BF_2N_3O_4$: 475.34; found: 474.78$(M-H)^+$.



1-2c

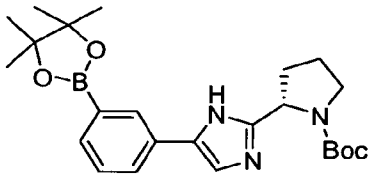
^{1}H NMR (500 MHz, DMSO-d_6) δ ppm 11.97 (1H, m), 7.62-7.75 (5H, m), 5.05 (1H d, *J*=3.36 Hz), 4.82 (m, 1H), 4.35 (m, 1H), 3.58 (1H, m), 2.389 (1H, s), 2.17 (1 H, m), 1.38 (3H, s), 1.30 (12H, s), 1.1 (6H, s); LCMS – Phenomenex C-18 3.0 x 50mm, 0 to 100% B over 4.0 minute gradient, 1 minute hold time, A = 5% acetonitrile, 95% water, 10mm ammonium acetate, B = 95% acetonitrile, 5% water, 10mm ammonium acetate, RT= 3.63 minutes, Anal. Calcd. for $C_{24}H_{34}BN_3O_5$ 455.30; found 456.31 $(M+H)^+$.



1-3c

^{1}H NMR (500 MHz, DMSO-d_6) δ ppm 12.05-12.24 (1H, m), 7.61-7.73 (5H, m), 4.83-5.01 (1H, m), 4.33 (1H, s), 3.54-3.63 (1H, m), 3.39-3.80 (1H, m), 2.38-2.49 (1H, m), 1.98-2.01 (1H, m), 1.42 (3H, s), 1.34 (12H, s), 1.21 (6H, s); LCMS – Phenomenex C-18 3.0 x 50mm, 0 to 100% B over 4.0 minute gradient, 1 minute hold time, A = 10% methanol 90% water 0.1% TFA, B = 90% methanol 10% water 0.1% TFA,

RT= 3.64 minutes, Anal. Calcd. for $C_{24}H_{34}BN_3O_5$ 455.30; found 456.30 $(M+H)^+$.



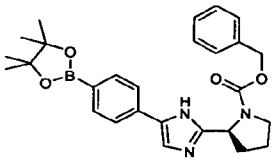
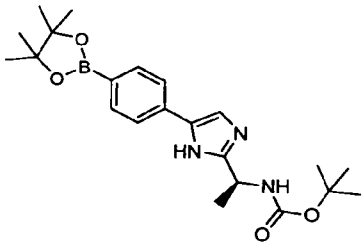
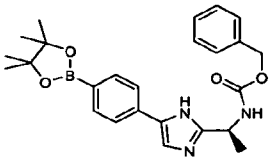
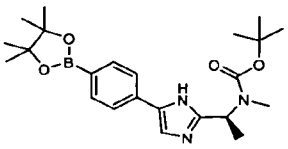
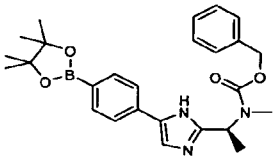
1-4c

^{1}H NMR (500 MHz, DMSO-d_6) δ ppm 1.02-1.54 (m, 21H), 1.75-2.07 (m, 3H), 2.09-2.33 (m, 1H), 3.32-3.44 (m, 1H), 3.55 (s, 1H), 4.69-4.94 (m, 1H), 7.33 (t, *J*=7.32 Hz, 1H), 7.41-7.57 (m, 2H), 7.84 (d, *J*=7.32 Hz, 1H), 8.08 (s, 1H), 11.62-12.07 (m, 1H). LC/MS $(M+H)^+$ = 440.32.

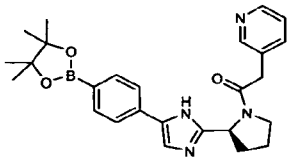
Additional boronic esters:

LCMS conditions: Phenomenex LUNA C-18 4.6 × 50 mm, 0 to 100% B over 3 minutes, 1 minute hold time, A = 90% water, 10% methanol, 0.1% TFA, B = 10% water, 90% methanol, 0.1% TFA, 220nm, 5 µL injection volume.

LCMS conditions (condition 2): Phenomenex LUNA C-18 4.6 × 50 mm, 0 to 100% B over 2 minutes, 1 minute hold time, A = 90% water, 10% methanol, 0.1% TFA, B = 10% water, 90% methanol, 0.1% TFA, 220nm, 5 µL injection volume.

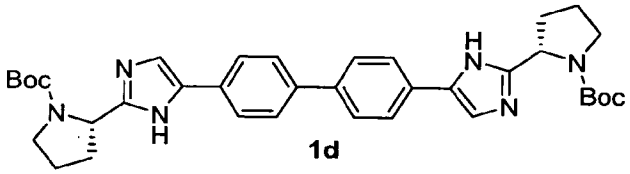
1-5c		RT = 1.84 minutes (condition 2); LCMS: Anal. Calcd. for $C_{27}H_{32}BN_3O_4$ 473; found: 474 $(M+H)^+$.
1-6c		RT = 1.84 minutes (condition 2); LCMS: Anal. Calcd. for $C_{22}H_{32}BN_3O_4$ 413; found: 414 $(M+H)^+$.
1-7c		RT = 1.85 minutes (condition 2); LCMS: Anal. Calcd. for $C_{25}H_{31}BN_3O_4$ 448; found: 448 $(M+H)^+$.
1-8c		RT = 2.49 (76%, boronic ester) and 1.81 (21.4%, boronic acid); LCMS: Anal. Calcd. for $C_{23}H_{35}N_3O_4B$ 428.27; found: 428.27 $(M+H)^+$; HRMS: Anal. Calcd. for $C_{23}H_{35}N_3O_4B$ 428.2721; found: 428.2716 $(M+H)^+$.
1-9c		RT = 2.54 (74.2%, boronic ester) and 1.93 (25.8%, boronic acid); LCMS: Anal. Calcd. for $C_{26}H_{33}N_3O_4B$ 462.26; found: 462.25 $(M+H)^+$; HRMS: Anal. Calcd. for $C_{26}H_{33}N_3O_4B$ 462.2564; found: 462.2570 $(M+H)^+$.

1-10c



RT = 1.91 (64.5 %, boronic ester) and 1.02 (33.8 %, boronic acid); LCMS: Anal. Calcd. for $C_{26}H_{32}N_4O_3{}^{10}B$ 458.26; found: 458.28 $(M+H)^+$; HRMS: Anal. Calcd. for $C_{26}H_{32}N_4O_3{}^{10}B$ 458.2604; found: 458.2617 $(M+H)^+$.

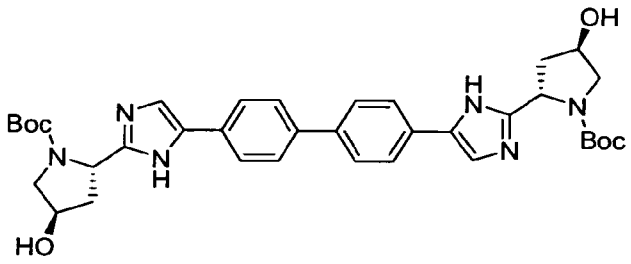
Example 1, Step d



1d

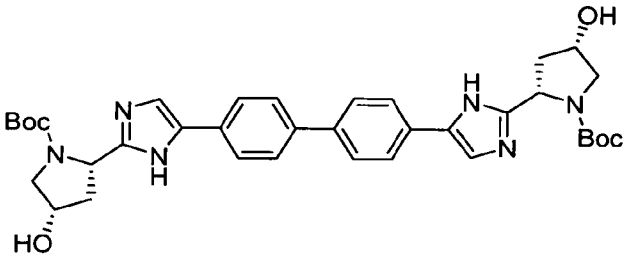
$Pd(Ph_3P)_4$ (59.9 mg, 0.0518 mmol) was added to a mixture of bromide **1b** (576.1 mg, 1.469 mmol), boronate **1c** (621.8 mg, 1.415 mmol), $NaHCO_3$ (400.4 mg, 4.766 mmol) in 1,2-dimethoxyethane (12 mL) and water (4 mL). The reaction mixture was flushed with nitrogen, heated with an oil bath at 80 °C for 5.75 hours, and then the volatile component was removed *in vacuo*. The residue was partitioned between 20% methanol/ $CHCl_3$ (60 mL) and water (30 mL), and the aqueous phase was extracted with 20% methanol/$CHCl_3$ (30 mL). The combined organic phase was washed with brine, dried ($MgSO_4$), filtered, and concentrated *in vacuo*. A silica gel mesh was prepared from the resulting crude material and submitted to flash chromatography (ethyl acetate) to provide dimer **1d**, contaminated with Ph_3PO, as an off-white solid (563 mg). ^1H NMR (DMSO-d_6, δ = 2.5 ppm, 400 MHz): δ 12.21-12-16/11.95-11.78 (m, 2H), 7.85-7.48/ 7.32-7.25 (m, 10H), 4.90-4.71 (m, 2H), 3.60-3.32 (m, 4H), 2.30-1.79 (m, 8H), 1.46-1.10 (m, 18H). LC (Cond. Ib): RT = 1.77 min; LC/MS: Anal. Calcd. for $[M+H]^+$ $C_{36}H_{45}BN_6O_4$: 625.35; found 625.48.

Additional symmetric analogs can be prepared in similar fashion.



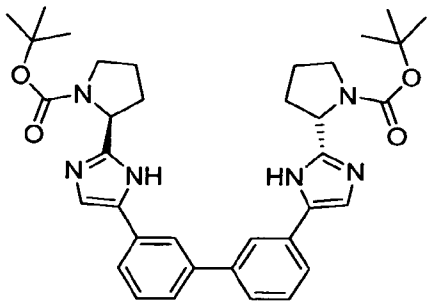
1-1d

Example **1-1d** was prepared using intermediates **1-2c** and **1-2b**. ^{1}H NMR (500 MHz, DMSO-d_6) δ ppm 11.94-12.22 (2H, m) 7.53-7.82 (10H, m) 4.82-4.92 (2 H, m) 4.34-4.43 (2 H, m) 3.55-3.64 (2 H, m) 3.36 (2 H, d, J=11.29 Hz) 2.12-2.22 (2 H, m) 2.02-2.11 (2 H, m) 1.40 (6 H, s) 1.14 (12 H, s); LCMS – Phenomenex C-18 3.0 x 50mm, 0 to 100% B over 4.0 minute gradient, 1 minute hold time, A = 10% methanol 90% water 0.1% TFA, B = 90% methanol 10% water 0.1% TFA, RT= 3.32min, Anal. Calcd. for 656.79; found 657.40 $(M+H)^+$. Nominal/LRMS – $(M+H)^+$ 657.42, $(M-H)^-$ -655.28.



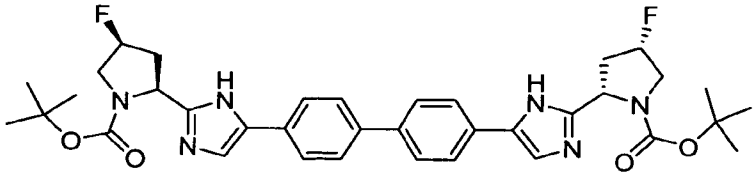
1-2d

Example **1-2d** was prepared using intermediates **1-3b** and **1-3c**. ^{1}H NMR (500 MHz, DMSO-d_6) δ ppm 12.00-12.20 (2H, m) 7.56-7.76 (10H, m) 4.90 (1H, s) 4.82 (1H, s) 4.25-4.34 (2H, m) 3.56 (2H, s) 3.34-3.47 (2H, m) 1.97-2.13 (4H, m) 1.39 (9H, m) 1.20 (9H, s); LCMS – Phenomenex C-18 3.0 x 50mm, 0 to 100% B over 4.0 minute gradient, 1 minute hold time, A = 10% methanol 90% water 0.1% TFA, B = 90% methanol 10% water 0.1% TFA; RT= 3.35min, Anal. Calcd. for 656.79; found 657.30 $(M+H)^+$.



1-2d-1

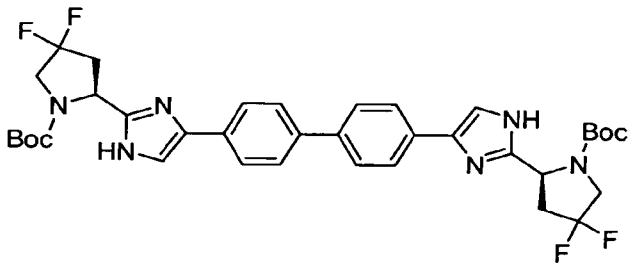
Example **1-2d-1** was prepared using intermediates **1-4c** and **1-4b**. ^{1}H NMR (500 MHz, DMSO-d_6) δ ppm 1.09-1.51 (m, 18H), 1.84-2.15 (m, 6H), 2.34-2.50 (m, 2H), 3.35-3.52 (m, 2H), 3.54-3.67 (m, 2H), 5.08 (d, J=5.49 Hz, 2H), 7.68 (t, J=7.78 Hz, 2H), 7.78-7.92 (m, 4H), 8.11-8.30 (m, 4H), 14.81 (s, 2H). LC/MS $(M+H)^+ = 625.48$.



1-2d-2

Diol **1-1d** (0.15g, 0.23mmol) was added as a solid to a solution of bis(2-methoxyethyl) aminosulfur trifluoride (0.1mL, 0.51mmol) in 1.0mL CH_2Cl_2 cooled to -78 °C. The reaction was stirred at -78 °C for two hours and then warmed to room temperature and stirred for 2 hours. The reaction was poured into saturated sodium bicarbonate solution and stirred until bubbling ceased. The layers were separated and the aqueous layer was extracted one time with CH_2Cl_2. The combined organics were washed with brine, dried ($MgSO_4$), filtered, and concentrated to give a yellow oil. The oil was triturated with CH_2Cl_2 and pentane to provide the desired product as a tan solid (0.092g, 61%). ^{1}H NMR (500 MHz, DMSO-d_6) δ ppm 11.76-11.94 (2H, m), 7.77 - 7.85 (4 H, m), 7.66 - 7.72 (4 H, m), 7.60 - 7.66 (2 H, m, J=11.60 Hz), 5.39 (1 H, s), 5.28 (1 H, s), 5.03 (2 H, s), 3.66 - 3.79 (4 H, m), 2.61 - 2.70 (2 H, m), 2.28 - 2.38 (2 H, m), 1.42 (10 H, s), 1.24 (8 H, s). LCMS – Phenomenex C-18 3.0 x 50mm, 0 to 100% B over 4.0 minute gradient, 1 minute hold time, A = 10% methanol 90%

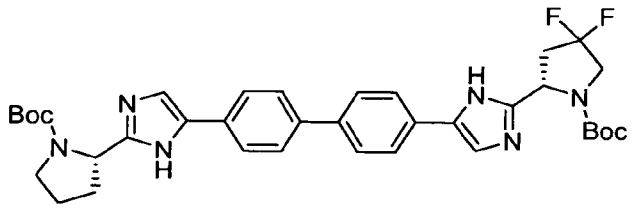
water 0.1% TFA, B = 90% methanol 10% water 0.1% TFA, (t_R= 3.58 min) Anal Calcd. for $C_{36}H_{42}F_2N_6O_4$ 660.70; found 661.68 $(M+H)^+$.



1-2d-3

Prepared from **1-1b** and **1-1c** in the same manner as the preparation of **1d** from **1b** and **1c**. ^{1}H NMR (500 MHz, DMSO-d_6) δ ppm 1.18/1.40 (two br. s., 18H), 2.53 - 2.75 (m, *J*=25.94 Hz, 2H), 2.86 - 3.06 (m, 2H), 3.78 - 4.02 (m, 4H), 5.04 (br s, 2H), 7.17 – 8.24 (m, 10H), 12.07/12.37 (two br. s., 2H); HPLC XTERRA C-18 3.0 × 50 mm, 0 to 100% B over 2 minutes, 1 minutes hold time, A = 90% water, 10% methanol, 0.2% H_3PO_4, B = 10% water, 90% methanol, 0.2% H_3PO_4, RT = 1.31 min, 99% homogeneity index. LCMS: Anal. Calcd. for $C_{36}H_{40}F_4N_6O_4$: 696.73; found: 967.64 $(M+H)^+$.

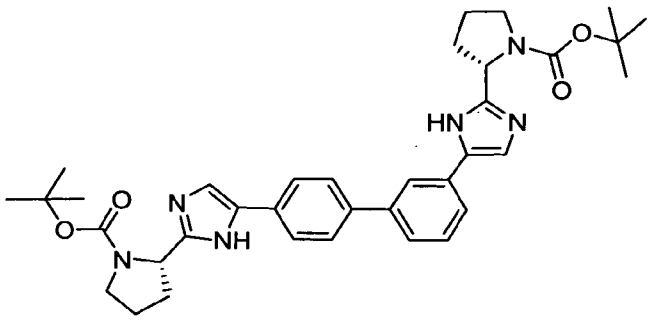
Dissymmetric compounds such as intermediate **1-3d** and **1-4d** can be prepared by the same method. For example, reaction of **1-1c** with **1b** in the same manner as described above for the preparation of **1d** provided **1-3d**. Similarly, reaction of **1-4c** with **1b** in the same manner as described above for the preparation of **1d** provideed **1-4d**.



1-3d

^{1}H NMR (500 MHz, DMSO-d_6) δ ppm 1.40/1.18 (two br s, 18H), 1.90-2.02 (m, 2H), 2.02-2.12 (m, 1H), 2.28-2.46 (m, 2H), 2.68-2.87 (m, 1H), 3.35-3.49 (m, 1H), 3.53-3.62 (m, 1H), 3.82-4.10 (m, 2H), 4.92-5.11 (m, 1H), 5.28 (s, 1H), 7.79-8.00 (m, 8H),

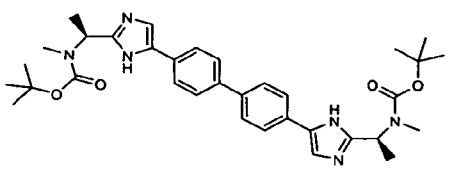
8.03-8.25 (m, 2H), 13.77-15.16 (m, 2H); HPLC XTERRA C-18 3.0 × 50 mm, 0 to 100% B over 4 minutes, 1 minute hold time, A = 90% water, 10% methanol, 0.2% H_3PO_4, B = 10% water, 90% methanol, 0.2% H_3PO_4, RT = 1.22 minutes, 99% homogeneity index. LCMS: Anal. Calcd. for $C_{36}H_{42}F_2N_6O_4$: 660.75; found: 661.98 $(M+H)^+$.

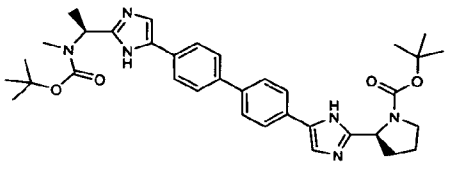
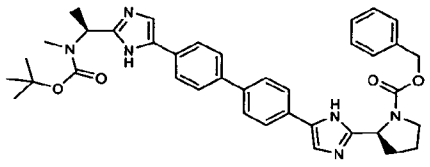


1-4d

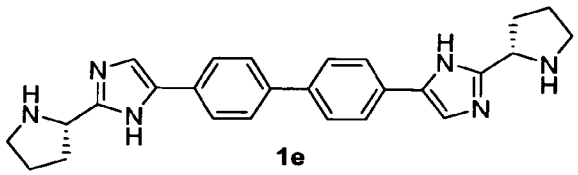
Example **1-4d** was prepared from **1-4c** and **1b** in similar fashion to the preparation of **1d** from **1b** and **1c**. ^1H NMR (500 MHz, DMSO-d_6) δ ppm 0.99 - 1.60 (m, 18 H) 1.75 - 2.11 (m, *J*=73.24 Hz, 6 H) 2.12 - 2.32 (m, 2 H) 3.32 - 3.41 (m, 2 H) 3.56 (s, 2 H) 4.63 - 5.02 (m, 2 H) 6.98 - 8.28 (m, 10 H) 11.67 - 12.33 (m, 2 H); LC conditions: Phenomenex Luna 3.0 X 5.0mm S10, Solvent A – 0.1% TFA in 10% MeOH/90%H_2O, Solvent B - 0.1% TFA in 90% MeOH/10% H_2O, 0 to 100% B over 2min, Stop time = 3min, Flow rate = 4ml/min, Wavelength = 220nm, LC/MS $(M+H)^+$ = 625.32. Retention time = 1.438 min

Additional biphenyl analogs were prepared similarly.

Example	Structure	Data
1-5d	 Prepared from **1-8c** and **1-6b**	RT = 1.64 minutes (>95%); LCMS: Anal. Calcd $C_{34}H_{45}N_6O_4$ 601.35; found: 601.48 $(M+H)^+$; LRMS: Anal. Calcd. for $C_{34}H_{44}N_6O_4$ 600.34; found: 601.32

		$(M+H)^+$.
1-6d	 Prepared from **1-8c** and **1b**	RT = 1.63 minutes (>95%); LCMS: Anal. Calcd $C_{35}H_{45}N_6O_4$ 613.34; found: 613.56 $(M+H)^+$; LRMS: Anal. Calcd. for $C_{35}H_{44}N_6O_4$ 612.34; found: 613.33 $(M+H)^+$.
1-7d	 Prepared from **1-6b** and **1-5c**	RT = 1.65 minutes (>95%); LCMS: Anal. Calcd $C_{38}H_{43}N_6O_4$ 647.33; found: 647.44 $(M+H)^+$; LRMS: Anal. Calcd. for $C_{38}H_{42}N_6O_4$ 646.33; found: 647.34 $(M+H)^+$.

Example 1, Step e

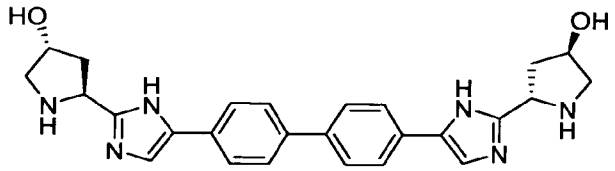


1e

A mixture of carbamate **1d** (560 mg) and 25% TFA/CH_2Cl_2 (9.0 mL) was stirred at ambient condition for 3.2 hours. The volatile component was removed *in vacuo*, and the resulting material was free based using an MCX column (methanol wash; 2.0 M NH_3/methanol elution) to provide pyrrolidine **1e** as a dull yellow solid (340 mg). ^{1}H NMR (DMSO-d_6, δ= 2.5 ppm, 400 MHz): δ 11.83 (br s, 2H), 7.80 (d, J = 8.1, 4H), 7.66 (d, J = 8.3, 4H), 7.46 (br s, 2H), 4.16 (app t, J = 7.2, 2H), 2.99-2.69 (m, 6H), 2.09-2.00 (m, 2H), 1.94-1.66 (m, 6H). LC (Cond. Ib): RT = 1.27 min; >

98% homogeneity index; LC/MS: Anal. Calcd. for $[M+H]^+$ $C_{26}H_{29}N_6$: 425.25; found 425.25; HRMS: Anal. Calcd. for $[M+H]^+$ $C_{26}H_{29}N_6$: 425.2454; found 425.2448

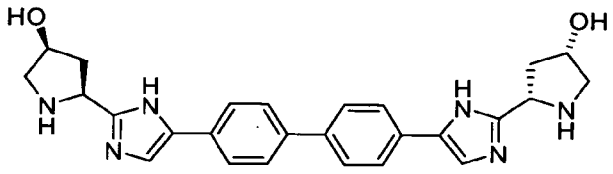
Additional analogs such as **1-1e** to **1-4e** can be prepared in a similar fashion.



· 4 HCl

1-1e

To a solution of **1-1d** (3R,3'R,5S,5'S)-tert-butyl 5,5'-(5,5'-(biphenyl-4,4'-diyl)bis(1H-imidazole-5,2-diyl))bis(3-hydroxypyrrolidine-1-carboxylate) in 3mL dioxane was added 0.8mL of a 4.0M solution of HCl in dioxane. The reaction was stirred for 2 hours at room temperature and concentrated under reduced pressure. The resulting tan solid was dried under vacuum to give **1-1e** (3R,3'R,5S,5'S)-5,5'-(5,5'-(biphenyl-4,4'-diyl)bis(1H-imidazole-5,2-diyl))dipyrrolidin-3-oltetrahydrochloride (0.55g, 100%yield). Used without further purification.^{1}H NMR (500 MHz, DMSO-d_6) δ ppm 10.33 (s, 2H), 9.85 (s, 2H), 8.09 (s, 2H), 8.01 (d, J=8.24 Hz, 4H), 7.88 (d, J=8.24 Hz, 4H), 5.14 (m, 2H), 4.62 (m, 2H), 3.61 (m, 2H), 3.23 (d, J=11.29 Hz, 2H), 2.64 (m, 2H), 2.44 (dd, J=13.43, 6.71 Hz, 2H); LCMS – Waters-Sunfire C-18 4.6 x 50mm, 0 to 100% B over 4.0 minute gradient, 1 minute hold time, A = 10% methanol 90% water 0.1% TFA, B = 90% methanol 10% water 0.1% TFA, RT= 1.35 minutes Anal. Calcd. for 456.30; found 457.25 $(M+H)^+$; Nominal/LRMS – $(M+H)^+$ 457.35.

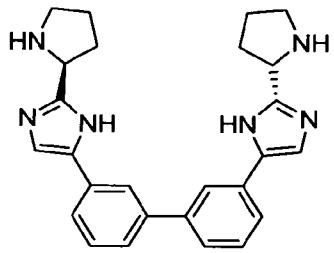


· 4 HCl

1-2e

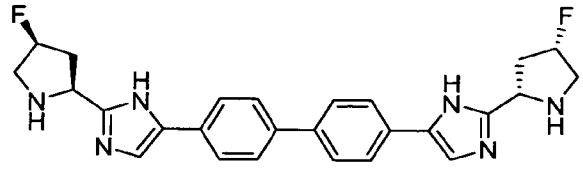
Example **1-2e** was prepared in similar fashion to the method described for the preparation of **1-1e**. ^{1}H NMR (500 MHz, DMSO-d_6) δ ppm 10.32 (1 H, s) 8.01 (2 H,

s) 7.97 (4 H, d, *J*=8.24 Hz) 7.86 (4 H, d, *J*=8.24 Hz) 5.01-5.10 (2 H, m) 4.52-4.60 (2 H, m) 3.36-3.45 (2 H, m) 3.25 (2 H, s) 2.60-2.68 (2 H, m) 2.40-2.48 (2 H, m); LCMS – Phenomenex C-18 3.0 x 50mm, 0 to 100% B over 4.0 minute gradient, 1 minute hold time, A = 10% methanol 90% water 0.1% TFA, B = 90% methanol 10% water 0.1% TFA, RT= 2.10min., Anal. Calcd. for 456.30; found 457.22 $(M+H)^+$



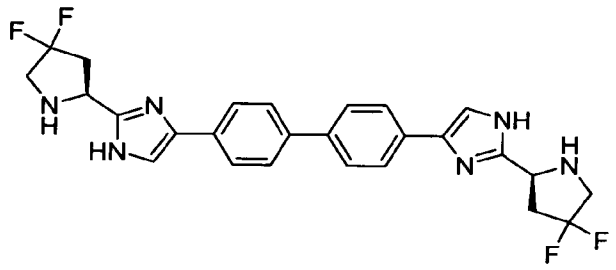
1-2e-1

Example **1-2e-1** was prepared from **1-2d-1** in similar fashion described for the preparation of **1-1e**. ^{1}H NMR (500 MHz, DMSO-d_6) δ ppm 1.74-2.44 (m, 12H), 4.83 (s, 2H), 7.37-7.72 (m, 4H), 7.74-8.03 (m, 4H), 8.10 (s, 2H), 9.14 (s, 2H), 9.81 (s, 2H). LC/MS $(M+H)^+$ = 425.30.



1-2e-2

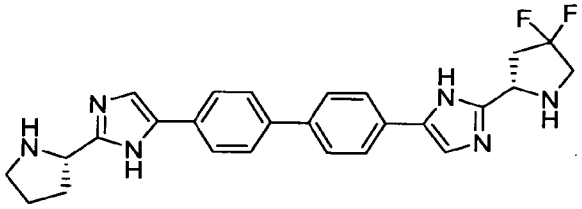
To a solution of **1-2d-2** (0.084g, 0.13mmol) in 1mL dioxane was added 0.5mL of a 4.0M solution of HCl in dioxane. The reaction was stirred for 2 hours at room temperature and concentrated under reduced pressure. The resulting tan solid was dried under vacuum to give **1-2e-2** (0.077g, 100%yield). The compound was used without further purification. ^{1}H NMR (500 MHz, DMSO-d_6) δ ppm 8.00 (2H, s), 7.97 (4H, d, *J*=8.55 Hz), 7.85 (4H, d, *J*=8.24 Hz), 5.63 (1H, s), 5.52 (1H, s), 5.09 - 5.17 (2H, m), 3.67 - 3.74 (2H, m), 3.63 - 3.67 (2H, m), 3.07 - 3.14 (1H, m), 2.89 - 2.96 (1H, m), 2.81 - 2.87 (2H, m); LCMS – Phenomenex C-18 3.0 x 50mm, 0 to 100% B over 4.0 minute gradient, 1 minute hold time, A = 10% methanol 90% water 0.1% TFA, B = 90% methanol 10% water 0.1% TFA, (t_R= 2.22 min) Anal Calcd. for $C_{26}H_{26}F_2N_6$ 460.53; found 461.37 $(M+H)^+$.



1-2e-3

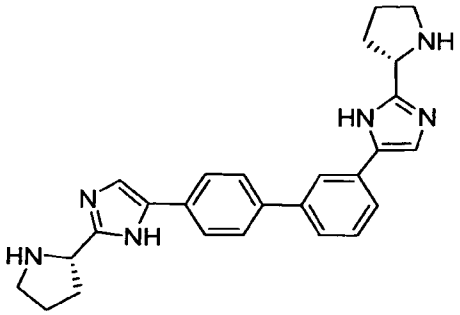
Prepared from **1-2d-3** in the same manner as the preparation of **1-1e** from **1-1d**. ^{1}H NMR (500 MHz, DMSO-d_6) δ ppm 2.97 - 3.13 (m, 4H), 3.64 - 3.91 (m, 4H), 5.16 (d, *J*=6.41 Hz, 2H), 7.84 (d, *J*=7.93 Hz, 4H), 7.96 (d, *J*=7.93 Hz, 4H), 8.00 (s, 2H); HPLC XTERRA C-18 3.0 × 50 mm, 0 to 100% B over 4 minutes, 1 minutes hold time, A = 90% water, 10% methanol, 0.2% H_3PO_4, B = 10% water, 90% methanol, 0.2% H_3PO_4, RT = 1.66 min, 92% homogeneity index. LCMS: Anal. Calcd. for $C_{26}H_{24}F_4N_6$: 496.50; found: 495.53 $(M-H)^-$.

Analogous dissymmetric compounds such as intermediates **1-3e** and **1-4e** can be prepared by the same method.



1-3e

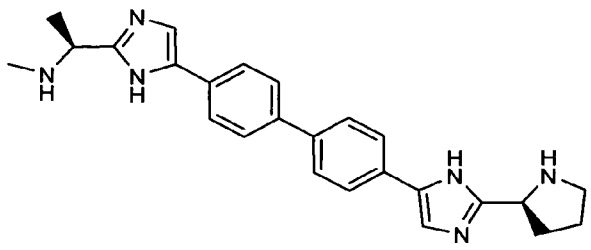
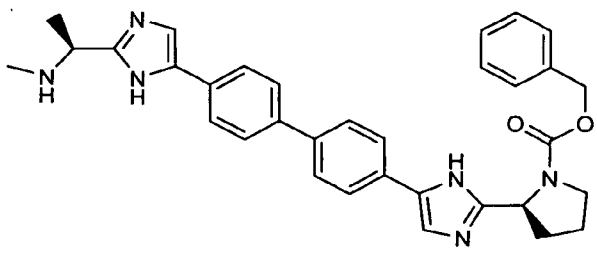
^{1}H NMR (500 MHz, DMSO-d_6) δ ppm 1.87-2.09 (m, 1H), 2.13-2.26 (m, 1H), 2.37-2.47 (m, 2H), 2.92-3.12 (m, 2H), 3.37 (s, 1H), 3.40-3.49 (m, 1H), 3.67-3.91 (m, 2H), 4.96-5.05 (m, 1H), 5.14 (t, *J*=8.70 Hz, 1H), 7.86 (t, *J*=9.00 Hz, 4H), 7.93-8.03 (m, 5H), 8.10 (s, 1H), 10.26/9.75 (two br s., 2H); HPLC XTERRA C-18 3.0 × 50 mm, 0 to 100% B over 4 minutes, 1 minute hold time, A = 90% water, 10% methanol, 0.2% H_3PO_4, B = 10% water, 90% methanol, 0.2% H_3PO_4, RT = 0.8622 minutes, 99% homogeneity index; LCMS: Anal. Calcd. for $C_{26}H_{26}F_2N_6$: 460.52; found: 461.45 $(M+H)^+$.



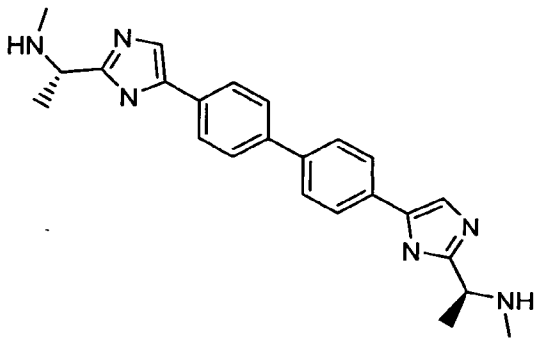
1-4e

Example **1-4e** was prepared from **1-4d** in similar fashion to that described for the preparation of **1-1e** from **1-1d**. ^{1}H NMR (500 MHz, DMSO-d_6) δ ppm 1.90 - 2.13 (m, 2 H) 2.12 - 2.31 (m, 2 H) 2.36 - 2.60 (m, 4 H) 3.29 - 3.55 (m, 4 H) 5.00 (s, 2 H) 7.35 - 8.50 (m, 10 H) 9.76 (s, 2 H) 10.12 - 10.45 (m, 2 H). LC conditions: Phenomenex Luna 3.0 X 5.0mm S10, Solvent A – 0.1% TFA in 10% MeOH/90%H_2O, Solvent B - 0.1% TFA in 90% MeOH/10% H_2O, 0 to 100% B over 2min, Stop time = 3min, Flow rate = 4ml/min, Wavelength = 220nm, LC/MS $(M+H)^+$ = 425.28. Retention time = 0.942 min

Additional analogs were prepared similarly:

Example	Structure	Data
1-5e	 Prepared from **1-6d**	RT = 1.37 min; LCMS: Anal. Calcd. for $C_{25}H_{28}N_6$ 412; found: 413 $(M+H)^+$.
1-6e	 Prepared from **1-7d**	RT = 1.43 min; LCMS: Anal. Calcd. for $C_{33}H_{35}N_6O_2$ 547; found: 547 $(M+H)^+$.

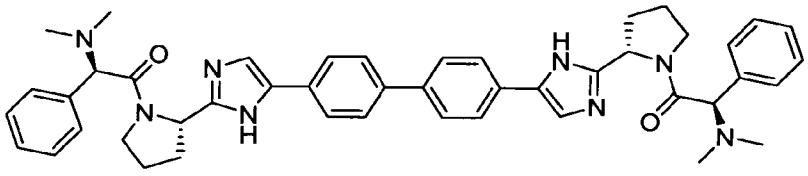
1-7e



RT = 1.12 min; LRMS: Anal. Calcd. for $C_{24}H_{28}N_6$ 400.24; found: 401.22 $(M+H)^+$.

Prepared from **1-5d**

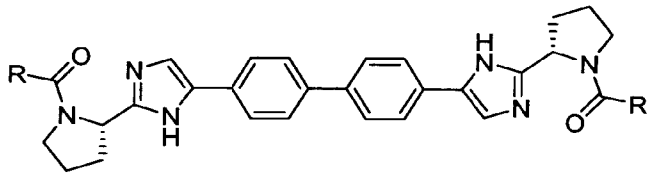
Conditions: Phenomenex LUNA C-18 4.6 × 50 mm, 0 to 100% B over 2 minutes, 1 minute hold time, A = 90% water, 10% methanol, 0.1% TFA, B = 10% water, 90% methanol, 0.1% TFA, 220nm, 5 µL injection volume.



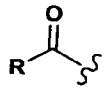
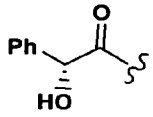
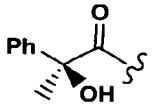
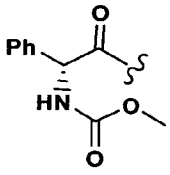
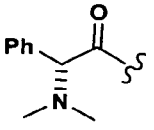
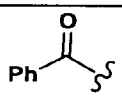
Example 1

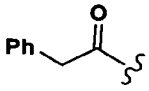
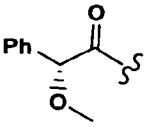
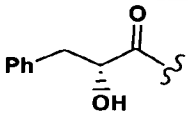
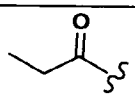
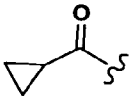
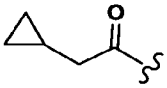
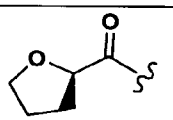
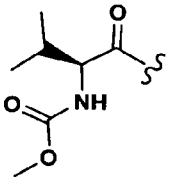
HATU (44.6 mg, 0.117 mmol) was added to a mixture of pyrrolidine **1e** (22.9 mg, 0.054 mmol), diisopropylethylamine (45 µL, 0.259 mmol) and **Cap-1** (28.1 mg, 0.13 mmol) in DMF (1.5 mL), and the resulting mixture was stirred at ambient for 90 minutes. The volatile component was removed *in vacuo*, and the residue was purified first by MCX (methanol wash; 2.0 M NH_3/methanol elution) and then by a reverse phase HPLC system (H_2O/methanol/TFA) to provide the TFA salt of **Example 1** as an off-white foam (44.1 mg). ^1H NMR (DMSO-d_6, δ= 2.5 ppm, 400 MHz): δ 10.25 (br s, 2H), 8.20-7.10 (m, 20H), 5.79-5.12 (m, 4H), 4.05-2.98 (m, 4H), 2.98-2.62 (m, 6H), 2.50-1.70 (m, 14H), [Note: the signal of the imidazole NH was too broad to assign a chemical shift]; LC (Cond.Ib): RT = 1.40 min; > 98% homogeneity index; LC/MS: Anal. Calcd. for $[M+H]^+$ $C_{46}H_{51}N_8O_2$: 747.41; found 747.58

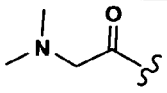
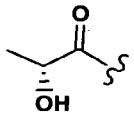
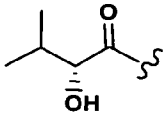
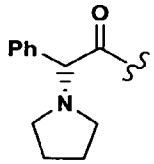
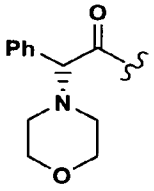
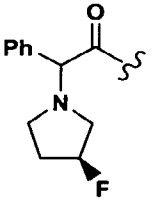
Examples 2 to 24-4d

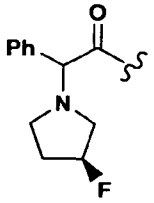
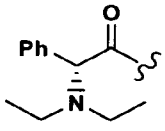
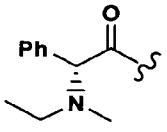
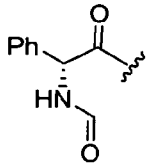
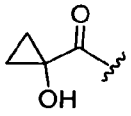
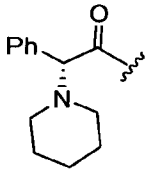


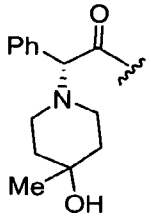
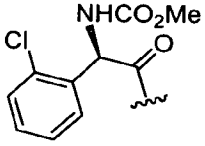
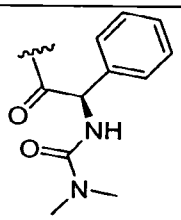
Examples 2 to 24-4h were prepared as TFA salts by substituting the respective acids for **Cap-1** using the same method described for **Example 1**. Caps in the following table without a number are commercially available.

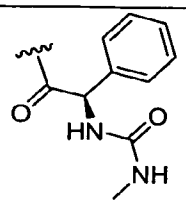
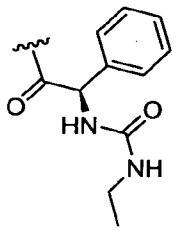
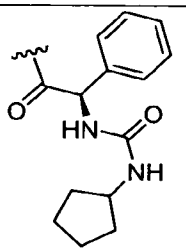
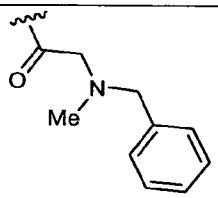
Example		RT (LC-Cond.); % homogeneity index; MS data
2		1.55 minutes (Cond. Ib); >98%; LC/MS: Anal. Calcd. for $[M+H]^+$ $C_{42}H_{41}N_6O_4$: 693.32; found 693.46; HRMS: Anal. Calcd. for $[M+H]^+$ $C_{42}H_{41}N_6O_4$: 693.3189; found 693.3182
3		1.77 minutes (Cond. Ib); >98%; LC/MS: Anal. Calcd. for $[M+H]^+$ $C_{44}H_{45}N_6O_4$: 721.35; found 721.52; HRMS: Anal. Calcd. for $[M+H]^+$ $C_{44}H_{45}N_6O_4$: 721.3502; found 721.3515
4	 cap-4	1.64 minutes (Cond. Ib); >98%; LC/MS: Anal. Calcd. for $[M+H]^+$ $C_{46}H_{47}N_8O_6$: 807.36; found 807.58
5	 cap-1	1.33 minutes (Cond. Ib); >98%; LC/MS: Anal. Calcd. for $[M+H]^+$ $C_{46}H_{51}N_8O_2$: 747.41; found 747.64; HRMS: Anal. Calcd. for $[M+H]^+$ $C_{46}H_{51}N_8O_2$: 747.4135; found 747.4103
6		1.65 minutes (Cond. Ib); >98%; LC/MS: Anal. Calcd. for $[M+H]^+$ $C_{40}H_{37}N_6O_2$: 633.30; found 633.51

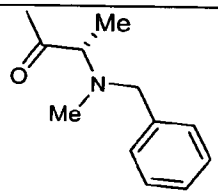
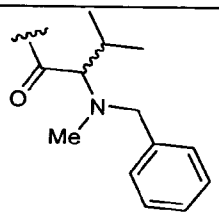
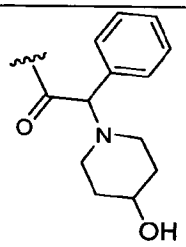
7		1.71 minutes (Cond. Ib); >98%; LC/MS: Anal. Calcd. for $[M+H]^+$ $C_{42}H_{41}N_6O_2$: 661.33; found 661.53; HRMS: Anal. Calcd. for $[M+H]^+$ $C_{42}H_{41}N_6O_2$: 661.3291; found 661.3300
8		1.63 minutes (Cond. Ib); >98%; LC/MS: Anal. Calcd. for $[M+H]^+$ $C_{44}H_{45}N_6O_4$: 721.35; found 721.59; HRMS: Anal. Calcd. for $[M+H]^+$ $C_{44}H_{45}N_6O_4$: 721.3502; found 721.3536
9		1.71 minutes (Cond. Ib); >98%; LC/MS: Anal. Calcd. for $[M+H]^+$ $C_{44}H_{45}N_6O_4$: 721.35; found 721.58; HRMS: Anal. Calcd. for $[M+H]^+$ $C_{44}H_{45}N_6O_4$: 721.3502; found 721.3497
10		1.47 minutes (Cond. Ib); >98%; LC/MS: Anal. Calcd. for $[M+H]^+$ $C_{32}H_{37}N_6O_2$: 537.30; found 537.40; HRMS: Anal. Calcd. for $[M+H]^+$ $C_{32}H_{37}N_6O_2$: 537.2978; found 537.2952
11		1.48 minutes (Cond. Ib); >98%; LC/MS: Anal. Calcd. for $[M+H]^+$ $C_{34}H_{37}N_6O_2$: 561.30; found 561.44
12		1.57 minutes (Cond. Ib); >98%; LC/MS: Anal. Calcd. for $[M+H]^+$ $C_{36}H_{41}N_6O_2$: 589.33; found 589.48; HRMS: Anal. Calcd. for $[M+H]^+$ $C_{36}H_{41}N_6O_2$: 589.3291; found 589.3268
13		1.44 minutes (Cond. Ib); >98%; LC/MS: Anal. Calcd. for $[M+H]^+$ $C_{36}H_{41}N_6O_4$: 621.32; found 621.52; HRMS: Anal. Calcd. for $[M+H]^+$ $C_{36}H_{41}N_6O_4$: 621.3189; found 621.3191
13a	 **cap-51**	RT = 1.27 min (Cond. I); >95% homogeneity index LC/MS: Anal. Calcd. for $[M+H]^+$ $C_{40}H_{51}N_8O_6$: 739.39; found, 739.65 HRMS: Anal. Calcd. for $[M+H]^+$ $C_{40}H_{51}N_8O_6$:

		739.3932; found, 739.3942
14		1.27 minutes (Cond. Ib); >98%; LC/MS: Anal. Calcd. for $[M+H]^+$ $C_{34}H_{43}N_8O_2$: 595.35; found 595.54; HRMS: Anal. Calcd. for $[M+H]^+$ $C_{34}H_{43}N_8O_2$: 595.3509; found 595.3503
15		1.36 minutes (Cond. Ib); >98%; LC/MS: Anal. Calcd. for $[M+H]^+$ $C_{32}H_{37}N_6O_4$: 569.29; found 569.44; HRMS: Anal. Calcd. for $[M+H]^+$ $C_{32}H_{37}N_6O_4$: 569.2876; found 569.2872
16		1.51 minutes (Cond. Ib); >98%; LC/MS: Anal. Calcd. for $[M+H]^+$ $C_{36}H_{45}N_6O_4$: 625.35; found 625.50; HRMS: Anal. Calcd. for $[M+H]^+$ $C_{36}H_{45}N_6O_4$: 625.3502; found 625.3517
17	 **cap-5**	1.13 minutes (Cond. I); >98%; LC/MS: Anal. Calcd. for $[M+H]^+$ $C_{50}H_{55}N_8O_2$: 799.45; found 799.67
18	 **cap-6**	1.11 minutes (Cond. I); >98%; LC/MS: Anal. Calcd. for $[M+H]^+$ $C_{50}H_{55}N_8O_4$: 831.44; found 831.71
19	 **Diastereomer-1 cap-9a**	1.17 minutes (Cond. I); 97%; LC/MS: Anal. Calcd. for $[M+H]^+$ $C_{50}H_{53}F_2N_8O_2$: 835.43; found 835.51; HRMS: Anal. Calcd. for $[M+H]^+$ $C_{50}H_{53}F_2N_8O_2$: 835.4260; found 835.4261

20	 **Diastereomer-2 cap-9b**	1.03 minutes (Cond. I); >98%; LC/MS: Anal. Calcd. for $[M+H]^+$ $C_{50}H_{53}F_2N_8O_2$: 835.43; found 835.51; HRMS: Anal. Calcd. for $[M+H]^+$ $C_{50}H_{53}F_2N_8O_2$: 835.4260; found 835.4266
21	 **cap-2**	1.13 minutes (Cond. I); >98%; LC/MS: Anal. Calcd. for $[M+H]^+$ $C_{50}H_{59}N_8O_2$: 803.48; found 803.56; HRMS: Anal. Calcd. for $[M+H]^+$ $C_{50}H_{59}N_8O_2$: 803.4761; found 803.4728
22	 **cap-3**	1.10 minutes (Cond. I); >98%; LC/MS: Anal. Calcd. for $[M+H]^+$ $C_{48}H_{55}N_8O_2$: 775.45; found 775.52; HRMS: Anal. Calcd. for $[M+H]^+$ $C_{50}H_{59}N_8O_2$: 775.4448; found 775.4456
23		1.22 minutes (Cond. I); >98%; LC/MS: Anal. Calcd. for $[M+H]^+$ $C_{44}H_{43}N_8O_4$: 747.34; found 747.38
24		1.77 minutes (Cond. II); >98%; LC/MS: Anal. Calcd. for $[M+H]^+$ $C_{34}H_{37}N_6O_4$: 593.29; found 593.16
24-1	 **cap-14**	^{1}HNMR (400 MHz, DMSO-d_6) δ 12.18 (m, 0.4H), 11.96 (m, 0.4H), 11.79 (m, 1.2H), 7.84-7.70 (m, 4H), 7.69-7.65 (m, 4H), 7.53-7.50 (m, 2H), 7.43-7.28 (m, 4H), 7.09-7.01 (m, 2H), 6.87-6.85 (m, 2H), 5.51-5.48 (m, 0.5H), 5.01-4.98 (m, 1.5H), 4.29 (m, 1.5H), 4.16 (m, 0.5H), 3.98 (m, 2H), 3.65-3.49 (m, 2H), 3.43-3.36 (m, 2H), 2.41-2.31 (m, 8H), 2.14-1.82 (m, 8H), 1.47-1.31 (m, 12H); LCMS: Anal. Calcd. for $C_{52}H_{58}N_8O_2$: 826; found: 827 $(M+H)^+$.

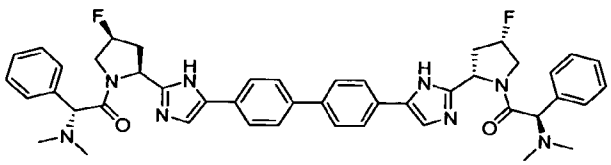
24-2	 **cap-15**	^{1}HNMR (400 MHz, DMSO-d_6) δ 12.02 (br s, 1H), 11.82 (br s, 1H), 7.90-7.79 (m, 4H), 7.79-7.65 (m, 5H), 7.55 (br s, 2H), 7.45 (d, J = 7.6 Hz, 2H), 7.39-7.25 (m, 3H), 7.34 (d, J = 7.6 Hz, 2H), 7.04 (t, J = 7.6 Hz, 2H), 6.85 (d, J = 8.1 Hz, 2H), 5.15-4.96 (m, 2H), 4.31-3.96 (m, 6H), 2.35-2.20 (m, 2H), 2.05-1.94 (m, 4H), 1.94-1.81 (m, 4H), 1.50-1.35 (m, 9H), 1.35-1.20 (m, 5H), 1.09 (s, 2H), 1.05 (s, 4H); LCMS: Anal. Calcd. for $C_{54}H_{62}N_8O_4$: 886; found: 887 $(M+H)^+$.
24-3	 **cap-40**	LCMS: Anal. Calcd. for $C_{46}H_{44}Cl_2N_8O_6$: 874; found: 875 $(M+H)^+$.
24-4a	 **cap-47**	^{1}H NMR (500 MHz, DMSO-d_6) δ ppm 1.89-2.00 (m, J=17.09, 7.02 Hz, 4H), 2.06-2.13 (m, J=14.95, 3.97 Hz, 3H), 2.24-2.33 (m, J=8.70, 6.56 Hz, 2H), 2.79-2.84 (m, 12H), 3.29 (q, 2H), 3.95-4.03 (m, 3H), 5.26 (dd, J=8.55, 2.14 Hz, 3H), 5.52 (d, J=5.80 Hz, 3H), 6.72 (d, J=6.10 Hz, 3H), 7.02-7.07 (m, 1H), 7.29-7.36 (m, 3H), 7.39 (t, J=7.17 Hz, 4H), 7.46 (d, J=7.02 Hz, 3H), 7.92 (s, 8H), 8.12 (s, 2H); HPLC XTERRA C-18 4.6 × 30 mm, 0 to 100% B over 4 minutes, 1 minute hold time, A = 90% water, 10% methanol, 0.2% H_3PO_4, B = 10% water, 90% methanol, 0.2% H_3PO_4, RT = 2.13 minutes, 96% homogeneity index; LCMS: Anal. Calcd. for $C_{48}H_{53}N_{10}O_4$: 832.42; found: 833.43 $(M+H)^+$; HRMS: Anal. Calcd. for $C_{48}H_{54}N_{10}O_4$ 833.4251; found: 833.4267

		$(M+H)^+$.
24-4b	 **cap-45**	RT = 4.45 minutes, method E; LCMS: Anal. Calcd. for $C_{46}H_{48}N_{10}O_4$ 804.95; found: 805.41 $(M+H)^+$; HRMS: Anal. Calcd. for $C_{46}H_{49}N_{10}O_4$ 805.3938; found: 805.3929 $(M+H)^+$.
24-4c	 **cap-46**	RT = 4.20 minutes , method E; LCMS: Anal. Calcd. for $C_{48}H_{52}N_{10}O_4$ 833.00; found: 833.48 $(M+H)^+$.
24-4d	 **cap-48**	RT = 4.92 minutes , method E; LCMS: Anal. Calcd. for $C_{54}H_{60}N_{10}O_4$ 912.49; found: 913.68 $(M+H)^+$; HRMS: Anal. Calcd. for $C_{54}H_{61}N_{10}O_4$ 913.4877; found: 913.4899 $(M+H)^+$.
24-4e	 **cap-49**	^1H NMR (500 MHz, DMSO-d_6) δ ppm 1.97-2.43 (m, 8H), 2.64-2.91 (m, 6H), 3.45-3.63 (m, 2H), 3.62-3.76 (m, 2H), 4.14 (dd, 4H), 4.22-4.45 (m, 4H), 5.29 (s, 2H), 7.28-7.65 (m, 10H), 7.90 (s, 8H), 8.06 (s, 2H), 14.62 (s, 2H); HPLC Xterra 4.6 X 50 mm, 0 to 100% B over 10 minutes, one minute hold time, A = 90% water, 10% methanol, 0.2% phosphoric acid, B = 10% water, 90% methanol, 0.2% phosphoric acid. RT = 3.06 min; LCMS: Anal. Calcd. for: $C_{46}H_{50}N_8O_2$ 746.96; Found: 747.41 $(M+H)^+$.

24-4f		RT = 2.95 minutes (99%); HPLC Xterra 4.6 X 50 mm, 0 to 100% B over 10 minutes, one minute hold time, A = 90% water, 10% methanol, 0.2% phosphoric acid, B = 10% water, 90% methanol, 0.2% phosphoric acid; LCMS: Anal. Calcd. for: $C_{48}H_{54}N_8O_2$ 775.02; Found: 775.45 $(M+H)^+$.
24-4g	 **cap-50**	RT = 3.86 minutes (100%); HPLC Xterra 4.6 X 50 mm, 0 to 100% B over 10 minutes, one minute hold time, A = 90% water, 10% methanol, 0.2% phosphoric acid, B = 10% water, 90% methanol, 0.2% phosphoric acid; LCMS: Anal. Calcd. for: $C_{52}H_{62}N_8O_2$ 831.13; Found: 831.51 $(M+H)^+$.
24-4h	 **cap-8**	RT = 2.86 minutes (100%); HPLC Xterra 4.6 X 50 mm, 0 to 100% B over 10 minutes, one minute hold time, A = 90% water, 10% methanol, 0.2% phosphoric acid, B = 10% water, 90% methanol, 0.2% phosphoric acid; LCMS: Anal. Calcd. for: $C_{52}H_{58}N_8O_4$ 859.09; Found: 859.45 $(M+H)^+$.

Examples 24-5 to 24-18

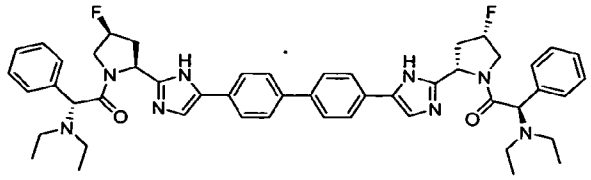
24-5



from 1-2e-2 and cap-1

Method E (RT=4.163 min); Nominal/LRMS – Calcd. for $C_{46}H_{48}F_2N_8O_2$ 782.93; found 783.40 $(M+H)^+$; Accurate/HRMS – Calcd. for $C_{46}H_{49}F_2N_8O_2$ 783.3946; 783.3934 $(M+H)^+$.

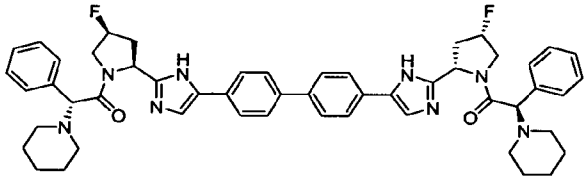
24-6



from 1-2e-2 and cap-2

Method F RT = 3.76 min; LCMS: Anal. Calcd. for $C_{50}H_{56}F_2N_8O_2$ 839.04; found: 839.49 $(M+H)^+$; HRMS: Anal. Calcd. for $C_{50}H_{57}F_2N_8O_2$ 839.4572; found: 839.4590 $(M+H)^+$.

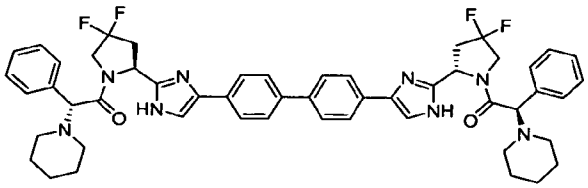
24-7



from 1-2e-2 and cap-14

Method F RT = 3.99 min; LCMS: Anal. Calcd. for $C_{52}H_{56}F_2N_8O_2$ 863.06; found: 863.47 $(M+H)^+$; HRMS: Anal. Calcd. for $C_{52}H_{57}F_2N_8O_2$ 863.4572; found: 863.4553 $(M+H)^+$.

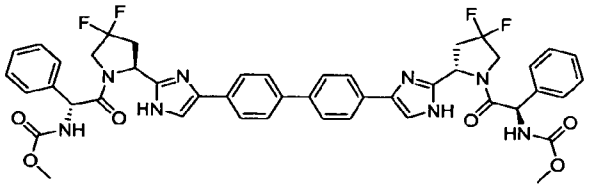
24-8



from 1-2e-3 and cap-14

RT = 1.64 minutes, method B; LCMS: Anal. Calcd. for $C_{52}H_{54}F_4N_8O_6$: 898.43; found: 899.46 $(M+H)^+$; HRMS: Anal. Calcd. for $C_{52}H_{55}F_4N_8O_6$ 899.4384; found: 899.4380 $(M+H)^+$.

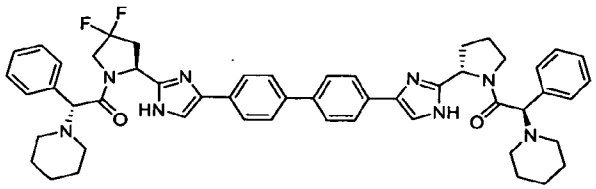
24-9



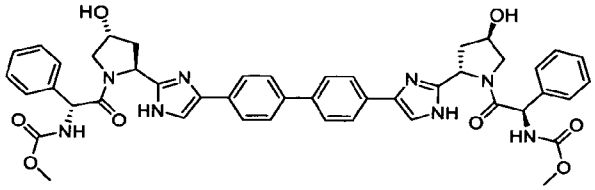
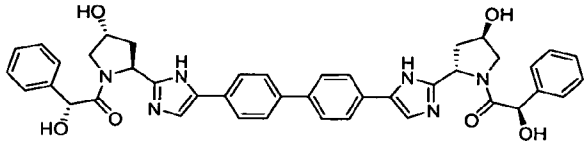
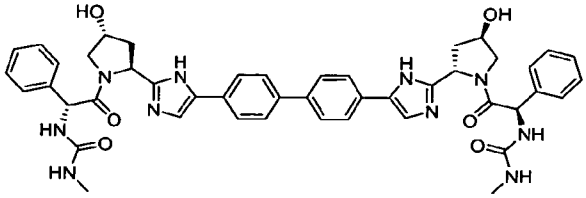
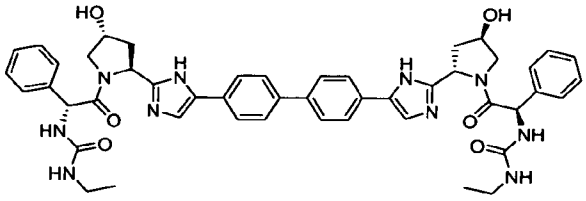
from 1-2e-3 and cap-4

RT = 2.62 minutes, method C; LCMS: Anal. Calcd. for $C_{46}H_{42}F_4N_8O_6$: 878.88; found: 879.81 $(M+H)^+$; HRMS: Anal. Calcd. for $C_{46}H_{43}F_4N_8O_6$ 879.33242; found: 879.3273 $(M+H)^+$.

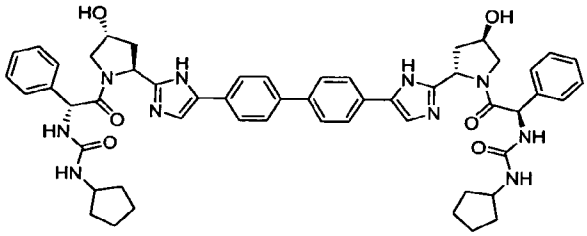
24-10



RT = 1.54 minutes, method B; LCMS: Anal. Calcd. for $C_{52}H_{56}F_2N_8O_6$: 862.45; found: 863.46 $(M+H)^+$; HRMS:

	from 1-3e and cap-14.	Anal. Calcd. for $C_{52}H_{57}F_2N_8O_6$ 863.4573; found: 863.4572 $(M+H)^+$.
24-11	 **from 1-1e and cap-4**	RT = 8.54 minutes, method A; LCMS: Anal. Calcd. for $C_{46}H_{46}N_8O_8$ 838.93; found: 839.41 $(M+H)^+$; HRMS: Anal. Calcd. for $C_{46}H_{47}N_8O_8$ 839.9300; found: 839.3527 $(M+H)^+$.
24-12	 **from 1-1e and mandelic acid**	RT = 6.92 minutes , method A; LCMS: Anal. Calcd. for $C_{42}H_{40}N_6O_6$ 724.81; found: 725.43 $(M+H)^+$; HRMS: Anal. Calcd. for $C_{42}H_{41}N_6O_6$ 725.3087; found: 725.3088 $(M+H)^+$.
24-13	 Prepared from **1-1e** and **cap-45**	RT = 3.80 minutes, method C; LCMS: Anal. Calcd. for $C_{46}H_{48}N_{10}O_6$ 836.95; found: 837.52 $(M+H)^+$; HRMS: Anal. Calcd. for $C_{46}H_{49}N_{10}O_6$ 837.3836; found: 837.3809 $(M+H)^+$.
24-14	 Prepared from **1-1e** and **cap-46**	RT = 4.39 minutes, method C; LRMS: Anal. Calcd. for $C_{48}H_{52}N_{10}O_6$ 865.003; found: 865.56 $(M+H)^+$; HRMS: Anal. Calcd. for $C_{48}H_{53}N_{10}O_6$ 865.4149; found: 865.4139 $(M+H)^+$.

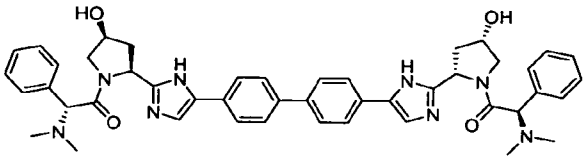
24-15



Prepared from **1-1e** and **cap-48**

RT = 4.88 minutes, method B; LRMS: Anal. Calcd. for $C_{54}H_{60}N_{10}O_6$ 944.13; found: 945.65 $(M+H)^+$; HRMS: Anal. Calcd. for $C_{54}H_{61}N_{10}O_6$ 945.4775; found: 945.4769 $(M+H)^+$.

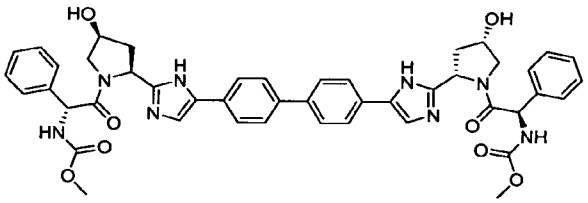
24-16



Prepared from **1-2e** and **cap-1**

RT = 3.66 minutes, method D; LRMS: Anal. Calcd. for $C_{46}H_{50}N_8O_4$ 778.39 found: 779.39 $(M+H)^+$; HRMS: Anal. Calcd. for $C_{46}H_{51}N_8O_4$ 779.4033; found: 779.4021 $(M+H)^+$.

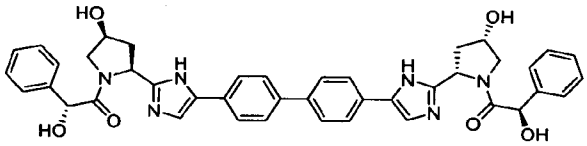
24-17



Prepared from **1-2e** and **cap-4**

RT = 5.75 minutes, method C; LRMS: Anal. Calcd. for $C_{46}H_{46}N_8O_8$ 838.93; found: 839.44 $(M+H)^+$; HRMS: Anal. Calcd. for $C_{46}H_{47}N_8O_8$ 839.3517 found: 839.3519 $(M+H)^+$.

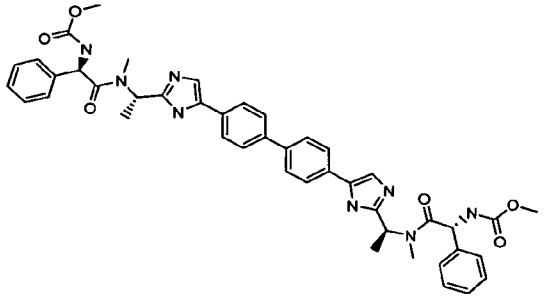
24-18



from 1-2e and mandelic acid

RT = 4.41 minutes, method D; LRMS: Anal. Calcd. for $C_{42}H_{40}N_6O_6$ 724.81; found: 725.13 $(M+H)^+$.

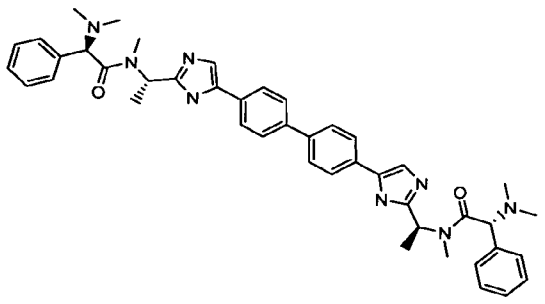
24-18-1



from 1-7e and cap-4

RT = 1.55 min[1]; LRMS: Anal. Calcd. for $C_{44}H_{46}N_8O_6$ 782.35; found: 783.37 $(M+H)^+$; HRMS: Anal. Calcd. for $C_{44}H_{47}N_8O_6$ 783.3619 found: 783.3630 $(M+H)^+$.

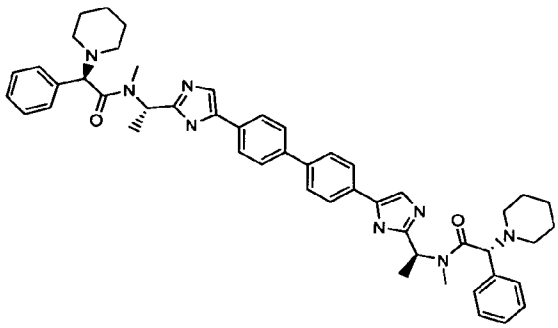
24-18-2



from 1-7e and cap-1

RT = 1.16 min[1]; LRMS: Anal. Calcd. for $C_{44}H_{50}N_8O_2$ 722.41; found: 723.41 $(M+H)^+$; HRMS: Anal. Calcd. for $C_{44}H_{51}N_8O_2$ 723.4135 found: 723.4152 $(M+H)^+$.

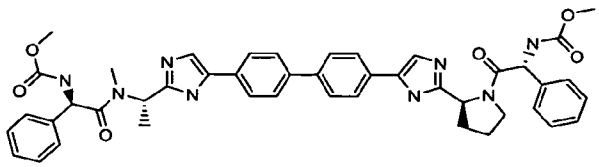
24-18-3



from 1-7e and cap-14

RT = 1.28 min[1]; LRMS: Anal. Calcd. for $C_{50}H_{58}N_8O_2$ 802.47; found: 803.50 $(M+H)^+$; HRMS: Anal. Calcd. for $C_{50}H_{59}N_8O_2$ 803.4761 found: 803.4778 $(M+H)^+$.

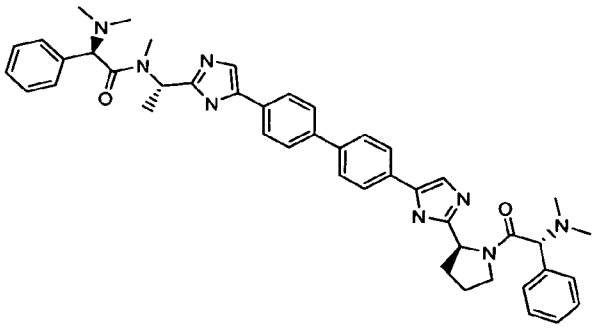
24-18-4



Prepared from 1-5e and cap-4

RT = 1.53 min[1]; LRMS: Anal. Calcd. for $C_{45}H_{46}N_8O_6$ 794.35; found: 795.39 $(M+H)^+$; HRMS: Anal. Calcd. for $C_{45}H_{47}N_8O_6$ 795.3619 found: 795.3616 $(M+H)^+$.

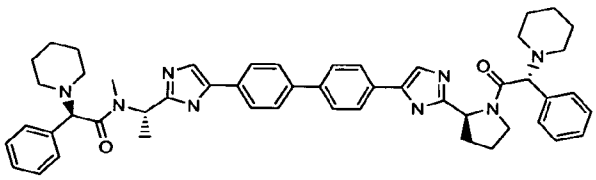
24-18-5



Prepared from 1-5e and cap-1

RT = 1.21[1]; LRMS: Anal. Calcd. for $C_{45}H_{50}N_8O_2$ 734.41; found: 735.46 $(M+H)^+$; HRMS: Anal. Calcd. for $C_{45}H_{51}N_8O_2$ 735.4135 found: 735.4136 $(M+H)^+$.

24-18-6

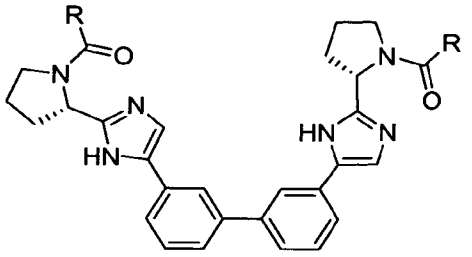


RT = 1.30[1]; LRMS: Anal. Calcd. for $C_{51}H_{58}N_8O_2$ 814.47; found: 815.48 $(M+H)^+$; HRMS: Anal. Calcd.

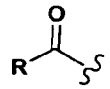
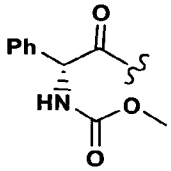
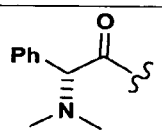
Prepared from 1-5e and cap-14 for $C_{51}H_{59}N_8O_2$ 815.4761 found: 815.4744 $(M+H)^+$.

[1]Phenomenex LUNA C-18 4.6 × 50 mm, 0 to 100% B over 2 minutes, 1 minute hold time, A = 90% water, 10% methanol, 0.1% TFA, B = 10% water, 90% methanol, 0.1% TFA, 220nm, 5 µL injection volume.

Examples 24-19 to 24-20



Example 24-19 and **24-20** were prepared as TFA salts from **1-2e-1** and the respective acids using the same method described for **Example 1**.

Example		Data
24-19	 **cap-4**	^{1}H NMR (500 MHz, DMSO-d_6) δ ppm 1.82-1.97 (m, 2H), 1.97-2.17 (m, 4H), 2.18-2.37 (m, 2H), 3.18 (d, *J*=9.77 Hz, 2H), 3.44-3.58 (m, 6H), 3.79-4.04 (m, 2H), 5.09-5.46 (m, 2H), 5.45-5.84 (m, 2H), 6.97-7.49 (m, 10H), 7.61-7.74 (m, 4H), 7.75-7.93 (m, 4H), 8.10-8.32 (m, 4H), 14.48 (app br s, 2H); RT = 1.34 min; LC/MS: Anal. Calcd. for $[M+H]^+$ $C_{46}H_{47}N_8O_6$: 807.36; found 807.40
24-20	 **cap-1**	^{1}H NMR (500 MHz, DMSO-d_6) δ ppm 1.71-2.32 (m, 8H), 3.33-3.68 (m, 2H), 3.89-4.16 (m, *J*=2.75 Hz, 2H), 4.96 (app br s, 12H), 5.26 (s, 2H), 5.45 (s, 2H), 7.03-7.78 (m, 12H), 7.84 (s,

		4H), 8.07-8.43 (m, 4H), 9.90-10.87 (m, 2H); RT = 1.10 min; LC/MS: Anal. Calcd. for $[M+H]^+$ $C_{46}H_{51}N_8O_2$: 747.41; found 747.45

LC conditions:

Column = Phenomenex-Luna 3.0X 50 mm S10

Start %B = 0

Final %B = 100

Gradient time = 2 min

Stop time = 3 min

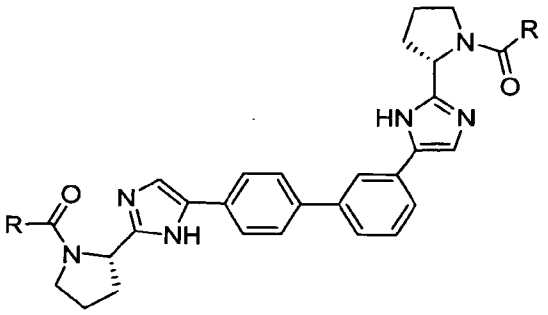
Flow Rate = 4 mL/min

Wavelength = 220 nm

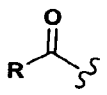
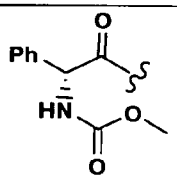
Slovent A = 0.1% TFA in 10% methanol/90%H_2O

Solvent B = 0.1% TFA in 90% methanol/10% H_2O

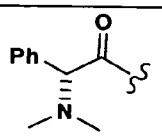
Examples 24-21 to 24-22



Example 24-21 and **24-22** were prepared as TFA salts from **1-4e** and the respective carboxylic acids using the same method described for **Example 1**.

Example		**Data**
24-21	 **cap-4**	^{1}H NMR (500 MHz, DMSO-d_6) δ ppm 1.73-2.37 (m, 8H), 3.13 (s, 2H), 3.36-4.29 (m, 8H), 5.26 (s, 2H), 5.53 (s, 2H), 6.99-8.61 (m, 22H), 14.51 (s, 2H); RT = 1.33min; LC/MS: Anal. Calcd. for $[M+H]^+$ $C_{46}H_{47}N_8O_6$: 807.36; found

807.58

24-22	 **cap-1**	^{1}H NMR (500 MHz, DMSO-d_6) δ ppm 1.84-2.32 (m, 8H), 2.92-3.10 (m, 2H), 3.92-4.08 (m, 2H), 4.43 (app br s, 12H), 5.16-5.37 (m, 2H), 5.39-5.58 (m, 2H), 7.16-8.24 (m, 20H), 9.60-10.46 (m, 2H); RT = 1.08 min; LC/MS: Anal. Calcd. for $[M+H]^+$ $C_{46}H_{51}N_8O_2$: 747.41; found 747.45

LC conditions:

Column = Phenomenex-Luna 3.0X 50 mm S10

Start %B = 0

Final %B = 100

Gradient time = 2 min

Stop time = 3 min

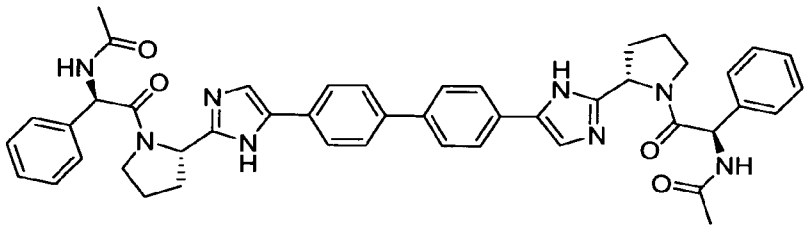
Flow Rate = 4 mL/min

Wavelength = 220 nm

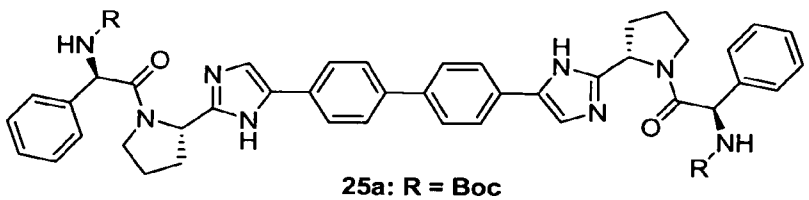
Slovent A = 0.1% TFA in 10% methanol/90%H_2O

Solvent B = 0.1% TFA in 90% methanol/10% H_2O

Example 25



Example 25, Step a & b



25a: R = Boc
25b: R = H

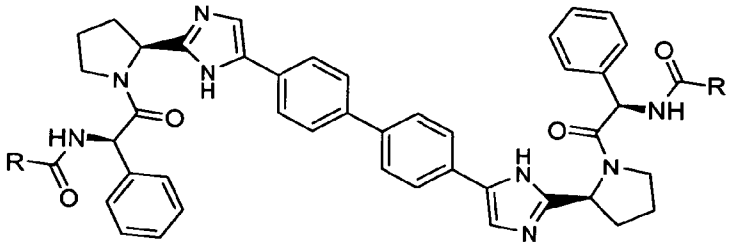
HATU (96.2 mg, 0.253 mmol) was added to a mixture of pyrrolidine **1e** (52.6 mg, 0.124 mmol), diisopropylethylamine (100 µL, 0.57 mmol) and Boc-D-Phg-OH (69 mg, 0.275 mmol) in DMF (3.0 mL). The reaction mixture was stirred for 25 minutes, and then diluted with methanol and purified by a reverse phase HPLC system (H_2O/methanol/TFA). The HPLC elute was neutralized with excess 2.0 M/NH_3 in CH_3OH and the volatile component was removed *in vacuo*. The residue was carefully partitioned between CH_2Cl_2 and saturated $NaHCO_3$. The aqueous phase was extracted with more CH_2Cl_2 (2x). The combined organic phase was dried ($MgSO_4$), filtered, and concentrated *in vacuo* to provide **25a** as a film of semisolid oil (78.8 mg). LC (Cond. Ib): RT = 1.99 min; >98% homogeneity index. LC/MS: Anal. Calcd. for $[M+H]^+$ $C_{52}H_{59}N_8O_6$: 891.46; found 891.55.

Carbamate **25a** was converted to amine **25b** according to the procedure described for the preparation of **1e**. LC(Cond. Ib): RT = 1.44 min; 97% homogeneity index. LC/MS: Anal. Calcd. for $[M+H]^+$ $C_{42}H_{43}N_8O_2$: 691.35; found 691.32

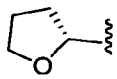
Example 25

Acetic anhydride (20 µL, 0.21 mmol) was added to a DMF (1.5 mL) solution of amine **25b** (29 mg, 0.042 mmol)and triethylamine (30 µL, 0.22 mmol) and stirred for 2.5 hours. The reaction mixture was then treated with NH_3/methanol (1 mL of 2 M) and stirred for an additional 1.5 hours. The volatile component was removed *in vacuo* and the residue was purified by a reverse phase HPLC system (H_2O/methanol/ TFA) to provide the TFA salt of **Example 25** as a white foam (28.1 mg). LC (Cond.Ib): RT = 1.61 min; >98% homogeneity index; LC/MS: Anal. Calcd. for $[M+H]^+$ $C_{46}H_{47}N_8O_4$: 775.37; found 775.40; HRMS: Anal. Calcd. for $[M+H]^+$ $C_{46}H_{47}N_8O_4$: 775.3720; found 775.3723

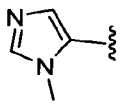
Example 25-1 to 25-5



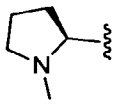
Examples **25-1** to **25-5** were prepared from **25b** and the appropriate carboxylic acid using standard amide forming conditions similar to that described for the preparation of example **1** from **1e**. Examples **25-6** to **25-8** were prepared from **25b** and the appropriate carbamoyl chloride or isocyanate.

25-1 

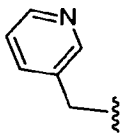
RT = 5.68 minutes; HPLC Xterra 4.6 X 50 mm, 0 to 100% B over 10 minutes, one minute hold time, A = 90% water, 10% methanol, 0.2% phosphoric acid, B = 10% water, 90% methanol, 0.2% phosphoric acid; LCMS: Anal. Calcd. for: $C_{52}H_{54}N_8O_6$: 887.06; Found: 887.58 $(M+H)^+$

25-2 

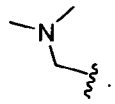
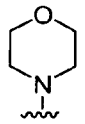
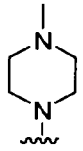
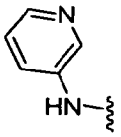
RT = 3.54 minutes; HPLC Xterra 4.6 X 50 mm, 0 to 100% B over 10 minutes, one minute hold time, A = 90% water, 10% methanol, 0.2% phosphoric acid, B = 10% water, 90% methanol, 0.2% phosphoric acid; LCMS: Anal. Calcd. for: $C_{52}H_{50}N_{12}O_4$: 907.06; Found: 907.42 $(M+H)^+$

25-3 

RT = 3.1 minutes; HPLC Xterra 4.6 X 50 mm, 0 to 100% B over 10 minutes, one minute hold time, A = 90% water, 10% methanol, 0.2% phosphoric acid, B = 10% water, 90% methanol, 0.2% phosphoric acid; LCMS: Anal. Calcd. for: $C_{54}H_{60}N_{10}O_4$ 913.14; Found: 913.54 $(M+H)^+$

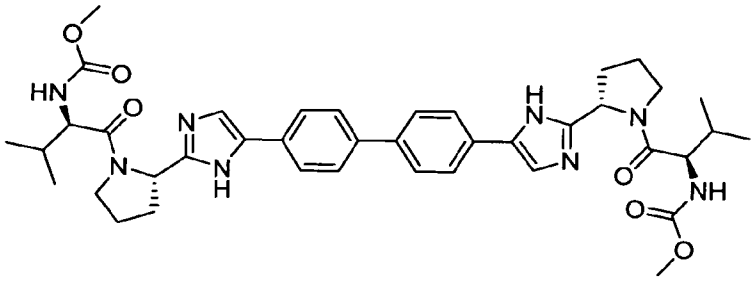
25-4 

RT = 3.37 minutes; HPLC Xterra 4.6 X 50 mm, 0 to 100% B over 10 minutes, one minute hold time, A = 90% water, 10% methanol, 0.2% phosphoric acid, B = 10% water, 90% methanol, 0.2%

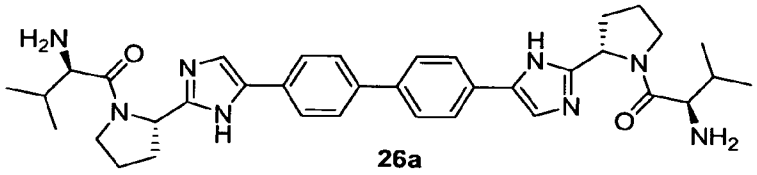
		phosphoric acid; LCMS: Anal. Calcd. for: $C_{56}H_{52}N_{10}O_4$ 929.10 Found: 929.42 $(M+H)^+$
25-5		RT = 7.07 minutes; HPLC Xterra 4.6 X 50 mm, 0 to 100% B over 10 minutes, one minute hold time, A = 90% water, 10% methanol, 0.2% phosphoric acid, B = 10% water, 90% methanol, 0.2% phosphoric acid; LCMS: Anal. Calcd. for: $C_{50}H_{56}N_{10}O_4$ 861.07 Found: 859.69 $(M+H)^+$
25-6		^{1}H NMR (500 MHz, DMSO-d_6) δ ppm 1.86-2.18 (m, 6H), 2.23-2.39 (m, 2H), 3.20-3.40 (m, 8H), 3.40-3.61 (m, 8H), 3.90-4.19 (m, 4H), 5.27 (dd, *J*=8.09, 3.51 Hz, 2H), 5.37-5.63 (m, 2H), 6.92-7.11 (m, 3H), 7.30-7.45 (m, 5H), 7.44-7.56 (m, 4H), 7.83-8.04 (m, 8H), 8.15 (s, 2H), 14.29 (s, 2H); HPLC Xterra 4.6 X 50 mm, 0 to 100% B over 10 minutes, one minute hold time, A = 90% water, 10% methanol, 0.2% phosphoric acid, B = 10% water, 90% methanol, 0.2% phosphoric acid, RT = 6.01 minutes; LCMS: Anal. Calcd. for: $C_{52}H_{56}N_{10}O_6$ 917.09; Found: 917.72 $(M+H)^+$
25-7		RT = 3.74 minutes; HPLC Xterra 4.6 X 50 mm, 0 to 100% B over 10 minutes, one minute hold time, A = 90% water, 10% methanol, 0.2% phosphoric acid, B = 10% water, 90% methanol, 0.2% phosphoric acid; LCMS: Anal. Calcd. for: $C_{54}H_{62}N_{12}O_4$ 943.17; Found: 943.84 $(M+H)^+$
25-8		^{1}H NMR (500 MHz, DMSO-d_6) δ ppm 1.79-2.17 (m, 6H), 2.29 (d, *J*=9.77 Hz, 2H), 3.06-3.39 (m, 2H), 3.72-4.14 (m, 2H), 5.27 (dd, *J*=8.24, 2.75 Hz, 2H), 5.66 (d, *J*=7.02 Hz, 2H), 7.26-7.65 (m, 12H),

7.82-8.11 (m, 12H), 8.17 (s, 2H), 8.23-8.45 (m, 2H), 8.61-8.97 (m, 2H), 9.38 (s, 2H), 14.51 (s, 2H); HPLC Xterra 4.6 X 50 mm, 0 to 100% B over 10 minutes, one minute hold time, A = 90% water, 10% methanol, 0.2% phosphoric acid, B = 10% water, 90% methanol, 0.2% phosphoric acid, RT = 4.05 minutes; LCMS: Anal. Calcd. for: $C_{54}H_{50}N_{12}O_4$ 931.08; Found: 931.78 $(M+H)^+$.

Example 26



Example 26, Step a



26a

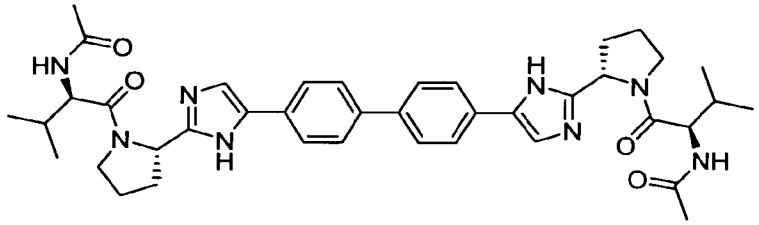
Diamine **26a** was prepared starting from pyrrolidine **1e** and BOC-D-Val-OH according to the procedure described for the synthesis of diamine **25b**.

Example 26

Methyl chloroformate (18 μL, 0.23 mmol) was added to a THF (1.5 mL) solution of diamine **26a** (30 mg, 0.048 mmol) and triethylamine (30 μL, 0.22 mmol), and the reaction mixture was stirred at ambient condition for 3 hours. The volatile components was removed *in vacuo*, and the residue was treated with NH_3/methanol (2 mL of 2 M) and stirred at ambient conditions for 15 minutes. All the volatile component was removed *in vacuo*, and the crude product was purified by reverse phase prep-HPLC (H_2O/methanol/TFA) to provide the TFA salt of **Example 26** as a

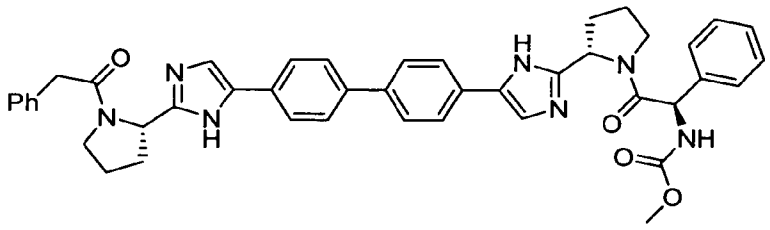
white solid (13.6 mg). LC (Cond.II): RT = 2.00 min; >98% homogeneity index; LC/MS: Anal. Calcd. for $[M+H]^+$ $C_{40}H_{51}N_8O_6$: 739.39; found 739.67; HRMS: Anal. Calcd. for $[M+H]^+$ $C_{40}H_{51}N_8O_6$: 739.3932; found 739.3966.

Example 27

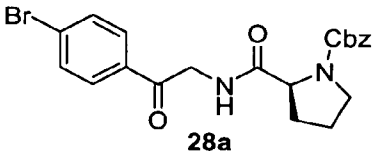


Diamine **26a** was converted to **Example 27** (TFA salt) according to a method described in the preparation of **Example 25**. LC (Cond.II): RT = 1.93min; >98% homogeneity index; LC/MS: Anal. Calcd. for $[M+H]^+$ $C_{40}H_{51}N_8O_4$: 707.40; found 707.59; HRMS: Anal. Calcd. for $[M+H]^+$ $C_{40}H_{51}N_8O_4$: 707.4033; found 707.4054.

Example 28



Example 28, Step a

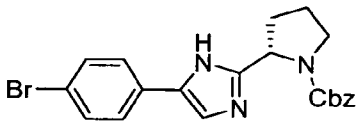


28a

HATU (19.868g, 52.25 mmol) was added to a heterogeneous mixture of *N*-Cbz-L- proline (12.436 g, 49.89 mmol) and the HCl salt of 2-amino-1-(4-bromophenyl) ethanone (12.157 g, 48.53 mmol) in DMF (156 mL). The mixture was lowered in an ice-water bath, and immediately afterward *N,N*-diisopropylethylamine (27 mL, 155 mmol) was added dropwise to it over 13 minutes. After the addition of the base was completed, the cooling bath was removed and the reaction mixture was stirred for an additional 50 minutes. The volatile component was removed *in vacuo*;

water (125 mL) was added to the resulting crude solid and stirred for about 1 hour. The off-white solid was filtered and washed with copious water, and dried *in vacuo* to provide ketoamide **28a** as a white solid (20.68 g). ^{1}H NMR (DMSO-d_6, δ= 2.5 ppm, 400 MHz): δ 8.30 (m, 1H), 7.91 (m, 2H), 7.75 (d, J = 8.5, 2H), 7.38-7.25 (m, 5H), 5.11-5.03 (m, 2H), 4.57-4.48 (m, 2H), 4.33-4.26 (m, 1H), 3.53-3.36 (m, 2H), 2.23-2.05 (m, 1H), 1.94-1.78 (m, 3H); LC (Cond. I): RT = 1.65 min; 98% homogeneity index; LC/MS: Anal. Calcd. for $[M+H]^+$ $C_{21}H_{22}BrN_2O_4$: 445.08; found 445.31.

Example 28, Step b



28b

Ketoamide **28a** (10.723g, 24.08 mmol) was converted to **28b** according to the procedure described for the synthesis of carbamate **1b**, with the exception that the crude material was purified by flash chromatography (sample was loaded with eluting solvent; 50% ethyl acetate/hexanes). Bromide **28b** was retrieved as an off-white foam (7.622 g). ^{1}H NMR (DMSO-d_6, δ= 2.5 ppm, 400 MHz): δ 12.23/12.04/11.97 (m, 1H), 7.73-6.96 (m, 10H), 5.11-4.85 (m, 3H), 3.61 (m, 1H), 3.45 (m, 1H), 2.33-184(m, 4H). LC (Cond.I): RT = 1.42 min; >95% homogeneity index; LC/MS: Anal. Calcd. for $[M+H]^+$ $C_{21}H_{21}BrN_3O_2$: 426.08; found 426.31; HRMS: Anal. Calcd. for $[M+H]^+$ $C_{21}H_{21}BrN_3O_2$: 426.0817; found: 426.0829. The optical purity of **28b** was assessed using the following chiral HPLC methods, and an ee of 99% was observed.

Column: Chiralpak AD, 10 um, 4.6 x 50 mm

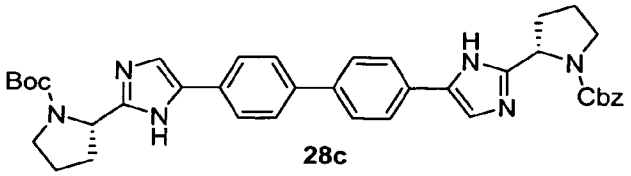
Solvent: 20% ethanol/heptane (isocratic)

Flow rate: 1 mL/min

Wavelength: 254 nm

Relative retention time: 1.82 minutes (*R*), 5.23 minutes (*S*)

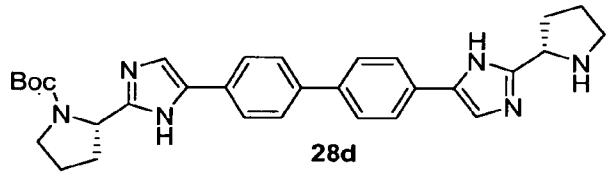
Example 28, Step c



28c

$Pd(Ph_3P)_4$ (711.4 mg, 0.616 mmol) was added to a mixture of boronate ester **1c** (7.582 g, ~ 17 mmol), bromide **28b** (7.62 g, 17.87 mmol), $NaHCO_3$ (4.779 g, 56.89 mmol) in 1,2-dimethoxyethane (144 mL) and water (48 mL). The reaction mixture was purged with N_2 and heated with an oil bath at 80 °C for 15.5 hours, and then the volatile component was removed *in vacuo*. The residue was partitioned between CH_2Cl_2 and water, and the aqueous layer was extracted with CH_2Cl_2. The combined organic phase was dried ($MgSO_4$), filtered, and concentrated *in vacuo*. The resulting material was submitted to flash chromatography (sample was loaded as a silica gel mesh; ethyl acetate used as eluent) to provide biphenyl **28c** as an off-white foam containing Ph_3PO impurity (7.5 g). ^1H NMR (DMSO-d_6, δ= 2.5 ppm, 400 MHz): δ 12.24-12.19 (m, 0.36H), 12.00-11.82 (m, 1.64H), 7.85-6.98 (15H), 5.12-4.74 (4H), 3.68-3.34(4H), 2.34-1.79 (8H), 1.41/1.17 (two br S, 9H); LC (Cond.I): RT = 1.41 minutes; LC/MS: Anal. Calcd. for $[M+H]^+$ $C_{39}H_{43}N_6O_4$: 659.34; found 659.52; HRMS: Anal. Calcd. for $[M+H]^+$ $C_{39}H_{43}N_6O_4$: 659.3346; found 659.3374.

Example 28, Step d

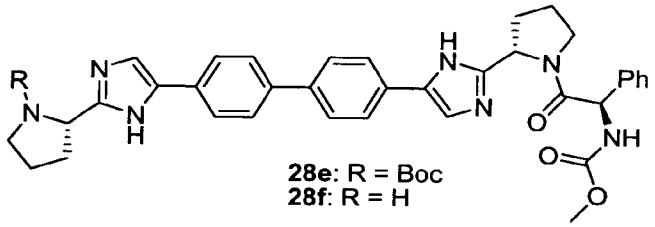


28d

K_2CO_3 (187.8 mg, 1.36 mmol) was added to a mixture of catalyst (10% Pd/C; 205.3 mg), carbamate **28c** (1.018 g, ~ 1.5 mmol), methanol (20 mL) and 3 pipet-drops of water. A balloon of H_2 was attached and the mixture was stirred for 6 hours. Then, additional catalyst (10% Pd/C, 100.8 mg) and K_2CO_3 (101.8 mg, 0.738 mmol) were added and stirring continued for 3.5 hours. During the hydrogenation process, the balloon of H_2 was changed at intervals three times. The reaction mixture was filtered through a pad of diatomaceous earth (Celite® 521), and the filterate was removed *in vacuo*. The resulting crude material was submitted to flash

chromatography using a short column (sample was loaded as a silica gel mesh; 0-20% methanol/CH_2Cl_2 used as eluent) to provide **28d** as a light-yellow foam (605.6 mg). ^{1}H NMR (DMSO-d_6, δ= 2.5 ppm, 400 MHz): δ 12.18/11.89/11.82 (three br s, 2H), 7.83-7.29 (m, 10H), 4.89-4.73 (m, 1H), 4.19 (app t, J = 7.2, 1H), 3.55 (app br s, 1H), 3.40-3.35 (m, 1H), 3.02-2.96 (m, 1H), 2.91-2.84(m, 1H), 2.30-1.69(m, 8H), 1.41/1.16 (two br s, 9H). Note: the signal of pyrrolidine NH appears to have overlapped with signals in the 3.6-3.2 ppm region; LC (Cond.I): RT = 1.21 min; >95% homogeneity index; LC/MS: Anal. Calcd. for $[M+H]^+$ $C_{31}H_{37}N_6O_2$: 525.30; found 525.40.

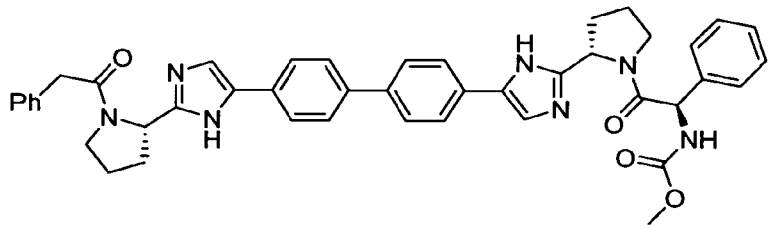
Example 28, Step e-f



HATU (316.6 mg, 0.833 mmol) was added to a DMF (7.0 mL) solution of pyrrolidine **28d** (427 mg, 0.813 mmol), **Cap-4** (177.6 mg, 0.849 mmol) and diisopropylethylamine (0.32 mL, 1.84 mmol), and the reaction mixture was stirred for 45 minutes. The volatile component was removed *in vacuo*, and the residue was partitioned between CH_2Cl_2 (50 mL) and an aqueous medium (20 mL H_2O + 1 mL saturated $NaHCO_3$ solution). The aqueous phase was re-extracted with CH_2Cl_2, and the combined organic phase was dried ($MgSO_4$), filtered, and concentrated *in vacuo*. The resulting yellow oil was purified by flash chromatography (silica gel; ethyl acetate) to provide **28e** as a yellow foam (336 mg). LC (Cond. Ib): RT = 1.68min; 91% homogeneity index; LC/MS: Anal. Calcd. for $[M+H]^+$ $C_{41}H_{46}N_7O_5$: 716.35; found 716.53.

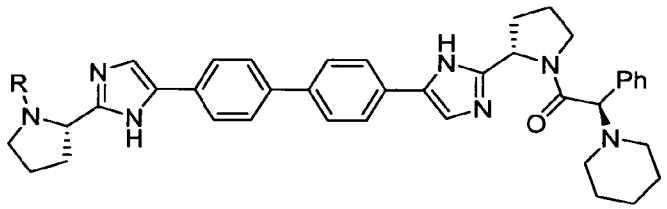
Carbamate **28e** was elaborated to amine **28f** by employing the procedure described in the conversion of **1d** to **1e**. LC (Cond. Ib): RT = 1.49min; >98% homogeneity index. LC/MS: Anal. Calcd. for $[M+H]^+$ $C_{36}H_{38}N_7O_3$: 616.30; found 616.37; HRMS: Anal. Calcd. for $[M+H]^+$ $C_{36}H_{38}N_7O_3$: 616.3036; found 616.3046.

Example 28



Amine **28f** was converted to the TFA salt of **Example 28** by employing the last step of the synthesis of **Example 1**. ^{1}H NMR (DMSO-d_6, δ= 2.5 ppm, 400 MHz): δ 8.21-7.03 (m, 21H), 5.78-5.14 (3H), 3.98-3.13 (m, 9H; includes the signal for OCH_3 at 3.54 & 3.53), 2.45-1.72 (m, 8H). LC (Cond. Ib): RT = 1.66 minutes, >98% homogeneity index; LC/MS: Anal. Calcd. for $[M+H]^+$ $C_{44}H_{44}N_7O_4$: 734.35; found 734.48; HRMS: Anal. Calcd. for $[M+H]^+$ $C_{44}H_{44}N_7O_4$: 734.3455; 734.3455.

Example 28-1 to 28-4



Examples **28-1** through **28-4** (R groups shown in the table below) were prepared in similar fashion to example **28** via the intermediacy of intermediate **28d**.

Example 28-1

Cap-1 was appended, the Boc carbamate was removed with TFA or HCl , and **cap-14** was appended.

Example 28-2

Tetrahydrofuroic acid was appended, the Boc carbamate was removed with TFA or HCl , and **cap-14** was appended.

Example 28-3

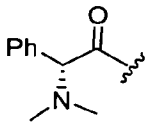
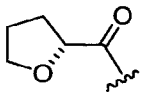
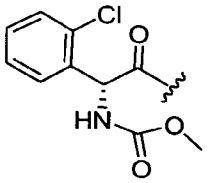
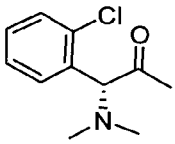
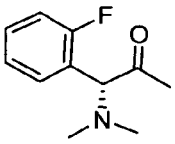
Cap-40 was appended, the Boc carbamate was removed with TFA or HCl , and **cap-14** was appended.

Example 28-4

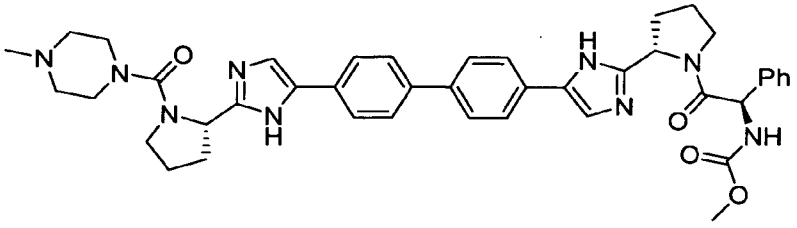
Cap-39 was appended, the Boc carbamate was removed with TFA or HCl , and **cap-14** was appended.

Example 28-5

Cap-38 was appended, the Boc carbamate was removed with TFA or HCl , and **cap-14** was appended.

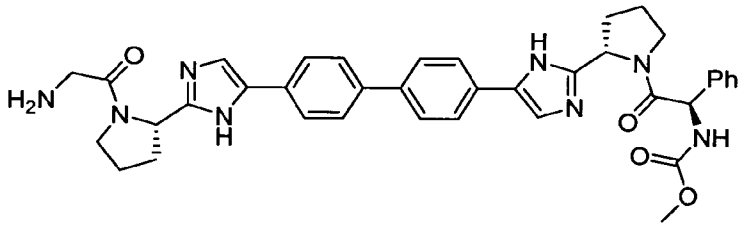
Example	R	Data
28-1		LCMS: Anal. Calcd. for $C_{49}H_{54}N_8O_2$: 786; found: 787 $(M+H)^+$.
28-2		LCMS: Anal. Calcd. for $C_{44}H_{49}N_7O_3$: 723; found: 724 $(M+H)^+$.
28-3		LCMS: Anal. Calcd. for $C_{49}H_{51}ClN_8O_4$: 850; found: 851 $(M+H)^+$.
28-4		LCMS: Anal. Calcd. for $C_{49}H_{53}ClN_8O_2$: 820; found: 821 $(M+H)^+$.
28-5		LCMS: Anal. Calcd. for $C_{49}H_{53}FN_8O_2$: 804; found: 805 $(M+H)^+$.

Example 29

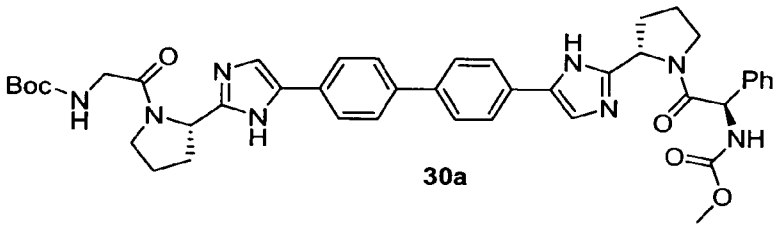


4-Methylpiperazine-1-carbonyl chloride/HCl (11.6 mg, 0.58 mmol) was added to a mixture of **28f** (30 mg, 0.049 mmol), triethylamine (15 µl, 0.11 mmol) and THF (1.0 mL), and stirred at ambient conditions for 1 hour. The volatile component was removed *in vacuo*, and the residue was purified by a reverse phase HPLC (H_2O/methanol/TFA) to provide the TFA salt of **Example 29** as a light yellow foam (29.3 mg). LC (Cond. II): RT = 1.82 minutes, >98% homogeneity index; LC/MS: Anal. Calcd. for $[M+H]^+$ $C_{42}H_{48}N_9O_4$: 742.38; found 742.49.

Example 30



Example 30, Step a



30a

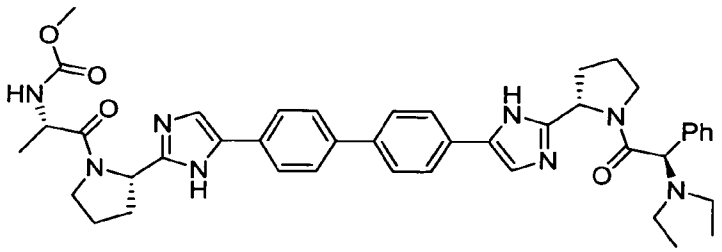
Carbamate **30a** was prepared from pyrrolidine **28f** and Boc-Glycine by using the procedure described for the preparation of **25a** from **1e**. LC (Cond. II): RT = 2.12 minutes, >98% homogeneity index; LC/MS: Anal. Calcd. for $[M+H]^+$ $C_{43}H_{49}N_8O_6$: 773.38; found 773.46

Example 30

Carbamate **30a** was converted to **Example 30** according to the procedure described for the preparation of **1e** from **1d**. LC (Cond. II): RT = 1.81 minutes, >98% homogeneity index; LC/MS: Anal. Calcd. for $[M+H]^+$ $C_{38}H_{41}N_8O_4$: 673.33; found 673.43

HRMS: Anal. Calcd. for $[M+H]^+$ $C_{38}H_{41}N_8O_4$: 673.3251; found 673.3262

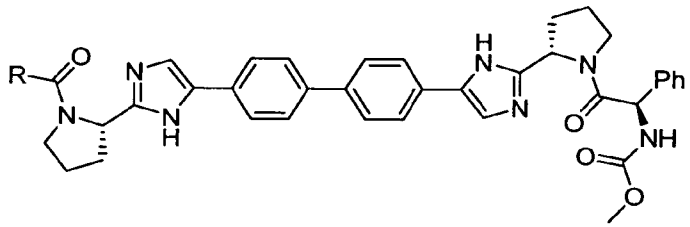
Example 30-1

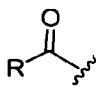


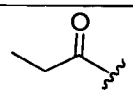
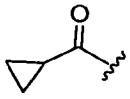
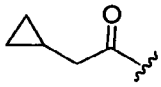
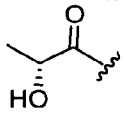
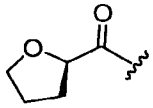
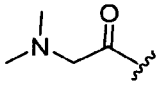
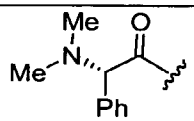
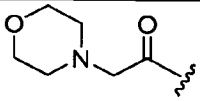
Example 30-1 was prepared in three steps from example **28d**. Step one: Append **cap-2** using the procedure describing the synthesis of **28e** from **28d**. Step two: Hydrolyze the Boc carbamate using the procedure describing the synthesis of **28f** from **28e**. Step three: Append **cap-52** using the procedure describing the synthesis of **28e** from **28d**. RT = 1.70 min (Cond. Ib); >95% homogeneity index. LC/MS: Anal. Calcd. for $[M+H]^+$ $C_{43}H_{51}N_8O_4$: 743.40; found, 743.50. HRMS: Anal. Calcd. for $[M+H]^+$ $C_{43}H_{51}N_8O_4$: 743.4033; found, 743.4053

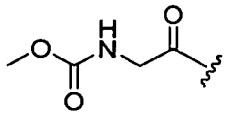
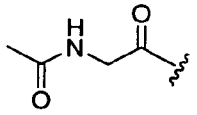
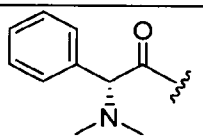
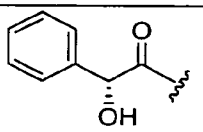
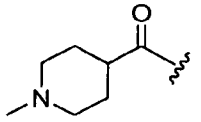
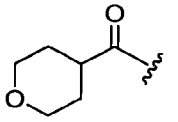
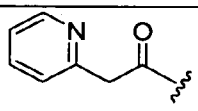
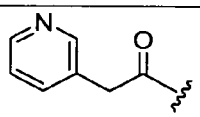
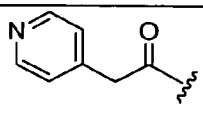
Substituting the appropriate acid chloride or carboxylic acid into **Example 29 or 30,** the following compounds (**Example 31-107**) were prepared as TFA salts.

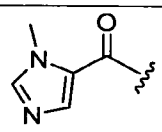
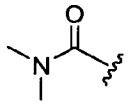
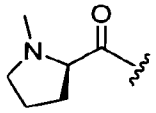
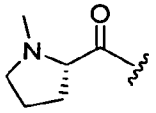
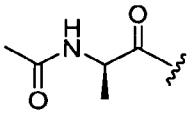
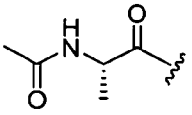
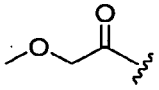
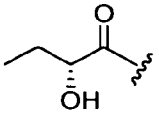
Example 31 to 84-88

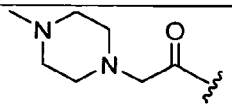
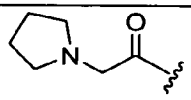
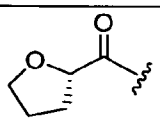
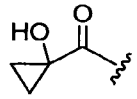
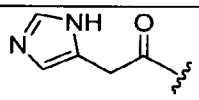
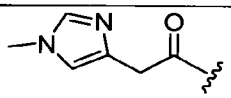
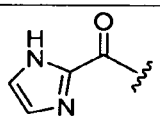
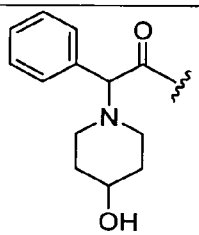


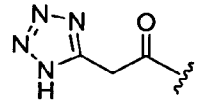
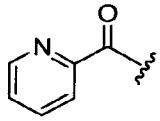
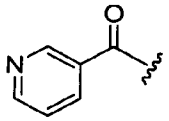
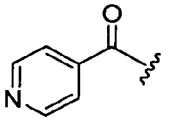
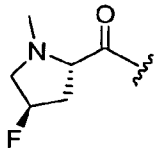
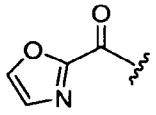
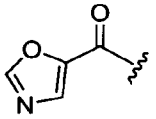
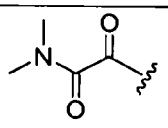
Example		**Retention time (LC-Condition); homogeneity index MS data**
31		1.54 minutes (Cond. Ib); >98%; LC/MS: Anal. Calcd. for $[M+H]^+$ $C_{38}H_{40}N_7O_4$: 658.31; found 658.42; HRMS: Anal. Calcd. for $[M+H]^+$ $C_{38}H_{40}N_7O_4$:

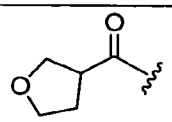
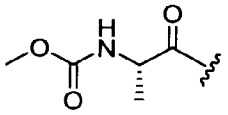
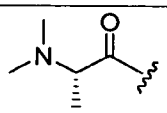
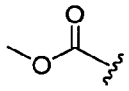
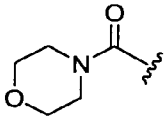
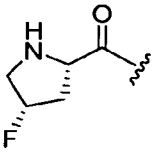
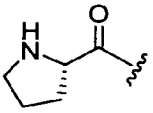
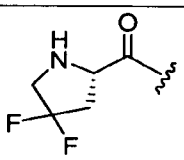
		658.3142; found 658.3135
32		1.57 minutes (Cond. Ib); >98%; LC/MS: Anal. Calcd. for $[M+H]^+$ $C_{39}H_{42}N_7O_4$: 672.33; found 672.46; HRMS: Anal. Calcd. for $[M+H]^+$ $C_{39}H_{42}N_7O_4$: 672.3298; found 672.3299
33		1.59 minutes (Cond. Ib); >98%; LC/MS: Anal. Calcd. for $[M+H]^+$ $C_{40}H_{42}N_7O_4$: 684.33; found 684.44; HRMS: Anal. Calcd. for $[M+H]^+$ $C_{40}H_{42}N_7O_4$: 684.3298; found 684.3324
34		1.61 minutes (Cond. Ib); >98%; LC/MS: Anal. Calcd. for $[M+H]^+$ $C_{40}H_{42}N_7O_4$: 698.35; found 698.48; HRMS: Anal. Calcd. for $[M+H]^+$ $C_{40}H_{42}N_7O_4$: 698.3455; found 698.3489
35		1.54 minutes (Cond. Ib); >98%; LC/MS: Anal. Calcd. for $[M+H]^+$ $C_{39}H_{42}N_7O_5$: 688.33; found 688.47
36		1.59 minutes (Cond. Ib); >98%; LC/MS: Anal. Calcd. for $[M+H]^+$ $C_{41}H_{44}N_7O_5$: 714.34; found 714.49; HRMS: Anal. Calcd. for $[M+H]^+$ $C_{41}H_{44}N_7O_5$: 714.3404; found 714.3430
37		1.48 minutes (Cond. Ib); >98%; LC/MS: Anal. Calcd. for $[M+H]^+$ $C_{40}H_{45}N_8O_4$: 701.36; found 701.49; HRMS: Anal. Calcd. for $[M+H]^+$ $C_{40}H_{45}N_8O_4$: 701.3564; found 701.3553
38	 **cap-1**	1.20 minutes (Cond. I); >98%; LC/MS: Anal. Calcd. for $[M+H]^+$ $C_{46}H_{49}N_8O_4$: 777.39; found 777.61; HRMS: Anal. Calcd. for $[M+H]^+$ $C_{46}H_{49}N_8O_4$: 777.3877; found 777.3909
39		1.79 minutes (Cond. II); >98%; LC/MS: Anal. Calcd. for $[M+H]^+$ $C_{42}H_{47}N_8O_5$: 743.37; found 743.49; HRMS: Anal. Calcd. for $[M+H]^+$ $C_{42}H_{47}N_8O_5$: 743.3669; found 743.3672

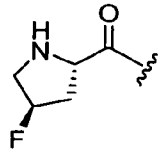
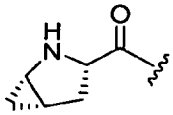
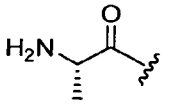
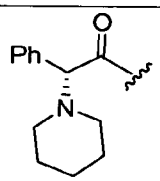
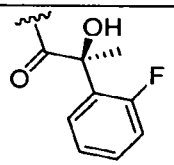
40		1.92 minutes (Cond. II); >98%; LC/MS: Anal. Calcd. for $[M+H]^+$ $C_{40}H_{43}N_8O_6$: 731.33; found 731.42; HRMS: Anal. Calcd. for $[M+H]^+$ $C_{40}H_{43}N_8O_6$: 731.3306; found 731.3333
41		1.86 minutes (Cond. II); >98%; LC/MS: Anal. Calcd. for $[M+H]^+$ $C_{40}H_{43}N_8O_5$: 715.34; found 715.49; HRMS: Anal. Calcd. for $[M+H]^+$ $C_{40}H_{43}N_8O_5$: 715.3356; found 715.3369
42		1.85 minutes (Cond. II); >98%; LC/MS: Anal. Calcd. for $[M+H]^+$ $C_{46}H_{49}N_8O_4$: 777.39; found 777.56
43		1.96 minutes (Cond. II); >98%; LC/MS: Anal. Calcd. for $[M+H]^+$ $C_{44}H_{44}N_7O_5$: 750.34; found 750.51; HRMS: Anal. Calcd. for $[M+H]^+$ $C_{44}H_{44}N_7O_5$: 750.3404; found 750.3437
44		1.78 minutes (Cond. II); >98%; LC/MS: Anal. Calcd. for $[M+H]^+$ $C_{43}H_{49}N_8O_4$: 741.39; found 741.55; HRMS: Anal. Calcd. for $[M+H]^+$ $C_{43}H_{49}N_8O_4$: 741.3877; found 741.3893
45		1.87 minutes (Cond. II); >98%; LC/MS: Anal. Calcd. for $[M+H]^+$ $C_{42}H_{46}N_7O_5$: 728.36; found 728.52; HRMS: Anal. Calcd. for $[M+H]^+$ $C_{42}H_{46}N_7O_5$: 728.3560; found 728.3587
46		1.80 minutes (Cond. II); >98%; LC/MS: Anal. Calcd. for $[M+H]^+$ $C_{43}H_{43}N_8O_4$: 735.34; found 735.51; HRMS: Anal. Calcd. for $[M+H]^+$ $C_{43}H_{43}N_8O_4$: 735.3407; found 735.3416
47		1.76 minutes (Cond. II); >98%; LC/MS: Anal. Calcd. for $[M+H]^+$ $C_{43}H_{43}N_8O_4$: 735.34; found 735.52
48		1.77 minutes (Cond. II); >98%; LC/MS: Anal. Calcd. for $[M+H]^+$ $C_{43}H_{43}N_8O_4$: 735.34; found 735.50; HRMS: Anal. Calcd. for $[M+H]^+$ $C_{43}H_{43}N_8O_4$:

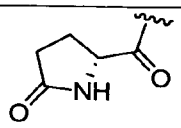
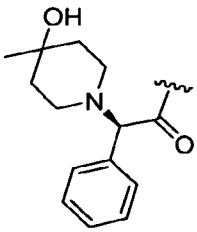
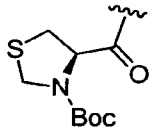
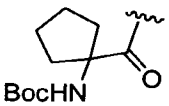
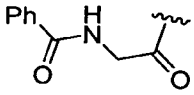
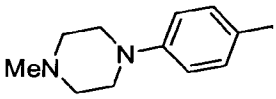
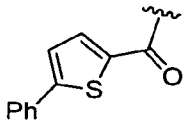
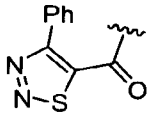
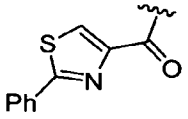
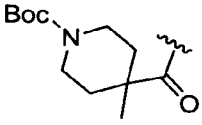
		735.3407; found 735.3405
49		1.77 minutes (Cond. II); >98%; LC/MS: Anal. Calcd. for $[M+H]^+$ $C_{41}H_{42}N_9O_4$: 724.34; found 724.51; HRMS: Anal. Calcd. for $[M+H]^+$ $C_{41}H_{42}N_9O_4$: 724.3360; found 724.3380
50		1.91 minutes (Cond. II); >98%; LC/MS: Anal. Calcd. for $[M+H]^+$ $C_{39}H_{43}N_8O_4$: 687.34; found 687.49; HRMS: Anal. Calcd. for $[M+H]^+$ $C_{39}H_{43}N_8O_4$: 687.3407; found 687.3414
51 **cap-10**		1.79 minutes (Cond. II); >98%; LC/MS: Anal. Calcd. for $[M+H]^+$ $C_{42}H_{47}N_8O_4$: 727.37; found 727.34; HRMS: Anal. Calcd. for $[M+H]^+$ $C_{42}H_{47}N_8O_4$: 727.3720; found 727.3719
52 **enantiomer of cap-10**		1.77 minutes (Cond. II); >98%; LC/MS: Anal. Calcd. for $[M+H]^+$ $C_{42}H_{47}N_8O_4$: 727.37; found 727.33; HRMS: Anal. Calcd. for $[M+H]^+$ $C_{42}H_{47}N_8O_4$: 727.3720; found 727.3738
53		1.92 minutes (Cond. II); >98%; LC/MS: Anal. Calcd. for $[M+H]^+$ $C_{41}H_{45}N_8O_5$: 729.35; found 729.33; HRMS: Anal. Calcd. for $[M+H]^+$ $C_{41}H_{45}N_8O_5$: 729.3513; found 729.3530
54		1.87 minutes (Cond. II); >98%; LC/MS: Anal. Calcd. for $[M+H]^+$ $C_{41}H_{45}N_8O_5$: 729.35; found 729.33
55		1.89 minutes (Cond. II); >98%; LC/MS: Anal. Calcd. for $[M+H]^+$ $C_{39}H_{42}N_7O_5$: 688.32; found 688.28; HRMS: Anal. Calcd. for $[M+H]^+$ $C_{39}H_{42}N_7O_5$: 688.3247; found 688.3231
56		1.91 minutes (Cond. II); >98%; LC/MS: Anal. Calcd. for $[M+H]^+$ $C_{40}H_{44}N_7O_5$: 702.34; found 702.30; HRMS: Anal. Calcd. for $[M+H]^+$ $C_{40}H_{44}N_7O_5$: 702.3404; found 702.3393

57		1.80 minutes (Cond. II); >98%; LC/MS: Anal. Calcd. for $[M+H]^+$ $C_{43}H_{50}N_9O_4$: 756.40; found 756.36; HRMS: Anal. Calcd. for $[M+H]^+$ $C_{43}H_{50}N_9O_4$: 756.3986; found 756.3965
58		1.82 minutes (Cond. II); >98%; LC/MS: Anal. Calcd. for $[M+H]^+$ $C_{42}H_{47}N_8O_4$: 727.37; found 727.33; HRMS: Anal. Calcd. for $[M+H]^+$ $C_{42}H_{47}N_8O_4$: 727.3720; found 727.3696
59		1.94 minutes (Cond. II); >98%; LC/MS: Anal. Calcd. for $[M+H]^+$ $C_{41}H_{43}N_7O_5$: 714.34; found 714.24
60		1.93 minutes (Cond. II); >98%; LC/MS: Anal. Calcd. for $[M+H]^+$ $C_{40}H_{42}N_7O_5$: 700.32; found 700.23; HRMS: Anal. Calcd. for $[M+H]^+$ $C_{40}H_{42}N_7O_5$: 700.3247; found 700.3265
61		1.84 minutes (Cond. II); >98%; LC/MS: Anal. Calcd. for $[M+H]^+$ $C_{41}H_{42}N_9O_4$: 724.34; found 724.21; HRMS: Anal. Calcd. for $[M+H]^+$ $C_{41}H_{42}N_9O_4$: 724.3360; found 724.3365
62		1.85 minutes (Cond. II); >98%; LC/MS: Anal. Calcd. for $[M+H]^+$ $C_{42}H_{44}N_9O_4$: 738.35; found 738.22; HRMS: Anal. Calcd. for $[M+H]^+$ $C_{42}H_{44}N_9O_4$: 738.3516; found 738.3539
63		1.95 minutes (Cond. II); >98%; LC/MS: Anal. Calcd. for $[M+H]^+$ $C_{40}H_{41}N_9O_4$: 710.32; found 710.17
64	 **cap-8** A single	1.92 minutes (Cond. II); >98%; LC/MS: Anal. Calcd. for $[M+H]^+$ $C_{49}H_{53}N_8O_5$: 833.41; found 833.32; HRMS: Anal. Calcd. for $[M+H]^+$ $C_{49}H_{53}N_8O_5$: 833.4139; found 833.4163

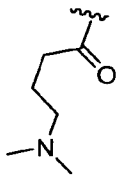
	diastereomer	
65		1.92 minutes (Cond. II); >98%; LC/MS: Anal. Calcd. for $[M+H]^+$ $C_{39}H_{40}N_{11}O_4$: 726.33; found 726.22; HRMS: Anal. Calcd. for $[M+H]^+$ $C_{39}H_{40}N_{11}O_4$: 726.3265; found 726.3290
67		2.03 minutes (Cond. II); >98%; LC/MS: Anal. Calcd. for $[M+H]^+$ $C_{42}H_{41}N_8O_4$: 721.33; found 721.31; HRMS: Anal. Calcd. for $[M+H]^+$ $C_{42}H_{41}N_8O_4$: 721.3251; found 721.3247
68		1.91 minutes (Cond. II); >98%; LC/MS: Anal. Calcd. for $[M+H]^+$ $C_{42}H_{41}N_8O_4$: 721.33; found 721.31; HRMS: Anal. Calcd. for $[M+H]^+$ $C_{42}H_{41}N_8O_4$: 721.3251; found 721.3226
69		1.89 minutes (Cond. II); >98%; LC/MS: Anal. Calcd. for $[M+H]^+$ $C_{42}H_{41}N_8O_4$: 721.33; found 721.29; HRMS: Anal. Calcd. for $[M+H]^+$ $C_{42}H_{41}N_8O_4$: 721.3251; found 721.3251
70	 **cap-11**	1.84 minutes (Cond. II); >98%; LC/MS: Anal. Calcd. for $[M+H]^+$ $C_{42}H_{46}FN_8O_4$: 745.36; found 745.27; HRMS: Anal. Calcd. for $[M+H]^+$ $C_{42}H_{46}FN_8O_4$: 745.3626; found 745.3658
71		1.97 minutes (Cond. II); >98%; LC/MS: Anal. Calcd. for $[M+H]^+$ $C_{40}H_{39}N_8O_5$: 711.30; found 711.27
72		1.95 minutes (Cond. II); >98%; LC/MS: Anal. Calcd. for $[M+H]^+$ $C_{40}H_{39}N_8O_5$: 711.30; found 711.27; HRMS: Anal. Calcd. for $[M+H]^+$ $C_{40}H_{39}N_8O_5$: 711.3043; found 711.3078
73		1.92 minutes (Cond. II); >98%; LC/MS: Anal. Calcd. for $[M+H]^+$ $C_{40}H_{43}N_8O_5$: 715.34; found 715.40

74		1.91 minutes (Cond. II); >98%; LC/MS: Anal. Calcd. for $[M+H]^+$ $C_{41}H_{44}N_7O_5$: 714.34; found 714.39; HRMS: Anal. Calcd. for $[M+H]^+$ $C_{41}H_{44}N_7O_5$: 714.3404; found 714.3433
75	 **cap-12**	1.94 minutes (Cond. II); >98%; LC/MS: Anal. Calcd. for $[M+H]^+$ $C_{41}H_{45}N_8O_6$: 745.35 found 745.34; HRMS: Anal. Calcd. for $[M+H]^+$ $C_{41}H_{45}N_8O_6$: 745.3462; found 745.3486
76		1.80 minutes (Cond. II); >98%; LC/MS: Anal. Calcd. for $[M+H]^+$ $C_{41}H_{47}N_8O_4$ 715.37; found 715.35 ; HRMS: Anal. Calcd. for $[M+H]^+$ $C_{41}H_{47}N_8O_4$ 715.3720; found 715.3737
77		1.97 minutes (Cond. II); >98%; LC/MS: Anal. Calcd. for $[M+H]^+$ $C_{38}H_{40}N_7O_5$: 674.31; found 674.66; HRMS: Anal. Calcd. for $[M+H]^+$ $C_{38}H_{40}N_7O_5$: 674.3091; found 674.3110
78		1.95 minutes (Cond. II); >98%; LC/MS: Anal. Calcd. for $[M+H]^+$ $C_{41}H_{45}N_8O_5$: 729.35; found 729.40; HRMS: Anal. Calcd. for $[M+H]^+$ $C_{41}H_{45}N_8O_5$: 729.3513; found 729.3502
79		1.80 minutes (Cond. II); >98%; LC/MS: Anal. Calcd. for $[M+H]^+$ $C_{41}H_{44}FN_8O_4$: 731.84; found 731.26
80		1.84 minutes (Cond. II); >98%; LC/MS: Anal. Calcd. for $[M+H]^+$ $C_{41}H_{45}N_8O_4$: 713.36; found 713.36; HRMS: Anal. Calcd. for $[M+H]^+$ $C_{41}H_{45}N_8O_4$: 713.3564; found 713.3563
81		1.88 minutes (Cond. II); >98%; LC/MS: Anal. Calcd. for $[M+H]^+$ $C_{41}H_{43}F_2N_8O_4$: 749.34; found 749.31; HRMS: Anal. Calcd. for $[M+H]^+$ $C_{41}H_{43}F_2N_8O_4$: 749.3375; found 749.3390

82		1.83 minutes (Cond. II); >98%; LC/MS: Anal. Calcd. for $[M+H]^+$ $C_{41}H_{44}FN_8O_4$: 731.35; found 731.37; HRMS: Anal. Calcd. for $[M+H]^+$ $C_{41}H_{44}FN_8O_4$: 731.3470; found 731.3502
83		1.82 minutes (Cond. II); >98%; LC/MS: Anal. Calcd. for $[M+H]^+$ $C_{42}H_{45}N_8O_4$: 725.36; found 725.39; HRMS: Anal. Calcd. for $[M+H]^+$ $C_{42}H_{45}N_8O_4$: 725.3564; found 725.3574
84		1.82 minutes (Cond. II); >98%; LC/MS: Anal. Calcd. for $[M+H]^+$ $C_{39}H_{43}N_8O_4$: 687.34; found 687.32; HRMS: Anal. Calcd. for $[M+H]^+$ $C_{39}H_{43}N_8O_4$: 687.3407; found 687.3435
84-1	 **cap-14**	^{1}HNMR (400 MHz, CD_3OD) δ 7.90-7.85 (m, 9H), 7.81-7.79 (m, 1H), 7.63-7.57 (m, 5H), 7.45-7.32 (m, 6H), 5.51 (s, 1H), 5.45 (s, 1H), 5.33-5.29 (m, 2H), 4.06-4.01 (m, 2H), 3.63 (d, J = 4.04 Hz, 3H), 3.59-3.50 (m, 2H), 3.19-3.12 (m, 1H), 3.07-3.01 (m, 1H), 2.93-2.76 (m, 2H), 2.57-2.51 (m, 1H), 2.40-2.31 (m, 2H), 2.22-2.06 (m, 4H), 2.00-1.90 (m, 3H), 1.84-1.64 (m, 4H), 1.52-1.43 (m, 2H); LCMS: Anal. Calcd. for $C_{49}H_{52}N_8O_4$: 816; found: 817 $(M+H)^+$.
84-2		^{1}HNMR (400 MHz, CD_3OD) δ 7.89-7.85 (m, 8H), 7.81-7.73 (2H), 7.67-7.65 (m, 1H), 7.45-7.26 (m, 7H), 7.13-7.08 (m, 1H), 6.94-6.89 (m, 0.5H), 6.72-6.67 (0.5H), 6.09-6.07 (m, 0.4H), 5.51 (s, 1H), 5.32-5.25 (m, 1.6H), 4.08-3.95 (m, 2H), 3.85-3.79 (1H), 3.64-3.63 (m, 3H), 3.56-3.49 (1H), 3.09-3.03 (m, 1H), 2.59-2.50 (m, 1H), 2.42-2.33 (m, 2H), 2.21-2.00 (m, 6H), 1.82-1.74 (m, 1H), 1.66 (d, J = 4.55 Hz, 3H); LCMS: Anal. Calcd. for $C_{45}H_{46}FN_7O_3$: 781; found: 782 $(M+H)^+$.

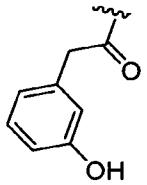
84-3		LCMS: Anal. Calcd. for $C_{41}H_{42}N_8O_5$: 726; found: 727 $(M+H)^+$.
84-4		LCMS: Anal. Calcd. for $C_{50}H_{54}N_8O_5$: 846; found: 847 $(M+H)^+$.
cap-15		
84-5		LCMS: Anal. Calcd. for $C_{45}H_{50}N_8O_6S$: 830; found: 831 $(M+H)^+$.
84-6		LCMS: Anal. Calcd. for $C_{47}H_{54}FN_8O_6$: 826; found: 827 $(M+H)^+$.
84-7		LCMS: Anal. Calcd. for $C_{45}H_{44}FN_8O_5$: 776; found: 777 $(M+H)^+$.
84-8		LCMS: Anal. Calcd. for $C_{48}H_{51}N_9O_4$: 817; found: 818 $(M+H)^+$.
84-9		LCMS: Anal. Calcd. for $C_{47}H_{43}N_7O_4S$: 801; found: 802 $(M+H)^+$.
84-10		LCMS: Anal. Calcd. for $C_{45}H_{41}N_9O_4S$: 803; found: 804 $(M+H)^+$.
84-11		LCMS: Anal. Calcd. for $C_{46}H_{42}N_8O_4S$: 802; found: 803 $(M+H)^+$.
84-12		LCMS: Anal. Calcd. for $C_{48}H_{56}N_8O_6$: 840; found: 841 $(M+H)^+$.

84-13



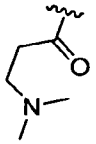
LCMS: Anal. Calcd. for $C_{42}H_{48}N_8O_4$: 728; found: 729 $(M+H)^+$.

84-14



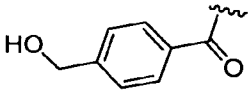
LCMS: Anal. Calcd. for $C_{44}H_{43}N_7O_5$: 749; found: 750 $(M+H)^+$.

84-15



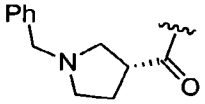
LCMS: Anal. Calcd. for $C_{41}H_{46}N_8O_4$: 714; found: 715 $(M+H)^+$.

84-16



LCMS: Anal. Calcd. for $C_{44}H_{43}N_7O_5$: 749; found: 750 $(M+H)^+$.

84-17



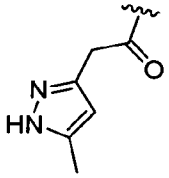
LCMS: Anal. Calcd. for $C_{48}H_{50}N_8O_4$: 802; found: 803 $(M+H)^+$.

84-18



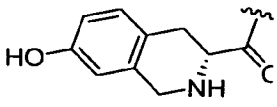
LCMS: Anal. Calcd. for $C_{47}H_{54}N_8O_6$: 826; found: 827 $(M+H)^+$.

84-19



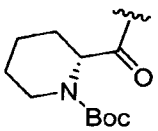
LCMS: Anal. Calcd. for $C_{42}H_{43}N_9O_4$: 737; found: 738 $(M+H)^+$.

84-20



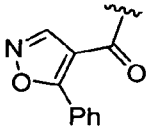
LCMS: Anal. Calcd. for $C_{46}H_{46}N_8O_5$: 790; found: 791 $(M+H)^+$.

84-21

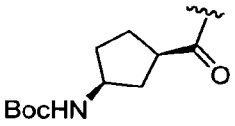
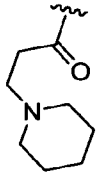
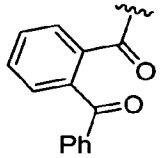
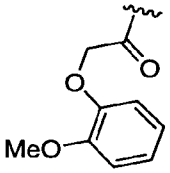
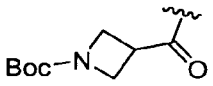
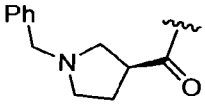
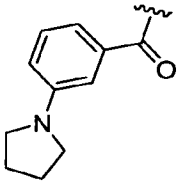
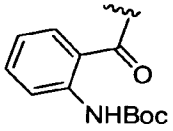
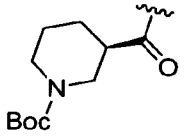
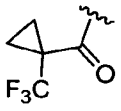


LCMS: Anal. Calcd. for $C_{47}H_{54}N_8O_6$: 826; found: 827 $(M+H)^+$.

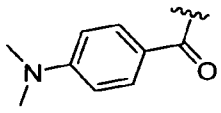
84-22



LCMS: Anal. Calcd. for $C_{46}H_{42}N_8O_5$: 786; found: 787 $(M+H)^+$.

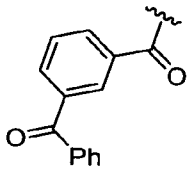
84-23		LCMS: Anal. Calcd. for $C_{47}H_{54}N_8O_6$: 826; found: 827 $(M+H)^+$.
84-24		LCMS: Anal. Calcd. for $C_{44}H_{50}N_8O_4$: 754; found: 755 $(M+H)^+$.
84-25		LCMS: Anal. Calcd. for $C_{50}H_{45}N_7O_5$: 823; found: 824 $(M+H)^+$.
84-26		LCMS: Anal. Calcd. for $C_{45}H_{45}N_7O_6$: 779; found: 780 $(M+H)^+$.
84-27		LCMS: Anal. Calcd. for $C_{45}H_{50}N_8O_6$: 798; found: 799 $(M+H)^+$.
84-28		LCMS: Anal. Calcd. for $C_{48}H_{50}N_8O_4$: 802; found: 803 $(M+H)^+$.
84-29		LCMS: Anal. Calcd. for $C_{47}H_{48}N_8O_4$: 788; found: 789 $(M+H)^+$.
84-30		LCMS: Anal. Calcd. for $C_{48}H_{50}N_8O_6$: 834; found: 835 $(M+H)^+$.
84-31		LCMS: Anal. Calcd. for $C_{47}H_{54}N_8O_6$: 826; found: 827 $(M+H)^+$.
84-32		LCMS: Anal. Calcd. for $C_{41}H_{40}F_3N_7O_4$: 751; found: 752 $(M+H)^+$.

84-33



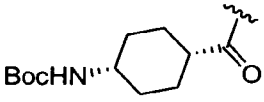
LCMS: Anal. Calcd. for $C_{45}H_{46}N_8O_4$: 762; found: 763 $(M+H)^+$.

84-34



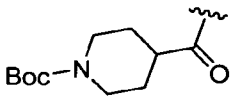
LCMS: Anal. Calcd. for $C_{50}H_{45}N_7O_5$: 823; found: 824 $(M+H)^+$.

84-35



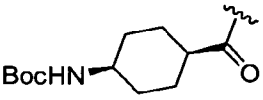
LCMS: Anal. Calcd. for $C_{48}H_{56}N_8O_6$: 840; found: 841 $(M+H)^+$.

84-36



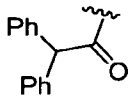
LCMS: Anal. Calcd. for $C_{47}H_{54}N_8O_6$: 826; found: 827 $(M+H)^+$.

84-37



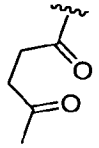
LCMS: Anal. Calcd. for $C_{48}H_{56}N_8O_6$: 840; found: 841 $(M+H)^+$.

84-38



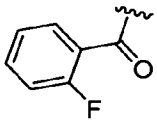
LCMS: Anal. Calcd. for $C_{50}H_{47}N_7O_4$: 809; found: 810 $(M+H)^+$.

84-39



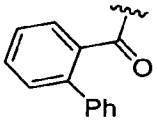
LCMS: Anal. Calcd. for $C_{41}H_{43}N_7O_5$: 713; found: 714 $(M+H)^+$.

84-40



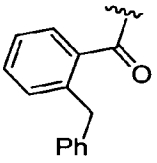
LCMS: Anal. Calcd. for $C_{43}H_{40}FN_7O_4$: 737; found: 738 $(M+H)^+$.

84-41



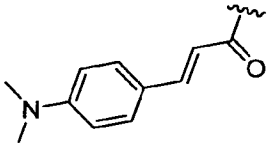
LCMS: Anal. Calcd. for $C_{49}H_{45}N_7O_4$: 795; found: 796 $(M+H)^+$.

84-42



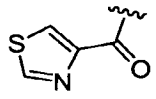
LCMS: Anal. Calcd. for $C_{50}H_{47}N_7O_4$: 809; found: 810 $(M+H)^+$.

84-43



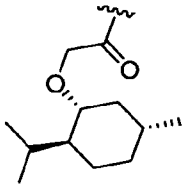
LCMS: Anal. Calcd. for $C_{47}H_{48}N_8O_4$: 788; found: 789 $(M+H)^+$.

84-44



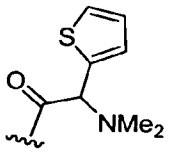
LCMS: Anal. Calcd. for $C_{40}H_{38}N_8O_4S$: 726; found: 727 $(M+H)^+$.

84-45



LCMS: Anal. Calcd. for $C_{48}H_{57}N_7O_5$: 811; found: 812 $(M+H)^+$.

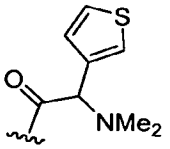
84-46



LCMS: Anal. Calcd. for $C_{44}H_{46}N_8O_4S$: 782; found: 782 $(M+H)^+$.

cap-32

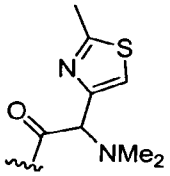
84-47



LCMS: Anal. Calcd. for $C_{44}H_{46}N_8O_4S$: 782; found: 782 $(M+H)^+$.

cap-33

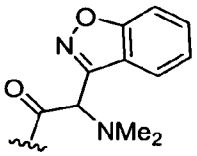
84-48



LCMS: Anal. Calcd. for $C_{44}H_{47}N_9O_4S$: 797; found: 798 $(M+H)^+$.

cap-31

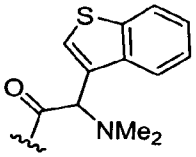
84-49



LCMS: Anal. Calcd. for $C_{47}H_{47}N_9O_5$: 817; found: 818 $(M+H)^+$.

cap-34

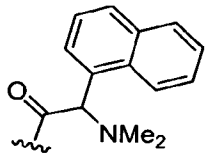
84-50



LCMS: Anal. Calcd. for $C_{48}H_{48}N_8O_4S$: 832; found: 833 $(M+H)^+$.

cap-35

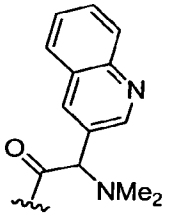
84-51



LCMS: Anal. Calcd. for $C_{50}H_{50}N_8O_4$: 826; found: 827 $(M+H)^+$.

cap-23

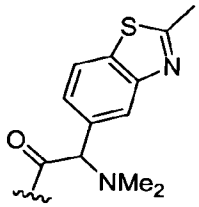
84-52



LCMS: Anal. Calcd. for $C_{49}H_{49}N_9O_4$: 827; found: 828 $(M+H)^+$.

cap-37

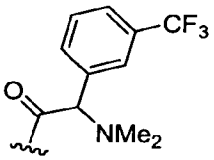
84-53



LCMS: Anal. Calcd. for $C_{48}H_{49}N_9O_4S$: 847; found: 848 $(M+H)^+$.

cap-36

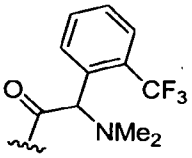
84-54



LCMS: Anal. Calcd. for $C_{47}H_{47}F_3N_8O_4$: 844; found: 845 $(M+H)^+$.

cap-24

84-55



LCMS: Anal. Calcd. for $C_{47}H_{47}F_3N_8O_4$: 844; found: 845 $(M+H)^+$.

cap-25

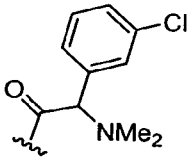
84-56



LCMS: Anal. Calcd. for $C_{46}H_{47}ClN_8O_4$: 810; found: 811 $(M+H)^+$.

cap-29

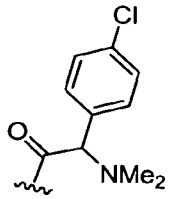
84-57



LCMS: Anal. Calcd. for $C_{46}H_{47}ClN_8O_4$: 810; found: 811 $(M+H)^+$.

cap-28

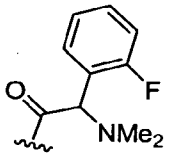
84-58



LCMS: Anal. Calcd. for $C_{46}H_{47}ClN_8O_4$: 810; found: 811 $(M+H)^+$.

cap-30

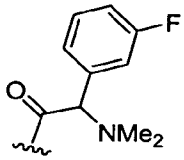
84-59



LCMS: Anal. Calcd. for $C_{46}H_{47}FN_8O_4$: 794; found: 795 $(M+H)^+$.

cap-26

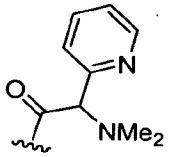
84-60



LCMS: Anal. Calcd. for $C_{46}H_{47}FN_8O_4$: 794; found: 795 $(M+H)^+$.

cap-27

84-61



LCMS: Anal. Calcd. for $C_{45}H_{47}N_9O_4$: 777; found: 778 $(M+H)^+$.

cap-20

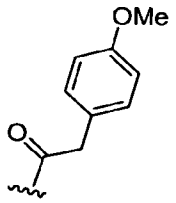
84-62



LCMS: Anal. Calcd. for $C_{45}H_{47}N_9O_4$: 777; found: 778 $(M+H)^+$.

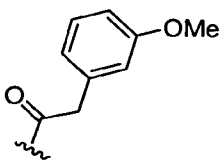
cap-19

84-63



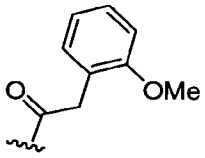
LCMS: Anal. Calcd. for $C_{45}H_{45}N_7O_5$: 763; found: 764 $(M+H)^+$.

84-64



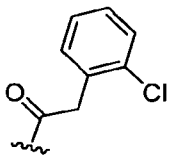
LCMS: Anal. Calcd. for $C_{45}H_{45}N_7O_5$: 763; found: 764 $(M+H)^+$.

84-65



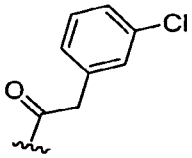
LCMS: Anal. Calcd. for $C_{45}H_{45}N_7O_5$: 763; found: 764 $(M+H)^+$.

84-66



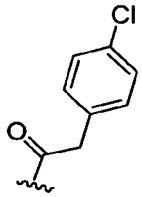
LCMS: Anal. Calcd. for $C_{44}H_{42}ClN_7O_4$: 767; found: 768 $(M+H)^+$.

84-67



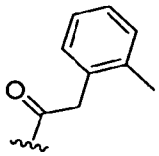
LCMS: Anal. Calcd. for $C_{44}H_{42}ClN_7O_4$: 767; found: 768 $(M+H)^+$.

84-68



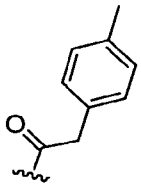
LCMS: Anal. Calcd. for $C_{44}H_{42}ClN_7O_4$: 767; found: 768 $(M+H)^+$.

84-69



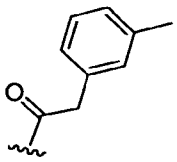
LCMS: Anal. Calcd. for $C_{45}H_{45}N_7O_4$: 747; found: 748 $(M+H)^+$.

84-70



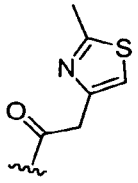
LCMS: Anal. Calcd. for $C_{45}H_{45}N_7O_4$: 747; found: 748 $(M+H)^+$.

84-71



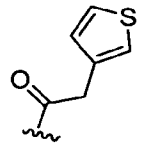
LCMS: Anal. Calcd. for $C_{45}H_{45}N_7O_4$: 747; found: 748 $(M+H)^+$.

84-72



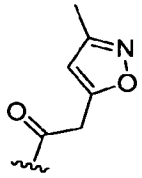
LCMS: Anal. Calcd. for $C_{42}H_{42}N_8O_4S$: 754; found: 755 $(M+H)^+$.

84-73



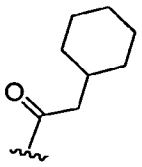
LCMS: Anal. Calcd. for $C_{42}H_{41}N_7O_4S$: 739; found: 740 $(M+H)^+$.

84-74



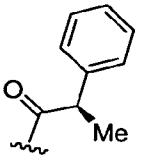
LCMS: Anal. Calcd. for $C_{42}H_{42}N_8O_5$: 738; found: 739 $(M+H)^+$.

84-75



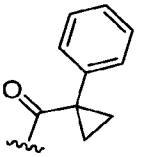
LCMS: Anal. Calcd. for $C_{44}H_{49}N_7O_4$: 739; found: 740 $(M+H)^+$.

84-76



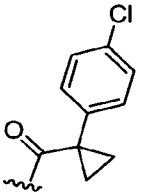
LCMS: Anal. Calcd. for $C_{45}H_{45}N_7O_4$: 747; found: 748 $(M+H)^+$.

84-77



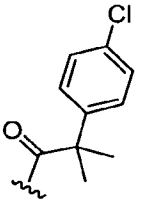
LCMS: Anal. Calcd. for $C_{46}H_{45}N_7O_4$: 759; found: 760 $(M+H)^+$.

84-78



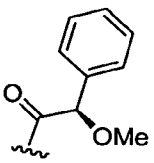
LCMS: Anal. Calcd. for $C_{46}H_{44}ClN_7O_4$: 793; found: 794 $(M+H)^+$.

84-79



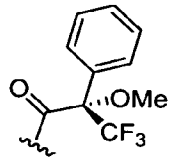
LCMS: Anal. Calcd. for $C_{46}H_{46}ClN_7O_4$: 795; found: 796 $(M+H)^+$.

84-80



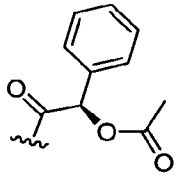
LCMS: Anal. Calcd. for $C_{45}H_{45}N_7O_5$: 763; found: 764 $(M+H)^+$.

84-81



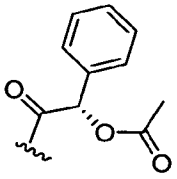
LCMS: Anal. Calcd. for $C_{46}H_{44}F_3N_7O_5$: 831; found: 832 $(M+H)^+$.

84-82

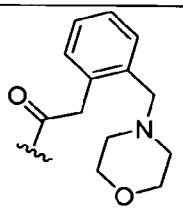
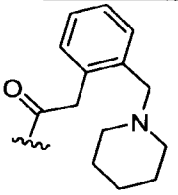
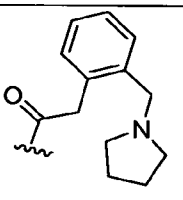


LCMS: Anal. Calcd. for $C_{46}H_{45}N_7O_6$: 791; found: 792 $(M+H)^+$.

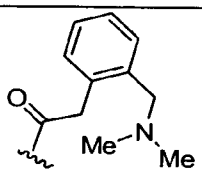
84-83



LCMS: Anal. Calcd. for $C_{46}H_{45}N_7O_6$: 791; found: 792 $(M+H)^+$.

84-84	 **cap-41**	LCMS: Anal. Calcd. for $C_{49}H_{52}N_8O_5$: 832; found: 833 $(M+H)^+$.
84-85	 **cap-42**	LCMS: Anal. Calcd. for $C_{50}H_{54}N_8O_4$: 830; found: 831 $(M+H)^+$.
84-86	 **cap-43**	LCMS: Anal. Calcd. for $C_{49}H_{52}N_8O_4$: 816; found: 816 $(M+H)^+$.

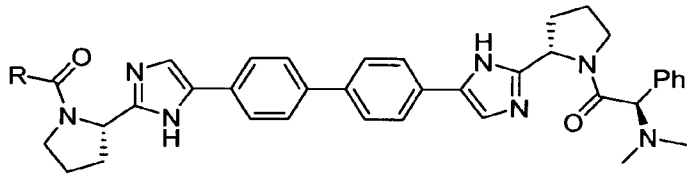
84-87



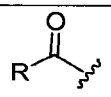
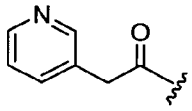
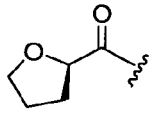
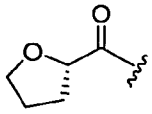
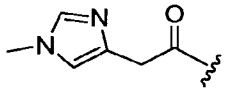
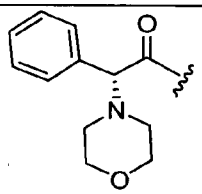
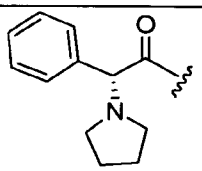
cap-44

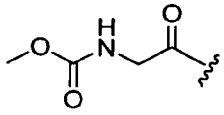
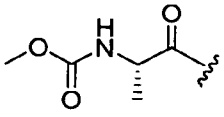
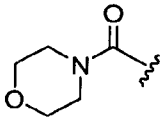
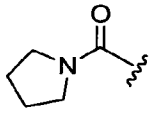
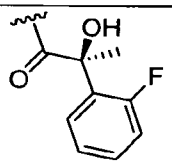
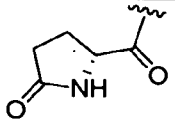
LCMS: Anal. Calcd. for $C_{47}H_{50}N_8O_4$: 790; found: 791 $(M+H)^+$.

Example 85-94

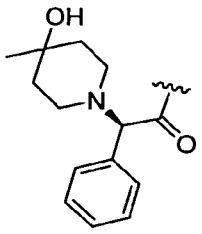


prepared from cap-1 and the appropriate cap/amino acid as indicated below

Example		Retention time (LC-Condition); homogeneity index MS data
85		1.64 minutes (Cond. II); >98%; LC/MS: Anal. Calcd. for $[M+H]^+$ $C_{43}H_{45}N_8O_2$: 705.37; found 705.43; HRMS: Anal. Calcd. for $[M+H]^+$ $C_{43}H_{45}N_8O_2$: 705.3665; found 705.3675
86		1.73 minutes (Cond. II); >98%; LC/MS: Anal. Calcd. for $[M+H]^+$ $C_{41}H_{46}N_7O_3$: 684.37; found 684.44; HRMS: Anal. Calcd. for $[M+H]^+$ $C_{41}H_{46}N_7O_3$: 684.3662; found 684.3671
87		1.12 minutes (Cond. I); >98%; LC/MS: Anal. Calcd. for $[M+H]^+$ $C_{41}H_{46}N_7O_3$: 684.37; found 684.68; HRMS: Anal. Calcd. for $[M+H]^+$ $C_{41}H_{46}N_7O_3$: 684.3662; found 684.3692
88		1.66 minutes (Cond. II); >98%; LC/MS: Anal. Calcd. for $[M+H]^+$ $C_{42}H_{46}N_9O_2$: 708.38; found 708.36
89	 cap-6	1.70 minutes (Cond. II); >98%; LC/MS: Anal. Calcd. for $[M+H]^+$ $C_{40}H_{45}N_8O_4$: 701.36; found 701.34; HRMS: Anal. Calcd. for $[M+H]^+$ $C_{40}H_{45}N_8O_4$: 701.3564; found 701.3576
90		1.80 minutes (Cond. II); >98%; LC/MS: Anal. Calcd. for $[M+H]^+$ $C_{48}H_{53}N_8O_2$: 773.43; found 773.42; HRMS: Anal. Calcd. for $[M+H]^+$ $C_{48}H_{53}N_6O_2$: 773.4291; found 773.4309

	cap-5	
91		1.66 minutes (Cond. II); >98%; LC/MS: Anal. Calcd. for $[M+H]^+$ $C_{42}H_{46}N_9O_2$: 708.38; found 708.36; HRMS: Anal. Calcd. for $[M+H]^+$ $C_{42}H_{46}N_9O_2$: 708.3744; found 708.3770
92	 **cap-12**	1.73 minutes (Cond. II); >98%; LC/MS: Anal. Calcd. for $[M+H]^+$ $C_{41}H_{47}N_8O_4$: 715.37; found 715.41; HRMS: Anal. Calcd. for $[M+H]^+$ $C_{41}H_{47}N_8O_4$: 715.3720; found 715.3729
93		1.76 minutes (Cond. II); >98%; LC/MS: Anal. Calcd. for $[M+H]^+$ $C_{41}H_{47}N_8O_3$: 699.38; found 699.45; HRMS: Anal. Calcd. for $[M+H]^+$ $C_{41}H_{47}N_8O_3$: 699.3771; found 699.3803
94		1.86 minutes (Cond. II); >98%; LC/MS: Anal. Calcd. for $[M+H]^+$ $C_{41}H_{47}N_8O_2$: 683.38; found 683.46; HRMS: Anal. Calcd. for $[M+H]^+$ $C_{41}H_{47}N_8O_2$: 683.3822; found 683.3835
94-1		^{1}HNMR (400 MHz, CD_3OD) δ 7.90-7.84 (m, 9H), 7.79-7.73 (m, 2H), 7.67-7.65 (m, 1H), 7.63-7.52 (m, 5H), 7.39-7.36 (m, 1H), 7.30-7.26 (m, 1H), 7.13-7.08 (m, 1H), 6.93-6.88 (m, 0.5H), 6.72-6.67 (m, 0.5H), 5.51 (s, 0.2H), 5.46 (s, 0.8H), 5.33-5.30 (m, 1H), 5.28-5.24 (m, 1H), 4.05-3.94 (m, 2H), 3.84-3.73 (m, 1H), 3.69-3.55 (m, 1H), 3.21-3.04 (m, 2H), 2.79 (br s, 6H), 2.39-2.33 (m, 2H), 2.21-1.93 (m, 5H), 1.65 (d, J = 4.55 Hz, 3H).; LCMS: Anal. Calcd. for $C_{45}H_{46}FN_7O_3$: 751; found: 752 $(M+H)^+$.
94-2		LCMS: Anal. Calcd. for $C_{41}H_{44}N_8O_3$: 696; found: 697 $(M+H)^+$.

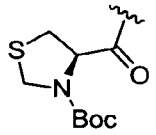
94-3



LCMS: Anal. Calcd. for $C_{50}H_{56}N_8O_3$: 816; found: 817 $(M+H)^+$.

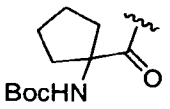
cap-15

94-4



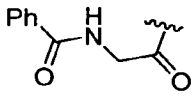
LCMS: Anal. Calcd. for $C_{45}H_{52}N_8O_4S$: 800; found: 801 $(M+H)^+$.

94-5



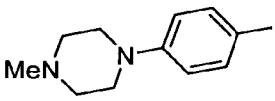
LCMS: Anal. Calcd. for $C_{47}H_{56}FN_8O_4$: 796; found: 797 $(M+H)^+$.

94-6



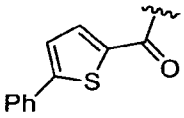
LCMS: Anal. Calcd. for $C_{45}H_{46}FN_8O_3$: 746; found: 747 $(M+H)^+$.

94-7



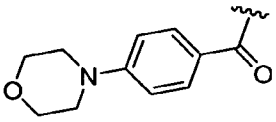
LCMS: Anal. Calcd. for $C_{48}H_{53}N_9O_2$: 787; found: 788 $(M+H)^+$.

94-8



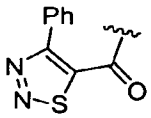
LCMS: Anal. Calcd. for $C_{47}H_{45}N_7O_2S$: 771; found: 772 $(M+H)^+$.

94-9



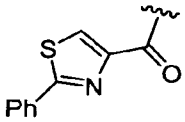
LCMS: Anal. Calcd. for $C_{47}H_{50}N_8O_3$: 774; found: 775 $(M+H)^+$.

94-10



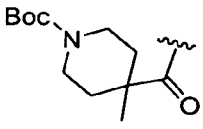
LCMS: Anal. Calcd. for $C_{45}H_{43}N_9O_2S$: 773; found: 774 $(M+H)^+$.

94-11



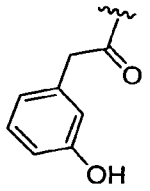
LCMS: Anal. Calcd. for $C_{46}H_{44}N_8O_2S$: 772; found: 773 $(M+H)^+$.

94-12



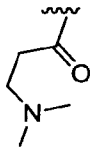
LCMS: Anal. Calcd. for $C_{48}H_{58}N_8O_4$: 810; found: 811 $(M+H)^+$.

94-13



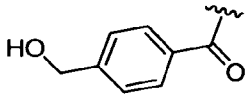
LCMS: Anal. Calcd. for $C_{44}H_{45}N_7O_3$: 719; found: 720 $(M+H)^+$.

94-14



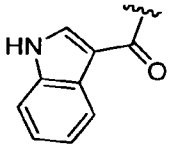
LCMS: Anal. Calcd. for $C_{41}H_{48}N_8O_2$: 684; found: 685 $(M+H)^+$.

94-15



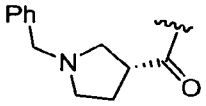
LCMS: Anal. Calcd. for $C_{44}H_{45}N_7O_3$: 719; found: 720 $(M+H)^+$.

94-16



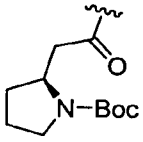
LCMS: Anal. Calcd. for $C_{45}H_{44}N_8O_2$: 728; found: 729 $(M+H)^+$.

94-17



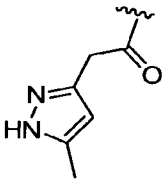
LCMS: Anal. Calcd. for $C_{48}H_{52}N_8O_2$: 772; found: 773 $(M+H)^+$.

94-18



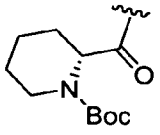
LCMS: Anal. Calcd. for $C_{47}H_{56}N_8O_4$: 796; found: 797 $(M+H)^+$.

94-19



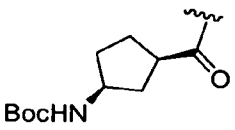
LCMS: Anal. Calcd. for $C_{42}H_{45}N_9O_2$: 707; found: 708 $(M+H)^+$.

94-20



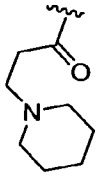
LCMS: Anal. Calcd. for $C_{47}H_{56}N_8O_4$: 796; found: 797 $(M+H)^+$.

94-21



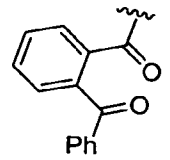
LCMS: Anal. Calcd. for $C_{47}H_{56}N_8O_4$: 796; found: 797 $(M+H)^+$.

94-22



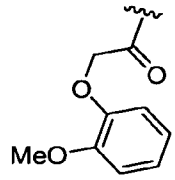
LCMS: Anal. Calcd. for $C_{44}H_{52}N_8O_2$: 724; found: 725 $(M+H)^+$.

94-23



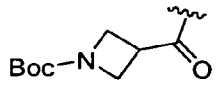
LCMS: Anal. Calcd. for $C_{50}H_{47}N_7O_3$: 793; found: 794 $(M+H)^+$.

94-24



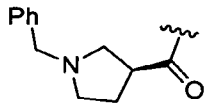
LCMS: Anal. Calcd. for $C_{45}H_{47}N_7O_4$: 749; found: 750 $(M+H)^+$.

94-25



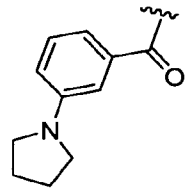
LCMS: Anal. Calcd. for $C_{45}H_{52}N_8O_4$: 768; found: 769 $(M+H)^+$.

94-26



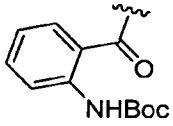
LCMS: Anal. Calcd. for $C_{48}H_{52}N_8O_2$: 772; found: 773 $(M+H)^+$.

94-27



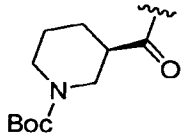
LCMS: Anal. Calcd. for $C_{47}H_{50}N_8O_2$: 758; found: 759 $(M+H)^+$.

94-28



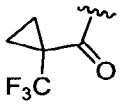
LCMS: Anal. Calcd. for $C_{48}H_{52}N_8O_4$: 804; found: 805 $(M+H)^+$.

94-29



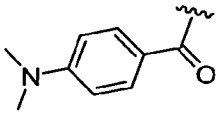
LCMS: Anal. Calcd. for $C_{47}H_{56}N_8O_4$: 796; found: 797 $(M+H)^+$.

94-30



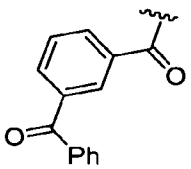
LCMS: Anal. Calcd. for $C_{41}H_{42}F_3N_7O_2$: 721; found: 722 $(M+H)^+$.

94-31



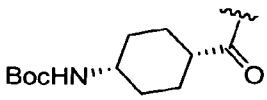
LCMS: Anal. Calcd. for $C_{45}H_{48}N_8O_2$: 732; found: 733 $(M+H)^+$.

94-32



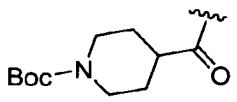
LCMS: Anal. Calcd. for $C_{50}H_{47}N_7O_3$: 793; found: 794 $(M+H)^+$.

94-33



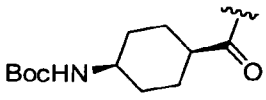
LCMS: Anal. Calcd. for $C_{48}H_{58}N_8O_4$: 810; found: 811 $(M+H)^+$.

94-34



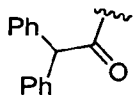
LCMS: Anal. Calcd. for $C_{47}H_{56}N_8O_4$: 796; found: 797 $(M+H)^+$.

94-35



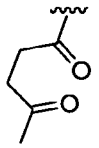
LCMS: Anal. Calcd. for $C_{48}H_{58}N_8O_4$: 810; found: 811 $(M+H)^+$.

94-36



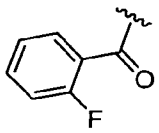
LCMS: Anal. Calcd. for $C_{50}H_{49}N_7O_2$: 779; found: 780 $(M+H)^+$.

94-37



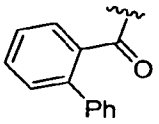
LCMS: Anal. Calcd. for $C_{41}H_{45}N_7O_3$: 683; found: 684 $(M+H)^+$.

94-38



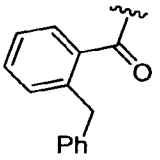
LCMS: Anal. Calcd. for $C_{43}H_{42}FN_7O_2$: 707; found: 708 $(M+H)^+$.

94-39



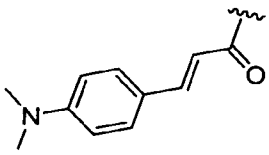
LCMS: Anal. Calcd. for $C_{49}H_{47}N_7O_2$: 765; found: 766 $(M+H)^+$.

94-40



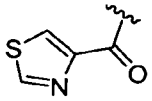
LCMS: Anal. Calcd. for $C_{50}H_{49}N_7O_2$: 779; found: 780 $(M+H)^+$.

94-41



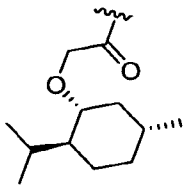
LCMS: Anal. Calcd. for $C_{47}H_{50}N_8O_2$: 758; found: 759 $(M+H)^+$.

94-42

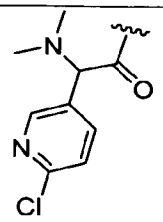
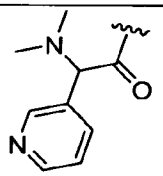
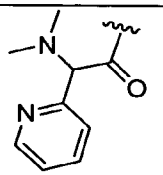
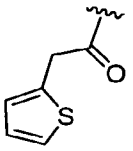
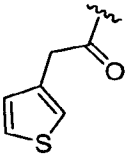
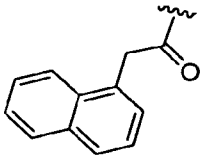
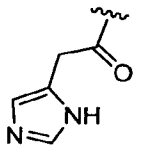
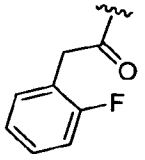


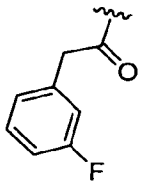
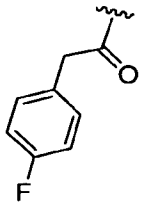
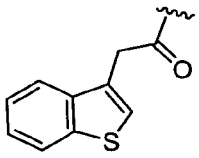
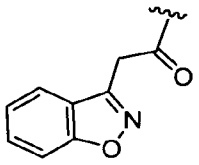
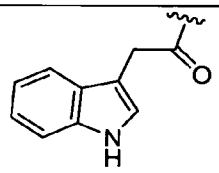
LCMS: Anal. Calcd. for $C_{40}H_{40}N_8O_2S$: 696; found: 697 $(M+H)^+$.

94-43

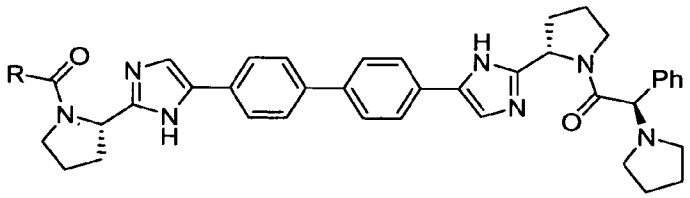


LCMS: Anal. Calcd. for $C_{48}H_{59}N_7O_3$: 781; found: 782 $(M+H)^+$.

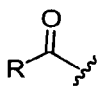
94-44	 **cap-21**	LCMS: Anal. Calcd. for $C_{45}H_{48}ClN_9O_2$: 781; found: 782 $(M+H)^+$.
94-45	 **cap-19**	LCMS: Anal. Calcd. for $C_{45}H_{49}N_9O_2$: 747; found: 748 $(M+H)^+$.
94-46	 **cap-20**	LCMS: Anal. Calcd. for $C_{45}H_{49}N_9O_2$: 747; found: 748 $(M+H)^+$.
94-47		LCMS: Anal. Calcd. for $C_{42}H_{43}N_7O_2S$: 709; found: 710 $(M+H)^+$.
94-48		LCMS: Anal. Calcd. for $C_{42}H_{43}N_7O_2S$: 709; found: 710 $(M+H)^+$.
94-49		LCMS: Anal. Calcd. for $C_{48}H_{47}N_7O_2$: 753; found: 754 $(M+H)^+$.
94-50		LCMS: Anal. Calcd. for $C_{41}H_{43}N_9O_2$: 693; found: 694 $(M+H)^+$.
94-51		LCMS: Anal. Calcd. for $C_{44}H_{44}FN_7O_2$: 721; found: 722 $(M+H)^+$.

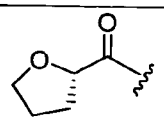
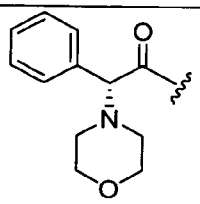
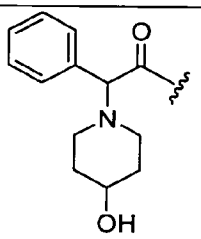
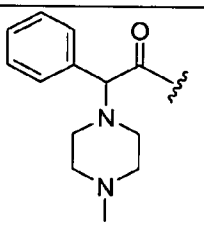
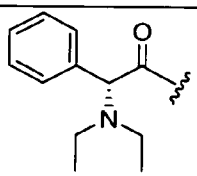
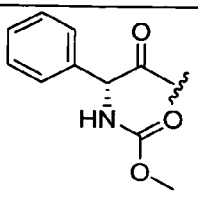
94-52		LCMS: Anal. Calcd. for $C_{44}H_{44}FN_7O_2$: 721; found: 722 $(M+H)^+$.
94-53		LCMS: Anal. Calcd. for $C_{44}H_{44}FN_7O_2$: 721; found: 722 $(M+H)^+$.
94-54		LCMS: Anal. Calcd. for $C_{46}H_{45}N_7O_2S$: 759; found: 760 $(M+H)^+$.
94-55		LCMS: Anal. Calcd. for $C_{45}H_{44}N_8O_3$: 744; found: 745 $(M+H)^+$.
94-56		LCMS: Anal. Calcd. for $C_{46}H_{46}N_8O_2$: 742; found: 743 $(M+H)^+$.

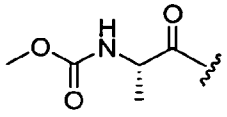
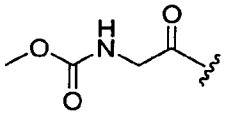
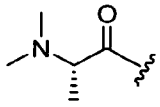
Example 95-103



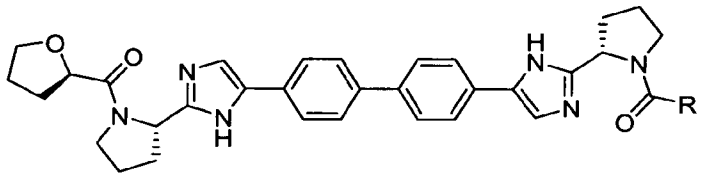
prepared from cap-5 and the appropriate amino acid/cap as indicated below

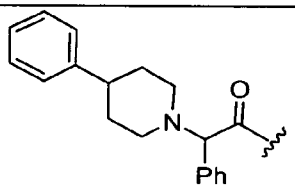
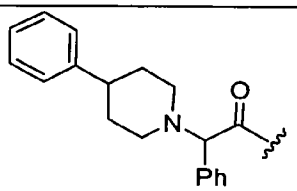
Example		**Retention time (LC-Condition); homogeneity index** **MS data**

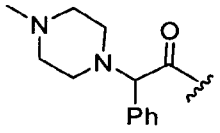
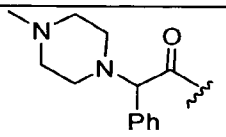
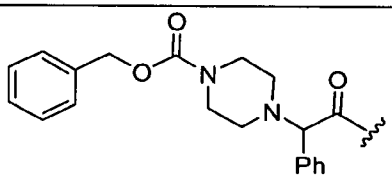
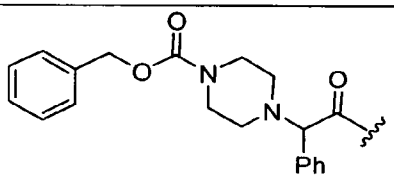
95		1.16 minutes (Cond. I); >98%; LC/MS: Anal. Calcd. for $[M+H]^+$ $C_{43}H_{48}N_7O_3$: 710.38; found 710.60
96	 **cap-6**	1.82 minutes (Cond. II); >98%; LC/MS: Anal. Calcd. for $[M+H]^+$ $C_{50}H_{55}N_8O_3$: 815.44; found 815.45; HRMS: Anal. Calcd. for $[M+H]^+$ $C_{50}H_{55}N_8O_3$: 815.4397; found 815.4395
97	 A single diastereomer **cap-8**	1.79 minutes (Cond. II); >98%; LC/MS: Anal. Calcd. for $[M+H]^+$ $C_{51}H_{57}N_8O_3$: 829.46; found 829.43; HRMS: Anal. Calcd. for $[M+H]^+$ $C_{51}H_{57}N_8O_3$: 829.4554; found 829.4585
98	 A single diastereomer **cap-17c**	1.84 minutes (Cond. II); >98%; LC/MS: Anal. Calcd. for $[M+H]^+$ $C_{51}H_{58}N_9O_2$: 828.47; found 828.45; HRMS: Anal. Calcd. for $[M+H]^+$ $C_{51}H_{58}N_9O_2$: 828.4713; found 828.4722
99	 **cap-2**	1.86 minutes (Cond. II); >98%; LC/MS: Anal. Calcd. for $[M+H]^+$ $C_{50}H_{57}N_8O_2$: 801.46; found 801.44; HRMS: Anal. Calcd. for $[M+H]^+$ $C_{50}H_{57}N_8O_2$: 801.4604; found 801.4595
100		1.93 minutes (Cond. II); LC/MS: Anal. Calcd. for $[M+H]^+$ $C_{48}H_{51}N_8O_4$: 803.40; found 803.47 ; HRMS: Anal. Calcd. for $[M+H]^+$ $C_{48}H_{51}N_8O_4$: 803.4033; found 803.4058

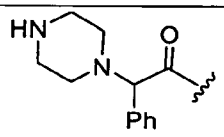
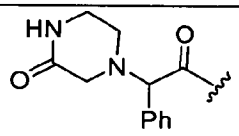
	cap-4	
101	 **cap-12**	1.80 minutes (Cond. II); LC/MS: Anal. Calcd. for $[M+H]^+$ $C_{43}H_{49}N_8O_4$: 741.39; found 741.33; HRMS: Anal. Calcd. for $[M+H]^+$ $C_{43}H_{49}N_8O_4$: 741.3877; found 741.3900
102		1.80 minutes (Cond. II); LC/MS: Anal. Calcd. for $[M+H]^+$ $C_{42}H_{47}N_8O_4$: 727.37; found 727.24; HRMS: Anal. Calcd. for $[M+H]^+$ $C_{42}H_{47}N_8O_4$: 727.3720; found 727.3743
103	 **cap-13**	1.69 minutes (Cond. II); LC/MS: Anal. Calcd. for $[M+H]^+$ $C_{43}H_{51}N_8O_2$: 711.41; found 711.37; HRMS: Anal. Calcd. for $[M+H]^+$ $C_{43}H_{51}N_8O_2$: 711.4135; found 711.4154

Example 103-1 to 103-8

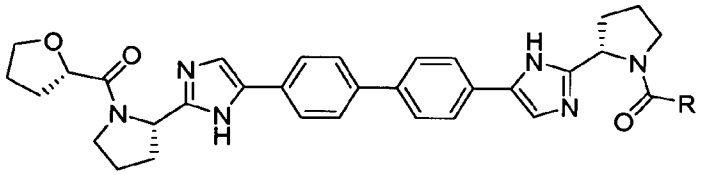


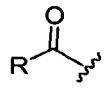
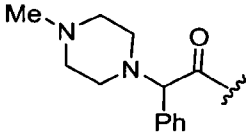
103-1	 Diastereomer 1 **cap-17d**	RT = 4.80 minutes; HPLC Xterra 4.6 X 50 mm, 0 to 100% B over 10 minutes, one minute hold time, A = 90% water, 10% methanol, 0.2% phosphoric acid, B = 10% water, 90% methanol, 0.2% phosphoric acid; LCMS: Anal. Calcd. for: $C_{50}H_{53}N_7O_3$ 800.03 Found: 800.49 $(M+H)^+$
103-2	 Diastereomer 2	RT = 4.59 minutes; HPLC Xterra 4.6 X 50 mm, 0 to 100% B over 10 minutes, one minute hold time, A = 90% water, 10% methanol, 0.2% phosphoric acid, B = 10% water, 90% methanol, 0.2% phosphoric acid;

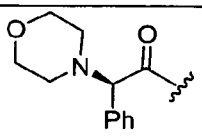
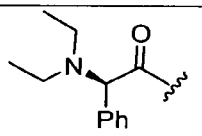
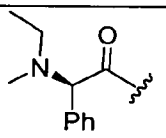
	cap-17d	LCMS: Anal. Calcd. for: $C_{50}H_{53}N_7O_3$ 800.03 Found: 800.48 $(M+H)^+$
103-3	 Diastereomer 1 **cap-17c**	RT = 3.36; HPLC Xterra 4.6 X 50 mm, 0 to 100% B over 10 minutes, one minute hold time, A = 90% water, 10% methanol, 0.2% phosphoric acid, B = 10% water, 90% methanol, 0.2% phosphoric acid; LCMS: Anal. Calcd. for: $C_{44}H_{50}N_8O_3$ 738.94 Found: 739.49 $(M+H)^+$
103-4	 Diastereomer 2 **cap-17c**	RT = 3.47 minutes; HPLC Xterra 4.6 X 50 mm, 0 to 100% B over 10 minutes, one minute hold time, A = 90% water, 10% methanol, 0.2% phosphoric acid, B = 10% water, 90% methanol, 0.2% phosphoric acid; LCMS: Anal. Calcd. for: $C_{44}H_{50}N_8O_3$ 738.94 Found: 739.51 $(M+H)^+$
103-5	 Diastereomer 1 **cap-17a**	RT = 5.00 minutes; HPLC Xterra 4.6 X 50 mm, 0 to 100% B over 10 minutes, one minute hold time, A = 90% water, 10% methanol, 0.2% phosphoric acid, B = 10% water, 90% methanol, 0.2% phosphoric acid; LCMS: Anal. Calcd. for: $C_{51}H_{54}N_8O_5$ 859.05 Found: 859.51 $(M+H)^+$
103-6	 Diastereomer 2 **cap-17a**	RT = 5.10 minutes; HPLC Xterra 4.6 X 50 mm, 0 to 100% B over 10 minutes, one minute hold time, A = 90% water, 10% methanol, 0.2% phosphoric acid, B = 10% water, 90% methanol, 0.2% phosphoric acid; LCMS: Anal. Calcd. for: $C_{51}H_{54}N_8O_5$ 859.05 Found: 859.49 $(M+H)^+$

103-7	 prepared by hydrogenolyzing **103-5**	RT = 3.61 minutes; HPLC Xterra 4.6 X 50 mm, 0 to 100% B over 10 minutes, one minute hold time, A = 90% water, 10% methanol, 0.2% phosphoric acid, B = 10% water, 90% methanol, 0.2% phosphoric acid; LCMS: Anal. Calcd. for: $C_{43}H_{48}N_8O_3$ 724.91 Found: 725.47 $(M+H)^+$
103-8	 **cap-17b**	RT = 3.97; HPLC Xterra 4.6 X 50 mm, 0 to 100% B over 10 minutes, one minute hold time, A = 90% water, 10% methanol, 0.2% phosphoric acid, B = 10% water, 90% methanol, 0.2% phosphoric acid; LCMS: Anal. Calcd. for: $C_{43}H_{46}N_8O_4$ 738.90 Found: 739.56 $(M+H)^+$

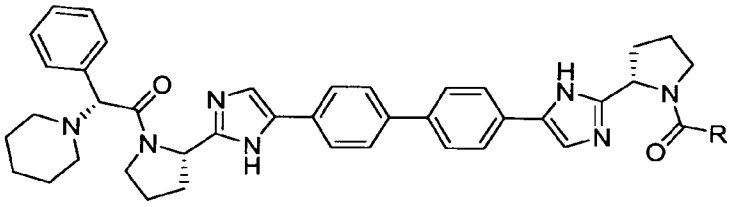
Example 104-107



Example		**Retention time (LC-Condition); homogeneity index MS data**
104	 A single diastereomer **cap-17c**	1.12 minutes (Cond. I); >98%; LC/MS: Anal. Calcd. for $[M+H]^+$ $C_{44}H_{51}N_8O_3$: 739.41; found 739.63; HRMS: Anal. Calcd. for $[M+H]^+$ $C_{44}H_{51}N_8O_3$: 739.4084; found 739.4054

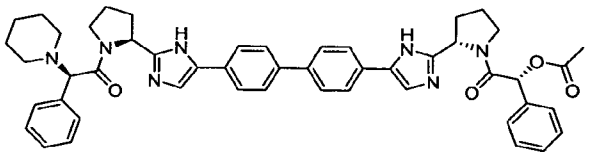
105	 **cap-6**	1.13 minutes (Cond. I); >98%; LC/MS: Anal. Calcd. for $[M+H]^+$ $C_{43}H_{48}N_7O_4$: 726.38; found 726.63; HRMS: Anal. Calcd. for $[M+H]^+$ $C_{43}H_{48}N_7O_4$: 726.3768; found 726.3803
106	 **cap-2**	1.12 minutes (Cond. I); 97%; LC/MS: Anal. Calcd. for $[M+H]^+$ $C_{43}H_{50}N_7O_3$: 712.40; found 712.45; HRMS: Anal. Calcd. for $[M+H]^+$ $C_{43}H_{50}N_7O_3$: 712.3975; found 712.3998
107	 **cap-3**	1.10 minutes (Cond. I); >98%; LC/MS: Anal. Calcd. for $[M+H]^+$ $C_{42}H_{48}N_7O_3$: 698.38; found 698.45; HRMS: Anal. Calcd. for $[M+H]^+$ $C_{42}H_{48}N_7O_3$: 698.3819; 698.3823

Example 107-1 to 107-30



prepared from cap-17 and the appropriate amino acid/cap as indicated below

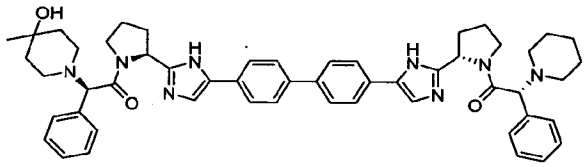
Example 107-1



^{1}HNMR (400 MHz, $CDCl_3$) δ 7.63-7.85 (m, 8H), 7.48- 7.54 (m, 2H), 7.26- 7.46 (m, 7H), 6.94- 7.17 (m, 3H), 6.22 and 6.18 (s, 1H, rotamers, 1:1), 5.99 and 5.68 (s, 1H, rotamers, 1:1), 5.61 and 5.54 (d, J = 7.8 Hz, 1H, rotamers, 1:1), 5.20- 5.23 and 5.10-

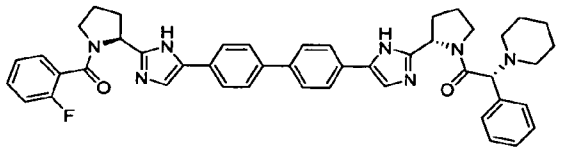
5.13 (m, 1H, rotamers, 1:1), 4.46 and 4.43 (s, 1H, rotamers, 1:1), 3.97-4.06 (m, 1H), 3.89- 3.93 and 3.78-3.84 (m, 1H, rotamers, 1:1), 3.63- 3.72 and 3.46- 3.60 (m, 1H, rotamers, 1:1), 3.23-3.32 (m, 2H), 2.41-2.59 (m, 4H), 2.13-2.26 (m, 2H), 2.11 and 2.10 (s, 3H, rotamers, 1:1), 2.05-2.09 (m, 2H), 1.97-1.98 (m, 1H), 1.82-1.90 (m, 1H), 1.58 (br s, 4H), 1.45 (br s, 2H); LCMS: Anal. Calcd. for $C_{49}H_{51}N_7O_4$: 801; found: 802 $(M+H)^+$.

Example 107-2



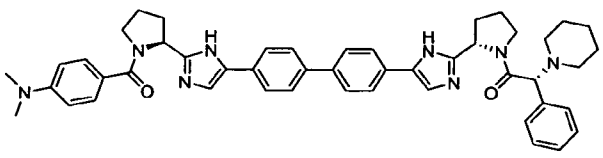
LCMS: Anal. Calcd. for $C_{53}H_{60}N_8O_3$: 856; found: 857 $(M+H)^+$.

Example 107-3

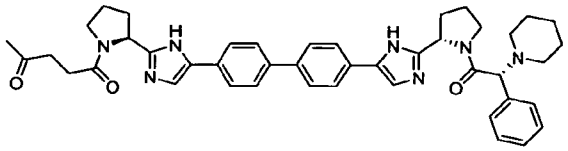
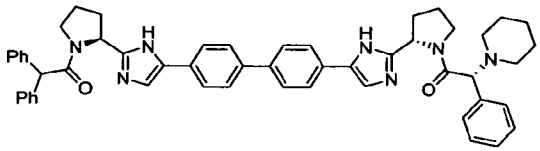
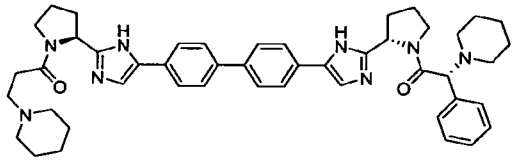
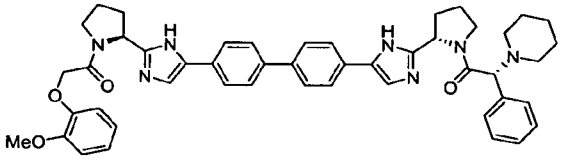
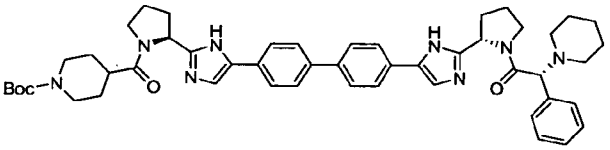
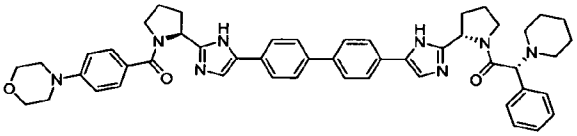
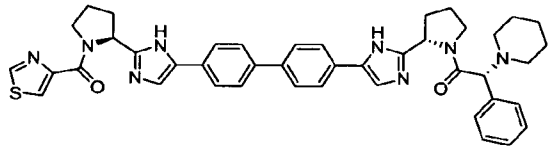
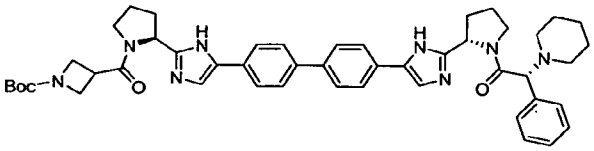
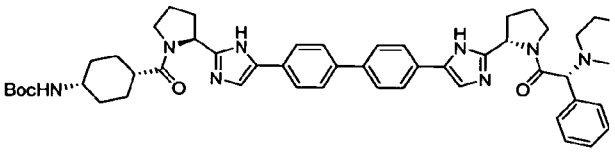


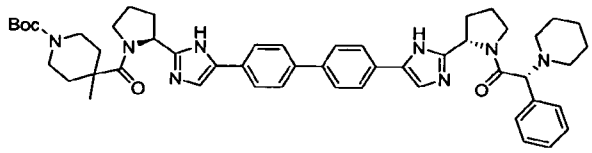
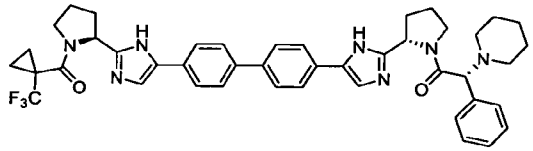
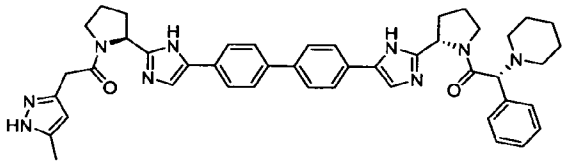
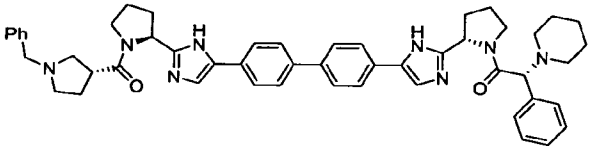
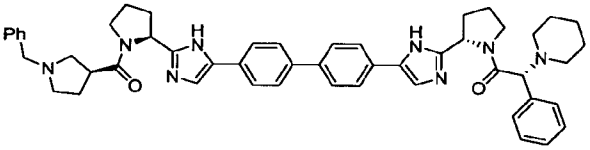
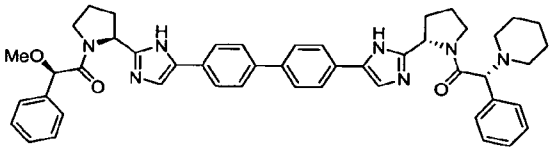
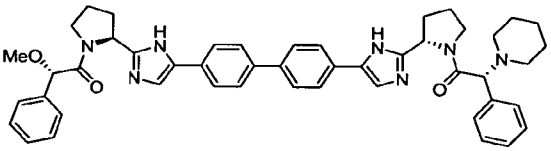
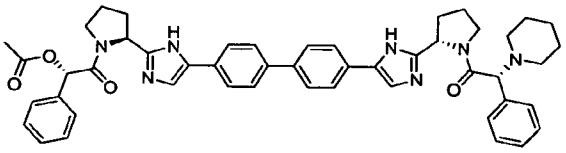
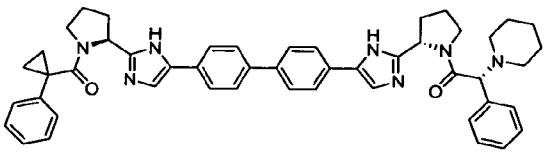
LCMS: Anal. Calcd. for $C_{46}H_{56}FN_7O_2$: 747; found: 748 $(M+H)^+$.

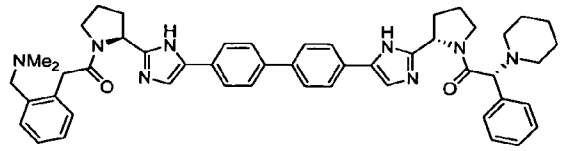
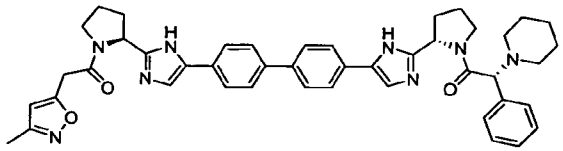
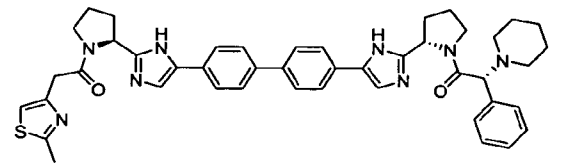
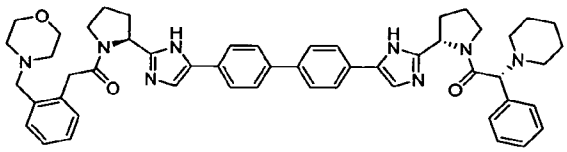
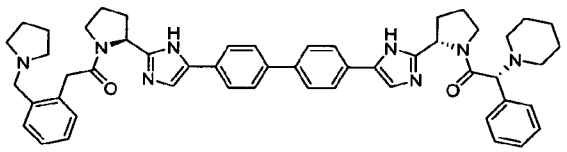
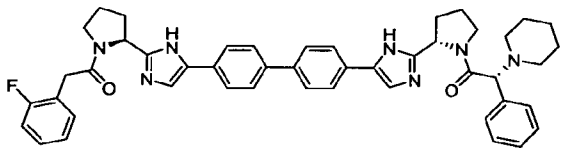
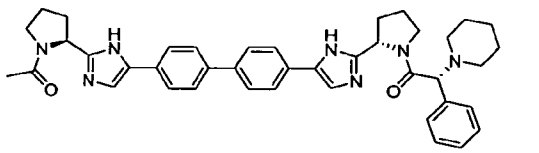
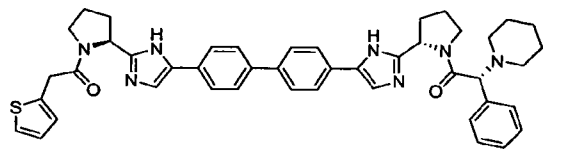
Example 107-4



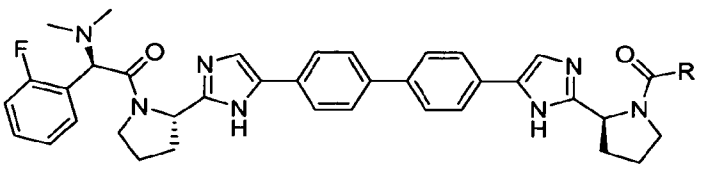
LCMS: Anal. Calcd. for $C_{48}H_{52}N_8O_2$: 772; found: 773 $(M+H)^+$.

Example 107-5		LCMS: Anal. Calcd. for $C_{44}H_{49}N_7O_3$: 723; found: 724 $(M+H)^+$.
Example 107-6		LCMS: Anal. Calcd. for $C_{53}H_{53}N_7O_2$: 819; found: 820 $(M+H)^+$.
Example 107-7		LCMS: Anal. Calcd. for $C_{47}H_{56}N_8O_2$: 764; found: 765 $(M+H)^+$.
Example 107-8		LCMS: Anal. Calcd. for $C_{48}H_{51}N_7O_4$: 789; found: 790 $(M+H)^+$.
Example 107-9		LCMS: Anal. Calcd. for $C_{50}H_{60}N_8O_4$: 836; found: 837 $(M+H)^+$.
Example 107-10		LCMS: Anal. Calcd. for $C_{50}H_{54}N_8O_3$: 814; found: 815 $(M+H)^+$.
Example 107-11		LCMS: Anal. Calcd. for $C_{43}H_{44}N_8O_2S$: 736; found: 737$(M+H)^+$.
Example 107-12		LCMS: Anal. Calcd. for $C_{48}H_{56}N_8O_4$: 808; found: 809 $(M+H)^+$.
Example 107-13		LCMS: Anal. Calcd. for $C_{51}H_{62}N_8O_4$: 850; found: 851 $(M+H)^+$.

Example 107-14		LCMS: Anal. Calcd. for $C_{51}H_{62}N_8O_4$: 850; found: 851 $(M+H)^+$.
Example 107-15		LCMS: Anal. Calcd. for $C_{44}H_{46}F_3N_7O_2$: 761; found: 762 $(M+H)^+$.
Example 107-16		LCMS: Anal. Calcd. for $C_{45}H_{49}N_9O_2$: 747; found: 748 $(M+H)^+$.
Example 107-17		LCMS: Anal. Calcd. for $C_{51}H_{56}N_8O_2$: 812; found: 813 $(M+H)^+$.
Example 107-18		LCMS: Anal. Calcd. for $C_{51}H_{56}N_8O_2$: 812; found: 813 $(M+H)^+$.
Example 107-19		LCMS: Anal. Calcd. for $C_{48}H_{51}N_7O_3$: 773; found: 774 $(M+H)^+$.
Example 107-20		LCMS: Anal. Calcd. for $C_{48}H_{51}N_7O_3$: 773; found: 774 $(M+H)^+$.
Example 107-21		LCMS: Anal. Calcd. for $C_{49}H_{51}N_7O_4$: 801; found: 802 $(M+H)^+$.
Example 107-22		LCMS: Anal. Calcd. for $C_{49}H_{51}N_7O_2$: 769; found: 770 $(M+H)^+$.

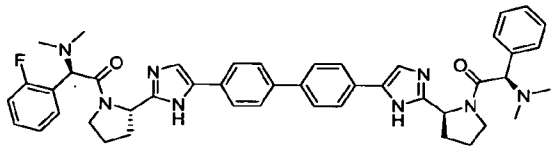
Example 107-23		LCMS: Anal. Calcd. for $C_{50}H_{56}N_8O_2$: 800; found: 801 $(M+H)^+$.
Example 107-24		LCMS: Anal. Calcd. for $C_{45}H_{48}N_8O_3$: 748; found: 749 $(M+H)^+$.
Example 107-25		LCMS: Anal. Calcd. for $C_{45}H_{48}N_8O_2S$: 764; found: 765 $(M+H)^+$.
Example 107-26		LCMS: Anal. Calcd. for $C_{52}H_{58}N_8O_3$: 842; found: 843 $(M+H)^+$.
Example 107-27		LCMS: Anal. Calcd. for $C_{52}H_{58}N_8O_2$: 826; found: 827 $(M+H)^+$.
Example 107-28		LCMS: Anal. Calcd. for $C_{47}H_{48}FN_7O_2$: 800; found: 801 $(M+H)^+$.
Example 107-29		LCMS: Anal. Calcd. for $C_{41}H_{45}FN_7O_2$: 667; found: 668 $(M+H)^+$.
Example 107-30		LCMS: Anal. Calcd. for $C_{45}H_{47}N_7O_2S$: 749; found: 750 $(M+H)^+$.

Example 107-31 to 107-34



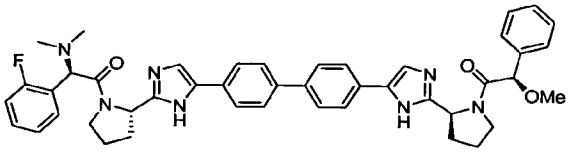
Examples **107-31** through **107-34** were prepared in similar fashion to example **28**. **Cap-38** was appended to intermediate **28d**, the Boc carbamate was removed with TFA or HCl and the appropriate carboxylic acid was coupled.

Example 107-31



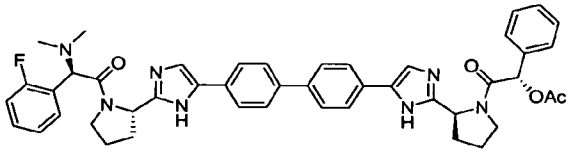
LCMS: Anal. Calcd. for $C_{46}H_{49}FN_8O_2$: 764; found: 765 $(M+H)^+$.

Example 107-32



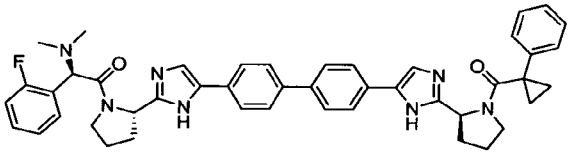
LCMS: Anal. Calcd. for $C_{45}H_{46}FN_7O_3$: 751; found: 752 $(M+H)^+$.

Example 107-33



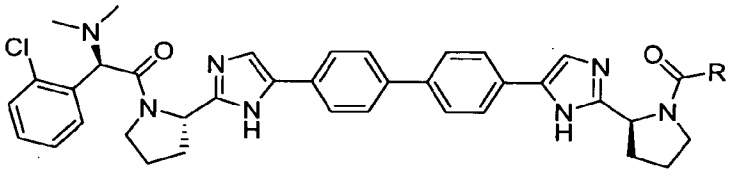
LCMS: Anal. Calcd. for $C_{46}H_{46}FN_7O_4$: 779; found: 780 $(M+H)^+$.

Example 107-34



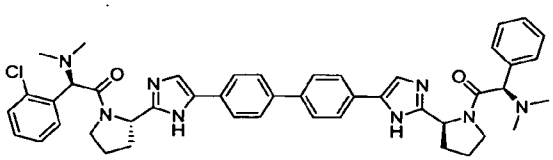
LCMS: Anal. Calcd. for $C_{46}H_{46}FN_7O_2$: 747; found: 748 $(M+H)^+$.

Example 107-35 to 107-38

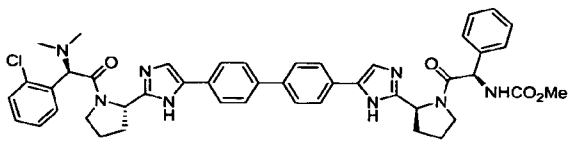
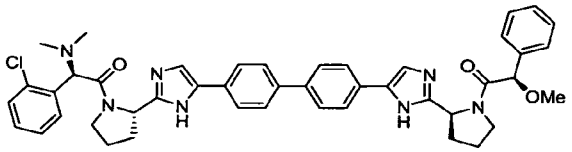
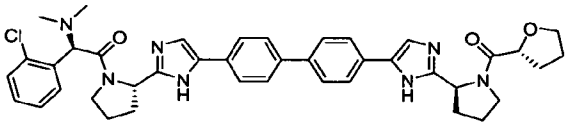


Examples **107-35** through **107-38** were prepared in similar fashion to example **28**. **Cap-39** was appended to intermediate **28d**, the Boc carbamate was removed with TFA or HCl and the appropriate carboxylic acid was coupled.

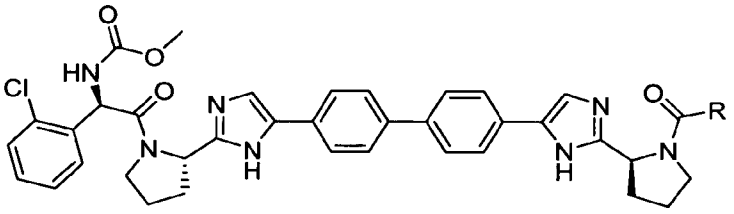
Example 107-35



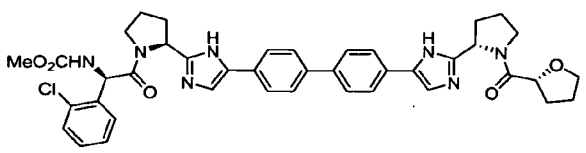
LCMS: Anal. Calcd. for $C_{46}H_{49}ClN_8O_2$: 780; found: 781 $(M+H)^+$.

Example 107-36		LCMS: Anal. Calcd. for $C_{46}H_{47}ClN_8O_4$: 810; found: 811 $(M+H)^+$.
Example 107-37		LCMS: Anal. Calcd. for $C_{45}H_{46}ClN_7O_3$: 767; found: 768 $(M+H)^+$.
Example 107-38		LCMS: Anal. Calcd. for $C_{41}H_{44}ClN_7O_3$: 717; found: 718 $(M+H)^+$.

Example 107-39 to 107-43

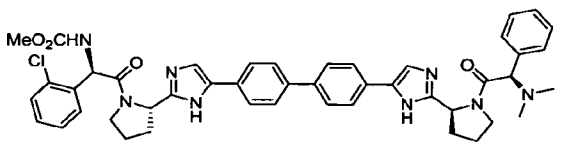


Examples **107-39** through **107-44** were prepared in similar fashion to example **28**. **Cap-40** was appended to intermediate **28d**, the Boc carbamate was removed with TFA or HCl and the appropriate carboxylic acid was coupled.

Example 107-39		^{1}HNMR (400 MHz, CD_3OD) δ 7.58-7.77 (m, 8H), 7.42- 7.55 (m, 2H), 7.19-7.39 (m, 4H), 5.94 and 5.89 (s, 1H, rotamers, 1:1), 5.80 and 5.61 (s, 1H, rotamers, 1:1), 5.43-5.47 and 5.35-5.38 (m, 1H, rotamers, 1:1),

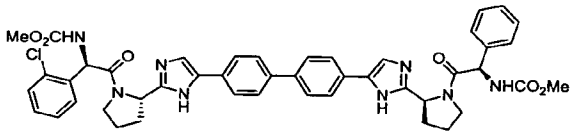
5.20-5.24 (m, 1H), 5.15- 5.18 (m, 1H), 4.67-4.70 and 4.39-4.42 (m, 1H, rotamers, 1:1), 3.92-3.98 (m, 1H), 3.85-3.90 (m, 1H), 3.69-3.84 (m, 2H), 3.64 and 3.63 (s, 3H, rotamers, 1:1), 3.53-3.59 (m, 1H), 2.35-2.46 (m, 1H), 2.21-2.29 (m, 2H), 2.06-2.17 (m, 3H), 1.84-2.01 (m, 4H), 1.66-1.76 and 1.41-1.47 (m, 1H, rotamers, 1:1); LCMS: Anal. Calcd. for $C_{41}H_{42}ClN_7O_5$: 747; found: 748 $(M+H)^+$.

Example 107-40



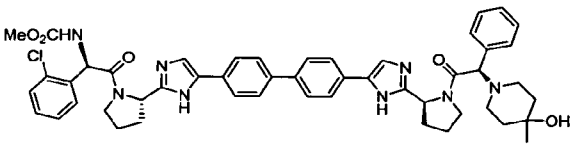
LCMS: Anal. Calcd. for $C_{46}H_{47}ClN_8O_4$: 810; found: 811 $(M+H)^+$.

Example 107-41

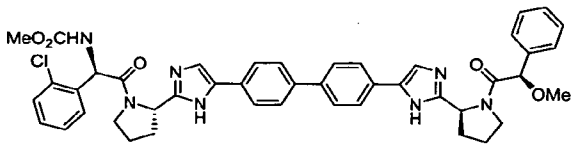
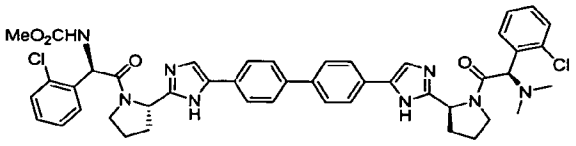


LCMS: Anal. Calcd. for $C_{46}H_{45}ClN_8O_6$: 840; found: 841 $(M+H)^+$.

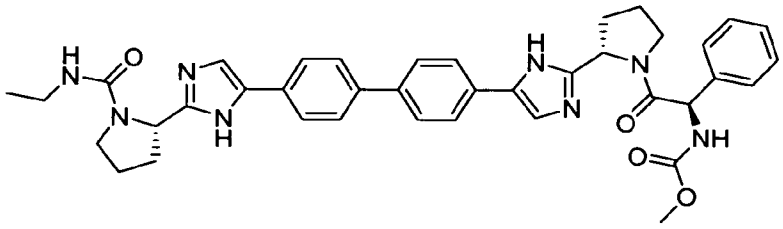
Example 107-42



LCMS: Anal. Calcd. for $C_{50}H_{53}ClN_8O_5$: 880; found: 881 $(M+H)^+$.

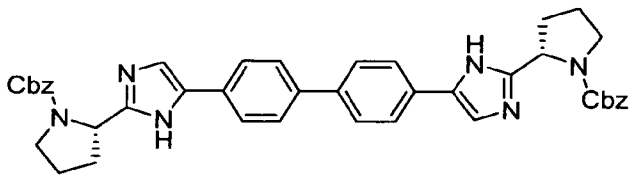
Example 107-43		LCMS: Anal. Calcd. for $C_{45}H_{44}ClN_7O_5$: 797; found: 798 $(M+H)^+$.
Example 107-44		LCMS: Anal. Calcd. for $C_{46}H_{46}Cl_2N_8O_4$: 844; found: 845 $(M+H)^+$.

Example 108

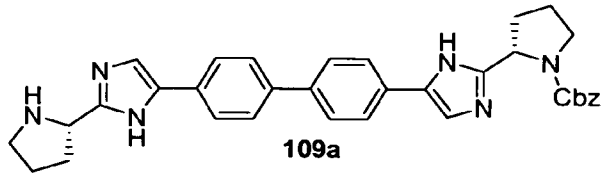


Ethyl isocyanate (5 μL, 0.063 mmol) was added to a methanol (1.0 mL) solution of **28f** (30 mg, 0.049 mmol) and stirred at ambient condition for 1.8 hours. The residue was treated with 2.0 M NH_3/methanol (2 mL) and stirred for an additional 30 minutes, and all the volatile components were removed *in vacuo*. The resulting material was purified by a reverse phase HPLC (H_2O/methanol/TFA) to provide the TFA salt of **Example 108** as a light yellow foam (16.7 mg) LC: 1.95 minutes (Cond. II); >98% homogeneity index; LC/MS: Anal. Calcd. for [M+H]+ $C_{39}H_{43}N_8O_4$: 687.34; found 687.53; HRMS: Anal. Calcd. for $[M+H]^+$ $C_{39}H_{43}N_8O_4$: 687.3407; found 687.3417.

Example 109



Example 109, Step a



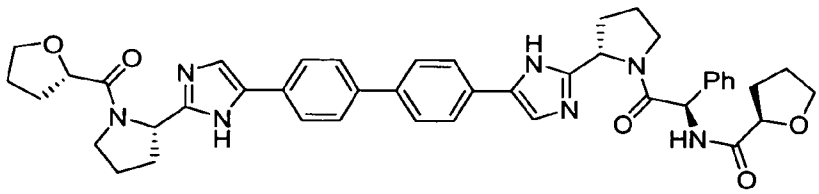
109a

The Boc-deprotection of **28c** using the procedure described for the synthesis of pyrrolidine **1e** from carbamate **1d** provided **109a**. RT = 1.92 minutes (Cond II); > 98% homogeneity index; LC/MS: Anal. Calcd. $C_{34}H_{35}N_6O_2$: 559.28; found 559.44

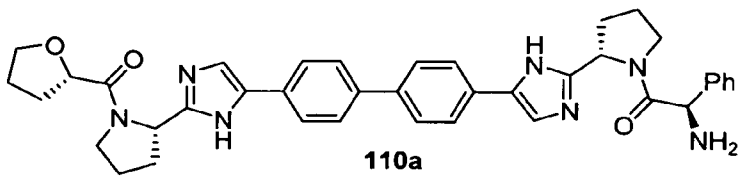
Example 109

Benzyl chloroformate (10.5 μL, 0.0736 mmol) was added to a THF (2.0 mL) solution of **109a** (37.1 mg, 0.664 mmol) and triethylamine (15 μl, 0.107 mmol), and stirred under ambient conditions for 6 hours. The volatile component was removed *in vacuo*, and the residue was treated with 2N NH_3/methanol (2 mL) and stirred for 15 minutes. The volatile component was removed *in vacuo*, and the residue purified by a reverse phase HPLC (H_2O/methanol/TFA) to provide the TFA salt of **Example 109** as an off-white foam (37.9 mg). LC (Cond. II): RT = 2.25 min; >98% homogeneity index; LC/MS: Anal. Calcd. for $[M+H]^+$ $C_{42}H_{41}N_6O_4$: 693.32; found 693.59; HRMS: Anal. Calcd. for $[M+H]^+$ $C_{42}H_{41}N_6O_4$: 693.3189; found 693.3220.

Example 110



Example 110, Step a



110a

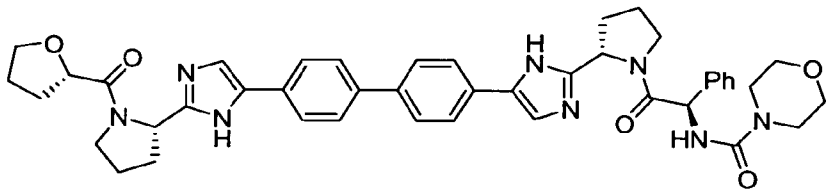
Amine **110a** was synthesized starting from **28d** and (*S*)-tetrahydrofuran-2-carboxylic by sequentially employing procedures described in the preparation of 28f (from 28d) and 25b (from 1e). LC (Cond. I): RT = 1.13 min; >98% homogeneity

index; LC/MS: Anal. Calcd. for $[M+H]^+$ $C_{39}H_{42}N_7O_3$: 656.34; found 656.49; HRMS: Anal. Calcd. for $[M+H]^+$ $C_{39}H_{42}N_7O_3$: 656.3349; found 656.3377.

Example 110

Example 110 (TFA salt) was prepared from Example 110a and (*S*)-tetrahydrofuran-2-carboxylic acid using the conditions described for the synthesis **Example 1** from amine **1e**. LC (Cond. I): RT = 1.28 min; >98% homogeneity index; LC/MS: Anal. Calcd. for $[M+H]^+$ $C_{44}H_{48}N_7O_5$: 754.37; found 754.60; HRMS: Anal. Calcd. for $[M+H]^+$ $C_{44}H_{48}N_7O_5$: 754.3717; found 754.3690.

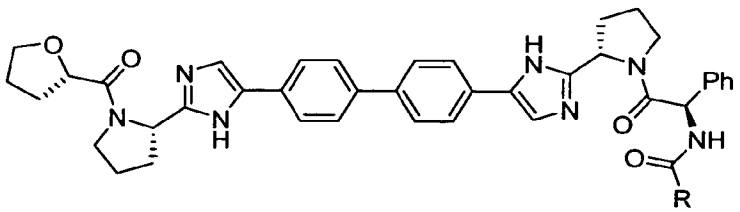
Example 111

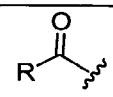


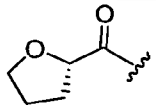
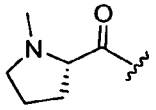
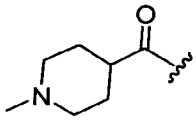
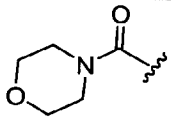
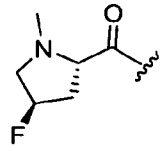
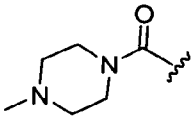
Example 111 (TFA salt) was prepared from amine **110a** and morpholine 4-carbonyl chloride using the procedure described for the synthesis of **Example 29** from amine **28f**. LC (Cond. I): RT = 1.28 min; >98% homogeneity index; LC/MS: Anal. Calcd. for $[M+H]^+$ $C_{44}H_{49}N_8O_5$: 769.38; found 769.60.

Using similar methods described for the preparation of **Example 111**, the following compounds (**Example 112-120**) were synthesized as TFA salts.

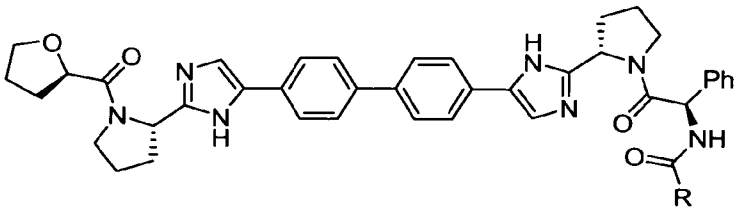
Example 112-117



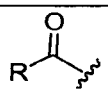
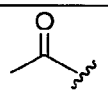
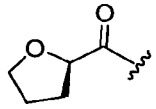
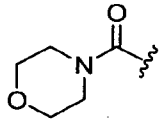
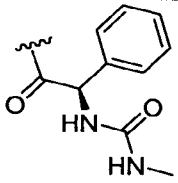
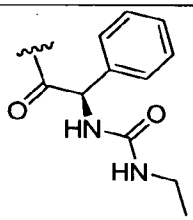
Example		Retention time (LC-Condition); homogeneity index MS data

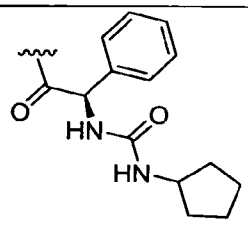
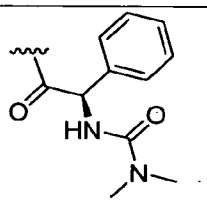
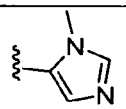
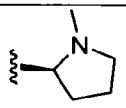
112		1.28 minutes (Cond. I); >98%; LC/MS: Anal. Calcd. for $[M+H]^+$ $C_{44}H_{48}N_7O_5$: 754.37; found 754.59; HRMS: Anal. Calcd. for $[M+H]^+$ $C_{44}H_{48}N_7O_5$: 754.3717; found 754.3731
113		1.14 minutes (Cond. I); >98%; LC/MS: Anal. Calcd. for $[M+H]^+$ $C_{44}H_{51}N_8O_4$: 767.40; found 767.68; HRMS: Anal. Calcd. for $[M+H]^+$ $C_{44}H_{51}N_8O_4$: 767.4033; found 767.4035
114		1.12 minutes (Cond. I); >98%; LC/MS: Anal. Calcd. for $[M+H]^+$ $C_{46}H_{53}N_8O_4$: 781.42; found 781.67; HRMS: Anal. Calcd. for $[M+H]^+$ $C_{46}H_{53}N_8O_4$: 781.4190; found 781.4195
115		1.24 minutes (Cond. I); >98%; LC/MS: Anal. Calcd. for $[M+H]^+$ $C_{45}H_{50}N_7O_5$: 768.39; found 768.66; HRMS: Anal. Calcd. for $[M+H]^+$ $C_{45}H_{50}N_7O_5$: 768.3873; found 768.3897
116 **cap-11**		1.16 minutes (Cond. I); >98%; LC/MS: Anal. Calcd. for $[M+H]^+$ $C_{45}H_{50}FN_8O_4$: 785.39; found 785.63; HRMS: Anal. Calcd. for $[M+H]^+$ $C_{45}H_{50}FN_8O_4$: 785.3939; found: 785.3940
117		1.15 minutes (Cond. I); 97.6%; LC/MS: Anal. Calcd. for $[M+H]^+$ $C_{45}H_{52}N_9O_4$: 782.41; found 782.64; HRMS: Anal. Calcd. for $[M+H]^+$ $C_{45}H_{52}N_9O_4$: 782.4142; found 782.4161

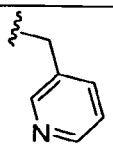
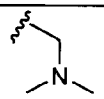
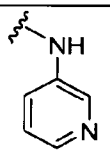
Example 118 to 120-9



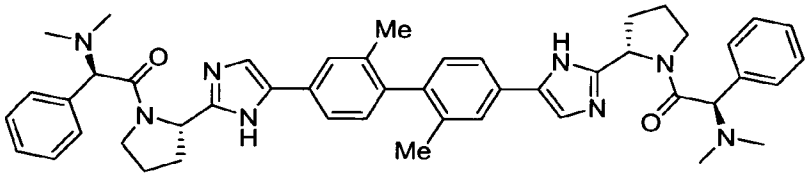
Example **118** to **120-9** were prepared as described in the preparation of Example **110a** substituting (R)-tetrahydrofuryl carboxylic acid and the appropriate carboxylic acid, carboxylic acid chloride, carbamoyl chloride, or isocyanate.

Example		**Retention time (LC-Condition); homogeneity index; MS data**
118		1.89 minutes (Cond. II); >98%; LC/MS: Anal. Calcd. for $[M+H]^+$ $C_{41}H_{44}N_7O_4$: 698.35; found 698.25; HRMS: Anal. Calcd. for $[M+H]^+$ $C_{41}H_{44}N_7O_4$: 698.3455; found 698.3474
119		1.99 minutes (Cond. II); >98%; LC/MS: Anal. Calcd. for $[M+H]^+$ $C_{44}H_{48}N_7O_5$: 754.37; found 754.28; HRMS: Anal. Calcd. for $[M+H]^+$ $C_{44}H_{48}N_7O_5$: 754.3717; found 754.3705
120		2.00 minutes (Cond. II); >98%; LC/MS: Anal. Calcd. for $[M+H]^+$ $C_{44}H_{49}N_8O_5$: 769.38; found 769.32
120-1	 employed **cap-45**	HPLC XTERRA C-18 4.6 × 30 mm, 0 to 100% B over 4 minutes, 1 minute hold time, A = 90% water, 10% methanol, 0.2% H_3PO_4, B = 10% water, 90% methanol, 0.2% H_3PO_4, RT = 1.81 minutes, 96% homogeneity index.; LCMS: Anal. Calcd. for $C_{41}H_{44}N_8O_4$: 712.84; found: 713.37 $(M+H)^+$; HRMS: Anal. Calcd. for $C_{41}H_{45}N_8O_4$ 713.3564; found: 713.3564 $(M+H)^+$.
120-2	 employed **cap-46**	HPLC XTERRA C-18 4.6 × 30 mm, 0 to 100% B over 2 minutes, 1 minute hold time, A = 90% water, 10% methanol, 0.2% H_3PO_4, B = 10% water, 90% methanol, 0.2% H_3PO_4, RT = 1.88 minutes, 95% homogeneity index; LCMS: Anal. Calcd. for $C_{42}H_{46}N_8O_4$: 726.87; found: 727.71 $(M+H)^+$; HRMS:

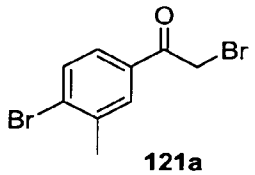
		Anal. Calcd. for $C_{42}H_{47}N_8O_4$ 727.3720; found: 727.3695 $(M+H)^+$.
120-3	 employed **cap-48**	HPLC XTERRA C-18 4.6 × 30 mm, 0 to 100% B over 2 minutes, 1 minute hold time, A = 90% water, 10% methanol, 0.2% H_3PO_4, B = 10% water, 90% methanol, 0.2% H_3PO_4, RT = 2.11 minutes, 96% homogeneity index; LCMS: Anal. Calcd. for $C_{45}H_{50}N_8O_4$: 766.93; found: 767.45 $(M+H)^+$; HRMS: Anal. Calcd. for $C_{45}H_{51}N_8O_4$ 767.4033; found: 767.4032 $(M+H)^+$.
120-4	 employed **cap-47**	HPLC XTERRA C-18 4.6 × 30 mm, 0 to 100% B over 2 minutes, 1 minute hold time, A = 90% water, 10% methanol, 0.2% H_3PO_4, B = 10% water, 90% methanol, 0.2% H_3PO_4, RT = 1.87 minutes, 97% homogeneity index; LCMS: Anal. Calcd. for $C_{42}H_{46}N_8O_4$: 726.87; found: 727.38 $(M+H)^+$; HRMS: Anal. Calcd. for $C_{42}H_{47}N_8O_4$ 727.3720; found: 727.3723 $(M+H)^+$.
120-5		RT = 4.02 (97%); HPLC XTERRA C-18 4.6 × 30 mm, 0 to 100% B over 2 minutes, 1 minute hold time, A = 90% water, 10% methanol, 0.2% H_3PO_4, B = 10% water, 90% methanol, 0.2% H_3PO_4, RT = 1.87 minutes, 97% homogeneity index; LCMS: Anal. Calcd. for: $C_{44}H_{45}N_9O_4$ 763.91; Found: 764.52 $(M+H)^+$
120-6		RT = 3.68 (99%); HPLC XTERRA C-18 4.6 × 30 mm, 0 to 100% B over 2 minutes, 1 minute hold time, A = 90% water, 10% methanol, 0.2% H_3PO_4, B = 10% water, 90% methanol, 0.2% H_3PO_4, RT = 1.87 minutes, 97% homogeneity index; LCMS: Anal. Calcd. for: $C_{45}H_{50}N_8O_4$ 766.95; Found: 767.47 $(M+H)^+$

120-7		RT = 3.81 (99%); HPLC XTERRA C-18 4.6 × 30 mm, 0 to 100% B over 2 minutes, 1 minute hold time, A = 90% water, 10% methanol, 0.2% H_3PO_4, B = 10% water, 90% methanol, 0.2% H_3PO_4, RT = 1.87 minutes, 97% homogeneity index; LCMS: Anal. Calcd. for: $C_{46}H_{46}N_8O_4$ 774.93; Found: 775.47 $(M+H)^+$
120-8		^{1}H NMR (500 MHz, DMSO-d_6) δ ppm 1.71-2.44 (m, 12H), 2.65-2.89 (m, 6H), 3.04-3.21 (m, *J*=8.55 Hz, 1H), 3.46-3.68 (m, 1H), 3.64-4.07 (m, 6H), 4.64 (dd, *J*=8.09, 5.34 Hz, 1H), 5.09-5.30 (m, 2H), 5.66-5.86 (m, 1H), 7.32-7.49 (m, 4H), 7.82-8.22 (m, 10H), 9.15-9.38 (m, 1H), 9.68 (s, 1H), 14.60 (s, 2H); HPLC Xterra 4.6 X 50 mm, 0 to 100% B over 10 minutes, one minute hold time, A = 90% water, 10% methanol, 0.2% phosphoric acid, B = 10% water, 90% methanol, 0.2% phosphoric acid, RT = 3.61 min; LCMS: Anal. Calcd. for: $C_{52}H_{56}N_{10}O_6$ 740.91; Found: 741.48 $(M+H)^+$.
120-9		^{1}H NMR (500 MHz, DMSO-d_6) δ ppm 1.64-2.40 (m, 12H), 3.11-3.27 (m, 1H), 3.51-3.65 (m, 1H), 3.80 (dd, *J*=18.46, 6.87 Hz, 3H), 3.96-4.11 (m, 1H), 4.64 (dd, *J*=7.78, 5.34 Hz, 1H), 5.13-5.23 (m, 1H), 5.21-5.35 (m, 1H), 5.66 (d, *J*=7.02 Hz, 1H), 7.29-7.57 (m, 7H), 7.82-8.07 (m, 10H), 8.14 (s, 1H), 8.22 (d, *J*=4.58 Hz, 1H), 8.68 (s, 1H), 9.32 (s, 1H), 14.46 (s, 2H); HPLC Xterra 4.6 X 50 mm, 0 to 100% B over 10 minutes, one minute hold time, A = 90% water, 10% methanol, 0.2% phosphoric acid, B = 10% water, 90% methanol, 0.2% phosphoric acid, RT = 3.83 min; LCMS: Anal. Calcd. for: $C_{45}H_{45}N_9O_4$ 775.92; Found: 776.53 $(M+H)^+$.

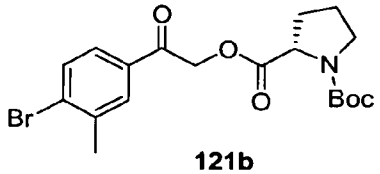
Example 121



Example 121, Step a-b



121a



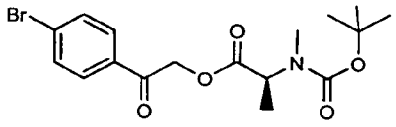
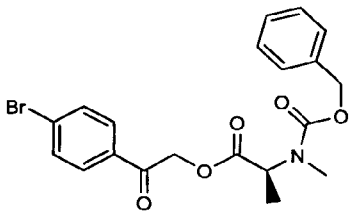
121b

$PdCl_2(Ph_3P)_2$ (257 mg, 0.367 mmol) was added to a dioxane (45 mL) solution of 1-bromo-4-iodo-2-methylbenzene (3.01 g, 10.13 mmol) and tri-*n*-butyl(1-ethoxyvinyl)stannane (3.826 g, 10.59 mmol) and heated at 80 °C for ~17 hours. The reaction mixture was treated with water (15 mL), cooled to ~0 °C (ice/water), and then NBS (1.839 g, 10.3 mmol) was added in batches over 7 minutes. After about 25 minutes of stirring, the volatile component was removed *in vacuo*, and the residue was partitioned between CH_2Cl_2 and water. The aqueous layer was extracted with CH_2Cl_2, and the combined organic phase was dried ($MgSO_4$), filtered, and concentrated *in vacuo*. The resulting crude material was purified by a gravity chromatography (silica gel; 4% ethyl acetate/hexanes)to provide bromide **121a** as a brownish-yellow solid (2.699 g); the sample is impure and contains stannane-derived impurities, among others. ^{1}H NMR ($CDCl_3$, δ = 7.24, 400 MHz): 7.83 (s, 1H), 7.63 (s, 2H), 4.30 (s, 2H), 2.46 (s, 3H).

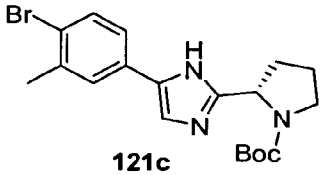
A CH_3CN (15 mL) solution of **121a** (2.69 g, < 9.21 mmol) was added dropwise over 3 minutes to a CH_3CN (30 mL) solution of (*S*)-Boc-proline (2.215 g, 10.3 mmol) and triethylamine (1.40 mL, 10.04 mmol), and stirred for 90 minutes. The volatile component was removed *in vacuo*, and the residue was partitioned between water and CH_2Cl_2, and the organic phase was dried ($MgSO_4$), filtered, and concentrated *in vacuo*. The resulting crude material was purified by a flash chromatography (silica gel; 15-20% ethyl acetate/hexanes) to provide **121b** as a colorless viscous oil (2.74g). ^{1}H NMR (DMSO-d_6, δ = 2.50, 400 MHz): δ 7.98 (m,

1H), 7.78 (d, J = 8.3, 1H), 7.72-7.69 (m, 1H), 5.61-5.41 (m, 2H), 4.35-4.30 (m, 1H), 3.41-3.30 (m, 2H), 2.43 (s, 3H), 2.33-2.08 (m, 2H), 1.93-1.83 (m, 2H), 1.40/1.36 (s, 9H); LC (Cond. I): RT = 1.91 min; >95% homogeneity index; LC/MS: Anal. Calcd. for $[M+Na]^+$ $C_{19}H_{24}BrNNaO_5$ 448.07; found 448.10.

Additional keto-esters can be prepared in analogous fashion:

Example	Structure	Data
121b-1		RT = 2.15 minutes (condition 2, 98%); LRMS: Anal. Calcd. for $C_{17}H_{22}NO_5$ 399.07; found: 400.10 $(M+H)^+$.
121b-2		RT = 2.78 minutes (>90%); LCMS: Anal. Calcd. for $C_{20}H_{20}{}^{37}BrNO_5$ 435.05 found: 458.02 $(M+Na)^+$.

Example 121, Step c

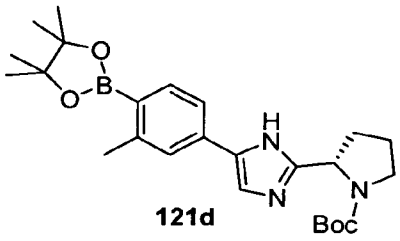


121c

A mixture of ketoester **121b** (1.445 g, 3.39 mmol) and NH_4OAc (2.93 g, 38.0 mmol) in xylenes (18 mL) was heated with a microwave at 140 °C for 80 minutes. The volatile component was removed *in vacuo*, and the residue was carefully partitioned between CH_2Cl_2 and water, where enough saturated $NaHCO_3$ solution was added to neutralize the aqueous medium. The aqueous phase was extracted with CH_2Cl_2, and the combined organic phase was dried ($MgSO_4$), filtered, and concentrated *in vacuo*. The crude product was purified by a flash chromatography (silica gel, 40% ethyl acetate/hexanes) to provide imidzaole **121c** as an off-white solid (1.087 g). ^1H NMR (DMSO-d_6, δ = 2.50, 400 MHz): 12.15/11.91/11.84 (br s, 1H), 7.72-7.24 (m, 4H), 4.78 (m, 1H), 3.52 (m, 1H), 3.38-3.32 (m, 1H), 2.35 (s, 3H),

2.28-1.77 (m, 4H), 1.40/1.14 (s, 9H); LC (Cond. Ib): RT = 1.91 min; >98% homogeneity index; LC/MS: Anal. Calcd. for $[M+H]^+$ $C_{19}H_{25}BrN_3O_2$ 405.96; found 406.11.

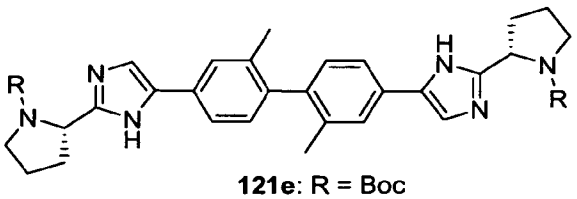
Example 121, Step d



121d

$PdCl_2dppf{\cdot}CH_2Cl_2$ (50.1 mg, 0.061 mmol) was added to a pressure tube containing a mixture of bromide **121c** (538.3 mg, 1.325 mmol), bis(pinacolato)diboron (666.6 mg, 2.625 mmol), potassium acetate (365.8 mg, 3.727 mmol) and DMF (10 mL). The reaction mixture was flushed with N_2 and heated at 80 °C for 24.5 hours. The volatile component was removed *in vacuo* and the residue was partitioned between CH_2Cl_2 and water, where enough saturated $NaHCO_3$ solution was added to make the pH of the aqueous medium neutral. The aqueous phase was extracted with CH_2Cl_2, and the combined organic phase was dried ($MgSO_4$), filtered, and concentrated *in vacuo*. The resulting material was purfied by a Biotage system (silica gel, 40-50% ethyl acetate/hexanes) to provide boronate **121d** as a white foam (580 mg). According to ^1H NMR the sample contains residual pinacol in a product/pinacol ratio of ~3. ^1H NMR (DMSO-d_6, δ = 2.50, 400 MHz): δ 12.16/11.91/11.83 (br s, 1H), 7.63-7.25 (m, 4H), 4.78 (m, 1H), 3.53 (m, 1H), 3.39-3.32 (m, 1H), 2.48/2.47 (s, 3H), 2.28-1.78 (m, 4H), 1.40/1.14/1.12 (br s, 9H), 1.30 (s, 12H); LC (Cond. I): RT = 1.62 min; LC/MS: Anal. Calcd. for $[M+H]^+$ $C_{25}H_{37}BN_3O_4$ 454.29; found 454.15

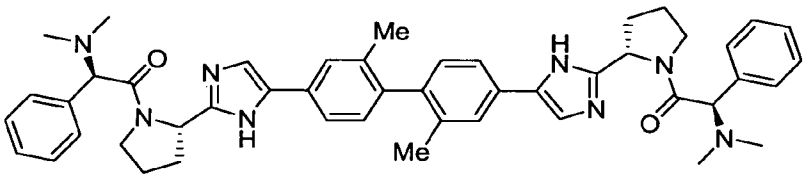
Example 121, Step e-f



121e: R = Boc
121f: R = H

Carbamate **121e** was prepared from bromide **121c** and boronate **121d** according to the preparation of dimer **1d**; LC (Cond. I): RT = 1.43 min; LC/MS: Anal. Calcd. for $[M+H]^+$ $C_{38}H_{49}N_6O_4$ 653.38; found 653.65.

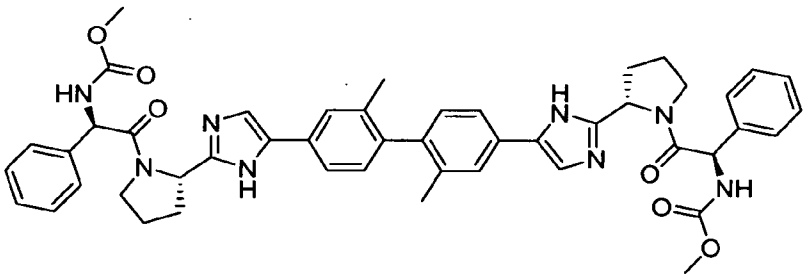
The deprotection of carbamate **121e**, according to the preparation of pyrrolidine **1e**, provideed **121f** as an off-white foam. ^1H NMR (DMSO-d_6, δ = 2.50, 400 MHz): 11.79 (br s, 2H), 7.66 (s, 2H), 7.57 (d, J = 7.8, 2H), 7.41 (br s, 2H), 7.02 (d, J = 7.8, 2H), 4.15 (app t, J = 7.2, 2H), 3.00-2.94 (m, 2H), 2.88-2.82 (m, 2H), 2.09-2.01 (m, 2H), 2.04 (s, 6H), 1.93-1.85 (m, 2H), 1.82-1.66 (m, 4H). Note: although broad signals corresponding to the pyrrolidine NH appear in the 2.8-3.2 ppm region, the actual range for their chemical shift could not be determined. LC (Cond. I): RT = 1.03 min; LC/MS: Anal. Calcd. for $[M+H]^+$ $C_{28}H_{33}N_6$ 453.28; found 453.53



Example 121

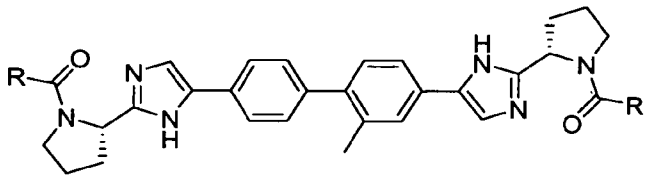
Example 121 (TFA salt) was synthesized from **121f** according to the preparation of **Example 1** from **1e**; LC (Cond. I): RT = 1.14 min; >98% homogeneity index; LC/MS: Anal. Calcd. for $[M+H]^+$ $C_{48}H_{55}N_8O_2$ 775.45; 775.75; HRMS: Anal. Calcd. for $[M+H]^+$ $C_{48}H_{55}N_8O_2$ 775.4448; found 775.4473

Example 122

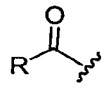
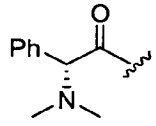
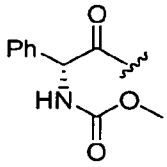
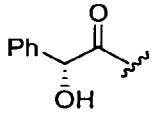


Example 122 (TFA salt) was prepared from pyrrolidine **121f** and **cap-4** by using the procedure described for the preparation of **Example 1** from pyrrolidine **1e**. LC (Cond. I): RT = 1.35 min; >98% homogeneity index; HRMS: Anal. Calcd. for $[M+H]^+$ $C_{48}H_{51}N_8O_6$ 835.3932; found 835.3954

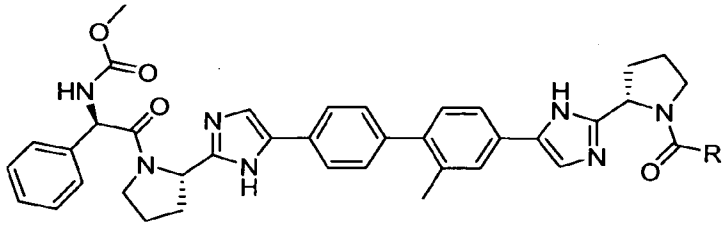
Example 123-125



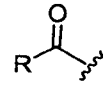
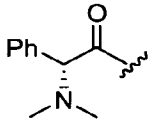
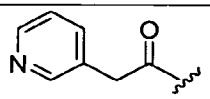
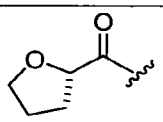
Example 123-125 were prepared starting from boronate **1c** and bromide **121c** by using the methods described in Example 1, step d, Example 1, step e, and in the step describing the preparation of Example 1.

Example		**RT (LC-Cond.); % homogeneity index; MS data**
123	 **cap-1**	1.12 minutes (Cond. I); >98%; LC/MS: Anal. Calcd. for $[M+H]^+$ $C_{47}H_{53}N_8O_2$: 761.43; found 761.49; HRMS: Anal. Calcd. for $[M+H]^+$ $C_{47}H_{53}N_8O_2$: 761.4291; found 761.4311
124	 **cap-4**	1.34 minutes (Cond. I); >98%; LC/MS: Anal. Calcd. for $[M+H]^+$ $C_{47}H_{49}N_8O_6$: 821.38; found 821.45; HRMS: Anal. Calcd. for $[M+H]^+$ $C_{47}H_{49}N_8O_6$: 821.3775; found 821.3785
125		1.23 minutes (Cond. I); >98%; LC/MS: Anal. Calcd. for $[M+H]^+$ $C_{43}H_{43}N_6O_4$: 707.34; found 707.38; HRMS: Anal. Calcd. for $[M+H]^+$ $C_{43}H_{43}N_6O_4$: 707.3346; found 707.3356

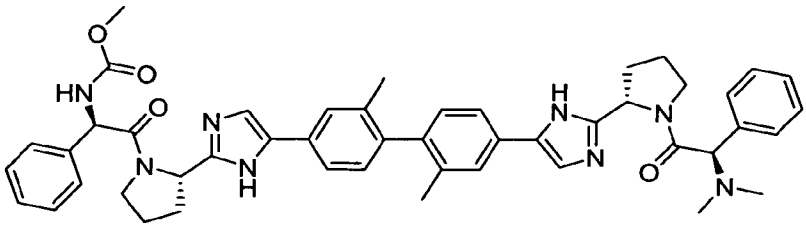
Example 126-128



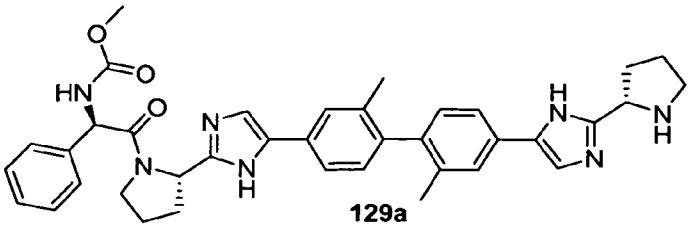
Example 126-128 were prepared starting from bromide **28b** and boronate **121d** by using the methods described in **Example 28 step c, step d, step e-f, and in the step describing the preparation of Example 28.**

Example		**RT (LC-Cond.); % homogeneity index; MS data**
126	 **cap-1**	1.22min (Cond. I); >98%; LC/MS: Anal. Calcd. for $[M+H]^+$ $C_{47}H_{51}N_8O_4$: 791.40; found 791.70; HRMS: Anal. Calcd. for $[M+H]^+$ $C_{47}H_{51}N_8O_4$: 791.4033; found 791.4061
127		1.19 minutes (Cond. I); >98%; LC/MS: Anal. Calcd. for $[M+H]^+$ $C_{44}H_{45}N_8O_4$: 749.36; found 749.62; HRMS: Anal. Calcd. for $[M+H]^+$ $C_{44}H_{45}N_8O_4$: 749.3564; found 749.3592
128		1.27 minutes (Cond. I); >98%; LC/MS: Anal. Calcd. for $[M+H]^+$ $C_{42}H_{46}N_7O_5$: 728.36; found 728.59; HRMS: Anal. Calcd. for $[M+H]^+$ $C_{42}H_{46}N_7O_5$: 728.3560; found 728.3593

Example 129



Example 129, Step a



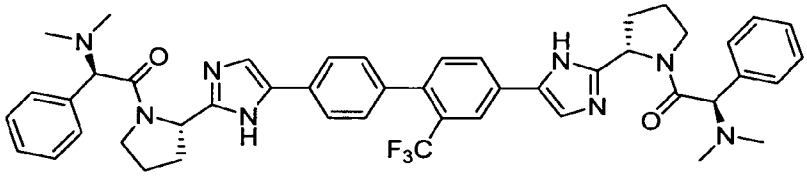
129a

HATU (104.3 mg, 0.274 mmol) was added to a mixture of **121f**, **Cap-4** (58.8 mg, 0.281 mmol) and diisopropylethylamine (110 µL, 0.631 mmol) in DMF (6.0 mL), and stirred for 90 minutes. The volatile component was removed *in vacuo* and the resulting crude material was purified by reverse phase HPLC (H_2O/methanol/TFA), and free-based by MCX column (methanol wash; 2.0 M NH_3/methanol) to provide **129a** (89.9 mg). LC (Cond. I): RT = 1.22 min; 95% homogeneity index; LC/MS: Anal. Calcd. for $[M+H]^+$ $C_{38}H_{42}N_7O_3$ 644.34; found 644.55.

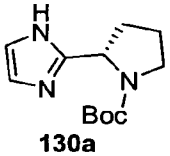
Example 129

Example 129 (TFA salt) was prepared from **129a** by the method used to convert Example 1e to Example 1. LC (Cond. I): RT = 1.27 min; 97% homogeneity index; LC/MS: Anal. Calcd. for $[M+H]^+$ $C_{48}H_{53}N_8O_4$ 805.42; found 805.61.

Example 130



Example 130, Step a



130a

Glyoxal (2.0 mL of 40% in water) was added dropwise over 11 minutes to a methanol solution of NH_4OH (32 mL) and (S)-Boc-prolinal (8.564 g, 42.98 mmol) and stirred at ambient temperature for 19 hours. The volatile component was removed *in vacuo* and the residue was purified by a flash chromatography (silica gel, ethyl acetate) followed by a recrystallization (ethyl acetate, room temperature) to provide imidazole **130a** as a white fluffy solid (4.43g). ^1H NMR (DMSO-d_6, δ = 2.50, 400 MHz): 11.68/11.59 (br s, 1H), 6.94 (s, 1H), 6.76 (s, 1H), 4.76 (m, 1H), 3.48 (m, 1H), 3.35-3.29 (m, 1H), 2.23-1.73 (m, 4H), 1.39/1.15 (s, 9H). LC (Cond. I): RT

= 0.87 min; >95% homogeneity index; LC/MS: Anal. Calcd. for $[M+H]^+$ $C_{12}H_{20}N_3O_2$ 238.16; found 238.22. Imidazole **130a** had an ee of 98.9% when analyzed under chiral HPLC condition noted below.

Column: Chiralpak AD, 10 um, 4.6 x 50 mm

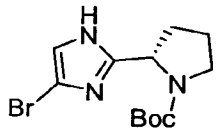
Solvent: 1.7% ethanol/heptane (isocratic)

Flow rate: 1 mL/min

Wavelength: either 220 or 256 nm

Relative retention time: 3.25min (*R*), 5.78 minutes (*S*)

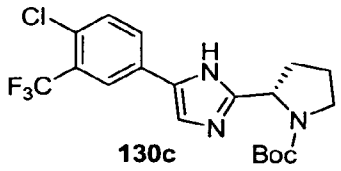
Example 130, Step b



130b

N-Bromosuccinimide (838.4 mg, 4.71 mmol) was added in batches, over 15 minutes, to a cooled (ice/water) CH_2Cl_2 (20 mL) solution of imidazole **130a** (1.0689 g, 4.504 mmol), and stirred at similar temperature for 75 minutes. The volatile component was removed *in vacuo*. The crude material was purified by a reverse phase HPLC system (H_2O/methanol/TFA) to separate bromide **130b** from its dibromo-analog and the non-consumed starting material. The HPLC elute was neutralized with excess NH_3/methanol and the volatile component was removed *in vacuo*. The residue was partitioned between CH_2Cl_2 and water, and the aqueous layer was extracted with water. The combined organic phase was dried ($MgSO_4$), filtered, and concentrated *in vacuo* to provide **130b** as a white solid (374 mg). ^1H NMR (DMSO-d_6, δ = 2.50, 400 MHz): 12.12 (br s, 1H), 7.10 (m, 1H), 4.70 (m, 1H), 3.31 (m, 1H; overlapped with water signal), 2.25-1.73 (m, 4H), 1.39/1.17 (s, 3.8H + 5.2H). LC (Cond. I): RT = 1.10 min; >95% homogeneity index; LC/MS: Anal. Calcd. for $[M+H]^+$ $C_{12}H_{19}BrN_3O_2$ 316.07; found 316.10.

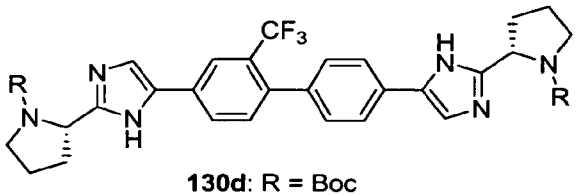
Example 130, Step c



130c

$Pd(Ph_3P)_4$ (78.5 mg, 0.0679 mmol) was added to a mixture of bromide **130b** (545 mg, 1.724 mmol), 2-(4-chloro-3-(trifluoromethyl)phenyl-4,4,5,5-tetramethyl-1,3,2-dioxaborolane (542.8 mg, 1.771 mmol) (commercially available), $NaHCO_3$ (477 mg, 5.678 mmol) in 1,2-dimethoxyethane (12.5 mL) and water (4.2 mL). The reaction mixture was purged with nitrogen, heated with an oil bath at 80 °C for 27 hours, and then the volatile component was removed *in vacuo*. The residue was partitioned between CH_2Cl_2 and water, and the organic layer was dried ($MgSO_4$), filtered, and concentrated *in vacuo*. The resulting crude material was purified by a Biotage system (silica gel, 40-50% ethyl acetate/hexanes) followed by a reverse phase HPLC (water/ methanol/TFA). The HPLC elute was treated with excess NH_3/methanol and concentrated. The residue was partitioned between water and CH_2Cl_2, and the organic layer was dried ($MgSO_4$), filtered, and concentrated *in vacuo* to provide **130c** as a white foam (317.4 mg). ^1H NMR (DMSO-d_6, δ = 2.50, 400 MHz): 12.36/12.09/12.03 (br s, 1H), 8.15 (d, J = 1.8, 0.93H), 8.09 (br s, 0.07H), 8.01 (dd, J = 8.3/1.3, 0.93H), 7.93 (m, 0.07H), 7.74 (m, 1H), 7.66 (d, J = 8.3, 0.93H), 7.46 (m, 0.07H), 4.80 (m, 1H), 3.53 (m, 1H), 3.36 (m, 1H), 2.30-1.77 (m, 4h), 1.40/1.15 (s, 3.8H+5.2H). LC (Cond. I): RT = 1.52 min; >95% homogeneity index; LC/MS: Anal. Calcd. for $[M+H]^+$ $C_{19}H_{22}ClF_3N_3O_2$ 416.14; found 416.17.

Example 130, Step d-e



130d: R = Boc
130e: R = H

$Pd[P(t\text{-}Bu)_3]_2$ (48 mg, 0.094 mmol) was added to a mixture of chloride **130c** (245 mg, 0.589 mmol), boronate **1c** (277.1 mg, 0.631 mmol), KF (106.7 mg, 1.836 mmol) in DMF (6 mL), and heated at 110 °C for ~30 hours. The volatile component was removed *in vacuo*, and the residue was partitioned between CH_2Cl_2 (50 mL),

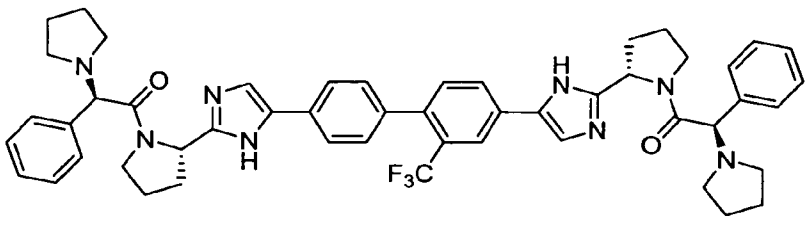
water (20 mL) and saturated $NaHCO_3$ (1 mL). The aquous layer was extracted with CH_2Cl_2 (2x), and the combined organic phase was dried ($MgSO_4$), filtered, and concentrated *in vacuo*. The resulting material was purified by a Biotage system (silica gel, ethyl acetate) to provide carbamate **130d** as an off-white foam (297 mg). LC (Cond. I): RT = 1.44 min; >95% homogeneity index; LC/MS: Anal. Calcd. for $[M+H]^+$ $C_{37}H_{44}F_3N_6O_4$ 693.34; found 693.34.

The deprotection of **130d**, which was conducted according to the preparation of pyrrolidine **1e**, provideed **130e** as a light yellow foam. ^1H NMR (DMSO-d_6, δ = 2.50, 400 MHz): 11.88 (br s, 2H), 8.16 (d, J = 1.5, 1H), 8.02 (d, J = 7.8, 1H), 7.78 (d, J = 8.1, 2H), 7.66 (br s, 1H), 7.48 (br s, 1H), 7.37 (d, J = 8.1, 1H), 7.28 (d, J = 8.3, 2H), 4.18 (m, 2H), 2.99-2.93 (m, 2H), 2.89-2.83 (m, 2H), 2.11-2.01 (m, 2H), 1.94-1.85 (m, 2H), 1.82-1.67 (m, 4H). Note: although broad signals corresponding to the pyrrolidine NH appear in the 2.8-3.2 ppm region, the actual range for their chemical shift could not be determined. LC (Cond. I): RT = 1.12 min; >95% homogeneity index; LC/MS: Anal. Calcd. for $[M+H]^+$ $C_{27}H_{28}F_3N_6$ 493.23; found 493.14.

Example 130

Example 130 (TFA salt) was prepared from **130e** according to the preparation of **Example 1** from pyrrolidine **1e**. LC (Cond. I): RT = 1.17 min; >98% homogeneity index; LC/MS: Anal. Calcd. for $[M+H]^+$ $C_{47}H_{50}F_3N_8O_2$ 815.40; found 815.44; HRMS: Anal. Calcd. for $[M+H]^+$ $C_{47}H_{50}F_3N_8O_2$ 815.4009; found 815.4013

Example 131



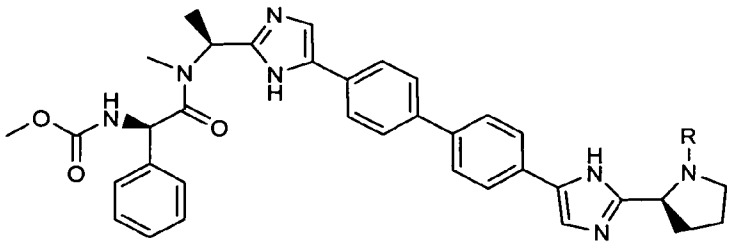
Example 131 (TFA salt) was synthesized from **130e** according to the preparation of **Example 130**.

LC (Cond. Ia): RT = 1.19 min; >98% homogeneity index

LC/MS: Anal. Calcd. for $[M+H]^+$ $C_{51}H_{54}F_3N_8O_2$ 867.43; found 867.51

HRMS: Anal. Calcd. for $[M+H]^+$ $C_{51}H_{54}F_3N_8O_2$ 867.4322; found 867.4315

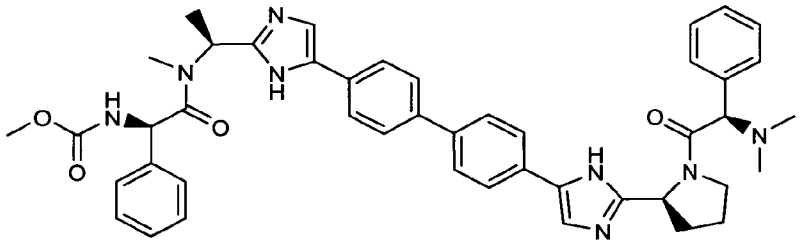
Example 131.1-1 to 131.1-2



Examples **131.1-1** through **131.1-2** were prepared in similar fashion to example **28** via the intermediacy of intermediate **1-6e** after appending **cap-4**.

Example 131.1-1

Cap-1 was appended after the CBz carbamate was removed from **1-6e** with $Pd/C/H_2$.



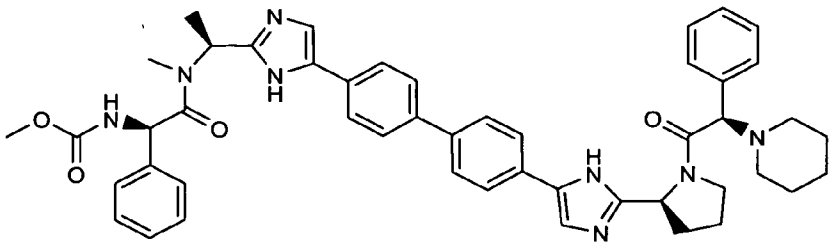
t_R = 1.42 min

LRMS: Anal. Calcd. for $C_{45}H_{49}N_8O_4$ 765.39; found: 765.38 $(M+H)^+$.

HRMS: Anal. Calcd. for $C_{45}H_{49}N_8O_4$ Calcd 765.3877 found: 765.3905 $(M+H)^+$.

Example 131.1-2

Cap-14 was appended after the CBz carbamate was removed from **1-6e** with $Pd/C/H_2$.



t_R = 1.45 min (>95 %)

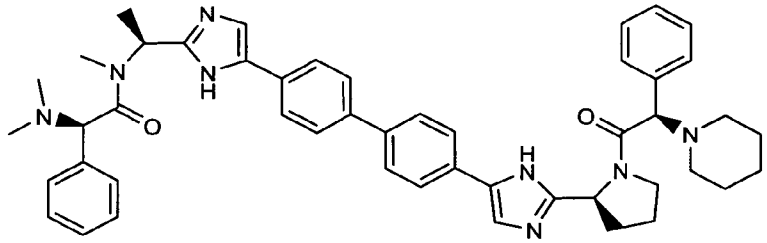
LRMS: Anal. Calcd. for $C_{48}H_{52}N_8O_4$ 805.42; found: 805.41 $(M+H)^+$.

HRMS: Anal. Calcd. $C_{48}H_{52}N_8O_4$ Calcd 805.4190 found: 805.4214 $(M+H)^+$.

Example 131.2

Example **131. 2** was prepared in similar fashion to example **28** via the intermediacy of intermediate **1-6e** after appending **cap-1**.

Cap-14 was appended after the CBz carbamate was removed with $Pd/C/H_2$.

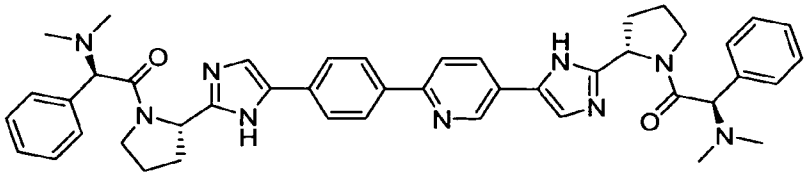


t_R = 1.28 min

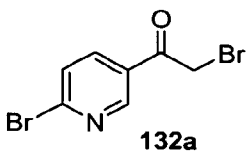
LRMS: Anal. Calcd. for $C_{48}H_{54}N_8O_2$ 775.44; found: 775.45 $(M+H)^+$.

HRMS: Anal. Calcd. $C_{48}H_{54}N_8O_2$ Calcd 775.4448 found: 775.4460 $(M+H)^+$.

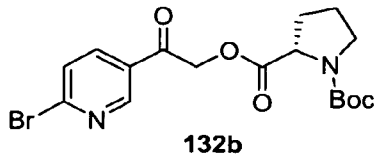
Example 132



Example 132, Step a-b



132a



132b

A CH_2Cl_2 (10 mL) solution of Br_2 (7.63 g, 47.74 mmol) was added-drop wise over 5 min to a cooled (ice/water) CH_2Cl_2 (105 mL) solution of 1-(6-bromopyridine-3-yl)ethanone (9.496 g, 47.47 mmol) and 48% HBr (0.4 mL). The cooling bath was removed 40 min later, and stirring was continued at ambient temperature for about 66 hr. The cake of solid that formed was filtered, washed with CH_2Cl_2 and dried in vacuo to afford impure **132a** as an off-white solid (15.94 g).

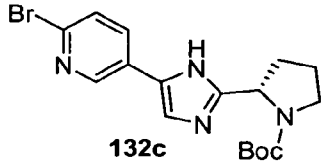
Boc-L-proline (9.70 g, 45.06 mmol) was added in one batch to a heterogeneous mixture of crude **132a** (15.4 g) and CH_3CN (150 mL), and immediately afterward Et_3N (13.0 mL, 93.2 mmol) was added drop-wise over 6 min. The reaction mixture was stirred for 50 min, the volatile component was removed in vacuo and the residue was partitioned between CH_2Cl_2 and water. The CH_2Cl_2 layer was dried ($MgSO_4$) and evaporated in vacuo, and the resultant material was purified by flash chromatography (silica gel; sample was loaded with eluting solvent; 25% EtOAc/hexanes) to afford **132b** as a highly viscous yellow oil (11.44g). ^1H NMR (DMSO, δ = 2.5 ppm; 400 MHz): 8.95 (m, 1H), 8.25-8.21 (m, 1H), 7.88 (d, J = 8.3, 1H), 5.65-5.46 (m, 2H), 4.36-4.31 (m, 1H), 3.41-3.29 (m, 2H), 2.36-2.22 (m, 1H), 2.14-2.07 (m, 1H), 1.93-1.83 (m, 2H), 1.40 & 1.36 (two s, 9H).

LC (Cond. Ib): RT = 2.01 min; >90% homogeneity index

LC/MS: Anal. Calcd. for $[M+Na]^+$ $C_{17}H_{21}NaBrN_2O_5$: 435.05; found 435.15

HRMS: Anal. Calcd. for $[M+H]^+$ $C_{17}H_{22}BrN_2O_5$: 413.0712; found 413.0717

Example 132, Step c



132c

A mixture of ketoester **132b** (1.318 g, 3.19 mmol) and NH_4OAc (2.729 g, 35.4 mmol) in xylenes (18 mL) was heated with a microwave at 140 °C for 90 min. The volatile component was removed in vacuo and the residue was partitioned between CH_2Cl_2 and water, where enough saturated $NaHCO_3$ solution was added to neutralize the aqueous medium. The aqueous phase was extracted with CH_2Cl_2, and the combined organic phase was dried ($MgSO_4$) and evaporated in vacuo. The resulting crude material was purified by a Biotage system (silica gel; 50%

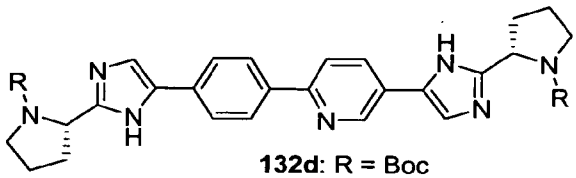
EtOAc/hexanes) to afford imidzaole **132c** as an off-white foam (1.025 g). ^{1}H NMR (DMSO, δ = 2.5 ppm, 400 MHz): 12.33/12.09/12.02 (br m, 1H), 8.74 (d, J = 2.3, 0.93H), 8.70 (app br s, 0.07H), 8.03/7.98 (dd for the first peak, J = 8.3, 1H), 7.69/7.67 (br m, 1H), 7.58/7.43 (d for the first peak, J = 8.3, 1H), 4.80 (m, 1H), 3.53 (m, 1H), 3.36 (m, 1H), 2.33-2.11 (m, 1H), 2.04-1.79 (m, 3H), 1.39/1.15 (app br s, 3.9H+5.1H).

LC (Cond.Ib): RT = 1.52 min; >98% homogeneity index

LC/MS: Anal. Calcd. for $[M+H]^+$ $C_{17}H_{22}BrN_4O_2$: 393.09; found 393.19

HRMS: Anal. Calcd. for $[M+H]^+$ $C_{17}H_{22}BrN_4O_2$: 393.0926; found 393.0909

Example 132, Step d-e



132d: R = Boc
132e: R = H

$Pd(Ph_3P)_4$ (115.1 mg, 0.10 mmol) was added to a mixture of bromide **132c** (992mg, 2.52 mmol), boronate **1c** (1.207 g, 2.747 mmol), $NaHCO_3$ (698.8 mg, 8.318 mmol) in 1,2-dimethoxyethane (18 mL) and water (4 mL). The reaction mixture was flushed with nitrogen, heated with an oil bath at 90 °C for 37 hr and allowed to cool to ambient temperature. The suspension that formed was filtered and washed with water followed by 1,2-dimethoxyethane, and dried in vacuo. A silica gel mesh was prepared from the crude solid and submitted to flash chromatography (silica gel; EtOAc) to afford carbamate **132d** as a white solid, which yellowed slightly upon standing at ambient conditions (1.124g). ^{1}H NMR indicated that the sample contains residual MeOH in a product/MeOH mole ratio of 1.3.

LC (Cond. Ib): RT = 1.71 min; >98% homogeneity index

LC/MS: Anal. Calcd. for $[M+H]^+$ $C_{35}H_{44}N_7O_4$: 626.35; found 626.64

HRMS: Anal. Calcd. for $[M+H]^+$ $C_{35}H_{44}N_7O_4$: 626.3455; 626.3479

Carbamate **132d** (217 mg) was treated with 25% TFA/CH_2Cl_2 (3.6 mL) and stirred at ambient condition for 6 hr. The volatile component was removed in vacuo,

and the resultant material was free based by MCX column (MeOH wash; 2.0 M NH_3/MeOH elution) to afford **132e** as a dull yellow foam that solidified gradually upon standing (150.5 mg; mass is above theoretical yield). ^{1}H NMR (DMSO, δ = 2.5 ppm; 400 MHz): 11.89 (very broad, 2H), 9.01 (d, J = 1.8, 1H), 8.13 (dd, J = 8.3, 2.2, 1H), 8.07 (d, J = 8.6, 2H), 7.92 (d, J = 8.3, 1H), 7.83 (d, J = 8.5, 2H), 7.61 (br s, 1H), 7.50 (br s, 1H), 4.18 (m, 2H), 3.00-2.93 (m, 2H), 2.90-2.82 (m, 2H), 2.11-2.02 (m, 2H), 1.94-1.85 (m, 2H), 1.83-1.67 (m, 4H). [Note: the exchangeable pyrrolidine hydrogens were not observed]

LC (Cond. Ib): RT = 1.21min; >98% homogeneity index

LC/MS: Anal. Calcd. for $[M+H]^+$ $C_{25}H_{28}N_7$: 426.24; found 426.40

HRMS: Anal. Calcd. for $[M+H]^+$ $C_{25}H_{28}N_7$: 426.2406; found 426.2425

Example 132

HATU (41.4 mg, 0.109 mmol) was added to a mixture of pyrrolidine **132e** (23.1 mg, 0.054 mmol), (i-Pr)$_2$EtN (40 µL, 0.23 mmol) and **Cap-1** (25.3 mg, 0.117 mmol) in DMF (1.5 mL), and the mixture was stirred at ambient for 1 hr. The volatile component was removed in vacuo, and the residue was purified first by MCX (MeOH wash; 2.0 M NH_3/MeOH elution) and then by a reverse phase HPLC (H_2O/MeOH/TFA) to afford the TFA salt of **Example 132** as a yellow foam (39.2 mg).

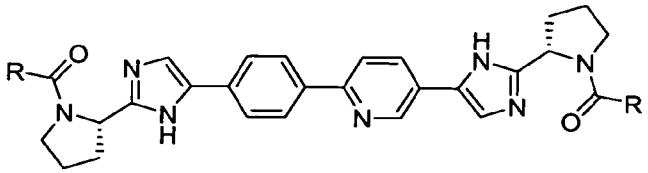
LC (Cond. Ib): RT = 1.37min; >98% homogeneity index

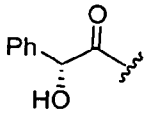
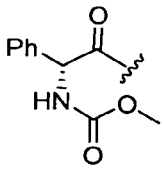
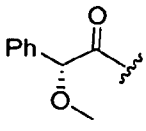
LC/MS: Anal. Calcd. for $[M+H]^+$ $C_{45}H_{50}N_9O_2$: 748.41; found 748.53

HRMS: Anal. Calcd. for $[M+H]^+$ $C_{45}H_{50}N_9O_2$: 748.4087; found 748.4090

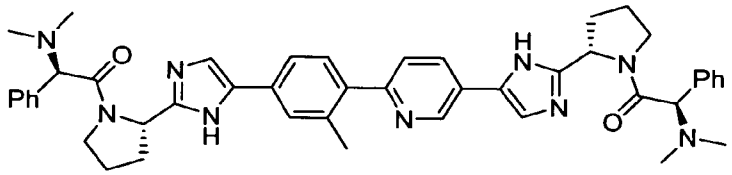
Example 133-135 were prepared as TFA salts from **132e** by using the same method of preparations as **Example 132** and appropriate reagents.

Example 133-135

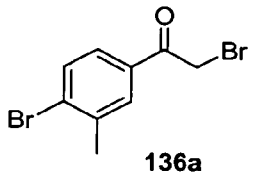


Example		RT (LC-Cond.); % homogeneity index; MS data
133		1.49 min (Cond. Ib); >98% LC/MS: Anal. Calcd. for $[M+H]^+$ $C_{41}H_{40}N_7O_4$: 694.31; found 694.42 HRMS: Anal. Calcd. for $[M+H]^+$ $C_{41}H_{40}N_7O_4$: 694.3142, found: 694.3164
134	 **cap-4**	1.60 min (Cond. Ib); >98% LC/MS: Anal. Calcd. for $[M+H]^+$ $C_{45}H_{46}N_9O_6$: 808.36; found 808.51 HRMS: Anal. Calcd. for $[M+H]^+$ $C_{45}H_{46}N_9O_6$: 808.3571; found 808.3576
135		1.60 min (Cond. Ib); >98% LC/MS: Anal. Calcd. for $[M+H]^+$ $C_{43}H_{44}N_7O_4$: 722.35; found 722.40 HRMS: Anal. Calcd. for $[M+H]^+$ $C_{43}H_{44}N_7O_4$: 722.3455; found 722.3464

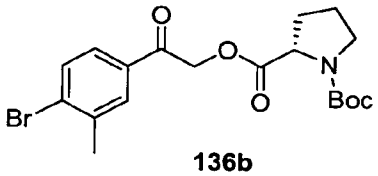
Example 136



Example 136, Step a and b



136a



136b

$PdCl_2(Ph_3P)_2$ (257 mg, 0.367 mmol) was added to a dioxane (45 mL) solution of 1-bromo-4-iodo-2-methylbenzene (3.01 g, 10.13 mmol) and tri-*n*-butyl(1-ethoxyvinyl)stannane (3.826 g, 10.59 mmol) and heated at 80 °C for ~17 hr. The reaction mixture was treated with water (15 mL), cooled to ~0 °C (ice/water), and then NBS (1.839 g, 10.3 mmol) was added in batches over 7 min. About 25 min of stirring, the volatile component was removed in vacuo, and the residue was partitioned between CH_2Cl_2 and water. The aqueous layer was extracted with CH_2Cl_2, and the combined organic phase was dried ($MgSO_4$) and evaporated in vacuo. The resulting crude material was purified by a gravity chromatography (silica gel; 4% EtOAc/hexanes)to afford bromide **136a** as a brownish-yellow solid (2.699 g); the sample is impure and contains stannane-derived impurities, among others. ^1H NMR ($CDCl_3$, $\delta = 7.24$, 400 MHz): 7.83 (s, 1H), 7.63 (s, 2H), 4.30 (s, 2H), 2.46 (s, 3H).

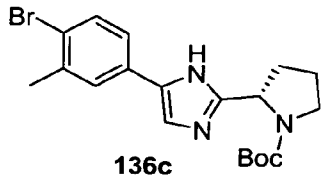
An CH_3CN (15 mL) solution of **136a** (2.69 g, < 9.21 mmol) was added drop wise over 3 min to a CH_3CN (30 mL) solution of (*S*)-Boc-proline (2.215 g, 10.3 mmol) and Et_3N (1.40 mL, 10.04 mmol), and stirred for 90 min. The volatile component was removed in vacuo, and the residue was partitioned between water and CH_2Cl_2, and the organic phase was dried ($MgSO_4$) and evaporated in vacuo. The resultant crude material was purified by a flash chromatography (silica gel; 15-20% EtOAc/hexanes) to afford **136b** as a colorless viscous oil (2.74g). ^1H NMR (DMSO-D_6, $\delta = 2.50$, 400 MHz): 7.98 (m, 1H), 7.78 (d, J = 8.3, 1H), 7.72-7.69 (m, 1H), 5.61-

5.41 (m, 2H), 4.35-4.30 (m, 1H), 3.41-3.30 (m, 2H), 2.43 (s, 3H), 2.33-2.08 (m, 2H), 1.93-1.83 (m, 2H), 1.40/1.36 (s, 9H).

LC (Cond. Ia): RT = 1.91 min; >95% homogeneity index

LC/MS: Anal. Calcd. for $[M+Na]^+$ $C_{19}H_{24}BrNNaO_5$ 448.07; found 448.10

Example 136, Step c



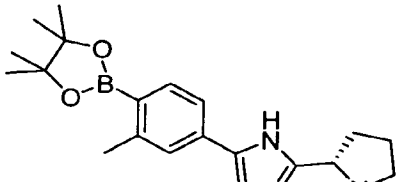
136c

A mixture of ketoester **136b** (1.445 g, 3.39 mmol) and NH_4OAc (2.93 g, 38.0 mmol) in xylenes (18 mL) was heated with a microwave at 140 °C for 80 min. The volatile component was removed in vacuo, and the residue was carefully partitioned between CH_2Cl_2 and water, where enough saturated $NaHCO_3$ solution was added to neutralize the aqueous medium. The aqueous phase was extracted with CH_2Cl_2, and the combined organic phase was dried ($MgSO_4$) and evaporated in vacuo. The crude was purified by a flash chromatography (silica gel, 40% EtOAc/hexanes) to afford imidzaole **136c** as an off-white solid (1.087 g). ^1H NMR (DMSO-D_6, δ = 2.50, 400 MHz): 12.15/11.91/11.84 (br s, 1H), 7.72-7.24 (m, 4H), 4.78 (m, 1H), 3.52 (m, 1H), 3.38-3.32 (m, 1H), 2.35 (s, 3H), 2.28-1.77 (m, 4H), 1.40/1.14 (s, 9H).

LC (Cond. Ib): RT = 1.91 min; >98% homogeneity index

LC/MS: Anal. Calcd. for $[M+H]^+$ $C_{19}H_{25}BrN_3O_2$ 405.96; found 406.11

Example 136, Step d



136d

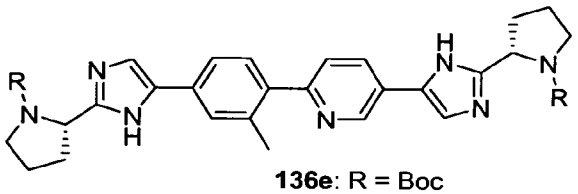
$PdCl_2dppf.CH_2Cl_2$ (50.1 mg, 0.061 mmol) was added to a pressure tube containing a mixture of bromide **136c** (538.3 mg, 1.325 mmol), bis(pinacolato)diboron (666.6 mg, 2.625 mmol), KOAc (365.8 mg, 3.727 mmol) and DMF (10 mL). The reaction mixture was flushed with N_2 and heated at 80 °C for

24.5 hr. The volatile component was removed in vacuo and the residue was partitioned between CH_2Cl_2 and water, where enough saturated $NaHCO_3$ solution was added to make the pH of the aqueous medium neutral. The aqueous phase was extracted with CH_2Cl_2, and the combined organic phase was dried ($MgSO_4$) and evaporated in vacuo. The resulting material was purfied by a Biotage system (silica gel, 40-50% EtOAc/hexanes) to afford boronate **136d** as a white foam (580 mg). According to ^1H NMR the sample contains residual pinacol in a product/pinacol ratio of ~3. ^1H NMR (DMSO-D_6, δ = 2.50, 400 MHz): 12.16/11.91/11.83 (br s, 1H), 7.63-7.25 (m, 4H), 4.78 (m, 1H), 3.53 (m, 1H), 3.39-3.32 (m, 1H), 2.48/2.47 (s, 3H), 2.28-1.78 (m, 4H), 1.40/1.14/1.12 (br s, 9H), 1.30 (s, 12H).

LC (Cond. Ia): RT = 1.62 min

LC/MS: Anal. Calcd. for $[M+H]^+$ $C_{25}H_{37}BN_3O_4$ 454.29; found 454.15

Example 136, Step e-f



136e: R = Boc
136f: R = H

Biaryl **136e** was prepared from bromide **132c** and boronate **136d** according to the coupling condition described for the preparation of biaryl **132d**.

LC (Cond. Ia): RT = 1.32 min; >90% homogeneity index

LC/MS: Anal. Calcd. for $[M+H]^+$ $C_{36}H_{45}N_7O_4$ 640.36; found 640.66

The deprotection of biaryl **136e** was done according to the preparation of pyrrolidine **132e** to afford **136f** as a light yellow foam. ^1H NMR (DMSO-D_6, δ = 2.50, 400 MHz): 11.88 (br s, 2H), 9.02 (d, J = 2, 1H), 8.12 (dd, J = 8.4, 2.3, 1H), 7.67 (s, 1H), 7.64-7.62 (m, 2H), 7.50 (d, J = 8.3, 1H), 7.46 (br s, 1H), 7.40 (d, J = 7.8, 1H), 4.21-4.14 (m, 2H), 3.00-2.93 (m, 2H), 2.90-2.82 (m, 2H), 2.40 (s, 3H), 2.11-2.01 (m, 2H), 1.94-1.85 (m, 2H), 1.82-1.66 (m, 4H). [Note: the signal for the pyrrolidine NH appears in the region 3.22-2.80 and is too broad to make a chemical shift assignment.]

LC (Cond. Ia): RT = 0.84 min

LC/MS: Anal. Calcd. for $[M+H]^+$ $C_{26}H_{30}N_7$ 440.26; found 440.50

Example 136

Example 136 (TFA salt) was synthesized from **136f** according to the preparation of **Example 132** from **132e**.

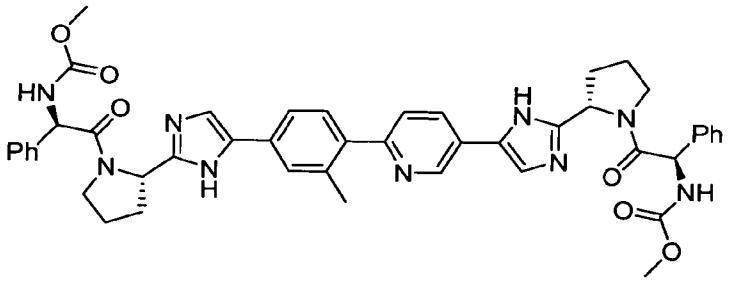
1.05 min (Cond. Ia); >98%

LC/MS: Anal. Calcd. for $[M+H]^+$ $C_{46}H_{52}N_9O_2$: 762.42, found: 762.77

HRMS: Anal. Calcd. for $[M+H]^+$ $C_{46}H_{52}N_9O_2$: 762.4244; found 762.4243

Example 138 was prepared similarly from pyrrolidine **136f** and **Cap-4**.

Example 138

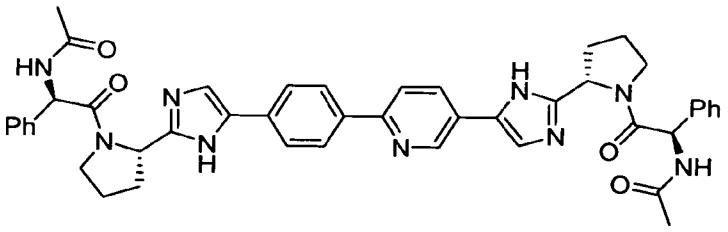


1.60 min (Cond. Ia); >98%

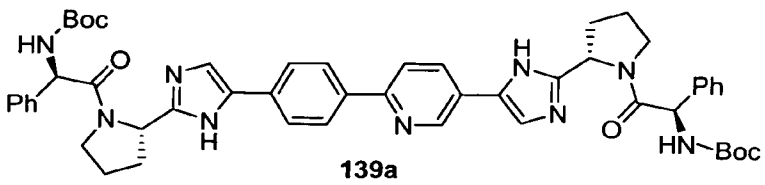
LC/MS: Anal. Calcd. for $[M+H]^+$ $C_{46}H_{48}N_9O_6$: 822.37; found 822.74

HRMS: Anal. Calcd. for $[M+H]^+$ $C_{46}H_{48}N_9O_6$: 822.3728; found 822.3760

Example 139



Example 139, Step a



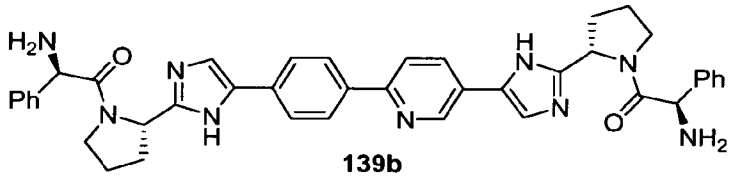
139a

HATU (99.8 mg, 0.262 mmol) was added to a mixture of **132e** (54.1 mg, 0.127 mmol), (*R*)-2-(*t*-butoxycarbonylamino)-2-phenylacetic acid (98.5 mg, 0.392 mmol) and *i*-Pr_2EtN (100 μL, 0.574 mol), and the reaction mixture was stirred for 70 min. The volatile component was removed in vacuo, and the residue was purified by a reverse phase HPLC (H_2O/MeOH/TFA), where the HPLC elute was treated with excess 2.0 N NH_3/MeOH before the removal of the volatile component in vacuo. The resulting material was partitioned between CH_2Cl_2 and water, and the aqueous phase was extracted with CH_2Cl_2 (2x). The combined organic phase was dried ($MgSO_4$) and evaporated in vacuo. Carbamate **139a** was obtained as a white film of foam (82.3 mg).

LC (Cond. Ib): RT = 1.97 min; >95% homogeneity index.

LC/MS: Anal. Calcd. for $[M+H]^+$ $C_{51}H_{58}N_9O_6$: 892.45; found 892.72

Example 139b, Step b



139b

Carbamate **139a** was deprotected to amine **139b** by using the procedure described for the preparation of pyrrolidine **132e** from **132d**.

LC (Cond. Ib): RT = 1.37 min; >95% homogeneity index

LC/MS: Anal. Calcd. for $[M+H]^+$ $C_{41}H_{42}N_9O_2$: 692.35; found 692.32

Example 139

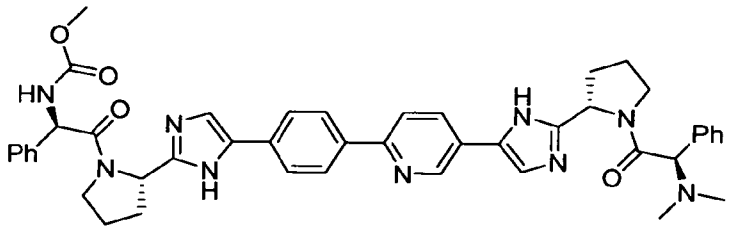
Acetic anhydride (20 μL, 0.212 mmol) was added to a DMF (1.5 mL) solution of **139b** (31.2 mg, 0.045 mmol), and the reaction mixture was stirred for 1 hr. NH_3/MeOH (1.0 mL of 2N) was added to the reaction mixture and stirring continued for 100 min. The volatile component was removed in vacuo and the resulting crude material was purified by a reverse phase HPLC (H_2O/MeOH/TFA) to afford the TFA salt of **Example 139** as a light yellow solid (24.1 mg).

LC (Cond. Ib): RT = 1.53 min; >98% homogeneity index

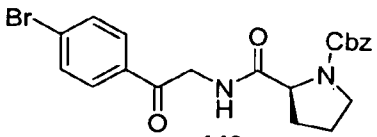
LC/MS: Anal. Calcd. for $[M+H]^+$ $C_{45}H_{46}N_9O_4$: 776.37; found 776.38

HRMS: Anal. Calcd. for $[M+H]^+$ $C_{45}H_{46}N_9O_4$: 776.3673; found 776.3680

Example 140



Example 140, Step a



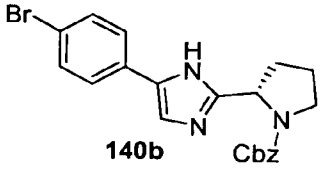
140a

HATU (19.868g, 52.25 mmol) was added to a heterogeneous mixture of *N*-Cbz-L-proline (12.436 g, 49.89 mmol) and the HCl salt of 2-amino-1-(4-bromophenyl) ethanone (12.157 g, 48.53 mmol) in DMF (156 mL). The mixture was lowered in an ice-water bath, and immediately afterward *N,N*-diisopropylethylamine (27 mL, 155 mmol) was added drop wise to it over 13 min. After the addition of the base was completed, the cooling bath was removed and the reaction mixture was stirred for an additional 50 min. The volatile component was removed in vacuo; water (125 mL) was added to the resultant crude solid and stirred for about 1 hr. The off-white solid was filtered and washed with copious water, and dried in vacuo to afford ketoamide **140a** as a white solid (20.68 g). ^{1}H NMR (DMSO-d_6, δ= 2.5 ppm, 400 MHz): 8.30 (m, 1H), 7.91 (m, 2H), 7.75 (d, J= 8.5, 2H), 7.38-7.25 (m, 5H), 5.11-5.03 (m, 2H), 4.57-4.48 (m, 2H), 4.33-4.26 (m, 1H), 3.53-3.36 (m, 2H), 2.23-2.05 (m, 1H), 1.94-1.78 (m, 3H).

LC (Cond. Ia): RT = 1.65 min; 98% homogeneity index

LC/MS: Anal. Calcd. for $[M+H]^+$ $C_{21}H_{22}BrN_2O_4$: 445.08; found 445.31

Example 140, Step b



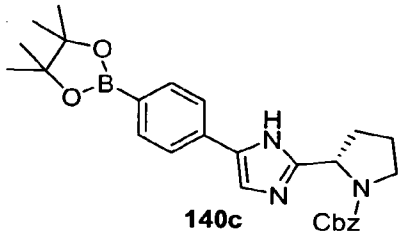
140b

Ketoamide **140a** (10.723g, 24.08 mmol) was converted to **140b** according to the procedure described for the synthesis of carbamate **132c**, with the exception that the crude material was purified by flash chromatography (silica gel; 50% EtOAc/hexanes). Bromide **140b** was retrieved as an off-white foam (7.622 g). ^{1}H NMR (DMSO-d_6, δ= 2.5 ppm, 400 MHz): 12.23/12.04/11.97 (m, 1H), 7.73-6.96 (m, 10H), 5.11-4.85 (m, 3H), 3.61 (m, 1H), 3.45 (m, 1H), 2.33-184(m, 4H).
LC (Cond.Ia): RT = 1.42 min; >95% homogeneity index
LC/MS: Anal. Calcd. for $[M+H]^+$ $C_{21}H_{21}BrN_3O_2$: 426.08; found 426.31
HRMS: Anal. Calcd. for $[M+H]^+$ $C_{21}H_{21}BrN_3O_2$: 426.0817; found: 426.0829

The optical purity of **140b** was assessed using the following chiral HPLC methods, and an ee of 99% was observed.

Column: Chiralpak AD, 10 um, 4.6 x 50 mm
Solvent: 20% ethanol/heptane (isocratic)
Flow rate: 1 ml/min
Wavelength: 254 nm
Relative retention time: 1.82 min (*R*), 5.23 min (*S*)

Example 140, Step c



140c

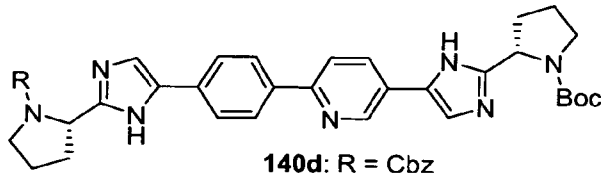
$Pd(Ph_3P)_4$ (208 mg, 0.180 mmol) was added to a pressure tube containing a mixture of bromide **140b** (1.80 g, 4.22 mmol), bis(pinacolato)diboron (2.146 g, 8.45 mmol), KOAc (1.8 g, 11.0 mmol) and 1,4-dioxane (34 mL). The reaction flask was purged with nitrogen, capped and heated with an oil bath at 80 °C for 23 hr. The volatile component was removed in vacuo, and the residue was partitioned carefully between CH_2Cl_2 (70 mL) and an aqueous medium (22 mL water + 5 mL saturated $NaHCO_3$ solution). The aqueous layer was extracted with CH_2Cl_2, and the combined organic phase was dried ($MgSO_4$) and evaporated in vacuo. The oily resdue was

crystallized from EtOAc/hexanes to afford two crops of boronate **140c** as a yellow solid (1.52 g). The mother liquor was evaporated in vacuo and the resulting material was purified by flash chromatography (silica gel; 20-35% EtOAc/CH_2Cl_2) to afford additional **140c** as an off-white solid, containing residual pinacol (772 mg).

LC (Cond. Ib): RT = 1.95 min

LC/MS: Anal. Calcd. for $[M+H]^+$ $C_{27}H_{33}BN_3O_4$: 474.26; found 474.31

Example 140, Step d-e



140d: R = Cbz
140e: R = H

Arylbromide **132c** was coupled with boronate **140c** to afford **140d** by using the same procedure described for the synthesis of biaryl **132d**. The sample contains the desbromo version of **132c** as an impurity. Proceeded to the next step without further purification.

LC (Cond. Ib): RT = 1.72 min; ~85% homogeneity index

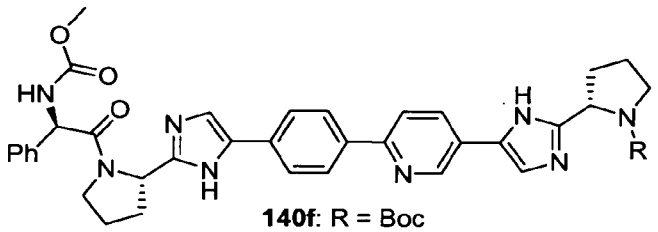
LC/MS: Anal. Calcd. for $[M+H]^+$ $C_{38}H_{42}N_7O_4$: 660.33; found 660.30

A mixture of 10% Pd/C (226 mg), biaryl **140d** (1.25 g) and MeOH (15 mL) was stirred under a balloon of hydrogen for ~160 hr, where the hydrogen supply was replenished periodically as needed. The reaction mixture was filtered through a pad of diatomaceous earth (Celite®), and the filtrate was evaporated in vacuo to afford crude **140e** as a yellowish-brown foam (911 mg). Proceeded to the next step without further purification.

LC (Cond. Ib): RT = 1.53 min

LC/MS: Anal. Calcd. for $[M+H]^+$ $C_{30}H_{36}N_7O_2$: 526.29; found 526.23

Example 140, Step f-g



140f: R = Boc
140g: R = H

Pyrrolidine **140g** was prepared from **140e** and **Cap-4**, via the intermediacy of carbamate **140f**, by sequentially employing the amide forming and Boc-deprotection protocols used in the synthesis of **Example 132**.

LC (Cond. Ia): RT = 1.09 min; ~94% homogeneity index

LC/MS: Anal. Calcd. for $[M+H]^+$ $C_{35}H_{37}N_8O_3$: 617.30; found 617.38

Example 140

The TFA salt of **Example 140** was synthesized from pyrrolidine **140g** and **Cap-1** by using the procedure described for the preparation of **Example 132** from intermediate **132e**.

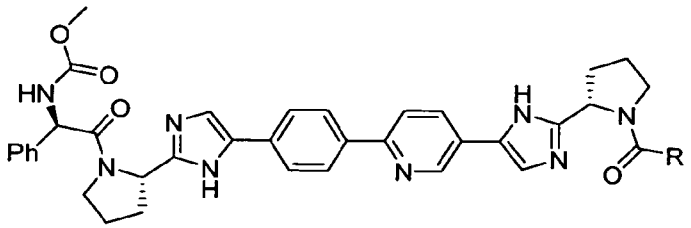
1.15 min (Cond. Ia); >98% homogeneity index

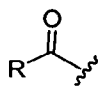
LC/MS: Anal. Calcd. for $[M+H]^+$ $C_{45}H_{40}N_7O_4$: 778.38; found 778.48

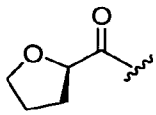
HRMS: Anal. Calcd. for $[M+H]^+$ $C_{45}H_{40}N_7O_4$: 778.3829; found 778.3849

The TFA salt of **Example 141-143** were synthesized from intermediate **140g** and appropriate reagents in a similar manner.

Example 141-143



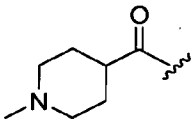
Example		**RT (LC-Cond.); % homogeneity index; MS data**

141 

1.15 min (Cond. Ia); >98%

LC/MS: Anal. Calcd. for $[M+H]^+$ $C_{40}H_{43}N_8O_5$: 715.34; found 715.44

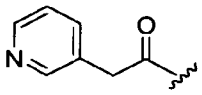
HRMS: Anal. Calcd. for $[M+H]^+$ $C_{40}H_{43}N_8O_5$: 715.3356; found 715.3381

142 

1.07 min (Cond. Ia); >98%

LC/MS: Anal. Calcd. for $[M+H]^+$ $C_{42}H_{48}N_9O_4$: 742.38; found 742.48

HRMS: Anal. Calcd. for $[M+H]^+$ $C_{42}H_{48}N_9O_4$: 742.3829; found 742.3859

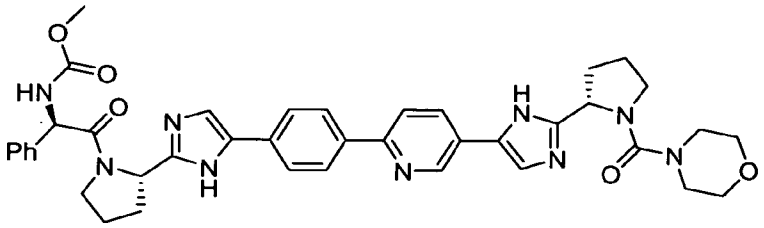
143 

1.09 min (Cond. Ia); >98%

LC/MS: Anal. Calcd. for $[M+H]^+$ $C_{42}H_{42}N_9O_4$: 736.34; found 736.44

HRMS: Anal. Calcd. for $[M+H]^+$ $C_{42}H_{42}N_9O_4$: 736.3360; 736.3344

Example 144



A DMF (1.5 mL) solution of morpholine-4-carbonyl chloride (8.5 mg, 0.057 mmol) was added to a mixture of *i*-Pr_2EtN (20 μL, 0.115 mmol) and **140g** (27.3 mg,

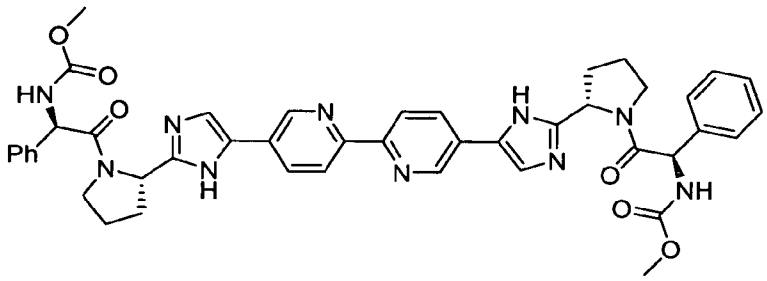
0.044 mmol), and stirred for 100 min. The volatile component was removed in vacuo and the residue was purified by a reverse phase HPLC (H_2O/MeOH/TFA) to afford the TFA salt of **Example 144** as a yellow foam (34.6 mg).

1.17 min (Cond. Ia); >98%

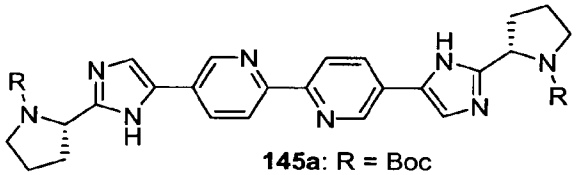
LC/MS: Anal. Calcd. for $[M+H]^+$ $C_{40}H_{44}N_9O_5$: 730.35; found 730.42

HRMS: Anal. Calcd. for $[M+H]^+$ $C_{40}H_{44}N_9O_5$: 730.3465; found 730.3477

Example 145



Example 145, Step a-b



145a: R = Boc
145b: R = H

$Pd(Ph_3P)_4$ (9.6 mg, 0.008 mmol) and LiCl (28 mg, 0.67 mmol) were added to a mixture of arylbromide **132c** (98.7 mg, 0.251 mmol) and hexamethylditin (51.6 mg, 0.158 mmol), and heated at 80 °C for ~ 3 days. The volatile component was removed in vacuo and the resultant crude material was purified by flash chromatography (silica gel; 0-10% MeOH/EtOAc) followed by a reverse phase HPLC (H_2O/MeOH/TFA). The HPLC elute was neutralized with excess 2.0 N NH_3/MeOH, and the volatile component was removed in vacuo. The residue was partitioned between CH_2Cl_2 and water, and the aqueous phase was washed with CH_2Cl_2 (2x). The combined organic phase was dried ($MgSO_4$) and evaporated in vacuo to afford carbamate **145a** as a film of oil (8.7 mg).

LC (Cond. Ib): RT = 1.68 min; >98% homogeneity index

LC/MS: Anal. Calcd. for $[M+H]^+$ $C_{34}H_{43}N_8O_4$: 627.34; found 627.47

Carbamate **145a** was elaborated to pyrrolidine **145b** according to the preparation of **132e** from **132d**. ^{1}H NMR (DMSO, δ = 2.5 ppm; 400 MHz): 12.02 (br signal, 2H), 9.04 (d, J = 1.6, 2H), 8.34 (d, J = 8.3, 2H), 8.20 (dd, J = 8.3, 2.3, 2H), 7.67 (br s, 1H), 4.21 (m, 2H), 3.00-2.85 (m, 4H), 2.12-2.04 (m, 2H), 1.95-1.68 (m, 6H). [Note: the pyrrolidine-NH signal was not observed].

LC (Cond. Ib): RT = 1.17 min; >98% homogeneity index

LC/MS: Anal. Calcd. for $[M+H]^+$ $C_{24}H_{27}N_8$: 427.24; found 427.13

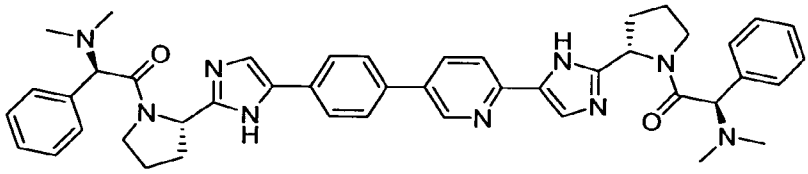
Example 145

Example 145 (TFA salt) was synthesized from **145b** according to the preparation of **Example 132** from **132e**.

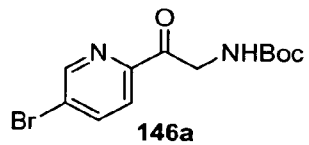
LC (Cond. Ib): RT = 1.63 min; 98% homogeneity index

LC/MS: Anal. Calcd. for $[M+H]^+$ $C_{44}H_{45}N_{10}O_6$: 809.35; found 809.40

Example 146



Example 146, Step a

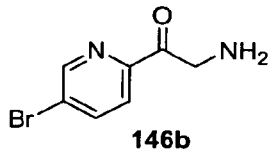


146a

n-BuLi (12.0 mL of 2.5M/hexanes, 30 mmol) was added drop-wise over 15 min to a cooled (-78 °C) toluene (300 mL) semi-solution of 2,5-dibromopyridine (6.040 g, 25.5 mmol), and stirred for 2.5 hr. *t*-Butyl 2-(methoxy(methyl)amino)-2-oxoethylcarbamate (2.809 g, 12.87 mmol) was added in batches over 7 min, and stirring continued for 1.5 hr at -78 °C. The -78 °C bath was replaced with -60 °C bath, which was allowed to warm up to -15 °C over 2.5 hr. The reaction was quenched

with saturated NH_4Cl solution (20 mL), and the mixture was allowed to thaw to ambient temperature and the organic layer was separated and evaporated in vacuo. The resulting crude material was purified by flash chromatography (silica gel; 15 % EtOAc/hexanes) to afford a reddish brown semisolid, which was washed with hexanes to removed the colored residue. Pyridine **146a** was retrieved as an ash colored solid (842 mg). ^{1}H NMR (DMSO, δ = 2.5 ppm; 400 MHz): 8.89 (d, J = 2.3, 1H), 8.30 (dd, J = 8.4, 2.4, 1H), 7.90 (d, J = 8.3, 1H), 7.03(br t, J = 5.7; 0.88H), 6.63 (app br s, 0.12H), 4.55 (d, J = 5.8, 2H), 1.40/1.28 (two app s, 7.83H + 1.17H).
LC (Cond. Ib): RT = 2.00 min; >95% homogeneity index
LC/MS: Anal. Calcd. for $[M+Na]^+$ $C_{12}H_{15}BrNaN_2O_3$: 337.02; found 337.13

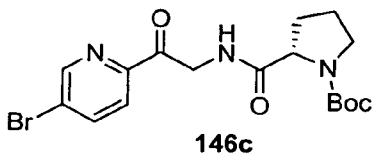
Example 146, Step b



146b

48% HBr (1.0 mL) was added drop-wise to a dioxane (5.0 mL) solution of carbamate **146a** (840 mg, 2.66 mmol) over 3 min, and the reaction mixture was stirred at ambient temperature for 17.5 hr. The precipitate was filtered and washed with dioxane, and dried in vacuo to afford amine the HBr salt of **146b** as an off-white solid (672.4 mg; the exact mole equivalent of the HBr salt was not determined). ^{1}H NMR (DMSO, δ = 2.5 ppm; 400 MHz): 8.95 (d, J = 2.3, 1 H), 8.37 (dd, J = 8.4, 2.3, 1H), 8.2 (br s, 3H), 8.00 (d, J = 8.3, 1H), 4.61 (s, 2H).
LC (Cond. Ib): RT = 0.53 min
LC/MS: Anal. Calcd. for $[M+H]^+$ $C_7H_8BrN_2O$: 214.98; found 215.00

Example 146, Step c



146c

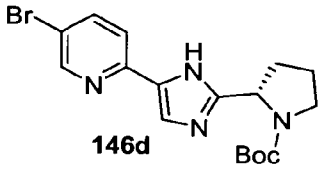
i-Pr_2EtN (2.3 mL, 13.2 mmol) was added drop-wise over 15 min to a heterogonous mixture of amine **146b** (1.365g), (*S*)-Boc-proline (0.957 g, 4.44 mmol) and HATU (1.70 g, 4.47 mmol) in DMF (13.5 mL), and stirred at ambient

temperature for 1 hr. The volatile component was removed in vacuo and the residue was partitioned between EtOAc (40 mL) and an aqueous medium (20 mL water + 1 ml saturated $NaHCO_3$ solution). The aqueous layer was washed with EtOAc (20 mL), and the combined organic phase was dried (brine; $MgSO_4$) and evaporated in vacuo. The resultant crude material was purified by flash chromatography (silica gel; 40-50% EtOAc/hexanes) to afford ketoamide **146c** as a faint-yellow foam (1.465g). ^1H NMR (DMSO, δ = 2.5 ppm; 400 MHz): 8.90 (d, J = 2.3, 1H), 8.30 (dd, J = 8.5, 2.4, 1H), 8.01-8.07 (m, 1H), 7.90 (d, J = 8.3, 1H), 4.6 (m, 1H), 4.64 (dd, J = 19.1, 5.5, 1H); 4.19 (m, 1H), 3.39 (m, 1H), 3.32-3.26 (m, 1H), 2.20-2.01 (m, 1H), 1.95-1.70 (m, 3H),1.40/1.35 (two app s, 9H).

LC (Cond. Ib): RT = 1.91 min

LC/MS: Anal. Calcd. for $[M+Na]^+$ $C_{17}H_{22}BrN_3NaO_4$: 434.07; found 433.96.

Example 146, Step d



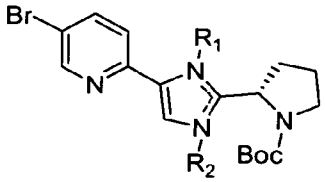
146d

A mixture of ketoamide **146c** (782.2 mg, 1.897 mmol) and NH_4OAc (800 mg, 10.4 mmol) in xylenes was heated with a microwave (140 °C) for 90 min. The volatile component was removed in vacuo and the residue was carefully partitioned between CH_2Cl_2 and water, where enough saturated $NaHCO_3$ solution was added to neutralize it. The aqueous phase was extracted with CH_2Cl_2 (2x), and the combined organic phase was dried ($MgSO_4$) and evaporated in vacuo. The resultant crude material was purified by flash chromatography (silica gel; 50% CH_2Cl_2/EtOAc) to afford imidazole **146d** as an off-white solid (552.8 mg). ^1H NMR (DMSO, δ = 2.5 ppm; 400 MHz): 12.49/12.39/12.15/12.06 (br s, 1H), 8.62 (app br s, 0.2H), 8.56 (d, J = 2, 0.8H), 8.02 (br d, J = 8.5, 0.2H), 7.97 (br d, J = 7.8, 0.8H), 7.77 (d, J = 8.6, 0.8H), 7.72 (d, J = 8.6, 0.2H), 7.61-7.49 (m, 1H), 4.93-4.72 (m, 1H), 3.53 (m, 1H), 3.41-3.32 (m, 1H), 2.33-1.77 (m, 4H), 1.39/1.14 (app br s, 3.7H+5.3H).

LC (Cond. Ib): RT = 1.67 min; >95% homogeneity index

LC/MS: Anal. Calcd. for $[M+Na]^+$ $C_{17}H_{21}BrN_4NaO_2$: 415.08; found 415.12

Example 146, Step e



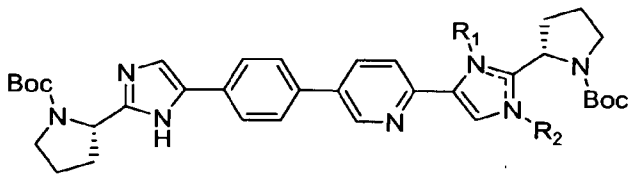
146e (R_1 = H, R_2 = SEM) or (R_1 = SEM, R_2 = H)

NaH (60%; 11.6 mg, 0.29 mmol) was added in one batch to a heterogeneous mixture of imidazole **146d** (80 mg, 0.203 mmol) and DMF (1.5 mL), and stirred at ambient condition for 30 min. SEM-Cl (40 μL, 0.226 mmol) was added drop-wise over 2 min to the above reaction mixture, and stirring was continued for 14 hr. The volatile component was removed in vacuo and the residue was partitioned between water and CH_2Cl_2. The aqueous layer was extracted with CH_2Cl_2, and the combined organic phase was dried ($MgSO_4$) and evaporated in vacuo. The crude material was purified by a flash chromatography (silica gel; 20% EtOAc/hexanes) to afford **146e** as a colorless viscous oil (87.5 mg). The exact regiochemistry of **146e** was not determined. ^{1}H NMR ($CDCl_3$, δ = 7.4 ppm; 400 MHz): 8.53 (d, J = 2.2, 1H), 7.90-7.72 (m, 2H), 7.52 (s, 1H), 5.87 (m, 0.46H), 5.41 (m, 0.54H), 5.16 (d, J = 10.8, 1H), 5.03-4.85 (m, 1H), 3.76-3.42 (m, 4H), 2.54-1.84 (m, 4H), 1.38/1.19 (br s, 4.3H + 4.7H), 0.97-0.81 (m, 2H), -0.03 (s, 9H).

LC (Cond. Ia): RT = 2.1 min

LC/MS: Anal. Calcd. for $[M+H]^+$ $C_{23}H_{36}BrN_4O_3Si$: 523.17; found 523.24

Example 146, Step f



146f: (R_1 = H, R_2 = SEM) or (R_1 = SEM, R_2 = H)

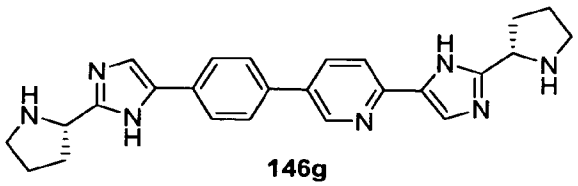
$Pd(Ph_3P)_4$ (24.4 mg, 0.021 mmol) was added to a mixture of imidazole **146e** (280 mg, 0.535 mmol), **1c** (241.5 mg, 0.55 mmol) and $NaHCO_3$ (148.6 mg, 1.769 mmol) in 1,2-dimethoxyethane (4.8 mL) and water (1.6 mL). The reaction mixture was flushed with nitrogen, heated with an oil bath at 80 °C for ~24 hr and then the volatile component was removed in vacuo. The residue was partitioned between

CH_2Cl_2 and water, and the organic phase was dried ($MgSO_4$) and evaporated in vacuo. The crude material was purified by a Biotage system (silica gel; 75-100% EtOAc/hexanes) followed by a reverse phase HPLC (H_2O/MeOH/TFA). The HPLC elute was neutralized with 2M NH_3/MeOH and evaporated in vacuo, and the residue was partitioned between water and CH_2Cl_2. The organic layer was dried ($MgSO_4$) and evaporated in vacuo to afford **146f** as a white foam (162 mg).

LC (Cond. Ib): RT = 2.1 min

LC/MS: Anal. Calcd. for $[M+H]^+$ $C_{41}H_{58}N_7O_5Si$: 756.43; found 756.55

Example 146, Step g



146g

Carbamate **146f** (208 mg, 0.275 mmol) was treated with 25% TFA/CH_2Cl_2 (4.0 mL) and stirred at ambient temperature for 10 hr. The volatile component was removed in vacuo and the residue was first free-based by MCX (MeOH wash; 2.0 M NH_3/MeOH elution) and then purified by a reverse phase HPLC (H_2O/MeOH/TFA), and the resultant material was free-based again (MCX) to afford pyrrolidine **146g** as a film of oil (53.7 mg). ^1H NMR (DMSO, δ = 2.5 ppm; 400 MHz): 1.88 (app br s, 2H), 8.83 (d, J = 2.1, 1H), 8.07 (dd, J = 8.3/2.3, 1H0, 7.87 (d, J = 8.5, 1H), 7.84 (d, J = 8.3, 2H), 7.71 (d, J = 8.3, 2H), 7.55 (s, 1H), 7.50 (br s, 1H), 4.18 (m, 2H), 3.00-2.94 (m, 2H), 2.89-2.83 (m, 2H), 2.11-2.02 (m, 2H), 1.95-1.86 (m, 2H), 1.83-1.67 (m, 4H).

LC (Cond. Ia): RT = 0.95 min; >98% homogeneity index

LC/MS: Anal. Calcd. for $[M+H]^+$ $C_{25}H_{28}N_7$: 426.24; found 426.27

Example 146

Example 146 (TFA salt) was synthesized from pyrrolidine **146g** according to the preparation of **Example 132** from intermediate **132e**.

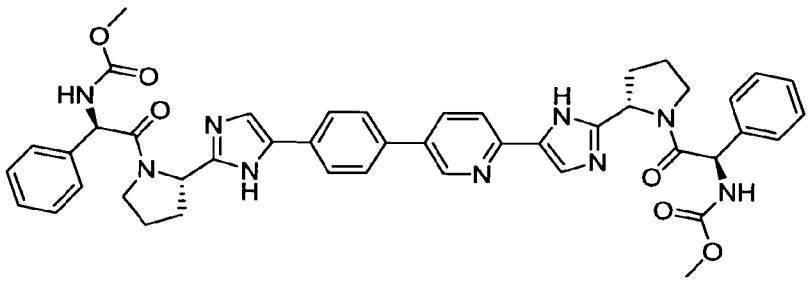
LC (Cond. Ib): RT = 1.42 min; 96.5% homogenity index

LC/MS: Anal. Calcd. for $[M+H]^+$ $C_{45}H_{50}N_9O_2$: 748.41; found 748.57

HRMS: Anal. Calcd. for $[M+H]^+$ $C_{45}H_{50}N_9O_2$: 748.4087; found 748.4100

The TFA salt of **Example 147** was prepared similarly from intermediate **146g** by using **Cap-4**.

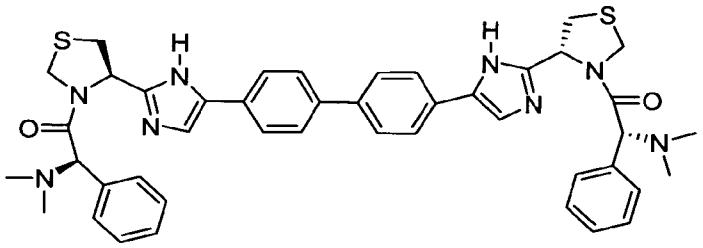
Example 147



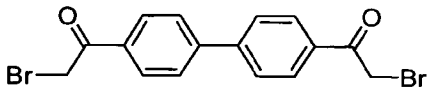
LC (Cond. Ib): RT = 1.66 min; 95% homogenity index

LC/MS: Anal. Calcd. for $[M+H]^+$ $C_{45}H_{46}N_9O_6$: 808.36; found 808.55

Example 148



Example 148, Step a; 1,1'-(biphenyl-4,4'-diyl)bis(2-bromoethanone)



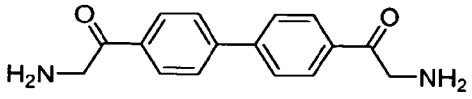
Example 148a

A solution of bromine (1.3mL, 25.0mmol) in 15mL glacial acetic acid was added drop-wise to a solution of 4-4'-diacetylbiphenyl (3.0g, 12.5mmol) in 40mL acetic acid at 50°C. Upon completion of addition the mixture was stirred at room temperature overnight. The precipitated product was filtered off and re-crystallized from chloroform to give 1,1'-(biphenyl-4,4'-diyl)bis(2-bromoethanone) (3.84g, 77.5%) as a white solid.

^{1}H NMR (500 MHz, CHLOROFORM-D) δ ppm 8.09 (4 H, d, *J*=7.93 Hz) 7.75 (4 H, d, *J*=8.24 Hz) 4.47 (4 H, s)

Nominal/LRMS – Anal. Calcd. for 369.07 found; $(M+H)^+$ - 397.33, $(M-H)^-$ - 395.14

Example 148, Step b; 1,1'-(biphenyl-4,4'-diyl)bis(2-aminoethanone) dihydrochloride



.2HCl

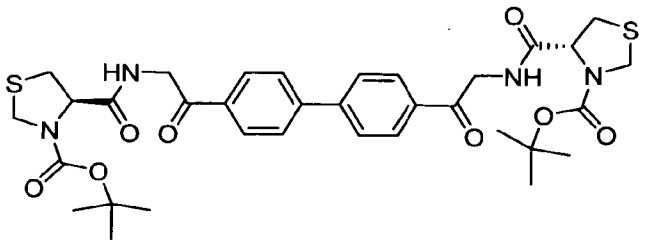
Example 148b

Sodium diformylamide (3.66g, 38.5mmol) was added to a suspension of 1,1'-(biphenyl-4,4'-diyl)bis(2-bromoethanone) (6.1g, 15.4mmol) in 85mL acetonitrile. The mixture was heated at reflux for 4 hours and concentrated under reduced pressure. The residue was suspended in 300mL 5% HCl in ethanol and heated at reflux for 3.5 hours. Reaction was cooled to room temperature and placed in the freezer for 1 hour. Precipitated solid was collected, washed with 200mL 1:1 ethanol/ether followed by 200mL pentane, and dried under vacuum to give 1,1'-(biphenyl-4,4'-diyl)bis(2-aminoethanone) dihydrochloride (4.85g, 92%). Carried on without further purification.

^{1}H NMR (300 MHz, DMSO-d_6) δ ppm 8.47-8.55 (4H, m) 8.11 - 8.17 (4 H, m) 8.00 (4 H, d, *J*=8.42 Hz) 4.59 - 4.67 (4 H, m).

LCMS – Phenomenex C-18 3.0 x 50mm, 0 to 100% B over 4.0 minute gradient, 1 minute hold time, A = 10% methanol 90% water 0.1% TFA, B = 90% methanol 10% water 0.1% TFA, t_R = 0.44 minutes, Anal. Calcd. for $C_{16}H_{16}N_2O_2$ 268.31 found; 269.09 $(M+H)^+$.

Example 148, Step c; (4S,4'S)-tert-butyl 4,4'-(2,2'-(biphenyl-4,4'-diyl)bis(2-oxoethane-2,1-diyl))bis(azanediyl)bis(oxomethylene)dithiazolidine-3-carboxylate



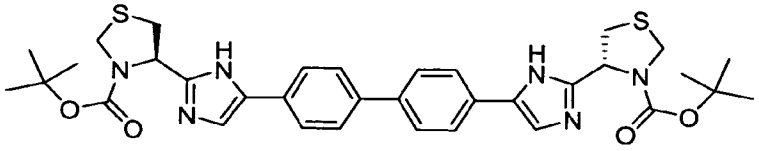
Example 148c

To a stirred solution of 1,1'-(biphenyl-4,4'-diyl)bis(2-aminoethanone) dihydrochloride (0.7g, 2.1mmol), N-(tert-butoxy carbonyl) –L-thioproline (0.96g, 4.2mmol), and HATU(1.68g, 4.4mmol) in 14mL DMF was added diisopropylethyl amine (1.5mL, 8.4mmol) drop-wise over 5 minutes. The resulting clear yellow solution was stirred at room temperature overnight (14 hours) and concentrated under reduced pressure. The residue was partitioned between 20%methanol/chloroform and water. The aqueous phase was washed once with 20%methanol/chloroform. The combined organics were washed with brine, dried ($MgSO_4$), and concentrated under reduced pressure. The crude product was chromatographed on silica gel by gradient elution with 10-50% ethyl acetate/CH_2Cl_2 to give (4S,4'S)-tert-butyl 4,4'-(2,2'-(biphenyl-4,4'-diyl)bis(2-oxoethane-2,1-diyl))bis(azanediyl)bis(oxomethylene)dithiazolidine-3-carboxylate (0.39g, 27%) as an orange foam.

^{1}H NMR (400 MHz, DMSO-d_6) δ ppm 8.38 (2 H, s) 8.12 (4 H, d, *J*=8.56 Hz) 7.94 (4 H, d, *J*=8.56 Hz) 4.60 - 4.68 (4 H, m) 4.33 - 4.38 (2 H, m) 3.58 - 3.68 (2 H, m) 3.38 (2 H, s) 3.08 - 3.18 (2 H, m) 1.40 (18 H, s)

LCMS – Water-Sunfire C-18 4.6 x 50mm, 0 to 100% B over 4.0 minute gradient, 1 minute hold time, A = 10% methanol 90% water 0.1% TFA, B = 90% methanol 10% water 0.1% TFA, t_R = 3.69 min., Anal. Calcd. for $C_{34}H_{42}N_4O_8S_2$ 698.85 found; 699.12 $(M+H)^+$.

Example 148, Step d; (4S,4'S)-tert-butyl 4,4'-(5,5'-(biphenyl-4,4'-diyl)bis(1H-imidazole-5,2- diyl))dithiazolidine-3-carboxylate

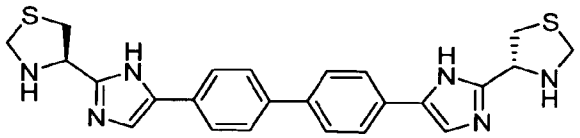


148d

(4S,4'S)-tert-butyl 4,4'-(5,5'-(biphenyl-4,4'-diyl)bis(1H-imidazole-5,2-diyl))dithiazolidine-3-carboxylate (0.39g, 0.56mmol) and ammonium acetate (0.43g, 5.6mmol) were suspended in 8mL o-xylene in a microwave reaction vessel. The mixture was heated under standard microwave conditions at 140°C for 70 minutes and concentrated under reduced pressure. The residue was dissolved in 30mL 20% methanol/chloroform and washed with 10% $NaHCO_3$(aq). The organic layer was washed with brine, dried ($MgSO_4$), and concentrated under reduced pressure. The crude product was chromatographed on silica gel by gradient elution with 1-6% methanol/CH_2Cl_2 to give (4S,4'S)-tert-butyl 4,4'-(5,5'-(biphenyl-4,4'-diyl)bis(1H-imidazole-5,2- diyl))dithiazolidine-3-carboxylate (0.15g, 41%) as a yellow solid. ^{1}H NMR (500 MHz, DMSO-d_6) δ ppm 12.02 (2 H, s) 7.70 - 7.88 (10 H, m) 5.28 - 5.37 (2 H, m) 4.68 (2 H, d, *J*=9.16 Hz) 4.47 - 4.55 (2 H, m) 3.46 (2 H, s) 3.23 (2 H, s) 1.26 – 1.43 (18 H, m)

LCMS - Luna C-18 3.0 x 50mm, 0 to 100% B over 3.0 minute gradient, 1 minute hold time, A = 5% acetonitrile, 95% water, 10mm ammonium acetate, B = 95% acetonitrile, 5% water, 10mm ammonium acetate, t_R = 1.96 min., Anal. Calcd. for $C_{34}H_{40}N_6O_4S_2$ 660.85 found; 661.30 $(M+H)^+$, 659.34 $(M-H)^-$

Example 148, Step e; 4,4'-bis(2-((S)-thiazolidin-4-yl)-1H-imidazol-5-yl)biphenyl tetrahydrochloride



.4HCl

148e

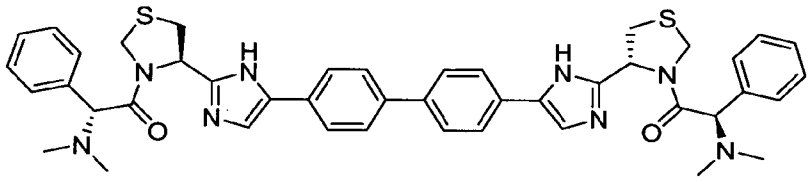
To a solution of (4S,4'S)-tert-butyl 4,4'-(5,5'-(biphenyl-4,4'-diyl)bis(1H-imidazole-5,2- diyl))dithiazolidine-3-carboxylate in 1mL dioxane was added 0.3mL of a 4.0M solution of HCl in dioxane. The reaction was stirred for 3 hours at room temperature

and concentrated under reduced pressure. The resulting tan solid was dried under vacuum to give 4,4'-bis(2-((S)-thiazolidin-4-yl)-1H-imidazol-5-yl)biphenyl tetrahydrochloride (0.12g, 100%) as a yellow solid.

^{1}H NMR (500 MHz, DMSO-d_6) δ ppm 8.09 (2 H, s) 8.01 (4 H, d, *J*=8.55 Hz) 7.90 (4 H, d, *J*=8.55 Hz) 5.08 (2 H, t, *J*=6.10 Hz) 4.38 (2 H, d, *J*=9.16 Hz) 4.23 (2 H, d, *J*=9.46 Hz) 3.48 - 3.54 (2 H, m,) 3.35 - 3.41 (2 H, m)

LCMS - Luna C-18 3.0 x 50mm, 0 to 100% B over 4.0 minute gradient, 1 minute hold time, A = 5% acetonitrile, 95% water, 10mm ammonium acetate, B = 95% acetonitrile, 5% water, 10mm ammonium acetate, t_R = 1.70 min., Anal. Calcd. for $C_{24}H_{24}N_6S_2$ 460.62 found; 461.16 $(M+H)^+$, 459.31 $(M-H)^-$

Example 148; (2R,2'R)-1,1'-((4S,4'S)-4,4'-(5,5'-(biphenyl-4,4'-diyl)bis(1H-imidazole-5,2-diyl))bis(thiazolidine-4,3-diyl))bis(2-(dimethylamino)-2-phenylethanone)



148

To a stirred solution of (4,4'-bis(2-((S)-thiazolidin-4-yl)-1H-imidazol-5-yl)biphenyl tetrahydrochloride (0.028g, 0.046mmol), (R)-2-(dimethylamino)-2-phenylacetic acid (**cap-1**, 0.017g, 0.0.10mmol), and HATU (0.039g, 0.10mmol) in 2mL DMF was added diisopropylethyl amine (0.05mL, 0.28mmol).The reaction was stirred at room temperature overnight (16 hours) and concentrated under reduced pressure. The crude product was purified by reverse-phase preparative HPLC to provide (2R,2'R)-1,1'-((4S,4'S)-4,4'-(5,5'-(biphenyl-4,4'-diyl)bis(1H-imidazole-5,2-diyl))bis(thiazolidine-4,3-diyl))bis(2-(dimethylamino)-2-phenylethanone), TFA salt (0.012g, 21%)

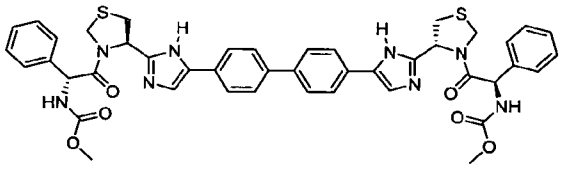
^{1}H NMR (500 MHz, DMSO-d_6) δ ppm 7.59 - 7.91 (20 H, m) 5.62 (2 H, dd, *J*=6.56, 2.59 Hz) 4.99 (2 H, d, *J*=8.85 Hz) 4.82/4.35 (2 H, s) 4.22 (2 H, s) 3.42 (2 H, s) 3.25 (2 H, s) 2.35-2.61 (12H, m)

LCMS - Luna C-18 3.0 x 50mm, 0 to 100% B over 7.0 minute gradient, 1 minute hold time, A = 5% acetonitrile, 95% water, 10mm ammonium acetate, B = 95% acetonitrile, 5% water, 10mm ammonium acetate mobile phase t_R = 3.128 min.

Nominal/LRMS – Calcd. for $C_{44}H_{46}N_8O_2S_2$ 783.03; found 783.28 $(M+H)^+$
Accurate/HRMS – Calcd. for $C_{44}H_{47}N_8O_2S_2$ 783.3263; 783.3246 $(M+H)^+$

Examples **149** and **150** were prepared in similar fashion as described for the preparation of example **148.**

Example 149



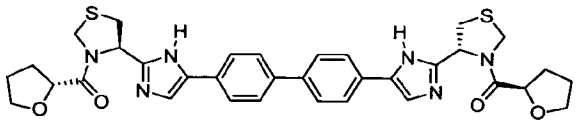
from **148e** and **cap-4**

t_R = 3.36 min , method F

LCMS: Anal. Calcd. for $C_{44}H_{42}N_8O_6S_2$ 842.99
found: 843.25 $(M+H)^+$

HRMS: Anal. Calcd. for $C_{44}H_{43}N_8O_6S_2$ 843.2747
found: 843.2724 $(M+H)^+$

Example 150

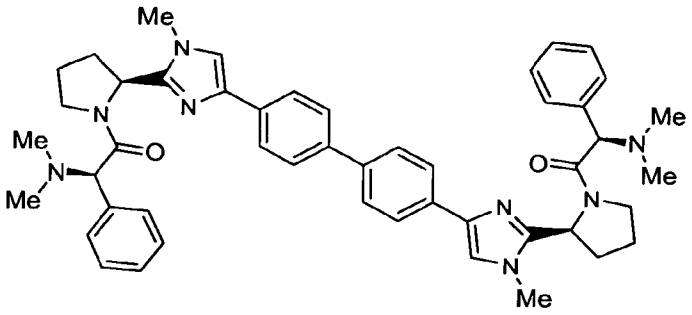


from **148e** and tetrahydrofuroic acid

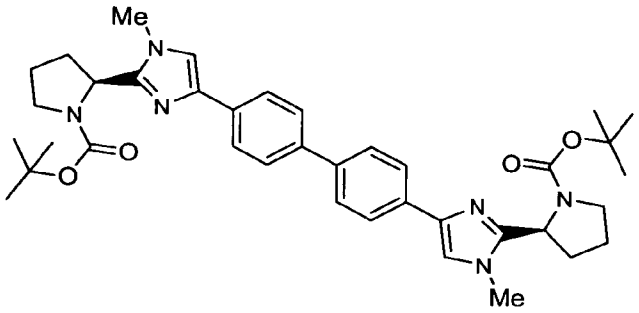
t_R = 4.32 min, method B

LRMS: Anal. Calcd. for $C_{34}H_{36}N_6O_4S_2$ 656.83
found: 657.32 $(M+H)^+$

Example 151



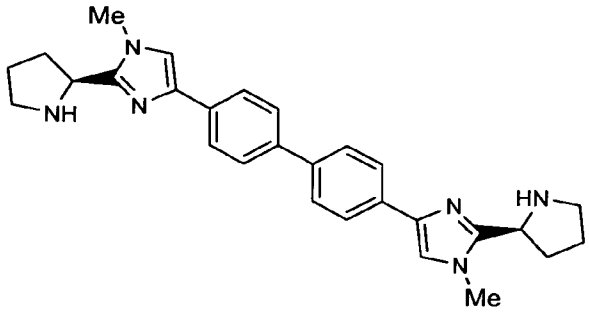
Example 151, Step a



151a

To a stirred solution of **1d**, (2S,2'S)-tert-butyl 2,2'-(4,4'-(biphenyl-4,4'-diyl)bis(1H-imidazole-4,2-diyl))dipyrrolidine-1-carboxylate (100 mg, 0.16 mmole) and iodomethane (40 µL, 0.16 mmole) in CH_2Cl_2 (2 mL) was added sodium hydride (40%) (21.2 mg, 0.352 mmole). After five hours at ambient temperature, it was concentrated under reduced pressure. The crude reaction product **151a**, (2S,2'S)-tert-butyl 2,2'-(4,4'-(biphenyl-4,4'-diyl)bis(1-methyl-1H-imidazole-4,2-diyl))dipyrrolidine-1-carboxylate (~ 90 mg) was moved onto next step without further purification (purity ~ 85%) LCMS: Anal. Calcd. for: $C_{38}H_{48}N_6O_4$ 652.83; Found: 653.51 $(M+H)^+$. It should be recognized that multiple methylation isomers are possible in this reaction and no attempt to assign these was made.

Example 151, Step b



151b

151a, (2S,2'S)-tert-butyl 2,2'-(4,4'-(biphenyl-4,4'-diyl)bis(1-methyl-1H-imidazole-4,2-diyl))dipyrrolidine-1-carboxylate (100 mg, 0.153 mmole) treated with 4 M HCl/dioxane (20 mL). After three hours at ambient temperature, it was concentrated under reduced pressure. The crude reaction product, 4,4'-bis(1-methyl-2-((S)-pyrrolidin-2-yl)-1H-imidazol-4-yl)biphenyl(~110 mg, HCl salt) was moved onto the next step without further purification (purity ~ 85%) LCMS: Anal. Calcd. for: $C_{28}H_{32}N_6$ 452.59; Found: 453.38 $(M+H)^+$. Multiple imidazole isomers were present and carried forward.

Example 151

HATU (58.9 mg, 0.150 mmol) was added to a mixture of **151b**, 4,4'-bis(1-methyl-2-((S)-pyrrolidin-2-yl)-1H-imidazol-4-yl)biphenyl (45.0 mg, 0.075 mmol), $(i\text{-Pr})_2$EtN (78 µL, 0.451 mmol) and **cap-1**, (*R*)-2-(dimethylamino)-2-phenylacetic acid (0.026 mg 0.150mmol) in DMF (1.0 mL). The resultant mixture was stirred at ambient temperature until the coupling was complete as determined by LC/MS analysis. Purification was accomplished by reverse-phase preparative HPLC (Waters-Sunfire 30 X 100mm S5, detection at 220 nm, flow rate 30 mL/min, 0 to 90% B over 14 min; A = 90% water, 10 % ACN, 0.1% TFA, B = 10% water, 90 % ACN, 0.1% TFA) to provide two isomer of **151,** (2R,2'R)-1,1'-((2S,2'S)-2,2'-(4,4'-(biphenyl-4,4'-diyl)bis(1-methyl-1H-imidazole-4,2-diyl))bis(pyrrolidine-2,1-diyl))bis(2-(dimethylamino)-2-phenylethanone), TFA salts.

Isomer 1 (8 mg, 8.6%) as a colorless wax.

^{1}H NMR (500 MHz, DMSO-d_6) δ ppm 1.84 - 2.25 (m, 8 H) 2.32 - 2.90 (m, 12 H) 3.67 - 3.92 (m, 8 H) 4.07 (s, 2 H) 5.23 (s, 2 H) 5.51 (s, 2 H) 7.51 - 7.91 (m, 20 H)

HPLC Xterra 4.6 X 50 mm, 0 to 100% B over 10 minutes, one minutes hold time, A = 90% water, 10% methanol, 0.2% phosphoric acid, B = 10% water, 90% methanol, 0.2% phosphoric acid, RT = 2.74 min, 98%.

LCMS: Anal. Calcd. for: $C_{48}H_{54}N_8O_2$ 775.02; Found: 775.50 $(M+H)^+$.

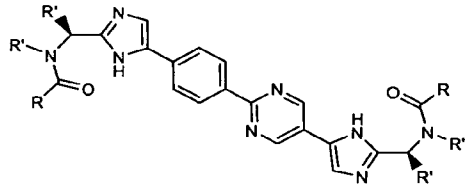
Isomer 2 (10.2 mg, 11%) as a colorless wax.

^{1}H NMR (500 MHz, DMSO-d_6) δ ppm 1.83 - 2.26 (m, 8 H) 2.30 - 2.92 (m, 12 H) 3.68 - 3.94 (m, 8 H) 4.06 (s, 2 H) 5.25 (d, *J*=2.14 Hz, 2 H) 5.50 (s, 2 H) 7.52 - 7.91 (m, 20 H).

HPLC Xterra 4.6 X 50 mm, 0 to 100% B over 10 minutes, one minutes hold time, A = 90% water, 10% methanol, 0.2% phosphoric acid, B = 10% water, 90% methanol, 0.2% phosphoric acid, RT = 2.75 min, 90%.

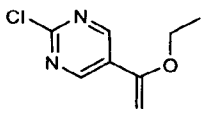
LCMS: Anal. Calcd. for: $C_{48}H_{54}N_8O_2$ 775.02; Found: 775.52 $(M+H)^+$.

Example 152



Example 152a-1 step a.

2-Chloro-5-(1-ethoxyvinyl)pyrimidine



To a solution of 5-bromo-2-chloropyrimidine (12.5 g, 64.62 mmol) in dry DMF (175 mL) under N_2 was added tributyl(1-ethoxyvinyl)tin (21.8 mL, 64.62 mmol) and dichlorobis(triphenylphosphine)palladium (II) (2.27 g, 3.23 mmol). The mixture was heated at 100°C for 3h before being allowed to stir at room temperature for 16 hr.. The mixture was then diluted with ether (200 mL) and treated with aqueous KF soln (55 g of potassium fluoride in 33 mL of water). The

two phase mixture was stirred vigorously for 1h at room temperature before being filtered through diatomaceous earth (Celite®). The fitrate was washed with sat'd $NaHCO_3$ soln and brine prior to drying (Na_2SO_4). The original aqueous phase was extracted with ether (2x) and the organic phase was treated as above. Repetition on 13.5 g of 5-bromo-2-chloropyrimidine and combined purification by Biotage™ flash chromatography on silica gel (gradient elution on a 65M column using 3% ethyl acetate in hexanes to 25% ethyl acetate in hexanes with 3.0 L) afforded the title compound as a white, crystalline solid (18.2 g, 73%).

^{1}H NMR (500 MHz, DMSO-d_6) δ 8.97 (s, 2H), 5.08 (d, *J*=3.7 Hz, 1H), 4.56 (d, *J*=3.4 Hz, 1H), 3.94 (q, *J*=7.0 Hz, 2H), 1.35 (t, *J*=7.0 Hz, 3H)..

LCMS Phenomenex LUNA C-18 4.6 × 50 mm, 0 to 100% B over 3 minutes, 1 minute hold time, A = 90% water, 10% methanol, 0.1% TFA, B = 10% water, 90% methanol, 0.1% TFA, RT = 2.53 min, 98.8% homogeneity index.

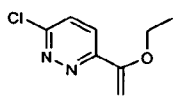
LCMS: Anal. Calcd. for $C_8H_{10}ClN_2O$ 185.05; found: 185.04 $(M+H)^+$.

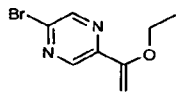
HRMS: Anal. Calcd. for $C_8H_{10}ClN_2O$ 185.0482; found: 185.0490 $(M+H)^+$.

The same method was used for the preparation of **Examples 152a-2 & 152a-3:**

LCMS conditions: Phenomenex LUNA C-18 4.6 × 50 mm, 0 to 100% B over 3 minutes, 1 minute hold time, A = 90% water, 10% methanol, 0.1% TFA, B = 10% water, 90% methanol, 0.1% TFA, 220nm, 5 µL injection volume.

LCMS conditions (condition 2): Phenomenex LUNA C-18 4.6 × 50 mm, 0 to 100% B over 2 minutes, 1 minute hold time, A = 90% water, 10% methanol, 0.1% TFA, B = 10% water, 90% methanol, 0.1% TFA, 220nm, 5 µL injection volume.

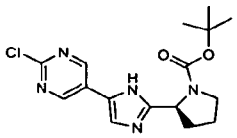
Example 152a-2	 from dichloropyridazine	t_R = 2.24 min 96.4%) LCMS: Anal. Calcd. for $C_8H_{10}ClN_2O$ 185.05; found: 185.06 $(M+H)^+$. HRMS: Anal. Calcd. for

		$C_8H_{10}ClN_2O$ 185.0482; found: 185.0476 $(M+H)^+$.
Example 152a-3	 from dibromopyrazine	t_R = 2.82 min (52.7%, inseparable with 2,5-dibrompyrazine (t_R =1.99 min, 43.2%)) LCMS: Anal. Calcd. for $C_8H_{10}BrN_2O$ 229.00; found: 228.93 $(M+H)^+$.

Example 152d-1 to 152d-6

Example 152b-1, step b.

(S)-*tert*-Butyl 2-(5-(2-chloropyrimidin-5-yl)-1*H*-imidazol-2-yl)pyrrolidine-1-carboxylate or (S)-2-[5-(2-Chloro-pyrimidin-5-yl)-1*H*-imidazol-2-yl]-pyrrolidine-1-carboxylic acid *tert*-butyl ester

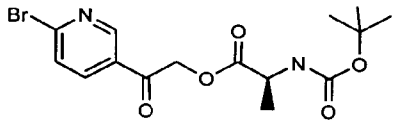
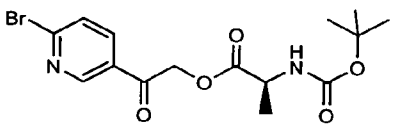


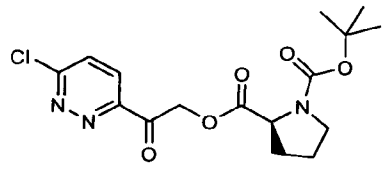
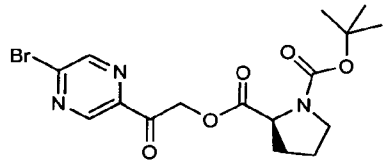
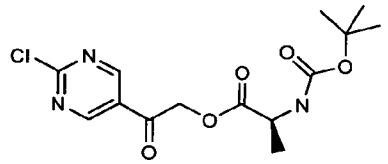
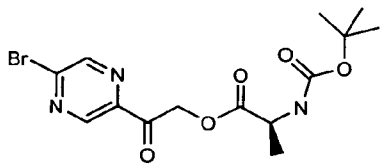
NBS (16.1 g, 90.7 mmol) was added in one portion to a stirred solution of 2-chloro-5-(1-ethoxyvinyl)pyrimidine (**152a-1**, 18.2 g, 98.6 mmol) in THF (267 mL) and H_2O (88 mL) at 0°C under N_2. The mixture was stirred for 1h at 0°C before it was diluted with more H_2O and extracted with ethyl acetate (2x). The combined extracts were washed with sat'd $NaHCO_3$ soln and brine prior to drying (Na_2SO_4) and solvent evaporation. LCMS Phenomenex LUNA C-18 4.6 × 50 mm, 0 to 100% B over 3 minutes, 1 minute hold time, A = 90% water, 10% methanol, 0.1% TFA, B = 10% water, 90% methanol, 0.1% TFA, RT = 1.52 min (unsymmetrical peak). LCMS: Anal. Calcd. for $C_6H_{14}BrClN_2O$ 235.92; found: 236.85 $(M+H)^+$.

Example 152c-1, step c.

Half of the crude residue (2-bromo-1-(2-chloropyrimidin-5-yl)ethanone, ~14.5g) was dissolved into anhydrous acetonitrile (150 mL) and treated directly with N-Boc-L-proline (9.76 g, 45.35 mmol) and diisopropylethylamine (7.9 mL, 45.35 mmol). After being stirred for 3h, the solvent was removed *in vacuo* and the residue was partitioned into ethyl acetate and water. The organic phase was washed with 0.1N hydrochloric acid, sat'd $NaHCO_3$ soln and brine prior to drying (Na_2SO_4) and concentration. LCMS Phenomenex LUNA C-18 4.6 × 50 mm, 0 to 100% B over 3 minutes, 1 minute hold time, A = 90% water, 10% methanol, 0.1% TFA, B = 10% water, 90% methanol, 0.1% TFA, RT = 2.66 min.

LCMS conditions: Phenomenex LUNA C-18 4.6 × 50 mm, 0 to 100% B over 3 minutes, 1 minute hold time, A = 90% water, 10% methanol, 0.1% TFA, B = 10% water, 90% methanol, 0.1% TFA, 220nm, 5 µL injection volume.
LCMS conditions (condition 2): Phenomenex LUNA C-18 4.6 × 50 mm, 0 to 100% B over 2 minutes, 1 minute hold time, A = 90% water, 10% methanol, 0.1% TFA, B = 10% water, 90% methanol, 0.1% TFA, 220nm, 5 µL injection volume.

Example 152c-2		t_R = 1.81 min (condition 2, ~95 %) LRMS: Anal. Calcd. for $C_{15}H_{19}BrN_4O_2$ 386.05 found: 387.07 $(M+H)^+$.
Example 152c-3		t_R = 1.84 min (condition 2, 94%) LRMS: Anal. Calcd. for $C_{15}H_{19}BrN_2O_5$ 386.05;

		found: 387.07 $(M+H)^+$.
Example 152c-3a		t_R = 2.65 min LCMS: Anal. Calcd. for $C_{16}H_{20}ClN_3O_5$ 369.11 found: 391.89 $(M+Na)^+$.
Example 152c-4		t_R = 1.94 min, (condition 2) LCMS: Anal. Calcd. for $C_{16}H_{21}BrN_3O_5$ 414.07 found: 414.11 $(M+H)^+$.
Example 152c-5		t_R = 2.22 min LCMS: Anal. Calcd. for $C_{14}H_{18}ClN_3O_5$ 343.09 found: undetermined.
Example 152c-6		t_R = 2.41 min LCMS: Anal. Calcd. for $C_{14}H_{18}{}^{37}BrN_3O_5$ 389.04 found: 412.03 $(M+Na)^+$.

Example 152d-1, step d.

This residue ((S)-1-tert-butyl 2-(2-(2-chloropyrimidin-5-yl)-2-oxoethyl) pyrrolidine-1,2-dicarboxylate) was taken up in xylenes (200 mL) and treated to NH_4OAc (17.5 g, 0.23 mol). The mixture was heated at 140°C for 2 hr in a thick-walled, screw-top flask before it was cooled to ambient temperature and suction-filtered. The filtrate was then concentrated, partitioned into ethyl acetate and sat'd $NaHCO_3$ soln and washed with brine prior to drying (Na_2SO_4) and concentration The original precipitate was partitioned into aqueous $NaHCO_3$ soln and ethyl acetate and sonicated for 2 min before being suction-filtered. The filtrate was washed with brine, dried over (Na_2SO_4) and evaporated down to dryness. Purification of the combined residues by Biotage™ flash chromatography on silica gel (65M column, preequilibration with 2%B for 900mL followed by gradient elution with 2%B to 2%B for 450 ml followed by 2%B to 40%B for 3000mL where B=methanol and A=dichloromethane) afforded the title compound (7.0 g, 44% yield, 2 steps, pure fraction) as an yellowish orange foam. The mixed fractions were subjected to a second Biotage™ chromatography on silica gel (40M column, preequilibration with 1%B for 600mL followed by gradient elution with 1%B to 1%B for 150 ml followed by 1%B to 10%B for 1500mL where B=MeOH and A=CH_2Cl_2) afforded additional title compound (2.8 g, 18%) as a brownish-orange foam. ^1H NMR (500 MHz, DMSO-d_6) □ 12.24-12.16 (m, 1H), 9.05 (s, 2H), 7.84-7.73 (m, 1H), 4.90-4.73 (m, 1H), 3.59-3.46 (m, 1H), 3.41-3.31 (m, 1H), 2.32-2.12 (m, 1H), 2.03-1.77 (m, 3H), 1.39 and 1.15 (2s, 9H)..

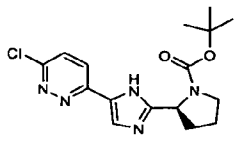
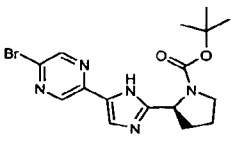
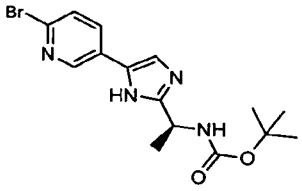
LCMS Phenomenex LUNA C-18 4.6 × 50 mm, 0 to 100% B over 3 minutes, 1 minute hold time, A = 90% water, 10% methanol, 0.1% TFA, B = 10% water, 90% methanol, 0.1% TFA, RT = 1.92 min, 94.7% homogeneity index.

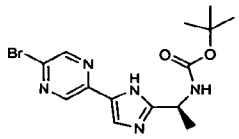
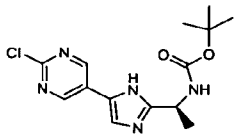
LCMS: Anal. Calcd. for $C_{16}H_{21}ClN_5O_2$ 350.14; found: 350.23 $(M+H)^+$.

HRMS: Anal. Calcd. for $C_{16}H_{21}ClN_5O_2$ 350.1384; found: 350.1398 $(M+H)^+$.

LCMS conditions: Phenomenex LUNA C-18 4.6 × 50 mm, 0 to 100% B over 3 minutes, 1 minute hold time, A = 90% water, 10% methanol, 0.1% TFA, B = 10% water, 90% methanol, 0.1% TFA, 220nm, 5 µL injection volume.

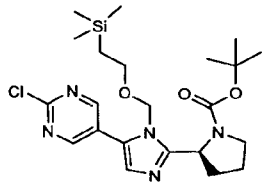
LCMS conditions (condition 2): Phenomenex LUNA C-18 4.6 × 50 mm, 0 to 100% B over 2 minutes, 1 minute hold time, A = 90% water, 10% methanol, 0.1% TFA, B = 10% water, 90% methanol, 0.1% TFA, 220nm, 5 µL injection volume.

Example 152d-2	 from **152c-3a**	t_R = 1.92 min (86.5%) LCMS: Anal. Calcd. for $C_{16}H_{21}ClN_5O_2$ 350.14; found: 350.23 $(M+H)^+$. HRMS: Anal. Calcd. for $C_{16}H_{21}ClN_5O_2$ 350.1384; found: 350.1393 $(M+H)^+$.
Example 152d-3	 from **152c-4**	t_R = 1.90min (>95%) LCMS: Anal. Calcd. for $C_{16}H_{21}BrN_5O_2$ 394.09; found: 393.82 $(M+H)^+$. HRMS: Anal. Calcd. for $C_{16}H_{21}BrN_5O_2$ 394.0879; found: 394.0884 $(M+H)^+$.
Example 152d-4	 from **152c-3**	t_R = 1.45 min (condition 2, 100%) LRMS: Anal. Calcd. for $C_{15}H_{19}BrN_4O_2$ 366.07 found: 367.07 $(M+H)^+$.

Example 152d-5	 from **152c-6**	t_R = 1.88 min (>95%) LCMS: Anal. Calcd. for $C_{14}H_{18}BrN_5O_2$ 367.06; found: 368.10 $(M+H)^+$.
Example 152d-6	 from **152c-5**	t_R = 1.66 min (85%) LCMS: Anal. Calcd. for $C_{14}H_{18}ClN_5O_2$ 323.11; found: 324.15 $(M+H)^+$.

Example 152e-1, step e.

Example 152e-1: (S)-*tert*-Butyl 2-(5-(2-chloropyrimidin-5-yl)-1-((2-(trimethylsilyl)ethoxy)methyl)-1*H*-imidazol-2-yl)pyrrolidine-1-carboxylate



Sodium hydride (60% dispersion in mineral oil , 0.23 g, 5.72 mmol) was added in one portion to a stirred solution of (S)-tert-butyl 2-(5-(2-chloropyrimidin-5-yl)-1H-imidazol-2-yl)pyrrolidine-1-carboxylate (**152d-1**, 2.0 g, 5.72 mmol) in dry DMF (45 mL) at ambient temperature under N_2. The mixture was stirred for 5 min. before SEM chloride (1.01 mL, 5.72 mmol) was added in approx. 0.1 mL increments. The mixture was stirred for 3h before being quenched with sat'd NH_4Cl soln and diluted with ethyl acetate. The organic phase was washed with sat'd $NaHCO_3$ soln and brine, dried over (Na_2SO_4), and concentrated. The original aqueous phase was extracted twice more and the combined residue was

purified by Biotage™ flash chromatography (40M column, 50 mL/min, preequilibration with 5%B for 750mL, followed by step gradient elution with 5%B to 5%B for 150 mL, 5%B to 75%B for 1500 mL, then 75%B to 100%B for 750 mL where solvent B is ethyl acetate and solvent A is hexanes). Concentration of the eluant furnished the title compound as a pale yellow foam (2.35 g, 85%).

^{1}H NMR (500 MHz, DMSO-d_6) δ 9.04 (s, 2H), 7.98-7.95 (m, 1H), 5.70-5.31 (3m, 2H), 5.02-4.91 (m, 1H), 3.59-3.49 (m, 3H), 3.45-3.35 (m, 1H), 2.30-2.08 (m, 2H), 1.99-1.83 (m, 2H), 1.36 and 1.12 (2s, 9H), 0.93-0.82 (m, 2H), -0.02 (s, 9H).

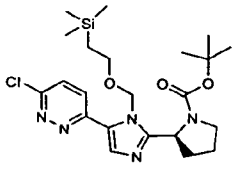
LCMS Phenomenex LUNA C-18 4.6 × 50 mm, 0 to 100% B over 2 minutes, 2 minute hold time, A = 90% water, 10% methanol, 0.1% TFA, B = 10% water, 90% methanol, 0.1% TFA, RT = 2.38 min, 95% homogeneity index.

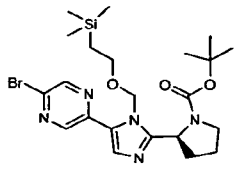
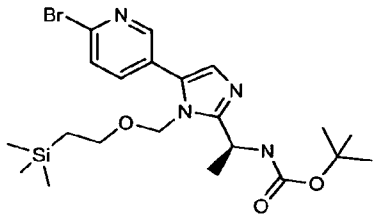
LCMS: Anal. Calcd. for $C_{22}H_{35}ClN_5O_3S_i$ 480.22; found: 480.23 $(M+H)^+$.

HRMS: Anal. Calcd. for $C_{22}H_{35}ClN_5O_3S_i$ 480.2198; found: 480.2194 $(M+H)^+$.

LCMS conditions: Phenomenex LUNA C-18 4.6 × 50 mm, 0 to 100% B over 3 minutes, 1 minute hold time, A = 90% water, 10% methanol, 0.1% TFA, B = 10% water, 90% methanol, 0.1% TFA, 220nm, 5 µL injection volume.

LCMS conditions (condition 2): Phenomenex LUNA C-18 4.6 × 50 mm, 0 to 100% B over 2 minutes, 1 minute hold time, A = 90% water, 10% methanol, 0.1% TFA, B = 10% water, 90% methanol, 0.1% TFA, 220nm, 5 µL injection volume.

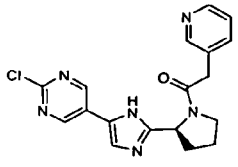
Example 152e-2	 from **152d-2**	t_R = 2.34 min (85.7%) LCMS: Anal. Calcd. for $C_{22}H_{35}ClN_5O_3Si$ 480.22; found: 480.22 $(M+H)^+$. HRMS: Anal. Calcd. for $C_{22}H_{35}ClN_5O_3Si$ 480.2198 found: 480.2198 $(M+H)^+$.

Example 152e-3	 from **152d-3**	t_R = 3.18 min (>95%) LCMS: Anal. Calcd. for $C_{22}H_{35}{}^{37}BrN_5O_3Si$ 526.17; found: 525.99 $(M+H)^+$. HRMS: Anal. Calcd. for $C_{22}H_{35}{}^{37}BrN_5O_3Si$ 526.1692; found: 526.1674 $(M+H)^+$.
Example 152e-4	 from **152d-4**	t_R = 2.14 min (condition 2, 96%) LRMS: Anal. Calcd. For $C_{21}H_{33}BrN_4O_3Si$ 496.15 found: 497.13 $(M+H)^+$.

Examples 152f-1 to 152f-2

Example 152f-1

(S)-1-(2-(5-(2-chloropyrimidin-5-yl)-1*H*-imidazol-2-yl)pyrrolidin-1-yl)-2-(pyridin-3-yl)ethanone



Cold (0°C) 4 *N* HCl in dioxanes (5 mL) was added via syringe to (S)-tert-butyl 2-(5-(2-chloropyrimidin-5-yl)-1*H*-imidazol-2-yl)pyrrolidine-1-carboxylate (**152d-1**, 0.50 g, 1.43 mmol) in a 100 mL pear-shaped flask followed by MeOH (1.0 mL). The suspension was stirred at room temperature for 4h before it was concentrated down to dryness and placed under high vacuum for 1h. There was isolated intermediate (S)-2-chloro-5-(2-(pyrrolidin-2-yl)-1*H*-imidazol-5-yl)pyrimidine trihydrochloride as a pale yellow solid (with an orange tint) which was used without further purification.

HATU (0.60 g, 1.57 mmol) was added in one portion to a stirred solution of intermediate (S)-2-chloro-5-(2-(pyrrolidin-2-yl)-1H-imidazol-5-yl)pyrimidine trihydrochloride (0.46 g, 1.43 mmol, theoretical amount), 2-(pyridin-3-yl)acetic acid (0.25 g, 1.43 mmol) and DIEA (1.0 mL, 5.72 mmol) in anhydrous DMF (10 mL) at ambient temperature. The mixture was stirred at room temperature for 2h before the DMF was removed *in vacuo*. The residue was taken up in CH_2Cl_2 and subjected to Biotage™ flash chromatography on silica gel (40M column, preequilibration with 0%B for 600mL followed by step gradient elution with 0%B to 0%B for 150 mL followed by 0%B to 15%B for 1500mL followed by 15%B to 25% B for 999 mL where B= MeOH and A= CH_2Cl_2). There was isolated the title compound (0.131 g, 25%, 2 steps) as a yellow solid.

^{1}H NMR (500 MHz, DMSO-d_6) δ 9.10-9.08 (2s, 2H), 8.72-8.55 (series of m, 2H), 8.21-8.20 and 8.11-8.10 (2m, 1H), 8.00 and 7.93 (2s, 1H), 7.84-7.77 (series of m, 1H), 5.43-5.41 and 5.17-5.15 (2m, 1H), 4.02-3.94 (3m, 2H), 3.90-3.58 (3m, 2H), 2.37-2.26 (m, 1H), 2.16-1.85 (2m, 3H).

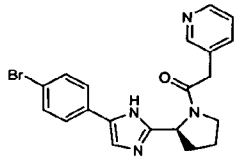
LCMS Phenomenex LUNA C-18 4.6 × 50 mm, 0 to 100% B over 3 minutes, 1 minute hold time, A = 90% water, 10% methanol, 0.1% TFA, B = 10% water, 90% methanol, 0.1% TFA, RT = 0.92 min, 95.1 % homogeneity index.

LCMS: Anal. Calcd. for $C_{18}H_{18}ClN_6O$ 369.12; found: 369.11 $(M+H)^+$.

HRMS: Anal. Calcd. for $C_{18}H_{18}ClN_6O$ 369.1231; found: 369.1246 $(M+H)^+$.

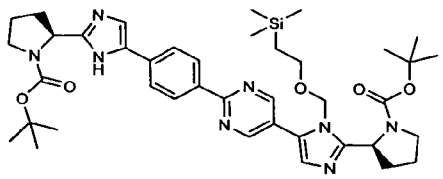
LCMS conditions: Phenomenex LUNA C-18 4.6 × 50 mm, 0 to 100% B over 3 minutes, 1 minute hold time, A = 90% water, 10% methanol, 0.1% TFA, B = 10% water, 90% methanol, 0.1% TFA, 220nm, 5 μL injection volume.

LCMS conditions (condition 2): Phenomenex LUNA C-18 4.6 × 50 mm, 0 to 100% B over 2 minutes, 1 minute hold time, A = 90% water, 10% methanol, 0.1% TFA, B = 10% water, 90% methanol, 0.1% TFA, 220nm, 5 µL injection volume.

Example 152f-2	 prepared from **1b** with same procedure describing the preparation of **152f-1** from **152d-1**	t_R = 1.56min (>95%) LCMS: Anal. Calcd. for $C_{20}H_{20}BrN_4O$ 413.08; found: 412.99 $(M+H)^+$. HRMS: Anal. Calcd. for $C_{20}H_{20}BrN_4O$ not done; found: not done $(M+H)^+$.

Examples 152g-1 to 152g-16

Example 152g-1 from **1c** and **152e-1.** (S)-2-[5-(2-{4-[2-((S)-1-*tert*-Butoxycarbonyl-pyrrolidin-2-yl)-3*H*-imidazol-4-yl]-phenyl}-pyrimidin-5-yl)-1-(2-trimethylsilanyl-ethoxymethyl)-1*H*-imidazol-2-yl]-pyrrolidine-1-carboxylic acid *tert*-butyl ester



Pd $(Ph_3)_4$ (0.12 g, 0.103 mmol) was added in one portion to a stirred suspension of (S)-tert-butyl 2-(5-(4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)phenyl)-1H-imidazol-2-yl)pyrrolidine-1-carboxylate (**1c**, 1.00 g, 2.27 mmol), (S)-tert-butyl 2-(5-(2-chloropyrimidin-5-yl)-1-((2-(trimethylsilyl)ethoxy)methyl)-1H-imidazol-2-yl)pyrrolidine-1-carboxylate (**152c-1**, 0.99 g, 2.06 mmol) and Na_2CO_2 (0.87 g, 10.3 mmol) in a solution of DME (20 mL) and H_2O (6 mL) at room temperature under N_2. The vessel was sealed and the mixture was placed into a preheated (80°C) oil bath and stirred at 80°C for 16h before additional catalyst (0.12 g) was added. After

heating the mixture for an additional 12h at 80°C, the mixture was cooled to ambient temperature, diluted with ethyl acetate and washed with sat'd $NaHCO_3$ soln and brine prior to drying over anhydrous sodium sulfate and solvent concentration. Purification of the residue by Biotage™ flash chromatography on silica gel using a 40M column (preequilibrated with 40% B followed by step gradient elution with 40%B to 40%B for 150mL, 40%B to 100%B for 1500mL, 100%B to 100%B for 1000mL where B=ethyl acetate and A=hexanes) furnished the title compound as a yellow foam (1.533 g, 98%). A small amount of the yellow foam was further purified for characterization purposes by pHPLC (Phenomenex GEMINI, 30 × 100 mm, S10, 10 to 100% B over 13 minutes, 3 minute hold time, 40 mL/min, A = 95% water, 5% acetonitrile, 10mM NH_4OAc, B = 10% water, 90% acetonitrile, 10mM NH_4OAc) to yield 95% pure title compound as a white solid.

^1H NMR (500 MHz, DMSO-d_6) δ 12.30-11.88 (3m, 1H), 9.17-9.16 (m, 2H), 8.43-8.31 (m, 2H), 7.99-7.35 (series of m, 4H), 5.72-5.30 (3m, 2H), 5.03-4.76 (2m, 2H), 3.64-3.50 (m, 4H), 3.48-3.31 (m, 2H), 2.36-2.07 (m, 2H), 2.05-1.80 (m, 4H), 1.46-1.08 (2m, 18H), 0.95-0.84 (m, 2H), -0.01 (s, 9H).

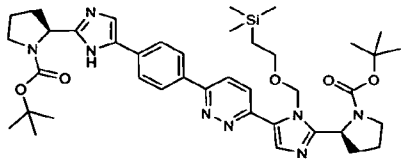
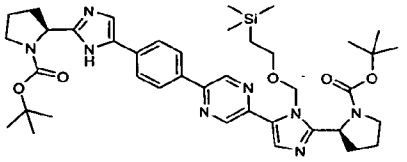
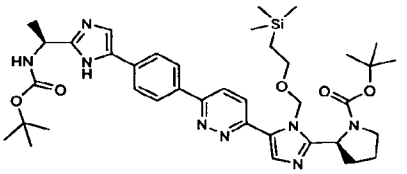
HPLC Phenomenex LUNA C-18 4.6 × 50 mm, 0 to 100% B over 3 minutes, 1 minute hold time, A = 90% water, 10% methanol, 0.1% TFA, B = 10% water, 90% methanol, 0.1% TFA, RT = 2.91 min, 95% homogeneity index.

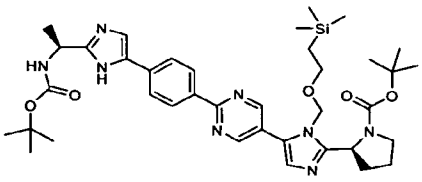
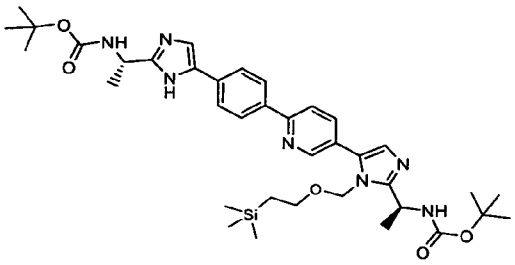
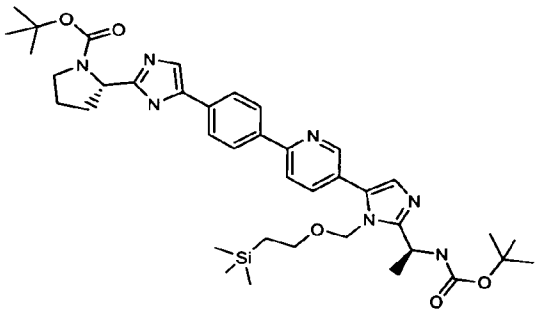
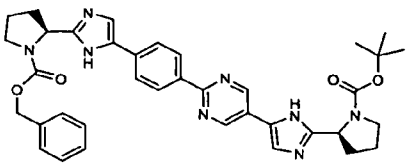
LCMS: Anal. Calcd. for $C_{40}H_{57}N_8O_5Si$ 757.42; found: 757.42 $(M+H)^+$.

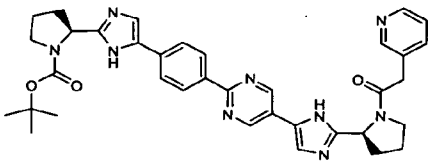
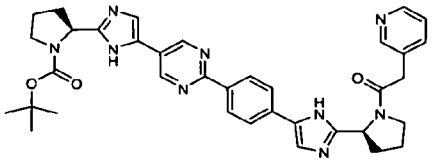
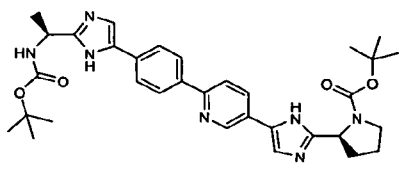
HRMS: Anal. Calcd. for $C_{40}H_{57}N_8O_5Si$ 757.4221; found: 757.4191 $(M+H)^+$.

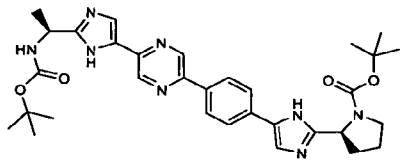
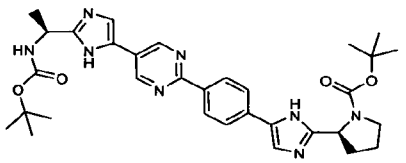
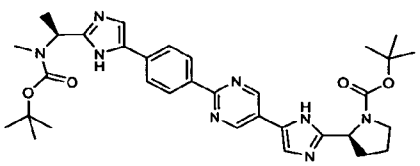
LCMS conditions: Phenomenex LUNA C-18 4.6 × 50 mm, 0 to 100% B over 3 minutes, 1 minute hold time, A = 90% water, 10% methanol, 0.1% TFA, B = 10% water, 90% methanol, 0.1% TFA, 220nm, 5 µL injection volume.

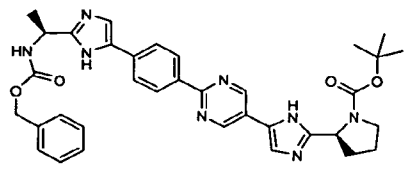
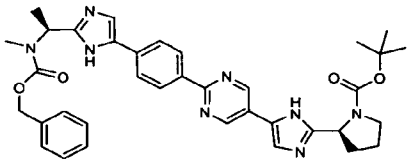
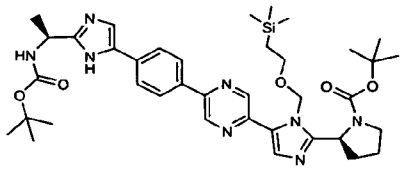
LCMS conditions (condition 2): Phenomenex LUNA C-18 4.6 × 50 mm, 0 to 100% B over 2 minutes, 1 minute hold time, A = 90% water, 10% methanol, 0.1% TFA, B = 10% water, 90% methanol, 0.1% TFA, 220nm, 5 µL injection volume.

Example 152g-2	 Prepared from **1c** and **152e-2**	t_R = 2.81 min (79%) LCMS: Anal. Calcd. for $C_{40}H_{57}N_8O_5Si$ 757.42; found: 758.05 $(M+H)^+$. HRMS: Anal. Calcd. for $C_{40}H_{57}N_8O_5Si$ 757.4221; found: 757.4196 $(M+H)^+$.
Example 152g-3	 Prepared from **1c** and **152e-3**	t_R = 2.89 min (>95%) LCMS: Anal. Calcd. for $C_{40}H_{57}N_8O_5Si$ 757.42; found: 757.35 $(M+H)^+$. HRMS: Anal. Calcd. for $C_{40}H_{57}N_8O_5Si$ 757.4221; found: 757.4191 $(M+H)^+$.
Example 152g-4	 Prepared from **1-6c** and **152e-2**	t_R = 2.87 min (97%) LCMS: Anal. Calcd. for $C_{38}H_{55}N_8O_5S_i$ 731.41; found: 731.26 $(M+H)^+$. HRMS: Anal. Calcd. for $C_{38}H_{55}N_8O_5S_i$ 731.4065; found: 731.4070 $(M+H)^+$.

Example 152g-5	 Prepared from **1-6c** and **152e-1**	t_R = 2.94 min (>95%) LCMS: Anal. Calcd. for $C_{38}H_{55}N_8O_5Si$ 731.41; found: 731.26 $(M+H)^+$. HRMS: Anal. Calcd. for $C_{38}H_{55}N_8O_5Si$ 731.4065; found: 731.4046 $(M+H)^+$.
Example 152g-6	 Prepared from **1-6c** and **152e-4**	t_R = 1.99 min (condition 2, 96%) LRMS: Anal. Calcd. for $C_{37}H_{53}N_7O_2Si$ 703.39; found: 704.34 $(M+H)^+$.
Example 152g-7	 Prepared from **1c** and **152e-4**	t_R = 1.99 min (condition 2, 96%) LRMS: Anal. Calcd. for $C_{39}H_{55}N_7O_5Si$ 729.40 found: 730.42 $(M+H)^+$.
Example 152g-8	 Prepared from **1-5c** and **152d-1**	t_R = 2.15 min (>95%) LCMS: Anal. Calcd. for $C_{37}H_{41}N_8O_4$ 661.33; found: 661.39 $(M+H)^+$.

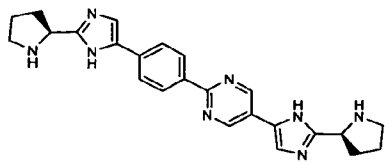
		HRMS: Anal. Calcd. for $C_{37}H_{41}N_8O_4$ 661.3251; found: 661.3268 $(M+H)^+$.
Example 152g-9	 Prepared from **1c** and **152f-1**	t_R = 1.71 min (>95%) LCMS: Anal. Calcd. for $C_{36}H_{40}N_9O_3$ 646.76; found: 646.47 $(M+H)^+$. HRMS: Anal. Calcd. for $C_{36}H_{40}N_9O_3$ not done found: not done $(M+H)^+$.
Example 152g-10	 Prepared from **152d-1** and **1-10c**	t_R = 1.71 min (>95%) LCMS: Anal. Calcd. for $C_{36}H_{40}N_9O_3$ 646.33; found: 646.37 $(M+H)^+$. HRMS: Anal. Calcd. for $C_{36}H_{40}N_9O_3$ 646.3254; found: 646.3240 $(M+H)^+$.
Example 152g-11	 Prepared from **1-6c** and **152e-4**	t_R = 2.12 min (>93.9%) LCMS: Anal. Calcd. for $C_{33}H_{42}N_7O_4$ 600.33; found: 600.11 $(M+H)^+$. HRMS: Anal. Calcd. for $C_{33}H_{42}N_7O_4$ 600.3298;

		found: 600.3312 $(M+H)^+$.
Example 152g-12	 Prepared from **1c** and **152d-5**	t_R = 2.13 min (97.3%) LCMS: Anal. Calcd. for $C_{32}H_{41}N_8O_4$ 601.33; found: 601.36 $(M+H)^+$. HRMS: Anal. Calcd. for $C_{32}H_{41}N_8O_4$ 601.3251; found: 601.3253 $(M+H)^+$.
Example 152g-13	 Prepared from **1c** and **152d-6**	t_R = 2.11 min (98.5%) LCMS: Anal. Calcd. for $C_{32}H_{41}N_8O_4$ 601.33; found: 601.36 $(M+H)^+$. HRMS: Anal. Calcd. for $C_{32}H_{41}N_8O_4$ 601.3251; found: 601.3253 $(M+H)^+$.
Example 152g-14	 Prepared from **1-8c** and **152d-1**	t_R = 2.18 min (>95%) LCMS: Anal. Calcd. for $C_{33}H_{43}N_8O_4$ 615.34; found: 615.38 $(M+H)^+$. HRMS: Anal. Calcd. for $C_{33}H_{43}N_8O_4$ 615.3407; found: 615.3433 $(M+H)^+$.

Example 152g-15	 Prepared from **1c** and **152d-1**	t_R = 2.20 min (97.7%) LCMS: Anal. Calcd. for $C_{35}H_{39}N_8O_4$ 635.31; found: 635.36 $(M+H)^+$. HRMS: Anal. Calcd. for $C_{35}H_{39}N_8O_4$ 635.3094; found: 635.3119 $(M+H)^+$.
Example 152g-16	 Prepared from **1-9c** and **152d-1**	t_R = 2.26 min (>95%) LCMS: Anal. Calcd $C_{36}H_{41}N_8O_4$ 649.33; found: 649.39 $(M+H)^+$. HRMS: Anal. Calcd. for $C_{36}H_{41}N_8O_4$ 649.3251; found: 649.3276 $(M+H)^+$.
Example 152g-17	 Prepared from **1-6c** and **152e-3**	t_R = 2.98 min (98.5%) LCMS: Anal. Calcd. for $C_{38}H_{54}N_8O_5Si$ 730.39; found: 731.40 $(M+H)^+$. HRMS: Anal. Calcd. for $C_{38}H_{54}N_8O_5Si$ 731.4065; found: 731.4045 $(M+H)^+$.

Example 152h-1-152h-7

Example **152h-1** from **152g-1**. 5-((S)-2-Pyrrolidin-2-yl-3*H*-imidazol-4-yl)-2-[4-((S)-2-pyrrolidin-2-yl-3*H*-imidazol-4-yl)-phenyl]-pyrimidine



TFA (8 mL) was added in one portion to a stirred solution of (S)-2-[5-(2-{4-[2-((S)-1-*tert*-butoxycarbonyl-pyrrolidin-2-yl)-3*H*-imidazol-4-yl]-phenyl}-pyrimidin-5-yl)-1-(2-trimethylsilanyl-ethoxymethyl)-1*H*-imidazol-2-yl]-pyrrolidine-1-carboxylic acid *tert*-butyl ester (1.50 g, 1.98 mmol) in dry CH_2Cl_2 (30 mL) at room temperature. The flask was sealed and the mixture was stirred at room temperature for 16h before the solvent(s) were removed *in vacuo*. The residue was taken up in methanol, filtered through a PVDF syringe filter (13mm x 0.45μm), distributed to 8 pHPLC vials and chromatographed by HPLC (gradient elution from 10%B to 100%B over 13 min on a Phenomenex C18 column, 30 x 100mm, 10μm, where A = 90% water, 10% methanol, 0.1% TFA, B = 10% water, 90% methanol, 0.1% TFA). After concentration of the selected test tubes by speed vacuum evaporation, the product was dissolved in methanol and neutralized by passing the solution through an UCT CHQAX 110M75 anion exchange cartridge. There was isolated the title compound as a yellow mustard-colored solid (306.7 mg, 36% yield) upon concentration of the eluant.

^{1}H NMR (500 MHz, DMSO-d_6) μ 12.50-11.80 (br m, 2H), 9.18 (s, 2H), 8.36 (d, *J*=8.5 Hz, 2H), 7.89 (d, *J*=8.2 Hz, 2H), 7.77 (s, 1H), 7.61 (s, 1H), 4.34-4.24 (m, 2H), 3.09-2.89 (m, 4H), 2.18-2.07 (m, 2H), 2.02-1.89 (m, 2H), 1.88-1.72 (m, 4H).

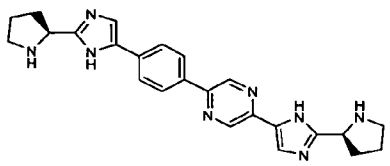
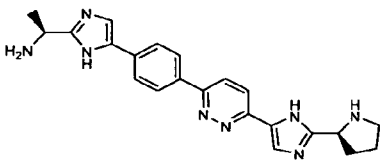
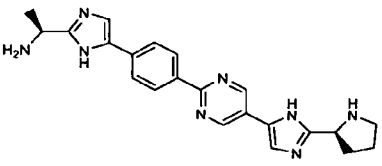
LCMS Phenomenex LUNA C-18 4.6 × 50 mm, 0 to 100% B over 3 minutes, 1 minute hold time, A = 90% water, 10% methanol, 0.1% TFA, B = 10% water, 90% methanol, 0.1% TFA, RT = 1.33 min, >95% homogeneity index.

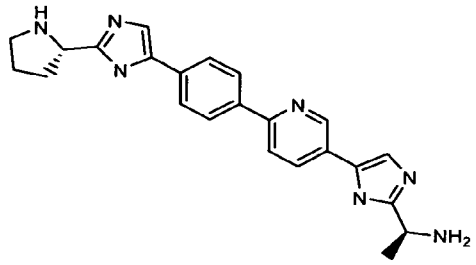
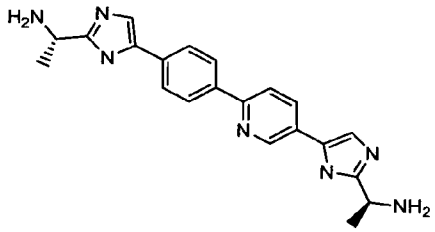
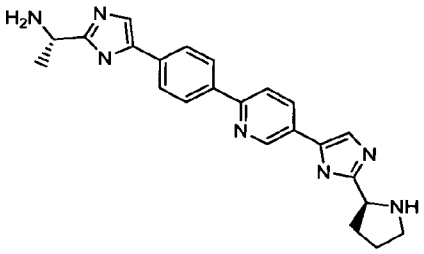
LCMS: Anal. Calcd. for $C_{24}H_{27}N_8$ 427.24; found: 427.01 $(M+H)^+$.

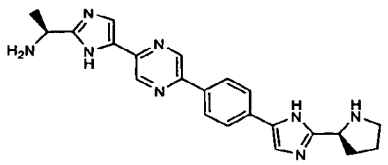
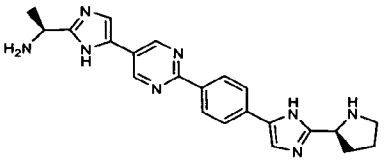
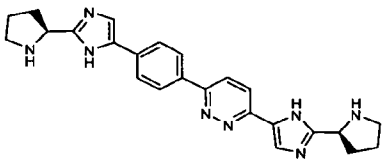
HRMS: Anal. Calcd. for $C_{24}H_{27}N_8$ 427.2359; found: 427.2363 $(M+H)^+$.

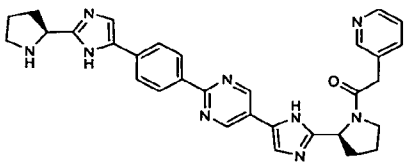
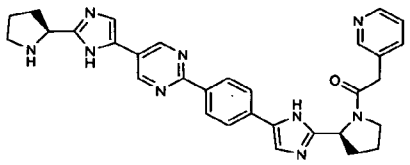
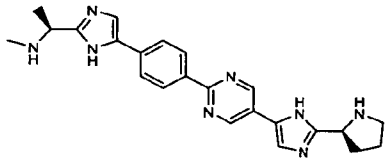
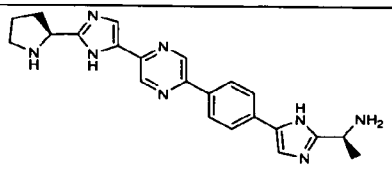
LCMS conditions: Phenomenex LUNA C-18 4.6 × 50 mm, 0 to 100% B over 3 minutes, 1 minute hold time, A = 90% water, 10% methanol, 0.1% TFA, B = 10% water, 90% methanol, 0.1% TFA, 220nm, 5 µL injection volume.

LCMS conditions (condition 2): Phenomenex LUNA C-18 4.6 × 50 mm, 0 to 100% B over 2 minutes, 1 minute hold time, A = 90% water, 10% methanol, 0.1% TFA, B = 10% water, 90% methanol, 0.1% TFA, 220nm, 5 µL injection volume.

Example 152h-2	 Prepared from **152g-3**	t_R = 1.36 min (98%) LCMS: Anal. Calcd. for $C_{24}H_{27}N_8$ 427.24; found: 427.48 $(M+H)^+$. HRMS: Anal. Calcd. for $C_{24}H_{27}N_8$ 427.2359; found: 427.2339 $(M+H)^+$.
Example 152h-3	 Preapared from **152g-4**	t_R = 1.17 min (>95%) LCMS: Anal. Calcd. for $C_{22}H_{25}N_8$ 401.22; found: 401.16 $(M+H)^+$. HRMS: Anal. Calcd. for $C_{22}H_{25}N_8$ 401.2202; found: 401.2193 $(M+H)^+$.
Example 152h-4	 Prepared from **152g-5**	t_R = 1.28 min (89.3%) LCMS: Anal. Calcd. for $C_{22}H_{25}N_8$ 401.22; found: 401.16 $(M+H)^+$.

		HRMS: Anal. Calcd. for $C_{22}H_{25}N_8$ 401.2202; found: 401.2201 $(M+H)^+$.
Example 152h-5	 Prepared from **152g-7**	t_R = 0.93 min LCMS: Anal. Calcd. for $C_{23}H_{25}N_7$ 399; found: 400 $(M+H)^+$.
Example 152h-6	 Prepared from **152g-6**	t_R = 0.81 min LCMS: Anal. Calcd. for $C_{21}H_{23}N_7$ 373; found: 374 $(M+H)^+$.
Example 152h-7	 Prepared from **152g-11**	t_R = 1.14 min (>95%) LCMS: Anal. Calcd. for $C_{23}H_{26}N_7$ 400.23; found: 400.14 $(M+H)^+$. HRMS: Anal. Calcd. for $C_{23}H_{26}N_7$ 400.2250; found: 400.2234 $(M+H)^+$.

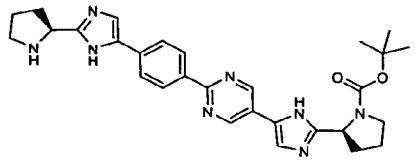
Example 152h-8	 Prepared from **152g-12**	t_R = 1.29 min (>95%) LCMS: Anal. Calcd. for $C_{22}H_{25}N_8$ 401.22; found: 401.21 $(M+H)^+$. HRMS: Anal. Calcd. for $C_{22}H_{25}N_8$ 401.2202; found: 401.2204 $(M+H)^+$.
Example 152h-9	 Prepared from **152g-13**	t_R = 1.29 min (97.6%) LCMS: Anal. Calcd. for $C_{22}H_{25}N_8$ 401.22; found: 401.21 $(M+H)^+$. HRMS: Anal. Calcd. for $C_{22}H_{25}N_8$ 401.2202; found: 401.2220 $(M+H)^+$.
Example 152h-10	 Prepared from **152g-2**	t_R = 1.26 min (86.4%) LCMS: Anal. Calcd. for $C_{24}H_{27}N_8$ 427.24; found: 427.48 $(M+H)^+$. HRMS: Anal. Calcd. for $C_{24}H_{27}N_8$ 427.2359; found: 427.2339 $(M+H)^+$.

Example 152h-11	 Prepared from **152g-9**	t_R = 1.26 min (>95%) LCMS: Anal. Calcd. for $C_{31}H_{32}N_9O$ 546.27; found: 546.28 $(M+H)^+$. HRMS: Anal. Calcd. for $C_{31}H_{32}N_9O$ 546.2730 found: 546.2739 $(M+H)^+$.
Example 152h-12	 Prepared from **152g-10**	t_R = 1.39 min (95%) LCMS: Anal. Calcd. for $C_{31}H_{32}N_9O$ 546.27; found: 546.32 $(M+H)^+$. HRMS: Anal. Calcd. for $C_{31}H_{32}N_9O$ 546.2730; found: 546.2719 $(M+H)^+$.
Example 152h-13	 Prepared from **152g-14**	t_R = 1.42 min LCMS: Anal. Calcd. for $C_{23}H_{26}N_8$ 414.24; found: 415.27 $(M+H)^+$. HRMS: Anal. Calcd. for $C_{23}H_{26}N_8$ 415.2359; found: 415.2371 $(M+H)^+$.
Example 152h-14		t_R = 1.30 min LCMS: Anal. Calcd. for

	Prepared from **152g-17**	$C_{22}H_{24}N_8$ 400.21; found: 401.24 $(M+H)^+$. HRMS: Anal. Calcd. for $C_{22}H_{24}N_8$ 401.2202; found: 401.2198 $(M+H)^+$.

Example 152i-1 to 152i-3

Example **152i-1** from **152g-8**. (S)-2-(5-{2-[4-((S)-2-Pyrrolidin-2-yl-3*H*-imidazol-4-yl)-phenyl]-pyrimidin-5-yl}-1*H*-imidazol-2-yl)-pyrrolidine-1-carboxylic acid *tert*-butyl ester.



A solution of (S)-2-[5-(2-{4-[2-((S)-1-Benzyloxycarbonyl-pyrrolidin-2-yl)-3*H*-imidazol-4-yl]-phenyl}-pyrimidin-5-yl)-1*H*-imidazol-2-yl]-pyrrolidine-1-carboxylic acid *tert*-butyl ester (317.1 mg, 0.48 mmol) in MeOH (1 mL) was added to a stirred suspension of 10% palladium on carbon (60 mg) and K_2CO_3 (70 mg) in a solution of MeOH (5 mL) and H_2O (0.1 mL) at room temperature under N_2. The flask was charged and evacuated three times with H_2 and stirred for 3h at atmosphere pressure. Additional catalyst (20 mg) was then added and the reaction mixture was stirred further for 3h before it was suction-filtered through Celite and concentrated. The residue was diluted with MeOH, filtered through a PVDF syringe filter (13mm x 0.45□m), distributed into 4 pHPLC vials and chromatographed (gradient elution from 20%B to 100%B over 10 min on a Phenomenex-Gemini C18 column (30 x 100mm, 10□m) where A = 95% water, 5% acetonitrile, 10mM NH_4OAc, B = 10% water, 90% acetonitrile, 10mM NH_4OAc). After concentration of the selected test tubes by speed vacuum evaporation, there was isolated the title compound as a yellow solid (142.5 mg, 56% yield).

^{1}H NMR (400 MHz, DMSO-d_6) δ 12.35-12.09 (br m, 1H), 9.17 (s, 2H), 8.35 (d, *J*=8.3Hz, 2H), 7.87 (d, *J*=8.3Hz, 2H), 7.80-7.72 (m, 1H), 7.56 (s, 1H), 4.92-4.77 (m, 1H), 4.21-4.13 (m, 1H), 3.61-3.05 (2m, 4H), 3.02-2.80 (2m, 2H), 2.37-1.67 (series of m, 6H), 1.41 and 1.17 (2s, 9H).

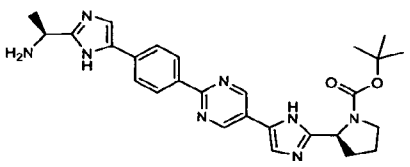
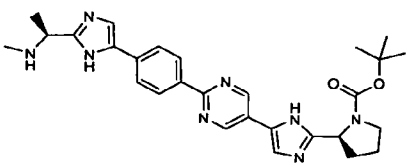
LCMS Phenomenex LUNA C-18 4.6 × 50 mm, 0 to 100% B over 3 minutes, 1 minute hold time, A = 90% water, 10% methanol, 0.1% TFA, B = 10% water, 90% methanol, 0.1% TFA, RT = 1.77 min, >95 % homogeneity index.

LCMS: Anal. Calcd. for $C_{29}H_{35}N_8O_2$ 527.29; found: 527.34 $(M+H)^+$.

HRMS: Anal. Calcd. for $C_{29}H_{35}N_8O_2$ 527.2883; found: 527.2874 $(M+H)^+$.

LCMS conditions: Phenomenex LUNA C-18 4.6 × 50 mm, 0 to 100% B over 3 minutes, 1 minute hold time, A = 90% water, 10% methanol, 0.1% TFA, B = 10% water, 90% methanol, 0.1% TFA, 220nm, 5 µL injection volume.

LCMS conditions (condition 2): Phenomenex LUNA C-18 4.6 × 50 mm, 0 to 100% B over 2 minutes, 1 minute hold time, A = 90% water, 10% methanol, 0.1% TFA, B = 10% water, 90% methanol, 0.1% TFA, 220nm, 5 µL injection volume.

Example 152i-2	 Prepared from **152g-15**	t_R = 1.70 min (95.7%) LCMS: Anal. Calcd. for $C_{27}H_{33}N_8O_2$ 501.27; found: 501.35 $(M+H)^+$. HRMS: Anal. Calcd. for $C_{27}H_{33}N_8O_2$ 501.2726 found: 501.2709 $(M+H)^+$.
Example 152i-3	 Prepared from **152g-16**	t_R = 1.77 min (>95%) LCMS: Anal. Calcd. for $C_{28}H_{35}N_8O_2$ 515.29; found: 515.37 $(M+H)^+$.

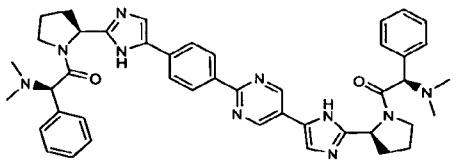
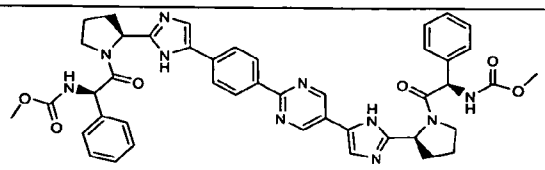
		HRMS: Anal. Calcd. for $C_{28}H_{35}N_8O_2$ 515.2883 found: 515.2869 $(M+H)^+$.

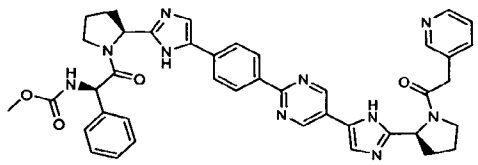
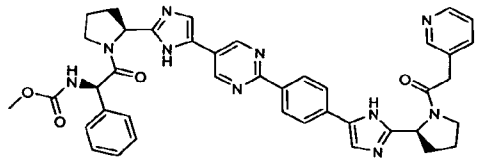
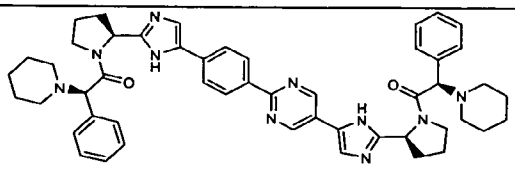
Examples 152j-1 to 152j-28

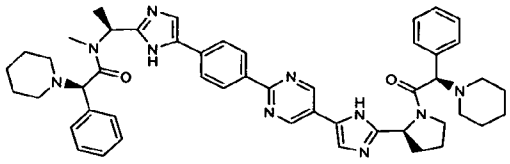
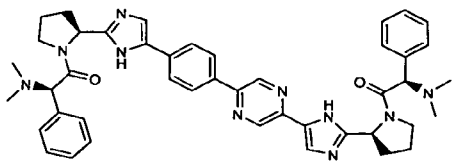
Examples 152j were isolated as TFA or AcOH salts prepared according to the method of example **148** above.

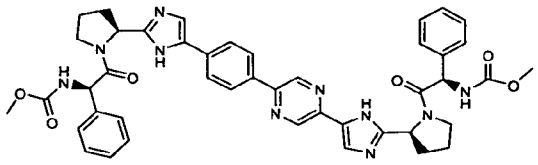
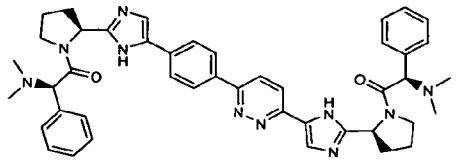
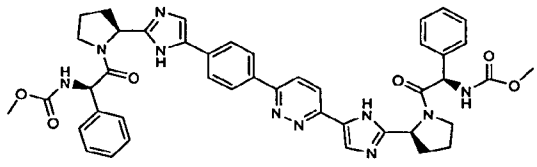
LCMS conditions: Phenomenex LUNA C-18 4.6 × 50 mm, 0 to 100% B over 3 minutes, 1 minute hold time, A = 90% water, 10% methanol, 0.1% TFA, B = 10% water, 90% methanol, 0.1% TFA, 220nm, 5 µL injection volume.

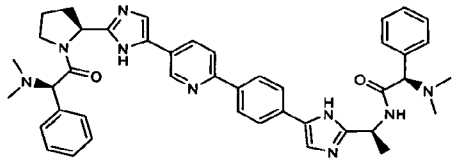
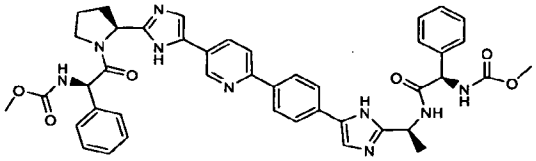
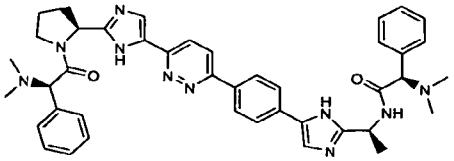
LCMS conditions (condition 2): Phenomenex LUNA C-18 4.6 × 50 mm, 0 to 100% B over 2 minutes, 1 minute hold time, A = 90% water, 10% methanol, 0.1% TFA, B = 10% water, 90% methanol, 0.1% TFA, 220nm, 5 µL injection volume.

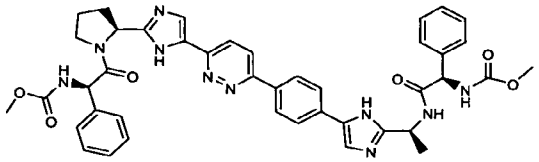
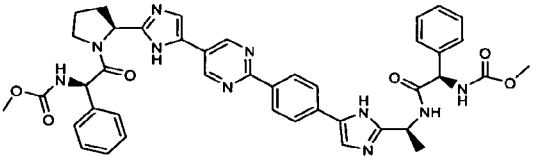
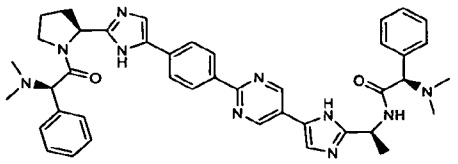
Example 152j-1	 Prepared from **152h-1** and **cap 1.**	t_R = 1.61 min (>95%) LCMS: Anal. Calcd. for $C_{44}H_{49}N_{10}O_2$ 749.40 found: 749.32 $(M+H)^+$ HRMS: Anal. Calcd. for $C_{44}H_{49}N_{10}O_2$ 749.4040 found: 749.4042 $(M+H)^+$
Example 152j-2	 Prepared from **152h-1** and **cap 4**	t_R = 1.99 min (>95%) LCMS: Anal. Calcd. for $C_{44}H_{45}N_{10}O_6$ 809.35 found:

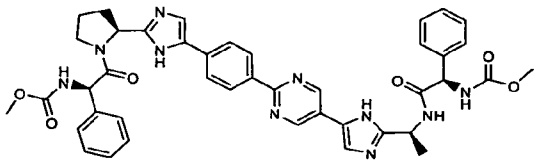
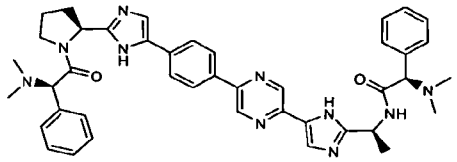
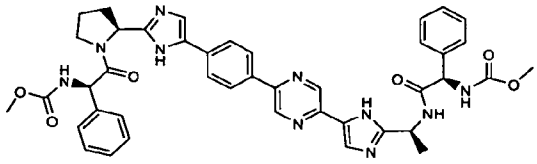
		809.17 $(M+H)^+$ HRMS: Anal. Calcd. for $C_{44}H_{45}N_{10}O_6$ 809.3524 found: 809.3505 $(M+H)^+$
Example 152j-3	 Prepared from **152h-11** and **cap 4**	t_R = 1.65 min (92.3%) LCMS: Anal. Calcd. for $C_{41}H_{41}N_{10}O_2$ 737.33 found: 737.49 $(M+H)^+$ HRMS: Anal. Calcd. for $C_{41}H_{41}N_{10}O_4$ 737.3312 found: 737.3342 $(M+H)^+$
Example 152j-4	 Prepared from **152h-12** and **cap 4**	t_R = 1.64 min (>95%) LCMS: Anal. Calcd. for $C_{41}H_{41}N_{10}O_4$ 737.33 found: 737.75 $(M+H)^+$ HRMS: Anal. Calcd. for $C_{41}H_{41}N_{10}O_4$ 737.3312 found: 737.3284 $(M+H)^+$
Example 152j-5		t_R = 1.70 min (>95%) LCMS: Anal. Calcd. for

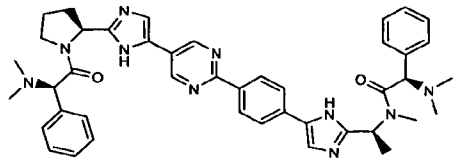
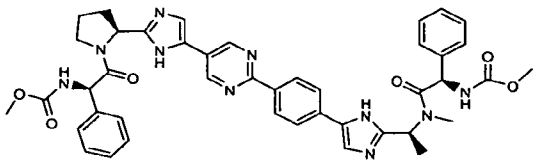
	Prepared from **152h-1** and **cap 14**	$C_{50}H_{57}N_{10}O_2$ 829.47 found: 829.39 $(M+H)^+$ HRMS: Anal. Calcd. for $C_{50}H_{57}N_{10}O_2$ 829.4666 found: 829.4658 $(M+H)^+$
Example 152j-6	 Prepared from **152h-13** and **cap 14**	t_R = 1.66 min (>95%) LCMS: Anal. Calcd. for $C_{49}H_{57}N_{10}O_2$ 817.47 found: 817.44 $(M+H)^+$ HRMS: Anal. Calcd. for $C_{49}H_{57}N_{10}O_2$ 817.4666 found: 817.4673 $(M+H)^+$
Example 152j-7	 Prepared from **152h-2** and **cap 1**	t_R = 1.60 min (>95%) LCMS: Anal. Calcd. for $C_{41}H_{49}N_{10}O_2$ 749.40 found: 749.31 $(M+H)^+$ HRMS: Anal. Calcd. for $C_{44}H_{49}N_{10}O_2$ 749.4040 found: 749.4031 $(M+H)^+$

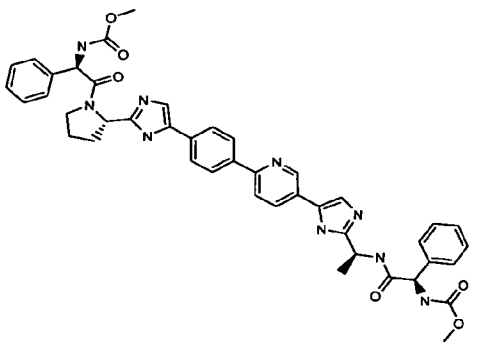
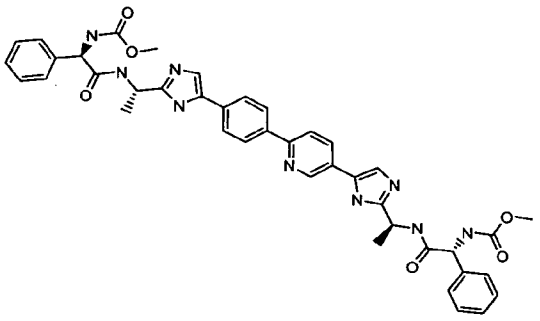
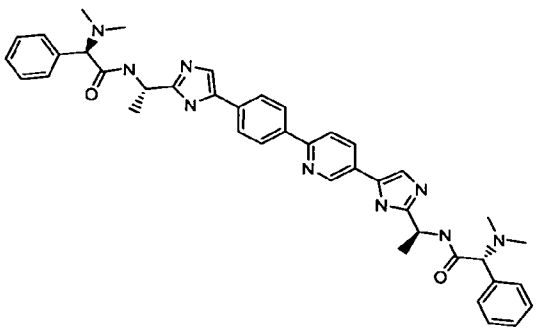
Example 152j-8	 Prepared from **152h-2** and **cap 4**	t_R = 2.01 min (>95%) LCMS: Anal. Calcd. for $C_{44}H_{45}N_{10}O_6$ 809.35 found: 809.24 $(M+H)^+$ HRMS: Anal. Calcd. for $C_{44}H_{45}N_{10}O_6$ 809.3523 found: 809.3493 $(M+H)^+$
Example 152j-9	 Prepared from **152h-10** and **cap 1**	t_R = 1.76 min (>95%) LCMS: Anal. Calcd. for $C_{44}H_{49}N_{10}O_2$ 749.40 found: not obsd $(M+H)^+$ HRMS: Anal. Calcd. for $C_{44}H_{49}N_{10}O_2$ 749.4040 found: 749.4056 $(M+H)^+$
Example 152j-10	 Prepared from **152h-10** and **cap 4**	t_R = 2.17 min (>95%) LCMS: Anal. Calcd. for $C_{44}H_{45}N_{10}O_6$ 809.35 found: 809.59 $(M+H)^+$ HRMS: Anal. Calcd. for $C_{44}H_{45}N_{10}O_6$ 809.3524 found: 809.3499 $(M+H)^+$

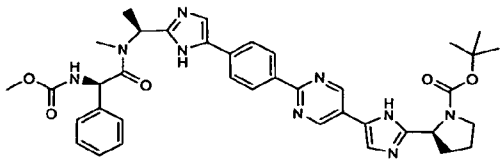
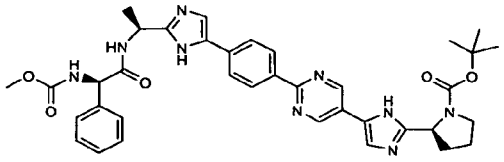
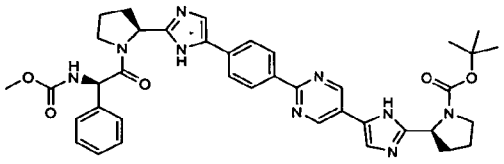
Example 152j-11	 Prepared from **152h-7** and **cap 1**	t_R = 1.56 min (>95%) LCMS: Anal. Calcd. for $C_{43}H_{48}N_9O_2$ 722.39 found: 722.89 $(M+H)^+$ HRMS: Anal. Calcd. for $C_{43}H_{48}N_9O_2$ 722.3931 found: 722.3930 $(M+H)^+$
Example 152j-12	 Prepared from **152h-7** and **cap 4**	t_R = 1.95 min (>95%) LCMS: Anal. Calcd. for $C_{43}H_{44}N_9O_6$ 782.34 found: 782.93 $(M+H)^+$ HRMS: Anal. Calcd. for $C_{43}H_{44}N_9O_6$ 782.3415 found: 782.3398 $(M+H)^+$
Example 152j-13	 Prepared from **152h-3** and **cap 1**	t_R = 1.55 min (>95%) LCMS: Anal. Calcd. for $C_{42}H_{47}N_{10}O_2$ 723.39 found: 723.88 $(M+H)^+$ HRMS: Anal. Calcd. for $C_{42}H_{47}N_{10}O_2$ 723.3883 found: 723.3903

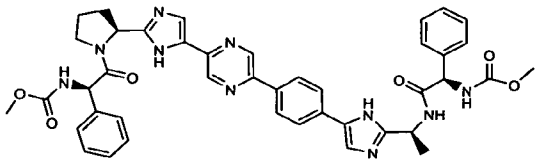
		$(M+H)^+$
Example 152j-14	 Prepared from **152h-3** and **cap 4**	t_R = 1.95 min (>95%) LCMS: Anal. Calcd. for $C_{42}H_{43}N_{10}O_6$ 783.34 found: 783.95 $(M+H)^+$ HRMS: Anal. Calcd. for $C_{42}H_{43}N_{10}O_6$ 783.3367 found: 783.3337 $(M+H)^+$
Example 152j-15	 Prepared from **152h-4** and **cap 4**	t_R = 1.97 min (>95%) LCMS: Anal. Calcd. for $C_{42}H_{43}N_{10}O_6$ 783.34 found: 783.97 $(M+H)^+$ HRMS: Anal. Calcd. for $C_{42}H_{43}N_{10}O_6$ 783.3367 found: 783.3357 $(M+H)^+$
Example 152j-16	 Prepared from **152h-9** and **cap 1**	t_R = 1.61 min (>95%) LCMS: Anal. Calcd. for $C_{42}H_{47}N_{10}O_2$ 723.39 found: 723.52 $(M+H)^+$ HRMS: Anal. Calcd. for $C_{42}H_{47}N_{10}O_2$

		723.3883 found: 723.3893 $(M+H)^+$
Example 152j-17	 Prepared from **152h-9** and **cap 4**	t_R = 1.99 min (95.6%) LCMS: Anal. Calcd. for $C_{42}H_{43}N_{10}O_6$ 783.34 found: 783.44 $(M+H)^+$ HRMS: Anal. Calcd. for $C_{42}H_{43}N_{10}O_6$ 783.3367 found: 783.3328 $(M+H)^+$
Example 152j-18	 Prepared from **152h-8** and **cap 1**	t_R = 1.60 min (>95%) LCMS: Anal. Calcd. for $C_{42}H_{47}N_{10}O_2$ 723.39 found: 723.47 $(M+H)^+$ HRMS: Anal. Calcd. for $C_{42}H_{47}N_{10}O_2$ 723.3883 found: 723.3861 $(M+H)^+$
Example 152j-19	 Prepared from **152h-8** and **cap 4**	t_R = 1.97 min (94.7%) LCMS: Anal. Calcd. for $C_{42}H_{43}N_{10}O_6$ 783.34 found: 783.69 $(M+H)^+$ HRMS: Anal. Calcd. for

		$C_{42}H_{43}N_{10}O_6$ 783.3367 found: 783.3345 $(M+H)^+$
Example 152j-20	 Prepared from **152h-13** and **cap 1**	t_R = 1.54 min (>95%) LCMS: Anal. Calcd. for $C_{43}H_{49}N_{10}O_2$ 737.40 found: 737.54 $(M+H)^+$ HRMS: Anal. Calcd. for $C_{43}H_{49}N_{10}O_2$ 737.4040 found: 7374066 $(M+H)^+$
Example 152j-21	 Prepared from **152h-13** and **cap 4**	t_R = 2.00 min (>95%) LCMS: Anal. Calcd. for $C_{43}H_{45}N_{10}O_6$ 797.35 found: 797.38 $(M+H)^+$ HRMS: Anal. Calcd. for $C_{43}H_{45}N_{10}O_6$ 797.3524 found: 797.3528 $(M+H)^+$

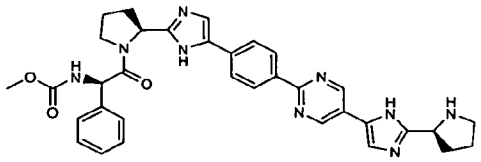
Example 152j-22	 Prepared from **152h-5** and **cap 4**	t_R = 1.46 min (condition 2, 98%) LRMS: Anal. Calcd. for $C_{43}H_{43}N_9O_6$ 781.33; found: 782.34 $(M+H)^+$. HRMS: Anal. Calcd. for $C_{43}H_{44}N_9O_6$ 782.3415 found: 782.3417 $(M+H)^+$
Example 152j-23	 Prepared from **152h-6** and **cap 4**	t_R = 1.44 min condition 2, 90%) LRMS: Anal. Calcd. for $C_{41}H_{41}N_9O_6$ 755.32; found: 756.35 $(M+H)^+$. HRMS: Anal. Calcd. for $C_{41}H_{42}N_9O_6$ 756.3258 found: 756.3239 $(M+H)^+$.
Example 152j-24	 Prepared from **152h-6** and **cap1**	t_R = 1.18 min (condition 2, 91%) LRMS: Anal. Calcd. for $C_{41}H_{45}N_9O_2$ 695.37; found: 696.37 $(M+H)^+$. HRMS: Anal. Calcd. for $C_{41}H_{46}N_9O_2$ 696.3774 found: 696.3806 $(M+H)^+$.

Example 152j-25	 Prepared from **152i-3** and **cap 4**	t_R = 2.08 min (95.8 %) LRMS: Anal. Calcd. for $C_{38}H_{44}N_9O_5$ 706.35; found: 706.53 $(M+H)^+$. HRMS: Anal. Calcd. for $C_{38}H_{44}N_9O_5$ 706.3465; found: 706.3492 $(M+H)^+$.
Example 152j-26	 Prepared from **152i-2** and **cap 4**	t_R = 2.04 min (96.4 %) LRMS: Anal. Calcd. for $C_{37}H_{42}N_9O_5$ 692.33; found: 692.49 $(M+H)^+$. HRMS: Anal. Calcd. for $C_{37}H_{42}N_9O_5$ 692.3309; found: 692.3322 $(M+H)^+$.
Example 152j-27	 Prepared from **152i-1** and **cap 4**	t_R = 2.04 min (>95 %) LRMS: Anal. Calcd. for $C_{39}H_{44}N_9O_5$ 718.35; found: 718.49 $(M+H)^+$. HRMS: Anal. Calcd. for $C_{39}H_{44}N_9O_5$ 718.3465; found: 718.3483 $(M+H)^+$.

Example 152j-28	 Prepared from **152h-14** and **cap 4**	t_R = 2.00 min (>95%) LCMS: Anal. Calcd. for $C_{42}H_{43}N_{10}O_6$ 783.34 found: 783.96 $(M+H)^+$ HRMS: Anal. Calcd. for $C_{42}H_{43}N_{10}O_6$ 783.3367 found: 783.3375 $(M+H)^+$

Examples 152k-1 to 152k-

Example 152k-1 from **152j-27**. {(R)-2-Oxo-1-phenyl-2-[(S)-2-(5-{4-[5-((S)-2-pyrrolidin-2-yl-3*H*-imidazol-4-yl)-pyrimidin-2-yl]-phenyl}-1*H*-imidazol-2-yl)-pyrrolidin-1-yl]-ethyl}-carbamic acid methyl ester



Cold (0°C) 4 *N* HCl in dioxanes (4 mL) was added via syringe to (S)-2-{5-[2-(4-{2-[(S)-1-((R)-2-methoxycarbonylamino-2-phenyl-acetyl)-pyrrolidin-2-yl]-3*H*-imidazol-4-yl}-phenyl)-pyrimidin-5-yl]-1*H*-imidazol-2-yl}-pyrrolidine-1-carboxylic acid *tert*-butyl ester (104.6 mg, 0.146 mmol) in a 100 mL pear-shaped flask followed by MeOH (0.5 mL). The homogeneous mixture was stirred at room temperature for 15 min before a precipitate was observed. After stirring further for 1.75h, the suspension was diluted with ether and hexanes. Suction-filtration of a small portion of the suspension yielded the title compound as a yellow solid which was used for characterization purposes. The balance of the suspension was concentrated down to dryness and placed under high vacuum for 16h. There was isolated the rest of the title

compound also as a yellow solid (137.7 mg, 123%) which was used without further purification.

^{1}H NMR (500 MHz, DMSO-d_6) δ 15.20 and 14.66 (2m, 1H), 10,29 (br s, 0.7H), 9.38-9.36 (m, 2H), 8.55-8.00 (series of m, 4H), 7.42-7.28 (2m, 3H), 5.53-4.00 (series of m, 7H), 3.99-3.13 (series of m, 4H), 3.57 and 3.52 (2s, 3H), 2.50-1.84 (series of m, 8H).

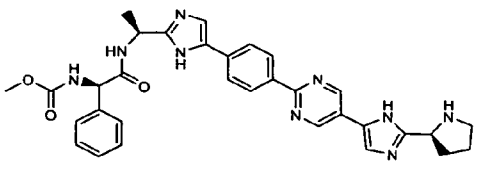
LCMS Phenomenex LUNA C-18 4.6 × 50 mm, 0 to 100% B over 3 minutes, 1 minute hold time, A = 90% water, 10% methanol, 0.1% TFA, B = 10% water, 90% methanol, 0.1% TFA, RT = 1.79 min, >95 % homogeneity index.

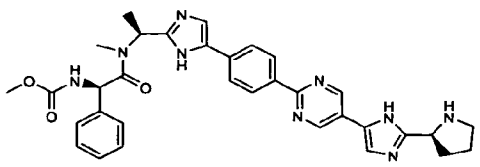
LCMS: Anal. Calcd. for $C_{34}H_{36}N_9O_3$ 618.29; found: 618.42 $(M+H)^+$.

HRMS: Anal. Calcd. for $C_{34}H_{36}N_9O_3$ 618.2921; found: 618.2958 $(M+H)^+$.

LCMS conditions: Phenomenex LUNA C-18 4.6 × 50 mm, 0 to 100% B over 3 minutes, 1 minute hold time, A = 90% water, 10% methanol, 0.1% TFA, B = 10% water, 90% methanol, 0.1% TFA, 220nm, 5 µL injection volume.

LCMS conditions (condition 2): Phenomenex LUNA C-18 4.6 × 50 mm, 0 to 100% B over 2 minutes, 1 minute hold time, A = 90% water, 10% methanol, 0.1% TFA, B = 10% water, 90% methanol, 0.1% TFA, 220nm, 5 µL injection volume.

Example 152k-2	 Prepared from **152j-26**	t_R = 1.74 min (>95 %) LCMS: Anal. Calcd. for $C_{32}H_{34}N_9O_3$ 592.28; found: 592.41 $(M+H)^+$. HRMS: Anal. Calcd. for $C_{32}H_{34}N_9O_3$ 592.2785; found: 592.2775 $(M+H)^+$.

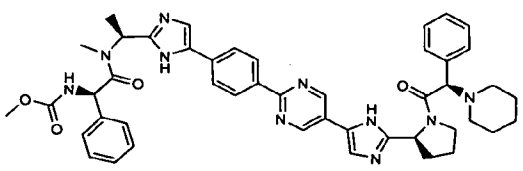
Example 152k-3	 Prepared from **152j-25**	t_R = 1.79 min (>95 %) LCMS: Anal. Calcd. for $C_{33}H_{36}N_9O_3$ 606.29; found: 606.43 $(M+H)^+$. HRMS: Anal. Calcd. for $C_{33}H_{36}N_9O_3$ 606.2941; found: 606.2925 $(M+H)^+$.

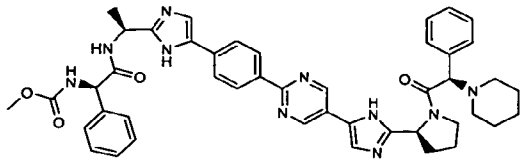
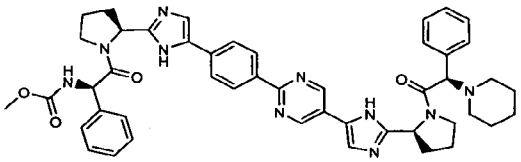
Examples 152l-1 to 152l-

Examples 152l were isolated as TFA or AcOH salts prepared according to the method of example **148** above.

LCMS conditions: Phenomenex LUNA C-18 4.6 × 50 mm, 0 to 100% B over 3 minutes, 1 minute hold time, A = 90% water, 10% methanol, 0.1% TFA, B = 10% water, 90% methanol, 0.1% TFA, 220nm, 5 µL injection volume.

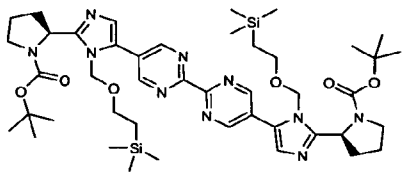
LCMS conditions (condition 2): Phenomenex LUNA C-18 4.6 × 50 mm, 0 to 100% B over 2 minutes, 1 minute hold time, A = 90% water, 10% methanol, 0.1% TFA, B = 10% water, 90% methanol, 0.1% TFA, 220nm, 5 µL injection volume.

Example 152l-1	 Prepared from **152k-3** and **cap 14**	t_R = 1.87 min (>95%) LCMS: Anal. Calcd. for $C_{46}H_{51}N_{10}O_4$ 807.41 found: 807.57 $(M+H)^+$ HRMS: Anal. Calcd. for $C_{46}H_{51}N_{10}O_4$

		807.4095 found: 807.4128 $(M+H)^+$
Example 152l-2	 Prepared from **152k-2** and **cap 14**	t_R = 1.83 min (>95%) LCMS: Anal. Calcd. for $C_{45}H_{49}N_{10}O_4$ 793.39 found: 793.52 $(M+H)^+$ HRMS: Anal. Calcd. for $C_{45}H_{49}N_{10}O_4$ 793.3938 found: 793.3934 $(M+H)^+$
Example 152l-3	 Prepared from **152k-1** and **cap 14**	t_R = 1.87 min (>95%) LCMS: Anal. Calcd. for $C_{47}H_{51}N_{10}O_4$ 819.41 found: 819.50 $(M+H)^+$ HRMS: Anal. Calcd. for $C_{47}H_{51}N_{10}O_4$ 819.4095 found: 819.4127 $(M+H)^+$

Example 153a-1 from 153a-4.

Example 153a-1 prepared from **152e-1**. (S)-2-[5-{5'-[2-((S)-1-*tert*-Butoxycarbonyl-pyrrolidin-2-yl)-3-(2-trimethylsilanyl-ethoxymethyl)-3*H*-imidazol-4-yl]-[2,2']bipyrimidinyl-5-yl}-1-(2-trimethylsilanyl-ethoxymethyl)-1*H*-imidazol-2-yl]-pyrrolidine-1-carboxylic acid *tert*-butyl ester



To a stirred solution of (S)-tert-butyl 2-(5-(2-chloropyrimidin-5-yl)-1-((2-(trimethylsilyl)ethoxy)methyl)-1H-imidazol-2-yl)pyrrolidine-1-carboxylate (1.0 g, 2.08 mmol) and dichlorobis(benzonitrile) palladium (40 mg, 0.104 mmol) in dry DMF (10 mL) at room temperature under argon was added neat tetrakis(dimethylamino)ethylene (1.0 mL, 4.16 mmol). The mixture was heated to 60°C for 15h before it was diluted with ethyl acetate and suction-filtered through Celite. The filtrate was washed with sat'd $NaHCO_3$ soln and brine prior to drying over Na_2SO_4 and solvent evaporation. Purification of the residue by Biotage™ flash chromatography on silica gel (step gradient elution with 15%B to 15%B for 150 mL, 15%B to 75%B for 1500 mL, 75%B to 100%B for 1000 mL, 100%B to 100%B for 1000 mL where B=ethyl acetate and A=hexane followed by a second gradient elution with 10%B to 100%B for 700 mL where B=methanol and A=ethyl acetate) furnished the title compound as a caramel-colored, viscous oil (487.8 mg, 26% yield).

^1H NMR (500 MHz, DMSO-d_6) δ 9.27 (s, 4H), 8.09-8.06 (m, 2H), 5.73-5.66 and 5.50-5.44 (2m, 2H), 5.06-4.93 (m, 2H), 3.60-3.39 (2m, 8H), 2.32-2.08 (3m, 4H), 2.00-1.85 (m, 4H), 1.37 and 1.14 (2s, 18H), 0.95-0.84 (m, 4H), -0.01 (s, 18H).

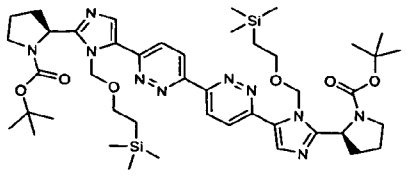
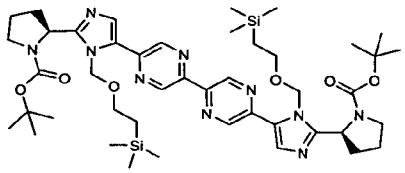
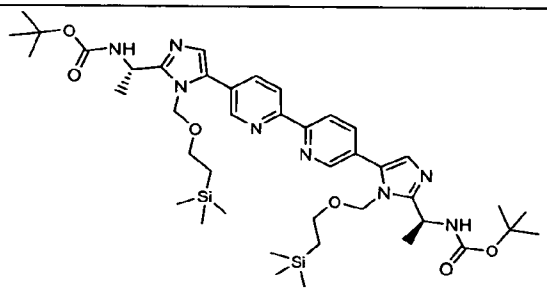
LCMS Phenomenex LUNA C-18 4.6 × 50 mm, 0 to 100% B over 3 minutes, 1 minute hold time, A = 90% water, 10% methanol, 0.1% TFA, B = 10% water, 90% methanol, 0.1% TFA, RT = 3.37min, >95% homogeneity index.

LCMS: Anal. Calcd. for $C_{44}H_{69}N_{10}O_6Si_2$ 889.49; found: 889.57 $(M+H)^+$.

HRMS: Anal. Calcd. for $C_{44}H_{69}N_{10}O_6Si_2$ 889.4940; found: 889.4920 $(M+H)^+$.

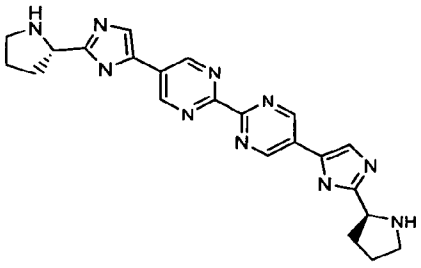
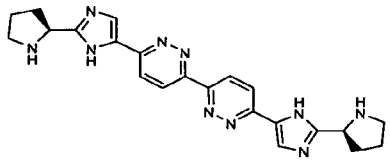
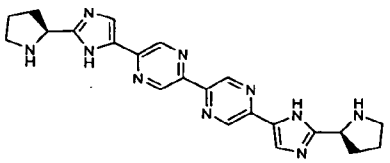
LCMS conditions: Phenomenex LUNA C-18 4.6 × 50 mm, 0 to 100% B over 3 minutes, 1 minute hold time, A = 90% water, 10% methanol, 0.1% TFA, B = 10% water, 90% methanol, 0.1% TFA, 220nm, 5 µL injection volume.

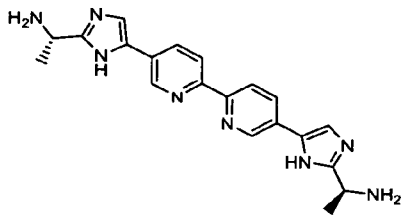
LCMS conditions (condition 2): Phenomenex LUNA C-18 4.6 × 50 mm, 0 to 100% B over 2 minutes, 1 minute hold time, A = 90% water, 10% methanol, 0.1% TFA, B = 10% water, 90% methanol, 0.1% TFA, 220nm, 5 µL injection volume.

Example 153a-2	 Prepared from **152e-2**	t_R = 3.37 min (89.6%) LCMS: Anal. Calcd. for $C_{44}H_{69}N_{10}O_6Si_2$ 889.49; found: 889.56 $(M+H)^+$. HRMS: Anal. Calcd. for $C_{44}H_{69}N_{10}O_6Si_2$ 889.494; found: 889.4951 $(M+H)^+$.
Example 153a-3	 Prepared from **152e-3**	t_R = 3.37 min (95%) LCMS: Anal. Calcd. for $C_{44}H_{69}N_{10}O_6Si_2$ 889.49; found: 889.51 $(M+H)^+$. HRMS: Anal. Calcd. for $C_{44}H_{69}N_{10}O_6Si_2$ 889.4940; found: 889.4915 $(M+H)^+$.
Example 153a-4	 Prepared from **152e-4**	t_R = 2.3 min (condition 2) LCMS: Anal. Calcd. for $C_{42}H_{66}N_8Si_2$ 834; found: 835 $(M+H)^+$.

Example 153b-1-153b-3

The hydrolysis reactions was performed as above for example Example **152h.**

Example 153b-1	 Prepared from **153a-1**	t_R = 1.18 min (>95%) LCMS: Anal. Calcd. for $C_{22}H_{25}N_{10}$ 429.23; found: 429.01 $(M+H)^+$. HRMS: Anal. Calcd. for $C_{22}H_{25}N_{10}$ 429.2264; found: 429.2259 $(M+H)^+$.
Example 153b-2	 Prepared from **153a-2**	t_R = 1.26 min (>95%) LCMS: Anal. Calcd. for $C_{41}H_{41}N_{10}O_2$ 737.33 found: 737.49 $(M+H)^+$ HRMS: Anal. Calcd. for $C_{41}H_{41}N_{10}O_4$ 737.3312 found: 737.3342 $(M+H)^+$
Example 153b-3	 Prepared from **153a-3**	t_R = 1.40 min (>95%) LCMS: Anal. Calcd. for $C_{22}H_{25}N_{10}$ 429.23; found: 429.20 $(M+H)^+$.

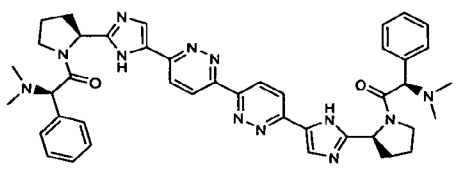
Example 153b-4	 Prepared from **153a-4**	t_R = 0.85 min (condition 2) LCMS: Anal. Calcd. for $C_{20}H_{22}N_8$ 374; found: 375 $(M+H)^+$.

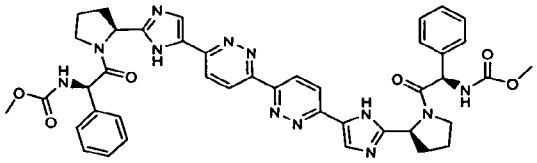
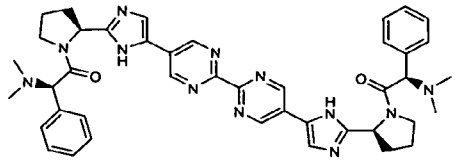
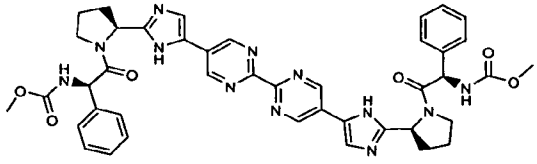
Examples 153c-1 to 153c-

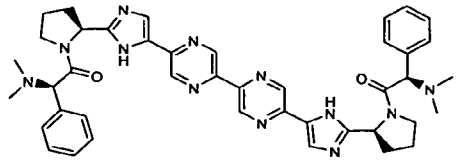
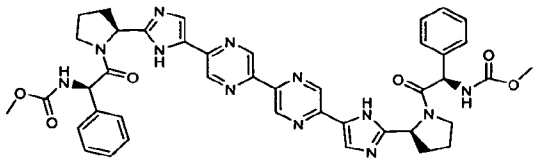
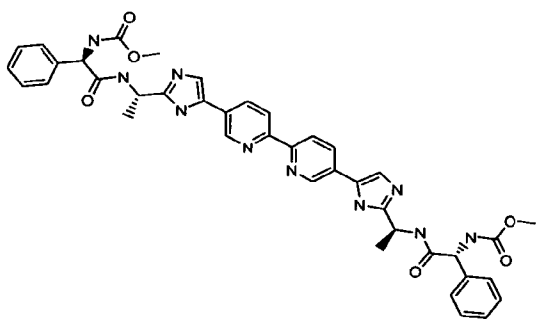
Examples 152l were isolated as TFA or AcOH salts prepared according to the method of example **148** above.

LCMS conditions: Phenomenex LUNA C-18 4.6 × 50 mm, 0 to 100% B over 3 minutes, 1 minute hold time, A = 90% water, 10% methanol, 0.1% TFA, B = 10% water, 90% methanol, 0.1% TFA, 220nm, 5 µL injection volume.

LCMS conditions (condition 2): Phenomenex LUNA C-18 4.6 × 50 mm, 0 to 100% B over 2 minutes, 1 minute hold time, A = 90% water, 10% methanol, 0.1% TFA, B = 10% water, 90% methanol, 0.1% TFA, 220nm, 5 µL injection volume.

Example 153c-1	 Prepared from **153b-2** and **cap 1**	t_R = 1.55 min (>95%) LCMS: Anal. Calcd. for $C_{42}H_{47}N_{12}O_2$ 751.39 found: 751.64 $(M+H)^+$ HRMS: Anal. Calcd. for $C_{42}H_{47}N_{12}O_2$ 751.3945 found: 751.3936 $(M+H)^+$

Example 153c-2	 Prepared from **153b-2** and **cap 4**	t_R = 1.95 min (>95%) LCMS: Anal. Calcd. for $C_{42}H_{43}N_{12}O_6$ 811.34 found: 811.22 $(M+H)^+$ HRMS: Anal. Calcd. for $C_{42}H_{43}N_{12}O_6$ 811.3429 found: 811.3406 $(M+H)^+$
Example 153c-3	 Prepared from **153b-1** anc **cap 1**	t_R = 1.51 min (>90%*) LCMS: Anal. Calcd. for $C_{42}H_{47}N_{12}O_2$ 751.39 found: 751.21 $(M+H)^+$ HRMS: Anal. Calcd. for $C_{42}H_{47}N_{12}O_2$ 751.3945 found: 751.3921 $(M+H)^+$
Example 153c-4	 Prepared from **153b-1** and **cap 4**	t_R = 1.88 min (>95%) LCMS: Anal. Calcd. for $C_{42}H_{43}N_{12}O_6$ 811.34 found: 811.10 $(M+H)^+$ HRMS: Anal. Calcd. for $C_{42}H_{43}N_{12}O_6$ 811.3429 found: 811.3401 $(M+H)^+$

Example 153c-5	 Prepared from **153b-3** and **cap 1**	t_R = 1.61 min (>95%) LCMS: Anal. Calcd. for $C_{42}H_{47}N_{12}O_2$ 751.39 found: 751.30 $(M+H)^+$ HRMS: Anal. Calcd. for $C_{42}H_{47}N_{12}O_2$ 751.3945 found: 751.3943 $(M+H)^+$
Example 153c-6	 Prepared from **153b-3** and **cap 4**	t_R = 2.00 min (>95%) LCMS: Anal. Calcd. for $C_{42}H_{43}N_{12}O_6$ 811.34 found: 811.23 $(M+H)^+$ HRMS: Anal. Calcd. for $C_{42}H_{43}N_{12}O_6$ 811.3429 found: 811.3407 $(M+H)^+$
Example 153c-7	 Prepared from **153b-4** and **cap 4**	t_R = 1.42 min (condition 2, 94%) LRMS: Anal. Calcd. for $C_{40}H_{40}N_{10}O_6$ 756.31; found: 757.34 $(M+H)^+$. HRMS: Anal. Calcd. for $C_{40}H_{41}N_{10}O_6$ 757.3211

		found: 757.3180 $(M+H)^+$.

BIOLOGICAL ACTIVITY

An HCV Replion assay was utilized in the present disclosure, and was prepared, conducted and validated as described in commonly owned PCT/US2006/022197 and in O'Boyle et. al. *Antimicrob Agents Chemother.* 2005 Apr;49(4):1346-53.

HCV 1b-377-neo replicon cells were used to test the currently described compound series as well as cells resistant to compound A due to a Y2065H mutation in NS5A (described in application PCT/US2006/022197 and commonly owned WO/O4014852). The compounds were determined to have more than 10-fold less inhibitory activity on cells resistant to compound A than wild-type cells indicating a related mechanism of action between the two compound series. Thus, the compounds of the present disclosure can be effective to inhibit the function of the HCV NS5A protein and are understood to be as effective in combinations as previously described in application PCT/US2006/022197 and commonly owned WO/O4014852. Further, the compounds of the present disclosure can be effective against the HCV 1b genotype. It should also be understood that the compounds of the present disclosure can inhibit multiple genotypes of HCV. Table 2 shows the EC50 values of representative compounds of the present disclosure against the HCV 1b genotype. Ranges are as follows: A = 1-10 μM; B = 100-999 nM; C = 1-99 nM; and D = 10-999 pM.

The compounds of the present disclosure may inhibit HCV by mechanisms in addition to or other than NS5A inhibition. In one embodiment the compounds of the present disclosure inhibit HCV replicon and in another embodiment the compounds of the present disclosure inhibit NS5A.

Table 2

Example	Range
1	D
24-4e	C
24-4f	B
24-4g	A
25-1	D
25-2	D
25-3	D
25-4	D
25-5	D
25-6	C
25-7	C
25-8	D
24-4h	D
120-9	D
120	D
120-5	C
120-6	C
120-7	D
120-8	C
103-3	D
103-4	D
103-1	D
103-2	D
103-5	D
103-6	C
103-8	D
103-7	D
151 isomer 1	C
151 isomer 2	B
152j-9	C
152j-10	C
152j-1	C
152j-2	D
153c-5	C
153c-6	C
153c-2	C
153c-1	C
152j-7	C
152j-8	D
153c-3	A
153c-4	A
152j-11	D
152j-12	D
152j-15	D

Example	Range
152j-28	D
152j-13	C
152j-14	C
152j-19	D
152j-16	D
152j-3	D
152j-20	C
152j-17	D
152j-18	D
152j-3	D
152j-5	D
152j-6	D
152l-2	D
152l-1	D
152j-24	D
152j-23	D
153c-7	C
152j-22	D
24-18-2	D
24-18-1	D
24-18-4	D
24-18-5	D
24-18-6	D
24-18-3	D
152j-21	D
152l-3	D
131.1-2	D
131.1-1	D
24-4a	D
120-1	D
120-2	D
120-3	D
120-4	D
24-10	D
24-9	D
24-8	D
24-11	C
24-12	C
11	C
24-16	D
24-18	D
24-17	D
24-15	C
24-13	B

Example	Range
24-14	C
24-4b	C
24-4c	D
24-4d	D
148	C
149	D
150	C
24-5	D
24-6	D
24-7	D
24-1	D
24-2	D
24-3	D
28-1	D
28-2	D
28-3	D
28-4	D
28-5	D
84-1	D
84-2	D
84-3	D
84-4	D
84-7	C
84-10	C
84-12	D
84-14	C
84-15	C
84-17	D
84-18	C
84-19	C
84-20	C
84-24	D
84-26	D
84-27	D
84-28	D
84-32	D
84-33	D
84-34	C
84-35	D
84-36	D
84-38	D
84-39	D
84-40	D
84-44	D

84-46	D
84-47	D
84-48	D
84-49	D
84-50	D
84-51	D
84-52	D
84-53	D
84-54	D
84-55	D
84-56	D
84-57	D
84-58	D
84-59	D
84-60	D
84-61	D
84-62	D
84-63	D
84-64	D
84-65	C-D
84-66	C-D
84-67	D
84-68	C
84-69	D
84-70	C
84-71	C
84-72	C
84-73	C
84-74	D
84-75	C
84-76	D
84-77	D
84-78	D
84-79	D
84-80	D
84-81	D
84-82	D
84-83	D
84-84	D
84-85	D
84-86	D
84-87	D
94-1	D
94-2	C
94-3	D

94-6	C-D
94-9	D
94-10	D
94-12	C
94-13	D
94-17	D
94-19	D
94-20	C
94-24	D
94-25	D
94-26	D
94-27	C
94-30	D
94-32	C
94-33	C
94-34	C
94-36	D
94-37	C
94-38	D
94-42	D
94-44	D
94-45	D
94-46	D
94-47	D
94-48	D
94-49	D
94-50	D
94-51	D
94-52	D
94-53	D
94-54	D
94-55	D
94-56	D
107-1	D
107-2	D
107-3	D
107-4	D
107-5	D
107-6	D
107-7	D
107-8	D
107-9	D
107-10	D
107-11	D
107-12	D

107-13	D
107-14	D
107-15	D
107-16	D
107-17	D
107-18	D
107-19	D
107-20	D
107-21	D
107-22	D
107-23	D
107-24	D
107-25	D
107-26	D
107-27	D
107-28	D
107-29	D
107-30	D
107-31	D
107-32	D
107-33	D
107-34	D
107-35	D
107-36	D
107-37	D
107-38	D
107-39	D
107-40	D
107-41	D
107-42	D
107-43	D
107-44	D
2	D
3	D
4	D
5	C
6	C
7	D
8	D
9	C
10	C
11	C

12	C
13	C
14	B
15	C
16	C
17	D
18	D
19	D
20	C
21	D
22	D
23	D
24	C
25	D
26	C
27	C
28	C
29	D
30	C
31	D
32	C
33	D
34	D
35	D
36	D
37	D
38	D
39	D
40	D
41	D
42	D
43	D
44	D
45	D
46	D
47	D
48	D
49	D
50	B
51	D
52	D
53	D
54	D
55	D
56	D

57	DD
58	D
59	D
60	D
61	D
62	D
63	D
64	D
65	C
67	D
68	D
69	D
70	C
71	D
72	C
73	D
74	D
75	D
76	D
77	D
78	D
79	D
80	D
81	D
82	D
83	D
84	D
85	D
86	D
87	D
88	D
89	D
90	D
91	D
92	D
93	D
94	D
95	D
96	D
97	D
98	D
99	D
100	D
101	D
102	D

103	D
104	D
105	D
106	D
107	D
108	D
109	C
110	D
111	D
112	D
113	D
114	D
115	D
116	D
117	D
118	D
119	D
120	D
121	D
122	D
123	D
124	D
125	D
126	D
127	D
128	D
129	D
130	D
131	D
132	D
133	C
134	D
135	D
136	D
138	D
139	D
140	D
141	D
142	C
143	D
144	D
145	D

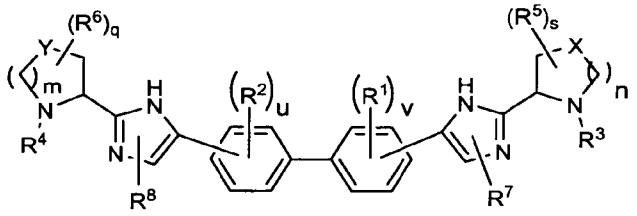
146	D
147	D

It will be evident to one skilled in the art that the present disclosure is not limited to the foregoing illustrative examples, and that it can be embodied in other specific forms without departing from the essential attributes thereof. It is therefore desired that the examples be considered in all respects as illustrative and not restrictive, reference being made to the appended claims, rather than to the foregoing examples, and all changes which come within the meaning and range of equivalency of the claims are therefore intended to be embraced therein.

The compounds of the present disclosure may inhibit HCV by mechanisms in addition to or other than NS5A inhibition. In one embodiment the compounds of the present disclosure inhibit HCV replicon and in another embodiment the compounds of the present disclosure inhibit NS5A. Compounds of the present disclosure may inhibit multiple genotypes of HCV.

WHAT IS CLAIMED IS:

1. A compound of Formula (I)



(I),

or a pharmaceutically acceptable salt thereof, wherein

m and n are independently 0, 1, or 2;

q and s are independently 0, 1, 2, 3, or 4;

u and v are independently 0, 1, 2, or 3;

X is selected from O, S, S(O), SO_2, CH_2, CHR^5, and $C(R^5)_2$;

provided that when m is 0, X is selected from CH_2, CHR^5, and $C(R^5)_2$;

Y is selected from O, S, S(O), SO_2, CH_2, CHR^6, and $C(R^6)_2$;

provided that when n is 0, Y is selected from CH_2, CHR^6, and $C(R^6)_2$;

each R^1 and R^2 are each independently selected from alkoxy, alkoxycarbonyl, alkyl, carboxy, halo, haloalkyl, hydroxy, $-NR^aR^b$, (NR^aR^b)alkyl, and (NR^aR^b)carbonyl;

R^3 and R^4 are each independently selected from hydrogen and R^9-C(O)-;

each R^5 and R^6 is independently selected from alkoxy, alkyl, halo, haloalkyl, hydroxy, and $-NR^aR^b$, wherein the alkyl can optionally form a fused cyclopropyl ring with an adjacent carbon atom;

R^7 and R^8 are each independently selected from hydrogen, alkoxycarbonyl, alkyl, carboxy, haloalkyl, (NR^aR^b)carbonyl, and trialkylsilylalkoxyalkyl; and

each R^9 is independently selected from alkoxy, alkoxyalkyl, alkoxycarbonyl, alkoxycarbonylalkyl, alkyl, alkylcarbonylalkyl, aryl, arylalkenyl, arylalkoxy, arylalkyl, aryloxyalkyl, cycloalkyl, (cycloalkyl)alkenyl, (cycloalkyl)alkyl, cycloalkyloxyalkyl, haloalkyl, heterocyclyl, heterocyclylalkenyl, heterocyclylalkoxy, heterocyclylalkyl, heterocyclyloxyalkyl, hydroxyalkyl, $-NR^cR^d$, (NR^cR^d)alkyl, and (NR^cR^d)carbonyl.

2. A compound of claim 1 wherein m and n are each 1.

3. A compound of claim 2 wherein at least one of X and Y is S.

4. A compound of claim 2 wherein X and Y are each S.

5. A compound of claim 4 wherein
q and s are each 0; and
u and v are each 0.

6. A compound of claim 5 wherein at least one of R^3 and R^4 is hydrogen.

7. A compound of claim 5 wherein R^3 and R^4 are -C(O)-R^9.

8. A compound of claim 7 wherein each R^9 is independently selected from arylalkyl and heterocyclyl.

9. A compound of claim 2 wherein X is selected from CHR^5, and $C(R^5)_2$; and Y is selected from CH_2, CHR^6, and $C(R^6)_2$.

10. A compound of claim 9 wherein each R^5 and R^6 is independently selected from halo and hydroxy.

11. A compound of claim 10 wherein each R^1 and R^2 is independently selected from hydrogen, C_1 alkyl, and halo.

12. A compound of claim 11 wherein R^1 and R^2 are hydrogen.

13. A compound of claim 12 wherein at least one of R^3 and R^4 is hydrogen.

14. A compound of claim 12 wherein R^3 and R^4 -C(O)-R^9.

15. A compound of claim 14 wherein each R^9 is independently selected from

alkoxy and arylalkyl.

16. A compound of claim 2 wherein X and Y are each CH_2.

17. A copound of claim 16 wherein at least one of q and s is 0.

18. A compound of claim 17 wherein q and s are each 0.

19. A compound of claim 18 wherein R^1 and R^2 are independently selected from hydrogen, alkyl, halo, and haloalkyl.

20. A compound of claim 19 wherein at least one of R^3 and R^4 is hydrogen.

21. A compound of claim 19 wherein R^3 and R^4 are -C(O)-R^9.

22. A compound of claim 21 wherein each R^9 is independently selected from alkoxy, alkoxyalkyl, alkyl, alkylcarbonylalkyl, aryl, arylalkenyl, arylalkoxy, arylalkyl, aryloxyalkyl, cycloalkyl, (cycloalkyl)alkyl, cycloalkyloxyalkyl, heterocyclyl, heterocyclylalkyl, hydroxyalkyl, (NR^cR^d)alkyl, and (NR^cR^d)carbonyl.

23. A compound of claim 21 wherein each R^9 is arylalkyl.

24. A compound of claim 21 wherein one R^9 is heterocyclyl and the other is arylalkyl.

25. A compound of claim 21 wherein one R^9 is heterocyclylalkyl and the other is arylalkyl.

26. A compound of claim 21 wherein each R^9 is (NR^cR^d)alkyl.

27. A compound of claim 21 wherein one R^9 is (NR^cR^d)alkyl and the other is arylalkyl.

28. A compound of claim 21 wherein one R^9 is selected from alkoxy, alkyl, aryl, arylalkoxy, arylalkyl, cycloalkyl, (cycloalkyl)alkyl, heterocyclyl, and hydroxyalkyl; and the other is selected from alkoxy, alkoxyalkyl, alkyl, alkylcarbonylalkyl, arylalkenyl, aryl, arylalkoxy, aryloxyalkyl, cycloalkyl, (cycloalkyl)alkyl, cycloalkyloxyalkyl, heterocyclyl, hydroxyalkyl, $-NR^cR^d$, and (NR^cR^d)carbonyl.

29. A composition comprising a compound of claim 1 and a pharmaceutically acceptable carrier.

30. The composition of claim 29 further comprising an interferon and ribavirin.

31. The composition of claim 30 further comprising a second compound having anti-HCV activity.

32. The composition of claim 31 wherein the second compound having anti-HCV activity is an interferon.

33. The composition of claim 32 wherein the interferon is selected from interferon alpha 2B, pegylated interferon alpha, consensus interferon, interferon alpha 2A, and lymphoblastiod interferon tau.

34. The composition of claim 31 wherein the second compound having anti-HCV activity is selected from interleukin 2, interleukin 6, interleukin 12, a compound that enhances the development of a type 1 helper T cell response, interfering RNA, anti-sense RNA, Imiqimod, ribavirin, an inosine 5'-monophospate dehydrogenase inhibitor, amantadine, and rimantadine.

35. A method of inhibiting the function of HCV NS5A protein comprising contacting the HCV NS5A protein with a compound of claim 1.

36. A method of treating an HCV infection in a patient, comprising administering to the patient a therapeutically effective amount of a compound of claim 1.

37. The method of claim 36 further comprising administering a second compound having anti-HCV activity prior to, after or simultaneously with the compound of claim 1.

38. The method of claim 37 wherein the second compound having anti-HCV activity is an interferon.

39. The method of claim 38 wherein the interferon is selected from interferon alpha 2B, pegylated interferon alpha, consensus interferon, interferon alpha 2A, and lymphoblastiod interferon tau.

40. The method of claim 37 wherein the second compound having anti-HCV activity is selected from interleukin 2, interleukin 6, interleukin 12, a compound that enhances the development of a type 1 helper T cell response, interfering RNA, anti-sense RNA, Imiqimod, ribavirin, an inosine 5'-monophospate dehydrogenase inhibitor, amantadine, and rimantadine.

ABSTRACT

The present disclosure relates to tripeptide compounds, compositions and methods for the treatment of hepatitis C virus (HCV) infection. Also disclosed are pharmaceutical compositions containing such compounds and methods for using these compounds in the treatment of HCV infection.

Document made available under the Patent Cooperation Treaty (PCT)

International application number: PCT/US2007/075544

International filing date: 09 August 2007 (09.08.2007)

Document type: Certified copy of priority document

Document details: Country/Office: US
Number: 11/835,462
Filing date: 08 August 2007 (08.08.2007)

Date of receipt at the International Bureau: 26 September 2007 (26.09.2007)

Remark: Priority document submitted or transmitted to the International Bureau in compliance with Rule 17.1(a) or (b)

World Intellectual Property Organization (WIPO) - Geneva, Switzerland
Organisation Mondiale de la Propriété Intellectuelle (OMPI) - Genève, Suisse

4409

THE UNITED STATES OF AMERICA

TO ALL TO WHOM THESE PRESENTS SHALL COME:

UNITED STATES DEPARTMENT OF COMMERCE

United States Patent and Trademark Office

September 26, 2007

THIS IS TO CERTIFY THAT ANNEXED HERETO IS A TRUE COPY FROM THE RECORDS OF THE UNITED STATES PATENT AND TRADEMARK OFFICE OF THOSE PAPERS OF THE BELOW IDENTIFIED PATENT APPLICATION THAT MET THE REQUIREMENTS TO BE GRANTED A FILING DATE.

APPLICATION NUMBER: *11/835,462*
FILING DATE: *August 08, 2007*
RELATED PCT APPLICATION NUMBER: *PCT/US07/75544*

THE COUNTRY CODE AND NUMBER OF YOUR PRIORITY APPLICATION, TO BE USED FOR FILING ABROAD UNDER THE PARIS CONVENTION, IS *US11/835,462*

Certified by

Under Secretary of Commerce
for Intellectual Property
and Director of the United States
Patent and Trademark Office

Application Data Sheet 37 CFR 1.76

Application Information

Title of the Invention	HEPATITIS C VIRUS INHIBITORS
Attorney Docket Number	10889-US-NP
Large Entity Status Claimed	YES
Application Type	NON-PROVISIONAL
Subject Matter	UTILITY
Total Number of Drawing Sheets (if any)	NONE
Sequence Submissions (if any)	NONE

Inventor Information

Authority Type	INVENTOR
Primary Citizenship Country	Canada
Given Name	Carol
Middle Name/Initial	
Family Name	Bachand
Residence City	Candiac
Residence State/Province	Quebec
Country of Residence	Canada
Mailing Address	119 Place Mercure
Mailing Address City	Candiac
Mailing Address Postal Code	J5R 1B1
Mailing Address State/Province	Quebec
Mailing Address Country	Canada

Inventor Information

Authority Type	INVENTOR
Primary Citizenship Country	Ethiopia
Given Name	Makonen
Middle Name/Initial	
Family Name	Belema
Residence City	North Haven
Residence State/Province	Connecticut
Country of Residence	United States of America
Mailing Address	5 Research Parkway
Mailing Address City	Wallingford
Mailing Address Postal Code	06492
Mailing Address State/Province	Connecticut
Mailing Address Country	United States of America

Application Data Sheet 37 CFR 1.76

Inventor Information

Authority Type	INVENTOR
Primary Citizenship Country	Canada
Given Name	Daniel
Middle Name/Initial	H.
Family Name	Deon
Residence City	Brossard
Residence State/Province	Quebec
Country of Residence	Canada
Mailing Address	#401-4905 Av Colomb
Mailing Address City	Brossard
Mailing Address Postal Code	J4Z 3T2
Mailing Address State/Province	Quebec
Mailing Address Country	Canada

Inventor Information

Authority Type	INVENTOR
Primary Citizenship Country	Great Britain
Given Name	Andrew
Middle Name/Initial	C.
Family Name	Good
Residence City	Wallingford
Residence State/Province	Connecticut
Country of Residence	United States of America
Mailing Address	5 Research Parkway
Mailing Address City	Wallingford
Mailing Address Postal Code	06492
Mailing Address State/Province	Connecticut
Mailing Address Country	United States of America

Inventor Information

Authority Type	INVENTOR
Primary Citizenship Country	United States of America
Given Name	Jason
Middle Name/Initial	
Family Name	Goodrich
Residence City	Meriden
Residence State/Province	Connecticut
Country of Residence	United States of America
Mailing Address	5 Research Parkway
Mailing Address City	Wallingford
Mailing Address Postal Code	06492
Mailing Address State/Province	Connecticut
Mailing Address Country	United States of America

Application Data Sheet 37 CFR 1.76

Inventor Information

Authority Type	INVENTOR
Primary Citizenship Country	Canada
Given Name	Clint
Middle Name/Initial	A.
Family Name	James
Residence City	Longueuil
Residence State/Province	Quebec
Country of Residence	Canada
Mailing Address	5 Research Parkway
Mailing Address City	Wallingford
Mailing Address Postal Code	06492
Mailing Address State/Province	Connecticut
Mailing Address Country	United States of America

Inventor Information

Authority Type	INVENTOR
Primary Citizenship Country	Canada
Given Name	Rico
Middle Name/Initial	
Family Name	Lavoie
Residence City	Candiac
Residence State/Province	Quebec
Country of Residence	Canada
Mailing Address	5 Research Parkway
Mailing Address City	Wallingford
Mailing Address Postal Code	06492
Mailing Address State/Province	Connecticut
Mailing Address Country	United States of America

Inventor Information

Authority Type	INVENTOR
Primary Citizenship Country	Argentina
Given Name	Omar
Middle Name/Initial	D.
Family Name	Lopez
Residence City	Wallingford
Residence State/Province	Connecticut
Country of Residence	United States of America
Mailing Address	5 Research Parkway
Mailing Address City	Wallingford
Mailing Address Postal Code	06492
Mailing Address State/Province	Connecticut
Mailing Address Country	United States of America

Application Data Sheet 37 CFR 1.76

Inventor Information

Authority Type	INVENTOR
Primary Citizenship Country	Canada
Given Name	Alain
Middle Name/Initial	
Family Name	Martel
Residence City	Delson
Residence State/Province	Quebec
Country of Residence	Canada
Mailing Address	29 Rue Monette
Mailing Address City	Delson
Mailing Address Postal Code	J5B 1G8
Mailing Address State/Province	Quebec
Mailing Address Country	Canada

Inventor Information

Authority Type	INVENTOR
Primary Citizenship Country	United States of America
Given Name	Nicholas
Middle Name/Initial	A.
Family Name	Meanwell
Residence City	East Hampton
Residence State/Province	Connecticut
Country of Residence	United States of America
Mailing Address	5 Research Parkway
Mailing Address City	Wallingford
Mailing Address Postal Code	06492
Mailing Address State/Province	Connecticut
Mailing Address Country	United States of America

Inventor Information

Authority Type	INVENTOR
Primary Citizenship Country	United States of America
Given Name	Van
Middle Name/Initial	N.
Family Name	Nguyen
Residence City	New Britain
Residence State/Province	Connecticut
Country of Residence	United States of America
Mailing Address	5 Research Parkway
Mailing Address City	Wallingford
Mailing Address Postal Code	06492
Mailing Address State/Province	Connecticut
Mailing Address Country	United States of America

Application Data Sheet 37 CFR 1.76

Inventor Information

Authority Type	INVENTOR
Primary Citizenship Country	United States of America
Given Name	Jeffrey
Middle Name/Initial	Lee
Family Name	Romine
Residence City	Meriden
Residence State/Province	Connecticut
Country of Residence	United States of America
Mailing Address	5 Research Parkway
Mailing Address City	Wallingford
Mailing Address Postal Code	06492
Mailing Address State/Province	Connecticut
Mailing Address Country	United States of America

Inventor Information

Authority Type	INVENTOR
Primary Citizenship Country	Canada
Given Name	Edward
Middle Name/Initial	H.
Family Name	Ruediger
Residence City	Greenfield Park
Residence State/Province	Quebec
Country of Residence	Canada
Mailing Address	133 St. Charles
Mailing Address City	Greenfield Park
Mailing Address Postal Code	J4V 2K3
Mailing Address State/Province	Quebec
Mailing Address Country	Canada

Inventor Information

Authority Type	INVENTOR
Primary Citizenship Country	United States of America
Given Name	Lawrence
Middle Name/Initial	B.
Family Name	Snyder
Residence City	Killingworth
Residence State/Province	Connecticut
Country of Residence	United States of America
Mailing Address	5 Research Parkway
Mailing Address City	Wallingford
Mailing Address Postal Code	06492
Mailing Address State/Province	Connecticut
Mailing Address Country	United States of America

Application Data Sheet 37 CFR 1.76

Inventor Information

Authority Type	INVENTOR
Primary Citizenship Country	United States of America
Given Name	Denis
Middle Name/Initial	R.
Family Name	St. Laurent
Residence City	Newington
Residence State/Province	Connecticut
Country of Residence	United States of America
Mailing Address	5 Research Parkway
Mailing Address City	Wallingford
Mailing Address Postal Code	06492
Mailing Address State/Province	Connecticut
Mailing Address Country	United States of America

Inventor Information

Authority Type	INVENTOR
Primary Citizenship Country	People's Republic of China
Given Name	Fukang
Middle Name/Initial	
Family Name	Yang
Residence City	Madison
Residence State/Province	Connecticut
Country of Residence	United States of America
Mailing Address	5 Research Parkway
Mailing Address City	Wallingford
Mailing Address Postal Code	06492
Mailing Address State/Province	Connecticut
Mailing Address Country	United States of America

Inventor Information

Authority Type	INVENTOR
Primary Citizenship Country	United States of America
Given Name	David
Middle Name/Initial	R.
Family Name	Langley
Residence City	Meriden
Residence State/Province	Connecticut
Country of Residence	United States of America
Mailing Address	5 Research Parkway
Mailing Address City	Wallingford
Mailing Address Postal Code	06492
Mailing Address State/Province	Connecticut
Mailing Address Country	United States of America

Application Data Sheet 37 CFR 1.76

Inventor Information

Authority Type	INVENTOR
Primary Citizenship Country	People's Republic of China
Given Name	Gan
Middle Name/Initial	
Family Name	Wang
Residence City	Wallingford
Residence State/Province	Connecticut
Country of Residence	United States of America
Mailing Address	5 Research Parkway
Mailing Address City	Wallingford
Mailing Address Postal Code	06492
Mailing Address State/Province	Wallingford
Mailing Address Country	United States of America

Inventor Information

Authority Type	INVENTOR
Primary Citizenship Country	United States of America
Given Name	Lawrence
Middle Name/Initial	G.
Family Name	Hamann
Residence City	North Grafton
Residence State/Province	Massachusetts
Country of Residence	United States of America
Mailing Address	5 Research Parkway
Mailing Address City	Wallingford
Mailing Address Postal Code	06492
Mailing Address State/Province	Wallingford
Mailing Address Country	United States of America

Correspondence Information:

Customer Number	23914
Main E-Mail address	patents@bms.com

Representative Information:

Customer Number	23914

Application Data Sheet 37 CFR 1.76

Domestic Priority Information:

Application No	Continuity Type	Parent Application No.	Parent Filing Date
This Application	is a non-provisional	of 60/836,996	August 11, 2006

Assignee Information:

Assignee	Bristol-Myers Squibb Company
Assignee is an Organization	Yes

Signature:

Signature	/pamela a mingo/
Date	August 8, 2007
Attorney/Agent Name	Pamela A. Mingo, Ph.D.
Registration Number	48,256
Telephone Number	203-677-7669

HEPATITIS C VIRUS INHIBITORS

CROSS-REFERENCE TO RELATED APPLICATIONS

This application claims the benefit of U.S. Provisional Application Serial Number 60/836,996 filed August 11, 2006.

The present disclosure is generally directed to antiviral compounds, and more specifically directed to compounds which can inhibit the function of the NS5A protein encoded by Hepatitis C virus (HCV), compositions comprising such compounds, and methods for inhibiting the function of the NS5A protein.

HCV is a major human pathogen, infecting an estimated 170 million persons worldwide - roughly five times the number infected by human immunodeficiency virus type 1. A substantial fraction of these HCV infected individuals develop serious progressive liver disease, including cirrhosis and hepatocellular carcinoma.

Presently, the most effective HCV therapy employs a combination of alpha-interferon and ribavirin, leading to sustained efficacy in 40% of patients. Recent clinical results demonstrate that pegylated alpha-interferon is superior to unmodified alpha-interferon as monotherapy. However, even with experimental therapeutic regimens involving combinations of pegylated alpha-interferon and ribavirin, a substantial fraction of patients do not have a sustained reduction in viral load. Thus, there is a clear and long-felt need to develop effective therapeutics for treatment of HCV infection.

HCV is a positive-stranded RNA virus. Based on a comparison of the deduced amino acid sequence and the extensive similarity in the 5' untranslated region, HCV has been classified as a separate genus in the Flaviviridae family. All members of the Flaviviridae family have enveloped virions that contain a positive stranded RNA genome encoding all known virus-specific proteins *via* translation of a single, uninterrupted, open reading frame.

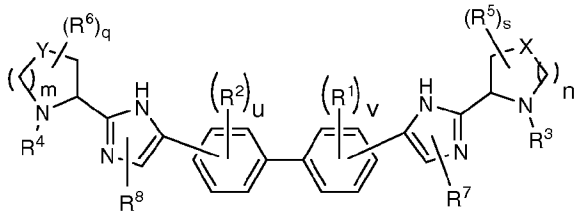
Considerable heterogeneity is found within the nucleotide and encoded amino acid sequence throughout the HCV genome. At least six major genotypes have been characterized, and more than 50 subtypes have been described. The major genotypes of HCV differ in their distribution worldwide, and the clinical significance of the genetic heterogeneity of HCV remains elusive despite numerous studies of the

possible effect of genotypes on pathogenesis and therapy.

The single strand HCV RNA genome is approximately 9500 nucleotides in length and has a single open reading frame (ORF) encoding a single large polyprotein of about 3000 amino acids. In infected cells, this polyprotein is cleaved at multiple sites by cellular and viral proteases to produce the structural and non-structural (NS) proteins. In the case of HCV, the generation of mature non-structural proteins (NS2, NS3, NS4A, NS4B, NS5A, and NS5B) is effected by two viral proteases. The first one is believed to be a metalloprotease and cleaves at the NS2-NS3 junction; the second one is a serine protease contained within the N-terminal region of NS3 (also referred to herein as NS3 protease) and mediates all the subsequent cleavages downstream of NS3, both in cis, at the NS3-NS4A cleavage site, and in trans, for the remaining NS4A-NS4B, NS4B-NS5A, NS5A-NS5B sites. The NS4A protein appears to serve multiple functions, acting as a cofactor for the NS3 protease and possibly assisting in the membrane localization of NS3 and other viral replicase components. The complex formation of the NS3 protein with NS4A seems necessary to the processing events, enhancing the proteolytic efficiency at all of the sites. The NS3 protein also exhibits nucleoside triphosphatase and RNA helicase activities. NS5B (also referred to herein as HCV polymerase) is a RNA-dependent RNA polymerase that is involved in the replication of HCV.

Compounds useful for treating HCV-infected patients are desired which selectively inhibit HCV viral replication. In particular, compounds which are effective to inhibit the function of the NS5A protein are desired. The HCV NS5A protein is described, for example, in Tan, S.-L., Katzel, M.G. *Virology* 2001, *284*, 1-12; and in Park, K.-J.; Choi, S.-H, *J. Biological Chemistry* 2003.

In a first aspect the present disclosure provides a compound of Formula (I)



(I),

or a pharmaceutically acceptable salt thereof, wherein

m and n are independently 0, 1, or 2;

q and s are independently 0, 1, 2, 3, or 4;

u and v are independently 0, 1, 2, or 3;

X is selected from O, S, S(O), SO_2, CH_2, CHR^5, and $C(R^5)_2$;

provided that when n is 0, X is selected from CH_2, CHR^5, and $C(R^5)_2$;

Y is selected from O, S, S(O), SO_2, CH_2, CHR^6, and $C(R^6)_2$;

provided that when m is 0, Y is selected from CH_2, CHR^6, and $C(R^6)_2$;

each R^1 and R^2 is independently selected from alkoxy, alkoxyalkyl, alkoxycarbonyl, alkyl, arylalkoxycarbonyl, carboxy, formyl, halo, haloalkyl, hydroxy, hydroxyalkyl, $-NR^aR^b$, (NR^aR^b)alkyl, and (NR^aR^b)carbonyl;

R^3 and R^4 are each independently selected from hydrogen, R^9-C(O)-, and R^9-C(S)-;

each R^5 and R^6 is independently selected from alkoxy, alkyl, aryl, halo, haloalkyl, hydroxy, and $-NR^aR^b$, wherein the alkyl can optionally form a fused three- to six-membered ring with an adjacent carbon atom, wherein the three- to six-membered ring is optionally substituted with one or two alkyl groups;

R^7 and R^8 are each independently selected from hydrogen, alkoxycarbonyl, alkyl, arylalkoxycarbonyl, carboxy, haloalkyl, (NR^aR^b)carbonyl, and trialkylsilylalkoxyalkyl; and

each R^9 is independently selected from alkoxy, alkoxyalkyl, alkoxycarbonyl, alkoxycarbonylalkyl, alkyl, alkylcarbonylalkyl, aryl, arylalkenyl, arylalkoxy, arylalkyl, aryloxyalkyl, cycloalkyl, (cycloalkyl)alkenyl, (cycloalkyl)alkyl, cycloalkyloxyalkyl, haloalkyl, heterocyclyl, heterocyclylalkenyl, heterocyclylalkoxy, heterocyclylalkyl, heterocyclyloxyalkyl, hydroxyalkyl, $-NR^cR^d$, (NR^cR^d)alkenyl, (NR^cR^d)alkyl, and (NR^cR^d)carbonyl.

In a first embodiment of the first aspect the present disclosure provides a compound of formula (I), or a pharmaceutically acceptable salt thereof, wherein m and n are each 1.

In a second embodiment of the first aspect the present disclosure provides a compound of formula (I), or a pharmaceutically acceptable salt thereof, wherein

u and v are each independently 0, 1, or 2; and

each R^1 and R^2 is independently selected from alkoxy, alkoxyalkyl, alkyl, arylalkoxycarbonyl, carboxy, formyl, halo, haloalkyl, hydroxyalkyl, (NR^aR^b)alkyl, and (NR^aR^b)carbonyl.

In a third embodiment of the first aspect the present disclosure provides a compound of formula (I), or a pharmaceutically acceptable salt thereof, wherein

u and v are each independently 0 or 1; and

when present, R^1 and/or R^2 are halo.

In a fourth embodiment of the first aspect the present disclosure provides a compound of formula (I), or a pharmaceutically acceptable salt thereof, wherein

u and v are each independently 0 or 1; and

when present, R^1 and/or R^2 are halo, wherein the halo is fluoro.

In a fifth embodiment of the first aspect the present disclosure provides a compound of formula (I), or a pharmaceutically acceptable salt thereof, wherein at least one of X and Y is S.

In a sixth embodiment of the first aspect the present disclosure provides a compound of formula (I), or a pharmaceutically acceptable salt thereof, wherein X and Y are each S.

In a seventh embodiment of the first aspect the present disclosure provides a compound of formula (I), or a pharmaceutically acceptable salt thereof, wherein X is selected from CHR^5, and $C(R^5)_2$; and Y is selected from CH_2, CHR^6, and $C(R^6)_2$.

In an eighth embodiment of the first aspect the present disclosure provides a compound of formula (I), or a pharmaceutically acceptable salt thereof, wherein R^7 and R^8 are independently selected from hydrogen, alkoxycarbonyl, alkyl, arylalkoxycarbonyl, carboxy, haloalkyl, and (NR^aR^b)carbonyl.

In a ninth embodiment of the first aspect the present disclosure provides a compound of formula (I), or a pharmaceutically acceptable salt thereof, wherein R^7 and R^8 are each hydrogen.

In a tenth embodiment of the first aspect the present disclosure provides a compound of formula (I), or a pharmaceutically acceptable salt thereof, wherein

q and s are independently 0, 1, or 2; and

each R^5 and R^6 is independently selected from alkyl, aryl, halo, and hydroxy, wherein the alkyl can optionally form a fused three- to six-membered ring with an adjacent carbon atom, wherein the three- to six-membered ring is optionally substituted with one or two alkyl groups.

In an eleventh embodiment of the first aspect the present disclosure provides a compound of formula (I), or a pharmaceutically acceptable salt thereof, wherein

q and s are independently 0 or 1; and

when present, R^5 and/or R^6 are each halo.

In a twelfth embodiment of the first aspect the present disclosure provides a compound of formula (I), or a pharmaceutically acceptable salt thereof, wherein

q and s are independently 0 or 1; and

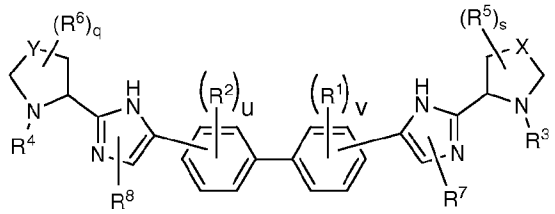
when present, R^5 and/or R^6 are each halo, wherein the halo is fluoro.

In a thirteenth embodiment of the first aspect the present disclosure provides a compound of formula (I), or a pharmaceutically acceptable salt thereof, wherein at least one of R^3 and R^4 is hydrogen.

In a fourteenth embodiment of the first aspect the present disclosure provides a compound of formula (I), or a pharmaceutically acceptable salt thereof, wherein R^3 and R^4 are each R^9-C(O)-.

In a fifteenth embodiment of the first aspect the present disclosure provides a compound of formula (I), or a pharmaceutically acceptable salt thereof, wherein each R^9 is independently selected from alkoxy, alkoxyalkyl, alkyl, alkylcarbonylalkyl, aryl, arylalkenyl, arylalkoxy, arylalkyl, aryloxyalkyl, cycloalkyl, (cycloalkyl)alkyl, cycloalkyloxyalkyl, heterocyclyl, heterocyclylalkyl, hydroxyalkyl, -NR^cR^d, (NR^cR^d)alkenyl, (NR^cR^d)alkyl, and (NR^cR^d)carbonyl.

In a second aspect the present disclosure provides a compound of Formula (II)



(II),

or a pharmaceutically acceptable salt thereof, wherein

q and s are independently 0, 1, or 2;

u and v are independently 0, 1, or 2;

X is selected from S, CH_2, CHR^5, and $C(R^5)_2$;

Y is selected from S, CH_2, CHR^6, and $C(R^6)_2$;

each R^1 and R^2 is independently selected from alkoxy, alkoxyalkyl, alkyl, arylalkoxycarbonyl, carboxy, formyl, halo, haloalkyl, hydroxyalkyl, (NR^aR^b)alkyl,

and (NR^aR^b)carbonyl;

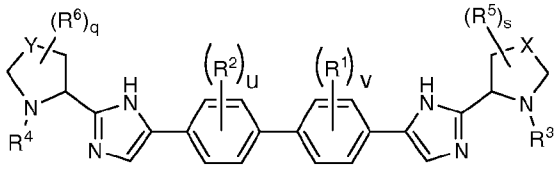
R^3 and R^4 are each independently selected from hydrogen and R^9-C(O)-;

each R^5 and R^6 is independently selected from alkyl, aryl, halo, and hydroxy, wherein the alkyl can optionally form a fused three- to six-membered ring with an adjacent carbon atom, wherein the three- to six-membered ring is optionally substituted with one or two alkyl groups;

R^7 and R^8 are each independently selected from hydrogen, alkoxycarbonyl, alkyl, arylalkoxycarbonyl, carboxy, haloalkyl, and (NR^aR^b)carbonyl; and

each R^9 is independently selected from alkoxy, alkoxyalkyl, alkyl, alkylcarbonylalkyl, aryl, arylalkenyl, arylalkoxy, arylalkyl, aryloxyalkyl, cycloalkyl, (cycloalkyl)alkyl, cycloalkyloxyalkyl, heterocyclyl, heterocyclylalkyl, hydroxyalkyl, -NR^cR^d, (NR^cR^d)alkenyl, (NR^cR^d)alkyl, and (NR^cR^d)carbonyl.

In a third aspect the present disclosure provides a compound of Formula (III)



(III),

or a pharmaceutically acceptable salt thereof, wherein

q and s are independently 0, 1, or 2;

u and v are independently 0 or 1;

X is selected from CH_2, CHR^5, and $C(R^5)_2$;

Y is selected from CH_2, CHR^6, and $C(R^6)_2$;

when present, R^1 and/or R^2 are halo, wherein the halo is fluoro;

R^3 and R^4 are each R^9-C(O)-;

when present, R^5 and/or R^6 are halo, wherein the halo is fluoro; and

each R^9 is independently selected from alkoxy, alkoxyalkyl, alkoxycarbonyl, alkoxycarbonylalkyl, alkyl, alkylcarbonylalkyl, aryl, arylalkenyl, arylalkoxy, arylalkyl, aryloxyalkyl, cycloalkyl, (cycloalkyl)alkenyl, (cycloalkyl)alkyl, cycloalkyloxyalkyl, haloalkyl, heterocyclyl, heterocyclylalkenyl, heterocyclylalkoxy, heterocyclylalkyl, heterocyclyloxyalkyl, hydroxyalkyl, -NR^cR^d, (NR^cR^d)alkenyl, (NR^cR^d)alkyl, and (NR^cR^d)carbonyl.

In a fourth aspect the present disclosure provides a compound selected from

methyl ((1S)-1-(((2S)-2-(5-(4'-(2-((2S)-1-((2S)-2-((methoxycarbonyl)amino)-3-methylbutanoyl)-2-pyrrolidinyl)-1H-imidazol-5-yl)-4-biphenylyl)-1H-imidazol-2-yl)-1-pyrrolidinyl)carbonyl)-2-methylpropyl)carbamate;

(1R,1'R)-2,2'-(4,4'-biphenyldiylbis(1H-imidazole-5,2-diyl(2S)-2,1-pyrrolidinediyl))bis(N,N-dimethyl-2-oxo-1-phenylethanamine);

methyl ((1S)-2-((2S)-2-(5-(4'-(2-((2S)-1-((2R)-2-(diethylamino)-2-phenylacetyl)-2-pyrrolidinyl)-1H-imidazol-5-yl)-4-biphenylyl)-1H-imidazol-2-yl)-1-pyrrolidinyl)-1-methyl-2-oxoethyl)carbamate;

methyl ((1S)-1-(((2S)-2-(4-(4'-(2-((2S)-4,4-difluoro-1-((2S)-2-((methoxycarbonyl)amino)-3-methylbutanoyl)-2-pyrrolidinyl)-1H-imidazol-4-yl)-4-biphenylyl)-1H-imidazol-2-yl)-4,4-difluoro-1-pyrrolidinyl)carbonyl)-2-methylpropyl)carbamate;

methyl ((1S)-1-(((1R,3R,5R)-3-(5-(4'-(2-((1R,3R,5R)-2-((2S)-2-((methoxycarbonyl)amino)-3-methylbutanoyl)-2-azabicyclo[3.1.0]hex-3-yl)-1H-imidazol-5-yl)-4-biphenylyl)-1H-imidazol-2-yl)-2-azabicyclo[3.1.0]hex-2-yl)carbonyl)-2-methylpropyl)carbamate;

methyl ((1R)-2-oxo-1-phenyl-2-((2S)-2-(5-(4'-(2-((2S)-1-((2R)-tetrahydro-2-furanylcarbonyl)-2-pyrrolidinyl)-1H-imidazol-5-yl)-4-biphenylyl)-1H-imidazol-2-yl)-1-pyrrolidinyl)ethyl)carbamate;

methyl ((1S)-2-methyl-1-(((2S)-2-(5-(4'-(2-((2S)-1-(N-2-pyrimidinyl-D-valyl)-2-pyrrolidinyl)-1H-imidazol-5-yl)-4-biphenylyl)-1H-imidazol-2-yl)-1-pyrrolidinyl)carbonyl)propyl)carbamate;

methyl ((1R)-2-((2S)-2-(5-(4'-(2-((2S)-1-((2R)-2-(dimethylamino)-2-phenylacetyl)-2-pyrrolidinyl)-1H-imidazol-5-yl)-4-biphenylyl)-1H-imidazol-2-yl)-1-pyrrolidinyl)-2-oxo-1-phenylethyl)carbamate;

dimethyl (4,4'-biphenyldiylbis(1H-imidazole-5,2-diyl(2S)-2,1-pyrrolidinediyl((1R)-2-oxo-1-phenyl-2,1-ethanediyl)))biscarbamate;

(1R)-N,N-dimethyl-2-oxo-1-phenyl-2-((2S)-2-(5-(4'-(2-((2S)-1-((2R)-tetrahydro-2-furanylcarbonyl)-2-pyrrolidinyl)-1H-imidazol-5-yl)-4-biphenylyl)-1H-imidazol-2-yl)-1-pyrrolidinyl)ethanamine;

methyl ((1S)-2-((2S)-2-(5-(4'-(2-((2S)-1-(N-(methoxycarbonyl)-L-alanyl)-2-pyrrolidinyl)-1H-imidazol-5-yl)-4-biphenylyl)-1H-imidazol-2-yl)-1-pyrrolidinyl)-1-methyl-2-oxoethyl)carbamate; and

methyl ((1S)-1-(((2S)-2-(5-(4'-(2-((2S)-1-((2S)-2-((methoxycarbonyl)amino)-3,3-dimethylbutanoyl)-2-pyrrolidinyl)-1H-imidazol-5-yl)-4-biphenylyl)-1H-imidazol-2-yl)-1-pyrrolidinyl)carbonyl)-2,2-dimethylpropyl)carbamate;

or a pharmaceutically acceptable salt thereof.

In a first embodiment of the fifth aspect the pharmaceutically acceptable salt is a dihydrochloride salt.

In a sixth aspect the present disclosure provides a composition comprising a compound of formula (I), or a pharmaceutically acceptable salt thereof, and a pharmaceutically acceptable carrier.

In a first embodiment of the sixth aspect the composition further comprises one or two additional compounds having anti-HCV activity. In a second embodiment at least one of the additional compounds is an interferon or a ribavirin. In a third embodiment the interferon is selected from interferon alpha 2B, pegylated interferon alpha, consensus interferon, interferon alpha 2A, and lymphoblastiod interferon tau.

In a fourth embodiment of the sixth aspect the composition further comprises one or two additional compounds having anti-HCV activity wherein at least one of the additional compounds is selected from interleukin 2, interleukin 6, interleukin 12, a compound that enhances the development of a type 1 helper T cell response, interfering RNA, anti-sense RNA, Imiqimod, ribavirin, an inosine 5'-monophospate dehydrogenase inhibitor, amantadine, and rimantadine.

In a fifth embodiment of the sixth aspect the composition further comprises one or two additional compounds having anti-HCV activity wherein at least one of the additional compounds is effective to inhibit the function of a target selected from HCV metalloprotease, HCV serine protease, HCV polymerase, HCV helicase, HCV NS4B protein, HCV entry, HCV assembly, HCV egress, HCV NS5A protein, and IMPDH for the treatment of an HCV infection.

In an seventh aspect the present disclosure provides a method of treating an HCV infection in a patient, comprising administering to the patient a therapeutically effective amount of a compound of formula (I), or a pharmaceutically acceptable salt thereof.

In a first embodiment of the seventh aspect the method further comprises administering one or two additional compounds having anti-HCV activity prior to, after or simultaneously with the compound of formula (I), or a pharmaceutically

acceptable salt thereof. In a second embodiment at least one of the additional compounds is an interferon or a ribavirin. In a third embodiment the interferon is selected from interferon alpha 2B, pegylated interferon alpha, consensus interferon, interferon alpha 2A, and lymphoblastiod interferon tau.

In a fourth embodiment the method further comprises administering one or two additional compounds having anti-HCV activity prior to, after or simultaneously with the compound of formula (I), or a pharmaceutically acceptable salt thereof, wherein at least one of the additional compounds is selected from interleukin 2, interleukin 6, interleukin 12, a compound that enhances the development of a type 1 helper T cell response, interfering RNA, anti-sense RNA, Imiqimod, ribavirin, an inosine 5'-monophospate dehydrogenase inhibitor, amantadine, and rimantadine.

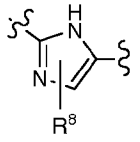
In a fifth embodiment the method further comprises administering one or two additional compounds having anti-HCV activity prior to, after or simultaneously with the compound of formula (I), or a pharmaceutically acceptable salt thereof, wherein at least one of the additional compounds is effective to inhibit the function of a target selected from HCV metalloprotease, HCV serine protease, HCV polymerase, HCV helicase, HCV NS4B portein, HCV entry, HCV assembly, HCV egress, HCV NS5A protein, and IMPDH for the treatment of an HCV infection.

Other embodiments of the present disclosure may comprise suitable combinations of two or more of embodiments and/or aspects disclosed herein.

Yet other embodiments and aspects of the disclosure will be apparent according to the description provided below.

The compounds of the present disclosure also exist as tautomers; therefore the present disclosure also encompasses all tautomeric forms.

The description of the present disclosure herein should be construed in congruity with the laws and principals of chemical bonding. In some instances it may be necessary to remove a hydrogen atom in order accommodate a substitutent at any given location. For example, in the structure shown below



R^8 may be attached to either the carbon atom in the imidazole ring or, alternatively, R^8 may take the place of the hydrogen atom on the nitrogen ring to form an N-substituted imidazole.

It should be understood that the compounds encompassed by the present disclosure are those that are suitably stable for use as pharmaceutical agent.

It is intended that the definition of any substituent or variable (e.g., R^1, R^2, R^5, R^6, etc.) at a particular location in a molecule be independent of its definitions elsewhere in that molecule. For example, when u is 2, each of the two R^1 groups may be the same or different.

All patents, patent applications, and literature references cited in the specification are herein incorporated by reference in their entirety. In the case of inconsistencies, the present disclosure, including definitions, will prevail.

As used in the present specification, the following terms have the meanings indicated:

As used herein, the singular forms "a", "an", and "the" include plural reference unless the context clearly dictates otherwise.

Unless stated otherwise, all aryl, cycloalkyl, and heterocyclyl groups of the present disclosure may be substituted as described in each of their respective definitions. For example, the aryl part of an arylalkyl group may be substituted as described in the definition of the term 'aryl'.

The term "alkenyl," as used herein, refers to a straight or branched chain group of two to six carbon atoms containing at least one carbon-carbon double bond.

The term "alkenyloxy," as used herein, refers to an alkenyl group attached to the parent molecular moiety through an oxygen atom.

The term "alkenyloxycarbonyl," as used herein, refers to an alkenyloxy group attached to the parent molecular moiety through a carbonyl group.

The term "alkoxy," as used herein, refers to an alkyl group attached to the parent molecular moiety through an oxygen atom.

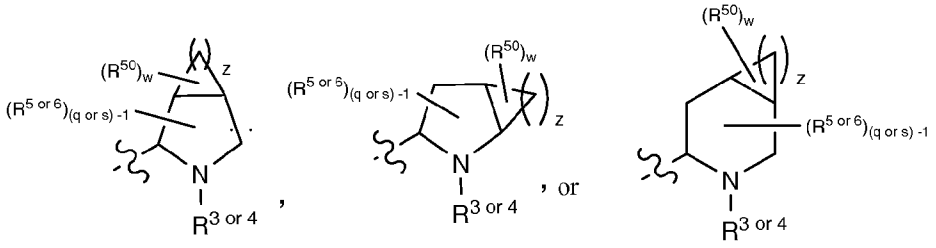
The term "alkoxyalkyl," as used herein, refers to an alkyl group substituted with one, two, or three alkoxy groups.

The term "alkoxyalkylcarbonyl," as used herein, refers to an alkoxyalkyl group attached to the parent molecular moiety through a carbonyl group.

The term "alkoxycarbonyl," as used herein, refers to an alkoxy group attached to the parent molecular moiety through a carbonyl group.

The term "alkoxycarbonylalkyl," as used herein, refers to an alkyl group substituted with one, two, or three alkoxycarbonyl groups.

The term "alkyl," as used herein, refers to a group derived from a straight or branched chain saturated hydrocarbon containing from one to six carbon atoms. In the compounds of the present disclosure, when m and/or n is 1 or 2; X and/or Y is CHR^5 and/or CHR^6, respectively, and R^5 and/or R^6 is alkyl, each alkyl can optionally form a fused three- to six-membered ring with an adjacent carbon atom to provide one of the structures shown below:



;

where z is 1, 2, 3, or 4, w is 0, 1, or 2, and R^{50} is alkyl. When w is 2, the two R^{50} alkyl groups may be the same or different.

The term "alkylcarbonyl," as used herein, refers to an alkyl group attached to the parent molecular moiety through a carbonyl group.

The term "alkylcarbonylalkyl," as used herein, refers to an alkyl group substituted with one, two, or three alkylcarbonyl groups.

The term "alkylcarbonyloxy," as used herein, refers to an alkylcarbonyl group attached to the parent molecular moiety through an oxygen atom.

The term "alkylsulfanyl," as used herein, refers to an alkyl group attached to the parent molecular moiety through a sulfur atom.

The term "alkylsulfonyl," as used herein, refers to an alkyl group attached to the parent molecular moiety through a sulfonyl group.

The term "aryl," as used herein, refers to a phenyl group, or a bicyclic fused ring system wherein one or both of the rings is a phenyl group. Bicyclic fused ring systems consist of a phenyl group fused to a four- to six-membered aromatic or non-aromatic carbocyclic ring. The aryl groups of the present disclosure can be attached to the parent molecular moiety through any substitutable carbon atom in the group.

Representative examples of aryl groups include, but are not limited to, indanyl, indenyl, naphthyl, phenyl, and tetrahydronaphthyl. The aryl groups of the present disclosure are optionally substituted with one, two, three, four, or five substituents independently selected from alkoxy, alkoxyalkyl, alkoxycarbonyl, alkyl, alkylcarbonyl, a second aryl group, arylalkoxy, arylalkyl, arylcarbonyl, cyano, halo, haloalkoxy, haloalkyl, heterocyclyl, heterocyclylalkyl, heterocyclylcarbonyl, hydroxy, hydroxyalkyl, nitro, $-NR^xR^y$, (NR^xR^y)alkyl, oxo, and $-P(O)OR_2$, wherein each R is independently selected from hydrogen and alkyl; and wherein the alkyl part of the arylalkyl and the heterocyclylalkyl are unsubstituted and wherein the second aryl group, the aryl part of the arylalkyl, the aryl part of the arylcarbonyl, the heterocyclyl, and the heterocyclyl part of the heterocyclylalkyl and the heterocyclylcarbonyl are further optionally substituted with one, two, or three substituents independently selected from alkoxy, alkyl, cyano, halo, haloalkoxy, haloalkyl, and nitro.

The term "arylalkenyl," as used herein, refers to an alkenyl group substituted with one, two, or three aryl groups.

The term "arylalkoxy," as used herein, refers to an aryl group attached to the parent molecular moiety through an alkoxy group.

The term "arylalkoxyalkyl," as used herein, refers to an alkyl group substituted with one, two, or three arylalkoxy groups.

The term "arylalkoxyalkylcarbonyl," as used herein, refers to an arylalkoxyalkyl group attached to the parent molecular moiety through a carbonyl group.

The term "arylalkoxycarbonyl," as used herein, refers to an arylalkoxy group attached to the parent molecular moiety through a carbonyl group.

The term "arylalkyl," as used herein, refers to an alkyl group substituted with one, two, or three aryl groups. The alkyl part of the arylalkyl is further optionally substituted with one or two additional groups independently selected from alkoxy, alkylcarbonyloxy, halo, haloalkoxy, haloalkyl, heterocyclyl, hydroxy, and $-NR^cR^d$, wherein the heterocyclyl is further optionally substitued with one or two substituents independently selected from alkoxy, alkyl, unsubstituted aryl, unsubstituted arylalkoxy, unsubstituted arylalkoxycarbonyl, halo, haloalkoxy, haloalkyl, hydroxy, and $-NR^xR^y$.

The term "arylalkylcarbonyl," as used herein, refers to an arylalkyl group attached to the parent molecular moiety through a carbonyl group.

The term "arylcarbonyl," as used herein, refers to an aryl group attached to the parent molecular moiety through a carbonyl group.

The term "aryloxy," as used herein, refers to an aryl group attached to the parent molecular moiety through an oxygen atom.

The term "aryloxyalkyl," as used herein, refers to an alkyl group substituted with one, two, or three aryloxy groups.

The term "aryloxycarbonyl," as used herein, refers to an aryloxy group attached to the parent molecular moiety through a carbonyl group.

The term "arylsulfonyl," as used herein, refers to an aryl group attached to the parent molecular moiety through a sulfonyl group.

The terms "Cap" and "cap" as used herein, refer to the group which is placed on the nitrogen atom of the terminal nitrogen-containing ring, i.e., the pyrrolidine rings of compound 1e. It should be understood that "Cap" or "cap" can refer to the reagent used to append the group to the terminal nitrogen-containing ring or to the fragment in the final product, i.e., "Cap-51" or "The Cap-51 fragment found in LS-19".

The term "carbonyl," as used herein, refers to -C(O)-.

The term "carboxy," as used herein, refers to $-CO_2H$.

The term "cyano," as used herein, refers to -CN.

The term "cycloalkyl," as used herein, refers to a saturated monocyclic, hydrocarbon ring system having three to seven carbon atoms and zero heteroatoms. Representative examples of cycloalkyl groups include, but are not limited to, cyclopropyl, cyclopentyl, and cyclohexyl. The cycloalkyl groups of the present disclosure are optionally substituted with one, two, three, four, or five substituents independently selected from alkoxy, alkyl, aryl, cyano, halo, haloalkoxy, haloalkyl, heterocyclyl, hydroxy, hydroxyalkyl, nitro, and $-NR^xR^y$, wherein the aryl and the heterocyclyl are futher optionally substituted with one, two, or three substituents independently selected from alkoxy, alkyl, cyano, halo, haloalkoxy, haloalkyl, hydroxy, and nitro.

The term "(cycloalkyl)alkenyl," as used herein, refers to an alkenyl group substituted with one, two, or three cycloalkyl groups.

The term "(cycloalkyl)alkyl," as used herein, refers to an alkyl group substituted with one, two, or three cycloalkyl groups. The alkyl part of the (cycloalkyl)alkyl is further optionally substituted with one or two groups independently selected from hydroxy and $-NR^cR^d$.

The term "cycloalkyloxy," as used herein, refers to a cycloalkyl group attached to the parent molecular moiety through an oxygen atom.

The term "cycloalkyloxyalkyl," as used herein, refers to an alkyl group substituted with one, two, or three cycloalkyloxy groups.

The term "cycloalkylsulfonyl," as used herein, refers to a cycloalkyl group attached to the parent molecular moiety through a sulfonyl group.

The term "formyl," as used herein, refers to -CHO.

The terms "halo" and "halogen," as used herein, refer to F, Cl, Br, or I.

The term "haloalkoxy," as used herein, refers to a haloalkyl group attached to the parent molecular moiety through an oxygen atom.

The term "haloalkoxycarbonyl," as used herein, refers to a haloalkoxy group attached to the parent molecular moiety through a carbonyl group.

The term "haloalkyl," as used herein, refers to an alkyl group substituted by one, two, three, or four halogen atoms.

The term "heterocyclyl," as used herein, refers to a four-, five-, six-, or seven-membered ring containing one, two, three, or four heteroatoms independently selected from nitrogen, oxygen, and sulfur. The four-membered ring has zero double bonds, the five-membered ring has zero to two double bonds, and the six- and seven-membered rings have zero to three double bonds. The term "heterocyclyl" also includes bicyclic groups in which the heterocyclyl ring is fused to another monocyclic heterocyclyl group, or a four- to six-membered aromatic or non-aromatic carbocyclic ring; as well as bridged bicyclic groups such as 7-azabicyclo[2.2.1]hept-7-yl, 2-azabicyclo[2.2.2]oc-2-tyl, and 2-azabicyclo[2.2.2]oc-3-tyl. The heterocyclyl groups of the present disclosure can be attached to the parent molecular moiety through any carbon atom or nitrogen atom in the group. Examples of heterocyclyl groups include, but are not limited to, benzothienyl, furyl, imidazolyl, indolinyl, indolyl, isothiazolyl, isoxazolyl, morpholinyl, oxazolyl, piperazinyl, piperidinyl, pyrazolyl, pyridinyl, pyrrolidinyl, pyrrolopyridinyl, pyrrolyl, thiazolyl, thienyl, thiomorpholinyl, 7-azabicyclo[2.2.1]hept-7-yl, 2-azabicyclo[2.2.2]oc-2-tyl, and 2-

azabicyclo[2.2.2]oc-3-tyl. The heterocyclyl groups of the present disclosure are optionally substituted with one, two, three, four, or five substituents independently selected from alkoxy, alkoxyalkyl, alkoxycarbonyl, alkyl, alkylcarbonyl, aryl, arylalkyl, arylcarbonyl, cyano, halo, haloalkoxy, haloalkyl, a second heterocyclyl group, heterocyclylalkyl, heterocyclylcarbonyl, hydroxy, hydroxyalkyl, nitro, -NR^xR^y, (NR^xR^y)alkyl, and oxo, wherein the alkyl part of the arylalkyl and the heterocyclylalkyl are unsubstituted and wherein the aryl, the aryl part of the arylalkyl, the aryl part of the arylcarbonyl, the second heterocyclyl group, and the heterocyclyl part of the heterocyclylalkyl and the heterocyclylcarbonyl are further optionally substituted with one, two, or three substituents independently selected from alkoxy, alkyl, cyano, halo, haloalkoxy, haloalkyl, and nitro.

The term "heterocyclylalkenyl," as used herein, refers to an alkenyl group substituted with one, two, or three heterocyclyl groups.

The term "heterocyclylalkoxy," as used herein, refers to a heterocyclyl group attached to the parent molecular moiety through an alkoxy group.

The term "heterocyclylalkoxycarbonyl," as used herein, refers to a heterocyclylalkoxy group attached to the parent molecular moiety through a carbonyl group.

The term "heterocyclylalkyl," as used herein, refers to an alkyl group substituted with one, two, or three heterocyclyl groups. The alkyl part of the heterocyclylalkyl is further optionally substituted with one or two additional groups independently selected from alkoxy, alkylcarbonyloxy, aryl, halo, haloalkoxy, haloalkyl, hydroxy, and -NR^cR^d, wherein the aryl is further optionally substitued with one or two substituents independently selected from alkoxy, alkyl, unsubstituted aryl, unsubstitued arylalkoxy, unsubstituted arylalkoxycarbonyl, halo, haloalkoxy, haloalkyl, hydroxy, and -NR^xR^y.

The term "heterocyclylalkylcarbonyl," as used herein, refers to a heterocyclylalkyl group attached to the parent molecular moiety through a carbonyl group.

The term "heterocyclylcarbonyl," as used herein, refers to a heterocyclyl group attached to the parent molecular moiety through a carbonyl group.

The term "heterocyclyloxy," as used herein, refers to a heterocyclyl group attached to the parent molecular moiety through an oxygen atom.

The term "heterocyclyloxyalkyl," as used herein, refers to an alkyl group substituted with one, two, or three heterocyclyloxy groups.

The term "heterocyclyloxycarbonyl," as used herein, refers to a heterocyclyloxy group attached to the parent molecular moiety through a carbonyl group.

The term "hydroxy," as used herein, refers to -OH.

The term "hydroxyalkyl," as used herein, refers to an alkyl group substituted with one, two, or three hydroxy groups.

The term "hydroxyalkylcarbonyl," as used herein, refers to a hydroxyalkyl group attached to the parent molecular moiety through a carbonyl group.

The term "nitro," as used herein, refers to $-NO_2$.

The term "$-NR^aR^b$," as used herein, refers to two groups, R^a and R^b, which are attached to the parent molecular moiety through a nitrogen atom. R^a and R^b are independently selected from hydrogen, alkenyl, and alkyl.

The term "(NR^aR^b)alkyl," as used herein, refers to an alkyl group substituted with one, two, or three $-NR^aR^b$ groups.

The term "(NR^aR^b)carbonyl," as used herein, refers to an $-NR^aR^b$ group attached to the parent molecular moiety through a carbonyl group.

The term "$-NR^cR^d$," as used herein, refers to two groups, R^c and R^d, which are attached to the parent molecular moiety through a nitrogen atom. R^c and R^d are independently selected from hydrogen, alkenyloxycarbonyl, alkoxyalkylcarbonyl, alkoxycarbonyl, alkyl, alkylcarbonyl, alkylsulfonyl, aryl, arylalkoxycarbonyl, arylalkyl, arylalkylcarbonyl, arylcarbonyl, aryloxycarbonyl, arylsulfonyl, cycloalkyl, cycloalkylsulfonyl, formyl, haloalkoxycarbonyl, heterocyclyl, heterocyclylalkoxycarbonyl, heterocyclylalkyl, heterocyclylalkylcarbonyl, heterocyclylcarbonyl, heterocyclyloxycarbonyl, hydroxyalkylcarbonyl, (NR^eR^f)alkyl, (NR^eR^f)alkylcarbonyl, (NR^eR^f)carbonyl, (NR^eR^f)sulfonyl, -C(NCN)OR', and -C(NCN)NR^xR^y, wherein R' is selected from alkyl and unsubstituted phenyl, and wherein the alkyl part of the arylalkyl, the arylalkylcarbonyl, the heterocyclylalkyl, and the heterocyclylalkylcarbonyl are further optionally substituted with one $-NR^eR^f$ group; and wherein the aryl, the aryl part of the arylalkoxycarbonyl, the arylalkyl, the arylalkylcarbonyl, the arylcarbonyl, the aryloxycarbonyl, and the arylsulfonyl, the heterocyclyl, and the heterocyclyl part of the heterocyclylalkoxycarbonyl, the

heterocyclylalkyl, the heterocyclylalkylcarbonyl, the heterocyclylcarbonyl, and the heterocyclyloxycarbonyl are further optionally substituted with one, two, or three substituents independently selected from alkoxy, alkyl, cyano, halo, haloalkoxy, haloalkyl, and nitro.

The term "(NR^cR^d)alkenyl," as used herein, refers to an alkenyl group substituted with one, two, or three -NR^cR^d groups.

The term "(NR^cR^d)alkyl," as used herein, refers to an alkyl group substituted with one, two, or three -NR^cR^d groups. The alkyl part of the (NR^cR^d)alkyl is further optionally substituted with one or two additional groups selected from alkoxy, alkoxyalkylcarbonyl, alkoxycarbonyl, alkylsulfanyl, arylalkoxyalkylcarbonyl, carboxy, heterocyclyl, heterocyclylcarbonyl, hydroxy, and (NR^eR^f)carbonyl; wherein the heterocyclyl is further optionally substituted with one, two, three, four, or five substituents independently selected from alkoxy, alkyl, cyano, halo, haloalkoxy, haloalkyl, and nitro.

The term "(NR^cR^d)carbonyl," as used herein, refers to an -NR^cR^d group attached to the parent molecular moiety through a carbonyl group.

The term "-NR^eR^f," as used herein, refers to two groups, R^e and R^f, which are attached to the parent molecular moiety through a nitrogen atom. R^e and R^f are independently selected from hydrogen, alkyl, unsubstituted aryl, unsubstituted arylalkyl, unsubstituted cycloalkyl, unsubstituted (cyclolalkyl)alkyl, unsubstituted heterocyclyl, unsubstituted heterocyclylalkyl, (NR^xR^y)alkyl, and (NR^xR^y)carbonyl.

The term "(NR^eR^f)alkyl," as used herein, refers to an alkyl group substituted with one, two, or three -NR^eR^f groups.

The term "(NR^eR^f)alkylcarbonyl," as used herein, refers to an (NR^eR^f)alkyl group attached to the parent molecular moiety through a carbonyl group.

The term "(NR^eR^f)carbonyl," as used herein, refers to an -NR^eR^f group attached to the parent molecular moiety through a carbonyl group.

The term "(NR^eR^f)sulfonyl," as used herein, refers to an -NR^eR^f group attached to the parent molecular moiety through a sulfonyl group.

The term "-NR^xR^y," as used herein, refers to two groups, R^x and R^y, which are attached to the parent molecular moiety through a nitrogen atom. R^x and R^y are independently selected from hydrogen, alkoxycarbonyl, alkyl, alkylcarbonyl, unsubstituted aryl, unsubstituted arylalkoxycarbonyl, unsubstituted arylalkyl,

unsubstituted cycloalkyl, unsubstituted heterocyclyl, and ($NR^{x'}R^{y'}$)carbonyl, wherein $R^{x'}$ and $R^{y'}$ are independently selected from hydrogen and alkyl.

The term "(NR^xR^y)alkyl," as used herein, refers to an alkyl group substituted with one, two, or three -NR^xR^y groups.

The term "oxo," as used herein, refers to =O.

The term "sulfonyl," as used herein, refers to -SO_2-.

The term "trialkylsilyl," as used herein, refers to -SiR_3, wherein R is alkyl. The R groups may be the same or different.

The term "trialkylsilylalkyl," as used herein, refers to an alkyl group substituted with one, two, or three trialkylsilyl groups.

The term "trialkylsilylalkoxy," as used herein, refers to a trialkylsilylalkyl group attached to the parent molecular moiety through an oxygen atom.

The term "trialkylsilylalkoxyalkyl," as used herein, refers to an alkyl group substituted with one, two, or three trialkylsilylalkoxy groups.

Asymmetric centers exist in the compounds of the present disclosure. These centers are designated by the symbols "R" or "S", depending on the configuration of substituents around the chiral carbon atom. It should be understood that the disclosure encompasses all stereochemical isomeric forms, or mixtures thereof, which possess the ability to inhibit NS5A. Individual stereoisomers of compounds can be prepared synthetically from commercially available starting materials which contain chiral centers or by preparation of mixtures of enantiomeric products followed by separation such as conversion to a mixture of diastereomers followed by separation or recrystallization, chromatographic techniques, or direct separation of enantiomers on chiral chromatographic columns. Starting compounds of particular stereochemistry are either commercially available or can be made and resolved by techniques known in the art.

Certain compounds of the present disclosure may also exist in different stable conformational forms which may be separable. Torsional asymmetry due to restricted rotation about an asymmetric single bond, for example because of steric hindrance or ring strain, may permit separation of different conformers. The present disclosure includes each conformational isomer of these compounds and mixtures thereof.

The term "compounds of the present disclosure", and equivalent expressions,

are meant to embrace compounds of Formula (I), and pharmaceutically acceptable enantiomers, diastereomers, and salts thereof. Similarly, references to intermediates are meant to embrace their salts where the context so permits.

The compounds of the present disclosure can exist as pharmaceutically acceptable salts. The term "pharmaceutically acceptable salt," as used herein, represents salts or zwitterionic forms of the compounds of the present disclosure which are water or oil-soluble or dispersible, which are, within the scope of sound medical judgment, suitable for use in contact with the tissues of patients without excessive toxicity, irritation, allergic response, or other problem or complication commensurate with a reasonable benefit/risk ratio, and are effective for their intended use The salts can be prepared during the final isolation and purification of the compounds or separately by reacting a suitable nitrogen atom with a suitable acid. Representative acid addition salts include acetate, adipate, alginate, citrate, aspartate, benzoate, benzenesulfonate, bisulfate, butyrate, camphorate, camphorsulfonate; digluconate, dihydrobromide, diydrochloride, dihydroiodide, glycerophosphate, hemisulfate, heptanoate, hexanoate, formate, fumarate, hydrochloride, hydrobromide, hydroiodide, 2-hydroxyethanesulfonate, lactate, maleate, mesitylenesulfonate, methanesulfonate, naphthylenesulfonate, nicotinate, 2-naphthalenesulfonate, oxalate, palmoate, pectinate, persulfate, 3-phenylproprionate, picrate, pivalate, propionate, succinate, tartrate, trichloroacetate, trifluoroacetate, phosphate, glutamate, bicarbonate, para-toluenesulfonate, and undecanoate. Examples of acids which can be employed to form pharmaceutically acceptable addition salts include inorganic acids such as hydrochloric, hydrobromic, sulfuric, and phosphoric, and organic acids such as oxalic, maleic, succinic, and citric.

Basic addition salts can be prepared during the final isolation and purification of the compounds by reacting a carboxy group with a suitable base such as the hydroxide, carbonate, or bicarbonate of a metal cation or with ammonia or an organic primary, secondary, or tertiary amine. The cations of pharmaceutically acceptable salts include lithium, sodium, potassium, calcium, magnesium, and aluminum, as well as nontoxic quaternary amine cations such as ammonium, tetramethylammonium, tetraethylammonium, methylamine, dimethylamine, trimethylamine, triethylamine, diethylamine, ethylamine, tributylamine, pyridine, N,N-dimethylaniline, N-methylpiperidine, N-methylmorpholine, dicyclohexylamine,

procaine, dibenzylamine, N,N-dibenzylphenethylamine, and N,N'-dibenzylethylenediamine. Other representative organic amines useful for the formation of base addition salts include ethylenediamine, ethanolamine, diethanolamine, piperidine, and piperazine.

When it is possible that, for use in therapy, therapeutically effective amounts of a compound of formula (I), as well as pharmaceutically acceptable salts thereof, may be administered as the raw chemical, it is possible to present the active ingredient as a pharmaceutical composition. Accordingly, the disclosure further provides pharmaceutical compositions, which include therapeutically effective amounts of compounds of formula (I) or pharmaceutically acceptable salts thereof, and one or more pharmaceutically acceptable carriers, diluents, or excipients. The term "therapeutically effective amount," as used herein, refers to the total amount of each active component that is sufficient to show a meaningful patient benefit, e.g., a reduction in viral load. When applied to an individual active ingredient, administered alone, the term refers to that ingredient alone. When applied to a combination, the term refers to combined amounts of the active ingredients that result in the therapeutic effect, whether administered in combination, serially, or simultaneously. The compounds of formula (I) and pharmaceutically acceptable salts thereof, are as described above. The carrier(s), diluent(s), or excipient(s) must be acceptable in the sense of being compatible with the other ingredients of the formulation and not deleterious to the recipient thereof. In accordance with another aspect of the present disclosure there is also provided a process for the preparation of a pharmaceutical formulation including admixing a compound of formula (I), or a pharmaceutically acceptable salt thereof, with one or more pharmaceutically acceptable carriers, diluents, or excipients. The term "pharmaceutically acceptable," as used herein, refers to those compounds, materials, compositions, and/or dosage forms which are, within the scope of sound medical judgment, suitable for use in contact with the tissues of patients without excessive toxicity, irritation, allergic response, or other problem or complication commensurate with a reasonable benefit/risk ratio, and are effective for their intended use.

Pharmaceutical formulations may be presented in unit dose forms containing a predetermined amount of active ingredient per unit dose. Dosage levels of between about 0.01 and about 250 milligram per kilogram ("mg/kg") body weight per day,

preferably between about 0.05 and about 100 mg/kg body weight per day of the compounds of the present disclosure are typical in a monotherapy for the prevention and treatment of HCV mediated disease. Typically, the pharmaceutical compositions of this disclosure will be administered from about 1 to about 5 times per day or alternatively, as a continuous infusion. Such administration can be used as a chronic or acute therapy. The amount of active ingredient that may be combined with the carrier materials to produce a single dosage form will vary depending on the condition being treated, the severity of the condition, the time of administration, the route of administration, the rate of excretion of the compound employed, the duration of treatment, and the age, gender, weight, and condition of the patient. Preferred unit dosage formulations are those containing a daily dose or sub-dose, as herein above recited, or an appropriate fraction thereof, of an active ingredient. Treatment may be initiated with small dosages substantially less than the optimum dose of the compound. Thereafter, the dosage is increased by small increments until the optimum effect under the circumstances is reached. In general, the compound is most desirably administered at a concentration level that will generally afford antivirally effective results without causing any harmful or deleterious side effects.

When the compositions of this disclosure comprise a combination of a compound of the present disclosure and one or more additional therapeutic or prophylactic agent, both the compound and the additional agent are usually present at dosage levels of between about 10 to 150%, and more preferably between about 10 and 80% of the dosage normally administered in a monotherapy regimen.

Pharmaceutical formulations may be adapted for administration by any appropriate route, for example by the oral (including buccal or sublingual), rectal, nasal, topical (including buccal, sublingual, or transdermal), vaginal, or parenteral (including subcutaneous, intracutaneous, intramuscular, intra-articular, intrasynovial, intrasternal, intrathecal, intralesional, intravenous, or intradermal injections or infusions) route. Such formulations may be prepared by any method known in the art of pharmacy, for example by bringing into association the active ingredient with the carrier(s) or excipient(s). Oral administration or administration by injection are preferred.

Pharmaceutical formulations adapted for oral administration may be presented as discrete units such as capsules or tablets; powders or granules; solutions or

suspensions in aqueous or non-aqueous liquids; edible foams or whips; or oil-in-water liquid emulsions or water-in-oil emulsions.

For instance, for oral administration in the form of a tablet or capsule, the active drug component can be combined with an oral, non-toxic pharmaceutically acceptable inert carrier such as ethanol, glycerol, water, and the like. Powders are prepared by comminuting the compound to a suitable fine size and mixing with a similarly comminuted pharmaceutical carrier such as an edible carbohydrate, as, for example, starch or mannitol. Flavoring, preservative, dispersing, and coloring agent can also be present.

Capsules are made by preparing a powder mixture, as described above, and filling formed gelatin sheaths. Glidants and lubricants such as colloidal silica, talc, magnesium stearate, calcium stearate, or solid polyethylene glycol can be added to the powder mixture before the filling operation. A disintegrating or solubilizing agent such as agar-agar, calcium carbonate, or sodium carbonate can also be added to improve the availability of the medicament when the capsule is ingested.

Moreover, when desired or necessary, suitable binders, lubricants, disintegrating agents, and coloring agents can also be incorporated into the mixture. Suitable binders include starch, gelatin, natural sugars such as glucose or beta-lactose, corn sweeteners, natural and synthetic gums such as acacia, tragacanth or sodium alginate, carboxymethylcellulose, polyethylene glycol, and the like. Lubricants used in these dosage forms include sodium oleate, sodium chloride, and the like. Disintegrators include, without limitation, starch, methyl cellulose, agar, betonite, xanthan gum, and the like. Tablets are formulated, for example, by preparing a powder mixture, granulating or slugging, adding a lubricant and disintegrant, and pressing into tablets. A powder mixture is prepared by mixing the compound, suitable comminuted, with a diluent or base as described above, and optionally, with a binder such as carboxymethylcellulose, an aliginate, gelating, or polyvinyl pyrrolidone, a solution retardant such as paraffin, a resorption accelerator such as a quaternary salt and/or and absorption agent such as betonite, kaolin, or dicalcium phosphate. The powder mixture can be granulated by wetting with a binder such as syrup, starch paste, acadia mucilage, or solutions of cellulosic or polymeric materials and forcing through a screen. As an alternative to granulating, the powder mixture can be run through the tablet machine and the result is

imperfectly formed slugs broken into granules. The granules can be lubricated to prevent sticking to the tablet forming dies by means of the addition of stearic acid, a stearate salt, talc, or mineral oil. The lubricated mixture is then compressed into tablets. The compounds of the present disclosure can also be combined with a free flowing inert carrier and compressed into tablets directly without going through the granulating or slugging steps. A clear or opaque protective coating consisting of a sealing coat of shellac, a coating of sugar or polymeric material, and a polish coating of wax can be provided. Dyestuffs can be added to these coatings to distinguish different unit dosages.

Oral fluids such as solution, syrups, and elixirs can be prepared in dosage unit form so that a given quantity contains a predetermined amount of the compound. Syrups can be prepared by dissolving the compound in a suitably flavored aqueous solution, while elixirs are prepared through the use of a non-toxic vehicle. Solubilizers and emulsifiers such as ethoxylated isostearyl alcohols and polyoxyethylene sorbitol ethers, preservatives, flavor additive such as peppermint oil or natural sweeteners, or saccharin or other artificial sweeteners, and the like can also be added.

Where appropriate, dosage unit formulations for oral administration can be microencapsulated. The formulation can also be prepared to prolong or sustain the release as for example by coating or embedding particulate material in polymers, wax, or the like.

The compounds of formula (I), and pharmaceutically acceptable salts thereof, can also be administered in the form of liposome delivery systems, such as small unilamellar vesicles, large unilamellar vesicles, and multilamellar vesicles. Liposomes can be formed from a variety of phopholipids, such as cholesterol, stearylamine, or phophatidylcholines.

The compounds of formula (I) and pharmaceutically acceptable salts thereof may also be delivered by the use of monoclonal antibodies as individual carriers to which the compound molecules are coupled. The compounds may also be coupled with soluble polymers as targetable drug carriers. Such polymers can include polyvinylpyrrolidone, pyran copolymer, polyhydroxypropylmethacrylamidephenol, polyhydroxyethylaspartamidephenol, or polyethyleneoxidepolylysine substituted with palitoyl residues. Furthermore, the compounds may be coupled to a class of

biodegradable polymers useful in achieving controlled release of a drug, for example, polylactic acid, polepsilon caprolactone, polyhydroxy butyric acid, polyorthoesters, polyacetals, polydihydropyrans, polycyanoacrylates, and cross-linked or amphipathic block copolymers of hydrogels.

Pharmaceutical formulations adapted for transdermal administration may be presented as discrete patches intended to remain in intimate contact with the epidermis of the recipient for a prolonged period of time. For example, the active ingredient may be delivered from the patch by iontophoresis as generally described in *Pharmaceutical Research* 1986, *3*(6), 318.

Pharmaceutical formulations adapted for topical administration may be formulated as ointments, creams, suspensions, lotions, powders, solutions, pastes, gels, sprays, aerosols, or oils.

Pharmaceutical formulations adapted for rectal administration may be presented as suppositories or as enemas.

Pharmaceutical formulations adapted for nasal administration wherein the carrier is a solid include a course powder having a particle size for example in the range 20 to 500 microns which is administered in the manner in which snuff is taken, *i.e.*, by rapid inhalation through the nasal passage from a container of the powder held close up to the nose. Suitable formulations wherein the carrier is a liquid, for administration as a nasal spray or nasal drops, include aqueous or oil solutions of the active ingredient.

Pharmaceutical formulations adapted for administration by inhalation include fine particle dusts or mists, which may be generated by means of various types of metered, dose pressurized aerosols, nebulizers, or insufflators.

Pharmaceutical formulations adapted for vaginal administration may be presented as pessaries, tampons, creams, gels, pastes, foams, or spray formulations.

Pharmaceutical formulations adapted for parenteral administration include aqueous and non-aqueous sterile injection solutions which may contain anti-oxidants, buffers, bacteriostats, and soutes which render the formulation isotonic with the blood of the intended recipient; and aqueous and non-aqueous sterile suspensions which may include suspending agents and thickening agents. The formulations may be presented in unit-dose or multi-dose containers, for example sealed ampoules and vials, and may be stored in a freeze-dried (lyophilized) condition requiring only the

addition of the sterile liquid carrier, for example water for injections, immediately prior to use. Extemporaneous injection solutions and suspensions may be prepared from sterile powders, granules, and tablets.

It should be understood that in addition to the ingredients particularly mentioned above, the formulations may include other agents conventional in the art having regard to the type of formulation in question, for example those suitable for oral administration may include flavoring agents.

The term "patient" includes both human and other mammals.

The term "treating" refers to: (i) preventing a disease, disorder or condition from occurring in a patient that may be predisposed to the disease, disorder, and/or condition but has not yet been diagnosed as having it; (ii) inhibiting the disease, disorder, or condition, i.e., arresting its development; and (iii) relieving the disease, disorder, or condition, i.e., causing regression of the disease, disorder, and/or condition.

The compounds of the present disclosure can also be administered with a cyclosporin, for example, cyclosporin A. Cyclosporin A has been shown to be active against HCV in clinical trials (*Hepatology* 2003, *38*, 1282; *Biochem. Biophys. Res. Commun.* 2004, *313*, 42; *J. Gastroenterol.* 2003, *38*, 567).

Table 1 below lists some illustrative examples of compounds that can be administered with the compounds of this disclosure. The compounds of the disclosure can be administered with other anti-HCV activity compounds in combination therapy, either jointly or separately, or by combining the compounds into a composition.

Table 1

Brand Name	*Physiological Class*	*Type of Inhibitor or Target*	*Source Company*
NIM811		Cyclophilin Inhibitor	Novartis
Zadaxin		Immunomodulator	Sciclone
Suvus		Methylene blue	Bioenvision
Actilon (CPG10101)		TLR9 agonist	Coley
Batabulin (T67)	Anticancer	β-tubulin inhibitor	Tularik Inc., South San Francisco, CA

Brand Name	*Physiological Class*	*Type of Inhibitor or Target*	*Source Company*
ISIS 14803	Antiviral	antisense	ISIS Pharmaceuticals Inc, Carlsbad, CA/Elan Phamaceuticals Inc., New York, NY
Summetrel	Antiviral	antiviral	Endo Pharmaceuticals Holdings Inc., Chadds Ford, PA
GS-9132 (ACH-806)	Antiviral	HCV Inhibitor	Achillion / Gilead
Pyrazolopyrimidine compounds and salts From WO-2005047288 26 May 2005	Antiviral	HCV Inhibitors	Arrow Therapeutics Ltd.
Levovirin	Antiviral	IMPDH inhibitor	Ribapharm Inc., Costa Mesa, CA
Merimepodib (VX-497)	Antiviral	IMPDH inhibitor	Vertex Pharmaceuticals Inc., Cambridge, MA
XTL-6865 (XTL-002)	Antiviral	monoclonal antibody	XTL Biopharmaceuticals Ltd., Rehovot, Isreal
Telaprevir (VX-950, LY-570310)	Antiviral	NS3 serine protease inhibitor	Vertex Pharmaceuticals Inc., Cambridge, MA/ Eli Lilly and Co. Inc., Indianapolis, IN
HCV-796	Antiviral	NS5B Replicase Inhibitor	Wyeth / Viropharma
NM-283	Antiviral	NS5B Replicase Inhibitor	Idenix / Novartis
GL-59728	Antiviral	NS5B Replicase Inhibitor	Gene Labs / Novartis
GL-60667	Antiviral	NS5B Replicase Inhibitor	Gene Labs / Novartis
2'C MeA	Antiviral	NS5B Replicase Inhibitor	Gilead

Brand Name	*Physiological Class*	*Type of Inhibitor or Target*	*Source Company*
PSI 6130	Antiviral	NS5B Replicase Inhibitor	Roche
R1626	Antiviral	NS5B Replicase Inhibitor	Roche
2'C Methyl adenosine	Antiviral	NS5B Replicase Inhibitor	Merck
JTK-003	Antiviral	RdRp inhibitor	Japan Tobacco Inc., Tokyo, Japan
Levovirin	Antiviral	ribavirin	ICN Pharmaceuticals, Costa Mesa, CA
Ribavirin	Antiviral	ribavirin	Schering-Plough Corporation, Kenilworth, NJ
Viramidine	Antiviral	Ribavirin Prodrug	Ribapharm Inc., Costa Mesa, CA
Heptazyme	Antiviral	ribozyme	Ribozyme Pharmaceuticals Inc., Boulder, CO
BILN-2061	Antiviral	serine protease inhibitor	Boehringer Ingelheim Pharma KG, Ingelheim, Germany
SCH 503034	Antiviral	serine protease inhibitor	Schering Plough
Zadazim	Immune modulator	Immune modulator	SciClone Pharmaceuticals Inc., San Mateo, CA
Ceplene	Immunomodulator	immune modulator	Maxim Pharmaceuticals Inc., San Diego, CA
CellCept	Immunosuppressant	HCV IgG immunosuppressant	F. Hoffmann-La Roche LTD, Basel, Switzerland
Civacir	Immunosuppressant	HCV IgG immunosuppressant	Nabi Biopharmaceuticals Inc., Boca Raton, FL

Brand Name	*Physiological Class*	*Type of Inhibitor or Target*	*Source Company*
Albuferon - α	Interferon	albumin IFN-α2b	Human Genome Sciences Inc., Rockville, MD
Infergen A	Interferon	IFN alfacon-1	InterMune Pharmaceuticals Inc., Brisbane, CA
Omega IFN	Interferon	IFN-ω	Intarcia Therapeutics
IFN-β and EMZ701	Interferon	IFN-β and EMZ701	Transition Therapeutics Inc., Ontario, Canada
Rebif	Interferon	IFN-β1a	Serono, Geneva, Switzerland
Roferon A	Interferon	IFN-α2a	F. Hoffmann-La Roche LTD, Basel, Switzerland
Intron A	Interferon	IFN-α2b	Schering-Plough Corporation, Kenilworth, NJ
Intron A and Zadaxin	Interferon	IFN-α2b/α1-thymosin	RegeneRx Biopharmiceuticals Inc., Bethesda, MD/ SciClone Pharmaceuticals Inc, San Mateo, CA
Rebetron	Interferon	IFN-α2b/ribavirin	Schering-Plough Corporation, Kenilworth, NJ
Actimmune	Interferon	INF-γ	InterMune Inc., Brisbane, CA
Interferon-β	Interferon	Interferon-β-1a	Serono
Multiferon	Interferon	Long lasting IFN	Viragen/Valentis
Wellferon	Interferon	lymphoblastoid IFN-αn1	GlaxoSmithKline plc, Uxbridge, UK

Brand Name	*Physiological Class*	*Type of Inhibitor or Target*	*Source Company*
Omniferon	Interferon	natural IFN-α	Viragen Inc., Plantation, FL
Pegasys	Interferon	PEGylated IFN-α2a	F. Hoffmann-La Roche LTD, Basel, Switzerland
Pegasys and Ceplene	Interferon	PEGylated IFN-α2a/ immune modulator	Maxim Pharmaceuticals Inc., San Diego, CA
Pegasys and Ribavirin	Interferon	PEGylated IFN-α2a/ribavirin	F. Hoffmann-La Roche LTD, Basel, Switzerland
PEG-Intron	Interferon	PEGylated IFN-α2b	Schering-Plough Corporation, Kenilworth, NJ
PEG-Intron / Ribavirin	Interferon	PEGylated IFN-α2b/ribavirin	Schering-Plough Corporation, Kenilworth, NJ
IP-501	Liver protection	antifibrotic	Indevus Pharmaceuticals Inc., Lexington, MA
IDN-6556	Liver protection	caspase inhibitor	Idun Pharmaceuticals Inc., San Diego, CA
ITMN-191 (R-7227)	Antiviral	serine protease inhibitor	InterMune Pharmaceuticals Inc., Brisbane, CA
GL-59728	Antiviral	NS5B Replicase Inhibitor	Genelabs
ANA-971	Antiviral	TLR-7 agonist	Anadys

The compounds of the present disclosure may also be used as laboratory reagents. Compounds may be instrumental in providing research tools for designing of viral replication assays, validation of animal assay systems and structural biology studies to further enhance knowledge of the HCV disease mechanisms. Further, the compounds of the present disclosure are useful in establishing or determining the binding site of other antiviral compounds, for example, by competitive inhibition.

The compounds of this disclosure may also be used to treat or prevent viral contamination of materials and therefore reduce the risk of viral infection of laboratory or medical personnel or patients who come in contact with such materials, e.g., blood, tissue, surgical instruments and garments, laboratory instruments and garments, and blood collection or transfusion apparatuses and materials.

This disclosure is intended to encompass compounds having formula (I) when prepared by synthetic processes or by metabolic processes including those occurring in the human or animal body (*in vivo*) or processes occurring *in vitro*.

The abbreviations used in the present application, including particularly in the illustrative schemes and examples which follow, are well-known to those skilled in the art. Some of the abbreviations used are as follows: HATU for O-(7-azabenzotriazol-1-yl)-N,N,N',N'-tetramethyluronium hexafluorophosphate; Boc or BOC for tert-butoxycarbonyl; NBS for N-bromosuccinimide; tBu or t-Bu for tert-butyl; SEM for -(trimethylsilyl)ethoxymethyl; DMSO for dimethylsulfoxide; MeOH for methanol; TFA for trifluoroacetic acid; RT for room temperature or retention time (context will dictate); t_R for retention time; EDCI for 1-(3-dimethylaminopropyl)-3-ethylcarbodiimide hydrochloride; DMAP for 4-dimethylaminopyridine; THF for tetrahydrofuran; DBU for 1,8-diazabicyclo[5.4.0]undec-7-ene; *t*-Bu; DEA for diethylamine; HMDS for hexamethyldisilazide; DMF for N,N-dimethylformamide; Bzl for benzyl; EtOH for ethanol; iPrOH or i-PrOH for isopropanol; Me_2S for dimethylsulfide; Et_3N or TEA for triethylamine; Ph for phenyl; OAc for acetate; EtOAc for ethyl acetate; dppf for 1,1'-bis(diphenylphosphino)ferrocene; iPr_2EtN or DIPEA for diisopropylethylamine; Cbz for carbobenzyloxy; n-BuLi for n-butyllithium; ACN for acetonitrile; h or hr for hours; m or min for minutes; s for seconds; LiHMDS for lithium hexamethyldisilazide; DIBAL for diisobutyl aluminum hydride; TBDMSCl for tert-butyldimethylsilyl chloride; Me for methyl; ca. for about; OAc for acetate; iPr for isopropyl; Et for ethyl; Bn for benzyl; and HOAT for 1-hydroxy-7-azabenzotriazole.

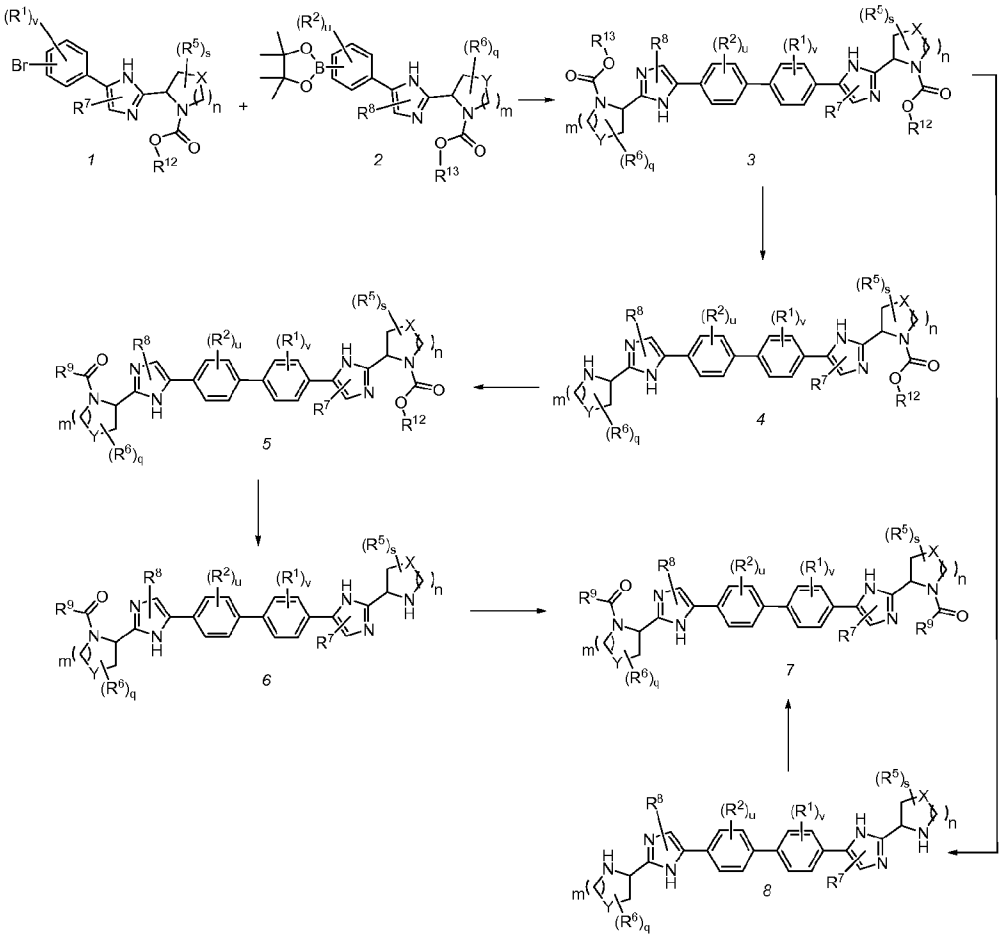
The abbreviations used in the present application, including particularly in the illustrative schemes and examples which follow, are well-known to those skilled in the art. Some of the abbreviations used are as follows:

The compounds and processes of the present disclosure will be better understood in connection with the following synthetic schemes which illustrate the

methods by which the compounds of the present disclosure may be prepared. Starting materials can be obtained from commercial sources or prepared by well-established literature methods known to those of ordinary skill in the art. It will be readily apparent to one of ordinary skill in the art that the compounds defined above can be synthesized by substitution of the appropriate reactants and agents in the syntheses shown below. It will also be readily apparent to one skilled in the art that the selective protection and deprotection steps, as well as the order of the steps themselves, can be carried out in varying order, depending on the nature of the variables to successfully complete the syntheses below. The variables are as defined above unless otherwise noted below.

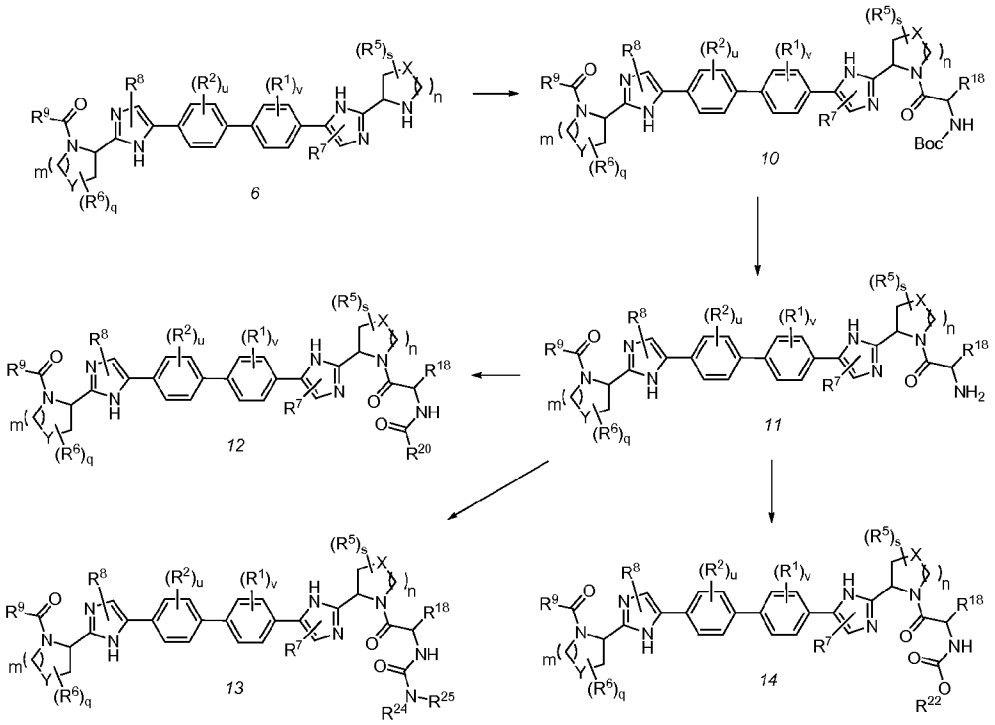
Scheme 1: Symmetric or Asymmetric Biphenyls

Aryl halide *1* and boronic ester *2* can be coupled to produce biaryl *3* using standard Suzuki-Miayura coupling conditions (*Angew Chem. Int. Ed. Engl* 2001, 40, 4544). It should be noted that the boronic acid analog of *2* may be used in place of the ester. Mono-deprotection of the pyrrolidine moiety may be accomplished when R^{12} and R^{13} are different. When R^{12} = benzyl, and R^{13} = t-butyl treatment to hydrogenolytic conditions produces *4*. For example, Pd/C catalyst in the presence of a base such as potassium carbonate can be used. Acylation of *4* can be accomplished under standard acylation conditions. A coupling reagent such as HATU in combination with an amine base such as Hunig's base can be used in this regard. Alternatively, *4* may be reacted with an isocyanate or carbamoyl chloride to provide compounds of formula *5* where R^9 is an amine. Further deprotection of *5* can be accomplished by treatment with strong acid such as HCl or trifluoroacetic acid. Standard conditions analogous to those used to convert *4* to *5* can be used to prepare *7* from *6*. In another embodiment where $R^{12} = R^{13}$ = t-Bu, direct conversion to *8* can be accomplished by treatment of *3* with strong acid such as HCl or trifluoroacetic acid. Conversion of *8* to *7* is accomplished in analogous fashion to the methods used to prepare *5* from *4* or *7* from *6*. In this instance however, the caps in *7* will be identical.



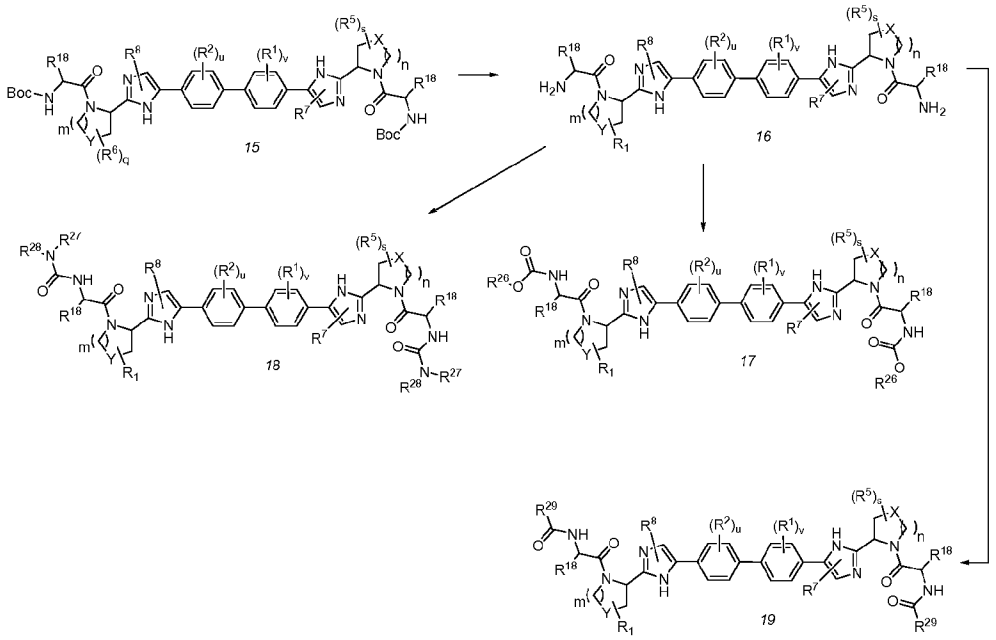
Scheme 2: Asymmetrically Capped Biphenyls

Conversion of *6* (from Scheme 1) to *10* can be done using standard amide coupling conditions such as HATU with an amine base, such as Hunig's base. Deprotection can be accomplished with strong acid such as HCl or trifluoroacetic acid affording *11*. Compound *11* can then be converted to *12*, *13*, or *14* using an acid chloride, an isocyanate or carbamoyl chloride, or a chloroformate respectively.



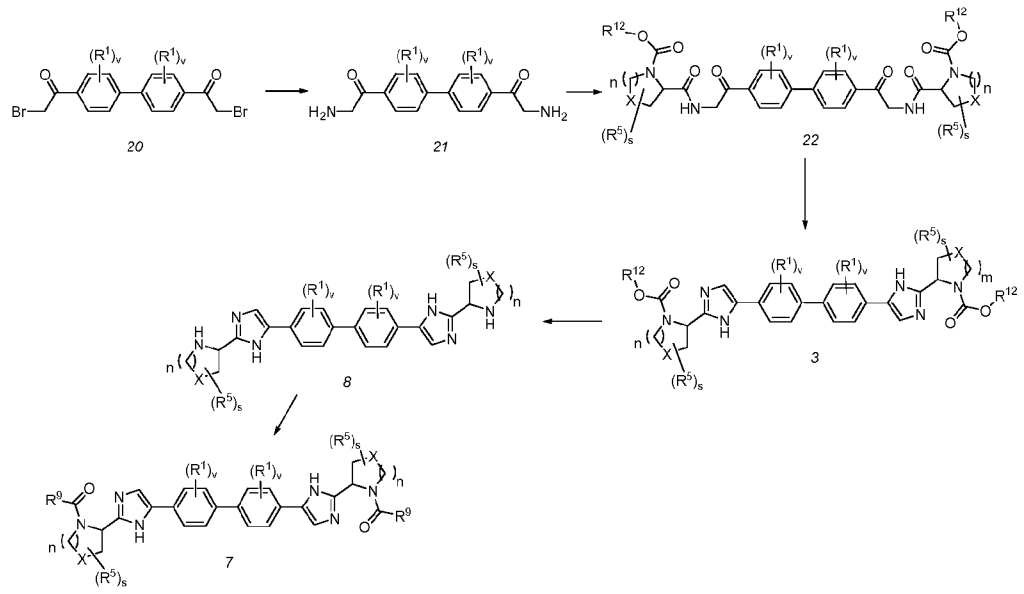
Scheme 3: Symmetric Cap Elaborated Biphenyls

Compound *15* (*15* = *7* (Scheme 1) wherein each R^9 is -CH(NHBoc)R^{18})can be converted to *16 via* treatment with strong acid such as HCl or trifluoroacetic acid. Compounds *17*, *18*, and *19* can be prepared from *16* by treating *16* with an appropriate chloroformate, isocyanate or carbamoyl chloride, or an acid chloride respectively.



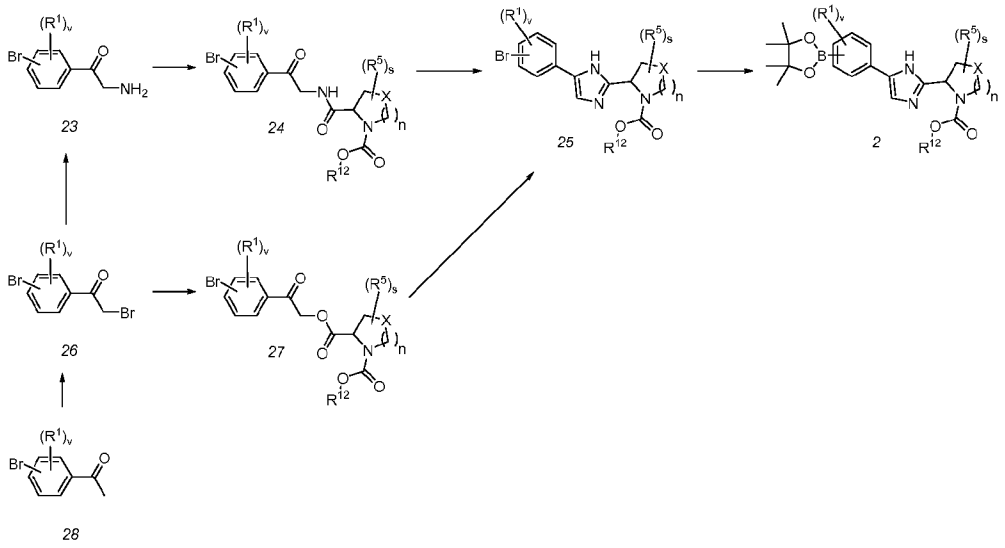
Scheme 4: Symmetric Biphenyls

Symmetrical biphenyl analogs (compounds of formula *7* where both halves of the molecule are equivalent) can be synthesized starting from bromoketone *20*. Amination by displacement with a nucleophile such as azide, phthalimide or preferably sodium diformylamide (Yinglin and Hongwen, *Synthesis* 1990, 122) followed by deprotection affords *21*. Condensation under standard amination conditions such as HATU and Hunig's base with an appropriately protected amino acid provides *22*. Heating with ammonium acetate under thermal or microwave conditions results in the formation of *3* which can be deprotected with strong acid such as HCl or trifluoroacetic acid ($R^{12} = R^{13}$ = t-Bu) or by hydrogenolysis with hydrogen gas and a transition metal catalyst such as Pd/C ($R^{12} = R^{13}$ = benzyl). Acylation can be affected with a carboxylic acid (R^9CO_2H) in a manner similar to the conversion of *21* to *22*. Urea formation can be accomplished by treatment with an appropriate isocycante ($R^9 = R^{24}R^{25}N$; R^{25} =H) or carbamoyl chloride ($R^9 = R^{24}R^{25}N$; R^{25} is other than hydrogen).



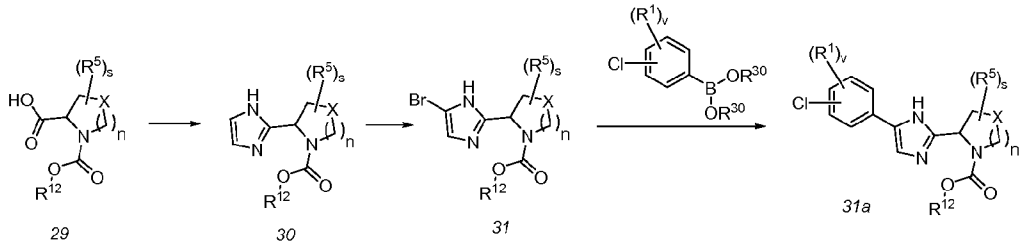
Scheme 5: Starting Materials 25 and 2

Scheme 5 describes the preparation of some of the starting materials required for the synthetic sequences depicted in Schemes 1-4. Key intermediate *25* (analogous to *1* in Scheme 1) is prepared from keto-amide *24* or keto-ester *27 via* heating with ammonium acetate under thermal or microwave conditions. Keto-amide *24* can be prepared from *23 via* condensation with an appropriate cyclic or acyclic amino acid under standard amide formation conditions. Bromide *26* can give rise to *23* by treatment with a nucleophile such as azide, phthalimide or sodium diformylamide (*Synthesis* 1990, 122) followed by deprotection. Bromide *26* can also be converted to *27* by reacting with an appropriate cyclic or acyclic N-protected amino acid in the presence of base such as potassium carbonate or sodium bicarbonate. Bromination of *28* with a source of bromonium ion such as bromine, NBS, or CBr_4 results in the formation of *26*. Bromide *25* can be converted to boronic ester *2 via* treatment with bis-pinacalotodiboron under palladium catalysis according to the method described in *Journal of Organic Chemistry* 1995, *60*, 7508, or variations thereof.



Scheme 6: Starting Material 31a

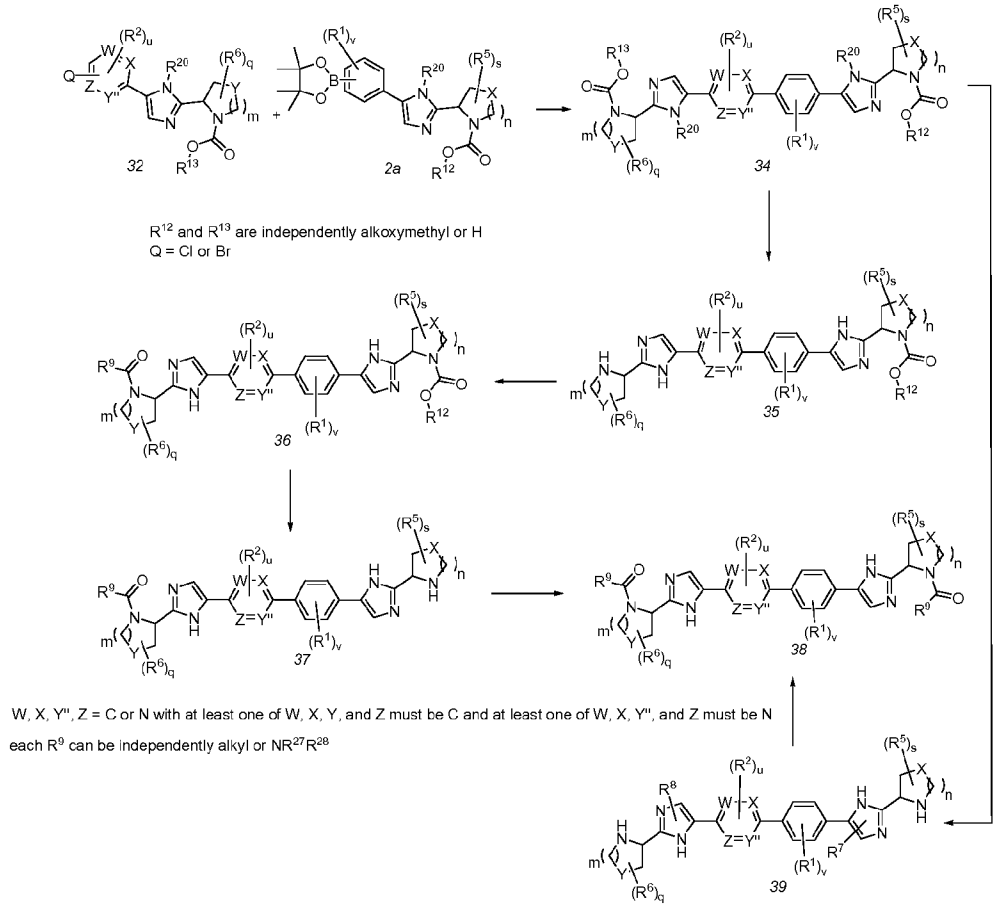
In another embodiment, starting materials such as *31a* (analogous to *25* in Scheme 5 and *1* in Scheme 1) may be prepared by reacting bromoimidazole derivatives *31* under Suzuki-type coupling conditions with a variety of chloro-substituted aryl boronic acids which can either be prepared by standard methodologies (see, for example, *Organic Letters* 2006, *8*, 305 and references cited therein) or purchased from commercial suppliers. Bromoimidazole *31* can be obtained by brominating imidazole *30* with a source of bromonium ion such as bromine, CBr_4, or N-bromosuccinimide. Imidazole *30* can be prepared from N-protected amino acids which are appropriately substituted by reacting with glyoxal in a methanolic solution of ammonium hydroxide.



Scheme 7: Heteroaryls

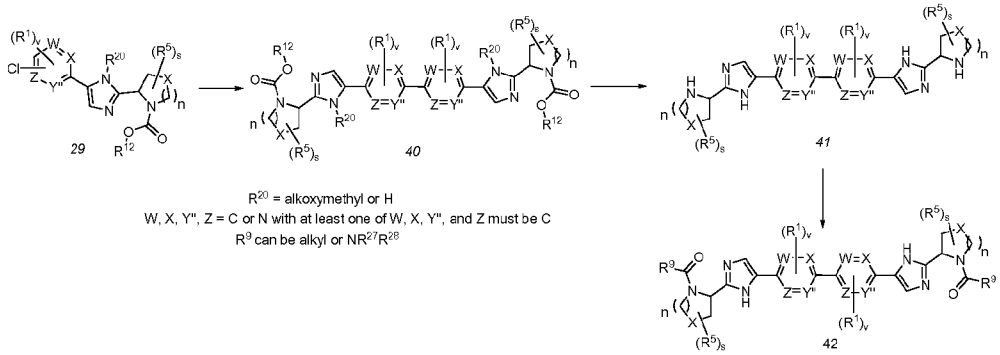
In yet another embodiment of the current disclosure, aryl halide *32* can be coupled under Suzuki-Miyaura palladium catalyzed conditions to form the heteroaryl derivative *34*. Compound *34* can be elaborated to *35* by treatment to hydrogenolytic conditions with hydrogen and a transition metal catalyst such as palladium on carbon

(R^{13} = benzyl). Acylation of *35* can be accomplished with an appropriate acid chloride (R^9COCl) in the presence of a base such as triethylamine, with an appropriately substituted carboxylic acid (R^9CO_2H) in the presence of a standard coupling reagent such as HATU, or with an isocyanate ($R^{27}NCO$ wherein R^9 = $R^{27}R^{28}N$-; R^{28} =H)or carbamoyl chloride ($R^{27}R^{28}NCOCl$ wherein R^9 = $R^{27}R^{28}N$-). Compound *37* can be prepared from 36 (R^{12} = t-Bu) *via* treatment with strong acid such as HCl or trifluoroacctic acid. Acylation of the resulting amine in *37* to give *38* can be accomplished as in the transformation of *35* to *36*. In cases where $R^{12} = R^{13}$, *34* can be directly transformed into *39* by treatment with strong acid such as HCl or trifluoroacetic acid ($R^{12} = R^{13}$ = t-Bu) or by employing hydrogenolytic conditions with hydrogen and a transition metal catalyst such as palladium on carbon ($R^{12} = R^{13}$ = benzyl). Acylation of *39* can be accomplished in analogous fashion to that described for the transformation of *35* to *36*.



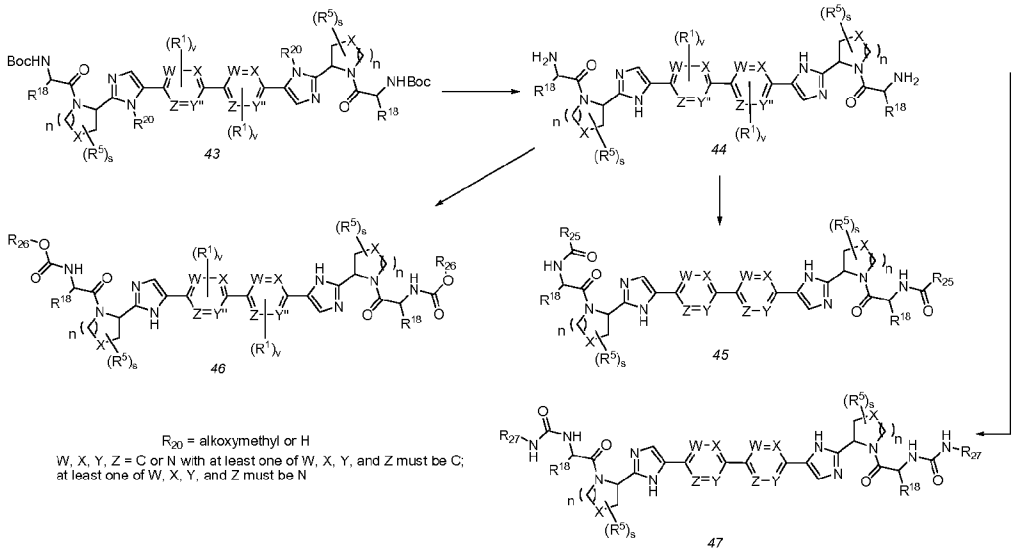
Scheme 8

Heteroaryl chloride *29* can be converted to symmetrical analog *40 via* treatment with a source of palladium such as dichlorobis(benzonitrile) palladium in the presence of tetrakis(dimethylamino)ethylene at elevated temperature. Removal of the SEM ether and Boc carbamates found in *40* can be accomplished in one step by treatment with a strong acid such as HCl or trifluoroacetic acid providing *41*. Conversion to *42* can be accomplished in similar fashion to the conditions used to convert *38* to *39* in Scheme 7.



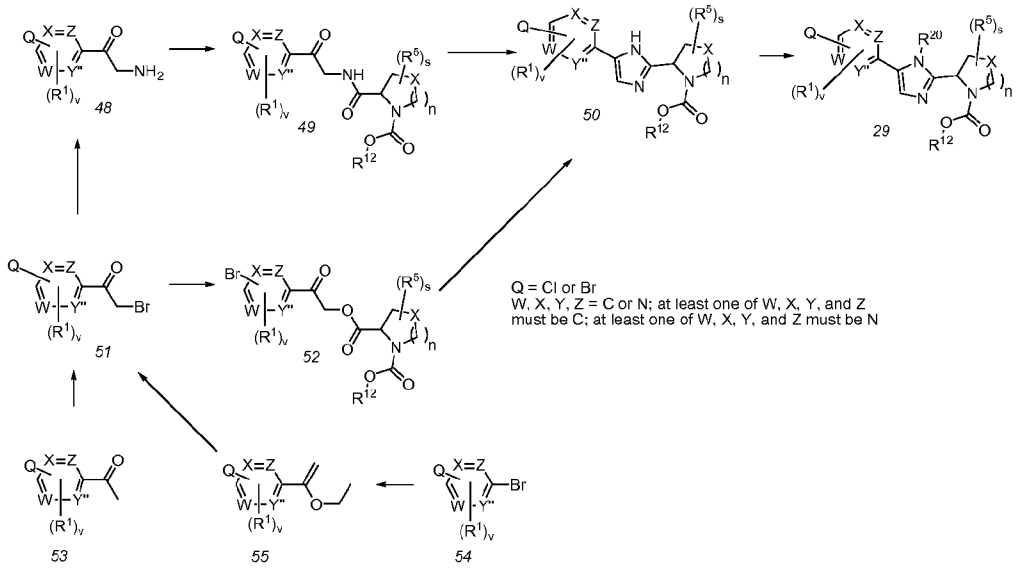
Scheme 9: Symmetric Cap Substituted Heteroaryls

Compound *43* (analogous to *42* wherein R_{23} = -CH(NHBoc)R_{24}) may be elaborated to *45*, *46*, and *47 via* similar methodologies to those described in Scheme 3. In cases where R_{20} = alkoxymethyl (ie; SEM), removal can be accomplished simultaneously with removal of the Boc carbamate (cf; *43* to *44*) using strong acid such as HCl or trifluoroacetic acid.



Scheme 10: Starting Material 29

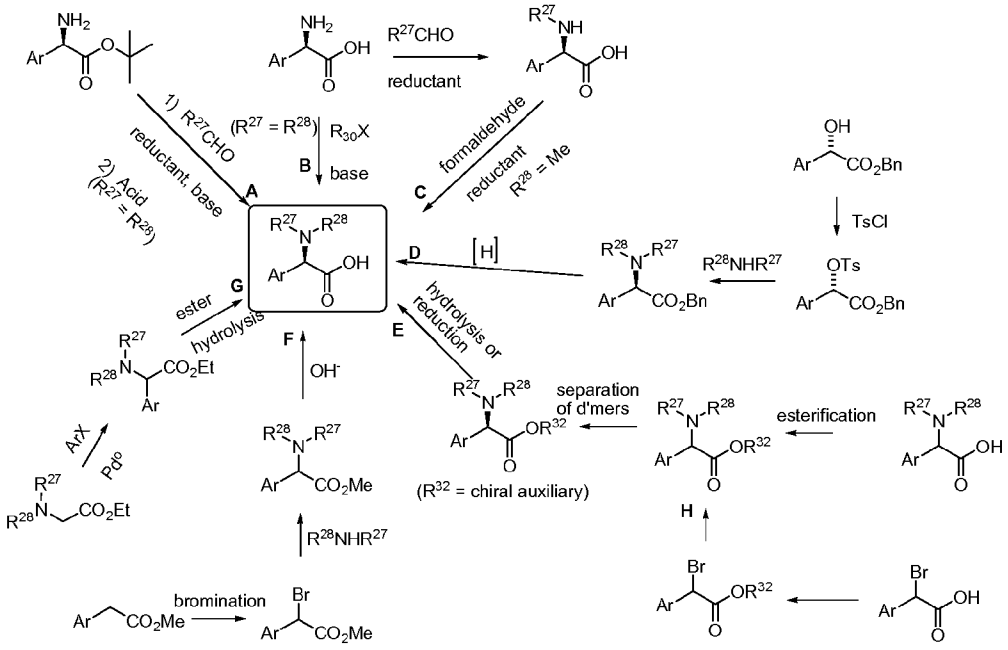
Heteroaryl bromides *54* may be reacted with a vinyl stannane such as tributyl(1-ethoxyvinyl)tin in the presence of a source of palladium such as dichlorobis(triphenylphosphine)palladium (II) to provide *55* which can be subsequently transformed into bromoketone *51 via* treatment with a source of bromonium ion such as N-bormosuccinimide, CBr_4, or bromine. Alternatively, keto-substituted heteroaryl bromides *53* may be directly converted to *51 via* treatment with a source of bromonium ion such as bromine, CBr_4, or N-bromosuccinimide. Bromide *51* can be converted to aminoketone *48 via* addition of sodium azide, potassium phthalimide or sodium diformylamide (*Synthesis* 1990 122) followed by deprotection. Aminoketone *48* can then be coupled with an appropriately substituted amino acid under standard amide formation conditions (i.e.; a coupling reagent such as HATU in the presence of a mild base such as Hunig's base) to provide *49*. Compound *49* can then be further transformed into imidazole *50 via* reacting with ammonium acetate under thermal or microwave conditions. Alternatively, *51* can be directly reacted with an appropriately substituted amino acid in the presence of a base such as sodium bicarbonate or potassium carbonate providing *52* which can in turn be reacted with ammonium acetate under thermal or microwave conditions to provide *50*. Imidazole *50* can be protected with an alkoxylmethyl group by treatment with the appropriate alkoxymethyl halide such as 2-(trimethylsilyl)ethoxymethyl chloride after first being deprotonated with a strong base such as sodium hydride.



Scheme 11: Substituted Phenylglycine Derivatives

Substituted phenylglycine derivatives can be prepared by a number of methods shown below. Phenylglycine t-butyl ester can be reductively alkylated (pathyway A) with an appropriate aldehyde and a reductant such as sodium cyanoborohydride in acidic medium. Hydrolysis of the t-butyl ester can be accomplished with strong acid such as HCl or trifluoroacetic acid. Alternatively, phenylglycine can be alkylated with an alkyl halide such as ethyl iodide and a base such as sodium bicarbonate or potassium carbonate (pathway B). Pathway C illustrates reductive alkylation of phenylglycine as in pathway A followed by a second reductive alkylation with an alternate aldehyde such as formaldehyde in the presence of a reducing agent and acid. Pathway D illustrates the synthesis of substituted phenylglycines *via* the corresponding mandelic acid analogs. Conversion of the secondary alcohol to a competent leaving group can be accomplished with p-toluensulfonyl chloride. Displacement of the tosylate group with an appropriate amine followed by reductive removal of the benzyl ester can provide substituted phenylglycine derivatives. In pathway E a racemic substituted phenylglycine derivative is resolved by esterification with an enantiomerically pure chiral auxiliary such as but not limited to (+)-1-phenylethanol, (-)-1-phenylethanol, an Evan's oxazolidinone, or enantiomerically pure pantolactone. Separation of the diastereomers is accomplished *via* chromatography (silica gel, HPLC, crystallization,

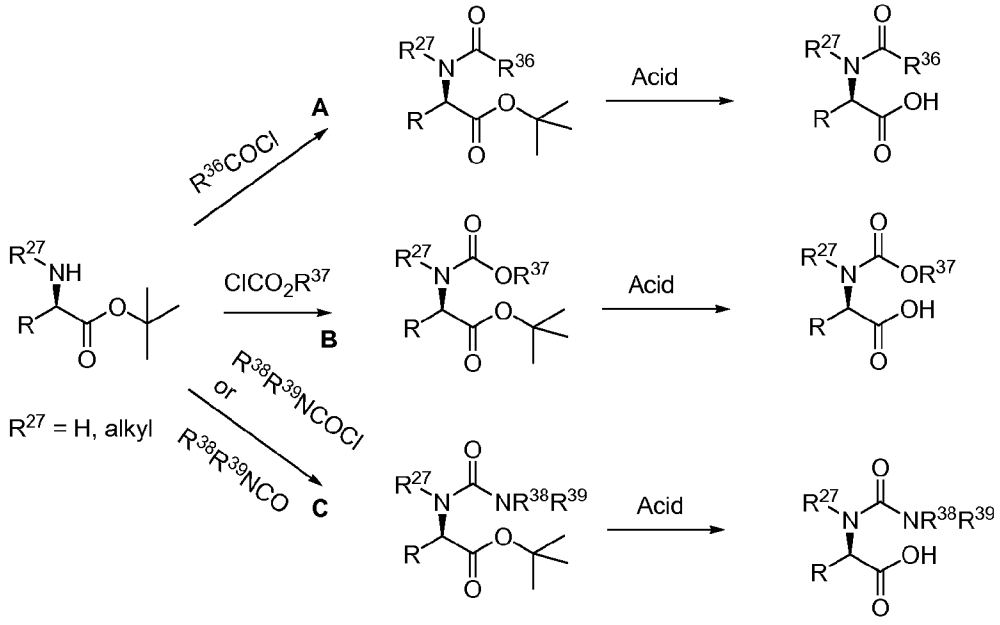
etc) followed by removal of the chiral auxiliary providing enantiomerically pure phenylglycine derivatives. Pathway H illustrates a synthetic sequence which intersects with pathway E wherein the aforementioned chiral auxiliary is installed prior to amine addition. Alternatively, an ester of an arylacetic acid can be brominated with a source of bromonium ion such as bromine, N-bromosuccinimide, or CBr_4. The resultant benzylic bromide can be displaced with a variety of mono- or disubstituted amines in the presence of a tertiary amine base such as triethylamine or Hunig's base. Hydrolysis of the methyl ester *via* treatment with lithium hydroxide at low temperature or 6N HCl at elevated temperature provides the substituted phenylglycine derivatives. Another method is shown in pathway G. Glycine analogs can be derivatized with a variety of aryl halides in the presence of a source of palladium (0) such as palladium bis(tributylphosphine) and base such as potassium phosphate. The resultant ester can then be hydrolyzed by treatment with base or acid. It should be understood that other well known methods to prepare phenylglycine derivatives exist in the art and can be amended to provide the desired compounds in this description. It should also be understood that the final phenylglycine derivatives can be purified to enantiomeric purity greater than 98%ee *via* preparative HPLC.



Scheme 12: Acylated Amino Acid Derivatives

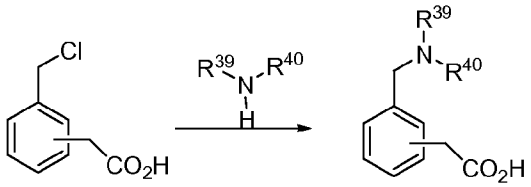
In another embodiment of the present disclosure, acylated phenylglycine derivatives may be prepared as illustrated below. Phenylglycine derivatives wherein

the carboxylic acid is protected as an easily removed ester, may be acylated with an acid chloride in the presence of a base such as triethylamine to provide the corresponding amides (pathway A). Pathway B illustrates the acylation of the starting phenylglycine derivative with an appropriate chloroformate while pathway C shows reaction with an appropriate isocyanate or carbamoyl chloride. Each of the three intermediates shown in pathways A – C may be deprotected by methods known by those skilled in the art (ie; treatment of the t-butyl ester with strong base such as HCl or trifluoroacetic acid).



Scheme 13

Amino-substituted phenylacetic acids may be prepared by treatment of a chloromethylphenylacetic acid with an excess of an amine.



Compound analysis conditions

Purity assessment and low resolution mass analysis were conducted on a Shimadzu LC system coupled with Waters Micromass ZQ MS system. It should be

noted that retention times may vary slightly between machines. The LC conditions employed in determining the retention time (RT) were:

Condition 1

Column = Phenomenex-Luna 3.0X 50 mm S10
Start %B = 0
Final %B = 100
Gradient time = 2 min
Stop time = 3 min
Flow Rate = 4 mL/min
Wavelength = 220 nm
Slovent A = 0.1% TFA in 10% methanol/90%H_2O
Solvent B = 0.1% TFA in 90% methanol/10% H_2O

Condition 2

Column = Phenomenex-Luna 4.6X50 mm S10
Start %B = 0
Final %B = 100
Gradient time = 2 min
Stop time = 3 min
Flow Rate = 5 mL/min
Wavelength = 220 nm
Slovent A = 0.1% TFA in 10% methanol/90%H_2O
Solvent B = 0.1% TFA in 90% methanol/10% H_2O

Condition 3

Column = HPLC XTERRA C18 3.0 x 50mm S7
Start %B = 0
Final %B = 100
Gradient time = 3 min
Stop time = 4 min
Flow Rate = 4 mL/min
Wavelength = 220 nm

Slovent A = 0.1% TFA in 10% methanol/90%H_2O

Solvent B = 0.1% TFA in 90% methanol/10% H_2O

Condition M1

Column: Luna 4.6X 50 mm S10

Start %B = 0

Final %B = 100

Gradient time = 3 min

Stop time = 4 min

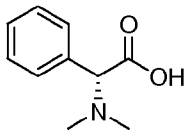
Flow rate = 4 mL/min

Solvent A: = 95% H_20: 5% CH_3CN, 10 mm Ammonium acetate

Solvent B: = 5% H_2O : 95% CH_3CN; 10 mm Ammonium acetate

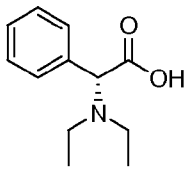
Synthesis of common caps

Cap-1



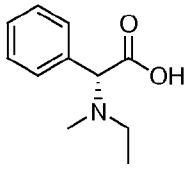
A suspension of 10% Pd/C (2.0g) in methanol (10 mL) was added to a mixture of (R)-2-phenylglycine (10g, 66.2 mmol), formaldehyde (33 mL of 37% wt. in water), 1N HCl (30 mL) and methanol (30 mL), and exposed to H_2 (60 psi) for 3 hours. The reaction mixture was filtered through diatomaceous earth (Celite®), and the filtrate was concentrated *in vacuo*. The resulting crude material was recrystallized from isopropanol to provide the HCl salt of *Cap*-1 as a white needle (4.0 g). Optical rotation: -117.1° [c = 9.95 mg/mL in H_2O; λ = 589 nm]. ^1H NMR (DMSO-d_6, δ = 2.5 ppm, 500 MHz): δ 7.43-7.34 (m, 5H), 4.14 (s, 1H), 2.43 (s, 6H); LC (Cond. 1): RT = 0.25; LC/MS: Anal. Calcd. for $[M+H]^+$ $C_{10}H_{14}NO_2$ 180.10; found 180.17; HRMS: Anal. Calcd. for $[M+H]^-$ $C_{10}H_{14}NO_2$ 180.1025; found 180.1017.

Cap-2



$NaBH_3CN$ (6.22g, 94 mmol) was added in portions over a few minutes to a cooled (ice/water) mixture of (R)-2-Phenylglycine (6.02 g, 39.8 mmol) and MeOH (100 mL), and stirred for 5 min. Acetaldehyde (10 mL) was added drop-wise over 10 min and stirring was continued at the same cooled temperature for 45 min and at ambient temperature for ~6.5 hr. The reaction mixture was cooled back with ice-water bath, treated with water (3 mL) and then quenched with a drop-wise addition of concentrated HCl over ~ 45 min until the pH of the mixture is ~ 1.5 – 2.0. The cooling bath was removed and the stirring was continued while adding concentrated HCl in order to maintain the pH of the mixture around 1.5-2.0. The reaction mixture was stirred over night, filtered to remove the white suspension, and the filtrate was concentrated *in vacuo*. The crude material was recrystallized from ethanol to afford the HCl salt of *Cap*-2 as a shining white solid in two crops (crop-1: 4.16 g; crop-2: 2.19 g). ^1H NMR (DMSO-d_6, δ = 2.5 ppm, 400 MHz): 10.44 (1.00, br s, 1H), 7.66 (m, 2H), 7.51 (m, 3H), 5.30 (s, 1H), 3.15 (br m, 2H), 2.98 (br m, 2H), 1.20 (app br s, 6H). Crop-1: $[\alpha]^{25}$ -102.21° (c = 0.357, H_2O); crop-2: $[\alpha]^{25}$ -99.7° (c = 0.357, H_2O). LC (Cond. 1): RT = 0.43 min; LC/MS: Anal. Calcd. for $[M+H]^+$ $C_{12}H_{18}NO_2$: 208.13; found 208.26

Cap-3

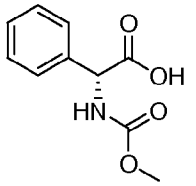


Acetaldehyde (5.0 mL, 89.1 mmol) and a suspension of 10% Pd/C (720 mg) in methanol/H_2O (4mL/1 mL) was sequentially added to a cooled (~ 15 °C) mixture of (R)-2-phenylglycine (3.096g, 20.48 mmol), 1N HCl (30 mL) and methanol (40 mL). The cooling bath was removed and the reaction mixture was stirred under a balloon of H_2 for 17 hours. An additional acetaldehyde (10 mL, 178.2 mmol) was

added and stirring continued under H_2 atmosphere for 24 hours [Note: the supply of H_2 was replenished as needed throughout the reaction]. The reaction mixture was filtered through diatomaceous earth (Celite®), and the filtrate was concentrated *in vacuo*. The resulting crude material was recrystallized from isopropanol to provide the HCl salt of (R)-2-(ethylamino)-2-phenylacetic acid as a shining white solid (2.846g). ^{1}H NMR (DMSO-d_6, δ = 2.5 ppm, 400 MHz): δ 14.15 (br s, 1H), 9.55 (br s, 2H), 7.55-7.48 (m, 5H), 2.88 (br m, 1H), 2.73 (br m, 1H), 1.20 (app t, J = 7.2, 3H). LC (Cond. 1): RT = 0.39 min; >95 % homogeneity index; LC/MS: Anal. Calcd. for $[M+H]^+$ $C_{10}H_{14}NO_2$: 180.10; found 180.18.

A suspension of 10% Pd/C (536 mg) in methanol/H_2O (3 mL/1 mL) was added to a mixture of (R)-2-(ethylamino)-2-phenylacetic acid/HCl (1.492g, 6.918 mmol), formaldehyde (20 mL of 37% wt. in water), 1N HCl (20 mL) and methanol (23 mL). The reaction mixture was stirred under a balloon of H_2 for ~72 hours, where the H_2 supply was replenished as needed. The reaction mixture was filtered through diatomaceous earth (Celite®) and the filtrate was concentrated *in vacuo*. The resulting crude material was recrystallized from isopropanol (50 mL) to provide the HCl salt of *Cap*-3 as a white solid (985 mg). ^{1}H NMR (DMSO-d_6, δ = 2.5 ppm, 400 MHz): δ 10.48 (br s, 1H), 7.59-7.51 (m, 5H), 5.26 (s, 1H), 3.08 (app br s, 2H), 2.65 (br s, 3H), 1.24 (br m, 3H). LC (Cond. 1): RT = 0.39 min; >95 % homogeneity index; LC/MS: Anal. Calcd. for $[M+H]^+$ $C_{11}H_{16}NO_2$: 194.12; found 194.18; HRMS: Anal. Calcd. for $[M+H]^+$ $C_{11}H_{16}NO_2$: 194.1180; found 194.1181.

Cap-4

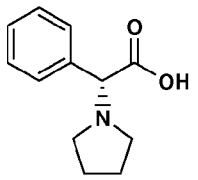


$ClCO_2Me$ (3.2 mL, 41.4 mmol) was added dropwise to a cooled (ice/water) THF (410 mL) semi-solution of (R)-tert-butyl 2-amino-2-phenylacetate/HCl (9.877 g, 40.52 mmol) and diisopropylethylamine (14.2 mL, 81.52 mmol) over 6 min, and stirred at similar temperature for 5.5 hours. The volatile component was removed *in vacuo*, and the residue was partitioned between water (100 mL) and ethyl acetate

(200 mL). The organic layer was washed with 1N HCl (25 mL) and saturated $NaHCO_3$ solution (30 mL), dried ($MgSO_4$), filtered, and concentrated *in vacuo*. The resultant colorless oil was triturated from hexanes, filtered and washed with hexanes (100 mL) to provide (R)-tert-butyl 2-(methoxycarbonylamino)-2-phenylacetate as a white solid (7.7 g). ^1H NMR (DMSO-d_6, δ = 2.5 ppm, 400 MHz): 7.98 (d, J = 8.0, 1H), 7.37-7.29 (m, 5H), 5.09 (d, J = 8, 1H), 3.56 (s, 3H), 1.33 (s, 9H). LC (Cond. 1): RT = 1.53 min; ~90 % homogeneity index; LC/MS: Anal. Calcd. for $[M+Na]^+$ $C_{14}H_{19}NNaO_4$: 288.12; found 288.15.

TFA (16 mL) was added dropwise to a cooled (ice/water) CH_2Cl_2 (160 mL) solution of the above product over 7 minutes, and the cooling bath was removed and the reaction mixture was stirred for 20 hours. Since the deprotection was still not complete, an additional TFA (1.0 mL) was added and stirring continued for an additional 2 hours. The volatile component was removed *in vacuo*, and the resulting oil residue was treated with diethyl ether (15 mL) and hexanes (12 mL) to provide a precipitate. The precipitate was filtered and washed with diethyl ether/hexanes (~1:3 ratio; 30 mL) and dried *in vacuo* to provide *Cap*-4 as a fluffy white solid (5.57 g). Optical rotation: -176.9° [c = 3.7 mg/mL in H_2O; λ = 589 nm]. ^1H NMR (DMSO-d_6, δ = 2.5 ppm, 400 MHz): δ 12.84 (br s, 1H), 7.96 (d, J = 8.3, 1H), 7.41-7.29 (m, 5H), 5.14 (d, J = 8.3, 1H), 3.55 (s, 3H). LC (Cond. 1): RT = 1.01 min; >95 % homogeneity index; LC/MS: Anal. Calcd. for $[M+H]^+$ $C_{10}H_{12}NO_4$ 210.08; found 210.17; HRMS: Anal. Calcd. for $[M+H]^+$ $C_{10}H_{12}NO_4$ 210.0766; found 210.0756.

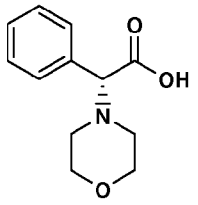
Cap-5



A mixture of (R)- 2-phenylglycine (1.0 g, 6.62 mmol), 1,4-dibromobutane (1.57 g, 7.27 mmol) and Na_2CO_3 (2.10 g, 19.8 mmol) in ethanol (40 mL) was heated at 100 °C for 21 hours. The reaction mixture was cooled to ambient temperature and filtered, and the filtrate was concentrated *in vacuo*. The residue was dissolved in ethanol and acidified with 1N HCl to pH 3-4, and the volatile component was removed *in vacuo*. The resulting crude material was purified by a reverse phase

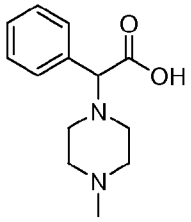
HPLC (water/methanol/TFA) to provide the TFA salt of *Cap*-5 as a semi-viscous white foam (1.0 g). ^{1}H NMR (DMSO-d_6, δ = 2.5, 500 MHz) δ 10.68 (br s, 1H), 7.51 (m, 5H), 5.23 (s, 1H), 3.34 (app br s, 2H), 3.05 (app br s, 2H), 1.95 (app br s, 4H); RT = 0.30 min (Cond. 1); >98% homogeneity index; LC/MS: Anal. Calcd. for $[M+H]^+$ $C_{12}H_{16}NO_2$: 206.12; found 206.25.

Cap-6



The TFA salt of *Cap*-6 was synthesized from (R)-2-phenylglycine and 1-bromo-2-(2-bromoethoxy)ethane by using the method of preparation of *Cap*-5. ^{1}H NMR (DMSO-d_6, δ = 2.5, 500 MHz) δ 12.20 (br s, 1H), 7.50 (m, 5H), 4.92 (s, 1H), 3.78 (app br s, 4H), 3.08 (app br s, 2H), 2.81 (app br s, 2H); RT = 0.32 min (Cond. 1); >98%; LC/MS: Anal. Calcd. for $[M+H]^+$ $C_{12}H_{16}NO_3$: 222.11; found 222.20; HRMS: Anal. Calcd. for $[M+H]^+$ $C_{12}H_{16}NO_3$: 222.1130; found 222.1121.

Cap-7



Cap-7a: enantiomer-1
Cap-7b: enantiomer-2

A CH_2Cl_2 (200 mL) solution of p-toluenesulfonyl chloride (8.65 g, 45.4 mmol) was added dropwise to a cooled (-5 °C) CH_2Cl_2 (200 mL) solution of (S)-benzyl 2-hydroxy-2-phenylacetate (10.0 g, 41.3 mmol), triethylamine (5.75 mL, 41.3 mmol) and 4-dimethylaminopyridine (0.504 g, 4.13 mmol), while maintaining the temperature between -5 °C and 0 °C. The reaction was stirred at 0 °C for 9 hours, and then stored in a freezer (-25 °C) for 14 hours. It was allowed to thaw to ambient temperature and washed with water (200 mL), 1N HCl (100 mL) and brine (100 mL), dried ($MgSO_4$), filtered, and concentrated *in vacuo* to provide benzyl 2-phenyl-2-

(tosyloxy)acetate as a viscous oil which solidified upon standing (16.5 g). The chiral integrity of the product was not checked and that product was used for the next step without further purification. ^{1}H NMR (DMSO-d_6, δ = 2.5, 500 MHz) δ 7.78 (d, *J* = 8.6, 2H), 7.43-7.29 (m, 10H), 7.20 (m, 2H), 6.12 (s, 1H), 5.16 (d, *J* = 12.5, 1H), 5.10 (d, *J* = 12.5, 1H), 2.39 (s, 3H). RT = 3.00 (Cond. 3); >90% homogeneity index; LC/MS: Anal. Calcd. for $[M+H]^+$ $C_{22}H_{20}NaO_5S$: 419.09; found 419.04.

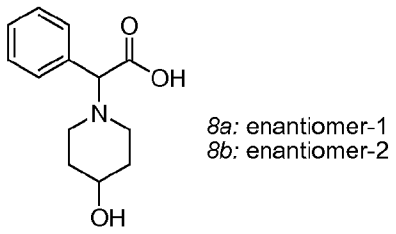
A THF (75 mL) solution of benzyl 2-phenyl-2-(tosyloxy)acetate (6.0 g, 15.1 mmol), 1-methylpiperazine (3.36 mL, 30.3 mmol) and N,N-diisopropylethylamine (13.2 mL, 75.8 mmol) was heated at 65 °C for 7 hours. The reaction was allowed to cool to ambient temperature and the volatile component was removed *in vacuo*. The residue was partitioned between ethylacetate and water, and the organic layer was washed with water and brine, dried ($MgSO_4$), filtered, and concentrated *in vacuo*. The resulting crude material was purified by flash chromatography (silica gel, ethyl acetate) to provide benzyl 2-(4-methylpiperazin-1-yl)-2-phenylacetate as an orangish-brown viscous oil (4.56 g). Chiral HPLC analysis (Chiralcel OD-H) indicated that the sample is a mixture of enantiomers in a 38.2 to 58.7 ratio. The separation of the enantiomers were effected as follow: the product was dissolved in 120 mL of ethanol/heptane (1:1) and injected (5 mL/injection) on chiral HPLC column (Chiracel OJ, 5 cm ID x 50 cm L, 20 μm) eluting with 85:15 Heptane/ethanol at 75 mL/min, and monitored at 220 nm. Enantiomer-1 (1.474 g) and enantiomer-2 (2.2149 g) were retrieved as viscous oil. ^{1}H NMR ($CDCl_3$, δ = 7.26, 500 MHz) 7.44-7.40 (m, 2H), 7.33-7.24 (m, 6H), 7.21-7.16 (m, 2H), 5.13 (d, *J* = 12.5, 1H), 5.08 (d, *J* = 12.5, 1H), 4.02 (s, 1H), 2.65-2.38 (app br s, 8H), 2.25 (s, 3H). RT = 2.10 (Cond. 3); >98% homogeneity index; LC/MS: Anal. Calcd. for $[M+H]^+$ $C_{20}H_{25}N_2O_2$: 325.19; found 325.20.

A methanol (10 mL) solution of either enantiomer of benzyl 2-(4-methylpiperazin-1-yl)-2-phenylacetate (1.0 g, 3.1 mmol) was added to a suspension of 10% Pd/C (120 mg) in methanol (5.0 mL). The reaction mixture was exposed to a balloon of hydrogen, under a careful monitoring, for <50 min. Immediately after the completion of the reaction, the catalyst was filtered through diatomaceous earth (Celite®) and the filtrate was concentrated *in vacuo* to provide *Cap*-7, contaminated with phenylacetic acid as a tan foam (867.6 mg; mass is above the theoretical yield).

The product was used for the next step without further purification. ^{1}H NMR (DMSO-d_6, δ = 2.5, 500 MHz) δ 7.44-7.37 (m, 2H), 7.37-7.24 (m, 3H), 3.92 (s, 1H), 2.63-2.48 (app. bs, 2H), 2.48-2.32 (m, 6H), 2.19 (s, 3H); RT = 0.31 (Cond. 2); >90% homogeneity index; LC/MS: Anal. Calcd. for $[M+H]^+$ $C_{13}H_{19}N_2O_2$: 235.14; found 235.15; HRMS: Anal. Calcd. for $[M+H]^+$ $C_{13}H_{19}N_2O_2$: 235.1447; found 235.1440.

The synthesis of *Cap*-8 and *Cap*-9 was conducted according to the synthesis of *Cap*-7 by using appropriate amines for the SN_2 displacement step (i.e., 4-hydroxypiperidine for *Cap*-8 and (S)-3-fluoropyrrolidine for *Cap*-9) and modified conditions for the separation of the respective stereoisomeric intermedites, as described below.

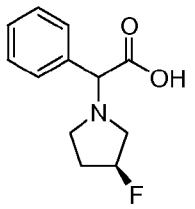
Cap-8



8a: enantiomer-1
8b: enantiomer-2

The enantiomeric separation of the intermediate benzyl 2-(4-hydroxypiperidin-1-yl)-2-phenyl acetate was effected by employing the following conditions: the compound (500 mg) was dissolved in ethanol/heptane (5 mL/45 mL). The resulting solution was injected (5 mL/injection) on a chiral HPLC column (Chiracel OJ, 2 cm ID x 25 cm L, 10 μm) eluting with 80:20 heptane/ethanol at 10 mL/min, monitored at 220 nm, to provide 186.3 mg of enantiomer-1 and 209.1 mg of enantiomer-2 as light-yellow viscous oils. These benzyl ester was hydrogenolysed according to the preparation of *Cap*-7 to provide *Cap*-8: ^{1}H NMR (DMSO-d_6, δ = 2.5, 500 MHz) 7.40 (d, *J* = 7, 2H), 7.28-7.20 (m, 3H), 3.78 (s 1H), 3.46 (m, 1H), 2.93 (m, 1H), 2.62 (m, 1H), 2.20 (m, 2H), 1.70 (m, 2H), 1.42 (m, 2H). RT = 0.28 (Cond. 2); >98% homogeneity index; LC/MS: Anal. Calcd. for $[M+H]^+$ $C_{13}H_{18}NO_3$: 236.13; found 236.07; HRMS: Calcd. for $[M+H]^+$ $C_{13}H_{18}NO_3$: 236.1287; found 236.1283.

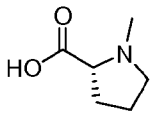
Cap-9



9a: diastereomer-1
9b: diastereomer-2

The diastereomeric separation of the intermediate benzyl 2-((S)-3-fluoropyrrolidin-1-yl)-2-phenylacetate was effected by employing the following conditions: the ester (220 mg) was separated on a chiral HPLC column (Chiracel OJ-H, 0.46 cm ID x 25 cm L, 5 μm) eluting with 95% CO_2 / 5% methanol with 0.1% TFA, at 10 bar pressure, 70 mL/min flow rate, and a temperature of 35 °C. The HPLC elute for the respective stereiosmers was concentrated, and the residue was dissolved in CH_2Cl_2 (20 mL) and washed with an aqueous medium (10 mL water + 1 mL saturated $NaHCO_3$ solution). The organic phase was dried ($MgSO_4$), filtered, and concentrated *in vacuo* to provide 92.5 mg of fraction-1 and 59.6 mg of fraction-2. These benzyl esters were hydrogenolysed according to the preparation of *Cap*-7 to prepare Caps 9a and 9b. *Cap*-9a (diastereomer-1; the sample is a TFA salt as a result of purification on a reverse phase HPLC using H_2O/methanol/TFA solvent): ^{1}H NMR (DMSO-d_6, δ = 2.5, 400 MHz) 7.55-7.48 (m, 5H), 5.38 (d of m, *J* = 53.7, 1H), 5.09 (br s, 1H), 3.84-2.82 (br m, 4H), 2.31-2.09 (m, 2H). RT = 0.42 (Cond. 1); >95% homogeneity index; LC/MS: Anal. Calcd. for $[M+H]^+$ $C_{12}H_{15}FNO_2$: 224.11; found 224.14; *Cap*-9b (diastereomer-2): ^{1}H NMR (DMSO-d_6, δ = 2.5, 400 MHz) 7.43-7.21 (m, 5H), 5.19 (d of m, *J* = 55.9, 1H), 3.97 (s, 1H), 2.95-2.43 (m, 4H), 2.19-1.78 (m, 2H). RT = 0.44 (Cond. 1); LC/MS: Anal. Calcd. for $[M+H]^+$ $C_{12}H_{15}FNO_2$: 224.11; found 224.14.

Cap-10



To a solution of D-proline (2.0 g, 17 mmol) and formaldehyde (2.0 mL of 37% wt. in H_2O) in methanol (15 mL) was added a suspension of 10% Pd/C (500 mg) in methanol (5 mL). The mixture was stirred under a balloon of hydrogen for 23

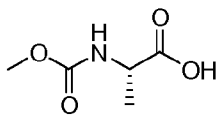
hours. The reaction mixture was filtered through diatomaceous earth (Celite®) and concentrated *in vacuo* to provide *Cap*-10 as an off-white solid (2.15 g). ^{1}H NMR (DMSO-d_6, δ = 2.5, 500 MHz) 3.42 (m, 1H), 3.37 (dd, *J* = 9.4, 6.1, 1H), 2.85-2.78 (m, 1H), 2.66 (s, 3H), 2.21-2.13 (m, 1H), 1.93-1.84 (m, 2H), 1.75-1.66 (m, 1H). RT = 0.28 (Cond. 2); >98% homogeneity index; LC/MS: Anal. Calcd. for $[M+H]^+$ $C_6H_{12}NO_2$: 130.09; found 129.96.

Cap-11



A mixture of (2S,4R)-4-fluoropyrrolidine-2-carboxylic acid (0.50 g, 3.8 mmol), formaldehyde (0.5 mL of 37% wt. in H_2O), 12 N HCl (0.25 mL) and 10% Pd/C (50 mg) in methanol (20 mL) was stirred under a balloon of hydrogen for 19 hours. The reaction mixture was filtered through diatomaceous earth (Celite®) and the filtrate was concentrated *in vacuo*. The residue was recrystallized from isopropanol to provide the HCl salt of *Cap*-11 as a white solid (337.7 mg). ^{1}H NMR (DMSO-d_6, δ = 2.5, 500 MHz) 5.39 (d m, *J* = 53.7, 1H), 4.30 (m, 1H), 3.90 (ddd, *J* = 31.5, 13.5, 4.5, 1H), 3.33 (dd, *J* = 25.6, 13.4, 1H), 2.85 (s, 3H), 2.60-2.51 (m, 1H), 2.39-2.26 (m, 1H). RT = 0.28 (Cond. 2); >98% homogeneity index; LC/MS: Anal. Calcd. for $[M+H]^+$ $C_6H_{11}FNO_2$: 148.08; found 148.06.

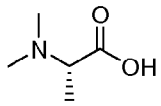
Cap-12



L-Alanine (2.0 g, 22.5 mmol) was dissolved in 10% aqueous sodium carbonate solution (50 mL), and a THF (50 mL) solution of methyl chloroformate (4.0 mL) was added to it. The reaction mixture was stirred under ambient conditions for 4.5 hours and concentrated *in vacuo*. The resulting white solid was dissolved in water and acidified with 1N HCl to a pH ~ 2-3. The resulting solutions was extracted with ethyl acetate (3 x 100 mL), and the combined organic phase was dried (Na_2SO_4),

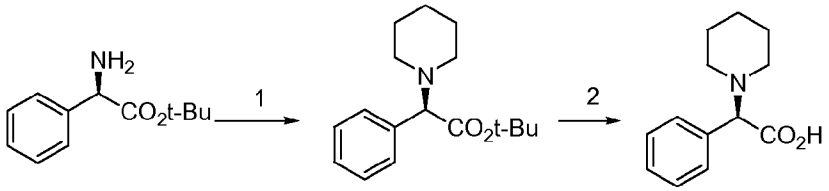
filtered, and concentrated *in vacuo* to provide a colorless oil (2.58 g). 500 mg of this material was purified by a reverse phase HPLC (H_2O/methanol/TFA) to provide 150 mg of *Cap*-12 as a colorless oil . ^{1}H NMR (DMSO-d_6, δ = 2.5, 500 MHz) 7.44 (d, *J* = 7.3, 0.8H), 7.10 (br s, 0.2H), 3.97 (m, 1H), 3.53 (s, 3H), 1.25 (d, *J* = 7.3, 3H).

Cap-13



A mixture of L-alanine (2.5 g, 28 mmol), formaldehyde (8.4 g, 37 wt. %), 1N HCl (30 mL) and 10% Pd/C (500 mg) in methanol (30 mL) was stirred under a hydrogen atmosphere (50 psi) for 5 hours. The reaction mixture was filtered through diatomaceous earth (Celite®) and the filtrate was concentrated *in vacuo* to provide the HCl salt of *Cap*-13 as an oil which solidified upon standing under vacuum (4.4 g; the mass is above theoretical yield). The product was used without further purification. ^{1}H NMR (DMSO-d_6, δ = 2.5, 500 MHz) δ 12.1 (br s, 1H), 4.06 (q, *J* = 7.4, 1H), 2.76 (s, 6H), 1.46 (d, *J* = 7.3, 3H).

Cap-14



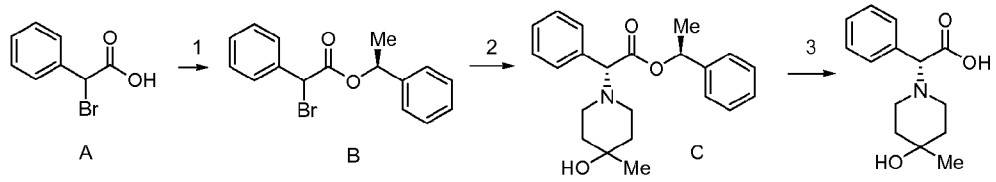
Cap-14

Step 1: A mixture of (R)-(-)-D-phenylglycine tert-butyl ester (3.00 g, 12.3 mmol), $NaBH_3CN$ (0.773 g, 12.3 mmol), KOH (0.690 g, 12.3 mmol) and acetic acid (0.352 mL, 6.15 mmol) were stirred in methanol at 0 °C. To this mixture was added glutaric dialdehyde (2.23 mL, 12.3 mmol) dropwise over 5 minutes. The reaction mixture was stirred as it was allowed to warm to ambient temperature and stirring was continued at the same temperature for 16 hours. The solvent was subsequently removed and the residue was partitioned with 10% aqueous NaOH and ethyl acetate. The organic phase was separated, dried ($MgSO_4$), filtered and concentrated to dryness to provide a clear oil. This material was purified by reverse-phase

preparative HPLC (Primesphere C-18, 30 x 100mm; CH_3CN-H_2O-0.1% TFA) to give the intermediate ester (2.70 g, 56%) as a clear oil. ^{1}HNMR (400 MHz, $CDCl_3$) δ 7.53-7.44 (m, 3H), 7.40-7.37 (m, 2H), 3.87 (d, J = 10.9 Hz, 1H), 3.59 (d, J = 10.9 Hz, 1H), 2.99 (t, J = 11.2 Hz, 1H), 2.59 (t, J = 11.4 Hz, 1H), 2.07-2.02 (m, 2H), 1.82 (d, J = 1.82 Hz, 3H), 1.40 (s, 9H). LC/MS: Anal. Calcd. for $C_{17}H_{25}NO_2$: 275; found: 276 $(M+H)^+$.

Step 2: To a stirred solution of the intermediate ester (1.12g, 2.88mmol) in dichloromethane (10 mL) was added TFA (3 mL). The reaction mixture was stirred at ambient temperature for 4 hours and then it was concentrated to dryness to give a light yellow oil. The oil was purified using reverse-phase preparative HPLC (Primesphere C-18, 30 x 100mm; CH_3CN-H_2O-0.1% TFA). The appropriate fractions were combined and concentrated to dryness *in vacuo*. The residue was then dissolved in a minimum amount of methanol and applied to applied to MCX LP extraction cartridges (2 x 6 g). The cartridges were rinsed with methanol (40 mL) and then the desired compound was eluted using 2M ammonia in methanol (50 mL). Product-containing fractions were combined and concentrated and the residue was taken up in water. Lyophilization of this solution provided the title compound (0.492 g, 78%) as a light yellow solid. ^{1}HNMR (DMSO-d_6) δ 7.50 (s, 5H), 5.13 (s, 1H), 3.09 (br s, 2H), 2.92-2.89 (m, 2H), 1.74 (m, 4H), 1.48 (br s, 2H). LC/MS: Anal. Calcd. for $C_{13}H_{17}NO_2$: 219; found: 220 $(M+H)^+$.

Cap-15



Step 1; (S)-1-Phenylethyl 2-bromo-2-phenylacetate: To a mixture of α-bromophenylacetic acid (10.75 g, 0.050 mol), (S)-(-)-1-phenylethanol (7.94 g, 0.065 mol) and DMAP (0.61 g, 5.0 mmol) in dry dichloromethane (100 mL) was added solid EDCI (12.46 g, 0.065 mol) all at once. The resulting solution was stirred at room temperature under Ar for 18 hours and then it was diluted with ethyl acetate, washed (H_2O x 2, brine), dried (Na_2SO_4), filtered, and concentrated to give a pale

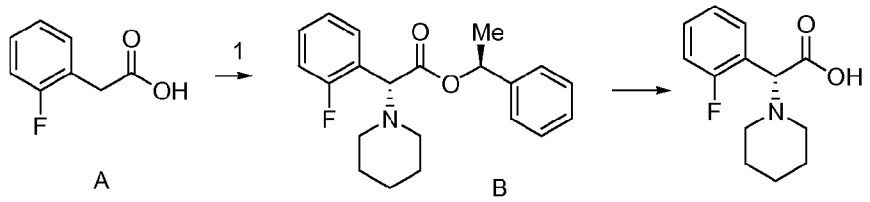
yellow oil. Flash chromatography (SiO_2/ hexane-ethyl acetate, 4:1) of this oil provided the title compound (11.64 g, 73%) as a white solid. ^{1}HNMR (400 MHz, $CDCl_3$) δ 7.53-7.17 (m, 10H), 5.95 (q, J = 6.6 Hz, 0.5H), 5.94 (q, J = 6.6 Hz, 0.5H), 5.41 (s, 0.5H), 5.39 (s, 0.5H), 1.58 (d, J = 6.6 Hz, 1.5H), 1.51 (d, J = 6.6 Hz, 1.5H).

Step 2; (S)-1-Phenylethyl (R)-2-(4-hydroxy-4-methylpiperidin-1-yl)- 2-phenylacetate: To a solution of (S)-1-phenylethyl 2-bromo-2-phenylacetate (0.464 g, 1.45 mmol) in THF (8 mL) was added triethylamine (0.61 mL, 4.35 mmol), followed by tetrabutylammonium iodide (0.215 g, 0.58 mmol). The reaction mixture was stirred at room temperature for 5 minutes and then a solution of 4-methyl-4-hydroxypiperidine (0.251 g, 2.18 mmol) in THF (2 mL) was added. The mixture was stirred for 1 hour at room temperature and then it was heated at 55-60 °C (oil bath temperature) for 4 hours. The cooled reaction mixture was then diluted with ethyl acetate (30 mL), washed (H_2O x2, brine), dried ($MgSO_4$), filtered and concentrated. The residue was purified by silica gel chromatography (0-60% ethyl acetate-hexane) to provide first the (S,R)-isomer of the title compound (0.306 g, 60%) as a white solid and then the corresponding (S,S)-isomer (0.120 g, 23%), also as a white solid. (S,R)-isomer: ^{1}HNMR (CD_3OD) δ 7.51-7.45 (m, 2H), 7.41-7.25 (m, 8H), 5.85 (q, J = 6.6 Hz, 1H), 4.05 (s, 1H), 2.56-2.45 (m, 2H), 2.41-2.29 (m, 2H), 1.71-1.49 (m, 4H), 1.38 (d, J = 6.6 Hz, 3H), 1.18 (s, 3H). LCMS: Anal. Calcd. for $C_{22}H_{27}NO_3$: 353; found: 354 $(M+H)^+$. (S,S)-isomer: ^{1}HNMR (CD_3OD) δ 7.41-7.30 (m, 5H), 7.20-7.14 (m, 3H), 7.06-7.00 (m, 2H), 5.85 (q, J = 6.6 Hz, 1H), 4.06 (s, 1H), 2.70-2.60 (m, 1H), 2.51 (dt, J = 6.6, 3.3 Hz, 1H), 2.44-2.31 (m, 2H), 1.75-1.65 (m, 1H), 1.65-1.54 (m, 3H), 1.50 (d, J = 6.8 Hz, 3H), 1.20 (s, 3H). LCMS: Anal. Calcd. for $C_{22}H_{27}NO_3$: 353; found: 354 $(M+H)^+$.

Step 3; (R)-2-(4-Hydroxy-4-methylpiperidin-1-yl)-2-phenylacetic acid: To a solution of (S)-1-phenylethyl (R)-2-(4-hydroxy-4-methylpiperidin-1-yl)-2-phenylacetate (0.185 g, 0.52 mmol) in dichloromethane (3 mL) was added trifluoroacetic acid (1 mL) and the mixture was stirred at room temperature for 2 hours. The volatiles were subsequently removed *in vacuo* and the residue was purified by reverse-phase preparative HPLC (Primesphere C-18, 20 x 100mm; CH_3CN-H_2O-0.1% TFA) to give the title compound (as TFA salt) as a pale bluish

solid (0,128 g, 98%). LCMS: Anal. Calcd. for $C_{14}H_{19}NO_3$: 249; found: 250 $(M+H)^+$.

Cap-16



A B *(R)-Cap-16*

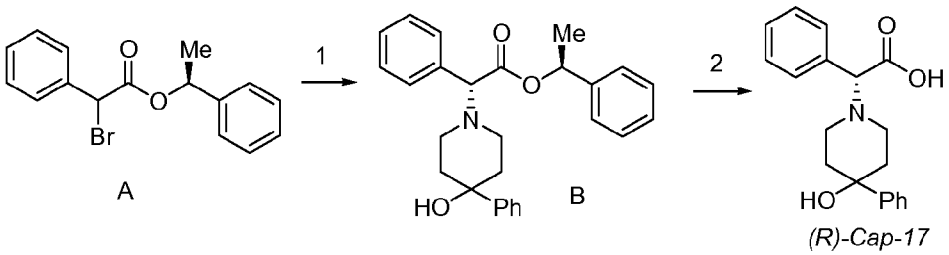
Step 1; (S)-1-Phenylethyl 2-(2-fluorophenyl)acetate: A mixture of 2-fluorophenylacetic acid (5.45 g, 35.4 mmol), (S)-1-phenylethanol (5.62 g, 46.0 mmol), EDCI (8.82 g, 46.0 mmol) and DMAP (0.561 g, 4.60 mmol) in CH_2Cl_2 (100 mL) was stirred at room temperature for 12 hours. The solvent was then concentrated and the residue partitioned with H_2O-ethyl acetate. The phases were separated and the aqueous layer back-extracted with ethyl acetate (2x). The combined organic phases were washed (H_2O, brine), dried (Na_2SO_4), filtered, and concentrated *in vacuo*. The residue was purified by silica gel chromatography (Biotage/ 0-20% ethyl acetate-hexane) to provide the title compound as a colorless oil (8.38 g, 92%). ^{1}HNMR (400 MHz, CD_3OD) δ 7.32 - 7.23 (m, 7H), 7.10-7.04 (m, 2), 5.85 (q, J = 6.5 Hz, 1H), 3.71 (s, 2H), 1.48 (d, J = 6.5 Hz, 3H).

Step 2; (R)-((S)-1-Phenylethyl) 2-(2-fluorophenyl)-2-(piperidin-1-yl)acetate: To a solution of (S)-1-phenylethyl 2-(2-fluorophenyl)acetate (5.00 g, 19.4 mmol) in THF (1200 mL) at 0°C was added DBU (6.19 g, 40.7 mmol) and the solution was allowed to warm to room temperature while stirring for 30 minutes. The solution was then cooled to -78 °C and a solution of CBr_4 (13.5 g, 40.7 mmol) in THF (100 mL) was added and the mixture was allowed to warm to -10 °C and stirred at this temperature for 2 hours. The reaction mixture was quenched with saturated aq. NH_4Cl and the layers were separated. The aqueous layer was back-extracted with ethyl acetate (2x) and the combined organic phases were washed (H_2O, brine), dried (Na_2SO_4), filtered, and concentrated *in vacuo*. To the residue was added piperidine (5.73 mL, 58.1 mmol) and the solution was stirred at room temperature for 24 hours. The volatiles were then concentrated *in vacuo* and the residue was purified by silica

gel chromatography (Biotage/ 0-30% diethyl ether-hexane) to provide a pure mixture of diastereomers (2:1 ratio by ^{1}HNMR) as a yellow oil (2.07 g, 31%), along with unreacted starting material (2.53 g, 51%). Further chromatography of the diastereomeric mixture (Biotage/ 0-10% diethyl ether-toluene) provided the title compound as a colorless oil (0.737 g, 11%). ^{1}HNMR (400 MHz, CD_3OD) δ 7.52 (ddd, J = 9.4, 7.6, 1.8 Hz, 1H), 7.33 – 7.40 (m, 1), 7.23 – 7.23 (m, 4H), 7.02 – 7.23 (m, 4H), 5.86 (q, J = 6.6 Hz, 1H), 4.45 (s, 1H), 2.39 – 2.45 (m, 4H), 1.52 – 1.58 (m, 4H), 1.40 – 1.42 (m, 1H), 1.38 (d, J = 6.6 Hz, 3H). LCMS: Anal. Calcd. for $C_{21}H_{24}FNO_2$: 341; found: 342 $(M+H)^+$.

Step 3; (R)-2-(2-fluorophenyl)-2-(piperidin-1-yl)acetic acid: A mixture of (R)-((S)-1-phenylethyl) 2-(2-fluorophenyl)-2-(piperidin-1-yl)acetate (0.737 g, 2.16 mmol) and 20% $Pd(OH)_2/C$ (0.070 g) in ethanol (30 mL) was hydrogenated at room temperature and atmospheric pressure (H_2 balloon) for 2 hours. The solution was then purged with Ar, filtered through diatomaceous earth (Celite®), and concentrated *in vacuo*. This provided the title compound as a colorless solid (0.503 g, 98%). ^{1}HNMR (400 MHz, CD_3OD) δ 7.65 (ddd, J = 9.1, 7.6, 1.5 Hz, 1H), 7.47-7.53 (m, 1H), 7.21-7.30 (m, 2H), 3.07-3.13 (m, 4H), 1.84 (br s, 4H), 1.62 (br s, 2H). LCMS: Anal. Calcd. for $C_{13}H_{16}FNO_2$: 237; found: 238 $(M+H)^+$.

Cap-17

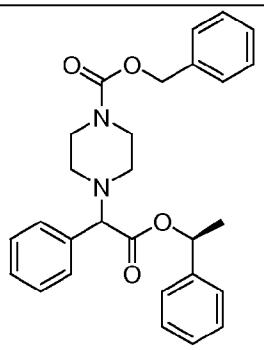


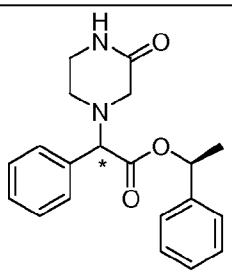
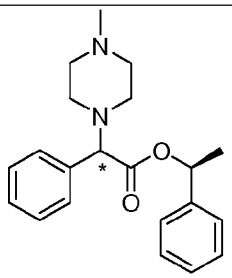
A B *(R)-Cap-17*

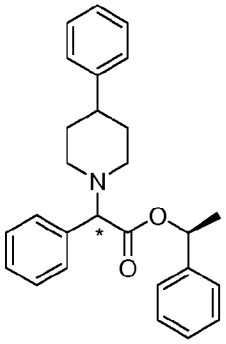
Step 1; (S)-1-Phenylethyl (R)-2-(4-hydroxy-4-phenylpiperidin-1-yl)- 2-phenylacetate: To a solution of (S)-1-phenylethyl 2-bromo-2-phenylacetate (1.50 g, 4.70 mmol) in THF (25 mL) was added triethylamine (1.31 mL, 9.42 mmol), followed by tetrabutylammonium iodide (0.347 g, 0.94 mmol). The reaction mixture was stirred at room temperature for 5 minutes and then a solution of 4-phenyl-4-hydroxypiperidine (1.00 g, 5.64 mmol) in THF (5 mL) was added. The mixture was stirred for 16 hours and then it was diluted with ethyl acetate (100 mL), washed (H_2O

x2, brine), dried ($MgSO_4$), filtered and concentrated. The residue was purified on a silica gel column (0-60% ethyl acetate-hexane) to provide an approximately 2:1 mixture of diastereomers, as judged by ^{1}HNMR. Separation of these isomers was performed using supercritical fluid chromatography (Chiralcel OJ-H, 30 x 250mm; 20% ethanol in CO_2 at 35 °C), to give first the (R)-isomer of the title compound (0.534 g, 27%) as a yellow oil and then the corresponding (S)-isomer (0.271 g, 14%), also as a yellow oil. (S,R)-isomer: ^{1}HNMR (400 MHz, CD_3OD) δ 7.55-7.47 (m, 4H), 7.44-7.25 (m, 10H), 7.25-7.17 (m, 1H), 5.88 (q, *J* = 6.6 Hz, 1H), 4.12 (s, 1H), 2.82-2.72 (m, 1H), 2.64 (dt, *J* = 11.1, 2.5 Hz, 1H), 2.58-2.52 (m, 1H), 2.40 (dt, *J* = 11.1, 2.5 Hz, 1H), 2.20 (dt, *J* = 12.1, 4.6 Hz, 1H), 2.10 (dt, *J* = 12.1, 4.6 Hz, 1H), 1.72-1.57 (m, 2H), 1.53 (d, *J* = 6.5 Hz, 3H). LCMS: Anal. Calcd. for $C_{27}H_{29}NO_3$: 415; found: 416 $(M+H)^+$; (S,S)-isomer: ^{1}HNMR (400 MHz, CD_3OD) δ 7.55-7.48 (m, 2H), 7.45-7.39 (m, 2H), 7.38-7.30 (m, 5H), 7.25-7.13 (m, 4H), 7.08-7.00 (m, 2H), 5.88 (q, *J* = 6.6 Hz, 1H), 4.12 (s, 1H), 2.95-2.85 (m, 1H), 2.68 (dt, *J* = 11.1, 2.5 Hz, 1H), 2.57-2.52 (m, 1H), 2.42 (dt, *J* = 11.1, 2.5 Hz, 1H), 2.25 (dt, *J* = 12.1, 4.6 Hz, 1H), 2.12 (dt, *J* = 12.1, 4.6 Hz, 1H), 1.73 (dd, *J* = 13.6, 3.0 Hz, 1H), 1.64 (dd, *J* = 13.6, 3.0 Hz, 1H), 1.40 (d, *J* = 6.6 Hz, 3H). LCMS: Anal. Calcd. for $C_{27}H_{29}NO_3$: 415; found: 416 $(M+H)^+$.

The following esters were prepared in similar fashion employing step 1 in the synthesis of *Cap*-17.

Intermediate-17a		Diastereomer 1: ^{1}H NMR (500 MHz, DMSO-d_6) δ ppm 1.36 (d, *J*=6.41 Hz, 3H) 2.23 - 2.51 (m, 4H) 3.35 (s, 4H) 4.25 (s, 1H) 5.05 (s, 2H) 5.82 (d, *J*=6.71 Hz, 1H) 7.15 - 7.52 (m, 15H). LCMS: Anal. Calcd. for: $C_{28}H_{30}N_2O_4$ 458.55; Found: 459.44 $(M+H)^+$.

		Diastereomer 2: ^{1}H NMR (500 MHz, DMSO-d_6) δ ppm 1.45 (d, *J*=6.71 Hz, 3H) 2.27 - 2.44 (m, 4H) 3.39 (s, 4H) 4.23 (s, 1H) 5.06 (s, 2H) 5.83 (d, *J*=6.71 Hz, 1H) 7.12 (dd, *J*=6.41, 3.05 Hz, 2H) 7.19 - 7.27 (m, 3H) 7.27 - 7.44 (m, 10H). LCMS: Anal. Calcd. for: $C_{28}H_{30}N_2O_4$ 458.55; Found: 459.44 $(M+H)^+$.
Intermediate -17b		Diasteromer 1: RT = 11.76 min (Cond'n II); LCMS: Anal. Calcd. for: $C_{20}H_{22}N_2O_3$ 338.4 Found: 339.39 $(M+H)^+$; Diastereomer 2: RT = 10.05 min (Cond'n II); LCMS: Anal. Calcd. for: $C_{20}H_{22}N_2O_3$ 338.4; Found: 339.39 $(M+H)^+$.
Intermediate -17c		Diastereomer 1: T_R = 4.55 min (Cond'n I); LCMS: Anal. Calcd. for: $C_{21}H_{26}N_2O_2$ 338.44 Found: 339.45 $(M+H)^+$; Diastereomer 2: T_R = 6.00 min (Cond'n I); LCMS: Anal. Calcd. for: $C_{21}H_{26}N_2O_2$ 338.44 Found: 339.45 $(M+H)^+$.

Intermediate -17d		Diastereomer 1: RT = 7.19 min (Cond'n I); LCMS: Anal. Calcd. for: $C_{27}H_{29}NO_2$ 399.52 Found: 400.48 $(M+H)^+$; Diastereomer 2: RT = 9.76 min (Cond'n I); LCMS: Anal. Calcd. for: $C_{27}H_{29}NO_2$ 399.52 Found: 400.48 $(M+H)^+$.

Chiral SFC Conditions for determining retention time for intermediates 17b-17d

Condition 1

Column: Chiralpak AD-H Column, 4.6X250 mm, 5µm

Solvents: 90% CO2 - 10% methanol with 0.1%DEA

Temp: 35 °C

Pressure: 150 bar

Flow rate: 2.0 mL/min.

UV monitored @ 220 nm

Injection: 1.0 mg/3mL methanol

Condition 2

Column: Chiralcel OD-H Column, 4.6X250 mm, 5µm

Solvents: 90% CO2 - 10% methanol with 0.1%DEA

Temp: 35 °C

Pressure: 150 bar

Flow rate: 2.0 mL/min.

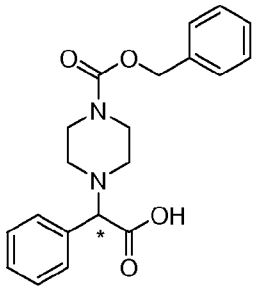
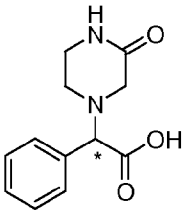
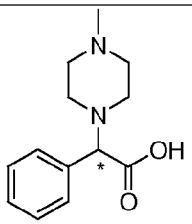
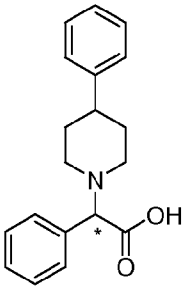
UV monitored @ 220 nm

Injection: 1.0 mg/mL methanol

Cap-17, Step 2; (R)-2-(4-Hydroxy-4-phenylpiperidin-1-yl)-2-phenylacetic acid: To a solution of (S)-1-phenylethyl (R)-2-(4-hydroxy-4-phenylpiperidin-1-yl)-2-

phenylacetate (0.350 g, 0.84 mmol) in dichloromethane (5 mL) was added trifluoroacetic acid (1 mL) and the mixture was stirred at room temperature for 2 hours. The volatiles were subsequently removed *in vacuo* and the residue was purified by reverse-phase preparative HPLC (Primesphere C-18, 20 x 100mm; CH_3CN-H_2O-0.1% TFA) to give the title compound (as TFA salt) as a white solid (0.230 g, 88%). LCMS: Anal. Calcd. for $C_{19}H_{21}NO_3$: 311; found: 312 $(M+H)^+$.

The following carboxylic acids were prepared in a similar fashion:

Cap-17a		RT = 2.21 (Cond'n II); ^1H NMR (500 MHz, DMSO-d_6) δ ppm 2.20 - 2.35 (m, 2H) 2.34 - 2.47 (m, 2H) 3.37 (s, 4H) 3.71 (s, 1H) 5.06 (s, 2H) 7.06 - 7.53 (m, 10H). LCMS: Anal. Calcd. for: $C_{20}H_{22}N_2O_4$ 354.40; Found: 355.38 $(M+H)^+$.
Cap-17b		RT = 0.27 (Cond'n III); LCMS: Anal. Calcd. for: $C_{12}H_{14}N_2O_3$ 234.25; Found: 235.22 $(M+H)^+$.
Cap-17c		RT = 0.48 (Cond'n II); LCMS: Anal. Calcd. for: $C_{13}H_{18}N_2O_2$ 234.29; Found: 235.31 $(M+H)^+$.
Cap-17d		RT = 2.21 (Cond'n I); LCMS: Anal. Calcd. for: $C_{19}H_{21}NO_2$ 295.38; Found: 296.33 $(M+H)^+$.

LCMS Conditions for determining retention time for Caps 17a-17d

Condition 1

Column: Phenomenex-Luna 4.6 X 50 mm S10

Start % B = 0

Fianl % B = 100

Gradicnt Timc = 4 min

Flow Rate = 4 mL/min

Wavelength = 220

Solvent A = 10% methanol – 90% H_2O – 0.1% TFA

Solvent B = 90% methanol – 10% H_2O – 0.1% TFA

Condition 2

Column: Waters-Sunfire 4.6 X 50 mm S5

Start % B = 0

Fianl % B = 100

Gradient Time = 2 min

Flow Rate = 4 mL/min

Wavelength = 220

Solvent A = 10% methanol – 90% H_2O – 0.1% TFA

Solvent B = 90% methanol – 10% H_2O – 0.1% TFA

Condition 3

Column: Phenomenex 10µ 3.0 X 50 mm

Start % B = 0

Fianl % B = 100

Gradient Time = 2 min

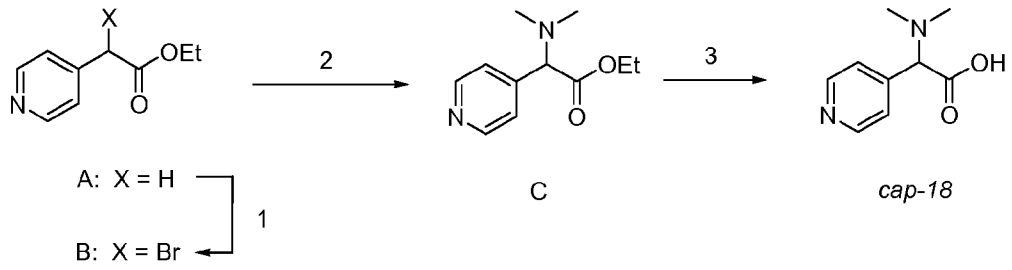
Flow Rate = 4 mL/min

Wavelength = 220

Solvcnt A = 10% mcthanol – 90% H_2O – 0.1% TFA

Solvent B = 90% methanol – 10% H_2O – 0.1% TFA

Cap-18



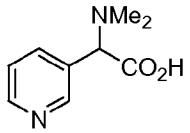
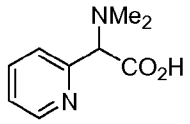
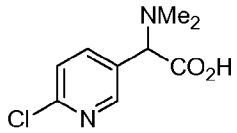
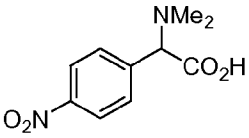
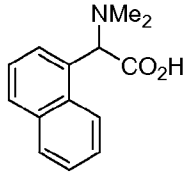
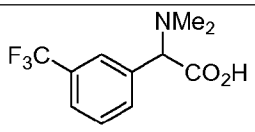
Step 1; (R,S)-Ethyl 2-(4-pyridyl)-2-bromoacetate: To a solution of ethyl 4-pyridylacetate (1.00 g, 6.05 mmol) in dry THF (150 mL) at 0 °C under argon was added DBU (0.99 mL, 6.66 mmol). The reaction mixture was allowed to warm to room temperature over 30 minutes and then it was cooled to -78 °C. To this mixture was added CBr_4 (2.21 g, 6.66 mmol) and stirring was continued at -78 °C for 2 hours. The reaction mixture was then quenched with sat. aq. NH_4Cl and the phases were separated. The organic phase was washed (brine), dried (Na_2SO_4), filtered, and concentrated *in vacuo*. The resulting yellow oil was immediately purified by flash chromatography (SiO_2/ hexane-ethyl acetate, 1:1) to provide the title compound (1.40 g, 95%) as a somewhat unstable yellow oil. ^{1}HNMR (400 MHz, $CDCl_3$) δ 8.62 (dd, *J* = 4.6, 1.8 Hz, 2H), 7.45 (dd, *J* = 4.6, 1.8 Hz, 2H), 5.24 (s, 1H), 4.21-4.29 (m, 2H), 1.28 (t, *J* = 7.1 Hz, 3H). LCMS: Anal. Calcd. for $C_9H_{10}BrNO_2$: 242, 244; found: 243, 245 $(M+H)^+$.

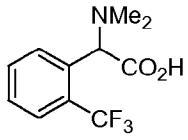
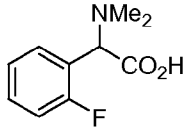
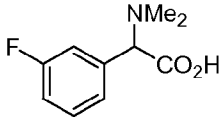
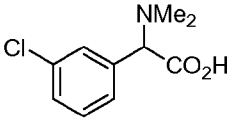
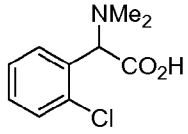
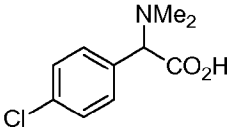
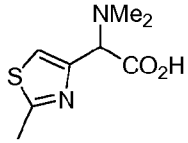
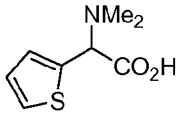
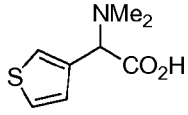
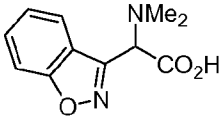
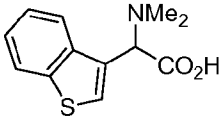
Step 2; (R,S)-Ethyl 2-(4-pyridyl)-2-(N,N-dimethylamino)acetate: To a solution of (R,S)-ethyl 2-(4-pyridyl)-2-bromoacetate (1.40 g, 8.48 mmol) in DMF (10 mL) at room temperature was added dimethylamine (2M in THF, 8.5 mL, 17.0 mmol). After completion of the reaction (as judged by tlc) the volatiles were removed *in vacuo* and the residue was purified by flash chromatography (Biotage, 40+M SiO_2 column; 50%-100% ethyl acetate-hexane) to provide the title compound (0.539 g, 31%) as a light yellow oil. ^{1}HNMR (400 MHz, $CDCl_3$) δ 8.58 (d, *J* = 6.0 Hz, 2H), 7.36 (d, *J* = 6.0 Hz, 2H), 4.17 (m, 2H), 3.92 (s, 1H), 2.27 (s, 6H), 1.22 (t, *J* = 7.0 Hz). LCMS: Anal. Calcd. for $C_{11}H_{16}N_2O_2$: 208; found: 209 $(M+H)^+$.

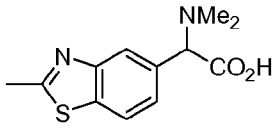
Step 3; (R,S)-2-(4-Pyridyl)-2-(N,N-dimethylamino)acetic acid: To a solution of (R,S)-ethyl 2-(4-pyridyl)-2-(N,N-dimethylamino)acetate (0.200 g, 0.960 mmol) in a mixture of THF-methanol-H_2O (1:1:1, 6 mL) was added powdered LiOH (0.120 g,

4.99 mmol) at room temperature. The solution was stirred for 3 hours and then it was acidified to pH 6 using 1N HCl. The aqueous phase was washed with ethyl acetate and then it was lyophilized to give the dihydrochloride of the title compound as a yellow solid (containing LiCl). The product was used as such in subsequent steps. ^{1}HNMR (400 MHz, DMSO-d_6) δ 8.49 (d, J = 5.7 Hz, 2H), 7.34 (d, J = 5.7 Hz, 2H), 3.56 (s, 1H), 2.21 (s, 6H).

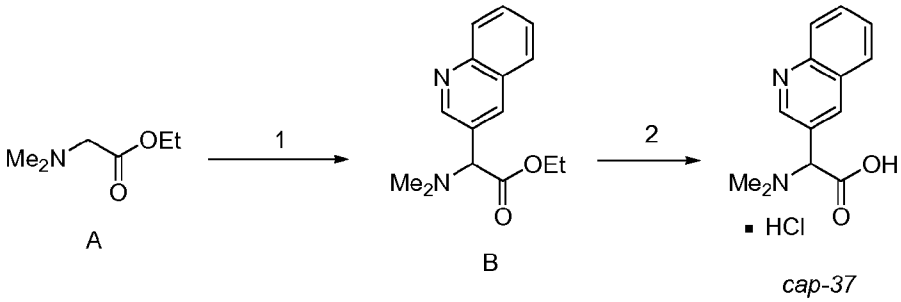
The following examples were prepared in similar fashion using the method described in Example 4;

Cap-19		LCMS: Anal. Calcd. for $C_9H_{12}N_2O_2$: 180; found: 181 $(M+H)^+$.
Cap-20		LCMS: no ionization. ^{1}HNMR (400 MHz, CD_3OD) δ 8.55 (d, J = 4.3 Hz, 1H), 7.84 (app t, J = 5.3 Hz, 1H), 7.61 (d, J = 7.8 Hz, 1H), 7.37 (app t, J = 5.3 Hz, 1H), 4.35 (s, 1H), 2.60 (s, 6H).
Cap-21		LCMS: Anal. Calcd. for $C_9H_{11Cl}N_2O_2$: 214, 216; found: 215, 217 $(M+H)^+$.
Cap-22		LCMS: Anal. Calcd. for $C_{10}H_{12}N_2O_4$: 224; found: 225 $(M+H)^+$.
Cap-23		LCMS: Anal. Calcd. for $C_{14}H_{15}NO_2$: 247; found: 248 $(M+H)^+$.
Cap-24		LCMS: Anal. Calcd. for $C_{11}H_{12}F_3NO_2$: 247; found: 248 $(M+H)^+$.

Cap-25		LCMS: Anal. Calcd. for $C_{11}H_{12}F_3NO_2$: 247; found: 248 $(M+H)^+$.
Cap-26		LCMS: Anal. Calcd. for $C_{10}H_{12}FNO_2$: 247; found: 248 $(M+H)^+$.
Cap-27		LCMS: Anal. Calcd. for $C_{10}H_{12}FNO_2$: 247; found: 248 $(M+H)^+$.
Cap-28		LCMS: Anal. Calcd. for $C_{10}H_{12}ClNO_2$: 213, 215; found: 214, 217 $(M+H)^+$.
Cap-29		LCMS: Anal. Calcd. for $C_{10}H_{12}ClNO_2$: 213, 215; found: 214, 217 $(M+H)^+$.
Cap-30		LCMS: Anal. Calcd. for $C_{10}H_{12}ClNO_2$: 213, 215; found: 214, 217 $(M+H)^+$.
Cap-31		LCMS: Anal. Calcd. for $C_8H_{11}N_2O_2S$: 200; found: 201 $(M+H)^+$.
Cap-32		LCMS: Anal. Calcd. for $C_8H_{11}NO_2S$: 185; found: 186 $(M+H)^+$.
Cap-33		LCMS: Anal. Calcd. for $C_8H_{11}NO_2S$: 185; found: 186 $(M+H)^+$.
Cap-34		LCMS: Anal. Calcd. for $C_{11}H_{12}N_2O_3$: 220; found: 221 $(M+H)^+$.
Cap-35		LCMS: Anal. Calcd. for $C_{12}H_{13}NO_2S$: 235; found: 236 $(M+H)^+$.

Cap-36		LCMS: Anal. Calcd. for $C_{12}H_{14}N_2O_2S$: 250; found: 251 $(M+H)^+$.

Cap-37



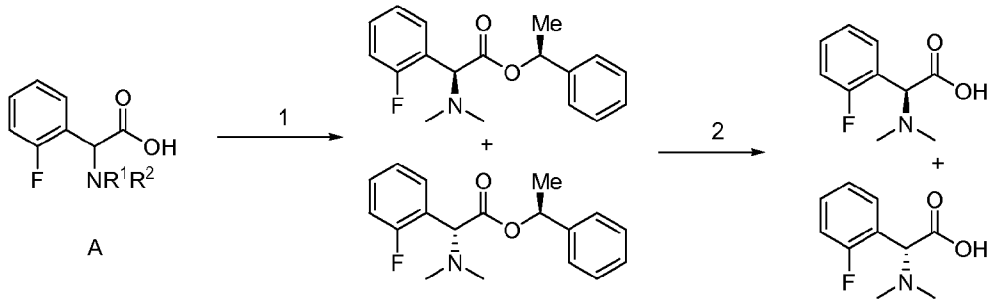
A B *cap-37*

Step 1; (R,S)-Ethyl 2-(quinolin-3-yl)-2-(N,N-dimethylamino)-acetate: A mixture of ethyl N,N-dimethylaminoacetate (0.462 g, 3.54 mmol), K_3PO_4 (1.90 g, 8.95 mmol), $Pd(t\text{-}Bu_3P)_2$ (0.090 g, 0.176 mmol) and toluene (10 mL) was degassed with a stream of Ar bubbles for 15 minutes. The reaction mixture was then heated at 100 °C for 12 hours, after which it was cooled to room temperature and poured into H_2O. The mixture was extracted with ethyl acetate (2x) and the combined organic phases were washed (H_2O, brine), dried (Na_2SO_4), filtered, and concentrated *in vacuo*. The residue was purified first by reverse-phase preparative HPLC (Primesphere C-18, 30 x 100mm; CH_3CN-H_2O-5 mM NH_4OAc) and then by flash chromatography (SiO_2/ hexane-ethyl acetate, 1:1) to provide the title compound (0.128 g, 17%) as an orange oil. ^{1}HNMR (400 MHz, $CDCl_3$) δ 8.90 (d, J = 2.0 Hz, 1H), 8.32 (d, J = 2.0 Hz, 1H), 8.03-8.01 (m, 2H), 7.77 (ddd, J = 8.3, 6.8, 1.5 Hz, 1H), 7.62 (ddd, J = 8.3, 6.8, 1.5 Hz, 1H), 4.35 (s, 1H), 4.13 (m, 2H), 2.22 (s, 6H), 1.15 (t, J = 7.0 Hz, 3H). LCMS: Anal. Calcd. for $C_{15}H_{18}N_2O_2$: 258; found: 259 $(M+H)^+$.

Step 2; (R,S) 2-(Quinolin-3-yl)-2-(N,N-dimethylamino)acetic acid: A mixture of (R,S)-ethyl 2-(quinolin-3-yl)-2-(N,N-dimethylamino)acetate (0.122 g, 0.472 mmol) and 6M HCl (3 mL) was heated at 100 °C for 12 hours. The solvent was removed *in vacuo* to provide the dihydrochloride of the title compound (0.169 g, >100%) as a light yellow foam. The unpurified material was used in subsequent

steps without further purification. LCMS: Anal. Calcd. for $C_{13}H_{14}N_2O_2$: 230; found: 231 $(M+H)^+$.

Cap-38



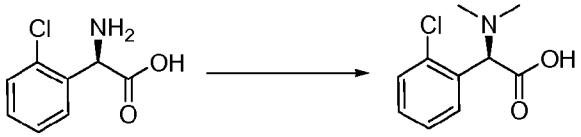
Step 1; (R)-((S)-1-phenylethyl) 2-(dimethylamino)-2-(2-fluorophenyl)acetate and (S)-((S)-1-phenylethyl) 2-(dimethylamino)-2-(2-fluorophenyl)acetate: To a mixture of (RS)-2-(dimethylamino)-2-(2-fluorophenyl)acetic acid (2.60 g, 13.19 mmol), DMAP (0.209 g, 1.71 mmol) and (S)-1-phenylethanol (2.09 g, 17.15 mmol) in CH_2Cl_2 (40 mL) was added EDCI (3.29 g, 17.15 mmol) and the mixture was allowed to stir at room temperature for 12 hours. The solvent was then removed *in vacuo* and the residue partitioned with ethyl acetate-H_2O. The layers were separated, the aqueous layer was back-extracted with ethyl acetate (2x) and the combined organic phases were washed (H_2O, brine), dried (Na_2SO_4), filtered, and concentrated *in vacuo*. The residue was purified by silica gel chromatography (Biotage/ 0-50% diethyl ether-hexane). The resulting pure diastereomeric mixture was then separated by reverse-phase preparative HPLC (Primesphere C-18, 30 x 100mm; CH_3CN-H_2O-0.1% TFA) to give first (S)-1-phenethyl (R)-2-(dimethylamino)-2-(2-fluorophenyl)acetate (0.501 g, 13%) and then (S)-1-phenethyl (S)-2-(dimethylamino)-2-(2-fluorophenyl)-acetate (0.727 g. 18%), both as their TFA salts. (S,R)-isomer: ^{1}HNMR (400 MHz, CD_3OD) δ 7.65 - 7.70 (m, 1H), 7.55-7.60 (ddd, J = 9.4, 8.1, 1.5 Hz, 1H), 7.36-7.41 (m, 2H), 7.28-7.34 (m, 5H), 6.04 (q, J = 6.5 Hz, 1H), 5.60 (s, 1H), 2.84 (s, 6H), 1.43 (d, J = 6.5 Hz, 3H). LCMS: Anal. Calcd. for $C_{18}H_{20}FNO_2$: 301; found: 302 $(M+H)^+$; (S,S)-isomer: ^{1}HNMR (400 MHz, CD_3OD) δ 7.58-7.63 (m, 1H), 7.18-7.31 (m, 6H), 7.00 (dd, J = 8.5, 1.5 Hz, 2H), 6.02 (q, J = 6.5

Hz, 1H), 5.60 (s, 1H), 2.88 (s, 6H), 1.54 (d, J = 6.5 Hz, 3H). LCMS: Anal. Calcd. for $C_{18}H_{20}FNO_2$: 301; found: 302 $(M+H)^+$.

Step 2; (R)-2-(dimethylamino)-2-(2-fluorophenyl)acetic acid: A mixture of (R)-((S)-1-phenylethyl) 2-(dimethylamino)-2-(2-fluorophenyl)acetate TFA salt (1.25 g, 3.01 mmol) and 20% $Pd(OH)_2/C$ (0.125 g) in ethanol (30 mL) was hydrogenated at room temperature and atmospheric pressure (H_2 balloon) for 4 hours. The solution was then purged with Ar, filtered through diatomaceous earth (Celite®), and concentrated *in vacuo*. This gave the title compound as a colorless solid (0.503 g, 98%). ^{1}HNMR (400 MHz, CD_3OD) δ 7.53-7.63 (m, 2H), 7.33-7.38 (m, 2H), 5.36 (s, 1H), 2.86 (s, 6H). LCMS: Anal. Calcd. for $C_{10}H_{12}FNO_2$: 197; found: 198 $(M+H)^+$.

The S-isomer could be obtained from (S)-((S)-1-phenylethyl) 2-(dimethylamino)-2-(2-fluorophenyl)acetate TFA salt in similar fashion.

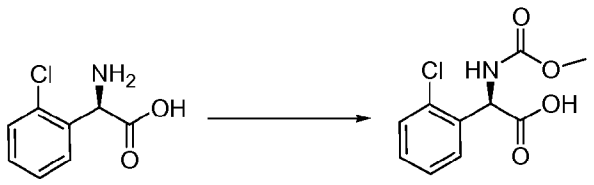
Cap-39



cap-39

A mixture of (R)-(2-chlorophenyl)glycine (0.300 g, 1.62 mmol), formaldehyde (35% aqueous solution, 0.80 mL, 3.23 mmol) and 20% $Pd(OH)_2/C$ (0.050 g) was hydrogenated at room temperature and atmospheric pressure (H_2 balloon) for 4 hours. The solution was then purged with Ar, filtered through diatomaceous earth (Celite®) and concentrated *in vacuo*. The residue was purified by reverse-phase preparative HPLC (Primesphere C-18, 30 x 100mm; CH_3CN-H_2O-0.1% TFA) to give theTFA salt of the title compound (R)-2-(dimethylamino)-2-(2-chlorophenyl)acetic acid as a colorless oil (0.290 g, 55%). ^{1}H NMR (400 MHz, CD_3OD) δ 7.59-7.65 (m, 2H), 7.45-7.53 (m, 2H), 5.40 (s, 1H), 2.87 (s, 6H). LCMS: Anal. Calcd. for $C_{10}H_{12}ClNO_2$: 213, 215; found: 214, 216 $(M+H)^+$.

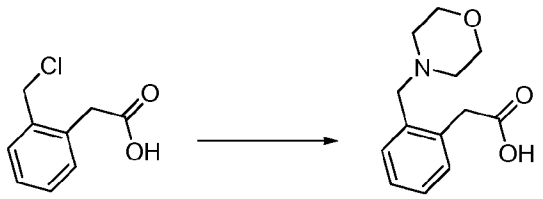
Cap-40



cap-40

To an ice-cold solution of (R)-(2-chlorophenyl)glycine (1.00 g, 5.38 mmol) and NaOH (0.862 g, 21.6 mmol) in H_2O (5.5 mL) was added methyl chloroformate (1.00 mL, 13.5 mmol) dropwise. The mixture was allowed to stir at 0 °C for 1 hour and then it was acidified by the addition of conc. HCl (2.5 mL). The mixture was extracted with ethyl acetate (2x) and the combined organic phase was washed (H_2O, brine), dried (Na_2SO_4), filtered, and concentrated *in vacuo* to give the title compound (R)-2-(methoxycarbonylamino)-2-(2-chlorophenyl)acetic acid as a yellow-orange foam (1.31 g, 96%). ^{1}H NMR (400 MHz, CD_3OD) δ 7.39 – 7.43 (m, 2H), 7.29 – 7.31 (m, 2H), 5.69 (s, 1H), 3.65 (s, 3H). LCMS: Anal. Calcd. for $C_{10}H_{10}ClNO_4$: 243, 245; found: 244, 246 $(M+H)^+$.

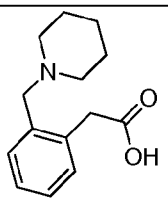
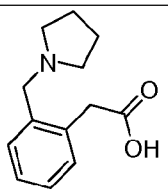
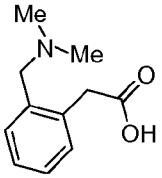
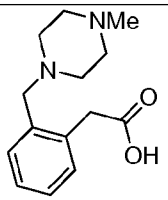
Cap-41



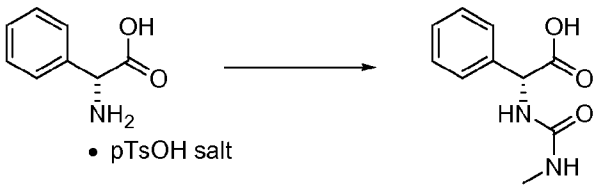
cap-41

To a suspension of 2-(2-(chloromethyl)phenyl)acetic acid (2.00 g, 10.8 mmol) in THF (20 mL) was added morpholine (1.89 g, 21.7 mmol) and the solution was stirred at room temperature for 3 hours. The reaction mixture was then diluted with ethyl acetate and extracted with H_2O (2x). The aqueous phase was lyophilized and the residue was purified by silica gel chromatography (Biotage/ 0-10% methanol-CH_2Cl_2) to give the title compound 2-(2-(Morpholinomethyl)phenyl)acetic acid as a colorless solid (2.22 g, 87%). ^{1}HNMR (400 MHz, CD_3OD) δ 7.37-7.44 (m, 3H), 7.29-7.33 (m, 1H), 4.24 (s, 2H), 3.83 (br s, 4H), 3.68 (s, 2H), 3.14 (br s, 4H). LCMS: Anal. Calcd. for $C_{13}H_{17}NO_3$: 235; found: 236 $(M+H)^+$.

The following examples were similarly prepared using the method described for *Cap*-41:

Cap-42		LCMS: Anal. Calcd. for $C_{14}H_{19}NO_2$: 233; found: 234 $(M+H)^+$.
Cap-43		LCMS: Anal. Calcd. for $C_{13}H_{17}NO_2$: 219; found: 220 $(M+H)^+$.
Cap-44		LCMS: Anal. Calcd. for $C_{11}H_{15}NO_2$: 193; found: 194 $(M+H)^+$.
Cap-45		LCMS: Anal. Calcd. for $C_{14}H_{20}N_2O_2$: 248; found: 249 $(M+H)^+$.

Cap-45

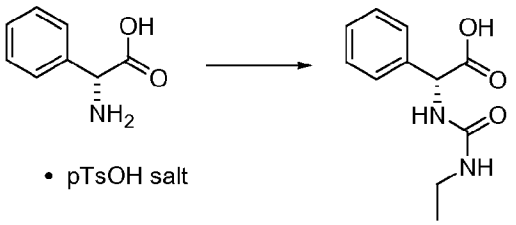


Cap-45

HMDS (1.85 mL, 8.77 mmol) was added to a suspension of (R)-2-amino-2-phenylacetic acid p-toluenesulfonate (2.83 g, 8.77 mmol) in CH_2Cl_2 (10 mL) and the mixture was stirred at room temperature for 30 minutes. Methyl isocyanate (0.5 g, 8.77 mmol) was added in one portion stirring continued for 30 minutes. The reaction was quenched by addition of H_2O (5 mL) and the resulting precipitate was filtered, washed with H_2O and n-hexanes, and dried under vacuum. (R)-2-(3-methylureido)-

2-phenylacetic acid (1.5 g; 82 %).was recovered as a white solid and it was used without further purification. ^{1}H NMR (500 MHz, DMSO-d_6) δ ppm 2.54 (d, *J*=4.88 Hz, 3H) 5.17 (d, *J*=7.93 Hz, 1H) 5.95 (q, *J*=4.48 Hz, 1H) 6.66 (d, *J*=7.93 Hz, 1H) 7.26 - 7.38 (m, 5H) 12.67 (s, 1H). LCMS: Anal. Calcd. for $C_{10}H_{12}N_2O_3$ 208.08 found 209.121 $(M+H)^+$; HPLC Phenomenex C-18 3.0 × 46 mm, 0 to 100% B over 2 minutes, 1 minute hold time, A = 90% water, 10% methanol, 0.1% TFA, B = 10% water, 90% methanol, 0.1% TFA, RT = 1.38 min, 90% homogeneity index.

Cap-46

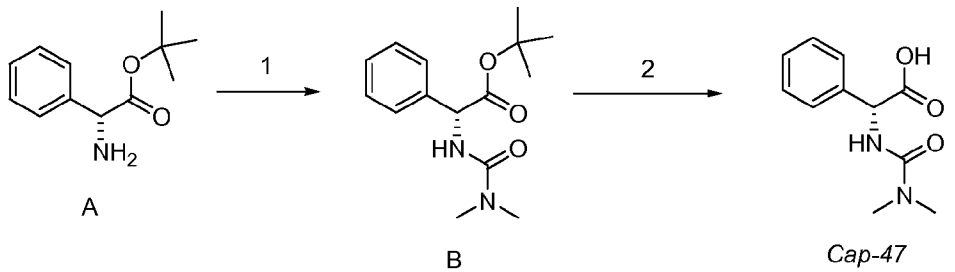


cap-46

The desired product was prepared according to the method described for *Cap-45*. ^{1}H NMR (500 MHz, DMSO-d_6) δ ppm 0.96 (t, *J*=7.17 Hz, 3H) 2.94 - 3.05 (m, 2H) 5.17 (d, *J*=7.93 Hz, 1H) 6.05 (t, *J*=5.19 Hz, 1H) 6.60 (d, *J*=7.63 Hz, 1H) 7.26 - 7.38 (m, 5H) 12.68 (s, 1H). LCMS: Anal. Calcd. for $C_{11}H_{14}N_2O_3$ 222.10 found 209.121 $(M+H)^+$.

HPLC XTERRA C-18 3.0 × 506 mm, 0 to 100% B over 2 minutes, 1 minutes hold time, A = 90% water, 10% methanol, 0.2% H_3PO_4, B = 10% water, 90% methanol, 0.2% H_3PO_4, RT = 0.87 min, 90% homogeneity index.

Cap-47



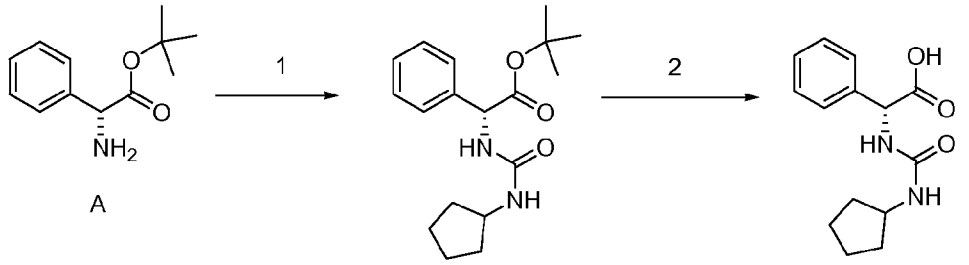
A B *Cap-47*

Step 1; (R)-tert-butyl 2-(3,3-dimethylureido)-2-phenylacetate: To a stirred solution of (R)-tert–butyl-2-amino-2-phenylacetate (1.0 g, 4.10 mmol) and Hunig's

base (1.79 mL, 10.25 mmol) in DMF (40 mL) was added dimethylcarbamoyl chloride (0.38 mL, 4.18 mmol) dropwise over 10 minutes. After stirring at room temperature for 3 hours, the reaction was concentrated under reduced pressure and the resulting residue was dissolved in ethyl acetate. The organic layer was washed with H_2O, 1N aq. HCl and brine, dried ($MgSO_4$), filtered and concentrated under reduced pressure. (R)-tert-butyl 2-(3,3-dimethylureido)-2-phenylacetate was obtained as a white solid (0.86 g; 75%) and used without further purification. ^1H NMR (500 MHz, DMSO-d_6) δ ppm 1.33 (s, 9H) 2.82 (s, 6H) 5.17 (d, *J*=7.63 Hz, 1H) 6.55 (d, *J*=7.32 Hz, 1H) 7.24 - 7.41 (m, 5H). LCMS: Anal. Calcd. for $C_{15}H_{22}N_2O_3$ 278.16 found 279.23 $(M+H)^+$; HPLC Phenomenex LUNA C-18 4.6 × 50 mm, 0 to 100% B over 4 minutes, 1 minutes hold time, A = 90% water, 10% methanol, 0.1% TFA, B = 10% water, 90% methanol, 0.1% TFA, RT = 2.26 min, 97% homogeneity index.

Step 2; (R)-2-(3,3-dimethylureido)-2-phenylacetic acid: To a stirred solution of ((R)-tert-butyl 2-(3,3-dimethylureido)-2-phenylacetate (0.86 g, 3.10 mmol) in CH_2Cl_2 (250 mL) was added TFA (15 mL) dropwise and the resulting solution was stirred at rt for 3 h. The desired compound was then precipitated out of solution with a mixture of EtOAC:Hexanes (5:20), filtered off and dried under reduced pressure. (R)-2-(3,3-dimethylureido)-2-phenylacetic acid was isolated as a white solid (0.59g, 86%) and used without further purification. ^1H NMR (500 MHz, DMSO-d_6) δ ppm 2.82 (s, 6H) 5.22 (d, *J*=7.32 Hz, 1H) 6.58 (d, *J*=7.32 Hz, 1H) 7.28 (t, *J*=7.17 Hz, 1H) 7.33 (t, *J*=7.32 Hz, 2H) 7.38 - 7.43 (m, 2H) 12.65 (s, 1H). LCMS: Anal. Calcd. for $C_{11}H_{14}N_2O_3$: 222.24; found: 223.21 $(M+H)^+$. HPLC XTERRA C-18 3.0 × 50 mm, 0 to 100% B over 2 minutes, 1 minutes hold time, A = 90% water, 10% methanol, 0.2% H_3PO_4, B = 10% water, 90% methanol, 0.2% H_3PO_4, RT = 0.75 min, 93% homogeneity index.

Cap-48



Step 1; (R)-tert-butyl 2-(3-cyclopentylureido)-2-phenylacetate: To a stirred solution of (R)-2-amino-2-phenylacetic acid hydrochloride (1.0 g, 4.10 mmol) and Hunig's base (1.0 mL, 6.15 mmol) in DMF (15 mL) was added cyclopentyl isocyanate (0.46 mL, 4.10 mmol) dropwise and over 10 minutes. After stirring at room temperature for 3 hours, the reaction was concentrated under reduced pressure and the resulting residue was taken up in ethyl acetate. The organic layer was washed with H_2O and brine, dried ($MgSO_4$), filtered, and concentrated under reduced pressure. (R)-tert-butyl 2-(3-cyclopentylureido)-2-phenylacetate was obtained as an opaque oil (1.32 g; 100 %) and used without further purification. ^{1}H NMR (500 MHz, CD_3Cl-D) δ ppm 1.50 - 1.57 (m, 2H) 1.58 - 1.66 (m, 2H) 1.87 - 1.97 (m, 2H) 3.89 - 3.98 (m, 1H) 5.37 (s, 1H) 7.26 - 7.38 (m, 5H). LCMS: Anal. Calcd. for $C_{18}H_{26}N_2O_3$ 318.19 found 319.21 $(M+H)^+$; HPLC XTERRA C-18 3.0 × 50 mm, 0 to 100% B over 4 minutes, 1 minutes hold time, A = 90% water, 10% methanol, 0.1% TFA, B = 10% water, 90% methanol, 0.1% TFA, RT = 2.82 min, 96% homogeneity index.

Step 2; (R)-2-(3-cyclopentylureido)-2-phenylacetic acid: To a stirred solution of (R)-tert-butyl 2-(3-cyclopentylureido)-2-phenylacetate (1.31 g, 4.10 mmol) in CH_2Cl_2 (25 mL) was added TFA (4 mL) and triethylsilane (1.64 mL; 10.3 mmol) dropwise, and the resulting solution was stirred at room temperature for 6 hours. The volatile components were removed under reduced pressure and the crude product was recrystallized in ethyl acetate/pentanes to yield (R)-2-(3-cyclopentylureido)-2-phenylacetic acid as a white solid (0.69 g, 64%). ^{1}H NMR (500 MHz, DMSO-d_6) δ ppm 1.17 - 1.35 (m, 2H) 1.42 - 1.52 (m, 2H) 1.53 - 1.64 (m, 2H) 1.67 - 1.80 (m, 2H) 3.75 - 3.89 (m, 1H) 5.17 (d, *J*=7.93 Hz, 1H) 6.12 (d, *J*=7.32 Hz, 1H) 6.48 (d, *J*=7.93 Hz, 1H) 7.24 - 7.40 (m, 5H) 12.73 (s, 1H). LCMS: Anal. Calcd. for $C_{14}H_{18}N_2O_3$:

262.31; found: 263.15 $(M+H)^+$. HPLC XTERRA C-18 3.0 × 50 mm, 0 to 100% B over 2 minutes, 1 minutes hold time, A = 90% water, 10% methanol, 0.2% H_3PO_4, B = 10% water, 90% methanol, 0.2% H_3PO_4, RT = 1.24 min, 100% homogeneity index.

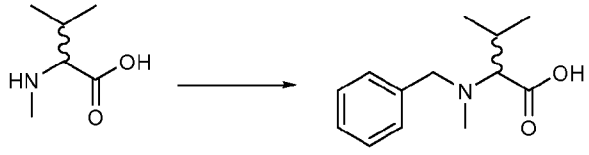
Cap-49



cap-49

To a stirred solution of 2-(benzylamino)acetic acid (2.0 g, 12.1 mmol) in formic acid (91 mL) was added formaldehyde (6.94 mL, 93.2 mmol). After five hours at 70 °C, the reaction mixture was concentrated under reduced pressure to 20 mL and a white solid precipitated. Following filtration, the mother liquors were collected and further concentrated under reduced pressure providing the crude product. Purification by reverse-phase preparative HPLC (Xterra 30 X 100 mm, detection at 220 nm, flow rate 35 mL/min, 0 to 35% B over 8 min; A = 90% water, 10 % methanol, 0.1% TFA, B = 10% water, 90 % methanol, 0.1% TFA) provided the title compound 2-(benzyl(methyl)-amino)acetic acid as its TFA salt (723 mg, 33%) as a colorless wax. ^1H NMR (300 MHz, DMSO-d_6) δ ppm 2.75 (s, 3H) 4.04 (s, 2H) 4.34 (s, 2H) 7.29 - 7.68 (m, 5H). LCMS: Anal. Calcd. for: $C_{10}H_{13}NO_2$ 179.22; Found: 180.20 $(M+H)^+$.

Cap-50

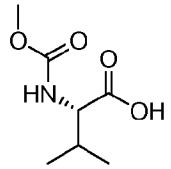


Cap-50

To a stirred solution of 3-methyl-2-(methylamino)butanoic acid (0.50 g, 3.81 mmol) in water (30 mL) was added K_2CO_3 (2.63 g, 19.1 mmol) and benzyl chloride (1.32 g, 11.4 mmol). The reaction mixture was stirred at ambient temperature for 18 hours. The reaction mixture was extracted with ethyl acetate (30 mL x 2) and the aqueous layer was concentrated under reduced pressure providing the crude product which was purified by reverse-phase preparative HPLC (Xterra 30 x 100mm,

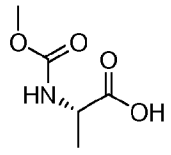
detection at 220 nm, flow rate 40 mL/min, 20 to 80% B over 6 min; A = 90% water, 10 % methanol, 0.1% TFA, B = 10% water, 90 % methanol, 0.1% TFA) to provide 2-(benzyl(methyl)amino)-3-methylbutanoic acid, TFA salt (126 mg, 19%) as a colorless wax. ^{1}H NMR (500 MHz, DMSO-d_6) δ ppm 0.98 (d, 3H) 1.07 (d, 3H) 2.33 - 2.48 (m, 1H) 2.54 - 2.78 (m, 3H) 3.69 (s, 1H) 4.24 (s, 2H) 7.29 - 7.65 (m, 5H). LCMS: Anal. Calcd. for: $C_{13}H_{19}NO_2$ 221.30; Found: 222.28 $(M+H)^+$.

Cap-51



Na_2CO_3 (1.83g, 17.2 mmol) was added to NaOH (33 mL of 1M/H_2O, 33 mmol) solution of L-valine (3.9 g, 33.29 mmol) and the resulting solution was cooled with ice-water bath. Methyl chloroformate (2.8 mL, 36.1 mmol) was added drop-wise over 15 min, the cooling bath was removed and the reaction mixture was stirred at ambient temperature for 3.25 hr. The reaction mixture was washed with ether (50 mL, 3x), and the aqueous phase was cooled with ice-water bath and acidified with concentrated HCl to a pH region of 1-2, and extracted with CH_2Cl_2 (50 mL, 3x). The organic phase was dried ($MgSO_4$), filtered, and concentrated *in vacuo* to afford *Cap*-51 as a white solid (6 g). ^{1}H NMR for the dominant rotamer (DMSO-d_6, δ = 2.5 ppm, 500 MHz): 12.54 (s, 1H), 7.33 (d, J = 8.6, 1H), 3.84 (dd, J = 8.4, 6.0, 1H), 3.54 (s, 3H), 2.03 (m, 1H), 0.87 (m, 6H). HRMS: Anal. Calcd. for $[M+H]^+$ $C_7H_{14}NO_4$: 176.0923; found 176.0922

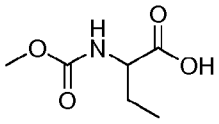
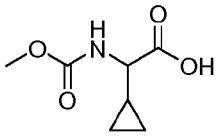
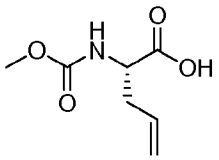
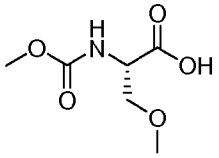
Cap-52

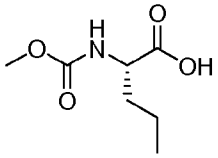
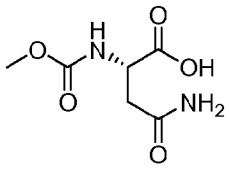
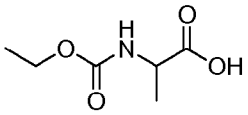
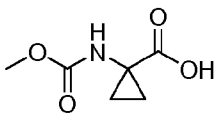
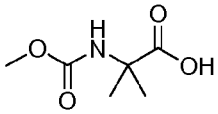


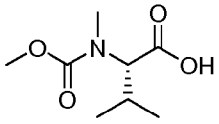
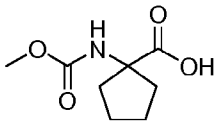
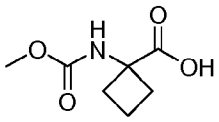
Cap-52 was synthesized from L-alanine according to the procedure described for the synthesis of *Cap*-51. For characterization purposes, a portion of the crude material was purified by a reverse phase HPLC (H_2O/MeOH/TFA) to afford *Cap*-52 as a colorless viscous oil. ^{1}H NMR (DMSO-d_6, δ = 2.5 ppm, 500 MHz): 12.49 (br s,

1H), 7.43 (d, J = 7.3, 0.88H), 7.09 (app br s, 0.12H), 3.97 (m, 1H), 3.53 (s, 3H), 1.25 (d, J = 7.3, 3H).

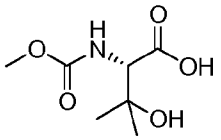
Cap-53 to -64 were prepared from appropriate starting materials according to the procedure described for the synthesis of *Cap*-51, with noted modifications if any.

Cap	Structure	Data
Cap-53a: (R) *Cap-53b*: (S)		^{1}H NMR (DMSO-d_6, δ = 2.5 ppm, 500 MHz): δ 12.51 (br s, 1H), 7.4 (d, J = 7.9, 0.9H), 7.06 (app s, 0.1H), 3.86-3.82 (m, 1H), 3.53 (s, 3H), 1.75-1.67 (m, 1H), 1.62-1.54 (m, 1H), 0.88 (d, J = 7.3, 3H). RT = 0.77 minutes (Cond. 2); LC/MS: Anal. Calcd. for [M+Na]$^+$ $C_6H_{11}NNaO_4$: 184.06; found 184.07. HRMS Calcd. for [M+Na]$^+$ $C_6H_{11}NNaO_4$: 184.0586; found 184.0592.
Cap-54a: (R) *Cap-54b*: (S)		^{1}H NMR (DMSO-d_6, δ = 2.5 ppm, 500 MHz): δ 12.48 (s, 1H), 7.58 (d, J = 7.6, 0.9H), 7.25 (app s, 0.1H), 3.52 (s, 3H), 3.36-3.33 (m, 1H), 1.10-1.01 (m, 1H), 0.54-0.49 (m, 1H), 0.46-0.40 (m, 1H), 0.39-0.35 (m, 1H), 0.31-0.21 (m, 1H). HRMS Calcd. for [M+H]$^+$ $C_7H_{12}NO_4$: 174.0766; found 174.0771
Cap-55		^{1}H NMR (DMSO-d_6, δ = 2.5 ppm, 500 MHz): δ 12.62 (s, 1H), 7.42 (d, J = 8.2, 0.9H), 7.07 (app s, 0.1H), 5.80-5.72 (m, 1H), 5.10 (d, J = 17.1, 1H), 5.04 (d, J = 10.4, 1H), 4.01-3.96 (m, 1H), 3.53 (s, 3H), 2.47-2.42 (m, 1H), 2.35-2.29 (m, 1H).
Cap-56		^{1}H NMR (DMSO-d_6, δ = 2.5 ppm, 500 MHz): δ 12.75 (s, 1H), 7.38 (d, J = 8.3, 0.9H), 6.96 (app s, 0.1H), 4.20-4.16 (m, 1H), 3.60-3.55 (m, 2H), 3.54 (s, 3H), 3.24 (s, 3H).

Cap-57		^{1}H NMR (DMSO-d_6, δ = 2.5 ppm, 500 MHz): δ 12.50 (s, 1H), 8.02 (d, *J* = 7.7, 0.08H), 7.40 (d, *J* = 7.9, 0.76H), 7.19 (d, *J* = 8.2, 0.07H), 7.07 (d, *J* = 6.7, 0.09H), 4.21-4.12 (m, 0.08H), 4.06-3.97 (m, 0.07H), 3.96-3.80 (m, 0.85H), 3.53 (s, 3H), 1.69-1.51 (m, 2H), 1.39-1.26 (m, 2H), 0.85 (t, *J* = 7.4, 3H). LC (Cond. 2): RT = 1.39 LC/MS: Anal. Calcd. for $[M+H]^-$ $C_7H_{14}NO_4$: 176.09; found 176.06.
Cap-58		^{1}H NMR (DMSO-d_6, δ = 2.5 ppm, 500 MHz): δ 12.63 (bs, 1H), 7.35 (s,1H), 7.31 (d, *J* = 8.2, 1H), 6.92 (s, 1H), 4.33-4.29 (m, 1H), 3.54 (s, 3H), 2.54(dd, *J* = 15.5, 5.4, 1H), 2.43 (dd, *J* = 15.6, 8.0, 1H). RT = 0.16 min (Cond. 2); LC/MS: Anal. Calcd. for $[M+H]^+$ $C_6H_{11}N_2O_5$: 191.07; found 191.14.
Cap-59a: (R) *Cap-59b*: (S)		^{1}H NMR (DMSO-d_6, δ = 2.5 ppm, 400 MHz): δ 12.49 (br s, 1H), 7.40 (d, *J* = 7.3, 0.89H), 7.04 (br s, 0.11H), 4.00-3.95 (m, 3H), 1.24 (d, *J* = 7.3, 3H), 1.15 (t, *J* = 7.2, 3H). HRMS: Anal. Calcd. for $[M+H]^+$ $C_6H_{12}NO_4$: 162.0766; found 162.0771.
Cap-60		The crude material was purified with a reverse phase HPLC (H_2O/MeOH/TFA) to afford a colorless viscous oil that crystallized to a white solid upon exposure to high vacuum. ^{1}H NMR (DMSO-d_6, δ = 2.5 ppm, 400 MHz): δ 12.38 (br s, 1H), 7.74 (s, 0.82H), 7.48 (s, 0.18H), 3.54/3.51 (two s, 3H), 1.30 (m, 2H), 0.98 (m, 2H). HRMS: Anal. Calcd. for $[M+H]^+$ $C_6H_{10}NO_4$: 160.0610; found 160.0604.
Cap-61		^{1}H NMR (DMSO-d_6, δ = 2.5 ppm, 400 MHz): δ 12.27 (br s, 1H), 7.40 (br s, 1H), 3.50 (s, 3H), 1.32 (s, 6H). HRMS: Anal. Calcd. for $[M+H]^+$ $C_6H_{12}NO_4$: 162.0766; found 162.0765.

Cap-62		^{1}H NMR (DMSO-d_6, δ = 2.5 ppm, 400 MHz): δ 12.74 (br s, 1H), 4.21 (d, *J* = 10.3, 0.6H), 4.05 (d, *J* = 10.0, 0.4H), 3.62/3.60 (two singlets, 3H), 3.0 (s, 3H), 2.14-2.05 (m, 1H), 0.95 (d, *J* = 6.3, 3H), 0.81 (d, *J* = 6.6, 3H). LC/MS: Anal. Calcd. for $[M-H]^-$ $C_8H_{14}NO_4$: 188.09; found 188.05.
Cap-63		[Note: the reaction was allowed to run for longer than what was noted for the general procedure.] ^{1}H NMR (DMSO-d_6, δ = 2.5 ppm, 400 MHz): 12.21 (br s, 1H), 7.42 (br s, 1H), 3.50 (s, 3H), 2.02-1.85 (m, 4H), 1.66-1.58 (m, 4H). LC/MS: Anal. Calcd. for $[M+H]^+$ $C_8H_{14}NO_4$: 188.09; found 188.19.
Cap-64		[Note: the reaction was allowed to run for longer than what was noted for the general procedure.] ^{1}H NMR (DMSO-d_6, δ = 2.5 ppm, 400 MHz): 12.35 (br s, 1H), 7.77 (s, 0.82H), 7.56/7.52 (overlapping br s, 0.18H), 3.50 (s, 3H), 2.47-2.40 (m, 2H), 2.14-2.07 (m, 2H), 1.93-1.82 (m, 2H).

Cap-65

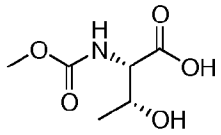


Methyl chloroformate (0.65 mL, 8.39 mmol) was added dropwise over 5 min to a cooled (ice-water) mixture of Na_2CO_3 (0.449 g, 4.23 mmol), NaOH (8.2 mL of 1M/H_2O, 8.2 mmol) and (*S*)-3-hydroxy-2-(methoxycarbonylamino)-3-methylbutanoic acid (1.04 g, 7.81 mmol). The reaction mixture was stirred for 45 min, and then the cooling bath was removed and stirring was continued for an additional 3.75 hr. The reaction mixture was washed with CH_2Cl_2, and the aqueous phase was cooled with ice-water bath and acidified with concentrated HCl to a pH region of 1-2. The volatile component was removed *in vacuo* and the residue was

taken up in a 2:1 mixture of MeOH/CH_2Cl_2 (15 mL) and filtered, and the filterate was rotervaped to afford *Cap*-65 as a white semi-viscous foam (1.236 g). ^{1}H NMR (DMSO-d_6, δ = 2.5 ppm, 400 MHz): δ 6.94 (d, *J* = 8.5, 0.9 H), 6.53 (br s, 0.1H), 3.89 (d, *J* = 8.8, 1H), 2.94 (s, 3H), 1.15 (s, 3H), 1.13 (s, 3H).

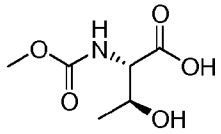
Cap-66 and -67 were prepared from appropriate commercially available starting materials by employing the procedure described for the synthesis of *Cap*-65.

Cap-66



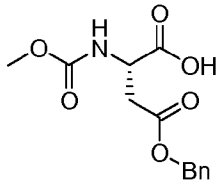
^{1}H NMR (DMSO-d_6, δ = 2.5 ppm, 400 MHz): δ 12.58 (br s, 1H), 7.07 (d, *J* = 8.3, 0.13H), 6.81 (d, *J* = 8.8, 0.67H), 4.10-4.02 (m, 1.15H), 3.91 (dd, *J* = 9.1, 3.5, 0.85H), 3.56 (s, 3H), 1.09 (d, *J* = 6.2, 3H). [Note: only the dominant signals of NH were noted].

Cap-67



^{1}H NMR (DMSO-d_6, δ = 2.5 ppm, 400 MHz): 12.51 (br s, 1H), 7.25 (d, *J* = 8.4, 0.75H), 7.12 (br d, *J* = 0.4, 0.05H), 6.86 (br s, 0.08H), 3.95-3.85 (m, 2H), 3.54 (s, 3H), 1.08 (d, *J* = 6.3, 3H). [Note: only the dominant signals of NH were noted]

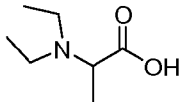
Cap-68



Methyl chloroformate (0.38 ml, 4.9 mmol) was added drop-wise to a mixture of 1N NaOH (aq) (9.0 ml, 9.0 mmol), 1M $NaHCO_3$ (aq) (9.0 ml, 9.0 mol), L-aspartic acid β-benzyl ester (1.0 g, 4.5 mmol) and Dioxane (9 ml). The reaction mixture was

stirred at ambient conditions for 3 hr, and then washed with Ethyl acetate (50 ml, 3x). The aqueous layer was acidified with 12N HCl to a pH ~ 1-2, and extracted with ethyl acetate (3 x 50 ml). The combined organic layers were washed with brine, dried (Na_2SO_4), filtered, and concentrated *in vacuo* to afford *Cap*-68 as a light yellow oil (1.37g; mass is above theoretical yield, and the product was used without further purification). ^{1}H NMR (DMSO-d_6, δ = 2.5 ppm, 500 MHz): δ 12.88 (br s, 1H), 7.55 (d, *J* = 8.5, 1H), 7.40-7.32 (m, 5H), 5.13 (d, *J* = 12.8, 1H), 5.10 (d, *J* = 12.9, 1H), 4.42-4.38 (m, 1H), 3.55 (s, 3H), 2.87 (dd, *J* = 16.2, 5.5, 1H), 2.71 (dd, *J* =16.2, 8.3, 1H). LC (Cond. 2): RT = 1.90 min; LC/MS: Anal. Calcd. For $[M+H]^+$ $C_{13}H_{16}NO_6$: 282.10; found 282.12.

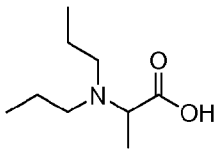
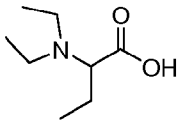
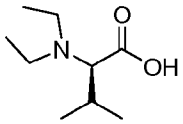
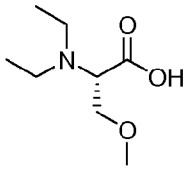
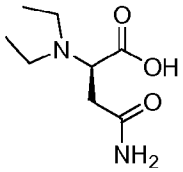
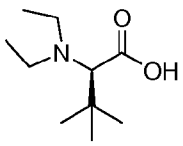
Cap-69a and -69b



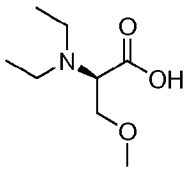
Cap-69a: (R)-enantiomer
Cap-69b: (S)-enantiomer

$NaCNBH_3$ (2.416 g, 36.5 mmol) was added in batches to a chilled (~15 °C) water (17 mL)/MeOH (10 mL) solution of alanine (1.338 g, 15.0 mmol). A few minutes later acetaldehyde (4.0 mL, 71.3 mmol) was added drop-wise over 4 min, the cooling bath was removed, and the reaction mixture was stirred at ambient condition for 6 hr. An additional acetaldehyde (4.0 mL) was added and the reaction was stirred for 2 hr. Concentrated HCl was added slowly to the reaction mixture until the pH reached ~ 1.5, and the resulting mixture was heated for 1 hr at 40 °C. Most of the volatile component was removed *in vacuo* and the residue was purified with a Dowex ® 50WX8-100 ion-exchange resin (column was washed with water, and the compound was eluted with dilute NH_4OH, prepared by mixing 18 ml of NH_4OH and 282 ml of water) to afford *Cap*-69 (2.0 g) as an off-white soft hygroscopic solid. ^{1}H NMR (DMSO-d_6, δ = 2.5 ppm, 400 MHz): δ 3.44 (q, *J* = 7.1, 1H), 2.99-2.90 (m, 2H), 2.89-2.80 (m, 2H), 1.23 (d, *J* = 7.1, 3H), 1.13 (t, *J* = 7.3, 6H).

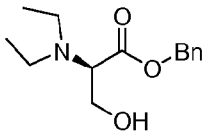
Cap-70 to -74 were prepared according to the procedure described for the synthesis of *Cap*-69 by employing appropriate starting materials.

Cap-70a: (R) *Cap-70b*: (S)		^{1}H NMR (DMSO-d_6, δ = 2.5 ppm, 400 MHz): δ 3.42 (q, *J* = 7.1, 1H), 2.68-2.60 (m, 4H), 1.53-1.44 (m, 4H), 1.19 (d, *J* = 7.3, 3H), 0.85 (t, *J* = 7.5, 6H). LC/MS: Anal. Calcd. for $[M+H]^+$ $C_9H_{20}NO_2$: 174.15; found 174.13.
Cap-71a: (R) *Cap-71b*: (S)		^{1}H NMR (DMSO-d_6, δ = 2.5 ppm, 500 MHz): δ 3.18-3.14 (m, 1H), 2.84-2.77 (m, 2H), 2.76-2.68 (m, 2H), 1.69-1.54 (m, 2H), 1.05 (t, *J* = 7.2, 6H), 0.91 (t, *J* = 7.3, 3H). LC/MS: Anal. Calcd. for $[M+H]^+$ $C_8H_{18}NO_2$: 160.13; found 160.06.
Cap-72		^{1}H NMR (DMSO-d_6, δ = 2.5 ppm, 400 MHz): δ 2.77-2.66 (m, 3H), 2.39-2.31 (m, 2H), 1.94-1.85 (m, 1H), 0.98 (t, *J* = 7.1, 6H), 0.91 (d, *J* = 6.5, 3H), 0.85 (d, *J* = 6.5, 3H). LC/MS: Anal. Calcd. for $[M+H]^+$ $C_9H_{20}NO_2$: 174.15; found 174.15.
Cap-73		^{1}H NMR (DMSO-d_6, δ = 2.5 ppm, 500 MHz): δ 9.5 (br s, 1H), 3.77 (dd, *J* = 10.8, 4.1,1H), 3.69-3.61 (m, 2H), 3.26 (s, 3H), 2.99-2.88 (m, 4H), 1.13 (t, *J* = 7.2, 6H).
Cap-74		^{1}H NMR (DMSO-d_6, δ = 2.5 ppm, 500 MHz): δ 7.54 (s, 1H), 6.89 (s, 1H), 3.81 (t, *J* = 6.6, k,1H), 2.82-2.71 (m, 4H), 2.63 (dd, *J* = 15.6, 7.0, 1H), 2.36 (dd, *J* = 15.4, 6.3, 1H), 1.09 (t, *J* = 7.2, 6H). RT = 0.125 minutes (Cond. 2); LC/MS: Anal. Calcd. for $[M+H]^+$ $C_8H_{17}N_2O_3$: 189.12; found 189.13.
Cap-74x		LC/MS: Anal. Calcd. for $[M+H]^+$ $C_{10}H_{22}NO_2$: 188.17; found 188.21

Cap-75



Cap-75, step a



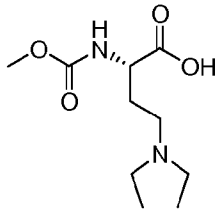
NaBH$_3$CN (1.6 g, 25.5 mmol) was added to a cooled (ice/water bath) water (25 ml)/methanol (15 ml) solution of H-D-Ser-OBzl HCl (2.0 g, 8.6 mmol). Acetaldehyde (1.5 ml, 12.5 mmol) was added drop-wise over 5 min, the cooling bath was removed, and the reaction mixture was stirred at ambient condition for 2 hr. The reaction was carefully quenched with 12N HCl and concentrated *in vacuo*. The residue was dissolved in water and purified with a reverse phase HPLC (MeOH/H_2O/TFA) to afford the TFA salt of (R)-benzyl 2-(diethylamino)-3-hydroxypropanoate as a colorless viscous oil (1.9g). ^{1}H NMR (DMSO-d_6, δ = 2.5 ppm, 500 MHz): δ 9.73 (br s, 1H), 7.52-7.36 (m, 5H), 5.32 (d, J = 12.2, 1H), 5.27 (d, J = 12.5, 1H), 4.54-4.32 (m, 1H), 4.05-3.97 (m, 2H), 3.43-3.21 (m, 4H), 1.23 (t, J = 7.2, 6H). LC/MS (Cond. 2): RT = 1.38 min; LC/MS: Anal. Calcd. for $[M+H]^+$ $C_{14}H_{22}NO_3$: 252.16; found 252.19.

Cap-75

NaH (0.0727 g, 1.82 mmol, 60%) was added to a cooled (ice-water) THF (3.0 mL) solution of the TFA salt (R)-benzyl 2-(diethylamino)-3-hydroxypropanoate (0.3019 g, 0.8264 mmol) prepared above, and the mixture was stirred for 15 min. Methyl iodide (56 µL, 0.90 mmol) was added and stirring was continued for 18 hr while allowing the bath to thaw to ambient condition. The reaction was quenched with water and loaded onto a MeOH pre-conditioned MCX (6 g) cartridge, and washed with methanol followed by compound elution with 2N NH_3/Methanol. Removal of the volatile component *in vacuo* afforded *Cap*-75, contaminated with

(R)-2-(diethylamino)-3-hydroxypropanoic acid, as a yellow semi-solid (100 mg). The product was used as is without further purification.

Cap-76

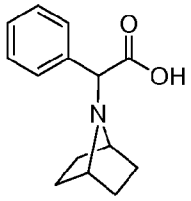


$NaCNBH_3$ (1.60 g, 24.2 mmol) was added in batches to a chilled (~15 °C) water/MeOH (12 mL each) solution of (*S*)-4-amino-2-(tert-butoxycarbonylamino) butanoic acid (2.17 g, 9.94 mmol). A few minutes later acetaldehyde (2.7 mL, 48.1 mmol) was added drop-wise over 2 min, the cooling bath was removed, and the reaction mixture was stirred at ambient condition for 3.5 hr. An additional acetaldehyde (2.7 mL, 48.1 mmol) was added and the reaction was stirred for 20.5 hr. Most of the MeOH component was removed *in vacuo*, and the remaining mixture was treated with concentrated HCl until its pH reached ~ 1.0 and then heated for 2 hr at 40 °C. The volatile component was removed *in vacuo*, and the residue was treated with 4 M HCl/dioxane (20 mL) and stirred at ambient condition for 7.5 hr. The volatile component was removed *in vacuo* and the residue was purified with Dowex ® 50WX8-100 ion-exchange resin (column was washed with water and the compound was eluted with dilute NH_4OH, prepared from 18 ml of NH_4OH and 282 ml of water) to afford intermediate (S)-2-amino-4-(diethylamino)butanoic acid as an off-white solid (1.73 g).

Methyl chloroformate (0.36 mL, 4.65 mmol) was added drop-wise over 11 min to a cooled (ice-water) mixture of Na_2CO_3 (0.243 g, 2.29 mmol), NaOH (4.6 mL of 1M/H_2O, 4.6 mmol) and the above product (802.4 mg). The reaction mixture was stirred for 55 min, and then the cooling bath was removed and stirring was continued for an additional 5.25 hr. The reaction mixture was diluted with equal volume of water and washed with CH_2Cl_2 (30 mL, 2x), and the aqueous phase was cooled with ice-water bath and acidified with concentrated HCl to a pH region of 2. The volatile component was then removed *in vacuo* and the crude material was free-based with MCX resin (6.0g; column was washed with water, and sample was eluted with 2.0 M

NH_3/MeOH) to afford impure *Cap*-76 as an off-white solid (704 mg). ^{1}H NMR (MeOH-d_4, δ = 3.29 ppm, 400 MHz): δ 3.99 (dd, *J* = 7.5, 4.7, 1H), 3.62 (s, 3H), 3.25-3.06 (m, 6H), 2.18-2.09 (m, 1H), 2.04-1.96 (m, 1H), 1.28 (t, *J* = 7.3, 6H). LC/MS: Anal. Calcd. for $[M+H]^+$ $C_{10}H_{21}N_2O_4$: 233.15; found 233.24.

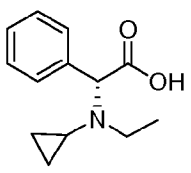
Cap-77a and -77b



Cap-77a: enantiomer-1
Cap-77b: enantiomer-2

The synthesis of *Cap*-77 was conducted according to the procedure described for *Cap*-7 by using 7-azabicyclo[2.2.1]heptane for the SN_2 displacement step, and by effecting the enantiomeric separation of the intermediate benzyl 2-(7-azabicyclo[2.2.1]heptan-7-yl)-2-phenylacetate using the following condition: the intermediate (303.7 mg) was dissolved in ethanol, and the resulting solution was injected on a chiral HPLC column (Chiracel AD-H column, 30 x 250 mm, 5 um) eluting with 90% CO_2-10% EtOH at 70 mL/min, and a temperature of 35 °C to provide 124.5 mg of enantiomer-1 and 133.8 mg of enantiomer-2. These benzyl esters were hydrogenolysed according to the preparation of *Cap*-7 to provide *Cap*-77: ^{1}H NMR (DMSO-d_6, δ = 2.5 ppm, 400 MHz): δ 7.55 (m, 2H), 7.38-7.30 (m, 3H), 4.16 (s, 1H), 3.54 (app br s, 2H), 2.08-1.88 (m, 4 H), 1.57-1.46 (m, 4H). LC (Cond. 1): RT = 0.67 min; LC/MS: Anal. Calcd. for $[M+H]^+$ $C_{14}H_{18}BrNO_2$: 232.13; found 232.18. HRMS: Anal. Calcd. for $[M+H]^+$ $C_{14}H_{18}BrNO_2$: 232.1338; found 232.1340.

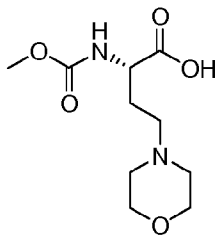
Cap-78



$NaCNBH_3$ (0.5828 g, 9.27 mmol) was added to a mixture of the HCl salt of (*R*)-2-(ethylamino)-2-phenylacetic acid (an intermediate in the synthesis of *Cap*-3; 0.9923 mg, 4.60 mmol) and (1-ethoxycyclopropoxy)trimethylsilane (1.640 g, 9.40

mmol) in MeOH (10 mL), and the semi-heterogeneous mixture was heated at 50 °C with an oil bath for 20 hr. More (1-ethoxycyclopropoxy)trimethylsilane (150 mg, 0.86 mmol) and $NaCNBH_3$ (52 mg, 0.827 mmol) were added and the reaction mixture was heated for an additional 3.5 hr. It was then allowed to cool to ambient temperature and acidified to a ~ pH region of 2 with concentrated HCl, and the mixture was filtered and the filtrate was rotervaped. The resulting crude material was taken up in *i*-PrOH (6 mL) and heated to effect dissolution, and the non-dissolved part was filtered off and the filtrate concentrated *in vacuo*. About 1/3 of the resultant crude material was purified with a reverse phase HPLC (H_2O/MeOH/TFA) to afford the TFA salt of *Cap*-78 as a colorless viscous oil (353 mg). ^1H NMR (DMSO-d_6, δ = 2.5 ppm, 400 MHz; after D_2O exchange): δ 7.56-7.49 (m, 5H), 5.35 (S, 1H), 3.35 (m, 1H), 3.06 (app br s, 1H), 2.66 (m, 1H), 1.26 (t, J = 7.3, 3H), 0.92 (m, 1H), 0.83-0.44 (m, 3H). LC (Cond. 1): RT = 0.64 min; LC/MS: Anal. Calcd. for $[M+H]^+$ $C_{13}H_{18}NO_2$: 220.13; found 220.21. HRMS: Anal. Calcd. for $[M+H]^+$ $C_{13}H_{18}NO_2$: 220.1338; found 220.1343.

Cap-79



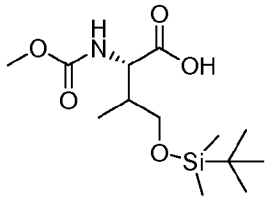
Ozone was bubbled through a cooled (-78 °C) CH_2Cl_2 (5.0 mL) solution *Cap*-55 (369 mg, 2.13 mmol) for about 50 min until the reaction mixture attained a tint of blue color. Me_2S (10 pipet drops) was added, and the reaction mixture was stirred for 35 min. The -78 °C bath was replaced with a -10 °C bath and stirring continued for an additional 30 min, and then the volatile component was removed *in vacuo* to afford a colorless viscous oil.

$NaBH_3CN$ (149 mg, 2.25 mmol) was added to a MeOH (5.0 mL) solution of the above crude material and morpholine (500 μL, 5.72 mmol) and the mixture was stirred at ambient condition for 4 hr. It was cooled to ice-water temperature and treated with concentrated HCl to bring its pH to ~2.0, and then stirred for 2.5 hr. The

volatile component was removed *in vacuo*, and the residue was purified with a combination of MCX resin (MeOH wash; 2.0 N NH_3/MeOH elution) and a reverse phase HPLC (H_2O/MeOH/TFA) to afford *Cap*-79 containing unknown amount of morpholine.

In order to consume the morpholine contaminant, the above material was dissolved in CH_2Cl_2 (1.5 mL) and treated with Et_3N (0.27 mL, 1.94 mmol) followed by acetic anhydride (0.10 mL, 1.06 mmol) and stirred at ambient condition for 18 hr. THF (1.0 mL) and H_2O (0.5 mL) were added and stirring continued for 1.5 hr. The volatile component was removed *in vacuo*, and the resultant residue was passed through MCX resin (MeOH wash; 2.0 N NH_3/MeOH elution) to afford impure *Cap*-79 as a brown viscous oil, which was used for the next step without further purification.

Cap-80a and -80b



Cap-80a: S/S-diastereomer
Cap-80b: S/R-diastereomer

$SOCl_2$ (6.60 mL, 90.5 mmol) was added drop-wise over 15 min to a cooled (ice-water) mixture of (S)-3-amino-4-(benzyloxy)-4-oxobutanoic acid (10.04g, 44.98 mmol) and MeOH (300 mL), the cooling bath was removed and the reaction mixture was stirred at ambient condition for 29 hr. Most of the volatile component was removed *in vacuo* and the residue was carefully partitioned between EtOAc (150 mL) and saturated $NaHCO_3$ solution. The aqueous phase was extracted with EtOAc (150 mL, 2x), and the combined organic phase was dried ($MgSO_4$), filtered, and concentrated *in vacuo* to afford (S)-1-benzyl 4-methyl 2-aminosuccinate as a colorless oil (9.706g). ^{1}H NMR (DMSO-d_6, δ = 2.5 ppm, 400 MHz): δ 7.40-7.32 (m, 5H), 5.11 (s, 2H), 3.72 (app t, J = 6.6, 1H), 3.55 (s, 3H), 2.68 (dd, J = 15.9, 6.3, 1H), 2.58 (dd, J = 15.9, 6.8, 1H), 1.96 (s, 2H). LC (Cond. 1): RT = 0.90 min; LC/MS: Anal. Calcd. for $[M+H]^+$ $C_{12}H_{16}NO_4$: 238.11; found 238.22.

$Pb(NO_3)_2$ (6.06 g, 18.3 mmol) was added over 1 min to a CH_2Cl_2 (80 mL) solution of (S)-1-benzyl 4-methyl 2-aminosuccinate (4.50 g, 19.0 mmol), 9-bromo-9-

phenyl-9*H*-fluorene (6.44 g, 20.0 mmol) and Et_3N (3.0 mL, 21.5 mmol), and the heterogeneous mixture was stirred at ambient condition for 48 hr. The mixture was filtered and the filtrate was treated with $MgSO_4$ and filtered again, and the final filtrate was concentrated. The resulting crude material was submitted to a Biotage purification (350 g silica gel, CH_2Cl_2 elution) to afford (S)-1-benzyl 4-methyl 2-(9-phenyl-9H-fluoren-9-ylamino)succinate as highly viscous colorless oil (7.93 g). ^1H NMR (DMSO-d_6, δ = 2.5 ppm, 400 MHz): δ 7.82 (m, 2H), 7.39-7.13 (m, 16H), 4.71 (d, J = 12.4, 1H), 4.51 (d, J = 12.6, 1H), 3.78 (d, J = 9.1, NH), 3.50 (s, 3H), 2.99 (m, 1H), 2.50-2.41 (m, 2H, partially overlapped with solvent). LC (Cond. 1): RT = 2.16 min; LC/MS: Anal. Calcd. for $[M+H]^+$ $C_{31}H_{28}NO_4$: 478.20; found 478.19.

LiHMDS (9.2 mL of 1.0 M/THF, 9.2 mmol) was added drop-wise over 10 min to a cooled (-78 °C) THF (50 mL) solution of (S)-1-benzyl 4-methyl 2-(9-phenyl-9H-fluoren-9-ylamino)succinate (3.907 g, 8.18 mmol) and stirred for ~1 hr. MeI (0.57 mL, 9.2 mmol) was added drop-wise over 8 min to the mixture, and stirring was continued for 16.5 hr while allowing the cooling bath to thaw to room temperature. After quenching with saturated NH_4Cl solution (5 mL), most of the organic component was removed *in vacuo* and the residue was partitioned between CH_2Cl_2 (100 mL) and water (40 mL). The organic layer was dried ($MgSO_4$), filtered, and concentrated *in vacuo*, and the resulting crude material was purified with a Biotage (350 g silica gel; 25% EtOAc/hexanes) to afford 3.65 g of a 2S/3S and 2S/3R diastereomeric mixtures of 1-benzyl 4-methyl 3-methyl-2-(9-phenyl-9H-fluoren-9-ylamino)succinate in ~1.0:0.65 ratio (^1H NMR). The stereochemistry of the dominant isomer was not determined at this juncture, and the mixture was submitted to the next step without separation. Partial ^1H NMR data (DMSO-d_6, δ = 2.5 ppm, 400 MHz): major diastereomer, δ 4.39 (d, J = 12.3, 1H of CH_2), 3.33 (s, 3H, overlapped with H_2O signal), 3.50 (d, J = 10.9, NH), 1.13 (d, J = 7.1, 3H); minor diastereomer, δ 4.27 (d, J =12.3, 1H of CH_2), 3.76 (d, J = 10.9, NH), 3.64 (s, 3H), 0.77 (d, J = 7.0, 3H). LC (Cond. 1): RT = 2.19 min; LC/MS: Anal. Calcd. for $[M+H]^+$ $C_{32}H_{30}NO_4$: 492.22; found 492.15.

Diisobutylaluminum hydride (20.57 ml of 1.0 M in hexanes, 20.57 mmol) was added drop-wise over 10 min to a cooled (-78 °C) THF (120 mL) solution of (2S)-1-benzyl 4-methyl 3-methyl-2-(9-phenyl-9H-fluoren-9-ylamino)succinate (3.37

g, 6.86 mmol) prepared above, and stirred at -78 °C for 20 hr. The reaction mixture was removed from the cooling bath and rapidly poured into ~1M H_3PO_4/H_2O (250 mL) with stirring, and the mixture was extracted with ether (100 mL, 2x). The combined organic phase was washed with brine, dried ($MgSO_4$), filtered and concentrated *in vacuo*. A silica gel mesh of the crude material was prepared and submitted to chromatography (25% EtOAc/hexanes; gravity elution) to afford 1.1g of (2S,3S)-benzyl 4-hydroxy-3-methyl-2-(9-phenyl-9*H*-fluoren-9-ylamino)butanoate, contaminated with benzyl alcohol, as a colorless viscous oil and (2S,3R)-benzyl 4-hydroxy-3-methyl-2-(9-phenyl-9*H*-fluoren-9-ylamino)butanoate containing the (2S,3R) stereoisomer as an impurity. The later sample was resubmitted to the same column chromatography purification conditions to afford 750 mg of purified material as a white foam. [Note: the (2S, 3S) isomer elutes before the (2S,3R) isomer under the above condition]. (2S, 3S) isomer: ^{1}H NMR (DMSO-d_6, δ = 2.5 ppm, 400 MHz): 7.81 (m, 2H), 7.39-7.08 (m, 16H), 4.67 (d, J = 12.3, 1H), 4.43 (d, J = 12.4, 1H), 4.21 (app t, J = 5.2, OH), 3.22 (d, J = 10.1, NH), 3.17 (m, 1H), 3.08 (m, 1H), ~2.5 (m, 1H, overlapped with the solvent signal), 1.58 (m, 1H), 0.88 (d, J = 6.8, 3H). LC (Cond. 1): RT = 2.00 min; LC/MS: Anal. Calcd. for $[M+H]^+$ $C_{31}H_{30}NO_3$: 464.45; found 464.22. (2S, 3R) isomer: ^{1}H NMR (DMSO-d_6, δ = 2.5 ppm, 400 MHz): 7.81 (d, J = 7.5, 2H), 7.39-7.10 (m, 16H), 4.63 (d, J= 12.1, 1H), 4.50 (app t, J = 4.9, 1H), 4.32 (d, J = 12.1, 1H), 3.59-3.53 (m, 2H), 3.23 (m, 1H), 2.44 (dd, J = 9.0, 8.3, 1H), 1.70 (m, 1H), 0.57 (d, J = 6.8, 3H). LC (Cond. 1): RT = 1.92 min; LC/MS: Anal. Calcd. for $[M+H]^+$ $C_{31}H_{30}NO_3$: 464.45; found 464.52.

The relative stereochemical assignments of the DIBAL-reduction products were made based on NOE studies conducted on lactone derivatives prepared from each isomer by employing the following protocol: LiHMDS (50 µL of 1.0 M/THF, 0.05 mmol) was added to a cooled (ice-water) THF (2.0 mL) solution of (2S,3S)-benzyl 4-hydroxy-3-methyl-2-(9-phenyl-9*H*-fluoren-9-ylamino)butanoate (62.7 mg, 0.135 mmol), and the reaction mixture was stirred at similar temperature for ~2 hr. The volatile component was removed *in vacuo* and the residue was partitioned between CH_2Cl_2 (30 mL), water (20 mL) and saturated aqueous NH_4Cl solution (1 mL). The organic layer was dried ($MgSO_4$), filtered, and concentrated *in vacuo*, and the resulting crude material was submitted to a Biotage purification (40 g silica gel; 10-15% EtOAc/hexanes) to afford (3S,4S)-4-methyl-3-(9-phenyl-9*H*-fluoren-9-

ylamino)dihydrofuran-2(3*H*)-one as a colorless film of solid (28.1 mg). (2S,3R)-benzyl 4-hydroxy-3-methyl-2-(9-phenyl-9*H*-fluoren-9-ylamino)butanoate was elaborated similarly to (3S,4R)-4-methyl-3-(9-phenyl-9*H*-fluoren-9-ylamino)dihydrofuran-2(3*H*)-one. (3S,4S)-lactone isomer: ^{1}H NMR (DMSO-d_6, δ = 2.5 ppm, 400 MHz), 7.83 (d, *J* = 7.5, 2H), 7.46-7.17 (m, 11H), 4.14 (app t, *J* = 8.3, 1H), 3.60 (d, *J* = 5.8, NH), 3.45 (app t, *J* = 9.2, 1H), ~2.47 (m, 1H, partially overlapped with solvent signal), 2.16 (m, 1H), 0.27 (d, *J* = 6.6, 3H). LC (Cond. 1): RT = 1.98 min; LC/MS: Anal. Calcd. for $[M+Na]^+$ $C_{24}H_{21}NNaO_2$: 378.15; found 378.42. (3S,4R)-lactone isomer: ^{1}H NMR (DMSO-d_6, δ = 2.5 ppm, 400 MHz), 7.89 (d, *J* = 7.6, 1H), 7.85 (d, *J* = 7.3, 1H), 7.46-7.20 (m, 11H), 3.95 (dd, *J* = 9.1, 4.8, 1H), 3.76 (d, *J* = 8.8, 1H), 2.96 (d, *J* = 3.0, NH), 2.92 (dd, *J* = 6.8, 3, NCH), 1.55 (m, 1H), 0.97 (d, *J* = 7.0, 3H). LC (Cond. 1): RT = 2.03 min; LC/MS: Anal. Calcd. for $[M+Na]^+$ $C_{24}H_{21}NNaO_2$: 378.15; found 378.49.

TBDMS-Cl (48 mg, 0.312 mmol) followed by imidazole (28.8 mg, 0.423 mmol) were added to a CH_2Cl_2 (3 ml) solution of (2S,3S)-benzyl 4-hydroxy-3-methyl-2-(9-phenyl-9H-fluoren-9-ylamino)butanoate (119.5 mg, 0.258 mmol), and the mixture was stirred at ambient condition for 14.25 hr. The reaction mixture was then diluted with CH_2Cl_2 (30 mL) and washed with water (15 mL), and the organic layer was dried ($MgSO_4$), filtered, and concentrated *in vacuo*. The resultant crude material was purified with a Biotage (40 g silica gel; 5% EtOAc/hexanes) to afford (2S,3S)-benzyl 4-(tert-butyldimethylsilyloxy)-3-methyl-2-(9-phenyl-9H-fluoren-9-ylamino)butanoate, contaminated with TBDMS based impurities, as a colorless viscous oil (124.4 mg). (2S,3R)-benzyl 4-hydroxy-3-methyl-2-(9-phenyl-9H-fluoren-9-ylamino)butanoate was elaborated similarly to (2S,3R)-benzyl 4-(tert-butyldimethylsilyloxy)-3-methyl-2-(9-phenyl-9H-fluoren-9-ylamino)butanoate. (2S,3S)-silyl ether isomer: ^{1}H NMR (DMSO-d_6, δ = 2.5 ppm, 400 MHz), 7.82 (d, *J* = 4.1, 1H), 7.80 (d, *J* = 4.0, 1H), 7.38-7.07 (m, 16 H), 4.70 (d, *J* = 12.4, 1H), 4.42 (d, *J* = 12.3, 1H), 3.28-3.19 (m, 3H), 2.56 (dd, *J* = 10.1, 5.5, 1H), 1.61 (m, 1H), 0.90 (d, *J* = 6.8, 3H), 0.70 (s, 9H), -0.13 (s, 3H), -0.16 (s, 3H). LC (Cond. 1, where the run time was extended to 4 min): RT = 3.26 min; LC/MS: Anal. Calcd. for $[M+H]^+$ $C_{37}H_{44}NO_3Si$: 578.31; found 578.40. (2S,3R)-silyl ether isomer: ^{1}H NMR (DMSO-d_6, δ = 2.5 ppm, 400 MHz), 7.82 (d, *J* = 3.0, 1H), 7.80 (d, *J* = 3.1, 1H), 7.39-7.10 (m,

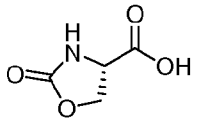
16H), 4.66 (d, J = 12.4, 1H), 4.39 (d, J = 12.4, 1H), 3.61 (dd, J = 9.9, 5.6, 1H), 3.45 (d, J = 9.5, 1H), 3.41 (dd, J = 10, 6.2, 1H), 2.55 (dd, J = 9.5, 7.3, 1H), 1.74 (m, 1H), 0.77 (s, 9H), 0.61 (d, J = 7.1, 3H), -0.06 (s, 3H), -0.08 (s, 3H).

A balloon of hydrogen was attached to a mixture of (2S,3S)-benzyl 4-(tert-butyldimethylsilyloxy)-3-methyl-2-(9-phenyl-9*H*-fluoren-9-ylamino)butanoate (836 mg, 1.447 mmol) and 10% Pd/C (213 mg) in EtOAc (16 mL) and the mixture was stirred at room temperature for ~ 21 hr, where the balloon was recharged with H_2 as necessary. The reaction mixture was diluted with CH_2Cl_2 and filtered through a pad of diatomaceous earth (Celite-545®), and the pad was washed with EtOAc (200 mL), EtOAc/MeOH (1:1 mixture, 200 mL) and MeOH (750 mL). The combined organic phase was concentrated, and a silica gel mesh was prepared from the resulting crude material and submitted to a flash chromatography (8:2:1 mixture of EtOAc/i-PrOH/H_2O) to afford (2S,3S)-2-amino-4-(tert-butyldimethylsilyloxy)-3-methylbutanoic acid as a white fluffy solid (325 mg). (2S,3R)-benzyl 4-(tert-butyldimethylsilyloxy)-3-methyl-2-(9-phenyl-9H-fluoren-9-ylamino)butanoate was similarly elaborated to (2S,3R)-2-amino-4-(tert-butyldimethylsilyloxy)-3-methylbutanoic acid. (2S,3S)-amino acid isomer: ^{1}H NMR (Methanol-d_4, δ = 3.29 ppm, 400 MHz), 3.76 (dd, J = 10.5, 5.2, 1H), 3.73 (d, J = 3.0, 1H), 3.67 (dd, J = 10.5, 7.0, 1H), 2.37 (m, 1H), 0.97 (d, J = 7.0, 3H), 0.92 (s, 9H), 0.10 (s, 6H). LC/MS: Anal. Calcd. for $[M+H]^+$ $C_{11}H_{26}NO_3Si$: 248.17; found 248.44. (2S,3R)-amino acid isomer: ^{1}H NMR (Methanol-d_4, δ = 3.29 ppm, 400 MHz), 3.76-3.75 (m, 2H), 3.60 (d, J = 4.1, 1H), 2.16 (m, 1H), 1.06 (d, J = 7.3, 3H), 0.91 (s, 9H), 0.09 (s, 6H). Anal. Calcd. for $[M+H]^+$ $C_{11}H_{26}NO_3Si$: 248.17; found 248.44.

Water (1 mL) and NaOH (0.18 mL of 1.0 M/H_2O, 0.18 mmol) were added to a mixture of (2S,3S)-2-amino-4-(tert-butyldimethylsilyloxy)-3-methylbutanoic acid (41.9 mg, 0.169 mmol) and Na_2CO_3 (11.9 mg, 0.112 mmol), and sonicated for about 1 min to effect dissolution of reactants. The mixture was then cooled with an ice-water bath, methyl chloroformate (0.02 mL, 0.259 mmol) was added over 30 s, and vigorous stirring was continued at similar temperature for 40 min and then at ambient temperature for 2.7 hr. The reaction mixture was diluted with water (5 mL), cooled with ice-water bath and treated drop-wise with 1.0 N HCl aqueous solution (~0.23 mL). The mixture was further diluted with water (10 mL) and extracted with CH_2Cl_2

(15 mL, 2x). The combined organic phase was dried ($MgSO_4$), filtered, and concentrated *in vacuo* to afford *Cap*-80a as an off-white solid. (2S,3R)-2-amino-4-(tert-butyldimethylsilyloxy)-3-methylbutanoic acid was similarly elaborated to *Cap*-80b. *Cap*-80a: ^{1}H NMR (DMSO-d_6, δ = 2.5 ppm, 400 MHz), 12.57 (br s, 1H), 7.64 (d, J = 8.3, 0.3H), 7.19 (d, J = 8.8, 0.7H), 4.44 (dd, J = 8.1, 4.6, 0.3H), 4.23 (dd, J = 8.7, 4.4, 0.7H), 3.56/3.53 (two singlets, 3H), 3.48-3.40 (m, 2H), 2.22-2.10 (m, 1H), 0.85 (s, 9H), ~0.84 (d, 0.9H, overlapped with t-Bu signal), 0.79 (d, J = 7, 2.1H), 0.02/0.01/0.00 (three overlapping singlets, 6H). LC/MS: Anal. Calcd. for $[M+Na]^+$ $C_{13}H_{27}NNaO_5Si$: 328.16; found 328.46. *Cap*-80b: ^{1}H NMR ($CDCl_3$, δ = 7.24 ppm, 400 MHz), 6.00 (br d, J = 6.8, 1H), 4.36 (dd, J = 7.1, 3.1, 1H), 3.87 (dd, J = 10.5, 3.0, 1H), 3.67 (s, 3H), 3.58 (dd, J = 10.6, 4.8, 1H), 2.35 (m, 1H), 1.03 (d, J = 7.1, 3H), 0.90 (s, 9H), 0.08 (s, 6H). LC/MS: Anal. Calcd. for $[M+Na]^+$ $C_{13}H_{27}NNaO_5Si$: 328.16; found 328.53. The crude products were utilized without further purification.

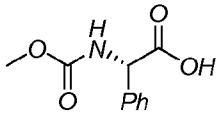
Cap-81



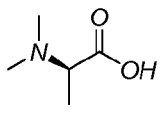
Prepared according to the protocol described by Falb et al. *Synthetic Communications* 1993, *23*, 2839.

Cap-82 to Cap-85

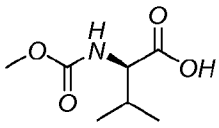
Cap-82 to *Cap*-85 were synthesized from appropriate starting materials according to the procedure described for *Cap*-51. The samples exhibited similar spectral profiles as that of their enantiomers (i.e., *Cap*-4, *Cap*-13, *Cap*-51 and *Cap*-52, respectively)



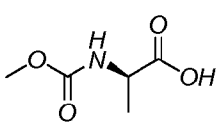
Cap-82



Cap-83

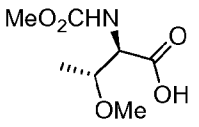


Cap-84



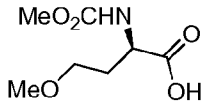
Cap-85

Cap-86



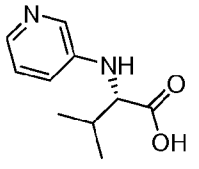
To a mixture of O-methyl-L-threonine (3.0 g, 22.55 mmol), NaOH (0.902 g, 22.55 mmol) in H_2O (15 mL) was added $ClCO_2Me$ (1.74 mL, 22.55 mmol) dropwise at 0°C. The mixture was allowed to stir for 12 h and acidified to pH 1 using 1N HCl. The aqueous phase was extracted with EtOAc and (2x250 mL) and 10% MeOH in CH_2Cl_2 (250 mL) and the combined organic phases were concentrated under *in vacuo* to afford a colorless oil (4.18 g, 97%) which was of sufficient purity for use in subsequent steps. ^{1}HNMR (400 MHz, $CDCl_3$) δ 4.19 (s, 1H), 3.92-3.97 (m, 1H), 3.66 (s, 3H), 1.17 (d, J = 7.7 Hz, 3H). LCMS: Anal. Calcd. for $C_7H_{13}NO_5$: 191; found: 190 $(M-H)^-$.

Cap-87



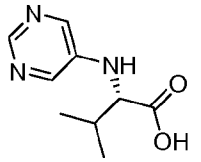
To a mixture of L-homoserine (2.0 g, 9.79 mmol), Na_2CO_3 (2.08 g, 19.59 mmol) in H_2O (15 mL) was added $ClCO_2Me$ (0.76 mL, 9.79 mmol) dropwise at 0°C. The mixture was allowed to stir for 48 h and acidified to pH 1 using 1N HCl. The aqueous phase was extracted with EtOAc and (2X250 mL) and the combined organic phases were concentrated under *in vacuo* to afford a colorless solid (0.719 g, 28%) which was of sufficient purity for use in subsequent steps. ^{1}HNMR (400 MHz, $CDCl_3$) δ 4.23 (dd, J = 4.5, 9.1 Hz, 1H), 3.66 (s, 3H), 3.43-3.49 (m, 2H), 2.08 – 2.14 (m, 1H), 1.82 – 1.89 (m, 1H). LCMS: Anal. Calcd. for $C_7H_{13}NO_5$: 191; found: 192 $(M+H)^+$.

Cap-88



A mixture of L-valine (1.0 g, 8.54 mmol), 3-bromopyridine (1.8 mL, 18.7 mmol), K_2CO_3 (2.45 g, 17.7 mmol) and CuI (169 mg, 0.887 mmol) in DMSO (10 mL) was heated at 100°C for 12h. The reaction mixture was cooled to rt, poured into H_2O (ca. 150 mL) and washed with EtOAc (x2). The organic layers were extracted with a small amount of H_2O and the combined aq phases were acidified to ca. pH 2 with 6N HCl. The volume was reduced to about one-third and 20g of cation exchange resin (Strata) was added. The slurry was allowed to stand for 20 min and loaded onto a pad of cation exchange resin (Strata) (ca. 25g). The pad was washed with H_2O (200 mL), MeOH (200 mL), and then NH_3 (3M in MeOH, 2X200 mL). The appropriate fractions was concentrated *in vacuo* and the residue (ca. 1.1 g) was dissolved in H_2O, frozen and lyophyllized. The title compound was obtained as a foam (1.02 g, 62%). ^{1}HNMR (400 MHz, DMSO-d_6) δ 8.00 (s, br, 1H), 7.68 – 7.71 (m, 1H), 7.01 (s, br, 1H), 6.88 (d, J = 7.5 Hz, 1H), 5.75 (s, br, 1H), 3.54 (s, 1H), 2.04 – 2.06 (m, 1H), 0.95 (d, J = 6.0 Hz, 3H), 0.91 (d, J = 6.6 Hz, 3H). LCMS: Anal. Calcd. for $C_{10}H_{14}N_2O_2$: 194; found: 195 $(M+H)^+$.

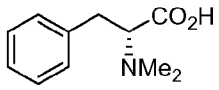
Cap-89



A mixture of L-valine (1.0 g, 8.54 mmol), 5-bromopyrimidine (4.03 g, 17.0 mmol), K_2CO_3 (2.40 g, 17.4 mmol) and CuI (179 mg, 0.94 mmol) in DMSO (10 mL) was heated at 100°C for 12h. The reaction mixture was cooled to RT, poured into H_2O (ca. 150 mL) and washed with EtOAc (x2). The organic layers were extracted with a small amount of H_2O and the combined aq phases were acidified to ca. pH 2 with 6N HCl. The volume was reduced to about one-third and 20g of cation exchange resin (Strata) was added. The slurry was allowed to stand for 20 min and loaded onto a pad of cation exchange resin (Strata) (ca. 25g). The pad was washed with H_2O (200 mL), MeOH (200 mL), and then NH_3 (3M in MeOH, 2x200 mL). The appropriate fractions was concentrated *in vacuo* and the residue (ca. 1.1 g) was dissolved in H_2O, frozen and lyophyllized. The title compound was obtained as a foam (1.02 g, 62%). ^{1}HNMR (400 MHz, CD_3OD) showed the mixture to contain valine and the purity

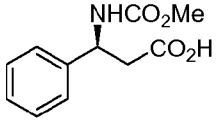
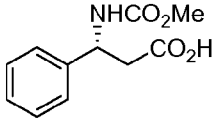
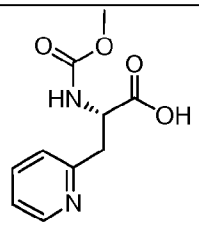
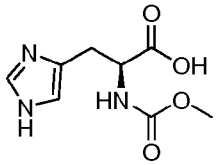
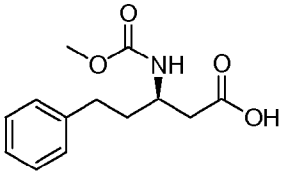
could not be estimated. The material was used as is in subsequent reactions. LCMS: Anal. Calcd. for $C_9H_{13}N_3O_2$: 195; found: 196 $(M+H)^+$.

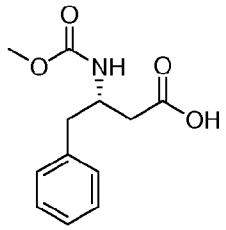
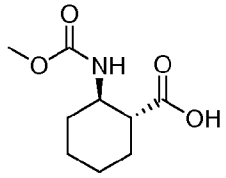
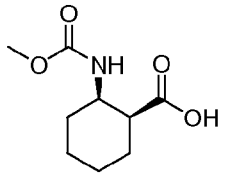
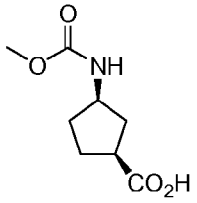
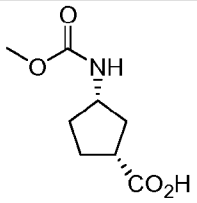
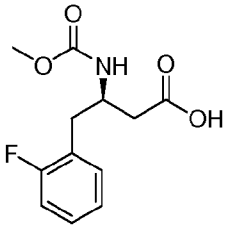
Cap–90

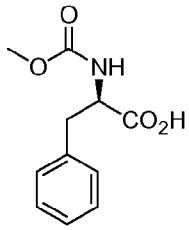
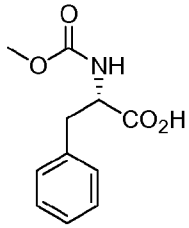
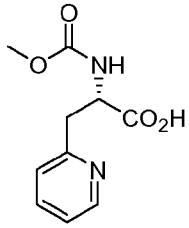
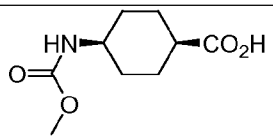
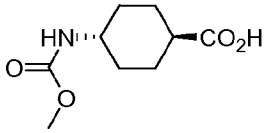
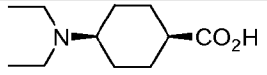


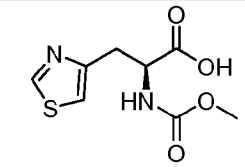
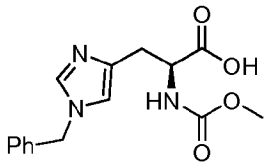
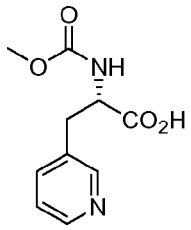
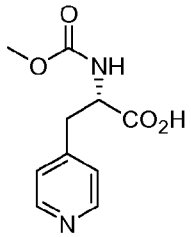
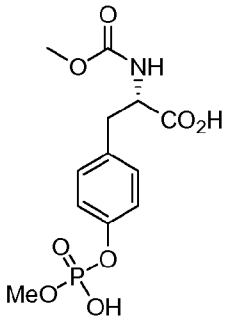
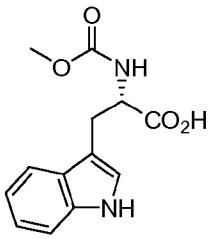
Cap-90 was prepared according to the method described for the preparation of *Cap*-1. The crude material was used as is in subsequent steps. LCMS: Anal. Calcd. for $C_{11}H_{15}NO_2$: 193; found: 192 $(M-H)^-$.

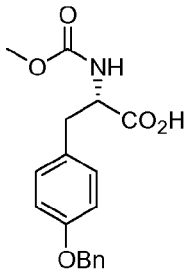
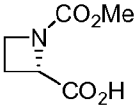
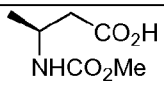
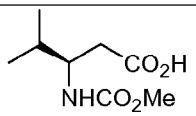
The following caps were prepared according to the method of example 51:

Cap	Structure	LCMS
Cap-91		LCMS: Anal. Calcd. for $C_{11}H_{13}NO_4$: 223; found: 222 $(M-H)^-$.
Cap-92		LCMS: Anal. Calcd. for $C_{11}H_{13}NO_4$: 223; found: 222 $(M-H)^-$.
Cap-93		LCMS: Anal. Calcd. for $C_{10}H_{12}N_2O_4$: 224; found: 225 $(M+H)^+$.
Cap-94		LCMS: Anal. Calcd. for $C_8H_{11}N_3O_4$: 213; found: 214 $(M+H)^+$.
Cap-95		LCMS: Anal. Calcd. for $C_{13}H_{17}NO_4$: 251; found: 250 $(M-H)^-$.

Cap-96		LCMS: Anal. Calcd. for $C_{12}H_{15}NO_4$: 237; found: 236 $(M-H)^-$.
Cap-97		LCMS: Anal. Calcd. for $C_9H_{15}NO_4$: 201; found: 200 $(M-H)^-$.
Cap-98		LCMS: Anal. Calcd. for $C_9H_{15}NO_4$: 201; found: 202 $(M+H)^+$.
Cap-99		^{1}HNMR (400 MHz, CD_3OD) δ 3.88 – 3.94 (m, 1H), 3.60, 3.61 (s, 3H), 2.80 (m, 1H), 2.20 (m 1H), 1.82 – 1.94 (m, 3H), 1.45 – 1.71 (m, 2H).
Cap-99a		^{1}HNMR (400 MHz, CD_3OD) δ 3.88 – 3.94 (m, 1H), 3.60, 3.61 (s, 3H), 2.80 (m, 1H), 2.20 (m 1H), 1.82 – 1.94 (m, 3H), 1.45 – 1.71 (m, 2H).
Cap-100		LCMS: Anal. Calcd. for $C_{12}H_{14}NO_4F$: 255; found: 256 $(M+H)^+$.

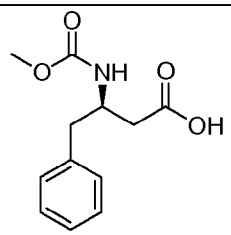
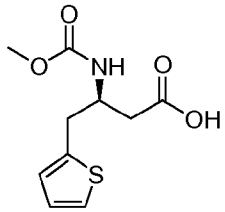
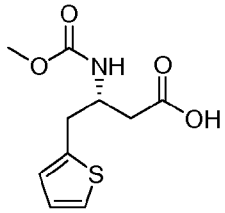
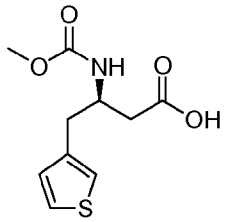
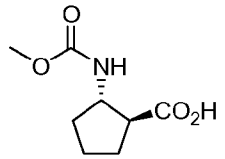
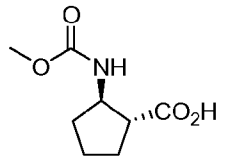
Cap-101		LCMS: Anal. Calcd. for $C_{11}H_{13}NO_4$: 223; found: 222 $(M-H)^-$.
Cap-102		LCMS: Anal. Calcd. for $C_{11}H_{13}NO_4$: 223; found: 222 $(M-H)^-$
Cap-103		LCMS: Anal. Calcd. for $C_{10}H_{12}N_2O_4$: 224; found: 225 $(M+H)^+$.
Cap-104		^{1}HNMR (400 MHz, CD_3OD) δ 3.60 (s, 3H), 3.50 – 3.53 (m, 1H), 2.66 – 2.69 and 2.44 – 2.49 (m, 1H), 1.91 – 2.01 (m, 2H), 1.62 – 1.74 (m, 4H), 1.51 – 1.62 (m, 2H).
Cap-105		^{1}HNMR (400 MHz, CD_3OD) δ 3.60 (s, 3H), 3.33 – 3.35 (m, 1H, partially obscured by solvent), 2.37 – 2.41 and 2.16 – 2.23 (m, 1H), 1.94 – 2.01 (m, 4H), 1.43 – 1.53 (m, 2H), 1.17 – 1.29 (m, 2H).
Cap-106		^{1}HNMR (400 MHz, CD_3OD) δ 3.16 (q, J = 7.3 Hz, 4H), 2.38 - 2.41 (m, 1H), 2.28 – 2.31 (m, 2H), 1.79 – 1.89 (m, 2H), 1.74 (app, ddd J = 3.5, 12.5, 15.9 Hz, 2H), 1.46 (app

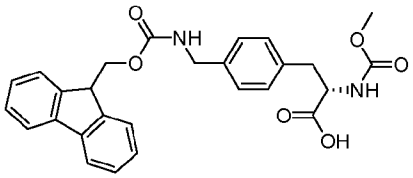
		dt J = 4.0, 12.9 Hz, 2H), 1.26 (t, J = 7.3 Hz, 6H).
Cap-107		LCMS: Anal. Calcd. for $C_8H_{10}N_2O_4S$: 230; found: 231 $(M+H)^+$.
Cap-108		LCMS: Anal. Calcd. for $C_{15}H_{17}N_3O_4$: 303; found: 304 $(M+H)^+$.
Cap-109		LCMS: Anal. Calcd. for $C_{10}H_{12}N_2O_4$: 224; found: 225 $(M+H)^+$.
Cap-110		LCMS: Anal. Calcd. for $C_{10}H_{12}N_2O_4$: 224; found: 225 $(M+H)^+$.
Cap-111		LCMS: Anal. Calcd. for $C_{12}H_{16}NO_8P$: 333; found: 334 $(M+H)^+$.
Cap-112		LCMS: Anal. Calcd. for $C_{13}H_{14}N_2O_4$: 262; found: 263 $(M+H)^+$.

Cap-113		LCMS: Anal. Calcd. for $C_{18}H_{19}NO_5$: 329; found: 330 $(M+H)^+$.
Cap-114		^{1}HNMR (400 MHz, $CDCl_3$) δ 4.82 – 4.84 (m, 1H), 4.00 – 4.05 (m, 2H), 3.77 (s, 3H), 2.56 (s, br, 2H)
Cap-115		^{1}HNMR (400 MHz, $CDCl_3$) δ 5.13 (s, br, 1H), 4.13 (s, br, 1H), 3.69 (s, 3H), 2.61 (d, *J* = 5.0 Hz, 2H), 1.28 (d, *J* = 9.1 Hz, 3H).
Cap-116		^{1}HNMR (400 MHz, $CDCl_3$) δ 5.10 (d, *J* = 8.6 Hz, 1H), 3.74 – 3.83 (m, 1H), 3.69 (s, 3H), 2.54 – 2.61 (m, 2H), 1.88 (sept, *J* = 7.0 Hz, 1H), 0.95 (d, *J* = 7.0 Hz, 6H).

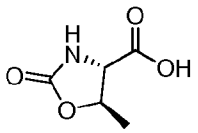
Cap-117 to Cap-123

For the preparation of caps *Cap*-117 to *Cap*-123 the the Boc amino acids were commercially available and were deprotected by treatment with 25% TFA in CH_2Cl_2. After complete reaction as judged by LCMS the solvents were removed *in vacuo* and the corresponding TFA salt of the amino acid was carbamoylated with methyl chloroformate according to the procedure for *Cap*-51.

Cap	Structure	LCMS
Cap-117		LCMS: Anal. Calcd. for $C_{12}H_{15}NO_4S$: 237; found: 238 $(M+H)^-$.
Cap-118		LCMS: Anal. Calcd. for $C_{10}H_{13}NO_4S$: 243; found: 244 $(M+H)^-$.
Cap-119		LCMS: Anal. Calcd. for $C_{10}H_{13}NO_4S$: 243; found: 244 $(M+H)^-$.
Cap-120		LCMS: Anal. Calcd. for $C_{10}H_{13}NO_4S$: 243; found: 244 $(M+H)^-$.
Cap-121		^{1}HNMR (400 MHz, $CDCl_3$) δ 4.06 – 4.16 (m, 1H), 3.63 (s, 3H), 3.43 (s, 1H), 2.82 and 2.66 (s, br, 1H), 1.86 – 2.10 (m, 3H), 1.64 – 1.76 (m, 2H), 1.44 – 1.53 (m, 1H).
Cap-122		^{1}HNMR (400 MHz, $CDCl_3$) δ 5.28 and 5.12 (s, br, 1H), 3.66 (s, 3H), 2.64 – 2.74 (m, 1H), 1.86 - 2.12 (m, 3H), 1.67 – 1.74 (m, 2H), 1.39 – 1.54 (m, 1H).

Cap-123		LCMS: Anal. Calcd. for $C_{27}H_{26}N_2O_6$: 474; found: 475 $(M+H)^-$.

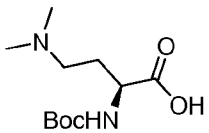
Preparation of *Cap*-124 . (4S,5R)-5-methyl-2-oxooxazolidine-4-carboxylic acid



cap-124

The hydrochloride salt of L-threonine tert-butyl ester was carbamoylated according to the procedure for *Cap*-51. The crude reaction mixture was acidified with 1N HCl to pH~1 and the mixture was extracted with EtOAc (2X50 mL). The combined organic phases were concentrated *in vacuo* to give a colorless which solidified on standing. The aqueous layer was concentrated *in vacuo* and the resulting mixture of product and inorganic salts was triturated with EtOAc-CH_2Cl_2-MeOH (1:1:0.1) and then the organic phase concentrated *in vacuo* to give a colorless oil which was shown by LCMS to be the desired product. Both crops were combined to give 0.52 g of a solid. ^{1}HNMR (400 MHz, CD_3OD) δ 4.60 (m, 1H), 4.04 (d, J = 5.0 Hz, 1H), 1.49 (d, J = 6.3 Hz, 3H). LCMS: Anal. Calcd. for $C_5H_7NO_4$: 145; found: 146 $(M+H)^+$.

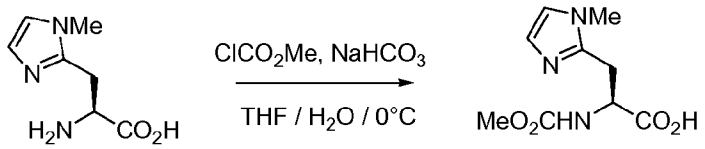
Preparation of *Cap*-125. (S)-2-(tert-butoxycarbonylamino)-4-(dimethylamino)butanoic acid.



cap-125

Cap-125 was prepared according to the procedure for the preparation of *Cap*-1. The crude product was used as is in subsequent reactions. LCMS: Anal. Calcd. for $C_{11}H_{22}N_2O_4$: 246; found: 247 $(M+H)^+$.

Preparation of (S)-2-(methoxycarbonylamino)-3-(1-methyl-1H-imidazol-2-yl)propanoic acid (*Cap*-126).



cj-25 *cap-126*

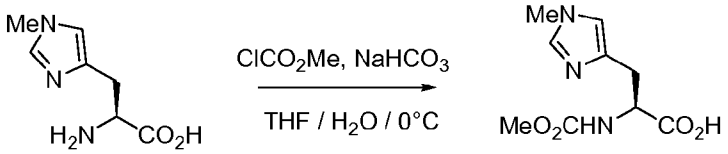
This procedure is a modification of that used to prepare *Cap*-51. To a suspension of (S)-2-amino-3-(1-methyl-1H-imidazol-2-yl)propanoic acid (0.80 g, 4.70 mmol) in THF (10mL) and H_2O (10 mL) at 0°C was added $NaHCO_3$ (0.88 g, 10.5 mmol). The resulting mixture was treated with $ClCO_2Me$ (0.40 mL, 5.20 mmol) and the mixture allowed to stir at 0°C. After stirring for ca. 2h LCMS showed no starting material remaining. The reaction was acidified to pH 2 with 6 N HCl.

The solvents were removed *in vacuo* and the residue was suspended in 20 mL of 20% MeOH in CH_2Cl_2. The mixture was filtered and concentrated to give a light yellow foam (1.21 g,). LCMS and ^1H NMR showed the material to be a 9:1 mixture of the methyl ester and the desired product. This material was taken up in THF (10mL) and H_2O (10mL), cooled to 0°C and LiOH (249.1 mg, 10.4 mmol) was added. After stirring ca. 1h LCMS showed no ester remaining. Therefore the mixture was acidified with 6N HCl and the solvents removed *in vacuo*. LCMS and ^1H NMR confirm the absence of the ester. The title compound was obtained as its HCl salt contaminated with inorganic salts (1.91 g, >100%). The compound was used as is in subsequent steps without further purification.

^{1}HNMR (400 MHz, CD_3OD) δ 8.84, (s, 1H), 7.35 (s, 1H), 4.52 (dd, J = 5.0, 9.1 Hz, 1H), 3.89 (s, 3H), 3.62 (s, 3H), 3.35 (dd, J = 4.5, 15.6 Hz, 1H, partially obscured by solvent), 3.12 (dd, J = 9.0, 15.6 Hz, 1H).

LCMS: Anal. Calcd. for $C_{17}H_{15}NO_2$: 392; found: 393 $(M+H)^+$.

Preparation of (S)-2-(methoxycarbonylamino)-3-(1-methyl-1H-imidazol-4-yl)propanoic acid (*Cap*-127).



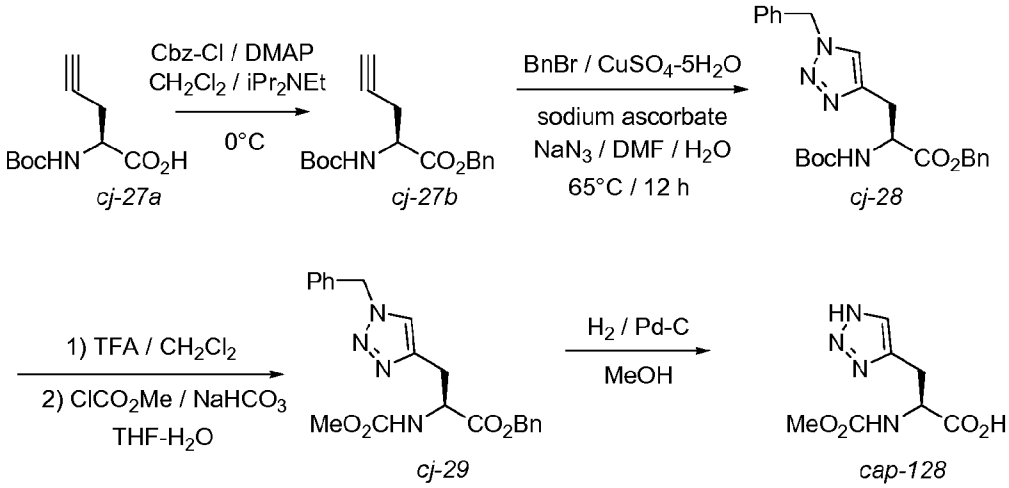
cj-26 *cap-127*

Cap-127 was prepared according to the method for *Cap*-126 above starting from (S)-2-amino-3-(1-methyl-1H-imidazol-4-yl)propanoic acid (1.11 g, 6.56 mmol), $NaHCO_3$ (1.21 g, 14.4 mmol) and $ClCO_2Me$ (0.56 mL, 7.28 mmol). The title compound was obtained as its HCl salt (1.79 g, >100%) contaminated with inorganic salts. LCMS and ^1H NMR showed the presence of ca. 5% of the methyl ester. The crude mixture was used as is without further purification.

^{1}HNMR (400 MHz, CD_3OD) δ 8.90 (s, 1H), 7.35 (s, 1H), 4.48 (dd, J = 5.0, 8.6 Hz, 1H), 3.89 (s, 3H), 3.62 (s, 3H), 3.35 (m, 1H), 3.08 (m, 1H).

LCMS: Anal. Calcd. for $C_{17}H_{15}NO_2$: 392; found: 393 $(M+H)^+$.

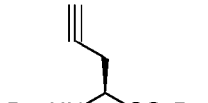
Preparation of (S)-2-(methoxycarbonylamino)-3-(1H-1,2,3-triazol-4-yl)propanoic acid (*Cap*-128).



cj-27a *cj-27b* *cj-28*

cj-29 *cap-128*

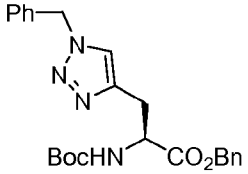
Step 1. Preparation of (S)-benzyl 2-(tert-butoxycarbonylamino)pent-4-ynoate (cj-27b).



cj-27b

To a solution of cj-27a (1.01 g, 4.74 mmol), DMAP (58 mg, 0.475 mmol) and iPr_2NEt (1.7 mL, 9.8 mmol) in CH_2Cl_2 (100 mL) at 0°C was added Cbz-Cl (0.68 mL, 4.83 mmol). The solution was allowed to stir for 4 h at 0°C, washed (1N $KHSO_4$, brine), dried (Na_2SO_4), filtered, and concentrated *in vacuo*. The residue was purified by flash column chromatography (TLC 6:1 hex:EtOAc) to give the title compound (1.30 g, 91%) as a colorless oil. ^{1}HNMR (400 MHz, $CDCl_3$) δ 7.35 (s, 5H), 5.35 (d, br, J = 8.1 Hz, 1H), 5.23 (d, J = 12.2 Hz, 1H), 5.17 (d, J = 12.2 Hz, 1H), 4.48 – 4.53 (m, 1H), 2.68 – 2.81 (m, 2H), 2.00 (t, J = 2.5 Hz, 1H), 1.44 (s, 9H). LCMS: Anal. Calcd. for $C_{17}H_{21}NO_4$: 303; found: 304 $(M+H)^+$.

Step 2. Preparation of (S)-benzyl 3-(1-benzyl-1H-1,2,3-triazol-4-yl)-2-(tert-butoxycarbonylamino)propanoate (cj-28).

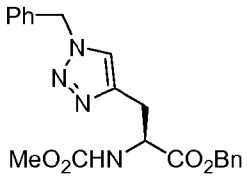


cj-28

To a mixture of (S)-benzyl 2-(tert-butoxycarbonylamino)pent-4-ynoate (0.50 g, 1.65 mmol), sodium ascorbate (0.036 g, 0.18 mmol), $CuSO_4$-$5H_2O$ (0.022 g, 0.09 mmol) and NaN_3 (0.13 g, 2.1 mmol) in DMF-H_2O (5 mL, 4:1) at rt was added BnBr (0.24 mL, 2.02 mmol) and the mixture was warmed to 65°C . After 5h LCMS indicated low conversion. A further portion of NaN_3 (100 mg) was added and heating was continued for 12h. The reaction was poured into EtOAc and H_2O and shaken. The layers were separated and the aqueous layer extracted 3x with EtOAc and the combined organic phases washed (H_2O x3, brine), dried (Na_2SO_4), filtered, and concentrated. The residue was purified by flash (Biotage, 40+M 0-5% MeOH in CH_2Cl_2; TLC 3% MeOH in CH_2Cl_2) to afford a light yellow oil which solidified on

standing (748.3 mg, 104%). The NMR was consistent with the desired product but suggests the presence of DMF. The material was used as is without further purification. ^{1}HNMR (400 MHz, DMSO-d_6) δ 7.84 (s, 1H), 7.27 – 7.32 (m, 10H), 5.54 (s, 2H), 5.07 (s, 2H), 4.25 (m, 1H), 3.16 (dd, J = 1.0, 5.3 Hz, 1H), 3.06 (dd, J = 5.3, 14.7 Hz), 2.96 (dd, J = 9.1, 14.7 Hz, 1H), 1.31 (s, 9H).
LCMS: Anal. Calcd. for $C_{24}H_{28}N_4O_4$: 436; found: 437 $(M+H)^+$.

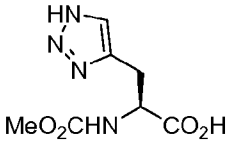
Step 2. Preparation of (S)-benzyl 3-(1-benzyl-1H-1,2,3-triazol-4-yl)-2-(methoxycarbonylamino)propanoate (cj-29).



cj-29

A solution of (S)-benzyl 3-(1-benzyl-1H-1,2,3-triazol-4-yl)-2-(tert-butoxycarbonylamino)propanoate (0.52 g, 1.15 mmol) in CH_2Cl_2 was added TFA (4 mL). The mixture was allowed to stir at room temperature for 2h. The mixture was concentrated *in vacuo* to give a colorless oil which solidified on standing. This material was dissolved in THF-H_2O and cooled to 0°C. Solid $NaHCO_3$ (0.25 g, 3.00 mmol) was added followed by $ClCO_2Me$ (0.25 mL, 3.25 mmol). After stirring for 1.5h the mixture was acidified to pH~2 with 6N HCl and then poured into H_2O-EtOAc. The layers were separated and the aq phase extracted 2x with EtOAc. The combined org layers were washed (H_2O, brine), dried (Na_2SO_4), filtered, and concentrated *in vacuo* to give a colorless oil (505.8 mg, 111%, NMR suggested the presence of an unidentified impurity) which solidified while standing on the pump. The material was used as is without further purification. ^{1}HNMR (400 MHz, DMSO-d_6) δ 7.87 (s, 1H), 7.70 (d, J = 8.1 Hz, 1H), 7.27 – 7.32 (m, 10H), 5.54 (s, 2H), 5.10 (d, J = 12.7 Hz, 1H), 5.06 (d, J = 12.7 Hz, 1H), 4.32 – 4.37 (m, 1H), 3.49 (s, 3H), 3.09 (dd, J = 5.6, 14.7 Hz, 1H), 2.98 (dd, J = 9.6, 14.7 Hz, 1H). LCMS: Anal. Calcd. for $C_{21}H_{22}N_4O_4$: 394; found: 395 $(M+H)^+$.

Step 3. Preparation of (S)-2-(methoxycarbonylamino)-3-(1H-1,2,3-triazol-4-yl)propanoic acid (*Cap*-128).

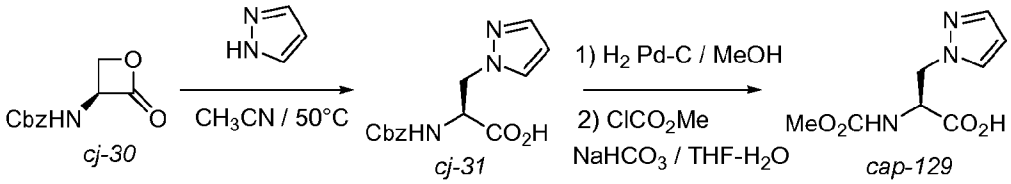


Cap-128

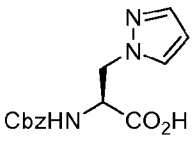
(S)-benzyl 3-(1-benzyl-1H-1,2,3-triazol-4-yl)-2-(methoxycarbonylamino)propanoate (502 mg, 1.11 mmol) was hydrogenated in the presence of Pd-C (82 mg) in MeOH (5 mL) at atmospheric pressure for 12h. The mixture was filtered through diatomaceous earth (Celite®) and concentrated *in vacuo*. (S)-2-(methoxycarbonylamino)-3-(1H-1,2,3-triazol-4-yl)propanoic acid was obtained as a colorless gum (266 mg, 111%) which was contaminated with ca. 10% of the methyl ester. The material was used as is without further purification.

^{1}HNMR (400 MHz, DMSO-d_6) δ 12.78 (s, br, 1H), 7.59 9s, 1H), 7.50 (d, J = 8.0 Hz, 1H), 4.19 – 4.24 (m, 1H), 3.49 (s, 3H), 3.12 (dd, J = 4.8 Hz, 14.9 Hz, 1H), 2.96 (dd, J = 9.9, 15.0 Hz, 1H). LCMS: Anal. Calcd. for $C_7H_{10}N_4O_4$: 214; found: 215 $(M+H)^+$.

Preparation of (S)-2-(methoxycarbonylamino)-3-(1H-pyrazol-1-yl)propanoic acid (*Cap*-129).



Step 1. Preparation of (S)-2-(benzyloxycarbonylamino)-3-(1H-pyrazol-1-yl)propanoic acid (cj-31).

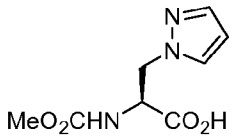


cj-31

A suspension of (S)-benzyl 2-oxooxetan-3-ylcarbamate (0.67 g, 3.03 mmol), and pyrazole (0.22 g, 3.29 mmol) in CH_3CN (12 mL) was heated at 50°C for 24h. The mixture was cooled to rt overnight and the solid filtered to afford (S)-2-(benzyloxycarbonylamino)-3-(1H-pyrazol-1-yl)propanoic acid (330.1 mg). The filtrate was concentrated *in vacuo* and then triturated with a small amount of CH_3CN (ca. 4 mL) to afford a second crop (43.5 mg). Total yield 370.4 mg (44%). m.p. 165.5 – 168°C. lit m.p. 168.5 – 169.5 Vederas et al. *J. Am. Chem. Soc.* 1985, *107*, 7105.

^{1}HNMR (400 MHz, CD_3OD) δ 7.51 (d, *J* = 2.0, 1H), 7.48 (s, *J* = 1.5 Hz, 1H), 7.24 – 7.34 (m, 5H), 6.23 m, 1H), 5.05 (d, 12.7 H, 1H), 5.03 (d, *J* = 12.7 Hz, 1H), 4.59 – 4.66 (m, 2H), 4.42 – 4.49 (m, 1H). LCMS: Anal. Calcd. for $C_{14}H_{15}N_3O_4$: 289; found: 290 $(M+H)^+$.

Step 2. Preparation of (S)-2-(methoxycarbonylamino)-3-(1H-pyrazol-1-yl)propanoic acid (*Cap*-129).

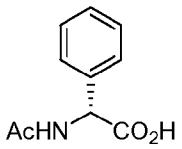


cap-129

(S)-2-(benzyloxycarbonylamino)-3-(1H-pyrazol-1-yl)propanoic acid (0.20 g, 0.70 mmol) was hydrogenated in the presence of Pd-C (45 mg) in MeOH (5 mL) at atmospheric pressure for 2h. The product appeared to be insoluble in MeOH, therefore the rxn mixture was diluted with 5mL H_2O and a few drops of 6N HCl. The homogeneous solution was filtered through diatomaceous earth (Celite®), and the MeOH removed *in vacuo*. The remaining solution was frozen and lyophyllized to give a yellow foam (188.9 mg). This material was suspended in THF-H_2O (1:1, 10mL) and then cooled to 0°C. To the cold mixture was added $NaHCO_3$ (146.0 mg, 1.74 mmol) carefully (evolution of CO_2). After gas evolution had ceased (ca. 15 min) $ClCO_2Me$ (0.06 mL, 0.78 mmol) was added dropwise. The mixture was allowed to stir for 2h and was acidified to pH~2 with 6N HCl and poured into EtOAc. The layers were separated and the aqueous phase extract with EtOAC (x5).

The combined organic layers were washed (brine), dried (Na_2SO_4), filtered, and concentrated to give the title compound as a colorless solid (117.8 mg, 79%). ^{1}HNMR (400 MHz, DMSO-d_6) δ 13.04 (s, 1H), 7.63 (d, J = 2.6 Hz, 1H), 7.48 (d, J = 8.1 Hz, 1H), 7.44 (d, J = 1.5 Hz, 1H), 6.19 (app t, J = 2.0 Hz, 1H), 4.47 (dd, J = 3.0, 12.9 Hz, 1H), 4.29 – 4.41 (m, 2H), 3.48 (s, 3H). LCMS: Anal. Calcd. for $C_8H_{11}N_3O_4$: 213; found: 214 $(M+H)^+$.

Cap-130. N-Acetyl –(R)-Phenylglycine



cap-130

Cap-130 was prepared by acylation of commercially available (R)-phenylglycine analgous to the procedure given in: Calmes, M.; Daunis, J.; Jacquier, R.; Verducci, J. *Tetrahedron*, 1987, *43*(10), 2285.

EXAMPLES

The present disclosure will now be described in connection with certain embodiments which are not intended to limit its scope. On the contrary, the present disclosure covers all alternatives, modifications, and equivalents as can be included within the scope of the claims. Thus, the following examples, which include specific embodiments, will illustrate one practice of the present disclosure, it being understood that the examples are for the purposes of illustration of certain embodiments and are presented to provide what is believed to be the most useful and readily understood description of its procedures and conceptual aspects.

Solution percentages express a weight to volume relationship, and solution ratios express a volume to volume relationship, unless stated otherwise. Nuclear magnetic resonance (NMR) spectra were recorded either on a Bruker 300, 400, or 500 MHz spectrometer; the chemical shifts (δ) are reported in parts per million. Flash chromatography was carried out on silica gel (SiO_2) according to Still's flash chromatography technique (*J. Org. Chem.* **1978**, *43*, 2923).

Purity assessment and low resolution mass analysis were conducted on a Shimadzu LC system coupled with Waters Micromass ZQ MS system. It should be noted that retention times may vary slightly between machines. The LC conditions employed in determining the retention time (RT) were:

Condition 1

Column = Phenomenex-Luna 3.0X 50 mm S10
Start %B = 0
Final %B = 100
Gradient time = 2 min
Stop time = 3 min
Flow Rate = 4 mL/min
Wavelength = 220 nm
Solvent A = 0.1% TFA in 10% methanol/90%H_2O
Solvent B = 0.1% TFA in 90% methanol/10% H_2O

Condition 2

Column = Phenomenex-Luna 4.6X50 mm S10
Start %B = 0
Final %B = 100
Gradient time = 2 min
Stop time = 3 min
Flow Rate = 5 mL/min
Wavelength = 220 nm
Solvent A = 0.1% TFA in 10% methanol/90%H_2O
Solvent B = 0.1% TFA in 90% methanol/10% H_2O

Condition 3

Column = HPLC XTERRA C18 3.0 x 50mm S7
Start %B = 0
Final %B = 100
Gradient time = 3 min
Stop time = 4 min
Flow Rate = 4 mL/min

Wavelength = 220 nm
Solvent A = 0.1% TFA in 10% methanol/90%H_2O
Solvent B = 0.1% TFA in 90% methanol/10% H_2O

Method A: LCMS – Xterra MS C-18 3.0 x 50mm, 0 to 100% B over 30.0 minute gradient, 1 minute hold time, A = 5% acetonitrile, 95% water, 10mm ammonium acetate, B = 95% acetonitrile, 5% water, 10mm ammonium acetate.

Method B: HPLC – X-Terra C-18 4.6 x 50mm, 0 to 100% B over 10.0 minute gradient, 1 minute hold time, A = 10% methanol 90% water 0.1% TFA, B = 90% methanol 10% water 0.1% TFA

Method C: HPLC – YMC C-18 4.6 x 50mm, 0 to 100% B over 10.0 minute gradient, 1 minute hold time, A = 10% methanol 90% water 0.2% H_3PO_4, B = 90% methanol 10% water 0.2% H_3PO_4.

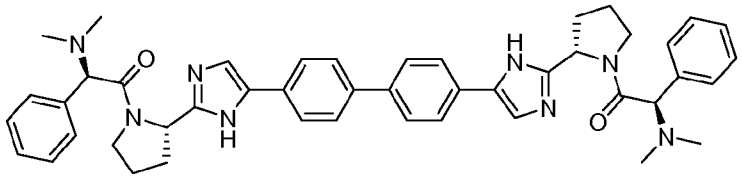
Method D: HPLC – Phenomenex C-18 4.6 x 150mm, 0 to 100% B over 10.0 minute gradient, 1 minute hold time, A = 10% methanol 90% water 0.2% H_3PO_4, B = 90% methanol 10% water 0.2% H_3PO_4

Method E: LCMS – Gemini C-18 4.6 x 50mm, 0 to 100% B over 10.0 minute gradient, 1 minute hold time, A = 5% acetonitrile, 95% water, 10mm ammonium acetate, B = 95% acetonitrile, 5% water, 10mm ammonium acetate.

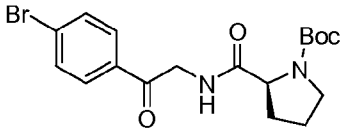
Method F: LCMS-Luna C-18 3.0 x 50mm, 0 to 100% B over 7.0 minute gradient, 1 minute hold time, A = 5% acetonitrile, 95% water, 10mm ammonium acetate, B = 95% acetonitrile, 5% water, 10mm ammonium acetate.

Example 1

(1R,1'R)-2,2'-(4,4'-biphenyldiylbis(1H-imidazole-5,2-diyl(2S)-2,1-pyrrolidinediyl))bis(N,N-dimethyl-2-oxo-1-phenylethanamine)



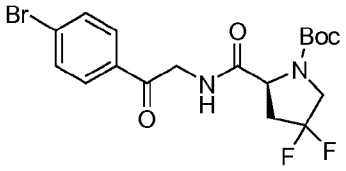
Example 1, Step a



1a

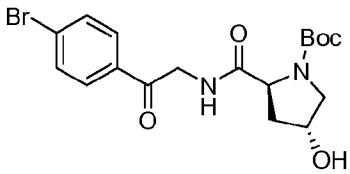
N,N-Diisopropylethylamine (18 mL, 103.3 mmol) was added dropwise, over 15 minutes, to a heterogeneous mixture of *N*-Boc-L-proline (7.139 g, 33.17 mmol), HATU (13.324 g, 35.04 mmol), the HCl salt of 2-amino-1-(4-bromophenyl)ethanone (8.127 g, 32.44 mmol), and DMF (105 mL), and stirred at ambient condition for 55 minutes. Most of the volatile component was removed *in vacuo*, and the resulting residue was partitioned between ethyl acetate (300 mL) and water (200 mL). The organic layer was washed with water (200 mL) and brine, dried ($MgSO_4$), filtered, and concentrated *in vacuo*. A silica gel mesh was prepared from the residue and submitted to flash chromatography (silica gel; 50-60 % ethyl acetate/hexanes) to provide ketoamide 1a as a white solid (12.8 g). ^{1}H NMR (DMSO-d_6, δ = 2.5 ppm, 400 MHz): δ 8.25-8.14 (m, 1H), 7.92 (br d, J = 8.0, 2H), 7.75 (br d, J = 8.6, 2H), 4.61 (dd, J = 18.3, 5.7, 1H), 4.53 (dd, J = 18.1, 5.6, 1H), 4.22-4.12 (m, 1H), 3.43-3.35 (m, 1H), 3.30-3.23 (m, 1H), 2.18-2.20 (m, 1H), 1.90-1.70 (m, 3H), 1.40/1.34 (two app br s, 9H). LC (Cond. 1): RT = 1.70 min; LC/MS: Anal. Calcd. for $[M+Na]^+$ $C_{18}H_{23}BrN_2NaO_4$: 433.07; found 433.09.

Analogous compounds such as intermediate 1-1a to 1-5a can be prepared by incorporating the appropriately substituted amino acid and aryl bromide isomer.



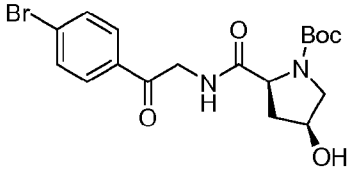
1-1a

^{1}H NMR (500 MHz, DMSO-d_6) δ ppm 1.35/1.40 (two br s, 9H), 2.27-2.42 (m, 1H), 2.73-2.95 (m, 1H), 3.62-3.89 (m, 2H), 4.36-4.50 (m, 1H), 4.51-4.60 (m, 1H), 4.62-4.73 (m, 1H), 7.75 (d, *J*=8.24 Hz, 2H), 7.92 (d, *J*=7.63 Hz, 2H), 8.31-8.49 (m, 1H). HPLC XTERRA C-18 4.6 × 30 mm, 0 to 100% B over 4 minutes, 1 minute hold time, A = 90% water, 10% methanol, 0.2% H_3PO_4, B = 10% water, 90% methanol, 0.2% H_3PO_4, RT = 1.59 minutes, 99% homogeneity index. LCMS: Anal. Calcd. for $C_{18}H_{21}BrF_2N_2O_4$: 446.06; found: 445.43 $(M-H)^-$.



1-2a

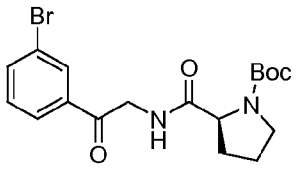
^{1}H NMR (500 MHz, DMSO-d_6) δ ppm (8.25 1H, s), 7.91 (2H, d, *J*=8.24Hz), 7.75 (2H, d, *J*=8.24 Hz), 4.98 (1H, s), 4.59-4.63 (1H, m), 4.46-4.52 (1H, m), 4.23 (1H, m), 3.37 (1H, s), 3.23-3.28 (1H, m), 2.06 (1H, m), 1.88 (1H, s), 1.38 (3H, s), 1.33 (6H, s). LCMS – Phenomenex C-18 3.0 x 50mm, 0 to 100% B over 4.0 minute gradient, 1 minute hold time, A = 10% methanol 90% water 0.1% TFA, B = 90% methanol 10% water 0.1% TFA mobile phase, RT = 3.34 minutes, Anal Calcd. for $C_{18}H_{23}BrN_2O_5$ 427.30; found 428.08 $(M+H)^+$.



1-3a

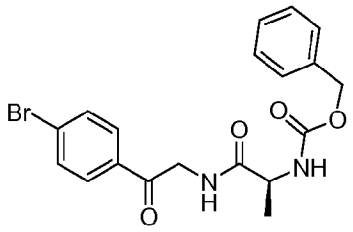
^{1}H NMR (500 MHz, DMSO-d_6) δ ppm 8.30 (1H, s) 7.93-7.96 (2H, m) 7.76 (2H d, *J*=8.24 Hz) 5.13 (1H, s) 4.66-4.71 (1H, m) 4.52-4.55 (1H, m) 4.17 (1H, m) 3.51 (1H,

s) 3.16-3.19 (1H, m) 2.36 (1H, m) 1.78 (1H, s) 1.40 (s, 3H), 1.34 (s, 6H). LCMS – Phenomenex C-18 3.0 x 50mm, 0 to 100% B over 4.0 minute gradient, 1 minute hold time, A = 10% methanol 90% water 0.1% TFA, B = 90% methanol 10% water 0.1% TFA, RT= 3.69 minutes, Anal Calcd. for $C_{18}H_{23}BrN_2O_5$ 427.30; found 428.16 $(M+H)^+$.



1-4a

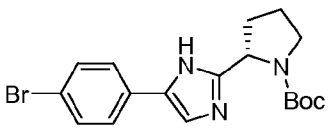
^{1}H NMR (500 MHz, DMSO-d_6) δ ppm 1.29-1.47 (m, 9H), 1.67-1.90 (m, 3H), 2.00-2.20 (m, 1H), 3.23-3.30 (m, 1H), 3.34-3.44 (m, 1H), 4.16 (dd, 1H), 4.57 (q, 2H), 7.51 (t, *J*=7.78 Hz, 1H), 7.86 (dd, *J*=7.93, 1.22 Hz, 1H), 7.98 (d, *J*=7.63 Hz, 1H), 8.11 (s, 1H), 8.15-8.29 (m, 1H). LC/MS $(M+Na)^+$ = 433.12/435.12.



1-5a

LCMS conditions: Phenomenex LUNA C-18 4.6 × 50 mm, 0 to 100% B over 2 minutes, 1 minute hold time, A = 90% water, 10% methanol, 0.1% TFA, B = 10% water, 90% methanol, 0.1% TFA, 220nm, 5 μL injection volume. RT = 1.93 min; LRMS: Anal. Calcd. for $C_{19}H_{18}BrN_2O_4$ 418.05; found: 419.07 $(M+H)^+$.

Example 1, Step b



1b

A mixture of ketoamide 1a (12.8 g, 31.12 mmol) and NH_4OAc (12.0 g, 155.7 mmol) in xylenes (155 mL) was heated in a sealed tube at 140 °C for 2 hours. The volatile component was removed *in vacuo*, and the residue was partitioned carefully between ethyl acetate and water, whereby enough saturated $NaHCO_3$ solution was added so as to make the pH of the aqueous phase slightly basic after the shaking of the biphasic system. The layers were separated, and the aqueous layer was extracted with an additional ethyl acetate. The combined organic phase was washed with brine, dried ($MgSO_4$), filtered, and concentrated *in vacuo*. The resulting material was recrystallized from ethyl acetate/hexanes to provide two crops of imidazole 1b as a light-yellow dense solid, weighing 5.85 g. The mother liquor was concentrated *in vacuo* and submitted to a flash chromatography (silica gel; 30% ethyl acetate/hexanes) to provide an additional 2.23 g of imidazole 1b. ^1H NMR (DMSO-d_6, δ = 2.5 ppm, 400 MHz): δ 12.17/11.92/11.86 (m, 1H), 7.72-7.46/7.28 (m, 5H), 4.86-4.70 (m, 1H), 3.52 (app br s, 1H), 3.36 (m, 1H), 2.30-1.75 (m, 4H), 1.40/1.15 (app br s, 9H). LC (Cond. 1): RT = 1.71 min; >98% homogeneity index; LC/MS: Anal. Calcd. for $[M+H]^+$ $C_{18}H_{23}BrN_3O_2$: 392.10; found 391.96; HRMS: Anal. Calcd. for $[M+H]^+$ $C_{18}H_{23}BrN_3O_2$: 392.0974; found 392.0959

The optical purity of the two samples of 1b were assessed using the chiral HPLC conditions noted below (ee > 99% for the combined crops; ee = 96.7% for the sample from flash chromatography):

Column: Chiralpak AD, 10 um, 4.6 x 50 mm

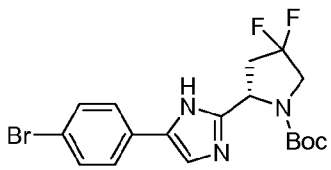
Solvent: 2% ethanol/heptane (isocratic)

Flow rate: 1 mL/min

Wavelength: either 220 or 254 nm

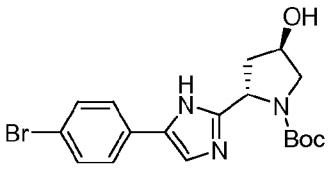
Relative retention time: 2.83 minutes (*R*), 5.34 minutes (*S*)

Analogous compounds such as intermediates 1-1b to 1-4b can be prepared by incorporating the appropriate ketoamide.



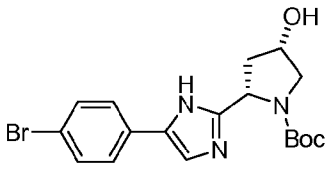
1-1b

^{1}H NMR (500 MHz, DMSO-d_6) δ ppm 1.17/1.40 (two br s, 9H), 2.50-2.74 (m, *J*=25.64 Hz, 1H), 2.84-3.07 (m, 1H), 3.88 (d, *J*=10.07 Hz, 2H), 5.03 (s, 1H), 7.50 (d, *J*=8.55 Hz, 2H), 7.60 (s, 1H), 7.70 (d, *J*=8.55 Hz, 2H), 12.10 (s, 1H). HPLC XTERRA C-18 4.6 × 30 mm, 0 to 100% B over 4 minutes, 1 minute hold time, A = 90% water, 10% methanol, 0.2% H_3PO_4, B = 10% water, 90% methanol, 0.2% H_3PO_4, RT = 1.59 minutes, 99% homogeneity index; LCMS: Anal. Calcd. for $C_{18}H_{20}BrF_2N_3O_2$: 428.27; found: 428.02 $(M)^+$.



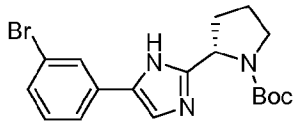
1-2b

^{1}H NMR (500 MHz, DMSO-d_6) δ ppm 11.89-11.99 (1H, m), 7.68 (2H, d, *J*=8.54 Hz), 7.52-7.59 (1H, m), 7.48 (2H, d, *J*=8.54 Hz), 4.80 (1H, m), 4.33 (1H, s), 3.51-3.60 (1H, m), 3.34 (1H, d, *J*=10.99 Hz), 2.14 (1H, s), 1.97-2.05 (1H, m), 1.37 (3H, s), 1.10 (6H, s); LCMS – Phenomenex C-18 3.0 x 50mm, 0 to 100% B over 4.0 minute gradient, 1 minute hold time, A = 10% methanol 90% water 0.1% TFA, B = 90% methanol 10% water 0.1% TFA, (RT= 3.23 min) Anal Calcd. for $C_{18}H_{22}BrN_3O_3$ 408.30; found 409.12 $(M+H)^+$.



1-3b

^{1}H NMR (500 MHz, DMSO-d_6) δ ppm 12.06-12.24 (1H, m), 7.58-7.69 (5H, m), 4.84-4.95 (1H, m), 4.34 (1H, s), 3.61 (1H, s), 3.34-3.40 (1H, m), 2.52 (1H, s), 1.92-2.20 (1H, m), 1.43 (3H, s), 1.22 (6H, s); LCMS – Phenomenex C-18 3.0 x 50mm, 0 to 100% B over 4.0 minute gradient, 1 minute hold time, A = 10% methanol 90% water 0.1% TFA, B = 90% methanol 10% water 0.1% TFA, (RT= 3.41 min) Anal Calcd. for $C_{18}H_{22}BrN_3O_3$ 408.30; found 409.15 $(M+H)^+$.



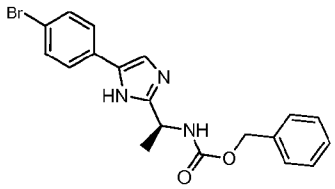
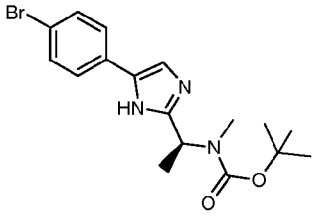
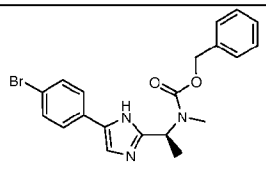
1-4b

^{1}H NMR (500 MHz, DMSO-d_6) δ ppm 0.98-1.51 (m, 9H), 1.82-2.12 (m, 3H), 2.31-2.48 (m, 1H), 3.30-3.51 (m, 1H), 3.52-3.66 (m, 1H), 4.88-5.16 (m, 1H), 7.47 (t, *J*=7.93 Hz, 1H), 7.61 (d, *J*=7.93 Hz, 1H), 7.81 (d, *J*=7.93 Hz, 1H), 8.04 (s, 1H), 8.12 (d, *J*=28.38 Hz, 1H), 14.65 (s, 1H). LC/MS $(M+H)^-$ = 391.96/393.96.

Additional imidazole analogs made following procedures similar to those described above.

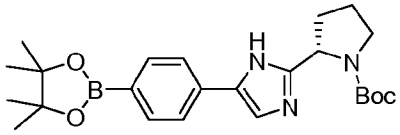
LC conditions: *Condition 1*: Phenomenex LUNA C-18 4.6 × 50 mm, 0 to 100% B over 3 minutes, 1 minute hold time, A = 90% water, 10% methanol, 0.1% TFA, B = 10% water, 90% methanol, 0.1% TFA, 220nm, 5 µL injection volume.

Condition 2: Phenomenex LUNA C-18 4.6 × 50 mm, 0 to 100% B over 2 minutes, 1 minute hold time, A = 90% water, 10% methanol, 0.1% TFA, B = 10% water, 90% methanol, 0.1% TFA, 220nm, 5 µL injection volume.

Example	Structure	Data
1-5b		RT = 1.70 minutes (condition 2, 98%); LRMS: Anal. Calcd. for $C_{19}H_{18}BrN_3O_2$ 399.05; found: 400.08 $(M+H)^+$.
1-6b		RT = 1.64 minutes (condtion 2, 98%); LRMS: Anal. Calcd. for $C_{17}H_{22}N_3O_2$ 379.09; found: 380.06 $(M+H)^+$.
1-7b		RT = 2.28 minutes (95%); LRMS: Anal. Calcd. for $C_{20}H_{21}BrN_3O_2$

		414.08; found: 414.08 $(M+H)^+$; HRMS: Anal. Calcd. for $C_{20}H_{21}BrN_3O_2$ 414.0817; found: 414.0798 $(M+H)^+$.

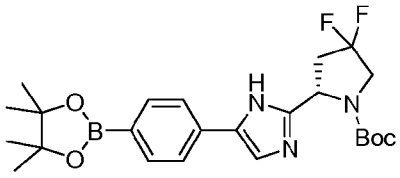
Example 1, Step c



1c

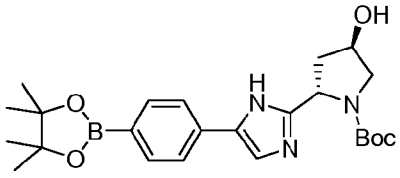
$Pd(Ph_3P)_4$ (469 mg, 0.406 mmol) was added to a pressure tube containing a mixture of bromide 1b (4.008 g, 10.22 mmol), bis(pinacolato)diboron (5.422 g, 21.35 mmol), potassium acetate (2.573g, 26.21 mmol) and 1,4-dioxane (80 mL). The reaction flask was purged with nitrogen, capped and heated with an oil bath at 80 °C for 16.5 hours. The reaction mixture was filtered and the filtrate was concentrated *in vacuo*. The crude material was partitioned carefully between CH_2Cl_2 (150 mL) and an aqueous medium (50 mL water + 10 mL saturated $NaHCO_3$ solution). The aqueous layer was extracted with CH_2Cl_2, and the combined organic phase was dried ($MgSO_4$), filtered, and concentrated *in vacuo*. The resulting material was purified with flash chromatography (sample was loaded with eluting solvent; 20-35% ethyl acetate/CH_2Cl_2) to provide boronate 1c, contaminated with pinacol, as an off-white dense solid; the relative mole ratio of 1c to pinacol was about 10:1 (^{1}H NMR). The sample weighed 3.925 g after ~2.5 days exposure to high vacuum. ^{1}H NMR (DMSO-d_6, δ= 2.5 ppm, 400 MHz): 12.22/11.94/ 11.87 (m, 1H), 7.79-7.50/ 7.34-7.27 (m, 5H), 4.86-4.70 (m, 1H), 3.52 (app br s, 1H), 3.36 (m, 1H), 2.27-1.77 (m, 4H), 1.45-1.10 (m, 21H). LC (Cond. 1): RT = 1.64 min; LC/MS: Anal. Calcd. for $[M+H]^+$ $C_{24}H_{35}BN_3O_4$: 440.27; found 440.23.

Analogous compounds such as intermediates 1-1c to 1-4c can be prepared by incorporating the appropriate aryl bromide.



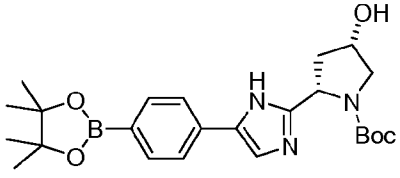
1-1c

^{1}H NMR (500 MHz, DMSO-d_6) δ ppm 1.16 (s, 8H), 1.29 (s, 13H), 2.51-2.72 (m, 1H), 2.84-3.03 (m, 1H), 3.79-4.00 (m, 2H), 4.88-5.21 (m, 1H), 7.62 (d, *J*=7.93 Hz, 2H), 7.67 (s, 1H), 7.76 (d, *J*=7.93 Hz, 2H), 12.11/12.40 (two br s, 1H). HPLC GEMINI C-18 4.6 × 50 mm, 0 to 100% B over 4 minutes, 1 minute hold time, A = 95% water, 5% acetonitrile, 0.1% NH_4OAc, B = 5% water, 95% acetonitrile, 0.1% NH_4OAc, RT = 1.62 minutes, 99% homogeneity index. LCMS: Anal. Calcd. for $C_{34}H_{32}BF_2N_3O_4$: 475.34; found: 474.78 $(M-H)^-$.



1-2c

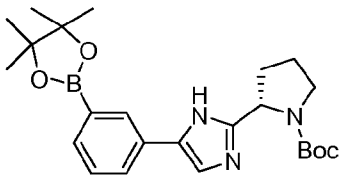
^{1}H NMR (500 MHz, DMSO-d_6) δ ppm 11.97 (1H, m), 7.62-7.75 (5H, m), 5.05 (1H d, *J*=3.36 Hz), 4.82 (m, 1H), 4.35 (m, 1H), 3.58 (1H, m), 2.389 (1H, s), 2.17 (1 H, m), 1.38 (3H, s), 1.30 (12H, s), 1.1 (6H, s); LCMS – Phenomenex C-18 3.0 x 50mm, 0 to 100% B over 4.0 minute gradient, 1 minute hold time, A = 5% acetonitrile, 95% water, 10mm ammonium acetate, B = 95% acetonitrile, 5% water, 10mm ammonium acetate, RT= 3.63 minutes, Anal. Calcd. for $C_{24}H_{34}BN_3O_5$ 455.30; found 456.31 $(M+H)^+$.



1-3c

^{1}H NMR (500 MHz, DMSO-d_6) δ ppm 12.05-12.24 (1H, m), 7.61-7.73 (5H, m), 4.83-5.01 (1H, m), 4.33 (1H, s), 3.54-3.63 (1H, m), 3.39-3.80 (1H, m), 2.38-2.49

(1H, m), 1.98-2.01 (1H, m), 1.42 (3H, s), 1.34 (12H, s), 1.21 (6H, s); LCMS – Phenomenex C-18 3.0 x 50mm, 0 to 100% B over 4.0 minute gradient, 1 minute hold time, A = 10% methanol 90% water 0.1% TFA, B = 90% methanol 10% water 0.1% TFA, RT= 3.64 minutes, Anal. Calcd. for $C_{24}H_{34}BN_3O_5$ 455.30; found 456.30 $(M+H)^+$.



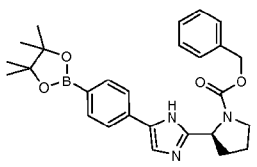
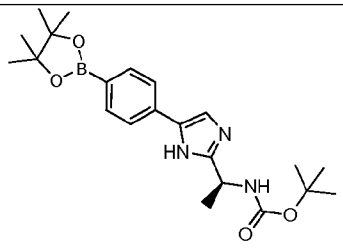
1-4c

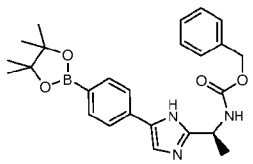
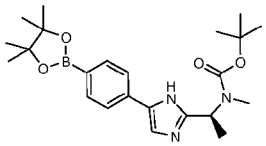
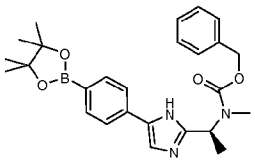
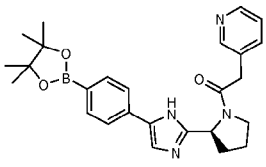
^1H NMR (500 MHz, DMSO-d_6) δ ppm 1.02-1.54 (m, 21H), 1.75-2.07 (m, 3H), 2.09-2.33 (m, 1H), 3.32-3.44 (m, 1H), 3.55 (s, 1H), 4.69-4.94 (m, 1H), 7.33 (t, *J*=7.32 Hz, 1H), 7.41-7.57 (m, 2H), 7.84 (d, *J*=7.32 Hz, 1H), 8.08 (s, 1H), 11.62-12.07 (m, 1H). LC/MS $(M+H)^+$ = 440.32.

Additional boronic esters: Conditions for 1-5c through 1-10c

LCMS conditions: *Condition 1*: Phenomenex LUNA C-18 4.6 × 50 mm, 0 to 100% B over 3 minutes, 1 minute hold time, A = 90% water, 10% methanol, 0.1% TFA, B = 10% water, 90% methanol, 0.1% TFA, 220nm, 5 µL injection volume.

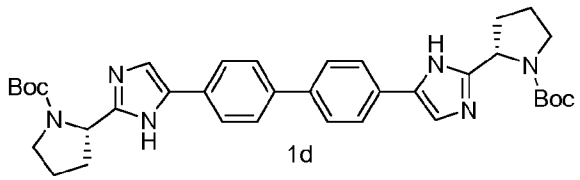
Condition 2: Phenomenex LUNA C-18 4.6 × 50 mm, 0 to 100% B over 2 minutes, 1 minute hold time, A = 90% water, 10% methanol, 0.1% TFA, B = 10% water, 90% methanol, 0.1% TFA, 220nm, 5 µL injection volume.

1-5c		RT = 1.84 minutes (condition 2); LCMS: Anal. Calcd. for $C_{27}H_{32}BN_3O_4$ 473; found: 474 $(M+H)^+$.
1-6c		RT = 1.84 minutes (condition 2); LCMS: Anal. Calcd. for $C_{22}H_{32}BN_3O_4$ 413; found: 414 $(M+H)^+$.

1-7c		RT = 1.85 minutes (condition 2); LRMS: Anal. Calcd. for $C_{25}H_{31}BN_3O_4$ 448; found: 448 $(M+H)^+$.
1-8c		RT = 2.49 (76%, boronic ester) and 1.81 (21.4%, boronic acid); LCMS: Anal. Calcd. for $C_{23}H_{35}N_3O_4B$ 428.27; found: 428.27 $(M+H)^+$; HRMS: Anal. Calcd. for $C_{23}H_{35}N_3O_4B$ 428.2721; found: 428.2716 $(M+H)^+$.
1-9c		RT = 2.54 (74.2%, boronic ester) and 1.93 (25.8%, boronic acid); LRMS: Anal. Calcd. for $C_{26}H_{33}N_3O_4B$ 462.26; found: 462.25 $(M+H)^+$; HRMS: Anal. Calcd. for $C_{26}H_{33}N_3O_4B$ 462.2564; found: 462.2570 $(M+H)^+$.
1-10c		RT = 1.91 (64.5 %, boronic ester) and 1.02 (33.8 %, boronic acid); LRMS: Anal. Calcd. for $C_{26}H_{32}N_4O_3{}^{10}B$ 458.26; found: 458.28 $(M+H)^+$; HRMS: Anal. Calcd. for $C_{26}H_{32}N_4O_3{}^{10}B$ 458.2604; found: 458.2617 $(M+H)^+$.

Example 1, Step d

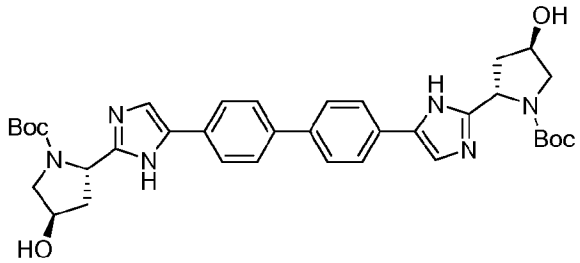
di-tert-butyl (2S,2'S)-2,2'-(4,4'-biphenyldiylbis(1H-imidazole-5,2-diyl))di(1-pyrrolidinecarboxylate)



1d

$Pd(Ph_3P)_4$ (59.9 mg, 0.0518 mmol) was added to a mixture of bromide 1b (576.1 mg, 1.469 mmol), boronate 1c (621.8 mg, 1.415 mmol), $NaHCO_3$ (400.4 mg, 4.766 mmol) in 1,2-dimethoxyethane (12 mL) and water (4 mL). The reaction mixture was flushed with nitrogen, heated with an oil bath at 80 °C for 5.75 hours, and then the volatile component was removed *in vacuo*. The residue was partitioned between 20% methanol/ $CHCl_3$ (60 mL) and water (30 mL), and the aqueous phase was extracted with 20% methanol/$CHCl_3$ (30 mL). The combined organic phase was washed with brine, dried ($MgSO_4$), filtered, and concentrated *in vacuo*. A silica gel mesh was prepared from the resulting crude material and submitted to flash chromatography (ethyl acetate) to provide dimer 1d, contaminated with Ph_3PO, as an off-white solid (563 mg). ^1H NMR (DMSO-d_6, δ = 2.5 ppm, 400 MHz): δ 12.21-12-16/11.95-11.78 (m, 2H), 7.85-7.48/ 7.32-7.25 (m, 10H), 4.90-4.71 (m, 2H), 3.60-3.32 (m, 4H), 2.30-1.79 (m, 8H), 1.46-1.10 (m, 18H). LC (Cond. 1b): RT = 1.77 min; LC/MS: Anal. Calcd. for $[M+H]^+$ $C_{36}H_{45}BN_6O_4$: 625.35; found 625.48.

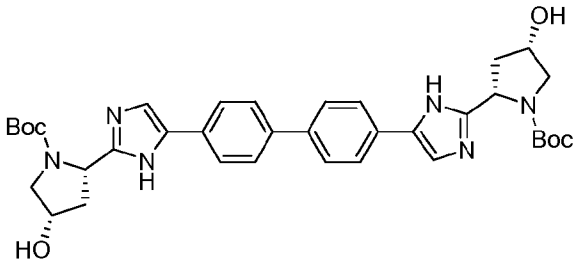
Additional symmetric analogs can be prepared in similar fashion.



1-1d

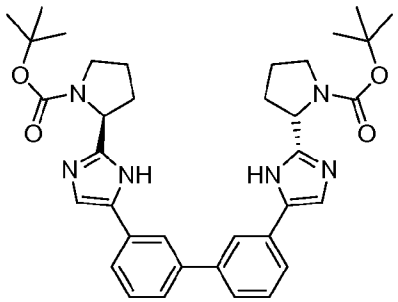
Example 1-1d was prepared using intermediates 1-2c and 1-2b. ^1H NMR (500 MHz, DMSO-d_6) δ ppm 11.94-12.22 (2H, m) 7.53-7.82 (10H, m) 4.82-4.92 (2 H, m) 4.34-4.43 (2 H, m) 3.55-3.64 (2 H, m) 3.36 (2 H, d, *J*=11.29 Hz) 2.12-2.22 (2 H, m) 2.02-

2.11 (2 H, m) 1.40 (6 H, s) 1.14 (12 H, s); LCMS – Phenomenex C-18 3.0 x 50mm, 0 to 100% B over 4.0 minute gradient, 1 minute hold time, A = 10% methanol 90% water 0.1% TFA, B = 90% methanol 10% water 0.1% TFA, RT= 3.32min, Anal. Calcd. for 656.79; found 657.40 $(M+H)^+$. Nominal/LRMS – $(M+H)^+$657.42, $(M-H)^-$ -655.28.



1-2d

Example 1-2d was prepared using intermediates 1-3b and 1-3c. ^{1}H NMR (500 MHz, DMSO-d_6) δ ppm 12.00-12.20 (2H, m) 7.56-7.76 (10H, m) 4.90 (1H, s) 4.82 (1H, s) 4.25-4.34 (2H, m) 3.56 (2H, s) 3.34-3.47 (2H, m) 1.97-2.13 (4H, m) 1.39 (9H, m) 1.20 (9H, s); LCMS – Phenomenex C-18 3.0 x 50mm, 0 to 100% B over 4.0 minute gradient, 1 minute hold time, A = 10% methanol 90% water 0.1% TFA, B = 90% methanol 10% water 0.1% TFA; RT= 3.35min, Anal. Calcd. for 656.79; found 657.30 $(M+H)^+$.

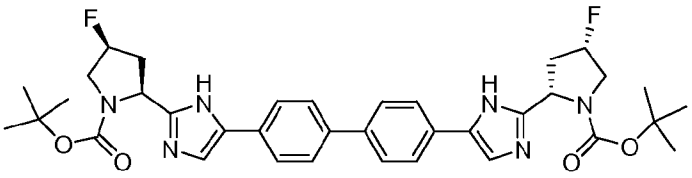


1-2d-1

tert-butyl (2S)-2-(4-(3'-(2-((2S)-1-(tert-butoxycarbonyl)-2-pyrrolidinyl)-1H-imidazol-5-yl)-3-biphenylyl)-1H-imidazol-2-yl)-1-pyrrolidinecarboxylate

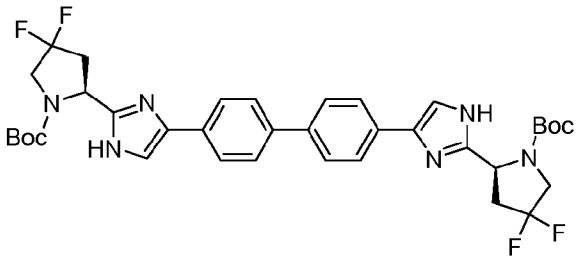
Example 1-2d-1 was prepared using intermediates 1-4c and 1-4b. ^{1}H NMR (500 MHz, DMSO-d_6) δ ppm 1.09-1.51 (m, 18H), 1.84-2.15 (m, 6H), 2.34-2.50 (m, 2H),

3.35-3.52 (m, 2H), 3.54-3.67 (m, 2H), 5.08 (d, *J*=5.49 Hz, 2H), 7.68 (t, *J*=7.78 Hz, 2H), 7.78-7.92 (m, 4H), 8.11-8.30 (m, 4H), 14.81 (s, 2H). LC/MS $(M+H)^+ = 625.48$.



1-2d-2

Diol 1-1d (0.15g, 0.23mmol) was added as a solid to a solution of bis(2-methoxyethyl) aminosulfur trifluoride (0.1mL, 0.51mmol) in 1.0mL CH_2Cl_2 cooled to -78 °C. The reaction was stirred at -78 °C for two hours and then warmed to room temperature and stirred for 2 hours. The reaction was poured into saturated sodium bicarbonate solution and stirred until bubbling ceased. The layers were separated and the aqueous layer was extracted one time with CH_2Cl_2. The combined organics were washed with brine, dried ($MgSO_4$), filtered, and concentrated to give a yellow oil. The oil was triturated with CH_2Cl_2 and pentane to provide the desired product as a tan solid (0.092g, 61%). ^{1}H NMR (500 MHz, DMSO-d_6) δ ppm 11.76-11.94 (2H, m), 7.77 - 7.85 (4 H, m), 7.66 - 7.72 (4 H, m), 7.60 - 7.66 (2 H, m, *J*=11.60 Hz), 5.39 (1 H, s), 5.28 (1 H, s), 5.03 (2 H, s), 3.66 - 3.79 (4 H, m), 2.61 - 2.70 (2 H, m), 2.28 - 2.38 (2 H, m), 1.42 (10 H, s), 1.24 (8 H, s). LCMS – Phenomenex C-18 3.0 x 50mm, 0 to 100% B over 4.0 minute gradient, 1 minute hold time, A = 10% methanol 90% water 0.1% TFA, B = 90% methanol 10% water 0.1% TFA, (t_R= 3.58 min) Anal Calcd. for $C_{36}H_{42}F_2N_6O_4$ 660.70; found 661.68 $(M+H)^+$.

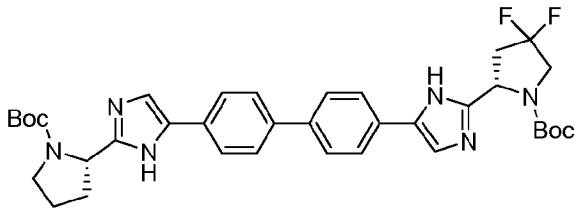


1-2d-3

Prepared from 1-1b and 1-1c in the same manner as the preparation of 1d from 1b and 1c. ^{1}H NMR (500 MHz, DMSO-d_6) δ ppm 1.18/1.40 (two br. s., 18H),

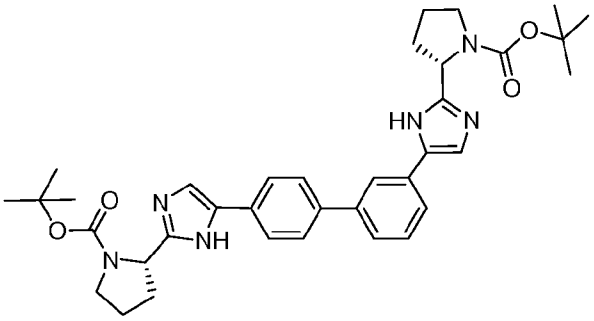
2.53 - 2.75 (m, *J*=25.94 Hz, 2H), 2.86 - 3.06 (m, 2H), 3.78 - 4.02 (m, 4H), 5.04 (br s, 2H), 7.17 – 8.24 (m, 10H), 12.07/12.37 (two br. s., 2H); HPLC XTERRA C-18 3.0 × 50 mm, 0 to 100% B over 2 minutes, 1 minutes hold time, A = 90% water, 10% methanol, 0.2% H_3PO_4, B = 10% water, 90% methanol, 0.2% H_3PO_4, RT = 1.31 min, 99% homogeneity index. LCMS: Anal. Calcd. for $C_{36}H_{40}F_4N_6O_4$: 696.73; found: 967.64 $(M+H)^+$.

Dissymmetric compounds such as intermediate 1-3d and 1-4d can be prepared by the same method. For example, reaction of 1-1c with 1b in the same manner as described above for the preparation of 1d provided 1-3d. Similarly, reaction of 1-4c with 1b in the same manner as described above for the preparation of 1d provideed 1-4d.



1-3d

^{1}H NMR (500 MHz, DMSO-d_6) δ ppm 1.40/1.18 (two br s, 18H), 1.90-2.02 (m, 2H), 2.02-2.12 (m, 1H), 2.28-2.46 (m, 2H), 2.68-2.87 (m, 1H), 3.35-3.49 (m, 1H), 3.53-3.62 (m, 1H), 3.82-4.10 (m, 2H), 4.92-5.11 (m, 1H), 5.28 (s, 1H), 7.79-8.00 (m, 8H), 8.03-8.25 (m, 2H), 13.77-15.16 (m, 2H); HPLC XTERRA C-18 3.0 × 50 mm, 0 to 100% B over 4 minutes, 1 minute hold time, A = 90% water, 10% methanol, 0.2% H_3PO_4, B = 10% water, 90% methanol, 0.2% H_3PO_4, RT = 1.22 minutes, 99% homogeneity index. LCMS: Anal. Calcd. for $C_{36}H_{42}F_2N_6O_4$: 660.75; found: 661.98 $(M+H)^+$.



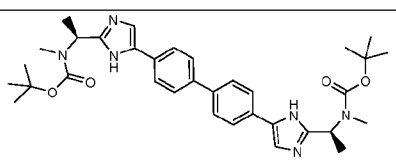
1-4d

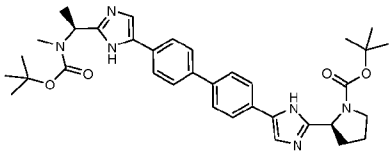
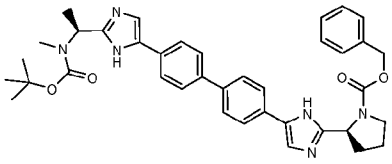
Example 1-4d was prepared from 1-4c and 1b in similar fashion to the preparation of 1d from 1b and 1c. ^{1}H NMR (500 MHz, DMSO-d_6) δ ppm 0.99 - 1.60 (m, 18 H) 1.75 - 2.11 (m, *J*=73.24 Hz, 6 H) 2.12 - 2.32 (m, 2 H) 3.32 - 3.41 (m, 2 H) 3.56 (s, 2 H) 4.63 - 5.02 (m, 2 H) 6.98 - 8.28 (m, 10 H) 11.67 - 12.33 (m, 2 H); LC conditions: Phenomenex Luna 3.0 X 5.0mm S10, Solvent A – 0.1% TFA in 10% MeOH/90%H_2O, Solvent B - 0.1% TFA in 90% MeOH/10% H_2O, 0 to 100% B over 2min, Stop time = 3min, Flow rate = 4ml/min, Wavelength = 220nm, LC/MS $(M+H)^+$ = 625.32. Retention time = 1.438 min

Additional biphenyl analogs were prepared similarly.

LC conditions for Examples 1-5d through 1-7d: *Condition 1*: Phenomenex LUNA C-18 4.6 × 50 mm, 0 to 100% B over 3 minutes, 1 minute hold time, A = 90% water, 10% methanol, 0.1% TFA, B = 10% water, 90% methanol, 0.1% TFA, 220nm, 5 µL injection volume.

Condition 2: Phenomenex LUNA C-18 4.6 × 50 mm, 0 to 100% B over 2 minutes, 1 minute hold time, A = 90% water, 10% methanol, 0.1% TFA, B = 10% water, 90% methanol, 0.1% TFA, 220nm, 5 µL injection volume.

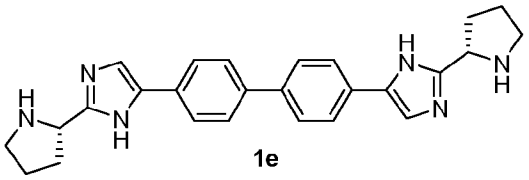
Example	*Compound Name*	*Structure*	*Characterization Data*
1-5d	di-tert-butyl (4,4'-biphenyldiylbis(1H-imidazole-5,2-diyl(1S)-1,1-ethanediyl))bis(meth	 Prepared from 1-8c and 1-6b	RT = 1.64 minutes (>95%); Condition 2; LCMS: Anal. Calcd $C_{34}H_{45}N_6O_4$

	ylcarbamate)		601.35; found: 601.48 $(M+H)^+$; LRMS: Anal. Calcd. for $C_{34}H_{44}N_6O_4$ 600.34; found: 601.32 $(M+H)^+$.
1-6d	tert-butyl (2S)-2-(5-(4'-(2-((1S)-1-((tert-butoxycarbonyl)(methyl)amino)ethyl)-1H-imidazol-5-yl)-4-biphenylyl)-1H-imidazol-2-yl)-1-pyrrolidinecarboxylate	 Prepared from 1-8c and 1b	RT = 1.63 minutes (>95%); Condition 2; LCMS: Anal. Calcd $C_{35}H_{45}N_6O_4$ 613.34; found: 613.56 $(M+H)^+$; LRMS: Anal. Calcd. for $C_{35}H_{44}N_6O_4$ 612.34; found: 613.33 $(M+H)^+$.
1-7d	benzyl (2S)-2-(5-(4'-(2-((1S)-1-((tert-butoxycarbonyl)(methyl)amino)ethyl)-1H-imidazol-5-yl)-4-biphenylyl)-1H-imidazol-2-yl)-1-pyrrolidinecarboxylate	 Prepared from 1-6b and 1-5c	RT = 1.65 minutes (>95%); Condition 2; LCMS: Anal. Calcd $C_{38}H_{43}N_6O_4$ 647.33; found: 647.44 $(M+H)^+$; LRMS: Anal. Calcd. for $C_{38}H_{42}N_6O_4$ 646.33; found: 647.34 $(M+H)^+$.

5

Example 1, Step e

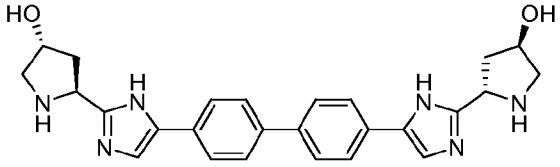
5,5'-(4,4'-biphenyldiyl)bis(2-((2S)-2-pyrrolidinyl)-1H-imidazole)



1e

A mixture of carbamate 1d (560 mg) and 25% TFA/CH_2Cl_2 (9.0 mL) was stirred at ambient condition for 3.2 hours. The volatile component was removed *in vacuo*, and the resulting material was free based using an MCX column (methanol wash; 2.0 M NH_3/methanol elution) to provide pyrrolidine 1e as a dull yellow solid (340 mg). ^{1}H NMR (DMSO-d_6, δ = 2.5 ppm, 400 MHz): δ 11.83 (br s, 2H), 7.80 (d, J = 8.1, 4H), 7.66 (d, J = 8.3, 4H), 7.46 (br s, 2H), 4.16 (app t, J = 7.2, 2H), 2.99-2.69 (m, 6H), 2.09-2.00 (m, 2H), 1.94-1.66 (m, 6H). LC (Cond. 1): RT = 1.27 min; > 98% homogeneity index; LC/MS: Anal. Calcd. for $[M+H]^+$ $C_{26}H_{29}N_6$: 425.25; found 425.25; HRMS: Anal. Calcd. for $[M+H]^-$ $C_{26}H_{29}N_6$: 425.2454; found 425.2448

Additional analogs such as 1-1e to 1-4e can be prepared in a similar fashion.

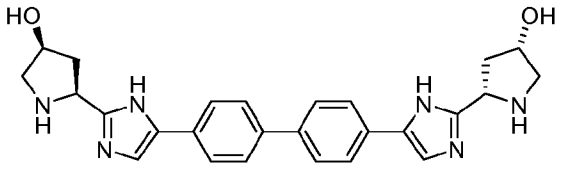


• 4 HCl

1-1e

To a solution of 1-1d (3R,3'R,5S,5'S)-tert-butyl 5,5'-(5,5'-(biphenyl-4,4'-diyl)bis(1H-imidazole-5,2-diyl))bis(3-hydroxypyrrolidine-1-carboxylate) in 3mL dioxane was added 0.8mL of a 4.0M solution of HCl in dioxane. The reaction was stirred for 2 hours at room temperature and concentrated under reduced pressure. The resulting tan solid was dried under vacuum to give 1-1e (3R,3'R,5S,5'S)-5,5'-(5,5'-(biphenyl-4,4'-diyl)bis(1H-imidazole-5,2-diyl))dipyrrolidin-3-oltetrahydrochloride (0.55g, 100%yield). Used without further purification.^{1}H NMR (500 MHz, DMSO-d_6) δ ppm 10.33 (s, 2H), 9.85 (s, 2H), 8.09 (s, 2H), 8.01 (d, J=8.24 Hz, 4H), 7.88 (d, J=8.24 Hz, 4H), 5.14 (m, 2H), 4.62 (m, 2H), 3.61 (m, 2H),

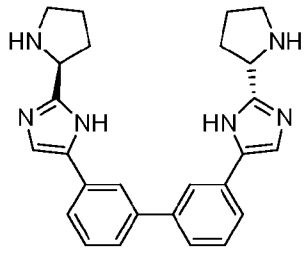
3.23 (d, *J*=11.29 Hz, 2H), 2.64 (m, 2H), 2.44 (dd, *J*=13.43, 6.71 Hz, 2H); LCMS – Waters-Sunfire C-18 4.6 x 50mm, 0 to 100% B over 4.0 minute gradient, 1 minute hold time, A = 10% methanol 90% water 0.1% TFA, B = 90% methanol 10% water 0.1% TFA, RT= 1.35 minutes Anal. Calcd. for 456.30; found 457.25 $(M+H)^+$; Nominal/LRMS – $(M+H)^+$ 457.35.



• 4 HCl

1-2e

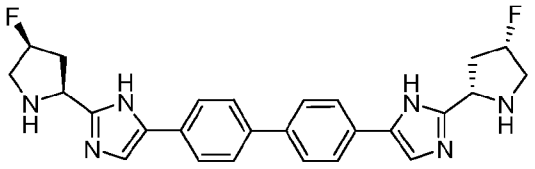
Example 1-2e was prepared in similar fashion to the method described for the preparation of 1-1e. ^{1}H NMR (500 MHz, DMSO-d_6) δ ppm 10.32 (1 H, s) 8.01 (2 H, s) 7.97 (4 H, d, *J*=8.24 Hz) 7.86 (4 H, d, *J*=8.24 Hz) 5.01-5.10 (2 H, m) 4.52-4.60 (2 H, m) 3.36-3.45 (2 H, m) 3.25 (2 H, s) 2.60-2.68 (2 H, m) 2.40-2.48 (2 H, m); LCMS – Phenomenex C-18 3.0 x 50mm, 0 to 100% B over 4.0 minute gradient, 1 minute hold time, A = 10% methanol 90% water 0.1% TFA, B = 90% methanol 10% water 0.1% TFA, RT= 2.10min., Anal. Calcd. for 456.30; found 457.22 $(M+H)^+$



1-2e-1

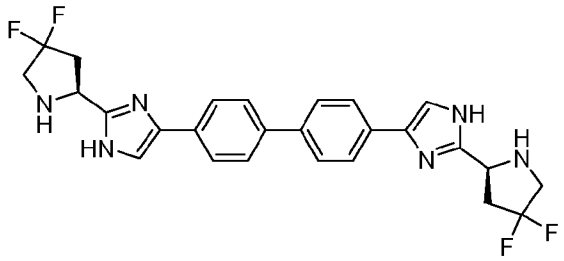
2-((2S)-2-pyrrolidinyl)-4-(3'-(2-((2S)-2-pyrrolidinyl)-1H-imidazol-5-yl)-3-biphenylyl)-1H-imidazole

Example 1-2e-1 was prepared from 1-2d-1 in similar fashion described for the preparation of 1-1e. ^{1}H NMR (500 MHz, DMSO-d_6) δ ppm 1.74-2.44 (m, 12H), 4.83 (s, 2H), 7.37-7.72 (m, 4H), 7.74-8.03 (m, 4H), 8.10 (s, 2H), 9.14 (s, 2H), 9.81 (s, 2H). LC/MS $(M+H)^+$ = 425.30.



1-2e-2

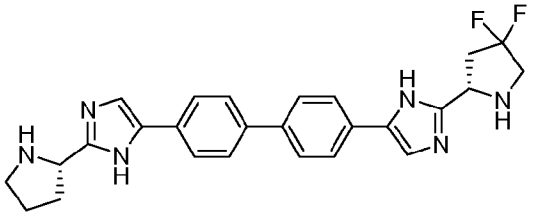
To a solution of 1-2d-2 (0.084g, 0.13mmol) in 1mL dioxane was added 0.5mL of a 4.0M solution of HCl in dioxane. The reaction was stirred for 2 hours at room temperature and concentrated under reduced pressure. The resulting tan solid was dried under vacuum to give 1-2e-2 (0.077g, 100%yield). The compound was used without further purification. ^{1}H NMR (500 MHz, DMSO-d_6) δ ppm 8.00 (2H, s), 7.97 (4H, d, *J*=8.55 Hz), 7.85 (4H, d, *J*=8.24 Hz), 5.63 (1H, s), 5.52 (1H, s), 5.09 - 5.17 (2H, m), 3.67 - 3.74 (2H, m), 3.63 - 3.67 (2H, m), 3.07 - 3.14 (1H, m), 2.89 - 2.96 (1H, m), 2.81 - 2.87 (2H, m); LCMS – Phenomenex C-18 3.0 x 50mm, 0 to 100% B over 4.0 minute gradient, 1 minute hold time, A = 10% methanol 90% water 0.1% TFA, B = 90% methanol 10% water 0.1% TFA, (t_R= 2.22 min) Anal Calcd. for $C_{26}H_{26}F_2N_6$ 460.53; found 461.37 $(M+H)^+$.



1-2e-3

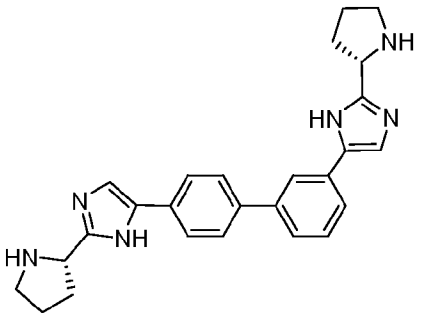
Prepared from 1-2d-3 in the same manner as the preparation of 1-1e from 1-1d. ^{1}H NMR (500 MHz, DMSO-d_6) δ ppm 2.97 - 3.13 (m, 4H), 3.64 - 3.91 (m, 4H), 5.16 (d, *J*=6.41 Hz, 2H), 7.84 (d, *J*=7.93 Hz, 4H), 7.96 (d, *J*=7.93 Hz, 4H), 8.00 (s, 2H); HPLC XTERRA C-18 3.0 × 50 mm, 0 to 100% B over 4 minutes, 1 minutes hold time, A = 90% water, 10% methanol, 0.2% H_3PO_4, B = 10% water, 90% methanol, 0.2% H_3PO_4, RT = 1.66 min, 92% homogeneity index. LCMS: Anal. Calcd. for $C_{26}H_{24}F_4N_6$: 496.50; found: 495.53 $(M-H)^-$.

Analogous dissymmetric compounds such as intermediates 1-3e and 1-4e can be prepared by the same method.



1-3e

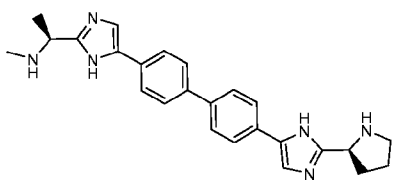
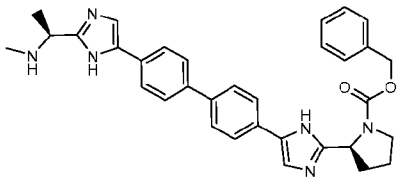
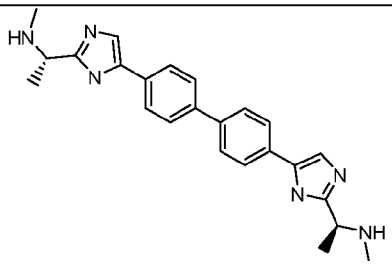
^{1}H NMR (500 MHz, DMSO-d_6) δ ppm 1.87-2.09 (m, 1H), 2.13-2.26 (m, 1H), 2.37-2.47 (m, 2H), 2.92-3.12 (m, 2H), 3.37 (s, 1H), 3.40-3.49 (m, 1H), 3.67-3.91 (m, 2H), 4.96-5.05 (m, 1H), 5.14 (t, *J*=8.70 Hz, 1H), 7.86 (t, *J*=9.00 Hz, 4H), 7.93-8.03 (m, 5H), 8.10 (s, 1H), 10.26/9.75 (two br s., 2H); HPLC XTERRA C-18 3.0 × 50 mm, 0 to 100% B over 4 minutes, 1 minute hold time, A = 90% water, 10% methanol, 0.2% H_3PO_4, B = 10% water, 90% methanol, 0.2% H_3PO_4, RT = 0.8622 minutes, 99% homogeneity index; LCMS: Anal. Calcd. for $C_{26}H_{26}F_2N_6$: 460.52; found: 461.45 $(M+H)^+$.



1-4e

Example 1-4e was prepared from 1-4d in similar fashion to that described for the preparation of 1-1e from 1-1d. ^{1}H NMR (500 MHz, DMSO-d_6) δ ppm 1.90 - 2.13 (m, 2 H) 2.12 - 2.31 (m, 2 H) 2.36 - 2.60 (m, 4 H) 3.29 - 3.55 (m, 4 H) 5.00 (s, 2 H) 7.35 - 8.50 (m, 10 H) 9.76 (s, 2 H) 10.12 - 10.45 (m, 2 H). LC conditions: Phenomenex Luna 3.0 X 5.0mm S10, Solvent A – 0.1% TFA in 10% MeOH/90%H_2O, Solvent B - 0.1% TFA in 90% MeOH/10% H_2O, 0 to 100% B over 2min, Stop time = 3min, Flow rate = 4ml/min, Wavelength = 220nm, LC/MS $(M+H)^+$ = 425.28. Retention time = 0.942 min

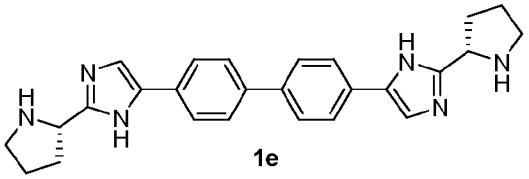
Additional analogs were prepared similarly:

Example	Compound Name	Structure	Data
1-5e		 Prepared from 1-6d	RT = 1.37 min; LCMS: Anal. Calcd. for $C_{25}H_{28}N_6$ 412; found: 413 $(M+H)^+$.
1-6e		 Prepared from 1-7d	RT = 1.43 min; LCMS: Anal. Calcd. for $C_{33}H_{35}N_6O_2$ 547; found: 547 $(M+H)^+$.
1-7e		 Prepared from 1-5d	RT = 1.12 min; LRMS: Anal. Calcd. for $C_{24}H_{28}N_6$ 400.24; found: 401.22 $(M+H)^+$.

LC Conditions for 1-5e through 1-7e: Phenomenex LUNA C-18 4.6 × 50 mm, 0 to 100% B over 2 minutes, 1 minute hold time, A = 90% water, 10% methanol, 0.1% TFA, B = 10% water, 90% methanol, 0.1% TFA, 220nm, 5 µL injection volume.

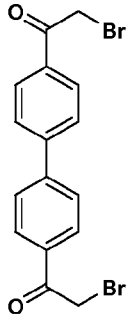
Alternative Synthesis of Example 1, Step e

5,5'-(4,4'-biphenyldiyl)bis(2-((2S)-2-pyrrolidinyl)-1H-imidazole)



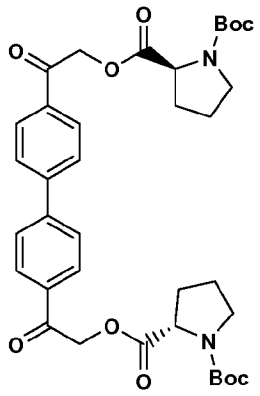
1e

Example A-1e-1



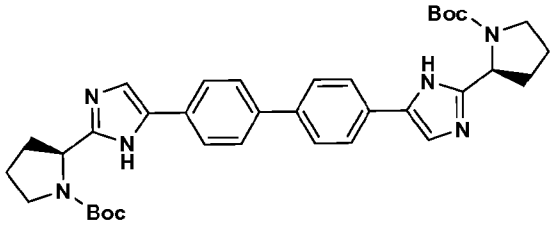
A 1 L, 3-neck round bottom flask, fitted with a nitrogen line, overhead stirrer and thermocouple was charged with 20 g (83.9 mmol, 1 equiv) 1,1'-(biphenyl-4,4'-diyl)diethanone, 200 mL CH_2Cl_2 and 8.7 mL (27.1g, 169.3 mmol, 2.02 quiv) bromine. The mixture was allowed to stir under nitrogen for about 20h under ambient conditions. The resulting slurry was charged with 200 mL CH_2Cl_2 and concentrated down to about 150 mL *via* vacuum distillation. The slurry was then solvent exchanged into THF to a target volume of 200 mL *via* vacuum distillation. The slurry was cooled to 20-25 °C over 1h and allowed to stir at 20-25 °C for an additional hour. The off-white crystalline solids were filtered and washed with 150 mL CH_2Cl_2. The product was dried under vacuum at 60 °C to provide 27.4 g (69.2 mmol, 82%) of the desired product: ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.95-7.85 (m, 4H), 7.60-7.50 (m, 4H), 4.26 (s, 4H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 191.0, 145.1, 133.8, 129.9, 127.9, 30.8; IR (KBr, cm-1) 3007, 2950, 1691, 1599, 1199; Anal calcd for $C_{16}H_{12}Br_2O_2$: C, 48.52; H, 3.05; Br, 40.34. Found: C, 48.53; H, 3.03; Br, 40.53. HRMS calcd for $C_{16}H_{13}Br_2O_2$ (M + H; DCI^+): 394.9282. Found: 394.9292. mp 224-226 °C.

Example A-1e-2



A 500 mL jacketed flask, fitted with a nitrogen line, thermocouple and overhead stirrer, was charged with 20 g (50.5 mmol, 1 equiv) of Example A-1e-1, 22.8 g (105.9 moles, 2.10 equiv) 1-(*tert*-butoxycarbonyl)-L-proline, and 200 mL acetonitrile. The slurry was cooled to 20 °C followed by the addition of 18.2 mL (13.5 g, 104.4 mmol, 2.07 equiv) DIPEA. The slurry was warmed to 25 °C and allowed to stir for 3h. The resulting clear, organic solution was washed with 3 x 100 mL 13 wt% aqueous NaCl. The rich acetonitrile solution was solvent exchanged into toluene (target volume = 215 mL) by vacuum distillation until there was less than 0.5 vol% acetonitrile.

Example A-1e-3

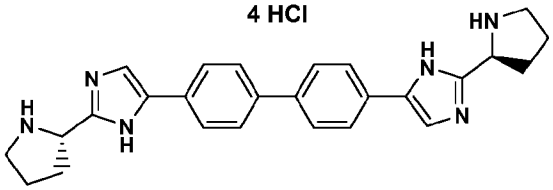


The above toluene solution of Example A-1e-2 was charged with 78 g (1.011 moles, 20 equiv) ammonium acetate and heated to 95-100 °C. The mixture was allowed to stir at 95-100 °C for 15h. After reaction completion, the mixture was cooled to 70-80 °C and charged with 7 mL acetic acid, 40 mL n-butanol, and 80 mL of 5 vol% aqueous acetic acid. The resulting biphasic solution was split while maintaining a temperature > 50 °C. The rich organic phase was charged with 80 mL of 5 vol% aqueous acetic acid, 30 mL acetic acid and 20 mL n-butanol while

maintaining a temperature > 50 °C. The resulting biphasic solution was split while maintaining a temperature > 50 °C and the rich organic phase was washed with an additional 80 mL of 5 vol% aqueous acetic acid. The rich organic phase was then solvent exchanged into toluene to a target volume of 215 mL by vacuum distillation. While maintaining a temperature > 60 °C, 64 mL MeOH was charged. The resulting slurry was heated to 70-75 °C and aged for 1h. The slurry was cooled to 20-25 °C over 1h and aged at that temperature for an additional hour. The slurry was filtered and the cake was washed with 200 mL 10:3 toluene:MeOH. The product was dried under vacuum at 70 °C, resulting in 19.8 g (31.7 mmol, 63%) of the desired product: ^{1}H NMR (400 MHz, DMSO-d_6) δ 13.00-11.00 (s, 2H), 7.90-7.75 (m, 4H), 7.75-7.60 (m, 4H), 7.60-7.30 (s, 2H), 4.92-4.72 (m, 2H), 3.65-3.49 (m, 2H), 3.49-3.28 (m, 2H), 2.39-2.1 (m, 2H), 2.10-1.87 (m, 6H), 1.60-1.33 (s, 8H), 1.33-1.07 (s, 10H); ^{13}C NMR (100 MHz, DMSO-d_6) δ 154.1, 153.8, 137.5, 126.6, 125.0, 78.9, 78.5, 55.6, 55.0, 47.0, 46.7, 33.7, 32.2, 28.5, 28.2, 24.2, 23.5; IR (KBr, cm-1) 2975, 2876, 1663, 1407, 1156, 1125; HRMS calcd for $C_{36}H_{45}N_6O_4$ (M + H; ESI$^+$): 625.3502. Found: 625.3502. mp 190-195 °C (decomposed).

Example A-1e-4

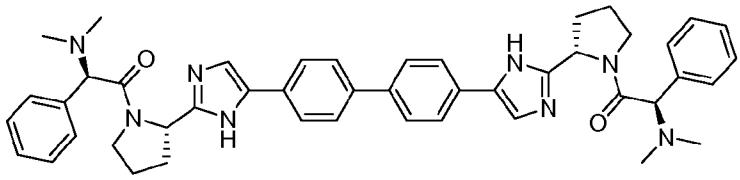
4 HCl



To a 250 ml reactor equipped with a nitrogen line and overhead stirrer, 25.0 g of Example A-1e-3 (40.01 mmol, 1 equiv) was charged followed by 250 mL methanol and 32.85 mL (400.1 mmol, 10 equiv) 6M aqueous hydrogen chloride. The temperature was increased to 50 °C and agitated at 50 °C for 5h. The resulting slurry was cooled to 20-25 °C and held with agitation for ca. 18h. Filtration of the slurry afforded a solid which was washed successively with 100 ml 90% methanol/water (V/V) and 2x100 ml of methanol. The wet cake was dried in a vacuum oven at 50 °C overnight to give 18.12 g (31.8 mmol, 79.4%) of the desired product.

Recrystallization of Example A-1e-4

To a 250 ml reactor equipped with a nitrogen line and an overhead stirrer, 17.8g of crude Example A-1e-4 was charged followed by 72 mL methanol. The resulting slurry was agitated at 50 °C for 4h, cooled to 20-25 °C and held with agitation at 20-25 °C for 1h. Filtration of the slurry afforded a crystalline solid which was washed with 60 ml methanol. The resulting wet cake was dried in a vacuum oven at 50 °C for 4 days to yield 14.7 g (25.7 mmol, 82.6%) of the desired product: ^{1}H NMR (400 MHz, DMSO-d_6) δ 10.5-10.25 (br, 2H), 10.1-9.75 (br, 2H), 8.19 (s, 2H), 7.05 (d, J = 8.4, 4H), 7.92 (d, J = 8.5, 4H), 5.06 (m, 2H), 3.5-3.35 (m, 4H), 2.6-2.3 (m, 4H), 2.25-2.15 (m, 2H), 2.18-1.96 (m, 2H); ^{13}C NMR (100 MHz, DMSO- d_6) δ 156.6, 142.5, 139.3, 128.1, 127.5, 126.1, 116.9, 53.2, 45.8, 29.8, 24.3; IR (KBr, cm^{-1}) 3429, 2627, 1636, 1567, 1493, 1428, 1028. Anal calcd for $C_{26}H_{32}N_6Cl_4$: C, 54.75; H, 5.65; Cl, 24.86; Adjusted for 1.9% water: C, 53.71; H, 5.76; N, 14.46; Cl, 24.39. Found: C, 53.74; H, 5.72; N, 14.50; Cl, 24.49; KF = 1.9. mp 240 °C (decomposed)



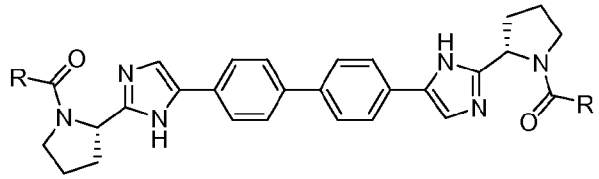
Example 1

(1R,1'R)-2,2'-(4,4'-biphenyldiylbis(1H-imidazole-5,2-diyl(2S)-2,1-pyrrolidinediyl))bis(N,N-dimethyl-2-oxo-1-phenylethanamine)

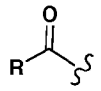
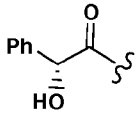
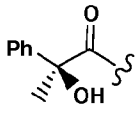
HATU (44.6 mg, 0.117 mmol) was added to a mixture of pyrrolidine 1e (22.9 mg, 0.054 mmol), diisopropylethylamine (45 μL, 0.259 mmol) and *Cap*-1 (28.1 mg, 0.13 mmol) in DMF (1.5 mL), and the resulting mixture was stirred at ambient for 90 minutes. The volatile component was removed *in vacuo*, and the residue was purified first by MCX (methanol wash; 2.0 M NH_3/methanol elution) and then by a reverse phase HPLC system (H_2O/methanol/TFA) to provide the TFA salt of Example 1 as an off-white foam (44.1 mg). ^{1}H NMR (DMSO-d_6, δ= 2.5 ppm, 400 MHz): δ 10.25 (br s, 2H), 8.20-7.10 (m, 20H), 5.79-5.12 (m, 4H), 4.05-2.98 (m, 4H), 2.98-2.62 (m, 6H), 2.50-1.70 (m, 14H), [Note: the signal of the imidazole NH was

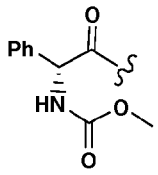
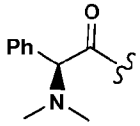
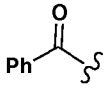
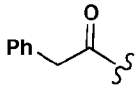
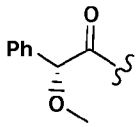
too broad to assign a chemical shift]; LC (Cond. 1): RT = 1.40 min; > 98% homogeneity index; LC/MS: Anal. Calcd. for $[M+H]^+$ $C_{46}H_{51}N_8O_2$: 747.41; found 747.58

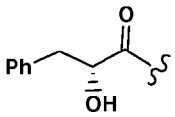
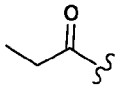
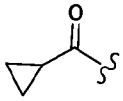
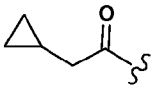
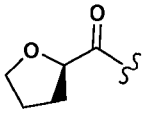
Examples 2 to 24-4d

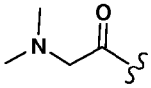
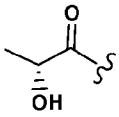
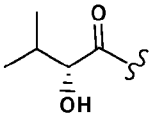
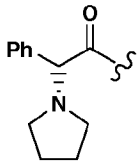
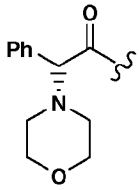


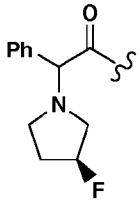
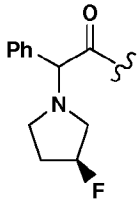
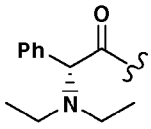
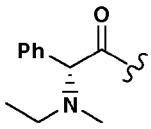
Examples 2 to 24-4h were prepared as TFA salts by substituting the respective acids for *Cap*-1 using the same method described for Example 1. Caps in the following table without a number are commercially available.

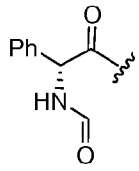
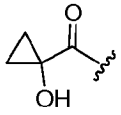
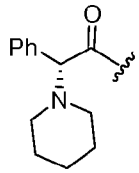
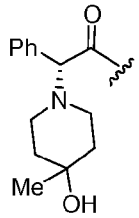
Example	*Compound Name*		*RT (LC-Cond.); % homogeneity index; MS data*
2	(1R,1'R)-2,2'-(4,4'-biphenyldiylbis(1H-imidazole-5,2-diyl(2S)-2,1-pyrrolidinediyl))bis(2-oxo-1-phenylethanol)		1.55 minutes (Cond. 1); >98%; LC/MS: Anal. Calcd. for $[M+H]^+$ $C_{42}H_{41}N_6O_4$: 693.32; found 693.46; HRMS: Anal. Calcd. for $[M+H]^+$ $C_{42}H_{41}N_6O_4$: 693.3189; found 693.3182
3	(2S,2'S)-1,1'-(4,4'-biphenyldiylbis(1H-imidazole-5,2-diyl(2S)-2,1-pyrrolidinediyl))bis(1-oxo-2-phenyl-2-propanol)		1.77 minutes (Cond. 1); >98%; LC/MS: Anal. Calcd. for $[M+H]^+$ $C_{44}H_{45}N_6O_4$: 721.35; found 721.52; HRMS: Anal. Calcd. for $[M+H]^+$ $C_{44}H_{45}N_6O_4$: 721.3502; found 721.3515

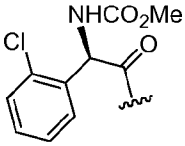
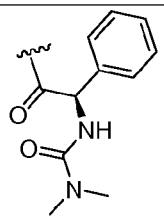
4	dimethyl (4,4'-biphenyldiylbis(1H-imidazole-5,2-diyl(2S)-2,1-pyrrolidinediyl((1R)-2-oxo-1-phenyl-2,1-ethanediyl)))biscarbamate	 *Cap-4*	1.64 minutes (Cond. 1); >98%; LC/MS: Anal. Calcd. for $[M+H]^+$ $C_{46}H_{47}N_8O_6$: 807.36; found 807.58
5	(1S,1'S)-2,2'-(4,4'-biphenyldiylbis(1H-imidazole-5,2-diyl(2S)-2,1-pyrrolidinediyl))bis(N,N-dimethyl-2-oxo-1-phenylethanamine)	 *ent of Cap-1*	1.33 minutes (Cond. 1); >98%; LC/MS: Anal. Calcd. for $[M+H]^+$ $C_{46}H_{51}N_8O_2$: 747.41; found 747.64; HRMS: Anal. Calcd. for $[M+H]^+$ $C_{46}H_{51}N_8O_2$: 747.4135; found 747.4103
6	5,5'-(4,4'-biphenyldiyl)bis(2-((2S)-1-benzoyl-2-pyrrolidinyl)-1H-imidazole)		1.65 minutes (Cond. 1); >98%; LC/MS: Anal. Calcd. for $[M+H]^+$ $C_{40}H_{37}N_6O_2$: 633.30; found 633.51
7	5,5'-(4,4'-biphenyldiyl)bis(2-((2S)-1-(phenylacetyl)-2-pyrrolidinyl)-1H-imidazole)		1.71 minutes (Cond. 1); >98%; LC/MS: Anal. Calcd. for $[M+H]^+$ $C_{42}H_{41}N_6O_2$: 661.33; found 661.53; HRMS: Anal. Calcd. for $[M+H]^+$ $C_{42}H_{41}N_6O_2$: 661.3291; found 661.3300
8	5,5'-(4,4'-biphenyldiyl)bis(2-((2S)-1-((2R)-2-methoxy-2-phenylacetyl)-2-pyrrolidinyl)-1H-imidazole)		1.63 minutes (Cond. 1); >98%; LC/MS: Anal. Calcd. for $[M+H]^+$ $C_{44}H_{45}N_6O_4$: 721.35; found 721.59; HRMS: Anal. Calcd. for $[M+H]^+$ $C_{44}H_{45}N_6O_4$: 721.3502; found 721.3536

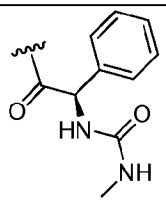
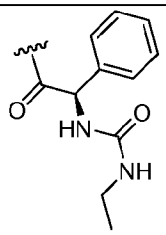
9	(2R,2'R)-1,1'-(4,4'-biphenyldiylbis(1H-imidazole-5,2-diyl(2S)-2,1-pyrrolidinediyl))bis(1-oxo-3-phenyl-2-propanol)		1.71 minutes (Cond. 1); >98%; LC/MS: Anal. Calcd. for $[M+H]^+$ $C_{44}H_{45}N_6O_4$: 721.35; found 721.58; HRMS: Anal. Calcd. for $[M+H]^+$ $C_{44}H_{45}N_6O_4$: 721.3502; found 721.3497
10	5,5'-(4,4'-biphenyldiyl)bis(2-((2S)-1-propionyl-2-pyrrolidinyl)-1H-imidazole)		1.47 minutes (Cond. 1); >98%; LC/MS: Anal. Calcd. for $[M+H]^+$ $C_{32}H_{37}N_6O_2$: 537.30; found 537.40; HRMS: Anal. Calcd. for $[M+H]^+$ $C_{32}H_{37}N_6O_2$: 537.2978; found 537.2952
11	5,5'-(4,4'-biphenyldiyl)bis(2-((2S)-1-(cyclopropylcarbonyl)-2-pyrrolidinyl)-1H-imidazole)		1.48 minutes (Cond. 1); >98%; LC/MS: Anal. Calcd. for $[M+H]^+$ $C_{34}H_{37}N_6O_2$: 561.30; found 561.44
12	5,5'-(4,4'-biphenyldiyl)bis(2-((2S)-1-(cyclopropylacetyl)-2-pyrrolidinyl)-1H-imidazole)		1.57 minutes (Cond. 1); >98%; LC/MS: Anal. Calcd. for $[M+H]^+$ $C_{36}H_{41}N_6O_2$: 589.33; found 589.48; HRMS: Anal. Calcd. for $[M+H]^+$ $C_{36}H_{41}N_6O_2$: 589.3291; found 589.3268
13	5,5'-(4,4'-biphenyldiyl)bis(2-((2S)-1-((2R)-tetrahydro-2-furanylcarbonyl)-2-pyrrolidinyl)-1H-imidazole)		1.44 minutes (Cond. 1); >98%; LC/MS: Anal. Calcd. for $[M+H]^+$ $C_{36}H_{41}N_6O_4$: 621.32; found 621.52; HRMS: Anal. Calcd. for $[M+H]^+$

			$C_{36}H_{41}N_6O_4$: 621.3189; found 621.3191
14	2,2'-(4,4'-biphenyldiylbis(1H-imidazole-5,2-diyl(2S)-2,1-pyrrolidinediyl))bis(N,N-dimethyl-2-oxoethanamine)		1.27 minutes (Cond. 1); >98%; LC/MS: Anal. Calcd. for $[M+H]^+$ $C_{34}H_{43}N_8O_2$: 595.35; found 595.54; HRMS: Anal. Calcd. for $[M+H]^+$ $C_{34}H_{43}N_8O_2$: 595.3509; found 595.3503
15	(2R,2'R)-1,1'-(4,4'-biphenyldiylbis(1H-imidazole-5,2-diyl(2S)-2,1-pyrrolidinediyl))bis(1-oxo-2-propanol)		1.36 minutes (Cond. 1); >98%; LC/MS: Anal. Calcd. for $[M+H]^+$ $C_{32}H_{37}N_6O_4$: 569.29; found 569.44; HRMS: Anal. Calcd. for $[M+H]^+$ $C_{32}H_{37}N_6O_4$: 569.2876; found 569.2872
16	(2R,2'R)-1,1'-(4,4'-biphenyldiylbis(1H-imidazole-5,2-diyl(2S)-2,1-pyrrolidinediyl))bis(3-methyl-1-oxo-2-butanol)		1.51 minutes (Cond. 1); >98%; LC/MS: Anal. Calcd. for $[M+H]^+$ $C_{36}H_{45}N_6O_4$: 625.35; found 625.50; HRMS: Anal. Calcd. for $[M+H]^+$ $C_{36}H_{45}N_6O_4$: 625.3502; found 625.3517
17	5,5'-(4,4'-biphenyldiyl)bis(2-((2S)-1-((2R)-2-phenyl-2-(1-pyrrolidinyl)acetyl)-2-pyrrolidinyl)-1H-imidazole)	 *Cap-5*	1.13 minutes (Cond. 1); >98%; LC/MS: Anal. Calcd. for $[M+H]^+$ $C_{50}H_{55}N_8O_2$: 799.45; found 799.67
18	4,4'-(4,4'-biphenyldiylbis(1H-imidazole-5,2-diyl(2S)-2,1-pyrrolidinediyl((1R)-2-oxo-1-phenyl-2,1-		1.11 minutes (Cond. 1); >98%; LC/MS: Anal. Calcd. for $[M+H]^+$ $C_{50}H_{55}N_8O_4$: 831.44; found

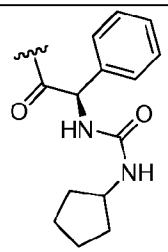
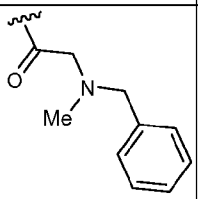
	ethanediyl)))dimorpholine	*Cap-6*	831.71
19	5,5'-(4,4'-biphenyldiyl)bis(2-((2S)-1-(((3S)-3-fluoro-1-pyrrolidinyl)(phenyl)acetyl)-2-pyrrolidinyl)-1H-imidazole)	 *Diastereomer-1* *Cap-9a*	1.17 minutes (Cond. 1); 97%; LC/MS: Anal. Calcd. for $[M+H]^+$ $C_{50}H_{53}F_2N_8O_2$: 835.43; found 835.51; HRMS: Anal. Calcd. for $[M+H]^+$ $C_{50}H_{53}F_2N_8O_2$: 835.4260; found 835.4261
20	5,5'-(4,4'-biphenyldiyl)bis(2-((2S)-1-(((3S)-3-fluoro-1-pyrrolidinyl)(phenyl)acetyl)-2-pyrrolidinyl)-1H-imidazole)	 *Diastereomer-2* *Cap-9b*	1.03 minutes (Cond. 1); >98%; LC/MS: Anal. Calcd. for $[M+H]^+$ $C_{50}H_{53}F_2N_8O_2$: 835.43; found 835.51; HRMS: Anal. Calcd. for $[M+H]^+$ $C_{50}H_{53}F_2N_8O_2$: 835.4260; found 835.4266
21	(1R,1'R)-2,2'-(4,4'-biphenyldiylbis(1H-imidazole-5,2-diyl(2S)-2,1-pyrrolidinediyl))bis(N,N-diethyl-2-oxo-1-phenylethanamine)	 *Cap-2*	1.13 minutes (Cond. 1); >98%; LC/MS: Anal. Calcd. for $[M+H]^+$ $C_{50}H_{59}N_8O_2$: 803.48; found 803.56; HRMS: Anal. Calcd. for $[M+H]^+$ $C_{50}H_{59}N_8O_2$: 803.4761; found 803.4728
22	(1R,1'R)-2,2'-(4,4'-biphenyldiylbis(1H-imidazole-5,2-diyl(2S)-2,1-pyrrolidinediyl))bis(N-ethyl-N-methyl-2-oxo-1-phenylethanamine)	 *Cap-3*	1.10 minutes (Cond. 1); >98%; LC/MS: Anal. Calcd. for $[M+H]^+$ $C_{48}H_{55}N_8O_2$: 775.45; found 775.52; HRMS: Anal. Calcd. for $[M+H]^+$ $C_{50}H_{59}N_8O_2$: 775.4448; found 775.4456

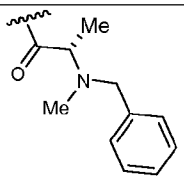
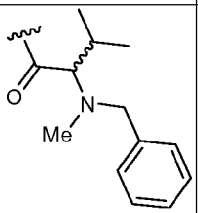
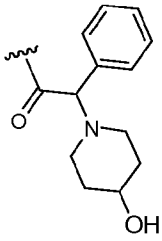
23	N,N'-(4,4'-biphenyldiylbis(1H-imidazole-5,2-diyl(2S)-2,1-pyrrolidinediyl((1R)-2-oxo-1-phenyl-2,1-ethanediyl)))diformamide		1.22 minutes (Cond. 1); >98%; LC/MS: Anal. Calcd. for $[M+H]^+$ $C_{44}H_{43}N_8O_4$: 747.34; found 747.38
24	1,1'-(4,4'-biphenyldiylbis(1H-imidazole-5,2-diyl(2S)-2,1-pyrrolidinediylcarbonyl))dicyclopropanol		1.77 minutes (Cond. 2); >98%; LC/MS: Anal. Calcd. for $[M+H]^+$ $C_{34}H_{37}N_6O_4$: 593.29; found 593.16
24-1	1,1'-(4,4'-biphenyldiylbis(1H-imidazole-5,2-diyl(2S)-2,1-pyrrolidinediyl((1R)-2-oxo-1-phenyl-2,1-ethanediyl)))dipiperidine	 *Cap-14*	^{1}HNMR (400 MHz, DMSO-d_6) δ 12.18 (m, 0.4H), 11.96 (m, 0.4H), 11.79 (m, 1.2H), 7.84-7.70 (m, 4H), 7.69-7.65 (m, 4H), 7.53-7.50 (m, 2H), 7.43-7.28 (m, 4H), 7.09-7.01 (m, 2H), 6.87-6.85 (m, 2H), 5.51-5.48 (m, 0.5H), 5.01-4.98 (m, 1.5H), 4.29 (m, 1.5H), 4.16 (m, 0.5H), 3.98 (m, 2H), 3.65-3.49 (m, 2H), 3.43-3.36 (m, 2H), 2.41-2.31 (m, 8H), 2.14-1.82 (m, 8H), 1.47-1.31 (m, 12H); LCMS: Anal. Calcd. for $C_{52}H_{58}N_8O_2$: 826; found: 827 $(M+H)^+$.
24-2	1,1'-(4,4'-biphenyldiylbis(1H-imidazole-5,2-diyl(2S)-2,1-pyrrolidinediyl((1R)-2-oxo-1-phenyl-2,1-ethanediyl)))bis(4-methyl-4-piperidinol)	 *Cap-15*	^{1}HNMR (400 MHz, DMSO-d_6) δ 12.02 (br s, 1H), 11.82 (br s, 1H), 7.90-7.79 (m, 4H), 7.79-7.65 (m, 5H), 7.55 (br s, 2H), 7.45 (d, J = 7.6 Hz, 2H), 7.39-7.25 (m, 3H),

			7.34 (d, J = 7.6 Hz, 2H), 7.04 (t, J = 7.6 Hz, 2H), 6.85 (d, J = 8.1 Hz, 2H), 5.15-4.96 (m, 2H), 4.31-3.96 (m, 6H), 2.35-2.20 (m, 2H), 2.05-1.94 (m, 4H), 1.94-1.81 (m, 4H), 1.50-1.35 (m, 9H), 1.35-1.20 (m, 5H), 1.09 (s, 2H), 1.05 (s, 4H); LCMS: Anal. Calcd. for $C_{54}H_{62}N_8O_4$: 886; found: 887 $(M+H)^+$.
24-3	dimethyl (4,4'-biphenyldiylbis(1H-imidazole-5,2-diyl(2S)-2,1-pyrrolidinediyl((1R)-1-(2-chlorophenyl)-2-oxo-2,1-ethanediyl)))biscarbamate		LCMS: Anal. Calcd. for $C_{46}H_{44}Cl_2N_8O_6$: 874; found: 875 $(M+H)^+$.
24-4a	N',N'''-(4,4'-biphenyldiylbis(1H-imidazole-4,2-diyl(2S)-2,1-pyrrolidinediyl((1R)-2-oxo-1-phenyl-2,1-ethanediyl)))bis(1,1-dimethylurea)	 *Cap-47*	^{1}H NMR (500 MHz, DMSO-d_6) δ ppm 1.89-2.00 (m, J=17.09, 7.02 Hz, 4H), 2.06-2.13 (m, J=14.95, 3.97 Hz, 3H), 2.24-2.33 (m, J=8.70, 6.56 Hz, 2H), 2.79-2.84 (m, 12H), 3.29 (q, 2H), 3.95-4.03 (m, 3H), 5.26 (dd, J=8.55, 2.14 Hz, 3H), 5.52 (d, J=5.80 Hz, 3H), 6.72 (d, J=6.10 Hz, 3H), 7.02-7.07 (m, 1H), 7.29-7.36 (m, 3H), 7.39 (t, J=7.17 Hz, 4H), 7.46 (d, J=7.02 Hz, 3H), 7.92 (s, 8H), 8.12 (s, 2H); HPLC XTERRA C-18 4.6 ×

			30 mm, 0 to 100% B over 4 minutes, 1 minute hold time, A = 90% water, 10% methanol, 0.2% H_3PO_4, B = 10% water, 90% methanol, 0.2% H_3PO_4, RT = 2.13 minutes, 96% homogeneity index; LCMS: Anal. Calcd. for $C_{48}H_{53}N_{10}O_4$: 832.42; found: 833.43 $(M+H)^+$; HRMS: Anal. Calcd. for $C_{48}H_{54}N_{10}O_4$ 833.4251; found: 833.4267 $(M+H)^+$.
24-4b	N',N'''-(4,4'-biphenyldiylbis(1H-imidazole-5,2-diyl(2S)-2,1-pyrrolidinediyl((1R)-2-oxo-1-phenyl-2,1-ethanediyl)))bis(1-methylurea)	 *Cap-45*	RT = 4.45 minutes (Gemini C-18 4.6 x 50mm, 0 to 100% B over 10.0 minute gradient, 1 minute hold time, A = 5% acetonitrile, 95% water, 10mm ammonium acetate, B = 95% acetonitrile, 5% water, 10mm ammonium acetate); LCMS: Anal. Calcd. for $C_{46}H_{48}N_{10}O_4$ 804.95; found: 805.41 $(M+H)^+$; HRMS: Anal. Calcd. for $C_{46}H_{49}N_{10}O_4$ 805.3938; found: 805.3929 $(M+H)^+$.
24-4c	N',N'''-(4,4'-biphenyldiylbis(1H-imidazole-5,2-diyl(2S)-2,1-pyrrolidinediyl((1R)-2-oxo-1-phenyl-2,1-ethanediyl)))bis(1-ethylurea)	 *Cap-46*	RT = 4.20 minutes (Gemini C-18 4.6 x 50mm, 0 to 100% B over 10.0 minute gradient, 1 minute hold time, A = 5% acetonitrile, 95% water, 10mm ammonium acetate, B = 95%

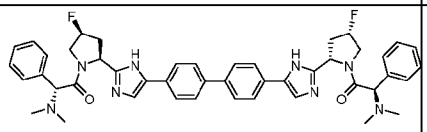
			acetonitrile, 5% water, 10mm ammonium acetate);LCMS: Anal. Calcd. for $C_{48}H_{52}N_{10}O_4$ 833.00; found: 833.48 $(M+H)^+$.

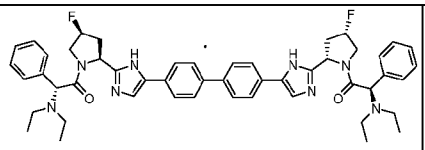
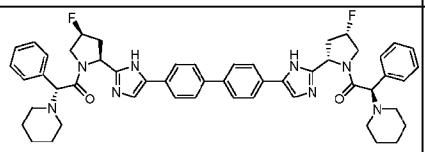
24-4d	N',N'''-(4,4'-biphenyldiylbis(1H-imidazole-5,2-diyl(2S)-2,1-pyrrolidinediyl((1R)-2-oxo-1-phenyl-2,1-ethanediyl)))bis(1-cyclopentylurea)	 *Cap-48*	RT = 4.92 minutes (Gemini C-18 4.6 x 50mm, 0 to 100% B over 10.0 minute gradient, 1 minute hold time, A = 5% acetonitrile, 95% water, 10mm ammonium acetate, B = 95% acetonitrile, 5% water, 10mm ammonium acetate); LCMS: Anal. Calcd. for $C_{54}H_{60}N_{10}O_4$ 912.49; found: 913.68 $(M+H)^+$; HRMS: Anal. Calcd. for $C_{54}H_{61}N_{10}O_4$ 913.4877; found: 913.4899 $(M+H)^+$.
24-4e	2,2'-(4,4'-biphenyldiylbis(1H-imidazole-5,2-diyl(2S)-2,1-pyrrolidinediyl))bis(N-benzyl-N-methyl-2-oxoethanamine)	 *Cap-49*	^{1}H NMR (500 MHz, DMSO-d_6) δ ppm 1.97-2.43 (m, 8H), 2.64-2.91 (m, 6H), 3.45-3.63 (m, 2H), 3.62-3.76 (m, 2H), 4.14 (dd, 4H), 4.22-4.45 (m, 4H), 5.29 (s, 2H), 7.28-7.65 (m, 10H), 7.90 (s, 8H), 8.06 (s, 2H), 14.62 (s, 2H); HPLC Xterra 4.6 X 50 mm, 0 to 100% B over 10 minutes, one minute hold time, A = 90% water, 10% methanol, 0.2% phosphoric acid, B =

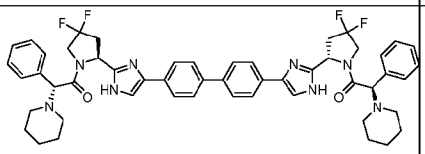
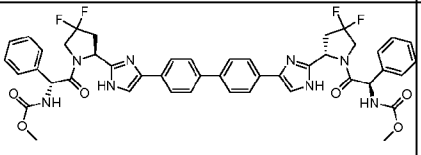
			10% water, 90% methanol, 0.2% phosphoric acid. RT = 3.06 min; LCMS: Anal. Calcd. for: $C_{46}H_{50}N_8O_2$ 746.96; Found: 747.41 $(M+H)^+$.
24-4f	(2S,2'S)-1,1'-(4,4'-biphenyldiylbis(1H-imidazole-5,2-diyl(2S)-2,1-pyrrolidinediyl))bis(N-benzyl-N-methyl-1-oxo-2-propanamine)		RT = 2.95 minutes (99%); HPLC Xterra 4.6 X 50 mm, 0 to 100% B over 10 minutes, one minute hold time, A = 90% water, 10% methanol, 0.2% phosphoric acid, B = 10% water, 90% methanol, 0.2% phosphoric acid; LCMS: Anal. Calcd. for: $C_{48}H_{54}N_8O_2$ 775.02; Found: 775.45 $(M+H)^+$.
24-4g	1,1'-(4,4'-biphenyldiylbis(1H-imidazole-5,2-diyl(2S)-2,1-pyrrolidinediyl))bis(N-benzyl-N,3-dimethyl-1-oxo-2-butanamine)	 *Cap-50*	RT = 3.86 minutes (100%); HPLC Xterra 4.6 X 50 mm, 0 to 100% B over 10 minutes, one minute hold time, A = 90% water, 10% methanol, 0.2% phosphoric acid, B = 10% water, 90% methanol, 0.2% phosphoric acid; LCMS: Anal. Calcd. for: $C_{52}H_{62}N_8O_2$ 831.13; Found: 831.51 $(M+H)^+$.
24-4h	1,1'-(4,4'-biphenyldiylbis(1H-imidazole-5,2-diyl(2S)-2,1-pyrrolidinediyl(2-oxo-1-phenyl-2,1-ethanediyl)))di(4-piperidinol)	 *Cap-8*	RT = 2.86 minutes (100%); HPLC Xterra 4.6 X 50 mm, 0 to 100% B over 10 minutes, one minute hold time, A = 90% water, 10% methanol, 0.2% phosphoric acid, B = 10% water, 90%

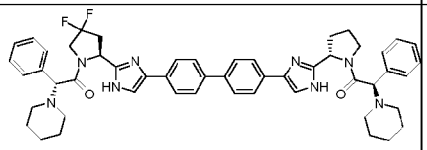
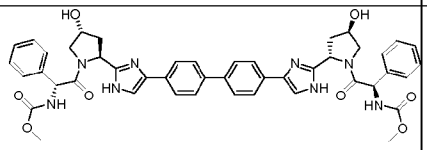
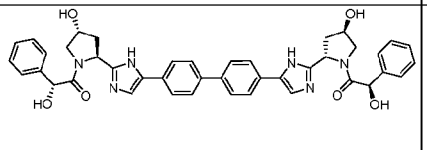
			methanol, 0.2% phosphoric acid; LCMS: Anal. Calcd. for: $C_{52}H_{58}N_8O_4$ 859.09; Found: 859.45 $(M+H)^+$.

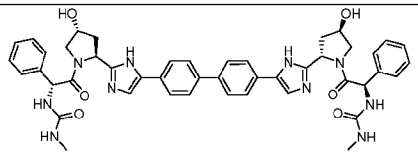
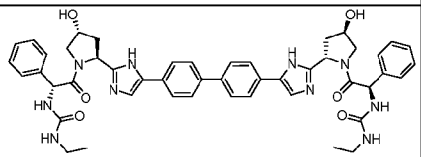
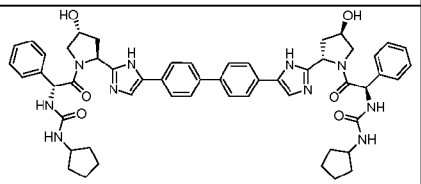
Examples 24-5 to 24-18

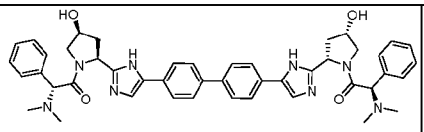
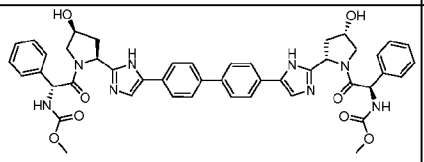
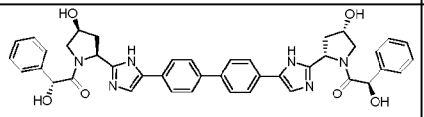
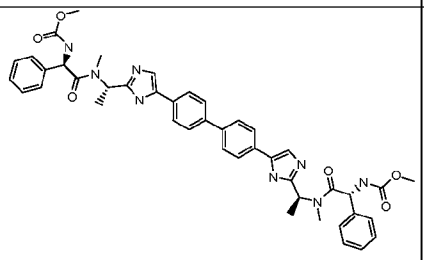
Example	*Compound Name*	*Structure*	*Data*
24-5	1,1'-(4,4'-biphenyldiylbis(1H-imidazole-5,2-diyl((2S,4S)-4-fluoro-2,1-pyrrolidinediyl)((1R)-2-oxo-1-phenyl-2,1-ethanediyl)))dipiperidine	 from 1-2e-2 and *Cap*-1	Gemini C-18 4.6 x 50mm, 0 to 100% B over 10.0 minute gradient, 1 minute hold time, A = 5% acetonitrile, 95% water, 10mm ammonium acetate, B = 95% acetonitrile, 5% water, 10mm ammonium acetate. (RT=4.163 min); Nominal/LRMS – Calcd. for $C_{46}H_{48}F_2N_8O_2$ 782.93; found 783.40 $(M+H)^+$; Accurate/HRMS – Calcd. for $C_{46}H_{49}F_2N_8O_2$ 783.3946; 783.3934 $(M+H)^+$.

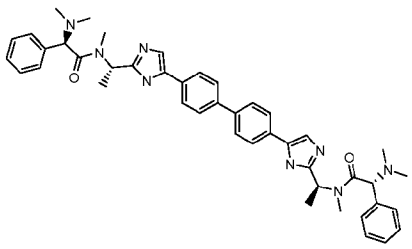
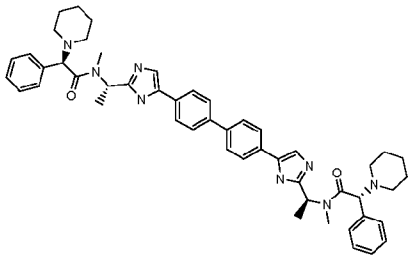
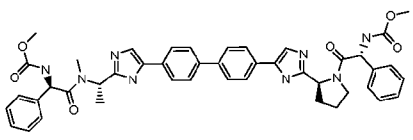
24-6	(1R,1'R)-2,2'-(4,4'-biphenyldiylbis(1H-imidazole-5,2-diyl((2S,4S)-4-fluoro-2,1-pyrrolidinediyl)))bis(N,N-diethyl-2-oxo-1-phenylethanamine)	 from 1-2e-2 and *Cap*-2	Gemini C-18 4.6 x 50mm, 0 to 100% B over 10.0 minute gradient, 1 minute hold time, A = 5% acetonitrile, 95% water, 10mm ammonium acetate, B = 95% acetonitrile, 5% water, 10mm ammonium acetate. (RT = 3.76 min); LCMS: Anal. Calcd. for $C_{50}H_{56}F_2N_8O_2$ 839.04; found: 839.49 $(M+H)^+$; HRMS: Anal. Calcd. for $C_{50}H_{57}F_2N_8O_2$ 839.4572; found: 839.4590 $(M+H)^+$.
24-7	(1R,1'R)-2,2'-(4,4'-biphenyldiylbis(1H-imidazole-5,2-diyl((2S,4S)-4-fluoro-2,1-pyrrolidinediyl)))bis(N,N-dimethyl-2-oxo-1-phenylethanamine	 from 1-2e-2 and *Cap*-14	Gemini C-18 4.6 x 50mm, 0 to 100% B over 10.0 minute gradient, 1 minute hold time, A = 5% acetonitrile, 95% water, 10mm ammonium

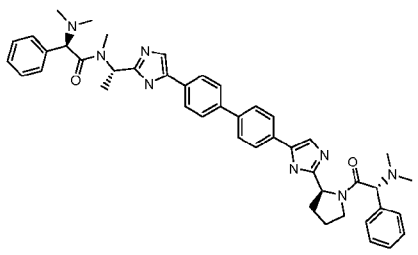
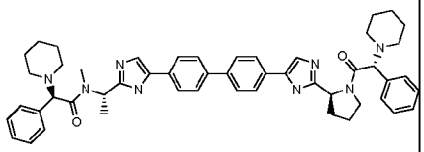
	)		acetate, B = 95% acetonitrile, 5% water, 10mm ammonium acetate. RT = 3.99 min; LCMS: Anal. Calcd. for $C_{52}H_{56}F_2N_8O_2$ 863.06; found: 863.47 $(M+H)^+$; HRMS: Anal. Calcd. for $C_{52}H_{57}F_2N_8O_2$ 863.4572; found: 863.4553 $(M+H)^+$.
24-8	1,1'-(4,4'-biphenyldiylbis(1H-imidazole-4,2-diyl((2S)-4,4-difluoro-2,1-pyrrolidinediyl)((1R)-2-oxo-1-phenyl-2,1-ethanediyl)))dipiperidine	 from 1-2e-3 and *Cap*-14	RT = 1.64 minutes, method B; LCMS: Anal. Calcd. for $C_{52}H_{54}F_4N_8O_6$: 898.43; found: 899.46 $(M+H)^+$; HRMS: Anal. Calcd. for $C_{52}H_{55}F_4N_8O_6$ 899.4384; found: 899.4380 $(M+H)^+$.
24-9	dimethyl (4,4'-biphenyldiylbis(1H-imidazole-4,2-diyl((2S)-4,4-difluoro-2,1-pyrrolidinediyl)((1R)-2-oxo-1-phenyl-2,1-ethanediyl)))biscar	 from 1-2e-3 and *Cap*-4	RT = 2.62 minutes, method C; LCMS: Anal. Calcd. for $C_{46}H_{42}F_4N_8O_6$: 878.88; found: 879.81 $(M+H)^+$; HRMS: Anal. Calcd. for

	bamate		$C_{46}H_{43}F_4N_8O_6$ 879.33242; found: 879.3273 $(M+H)^+$.
24-10	1-((1R)-2-((2S)-2-(4-(4'-(2-((2S)-4,4-difluoro-1-((2R)-2-phenyl-2-(1-piperidinyl)acetyl)-2-pyrrolidinyl)-1H-imidazol-4-yl)-4-biphenylyl)-1H-imidazol-2-yl)-1-pyrrolidinyl)-2-oxo-1-phenylethyl)piperidine	 from 1-3e and *Cap*-14.	RT = 1.54 minutes, method B; LCMS: Anal. Calcd. for $C_{52}H_{56}F_2N_8O_6$: 862.45; found: 863.46 $(M+H)^+$; HRMS: Anal. Calcd. for $C_{52}H_{57}F_2N_8O_6$ 863.4573; found: 863.4572 $(M+H)^+$.
24-11	dimethyl (4,4'-biphenyldiylbis(1H-imidazole-5,2-diyl((2S,4R)-4-hydroxy-2,1-pyrrolidinediyl)((1R)-2-oxo-1-phenyl-2,1-ethanediyl)))biscarbamate	 from 1-1e and *Cap*-4	RT = 8.54 minutes, method A; LCMS: Anal. Calcd. for $C_{46}H_{46}N_8O_8$ 838.93; found: 839.41 $(M+H)^+$; HRMS: Anal. Calcd. for $C_{46}H_{47}N_8O_8$ 839.9300; found: 839.3527 $(M+H)^+$.
24-12	(3R,5S,3'R,5'S)-5,5'-(4,4'-biphenyldiylbis(1H-imidazole-5,2-diyl))bis(1-((2R)-2-hydroxy-2-phenylacetyl)-3-	 from 1-1e and mandelic acid	RT = 6.92 minutes , method A; LCMS: Anal. Calcd. for $C_{42}H_{40}N_6O_6$ 724.81; found: 725.43 $(M+H)^+$; HRMS: Anal. Calcd. for

	pyrrolidinol)		$C_{42}H_{41}N_6O_6$ 725.3087; found: 725.3088 $(M+H)^+$.
24-13	N,N''-(4,4'-biphenyldiylbis(1H-imidazole-5,2-diyl((2S,4R)-4-hydroxy-2,1-pyrrolidinediyl)((1R)-2-oxo-1-phenyl-2,1-ethanediyl)))bis(3-methylurea)	 Prepared from 1-1e and *Cap*-45	RT = 3.80 minutes, method C; LCMS: Anal. Calcd. for $C_{46}H_{48}N_{10}O_6$ 836.95; found: 837.52 $(M+H)^+$; HRMS: Anal. Calcd. for $C_{46}H_{49}N_{10}O_6$ 837.3836; found: 837.3809 $(M+H)^+$.
24-14	N',N'''-(4,4'-biphenyldiylbis(1H-imidazole-5,2-diyl((2S,4R)-4-hydroxy-2,1-pyrrolidinediyl)((1R)-2-oxo-1-phenyl-2,1-ethanediyl)))bis(1-ethylurea)	 Prepared from 1-1e and *Cap*-46	RT = 4.39 minutes, method C; LRMS: Anal. Calcd. for $C_{48}H_{52}N_{10}O_6$ 865.003; found: 865.56 $(M+H)^+$; HRMS: Anal. Calcd. for $C_{48}H_{53}N_{10}O_6$ 865.4149; found: 865.4139 $(M+H)^+$.
24-15	N',N'''-(4,4'-biphenyldiylbis(1H-imidazole-5,2-diyl((2S,4R)-4-hydroxy-2,1-pyrrolidinediyl)((1R)-2-oxo-1-phenyl-2,1-ethanediyl)))bis(1-cyclopentylurea)	 Prepared from 1-1e and *Cap*-48	RT = 4.88 minutes, method B; LRMS: Anal. Calcd. for $C_{54}H_{60}N_{10}O_6$ 944.13; found: 945.65 $(M+H)^+$; HRMS: Anal. Calcd. for $C_{54}H_{61}N_{10}O_6$ 945.4775; found: 945.4769 $(M+H)^+$.

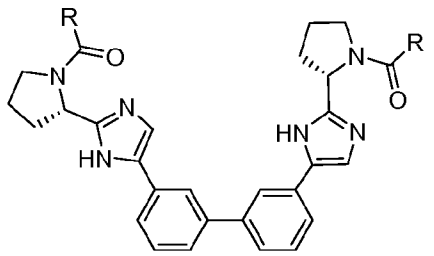
24-16	(3S,5S,3'S,5'S)-5,5'-(4,4'-biphenyldiylbis(1H-imidazole-5,2-diyl))bis(1-((2R)-2-(dimethylamino)-2-phenylacetyl)-3-pyrrolidinol)	 Prepared from 1-2e and *Cap*-1	RT = 3.66 minutes, method D; LRMS: Anal. Calcd. for $C_{46}H_{50}N_8O_4$ 778.39 found: 779.39 $(M+H)^+$; HRMS: Anal. Calcd. for $C_{46}H_{51}N_8O_4$ 779.4033; found: 779.4021 $(M+H)^+$.
24-17	dimethyl (4,4'-biphenyldiylbis(1H-imidazole-5,2-diyl((2S,4S)-4-hydroxy-2,1-pyrrolidinediyl)((1R)-2-oxo-1-phenyl-2,1-ethanediyl)))biscarbamate	 Prepared from 1-2e and *Cap*-4	RT = 5.75 minutes, method C; LRMS: Anal. Calcd. for $C_{46}H_{46}N_8O_8$ 838.93; found: 839.44 $(M+H)^+$; HRMS: Anal. Calcd. for $C_{46}H_{47}N_8O_8$ 839.3517 found: 839.3519 $(M+H)^+$.
24-18	(3S,5S,3'S,5'S)-5,5'-(4,4'-biphenyldiylbis(1H-imidazole-5,2-diyl))bis(1-((2R)-2-hydroxy-2-phenylacetyl)-3-pyrrolidinol)	 from 1-2e and mandelic acid	RT = 4.41 minutes, method D; LRMS: Anal. Calcd. for $C_{42}H_{40}N_6O_6$ 724.81; found: 725.13 $(M+H)^+$.
24-18-1	dimethyl (4,4'-biphenyldiylbis(1H-imidazole-5,2-diyl(1S)-1,1-ethanediyl(methylimino))((1R)-2-oxo-1-phenyl-2,1-	 from 1-7e and *Cap*-4	RT = 1.55 min[1]; LRMS: Anal. Calcd. for $C_{44}H_{46}N_8O_6$ 782.35; found: 783.37 $(M+H)^+$; HRMS: Anal. Calcd. for

	ethanediyl)))biscarbamate		$C_{44}H_{47}N_8O_6$ 783.3619 found: 783.3630 $(M+H)^+$.
24-18-2	(2R,2'R)-N,N'-(4,4'-biphenyldiylbis(1H-imidazole-5,2-diyl(1S)-1,1-ethanediyl))bis(2-(dimethylamino)-N-methyl-2-phenylacetamide)	 from 1-7e and *Cap*-1	RT = 1.16 min[1]; LRMS: Anal. Calcd. for $C_{44}H_{50}N_8O_2$ 722.41; found: 723.41 $(M+H)^+$; HRMS: Anal. Calcd. for $C_{44}H_{51}N_8O_2$ 723.4135 found: 723.4152 $(M+H)^+$.
24-18-3	(2R,2'R)-N,N'-(4,4'-biphenyldiylbis(1H-imidazole-5,2-diyl(1S)-1,1-ethanediyl))bis(N-methyl-2-phenyl-2-(1-piperidinyl)acetamide)	 from 1-7e and *Cap*-14	RT = 1.28 min[1]; LRMS: Anal. Calcd. for $C_{50}H_{58}N_8O_2$ 802.47; found: 803.50 $(M+H)^+$; HRMS: Anal. Calcd. for $C_{50}H_{59}N_8O_2$ 803.4761 found: 803.4778 $(M+H)^+$.
24-18-4	methyl ((1R)-2-((2S)-2-(5-(4'-(2-((1S)-1-(((2R)-2-((methoxycarbonyl)amino)-2-phenylacetyl)(methyl)amino)ethyl)-1H-imidazol-5-yl)-4-biphenylyl)-1H-imidazol-2-yl)-1-	 Prepared from 1-5e and *Cap*-4	RT = 1.53 min[1]; LRMS: Anal. Calcd. for $C_{45}H_{46}N_8O_6$ 794.35; found: 795.39 $(M+H)^+$; HRMS: Anal. Calcd. for $C_{45}H_{47}N_8O_6$ 795.3619 found: 795.3616 $(M+H)^+$.

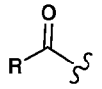
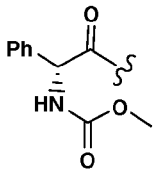
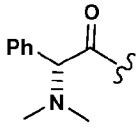
	pyrrolidinyl)-2-oxo-1-phenylethyl)carbamate		
24-18-5	(2R)-2-(dimethylamino)-N-((1S)-1-(5-(4'-(2-((2S)-1-((2R)-2-(dimethylamino)-2-phenylacetyl)-2-pyrrolidinyl)-1H-imidazol-5-yl)-4-biphenylyl)-1H-imidazol-2-yl)ethyl)-N-methyl-2-phenylacetamide	 Prepared from 1-5e and *Cap*-1	RT = 1.21[1]; LRMS: Anal. Calcd. for $C_{45}H_{50}N_8O_2$ 734.41; found: 735.46 $(M+H)^+$; HRMS: Anal. Calcd. for $C_{45}H_{51}N_8O_2$ 735.4135 found: 735.4136 $(M+H)^+$.
24-18-6	(2R)-N-methyl-2-phenyl-N-((1S)-1-(5-(4'-(2-((2S)-1-((2R)-2-phenyl-2-(1-piperidinyl)acetyl)-2-pyrrolidinyl)-1H-imidazol-5-yl)-4-biphenylyl)-1H-imidazol-2-yl)ethyl)-2-(1-piperidinyl)acetamide	 Prepared from 1-5e and *Cap*-14	RT = 1.30[1]; LRMS: Anal. Calcd. for $C_{51}H_{58}N_8O_2$ 814.47; found: 815.48 $(M+H)^+$; HRMS: Anal. Calcd. for $C_{51}H_{59}N_8O_2$ 815.4761 found: 815.4744 $(M+H)^+$.

[1]LC Conditions for 24-18-1 through 24-18-6: Phenomenex LUNA C-18 4.6 × 50 mm, 0 to 100% B over 2 minutes, 1 minute hold time, A = 90% water, 10% methanol, 0.1% TFA, B = 10% water, 90% methanol, 0.1% TFA, 220nm, 5 µL injection volume.

Examples 24-19 to 24-20



Example 24-19 and 24-20 were prepared as TFA salts from 1-2e-1 and the respective acids using the same method described for Example 1.

Example	*Compound Name*		*Data*
24-19	methyl ((1*R*)-2-((2*S*)-2-(4-(3'-(2-((2*S*)-1-((2*R*)-2-((methoxycarbonyl)amino)-2-phenylacetyl)-2-pyrrolidinyl)-1*H*-imidazol-5-yl)-3-biphenylyl)-1*H*-imidazol-2-yl)-1-pyrrolidinyl)-2-oxo-1-phenylethyl)carbamate	 *Cap*-4	^{1}H NMR (500 MHz, DMSO-d$_6$) δ ppm 1.82-1.97 (m, 2H), 1.97-2.17 (m, 4H), 2.18-2.37 (m, 2H), 3.18 (d, *J*=9.77 Hz, 2H), 3.44-3.58 (m, 6H), 3.79-4.04 (m, 2H), 5.09-5.46 (m, 2H), 5.45-5.84 (m, 2H), 6.97-7.49 (m, 10H), 7.61-7.74 (m, 4H), 7.75-7.93 (m, 4H), 8.10-8.32 (m, 4H), 14.48 (app br s, 2H); RT = 1.34 min; LC/MS: Anal. Calcd. for [M+H]$^+$ $C_{46}H_{47}N_8O_6$: 807.36; found 807.40
24-20	(1*R*)-2-((2*S*)-2-(4-(3'-(2-((2*S*)-1-((2*R*)-2-(dimethylamino)-2-phenylacetyl)-2-	 *Cap*-1	^{1}H NMR (500 MHz, DMSO-d$_6$) δ ppm 1.71-2.32 (m, 8H), 3.33-3.68 (m, 2H), 3.89-4.16 (m,

	pyrrolidinyl)-1*H*-imidazol-5-yl)-3-biphenylyl)-1*H*-imidazol-2-yl)-1-pyrrolidinyl)-*N*,*N*-dimethyl-2-oxo-1-phenylethanamine		*J*=2.75 Hz, 2H), 4.96 (app br s, 12H), 5.26 (s, 2H), 5.45 (s, 2H), 7.03-7.78 (m, 12H), 7.84 (s, 4H), 8.07-8.43 (m, 4H), 9.90-10.87 (m, 2H); RT = 1.10 min; LC/MS: Anal. Calcd. for $[M+H]^+$ $C_{46}H_{51}N_8O_2$: 747.41; found 747.45

LC conditions for 24-19 and 24-20:

Column = Phenomenex-Luna 3.0X 50 mm S10

Start %B = 0

Final %B = 100

Gradient time = 2 min

Stop time = 3 min

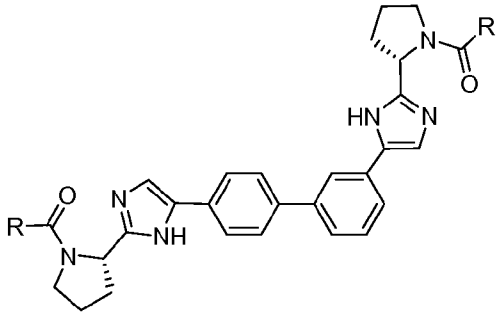
Flow Rate = 4 mL/min

Wavelength = 220 nm

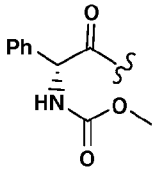
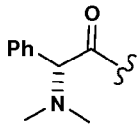
Slovent A = 0.1% TFA in 10% methanol/90%H_2O

Solvent B = 0.1% TFA in 90% methanol/10% H_2O

Examples 24-21 to 24-22



Example 24-21 and 24-22 were prepared as TFA salts from 1-4e and the respective carboxylic acids using the same method described for Example 1.

Example	*Compound Name*		*Data*
24-21	methyl ((1*R*)-2-((2*R*)-2-(4-(3'-(2-((2*S*)-1-((2*R*)-2-((methoxycarbonyl)amino)-2-phenylacetyl)-2-pyrrolidinyl)-1*H*-imidazol-4-yl)-4-biphenylyl)-1*H*-imidazol-2-yl)-1-pyrrolidinyl)-2-oxo-1-phenylethyl)carbamate	 *Cap*-4	^{1}H NMR (500 MHz, DMSO-d_6) δ ppm 1.73-2.37 (m, 8H), 3.13 (s, 2H), 3.36-4.29 (m, 8H), 5.26 (s, 2H), 5.53 (s, 2H), 6.99-8.61 (m, 22H), 14.51 (s, 2H); RT = 1.33min; LC/MS: Anal. Calcd. for $[M+H]^+$ $C_{46}H_{47}N_8O_6$: 807.36; found 807.58
24-22	(1*R*)-2-((2*R*)-2-(4-(3'-(2-((2*S*)-1-((2*R*)-2-(dimethylamino)-2-phenylacetyl)-2-pyrrolidinyl)-1*H*-imidazol-4-yl)-4-biphenylyl)-1*H*-imidazol-2-yl)-1-pyrrolidinyl)-*N*,*N*-dimethyl-2-oxo-1-phenylethanamine	 *Cap*-1	^{1}H NMR (500 MHz, DMSO-d_6) δ ppm 1.84-2.32 (m, 8H), 2.92-3.10 (m, 2H), 3.92-4.08 (m, 2H), 4.43 (app br s, 12H), 5.16-5.37 (m, 2H), 5.39-5.58 (m, 2H), 7.16-8.24 (m, 20H),

			9.60-10.46 (m, 2H); RT = 1.08 min; LC/MS: Anal. Calcd. for $[M+H]^+$ $C_{46}H_{51}N_8O_2$: 747.41; found 747.45

LC conditions for 24-21 and 24-22:

Column = Phenomenex-Luna 3.0X 50 mm S10

Start %B = 0

Final %B = 100

Gradient time = 2 min

Stop time = 3 min

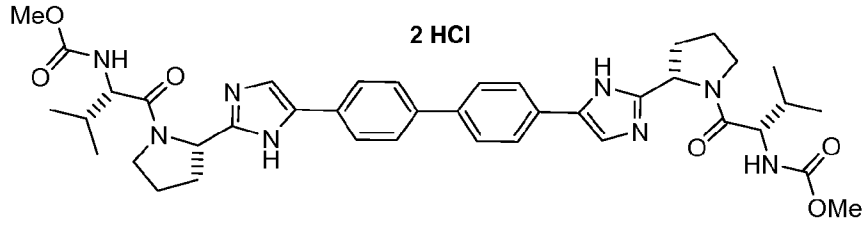
Flow Rate = 4 mL/min

Wavelength = 220 nm

Slovent A = 0.1% TFA in 10% methanol/90%H_2O

Solvent B = 0.1% TFA in 90% methanol/10% H_2O

Example 24-23



methyl ((1S)-1-(((2S)-2-(5-(4'-(2-((2S)-1-((2S)-2-((methoxycarbonyl)amino)-3-methylbutanoyl)-2-pyrrolidinyl)-1H-imidazol-5-yl)-4-biphenylyl)-1H-imidazol-2-yl)-1-pyrrolidinyl)carbonyl)-2-methylpropyl)carbamate

A 50 mL flask equipped with a stir bar was sequentially charged with 2.5 mL acetonitrile, 0.344 g (2.25 mmol, 2.5 equiv) hydroxy benzotriazole hydrate, 0.374 g (2.13 mmol, 2.4 equiv) *N*-(methoxycarbonyl)-L-valine, 0.400 g (2.09 mmol, 2.4 equiv) 1-(3-dimethyaminopropyl)-3-ethylcarbodiimide hydrochloride and an

additional 2.5 mL acetonitrile. The resulting solution was agitated at 20 °C for 1 hour and charged with 0.501 g (0.88 mmol, 1 equiv) Example A-1e-4. The slurry was cooled to about 0 °C and 0.45 g (3.48 mmol, 4 equiv) diisopropylethylamine was added over 30 minutes while maintaining a temperature below 10 °C. The solution was slowly heated to 15 °C over 3 hours and held at 15 °C for 16 hours. The temperature was increased to 20 °C and stirred for 3.25 hours. The resulting solution was charged with 3.3 g of 13 wt% aqueous NaCl and heated to 50 °C for 1 hour. After cooling to 20 °C, 2.5 mL of isopropyl acetate was added. The rich organic phase was washed with 2 x 6.9 g of a 0.5 N NaOH solution containing 13 wt% NaCl followed by 3.3 g of 13 wt% aqueous NaCl. The mixture was then solvent exchanged into isopropyl acetate by vacuum distillation to a target volume of 10 mL. The resulting hazy solution was cooled to 20 °C and filtered through a 0.45 μm filter. The clear solution was then solvent exchanged into ethanol by vacuum distillation with a target volume of 3 mL. 1.67 mL (2.02 mmol, 2.3 equiv) of 1.21 M HCl in ethanol was added. The mixture was then stirred at 25 °C for 15 hours. The resulting slurry was filtered and the wet cake was washed with 2.5 mL of 2:1 acetone:ethanol. The solids were dried in a vacuum oven at 50 °C to give 0.550 g (0.68 mmol, 77 %) of the desired product.

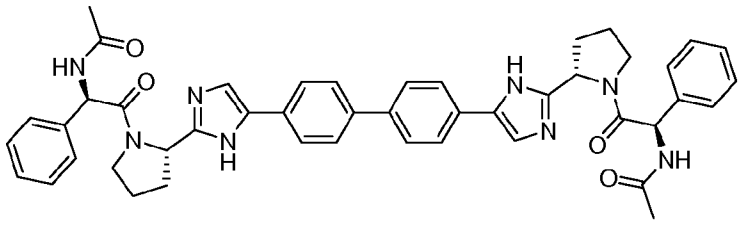
Recrystallization of Example 24-23

A solution of Example 24-23 prepared above was prepared by dissolving 0.520 g of the above product in 3.65 mL methanol. The solution was then charged with 0.078 g of type 3 Cuno Zeta loose carbon and allowed to stir for 0.25 hours. The mixture was then filtered and washed with 6 ml of methanol. The product rich solution was concentrated down to 2.6 mL by vacuum distillation. 7.8 mL acetone was added and allowed to stir at 25 °C for 15 h. The solids were filtered, washed with 2.5 mL 2:1 acetone:ethanol and dried in a vacuum oven at 70 °C to give 0.406 g (57.0%) of the desired product as white crystals: ^{1}H NMR (400 MHz, DMSO-d_6, 80 °C): 8.02 (d, *J*=8.34 Hz, 4 H), 7.97 (s, 2 H), 7.86 (d, *J*=8.34 Hz, 4 H), 6.75 (s, 2 H), 5.27 (t, *J*=6.44 Hz, 2 H), 4.17 (t, *J*=6.95 Hz, 2 H), 3.97 - 4.11 (m, 2 H), 3.74 - 3.90 (m, 2 H), 3.57 (s, 6 H), 2.32 - 2.46 (m, 2 H), 2.09 - 2.31 (m, 6 H), 1.91 - 2.07 (m, 2 H), 0.88 (d, *J*=6.57 Hz, 6 H), 0.79 (d, *J*=6.32 Hz, 6 H); ^{13}C NMR (75 MHz, DMSO-

d_6): δ 170.9, 156.9, 149.3, 139.1, 131.7, 127.1, 126.5, 125.9, 115.0, 57.9, 52.8, 51.5, 47.2, 31.1, 28.9, 24.9, 19.6, 17.7; IR (neat, cm^{-1}): 3385, 2971, 2873, 2669, 1731, 1650. Anal. Calcd for $C_{40}H_{52}N_8O_6Cl_2$: C, 59.18; H, 6.45; N, 13.80; Cl, 8.73. Found C, 59.98; H, 6.80; N, 13.68; Cl, 8.77. mp 267 °C (decomposed). Characteristic diffraction peak positions (degrees 2θ ± 0.1) @ RT, based on a high quality pattern collected with a diffractometer (CuKα) with a spinning capillary with 2θ calibrated with a NIST other suitable standard are as follows: 10.3, 12.4, 12.8, 13.3, 13.6, 15.5, 20.3, 21.2, 22.4, 22.7, 23.7.

Example 25

N,N'-(4,4'-biphenyldiylbis(1H-imidazole-5,2-diyl(2S)-2,1-pyrrolidinediyl((1R)-2-oxo-1-phenyl-2,1-ethanediyl)))diacetamide

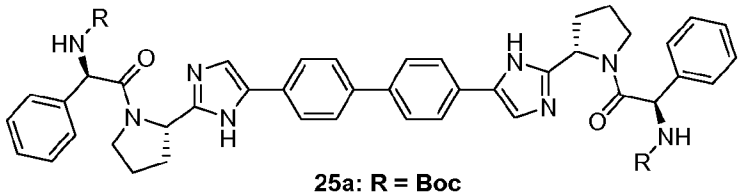


Example 25 Step a:

di-tert-butyl (4,4'-biphenyldiylbis(1H-imidazole-5,2-diyl(2S)-2,1-pyrrolidinediyl((1R)-2-oxo-1-phenyl-2,1-ethanediyl)))biscarbamate

and

Example 25 Step b:



25a: R = Boc
25b: R = H

HATU (96.2 mg, 0.253 mmol) was added to a mixture of pyrrolidine 1e (52.6 mg, 0.124 mmol), diisopropylethylamine (100 μL, 0.57 mmol) and Boc-D-Phg-OH (69 mg, 0.275 mmol) in DMF (3.0 mL). The reaction mixture was stirred for 25 minutes, and then diluted with methanol and purified by a reverse phase HPLC

system (H_2O/methanol/TFA). The HPLC elute was neutralized with excess 2.0 M/NH_3 in CH_3OH and the volatile component was removed *in vacuo*. The residue was carefully partitioned between CH_2Cl_2 and saturated $NaHCO_3$. The aqueous phase was extracted with more CH_2Cl_2 (2x). The combined organic phase was dried ($MgSO_4$), filtered, and concentrated *in vacuo* to provide 25a as a film of semisolid oil (78.8 mg). LC (Cond. 1): RT = 1.99 min; >98% homogeneity index. LC/MS: Anal. Calcd. for $[M+H]^+$ $C_{52}H_{59}N_8O_6$: 891.46; found 891.55.

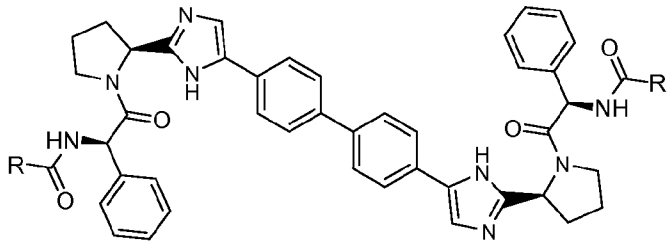
Carbamate 25a was converted to amine 25b according to the procedure described for the preparation of 1e. LC(Cond. 1): RT = 1.44 min; 97% homogeneity index. LC/MS: Anal. Calcd. for $[M+H]^+$ $C_{42}H_{43}N_8O_2$: 691.35; found 691.32

Example 25

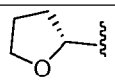
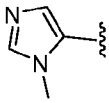
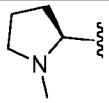
N,N'-(4,4'-biphenyldiylbis(1H-imidazole-5,2-diyl(2S)-2,1-pyrrolidinediyl((1R)-2-oxo-1-phenyl-2,1-ethanediyl)))diacetamide

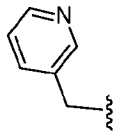
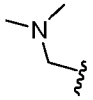
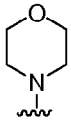
Acetic anhydride (20 µL, 0.21 mmol) was added to a DMF (1.5 mL) solution of amine 25b (29 mg, 0.042 mmol)and triethylamine (30 µL, 0.22 mmol) and stirred for 2.5 hours. The reaction mixture was then treated with NH_3/methanol (1 mL of 2 M) and stirred for an additional 1.5 hours. The volatile component was removed *in vacuo* and the residue was purified by a reverse phase HPLC system (H_2O/methanol/ TFA) to provide the TFA salt of Example 25 as a white foam (28.1 mg). LC (Cond.1): RT = 1.61 min; >98% homogeneity index; LC/MS: Anal. Calcd. for $[M+H]^+$ $C_{46}H_{47}N_8O_4$: 775.37; found 775.40; HRMS: Anal. Calcd. for $[M+H]^+$ $C_{46}H_{47}N_8O_4$: 775.3720; found 775.3723

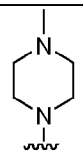
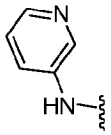
Example 25-1 to 25-5



Examples 25-1 to 25-5 were prepared from 25b and the appropriate carboxylic acid using standard amide forming conditions similar to that described for the preparation of example 1 from 1c. Examples 25-6 to 25-8 were prepared from 25b and the appropriate carbamoyl chloride or isocyanate.

Example Number	*Compound Name*	*R*	*RT (LC-Cond.); % homogeneity index; MS data*
25-1	(2R,2'R)-N,N'-(4,4'-biphenyldiylbis(1H-imidazole-5,2-diyl(2S)-2,1-pyrrolidinediyl((1R)-2-oxo-1-phenyl-2,1-ethanediyl)))ditetrahydro-2-furancarboxamide		RT = 5.68 minutes; HPLC Xterra 4.6 X 50 mm, 0 to 100% B over 10 minutes, one minute hold time, A = 90% water, 10% methanol, 0.2% phosphoric acid, B = 10% water, 90% methanol, 0.2% phosphoric acid; LCMS: Anal. Calcd. for: $C_{52}H_{54}N_8O_6$: 887.06; Found: 887.58 $(M+H)^+$
25-2	N,N'-(4,4'-biphenyldiylbis(1H-imidazole-5,2-diyl(2S)-2,1-pyrrolidinediyl((1R)-2-oxo-1-phenyl-2,1-ethanediyl)))bis(1-methyl-1H-imidazole-5-carboxamide)		RT = 3.54 minutes; HPLC Xterra 4.6 X 50 mm, 0 to 100% B over 10 minutes, one minute hold time, A = 90% water, 10% methanol, 0.2% phosphoric acid, B = 10% water, 90% methanol, 0.2% phosphoric acid; LCMS: Anal. Calcd. for: $C_{52}H_{50}N_{12}O_4$: 907.06; Found: 907.42 $(M+H)^+$
25-3	(2S,2'S)-N,N'-(4,4'-biphenyldiylbis(1H-imidazole-5,2-diyl(2S)-2,1-pyrrolidinediyl((1R)-2-oxo-1-phenyl-2,1-ethanediyl)))bis(1-methyl-2-pyrrolidinecarboxamide)		RT = 3.1 minutes; HPLC Xterra 4.6 X 50 mm, 0 to 100% B over 10 minutes, one minute hold time, A = 90% water, 10% methanol, 0.2% phosphoric acid, B = 10% water, 90% methanol, 0.2% phosphoric acid; LCMS: Anal. Calcd. for: $C_{54}H_{60}N_{10}O_4$ 913.14; Found: 913.54 $(M+H)^+$

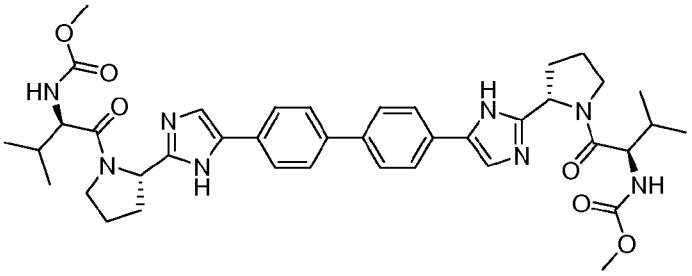
25-4	N,N'-(4,4'-biphenyldiylbis(1H-imidazole-5,2-diyl(2S)-2,1-pyrrolidinediyl((1R)-2-oxo-1-phenyl-2,1-ethanediyl)))bis(2-(3-pyridinyl)acetamide)		RT = 3.37 minutes; HPLC Xterra 4.6 X 50 mm, 0 to 100% B over 10 minutes, one minute hold time, A = 90% water, 10% methanol, 0.2% phosphoric acid, B = 10% water, 90% methanol, 0.2% phosphoric acid; LCMS: Anal. Calcd. for: $C_{56}H_{52}N_{10}O_4$ 929.10 Found: 929.42 $(M+H)^+$
25-5	N,N'-(4,4'-biphenyldiylbis(1H-imidazole-5,2-diyl(2S)-2,1-pyrrolidinediyl((1R)-2-oxo-1-phenyl-2,1-ethanediyl)))bis(2-(dimethylamino)acetamide) (non-preferred name)		RT = 7.07 minutes; HPLC Xterra 4.6 X 50 mm, 0 to 100% B over 10 minutes, one minute hold time, A = 90% water, 10% methanol, 0.2% phosphoric acid, B = 10% water, 90% methanol, 0.2% phosphoric acid; LCMS: Anal. Calcd. for: $C_{50}H_{56}N_{10}O_4$ 861.07 Found: 859.69 $(M+H)^+$
25-6	N,N'-(4,4'-biphenyldiylbis(1H-imidazole-5,2-diyl(2S)-2,1-pyrrolidinediyl((1R)-2-oxo-1-phenyl-2,1-ethanediyl)))di(4-morpholinecarboxamide)		^{1}H NMR (500 MHz, DMSO-d_6) δ ppm 1.86-2.18 (m, 6H), 2.23-2.39 (m, 2H), 3.20-3.40 (m, 8H), 3.40-3.61 (m, 8H), 3.90-4.19 (m, 4H), 5.27 (dd, *J*=8.09, 3.51 Hz, 2H), 5.37-5.63 (m, 2H), 6.92-7.11 (m, 3H), 7.30-7.45 (m, 5H), 7.44-7.56 (m, 4H), 7.83-8.04 (m, 8H), 8.15 (s, 2H), 14.29 (s, 2H); HPLC Xterra 4.6 X 50 mm, 0 to 100% B over 10 minutes, one minute hold time, A = 90% water, 10% methanol, 0.2% phosphoric acid, B = 10% water, 90% methanol, 0.2% phosphoric acid, RT = 6.01 minutes; LCMS: Anal. Calcd. for: $C_{52}H_{56}N_{10}O_6$ 917.09; Found:

			917.72 $(M+H)^+$
25-7	N,N'-(4,4'-biphenyldiylbis(1H-imidazole-5,2-diyl(2S)-2,1-pyrrolidinediyl((1R)-2-oxo-1-phenyl-2,1-ethanediyl)))bis(4-methyl-1-piperazinecarboxamide)		RT = 3.74 minutes; HPLC Xterra 4.6 X 50 mm, 0 to 100% B over 10 minutes, one minute hold time, A = 90% water, 10% methanol, 0.2% phosphoric acid, B = 10% water, 90% methanol, 0.2% phosphoric acid; LCMS: Anal. Calcd. for: $C_{54}H_{62}N_{12}O_4$ 943.17; Found: 943.84 $(M+H)^+$
25-8	N,N''-(4,4'-biphenyldiylbis(1H-imidazole-5,2-diyl(2S)-2,1-pyrrolidinediyl((1R)-2-oxo-1-phenyl-2,1-ethanediyl)))bis(3-(3-pyridinyl)urea)		^{1}H NMR (500 MHz, DMSO-d_6) δ ppm 1.79-2.17 (m, 6H), 2.29 (d, *J*=9.77 Hz, 2H), 3.06-3.39 (m, 2H), 3.72-4.14 (m, 2H), 5.27 (dd, *J*=8.24, 2.75 Hz, 2H), 5.66 (d, *J*=7.02 Hz, 2H), 7.26-7.65 (m, 12H), 7.82-8.11 (m, 12H), 8.17 (s, 2H), 8.23-8.45 (m, 2H), 8.61-8.97 (m, 2H), 9.38 (s, 2H), 14.51 (s, 2H); HPLC Xterra 4.6 X 50 mm, 0 to 100% B over 10 minutes, one minute hold time, A = 90% water, 10% methanol, 0.2% phosphoric acid, B = 10% water, 90% methanol, 0.2% phosphoric acid, RT = 4.05 minutes; LCMS: Anal. Calcd. for: $C_{54}H_{50}N_{12}O_4$ 931.08; Found: 931.78 $(M+H)^+$.

5

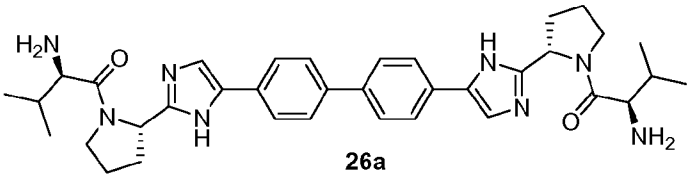
Example 26

methyl ((1R)-1-(((2S)-2-(5-(4'-(2-((2S)-1-((2R)-2-((methoxycarbonyl)amino)-3-methylbutanoyl)-2-pyrrolidinyl)-1H-imidazol-5-yl)-4-biphenylyl)-1H-imidazol-2-yl)-1-pyrrolidinyl)carbonyl)-2-methylpropyl)carbamate



Example 26, Step a

(2R,2'R)-1,1'-(4,4'-biphenyldiylbis(1H-imidazole-5,2-diyl(2S)-2,1-pyrrolidinediyl))bis(3-methyl-1-oxo-2-butanamine)



26a

Diamine 26a was prepared starting from pyrrolidine 1e and BOC-D-Val-OH according to the procedure described for the synthesis of diamine 25b.

Example 26

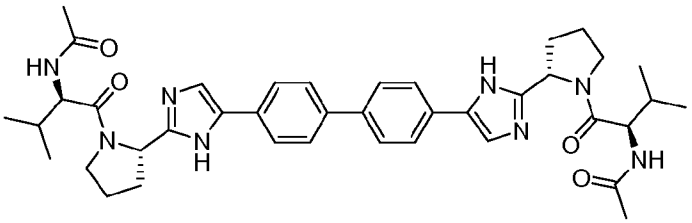
methyl ((1R)-1-(((2S)-2-(5-(4'-(2-((2S)-1-((2R)-2-((methoxycarbonyl)amino)-3-methylbutanoyl)-2-pyrrolidinyl)-1H-imidazol-5-yl)-4-biphenylyl)-1H-imidazol-2-yl)-1-pyrrolidinyl)carbonyl)-2-methylpropyl)carbamate

Methyl chloroformate (18 μL, 0.23 mmol) was added to a THF (1.5 mL) solution of diamine 26a (30 mg, 0.048 mmol) and triethylamine (30 μL, 0.22 mmol), and the reaction mixture was stirred at ambient condition for 3 hours. The volatile components was removed *in vacuo*, and the residue was treated with NH_3/methanol (2 mL of 2 M) and stirred at ambient conditions for 15 minutes. All the volatile component was removed *in vacuo*, and the crude product was purified by reverse phase prep-HPLC (H_2O/methanol/TFA) to provide the TFA salt of Example 26 as a white solid (13.6 mg). LC (Cond.2): RT = 2.00 min; >98% homogeneity index;

LC/MS: Anal. Calcd. for $[M+H]^+$ $C_{40}H_{51}N_8O_6$: 739.39; found 739.67; HRMS: Anal. Calcd. for $[M+H]^+$ $C_{40}H_{51}N_8O_6$: 739.3932; found 739.3966.

Example 27

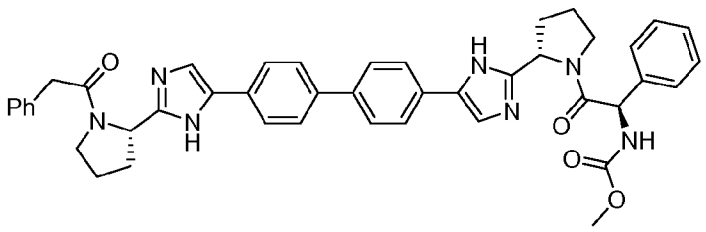
N-((1R)-1-(((2S)-2-(5-(4'-(2-((2S)-1-((2R)-2-acetamido-3-methylbutanoyl)-2-pyrrolidinyl)-1H-imidazol-5-yl)-4-biphenylyl)-1H-imidazol-2-yl)-1-pyrrolidinyl)carbonyl)-2-methylpropyl)acetamide



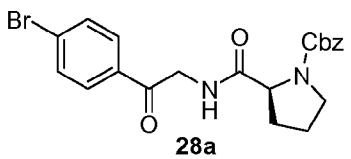
Diamine 26a was converted to Example 27 (TFA salt) according to a method described in the preparation of Example 25. LC (Cond.2): RT = 1.93min; >98% homogeneity index; LC/MS: Anal. Calcd. for $[M+H]^+$ $C_{40}H_{51}N_8O_4$: 707.40; found 707.59; HRMS: Anal. Calcd. for $[M+H]^+$ $C_{40}H_{51}N_8O_4$: 707.4033; found 707.4054.

Example 28

methyl ((1R)-2-oxo-1-phenyl-2-((2S)-2-(5-(4'-(2-((2S)-1-(phenylacetyl)-2-pyrrolidinyl)-1H-imidazol-5-yl)-4-biphenylyl)-1H-imidazol-2-yl)-1-pyrrolidinyl)ethyl)carbamate



Example 28, Step a

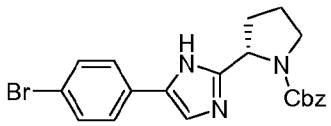


28a

HATU (19.868g, 52.25 mmol) was added to a heterogeneous mixture of *N*-Cbz-L- proline (12.436 g, 49.89 mmol) and the HCl salt of 2-amino-1-(4-

bromophenyl) ethanone (12.157 g, 48.53 mmol) in DMF (156 mL). The mixture was lowered in an ice-water bath, and immediately afterward *N,N*-diisopropylethylamine (27 mL, 155 mmol) was added dropwise to it over 13 minutes. After the addition of the base was completed, the cooling bath was removed and the reaction mixture was stirred for an additional 50 minutes. The volatile component was removed *in vacuo*; water (125 mL) was added to the resulting crude solid and stirred for about 1 hour. The off-white solid was filtered and washed with copious water, and dried *in vacuo* to provide ketoamide 28a as a white solid (20.68 g). ^{1}H NMR (DMSO-d_6, δ = 2.5 ppm, 400 MHz): δ 8.30 (m, 1H), 7.91 (m, 2H), 7.75 (d, J = 8.5, 2H), 7.38-7.25 (m, 5H), 5.11-5.03 (m, 2H), 4.57-4.48 (m, 2H), 4.33-4.26 (m, 1H), 3.53-3.36 (m, 2H), 2.23-2.05 (m, 1H), 1.94-1.78 (m, 3H); LC (Cond. 1): RT = 1.65 min; 98% homogeneity index; LC/MS: Anal. Calcd. for $[M+H]^+$ $C_{21}H_{22}BrN_2O_4$: 445.08; found 445.31.

Example 28, Step b



28b

Ketoamide 28a (10.723g, 24.08 mmol) was converted to 28b according to the procedure described for the synthesis of carbamate 1b, with the exception that the crude material was purified by flash chromatography (sample was loaded with eluting solvent; 50% ethyl acetate/hexanes). Bromide 28b was retrieved as an off-white foam (7.622 g). ^{1}H NMR (DMSO-d_6, δ = 2.5 ppm, 400 MHz): δ 12.23/12.04/11.97 (m, 1H), 7.73-6.96 (m, 10H), 5.11-4.85 (m, 3H), 3.61 (m, 1H), 3.45 (m, 1H), 2.33-184(m, 4H). LC (Cond.1): RT = 1.42 min; >95% homogeneity index; LC/MS: Anal. Calcd. for $[M+H]^+$ $C_{21}H_{21}BrN_3O_2$: 426.08; found 426.31; HRMS: Anal. Calcd. for $[M+H]^+$ $C_{21}H_{21}BrN_3O_2$: 426.0817; found: 426.0829. The optical purity of 28b was assessed using the following chiral HPLC methods, and an ee of 99% was observed.

Column: Chiralpak AD, 10 um, 4.6 x 50 mm

Solvent: 20% ethanol/heptane (isocratic)

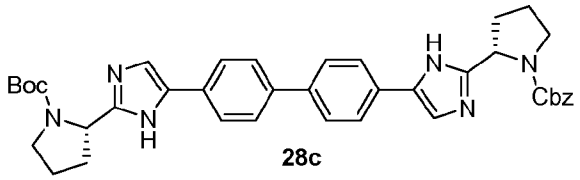
Flow rate: 1 mL/min

Wavelength: 254 nm

Relative retention time: 1.82 minutes (*R*), 5.23 minutes (*S*)

Example 28, Step c

benzyl tert-butyl (2S,2'S)-2,2'-(4,4'-biphenyldiylbis(1H-imidazole-5,2-diyl))di(1-pyrrolidinecarboxylate)

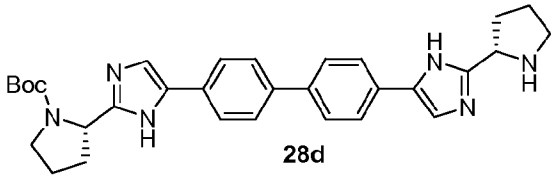


28c

$Pd(Ph_3P)_4$ (711.4 mg, 0.616 mmol) was added to a mixture of boronate ester 1c (7.582 g, ~ 17 mmol), bromide 28b (7.62 g, 17.87 mmol), $NaHCO_3$ (4.779 g, 56.89 mmol) in 1,2-dimethoxyethane (144 mL) and water (48 mL). The reaction mixture was purged with N_2 and heated with an oil bath at 80 °C for 15.5 hours, and then the volatile component was removed *in vacuo*. The residue was partitioned between CH_2Cl_2 and water, and the aqueous layer was extracted with CH_2Cl_2. The combined organic phase was dried ($MgSO_4$), filtered, and concentrated *in vacuo*. The resulting material was submitted to flash chromatography (sample was loaded as a silica gel mesh; ethyl acetate used as eluent) to provide biphenyl 28c as an off-white foam containing Ph_3PO impurity (7.5 g). ^1H NMR (DMSO-d_6, δ = 2.5 ppm, 400 MHz): δ 12.24-12.19 (m, 0.36H), 12.00-11.82 (m, 1.64H), 7.85-6.98 (15H), 5.12-4.74 (4H), 3.68-3.34(4H), 2.34-1.79 (8H), 1.41/1.17 (two br S, 9H); LC (Cond.1): RT = 1.41 minutes; LC/MS: Anal. Calcd. for $[M+H]^+$ $C_{39}H_{43}N_6O_4$: 659.34; found 659.52; HRMS: Anal. Calcd. for $[M+H]^+$ $C_{39}H_{43}N_6O_4$: 659.3346; found 659.3374.

Example 28, Step d

tert-butyl (2S)-2-(5-(4'-(2-((2S)-2-pyrrolidinyl)-1H-imidazol-5-yl)-4-biphenylyl)-1H-imidazol-2-yl)-1-pyrrolidinecarboxylate



28d

K_2CO_3 (187.8 mg, 1.36 mmol) was added to a mixture of catalyst (10% Pd/C; 205.3 mg), carbamate 28c (1.018 g, ~ 1.5 mmol), methanol (20 mL) and 3 pipet-drops of water. A balloon of H_2 was attached and the mixture was stirred for 6 hours. Then, additional catalyst (10% Pd/C, 100.8 mg) and K_2CO_3 (101.8 mg, 0.738 mmol) were added and stirring continued for 3.5 hours. During the hydrogenation process, the balloon of H_2 was changed at intervals three times. The reaction mixture was filtered through a pad of diatomaceous earth (Celite® 521), and the filtrate was removed *in vacuo*. The resulting crude material was submitted to flash chromatography using a short column (sample was loaded as a silica gel mesh; 0-20% methanol/CH_2Cl_2 used as eluent) to provide 28d as a light-yellow foam (605.6 mg). ^{1}H NMR (DMSO-d_6, δ = 2.5 ppm, 400 MHz): δ 12.18/11.89/11.82 (three br s, 2H), 7.83-7.29 (m, 10H), 4.89-4.73 (m, 1H), 4.19 (app t, J = 7.2, 1H), 3.55 (app br s, 1H), 3.40-3.35 (m, 1H), 3.02-2.96 (m, 1H), 2.91-2.84(m, 1H), 2.30-1.69(m, 8H), 1.41/1.16 (two br s, 9H). Note: the signal of pyrrolidine NH appears to have overlapped with signals in the 3.6-3.2 ppm region; LC (Cond.1): RT = 1.21 min; >95% homogeneity index; LC/MS: Anal. Calcd. for $[M+H]^+$ $C_{31}H_{37}N_6O_2$: 525.30; found 525.40.

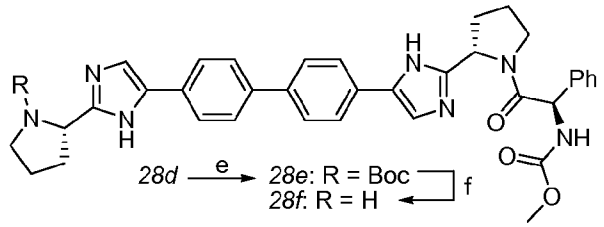
Example 28, Step e-f

Example 28 step e

tert-butyl (2S)-2-(5-(4'-(2-((2S)-1-((2R)-2-((methoxycarbonyl)amino)-2-phenylacetyl)-2-pyrrolidinyl)-1H-imidazol-5-yl)-4-biphenylyl)-1H-imidazol-2-yl)-1-pyrrolidinecarboxylate

Example 28 step f

methyl ((1R)-2-oxo-1-phenyl-2-((2S)-2-(5-(4'-(2-((2S)-2-pyrrolidinyl)-1H-imidazol-5-yl)-4-biphenylyl)-1H-imidazol-2-yl)-1-pyrrolidinyl)ethyl)carbamate

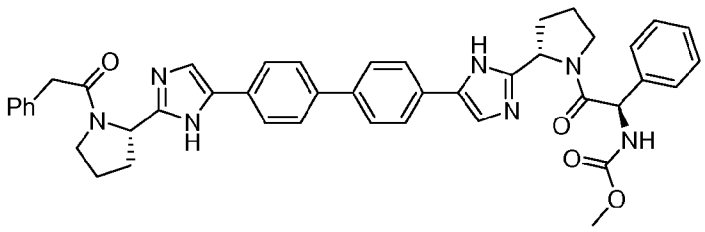


Step e: HATU (316.6 mg, 0.833 mmol) was added to a DMF (7.0 mL) solution of pyrrolidine 28d (427 mg, 0.813 mmol), *Cap*-4 (177.6 mg, 0.849 mmol) and diisopropylethylamine (0.32 mL, 1.84 mmol), and the reaction mixture was stirred for 45 minutes. The volatile component was removed *in vacuo*, and the residue was partitioned between CH_2Cl_2 (50 mL) and an aqueous medium (20 mL H_2O + 1 mL saturated $NaHCO_3$ solution). The aqueous phase was re-extracted with CH_2Cl_2, and the combined organic phase was dried ($MgSO_4$), filtered, and concentrated *in vacuo*. The resulting yellow oil was purified by flash chromatography (silica gel; ethyl acetate) to provide 28e as a yellow foam (336 mg). LC (Cond. 1): RT = 1.68min; 91% homogeneity index; LC/MS: Anal. Calcd. for $[M+H]^+$ $C_{41}H_{46}N_7O_5$: 716.35; found 716.53.

Step f: Carbamate 28e was elaborated to amine 28f by employing the procedure described in the conversion of 1d to 1e. LC (Cond. 1): RT = 1.49min; >98% homogeneity index. LC/MS: Anal. Calcd. for $[M+H]^+$ $C_{36}H_{38}N_7O_3$: 616.30; found 616.37; HRMS: Anal. Calcd. for $[M+H]^-$ $C_{36}H_{38}N_7O_3$: 616.3036; found 616.3046.

Example 28

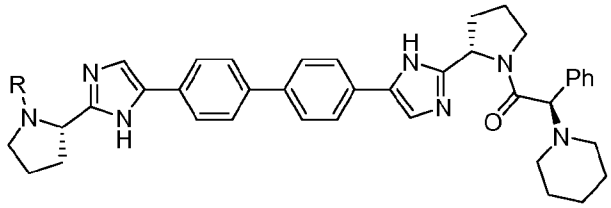
methyl ((1R)-2-oxo-1-phenyl-2-((2S)-2-(5-(4'-(2-((2S)-1-(phenylacetyl)-2-pyrrolidinyl)-1H-imidazol-5-yl)-4-biphenylyl)-1H-imidazol-2-yl)-1-pyrrolidinyl)ethyl)carbamate



Amine 28f was converted to the TFA salt of Example 28 by employing the last step of the synthesis of Example 1. ^1H NMR (DMSO-d_6, δ= 2.5 ppm, 400

MHz): δ 8.21-7.03 (m, 21H), 5.78-5.14 (3H), 3.98-3.13 (m, 9H; includes the signal for OCH_3 at 3.54 & 3.53), 2.45-1.72 (m, 8H). LC (Cond. 1): RT = 1.66 minutes, >98% homogeneity index; LC/MS: Anal. Calcd. for $[M+H]^+$ $C_{44}H_{44}N_7O_4$: 734.35; found 734.48; HRMS: Anal. Calcd. for $[M+H]^-$ $C_{44}H_{44}N_7O_4$: 734.3455; 734.3455.

Example 28-1 to 28-4



Examples 28-1 through 28-4 (R groups shown in the table below) were prepared in similar fashion to example 28 *via* the intermediacy of intermediate 28d.

Example 28-1

(1R)-N,N-dimethyl-2-oxo-1-phenyl-2-((2S)-2-(5-(4'-(2-((2S)-1-((2R)-2-phenyl-2-(1-piperidinyl)acetyl)-2-pyrrolidinyl)-1H-imidazol-5-yl)-4-biphenylyl)-1H-imidazol-2-yl)-1-pyrrolidinyl)ethanamine

Cap-1 was appended, the Boc carbamate was removed with TFA or HCl , and *Cap*-14 was appended.

Example 28-2

1-((1R)-2-oxo-1-phenyl-2-((2S)-2-(5-(4'-(2-((2S)-1-((2R)-tetrahydro-2-furanylcarbonyl)-2-pyrrolidinyl)-1H-imidazol-5-yl)-4-biphenylyl)-1H-imidazol-2-yl)-1-pyrrolidinyl)ethyl)piperidine

Tetrahydrofuroic acid was appended, the Boc carbamate was removed with TFA or HCl , and *Cap*-14 was appended.

Example 28-3

methyl ((1R)-1-(2-chlorophenyl)-2-oxo-2-((2S)-2-(5-(4'-(2-((2S)-1-((2R)-2-phenyl-2-(1-piperidinyl)acetyl)-2-pyrrolidinyl)-1H-imidazol-5-yl)-4-biphenylyl)-1H-imidazol-2-yl)-1-pyrrolidinyl)ethyl)carbamate

Cap-40 was appended, the Boc carbamate was removed with TFA or HCl , and *Cap*-14 was appended.

Example 28-4

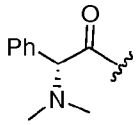
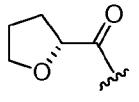
(1R)-1-(2-chlorophenyl)-N,N-dimethyl-2-oxo-2-((2S)-2-(5-(4'-(2-((2S)-1-((2R)-2-phenyl-2-(1-piperidinyl)acetyl)-2-pyrrolidinyl)-1H-imidazol-5-yl)-4-biphenylyl)-1H-imidazol-2-yl)-1-pyrrolidinyl)ethanamine

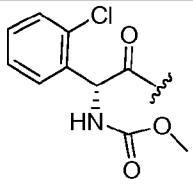
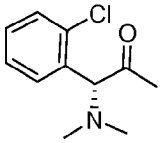
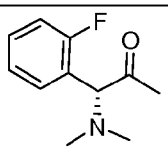
Cap-39 was appended, the Boc carbamate was removed with TFA or HCl , and *Cap*-14 was appended.

Example 28-5

(1R)-1-(2-fluorophenyl)-N,N-dimethyl-2-oxo-2-((2S)-2-(5-(4'-(2-((2S)-1-((2R)-2-phenyl-2-(1-piperidinyl)acetyl)-2-pyrrolidinyl)-1H-imidazol-5-yl)-4-biphenylyl)-1H-imidazol-2-yl)-1-pyrrolidinyl)ethanamine

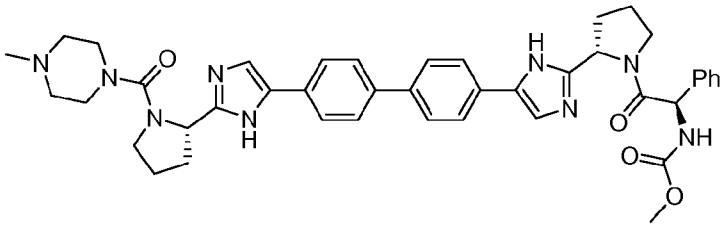
Cap-38 was appended, the Boc carbamate was removed with TFA or HCl , and *Cap*-14 was appended.

Example	*Compound Name*	*R*	*Data*
28-1	(1R)-N,N-dimethyl-2-oxo-1-phenyl-2-((2S)-2-(5-(4'-(2-((2S)-1-((2R)-2-phenyl-2-(1-piperidinyl)acetyl)-2-pyrrolidinyl)-1H-imidazol-5-yl)-4-biphenylyl)-1H-imidazol-2-yl)-1-pyrrolidinyl)ethanamine		LCMS: Anal. Calcd. for $C_{49}H_{54}N_8O_2$: 786; found: 787 $(M+H)^+$.
28-2	1-((1R)-2-oxo-1-phenyl-2-((2S)-2-(5-(4'-(2-((2S)-1-		LCMS: Anal. Calcd. for

	((2R)-tetrahydro-2-furanylcarbonyl)-2-pyrrolidinyl)-1H-imidazol-5-yl)-4-biphenylyl)-1H-imidazol-2-yl)-1-pyrrolidinyl)ethyl)piperidine		$C_{44}H_{49}N_7O_3$: 723; found: 724 $(M+H)^+$.
28-3	methyl ((1R)-1-(2-chlorophenyl)-2-oxo-2-((2S)-2-(5-(4'-(2-((2S)-1-((2R)-2-phenyl-2-(1-piperidinyl)acetyl)-2-pyrrolidinyl)-1H-imidazol-5-yl)-4-biphenylyl)-1H-imidazol-2-yl)-1-pyrrolidinyl)ethyl)carbamate		LCMS: Anal. Calcd. for $C_{49}H_{51}ClN_8O_4$: 850; found: 851 $(M+H)^+$.
28-4	(1R)-1-(2-chlorophenyl)-N,N-dimethyl-2-oxo-2-((2S)-2-(5-(4'-(2-((2S)-1-((2R)-2-phenyl-2-(1-piperidinyl)acetyl)-2-pyrrolidinyl)-1H-imidazol-5-yl)-4-biphenylyl)-1H-imidazol-2-yl)-1-pyrrolidinyl)ethanamine		LCMS: Anal. Calcd. for $C_{49}H_{53}ClN_8O_2$: 820; found: 821 $(M+H)^+$.
28-5	(1R)-1-(2-fluorophenyl)-N,N-dimethyl-2-oxo-2-((2S)-2-(5-(4'-(2-((2S)-1-((2R)-2-phenyl-2-(1-piperidinyl)acetyl)-2-pyrrolidinyl)-1H-imidazol-5-yl)-4-biphenylyl)-1H-imidazol-2-yl)-1-pyrrolidinyl)ethanamine		LCMS: Anal. Calcd. for $C_{49}H_{53}FN_8O_2$: 804; found: 805 $(M+H)^+$.

Example 29

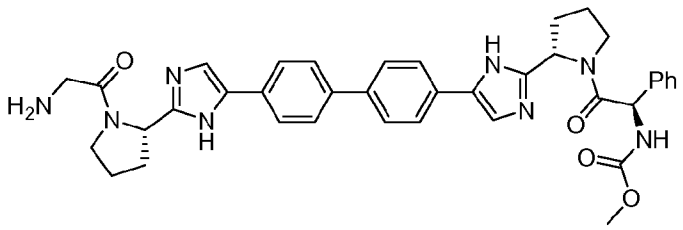
methyl ((1R)-2-((2S)-2-(5-(4'-(2-((2S)-1-((4-methyl-1-piperazinyl)carbonyl)-2-pyrrolidinyl)-1H-imidazol-5-yl)-4-biphenylyl)-1H-imidazol-2-yl)-1-pyrrolidinyl)-2-oxo-1-phenylethyl)carbamate



4-Methylpiperazine-1-carbonyl chloride/HCl (11.6 mg, 0.58 mmol) was added to a mixture of 28f (30 mg, 0.049 mmol), triethylamine (15 µl, 0.11 mmol) and THF (1.0 mL), and stirred at ambient conditions for 1 hour. The volatile component was removed *in vacuo*, and the residue was purified by a reverse phase HPLC (H_2O/methanol/TFA) to provide the TFA salt of Example 29 as a light yellow foam (29.3 mg). LC (Cond. 2): RT = 1.82 minutes, >98% homogeneity index; LC/MS: Anal. Calcd. for $[M+H]^+$ $C_{42}H_{48}N_9O_4$: 742.38; found 742.49.

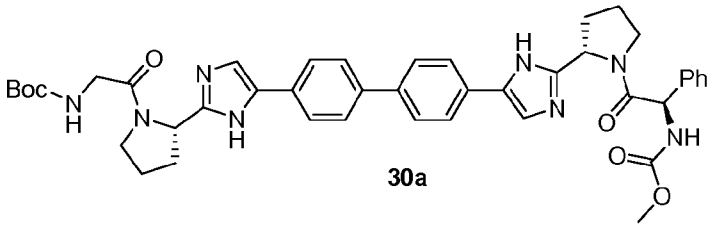
Example 30

methyl ((1R)-2-((2S)-2-(5-(4'-(2-((2S)-1-glycyl-2-pyrrolidinyl)-1H-imidazol-5-yl)-4-biphenylyl)-1H-imidazol-2-yl)-1-pyrrolidinyl)-2-oxo-1-phenylethyl)carbamate



Example 30, Step a

methyl ((1R)-2-((2S)-2-(5-(4'-(2-((2S)-1-(N-(tert-butoxycarbonyl)glycyl)-2-pyrrolidinyl)-1H-imidazol-5-yl)-4-biphenylyl)-1H-imidazol-2-yl)-1-pyrrolidinyl)-2-oxo-1-phenylethyl)carbamate



30a

Carbamate 30a was prepared from pyrrolidine 28f and Boc-Glycine by using the procedure described for the preparation of 25a from 1e. LC (Cond. 2): RT = 2.12 minutes, >98% homogeneity index; LC/MS: Anal. Calcd. for $[M+H]^+$ $C_{43}H_{49}N_8O_6$: 773.38; found 773.46

Example 30

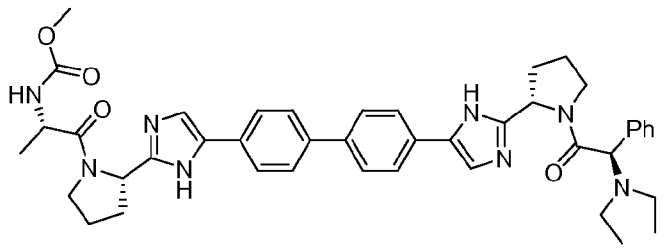
methyl ((1R)-2-((2S)-2-(5-(4'-(2-((2S)-1-glycyl-2-pyrrolidinyl)-1H-imidazol-5-yl)-4-biphenylyl)-1H-imidazol-2-yl)-1-pyrrolidinyl)-2-oxo-1-phenylethyl)carbamate

Carbamate 30a was converted to Example 30 according to the procedure described for the preparation of 1e from 1d. LC (Cond. 2): RT = 1.81 minutes, >98% homogeneity index; LC/MS: Anal. Calcd. for $[M+H]^+$ $C_{38}H_{41}N_8O_4$: 673.33; found 673.43

HRMS: Anal. Calcd. for $[M+H]^+$ $C_{38}H_{41}N_8O_4$: 673.3251; found 673.3262

Example 30-1

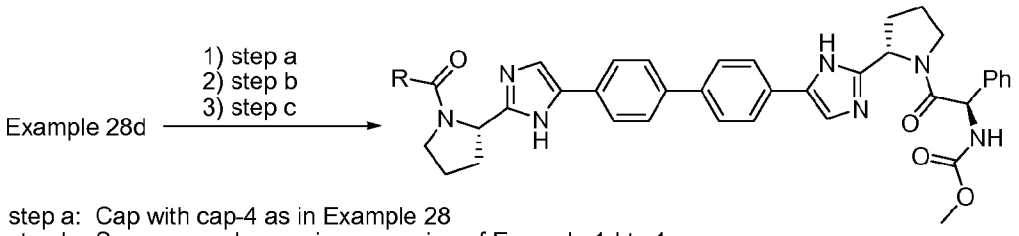
methyl ((1S)-2-((2S)-2-(5-(4'-(2-((2S)-1-((2R)-2-(diethylamino)-2-phenylacetyl)-2-pyrrolidinyl)-1H-imidazol-5-yl)-4-biphenylyl)-1H-imidazol-2-yl)-1-pyrrolidinyl)-1-methyl-2-oxoethyl)carbamate



Example 30-1 was prepared in three steps from Example 28d. Step one: Append *Cap*-2 using the procedure describing the synthesis of 28e from 28d. Step two: Hydrolyze the Boc carbamate using the procedure describing the synthesis of 28f from 28e. Step three: Append *Cap*-52 using the procedure describing the synthesis of 28e from 28d. RT = 1.70 min (Cond. 1b); >95% homogeneity index. LC/MS: Anal. Calcd. for $[M+H]^+$ $C_{43}H_{51}N_8O_4$: 743.40; found, 743.50. HRMS: Anal. Calcd. for $[M+H]^+$ $C_{43}H_{51}N_8O_4$: 743.4033; found, 743.4053

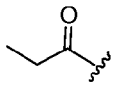
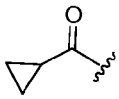
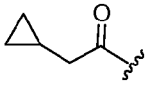
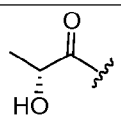
Substituting the appropriate acid chloride or carboxylic acid into Example 29 or 30, the following compounds (Example 31 to 84-87) were prepared as TFA salts.

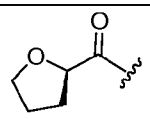
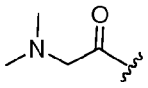
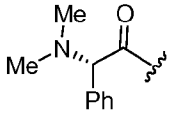
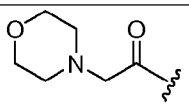
Example 31 to 84-88

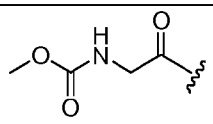
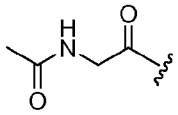
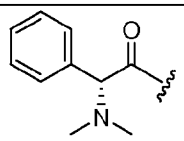
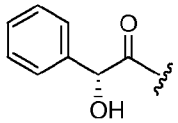


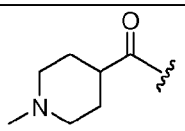
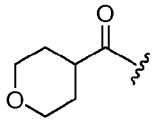
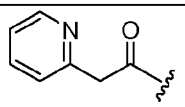
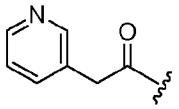
step a: Cap with cap-4 as in Example 28
step b: Same procedure as in conversion of Example 1d to 1e
step c: As in the last step of Example 1 using 1.1 equiv. of the appropriate carboxylic acid and HATU

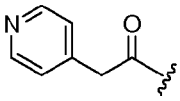
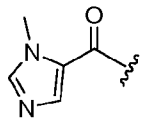
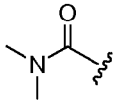
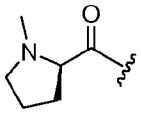
Example	*Compound Name*		*Retention time (LC-Condition); homogeneity index MS data*
31	methyl ((1R)-2-((2S)-2-(5-(4'-(2-((2S)-1-acetyl-2-pyrrolidinyl)-1H-imidazol-5-yl)-4-biphenylyl)-1H-imidazol-2-yl)-1-pyrrolidinyl)-2-oxo-1-phenylethyl)carbamate		1.54 minutes (Cond. 1); >98%; LC/MS: Anal. Calcd. for $[M+H]^+$ $C_{38}H_{40}N_7O_4$: 658.31; found 658.42; HRMS: Anal. Calcd. for $[M+H]^+$ $C_{38}H_{40}N_7O_4$: 658.3142; found 658.3135

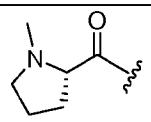
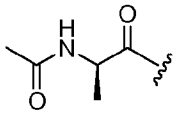
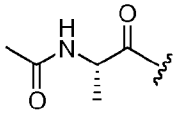
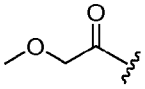
32	methyl ((1R)-2-oxo-1-phenyl-2-((2S)-2-(5-(4'-(2-((2S)-1-propionyl-2-pyrrolidinyl)-1H-imidazol-5-yl)-4-biphenylyl)-1H-imidazol-2-yl)-1-pyrrolidinyl)ethyl)carbamate		1.57 minutes (Cond. 1); >98%; LC/MS: Anal. Calcd. for $[M+H]^+$ $C_{39}H_{42}N_7O_4$: 672.33; found 672.46; HRMS: Anal. Calcd. for $[M+H]^+$ $C_{39}H_{42}N_7O_4$: 672.3298; found 672.3299
33	methyl ((1R)-2-((2S)-2-(5-(4'-(2-((2S)-1-(cyclopropylcarbonyl)-2-pyrrolidinyl)-1H-imidazol-5-yl)-4-biphenylyl)-1H-imidazol-2-yl)-1-pyrrolidinyl)-2-oxo-1-phenylethyl)carbamate		1.59 minutes (Cond. 1); >98%; LC/MS: Anal. Calcd. for $[M+H]^+$ $C_{40}H_{42}N_7O_4$: 684.33; found 684.44; HRMS: Anal. Calcd. for $[M+H]^+$ $C_{40}H_{42}N_7O_4$: 684.3298; found 684.3324
34	methyl ((1R)-2-((2S)-2-(5-(4'-(2-((2S)-1-(cyclopropylacetyl)-2-pyrrolidinyl)-1H-imidazol-5-yl)-4-biphenylyl)-1H-imidazol-2-yl)-1-pyrrolidinyl)-2-oxo-1-phenylethyl)carbamate		1.61 minutes (Cond. 1); >98%; LC/MS: Anal. Calcd. for $[M+H]^+$ $C_{40}H_{42}N_7O_4$: 698.35; found 698.48; HRMS: Anal. Calcd. for $[M+H]^+$ $C_{40}H_{42}N_7O_4$: 698.3455; found 698.3489
35	methyl ((1R)-2-((2S)-2-(5-(4'-(2-((2S)-1-((2R)-2-hydroxypropanoyl)-2-pyrrolidinyl)-1H-imidazol-5-yl)-4-biphenylyl)-1H-imidazol-2-yl)-1-pyrrolidinyl)-2-oxo-1-phenylethyl)carbamate		1.54 minutes (Cond. 1); >98%; LC/MS: Anal. Calcd. for $[M+H]^+$ $C_{39}H_{42}N_7O_5$: 688.33; found 688.47

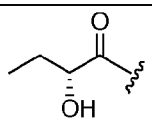
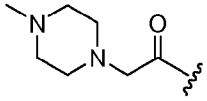
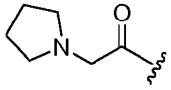
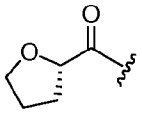
36	methyl ((1R)-2-oxo-1-phenyl-2-((2S)-2-(5-(4'-(2-((2S)-1-((2R)-tetrahydro-2-furanylcarbonyl)-2-pyrrolidinyl)-1H-imidazol-5-yl)-4-biphenylyl)-1H-imidazol-2-yl)-1-pyrrolidinyl)ethyl)carbamate		1.59 minutes (Cond. 1); >98%; LC/MS: Anal. Calcd. for $[M+H]^+$ $C_{41}H_{44}N_7O_5$: 714.34; found 714.49; HRMS: Anal. Calcd. for $[M+H]^+$ $C_{41}H_{44}N_7O_5$: 714.3404; found 714.3430
37	methyl ((1R)-2-((2S)-2-(5-(4'-(2-((2S)-1-(N,N-dimethylglycyl)-2-pyrrolidinyl)-1H-imidazol-5-yl)-4-biphenylyl)-1H-imidazol-2-yl)-1-pyrrolidinyl)-2-oxo-1-phenylethyl)carbamate		1.48 minutes (Cond. 1); >98%; LC/MS: Anal. Calcd. for $[M+H]^+$ $C_{40}H_{45}N_8O_4$: 701.36; found 701.49; HRMS: Anal. Calcd. for $[M+H]^+$ $C_{40}H_{45}N_8O_4$: 701.3564; found 701.3553
38	methyl ((1R)-2-((2S)-2-(5-(4'-(2-((2S)-1-((2S)-2-(dimethylamino)-2-phenylacetyl)-2-pyrrolidinyl)-1H-imidazol-5-yl)-4-biphenylyl)-1H-imidazol-2-yl)-1-pyrrolidinyl)-2-oxo-1-phenylethyl)carbamate	 *Cap-1*	1.20 minutes (Cond. 1); >98%; LC/MS: Anal. Calcd. for $[M+H]^+$ $C_{46}H_{49}N_8O_4$: 777.39; found 777.61; HRMS: Anal. Calcd. for $[M+H]^+$ $C_{46}H_{49}N_8O_4$: 777.3877; found 777.3909
39	methyl ((1R)-2-((2S)-2-(5-(4'-(2-((2S)-1-(4-morpholinylacetyl)-2-pyrrolidinyl)-1H-imidazol-5-yl)-4-biphenylyl)-1H-imidazol-2-yl)-1-pyrrolidinyl)-2-oxo-1-phenylethyl)carbamate		1.79 minutes (Cond. 2); >98%; LC/MS: Anal. Calcd. for $[M+H]^+$ $C_{42}H_{47}N_8O_5$: 743.37; found 743.49; HRMS: Anal. Calcd. for $[M+H]^+$ $C_{42}H_{47}N_8O_5$: 743.3669; found

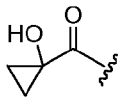
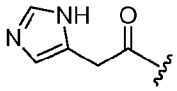
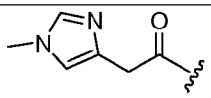
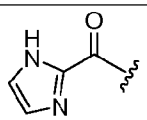
			743.3672
40	methyl (2-((2S)-2-(5-(4'-(2-((2S)-1-((2R)-2-((methoxycarbonyl)amino)-2-phenylacetyl)-2-pyrrolidinyl)-1H-imidazol-5-yl)-4-biphenylyl)-1H-imidazol-2-yl)-1-pyrrolidinyl)-2-oxoethyl)carbamate		1.92 minutes (Cond. 2); >98%; LC/MS: Anal. Calcd. for $[M+H]^+$ $C_{40}H_{43}N_8O_6$: 731.33; found 731.42; HRMS: Anal. Calcd. for $[M+H]^+$ $C_{40}H_{43}N_8O_6$: 731.3306; found 731.3333
41	methyl ((1R)-2-((2S)-2-(5-(4'-(2-((2S)-1-(N-acetylglycyl)-2-pyrrolidinyl)-1H-imidazol-5-yl)-4-biphenylyl)-1H-imidazol-2-yl)-1-pyrrolidinyl)-2-oxo-1-phenylethyl)carbamate		1.86 minutes (Cond. 2); >98%; LC/MS: Anal. Calcd. for $[M+H]^+$ $C_{40}H_{43}N_8O_5$: 715.34; found 715.49; HRMS: Anal. Calcd. for $[M+H]^+$ $C_{40}H_{43}N_8O_5$: 715.3356; found 715.3369
42	methyl ((1R)-2-((2S)-2-(5-(4'-(2-((2S)-1-((2R)-2-(dimethylamino)-2-phenylacetyl)-2-pyrrolidinyl)-1H-imidazol-5-yl)-4-biphenylyl)-1H-imidazol-2-yl)-1-pyrrolidinyl)-2-oxo-1-phenylethyl)carbamate		1.85 minutes (Cond. 2); >98%; LC/MS: Anal. Calcd. for $[M+H]^+$ $C_{46}H_{49}N_8O_4$: 777.39; found 777.56
43	methyl ((1R)-2-((2S)-2-(5-(4'-(2-((2S)-1-((2R)-2-hydroxy-2-phenylacetyl)-2-pyrrolidinyl)-1H-imidazol-5-yl)-4-biphenylyl)-1H-imidazol-2-yl)-1-pyrrolidinyl)-2-oxo-1-phenylethyl)carbamate		1.96 minutes (Cond. 2); >98%; LC/MS: Anal. Calcd. for $[M+H]^+$ $C_{44}H_{44}N_7O_5$: 750.34; found 750.51; HRMS: Anal. Calcd. for $[M+H]^+$ $C_{44}H_{44}N_7O_5$: 750.3404; found

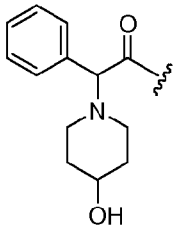
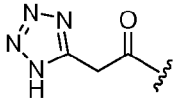
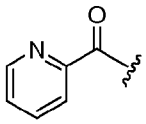
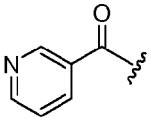
			750.3437
44	methyl ((1R)-2-((2S)-2-(5-(4'-(2-((2S)-1-((1-methyl-4-piperidinyl)carbonyl)-2-pyrrolidinyl)-1H-imidazol-5-yl)-4-biphenylyl)-1H-imidazol-2-yl)-1-pyrrolidinyl)-2-oxo-1-phenylethyl)carbamate		1.78 minutes (Cond. 2); >98%; LC/MS: Anal. Calcd. for $[M+H]^+$ $C_{43}H_{49}N_8O_4$: 741.39; found 741.55; HRMS: Anal. Calcd. for $[M+H]^+$ $C_{43}H_{49}N_8O_4$: 741.3877; found 741.3893
45	methyl ((1R)-2-oxo-1-phenyl-2-((2S)-2-(5-(4'-(2-((2S)-1-(tetrahydro-2H-pyran-4-ylcarbonyl)-2-pyrrolidinyl)-1H-imidazol-5-yl)-4-biphenylyl)-1H-imidazol-2-yl)-1-pyrrolidinyl)ethyl)carbamate		1.87 minutes (Cond. 2); >98%; LC/MS: Anal. Calcd. for $[M+H]^+$ $C_{42}H_{46}N_7O_5$: 728.36; found 728.52; HRMS: Anal. Calcd. for $[M+H]^+$ $C_{42}H_{46}N_7O_5$: 728.3560; found 728.3587
46	methyl ((1R)-2-oxo-1-phenyl-2-((2S)-2-(5-(4'-(2-((2S)-1-(2-pyridinylacetyl)-2-pyrrolidinyl)-1H-imidazol-5-yl)-4-biphenylyl)-1H-imidazol-2-yl)-1-pyrrolidinyl)ethyl)carbamate		1.80 minutes (Cond. 2); >98%; LC/MS: Anal. Calcd. for $[M+H]^+$ $C_{43}H_{43}N_8O_4$: 735.34; found 735.51; HRMS: Anal. Calcd. for $[M+H]^+$ $C_{43}H_{43}N_8O_4$: 735.3407; found 735.3416
47	methyl ((1R)-2-oxo-1-phenyl-2-((2S)-2-(5-(4'-(2-((2S)-1-(3-pyridinylacetyl)-2-pyrrolidinyl)-1H-imidazol-5-yl)-4-biphenylyl)-1H-imidazol-2-yl)-1-pyrrolidinyl)ethyl)carbamate		1.76 minutes (Cond. 2); >98%; LC/MS: Anal. Calcd. for $[M+H]^+$ $C_{43}H_{43}N_8O_4$: 735.34; found 735.52

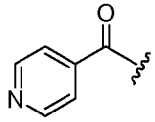
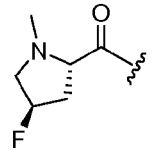
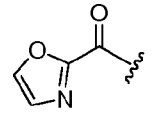
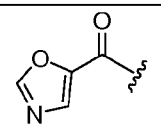
48	methyl ((1R)-2-oxo-1-phenyl-2-((2S)-2-(5-(4'-(2-((2S)-1-(4-pyridinylacetyl)-2-pyrrolidinyl)-1H-imidazol-5-yl)-4-biphenylyl)-1H-imidazol-2-yl)-1-pyrrolidinyl)ethyl)carbamate		1.77 minutes (Cond. 2); >98%; LC/MS: Anal. Calcd. for $[M+H]^+$ $C_{43}H_{43}N_8O_4$: 735.34; found 735.50; HRMS: Anal. Calcd. for $[M+H]^+$ $C_{43}H_{43}N_8O_4$: 735.3407; found 735.3405
49	methyl ((1R)-2-((2S)-2-(5-(4'-(2-((2S)-1-((1-methyl-1H-imidazol-5-yl)carbonyl)-2-pyrrolidinyl)-1H-imidazol-5-yl)-4-biphenylyl)-1H-imidazol-2-yl)-1-pyrrolidinyl)-2-oxo-1-phenylethyl)carbamate		1.77 minutes (Cond. 2); >98%; LC/MS: Anal. Calcd. for $[M+H]^+$ $C_{41}H_{42}N_9O_4$: 724.34; found 724.51; HRMS: Anal. Calcd. for $[M+H]^+$ $C_{41}H_{42}N_9O_4$: 724.3360; found 724.3380
50	methyl ((1R)-2-((2S)-2-(5-(4'-(2-((2S)-1-(dimethylcarbamoyl)-2-pyrrolidinyl)-1H-imidazol-5-yl)-4-biphenylyl)-1H-imidazol-2-yl)-1-pyrrolidinyl)-2-oxo-1-phenylethyl)carbamate		1.91 minutes (Cond. 2); >98%; LC/MS: Anal. Calcd. for $[M+H]^+$ $C_{39}H_{43}N_8O_4$: 687.34; found 687.49; HRMS: Anal. Calcd. for $[M+H]^+$ $C_{39}H_{43}N_8O_4$: 687.3407; found 687.3414
51	methyl ((1R)-2-((2S)-2-(5-(4'-(2-((2S)-1-(1-methyl-D-prolyl)-2-pyrrolidinyl)-1H-imidazol-5-yl)-4-biphenylyl)-1H-imidazol-2-yl)-1-pyrrolidinyl)-2-oxo-1-phenylethyl)carbamate	 *Cap-10*	1.79 minutes (Cond. 2); >98%; LC/MS: Anal. Calcd. for $[M+H]^+$ $C_{42}H_{47}N_8O_4$: 727.37; found 727.34; HRMS: Anal. Calcd. for $[M+H]^+$ $C_{42}H_{47}N_8O_4$: 727.3720; found

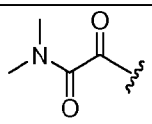
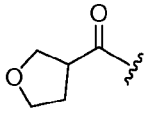
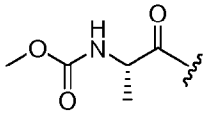
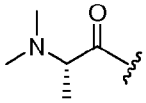
			727.3719
52	methyl ((1R)-2-((2S)-2-(5-(4'-(2-((2S)-1-(1-methyl-L-prolyl)-2-pyrrolidinyl)-1H-imidazol-5-yl)-4-biphenylyl)-1H-imidazol-2-yl)-1-pyrrolidinyl)-2-oxo-1-phenylethyl)carbamate	 *enantiomer of Cap-10*	1.77 minutes (Cond. 2); >98%; LC/MS: Anal. Calcd. for $[M+H]^+$ $C_{42}H_{47}N_8O_4$: 727.37; found 727.33; HRMS: Anal. Calcd. for $[M+H]^+$ $C_{42}H_{47}N_8O_4$: 727.3720; found 727.3738
53	methyl ((1R)-2-((2S)-2-(5-(4'-(2-((2S)-1-(N-acetyl-D-alanyl)-2-pyrrolidinyl)-1H-imidazol-5-yl)-4-biphenylyl)-1H-imidazol-2-yl)-1-pyrrolidinyl)-2-oxo-1-phenylethyl)carbamate		1.92 minutes (Cond. 2); >98%; LC/MS: Anal. Calcd. for $[M+H]^+$ $C_{41}H_{45}N_8O_5$: 729.35; found 729.33; HRMS: Anal. Calcd. for $[M+H]^+$ $C_{41}H_{45}N_8O_5$: 729.3513; found 729.3530
54	methyl ((1R)-2-((2S)-2-(5-(4'-(2-((2S)-1-(N-acetyl-L-alanyl)-2-pyrrolidinyl)-1H-imidazol-5-yl)-4-biphenylyl)-1H-imidazol-2-yl)-1-pyrrolidinyl)-2-oxo-1-phenylethyl)carbamate		1.87 minutes (Cond. 2); >98%; LC/MS: Anal. Calcd. for $[M+H]^+$ $C_{41}H_{45}N_8O_5$: 729.35; found 729.33
55	methyl ((1R)-2-((2S)-2-(5-(4'-(2-((2S)-1-(methoxyacetyl)-2-pyrrolidinyl)-1H-imidazol-5-yl)-4-biphenylyl)-1H-imidazol-2-yl)-1-pyrrolidinyl)-2-oxo-1-phenylethyl)carbamate		1.89 minutes (Cond. 2); >98%; LC/MS: Anal. Calcd. for $[M+H]^+$ $C_{39}H_{42}N_7O_5$: 688.32; found 688.28; HRMS: Anal. Calcd. for $[M+H]^+$ $C_{39}H_{42}N_7O_5$: 688.3247; found 688.3231

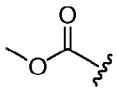
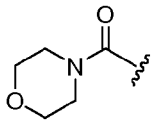
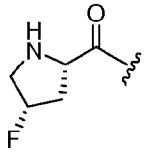
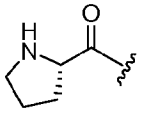
56	methyl ((1R)-2-((2S)-2-(5-(4'-(2-((2S)-1-((2R)-2-hydroxybutanoyl)-2-pyrrolidinyl)-1H-imidazol-5-yl)-4-biphenylyl)-1H-imidazol-2-yl)-1-pyrrolidinyl)-2-oxo-1-phenylethyl)carbamate		1.91 minutes (Cond. 2); >98%; LC/MS: Anal. Calcd. for $[M+H]^+$ $C_{40}H_{44}N_7O_5$: 702.34; found 702.30; HRMS: Anal. Calcd. for $[M+H]^+$ $C_{40}H_{44}N_7O_5$: 702.3404; found 702.3393
57	methyl ((1R)-2-((2S)-2-(5-(4'-(2-((2S)-1-((4-methyl-1-piperazinyl)acetyl)-2-pyrrolidinyl)-1H-imidazol-5-yl)-4-biphenylyl)-1H-imidazol-2-yl)-1-pyrrolidinyl)-2-oxo-1-phenylethyl)carbamate		1.80 minutes (Cond. 2); >98%; LC/MS: Anal. Calcd. for $[M+H]^+$ $C_{43}H_{50}N_9O_4$: 756.40; found 756.36; HRMS: Anal. Calcd. for $[M+H]^+$ $C_{43}H_{50}N_9O_4$: 756.3986; found 756.3965
58	methyl ((1R)-2-oxo-1-phenyl-2-((2S)-2-(5-(4'-(2-((2S)-1-(1-pyrrolidinylacetyl)-2-pyrrolidinyl)-1H-imidazol-5-yl)-4-biphenylyl)-1H-imidazol-2-yl)-1-pyrrolidinyl)ethyl)carbamate		1.82 minutes (Cond. 2); >98%; LC/MS: Anal. Calcd. for $[M+H]^+$ $C_{42}H_{47}N_8O_4$: 727.37; found 727.33; HRMS: Anal. Calcd. for $[M+H]^+$ $C_{42}H_{47}N_8O_4$: 727.3720; found 727.3696
59	methyl ((1R)-2-oxo-1-phenyl-2-((2S)-2-(5-(4'-(2-((2S)-1-((2S)-tetrahydro-2-furanylcarbonyl)-2-pyrrolidinyl)-1H-imidazol-5-yl)-4-biphenylyl)-1H-imidazol-2-yl)-1-pyrrolidinyl)ethyl)carbamate		1.94 minutes (Cond. 2); >98%; LC/MS: Anal. Calcd. for $[M+H]^+$ $C_{41}H_{43}N_7O_5$: 714.34; found 714.24

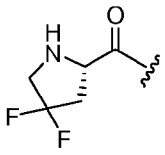
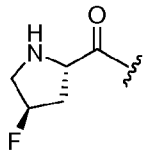
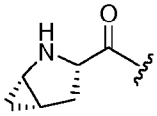
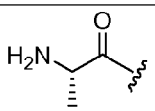
60	methyl ((1R)-2-((2S)-2-(5-(4'-(2-((2S)-1-((1-hydroxycyclopropyl)carbonyl)-2-pyrrolidinyl)-1H-imidazol-5-yl)-4-biphenylyl)-1H-imidazol-2-yl)-1-pyrrolidinyl)-2-oxo-1-phenylethyl)carbamate		1.93 minutes (Cond. 2); >98%; LC/MS: Anal. Calcd. for $[M+H]^+$ $C_{40}H_{42}N_7O_5$: 700.32; found 700.23; HRMS: Anal. Calcd. for $[M+H]^+$ $C_{40}H_{42}N_7O_5$: 700.3247; found 700.3265
61	methyl ((1R)-2-((2S)-2-(5-(4'-(2-((2S)-1-(1H-imidazol-5-ylacetyl)-2-pyrrolidinyl)-1H-imidazol-5-yl)-4-biphenylyl)-1H-imidazol-2-yl)-1-pyrrolidinyl)-2-oxo-1-phenylethyl)carbamate		1.84 minutes (Cond. 2); >98%; LC/MS: Anal. Calcd. for $[M+H]^+$ $C_{41}H_{42}N_9O_4$: 724.34; found 724.21; HRMS: Anal. Calcd. for $[M+H]^+$ $C_{41}H_{42}N_9O_4$: 724.3360; found 724.3365
62	methyl ((1R)-2-((2S)-2-(5-(4'-(2-((2S)-1-((1-methyl-1H-imidazol-4-yl)acetyl)-2-pyrrolidinyl)-1H-imidazol-5-yl)-4-biphenylyl)-1H-imidazol-2-yl)-1-pyrrolidinyl)-2-oxo-1-phenylethyl)carbamate		1.85 minutes (Cond. 2); >98%; LC/MS: Anal. Calcd. for $[M+H]^+$ $C_{42}H_{44}N_9O_4$: 738.35; found 738.22; HRMS: Anal. Calcd. for $[M+H]^+$ $C_{42}H_{44}N_9O_4$: 738.3516; found 738.3539
63	methyl ((1R)-2-((2S)-2-(5-(4'-(2-((2S)-1-(1H-imidazol-2-ylcarbonyl)-2-pyrrolidinyl)-1H-imidazol-5-yl)-4-biphenylyl)-1H-imidazol-2-yl)-1-pyrrolidinyl)-2-oxo-1-phenylethyl)carbamate		1.95 minutes (Cond. 2); >98%; LC/MS: Anal. Calcd. for $[M+H]^+$ $C_{40}H_{41}N_9O_4$: 710.32; found 710.17

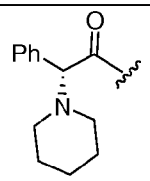
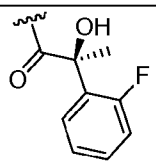
64	methyl ((1R)-2-((2S)-2-(5-(4'-(2-((2S)-1-((4-hydroxy-1-piperidinyl)(phenyl)acetyl)-2-pyrrolidinyl)-1H-imidazol-5-yl)-4-biphenylyl)-1H-imidazol-2-yl)-1-pyrrolidinyl)-2-oxo-1-phenylethyl)carbamate	 *Cap-8* A single diastereomer	1.92 minutes (Cond. 2); >98%; LC/MS: Anal. Calcd. for $[M+H]^+$ $C_{49}H_{53}N_8O_5$: 833.41; found 833.32; HRMS: Anal. Calcd. for $[M+H]^+$ $C_{49}H_{53}N_8O_5$: 833.4139; found 833.4163
65	methyl ((1R)-2-oxo-1-phenyl-2-((2S)-2-(5-(4'-(2-((2S)-1-(1H-tetrazol-5-ylacetyl)-2-pyrrolidinyl)-1H-imidazol-5-yl)-4-biphenylyl)-1H-imidazol-2-yl)-1-pyrrolidinyl)ethyl)carbamate		1.92 minutes (Cond. 2); >98%; LC/MS: Anal. Calcd. for $[M+H]^+$ $C_{39}H_{40}N_{11}O_4$: 726.33; found 726.22; HRMS: Anal. Calcd. for $[M+H]^+$ $C_{39}H_{40}N_{11}O_4$: 726.3265; found 726.3290
67	methyl ((1R)-2-oxo-1-phenyl-2-((2S)-2-(5-(4'-(2-((2S)-1-(2-pyridinylcarbonyl)-2-pyrrolidinyl)-1H-imidazol-5-yl)-4-biphenylyl)-1H-imidazol-2-yl)-1-pyrrolidinyl)ethyl)carbamate		2.03 minutes (Cond. 2); >98%; LC/MS: Anal. Calcd. for $[M+H]^+$ $C_{42}H_{41}N_8O_4$: 721.33; found 721.31; HRMS: Anal. Calcd. for $[M+H]^+$ $C_{42}H_{41}N_8O_4$: 721.3251; found 721.3247
68	methyl ((1R)-2-oxo-1-phenyl-2-((2S)-2-(5-(4'-(2-((2S)-1-(3-pyridinylcarbonyl)-2-pyrrolidinyl)-1H-imidazol-5-yl)-4-biphenylyl)-1H-imidazol-2-yl)-1-pyrrolidinyl)ethyl)carbamate		1.91 minutes (Cond. 2); >98%; LC/MS: Anal. Calcd. for $[M+H]^+$ $C_{42}H_{41}N_8O_4$: 721.33; found 721.31; HRMS: Anal. Calcd. for $[M+H]^+$ $C_{42}H_{41}N_8O_4$:

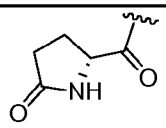
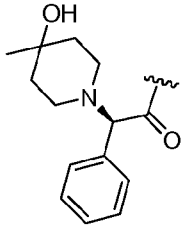
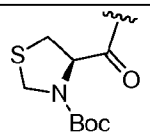
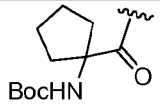
			721.3251; found 721.3226
69	methyl ((1R)-2-((2S)-2-(5-(4'-(2-((2S)-1-isonicotinoyl-2-pyrrolidinyl)-1H-imidazol-5-yl)-4-biphenylyl)-1H-imidazol-2-yl)-1-pyrrolidinyl)-2-oxo-1-phenylethyl)carbamate		1.89 minutes (Cond. 2); >98%; LC/MS: Anal. Calcd. for $[M+H]^+$ $C_{42}H_{41}N_8O_4$: 721.33; found 721.29; HRMS: Anal. Calcd. for $[M+H]^+$ $C_{42}H_{41}N_8O_4$: 721.3251; found 721.3251
70	methyl ((1R)-2-((2S)-2-(5-(4'-(2-((2S)-1-((4R)-4-fluoro-1-methyl-L-prolyl)-2-pyrrolidinyl)-1H-imidazol-5-yl)-4-biphenylyl)-1H-imidazol-2-yl)-1-pyrrolidinyl)-2-oxo-1-phenylethyl)carbamate	 *Cap*-11	1.84 minutes (Cond. 2); >98%; LC/MS: Anal. Calcd. for $[M+H]^+$ $C_{42}H_{46}FN_8O_4$: 745.36; found 745.27; HRMS: Anal. Calcd. for $[M+H]^+$ $C_{42}H_{46}FN_8O_4$: 745.3626; found 745.3658
71	methyl ((1R)-2-((2S)-2-(5-(4'-(2-((2S)-1-(1,3-oxazol-2-ylcarbonyl)-2-pyrrolidinyl)-1H-imidazol-5-yl)-4-biphenylyl)-1H-imidazol-2-yl)-1-pyrrolidinyl)-2-oxo-1-phenylethyl)carbamate		1.97 minutes (Cond. 2); >98%; LC/MS: Anal. Calcd. for $[M+H]^+$ $C_{40}H_{39}N_8O_5$: 711.30; found 711.27
72	methyl ((1R)-2-((2S)-2-(5-(4'-(2-((2S)-1-(1,3-oxazol-5-ylcarbonyl)-2-pyrrolidinyl)-1H-imidazol-5-yl)-4-biphenylyl)-1H-imidazol-2-yl)-1-pyrrolidinyl)-2-oxo-1-phenylethyl)carbamate		1.95 minutes (Cond. 2); >98%; LC/MS: Anal. Calcd. for $[M+H]^+$ $C_{40}H_{39}N_8O_5$: 711.30; found 711.27; HRMS: Anal. Calcd. for $[M+H]^+$ $C_{40}H_{39}N_8O_5$: 711.3043; found

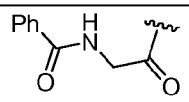
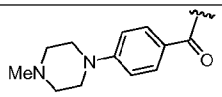
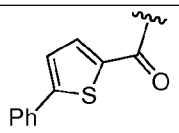
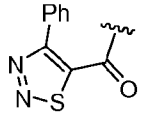
			711.3078
73	methyl ((1R)-2-((2S)-2-(5-(4'-(2-((2S)-1-((dimethylamino)(oxo)acetyl)-2-pyrrolidinyl)-1H-imidazol-5-yl)-4-biphenylyl)-1H-imidazol-2-yl)-1-pyrrolidinyl)-2-oxo-1-phenylethyl)carbamate		1.92 minutes (Cond. 2); >98%; LC/MS: Anal. Calcd. for $[M+H]^+$ $C_{40}H_{43}N_8O_5$: 715.34; found 715.40
74	methyl ((1R)-2-oxo-1-phenyl-2-((2S)-2-(5-(4'-(2-((2S)-1-(tetrahydro-3-furanylcarbonyl)-2-pyrrolidinyl)-1H-imidazol-5-yl)-4-biphenylyl)-1H-imidazol-2-yl)-1-pyrrolidinyl)ethyl)carbamate		1.91 minutes (Cond. 2); >98%; LC/MS: Anal. Calcd. for $[M+H]^+$ $C_{41}H_{44}N_7O_5$: 714.34; found 714.39; HRMS: Anal. Calcd. for $[M+H]^+$ $C_{41}H_{44}N_7O_5$: 714.3404; found 714.3433
75	methyl ((1R)-2-((2S)-2-(5-(4'-(2-((2S)-1-(N-(methoxycarbonyl)-L-alanyl)-2-pyrrolidinyl)-1H-imidazol-5-yl)-4-biphenylyl)-1H-imidazol-2-yl)-1-pyrrolidinyl)-2-oxo-1-phenylethyl)carbamate	 *Cap*-12	1.94 minutes (Cond. 2); >98%; LC/MS: Anal. Calcd. for $[M+H]^+$ $C_{41}H_{45}N_8O_6$: 745.35 found 745.34; HRMS: Anal. Calcd. for $[M+H]^+$ $C_{41}H_{45}N_8O_6$: 745.3462; found 745.3486
76	methyl ((1R)-2-((2S)-2-(5-(4'-(2-((2S)-1-(N,N-dimethyl-L-alanyl)-2-pyrrolidinyl)-1H-imidazol-5-yl)-4-biphenylyl)-1H-imidazol-2-yl)-1-pyrrolidinyl)-2-oxo-1-phenylethyl)carbamate		1.80 minutes (Cond. 2); >98%; LC/MS: Anal. Calcd. for $[M+H]^+$ $C_{41}H_{47}N_8O_4$ 715.37; found 715.35 ; HRMS: Anal. Calcd. for $[M+H]^+$ $C_{41}H_{47}N_8O_4$ 715.3720; found 715.3737

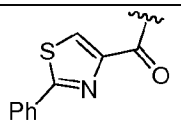
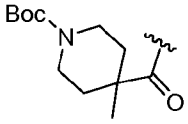
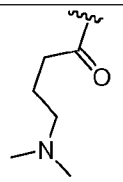
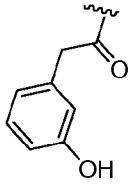
77	methyl (2S)-2-(5-(4'-(2-((2S)-1-((2R)-2-((methoxycarbonyl)amino)-2-phenylacetyl)-2-pyrrolidinyl)-1H-imidazol-5-yl)-4-biphenylyl)-1H-imidazol-2-yl)-1-pyrrolidinecarboxylate		1.97 minutes (Cond. 2); >98%; LC/MS: Anal. Calcd. for $[M+H]^+$ $C_{38}H_{40}N_7O_5$: 674.31; found 674.66; HRMS: Anal. Calcd. for $[M+H]^+$ $C_{38}H_{40}N_7O_5$: 674.3091; found 674.3110
78	methyl ((1R)-2-((2S)-2-(5-(4'-(2-((2S)-1-(4-morpholinylcarbonyl)-2-pyrrolidinyl)-1H-imidazol-5-yl)-4-biphenylyl)-1H-imidazol-2-yl)-1-pyrrolidinyl)-2-oxo-1-phenylethyl)carbamate		1.95 minutes (Cond. 2); >98%; LC/MS: Anal. Calcd. for $[M+H]^+$ $C_{41}H_{45}N_8O_5$: 729.35; found 729.40; HRMS: Anal. Calcd. for $[M+H]^+$ $C_{41}H_{45}N_8O_5$: 729.3513; found 729.3502
79	methyl ((1R)-2-((2S)-2-(5-(4'-(2-((2S)-1-((4S)-4-fluoro-L-prolyl)-2-pyrrolidinyl)-1H-imidazol-5-yl)-4-biphenylyl)-1H-imidazol-2-yl)-1-pyrrolidinyl)-2-oxo-1-phenylethyl)carbamate		1.80 minutes (Cond. 2); >98%; LC/MS: Anal. Calcd. for $[M+H]^+$ $C_{41}H_{44}FN_8O_4$: 731.84; found 731.26
80	methyl ((1R)-2-oxo-1-phenyl-2-((2S)-2-(5-(4'-(2-((2S)-1-L-prolyl-2-pyrrolidinyl)-1H-imidazol-5-yl)-4-biphenylyl)-1H-imidazol-2-yl)-1-pyrrolidinyl)ethyl)carbamate		1.84 minutes (Cond. 2); >98%; LC/MS: Anal. Calcd. for $[M+H]^+$ $C_{41}H_{45}N_8O_4$: 713.36; found 713.36; HRMS: Anal. Calcd. for $[M+H]^+$ $C_{41}H_{45}N_8O_4$: 713.3564; found 713.3563

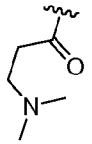
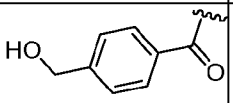
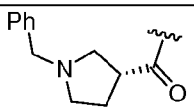
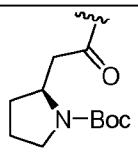
81	methyl ((1R)-2-((2S)-2-(5-(4'-(2-((2S)-1-(4,4-difluoro-L-prolyl)-2-pyrrolidinyl)-1H-imidazol-5-yl)-4-biphenylyl)-1H-imidazol-2-yl)-1-pyrrolidinyl)-2-oxo-1-phenylethyl)carbamate		1.88 minutes (Cond. 2); >98%; LC/MS: Anal. Calcd. for $[M+H]^+$ $C_{41}H_{43}F_2N_8O_4$: 749.34; found 749.31; HRMS: Anal. Calcd. for $[M+H]^+$ $C_{41}H_{43}F_2N_8O_4$: 749.3375; found 749.3390
82	methyl ((1R)-2-((2S)-2-(5-(4'-(2-((2S)-1-((4R)-4-fluoro-L-prolyl)-2-pyrrolidinyl)-1H-imidazol-5-yl)-4-biphenylyl)-1H-imidazol-2-yl)-1-pyrrolidinyl)-2-oxo-1-phenylethyl)carbamate		1.83 minutes (Cond. 2); >98%; LC/MS: Anal. Calcd. for $[M+H]^+$ $C_{41}H_{44}FN_8O_4$: 731.35; found 731.37; HRMS: Anal. Calcd. for $[M+H]^+$ $C_{41}H_{44}FN_8O_4$: 731.3470; found 731.3502
83	methyl ((1R)-2-((2S)-2-(5-(4'-(2-((2S)-1-((1S,3S,5S)-2-azabicyclo[3.1.0]hex-3-ylcarbonyl)-2-pyrrolidinyl)-1H-imidazol-5-yl)-4-biphenylyl)-1H-imidazol-2-yl)-1-pyrrolidinyl)-2-oxo-1-phenylethyl)carbamate		1.82 minutes (Cond. 2); >98%; LC/MS: Anal. Calcd. for $[M+H]^+$ $C_{42}H_{45}N_8O_4$: 725.36; found 725.39; HRMS: Anal. Calcd. for $[M+H]^+$ $C_{42}H_{45}N_8O_4$: 725.3564; found 725.3574
84	methyl ((1R)-2-((2S)-2-(5-(4'-(2-((2S)-1-L-alanyl-2-pyrrolidinyl)-1H-imidazol-5-yl)-4-biphenylyl)-1H-imidazol-2-yl)-1-pyrrolidinyl)-2-oxo-1-phenylethyl)carbamate		1.82 minutes (Cond. 2); >98%; LC/MS: Anal. Calcd. for $[M+H]^+$ $C_{39}H_{43}N_8O_4$: 687.34; found 687.32; HRMS: Anal. Calcd. for $[M+H]^+$ $C_{39}H_{43}N_8O_4$: 687.3407; found

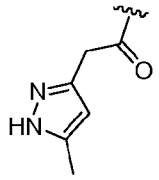
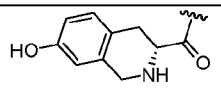
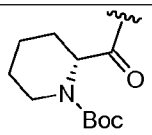
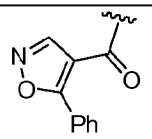
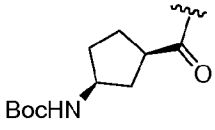
			687.3435
84-1	methyl ((1R)-2-oxo-1-phenyl-2-((2S)-2-(5-(4'-(2-((2S)-1-((2R)-2-phenyl-2-(1-piperidinyl)acetyl)-2-pyrrolidinyl)-1H-imidazol-5-yl)-4-biphenylyl)-1H-imidazol-2-yl)-1-pyrrolidinyl)ethyl)carbamate	 *Cap-14*	^{1}HNMR (400 MHz, CD_3OD) δ 7.90-7.85 (m, 9H), 7.81-7.79 (m, 1H), 7.63-7.57 (m, 5H), 7.45-7.32 (m, 6H), 5.51 (s, 1H), 5.45 (s, 1H), 5.33-5.29 (m, 2H), 4.06-4.01 (m, 2H), 3.63 (d, J = 4.04 Hz, 3H), 3.59-3.50 (m, 2H), 3.19-3.12 (m, 1H), 3.07-3.01 (m, 1H), 2.93-2.76 (m, 2H), 2.57-2.51 (m, 1H), 2.40-2.31 (m, 2H), 2.22-2.06 (m, 4H), 2.00-1.90 (m, 3H), 1.84-1.64 (m, 4H), 1.52-1.43 (m, 2H); LCMS: Anal. Calcd. for $C_{49}H_{52}N_8O_4$: 816; found: 817 $(M+H)^+$.
84-2	methyl ((1R)-2-((2S)-2-(5-(4'-(2-((2S)-1-((2S)-2-(2-fluorophenyl)-2-hydroxypropanoyl)-2-pyrrolidinyl)-1H-imidazol-5-yl)-4-biphenylyl)-1H-imidazol-2-yl)-1-pyrrolidinyl)-2-oxo-1-phenylethyl)carbamate		^{1}HNMR (400 MHz, CD_3OD) δ 7.89-7.85 (m, 8H), 7.81-7.73 (2H), 7.67-7.65 (m, 1H), 7.45-7.26 (m, 7H), 7.13-7.08 (m, 1H), 6.94-6.89 (m, 0.5H), 6.72-6.67 (0.5H), 6.09-6.07 (m, 0.4H), 5.51 (s, 1H), 5.32-5.25 (m, 1.6H), 4.08-3.95 (m, 2H), 3.85-3.79 (1H), 3.64-3.63 (m, 3H), 3.56-3.49 (1H), 3.09-3.03 (m, 1H), 2.59-2.50 (m, 1H),

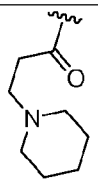
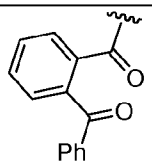
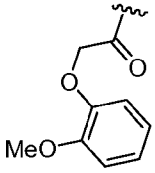
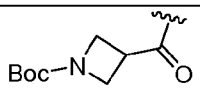
			2.42-2.33 (m, 2H), 2.21-2.00 (m, 6H), 1.82-1.74 (m, 1H), 1.66 (d, J = 4.55 Hz, 3H); LCMS: Anal. Calcd. for $C_{45}H_{46}FN_7O_3$: 781; found: 782 $(M+H)^+$.
84-3	methyl ((1R)-2-oxo-2-((2S)-2-(5-(4'-(2-((2S)-1-(5-oxo-D-prolyl)-2-pyrrolidinyl)-1H-imidazol-5-yl)-4-biphenylyl)-1H-imidazol-2-yl)-1-pyrrolidinyl)-1-phenylethyl)carbamate		LCMS: Anal. Calcd. for $C_{41}H_{42}N_8O_5$: 726; found: 727 $(M+H)^+$.
84-4	methyl ((1R)-2-((2S)-2-(5-(4'-(2-((2S)-1-((2R)-2-(4-hydroxy-4-methyl-1-piperidinyl)-2-phenylacetyl)-2-pyrrolidinyl)-1H-imidazol-5-yl)-4-biphenylyl)-1H-imidazol-2-yl)-1-pyrrolidinyl)-2-oxo-1-phenylethyl)carbamate	 *Cap*-15	LCMS: Anal. Calcd. for $C_{50}H_{54}N_8O_5$: 846; found: 847 $(M+H)^+$.
84-5	tert-butyl (4R)-4-(((2S)-2-(5-(4'-(2-((2S)-1-((2R)-2-((methoxycarbonyl)amino)-2-phenylacetyl)-2-pyrrolidinyl)-1H-imidazol-5-yl)-4-biphenylyl)-1H-imidazol-2-yl)-1-pyrrolidinyl)carbonyl)-1,3-thiazolidine-3-carboxylate		LCMS: Anal. Calcd. for $C_{45}H_{50}N_8O_6S$: 830; found: 831 $(M+H)^+$.
84-6	methyl ((1R)-2-((2S)-2-(5-(4'-(2-((2S)-1-((1-((tert-butoxycarbonyl)amino)cyclopentyl)carbonyl)-2-		LCMS: Anal. Calcd. for $C_{47}H_{54}FN_8O_6$: 826; found: 827 $(M+H)^+$.

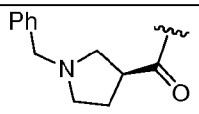
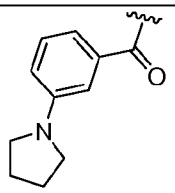
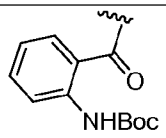
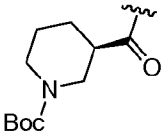
	pyrrolidinyl)-1H-imidazol-5-yl)-4-biphenylyl)-1H-imidazol-2-yl)-1-pyrrolidinyl)-2-oxo-1-phenylethyl)carbamate		
84-7	methyl ((1R)-2-((2S)-2-(5-(4'-(2-((2S)-1-(N-benzoylglycyl)-2-pyrrolidinyl)-1H-imidazol-5-yl)-4-biphenylyl)-1H-imidazol-2-yl)-1-pyrrolidinyl)-2-oxo-1-phenylethyl)carbamate		LCMS: Anal. Calcd. for $C_{45}H_{44}FN_8O_5$: 776; found: 777 $(M+H)^+$.
84-8	methyl ((1R)-2-((2S)-2-(5-(4'-(2-((2S)-1-(4-(4-methyl-1-piperazinyl)benzoyl)-2-pyrrolidinyl)-1H-imidazol-5-yl)-4-biphenylyl)-1H-imidazol-2-yl)-1-pyrrolidinyl)-2-oxo-1-phenylethyl)carbamate		LCMS: Anal. Calcd. for $C_{48}H_{51}N_9O_4$: 817; found: 818 $(M+H)^+$.
84-9	methyl ((1R)-2-oxo-1-phenyl-2-((2S)-2-(5-(4'-(2-((2S)-1-((5-phenyl-2-thienyl)carbonyl)-2-pyrrolidinyl)-1H-imidazol-5-yl)-4-biphenylyl)-1H-imidazol-2-yl)-1-pyrrolidinyl)ethyl)carbamate		LCMS: Anal. Calcd. for $C_{47}H_{43}N_7O_4S$: 801; found: 802 $(M+H)^+$.
84-10	methyl ((1R)-2-oxo-1-phenyl-2-((2S)-2-(5-(4'-(2-((2S)-1-((4-phenyl-1,2,3-thiadiazol-5-yl)carbonyl)-2-pyrrolidinyl)-1H-imidazol-5-yl)-4-biphenylyl)-1H-imidazol-2-yl)-1-pyrrolidinyl)ethyl)carbamate		LCMS: Anal. Calcd. for $C_{45}H_{41}N_9O_4S$: 803; found: 804 $(M+H)^+$.

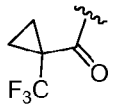
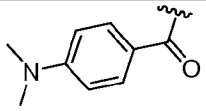
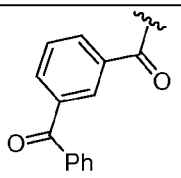
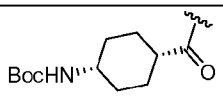
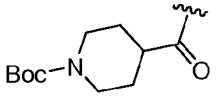
84-11	methyl ((1R)-2-oxo-1-phenyl-2-((2S)-2-(5-(4'-(2-((2S)-1-((2-phenyl-1,3-thiazol-4-yl)carbonyl)-2-pyrrolidinyl)-1H-imidazol-5-yl)-4-biphenylyl)-1H-imidazol-2-yl)-1-pyrrolidinyl)ethyl)carbamate		LCMS: Anal. Calcd. for $C_{46}H_{42}N_8O_4S$: 802; found: 803 $(M+H)^+$.
84-12	tert-butyl 4-(((2S)-2-(5-(4'-(2-((2S)-1-((2R)-2-((methoxycarbonyl)amino)-2-phenylacetyl)-2-pyrrolidinyl)-1H-imidazol-5-yl)-4-biphenylyl)-1H-imidazol-2-yl)-1-pyrrolidinyl)carbonyl)-4-methyl-1-piperidinecarboxylate		LCMS: Anal. Calcd. for $C_{48}H_{56}N_8O_6$: 840; found: 841 $(M+H)^+$.
84-13	methyl ((1R)-2-((2S)-2-(5-(4'-(2-((2S)-1-(4-(dimethylamino)butanoyl)-2-pyrrolidinyl)-1H-imidazol-5-yl)-4-biphenylyl)-1H-imidazol-2-yl)-1-pyrrolidinyl)-2-oxo-1-phenylethyl)carbamate		LCMS: Anal. Calcd. for $C_{42}H_{48}N_8O_4$: 728; found: 729 $(M+H)^+$.
84-14	methyl ((1R)-2-((2S)-2-(5-(4'-(2-((2S)-1-((3-hydroxyphenyl)acetyl)-2-pyrrolidinyl)-1H-imidazol-5-yl)-4-biphenylyl)-1H-imidazol-2-yl)-1-pyrrolidinyl)-2-oxo-1-phenylethyl)carbamate		LCMS: Anal. Calcd. for $C_{44}H_{43}N_7O_5$: 749; found: 750 $(M+H)^+$.

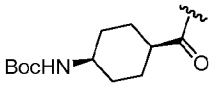
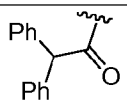
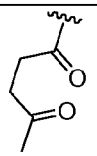
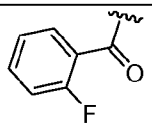
84-15	methyl ((1R)-2-((2S)-2-(5-(4'-(2-((2S)-1-(N,N-dimethyl-beta-alanyl)-2-pyrrolidinyl)-1H-imidazol-5-yl)-4-biphenylyl)-1H-imidazol-2-yl)-1-pyrrolidinyl)-2-oxo-1-phenylethyl)carbamate		LCMS: Anal. Calcd. for $C_{41}H_{46}N_8O_4$: 714; found: 715 $(M+H)^+$.
84-16	methyl ((1R)-2-((2S)-2-(5-(4'-(2-((2S)-1-(4-(hydroxymethyl)benzoyl)-2-pyrrolidinyl)-1H-imidazol-5-yl)-4-biphenylyl)-1H-imidazol-2-yl)-1-pyrrolidinyl)-2-oxo-1-phenylethyl)carbamate		LCMS: Anal. Calcd. for $C_{44}H_{43}N_7O_5$: 749; found: 750 $(M+H)^+$.
84-17	methyl ((1R)-2-((2S)-2-(5-(4'-(2-((2S)-1-(((3R)-1-benzyl-3-pyrrolidinyl)carbonyl)-2-pyrrolidinyl)-1H-imidazol-5-yl)-4-biphenylyl)-1H-imidazol-2-yl)-1-pyrrolidinyl)-2-oxo-1-phenylethyl)carbamate		LCMS: Anal. Calcd. for $C_{48}H_{50}N_8O_4$: 802; found: 803 $(M+H)^+$.
84-18	tert-butyl (2S)-2-(2-((2S)-2-(5-(4'-(2-((2S)-1-((2R)-2-((methoxycarbonyl)amino)-2-phenylacetyl)-2-pyrrolidinyl)-1H-imidazol-5-yl)-4-biphenylyl)-1H-imidazol-2-yl)-1-pyrrolidinyl)-2-oxoethyl)-1-pyrrolidinecarboxylate		LCMS: Anal. Calcd. for $C_{47}H_{54}N_8O_6$: 826; found: 827 $(M+H)^+$.

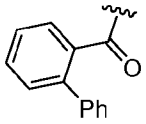
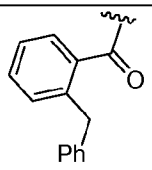
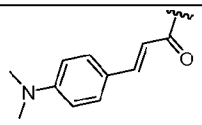
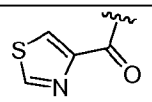
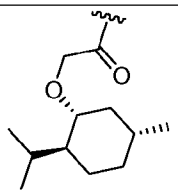
84-19	methyl ((1R)-2-((2S)-2-(5-(4'-(2-((2S)-1-((5-methyl-1H-pyrazol-3-yl)acetyl)-2-pyrrolidinyl)-1H-imidazol-5-yl)-4-biphenylyl)-1H-imidazol-2-yl)-1-pyrrolidinyl)-2-oxo-1-phenylethyl)carbamate		LCMS: Anal. Calcd. for $C_{42}H_{43}N_9O_4$: 737; found: 738 $(M+H)^+$.
84-20	methyl ((1R)-2-((2S)-2-(5-(4'-(2-((2S)-1-(((3S)-7-hydroxy-1,2,3,4-tetrahydro-3-isoquinolinyl)carbonyl)-2-pyrrolidinyl)-1H-imidazol-5-yl)-4-biphenylyl)-1H-imidazol-2-yl)-1-pyrrolidinyl)-2-oxo-1-phenylethyl)carbamate		LCMS: Anal. Calcd. for $C_{46}H_{46}N_8O_5$: 790; found: 791 $(M+H)^+$.
84-21	tert-butyl (2R)-2-(((2S)-2-(5-(4'-(2-((2S)-1-((2R)-2-((methoxycarbonyl)amino)-2-phenylacetyl)-2-pyrrolidinyl)-1H-imidazol-5-yl)-4-biphenylyl)-1H-imidazol-2-yl)-1-pyrrolidinyl)carbonyl)-1-piperidinecarboxylate		LCMS: Anal. Calcd. for $C_{47}H_{54}N_8O_6$: 826; found: 827 $(M+H)^+$.
84-22	methyl ((1R)-2-oxo-1-phenyl-2-((2S)-2-(5-(4'-(2-((2S)-1-((5-phenyl-4-isoxazolyl)carbonyl)-2-pyrrolidinyl)-1H-imidazol-5-yl)-4-biphenylyl)-1H-imidazol-2-yl)-1-pyrrolidinyl)ethyl)carbamate		LCMS: Anal. Calcd. for $C_{46}H_{42}N_8O_5$: 786; found: 787 $(M+H)^+$.
84-23	methyl ((1R)-2-((2S)-2-(5-(4'-(2-((2S)-1-(((1R,3S)-3-((tert-butoxycarbonyl)amino)cyclop		LCMS: Anal. Calcd. for $C_{47}H_{54}N_8O_6$: 826; found: 827 $(M+H)^+$.

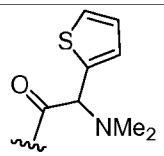
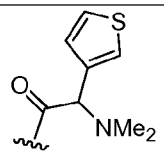
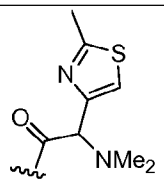
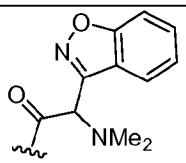
	entyl)carbonyl)-2-pyrrolidinyl)-1H-imidazol-5-yl)-4-biphenylyl)-1H-imidazol-2-yl)-1-pyrrolidinyl)-2-oxo-1-phenylethyl)carbamate		
84-24	methyl ((1R)-2-oxo-1-phenyl-2-((2S)-2-(5-(4'-(2-((2S)-1-(3-(1-piperidinyl)propanoyl)-2-pyrrolidinyl)-1H-imidazol-5-yl)-4-biphenylyl)-1H-imidazol-2-yl)-1-pyrrolidinyl)ethyl)carbamate		LCMS: Anal. Calcd. for $C_{44}H_{50}N_8O_4$: 754; found: 755 $(M+H)^+$.
84-25	methyl ((1R)-2-((2S)-2-(5-(4'-(2-((2S)-1-(2-benzoylbenzoyl)-2-pyrrolidinyl)-1H-imidazol-5-yl)-4-biphenylyl)-1H-imidazol-2-yl)-1-pyrrolidinyl)-2-oxo-1-phenylethyl)carbamate		LCMS: Anal. Calcd. for $C_{50}H_{45}N_7O_5$: 823; found: 824 $(M+H)^+$.
84-26	methyl ((1R)-2-((2S)-2-(5-(4'-(2-((2S)-1-((2-methoxyphenoxy)acetyl)-2-pyrrolidinyl)-1H-imidazol-5-yl)-4-biphenylyl)-1H-imidazol-2-yl)-1-pyrrolidinyl)-2-oxo-1-phenylethyl)carbamate		LCMS: Anal. Calcd. for $C_{45}H_{45}N_7O_6$: 779; found: 780 $(M+H)^+$.
84-27	tert-butyl 3-(((2S)-2-(5-(4'-(2-((2S)-1-((2R)-2-((methoxycarbonyl)amino)-2-phenylacetyl)-2-pyrrolidinyl)-1H-imidazol-5-yl)-4-biphenylyl)-1H-imidazol-2-		LCMS: Anal. Calcd. for $C_{45}H_{50}N_8O_6$: 798; found: 799 $(M+H)^+$.

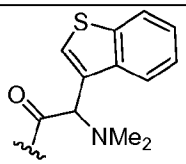
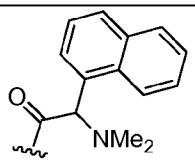
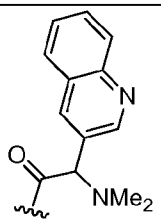
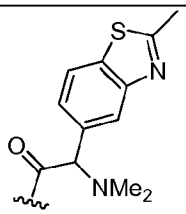
	yl)-1-pyrrolidinyl)carbonyl)-1-azetidinecarboxylate		
84-28	methyl ((1R)-2-((2S)-2-(5-(4'-(2-((2S)-1-(((3S)-1-benzyl-3-pyrrolidinyl)carbonyl)-2-pyrrolidinyl)-1H-imidazol-5-yl)-4-biphenylyl)-1H-imidazol-2-yl)-1-pyrrolidinyl)-2-oxo-1-phenylethyl)carbamate		LCMS: Anal. Calcd. for $C_{48}H_{50}N_8O_4$: 802; found: 803 $(M+H)^+$.
84-29	methyl ((1R)-2-oxo-1-phenyl-2-((2S)-2-(5-(4'-(2-((2S)-1-(3-(1-pyrrolidinyl)benzoyl)-2-pyrrolidinyl)-1H-imidazol-5-yl)-4-biphenylyl)-1H-imidazol-2-yl)-1-pyrrolidinyl)ethyl)carbamate		LCMS: Anal. Calcd. for $C_{47}H_{48}N_8O_4$: 788; found: 789 $(M+H)^+$.
84-30	methyl ((1R)-2-((2S)-2-(5-(4'-(2-((2S)-1-(2-((tert-butoxycarbonyl)amino)benzoyl)-2-pyrrolidinyl)-1H-imidazol-5-yl)-4-biphenylyl)-1H-imidazol-2-yl)-1-pyrrolidinyl)-2-oxo-1-phenylethyl)carbamate		LCMS: Anal. Calcd. for $C_{48}H_{50}N_8O_6$: 834; found: 835 $(M+H)^+$.
84-31	tert-butyl (3R)-3-(((2S)-2-(5-(4'-(2-((2S)-1-((2R)-2-((methoxycarbonyl)amino)-2-phenylacetyl)-2-pyrrolidinyl)-1H-imidazol-5-yl)-4-biphenylyl)-1H-imidazol-2-yl)-1-pyrrolidinyl)carbonyl)-1-piperidinecarboxylate		LCMS: Anal. Calcd. for $C_{47}H_{54}N_8O_6$: 826; found: 827 $(M+H)^+$.

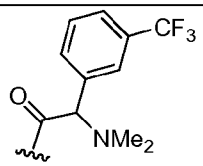
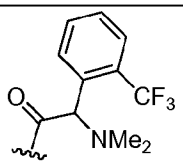
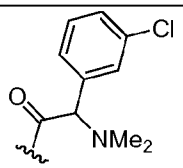
84-32	methyl ((1R)-2-oxo-1-phenyl-2-((2S)-2-(5-(4'-(2-((2S)-1-((1-(trifluoromethyl)cyclopropyl)carbonyl)-2-pyrrolidinyl)-1H-imidazol-5-yl)-4-biphenylyl)-1H-imidazol-2-yl)-1-pyrrolidinyl)ethyl)carbamate		LCMS: Anal. Calcd. for $C_{41}H_{40}F_3N_7O_4$: 751; found: 752 $(M+H)^+$.
84-33	methyl ((1R)-2-((2S)-2-(5-(4'-(2-((2S)-1-(4-(dimethylamino)benzoyl)-2-pyrrolidinyl)-1H-imidazol-5-yl)-4-biphenylyl)-1H-imidazol-2-yl)-1-pyrrolidinyl)-2-oxo-1-phenylethyl)carbamate		LCMS: Anal. Calcd. for $C_{45}H_{46}N_8O_4$: 762; found: 763 $(M+H)^+$.
84-34	methyl ((1R)-2-((2S)-2-(5-(4'-(2-((2S)-1-(3-benzoylbenzoyl)-2-pyrrolidinyl)-1H-imidazol-5-yl)-4-biphenylyl)-1H-imidazol-2-yl)-1-pyrrolidinyl)-2-oxo-1-phenylethyl)carbamate		LCMS: Anal. Calcd. for $C_{50}H_{45}N_7O_5$: 823; found: 824 $(M+H)^+$.
84-35	methyl ((1R)-2-((2S)-2-(5-(4'-(2-((2S)-1-((cis-4-((tert-butoxycarbonyl)amino)cyclohexyl)carbonyl)-2-pyrrolidinyl)-1H-imidazol-5-yl)-4-biphenylyl)-1H-imidazol-2-yl)-1-pyrrolidinyl)-2-oxo-1-phenylethyl)carbamate		LCMS: Anal. Calcd. for $C_{48}H_{56}N_8O_6$: 840; found: 841 $(M+H)^+$.
84-36	tert-butyl 4-(((2S)-2-(5-(4'-(2-((2S)-1-((2R)-2-((methoxycarbonyl)amino)-2-phenylacetyl)-2-pyrrolidinyl)-		LCMS: Anal. Calcd. for $C_{47}H_{54}N_8O_6$: 826; found: 827 $(M+H)^+$.

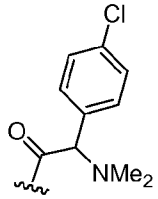
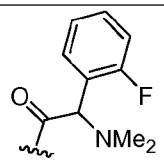
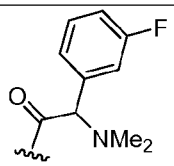
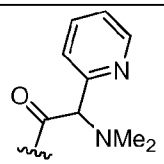
	1H-imidazol-5-yl)-4-biphenylyl)-1H-imidazol-2-yl)-1-pyrrolidinyl)carbonyl)-1-piperidinecarboxylate		
84-37	methyl ((1R)-2-((2S)-2-(5-(4'-(2-((2S)-1-((cis-4-((tert-butoxycarbonyl)amino)cyclohexyl)carbonyl)-2-pyrrolidinyl)-1H-imidazol-5-yl)-4-biphenylyl)-1H-imidazol-2-yl)-1-pyrrolidinyl)-2-oxo-1-phenylethyl)carbamate		LCMS: Anal. Calcd. for $C_{48}H_{56}N_8O_6$: 840; found: 841 $(M+H)^+$.
84-38	methyl ((1R)-2-((2S)-2-(5-(4'-(2-((2S)-1-(diphenylacetyl)-2-pyrrolidinyl)-1H-imidazol-5-yl)-4-biphenylyl)-1H-imidazol-2-yl)-1-pyrrolidinyl)-2-oxo-1-phenylethyl)carbamate		LCMS: Anal. Calcd. for $C_{50}H_{47}N_7O_4$: 809; found: 810 $(M+H)^+$.
84-39	methyl ((1R)-2-oxo-2-((2S)-2-(5-(4'-(2-((2S)-1-(4-oxopentanoyl)-2-pyrrolidinyl)-1H-imidazol-5-yl)-4-biphenylyl)-1H-imidazol-2-yl)-1-pyrrolidinyl)-1-phenylethyl)carbamate		LCMS: Anal. Calcd. for $C_{41}H_{43}N_7O_5$: 713; found: 714 $(M+H)^+$.
84-40	methyl ((1R)-2-((2S)-2-(5-(4'-(2-((2S)-1-(2-fluorobenzoyl)-2-pyrrolidinyl)-1H-imidazol-5-yl)-4-biphenylyl)-1H-imidazol-2-yl)-1-pyrrolidinyl)-2-oxo-1-phenylethyl)carbamate		LCMS: Anal. Calcd. for $C_{43}H_{40}FN_7O_4$: 737; found: 738 $(M+H)^+$.

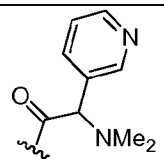
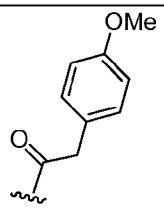
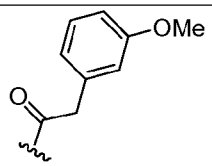
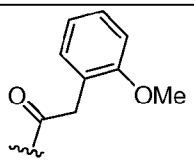
84-41	methyl ((1R)-2-((2S)-2-(5-(4'-(2-((2S)-1-(2-biphenylylcarbonyl)-2-pyrrolidinyl)-1H-imidazol-5-yl)-4-biphenylyl)-1H-imidazol-2-yl)-1-pyrrolidinyl)-2-oxo-1-phenylethyl)carbamate		LCMS: Anal. Calcd. for $C_{49}H_{45}N_7O_4$: 795; found: 796 $(M+H)^+$.
84-42	methyl ((1R)-2-((2S)-2-(5-(4'-(2-((2S)-1-(2-benzylbenzoyl)-2-pyrrolidinyl)-1H-imidazol-5-yl)-4-biphenylyl)-1H-imidazol-2-yl)-1-pyrrolidinyl)-2-oxo-1-phenylethyl)carbamate		LCMS: Anal. Calcd. for $C_{50}H_{47}N_7O_4$: 809; found: 810 $(M+H)^+$.
84-43	methyl ((1R)-2-((2S)-2-(5-(4'-(2-((2S)-1-((2E)-3-(4-(dimethylamino)phenyl)-2-propenoyl)-2-pyrrolidinyl)-1H-imidazol-5-yl)-4-biphenylyl)-1H-imidazol-2-yl)-1-pyrrolidinyl)-2-oxo-1-phenylethyl)carbamate		LCMS: Anal. Calcd. for $C_{47}H_{48}N_8O_4$: 788; found: 789 $(M+H)^+$.
84-44	methyl ((1R)-2-oxo-1-phenyl-2-((2S)-2-(5-(4'-(2-((2S)-1-(1,3-thiazol-4-ylcarbonyl)-2-pyrrolidinyl)-1H-imidazol-5-yl)-4-biphenylyl)-1H-imidazol-2-yl)-1-pyrrolidinyl)ethyl)carbamate		LCMS: Anal. Calcd. for $C_{40}H_{38}N_8O_4S$: 726; found: 727 $(M+H)^+$.
84-45	methyl ((1R)-2-((2S)-2-(5-(4'-(2-((2S)-1-((((1R,2S,5R)-2-isopropyl-5-methylcyclohexyl)oxy)acetyl)-2-pyrrolidinyl)-1H-imidazol-5-		LCMS: Anal. Calcd. for $C_{48}H_{57}N_7O_5$: 811; found: 812 $(M+H)^+$.

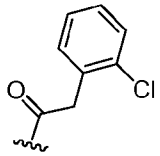
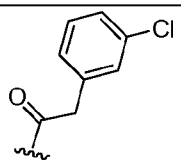
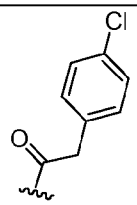
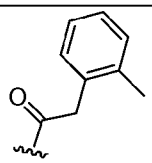
	yl)-4-biphenylyl)-1H-imidazol-2-yl)-1-pyrrolidinyl)-2-oxo-1-phenylethyl)carbamate		
84-46	methyl ((1R)-2-((2S)-2-(5-(4'-(2-((2S)-1-((dimethylamino)(2-thienyl)acetyl)-2-pyrrolidinyl)-1H-imidazol-5-yl)-4-biphenylyl)-1H-imidazol-2-yl)-1-pyrrolidinyl)-2-oxo-1-phenylethyl)carbamate	 *Cap*-32	LCMS: Anal. Calcd. for $C_{44}H_{46}N_8O_4S$: 782; found: 782 $(M+H)^+$.
84-47	methyl ((1R)-2-((2S)-2-(5-(4'-(2-((2S)-1-((dimethylamino)(3-thienyl)acetyl)-2-pyrrolidinyl)-1H-imidazol-5-yl)-4-biphenylyl)-1H-imidazol-2-yl)-1-pyrrolidinyl)-2-oxo-1-phenylethyl)carbamate	 *Cap*-33	LCMS: Anal. Calcd. for $C_{44}H_{46}N_8O_4S$: 782; found: 782 $(M+H)^+$.
84-48	methyl ((1R)-2-((2S)-2-(5-(4'-(2-((2S)-1-((dimethylamino)(2-methyl-1,3-thiazol-4-yl)acetyl)-2-pyrrolidinyl)-1H-imidazol-5-yl)-4-biphenylyl)-1H-imidazol-2-yl)-1-pyrrolidinyl)-2-oxo-1-phenylethyl)carbamate	 *Cap*-31	LCMS: Anal. Calcd. for $C_{44}H_{47}N_9O_4S$: 797; found: 798 $(M+H)^+$.
84-49	methyl ((1R)-2-((2S)-2-(5-(4'-(2-((2S)-1-(1,2-benzisoxazol-3-yl(dimethylamino)acetyl)-2-pyrrolidinyl)-1H-imidazol-5-yl)-4-biphenylyl)-1H-imidazol-2-yl)-1-pyrrolidinyl)-	 *Cap*-34	LCMS: Anal. Calcd. for $C_{47}H_{47}N_9O_5$: 817; found: 818 $(M+H)^+$.

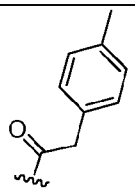
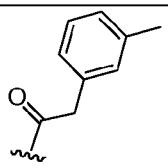
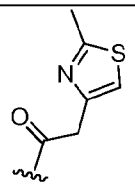
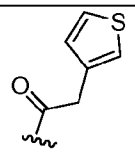
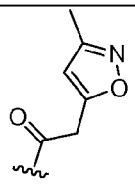
	2-oxo-1-phenylethyl)carbamate		
84-50	methyl ((1R)-2-((2S)-2-(5-(4'-(2-((2S)-1-(1-benzothiophen-3-yl(dimethylamino)acetyl)-2-pyrrolidinyl)-1H-imidazol-5-yl)-4-biphenylyl)-1H-imidazol-2-yl)-1-pyrrolidinyl)-2-oxo-1-phenylethyl)carbamate	 *Cap*-35	LCMS: Anal. Calcd. for $C_{48}H_{48}N_8O_4S$: 832; found: 833 $(M+H)^+$.
84-51	methyl ((1R)-2-((2S)-2-(5-(4'-(2-((2S)-1-((dimethylamino)(1-naphthyl)acetyl)-2-pyrrolidinyl)-1H-imidazol-5-yl)-4-biphenylyl)-1H-imidazol-2-yl)-1-pyrrolidinyl)-2-oxo-1-phenylethyl)carbamate	 *Cap*-23	LCMS: Anal. Calcd. for $C_{50}H_{50}N_8O_4$: 826; found: 827 $(M+H)^+$.
84-52	methyl ((1R)-2-((2S)-2-(5-(4'-(2-((2S)-1-((dimethylamino)(3-quinolinyl)acetyl)-2-pyrrolidinyl)-1H-imidazol-5-yl)-4-biphenylyl)-1H-imidazol-2-yl)-1-pyrrolidinyl)-2-oxo-1-phenylethyl)carbamate	 *Cap*-37	LCMS: Anal. Calcd. for $C_{49}H_{49}N_9O_4$: 827; found: 828 $(M+H)^+$.
84-53	methyl ((1R)-2-((2S)-2-(5-(4'-(2-((2S)-1-((dimethylamino)(2-methyl-1,3-benzothiazol-5-yl)acetyl)-2-pyrrolidinyl)-1H-imidazol-5-yl)-4-biphenylyl)-1H-imidazol-2-yl)-1-pyrrolidinyl)-	 *Cap*-36	LCMS: Anal. Calcd. for $C_{48}H_{49}N_9O_4S$: 847; found: 848 $(M+H)^+$.

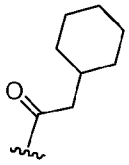
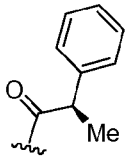
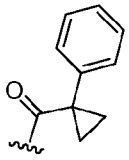
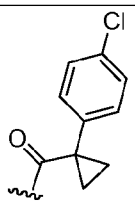
	2-oxo-1-phenylethyl)carbamate		
84-54	methyl ((1R)-2-((2S)-2-(5-(4'-(2-((2S)-1-((dimethylamino)(3-(trifluoromethyl)phenyl)acetyl)-2-pyrrolidinyl)-1H-imidazol-5-yl)-4-biphenylyl)-1H-imidazol-2-yl)-1-pyrrolidinyl)-2-oxo-1-phenylethyl)carbamate	 *Cap*-24	LCMS: Anal. Calcd. for $C_{47}H_{47}F_3N_8O_4$: 844; found: 845 $(M+H)^+$.
84-55	methyl ((1R)-2-((2S)-2-(5-(4'-(2-((2S)-1-((dimethylamino)(2-(trifluoromethyl)phenyl)acetyl)-2-pyrrolidinyl)-1H-imidazol-5-yl)-4-biphenylyl)-1H-imidazol-2-yl)-1-pyrrolidinyl)-2-oxo-1-phenylethyl)carbamate	 *Cap*-25	LCMS: Anal. Calcd. for $C_{47}H_{47}F_3N_8O_4$: 844; found: 845 $(M+H)^+$.
84-56	methyl ((1R)-2-((2S)-2-(5-(4'-(2-((2S)-1-((2-chlorophenyl)(dimethylamino)acetyl)-2-pyrrolidinyl)-1H-imidazol-5-yl)-4-biphenylyl)-1H-imidazol-2-yl)-1-pyrrolidinyl)-2-oxo-1-phenylethyl)carbamate	 *Cap*-29	LCMS: Anal. Calcd. for $C_{46}H_{47}ClN_8O_4$: 810; found: 811 $(M+H)^+$.
84-57	methyl ((1R)-2-((2S)-2-(5-(4'-(2-((2S)-1-((3-chlorophenyl)(dimethylamino)acetyl)-2-pyrrolidinyl)-1H-imidazol-5-yl)-4-biphenylyl)-1H-imidazol-2-yl)-1-pyrrolidinyl)-2-oxo-1-	 *Cap*-28	LCMS: Anal. Calcd. for $C_{46}H_{47}ClN_8O_4$: 810; found: 811 $(M+H)^+$.

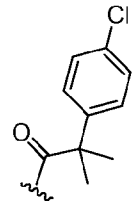
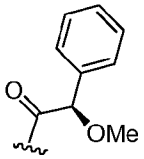
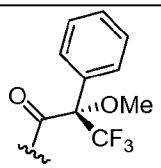
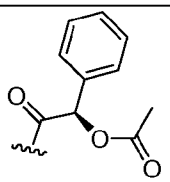
	phenylethyl)carbamate		
84-58	methyl ((1R)-2-((2S)-2-(5-(4'-(2-((2S)-1-((4-chlorophenyl)(dimethylamino)acetyl)-2-pyrrolidinyl)-1H-imidazol-5-yl)-4-biphenylyl)-1H-imidazol-2-yl)-1-pyrrolidinyl)-2-oxo-1-phenylethyl)carbamate	 *Cap*-30	LCMS: Anal. Calcd. for $C_{46}H_{47}ClN_8O_4$: 810; found: 811 $(M+H)^+$.
84-59	methyl ((1R)-2-((2S)-2-(5-(4'-(2-((2S)-1-((dimethylamino)(2-fluorophenyl)acetyl)-2-pyrrolidinyl)-1H-imidazol-5-yl)-4-biphenylyl)-1H-imidazol-2-yl)-1-pyrrolidinyl)-2-oxo-1-phenylethyl)carbamate	 *Cap*-26	LCMS: Anal. Calcd. for $C_{46}H_{47}FN_8O_4$: 794; found: 795 $(M+H)^+$.
84-60	methyl ((1R)-2-((2S)-2-(5-(4'-(2-((2S)-1-((dimethylamino)(3-fluorophenyl)acetyl)-2-pyrrolidinyl)-1H-imidazol-5-yl)-4-biphenylyl)-1H-imidazol-2-yl)-1-pyrrolidinyl)-2-oxo-1-phenylethyl)carbamate	 *Cap*-27	LCMS: Anal. Calcd. for $C_{46}H_{47}FN_8O_4$: 794; found: 795 $(M+H)^+$.
84-61	methyl ((1R)-2-((2S)-2-(5-(4'-(2-((2S)-1-((dimethylamino)(2-pyridinyl)acetyl)-2-pyrrolidinyl)-1H-imidazol-5-yl)-4-biphenylyl)-1H-imidazol-2-yl)-1-pyrrolidinyl)-2-oxo-1-	 *Cap*-20	LCMS: Anal. Calcd. for $C_{45}H_{47}N_9O_4$: 777; found: 778 $(M+H)^+$.

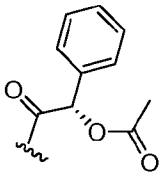
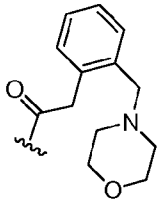
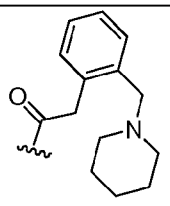
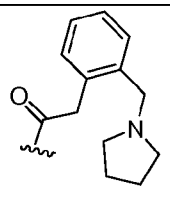
	phenylethyl)carbamate		
84-62	methyl ((1R)-2-((2S)-2-(4-(4'-(2-((2S)-1-((dimethylamino)(3-pyridinyl)acetyl)-2-pyrrolidinyl)-1H-imidazol-5-yl)-4-biphenylyl)-1H-imidazol-2-yl)-1-pyrrolidinyl)-2-oxo-1-phenylethyl)carbamate	 *Cap*-19	LCMS: Anal. Calcd. for $C_{45}H_{47}N_9O_4$: 777; found: 778 $(M+H)^+$.
84-63	methyl ((1R)-2-((2S)-2-(5-(4'-(2-((2S)-1-((4-methoxyphenyl)acetyl)-2-pyrrolidinyl)-1H-imidazol-5-yl)-4-biphenylyl)-1H-imidazol-2-yl)-1-pyrrolidinyl)-2-oxo-1-phenylethyl)carbamate		LCMS: Anal. Calcd. for $C_{45}H_{45}N_7O_5$: 763; found: 764 $(M+H)^+$.
84-64	methyl ((1R)-2-((2S)-2-(5-(4'-(2-((2S)-1-((3-methoxyphenyl)acetyl)-2-pyrrolidinyl)-1H-imidazol-5-yl)-4-biphenylyl)-1H-imidazol-2-yl)-1-pyrrolidinyl)-2-oxo-1-phenylethyl)carbamate		LCMS: Anal. Calcd. for $C_{45}H_{45}N_7O_5$: 763; found: 764 $(M+H)^+$.
84-65	methyl ((1R)-2-((2S)-2-(5-(4'-(2-((2S)-1-((2-methoxyphenyl)acetyl)-2-pyrrolidinyl)-1H-imidazol-5-yl)-4-biphenylyl)-1H-imidazol-2-yl)-1-pyrrolidinyl)-2-oxo-1-phenylethyl)carbamate		LCMS: Anal. Calcd. for $C_{45}H_{45}N_7O_5$: 763; found: 764 $(M+H)^+$.

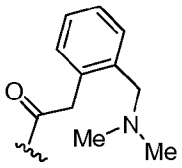
84-66	methyl ((1R)-2-((2S)-2-(5-(4'-(2-((2S)-1-((2-chlorophenyl)acetyl)-2-pyrrolidinyl)-1H-imidazol-5-yl)-4-biphenylyl)-1H-imidazol-2-yl)-1-pyrrolidinyl)-2-oxo-1-phenylethyl)carbamate		LCMS: Anal. Calcd. for $C_{44}H_{42}ClN_7O_4$: 767; found: 768 $(M+H)^+$.
84-67	methyl ((1R)-2-((2S)-2-(5-(4'-(2-((2S)-1-((3-chlorophenyl)acetyl)-2-pyrrolidinyl)-1H-imidazol-5-yl)-4-biphenylyl)-1H-imidazol-2-yl)-1-pyrrolidinyl)-2-oxo-1-phenylethyl)carbamate		LCMS: Anal. Calcd. for $C_{44}H_{42}ClN_7O_4$: 767; found: 768 $(M+H)^+$.
84-68	methyl ((1R)-2-((2S)-2-(5-(4'-(2-((2S)-1-((4-chlorophenyl)acetyl)-2-pyrrolidinyl)-1H-imidazol-5-yl)-4-biphenylyl)-1H-imidazol-2-yl)-1-pyrrolidinyl)-2-oxo-1-phenylethyl)carbamate		LCMS: Anal. Calcd. for $C_{44}H_{42}ClN_7O_4$: 767; found: 768 $(M+H)^+$.
84-69	methyl ((1R)-2-((2S)-2-(5-(4'-(2-((2S)-1-((2-methylphenyl)acetyl)-2-pyrrolidinyl)-1H-imidazol-5-yl)-4-biphenylyl)-1H-imidazol-2-yl)-1-pyrrolidinyl)-2-oxo-1-phenylethyl)carbamate		LCMS: Anal. Calcd. for $C_{45}H_{45}N_7O_4$: 747; found: 748 $(M+H)^+$.

84-70	methyl ((1R)-2-((2S)-2-(5-(4'-(2-((2S)-1-((4-methylphenyl)acetyl)-2-pyrrolidinyl)-1H-imidazol-5-yl)-4-biphenylyl)-1H-imidazol-2-yl)-1-pyrrolidinyl)-2-oxo-1-phenylethyl)carbamate		LCMS: Anal. Calcd. for $C_{45}H_{45}N_7O_4$: 747; found: 748 $(M+H)^+$.
84-71	methyl ((1R)-2-((2S)-2-(5-(4'-(2-((2S)-1-((3-methylphenyl)acetyl)-2-pyrrolidinyl)-1H-imidazol-5-yl)-4-biphenylyl)-1H-imidazol-2-yl)-1-pyrrolidinyl)-2-oxo-1-phenylethyl)carbamate		LCMS: Anal. Calcd. for $C_{45}H_{45}N_7O_4$: 747; found: 748 $(M+H)^+$.
84-72	methyl ((1R)-2-((2S)-2-(5-(4'-(2-((2S)-1-((2-methyl-1,3-thiazol-4-yl)acetyl)-2-pyrrolidinyl)-1H-imidazol-5-yl)-4-biphenylyl)-1H-imidazol-2-yl)-1-pyrrolidinyl)-2-oxo-1-phenylethyl)carbamate		LCMS: Anal. Calcd. for $C_{42}H_{42}N_8O_4S$: 754; found: 755 $(M+H)^+$.
84-73	methyl ((1R)-2-oxo-1-phenyl-2-((2S)-2-(5-(4'-(2-((2S)-1-(3-thienylacetyl)-2-pyrrolidinyl)-1H-imidazol-5-yl)-4-biphenylyl)-1H-imidazol-2-yl)-1-pyrrolidinyl)ethyl)carbamate		LCMS: Anal. Calcd. for $C_{42}H_{41}N_7O_4S$: 739; found: 740 $(M+H)^+$.
84-74	methyl ((1R)-2-((2S)-2-(5-(4'-(2-((2S)-1-((3-methyl-5-isoxazolyl)acetyl)-2-pyrrolidinyl)-1H-imidazol-5-		LCMS: Anal. Calcd. for $C_{42}H_{42}N_8O_5$: 738; found: 739 $(M+H)^+$.

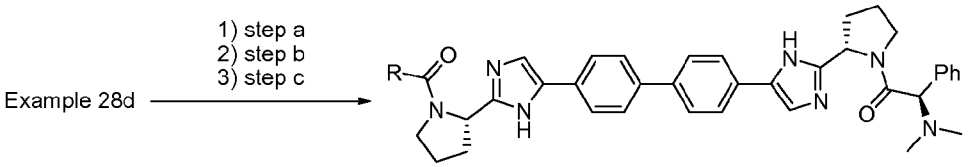
	yl)-4-biphenylyl)-1H-imidazol-2-yl)-1-pyrrolidinyl)-2-oxo-1-phenylethyl)carbamate		
84-75	methyl ((1R)-2-((2S)-2-(5-(4'-(2-((2S)-1-(cyclohexylacetyl)-2-pyrrolidinyl)-1H-imidazol-5-yl)-4-biphenylyl)-1H-imidazol-2-yl)-1-pyrrolidinyl)-2-oxo-1-phenylethyl)carbamate		LCMS: Anal. Calcd. for $C_{44}H_{49}N_7O_4$: 739; found: 740 $(M+H)^+$.
84-76	methyl ((1R)-2-oxo-1-phenyl-2-((2S)-2-(5-(4'-(2-((2S)-1-((2R)-2-phenylpropanoyl)-2-pyrrolidinyl)-1H-imidazol-5-yl)-4-biphenylyl)-1H-imidazol-2-yl)-1-pyrrolidinyl)ethyl)carbamate		LCMS: Anal. Calcd. for $C_{45}H_{45}N_7O_4$: 747; found: 748 $(M+H)^+$.
84-77	methyl ((1R)-2-oxo-1-phenyl-2-((2S)-2-(5-(4'-(2-((2S)-1-((1-phenylcyclopropyl)carbonyl)-2-pyrrolidinyl)-1H-imidazol-5-yl)-4-biphenylyl)-1H-imidazol-2-yl)-1-pyrrolidinyl)ethyl)carbamate		LCMS: Anal. Calcd. for $C_{46}H_{45}N_7O_4$: 759; found: 760 $(M+H)^+$.
84-78	methyl ((1R)-2-((2S)-2-(5-(4'-(2-((2S)-1-((1-(4-chlorophenyl)cyclopropyl)carbonyl)-2-pyrrolidinyl)-1H-imidazol-5-yl)-4-biphenylyl)-1H-imidazol-2-yl)-1-pyrrolidinyl)-2-oxo-1-phenylethyl)carbamate		LCMS: Anal. Calcd. for $C_{46}H_{44}ClN_7O_4$: 793; found: 794 $(M+H)^+$.

84-79	methyl ((1R)-2-((2S)-2-(5-(4'-(2-((2S)-1-(2-(4-chlorophenyl)-2-methylpropanoyl)-2-pyrrolidinyl)-1H-imidazol-5-yl)-4-biphenylyl)-1H-imidazol-2-yl)-1-pyrrolidinyl)-2-oxo-1-phenylethyl)carbamate		LCMS: Anal. Calcd. for $C_{46}H_{46}ClN_7O_4$: 795; found: 796 $(M+H)^+$.
84-80	methyl ((1R)-2-((2S)-2-(5-(4'-(2-((2S)-1-((2R)-2-methoxy-2-phenylacetyl)-2-pyrrolidinyl)-1H-imidazol-5-yl)-4-biphenylyl)-1H-imidazol-2-yl)-1-pyrrolidinyl)-2-oxo-1-phenylethyl)carbamate		LCMS: Anal. Calcd. for $C_{45}H_{45}N_7O_5$: 763; found: 764 $(M+H)^+$.
84-81	methyl ((1R)-2-oxo-1-phenyl-2-((2S)-2-(5-(4'-(2-((2S)-1-((2S)-3,3,3-trifluoro-2-methoxy-2-phenylpropanoyl)-2-pyrrolidinyl)-1H-imidazol-5-yl)-4-biphenylyl)-1H-imidazol-2-yl)-1-pyrrolidinyl)ethyl)carbamate		LCMS: Anal. Calcd. for $C_{46}H_{44}F_3N_7O_5$: 831; found: 832 $(M+H)^+$.
84-82	(1R)-2-((2S)-2-(5-(4'-(2-((2S)-1-((2R)-2-((methoxycarbonyl)amino)-2-phenylacetyl)-2-pyrrolidinyl)-1H-imidazol-5-yl)-4-biphenylyl)-1H-imidazol-2-yl)-1-pyrrolidinyl)-2-oxo-1-phenylethyl acetate		LCMS: Anal. Calcd. for $C_{46}H_{45}N_7O_6$: 791; found: 792 $(M+H)^+$.

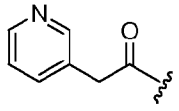
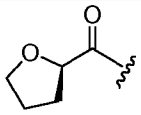
84-83	(1S)-2-((2S)-2-(5-(4'-(2-((2S)-1-((2R)-2-((methoxycarbonyl)amino)-2-phenylacetyl)-2-pyrrolidinyl)-1H-imidazol-5-yl)-4-biphenylyl)-1H-imidazol-2-yl)-1-pyrrolidinyl)-2-oxo-1-phenylethyl acetate		LCMS: Anal. Calcd. for $C_{46}H_{45}N_7O_6$: 791; found: 792 $(M+H)^+$.
84-84	methyl ((1R)-2-((2S)-2-(5-(4'-(2-((2S)-1-((2-(4-morpholinylmethyl)phenyl)acetyl)-2-pyrrolidinyl)-1H-imidazol-5-yl)-4-biphenylyl)-1H-imidazol-2-yl)-1-pyrrolidinyl)-2-oxo-1-phenylethyl)carbamate	 *Cap-41*	LCMS: Anal. Calcd. for $C_{49}H_{52}N_8O_5$: 832; found: 833 $(M+H)^+$.
84-85	methyl ((1R)-2-oxo-1-phenyl-2-((2S)-2-(5-(4'-(2-((2S)-1-((2-(1-piperidinylmethyl)phenyl)acetyl)-2-pyrrolidinyl)-1H-imidazol-5-yl)-4-biphenylyl)-1H-imidazol-2-yl)-1-pyrrolidinyl)ethyl)carbamate	 *Cap-42*	LCMS: Anal. Calcd. for $C_{50}H_{54}N_8O_4$: 830; found: 831 $(M+H)^+$.
84-86	methyl ((1R)-2-oxo-1-phenyl-2-((2S)-2-(5-(4'-(2-((2S)-1-((2-(1-pyrrolidinylmethyl)phenyl)acetyl)-2-pyrrolidinyl)-1H-imidazol-5-yl)-4-biphenylyl)-1H-imidazol-2-yl)-1-pyrrolidinyl)ethyl)carbamate	 *Cap-43*	LCMS: Anal. Calcd. for $C_{49}H_{52}N_8O_4$: 816; found: 816 $(M+H)^+$.

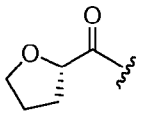
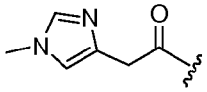
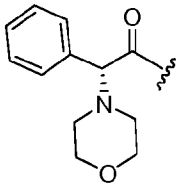
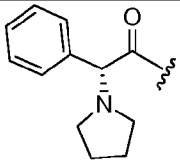
84-87	methyl ((1R)-2-((2S)-2-(5-(4'-(2-((2S)-1-((2-((dimethylamino)methyl)phenyl)acetyl)-2-pyrrolidinyl)-1H-imidazol-5-yl)-4-biphenylyl)-1H-imidazol-2-yl)-1-pyrrolidinyl)-2-oxo-1-phenylethyl)carbamate	 *Cap-44*	LCMS: Anal. Calcd. for $C_{47}H_{50}N_8O_4$: 790; found: 791 $(M+H)^+$.

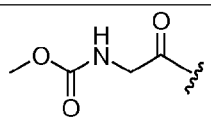
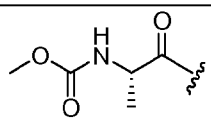
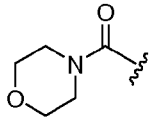
Examples 85-94

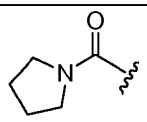
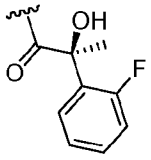


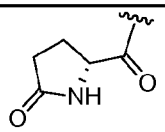
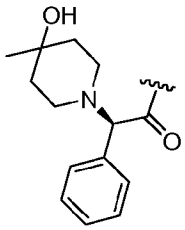
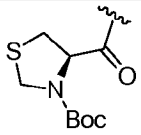
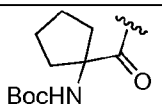
step a: Cap with cap-1 as in Example 28
step b: Same procedure as in conversion of Example 1d to 1e
step c: As in the last step of Example 1 using 1.1 equiv. of the appropriate carboxylic acid and HATU

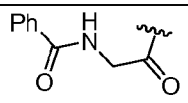
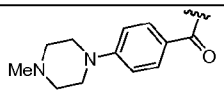
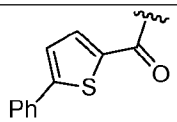
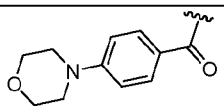
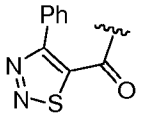
Example	*Compound Name*		*Retention time (LC-Condition); homogeneity index MS data*
85	(1R)-N,N-dimethyl-2-oxo-1-phenyl-2-((2S)-2-(5-(4'-(2-((2S)-1-(3-pyridinylacetyl)-2-pyrrolidinyl)-1H-imidazol-5-yl)-4-biphenylyl)-1H-imidazol-2-yl)-1-pyrrolidinyl)ethanamine		1.64 minutes (Cond. 2); >98%; LC/MS: Anal. Calcd. for $[M+H]^+$ $C_{43}H_{45}N_8O_2$: 705.37; found 705.43; HRMS: Anal. Calcd. for $[M+H]^+$ $C_{43}H_{45}N_8O_2$: 705.3665; found 705.3675
86	(1R)-N,N-dimethyl-2-oxo-1-phenyl-2-((2S)-2-(5-(4'-(2-((2S)-1-((2R)-tetrahydro-2-furanylcarbonyl)-2-pyrrolidinyl)-1H-imidazol-5-yl)-4-biphenylyl)-1H-imidazol-2-		1.73 minutes (Cond. 2); >98%; LC/MS: Anal. Calcd. for $[M+H]^+$ $C_{41}H_{46}N_7O_3$: 684.37; found 684.44; HRMS: Anal.

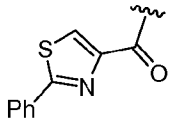
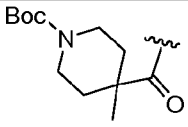
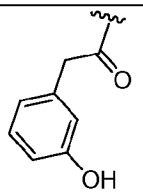
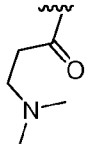
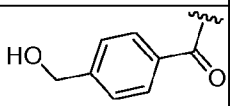
	yl)-1-pyrrolidinyl)ethanamine		Calcd. for $[M+H]^+$ $C_{41}H_{46}N_7O_3$: 684.3662; found 684.3671
87	(1R)-N,N-dimethyl-2-oxo-1-phenyl-2-((2S)-2-(5-(4'-(2-((2S)-1-((2S)-tetrahydro-2-furanylcarbonyl)-2-pyrrolidinyl)-1H-imidazol-5-yl)-4-biphenylyl)-1H-imidazol-2-yl)-1-pyrrolidinyl)ethanamine		1.12 minutes (Cond. 2); >98%; LC/MS: Anal. Calcd. for $[M+H]^+$ $C_{41}H_{46}N_7O_3$: 684.37; found 684.68; HRMS: Anal. Calcd. for $[M+H]^+$ $C_{41}H_{46}N_7O_3$: 684.3662; found 684.3692
88	(1R)-N,N-dimethyl-2-((2S)-2-(5-(4'-(2-((2S)-1-((1-methyl-1H-imidazol-4-yl)acetyl)-2-pyrrolidinyl)-1H-imidazol-5-yl)-4-biphenylyl)-1H-imidazol-2-yl)-1-pyrrolidinyl)-2-oxo-1-phenylethanamine		1.66 minutes (Cond. 2); >98%; LC/MS: Anal. Calcd. for $[M+H]^+$ $C_{42}H_{46}N_9O_2$: 708.38; found 708.36
89	(1R)-N,N-dimethyl-2-((2S)-2-(5-(4'-(2-((2S)-1-((2R)-2-(4-morpholinyl)-2-phenylacetyl)-2-pyrrolidinyl)-1H-imidazol-5-yl)-4-biphenylyl)-1H-imidazol-2-yl)-1-pyrrolidinyl)-2-oxo-1-phenylethanamine	 *Cap-6*	1.70 minutes (Cond. 2); >98%; LC/MS: Anal. Calcd. for $[M+H]^+$ $C_{40}H_{45}N_8O_4$: 701.36; found 701.34; HRMS: Anal. Calcd. for $[M+H]^+$ $C_{40}H_{45}N_8O_4$: 701.3564; found 701.3576
90	(1R)-N,N-dimethyl-2-oxo-1-phenyl-2-((2S)-2-(5-(4'-(2-((2S)-1-((2R)-2-phenyl-2-(1-pyrrolidinyl)acetyl)-2-		1.80 minutes (Cond. 2); >98%; LC/MS: Anal. Calcd. for $[M+H]^+$ $C_{48}H_{53}N_8O_2$:

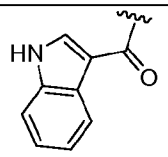
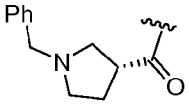
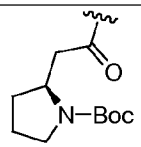
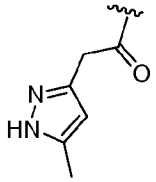
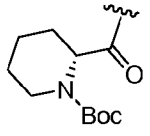
	pyrrolidinyl)-1H-imidazol-5-yl)-4-biphenylyl)-1H-imidazol-2-yl)-1-pyrrolidinyl)ethanamine	*Cap-5*	773.43; found 773.42; HRMS: Anal. Calcd. for $[M+H]^+$ $C_{48}H_{53}N_6O_2$: 773.4291; found 773.4309
91	methyl (2-((2S)-2-(5-(4'-(2-((2S)-1-((2R)-2-(dimethylamino)-2-phenylacetyl)-2-pyrrolidinyl)-1H-imidazol-5-yl)-4-biphenylyl)-1H-imidazol-2-yl)-1-pyrrolidinyl)-2-oxoethyl)carbamate		1.66 minutes (Cond. 2); >98%; LC/MS: Anal. Calcd. for $[M+H]^+$ $C_{42}H_{46}N_9O_2$: 708.38; found 708.36; HRMS: Anal. Calcd. for $[M+H]^+$ $C_{42}H_{46}N_9O_2$: 708.3744; found 708.3770
92	methyl ((1S)-2-((2S)-2-(5-(4'-(2-((2S)-1-((2R)-2-(dimethylamino)-2-phenylacetyl)-2-pyrrolidinyl)-1H-imidazol-5-yl)-4-biphenylyl)-1H-imidazol-2-yl)-1-pyrrolidinyl)-1-methyl-2-oxoethyl)carbamate	 *Cap-12*	1.73 minutes (Cond. 2); >98%; LC/MS: Anal. Calcd. for $[M+H]^+$ $C_{41}H_{47}N_8O_4$: 715.37; found 715.41; HRMS: Anal. Calcd. for $[M+H]^+$ $C_{41}H_{47}N_8O_4$: 715.3720; found 715.3729
93	(1R)-N,N-dimethyl-2-((2S)-2-(5-(4'-(2-((2S)-1-(4-morpholinylcarbonyl)-2-pyrrolidinyl)-1H-imidazol-5-yl)-4-biphenylyl)-1H-imidazol-2-yl)-1-pyrrolidinyl)-2-oxo-1-phenylethanamine		1.76 minutes (Cond. 2); >98%; LC/MS: Anal. Calcd. for $[M+H]^+$ $C_{41}H_{47}N_8O_3$: 699.38; found 699.45; HRMS: Anal. Calcd. for $[M+H]^+$ $C_{41}H_{47}N_8O_3$: 699.3771; found

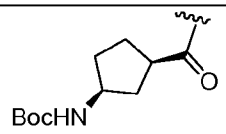
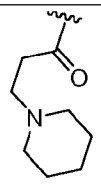
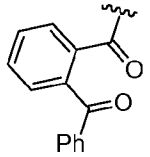
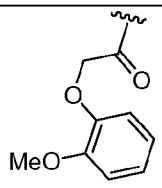
			699.3803
94	(1R)-N,N-dimethyl-2-oxo-1-phenyl-2-((2S)-2-(5-(4'-(2-((2S)-1-(1-pyrrolidinylcarbonyl)-2-pyrrolidinyl)-1H-imidazol-5-yl)-4-biphenylyl)-1H-imidazol-2-yl)-1-pyrrolidinyl)ethanamine		1.86 minutes (Cond. 2); >98%; LC/MS: Anal. Calcd. for $[M+H]^+$ $C_{41}H_{47}N_8O_2$: 683.38; found 683.46; HRMS: Anal. Calcd. for $[M+H]^+$ $C_{41}H_{47}N_8O_2$: 683.3822; found 683.3835
94-1	(2S)-1-((2S)-2-(5-(4'-(2-((2S)-1-((2R)-2-(dimethylamino)-2-phenylacetyl)-2-pyrrolidinyl)-1H-imidazol-5-yl)-4-biphenylyl)-1H-imidazol-2-yl)-1-pyrrolidinyl)-2-(2-fluorophenyl)-1-oxo-2-propanol		^{1}HNMR (400 MHz, CD_3OD) δ 7.90-7.84 (m, 9H), 7.79-7.73 (m, 2H), 7.67-7.65 (m, 1H), 7.63-7.52 (m, 5H), 7.39-7.36 (m, 1H), 7.30-7.26 (m, 1H), 7.13-7.08 (m, 1H), 6.93-6.88 (m, 0.5H), 6.72-6.67 (m, 0.5H), 5.51 (s, 0.2H), 5.46 (s, 0.8H), 5.33-5.30 (m, 1H), 5.28-5.24 (m, 1H), 4.05-3.94 (m, 2H), 3.84-3.73 (m, 1H), 3.69-3.55 (m, 1H), 3.21-3.04 (m, 2H), 2.79 (br s, 6H), 2.39-2.33 (m, 2H), 2.21-1.93 (m, 5H), 1.65 (d, J = 4.55 Hz, 3H).; LCMS: Anal. Calcd. for $C_{45}H_{46}FN_7O_3$:

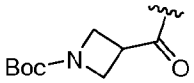
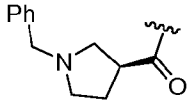
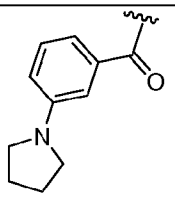
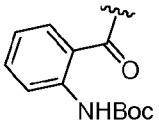
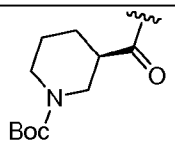
			751; found: 752 $(M+H)^+$.
94-2	(5R)-5-(((2S)-2-(5-(4'-(2-((2S)-1-((2R)-2-(dimethylamino)-2-phenylacetyl)-2-pyrrolidinyl)-1H-imidazol-5-yl)-4-biphenylyl)-1H-imidazol-2-yl)-1-pyrrolidinyl)carbonyl)-2-pyrrolidinone		LCMS: Anal. Calcd. for $C_{41}H_{44}N_8O_3$: 696; found: 697 $(M+H)^+$.
94-3	1-((1R)-2-((2S)-2-(5-(4'-(2-((2S)-1-((2R)-2-(dimethylamino)-2-phenylacetyl)-2-pyrrolidinyl)-1H-imidazol-5-yl)-4-biphenylyl)-1H-imidazol-2-yl)-1-pyrrolidinyl)-2-oxo-1-phenylethyl)-4-methyl-4-piperidinol	 *Cap-15*	LCMS: Anal. Calcd. for $C_{50}H_{56}N_8O_3$: 816; found: 817 $(M+H)^+$.
94-4	tert-butyl (4R)-4-(((2S)-2-(5-(4'-(2-((2S)-1-((2R)-2-(dimethylamino)-2-phenylacetyl)-2-pyrrolidinyl)-1H-imidazol-5-yl)-4-biphenylyl)-1H-imidazol-2-yl)-1-pyrrolidinyl)carbonyl)-1,3-thiazolidine-3-carboxylate		LCMS: Anal. Calcd. for $C_{45}H_{52}N_8O_4S$: 800; found: 801 $(M+H)^+$.
94-5	tert-butyl (1-(((2S)-2-(5-(4'-(2-((2S)-1-((2R)-2-(dimethylamino)-2-phenylacetyl)-2-pyrrolidinyl)-1H-imidazol-5-yl)-4-biphenylyl)-1H-imidazol-2-yl)-1-pyrrolidinyl)carbonyl)cyclopentyl)carbamate		LCMS: Anal. Calcd. for $C_{47}H_{56}FN_8O_4$: 796; found: 797 $(M+H)^+$.

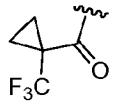
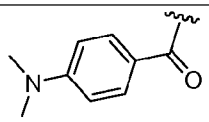
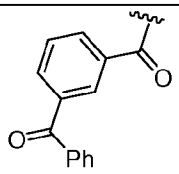
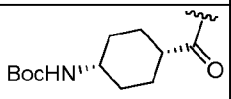
94-6	N-(2-((2S)-2-(5-(4'-(2-((2S)-1-((2R)-2-(dimethylamino)-2-phenylacetyl)-2-pyrrolidinyl)-1H-imidazol-5-yl)-4-biphenylyl)-1H-imidazol-2-yl)-1-pyrrolidinyl)-2-oxoethyl)benzamide		LCMS: Anal. Calcd. for $C_{45}H_{46}FN_8O_3$: 746; found: 747 $(M+H)^+$.
94-7	(1R)-N,N-dimethyl-2-((2S)-2-(5-(4'-(2-((2S)-1-(4-(4-methyl-1-piperazinyl)benzoyl)-2-pyrrolidinyl)-1H-imidazol-5-yl)-4-biphenylyl)-1H-imidazol-2-yl)-1-pyrrolidinyl)-2-oxo-1-phenylethanamine		LCMS: Anal. Calcd. for $C_{48}H_{53}N_9O_2$: 787; found: 788 $(M+H)^+$.
94-8	(1R)-N,N-dimethyl-2-oxo-1-phenyl-2-((2S)-2-(5-(4'-(2-((2S)-1-((5-phenyl-2-thienyl)carbonyl)-2-pyrrolidinyl)-1H-imidazol-5-yl)-4-biphenylyl)-1H-imidazol-2-yl)-1-pyrrolidinyl)ethanamine		LCMS: Anal. Calcd. for $C_{47}H_{45}N_7O_2S$: 771; found: 772 $(M+H)^+$.
94-9	(1R)-N,N-dimethyl-2-((2S)-2-(5-(4'-(2-((2S)-1-(4-(4-morpholinyl)benzoyl)-2-pyrrolidinyl)-1H-imidazol-5-yl)-4-biphenylyl)-1H-imidazol-2-yl)-1-pyrrolidinyl)-2-oxo-1-phenylethanamine		LCMS: Anal. Calcd. for $C_{47}H_{50}N_8O_3$: 774; found: 775 $(M+H)^+$.
94-10	(1R)-N,N-dimethyl-2-oxo-1-phenyl-2-((2S)-2-(5-(4'-(2-((2S)-1-((4-phenyl-1,2,3-thiadiazol-5-yl)carbonyl)-2-pyrrolidinyl)-1H-imidazol-5-yl)-4-biphenylyl)-1H-imidazol-2-yl)-1-pyrrolidinyl)ethanamine		LCMS: Anal. Calcd. for $C_{45}H_{43}N_9O_2S$: 773; found: 774 $(M+H)^+$.

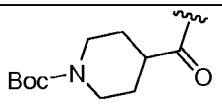
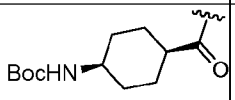
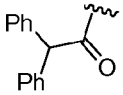
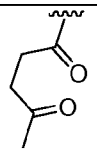
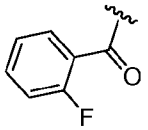
94-11	(1R)-N,N-dimethyl-2-oxo-1-phenyl-2-((2S)-2-(5-(4'-(2-((2S)-1-((2-phenyl-1,3-thiazol-4-yl)carbonyl)-2-pyrrolidinyl)-1H-imidazol-5-yl)-4-biphenylyl)-1H-imidazol-2-yl)-1-pyrrolidinyl)ethanamine		LCMS: Anal. Calcd. for $C_{46}H_{44}N_8O_2S$: 772; found: 773 $(M+H)^+$.
94-12	tert-butyl 4-(((2S)-2-(5-(4'-(2-((2S)-1-((2R)-2-(dimethylamino)-2-phenylacetyl)-2-pyrrolidinyl)-1H-imidazol-5-yl)-4-biphenylyl)-1H-imidazol-2-yl)-1-pyrrolidinyl)carbonyl)-4-methyl-1-piperidinecarboxylate		LCMS: Anal. Calcd. for $C_{48}H_{58}N_8O_4$: 810; found: 811 $(M+H)^+$.
94-13	3-(2-((2S)-2-(5-(4'-(2-((2S)-1-((2R)-2-(dimethylamino)-2-phenylacetyl)-2-pyrrolidinyl)-1H-imidazol-5-yl)-4-biphenylyl)-1H-imidazol-2-yl)-1-pyrrolidinyl)-2-oxoethyl)phenol		LCMS: Anal. Calcd. for $C_{44}H_{45}N_7O_3$: 719; found: 720 $(M+H)^+$.
94-14	3-((2S)-2-(5-(4'-(2-((2S)-1-((2R)-2-(dimethylamino)-2-phenylacetyl)-2-pyrrolidinyl)-1H-imidazol-5-yl)-4-biphenylyl)-1H-imidazol-2-yl)-1-pyrrolidinyl)-N,N-dimethyl-3-oxo-1-propanamine		LCMS: Anal. Calcd. for $C_{41}H_{48}N_8O_2$: 684; found: 685 $(M+H)^+$.
94-15	(4-(((2S)-2-(5-(4'-(2-((2S)-1-((2R)-2-(dimethylamino)-2-phenylacetyl)-2-pyrrolidinyl)-1H-imidazol-5-yl)-4-biphenylyl)-1H-imidazol-2-yl)-1-		LCMS: Anal. Calcd. for $C_{44}H_{45}N_7O_3$: 719; found: 720 $(M+H)^+$.

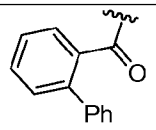
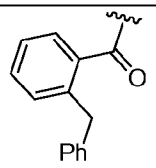
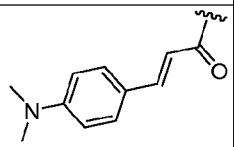
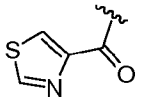
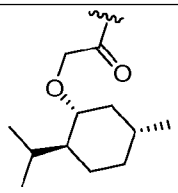
	pyrrolidinyl)carbonyl)phenyl)methanol		
94-16	(1R)-2-((2S)-2-(5-(4'-(2-((2S)-1-(1H-indol-3-ylcarbonyl)-2-pyrrolidinyl)-1H-imidazol-5-yl)-4-biphenylyl)-1H-imidazol-2-yl)-1-pyrrolidinyl)-N,N-dimethyl-2-oxo-1-phenylethanamine		LCMS: Anal. Calcd. for $C_{45}H_{44}N_8O_2$: 728; found: 729 $(M+H)^+$.
94-17	(1R)-2-((2S)-2-(5-(4'-(2-((2S)-1-(((3R)-1-benzyl-3-pyrrolidinyl)carbonyl)-2-pyrrolidinyl)-1H-imidazol-5-yl)-4-biphenylyl)-1H-imidazol-2-yl)-1-pyrrolidinyl)-N,N-dimethyl-2-oxo-1-phenylethanamine		LCMS: Anal. Calcd. for $C_{48}H_{52}N_8O_2$: 772; found: 773 $(M+H)^+$.
94-18	tert-butyl (2S)-2-(2-((2S)-2-(5-(4'-(2-((2S)-1-((2R)-2-(dimethylamino)-2-phenylacetyl)-2-pyrrolidinyl)-1H-imidazol-5-yl)-4-biphenylyl)-1H-imidazol-2-yl)-1-pyrrolidinyl)-2-oxoethyl)-1-pyrrolidinecarboxylate		LCMS: Anal. Calcd. for $C_{47}H_{56}N_8O_4$: 796; found: 797 $(M+H)^+$.
94-19	(1R)-N,N-dimethyl-2-((2S)-2-(5-(4'-(2-((2S)-1-((5-methyl-1H-pyrazol-3-yl)acetyl)-2-pyrrolidinyl)-1H-imidazol-5-yl)-4-biphenylyl)-1H-imidazol-2-yl)-1-pyrrolidinyl)-2-oxo-1-phenylethanamine		LCMS: Anal. Calcd. for $C_{42}H_{45}N_9O_2$: 707; found: 708 $(M+H)^+$.
94-20	tert-butyl (2R)-2-(((2S)-2-(5-(4'-(2-((2S)-1-((2R)-2-(dimethylamino)-2-		LCMS: Anal. Calcd. for $C_{47}H_{56}N_8O_4$: 796; found: 797 $(M+H)^+$.

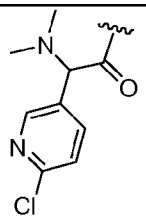
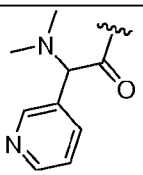
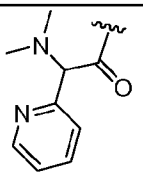
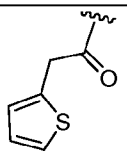
	phenylacetyl)-2-pyrrolidinyl)-1H-imidazol-5-yl)-4-biphenylyl)-1H-imidazol-2-yl)-1-pyrrolidinyl)carbonyl)-1-piperidinecarboxylate		
94-21	tert-butyl ((1S,3R)-3-(((2S)-2-(5-(4'-(2-((2S)-1-((2R)-2-(dimethylamino)-2-phenylacetyl)-2-pyrrolidinyl)-1H-imidazol-5-yl)-4-biphenylyl)-1H-imidazol-2-yl)-1-pyrrolidinyl)carbonyl)cyclopentyl)carbamate		LCMS: Anal. Calcd. for $C_{47}H_{56}N_8O_4$: 796; found: 797 $(M+H)^+$.
94-22	(1R)-N,N-dimethyl-2-oxo-1-phenyl-2-((2S)-2-(5-(4'-(2-((2S)-1-(3-(1-piperidinyl)propanoyl)-2-pyrrolidinyl)-1H-imidazol-5-yl)-4-biphenylyl)-1H-imidazol-2-yl)-1-pyrrolidinyl)ethanamine		LCMS: Anal. Calcd. for $C_{44}H_{52}N_8O_2$: 724; found: 725 $(M+H)^+$.
94-23	(2-(((2S)-2-(5-(4'-(2-((2S)-1-((2R)-2-(dimethylamino)-2-phenylacetyl)-2-pyrrolidinyl)-1H-imidazol-5-yl)-4-biphenylyl)-1H-imidazol-2-yl)-1-pyrrolidinyl)carbonyl)phenyl)(phenyl)methanone		LCMS: Anal. Calcd. for $C_{50}H_{47}N_7O_3$: 793; found: 794 $(M+H)^+$.
94-24	(1R)-2-((2S)-2-(5-(4'-(2-((2S)-1-((2-methoxyphenoxy)acetyl)-2-pyrrolidinyl)-1H-imidazol-5-yl)-4-biphenylyl)-1H-imidazol-2-yl)-1-pyrrolidinyl)-N,N-dimethyl-2-oxo-1-phenylethanamine		LCMS: Anal. Calcd. for $C_{45}H_{47}N_7O_4$: 749; found: 750 $(M+H)^+$.

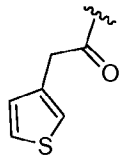
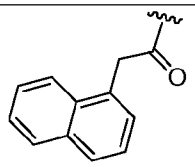
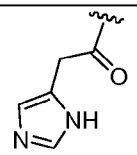
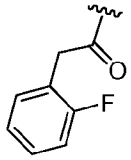
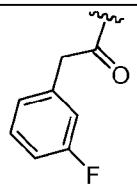
94-25	tert-butyl 3-(((2S)-2-(5-(4'-(2-((2S)-1-((2R)-2-(dimethylamino)-2-phenylacetyl)-2-pyrrolidinyl)-1H-imidazol-5-yl)-4-biphenylyl)-1H-imidazol-2-yl)-1-pyrrolidinyl)carbonyl)-1-azetidinecarboxylate		LCMS: Anal. Calcd. for $C_{45}H_{52}N_8O_4$: 768; found: 769 $(M+H)^+$.
94-26	(1R)-2-((2S)-2-(5-(4'-(2-((2S)-1-(((3S)-1-benzyl-3-pyrrolidinyl)carbonyl)-2-pyrrolidinyl)-1H-imidazol-5-yl)-4-biphenylyl)-1H-imidazol-2-yl)-1-pyrrolidinyl)-N,N-dimethyl-2-oxo-1-phenylethanamine		LCMS: Anal. Calcd. for $C_{48}H_{52}N_8O_2$: 772; found: 773 $(M+H)^+$.
94-27	(1R)-N,N-dimethyl-2-oxo-1-phenyl-2-((2S)-2-(5-(4'-(2-((2S)-1-(3-(1-pyrrolidinyl)benzoyl)-2-pyrrolidinyl)-1H-imidazol-5-yl)-4-biphenylyl)-1H-imidazol-2-yl)-1-pyrrolidinyl)ethanamine		LCMS: Anal. Calcd. for $C_{47}H_{50}N_8O_2$: 758; found: 759 $(M+H)^+$.
94-28	tert-butyl (2-(((2S)-2-(5-(4'-(2-((2S)-1-((2R)-2-(dimethylamino)-2-phenylacetyl)-2-pyrrolidinyl)-1H-imidazol-5-yl)-4-biphenylyl)-1H-imidazol-2-yl)-1-pyrrolidinyl)carbonyl)phenyl)carbamate		LCMS: Anal. Calcd. for $C_{48}H_{52}N_8O_4$: 804; found: 805 $(M+H)^+$.
94-29	tert-butyl (3R)-3-(((2S)-2-(5-(4'-(2-((2S)-1-((2R)-2-(dimethylamino)-2-phenylacetyl)-2-pyrrolidinyl)-		LCMS: Anal. Calcd. for $C_{47}H_{56}N_8O_4$: 796; found: 797 $(M+H)^+$.

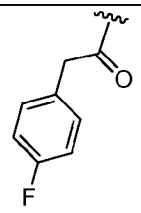
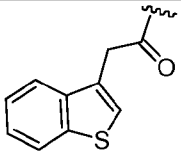
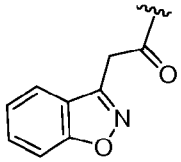
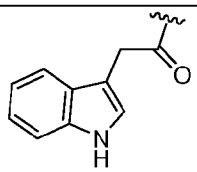
	1H-imidazol-5-yl)-4-biphenylyl)-1H-imidazol-2-yl)-1-pyrrolidinyl)carbonyl)-1-piperidinecarboxylate		
94-30	(1R)-N,N-dimethyl-2-oxo-1-phenyl-2-((2S)-2-(5-(4'-(2-((2S)-1-((1-(trifluoromethyl)cyclopropyl)carbonyl)-2-pyrrolidinyl)-1H-imidazol-5-yl)-4-biphenylyl)-1H-imidazol-2-yl)-1-pyrrolidinyl)ethanamine		LCMS: Anal. Calcd. for $C_{41}H_{42}F_3N_7O_2$: 721; found: 722 $(M+H)^+$.
94-31	4-(((2S)-2-(5-(4'-(2-((2S)-1-((2R)-2-(dimethylamino)-2-phenylacetyl)-2-pyrrolidinyl)-1H-imidazol-5-yl)-4-biphenylyl)-1H-imidazol-2-yl)-1-pyrrolidinyl)carbonyl)-N,N-dimethylaniline		LCMS: Anal. Calcd. for $C_{45}H_{48}N_8O_2$: 732; found: 733 $(M+H)^+$.
94-32	(3-(((2S)-2-(5-(4'-(2-((2S)-1-((2R)-2-(dimethylamino)-2-phenylacetyl)-2-pyrrolidinyl)-1H-imidazol-5-yl)-4-biphenylyl)-1H-imidazol-2-yl)-1-pyrrolidinyl)carbonyl)phenyl)(phenyl)methanone		LCMS: Anal. Calcd. for $C_{50}H_{47}N_7O_3$: 793; found: 794 $(M+H)^+$.
94-33	tert-butyl (cis-4-(((2S)-2-(5-(4'-(2-((2S)-1-((2R)-2-(dimethylamino)-2-phenylacetyl)-2-pyrrolidinyl)-1H-imidazol-5-yl)-4-biphenylyl)-1H-imidazol-2-yl)-1-pyrrolidinyl)carbonyl)cyclohexyl		LCMS: Anal. Calcd. for $C_{48}H_{58}N_8O_4$: 810; found: 811 $(M+H)^+$.

	)carbamate		
94-34	'tert-butyl 4-(((2S)-2-(5-(4'-(2-((2S)-1-((2R)-2-(dimethylamino)-2-phenylacetyl)-2-pyrrolidinyl)-1H-imidazol-5-yl)-4-biphenylyl)-1H-imidazol-2-yl)-1-pyrrolidinyl)carbonyl)-1-piperidinecarboxylate		LCMS: Anal. Calcd. for $C_{47}H_{56}N_8O_4$: 796; found: 797 $(M+H)^+$.
94-35	tert-butyl (cis-4-(((2S)-2-(5-(4'-(2-((2S)-1-((2R)-2-(dimethylamino)-2-phenylacetyl)-2-pyrrolidinyl)-1H-imidazol-5-yl)-4-biphenylyl)-1H-imidazol-2-yl)-1-pyrrolidinyl)carbonyl)cyclohexyl)carbamate		LCMS: Anal. Calcd. for $C_{48}H_{58}N_8O_4$: 810; found: 811 $(M+H)^+$.
94-36	(1R)-2-((2S)-2-(5-(4'-(2-((2S)-1-(diphenylacetyl)-2-pyrrolidinyl)-1H-imidazol-5-yl)-4-biphenylyl)-1H-imidazol-2-yl)-1-pyrrolidinyl)-N,N-dimethyl-2-oxo-1-phenylethanamine		LCMS: Anal. Calcd. for $C_{50}H_{49}N_7O_2$: 779; found: 780 $(M+H)^+$.
94-37	5-((2S)-2-(5-(4'-(2-((2S)-1-((2R)-2-(dimethylamino)-2-phenylacetyl)-2-pyrrolidinyl)-1H-imidazol-5-yl)-4-biphenylyl)-1H-imidazol-2-yl)-1-pyrrolidinyl)-5-oxo-2-pentanone		LCMS: Anal. Calcd. for $C_{41}H_{45}N_7O_3$: 683; found: 684 $(M+H)^+$.
94-38	(1R)-2-((2S)-2-(5-(4'-(2-((2S)-1-(2-fluorobenzoyl)-2-pyrrolidinyl)-1H-imidazol-5-yl)-4-biphenylyl)-1H-imidazol-2-		LCMS: Anal. Calcd. for $C_{43}H_{42}FN_7O_2$: 707; found: 708 $(M+H)^+$.

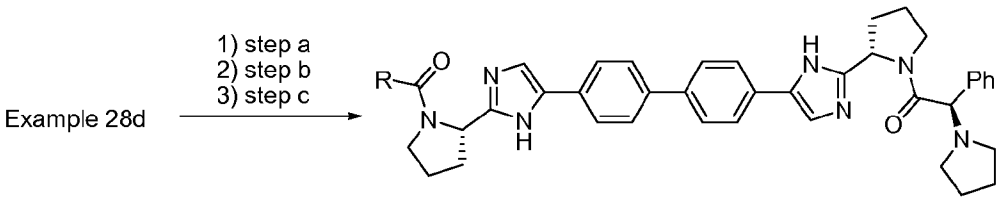
	yl)-1-pyrrolidinyl)-N,N-dimethyl-2-oxo-1-phenylethanamine		
94-39	(1R)-2-((2S)-2-(5-(4'-(2-((2S)-1-(2-biphenylylcarbonyl)-2-pyrrolidinyl)-1H-imidazol-5-yl)-4-biphenylyl)-1H-imidazol-2-yl)-1-pyrrolidinyl)-N,N-dimethyl-2-oxo-1-phenylethanamine		LCMS: Anal. Calcd. for $C_{49}H_{47}N_7O_2$: 765; found: 766 $(M+H)^+$.
94-40	(1R)-2-((2S)-2-(5-(4'-(2-((2S)-1-(2-benzylbenzoyl)-2-pyrrolidinyl)-1H-imidazol-5-yl)-4-biphenylyl)-1H-imidazol-2-yl)-1-pyrrolidinyl)-N,N-dimethyl-2-oxo-1-phenylethanamine		LCMS: Anal. Calcd. for $C_{50}H_{49}N_7O_2$: 779; found: 780 $(M+H)^+$.
94-41	4-((1E)-3-((2S)-2-(5-(4'-(2-((2S)-1-((2R)-2-(dimethylamino)-2-phenylacetyl)-2-pyrrolidinyl)-1H-imidazol-5-yl)-4-biphenylyl)-1H-imidazol-2-yl)-1-pyrrolidinyl)-3-oxo-1-propen-1-yl)-N,N-dimethylaniline		LCMS: Anal. Calcd. for $C_{47}H_{50}N_8O_2$: 758; found: 759 $(M+H)^+$.
94-42	(1R)-N,N-dimethyl-2-oxo-1-phenyl-2-((2S)-2-(5-(4'-(2-((2S)-1-(1,3-thiazol-4-ylcarbonyl)-2-pyrrolidinyl)-1H-imidazol-5-yl)-4-biphenylyl)-1H-imidazol-2-yl)-1-pyrrolidinyl)ethanamine		LCMS: Anal. Calcd. for $C_{40}H_{40}N_8O_2S$: 696; found: 697 $(M+H)^+$.
94-43	(1R)-2-((2S)-2-(5-(4'-(2-((2S)-1-((((1R,2S,5R)-2-isopropyl-5-methylcyclohexyl)oxy)acetyl)-2-pyrrolidinyl)-1H-imidazol-5-yl)-		LCMS: Anal. Calcd. for $C_{48}H_{59}N_7O_3$: 781; found: 782 $(M+H)^+$.

	4-biphenylyl)-1H-imidazol-2-yl)-1-pyrrolidinyl)-N,N-dimethyl-2-oxo-1-phenylethanamine		
94-44	1-(6-chloro-3-pyridinyl)-2-((2S)-2-(5-(4'-(2-((2S)-1-((2R)-2-(dimethylamino)-2-phenylacetyl)-2-pyrrolidinyl)-1H-imidazol-5-yl)-4-biphenylyl)-1H-imidazol-2-yl)-1-pyrrolidinyl)-N,N-dimethyl-2-oxoethanamine	 *Cap-21*	LCMS: Anal. Calcd. for $C_{45}H_{48}ClN_9O_2$: 781; found: 782 $(M+H)^+$.
94-45	2-((2S)-2-(5-(4'-(2-((2S)-1-((2R)-2-(dimethylamino)-2-phenylacetyl)-2-pyrrolidinyl)-1H-imidazol-5-yl)-4-biphenylyl)-1H-imidazol-2-yl)-1-pyrrolidinyl)-N,N-dimethyl-2-oxo-1-(3-pyridinyl)ethanamine	 *Cap-19*	LCMS: Anal. Calcd. for $C_{45}H_{49}N_9O_2$: 747; found: 748 $(M+H)^+$.
94-46	2-((2S)-2-(5-(4'-(2-((2S)-1-((2R)-2-(dimethylamino)-2-phenylacetyl)-2-pyrrolidinyl)-1H-imidazol-5-yl)-4-biphenylyl)-1H-imidazol-2-yl)-1-pyrrolidinyl)-N,N-dimethyl-2-oxo-1-(2-pyridinyl)ethanamine	 *Cap*-20	LCMS: Anal. Calcd. for $C_{45}H_{49}N_9O_2$: 747; found: 748 $(M+H)^+$.
94-47	(1R)-N,N-dimethyl-2-oxo-1-phenyl-2-((2S)-2-(5-(4'-(2-((2S)-1-(2-thienylacetyl)-2-pyrrolidinyl)-1H-imidazol-5-yl)-4-biphenylyl)-1H-imidazol-2-yl)-1-pyrrolidinyl)ethanamine		LCMS: Anal. Calcd. for $C_{42}H_{43}N_7O_2S$: 709; found: 710 $(M+H)^+$.

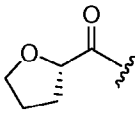
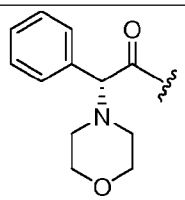
94-48	(1R)-N,N-dimethyl-2-oxo-1-phenyl-2-((2S)-2-(5-(4'-(2-((2S)-1-(3-thienylacetyl)-2-pyrrolidinyl)-1H-imidazol-5-yl)-4-biphenylyl)-1H-imidazol-2-yl)-1-pyrrolidinyl)ethanamine		LCMS: Anal. Calcd. for $C_{42}H_{43}N_7O_2S$: 709; found: 710 $(M+H)^+$.
94-49	(1R)-N,N-dimethyl-2-((2S)-2-(5-(4'-(2-((2S)-1-(1-naphthylacetyl)-2-pyrrolidinyl)-1H-imidazol-5-yl)-4-biphenylyl)-1H-imidazol-2-yl)-1-pyrrolidinyl)-2-oxo-1-phenylethanamine		LCMS: Anal. Calcd. for $C_{48}H_{47}N_7O_2$: 753; found: 754 $(M+H)^+$.
94-50	(1R)-2-((2S)-2-(5-(4'-(2-((2S)-1-(1H-imidazol-5-ylacetyl)-2-pyrrolidinyl)-1H-imidazol-5-yl)-4-biphenylyl)-1H-imidazol-2-yl)-1-pyrrolidinyl)-N,N-dimethyl-2-oxo-1-phenylethanamine		LCMS: Anal. Calcd. for $C_{41}H_{43}N_9O_2$: 693; found: 694 $(M+H)^+$.
94-51	(1R)-2-((2S)-2-(5-(4'-(2-((2S)-1-((2-fluorophenyl)acetyl)-2-pyrrolidinyl)-1H-imidazol-5-yl)-4-biphenylyl)-1H-imidazol-2-yl)-1-pyrrolidinyl)-N,N-dimethyl-2-oxo-1-phenylethanamine		LCMS: Anal. Calcd. for $C_{44}H_{44}FN_7O_2$: 721; found: 722 $(M+H)^+$.
94-52	(1R)-2-((2S)-2-(5-(4'-(2-((2S)-1-((3-fluorophenyl)acetyl)-2-pyrrolidinyl)-1H-imidazol-5-yl)-4-biphenylyl)-1H-imidazol-2-yl)-1-pyrrolidinyl)-N,N-dimethyl-2-oxo-1-phenylethanamine		LCMS: Anal. Calcd. for $C_{44}H_{44}FN_7O_2$: 721; found: 722 $(M+H)^+$.

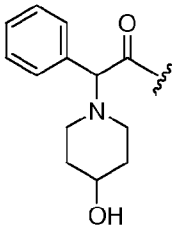
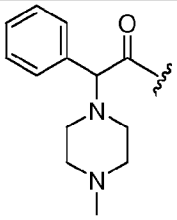
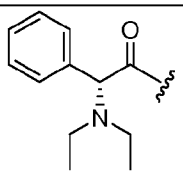
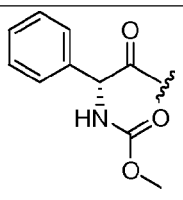
94-53	(1R)-2-((2S)-2-(5-(4'-(2-((2S)-1-((4-fluorophenyl)acetyl)-2-pyrrolidinyl)-1H-imidazol-5-yl)-4-biphenylyl)-1H-imidazol-2-yl)-1-pyrrolidinyl)-N,N-dimethyl-2-oxo-1-phenylethanamine		LCMS: Anal. Calcd. for $C_{44}H_{44}FN_7O_2$: 721; found: 722 $(M+H)^+$.
94-54	(1R)-2-((2S)-2-(5-(4'-(2-((2S)-1-(1-benzothiophen-3-ylacetyl)-2-pyrrolidinyl)-1H-imidazol-5-yl)-4-biphenylyl)-1H-imidazol-2-yl)-1-pyrrolidinyl)-N,N-dimethyl-2-oxo-1-phenylethanamine		LCMS: Anal. Calcd. for $C_{46}H_{45}N_7O_2S$: 759; found: 760 $(M+H)^+$.
94-55	(1R)-2-((2S)-2-(5-(4'-(2-((2S)-1-(1,2-benzisoxazol-3-ylacetyl)-2-pyrrolidinyl)-1H-imidazol-5-yl)-4-biphenylyl)-1H-imidazol-2-yl)-1-pyrrolidinyl)-N,N-dimethyl-2-oxo-1-phenylethanamine		LCMS: Anal. Calcd. for $C_{45}H_{44}N_8O_3$: 744; found: 745 $(M+H)^+$.
94-56	(1R)-2-((2S)-2-(5-(4'-(2-((2S)-1-(1H-indol-3-ylacetyl)-2-pyrrolidinyl)-1H-imidazol-5-yl)-4-biphenylyl)-1H-imidazol-2-yl)-1-pyrrolidinyl)-N,N-dimethyl-2-oxo-1-phenylethanamine		LCMS: Anal. Calcd. for $C_{46}H_{46}N_8O_2$: 742; found: 743 $(M+H)^+$.

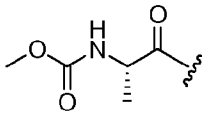
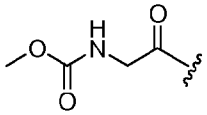
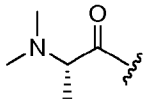
Examples 95-103



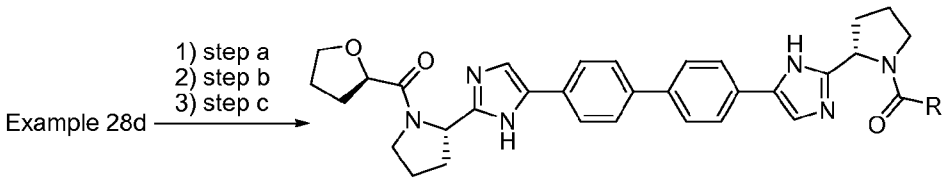
step a: Cap w/ cap-5 as in Example 28
step b: Same procedure as in conversion of Example 1d to 1e
step c: As in the last step of Example 1 using 1.1 equiv. of the appropriate carboxylic acid and HATU

Example	*Compound Name*		*Retention time (LC-Condition); homogeneity index MS data*
95	2-((2S)-1-((2R)-2-phenyl-2-(1-pyrrolidinyl)acetyl)-2-pyrrolidinyl)-5-(4'-(2-((2S)-1-((2S)-tetrahydro-2-furanylcarbonyl)-2-pyrrolidinyl)-1H-imidazol-5-yl)-4-biphenylyl)-1H-imidazole		1.16 minutes (Cond. 1); >98%; LC/MS: Anal. Calcd. for $[M+H]^+$ $C_{43}H_{48}N_7O_3$: 710.38; found 710.60
96	4-((1R)-2-oxo-1-phenyl-2-((2S)-2-(5-(4'-(2-((2S)-1-((2R)-2-phenyl-2-(1-pyrrolidinyl)acetyl)-2-pyrrolidinyl)-1H-imidazol-5-yl)-4-biphenylyl)-1H-imidazol-2-yl)-1-pyrrolidinyl)ethyl)morpholine	 *Cap-6*	1.82 minutes (Cond. 1); >98%; LC/MS: Anal. Calcd. for $[M+H]^+$ $C_{50}H_{55}N_8O_3$: 815.44; found 815.45; HRMS: Anal. Calcd. for $[M+H]^+$ $C_{50}H_{55}N_8O_3$: 815.4397; found 815.4395

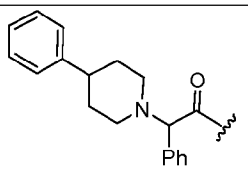
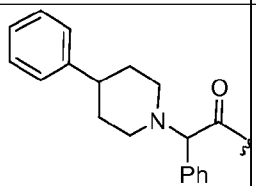
97	1-(2-oxo-1-phenyl-2-((2S)-2-(5-(4'-(2-((2S)-1-((2R)-2-phenyl-2-(1-pyrrolidinyl)acetyl)-2-pyrrolidinyl)-1H-imidazol-5-yl)-4-biphenylyl)-1H-imidazol-2-yl)-1-pyrrolidinyl)ethyl)-4-piperidinol	 A single diastereomer *Cap-8*	1.79 minutes (Cond. 2); >98%; LC/MS: Anal. Calcd. for $[M+H]^+$ $C_{51}H_{57}N_8O_3$: 829.46; found 829.43; HRMS: Anal. Calcd. for $[M+H]^+$ $C_{51}H_{57}N_8O_3$: 829.4554; found 829.4585
98	1-methyl-4-(2-oxo-1-phenyl-2-((2S)-2-(5-(4'-(2-((2S)-1-((2R)-2-phenyl-2-(1-pyrrolidinyl)acetyl)-2-pyrrolidinyl)-1H-imidazol-5-yl)-4-biphenylyl)-1H-imidazol-2-yl)-1-pyrrolidinyl)ethyl)piperazine	 A single diastereomer *Cap-17c*	1.84 minutes (Cond. 2); >98%; LC/MS: Anal. Calcd. for $[M+H]^+$ $C_{51}H_{58}N_9O_2$: 828.47; found 828.45; HRMS: Anal. Calcd. for $[M+H]^+$ $C_{51}H_{58}N_9O_2$: 828.4713; found 828.4722
99	(1R)-N,N-diethyl-2-oxo-1-phenyl-2-((2S)-2-(5-(4'-(2-((2S)-1-((2R)-2-phenyl-2-(1-pyrrolidinyl)acetyl)-2-pyrrolidinyl)-1H-imidazol-5-yl)-4-biphenylyl)-1H-imidazol-2-yl)-1-pyrrolidinyl)ethanamine	 *Cap-2*	1.86 minutes (Cond. 2); >98%; LC/MS: Anal. Calcd. for $[M+H]^+$ $C_{50}H_{57}N_8O_2$: 801.46; found 801.44; HRMS: Anal. Calcd. for $[M+H]^+$ $C_{50}H_{57}N_8O_2$: 801.4604; found 801.4595
100	methyl ((1R)-2-oxo-1-phenyl-2-((2S)-2-(5-(4'-(2-((2S)-1-((2R)-2-phenyl-2-(1-pyrrolidinyl)acetyl)-2-pyrrolidinyl)-1H-imidazol-5-yl)-	 *Cap-4*	1.93 minutes (Cond. 2); LC/MS: Anal. Calcd. for $[M+H]^+$ $C_{48}H_{51}N_8O_4$: 803.40; found 803.47 ;

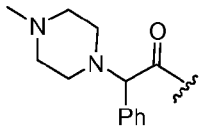
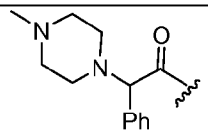
	4-biphenylyl)-1H-imidazol-2-yl)-1-pyrrolidinyl)ethyl)carbamate		HRMS: Anal. Calcd. for $[M+H]^+$ $C_{48}H_{51}N_8O_4$: 803.4033; found 803.4058
101	methyl ((1S)-1-methyl-2-oxo-2-((2S)-2-(5-(4'-(2-((2S)-1-((2R)-2-phenyl-2-(1-pyrrolidinyl)acetyl)-2-pyrrolidinyl)-1H-imidazol-5-yl)-4-biphenylyl)-1H-imidazol-2-yl)-1-pyrrolidinyl)ethyl)carbamate	 *Cap*-12	1.80 minutes (Cond. 2); LC/MS: Anal. Calcd. for $[M+H]^+$ $C_{43}H_{49}N_8O_4$: 741.39; found 741.33; HRMS: Anal. Calcd. for $[M+H]^+$ $C_{43}H_{49}N_8O_4$: 741.3877; found 741.3900
102	methyl (2-oxo-2-((2S)-2-(5-(4'-(2-((2S)-1-((2R)-2-phenyl-2-(1-pyrrolidinyl)acetyl)-2-pyrrolidinyl)-1H-imidazol-5-yl)-4-biphenylyl)-1H-imidazol-2-yl)-1-pyrrolidinyl)ethyl)carbamate		1.80 minutes (Cond. 2); LC/MS: Anal. Calcd. for $[M+H]^+$ $C_{42}H_{47}N_8O_4$: 727.37; found 727.24; HRMS: Anal. Calcd. for $[M+H]^+$ $C_{42}H_{47}N_8O_4$: 727.3720; found 727.3743
103	(2S)-N,N-dimethyl-1-oxo-1-((2S)-2-(5-(4'-(2-((2S)-1-((2R)-2-phenyl-2-(1-pyrrolidinyl)acetyl)-2-pyrrolidinyl)-1H-imidazol-5-yl)-4-biphenylyl)-1H-imidazol-2-yl)-1-pyrrolidinyl)-2-propanamine	 *Cap*-13	1.69 minutes (Cond. 2); LC/MS: Anal. Calcd. for $[M+H]^+$ $C_{43}H_{51}N_8O_2$: 711.41; found 711.37; HRMS: Anal. Calcd. for $[M+H]^+$ $C_{43}H_{51}N_8O_2$: 711.4135; found 711.4154

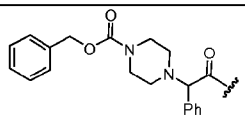
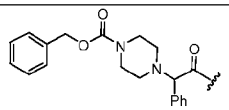
Examples 103-1 to 103-12

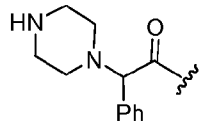
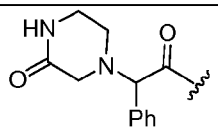
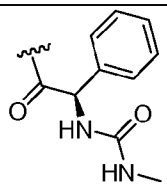


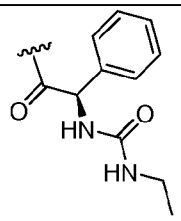
step a: Cap with (R)-2-tetrahydrofuroic acid as in Example 28
step b: Same procedure as in the conversion of Example 1d to 1e
step c: As in the last step of Example 1 using 1.1 equiv. of the appropriate carboxylic acid and HATU

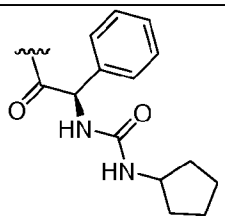
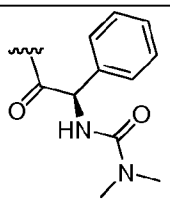
103-1	1-(2-oxo-1-phenyl-2-((2S)-2-(5-(4'-(2-((2S)-1-((2R)-tetrahydro-2-furanylcarbonyl)-2-pyrrolidinyl)-1H-imidazol-4-yl)-4-biphenylyl)-1H-imidazol-2-yl)-1-pyrrolidinyl)ethyl)-4-phenylpiperidine	 Diastereomer 1 *Cap-17d*	RT = 4.80 minutes; HPLC Xterra 4.6 X 50 mm, 0 to 100% B over 10 minutes, one minute hold time, A = 90% water, 10% methanol, 0.2% phosphoric acid, B = 10% water, 90% methanol, 0.2% phosphoric acid; LCMS: Anal. Calcd. for: $C_{50}H_{53}N_7O_3$ 800.03 Found: 800.49 $(M+H)^+$
103-2	1-(2-oxo-1-phenyl-2-((2S)-2-(5-(4'-(2-((2S)-1-((2R)-tetrahydro-2-furanylcarbonyl)-2-pyrrolidinyl)-1H-imidazol-4-yl)-4-biphenylyl)-1H-imidazol-2-yl)-1-pyrrolidinyl)ethyl)-4-phenylpiperidine	 Diastereomer 2 *Cap-17d*	RT = 4.59 minutes; HPLC Xterra 4.6 X 50 mm, 0 to 100% B over 10 minutes, one minute hold time, A = 90% water, 10% methanol, 0.2% phosphoric acid, B = 10% water, 90% methanol, 0.2%

			phosphoric acid; LCMS: Anal. Calcd. for: $C_{50}H_{53}N_7O_3$ 800.03 Found: 800.48 $(M+H)^+$
103-3	1-methyl-4-(2-oxo-1-phenyl-2-((2S)-2-(5-(4'-(2-((2S)-1-((2R)-tetrahydro-2-furanylcarbonyl)-2-pyrrolidinyl)-1H-imidazol-4-yl)-4-biphenylyl)-1H-imidazol-2-yl)-1-pyrrolidinyl)ethyl)piperazine	 Diastereomer 1 *Cap-17c*	RT = 3.36; HPLC Xterra 4.6 X 50 mm, 0 to 100% B over 10 minutes, one minute hold time, A = 90% water, 10% methanol, 0.2% phosphoric acid, B = 10% water, 90% methanol, 0.2% phosphoric acid; LCMS: Anal. Calcd. for: $C_{44}H_{50}N_8O_3$ 738.94 Found: 739.49 $(M+H)^+$
103-4	1-methyl-4-(2-oxo-1-phenyl-2-((2S)-2-(5-(4'-(2-((2S)-1-((2R)-tetrahydro-2-furanylcarbonyl)-2-pyrrolidinyl)-1H-imidazol-4-yl)-4-biphenylyl)-1H-imidazol-2-yl)-1-pyrrolidinyl)ethyl)piperazine	 Diastereomer 2 *Cap-17c*	RT = 3.47 minutes; HPLC Xterra 4.6 X 50 mm, 0 to 100% B over 10 minutes, one minute hold time, A = 90% water, 10% methanol, 0.2% phosphoric acid, B = 10% water, 90% methanol, 0.2% phosphoric acid; LCMS: Anal. Calcd. for: $C_{44}H_{50}N_8O_3$ 738.94

			Found: 739.51 $(M+H)^+$
103-5	benzyl 4-(2-oxo-1-phenyl-2-((2S)-2-(5-(4'-(2-((2S)-1-((2R)-tetrahydro-2-furanylcarbonyl)-2-pyrrolidinyl)-1H-imidazol-4-yl)-4-biphenylyl)-1H-imidazol-2-yl)-1-pyrrolidinyl)ethyl)-1-piperazinecarboxylate	 Diastereomer 1 *Cap-17a*	RT = 5.00 minutes; HPLC Xterra 4.6 X 50 mm, 0 to 100% B over 10 minutes, one minute hold time, A = 90% water, 10% methanol, 0.2% phosphoric acid, B = 10% water, 90% methanol, 0.2% phosphoric acid; LCMS: Anal. Calcd. for: $C_{51}H_{54}N_8O_5$ 859.05 Found: 859.51 $(M+H)^+$
103-6	benzyl 4-(2-oxo-1-phenyl-2-((2S)-2-(5-(4'-(2-((2S)-1-((2R)-tetrahydro-2-furanylcarbonyl)-2-pyrrolidinyl)-1H-imidazol-4-yl)-4-biphenylyl)-1H-imidazol-2-yl)-1-pyrrolidinyl)ethyl)-1-piperazinecarboxylate	 Diastereomer 2 *Cap-17a*	RT = 5.10 minutes; HPLC Xterra 4.6 X 50 mm, 0 to 100% B over 10 minutes, one minute hold time, A = 90% water, 10% methanol, 0.2% phosphoric acid, B = 10% water, 90% methanol, 0.2% phosphoric acid; LCMS: Anal. Calcd. for: $C_{51}H_{54}N_8O_5$ 859.05 Found: 859.49 $(M+H)^+$

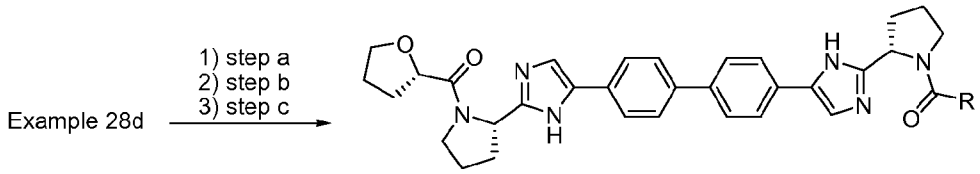
103-7	1-(2-oxo-1-phenyl-2-((2S)-2-(5-(4'-(2-((2S)-1-((2R)-tetrahydro-2-furanylcarbonyl)-2-pyrrolidinyl)-1H-imidazol-4-yl)-4-biphenylyl)-1H-imidazol-2-yl)-1-pyrrolidinyl)ethyl)piperazine	 prepared by hydrogenolyzing 103-5	RT = 3.61 minutes; HPLC Xterra 4.6 X 50 mm, 0 to 100% B over 10 minutes, one minute hold time, A = 90% water, 10% methanol, 0.2% phosphoric acid, B = 10% water, 90% methanol, 0.2% phosphoric acid; LCMS: Anal. Calcd. for: $C_{43}H_{48}N_8O_3$ 724.91 Found: 725.47 $(M+H)^+$
103-8	4-(2-oxo-1-phenyl-2-((2S)-2-(5-(4'-(2-((2S)-1-((2R)-tetrahydro-2-furanylcarbonyl)-2-pyrrolidinyl)-1H-imidazol-4-yl)-4-biphenylyl)-1H-imidazol-2-yl)-1-pyrrolidinyl)ethyl)-2-piperazinone	 *Cap-17b*	RT = 3.97; HPLC Xterra 4.6 X 50 mm, 0 to 100% B over 10 minutes, one minute hold time, A = 90% water, 10% methanol, 0.2% phosphoric acid, B = 10% water, 90% methanol, 0.2% phosphoric acid; LCMS: Anal. Calcd. for: $C_{43}H_{46}N_8O_4$ 738.90 Found: 739.56 $(M+H)^+$
103-9	1-methyl-3-((1R)-2-oxo-1-phenyl-2-((2S)-2-(4-(4'-(2-((2S)-1-((2R)-tetrahydro-2-furanylcarbonyl)-2-		HPLC XTERRA C-18 4.6 × 30 mm, 0 to 100% B over 4 minutes, 1 minute

	pyrrolidinyl)-1H-imidazol-4-yl)-4-biphenylyl)-1H-imidazol-2-yl)-1-pyrrolidinyl)ethyl)urea	employed *Cap-45*	hold time, A = 90% water, 10% methanol, 0.2% H_3PO_4, B = 10% water, 90% methanol, 0.2% H_3PO_4, RT = 1.81 minutes, 96% homogeneity index.; LCMS: Anal. Calcd. for $C_{41}H_{44}N_8O_4$: 712.84; found: 713.37 $(M+H)^+$; HRMS: Anal. Calcd. for $C_{41}H_{45}N_8O_4$ 713.3564; found: 713.3564 $(M+H)^+$.
103-10	1-ethyl-3-((1R)-2-oxo-1-phenyl-2-((2S)-2-(4-(4'-(2-((2S)-1-((2R)-tetrahydro-2-furanylcarbonyl)-2-pyrrolidinyl)-1H-imidazol-4-yl)-4-biphenylyl)-1H-imidazol-2-yl)-1-pyrrolidinyl)ethyl)urea	 employed *Cap-46*	HPLC XTERRA C-18 4.6 × 30 mm, 0 to 100% B over 2 minutes, 1 minute hold time, A = 90% water, 10% methanol, 0.2% H_3PO_4, B = 10% water, 90% methanol, 0.2% H_3PO_4, RT = 1.88 minutes, 95% homogeneity index; LCMS: Anal. Calcd. for $C_{42}H_{46}N_8O_4$: 726.87; found: 727.71 $(M+H)^+$; HRMS: Anal. Calcd. for $C_{42}H_{47}N_8O_4$ 727.3720; found:

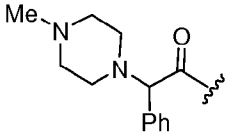
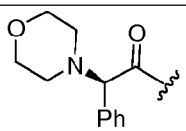
			727.3695 $(M+H)^+$.
103-11	1-cyclopentyl-3-((1R)-2-oxo-1-phenyl-2-((2S)-2-(4-(4'-(2-((2S)-1-((2R)-tetrahydro-2-furanylcarbonyl)-2-pyrrolidinyl)-1H-imidazol-4-yl)-4-biphenylyl)-1H-imidazol-2-yl)-1-pyrrolidinyl)ethyl)urea	 employed *Cap-48*	HPLC XTERRA C-18 4.6 × 30 mm, 0 to 100% B over 2 minutes, 1 minute hold time, A = 90% water, 10% methanol, 0.2% H_3PO_4, B = 10% water, 90% methanol, 0.2% H_3PO_4, RT = 2.11 minutes, 96% homogeneity index; LCMS: Anal. Calcd. for $C_{45}H_{50}N_8O_4$: 766.93; found: 767.45 $(M+H)^+$; HRMS: Anal. Calcd. for $C_{45}H_{51}N_8O_4$ 767.4033; found: 767.4032 $(M+H)^+$.
103-12	1,1-dimethyl-3-((1R)-2-oxo-1-phenyl-2-((2S)-2-(4-(4'-(2-((2S)-1-((2R)-tetrahydro-2-furanylcarbonyl)-2-pyrrolidinyl)-1H-imidazol-4-yl)-4-biphenylyl)-1H-imidazol-2-yl)-1-pyrrolidinyl)ethyl)urea	 employed *Cap-47*	HPLC XTERRA C-18 4.6 × 30 mm, 0 to 100% B over 2 minutes, 1 minute hold time, A = 90% water, 10% methanol, 0.2% H_3PO_4, B = 10% water, 90% methanol, 0.2% H_3PO_4, RT = 1.87 minutes, 97% homogeneity index; LCMS: Anal. Calcd. for $C_{42}H_{46}N_8O_4$:

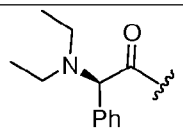
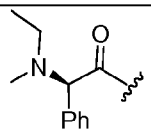
			726.87; found: 727.38 $(M+H)^+$; HRMS: Anal. Calcd. for $C_{42}H_{47}N_8O_4$ 727.3720; found: 727.3723 $(M+H)^+$.

Examples 104-107

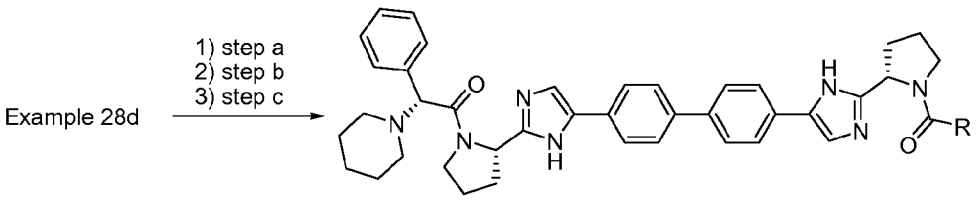


step a: Cap with (S)-2-tetrahydrofuroic acid as in Example 28
step b: Same procedure as in the conversion of Example 1d to Example 1e
step c: As in the last step of Example 1 using 1.1 equiv. of the appropriate carboxylic acid and HATU

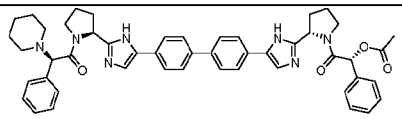
Example	*Compound Name*		*Retention time (LC-Condition); homogeneity index MS data*
104	1-methyl-4-(2-oxo-1-phenyl-2-((2S)-2-(5-(4'-(2-((2S)-1-((2S)-tetrahydro-2-furanylcarbonyl)-2-pyrrolidinyl)-1H-imidazol-5-yl)-4-biphenylyl)-1H-imidazol-2-yl)-1-pyrrolidinyl)ethyl)piperazine	 A single diastereomer *Cap-17c*	1.12 minutes (Cond. 1); >98%; LC/MS: Anal. Calcd. for $[M+H]^+$ $C_{44}H_{51}N_8O_3$: 739.41; found 739.63; HRMS: Anal. Calcd. for $[M+H]^+$ $C_{44}H_{51}N_8O_3$: 739.4084; found 739.4054
105	4-((1R)-2-oxo-1-phenyl-2-((2S)-2-(5-(4'-(2-((2S)-1-((2S)-tetrahydro-2-furanylcarbonyl)-2-pyrrolidinyl)-1H-imidazol-5-	 *Cap-6*	1.13 minutes (Cond. 1); >98%; LC/MS: Anal. Calcd. for $[M+H]^+$ $C_{43}H_{48}N_7O_4$:

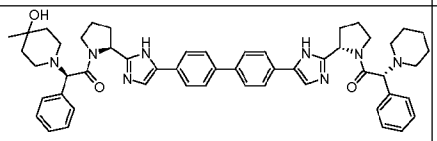
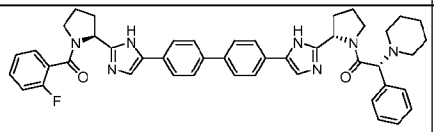
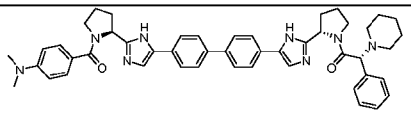
	yl)-4-biphenylyl)-1H-imidazol-2-yl)-1-pyrrolidinyl)ethyl)morpholine		726.38; found 726.63; HRMS: Anal. Calcd. for $[M+H]^+$ $C_{43}H_{48}N_7O_4$: 726.3768; found 726.3803
106	(1R)-N,N-diethyl-2-oxo-1-phenyl-2-((2S)-2-(5-(4'-(2-((2S)-1-((2S)-tetrahydro-2-furanylcarbonyl)-2-pyrrolidinyl)-1H-imidazol-5-yl)-4-biphenylyl)-1H-imidazol-2-yl)-1-pyrrolidinyl)ethanamine	 *Cap-2*	1.12 minutes (Cond. 1); 97%; LC/MS: Anal. Calcd. for $[M+H]^+$ $C_{43}H_{50}N_7O_3$: 712.40; found 712.45; HRMS: Anal. Calcd. for $[M+H]^+$ $C_{43}H_{50}N_7O_3$: 712.3975; found 712.3998
107	(1R)-N-ethyl-N-methyl-2-oxo-1-phenyl-2-((2S)-2-(5-(4'-(2-((2S)-1-((2S)-tetrahydro-2-furanylcarbonyl)-2-pyrrolidinyl)-1H-imidazol-5-yl)-4-biphenylyl)-1H-imidazol-2-yl)-1-pyrrolidinyl)ethanamine	 *Cap-3*	1.10 minutes (Cond. 1); >98%; LC/MS: Anal. Calcd. for $[M+H]^+$ $C_{42}H_{48}N_7O_3$: 698.38; found 698.45; HRMS: Anal. Calcd. for $[M+H]^+$ $C_{42}H_{48}N_7O_3$: 698.3819; 698.3823

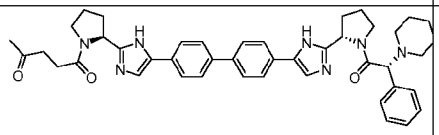
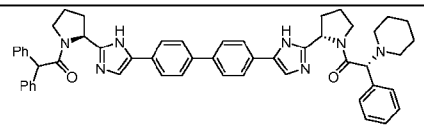
Examples 107-1 to 107-30

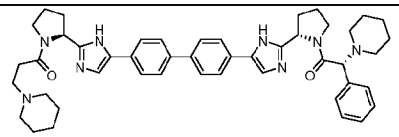
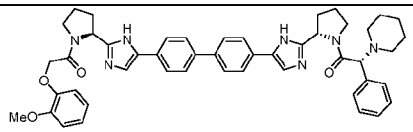
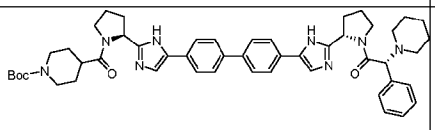


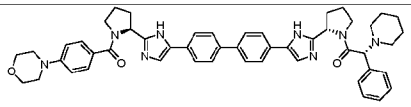
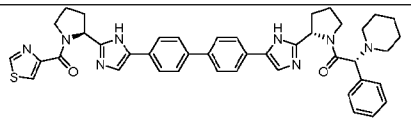
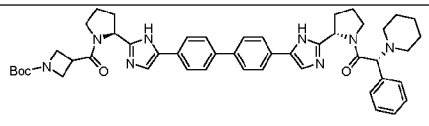
step a: Cap with cap-14 as in Example 28
step b: Same procedure as in the conversion of Example 1d to 1e
step c: As in the last step of Example 1 using 1.1 equiv. of the appropriate carboxylic acid and HATU

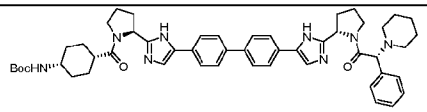
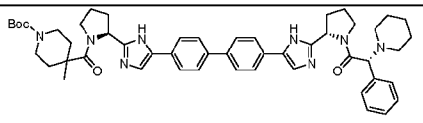
Example Number	*Compound Name*	*Structure*	*Data*
Example 107-1	(1S)-2-oxo-1-phenyl-2-((2S)-2-(5-(4'-(2-((2S)-1-((2R)-2-phenyl-2-(1-piperidinyl)acetyl)-2-pyrrolidinyl)-1H-imidazol-5-yl)-4-biphenylyl)-1H-imidazol-2-yl)-1-pyrrolidinyl)ethyl acetate		^{1}HNMR (400 MHz, $CDCl_3$) δ 7.63-7.85 (m, 8H), 7.48- 7.54 (m, 2H), 7.26- 7.46 (m, 7H), 6.94- 7.17 (m, 3H), 6.22 and 6.18 (s, 1H, rotamers, 1:1), 5.99 and 5.68 (s, 1H, rotamers, 1:1), 5.61 and 5.54 (d, J = 7.8 Hz, 1H, rotamers, 1:1), 5.20- 5.23 and 5.10- 5.13 (m, 1H, rotamers, 1:1), 4.46 and 4.43 (s, 1H, rotamers, 1:1), 3.97-4.06 (m, 1H), 3.89- 3.93 and 3.78- 3.84 (m, 1H, rotamers, 1:1), 3.63- 3.72 and 3.46- 3.60 (m, 1H, rotamers, 1:1), 3.23-3.32 (m, 2H), 2.41-2.59 (m, 4H), 2.13- 2.26 (m, 2H), 2.11 and 2.10 (s, 3H, rotamers, 1:1), 2.05-2.09 (m, 2H), 1.97-1.98 (m, 1H), 1.82-1.90 (m, 1H), 1.58 (br s, 4H),

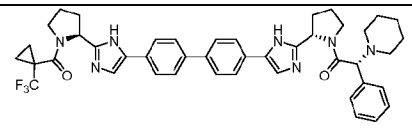
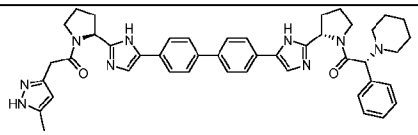
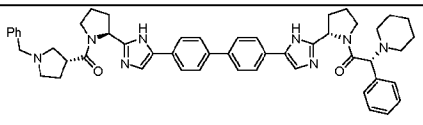
			1.45 (br s, 2H); LCMS: Anal. Calcd. for $C_{49}H_{51}N_7O_4$: 801; found: 802 $(M+H)^+$.
Example 107-2	4-methyl-1-((1R)-2-oxo-1-phenyl-2-((2S)-2-(5-(4'-(2-((2S)-1-((2R)-2-phenyl-2-(1-piperidinyl)acetyl)-2-pyrrolidinyl)-1H-imidazol-5-yl)-4-biphenylyl)-1H-imidazol-2-yl)-1-pyrrolidinyl)ethyl)-4-piperidinol		LCMS: Anal. Calcd. for $C_{53}H_{60}N_8O_3$: 856; found: 857 $(M+H)^+$.
Example 107-3	1-((1R)-2-((2S)-2-(5-(4'-(2-((2S)-1-(2-fluorobenzoyl)-2-pyrrolidinyl)-1H-imidazol-5-yl)-4-biphenylyl)-1H-imidazol-2-yl)-1-pyrrolidinyl)-2-oxo-1-phenylethyl)piperidine		LCMS: Anal. Calcd. for $C_{46}H_{56}FN_7O_2$: 747; found: 748 $(M+H)^+$.
Example 107-4	N,N-dimethyl-4-(((2S)-2-(5-(4'-(2-((2S)-1-((2R)-		LCMS: Anal. Calcd. for $C_{48}H_{52}N_8O_2$: 772;

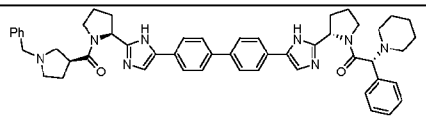
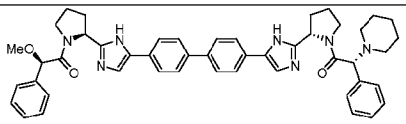
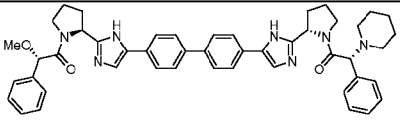
	2-phenyl-2-(1-piperidinyl)acetyl)-2-pyrrolidinyl)-1H-imidazol-5-yl)-4-biphenylyl)-1H-imidazol-2-yl)-1-pyrrolidinyl)carbonyl)aniline		found: 773 $(M+H)^+$.
Example 107-5	5-oxo-5-((2S)-2-(5-(4'-(2-((2S)-1-((2R)-2-phenyl-2-(1-piperidinyl)acetyl)-2-pyrrolidinyl)-1H-imidazol-5-yl)-4-biphenylyl)-1H-imidazol-2-yl)-1-pyrrolidinyl)-2-pentanone		LCMS: Anal. Calcd. for $C_{44}H_{49}N_7O_3$: 723; found: 724 $(M+H)^+$.
Example 107-6	1-((1R)-2-((2S)-2-(5-(4'-(2-((2S)-1-(diphenylacetyl)-2-pyrrolidinyl)-1H-imidazol-5-yl)-4-biphenylyl)-1H-imidazol-2-yl)-1-pyrrolidinyl)-2-oxo-1-phenylethyl)piperidine		LCMS: Anal. Calcd. for $C_{53}H_{53}N_7O_2$: 819; found: 820 $(M+H)^+$.

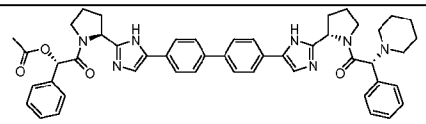
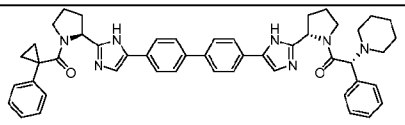
Example 107-7	1-(3-oxo-3-((2S)-2-(5-(4'-(2-((2S)-1-((2R)-2-phenyl-2-(1-piperidinyl)acetyl)-2-pyrrolidinyl)-1H-imidazol-5-yl)-4-biphenylyl)-1H-imidazol-2-yl)-1-pyrrolidinyl)propyl)piperidine		LCMS: Anal. Calcd. for $C_{47}H_{56}N_8O_2$: 764; found: 765 $(M+H)^+$.
Example 107-8	1-((1R)-2-((2S)-2-(5-(4'-(2-((2S)-1-((2-methoxyphenoxy)acetyl)-2-pyrrolidinyl)-1H-imidazol-5-yl)-4-biphenylyl)-1H-imidazol-2-yl)-1-pyrrolidinyl)-2-oxo-1-phenylethyl)piperidine		LCMS: Anal. Calcd. for $C_{48}H_{51}N_7O_4$: 789; found: 790 $(M+H)^+$.
Example 107-9	tert-butyl 4-(((2S)-2-(5-(4'-(2-((2S)-1-((2R)-2-phenyl-2-(1-piperidinyl)acetyl)-2-pyrrolidinyl)-1H-imidazol-5-yl)-4-biphenylyl)-1H-imidazol-2-yl)-1-		LCMS: Anal. Calcd. for $C_{50}H_{60}N_8O_4$: 836; found: 837 $(M+H)^+$.

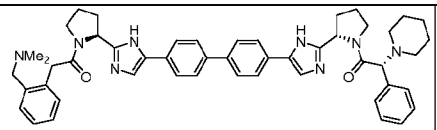
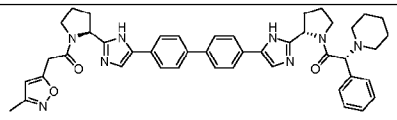
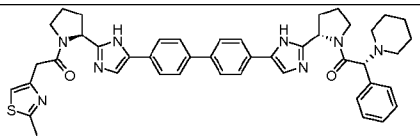
	pyrrolidinyl)carbonyl)-1-piperidinecarboxylate		
Example 107-10	4-(4-(((2S)-2-(5-(4'-(2-((2S)-1-((2R)-2-phenyl-2-(1-piperidinyl)acetyl)-2-pyrrolidinyl)-1H-imidazol-5-yl)-4-biphenylyl)-1H-imidazol-2-yl)-1-pyrrolidinyl)carbonyl)phenyl)morpholine		LCMS: Anal. Calcd. for $C_{50}H_{54}N_8O_3$: 814; found: 815 $(M+H)^+$.
Example 107-11	1-((1R)-2-oxo-1-phenyl-2-((2S)-2-(5-(4'-(2-((2S)-1-(1,3-thiazol-4-ylcarbonyl)-2-pyrrolidinyl)-1H-imidazol-5-yl)-4-biphenylyl)-1H-imidazol-2-yl)-1-pyrrolidinyl)ethyl)piperidine		LCMS: Anal. Calcd. for $C_{43}H_{44}N_8O_2S$: 736; found: 737$(M+H)^+$.
Example 107-12	tert-butyl 3-(((2S)-2-(5-(4'-(2-((2S)-1-((2R)-2-phenyl-2-(1-piperidinyl)acetyl)-2-pyrrolidinyl)-1H-imidazol-5-		LCMS: Anal. Calcd. for $C_{48}H_{56}N_8O_4$: 808; found: 809 $(M+H)^+$.

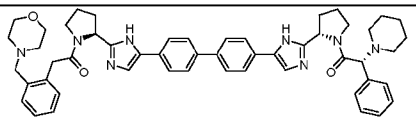
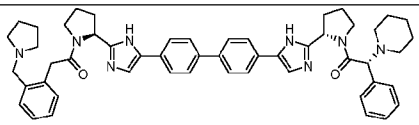
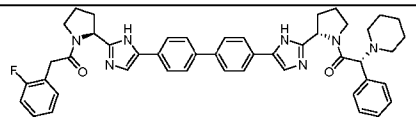
	yl)-4-biphenylyl)-1H-imidazol-2-yl)-1-pyrrolidinyl)carbonyl)-1-azetidinecarboxylate		
Example 107-13	tert-butyl (cis-4-(((2S)-2-(5-(4'-(2-((2S)-1-((2R)-2-phenyl-2-(1-piperidinyl)acetyl)-2-pyrrolidinyl)-1H-imidazol-5-yl)-4-biphenylyl)-1H-imidazol-2-yl)-1-pyrrolidinyl)carbonyl)cyclohexyl)carbamate		LCMS: Anal. Calcd. for $C_{51}H_{62}N_8O_4$: 850; found: 851 $(M+H)^+$.
Example 107-14	tert-butyl 4-methyl-4-(((2S)-2-(5-(4'-(2-((2S)-1-((2R)-2-phenyl-2-(1-piperidinyl)acetyl)-2-pyrrolidinyl)-1H-imidazol-5-yl)-4-biphenylyl)-1H-imidazol-2-yl)-1-pyrrolidinyl)carbonyl)-1-piperidinecarboxylate		LCMS: Anal. Calcd. for $C_{51}H_{62}N_8O_4$: 850; found: 851 $(M+H)^+$.

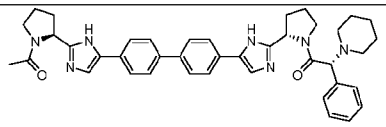
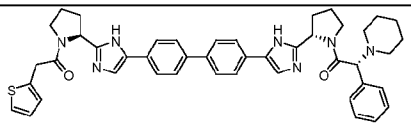
Example 107-15	1-((1R)-2-oxo-1-phenyl-2-((2S)-2-(5-(4'-(2-((2S)-1-((1-(trifluoromethyl)cyclopropyl)carbonyl)-2-pyrrolidinyl)-1H-imidazol-5-yl)-4-biphenylyl)-1H-imidazol-2-yl)-1-pyrrolidinyl)ethyl)piperidine		LCMS: Anal. Calcd. for $C_{44}H_{46}F_3N_7O_2$: 761; found: 762 $(M+H)^+$.
Example 107-16	1-((1R)-2-((2S)-2-(5-(4'-(2-((2S)-1-((5-methyl-1H-pyrazol-3-yl)acetyl)-2-pyrrolidinyl)-1H-imidazol-5-yl)-4-biphenylyl)-1H-imidazol-2-yl)-1-pyrrolidinyl)-2-oxo-1-phenylethyl)piperidine		LCMS: Anal. Calcd. for $C_{45}H_{49}N_9O_2$: 747; found: 748 $(M+H)^+$.
Example 107-17	1-((1R)-2-((2S)-2-(5-(4'-(2-((2S)-1-(((3R)-1-benzyl-3-pyrrolidinyl)carbonyl)-2-pyrrolidinyl)-1H-imidazol-5-yl)-4-biphenylyl)-1H-		LCMS: Anal. Calcd. for $C_{51}H_{56}N_8O_2$: 812; found: 813 $(M+H)^+$.

	imidazol-2-yl)-1-pyrrolidinyl)-2-oxo-1-phenylethyl)piperidine		
Example 107-18	1-((1R)-2-((2S)-2-(5-(4'-(2-((2S)-1-(((3S)-1-benzyl-3-pyrrolidinyl)carbonyl)-2-pyrrolidinyl)-1H-imidazol-5-yl)-4-biphenylyl)-1H-imidazol-2-yl)-1-pyrrolidinyl)-2-oxo-1-phenylethyl)piperidine		LCMS: Anal. Calcd. for $C_{51}H_{56}N_8O_2$: 812; found: 813 $(M+H)^+$.
Example 107-19	1-((1R)-2-((2S)-2-(5-(4'-(2-((2S)-1-((2R)-2-methoxy-2-phenylacetyl)-2-pyrrolidinyl)-1H-imidazol-5-yl)-4-biphenylyl)-1H-imidazol-2-yl)-1-pyrrolidinyl)-2-oxo-1-phenylethyl)piperidine		LCMS: Anal. Calcd. for $C_{48}H_{51}N_7O_3$: 773; found: 774 $(M+H)^+$.
Example 107-20	1-((1R)-2-((2S)-2-(5-(4'-(2-((2S)-1-((2S)-2-		LCMS: Anal. Calcd. for $C_{48}H_{51}N_7O_3$: 773;

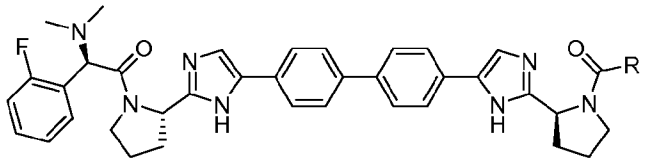
	methoxy-2-phenylacetyl)-2-pyrrolidinyl)-1H-imidazol-5-yl)-4-biphenylyl)-1H-imidazol-2-yl)-1-pyrrolidinyl)-2-oxo-1-phenylethyl)piperidine		found: 774 $(M+H)^+$.
Example 107-21	(1R)-2-oxo-1-phenyl-2-((2S)-2-(5-(4'-(2-((2S)-1-((2R)-2-phenyl-2-(1-piperidinyl)acetyl)-2-pyrrolidinyl)-1H-imidazol-5-yl)-4-biphenylyl)-1H-imidazol-2-yl)-1-pyrrolidinyl)ethyl acetate		LCMS: Anal. Calcd. for $C_{49}H_{51}N_7O_4$: 801; found: 802 $(M+H)^+$.
Example 107-22	1-((1R)-2-oxo-1-phenyl-2-((2S)-2-(5-(4'-(2-((2S)-1-((1-phenylcyclopropyl)carbonyl)-2-pyrrolidinyl)-1H-imidazol-5-yl)-4-biphenylyl)-1H-imidazol-2-yl)-1-pyrrolidinyl)ethyl)piperidine		LCMS: Anal. Calcd. for $C_{49}H_{51}N_7O_2$: 769; found: 770 $(M+H)^+$.

Example 107-23	N,N-dimethyl-1-(2-(2-oxo-2-((2S)-2-(5-(4'-(2-((2S)-1-((2R)-2-phenyl-2-(1-piperidinyl)acetyl)-2-pyrrolidinyl)-1H-imidazol-5-yl)-4-biphenylyl)-1H-imidazol-2-yl)-1-pyrrolidinyl)ethyl)phenyl)methanamine		LCMS: Anal. Calcd. for $C_{50}H_{56}N_8O_2$: 800; found: 801 $(M+H)^+$.
Example 107-24	1-((1R)-2-((2S)-2-(5-(4'-(2-((2S)-1-((3-methyl-5-isoxazolyl)acetyl)-2-pyrrolidinyl)-1H-imidazol-5-yl)-4-biphenylyl)-1H-imidazol-2-yl)-1-pyrrolidinyl)-2-oxo-1-phenylethyl)piperidine		LCMS: Anal. Calcd. for $C_{45}H_{48}N_8O_3$: 748; found: 749 $(M+H)^+$.
Example 107-25	1-((1R)-2-((2S)-2-(5-(4'-(2-((2S)-1-((2-methyl-1,3-thiazol-4-yl)acetyl)-2-pyrrolidinyl)-1H-imidazol-5-yl)-4-biphenylyl)-1H-		LCMS: Anal. Calcd. for $C_{45}H_{48}N_8O_2S$: 764; found: 765 $(M+H)^+$.

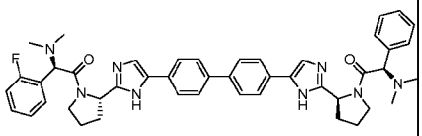
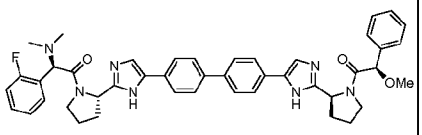
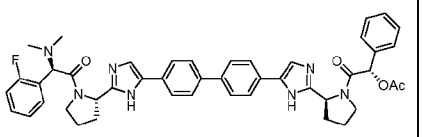
	imidazol-2-yl)-1-pyrrolidinyl)-2-oxo-1-phenylethyl)piperidine		
Example 107-26	4-(2-(2-oxo-2-((2S)-2-(5-(4'-(2-((2S)-1-((2R)-2-phenyl-2-(1-piperidinyl)acetyl)-2-pyrrolidinyl)-1H-imidazol-5-yl)-4-biphenylyl)-1H-imidazol-2-yl)-1-pyrrolidinyl)ethyl)benzyl)morpholine		LCMS: Anal. Calcd. for $C_{52}H_{58}N_8O_3$: 842; found: 843 $(M+H)^+$.
Example 107-27	1-((1R)-2-oxo-1-phenyl-2-((2S)-2-(5-(4'-(2-((2S)-1-((2-(1-pyrrolidinylmethyl)phenyl)acetyl)-2-pyrrolidinyl)-1H-imidazol-5-yl)-4-biphenylyl)-1H-imidazol-2-yl)-1-pyrrolidinyl)ethyl)piperidine		LCMS: Anal. Calcd. for $C_{52}H_{58}N_8O_2$: 826; found: 827 $(M+H)^+$.
Example 107-28	1-((1R)-2-((2S)-2-(5-(4'-(2-((2S)-1-((2-fluorophenyl)acet		LCMS: Anal. Calcd. for $C_{47}H_{48}FN_7O_2$: 800; found: 801

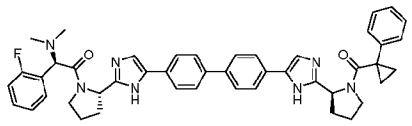
	yl)-2-pyrrolidinyl)-1H-imidazol-5-yl)-4-biphenylyl)-1H-imidazol-2-yl)-1-pyrrolidinyl)-2-oxo-1-phenylethyl)piperidine		$(M+H)^+$.
Example 107-29	1-((1R)-2-((2S)-2-(5-(4'-(2-((2S)-1-acetyl-2-pyrrolidinyl)-1H-imidazol-5-yl)-4-biphenylyl)-1H-imidazol-2-yl)-1-pyrrolidinyl)-2-oxo-1-phenylethyl)piperidine		LCMS: Anal. Calcd. for $C_{41}H_{45}FN_7O_2$: 667; found: 668 $(M+H)^+$.
Example 107-30	1-((1R)-2-oxo-1-phenyl-2-((2S)-2-(5-(4'-(2-((2S)-1-(2-thienylacetyl)-2-pyrrolidinyl)-1H-imidazol-5-yl)-4-biphenylyl)-1H-imidazol-2-yl)-1-pyrrolidinyl)ethyl)piperidine		LCMS: Anal. Calcd. for $C_{45}H_{47}N_7O_2S$: 749; found: 750 $(M+H)^+$.

Example 107-31 to 107-34

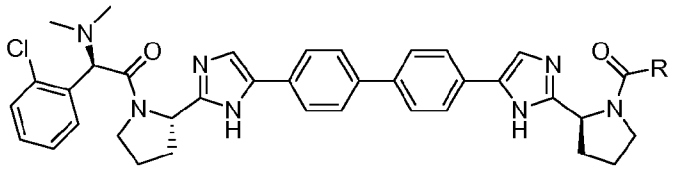


Examples 107-31 through 107-34 were prepared in similar fashion to example 28. *Cap*-38 was appended to intermediate 28d, the Boc carbamate was removed with TFA or HCl and the appropriate carboxylic acid was coupled.

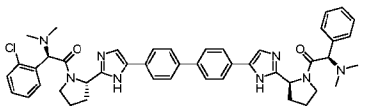
Example	*Compound Name*	*Structure*	*Data*
Example 107-31	(1R)-2-((2S)-2-(5-(4'-(2-((2S)-1-((2R)-2-(dimethylamino)-2-(2-fluorophenyl)acetyl)-2-pyrrolidinyl)-1H-imidazol-5-yl)-4-biphenylyl)-1H-imidazol-2-yl)-1-pyrrolidinyl)-N,N-dimethyl-2-oxo-1-phenylethanamine		LCMS: Anal. Calcd. for $C_{46}H_{49}FN_8O_2$: 764; found: 765 $(M+H)^+$.
Example 107-32	(1R)-1-(2-fluorophenyl)-2-((2S)-2-(5-(4'-(2-((2S)-1-((2R)-2-methoxy-2-phenylacetyl)-2-pyrrolidinyl)-1H-imidazol-5-yl)-4-biphenylyl)-1H-imidazol-2-yl)-1-pyrrolidinyl)-N,N-dimethyl-2-oxoethanamine		LCMS: Anal. Calcd. for $C_{45}H_{46}FN_7O_3$: 751; found: 752 $(M+H)^+$.
Example 107-33	(1R)-2-((2S)-2-(5-(4'-(2-((2S)-1-((2R)-2-(dimethylamino)-2-(2-fluorophenyl)acetyl)-2-pyrrolidinyl)-1H-imidazol-5-yl)-4-biphenylyl)-1H-		LCMS: Anal. Calcd. for $C_{46}H_{46}FN_7O_4$: 779; found: 780

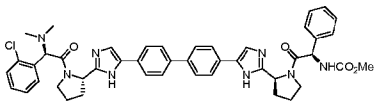
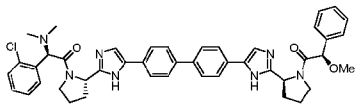
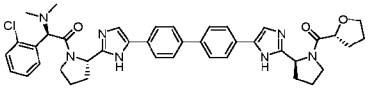
	imidazol-2-yl)-1-pyrrolidinyl)-2-oxo-1-phenylethyl acetate		$(M+H)^+$.
Example 107-34	(1R)-1-(2-fluorophenyl)-N,N-dimethyl-2-oxo-2-((2S)-2-(5-(4'-(2-((2S)-1-((1-phenylcyclopropyl)carbonyl)-2-pyrrolidinyl)-1H-imidazol-5-yl)-4-biphenylyl)-1H-imidazol-2-yl)-1-pyrrolidinyl)ethanamine		LCMS: Anal. Calcd. for $C_{46}H_{46}FN_7O_2$: 747; found: 748 $(M+H)^+$.

Example 107-35 to 107-38

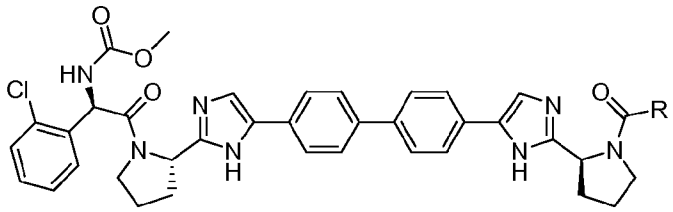


Examples 107-35 through 107-38 were prepared in similar fashion to example 28. *Cap*-39 was appended to intermediate 28d, the Boc carbamate was removed with TFA or HCl and the appropriate carboxylic acid was coupled.

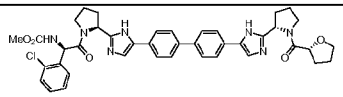
Example	*Compound Name*	*Structure*	*Data*
Example 107-35	(1R)-1-(2-chlorophenyl)-2-((2S)-2-(5-(4'-(2-((2S)-1-((2R)-2-(dimethylamino)-2-phenylacetyl)-2-pyrrolidinyl)-1H-imidazol-5-yl)-4-biphenylyl)-1H-imidazol-2-yl)-1-pyrrolidinyl)-N,N-dimethyl-2-oxoethanamine		LCMS: Anal. Calcd. for $C_{46}H_{49}ClN_8O_2$: 780; found: 781 $(M+H)^+$.

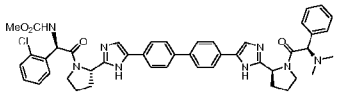
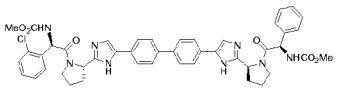
Example 107-36	methyl ((1R)-2-((2S)-2-(5-(4'-(2-((2S)-1-((2R)-2-(2-chlorophenyl)-2-(dimethylamino)acetyl)-2-pyrrolidinyl)-1H-imidazol-5-yl)-4-biphenylyl)-1H-imidazol-2-yl)-1-pyrrolidinyl)-2-oxo-1-phenylethyl)carbamate		LCMS: Anal. Calcd. for $C_{46}H_{47}ClN_8O_4$: 810; found: 811 $(M+H)^+$.
Example 107-37	(1R)-1-(2-chlorophenyl)-2-((2S)-2-(5-(4'-(2-((2S)-1-((2R)-2-methoxy-2-phenylacetyl)-2-pyrrolidinyl)-1H-imidazol-5-yl)-4-biphenylyl)-1H-imidazol-2-yl)-1-pyrrolidinyl)-N,N-dimethyl-2-oxoethanamine		LCMS: Anal. Calcd. for $C_{45}H_{46}ClN_7O_3$: 767; found: 768 $(M+H)^+$.
Example 107-38	(1R)-1-(2-chlorophenyl)-N,N-dimethyl-2-oxo-2-((2S)-2-(5-(4'-(2-((2S)-1-((2R)-tetrahydro-2-furanylcarbonyl)-2-pyrrolidinyl)-1H-imidazol-5-yl)-4-biphenylyl)-1H-imidazol-2-yl)-1-pyrrolidinyl)ethanamine		LCMS: Anal. Calcd. for $C_{41}H_{44}ClN_7O_3$: 717; found: 718 $(M+H)^+$.

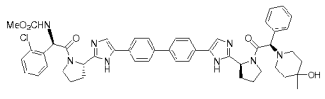
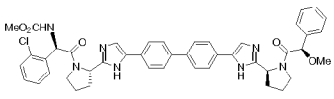
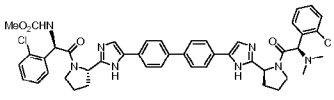
Example 107-39 to 107-43



Examples 107-39 through 107-44 were prepared in similar fashion to example 28. *Cap*-40 was appended to intermediate 28d, the Boc carbamate was removed with TFA or HCl and the appropriate carboxylic acid was coupled.

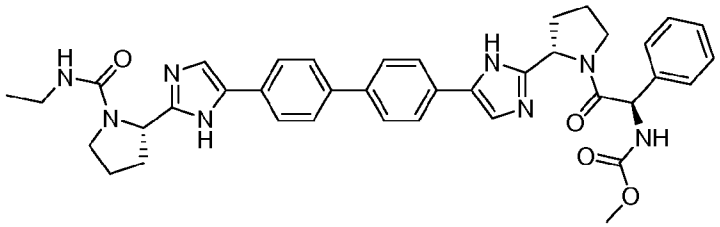
Example	*Compound Name*	*Structure*	*Data*
Example 107-39	methyl ((1R)-1-(2-chlorophenyl)-2-oxo-2-((2S)-2-(5-(4'-(2-((2S)-1-((2R)-tetrahydro-2-furanylcarbonyl)-2-pyrrolidinyl)-1H-imidazol-5-yl)-4-biphenylyl)-1H-imidazol-2-yl)-1-pyrrolidinyl)ethyl)carbamate		^{1}HNMR (400 MHz, CD_3OD) δ 7.58-7.77 (m, 8H), 7.42- 7.55 (m, 2H), 7.19-7.39 (m, 4H), 5.94 and 5.89 (s, 1H, rotamers, 1:1), 5.80 and 5.61 (s, 1H, rotamers, 1:1), 5.43-5.47 and 5.35-5.38 (m, 1H, rotamers, 1:1), 5.20-5.24 (m, 1H), 5.15- 5.18 (m, 1H), 4.67-4.70 and 4.39-4.42 (m, 1H, rotamers, 1:1), 3.92-3.98 (m, 1H), 3.85-3.90 (m, 1H), 3.69-3.84 (m, 2H),

			3.64 and 3.63 (s, 3H, rotamers, 1:1), 3.53-3.59 (m, 1H), 2.35-2.46 (m, 1H), 2.21-2.29 (m, 2H), 2.06-2.17 (m, 3H), 1.84-2.01 (m, 4H), 1.66-1.76 and 1.41-1.47 (m, 1H, rotamers, 1:1); LCMS: Anal. Calcd. for $C_{41}H_{42}ClN_7O_5$: 747; found: 748 $(M+H)^+$.
Example 107-40	methyl ((1R)-1-(2-chlorophenyl)-2-((2S)-2-(5-(4'-(2-((2S)-1-((2R)-2-(dimethylamino)-2-phenylacetyl)-2-pyrrolidinyl)-1H-imidazol-5-yl)-4-biphenylyl)-1H-imidazol-2-yl)-1-pyrrolidinyl)-2-oxoethyl)carbamate		LCMS: Anal. Calcd. for $C_{46}H_{47}ClN_8O_4$: 810; found: 811 $(M+H)^+$.
Example 107-41	methyl ((1R)-2-((2S)-2-(5-(4'-(2-((2S)-1-((2R)-2-(2-chlorophenyl)-2-((methoxycarbonyl)amino)acetyl)-2-pyrrolidinyl)-1H-imidazol-5-yl)-4-biphenylyl)-1H-imidazol-2-yl)-1-pyrrolidinyl)-2-oxo-1-		LCMS: Anal. Calcd. for $C_{46}H_{45}ClN_8O_6$: 840; found: 841 $(M+H)^+$.

	phenylethyl)carbamate		
Example 107-42	methyl ((1R)-1-(2-chlorophenyl)-2-((2S)-2-(5-(4'-(2-((2S)-1-((2R)-2-(4-hydroxy-4-methyl-1-piperidinyl)-2-phenylacetyl)-2-pyrrolidinyl)-1H-imidazol-5-yl)-4-biphenylyl)-1H-imidazol-2-yl)-1-pyrrolidinyl)-2-oxoethyl)carbamate		LCMS: Anal. Calcd. for $C_{50}H_{53}ClN_8O_5$: 880; found: 881 $(M+H)^+$.
Example 107-43	methyl ((1R)-1-(2-chlorophenyl)-2-((2S)-2-(5-(4'-(2-((2S)-1-((2R)-2-methoxy-2-phenylacetyl)-2-pyrrolidinyl)-1H-imidazol-5-yl)-4-biphenylyl)-1H-imidazol-2-yl)-1-pyrrolidinyl)-2-oxoethyl)carbamate		LCMS: Anal. Calcd. for $C_{45}H_{44}ClN_7O_5$: 797; found: 798 $(M+H)^+$.
Example 107-44	methyl ((1R)-1-(2-chlorophenyl)-2-((2S)-2-(5-(4'-(2-((2S)-1-((2R)-2-(2-chlorophenyl)-2-(dimethylamino)acetyl)-2-pyrrolidinyl)-1H-imidazol-5-yl)-4-biphenylyl)-1H-imidazol-2-yl)-1-pyrrolidinyl)-2-oxoethyl)carbamate		LCMS: Anal. Calcd. for $C_{46}H_{46}Cl_2N_8O_4$: 844; found: 845 $(M+H)^+$.

Example 108

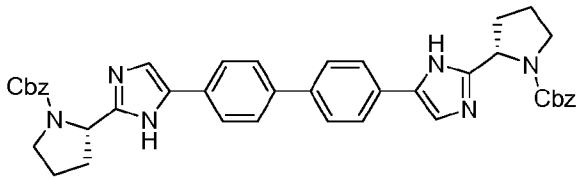
methyl ((1R)-2-((2S)-2-(5-(4'-(2-((2S)-1-(ethylcarbamoyl)-2-pyrrolidinyl)-1H-imidazol-5-yl)-4-biphenylyl)-1H-imidazol-2-yl)-1-pyrrolidinyl)-2-oxo-1-phenylethyl)carbamate



Ethyl isocyanate (5 μL, 0.063 mmol) was added to a methanol (1.0 mL) solution of 28f (30 mg, 0.049 mmol) and stirred at ambient condition for 1.8 hours. The residue was treated with 2.0 M NH_3/methanol (2 mL) and stirred for an additional 30 minutes, and all the volatile components were removed *in vacuo*. The resulting material was purified by a reverse phase HPLC (H_2O/methanol/TFA) to provide the TFA salt of Example 108 as a light yellow foam (16.7 mg) LC: 1.95 minutes (Cond. 2); >98% homogeneity index; LC/MS: Anal. Calcd. for [M+H]+ $C_{39}H_{43}N_8O_4$: 687.34; found 687.53; HRMS: Anal. Calcd. for $[M+H]^+$ $C_{39}H_{43}N_8O_4$: 687.3407; found 687.3417.

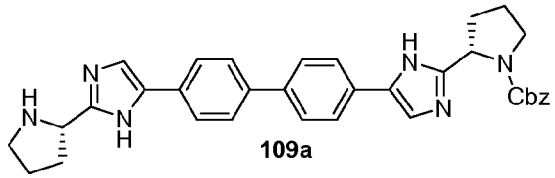
Example 109

dibenzyl (2S,2'S)-2,2'-(4,4'-biphenyldiylbis(1H-imidazole-5,2-diyl))di(1-pyrrolidinecarboxylate)



Example 109, Step a

benzyl (2S)-2-(5-(4'-(2-((2S)-2-pyrrolidinyl)-1H-imidazol-5-yl)-4-biphenylyl)-1H-imidazol-2-yl)-1-pyrrolidinecarboxylate

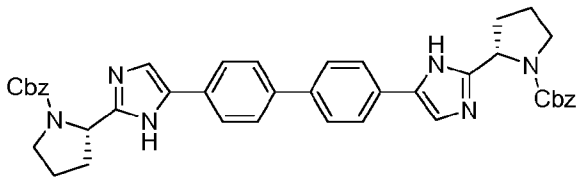


109a

The Boc-deprotection of 28c using the procedure described for the synthesis of pyrrolidine 1e from carbamate 1d provided 109a. RT = 1.92 minutes (Cond 2); > 98% homogeneity index; LC/MS: Anal. Calcd. $C_{34}H_{35}N_6O_2$: 559.28; found 559.44

Example 109

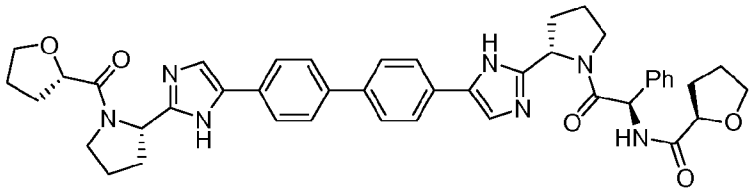
dibenzyl (2S,2'S)-2,2'-(4,4'-biphenyldiylbis(1H-imidazole-5,2-diyl))di(1-pyrrolidinecarboxylate)



Benzyl chloroformate (10.5 μL, 0.0736 mmol) was added to a THF (2.0 mL) solution of 109a (37.1 mg, 0.664 mmol) and triethylamine (15 μl, 0.107 mmol), and stirred under ambient conditions for 6 hours. The volatile component was removed *in vacuo*, and the residue was treated with 2N NH_3/methanol (2 mL) and stirred for 15 minutes. The volatile component was removed *in vacuo*, and the residue purified by a reverse phase HPLC (H_2O/methanol/TFA) to provide the TFA salt of Example 109 as an off-white foam (37.9 mg). LC (Cond. 2): RT = 2.25 min; >98% homogeneity index; LC/MS: Anal. Calcd. for $[M+H]^+$ $C_{42}H_{41}N_6O_4$: 693.32; found 693.59; HRMS: Anal. Calcd. for $[M+H]^+$ $C_{42}H_{41}N_6O_4$: 693.3189; found 693.3220.

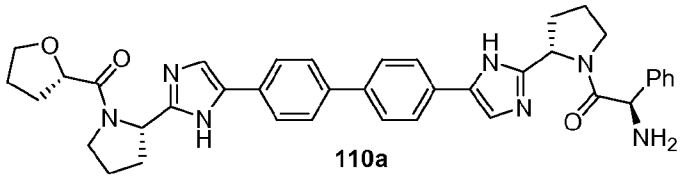
Example 110

(2R)-N-((1R)-2-oxo-1-phenyl-2-((2S)-2-(5-(4'-(2-((2S)-1-((2S)-tetrahydro-2-furanylcarbonyl)-2-pyrrolidinyl)-1H-imidazol-5-yl)-4-biphenylyl)-1H-imidazol-2-yl)-1-pyrrolidinyl)ethyl)tetrahydro-2-furancarboxamide



Example 110, Step a

(1R)-2-oxo-1-phenyl-2-((2S)-2-(5-(4'-(2-((2S)-1-((2S)-tetrahydro-2-furanylcarbonyl)-2-pyrrolidinyl)-1H-imidazol-5-yl)-4-biphenylyl)-1H-imidazol-2-yl)-1-pyrrolidinyl)ethanamine

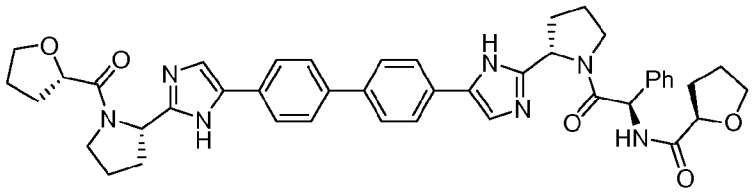


110a

Amine 110a was synthesized starting from 28d and (*S*)-tetrahydrofuran-2-carboxylic by sequentially employing procedures described in the preparation of 28f (from 28d) and 25b (from 1e). LC (Cond. 1): RT = 1.13 min; >98% homogeneity index; LC/MS: Anal. Calcd. for $[M+H]^+$ $C_{39}H_{42}N_7O_3$: 656.34; found 656.49; HRMS: Anal. Calcd. for $[M+H]^+$ $C_{39}H_{42}N_7O_3$: 656.3349; found 656.3377.

Example 110

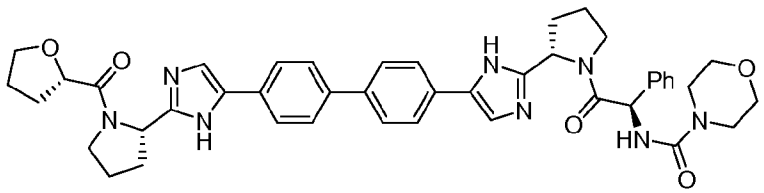
(2R)-N-((1R)-2-oxo-1-phenyl-2-((2S)-2-(5-(4'-(2-((2S)-1-((2S)-tetrahydro-2-furanylcarbonyl)-2-pyrrolidinyl)-1H-imidazol-5-yl)-4-biphenylyl)-1H-imidazol-2-yl)-1-pyrrolidinyl)ethyl)tetrahydro-2-furancarboxamide



Example 110 (TFA salt) was prepared from Example 110a and (*S*)-tetrahydrofuran-2-carboxylic acid using the conditions described for the synthesis Example 1 from amine 1c. LC (Cond. 1): RT = 1.28 min; >98% homogeneity index; LC/MS: Anal. Calcd. for $[M+H]^+$ $C_{44}H_{48}N_7O_5$: 754.37; found 754.60; HRMS: Anal. Calcd. for $[M+H]^+$ $C_{44}H_{48}N_7O_5$: 754.3717; found 754.3690.

Example 111

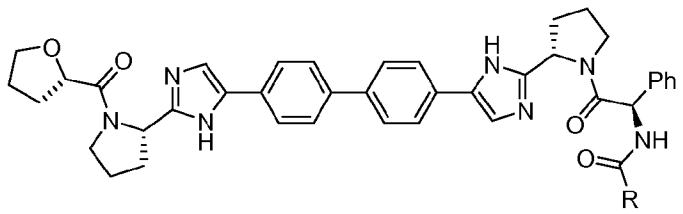
N-((1R)-2-oxo-1-phenyl-2-((2S)-2-(5-(4'-(2-((2S)-1-((2S)-tetrahydro-2-furanylcarbonyl)-2-pyrrolidinyl)-1H-imidazol-5-yl)-4-biphenylyl)-1H-imidazol-2-yl)-1-pyrrolidinyl)ethyl)-4-morpholinecarboxamide

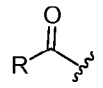
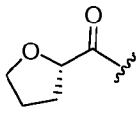
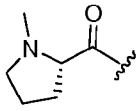
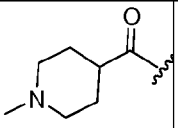


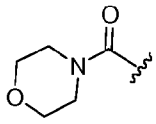
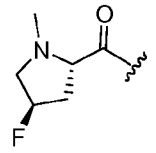
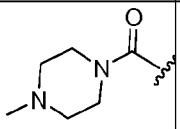
Example 111 (TFA salt) was prepared from amine 110a and morpholine 4-carbonyl chloride using the procedure described for the synthesis of Example 29 from amine 28f. LC (Cond. 1): RT = 1.28 min; >98% homogeneity index; LC/MS: Anal. Calcd. for $[M+H]^+$ $C_{44}H_{49}N_8O_5$: 769.38; found 769.60.

Using similar methods described for the preparation of Example 111, the following compounds (Example 112-120) were synthesized as TFA salts.

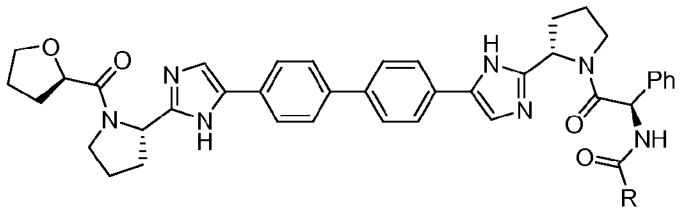
Example 112-117



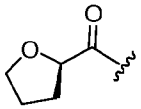
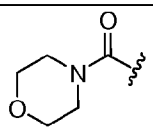
Example	*Compound Name*		*Retention time (LC-Condition); homogeneity index MS data*
112	(2S)-N-((1R)-2-oxo-1-phenyl-2-((2S)-2-(5-(4'-(2-((2S)-1-((2S)-tetrahydro-2-furanylcarbonyl)-2-pyrrolidinyl)-1H-imidazol-5-yl)-4-biphenylyl)-1H-imidazol-2-yl)-1-pyrrolidinyl)ethyl)tetrahydro-2-furancarboxamide		1.28 minutes (Cond. 1); >98%; LC/MS: Anal. Calcd. for $[M+H]^+$ $C_{44}H_{48}N_7O_5$: 754.37; found 754.59; HRMS: Anal. Calcd. for $[M+H]^+$ $C_{44}H_{48}N_7O_5$: 754.3717; found 754.3731
113	1-methyl-N-((1R)-2-oxo-1-phenyl-2-((2S)-2-(5-(4'-(2-((2S)-1-((2S)-tetrahydro-2-furanylcarbonyl)-2-pyrrolidinyl)-1H-imidazol-5-yl)-4-biphenylyl)-1H-imidazol-2-yl)-1-pyrrolidinyl)ethyl)-L-prolinamide		1.14 minutes (Cond. 1); >98%; LC/MS: Anal. Calcd. for $[M+H]^+$ $C_{44}H_{51}N_8O_4$: 767.40; found 767.68; HRMS: Anal. Calcd. for $[M+H]^+$ $C_{44}H_{51}N_8O_4$: 767.4033; found 767.4035
114	1-methyl-N-((1R)-2-oxo-1-phenyl-2-((2S)-2-(5-(4'-(2-((2S)-1-((2S)-tetrahydro-2-furanylcarbonyl)-2-pyrrolidinyl)-1H-imidazol-5-yl)-4-biphenylyl)-1H-imidazol-2-yl)-1-pyrrolidinyl)ethyl)-4-piperidinecarboxamide		1.12 minutes (Cond. 1); >98%; LC/MS: Anal. Calcd. for $[M+H]^+$ $C_{46}H_{53}N_8O_4$: 781.42; found 781.67; HRMS: Anal. Calcd. for $[M+H]^+$ $C_{46}H_{53}N_8O_4$: 781.4190; found 781.4195

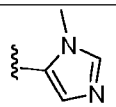
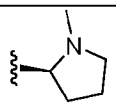
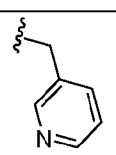
115	N-((1R)-2-oxo-1-phenyl-2-((2S)-2-(5-(4'-(2-((2S)-1-((2S)-tetrahydro-2-furanylcarbonyl)-2-pyrrolidinyl)-1H-imidazol-5-yl)-4-biphenylyl)-1H-imidazol-2-yl)-1-pyrrolidinyl)ethyl)tetrahydro-2H-pyran-4-carboxamide		1.24 minutes (Cond. 1); >98%; LC/MS: Anal. Calcd. for $[M+H]^+$ $C_{45}H_{50}N_7O_5$: 768.39; found 768.66; HRMS: Anal. Calcd. for $[M+H]^+$ $C_{45}H_{50}N_7O_5$: 768.3873; found 768.3897
116	(4R)-4-fluoro-1-methyl-N-((1R)-2-oxo-1-phenyl-2-((2S)-2-(5-(4'-(2-((2S)-1-((2S)-tetrahydro-2-furanylcarbonyl)-2-pyrrolidinyl)-1H-imidazol-5-yl)-4-biphenylyl)-1H-imidazol-2-yl)-1-pyrrolidinyl)ethyl)-L-prolinamide	 *Cap*-11	1.16 minutes (Cond. 1); >98%; LC/MS: Anal. Calcd. for $[M+H]^+$ $C_{45}H_{50}FN_8O_4$: 785.39; found 785.63; HRMS: Anal. Calcd. for $[M+H]^+$ $C_{45}H_{50}FN_8O_4$: 785.3939; found: 785.3940
117	4-methyl-N-((1R)-2-oxo-1-phenyl-2-((2S)-2-(5-(4'-(2-((2S)-1-((2S)-tetrahydro-2-furanylcarbonyl)-2-pyrrolidinyl)-1H-imidazol-5-yl)-4-biphenylyl)-1H-imidazol-2-yl)-1-pyrrolidinyl)ethyl)-1-piperazinecarboxamide		1.15 minutes (Cond. 1); 97.6%; LC/MS: Anal. Calcd. for $[M+H]^+$ $C_{45}H_{52}N_9O_4$: 782.41; found 782.64; HRMS: Anal. Calcd. for $[M+H]^+$ $C_{45}H_{52}N_9O_4$: 782.4142; found 782.4161

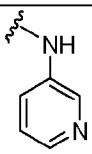
Examples 118 to 120-9



Examples 118 to 120-9 were prepared as described in the preparation of Example 110a substituting (R)-tetrahydrofuryl carboxylic acid and the appropriate carboxylic acid, carboxylic acid chloride, carbamoyl chloride, or isocyanate.

Example	*Compound Name*		*Retention time (LC-Condition); homogeneity index; MS data*
118	N-((1R)-2-oxo-1-phenyl-2-((2S)-2-(5-(4'-(2-((2S)-1-((2R)-tetrahydro-2-furanylcarbonyl)-2-pyrrolidinyl)-1H-imidazol-5-yl)-4-biphenylyl)-1H-imidazol-2-yl)-1-pyrrolidinyl)ethyl)acetamide		1.89 minutes (Cond. 2); >98%; LC/MS: Anal. Calcd. for $[M+H]^+$ $C_{41}H_{44}N_7O_4$: 698.35; found 698.25; HRMS: Anal. Calcd. for $[M+H]^+$ $C_{41}H_{44}N_7O_4$: 698.3455; found 698.3474
119	(2R)-N-((1R)-2-oxo-1-phenyl-2-((2S)-2-(5-(4'-(2-((2S)-1-((2R)-tetrahydro-2-furanylcarbonyl)-2-pyrrolidinyl)-1H-imidazol-5-yl)-4-biphenylyl)-1H-imidazol-2-yl)-1-pyrrolidinyl)ethyl)tetrahydro-2-furancarboxamide		1.99 minutes (Cond. 2); >98%; LC/MS: Anal. Calcd. for $[M+H]^+$ $C_{44}H_{48}N_7O_5$: 754.37; found 754.28; HRMS: Anal. Calcd. for $[M+H]^+$ $C_{44}H_{48}N_7O_5$: 754.3717; found 754.3705
120	N-((1R)-2-oxo-1-phenyl-2-((2S)-2-(5-(4'-(2-((2S)-1-((2R)-tetrahydro-2-		2.00 minutes (Cond. 2); >98%; LC/MS: Anal. Calcd. for $[M+H]^+$ $C_{44}H_{49}N_8O_5$:

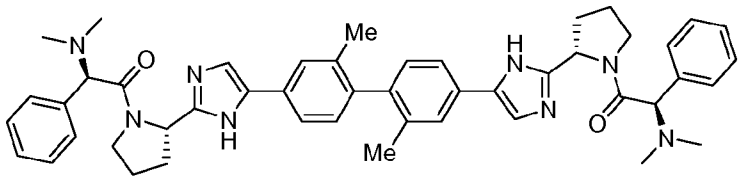
	furanylcarbonyl)-2-pyrrolidinyl)-1H-imidazol-5-yl)-4-biphenylyl)-1H-imidazol-2-yl)-1-pyrrolidinyl)ethyl)-4-morpholinecarboxamide		769.38; found 769.32
120-5	1-methyl-N-((1R)-2-oxo-1-phenyl-2-((2S)-2-(5-(4'-(2-((2S)-1-((2R)-tetrahydro-2-furanylcarbonyl)-2-pyrrolidinyl)-1H-imidazol-4-yl)-4-biphenylyl)-1H-imidazol-2-yl)-1-pyrrolidinyl)ethyl)-1H-imidazole-5-carboxamide		RT = 4.02 (97%); HPLC XTERRA C-18 4.6 × 30 mm, 0 to 100% B over 2 minutes, 1 minute hold time, A = 90% water, 10% methanol, 0.2% H_3PO_4, B = 10% water, 90% methanol, 0.2% H_3PO_4, RT = 1.87 minutes, 97% homogeneity index; LCMS: Anal. Calcd. for: $C_{44}H_{45}N_9O_4$ 763.91; Found: 764.52 $(M+H)^+$
120-6	1-methyl-N-((1R)-2-oxo-1-phenyl-2-((2S)-2-(5-(4'-(2-((2S)-1-((2R)-tetrahydro-2-furanylcarbonyl)-2-pyrrolidinyl)-1H-imidazol-4-yl)-4-biphenylyl)-1H-imidazol-2-yl)-1-pyrrolidinyl)ethyl)-L-prolinamide		RT = 3.68 (99%); HPLC XTERRA C-18 4.6 × 30 mm, 0 to 100% B over 2 minutes, 1 minute hold time, A = 90% water, 10% methanol, 0.2% H_3PO_4, B = 10% water, 90% methanol, 0.2% H_3PO_4, RT = 1.87 minutes, 97% homogeneity index; LCMS: Anal. Calcd. for: $C_{45}H_{50}N_8O_4$ 766.95; Found: 767.47 $(M+H)^+$
120-7	N-((1R)-2-oxo-1-phenyl-2-((2S)-2-(5-(4'-(2-((2S)-1-((2R)-tetrahydro-2-furanylcarbonyl)-2-pyrrolidinyl)-1H-imidazol-		RT = 3.81 (99%); HPLC XTERRA C-18 4.6 × 30 mm, 0 to 100% B over 2 minutes, 1 minute hold time, A = 90% water, 10% methanol, 0.2%

	4-yl)-4-biphenylyl)-1H-imidazol-2-yl)-1-pyrrolidinyl)ethyl)-2-(3-pyridinyl)acetamide		H_3PO_4, B = 10% water, 90% methanol, 0.2% H_3PO_4, RT = 1.87 minutes, 97% homogeneity index; LCMS: Anal. Calcd. for: $C_{46}H_{46}N_8O_4$ 774.93; Found: 775.47 $(M+H)^+$
120-8	N^2,N^2-dimethyl-N-((1R)-2-oxo-1-phenyl-2-((2S)-2-(5-(4'-(2-((2S)-1-((2R)-tetrahydro-2-furanylcarbonyl)-2-pyrrolidinyl)-1H-imidazol-4-yl)-4-biphenylyl)-1H-imidazol-2-yl)-1-pyrrolidinyl)ethyl)glycinamide		^{1}H NMR (500 MHz, DMSO-d_6) δ ppm 1.71-2.44 (m, 12H), 2.65-2.89 (m, 6H), 3.04-3.21 (m, *J*=8.55 Hz, 1H), 3.46-3.68 (m, 1H), 3.64-4.07 (m, 6H), 4.64 (dd, *J*=8.09, 5.34 Hz, 1H), 5.09-5.30 (m, 2H), 5.66-5.86 (m, 1H), 7.32-7.49 (m, 4H), 7.82-8.22 (m, 10H), 9.15-9.38 (m, 1H), 9.68 (s, 1H), 14.60 (s, 2H); HPLC Xterra 4.6 X 50 mm, 0 to 100% B over 10 minutes, one minute hold time, A = 90% water, 10% methanol, 0.2% phosphoric acid, B = 10% water, 90% methanol, 0.2% phosphoric acid, RT = 3.61 min; LCMS: Anal. Calcd. for: $C_{52}H_{56}N_{10}O_6$ 740.91; Found: 741.48 $(M+H)^+$.
120-9	1-((1R)-2-oxo-1-phenyl-2-((2S)-2-(5-(4'-(2-((2S)-1-((2R)-tetrahydro-2-furanylcarbonyl)-2-pyrrolidinyl)-1H-imidazol-4-yl)-4-biphenylyl)-1H-		^{1}H NMR (500 MHz, DMSO-d_6) δ ppm 1.64-2.40 (m, 12H), 3.11-3.27 (m, 1H), 3.51-3.65 (m, 1H), 3.80 (dd, *J*=18.46, 6.87 Hz, 3H), 3.96-4.11 (m, 1H), 4.64 (dd,

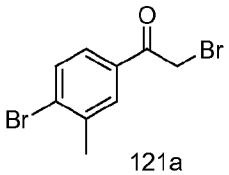
	imidazol-2-yl)-1-pyrrolidinyl)ethyl)-3-(3-pyridinyl)urea		*J*=7.78, 5.34 Hz, 1H), 5.13-5.23 (m, 1H), 5.21-5.35 (m, 1H), 5.66 (d, *J*=7.02 Hz, 1H), 7.29-7.57 (m, 7H), 7.82-8.07 (m, 10H), 8.14 (s, 1H), 8.22 (d, *J*=4.58 Hz, 1H), 8.68 (s, 1H), 9.32 (s, 1H), 14.46 (s, 2H); HPLC Xterra 4.6 X 50 mm, 0 to 100% B over 10 minutes, one minute hold time, A = 90% water, 10% methanol, 0.2% phosphoric acid, B = 10% water, 90% methanol, 0.2% phosphoric acid, RT = 3.83 min; LCMS: Anal. Calcd. for: $C_{45}H_{45}N_9O_4$ 775.92; Found: 776.53 $(M+H)^+$.

Example 121

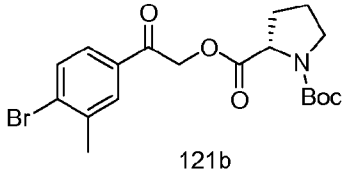
(1R,1'R)-2,2'-((2,2'-dimethyl-4,4'-biphenyldiyl)bis(1H-imidazole-5,2-diyl(2S)-2,1-pyrrolidinediyl))bis(N,N-dimethyl-2-oxo-1-phenylethanamine)



Example 121, Step a-b



121a



121b

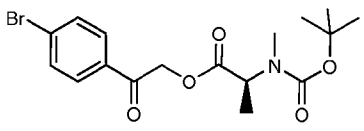
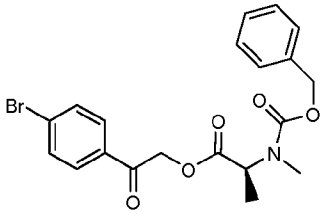
$PdCl_2(Ph_3P)_2$ (257 mg, 0.367 mmol) was added to a dioxane (45 mL) solution of 1-bromo-4-iodo-2-methylbenzene (3.01 g, 10.13 mmol) and tri-*n*-butyl(1-

ethoxyvinyl)stannane (3.826 g, 10.59 mmol) and heated at 80 °C for ~17 hours. The reaction mixture was treated with water (15 mL), cooled to ~0 °C (ice/water), and then NBS (1.839 g, 10.3 mmol) was added in batches over 7 minutes. After about 25 minutes of stirring, the volatile component was removed *in vacuo*, and the residue was partitioned between CH_2Cl_2 and water. The aqueous layer was extracted with CH_2Cl_2, and the combined organic phase was dried ($MgSO_4$), filtered, and concentrated *in vacuo*. The resulting crude material was purified by a gravity chromatography (silica gel; 4% ethyl acetate/hexanes)to provide bromide 121a as a brownish-yellow solid (2.699 g); the sample is impure and contains stannane-derived impurities, among others. ^{1}H NMR ($CDCl_3$, δ = 7.24, 400 MHz): 7.83 (s, 1H), 7.63 (s, 2H), 4.30 (s, 2H), 2.46 (s, 3H).

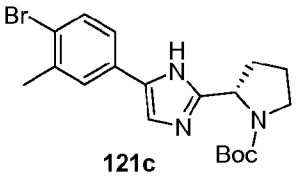
A CH_3CN (15 mL) solution of 121a (2.69 g, < 9.21 mmol) was added dropwise over 3 minutes to a CH_3CN (30 mL) solution of (*S*)-Boc-proline (2.215 g, 10.3 mmol) and triethylamine (1.40 mL, 10.04 mmol), and stirred for 90 minutes. The volatile component was removed *in vacuo*, and the residue was partitioned between water and CH_2Cl_2, and the organic phase was dried ($MgSO_4$), filtered, and concentrated *in vacuo*. The resulting crude material was purified by a flash chromatography (silica gel; 15-20% ethyl acetate/hexanes) to provide 121b as a colorless viscous oil (2.74g). ^{1}H NMR (DMSO-d_6, δ = 2.50, 400 MHz): δ 7.98 (m, 1H), 7.78 (d, *J* = 8.3, 1H), 7.72-7.69 (m, 1H), 5.61-5.41 (m, 2H), 4.35-4.30 (m, 1H), 3.41-3.30 (m, 2H), 2.43 (s, 3H), 2.33-2.08 (m, 2H), 1.93-1.83 (m, 2H), 1.40/1.36 (s, 9H); LC (Cond. 1): RT = 1.91 min; >95% homogeneity index; LC/MS: Anal. Calcd. for $[M+Na]^+$ $C_{19}H_{24}BrNNaO_5$ 448.07; found 448.10.

Additional keto-esters can be prepared in analogous fashion.

LC conditions: *Condition 1*: Phenomenex LUNA C-18 4.6 × 50 mm, 0 to 100% B over 3 minutes, 1 minute hold time, A = 90% water, 10% methanol, 0.1% TFA, B = 10% water, 90% methanol, 0.1% TFA, 220nm, 5 µL injection volume.
Condition 2: Phenomenex LUNA C-18 4.6 × 50 mm, 0 to 100% B over 2 minutes, 1 minute hold time, A = 90% water, 10% methanol, 0.1% TFA, B = 10% water, 90% methanol, 0.1% TFA, 220nm, 5 µL injection volume.

Example	*Structure*	*Data*
121b-1		RT = 2.15 minutes (condition 2, 98%); LRMS: Anal. Calcd. for $C_{17}H_{22}NO_5$ 399.07; found: 400.10 $(M+H)^+$.
121b-2		RT = 2.78 minutes (condition 1, >90%); LRMS: Anal. Calcd. for $C_{20}H_{20}{}^{37}BrNO_5$ 435.05 found: 458.02 $(M+Na)^+$.

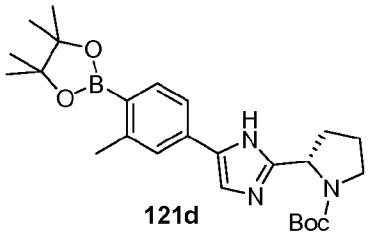
Example 121, Step c



121c

A mixture of ketoester 121b (1.445 g, 3.39 mmol) and NH_4OAc (2.93 g, 38.0 mmol) in xylenes (18 mL) was heated with a microwave at 140 °C for 80 minutes. The volatile component was removed *in vacuo*, and the residue was carefully partitioned between CH_2Cl_2 and water, where enough saturated $NaHCO_3$ solution was added to neutralize the aqueous medium. The aqueous phase was extracted with CH_2Cl_2, and the combined organic phase was dried ($MgSO_4$), filtered, and concentrated *in vacuo*. The crude product was purified by a flash chromatography (silica gel, 40% ethyl acetate/hexanes) to provide imidzaole 121c as an off-white solid (1.087 g). ^1H NMR (DMSO-d_6, δ = 2.50, 400 MHz): 12.15/11.91/11.84 (br s, 1H), 7.72-7.24 (m, 4H), 4.78 (m, 1H), 3.52 (m, 1H), 3.38-3.32 (m, 1H), 2.35 (s, 3H), 2.28-1.77 (m, 4H), 1.40/1.14 (s, 9H); LC (Cond. 1): RT = 1.91 min; >98% homogeneity index; LC/MS: Anal. Calcd. for $[M+H]^+$ $C_{19}H_{25}BrN_3O_2$ 405.96; found 406.11.

Example 121, Step d



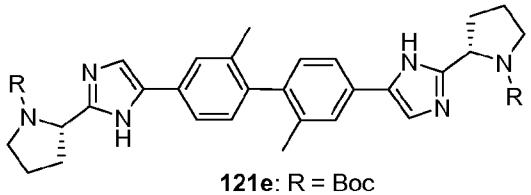
121d

$PdCl_2dppf{\cdot}CH_2Cl_2$ (50.1 mg, 0.061 mmol) was added to a pressure tube containing a mixture of bromide 121c (538.3 mg, 1.325 mmol), bis(pinacolato)diboron (666.6 mg, 2.625 mmol), potassium acetate (365.8 mg, 3.727 mmol) and DMF (10 mL). The reaction mixture was flushed with N_2 and heated at 80 °C for 24.5 hours. The volatile component was removed *in vacuo* and the residue was partitioned between CH_2Cl_2 and water, where enough saturated $NaHCO_3$ solution was added to make the pH of the aqueous medium neutral. The aqueous phase was extracted with CH_2Cl_2, and the combined organic phase was dried ($MgSO_4$), filtered, and concentrated *in vacuo*. The resulting material was purfied by a Biotage system (silica gel, 40-50% ethyl acetate/hexanes) to provide boronate 121d as a white foam (580 mg). According to ^1H NMR the sample contains residual pinacol in a product/pinacol ratio of ~3. ^1H NMR (DMSO-d_6, δ = 2.50, 400 MHz): δ 12.16/11.91/11.83 (br s, 1H), 7.63-7.25 (m, 4H), 4.78 (m, 1H), 3.53 (m, 1H), 3.39-3.32 (m, 1H), 2.48/2.47 (s, 3H), 2.28-1.78 (m, 4H), 1.40/1.14/1.12 (br s, 9H), 1.30 (s, 12H); LC (Cond. 1): RT = 1.62 min; LC/MS: Anal. Calcd. for $[M+H]^+$ $C_{25}H_{37}BN_3O_4$ 454.29; found 454.15

Example 121, Step e

and

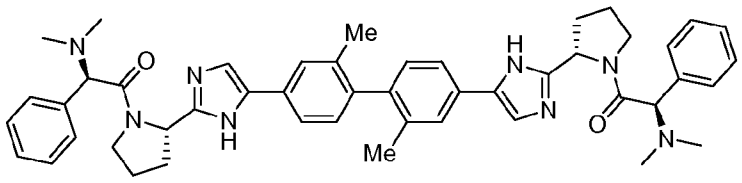
Example 121, Step f



121e: R = Boc
121f: R = H

Carbamate 121e was prepared from bromide 121c and boronate 121d according to the preparation of dimer 1d; LC (Cond. 1): RT = 1.43 min; LC/MS: Anal. Calcd. for $[M+H]^+$ $C_{38}H_{49}N_6O_4$ 653.38; found 653.65.

The deprotection of carbamate 121e, according to the preparation of pyrrolidine 1e, provided 121f as an off-white foam. ^1H NMR (DMSO-d_6, δ = 2.50, 400 MHz): 11.79 (br s, 2H), 7.66 (s, 2H), 7.57 (d, J = 7.8, 2H), 7.41 (br s, 2H), 7.02 (d, J = 7.8, 2H), 4.15 (app t, J = 7.2, 2H), 3.00-2.94 (m, 2H), 2.88-2.82 (m, 2H), 2.09-2.01 (m, 2H), 2.04 (s, 6H), 1.93-1.85 (m, 2H), 1.82-1.66 (m, 4H). Note: although broad signals corresponding to the pyrrolidine NH appear in the 2.8-3.2 ppm region, the actual range for their chemical shift could not be determined. LC (Cond. 1): RT = 1.03 min; LC/MS: Anal. Calcd. for $[M+H]^+$ $C_{28}H_{33}N_6$ 453.28; found 453.53



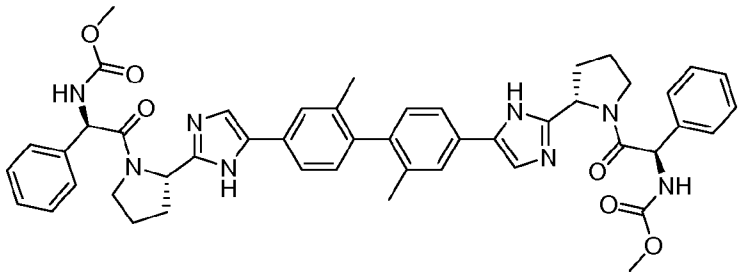
Example 121

(1R,1'R)-2,2'-((2,2'-dimethyl-4,4'-biphenyldiyl)bis(1H-imidazole-5,2-diyl(2S)-2,1-pyrrolidinediyl))bis(N,N-dimethyl-2-oxo-1-phenylethanamine)

Example 121 (TFA salt) was synthesized from 121f according to the preparation of Example 1 from 1e; LC (Cond. 1): RT = 1.14 min; >98% homogeneity index; LC/MS: Anal. Calcd. for $[M+H]^+$ $C_{48}H_{55}N_8O_2$ 775.45; 775.75; HRMS: Anal. Calcd. for $[M+H]^+$ $C_{48}H_{55}N_8O_2$ 775.4448; found 775.4473

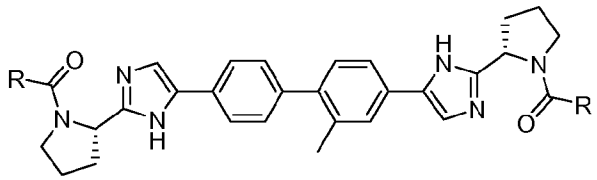
Example 122

dimethyl ((2,2'-dimethyl-4,4'-biphenyldiyl)bis(1H-imidazole-5,2-diyl(2S)-2,1-pyrrolidinediyl((1R)-2-oxo-1-phenyl-2,1-ethanediyl)))biscarbamate

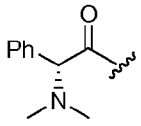


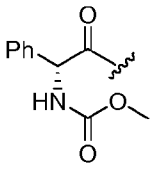
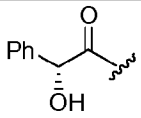
Example 122 (TFA salt) was prepared from pyrrolidine 121f and *Cap*-4 by using the procedure described for the preparation of Example 1 from pyrrolidine 1e. LC (Cond. 1): RT = 1.35 min; >98% homogeneity index; HRMS: Anal. Calcd. for $[M+H]^+$ $C_{48}H_{51}N_8O_6$ 835.3932; found 835.3954

Example 123-125

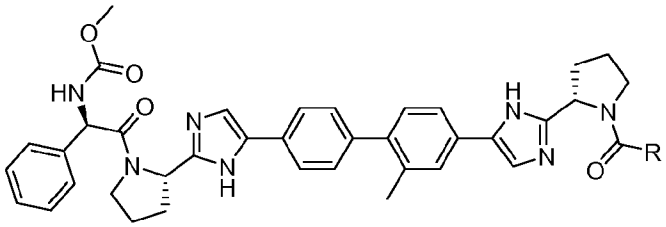


Example 123-125 were prepared starting from boronate 1c and bromide 121c by using the methods described in Example 1, step d, Example 1, step e, and in the step describing the final preparation of Example 1.

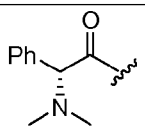
Example	*Compound Name*		*RT (LC-Cond.); % homogeneity index; MS data*
123	(1R,1'R)-2,2'-((2-methyl-4,4'-biphenyldiyl)bis(1H-imidazole-5,2-diyl(2S)-2,1-pyrrolidinediyl))bis(N,N-dimethyl-2-oxo-1-phenylethanamine)	 *Cap-1*	1.12 minutes (Cond. 1); >98%; LC/MS: Anal. Calcd. for $[M+H]^+$ $C_{47}H_{53}N_8O_2$: 761.43; found 761.49; HRMS: Anal. Calcd. for $[M+H]^+$ $C_{47}H_{53}N_8O_2$: 761.4291; found 761.4311

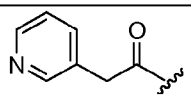
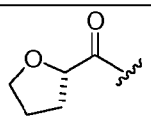
124	dimethyl ((2-methyl-4,4'-biphenyldiyl)bis(1H-imidazole-5,2-diyl(2S)-2,1-pyrrolidinediyl((1R)-2-oxo-1-phenyl-2,1-ethanediyl)))biscarbamate	 *Cap-4*	1.34 minutes (Cond. 1); >98%; LC/MS: Anal. Calcd. for $[M+H]^+$ $C_{47}H_{49}N_8O_6$: 821.38; found 821.45; HRMS: Anal. Calcd. for $[M+H]^+$ $C_{47}H_{49}N_8O_6$: 821.3775; found 821.3785
125	(1R,1'R)-2,2'-((2-methyl-4,4'-biphenyldiyl)bis(1H-imidazole-5,2-diyl(2S)-2,1-pyrrolidinediyl))bis(2-oxo-1-phenylethanol)		1.23 minutes (Cond. 1); >98%; LC/MS: Anal. Calcd. for $[M+H]^+$ $C_{43}H_{43}N_6O_4$: 707.34; found 707.38; HRMS: Anal. Calcd. for $[M+H]^+$ $C_{43}H_{43}N_6O_4$: 707.3346; found 707.3356

Examples 126-128



Example 126-128 were prepared starting from bromide 28b and boronate 121d by using the methods described in Example 28 starting with step c.

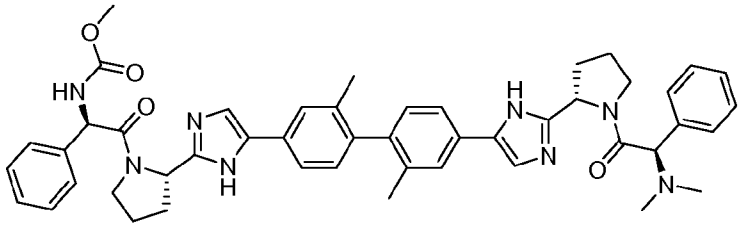
Example	*Compound Name*		*RT (LC-Cond.); % homogeneity index; MS data*
126	methyl ((1R)-2-((2S)-2-(5-(4'-(2-((2S)-1-((2R)-2-(dimethylamino)-2-phenylacetyl)-2-pyrrolidinyl)-1H-	 *Cap-1*	1.22min (Cond. 1); >98%; LC/MS: Anal. Calcd. for $[M+H]^+$ $C_{47}H_{51}N_8O_4$: 791.40; found 791.70; HRMS: Anal. Calcd. for $[M+H]^-$ $C_{47}H_{51}N_8O_4$: 791.4033; found 791.4061

	imidazol-5-yl)-2'-methyl-4-biphenylyl)-1H-imidazol-2-yl)-1-pyrrolidinyl)-2-oxo-1-phenylethyl)carbamate		
127	methyl ((1R)-2-((2S)-2-(5-(2'-methyl-4'-(2-((2S)-1-(3-pyridinylacetyl)-2-pyrrolidinyl)-1H-imidazol-5-yl)-4-biphenylyl)-1H-imidazol-2-yl)-1-pyrrolidinyl)-2-oxo-1-phenylethyl)carbamate		1.19 minutes (Cond. 1); >98%; LC/MS: Anal. Calcd. for $[M+H]^+$ $C_{44}H_{45}N_8O_4$: 749.36; found 749.62; HRMS: Anal. Calcd. for $[M+H]^-$ $C_{44}H_{45}N_8O_4$: 749.3564; found 749.3592
128	methyl ((1R)-2-((2S)-2-(5-(2'-methyl-4'-(2-((2S)-1-((2S)-tetrahydro-2-furanylcarbonyl)-2-pyrrolidinyl)-1H-imidazol-5-yl)-4-biphenylyl)-1H-imidazol-2-yl)-1-pyrrolidinyl)-2-oxo-1-phenylethyl)carbamate		1.27 minutes (Cond. 1); >98%; LC/MS: Anal. Calcd. for $[M+H]^+$ $C_{42}H_{46}N_7O_5$: 728.36; found 728.59; HRMS: Anal. Calcd. for $[M+H]^-$ $C_{42}H_{46}N_7O_5$: 728.3560; found 728.3593

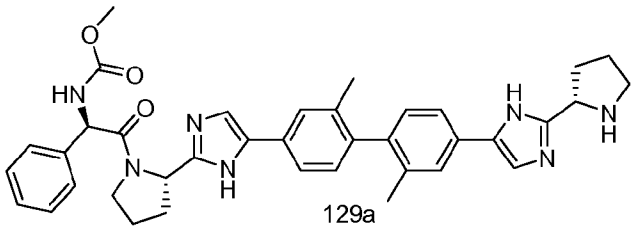
5

Example 129

methyl ((1R)-2-((2S)-2-(5-(4'-(2-((2S)-1-((2R)-2-(dimethylamino)-2-phenylacetyl)-2-pyrrolidinyl)-1H-imidazol-5-yl)-2,2'-dimethyl-4-biphenylyl)-1H-imidazol-2-yl)-1-pyrrolidinyl)-2-oxo-1-phenylethyl)carbamate



Example 129, Step a

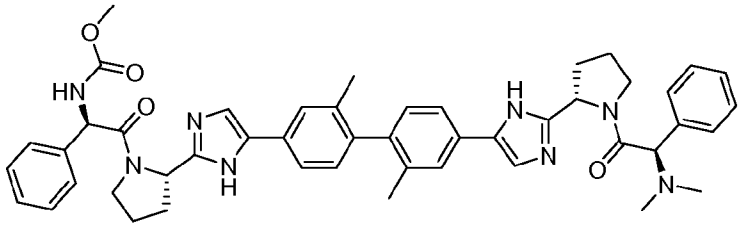


129a

HATU (104.3 mg, 0.274 mmol) was added to a mixture of 121f, *Cap*-4 (58.8 mg, 0.281 mmol) and diisopropylethylamine (110 μL, 0.631 mmol) in DMF (6.0 mL), and stirred for 90 minutes. The volatile component was removed *in vacuo* and the resulting crude material was purified by reverse phase HPLC (H_2O/methanol/TFA), and free-based by MCX column (methanol wash; 2.0 M NH_3/methanol) to provide 129a (89.9 mg). LC (Cond. 1): RT = 1.22 min; 95% homogeneity index; LC/MS: Anal. Calcd. for $[M+H]^+$ $C_{38}H_{42}N_7O_3$ 644.34; found 644.55.

Example 129

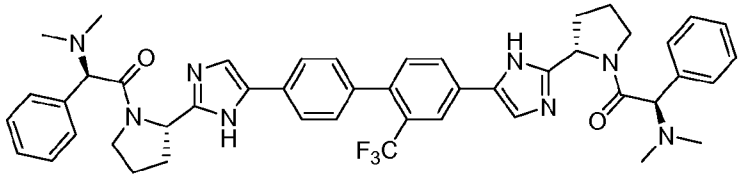
methyl ((1R)-2-((2S)-2-(5-(4'-(2-((2S)-1-((2R)-2-(dimethylamino)-2-phenylacetyl)-2-pyrrolidinyl)-1H-imidazol-5-yl)-2,2'-dimethyl-4-biphenylyl)-1H-imidazol-2-yl)-1-pyrrolidinyl)-2-oxo-1-phenylethyl)carbamate



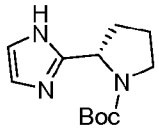
Example 129 (TFA salt) was prepared from 129a by the method used to convert Example 1e to Example 1. LC (Cond. 1): RT = 1.27 min; 97% homogeneity index; LC/MS: Anal. Calcd. for $[M+H]^+$ $C_{48}H_{53}N_8O_4$ 805.42; found 805.61.

Example 130

(1R,1'R)-2,2'-((2-(trifluoromethyl)-4,4'-biphenyldiyl)bis(1H-imidazole-5,2-diyl(2S)-2,1-pyrrolidinediyl))bis(N,N-dimethyl-2-oxo-1-phenylethanamine)



Example 130, Step a



130a

Glyoxal (2.0 mL of 40% in water) was added dropwise over 11 minutes to a methanol solution of NH_4OH (32 mL) and (S)-Boc-prolinal (8.564 g, 42.98 mmol) and stirred at ambient temperature for 19 hours. The volatile component was removed *in vacuo* and the residue was purified by a flash chromatography (silica gel, ethyl acetate) followed by a recrystallization (ethyl acetate, room temperature) to provide imidazole 130a as a white fluffy solid (4.43g). ^1H NMR (DMSO-d_6, δ = 2.50, 400 MHz): 11.68/11.59 (br s, 1H), 6.94 (s, 1H), 6.76 (s, 1H), 4.76 (m, 1H), 3.48

(m, 1H), 3.35-3.29 (m, 1H), 2.23-1.73 (m, 4H), 1.39/1.15 (s, 9H). LC (Cond. 1): RT = 0.87 min; >95% homogeneity index; LC/MS: Anal. Calcd. for $[M+H]^+$ $C_{12}H_{20}N_3O_2$ 238.16; found 238.22. Imidazole 130a had an ee of 98.9% when analyzed under chiral HPLC condition noted below.

Column: Chiralpak AD, 10 um, 4.6 x 50 mm

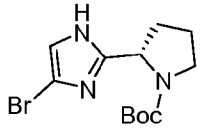
Solvent: 1.7% ethanol/heptane (isocratic)

Flow rate: 1 mL/min

Wavelength: either 220 or 256 nm

Relative retention time: 3.25min (*R*), 5.78 minutes (*S*)

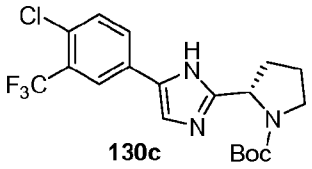
Example 130, Step b



130b

N-Bromosuccinimide (838.4 mg, 4.71 mmol) was added in batches, over 15 minutes, to a cooled (ice/water) CH_2Cl_2 (20 mL) solution of imidazole 130a (1.0689 g, 4.504 mmol), and stirred at similar temperature for 75 minutes. The volatile component was removed *in vacuo*. The crude material was purified by a reverse phase HPLC system (H_2O/methanol/TFA) to separate bromide 130b from its dibromo-analog and the non-consumed starting material. The HPLC elute was neutralized with excess NH_3/methanol and the volatile component was removed *in vacuo*. The residue was partitioned between CH_2Cl_2 and water, and the aqueous layer was extracted with water. The combined organic phase was dried ($MgSO_4$), filtered, and concentrated *in vacuo* to provide 130b as a white solid (374 mg). ^1H NMR (DMSO-d_6, δ = 2.50, 400 MHz): 12.12 (br s, 1H), 7.10 (m, 1H), 4.70 (m, 1H), 3.31 (m, 1H; overlapped with water signal), 2.25-1.73 (m, 4H), 1.39/1.17 (s, 3.8H + 5.2H). LC (Cond. 1): RT = 1.10 min; >95% homogeneity index; LC/MS: Anal. Calcd. for $[M+H]^+$ $C_{12}H_{19}BrN_3O_2$ 316.07; found 316.10.

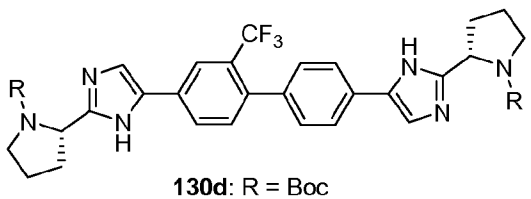
Example 130, Step c



130c

$Pd(Ph_3P)_4$ (78.5 mg, 0.0679 mmol) was added to a mixture of bromide 130b (545 mg, 1.724 mmol), 2-(4-chloro-3-(trifluoromethyl)phenyl-4,4,5,5-tetramethyl-1,3,2-dioxaborolane (542.8 mg, 1.771 mmol) (commercially available), $NaHCO_3$ (477 mg, 5.678 mmol) in 1,2-dimethoxyethane (12.5 mL) and water (4.2 mL). The reaction mixture was purged with nitrogen, heated with an oil bath at 80 °C for 27 hours, and then the volatile component was removed *in vacuo*. The residue was partitioned between CH_2Cl_2 and water, and the organic layer was dried ($MgSO_4$), filtered, and concentrated *in vacuo*. The resulting crude material was purified by a Biotage system (silica gel, 40-50% ethyl acetate/hexanes) followed by a reverse phase HPLC (water/ methanol/TFA). The HPLC elute was treated with excess NH_3/methanol and concentrated. The residue was partitioned between water and CH_2Cl_2, and the organic layer was dried ($MgSO_4$), filtered, and concentrated *in vacuo* to provide 130c as a white foam (317.4 mg). ^1H NMR (DMSO-d_6, δ = 2.50, 400 MHz): 12.36/12.09/12.03 (br s, 1H), 8.15 (d, J = 1.8, 0.93H), 8.09 (br s, 0.07H), 8.01 (dd, J = 8.3/1.3, 0.93H), 7.93 (m, 0.07H), 7.74 (m, 1H), 7.66 (d, J = 8.3, 0.93H), 7.46 (m, 0.07H), 4.80 (m, 1H), 3.53 (m, 1H), 3.36 (m, 1H), 2.30-1.77 (m, 4h), 1.40/1.15 (s, 3.8H+5.2H). LC (Cond. 1): RT = 1.52 min; >95% homogeneity index; LC/MS: Anal. Calcd. for $[M+H]^+$ $C_{19}H_{22}ClF_3N_3O_2$ 416.14; found 416.17.

Example 130, Step d-e



130d: R = Boc
130e: R = H

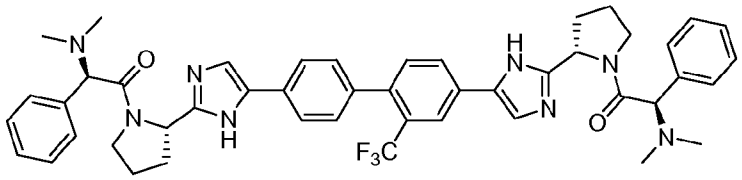
$Pd[P(t\text{-}Bu)_3]_2$ (48 mg, 0.094 mmol) was added to a mixture of chloride 130c (245 mg, 0.589 mmol), boronate 1c (277.1 mg, 0.631 mmol), KF (106.7 mg, 1.836 mmol) in DMF (6 mL), and heated at 110 °C for ~30 hours. The volatile component

was removed *in vacuo*, and the residue was partitioned between CH_2Cl_2 (50 mL), water (20 mL) and saturated $NaHCO_3$ (1 mL). The aqueous layer was extracted with CH_2Cl_2 (2x), and the combined organic phase was dried ($MgSO_4$), filtered, and concentrated *in vacuo*. The resulting material was purified by a Biotage system (silica gel, ethyl acetate) to provide carbamate 130d as an off-white foam (297 mg). LC (Cond. 1): RT = 1.44 min; >95% homogeneity index; LC/MS: Anal. Calcd. for $[M+H]^+$ $C_{37}H_{44}F_3N_6O_4$ 693.34; found 693.34.

The deprotection of 130d, which was conducted according to the preparation of pyrrolidine 1e, provideed 130e as a light yellow foam. ^1H NMR (DMSO-d_6, δ = 2.50, 400 MHz): 11.88 (br s, 2H), 8.16 (d, J = 1.5, 1H), 8.02 (d, J = 7.8, 1H), 7.78 (d, J = 8.1, 2H), 7.66 (br s, 1H), 7.48 (br s, 1H), 7.37 (d, J = 8.1, 1H), 7.28 (d, J = 8.3, 2H), 4.18 (m, 2H), 2.99-2.93 (m, 2H), 2.89-2.83 (m, 2H), 2.11-2.01 (m, 2H), 1.94-1.85 (m, 2H), 1.82-1.67 (m, 4H). Note: although broad signals corresponding to the pyrrolidine NH appear in the 2.8-3.2 ppm region, the actual range for their chemical shift could not be determined. LC (Cond. 1): RT = 1.12 min; >95% homogeneity index; LC/MS: Anal. Calcd. for $[M+H]^+$ $C_{27}H_{28}F_3N_6$ 493.23; found 493.14.

Example 130

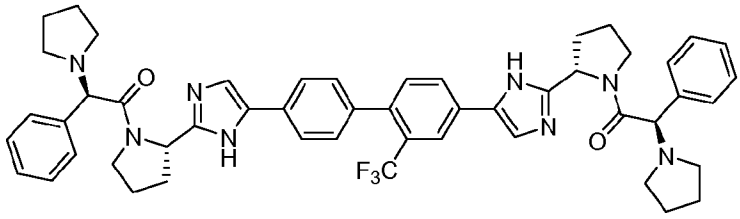
(1R,1'R)-2,2'-((2-(trifluoromethyl)-4,4'-biphenyldiyl)bis(1H-imidazole-5,2-diyl(2S)-2,1-pyrrolidinediyl))bis(N,N-dimethyl-2-oxo-1-phenylethanamine)



Example 130 (TFA salt) was prepared from 130e and *Cap*-1 according to the preparation of Example 1 from pyrrolidine 1e. LC (Cond. 1): RT = 1.17 min; >98% homogeneity index; LC/MS: Anal. Calcd. for $[M+H]^+$ $C_{47}H_{50}F_3N_8O_2$ 815.40; found 815.44; HRMS: Anal. Calcd. for $[M+H]^+$ $C_{47}H_{50}F_3N_8O_2$ 815.4009; found 815.4013

Example 131

5,5'-(2-(trifluoromethyl)-4,4'-biphenyldiyl)bis(2-((2S)-1-((2R)-2-phenyl-2-(1-pyrrolidinyl)acetyl)-2-pyrrolidinyl)-1H-imidazole)



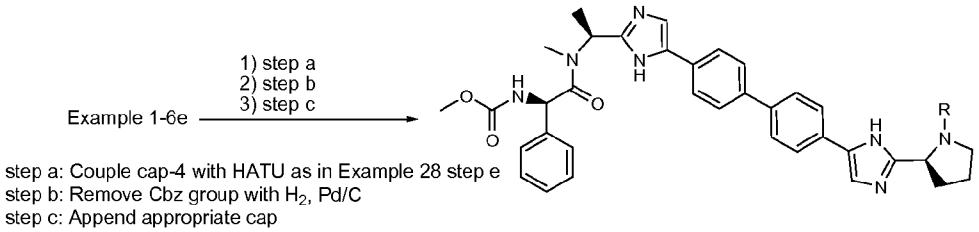
Example 131 (TFA salt) was synthesized from 130c and *Cap*-5 according to the preparation of Example 130.

LC (Cond. 1): RT = 1.19 min; >98% homogeneity index

LC/MS: Anal. Calcd. for $[M+H]^+$ $C_{51}H_{54}F_3N_8O_2$ 867.43; found 867.51

HRMS: Anal. Calcd. for $[M+H]^+$ $C_{51}H_{54}F_3N_8O_2$ 867.4322; found 867.4315

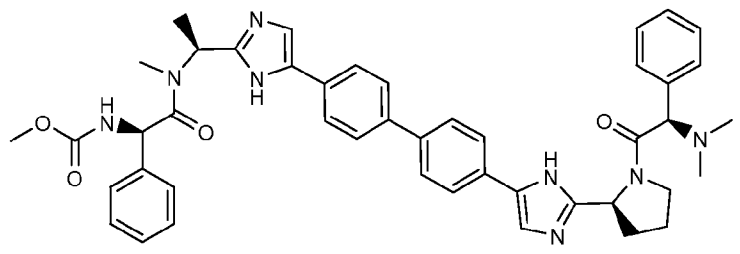
Example 131.1-1 to 131.1-2



Examples 131.1-1 through 131.1-2 were prepared in similar fashion to example 28 *via* the intermediacy of intermediate 1-6e after appending *Cap*-4.

Example 131.1-1

methyl ((1R)-2-(((1S)-1-(5-(4'-(2-((2S)-1-((2R)-2-(dimethylamino)-2-phenylacetyl)-2-pyrrolidinyl)-1H-imidazol-5-yl)-4-biphenylyl)-1H-imidazol-2-yl)ethyl)(methyl)amino)-2-oxo-1-phenylethyl)carbamate



Cap-1 was appended after the CBz carbamate was removed from 1-6e with $Pd/C/H_2$.

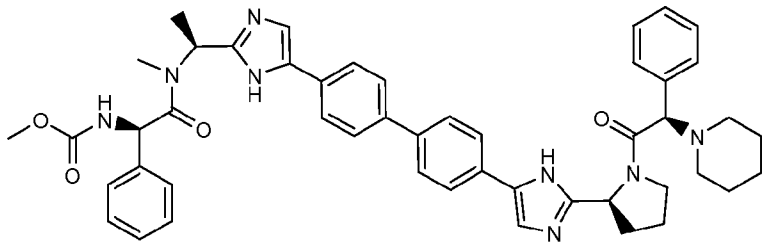
LCMS conditions: Phenomenex LUNA C-18 4.6 × 50 mm, 0 to 100% B over 3 minutes, 1 minute hold time, A = 90% water, 10% methanol, 0.1% TFA, B = 10% water, 90% methanol, 0.1% TFA, 220nm, 5 μL injection volume. t_R = 1.42 min

LRMS: Anal. Calcd. for $C_{45}H_{49}N_8O_4$ 765.39; found: 765.38 $(M+H)^+$.

HRMS: Anal. Calcd. for $C_{45}H_{49}N_8O_4$ Calcd 765.3877 found: 765.3905 $(M+H)^+$.

Example 131.1-2

methyl ((1R)-2-(methyl((1S)-1-(5-(4'-(2-((2S)-1-((2R)-2-phenyl-2-(1-piperidinyl)acetyl)-2-pyrrolidinyl)-1H-imidazol-5-yl)-4-biphenylyl)-1H-imidazol-2-yl)ethyl)amino)-2-oxo-1-phenylethyl)carbamate



Cap-14 was appended after the CBz carbamate was removed from 1-6e with $Pd/C/H_2$.

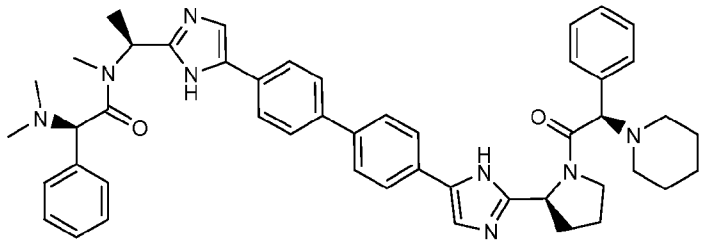
LCMS conditions: Phenomenex LUNA C-18 4.6 × 50 mm, 0 to 100% B over 3 minutes, 1 minute hold time, A = 90% water, 10% methanol, 0.1% TFA, B = 10% water, 90% methanol, 0.1% TFA, 220nm, 5 μL injection volume. t_R = 1.45 min (>95 %)

LRMS: Anal. Calcd. for $C_{48}H_{52}N_8O_4$ 805.42; found: 805.41 $(M+H)^+$.

HRMS: Anal. Calcd. $C_{48}H_{52}N_8O_4$ Calcd 805.4190 found: 805.4214 $(M+H)^+$.

Example 131.2

(2R)-2-(dimethylamino)-N-methyl-2-phenyl-N-((1S)-1-(5-(4'-(2-((2S)-1-((2R)-2-phenyl-2-(1-piperidinyl)acetyl)-2-pyrrolidinyl)-1H-imidazol-5-yl)-4-biphenylyl)-1H-imidazol-2-yl)ethyl)acetamide



Example 131. 2 was prepared in similar fashion to example 131.1-1 and example 131.1-2 *via* the intermediacy of intermediate 1-6e after appending *Cap*-1. *Cap*-14 was appended after the CBz carbamate was removed with $Pd/C/H_2$.

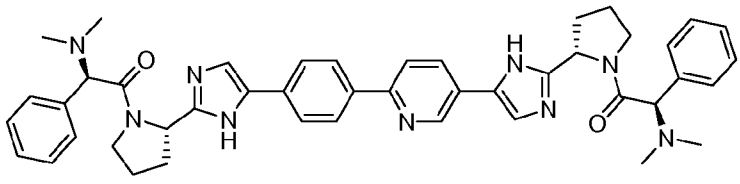
LCMS conditions: Phenomenex LUNA C-18 4.6 × 50 mm, 0 to 100% B over 3 minutes, 1 minute hold time, A = 90% water, 10% methanol, 0.1% TFA, B = 10% water, 90% methanol, 0.1% TFA, 220nm, 5 μL injection volume. t_R = 1.28 min

LRMS: Anal. Calcd. for $C_{48}H_{54}N_8O_2$ 775.44; found: 775.45 $(M+H)^+$.

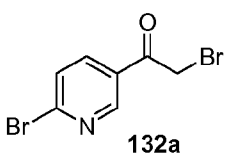
HRMS: Anal. Calcd. $C_{48}H_{54}N_8O_2$ Calcd 775.4448 found: 775.4460 $(M+H)^+$.

Example 132

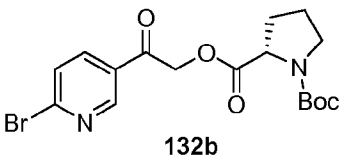
(1R)-2-((2S)-2-(5-(6-(4-(2-((2S)-1-((2R)-2-(dimethylamino)-2-phenylacetyl)-2-pyrrolidinyl)-1H-imidazol-5-yl)phenyl)-3-pyridinyl)-1H-imidazol-2-yl)-1-pyrrolidinyl)-N,N-dimethyl-2-oxo-1-phenylethanamine



Example 132, Step a-b



132a



132b

A CH_2Cl_2 (10 mL) solution of Br_2 (7.63 g, 47.74 mmol) was added-drop wise over 5 min to a cooled (ice/water) CH_2Cl_2 (105 mL) solution of 1-(6-bromopyridine-3-yl)ethanone (9.496 g, 47.47 mmol) and 48% HBr (0.4 mL). The cooling bath was removed 40 min later, and stirring was continued at ambient temperature for about 66 hr. The cake of solid that formed was filtered, washed with CH_2Cl_2 and dried *in vacuo* to afford impure 132a as an off-white solid (15.94 g).

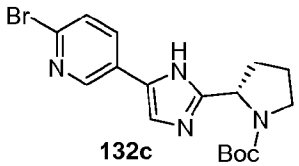
Boc-L-proline (9.70 g, 45.06 mmol) was added in one batch to a heterogeneous mixture of crude 132a (15.4 g) and CH_3CN (150 mL), and immediately afterward Et_3N (13.0 mL, 93.2 mmol) was added drop-wise over 6 min. The reaction mixture was stirred for 50 min, the volatile component was removed *in vacuo* and the residue was partitioned between CH_2Cl_2 and water. The CH_2Cl_2 layer was dried ($MgSO_4$), filtered and concentrated *in vacuo*, and the resultant material was purified by flash chromatography (silica gel; sample was loaded with eluting solvent; 25% EtOAc/hexanes) to afford 132b as a highly viscous yellow oil (11.44g). ^1H NMR (DMSO, δ = 2.5 ppm; 400 MHz): 8.95 (m, 1H), 8.25-8.21 (m, 1H), 7.88 (d, J = 8.3, 1H), 5.65-5.46 (m, 2H), 4.36-4.31 (m, 1H), 3.41-3.29 (m, 2H), 2.36-2.22 (m, 1H), 2.14-2.07 (m, 1H), 1.93-1.83 (m, 2H), 1.40 & 1.36 (two s, 9H).

LC (Cond. 1): RT = 2.01 min; >90% homogeneity index

LC/MS: Anal. Calcd. for $[M+Na]^+$ $C_{17}H_{21}NaBrN_2O_5$: 435.05; found 435.15

HRMS: Anal. Calcd. for $[M+H]^+$ $C_{17}H_{22}BrN_2O_5$: 413.0712; found 413.0717

Example 132, Step c



132c

A mixture of ketoester 132b (1.318 g, 3.19 mmol) and NH_4OAc (2.729 g, 35.4 mmol) in xylenes (18 mL) was heated with a microwave at 140 °C for 90 min. The volatile component was removed *in vacuo* and the residue was partitioned between CH_2Cl_2 and water, where enough saturated $NaHCO_3$ solution was added to neutralize the aqueous medium. The aqueous phase was extracted with CH_2Cl_2, and the combined organic phase was dried ($MgSO_4$), filtered, and concentrated *in vacuo*. The resulting crude material was purified by a Biotage system (silica gel; 50%

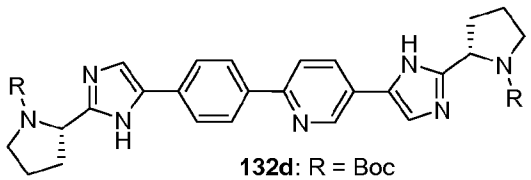
EtOAc/hexanes) to afford imidzaole 132c as an off-white foam (1.025 g). ^{1}H NMR (DMSO, δ = 2.5 ppm, 400 MHz): 12.33/12.09/12.02 (br m, 1H), 8.74 (d, J = 2.3, 0.93H), 8.70 (app br s, 0.07H), 8.03/7.98 (dd for the first peak, J = 8.3, 1H), 7.69/7.67 (br m, 1H), 7.58/7.43 (d for the first peak, J = 8.3, 1H), 4.80 (m, 1H), 3.53 (m, 1H), 3.36 (m, 1H), 2.33-2.11 (m, 1H), 2.04-1.79 (m, 3H), 1.39/1.15 (app br s, 3.9H+5.1H).

LC (Cond.1): RT = 1.52 min; >98% homogeneity index

LC/MS: Anal. Calcd. for $[M+H]^+$ $C_{17}H_{22}BrN_4O_2$: 393.09; found 393.19

HRMS: Anal. Calcd. for $[M+H]^+$ $C_{17}H_{22}BrN_4O_2$: 393.0926; found 393.0909

Example 132, Step d-e



132d: R = Boc
132e: R = H

$Pd(Ph_3P)_4$ (115.1 mg, 0.10 mmol) was added to a mixture of bromide 132c (992mg, 2.52 mmol), boronate 1c (1.207 g, 2.747 mmol), $NaHCO_3$ (698.8 mg, 8.318 mmol) in 1,2-dimethoxyethane (18 mL) and water (4 mL). The reaction mixture was flushed with nitrogen, heated with an oil bath at 90 °C for 37 hr and allowed to cool to ambient temperature. The suspension that formed was filtered and washed with water followed by 1,2-dimethoxyethane, and dried *in vacuo*. A silica gel mesh was prepared from the crude solid and submitted to flash chromatography (silica gel; EtOAc) to afford carbamate 132d as a white solid, which yellowed slightly upon standing at ambient conditions (1.124g). ^{1}H NMR indicated that the sample contains residual MeOH in a product/MeOH mole ratio of 1.3.

LC (Cond. 1): RT = 1.71 min; >98% homogeneity index

LC/MS: Anal. Calcd. for $[M+H]^+$ $C_{35}H_{44}N_7O_4$: 626.35; found 626.64

HRMS: Anal. Calcd. for $[M+H]^+$ $C_{35}H_{44}N_7O_4$: 626.3455; 626.3479

Carbamate 132d (217 mg) was treated with 25% TFA/CH_2Cl_2 (3.6 mL) and stirred at ambient condition for 6 hr. The volatile component was removed *in vacuo*, and the resultant material was free based by MCX column (MeOH wash; 2.0 M NH_3/MeOH elution) to afford 132e as a dull yellow foam that solidified gradually

upon standing (150.5 mg; mass is above theoretical yield). ^{1}H NMR (DMSO, δ = 2.5 ppm; 400 MHz): 11.89 (very broad, 2H), 9.01 (d, J = 1.8, 1H), 8.13 (dd, J = 8.3, 2.2, 1H), 8.07 (d, J = 8.6, 2H), 7.92 (d, J = 8.3, 1H), 7.83 (d, J = 8.5, 2H), 7.61 (br s, 1H), 7.50 (br s, 1H), 4.18 (m, 2H), 3.00-2.93 (m, 2H), 2.90-2.82 (m, 2H), 2.11-2.02 (m, 2H), 1.94-1.85 (m, 2H), 1.83-1.67 (m, 4H). [Note: the exchangeable pyrrolidine hydrogens were not observed]

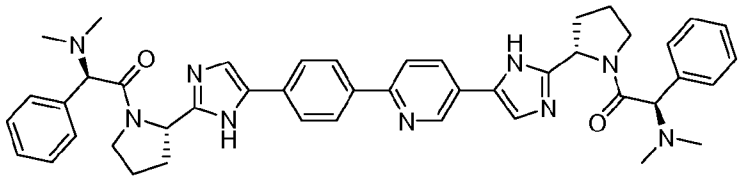
LC (Cond. 1): RT = 1.21min; >98% homogeneity index

LC/MS: Anal. Calcd. for $[M+H]^+$ $C_{25}H_{28}N_7$: 426.24; found 426.40

HRMS: Anal. Calcd. for $[M+H]^+$ $C_{25}H_{28}N_7$: 426.2406; found 426.2425

Example 132

(1R)-2-((2S)-2-(5-(6-(4-(2-((2S)-1-((2R)-2-(dimethylamino)-2-phenylacetyl)-2-pyrrolidinyl)-1H-imidazol-5-yl)phenyl)-3-pyridinyl)-1H-imidazol-2-yl)-1-pyrrolidinyl)-N,N-dimethyl-2-oxo-1-phenylethanamine



HATU (41.4 mg, 0.109 mmol) was added to a mixture of pyrrolidine 132e (23.1 mg, 0.054 mmol), (i-Pr)$_2$EtN (40 µL, 0.23 mmol) and *Cap*-1 (25.3 mg, 0.117 mmol) in DMF (1.5 mL), and the mixture was stirred at ambient for 1 hr. The volatile component was removed *in vacuo*, and the residue was purified first by MCX (MeOH wash; 2.0 M NH_3/MeOH elution) and then by a reverse phase HPLC (H_2O/MeOH/TFA) to afford the TFA salt of Example 132 as a yellow foam (39.2 mg).

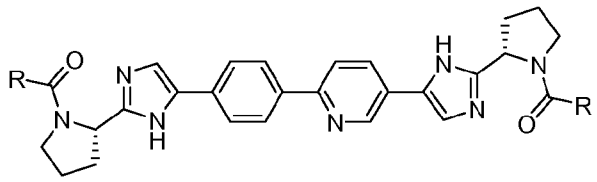
LC (Cond. 1): RT = 1.37min; >98% homogeneity index

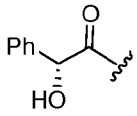
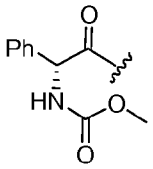
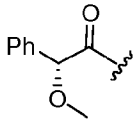
LC/MS: Anal. Calcd. for $[M+H]^+$ $C_{45}H_{50}N_9O_2$: 748.41; found 748.53

HRMS: Anal. Calcd. for $[M+H]^+$ $C_{45}H_{50}N_9O_2$: 748.4087; found 748.4090

Example 133-135 were prepared as TFA salts from 132e by using the same method of preparations as Example 132 and appropriate reagents.

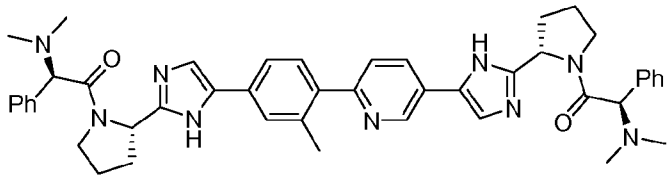
Example 133-135



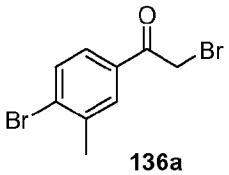
Example	*Compound Name*		*RT (LC-Cond.); % homogeneity index; MS data*
133	(1R)-2-((2S)-2-(5-(6-(4-(2-((2S)-1-((2R)-2-hydroxy-2-phenylacetyl)-2-pyrrolidinyl)-1H-imidazol-5-yl)phenyl)-3-pyridinyl)-1H-imidazol-2-yl)-1-pyrrolidinyl)-2-oxo-1-phenylethanol		1.49 min (Cond. 1); >98% LC/MS: Anal. Calcd. for $[M+H]^+$ $C_{41}H_{40}N_7O_4$: 694.31; found 694.42 HRMS: Anal. Calcd. for $[M+H]^+$ $C_{41}H_{40}N_7O_4$: 694.3142, found: 694.3164
134	methyl ((1R)-2-((2S)-2-(5-(6-(4-(2-((2S)-1-((2R)-2-((methoxycarbonyl)amino)-2-phenylacetyl)-2-pyrrolidinyl)-1H-imidazol-5-yl)phenyl)-3-pyridinyl)-1H-imidazol-2-yl)-1-pyrrolidinyl)-2-oxo-1-phenylethyl)carbamate	 *Cap-4*	1.60 min (Cond. 1); >98% LC/MS: Anal. Calcd. for $[M+H]^+$ $C_{45}H_{46}N_9O_6$: 808.36; found 808.51 HRMS: Anal. Calcd. for $[M+H]^+$ $C_{45}H_{46}N_9O_6$: 808.3571; found 808.3576
135	5-(2-((2S)-1-((2R)-2-methoxy-2-phenylacetyl)-2-pyrrolidinyl)-1H-imidazol-5-yl)-2-(4-(2-((2S)-1-((2R)-2-methoxy-2-phenylacetyl)-2-pyrrolidinyl)-1H-imidazol-5-yl)phenyl)pyridine		1.60 min (Cond. 1); >98% LC/MS: Anal. Calcd. for $[M+H]^+$ $C_{43}H_{44}N_7O_4$: 722.35; found 722.40 HRMS: Anal. Calcd. for $[M+H]^+$ $C_{43}H_{44}N_7O_4$: 722.3455; found 722.3464

Example 136

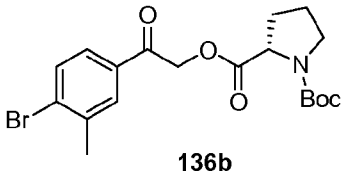
(1R)-2-((2S)-2-(5-(6-(4-(2-((2S)-1-((2R)-2-(dimethylamino)-2-phenylacetyl)-2-pyrrolidinyl)-1H-imidazol-5-yl)-2-methylphenyl)-3-pyridinyl)-1H-imidazol-2-yl)-1-pyrrolidinyl)-N,N-dimethyl-2-oxo-1-phenylethanamine



Example 136, Step a and b



136a



136b

$PdCl_2(Ph_3P)_2$ (257 mg, 0.367 mmol) was added to a dioxane (45 mL) solution of 1-bromo-4-iodo-2-methylbenzene (3.01 g, 10.13 mmol) and tri-*n*-butyl(1-ethoxyvinyl)stannane (3.826 g, 10.59 mmol) and heated at 80 °C for ~17 hr. The reaction mixture was treated with water (15 mL), cooled to ~0 °C (ice/water), and then NBS (1.839 g, 10.3 mmol) was added in batches over 7 min. About 25 min of stirring, the volatile component was removed *in vacuo*, and the residue was partitioned between CH_2Cl_2 and water. The aqueous layer was extracted with CH_2Cl_2, and the combined organic phase was dried ($MgSO_4$), filtered, and concentrated *in vacuo*. The resulting crude material was purified by a gravity chromatography (silica gel; 4% EtOAc/hexanes)to afford bromide 136a as a brownish-yellow solid (2.699 g); the sample is impure and contains stannane-derived impurities, among others. ^1H NMR ($CDCl_3$, $\delta = 7.24$, 400 MHz): 7.83 (s, 1H), 7.63 (s, 2H), 4.30 (s, 2H), 2.46 (s, 3H).

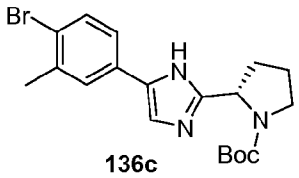
An CH_3CN (15 mL) solution of 136a (2.69 g, < 9.21 mmol) was added drop wise over 3 min to a CH_3CN (30 mL) solution of (*S*)-Boc-proline (2.215 g, 10.3 mmol) and Et_3N (1.40 mL, 10.04 mmol), and stirred for 90 min. The volatile component was removed *in vacuo*, and the residue was partitioned between water and CH_2Cl_2, and the organic phase was dried ($MgSO_4$), filtered, and concentrated *in vacuo*. The resultant crude material was purified by a flash chromatography (silica

gel; 15-20% EtOAc/hexanes) to afford 136b as a colorless viscous oil (2.74g). ^{1}H NMR (DMSO-d_6, δ = 2.50, 400 MHz): 7.98 (m, 1H), 7.78 (d, J = 8.3, 1H), 7.72-7.69 (m, 1H), 5.61-5.41 (m, 2H), 4.35-4.30 (m, 1H), 3.41-3.30 (m, 2H), 2.43 (s, 3H), 2.33-2.08 (m, 2H), 1.93-1.83 (m, 2H), 1.40/1.36 (s, 9H).

LC (Cond. 1): RT = 1.91 min; >95% homogeneity index

LC/MS: Anal. Calcd. for $[M+Na]^+$ $C_{19}H_{24}BrNNaO_5$ 448.07; found 448.10

Example 136, Step c



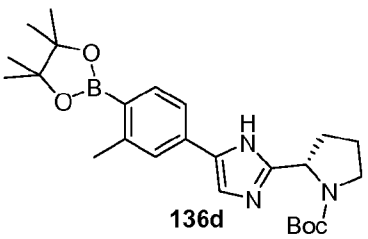
136c

A mixture of ketoester 136b (1.445 g, 3.39 mmol) and NH_4OAc (2.93 g, 38.0 mmol) in xylenes (18 mL) was heated with a microwave at 140 °C for 80 min. The volatile component was removed *in vacuo*, and the residue was carefully partitioned between CH_2Cl_2 and water, where enough saturated $NaHCO_3$ solution was added to neutralize the aqueous medium. The aqueous phase was extracted with CH_2Cl_2, and the combined organic phase was dried ($MgSO_4$), filtered, and concentrated *in vacuo*. The crude was purified by a flash chromatography (silica gel, 40% EtOAc/hexanes) to afford imidzaole 136c as an off-white solid (1.087 g). ^{1}H NMR (DMSO-d_6, δ = 2.50, 400 MHz): 12.15/11.91/11.84 (br s, 1H), 7.72-7.24 (m, 4H), 4.78 (m, 1H), 3.52 (m, 1H), 3.38-3.32 (m, 1H), 2.35 (s, 3H), 2.28-1.77 (m, 4H), 1.40/1.14 (s, 9H).

LC (Cond. 1): RT = 1.91 min; >98% homogeneity index

LC/MS: Anal. Calcd. for $[M+H]^+$ $C_{19}H_{25}BrN_3O_2$ 405.96; found 406.11

Example 136, Step d



136d

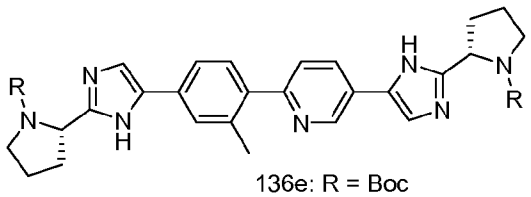
$PdCl_2$dppf.CH_2Cl_2 (50.1 mg, 0.061 mmol) was added to a pressure tube containing a mixture of bromide 136c (538.3 mg, 1.325 mmol),

bis(pinacolato)diboron (666.6 mg, 2.625 mmol), KOAc (365.8 mg, 3.727 mmol) and DMF (10 mL). The reaction mixture was flushed with N_2 and heated at 80 °C for 24.5 hr. The volatile component was removed *in vacuo* and the residue was partitioned between CH_2Cl_2 and water, where enough saturated $NaHCO_3$ solution was added to make the pH of the aqueous medium neutral. The aqueous phase was extracted with CH_2Cl_2, and the combined organic phase was dried ($MgSO_4$), filtered, and concentrated *in vacuo*. The resulting material was purfied by a Biotage system (silica gel, 40-50% EtOAc/hexanes) to afford boronate 136d as a white foam (580 mg). According to ^{1}H NMR the sample contains residual pinacol in a product/pinacol ratio of ~3. ^{1}H NMR (DMSO-d_6, δ = 2.50, 400 MHz): 12.16/11.91/11.83 (br s, 1H), 7.63-7.25 (m, 4H), 4.78 (m, 1H), 3.53 (m, 1H), 3.39-3.32 (m, 1H), 2.48/2.47 (s, 3H), 2.28-1.78 (m, 4H), 1.40/1.14/1.12 (br s, 9H), 1.30 (s, 12H).

LC (Cond. 1): RT = 1.62 min

LC/MS: Anal. Calcd. for $[M+H]^+$ $C_{25}H_{37}BN_3O_4$ 454.29; found 454.15

Example 136, Step e-f



136e: R = Boc
136f: R = H

Biaryl 136e was prepared from bromide 132c and boronate 136d according to the coupling condition described for the preparation of biaryl 132d.

LC (Cond. 1a): RT = 1.32 min; >90% homogeneity index

LC/MS: Anal. Calcd. for $[M+H]^+$ $C_{36}H_{45}N_7O_4$ 640.36; found 640.66

The deprotection of biaryl 136e was done according to the preparation of pyrrolidine 132e to afford 136f as a light yellow foam. ^{1}H NMR (DMSO-d_6, δ = 2.50, 400 MHz): 11.88 (br s, 2H), 9.02 (d, J = 2, 1H), 8.12 (dd, J = 8.4, 2.3, 1H), 7.67 (s, 1H), 7.64-7.62 (m, 2H), 7.50 (d, J = 8.3, 1H), 7.46 (br s, 1H), 7.40 (d, J = 7.8, 1H), 4.21-4.14 (m, 2H), 3.00-2.93 (m, 2H), 2.90-2.82 (m, 2H), 2.40 (s, 3H), 2.11-2.01 (m, 2H), 1.94-1.85 (m, 2H), 1.82-1.66 (m, 4H). [Note: the signal for the pyrrolidine NH

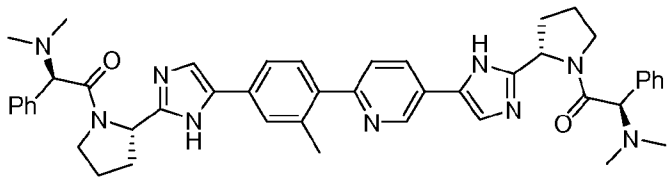
appears in the region 3.22-2.80 and is too broad to make a chemical shift assignment.]

LC (Cond. 1): RT = 0.84 min

LC/MS: Anal. Calcd. for $[M+H]^+$ $C_{26}H_{30}N_7$ 440.26; found 440.50

Example 136

(1R)-2-((2S)-2-(5-(6-(4-(2-((2S)-1-((2R)-2-(dimethylamino)-2-phenylacetyl)-2-pyrrolidinyl)-1H-imidazol-5-yl)-2-methylphenyl)-3-pyridinyl)-1H-imidazol-2-yl)-1-pyrrolidinyl)-N,N-dimethyl-2-oxo-1-phenylethanamine



Example 136 (TFA salt) was synthesized from 136f according to the preparation of Example 132 from 132e.

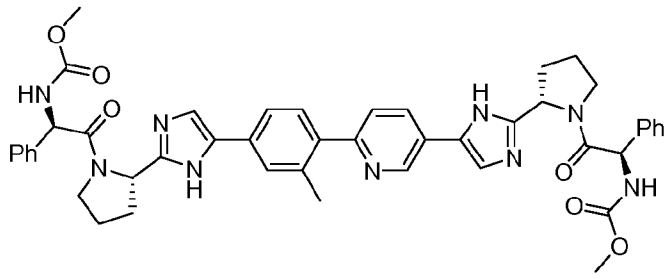
1.05 min (Cond.1); >98%

LC/MS: Anal. Calcd. for $[M+H]^+$ $C_{46}H_{52}N_9O_2$: 762.42, found: 762.77

HRMS: Anal. Calcd. for $[M+H]^+$ $C_{46}H_{52}N_9O_2$: 762.4244; found 762.4243

Example 138

methyl ((1R)-2-((2S)-2-(5-(6-(4-(2-((2S)-1-((2R)-2-((methoxycarbonyl)amino)-2-phenylacetyl)-2-pyrrolidinyl)-1H-imidazol-5-yl)-2-methylphenyl)-3-pyridinyl)-1H-imidazol-2-yl)-1-pyrrolidinyl)-2-oxo-1-phenylethyl)carbamate



Example 138 was prepared similarly from pyrrolidine 136f and *Cap*-4.

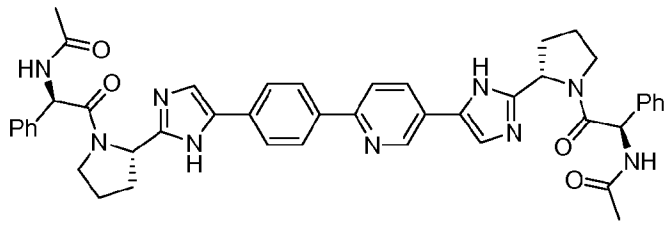
1.60 min (Cond. 1); >98%

LC/MS: Anal. Calcd. for $[M+H]^+$ $C_{46}H_{48}N_9O_6$: 822.37; found 822.74

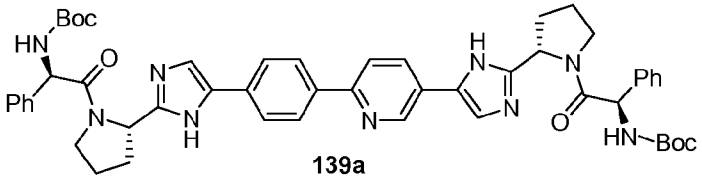
HRMS: Anal. Calcd. for $[M+H]^+$ $C_{46}H_{48}N_9O_6$: 822.3728; found 822.3760

Example 139

N-((1R)-2-((2S)-2-(5-(6-(4-(2-((2S)-1-((2R)-2-acetamido-2-phenylacetyl)-2-pyrrolidinyl)-1H-imidazol-5-yl)phenyl)-3-pyridinyl)-1H-imidazol-2-yl)-1-pyrrolidinyl)-2-oxo-1-phenylethyl)acetamide



Example 139, Step a



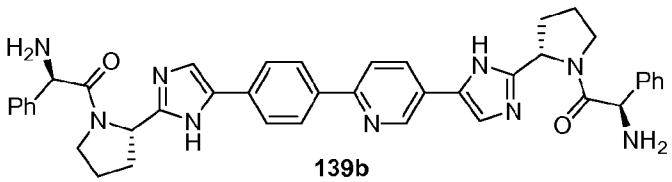
139a

HATU (99.8 mg, 0.262 mmol) was added to a mixture of 132e (54.1 mg, 0.127 mmol), (*R*)-2-(*t*-butoxycarbonylamino)-2-phenylacetic acid (98.5 mg, 0.392 mmol) and *i*-Pr_2EtN (100 μL, 0.574 mol), and the reaction mixture was stirred for 70 min. The volatile component was removed *in vacuo*, and the residue was purified by a reverse phase HPLC (H_2O/MeOH/TFA), where the HPLC elute was treated with excess 2.0 N NH_3/McOH before the removal of the volatile component *in vacuo*. The resulting material was partitioned between CH_2Cl_2 and water, and the aqueous phase was extracted with CH_2Cl_2 (2x). The combined organic phase was dried ($MgSO_4$), filtered, and concentrated *in vacuo*. Carbamate 139a was obtained as a white film of foam (82.3 mg).

LC (Cond. 1): RT = 1.97 min; >95% homogeneity index.

LC/MS: Anal. Calcd. for $[M+H]^+$ $C_{51}H_{58}N_9O_6$: 892.45; found 892.72

Example 139b, Step b



139b

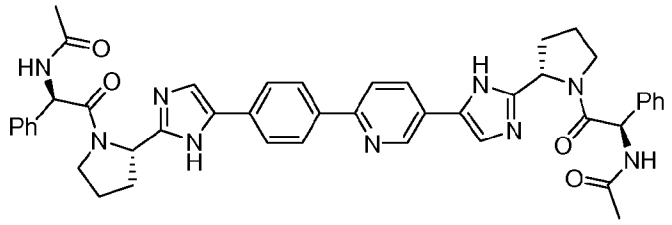
Carbamate 139a was deprotected to amine 139b by using the procedure described for the preparation of pyrrolidine 132e from 132d.

LC (Cond. 1): RT = 1.37 min; >95% homogeneity index

LC/MS: Anal. Calcd. for $[M+H]^+$ $C_{41}H_{42}N_9O_2$: 692.35; found 692.32

Example 139

N-((1R)-2-((2S)-2-(5-(6-(4-(2-((2S)-1-((2R)-2-acetamido-2-phenylacetyl)-2-pyrrolidinyl)-1H-imidazol-5-yl)phenyl)-3-pyridinyl)-1H-imidazol-2-yl)-1-pyrrolidinyl)-2-oxo-1-phenylethyl)acetamide



Acetic anhydride (20 μL, 0.212 mmol) was added to a DMF (1.5 mL) solution of 139b (31.2 mg, 0.045 mmol), and the reaction mixture was stirred for 1 hr. NH_3/MeOH (1.0 mL of 2N) was added to the reaction mixture and stirring continued for 100 min. The volatile component was removed *in vacuo* and the resulting crude material was purified by a reverse phase HPLC (H_2O/MeOH/TFA) to afford the TFA salt of Example 139 as a light yellow solid (24.1 mg).

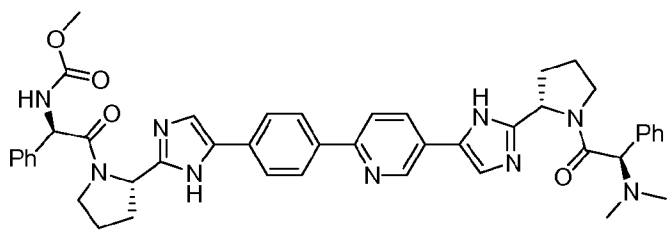
LC (Cond. 1): RT = 1.53 min; >98% homogeneity index

LC/MS: Anal. Calcd. for $[M+H]^+$ $C_{45}H_{46}N_9O_4$: 776.37; found 776.38

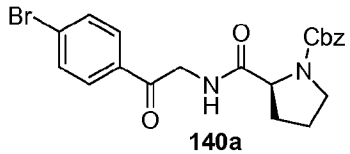
HRMS: Anal. Calcd. for $[M+H]^+$ $C_{45}H_{46}N_9O_4$: 776.3673; found 776.3680

Example 140

methyl ((1R)-2-((2S)-2-(5-(4-(5-(2-((2S)-1-((2R)-2-(dimethylamino)-2-phenylacetyl)-2-pyrrolidinyl)-1H-imidazol-5-yl)-2-pyridinyl)phenyl)-1H-imidazol-2-yl)-1-pyrrolidinyl)-2-oxo-1-phenylethyl)carbamate



Example 140, Step a



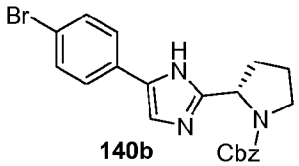
140a

HATU (19.868g, 52.25 mmol) was added to a heterogeneous mixture of *N*-Cbz-L-proline (12.436 g, 49.89 mmol) and the HCl salt of 2-amino-1-(4-bromophenyl) ethanone (12.157 g, 48.53 mmol) in DMF (156 mL). The mixture was lowered in an ice-water bath, and immediately afterward *N,N*-diisopropylethylamine (27 mL, 155 mmol) was added drop wise to it over 13 min. After the addition of the base was completed, the cooling bath was removed and the reaction mixture was stirred for an additional 50 min. The volatile component was removed *in vacuo*; water (125 mL) was added to the resultant crude solid and stirred for about 1 hr. The off-white solid was filtered and washed with copious water, and dried *in vacuo* to afford ketoamide 140a as a white solid (20.68 g). ^{1}H NMR (DMSO-d_6, δ= 2.5 ppm, 400 MHz): 8.30 (m, 1H), 7.91 (m, 2H), 7.75 (d, J = 8.5, 2H), 7.38-7.25 (m, 5H), 5.11-5.03 (m, 2H), 4.57-4.48 (m, 2H), 4.33-4.26 (m, 1H), 3.53-3.36 (m, 2H), 2.23-2.05 (m, 1H), 1.94-1.78 (m, 3H).

LC (Cond. 1): RT = 1.65 min; 98% homogeneity index

LC/MS: Anal. Calcd. for $[M+H]^+$ $C_{21}H_{22}BrN_2O_4$: 445.08; found 445.31

Example 140, Step b



140b

Ketoamide 140a (10.723g, 24.08 mmol) was converted to 140b according to the procedure described for the synthesis of carbamate 132c, with the exception that the crude material was purified by flash chromatography (silica gel; 50% EtOAc/hexanes). Bromide 140b was retrieved as an off-white foam (7.622 g). ^{1}H NMR (DMSO-d_6, δ= 2.5 ppm, 400 MHz): 12.23/12.04/11.97 (m, 1H), 7.73-6.96 (m, 10H), 5.11-4.85 (m, 3H), 3.61 (m, 1H), 3.45 (m, 1H), 2.33-184(m, 4H).

LC (Cond.1): RT = 1.42 min; >95% homogeneity index

LC/MS: Anal. Calcd. for $[M+H]^+$ $C_{21}H_{21}BrN_3O_2$: 426.08; found 426.31

HRMS: Anal. Calcd. for $[M+H]^+$ $C_{21}H_{21}BrN_3O_2$: 426.0817; found: 426.0829

The optical purity of 140b was assessed using the following chiral HPLC methods, and an ee of 99% was observed.

Column: Chiralpak AD, 10 um, 4.6 x 50 mm

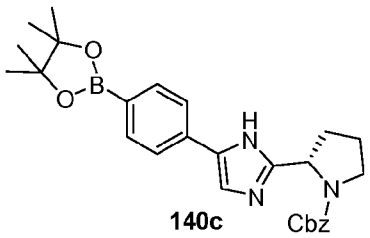
Solvent: 20% ethanol/heptane (isocratic)

Flow rate: 1 ml/min

Wavelength: 254 nm

Relative retention time: 1.82 min (*R*), 5.23 min (*S*)

Example 140, Step c



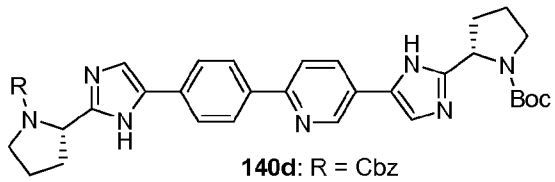
140c

$Pd(Ph_3P)_4$ (208 mg, 0.180 mmol) was added to a pressure tube containing a mixture of bromide 140b (1.80 g, 4.22 mmol), bis(pinacolato)diboron (2.146 g, 8.45 mmol), KOAc (1.8 g, 11.0 mmol) and 1,4-dioxane (34 mL). The reaction flask was purged with nitrogen, capped and heated with an oil bath at 80 °C for 23 hr. The volatile component was removed *in vacuo*, and the residue was partitioned carefully between CH_2Cl_2 (70 mL) and an aqueous medium (22 mL water + 5 mL saturated $NaHCO_3$ solution). The aqueous layer was extracted with CH_2Cl_2, and the combined organic phase was dried ($MgSO_4$), filtered, and concentrated *in vacuo*. The oily resdue was crystallized from EtOAc/hexanes to afford two crops of boronate 140c as a yellow solid (1.52 g). The mother liquor was evaporated *in vacuo* and the resulting material was purified by flash chromatography (silica gel; 20-35% EtOAc/CH_2Cl_2) to afford additional 140c as an off-white solid, containing residual pinacol (772 mg).

LC (Cond. 1): RT = 1.95 min

LC/MS: Anal. Calcd. for $[M+H]^+$ $C_{27}H_{33}BN_3O_4$: 474.26; found 474.31

Example 140, Step d-e



140d: R = Cbz
140e: R = H

Arylbromide 132c was coupled with boronate 140c to afford 140d by using the same procedure described for the synthesis of biaryl 132d. The sample contains the desbromo version of 132c as an impurity. Proceeded to the next step without further purification.

LC (Cond. 1): RT = 1.72 min; ~85% homogeneity index

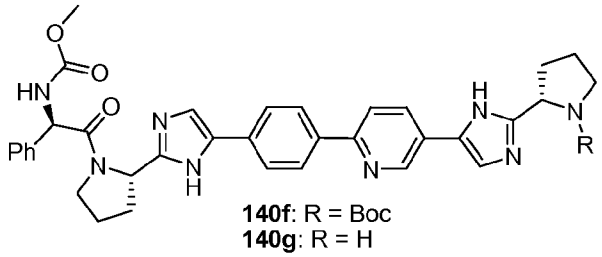
LC/MS: Anal. Calcd. for $[M+H]^+$ $C_{38}H_{42}N_7O_4$: 660.33; found 660.30

A mixture of 10% Pd/C (226 mg), biaryl 140d (1.25 g) and MeOH (15 mL) was stirred under a balloon of hydrogen for ~160 hr, where the hydrogen supply was replenished periodically as needed. The reaction mixture was filtered through a pad of diatomaceous earth (Celite®), and the filtrate was evaporated *in vacuo* to afford crude 140e as a yellowish-brown foam (911 mg). Proceeded to the next step without further purification.

LC (Cond. 1): RT = 1.53 min

LC/MS: Anal. Calcd. for $[M+H]^+$ $C_{30}H_{36}N_7O_2$: 526.29; found 526.23

Example 140, Step f-g



140f: R = Boc
140g: R = H

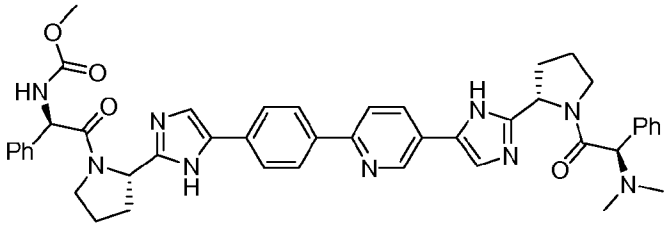
Pyrrolidine 140g was prepared from 140e and *Cap*-4, *via* the intermediacy of carbamate 140f, by sequentially employing the amide forming and Boc-deprotection protocols used in the synthesis of Example 132.

LC (Cond. 1): RT = 1.09 min; ~94% homogeneity index

LC/MS: Anal. Calcd. for $[M+H]^+$ $C_{35}H_{37}N_8O_3$: 617.30; found 617.38

Example 140

methyl ((1R)-2-((2S)-2-(5-(4-(5-(2-((2S)-1-((2R)-2-(dimethylamino)-2-phenylacetyl)-2-pyrrolidinyl)-1H-imidazol-5-yl)-2-pyridinyl)phenyl)-1H-imidazol-2-yl)-1-pyrrolidinyl)-2-oxo-1-phenylethyl)carbamate



The TFA salt of Example 140 was synthesized from pyrrolidine 140g and *Cap*-1 by using the procedure described for the preparation of Example 132 from intermediate 132e.

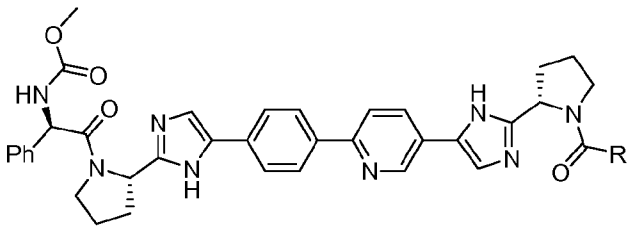
1.15 min (Cond. 1); >98% homogeneity index

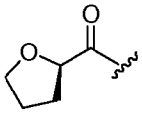
LC/MS: Anal. Calcd. for $[M+H]^+$ $C_{45}H_{40}N_7O_4$: 778.38; found 778.48

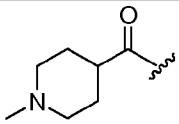
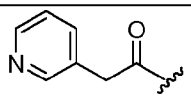
HRMS: Anal. Calcd. for $[M+H]^+$ $C_{45}H_{40}N_7O_4$: 778.3829; found 778.3849

The TFA salt of Example 141-143 were synthesized from intermediate 140g and appropriate reagents in a similar manner.

Example 141-143

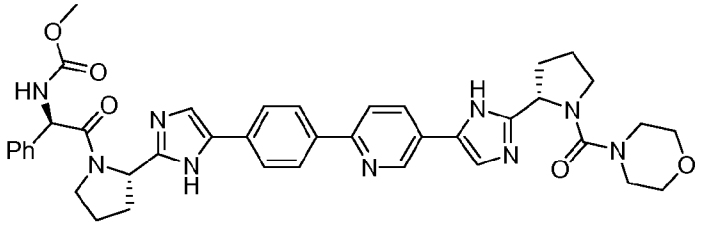


Example	*Compound Name*		*RT (LC-Cond.); % homogeneity index; MS data*
141	methyl ((1R)-2-oxo-1-phenyl-2-((2S)-2-(5-(4-(5-(2-((2S)-1-((2R)-tetrahydro-		1.15 min (Cond. 1); >98% LC/MS: Anal. Calcd. for

	2-furanylcarbonyl)-2-pyrrolidinyl)-1H-imidazol-5-yl)-2-pyridinyl)phenyl)-1H-imidazol-2-yl)-1-pyrrolidinyl)ethyl)carbamate		$[M+H]^+$ $C_{40}H_{43}N_8O_5$: 715.34; found 715.44 HRMS: Anal. Calcd. for $[M+H]^+$ $C_{40}H_{43}N_8O_5$: 715.3356; found 715.3381
142	methyl ((1R)-2-((2S)-2-(5-(4-(5-(2-((2S)-1-((1-methyl-4-piperidinyl)carbonyl)-2-pyrrolidinyl)-1H-imidazol-5-yl)-2-pyridinyl)phenyl)-1H-imidazol-2-yl)-1-pyrrolidinyl)-2-oxo-1-phenylethyl)carbamate		1.07 min (Cond. 1); >98% LC/MS: Anal. Calcd. for $[M+H]^+$ $C_{42}H_{48}N_9O_4$: 742.38; found 742.48 HRMS: Anal. Calcd. for $[M+H]^+$ $C_{42}H_{48}N_9O_4$: 742.3829; found 742.3859
143	methyl ((1R)-2-oxo-1-phenyl-2-((2S)-2-(5-(4-(5-(2-((2S)-1-(3-pyridinylacetyl)-2-pyrrolidinyl)-1H-imidazol-5-yl)-2-pyridinyl)phenyl)-1H-imidazol-2-yl)-1-pyrrolidinyl)ethyl)carbamate		1.09 min (Cond. 1); >98% LC/MS: Anal. Calcd. for $[M+H]^+$ $C_{42}H_{42}N_9O_4$: 736.34; found 736.44 HRMS: Anal. Calcd. for $[M+H]^+$ $C_{42}H_{42}N_9O_4$: 736.3360; 736.3344

Example 144

methyl ((1R)-2-((2S)-2-(5-(4-(5-(2-((2S)-1-(4-morpholinylcarbonyl)-2-pyrrolidinyl)-1H-imidazol-5-yl)-2-pyridinyl)phenyl)-1H-imidazol-2-yl)-1-pyrrolidinyl)-2-oxo-1-phenylethyl)carbamate



A DMF (1.5 mL) solution of morpholine-4-carbonyl chloride (8.5 mg, 0.057 mmol) was added to a mixture of *i*-Pr_2EtN (20 μL, 0.115 mmol) and 140g (27.3 mg, 0.044 mmol), and stirred for 100 min. The volatile component was removed *in vacuo* and the residue was purified by a reverse phase HPLC (H_2O/MeOH/TFA) to afford the TFA salt of Example 144 as a yellow foam (34.6 mg).

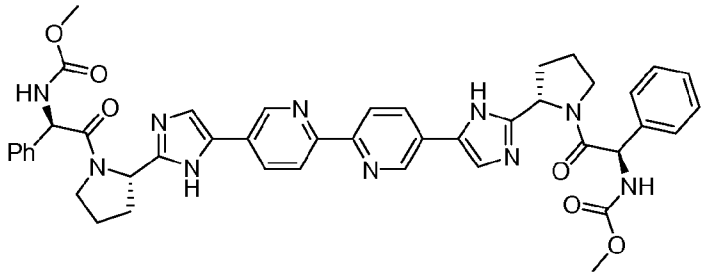
1.17 min (Cond. 1); >98%

LC/MS: Anal. Calcd. for $[M+H]^+$ $C_{40}H_{44}N_9O_5$: 730.35; found 730.42

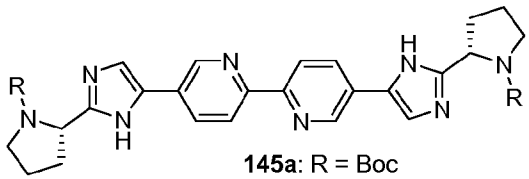
HRMS: Anal. Calcd. for $[M+H]^+$ $C_{40}H_{44}N_9O_5$: 730.3465; found 730.3477

Example 145

dimethyl (2,2'-bipyridine-5,5'-diylbis(1H-imidazole-5,2-diyl(2S)-2,1-pyrrolidinediyl((1R)-2-oxo-1-phenyl-2,1-ethanediyl)))biscarbamate



Example 145, Step a-b



145a: R = Boc
145b: R = H

$Pd(Ph_3P)_4$ (9.6 mg, 0.008 mmol) and LiCl (28 mg, 0.67 mmol) were added to a mixture of arylbromide 132c (98.7 mg, 0.251 mmol) and hexamethylditin (51.6 mg, 0.158 mmol), and heated at 80 °C for ~ 3 days. The volatile component was removed *in vacuo* and the resultant crude material was purified by flash chromatography (silica gel; 0-10% MeOH/EtOAc) followed by a reverse phase HPLC (H_2O/MeOH/TFA). The HPLC elute was neutralized with excess 2.0 N NH_3/MeOH, and the volatile component was removed *in vacuo*. The residue was partitioned between CH_2Cl_2 and water, and the aqueous phase was washed with CH_2Cl_2 (2x).

The combined organic phase was dried ($MgSO_4$), filtered, and concentrated *in vacuo* to afford carbamate 145a as a film of oil (8.7 mg).

LC (Cond. 1): RT = 1.68 min; >98% homogeneity index

LC/MS: Anal. Calcd. for $[M+H]^+$ $C_{34}H_{43}N_8O_4$: 627.34; found 627.47

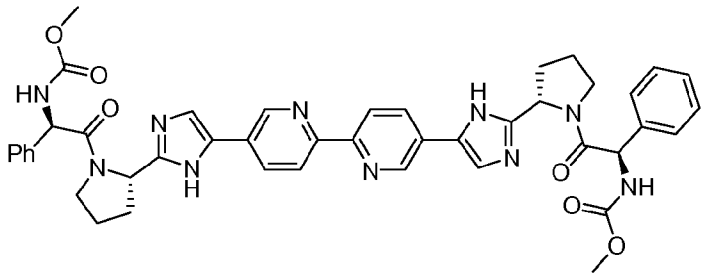
Carbamate 145a was elaborated to pyrrolidine 145b according to the preparation of 132c from 132d. ^1H NMR (DMSO, δ = 2.5 ppm; 400 MHz): 12.02 (br signal, 2H), 9.04 (d, J = 1.6, 2H), 8.34 (d, J = 8.3, 2H), 8.20 (dd, J = 8.3, 2.3, 2H), 7.67 (br s, 1H), 4.21 (m, 2H), 3.00-2.85 (m, 4H), 2.12-2.04 (m, 2H), 1.95-1.68 (m, 6H). [Note: the pyrrolidine-NH signal was not observed].

LC (Cond.1): RT = 1.17 min; >98% homogeneity index

LC/MS: Anal. Calcd. for $[M+H]^+$ $C_{24}H_{27}N_8$: 427.24; found 427.13

Example 145

dimethyl (2,2'-bipyridine-5,5'-diylbis(1H-imidazole-5,2-diyl(2S)-2,1-pyrrolidinediyl((1R)-2-oxo-1-phenyl-2,1-ethanediyl)))biscarbamate



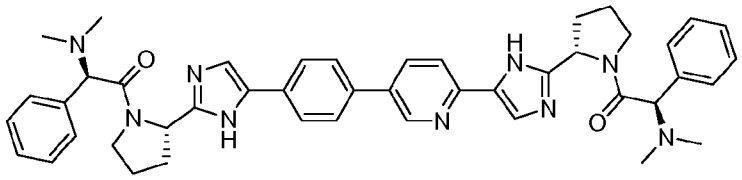
Example 145 (TFA salt) was synthesized from 145b according to the preparation of Example 132 from 132e.

LC (Cond. 1): RT = 1.63 min; 98% homogeneity index

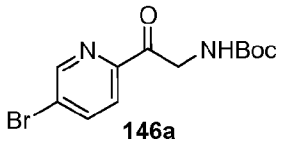
LC/MS: Anal. Calcd. for $[M+H]^+$ $C_{44}H_{45}N_{10}O_6$: 809.35; found 809.40

Example 146

(1R)-2-((2S)-2-(5-(5-(4-(2-((2S)-1-((2R)-2-(dimethylamino)-2-phenylacetyl)-2-pyrrolidinyl)-1H-imidazol-5-yl)phenyl)-2-pyridinyl)-1H-imidazol-2-yl)-1-pyrrolidinyl)-N,N-dimethyl-2-oxo-1-phenylethanamine



Example 146, Step a



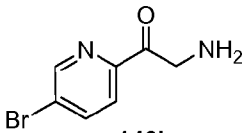
146a

n-BuLi (12.0 mL of 2.5M/hexanes, 30 mmol) was added drop-wise over 15 min to a cooled (-78 °C) toluene (300 mL) semi-solution of 2,5-dibromopyridine (6.040 g, 25.5 mmol), and stirred for 2.5 hr. *t*-Butyl 2-(methoxy(methyl)amino)-2-oxoethylcarbamate (2.809 g, 12.87 mmol) was added in batches over 7 min, and stirring continued for 1.5 hr at -78 °C. The -78 °C bath was replaced with -60 °C bath, which was allowed to warm up to -15 °C over 2.5 hr. The reaction was quenched with saturated NH_4Cl solution (20 mL), and the mixture was allowed to thaw to ambient temperature and the organic layer was separated and evaporated *in vacuo*. The resulting crude material was purified by flash chromatography (silica gel; 15 % EtOAc/hexanes) to afford a reddish brown semisolid, which was washed with hexanes to removed the colored residue. Pyridine 146a was retrieved as an ash colored solid (842 mg). ^{1}H NMR (DMSO, δ = 2.5 ppm; 400 MHz): 8.89 (d, J = 2.3, 1H), 8.30 (dd, J = 8.4, 2.4, 1H), 7.90 (d, J = 8.3, 1H), 7.03(br t, J = 5.7; 0.88H), 6.63 (app br s, 0.12H), 4.55 (d, J = 5.8, 2H), 1.40/1.28 (two app s, 7.83H + 1.17H).

LC (Cond. 1): RT = 2.00 min; >95% homogeneity index

LC/MS: Anal. Calcd. for $[M+Na]^+$ $C_{12}H_{15}BrNaN_2O_3$: 337.02; found 337.13

Example 146, Step b



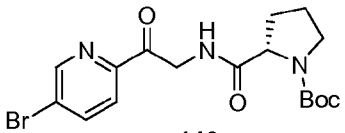
146b

48% HBr (1.0 mL) was added drop-wise to a dioxane (5.0 mL) solution of carbamate 146a (840 mg, 2.66 mmol) over 3 min, and the reaction mixture was stirred at ambient temperature for 17.5 hr. The precipitate was filtered and washed with dioxane, and dried *in vacuo* to afford amine the HBr salt of 146b as an off-white solid (672.4 mg; the exact mole equivalent of the HBr salt was not determined). ^{1}H NMR (DMSO, δ = 2.5 ppm; 400 MHz): 8.95 (d, J = 2.3, 1 H), 8.37 (dd, J = 8.4, 2.3, 1H), 8.2 (br s, 3H), 8.00 (d, J = 8.3, 1H), 4.61 (s, 2H).

LC (Cond. 1): RT = 0.53 min

LC/MS: Anal. Calcd. for $[M+H]^+$ $C_7H_8BrN_2O$: 214.98; found 215.00

Example 146, Step c



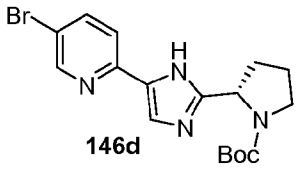
146c

i-Pr_2EtN (2.3 mL, 13.2 mmol) was added drop-wise over 15 min to a heterogonous mixture of amine 146b (1.365g), (*S*)-Boc-proline (0.957 g, 4.44 mmol) and HATU (1.70 g, 4.47 mmol) in DMF (13.5 mL), and stirred at ambient temperature for 1 hr. The volatile component was removed *in vacuo* and the residue was partitioned between EtOAc (40 mL) and an aqueous medium (20 mL water + 1 ml saturated $NaHCO_3$ solution). The aqueous layer was washed with EtOAc (20 mL), and the combined organic phase was dried ($MgSO_4$), filtered, and concentrated *in vacuo*. The resultant crude material was purified by flash chromatography (silica gel; 40-50% EtOAc/hexanes) to afford ketoamide 146c as a faint-yellow foam (1.465g). ^{1}H NMR (DMSO, δ = 2.5 ppm; 400 MHz): 8.90 (d, J = 2.3, 1H), 8.30 (dd, J = 8.5, 2.4, 1H), 8.01-8.07 (m, 1H), 7.90 (d, J = 8.3, 1H), 4.6 (m, 1H), 4.64 (dd, J = 19.1, 5.5, 1H); 4.19 (m, 1H), 3.39 (m, 1H), 3.32-3.26 (m, 1H), 2.20-2.01 (m, 1H), 1.95-1.70 (m, 3H),1.40/1.35 (two app s, 9H).

LC (Cond. 1): RT = 1.91 min

LC/MS: Anal. Calcd. for $[M+Na]^+$ $C_{17}H_{22}BrN_3NaO_4$: 434.07; found 433.96.

Example 146, Step d



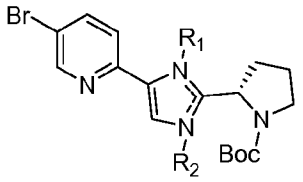
146d

A mixture of ketoamide 146c (782.2 mg, 1.897 mmol) and NH_4OAc (800 mg, 10.4 mmol) in xylenes was heated with a microwave (140 °C) for 90 min. The volatile component was removed *in vacuo* and the residue was carefully partitioned between CH_2Cl_2 and water, where enough saturated $NaHCO_3$ solution was added to neutralize it. The aqueous phase was extracted with CH_2Cl_2 (2x), and the combined organic phase was dried ($MgSO_4$), filtered, and concentrated *in vacuo*. The resultant crude material was purified by flash chromatography (silica gel; 50% CH_2Cl_2/EtOAc) to afford imidazole 146d as an off-white solid (552.8 mg). ^1H NMR (DMSO, δ = 2.5 ppm; 400 MHz): 12.49/12.39/12.15/12.06 (br s, 1H), 8.62 (app br s, 0.2H), 8.56 (d, J = 2, 0.8H), 8.02 (br d, J = 8.5, 0.2H), 7.97 (br d, J = 7.8, 0.8H), 7.77 (d, J = 8.6, 0.8H), 7.72 (d, J = 8.6, 0.2H), 7.61-7.49 (m, 1H), 4.93-4.72 (m, 1H), 3.53 (m, 1H), 3.41-3.32 (m, 1H), 2.33-1.77 (m, 4H), 1.39/1.14 (app br s, 3.7H+5.3H).

LC (Cond. 1): RT = 1.67 min; >95% homogeneity index

LC/MS: Anal. Calcd. for $[M+Na]^+$ $C_{17}H_{21}BrN_4NaO_2$: 415.08; found 415.12

Example 146, Step e



146e (R_1 = H, R_2 = SEM) or (R_1 = SEM, R_2 = H)

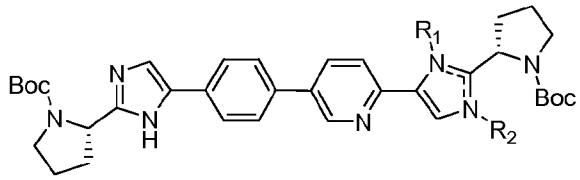
NaH (60%; 11.6 mg, 0.29 mmol) was added in one batch to a heterogeneous mixture of imidazole 146d (80 mg, 0.203 mmol) and DMF (1.5 mL), and stirred at ambient condition for 30 min. SEM-Cl (40 µL, 0.226 mmol) was added drop-wise over 2 min to the above reaction mixture, and stirring was continued for 14 hr. The volatile component was removed *in vacuo* and the residue was partitioned between

water and CH_2Cl_2. The aqueous layer was extracted with CH_2Cl_2, and the combined organic phase was dried ($MgSO_4$), filtered, and concentrated *in vacuo*. The crude material was purified by a flash chromatography (silica gel; 20% EtOAc/hexanes) to afford 146e as a colorless viscous oil (87.5 mg). The exact regiochemistry of 146e was not determined. ^1H NMR ($CDCl_3$, δ = 7.4 ppm; 400 MHz): 8.53 (d, J = 2.2, 1H), 7.90-7.72 (m, 2H), 7.52 (s, 1H), 5.87 (m, 0.46H), 5.41 (m, 0.54H), 5.16 (d, J = 10.8, 1H), 5.03-4.85 (m, 1H), 3.76-3.42 (m, 4H), 2.54-1.84 (m, 4H), 1.38/1.19 (br s, 4.3H + 4.7H), 0.97-0.81 (m, 2H), -0.03 (s, 9H).

LC (Cond. 1): RT = 2.1 min

LC/MS: Anal. Calcd. for $[M+H]^+$ $C_{23}H_{36}BrN_4O_3Si$: 523.17; found 523.24

Example 146, Step f



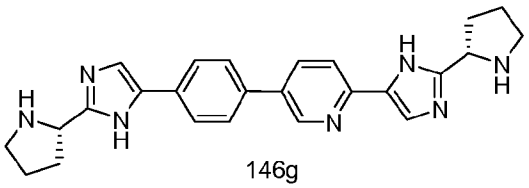
146f: (R_1 = H, R_2 = SEM) or (R_1 = SEM, R_2 = H)

$Pd(Ph_3P)_4$ (24.4 mg, 0.021 mmol) was added to a mixture of imidazole 146e (280 mg, 0.535 mmol), 1c (241.5 mg, 0.55 mmol) and $NaHCO_3$ (148.6 mg, 1.769 mmol) in 1,2-dimethoxyethane (4.8 mL) and water (1.6 mL). The reaction mixture was flushed with nitrogen, heated with an oil bath at 80 °C for ~24 hr and then the volatile component was removed *in vacuo*. The residue was partitioned between CH_2Cl_2 and water, and the organic phase was dried ($MgSO_4$), filtered, and concentrated *in vacuo*. The crude material was purified by a Biotage system (silica gel; 75-100% EtOAc/hexanes) followed by a reverse phase HPLC (H_2O/MeOH/TFA). The HPLC elute was neutralized with 2M NH_3/MeOH and evaporated *in vacuo*, and the residue was partitioned between water and CH_2Cl_2. The organic layer was dried ($MgSO_4$), filtered, and concentrated *in vacuo* to afford 146f as a white foam (162 mg).

LC (Cond. 1): RT = 2.1 min

LC/MS: Anal. Calcd. for $[M+H]^+$ $C_{41}H_{58}N_7O_5Si$: 756.43; found 756.55

Example 146, Step g



146g

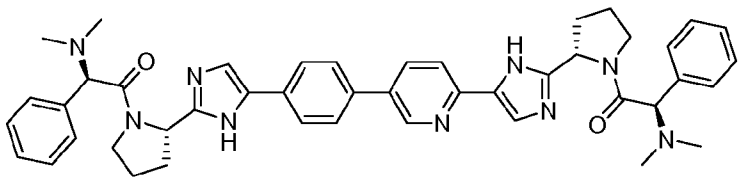
Carbamate 146f (208 mg, 0.275 mmol) was treated with 25% TFA/CH_2Cl_2 (4.0 mL) and stirred at ambient temperature for 10 hr. The volatile component was removed *in vacuo* and the residue was first free-based by MCX (MeOH wash; 2.0 M NH_3/MeOH elution) and then purified by a reverse phase HPLC (H_2O/MeOH/TFA), and the resultant material was free-based again (MCX) to afford pyrrolidine 146g as a film of oil (53.7 mg). ^{1}H NMR (DMSO, δ = 2.5 ppm; 400 MHz): 1.88 (app br s, 2H), 8.83 (d, J = 2.1, 1H), 8.07 (dd, J = 8.3/2.3, 1H0, 7.87 (d, J = 8.5, 1H), 7.84 (d, J = 8.3, 2H), 7.71 (d, J = 8.3, 2H), 7.55 (s, 1H), 7.50 (br s, 1H), 4.18 (m, 2H), 3.00-2.94 (m, 2H), 2.89-2.83 (m, 2H), 2.11-2.02 (m, 2H), 1.95-1.86 (m, 2H), 1.83-1.67 (m, 4H).

LC (Cond. 1): RT = 0.95 min; >98% homogeneity index

LC/MS: Anal. Calcd. for $[M+H]^+$ $C_{25}H_{28}N_7$: 426.24; found 426.27

Example 146

(1R)-2-((2S)-2-(5-(5-(4-(2-((2S)-1-((2R)-2-(dimethylamino)-2-phenylacetyl)-2-pyrrolidinyl)-1H-imidazol-5-yl)phenyl)-2-pyridinyl)-1H-imidazol-2-yl)-1-pyrrolidinyl)-N,N-dimethyl-2-oxo-1-phenylethanamine



Example 146 (TFA salt) was synthesized from pyrrolidine 146g according to the preparation of Example 132 from intermediate 132e.

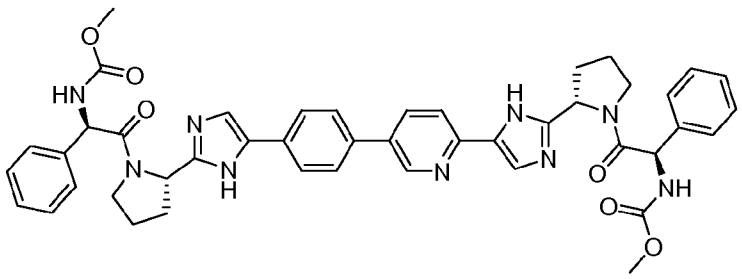
LC (Cond. 1): RT = 1.42 min; 96.5% homogenity index

LC/MS: Anal. Calcd. for $[M+H]^+$ $C_{45}H_{50}N_9O_2$: 748.41; found 748.57

HRMS: Anal. Calcd. for $[M+H]^+$ $C_{45}H_{50}N_9O_2$: 748.4087; found 748.4100

Example 147

methyl ((1R)-2-((2S)-2-(5-(5-(4-(2-((2S)-1-((2R)-2-((methoxycarbonyl)amino)-2-phenylacetyl)-2-pyrrolidinyl)-1H-imidazol-5-yl)phenyl)-2-pyridinyl)-1H-imidazol-2-yl)-1-pyrrolidinyl)-2-oxo-1-phenylethyl)carbamate



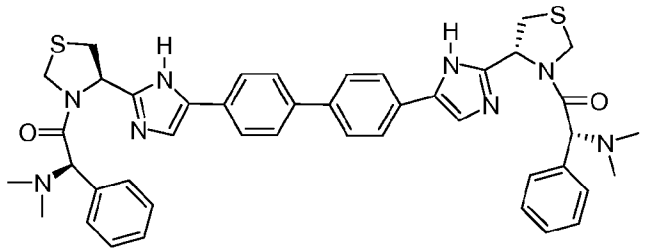
The TFA salt of Example 147 was prepared similarly from intermediate 146g by using *Cap*-4.

LC (Cond. 1): RT = 1.66 min; 95% homogenity index

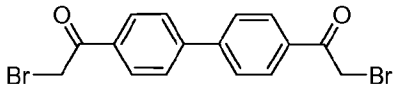
LC/MS: Anal. Calcd. for $[M+H]^+$ $C_{45}H_{46}N_9O_6$: 808.36; found 808.55

Example 148

(1R,1'R)-2,2'-(4,4'-biphenyldiylbis(1H-imidazole-5,2-diyl(4R)-1,3-thiazolidine-4,3-diyl))bis(N,N-dimethyl-2-oxo-1-phenylethanamine)



Example 148, Step a



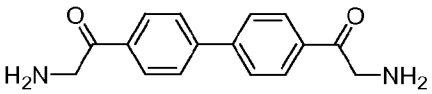
A solution of bromine (1.3mL, 25.0mmol) in 15mL glacial acetic acid was added drop-wise to a solution of 4-4'-diacetylbiphenyl (3.0g, 12.5mmol) in 40mL acetic acid at 50°C. Upon completion of addition the mixture was stirred at room temperature overnight. The precipitated product was filtered off and re-crystallized

from chloroform to give 1,1'-(biphenyl-4,4'-diyl)bis(2-bromoethanone) (3.84g, 77.5%) as a white solid.

^{1}H NMR (500 MHz, CHLOROFORM-D) δ ppm 8.09 (4 H, d, *J*=7.93 Hz) 7.75 (4 H, d, *J*=8.24 Hz) 4.47 (4 H, s)

Nominal/LRMS – Anal. Calcd. for 369.07 found; $(M+H)^+$ - 397.33, $(M-H)^-$ - 395.14

Example 148, Step b



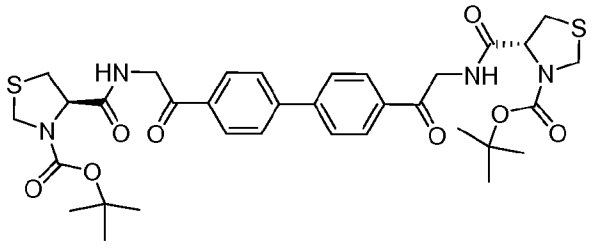
.2HCl

Sodium diformylamide (3.66g, 38.5mmol) was added to a suspension of 1,1'-(biphenyl-4,4'-diyl)bis(2-bromoethanone) (6.1g, 15.4mmol) in 85mL acetonitrile. The mixture was heated at reflux for 4 hours and concentrated under reduced pressure. The residue was suspended in 300mL 5% HCl in ethanol and heated at reflux for 3.5 hours. Reaction was cooled to room temperature and placed in the freezer for 1 hour. Precipitated solid was collected, washed with 200mL 1:1 ethanol/ether followed by 200mL pentane, and dried under vacuum to give 1,1'-(biphenyl-4,4'-diyl)bis(2-aminoethanone) dihydrochloride (4.85g, 92%). Carried on without further purification.

^{1}H NMR (300 MHz, DMSO-d_6) δ ppm 8.47-8.55 (4H, m) 8.11 - 8.17 (4 H, m) 8.00 (4 H, d, *J*=8.42 Hz) 4.59 - 4.67 (4 H, m).

LCMS – Phenomenex C-18 3.0 x 50mm, 0 to 100% B over 4.0 minute gradient, 1 minute hold time, A = 10% methanol 90% water 0.1% TFA, B = 90% methanol 10% water 0.1% TFA, t_R = 0.44 minutes, Anal. Calcd. for $C_{16}H_{16}N_2O_2$ 268.31 found; 269.09 $(M+H)^+$.

Example 148, Step c

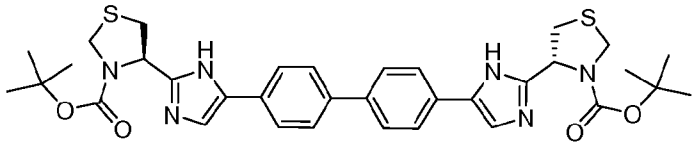


To a stirred solution of 1,1'-(biphenyl-4,4'-diyl)bis(2-aminoethanone) dihydrochloride (0.7g, 2.1mmol), N-(tert-butoxy carbonyl) –L-thioproline (0.96g, 4.2mmol), and HATU(1.68g, 4.4mmol) in 14mL DMF was added diisopropylethyl amine (1.5mL, 8.4mmol) drop-wise over 5 minutes. The resulting clear yellow solution was stirred at room temperature overnight (14 hours) and concentrated under reduced pressure. The residue was partitioned between 20%methanol/chloroform and water. The aqueous phase was washed once with 20%methanol/chloroform. The combined organics were washed with brine, dried ($MgSO_4$), filtered, and concentrated under reduced pressure. The crude product was chromatographed on silica gel by gradient elution with 10-50% ethyl acetate/CH_2Cl_2 to give (4S,4'S)-tert-butyl 4,4'-(2,2'-(biphenyl-4,4'-diyl)bis(2-oxoethane-2,1-diyl))bis(azanediyl)bis(oxomethylene)dithiazolidine-3-carboxylate (0.39g, 27%) as an orange foam.

^{1}H NMR (400 MHz, DMSO-d_6) δ ppm 8.38 (2 H, s) 8.12 (4 H, d, *J*=8.56 Hz) 7.94 (4 H, d, *J*=8.56 Hz) 4.60 - 4.68 (4 H, m) 4.33 - 4.38 (2 H, m) 3.58 - 3.68 (2 H, m) 3.38 (2 H, s) 3.08 - 3.18 (2 H, m) 1.40 (18 H, s)

LCMS – Water-Sunfire C-18 4.6 x 50mm, 0 to 100% B over 4.0 minute gradient, 1 minute hold time, A = 10% methanol 90% water 0.1% TFA, B = 90% methanol 10% water 0.1% TFA, t_R = 3.69 min., Anal. Calcd. for $C_{34}H_{42}N_4O_8S_2$ 698.85 found; 699.12 $(M+H)^+$.

Example 148, Step d



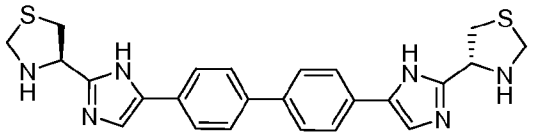
(4S,4'S)-tert-butyl 4,4'-(5,5'-(biphenyl-4,4'-diyl)bis(1H-imidazole-5,2-diyl))dithiazolidine-3-carboxylate (0.39g, 0.56mmol) and ammonium acetate (0.43g, 5.6mmol) were suspended in 8mL o-xylene in a microwave reaction vessel. The mixture was heated under standard microwave conditions at 140°C for 70 minutes and concentrated under reduced pressure. The residue was dissolved in 30mL 20% methanol/chloroform and washed with 10% $NaHCO_3$(aq). The organic layer was washed with brine, dried ($MgSO_4$), filtered, and concentrated under reduced pressure.

The crude product was chromatographed on silica gel by gradient elution with 1-6% methanol/CH_2Cl_2 to give (4S,4'S)-tert-butyl 4,4'-(5,5'-(biphenyl-4,4'-diyl)bis(1H-imidazole-5,2- diyl))dithiazolidine-3-carboxylate (0.15g, 41%) as a yellow solid.

^{1}H NMR (500 MHz, DMSO-d_6) δ ppm 12.02 (2 H, s) 7.70 - 7.88 (10 H, m) 5.28 - 5.37 (2 H, m) 4.68 (2 H, d, *J*=9.16 Hz) 4.47 - 4.55 (2 H, m) 3.46 (2 H, s) 3.23 (2 H, s) 1.26 – 1.43 (18 H, m)

LCMS - Luna C-18 3.0 x 50mm, 0 to 100% B over 3.0 minute gradient, 1 minute hold time, A = 5% acetonitrile, 95% water, 10mm ammonium acetate, B = 95% acetonitrile, 5% water, 10mm ammonium acetate, t_R = 1.96 min., Anal. Calcd. for $C_{34}H_{40}N_6O_4S_2$ 660.85 found; 661.30 $(M+H)^+$, 659.34 $(M-H)^-$

Example 148, Step e



.4HCl

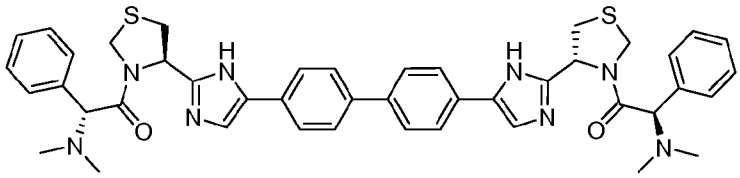
To a solution of (4S,4'S)-tert-butyl 4,4'-(5,5'-(biphenyl-4,4'-diyl)bis(1H-imidazole-5,2- diyl))dithiazolidine-3-carboxylate in 1mL dioxane was added 0.3mL of a 4.0M solution of HCl in dioxane. The reaction was stirred for 3 hours at room temperature and concentrated under reduced pressure. The resulting tan solid was dried under vacuum to give 4,4'-bis(2-((S)-thiazolidin-4-yl)-1H-imidazol-5-yl)biphenyl tetrahydrochloride (0.12g, 100%) as a yellow solid.

^{1}H NMR (500 MHz, DMSO-d_6) δ ppm 8.09 (2 H, s) 8.01 (4 H, d, *J*=8.55 Hz) 7.90 (4 H, d, *J*=8.55 Hz) 5.08 (2 H, t, *J*=6.10 Hz) 4.38 (2 H, d, *J*=9.16 Hz) 4.23 (2 H, d, *J*=9.46 Hz) 3.48 - 3.54 (2 H, m,) 3.35 - 3.41 (2 H, m)

LCMS - Luna C-18 3.0 x 50mm, 0 to 100% B over 4.0 minute gradient, 1 minute hold time, A = 5% acetonitrile, 95% water, 10mm ammonium acetate, B = 95% acetonitrile, 5% water, 10mm ammonium acetate, t_R = 1.70 min., Anal. Calcd. for $C_{24}H_{24}N_6S_2$ 460.62 found; 461.16 $(M+H)^+$, 459.31 $(M-H)^-$

Example 148

(1R,1'R)-2,2'-(4,4'-biphenyldiylbis(1H-imidazole-5,2-diyl(4R)-1,3-thiazolidine-4,3-diyl))bis(N,N-dimethyl-2-oxo-1-phenylethanamine)



To a stirred solution of (4,4'-bis(2-((S)-thiazolidin-4-yl)-1H-imidazol-5-yl)biphenyl tetrahydrochloride (0.028g, 0.046mmol), (R)-2-(dimethylamino)-2-phenylacetic acid (*Cap*-1, 0.017g, 0.0.10mmol), and HATU (0.039g, 0.10mmol) in 2mL DMF was added diisopropylethyl amine (0.05mL, 0.28mmol).The reaction was stirred at room temperature overnight (16 hours) and concentrated under reduced pressure. The crude product was purified by reverse-phase preparative HPLC to provide (2R,2'R)-1,1'-((4S,4'S)-4,4'-(5,5'-(biphenyl-4,4'-diyl)bis(1H-imidazole-5,2-diyl))bis(thiazolidine-4,3-diyl))bis(2-(dimethylamino)-2-phenylethanone), TFA salt (0.012g, 21%)

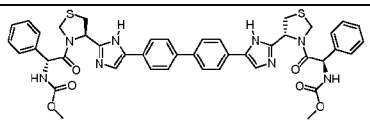
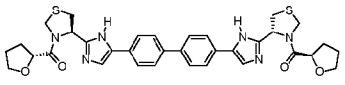
^{1}H NMR (500 MHz, DMSO-d_6) δ ppm 7.59 - 7.91 (20 H, m) 5.62 (2 H, dd, *J*=6.56, 2.59 Hz) 4.99 (2 H, d, *J*=8.85 Hz) 4.82/4.35 (2 H, s) 4.22 (2 H, s) 3.42 (2 H, s) 3.25 (2 H, s) 2.35-2.61 (12H, m)

LCMS - Luna C-18 3.0 x 50mm, 0 to 100% B over 7.0 minute gradient, 1 minute hold time, A = 5% acetonitrile, 95% water, 10mm ammonium acetate, B = 95% acetonitrile, 5% water, 10mm ammonium acetate mobile phase t_R = 3.128 min.

Nominal/LRMS – Calcd. for $C_{44}H_{46}N_8O_2S_2$ 783.03; found 783.28 $(M+H)^+$
Accurate/HRMS – Calcd. for $C_{44}H_{47}N_8O_2S_2$ 783.3263; 783.3246 $(M+H)^+$

Examples 149 and 150 were prepared in similar fashion as described for the preparation of example 148.

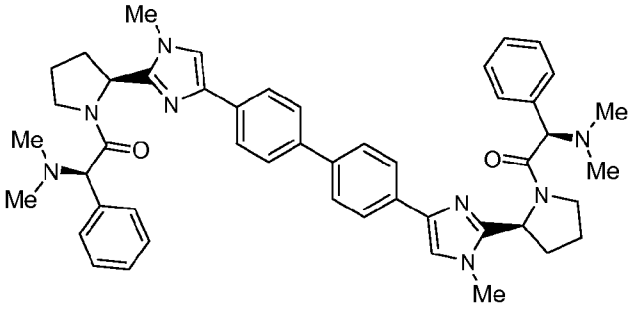
Example	*Compound Name*	*Structure*	*Data*
Example 149	dimethyl (4,4'-biphenyldiylbis(1H-		t_R = 3.36 min (LCMS - Luna C-

	imidazole-5,2-diyl(4R)-1,3-thiazolidine-4,3-diyl((1R)-2-oxo-1-phenyl-2,1-ethanediyl)))biscarbamate	 from 148e and *Cap*-4	18 3.0 x 50mm, 0 to 100% B over 7.0 minute gradient, 1 minute hold time, A = 5% acetonitrile, 95% water, 10mm ammonium acetate, B = 95% acetonitrile, 5% water, 10mm ammonium acetate) LRMS: Anal. Calcd. for $C_{44}H_{42}N_8O_6S_2$ 842.99 found: 843.25 $(M+H)^+$ HRMS: Anal. Calcd. for $C_{44}H_{43}N_8O_6S_2$ 843.2747 found: 843.2724 $(M+H)^+$
Example 150	(4R,4'R)-4,4'-(4,4'-biphenyldiylbis(1H-imidazole-5,2-diyl))bis(3-((2R)-tetrahydro-2-furanylcarbonyl)-1,3-thiazolidine)	 from 148e and tetrahydrofuroic acid	t_R = 4.32 min (HPLC – X-Terra C-18 4.6 x 50mm, 0 to 100% B over 10.0 minute gradient, 1 minute hold

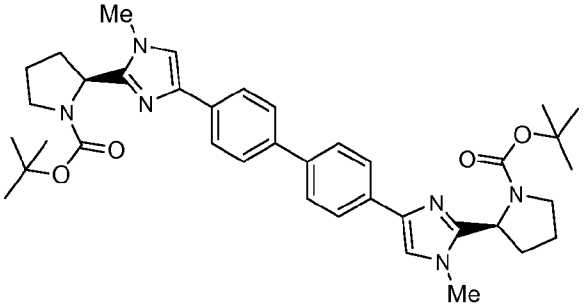
			time, A = 10% methanol 90% water 0.1% TFA, B = 90% methanol 10% water 0.1% TFA) LRMS: Anal. Calcd. for $C_{34}H_{36}N_6O_4S_2$ 656.83 found: 657.32 $(M+H)^+$

Example 151

(1R,1'R)-2,2'-(4,4'-biphenyldiylbis((1-methyl-1H-imidazole-4,2-diyl)(2S)-2,1-pyrrolidinediyl))bis(N,N-dimethyl-2-oxo-1-phenylethanamine)



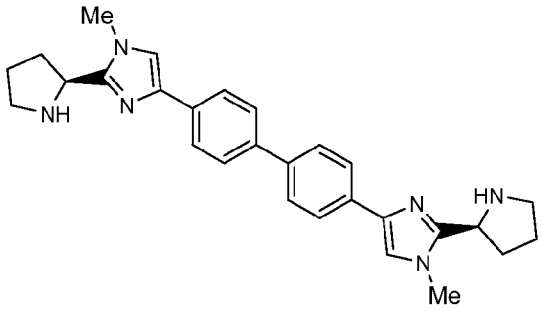
Example 151, Step a



To a stirred solution of 1d, (2S,2'S)-tert-butyl 2,2'-(4,4'-(biphenyl-4,4'-diyl)bis(1H-imidazole-4,2-diyl))dipyrrolidine-1-carboxylate (100 mg, 0.16 mmole)

and iodomethane (40 μL, 0.16 mmole) in CH_2Cl_2 (2 mL) was added sodium hydride (40%) (21.2 mg, 0.352 mmole). After five hours at ambient temperature, it was concentrated under reduced pressure. The crude reaction product 151a, (2S,2'S)-tert-butyl 2,2'-(4,4'-(biphenyl-4,4'-diyl)bis(1-methyl-1H-imidazole-4,2-diyl))dipyrrolidine-1-carboxylate (~ 90 mg) was moved onto next step without further purification (purity ~ 85%) LCMS: Anal. Calcd. for: $C_{38}H_{48}N_6O_4$ 652.83; Found: 653.51 $(M+H)^+$. It should be recognized that multiple methylation isomers are possible in this reaction and no attempt to assign these was made.

Example 151, Step b



151a, (2S,2'S)-tert-butyl 2,2'-(4,4'-(biphenyl-4,4'-diyl)bis(1-methyl-1H-imidazole-4,2-diyl))dipyrrolidine-1-carboxylate (100 mg, 0.153 mmole) treated with 4 M HCl/dioxane (20 mL). After three hours at ambient temperature, it was concentrated under reduced pressure. The crude reaction product, 4,4'-bis(1-methyl-2-((S)-pyrrolidin-2-yl)-1H-imidazol-4-yl)biphenyl(~110 mg, HCl salt) was moved onto the next step without further purification (purity ~ 85%) LCMS: Anal. Calcd. for: $C_{28}H_{32}N_6$ 452.59; Found: 453.38 $(M+H)^+$. Multiple imidazole isomers were present and carried forward.

Example 151

HATU (58.9 mg, 0.150 mmol) was added to a mixture of 151b, 4,4'-bis(1-methyl-2-((S)-pyrrolidin-2-yl)-1H-imidazol-4-yl)biphenyl (45.0 mg, 0.075 mmol), (*i*-Pr)$_2$EtN (78 μL, 0.451 mmol) and *Cap*-1, (*R*)-2-(dimethylamino)-2-phenylacetic acid (0.026 mg 0.150mmol) in DMF (1.0 mL). The resultant mixture was stirred at ambient temperature until the coupling was complete as determined by LC/MS analysis. Purification was accomplished by reverse-phase preparative HPLC

(Waters-Sunfire 30 X 100mm S5, detection at 220 nm, flow rate 30 mL/min, 0 to 90% B over 14 min; A = 90% water, 10 % ACN, 0.1% TFA, B = 10% water, 90 % ACN, 0.1% TFA) to provide two isomer of 151, (2R,2'R)-1,1'-((2S,2'S)-2,2'-(4,4'-(biphenyl-4,4'-diyl)bis(1-methyl-1H-imidazole-4,2-diyl))bis(pyrrolidine-2,1-diyl))bis(2-(dimethylamino)-2-phenylethanone), TFA salts.

Isomer 1: *(1R,1'R)-2,2'-(4,4'-biphenyldiylbis((1-methyl-1H-imidazole-4,2-diyl)(2S)-2,1-pyrrolidinediyl))bis(N,N-dimethyl-2-oxo-1-phenylethanamine)*

(8 mg, 8.6%) as a colorless wax.

^{1}H NMR (500 MHz, DMSO-d_6) δ ppm 1.84 - 2.25 (m, 8 H) 2.32 - 2.90 (m, 12 H) 3.67 - 3.92 (m, 8 H) 4.07 (s, 2 H) 5.23 (s, 2 H) 5.51 (s, 2 H) 7.51 - 7.91 (m, 20 H)

HPLC Xterra 4.6 X 50 mm, 0 to 100% B over 10 minutes, one minutes hold time, A = 90% water, 10% methanol, 0.2% phosphoric acid, B = 10% water, 90% methanol, 0.2% phosphoric acid, RT = 2.74 min, 98%.

LCMS: Anal. Calcd. for: $C_{48}H_{54}N_8O_2$ 775.02; Found: 775.50 $(M+H)^+$.

Isomer 2: *(1R,1'R)-2,2'-(4,4'-biphenyldiylbis((1-methyl-1H-imidazole-4,2-diyl)(2S)-2,1-pyrrolidinediyl))bis(N,N-dimethyl-2-oxo-1-phenylethanamine)*

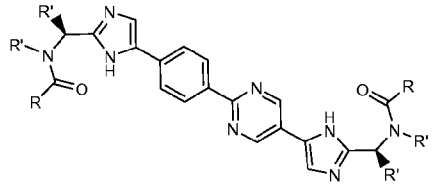
(10.2 mg, 11%) as a colorless wax.

^{1}H NMR (500 MHz, DMSO-d_6) δ ppm 1.83 - 2.26 (m, 8 H) 2.30 - 2.92 (m, 12 H) 3.68 - 3.94 (m, 8 H) 4.06 (s, 2 H) 5.25 (d, *J*=2.14 Hz, 2 H) 5.50 (s, 2 H) 7.52 - 7.91 (m, 20 H).

HPLC Xterra 4.6 X 50 mm, 0 to 100% B over 10 minutes, one minutes hold time, A = 90% water, 10% methanol, 0.2% phosphoric acid, B = 10% water, 90% methanol, 0.2% phosphoric acid, RT = 2.75 min, 90%.

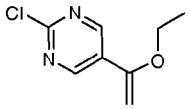
LCMS: Anal. Calcd. for: $C_{48}H_{54}N_8O_2$ 775.02; Found: 775.52 $(M+H)^+$.

Example 152



Example 152a-1 step a.

2-Chloro-5-(1-ethoxyvinyl)pyrimidine



To a solution of 5-bromo-2-chloropyrimidine (12.5 g, 64.62 mmol) in dry DMF (175 mL) under N_2 was added tributyl(1-ethoxyvinyl)tin (21.8 mL, 64.62 mmol) and dichlorobis(triphenylphosphine)palladium (II) (2.27 g, 3.23 mmol). The mixture was heated at 100°C for 3h before being allowed to stir at room temperature for 16 hr.. The mixture was then diluted with ether (200 mL) and treated with aqueous KF soln (55 g of potassium fluoride in 33 mL of water). The two phase mixture was stirred vigorously for 1h at room temperature before being filtered through diatomaceous earth (Celite®). The fitrate was washed with sat'd $NaHCO_3$ soln and brine prior to drying (Na_2SO_4). The original aqueous phase was extracted with ether (2x) and the organic phase was treated as above. Repetition on 13.5 g of 5-bromo-2-chloropyrimidine and combined purification by Biotage™ flash chromatography on silica gel (gradient elution on a 65M column using 3% ethyl acetate in hexanes to 25% ethyl acetate in hexanes with 3.0 L) afforded the title compound as a white, crystalline solid (18.2 g, 73%).

^{1}H NMR (500 MHz, DMSO-d_6) δ 8.97 (s, 2H), 5.08 (d, *J*=3.7 Hz, 1H), 4.56 (d, *J*=3.4 Hz, 1H), 3.94 (q, *J*=7.0 Hz, 2H), 1.35 (t, *J*=7.0 Hz, 3H)..

LCMS Phenomenex LUNA C-18 4.6 × 50 mm, 0 to 100% B over 3 minutes, 1 minute hold time, A = 90% water, 10% methanol, 0.1% TFA, B = 10% water, 90% methanol, 0.1% TFA, RT = 2.53 min, 98.8% homogeneity index.

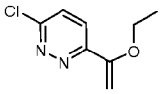
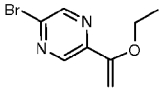
LCMS: Anal. Calcd. for $C_8H_{10}ClN_2O$ 185.05; found: 185.04 $(M+H)^+$.

HRMS: Anal. Calcd. for $C_8H_{10}ClN_2O$ 185.0482; found: 185.0490 $(M+H)^+$.

The same method was used for the preparation of Examples 152a-2 & 152a-3:

LC conditions: *Condition 1*: Phenomenex LUNA C-18 4.6 × 50 mm, 0 to 100% B over 3 minutes, 1 minute hold time, A = 90% water, 10% methanol, 0.1% TFA, B = 10% water, 90% methanol, 0.1% TFA, 220nm, 5 µL injection volume.

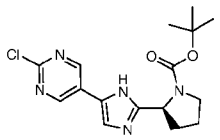
Condition 2: Phenomenex LUNA C-18 4.6 × 50 mm, 0 to 100% B over 2 minutes, 1 minute hold time, A = 90% water, 10% methanol, 0.1% TFA, B = 10% water, 90% methanol, 0.1% TFA, 220nm, 5 µL injection volume.

Example 152a-2	 from dichloropyridazine	t_R = 2.24 min 96.4%, condition 1 LRMS: Anal. Calcd. for $C_8H_{10}ClN_2O$ 185.05; found: 185.06 $(M+H)^+$. HRMS: Anal. Calcd. for $C_8H_{10}ClN_2O$ 185.0482; found: 185.0476 $(M+H)^+$.
Example 152a-3	 from dibromopyrazine	t_R = 2.82 min (52.7%, inseparable with 2,5-dibrompyrazine (t_R =1.99 min, 43.2%)); condition 1 LRMS: Anal. Calcd. for $C_8H_{10}BrN_2O$ 229.00; found: 228.93 $(M+H)^+$.

Example 152d-1 to 152d-6

Example 152b-1, step b.

(S)-tert-Butyl 2-(5-(2-chloropyrimidin-5-yl)-1H-imidazol-2-yl)pyrrolidine-1-carboxylate or (S)-2-[5-(2-Chloro-pyrimidin-5-yl)-1H-imidazol-2-yl]-pyrrolidine-1-carboxylic acid tert-butyl ester



NBS (16.1 g, 90.7 mmol) was added in one portion to a stirred solution of 2-chloro-5-(1-ethoxyvinyl)pyrimidine (152a-1, 18.2 g, 98.6 mmol) in THF (267 mL) and H_2O (88 mL) at 0°C under N_2. The mixture was stirred for 1h at 0°C before it was diluted with more H_2O and extracted with ethyl acetate (2x). The combined extracts were washed with sat'd $NaHCO_3$ soln and brine prior to drying (Na_2SO_4), filtration, and solvent evaporation. LCMS Phenomenex LUNA C-18 4.6 × 50 mm, 0 to 100% B over 3 minutes, 1 minute hold time, A = 90% water, 10% methanol, 0.1% TFA, B = 10% water, 90% methanol, 0.1% TFA, RT = 1.52 min (unsymmetrical peak). LCMS: Anal. Calcd. for $C_6H_{14}BrClN_2O$ 235.92; found: 236.85 $(M+H)^+$.

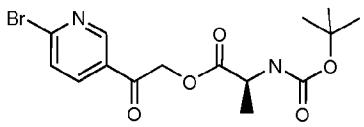
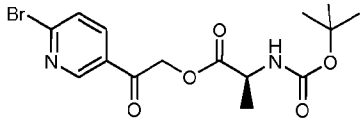
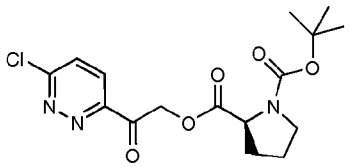
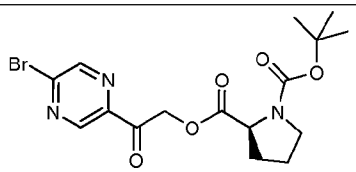
Example 152c-1, step c.

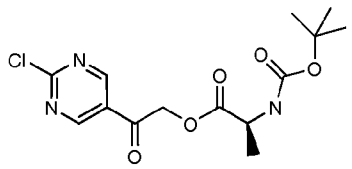
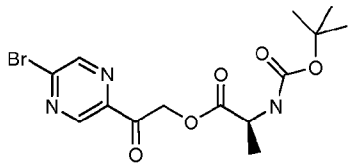
Half of the crude residue (2-bromo-1-(2-chloropyrimidin-5-yl)ethanone, ~14.5g) was dissolved into anhydrous acetonitrile (150 mL) and treated directly with N-Boc-L-proline (9.76 g, 45.35 mmol) and diisopropylethylamine (7.9 mL, 45.35 mmol). After being stirred for 3h, the solvent was removed *in vacuo* and the residue was partitioned into ethyl acetate and water. The organic phase was washed with 0.1N hydrochloric acid, sat'd $NaHCO_3$ soln and brine prior to drying (Na_2SO_4), filtration, and concentration. LCMS Phenomenex LUNA C-18 4.6 × 50 mm, 0 to 100% B over 3 minutes, 1 minute hold time, A = 90% water, 10% methanol, 0.1% TFA, B = 10% water, 90% methanol, 0.1% TFA, RT = 2.66 min.

The same method was used to prepare Examples 152c through 152c-6.

LC conditions: *Condition 1*: Phenomenex LUNA C-18 4.6 × 50 mm, 0 to 100% B over 3 minutes, 1 minute hold time, A = 90% water, 10% methanol, 0.1% TFA, B = 10% water, 90% methanol, 0.1% TFA, 220nm, 5 µL injection volume.

Condition 2: Phenomenex LUNA C-18 4.6 × 50 mm, 0 to 100% B over 2 minutes, 1 minute hold time, A = 90% water, 10% methanol, 0.1% TFA, B = 10% water, 90% methanol, 0.1% TFA, 220nm, 5 µL injection volume.

Example 152c-2		t_R = 1.81 min (condition 2, ~95 %) LRMS: Anal. Calcd. for $C_{15}H_{19}BrN_4O_2$ 386.05 found: 387.07 $(M+H)^+$.
Example 152c-3		t_R = 1.84 min (condition 2, 94%) LRMS: Anal. Calcd. for $C_{15}H_{19}BrN_2O_5$ 386.05; found: 387.07 $(M+H)^+$.
Example 152c-3a		t_R = 2.65 min; condition 1 LCMS: Anal. Calcd. for $C_{16}H_{20}ClN_3O_5$ 369.11 found: 391.89 $(M+Na)^+$.
Example 152c-4		t_R = 1.94 min, (condition 2) LCMS: Anal. Calcd. for

		$C_{16}H_{21}BrN_3O_5$ 414.07 found: 414.11 $(M+H)^+$.
Example 152c-5		t_R = 2.22 min; condition 1 LCMS: Anal. Calcd. for $C_{14}H_{18}ClN_3O_5$ 343.09 found: undetermined.
Example 152c-6		t_R = 2.41 min, condition 1 LCMS: Anal. Calcd. for $C_{14}H_{18}{}^{37}BrN_3O_5$ 389.04 found: 412.03 $(M+Na)^+$.

Example 152d-1, step d.

This residue ((S)-1-tert-butyl 2-(2-(2-chloropyrimidin-5-yl)-2-oxoethyl) pyrrolidine-1,2-dicarboxylate) was taken up in xylenes (200 mL) and treated to NH_4OAc (17.5 g, 0.23 mol). The mixture was heated at 140°C for 2 hr in a thick-walled, screw-top flask before it was cooled to ambient temperature and suction-filtered. The filtrate was then concentrated, partitioned into ethyl acetate and sat'd $NaHCO_3$ soln and washed with brine prior to drying (Na_2SO_4), filtration, and concentration The original precipitate was partitioned into aqueous $NaHCO_3$ soln and ethyl acetate and sonicated for 2 min before being suction-filtered. The filtrate was washed with brine, dried over (Na_2SO_4), filtered, and concentrated to dryness. Purification of the combined residues by Biotage™ flash chromatography on silica gel (65M column, preequilibration with 2%B for 900mL followed by gradient elution with 2%B to 2%B for 450 ml followed by 2%B to 40%B for 3000mL where B=methanol and A=dichloromethane) afforded the title compound (7.0 g, 44% yield, 2 steps, pure fraction) as an yellowish orange foam. The mixed fractions were

subjected to a second Biotage™ chromatography on silica gel (40M column, preequilibration with 1%B for 600mL followed by gradient elution with 1%B to 1%B for 150 ml followed by 1%B to 10%B for 1500mL where B=MeOH and A=CH_2Cl_2) afforded additional title compound (2.8 g, 18%) as a brownish-orange foam. ^{1}H NMR (500 MHz, DMSO-d_6) δ 12.24-12.16 (m, 1H), 9.05 (s, 2H), 7.84-7.73 (m, 1H), 4.90-4.73 (m, 1H), 3.59-3.46 (m, 1H), 3.41-3.31 (m, 1H), 2.32-2.12 (m, 1H), 2.03-1.77 (m, 3H), 1.39 and 1.15 (2s, 9H)..

LCMS Phenomenex LUNA C-18 4.6 × 50 mm, 0 to 100% B over 3 minutes, 1 minute hold time, A = 90% water, 10% methanol, 0.1% TFA, B = 10% water, 90% methanol, 0.1% TFA, RT = 1.92 min, 94.7% homogeneity index.

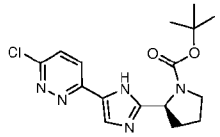
LRMS: Anal. Calcd. for $C_{16}H_{21}ClN_5O_2$ 350.14; found: 350.23 $(M+H)^+$.

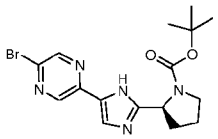
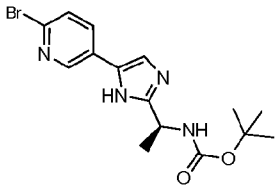
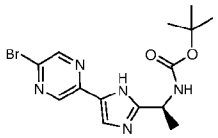
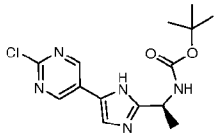
HRMS: Anal. Calcd. for $C_{16}H_{21}ClN_5O_2$ 350.1384; found: 350.1398 $(M+H)^+$.

The same method was used to prepare Examples 152d-2 through 152d-6.

LC conditions: *Condition 1*: Phenomenex LUNA C-18 4.6 × 50 mm, 0 to 100% B over 3 minutes, 1 minute hold time, A = 90% water, 10% methanol, 0.1% TFA, B = 10% water, 90% methanol, 0.1% TFA, 220nm, 5 µL injection volume.

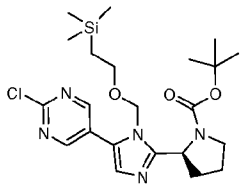
Condition 2: Phenomenex LUNA C-18 4.6 × 50 mm, 0 to 100% B over 2 minutes, 1 minute hold time, A = 90% water, 10% methanol, 0.1% TFA, B = 10% water, 90% methanol, 0.1% TFA, 220nm, 5 µL injection volume.

Example 152d-2	 from 152c-3a	t_R = 1.92 min (86.5%); condition 1 LRMS: Anal. Calcd. for $C_{16}H_{21}ClN_5O_2$ 350.14; found: 350.23 $(M+H)^+$. HRMS: Anal. Calcd. for $C_{16}H_{21}ClN_5O_2$ 350.1384; found: 350.1393 $(M+H)^+$.

Example 152d-3	 from 152c-4	t_R = 1.90min (>95%); condition 1 LRMS: Anal. Calcd. for $C_{16}H_{21}BrN_5O_2$ 394.09; found: 393.82 $(M+H)^+$. HRMS: Anal. Calcd. for $C_{16}H_{21}BrN_5O_2$ 394.0879; found: 394.0884 $(M+H)^-$.
Example 152d-4	 from 152c-3	t_R = 1.45 min (condition 2, 100%) LRMS: Anal. Calcd. for $C_{15}H_{19}BrN_4O_2$ 366.07 found: 367.07 $(M+H)^+$.
Example 152d-5	 from 152c-6	t_R = 1.88 min (>95%); condition 1 LRMS: Anal. Calcd. for $C_{14}H_{18}BrN_5O_2$ 367.06; found: 368.10 $(M+H)^+$.
Example 152d-6	 from 152c-5	t_R = 1.66 min (85%); condition 1 LRMS: Anal. Calcd. for $C_{14}H_{18}ClN_5O_2$ 323.11; found: 324.15 $(M+H)^+$.

Example 152e-1, step e.

Example 152e-1: (S)-tert-Butyl 2-(5-(2-chloropyrimidin-5-yl)-1-((2-(trimethyl-silyl)ethoxy)methyl)-1H-imidazol-2-yl)pyrrolidine-1-carboxylate



Sodium hydride (60% dispersion in mineral oil , 0.23 g, 5.72 mmol) was added in one portion to a stirred solution of (S)-tert-butyl 2-(5-(2-chloropyrimidin-5-yl)-1H-imidazol-2-yl)pyrrolidine-1-carboxylate (152d-1, 2.0 g, 5.72 mmol) in dry DMF (45 mL) at ambient temperature under N_2. The mixture was stirred for 5 min. before SEM chloride (1.01 mL, 5.72 mmol) was added in approx. 0.1 mL increments. The mixture was stirred for 3h before being quenched with sat'd NH_4Cl soln and diluted with ethyl acetate. The organic phase was washed with sat'd $NaHCO_3$ soln and brine, dried over (Na_2SO_4), filtered, and concentrated. The original aqueous phase was extracted twice more and the combined residue was purified by Biotage™ flash chromatography (40M column, 50 mL/min, prccquilibration with 5%B for 750mL, followed by step gradient elution with 5%B to 5%B for 150 mL, 5%B to 75%B for 1500 mL, then 75%B to 100%B for 750 mL where solvent B is ethyl acetate and solvent A is hexanes). Concentration of the eluant furnished the title compound as a palc yellow foam (2.35 g, 85%).

^{1}H NMR (500 MHz, DMSO-d_6) δ 9.04 (s, 2H), 7.98-7.95 (m, 1H), 5.70-5.31 (3m, 2H), 5.02-4.91 (m, 1H), 3.59-3.49 (m, 3H), 3.45-3.35 (m, 1H), 2.30-2.08 (m, 2H), 1.99-1.83 (m, 2H), 1.36 and 1.12 (2s, 9H), 0.93-0.82 (m, 2H), -0.02 (s, 9H).

LCMS Phenomenex LUNA C-18 4.6 × 50 mm, 0 to 100% B over 2 minutes, 2 minute hold time, A = 90% water, 10% methanol, 0.1% TFA, B = 10% water, 90% methanol, 0.1% TFA, RT = 2.38 min, 95% homogeneity index.

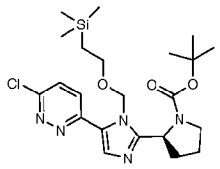
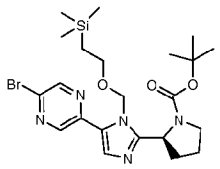
LRMS: Anal. Calcd. for $C_{22}H_{35}ClN_5O_3S_i$ 480.22; found: 480.23 $(M+H)^+$.

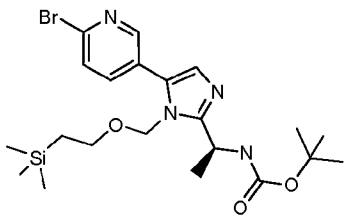
HRMS: Anal. Calcd. for $C_{22}H_{35}ClN_5O_3S_i$ 480.2198; found: 480.2194 $(M+H)^+$.

The same method was used to prepare 152e-2 through 152e-4

LC conditions: *Condition 1*: Phenomenex LUNA C-18 4.6 × 50 mm, 0 to 100% B over 3 minutes, 1 minute hold time, A = 90% water, 10% methanol, 0.1% TFA, B = 10% water, 90% methanol, 0.1% TFA, 220nm, 5 µL injection volume.

Condition 2: Phenomenex LUNA C-18 4.6 × 50 mm, 0 to 100% B over 2 minutes, 1 minute hold time, A = 90% water, 10% methanol, 0.1% TFA, B = 10% water, 90% methanol, 0.1% TFA, 220nm, 5 µL injection volume.

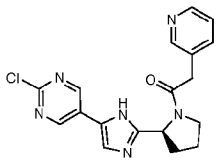
Example 152e-2	 from 152d-2	t_R = 2.34 min (85.7%); condition 1 LCMS: Anal. Calcd. for $C_{22}H_{35}ClN_5O_3Si$ 480.22; found: 480.22 $(M+H)^+$. HRMS: Anal. Calcd. for $C_{22}H_{35}ClN_5O_3Si$ 480.2198 found: 480.2198 $(M+H)^+$.
Example 152e-3	 from 152d-3	t_R = 3.18 min (>95%); condition 1 LCMS: Anal. Calcd. for $C_{22}H_{35}{}^{37}BrN_5O_3Si$ 526.17; found: 525.99 $(M+H)^+$. HRMS: Anal. Calcd. for $C_{22}H_{35}{}^{37}BrN_5O_3Si$ 526.1692; found: 526.1674 $(M+H)^+$.

Example 152e-4	 from 152d-4	t_R = 2.14 min (condition 2, 96%) LRMS: Anal. Calcd. For $C_{21}H_{33}BrN_4O_3Si$ 496.15 found: 497.13 $(M+H)^+$.

Examples 152f-1 to 152f-2

Example 152f-1

(S)-1-(2-(5-(2-chloropyrimidin-5-yl)-1H-imidazol-2-yl)pyrrolidin-1-yl)-2-(pyridin-3-yl)ethanone



Cold (0°C) 4 *N* HCl in dioxanes (5 mL) was added *via* syringe to (S)-tert-butyl 2-(5-(2-chloropyrimidin-5-yl)-1*H*-imidazol-2-yl)pyrrolidine-1-carboxylate (152d-1, 0.50 g, 1.43 mmol) in a 100 mL pear-shaped flask followed by MeOH (1.0 mL). The suspension was stirred at room temperature for 4h before it was concentrated down to dryness and placed under high vacuum for 1h. There was isolated intermediate (S)-2-chloro-5-(2-(pyrrolidin-2-yl)-1*H*-imidazol-5-yl)pyrimidine trihydrochloride as a pale yellow solid (with an orange tint) which was used without further purification.

HATU (0.60 g, 1.57 mmol) was added in one portion to a stirred solution of intermediate (S)-2-chloro-5-(2-(pyrrolidin-2-yl)-1H-imidazol-5-yl)pyrimidine trihydrochloride (0.46 g, 1.43 mmol, theoretical amount), 2-(pyridin-3-yl)acetic acid (0.25 g, 1.43 mmol) and DIEA (1.0 mL, 5.72 mmol) in anhydrous DMF (10 mL) at ambient temperature. The mixture was stirred at room temperature for 2h before the DMF was removed *in vacuo*. The residue was taken up in CH_2Cl_2 and subjected to

Biotage™ flash chromatography on silica gel (40M column, preequilibration with 0%B for 600mL followed by step gradient elution with 0%B to 0%B for 150 mL followed by 0%B to 15%B for 1500mL followed by 15%B to 25% B for 999 mL where B= MeOH and A= CH_2Cl_2). There was isolated the title compound (0.131 g, 25%, 2 steps) as a yellow solid.

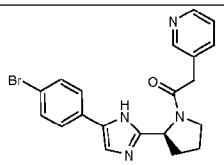
^{1}H NMR (500 MHz, DMSO-d_6) δ 9.10-9.08 (2s, 2H), 8.72-8.55 (series of m, 2H), 8.21-8.20 and 8.11-8.10 (2m, 1H), 8.00 and 7.93 (2s, 1H), 7.84-7.77 (series of m, 1H), 5.43-5.41 and 5.17-5.15 (2m, 1H), 4.02-3.94 (3m, 2H), 3.90-3.58 (3m, 2H), 2.37-2.26 (m, 1H), 2.16-1.85 (2m, 3H).

LCRMS Phenomenex LUNA C-18 4.6 × 50 mm, 0 to 100% B over 3 minutes, 1 minute hold time, A = 90% water, 10% methanol, 0.1% TFA, B = 10% water, 90% methanol, 0.1% TFA, RT = 0.92 min, 95.1 % homogeneity index.

LRMS: Anal. Calcd. for $C_{18}H_{18}ClN_6O$ 369.12; found: 369.11 $(M+H)^+$.

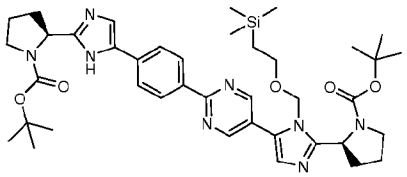
HRMS: Anal. Calcd. for $C_{18}H_{18}ClN_6O$ 369.1231; found: 369.1246 $(M+H)^+$.

Example 152f-2 LCMS conditions: Phenomenex LUNA C-18 4.6 × 50 mm, 0 to 100% B over 3 minutes, 1 minute hold time, A = 90% water, 10% methanol, 0.1% TFA, B = 10% water, 90% methanol, 0.1% TFA, 220nm, 5 μL injection volume.

Example 152f-2	 prepared from 1b with same procedure describing the preparation of 152f-1 from 152d-1	t_R = 1.56min (>95%) LRMS: Anal. Calcd. for $C_{20}H_{20}BrN_4O$ 413.08; found: 412.99 $(M+H)^+$.

Examples 152g-1 to 152g-16

Example 152g-1 from 1c and 152e-1. (S)-2-[5-(2-{4-[2-((S)-1-tert-Butoxycarbonyl-pyrrolidin-2-yl)-3H-imidazol-4-yl]-phenyl}-pyrimidin-5-yl)-1-(2-trimethylsilanyl-ethoxymethyl)-1H-imidazol-2-yl]-pyrrolidine-1-carboxylic acid tert-butyl ester



Pd $(Ph_3)_4$ (0.12 g, 0.103 mmol) was added in one portion to a stirred suspension of (S)-tert-butyl 2-(5-(4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)phenyl)-1H-imidazol-2-yl)pyrrolidine-1-carboxylate (1c, 1.00 g, 2.27 mmol), (S)-tert-butyl 2-(5-(2-chloropyrimidin-5-yl)-1-((2-(trimethylsilyl)ethoxy)methyl)-1H-imidazol-2-yl)pyrrolidine-1-carboxylate (152c-1, 0.99 g, 2.06 mmol) and $NaHCO_3$ (0.87 g, 10.3 mmol) in a solution of DME (20 mL) and H_2O (6 mL) at room temperature under N_2. The vessel was sealed and the mixture was placed into a preheated (80°C) oil bath and stirred at 80°C for 16h before additional catalyst (0.12 g) was added. After heating the mixture for an additional 12h at 80°C, the mixture was cooled to ambient temperature, diluted with ethyl acetate and washed with sat'd $NaHCO_3$ soln and brine prior to drying over anhydrous sodium sulfate and solvent concentration. Purification of the residue by Biotage™ flash chromatography on silica gel using a 40M column (preequilibrated with 40% B followed by step gradient elution with 40%B to 40%B for 150mL, 40%B to 100%B for 1500mL, 100%B to 100%B for 1000mL where B=ethyl acetate and A=hexanes) furnished the title compound as a yellow foam (1.533 g, 98%). A small amount of the yellow foam was further purified for characterization purposes by pHPLC (Phenomenex GEMINI, 30 × 100 mm, S10, 10 to 100% B over 13 minutes, 3 minute hold time, 40 mL/min, A = 95% water, 5% acetonitrile, 10mM NH_4OAc, B = 10% water, 90% acetonitrile, 10mM NH_4OAc) to yield 95% pure title compound as a white solid.

^1H NMR (500 MHz, DMSO-d_6) δ 12.30-11.88 (3m, 1H), 9.17-9.16 (m, 2H), 8.43-8.31 (m, 2H), 7.99-7.35 (series of m, 4H), 5.72-5.30 (3m, 2H), 5.03-4.76 (2m, 2H), 3.64-3.50 (m, 4H), 3.48-3.31 (m, 2H), 2.36-2.07 (m, 2H), 2.05-1.80 (m, 4H), 1.46-1.08 (2m, 18H), 0.95-0.84 (m, 2H), -0.01 (s, 9H).

HPLC Phenomenex LUNA C-18 4.6 × 50 mm, 0 to 100% B over 3 minutes, 1 minute hold time, A = 90% water, 10% methanol, 0.1% TFA, B = 10% water, 90% methanol, 0.1% TFA, RT = 2.91 min, 95% homogeneity index.

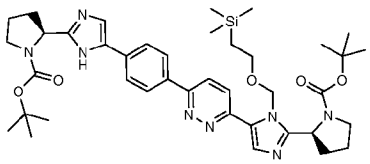
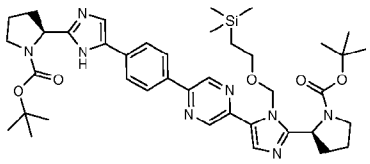
LRMS: Anal. Calcd. for $C_{40}H_{57}N_8O_5Si$ 757.42; found: 757.42 $(M+H)^+$.

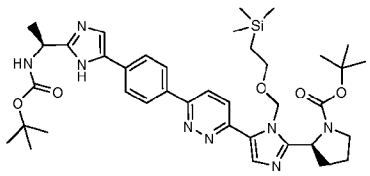
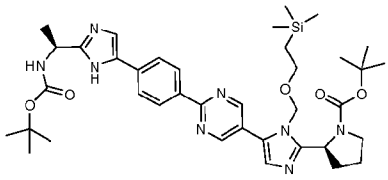
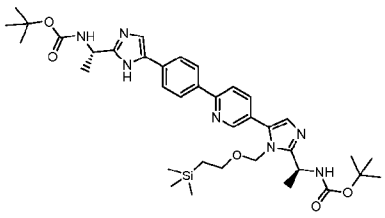
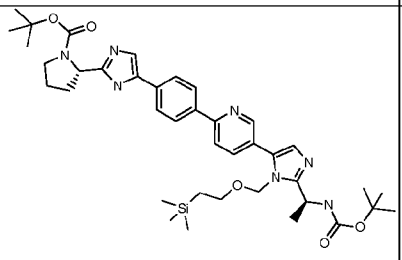
HRMS: Anal. Calcd. for $C_{40}H_{57}N_8O_5Si$ 757.4221; found: 757.4191 $(M+H)^+$.

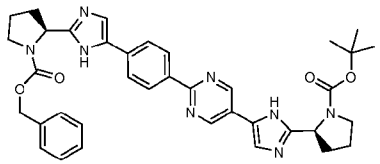
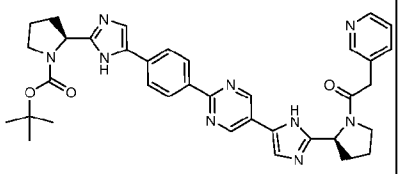
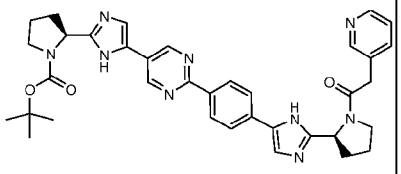
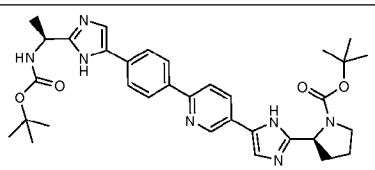
The same procedure was used to prepare Examples 152g-2 through 152g-17:

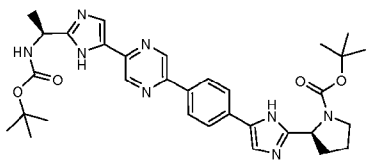
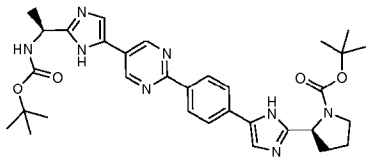
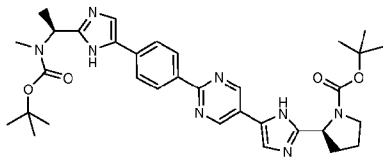
LC conditions: *Condition 1*: Phenomenex LUNA C-18 4.6 × 50 mm, 0 to 100% B over 3 minutes, 1 minute hold time, A = 90% water, 10% methanol, 0.1% TFA, B = 10% water, 90% methanol, 0.1% TFA, 220nm, 5 µL injection volume.

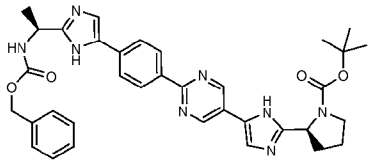
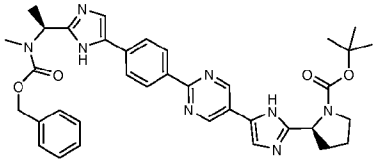
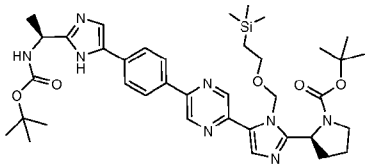
Condition 2: Phenomenex LUNA C-18 4.6 × 50 mm, 0 to 100% B over 2 minutes, 1 minute hold time, A = 90% water, 10% methanol, 0.1% TFA, B = 10% water, 90% methanol, 0.1% TFA, 220nm, 5 µL injection volume.

Example 152g-2	 Prepared from 1c and 152e-2	t_R = 2.81 min (79%); Condition 1 LRMS: Anal. Calcd. for $C_{40}H_{57}N_8O_5Si$ 757.42; found: 758.05 $(M+H)^+$. HRMS: Anal. Calcd. for $C_{40}H_{57}N_8O_5Si$ 757.4221; found: 757.4196 $(M+H)^+$.
Example 152g-3	 Prepared from 1c and 152e-3	t_R = 2.89 min (>95%); Condition 1 LRMS: Anal. Calcd. for $C_{40}H_{57}N_8O_5Si$ 757.42; found: 757.35 $(M+H)^+$. HRMS: Anal. Calcd. for $C_{40}H_{57}N_8O_5Si$ 757.4221; found: 757.4191 $(M+H)^+$.

Example 152g-4	 Prepared from 1-6c and 152e-2	t_R = 2.87 min (97%); Condition 1 LRMS: Anal. Calcd. for $C_{38}H_{55}N_8O_5S_i$ 731.41; found: 731.26 $(M+H)^+$. HRMS: Anal. Calcd. for $C_{38}H_{55}N_8O_5S_i$ 731.4065; found: 731.4070 $(M+H)^+$.
Example 152g-5	 Prepared from 1-6c and 152e-1	t_R = 2.94 min (>95%); Condition 1 LRMS: Anal. Calcd. for $C_{38}H_{55}N_8O_5Si$ 731.41; found: 731.26 $(M+H)^+$. HRMS: Anal. Calcd. for $C_{38}H_{55}N_8O_5Si$ 731.4065; found: 731.4046 $(M+H)^+$.
Example 152g-6	 Prepared from 1-6c and 152e-4	t_R = 1.99 min (condition 2, 96%) LRMS: Anal. Calcd. for $C_{37}H_{53}N_7O_2Si$ 703.39; found: 704.34 $(M+H)^+$.
Example 152g-7	 Prepared from 1c and 152e-4	t_R = 1.99 min (condition 2, 96%) LRMS: Anal. Calcd. for $C_{39}H_{55}N_7O_5Si$ 729.40 found: 730.42 $(M+H)^+$.

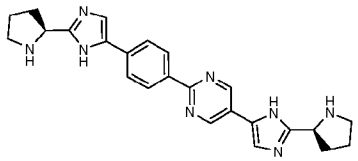
Example 152g-8	 Prepared from 1-5c and 152d-1	t_R = 2.15 min (>95%); Condition 1 LRMS: Anal. Calcd. for $C_{37}H_{41}N_8O_4$ 661.33; found: 661.39 $(M+H)^+$. HRMS: Anal. Calcd. for $C_{37}H_{41}N_8O_4$ 661.3251; found: 661.3268 $(M+H)^+$.
Example 152g-9	 Prepared from 1c and 152f-1	t_R = 1.71 min (>95%); Condition 1 LRMS: Anal. Calcd. for $C_{36}H_{40}N_9O_3$ 646.76; found: 646.47 $(M+H)^+$. HRMS: Anal. Calcd. for $C_{36}H_{40}N_9O_3$ not done found: not done $(M+H)^+$.
Example 152g-10	 Prepared from 152d-1 and 1-10c	t_R = 1.71 min (>95%); Condition 1 LRMS: Anal. Calcd. for $C_{36}H_{40}N_9O_3$ 646.33; found: 646.37 $(M+H)^+$. HRMS: Anal. Calcd. for $C_{36}H_{40}N_9O_3$ 646.3254; found: 646.3240 $(M+H)^+$.
Example 152g-11	 Prepared from 1-6c and 152e-4	t_R = 2.12 min (>93.9%); Condition 1 LRMS: Anal. Calcd. for $C_{33}H_{42}N_7O_4$ 600.33; found: 600.11

		$(M+H)^+$. HRMS: Anal. Calcd. for $C_{33}H_{42}N_7O_4$ 600.3298; found: 600.3312 $(M+H)^+$.
Example 152g-12	 Prepared from 1c and 152d-5	t_R = 2.13 min (97.3%); Condition 1 LRMS: Anal. Calcd. for $C_{32}H_{41}N_8O_4$ 601.33; found: 601.36 $(M+H)^+$. HRMS: Anal. Calcd. for $C_{32}H_{41}N_8O_4$ 601.3251; found: 601.3253 $(M+H)^+$.
Example 152g-13	 Prepared from 1c and 152d-6	t_R = 2.11 min (98.5%); Condition 1 LRMS: Anal. Calcd. for $C_{32}H_{41}N_8O_4$ 601.33; found: 601.36 $(M+H)^+$. HRMS: Anal. Calcd. for $C_{32}H_{41}N_8O_4$ 601.3251; found: 601.3253 $(M+H)^+$.
Example 152g-14	 Prepared from 1-8c and 152d-1	t_R = 2.18 min (>95%); Condition 1 LRMS: Anal. Calcd. for $C_{33}H_{43}N_8O_4$ 615.34; found: 615.38 $(M+H)^+$. HRMS: Anal. Calcd. for $C_{33}H_{43}N_8O_4$ 615.3407; found: 615.3433 $(M+H)^+$.

Example 152g-15	 Prepared from 1c and 152d-1	t_R = 2.20 min (97.7%); Condition 1 LRMS: Anal. Calcd. for $C_{35}H_{39}N_8O_4$ 635.31; found: 635.36 $(M+H)^+$. HRMS: Anal. Calcd. for $C_{35}H_{39}N_8O_4$ 635.3094; found: 635.3119 $(M+H)^+$.
Example 152g-16	 Prepared from 1-9c and 152d-1	t_R = 2.26 min (>95%); Condition 1 LRMS: Anal. Calcd $C_{36}H_{41}N_8O_4$ 649.33; found: 649.39 $(M+H)^+$. HRMS: Anal. Calcd. for $C_{36}H_{41}N_8O_4$ 649.3251; found: 649.3276 $(M+H)^+$.
Example 152g-17	 Prepared from 1-6c and 152e-3	t_R = 2.98 min (98.5%); Condition 1 LRMS: Anal. Calcd. for $C_{38}H_{54}N_8O_5Si$ 730.39; found: 731.40 $(M+H)^+$. HRMS: Anal. Calcd. for $C_{38}H_{54}N_8O_5Si$ 731.4065; found: 731.4045 $(M+H)^+$.

Example 152h-1-152h-7

Example 152h-1 from 152g-1. 5-((S)-2-Pyrrolidin-2-yl-3H-imidazol-4-yl)-2-[4-((S)-2-pyrrolidin-2-yl-3H-imidazol-4-yl)-phenyl]-pyrimidine



TFA (8 mL) was added in one portion to a stirred solution of (S)-2-[5-(2-{4-[2-((S)-1-*tert*-butoxycarbonyl-pyrrolidin-2-yl)-3*H*-imidazol-4-yl]-phenyl}-pyrimidin-5-yl)-1-(2-trimethylsilanyl-ethoxymethyl)-1*H*-imidazol-2-yl]-pyrrolidine-1-carboxylic acid *tert*-butyl ester (1.50 g, 1.98 mmol) in dry CH_2Cl_2 (30 mL) at room temperature. The flask was sealed and the mixture was stirred at room temperature for 16h before the solvent(s) were removed *in vacuo*. The residue was taken up in methanol, filtered through a PVDF syringe filter (13mm x 0.45μm), distributed to 8 pHPLC vials and chromatographed by HPLC (gradient elution from 10%B to 100%B over 13 min on a Phenomenex C18 column, 30 x 100mm, 10μm, where A = 90% water, 10% methanol, 0.1% TFA, B = 10% water, 90% methanol, 0.1% TFA). After concentration of the selected test tubes by speed vacuum evaporation, the product was dissolved in methanol and neutralized by passing the solution through an UCT CHQAX 110M75 anion exchange cartridge. There was isolated the title compound as a yellow mustard-colored solid (306.7 mg, 36% yield) upon concentration of the eluant.

^{1}H NMR (500 MHz, DMSO-d_6) μ 12.50-11.80 (br m, 2H), 9.18 (s, 2H), 8.36 (d, *J*=8.5 Hz, 2H), 7.89 (d, *J*=8.2 Hz, 2H), 7.77 (s, 1H), 7.61 (s, 1H), 4.34-4.24 (m, 2H), 3.09-2.89 (m, 4H), 2.18-2.07 (m, 2H), 2.02-1.89 (m, 2H), 1.88-1.72 (m, 4H).

LCMS Phenomenex LUNA C-18 4.6 × 50 mm, 0 to 100% B over 3 minutes, 1 minute hold time, A = 90% water, 10% methanol, 0.1% TFA, B = 10% water, 90% methanol, 0.1% TFA, RT = 1.33 min, >95% homogeneity index.

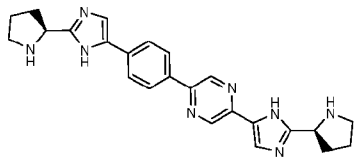
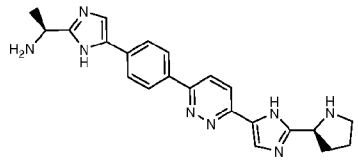
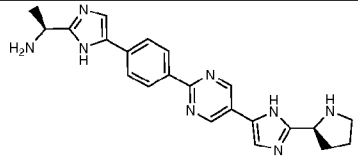
LRMS: Anal. Calcd. for $C_{24}H_{27}N_8$ 427.24; found: 427.01 $(M+H)^+$.

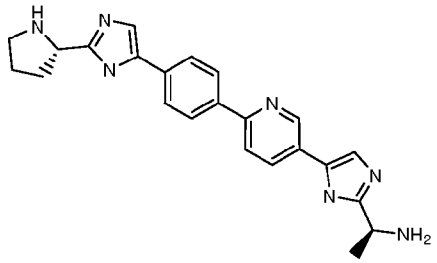
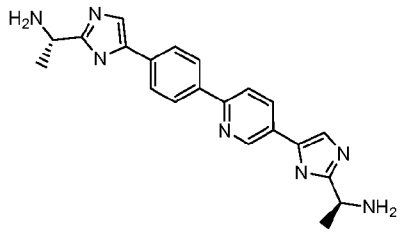
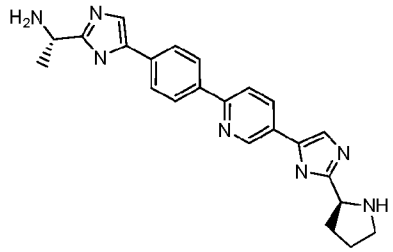
HRMS: Anal. Calcd. for $C_{24}H_{27}N_8$ 427.2359; found: 427.2363 $(M+H)^+$.

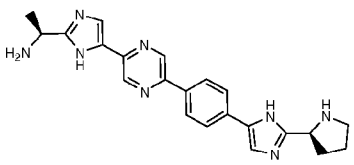
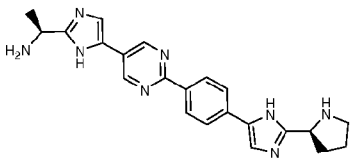
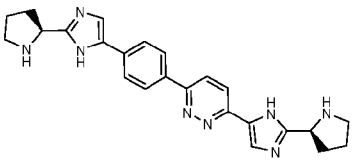
The same conditions were used to prepare Examples 152h-2 through 152h-14.

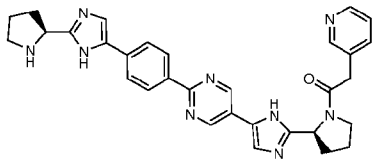
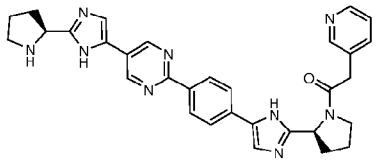
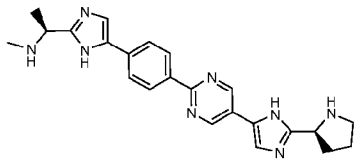
LC conditions: *Condition 1*: Phenomenex LUNA C-18 4.6 × 50 mm, 0 to 100% B over 3 minutes, 1 minute hold time, A = 90% water, 10% methanol, 0.1% TFA, B = 10% water, 90% methanol, 0.1% TFA, 220nm, 5 µL injection volume.

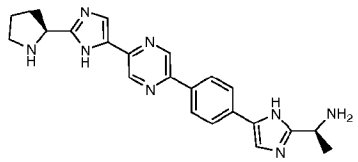
Condition 2: Phenomenex LUNA C-18 4.6 × 50 mm, 0 to 100% B over 2 minutes, 1 minute hold time, A = 90% water, 10% methanol, 0.1% TFA, B = 10% water, 90% methanol, 0.1% TFA, 220nm, 5 µL injection volume.

Example 152h-2	 Prepared from 152g-3	t_R = 1.36 min (98%); Condition 1 LRMS: Anal. Calcd. for $C_{24}H_{27}N_8$ 427.24; found: 427.48 $(M+H)^+$. HRMS: Anal. Calcd. for $C_{24}H_{27}N_8$ 427.2359; found: 427.2339 $(M+H)^+$.
Example 152h-3	 Preapared from 152g-4	t_R = 1.17 min (>95%); Condition 1 LRMS: Anal. Calcd. for $C_{22}H_{25}N_8$ 401.22; found: 401.16 $(M+H)^+$. HRMS: Anal. Calcd. for $C_{22}H_{25}N_8$ 401.2202; found: 401.2193 $(M+H)^+$.
Example 152h-4		t_R = 1.28 min (89.3%); Condition 1

	Prepared from 152g-5	LRMS: Anal. Calcd. for $C_{22}H_{25}N_8$ 401.22; found: 401.16 $(M+H)^+$. HRMS: Anal. Calcd. for $C_{22}H_{25}N_8$ 401.2202; found: 401.2201 $(M+H)^+$.
Example 152h-5	 Prepared from 152g-7	t_R = 0.93 min; Condition 2 LRMS: Anal. Calcd. for $C_{23}H_{25}N_7$ 399; found: 400 $(M+H)^+$.
Example 152h-6	 Prepared from 152g-6	t_R = 0.81 min; Condition 2 LRMS: Anal. Calcd. for $C_{21}H_{23}N_7$ 373; found: 374 $(M+H)^+$.
Example 152h-7	 Prepared from 152g-11	t_R = 1.14 min (>95%); Condition 1 LRMS: Anal. Calcd. for $C_{23}H_{26}N_7$ 400.23; found: 400.14 $(M+H)^+$. HRMS: Anal. Calcd. for $C_{23}H_{26}N_7$ 400.2250; found: 400.2234

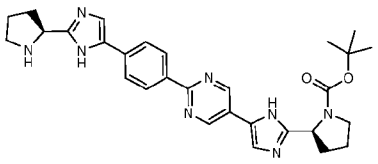
		$(M+H)^+$.
Example 152h-8	 Prepared from 152g-12	t_R = 1.29 min (>95%); Condition 1 LRMS: Anal. Calcd. for $C_{22}H_{25}N_8$ 401.22; found: 401.21 $(M+H)^+$. HRMS: Anal. Calcd. for $C_{22}H_{25}N_8$ 401.2202; found: 401.2204 $(M+H)^+$.
Example 152h-9	 Prepared from 152g-13	t_R = 1.29 min (97.6%); Condition 1 LRMS: Anal. Calcd. for $C_{22}H_{25}N_8$ 401.22; found: 401.21 $(M+H)^+$. HRMS: Anal. Calcd. for $C_{22}H_{25}N_8$ 401.2202; found: 401.2220 $(M+H)^+$.
Example 152h-10	 Prepared from 152g-2	t_R = 1.26 min (86.4%); Condition 1 LRMS: Anal. Calcd. for $C_{24}H_{27}N_8$ 427.24; found: 427.48 $(M+H)^+$.

		HRMS: Anal. Calcd. for $C_{24}H_{27}N_8$ 427.2359; found: 427.2339 $(M+H)^+$.
Example 152h-11	 Prepared from 152g-9	t_R = 1.26 min (>95%); Condition 1 LRMS: Anal. Calcd. for $C_{31}H_{32}N_9O$ 546.27; found: 546.28 $(M+H)^+$. HRMS: Anal. Calcd. for $C_{31}H_{32}N_9O$ 546.2730 found: 546.2739 $(M+H)^+$.
Example 152h-12	 Prepared from 152g-10	t_R = 1.39 min (95%); Condition 1 LRMS: Anal. Calcd. for $C_{31}H_{32}N_9O$ 546.27; found: 546.32 $(M+H)^+$. HRMS: Anal. Calcd. for $C_{31}H_{32}N_9O$ 546.2730; found: 546.2719 $(M+H)^+$.
Example 152h-13	 Prepared from 152g-14	t_R = 1.42 min; Condition 1 LRMS: Anal. Calcd. for $C_{23}H_{26}N_8$ 414.24; found: 415.27 $(M+H)^+$.

		HRMS: Anal. Calcd. for $C_{23}H_{26}N_8$ 415.2359; found: 415.2371 $(M+H)^+$.
Example 152h-14	 Prepared from 152g-17	t_R = 1.30 min; Condition 1 LRMS: Anal. Calcd. for $C_{22}H_{24}N_8$ 400.21; found: 401.24 $(M+H)^+$. HRMS: Anal. Calcd. for $C_{22}H_{24}N_8$ 401.2202; found: 401.2198 $(M+H)^+$.

Example 152i-1 to 152i-3

Example 152i-1 from 152g-8. (S)-2-(5-{2-[4-((S)-2-Pyrrolidin-2-yl-3H-imidazol-4-yl)-phenyl]-pyrimidin-5-yl}-1H-imidazol-2-yl)-pyrrolidine-1-carboxylic acid tert-butyl ester



A solution of (S)-2-[5-(2-{4-[2-((S)-1-Benzyloxycarbonyl-pyrrolidin-2-yl)-3*H*-imidazol-4-yl]-phenyl}-pyrimidin-5-yl)-1*H*-imidazol-2-yl]-pyrrolidine-1-carboxylic acid *tert*-butyl ester (317.1 mg, 0.48 mmol) in MeOH (1 mL) was added to a stirred suspension of 10% palladium on carbon (60 mg) and K_2CO_3 (70 mg) in a solution of MeOH (5 mL) and H_2O (0.1 mL) at room temperature under N_2. The flask was charged and evacuated three times with H_2 and stirred for 3h at atmosphere pressure. Additional catalyst (20 mg) was then added and the reaction mixture was stirred further for 3h before it was suction-filtered through diatomaceous earth

(Celite®) and concentrated. The residue was diluted with MeOH, filtered through a PVDF syringe filter (13mm x 0.45μm), distributed into 4 pHPLC vials and chromatographed (gradient elution from 20%B to 100%B over 10 min on a Phenomenex-Gemini C18 column (30 x 100mm, 10μm) where A = 95% water, 5% acetonitrile, 10mM NH_4OAc, B = 10% water, 90% acetonitrile, 10mM NH_4OAc). After concentration of the selected test tubes by speed vacuum evaporation, there was isolated the title compound as a yellow solid (142.5 mg, 56% yield).

^1H NMR (400 MHz, DMSO-d_6) δ 12.35-12.09 (br m, 1H), 9.17 (s, 2H), 8.35 (d, *J*=8.3Hz, 2H), 7.87 (d, *J*=8.3Hz, 2H), 7.80-7.72 (m, 1H), 7.56 (s, 1H), 4.92-4.77 (m, 1H), 4.21-4.13 (m, 1H), 3.61-3.05 (2m, 4H), 3.02-2.80 (2m, 2H), 2.37-1.67 (series of m, 6H), 1.41 and 1.17 (2s, 9H).

LCMS Phenomenex LUNA C-18 4.6 × 50 mm, 0 to 100% B over 3 minutes, 1 minute hold time, A = 90% water, 10% methanol, 0.1% TFA, B = 10% water, 90% methanol, 0.1% TFA, RT = 1.77 min, >95 % homogeneity index.

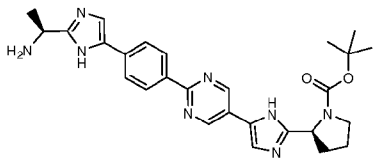
LRMS: Anal. Calcd. for $C_{29}H_{35}N_8O_2$ 527.29; found: 527.34 $(M+H)^+$.

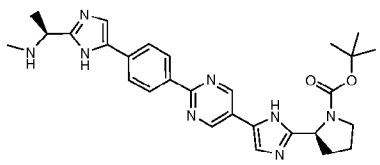
HRMS: Anal. Calcd. for $C_{29}H_{35}N_8O_2$ 527.2883; found: 527.2874 $(M+H)^+$.

The same procedure was used to prepare Examples 152i-2 through 152i-3.

LC conditions: *Condition 1*: Phenomenex LUNA C-18 4.6 × 50 mm, 0 to 100% B over 3 minutes, 1 minute hold time, A = 90% water, 10% methanol, 0.1% TFA, B = 10% water, 90% methanol, 0.1% TFA, 220nm, 5 μL injection volume.

Condition 2: Phenomenex LUNA C-18 4.6 × 50 mm, 0 to 100% B over 2 minutes, 1 minute hold time, A = 90% water, 10% methanol, 0.1% TFA, B = 10% water, 90% methanol, 0.1% TFA, 220nm, 5 μL injection volume.

Example 152i-2	 Prepared from 152g-15	t_R = 1.70 min (95.7%); Condition 1 LRMS: Anal. Calcd. for $C_{27}H_{33}N_8O_2$ 501.27; found: 501.35 $(M+H)^+$.

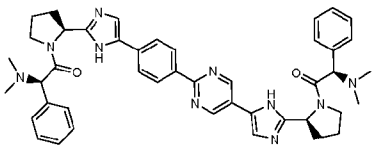
		HRMS: Anal. Calcd. for $C_{27}H_{33}N_8O_2$ 501.2726 found: 501.2709 $(M+H)^+$.
Example 152i-3	 Prepared from 152g-16	t_R = 1.77 min (>95%); Condition 1 LRMS: Anal. Calcd. for $C_{28}H_{35}N_8O_2$ 515.29; found: 515.37 $(M+H)^+$. HRMS: Anal. Calcd. for $C_{28}H_{35}N_8O_2$ 515.2883 found: 515.2869 $(M+H)^+$.

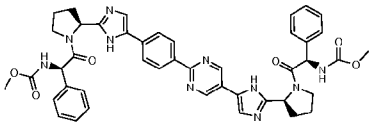
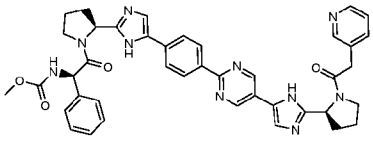
Examples 152j-1 to 152j-28

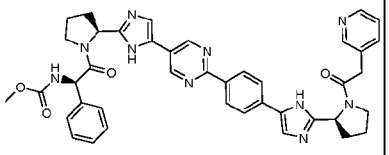
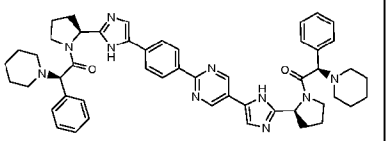
Examples 152j were isolated as TFA or AcOH salts prepared using the procedure to convert Example 148e to 148.

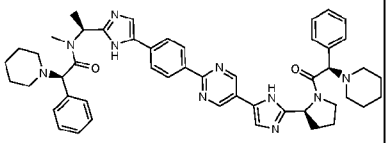
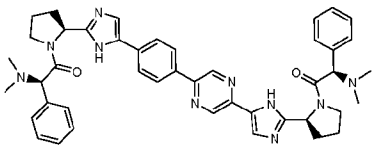
LC conditions: *Condition 1*: Phenomenex LUNA C-18 4.6 × 50 mm, 0 to 100% B over 3 minutes, 1 minute hold time, A = 90% water, 10% methanol, 0.1% TFA, B = 10% water, 90% methanol, 0.1% TFA, 220nm, 5 µL injection volume.

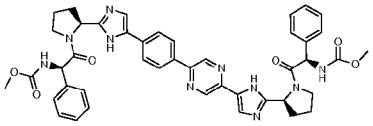
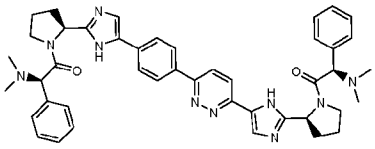
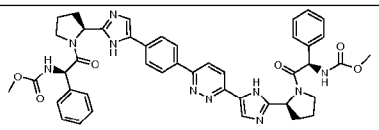
Condition 2: Phenomenex LUNA C-18 4.6 × 50 mm, 0 to 100% B over 2 minutes, 1 minute hold time, A = 90% water, 10% methanol, 0.1% TFA, B = 10% water, 90% methanol, 0.1% TFA, 220nm, 5 µL injection volume.

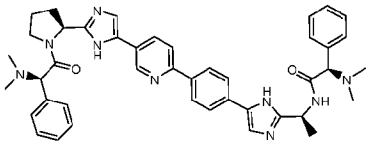
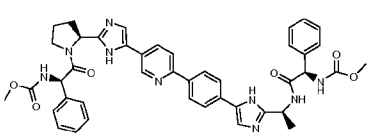
Example	*Compound Name*	*Structure*	*Data*
Example 152j-1	(1R)-2-((2S)-2-(5-(2-(4-(2-((2S)-1-((2R)-2-(dimethylamino)-2-phenylacetyl)-2-pyrrolidinyl)-1H-imidazol-5-yl)phenyl)-5-	 Prepared from 152h-1 and *Cap*-1.	t_R = 1.61 min; (>95%); Condition 1 LRMS: Anal. Calcd. for $C_{44}H_{49}N_{10}O_2$

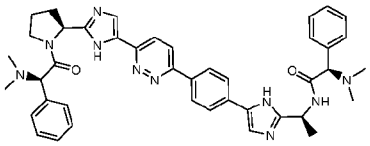
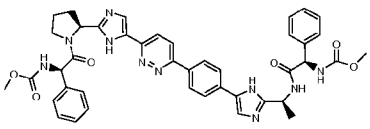
	pyrimidinyl)-1H-imidazol-2-yl)-1-pyrrolidinyl)-N,N-dimethyl-2-oxo-1-phenylethanamine		749.40 found: 749.32 $(M+H)^+$ HRMS: Anal. Calcd. for $C_{44}H_{49}N_{10}O_2$ 749.4040 found: 749.4042 $(M+H)^+$
Example 152j-2	methyl ((1R)-2-((2S)-2-(5-(2-(4-(2-((2S)-1-((2R)-2-((methoxycarbonyl)amino)-2-phenylacetyl)-2-pyrrolidinyl)-1H-imidazol-5-yl)phenyl)-5-pyrimidinyl)-1H-imidazol-2-yl)-1-pyrrolidinyl)-2-oxo-1-phenylethyl)carbamate	 Prepared from 152h-1 and *Cap*-4	t_R = 1.99 min (>95%); Condition 1 LRMS: Anal. Calcd. for $C_{44}H_{45}N_{10}O_6$ 809.35 found: 809.17 $(M+H)^+$ HRMS: Anal. Calcd. for $C_{44}H_{45}N_{10}O_6$ 809.3524 found: 809.3505 $(M+H)^+$
Example 152j-3	methyl ((1R)-2-oxo-1-phenyl-2-((2S)-2-(5-(4-(5-(2-((2S)-1-(3-pyridinylacetyl)-2-pyrrolidinyl)-1H-imidazol-5-yl)-2-pyrimidinyl)phenyl)-1H-imidazol-2-yl)-1-pyrrolidinyl)ethyl)carbamate	 Prepared from 152h-11 and *Cap*-4	t_R = 1.65 min (92.3%); Condition 1 LRMS: Anal. Calcd. for $C_{41}H_{41}N_{10}O_2$ 737.33 found: 737.49 $(M+H)^+$

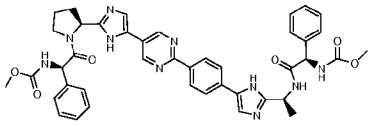
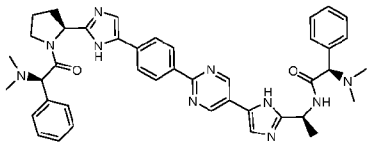
			HRMS: Anal. Calcd. for $C_{41}H_{41}N_{10}O_4$ 737.3312 found: 737.3342 $(M+H)^+$
Example 152j-4	methyl ((1R)-2-oxo-1-phenyl-2-((2S)-2-(5-(2-(4-(2-((2S)-1-(3-pyridinylacetyl)-2-pyrrolidinyl)-1H-imidazol-5-yl)phenyl)-5-pyrimidinyl)-1H-imidazol-2-yl)-1-pyrrolidinyl)ethyl)carbamate	 Prepared from 152h-12 and *Cap*-4	t_R = 1.64 min (>95%); Condition 1 LRMS: Anal. Calcd. for $C_{41}H_{41}N_{10}O_4$ 737.33 found: 737.75 $(M+H)^+$ HRMS: Anal. Calcd. for $C_{41}H_{41}N_{10}O_4$ 737.3312 found: 737.3284 $(M+H)^+$
Example 152j-5	5-(2-((2S)-1-((2R)-2-phenyl-2-(1-piperidinyl)acetyl)-2-pyrrolidinyl)-1H-imidazol-5-yl)-2-(4-(2-((2S)-1-((2R)-2-phenyl-2-(1-piperidinyl)acetyl)-2-pyrrolidinyl)-1H-imidazol-4-yl)phenyl)pyrimidine	 Prepared from 152h-1 and *Cap*-14	t_R = 1.70 min (>95%); Condition 1 LRMS: Anal. Calcd. for $C_{50}H_{57}N_{10}O_2$ 829.47 found: 829.39 $(M+H)^+$ HRMS: Anal. Calcd. for $C_{50}H_{57}N_{10}O_2$

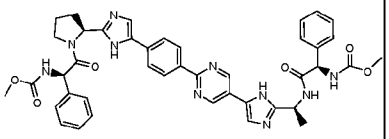
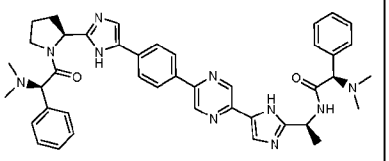
			829.4666 found: 829.4658 $(M+H)^+$
Example 152j-6	(2R)-N-methyl-2-phenyl-N-((1S)-1-(4-(4-(5-(2-((2S)-1-((2R)-2-phenyl-2-(1-piperidinyl)acetyl)-2-pyrrolidinyl)-1H-imidazol-5-yl)-2-pyrimidinyl)phenyl)-1H-imidazol-2-yl)ethyl)-2-(1-piperidinyl)acetamide	 Prepared from 152h-13 and *Cap*-14	t_R = 1.66 min (>95%); Condition 1 LRMS: Anal. Calcd. for $C_{49}H_{57}N_{10}O_2$ 817.47 found: 817.44 $(M+H)^+$ HRMS: Anal. Calcd. for $C_{49}H_{57}N_{10}O_2$ 817.4666 found: 817.4673 $(M+H)^+$
Example 152j-7	(1R)-2-((2S)-2-(5-(5-(4-(2-((2S)-1-((2R)-2-(dimethylamino)-2-phenylacetyl)-2-pyrrolidinyl)-1H-imidazol-5-yl)phenyl)-2-pyrazinyl)-1H-imidazol-2-yl)-1-pyrrolidinyl)-N,N-dimethyl-2-oxo-1-phenylethanamine	 Prepared from 152h-2 and *Cap*-1	t_R = 1.60 min (>95%); Condition 1 LRMS: Anal. Calcd. for $C_{41}H_{49}N_{10}O_2$ 749.40 found: 749.31 $(M+H)^+$ HRMS: Anal. Calcd. for $C_{44}H_{49}N_{10}O_2$ 749.4040 found: 749.4031 $(M+H)^+$

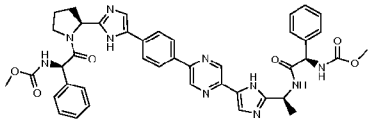
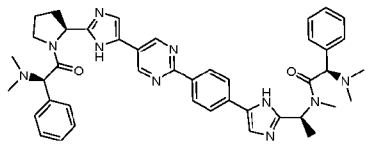
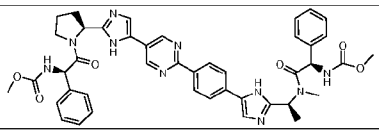
Example 152j-8	methyl ((1R)-2-((2S)-2-(5-(5-(4-(2-((2S)-1-((2R)-2-((methoxycarbonyl)amino)-2-phenylacetyl)-2-pyrrolidinyl)-1H-imidazol-5-yl)phenyl)-2-pyrazinyl)-1H-imidazol-2-yl)-1-pyrrolidinyl)-2-oxo-1-phenylethyl)carbamate	 Prepared from 152h-2 and *Cap*-4	t_R = 2.01 min (>95%); Condition 1 LRMS: Anal. Calcd. for $C_{44}H_{45}N_{10}O_6$ 809.35 found: 809.24 $(M+H)^+$ HRMS: Anal. Calcd. for $C_{44}H_{45}N_{10}O_6$ 809.3523 found: 809.3493 $(M+H)^+$
Example 152j-9	(1R)-2-((2S)-2-(5-(6-(4-(2-((2S)-1-((2R)-2-(dimethylamino)-2-phenylacetyl)-2-pyrrolidinyl)-1H-imidazol-5-yl)phenyl)-3-pyridazinyl)-1H-imidazol-2-yl)-1-pyrrolidinyl)-N,N-dimethyl-2-oxo-1-phenylethanamine	 Prepared from 152h-10 and *Cap*-1	t_R = 1.76 min (>95%); Condition 1 LRMS: Anal. Calcd. for $C_{44}H_{49}N_{10}O_2$ 749.40 found: not obsd $(M+H)^+$ HRMS: Anal. Calcd. for $C_{44}H_{49}N_{10}O_2$ 749.4040 found: 749.4056 $(M+H)^+$
Example 152j-10	methyl ((1R)-2-((2S)-2-(5-(6-(4-(2-((2S)-1-((2R)-2-		t_R = 2.17 min (>95%); Condition 1

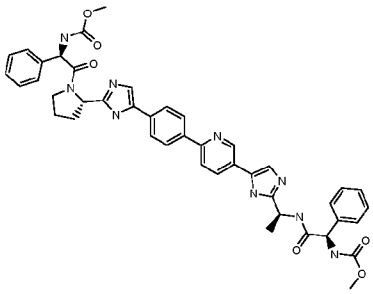
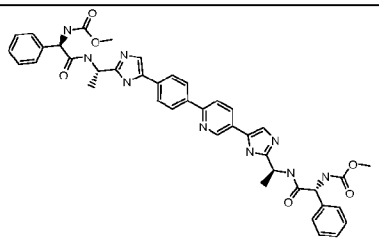
	((methoxycarbonyl)amino)-2-phenylacetyl)-2-pyrrolidinyl)-1H-imidazol-5-yl)phenyl)-3-pyridazinyl)-1H-imidazol-2-yl)-1-pyrrolidinyl)-2-oxo-1-phenylethyl)carbamate	Prepared from 152h-10 and *Cap*-4	LRMS: Anal. Calcd. for $C_{44}H_{45}N_{10}O_6$ 809.35 found: 809.59 $(M+H)^+$ HRMS: Anal. Calcd. for $C_{44}H_{45}N_{10}O_6$ 809.3524 found: 809.3499 $(M+H)^+$
Example 152j-11	(2R)-2-(dimethylamino)-N-((1S)-1-(5-(4-(5-(2-((2S)-1-((2R)-2-(dimethylamino)-2-phenylacetyl)-2-pyrrolidinyl)-1H-imidazol-5-yl)-2-pyridinyl)phenyl)-1H-imidazol-2-yl)ethyl)-2-phenylacetamide	 Prepared from 152h-7 and *Cap*-1	t_R = 1.56 min (>95%); Condition 1 LRMS: Anal. Calcd. for $C_{43}H_{48}N_9O_2$ 722.39 found: 722.89 $(M+H)^+$ HRMS: Anal. Calcd. for $C_{43}H_{48}N_9O_2$ 722.3931 found: 722.3930 $(M+H)^+$
Example 152j-12	methyl ((1R)-2-((2S)-2-(5-(6-(4-(2-((1S)-1-(((2R)-2-((methoxycarbonyl)amino)-2-phenylacetyl)amino)e	 Prepared from 152h-7 and *Cap*-4	t_R = 1.95 min (>95%); Condition 1 LRMS: Anal. Calcd. for

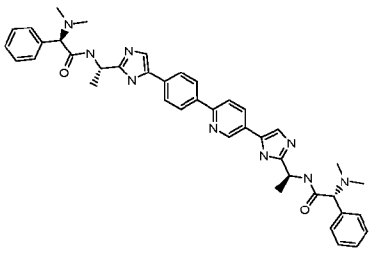
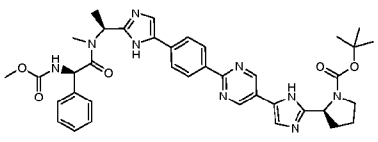
	thyl)-1H-imidazol-5-yl)phenyl)-3-pyridinyl)-1H-imidazol-2-yl)-1-pyrrolidinyl)-2-oxo-1-phenylethyl)carbamate		$C_{43}H_{44}N_9O_6$ 782.34 found: 782.93 $(M+H)^+$ HRMS: Anal. Calcd. for $C_{43}H_{44}N_9O_6$ 782.3415 found: 782.3398 $(M+H)^+$
Example 152j-13	(2R)-2-(dimethylamino)-N-((1S)-1-(5-(4-(6-(2-((2S)-1-((2R)-2-(dimethylamino)-2-phenylacetyl)-2-pyrrolidinyl)-1H-imidazol-5-yl)-3-pyridazinyl)phenyl)-1H-imidazol-2-yl)ethyl)-2-phenylacetamide	 Prepared from 152h-3 and *Cap*-1	t_R = 1.55 min (>95%); Condition 1 LRMS: Anal. Calcd. for $C_{42}H_{47}N_{10}O_2$ 723.39 found: 723.88 $(M+H)^+$ HRMS: Anal. Calcd. for $C_{42}H_{47}N_{10}O_2$ 723.3883 found: 723.3903 $(M+H)^+$
Example 152j-14	methyl ((1R)-2-((2S)-2-(5-(6-(4-(2-((1S)-1-(((2R)-2-((methoxycarbonyl)amino)-2-phenylacetyl)amino)ethyl)-1H-imidazol-5-yl)phenyl)-3-pyridazinyl)-1H-	 Prepared from 152h-3 and *Cap*-4	t_R = 1.95 min (>95%); Condition 1 LRMS: Anal. Calcd. for $C_{42}H_{43}N_{10}O_6$ 783.34 found: 783.95 $(M+H)^+$

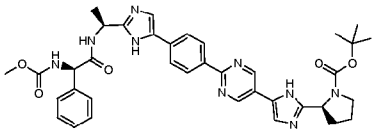
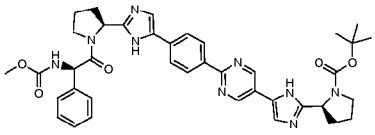
	imidazol-2-yl)-1-pyrrolidinyl)-2-oxo-1-phenylethyl)carbamate		HRMS: Anal. Calcd. for $C_{42}H_{43}N_{10}O_6$ 783.3367 found: 783.3337 $(M+H)^+$
Example 152j-15	methyl ((1R)-2-((2S)-2-(5-(2-(4-(2-((1S)-1-(((2R)-2-((methoxycarbonyl)amino)-2-phenylacetyl)amino)ethyl)-1H-imidazol-5-yl)phenyl)-5-pyrimidinyl)-1H-imidazol-2-yl)-1-pyrrolidinyl)-2-oxo-1-phenylethyl)carbamate	 Prepared from 152h-4 and *Cap*-4	t_R = 1.97 min (>95%); Condition 1 LRMS: Anal. Calcd. for $C_{42}H_{43}N_{10}O_6$ 783.34 found: 783.97 $(M+H)^+$ HRMS: Anal. Calcd. for $C_{42}H_{43}N_{10}O_6$ 783.3367 found: 783.3357 $(M+H)^+$
Example 152j-16	(2R)-2-(dimethylamino)-N-((1S)-1-(5-(2-(4-(2-((2S)-1-((2R)-2-(dimethylamino)-2-phenylacetyl)-2-pyrrolidinyl)-1H-imidazol-5-yl)phenyl)-5-pyrimidinyl)-1H-imidazol-2-yl)ethyl)-2-phenylacetamide	 Prepared from 152h-9 and *Cap*-1	t_R = 1.61 min (>95%); Condition 1 LRMS: Anal. Calcd. for $C_{42}H_{47}N_{10}O_2$ 723.39 found: 723.52 $(M+H)^+$ HRMS: Anal. Calcd. for

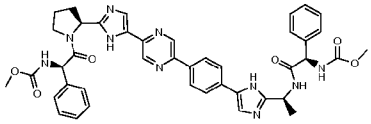
			$C_{42}H_{47}N_{10}O_2$ 723.3883 found: 723.3893 $(M+H)^+$
Example 152j-17	methyl ((1R)-2-((2S)-2-(5-(4-(5-(2-((1S)-1-(((2R)-2-((methoxycarbonyl)amino)-2-phenylacetyl)amino)ethyl)-1H-imidazol-5-yl)-2-pyrimidinyl)phenyl)-1H-imidazol-2-yl)-1-pyrrolidinyl)-2-oxo-1-phenylethyl)carbamate	 Prepared from 152h-9 and *Cap*-4	t_R = 1.99 min (95.6%); Condition 1 LRMS: Anal. Calcd. for $C_{42}H_{43}N_{10}O_6$ 783.34 found: 783.44 $(M+H)^+$ HRMS: Anal. Calcd. for $C_{42}H_{43}N_{10}O_6$ 783.3367 found: 783.3328 $(M+H)^+$
Example 152j-18	(2R)-2-(dimethylamino)-N-((1S)-1-(5-(5-(4-(2-((2S)-1-((2R)-2-(dimethylamino)-2-phenylacetyl)-2-pyrrolidinyl)-1H-imidazol-5-yl)phenyl)-2-pyrazinyl)-1H-imidazol-2-yl)ethyl)-2-phenylacetamide	 Prepared from 152h-8 and *Cap*-1	t_R = 1.60 min (>95%); Condition 1 LRMS: Anal. Calcd. for $C_{42}H_{47}N_{10}O_2$ 723.39 found: 723.47 $(M+H)^+$ HRMS: Anal. Calcd. for $C_{42}H_{47}N_{10}O_2$ 723.3883 found: 723.3861 $(M+H)^+$

Example 152j-19	methyl ((1R)-2-((2S)-2-(5-(4-(5-(2-((1S)-1-(((2R)-2-((methoxycarbonyl)amino)-2-phenylacetyl)amino)ethyl)-1H-imidazol-5-yl)-2-pyrazinyl)phenyl)-1H-imidazol-2-yl)-1-pyrrolidinyl)-2-oxo-1-phenylethyl)carbamate	 Prepared from 152h-8 and *Cap*-4	t_R = 1.97 min (94.7%); Condition 1 LRMS: Anal. Calcd. for $C_{42}H_{43}N_{10}O_6$ 783.34 found: 783.69 $(M+H)^+$ HRMS: Anal. Calcd. for $C_{42}H_{43}N_{10}O_6$ 783.3367 found: 783.3345 $(M+H)^+$
Example 152j-20	(2R)-2-(dimethylamino)-N-((1S)-1-(5-(4-(5-(2-((2S)-1-((2R)-2-(dimethylamino)-2-phenylacetyl)-2-pyrrolidinyl)-1H-imidazol-5-yl)-2-pyrimidinyl)phenyl)-1H-imidazol-2-yl)ethyl)-N-methyl-2-phenylacetamide	 Prepared from 152h-13 and *Cap*-1	t_R = 1.54 min (>95%); Condition 1 LRMS: Anal. Calcd. for $C_{43}H_{49}N_{10}O_2$ 737.40 found: 737.54 $(M+H)^+$ HRMS: Anal. Calcd. for $C_{43}H_{49}N_{10}O_2$ 737.4040 found: 7374066 $(M+H)^+$
Example 152j-21	methyl ((1R)-2-((2S)-2-(5-(2-(4-(2-((1S)-1-		t_R = 2.00 min (>95%); Condition

	(((2R)-2-((methoxycarbonyl)amino)-2-phenylacetyl)(methyl)amino)ethyl)-1H-imidazol-5-yl)phenyl)-5-pyrimidinyl)-1H-imidazol-2-yl)-1-pyrrolidinyl)-2-oxo-1-phenylethyl)carbamate	Prepared from 152h-13 and *Cap*-4	1 LRMS: Anal. Calcd. for $C_{43}H_{45}N_{10}O_6$ 797.35 found: 797.38 $(M+H)^+$ HRMS: Anal. Calcd. for $C_{43}H_{45}N_{10}O_6$ 797.3524 found: 797.3528 $(M+H)^+$
Example 152j-22	methyl ((1R)-2-((2S)-2-(5-(4-(5-(2-((1S)-1-(((2R)-2-((methoxycarbonyl)amino)-2-phenylacetyl)amino)ethyl)-1H-imidazol-5-yl)-2-pyridinyl)phenyl)-1H-imidazol-2-yl)-1-pyrrolidinyl)-2-oxo-1-phenylethyl)carbamate	 Prepared from 152h-5 and *Cap*-4	t_R = 1.46 min (condition 2, 98%) LRMS: Anal. Calcd. for $C_{43}H_{43}N_9O_6$ 781.33; found: 782.34 $(M+H)^+$. HRMS: Anal. Calcd. for $C_{43}H_{44}N_9O_6$ 782.3415 found: 782.3417 $(M+H)^+$
Example 152j-23	methyl ((1R)-2-(((1S)-1-(5-(6-(4-(2-((1S)-1-(((2R)-2-((methoxycarbonyl)amino)-2-phenylacetyl)amino)e	 Prepared from 152h-6 and *Cap*-4	t_R = 1.44 min condition 2, 90%) LRMS: Anal. Calcd. for $C_{41}H_{41}N_9O_6$

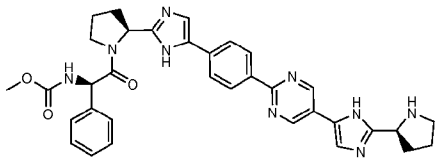
	thyl)-1H-imidazol-5-yl)phenyl)-3-pyridinyl)-1H-imidazol-2-yl)ethyl)amino)-2-oxo-1-phenylethyl)carbamate		755.32; found: 756.35 $(M+H)^+$. HRMS: Anal. Calcd. for $C_{41}H_{42}N_9O_6$ 756.3258 found: 756.3239 $(M+H)^+$.
Example 152j-24	(2R)-2-(dimethylamino)-N-((1S)-1-(5-(6-(4-(2-((1S)-1-(((2R)-2-(dimethylamino)-2-phenylacetyl)amino)ethyl)-1H-imidazol-5-yl)phenyl)-3-pyridinyl)-1H-imidazol-2-yl)ethyl)-2-phenylacetamide	 Prepared from 152h-6 and Cap1	t_R = 1.18 min (condition 2, 91%) LRMS: Anal. Calcd. for $C_{41}H_{45}N_9O_2$ 695.37; found: 696.37 $(M+H)^+$. HRMS: Anal. Calcd. for $C_{41}H_{46}N_9O_2$ 696.3774 found: 696.3806 $(M+H)^+$.
Example 152j-25		 Prepared from 152i-3 and *Cap*-4	t_R = 2.08 min (95.8 %); Condition 1 LRMS: Anal. Calcd. for $C_{38}H_{44}N_9O_5$ 706.35; found: 706.53 $(M+H)^+$. HRMS: Anal. Calcd. for

			$C_{38}H_{44}N_9O_5$ 706.3465; found: 706.3492 $(M+H)^+$.
Example 152j-26		 Prepared from 152i-2 and *Cap*-4	t_R = 2.04 min (96.4 %); Condition 1 LRMS: Anal. Calcd. for $C_{37}H_{42}N_9O_5$ 692.33; found: 692.49 $(M+H)^+$. HRMS: Anal. Calcd. for $C_{37}H_{42}N_9O_5$ 692.3309; found: 692.3322 $(M+H)^+$.
Example 152j-27		 Prepared from 152i-1 and *Cap*-4	t_R = 2.04 min (>95 %); Condition 1 LRMS: Anal. Calcd. for $C_{39}H_{44}N_9O_5$ 718.35; found: 718.49 $(M+H)^+$. HRMS: Anal. Calcd. for $C_{39}H_{44}N_9O_5$ 718.3465; found: 718.3483 $(M+H)^+$.

Example 152j-28	methyl ((1R)-2-((2S)-2-(5-(5-(4-(2-((1S)-1-(((2R)-2-((methoxycarbonyl)amino)-2-phenylacetyl)amino)ethyl)-1H-imidazol-5-yl)phenyl)-2-pyrazinyl)-1H-imidazol-2-yl)-1-pyrrolidinyl)-2-oxo-1-phenylethyl)carbamate	 Prepared from 152h-14 and *Cap-4*	t_R = 2.00 min (>95%); Condition 1 LRMS: Anal. Calcd. for $C_{42}H_{43}N_{10}O_6$ 783.34 found: 783.96 $(M+H)^+$ HRMS: Anal. Calcd. for $C_{42}H_{43}N_{10}O_6$ 783.3367 found: 783.3375 $(M+H)^+$

Examples 152k-1 to 152k-

Example 152k-1 from 152j-27. {(R)-2-Oxo-1-phenyl-2-[(S)-2-(5-{4-[5-((S)-2-pyrrolidin-2-yl-3H-imidazol-4-yl)-pyrimidin-2-yl]-phenyl}-1H-imidazol-2-yl)-pyrrolidin-1-yl]-ethyl}-carbamic acid methyl ester



Cold (0°C) 4 *N* HCl in dioxanes (4 mL) was added *via* syringe to (S)-2-{5-[2-(4-{2-[(S)-1-((R)-2-methoxycarbonylamino-2-phenyl-acetyl)-pyrrolidin-2-yl]-3*H*-imidazol-4-yl}-phenyl)-pyrimidin-5-yl]-1*H*-imidazol-2-yl}-pyrrolidine-1-carboxylic acid *tert*-butyl ester (104.6 mg, 0.146 mmol) in a 100 mL pear-shaped flask followed by MeOH (0.5 mL). The homogeneous mixture was stirred at room temperature for 15 min before a precipitate was observed. After stirring further for 1.75h, the suspension was diluted with ether and hexanes. Suction-filtration of a small portion of the suspension yielded the title compound as a yellow solid which was used for characterization purposes. The balance of the suspension was concentrated down to

dryness and placed under high vacuum for 16h. There was isolated the rest of the title compound also as a yellow solid (137.7 mg, 123%) which was used without further purification.

^{1}H NMR (500 MHz, DMSO-d_6) δ 15.20 and 14.66 (2m, 1H), 10,29 (br s, 0.7H), 9.38-9.36 (m, 2H), 8.55-8.00 (series of m, 4H), 7.42-7.28 (2m, 3H), 5.53-4.00 (series of m, 7H), 3.99-3.13 (series of m, 4H), 3.57 and 3.52 (2s, 3H), 2.50-1.84 (series of m, 8H) .

LCMS Phenomenex LUNA C-18 4.6 × 50 mm, 0 to 100% B over 3 minutes, 1 minute hold time, A = 90% water, 10% methanol, 0.1% TFA, B = 10% water, 90% methanol, 0.1% TFA, RT = 1.79 min, >95 % homogeneity index.

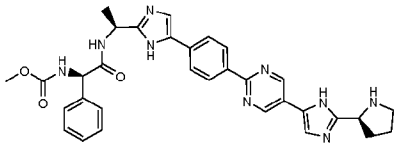
LRMS: Anal. Calcd. for $C_{34}H_{36}N_9O_3$ 618.29; found: 618.42 $(M+H)^+$.

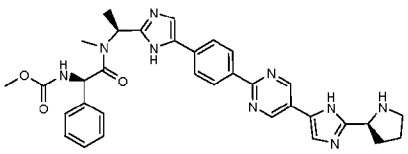
HRMS: Anal. Calcd. for $C_{34}H_{36}N_9O_3$ 618.2921; found: 618.2958 $(M+H)^+$.

The same procedure was used to prepare Examples 152k-2 through 152k-3.

LC conditions: *Condition 1*: Phenomenex LUNA C-18 4.6 × 50 mm, 0 to 100% B over 3 minutes, 1 minute hold time, A = 90% water, 10% methanol, 0.1% TFA, B = 10% water, 90% methanol, 0.1% TFA, 220nm, 5 µL injection volume.

Condition 2: Phenomenex LUNA C-18 4.6 × 50 mm, 0 to 100% B over 2 minutes, 1 minute hold time, A = 90% water, 10% methanol, 0.1% TFA, B = 10% water, 90% methanol, 0.1% TFA, 220nm, 5 µL injection volume.

Example	*Compound Name*	*Structure*	*Data*
Example 152k-2		 Prepared from 152j-26	t_R = 1.74 min (>95 %); Condition 1 LRMS: Anal. Calcd. for $C_{32}H_{34}N_9O_3$ 592.28; found: 592.41 $(M+H)^+$. HRMS: Anal.

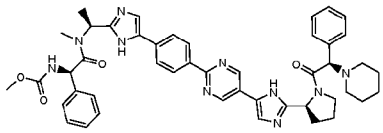
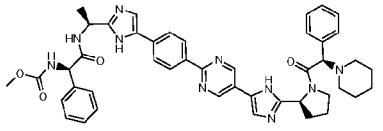
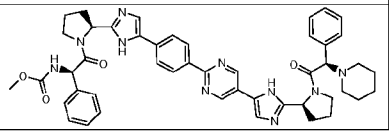
			Calcd. for $C_{32}H_{34}N_9O_3$ 592.2785; found: 592.2775 $(M+H)^+$.
Example 152k-3		 Prepared from 152j-25	t_R = 1.79 min (>95 %); Condition 1 LRMS: Anal. Calcd. for $C_{33}H_{36}N_9O_3$ 606.29; found: 606.43 $(M+H)^+$. HRMS: Anal. Calcd. for $C_{33}H_{36}N_9O_3$ 606.2941; found: 606.2925 $(M+H)^+$.

Examples 152l-1 to 152l-

Examples 152l-1 through 152l-3 were isolated as TFA or AcOH salts prepared using the same procedure to convert Example 148e to 148.

LC conditions: *Condition 1*: Phenomenex LUNA C-18 4.6 × 50 mm, 0 to 100% B over 3 minutes, 1 minute hold time, A = 90% water, 10% methanol, 0.1% TFA, B = 10% water, 90% methanol, 0.1% TFA, 220nm, 5 µL injection volume.

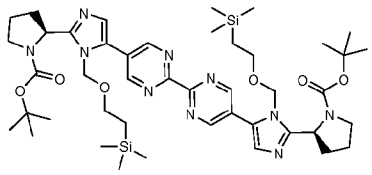
Condition 2: Phenomenex LUNA C-18 4.6 × 50 mm, 0 to 100% B over 2 minutes, 1 minute hold time, A = 90% water, 10% methanol, 0.1% TFA, B = 10% water, 90% methanol, 0.1% TFA, 220nm, 5 µL injection volume.

Example	*Compound Name*	*Structure*	*Data*
Example 152l-1	methyl ((1R)-2-(methyl((1S)-1-(4-(4-(5-(2-((2S)-1-((2R)-2-phenyl-2-(1-piperidinyl)acetyl)-2-pyrrolidinyl)-1H-imidazol-5-yl)-2-pyrimidinyl)phenyl)-1H-imidazol-2-yl)ethyl)amino)-2-oxo-1-phenylethyl)carbamate	 Prepared from 152k-3 and *Cap*-14	t_R = 1.87 min (>95%); Condition 1 LRMS: Anal. Calcd. for $C_{46}H_{51}N_{10}O_4$ 807.41 found: 807.57 $(M+H)^+$ HRMS: Anal. Calcd. for $C_{46}H_{51}N_{10}O_4$ 807.4095 found: 807.4128 $(M+H)^+$
Example 152l-2	methyl ((1R)-2-oxo-1-phenyl-2-(((1S)-1-(4-(4-(5-(2-((2S)-1-((2R)-2-phenyl-2-(1-piperidinyl)acetyl)-2-pyrrolidinyl)-1H-imidazol-5-yl)-2-pyrimidinyl)phenyl)-1H-imidazol-2-yl)ethyl)amino)ethyl)carbamate	 Prepared from 152k-2 and *Cap*-14	t_R = 1.83 min (>95%); Condition 1 LRMS: Anal. Calcd. for $C_{45}H_{49}N_{10}O_4$ 793.39 found: 793.52 $(M+H)^+$ HRMS: Anal. Calcd. for $C_{45}H_{49}N_{10}O_4$ 793.3938 found: 793.3934 $(M+H)^+$
Example 152l-3	methyl ((1R)-2-oxo-1-phenyl-2-((2S)-2-(4-(4-		t_R = 1.87 min (>95%); Condition

	(5-(2-((2S)-1-((2R)-2-phenyl-2-(1-piperidinyl)acetyl)-2-pyrrolidinyl)-1H-imidazol-5-yl)-2-pyrimidinyl)phenyl)-1H-imidazol-2-yl)-1-pyrrolidinyl)ethyl)carbamate	Prepared from 152k-1 and *Cap*-14	1 LRMS: Anal. Calcd. for $C_{47}H_{51}N_{10}O_4$ 819.41 found: 819.50 $(M+H)^+$ HRMS: Anal. Calcd. for $C_{47}H_{51}N_{10}O_4$ 819.4095 found: 819.4127 $(M+H)^+$

Example 153a-1 from 153a-4.

Example 153a-1 prepared from 152e-1. (S)-2-[5-{5'-[2-((S)-1-tert-Butoxycarbonyl-pyrrolidin-2-yl)-3-(2-trimethylsilanyl-ethoxymethyl)-3H-imidazol-4-yl]-[2,2']bipyrimidinyl-5-yl}-1-(2-trimethylsilanyl-ethoxymethyl)-1H-imidazol-2-yl]-pyrrolidine-1-carboxylic acid tert-butyl ester



To a stirred solution of (S)-tert-butyl 2-(5-(2-chloropyrimidin-5-yl)-1-((2-(trimethylsilyl)ethoxy)methyl)-1H-imidazol-2-yl)pyrrolidine-1-carboxylate (1.0 g, 2.08 mmol) and dichlorobis(benzonitrile) palladium (40 mg, 0.104 mmol) in dry DMF (10 mL) at room temperature under argon was added neat tetrakis(dimethylamino)ethylene (1.0 mL, 4.16 mmol). The mixture was heated to 60°C for 15h before it was diluted with ethyl acetate and suction-filtered through diatomaceous earth (Celite®). The filtrate was washed with sat'd $NaHCO_3$ soln and brine prior to drying over Na_2SO_4 and solvent evaporation. Purification of the residue by Biotage™ flash chromatography on silica gel (step gradient elution with 15%B to 15%B for 150 mL, 15%B to 75%B for 1500 mL, 75%B to 100%B for 1000

mL, 100%B to 100%B for 1000 mL where B=ethyl acetate and A=hexane followed by a second gradient elution with 10%B to 100%B for 700 mL where B=methanol and A=ethyl acetate) furnished the title compound as a caramel-colored, viscous oil (487.8 mg, 26% yield).

^{1}H NMR (500 MHz, DMSO-d_6) δ 9.27 (s, 4H), 8.09-8.06 (m, 2H), 5.73-5.66 and 5.50-5.44 (2m, 2H), 5.06-4.93 (m, 2H), 3.60-3.39 (2m, 8H), 2.32-2.08 (3m, 4H), 2.00-1.85 (m, 4H), 1.37 and 1.14 (2s, 18H), 0.95-0.84 (m, 4H), -0.01 (s, 18H).

LCMS Phenomenex LUNA C-18 4.6 × 50 mm, 0 to 100% B over 3 minutes, 1 minute hold time, A = 90% water, 10% methanol, 0.1% TFA, B = 10% water, 90% methanol, 0.1% TFA, RT = 3.37min, >95% homogeneity index.

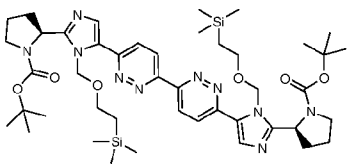
LRMS: Anal. Calcd. for $C_{44}H_{69}N_{10}O_6Si_2$ 889.49; found: 889.57 $(M+H)^+$.

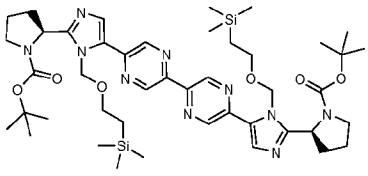
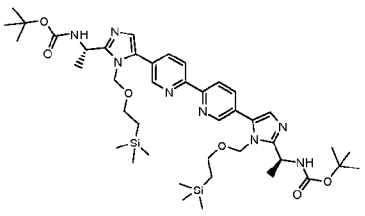
HRMS: Anal. Calcd. for $C_{44}H_{69}N_{10}O_6Si_2$ 889.4940; found: 889.4920 $(M+H)^+$.

The same procedure was used to prepare Examples 153a-2 through 153a-4.

LC conditions: *Condition 1*: Phenomenex LUNA C-18 4.6 × 50 mm, 0 to 100% B over 3 minutes, 1 minute hold time, A = 90% water, 10% methanol, 0.1% TFA, B = 10% water, 90% methanol, 0.1% TFA, 220nm, 5 µL injection volume.

Condition 2: Phenomenex LUNA C-18 4.6 × 50 mm, 0 to 100% B over 2 minutes, 1 minute hold time, A = 90% water, 10% methanol, 0.1% TFA, B = 10% water, 90% methanol, 0.1% TFA, 220nm, 5 µL injection volume.

Example	*Compound Name*	*Structure*	*Data*
Example 153a-2		 Prepared from 152e-2	t_R = 3.37 min (89.6%); Condition 1 LRMS: Anal. Calcd. for $C_{44}H_{69}N_{10}O_6Si_2$ 889.49; found: 889.56 $(M+H)^+$. HRMS: Anal.

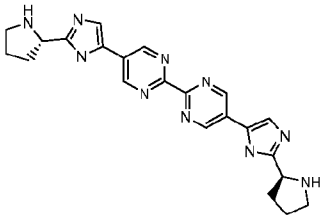
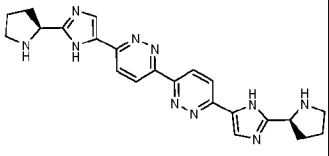
			Calcd. for $C_{44}H_{69}N_{10}O_6Si_2$ 889.494; found: 889.4951 $(M+H)^+$.
Example 153a-3		 Prepared from 152e-3	t_R = 3.37 min (95%); Condition 1 LRMS: Anal. Calcd. for $C_{44}H_{69}N_{10}O_6Si_2$ 889.49; found: 889.51 $(M+H)^+$. HRMS: Anal. Calcd. for $C_{44}H_{69}N_{10}O_6Si_2$ 889.4940; found: 889.4915 $(M+H)^+$.
Example 153a-4		 Prepared from 152e-4	t_R = 2.3 min (condition 2) LRMS: Anal. Calcd. for $C_{42}H_{66}N_8Si_2$ 834; found: 835 $(M+H)^+$.

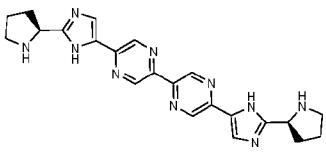
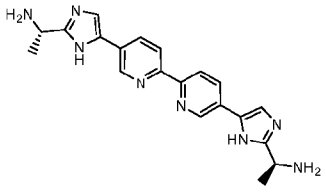
Example 153b-1-153b-3

The hydrolysis reactions was performed as above for Example 152h.

LC conditions: *Condition 1*: Phenomenex LUNA C-18 4.6 × 50 mm, 0 to 100% B over 3 minutes, 1 minute hold time, A = 90% water, 10% methanol, 0.1% TFA, B = 10% water, 90% methanol, 0.1% TFA, 220nm, 5 µL injection volume.

Condition 2: Phenomenex LUNA C-18 4.6 × 50 mm, 0 to 100% B over 2 minutes, 1 minute hold time, A = 90% water, 10% methanol, 0.1% TFA, B = 10% water, 90% methanol, 0.1% TFA, 220nm, 5 μL injection volume.

Example	*Compound Name*	*Structure*	*Data*
Example 153b-1		 Prepared from 153a-1	t_R = 1.18 min (>95%); Condition 1 LRMS: Anal. Calcd. for $C_{22}H_{25}N_{10}$ 429.23; found: 429.01 $(M+H)^+$. HRMS: Anal. Calcd. for $C_{22}H_{25}N_{10}$ 429.2264; found: 429.2259 $(M+H)^+$.
Example 153b-2		 Prepared from 153a-2	t_R = 1.26 min (>95%); Condition 1 LRMS: Anal. Calcd. for $C_{41}H_{41}N_{10}O_2$ 737.33 found: 737.49 $(M+H)^+$ HRMS: Anal. Calcd. for $C_{41}H_{41}N_{10}O_4$ 737.3312 found: 737.3342 $(M+H)^+$

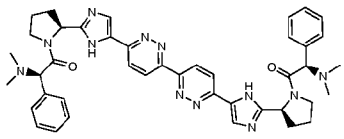
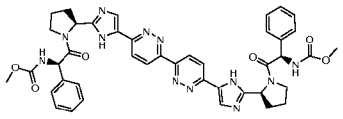
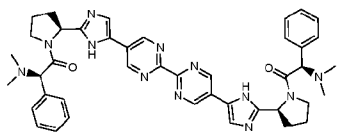
Example 153b-3		 Prepared from 153a-3	t_R = 1.40 min (>95%); Condition 1 LRMS: Anal. Calcd. for $C_{22}H_{25}N_{10}$ 429.23; found: 429.20 $(M+H)^+$. HRMS: Anal. Calcd. for $C_{22}H_{25}N_{10}$: 429.2264; Found: 429.2254 $(M+H)^+$
Example 153b-4		 Prepared from 153a-4	t_R = 0.85 min (condition 1) LCMS: Anal. Calcd. for $C_{20}H_{22}N_8$ 374; found: 375 $(M+H)^+$.

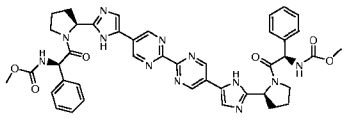
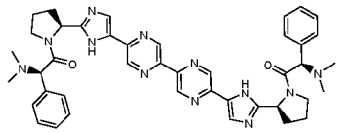
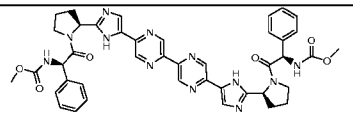
Examples 153c-1 to 153c-7

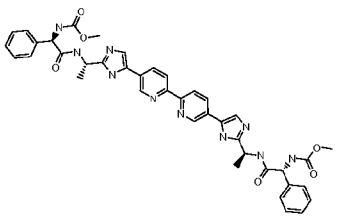
Examples 153c-1 through 153c-7 were isolated as TFA or AcOH salts using the procedure used to convert Example 148e to 148.

LC conditions: *Condition 1*: Phenomenex LUNA C-18 4.6 × 50 mm, 0 to 100% B over 3 minutes, 1 minute hold time, A = 90% water, 10% methanol, 0.1% TFA, B = 10% water, 90% methanol, 0.1% TFA, 220nm, 5 µL injection volume.

Condition 2: Phenomenex LUNA C-18 4.6 × 50 mm, 0 to 100% B over 2 minutes, 1 minute hold time, A = 90% water, 10% methanol, 0.1% TFA, B = 10% water, 90% methanol, 0.1% TFA, 220nm, 5 µL injection volume.

Example	*Compound Name*	*Structure*	*Data*
Example 153c-1	(1R,1'R)-2,2'-(3,3'-bipyridazine-6,6'-diylbis(1H-imidazole-5,2-diyl(2S)-2,1-pyrrolidinediyl))bis(N,N-dimethyl-2-oxo-1-phenylethanamine)	 Prepared from 153b-2 and *Cap*-1	t_R = 1.55 min (>95%); Condition 1 LRMS: Anal. Calcd. for $C_{42}H_{47}N_{12}O_2$ 751.39 found: 751.64 $(M+H)^+$ HRMS: Anal. Calcd. for $C_{42}H_{47}N_{12}O_2$ 751.3945 found: 751.3936 $(M+H)^+$
Example 153c-2	dimethyl (3,3'-bipyridazine-6,6'-diylbis(1H-imidazole-5,2-diyl(2S)-2,1-pyrrolidinediyl((1R)-2-oxo-1-phenyl-2,1-ethanediyl)))biscarbamate	 Prepared from 153b-2 and *Cap*-4	t_R = 1.95 min (>95%); Condition 1 LRMS: Anal. Calcd. for $C_{42}H_{43}N_{12}O_6$ 811.34 found: 811.22 $(M+H)^+$ HRMS: Anal. Calcd. for $C_{42}H_{43}N_{12}O_6$ 811.3429 found: 811.3406 $(M+H)^+$
Example 153c-3	(1R,1'R)-2,2'-(2,2'-bipyrimidine-5,5'-diylbis(1H-imidazole-5,2-diyl(2S)-2,1-pyrrolidinediyl))bis(N,N-dimethyl-2-oxo-1-phenylethanamine)	 Prepared from 153b-1 and *Cap*-1	t_R = 1.51 min (>90%*); Condition 1 LRMS: Anal. Calcd. for $C_{42}H_{47}N_{12}O_2$ 751.39 found: 751.21 $(M+H)^+$

			HRMS: Anal. Calcd. for $C_{42}H_{47}N_{12}O_2$ 751.3945 found: 751.3921 $(M+H)^+$
Example 153c-4	dimethyl (2,2'-bipyrimidine-5,5'-diylbis(1H-imidazole-5,2-diyl(2S)-2,1-pyrrolidinediyl((1R)-2-oxo-1-phenyl-2,1-ethanediyl)))biscarbamate	 Prepared from 153b-1 and *Cap*-4	t_R = 1.88 min (>95%); Condition 1 LRMS: Anal. Calcd. for $C_{42}H_{43}N_{12}O_6$ 811.34 found: 811.10 $(M+H)^+$ HRMS: Anal. Calcd. for $C_{42}H_{43}N_{12}O_6$ 811.3429 found: 811.3401 $(M+H)^+$
Example 153c-5	(1R,1'R)-2,2'-(2,2'-bipyrazine-5,5'-diylbis(1H-imidazole-5,2-diyl(2S)-2,1-pyrrolidinediyl))bis(N,N-dimethyl-2-oxo-1-phenylethanamine)	 Prepared from 153b-3 and *Cap*-1	t_R = 1.61 min (>95%); Condition 1 LRMS: Anal. Calcd. for $C_{42}H_{47}N_{12}O_2$ 751.39 found: 751.30 $(M+H)^+$ HRMS: Anal. Calcd. for $C_{42}H_{47}N_{12}O_2$ 751.3945 found: 751.3943 $(M+H)^+$
Example 153c-6	dimethyl (2,2'-bipyrazine-5,5'-diylbis(1H-imidazole-5,2-diyl(2S)-2,1-	 Prepared from 153b-3 and *Cap*-4	t_R = 2.00 min (>95%); Condition 1 LRMS: Anal. Calcd.

	pyrrolidinediyl((1R)-2-oxo-1-phenyl-2,1-ethanediyl)))biscarbamate		for $C_{42}H_{43}N_{12}O_6$ 811.34 found: 811.23 $(M+H)^+$ HRMS: Anal. Calcd. for $C_{42}H_{43}N_{12}O_6$ 811.3429 found: 811.3407 $(M+H)^+$
Example 153c-7	dimethyl (2,2'-bipyridine-5,5'-diylbis(1H-imidazole-5,2-diyl(1S)-1,1-ethanediylimino((1R)-2-oxo-1-phenyl-2,1-ethanediyl)))biscarbamate	 Prepared from 153b-4 and *Cap*-4	t_R = 1.42 min (condition 2, 94%) LRMS: Anal. Calcd. for $C_{40}H_{40}N_{10}O_6$ 756.31; found: 757.34 $(M+H)^+$. HRMS: Anal. Calcd. for $C_{40}H_{41}N_{10}O_6$ 757.3211 found: 757.3180 $(M+H)^+$.

Section LS LC Conditions:

Condition 1: Solvent A: 10%methanol/90% water/0.1% TFA; Solvent B: 90% methanol/10% water/0.1% TFA; Column: Phenomenex-Luna 3.0 x 5.0mm S10; Wavelength: 220nM; Flow rate: 4mL/min; 0%B to 100% B over 4min with a 1min hold time

Condition 2: Solvent A: 10%methanol/90% water/0.1% TFA; Solvent B: 90% methanol/10% water/0.1% TFA; Column: Phenomenex 10u C18 3.0 x 5.0mm; Wavelength: 220nM; Flow rate: 4mL/min; 0%B to 100% B over 4min with a 1min hold time

Condition 3: Solvent A: 5% acetonitrile/95% water/10mmol ammonium acetate; Solvent B: 95% acetonitrile/5% water/10mmol ammonium acetate; Column: Phenomenex 10u C18 4.6 x 5.0mm; Wavelength: 220nM; Flow rate: 4mL/min; 0%B to 100% B over 4min with a 1min hold time

Condition 4: Solvent A: 5% acetonitrile/95% water/10mmol ammonium acetate; Solvent B: 95% acetonitrile/5% water/10mmol ammonium acetate; Column: Luna 4.6 x 50mm S10; Wavelength: 220nM; Flow rate: 4mL/min; 0%B to 100% B over 3min with a 1min hold time

Condition 5: Solvent A: 10%methanol/90% water/0.1% TFA; Solvent B: 90% methanol/10% water/0.1% TFA; Column: Phenomenex 10u C18 3.0 x 5.0mm; Wavelength: 220nM; Flow rate: 4mL/min; 0%B to 100% B over 3min with a 1min hold time

Condition 6: Solvent A: 5% acetonitrile/95% water/10mmol ammonium acetate; Solvent B: 95% acetonitrile/5% water/10mmol ammonium acetate; Column: Phenomenex-Luna 3.0 x 50mm S10; Wavelength: 220nM; Flow rate: 4mL/min; 0%B to 100% B over 8min with a 2min hold time

Condition 7: Solvent A: 10%methanol/90% water/0.1% TFA; Solvent B: 90% methanol/10% water/0.1% TFA; Column: Phenomenex-Luna 3.0 x 5.0mm S10; Wavelength: 220nM; Flow rate: 4mL/min; 0%B to 100% B over 3min with a 1min hold time

Condition 8: Solvent A: 10%methanol/90% water/0.2% H_3PO_4; Solvent B: 90% methanol/10% water/0.2% H_3PO_4; Column: YMC ODS-A 4.6 x 50mm S5; Wavelength: 220nM; Flow rate: 4mL/min; 0%B to 100% B over 4min with a 1min hold time

Condition 9: Solvent A: 10%methanol/90% water/0.2% H_3PO_4; Solvent B: 90% methanol/10% water/0.2% H_3PO_4; Column: YMC ODS-A 4.6 x 50mm S5;

Wavelength: 220nM; Flow rate: 2.5mL/min; 0%B to 50% B over 8min with a 3min hold time

Condition 10: Xbridge C18, 150 x4.6 mm I.D. S-3.5um; Mobile Phase A: 95%Water-5% Acetonitrile with 10 mM ammonium acetate (pH=5); Mobile phase B: 95% Acetonitrile-5% Water with 10 mM ammonium acetate (pH=5); Isocratic 30% B for 20 min; Flow rate: 1 mL/min; UV detection: 220 nm

Condition 11: Solvent A: 10%methanol/90% water/0.1% TFA; Solvent B: 90% methanol/10% water/0.1% TFA; Column: Phenomenex 10u C18 3.0 x 5.0mm; Wavelength: 220nM; Flow rate: 4mL/min; 30%B to 100% B over 4min with a 1min hold time

Condition 12: Solvent A: 10%methanol/90% water/0.1% TFA; Solvent B: 90% methanol/10% water/0.1% TFA; Column: Phenomenex 10u C18 3.0 x 5.0mm; Wavelength: 220nM; Flow rate: 4mL/min; 20%B to 100% B over 4min with a 1min hold time

Condition 13: Solvent A: 10%methanol/90% water/0.2% H_3PO_4; Solvent B: 90% methanol/10% water/0.2% H_3PO_4; Column: YMC ODS-A 4.6 x 50mm S5; Wavelength: 220nM; Flow rate: 2.5mL/min; 0%B to 100% B over 8min with a 3min hold time

Section LS Preparative HPLC Conditions:

Condition 1: Solvent A: 10%methanol/90% water/0.1% TFA; Solvent B: 90% methanol/10% water/0.1% TFA; Column: Phenomenex-Luna 30 x 100mm S10; Wavelength: 220nM; Flow rate: 30mL/min; 0%B to 100% B over 10min with a 2min hold time

Condition 2: Solvent A: 10%methanol/90% water/0.1% TFA; Solvent B: 90% methanol/10% water/0.1% TFA; Column: Xterra Prep MS C18 30 x 50mm 5u;

Wavelength: 220nM; Flow rate: 30mL/min; 0%B to 100% B over 8min with a 3min hold time

Condition 3: Solvent A: 10%methanol/90% water/0.1% TFA; Solvent B: 90% methanol/10% water/0.1% TFA; Column: Xterra Prep MS C18 30 x 50mm 5u; Wavelength: 220nM; Flow rate: 25mL/min; 10%B to 100% B over 8min with a 2min hold time

Condition 4: Solvent A: 10%methanol/90% water/0.1% TFA; Solvent B: 90% methanol/10% water/0.1% TFA; Column: Xterra 19 x 100mm S5; Wavelength: 220nM; Flow rate: 20mL/min; 30%B to 100% B over 5min with a 3min hold time

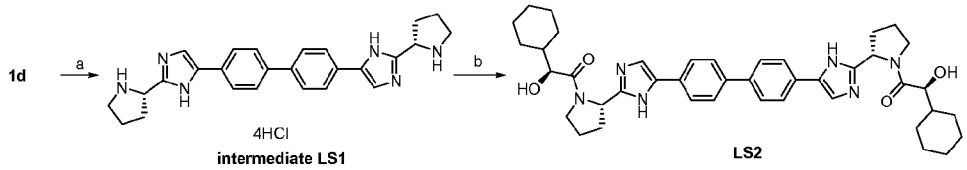
Condition 5: Solvent A: 10%methanol/90% water/0.1% TFA; Solvent B: 90% methanol/10% water/0.1% TFA; Column: Phenomenex-Luna 30 x 100mm S10; Wavelength: 220nM; Flow rate: 30mL/min; 10%B to 100% B over 8min with a 2min hold time

Condition 6: Solvent A: 10% Acetonitrile/90% water/0.1% TFA; Solvent B: 90% Acetonitrile/10% water/0.1% TFA; Column: Phenomenex-Luna 21 x 100mm S10; Wavelength: 220nM; Flow rate: 25mL/min; 0%B to 60% B over 10min with a 5min hold time

Experimentals:

Compound LS2

(1S,1'S)-2,2'-(4,4'-biphenyldiylbis(1H-imidazole-5,2-diyl(2S)-2,1-pyrrolidinediyl))bis(1-cyclohexyl-2-oxoethanol)

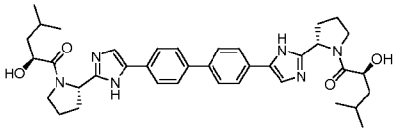


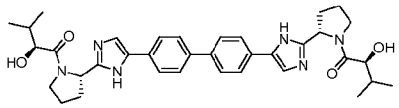
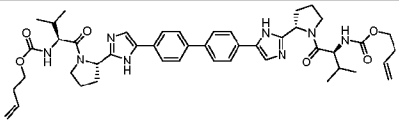
Step a: To 1d (1.4g; 2.24mmol) was added 30mL 4N HCl in dioxane. After 3h, 60mL ether was added and the precipitate was filtered and dried under high vacuum providing 1.02g (80%) intermediate LS1 as a pale yellow powder. ^{1}H NMR (DMSO-

d_6, δ = 2.5 ppm, 500 MHz): δ 10.41 (s, 2H), 9.98 (s, 2H), 8.22 (s, 2H), 8.06 (d, *J* = 8.54Hz, 4H), 7.92 (d, *J* = 8.55Hz, 4H), 5.07 (s, 2H), 3.43-3.54 (m, 2H), 3.33-3.43 (m, 2H), 2.43-2.59 (m, 4H), 2.16-2.28 (m, 2H), 1.94-2.09 (m, 2H). LC (Cond. 1): RT = 1.28 min; MS: Anal. Calcd. for $[M+H]^+$ $C_{26}H_{28}N_6$: 425.24; found 425.56.

Step b: To intermediate LS1 (200mg; 0.35mmol) in 2mL DMF was added DIPEA (0.30mL; 1.75mmol), (S)-2-cyclohexyl-2-hydroxyacetic acid (61mg; 0.39mmol), followed by HATU (147mg; 0.38mmol). After stirring at ambient temperature for 18h, the reaction mixture was split into two portions and purified *via* preparative HPLC (Cond'n 1). Fractions containing desired product were pooled and passed through an MCX cartridge (Oasis; 6g; preconditioned with two column lengths of methanol). The cartridge was washed with two column lengths of methanol and product was eluted with ammonia/methanol. Concentration provided 65mg of LS2 (26%) as a colorless powder. ^{1}H NMR (500 MHz, DMSO-d_6) δ ppm 0.87-1.30 (m, 12H) 1.38-1.53 (m, *J*=24.72, 11.90 Hz, 4H) 1.54-1.75 (m, 8H) 1.95-2.21 (m, 6H) 3.72-3.86 (m, 6H) 5.13 (t, *J*=6.56 Hz, 2H) 7.87 (d, *J*=7.93 Hz, 4H) 7.96 (d, *J*=6.41 Hz, 4H) 8.13 (s, 2H) (imidazole NH and hydroxyl protons unaccounted for). LC (Cond'n 2): RT = 3.07 min; MS: Anal. Calcd. for $[M+H]^+$ $C_{42}H_{52}N_6O_4$: 705.9; found 705.6.

The following analogs were prepared in similar fashion to the preparation of LS2 from intermediate LS1 employing the appropriate carboxylic acid:

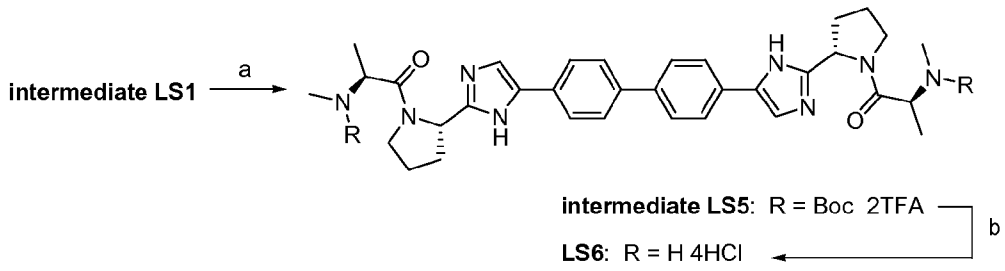
Example Number	*Compound Name*	*Structure*	*Analytical Data*
LS3	(2S,2'S)-1,1'-(4,4'-biphenyldiylbis(1H-imidazole-5,2-diyl(2S)-2,1-pyrrolidinediyl))bis(4-methyl-1-oxo-2-pentanol)		LC/MS: 2.02 min (Cond'n 1); Anal. Calcd. for $[M+H]^+$ $C_{38}H_{48}N_6O_4$: 653.4; found 653.2.

LS4	(2S,2'S)-1,1'-(4,4'-biphenyldiylbis(1H-imidazole-5,2-diyl(2S)-2,1-pyrrolidinediyl))bis(3-methyl-1-oxo-2-butanol)		LC/MS: 1.99 min (Cond'n 3); Anal. Calcd. for $[M+H]^+$ $C_{36}H_{44}N_6O_4$: 625.3; found 625.3.
LS16	3-buten-1-yl ((1S)-1-(((2S)-2-(5-(4'-(2-((2S)-1-((2S)-2-(((3-buten-1-yloxy)carbonyl)amino)-3-methylbutanoyl)-2-pyrrolidinyl)-1H-imidazol-5-yl)-4-biphenylyl)-1H-imidazol-2-yl)-1-pyrrolidinyl)carbonyl)-2-methylpropyl)carbamate	 from intermediate LS1 and (S)-2-((but-3-enyloxy)carbonylamino)-3-methylbutanoic which was prepared from L-valine and butenylchloroformate in similar fashion to the preparation of *Cap-51*	^{1}H NMR (500 MHz, CH_3OD) δ ppm 0.81-1.10 (m, 12H) 1.90-2.15 (m, 4H) 2.15-2.51 (m, 8H) 3.82-3.96 (m, 2H) 3.97-4.05 (m, 2H) 4.05-4.19 (m, 4H) 4.25 (d, *J*=7.02 Hz, 2H) 4.62 (s, 2H) 5.00-5.17 (m, 4H) 5.20 (t, *J*=5.65 Hz, 2H) 5.79-5.93 (m, 2H) 7.20-7.47 (m, 2H) 7.59-7.90 (m, 8H)

5

Example LS6

(2S,2'S)-1,1'-(4,4'-biphenyldiylbis(1H-imidazole-5,2-diyl(2S)-2,1-pyrrolidinediyl))bis(N-methyl-1-oxo-2-propanamine)

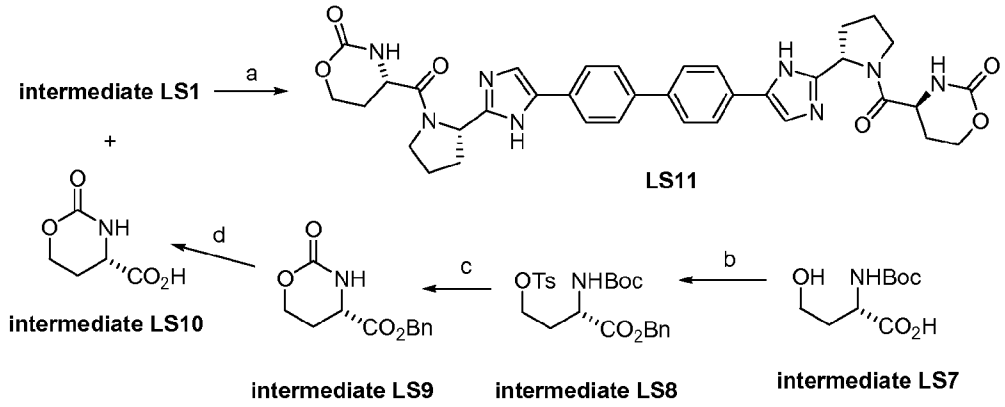


Step a: To intermediate LS1 (64mg; 0.11mmol) in 1 mL DMF was added (S)-2-(tert-butoxycarbonyl(methyl)amino)propanoic acid (48mg; 0.24mmol), Hunig's base (0.12mL; 0.67mmol) and HATU (90mg; 0.24mmol). After 3h, the reaction was purified *via* preparative HPLC (Cond'n 2). Fractions containing intermediate LS5 were pooled and concentrated providing intermediate LS5 as a colorless powder (43mg; 48%) after drying under high vacuum. LC (Cond'n 4): RT = 2.12 min; MS: Anal. Calcd. for $[M+H]^+$ $C_{44}H_{58}N_8O_6$: 795.4; found 795.5.

Step b: Intermediate LS5 was allowed to stir in 2mL HCl/Dioxane (4N) for 18h at which time 10mL ether was added and the resultant precipitate was filtered and dried under high vacuum providing LS6 (45mg; 155%) as a colorless solid. ^{1}H NMR (500 MHz, DMSO-d_6) δ ppm 2.00-2.11 (m, 2H) 2.12-2.27 (m, 4H) 2.38-2.47 (m, 2H) 2.39-2.48 (m, 2H) 2.58 (t, *J*=5.19 Hz, 2H) 3.78-3.85 (m, 2H) 3.91-4.02 (m, 2H) 4.21-4.32 (m, 2H) 5.26 (t, *J*=7.17 Hz, 2H) 7.93 (d, *J*=7.32 Hz, 4H) 8.02 (d, *J*=7.94 Hz, 4H) 8.12-8.21 (m, 2H) 8.69-8.81 (m, 2H) 9.09-9.17 (m, 2H); N-Me protons obscured by DMSO peak with 2 other protons unaccounted for. LC (Cond'n 5): RT = 1.71 min; MS: Anal. Calcd. for $[M+H]^+$ $C_{34}H_{42}N_8O_2$: 595.3; found 595.6.

Example LS11

(4S,4'S)-4,4'-(4,4'-biphenyldiylbis(1H-imidazole-5,2-diyl(2S)-2,1-pyrrolidinediylcarbonyl))bis(1,3-oxazinan-2-one)



Step a: To intermediate LS1 (65mg; 0.11mmol) in 1mL DMF was added HATU (91mg; 0.24mmol), (S)-2-oxo-1,3-oxazinane-4-carboxylic acid (intermediate LS10; 35mg; 0.24mmol), followed by DIPEA (0.12mL; 0.68mmol. After 3h, the reaction mixture was twice purified *via* preparative HPLC (Cond'n 3). Appropriate fractions were pooled and concentrated under high vacuum providing 8mg (10%) bis TFA LS11 as a colorless oil. ^{1}H NMR (500 MHz, CH_3OD) δ ppm ^{1}H NMR (500 MHz, CH_3OD) δ ppm 1.99-2.43 (m, 10H) 2.48-2.66 (m, 1.98 Hz, 2H) 3.82-3.95 (m, 4H) 4.17-4.40 (m, 4H) 4.57 (t, *J*=5.80 Hz, 2H) 5.23-5.41 (m, 2H) 7.73-7.97 (m, 10H); imidazole and carbamate NH protons are unaccounted for. LC (Cond'n 6): RT = 2.28 min; MS: Anal. Calcd. for $[M+H]^+$ $C_{34}H_{42}N_8O_2$: 679.3; found 679.4.

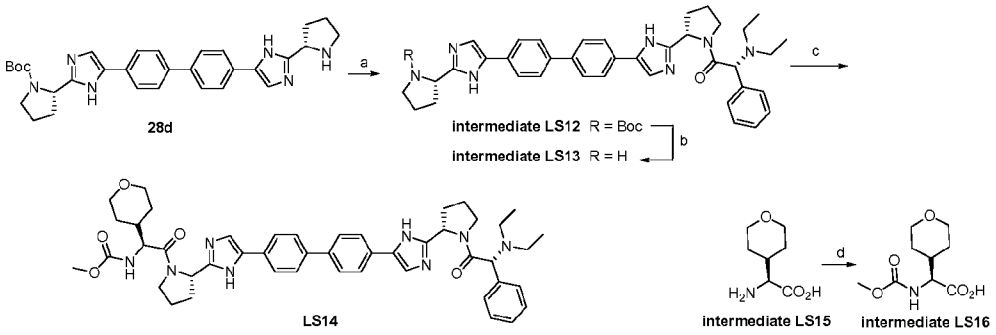
Step b: Performed as in Baldwin et al, *Tetrahedron* 1988, *44*, 637

Step c: Performed as in Sakaitani and Ohfune, *J. Am. Chem. Soc.* 1990, *112*, 1150 for the conversion of compound 1 to 5. Purification *via* Biotage (40M cartridge; 1:1 ether/ethyl acetate) then preparative HPLC (Cond'n 4) provided 77mg (8%) intermediate LS9 as a viscous oil. ^{1}H NMR (300 MHz, $CDCl_3$) δ ppm 2.02-2.21 (m, 1H) 2.23-2.41 (m, 1H) 4.11-4.38 (m, 3H) 5.11-5.31 (m, 2H) 6.15 (s, 1H) 7.27-7.46 (m, 5H). LC (Cond'n 7): RT = 1.24 min; MS: Anal. Calcd. for $[M+H]^+$ $C_{34}H_{42}N_8O_2$: 236.1; found 236.4.

Step d: Intermediate LS9 was hydrogenated under 1 atm H_2 in 3mL methanol with 10mg Pd/C (10%) for 18h. The reaction mixture was filtered through a pad of diatomaceous earth (Celite®) and concentrated to provide intermediate LS10 (40mg; 83%) as a colorless powder. ^{1}H NMR (500 MHz, CH_3OD) δ ppm 2.08-2.18 (m, 1H) 2.26-2.38 (m, 1H) 4.19 (t, *J*=5.95 Hz, 1H) 4.25-4.40 (m, 2H).

Example LS14

methyl ((1S)-2-((2S)-2-(5-(4'-(2-((2S)-1-((2R)-2-(diethylamino)-2-phenylacetyl)-2-pyrrolidinyl)-1H-imidazol-5-yl)-4-biphenylyl)-1H-imidazol-2-yl)-1-pyrrolidinyl)-2-oxo-1-(tetrahydro-2H-pyran-4-yl)ethyl)carbamate



Step a: To 28 (1.5g; 2.86mmol) in 25mL DMF was added sequentially *Cap*-2 (697mg; 2.86mmol), HATU (1.2g; 3.14mmol), and Hunig's base (1.5mL; 8.57mmol). After 3h, the solution was concentrated to 10mL and partitioned between chloroform and water. The organic layer was washed with brine, dried over magnesium sulfate, filtered, and concentrated *in vacuo* to an amber oil which was subjected to silica gel chromatography (Biotage; loaded on 40 samplet with dichloromethane; eluted on 40M cartridge with 0 to 12% dichloromethane/methanol over 1200mL). Fractions containing intermediate LS12 were pooled and concentrated to provide material which contained residual DMF. This material was redissolved in dichloromethane and washed with water (3 x 50mL) and then brine. The organic layer was dried over magnesium sulfate, filtered, and concentrated to 761mg powder which was repurified *via* silica gel chromatography (Biotage; loaded on 40 samplet with dichloromethane; eluted on 40M cartridge with 0 to 80% 4:1 chloroform : methanol/ethyl acetate over 1500mL) to provide intermediate LS12 (501mg; 25%) as a colorless powder. LC (Cond'n 8): RT = 1.24 min.

Step b: To intermediate LS12 (490mg; 0.69mmol) was added 6mL HCl/Dioxane followed by 25mL dichloromethane. After 24h, 75mL ether was added, the reaction mixture was filtered and the precipitate was dried under vacuum providing intermediate LS13 · 4HCl (434mg; quant) as a tan solid. ^{1}H NMR (300 MHz, CH_3OD) δ ppm 1.16-1.29 (m, 3H) 1.37 (t, *J*=6.95 Hz, 3H) 1.89-2.06 (m, 6.95 Hz, 1H) 2.12-2.51 (m, 5H) 2.52-2.85 (m, 4H) 3.02-3.24 (m, 2H) 3.42-3.55 (m, 7.32 Hz, 1H) 3.58-3.71 (m, 2H) 4.26-4.41 (m, 1H) 5.18-5.37 (m, 2H) 5.65 (s, 1H) 7.57-7.66 (m, 3H) 7.67-7.75 (m, 1H) 7.86-8.04 (m, 10H) 8.14 (s, 1H). LC (Cond'n 8): RT = 1.92 min.

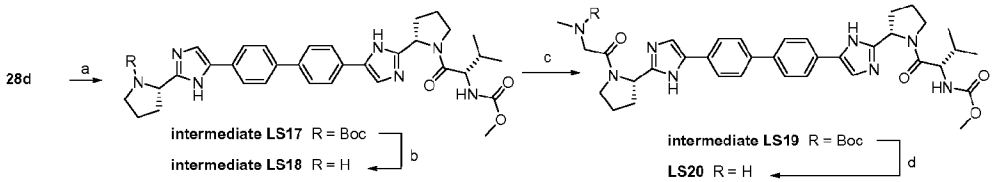
Step c: To intermediate LS13 · 4HCl (75mg; 0.099mmol) in 0.7mL DMF was added sequentially intermediate LS16 (26mg; 0.118mmol), HATU (45mg; 0.118mmol), and Hunig's base (0.10mL; 0.591mmol). After 2h, the reaction mixture was filtered through diatomaceous earth (Celite®), the pad washed with 0.3mL methanol and the resultant filtrate was purified *via* preparative HPLC (Cond'n 5) in two separate injections. The fractions containing desired product were passed through an MCX cartridge (Oasis; 1g; preconditioned with two column lengths of methanol). The cartridge was washed with two column lengths of methanol and product was eluted with ammonia/methanol. Concentration provided 36mg of LS14 as a colorless powder which was assayed to be of 82% diastereomeric purity (most likely epimeric at the stereogenic carbon in intermediate 16). Resubjected to preparative HPLC purification (2x) providing LS14 (13mg; 16%) as a colorless solid. ^{1}H NMR (500 MHz, CH_3OD) δ ppm 0.99 (q, *J*=6.92 Hz, 6H) 1.25-1.72 (m, 5H) 1.80-2.42 (m, 10H) 2.47-2.61 (m, 3H) 2.66-2.78 (m, 2H) 3.35-3.43 (m, 2H) 3.65-3.71 (m, 3H) 3.89-4.01 (m, 4H) 4.01-4.10 (m, 1H) 4.32 (d, *J*=8.24 Hz, 1H) 5.11-5.22 (m, 1H) 6.95-7.17 (m, 3H) 7.30-7.44 (m, 3H) 7.53 (d, *J*=7.02 Hz, 1H) 7.62-7.89 (m, 8H). LC (Cond'n 9): RT = 5.31 min.

Step d: Intermediate LS16 was prepared in analogous fashion to the procedure describing the synthesis of *Cap*-51 substituting (S)-2-amino-2-(tetrahydro-2H-pyran-4-yl)acetic acid (available from Astatech) for L-Valine. ^{1}H NMR (300 MHz, DMSO-

d_6) δ ppm 1.15-1.63 (m, 5H) 1.75-2.03 (m, 1H) 3.54 (s, 3H) 3.76-3.98 (m, 4H) 7.45 (d, *J*=8.42 Hz, 1H); one proton obscured by water peak.

Example LS20

methyl ((1S)-2-methyl-1-(((2S)-2-(5-(4'-(2-((2S)-1-(N-methylglycyl)-2-pyrrolidinyl)-1H-imidazol-5-yl)-4-biphenylyl)-1H-imidazol-2-yl)-1-pyrrolidinyl)carbonyl)propyl)carbamate

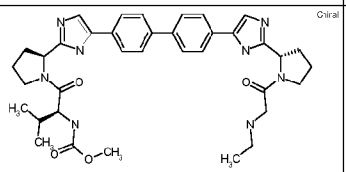
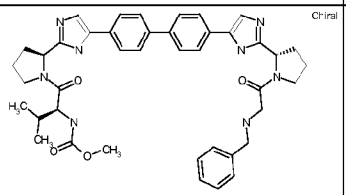
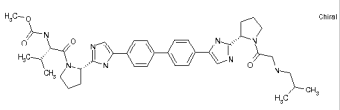


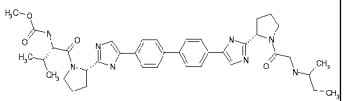
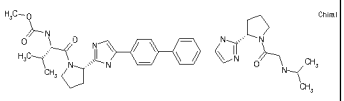
Step a & b: Intermediate LS18 was prepared in analogous fashion to the procedure describing the synthesis of intermediate LS13 substituting *Cap*-51 for *Cap*-2.

Step c: To intermediate LS18 (100mg; 0.14mmol) in 1.4mL DMF was added sequentially N-Boc Sarcosine (30mg; 0.16mmol), Hunig's base (0.13mL; 0.72mmol) and HATU (60mg; 0.16mmol). After 2h the reaction mixture was partitioned into dichloromethane, washed with $NaHCO_3$ (aq), brine, dried over magnesium sulfate, filtered and concentrated to crude intermediate LS19 which was used directly in the next step. LC (Cond'n 5): RT = 2.42 min; MS: Anal. Calcd. for $[M+H]^+$ $C_{41}H_{52}N_8O_6$: 753.4; found 753.9.

Step d: Crude intermediate LS19 was dissolved in 0.5mL methanol and 5mL 4N HCl/Dioxane. After stirring for 1h, the reaction was concentrated and purified *via* preparative HPLC (Cond'n 6) and the fractions containing desired product were passed through an MCX cartridge (Oasis; 1g; preconditioned with two column lengths of methanol). The cartridge was washed with two column lengths of methanol and product was eluted with ammonia/methanol. Concentration provided LS20 (32mg; 34%). ^1H NMR (500 MHz, DMSO-d_6) δ ppm 0.74-0.98 (m, 6H) 1.79-2.24 (m, 9H) 2.29-2.38 (m, 2H) 3.19-3.51 (m, 8H) 3.50-3.56 (m, 3H) 3.59-3.71 (m, 1H) 3.81 (s, 1H) 3.97-4.17 (m, 1H) 5.01-5.16 (m, 2H) 7.30 (d, *J*=7.93 Hz, 1H) 7.51 (s, 1H) 7.59-7.74 (m, 4H) 7.79 (d, *J*=7.63 Hz, 4H) 11.78 (s, 1H). LC (Cond'n 5): RT = 2.00 min; MS: Anal. Calcd. for $[M+H]^+$ $C_{36}H_{44}N_8O_4$: 653.4; found 653.7.

The following analogs were prepared in similar fashion to the preparation of LS20 from LS18 substituting the appropriate carboxylic acid for N-Boc Sarcosine :

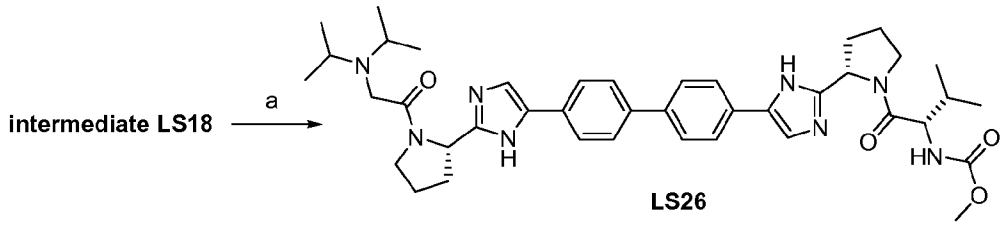
Example Number	*Compound Name*	*Structure*	*Analytical Data*
LS21	methyl ((1S)-1-(((2S)-2-(5-(4'-(2-((2S)-1-(N-ethylglycyl)-2-pyrrolidinyl)-1H-imidazol-5-yl)-4-biphenylyl)-1H-imidazol-2-yl)-1-pyrrolidinyl)carbonyl)-2-methylpropyl)carbamate		LC/MS: 2.34 min (Cond'n 2); Anal. Calcd. for $[M+H]^+$ $C_{37}H_{46}N_8O_4$: 667.4; found 667.7.
LS22	methyl ((1S)-1-(((2S)-2-(5-(4'-(2-((2S)-1-(N-benzylglycyl)-2-pyrrolidinyl)-1H-imidazol-5-yl)-4-biphenylyl)-1H-imidazol-2-yl)-1-pyrrolidinyl)carbonyl)-2-methylpropyl)carbamate		LC/MS: 2.34 min (Cond'n 5); Anal. Calcd. for $[M+H]^+$ $C_{42}H_{48}N_8O_4$: 729.4; found 729.8.
LS23	methyl ((1S)-1-(((2S)-2-(5-(4'-(2-((2S)-1-(N-isobutylglycyl)-2-pyrrolidinyl)-1H-imidazol-5-yl)-4-		LC/MS: 2.07 min (Cond'n 5); Anal. Calcd. for $[M+H]^+$ $C_{39}H_{50}N_8O_4$: 695.4; found 695.8.

	biphenylyl)-1H-imidazol-2-yl)-1-pyrrolidinyl)carbonyl)-2-methylpropyl)carbamate		
LS24	methyl ((1S)-1-(((2S)-2-(5-(4'-(2-((2S)-1-(N-sec-butylglycyl)-2-pyrrolidinyl)-1H-imidazol-5-yl)-4-biphenylyl)-1H-imidazol-2-yl)-1-pyrrolidinyl)carbonyl)-2-methylpropyl)carbamate		LC/MS: 2.03 min (Cond'n 5); Anal. Calcd. for $[M+H]^+$ $C_{39}H_{50}N_8O_4$: 695.4; found 695.9.
LS25	methyl ((1S)-1-(((2S)-2-(5-(4'-(2-((2S)-1-(N-isopropylglycyl)-2-pyrrolidinyl)-1H-imidazol-5-yl)-4-biphenylyl)-1H-imidazol-2-yl)-1-pyrrolidinyl)carbonyl)-2-methylpropyl)carbamate		LC/MS: 1.97 min (Cond'n 5); Anal. Calcd. for $[M+H]^+$ $C_{38}H_{48}N_8O_4$: 681.4; found 681.7.

5

Example LS26

methyl ((1S)-1-(((2S)-2-(5-(4'-(2-((2S)-1-(N,N-diisopropylglycyl)-2-pyrrolidinyl)-1H-imidazol-5-yl)-4-biphenylyl)-1H-imidazol-2-yl)-1-pyrrolidinyl)carbonyl)-2-methylpropyl)carbamate



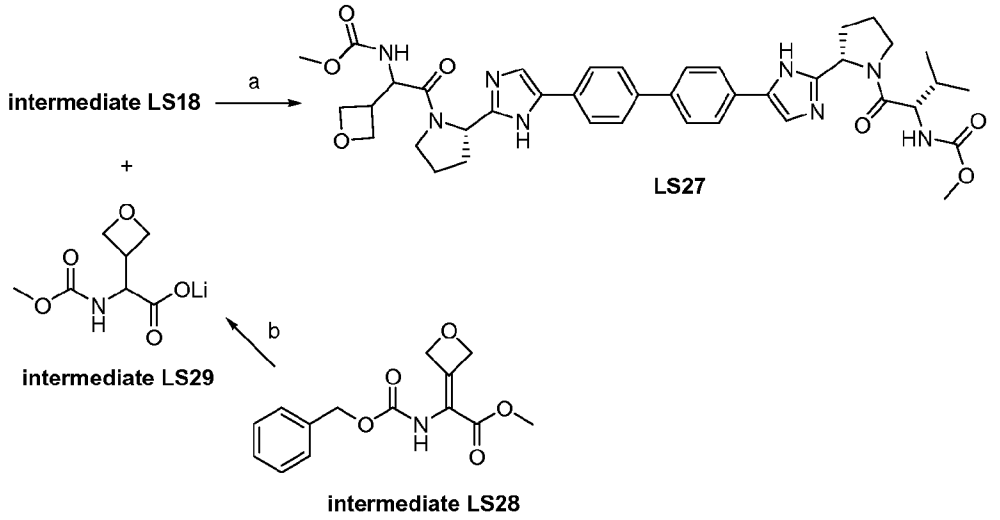
Step a: Compound LS26 was prepared in a similar fashion to the preparation of intermediate LS19 employing 2-(diisopropylamino)acetic acid as the carboxylic acid coupling partner. ^{1}H NMR (500 MHz, DMSO-d_6) δ ppm 0.74-1.04 (m, 18H) 1.74-2.21 (m, 13H) 2.86-3.09 (m, 3H) 3.54 (s, 3H) 3.71-3.89 (m, 3H) 4.06 (t, *J*=8.55 Hz, 1H) 4.98-5.13 (m, 2H) 5.56 (d, *J*=8.55 Hz, 1H) 7.21-7.34 (m, 1H) 7.42-7.54 (m, 1H) 7.61-7.87 (m, 8H). LC (Cond'n 5): RT = 1.98 min; MS: Anal. Calcd. for $[M+H]^+$ $C_{41}H_{54}N_8O_4$: 723.4; found 723.4.

Example LS27 Diastereomer 1

methyl ((1S)-1-(((2S)-2-(5-(4'-(2-((2S)-1-((2R)-2-((methoxycarbonyl)amino)-2-(3-oxetanyl)acetyl)-2-pyrrolidinyl)-1H-imidazol-5-yl)-4-biphenylyl)-1H-imidazol-2-yl)-1-pyrrolidinyl)carbonyl)-2-methylpropyl)carbamate

Example LS27 Diastereomer 2

methyl ((1S)-1-(((2S)-2-(5-(4'-(2-((2S)-1-((2S)-2-((methoxycarbonyl)amino)-2-(3-oxetanyl)acetyl)-2-pyrrolidinyl)-1H-imidazol-5-yl)-4-biphenylyl)-1H-imidazol-2-yl)-1-pyrrolidinyl)carbonyl)-2-methylpropyl)carbamate

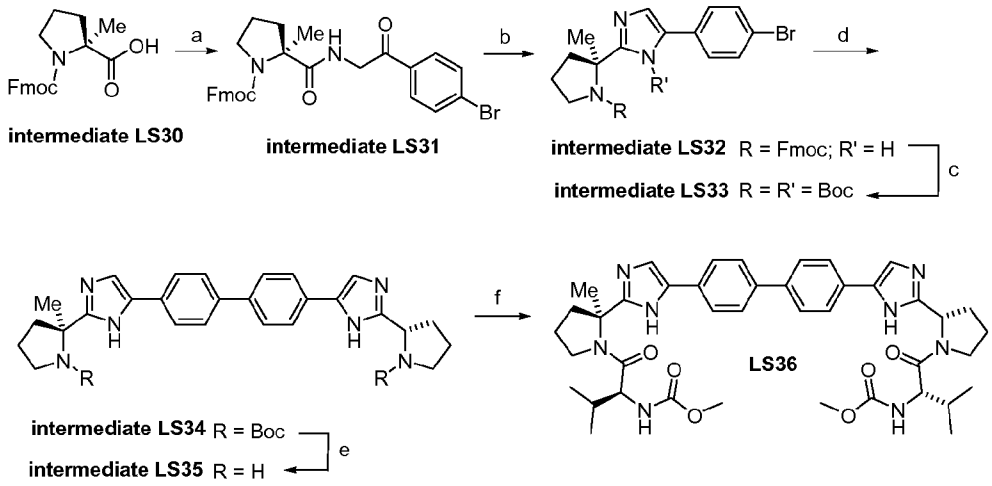


Step a: Compound LS27 was prepared in a similar fashion to the preparation of intermediate LS19 employing 2-(methoxycarbonylamino)-2-(oxetan-3-yl)acetic acid (intermediate LS29) as the carboxylic acid coupling partner. The two diastereomers of LS27 were separated *via* preparative HPLC (Xbridge C18, 100 x 19 mm I.D. S-5μm; Mobile Phase A: 95%Water-5% Acetonitrile with 10 mM ammonium acetate (pH=5); Mobile phase B: 95%Acetonitrile-5% Water with 10 mM ammonium acetate (pH=5); Isocratic 30% B for 7 min; Flow rate: 25 mL/min; UV detection: 220 nm; Sample amount: ~5 mg/each injection, 300 μl sample solution in methanol (~17 mg/mL)). Diastereomer 1: ^{1}H NMR (500 MHz, DMSO-d_6) δ ppm 0.80-0.96 (m, 6H) 1.91-2.06 (m, 6H) 2.09-2.21 (m, 3H) 3.54 (s, 3H) 3.59 (s, 3H) 3.77-3.83 (m, 2H) 3.87 (t, *J*=7.63 Hz, 1H) 4.06 (t, *J*=8.24 Hz, 1H) 4.31 (t, *J*=6.41 Hz, 1H) 4.43 (t, *J*=6.10 Hz, 1H) 4.49 (t, *J*=7.17 Hz, 1H) 4.51-4.57 (m, 1H) 4.80 (t, *J*=8.55 Hz, 1H) 5.00-5.05 (m, 1H) 5.06-5.11 (m, 1H) 7.30 (d, *J*=8.55 Hz, 1H) 7.50 (s, 1H) 7.58-7.89 (m, 8H) 11.77 (s, 2H). LC (Cond'n 10): RT = 7.14 min; MS: Anal. Calcd. for $[M+H]^+$ $C_{40}H_{48}N_8O_7$: 753.4; found 753.9. Diastereomer 2: ^{1}H NMR (500 MHz, DMSO-d_6) δ ppm 0.79-0.98 (m, 6H) 1.91-2.06 (m, 4H) 2.07-2.23 (m, 4H) 3.51-3.69 (m, 8H) 3.74-3.90 (m, 2H) 4.06 (t, *J*=7.48 Hz, 1H) 4.20-4.33 (m, 1H) 4.36-4.49 (m, 2H) 4.55 (s, 2H) 4.71 (s, 1H) 4.97-5.05 (m, 1H) 5.08 (s, 1H) 5.53 (s, 1H) 7.30 (d, *J*=7.93 Hz, 1H) 7.51 (s, 1H) 7.58-7.91 (m, 8H) 11.53 (s, 1H) 11.78 (s, 1H). LC (Cond'n 10): RT = 8.79 min; MS: Anal. Calcd. for $[M+H]^+$ $C_{40}H_{48}N_8O_7$: 753.4; found 753.9.

Step b: A solution of methyl 2-(benzyloxycarbonylamino)-2-(oxetan-3-ylidene)acetate (intermediate LS28; Source: Moldes et al, *Il Farmaco*, 2001, *56*, 609 and Wuitschik et al, *Ang. Chem. Int. Ed. Engl*, 2006, *45*, 7736; 200 mg, 0.721 mmol) in ethyl acetate (7 mL) and CH_2Cl_2 (4.00 mL) was degassed by bubbling nitrogen for 10min. Dimethyl dicarbonate (0.116 mL, 1.082 mmol) and Pd/C (20 mg, 0.019 mmol) were then added, the reaction mixture was fitted with a hydrogen balloon and allowed to stir at ambient temperature overnight. The reaction mixture was filtered through diatomaceous earth (Celite®) and concentrated. The residue was purified *via* Biotage (load with dichloromethane on 25 samplet; elute on 25S column with dichloromethane for 3CV then 0 to 5% methanol/dichloromethane over 250mL then hold at 5% methanol/dichloromethane for 250mL; 9mL fractions). Fractions containing the desired product were concentrated to provide 167mg methyl 2-(methoxycarbonylamino)-2-(oxetan-3-yl)acetate as a colorless oil which solidified on standing. ^{1}H NMR (500 MHz, CHLOROFORM-D) δ ppm 3.29-3.40 (m, 1H) 3.70 (s, 3H) 3.74 (s, 3H) 4.55 (t, *J*=6.41 Hz, 1H) 4.58-4.68 (m, 2H) 4.67-4.78 (m, 2H) 5.31 (br s, 1H). MS: Anal. Calcd. for $[M+H]^+$ $C_8H_{13}NO_5$: 204.1; found 204.0. To methyl 2-(methoxycarbonylamino)-2-(oxetan-3-yl)acetate (50 mg, 0.246 mmol) in THF (2mL) and Water (0.5mL) was added lithium hydroxide monohydrate (10.33 mg, 0.246 mmol). The resultant solution was allowed to stir overnite at ambient temperature then concentrated to dryness to provide intermediate LS29 as a colorless powder. ^{1}H NMR (500 MHz, CH_3OD) δ ppm 3.38-3.50 (m, 1H) 3.67 (s, 3H) 4.28 (d, *J*=7.63 Hz, 1H) 4.57-4.79 (m, 4H).

Example LS36

methyl ((1S)-1-(((2S)-2-(5-(4'-(2-((2S)-1-((2S)-2-((methoxycarbonyl)amino)-3-methylbutanoyl)-2-pyrrolidinyl)-1H-imidazol-5-yl)-4-biphenylyl)-1H-imidazol-2-yl)-2-methyl-1-pyrrolidinyl)carbonyl)-2-methylpropyl)carbamate



Step a: To (S)-1-(((9H-fluoren-9-yl)methoxy)carbonyl)-2-methylpyrrolidine-2-carboxylic acid (intermediate LS30; 1.5g; 4.3mmol) in 50mL DMF was added sequentially 2-amino-1-(4-bromophenyl)ethanone hydrochloride (1.2g; 4.7mmol), HOAT (290mg; 2.1mmol), Hunig's base (0.7mL; 4.3mmol) and EDCI (1.2g; 6.4mmol). After 1h, the reaction mixture was poured into 150mL water and allowed to stir for 15min before filtering the resultant precipitate which was dissolved in dichloromethane and dried over magnesium sulfate. The dichloromethane mixture was filtered and applied to a Biotage 40 samplet. Chromatography on a 40M column (25 to 60% ethyl acetate/hexane over 1200mL) provided (S)-(9H-fluoren-9-yl)methyl 2-(2-(4-bromophenyl)-2-oxoethylcarbamoyl)-2-methylpyrrolidine-1-carboxylate (intermediate LS31; 2.4g; quant) as a yellow foam. LC (Cond'n 11): RT = 3.75 min; MS: Anal. Calcd. for $[M+H]^+$ $C_{29}H_{27}BrN_2O_4$: 547.1; found 547.0.

Step b: A mixture of ammonium acetate (844mg; 10.97mmol) and (S)-(9H-fluoren-9-yl)methyl 2-(2-(4-bromophenyl)-2-oxoethylcarbamoyl)-2-methylpyrrolidine-1-carboxylate (intermediate LS31; 1.00g; 1.83mmol) was heated to 140°C in 25mL xylene for 2.5h at which time the reaction mixture was concentrated and loaded with dichloromethane onto a Biotage 40 samplet. Purification *via* Biotage (5 to 60% ethyl acetate /hexane over 1000mL with 400mL hold time) provided (S)-(9H-fluoren-9-

yl)methyl 2-(5-(4-bromophenyl)-1H-imidazol-2-yl)-2-methylpyrrolidine-1-carboxylate (intermediate LS32; 469mg; 49%) as an amber liquid. LC (Cond'n 12): RT = 3.09 min; MS: Anal. Calcd. for $[M+H]^+$ $C_{29}H_{26}BrN_3O_2$: 528.1; found 528.5.

Step c: To (S)-(9H-fluoren-9-yl)methyl 2-(5-(4-bromophenyl)-1H-imidazol-2-yl)-2-methylpyrrolidine-1-carboxylate (intermediate LS32; 329mg; 0.62mmol) in 3mL DMF was added 1.5mL piperidine. The reaction mixture was concentrated *via* a nitrogen stream overnite. The resultant residue was washed with hexane and passed through an MCX cartridge (Oasis; 6g; preconditioned with two column lengths of methanol). The cartridge was washed with two column lengths of methanol and product was eluted with ammonia/methanol. Concentration provided 193mg of (S)-5-(4-bromophenyl)-2-(2-methylpyrrolidin-2-yl)-1H-imidazole which was dissolved in 6mL dichloromethane and combined with di-t-butyldicarbonate (413mg; 1.89mmol), DMAP (15mg; 0.13mmol) and TEA (0.17mL; 1.30mmol). After 48h, the reaction mixture was concentrated and purified *via* chromatography on a Biotage system providing (S)-tert-butyl 5-(4-bromophenyl)-2-(1-(tert-butoxycarbonyl)-2-methylpyrrolidin-2-yl)-1H-imidazole-1-carboxylate (intermediate LS33; 150mg; 48%) as an off white solid. LC (Cond'n 5): RT = 3.75 min; MS: Anal. Calcd. for $[M+H]^+$ $C_{24}H_{32}BrN_3O_4$: 506.2; found 506.4

Step d: (S)-tert-butyl 2-(5-(4'-(2-((S)-1-(tert-butoxycarbonyl)pyrrolidin-2-yl)-1H-imidazol-5-yl)biphenyl-4-yl)-1H-imidazol-2-yl)-2-methylpyrrolidine-1-carboxylate (intermediate LS34) was prepared in a similar fashion to the preparation of 1d employing intermediate LS33 in place of 1b. ^{1}H NMR (300 MHz, DMSO-d_6; 100°C) δ ppm 1.18-1.29 (m, 9H) 1.29-1.40 (m, 9H) 1.75-1.82 (m, 3H) 1.81-2.39 (m, 8H) 3.35-3.75 (m, 4H) 4.81-4.92 (m, 1H) 7.36-7.45 (m, 1H) 7.57-7.74 (m, 5H) 7.76-7.89 (m, 4H) 11.29-11.63 (m, 2H). LC (Cond'n 5): RT = 2.49 min; MS: Anal. Calcd. for $[M+H]^+$ $C_{37}H_{46}N_6O_4$: 639.4; found 639.9.

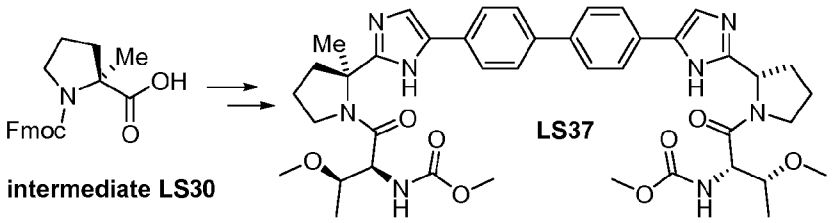
Step e: 2-((S)-2-methylpyrrolidin-2-yl)-5-(4'-(2-((S)-pyrrolidin-2-yl)-1H-imidazol-5-yl)biphenyl-4-yl)-1H-imidazole (intermediate LS35) was prepared in a similar fashion to the preparation of 1e employing intermediate LS34 in place of 1d. ^{1}H NMR (500 MHz, DMSO-d_6) δ ppm 1.76-1.83 (m, 3H) 1.92-2.23 (m, 6H) 3.31-3.49

(m, 4H) 4.88-4.97 (m, 1H) 7.76-7.88 (m, 5H) 7.90-8.04 (m, 5H) 9.72-9.82 (m, 1H) 10.04-10.16 (m, 1H); imidazole and pyrrolidine NH protons unaccounted for. LC (Cond'n 5): RT = 1.79 min; MS: Anal. Calcd. for $[M+H]^+$ $C_{27}H_{30}N_6$: 439.2; found 439.5.

Step f: Compound LS36 was prepared in a similar fashion to the preparation of example 1 employing intermediate LS35 in place of 1c and *Cap*-51 in place of *Cap*-1. ^{1}H NMR (500 MHz, DMSO-d_6) δ ppm 0.72-0.97 (m, 12H) 1.77 (s, 3H) 1.86-2.08 (m, 8H) 2.09-2.19 (m, 2H) 2.25-2.39 (m, 2H) 3.49-3.59 (m, 6H) 3.81 (d, *J*=6.71 Hz, 4H) 4.06 (q, *J*=7.83 Hz, 2H) 5.08 (dd, *J*=7.02, 3.05 Hz, 1H) 7.12 (d, *J*=8.85 Hz, 1H) 7.27-7.34 (m, 1H) 7.46-7.55 (m, 1H) 7.59-7.73 (m, 4H) 7.75-7.86 (m, 3H) 11.66 (s, 1H) 11.77 (s, 1H). LC (Cond'n 5): RT = 2.25 min; MS: Anal. Calcd. for $[M+H]^+$ $C_{41}H_{52}N_8O_6$: 753.4; found 754.0.

Example LS37

methyl ((1S,2R)-2-methoxy-1-(((2S)-2-(5-(4'-(2-((2S)-1-(N-(methoxycarbonyl)-O-methyl-L-threonyl)-2-pyrrolidinyl)-1H-imidazol-5-yl)-4-biphenylyl)-1H-imidazol-2-yl)-2-methyl-1-pyrrolidinyl)carbonyl)propyl)carbamate



Compound LS37 was prepared in a similar fashion to the preparation of LS36 from intermediate LS30 using *Cap-86* in place of *Cap*-51. ^{1}H NMR (500 MHz, DMSO-d_6) δ ppm 0.99-1.17 (m, 6H) 1.76 (s, 3H) 1.87-2.09 (m, 4H) 2.10-2.23 (m, 2H) 2.34-2.38 (m, 2H) 2.56-2.60 (m, 1H) 2.63 (d, *J*=1.83 Hz, 1H) 3.17 (s, 3H) 3.19 (s, 3H) 3.37-3.51 (m, 2H) 3.54 (s, 6H) 3.75-3.96 (m, 4H) 4.13-4.36 (m, 2H) 5.07 (dd, *J*=7.48, 3.20 Hz, 1H) 7.20 (d, *J*=8.54 Hz, 1H) 7.24-7.34 (m, 1H) 7.50 (dd, *J*=7.17, 1.98 Hz, 1H) 7.59-7.73 (m, 4H) 7.76-7.86 (m, 3H) 11.65 (s, 1H) 11.77 (s, 1H). LC (Cond'n 13): RT = 4.30 min; MS: Anal. Calcd. for $[M+H]^+$ $C_{41}H_{52}N_8O_8$: 785.4; found 785.4.

Section F LC Conditions for determining retention time

Condition 1

Column: Phenomenex-Luna 4.6 X 50 mm S10

Start % B = 0

Final % B = 100

Gradient Time = 4 min

Flow Rate = 4 mL/Min

Wavelength = 220

Solvent A = 10% methanol – 90% H_2O – 0.1% TFA

Solvent B = 90% methanol – 10% H_2O – 0.1% TFA

Condition 2

Column: Waters-Sunfire 4.6 X 50 mm S5

Start % B = 0

Final % B = 100

Gradient Time = 2 min

Flow Rate = 4 mL/Min

Wavelength = 220

Solvent A = 10% methanol – 90% H_2O – 0.1% TFA

Solvent B = 90% methanol – 10% H_2O – 0.1% TFA

Condition 3

Column: Phenomenex 10u 3.0 X 50 mm

Start % B = 0

Final % B = 100

Gradient Time = 2 min

Flow Rate = 4 mL/Min

Wavelength = 220

Solvent A = 10% methanol – 90% H_2O – 0.1% TFA

Solvent B = 90% methanol – 10% H_2O – 0.1% TFA

Condition 4

Column: Phenomenex-Luna 3.0 X 50 mm S10

Start % B = 0

Final % B = 100

Gradient Time = 3 min

Flow Rate = 4 mL/Min

Wavelength = 220

Solvent A = 10% methanol – 90% H_2O – 0.1% TFA

Solvent B = 90% methanol – 10% H_2O – 0.1% TFA

Condition 5

Column: Phenomenex-Luna 4.6 X 50 mm S10

Start % B = 0

Final % B = 100

Gradient Time = 3 min

Flow Rate = 4 mL/Min

Wavelength = 220

Solvent A = 10% methanol – 90% H_2O – 0.1% TFA

Solvent B = 90% methanol – 10% H_2O – 0.1% TFA

Condition 6

Column: Xbridge C18 4.6 X 50 mm S5

Start % B = 0

Final % B = 100

Gradient Time = 3 min

Flow Rate = 4 mL/Min

Wavelength = 220

Solvent A = H_2O : ACN 95% : 5% 10 mm Ammonium Acetate

Solvent B = H_2O : ACN 5% : 95% 10 mm Ammonium Acetate

Condition 7

Column: Phenomenex C18 10u 4.6 X 30 mm

Start % B = 0

Final % B = 100

Gradient Time = 3 min

Flow Ratc = 4 mL/Min

Wavelength = 220

Solvent A = 10% methanol – 90% H_2O – 0.1% TFA

Solvent B = 90% methanol – 10% H_2O – 0.1% TFA

Condition 8

Column: Phenomenex LunaC18 10u 4.6 X 30 mm

Start % B = 0

Final % B = 100

Gradient Time = 2 min

Flow Rate = 5 mL/Min

Wavelength = 220

Solvent A = 10% methanol – 90% H_2O – 0.1% TFA

Solvent B = 90% methanol – 10% H_2O – 0.1% TFA

Condition 9

Column: Phenomenex C18 10u 4.6 X 30 mm

Start % B = 0

Final % B = 100

Gradient Time = 10min

Flow Rate = 4 mL/Min

Wavelength = 220

Solvent A = H_2O : ACN 95% : 5% 10 mm Ammonium Acetate

Solvent B = H_2O : ACN 5% : 95% 10 mm Ammonium Acetate

Condition 10

Column: Phenomenex 10u 3.0 X 50 mm

Start % B = 0

Final % B = 100

Gradient Time = 3min

Flow Rate = 4 mL/Min

Wavelength = 220

Solvent A = 10% methanol – 90% H_2O – 0.1% TFA

Solvent B = 90% methanol – 10% H_2O – 0.1% TFA

Condition 11

Column: Xterra 4.6 X 30 mm S5

Start % B = 0

Final % B = 100

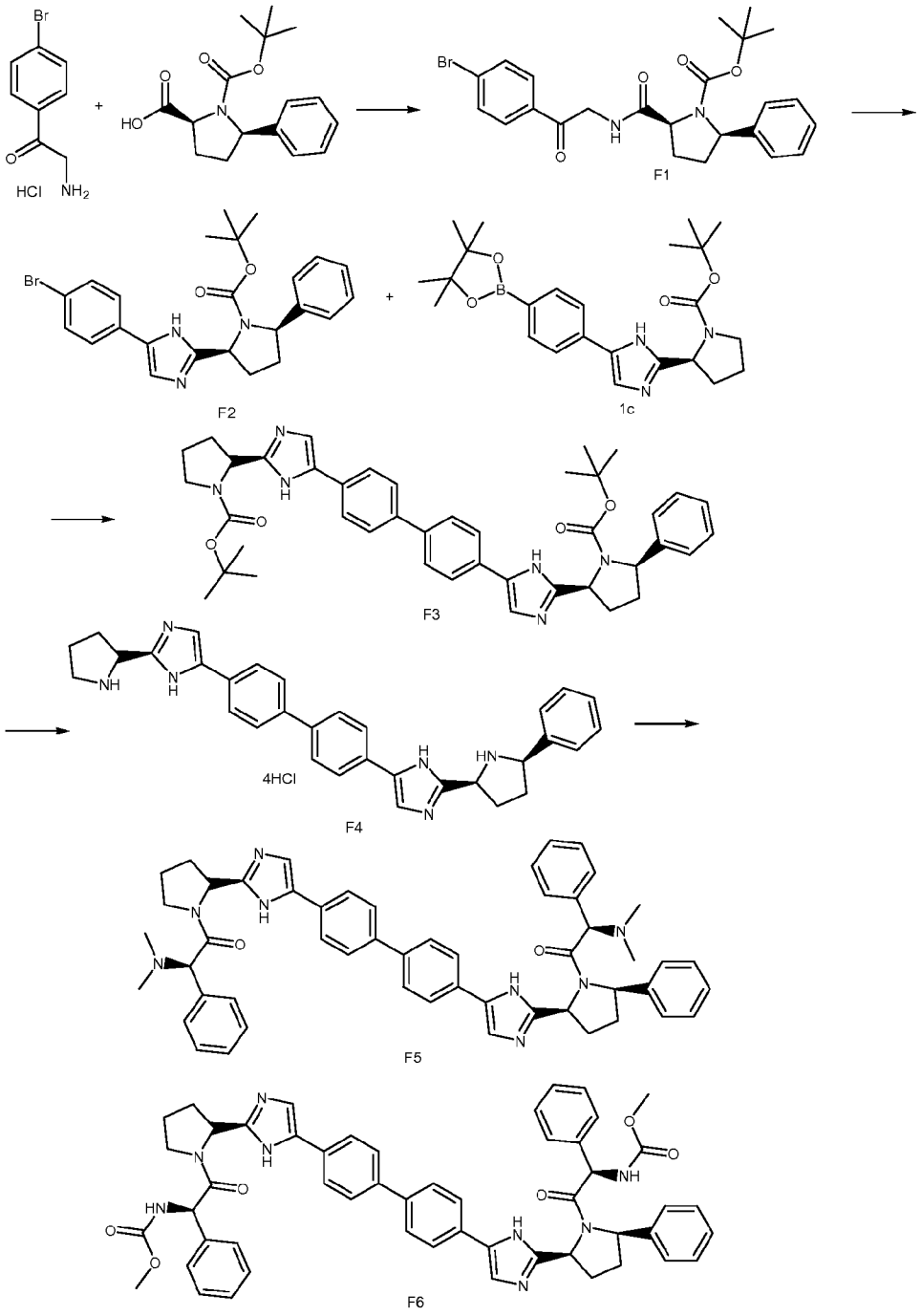
Gradient Time = 2min

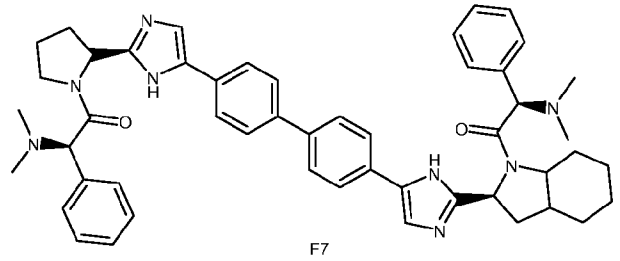
Flow Rate = 5 mL/Min

Wavelength = 220

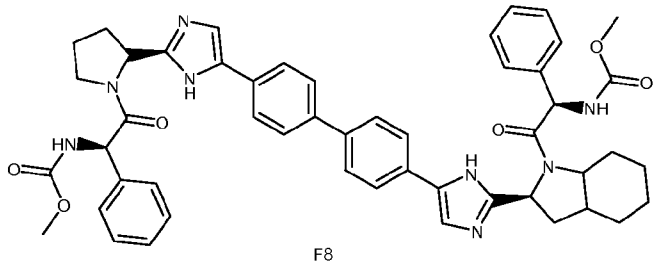
Solvent A = H_2O : ACN 95% : 5% 10 mm Ammonium Acetate

Solvent B = H_2O : ACN 5% : 95% 10 mm Ammonium Acetate


Br
HCl NH2
HO
F1
F2
1c
F3
4HCl
F4
F5
F6



F7



F8

Compound F1 was prepared in analogous fashion to the procedure used to synthesize 1a with following modification: (2S,5R)-1-(tert-butoxycarbonyl)-5-phenylpyrrolidine-2-carboxylic acid was used in place of N-Boc-L-proline.

Compound F2 was prepared in analogous fashion to the procedure used to sythesize 1b.

Compound F3 was prepared in analogous fashion to the procedure used to sythesize 1d.

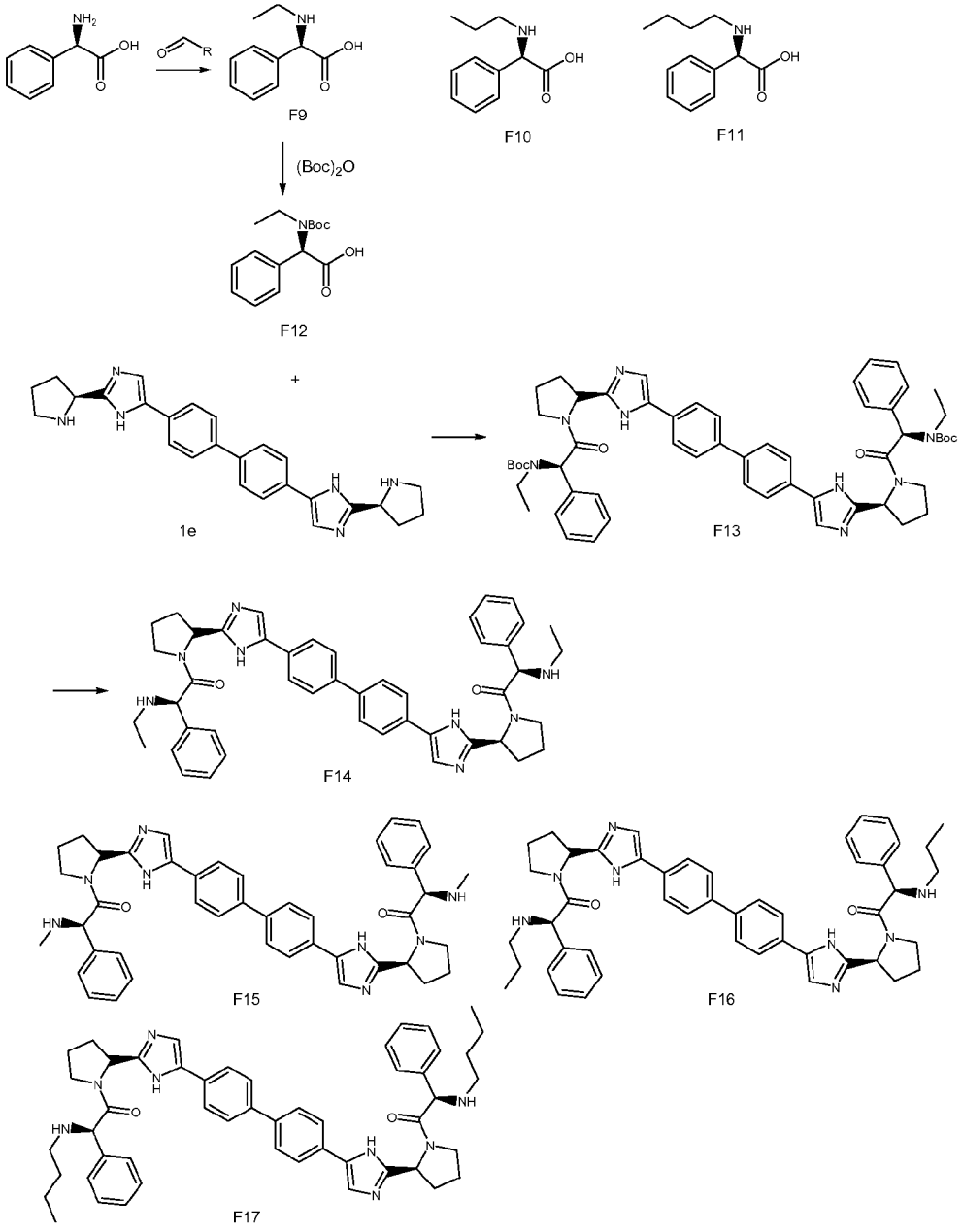
Compound F4 was prepared in analogous fashion to the procedure used to sythesize 1e.

Compound F5, F6 was prepared in analogous fashion to the procedure used to sythesize example 1from Compound F4.

Compound F7, F8 was prepared in analogous fashsion to the procedure used to sythesize F5 with following modification: (2S)-1-(tert-butoxycarbonyl)octahydro-1H-indole-2-carboxylic acid was used in place of (2S,5R)-1-(tert-butoxycarbonyl)-5-phenylpyrrolidine-2-carboxylic acid.

Entry	*Compound Name*	*Retention time (LC-Condition); homogeneity index MS data*
F1		RT = 3.838 minutes (condition 1, 94%); LRMS: Anal. Calcd. for C24H27BrN2O4 486.12; found: 487.26 $(M+H)^+$.
F2		RT = 3.175 minutes (condition 1, 83%); LRMS: Anal. Calcd. for C24H27BrN2O4 467.12; found: 468.26 $(M+H)^+$.
F3		RT = 2.965 minutes (condition 1, 93%); LRMS: Anal. Calcd. for C42H48N6O4 700.37; found: 701.49 $(M+H)^+$.
F4		RT = 2.083 minutes (condition 1, 98%); LRMS: Anal. Calcd. for C32H32N6 500.27; found: 501.40 $(M+H)^+$.
F5		RT = 1.222 minutes (condition 3, 98%); LRMS: Anal. Calcd. for C52H54N8O2 822.44; found: 823.5 $(M+H)^+$.
F6	methyl ((1*R*)-2-((2*R*)-2-(5-(4'-(2-((2*S*,5*R*)-1-((2*R*)-2-((methoxycarbonyl)amino)-2-phenylacetyl)-5-phenyl-2-pyrrolidinyl)-1*H*-imidazol-5-yl)-4-biphenylyl)-1*H*-imidazol-2-yl)-1-pyrrolidinyl)-2-oxo-1-phenylethyl)carbamate	RT = 1.512 minutes (condition 3, 98%); LRMS: Anal. Calcd. for C52H50N8O6 882.39; found: 883.45 $(M+H)^+$.
F7	*rel*-(1*R*)-2-((2*S*)-2-(4-(4'-(2-((2*S*)-1-((2*R*)-2-	RT = 1.223 minutes (condition 3, 98%); LRMS: Anal. Calcd.

	(dimethylamino)-2-phenylacetyl)octahydro-1*H*-indol-2-yl)-1*H*-imidazol-5-yl)-4-biphenylyl)-1*H*-imidazol-2-yl)-1-pyrrolidinyl)-*N*,*N*-dimethyl-2-oxo-1-phenylethanamine	for C50H56N8O2 800.45; found: 801.51 $(M+H)^+$.
F8	methyl *rel*-((1*R*)-2-((2*S*)-2-(4-(4'-(2-((2*S*)-1-((2*R*)-2-((methoxycarbonyl)amino)-2-phenylacetyl)octahydro-1*H*-indol-2-yl)-1*H*-imidazol-5-yl)-4-biphenylyl)-1*H*-imidazol-2-yl)-1-pyrrolidinyl)-2-oxo-1-phenylethyl)carbamate	RT = 1.513 minutes (condition 3, 98%); LRMS: Anal. Calcd. for C50H56N8O2 860.40; found: 861.42 $(M+H)^+$.



Compound F9, F10, and F11 was prepared in analogous fashion to the procedure used to sythesize *Cap*-3 first half procedure using acetaldehyde, propionaldehyde, and butyraldehyde respectively.

Compound F12

$(Boc)_2O$ (2.295 g, 10.20 mmol) was added to a mixture of compound F9 (1.0 g, 4.636 mmol), hunig's base (1.78 mL, 10.20 mmol) in CH_2Cl_2 (12 mL), and the

resulting mixture was stirred over night. The volatile component was removed *in vacuo*, and the residue was purified by a reverse phase HPLC system (H_2O/methanol/TFA) to provide compound F12 as a clear wax (0.993 g). LC (Cond.3): RT = 1.663 min; >95% homogeneity index; LC/MS: Anal. Calcd. for $[M+H]^+$ C15H21NO4: 279.33; found $[M+Na]^+$ 302.30

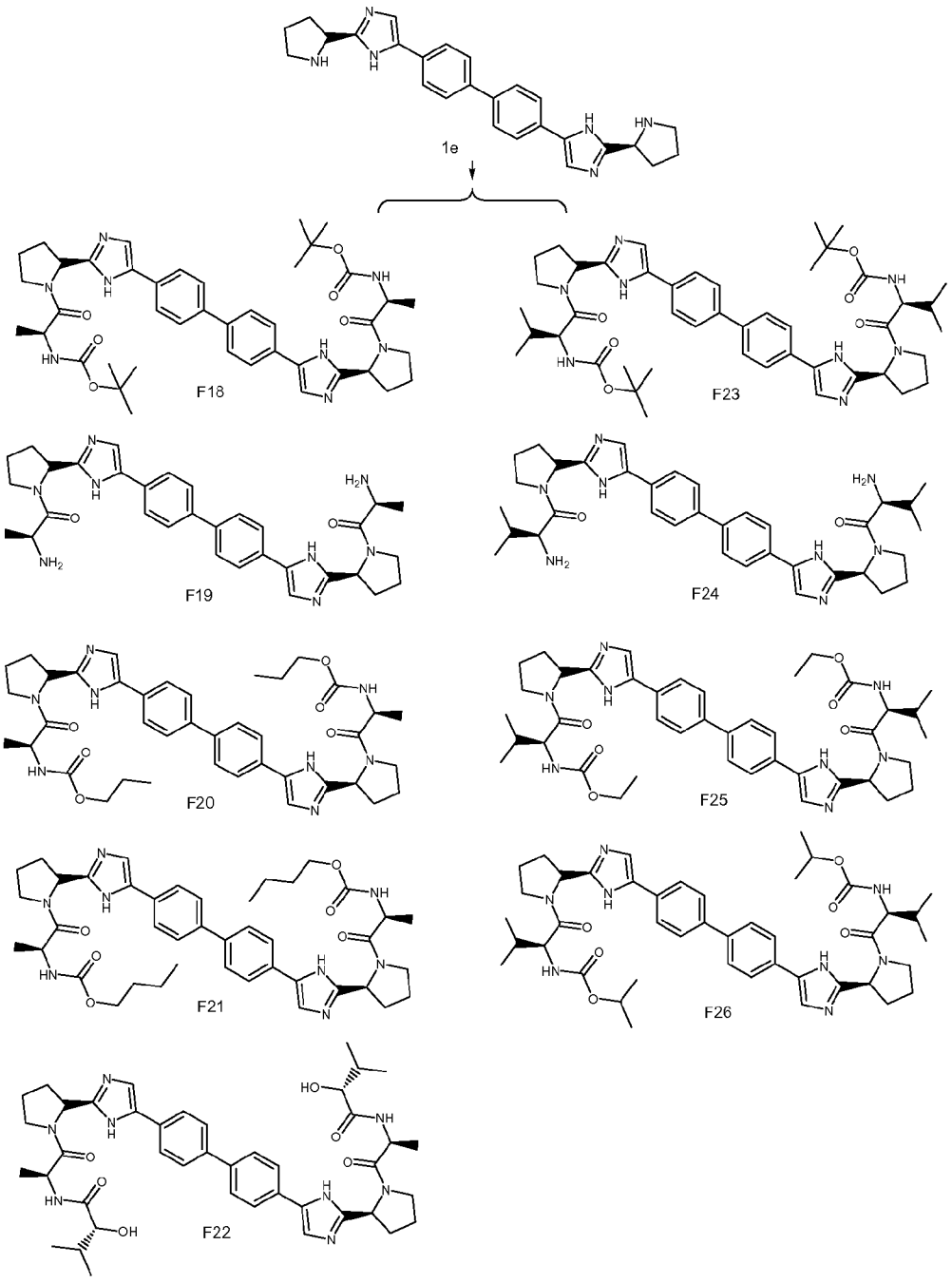
Compound F13 was prepared in analogous fashion to the procedure used to sythesized example 1 from Compound 1e and F12.

Compound F14 was prepared in analogous fashion to the procedure used to sythesized 132e.

Compound F15, F16, and F17 was prepared in analogous fashion to the procedure used to sythesize F14.

Entry	*Compound Name*	*Retention time (LC-Condition); homogeneity index MS data*
F9		RT = 0.580 minutes (condition 1, 94%); LRMS: Anal. Calcd. for C10H13NO2 179.09; found: 180.26 $(M+H)^+$.
F10		RT = 0.563 minutes (condition 3, 94%); LRMS: Anal. Calcd. for C11H15NO2 193.11; found: 194.26 $(M+H)^+$.
F11		RT = 1.023 minutes (condition 3, 94%); LRMS: Anal. Calcd. for C12H17NO2 207.13; found: 208.31 $(M+H)^+$.
F12		RT = 1.663 minutes (condition 3, 95%); LRMS: Anal. Calcd. for C15H21NO4 279.15; found: 302.30 $(Na+H)^+$.
F13		RT = 2.595 minutes (condition 4,

		94%); LRMS: Anal. Calcd. for C56H66N8O6 946.51; found: 947.64 $(M+H)^+$.
F14	(1*R*)-*N*-ethyl-2-((2*S*)-2-(4-(4'-(2-((2*S*)-1-((2*R*)-2-(ethylamino)-2-phenylacetyl)-2-pyrrolidinyl)-1*H*-imidazol-5-yl)-4-biphenylyl)-1*H*-imidazol-2-yl)-1-pyrrolidinyl)-2-oxo-1-phenylethanamine	RT = 1.55 minutes (condition 5, 90%); LRMS: Anal. Calcd. for C46H50N8O2 746.41; found: 747.72 $(M+H)^+$.
F15	(1*R*)-*N*-methyl-2-((2*S*)-2-(4-(4'-(2-((2*S*)-1-((2*R*)-2-(methylamino)-2-phenylacetyl)-2-pyrrolidinyl)-1*H*-imidazol-5-yl)-4-biphenylyl)-1*H*-imidazol-2-yl)-1-pyrrolidinyl)-2-oxo-1-phenylethanamine	RT = 1.50 minutes (condition 5, 94%); LRMS: Anal. Calcd. for C44H46N8O2 718.37; found: 719.69 $(M+H)^+$.
F16	*N*-((1*R*)-2-oxo-1-phenyl-2-((2*S*)-2-(4-(4'-(2-((2*S*)-1-((2*R*)-2-phenyl-2-(propylamino)acetyl)-2-pyrrolidinyl)-1*H*-imidazol-5-yl)-4-biphenylyl)-1*H*-imidazol-2-yl)-1-pyrrolidinyl)ethyl)-1-propanamine	RT = 1.63 minutes (condition 5, 90%); LRMS: Anal. Calcd. for C48H54N8O2 774.43; found: 775.76$(M+H)^+$.
F17	*N*-((1*R*)-2-((2*S*)-2-(4-(4'-(2-((2*S*)-1-((2*R*)-2-(butylamino)-2-phenylacetyl)-2-pyrrolidinyl)-1*H*-imidazol-5-yl)-4-biphenylyl)-1*H*-imidazol-2-yl)-1-pyrrolidinyl)-2-oxo-1-phenylethyl)-1-butanamine	RT = 1.81 minutes (condition 5, 85%); LRMS: Anal. Calcd. for C50H58N8O2 802.47; found: 803.79 $(M+H)^+$.



Compound F18 and F23 was prepared in analogous fashion to the procedure used to sythesize example1 with following modification: N-Boc-L-alanine and N-Boc-L-valine was used in place of N-Boc-L-proline respectively.

Compound F22 was prepared in analogous fashion to the procedure used to sythesize example 1from Compound F19.

Compound F19, F24 was prepared in analogous fashion to the procedure used to sythesize 132e.

Compound F25

ethyl ((1S)-1-(((2S)-2-(4-(4'-(2-((2S)-1-((2S)-2-((ethoxycarbonyl)amino)-3-methylbutanoyl)-2-pyrrolidinyl)-1H-imidazol-4-yl)-4-biphenylyl)-1H-imidazol-2-yl)-1-pyrrolidinyl)carbonyl)-2-methylpropyl)carbamate

To a solution of F24 (0.06 g, 0.074 mmol) in DMF (1 mL) was added Hunig's base (0.105 mL, 0.593 mmol) and ethyl carbonochloridate (0.016 mL, 0.163 mmol) then stirred it at room temperature. Two hours later, checked it by LCMS. There were three major peaks which indicated desired compound, tri-coupled, and tetra-coupled compound. Stopped reaction and concentrated it by reduced pressure to get light brown oil which was treated with 10 mL of 2 M NH_3 in methanol for 20 minutes then concentrated it again to a yellow solid which was purified by preparative LC to provide compound F25 as a white TFA salt (57.6 mg).

LC (Cond.6): RT = 1.932 min, LC/MS: Anal. Calcd. for $[M+H]^+$ C42H54N8O6: 766.42; found 767.55.

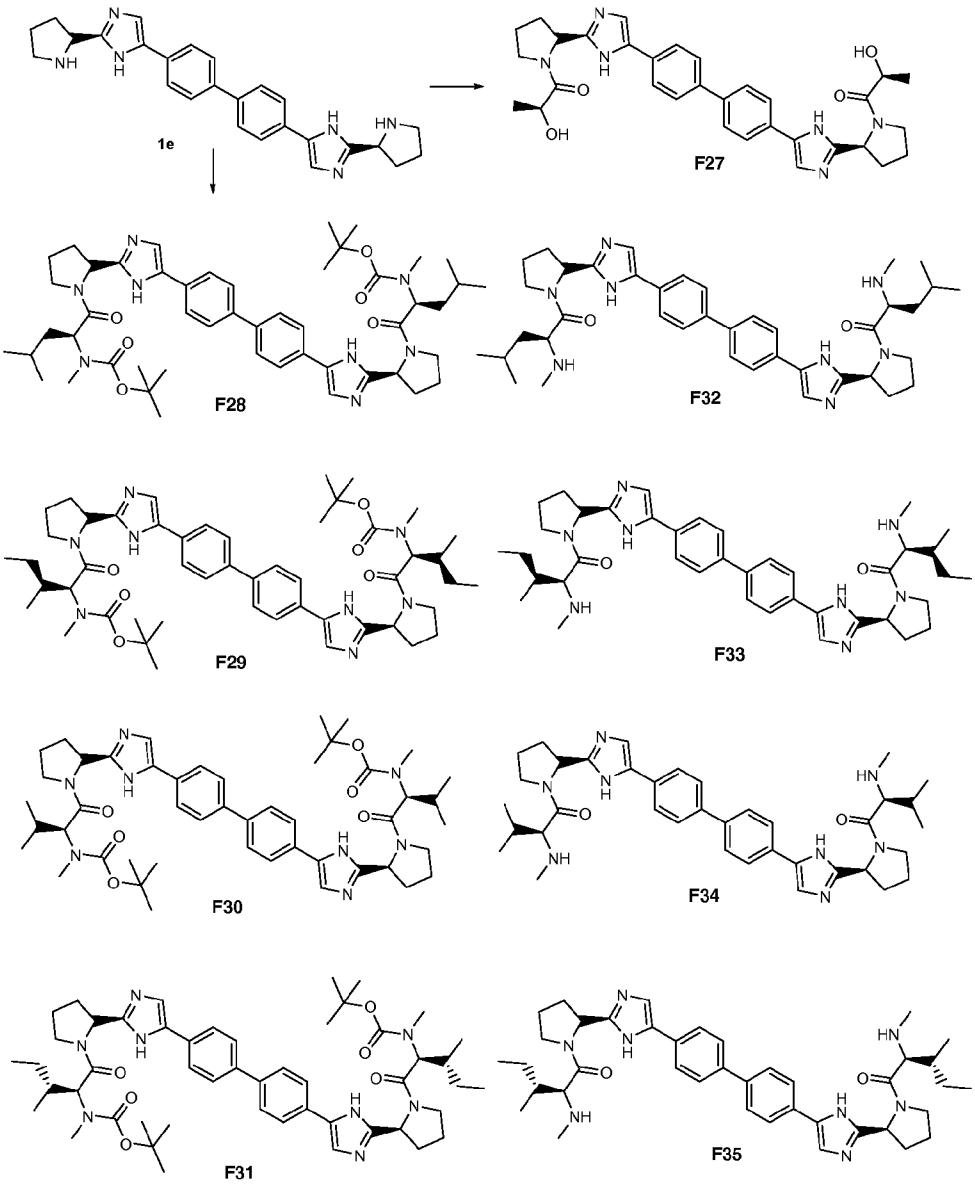
^{1}H NMR (500 MHz, DMSO-d_6) δ ppm 0.69-0.94 (m, 12H) 1.16 (t, *J*=7.02 Hz, 6H) 1.90-2.26 (m, 8H) 2.40 (d, *J*=4.88 Hz, 2H) 3.73-3.92 (m, 4H) 3.94-4.08 (m, 4H) 4.12 (t, *J*=7.78 Hz, 2H) 5.15 (t, *J*=7.02 Hz, 2H) 7.26 (d, *J*=8.54 Hz, 2H) 7.85-7.93 (m, 4H) 7.93-8.01 (m, 4H) 8.13 (s, 2H) 14.68 (s, 2H)

Compound F20, F21, and F26 was prepared in analogous fashion to the procedure used to sythesize example1.

Entry	*Compound Name*	*Retention time (LC-Condition); homogeneity index MS data*
F18		RT = 2.257 minutes (condition 5, 96%); LRMS: Anal. Calcd. for C42H54N8O6 766.42; found: 767.88 $(M+H)^+$.

F19		RT = 1.462 minutes (condition 5, 95%); LRMS: Anal. Calcd. for C32H38N8O2 566.31; found: 567.79 $(M+H)^+$.
F20	propyl ((1S)-1-methyl-2-oxo-2-((2S)-2-(4-(4'-(2-((2S)-1-(N-(propoxycarbonyl)-L-alanyl)-2-pyrrolidinyl)-1H-imidazol-5-yl)-4-biphenylyl)-1H-imidazol-2-yl)-1-pyrrolidinyl)ethyl)carbamate	RT = 1.338 minutes (condition 3, 89%); LRMS: Anal. Calcd. for C40H50N8O6 738.39; found: 739.95 $(M+H)^+$.
F21	butyl ((1S)-2-((2S)-2-(4-(4'-(2-((2S)-1-(N-(butoxycarbonyl)-L-alanyl)-2-pyrrolidinyl)-1H-imidazol-5-yl)-4-biphenylyl)-1H-imidazol-2-yl)-1-pyrrolidinyl)-1-methyl-2-oxoethyl)carbamate	RT = 1.447 minutes (condition 3, 96%); LRMS: Anal. Calcd. for C42H54N8O6 766.93; found: 768.02 $(M+H)^+$.
F22	(2S)-2-hydroxy-N-((1S)-2-((2S)-2-(5-(4'-(2-((2S)-1-(N-((2S)-2-hydroxy-3-methylbutanoyl)-L-alanyl)-2-pyrrolidinyl)-1H-imidazol-4-yl)-4-biphenylyl)-1H-imidazol-2-yl)-1-pyrrolidinyl)-1-methyl-2-oxoethyl)-3-methylbutanamide	RT = 1.703 minutes (condition 4, 98%); LRMS: Anal. Calcd. for C42H54N8O 766.93; found: 768.02 $(M+H)^+$.
F23		RT = 2.881 minutes (condition 7, 93%); LRMS: Anal. Calcd. for C46H62N8O6 822.48; found: 823.95 $(M+H)^+$.
F24		RT = 1.743 minutes (condition 7, 98%); LRMS: Anal. Calcd. for C36H46N8O2 622.37; found: 624.07 $(M+H)^+$.
F25	ethyl ((1S)-1-(((2S)-2-(4-(4'-(2-	RT = 1.932 minutes (condition 6,

	((2S)-1-((2S)-2-((ethoxycarbonyl)amino)-3-methylbutanoyl)-2-pyrrolidinyl)-1H-imidazol-4-yl)-4-biphenylyl)-1H-imidazol-2-yl)-1-pyrrolidinyl)carbonyl)-2-methylpropyl)carbamate	97%); LRMS: Anal. Calcd. for C42H54N8O6 766.42; found: 767.55 $(M+H)^+$.
F26	isopropyl ((1S)-1-(((2S)-2-(4-(4'-(2-((2S)-1-((2S)-2-((isopropoxycarbonyl)amino)-3-methylbutanoyl)-2-pyrrolidinyl)-1H-imidazol-4-yl)-4-biphenylyl)-1H-imidazol-2-yl)-1-pyrrolidinyl)carbonyl)-2-methylpropyl)carbamate	RT = 2.122 minutes (condition 6, 98%); LRMS: Anal. Calcd. for C44H58N8O6 794.45; found: 795.58 $(M+H)^+$.



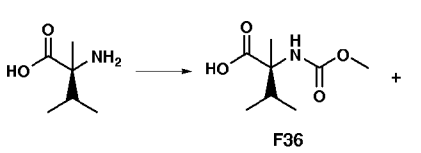
Entry	*Compound Name*	*Retention time (LC-Condition); homogeneity index MS data*
F27	(2S)-1-((2S)-2-(4-(4'-(2-((2S)-1-((2S)-2-hydroxypropanoyl)-2-pyrrolidinyl)-1H-imidazol-5-yl)-4-biphenylyl)-1H-imidazol-2-yl)-1-pyrrolidinyl)-1-oxo-2-propanol	RT = 1.03 minutes (condition 3, 98%); LRMS: Anal. Calcd. for C32H36N6O4 568.28; found: 569.76 $(M+H)^+$.
F28	tert-butyl ((1S)-1-(((2S)-2-(5-(4'-(2-((2S)-1-((2S)-2-((tert-	RT = 1.847 minutes (condition 3, 95%); LRMS: Anal. Calcd. for

	butoxycarbonyl)(methyl)amino)-4-methylpentanoyl)-2-pyrrolidinyl)-1H-imidazol-4-yl)-4-biphenylyl)-1H-imidazol-2-yl)-1-pyrrolidinyl)carbonyl)-3-methylbutyl)methylcarbamate	C50H70N8O6 878.54; found: 879.53 $(M+H)^+$.
F29	tert-butyl ((1S)-1-(((2S)-2-(5-(4'-(2-((2S)-1-((2S)-2-((tert-butoxycarbonyl)(methyl)amino)-3-methylpentanoyl)-2-pyrrolidinyl)-1H-imidazol-4-yl)-4-biphenylyl)-1H-imidazol-2-yl)-1-pyrrolidinyl)carbonyl)-2-methylbutyl)methylcarbamate	RT = 2.202 minutes (condition 8, 98%); LRMS: Anal. Calcd. for C50H70N8O6 878.54; found: 879.57 $(M+H)^+$.
F30	tert-butyl ((1S)-1-(((2S)-2-(5-(4'-(2-((2S)-1-((2S)-2-((tert-butoxycarbonyl)(methyl)amino)-3-methylbutanoyl)-2-pyrrolidinyl)-1H-imidazol-4-yl)-4-biphenylyl)-1H-imidazol-2-yl)-1-pyrrolidinyl)carbonyl)-2-methylpropyl)methylcarbamate	RT = 1.743 minutes (condition 8, 96%); LRMS: Anal. Calcd. for C48H66N8O6 850.51; found: 851.52 $(M+H)^+$.
F31	tert-butyl ((1S,2R)-1-(((2S)-2-(4-(4'-(2-((2S)-1-(N-(tert-butoxycarbonyl)-N-methyl-L-alloisoleucyl)-2-pyrrolidinyl)-1H-imidazol-5-yl)-4-biphenylyl)-1H-imidazol-2-yl)-1-pyrrolidinyl)carbonyl)-2-methylbutyl)methylcarbamate	RT = 1.82 minutes (condition 8, 98%); LRMS: Anal. Calcd. for C50H70N8O6 878.54; found: 879.54 $(M+H)^+$.
F32	(2S)-N,4-dimethyl-1-((2S)-2-(4-(4'-(2-((2S)-1-((2S)-4-methyl-2-(methylamino)pentanoyl)-2-pyrrolidinyl)-1H-imidazol-5-yl)-4-biphenylyl)-1H-imidazol-2-yl)-	RT = 3.715 minutes (condition 9, 98%); LRMS: Anal. Calcd. for C40H54N8O2 678.44; found: 679.46 $(M+H)^+$.

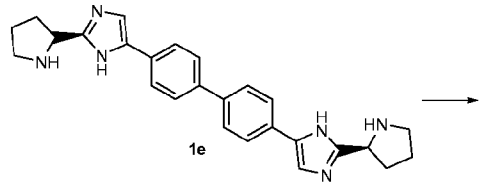
	1-pyrrolidinyl)-1-oxo-2-pentanamine	
F33	(2S)-N,3-dimethyl-1-((2S)-2-(4-(4'-(2-((2S)-1-((2S)-3-methyl-2-(methylamino)pentanoyl)-2-pyrrolidinyl)-1H-imidazol-5-yl)-4-biphenylyl)-1H-imidazol-2-yl)-1-pyrrolidinyl)-1-oxo-2-pentanamine	RT = 3.058 minutes (condition 9, 99%); LRMS: Anal. Calcd. for C36H46N8O2 678.44; found: 679.61 $(M+H)^+$.
F34	(2S)-N,3-dimethyl-1-((2S)-2-(4-(4'-(2-((2S)-1-((2S)-3-methyl-2-(methylamino)butanoyl)-2-pyrrolidinyl)-1H-imidazol-5-yl)-4-biphenylyl)-1H-imidazol-2-yl)-1-pyrrolidinyl)-1-oxo-2-butanamine	RT = 3.206 minutes (condition 9, 99%); LRMS: Anal. Calcd. for C38H50N8O2 650.41; found: 651.41 $(M+H)^+$.
F35	(2S,3R)-N,3-dimethyl-1-((2S)-2-(4-(4'-(2-((2S)-1-((2S,3R)-3-methyl-2-(methylamino)pentanoyl)-2-pyrrolidinyl)-1H-imidazol-5-yl)-4-biphenylyl)-1H-imidazol-2-yl)-1-pyrrolidinyl)-1-oxo-2-pentanamine	RT = 3.43 minutes (condition 9, 98%); LRMS: Anal. Calcd. for C40H54N8O2 678.44; found: 679.44 $(M+H)^+$.

Compound F27 to F31 was prepared in analogous fashion to the procedure used to sythesize example 1.

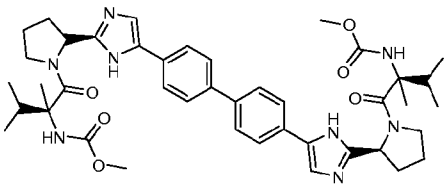
Compound F32 to F35 was prepared in analogous fashsion to the procedure used to synthesize 1e.



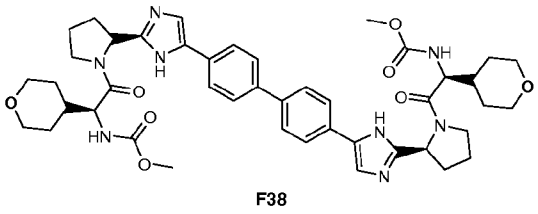
F36



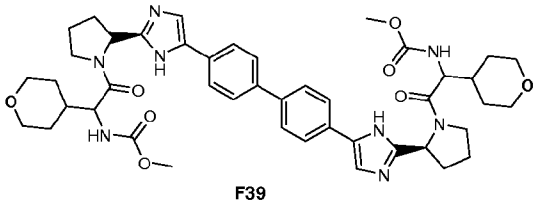
1e



F37



F38



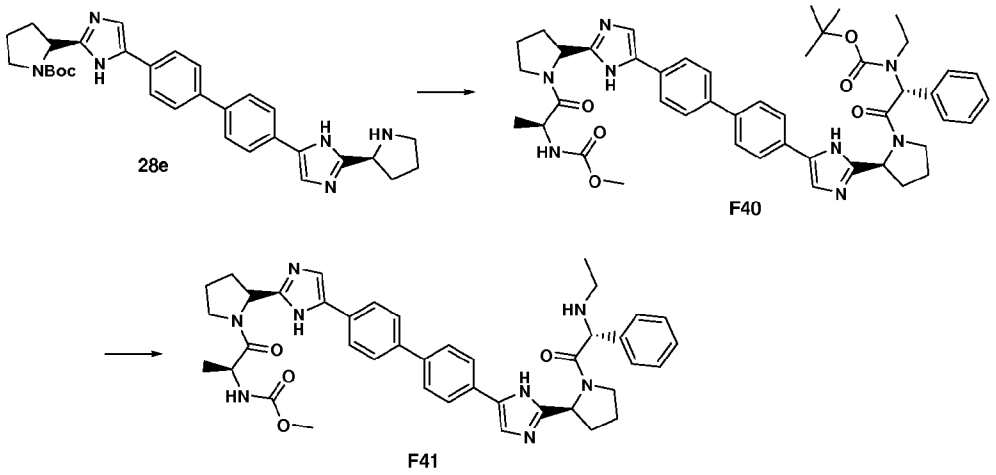
F39

Compound F36 was prepared in analogous fashion to the procedure used to sythesize *Cap*-52.

Compound F37, F38, and F39 was prepared in analogous fashion to the procedure used to synthesize example 1 from Compound F36 and LS16 respectively.

Entry	*Compound*	*Retention time (LC-Condition); homogeneity index MS data*
F36		RT = 1.55 minutes (condition 10); LRMS: Anal. Calcd. for C10H13NO2 189.1; found: 190.13 $(M+H)^+$. ^1H NMR (500 MHz, DMSO-d_6) δ ppm 0.71-1.00 (m, 6H) 1.16-1.41 (m, 3H) 1.75-2.09 (m, 1H) 3.39-3.64 (m, 3H) 7.13 (s, 1H) 12.27 (s, 1H)
F37	methyl ((1S)-1-(((2S)-2-(4-(4'-(2-((2S)-1-((2S)-2-((methoxycarbonyl)amino)-2,3-dimethylbutanoyl)-2-pyrrolidinyl)-	RT = 2.572 minutes (condition 4, 98%); LRMS: Anal. Calcd. for C42H54N8O6 766.42;

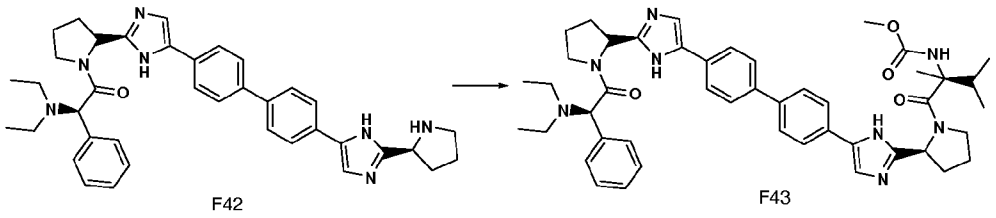
	1H-imidazol-5-yl)-4-biphenylyl)-1H-imidazol-2-yl)-1-pyrrolidinyl)carbonyl)-1,2-dimethylpropyl)carbamate	found: 767.48 $(M+H)^+$.
F38	methyl ((1S)-2-((2S)-2-(4-(4'-(2-((2S)-1-((2S)-2-((methoxycarbonyl)amino)-2-(tetrahydro-2H-pyran-4-yl)acetyl)-2-pyrrolidinyl)-1H-imidazol-5-yl)-4-biphenylyl)-1H-imidazol-2-yl)-1-pyrrolidinyl)-2-oxo-1-(tetrahydro-2H-pyran-4-yl)ethyl)carbamate	RT = 2.128 minutes (condition 7, 98%); LRMS: Anal. Calcd. for C44H54N8O8 822.41; found: 823.45 $(M+H)^+$.
F39	methyl (2-((2S)-2-(4-(4'-(2-((2S)-1-(((methoxycarbonyl)amino)(tetrahydro-2H-pyran-4-yl)acetyl)-2-pyrrolidinyl)-1H-imidazol-5-yl)-4-biphenylyl)-1H-imidazol-2-yl)-1-pyrrolidinyl)-2-oxo-1-(tetrahydro-2H-pyran-4-yl)ethyl)carbamate	RT = 2.162 minutes (condition 7, 98%); LRMS: Anal. Calcd. for C44H54N8O8 822.42; found: 823.49 $(M+H)^+$.



Compound F41 was prepared in analogous fashion to the procedure used to sythesize example 1.

Compound F42 was prepared in analogous fashsion to the procedure used to sythesize 1e.

Entry	*Compound Name*	*Retention time (LC-Condition); homogeneity index MS data*
F40		RT = 2.72 minutes (condition 10); LRMS: Anal. Calcd. for C46H54N8O6 814.42; found: 815.98 $(M+H)^+$.
F41	methyl ((1S)-2-((2S)-2-(4-(4'-(2-((2S)-1-((2R)-2-(ethylamino)-2-phenylacetyl)-2-pyrrolidinyl)-1H-imidazol-5-yl)-4-biphenylyl)-1H-imidazol-2-yl)-1-pyrrolidinyl)-1-methyl-2-oxoethyl)carbamate	RT = 2.048 minutes (condition 10, 95%); LRMS: Anal. Calcd. for C41H46N8O4 714.36; found: 715.84 $(M+H)^+$.

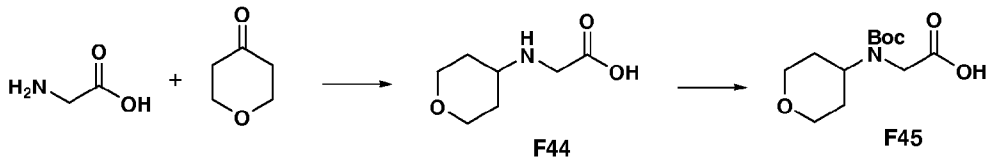


Compound F42 was prepared in analogous fashion to the procedure used to sythesize example 28f employing *Cap*-2 in place of *Cap*-4.

Compound F43 was prepared in analogous fashion to the procedure used to sythesize 2 from Compound F42.

Entry	*Compound Name*	*Retention time (LC-Condition); homogeneity index MS data*
F42		RT = 2.0 minutes (condition 10, 95%); LRMS: Anal. Calcd. for C38H43N7O 613.35; found: 614.40 $(M+H)^+$.
F43	methyl ((1S)-1-(((2S)-2-(5-(4'-(2-((2S)-1-((2R)-2-(diethylamino)-2-phenylacetyl)-2-pyrrolidinyl)-1H-imidazol-4-yl)-4-biphenylyl)-1H-imidazol-	RT = 2.308 minutes (condition 10, 98%); LRMS: Anal. Calcd. for C50H70N8O6 784.44; found: 785.49 $(M+H)^+$.

	2-yl)-1-pyrrolidinyl)carbonyl)-1,2-dimethylpropyl)carbamate	



Compound F44 was prepared following below paper with following modification: glycine was used in place of leucine.

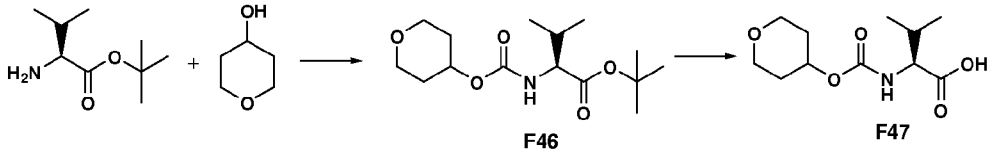
A simple method for preparation of *N*-mono- and *N*,*N*-di-alkylated α-amino acids Yuntao Song et al., *Tetrahedron Lett.* 41, October 2000, Pages 8225-8230.

^{1}H NMR (500 MHz, DMSO-d_6) δ ppm 1.37-1.62 (m, 2H) 1.86 (dd, *J*=12.36, 1.98 Hz, 2H) 3.01-3.12 (m, 1H) 3.15 (s, 2H) 3.25 (t, *J*=11.75 Hz, 2H) 3.86 (dd, *J*=11.44, 4.12 Hz, 2H) 7.67-8.48 (m, 1H).

Compound F45

2-(tetrahydro-2H-pyran-4-ylamino)acetic acid (0.2 g, 1.256 mmol) F44 was dissolved in DMF (22.5 mL) and Et_3N (2.5 mL, 17.94 mmol) .After 5 minutes BOC_2O (0.583 mL, 2.51 mmol) was added and the reaction solution was heated to 60 °C for 1 h. The reaction was concentrated by reduced pressure providing a light yellow oil to which was added 20 mL HCl/H2O which was adjusted to PH3 at 0 °C and stirred for 10 minutes. The reaction mixture was extracted by ethyl acetate 3 X 20 mL, dried ($MgSO_4$), filtered, and concentrated to dryness. Ether was added and the mixture was sonicated and filtered providing a white solid F45 2-(tert-butoxycarbonyl(tetrahydro-2H-pyran-4-yl)amino)acetic acid (0.14 g, 0.540 mmol, 43.0 % yield).

^{1}H NMR (300 MHz, DMSO-d_6) δ ppm 1.27-1.44 (m, 9H) 1.43-1.69 (m, 4H) 3.19-3.39 (m, 2H) 3.74 (s, 2H) 3.79-3.92 (m, 2H) 3.97-4.16 (m, 1H) 12.46 (s, 1H).



Compound F46 was prepared following the below referenced procedure with following modification: (S)-tert-butyl 2-amino-3-methylbutanoate was used in place of (S)-methyl 2-(((9H-fluoren-9-yl)methoxy)carbonylamino)-3-methylbutanoate.

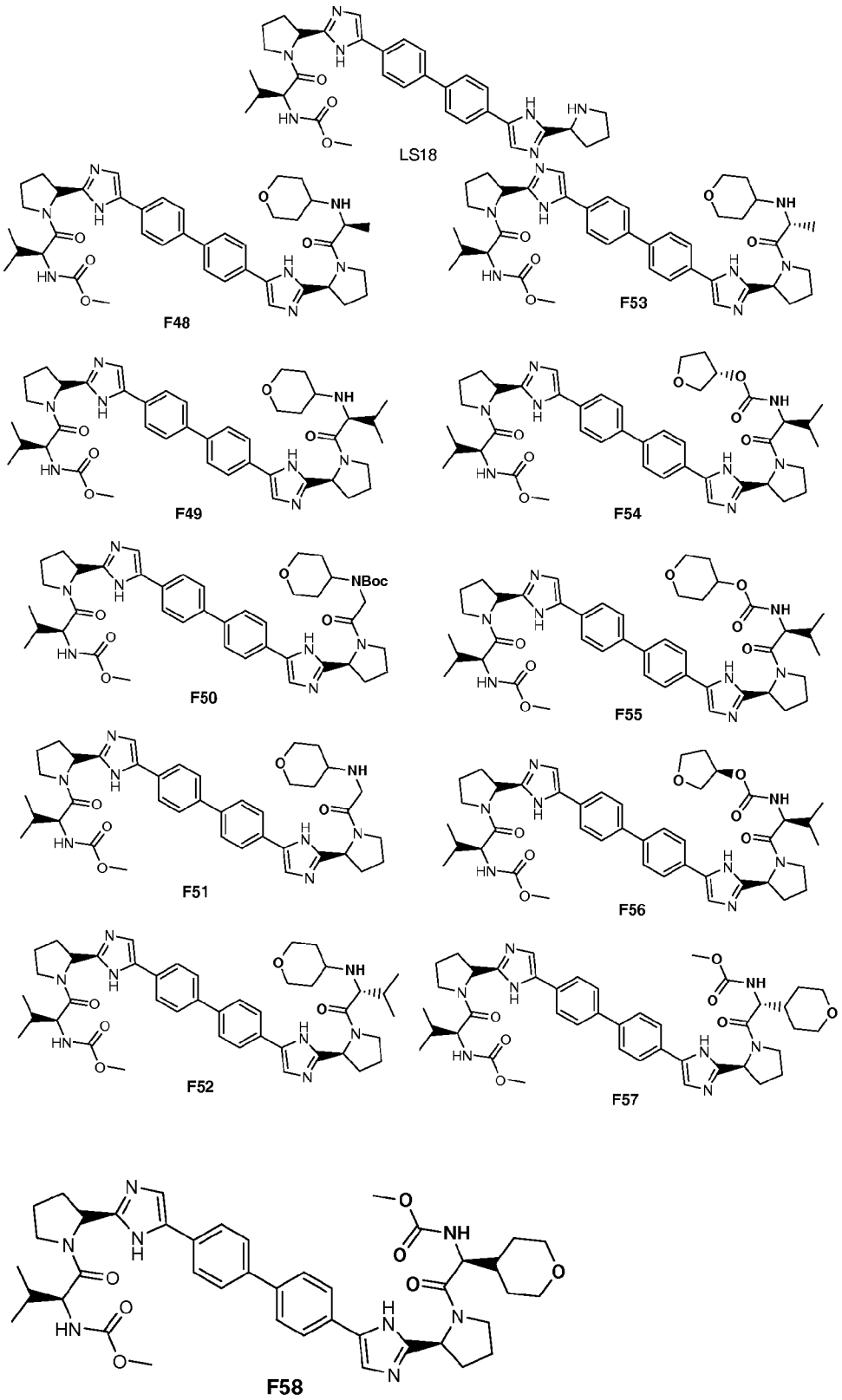
Hans-Joachim Knölker, et al. *Synlett* 1997; 925-928

^{1}H NMR (500 MHz, DMSO-d_6) δ ppm 0.77-0.97 (m, 6H) 1.32-1.45 (m, 9H) 1.45-1.56 (m, 2H) 1.74-1.91 (m, 2H) 1.94-2.11 (m, 1H) 3.36-3.53 (m, 2H) 3.76 (dd, *J*=8.09, 6.26 Hz, 1H) 3.77-3.90 (m, 2H) 4.69 (dd, *J*=9.00, 4.73 Hz, 1H) 7.35 (d, *J*=8.24 Hz, 1H)

Compound F47

To a Compound 46 (S)-tert-butyl 3-methyl-2-((tetrahydro-2H-pyran-4-yloxy)carbonylamino)butanoate (0.21 g, 0.697 mmol) was added HCl in dioxane (15 mL, 60.0 mmol) and the mixture was stirred at room temperature under nitrogen for three hours. The reaction was done and concentrated under reduced pressure to provide F47(S)-3-methyl-2-((tetrahydro-2H-pyran-4-yloxy)carbonylamino)butanoic acid (0.1694g, 0.691 mmol, 100 % yield) as a clear wax.

^{1}H NMR (500 MHz, DMSO-d_6) δ ppm 0.88 (t, *J*=6.71 Hz, 6H) 1.41-1.60 (m, 2H) 1.85 (d, *J*=12.21 Hz, 2H) 1.97-2.08 (m, 1H) 3.41 (t, *J*=10.68 Hz, 1H) 3.45-3.52 (m, 1H) 3.64-3.74 (m, 1H) 3.77-3.89 (m, 2H) 4.63-4.72 (m, 1H) 7.32 (d, *J*=8.55 Hz, 1H) 12.52 (s, 1H)


LS18
F48
F53
F49
F54
F50
F55
F51
F56
F52
F57
F58

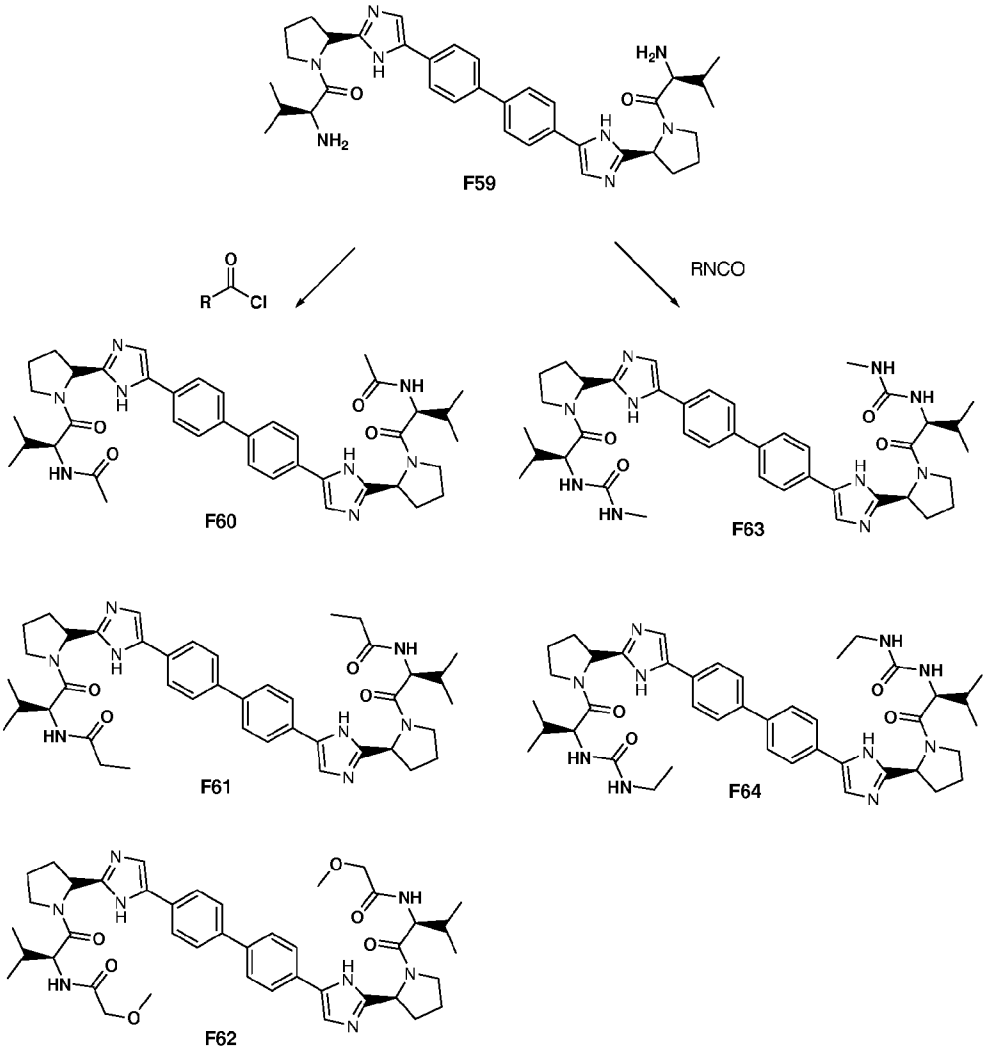
Compound F48 to F58 except F51 was prepared in analogous fashion to the procedure used to sythesize example 1 from LS18.

Compound F51 was prepared in analogous fashion to the procedure used to sythesize 1e from F50.

Entry	*Compound Name*	*Retention time (LC-Condition); homogeneity index MS data*
F48	methyl ((1S)-2-methyl-1-(((2S)-2-(4-(4'-(2-((2S)-1-(N-(tetrahydro-2H-pyran-4-yl)-L-alanyl)-2-pyrrolidinyl)-1H-imidazol-4-yl)-4-biphenylyl)-1H-imidazol-2-yl)-1-pyrrolidinyl)carbonyl)propyl)carbamate	RT = 2.103 minutes (condition 7, 98%); LRMS: Anal. Calcd. for C41H52N8O5 736.41; found: 737.07 $(M+H)^+$.
F49	methyl ((1S)-2-methyl-1-(((2S)-2-(4-(4'-(2-((2S)-1-(N-(tetrahydro-2H-pyran-4-yl)-L-valyl)-2-pyrrolidinyl)-1H-imidazol-4-yl)-4-biphenylyl)-1H-imidazol-2-yl)-1-pyrrolidinyl)carbonyl)propyl)carbamate	RT = 2.117 minutes (condition 7, 98%); LRMS: Anal. Calcd. for C43H56N8O5 764.44; found: 765.75 $(M+H)^+$.
F50		RT = 2.547 minutes (condition 7, 98%); LRMS: Anal. Calcd. for C45H58N8O7 822.44; found: 823.17 $(M+H)^+$.
F51	methyl ((1S)-2-methyl-1-(((2S)-2-(4-(4'-(2-((2S)-1-(N-(tetrahydro-2H-pyran-4-yl)glycyl)-2-pyrrolidinyl)-1H-imidazol-4-yl)-4-biphenylyl)-1H-imidazol-2-yl)-1-pyrrolidinyl)carbonyl)propyl)carbamate	RT = 2.138 minutes (condition 7, 96%); LRMS: Anal. Calcd. for C40H50N8O5 722.39; found: 723.63 $(M+H)^+$.
F52	methyl ((1S)-2-methyl-1-(((2S)-2-(4-(4'-(2-((2S)-1-(N-(tetrahydro-2H-pyran-4-yl)-D-valyl)-2-pyrrolidinyl)-1H-imidazol-4-yl)-4-biphenylyl)-1H-imidazol-2-yl)-1-pyrrolidinyl)carbonyl)propyl)carbamate	RT = 2.083 minutes (condition 7, 98%); LRMS: Anal. Calcd. for C43H56N8O5 764.44; found: 765.78 $(M+H)^+$.

F53	methyl ((1S)-2-methyl-1-(((2S)-2-(4-(4'-(2-((2S)-1-(N-(tetrahydro-2H-pyran-4-yl)-D-alanyl)-2-pyrrolidinyl)-1H-imidazol-4-yl)-4-biphenylyl)-1H-imidazol-2-yl)-1-pyrrolidinyl)carbonyl)propyl)carbamate	RT = 0.963 minutes (condition 11, 95%); LRMS: Anal. Calcd. for C43H54N8O7 736.41; found: 737.54 $(M+H)^+$.
F54	(3S)-tetrahydro-3-furanyl ((1S)-1-(((2S)-2-(4-(4'-(2-((2S)-1-(N-(methoxycarbonyl)-L-valyl)-2-pyrrolidinyl)-1H-imidazol-4-yl)-4-biphenylyl)-1H-imidazol-2-yl)-1-pyrrolidinyl)carbonyl)-2-methylpropyl)carbamate	RT = 2.378 minutes (condition 7, 95%); LRMS: Anal. Calcd. for C43H54N8O7 794.41; found: 795.94 $(M+H)^+$.
F55	tetrahydro-2H-pyran-4-yl ((1S)-1-(((2S)-2-(4-(4'-(2-((2S)-1-(N-(methoxycarbonyl)-L-valyl)-2-pyrrolidinyl)-1H-imidazol-4-yl)-4-biphenylyl)-1H-imidazol-2-yl)-1-pyrrolidinyl)carbonyl)-2-methylpropyl)carbamate	RT = 2.447 minutes (condition 7, 99%); LRMS: Anal. Calcd. for C44H56N8O7 808.43; found: 809.42 $(M+H)^+$.
F56	(3R)-tetrahydro-3-furanyl ((1S)-1-(((2S)-2-(4-(4'-(2-((2S)-1-(N-(methoxycarbonyl)-L-valyl)-2-pyrrolidinyl)-1H-imidazol-4-yl)-4-biphenylyl)-1H-imidazol-2-yl)-1-pyrrolidinyl)carbonyl)-2-methylpropyl)carbamate	RT = 2.398 minutes (condition 7, 96%); LRMS: Anal. Calcd. for C43H54N8O7 794.41; found: 795.36 $(M+H)^+$.
F57	methyl ((1S)-1-(((2S)-2-(4-(4'-(2-((2S)-1-((2R)-2-((methoxycarbonyl)amino)-2-(tetrahydro-2H-pyran-4-yl)acetyl)-2-pyrrolidinyl)-1H-imidazol-5-yl)-4-biphenylyl)-1H-imidazol-2-yl)-1-pyrrolidinyl)carbonyl)-2-methylpropyl)carbamate	RT = 2.272 minutes (condition 7, 98%); LRMS: Anal. Calcd. for C42H52N8O7 780.40; found: 781.34 $(M+H)^+$.
F58	methyl ((1S)-1-(((2S)-2-(4-(4'-(2-((2S)-	RT = 2.225 minutes (condition

	1-((2S)-2-((methoxycarbonyl)amino)-2-(tetrahydro-2H-pyran-4-yl)acetyl)-2-pyrrolidinyl)-1H-imidazol-5-yl)-4-biphenylyl)-1H-imidazol-2-yl)-1-pyrrolidinyl)carbonyl)-2-methylpropyl)carbamate	7, 98%); LRMS: Anal. Calcd. for C42H52N8O7 780.40; found: 781.27 $(M+H)^+$.



Compound F59

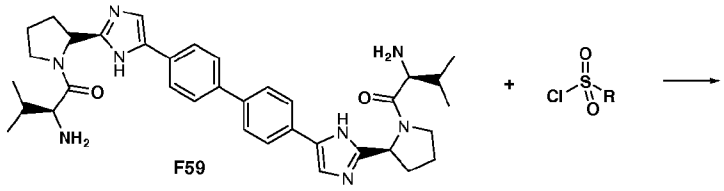
Compound F59 was prepared in analogous fashion to the procedure used to sythesize 26a with following modification: Boc-L-val-OH was used in place of Boc-D-val-OH.

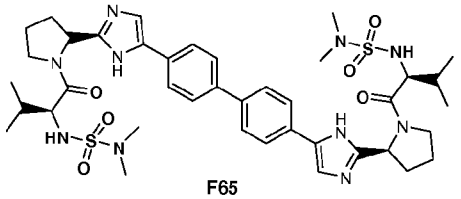
Compound F60 to F62 were prepared in analogous fashion to the procedure used to sythesize example 29 from F59.

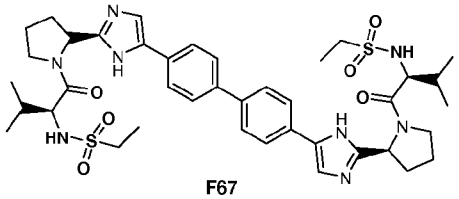
Compound F63 and F64 were prepared in analogous fashion to the procedure used to sythesized Cap45.

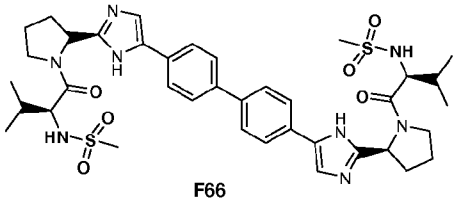
Entry	*Compound Name*	*Retention time (LC-Condition); homogeneity index MS data*
F59		RT = 1.743 minutes (condition 7, 98%); LRMS: Anal. Calcd. for C36H46N8O2 622.37; found: 624.07 $(M+H)^+$.
F60	N-((1S)-1-(((2S)-2-(4-(4'-(2-((2S)-1-((2S)-2-acetamido-3-methylbutanoyl)-2-pyrrolidinyl)-1H-imidazol-4-yl)-4-biphenylyl)-1H-imidazol-2-yl)-1-pyrrolidinyl)carbonyl)-2-methylpropyl)acetamide	RT = 2.047 minutes (condition 10, 98%); LRMS: Anal. Calcd. for C40H50N8O4 706.44; found: 707.77 $(M+H)^+$.
F61	N-((1S)-2-methyl-1-(((2S)-2-(4-(4'-(2-((2S)-1-((2S)-3-methyl-2-(propionylamino)butanoyl)-2-pyrrolidinyl)-1H-imidazol-4-yl)-4-biphenylyl)-1H-imidazol-2-yl)-1-pyrrolidinyl)carbonyl)propyl)propanamide	RT = 2.215 minutes (condition 10 98%); LRMS: Anal. Calcd. for C42H54N8O4 734.43; found: 735.87$(M+H)^+$.
F62	2-methoxy-N-((1S)-1-(((2S)-2-(4-(4'-(2-((2S)-1-((2S)-2-((methoxyacetyl)amino)-3-methylbutanoyl)-2-pyrrolidinyl)-1H-imidazol-4-yl)-4-biphenylyl)-1H-imidazol-2-yl)-1-pyrrolidinyl)carbonyl)-2-methylpropyl)acetamide	RT = 2.232 minutes (condition 10, 99%); LRMS: Anal. Calcd. for C42H54N8O6 766.93; found: 768.05 $(M+H)^+$.
F63	1-methyl-3-((1S)-2-methyl-1-(((2S)-2-(4-(4'-(2-((2S)-1-(N-(methylcarbamoyl)-L-valyl)-2-pyrrolidinyl)-1H-imidazol-4-yl)-4-biphenylyl)-1H-imidazol-2-yl)-1-	RT = 2.082 minutes (condition 10, 95%); LRMS: Anal. Calcd. for C40H52N10O4 736.42; found: 737.86

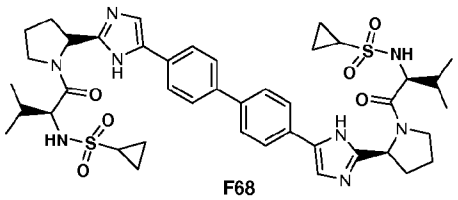
	pyrrolidinyl)carbonyl)propyl)urea	$(M+H)^+$.
F64	1-ethyl-3-((1S)-1-(((2S)-2-(4-(4'-(2-((2S)-1-((2S)-2-((ethylcarbamoyl)amino)-3-methylbutanoyl)-2-pyrrolidinyl)-1H-imidazol-4-yl)-4-biphenylyl)-1H-imidazol-2-yl)-1-pyrrolidinyl)carbonyl)-2-methylpropyl)urea	RT = 1.617 minutes (condition 12, 93%); LRMS: Anal. Calcd. for C42H56N10O4 764.45; found: 765.57 $(M+H)^+$.

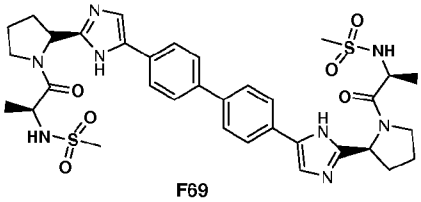












Compound F65

To a solution of F59 (0.06 g, 0.074 mmol in DMF (1 mL) was added dimethylsulfamoyl chloride (0.016 mL, 0.148 mmol) and Hunig'sBase (0.078 mL, 0.445 mmol) then stirred it at room temperature for 3 h. Solvent was removed by reduced pressure to get light brown oil which was purified by PreHPLC providing F65 N-((S)-1-((S)-2-(5-(4'-(2-((S)-1-((S)-2-(N,N-dimethylsulfamoylamino)-3-methylbutanoyl)pyrrolidin-2-yl)-1H-imidazol-5-yl)biphenyl-4-yl)-1H-imidazol-2-

yl)pyrrolidin-1-yl)-3-methyl-1-oxobutan-2-yl)propane-2-sulfonamide (19.0 mg, 0.018 mmol, 24.08 % yield)

^{1}H NMR (500 MHz, DMSO-d_6) δ ppm 0.65-1.03 (m, 12H) 1.87-2.08 (m, 4H) 2.06-2.27 (m, 4H) 2.37-2.46 (m, 2H) 2.56-2.69 (m, 12H) 3.66-3.92 (m, 6H) 5.14 (t, *J*=7.63 Hz, 2H) 7.49 (d, *J*=9.16 Hz, 2H) 7.89 (d, *J*=8.24 Hz, 4H) 7.96 (s, 4H) 8.14 (s, 2H) 14.72 (s, 2H)

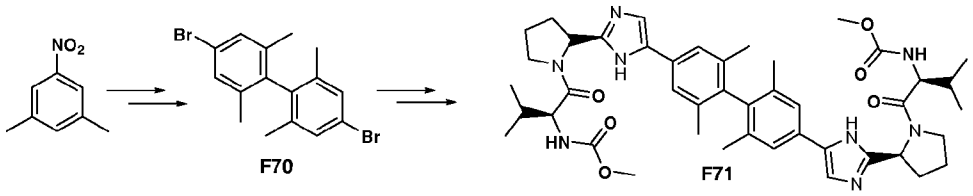
RT = 2.047 minutes (condition 10, 98%); LRMS: Anal. Calcd. for C40H50N8O4 706.38; found: 707.77 $(M+H)^+$.

1b Fret (EC50,uM) = 0.21

Compound F66 to F69 was prepared in analogous fashion to the procedure used to sythesize F65 from Compound F59.

Entry	*Compound Name*	*Retention time (LC-Condition); homogeneity index MS data*
F66	N-((1S)-2-methyl-1-(((2S)-2-(4-(4'-(2-((2S)-1-((2S)-3-methyl-2-((methylsulfonyl)amino)butanoyl)-2-pyrrolidinyl)-1H-imidazol-4-yl)-4-biphenylyl)-1H-imidazol-2-yl)-1-pyrrolidinyl)carbonyl)propyl)methanesulfonamide	RT = 2.02 minutes (condition 10, 98%); LRMS: Anal. Calcd. for C38H50N8O6S2 778.38; found: 779.60 $(M+H)^+$.
F67	N-((1S)-1-(((2S)-2-(4-(4'-(2-((2S)-1-((2S)-2-((ethylsulfonyl)amino)-3-methylbutanoyl)-2-pyrrolidinyl)-1H-imidazol-4-yl)-4-biphenylyl)-1H-imidazol-2-yl)-1-pyrrolidinyl)carbonyl)-2-methylpropyl)ethanesulfonamide	RT = 2.172 minutes (condition 10 98%); LRMS: Anal. Calcd. for C40H54N8O6S2 807.04; found: 808.42 $(M+H)^+$.
F68	N-((1S)-1-(((2S)-2-(4-(4'-(2-((2S)-1-((2S)-2-((cyclopropylsulfonyl)amino)-3-methylbutanoyl)-2-pyrrolidinyl)-1H-imidazol-4-yl)-4-biphenylyl)-1H-imidazol-2-yl)-1-pyrrolidinyl)carbonyl)-2-	RT = 2.217 minutes (condition 10, 93%); LRMS: Anal. Calcd. for C42H54N8O6S2 831.06; found: 832.49 $(M+H)^+$.

	methylpropyl)cyclopropanesulfonamide	
F69	N-((1S)-1-methyl-2-((2S)-2-(5-(4'-(2-((2S)-1-(N-(methylsulfonyl)-L-alanyl)-2-pyrrolidinyl)-1H-imidazol-4-yl)-4-biphenylyl)-1H-imidazol-2-yl)-1-pyrrolidinyl)-2-oxoethyl)methanesulfonamide	RT = 1.983 minutes (condition 10, 95%); LRMS: Anal. Calcd. for C34H42N8O6S2 722.27; found: 723.68 $(M+H)^+$.



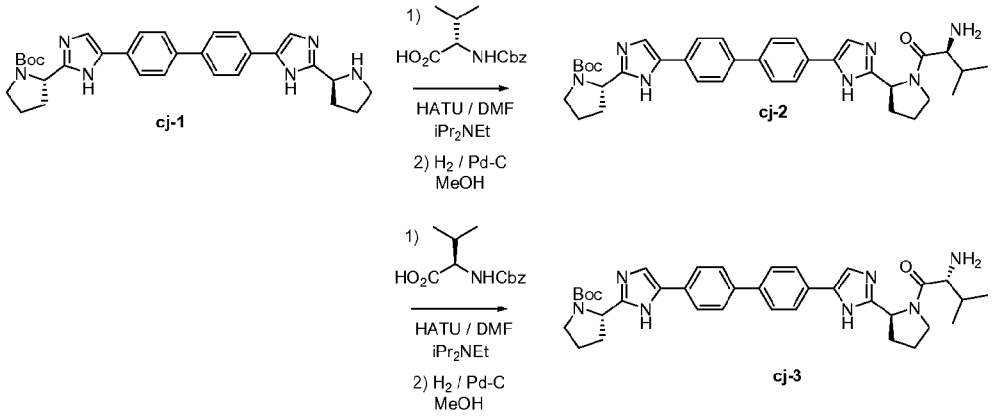
Compound F70 was prepared following the procedure described in Anna Helms et al., *J. Am. Chem. Soc.* 1992 114(15) pp 6227-6238.

Compound F71 was prepared in analogous fashion to the procedure used to sythesize Example 1.

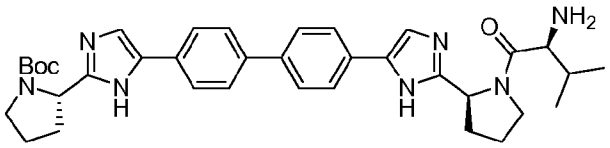
^{1}H NMR (500 MHz, DMSO-d_6) δ ppm 0.69-0.95 (m, 12H) 1.92 (s, 12H) 1.97-2.27 (m, 8H) 2.40 (s, 2H) 3.55 (s, 6H) 3.73-3.97 (m, 4H) 4.12 (t, *J*=7.78 Hz, 2H) 5.14 (t, *J*=7.02 Hz, 2H) 7.34 (d, *J*=8.24 Hz, 2H) 7.49-7.70 (m, 4H) 8.04 (s, 2H) 14.59 (s, 2H) RT = 2.523 minutes (condition 7, 96%); LRMS: Anal. Calcd. for C44H58N8O6 794.45; found: 795.48 $(M+H)^+$.

Section cj: Synthesis of Carbamate Replacements

Example cj-2 and cj-3



Preparation of (*S*)-*tert*-Butyl 2-(5-(4'-(2-((*S*)-1-((*S*)-2-amino-3-methylbutanoyl)pyrrolidin-2-yl)-1*H*-imidazol-5-yl)biphenyl-4-yl)-1*H*-imidazol-2-yl)pyrrolidine-1-carboxylate (cj-2)

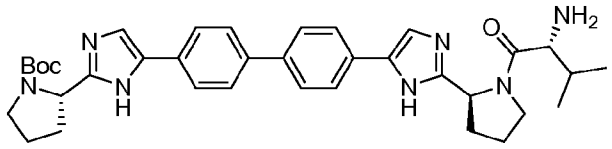


To a solution of (*S*)-*tert*-butyl 2-(5-(4'-(2-((*S*)-pyrrolidin-2-yl)-1*H*-imidazol-5-yl)biphenyl-4-yl)-1*H*-imidazol-2-yl)pyrrolidine-1-carboxylate (cj-1) (1.00 g, 1.91 mmol), iPr_2NEt (1.60 mL, 9.19 mmol) and *N*-Z-valine (0.62 g, 2.47 mmol) in DMF (10 mL) was added HATU (0.92 g, 2.42 mmol). The solution was allowed to stir at rt for 1 h and then it was poured into ice water (*ca.* 250 mL) and allowed to stand for 20 min. The mixture was filtered and the solid washed with water and then dried *in vacuo* overnight to afford a colorless solid (1.78 g) which was used as such in the next step. LCMS: Anal. Calcd. for $C_{44}H_{51}N_7O_5$: 757; found: 758 $(M+H)^+$.

A mixture of this material (1.70 g) and 10% Pd-C (0.37 g) in MeOH (100 mL) was hydrogenated (balloon pressure) for 12 h. The mixture was then filtered and the solvent removed *in vacuo*. The residue was purified by silica gel chromatography (Biotage system/ 0-10% MeOH-CH_2Cl_2) to afford the title compound as a light yellow foam (0.90 g, 76%).

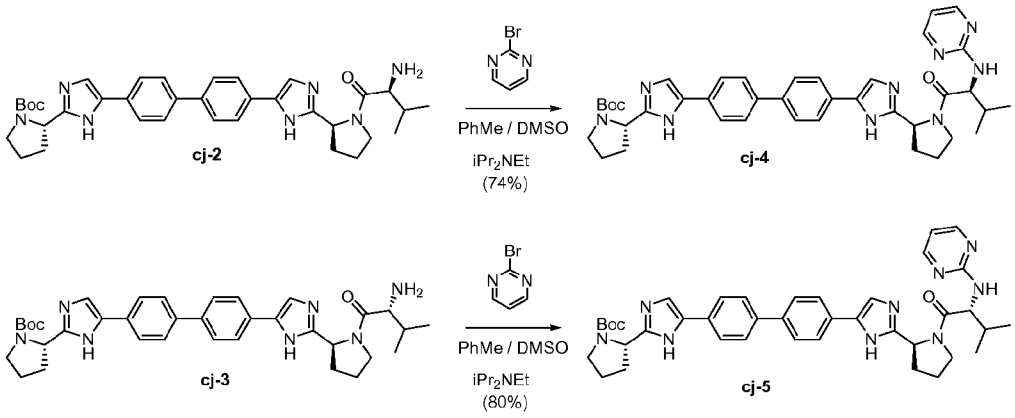
^{1}HNMR (400 MHz, DMSO-d_6) δ 12.18 (s, 0.35H), 11.73 (s, 0.65H), 11.89 (s, 0.65H), 11.82 (s, 0.35H), 7.77–7.81 (m, 3H), 7.57–7.71 (m, 5H), 7.50–7.52 (m, 2H), 5.17 (dd, *J* = 3.6, 6.5 Hz, 0.3H), 5.08 (dd, *J* = 3.6, 6.5 Hz, 0.7H), 4.84 (m, 0.3H), 4.76 (m, 0.7H), 3.67–3.69 (m, 1H), 3.50-3.62 (m, 1H), 3.34–3.47 (m, 2H), 2.22-2.28 (m, 2H), 2.10-2.17 (m, 2H), 1.74–2.05 (m, 6H), 1.40 (s, 4H), 1.15 (s, 5H), 0.85 – 0.91 (m, 4H), 0.79 (d, *J* = 6.5 Hz, 2H).
LCMS: Anal. Calcd. for $C_{36}H_{45}N_7O_3$: 623; found: 624 $(M+H)^+$.

Preparation of (*S*)-*tert*-Butyl 2-(5-(4'-(2-((*S*)-1-((*R*)-2-amino-3-methylbutanoyl)pyrrolidin-2-yl)-1*H*-imidazol-5-yl)biphenyl-4-yl)-1*H*-imidazol-2-yl)pyrrolidine-1-carboxylate (cj-3)

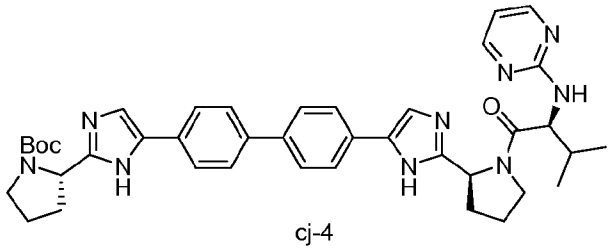


(*S*)-*tert*-Butyl 2-(5-(4'-(2-((*S*)-1-((*R*)-2-amino-3-methylbutanoyl)pyrrolidin-2-yl)-1*H*-imidazol-5-yl)biphenyl-4-yl)-1*H*-imidazol-2-yl)pyrrolidine-1-carboxylate (cj-3) was prepared using the same method used to prepare cj-2 to give a colorless foam (1.15 g, 76%). ^{1}HNMR (400 MHz, DMSO-d_6) δ 12.17 (s, 0.35H), 12.04 (s, 0.65H), 11.89 (s, 0.65H), 11.81 (s, 0.35H), 7.78–7.83 (m, 3H), 7.60–7.71 (m, 5H), 7.43–7.52 (m, 2H), 5.22–5.25 (m, 0.4H), 5.05–5.07 (m, 0.6H), 4.83–4.86 (m, 0.5H), 4.72–4.78 (m, 0.5H), 3.78–3.84 (m, 1H), 3.49-3.64 (m, 2H), 3.35–3.43 (m, 2H), 2.19 -2.32 (m, 1H), 2.04-2.17 (m, 3H), 1.95–2.04 (m, 2H), 1.76–1.90 (m, 3H), 1.40 (s, 4H), 1.15 (s, 5H), 0.85–0.91 (m, 4H), 0.67 (d, *J* = 6.5 Hz, 1H), 0.35 (d, *J* = 6.5 Hz, 1H). LCMS: Anal. Calcd. for $C_{36}H_{45}N_7O_3$: 623; found: 624 $(M+H)^+$.

Example cj-4 and cj-5



Preparation of (*S*)-*tert*-Butyl 2-(5-(4'-(2-((*S*)-1-((*S*)-3-methyl-2-(pyrimidin-2-ylamino)butanoyl)pyrrolidin-2-yl)-1*H*-imidazol-5-yl)biphenyl-4-yl)-1*H*-imidazol-2-yl)pyrrolidine-1-carboxylate (cj-4)



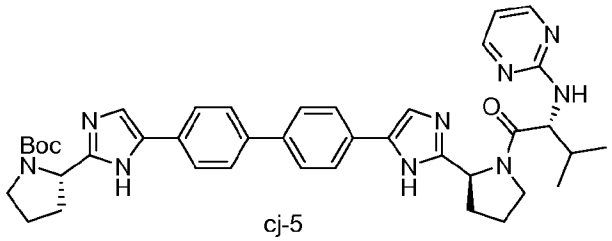
A mixture of (*S*)-*tert*-butyl 2-(5-(4'-(2-((*S*)-1-((*S*)-2-amino-3-methylbutanoyl)pyrrolidin-2-yl)-1*H*-imidazol-5-yl)biphenyl-4-yl)-1*H*-imidazol-2-yl)pyrrolidine-1-carboxylate (cj-2) (0.45 g, 0.72 mmol), 2-bromopyrimidine (0.37 g, 2.34 mmol) and iPr_2NEt (0.20 mL, 1.18 mmol) in toluene-DMSO (4:1, 5 mL) was heated at 90°C overnight. The volatiles were removed *in vacuo* and the residue was purified by preparative HPLC (YMC Pack C-18, 30X100mm/MeCN-H_2O-TFA). The title compound (0.56 g, 74%), as its TFA salt, was obtained as a yellow-orange glass.

^{1}HNMR (400 MHz, DMSO-d_6) δ 14.56 (br s, 2H), 8.28 (d, *J* = 5.0 Hz, 1H), 8.12 – 8.20 (m, 2H), 7.94 – 7.97 (m, 3H), 7.83 – 7.91 (m, 5H), 7.06 (d, *J* = 8.1 Hz, 1H), 6.62 (app t, *J* = 5.0 Hz, 1H), 4.99 – 5.10 (m, 2H), 4.50 (app t, *J* = 7.7 Hz, 1H), 4.07 – 4.12 (m, 2H), 3.83 – 3.87 (m, 1H), 3.56 – 3.62 (m, 1H), 3.40 – 3.47 (m, 2H), 2.36 –

2.41 (m, 1H), 1.94 – 2.22 (m, 6H), 1.40 (s, 4H), 1.17 (s, 5H), 0.88 (app t, *J* = 6.5 Hz, 6H).

LCMS: Anal. Calcd. for $C_{40}H_{47}N_9O_3$: 701; found: 702 $(M+H)^+$.

Preparation of (*S*)-tert-Butyl -2-(5-(4'-(2-((*S*)-1-((*R*)-3-methyl-2-(pyrimidin-2-ylamino)butanoyl)pyrrolidin-2-yl)-1*H*-imidazol-5-yl)biphenyl-4-yl)-1*H*-imidazol-2-yl)pyrrolidine-1-carboxylate (cj-5)



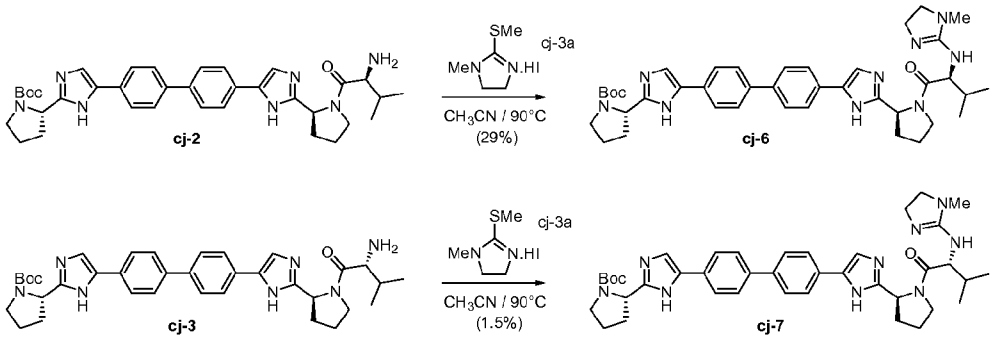
cj-5

The TFA salt of the title compound was prepared following the same method method used to prepare cj-4 to give a light yellow solid (0.375 g, 59%).

^{1}HNMR (400 MHz, DMSO-d_6) δ 14.67 (br s, 2H), 8.30 (d, *J* = 4.3 Hz, 1H), 8.04 – 8.19 (m, 2H), 7.84 – 7.96 (m, 8H), 6.88 (d, *J* = 8.6 Hz, 1H), 6.61 (app t, *J* = 4.5 Hz, 1H), 5.17 (dd, *J* = 4.4, 8.0 Hz, 1H), 5.00 – 5.07 (m, 1H), 4.67 (dd, *J* = 7.3, 8.1 Hz, 1H), 3.91 – 3.96 (m, 1H), 3.70-3.75 (m, 1H), 3.56 – 3.62 (m, 1H), 3.42 – 3.45 (m, 1H), 2.39 – 2.43 (m, 2H), 2.04 – 2.16 (m, 5H), 1.94 – 1.97 (m, 2H), 1.40 (s, 4H), 1.17 (s, 5H), 0.95 (d, *J* = 6.6 Hz, 2.5H), 0.91 (d, *J* = 6.6 Hz, 2.5H), 0.86 (d, *J* = 6.6 Hz, 0.5H), 0.81 (d, *J* = 6.6 Hz, 0.5H).

LCMS: Anal. Calcd. for $C_{40}H_{47}N_9O_3$: 701; found: 702 $(M+H)^+$.

Example cj-6 and cj-7



Preparation of 1-Methyl-2-(methylthio)-4,5-dihydro-1*H*-imidazole hydroiodide



cj-3a

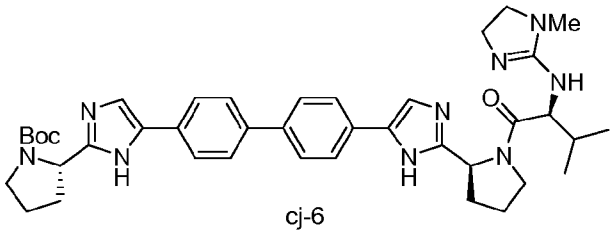
The title compound was prepared according to : Kister, J.; Assef, G.; Dou, H. J.-M.; Metzger, J. *Tetrahedron* 1976, *32*, 1395. Thus, a solution of *N*-methylethylenediamine (10.8 g, 146 mmol) in EtOH-H_2O (1:1, 90 mL) was preheated to 60°C and CS_2 (9.0 mL, 150 mmol) was added dropwise. The resulting mixture was heated at 60°C for 3 h and then conc. HCl (4.7 mL) was slowly added. The temperature was raised to 90°C and stirring was continued for 6 h. After the cooled mixture had been stored at -20°C, it was filtered and the resulting solid dried *in vacuo* to afford 1-methylimidazolidine-2-thione (8.43g, 50%) as a beige solid.

^{1}HNMR (400 MHz, $CDCl_3$) δ 5.15 (s, br, 1H), 3.67 – 3.70 (m, 2H), 3.53 – 3.58 (m, 2H), 3.11 (s, 3H).

To a suspension of 1-methylimidazolidine-2-thione (5.17 g, 44.5 mmol) in acetone (50 mL) was added MeI (2.9 mL, 46.6 mmol). The solution was allowed to stir at room temperature for 4 h and the resulting solid was quickly filtered and then dried *in vacuo* to give 1-methyl-2-(methylthio)-4,5-dihydro-1*H*-imidazole hydroiodide (8.79 g, 77%) as beige solid.

^{1}HNMR (400 MHz, $CDCl_3$) δ 9.83 (s, br, 1H), 3.99 – 4.12 (m, 4H), 3.10 (s, 3H), 2.99 (s, 3H).

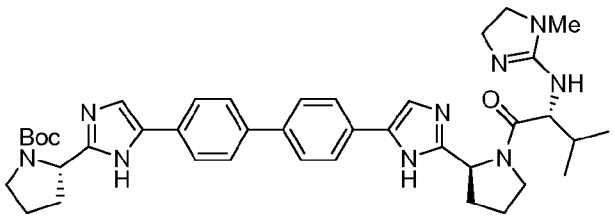
Preparation of (*S*)-*tert*-Butyl 2-(5-(4'-(2-((*S*)-1-((*S*)-3-methyl-2-(1-methyl-4-5-dihydroimidazol-2-ylamino)butanoyl)pyrrolidin-2-yl)-1*H*-imidazol-5-yl)biphenyl-4-yl)-1*H*-imidazol-2-yl)pyrrolidine-1-carboxylate (cj-6)



cj-6

A mixture of (*S*)-*tert*-butyl 2-(5-(4'-(2-((*S*)-1-((*S*)-2-amino-3-methylbutanoyl)pyrrolidin-2-yl)-1*H*-imidazol-5-yl)biphenyl-4-yl)-1*H*-imidazol-2-yl)-pyrrolidine-1-carboxylate (cj-2) (0.280 g, 0.448 mmol) and 1-methyl-2-(methylthio)-4,5-dihydro-1*H*-imidazole hydroiodide (cj-3a) (0.121 g, 0.468 mmol) in CH_3CN (5 mL) was heated at 90°C for 12 h. Another 0.030 g of 1-methyl-2-(methylthio)-4,5-dihydro-1*H*-imidazole hydroiodide (cj-3a) was added and heating continued for a further 12 h. The crude reaction mixture was directly purified by prep HPLC (Luna C-18/MeCN-H_2O-TFA) to give the TFA salt of the title compound (0.089 g) as a light yellow solid which was used as such in the subsequent steps.
LCMS: Anal. Calcd. for $C_{40}H_{51}N_9O_3$: 705; found: 706 $(M+H)^+$.

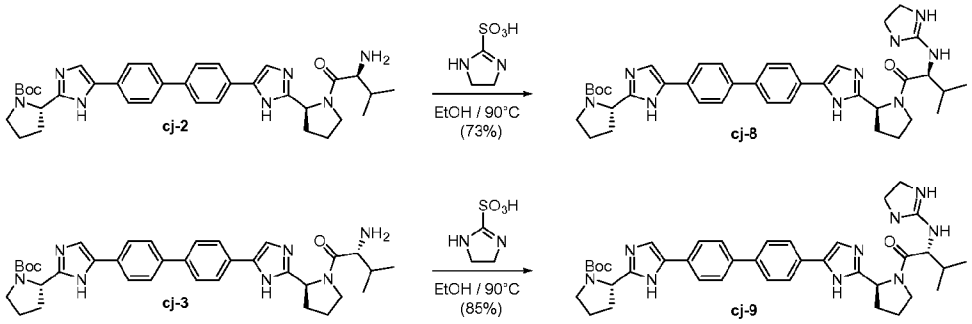
Preparation of (S)-*tert*-Butyl 2-(5-(4'-(2-((*S*)-1-((*R*)-3-methyl-2-(1-methyl-4-5-dihydroimidazol-2-ylamino)butanoyl)pyrrolidin-2-yl)-1*H*-imidazol-5-yl)biphenyl-4-yl)-1*H*-imidazol-2-yl)pyrrolidine-1-carboxylate (cj-7)



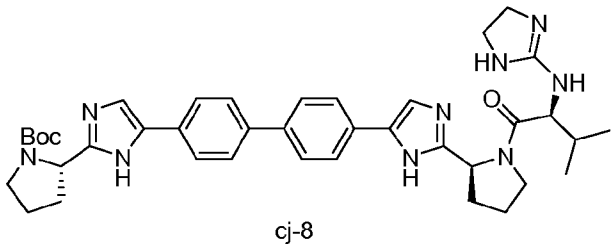
cj-7

The title compound was prepared from cj-3 according to the method described for the synthesis of cj-6, except that the reaction mixture was initially purified by prep HPLC (YMC-Pack 25X250mm/MeCN-H_2O-NH_4OAc) and then repurified by prep HPLC (Luna Phenyl-hexyl//MeCN-H_2O-NH_4OAc). This gave the desired product (0.005 g) as a foam which was used as such in the subsequent steps.
LCMS: Anal. Calcd. for $C_{40}H_{51}N_9O_3$: 705; found: 706 $(M+H)^+$.

Example cj-8 and cj-9



Preparation of (*S*)-*tert*-Butyl 2-(5-(4'-(2-((*S*)-1-((*S*)-3-methyl-2-(3,4-dihydroimidazol-2-ylamino)butanoyl)pyrrolidin-2-yl)-1*H*-imidazol-5-yl)biphenyl-4-yl)-1*H*-imidazol-2-yl)pyrrolidine-1-carboxylate (cj-8)

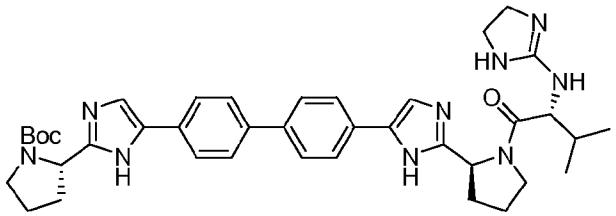


cj-8

A mixture of (*S*)-*tert*-butyl 2-(5-(4'-(2-((*S*)-1-((*S*)-2-amino-3-methylbutanoyl)pyrrolidin-2-yl)-1*H*-imidazol-5-yl)biphenyl-4-yl)-1*H*-imidazol-2-yl)pyrrolidine-1-carboxylate (cj-2) (0.298 g, 0.480 mmol), 4,5-dihydro-1*H*-imidazole-2-sulfonic acid (AstaTech) (0.090 g, 0.60 mmol) and iPr_2NEt (0.083 mL, 0.48 mmol) in EtOH (4 mL) was heated at 100°C for 12 h. The cooled mixture was evaporated to dryness and the residue was purified by prep HPLC (Luna 5u C18/MeCN-H_2O-TFA, x2) to afford the TFA salt of the title compound (0.390 g, 73%) as a light yellow solid.

^{1}HNMR (400 MHz, DMSO-d_6) δ 14.66 (br s, 2H), 8.51 (br s, 1H), 8.20 (d, *J* = 10.1 Hz, 2H), 8.10 (br s, 1H), 7.82 – 7.91 (m, 7H), 7.30 (br s, 1H), 5.12 (t, *J* = 7.1 Hz, 1H), 4.97 – 5.05 (m, 2H), 4.37 (dd, *J* = 4.3, 10.1 Hz, 2H), 3.82 – 3.86 (m, 2H), 3.73 – 3.77 (m, 2H), 3.59 (s, 4H), 3.39 – 3.48 (m, 2H), 2.15 – 2.25 (m, 2H), 1.93 – 2.07 (m, 5H), 1.40 (s, 4H), 1.17 (s, 5H), 0.93 (d, *J* = 6.6 Hz, 3H), 0.69 (br s, 3H).
LCMS: Anal. Calcd. for $C_{39}H_{49}N_9O_3$: 691; found: 692 $(M+H)^+$.

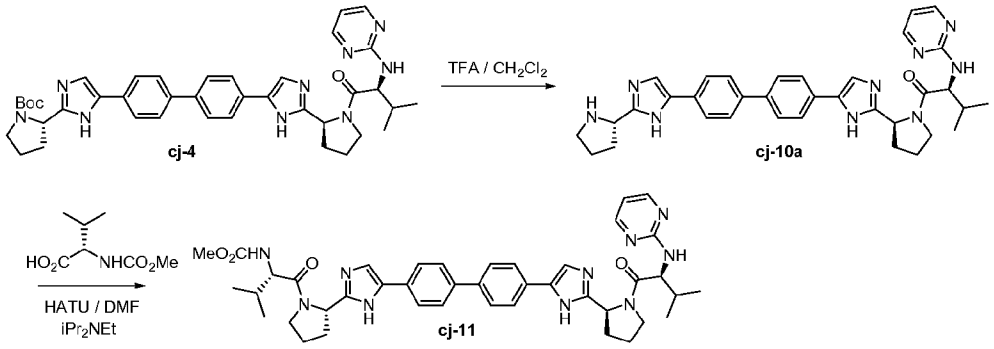
Preparation of (*S*)-*tert*-Butyl 2-(5-(4'-(2-((*S*)-1-((*R*)-3-methyl-2-(3,4-dihydroimidazol-2-ylamino)butanoyl)pyrrolidin-2-yl)-1*H*-imidazol-5-yl)biphenyl-4-yl)-1*H*-imidazol-2-yl)pyrrolidine-1-carboxylate (cj-9)



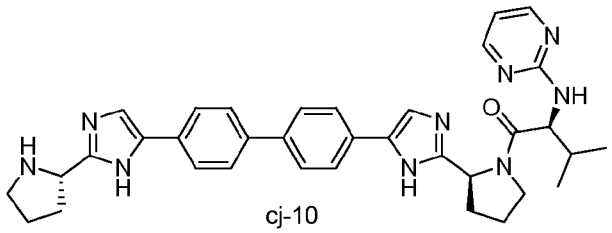
cj-9

The title compound was prepared from cj-3 according to the same method used to prepare cj-8 to afford the TFA salt (0.199 g, 57%) as a yellow glass.
^{1}HNMR (400 MHz, DMSO-d_6) δ 14.58 (br s, 4H), 8.23 (d, *J* = 9.6 Hz, 1H), 8.11 (s, 1H), 7.87 – 7.89 (m, 6H), 7.25 (br s, 1H), 5.17 – 5.20 (m, 1H), 4.96 – 5.04 (m, 1H), 4.37 (dd, *J* = 5.5, 9.6 Hz, 1H), 3.91-3.95 (m, 2H), 3.37 – 3.46 (m, partially obscured by H_2O, 4H), 2.39 – 2.42 (m, partially obscured by solvent, 2H), 2.01 – 2.09 (m, 4H), 1.94 – 1.98 (m, 2H), 1.40 (s, 3H), 1.17 (s, 6H), 0.95 (d, *J* = 6.5 Hz, 2.5H), 0.85 (d, *J* = 6.5 Hz, 2.5H), 0.66 (d, *J* = 7.0 Hz, 0.5H), 0.54 (d, *J* = 6.5 Hz, 0.5H).
LCMS: Anal. Calcd. for $C_{39}H_{49}N_9O_3$: 691; found: 692 $(M+H)^+$.

Example cj-11



Preparation of (*S*)-3-Methyl-2-(pyrimidin-2-ylamino)-1-((*S*)-2-(5-(4'-(2-((*S*)-pyrrolidin-2-yl)-1*H*-imidazol-5-yl)biphenyl-4-yl)-1*H*-imidazol-2-yl)pyrrolidin-1-yl)butan-1-one (cj-10a).

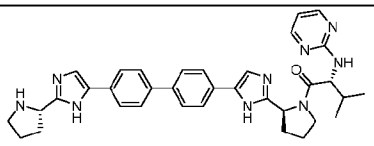
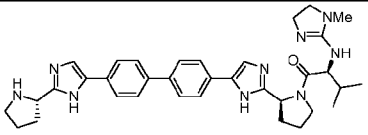
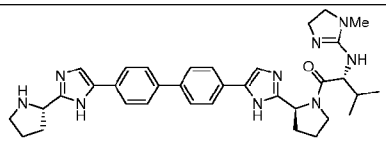
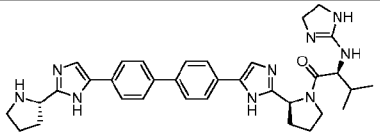
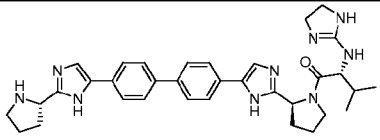


Step 1: A solution of the TFA salt of (*S*)-*tert*-butyl 2-(5-(4'-(2-((*S*)-1-((*S*)-3-methyl-2-(pyrimidin-2-ylamino)butanoyl)pyrrolidin-2-yl)-1*H*-imidazol-5-yl)biphenyl-4-yl)-1*H*-imidazol-2-yl)pyrrolidine-1-carboxylate (cj-4) (0.208 g, 0.199 mmol) in a mixture CH_2Cl_2 (4 mL) and TFA (3 mL) was stirred at room temperature for 1.5 h. The solvents were then removed *in vacuo* and the residue was purified by prep HPLC (Luna 5u C18/MeCN-H_2O-TFA) to give the TFA salt of the title compound (0.391 g) as an orange gum.

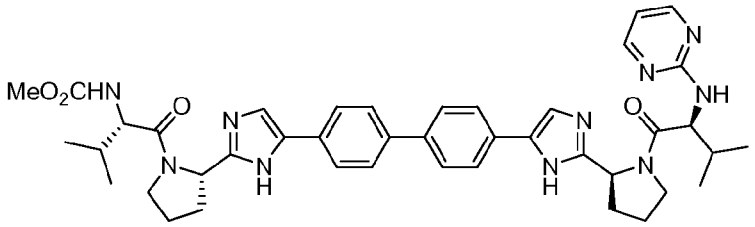
^{1}HNMR (400 MHz, DMSO-d_6) δ 14.53 (br s, 3H), 9.52 – 9.57 (m, 2H), 8.98 – 9.04 (m, 2H), 8.28 (d, *J* = 4.6 Hz, 2H), 8.13 (br s, 1H), 7.79 – 7.91 (m, 7H), 7.07 (d, *J* = 8.1 Hz, 1H), 6.62 (app t, *J* = 4.8 Hz, 1H), 5.07 (t, *J* = 7.1 Hz, 1H), 4.72 – 4.78 (m, 2H), 4.48 – 4.51 (m, 1H), 4.08-4.12 (m, 2H), 3.28 – 3.36 (m, 2H), 2.37 – 2.42 (m, 2H), 1.97 – 2.22 (m, 6H), 0.88 (app t, *J* = 4.5 Hz, 6H).

LCMS: Anal. Calcd. for $C_{35}H_{39}N_9O$: 601; found: 602 $(M+H)^+$.

Similarly, the following examples were prepared according to the representative method above;

Example	*Structure*	*LCMS*
cj-10a (from cj-3)		LCMS: Anal. Calcd. for $C_{35}H_{39}N_9O$: 601; found: 602 $(M+H)^+$.
cj-10b (from cj-2)		LCMS: Anal. Calcd. for $C_{35}H_{43}N_9O$: 605; found: 606 $(M+H)^+$.
cj-10c (from cj-3)		LCMS: Anal. Calcd. for $C_{35}H_{43}N_9O$: 605; found: 606 $(M+H)^+$.
cj-10d (from cj-2)		LCMS: Anal. Calcd. for $C_{34}H_{41}N_9O$: 591; found: 592 $(M+H)^+$.
cj-10e (from cj-3)		LCMS: Anal. Calcd. for $C_{34}H_{41}N_9O$: 591; found: 592 $(M+H)^+$.

Preparation of methyl ((1S)-2-methyl-1-(((2S)-2-(5-(4'-(2-((2S)-1-(N-2-pyrimidinyl-L-valyl)-2-pyrrolidinyl)-1H-imidazol-5-yl)-4-biphenylyl)-1H-imidazol-2-yl)-1-pyrrolidinyl)carbonyl)propyl)carbamate (cj-11)



cj-11

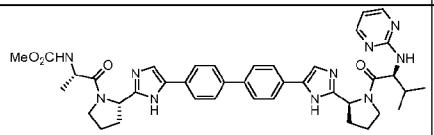
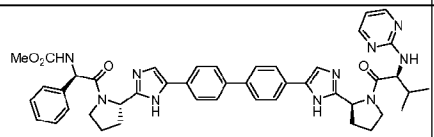
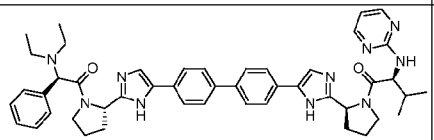
methyl ((1S)-2-methyl-1-(((2S)-2-(5-(4'-(2-((2S)-1-(N-2-pyrimidinyl-L-valyl)-2-pyrrolidinyl)-1H-imidazol-5-yl)-4-biphenylyl)-1H-imidazol-2-yl)-1-pyrrolidinyl)carbonyl)propyl)carbamate

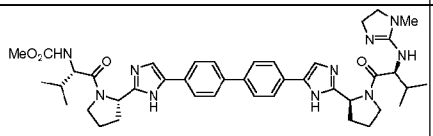
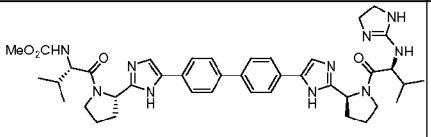
Step 2: To a solution of the TFA salt of (*S*)-3-methyl-2-(pyrimidin-2-ylamino)-1-((*S*)-2-(5-(4'-(2-((*S*)-pyrrolidin-2-yl)-1*H*-imidazol-5-yl)biphenyl-4-yl)-1*H*-imidazol-2-yl)pyrrolidin-1-yl)butan-1-one (cj-10) (0.208 g, 0.197 mmol) in DMF (4 mL) was added iPr_2NEt (0.20 mL, 1.15 mmol), (*S*)-2-(methoxycarbonylamino)-3-methylbutanoic acid (0.049 g, 0.28 mmol) and HATU (0.105 g, 0.276 mmol). The solution was stirred for 1.5 h at room temperature, diluted with MeOH (2 mL) and purified directly by prep HPLC (Luna 5u C18/MeCN-H_2O-NH_4OAc). This material was repurified by flash chromatography (SiO_2/2-10% MeOH-CH_2Cl_2) to give a solid which was lyophilized from CH_3CN-H_2O to give the title compound (48.6 mg, 32%) as a colourless solid.

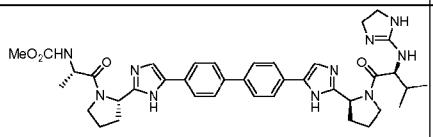
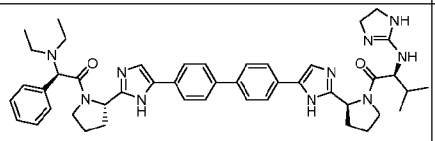
^{1}HNMR (400 MHz, DMSO-d_6) δ 11.78 (br s, 1H), 8.28 (d, *J* = 4.5 Hz, 1H), 7.76 – 7.79 (m, 4H), 7.66 – 7.69 (m, 4H), 7.48-7.51 (m, 2H), 7.29 (d, *J* = 8.6 Hz, 1H), 6.93 (d, *J* = 8.1 Hz, 1H), 6.60 (app t, *J* = 4.5 Hz, 1H), 5.03 – 5.09 (m, 2H), 4.48 (t. *J* = 8.1 Hz, 1H), 3.99 – 4.08 (m, 2H), 3.78 – 3.85 (m, 2H) 3.53 (s, 3H), 2.12 – 2.21 (m, 4H), 1.87 – 2.05 (m, 7H), 0.83 – 0.97 (m, 12H).

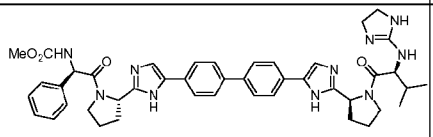
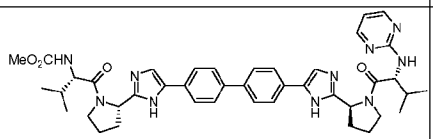
LCMS: Anal. Calcd. for $C_{42}H_{50}N_{10}O_4$:758; found: 759 $(M+H)^+$.

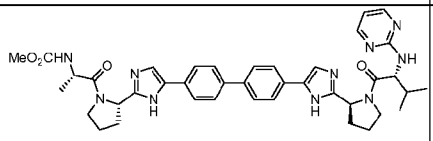
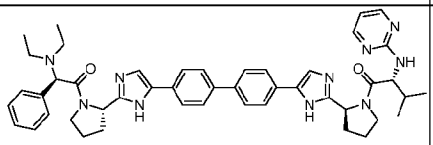
Similarly, the following examples were prepared according to the representative method above;

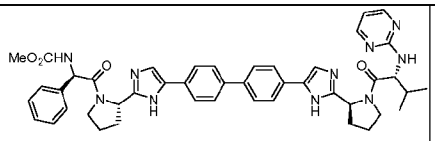
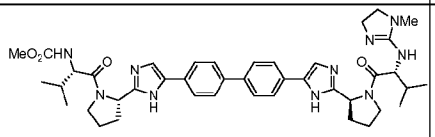
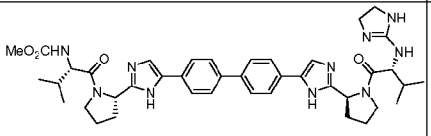
Example	*Compound Name*	*Structure*	*LCMS*
cj-11a (from cj-10 and *Cap*-52)	methyl ((1S)-1-methyl-2-oxo-2-((2S)-2-(5-(4'-(2-((2S)-1-(N-2-pyrimidinyl-L-valyl)-2-pyrrolidinyl)-1H-imidazol-5-yl)-4-biphenylyl)-1H-imidazol-2-yl)-1-pyrrolidinyl)ethyl)carbamate		LCMS: Anal. Calcd. for $C_{40}H_{46}N_{10}O_4$: 730; found: 731 $(M+H)^+$.
cj-11b (from cj-10 and *Cap*-4)	methyl ((1R)-2-oxo-1-phenyl-2-((2S)-2-(5-(4'-(2-((2S)-1-(N-2-pyrimidinyl-L-valyl)-2-pyrrolidinyl)-1H-imidazol-5-yl)-4-biphenylyl)-1H-imidazol-2-yl)-1-pyrrolidinyl)ethyl)carbamate		LCMS: Anal. Calcd. for $C_{45}H_{48}N_{10}O_4$: 792; found: 793 $(M+H)^+$.
cj-11c (from cj-10 and *Cap*-2)	N-((1S)-1-(((2S)-2-(5-(4'-(2-((2S)-1-((2R)-2-(diethylamino)-		LCMS: Anal. Calcd. for $C_{47}H_{54}N_{10}O_2$: 790; found: 791 $(M+H)^+$.

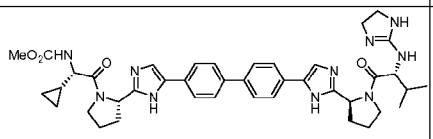
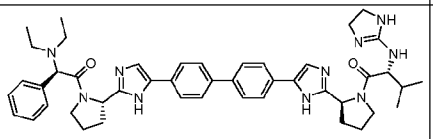
	2-phenylacetyl)-2-pyrrolidinyl)-1H-imidazol-5-yl)-4-biphenylyl)-1H-imidazol-2-yl)-1-pyrrolidinyl)carbonyl)-2-methylpropyl)-2-pyrimidinamine		
cj-11d (from cj-10b and *Cap*-51)	methyl ((1S)-2-methyl-1-(((2S)-2-(5-(4'-(2-((2S)-1-(N-(1-methyl-4,5-dihydro-1H-imidazol-2-yl)-L-valyl)-2-pyrrolidinyl)-1H-imidazol-5-yl)-4-biphenylyl)-1H-imidazol-2-yl)-1-pyrrolidinyl)carbonyl)propyl)carbamate		LCMS: Anal. Calcd. for $C_{42}H_{54}N_{10}O_4$: 762; found: 763 $(M+H)^+$.
cj-11e (from cj-10d and *Cap*-51)	methyl ((1S)-1-(((2S)-2-(5-(4'-(2-((2S)-1-(N-(4,5-dihydro-1H-imidazol-2-yl)-L-valyl)-2-		LCMS: Anal. Calcd. for $C_{41}H_{52}N_{10}O_4$: 748; found: 749 $(M+H)^+$.

	pyrrolidinyl)-1H-imidazol-5-yl)-4-biphenylyl)-1H-imidazol-2-yl)-1-pyrrolidinyl)carbonyl)-2-methylpropyl)carbamate		
cj-11f (from cj-10d and *Cap*-52)	methyl ((1S)-2-((2S)-2-(5-(4'-(2-((2S)-1-(N-(4,5-dihydro-1H-imidazol-2-yl)-L-valyl)-2-pyrrolidinyl)-1H-imidazol-5-yl)-4-biphenylyl)-1H-imidazol-2-yl)-1-pyrrolidinyl)-1-methyl-2-oxoethyl)carbamate		LCMS: Anal. Calcd. for $C_{39}H_{48}N_{10}O_4$: 720; found: 721 $(M+H)^+$.
cj-11g (from cj-10d and *Cap*-2)	N-((1S)-1-(((2S)-2-(5-(4'-(2-((2S)-1-((2R)-2-(diethylamino)-2-phenylacetyl)-2-pyrrolidinyl)-1H-imidazol-5-yl)-4-biphenylyl)-1H-		LCMS: Anal. Calcd. for $C_{46}H_{56}N_{10}O_2$: 780; found: 781 $(M+H)^+$.

	imidazol-2-yl)-1-pyrrolidinyl)carbonyl)-2-methylpropyl)-4,5-dihydro-1H-imidazol-2-amine		
cj11h (from cj-10d and *Cap*-4)	methyl ((1R)-2-oxo-1-phenyl-2-((2S)-2-(5-(4'-(2-((2S)-1-(N-2-pyrimidinyl-D-valyl)-2-pyrrolidinyl)-1H-imidazol-5-yl)-4-biphenylyl)-1H-imidazol-2-yl)-1-pyrrolidinyl)ethyl)carbamate		LCMS: Anal. Calcd. for $C_{44}H_{50}N_{10}O_4$: 782; found: 783 $(M+H)^+$.
cj-11i (from cj-10a and *Cap*-51)	methyl ((1S)-2-methyl-1-(((2S)-2-(5-(4'-(2-((2S)-1-(N-2-pyrimidinyl-D-valyl)-2-pyrrolidinyl)-1H-imidazol-5-yl)-4-biphenylyl)-1H-imidazol-2-yl)-1-pyrrolidinyl)carb		LCMS: Anal. Calcd. for $C_{42}H_{50}N_{10}O_4$: 758; found: 759 $(M+H)^+$.

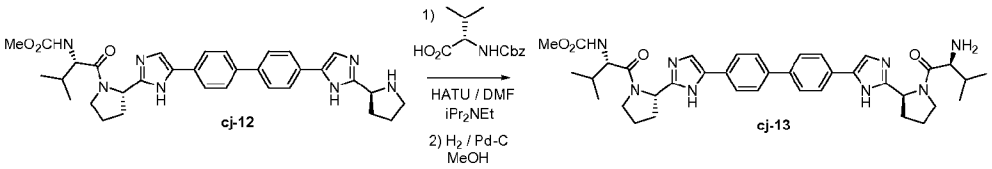
	onyl)propyl)carbamate		
cj-11j (from cj-10a and *Cap*-52)	methyl ((1S)-1-methyl-2-oxo-2-((2S)-2-(5-(4'-(2-((2S)-1-(N-2-pyrimidinyl-D-valyl)-2-pyrrolidinyl)-1H-imidazol-5-yl)-4-biphenylyl)-1H-imidazol-2-yl)-1-pyrrolidinyl)ethyl)carbamate		LCMS: Anal. Calcd. for $C_{40}H_{46}N_{10}O_4$: 730; found: 731 $(M+H)^+$.
cj-11k (from cj-10a and *Cap*-2)	N-((1R)-1-(((2S)-2-(5-(4'-(2-((2S)-1-((2R)-2-(diethylamino)-2-phenylacetyl)-2-pyrrolidinyl)-1H-imidazol-5-yl)-4-biphenylyl)-1H-imidazol-2-yl)-1-pyrrolidinyl)carbonyl)-2-methylpropyl)-2-pyrimidinamine		LCMS: Anal. Calcd. for $C_{47}H_{54}N_{10}O_2$: 790; found: 791 $(M+H)^+$.

cj-11l (from cj-10a and *Cap*-4)			LCMS: Anal. Calcd. for $C_{45}H_{48}N_{10}O_4$: 792; found: 793 $(M+H)^+$.
cj-11m (from cj-10c and *Cap*-51)	methyl ((1S)-2-methyl-1-(((2S)-2-(5-(4'-(2-((2S)-1-(N-(1-methyl-4,5-dihydro-1H-imidazol-2-yl)-D-valyl)-2-pyrrolidinyl)-1H-imidazol-5-yl)-4-biphenylyl)-1H-imidazol-2-yl)-1-pyrrolidinyl)carbonyl)propyl)carbamate		LCMS: Anal. Calcd. for $C_{42}H_{54}N_{10}O_4$: 762; found: 763 $(M+H)^+$.
cj-11n (from cj-10e and *Cap*-51)	methyl ((1S)-1-(((2S)-2-(5-(4'-(2-((2S)-1-(N-(4,5-dihydro-1H-imidazol-2-yl)-D-valyl)-2-pyrrolidinyl)-1H-imidazol-5-yl)-4-biphenylyl)-1H-imidazol-2-yl)-1-pyrrolidinyl)carb		LCMS: Anal. Calcd. for $C_{41}H_{52}N_{10}O_4$: 748; found: 749 $(M+H)^+$.

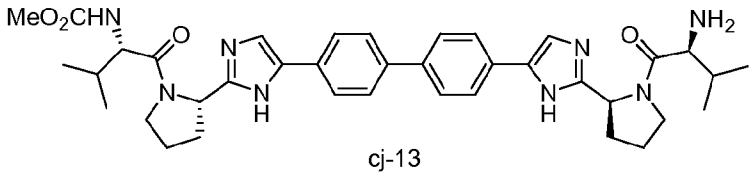
	onyl)-2-methylpropyl)carbamate		
cj-11o (from cj-10e and *Cap*-54b)	methyl ((1S)-1-cyclopropyl-2-((2S)-2-(5-(4'-(2-((2S)-1-(N-(4,5-dihydro-1H-imidazol-2-yl)-D-valyl)-2-pyrrolidinyl)-1H-imidazol-5-yl)-4-biphenylyl)-1H-imidazol-2-yl)-1-pyrrolidinyl)-2-oxoethyl)carbamate		LCMS: Anal. Calcd. for $C_{41}H_{50}N_{10}O_4$: 746; found: 747 $(M+H)^+$.
cj-11p (from cj-10e and *Cap*-2)	N-((1R)-1-(((2S)-2-(5-(4'-(2-((2S)-1-((2R)-2-(diethylamino)-2-phenylacetyl)-2-pyrrolidinyl)-1H-imidazol-5-yl)-4-biphenylyl)-1H-imidazol-2-yl)-1-pyrrolidinyl)carbonyl)-2-methylpropyl)-4,5-dihydro-1H-		LCMS: Anal. Calcd. for $C_{46}H_{56}N_{10}O_2$: 780; found: 781 $(M+H)^+$.

	imidazol-2-amine		

Example-cj-13



Preparation of Methyl (*S*)-1-((*S*)-2-(5-(4'-(2-((*S*)-1-((*S*)-2-amino-3-methylbutanoyl)pyrrolidin-2-yl)-1*H*-imidazol-5-yl)biphenyl-4-yl)-1*H*-imidazol-2-yl)pyrrolidin-1-yl)-3-methyl-1-oxobutan-2-ylcarbamate (cj-13)



cj-13

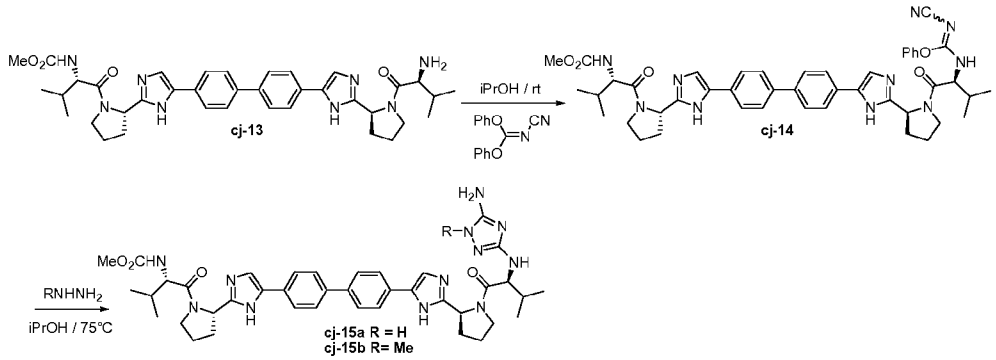
To a solution of methyl (*S*)-3-methyl-1-oxo-1-((*S*)-2-(5-(4'-(2-((*S*)-pyrrolidin-2-yl)-1*H*-imidazol-5-yl)biphenyl-4-yl)-1*H*-imidazol-2-yl)pyrrolidin-1-yl)butan-2-ylcarbamate (cj-12) (1.16 g, 1.99 mmol), Z-Val-OH (0.712 g, 2.83 mmol) and iPr_2NEt (0.70 mL, 5.42 mmol) in DMF (40 mL) was added HATU (1.10 g, 2.89 mmol) portionwise. The mixture was allowed to stir at room temperature for 1 h and was then poured into ice-water (400 mL) and allowed to stand for 20 min. The mixture was filtered and the solid washed with cold water and allowed to air dry overnight to give the Z-protected intermediate. LCMS: Anal. Calcd. for $C_{46}H_{54}N_8O_6$: 814; found: 815 $(M+H)^+$.

The obtained solid was dissolved in MeOH (80 mL), 10% Pd-C (1.0 g) was added and the mixture was hydrogenated at room temperature and atmospheric pressure for 3 h. The mixture was then filtered and the filtrate concentrated *in vacuo*. The resulting residue was purified by flash chromatography (SiO_2/ 5-20% MeOH-CH_2Cl_2) to afford the title compound (1.05 g, 77%) as a colorless foam. ^{1}HNMR (400 MHz, DMSO-d_6) δ 11.75 (s, 1H), 7.75 – 7.79 (m, 3H), 7.61 – 7.67 (m, 5H), 7.49 (s, 1H), 7.26 – 7.28 (m, 1H), 5.05 – 5.09 (m, 2H), 4.03 – 4.09 (m, 2H), 3.77 –

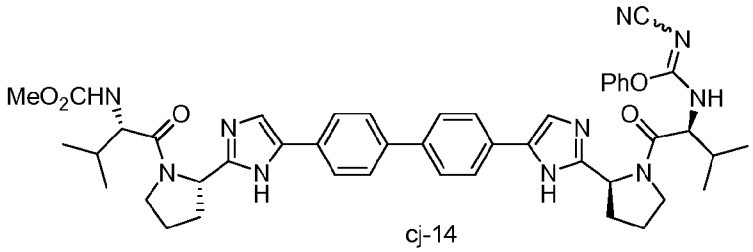
3.80 (m, 1H), 3.66 – 3.70 (m, 1H), 3.52 (s, 3H), 3.40 – 3.47 (m, 2H), 2.21 – 2.26 (m, 1H), 2.10 – 2.17 (m, 3H), 1.81 – 2.02 (m, 6H), 0.77 – 0.92 (m, 12H).

LCMS: Anal. Calcd. for $C_{38}H_{48}N_8O_4$: 680; found: 681 $(M+H)^+$.

Example cj-15



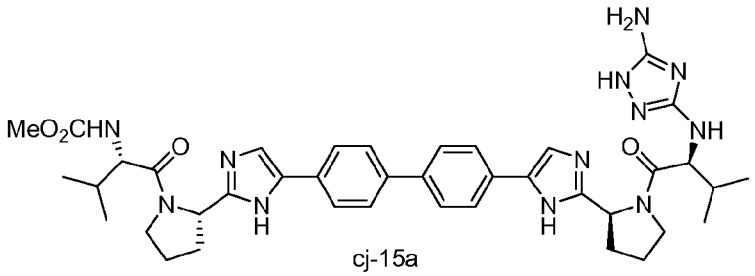
Preparation of Methyl (*S*)-1-((*S*)-2-(5-(4'-(2-((*S*)-1-((*S*)-2-((*Z/E*)-(cyanoimino)(phenoxy)methylamino)-3-methylbutanoyl)pyrrolidin-2-yl)-1*H*-imidazol-5-yl)biphenyl-4-yl)-1*H*-imidazol-2-yl)pyrrolidin-1-yl)-3-methyl-1-oxobutan-2-ylcarbamate (cj-14)



A mixture of methyl (*S*)-1-((*S*)-2-(5-(4'-(2-((*S*)-1-((*S*)-2-amino-3-methylbutanoyl)pyrrolidin-2-yl)-1*H*-imidazol-5-yl)biphenyl-4-yl)-1*H*-imidazol-2-yl)pyrrolidin-1-yl)-3-methyl-1-oxobutan-2-ylcarbamate (cj-13) (0.329 g, 0.527 mmol) and diphenyl cyanocarbonimidate (0.128 g, 0.537 mmol) in iPrOH (10 mL) was stirred at room temperature for 12 h. The resulting solid was filtered and air-dried to give the title compound (0.187 g, 43%) as a cream-colored solid. This material was used as such in the next step without further purification.

LCMS: Anal. Calcd. for $C_{46}H_{52}N_{10}O_5$: 824; found: 825 $(M+H)^+$.

Preparation of *methyl ((1S)-1-(((2S)-2-(5-(4'-(2-((2S)-1-(N-(5-amino-1-methyl-1H-1,2,4-triazol-3-yl)-L-valyl)-2-pyrrolidinyl)-1H-imidazol-5-yl)-4-biphenylyl)-1H-imidazol-2-yl)-1-pyrrolidinyl)carbonyl)-2-methylpropyl)carbamate* (cj-15a, R=H)

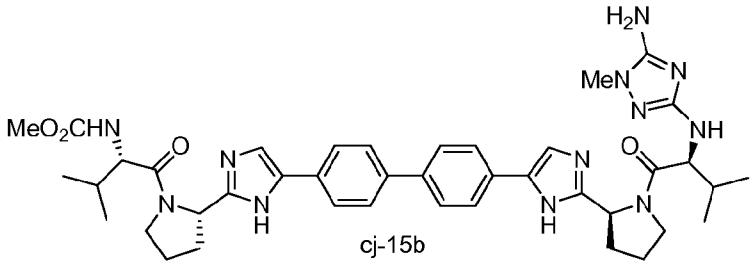


A solution of methyl (*S*)-1-((*S*)-2-(5-(4'-(2-((*S*)-1-((*S*)-2-((*Z/E*)-(cyanoimino)(phenoxy)methylamino)-3-methylbutanoyl)pyrrolidin-2-yl)-1*H*-imidazol-5-yl)biphenyl-4-yl)-1*H*-imidazol-2-yl)pyrrolidin-1-yl)-3-methyl-1-oxobutan-2-ylcarbamate (cj-14) (0.074 g, 0.090 mmol) and hydrazine hydrate (0.05 mL, 0.88 mmol) in iPrOH (2 mL) was heated at 75°C for 7 h. The solvent was then removed *in vacuo* and the residue was purified by prep HPLC (Luna 5u C18/MeCN-H_2O-NH_4OAc) to give foam which was lyophilized from CH_3CN-H_2O to give the title compound (0.032 g, 46%) as a colorless solid.

^{1}HNMR (400 MHz, DMSO-d_6) δ 12.17 (s, 1H), 11.75 (m, 2H), 10.66 – 10.84 (m, 2H), 7.76 – 7.79 (m, 3H), 7.62 – 7.74 (m, 4H), 7.49 – 7.51 (m, 1H), 7.24 – 7.29 (m, 2H), 5.28 – 5.32 (m, 1H), 5.05 – 5.08 (m, 2H), 4.04 – 4.09 (m, 3H), 3.87 – 3.94 (m, 2H), 3.72 – 3.81 (m, 2H), 3.53 (s, 3H), 2.09 – 2.17 (m, 2H), 1.90 – 2.02 (m, 6H), 0.81 – 0.99 (m, 12H).

LCMS: Anal. Calcd. for $C_{40}H_{50}N_{12}O_4$: 762; found: 763 $(M+H)^+$.

Preparation of Methyl (*S*)-1-((*S*)-2-(5-(4'-(2-((*S*)-1-((*S*)-2-(5-amino-1-methyl-1*H*-1,2,4-triazol-3-ylamino)-3-methylbutanoyl)pyrrolidin-2-yl)-1*H*-imidazol-5-yl)biphenyl-4-yl)-1*H*-imidazol-2-yl)pyrrolidin-1-yl)-3-methyl-1-oxobutan-2-ylcarbamate (cj-15b, R= Me)



cj-15b

A solution of methyl (*S*)-1-((*S*)-2-(5-(4'-(2-((*S*)-1-((*S*)-2-((*Z/E*)-(cyanoimino)(phenoxy)methylamino)-3-methylbutanoyl)pyrrolidin-2-yl)-1*H*-imidazol-5-yl)biphenyl-4-yl)-1*H*-imidazol-2-yl)pyrrolidin-1-yl)-3-methyl-1-oxobutan-2-ylcarbamate (cj-14) (0.105 g, 0.128 mmol) and N-methylhydrazine (0.010 mL, 0.188 mmol) in iPrOH (2 mL) was heated at 75°C for 3 h. A second portion of N-methylhydrazine (0.010 mL, 0.188 mmol) was added and heating was continued for 7 h. The volatiles were then removed *in vacuo* and the residue was purified by prep HPLC (Luna 5u C18/MeCN-H_2O-NH_4OAc) to give a foam which was further purified by flash chromatography (SiO_2/0-20% MeOH-CH_2Cl_2). The resulting material was lyophilized from CH_3CN-H_2O to give the title compound (0.029 g, 29%) as a colorless solid.

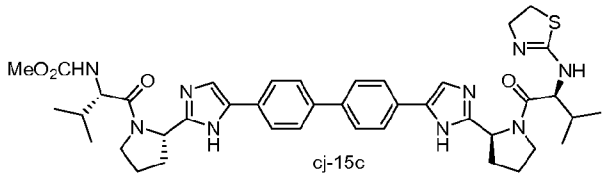
^{1}HNMR (400 MHz, DMSO-d_6) δ 13.79 (s, 0.4H), 12.19 (s, 1H), 11.76 (m, 1.6H), 7.77 – 7.85 (m, 4H), 7.62 – 7.71 (m, 4H), 7.49 – 7.51 (m, 1H), 7.24 – 7.29 (m, 1H), 6.31 (d, *J* = 9.1 Hz, 0.5H), 6.09 (d, *J* = 9.1 Hz, 1.5H), 5.87 (s, 1H), 5.34 – 5.36 (m, 1H), 5.04 – 5.08 (m, 2H), 4.89 (s, 1H), 4.75 (s, 2H), 3.53 (s, 3H), 2.10 – 2.17 (s, 3H), 1.94 – 2.02 (m, 6H), 0.81 – 0.98 (m, 12H).

LCMS: Anal. Calcd. for $C_{41}H_{52}N_{12}O_4$: 776; found: 777 $(M+H)^+$.

HRMS: Anal. Calcd. for $C_{41}H_{52}N_{12}O_4$: 776.4234; found: 777.4305 $(M+H)^+$.

Example cj-15c

methyl ((1S)-1-(((2S)-2-(5-(4'-(2-((2S)-1-(N-(4,5-dihydro-1,3-thiazol-2-yl)-L-valyl)-2-pyrrolidinyl)-1H-imidazol-5-yl)-4-biphenylyl)-1H-imidazol-2-yl)-1-pyrrolidinyl)carbonyl)-2-methylpropyl)carbamate

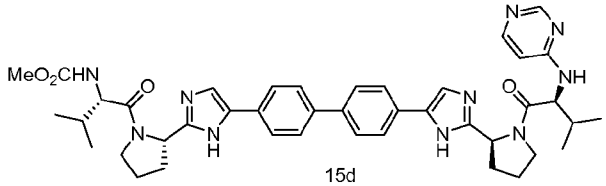


cj-15c

Example cj-15c was prepared by the condensation of Intermediate cj-13 with 2-(methylthio)-4,5-dihydrothiazole (Aldrich) using conditions analgous to those in the preparation of Intermediate cj-4. LCMS: Anal. Calcd. for $C_{41}H_{51}N_9O_4S$: 765; found: 766 $(M+H)^+$.

Example 15-d

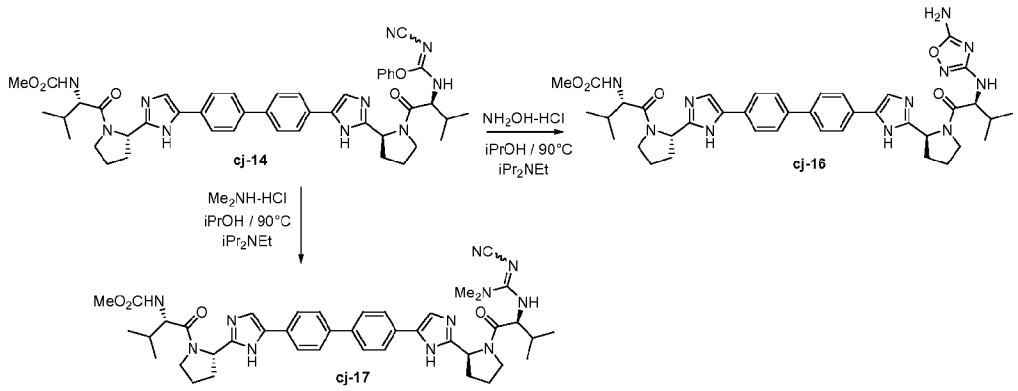
methyl ((1S)-2-methyl-1-(((2S)-2-(5-(4'-(2-((2S)-1-(N-4-pyrimidinyl-L-valyl)-2-pyrrolidinyl)-1H-imidazol-5-yl)-4-biphenylyl)-1H-imidazol-2-yl)-1-pyrrolidinyl)carbonyl)propyl)carbamate



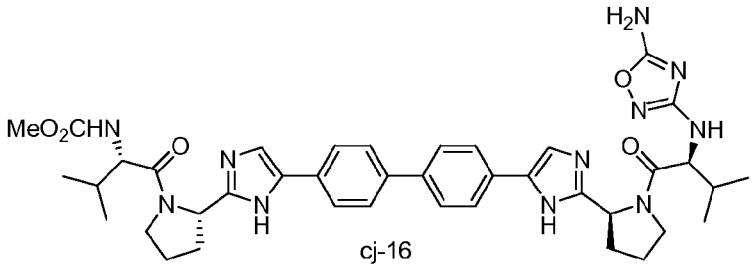
15d

Example cj-15d was prepared by the condensation of Intermediate cj-13 with 4,6-dichloropyrimidine (Aldrich) using conditions analgous to those in the preparation of Intermediate cj-4, followed by hydrogenation with 10% Pd-C. LCMS: Anal. Calcd. for $C_{42}H_{50}N_{10}O_4$: 758; found: 759 $(M+H)^+$.

Example cj-16 and cj-17



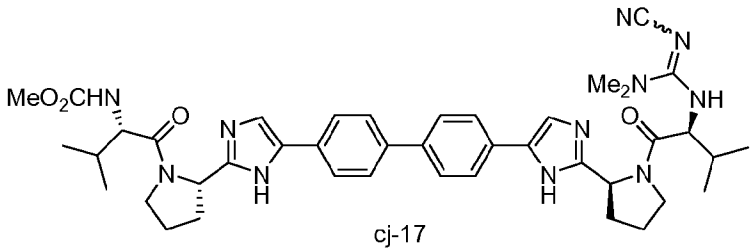
Preparation of methyl ((1S)-1-(((2S)-2-(5-(4'-(2-((2S)-1-(N-(5-amino-1,2,4-oxadiazol-3-yl)-L-valyl)-2-pyrrolidinyl)-1H-imidazol-5-yl)-4-biphenylyl)-1H-imidazol-2-yl)-1-pyrrolidinyl)carbonyl)-2-methylpropyl)carbamate (cj-16)



A solution of methyl (*S*)-1-((*S*)-2-(5-(4'-(2-((*S*)-1-((*S*)-2-((*Z/E*)-(cyanoimino)(phenoxy)methylamino)-3-methylbutanoyl)pyrrolidin-2-yl)-1*H*-imidazol-5-yl)biphenyl-4-yl)-1*H*-imidazol-2-yl)pyrrolidin-1-yl)-3-methyl-1-oxobutan-2-ylcarbamate (cj-14) (0.120 g, 0.205 mmol) and hydroxylamine hydrochloride (0.0213 g, 0.307 mmol) in iPrOH (5 mL) was heated at 75°C for 3 h. A second portion of hydroxylamine hydrochloride (0.0213 g, 0.307 mmol) was added and heating continued for 7 h. The volatiles were then removed *in vacuo* and the residue was purified by prep HPLC (Luna 5u C18/MeCN-H_2O-NH_4OAc) to give a foam which was further purified by flash chromatography (SiO_2/5% MeOH-CH_2Cl_2). The resulting colorless wax was lyophilized from CH_3CN-H_2O to give the title compound (0.0344 g, 22%) as a colorless solid.

^{1}HNMR (400 MHz, DMSO-d_6) δ 12.18 – 12.22 (m, 1H), 11.80 (s, 1H), 11.75 (s, 1h), 8.03 – 8.06 (m, 1H), 7.77 (app d, *J* = 8.1 Hz, 2H), 7.62 – 7.73 (m, 4H), 7.50 (dd, *J* = 2.0, 5.5 Hz, 1H), 7.24 – 7.29 (m, 2H), 5.69 (s, 1H), 5.06 – 5.11 (m, 2H), 4.14 (t, *J* = 8.6 Hz, 1H), 4.06 (unresolved dd, *J* = 8.0, 8.6Hz, 1H), 3.78 – 3.90 (m, 3H), 3.53 (s, 3H), 3.01 (br s, 2H), 2.10 – 2.19 (m, 3H), 1.90 – 2.04 (m, 5H), 0.81 – 0.96 (m, 12H). LCMS: Anal. Calcd. for $C_{40}H_{49}N_{11}O_5$: 763; found: 764 $(M+H)^+$.

Preparation of methyl ((1S)-1-(((2S)-2-(5-(4'-(2-((2S)-1-(N-(cyano(dimethyl)carbamimidoyl)-L-valyl)-2-pyrrolidinyl)-1H-imidazol-5-yl)-4-biphenylyl)-1H-imidazol-2-yl)-1-pyrrolidinyl)carbonyl)-2-methylpropyl)carbamate (cj-17)



cj-17

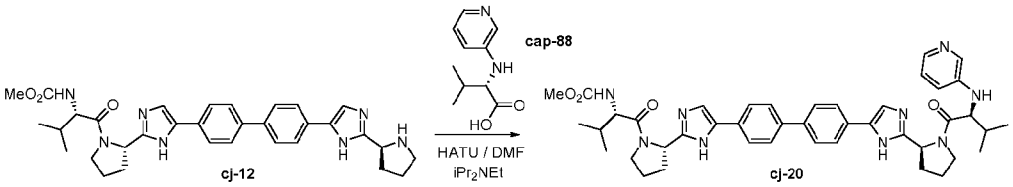
A solution of methyl (*S*)-1-((*S*)-2-(5-(4'-(2-((*S*)-1-((*S*)-2-((*Z*/*E*)-(cyanoimino)(phenoxy)methylamino)-3-methylbutanoyl)pyrrolidin-2-yl)-1*H*-imidazol-5-yl)biphenyl-4-yl)-1*H*-imidazol-2-yl)pyrrolidin-1-yl)-3-methyl-1-oxobutan-2-ylcarbamate (cj-14) (0.115 g, 0.198 mmol) and dimethylamine hydrochloride (0.0257 g, 0.315 mmol) in iPrOH (5 mL) was heated at 90°C for 12 h. A second portion of dimethylamine hydrochloride (0.0257 g, 0.315 mmol) was added and heating was continued for 48 h. The volatiles were then removed *in vacuo* and the residue was purified by prep HPLC (Luna 5u C18/MeCN-H_2O-NH_4OAc) and then repurified by flash chromatography (SiO_2/5% MeOH-CH_2Cl_2). The resulting colorless wax was lyophilized from CH_3CN-H_2O to give the title compound (0.0318 g, 21%) as a colorless solid.

^{1}HNMR (400 MHz, DMSO-d_6) δ 12.22 (m, 0.6H), 11.81 (s, 1H), 11.75 (s, 1H), 12.17 – 12.22 (m, 0.5H), 11.99 – 12.04 (m, 0.5H), 11.75-11.81 (m, 1H), 7.76 – 7.79 (m, 3H), 7.62 – 7.73 (m, 5H), 7.50 (t, *J* = 2.0 Hz, 1H), 7.23 – 7.29 (m, 1H), 6.64 (d, *J* =

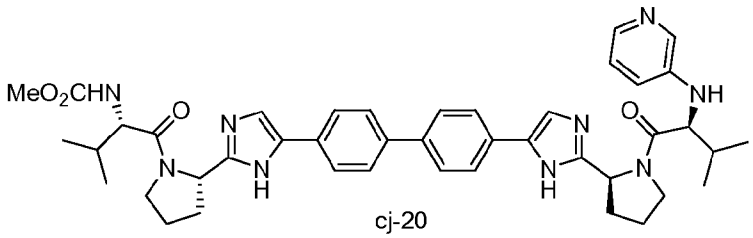
8.1 Hz, 1H), 5.06 – 5.08 (m, 2H), 4.47 (t, *J* = 8.1 Hz, 2H), 4.06 (unresolved dd, *J* = 8.0, 8.6 Hz, 1H), 3.84 – 3.90 (m, 2H), 3.76 – 3.82 (m, 3H), 3.53 (s, 3H), 3.00 (s, 6H), 2.11 – 2.20 (m, 3H), 1.90 – 2.04 (m, 5H), 0.97 (d, *J* = 6.5 Hz, 3H), 0.89 – 0.91 (m, 6H), 0.84 (d, *J* = 6.5 Hz, 3H).

LCMS: Anal. Calcd. for $C_{42}H_{53}N_{11}O_4$: 775; found: 776 $(M+H)^+$

Examplc cj-20



Preparation of methyl ((1S)-2-methyl-1-(((2S)-2-(5-(4'-(2-((2S)-1-(N-3-pyridinyl-L-valyl)-2-pyrrolidinyl)-1H-imidazol-5-yl)-4-biphenylyl)-1H-imidazol-2-yl)-1-pyrrolidinyl)carbonyl)propyl)carbamate (cj-20)



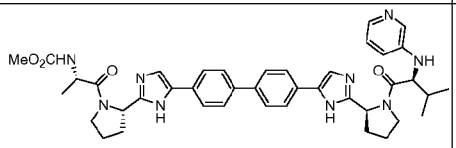
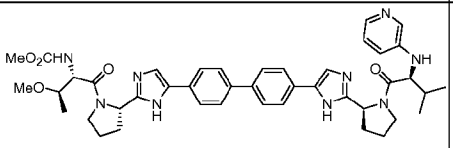
To a solution of methyl (*S*)-3-methyl-1-oxo-1-((*S*)-2-(5-(4'-(2-((*S*)-pyrrolidin-2-yl)-1*H*-imidazol-5-yl)biphenyl-4-yl)-1*H*-imidazol-2-yl)pyrrolidin-1-yl)butan-2-ylcarbamate (cj-13) (0.060 g, 0.103 mmol) in DMF (2 mL) was added iPr_2NEt (0.18 mL, 1.02 mmol), (*S*)-3-methyl-2-(pyridin-3-ylamino)butanoic acid (*Cap*-88) (0.040 g, 0.206 mmol) and HATU (0.078 g, 0.205 mmol). The reaction mixture was stirred for 1.5 h at room temperature and then it was directly purified by prep HPLC (Luna 5u C18/MeCN-H_2O-NH_4OAc). The resulting solid was repurified by flash chromatography (SiO_2/0-10% MeOH-CH_2Cl_2) and the obtained product was lyophilized from CH_3CN-H_2O to give the title compound (0.044 g, 56%) as a solid.

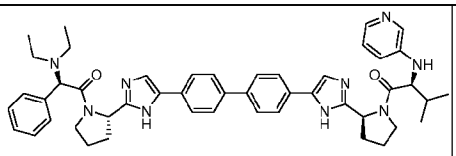
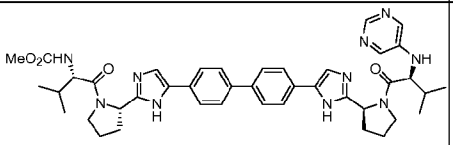
^{1}HNMR (400 MHz, DMSO-d_6) δ 12.19 (s, 1H), 11.76 (s, 1H), 8.07 (d, *J* = 2.6 Hz, 1H), 7.62 – 7.85 (m, 8H), 7.49 – 7.51 (m, 2H), 7.24 – 7.29 (m, 1H), 6.99 – 7.06 (m,

2H), 6.46 – 6.49 (m, 0.5H), 5.97 – 5.99 (m, 0.5H), 5.71 (d, *J* = 9.0 Hz, 1H), 5.55 (d, *J* = 10.6 Hz, 1H), 5.22 – 5.44 (m, 1H), 5.03 – 5.09 (m, 2H), 4.04 – 4.13 (m, 2H), 3.78 – 3.90 (m, 3H), 3.66 – 3.71 (m, 1H), 3.53 (s, 3H), 2.03 – 2.19 (m, 2H), 1.84 – 2.01 (m, 4H), 0.81 – 1.01 (m, 12H).

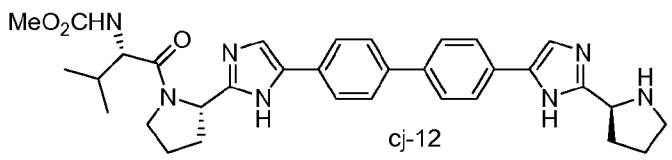
LCMS: Anal. Calcd. for $C_{43}H_{51}N_9O_4$: 757; found: 758 $(M+H)^+$.

Similarly, the following examples were prepared according to the representative method above;

Example	*Compound Name*	*Structure*	*LCMS*
cj-20a (from cj-22 and *Cap*-88)	methyl ((1S)-1-methyl-2-oxo-2-((2S)-2-(5-(4'-(2-((2S)-1-(N-3-pyridinyl-L-valyl)-2-pyrrolidinyl)-1H-imidazol-5-yl)-4-biphenylyl)-1H-imidazol-2-yl)-1-pyrrolidinyl)ethyl)carbamate		LCMS: Anal. Calcd. for $C_{41}H_{47}N_9O_4$: 729; found: 730 $(M+H)^+$.
cj-20b (from cj-23 and *Cap*-88)	methyl ((1S,2R)-2-methoxy-1-(((2S)-2-(5-(4'-(2-((2S)-1-(N-3-pyridinyl-L-valyl)-2-pyrrolidinyl)-1H-imidazol-5-yl)-4-biphenylyl)-1H-imidazol-2-yl)-1-pyrrolidinyl)carbonyl)propyl)carbamate		LCMS: Anal. Calcd. for $C_{43}H_{51}N_9O_5$: 773; found: 774 $(M+H)^+$.

cj-20c (from cj-24 and *Cap*-88)	N-((1S)-1-(((2S)-2-(5-(4'-(2-((2S)-1-((2R)-2-(diethylamino)-2-phenylacetyl)-2-pyrrolidinyl)-1H-imidazol-5-yl)-4-biphenylyl)-1H-imidazol-2-yl)-1-pyrrolidinyl)carbonyl)-2-methylpropyl)-3-pyridinamine		LCMS: Anal. Calcd. for $C_{48}H_{55}N_9O_2$: 789; found: 790 $(M+H)^+$.
cj-20d (from cj-12 and *Cap*-88)	methyl ((1S)-2-methyl-1-(((2S)-2-(5-(4'-(2-((2S)-1-(N-5-pyrimidinyl-L-valyl)-2-pyrrolidinyl)-1H-imidazol-5-yl)-4-biphenylyl)-1H-imidazol-2-yl)-1-pyrrolidinyl)carbonyl)propyl)carbamate		LCMS: Anal. Calcd. for $C_{42}H_{50}N_{10}O_4$: 758; found: 759 $(M+H)^+$.

Preparation of Methyl (*S*)-3-methyl-1-oxo-1-((*S*)-2-(5-(4'-(2-((*S*)-pyrrolidin-2-yl)-1*H*-imidazol-5-yl)biphenyl-4-yl)-1*H*-imidazol-2-yl)pyrrolidin-1-yl)butan-2-ylcarbamate (cj-12)



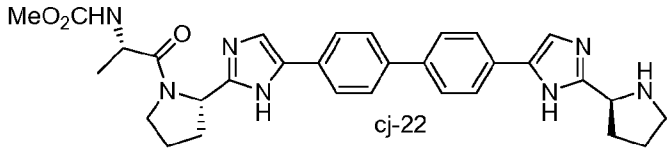
cj-12

Synthesized from Intermediate-28d and *Cap*-51 as in Example 28e, followed by Boc removal with TFA/CH_2Cl_2 and free base formation with MCX resin.

^{1}HNMR (400 MHz, MeOH-d_4) δ 7.79 – 7.82 (m, 3H), 7.65 – 7.75 (m, 5H), 7.48 (s, 1H), 7.32 (s, 1H), 5.19 (dd, *J* = 5.5, 5.7 Hz, 1H), 4.75 (t, *J* = 7.8 Hz, 1H), 4.25 (d, *J* = 7.3 Hz, 1H), 3.88 – 4.04 (m, 2H), 3.67 (s, 3H), 3.35 – 3.51 (m, 3H), 2.43 – 2.51 (m, 1H), 2.02-2.38 (m, 7H), 0.97 (d, *J* = 6.5 Hz, 3H), 0.92 (d, *J* = 6.9 Hz, 3H).

LCMS: Anal. Calcd. for $C_{33}H_{39}N_7O_3$: 581; found: 582 $(M+H)^+$.

Preparation of Methyl (*S*)-1-oxo-1-((*S*)-2-(5-(4'-(2-((*S*)-pyrrolidin-2-yl)-1*H*-imidazol-5-yl)biphenyl-4-yl)-1*H*-imidazol-2-yl)pyrrolidin-1-yl)propan-2-ylcarbamate (cj-22).



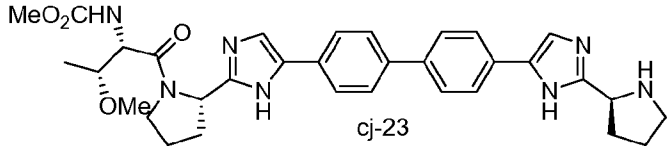
cj-22

Synthesized from Intermediate-28d and *Cap*-52 as in Example 28e, followed by Boc removal with TFA/CH_2Cl_2 and free base formation with MCX resin.

^{1}HNMR (400 MHz, MeOH-d_4) δ 7.68 – 7.79 (m, 4H), 7.59-7.65 (m, 4H), 7.44 (d, *J* = 6.6 Hz, 1H), 7.37 (s, 0.3H), 7.27 (s, 0.7H), 5.18 (dd, *J* = 4.0, 7.6 Hz, 1H), 4.74 (t, *J* = 8.0 Hz, 1H), 4.46 (dd, *J* = 6.8, 13.9 Hz, 1H), 3.84 (unresolved dd, *J* = 6.1, 6.5 Hz, 1H), 3.62 (s, 3H), 3.54 (s, 1H), 3.32 – 3.46 (m, 3H), 2.40 – 2.46 (m, 1H), 2.26 – 2.39 (m, 2H), 2.14 – 2.24 (m, 2H), 2.01 – 2.12 (m, 2H), 0.32 (d, *J* = 7.1 Hz, 3H).

LCMS: Anal. Calcd. for $C_{31}H_{35}N_7O_3$: 553; found: 554 $(M+H)^+$.

Preparation of Methyl (2*S*,3*R*)-3-methoxy-1-oxo-1-((*S*)-2-(5-(4'-(2-((*S*)-pyrrolidin-2-yl)-1*H*-imidazol-5-yl)biphenyl-4-yl)-1*H*-imidazol-2-yl)pyrrolidin-1-yl)butan-2-ylcarbamate (cj-23).



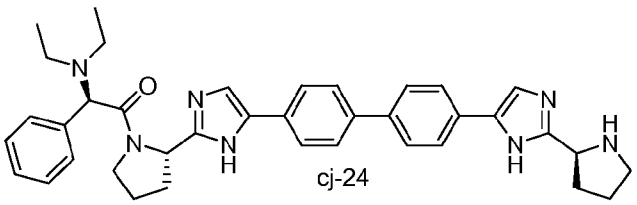
cj-23

Synthesized from Intermediate-28d and *Cap*-86 as in Example 28e, followed by Boc removal with TFA/CH_2Cl_2 and free base formation with MCX resin.

^{1}HNMR (400 MHz, MeOH-d_4) δ 7.72 (m, 4H), 7.64 -7.69 (m, 4H), 7.48 (d, J = 4.1 Hz, 1H), 7.38 (s, 0.3H), 7.33 (s, 0.7H), 5.51 – 5.54 (m, 0.2H), 5.22 (dd, J = 4.9, 7.6 Hz, 0.8H), 4.76 (t, J = 8.0 Hz, 1H), 4.48 (d, J = 5.1 Hz, 0.8H), 4.35 – 4.36 (m, 0.2H), 3.90 – 3.99 (m, 1H), 3.68 (s, 3H), 3.54 (s, 1H), 3.35 – 3.48 (m, 4H), 3.29 (s, 3H), 2.42 – 2.50 (m, 1H), 2.30 – 2.37 (m, 2H), 2.19 – 2.26 (m, 2H), 2.05 – 2.15 (m, 2H), 1.19 (d, J = 6.1 Hz, 3H).

LCMS: Anal. Calcd. for $C_{33}H_{39}N_7O_4$: 597; found: 598 $(M+H)^+$.

Preparation of (*R*)-2-(Diethylamino)-2-phenyl-1-((*S*)-2-(5-(4'-(2-((*S*)-pyrrolidin-2-yl)-1*H*-imidazol-5-yl)biphenyl-4-yl)-1*H*-imidazol-2-yl)pyrrolidin-1-yl)ethanone (cj-24).



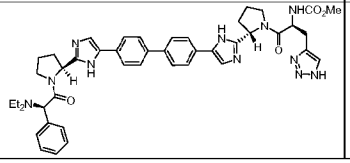
cj-24

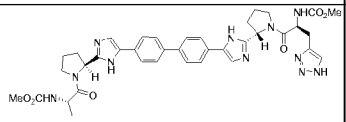
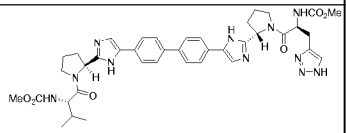
Synthesized from Intermediate-28d and *Cap*-2 as in Example 28e, followed by Boc removal with TFA/CH_2Cl_2 and free base formation with MCX resin.

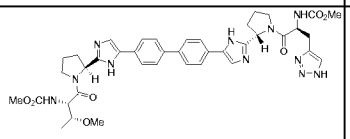
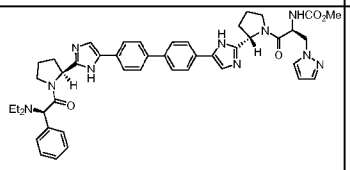
^{1}HNMR (400 MHz, MeOH-d_4) δ 7.59 – 7.82 (m, 10H), 7.36 – 7.51 (m, 4H), 7.01 – 7.15 (m, 1H), 5.09 – 5.13 (m, 2H), 4.77 (t, J = 8.5 Hz, 1H), 4.03 – 4.05 (m, 1H), 3.67 – 3.93 (m, 1H), 3.35 – 3.47 (m, 2H), 3.18 – 3.23 (m, 1H), 2.91-3.07 (m, 2H), 2.70 – 2.84 (m, 2H), 2.34 – 2.60 (m, 2H), 1.97 – 2.24 (m, 5H), 1.07 – 1.17 (m, 6H).

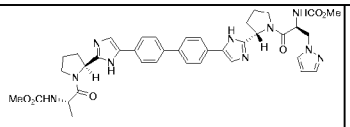
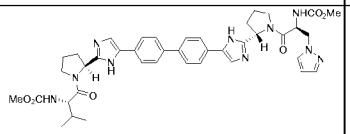
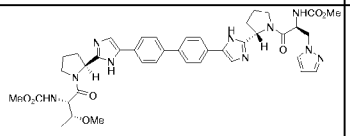
LCMS: Anal. Calcd. for $C_{38}H_{43}N_7O$: 613; found: 614 $(M+H)^+$.

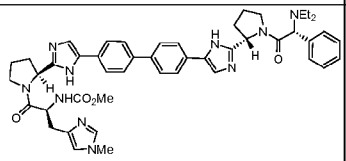
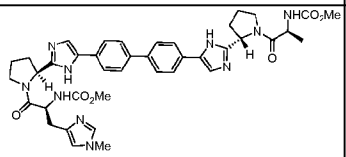
The following were prepared according to the procedure in example 28 starting with 28d. The caps are given in the table in the order they were appended to 28d. Where a cap number is not given the corresponding carboxylic acid is commercially available.

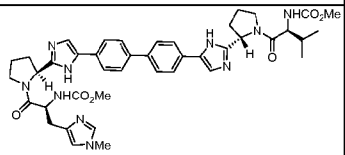
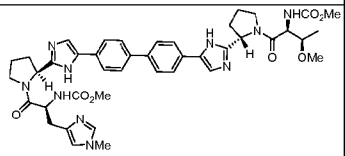
Example	*Compound Name*	*Structure*	*LCMS*	*Cap*
cj-32	methyl ((1S)-2-((2S)-2-(5-(4'-(2-((2S)-1-((2R)-2-		LCMS: Anal. Calcd. for $C_{45}H_{51}N_{11}O_4$:	2/128

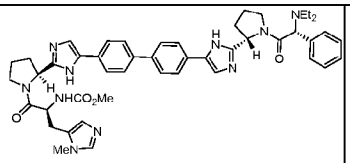
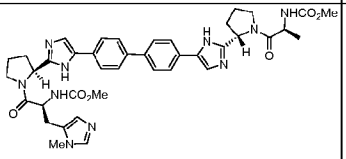
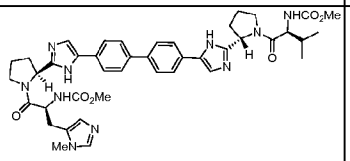
	(diethylamino)-2-phenylacetyl)-2-pyrrolidinyl)-1H-imidazol-5-yl)-4-biphenylyl)-1H-imidazol-2-yl)-1-pyrrolidinyl)-2-oxo-1-(1H-1,2,3-triazol-4-ylmethyl)ethyl)carbamate		809; found: 810 $(M+H)^+$.	
cj-33	methyl ((1S)-2-((2S)-2-(5-(4'-(2-((2S)-1-(N-(methoxycarbonyl)-L-alanyl)-2-pyrrolidinyl)-1H-imidazol-5-yl)-4-biphenylyl)-1H-imidazol-2-yl)-1-pyrrolidinyl)-2-oxo-1-(1H-1,2,3-triazol-4-ylmethyl)ethyl)carbamate		LCMS: Anal. Calcd. for $C_{38}H_{43}N_{11}O_6$: 749; found: 750 $(M+H)^+$.	52/128
cj-34	methyl ((1S)-1-(((2S)-2-(5-(4'-(2-((2S)-1-((2S)-2-((methoxycarbonyl)amino)-3-(1H-1,2,3-triazol-4-yl)propanoyl)-2-pyrrolidinyl)-1H-imidazol-5-yl)-4-biphenylyl)-1H-		LCMS: Anal. Calcd. for $C_{40}H_{47}N_{11}O_6$: 777; found: 777 $(M+H)^+$.	51/128

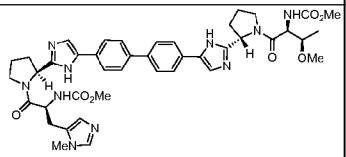
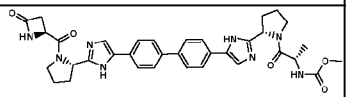
	imidazol-2-yl)-1-pyrrolidinyl)carbonyl)-2-methylpropyl)carbamate			
cj-35	methyl ((1S)-2-((2S)-2-(5-(4'-(2-((2S)-1-((2S,3R)-3-methoxy-2-((methoxycarbonyl)amino)butanoyl)-2-pyrrolidinyl)-1H-imidazol-5-yl)-4-biphenylyl)-1H-imidazol-2-yl)-1-pyrrolidinyl)-2-oxo-1-(1H-1,2,3-triazol-4-ylmethyl)ethyl)carbamate		LCMS: Anal. Calcd. for $C_{40}H_{47}N_{11}O_7$: 793; found: 794 $(M+H)^+$.	86/128
cj-36	methyl ((1S)-2-((2S)-2-(5-(4'-(2-((2S)-1-((2R)-2-(diethylamino)-2-phenylacetyl)-2-pyrrolidinyl)-1H-imidazol-5-yl)-4-biphenylyl)-1H-imidazol-2-yl)-1-pyrrolidinyl)-2-oxo-1-(1H-pyrazol-1-ylmethyl)ethyl)carbamate		LCMS: Anal. Calcd. for $C_{46}H_{52}N_{10}O_4$: 808; found: 809 $(M+H)^+$.	2/129

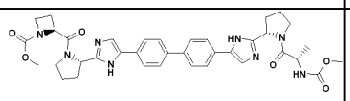
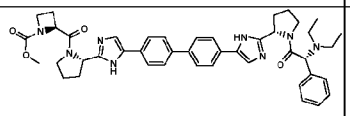
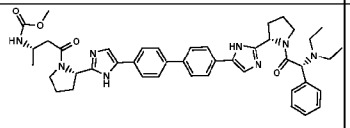
cj-37	methyl ((1S)-2-((2S)-2-(5-(4'-(2-((2S)-1-(N-(methoxycarbonyl)-L-alanyl)-2-pyrrolidinyl)-1H-imidazol-5-yl)-4-biphenylyl)-1H-imidazol-2-yl)-1-pyrrolidinyl)-2-oxo-1-(1H-pyrazol-1-ylmethyl)ethyl)carbamate		LCMS: Anal. Calcd. for C39H44N10O6: 748; found: 749 $(M+H)^+$.	52/129
cj-38	methyl ((1S)-1-(((2S)-2-(5-(4'-(2-((2S)-1-((2S)-2-((methoxycarbonyl)amino)-3-(1H-pyrazol-1-yl)propanoyl)-2-pyrrolidinyl)-1H-imidazol-5-yl)-4-biphenylyl)-1H-imidazol-2-yl)-1-pyrrolidinyl)carbonyl)-2-methylpropyl)carbamate		LCMS: Anal. Calcd. for $C_{40}H_{47}N_{11}O_7$: 776; found: 777 $(M+H)^+$.	51/129
cj-39	methyl ((1S)-2-((2S)-2-(5-(4'-(2-((2S)-1-(N-(methoxycarbonyl)-O-methyl-L-threonyl)-2-		LCMS: Anal. Calcd. for $C_{41}H_{48}N_{10}O_7$: 792; found: 793 $(M+H)^+$.	86/129

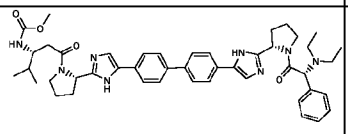
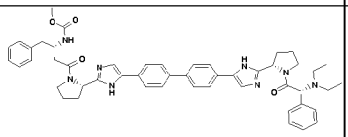
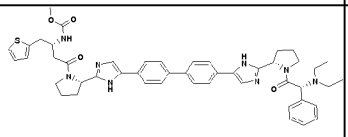
	pyrrolidinyl)-1H-imidazol-5-yl)-4-biphenylyl)-1H-imidazol-2-yl)-1-pyrrolidinyl)-2-oxo-1-(1H-pyrazol-1-ylmethyl)ethyl)carbamate			
cj-40	methyl ((1S)-2-((2S)-2-(5-(4'-(2-((2S)-1-((2R)-2-(diethylamino)-2-phenylacetyl)-2-pyrrolidinyl)-1H-imidazol-5-yl)-4-biphenylyl)-1H-imidazol-2-yl)-1-pyrrolidinyl)-1-((1-methyl-1H-imidazol-4-yl)methyl)-2-oxoethyl)carbamate		LCMS: Anal. Calcd. for $C_{47}H_{54}N_{10}O_4$: 822; found: 823 $(M+H)^+$.	2/127
cj-41	methyl ((1S)-2-((2S)-2-(5-(4'-(2-((2S)-1-(N-(methoxycarbonyl)-L-alanyl)-2-pyrrolidinyl)-1H-imidazol-5-yl)-4-biphenylyl)-1H-imidazol-2-yl)-1-pyrrolidinyl)-1-((1-methyl-1H-imidazol-4-		LCMS: Anal. Calcd. for $C_{40}H_{46}N_{10}O_6$: 762; found: 763 $(M+H)^+$.	52/127

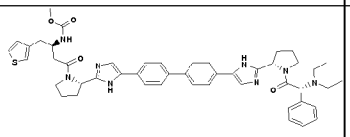
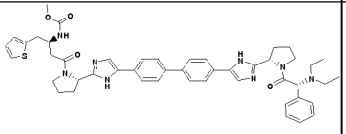
	yl)methyl)-2-oxoethyl)carbamate			
cj-42	methyl ((1S)-1-(((2S)-2-(5-(4'-(2-((2S)-1-((2S)-2-((methoxycarbonyl)amino)-3-(1-methyl-1H-imidazol-4-yl)propanoyl)-2-pyrrolidinyl)-1H-imidazol-5-yl)-4-biphenylyl)-1H-imidazol-2-yl)-1-pyrrolidinyl)carbonyl)-2-methylpropyl)carbamate		LCMS: Anal. Calcd. for $C_{42}H_{50}N_{10}O_6$ 790; found: 791 $(M+H)^+$.	51/127
cj-43	methyl ((1S)-2-((2S)-2-(5-(4'-(2-((2S)-1-((2S,3R)-3-methoxy-2-((methoxycarbonyl)amino)butanoyl)-2-pyrrolidinyl)-1H-imidazol-5-yl)-4-biphenylyl)-1H-imidazol-2-yl)-1-pyrrolidinyl)-1-((1-methyl-1H-imidazol-4-yl)methyl)-2-oxoethyl)carbamate		LCMS: Anal. Calcd. for $C_{42}H_{50}N_{10}O_7$ 806; found: 806 $(M+H)^+$.	86/127

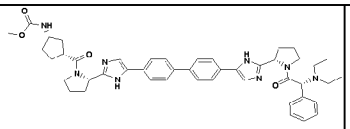
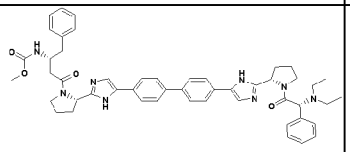
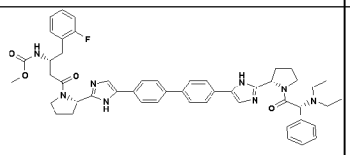
cj-44	methyl ((1S)-2-((2S)-2-(5-(4'-(2-((2S)-1-((2R)-2-(diethylamino)-2-phenylacetyl)-2-pyrrolidinyl)-1H-imidazol-5-yl)-4-biphenylyl)-1H-imidazol-2-yl)-1-pyrrolidinyl)-1-((1-methyl-1H-imidazol-5-yl)methyl)-2-oxoethyl)carbamate		LCMS: Anal. Calcd. for $C_{47}H_{54}N_{10}O_4$ 822; found: 823 $(M+H)^+$.	2/126
cj-45	methyl ((1S)-2-((2S)-2-(5-(4'-(2-((2S)-1-(N-(methoxycarbonyl)-L-alanyl)-2-pyrrolidinyl)-1H-imidazol-5-yl)-4-biphenylyl)-1H-imidazol-2-yl)-1-pyrrolidinyl)-1-((1-methyl-1H-imidazol-5-yl)methyl)-2-oxoethyl)carbamate		LCMS: Anal. Calcd. for $C_{40}H_{46}N_{10}O_6$: 762; found: 763 $(M+H)^+$.	52/126
cj-46	methyl ((1S)-1-(((2S)-2-(5-(4'-(2-((2S)-1-((2S)-2-((methoxycarbonyl)amino)-3-(1-methyl-1H-imidazol-5-		LCMS: Anal. Calcd. for $C_{42}H_{50}N_{10}O_6$ 790; found: 791	51/126

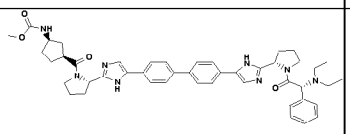
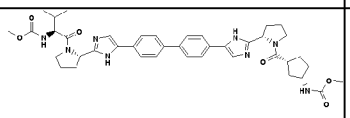
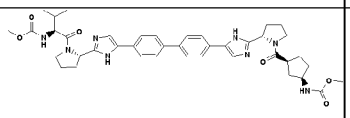
	yl)propanoyl)-2-pyrrolidinyl)-1H-imidazol-5-yl)-4-biphenylyl)-1H-imidazol-2-yl)-1-pyrrolidinyl)carbonyl)-2-methylpropyl)carbamate			
cj-47	methyl ((1S)-2-((2S)-2-(5-(4'-(2-((2S)-1-((2S,3R)-3-methoxy-2-((methoxycarbonyl)amino)butanoyl)-2-pyrrolidinyl)-1H-imidazol-5-yl)-4-biphenylyl)-1H-imidazol-2-yl)-1-pyrrolidinyl)-1-((1-methyl-1H-imidazol-5-yl)methyl)-2-oxoethyl)carbamate		LCMS: Anal. Calcd. for $C_{42}H_{50}N_{10}O_7$ 806; found: 807 $(M+H)^+$.	86/126
cj-48	methyl ((1S)-1-methyl-2-oxo-2-((2S)-2-(5-(4'-(2-((2S)-1-(((2S)-4-oxo-2-azetidinyl)carbonyl)-2-pyrrolidinyl)-1H-imidazol-5-yl)-4-biphenylyl)-1H-imidazol-2-yl)-1-pyrrolidinyl)ethyl)c		LCMS: Anal. Calcd. for $C_{35}H_{38}N_8O_5$ 650; found: 651 $(M+H)^+$.	52/-

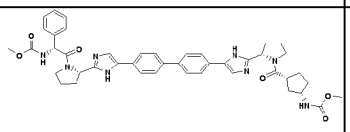
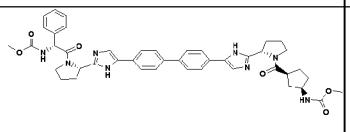
	arbamate			
cj-49	methyl (2S)-2-(((2S)-2-(5-(4'-(2-((2S)-1-(N-(methoxycarbonyl)-L-alanyl)-2-pyrrolidinyl)-1H-imidazol-5-yl)-4-biphenylyl)-1H-imidazol-2-yl)-1-pyrrolidinyl)carbonyl)-1-azetidinecarboxylate		LCMS: Anal. Calcd. for $C_{37}H_{42}N_8O_6$ 694; found: 695 $(M+H)^+$.	52/114
cj-50	methyl (2S)-2-(((2S)-2-(5-(4'-(2-((2S)-1-((2R)-2-(diethylamino)-2-phenylacetyl)-2-pyrrolidinyl)-1H-imidazol-5-yl)-4-biphenylyl)-1H-imidazol-2-yl)-1-pyrrolidinyl)carbonyl)-1-azetidinecarboxylate		LCMS: Anal. Calcd. for $C_{44}H_{50}N_8O_4$ 754; found: 755 $(M+H)^+$.	2/114
cj-51	methyl ((1S)-3-((2S)-2-(5-(4'-(2-((2S)-1-((2R)-2-(diethylamino)-2-phenylacetyl)-2-pyrrolidinyl)-1H-imidazol-5-yl)-4-biphenylyl)-1H-		LCMS: Anal. Calcd. for $C_{44}H_{52}N_8O_4$ 756; found: 757 $(M+H)^+$.	2/115

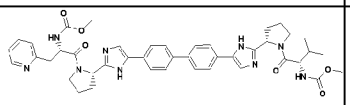
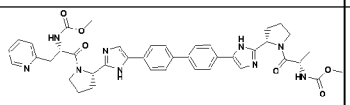
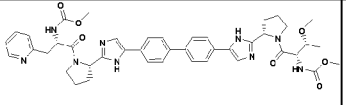
	imidazol-2-yl)-1-pyrrolidinyl)-1-methyl-3-oxopropyl)carbamate			
cj-52	methyl ((1R)-3-((2S)-2-(5-(4'-(2-((2S)-1-((2R)-2-(diethylamino)-2-phenylacetyl)-2-pyrrolidinyl)-1H-imidazol-5-yl)-4-biphenylyl)-1H-imidazol-2-yl)-1-pyrrolidinyl)-1-isopropyl-3-oxopropyl)carbamate		LCMS: Anal. Calcd. for $C_{46}H_{56}N_8O_4$ 784; found: 785 $(M+H)^+$.	2/116
cj-53	methyl ((1S)-1-benzyl-3-((2S)-2-(5-(4'-(2-((2S)-1-((2R)-2-(diethylamino)-2-phenylacetyl)-2-pyrrolidinyl)-1H-imidazol-5-yl)-4-biphenylyl)-1H-imidazol-2-yl)-1-pyrrolidinyl)-3-oxopropyl)carbamate		LCMS: Anal. Calcd. for $C_{50}H_{56}N_8O_4$ 833; found: 834 $(M+H)^+$.	2/96
cj-54	methyl ((1R)-3-((2S)-2-(5-(4'-(2-((2S)-1-((2R)-2-(diethylamino)-2-		LCMS: Anal. Calcd. for $C_{48}H_{54}N_8O_4S$ 838; found:	2/119

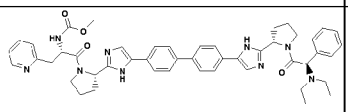
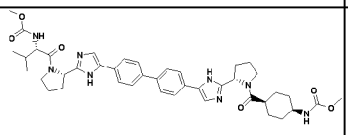
	phenylacetyl)-2-pyrrolidinyl)-1H-imidazol-5-yl)-4-biphenylyl)-1H-imidazol-2-yl)-1-pyrrolidinyl)-3-oxo-1-(2-thienylmethyl)propyl)carbamate		839 $(M+H)^+$.	
cj-55	methyl ((1R)-3-((2S)-2-(5-(4'-(2-((2S)-1-((2R)-2-(diethylamino)-2-phenylacetyl)-2-pyrrolidinyl)-1H-imidazol-5-yl)-4-biphenylyl)-1H-imidazol-2-yl)-1-pyrrolidinyl)-3-oxo-1-(3-thienylmethyl)propyl)carbamate		LCMS: Anal. Calcd. for $C_{48}H_{54}N_8O_4S$ 838; found: 839 $(M+H)^+$.	2/120
cj-56	methyl ((1S)-3-((2S)-2-(5-(4'-(2-((2S)-1-((2R)-2-(diethylamino)-2-phenylacetyl)-2-pyrrolidinyl)-1H-imidazol-5-yl)-4-biphenylyl)-1H-imidazol-2-yl)-1-pyrrolidinyl)-3-oxo-1-(2-thienylmethyl)propyl)carbamate		LCMS: Anal. Calcd. for $C_{48}H_{54}N_8O_4S$ 838; found: 839 $(M+H)^+$.	2/118

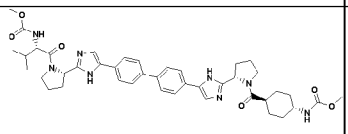
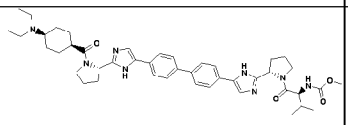
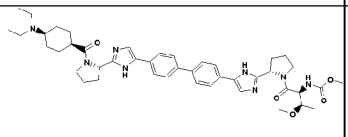
cj-57	methyl ((1S,3R)-3-(((2S)-2-(5-(4'-(2-((2S)-1-((2R)-2-(diethylamino)-2-phenylacetyl)-2-pyrrolidinyl)-1H-imidazol-5-yl)-4-biphenylyl)-1H-imidazol-2-yl)-1-pyrrolidinyl)carbonyl)cyclopentyl)carbamate		LCMS: Anal. Calcd. for $C_{46}H_{54}N_8O_4$ 782; found: 783 $(M+H)^+$.	2/99a
cj-58	methyl ((1R)-1-benzyl-3-((2S)-2-(5-(4'-(2-((2S)-1-((2R)-2-(diethylamino)-2-phenylacetyl)-2-pyrrolidinyl)-1H-imidazol-5-yl)-4-biphenylyl)-1H-imidazol-2-yl)-1-pyrrolidinyl)-3-oxopropyl)carbamate		LCMS: Anal. Calcd. for $C_{50}H_{56}N_8O_4$ 832; found: 833 $(M+H)^+$.	2/117
cj-59	methyl ((1R)-3-((2S)-2-(5-(4'-(2-((2S)-1-((2R)-2-(diethylamino)-2-phenylacetyl)-2-pyrrolidinyl)-1H-imidazol-5-yl)-4-biphenylyl)-1H-imidazol-2-yl)-1-pyrrolidinyl)-1-(2-		LCMS: Anal. Calcd. for $C_{50}H_{55}N_8O_4F$ 850; found: 851 $(M+H)^+$.	2/100

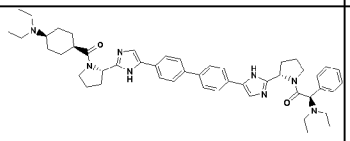
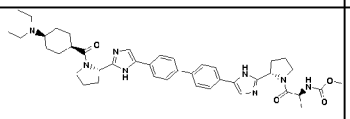
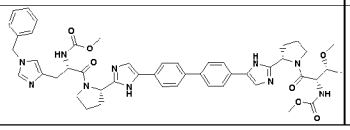
	fluorobenzyl)-3-oxopropyl)carbamate			
cj-60	methyl ((1R,3S)-3-(((2S)-2-(5-(4'-(2-((2S)-1-((2R)-2-(diethylamino)-2-phenylacetyl)-2-pyrrolidinyl)-1H-imidazol-5-yl)-4-biphenylyl)-1H-imidazol-2-yl)-1-pyrrolidinyl)carbonyl)cyclopentyl)carbamate		LCMS: Anal. Calcd. for $C_{46}H_{54}N_8O_4$ 782; found: 783 $(M+H)^+$.	2/99
cj-61	methyl ((1S)-1-(((2S)-2-(5-(4'-(2-((2S)-1-(((1R,3S)-3-((methoxycarbonyl)amino)cyclopentyl)carbonyl)-2-pyrrolidinyl)-1H-imidazol-5-yl)-4-biphenylyl)-1H-imidazol-2-yl)-1-pyrrolidinyl)carbonyl)-2-methylpropyl)carbamate		LCMS: Anal. Calcd. for $C_{41}H_{50}N_8O_6$ 750; found: 751 $(M+H)^+$.	52/99a
cj-62	methyl ((1S)-1-(((2S)-2-(5-(4'-(2-((2S)-1-(((1S,3R)-3-((methoxycarbonyl)		LCMS: Anal. Calcd. for $C_{41}H_{50}N_8O_6$ 750; found: 751 $(M+H)^+$.	52/99

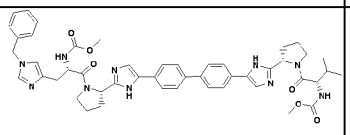
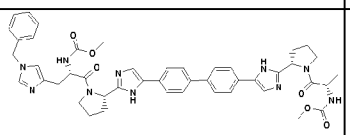
	amino)cyclopentyl) carbonyl)-2-pyrrolidinyl)-1H-imidazol-5-yl)-4-biphenylyl)-1H-imidazol-2-yl)-1-pyrrolidinyl)carbonyl)-2-methylpropyl)carbamate			
cj-63	methyl ((1R)-2-((2S)-2-(5-(4'-(2-((2S)-1-(((1R,3S)-3-((methoxycarbonyl) amino)cyclopentyl) carbonyl)-2-pyrrolidinyl)-1H-imidazol-5-yl)-4-biphenylyl)-1H-imidazol-2-yl)-1-pyrrolidinyl)-2-oxo-1-phenylethyl)carbamate		LCMS: Anal. Calcd. for $C_{44}H_{48}N_8O_6$ 784; found: 785 $(M+H)^+$.	4/99a
cj-64	methyl ((1R)-2-((2S)-2-(5-(4'-(2-((2S)-1-(((1S,3R)-3-((methoxycarbonyl) amino)cyclopentyl) carbonyl)-2-pyrrolidinyl)-1H-imidazol-5-yl)-4-biphenylyl)-1H-		LCMS: Anal. Calcd. for $C_{44}H_{48}N_8O_6$ 784; found: 785 $(M+H)^+$.	4/99

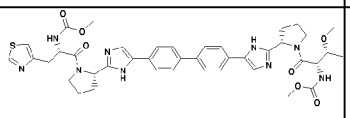
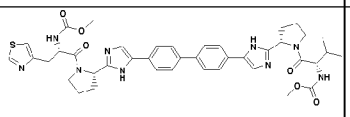
	imidazol-2-yl)-1-pyrrolidinyl)-2-oxo-1-phenylethyl)carbamate			
cj-65	methyl ((1S)-1-(((2S)-2-(5-(4'-(2-((2S)-1-((2S)-2-((methoxycarbonyl)amino)-3-(2-pyridinyl)propanoyl)-2-pyrrolidinyl)-1H-imidazol-5-yl)-4-biphenylyl)-1H-imidazol-2-yl)-1-pyrrolidinyl)carbonyl)-2-methylpropyl)carbamate		LCMS: Anal. Calcd. for $C_{43}H_{49}N_9O_6$ 787; found: 788 $(M+H)^+$.	51/93
cj-66	methyl ((1S)-2-((2S)-2-(5-(4'-(2-((2S)-1-(N-(methoxycarbonyl)-L-alanyl)-2-pyrrolidinyl)-1H-imidazol-5-yl)-4-biphenylyl)-1H-imidazol-2-yl)-1-pyrrolidinyl)-2-oxo-1-(2-pyridinylmethyl)ethyl)carbamate		LCMS: Anal. Calcd. for $C_{41}H_{45}N_9O_6$ 759; found: 760 $(M+H)^+$.	52/93
cj-67	methyl ((1S)-2-((2S)-2-(5-(4'-(2-((2S)-1-((2S,3R)-3-		LCMS: Anal. Calcd. for $C_{43}H_{49}N_9O_7$	86/93

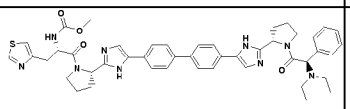
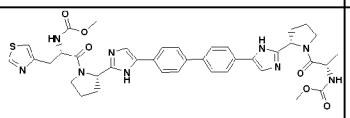
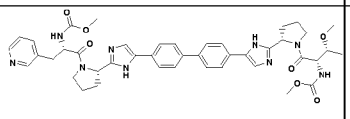
	methoxy-2-((methoxycarbonyl)amino)butanoyl)-2-pyrrolidinyl)-1H-imidazol-5-yl)-4-biphenylyl)-1H-imidazol-2-yl)-1-pyrrolidinyl)-2-oxo-1-(2-pyridinylmethyl)ethyl)carbamate		803; found: 804 $(M+H)^+$.	
cj-68	methyl ((1S)-2-((2S)-2-(5-(4'-(2-((2S)-1-((2R)-2-(diethylamino)-2-phenylacetyl)-2-pyrrolidinyl)-1H-imidazol-5-yl)-4-biphenylyl)-1H-imidazol-2-yl)-1-pyrrolidinyl)-2-oxo-1-(2-pyridinylmethyl)ethyl)carbamate		LCMS: Anal. Calcd. for $C_{48}H_{53}N_9O_4$ 819; found: 820 $(M+H)^+$.	2/93
cj-69	methyl ((1S)-1-(((2S)-2-(5-(4'-(2-((2S)-1-((cis-4-((methoxycarbonyl)amino)cyclohexyl)carbonyl)-2-pyrrolidinyl)-1H-imidazol-5-yl)-4-biphenylyl)-1H-imidazol-2-yl)-1-pyrrolidinyl)carbon		LCMS: Anal. Calcd. for $C_{42}H_{52}N_8O_6$ 764; found: 765 $(M+H)^+$.	51/104

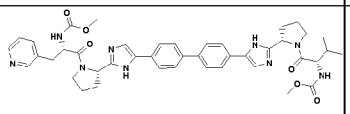
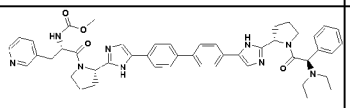
	yl)-2-methylpropyl)carbamate			
cj-70	methyl ((1S)-1-(((2S)-2-(5-(4'-(2-((2S)-1-((trans-4-((methoxycarbonyl)amino)cyclohexyl)carbonyl)-2-pyrrolidinyl)-1H-imidazol-5-yl)-4-biphenylyl)-1H-imidazol-2-yl)-1-pyrrolidinyl)carbonyl)-2-methylpropyl)carbamate		LCMS: Anal. Calcd. for $C_{42}H_{52}N_8O_6$ 764; found: 765 $(M+H)^+$.	51/105
cj-71	methyl ((1S)-1-(((2S)-2-(5-(4'-(2-((2S)-1-((cis-4-(diethylamino)cyclohexyl)carbonyl)-2-pyrrolidinyl)-1H-imidazol-5-yl)-4-biphenylyl)-1H-imidazol-2-yl)-1-pyrrolidinyl)carbonyl)-2-methylpropyl)carbamate		LCMS: Anal. Calcd. for $C_{44}H_{58}N_8O_4$ 762; found: 763 $(M+H)^+$.	51/106
cj-72	methyl ((1S,2R)-1-(((2S)-2-(5-(4'-(2-((2S)-1-((cis-4-(diethylamino)cyclohexyl)carbonyl)-		LCMS: Anal. Calcd. for $C_{44}H_{58}N_8O_5$ 778; found: 779 $(M+H)^+$.	86/106

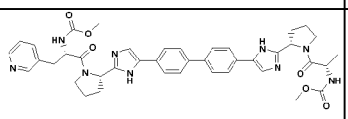
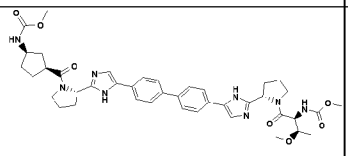
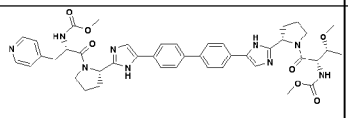
	2-pyrrolidinyl)-1H-imidazol-5-yl)-4-biphenylyl)-1H-imidazol-2-yl)-1-pyrrolidinyl)carbonyl)-2-methoxypropyl)carbamate			
cj-73	cis-4-(((2S)-2-(5-(4'-(2-((2S)-1-((2R)-2-(diethylamino)-2-phenylacetyl)-2-pyrrolidinyl)-1H-imidazol-5-yl)-4-biphenylyl)-1H-imidazol-2-yl)-1-pyrrolidinyl)carbonyl)-N,N-diethylcyclohexanamine		LCMS: Anal. Calcd. for $C_{49}H_{62}N_8O_2$ 794; found: 795 $(M+H)^+$.	2/106
cj-74	methyl ((1S)-2-((2S)-2-(5-(4'-(2-((2S)-1-((cis-4-(diethylamino)cyclohexyl)carbonyl)-2-pyrrolidinyl)-1H-imidazol-5-yl)-4-biphenylyl)-1H-imidazol-2-yl)-1-pyrrolidinyl)-1-methyl-2-oxoethyl)carbamate		LCMS: Anal. Calcd. for $C_{42}H_{54}N_8O_4$ 734; found: 735 $(M+H)^+$.	52/106
cj-75	methyl ((1S)-1-((1-benzyl-1H-		LCMS: Anal. Calcd. for	86/108

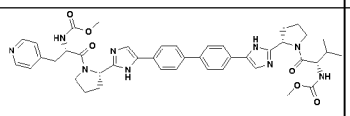
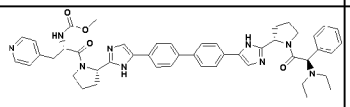
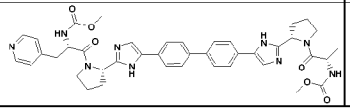
	imidazol-4-yl)methyl)-2-((2S)-2-(5-(4'-(2-((2S)-1-((2S,3R)-3-methoxy-2-((methoxycarbonyl)amino)butanoyl)-2-pyrrolidinyl)-1H-imidazol-5-yl)-4-biphenylyl)-1H-imidazol-2-yl)-1-pyrrolidinyl)-2-oxoethyl)carbamate		$C_{48}H_{54}N_{10}O_7$ 882; found: 883 $(M+H)^+$.	
cj-76	methyl ((1S)-1-(((2S)-2-(5-(4'-(2-((2S)-1-((2S)-3-(1-benzyl-1H-imidazol-4-yl)-2-((methoxycarbonyl)amino)propanoyl)-2-pyrrolidinyl)-1H-imidazol-5-yl)-4-biphenylyl)-1H-imidazol-2-yl)-1-pyrrolidinyl)carbonyl)-2-methylpropyl)carbamate		LCMS: Anal. Calcd. for $C_{48}H_{54}N_{10}O_6$ 866; found: 867 $(M+H)^+$.	51/108
cj-77	methyl ((1S)-2-((2S)-2-(5-(4'-(2-((2S)-1-((2S)-3-(1-benzyl-1H-imidazol-4-yl)-2-((methoxycarbonyl)amino)propanoyl)-		LCMS: Anal. Calcd. for $C_{46}H_{50}N_{10}O_6$ 838; found: 839 $(M+H)^+$.	52/108

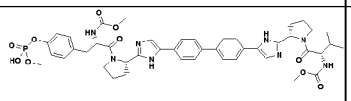
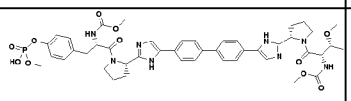
	2-pyrrolidinyl)-1H-imidazol-5-yl)-4-biphenylyl)-1H-imidazol-2-yl)-1-pyrrolidinyl)-1-methyl-2-oxoethyl)carbamate			
cj-78	methyl ((1S)-2-((2S)-2-(5-(4'-(2-((2S)-1-((2S,3R)-3-methoxy-2-((methoxycarbonyl)amino)butanoyl)-2-pyrrolidinyl)-1H-imidazol-5-yl)-4-biphenylyl)-1H-imidazol-2-yl)-1-pyrrolidinyl)-2-oxo-1-(1,3-thiazol-4-ylmethyl)ethyl)carbamate		LCMS: Anal. Calcd. for $C_{41}H_{47}N_9O_7S$ 809; found: 810 $(M+H)^+$.	86/107
cj-79	methyl ((1S)-1-(((2S)-2-(5-(4'-(2-((2S)-1-((2S)-2-((methoxycarbonyl)amino)-3-(1,3-thiazol-4-yl)propanoyl)-2-pyrrolidinyl)-1H-imidazol-5-yl)-4-biphenylyl)-1H-imidazol-2-yl)-1-pyrrolidinyl)carbonyl)-2-		LCMS: Anal. Calcd. for $C_{41}H_{47}N_9O_6S$ 793; found: 794 $(M+H)^+$.	51/107

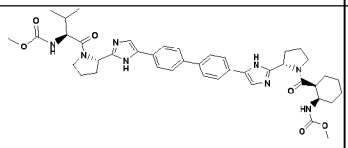
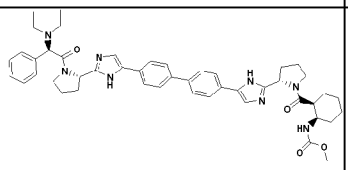
	methylpropyl)carbamate			
cj-80	methyl ((1S)-2-((2S)-2-(5-(4'-(2-((2S)-1-((2R)-2-(diethylamino)-2-phenylacetyl)-2-pyrrolidinyl)-1H-imidazol-5-yl)-4-biphenylyl)-1H-imidazol-2-yl)-1-pyrrolidinyl)-2-oxo-1-(1,3-thiazol-4-ylmethyl)ethyl)carbamate		LCMS: Anal. Calcd. for $C_{46}H_{51}N_9O_4S$ 825; found: 826 $(M+H)^+$.	2/107
cj-81	methyl ((1S)-2-((2S)-2-(5-(4'-(2-((2S)-1-(N-(methoxycarbonyl)-L-alanyl)-2-pyrrolidinyl)-1H-imidazol-5-yl)-4-biphenylyl)-1H-imidazol-2-yl)-1-pyrrolidinyl)-2-oxo-1-(1,3-thiazol-4-ylmethyl)ethyl)carbamate		LCMS: Anal. Calcd. for $C_{39}H_{43}N_9O_6S$ 765; found: 766 $(M+H)^+$.	51/107
cj-82	methyl ((1S)-2-((2S)-2-(5-(4'-(2-((2S)-1-((2S,3R)-3-methoxy-2-((methoxycarbonyl)		LCMS: Anal. Calcd. for $C_{43}H_{49}N_9O_7$ 803; found: 804$(M+H)^+$.	86/109

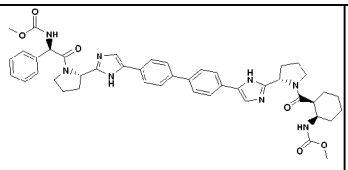
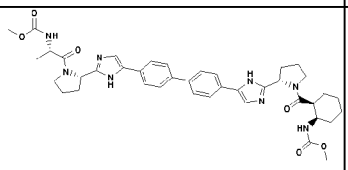
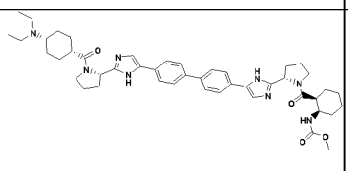
	amino)butanoyl)-2-pyrrolidinyl)-1H-imidazol-5-yl)-4-biphenylyl)-1H-imidazol-2-yl)-1-pyrrolidinyl)-2-oxo-1-(3-pyridinylmethyl)ethyl)carbamate			
cj-83	methyl ((1S)-2-((2S)-2-(5-(4'-(2-((2S)-1-((2S)-2-((methoxycarbonyl)amino)-3-methylbutanoyl)-2-pyrrolidinyl)-1H-imidazol-5-yl)-4-biphenylyl)-1H-imidazol-2-yl)-1-pyrrolidinyl)-2-oxo-1-(3-pyridinylmethyl)ethyl)carbamate		LCMS: Anal. Calcd. for $C_{43}H_{49}N_9O_6$ 787; found: 788 $(M+H)^+$.	51/109
cj-84	methyl ((1S)-2-((2S)-2-(5-(4'-(2-((2S)-1-((2R)-2-(diethylamino)-2-phenylacetyl)-2-pyrrolidinyl)-1H-imidazol-5-yl)-4-biphenylyl)-1H-imidazol-2-yl)-1-pyrrolidinyl)-2-oxo-1-(3-pyridinylmethyl)eth		LCMS: Anal. Calcd. for $C_{48}H_{53}N_9O_4$ 819; found: 820 $(M+H)^+$.	2/109

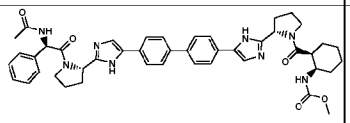
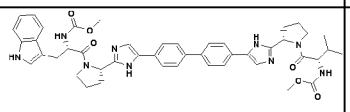
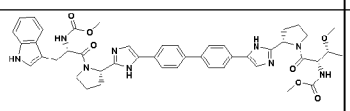
	yl)carbamate			
cj-85	methyl ((1S)-2-((2S)-2-(5-(4'-(2-((2S)-1-(N-(methoxycarbonyl)-L-alanyl)-2-pyrrolidinyl)-1H-imidazol-5-yl)-4-biphenylyl)-1H-imidazol-2-yl)-1-pyrrolidinyl)-2-oxo-1-(3-pyridinylmethyl)ethyl)carbamate		LCMS: Anal. Calcd. for $C_{41}H_{45}N_9O_6$ 759; found: 760 $(M+H)^+$.	52/109
cj-86	methyl ((1R,3S)-3-(((2S)-2-(5-(4'-(2-((2S)-1-((2S)-3-methoxy-2-((methoxycarbonyl)amino)butanoyl)-2-pyrrolidinyl)-1H-imidazol-5-yl)-4-biphenylyl)-1H-imidazol-2-yl)-1-pyrrolidinyl)carbonyl)cyclopentyl)carbamate		LCMS: Anal. Calcd. for $C_{42}H_{50}N_8O_7$ 766; found: 767 $(M+H)^+$.	86/99
cj-87	methyl ((1S)-2-((2S)-2-(5-(4'-(2-((2S)-1-((2S,3R)-3-methoxy-2-((methoxycarbonyl)amino)butanoyl)-2-pyrrolidinyl)-1H-imidazol-5-yl)-4-		LCMS: Anal. Calcd. for $C_{43}H_{49}N_9O_7$ 803; found: 804 $(M+H)^+$.	86/110

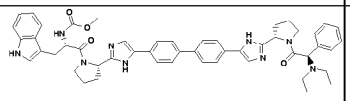
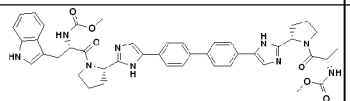
	biphenylyl)-1H-imidazol-2-yl)-1-pyrrolidinyl)-2-oxo-1-(4-pyridinylmethyl)ethyl)carbamate			
cj-88	methyl ((1S)-2-((2S)-2-(5-(4'-(2-((2S)-1-((2S)-2-((methoxycarbonyl)amino)-3-methylbutanoyl)-2-pyrrolidinyl)-1H-imidazol-5-yl)-4-biphenylyl)-1H-imidazol-2-yl)-1-pyrrolidinyl)-2-oxo-1-(4-pyridinylmethyl)ethyl)carbamate		LCMS: Anal. Calcd. for $C_{43}H_{49}N_9O_6$ 787; found: 788 $(M+H)^+$.	51/110
cj-89	methyl ((1S)-2-((2S)-2-(5-(4'-(2-((2S)-1-((2R)-2-(diethylamino)-2-phenylacetyl)-2-pyrrolidinyl)-1H-imidazol-5-yl)-4-biphenylyl)-1H-imidazol-2-yl)-1-pyrrolidinyl)-2-oxo-1-(4-pyridinylmethyl)ethyl)carbamate		LCMS: Anal. Calcd. for $C_{48}H_{53}N_9O_4$ 819; found: 820 $(M+H)^+$.	2/110
cj-90	methyl ((1S)-2-((2S)-2-(5-(4'-(2-		LCMS: Anal. Calcd. for	52/110

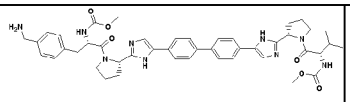
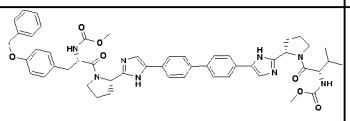
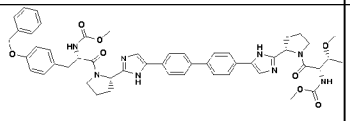
	((2S)-1-(N-(methoxycarbonyl)-L-alanyl)-2-pyrrolidinyl)-1H-imidazol-5-yl)-4-biphenylyl)-1H-imidazol-2-yl)-1-pyrrolidinyl)-2-oxo-1-(4-pyridinylmethyl)ethyl)carbamate		$C_{41}H_{45}N_9O_6$ 759; found: 760 $(M+H)^+$.	
cj-91	methyl ((1S)-1-(((2S)-2-(5-(4'-(2-((2S)-1-(O-(hydroxy(methoxy)phosphoryl)-N-(methoxycarbonyl)-L-tyrosyl)-2-pyrrolidinyl)-1H-imidazol-5-yl)-4-biphenylyl)-1H-imidazol-2-yl)-1-pyrrolidinyl)carbonyl)-2-methylpropyl)carbamate		LCMS: Anal. Calcd. for $C_{45}H_{53}N_8O_{10}P$ 896; found: 897 $(M+H)^+$.	51/111
cj-92	methyl ((1S,2R)-1-(((2S)-2-(5-(4'-(2-((2S)-1-(O-(hydroxy(methoxy)phosphoryl)-N-(methoxycarbonyl)-L-tyrosyl)-2-pyrrolidinyl)-1H-imidazol-5-yl)-4-		LCMS: Anal. Calcd. for $C_{45}H_{53}N_8O_{11}P$ 912; found: 913 $(M+H)^+$.	86/111

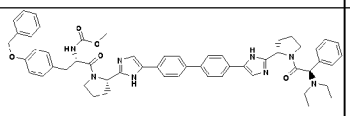
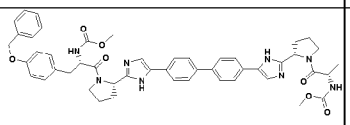
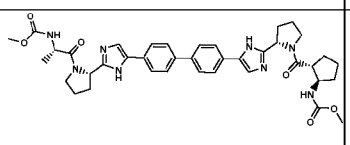
	biphenylyl)-1H-imidazol-2-yl)-1-pyrrolidinyl)carbonyl)-2-methoxypropyl)carbamate			
cj-93	methyl ((1S)-1-(((2S)-2-(5-(4'-(2-((2S)-1-(((1S,2R)-2-((methoxycarbonyl)amino)cyclohexyl)carbonyl)-2-pyrrolidinyl)-1H-imidazol-5-yl)-4-biphenylyl)-1H-imidazol-2-yl)-1-pyrrolidinyl)carbonyl)-2-methylpropyl)carbamate		LCMS: Anal. Calcd. for $C_{42}H_{52}N_8O_6$ 764; found: 765 $(M+H)^+$.	98/51
cj-94	methyl ((1R,2S)-2-(((2S)-2-(5-(4'-(2-((2S)-1-((2R)-2-(diethylamino)-2-phenylacetyl)-2-pyrrolidinyl)-1H-imidazol-5-yl)-4-biphenylyl)-1H-imidazol-2-yl)-1-pyrrolidinyl)carbonyl)cyclohexyl)carbamate		LCMS: Anal. Calcd. for $C_{47}H_{56}N_8O_4$ 796; found: 797 $(M+H)^+$.	98/2

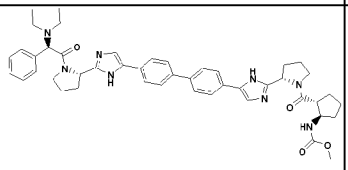
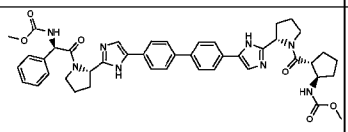
cj-95	methyl ((1R)-2-((2S)-2-(5-(4'-(2-((2S)-1-(((1S,2R)-2-((methoxycarbonyl)amino)cyclohexyl)carbonyl)-2-pyrrolidinyl)-1H-imidazol-5-yl)-4-biphenylyl)-1H-imidazol-2-yl)-1-pyrrolidinyl)-2-oxo-1-phenylethyl)carbamate		LCMS: Anal. Calcd. for $C_{45}H_{50}N_8O_6$ 798; found: 799 $(M+H)^+$.	98/4
cj-96	methyl ((1R,2S)-2-(((2S)-2-(5-(4'-(2-((2S)-1-(N-(methoxycarbonyl)-L-alanyl)-2-pyrrolidinyl)-1H-imidazol-5-yl)-4-biphenylyl)-1H-imidazol-2-yl)-1-pyrrolidinyl)carbonyl)cyclohexyl)carbamate		LCMS: Anal. Calcd. for $C_{40}H_{48}N_8O_6$ 736; found: 737 $(M+H)^+$.	98/51
cj-97	methyl ((1R,2S)-2-(((2S)-2-(5-(4'-(2-((2S)-1-((cis-4-(diethylamino)cyclohexyl)carbonyl)-2-pyrrolidinyl)-1H-imidazol-5-yl)-4-biphenylyl)-1H-		LCMS: Anal. Calcd. for $C_{46}H_{60}N_8O_4$ 788; found: 789 $(M+H)^+$.	98/106

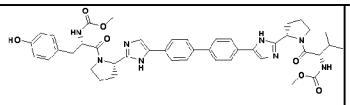
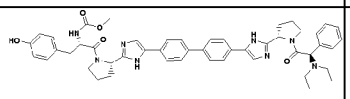
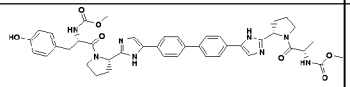
	imidazol-2-yl)-1-pyrrolidinyl)carbonyl)cyclohexyl)carbamate			
cj-98	methyl ((1R,2S)-2-(((2S)-2-(5-(4'-(2-((2S)-1-((2R)-2-acetamido-2-phenylacetyl)-2-pyrrolidinyl)-1H-imidazol-5-yl)-4-biphenylyl)-1H-imidazol-2-yl)-1-pyrrolidinyl)carbonyl)cyclohexyl)carbamate		LCMS: Anal. Calcd. for $C_{45}H_{50}N_8O_5$ 782; found: 783 $(M+H)^+$.	98/130
cj-99	methyl ((1S)-1-(((2S)-2-(5-(4'-(2-((2S)-1-((2S)-3-(1H-indol-3-yl)-2-((methoxycarbonyl)amino)propanoyl)-2-pyrrolidinyl)-1H-imidazol-5-yl)-4-biphenylyl)-1H-imidazol-2-yl)-1-pyrrolidinyl)carbonyl)-2-methylpropyl)carbamate		LCMS: Anal. Calcd. for $C_{56}H_{51}N_9O_6$ 825; found: 826 $(M+H)^+$.	51/112
cj-100	methyl ((1S)-1-(1H-indol-3-ylmethyl)-2-((2S)-2-(5-(4'-(2-((2S)-1-((2S,3R)-3-		LCMS: Anal. Calcd. for $C_{46}H_{51}N_9O_7$ 841; found: 842 $(M+H)^+$.	86/112

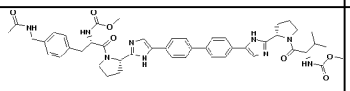
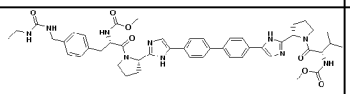
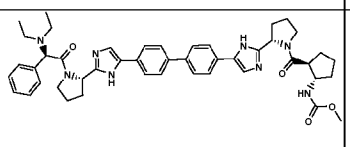
	methoxy-2-((methoxycarbonyl)amino)butanoyl)-2-pyrrolidinyl)-1H-imidazol-5-yl)-4-biphenylyl)-1H-imidazol-2-yl)-1-pyrrolidinyl)-2-oxoethyl)carbamate			
cj-101	methyl ((1S)-2-((2S)-2-(5-(4'-(2-((2S)-1-((2R)-2-(diethylamino)-2-phenylacetyl)-2-pyrrolidinyl)-1H-imidazol-5-yl)-4-biphenylyl)-1H-imidazol-2-yl)-1-pyrrolidinyl)-1-(1H-indol-3-ylmethyl)-2-oxoethyl)carbamate		LCMS: Anal. Calcd. for $C_{51}H_{55}N_9O_4$ 857; found: 858 $(M+H)^+$.	2/112
cj-102	methyl ((1S)-2-((2S)-2-(5-(4'-(2-((2S)-1-((2S)-3-(1H-indol-3-yl)-2-((methoxycarbonyl)amino)propanoyl)-2-pyrrolidinyl)-1H-imidazol-5-yl)-4-biphenylyl)-1H-imidazol-2-yl)-1-pyrrolidinyl)-1-methyl-2-oxoethyl)carbamate		LCMS: Anal. Calcd. for $C_{44}H_{47}N_9O_6$ 797; found: 798 $(M+H)^+$.	52/112

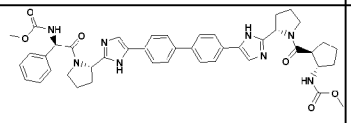
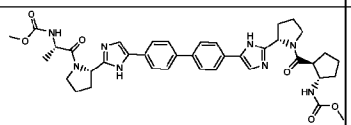
cj-103	methyl ((1S)-1-(4-(aminomethyl)benzyl)-2-((2S)-2-(5-(4'-(2-((2S)-1-((2S)-2-((methoxycarbonyl)amino)-3-methylbutanoyl)-2-pyrrolidinyl)-1H-imidazol-5-yl)-4-biphenylyl)-1H-imidazol-2-yl)-1-pyrrolidinyl)-2-oxoethyl)carbamate		LCMS: Anal. Calcd. for $C_{45}H_{53}N_9O_6$ 815; found: 816 $(M+H)^+$.	see text
cj-104	methyl ((1S)-1-(((2S)-2-(5-(4'-(2-((2S)-1-(O-benzyl-N-(methoxycarbonyl)-L-tyrosyl)-2-pyrrolidinyl)-1H-imidazol-5-yl)-4-biphenylyl)-1H-imidazol-2-yl)-1-pyrrolidinyl)carbonyl)-2-methylpropyl)carbamate		LCMS: Anal. Calcd. for $C_{51}H_{56}N_8O_7$ 892; found: 893 $(M+H)^+$.	51/113
cj-105	methyl ((1S,2R)-1-(((2S)-2-(5-(4'-(2-((2S)-1-(O-benzyl-N-(methoxycarbonyl)-L-tyrosyl)-2-pyrrolidinyl)-1H-imidazol-5-yl)-4-		LCMS: Anal. Calcd. for $C_{51}H_{56}N_8O_8$ 908; found: 909 $(M+H)^+$.	86/113

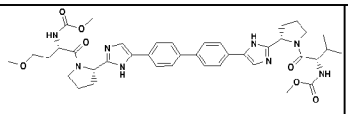
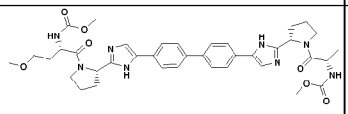
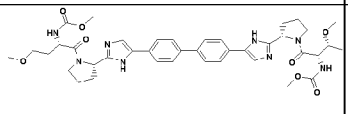
	biphenylyl)-1H-imidazol-2-yl)-1-pyrrolidinyl)carbonyl)-2-methoxypropyl)carbamate			
cj-106	methyl ((1S)-1-(4-(benzyloxy)benzyl)-2-((2S)-2-(5-(4'-(2-((2S)-1-((2R)-2-(diethylamino)-2-phenylacetyl)-2-pyrrolidinyl)-1H-imidazol-5-yl)-4-biphenylyl)-1H-imidazol-2-yl)-1-pyrrolidinyl)-2-oxoethyl)carbamate		LCMS: Anal. Calcd. for $C_{56}H_{60}N_8O_5$ 924; found: 925 $(M+H)^+$.	2/113
cj-107	methyl ((1S)-1-(4-(benzyloxy)benzyl)-2-((2S)-2-(5-(4'-(2-((2S)-1-(N-(methoxycarbonyl)-L-alanyl)-2-pyrrolidinyl)-1H-imidazol-5-yl)-4-biphenylyl)-1H-imidazol-2-yl)-1-pyrrolidinyl)-2-oxoethyl)carbamate		LCMS: Anal. Calcd. for $C_{49}H_{52}N_8O_7$ 864; found: 865 $(M+H)^+$.	52/113
cj-108	methyl ((1R,2R)-2-(((2S)-2-(5-(4'-(2-((2S)-1-(N-(methoxycarbonyl)-L-alanyl)-2-		LCMS: Anal. Calcd. for $C_{39}H_{46}N_8O_6$ 722; found: 723 $(M+H)^+$.	122/52

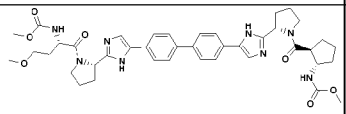
	pyrrolidinyl)-1H-imidazol-5-yl)-4-biphenylyl)-1H-imidazol-2-yl)-1-pyrrolidinyl)carbonyl)cyclopentyl)carbamate			
cj-109	methyl ((1R,2R)-2-(((2S)-2-(5-(4'-(2-((2S)-1-((2R)-2-(diethylamino)-2-phenylacetyl)-2-pyrrolidinyl)-1H-imidazol-5-yl)-4-biphenylyl)-1H-imidazol-2-yl)-1-pyrrolidinyl)carbonyl)cyclopentyl)carbamate		LCMS: Anal. Calcd. for $C_{46}H_{54}N_8O_4$ 782; found: 783 $(M+H)^+$.	122/2
cj-110	methyl ((1R)-2-((2S)-2-(5-(4'-(2-((2S)-1-(((1R,2R)-2-((methoxycarbonyl)amino)cyclopentyl)carbonyl)-2-pyrrolidinyl)-1H-imidazol-5-yl)-4-biphenylyl)-1H-imidazol-2-yl)-1-pyrrolidinyl)-2-oxo-1-phenylethyl)carbamate		LCMS: Anal. Calcd. for $C_{44}H_{48}N_8O_6$ 784; found: 785 $(M+H)^+$.	122/4

cj-111	methyl ((1S)-1-(4-hydroxybenzyl)-2-((2S)-2-(5-(4'-(2-((2S)-1-((2S)-2-((methoxycarbonyl)amino)-3-methylbutanoyl)-2-pyrrolidinyl)-1H-imidazol-5-yl)-4-biphenylyl)-1H-imidazol-2-yl)-1-pyrrolidinyl)-2-oxoethyl)carbamate		LCMS: Anal. Calcd. for $C_{44}H_{50}N_8O_7$ 802; found: 803 $(M+H)^+$.	see text
cj-112	methyl ((1S)-2-((2S)-2-(5-(4'-(2-((2S)-1-((2R)-2-(diethylamino)-2-phenylacetyl)-2-pyrrolidinyl)-1H-imidazol-5-yl)-4-biphenylyl)-1H-imidazol-2-yl)-1-pyrrolidinyl)-1-(4-hydroxybenzyl)-2-oxoethyl)carbamate		LCMS: Anal. Calcd. for $C_{49}H_{54}N_8O_5$ 834; found: 835 $(M+H)^+$.	see text
cj-113	methyl ((1S)-1-(4-hydroxybenzyl)-2-((2S)-2-(5-(4'-(2-((2S)-1-(N-(methoxycarbonyl)-L-alanyl)-2-pyrrolidinyl)-1H-imidazol-5-yl)-4-biphenylyl)-1H-imidazol-2-yl)-1-		LCMS: Anal. Calcd. for $C_{42}H_{46}N_8O_7$ 774; found: 775 $(M+H)^+$.	see text

	pyrrolidinyl)-2-oxoethyl)carbamate			
cj-114	methyl ((1S)-1-(4-(acetamidomethyl)benzyl)-2-((2S)-2-(5-(4'-(2-((2S)-1-((2S)-2-((methoxycarbonyl)amino)-3-methylbutanoyl)-2-pyrrolidinyl)-1H-imidazol-5-yl)-4-biphenylyl)-1H-imidazol-2-yl)-1-pyrrolidinyl)-2-oxoethyl)carbamate		LCMS: Anal. Calcd. for $C_{47}H_{55}N_9O_7$ 857; found: 585 $(M+H)^+$.	see text
cj-115	methyl ((1S)-1-(4-(((ethylcarbamoyl)amino)methyl)benzyl)-2-((2S)-2-(5-(4'-(2-((2S)-1-((2S)-2-((methoxycarbonyl)amino)-3-methylbutanoyl)-2-pyrrolidinyl)-1H-imidazol-5-yl)-4-biphenylyl)-1H-imidazol-2-yl)-1-pyrrolidinyl)-2-oxoethyl)carbamate		LCMS: Anal. Calcd. for $C_{48}H_{58}N_{10}O_7$ 886; found: 887 $(M+H)^+$.	see text
cj-116	methyl ((1S,2S)-2-(((2S)-2-(5-(4'-(2-((2S)-1-((2R)-2-(diethylamino)-2-phenylacetyl)-2-		LCMS: Anal. Calcd. for $C_{46}H_{54}N_8O_4$ 782; found: 783 $(M+H)^+$.	121/2

	pyrrolidinyl)-1H-imidazol-5-yl)-4-biphenylyl)-1H-imidazol-2-yl)-1-pyrrolidinyl)carbonyl)cyclopentyl)carbamate			
cj-117	methyl ((1R)-2-((2S)-2-(5-(4'-(2-((2S)-1-(((1S,2S)-2-((methoxycarbonyl)amino)cyclopentyl)carbonyl)-2-pyrrolidinyl)-1H-imidazol-5-yl)-4-biphenylyl)-1H-imidazol-2-yl)-1-pyrrolidinyl)-2-oxo-1-phenylethyl)carbamate		LCMS: Anal. Calcd. for $C_{44}H_{48}N_8O_6$ 784; found: 785 $(M+H)^+$.	121/4
cj-118	methyl ((1S,2S)-2-(((2S)-2-(5-(4'-(2-((2S)-1-(N-(methoxycarbonyl)-L-alanyl)-2-pyrrolidinyl)-1H-imidazol-5-yl)-4-biphenylyl)-1H-imidazol-2-yl)-1-pyrrolidinyl)carbonyl)cyclopentyl)carbamate		LCMS: Anal. Calcd. for $C_{39}H_{46}N_8O_6$ 722; found: 723 $(M+H)^+$.	121/52

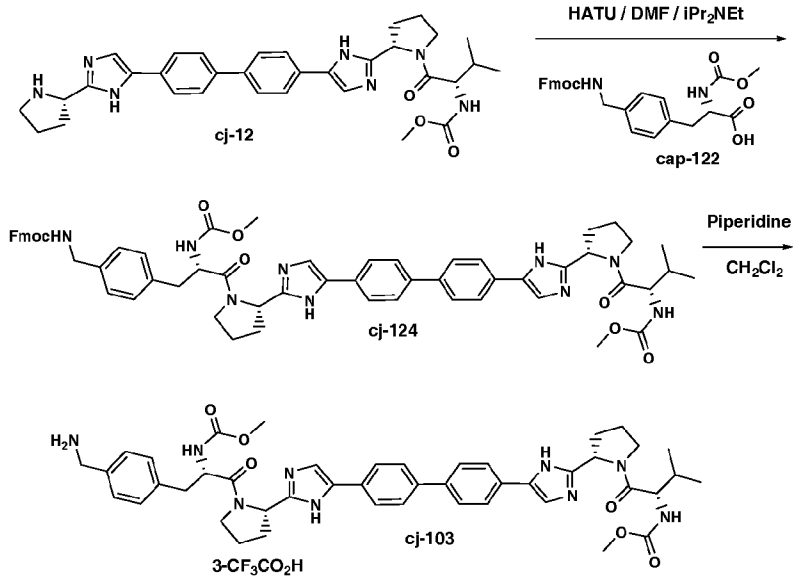
cj-119	methyl ((1S)-1-(((2S)-2-(5-(4'-(2-((2S)-1-(N-(methoxycarbonyl)-O-methyl-L-homoseryl)-2-pyrrolidinyl)-1H-imidazol-5-yl)-4-biphenylyl)-1H-imidazol-2-yl)-1-pyrrolidinyl)carbonyl)-2-methylpropyl)carbamate		LCMS: Anal. Calcd. for $C_{40}H_{50}N_8O_7$ 754; found: 755 $(M+H)^+$.	51/87
cj-120	methyl ((1S)-3-methoxy-1-(((2S)-2-(5-(4'-(2-((2S)-1-(N-(methoxycarbonyl)-L-alanyl)-2-pyrrolidinyl)-1H-imidazol-5-yl)-4-biphenylyl)-1H-imidazol-2-yl)-1-pyrrolidinyl)carbonyl)propyl)carbamate		LCMS: Anal. Calcd. for $C_{38}H_{46}N_8O_7$ 726; found: 727 $(M+H)^+$.	52/87
cj-121	methyl ((1S,2R)-2-methoxy-1-(((2S)-2-(5-(4'-(2-((2S)-1-(N-(methoxycarbonyl)-O-methyl-L-homoseryl)-2-pyrrolidinyl)-1H-		LCMS: Anal. Calcd. for $C_{40}H_{50}N_8O_8$ 770; found: 771 $(M+H)^+$.	86/87

	imidazol-5-yl)-4-biphenylyl)-1H-imidazol-2-yl)-1-pyrrolidinyl)carbonyl)propyl)carbamate			
cj-122	methyl ((1S,2S)-2-(((2S)-2-(5-(4'-(2-((2S)-1-(N-(methoxycarbonyl)-O-methyl-L-homoseryl)-2-pyrrolidinyl)-1H-imidazol-5-yl)-4-biphenylyl)-1H-imidazol-2-yl)-1-pyrrolidinyl)carbonyl)cyclopentyl)carbamate		LCMS: Anal. Calcd. for $C_{41}H_{50}N_8O_7$ 766; found: 767 $(M+H)^+$.	121/87

Examples cj-111 to cj-113.

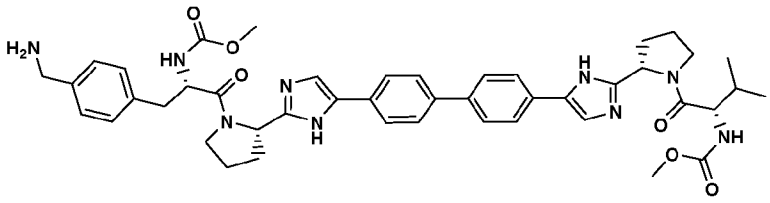
For Examples cj-111 to cj-113 the compounds of Examples cj-105 to cj-107 were hydrogenated under conditions analogous to those used in Example 28, step d (with the exception that K_2CO_3 was not employed).

Preparation of examples cj-103, cj-114 and cj-115.



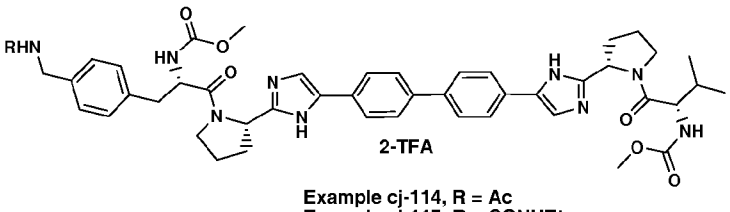
Intermediate cj-124 was prepared by coupling of intermediate cj-12 and *Cap*-122, as described in Example 28, step e. LCMS: Anal. Calcd. for $C_{60}H_{63}N_9O_8$ 1037; found: 520 $(1/2M+H)^+$. This corresponds to the doubly charged molecular ion.

Example cj-103.



Intermediate cj-124 (83.0 mg, 0.08 mmol) was dissolved in DMF (5 mL) and piperidine (1 mL) was added at room temperature. After 2h the volatiles were removed *in vacuo* and the residue was purified by preparative HPLC (YMC-Pack C-18, 30X100mm, CH_3CN-H_2O-TFA) to give the TFA salt of the amine (87.0 mg, 94%). LCMS: Anal. Calcd. for $C_{45}H_{53}N_9O_6$ 815; found: 816 $(M+H)^+$.

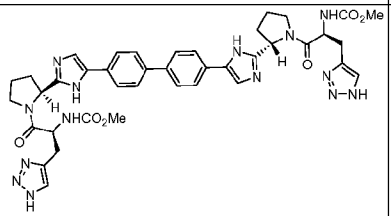
Examples cj-114 to cj-115.

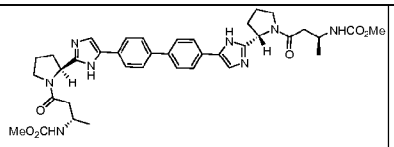
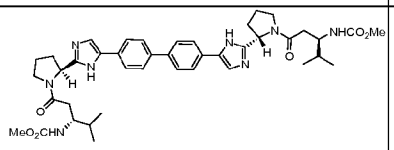
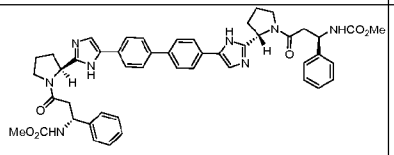
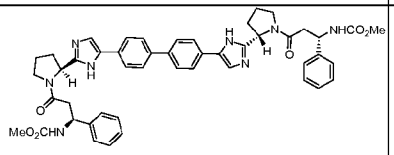


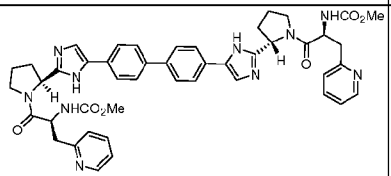
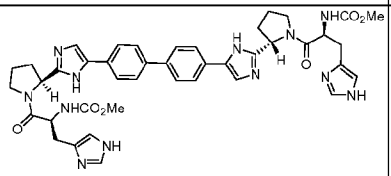
Example cj-114, R = Ac
Example cj-115, R = CONHEt

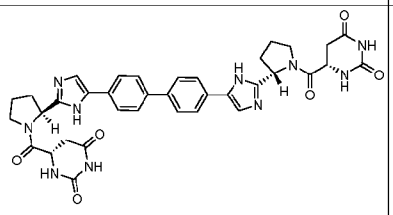
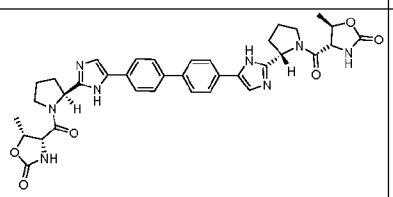
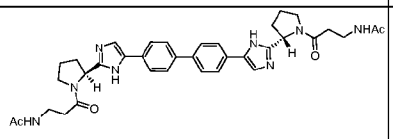
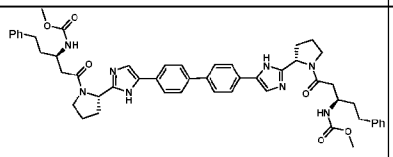
The product from Example cj-103 was acylated with either acetic anhydride or ethyl isocyanate as shown in scheme under conditions analogous to those in Example 25. Example cj-114, LCMS: Anal. Calcd. for $C_{47}H_{55}N_9O_7$ 857; found: 858 $(M+H)^+$. Example cj-115, LCMS: Anal. Calcd. for $C_{48}H_{58}N_{10}O_7$ 886; found: 887 $(M+H)^-$.

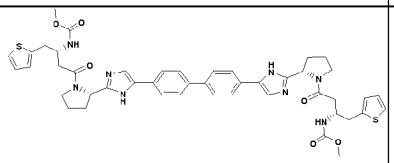
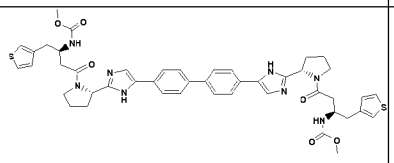
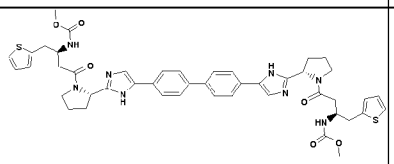
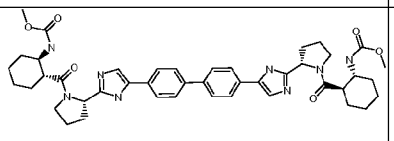
The following examples were prepared from intermediate 1e using a procedure analogous to Example 1. The appended cap is indicated in the Table and where no cap number is give the carboxylic acid was commercially available.

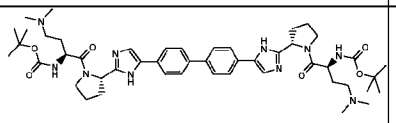
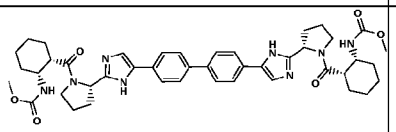
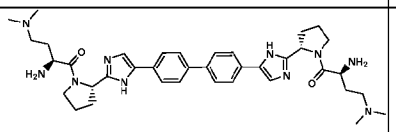
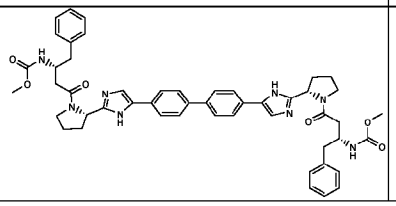
Example	*Compound Name*	*Structure*	*Cap*	*LCMS*
cj-125	methyl ((1S)-2-((2S)-2-(5-(4'-(2-((2S)-1-((2S)-2-((methoxycarbonyl)amino)-3-(1H-1,2,3-triazol-4-yl)propanoyl)-2-pyrrolidinyl)-1H-imidazol-5-yl)-4-biphenylyl)-1H-imidazol-2-yl)-1-pyrrolidinyl)-2-oxo-1-(1H-1,2,3-triazol-4-ylmethyl)ethyl)carbamate		128	LCMS: Anal. Calcd. for $C_{40}H_{44}N_{14}O_6$: 816; found: 817 $(M+H)^+$.

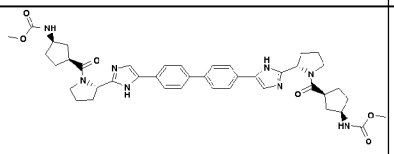
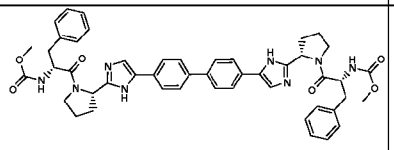
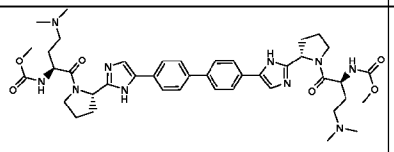
cj-126	dimethyl (4,4'-biphenyldiylbis(1H-imidazole-5,2-diyl(2S)-2,1-pyrrolidinediyl((2S)-4-oxo-4,2-butanediyl)))biscarbamate		115	LCMS: Anal. Calcd. for $C_{38}H_{46}N_8O_6$ 710; found: 711 $(M+H)^+$.
cj-127	dimethyl (4,4'-biphenyldiylbis(1H-imidazole-5,2-diyl(2S)-2,1-pyrrolidinediyl((3R)-4-methyl-1-oxo-1,3-pentanediyl)))biscarbamate		116	LCMS: Anal. Calcd. for $C_{42}H_{54}N_8O_6$ 766; found: 777 $(M+H)^+$.
cj-128	methyl ((1R)-3-((2S)-2-(5-(4'-(2-(1-((3R)-3-((methoxycarbonyl)amino)-3-phenylpropanoyl)-2-pyrrolidinyl)-1H-imidazol-5-yl)-4-biphenylyl)-1H-imidazol-2-yl)-1-pyrrolidinyl)-3-oxo-1-phenylpropyl)carbamate		92	LCMS: Anal. Calcd. for $C_{48}H_{50}N_8O_6$ 834; found: 835 $(M+H)^+$.
cj-129	methyl ((1S)-3-((2S)-2-(5-(4'-(2-(1-((3S)-3-((methoxycarbonyl)		91	LCMS: Anal. Calcd. for $C_{48}H_{50}N_8O_6$ 834; found:

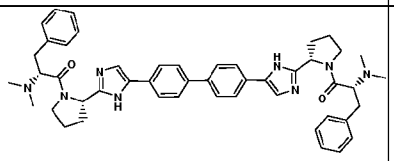
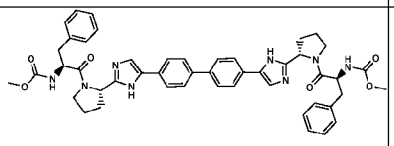
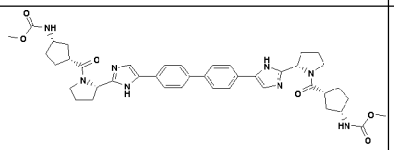
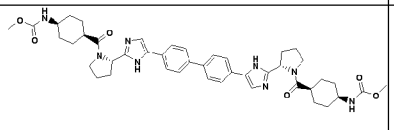
	amino)-3-phenylpropanoyl)-2-pyrrolidinyl)-1H-imidazol-5-yl)-4-biphenylyl)-1H-imidazol-2-yl)-1-pyrrolidinyl)-3-oxo-1-phenylpropyl)carbamate			835 $(M+H)^+$.
cj-130	methyl ((1S)-2-((2S)-2-(5-(4'-(2-((2S)-1-((2S)-2-((methoxycarbonyl)amino)-3-(2-pyridinyl)propanoyl)-2-pyrrolidinyl)-1H-imidazol-5-yl)-4-biphenylyl)-1H-imidazol-2-yl)-1-pyrrolidinyl)-2-oxo-1-(2-pyridinylmethyl)ethyl)carbamate		93	LCMS: Anal. Calcd. for $C_{46}H_{48}N_{10}O_6$ 836; found: 837 $(M+H)^+$.
cj-131	methyl ((1S)-2-((2S)-2-(5-(4'-(2-((2S)-1-((2S)-3-(1H-imidazol-4-yl)-2-((methoxycarbonyl)amino)propanoyl)-2-pyrrolidinyl)-1H-imidazol-5-yl)-4-biphenylyl)-1H-imidazol-2-yl)-1-		94	LCMS: Anal. Calcd. for $C_{42}H_{46}N_{12}O_6$ 814; found: 815 $(M+H)^+$.

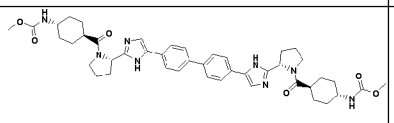
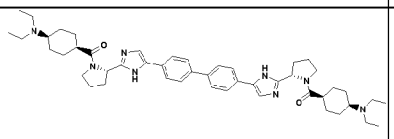
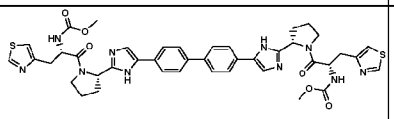
	pyrrolidinyl)-1-(1H-imidazol-4-ylmethyl)-2-oxoethyl)carbamate			
cj-132	(6S,6'S)-6,6'-(4,4'-biphenyldiylbis(1H-imidazole-5,2-diyl(2S)-2,1-pyrrolidinediylcarbonyl))didihydro-2,4(1H,3H)-pyrimidinedione		-	LCMS: Anal. Calcd. for $C_{36}H_{36}N_{10}O_6$ 704; found: 705 $(M+H)^+$.
cj-133	(4S,5R,4'S,5'R)-4,4'-(4,4'-biphenyldiylbis(1H-imidazole-5,2-diyl(2S)-2,1-pyrrolidinediylcarbonyl))bis(5-methyl-1,3-oxazolidin-2-one)		124	LCMS: Anal. Calcd. for $C_{37}H_{40}N_8O_5$ 676; found: 677 $(M+H)^+$.
cj-134	N-(3-((2S)-2-(5-(4'-(2-((2S)-1-(3-acetamidopropanoyl)-2-pyrrolidinyl)-1H-imidazol-5-yl)-4-biphenylyl)-1H-imidazol-2-yl)-1-pyrrolidinyl)-3-oxopropyl)acetamide		-	LCMS: Anal. Calcd. for $C_{36}H_{42}N_8O_4$ 650; found: 651 $(M+H)^+$.
cj-135	dimethyl (4,4'-biphenyldiylbis(1H-imidazole-5,2-diyl(2S)-2,1-		95	LCMS: Anal. Calcd. for $C_{52}H_{58}N_8O_6$ 890; found:

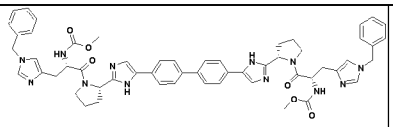
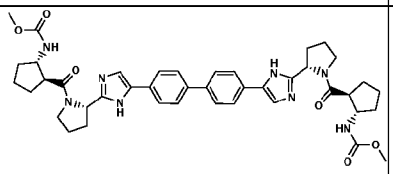
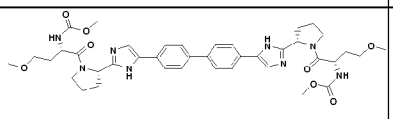
	pyrrolidinediyl((3R)-1-oxo-5-phenyl-1,3-pentanediyl)))biscarbamate			890 $(M+H)^+$.
cj-136	dimethyl (4,4'-biphenyldiylbis(1H-imidazole-5,2-diyl(2S)-2,1-pyrrolidinediyl((2R)-4-oxo-1-(2-thienyl)-4,2-butanediyl)))biscarbamate		119	LCMS: Anal. Calcd. for $C_{46}H_{50}N_8O_6S_2$ 874; found: 875 $(M+H)^+$.
cj-137	dimethyl (4,4'-biphenyldiylbis(1H-imidazole-5,2-diyl(2S)-2,1-pyrrolidinediyl((2R)-4-oxo-1-(3-thienyl)-4,2-butanediyl)))biscarbamate		120	LCMS: Anal. Calcd. for $C_{46}H_{50}N_8O_6S_2$ 874; found: 875 $(M+H)^+$.
cj-138	dimethyl (4,4'-biphenyldiylbis(1H-imidazole-5,2-diyl(2S)-2,1-pyrrolidinediyl((2S)-4-oxo-1-(2-thienyl)-4,2-butanediyl)))biscarbamate		118	LCMS: Anal. Calcd. for $C_{46}H_{50}N_8O_6S_2$ 874; found: 875 $(M+H)^+$.
cj-139	dimethyl (4,4'-biphenyldiylbis(1H-imidazole-5,2-		97	LCMS: Anal. Calcd. for $C_{44}H_{54}N_8O_6$

	diyl(2S)-2,1-pyrrolidinediylcarbonyl(1R,2R)-2,1-cyclohexanediyl))biscarbamate			790; found: 791 $(M+H)^+$.
cj-140	di-tert-butyl (4,4'-biphenyldiylbis(1H-imidazole-5,2-diyl(2S)-2,1-pyrrolidinediyl((2S)-4-(dimethylamino)-1-oxo-1,2-butanediyl)))biscarbamate		125	LCMS: Anal. Calcd. for $C_{48}H_{68}N_{10}O_6$ 880; found: 881 $(M+H)^+$.
cj-141	dimethyl (4,4'-biphenyldiylbis(1H-imidazole-5,2-diyl(2S)-2,1-pyrrolidinediylcarbonyl(1R,2S)-2,1-cyclohexanediyl))biscarbamate		98	LCMS: Anal. Calcd. for $C_{44}H_{54}N_8O_6$ 790; found: 791 $(M+H)^+$.
cj-142	(3S,3'S)-4,4'-(4,4'-biphenyldiylbis(1H-imidazole-5,2-diyl(2S)-2,1-pyrrolidinediyl))bis(N~1~,N~1~-dimethyl-4-oxo-1,3-butanediamine)		see text	LCMS: Anal. Calcd. for $C_{38}H_{52}N_{10}O_2$ 680; found: 681 $(M+H)^+$.
cj-143	dimethyl (4,4'-biphenyldiylbis(1H-imidazole-5,2-diyl(2S)-2,1-		117	LCMS: Anal. Calcd. for $C_{50}H_{54}N_8O_6$ 862; found:

	pyrrolidinediyl((2R)-4-oxo-1-phenyl-4,2-butanediyl)))biscarbamate			863 $(M+H)^+$.
cj-144	dimethyl (4,4'-biphenyldiylbis(1H-imidazole-5,2-diyl(2S)-2,1-pyrrolidinediylcarbonyl(1R,3S)-3,1-cyclopentanediyl))biscarbamate		99	LCMS: Anal. Calcd. for $C_{42}H_{50}N_8O_6$ 762; found: 763 $(M+H)^+$.
cj-145	methyl ((1R)-1-benzyl-2-((2S)-2-(5-(4'-(2-((2S)-1-((2R)-2-((methoxycarbonyl)amino)-3-phenylpropanoyl)-2-pyrrolidinyl)-1H-imidazol-5-yl)-4-biphenylyl)-1H-imidazol-2-yl)-1-pyrrolidinyl)-2-oxoethyl)carbamate		101	LCMS: Anal. Calcd. for $C_{48}H_{50}N_8O_6$ 834; found: 835 $(M+H)^+$.
cj-146	dimethyl (4,4'-biphenyldiylbis(1H-imidazole-5,2-diyl(2S)-2,1-pyrrolidinediyl((2S)-4-(dimethylamino)-1-oxo-1,2-butanediyl)))biscar		see text	LCMS: Anal. Calcd. for $C_{42}H_{56}N_{10}O_6$ 796; found: 797 $(M+H)^+$.

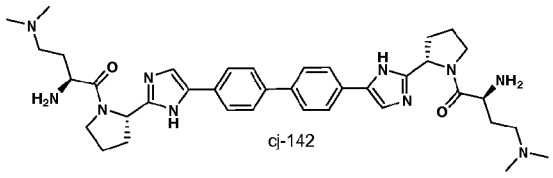
	bamate			
cj-147	(2R,2'R)-1,1'-(4,4'-biphenyldiylbis(1H-imidazole-5,2-diyl(2S)-2,1-pyrrolidinediyl))bis(N,N-dimethyl-1-oxo-3-phenyl-2-propanamine)		90	LCMS: Anal. Calcd. for $C_{48}H_{54}N_8O_2$ 774; found: 775 $(M+H)^+$.
cj-148	methyl ((1S)-1-benzyl-2-((2S)-2-(5-(4'-(2-((2S)-1-((2S)-2-((methoxycarbonyl)amino)-3-phenylpropanoyl)-2-pyrrolidinyl)-1H-imidazol-5-yl)-4-biphenylyl)-1H-imidazol-2-yl)-1-pyrrolidinyl)-2-oxoethyl)carbamate		102	LCMS: Anal. Calcd. for $C_{48}H_{50}N_8O_6$ 834; found: 835 $(M+H)^+$.
cj-149	dimethyl (4,4'-biphenyldiylbis(1H-imidazole-5,2-diyl(2S)-2,1-pyrrolidinediylcarbonyl(1R,3S)-3,1-cyclopentanediyl))biscarbamate		99a	LCMS: Anal. Calcd. for $C_{42}H_{50}N_8O_6$ 806; found: 807 $(M+H)^+$.
cj-150	dimethyl (4,4'-biphenyldiylbis(1H-imidazole-5,2-diyl(2S)-2,1-pyrrolidinediylcarb		104	LCMS: Anal. Calcd. for $C_{44}H_{54}N_8O_6$ 790; found: 791 $(M+H)^+$.

	onylcis-4,1-cyclohexanediyl))bi scarbamate			
cj-151	dimethyl (4,4'-biphenyldiylbis(1H -imidazole-5,2-diyl(2S)-2,1-pyrrolidinediylcarb onyltrans-4,1-cyclohexanediyl))bi scarbamate		105	LCMS: Anal. Calcd. for $C_{44}H_{54}N_8O_6$ 790; found: 791 $(M+H)^+$.
cj-152	({cis)-4,4'-(4,4'-biphenyldiylbis(1H -imidazole-5,2-diyl(2S)-2,1-pyrrolidinediylcarb onyl))bis(N,N-diethylcyclohexana mine)		106	LCMS: Anal. Calcd. for $C_{48}H_{66}N_8O_2$ 766; found: 777 $(M+H)^+$.
cj-153	methyl ((1S)-2-((2S)-2-(5-(4'-(2-((2S)-1-((2S)-2-((methoxycarbonyl) amino)-3-(1,3-thiazol-4-yl)propanoyl)-2-pyrrolidinyl)-1H-imidazol-5-yl)-4-biphenylyl)-1H-imidazol-2-yl)-1-pyrrolidinyl)-2-oxo-1-(1,3-thiazol-4-ylmethyl)ethyl)carb amate		107	LCMS: Anal. Calcd. for $C_{42}H_{44}N_{10}O_6S_2$ 848; found: 849 $(M+H)^+$.

cj-154	methyl ((1S)-2-((2S)-2-(5-(4'-(2-((2S)-1-((2S)-3-(1-benzyl-1H-imidazol-4-yl)-2-((methoxycarbonyl)amino)propanoyl)-2-pyrrolidinyl)-1H-imidazol-5-yl)-4-biphenylyl)-1H-imidazol-2-yl)-1-pyrrolidinyl)-1-((1-benzyl-1H-imidazol-4-yl)methyl)-2-oxoethyl)carbamate		108	LCMS: Anal. Calcd. for $C_{56}H_{58}N_{12}O_6$ 994; found: 995 $(M+H)^+$.
cj-155	dimethyl (4,4'-biphenyldiylbis(1H-imidazole-5,2-diyl(2S)-2,1-pyrrolidinediylcarbonyl(1S,2S)-2,1-cyclopentanediyl))biscarbamate		121	LCMS: Anal. Calcd. for $C_{42}H_{50}N_8O_6$ 762; found: 763 $(M+H)^+$.
cj-156	methyl ((1S)-3-methoxy-1-(((2S)-2-(5-(4'-(2-((2S)-1-(N-(methoxycarbonyl)-O-methyl-L-homoseryl)-2-pyrrolidinyl)-1H-imidazol-5-yl)-4-biphenylyl)-1H-imidazol-2-yl)-1-		87	LCMS: Anal. Calcd. for $C_{40}H_{50}N_8O_8$ 770; found: 771 $(M+H)^+$.

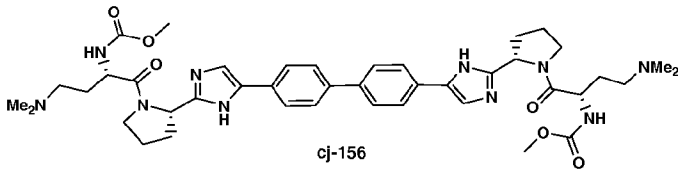
	pyrrolidinyl)carbonyl)propyl)carbamate			

Example cj-142.



Example cj-142 was prepared from the product obtained in Example cj-140 by treatment with 40% TFA in CH_2Cl_2. The mixture was allowed to stir for 3 h at room temperature and then concentrated *in vacuo*. The residue was purified by prep HPLC (YMC-Pack, C18 30X100mm, CH_3CN-H_2O-TFA).

Example cj-156.



The compound of Example-cj-156 was prepared by carbamoylation of the compound prepared in Example-cj-142 according to the method shown for *Cap*-51.

Section JG

Method A: LCMS – Xterra MS C-18 3.0 x 50mm, 0 to 100% B over 30.0 minute gradient, 1 minute hold time, A = 5% acetonitrile, 95% water, 10mm ammonium acetate, B = 95% acetonitrile, 5% water, 10mm ammonium acetate.

Method B: HPLC – X-Terra C-18 4.6 x 50mm, 0 to 100% B over 10.0 minute gradient, 1 minute hold time, A = 10% methanol 90% water 0.1% TFA, B = 90% methanol 10% water 0.1% TFA

Method C: HPLC – YMC C-18 4.6 x 50mm, 0 to 100% B over 10.0 minute gradient, 1 minute hold time, A = 10% methanol 90% water 0.2% H_3PO_4, B = 90% methanol 10% water 0.2% H_3PO_4.

Method D: HPLC – Phenomenex C-18 4.6 x 150mm, 0 to 100% B over 10.0 minute gradient, 1 minute hold time, A = 10% methanol 90% water 0.2% H_3PO_4, B = 90% methanol 10% water 0.2% H_3PO_4

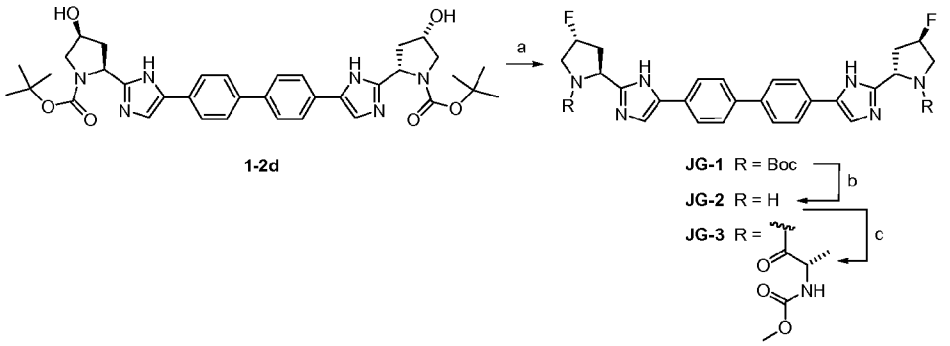
Method E: LCMS – Gemini C-18 4.6 x 50mm, 0 to 100% B over 10.0 minute gradient, 1 minute hold time, A = 5% acetonitrile, 95% water, 10mm ammonium acetate, B = 95% acetonitrile, 5% water, 10mm ammonium acetate.

Method F: LCMS-Luna C-18 3.0 x 50mm, 0 to 100% B over 7.0 minute gradient, 1 minute hold time, A = 5% acetonitrile, 95% water, 10mm ammonium acetate, B = 95% acetonitrile, 5% water, 10mm ammonium acetate.

Method G: HPLC – Phenomenex Gemini C-18 4.6 x 150mm, 10 to 80% B over 35 minute gradient, 1 minute hold time, A = 5% acetonitrile, 95% water, 10mm ammonium acetate, B = 95% acetonitrile, 5% water, 10mm ammonium acetate

Method H: HPLC – Phenomenex Gemini C-18 4.6 x 150mm, 10 to 80% B over 25 minute gradient, 1 minute hold time, A = 5% acetonitrile, 95% water, 10mm ammonium acetate, B = 95% acetonitrile, 5% water, 10mm ammonium acetate

Method I: HPLC –Waters-X-Bridge C-18 4.6 x 150mm, 10 to 70% B over 30 minute gradient, 1 minute hold time, A = 5% acetonitrile, 95% water, 10mm ammonium acetate, B = 95% acetonitrile, 5% water, 10mm ammonium acetate



Step a:

(3S,3'S,5S,5'S)-tert-butyl 5,5'-(5,5'-(biphenyl-4,4'-diyl)bis(1H-imidazole-5,2-diyl))bis(3-hydroxypyrrolidine-1-carboxylate) (1.40g, 2.13mmol) was added as a solid to a solution of bis(2-methoxyethyl) aminosulfur trifluoride (0.87mL, 4.69mmol) in 14.0mL CH_2Cl_2 cooled to -78°C. Reaction was stirred at -78°C for two hours and then warmed to room temperature and stirred for 2 hours. Reaction was poured into saturated sodium bicarbonate solution and stirred until bubbling ceased. Layers were separated and aqueous layer washed one time with CH_2Cl_2. Combined organics were washed with brine, dried ($MgSO_4$), filtered, and concentrated to give a yellow oil. The oil was triturated with CH_2Cl_2 and pentane to yield (3R,3'R,5S,5'S)-tert-butyl 5,5'-(5,5'-(biphenyl-4,4'-diyl)bis(1H-imidazole-5,2-diyl))bis(3-fluoropyrrolidine-1-carboxylate) JG-1 as a tan solid (0.98g, 71%).

^1H NMR (500 MHz, DMSO-d_6) δ ppm 12.10 (2H, m) 7.60-7.82 (8H, m) 7.35 (2H, m) 5.45 (1H, s) 5.35 (1H, s) 4.85-4.90 (2H, m) 3.69-3.79 (4H, m) 2.53-2.61 (2H, m) 2.28-2.37 (2H, m) 1.40 (8H, s) 1.12 (10H, s)

LCMS – Phenomenex C-18 3.0 x 50mm, 0 to 100% B over 4.0 minute gradient, 1 minute hold time, A = 10% methanol 90% water 0.1% TFA, B = 90% methanol 10% water 0.1% TFA, (t_R= 3.04 min) Anal Calcd. for $C_{36}H_{42}F_2N_6O_4$ 660.70; found 661.68 $(M+H)^+$

Step b:

To a solution of (3R,3'R,5S,5'S)-tert-butyl 5,5'-(5,5'-(biphenyl-4,4'-diyl)bis(1H-imidazole-5,2-diyl))bis(3-hydroxypyrrolidine-1-carboxylate) (0.098g, 1.48mmol) in 4mL dioxane was added 2.0mL of a 4.0M solution of HCl in dioxane. The reaction was stirred for 2 hours at room temperature and concentrated under reduced pressure.

The resulting tan solid was dried under vacuum to give 4,4'-bis(2-((2S,4S)-4-fluoropyrrolidin-2-yl)-1H-imidazol-5-yl)biphenyl tetrahydrochloride JG-2 (0.89g, 100%yield). No further purification.

^{1}H NMR (500 MHz, DMSO-d_6) δ ppm 9.05 (2H, s), 8.18 (2H, s), 8.00-8.09 (4H, m) 7.89 (4H, d, *J*=7.63 Hz) 5.71 (1H, s) 5.61 (1H, s) 5.24-5.33 (2H, m) 3.92 (2H, d, *J*=10.68Hz) 3.63-3.71 (2H, m) 2.79-2.89 (2H, m)

LCMS – Phenomenex C-18 3.0 x 50mm, 0 to 100% B over 4.0 minute gradient, 1 minute hold time, A = 10% methanol 90% water 0.1% TFA, B = 90% methanol 10% water 0.1% TFA, (t_R= 2.12 min) Anal Calcd. for $C_{26}H_{26}F_2N_6$ 460.53; found 461.37 $(M+H)^+$

Step c:

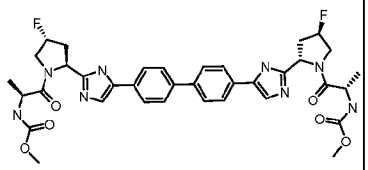
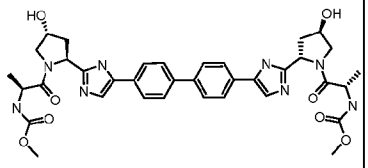
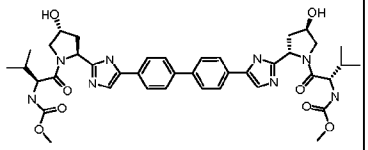
To a stirred solution of 4,4'-bis(2-((2S,4R)-4-fluoropyrrolidin-2-yl)-1H-imidazol-5-yl)biphenyltetrahydrochloride (0.060g, 0.10mmol), (S)-2-(methoxycarbonylamino)propanoic acid (0.031g, 0.21mmol), and HATU (0.081g, 0.21mmol) in 3mL DMF was added diisopropylethyl amine (0.11mL, 0..61mmol).The reaction was stirred at room temperature overnight (16 hours) and concentrated under reduced pressure. The crude product was purified by reverse-phase preparative HPLC and secondly by passing it through a Waters MCX extraction cartridge to provide Dimethyl (2S,2'S)-1,1'-((3R,3'R,5S,5'S)-5,5'-(5,5'-(biphenyl-4,4'-diyl)bis(1H-imidazole-5,2-diyl))bis(3-fluoropyrrolidine-5,1-diyl))bis(1-oxopropane-2,1-diyl)dicarbamate JG-3 , free base (0.0097g, 7.5%).

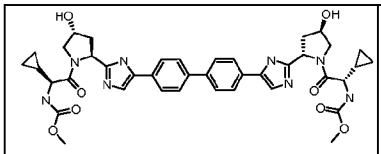
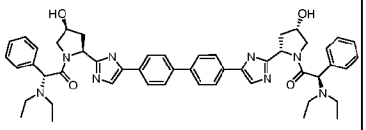
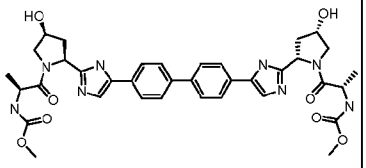
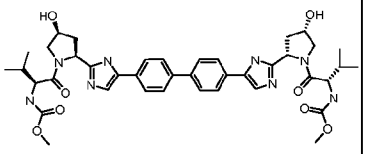
^{1}H NMR (500MHz, DMSO-d_6) δ ppm 11.91 (2H, m), 7.76-7.84 (3H, m), 7.64-7.84 (5H, m), 7.48-7.58 (2H, m), 5.55 (1H, s), 5.11 (1H, s), 4.29-4.38 (2H, m), 4.13 (2H, d, *J*=12.51 Hz), 3.89-3.98 (2H, m), 3.53 (6H, s), 2.54-2.64 4H, m), 1.21 (6H, s)

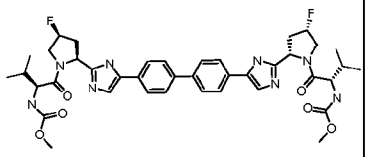
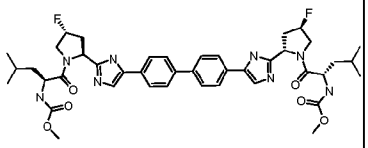
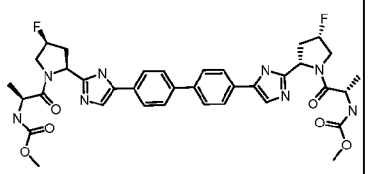
LCMS – Luna C-18 3.0 x 50mm, 0 to 100% B over 7.0 minute gradient, 1 minute hold time, A = 5% acetonitrile, 95% water, 10mm ammonium acetate, B = 95% acetonitrile, 5% water, 10mm ammonium acetate, (t_R=2.40 min)

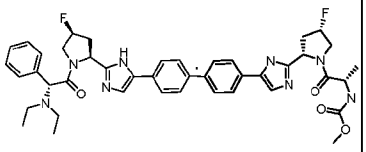
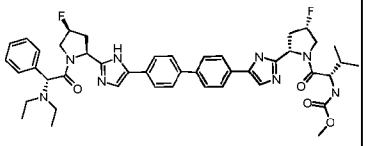
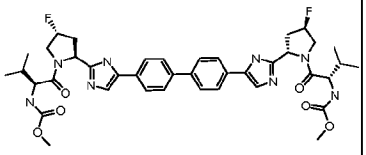
Nominal/LRMS – Calcd. for $C_{36}H_{40}F_2N_8O_6$ 718.30; found 719.24$(M+H)^+$

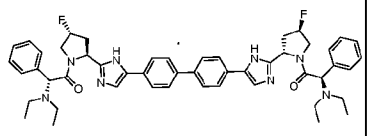
Accurate/HRMS – Calcd. for $C_{36}H_{41}F_2N_8O_6$ 719.3117; found 719.3114$(M+H)^+$

Structure	*Compound Name*	*Data*
JG-3 	methyl ((1S)-2-((2S,4R)-4-fluoro-2-(5-(4'-(2-((2S,4R)-4-fluoro-1-(N-(methoxycarbonyl)-L-alanyl)-2-pyrrolidinyl)-1H-imidazol-5-yl)-4-biphenylyl)-1H-imidazol-2-yl)-1-pyrrolidinyl)-1-methyl-2-oxoethyl)carbamate	RT = 13.60 min, method I LRMS: Anal. Calcd. for $C_{36}H_{40}F_2N_8O_6$ 718.30 found: 719.24 $(M+H)^+$ HRMS: Anal. Calcd. for $C_{36}H_{41}F_2N_8O_6$ 719.3117 found 719.3114 $(M+H)^+$
JG-4  From 1-1e and *Cap*-12	methyl ((1S)-2-((2S,4R)-4-hydroxy-2-(5-(4'-(2-((2S,4R)-4-hydroxy-1-(N-(methoxycarbonyl)-L-alanyl)-2-pyrrolidinyl)-1H-imidazol-5-yl)-4-biphenylyl)-1H-imidazol-2-yl)-1-pyrrolidinyl)-1-methyl-2-oxoethyl)carbamate	RT = 9.27 min, method H LRMS: Anal. Calcd. for $C_{36}H_{42}N_8O_8$ 714.77 found: 715.33 $(M+H)^+$ HRMS: Anal. Calcd. for $C_{36}H_{43}N_8O_8$ 715.3204 found: 715.3186 $(M+H)^+$
JG-5  From 1-1e and *Cap*-51	methyl ((1S)-1-(((2S,4R)-4-hydroxy-2-(5-(4'-(2-((2S,4R)-4-hydroxy-1-((2S)-2-((methoxycarbonyl)amino)-3-methylbutanoyl)-2-pyrrolidinyl)-1H-imidazol-5-yl)-4-biphenylyl)-1H-imidazol-2-yl)-1-pyrrolidinyl)carbonyl)-2-methylpropyl)carbamate	RT = 15.08 min, method G LRMS: Anal. Calcd. for $C_{40}H_{50}N_8O_8$ 770.88 found: 771.76 $(M+H)^+$ HRMS: Anal. Calcd. for $C_{40}H_{51}N_8O_8$ 771.3830 found: 771.3798 $(M+H)^+$
JG-6	dimethyl (4,4'-biphenyldiylbis(1H-	RT = 13.67 min, method G

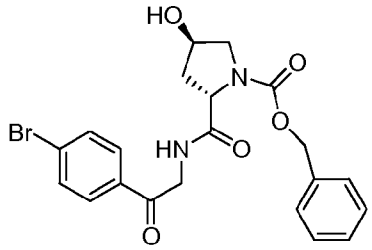
 From 1-1e and *Cap*-54b	imidazole-5,2-diyl((2S,4R)-4-hydroxy-2,1-pyrrolidinediyl)((1S)-1-cyclopropyl-2-oxo-2,1-ethanediyl)))biscarbamate	LRMS: Anal. Calcd. for $C_{40}H_{46}N_8O_8$ 766.85 found: 767.65 $(M+H)^+$ HRMS: Anal. Calcd. for $C_{40}H_{47}N_8O_8$ 767.3517 found: 767.3483 $(M+H)^+$
JG-7  From 1-2e and *Cap*-2	(3S,5S,3'S,5'S)-5,5'-(4,4'-biphenyldiylbis(1H-imidazole-5,2-diyl))bis(1-((2R)-2-(diethylamino)-2-phenylacetyl)-3-pyrrolidinol)	RT = 15.88min, method H LRMS: Anal. Calcd. for $C_{50}H_{58}N_8O_4$ 834.45 found: 835.38$(M+H)^+$ HRMS: Anal. Calcd. for $C_{50}H_{59}N_8O_4$ 835.4659 found: 835.4627$(M+H)^+$
JG-8  From 1-2e and *Cap*-52	methyl ((1S)-2-((2S,4S)-4-hydroxy-2-(5-(4'-(2-((2S,4S)-4-hydroxy-1-(N-(methoxycarbonyl)-L-alanyl)-2-pyrrolidinyl)-1H-imidazol-5-yl)-4-biphenylyl)-1H-imidazol-2-yl)-1-pyrrolidinyl)-1-methyl-2-oxoethyl)carbamate	RT = 9.99 min, method H LRMS: Anal. Calcd. for $C_{36}H_{42}N_8O_8$ 714.77 found: 715.71 $(M+H)^+$ HRMS: Anal. Calcd. for $C_{36}H_{43}N_8O_8$ 715.3204 found: 715.3188 $(M+H)^+$
JG-9  From 1-2e and *Cap*-51	methyl ((1S)-1-(((2S,4S)-4-hydroxy-2-(5-(4'-(2-((2S,4S)-4-hydroxy-1-((2S)-2-((methoxycarbonyl)amino)-3-methylbutanoyl)-2-pyrrolidinyl)-1H-imidazol-5-yl)-4-	RT = 14.12 min, method H LRMS: Anal. Calcd. for $C_{40}H_{50}N_8O_8$ 770.88 found: 771.74 $(M+H)^+$ HRMS: Anal. Calcd. for $C_{40}H_{51}N_8O_8$ 771.3830

	biphenylyl)-1H-imidazol-2-yl)-1-pyrrolidinyl)carbonyl)-2-methylpropyl)carbamate	found: 771.3799 $(M+H)^+$
JG-10  From 1-2e2 and *Cap*-51	methyl ((1S)-1-(((2S,4S)-4-fluoro-2-(5-(4'-(2-((2S,4S)-4-fluoro-1-((2S)-2-((methoxycarbonyl)amino)-3-methylbutanoyl)-2-pyrrolidinyl)-1H-imidazol-5-yl)-4-biphenylyl)-1H-imidazol-2-yl)-1-pyrrolidinyl)carbonyl)-2-methylpropyl)carbamate	RT = 17.66 min, method I LRMS: Anal. Calcd. for $C_{40}H_{48}F_2N_8O_6$ 774.86 found: 775.49 $(M+H)^+$ HRMS: Anal. Calcd. for $C_{40}H_{49}F_2N_8O_6$ 775.3743 found: 775.3717 $(M+H)^+$
JG-12  From (S)-2-(methoxycarbonylamino)-4-methylpentanoic acid and JG-2	methyl ((1S)-1-(((2S,4R)-4-fluoro-2-(5-(4'-(2-((2S,4R)-4-fluoro-1-((2S)-2-((methoxycarbonyl)amino)-4-methylpentanoyl)-2-pyrrolidinyl)-1H-imidazol-5-yl)-4-biphenylyl)-1H-imidazol-2-yl)-1-pyrrolidinyl)carbonyl)-3-methylbutyl)carbamate	RT = 9.69 min, method I LRMS: Anal. Calcd. for $C_{42}H_{52}F_2N_8O_6$ 802.92 found: 803.42 $(M+H)^+$ HRMS: Anal. Calcd. for $C_{42}H_{53}F_2N_8O_6$ 803.4056 found: 803.4018 $(M+H)^+$
JG-13  From 1-2e2 and *Cap*-52	methyl ((1S)-2-((2S,4S)-4-fluoro-2-(5-(4'-(2-((2S,4S)-4-fluoro-1-(N-(methoxycarbonyl)-L-alanyl)-2-pyrrolidinyl)-1H-imidazol-5-yl)-4-biphenylyl)-1H-imidazol-	RT = 13.60 min, method I LRMS: Anal. Calcd. for $C_{36}H_{40}F_2N_8O_6$ 718.30 found: 719.45 $(M+H)^+$ HRMS: Anal. Calcd. for

	2-yl)-1-pyrrolidinyl)-1-methyl-2-oxoethyl)carbamate	$C_{36}H_{41}F_2N_8O_6$ 719.3117 found 719.3090 $(M+H)^+$
JG-14  From JG-25 and *Cap*-52	methyl ((1S)-2-((2S,4S)-2-(5-(4'-(2-((2S,4S)-1-((2R)-2-(diethylamino)-2-phenylacetyl)-4-fluoro-2-pyrrolidinyl)-1H-imidazol-5-yl)-4-biphenylyl)-1H-imidazol-2-yl)-4-fluoro-1-pyrrolidinyl)-1-methyl-2-oxoethyl)carbamate	RT = 15.13 min, method I LCMS: Anal. Calcd. for $C_{43}H_{48}F_2N_8O_4$ 778.91 found: 779.79 $(M+H)^+$
JG-15  From JG-25 and *Cap*-51	methyl ((1S)-1-(((2S,4S)-2-(5-(4'-(2-((2S,4S)-1-((2R)-2-(diethylamino)-2-phenylacetyl)-4-fluoro-2-pyrrolidinyl)-1H-imidazol-5-yl)-4-biphenylyl)-1H-imidazol-2-yl)-4-fluoro-1-pyrrolidinyl)carbonyl)-2-methylpropyl)carbamate	RT = 17.51 min, method I LCMS: Anal. Calcd. for $C_{45}H_{52}F_2N_8O_4$ 806.96 found: 807.50 $(M+H)^+$
JG-16  From JG-2 and *Cap*-51	methyl ((1S)-1-(((2S,4R)-4-fluoro-2-(5-(4'-(2-((2S,4R)-4-fluoro-1-((2S)-2-((methoxycarbonyl)amino)-3-methylbutanoyl)-2-pyrrolidinyl)-1H-imidazol-5-yl)-4-biphenylyl)-1H-imidazol-2-yl)-1-pyrrolidinyl)carbonyl)-2-methylpropyl)carbamate	RT =16.51 min, method I LRMS: Anal. Calcd. for $C_{40}H_{48}F_2N_8O_6$ 774.86 found: 775.39 $(M+H)^+$ HRMS: Anal. Calcd. for $C_{40}H_{49}F_2N_8O_6$ 775.3743 found: 775.3740 $(M+H)^+$

JG-17  From JG-2 and *Cap*-2	(1R,1'R)-2,2'-(4,4'-biphenyldiylbis(1H-imidazole-5,2-diyl((2S,4R)-4-fluoro-2,1-pyrrolidinediyl)))bis(N,N-diethyl-2-oxo-1-phenylethanamine)	RT = 8.13 min, method I LCMS: Anal. Calcd. for $C_{50}H_{56}F_2N_8O_2$ 839.04 found: 839.46 $(M+H)^+$ HRMS: Anal. Calcd. for $C_{50}H_{57}F_2N_8O_2$ 839.4572 found: 839.4543 $(M+H)^+$

Synthesis of JG-18 as in Example 28 step a using hydroxyproline in place of proline.

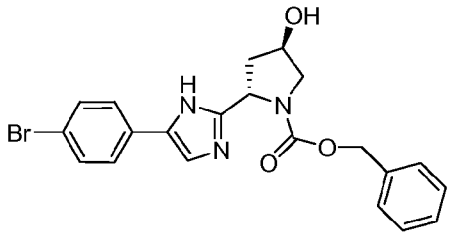


JG-18

^{1}H NMR (500 MHz, DMSO-d_6) δ ppm 7.89(2H, t, *J*=8.39 Hz) 7.74 (2H, t, *J*=8.24 Hz) 7.28-7.37 (5H, m) 5.01-5.08 (3H, m) 4.27-4.57 (4H, m) 3.44-3.53 (1H, m) 3.37(1H, d, *J*=10.99 Hz) 2.12 (1H, d, *J*=11.60 Hz) 1.93 (1H, dd, *J*=12.05 Hz, 6.56 Hz)

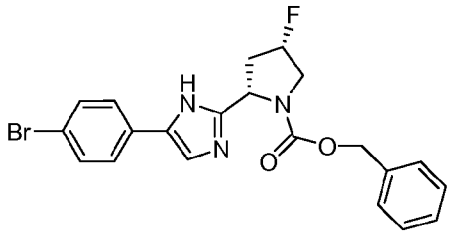
LCMS – Phenomenex C-18 3.0 x 50mm, 0 to 100% B over 4.0 minute gradient, 1 minute hold time, A = 10% methanol 90% water 0.1% TFA, B = 90% methanol 10% water 0.1% TFA mobile phase, t_R= 3.62 min, Anal Calcd. for $C_{21}H_{21}BrN_2O_5$ 461.32; found 462.64 $(M+H)^+$.

Synthesis of JG-19 from JG-18 as in Example 28 step b.



JG-19

LCMS – Luna C-18 3.0 x 50mm, 0 to 100% B over 4.0 minute gradient, 1 minute hold time, A = 5% acetonitrile, 95% water, 10mm ammonium acetate, B = 95% acetonitrile, 5% water, 10mm ammonium acetate, t_R= 1.88 min, Anal. Calcd. for $C_{21}H_{20}BN_3O_3$ 441.07; found 442.22 $(M+H)^+$

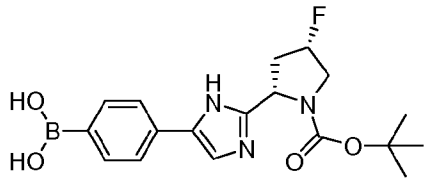


JG-20

(2S,4R)-benzyl 2-(5-(4-bromophenyl)-1H-imidazol-2-yl)-4-hydroxypyrrolidine-1-carboxylate (1.5g, 3.4mmol) was added as a solid to a solution of bis(2-methoxyethyl) aminosulfur trifluoride (0.98mL, 5.1mmol) in 15mL CH_2Cl_2 cooled to -78°C. Reaction was stirred at -78°C for two hours and then warmed to room temperature and stirred for 2 hours. Reaction was poured into saturated sodium bicarbonate solution and stirred until bubbling ceased. Layers were separated and aqueous layer washed one time with CH_2Cl_2. Combined organics were washed with brine, dried ($MgSO_4$), filtered, and concentrated to give a yellow oil. The oil was triturated with CH_2Cl_2 and pentane to yield (2S,4S)-benzyl 2-(5-(4-bromophenyl)-1H-imidazol-2-yl)-4-fluoropyrrolidine-1-carboxylate JG-20 as a yellow solid (0.96g, 62%).

^{1}H NMR (500 MHz, DMSO-d_6) δ ppm 7.70 (2H, d, *J*=7.02 Hz) 7.48-7.55 (3H, m) 7.41 -7.35 (3H, m) 7.19-7.11 (2H, m) 5.15 -5.02 (3H, m) 3.84 -3.78 (2H, m) 3.33 (2H, s) 2.53-2.61 (1H, m) 2.33-2.42 (1H, m)

LCMS – Luna C-18 3.0 x 50mm, 0 to 100% B over 4.0 minute gradient, 1 minute hold time, A = 5% acetonitrile, 95% water, 10mm ammonium acetate, B = 95% acetonitrile, 5% water, 10mm ammonium acetate, t_R= 2.10 min, Anal. Calcd. for $C_{21}H_{19}Br_1F_1N_3O_2$ 443.06; found 444.05 $(M+H)^+$

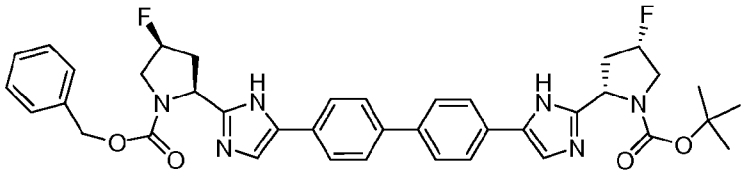


JG-21

(2S,4R)-tert-butyl 4-hydroxy-2-(5-(4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)phenyl)-1H-imidazol-2-yl)pyrrolidine-1-carboxylate, 1-2c (1.5g, 3.3mmol) was added as a solid to a solution of bis(2-methoxyethyl) aminosulfur trifluoride (0.91mL, 5.0mmol) in 15mL CH_2Cl_2 cooled to -78°C. Reaction was stirred at -78°C for two hours and then warmed to room temperature and stirred for 2 hours. Reaction was poured into saturated sodium bicarbonate solution and stirred until bubbling ceased. Layers were separated and aqueous layer washed one time with CH_2Cl_2. Combined organics were washed with brine, dried ($MgSO_4$), filtered, and concentrated to give a brown oil. The oil was chromatographed on silica gel with with 5% MeOH/CH_2Cl_2 to yield 4-(2-((2S,4S)-1-(tert-butoxycarbonyl)-4-fluoropyrrolidin-2-yl)-1H-imidazol-5-yl)phenylboronic acid as a tan solid (0.46g, 37%).

LCMS – Luna C-18 3.0 x 50mm, 0 to 100% B over 4.0 minute gradient, 1 minute hold time, A = 5% acetonitrile, 95% water, 10mm ammonium acetate, B = 95% acetonitrile, 5% water, 10mm ammonium acetate, t_R= 1.46 min, Anal. Calcd. for $C_{18}H_{23}B_1F_1N_3O_4$ 375.18; found 376.12 $(M+H)^+$

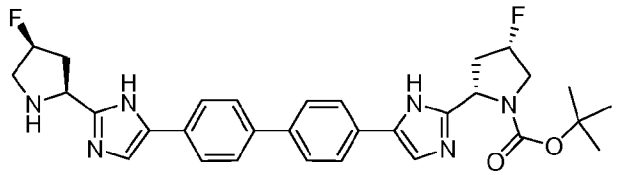
JG-22 is synthesized from JG-20 and JG-21 as described in Example 28 step c.



JG-22

LCMS – Luna C-18 3.0 x 50mm, 0 to 100% B over 4.0 minute gradient, 1 minute hold time, A = 5% acetonitrile, 95% water, 10mm ammonium acetate, B = 95% acetonitrile, 5% water, 10mm ammonium acetate, t_R= 2.27 min, Anal. Calcd. for $C_{39}H_{40}F_2N_6O_4$ 694.31; found 695.35 $(M+H)^+$

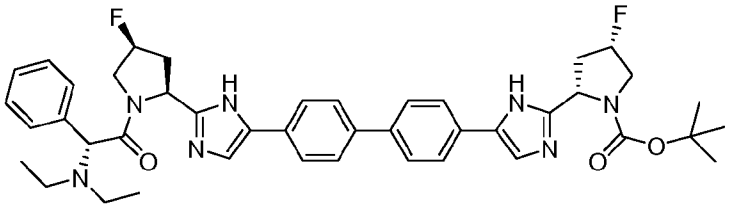
JG-23 is synthesized from JG-22 as described in Example 28 step d.



JG-23

LCMS – Phenomenex C-18 3.0 x 50mm, 0 to 100% B over 4.0 minute gradient, 1 minute hold time, A = 10% methanol 90% water 0.1% TFA, B = 90% methanol 10% water 0.1% TFA mobile phase, t_R= 2.62 min, Anal Calcd. for $C_{31}H_{34}F_2N_6O_2$ 560.27; found 561.52 $(M+H)^+$.

JG-24 is synthesized from JG-22 and *Cap*-2 as in Example 28 step e.

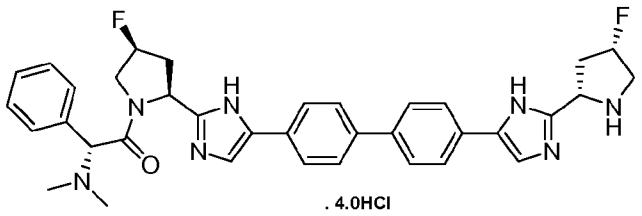


JG-24

LCMS – Luna C-18 3.0 x 50mm, 0 to 100% B over 4.0 minute gradient, 1 minute hold time, A = 5% acetonitrile, 95% water, 10mm ammonium acetate, B = 95%

acetonitrile, 5% water, 10mm ammonium acetate, t_R= 2.30 min, Anal. Calcd. for $C_{41}H_{45}F_2N_7O_3$ 721.36; found 722.42 $(M+H)^+$

JG-25 is synthesized from JG-24 *via* reaction with methanolic HCl as described in Example LS14 step b.



JG-25

LCMS – Luna C-18 3.0 x 50mm, 0 to 100% B over 4.0 minute gradient, 1 minute hold time, A = 5% acetonitrile, 95% water, 10mm ammonium acetate, B = 95% acetonitrile, 5% water, 10mm ammonium acetate, t_R= 1.98 min, Anal. Calcd. for $C_{36}H_{37}F_2N_7O_1$ 621.30; found 622.48 $(M+H)^+$

Section OL LC Conditions:

Condition 1: Solvent A: 5% acetonitrile / 95% water / 10mmol ammonium acetate; Solvent B: 95% acetonitrile / 5% water / 10mmol ammonium acetate; Column: Phenomenex GEMINI 5u C18 4.6 x 5.0mm; Wavelength: 220nM; Flow rate: 4 ml / min; 0%B to 100% B over 3 min with a 1 min hold time.

Condition 2: Solvent A: 5% acetonitrile / 95% water / 10mmol ammonium acetate; Solvent B: 95% acetonitrile / 5% water / 10mmol ammonium acetate; Column: Phenomenex GEMINI 5u C18 4.6 x 5.0mm; Wavelength: 220nM; Flow rate: 4 ml / min; 0%B to 100% B over 2 min with a 1 min hold time

Condition 3: Solvent A: 5% acetonitrile / 95% water / 10mmol ammonium acetate; Solvent B: 95% acetonitrile / 5% water / 10mmol ammonium acetate; Column:

Phenomenex GEMINI 5u C18 4.6 x 5.0mm; Wavelength: 220nM; Flow rate: 4 ml / min; 0%B to 100% B over 4 min with a 1 min hold time

Condition 4: Solvent A: 10%MeOH / 90% water / 0.1% TFA; Solvent B: 90% MeOH / 10% water / 0.1% TFA; Column: Phenomenex 10u C18 3.0 x 5.0mm; Wavelength: 220nM; Flow rate: 4ml / min; 0%B to 100% B over 4 min with a 1min hold time

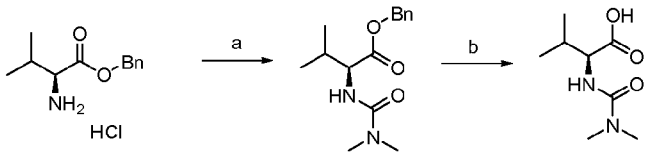
Condition 5: Solvent A: 5% acetonitrile / 95% water / 10mmol ammonium acetate; Solvent B: 95% acetonitrile / 5% water / 10mmol ammonium acetate; Column: Phenomenex GEMINI 5u C18 4.6 x 5.0mm; Wavelength: 220nM; Flow rate: 4 ml / min; 0%B to 100% B over 9 min with a 1 min hold time

Condition 6: Solvent A: 10%MeOH / 90% water / 0.2% H_3PO_4; Solvent B: 90% MeOH / 10% water / 0.2% H_3PO_4; Column: Phenomenex 5u C-18 4.6 x 50mm; Wavelength: 220nM; Flow rate: 1.5ml / min; 0%B to 100% B over 14 min with a 3min hold time

Condition 7: Solvent A: 10%MeOH / 90% water / 0.1% TFA; Solvent B: 90% MeOH / 10% water / 0.1% TFA; Column: Phenomenex 10u C18 3.0 x 5.0mm; Wavelength: 220nM; Flow rate: 4ml / min; 0%B to 100% B over 3 min with a 1min hold time

Condition 8: Solvent A: 10%MeOH / 90% water / 0.1% TFA; Solvent B: 90% MeOH / 10% water / 0.1% TFA; Column: Phenomenex 10u C18 3.0 x 5.0mm; Wavelength: 220nM; Flow rate: 4ml / min; 0%B to 100% B over 2 min with a 1min hold time

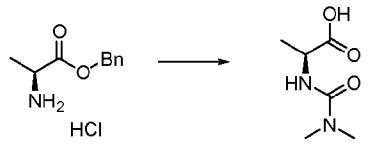
Experimentals Caps:



Intermediate Cap OL-1 Cap OL-2

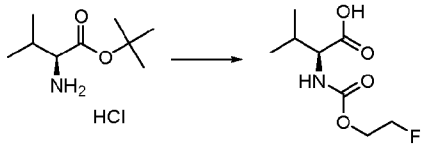
Step a: Dimethylcarbamoyl chloride (0.92 mL, 10 mmol) was added slowly to a solution of (S)-benzyl 2-amino-3-methylbutanoate hydrochloride (2.44 g; 10 mmol) and Hunig's base (3.67 mL, 21 mmol) in THF (50 mL). The resulting white suspension was stirred at room temperature overnight (16 hours) and concentrated under reduced pressure. The residue was partitioned between ethyl acetate and water. The organic layer was washed with brine, dried ($MgSO_4$), filtered, and concentrated under reduced pressure. The resulting yellow oil was purified by flash chromatography, eluting with ethyl acetate:hexanes (1:1). Collected fractions were concentrated under vacuum providing 2.35 g (85%) of Intermediate Cap OL-1 as a clear oil. ^{1}H NMR (300 MHz, DMSO-d_6) δ ppm 0.84 (d, *J*=6.95 Hz, 3H) 0.89 (d, *J*=6.59 Hz, 3H) 1.98-2.15 (m, 1H) 2.80 (s, 6H) 5.01-5.09 (m, *J*=12.44 Hz, 1H) 5.13 (d, *J*=12.44 Hz, 1H) 6.22 (d, *J*=8.05 Hz, 1H) 7.26-7.42 (m, 5H). LC (Cond. 1): RT = 1.76 min; MS: Anal. Calcd. for $[M+H]^+$ $C_{16}H_{22}N_2O_3$: 279.17; found 279.03.

Step b: To Intermediate Cap OL-1 (2.35 g; 8.45 mmol) in 50 ml MeOH was added Pd/C (10%;200 mg) and the resulting black suspension was flushed with N_2 (3x) and placed under 1 atm of H_2. The mixture was stirred at room temperature overnight and filtered though a microfiber filter to remove the catalyst. The resulting clear solution was then concentrated under reduced pressure to obtain 1.43 g (89%) of Cap OL-2 as a white foam, which was used without further purification. ^{1}H NMR (500 MHz, DMSO-d_6) δ ppm 0.87 (d, *J*=4.27 Hz, 3H) 0.88 (d, *J*=3.97 Hz, 3H) 1.93-2.11 (m, 1H) 2.80 (s, 6H) 3.90 (dd, *J*=8.39, 6.87 Hz, 1H) 5.93 (d, *J*=8.54 Hz, 1H) 12.36 (s, 1H).). LC (Cond. 1): RT = 0.33 min; MS: Anal. Calcd. for $[M+H]^+$ $C_8H_{17}N_2O_3$: 1898.12; found 189.04.



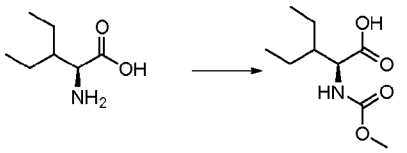
Cap OL-3

Cap OL-3 was prepared from (S)-benzyl 2-aminopropanoate hydrochloride according to the method described for Cap OL-2. ^{1}H NMR (500 MHz, DMSO-d_6) δ ppm 1.27 (d, *J*=7.32 Hz, 3H) 2.80 (s, 6H) 4.06 (qt, 1H) 6.36 (d, *J*=7.32 Hz, 1H) 12.27 (s, 1H). LC (Cond. 1): RT = 0.15 min; MS: Anal. Calcd. for $[M+H]^+$ $C_6H_{13}N_2O_3$: 161.09; found 161.00.



Cap OL-4

Cap OL-4 was prepared from (S)-tert-butyl 2-amino-3-methylbutanoate hydrochloride and 2-fluoroethyl chloroformate according to the method described for *Cap*-47. ^{1}H NMR (500 MHz, DMSO-d_6) δ ppm 0.87 (t, *J*=6.71 Hz, 6H) 1.97-2.10 (m, 1H) 3.83 (dd, *J*=8.39, 5.95 Hz, 1H) 4.14-4.18 (m, 1H) 4.20-4.25 (m, 1H) 4.50-4.54 (m, 1H) 4.59-4.65 (m, 1H) 7.51 (d, *J*=8.54 Hz, 1H) 12.54 (s, 1H)

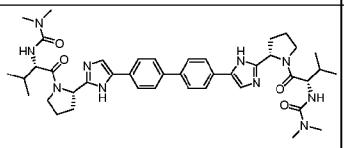
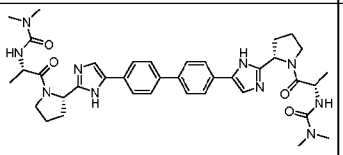
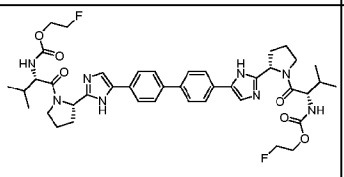


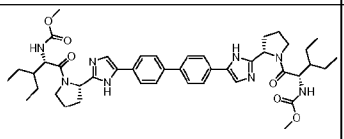
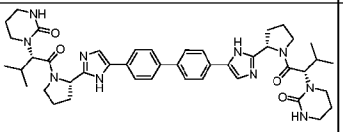
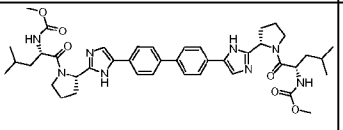
Cap OL-5

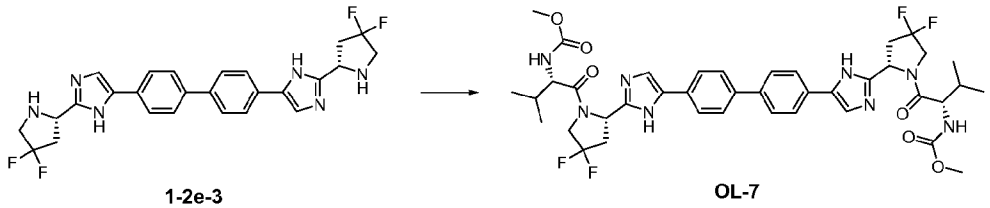
Cap OL-5 was prepared from (S)-diethyl alanine and methyl chloroformate according to the method described for *Cap*-51. ^{1}H NMR (500 MHz, DMSO-d_6) δ ppm 0.72-0.89 (m, 6H) 1.15-1.38 (m, 4H) 1.54-1.66 (m, 1H) 3.46-3.63 (m, 3H) 4.09 (dd, *J*=8.85, 5.19 Hz, 1H) 7.24 (d, *J*=8.85 Hz, 1H) 12.55 (s, 1H). LC (Cond. 2): RT = 0.66 min; MS: Anal. Calcd. for $[M+H]^+$ $C_9H_{18}NO_4$:204.12; found 204.02.

New Examples:

The following analogs were prepared from 1e in similar fashion to the preparation of Example 1 and employing the appropriate Cap.

Example Number	*Compound Name*	*Structure*	*Analytical Data*
OL-1	3-((1S)-1-(((2S)-2-(4-(4'-(2-((2S)-1-((2S)-2-((dimethylcarbamoyl)amino)-3-methylbutanoyl)-2-pyrrolidinyl)-1H-imidazol-4-yl)-4-biphenylyl)-1H-imidazol-2-yl)-1-pyrrolidinyl)carbonyl)-2-methylpropyl)-1,1-dimethylurea	 From 1e and Cap OL-2	LC/MS: 2.16 min (Cond'n 3); Anal. Calcd. for $[M+H]^+$ $C_{42}H_{57}N_{10}O_4$: 765.45; found 765.47.
OL-2	3-((1S)-2-((2S)-2-(4-(4'-(2-((2S)-1-(N-(dimethylcarbamoyl)-L-alanyl)-2-pyrrolidinyl)-1H-imidazol-4-yl)-4-biphenylyl)-1H-imidazol-2-yl)-1-pyrrolidinyl)-1-methyl-2-oxoethyl)-1,1-dimethylurea	 From 1e and Cap OL-3	LC/MS: 1.86 min (Cond'n 3); Anal. Calcd. for $[M+H]^+$ $C_{38}H_{49}N_{10}O_4$: 709.39; found 709.43.
OL-3	2-fluoroethyl ((1S)-1-(((2S)-2-(4-(4'-(2-((2S)-1-((2S)-2-(((2-fluoroethoxy)carbonyl)amino)-3-methylbutanoyl)-2-pyrrolidinyl)-1H-imidazol-4-yl)-4-biphenylyl)-1H-imidazol-	 From 1e and Cap OL-4	LC/MS: 2.83 min (Cond'n 4); Anal. Calcd. for $[M+H]^+$ $C_{42}H_{53}F_2N_8O_6$: 803.40; found 803.47.

	2-yl)-1-pyrrolidinyl)carbonyl)-2-methylpropyl)carbamate		
OL-4	methyl ((1S)-2-ethyl-1-(((2S)-2-(4-(4'-(2-((2S)-1-((2S)-3-ethyl-2-((methoxycarbonyl)amino)pentanoyl)-2-pyrrolidinyl)-1H-imidazol-4-yl)-4-biphenylyl)-1H-imidazol-2-yl)-1-pyrrolidinyl)carbonyl)butyl)carbamate	 From 1e and Cap OL-5	LC/MS: 2.64 min (Cond'n 3); Anal. Calcd. for $[M+H]^+$ $C_{44}H_{59}N_8O_6$: 795.45; found 795.48.
OL-5	1,1'-(4,4'-biphenyldiylbis(1H-imidazole-4,2-diyl(2S)-2,1-pyrrolidinediyl((2S)-3-methyl-1-oxo-1,2-butanediyl)))ditetrahydro-2(1H)-pyrimidinone	 From 1e and (S)-3-methyl-2-(2-oxotetrahydropyrimidin-1(2H)-yl)butanoic acid	LC/MS: 2.95 min (Cond'n 4); Anal. Calcd. for $[M+H]^+$ $C_{44}H_{57}N_{10}O_6$: 789.46; found 789.52.
OL-6	methyl ((1S)-1-(((2S)-2-(4-(4'-(2-((2S)-1-((2S)-2-((methoxycarbonyl)amino)-4-methylpentanoyl)-2-pyrrolidinyl)-1H-imidazol-4-yl)-4-biphenylyl)-1H-imidazol-2-yl)-1-pyrrolidinyl)carbonyl)-3-methylbutyl)carbamate	 From 1e and (S)-2-(methoxycarbonylamino)-4-methylpentanoic acid which was prepared from L-Isoleucine and methylchloroformate in similar fashion to the preparation of *Cap*-51	LC/MS: 2.95 min (Cond'n 3); Anal. Calcd. for $[M+H]^+$ $C_{42}H_{53}N_8O_6$: 767.42; found 767.43.



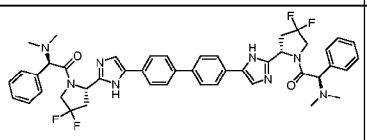
1-2e-3 OL-7

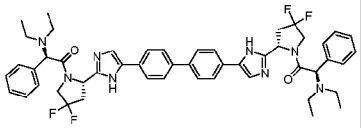
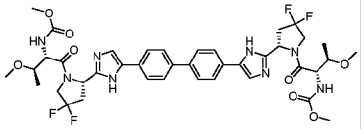
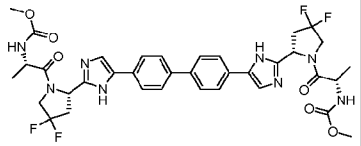
Example OL-7

methyl ((1S)-1-(((2S)-2-(4-(4'-(2-((2S)-4,4-difluoro-1-((2S)-2-((methoxycarbonyl)amino)-3-methylbutanoyl)-2-pyrrolidinyl)-1H-imidazol-4-yl)-4-biphenylyl)-1H-imidazol-2-yl)-4,4-difluoro-1-pyrrolidinyl)carbonyl)-2-methylpropyl)carbamate

Example OL-7 was prepared from 1-2e-3 in similar fashion to the preparation of Example 1, using *Cap*-51 as the coupling partner. ^{1}H NMR (500 MHz, DMSO-d_6) δ ppm 0.80 (dd, *J*=6.41, 2.44 Hz, 12H) 1.87-1.98 (m, 2H) 2.79-2.91 (m, 2H) 3.01-3.13 (m, 2H) 3.54 (s, 6H) 3.98 (t, *J*=7.93 Hz, 2H) 4.22-4.37 (m, 2H) 4.52 (t, *J*=14.19 Hz, 2H) 5.31 (t, *J*=8.39 Hz, 2H) 7.50 (d, *J*=7.93 Hz, 2H) 7.82-7.87 (m, 4H) 7.88-7.97 (m, 6H) 8.08 (s, 2H). LC (Cond'n 6): 7.64 min; MS: Anal. Calcd. for $[M+H]^+$ $C_{40}H_{47}F_4N_8O_6$: 811.35; found 811.46. HRMS: Anal. Calcd. for $(M+H)^+$ $C_{40}H_{47}F_4N_8O_6$ 811.3549 found 811.3553.

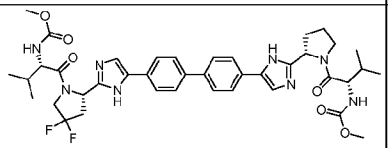
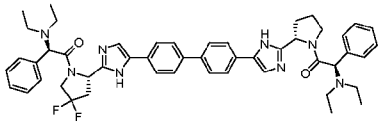
The following analogs were prepared from 1-2e-3 in similar fashion to the preparation of Example 1 and employing the appropriate Cap.

Example Number	*Compound Name*	*Structure*	*Analytical Data*
OL-8	(1R,1'R)-2,2'-(4,4'-biphenyldiylbis(1H-imidazole-4,2-diyl((2S)-4,4-difluoro-2,1-pyrrolidinediyl)))bis(N,N-dimethyl-2-oxo-1-phenylethanamine)	 From 1-2e-3 and *Cap*-1	LC/MS: 3.98 min (Cond'n 5); Anal. Calcd. for $[M+H]^+$ $C_{46}H_{47}F_4N_8O_2$: 819.37; found 819.78.

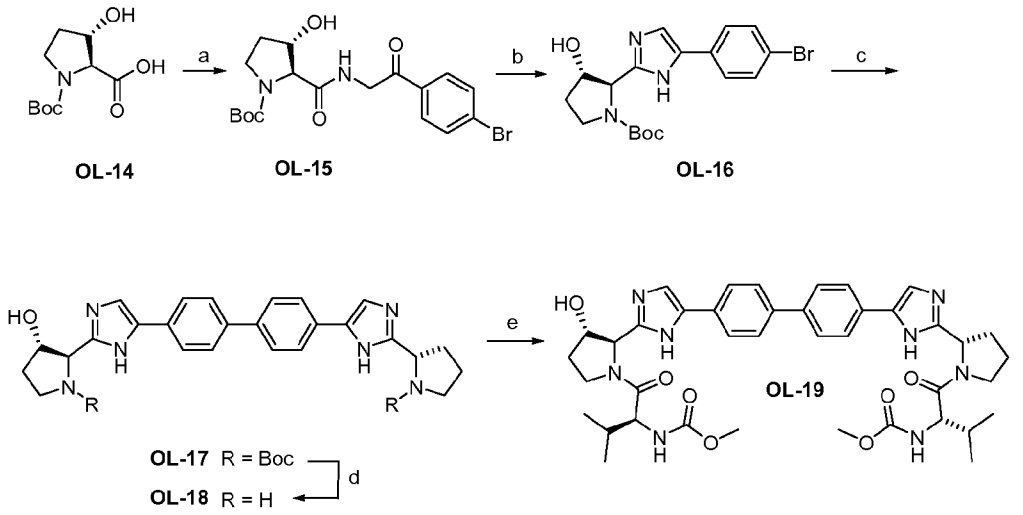
OL-9	(1R,1'R)-2,2'-(4,4'-biphenyldiylbis(1H-imidazole-4,2-diyl((2S)-4,4-difluoro-2,1-pyrrolidinediyl)))bis(N,N-diethyl-2-oxo-1-phenylethanamine)	 From 1-2e-3 and *Cap*-2	LC/MS: 4.58 min (Cond'n 5); Anal. Calcd. for $[M+H]^+$ $C_{50}H_{55}F_4N_8O_2$: 875.449; found 875.90.
OL-10	methyl ((1S,2R)-1-(((2S)-2-(4-(4'-(2-((2S)-4,4-difluoro-1-(N-(methoxycarbonyl)-O-methyl-L-threonyl)-2-pyrrolidinyl)-1H-imidazol-4-yl)-4-biphenylyl)-1H-imidazol-2-yl)-4,4-difluoro-1-pyrrolidinyl)carbonyl)-2-methoxypropyl)carbamate	 From 1-2e-3 and *Cap*-86	LC/MS: 2.18 min (Cond'n 7); Anal. Calcd. for $[M+H]^+$ $C_{40}H_{47}F_4N_8O_8$: 843.84; found 844.04.
OL-11	methyl ((1S)-2-((2S)-2-(4-(4'-(2-((2S)-4,4-difluoro-1-(N-(methoxycarbonyl)-L-alanyl)-2-pyrrolidinyl)-1H-imidazol-4-yl)-4-biphenylyl)-1H-imidazol-2-yl)-4,4-	 From 1-2e-3 and *Cap*-52	LC/MS: 2.04 min (Cond'n 7); Anal. Calcd. for $[M+H]^+$ $C_{36}H_{39}F_4N_8O_6$: 755.29; found 755.78.

	difluoro-1-pyrrolidinyl)-1-methyl-2-oxoethyl)carbamate		

The following analogs were prepared from 1-3e in similar fashion to the preparation of Example 1 and employing the appropriate Cap.

Example Number	*Compound Name*	*Structure*	*Analytical Data*
OL-12	methyl ((1S)-1-(((2S)-2-(4-(4'-(2-((2S)-4,4-difluoro-1-((2S)-2-((methoxycarbonyl)amino)-3-methylbutanoyl)-2-pyrrolidinyl)-1H-imidazol-4-yl)-4-biphenylyl)-1H-imidazol-2-yl)-1-pyrrolidinyl)carbonyl)-2-methylpropyl)carbamate	 From 1-3e and *Cap*-51	LC/MS: 2.33 min (Cond'n 3); Anal. Calcd. for $[M+H]^+$ $C_{40}H_{49}F_2N_8O_2$: 775.37; found 775.37.
OL-13	rac-(1R)-2-((2S)-2-(4-(4'-(2-((2S)-1-((2R)-2-(diethylamino)-2-phenylacetyl)-4,4-difluoro-2-pyrrolidinyl)-1H-imidazol-4-yl)-4-biphenylyl)-1H-	 From 1-3e and *Cap*-2	LC/MS: 3.93 min (Cond'n 5); Anal. Calcd. for $[M+H]^+$ $C_{50}H_{57}F_2N_8O_2$: 839.40; found 839.93.

	imidazol-2-yl)-1-pyrrolidinyl)-N,N-diethyl-2-oxo-1-phenylethanamine		



Example OL-19

methyl ((1S)-1-(((2R,3S)-3-hydroxy-2-(4-(4'-(2-((2S)-1-((2S)-2-((methoxycarbonyl)amino)-3-methylbutanoyl)-2-pyrrolidinyl)-1H-imidazol-4-yl)-4-biphenylyl)-1H-imidazol-2-yl)-1-pyrrolidinyl)carbonyl)-2-methylpropyl)carbamate

Step a: Intermediate OL-15 was prepared in similar fashion as intermediate 1a, where *N*-Boc-L-proline was substituted for *N*-Boc-*trans*-3-hydroxy-L-proline. ^{1}H NMR (500 MHz, DMSO-d_6) δ ppm 1.34/1.4) (2 br. s., 9H) 1.65-1.77 (m, 1H) 1.83-1.95 (m, 1H) 3.33-3.42 (m, 1H) 3.43-3.51 (m, 1H) 3.96-4.07 (m, 1H) 4.16 (s, 1H) 4.44-4.65 (m, 2H) 5.22-5.28 (m, 1H) 7.74 (d, *J*=8.54 Hz, 2H) 7.86-7.94 (m, 2H) 8.15-8.32 (m, 1H). LC (Cond. 4): RT = 3.33 min; MS: Anal. Calcd. for $[2M+Na]^+$ $C_{36}H_{46}Br_2N_4NaO_{10}$: 877.57; found 877.11.

Step b: Intermediate OL-16 was prepared from intermediate OL-15 in similar fashion as intermediate 1b. ^{1}H NMR (500 MHz, DMSO-d_6) δ ppm 1.16/1.39 (2 br. s., 9H) 1.71-1.81 (m, *J*=6.10 Hz, 1H) 2.01-2.17 (m, 1H) 3.37-3.50 (m, 1H) 3.50-3.62 (m, 1H) 4.15 (s, 1H) 4.49-4.70 (m, 1H) 5.36 (dd, *J*=6.71, 3.66 Hz, 1H) 7.44-7.62 (m, 3H)

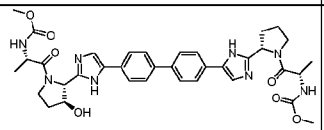
7.68 (d, *J*=7.02 Hz, 2H) 11.96/11.99/12.26/12.30 (m, 1H). LC (Cond. 8): RT = 1.87 min; MS: Anal. Calcd. for $[M+H]^+$ $C_{18}H_{23}BrN_3O_3$: 408.08; found 408.09.

Step c: Intermediate OL-17 was prepared by coupling intermediate OL-16 with 1c in similar fashion to the preparation of 1d. ^{1}H NMR (500 MHz, DMSO-d_6) δ ppm 1.09-1.49 (m, 18H) 1.71-2.04 (m, 4H) 2.06-2.28 (m, 2H) 3.33-3.40 (m, 1H) 3.41-3.65 (m, 3H) 4.18 (s, 1H) 4.52-4.69 (m, 1H) 4.70-4.88 (m, 1H) 5.38 (s, 1H) 6.64-7.35 (m, 1H) 7.39-7.96 (m, 9H) 11.71 – 12.0/12.10 – 12.36 (m, 2H). LC (Cond. 2): RT = 1.36 min; MS: Anal. Calcd. for $[M+H]^+$ $C_{36}H_{45}N_6O_5$: 641.77; found 641.39.

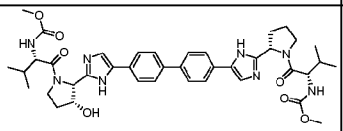
Step d: Intermediate OL-18 was prepared by deprotection of intermediate OL-17 with HCl in similar fashion to the preparation of 1-1e. ^{1}H NMR (500 MHz, DMSO-d_6) δ ppm 1.92-2.07 (m, 2H) 2.14-2.25 (m, 1H) 2.35-2.44 (m, 1H) 3.15 (s, 4H) 3.32-3.41 (m, *J*=7.02, 7.02, 7.02 Hz, 1H) 3.41-3.51 (m, *J*=7.32 Hz, 2H) 3.54-3.66 (m, 1H) 4.68 (d, *J*=4.27 Hz, 1H) 4.78-4.89 (m, *J*=4.88 Hz, 1H) 5.04 (s, 1H) 6.89/7.73 (2d, *J*= 8.70 Hz, 1H) 7.89 (dd, *J*=8.24, 4.58 Hz, 4H) 7.96-8.07 (m, 4H) 8.15 (d, *J*=23.19 Hz, 2H) 9.62-10.12 (m, 2H) 10.21-10.74 (m, 2H).). LC (Cond. 8): RT = 1.30 min; MS: Anal. Calcd. for $[M+H]^+$ $C_{26}H_{29}N_6O$: 441.24; found 441.18.

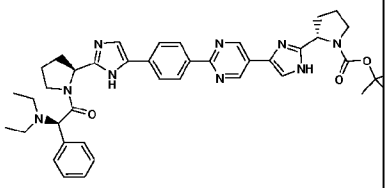
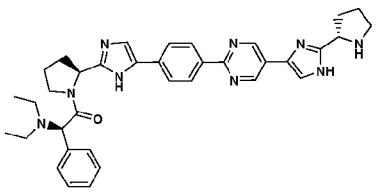
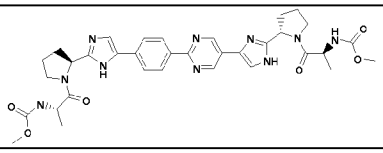
Step e: Example OL-19 was prepared by coupling of intermediate OL-18 with *Cap*-51 in similar fashion to the preparation of Example 1. ^{1}H NMR (500 MHz, DMSO-d_6) δ ppm 0.78 (d, *J*=6.41 Hz, 6H) 0.83 (d, *J*=6.71 Hz, 6H) 1.92-2.12 (m, 5H) 2.12-2.21 (m, 1H) 2.31 (dd, *J*=12.21, 5.80 Hz, 1H) 2.35-2.43 (m, 1H) 3.54 (d, *J*=4.27 Hz, 6H) 3.78-3.89 (m, 3H) 3.91-4.02 (m, 1H) 4.07-4.19 (m, 2H) 4.36-4.50 (m, 1H) 4.81 (d, *J*=3.66 Hz, 1H) 5.13 (t, *J*=7.17 Hz, 1H) 5.79 (s, 1H) 7.34 (dd, *J*=11.29, 8.85 Hz, 2H) 7.83-7.90 (m, 4H) 7.90-8.01 (m, 4H) 8.12 (s, 2H) [Note: the signal for the imidazole NH was too broad to assign a chemical shift].). LC (Cond. 4): RT = 2.76 min; MS: Anal. Calcd. for $[M+H]^+$ $C_{40}H_{51}N_8O_7$: 755.39; found 755.38. HRMS: Anal. Calcd. for $(M+H)^+$ $C_{40}H_{51}N_8O_7$ 755.3881 found 755.3873.

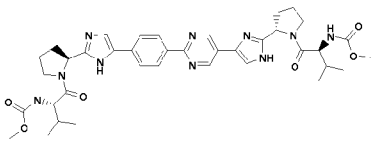
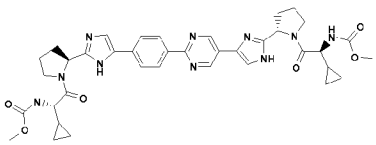
The following analog was prepared from intermediate OL-18 in similar fashion to the preparation of Example 1 and employing *Cap*-52.

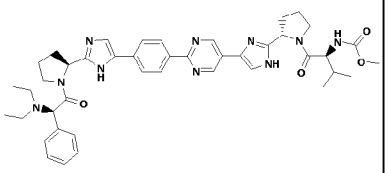
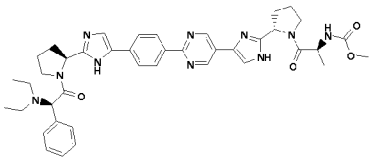
Example Number	*Compound Name*	*Structure*	*Analytical Data*
OL-20	methyl ((1S)-2-((2S)-2-(4-(4'-(2-((2R,3S)-3-hydroxy-1-(N-(methoxycarbonyl)-L-alanyl)-2-pyrrolidinyl)-1H-imidazol-4-yl)-4-biphenylyl)-1H-imidazol-2-yl)-1-pyrrolidinyl)-1-methyl-2-oxoethyl)carbamate	 From OL-18 and *Cap*-52	LC/MS: 2.32 min (Cond'n 4); Anal. Calcd. for $[M+H]^+$ $C_{36}H_{43}N_8O_7$: 699.78; found 699.32.

The following analog was prepared in similar fashion to the preparation of OL-19 but using *N*-Boc-*cis*-3-hydroxy-L-proline as starting material.

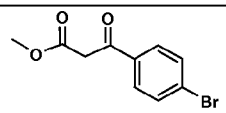
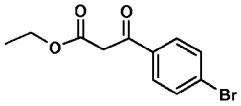
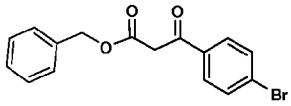
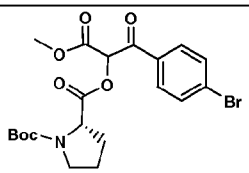
Example Number	*Compound Name*	*Structure*	*Analytical Data*
OL-21	methyl ((1S)-1-(((2R)-3-hydroxy-2-(4-(4'-(2-((2S)-1-((2S)-2-((methoxycarbonyl)amino)-3-methylbutanoyl)-2-pyrrolidinyl)-1H-imidazol-4-yl)-4-biphenylyl)-1H-imidazol-2-yl)-1-pyrrolidinyl)carbonyl)-2-methylpropyl)carbamate	 From *N*-Boc-*cis*-3-hydroxy-L-proline and *Cap*-51	LC/MS: 2.74 min (Cond'n 4); Anal. Calcd. for $[M+H]^+$ $C_{40}H_{51}N_8O_7$: 755.39; found 755.34.

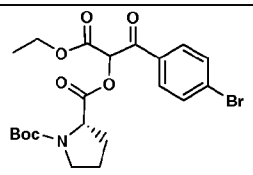
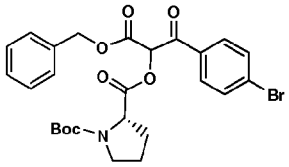
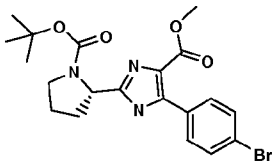
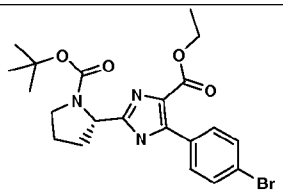
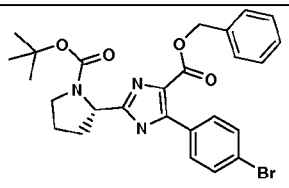
Example Number	*Compound Name*	*Heterocycles with New Caps*	*Analytical Data (Cond 1: 3 min gradient, 4 min run; Cond 2: 2 min gradient, 3 min run)*
D71	tert-butyl (2S)-2-(5-(2-(4-(2-((2S)-1-((2R)-2-(diethylamino)-2-phenylacetyl)-2-pyrrolidinyl)-1H-imidazol-5-yl)phenyl)-5-pyrimidinyl)-1H-imidazol-2-yl)-1-pyrrolidinecarboxylate	 Prepared from 152i-1 (in lieu of 148e) and *Cap*-2 using experimental conditions outlined in Example 148	t_R = 1.82 min, (97.7%), (Cond 1) LRMS: Anal. Calcd. for $C_{41}H_{50}N_9O_3$ 716.40; found: 716.44 $(M+H)^+$. HRMS: Anal. Calcd. for $C_{41}H_{50}N_9O_3$ 716.4037; found: 716.4056 $(M+H)^+$.
D72	(1R)-N,N-diethyl-2-oxo-1-phenyl-2-((2S)-2-(5-(4-(5-(2-((2S)-2-pyrrolidinyl)-1H-imidazol-5-yl)-2-pyrimidinyl)phenyl)-1H-imidazol-2-yl)-1-pyrrolidinyl)ethanamine	 Prepared from entry 71 (in lieu of 152j-27) using experimental conditions outlined in Example 152k-l.	t_R = 1.56 min, (~95.3%, has shoulder), (Cond 1) LRMS: Anal. Calcd. for $C_{36}H_{42}N_9O$ 616.35; found: 616.37 $(M+H)^+$. HRMS: Anal. Calcd. for $C_{36}H_{42}N_9O$ 616.3512; found: 616.3540 $(M+H)^+$.
D73	methyl ((1S)-2-((2S)-2-(5-(4-(5-(2-((2S)-1-(N-		t_R = 1.52 min, (96.2%), (Cond 1)

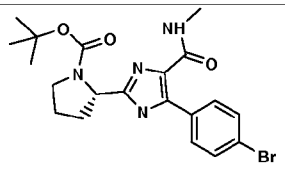
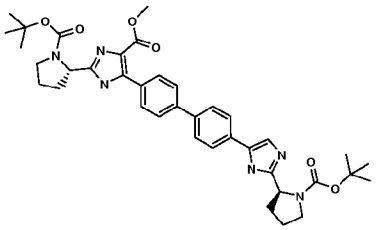
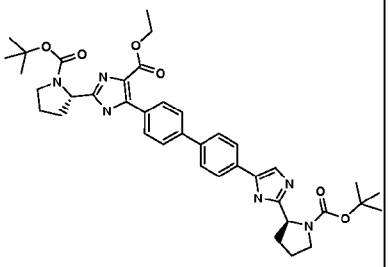
	(methoxycarbonyl)-L-alanyl)-2-pyrrolidinyl)-1H-imidazol-5-yl)-2-pyrimidinyl)phenyl)-1H-imidazol-2-yl)-1-pyrrolidinyl)-1-methyl-2-oxoethyl)carbamate	Prepared from 152h-1 (in lieu of 148e) and *Cap*-52 using experimental conditions outlined in Example 148	LRMS: Anal. Calcd. for $C_{34}H_{41}N_{10}O_6$ 685.32; found: 685.21 $(M+H)^+$. HRMS: Anal. Calcd. for $C_{34}H_{41}N_{10}O_6$ 685.3211; found: 685.3196 $(M+H)^+$.
D74	methyl ((1S)-1-(((2S)-2-(5-(2-(4-(2-((2S)-1-((2S)-2-((methoxycarbonyl)amino)-3-methylbutanoyl)-2-pyrrolidinyl)-1H-imidazol-5-yl)phenyl)-5-pyrimidinyl)-1H-imidazol-2-yl)-1-pyrrolidinyl)carbonyl)-2-methylpropyl)carbamate	 Prepared from 152h-1 (in lieu of 148e) and *Cap*-51 using experimental conditions outlined in Example 148	t_R = 2.09 min, (95%), (Cond 1) LRMS: Anal. Calcd. for $C_{38}H_{49}N_{10}O_6$ 741.38; found: 741.26 $(M+H)^+$. HRMS: Anal. Calcd. for $C_{38}H_{49}N_{10}O_6$ 741.3837; found: 741.3824 $(M+H)^+$.
D75	methyl ((1S)-1-cyclopropyl-2-((2S)-2-(5-(2-(4-(2-((2S)-1-((2S)-2-cyclopropyl-2-((methoxycarbonyl)amino)acetyl)-2-pyrrolidinyl)-1H-imidazol-5-yl)phenyl)-5-pyrimidinyl)-1H-	 Prepared from 152h-1 (in lieu of 148e) and *Cap*-54b using experimental conditions outlined in Example 148	t_R = 1.98 min, (95%), (Cond 1) LRMS: Anal. Calcd. for $C_{38}H_{45}N_{10}O_6$ 737.35; found: 737.22 $(M+H)^+$. HRMS: Anal. Calcd. for $C_{38}H_{45}N_{10}O_6$ 737.3524; found:

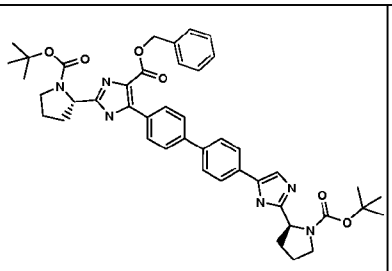
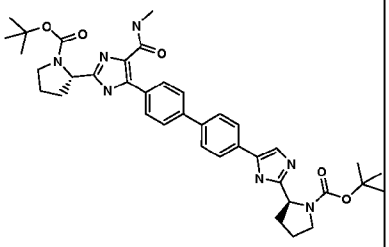
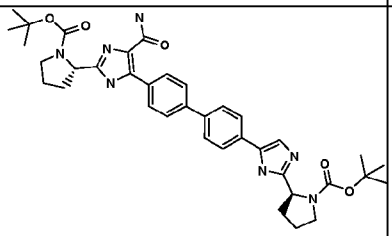
	imidazol-2-yl)-1-pyrrolidinyl)-2-oxoethyl)carbamate		737.3555 $(M+H)^+$.
D76	methyl ((1S)-1-(((2S)-2-(5-(2-(4-(2-((2S)-1-((2R)-2-(diethylamino)-2-phenylacetyl)-2-pyrrolidinyl)-1H-imidazol-5-yl)phenyl)-5-pyrimidinyl)-1H-imidazol-2-yl)-1-pyrrolidinyl)carbonyl)-2-methylpropyl)carbamate	 Prepared from entry D72 (in lieu of 148e) and *Cap*-51 using experimental conditions outlined in Example 148	t_R = 1.69 min, (95%), (Cond 1) LRMS: Anal. Calcd. for $C_{43}H_{53}N_{10}O_4$ 773.43; found: 773.30 $(M+H)^+$. HRMS: Anal. Calcd. for $C_{43}H_{53}N_{10}O_4$ 773.4251; found: 773.4280 $(M+H)^+$.
D77	methyl ((1S)-2-((2S)-2-(5-(2-(4-(2-((2S)-1-((2R)-2-(diethylamino)-2-phenylacetyl)-2-pyrrolidinyl)-1H-imidazol-5-yl)phenyl)-5-pyrimidinyl)-1H-imidazol-2-yl)-1-pyrrolidinyl)-1-methyl-2-oxoethyl)carbamate	 Prepared from entry D72 (in lieu of 148e) and *Cap*-52 using experimental conditions outlined in Example 148	t_R = 1.81 min, (97.5%), (Cond 1) LRMS: Anal. Calcd. for $C_{41}H_{49}N_{10}O_4$ 745.39; found: 745.27 $(M+H)^+$. HRMS: Anal. Calcd. for $C_{41}H_{49}N_{10}O_4$ 745.3938; found: 745.3939 $(M+H)^+$.

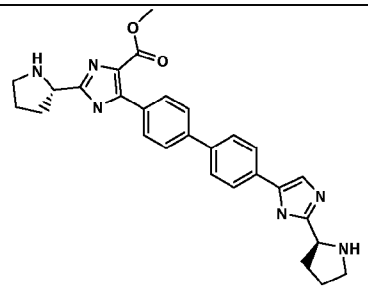
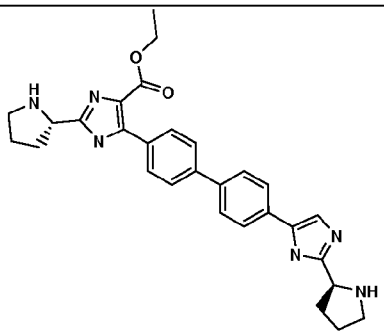
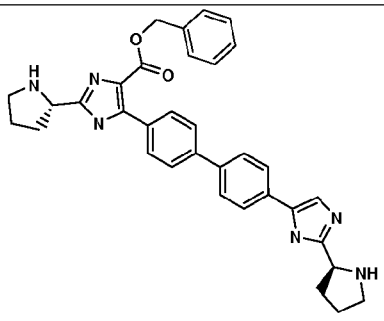
Section J

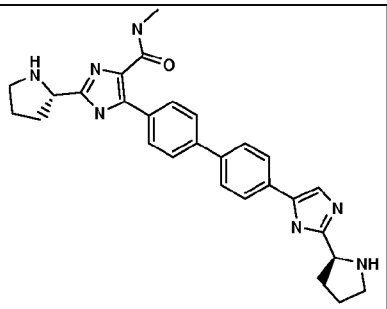
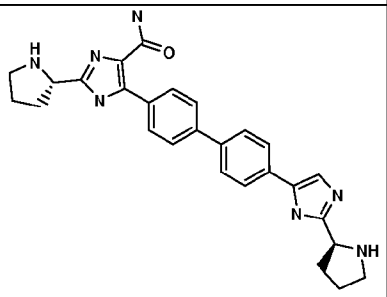
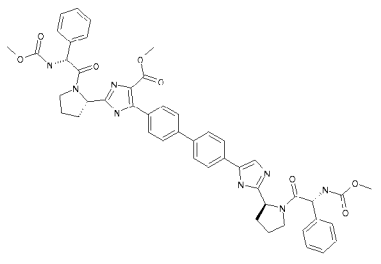
Example Number	*Compound Name*	*Structure*	*Analytical Data*
J.1a		 Prepared from 4-bromoacetophenone and dimethylcarbonate from Bioorg.Med.Chem.Lett (2001)11, 641	t_R = 1.7 min, (Cond 2); LCMS: $C_{10}H_9BrO_3$ found: 257 $(M+H)^+$.
J.1b		 Prepared from 4-bromoacetophenone and diethylcarbonate from Bioorg.Med.Chem.Lett (2001)11, 641.	t_R = 1.9 min, (Cond 2); LCMS: $C_{11}H_{11}BrO_3$ found: 271 $(M+H)^+$.
J.1c		 Prepared from 4-bromoacetophenone and dibenzylcarbonate from Bioorg.Med.Chem.Lett (2001)11, 641.	t_R = 2.1min, (Cond 2); LCMS: $C_{16}H_{13}BrO_3$ found: 332 $(M+H)^+$.
J1		 Prepared from entry J.1a (in lieu of J.1b) and proline using experimental conditions in Example J2.	t_R = 2.2min, (Cond 2); LCMS: $C_{20}H_{24}BrNO_7$ found: 470 $(M+H)^+$.

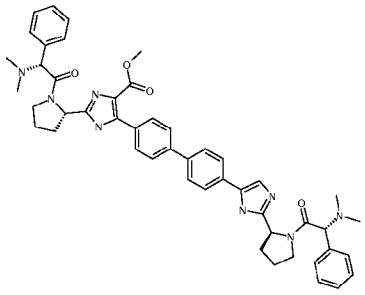
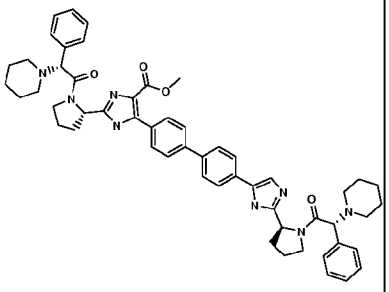
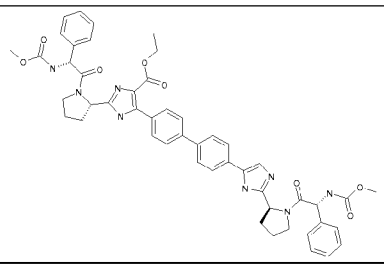
J2		 Prepared from entry J.1b and proline using experimental conditions in Example J2.	t_R = 2.2min, (Cond 2); LCMS: $C_{21}H_{26}BrNO_7$ found: 484 $(M+H)^+$.
J3		 Prepared from entry J.1c (in lieu of J.1b) and proline using experimental conditions in Example J2.	t_R = 2.3min, (Cond 2); LCMS: $C_{26}H_{28}BrNO_7$ found: 546 $(M+H)^+$.
J4		 Prepared from entry J.1 and (in lieu of J.2) using experimental conditions in Example J2.	t_R = 1.84 min, (100%) (Cond 2); LRMS: Anal. Calcd. for $C_{20}H_{24}BrN_3O_4$; 450.10; found: 450.13 and 452.13 $(M+H)^+$.
J5		 Prepared from entry J2 using experimental conditions in J5.	t_R = 1.93 min, (99%) (Cond 2); Reported in J5.
J6		 Prepared from entry J3 (in lieu of	t_R = 2.1 min, (93%) (Cond 2); LRMS: Anal. Calcd. for $C_{26}H_{29}BrN_3O_4$

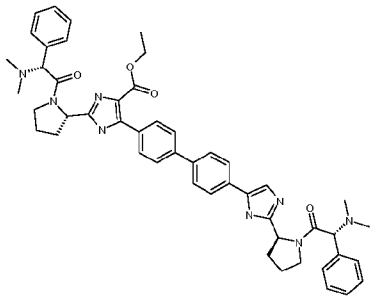
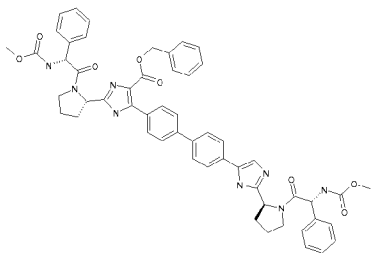
		entry J1) using experimental conditions in J5.	526.13; found: 526.16 and 528.16 $(M+H)^+$.
J7		 Prepared from entry J5 using experimental in J7.	t_R = 1.7 min, (100%) (Cond 2); Reported in J7.
J8	methyl 2-((2S)-1-(tert-butoxycarbonyl)-2-pyrrolidinyl)-5-(4'-(2-((2S)-1-(tert-butoxycarbonyl)-2-pyrrolidinyl)-1H-imidazol-5-yl)-4-biphenylyl)-1H-imidazole-4-carboxylate	 Prepared from entry J4 (in lieu of 152e-1) and 1c using experimental conditions outlined in Example 152g-1.	t_R = 1.70 min, (95%) (Cond 2); LRMS: Anal. Calcd. for $C_{38}H_{47}N_6O_6$ 683.36; found: 683.42 $(M+H)^+$.
J9	ethyl 2-((2S)-1-(tert-butoxycarbonyl)-2-pyrrolidinyl)-5-(4'-(2-((2S)-1-(tert-butoxycarbonyl)-2-pyrrolidinyl)-1H-imidazol-5-yl)-4-biphenylyl)-1H-imidazole-4-carboxylate	 Prepared from entry J5 (in lieu of 152e-1) and 1c using experimental conditions outlined in Example 152g-1.	t_R = 1.78 min, (97.5%) (Cond 2); LRMS: Anal. Calcd. for $C_{39}H_{49}N_6O_6$ 697.37; found: 697.38 $(M+H)^+$.

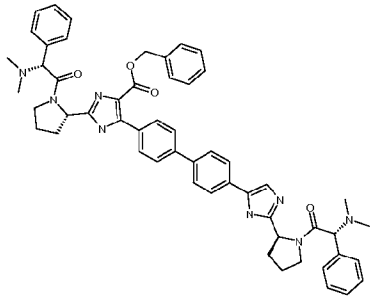
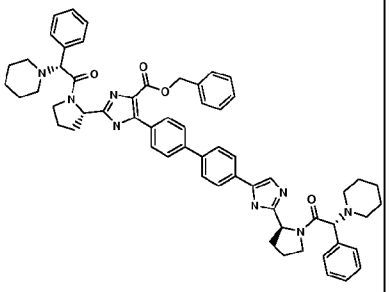
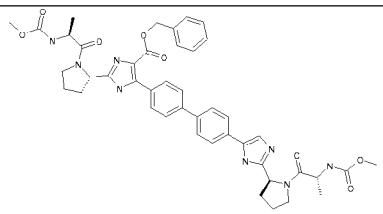
J10	benzyl 2-((2S)-1-(tert-butoxycarbonyl)-2-pyrrolidinyl)-5-(4'-(2-((2S)-1-(tert-butoxycarbonyl)-2-pyrrolidinyl)-1H-imidazol-5-yl)-4-biphenylyl)-1H-imidazole-4-carboxylate	 Prepared from entry J6 (in lieu of 152e-1) and 1c using experimental conditions outlined in Example 152g-1.	t_R = 1.88 min, (85%) (Cond 2); LRMS: Anal. Calcd. for $C_{44}H_{51}N_6O_6$ 759.39; found: 759.48 $(M+H)^+$.
J11	tert-butyl (2S)-2-(5-(4'-(2-((2S)-1-(tert-butoxycarbonyl)-2-pyrrolidinyl)-1H-imidazol-5-yl)-4-biphenylyl)-4-(methylcarbamoyl)-1H-imidazol-2-yl)-1-pyrrolidinecarboxylate	 Prepared from entry J7 (in lieu of 152e-1) and 1c using experimental conditions outlined in Example 152g-1.	t_R = 1.65 min, (90%) (Cond 2); LRMS: Anal. Calcd. for $C_{38}H_{48}N_7O_5$ 682.37; found: 682.42 $(M+H)^+$.
J11.a		 Prepared from entry J9 as described in J11.a.	t_R = 1.60 min, (Cond 2); LCMS: $C_{37}H_{46}N_7O_5$ found: 668 $(M+H)^+$.

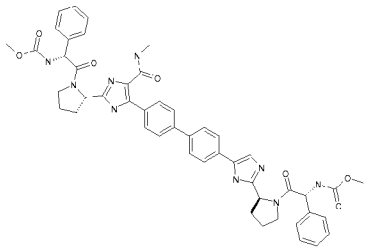
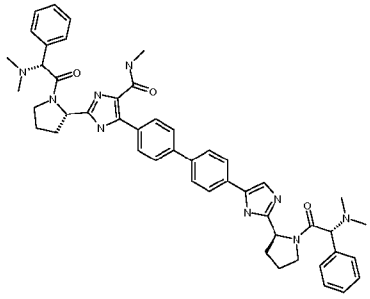
J12		 Prepared from entry J8 (in lieu of 152j-27) using experimental conditions outlined in Example 152k-1.	t_R = 1.25min, (97%) (Cond 2); LCMS: $C_{28}H_{31}N_6O_2$ found: 483 $(M+H)^+$.
J13		 Prepared from entry J9 (in lieu of 152j-27) using experimental conditions outlined in Example 152k-1.	t_R = 1.34 min, (Cond 2); LCMS: $C_{29}H_{33}N_6O_2$ found: 497 $(M+H)^+$.
J14		 Prepared from entry J10 (in lieu of 152j-27) using experimental conditions outlined in Example 152k-1.	t_R = 1.51 min, (90%) (Cond 2); LCMS: $C_{34}H_{35}N_6O_2$ found: 559$(M+H)^+$.

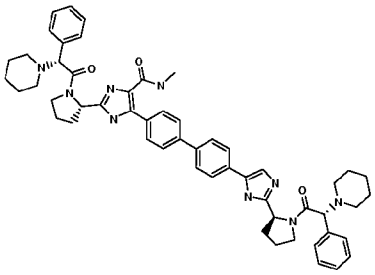
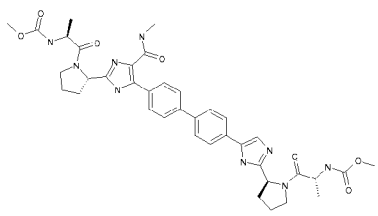
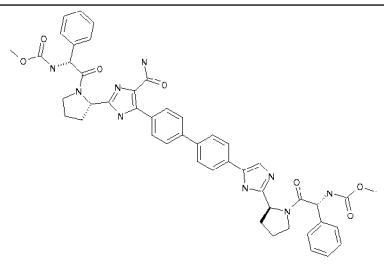
J15		 Prepared from entry J11 (in lieu of 152j-27) using experimental conditions outlined in Example 152k-1.	t_R = 1.32 min, (99%) (Cond 2); LCMS: $C_{28}H_{32}N_7O$ found: 482 $(M+H)^+$.
J15.a		 Prepared from entry J11.a (in lieu of 152j-27) using experimental conditions outlined in Example 152k-1.	t_R = 1.07 min, (98%) (Cond 2); LCMS: $C_{27}H_{30}N_7O$ found: 468 $(M+H)^+$.
J16	methyl 2-((2S)-1-((2R)-2-((methoxycarbonyl) amino)-2-phenylacetyl)-2-pyrrolidinyl)-5-(4'-(2-((2S)-1-((2R)-2-((methoxycarbonyl) amino)-2-phenylacetyl)-2-pyrrolidinyl)-1H-imidazol-5-yl)-4-	 Prepared from entry J12 (in lieu of 148e) and *Cap*-4 using experimental conditions outlined in Example 148.	t_R = 1.62 min, (99.5%) (Cond 2); LRMS: Anal. Calcd. for C48H49N8O8 865.37; found: 865.34 $(M+H)^+$. HRMS: Anal. Calcd. for C48H49N8O8 865.3673; found: 865.3715 $(M+H)^+$.

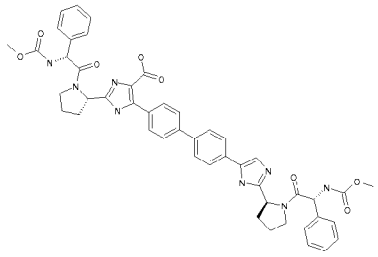
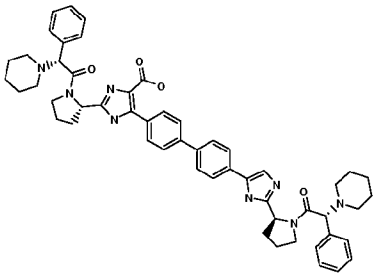
	biphenylyl)-1H-imidazole-4-carboxylate		
J17	methyl 2-((2S)-1-((2R)-2-(dimethylamino)-2-phenylacetyl)-2-pyrrolidinyl)-5-(4'-(2-((2S)-1-((2R)-2-(dimethylamino)-2-phenylacetyl)-2-pyrrolidinyl)-1H-imidazol-5-yl)-4-biphenylyl)-1H-imidazole-4-carboxylate	 Prepared from entry J12 (in lieu of 148c) and *Cap*-1 using experimental conditions outlined in Example 148.	t_R = 1.37 min, (92%) (Cond 2); LRMS: Anal. Calcd. for C48H53N8O4 804.42; found: 805.51 $(M+H)^+$. HRMS: Anal. Calcd. for C48H53N8O4 805.4190; found: 805.4211 $(M+H)^+$.
J18	methyl 2-((2S)-1-((2R)-2-phenyl-2-(1-piperidinyl)acetyl)-2-pyrrolidinyl)-5-(4'-(2-((2S)-1-((2R)-2-phenyl-2-(1-piperidinyl)acetyl)-2-pyrrolidinyl)-1H-imidazol-5-yl)-4-biphenylyl)-1H-imidazole-4-carboxylate	 Prepared from entry J12 (in lieu of 148e) and *Cap*-14 using experimental conditions outlined in Example 148.	t_R = 1.46 min, (94%) (Cond 2); LRMS: Anal. Calcd. for C54H61N8O6 885.48; found: 885.48 $(M+H)^+$. HRMS: Anal. Calcd. for C54H61N8O6 885.4816; found: 885.4852 $(M+H)^+$.
J19	ethyl 2-((2S)-1-((2R)-2-((methoxycarbonyl)amino)-2-phenylacetyl)-2-		t_R = 1.68 min, (99%) (Cond 2); LRMS: Anal. Calcd. for C49H51N8O8

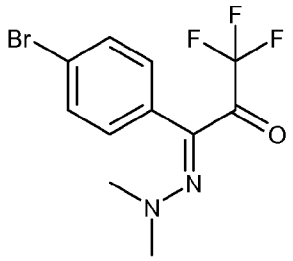
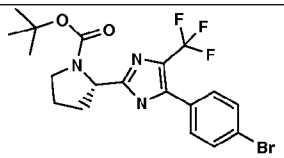
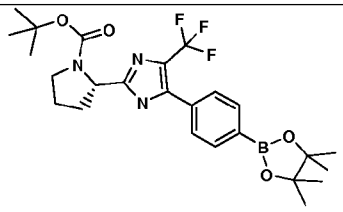
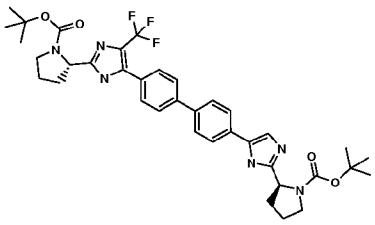
	pyrrolidinyl)-5-(4'-(2-((2S)-1-((2R)-2-((methoxycarbonyl)amino)-2-phenylacetyl)-2-pyrrolidinyl)-1H-imidazol-5-yl)-4-biphenylyl)-1H-imidazole-4-carboxylate	Prepared from entry J13 (in lieu of 148e) and *Cap*-4 using experimental conditions outlined in Example 148.	879.38; found: 879.37 $(M+H)^+$. HRMS: Anal. Calcd. for C49H51N8O8 879.3830; found: 879.3814 $(M+H)^+$.
J20	ethyl 2-((2S)-1-((2R)-2-(dimethylamino)-2-phenylacetyl)-2-pyrrolidinyl)-5-(4'-(2-((2S)-1-((2R)-2-(dimethylamino)-2-phenylacetyl)-2-pyrrolidinyl)-1H-imidazol-5-yl)-4-biphenylyl)-1H-imidazole-4-carboxylate	 Prepared from entry J13 (in lieu of 148e) and *Cap*-1 using experimental conditions outlined in Example 148.	t_R = 1.45 min, (89%) (Cond 2); LRMS: Anal. Calcd. for C49H55N8O4 818.44; found: 818.40 $(M+H)^+$. HRMS: Anal. Calcd. for C49H55N8O4 819.4346; found: 819.4340 $(M+H)^+$.
J21	benzyl 2-((2S)-1-((2R)-2-((methoxycarbonyl)amino)-2-phenylacetyl)-2-pyrrolidinyl)-5-(4'-(2-((2S)-1-((2R)-2-((methoxycarbonyl)amino)-2-phenylacetyl)-2-pyrrolidinyl)-1H-imidazol-5-yl)-4-	 Prepared from entry J14 (in lieu of 148e) and *Cap*-4 using experimental conditions outlined in Example 148.	t_R = 1.80 min, (92%) (Cond 2); LRMS: Anal. Calcd. for C54H53N8O8 941.40; found: 941.39 $(M+H)^+$. HRMS: Anal. Calcd. for C54H53N8O8 941.3986; found: 941.4033 $(M+H)^+$.

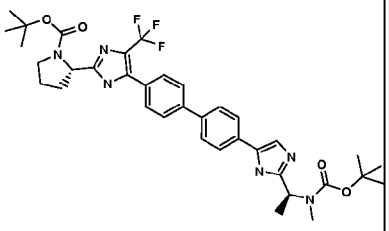
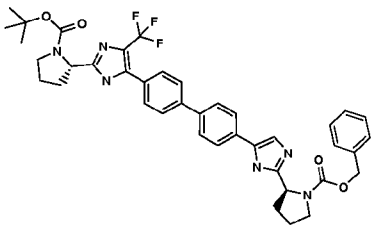
	biphenylyl)-1H-imidazole-4-carboxylate		
J22	benzyl 2-((2S)-1-((2R)-2-(dimethylamino)-2-phenylacetyl)-2-pyrrolidinyl)-5-(4'-(2-((2S)-1-((2R)-2-(dimethylamino)-2-phenylacetyl)-2-pyrrolidinyl)-1H-imidazol-5-yl)-4-biphenylyl)-1H-imidazole-4-carboxylate	 Prepared from entry J14 (in lieu of 148e) and *Cap*-1 using experimental conditions outlined in Example 148.	t_R = 1.56 min, (96%) (Cond 2); LRMS: Anal. Calcd. for C54H57N8O4 881.45; found: 881.46 $(M+H)^+$. HRMS: Anal. Calcd. for C54H57N8O4 881.4503; found: 881.4536 $(M+H)^+$.
J23	benzyl 2-((2S)-1-((2R)-2-phenyl-2-(1-piperidinyl)acetyl)-2-pyrrolidinyl)-5-(4'-(2-((2S)-1-((2R)-2-phenyl-2-(1-piperidinyl)acetyl)-2-pyrrolidinyl)-1H-imidazol-5-yl)-4-biphenylyl)-1H-imidazole-4-carboxylate	 Prepared from entry J14 (in lieu of 148e) and *Cap*-14 using experimental conditions outlined in Example 148.	t_R = 1.63 min, (96%) (Cond 2); LRMS: Anal. Calcd. for C60H65N8O4 961.51; found: 961.54 $(M+H)^+$. HRMS: Anal. Calcd. for C60H65N8O4 961.5129; found: 961.5164 $(M+H)^+$.
J24	benzyl 2-((2S)-1-(N-(methoxycarbonyl)-L-alanyl)-2-pyrrolidinyl)-5-(4'-		t_R = 1.64 min, (94%) (Cond 2); LRMS: Anal. Calcd. for C44H49N8O8

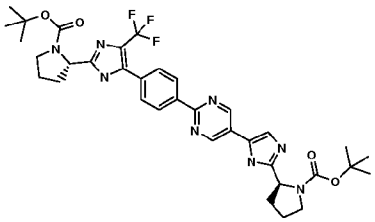
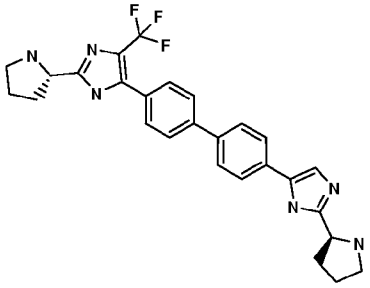
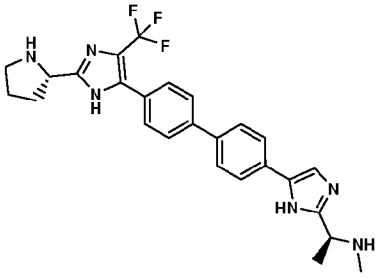
	(2-((2S)-1-(N-(methoxycarbonyl)-L-alanyl)-2-pyrrolidinyl)-1H-imidazol-5-yl)-4-biphenylyl)-1H-imidazole-4-carboxylate	Prepared from entry J14 (in lieu of 148e) and *Cap*-52 using experimental conditions outlined in Example 148.	817.37; found: 817.38 $(M+H)^+$. HRMS: Anal. Calcd. for C44H49N8O8 817.3673; found: 817.3675 $(M+H)^+$.
J25	methyl ((1R)-2-((2S)-2-(5-(4'-(2-((2S)-1-((2R)-2-((methoxycarbonyl)amino)-2-phenylacetyl)-2-pyrrolidinyl)-1H-imidazol-5-yl)-4-biphenylyl)-4-(methylcarbamoyl)-1H-imidazol-2-yl)-1-pyrrolidinyl)-2-oxo-1-phenylethyl)carbamate	 Prepared from entry J15 (in lieu of 148e) and *Cap*-4 using experimental conditions outlined in Example 148.	t_R = 1.58 min, (99.6%) (Cond 2); LRMS: Anal. Calcd. for C48H50N9O7 864.38; found: 864.47 $(M+H)^+$. HRMS: Anal. Calcd. for C48H50N9O7 864.3833; found: 864.3849 $(M+H)^+$.
J26	2-((2S)-1-((2R)-2-(dimethylamino)-2-phenylacetyl)-2-pyrrolidinyl)-5-(4'-(2-((2S)-1-((2R)-2-(dimethylamino)-2-phenylacetyl)-2-pyrrolidinyl)-1H-imidazol-5-yl)-4-biphenylyl)-N-methyl-1H-imidazole-4-	 Prepared from entry J15 (in lieu of 148e) and *Cap*-1 using experimental conditions outlined in Example 148.	t_R = 1.31 min, (93.2%) (Cond 2); LRMS: Anal. Calcd. for C48H54N9O3 804.44; found: 804.51 $(M+H)^+$. HRMS: Anal. Calcd. for C48H54N9O3 804.4350; found: 804.4369 $(M+H)^+$.

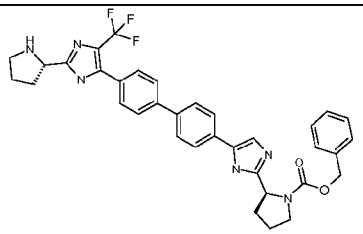
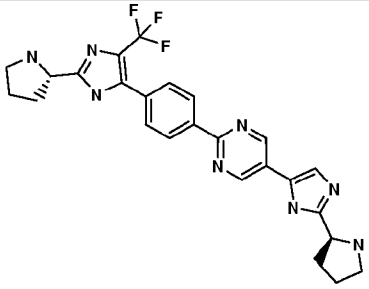
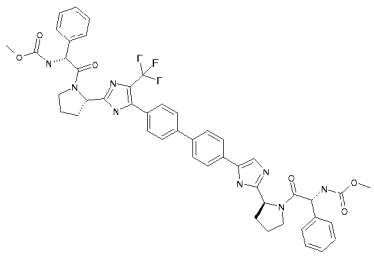
	carboxamide		
J27	N-methyl-2-((2S)-1-((2R)-2-phenyl-2-(1-piperidinyl)acetyl)-2-pyrrolidinyl)-5-(4'-(2-((2S)-1-((2R)-2-phenyl-2-(1-piperidinyl)acetyl)-2-pyrrolidinyl)-1H-imidazol-5-yl)-4-biphenylyl)-1H-imidazole-4-carboxamide	 Prepared from entry J15 (in lieu of 148c) and *Cap*-14 using experimental conditions outlined in Example 148.	t_R = 1.39 min, (95.4%) (Cond 2); LRMS: Anal. Calcd. for C54H62N9O3 884.50; found: 884.52 $(M+H)^+$. HRMS: Anal. Calcd. for C54H62N9O3 884.4976; found: 884.4973 $(M+H)^+$.
J28	methyl ((1S)-2-((2S)-2-(5-(4'-(2-((2S)-1-(N-(methoxycarbonyl)-L-alanyl)-2-pyrrolidinyl)-4-(methylcarbamoyl)-1H-imidazol-5-yl)-4-biphenylyl)-1H-imidazol-2-yl)-1-pyrrolidinyl)-1-methyl-2-oxoethyl)carbamate	 Prepared from entry J15 (in lieu of 148e) and *Cap*-52 using experimental conditions outlined in Example 148.	t_R = 1.34 min, (89.3%) (Cond 2); LRMS: Anal. Calcd. for C38H46N9O7 740.35; found: 740.31 $(M+H)^+$. HRMS: Anal. Calcd. for C38H46N9O7 740.3520; found: 740.3497 $(M+H)^+$.
J29	methyl ((1R)-2-((2S)-2-(4-carbamoyl-5-(4'-(2-((2S)-1-((2R)-2-((methoxycarbonyl)amino)-2-phenylacetyl)-2-	 Prepared from entry J15.a (in	t_R = 1.55 min, (96.4%) (Cond 2); LRMS: Anal. Calcd. for C47H48N9O7 740.35; found: 740.31 $(M+H)^+$.

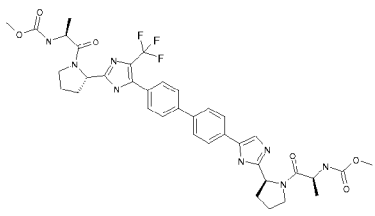
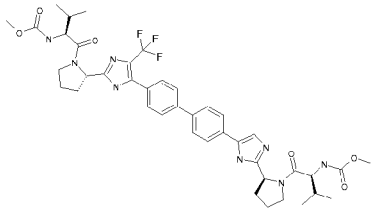
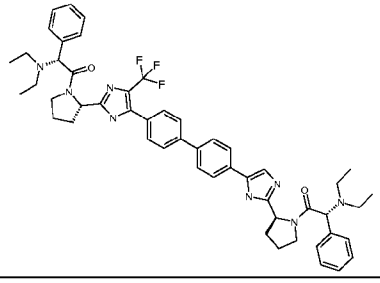
	pyrrolidinyl)-1H-imidazol-5-yl)-4-biphenylyl)-1H-imidazol-2-yl)-1-pyrrolidinyl)-2-oxo-1-phenylethyl)carbamate	lieu of 148e) and *Cap*-4 using experimental conditions outlined in Example 148.	HRMS: Anal. Calcd. for C47H48N9O7 740.3520; found: 740.3497 $(M+H)^+$.
J30	2-((2S)-1-((2R)-2-((methoxycarbonyl)amino)-2-phenylacetyl)-2-pyrrolidinyl)-5-(4'-(2-((2S)-1-((2R)-2-((methoxycarbonyl)amino)-2-phenylacetyl)-2-pyrrolidinyl)-1H-imidazol-5-yl)-4-biphenylyl)-1H-imidazole-4-carboxylic acid	 Prepared from entry 21 (in lieu of 28c) using experimental conditions outlined in Example 28 step d.	t_R = 1.52 min, (92.8%) (Cond 2); LRMS: Anal. Calcd. for C47H47N8O8 851.35; found: 851.37 $(M+H)^+$. HRMS: Anal. Calcd. for C47H47N8O8 851.3517; found: 851.3553 $(M+H)^+$.
J31	2-((2S)-1-((2R)-2-phenyl-2-(1-piperidinyl)acetyl)-2-pyrrolidinyl)-5-(4'-(2-((2S)-1-((2R)-2-phenyl-2-(1-piperidinyl)acetyl)-2-pyrrolidinyl)-1H-imidazol-5-yl)-4-biphenylyl)-1H-imidazole-4-carboxylic acid	 Prepared from entry 23 (in lieu of 28c) using experimental conditions outlined in Example 28 step d.	t_R = 1.36 min, (96.5%) (Cond 2); LRMS: Anal. Calcd. for C53H59N8O4 871.47; found: 871.47 $(M+H)^+$. HRMS: Anal. Calcd. for C53H59N8O4 871.4659; found: 871.4692 $(M+H)^+$.

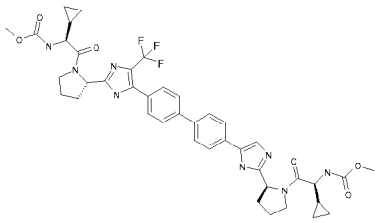
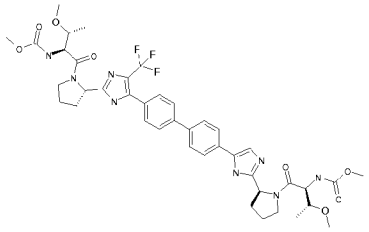
J32		 Prepared from 4-bromobenzaldehyde according to procedure described in J.Org.Chem. (1988), 53, 129.	t_R = 1.96 min, (96%) (Cond 2); LRMS: Anal. Calcd. for $C_{11}H_{11}BrF_3N_2O$ 323.00; found: 323.05 and 325.05 $(M+H)^+$. ^1H NMR (300 MHz, DMSO-d_6) δ 7.58 (d, J = 8.4 Hz, 2H), 7.21 (d, J = 8.4 Hz, 2H), 3.06 (s, 6H).
J32.a		 Prepared from entry J32 using experimental conditions in J32.a	t_R = 2.19 min, (96%) (Cond 2); Reported in J32.a
J32.b		 Prepared from entry J32.a (in lieu of 1b) using experimental conditions outlined in Example 1 step c.	t_R = 2.3 min, (73%) (Cond 2); LCMS: $C_{25}H_{34}BF_3N_3O_4$ found: 508 $(M+H)^+$.
J33	tert-butyl (2S)-2-(5-(4'-(2-((2S)-1-(tert-butoxycarbonyl)-2-pyrrolidinyl)-1H-imidazol-5-yl)-4-biphenylyl)-4-	 Prepared from entry J32.a (in	t_R = 2.7 min, (95%) (Cond 2); LRMS: Anal. Calcd. for $C_{37}H_{44}F_3N_6O_4$ 693.34; found: 693.33 $(M+H)^+$.

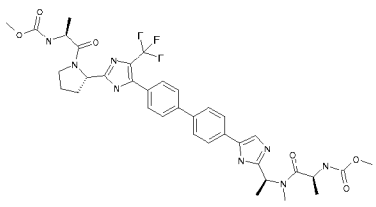
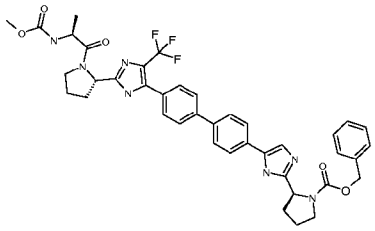
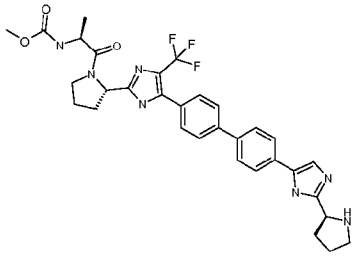
	(trifluoromethyl)-1H-imidazol-2-yl)-1-pyrrolidinecarboxylate	lieu of 152e-1) and 1c using experimental conditions outlined in Example 152g-1.	HRMS: Anal. Calcd. for $C_{37}H_{44}F_3N_6O_4$ 693.3376; found: 693.3370 $(M+H)^+$.
J33.a	tert-butyl (2S)-2-(5-(4'-(2-((1S)-1-((tert-butoxycarbonyl)(methyl)amino)ethyl)-1H-imidazol-5-yl)-4-biphenylyl)-4-(trifluoromethyl)-1H-imidazol-2-yl)-1-pyrrolidinecarboxylate	 Prepared from entry J32.a (in lieu of 152e-1) and 1-8c using experimental conditions outlined in Example 152g-1.	t_R = 1.97 min, (97%) (Cond 2); LRMS: Anal. Calcd. for $C_{36}H_{44}F_3N_6O_4$ 681.34; found: 681.31 $(M+H)^+$. HRMS: Anal. Calcd. for $C_{36}H_{44}F_3N_6O_4$ 681.3376; found: 681.3383 $(M+H)^+$.
J34	tert-butyl (2S)-2-(5-(4'-(2-((2S)-1-((benzyloxy)carbonyl)-2-pyrrolidinyl)-1H-imidazol-5-yl)-4-biphenylyl)-4-(trifluoromethyl)-1H-imidazol-2-yl)-1-pyrrolidinecarboxylate	 Prepared from entry J32.a (in lieu of 152e-1) and 1-5c using experimental conditions outlined in Example 152g-1.	t_R = 2.0 min, (95%) (Cond 2); LRMS: Anal. Calcd. for $C_{40}H_{42}F_3N_6O_4$ 727.32; found: 727.19 $(M+H)^+$. HRMS: Anal. Calcd. for $C_{40}H_{42}F_3N_6O_4$ 727.3220; found: 727.3251 $(M+H)^+$.

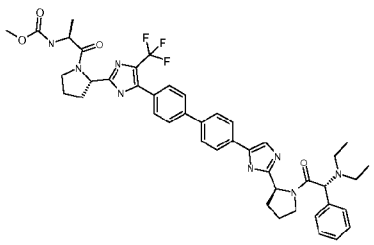
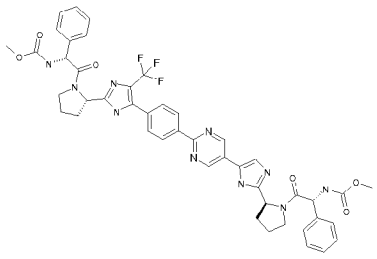
J34.a	tert-butyl (2S)-2-(5-(4-(5-(2-((2S)-1-(tert-butoxycarbonyl)-2-pyrrolidinyl)-1H-imidazol-5-yl)-2-pyrimidinyl)phenyl)-4-(trifluoromethyl)-1H-imidazol-2-yl)-1-pyrrolidinecarboxylate	 Prepared from entry J32.b (in lieu of 152e-1) and 152d-1 using experimental conditions outlined in Example 152g-1.	t_R = 1.97 min, (93%) (Cond 2); LRMS: Anal. Calcd. for $C_{35}H_{42}F_3N_8O_4$ 695.33; found: 695.28 $(M+H)^+$.
J35		 Prepared from entry J33 (in lieu of 152j-27) using experimental conditions outlined in Example 152k-1.	t_R = 1.46 min, (92%) (Cond 2); LCMS: $C_{27}H_{28}F_3N_6O$ found: 493 $(M+H)^+$.
J35.a		 Prepared from entry J33.a (in lieu of 152j-27) using experimental conditions outlined in Example 152k-1.	LCMS: $C_{26}H_{28}F_3N_6$ found: 481 $(M+H)^+$.

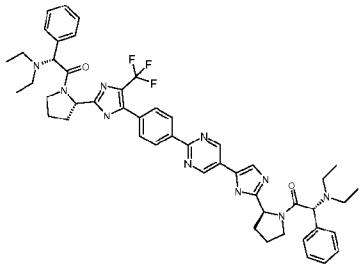
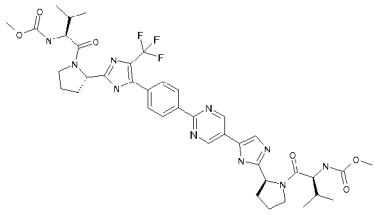
J36		 Prepared from entry J34 (in lieu of 152j-27) using experimental conditions outlined in Example 152k-1.	LCMS: $C_{35}H_{34}F_3N_6O_2$ found: 626 $(M+H)^+$.
J36.a		 Prepared from entry J34.a (in lieu of 152j-27) using experimental conditions outlined in Example 152k-1.	t_R = 1.45 min, (Cond 2); LCMS: $C_{25}H_{26}F_3N_8$ found: 495 $(M+H)^+$.
J37	methyl ((1R)-2-((2S)-2-(5-(4'-(2-((2S)-1-((2R)-2-((methoxycarbonyl)amino)-2-phenylacetyl)-2-pyrrolidinyl)-1H-imidazol-5-yl)-4-biphenylyl)-4-(trifluoromethyl)-1H-imidazol-2-yl)-1-pyrrolidinyl)-2-oxo-1-phenylethyl)carbamate	 Prepared from entry J35 (in lieu of 148e) and *Cap*-4 using experimental conditions outlined in Example 148.	t_R = 1.9 min, (95%) (Cond 2); LRMS: Anal. Calcd. for $C_{47}H_{46}F_3N_8O_4$ 875.35; found: 875.35 $(M+H)^+$. HRMS: Anal. Calcd. for $C_{47}H_{46}F_3N_8O_4$ 875.3492; found: 875.3504 $(M+H)^+$.

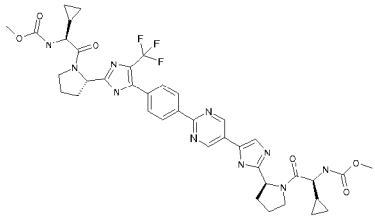
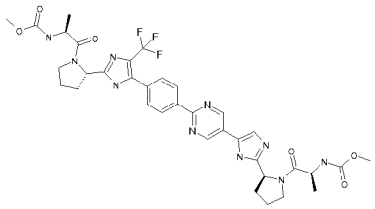
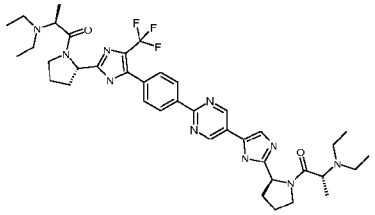
J38	methyl ((1S)-2-((2S)-2-(5-(4'-(2-((2S)-1-(N-(methoxycarbonyl)-L-alanyl)-2-pyrrolidinyl)-4-(trifluoromethyl)-1H-imidazol-5-yl)-4-biphenylyl)-1H-imidazol-2-yl)-1-pyrrolidinyl)-1-methyl-2-oxoethyl)carbamate	 Prepared from entry J35 (in lieu of 148e) and *Cap*-52 using experimental conditions outlined in Example 148.	t_R = 1.7 min, (95.5%) (Cond 2); LRMS: Anal. Calcd. for $C_{37}H_{42}F_3N_8O_6$ 751.32; found: 751.32 $(M+H)^+$. HRMS: Anal. Calcd. for $C_{37}H_{42}F_3N_8O_6$ 751.3179; found: 751.3163 $(M+H)^+$.
J39	methyl ((1S)-1-(((2S)-2-(5-(4'-(2-((2S)-1-((2S)-2-((methoxycarbonyl)amino)-3-methylbutanoyl)-2-pyrrolidinyl)-1H-imidazol-5-yl)-4-biphenylyl)-4-(trifluoromethyl)-1H-imidazol-2-yl)-1-pyrrolidinyl)carbonyl)-2-methylpropyl)carbamate	 Prepared from entry J35 (in lieu of 148e) and *Cap*-51 using experimental conditions outlined in Example 148.	t_R = 1.9 min, (96%) (Cond 2); LRMS: Anal. Calcd. for $C_{41}H_{50}F_3N_8O_6$ 807.38; found: 807.33 $(M+H)^+$. HRMS: Anal. Calcd. for $C_{41}H_{50}F_3N_8O_6$ 807.3805; found: 807.3773 $(M+H)^+$.
J40	(1R)-2-((2S)-2-(5-(4'-(2-((2S)-1-((2R)-2-(diethylamino)-2-phenylacetyl)-2-pyrrolidinyl)-1H-		t_R = 1.6 min, (95%) (Cond 2); LRMS: Anal. Calcd. for $C_{51}H_{58}F_3N_8O_2$ 871.46; found:

	imidazol-5-yl)-4-biphenylyl)-4-(trifluoromethyl)-1H-imidazol-2-yl)-1-pyrrolidinyl)-N,N-diethyl-2-oxo-1-phenylethanamine	Prepared from entry J35 (in lieu of 148e) and *Cap*-2 using experimental conditions outlined in Example 148.	871.48 $(M+H)^+$. HRMS: Anal. Calcd. for $C_{51}H_{58}F_3N_8O_2$ 871.4635; found: 871.4647 $(M+H)^+$.
J41	methyl ((1S)-1-cyclopropyl-2-((2S)-2-(5-(4'-(2-((2S)-1-((2S)-2-cyclopropyl-2-((methoxycarbonyl)amino)acetyl)-2-pyrrolidinyl)-1H-imidazol-5-yl)-4-biphenylyl)-4-(trifluoromethyl)-1H-imidazol-2-yl)-1-pyrrolidinyl)-2-oxoethyl)carbamate	 Prepared from entry J35 (in lieu of 148e) and *Cap*-54b using experimental conditions outlined in Example 148.	t_R = 1.8 min, (96.9%) (Cond 2); LRMS: Anal. Calcd. for $C_{41}H_{46}F_3N_8O_6$ 803.35; found: 803.35 $(M+H)^+$. HRMS: Anal. Calcd. for $C_{41}H_{46}F_3N_8O_6$ 803.3492; found: 803.3507 $(M+H)^+$.
J42	methyl ((1S,2R)-2-methoxy-1-(((2S)-2-(5-(4'-(2-((2S)-1-(N-(methoxycarbonyl)-O-methyl-L-threonyl)-2-pyrrolidinyl)-4-(trifluoromethyl)-1H-imidazol-5-yl)-4-biphenylyl)-1H-imidazol-2-yl)-1-pyrrolidinyl)carbon	 Prepared from entry J35 (in lieu of 148e) and *Cap*-86 using experimental conditions outlined in Example 148.	t_R = 1.8 min, (92%) (Cond 2); LRMS: Anal. Calcd. for $C_{41}H_{50}F_3N_8O_8$ 839.37; found: 839.30 $(M+H)^+$. HRMS: Anal. Calcd. for $C_{41}H_{50}F_3N_8O_8$ 839.3704; found: 839.3677 $(M+H)^+$.

	yl)propyl)carbamate		
J42.a	methyl ((1S)-2-((2S)-2-(5-(4'-(2-((1S)-1-((N-(methoxycarbonyl)-L-alanyl)(methyl)amino)ethyl)-1H-imidazol-5-yl)-4-biphenylyl)-4-(trifluoromethyl)-1H-imidazol-2-yl)-1-pyrrolidinyl)-1-methyl-2-oxoethyl)carbamate	 Prepared from entry J35.a (in lieu of 148e) and *Cap*-52 using experimental conditions outlined in Example 148.	t_R = 1.69 min, (100%) (Cond 2); LRMS: Anal. Calcd. for $C_{36}H_{42}F_3N_8O_6$ 739.32; found: 739.31 $(M+H)^+$. HRMS: Anal. Calcd. for $C_{36}H_{42}F_3N_8O_6$ 739.3179; found: 739.3195 $(M+H)^+$.
J43	benzyl (2S)-2-(5-(4'-(2-((2S)-1-(N-(methoxycarbonyl)-L-alanyl)-2-pyrrolidinyl)-4-(trifluoromethyl)-1H-imidazol-5-yl)-4-biphenylyl)-1H-imidazol-2-yl)-1-pyrrolidinecarboxylate	 Prepared from entry J36 (in lieu of 148e) and *Cap*-52 using experimental conditions outlined in Example 148.	t_R = 1.9 min, (95%) (Cond 2); LRMS: Anal. Calcd. for $C_{40}H_{41}F_3N_7O_5$ 756.31; found: 756.19 $(M+H)^+$. HRMS: Anal. Calcd. for $C_{40}H_{41}F_3N_7O_5$ 756.3121; found: 756.3127 $(M+H)^+$.
J44			LCMS: $C_{32}H_{35}F_3N_7O_3$ found: 622 $(M+H)^+$.

		Prepared from entry J43 (in lieu of 152g-8) using experimental conditions outlined in Example 152i-1.	
J45	methyl ((1S)-2-((2S)-2-(5-(4'-(2-((2S)-1-((2R)-2-(diethylamino)-2-phenylacetyl)-2-pyrrolidinyl)-1H-imidazol-5-yl)-4-biphenylyl)-4-(trifluoromethyl)-1H-imidazol-2-yl)-1-pyrrolidinyl)-1-methyl-2-oxoethyl)carbamate	 Prepared from entry J44 (in lieu of 148e) and *Cap*-2 using experimental conditions outlined in Example 148.	t_R = 1.7 min, (93%) (Cond 2); LRMS: Anal. Calcd. for $C_{44}H_{50}F_3N_8O_4$ 811.39; found: 811.34 $(M+H)^+$. HRMS: Anal. Calcd. for $C_{44}H_{50}F_3N_8O_4$ 811.3907; found: 811.3913 $(M+H)^+$.
J46	methyl ((1R)-2-((2S)-2-(5-(4-(5-(2-((2S)-1-((2R)-2-((methoxycarbonyl)amino)-2-phenylacetyl)-2-pyrrolidinyl)-1H-imidazol-5-yl)-2-pyrimidinyl)phenyl)-4-(trifluoromethyl)-1H-imidazol-2-yl)-1-pyrrolidinyl)-2-oxo-1-phenylethyl)carbamate	 Prepared from entry J34.a (in lieu of 148e) and *Cap*-4 using experimental conditions outlined in Example 148	t_R = 1.82 min, (98%) (Cond 2); LRMS: Anal. Calcd. for $C_{45}H_{44}F_3N_{10}O_6$ 877.34; found: 877.29 $(M+H)^+$. HRMS: Anal. Calcd. for $C_{45}H_{44}F_3N_{10}O_6$ 877.3397; found: 877.3403 $(M+H)^+$.

J47	(1R)-2-((2S)-2-(5-(4-(5-(2-((2S)-1-((2R)-2-(diethylamino)-2-phenylacetyl)-2-pyrrolidinyl)-1H-imidazol-5-yl)-2-pyrimidinyl)phenyl)-4-(trifluoromethyl)-1H-imidazol-2-yl)-1-pyrrolidinyl)-N,N-diethyl-2-oxo-1-phenylethanamine	 Prepared from entry J34.a (in lieu of 148e) and *Cap*-2 using experimental conditions outlined in Example 148	t_R = 1.58 min, (97%) (Cond 2); LRMS: Anal. Calcd. for $C_{49}H_{56}F_3N_{10}O_2$ 873.44; found: 873.40 $(M+H)^+$. HRMS: Anal. Calcd. for $C_{49}H_{56}F_3N_{10}O_2$ 873.4540; found: 873.4536 $(M+H)^+$.
J48	methyl ((1S)-1-(((2S)-2-(5-(2-(4-(2-((2S)-1-((2S)-2-((methoxycarbonyl)amino)-3-methylbutanoyl)-2-pyrrolidinyl)-4-(trifluoromethyl)-1H-imidazol-5-yl)phenyl)-5-pyrimidinyl)-1H-imidazol-2-yl)-1-pyrrolidinyl)carbonyl)-2-methylpropyl)carbamate	 Prepared from entry J34.a (in lieu of 148e) and *Cap*-51 using experimental conditions outlined in Example 148	t_R = 1.85 min, (99%) (Cond 2); LRMS: Anal. Calcd. for $C_{39}H_{48}F_3N_{10}O_6$ 809.37; found: 809.37 $(M+H)^+$. HRMS: Anal. Calcd. for $C_{39}H_{48}F_3N_{10}O_6$ 809.3710; found: 809.3683 $(M+H)^+$.

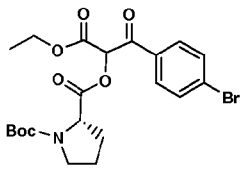
J49	methyl ((1S)-1-cyclopropyl-2-((2S)-2-(5-(4-(5-(2-((2S)-1-((2S)-2-cyclopropyl-2-((methoxycarbonyl)amino)acetyl)-2-pyrrolidinyl)-1H-imidazol-5-yl)-2-pyrimidinyl)phenyl)-4-(trifluoromethyl)-1H-imidazol-2-yl)-1-pyrrolidinyl)-2-oxoethyl)carbamate	 Prepared from entry J34.a (in lieu of 148e) and *Cap*-54b using experimental conditions outlined in Example 148	t_R = 1.75 min, (100%) (Cond 2); LRMS: Anal. Calcd. for $C_{39}H_{44}F_3N_{10}O_6$ 805.34; found: 805.34 $(M+H)^+$. HRMS: Anal. Calcd. for $C_{39}H_{44}F_3N_{10}O_6$ 805.3397; found: 805.3384 $(M+H)^+$.
J50	methyl ((1S)-2-((2S)-2-(5-(4-(5-(2-((2S)-1-(N-(methoxycarbonyl)-L-alanyl)-2-pyrrolidinyl)-1H-imidazol-5-yl)-2-pyrimidinyl)phenyl)-4-(trifluoromethyl)-1H-imidazol-2-yl)-1-pyrrolidinyl)-1-methyl-2-oxoethyl)carbamate	 Prepared from entry J34.a (in lieu of 148e) and *Cap*-52 using experimental conditions outlined in Example 148	t_R = 1.61 min, (94%) (Cond 2); LRMS: Anal. Calcd. for $C_{35}H_{40}F_3N_{10}O_6$ 753.31; found: 753.31 $(M+H)^+$. HRMS: Anal. Calcd. for $C_{35}H_{40}F_3N_{10}O_6$ 753.3084; found: 753.3099 $(M+H)^+$.
J51	(2R)-1-((2S)-2-(5-(4-(5-(2-((2S)-1-((2R)-2-(diethylamino)propanoyl)-2-pyrrolidinyl)-1H-	 Prepared from entry J34.a (in	t_R = 1.41 min, (92%) (Cond 2); LRMS: Anal. Calcd. for $C_{39}H_{52}F_3N_{10}O_2$ 749.42; found:

	imidazol-5-yl)-2-pyrimidinyl)phenyl)-4-(trifluoromethyl)-1H-imidazol-2-yl)-1-pyrrolidinyl)-N,N-diethyl-1-oxo-2-propanamine	lieu of 148e) and *Cap*-70b using experimental conditions outlined in Example 148	749.37 $(M+H)^+$. HRMS: Anal. Calcd. for $C_{39}H_{52}F_3N_{10}O_2$ 749.4227; found: 749.4223 $(M+H)^+$.

Cond 1: LCMS conditions: Phenomenex-Luna 4.6 x 50 mm S10, 0 to 100%B over 3 min, 4 min stop time, 4 mL/min, 220nm, A: 10% MeOH-90%H2O - 0.1% TFA; B: 90% MeOH-10%H2O-0.1% TFA

Cond 2: LCMS conditions: Phenomenex-Luna 4.6 x 50 mm S10, 0 to 100%B over 2 min, 3 min stop time, 4 mL/min, 220nm, A: 10% MeOH-90%H2O - 0.1% TFA; B: 90% MeOH-10%H2O-0.1% TFA

Example J2. (2S)-2-(1-(4-bromophenyl)-3-ethoxy-1,3-dioxopropan-2-yl) 1-tert-butyl pyrrolidine-1,2-dicarboxylate



J2

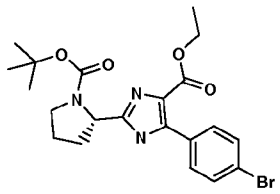
The ethyl 3-(4-bromophenyl)-3-oxopropanoate (15 g, 55 mmol) was dissolved in CH_2Cl_2 (600 mL) and freshly recrystallized NBS (9.8 g, 55 mmol) was added and the solution stirred 18 hr. The reaction mixture was washed with $NaHCO_3$ solution, brine, and dried ($MgSO_4$), filtered, and concentrated to give a residue which was not purified. Ethyl 2-bromo-3-(4-bromophenyl)-3-oxopropanoate (16.5 g, 48 mmol) and N-Boc-L-proline (10 g, 48 mmol) were taken up in acetonitrile (450 mL) and Hunig's base (16 mL, 95 mmol) was added and the solution stirred 18 hr. The solvent was removed by rotorary evaporation and the residue taken up in ethyl acetate, washed with 0.1 N HCl, and brine. ^1H NMR (300 MHz, DMSO-d_6) δ 7.95 (d, J = 8.4 Hz, 2H), 7.79 (d, J = 8.4 Hz, 2H), 6.68-6.65 (m, 1H), 4.39-4.30 (m, 1H),

4.21-4.12 (m, 2H), 2.27-2.21 (m, 1H), 2.0-1.95 (m, 1H), 1.90-1.76 (m, 2H), 1.39 (s, 2H), 1.31 (s, 9H), 1.11 (t, J = 7.3Hz, 3H).

LRMS: Anal. Calcd. for $C_{21}H_{26}BrNO_7$ 484.09; found: 410.08 $(M+H)^+$.

Example J5.

(S)-ethyl 5-(4-bromophenyl)-2-(1-(tert-butoxycarbonyl)pyrrolidin-2-yl)-1H-imidazolc-4-carboxylatc

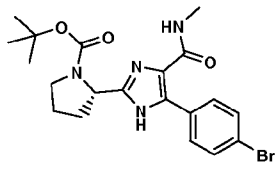


J5

A 1L pressure bottle was charged with (2S)-2-(1-(4-bromophenyl)-3-ethoxy-1,3-dioxopropan-2-yl) 1-tert-butyl pyrrolidine-1,2-dicarboxylate J2 (7 g, 35 mmol) and 11 g of NH_4OAc in 125 mL of Xylene, and the reaction was heated at 140°C for 3.5 hr. After being cooled, the solution was partition between ethyl actate and water. The organic layer was concentrated and the resultant residue applied to a Biotage 40 m silica gel cartridge and eluted by 20 -100% gradient, ethyl acetate/ Hex to give 3g (45%). ^{1}H NMR (300 MHz, $CDCl_3$) δ 12.75 (br. s, 7.82), (br. s, 2H), 7.50 (d, J = 8.4 Hz, 2H), 4.96-4.92 (m, 1H), 4.23 (q, J = 6.6 Hz, 2H), 3.68-3.50 (m, 1H), 3.40-3.32 (m, 1H), 2.19-2.15 (m, 1H), 1.99-1.89 (m, 3H), 1.48/1.13 (s, 9H), 1.23 (t, J = 7.3Hz, 3H). LRMS: Anal. Calcd. for $C_{21}H_{26}BrN_3O_4$ 464.12; found: 464.15 and 466.15 $(M+H)^+$.

Example J7.

(S)-tert-butyl 2-(5-(4-bromophenyl)-4-(methylcarbamoyl)-1H-imidazol-2-yl)pyrrolidine-1-carboxylate

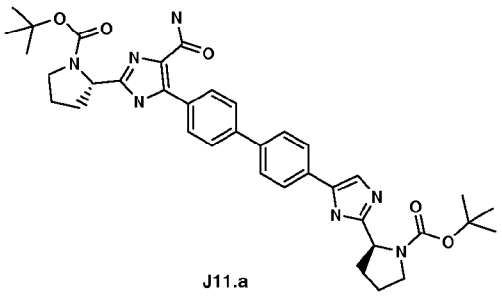


J7

(S)-ethyl 5-(4-bromophenyl)-2-(1-(tert-butoxycarbonyl)pyrrolidin-2-yl)-1H-imidazole-4-carboxylate (1g, 2.1 mmol) was dissolved in 2M methylamine in MeOH (35 mL) and heated in a pressure vessel at 70°C for 48 h. The reaction mixture was concentrated and the residue applied to a Biotage 25 m silica gel cartridge and eluted by 10 -100% gradient, ethyl acetate/ Hex to give 556 mg (57%). ^{1}H NMR (300 MHz, DMSO-d_6) δ 12.5 (br.s, 1H), 7.86-7.82 (m, 1H), 7.77 (d, J = 8.4 Hz, 2H), 7.61 (d, J = 8.7 Hz, 2H), 4.83-4.70 (m, 1H), 3.69-3.52 (br.s, 1H), 3.42-3.32 (m, 1H), 2.71 (d, 4.8 Hz, 3H), 2.30-1.78 (m, 4H), 1.19-1.14 (m, 9H).

LRMS: Anal. Calcd. for $C_{20}H_{26}BrN_4O_3$ 449.12; found: 449.15 and 451.14 $(M+H)^+$.

Example J11.a.

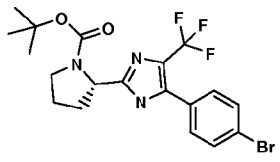


J11.a

Entry J9 (1.1g, 1.58 mmol) was taken up in ethanol (60 mL), 28% concentrated ammonium hydroxide soln (10 mL) was added, and the reaction heated in a pressure vessel at 75°C for 48 h. The solvent was removed by rotary evaporation and the residue taken up in ethyl acetate and washed with water, brine. Concentration and application to a 25 M Biotage cartridge, gradient elution with 10% - 100% ethyl acetate/CH_2Cl_2, gave J11.a 90 mg (8.5%) and recovered starting material J9 696 mg (63%).

Example J32.a.

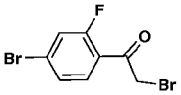
(S)-tert-butyl 2-(5-(4-bromophenyl)-4-(trifluoromethyl)-1H-imidazol-2-yl)pyrrolidine-1-carboxylate

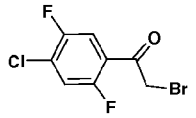
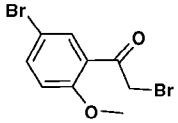
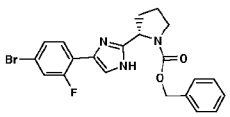


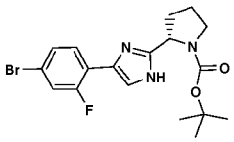
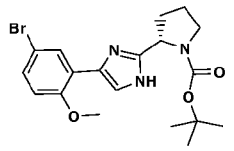
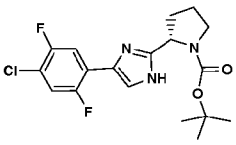
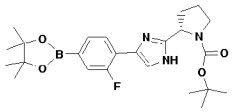
J32.a

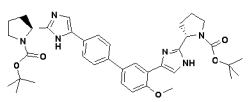
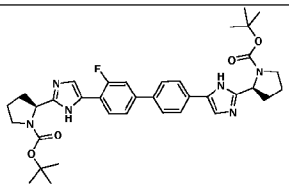
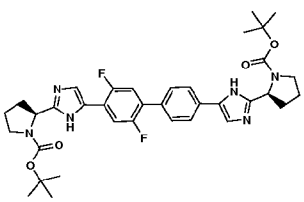
3-(4-bromophenyl)-3-(2,2-dimethylhydrazono)-1,1,1-trifluoropropan-2-one (2.0g, 6.2 mmol) was suspended in 5N sulfuric acid (60 mL) and heated at 45°C for 6 h. The temperature was raised to 85°C for 2 h, and upon cooling a precipitate formed. This material which was isolated by filtration to give 1-(4-bromophenyl)-3,3,3-trifluoropropane-1,2-dione 1.6g (92%) as a yellow solid. The dione (1.6g, 5.7 mmol) was taken up in methanol (30 mL), N-(tert-butoxycarbonyl)-L-prolinal (1g, 5.0 mmol) was added, followed by addition of 28% ammonium hydroxide solution (10 mL). The reaction was stirred at room temperature for 18 h, poured onto dichloromethane (200 mL), washed with water and dried with $MgSO_4$. Filtration, concentration and application to a 40 M Biotage cartridge, gradient elution with 5% - 30% ethyl acetate/Hexanes, gave J32.a 1.3g (50%). ^{1}H NMR (300 MHz, DMSO-d_6) δ 12.88 (br.s, 1H), 7.72 (d, J = 8.4 Hz, 2H), 7.39 (d, J = 8.0 Hz, 2H), 4.84-4.70 (m, 1H), 3.57-3.49 (m, 1H), 3.39-3.29 (m, 1H), 2.31-2.20 (m, 1H), 1.98-1.78 (m, 3H), 1.39/1.13 (m, 9H). LRMS: Anal. Calcd. for $C_{19}H_{20}BrF_3N_3O_2$ 458.07; found: 458.06 and 460.06 $(M-H)^-$. HRMS: Anal. Calcd. for $C_{19}H_{22}BrF_3N_3O_2$ 460.0847; found: 460.0866 and 462.0840 $(M+H)^+$.

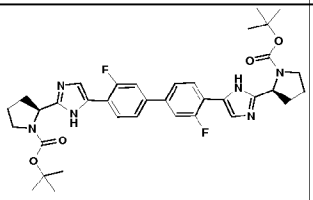
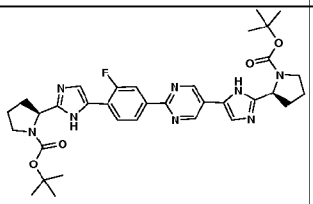
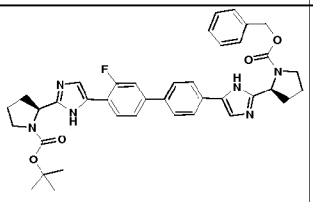
Section D

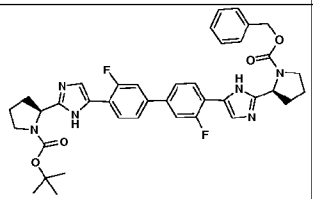
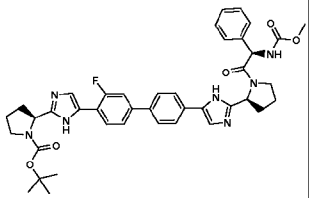
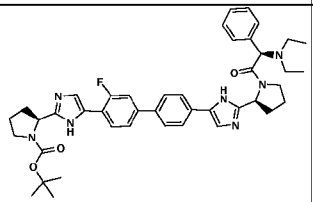
Entry	*Compound Name*	*Structure*	***Data*
D1		 Prepared from 1-(4-bromo-2-fluorophenyl)ethanone (Vendor: Marshalton	t_R = 2.65 min, (86.7%) LCMS: Anal. Calcd. for $C_8H_{15}BrFO$ 296.88; found: 296.91 $(M+H)^+$.

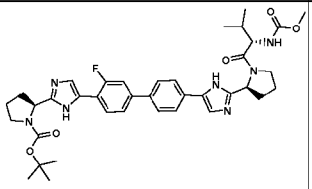
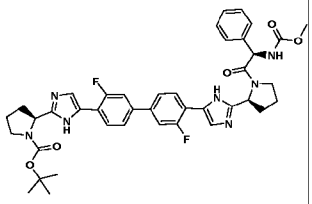
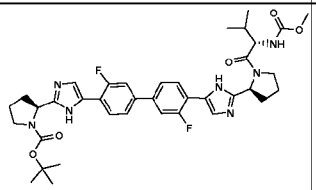
		50043) using bromination conditions outlined in D5.	
D2		 Prepared from 1-(4-chloro-2,5-difluorophenyl)ethanone (Vendor: Oakwood products, 001626) using bromination conditions outlined in D5.	t_R = 2.66 min, (80%) LCMS: Anal. Calcd. for $C_8H_4BrClFO$ 270.92; found: ND $(M+H)^+$.
D3		 Prepared from 2-bromo-1-(5-bromo-2-methoxyphenyl)ethanone (Andersh et al., Synth. Comm. 2000, 30 (12), 2091-98) using bromination conditions outlined in D5.	t_R = 2.57 min, (95%) LCMS: Anal. Calcd. for $C_9H_9BrO_2$ 228.99; found: 229.00 $(M+H)^+$.
D4		 Prepared from entry D1 and CBz-L-proline (in lieu of Boc-L-proline) using experimental conditions outlined in D5.	t_R = 2.38 min, (95.0%) LRMS: Anal. Calcd. for $C_{19}H_{20}{}^{79}BrFN_3O_2$ 444.07; found: 444.04 $(M+H)^+$. HRMS: Anal. Calcd. for $C_{19}H_{20}{}^{79}BrFN_3O_2$ 444.0721; found: 444.0736 $(M+H)^+$

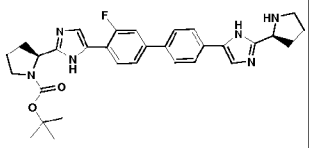
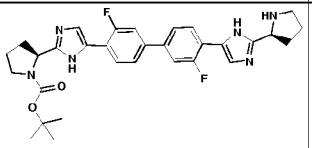
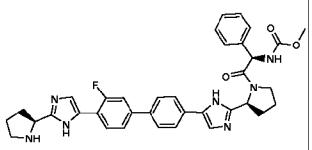
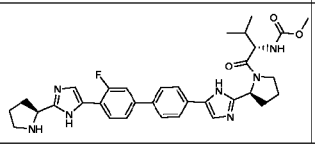
D5		 Experimental conditions in D5	t_R = 2.27min, (95%) LRMS: Anal. Calcd. for $C_{18}H_{22}BrFN_3O_2$ 410.09 and 412.08; found: 410.08 and 412.08 $(M+H)^+$. HRMS: Anal. Calcd. for $C_{18}H_{22}{}^{79}BrFN_3O_2$ 410.0879; found: 410.0893 $(M+H)^+$.
D6		 Prepared from entry D3 (in lieu of entry D1) using experimental conditions outlined in D5.	t_R = 2.26 min, (95%) LRMS: Anal. Calcd. for $C_{19}H_{25}BrN_3O_3$ 422.11 and 424.11; found: 422.10 and 424.10 $(M+H)^+$. HRMS: Anal. Calcd. for $C_{19}H_{25}{}^{79}BrN_3O_3$ 422.1079; found: 422.1089 $(M+H)^+$.
D7		 Prepared from entry D2 (in lieu of entry D1) using experimental conditions outlined in enclosed experiment.	t_R = 2.28 min, (95%) LRMS: Anal. Calcd. for $C_{18}H_{21}ClF_2N_3O_2$ 384.13; found: 384.13 $(M+H)^+$. HRMS: Anal. Calcd. for $C_{18}H_{21}ClF_2N_3O_2$ 384.1290; found: 384.1301 $(M+H)^+$.
D8		 Prep	t_R = 2.62 min, (~50%) and 1.95 min (~50%, boronic acid)

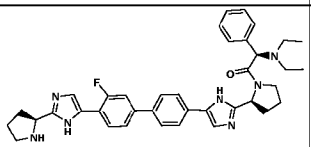
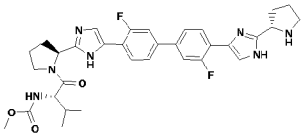
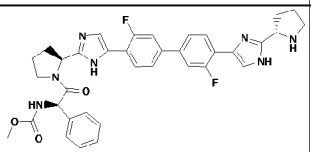
		ared from entry D5 (in lieu of 1b) using experimental conditions outlined in Example 1, Step c.	LRMS: Anal. Calcd. for $C_{24}H_{34}BFN_3O_4$ 458.26; found: 458.23 $(M+H)^+$. HRMS: Anal. Calcd. for $C_{24}H_{34}BFN_3O_4$ 458.2626; found: 458.2610 $(M+H)^+$.
D9	tert-butyl (2S)-2-(4-(4'-(2-((2S)-1-(tert-butoxycarbonyl)-2-pyrrolidinyl)-1H-imidazol-5-yl)-4-methoxy-3-biphenylyl)-1H-imidazol-2-yl)-1-pyrrolidinecarboxylate	 Prepared from entry D6 (in lieu of 152e-1) and 1c using experimental conditions outlined in Example 152g-1.	t_R = 2.28 min, (95%) LRMS: Anal. Calcd. for $C_{37}H_{47}N_6O_5$ 655.36; found: 655.37 $(M+H)^+$. HRMS: Anal. Calcd. for $C_{37}H_{47}N_6O_5$ 655.3608; found: 655.3627 $(M+H)^+$.
D10	di-tert-butyl (2S,2'S)-2,2'-((3-fluoro-4,4'-biphenyldiyl)bis(1H-imidazole-4,2-diyl))di(1-pyrrolidinecarboxylate)	 Prepared from entry D5 (in lieu of 152e-1) and 1c using experimental conditions outlined in Example 152g-1.	t_R = 2.21 min, (99.2%) LCMS: Anal. Calcd. for $C_{36}H_{44}FN_6O_4$ 643.34; found: 643.51 $(M+H)^+$. HRMS: Anal. Calcd. for $C_{36}H_{44}FN_6O_4$ 643.3403; found: 643.3390 $(M+H)^+$.
D11	tert-butyl (2S)-2-(4-(4'-(2-((2S)-1-(tert-butoxycarbonyl)-2-pyrrolidinyl)-1H-imidazol-5-yl)-2,5-difluoro-4-		t_R = 2.24 min, (95%) LRMS: Anal. Calcd. for $C_{36}H_{43}F_2N_6O_4$ 661.33; found: 661.35 $(M+H)^+$.

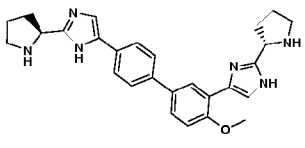
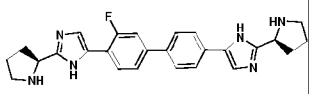
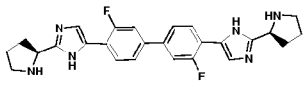
	biphenylyl)-1H-imidazol-2-yl)-1-pyrrolidinecarboxylate	Prepared from entry D7 (in lieu of 152e-1) and 1c using experimental conditions outlined in Example 152g-1.	HRMS: Anal. Calcd. for $C_{36}H_{43}F_2N_6O_4$ 661.3314; found: 661.3336 $(M+H)^+$.
D12	di-tert-butyl (2S,2'S)-2,2'-((3,3'-difluoro-4,4'-biphenyldiyl)bis(1H-imidazole-5,2-diyl))di(1-pyrrolidinecarboxylate)	 Prepared from entry D5 (in lieu of 152e-1) using experimental conditions outlined in Example 153a-1.	t_R = 2.20min, (95%) LRMS: Anal. Calcd. for $C_{36}H_{43}F_2N_6O_4$ 661.33; found: 661.22 $(M+H)^+$. HRMS: Anal. Calcd. for $C_{36}H_{43}F_2N_6O_4$ 661.3314; found: 661.3307 $(M+H)^+$.
D13	tert-butyl (2S)-2-(5-(2-(4-(2-((2S)-1-(tert-butoxycarbonyl)-2-pyrrolidinyl)-1H-imidazol-4-yl)-3-fluorophenyl)-5-pyrimidinyl)-1H-imidazol-2-yl)-1-pyrrolidinecarboxylate	 Prepared from entry D8 (in lieu of 1c) and 152b-1 using experimental conditions outlined in Example 152g-1.	t_R = 2.27min, (95%) LRMS: Anal. Calcd. for $C_{34}H_{42}FN_8O_4$ 645.33; found: 645.34 $(M+H)^+$. HRMS: Anal. Calcd. for $C_{34}H_{42}FN_8O_4$ 645.3313; found: 645.3323 $(M+H)^+$.
D14	tert-butyl (2S)-2-(4-(4'-(2-((2S)-1-((benzyloxy)carbonyl)-2-pyrrolidinyl)-1H-imidazol-5-yl)-3-fluoro-4-biphenylyl)-1H-imidazol-2-yl)-1-pyrrolidinecarboxylat	 Prepared from entry D5 (in lieu of 152e-1) and 1-5c using experimental	t_R = 2.26min, (95%) LRMS: Anal. Calcd. for $C_{39}H_{42}FN_6O_4$ 677.33; found: 677.33 $(M+H)^+$. HRMS: Anal. Calcd. for $C_{39}H_{42}FN_6O_4$

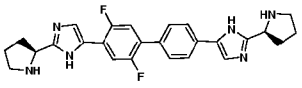
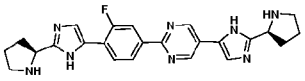
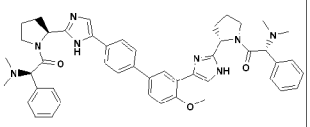
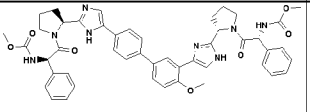
	e	conditions outlined in Example 152g-1.	677.3252; found: 677.3278 $(M+H)^+$.
D15	tert-butyl (2S)-2-(4-(4'-(2-((2S)-1-((benzyloxy)carbonyl)-2-pyrrolidinyl)-1H-imidazol-5-yl)-3,3'-difluoro-4-biphenylyl)-1H-imidazol-2-yl)-1-pyrrolidinecarboxylate	 Prepared from entry D8 (in lieu of 1c) and entry D4 using experimental conditions outlined in Example 152g-1.	t_R = 2.36min, (97.3%) LRMS: Anal. Calcd. for $C_{39}H_{41}F_2N_6O_4$ 695.32; found: 695.33 $(M+H)^+$. HRMS: Anal. Calcd. for $C_{39}H_{41}F_2N_6O_4$ 695.3157; found: 695.3151 $(M+H)^+$.
D16	tert-butyl (2S)-2-(5-(3-fluoro-4'-(2-((2S)-1-((2R)-2-((methoxycarbonyl)amino)-2-phenylacetyl)-2-pyrrolidinyl)-1H-imidazol-5-yl)-4-biphenylyl)-1H-imidazol-2-yl)-1-pyrrolidinecarboxylate	 Prepared from entry D21 (in lieu of 148e) and *Cap*-4 using experimental conditions outlined in Example 148.	t_R = 2.16 min, (91.0%) LRMS: Anal. Calcd. for $C_{41}H_{45}FN_7O_5$ 734.35; found: 734.36 $(M+H)^+$. HRMS: Anal. Calcd. for $C_{41}H_{45}FN_7O_5$ 734.3466; found: 734.3474 $(M+H)^+$.
D17	tert-butyl (2S)-2-(5-(4'-(2-((2S)-1-((2R)-2-(diethylamino)-2-phenylacetyl)-2-pyrrolidinyl)-1H-imidazol-5-yl)-3-fluoro-4-biphenylyl)-1H-imidazol-2-yl)-1-pyrrolidinecarboxylat	 Prepared from entry D21 (in lieu of 148e) and *Cap*-2 using experimental conditions outlined in	t_R = 1.95 min, (95%) LRMS: Anal. Calcd. for $C_{43}H_{51}FN_7O_3$ 732.40; found: 732.44 $(M+H)^+$. HRMS: Anal. Calcd. for $C_{43}H_{51}FN_7O_3$

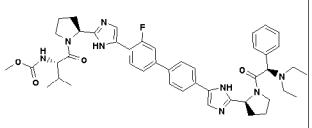
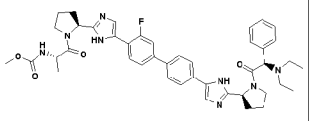
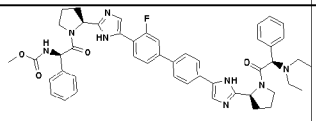
	e	Example 148.	732.4037; found: 732.4065 $(M+H)^+$.
D18	tert-butyl (2S)-2-(5-(3-fluoro-4'-(2-((2S)-1-(N-(methoxycarbonyl)-L-valyl)-2-pyrrolidinyl)-1H-imidazol-5-yl)-4-biphenylyl)-1H-imidazol-2-yl)-1-pyrrolidinecarboxylate	 Prepared from entry D21 (in lieu of 148e) and *Cap*-51 using experimental conditions outlined in Example 148.	t_R = 2.14 min, (95%) LRMS: Anal. Calcd. for $C_{38}H_{47}FN_7O_5$ 700.36; found: 700.37 $(M+H)^+$. HRMS: Anal. Calcd. for $C_{38}H_{47}FN_7O_5$ 700.3623; found: 700.3596 $(M+H)^+$.
D19	tert-butyl (2S)-2-(5-(3,3'-difluoro-4'-(2-((2S)-1-((2R)-2-((methoxycarbonyl)amino)-2-phenylacetyl)-2-pyrrolidinyl)-1H-imidazol-5-yl)-4-biphenylyl)-1H-imidazol-2-yl)-1-pyrrolidinecarboxylate	 Prepared from entry D22 (in lieu of 148c) and *Cap*-4 using experimental conditions outlined in Example 148.	t_R = 2.23 min, (95%) LRMS: Anal. Calcd. for $C_{41}H_{44}F_2N_7O_5$ 752.34; found: 752.35 $(M+H)^+$. HRMS: Anal. Calcd. for $C_{41}H_{44}F_2N_7O_5$ 752.3372; found: 752.3385 $(M+H)^+$.
D20	tert-butyl (2S)-2-(5-(3,3'-difluoro-4'-(2-((2S)-1-(N-(methoxycarbonyl)-L-valyl)-2-pyrrolidinyl)-1H-imidazol-5-yl)-4-biphenylyl)-1H-imidazol-2-yl)-1-pyrrolidinecarboxylat	 Prepared from entry D22 (in lieu of 148e) and *Cap*-51 using experimental conditions outlined in Example 148.	t_R = 2.16 min, (90%) LRMS: Anal. Calcd. for $C_{38}H_{46}F_2N_7O_5$ 718.35; found: 718.36 $(M+H)^+$. HRMS: Anal. Calcd. for $C_{38}H_{46}F_2N_7O_5$ 718.3528; found: 718.3505 $(M+H)^+$.

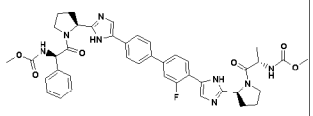
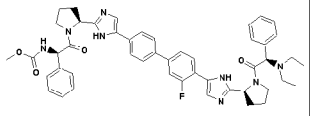
	e		
D21	tert-butyl (2S)-2-(5-(3-fluoro-4'-(2-((2S)-2-pyrrolidinyl)-1H-imidazol-5-yl)-4-biphenylyl)-1H-imidazol-2-yl)-1-pyrrolidinecarboxylate triacetate	 Prepared from entry D14 (in lieu of 152g-8) using experimental conditions outlined in Example 152i-1.	t_R = 1.94 min, (95%) LRMS: Anal. Calcd. for $C_{31}H_{36}FN_6O_2$ 543.29; found: 543.30. HRMS: Anal. Calcd. for $C_{31}H_{36}FN_6O_2$ 543.2884; found: 543.2872 $(M+H)^+$.
D22	tert-butyl (2S)-2-(5-(3,3'-difluoro-4'-(2-((2S)-2-pyrrolidinyl)-1H-imidazol-5-yl)-4-biphenylyl)-1H-imidazol-2-yl)-1-pyrrolidinecarboxylate	 Prepared from entry D15 (in lieu of 152g-8) using experimental conditions outlined in Example 152i-1.	t_R = 2.14 min, (95%) LRMS: Anal. Calcd. for $C_{31}H_{35}F_2N_6O_2$ 561.28; found: 561.29 $(M+H)^+$. HRMS: Anal. Calcd. for $C_{31}H_{35}F_2N_6O_2$ 561.2790; found: 561.2766 $(M+H)^+$.
D23	methyl ((1R)-2-((2S)-2-(5-(3'-fluoro-4'-(2-((2S)-2-pyrrolidinyl)-1H-imidazol-5-yl)-4-biphenylyl)-1H-imidazol-2-yl)-1-pyrrolidinyl)-2-oxo-1-phenylethyl)carbamate	 Prepared from entry D16 (in lieu of 152j-27) using experimental conditions outlined in Example 152k-1.	t_R = 1.90 min, (94%) LRMS: Anal. Calcd. for $C_{36}H_{37}FN_7O_3$ 634.29; found: 634.29 $(M+H)^+$. HRMS: Anal. Calcd. for $C_{36}H_{37}FN_7O_3$ 634.2942; found: 634.2948 $(M+H)^+$.
D24	methyl ((1S)-1-(((2S)-2-(5-(3'-fluoro-4'-(2-((2S)-2-		t_R = 1.89 min, (95%) LRMS: Anal. Calcd. for for

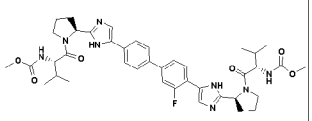
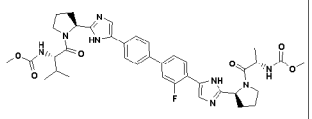
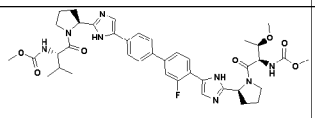
	pyrrolidinyl)-1H-imidazol-5-yl)-4-biphenylyl)-1H-imidazol-2-yl)-1-pyrrolidinyl)carbonyl)-2-methylpropyl)carbamate	Prepared from entry D18 (in lieu of 152j-27) using experimental conditions outlined in Example 152k-1.	$C_{33}H_{39}FN_7O_3$ 600.31; found: 600.32 $(M+H)^+$. HRMS: Anal. Calcd. for $C_{33}H_{39}FN_7O_3$ 600.3098; found: 600.3121 $(M+H)^+$.
D25	(1R)-N,N-diethyl-2-((2S)-2-(5-(3'-fluoro-4'-(2-((2S)-2-pyrrolidinyl)-1H-imidazol-5-yl)-4-biphenylyl)-1H-imidazol-2-yl)-1-pyrrolidinyl)-2-oxo-1-phenylethanamine	 Prepared from entry D17 (in lieu of 152j-27) using experimental conditions outlined in Example 152k-1.	t_R = 1.72 min, (90%) LRMS: Anal. Calcd. for $C_{38}H_{43}FN_7O$ 632.35; found: 632.36 $(M+H)^+$. HRMS: Anal. Calcd. for $C_{38}H_{43}FN_7O$ 632.3513; found: 632.3527 $(M+H)^+$.
D26	methyl ((1S)-1-(((2S)-2-(5-(3,3'-difluoro-4'-(2-((2S)-2-pyrrolidinyl)-1H-imidazol-5-yl)-4-biphenylyl)-1H-imidazol-2-yl)-1-pyrrolidinyl)carbonyl)-2-methylpropyl)carbamate	 Prepared from entry D20 (in lieu of 152j-27) using experimental conditions outlined in Example 152k-1.	t_R = 1.96 min, (95%) LRMS: Anal. Calcd. for $C_{33}H_{38}F_2N_7O_3$ 618.30; found: 618.31 $(M+H)^+$. HRMS: Anal. Calcd. for $C_{33}H_{38}F_2N_7O_3$ 618.3004; found: 618.3024 $(M+H)^+$.
D27	methyl ((1R)-2-((2S)-2-(5-(3,3'-difluoro-4'-(2-((2S)-2-pyrrolidinyl)-1H-imidazol-5-yl)-4-biphenylyl)-1H-	 Prepared from entry D19 (in lieu of 152j-27) using	t_R = 1.63 min, (95%) LRMS: Anal. Calcd. for $C_{36}H_{36}F_2N_7O_3$ 652.28; found: 652.29 $(M+H)^+$.

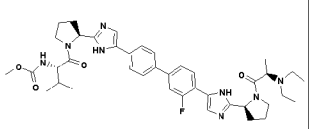
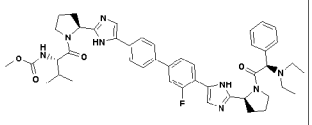
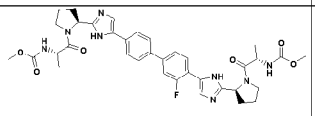
	imidazol-2-yl)-1-pyrrolidinyl)-2-oxo-1-phenylethyl)carbamate	experimental conditions outlined in Example 152k-1.	HRMS: Anal. Calcd. for $C_{36}H_{36}F_2N_7O_3$ 652.2848; found: 652.2858 $(M+H)^+$.
D28	5,5'-(4-methoxy-3,4'-biphenyldiyl)bis(2-((2S)-2-pyrrolidinyl)-1H-imidazole)	 Prepared from entry D9 (in lieu of 152j-27) using experimental conditions outlined in Example 152k-1.	t_R = 1.53 min, (98.2%) LRMS: Anal. Calcd. for $C_{27}H_{31}N_6O$ 455.26; found: 455.26 $(M+H)^+$. HRMS: Anal. Calcd. for $C_{27}H_{31}N_6O$ 455.2559; found: 455.2576 $(M+H)^+$.
D29	5,5'-(3-fluoro-4,4'-biphenyldiyl)bis(2-((2S)-2-pyrrolidinyl)-1H-imidazole) tetraacetate	 Prepared from entry 10 (in lieu of 152j-27) using experimental conditions outlined in Example 152k-1.	t_R = 1.55 min, (95%) LRMS: Anal. Calcd. for $C_{26}H_{28}FN_6$ 443.24; found: 443.24 $(M+H)^+$. HRMS: Anal. Calcd. for $C_{26}H_{28}FN_6$ 443.2359; found: 443.2371 $(M+H)^+$.
D30		 Prepared from entry D12 (in lieu of 152j-27) using experimental conditions outlined in Example 152k-1.	t_R = 1.72 min, (77.5%) LRMS: Anal. Calcd. for $C_{26}H_{27}F_2N_6$ 461.23; found: 461.25 $(M+H)^+$. HRMS: Anal. Calcd. for $C_{26}H_{27}F_2N_6$ 461.2265; found: 461.2272

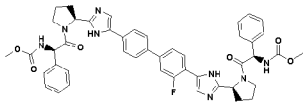
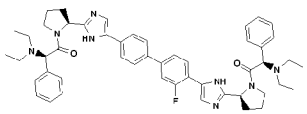
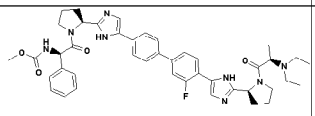
			$(M+H)^+$.
D31	5,5'-(2,5-difluoro-4,4'-biphenyldiyl)bis(2-((2S)-2-pyrrolidinyl)-1H-imidazole)	 Prepared from entry D11 (in lieu of 152j-27) using experimental conditions outlined in Example 152k-1.	t_R = 1.67 min, (95%) LRMS: Anal. Calcd. for $C_{26}H_{27}F_2N_6$ 461.23; found: 461.23 $(M+H)^+$. HRMS: Anal. Calcd. for $C_{26}H_{27}F_2N_6$ 461.2265; found: 461.2287 $(M+H)^+$.
D32	2-(3-fluoro-4-(2-((2S)-2-pyrrolidinyl)-1H-imidazol-5-yl)phenyl)-5-(2-((2S)-2-pyrrolidinyl)-1H-imidazol-5-yl)pyrimidine	 Prepared from entry D13 (in lieu of 152j-27) using experimental conditions outlined in Example 152k-1.	t_R = 1.63 min, (95%) LRMS: Anal. Calcd. for $C_{24}H_{26}FN_8$ 445.23; found: 445.23 $(M+H)^+$. HRMS: Anal. Calcd. for $C_{24}H_{26}FN_8$ 445.2264; found: 445.2268 $(M+H)^+$.
D33	(1R,1'R)-2,2'-((4-methoxy-3,4'-biphenyldiyl)bis(1H-imidazole-5,2-diyl(2S)-2,1-pyrrolidinediyl))bis(N,N-dimethyl-2-oxo-1-phenylethanamine)	 Prepared from entry D28 (in lieu of 148e) and *Cap*-1 using experimental conditions outlined in Example 148.	t_R = 1.71 min, (95%) LRMS: Anal. Calcd. for $C_{47}H_{53}N_8O_3$ 777.42; found: 777.41 $(M+H)^+$. HRMS: Anal. Calcd. for $C_{47}H_{53}N_8O_3$ 777.4241; found: 777.4254 $(M+H)^+$.
D34	dimethyl ((4-methoxy-3,4'-biphenyldiyl)bis(1H-imidazole-5,2-	 Prepared from entry D28	t_R = 2.09 min, (95%) LRMS: Anal. Calcd. for $C_{47}H_{49}N_8O_7$ 837.37; found:

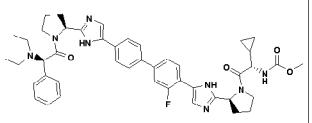
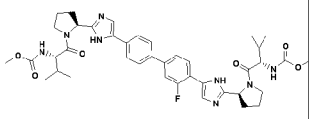
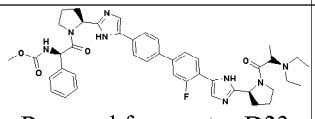
	diyl(2S)-2,1-pyrrolidinediyl((1R)-2-oxo-1-phenyl-2,1-ethanediyl)))biscarbamate	(in lieu of 148e) and *Cap*-4 using experimental conditions outlined in Example 148.	837.34 $(M+H)^+$. HRMS: Anal. Calcd. for $C_{47}H_{49}N_8O_7$ 837.3724; found: 837.3690 $(M+H)^+$.
D35	methyl ((1S)-1-(((2S)-2-(5-(4'-(2-((2S)-1-((2R)-2-(diethylamino)-2-phenylacetyl)-2-pyrrolidinyl)-1H-imidazol-5-yl)-3-fluoro-4-biphenylyl)-1H-imidazol-2-yl)-1-pyrrolidinyl)carbonyl)-2-methylpropyl)carbamate	 Prepared from entry D25 (in lieu of 148e) and *Cap*-51 using experimental conditions outlined in Example 148.	t_R = 1.85 min, (97.2%) LRMS: Anal. Calcd. for $C_{45}H_{54}FN_8O_4$ 789.43; found: 789.43 $(M+H)^+$. HRMS: Anal. Calcd. for $C_{45}H_{54}FN_8O_4$ 789.4252; found: 789.4225 $(M+H)^+$.
D36	methyl ((1S)-2-((2S)-2-(5-(4'-(2-((2S)-1-((2R)-2-(diethylamino)-2-phenylacetyl)-2-pyrrolidinyl)-1H-imidazol-5-yl)-3-fluoro-4-biphenylyl)-1H-imidazol-2-yl)-1-pyrrolidinyl)-1-methyl-2-oxoethyl)carbamate	 Prepared from entry D25 (in lieu of 148e) and *Cap*-52 using experimental conditions outlined in Example 148.	t_R = 1.76 min, (97.9%) LRMS: Anal. Calcd. for $C_{43}H_{50}FN_8O_4$ 761.39; found: 761.26 $(M+H)^+$. HRMS: Anal. Calcd. for $C_{43}H_{50}FN_8O_4$ 761.3939; found: 761.3967 $(M+H)^+$.
D37	methyl ((1R)-2-((2S)-2-(5-(4'-(2-((2S)-1-((2R)-2-(diethylamino)-2-	 Prepared from entry D25	t_R = 1.90 min, (98.6%) LRMS: Anal. Calcd. for $C_{48}H_{52}FN_8O_4$

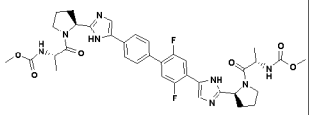
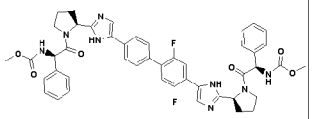
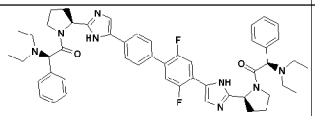
	phenylacetyl)-2-pyrrolidinyl)-1H-imidazol-5-yl)-3-fluoro-4-biphenylyl)-1H-imidazol-2-yl)-1-pyrrolidinyl)-2-oxo-1-phenylethyl)carbamate	(in lieu of 148e) and *Cap*-4 using experimental conditions outlined in Example 148.	823.41; found: 823.42 $(M+H)^+$. HRMS: Anal. Calcd. for $C_{48}H_{52}FN_8O_4$ 823.4096; found: 823.4102 $(M+H)^+$.
D38	methyl ((1R)-2-((2S)-2-(5-(3'-fluoro-4'-(2-((2S)-1-(N-(methoxycarbonyl)-L-alanyl)-2-pyrrolidinyl)-1H-imidazol-5-yl)-4-biphenylyl)-1H-imidazol-2-yl)-1-pyrrolidinyl)-2-oxo-1-phenylethyl)carbamate	 Prepared from entry D23 (in lieu of 148e) and *Cap*-52 using experimental conditions outlined in Example 148.	t_R = 1.89 min, (98.2%) LRMS: Anal. Calcd. for $C_{47}H_{49}N_8O_7$ 763.34; found: 763.32 $(M+H)^+$. HRMS: Anal. Calcd. for $C_{41}H_{44}FN_8O_6$ 763.3368; found: 763.3358 $(M+H)^+$.
D39	methyl ((1R)-2-((2S)-2-(5-(4'-(2-((2S)-1-((2R)-2-(diethylamino)-2-phenylacetyl)-2-pyrrolidinyl)-1H-imidazol-5-yl)-3'-fluoro-4-biphenylyl)-1H-imidazol-2-yl)-1-pyrrolidinyl)-2-oxo-1-phenylethyl)carbamate	 Prepared from entry D23 (in lieu of 148e) and *Cap*-2 using experimental conditions outlined in Example 148.	t_R = 1.88 min, (98.7%) LRMS: Anal. Calcd. for $C_{48}H_{52}FN_8O_4$ 823.41; found: 823.39 $(M+H)^+$. HRMS: Anal. Calcd. for $C_{48}H_{52}FN_8O_4$ 823.4096; found: 823.4127 $(M+H)^+$.

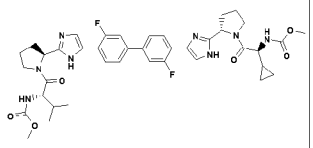
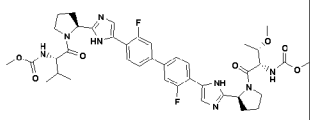
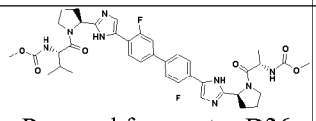
D40	methyl ((1S)-1-(((2S)-2-(5-(3'-fluoro-4'-(2-((2S)-1-((2S)-2-((methoxycarbonyl)amino)-3-methylbutanoyl)-2-pyrrolidinyl)-1H-imidazol-5-yl)-4-biphenylyl)-1H-imidazol-2-yl)-1-pyrrolidinyl)carbonyl)-2-methylpropyl)carbamate	 Prepared from entry D29 (in lieu of 148e) and *Cap*-51 using experimental conditions outlined in Example 148.	t_R = 1.97 min, (98.4%) LRMS: Anal. Calcd. for $C_{40}H_{50}FN_8O_6$ 757.38; found: 757.32 $(M+H)^+$. HRMS: Anal. Calcd. for $C_{40}H_{50}FN_8O_6$ 757.3837; found: 757.3815 $(M+H)^+$.
D41	methyl ((1S)-1-(((2S)-2-(5-(3'-fluoro-4'-(2-((2S)-1-(N-(methoxycarbonyl)-L-alanyl)-2-pyrrolidinyl)-1H-imidazol-5-yl)-4-biphenylyl)-1H-imidazol-2-yl)-1-pyrrolidinyl)carbonyl)-2-methylpropyl)carbamate	 Prepared from entry D24 (in lieu of 148e) and *Cap*-52 using experimental conditions outlined in Example 148.	t_R = 1.82 min, (95.0%) LRMS: Anal. Calcd. for $C_{38}H_{46}FN_8O_6$ 729.35; found: 729.29 $(M+H)^+$. HRMS: Anal. Calcd. for $C_{38}H_{46}FN_8O_6$ 729.3524; found: 729.3523 $(M+H)^+$.
D42	methyl ((1S,2R)-1-(((2S)-2-(5-(3-fluoro-4'-(2-((2S)-1-(N-(methoxycarbonyl)-L-valyl)-2-pyrrolidinyl)-1H-imidazol-5-yl)-4-biphenylyl)-1H-	 Prepared from entry D24 (in lieu of 148e) and *Cap*-86 using experimental conditions outlined in Example 148.	t_R = 1.91 min, (94.0%) LRMS: Anal. Calcd. for $C_{40}H_{50}FN_8O_7$ 773.38; found: 773.31 $(M+H)^+$. HRMS: Anal. Calcd. for $C_{40}H_{50}FN_8O_7$

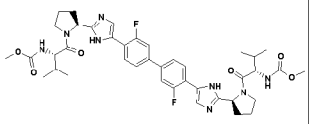
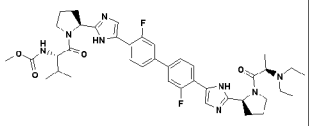
	imidazol-2-yl)-1-pyrrolidinyl)carbonyl)-2-methoxypropyl)carbamate		773.3786; found: 773.3759 $(M+H)^+$.
D43	methyl ((1S)-1-(((2S)-2-(5-(4'-(2-((2S)-1-(N,N-diethyl-D-alanyl)-2-pyrrolidinyl)-1H-imidazol-5-yl)-3'-fluoro-4-biphenylyl)-1H-imidazol-2-yl)-1-pyrrolidinyl)carbonyl)-2-methylpropyl)carbamate	 Prepared from entry D24 (in lieu of 148e) and *Cap*-69b using experimental conditions outlined in Example 148.	t_R = 1.72 min, (97.6%) LRMS: Anal. Calcd. for $C_{40}H_{52}FN_8O_4$ 727.41; found: 727.35 $(M+H)^+$. HRMS: Anal. Calcd. for $C_{40}H_{52}FN_8O_4$ 727.4096; found: 727.4091 $(M+H)^+$.
D44	methyl ((1S)-1-(((2S)-2-(5-(4'-(2-((2S)-1-((2R)-2-(diethylamino)-2-phenylacetyl)-2-pyrrolidinyl)-1H-imidazol-5-yl)-3'-fluoro-4-biphenylyl)-1H-imidazol-2-yl)-1-pyrrolidinyl)carbonyl)-2-methylpropyl)carbamate	 Prepared from entry D24 (in lieu of 148e) and *Cap*-2 using experimental conditions outlined in Example 148.	t_R = 1.83 min, (96.9%) LRMS: Anal. Calcd. for $C_{45}H_{54}FN_8O_4$ 789.43; found: 789.36 $(M+H)^+$. HRMS: Anal. Calcd. for $C_{45}H_{54}FN_8O_4$ 789.4252; found: 789.4225 $(M+H)^+$.
D45	methyl ((1S)-2-((2S)-2-(5-(3'-fluoro-4'-(2-((2S)-1-(N-(methoxycarbonyl)-L-alanyl)-2-	 Prepared from entry D29 (in lieu of 148e) and *Cap*-	t_R = 1.69 min, (97.7%) LRMS: Anal. Calcd. for for $C_{36}H_{42}FN_8O_6$ 701.32; found: 701.30 $(M+H)^+$.

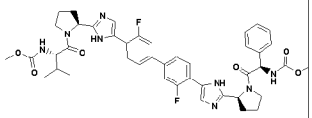
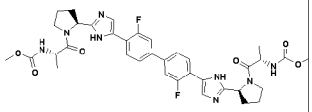
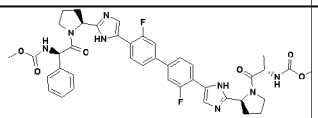
	pyrrolidinyl)-1H-imidazol-5-yl)-4-biphenylyl)-1H-imidazol-2-yl)-1-pyrrolidinyl)-1-methyl-2-oxoethyl)carbamate	52 using experimental conditions outlined in Example 148.	HRMS: Anal. Calcd. for $C_{36}H_{42}FN_8O_6$ 701.3222; found: 701.3211 $(M+H)^+$.
D46	dimethyl ((3-fluoro-4,4'-biphenyldiyl)bis(1H-imidazole-5,2-diyl(2S)-2,1-pyrrolidinediyl((1R)-2-oxo-1-phenyl-2,1-ethanediyl)))biscarbamate	 Prepared from entry D29 (in lieu of 148e) and *Cap*-4 using experimental conditions outlined in Example 148.	t_R = 2.05 min, (99.9%) LRMS: Anal. Calcd. for for $C_{46}H_{46}FN_8O_6$ 825.35; found: 825.35 $(M+H)^+$. HRMS: Anal. Calcd. for $C_{46}H_{46}FN_8O_6$ 825.3524; found: 825.3522 $(M+H)^+$.
D47	(1R,1'R)-2,2'-((3-fluoro-4,4'-biphenyldiyl)bis(1H-imidazole-5,2-diyl(2S)-2,1-pyrrolidinediyl))bis(N,N-diethyl-2-oxo-1-phenylethanamine)	 Prepared from entry D29 (in lieu of 148e) and *Cap*-2 using experimental conditions outlined in Example 148.	t_R = 1.72 min, (99.5%) LRMS: Anal. Calcd. for for $C_{50}H_{58}FN_8O_2$ 821.47; found: 821.44 $(M+H)^+$. HRMS: Anal. Calcd. for $C_{50}H_{58}FN_8O_2$ 821.4667; found: 821.4636 $(M+H)^+$.
D48	methyl ((1R)-2-((2S)-2-(5-(4'-(2-((2S)-1-(N,N-diethyl-D-alanyl)-2-pyrrolidinyl)-1H-imidazol-5-yl)-3'-fluoro-4-biphenylyl)-1H-imidazol-2-yl)-1-	 Prepared from entry D23 (in lieu of 148e) and *Cap*-69b using experimental conditions outlined in Example 148.	t_R = 1.76min, (99.7%) LRMS: Anal. Calcd. for $C_{43}H_{50}FN_8O_4$ 761.39; found: 761.27 $(M+H)^+$. HRMS: Anal. Calcd. for $C_{43}H_{50}FN_8O_4$

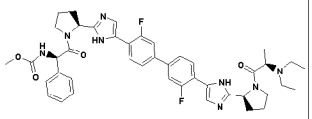
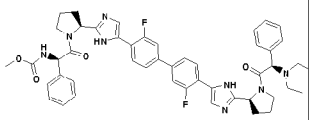
	pyrrolidinyl)-2-oxo-1-phenylethyl)carbamate		761.3939; found: 761.3952 $(M+H)^+$.
D49	methyl ((1S)-1-cyclopropyl-2-((2S)-2-(5-(4'-(2-((2S)-1-((2R)-2-(diethylamino)-2-phenylacetyl)-2-pyrrolidinyl)-1H-imidazol-5-yl)-3-fluoro-4-biphenylyl)-1H-imidazol-2-yl)-1-pyrrolidinyl)-2-oxoethyl)carbamate	 Prepared from entry D25 (in lieu of 148e) and *Cap*-54b using experimental conditions outlined in Example 148.	t_R = 1.92 min, (98.7%) LRMS: Anal. Calcd. for $C_{45}H_{52}FN_8O_4$ 787.41; found: 787.36 $(M+H)^+$. HRMS: Anal. Calcd. for $C_{45}H_{52}FN_8O_4$ 787.4096; found: 787.4074 $(M+H)^+$.
D50	methyl ((1S)-1-cyclopropyl-2-((2S)-2-(5-(3-fluoro-4'-(2-((2S)-1-(N-(methoxycarbonyl)-L-valyl)-2-pyrrolidinyl)-1H-imidazol-5-yl)-4-biphenylyl)-1H-imidazol-2-yl)-1-pyrrolidinyl)-2-oxoethyl)carbamate	 Prepared from entry D24 (in lieu of 148e) and *Cap*-54b using experimental conditions outlined in Example 148.	t_R = 1.94 min, (99.0%) LRMS: Anal. Calcd. for $C_{40}H_{48}F_2N_8O_7$ 755.37; found: 755.32 $(M+H)^+$. HRMS: Anal. Calcd. for $C_{40}H_{48}FN_8O_6$ 755.3681; found: 755.3670 $(M+H)^+$.
D51	methyl ((1R)-2-((2S)-2-(5-(4'-(2-((2S)-1-(N,N-diethyl-D-alanyl)-2-pyrrolidinyl)-1H-imidazol-5-yl)-3'-fluoro-4-biphenylyl)-	 Prepared from entry D23 (in lieu of 148e) and *Cap*-69b using experimental conditions outlined in Example 148.	t_R = 1.92 min, (98.3%) LRMS: Anal. Calcd. for $C_{43}H_{50}FN_8O_4$ 761.39; found: 761.35 $(M+H)^+$.

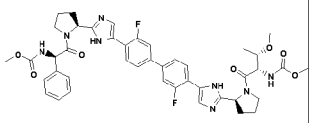
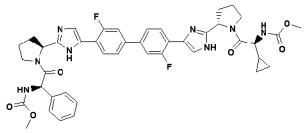
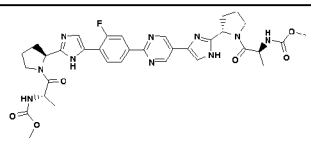
	1H-imidazol-2-yl)-1-pyrrolidinyl)-2-oxo-1-phenylethyl)carbamate		HRMS: Anal. Calcd. for $C_{43}H_{50}FN_8O_4$ 761.3939; found: 761.3956 $(M+H)^+$.
D52	methyl ((1S)-2-((2S)-2-(5-(2',5'-difluoro-4'-(2-((2S)-1-(N-(methoxycarbonyl)-L-alanyl)-2-pyrrolidinyl)-1H-imidazol-5-yl)-4-biphenylyl)-1H-imidazol-2-yl)-1-pyrrolidinyl)-1-methyl-2-oxoethyl)carbamate	 Prepared from entry D31 (in lieu of 148e) and *Cap*-52 using experimental conditions outlined in Example 148.	t_R = 1.69 min, (99.2%) LRMS: Anal. Calcd. for $C_{36}H_{41}F_2N_8O_6$ 719.31; found: 719.29 $(M+H)^+$. HRMS: Anal. Calcd. for $C_{36}H_{41}F_2N_8O_6$ 719.3117; found: 719.3109 $(M+H)^+$.
D53	dimethyl ((2,5-difluoro-4,4'-biphenyldiyl)bis(1H-imidazole-5,2-diyl(2S)-2,1-pyrrolidinediyl((1R)-2-oxo-1-phenyl-2,1-ethanediyl)))biscarbamate	 Prepared from entry D31 (in lieu of 148e) and *Cap*-4 using experimental conditions outlined in Example 148 of 10889PSP.	t_R = 2.08 min, (100.0%) LRMS: Anal. Calcd. for $C_{46}H_{45}F_2N_8O_6$ 843.34; found: 843.34 $(M+H)^+$. HRMS: Anal. Calcd. for $C_{46}H_{45}F_2N_8O_6$ 843.3430; found: 843.3458 $(M+H)^+$.
D54	(1R,1'R)-2,2'-((2,5-difluoro-4,4'-biphenyldiyl)bis(1H-imidazole-5,2-diyl(2S)-2,1-pyrrolidinediyl))bis(N,N-diethyl-2-oxo-1-	 Prepared from entry D31 (in lieu of 148e) and *Cap*-2 using experimental conditions outlined in Example 148.	t_R = 1.76 min, (99.8%) LRMS: Anal. Calcd. for $C_{50}H_{57}F_2N_8O_2$ 839.46; found: 839.43 $(M+H)^+$.

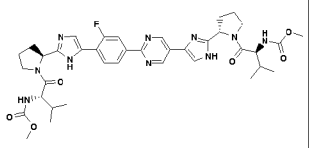
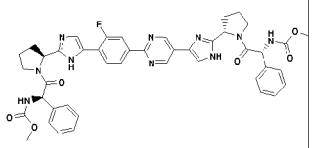
	phenylethanamine)		HRMS: Anal. Calcd. for $C_{50}H_{57}F_2N_8O_2$ 839.4573; found: 839.4585 $(M+H)^+$.
D55	methyl ((1S)-1-cyclopropyl-2-((2S)-2-(5-(3,3'-difluoro-4'-(2-((2S)-1-(N-(methoxycarbonyl)-L-valyl)-2-pyrrolidinyl)-1H-imidazol-5-yl)-4-biphenylyl)-1H-imidazol-2-yl)-1-pyrrolidinyl)-2-oxoethyl)carbamate	 Prepared from entry D26 (in lieu of 148e) and *Cap*-54b using experimental conditions outlined in Example 148.	t_R = 1.93 min, (98.5%) LRMS: Anal. Calcd. for $C_{40}H_{47}F_2N_8O_6$ 773.36; found: 773.31 $(M+H)^+$. HRMS: Anal. Calcd. for $C_{40}H_{47}F_2N_8O_6$ 773.3567; found: 773.3587 $(M+H)^+$.
D56	methyl ((1S,2R)-1-(((2S)-2-(5-(3,3'-difluoro-4'-(2-((2S)-1-(N-(methoxycarbonyl)-L-valyl)-2-pyrrolidinyl)-1H-imidazol-5-yl)-4-biphenylyl)-1H-imidazol-2-yl)-1-pyrrolidinyl)carbonyl)-2-methoxypropyl)carbamate	 Prepared from entry D26 (in lieu of 148e) and *Cap*-86 using experimental conditions outlined in Example 148.	t_R = 2.00 min, (98.0%) LRMS: Anal. Calcd. for $C_{40}H_{49}F_2N_8O_7$ 791.37; found: 791.32 $(M+H)^+$. HRMS: Anal. Calcd. for $C_{40}H_{49}F_2N_8O_7$ 791.3692; found: 791.3682 $(M+H)^+$.
D57	methyl ((1S)-1-(((2S)-2-(5-(3,3'-difluoro-4'-(2-((2S)-1-(N-(methoxycarbonyl)-	 Prepared from entry D26 (in lieu of 148e) and *Cap*-52 using experimental	t_R = 1.86 min, (95.6%) LRMS: Anal. Calcd. for $C_{38}H_{45}F_2N_8O_6$ 747.34; found: 747.30 $(M+H)^+$.

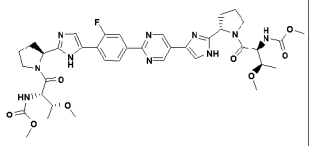
	L-alanyl)-2-pyrrolidinyl)-1H-imidazol-5-yl)-4-biphenylyl)-1H-imidazol-2-yl)-1-pyrrolidinyl)carbonyl)-2-methylpropyl)carbamate	conditions outlined in Example 148.	HRMS: Anal. Calcd. for $C_{38}H_{45}F_2N_8O_6$ 747.3430; found: 747.3425 $(M+H)^+$.
D58	methyl ((1S)-1-(((2S)-2-(5-(3,3'-difluoro-4'-(2-((2S)-1-((2S)-2-((methoxycarbonyl)amino)-3-methylbutanoyl)-2-pyrrolidinyl)-1H-imidazol-5-yl)-4-biphenylyl)-1H-imidazol-2-yl)-1-pyrrolidinyl)carbonyl)-2-methylpropyl)carbamate	 Prepared from entry D26 (in lieu of 148e) and *Cap*-51 using experimental conditions outlined in Example 148.	t_R = 2.02 min, (96.3%) LRMS: Anal. Calcd. for $C_{40}H_{49}F_2N_8O_6$ 775.37; found: 775.31 $(M+H)^+$. HRMS: Anal. Calcd. for $C_{40}H_{49}F_2N_8O_6$ 775.3743; found: 775.37.34 $(M+H)^+$.
D59	methyl ((1S)-1-(((2S)-2-(5-(4'-(2-((2S)-1-(N,N-diethyl-D-alanyl)-2-pyrrolidinyl)-1H-imidazol-5-yl)-3,3'-difluoro-4-biphenylyl)-1H-imidazol-2-yl)-1-pyrrolidinyl)carbonyl)-2-	 Prepared from entry D26 (in lieu of 148e) and *Cap*-69b using experimental conditions outlined in Example 148.	t_R = 1.78 min, (98.2%) LRMS: Anal. Calcd. for $C_{40}H_{51}F_2N_8O_4$ 745.40; found: 745.34 $(M+H)^+$. HRMS: Anal. Calcd. for $C_{40}H_{51}F_2N_8O_4$ 745.4001; found: 745.4008 $(M+H)^+$.

	methylpropyl)carbamate		
D60	methyl ((1S)-1-(((2S)-2-(5-(3,3'-difluoro-4'-(2-((2S)-1-((2R)-2-((methoxycarbonyl)amino)-2-phenylacetyl)-2-pyrrolidinyl)-1H-imidazol-5-yl)-4-biphenylyl)-1H-imidazol-2-yl)-1-pyrrolidinyl)carbonyl)-2-methylpropyl)carbamate	 Prepared from entry D26 (in lieu of 148e) and *Cap*-4 using experimental conditions outlined in Example 148.	t_R = 2.08 min, (99.1%) LRMS: Anal. Calcd. for $C_{43}H_{47}F_2N_8O_6$ 809.36; found: 809.29 $(M+H)^+$. HRMS: Anal. Calcd. for $C_{43}H_{47}F_2N_8O_6$ 809.3587; found: 809.3568 $(M+H)^+$.
D61	methyl ((1S)-2-((2S)-2-(5-(3,3'-difluoro-4'-(2-((2S)-1-(N-(methoxycarbonyl)-L-alanyl)-2-pyrrolidinyl)-1H-imidazol-5-yl)-4-biphenylyl)-1H-imidazol-2-yl)-1-pyrrolidinyl)-1-methyl-2-oxoethyl)carbamate	 Prepared from entry D30 (in lieu of 148e) and *Cap*-52 using experimental conditions outlined in Example 148.	t_R = 1.71min, (94.3%) LRMS: Anal. Calcd. for $C_{36}H_{41}F_2N_8O_6$ 719.31; found: 719.19 $(M+H)^+$. HRMS: Anal. Calcd. for $C_{36}H_{41}F_2N_8O_6$ 719.3117; found: 719.3115 $(M+H)^+$.
D62	methyl ((1R)-2-((2S)-2-(5-(3,3'-difluoro-4'-(2-((2S)-1-(N-(methoxycarbonyl)-L-alanyl)-2-pyrrolidinyl)-1H-	 Prepared from entry D27 (in lieu of 148e) and *Cap*-52 using experimental conditions outlined in	t_R = 1.94 min, (98.3%) LRMS: Anal. Calcd. for $C_{41}H_{43}F_2N_8O_6$ 781.33; found: 781.26 $(M+H)^+$.

	imidazol-5-yl)-4-biphenylyl)-1H-imidazol-2-yl)-1-pyrrolidinyl)-2-oxo-1-phenylethyl)carbamate	Example 148.	HRMS: Anal. Calcd. for $C_{41}H_{43}F_2N_8O_6$ 781.3274; found: 781.3264 $(M+H)^+$.
D63	methyl ((1R)-2-((2S)-2-(5-(4'-(2-((2S)-1-(N,N-diethyl-D-alanyl)-2-pyrrolidinyl)-1H-imidazol-5-yl)-3,3'-difluoro-4-biphenylyl)-1H-imidazol-2-yl)-1-pyrrolidinyl)-2-oxo-1-phenylethyl)carbamate	 Prepared from entry D27 (in lieu of 148e) and *Cap*-69b using experimental conditions outlined in Example 148.	t_R = 1.44 min, (99.0%) LRMS: Anal. Calcd. for $C_{43}H_{49}F_2N_8O_4$ 779.38; found: 779.32 $(M+H)^+$. HRMS: Anal. Calcd. for $C_{43}H_{49}F_2N_8O_4$ 779.3845; found: 779.3842 $(M+H)^+$.
D64	methyl ((1R)-2-((2S)-2-(5-(4'-(2-((2S)-1-((2R)-2-(diethylamino)-2-phenylacetyl)-2-pyrrolidinyl)-1H-imidazol-5-yl)-3,3'-difluoro-4-biphenylyl)-1H-imidazol-2-yl)-1-pyrrolidinyl)-2-oxo-1-phenylethyl)carbamate	 Prepared from entry D27 (in lieu of 148e) and *Cap*-2 using experimental conditions outlined in Example 148.	t_R = 1.94 min, (95.3%) LRMS: Anal. Calcd. for $C_{48}H_{51}F_2N_8O_4$ 841.40; found: 841.33 $(M+H)^+$. HRMS: Anal. Calcd. for $C_{48}H_{51}F_2N_8O_4$ 841.4001; found: 841.3991 $(M+H)^+$.

D65	methyl ((1S,2R)-1-(((2S)-2-(5-(3,3'-difluoro-4'-(2-((2S)-1-((2R)-2-((methoxycarbonyl)amino)-2-phenylacetyl)-2-pyrrolidinyl)-1H-imidazol-5-yl)-4-biphenylyl)-1H-imidazol-2-yl)-1-pyrrolidinyl)carbonyl)-2-methoxypropyl)carbamate bis(trifluoroacetate)	 Prepared from entry D27 (in lieu of 148e) and *Cap*-86 using experimental conditions outlined in Example 148.	t_R = 2.00 min, (96.2%) LRMS: Anal. Calcd. for $C_{43}H_{47}F_2N_8O_7$ 825.35; found: 825.28 $(M+H)^+$. HRMS: Anal. Calcd. for $C_{43}H_{47}F_2N_8O_7$ 825.3536; found: 825.3527 $(M+H)^+$.
D66	methyl ((1S)-1-cyclopropyl-2-((2S)-2-(5-(3,3'-difluoro-4'-(2-((2S)-1-((2R)-2-((methoxycarbonyl)amino)-2-phenylacetyl)-2-pyrrolidinyl)-1H-imidazol-5-yl)-4-biphenylyl)-1H-imidazol-2-yl)-1-pyrrolidinyl)-2-oxoethyl)carbamate	 Prepared from entry D27 (in lieu of 148e) and *Cap*-54b using experimental conditions outlined in Example 148.	t_R = 2.01 min, (99.5%) LRMS: Anal. Calcd. for $C_{43}H_{45}F_2N_8O_6$ 807.34; found: 807.29 $(M+H)^+$. HRMS: Anal. Calcd. for $C_{43}H_{45}F_2N_8O_6$ 807.3430; found: 807.3409 $(M+H)^+$.
D67	methyl ((1S)-2-((2S)-2-(5-(2-fluoro-4-(5-(2-((2S)-1-(N-(methoxycarbonyl)-L-alanyl)-2-pyrrolidinyl)-1H-	 Prepared from entry D32 (in lieu of 148e) and *Cap*-	t_R = 1.58 min, (91.1%) LRMS: Anal. Calcd. for $C_{34}H_{40}FN_{10}O_6$ 703.31; found: 703.27 $(M+H)^+$.

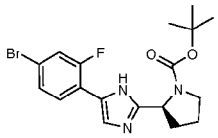
	imidazol-5-yl)-2-pyrimidinyl)phenyl)-1H-imidazol-2-yl)-1-pyrrolidinyl)-1-methyl-2-oxoethyl)carbamate	52 using experimental conditions outlined in Example 148.	HRMS: Anal. Calcd. for $C_{34}H_{40}FN_{10}O_6$ 703.3116; found: 703.3101 $(M+H)^+$.
D68	methyl ((1S)-1-(((2S)-2-(5-(2-fluoro-4-(5-(2-((2S)-1-((2S)-2-((methoxycarbonyl)amino)-3-methylbutanoyl)-2-pyrrolidinyl)-1H-imidazol-5-yl)-2-pyrimidinyl)phenyl)-1H-imidazol-2-yl)-1-pyrrolidinyl)carbonyl)-2-methylpropyl)carbamate	 Prepared from entry D32 (in lieu of 148e) and *Cap*-51 using experimental conditions outlined in Example 148.	t_R = 1.95 min, (99.3%) LRMS: Anal. Calcd. for $C_{38}H_{48}FN_{10}O_6$ 759.37; found: 759.30 $(M+H)^+$. HRMS: Anal. Calcd. for $C_{38}H_{48}FN_{10}O_6$ 759.3742; found: 759.3715 $(M+H)^+$.
D69	methyl ((1R)-2-((2S)-2-(5-(2-(3-fluoro-4-(2-((2S)-1-((2R)-2-((methoxycarbonyl)amino)-2-phenylacetyl)-2-pyrrolidinyl)-1H-imidazol-5-yl)phenyl)-5-pyrimidinyl)-1H-imidazol-2-yl)-1-pyrrolidinyl)-2-oxo-1-phenylethyl)carbamat	 Prepared from entry D32 (in lieu of 148e) and *Cap*-4 using experimental conditions outlined in Example 148.	t_R = 2.05 min, (99.3%) LRMS: Anal. Calcd. for $C_{44}H_{44}FN_{10}O_6$ 827.34; found: 827.27 $(M+H)^+$. HRMS: Anal. Calcd. for $C_{44}H_{44}FN_{10}O_6$ 827.3429; found: 827.3407 $(M+H)^+$.

	e		
D70	methyl ((1S,2R)-1-(((2S)-2-(5-(2-fluoro-4-(5-(2-((2S)-1-(N-(methoxycarbonyl)-O-methyl-L-threonyl)-2-pyrrolidinyl)-1H-imidazol-5-yl)-2-pyrimidinyl)phenyl)-1H-imidazol-2-yl)-1-pyrrolidinyl)carbonyl)-2-methoxypropyl)carbamate	 Prepared from entry D32 (in lieu of 148e) and *Cap*-86 using experimental conditions outlined in Example 148.	t_R = 1.79 min, (93.0%) LRMS: Anal. Calcd. for $C_{38}H_{48}FN_{10}O_8$ 791.36; found: 791.31 $(M+H)^+$. HRMS: Anal. Calcd. for $C_{38}H_{48}FN_{10}O_8$ 791.3641; found: 791.3636 $(M+H)^+$.

**LCMS conditions: Phenomenex-Luna 4.6 x 50 mm S10, 0 to 100%B over 3 min, 4 min stop time, 4 mL/min, 220nm, A: 10% MeOH-90%H2O - 0.1% TFA; B: 90% MeOH-10%H2O-0.1% TFA

Example D5.

(S)-tert-butyl 2-(5-(4-bromo-2-fluorophenyl)-1H-imidazol-2-yl)pyrrolidine-1-carboxylate



D5

Bromine (0.54 mL, 10.6 mmol) was added dropwise to a cold (0 ºC) solution of 4-bromo-2-fluoroacetophenone (2.30 g, 10.6 mmol) in dioxane (80 mL) and tetrahydrofuran (80 mL). The mixture was stirred for 1h at 0°C and warmed to RT for 15h. The mixture was diluted with ethyl acetate, washed with saturated $NaHCO_3$ solution, 5% sodium thiosulfate solution and brine prior to drying (Na_2SO_4). 2-Bromo-1-(4-bromo-2-fluorophenyl)ethanone (D1) was isolated as a colorless film which solidified upon further concentration under high vacuum. This solid was

dissolved into anhydrous acetonitrile (50 mL) and treated with N-Boc-L-proline (2.28 g, 10.6 mmol) and diisopropylethylamine (1.85 mL, 10.6 mmol). After being stirred for 3h at RT, the solvent was removed *in vacuo* and the residue was partitioned into ethyl acetate and water. The organic phase was washed with 0.1N hydrochloric acid, saturated $NaHCO_3$ solution and brine prior to drying (Na_2SO_4), filtration, and concentration. This residue was taken up in xylenes (50 mL) and treated to solid NH_4OAc (4.1 g, 53.0 mmol). The mixture was heated at 140°C for 2 hr in a thick-walled, screw-top flask before it was cooled to ambient temperature, diluted with ethyl acetate and washed with saturated $NaHCO_3$ solution and brine prior to drying (Na_2SO_4) and concentration. Purification of the residue by Biotage™ flash chromatography on silica gel (65M column, preequilibration with 16%B for 1800 mL followed by gradient elution with 16%B to 16%B for 450 mL, 16%B to 50%B for 2199 ml and finally 50%B to 100%B for 2199 mL) afforded title compound (D5) (3.61 g, 83%) as a brownish/caramel-colored oil. A small portion (40 mg) of the title compound was further purified by preparative HPLC (20%B to 100%B over 14 min where B is 10mM NH_4OAc in 10:90 H_2O/ACN and A is 10 mM NH_4OAc in 95:5 H_2O/CAN using a Phenomenex-Gemini 30 x 100 mm S10 column flowing at 40 mL/min) to afford pure title compound (31.8 mg) as a white solid.

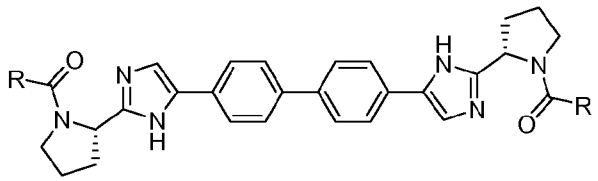
^1H NMR (500 MHz, DMSO-d_6) δ 12.13-11.95 (m, 1H), 7.94 (br s, 1H), 7.54 (d, J = 10.7 Hz, 1H), 7.42 (d, J = 7.9 Hz, 1H), 7.36-7.34 (m, 1H), 4.86-4.77 (2m, 1H), 3.54 (m, 1H), 3.38-3.32 (m, 1H), 2.28-2.14 (2m, 1H), 2.05-1.78 (2m, 3H), 1.39 and 1.14 (2s, 9H).

HPLC Phenomenex LUNA C-18 4.6 × 50 mm, 0 to 100% B over 3 minutes, 1 minute hold time, A = 90% water, 10% methanol, 0.1% TFA, B = 10% water, 90% methanol, 0.1% TFA, RT = 2.27 min, 95% homogeneity index.

LRMS: Anal. Calcd. for $C_{18}H_{22}BrFN_3O_2$ 410.09 and 412.09; found: 410.08 and 412.08 $(M+H)^+$.

HRMS: Anal. Calcd. for $C_{18}H_{22}BrFN_3O_2$ 410.0879; found: 410.0893 $(M+H)^+$.

Examples M1-M27



Example M1-M27 were prepared from 1e and the respective acids using the method described for Example 1. The products were prepared as TFA salts, unless noted otherwise. LC Conditions were as follows:

Condition 1

Column = Phenomenex-Luna 3.0X 50 mm S10
Start %B = 0
Final %B = 100
Gradient time = 2 min
Stop time = 3 min
Flow Rate = 4 mL/min
Wavelength = 220 nm
Slovent A = 0.1% TFA in 10% methanol/90%H_2O
Solvent B = 0.1% TFA in 90% methanol/10% H_2O

Condition 2

Column = Phenomenex-Luna 4.6X50 mm S10
Start %B = 0
Final %B = 100
Gradient time = 2 min
Stop time = 3 min
Flow Rate = 5 mL/min
Wavelength = 220 nm
Slovent A = 0.1% TFA in 10% methanol/90%H_2O
Solvent B = 0.1% TFA in 90% methanol/10% H_2O

Condition 3

Column = HPLC XTERRA C18 3.0 x 50mm S7
Start %B = 0

Final %B = 100

Gradient time = 3 min

Stop time = 4 min

Flow Rate = 4 mL/min

Wavelength = 220 nm

Slovent A = 0.1% TFA in 10% methanol/90%H_2O

Solvent B = 0.1% TFA in 90% methanol/10% H_2O

Condition M1

Column: Luna 4.6X 50 mm S10

Start %B = 0

Final %B = 100

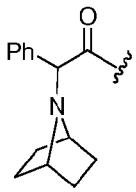
Gradient time = 3 min

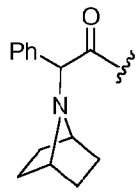
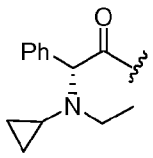
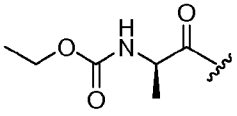
Stop time = 4 min

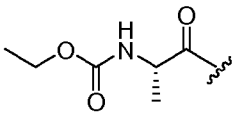
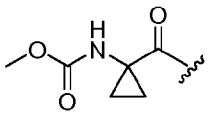
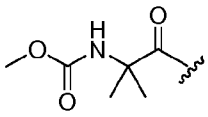
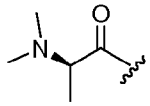
Flow rate = 4 mL/min

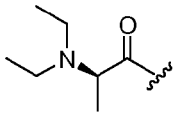
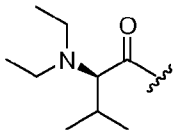
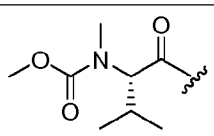
Solvent A: = 95% H_20: 5% CH_3CN, 10 mm Ammonium acetate

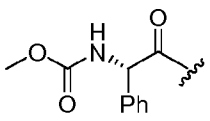
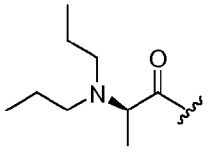
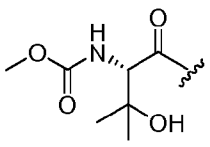
Solvent B: = 5% H_2O : 95% CH_3CN; 10 mm Ammonium acetate

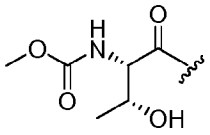
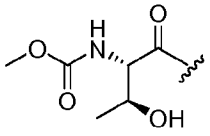
Example	*Compound Name*	 *(Source)*	*RT (LC-Cond.); % homogeneity index; MS data; ^1H NMR data*
M1	7,7'-(4,4'-biphenyldiylbis(1H-imidazole-5,2-diyl(2S)-2,1-pyrrolidinediyl(2-oxo-1-phenyl-2,1-ethanediyl)))bis(7-azabicyclo[2.2.1]heptane)	 (*Cap*-77a)	1.04 min (Cond. 1); >98%; LC/MS: Anal. Calcd. for $[M+H]^+$ $C_{54}H_{59}N_8O_2$: 851.48; found 851.55; HRMS: Anal. Calcd. for $[M+H]^+$ $C_{54}H_{59}N_8O_2$: 851.4761; found 851.4780

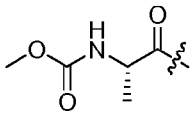
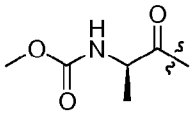
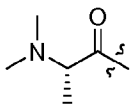
M2	7,7'-(4,4'-biphenyldiylbis(1H-imidazole-5,2-diyl(2S)-2,1-pyrrolidinediyl(2-oxo-1-phenyl-2,1-ethanediyl)))bis(7-azabicyclo[2.2.1]heptane)	 (*Cap*-77b)	1.13 min (Cond. 1); >98%; LC/MS: Anal. Calcd. for $[M+H]^+$ $C_{54}H_{59}N_8O_2$: 851.48; found 851.57; HRMS: Anal. Calcd. for $[M+H]^+$ $C_{54}H_{59}N_8O_2$: 851.4761; found 851.4792
M3	N,N'-(4,4'-biphenyldiylbis(1H-imidazole-5,2-diyl(2S)-2,1-pyrrolidinediyl((1R)-2-oxo-1-phenyl-2,1-ethanediyl)))bis(N-ethylcyclopropanamine)	 (*Cap*-78)	1.13 min (Cond. 1); >95%; LC/MS: Anal. Calcd. for $[M+H]^+$ $C_{52}H_{59}N_8O_2$: 827.48; found 827.69; HRMS: Anal. Calcd. for $[M+H]^+$ $C_{52}H_{59}N_8O_2$: 827.4761; found 827.4782
M4	ethyl ((1R)-2-((2S)-2-(5-(4'-(2-((2S)-1-(N-(ethoxycarbonyl)-D-alanyl)-2-pyrrolidinyl)-1H-imidazol-5-yl)-4-biphenylyl)-1H-imidazol-2-yl)-1-pyrrolidinyl)-1-methyl-2-oxoethyl)carbamate	 (*Cap*-59a)	1.20 min (Cond. 1); >97%; LC/MS: Anal. Calcd. for $[M+H]^+$ $C_{38}H_{47}N_8O_6$: 711.36; found 711.46; HRMS: Anal. Calcd. for $[M+H]^+$ $C_{38}H_{47}N_8O_6$: 711.3619; found 711.3638

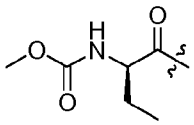
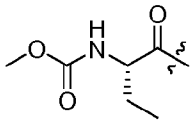
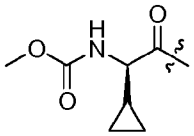
M5	ethyl ((1S)-2-((2S)-2-(5-(4'-(2-((2S)-1-(N-(ethoxycarbonyl)-L-alanyl)-2-pyrrolidinyl)-1H-imidazol-5-yl)-4-biphenylyl)-1H-imidazol-2-yl)-1-pyrrolidinyl)-1-methyl-2-oxoethyl)carbamate	 (*Cap*-59b)	1.16 min (Cond. 1); 97%; LC/MS: Anal. Calcd. for $[M+H]^+$ $C_{38}H_{47}N_8O_6$: 711.36; found 711.48; HRMS: Anal. Calcd. for $[M+H]^+$ $C_{38}H_{47}N_8O_6$: 711.3619; found 711.3621
M6	dimethyl (4,4'-biphenyldiylbis(1H-imidazole-5,2-diyl(2S)-2,1-pyrrolidinediylcarbonyl-1,1-cyclopropanediyl))biscarbamate	 (*Cap*-60)	1.12 min (Cond. 1); >98%; LC/MS: Anal. Calcd. for $[M+H]^+$ $C_{38}H_{43}N_8O_6$: 707.33; found 707.45; HRMS: Anal. Calcd. for $[M+H]^+$ $C_{38}H_{43}N_8O_6$: 707.3306; found 707.3309
M7	methyl (2-((2S)-2-(5-(4'-(2-((2S)-1-(2-((methoxycarbonyl)amino)-2-methylpropanoyl)-2-pyrrolidinyl)-1H-imidazol-5-yl)-4-biphenylyl)-1H-imidazol-2-yl)-1-pyrrolidinyl)-1,1-dimethyl-2-oxoethyl)carbamate	 (*Cap*-61)	1.21 min (Cond. 1); >98%; LC/MS: Anal. Calcd. for $[M+H]^+$ $C_{38}H_{47}N_8O_6$: 711.36; found 711.53; HRMS: Anal. Calcd. for $[M+H]^+$ $C_{38}H_{47}N_8O_6$: 711.3619; found 711.3652
M8	(2R,2'R)-1,1'-(4,4'-biphenyldiylbis(1H-imidazole-5,2-diyl(2S)-2,1-		0.91 min (Cond. 1); >80%; LC/MS: Anal. Calcd. for

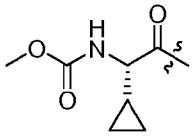
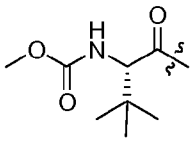
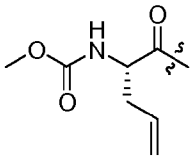
	pyrrolidinediyl))bis(N,N-dimethyl-1-oxo-2-propanamine)	(*Cap*-83)	$[M+H]^+$ $C_{36}H_{47}N_8O_2$: 623.38; found 623.46; HRMS: Anal. Calcd. for $[M+H]^+$ $C_{36}H_{47}N_8O_2$: 623.3822; found 623.3819
M9	(2R,2'R)-1,1'-(4,4'-biphenyldiylbis(1H-imidazole-5,2-diyl(2S)-2,1-pyrrolidinediyl))bis(N,N-diethyl-1-oxo-2-propanamine)	 (*Cap*-69a)	1.00 min (Cond. 1); >95%; LC/MS: Anal. Calcd. for $[M+H]^+$ $C_{40}H_{55}N_8O_2$: 623.38; found 679.67; HRMS: Anal. Calcd. for $[M+H]^+$ $C_{40}H_{55}N_8O_2$: 679.4448; found 679.4432
M10	(2R,2'R)-1,1'-(4,4'-biphenyldiylbis(1H-imidazole-5,2-diyl(2S)-2,1-pyrrolidinediyl))bis(N,N-diethyl-3-methyl-1-oxo-2-butanamine)	 (*Cap*-72)	1.03 min (Cond. 1); >98%; LC/MS: Anal. Calcd. for $[M+H]^+$ $C_{44}H_{63}N_8O_2$: 735.51; found 735.76; HRMS: Anal. Calcd. for $[M+H]^+$ $C_{44}H_{63}N_8O_2$: 735.5074; found 735.5060
M11	methyl ((1S)-1-(((2S)-2-(5-(4'-(2-((2S)-1-((2S)-2-((methoxycarbonyl)(methyl)amino)-3-methylbutanoyl)-2-pyrrolidinyl)-1H-	 (*Cap*-62)	1.46 min (Cond. 1); >98%; LC/MS: Anal. Calcd. for $[M+H]^+$ $C_{42}H_{55}N_8O_2$: 767.42;

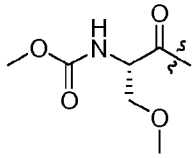
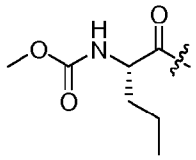
	imidazol-5-yl)-4-biphenylyl)-1H-imidazol-2-yl)-1-pyrrolidinyl)carbonyl)-2-methylpropyl)methylcarbamate		found 767.38; HRMS: Anal. Calcd. for $[M+H]^+$ $C_{42}H_{55}N_8O_2$: 767.4245; found 767.4252
M12	dimethyl (4,4'-biphenyldiylbis(1H-imidazole-5,2-diyl(2S)-2,1-pyrrolidinediyl((1S)-2-oxo-1-phenyl-2,1-ethanediyl)))biscarbamate	 (*Cap*-82)	1.32 min (Cond. 1); >98%; LC/MS: Anal. Calcd. for $[M+H]^+$ $C_{46}H_{47}N_8O_6$: 807.36; found 807.32; HRMS: Anal. Calcd. for $[M+H]^+$ $C_{46}H_{47}N_8O_6$: 807.3619; found 807.3651
M13	N,N'-(4,4'-biphenyldiylbis(1H-imidazole-5,2-diyl(2S)-2,1-pyrrolidinediyl((2R)-1-oxo-1,2-propanediyl)))bis(N-propyl-1-propanamine)	 (*Cap*-70a)	1.09 min (Cond. 1); >98%; LC/MS: Anal. Calcd. for $[M+H]^+$ $C_{44}H_{63}N_8O_2$: 735.51; found 735.46; HRMS: Anal. Calcd. for $[M+H]^+$ $C_{44}H_{63}N_8O_2$: 735.5074; found 735.5063
M14	methyl ((1S)-2-hydroxy-1-(((2S)-2-(5-(4'-(2-((2S)-1-((2S)-3-hydroxy-2-((methoxycarbonyl)amino)-3-methylbutanoyl)-2-pyrrolidinyl)-1H-imidazol-5-yl)-4-biphenylyl)-1H-	 (*Cap*-65)	1.13 min (Cond. 1); >98%; LC/MS: Anal. Calcd. for $[M+H]^+$ $C_{40}H_{51}N_8O_8$: 771.38; found 771.21

	imidazol-2-yl)-1-pyrrolidinyl)carbonyl)-2-methylpropyl)carbamate		
M15	methyl ((1S,2R)-2-hydroxy-1-(((2S)-2-(5-(4'-(2-((2S)-1-((2S,3R)-3-hydroxy-2-((methoxycarbonyl)amino)butanoyl)-2-pyrrolidinyl)-1H-imidazol-5-yl)-4-biphenylyl)-1H-imidazol-2-yl)-1-pyrrolidinyl)carbonyl)propyl)carbamate	 (*Cap*-66)	1.10 min (Cond. 1); >98%; LC/MS: Anal. Calcd. for $[M+H]^+$ $C_{38}H_{47}N_8O_8$: 743.35; found 743.23; ^1H NMR (DMSO-d_6, δ = 2.5 ppm, 400 MHz), ~14.5 (br s, 4H), 8.15 (s, 2H), 7.97 (d, *J* = 8.5, 4H), 7.89 (d, *J* = 8.4, 4H), 7.10/7.05 (two overlapping d, *J* = 8.0, 8.4, 1.82H), 6.57 (app br s, 0.18H), 5.78 (br d, *J* = 7.9, 0.18H), 5.16 (m, 1.82H), 4.27 (dd, *J* = 8.0, 5.3, 1.82H), 4.10 (m, 0.18H), 3.96-3.81 (m, 6H), 3.55 (s, 5.46H), 3.37 (s, 0.54H), 2.41 (m, 2H), 2.17-2.00 (m, 6H), 1.10 (d, *J* = 6.3, 0.54H), 1.04 (d, *J* = 6.3, 5.46H).
M16	methyl ((1S,2S)-2-hydroxy-1-(((2S)-2-(5-(4'-(2-((2S)-1-((2S,3S)-3-hydroxy-2-		1.11 min (Cond. 1); >98%; LC/MS: Anal. Calcd. for

	((methoxycarbonyl)amino)butanoyl)-2-pyrrolidinyl)-1H-imidazol-5-yl)-4-biphenylyl)-1H-imidazol-2-yl)-1-pyrrolidinyl)carbonyl)propyl)carbamate	(*Cap*-67)	$[M+H]^+$ $C_{38}H_{47}N_8O_8$: 743.35; found 743.23
M17	methyl ((1S)-2-((2S)-2-(5-(4'-(2-((2S)-1-(N-(methoxycarbonyl)-L-alanyl)-2-pyrrolidinyl)-1H-imidazol-5-yl)-4-biphenylyl)-1H-imidazol-2-yl)-1-pyrrolidinyl)-1-methyl-2-oxoethyl)carbamate	 (*Cap*-52)	1.64 min (Cond. 2); 99%; LC/MS: Anal. Calcd. for $[M+H]^+$ $C_{36}H_{43}N_8O_6$: 683.33; found 683.30; HRMS: Anal. Calcd. for $[M+H]^+$ $C_{36}H_{43}N_8O_6$: 683.3306; found 683.3305.
M18	methyl ((1R)-2-((2S)-2-(5-(4'-(2-((2S)-1-(N-(methoxycarbonyl)-D-alanyl)-2-pyrrolidinyl)-1H-imidazol-5-yl)-4-biphenylyl)-1H-imidazol-2-yl)-1-pyrrolidinyl)-1-methyl-2-oxoethyl)carbamate	 (*Cap*-85)	1.70 min (Cond. 2); 97%; LC/MS: Anal. Calcd. for $[M+H]^+$ $C_{36}H_{43}N_8O_6$: 683.33; found 683.32; HRMS: Anal. Calcd. for $[M+H]^+$ $C_{36}H_{43}N_8O_6$: 683.3306; found 683.3318.
M19	(2S,2'S)-1,1'-(4,4'-biphenyldiylbis(1H-imidazole-5,2-diyl(2S)-2,1-pyrrolidinediyl))bis(N,N-dimethyl-1-oxo-2-propanamine)	 (*Cap*-13)	1.43 min (Cond. 2); >99%; LC/MS: Anal. Calcd. for $[M+H]^+$ $C_{36}H_{47}N_8O_2$: 623.38; found 623.43; HRMS: Anal. Calcd. for $[M+H]^+$

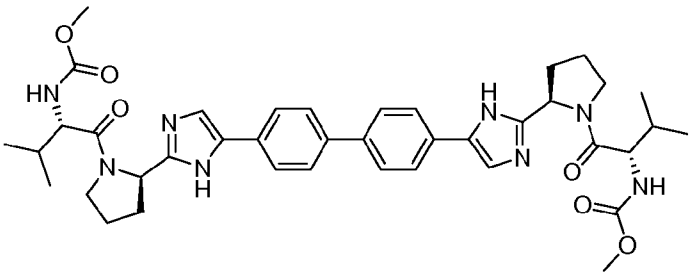
			$C_{36}H_{47}N_8O_2$: 623.3822; found 623.3837.
M20	dimethyl (4,4'-biphenyldiylbis(1H-imidazole-5,2-diyl(2S)-2,1-pyrrolidinediyl((2R)-1-oxo-1,2-butanediyl)))biscarbamate	 (*Cap*-53a)	1.82 min (Cond.2); >99%; LC/MS: Anal. Calcd. for $[M+H]^+$ $C_{38}H_{47}N_8O_6$: 711.36; found: 711.35; HRMS: Anal. Calcd. for $[M+H]^+$ $C_{38}H_{47}N_8O_6$: 711.3619; found 711.3649.
M21	dimethyl (4,4'-biphenyldiylbis(1H-imidazole-5,2-diyl(2S)-2,1-pyrrolidinediyl((2S)-1-oxo-1,2-butanediyl)))biscarbamate	 (*Cap*-53b)	1.81 min (Cond.2); >99%; LC/MS: Anal. Calcd. for $[M+H]^+$ $C_{38}H_{47}N_8O_6$: 711.36; found 711.35; HRMS: Anal. Calcd. for $[M+H]^+$ $C_{38}H_{47}N_8O_6$: 711.3619; found 711.3643.
M22	dimethyl (4,4'-biphenyldiylbis(1H-imidazole-5,2-diyl(2S)-2,1-pyrrolidinediyl((1R)-1-cyclopropyl-2-oxo-2,1-ethanediyl)))biscarbamate	 (*Cap*-54a)	1.83 min (Cond. 2); >99%; LC/MS: Anal. Calcd. for $[M+H]^+$ $C_{40}H_{47}N_8O_6$: 735.36; found 735.44; HRMS: Anal. Calcd. for $[M+H]^+$ $C_{40}H_{47}N_8O_6$: 735.3619; found:

			735.3614.
M23	dimethyl (4,4'-biphenyldiylbis(1H-imidazole-5,2-diyl(2S)-2,1-pyrrolidinediyl((1S)-1-cyclopropyl-2-oxo-2,1-ethanediyl)))biscarbamate	 (*Cap*-54b)	1.81 min (Cond. 2); >99%; LC/MS: Anal. Calcd. for $[M+H]^+$ $C_{40}H_{47}N_8O_6$: 735.36; found 735.43; HRMS: Anal. Calcd. for $[M+H]^+$ $C_{40}H_{47}N_8O_6$: 735.3619; found 735.3651.
M24	methyl ((1S)-1-(((2S)-2-(5-(4'-(2-((2S)-1-((2S)-2-((methoxycarbonyl)amino)-3,3-dimethylbutanoyl)-2-pyrrolidinyl)-1H-imidazol-5-yl)-4-biphenylyl)-1H-imidazol-2-yl)-1-pyrrolidinyl)carbonyl)-2,2-dimethylpropyl)carbamate		2.11 min (Cond. 2); >99%; LC/MS: Anal. Calcd. for $[M+H]^+$ $C_{42}H_{55}N_8O_6$: 767.42; found 767.58; HRMS: Anal. Calcd. for $C_{42}H_{55}N_8O_6$: 767.4245; found 767.4230.
M25	dimethyl (4,4'-biphenyldiylbis(1H-imidazole-5,2-diyl(2S)-2,1-pyrrolidinediyl((4S)-5-oxo-1-pentene-5,4-diyl)))biscarbamate	 (*Cap*-55)	1.91 min (Cond. 2); 98%; LC/MS: Anal. Calcd. for $[M+H]^+$ $C_{40}H_{47}N_8O_6$: 735.36; found 735.47; HRMS: Anal. Calcd. for $[M+H]^+$ $C_{40}H_{47}N_8O_6$: 735.3619; found 735.3630.

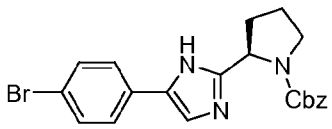
M26	methyl ((1S)-2-((2S)-2-(5-(4'-(2-((2S)-1-(N-(methoxycarbonyl)-O-methyl-L-seryl)-2-pyrrolidinyl)-1H-imidazol-5-yl)-4-biphenylyl)-1H-imidazol-2-yl)-1-pyrrolidinyl)-1-(methoxymethyl)-2-oxoethyl)carbamate	 (*Cap*-56)	1.72 min (Cond. 2); 97%; LC/MS: Anal. Calcd. for $[M+H]^+$ $C_{38}H_{47}N_8O_8$: 743.35; found 743.49; HRMS: Anal. Calcd. for $[M+H]^+$ $C_{38}H_{47}N_8O_8$: 743.3517; found 743.3489.
M27	methyl ((1S)-1-(((2S)-2-(5-(4'-(2-((2S)-1-((2S)-2-((methoxycarbonyl)amino)pentanoyl)-2-pyrrolidinyl)-1H-imidazol-5-yl)-4-biphenylyl)-1H-imidazol-2-yl)-1-pyrrolidinyl)carbonyl)butyl)carbamate	 (*Cap*-57)	1.98 min (Cond. 2); 98%; LC/MS: Anal. Calcd. for $[M+H]^+$ $C_{40}H_{51}N_8O_6$: 739.39; found 739.52; HRMS: Anal. Calcd. for $[M+H]^+$ $C_{40}H_{51}N_8O_6$: 739.3932; found 739.3904.

Example M28

methyl ((1S)-1-(((2R)-2-(5-(4'-(2-((2R)-1-((2S)-2-((methoxycarbonyl)amino)-3-methylbutanoyl)-2-pyrrolidinyl)-1H-imidazol-5-yl)-4-biphenylyl)-1H-imidazol-2-yl)-1-pyrrolidinyl)carbonyl)-2-methylpropyl)carbamate

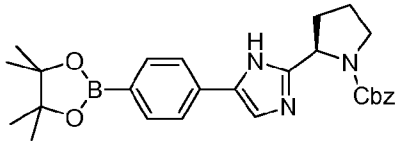


Example M28, Step a



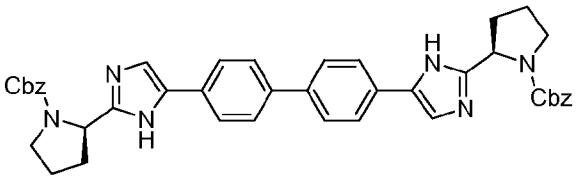
Bromide M28a was prepared from D-Proline according to the procedure described for its enantiomer 28b.

Example M28, Step b



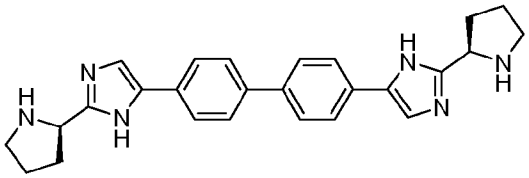
Boronate ester M28b was prepared from bromide M28a according to the procedure described for intermediate 1c. LC: RT = 1.57 min (Cond. 1); LC/MS: Anal. Calcd. for $[M+H]^+$ $C_{27}H_{33}BN_3O_4$: 474.26; found 474.24.

Example M28, Step c



Biphenyl M28c was prepared from bromide M28a and boronate M28b according to the procedure described for intermediate 1d. LC: RT = 1.43 min (Cond. 1); LC/MS: Anal. Calcd. for $[M+H]^+$ $C_{42}H_{41}N_6O_4$: 693.32; found 693.38.

Example M28, Step d



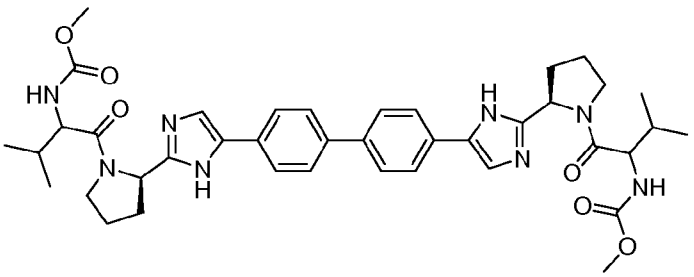
Pyrrolidine M28d was prepared from carbamate M28c according to the procedure described for intermediate 28d. ^{1}H NMR (DMSO-d_6, δ = 2.5 ppm, 400 MHz): δ 11.83 (br s, 2H), 7.80 (d, J = 8.3, 4H), 7.66 (d, J = 8.3, 4H), 7.46 (br s, 2H),

4.16 (app t, J = 7.2, 2H), 3.00-2.94 (m, 2H), 2.88-2.82 (m, 2H), 2.10-2.01 (m, 2H), 1.94-1.85 (m, 2H), 1.82-1.66 (m, 4H). [Note: in the region between 3.2-2.6 ppm there is a broad base-line signal that is believed to be that of the pyrrolidine NH]. LC: RT = 1.02 min (Cond. 1); LC/MS: Anal. Calcd. for $[M+H]^+$ $C_{26}H_{29}N_6$: 425.25; found 425.27.

Example M28

Example M28 was prepared as TFA salt from intermediate M28d and *Cap*-51 according to the procedure described for Example 1. LC: RT = 1.33 min (Cond. 1); 96% homogeneity index; LC/MS: Anal. Calcd. for $[M+H]^-$ $C_{40}H_{51}N_8O_6$: 739.32; found 739.43; HRMS: Anal. Calcd. for $[M+H]^-$ $C_{40}H_{51}N_8O_6$: 739.3932; found 739.3907.

Example M28-1



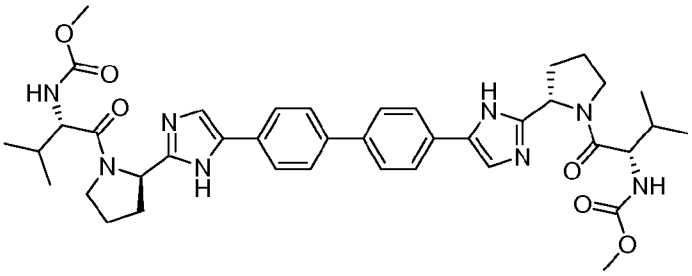
The TFA salt of Example M28-1 was prepared as a mixture of three stereoisomers from intermediate M28d and racemic version of *Cap*-51 according to the procedure described for Example 1. Three peaks with a retention time of 21.74 min, 22.62 min, and 23.40 min, and exhibiting the correct molecular weight, were observed when the sample was analyzed under the following condition:

Waters Acquity HPLC with Micromass ZQ MS (electrospray probe) and Waters 2996 PDA detection. (UV detection @ 315nm)
Column: Acquity UPLC; BEH C18; 1.7um; 100 X 2.1 mm ID; (at approx. 30C)
Mobile phase A: water, 25 mM ammonium acetate at pH=5
Mobile phase B: acetonitrile
Flow rate: 0.50 ml/min
10-50%B 0-35.0 min

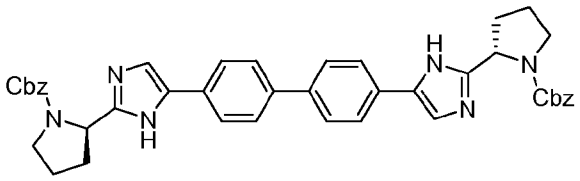
50-98%B	35.0-45.0min
Hold 98%B	45.0-48.0 min
98%B-100%B	48.0-48.5min
Hold 100%B	48.5-50.0min

Example M28-2

methyl ((1S)-1-(((2S)-2-(5-(4'-(2-((2R)-1-((2S)-2-((methoxycarbonyl)amino)-3-methylbutanoyl)-2-pyrrolidinyl)-1H-imidazol-5-yl)-4-biphenylyl)-1H-imidazol-2-yl)-1-pyrrolidinyl)carbonyl)-2-methylpropyl)carbamate

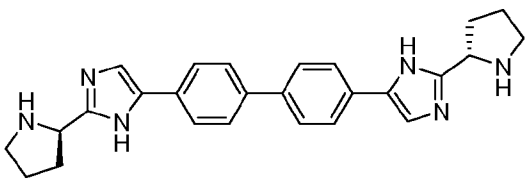


Example M28-2, Step a



Carbamate M28-2a was prepared from boronate ester M28b and bromide 28b according to the procedure described for intermediate 1d. ^{1}H NMR (DMSO-d_6, δ = 2.5 ppm, 400 MHz): δ 12.25/12.01/11.93 (three br s, 2H), 7.86-6.98 (m, 20H), 5.13-4.88 (m, 6H), 3.63 (m, 2H), 3.47 (m, 2H), 2.35-1.84 (M, 8H). LC: RT = 1.46 min (Cond. 1); LC/MS: Anal. Calcd. for $[M+H]^+$ $C_{42}H_{41}N_6O_4$: 693.32; found 693.34.

Example M28-2, Step b

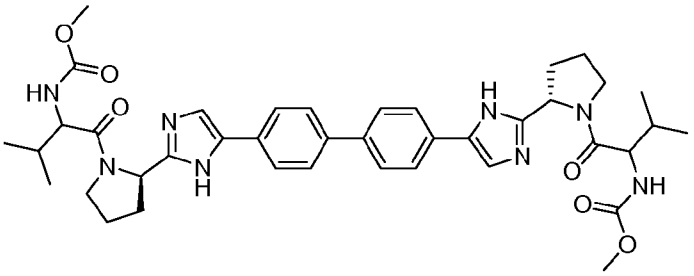


Pyrrolidine M28-2b was prepared from carbamate M28-2a according to the procedure described for intermediate 28d. ^{1}H NMR (DMSO-d_6, δ = 2.5 ppm, 400 MHz): δ 11.84 (br s, 2H), 7.80 (d, *J* = 8.3, 4H), 7.66 (d, *J* = 8.3, 4H), 7.46 (br s, 2H), 4.87 (m, 0.05H), 4.16 (app t, *J* = 7.2, 1.95H), 3.00-2.94 (m, 2H), 2.88-2.82 (m, 2H), 2.10-2.01 (m, 2H), 1.94-1.85 (m, 2H), 1.82-1.66 (m, 4H). [Note: in the region between ~3.1-2.6 ppm there is a broad base-line signal that is believed to be that of the pyrrolidine NH]. LC: RT = 0.96 min (Cond. 1); LC/MS: Anal. Calcd. for $[M+H]^+$ $C_{26}H_{29}N_6$: 425.25; found 425.28.

Example M28-2

Example M28-2 was prepared as TFA salt from intermediate M28-2b and *Cap*-51 according to the procedure described for Example 1. LC: RT = 1.96 minutes (Cond. 2); 98% homogeneity index; LC/MS: Anal. Calcd. for $[M+H]^+$ $C_{40}H_{51}N_8O_6$ 739.39; found 739.47.

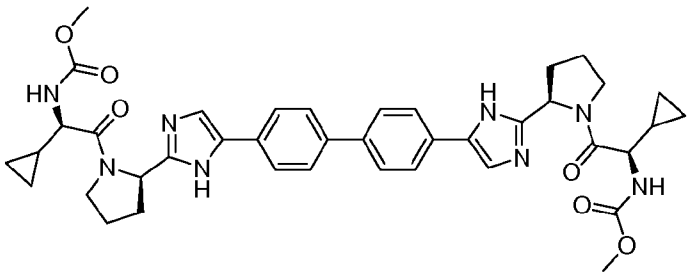
Example M28-3



The TFA salt of Example M28-3 was prepared as a mixture of four stereoisomers from intermediate M28-2b and racemic version of *Cap*-51 according to the procedure described for Example 1. Three peaks with a retention time of 21.28 min, 22.19 min, and 23.01 min, and exhibiting the correct molecular weight, were observed when the sample was analyzed under the LC/MS condition described for Example M28-1.

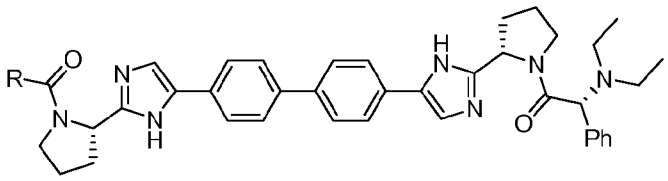
Example M29

dimethyl (4,4'-biphenyldiylbis(1H-imidazole-5,2-diyl(2R)-2,1-pyrrolidinediyl((1R)-1-cyclopropyl-2-oxo-2,1-ethanediyl)))biscarbamate

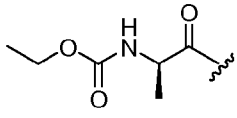


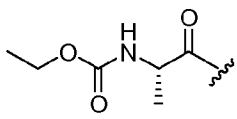
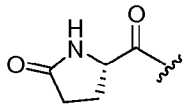
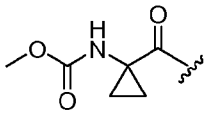
Example M29 was prepared as TFA salt from intermediate M28d and *Cap*-54a according to the procedure described for Example 1. LC: RT = 1.21 min (Cond. 1); >98% homogeneity index; LC/MS: Anal. Calcd. for $[M+H]^+$ $C_{40}H_{47}N_8O_6$: 735.36; found 735.42; HRMS: Anal. Calcd. for $[M+H]^+$ $C_{40}H_{47}N_8O_6$: 735.3619; found 735.3598.

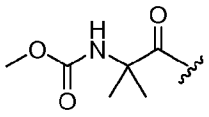
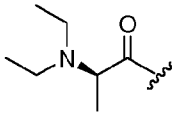
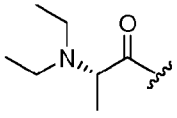
Example M30-M62

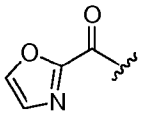
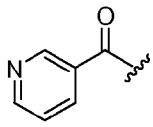
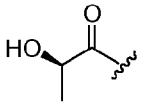


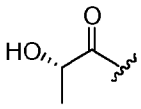
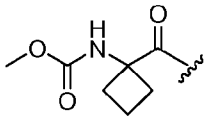
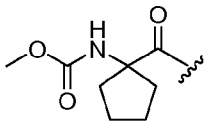
Example M30-M62 were prepared as TFA salts from CJ-24 and the respective caps using the same method described for Example 28.

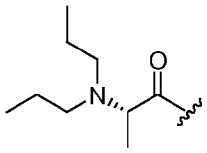
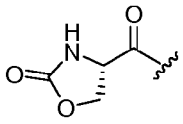
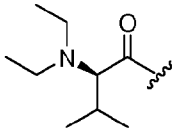
Example	*Compound Name*	 *(Source)*	*RT (LC-Cond.); % homogeneity index; MS data*
M30	ethyl ((1R)-2-((2S)-2-(5-(4'-(2-((2S)-1-((2R)-2-(diethylamino)-2-phenylacetyl)-2-pyrrolidinyl)-1H-imidazol-5-yl)-4-biphenylyl)-1H-imidazol-2-yl)-1-pyrrolidinyl)-1-	 (*Cap*-59a)	1.13 min (Cond. 1); >98%; LC/MS: Anal. Calcd. for $[M+H]^+$ $C_{44}H_{53}N_8O_4$: 757.42;

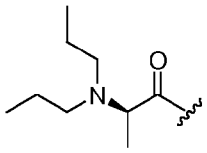
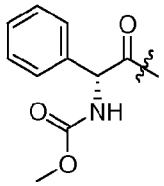
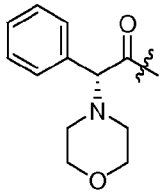
	methyl-2-oxoethyl)carbamate		found 757.50; HRMS: Anal. Calcd. for $[M+H]^+$ $C_{44}H_{53}N_8O_4$: 757.4190; found 757.4181
M31	ethyl ((1S)-2-((2S)-2-(5-(4'-(2-((2S)-1-((2R)-2-(diethylamino)-2-phenylacetyl)-2-pyrrolidinyl)-1H-imidazol-5-yl)-4-biphenylyl)-1H-imidazol-2-yl)-1-pyrrolidinyl)-1-methyl-2-oxoethyl)carbamate	 (*Cap*-59b)	1.07 min (Cond. 1); >98%; LC/MS: Anal. Calcd. for $[M+H]^+$ $C_{44}H_{53}N_8O_4$: 757.42; found 757.55; HRMS: Anal. Calcd. for $[M+H]^+$ $C_{44}H_{53}N_8O_4$: 757.4190; found 757.4225
M32	(5S)-5-(((2S)-2-(5-(4'-(2-((2S)-1-((2R)-2-(diethylamino)-2-phenylacetyl)-2-pyrrolidinyl)-1H-imidazol-5-yl)-4-biphenylyl)-1H-imidazol-2-yl)-1-pyrrolidinyl)carbonyl)-2-pyrrolidinone		1.02 min (Cond. 1); >98%; LC/MS: Anal. Calcd. for $[M+H]^+$ $C_{43}H_{49}N_8O_3$: 725.39; found 725.48; HRMS: Anal. Calcd. for $[M+H]^+$ $C_{43}H_{49}N_8O_3$: 725.3928; found 725.3926
M33	methyl (1-(((2S)-2-(5-(4'-(2-((2S)-1-((2R)-2-(diethylamino)-2-phenylacetyl)-2-pyrrolidinyl)-1H-imidazol-5-yl)-4-biphenylyl)-1H-imidazol-2-yl)-1-pyrrolidinyl)carbonyl)cyclopropyl)carbamate	 (*Cap*-60)	1.12 min (Cond. 1); >98%; LC/MS: Anal. Calcd. for $[M+H]^+$ $C_{44}H_{51}N_8O_4$: 755.40; found 755.61; HRMS: Anal.

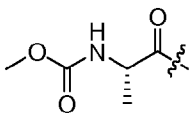
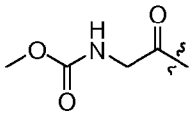
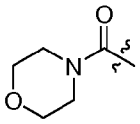
			Calcd. for $[M+H]^+$ $C_{44}H_{51}N_8O_4$: 755.4033; found 755.4066
M34	methyl (2-((2S)-2-(5-(4'-(2-((2S)-1-((2R)-2-(diethylamino)-2-phenylacetyl)-2-pyrrolidinyl)-1H-imidazol-5-yl)-4-biphenylyl)-1H-imidazol-2-yl)-1-pyrrolidinyl)-1,1-dimethyl-2-oxoethyl)carbamate	 (*Cap*-61)	1.16 min (Cond. 1); >98%; LC/MS: Anal. Calcd. for $[M+H]^+$ $C_{44}H_{53}N_8O_4$: 757.42; found 757.63; HRMS: Anal. Calcd. for $[M+H]^+$ $C_{44}H_{53}N_8O_4$: 757.4190; found 757.4164
M35	(2R)-1-((2S)-2-(5-(4'-(2-((2S)-1-((2R)-2-(diethylamino)-2-phenylacetyl)-2-pyrrolidinyl)-1H-imidazol-5-yl)-4-biphenylyl)-1H-imidazol-2-yl)-1-pyrrolidinyl)-N,N-diethyl-1-oxo-2-propanamine	 (*Cap*-69a)	1.06 min (Cond. 1); >98%; LC/MS: Anal. Calcd. for $[M+H]^+$ $C_{45}H_{57}N_8O_2$: 741.46; found 741.64; HRMS: Anal. Calcd. for $[M+H]^+$ $C_{45}H_{57}N_8O_2$: 741.4604; found 741.4597
M36	(2S)-1-((2S)-2-(5-(4'-(2-((2S)-1-((2R)-2-(diethylamino)-2-phenylacetyl)-2-pyrrolidinyl)-1H-imidazol-5-yl)-4-biphenylyl)-1H-imidazol-2-yl)-1-pyrrolidinyl)-N,N-diethyl-1-oxo-2-propanamine	 (*Cap*-69b)	1.04 min (Cond. 1); >98%; LC/MS: Anal. Calcd. for $[M+H]^+$ $C_{45}H_{57}N_8O_2$: 741.46; found 741.63; HRMS: Anal. Calcd. for $[M+H]^+$ $C_{45}H_{57}N_8O_2$:

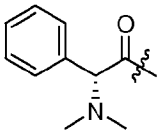
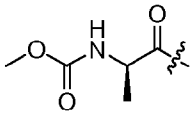
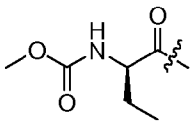
			741.4604; found 741.4581
M37	(1R)-N,N-diethyl-2-((2S)-2-(5-(4'-(2-((2S)-1-(1,3-oxazol-2-ylcarbonyl)-2-pyrrolidinyl)-1H-imidazol-5-yl)-4-biphenylyl)-1H-imidazol-2-yl)-1-pyrrolidinyl)-2-oxo-1-phenylethanamine		1.11 min (Cond. 1); >98%; LC/MS: Anal. Calcd. for $[M+H]^+$ $C_{42}H_{45}N_8O_3$: 709.36; found 709.51; HRMS: Anal. Calcd. for $[M+H]^+$ $C_{42}H_{45}N_8O_2$: 709.3615; found 709.3615
M38	(1R)-N,N-diethyl-2-oxo-1-phenyl-2-((2S)-2-(5-(4'-(2-((2S)-1-(3-pyridinylcarbonyl)-2-pyrrolidinyl)-1H-imidazol-5-yl)-4-biphenylyl)-1H-imidazol-2-yl)-1-pyrrolidinyl)ethanamine		1.09 min (Cond. 1); >98%; LC/MS: Anal. Calcd. for $[M+H]^+$ $C_{44}H_{47}N_8O_2$: 719.38; found 719.51; HRMS: Anal. Calcd. for $[M+H]^+$ $C_{44}H_{47}N_8O_2$: 719.3822; found 719.3829
M39	(2R)-1-((2S)-2-(5-(4'-(2-((2S)-1-((2R)-2-(diethylamino)-2-phenylacetyl)-2-pyrrolidinyl)-1H-imidazol-5-yl)-4-biphenylyl)-1H-imidazol-2-yl)-1-pyrrolidinyl)-1-oxo-2-propanol		1.09 min (Cond. 1); >98%; LC/MS: Anal. Calcd. for $[M+H]^+$ $C_{41}H_{48}N_7O_3$: 686.38; found 686.58; HRMS: Anal. Calcd. for $[M+H]^+$ $C_{41}H_{48}N_7O_3$: 686.3819; found 686.3843

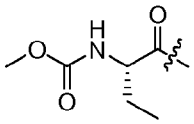
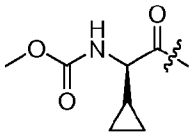
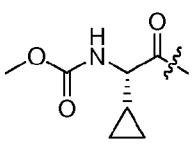
M40	(2S)-1-((2S)-2-(5-(4'-(2-((2S)-1-((2R)-2-(diethylamino)-2-phenylacetyl)-2-pyrrolidinyl)-1H-imidazol-5-yl)-4-biphenylyl)-1H-imidazol-2-yl)-1-pyrrolidinyl)-1-oxo-2-propanol		1.09 min (Cond. 1); >98%; LC/MS: Anal. Calcd. for $[M+H]^+$ $C_{41}H_{48}N_7O_3$: 686.38; found 686.57; HRMS: Anal. Calcd. for $[M+H]^+$ $C_{41}H_{48}N_7O_3$: 686.3819; found 686.3832
M41	methyl (1-(((2S)-2-(5-(4'-(2-((2S)-1-((2R)-2-(diethylamino)-2-phenylacetyl)-2-pyrrolidinyl)-1H-imidazol-5-yl)-4-biphenylyl)-1H-imidazol-2-yl)-1-pyrrolidinyl)carbonyl)cyclobutyl) carbamate	 (*Cap*-64)	1.19 min (Cond. 1); >98%; LC/MS: Anal. Calcd. for $[M+H]^+$ $C_{45}H_{53}N_8O_4$: 769.42; found 769.66; HRMS: Anal. Calcd. for $[M+H]^+$ $C_{45}H_{53}N_8O_4$: 769.419; found 769.4155
M42	methyl (1-(((2S)-2-(5-(4'-(2-((2S)-1-((2R)-2-(diethylamino)-2-phenylacetyl)-2-pyrrolidinyl)-1H-imidazol-5-yl)-4-biphenylyl)-1H-imidazol-2-yl)-1-pyrrolidinyl)carbonyl)cyclopentyl)carbamate	 (*Cap*-63)	1.25 min (Cond. 1); >98%; LC/MS: Anal. Calcd. for $[M+H]^+$ $C_{46}H_{55}N_8O_4$: 783.43; found 783.69; HRMS: Anal. Calcd. for $[M+H]^+$ $C_{46}H_{55}N_8O_4$: 783.4346; found 783.4357

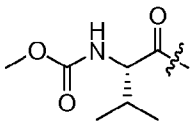
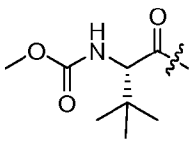
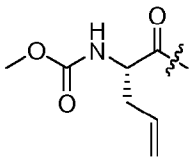
M43	N-((1S)-2-((2S)-2-(5-(4'-(2-((2S)-1-((2R)-2-(diethylamino)-2-phenylacetyl)-2-pyrrolidinyl)-1H-imidazol-5-yl)-4-biphenylyl)-1H-imidazol-2-yl)-1-pyrrolidinyl)-1-methyl-2-oxoethyl)-N-propyl-1-propanamine	 (*Cap*-70b)	1.10 min (Cond. 1); >98%; LC/MS: Anal. Calcd. for $[M+H]^+$ $C_{47}H_{61}N_8O_2$: 769.49; found 769.69; HRMS: Anal. Calcd. for $[M+H]^+$ $C_{47}H_{61}N_8O_2$: 769.4917; found 769.4925
M44	(4S)-4-(((2S)-2-(5-(4'-(2-((2S)-1-((2R)-2-(diethylamino)-2-phenylacetyl)-2-pyrrolidinyl)-1H-imidazol-5-yl)-4-biphenylyl)-1H-imidazol-2-yl)-1-pyrrolidinyl)carbonyl)-1,3-oxazolidin-2-one	 (*Cap*-81)	1.08 min (Cond.1); >98%; LC/MS: Anal. Calcd. for $[M+H]^+$ $C_{42}H_{47}N_8O_4$: 727.37; found 727.56; HRMS: Anal. Calcd. for $[M+H]^+$ $C_{42}H_{47}N_8O_4$: 727.3720; found 727.3740
M45	(2R)-1-((2S)-2-(5-(4'-(2-((2S)-1-((2R)-2-(diethylamino)-2-phenylacetyl)-2-pyrrolidinyl)-1H-imidazol-5-yl)-4-biphenylyl)-1H-imidazol-2-yl)-1-pyrrolidinyl)-N,N-diethyl-3-methyl-1-oxo-2-butanamine	 (*Cap*-72)	1.08 min (Cond. 1); >98%; LC/MS: Anal. Calcd. for $[M+H]^+$ $C_{47}H_{61}N_8O_2$: 769.49; found 769.73; HRMS: Anal. Calcd. for $[M+H]^+$ $C_{47}H_{61}N_8O_2$: 769.4917; found 769.4898

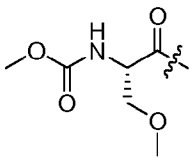
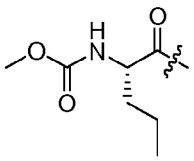
M46	N-((1R)-2-((2S)-2-(5-(4'-(2-((2S)-1-((2R)-2-(diethylamino)-2-phenylacetyl)-2-pyrrolidinyl)-1H-imidazol-5-yl)-4-biphenylyl)-1H-imidazol-2-yl)-1-pyrrolidinyl)-1-methyl-2-oxoethyl)-N-propyl-1-propanamine	 (*Cap*-70a)	1.12 min (Cond.1); >98%; LC/MS: Anal. Calcd. for $[M+H]^+$ $C_{47}H_{61}N_8O_2$: 769.49; found 769.45; HRMS: Anal. Calcd. for $[M+H]^+$ $C_{47}H_{61}N_8O_2$: 769.4917; found 769.4915
M47	methyl ((1R)-2-((2S)-2-(5-(4'-(2-((2S)-1-((2R)-2-(diethylamino)-2-phenylacetyl)-2-pyrrolidinyl)-1H-imidazol-5-yl)-4-biphenylyl)-1H-imidazol-2-yl)-1-pyrrolidinyl)-2-oxo-1-phenylethyl)carbamate	 (*Cap*-4)	1.85 min (Cond.2); 97%; LC/MS: Anal. Calcd. for $[M+H]^+$ $C_{48}H_{53}N_8O_4$: 805.42; found 805.4; HRMS: Anal. Calcd. for $[M+H]^+$: $C_{48}H_{53}N_8O_4$ 805.4190; found 805.4196.
M48	(1R)-N,N-diethyl-2-((2S)-2-(5-(4'-(2-((2S)-1-((2R)-2-(4-morpholinyl)-2-phenylacetyl)-2-pyrrolidinyl)-1H-imidazol-5-yl)-4-biphenylyl)-1H-imidazol-2-yl)-1-pyrrolidinyl)-2-oxo-1-phenylethanamine	 (*Cap*-6)	1.69 min (Cond. 2); 98%; LC/MS: Anal. Calcd. for $[M+H]^+$ $C_{50}H_{57}N_8O_3$: 817.45; found 817.48; HRMS: Anal. Calcd. for $[M+H]^+$ $C_{50}H_{57}N_8O_3$: 817.4554; found 817.4589.

M49	methyl ((1S)-2-((2S)-2-(5-(4'-(2-((2S)-1-((2R)-2-(diethylamino)-2-phenylacetyl)-2-pyrrolidinyl)-1H-imidazol-5-yl)-4-biphenylyl)-1H-imidazol-2-yl)-1-pyrrolidinyl)-1-methyl-2-oxoethyl)carbamate	 (*Cap*-52)	1.67 min (Cond. 2); 92%; LC/MS: Anal. Calcd. for $[M+H]^+$ $C_{43}H_{51}N_8O_4$: 743.40; found 743.42; HRMS: Anal. Calcd. for $[M+H]^+$ $C_{43}H_{51}N_8O_4$: 743.4033; found 743.4053.
M50	methyl (2-((2S)-2-(5-(4'-(2-((2S)-1-((2R)-2-(diethylamino)-2-phenylacetyl)-2-pyrrolidinyl)-1H-imidazol-5-yl)-4-biphenylyl)-1H-imidazol-2-yl)-1-pyrrolidinyl)-2-oxoethyl)carbamate		1.63 min (Cond. 2); 99%; LC/MS: Anal. Calcd. for $[M+H]^+$ $C_{42}H_{49}N_8O_4$: 729.39; found 729.39; HRMS: Anal. Calcd. for $[M+H]^+$ $C_{42}H_{49}N_8O_4$: 729.3877; found 729.3888.
M51	(1R)-N,N-diethyl-2-((2S)-2-(5-(4'-(2-((2S)-1-(4-morpholinylcarbonyl)-2-pyrrolidinyl)-1H-imidazol-5-yl)-4-biphenylyl)-1H-imidazol-2-yl)-1-pyrrolidinyl)-2-oxo-1-phenylethanamine		1.67 min (Cond.2); 99%; LC/MS: Anal. Calcd. for $[M+H]^+$ $C_{43}H_{51}N_8O_3$: 727.41; found 727.40; HRMS: Anal. Calcd. for $[M+H]^+$ $C_{43}H_{51}N_8O_3$: 727.4084; found

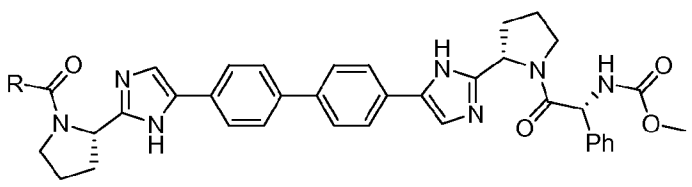
			727.4117.
M52	(1R)-2-((2S)-2-(5-(4'-(2-((2S)-1-((2R)-2-(diethylamino)-2-phenylacetyl)-2-pyrrolidinyl)-1H-imidazol-5-yl)-4-biphenylyl)-1H-imidazol-2-yl)-1-pyrrolidinyl)-N,N-dimethyl-2-oxo-1-phenylethanamine	 (*Cap*-1)	1.65 min (Cond. 2); 92%; LC/MS: Anal. Calcd. for $[M+H]^+$ $C_{48}H_{55}N_8O_2$: 775.44; found 775.48; HRMS: Anal. Calcd. for $[M+H]^+$ $C_{48}H_{55}N_8O_2$: 775.4448; found 775.4433.
M53	methyl ((1R)-2-((2S)-2-(5-(4'-(2-((2S)-1-((2R)-2-(diethylamino)-2-phenylacetyl)-2-pyrrolidinyl)-1H-imidazol-5-yl)-4-biphenylyl)-1H-imidazol-2-yl)-1-pyrrolidinyl)-1-methyl-2-oxoethyl)carbamate	 (*Cap*-85)	1.68 min (Cond.2); 98%; LC/MS: Anal. Calcd. for $[M+H]^+$ $C_{43}H_{51}N_8O_4$: 743.40; found 743.42; HRMS: Anal. Calcd. for $[M+H]^+$ $C_{43}H_{51}N_8O_4$: 743.4033; found 743.4055.
M54	methyl ((1R)-1-(((2S)-2-(5-(4'-(2-((2S)-1-((2R)-2-(diethylamino)-2-phenylacetyl)-2-pyrrolidinyl)-1H-imidazol-5-yl)-4-biphenylyl)-1H-imidazol-2-yl)-1-pyrrolidinyl)carbonyl)propyl)carbamate	 (*Cap*-53a)	1.78 min; (Cond. 2); >99%; LC/MS: Anal. Calcd. for $[M+H]^+$ $C_{44}H_{53}N_8O_4$: 757.42; found 757.42; HRMS: Anal. Calcd. for $[M+H]^+$ $C_{44}H_{53}N_8O_4$:

			757.4190; found 757.4216.
M55	methyl ((1S)-1-(((2S)-2-(5-(4'-(2-((2S)-1-((2R)-2-(diethylamino)-2-phenylacetyl)-2-pyrrolidinyl)-1H-imidazol-5-yl)-4-biphenylyl)-1H-imidazol-2-yl)-1-pyrrolidinyl)carbonyl)propyl)carbamate	 (*Cap*-53b)	1.74 min (Cond. 2); >99%; LC/MS: Anal. Calcd. for $[M+H]^+$ $C_{44}H_{53}N_8O_4$: 757.42; found 757.41; HRMS: Anal. Calcd. for $[M+H]^+$ $C_{44}H_{53}N_8O_4$: 757.4190; found 757.4212 .
M56	methyl ((1R)-1-cyclopropyl-2-((2S)-2-(5-(4'-(2-((2S)-1-((2R)-2-(diethylamino)-2-phenylacetyl)-2-pyrrolidinyl)-1H-imidazol-5-yl)-4-biphenylyl)-1H-imidazol-2-yl)-1-pyrrolidinyl)-2-oxoethyl)carbamate	 (*Cap*-54a)	1.74 min (Cond. 2); >99%; LC/MS: Anal. Calcd. for $[M+H]^+$ $C_{45}H_{53}N_8O_4$: 769.42; found 769.52; HRMS: Anal. Calcd. for $[M+H]^+$ $C_{45}H_{53}N_8O_4$: 769.4190; found 769.4188 .
M57	methyl ((1S)-1-cyclopropyl-2-((2S)-2-(5-(4'-(2-((2S)-1-((2R)-2-(diethylamino)-2-phenylacetyl)-2-pyrrolidinyl)-1H-imidazol-5-yl)-4-biphenylyl)-1H-imidazol-2-yl)-1-pyrrolidinyl)-2-oxoethyl)carbamate	 (*Cap*-54b)	1.72 min (Cond. 2); >99%; LC/MS: Anal. Calcd. for $[M+H]^+$ $C_{45}H_{53}N_8O_4$: 769.42; found 769.53; HRMS: Anal. Calcd. for $[M+H]^+$

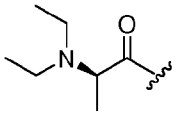
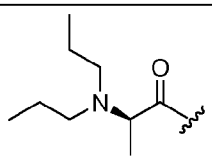
			$C_{45}H_{53}N_8O_4$: 769.4190; found 769.4218.
M58	methyl ((1S)-1-(((2S)-2-(5-(4'-(2-((2S)-1-((2R)-2-(diethylamino)-2-phenylacetyl)-2-pyrrolidinyl)-1H-imidazol-5-yl)-4-biphenylyl)-1H-imidazol-2-yl)-1-pyrrolidinyl)carbonyl)-2-methylpropyl)carbamate	 (*Cap*-51)	1.76 min (Cond. 2); >99%; LC/MS: Anal. Calcd. for $[M+H]^+$ $C_{45}H_{55}N_8O_4$: 771.43; found 771.54; HRMS: Anal. Calcd. for $[M+H]^+$ $C_{45}H_{53}N_8O_4$: 771.4346; found 771.4379.
M59	methyl ((1S)-1-(((2S)-2-(5-(4'-(2-((2S)-1-((2R)-2-(diethylamino)-2-phenylacetyl)-2-pyrrolidinyl)-1H-imidazol-5-yl)-4-biphenylyl)-1H-imidazol-2-yl)-1-pyrrolidinyl)carbonyl)-2,2-dimethylpropyl)carbamate		1.92 min (Cond. 2); 99%; LC/MS: Anal. Calcd. for $[M+H]^+$ $C_{46}H_{57}N_8O_6$: 785.45; found 785.63; HRMS: Anal. Calcd. for $[M+H]^+$ $C_{42}H_{57}N_8O_4$: 785.4503; found 785.4515.
M60	methyl ((1S)-1-(((2S)-2-(5-(4'-(2-((2S)-1-((2R)-2-(diethylamino)-2-phenylacetyl)-2-pyrrolidinyl)-1H-imidazol-5-yl)-4-biphenylyl)-1H-imidazol-2-yl)-1-pyrrolidinyl)carbonyl)-3-buten-1-yl)carbamate	 (*Cap*-55)	1.81 min (Cond.2); 99%; LC/MS: Anal. Calcd. for $[M+H]^+$ $C_{45}H_{53}N_8O_4$: 769.42; found 769.55; HRMS: Anal. Calcd. for

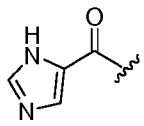
			$[M+H]^+$ $C_{45}H_{53}N_8O_4$: 769.4190; found 769.4157.
M61	methyl ((1S)-2-((2S)-2-(5-(4'-(2-((2S)-1-((2R)-2-(diethylamino)-2-phenylacetyl)-2-pyrrolidinyl)-1H-imidazol-5-yl)-4-biphenylyl)-1H-imidazol-2-yl)-1-pyrrolidinyl)-1-(methoxymethyl)-2-oxoethyl)carbamate	 (*Cap*-56)	1.73 min (Cond. 2); 99%; LC/MS: Anal. Calcd. for $[M+H]^+$ $C_{44}H_{53}N_8O_5$: 773.41; found 773.55; HRMS: Anal. Calcd. for $[M+H]^+$ $C_{44}H_{53}N_8O_5$: 773.4139; found 773.4107.
M62	methyl ((1S)-1-(((2S)-2-(5-(4'-(2-((2S)-1-((2R)-2-(diethylamino)-2-phenylacetyl)-2-pyrrolidinyl)-1H-imidazol-5-yl)-4-biphenylyl)-1H-imidazol-2-yl)-1-pyrrolidinyl)carbonyl)butyl)carbamate	 (*Cap*-57)	1.73 min (Cond. 2); 99%; LC/MS: Anal. Calcd. for $[M+H]^+$ $C_{45}H_{55}N_8O_4$: 771.43; found 771.56 $(M+H)^+$; HRMS: Anal. Calcd. for $[M+H]^+$ $C_{45}H_{55}N_8O_4$: 771.4346; found 771.4315.

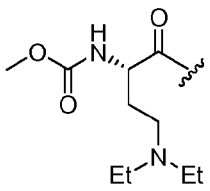
Example M63-M66

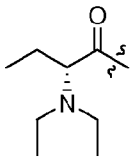


Example M63-M66x were prepared from 28f and the respective acids using the method described for Example 28. Products were prepared as TFA salts unless noted otherwise.

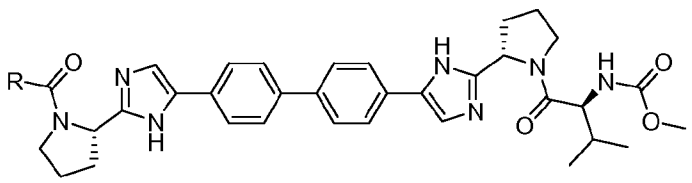
Example	*Compound Name*	 *(Source)*	*RT (LC-Cond.); % homogeneity index; MS data*
M63	methyl ((1R)-2-((2S)-2-(5-(4'-(2-((2S)-1-(N,N-diethyl-D-alanyl)-2-pyrrolidinyl)-1H-imidazol-5-yl)-4-biphenylyl)-1H-imidazol-2-yl)-1-pyrrolidinyl)-2-oxo-1-phenylethyl)carbamate	 (*Cap*-69a)	1.17 min (Cond. 1); >98%; LC/MS: Anal. Calcd. for $[M+H]^+$ $C_{43}H_{51}N_8O_4$: 743.40; found 743.41; HRMS: Anal. Calcd. for $[M+H]^+$ $C_{43}H_{51}N_8O_4$: 743.4033; found 743.4017
M64	methyl ((1R)-2-((2S)-2-(5-(4'-(2-((2S)-1-(N,N-dipropyl-D-alanyl)-2-pyrrolidinyl)-1H-imidazol-5-yl)-4-biphenylyl)-1H-imidazol-2-yl)-1-pyrrolidinyl)-2-oxo-1-phenylethyl)carbamate	 (*Cap*-70a)	1.22 min (Cond. 1); >98%; LC/MS: Anal. Calcd. for

			$[M+H]^+$ $C_{45}H_{55}N_8O_4$: 771.43; found 771.39; HRMS: Anal. Calcd. for $[M+H]^+$ $C_{45}H_{55}N_8O_4$: 771.4346; found 771.4361
M65	methyl ((1R)-2-((2S)-2-(5-(4'-(2-((2S)-1-(1H-imidazol-5-ylcarbonyl)-2-pyrrolidinyl)-1H-imidazol-5-yl)-4-biphenylyl)-1H-imidazol-2-yl)-1-pyrrolidinyl)-2-oxo-1-phenylethyl)carbamate		1.15 min (Cond. 1); >90%; LC/MS: Anal. Calcd. for $[M+H]^+$ $C_{40}H_{40}N_9O_4$: 710.32; found 710.31; HRMS: Anal. Calcd. for $[M+H]^+$ $C_{40}H_{40}N_9O_4$: 710.3203; found 710.3180

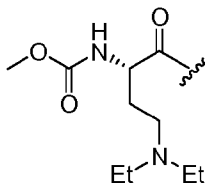
M66a & M66b	M66a: methyl ((1R)-2-((2S)-2-(5-(4'-(2-((2S)-1-(4-(diethylamino)-2-((methoxycarbonyl)amino)butanoyl)-2-pyrrolidinyl)-1H-imidazol-5-yl)-4-biphenylyl)-1H-imidazol-2-yl)-1-pyrrolidinyl)-2-oxo-1-phenylethyl)carbamate	 (*Cap*-76)	Two fractions enriched with one of two compounds exhibiting very similar spectral data were isolated. M66a: 1.19 min (Cond. 1); 97%; LC/MS: Anal. Calcd. for $[M+H]^+$ $C_{46}H_{56}N_9O_6$: 830.44; found 830.39 M66b: 1.21 min (Cond. 1); >97%; LC/MS: Anal. Calcd. for $[M+H]^+$ $C_{46}H_{56}N_9O_6$: 830.44; found 830.39;

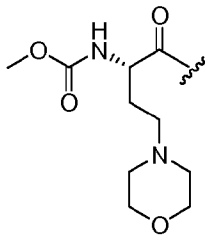
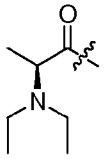
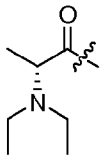
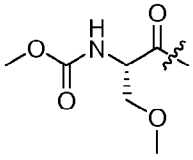
			HRMS: Anal. Calcd. for $[M+H]^+$ $C_{46}H_{56}N_9O_6$: 830.4354; found 830.4316
M66x (AcOH)	methyl ((1R)-2-((2S)-2-(5-(4'-(2-((2S)-1-((2R)-2-(diethylamino)butanoyl)-2-pyrrolidinyl)-1H-imidazol-5-yl)-4-biphenylyl)-1H-imidazol-2-yl)-1-pyrrolidinyl)-2-oxo-1-phenylethyl)carbamate		1.80 minutes (Cond.2); (98%); LC/MS: Anal. Calcd. for $[M+H]^+$ $C_{44}H_{53}N_8O_4$ 757.42; found 757.48; HRMS: Anal. Calcd for $[M+H]^+$ $C_{44}H_{53}N_8O_4$: 757.4190; found 757.4156

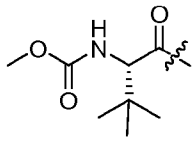
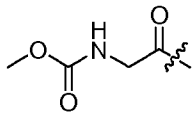
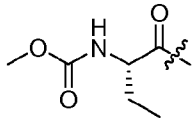
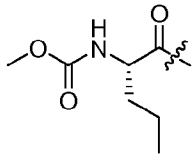
Example M67-M91

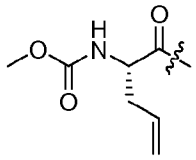
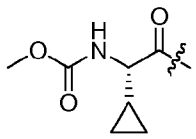
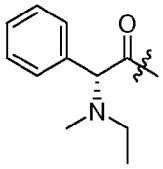
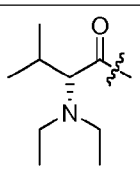


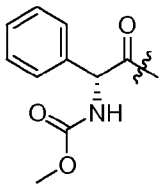
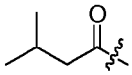
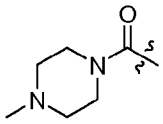
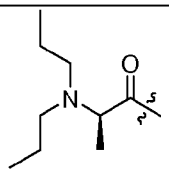
Example M67-M91y were prepared from 28d and the respective acids using the method described for Example 28. Final products were prepared as TFA salts, unless noted otherwise.

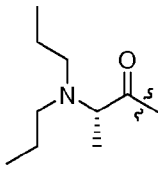
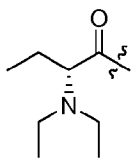
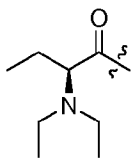
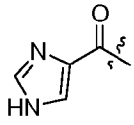
Example	*Compound Name*	 *(Source)*	*RT (LC-Cond.); % homogeneity index; MS data*
M67a & M67b	M67a: methyl ((1S)-1-(((2S)-2-(5-(4'-(2-((2S)-1-(4-(diethylamino)-2-((methoxycarbonyl)amino)butanoyl)-2-pyrrolidinyl)-1H-imidazol-5-yl)-4-biphenylyl)-1H-imidazol-2-yl)-1-pyrrolidinyl)carbonyl)-2-methylpropyl)carbamate	 (*Cap*-76)	Two fractions enriched with one of two compounds exhibiting very similar spectral data were isolated M67a: 1.16 min (Cond. 1); >98%; LC/MS: Anal. Calcd. for $[M+H]^+$ $C_{43}H_{58}N_9O_6$: 796.45; found 796.40 M67b: 1.17 min (Cond. 1); >96%; LC/MS: Anal. Calcd. for $[M+H]^+$ $C_{43}H_{58}N_9O_6$: 796.45; found 796.40; HRMS: Anal. Calcd. for $[M+H]^+$ $C_{43}H_{58}N_9O_6$: 796.4510; found 796.4537

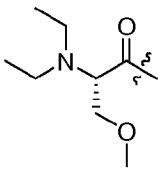
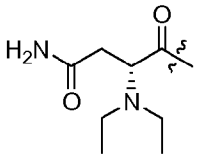
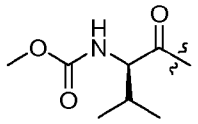
M68 (.AcOH)	methyl ((1S)-1-(((2S)-2-(5-(4'-(2-((2S)-1-((2S)-2-((methoxycarbonyl)amino)-3-methylbutanoyl)-2-pyrrolidinyl)-1H-imidazol-5-yl)-4-biphenylyl)-1H-imidazol-2-yl)-1-pyrrolidinyl)carbonyl)-3-(4-morpholinyl)propyl)carbamate	 (*Cap*-79)	1.10 min (Cond. 1); >96%; LC/MS: Anal. Calcd. for $[M+H]^+$ $C_{43}H_{56}N_9O_7$: 810.43; found 810.44; HRMS: Anal. Calcd. for $[M+H]^+$ $C_{43}H_{56}N_9O_7$: 810.4303; found 810.4333
M69	methyl ((1S)-1-(((2S)-2-(5-(4'-(2-((2S)-1-(N,N-diethyl-L-alanyl)-2-pyrrolidinyl)-1H-imidazol-5-yl)-4-biphenylyl)-1H-imidazol-2-yl)-1-pyrrolidinyl)carbonyl)-2-methylpropyl)carbamate	 (*Cap*-69b)	1.72 min (Cond. 2); 98%; LC/MS: Anal. Calcd. for $[M+H]^+$ $C_{40}H_{53}N_8O_4$: 709.42; found 709.56; HRMS: Anal. Calcd. for $[M+H]^+$ $C_{40}H_{53}N_8O_4$: 709.4190; found 709.4219.
M70	methyl ((1S)-1-(((2S)-2-(5-(4'-(2-((2S)-1-(N,N-diethyl-D-alanyl)-2-pyrrolidinyl)-1H-imidazol-5-yl)-4-biphenylyl)-1H-imidazol-2-yl)-1-pyrrolidinyl)carbonyl)-2-methylpropyl)carbamate	 (*Cap*-69a)	1.75 min (Cond. 2); 99%; LC/MS: Anal. Calcd. for $[M+H]^+$ $C_{40}H_{53}N_8O_4$: 709.42; found 709.55; HRMS: Anal. Calcd. for $[M+H]^+$ $C_{40}H_{53}N_8O_4$: 709.4190; found 709.4184.
M71	methyl ((1S)-2-((2S)-2-(5-(4'-(2-((2S)-1-(N-(methoxycarbonyl)-L-valyl)-2-pyrrolidinyl)-1H-imidazol-5-yl)-4-biphenylyl)-1H-imidazol-2-yl)-1-pyrrolidinyl)-1-	 (*Cap*-56)	1.81 min (Cond. 2); 97%; LC/MS: Anal. Calcd. for $[M+H]^+$ $C_{39}H_{49}N_8O_7$: 741.37; found 741.48; HRMS: Anal. Calcd. for $[M+H]^+$ $C_{39}H_{49}N_8O_7$:

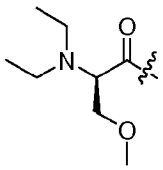
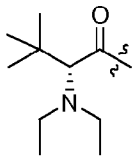
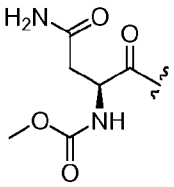
	(methoxymethyl)-2-oxoethyl)carbamate		741.3724; found 741.3738.
M72	methyl ((1S)-1-(((2S)-2-(5-(4'-(2-((2S)-1-((2S)-2-((methoxycarbonyl)amino)-3,3-dimethylbutanoyl)-2-pyrrolidinyl)-1H-imidazol-5-yl)-4-biphenylyl)-1H-imidazol-2-yl)-1-pyrrolidinyl)carbonyl)-2-methylpropyl)carbamate		2.07 min (Cond. 2); 97%; LC/MS: Anal. Calcd. for $[M+H]^+$ $C_{41}H_{53}N_8O_6$: 753.41; found 753.53; HRMS: Anal. Calcd. for $[M+H]^+$ $C_{41}H_{53}N_8O_6$: 753.4088; found 753.4111.
M73	methyl (2-((2S)-2-(5-(4'-(2-((2S)-1-((2S)-2-((methoxycarbonyl)amino)-3-methylbutanoyl)-2-pyrrolidinyl)-1H-imidazol-5-yl)-4-biphenylyl)-1H-imidazol-2-yl)-1-pyrrolidinyl)-2-oxoethyl)carbamate		1.80 min (Cond. 2); 97%; LC/MS: Anal. Calcd. for $[M+H]^+$ $C_{37}H_{45}N_8O_6$: 697.35; found 697.32; HRMS: Anal. Calcd. for $[M+H]^+$ $C_{37}H_{45}N_8O_6$: 697.3462; found 697.3443.
M74	methyl ((1S)-1-(((2S)-2-(5-(4'-(2-((2S)-1-((2S)-2-((methoxycarbonyl)amino)butanoyl)-2-pyrrolidinyl)-1H-imidazol-5-yl)-4-biphenylyl)-1H-imidazol-2-yl)-1-pyrrolidinyl)carbonyl)-2-methylpropyl)carbamate	 (*Cap*-53b)	1.90 min (Cond. 2); 98%; LC/MS: Anal. Calcd. for $[M+H]^+$ $C_{39}H_{49}N_8O_6$: 725.37; found 725.36; HRMS: Anal. Calcd. for $[M+H]^+$ $C_{39}H_{49}N_8O_6$: 725.3775; found 725.3742.
M75	methyl ((1S)-1-(((2S)-2-(5-(4'-(2-((2S)-1-((2S)-2-((methoxycarbonyl)amino)-3-methylbutanoyl)-2-pyrrolidinyl)-1H-imidazol-5-yl)-4-biphenylyl)-1H-	 (*Cap*-57)	1.96 min (Cond. 2); 98%; LC/MS: Anal. Calcd. for $[M+H]^+$ $C_{40}H_{51}N_8O_6$: 739.39; found 739.37; HRMS: Anal. Calcd. for

	imidazol-2-yl)-1-pyrrolidinyl)carbonyl)butyl) carbamate		$[M+H]^+$ $C_{40}H_{51}N_8O_6$: 739.3932; found 739.3953.
M76	methyl ((1S)-1-(((2S)-2-(5-(4'-(2-((2S)-1-((2S)-2-((methoxycarbonyl)amino)-3-methylbutanoyl)-2-pyrrolidinyl)-1H-imidazol-5-yl)-4-biphenylyl)-1H-imidazol-2-yl)-1-pyrrolidinyl)carbonyl)-3-buten-1-yl)carbamate	 (*Cap*-55)	1.91 min (Cond. 2); 98%; LC/MS: Anal. Calcd. for $[M+H]^+$ $C_{40}H_{49}N_8O_6$: 737.38; found 737.38; HRMS: Anal. Calcd. $C_{40}H_{49}N_8O_6$: 737.3775; found 737.3744.
M77	methyl ((1S)-1-(((2S)-2-(5-(4'-(2-((2S)-1-((2S)-2-cyclopropyl-2-((methoxycarbonyl)amino)acetyl)-2-pyrrolidinyl)-1H-imidazol-5-yl)-4-biphenylyl)-1H-imidazol-2-yl)-1-pyrrolidinyl)carbonyl)-2-methylpropyl)carbamate	 (*Cap*-54b)	1.90 min (Cond. 2); 98%; LC/MS: Anal. Calcd. for $[M+H]^+$ $C_{40}H_{49}N_8O_6$ 737.38; found 737.34; HRMS: Anal. Calcd. for $[M+H]^+$ $C_{40}H_{49}N_8O_6$ 737.3775; found 737.3764.
M78	methyl ((1S)-1-(((2S)-2-(5-(4'-(2-((2S)-1-((2R)-2-(ethyl(methyl)amino)-2-phenylacetyl)-2-pyrrolidinyl)-1H-imidazol-5-yl)-4-biphenylyl)-1H-imidazol-2-yl)-1-pyrrolidinyl)carbonyl)-2-methylpropyl)carbamate	 (*Cap*-3)	1.82 min (Cond. 2); 98%; LC/MS: Anal. Calcd. for $[M+H]^+$ $C_{44}H_{53}N_8O_4$ 757.42; found 757.42; HRMS: Anal. Calcd. for $[M+H]^+$ $C_{44}H_{53}N_8O_4$ 757.4190; found 757.4188.
M79	methyl ((1S)-1-(((2S)-2-(5-(4'-(2-((2S)-1-(N,N-diethyl-D-valyl)-2-pyrrolidinyl)-1H-imidazol-5-yl)-4-biphenylyl)-1H-imidazol-2-	 (*Cap*-72)	1.78 min (Cond. 2); 94%; LC/MS: Anal. Calcd. for $[M+H]^+$ $C_{42}H_{57}N_8O_4$ 737.45; found 737.45; HRMS:

	yl)-1-pyrrolidinyl)carbonyl)-2-methylpropyl)carbamate		Anal. Calcd. for $[M+H]^+$ $C_{42}H_{57}N_8O_4$ 737.4503; found 737.4488.
M80	methyl ((1S)-1-(((2S)-2-(5-(4'-(2-((2S)-1-((2R)-2-((methoxycarbonyl)amino)-2-phenylacetyl)-2-pyrrolidinyl)-1H-imidazol-5-yl)-4-biphenylyl)-1H-imidazol-2-yl)-1-pyrrolidinyl)carbonyl)-2-methylpropyl)carbamate	 (*Cap*-4)	2.05 min (Cond. 2); 99%; LC/MS: Anal. Calcd. for $[M+H]^+$ $C_{43}H_{49}N_8O_6$ 773.37; found 773.40; HRMS: Anal. Calcd. for $[M+H]^+$ $C_{43}H_{49}N_8O_6$ 773.375; found: 773.3759.
M81	methyl ((1S)-2-methyl-1-(((2S)-2-(5-(4'-(2-((2S)-1-(3-methylbutanoyl)-2-pyrrolidinyl)-1H-imidazol-5-yl)-4-biphenylyl)-1H-imidazol-2-yl)-1-pyrrolidinyl)carbonyl)propyl)carbamate		2.05 min (Cond. 2); 99%; LC/MS: Anal. Calcd. for $[M+H]^+$ $C_{38}H_{48}N_7O_4$ 666.38; found 666.37; HRMS: Anal. Calcd. for $[M+H]^+$ $C_{38}H_{48}N_7O_4$ 666.3768; found 666.3785.
M82	methyl ((1S)-2-methyl-1-(((2S)-2-(5-(4'-(2-((2S)-1-((4-methyl-1-piperazinyl)carbonyl)-2-pyrrolidinyl)-1H-imidazol-5-yl)-4-biphenylyl)-1H-imidazol-2-yl)-1-pyrrolidinyl)carbonyl)propyl)carbamate		1.75 min (Cond. 2); 98%; LC/MS: Anal. Calcd. for $[M+H]^+$ $C_{39}H_{50}N_9O_4$ 708.40; found 708.38; HRMS: Anal. Calcd. for $[M+H]^+$ $C_{39}H_{50}N_9O_4$ 708.3986; found 708.3974.
M83	methyl ((1S)-1-(((2S)-2-(5-(4'-(2-((2S)-1-(N,N-dipropyl-D-alanyl)-2-pyrrolidinyl)-1H-imidazol-5-		1.81 min (Cond. 2); 98%; LC/MS: Anal. Calcd. for $[M+H]^+$ $C_{42}H_{57}N_8O_4$ 737.45;

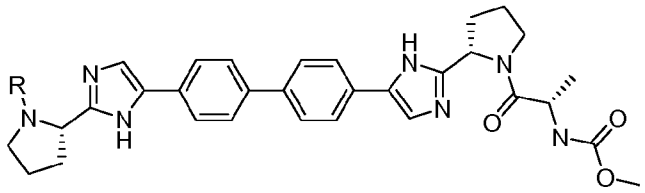
	yl)-4-biphenylyl)-1H-imidazol-2-yl)-1-pyrrolidinyl)carbonyl)-2-methylpropyl)carbamate	(*Cap*-70a)	found 737.47; HRMS: Anal. Calcd. for $[M+H]^+$ $C_{42}H_{57}N_8O_4$ 737.4503; found 737.4480.
M84	methyl ((1S)-1-(((2S)-2-(5-(4'-(2-((2S)-1-(N,N-dipropyl-L-alanyl)-2-pyrrolidinyl)-1H-imidazol-5-yl)-4-biphenylyl)-1H-imidazol-2-yl)-1-pyrrolidinyl)carbonyl)-2-methylpropyl)carbamate	 (*Cap*-70b)	1.78 min (Cond. 2); 99%; LC/MS: Anal. Calcd. for $[M+H]^+$ $C_{42}H_{57}N_8O_4$ 737.45; found 737.47; HRMS: Anal. Calcd. for $[M+H]^+$ $C_{42}H_{57}N_8O_4$ 737.4503; found 737.4491 .
M85	methyl ((1S)-1-(((2S)-2-(5-(4'-(2-((2S)-1-((2R)-2-(diethylamino)butanoyl)-2-pyrrolidinyl)-1H-imidazol-5-yl)-4-biphenylyl)-1H-imidazol-2-yl)-1-pyrrolidinyl)carbonyl)-2-methylpropyl)carbamate	 (*Cap*-71a)	1.76 min (Cond. 2); 98%; LC/MS: Anal. Calcd. for $[M+H]^+$ $C_{41}H_{55}N_8O_4$ 723.43; found 723.47; HRMS: Anal. Calcd. for $[M+H]^+$ $C_{41}H_{55}N_8O_4$ 723.4346; found 723.4335 .
M86	methyl ((1S)-1-(((2S)-2-(5-(4'-(2-((2S)-1-((2S)-2-(diethylamino)butanoyl)-2-pyrrolidinyl)-1H-imidazol-5-yl)-4-biphenylyl)-1H-imidazol-2-yl)-1-pyrrolidinyl)carbonyl)-2-methylpropyl)carbamate	 (*Cap*-71b)	1.73 min (Cond. 2); 98%; LC/MS: Anal. Calcd. for $[M+H]^+$ $C_{41}H_{55}N_8O_4$ 723.43; found 723.47; HRMS: Anal. Calcd. for $[M+H]^+$ $C_{41}H_{55}N_8O_4$ 723.4346; found 723.4343.
M87	methyl ((1S)-1-(((2S)-2-(5-(4'-(2-((2S)-1-(1H-imidazol-4-ylcarbonyl)-2-		1.67 min (Cond. 2); 99%; LC/MS: Anal. Calcd. for $[M+H]^+$

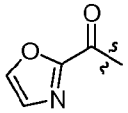
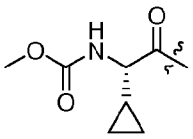
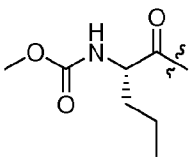
	pyrrolidinyl)-1H-imidazol-5-yl)-4-biphenylyl)-1H-imidazol-2-yl)-1-pyrrolidinyl)carbonyl)-2-methylpropyl)carbamate		$C_{37}H_{42}N_9O_4$ 676.34; found 676.45; HRMS: Anal. Calcd. for $[M+H]^+$ $C_{37}H_{42}N_9O_4$ 676.3360; found 676.3344.
M88	methyl ((1S)-1-(((2S)-2-(5-(4'-(2-((2S)-1-(N,N-diethyl-O-methyl-L-seryl)-2-pyrrolidinyl)-1H-imidazol-5-yl)-4-biphenylyl)-1H-imidazol-2-yl)-1-pyrrolidinyl)carbonyl)-2-methylpropyl)carbamate	 (*Cap*-73)	1.67 min (Cond. 2); 97%; LCMS: Anal. Calcd. for $[M+H]^+$ $C_{41}H_{55}N_8O_5$ 739.43; found 739.54; HRMS: Anal. Calcd. for $[M+H]^+$ $C_{41}H_{55}N_8O_5$ 739.4295; found 739.4327.
M89	methyl ((1S)-1-(((2S)-2-(5-(4'-(2-((2S)-1-(N^2,N^2-diethyl-D-asparaginyl)-2-pyrrolidinyl)-1H-imidazol-5-yl)-4-biphenylyl)-1H-imidazol-2-yl)-1-pyrrolidinyl)carbonyl)-2-methylpropyl)carbamate	 (*Cap*-74)	1.76 min (Cond. 2); 97%; LCMS: Anal. Calcd. for for $[M+H]^+$ $C_{41}H_{54}N_9O_5$ 752.42; found 752.43; HRMS: Anal. Calcd. for $[M+H]^+$ $C_{41}H_{54}N_9O_5$ 752.4248; found 752.4263.
M90	methyl ((1S)-1-(((2S)-2-(5-(4'-(2-((2R)-1-((2R)-2-((methoxycarbonyl)amino)-3-methylbutanoyl)-2-pyrrolidinyl)-1H-imidazol-5-yl)-4-biphenylyl)-1H-imidazol-2-yl)-1-pyrrolidinyl)carbonyl)-2-methylpropyl)carbamate	 (*Cap*-84)	2.00 min (Cond. 2); 98%; LC/MS: Anal. Calcd. for $[M+H]^+$ $C_{40}H_{51}N_8O_6$ 739.39; found 739.46; HRMS: Anal. Calcd for $[M+H]^+$ $C_{40}H_{51}N_8O_6$ 739.3932; found 739.3901.

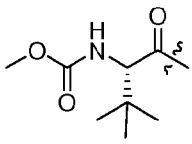
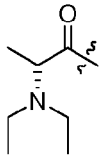
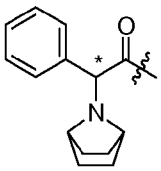
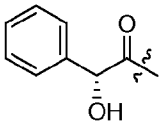
M91	methyl ((1S)-1-(((2S)-2-(5-(4'-(2-((2S)-1-(N,N-diethyl-O-methyl-D-seryl)-2-pyrrolidinyl)-1H-imidazol-5-yl)-4-biphenylyl)-1H-imidazol-2-yl)-1-pyrrolidinyl)carbonyl)-2-methylpropyl)carbamate	 (*Cap*-75)	1.73 min (Cond. 2); 99%; LC/MS: Anal. Calcd. for $[M+H]^+$ $C_{41}H_{55}N_8O_5$ 739.43; found 739.39; HRMS: Anal. Calcd for $[M+H]^+$ $C_{41}H_{55}N_8O_5$ 739.4295; found 739.4277.
M91x	methyl ((1S)-1-(((2S)-2-(5-(4'-(2-((2S)-1-(N,N-diethyl-3-methyl-D-valyl)-2-pyrrolidinyl)-1H-imidazol-5-yl)-4-biphenylyl)-1H-imidazol-2-yl)-1-pyrrolidinyl)carbonyl)-2-methylpropyl)carbamate		1.78 minutes (Cond. 2); (97%); LC/MS: Anal. Calcd. for $[M+H]^+$ $C_{43}H_{59}N_8O_4$ 751.47; found 751.50; HRMS: Anal. Calcd for $[M+H]^+$ $C_{43}H_{59}N_8O_4$: 751.4659; found: 751.4648.
M91y	methyl ((1S)-3-amino-1-(((2S)-2-(5-(4'-(2-((2S)-1-((2S)-2-((methoxycarbonyl)amino)-3-methylbutanoyl)-2-pyrrolidinyl)-1H-imidazol-5-yl)-4-biphenylyl)-1H-imidazol-2-yl)-1-pyrrolidinyl)carbonyl)-3-oxopropyl)carbamate (non-preferred name)	 (*Cap*-58)	1.92 min (Cond. 2); (>97%); LC/MS: Anal. Calcd. for $[M+H]^+$ $C_{39}H_{48}N_9O_7$ 754.37; found 754.42; HRMS: Anal. Calcd for $[M+H]^+$ $C_{39}H_{48}N_9O_7$: 754.3677; found: 754.3676.

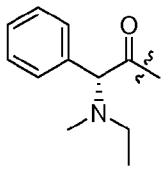
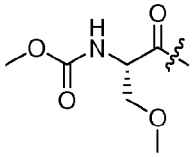
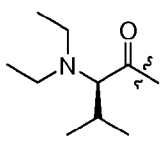
Example M92-M103

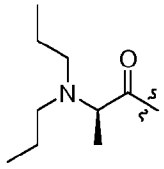
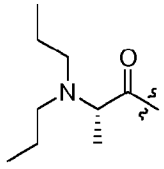
Example M92-M103 were prepared from 28d and the respective acids using the method described for Example 28. Final products were prepared as TFA salts, unless noted otherwise.



Example	*Compound Name*	*R* *(Source)*	*Analytical Data*
M92	methyl ((1S)-1-methyl-2-((2S)-2-(5-(4'-(2-((2S)-1-(1,3-oxazol-2-ylcarbonyl)-2-pyrrolidinyl)-1H-imidazol-5-yl)-4-biphenylyl)-1H-imidazol-2-yl)-1-pyrrolidinyl)-2-oxoethyl)carbamate		1.70 min (Cond. 2); 95%; LC/MS: Anal. Calcd. for $[M+H]^-$ $C_{35}H_{37}N_8O_5$ 649.29; found 649.41; HRMS: Anal. Calcd for $[M+H]^+$ $C_{35}H_{37}N_8O_5$ 649.2887; found 649.2867
M93	methyl ((1S)-1-cyclopropyl-2-((2S)-2-(5-(4'-(2-((2S)-1-(N-(methoxycarbonyl)-L-alanyl)-2-pyrrolidinyl)-1H-imidazol-5-yl)-4-biphenylyl)-1H-imidazol-2-yl)-1-pyrrolidinyl)-2-oxoethyl)carbamate	 (*Cap*-54b)	1.76 min (Cond. 2); 98%; LC/MS: Anal. Calcd. for $[M+H]^-$ $C_{38}H_{45}N_8O_6$ 709.35; found 709.50; HRMS: Anal. Calcd for $[M+H]^+$ $C_{38}H_{45}N_8O_6$ 709.3462; found 709.3478
M94	methyl ((1S)-1-(((2S)-2-(5-(4'-(2-((2S)-1-((2S)-2-((methoxycarbonyl)amino)propanoyl)-2-pyrrolidinyl)-1H-imidazol-5-yl)-4-biphenylyl)-1H-imidazol-2-yl)-1-pyrrolidinyl)carbonyl)butyl)carbamate	 (*Cap*-57)	1.84 min (Cond. 2); 99%; LC/MS: Anal. Calcd. for $[M+H]^-$ $C_{38}H_{47}N_8O_6$ 711.36; found 711.54; HRMS: Anal. Calcd for $[M+H]^+$ $C_{38}H_{47}N_8O_6$

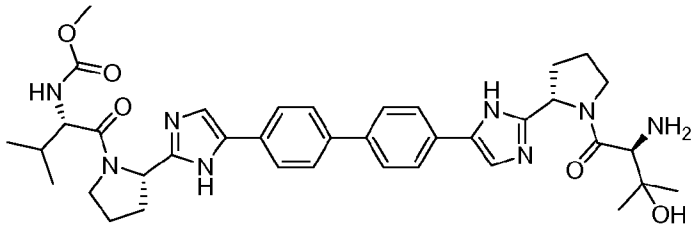
			711.3619; found 711.3590.
M95	methyl ((1S)-1-(((2S)-2-(5-(4'-(2-((2S)-1-(N-(methoxycarbonyl)-L-alanyl)-2-pyrrolidinyl)-1H-imidazol-5-yl)-4-biphenylyl)-1H-imidazol-2-yl)-1-pyrrolidinyl)carbonyl)-2,2-dimethylpropyl)carbamate		1.91 min (Cond. 2); 99%; LC/MS: Anal. Calcd. for $[M+H]^-$ $C_{39}H_{49}N_8O_6$ 725.37; found 725.54; HRMS: Anal. Calcd for $[M+H]^+$ $C_{39}H_{49}N_8O_6$ 725.3775; found 725.3809.
M96	methyl ((1S)-2-((2S)-2-(5-(4'-(2-((2S)-1-(N,N-diethyl-D-alanyl)-2-pyrrolidinyl)-1H-imidazol-5-yl)-4-biphenylyl)-1H-imidazol-2-yl)-1-pyrrolidinyl)-1-methyl-2-oxoethyl)carbamate	 (*Cap*-69a)	1.61 min (Cond. 2); 99%; LC/MS: Anal. Calcd. for $[M+H]^-$ $C_{38}H_{49}N_8O_4$ 681.39; found 681.54; HRMS: Anal. Calcd for $[M+H]^+$ $C_{38}H_{49}N_8O_4$ 681.3877; found 681.3867.
M97	methyl ((1S)-2-((2S)-2-(5-(4'-(2-((2S)-1-(7-azabicyclo[2.2.1]hept-7-yl(phenyl)acetyl)-2-pyrrolidinyl)-1H-imidazol-5-yl)-4-biphenylyl)-1H-imidazol-2-yl)-1-pyrrolidinyl)-1-methyl-2-oxoethyl)carbamate	 (*Cap*-77b)	1.72 min (Cond. 2); 98%; LC/MS: Anal. Calcd. for $[M+H]^-$ $C_{45}H_{51}N_8O_4$ 767.40; found 767.59; HRMS: Anal. Calcd for $[M+H]^+$ $C_{45}H_{51}N_8O_4$ 767.4033; found 767.4067.
M98	methyl ((1S)-2-((2S)-2-(5-(4'-(2-((2S)-1-((2R)-2-hydroxy-2-phenylacetyl)-2-pyrrolidinyl)-		1.80 min (Cond. 2); 99%; LC/MS: Anal. Calcd. for $[M+H]^-$

	1H-imidazol-5-yl)-4-biphenylyl)-1H-imidazol-2-yl)-1-pyrrolidinyl)-1-methyl-2-oxoethyl)carbamate		$C_{39}H_{42}N_7O_5$ 688.32; found 688.48; HRMS: Anal. Calcd for $[M+H]^+$ $C_{39}H_{42}N_7O_5$ 688.3247; found 688.3263.
M99	methyl ((1S)-2-((2S)-2-(5-(4'-(2-((2S)-1-((2R)-2-(ethyl(methyl)amino)-2-phenylacetyl)-2-pyrrolidinyl)-1H-imidazol-5-yl)-4-biphenylyl)-1H-imidazol-2-yl)-1-pyrrolidinyl)-1-methyl-2-oxoethyl)carbamate	 (*Cap*-3)	1.70 min (Cond. 2); 99%; LC/MS: Anal. Calcd. for $[M+H]^-$ $C_{42}H_{49}N_8O_4$ 729.39; found 729.56; HRMS: Anal. Calcd for $[M+H]^+$ $C_{42}H_{49}N_8O_4$ 729.3877; found 729.3887.
M100	methyl ((1S)-2-((2S)-2-(5-(4'-(2-((2S)-1-(N-(methoxycarbonyl)-L-alanyl)-2-pyrrolidinyl)-1H-imidazol-5-yl)-4-biphenylyl)-1H-imidazol-2-yl)-1-pyrrolidinyl)-1-(methoxymethyl)-2-oxoethyl)carbamate	 (*Cap*-56)	1.75 min (Cond. 2); 99%; LC/MS: Anal. Calcd. for $[M+H]^-$ $C_{37}H_{45}N_8O_7$ 713.34; found 713.34; HRMS: Anal. Calcd for $[M+H]^+$ $C_{37}H_{45}N_8O_7$ 713.3411; found 713.3386.
M101	methyl ((1S)-2-((2S)-2-(5-(4'-(2-((2S)-1-(N,N-diethyl-D-valyl)-2-pyrrolidinyl)-1H-imidazol-5-yl)-4-biphenylyl)-1H-imidazol-2-yl)-1-pyrrolidinyl)-1-methyl-2-oxoethyl)carbamate	 (*Cap*-72)	1.66 min (Cond. 2); 94%; LC/MS: Anal. Calcd. for $[M+H]^-$ $C_{40}H_{53}N_8O_4$ 709.42; found: 709.42; HRMS: Anal. Calcd for $[M+H]^+$ $C_{40}H_{53}N_8O_4$

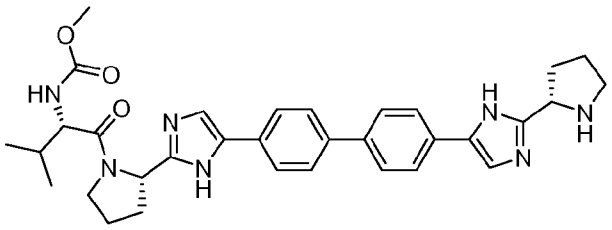
			709.4190; found 709.4166.
M102	methyl ((1S)-2-((2S)-2-(5-(4'-(2-((2S)-1-(N,N-dipropyl-D-alanyl)-2-pyrrolidinyl)-1H-imidazol-5-yl)-4-biphenylyl)-1H-imidazol-2-yl)-1-pyrrolidinyl)-1-methyl-2-oxoethyl)carbamate	 (*Cap*-70a)	1.71 min (Cond. 2); 98%; LC/MS: Anal. Calcd. for $[M+H]^-$ $C_{40}H_{53}N_8O_4$ 709.42; found 709.48; HRMS: Anal. Calcd for $[M+H]^+$ $C_{40}H_{53}N_8O_4$ 709.4190; found 709.4191.
M103	methyl ((1S)-2-((2S)-2-(5-(4'-(2-((2S)-1-(N,N-dipropyl-L-alanyl)-2-pyrrolidinyl)-1H-imidazol-5-yl)-4-biphenylyl)-1H-imidazol-2-yl)-1-pyrrolidinyl)-1-methyl-2-oxoethyl)carbamate	 (*Cap*-70b)	1.66 min (Cond. 2); 98%; LC/MS: Anal. Calcd. for $[M+H]^-$ $C_{40}H_{53}N_8O_4$ 709.42; found 709.42; HRMS: Anal. Calcd for $[M+H]^+$ $C_{40}H_{53}N_8O_4$ 709.4190; found 709.4198.

Example M104

methyl ((1S)-1-(((2S)-2-(5-(4'-(2-((2S)-1-(3-hydroxy-L-valyl)-2-pyrrolidinyl)-1H-imidazol-5-yl)-4-biphenylyl)-1H-imidazol-2-yl)-1-pyrrolidinyl)carbonyl)-2-methylpropyl)carbamate



Example M104, Step a



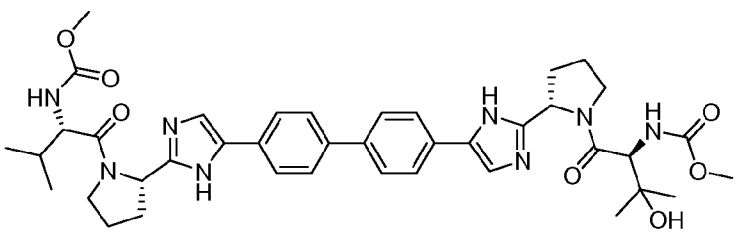
Pyrrolidine M104a was prepared from intermediate 28d and *Cap*-51 according to the procedure described for the synthesis of pyrrolidine 28f.

Example M104

HATU (96.3 mg, 0.253 mmol) was added to a DMF (5.0 mL) solution of pyrrolidine M104a (150 mg, 0.217 mmol), (S)-2-(tert-butoxycarbonylamino)-3-hydroxy-3-methylbutanoic acid (65.8 mg, 0.282 mmol) and *i*-Pr_2EtN (180 uL, 1.03 mmol), and the reaction mixture was stirred at ambient condition for 35 min. The volatile component was removed *in vacuo*, and the residue was purified with a reverse phase HPLC ($MeOH/H_2O$/TFA), and the fractions were concentrated *in vacuo*. The resultant residue was treated with 25% TFA/CH_2Cl_2 (6.0 mL) and stirred for 3.25 hr. The volatile component was removed *in vacuo* and the residue was free-based (MCX; MeOH wash; 2.0 M NH_3/MeOH elution) to afford Example M104 as an off-white foam (107 mg). LC (Cond. 2): RT = 1.03 min; >95% homogeneity index; LC/MS: Anal. Calcd. for $[M+H]^+$ $C_{38}H_{49}N_8O_5$ = 697.38; found 697.28.

Example M105

methyl ((1S)-1-(((2S)-2-(5-(4'-(2-((2S)-1-((2S)-3-hydroxy-2-((methoxycarbonyl)amino)-3-methylbutanoyl)-2-pyrrolidinyl)-1H-imidazol-5-yl)-4-biphenylyl)-1H-imidazol-2-yl)-1-pyrrolidinyl)carbonyl)-2-methylpropyl)carbamate

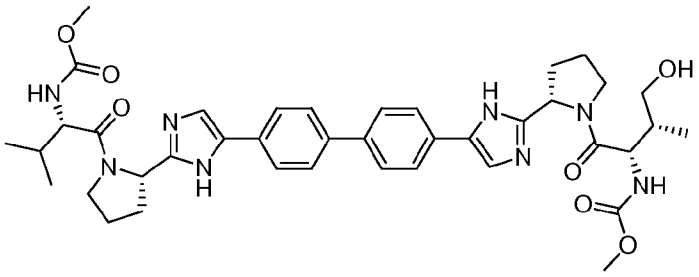


Methyl chloroformate (20 µL, 0.258 mmol) was added to a THF (2.0 mL) solution of Example M104 (82.9 mg, 0.119 mmol) and *i*-Pr_2EtN (50 uL, 0.287 mmol)

and stirred for 65 min. The mixture was then treated with 2.0 M NH_3/MeOH (3 mL), stirred for 2.75 hr, and the volatile component was removed *in vacuo*. The resultant residue was purified with a reverse phase HPLC (MeOH/H_2O/TFA) to afford the TFA salt of Example M105 as a white foam (64.1 mg). LC (Cond. 2): RT = 1.17 min; >98% homogeneity index; LC/MS: Anal. Calcd. for $[M+H]^+$ $C_{40}H_{51}N_8O_7$ = 755.39; found 755.25.

Example M106

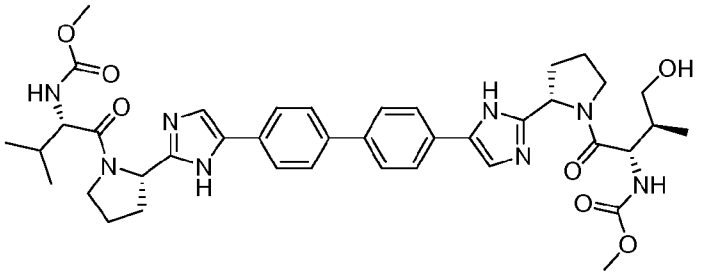
methyl ((1S)-1-(((2S)-2-(5-(4'-(2-((2S)-1-((2S,3R)-4-hydroxy-2-((methoxycarbonyl)amino)-3-methylbutanoyl)-2-pyrrolidinyl)-1H-imidazol-5-yl)-4-biphenylyl)-1H-imidazol-2-yl)-1-pyrrolidinyl)carbonyl)-2-methylpropyl)carbamate



HATU (69 mg, 0.181 mmol) was added to a DMF (3.0 mL) solution of pyrrolidine M104a (101 mg, 0.173 mmol), *Cap*-80b (55.9 mg, ~0.183 mmol) and *i*-Pr_2EtN (90 µL, 0.515 mmol), and the reaction mixture was stirred at ambient condition for 70 min. The volatile component was removed *in vacuo* and the residue was purified with a reverse phase HPLC (H_2O/MeOH/TFA) to retrieve the dominant signal. The collected fraction was allowed to stand at ambient condition for a few hours and then the volatile component was removed *in vacuo*, at which time total desilylation of the coupled product was achieved. The resultant product was submitted to a reverse phase HPLC purification (ACN/H_2O/NH_4OAc) to afford Example M106 as an off-white foam (32.2 mg). LC (Cond. 2): RT = 1.19 min; >95% homogeneity index; LC/MS: Anal. Calcd. for $[M+H]^+$ $C_{40}H_{51}N_8O_7$ = 755.39; found 755.85.

Example M107

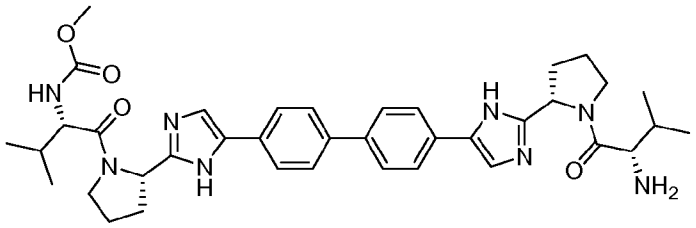
methyl ((1S)-1-(((2S)-2-(5-(4'-(2-((2S)-1-((2S,3S)-4-hydroxy-2-((methoxycarbonyl)amino)-3-methylbutanoyl)-2-pyrrolidinyl)-1H-imidazol-5-yl)-4-biphenylyl)-1H-imidazol-2-yl)-1-pyrrolidinyl)carbonyl)-2-methylpropyl)carbamate



Example M107 was prepared from pyrrolidine M104a and *Cap*-80a according to the procedure described for the synthesis of Example M106. LC (Cond. 2): RT = 1.20 min; ~95% homogeneity index; LC/MS: Anal. Calcd. for $[M+H]^+$ $C_{40}H_{51}N_8O_7$ = 755.39; found 755.78.

Example M108

methyl ((1S)-2-methyl-1-(((2S)-2-(5-(4'-(2-((2S)-1-L-valyl-2-pyrrolidinyl)-1H-imidazol-5-yl)-4-biphenylyl)-1H-imidazol-2-yl)-1-pyrrolidinyl)carbonyl)propyl)carbamate



HATU (70.1 mg, 0.184 mmol) was added to a DMF (3.0 mL) solution of pyrrolidine M104a (100.7 mg, 0.173 mmol), (L)-Boc-Valine (49.6 mg, 0.228 mmol) and *i*-Pr_2EtN (70 uL, 0.40 mmol), and the reaction mixture was stirred at ambient condition for 65 min. The volatile component was removed *in vacuo* and the residue was purified with a Biotage (60-100% EtOAc/hexanes) to afford 116.6 mg of the coupled product.

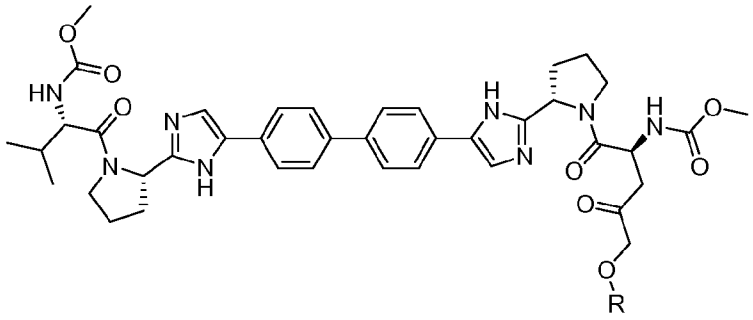
The above product (112 mg) was treated with 25% TFA/CH_2Cl_2 (2 mL) and the reaction mixture was stirred for 6 hr. The volatile component was removed *in vacuo* and the crude material was purified with a combination of MCX resin (MeOH wash; 2.0 M NH_3/MeOH elution) and reverse phase HPLC (H_2O/MeOH/TFA) to

afford the TFA salt of Example M108 as a white foam (98.5 mg). LC (Cond. 2): RT = 1.14 min; >98% homogeneity index; LC/MS: Anal. Calcd. for $[M+H]^+$ $C_{38}H_{49}N_8O_4$ = 681.39; found 681.36. HRMS Calcd. for $[M+H]^+$ $C_{38}H_{49}N_8O_4$: 681.3877; found 681.3865.

Example M109 (R = Bn) & M110 (R = Me)

M109: benzyl (3S)-3-((methoxycarbonyl)amino)-4-((2S)-2-(5-(4'-(2-((2S)-1-(N-(methoxycarbonyl)-L-valyl)-2-pyrrolidinyl)-1H-imidazol-5-yl)-4-biphenylyl)-1H-imidazol-2-yl)-1-pyrrolidinyl)-4-oxobutanoate

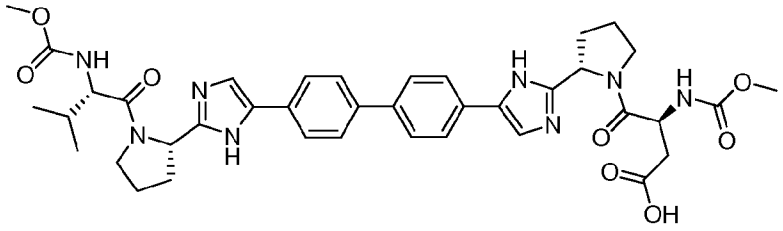
M110: methyl (3S)-3-((methoxycarbonyl)amino)-4-((2S)-2-(5-(4'-(2-((2S)-1-(N-(methoxycarbonyl)-L-valyl)-2-pyrrolidinyl)-1H-imidazol-5-yl)-4-biphenylyl)-1H-imidazol-2-yl)-1-pyrrolidinyl)-4-oxobutanoate



HATU (109 mg, 0.287 mmol) was added to DMF (1.5 ml) solution of pyrrolidine M104a (151 mg, 0.260 mmol), *Cap*-68 (109 mg, 387 mmol), and *i*-Pr_2EtN (100 µl, 0.574 mmol), and the reaction mixture was stirred at ambient condition for 3 hr. The volatile component was removed *in vacuo* and crude material was purified with a combination of MCX resin (MeOH wash; 2.0 M NH_3/MeOH elution) and reverse phase HPLC (H_2O/MeOH/TFA) to afford the TFA salt Example M109 (88.0 mg) and Example M110 (90.2 mg). Example M109: LC (Cond. 2): RT = 2.16; 97% homogenity index; LC/MS: Anal. Calcd. for $[M+H]^+$ $C_{46}H_{53}N_8O_8$: 845.40; found 845.51. HRMS Calcd. for $[M+H]^+$ $C_{46}H_{53}N_8O_8$: 845.3986; found 845.3983. Example M110: LC (Cond. 2): RT = 1.92; 97% homogenity index; LC/MS: Anal. Calcd. for $[M+H]^+$ $C_{40}H_{49}N_8O_4$: 769.47; found 769.46. HRMS Calcd. for $[M+H]^+$ $C_{40}H_{49}N_8O_4$: 769.3673; found 769.3682.

Example M111

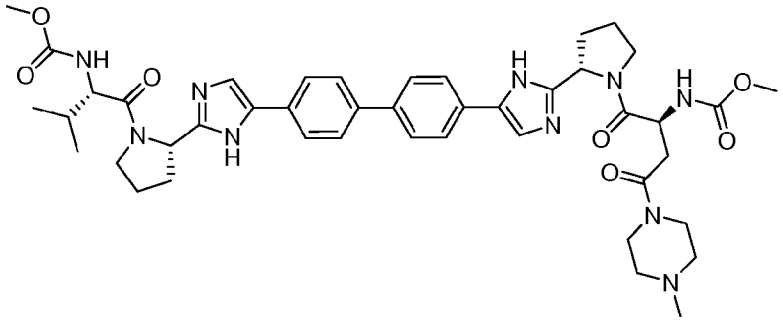
(3S)-3-((methoxycarbonyl)amino)-4-((2S)-2-(5-(4'-(2-((2S)-1-(N-(methoxycarbonyl)-L-valyl)-2-pyrrolidinyl)-1H-imidazol-5-yl)-4-biphenylyl)-1H-imidazol-2-yl)-1-pyrrolidinyl)-4-oxobutanoic acid



A mixture of Example M109 (69.7 mg, 0.082 mmol) and 10% Pd/C (10 mg) in methanol (5 ml) was stirred at room temperature under a balloon of H_2 for 1.5 h. The reaction was filtered through diatomaceous earth (Celite®) and concentrated *in vacuo*, and the resultant material was purified with a reverse phase HPLC (H_2O/MeOH/TFA) to afford the TFA salt of Example M111 as an off-white foam (54.0 mg). LC (Cond. 2): RT = 1.18; 99% homogenity index; LC/MS: Anal. Calcd. for $[M+H]^+$ $C_{39}H_{47}N_8O_8$: 755.35; found 755.32. HRMS Calcd. for $[M+H]^+$ $C_{39}H_{47}N_8O_8$: 755.3517; found 755.3525.

Example M112

methyl ((1S)-1-(((2S)-2-(5-(4'-(2-((2S)-1-((2S)-2-((methoxycarbonyl)amino)-4-(4-methyl-1-piperazinyl)-4-oxobutanoyl)-2-pyrrolidinyl)-1H-imidazol-5-yl)-4-biphenylyl)-1H-imidazol-2-yl)-1-pyrrolidinyl)carbonyl)-2-methylpropyl)carbamate

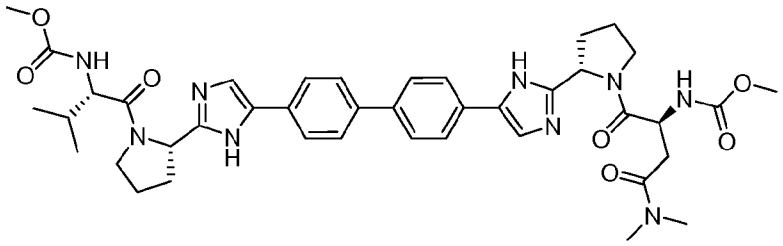


HATU (30.6 mg, 0.080 mmol) was added to a DMF (1.5 ml) solution of Example M111 (55.3 mg, 0.0733 mmol), *N*-methyl piperazine (11.0 mg, 0.11 mmol) and *i*-Pr_2EtN (25 µl, 0.14 mmol), and the reaction mixture was stirred at ambient

condition for 1.5 h. All volatile components were removed *in vacuo*, and the residue was purified with a combination of MCX resin and a reverse phase HPLC (H_2O/MeOH/TFA) to afford the TFA salt of Example M112 as an off-white foam (51.4 mg). LC (Cond. 2): RT = 1.75; 91% homogenity index; LC/MS: Anal. Calcd. for $[M+H]^+$ $C_{44}H_{57}N_{10}O_7$: 837.44; found 837.59. HRMS Calcd. for $[M+H]^+$ $C_{44}H_{57}N_{10}O_7$: 837.4412; found 837.4453.

Example M113

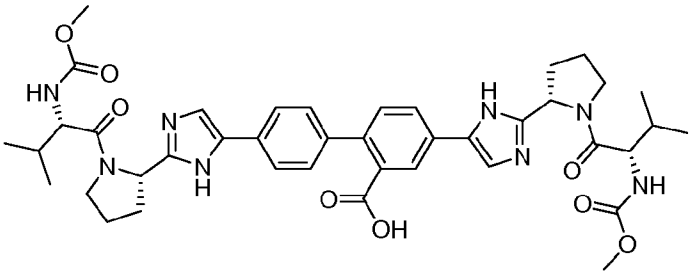
methyl ((1S)-3-(dimethylamino)-1-(((2S)-2-(5-(4'-(2-((2S)-1-((2S)-2-((methoxycarbonyl)amino)-3-methylbutanoyl)-2-pyrrolidinyl)-1H-imidazol-5-yl)-4-biphenylyl)-1H-imidazol-2-yl)-1-pyrrolidinyl)carbonyl)-3-oxopropyl)carbamate



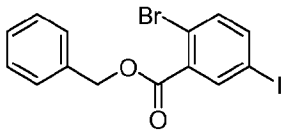
Example M118 was prepared from Example M111 and $Me_2N.HCl$ according to the procedure described for Example M112. LC (Cond. 2): RT = 1.89; 99% homogenity index. LC/MS: Anal. Calcd. for $[M+H]^-$ $C_{41}H_{52}N_9O_7$: 782.40; found 782.47. HRMS Calcd. for $[M+H]^+$ $C_{41}H_{52}N_9O_7$: 782.3990; found 782.4008.

Example M114

4,4'-bis(2-((2S)-1-(N-(methoxycarbonyl)-L-valyl)-2-pyrrolidinyl)-1H-imidazol-5-yl)-2-biphenylcarboxylic acid

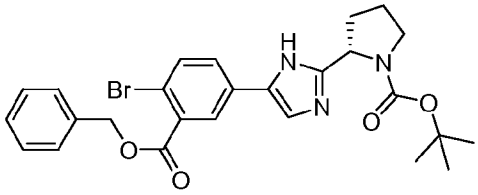


Example M114, Step a



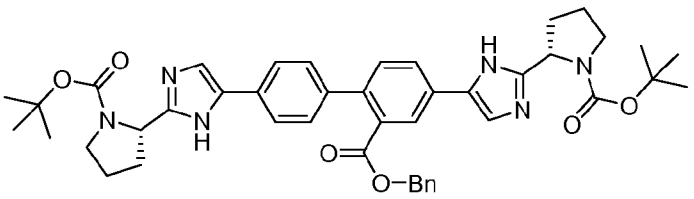
DMF (20 mL) was added to mixture of $KHCO_3$ (1.84g, 18.4 mmol) and 2-bromo-5-iodobenzoic acid (4.99 g, 15.3 mmol) and the resulting mixture was stirred for 15 min. Benzyl bromide (2.4 mL, 20.2 mmol) was added drop-wise over 5 min and stirring was continued at ambient condition for ~20 hr. Most of the volatile component was removed *in vacuo* and the residue was partitioned between CH_2Cl_2 (50 mL) and water (50 mL), and the organic layer was washed with water (50 mL), dried ($MgSO_4$), filtered, and concentrated. The resulting crude material was purified with flash chromatography (7% EtOAc/hexanes) to afford ester M114a as a colorless viscous oil (6.01 g). ^{1}H NMR (DMSO-d_6, δ = 2.5 ppm, 400 MHz): δ 8.07 (d, J = 2.0, 1H), 7.81 (dd, J = 8.4, 2.1, 1H), 7.53 (d, J = 8.4, 1H), 7.48 (m, 2H), 7.43-7.34 (m, 3H), 5.34 (s, 2H). LC (Cond. 1): RT = 2.1 min; LC/MS: Anal. Calcd. for $[M+Na]^+$ $C_{14}H_{10}BrINaO_2$: 438.88; found 438.83.

Example M114, Step b-d



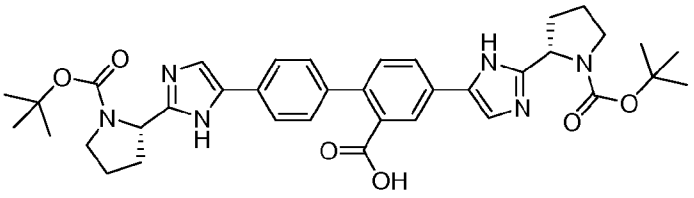
Ester M114a was elaborated to ester M114d by employing a three step protocol employed in the synthesis of bromide 121c from 1-bromo-4-iodo-2-methylbenzene. M114d: ^{1}H NMR (DMSO-d_6, δ = 2.5 ppm, 400 MHz): δ 12.04/11.97 (br s, 1H), 8.12 (d, J = 2.0, 0.92H), 7.99 (app br s, 0.08H), 7.81 (dd, J = 8.3, 2.0, 0.92H), 7.74-7.62 (m, 2.08H), 7.50 (app br d, J = 7.0, 2H), 7.44-7.35 (m, 3H), 5.38 (s, 2H), 4.79 (m, 1H), 3.52 (app br s, 1H), 3.36 (m, 1H), 2.24-1.79 (m, 4H), 1.39/5.11 (two s, 9H). LC (Cond. 1): RT = 1.66 min; LC/MS: Anal. Calcd. for $[M+H]^+$ $C_{26}H_{29}BrN_3O_4$: 526.13; found 526.16.

Example M114, Step e



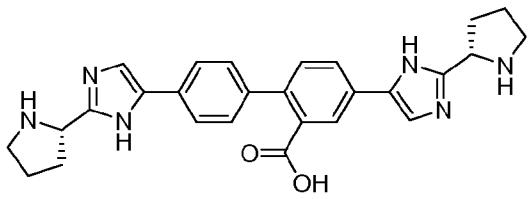
Ester M114e was prepared from bromide M114d and boronate 1c according to the preparation of dimer 1d. ^{1}H NMR (DMSO-d_6, δ = 2.5 ppm, 400 MHz): δ 12.18/12.00/11.91/11.83 (four br s, 2H), 8.11-7.03 (m, 14H), 5.10 (s, 2H), 4.85-4.78 (m, 2H), 3.55 (app br s, 2H), 3.37 (m, 2H), 2.29-1.80 (m, 8H), 1.41/1.16 (two s, 18H). LC (Cond. 1): RT = 1.54 min; LC/MS: Anal. Calcd. for $[M+H]^+$ $C_{44}H_{51}N_6O_6$: 759.39; found 759.63.

Example M114, Step f



A mixture of benzyl ester M114e (1.005 g, 1.325 mmol) and 10% Pd/C (236 mg) in MeOH (20 mL) was stirred under a balloon of H_2 for 5 hr. The reaction mixture was then treated with a 1:1 mixture of MeOH and CH_2Cl_2, filtered through a pad of diatomaceous earth (Celite®-521), and the filtrate was rotervaped to afford acid M114f (840 mg), contaminated with Ph_3PO which was a carryover from the Suzuki coupling step. ^{1}H NMR (DMSO-d_6, δ = 2.5 ppm, 400 MHz): δ 12.17/11.98/11.89/11.81 (four app br s, 2H), 8.04-7.31 (m, 9H), 4.85-4.78 (m, 2H), 3.55 (app br s, 2H), ~3.37 (m, 2H, overlaped with water signal) 2.27-1.84 (m, 8H), 1.41/1.16 (two s, 18H). LC (Cond. 1): RT = 1.37 min; LC/MS: Anal. Calcd. for $[M+H]^+$ $C_{37}H_{45}N_6O_6$: 669.34; found 669.53.

Example M114, Step g



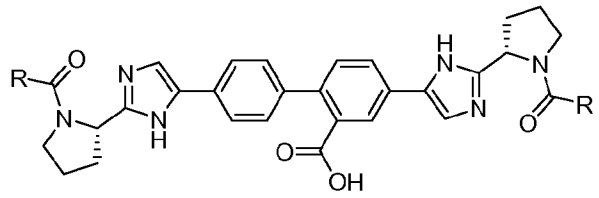
4N HCl/dioxane (8.0 mL) and CH_2Cl_2 (2.0 mL) were sequentially added to carbamate M114f (417 mg, 0.623 mmol), the mixture was vigorously stirred 5.5 hr, and then the volatile component was removed *in vacuo* to afford the HCl (.4x) salt of pyrrolidine M114g (487 mg), contaminated with Ph_3PO impurity. ^1H NMR (DMSO-d_6, δ = 2.5 ppm, 400 MHz) after D_2O exchange: δ 8.23 (d, J = 1.7, 1H), 8.09-8.04 (m, 3H), 7.92 (d, J = 8.3, 2H), 7.53 (d, J = 8.1, 1H), 7.48 (d, J = 8.3, 2H), 5.00 (app br t, J = 8.3, 1H), 4.90 (app br t, J = 8.4, 1H), 3.6-3.3 (m, 4H), 2.5-1.99 (m, 8H). LC (Cond. 1): RT = 0.92 min; LC/MS: Anal. Calcd. for $[M+H]^+$ $C_{27}H_{29}N_6O_2$: 469.24; found 469.31.

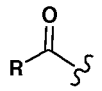
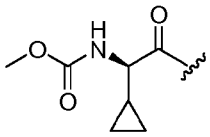
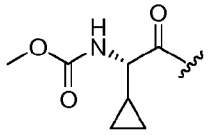
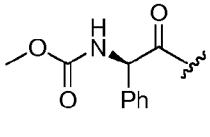
Example M114

HATU (79.9 mg, 0.21 mmol) was added to a DMF (3.0 mL) solution of pyrrolidine M114g.4HCl (80 mg, 0.13 mmol), *Cap*-51 (92.4 mg, 0.527 mmol) and *i*-Pr_2EtN (160 µL, 0.919 mmol), and the reaction mixture was stirred at ambient condition for 2 hr. The volatile component was removed *in vacuo* and the residue was purified with a combination of MCX (MeOH wash; 2.0 M NH_3/MeOH elution) and a reverse phase HPLC (CH_3CN/H_2O/ NH_4OAc) to afford the acetic acid salt of Example M114. LC (Cond. 1): RT = 1.20 min; >98 homogeneity index. LC/MS: Anal. Calcd. for $[M+H]^+$ $C_{41}H_{51}N_8O_8$: 783.38; found 783.34. HRMS Calcd. for $[M+H]^+$ $C_{41}H_{51}N_8O_8$: 783.3830; found 783.3793.

Example M115-M116

Examples M115-M116 were prepared using the same method as described for Example M114 and by substituting the appropriate acids for *Cap*-51. The products were isolated as either the acetic acid or TFA salt depending on the nature of the mobile phase of the HPLC purification step.

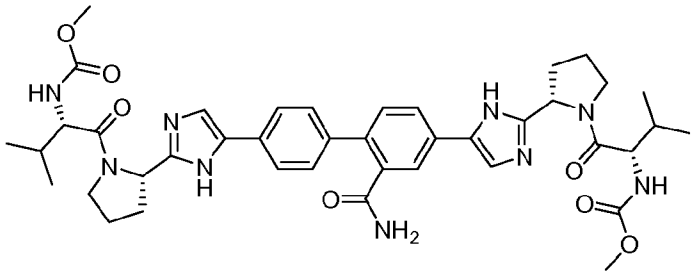


Example	*Compound Name*	 *(Source)*	*RT (LC-Cond.); % homogeneity index; MS data*
M115 (AcOH)	4,4'-bis(2-((2S)-1-((2R)-2-cyclopropyl-2-((methoxycarbonyl)amino)acetyl)-2-pyrrolidinyl)-1H-imidazol-5-yl)-2-biphenylcarboxylic acid	 (*Cap*-54a)	1.17 min (Cond. 1); >98%; LC/MS: Anal. Calcd. for $[M+H]^+$ $C_{41}H_{47}N_8O_8$: 779.35; found 779.33; HRMS: Anal. Calcd. for $[M+H]^+$ $C_{41}H_{47}N_8O_8$: 779.3517; found 779.3498
M116 (2.TFA)	4,4'-bis(2-((2S)-1-((2S)-2-cyclopropyl-2-((methoxycarbonyl)amino)acetyl)-2-pyrrolidinyl)-1H-imidazol-5-yl)-2-biphenylcarboxylic acid	 (*Cap*-54b)	1.13 min (Cond. 1); >98%; LC/MS: Anal. Calcd. for $[M+H]^+$ $C_{41}H_{47}N_8O_8$: 779.35; found 779.33; HRMS: Anal. Calcd. for $[M+H]^+$ $C_{41}H_{47}N_8O_8$: 779.3517; found 779.3551
M117 (2.TFA)	4,4'-bis(2-((2S)-1-((2R)-2-((methoxycarbonyl)amino)-2-phenylacetyl)-2-pyrrolidinyl)-1H-imidazol-5-yl)-2-biphenylcarboxylic acid	 (*Cap*-4)	1.29 min (Cond. 1); >98%; LC/MS: Anal. Calcd. for $[M+H]^+$ $C_{47}H_{47}N_8O_8$: 851.35; found 851.33; HRMS: Anal. Calcd. for $[M+H]^+$ $C_{47}H_{47}N_8O_8$: 851.3517; found

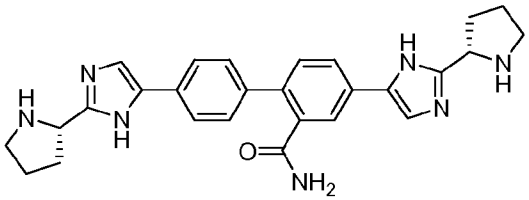
			851.3480

Example M118

methyl ((1S)-1-(((2S)-2-(5-(2'-carbamoyl-4'-(2-((2S)-1-((2S)-2-((methoxycarbonyl)amino)-3-methylbutanoyl)-2-pyrrolidinyl)-1H-imidazol-5-yl)-4-biphenylyl)-1H-imidazol-2-yl)-1-pyrrolidinyl)carbonyl)-2-methylpropyl)carbamate



Example M118, Step a



Et_3N (300 μL, 2.15 mmol) was added to a mixture of acid M114f (198.3 mg, 0.297 mmol), HOBt (94.2 mg, 0.697 mmol), EDCI (0.66 mmol), NH_4Cl (101 mg, 1.89 mmol) in DMF (8.0 mL) and stirred for 17 hr at ambient condition. The reaction mixture was filtered through 0.45 μm filter, the volatile component was removed *in vacuo* and the residue was partitioned between CH_2Cl_2 and water. The organic layer was concentrated and the resulting crude material was purified with a reverse phase HPLC ($MeOH/H_2O$/TFA).

The above product was treated with 25% TFA/CH_2Cl_2 (4.0 mL) and the reaction mixture was stirred for 2.5 hr at ambient condition. The volatile component was removed *in vacuo* and the residue was free-based (MCX; MeOH wash; 2.0 M NH_3/MeOH elution) to afford amide M118a (67.2 mg). ^1H NMR (DMSO-d_6, δ = 2.5 ppm, 400 MHz): δ 11.83 (br s, 2H), 7.81-7.80 (m, 2H), 7.73 (d, *J* = 8.3, 2H), 7.65 (br s, 1H), 7.52 (br S, 1H), 7.44 (br s, 1H), 7.41 (d, *J* = 8.3, 2H), 7.36 (d, *J* = 8.3, 1H), 7.31 (br s, 1H), 4.16 (app t, *J* = 7.2, 2H), 3.00-2.94 (m, 2H), 2.88-2.82 (m, 2H), 2.10-2.01 (m, 2H), 1.94-1.85 (m, 2H), 1.83-1.66 (m, 4H). LC (Cond. 1): RT = 0.89 min;

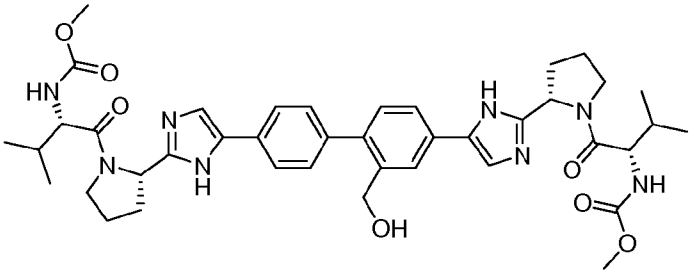
>95 homogeneity index. LC/MS: Anal. Calcd. for $[M+H]^+$ $C_{27}H_{30}N_7O$: 468.25; found 468.24.

Example M118

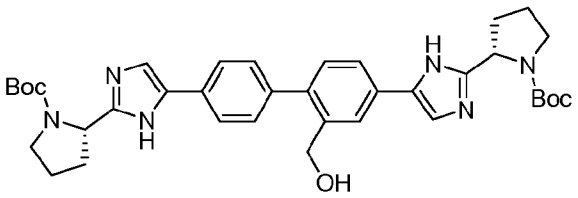
The TFA salt of Example M118 was prepared from intermediate M118a and *Cap*-51 according to the procedure described for Example 1. LC (Cond. 1): RT = 1.16 min; 97% homogeneity index. LC/MS: Anal. Calcd. for $[M+H]^+$ $C_{41}H_{52}N_9O_7$: 782.40; found 782.40. HRMS: Anal. Calcd. for $[M+H]^+$ $C_{41}H_{52}N_9O_7$: 782.3990; found 782.3979.

Example M119

methyl ((1S)-1-(((2S)-2-(5-(2-(hydroxymethyl)-4'-(2-((2S)-1-((2S)-2-((methoxycarbonyl)amino)-3-methylbutanoyl)-2-pyrrolidinyl)-1H-imidazol-5-yl)-4-biphenylyl)-1H-imidazol-2-yl)-1-pyrrolidinyl)carbonyl)-2-methylpropyl)carbamate



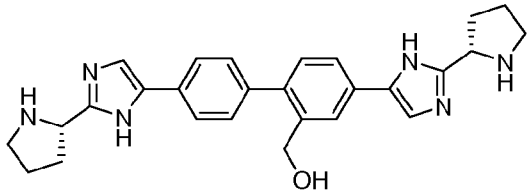
Example M119, step a



DIBAL-H (8.0 mL of 1.0 M/CH_2Cl_2, 8.0 mmol) was added drop-wise to an ice-water cooled CH_2Cl_2 (20 mL) solution of benzyl ester M114e (1.216 g, 1.60 mmol), and the reaction mixture was stirred for 1 hr and an additional DIBAL-H (0.5 mL of 1.0 M/CH_2Cl_2, 0.5 mmol) was added and stirring was continued for ~2.5 hr. The reaction was quenched with excess saturated NH_4Cl solution and the mixture was diluted with water and extracted with CH_2Cl_2 (3x). The combined organic phase was dried ($MgSO_4$), filtered, and concentrated *in vacuo*. The resulting crude material

was purified with a Biotage (100 g silica gel; 2-6% MeOH/EtOAc) to afford alcohol M119a as an off-white foam (610 mg). ^{1}H NMR (DMSO-d_6, δ = 2.5 ppm, 400 MHz): δ 12.23 (br s, 0.19 H), 12.17 (br s, 0.19H), 11.89 (br s, 0.81H), 11.82 (br s, 0.81H), 7.97 (s, 0.81H), 7.84 (s, 0.19H), 7.78 (d, *J* = 8.1, 1.62H), 7.69-7.20 (m, 6.38H), 5.21-5.15 (m, 1H), 4.86-4.78 (m, 2H), 4.49-4.45 (m, 2H), ~3.54 (m, 2H), 3.40-3.34 (m, 2H), 2.30-1.80 (m, 8H), 1.41/1.17 (two s, 18H). LC (Cond. 1): RT = 1.36 min. LC/MS: Anal. Calcd. for $[M+H]^+$ $C_{37}H_{47}N_6O_5$: 655.36; found 655.34.

Example M119, Step b



25% TFA/CH_2Cl_2 (3.0 mL) was added to carbamate M119a (105 mg, 0.160 mmol) and the mixture was stirred at ambient condition for 4.5 hr. The volatile component was removed *in vacuo* and the residue was free-based (MCX; MeOH wash; 2.0 M NH3/MeOH elution) to afford pyrrolidine M119b, contaminated with its trifluoroacetylated derivative of unknown regiochemistry. The sample was dissolved in MeOH (1.5 mL) and treated with 1.0 M NaOH/H_2O (300 μL, 0.3 mmol) and the mixture was stirred for 2.75 hr. It was then directly submitted to MCX purification (MeOH wash; 2.0 M NH_3/MeOH elution) to afford M119b as a film of white solid (63.8 mg). ^{1}H NMR (DMSO-d_6, δ = 2.5 ppm, 400 MHz): δ 11.82 (br s, 2H), 7.96 (s, 1H), 7.77 (d, *J* = 8.0, 2H), 7.66 (d, *J*= 8.0, 1H), 7.46 (br s, 1H), 7.42 (br s, 1H), 7.36 (d, *J* = 8.0, 2H), 7.21 (d, *J* = 8.0, 1H), 5.16 (app br s, 1H), 4.46 (s, 2H), 4.16 (app t, *J* = 7.1, 2H), 3.00-2.82 (two m, 4H; there is a broad base line signal in this region from the pyrrolidine NH that was not included in the integration), 2.10-2.01 (m, 2H), 1.94-1.85 (m, 2H), 1.83-1.67 (m, 4H). LC (Cond.1): RT = 0.78 min. LC/MS: Anal. Calcd. for $[M+H]^+$ $C_{27}H_{31}N_6O$: 455.26; found 455.27.

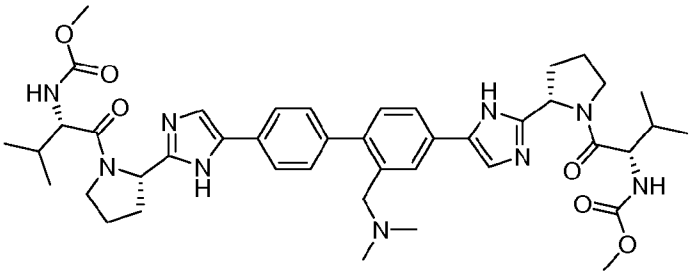
Example M119

Example M119 was prepared from M119b and *Cap*-51 according to the procedure described for Example 1, with the exception that a reverse phase HPLC

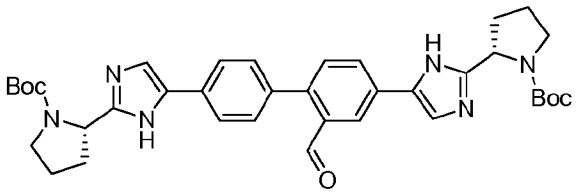
with ACN/H_2O/NH_4OAC solvent system was employed for the purification step. LC (Cond. 1): RT = 1.15 min; 98% homogeneity index. LC/MS: Anal. Calcd. for $[M+H]^+$ $C_{41}H_{53}N_8O_7$: 769.40; found 769.40. HRMS: Anal. Calcd. for $[M+H]^+$ $C_{41}H_{53}N_8O_7$: 769.4037; found 769.4023.

Example M120

methyl ((1S)-1-(((2S)-2-(5-(2-((dimethylamino)methyl)-4'-(2-((2S)-1-((2S)-2-((methoxycarbonyl)amino)-3-methylbutanoyl)-2-pyrrolidinyl)-1H-imidazol-5-yl)-4-biphenylyl)-1H-imidazol-2-yl)-1-pyrrolidinyl)carbonyl)-2-methylpropyl)carbamate

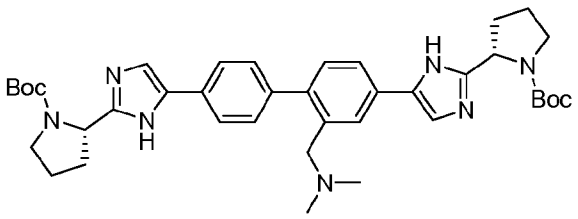


Example M120, step a



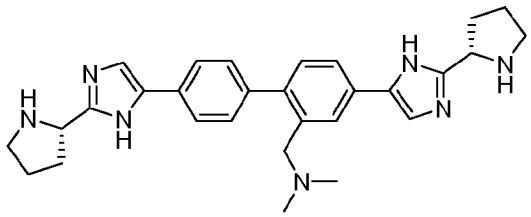
CH_2Cl_2 (6.0 mL) was added to a mixture alcohol M119a (501 mg, 0.765 mmol), TPAP (29.1, 0.083 mmol) and 4-methylmorpholine *N*-oxide (135.8 mg, 1.159 mmol), and the resultant heterogeneous mixture was vigorously stirred at ambient condition for 14.5 hr. Additional TPAP (11.0 mg, 0.031 mmol) and 4-methylmorpholine *N*-oxide (39 mg, 0.33 mmol) were added and stirring was continued for an additional 24 hr. The mixture was filtered through diatomaceous earth (Celite®), the filtrate was rotervaped and the resulting crude material was purified with a Biotage (2% MeOH/EtOAc) to afford aldehyde M120a as a yellow viscous oil (195.6 mg). LC (Cond. 1): RT = 1.37 min. LC/MS: Anal. Calcd. for $[M+H]^+$ $C_{37}H_{45}N_6O_5$: 653.35; found 653.40.

Example M120, Step b



$NaCNBH_3$ (33 mg, 0.50 mmol) was added in one batch to a MeOH (3.0 mL) solution of aldehyde M120a (195.6 mg, 0.30 mmol) and Me_2NH (200 μL of 40% solution in H_2O), and the reaction mixture was stirred for 4 hr. The volatile component was removed *in vacuo* and the residue was purified with a flash chromatography (sample was loaded as a silica gel mesh; 3-15% $MeOH/CH_2Cl_2$) to afford amine M120b as an off-white foam (120 mg). LC (Cond. 1): RT = 1.32 min. LC/MS: Anal. Calcd. for $[M+H]^+$ $C_{39}H_{52}N_7O_4$: 682.41; found 682.42.

Example M120, Step c



Carbamate M120b was converted to M120c by employing the protocol described for the preparation of 1e from 1d. ^1H NMR (DMSO-d_6, δ = 2.5 ppm, 400 MHz): δ 11.82 (br s, 2H), 7.87 (s, 1H), 7.77 (d, *J* = 8.0, 2H), 7.65 (d, *J* = 7.8, 1H), 7.45/7.43 (overlapping two br s, 2H), 7.37 (d, *J* = 7.8, 2H), 7.21 (d, *J* = 7.8, 1H), 4.87 (m, 0.1H), 4.17 (m, 1.90H), ~3.3 (signal of Me_2NCH_2 overlapped with that of water), 3.01-2.94 (m, 2H), 2.89-2.83 (m, 2H), 2.10 (s, 6H), 2.10-2.01 (m, 2H), 1.94-1.85 (m, 2H), 1.81-1.67 (m, 4H). LC (Cond. 1): RT = 0.79 min. LC/MS: Anal. Calcd. for $[M+H]^+$ $C_{29}H_{36}N_7$: 482.30; found 482.35.

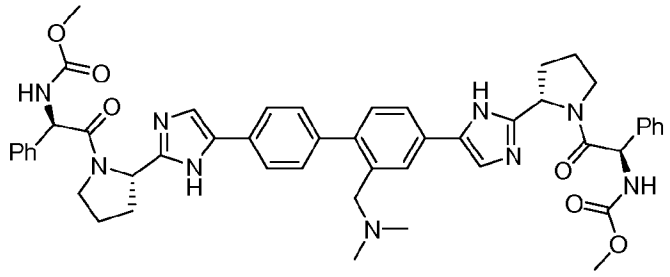
Example M120

The TFA salt of Example M120 was prepared from pyrrolidine M120c and *Cap*-51 according to the procedure described for Example 1. LC (Cond. 1): RT = 1.06 min; 96% homogeneity index. LC/MS: Anal. Calcd. for $[M+H]^+$ $C_{43}H_{58}N_9O_6$:

796.45; found 796.48. HRMS: Anal. Calcd. for $[M+H]^+$ $C_{43}H_{58}N_9O_6$: 796.4510; found 796.4515.

Example M121

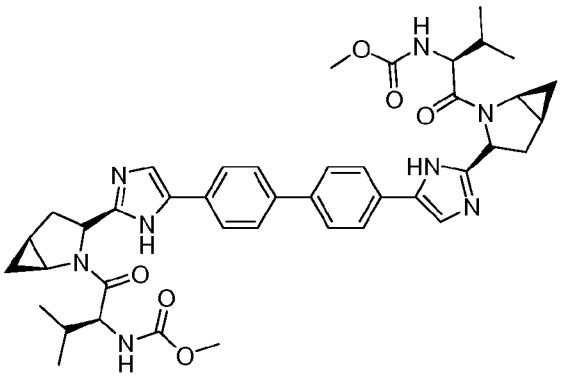
dimethyl ((2-((dimethylamino)methyl)-4,4'-biphenyldiyl)bis(1H-imidazole-5,2-diyl(2S)-2,1-pyrrolidinediyl((1R)-2-oxo-1-phenyl-2,1-ethanediyl)))biscarbamate



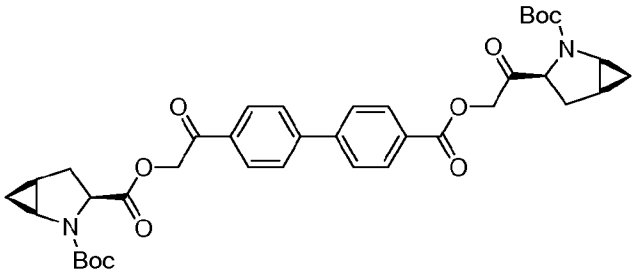
The TFA salt of Example M121 was prepared from M120c and *Cap*-4 according to the procedure described for Example 1. LC (Cond. 1): RT = 1.15 min; >98% homogeneity index. LC/MS: Anal. Calcd. for $[M+H]^+$ $C_{49}H_{54}N_9O_6$: 796.45; found 864.46. HRMS: Anal. Calcd. for $[M+H]^+$ $C_{49}H_{54}N_9O_6$: 864.4197; found 864.4222.

Example M122

methyl ((1S)-1-(((1S,3S,5S)-3-(5-(4'-(2-((1S,3S,5S)-2-((2S)-2-((methoxycarbonyl)amino)-3-methylbutanoyl)-2-azabicyclo[3.1.0]hex-3-yl)-1H-imidazol-5-yl)-4-biphenylyl)-1H-imidazol-2-yl)-2-azabicyclo[3.1.0]hex-2-yl)carbonyl)-2-methylpropyl)carbamate

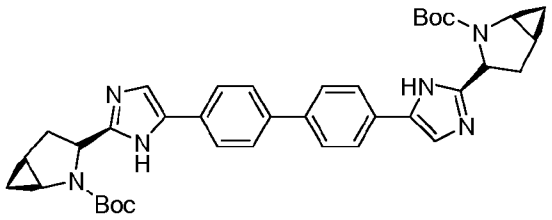


Example M122, step a



Diisopropyl ethylamine (1.81 mL, 10.4 mmol) was slowly added to acetonitrile (20 mL) solution of (1S,3S,5S)-2-(tert-butoxycarbonyl)-2-azabicyclo[3.1.0]hexane-3-carboxylic acid (2.36 g, 10.4 mmol) and (2-(4'-(2-bromoacetyl)biphenyl-4-yl)-2-oxoethyl)bromonium (2.0 g, 5.05 mmol), and the reaction mixture was stirred at ambient conditions for 16 hr. The solvent was evaporated and the residue was partitioned between ethyl acetate and water (1:1, 40 mL each). The organic layer was washed with Sat. $NaHCO_3$ (2 x 10 mL), brine, dried (Na_2SO_4), filtered, and concentrated *in vacuo* to afford ketoester M122a (3.58 g) as a viscous amber oil, which solidified upon storage in a refrigerator. ^1H NMR (DMSO-d_6, δ = 2.5 ppm, 400 MHz): δ 8.20 (m, 4H), 7.97 (d, J = 8.5, 4H), 5.71-5.48 (m, 4H), 4.69 (m, 2H), 3.44 (m, 2H), 3.3 (m, 2H), 2.76-2.67 (m, 2 H), 2.27 (m, 2H), 1.60 (m, 2H), 1.44/1.38 (two s, 18H), 0.78 (m, 2H), 0.70 (m, 2H). LC (Cond. 1): RT = 1.70 min; LC/MS: the molecular ion was not picked up.

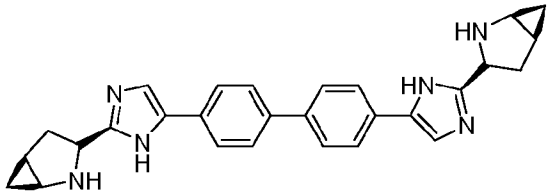
Example M122, Step b



Ammonium acetate (2.89 g, 37.5 mmol) was added to a toluene (20 mL) solution of ketoester M122a (2.58 g, 3.75 mmol), and the resulting mixture was heated at 120 °C for 4.5 hr, while azaetroping the water that is formed with a Dean-Stark set-up. The reaction mixture was cooled to room temperature and the volatile component was removed *in vacuo*. Sat. $NaHCO_3$ solution (10 mL) was added to the solid and the mixture was stirred for 30 min, and the solid was filtered, dried *in vacuo*

and submitted to a Biotage purification (28-100% EtOAc/hexanes) to afford imidazole M122b as light yellow solid (0.6 g). LC (Cond. 1): RT = 1.52 min; LC/MS: Anal. Calcd. for $[M+H]^+$ $C_{38}H_{45}N_6O_4$: 649.35; found 649.78.

Example M122, Step c



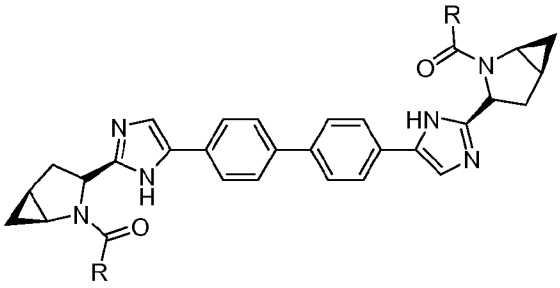
4 N HCl in dioxane (5 mL) was added to a ice-water cooled dioxane (16 mL) solution of carbamate M122b (0.8 g, 1.2 mmol), the ice-water bath was removed and the mixture was stirred at ambient condition for 4 hr. Big chunks of solid that formed during the reaction were broken up with a spatula. Removal of the volatile component *in vacuo* afforded pyrrolidine M122c (.4 HCl) as yellow solid (0.73 g). ^{1}H NMR (DMSO-d_6, δ = 2.5 ppm, 400 MHz): δ 7.90 (d, J = 8.3, 4H), 7.84 (br s, 2H), 7.79 (d, J = 8.3, 4H), 5.24 (m, 2H), 3.38 (m, 2H), 2.71 (m, 2H), ~2.50 (2H, overlapped with solvent signal), 1.93 (m, 2H), 1.38 (m, 2H), 0.96 (m, 2H). LC (Cond. 1): RT = 1.03 min; LC/MS: Anal. Calcd. for $[M+H]^+$ $C_{28}H_{29}N_6$: 449.25; found 449.59.

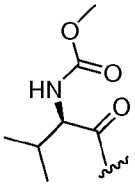
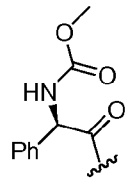
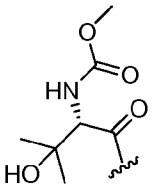
Example M122

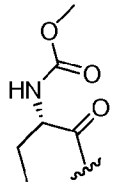
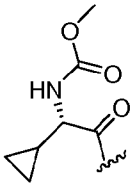
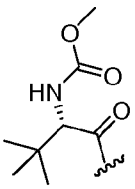
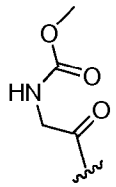
The TFA salt of Example M122 was prepared from M122c and *Cap*-51 according to the procedure described for Example 1. LC (Cond. 1): RT = 1.34 min; LC/MS: Anal. Calcd. for $[M+H]^+$ $C_{42}H_{51}N_8O_6$: 763.39; found 763.73.

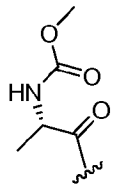
Example M123-M130

Example M123-M130 were prepared according to the procedure described for Example M122. Example M123-M129 were prepared as TFA salts, where as Example M130 was prepared as a free base.



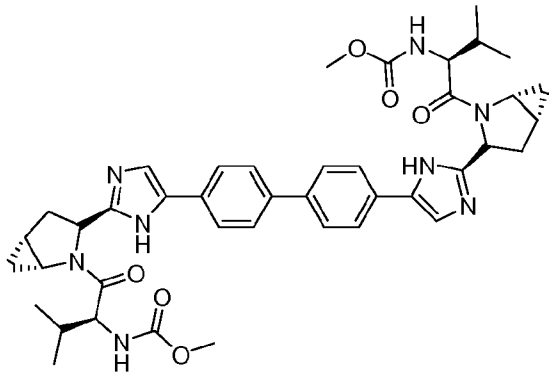
Example	*Compound Name*	 *(Source)*	*RT (LC-Cond.); % homogeneity index; MS data*
M123	methyl ((1R)-1-(((1S,3S,5S)-3-(5-(4'-(2-((1S,3S,5S)-2-((2R)-2-((methoxycarbonyl)amino)-3-methylbutanoyl)-2-azabicyclo[3.1.0]hex-3-yl)-1H-imidazol-5-yl)-4-biphenylyl)-1H-imidazol-2-yl)-2-azabicyclo[3.1.0]hex-2-yl)carbonyl)-2-methylpropyl)carbamate	 (*Cap*-84)	1.372 minutes (Cond. 1); >98%; LC/MS: Anal. Calcd. for $[M+H]^+$ $C_{42}H_{51}N_8O_6$: 763.39; found 763.73
M124	dimethyl (4,4'-biphenyldiylbis(1H-imidazole-5,2-diyl(1S,3S,5S)-2-azabicyclo[3.1.0]hexane-3,2-diyl((1R)-2-oxo-1-phenyl-2,1-ethanediyl)))biscarbamate	 (*Cap*-4)	2.28 minutes (Cond. M1); >98%; LC/MS: Anal. Calcd. for $[M+H]^+$ $C_{48}H_{47}N_8O_6$: 831.36; found 831.36
M125	methyl ((1S)-2-hydroxy-1-(((1S,3S,5S)-3-(5-(4'-(2-((1S,3S,5S)-2-((2S)-3-hydroxy-2-((methoxycarbonyl)amino)-3-methylbutanoyl)-2-azabicyclo[3.1.0]hex-3-yl)-1H-imidazol-5-yl)-4-biphenylyl)-1H-imidazol-2-yl)-2-	 (*Cap*-65)	1.76 minutes (Cond. M1); >98%; LC/MS: Anal. Calcd. for $[M+H]^+$ $C_{42}H_{51}N_8O_8$: 795.38; found 795.37

	azabicyclo[3.1.0]hex-2-yl)carbonyl)-2-methylpropyl)carbamate		
M126	dimethyl (4,4'-biphenyldiylbis(1H-imidazole-5,2-diyl(1S,3S,5S)-2-azabicyclo[3.1.0]hexane-3,2-diyl((2S)-1-oxo-1,2-butanediyl)))biscarbamate	 (*Cap*-53b)	1.25 minutes (Cond.1); >98%; LC/MS: Anal. Calcd. for $[M+H]^+$ $C_{40}H_{47}N_8O_6$: 735.36; found 735.68
M127	dimethyl (4,4'-biphenyldiylbis(1H-imidazole-5,2-diyl(1S,3S,5S)-2-azabicyclo[3.1.0]hexane-3,2-diyl((1S)-1-cyclopropyl-2-oxo-2,1-ethanediyl)))biscarbamate	 (*Cap*-54b)	1.27 minutes (Cond. 1); >98%; LC/MS: Anal. Calcd. for $[M+H]^+$ $C_{42}H_{47}N_8O_6$: 759.36; found 759.72
M128	methyl ((1S)-1-(((1S,3S,5S)-3-(5-(4'-(2-((1S,3S,5S)-2-((2S)-2-((methoxycarbonyl)amino)-3,3-dimethylbutanoyl)-2-azabicyclo[3.1.0]hex-3-yl)-1H-imidazol-5-yl)-4-biphenylyl)-1H-imidazol-2-yl)-2-azabicyclo[3.1.0]hex-2-yl)carbonyl)-2,2-dimethylpropyl)carbamate		2.48 minutes (Cond. M1); >98%; LC/MS: Anal. Calcd. for $[M+H]^+$ $C_{44}H_{55}N_8O_6$: 791.42; found 791.41
M129	methyl (2-((1S,3S,5S)-3-(5-(4'-(2-((1S,3S,5S)-2-(((methoxycarbonyl)amino)acetyl)-2-azabicyclo[3.1.0]hex-3-yl)-1H-imidazol-5-yl)-4-biphenylyl)-1H-imidazol-2-yl)-2-azabicyclo[3.1.0]hex-2-yl)-2-oxoethyl)carbamate		1.10 minutes (Cond.1); >98%; LC/MS: Anal. Calcd. for $[M+H]^+$ $C_{36}H_{39}N_8O_6$: 679.74; found 679.77

M130	methyl ((1S)-2-((1S,3S,5S)-3-(5-(4'-(2-((1S,3S,5S)-2-(N-(methoxycarbonyl)-L-alanyl)-2-azabicyclo[3.1.0]hex-3-yl)-1H-imidazol-5-yl)-4-biphenylyl)-1H-imidazol-2-yl)-2-azabicyclo[3.1.0]hex-2-yl)-1-methyl-2-oxoethyl)carbamate	 (*Cap*-52)	1.16 minutes (Cond. 1); >98%; LC/MS: Anal. Calcd. for $[M+H]^+$ $C_{38}H_{43}N_8O_6$: 707.33; found 707.69

Example M131

methyl ((1S)-1-(((1R,3R,5R)-3-(5-(4'-(2-((1R,3R,5R)-2-((2S)-2-((methoxycarbonyl)amino)-3-methylbutanoyl)-2-azabicyclo[3.1.0]hex-3-yl)-1H-imidazol-5-yl)-4-biphenylyl)-1H-imidazol-2-yl)-2-azabicyclo[3.1.0]hex-2-yl)carbonyl)-2-methylpropyl)carbamate



Example M131 was prepared according to the procedure described for its disatereomer Example M122 starting from (1R,3S,5R)-2-(*tert*-butoxycarbonyl)-2-azabicyclo[3.1.0]hexane-3-carboxylic acid, which was in turn synthesized by employing a literature protocol (Hanessian *et al., Angew. Chem., Int. Ed. Engl.* 1997, *36*, 1881-1884). LC (Cond. 1): RT = 1.273 min; LC/MS: Anal. Calcd. for $[M+H]^+$ $C_{42}H_{50}N_8O_6$: 763.39; found 763.94.

BIOLOGICAL ACTIVITY

An HCV Replion assay was utilized in the present disclosure, and was prepared, conducted and validated as described in commonly owned

PCT/US2006/022197 and in O'Boyle et. al. *Antimicrob Agents Chemother.* **2005** Apr;49(4):1346-53.

HCV 1b-377-neo replicon cells were used to test the currently described compound series as well as cells resistant to compound A due to a Y2065H mutation in NS5A (described in application PCT/US2006/022197). The compounds tested were determined to have more than 10-fold less inhibitory activity on cells resistant to compound A than wild-type cells indicating a related mechanism of action between the two compound series. Thus, the compounds of the present disclosure can be effective to inhibit the function of the HCV NS5A protein and are understood to be as effective in combinations as previously described in application PCT/US2006/022197 and commonly owned WO/O4014852. Further, the compounds of the present disclosure can be effective against the HCV 1b genotype. It should also be understood that the compounds of the present disclosure can inhibit multiple genotypes of HCV. Table 2 shows the EC50 values of representative compounds of the present disclosure against the HCV 1b genotype. In one embodiment compounds of the present disclosure are active against the 1a, 1b, 2a, 2b, 3a, 4a, and 5a genotypes. EC50 ranges against HCV 1b are as follows: A = 1-10 μM; B = 100-999 nM; C = 1-99 nM; and D = 10-999 pM.

The compounds of the present disclosure may inhibit HCV by mechanisms in addition to or other than NS5A inhibition. In one embodiment the compounds of the present disclosure inhibit HCV replicon and in another embodiment the compounds of the present disclosure inhibit NS5A.

Table 2

Example	Range
1	D
24-4e	C
24-4f	B
24-4g	A
25-1	D
25-2	D
25-3	D
25-4	D
25-5	D
25-6	C
25-7	C
25-8	D
24-4h	D
120-9	D
120	D
120-5	C
120-6	C
120-7	D
120-8	C
103-3	D
103-4	D
103-1	D
103-2	D
103-5	D
103-6	C
103-8	D
103-7	D
151 isomer 1	C
151 isomer 2	B
152j-9	C
152j-10	C
152j-1	C
152j-2	D
153c-5	C
153c-6	C
153c-2	C
153c-1	C
152j-7	C
152j-8	D
153c-3	A
153c-4	A
152j-11	D
152j-12	D
152j-15	D
152j-28	D
152j-13	C
152j-14	C
152j-19	D
152j-16	D

Example	Range
152j-3	D
152j-20	C
152j-17	D
152j-18	D
152j-3	D
152j-5	D
152j-6	D
152l-2	D
152l-1	D
152j-24	D
152j-23	D
153c-7	C
152j-22	D
24-18-2	D
24-18-1	D
24-18-4	D
24-18-5	D
24-18-6	D
24-18-3	D
152j-21	D
152l-3	D
131.1-2	D
131.1-1	D
24-4a	D
120-1	D
120-2	D
120-3	D
120-4	D
24-10	D
24-9	D
24-8	D
24-11	C
24-12	C
11	C
24-16	D
24-18	D
24-17	D
24-15	C
24-13	B
24-14	C
24-4b	C
24-4c	D
24-4d	D
148	C
149	D
150	C
24-5	D
24-6	D
24-7	D

Example	Range
24-1	D
24-2	D
24-3	D
28-1	D
28-2	D
28-3	D
28-4	D
28-5	D
84-1	D
84-2	D
84-3	D
84-4	D
84-7	C
84-10	C
84-12	D
84-14	C
84-15	C
84-17	D
84-18	C
84-19	C
84-20	C
84-24	D
84-26	D
84-27	D
84-28	D
84-32	D
84-33	D
84-34	C
84-35	D
84-36	D
84-38	D
84-39	D
84-40	D
84-44	D
84-46	D
84-47	D
84-48	D
84-49	D
84-50	D
84-51	D
84-52	D
84-53	D
84-54	D
84-55	D
84-56	D
84-57	D
84-58	D
84-59	D
84-60	D

Example	Range
84-61	D
84-62	D
84-63	D
84-64	D
84-65	C-D
84-66	C-D
84-67	D
84-68	C
84-69	D
84-70	C
84-71	C
84-72	C
84-73	C
84-74	D
84-75	C
84-76	D
84-77	D
84-78	D
84-79	D
84-80	D
84-81	D
84-82	D
84-83	D
84-84	D
84-85	D
84-86	D
84-87	D
94-1	D
94-2	C
94-3	D
94-6	C-D
94-9	D
94-10	D
94-12	C
94-13	D
94-17	D
94-19	D
94-20	C
94-24	D
94-25	D
94-26	D
94-27	C
94-30	D
94-32	C
94-33	C
94-34	C
94-36	D
94-37	C
94-38	D
94-42	D

Example	Range
94-44	D
94-45	D
94-46	D
94-47	D
94-48	D
94-49	D
94-50	D
94-51	D
94-52	D
94-53	D
94-54	D
94-55	D
94-56	D
107-1	D
107-2	D
107-3	D
107-4	D
107-5	D
107-6	D
107-7	D
107-8	D
107-9	D
107-10	D
107-11	D
107-12	D
107-13	D
107-14	D
107-15	D
107-16	D
107-17	D
107-18	D
107-19	D
107-20	D
107-21	D
107-22	D
107-23	D
107-24	D
107-25	D
107-26	D
107-27	D
107-28	D
107-29	D
107-30	D
107-31	D
107-32	D
107-33	D
107-34	D
107-35	D
107-36	D
107-37	D

Example	Range
107-38	D
107-39	D
107-40	D
107-41	D
107-42	D
107-43	D
107-44	D
2	D
3	D
4	D
5	C
6	C
7	D
8	D
24-23	D
9	C
10	C
11	C
12	C
13	C
14	B
15	C
16	C
17	D
18	D
19	D
20	C
21	D
22	D
23	D
24	C
25	D
26	C
27	C
28	C
29	D
30	C
31	D
32	C
33	D
34	D
35	D
36	D
37	D
38	D
39	D
40	D
41	D
42	D
43	D

44	D
45	D
46	D
47	D
48	D
49	D
50	B
51	D
52	D
53	D
54	D
55	D
56	D
57	D
58	D
59	D
60	D
61	D
62	D
63	D
64	D
65	C
67	D
68	D
69	D
70	C
71	D
72	C
73	D
74	D
75	D
76	D
77	D

78	D
79	D
80	D
81	D
82	D
83	D
84	D
85	D
86	D
87	D
88	D
89	D
90	D
91	D
92	D
93	D
94	D
95	D
96	D
97	D
98	D
99	D
100	D
101	D
102	D
103	D
104	D
105	D
106	D
107	D
108	D
109	C
110	D
111	D

112	D
113	D
114	D
115	D
116	D
117	D
118	D
119	D
120	D
121	D
122	D
123	D
124	D
125	D
126	D
127	D
128	D
129	D
130	D
131	D
132	D
133	C
134	D
135	D
136	D
138	D
139	D
140	D
141	D
142	C
143	D
144	D
145	D

146	D
147	D
LS2	C
LS3	C
LS4	C
LS16	C
LS6	B
LS11	A
LS14	D
LS20	D
LS21	D
LS22	D
LS23	D
LS24	D
LS25	D
LS26	D

LS27 D'mer 1	D
LS27 D'mer 2	D
LS36	D
LS37	D
F5	D
F6	D
F7	D
F8	D
F14	D
F15	D
F16	D
F17	D
F20	B
F21	B

F22	B
F25	D
F26	C
F27	C
F28	C
F29	C
F30	C
F32	B
F33	B
F34	C
F35	B
F37	B
F38	D
F39 Diastereomers	D

F41	D
F43	D
F48	D
F49	C
F51	D
F52	D
F53	D
F54	D
F55	D
F56	D
F57	D
F58	D
F60	D
F61	C
F62	C
F63	D
F64	C
F65	B
F66	C
F67	C
F69	B
F70	B
F71	D
cj-48	B
cj-49	C
cj-50	D
cj-51	D
cj-52	D
cj-53	D
cj-54	D
cj-55	D
cj-56	D
cj-57	D
cj-58	D
cj-59	D
cj-60	D
cj-61	D
cj-62	D
cj-63	D
cj-64	D
cj-65	D
cj-66	D
cj-67	D
cj-68	D
cj-69	D
cj-70	D
cj-71	D
cj-72	D
cj-73	D
cj-74	C
cj-75	D

cj-76	D
cj-77	D
cj-78	D
cj-79	D
cj-80	D
cj-81	D
cj-82	D
cj-83	D
cj-84	D
cj-85	D
cj-86	D
cj-87	D
cj-88	D
cj-89	D
cj-90	D
cj-91	D
cj-92	C
cj-93	D
cj-94	D
cj-95	D
cj-96	D
cj-97	D
cj-98	D
cj-99	D
cj-100	D
cj-101	D
cj-102	D
cj-103	D
cj-104	D
cj-105	D
cj-106	D
cj-107	D
cj-108	D
cj-109	D
cj-110	D
cj-111	D
cj-112	D
cj-113	D
cj-114	D
cj-115	D
cj-116	D
cj-117	D
cj-118	D
cj-119	D
cj-120	D
cj-121	D
cj-122	D
cj-45	D
cj-41	D
cj-47	C
cj-43	D

cj-44	D
cj-40	D
cj-46	D
cj-42	D
cj-36	D
cj-37	D
cj-38	D
cj-39	D
cj-32	D
cj-33	D
cj-34	D
cj-35	C
cj-136	D
cj-137	C
cj-138	A
cj-139	C
cj-140	B
cj-141	A
cj-142	A
cj-143	A
cj-144	D
cj-145	C
cj-146	B
cj-147	C
cj-148	C
cj-149	C
cj-150	C
cj-151	C
cj-152	C
cj-153	D
cj-154	D
cj-155	C
cj-156	D
cj-126	D
cj-127	C
cj-128	D
cj-129	D
cj-130	D
cj-131	C
cj-132	B
cj-133	C
cj-134	C
cj-135	C
cj-125	C
cj-15c	D
cj-20c	D
cj-20b	D
cj-20a	D
cj-17	D
cj-16	D
cj-20d	D

cj-20	D
cj-15a	D
cj-15	D
cj-15d	D
cj-11n	C
cj-11o	C
cj-11p	D
cj-11m	C
cj-11h	D
cj-11i	D
cj-11j	D
cj-11k	D
cj-11e	A
cj-11f	C
cj-11g	C
cj-11d	D
cj-11b	D
cj-11	D
cj-11a	D
cj-11c	D
JG-3	D
JG-4	C
JG-5	D
JG-6	C
JG-7	D
JG-8	D
JG-9	D
JG-10	C
JG-12	D
JG-13	C
JG-14	D
JG-15	D
JG-16	D
JG-17	D
OL-1	D
OL-2	D
OL-3	C
OL-4	D

OL-5	D
OL-6	D
OL-7	D
OL-8	D
OL-9	D
OL-10	D
OL-11	D
OL-12	D
OL-13	D
OL-19	D
OL-20	C
OL-21	D
D73	D
D74	D
D75	D
D76	D
D77	D
J16	D
J17	D
J18	D
J19	D
J20	D
J21	D
J22	D
J23	D
J24	D
J25	D
J26	D
J27	D
J28	C
J29	D
J30	C
J31	D
J37	D
J38	D
J39	D
J40	D
J41	D
J42	D
J42.a	D
J45	D
J46	D
J47	D
J48	D
J49	D
J50	D
J51	C
D33	D
D34	D
D35	D
D36	D

D37	D
D38	D
D39	D
D40	D
D41	D
D42	D
D43	D
D44	D
D45	D
D46	D
D47	D
D48	D
D49	D
D50	D
D51	D
D52	D
D53	D
D54	D
D55	D
D56	D
D57	D
D58	D
D59	D
D60	D
D61	D
D62	D
D63	D
D64	D
D65	D
D66	D
D67	D
D68	D
D69	D
D70	D
M1	>A
M2	C
M3	C
M4	B
M5	A
M6	A
M7	>A
M8	A
M9	B
M10	>A
M11	C
M12	C
M13	B
M14	B
M15	B
M16	A
M17	B

M18	A
M19	>A
M21	C
M22	A
M23	C
M24	C
M25	C
M26	B
M27	C
M28	A
M28-2	B
M29	>A
M30	C
M31	C
M32	B
M33	C
M34	C
M35	C
M36	C
M37	C
M38	C
M39	C
M40	C
M41	C
M42	C
M43	C
M44	B
M45	C
M46	C
M47	C
M48	C
M49	C
M50	C
M51	C
M52	C
M53	C
M54	C
M55	C
M56	C
M57	C

M58	C
M59	C
M60	C
M61	C
M62	C
M63	C
M64	C
M65	C
M66a	B
M66b	B
M66x	C
M67a	B
M67b	B
M68	B
M69	B
M70	C
M71	C
M72	C
M73	B
M74	C
M75	C
M76	C
M77	C
M78	C
M79	C
M80	C
M81	B
M82	C
M83	C
M84	C
M85	C
M86	C
M87	C
M88	C
M89	C
M90	A
M91	C
M91x	C
M91y	B
M92	A

M93	C
M94	C
M95	C
M96	B
M97	C
M98	C
M99	C
M100	C
M101	B
M102	C
M103	B
M104	B
M105	C
M106	C
M107	C
M108	C
M109	C
M110	C
M111	A
M112	C
M113	C
M114	>A
M115	>A
M116	>A
M117	>A
M118	>A
M119	B
M120	B
M121	B
M122	C
M123	A
M124	C
M125	C
M126	C
M127	C
M128	C
M129	A
M130	C

It will be evident to one skilled in the art that the present disclosure is not limited to the foregoing illustrative examples, and that it can be embodied in other specific forms without departing from the essential attributes thereof. It is therefore desired that the examples be considered in all respects as illustrative and not restrictive, reference being made to the appended claims, rather than to the foregoing examples, and all changes which come within the meaning and range of equivalency

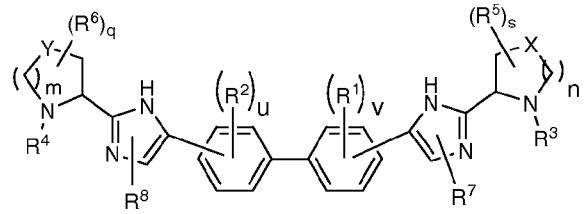
of the claims are therefore intended to be embraced therein.

The compounds of the present disclosure may inhibit HCV by mechanisms in addition to or other than NS5A inhibition. In one embodiment the compounds of the present disclosure inhibit HCV replicon and in another embodiment the compounds of the present disclosure inhibit NS5A. Compounds of the present disclosure may inhibit multiple genotypes of HCV.

CLAIMS

WHAT IS CLAIMED IS:

1. A compound of Formula (I)



(I),

or a pharmaceutically acceptable salt thereof, wherein

m and n are independently 0, 1, or 2;

q and s are independently 0, 1, 2, 3, or 4;

u and v are independently 0, 1, 2, or 3;

X is selected from O, S, S(O), SO_2, CH_2, CHR^5, and $C(R^5)_2$;

provided that when n is 0, X is selected from CH_2, CHR^5, and $C(R^5)_2$;

Y is selected from O, S, S(O), SO_2, CH_2, CHR^6, and $C(R^6)_2$;

provided that when m is 0, Y is selected from CH_2, CHR^6, and $C(R^6)_2$;

each R^1 and R^2 is independently selected from alkoxy, alkoxyalkyl, alkoxycarbonyl, alkyl, arylalkoxycarbonyl, carboxy, formyl, halo, haloalkyl, hydroxy, hydroxyalkyl, $-NR^aR^b$, (NR^aR^b)alkyl, and (NR^aR^b)carbonyl;

R^3 and R^4 are each independently selected from hydrogen and R^9-C(O)-, and R^9-C(S)-;

each R^5 and R^6 is independently selected from alkoxy, alkyl, aryl, halo, haloalkyl, hydroxy, and $-NR^aR^b$, wherein the alkyl can optionally form a fused three- to six-membered ring with an adjacent carbon atom, wherein the three- to six-membered ring is optionally substituted with one or two alkyl groups;

R^7 and R^8 are each independently selected from hydrogen, alkoxycarbonyl, alkyl, arylalkoxycarbonyl, carboxy, haloalkyl, (NR^aR^b)carbonyl, and trialkylsilylalkoxyalkyl; and

each R^9 is independently selected from alkoxy, alkoxyalkyl, alkoxycarbonyl, alkoxycarbonylalkyl, alkyl, alkylcarbonylalkyl, aryl, arylalkenyl, arylalkoxy, arylalkyl, aryloxyalkyl, cycloalkyl, (cycloalkyl)alkenyl, (cycloalkyl)alkyl,

cycloalkyloxyalkyl, haloalkyl, heterocyclyl, heterocyclylalkenyl, heterocyclylalkoxy, heterocyclylalkyl, heterocyclyloxyalkyl, hydroxyalkyl, -NR^cR^d, (NR^cR^d)alkenyl, (NR^cR^d)alkyl, and (NR^cR^d)carbonyl.

2. A compound of claim 1, or a pharmaceutically acceptable salt thereof, wherein m and n are each 1.

3. A compound of claim 1, or a pharmaceutically acceptable salt thereof, wherein

u and v are each independently 0, 1, or 2; and

each R^1 and R^2 is independently selected from alkoxy, alkoxyalkyl, alkyl, arylalkoxycarbonyl, carboxy, formyl, halo, haloalkyl, hydroxyalkyl, (NR^aR^b)alkyl, and (NR^aR^b)carbonyl.

4. A compound of claim 1, or a pharmaceutically acceptable salt thereof, wherein

u and v are each independently 0 or 1; and

when present, R^1 and/or R^2 are halo.

5. A compound of claim 4, or a pharmaceutically acceptable salt thereof, wherein the halo is fluoro.

6. A compound of claim 1, or a pharmaceutically acceptable salt thereof, wherein at least one of X and Y is S.

7. A compound of claim 6, or a pharmaceutically acceptable salt thereof, wherein X and Y are each S.

8. A compound of claim 1, or a pharmaceutically acceptable salt thereof, wherein X is selected from CHR^5, and $C(R^5)_2$; and Y is selected from CH_2, CHR^6, and $C(R^6)_2$.

9. A compound of claim 1, or a pharmaceutically acceptable salt thereof,

wherein R^7 and R^8 are independently selected from hydrogen, alkoxycarbonyl, alkyl, arylalkoxycarbonyl, carboxy, haloalkyl, and (NR^aR^b)carbonyl.

10. A compound of claim 9, or a pharmaceutically acceptable salt thereof, wherein R^7 and R^8 are each hydrogen.

11. A compound of claim 1, or a pharmaceutically acceptable salt thereof, wherein

q and s are independently 0, 1, or 2; and

each R^5 and R^6 is independently selected from alkyl, aryl, halo, and hydroxy, wherein the alkyl can optionally form a fused three- to six-membered ring with an adjacent carbon atom, wherein the three- to six-membered ring is optionally substituted with one or two alkyl groups.

12. A compound of claim 1, or a pharmaceutically acceptable salt thereof, wherein

q and s are independently 0 or 1; and

when present, R^5 and/or R^6 are halo.

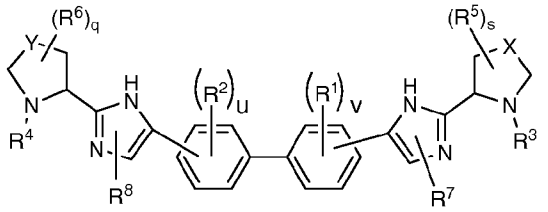
13. A compound of claim 12, or a pharmaceutically acceptable salt thereof, wherein the halo is fluoro.

14. A compound of claim 1, or a pharmaceutically acceptable salt thereof, wherein at least one of R^3 and R^4 is hydrogen.

15. A compound of claim 1, or a pharmaceutically acceptable salt thereof, wherein R^3 and R^4 are each R^9-C(O)-.

16. A compound of claim 15, or a pharmaceutically acceptable salt thereof, wherein each R^9 is independently selected from alkoxy, alkoxyalkyl, alkyl, alkylcarbonylalkyl, aryl, arylalkenyl, arylalkoxy, arylalkyl, aryloxyalkyl, cycloalkyl, (cycloalkyl)alkyl, cycloalkyloxyalkyl, heterocyclyl, heterocyclylalkyl, hydroxyalkyl, -NR^cR^d, (NR^cR^d)alkenyl, (NR^cR^d)alkyl, and (NR^cR^d)carbonyl.

17. A compound of Formula (II)



(II),

or a pharmaceutically acceptable salt thereof, wherein

q and s are independently 0, 1, or 2;

u and v are independently 0, 1, or 2;

X is selected from S, CH_2, CHR^5, and $C(R^5)_2$;

Y is selected from S, CH_2, CHR^6, and $C(R^6)_2$;

each R^1 and R^2 is independently selected from alkoxy, alkoxyalkyl, alkyl, arylalkoxycarbonyl, carboxy, formyl, halo, haloalkyl, hydroxyalkyl, (NR^aR^b)alkyl, and (NR^aR^b)carbonyl;

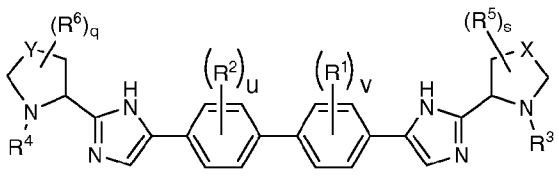
R^3 and R^4 are each independently selected from hydrogen and R^9-C(O)-;

each R^5 and R^6 is independently selected from alkyl, aryl, halo, and hydroxy, wherein the alkyl can optionally form a fused three- to six-membered ring with an adjacent carbon atom, wherein the three- to six-membered ring is optionally substituted with one or two alkyl groups;

R^7 and R^8 are each independently selected from hydrogen, alkoxycarbonyl, alkyl, arylalkoxycarbonyl, carboxy, haloalkyl, and (NR^aR^b)carbonyl; and

each R^9 is independently selected from alkoxy, alkoxyalkyl, alkyl, alkylcarbonylalkyl, aryl, arylalkenyl, arylalkoxy, arylalkyl, aryloxyalkyl, cycloalkyl, (cycloalkyl)alkyl, cycloalkyloxyalkyl, heterocyclyl, heterocyclylalkyl, hydroxyalkyl, $-NR^cR^d$, (NR^cR^d)alkenyl, (NR^cR^d)alkyl, and (NR^cR^d)carbonyl.

18. A compound of Formula (III)



(III),

or a pharmaceutically acceptable salt thereof, wherein

q and s are independently 0, 1, or 2;

u and v are independently 0 or 1;

X is selected from CH_2, CHR^5, and $C(R^5)_2$;

Y is selected from CH_2, CHR^6, and $C(R^6)_2$;

when present, R^1 and/or R^2 are halo, wherein the halo is fluoro;

R^3 and R^4 are each R^9-C(O)-;

when present, R^5 and/or R^6 are halo, wherein the halo is fluoro; and

each R^9 is independently selected from alkoxy, alkoxyalkyl, alkoxycarbonyl, alkoxycarbonylalkyl, alkyl, alkylcarbonylalkyl, aryl, arylalkenyl, arylalkoxy, arylalkyl, aryloxyalkyl, cycloalkyl, (cycloalkyl)alkenyl, (cycloalkyl)alkyl, cycloalkyloxyalkyl, haloalkyl, heterocyclyl, heterocyclylalkenyl, heterocyclylalkoxy, heterocyclylalkyl, heterocyclyloxyalkyl, hydroxyalkyl, $-NR^cR^d$, (NR^cR^d)alkenyl, (NR^cR^d)alkyl, and (NR^cR^d)carbonyl.

19. A compound selected from

di-tert-butyl (2S,2'S)-2,2'-(4,4'-biphenyldiylbis(1H-imidazole-5,2-diyl))di(1-pyrrolidinecarboxylate);

tert-butyl (2S)-2-(4-(3'-(2-((2S)-1-(tert-butoxycarbonyl)-2-pyrrolidinyl)-1H-imidazol-5-yl)-3-biphenylyl)-1H-imidazol-2-yl)-1-pyrrolidinecarboxylate;

5,5'-(4,4'-biphenyldiyl)bis(2-((2S)-2-pyrrolidinyl)-1H-imidazole);

2-((2S)-2-pyrrolidinyl)-4-(3'-(2-((2S)-2-pyrrolidinyl)-1H-imidazol-5-yl)-3-biphenylyl)-1H-imidazole;

(1R,1'R)-2,2'-(4,4'-biphenyldiylbis(1H-imidazole-5,2-diyl(2S)-2,1-pyrrolidinediyl))bis(N,N-dimethyl-2-oxo-1-phenylethanamine);

(1R,1'R)-2,2'-(4,4'-biphenyldiylbis(1H-imidazole-5,2-diyl(2S)-2,1-pyrrolidinediyl))bis(2-oxo-1-phenylethanol);

(2S,2'S)-1,1'-(4,4'-biphenyldiylbis(1H-imidazole-5,2-diyl(2S)-2,1-pyrrolidinediyl))bis(1-oxo-2-phenyl-2-propanol);

dimethyl (4,4'-biphenyldiylbis(1H-imidazole-5,2-diyl(2S)-2,1-pyrrolidinediyl((1R)-2-oxo-1-phenyl-2,1-ethanediyl)))biscarbamate;

(1S,1'S)-2,2'-(4,4'-biphenyldiylbis(1H-imidazole-5,2-diyl(2S)-2,1-pyrrolidinediyl))bis(N,N-dimethyl-2-oxo-1-phenylethanamine);

5,5'-(4,4'-biphenyldiyl)bis(2-((2S)-1-benzoyl-2-pyrrolidinyl)-1H-imidazole);
5,5'-(4,4'-biphenyldiyl)bis(2-((2S)-1-(phenylacetyl)-2-pyrrolidinyl)-1H-imidazole);
5,5'-(4,4'-biphenyldiyl)bis(2-((2S)-1-((2R)-2-methoxy-2-phenylacetyl)-2-pyrrolidinyl)-1H-imidazole);
(2R,2'R)-1,1'-(4,4'-biphenyldiylbis(1H-imidazole-5,2-diyl(2S)-2,1-pyrrolidinediyl))bis(1-oxo-3-phenyl-2-propanol);
5,5'-(4,4'-biphenyldiyl)bis(2-((2S)-1-propionyl-2-pyrrolidinyl)-1H-imidazole);
5,5'-(4,4'-biphenyldiyl)bis(2-((2S)-1-(cyclopropylcarbonyl)-2-pyrrolidinyl)-1H-imidazole);
5,5'-(4,4'-biphenyldiyl)bis(2-((2S)-1-(cyclopropylacetyl)-2-pyrrolidinyl)-1H-imidazole);
5,5'-(4,4'-biphenyldiyl)bis(2-((2S)-1-((2R)-tetrahydro-2-furanylcarbonyl)-2-pyrrolidinyl)-1H-imidazole);
2,2'-(4,4'-biphenyldiylbis(1H-imidazole-5,2-diyl(2S)-2,1-pyrrolidinediyl))bis(N,N-dimethyl-2-oxoethanamine);
(2R,2'R)-1,1'-(4,4'-biphenyldiylbis(1H-imidazole-5,2-diyl(2S)-2,1-pyrrolidinediyl))bis(1-oxo-2-propanol);
(2R,2'R)-1,1'-(4,4'-biphenyldiylbis(1H-imidazole-5,2-diyl(2S)-2,1-pyrrolidinediyl))bis(3-methyl-1-oxo-2-butanol);
5,5'-(4,4'-biphenyldiyl)bis(2-((2S)-1-((2R)-2-phenyl-2-(1-pyrrolidinyl)acetyl)-2-pyrrolidinyl)-1H-imidazole);
4,4'-(4,4'-biphenyldiylbis(1H-imidazole-5,2-diyl(2S)-2,1-pyrrolidinediyl((1R)-2-oxo-1-phenyl-2,1-ethanediyl)))dimorpholine;
5,5'-(4,4'-biphenyldiyl)bis(2-((2S)-1-(((3S)-3-fluoro-1-pyrrolidinyl)(phenyl)acetyl)-2-pyrrolidinyl)-1H-imidazole);
5,5'-(4,4'-biphenyldiyl)bis(2-((2S)-1-(((3S)-3-fluoro-1-pyrrolidinyl)(phenyl)acetyl)-2-pyrrolidinyl)-1H-imidazole);
(1R,1'R)-2,2'-(4,4'-biphenyldiylbis(1H-imidazole-5,2-diyl(2S)-2,1-pyrrolidinediyl))bis(N,N-diethyl-2-oxo-1-phenylethanamine);
(1R,1'R)-2,2'-(4,4'-biphenyldiylbis(1H-imidazole-5,2-diyl(2S)-2,1-pyrrolidinediyl))bis(N-ethyl-N-methyl-2-oxo-1-phenylethanamine);
N,N'-(4,4'-biphenyldiylbis(1H-imidazole-5,2-diyl(2S)-2,1-pyrrolidinediyl((1R)-2-oxo-1-phenyl-2,1-ethanediyl)))diformamide;

1,1'-(4,4'-biphenyldiylbis(1H-imidazole-5,2-diyl(2S)-2,1-pyrrolidinediylcarbonyl))dicyclopropanol;

1,1'-(4,4'-biphenyldiylbis(1H-imidazole-5,2-diyl(2S)-2,1-pyrrolidinediyl((1R)-2-oxo-1-phenyl-2,1-ethanediyl)))dipiperidine;

1,1'-(4,4'-biphenyldiylbis(1H-imidazole-5,2-diyl(2S)-2,1-pyrrolidinediyl((1R)-2-oxo-1-phenyl-2,1-ethanediyl)))bis(4-methyl-4-piperidinol);

dimethyl (4,4'-biphenyldiylbis(1H-imidazole-5,2-diyl(2S)-2,1-pyrrolidinediyl((1R)-1-(2-chlorophenyl)-2-oxo-2,1-ethanediyl)))biscarbamate;

N',N'''-(4,4'-biphenyldiylbis(1H-imidazole-4,2-diyl(2S)-2,1-pyrrolidinediyl((1R)-2-oxo-1-phenyl-2,1-ethanediyl)))bis(1,1-dimethylurea);

N',N'''-(4,4'-biphenyldiylbis(1H-imidazole-5,2-diyl(2S)-2,1-pyrrolidinediyl((1R)-2-oxo-1-phenyl-2,1-ethanediyl)))bis(1-methylurea);

N',N'''-(4,4'-biphenyldiylbis(1H-imidazole-5,2-diyl(2S)-2,1-pyrrolidinediyl((1R)-2-oxo-1-phenyl-2,1-ethanediyl)))bis(1-ethylurea);

N',N'''-(4,4'-biphenyldiylbis(1H-imidazole-5,2-diyl(2S)-2,1-pyrrolidinediyl((1R)-2-oxo-1-phenyl-2,1-ethanediyl)))bis(1-cyclopentylurea);

2,2'-(4,4'-biphenyldiylbis(1H-imidazole-5,2-diyl(2S)-2,1-pyrrolidinediyl))bis(N-benzyl-N-methyl-2-oxoethanamine);

(2S,2'S)-1,1'-(4,4'-biphenyldiylbis(1H-imidazole-5,2-diyl(2S)-2,1-pyrrolidinediyl))bis(N-benzyl-N-methyl-1-oxo-2-propanamine);

1,1'-(4,4'-biphenyldiylbis(1H-imidazole-5,2-diyl(2S)-2,1-pyrrolidinediyl))bis(N-benzyl-N,3-dimethyl-1-oxo-2-butanamine);

1,1'-(4,4'-biphenyldiylbis(1H-imidazole-5,2-diyl(2S)-2,1-pyrrolidinediyl(2-oxo-1-phenyl-2,1-ethanediyl)))di(4-piperidinol);

1,1'-(4,4'-biphenyldiylbis(1H-imidazole-5,2-diyl((2S,4S)-4-fluoro-2,1-pyrrolidinediyl)((1R)-2-oxo-1-phenyl-2,1-ethanediyl)))dipiperidine;

(1R,1'R)-2,2'-(4,4'-biphenyldiylbis(1H-imidazole-5,2-diyl((2S,4S)-4-fluoro-2,1-pyrrolidinediyl)))bis(N,N-diethyl-2-oxo-1-phenylethanamine);

(1R,1'R)-2,2'-(4,4'-biphenyldiylbis(1H-imidazole-5,2-diyl((2S,4S)-4-fluoro-2,1-pyrrolidinediyl)))bis(N,N-dimethyl-2-oxo-1-phenylethanamine);

1,1'-(4,4'-biphenyldiylbis(1H-imidazole-4,2-diyl((2S)-4,4-difluoro-2,1-pyrrolidinediyl)((1R)-2-oxo-1-phenyl-2,1-ethanediyl)))dipiperidine;

dimethyl (4,4'-biphenyldiylbis(1H-imidazole-4,2-diyl((2S)-4,4-difluoro-2,1-pyrrolidinediyl)((1R)-2-oxo-1-phenyl-2,1-ethanediyl)))biscarbamate;
1-((1R)-2-((2S)-2-(4-(4'-(2-((2S)-4,4-difluoro-1-((2R)-2-phenyl-2-(1-piperidinyl)acetyl)-2-pyrrolidinyl)-1H-imidazol-4-yl)-4-biphenylyl)-1H-imidazol-2-yl)-1-pyrrolidinyl)-2-oxo-1-phenylethyl)piperidine;
dimethyl (4,4'-biphenyldiylbis(1H-imidazole-5,2-diyl((2S,4R)-4-hydroxy-2,1-pyrrolidinediyl)((1R)-2-oxo-1-phenyl-2,1-ethanediyl)))biscarbamate;
(3R,5S,3'R,5'S)-5,5'-(4,4'-biphenyldiylbis(1H-imidazole-5,2-diyl))bis(1-((2R)-2-hydroxy-2-phenylacetyl)-3-pyrrolidinol);
N,N''-(4,4'-biphenyldiylbis(1H-imidazole-5,2-diyl((2S,4R)-4-hydroxy-2,1-pyrrolidinediyl)((1R)-2-oxo-1-phenyl-2,1-ethanediyl)))bis(3-methylurea);
N',N'''-(4,4'-biphenyldiylbis(1H-imidazole-5,2-diyl((2S,4R)-4-hydroxy-2,1-pyrrolidinediyl)((1R)-2-oxo-1-phenyl-2,1-ethanediyl)))bis(1-ethylurea);
N',N'''-(4,4'-biphenyldiylbis(1H-imidazole-5,2-diyl((2S,4R)-4-hydroxy-2,1-pyrrolidinediyl)((1R)-2-oxo-1-phenyl-2,1-ethanediyl)))bis(1-cyclopentylurea);
(3S,5S,3'S,5'S)-5,5'-(4,4'-biphenyldiylbis(1H-imidazole-5,2-diyl))bis(1-((2R)-2-(dimethylamino)-2-phenylacetyl)-3-pyrrolidinol);
dimethyl (4,4'-biphenyldiylbis(1H-imidazole-5,2-diyl((2S,4S)-4-hydroxy-2,1-pyrrolidinediyl)((1R)-2-oxo-1-phenyl-2,1-ethanediyl)))biscarbamate;
(3S,5S,3'S,5'S)-5,5'-(4,4'-biphenyldiylbis(1H-imidazole-5,2-diyl))bis(1-((2R)-2-hydroxy-2-phenylacetyl)-3-pyrrolidinol);
N,N'-(4,4'-biphenyldiylbis(1H-imidazole-5,2-diyl(2S)-2,1-pyrrolidinediyl((1R)-2-oxo-1-phenyl-2,1-ethanediyl)))diacetamide;
di-tert-butyl (4,4'-biphenyldiylbis(1H-imidazole-5,2-diyl(2S)-2,1-pyrrolidinediyl((1R)-2-oxo-1-phenyl-2,1-ethanediyl)))biscarbamate;
(2R,2'R)-N,N'-(4,4'-biphenyldiylbis(1H-imidazole-5,2-diyl(2S)-2,1-pyrrolidinediyl((1R)-2-oxo-1-phenyl-2,1-ethanediyl)))ditetrahydro-2-furancarboxamide;
N,N'-(4,4'-biphenyldiylbis(1H-imidazole-5,2-diyl(2S)-2,1-pyrrolidinediyl((1R)-2-oxo-1-phenyl-2,1-ethanediyl)))bis(1-methyl-1H-imidazole-5-carboxamide) (2S,2'S)-N,N'-(4,4'-biphenyldiylbis(1H-imidazole-5,2-diyl(2S)-2,1-pyrrolidinediyl((1R)-2-oxo-1-phenyl-2,1-ethanediyl)))bis(1-methyl-2-pyrrolidinecarboxamide);

N,N'-(4,4'-biphenyldiylbis(1H-imidazole-5,2-diyl(2S)-2,1-pyrrolidinediyl((1R)-2-oxo-1-phenyl-2,1-ethanediyl)))bis(2-(3-pyridinyl)acetamide);

N,N'-(4,4'-biphenyldiylbis(1H-imidazole-5,2-diyl(2S)-2,1-pyrrolidinediyl((1R)-2-oxo-1-phenyl-2,1-ethanediyl)))bis(2-(dimethylamino)acetamide);

N,N'-(4,4'-biphenyldiylbis(1H-imidazole-5,2-diyl(2S)-2,1-pyrrolidinediyl((1R)-2-oxo-1-phenyl-2,1-ethanediyl)))di(4-morpholinecarboxamide);

N,N'-(4,4'-biphenyldiylbis(1H-imidazole-5,2-diyl(2S)-2,1-pyrrolidinediyl((1R)-2-oxo-1-phenyl-2,1-ethanediyl)))bis(4-methyl-1-piperazinecarboxamide);

N,N''-(4,4'-biphenyldiylbis(1H-imidazole-5,2-diyl(2S)-2,1-pyrrolidinediyl((1R)-2-oxo-1-phenyl-2,1-ethanediyl)))bis(3-(3-pyridinyl)urea);

methyl ((1R)-1-(((2S)-2-(5-(4'-(2-((2S)-1-((2R)-2-((methoxycarbonyl)amino)-3-methylbutanoyl)-2-pyrrolidinyl)-1H-imidazol-5-yl)-4-biphenylyl)-1H-imidazol-2-yl)-1-pyrrolidinyl)carbonyl)-2-methylpropyl)carbamate;

(2R,2'R)-1,1'-(4,4'-biphenyldiylbis(1H-imidazole-5,2-diyl(2S)-2,1-pyrrolidinediyl))bis(3-methyl-1-oxo-2-butanamine);

N-((1R)-1-(((2S)-2-(5-(4'-(2-((2S)-1-((2R)-2-acetamido-3-methylbutanoyl)-2-pyrrolidinyl)-1H-imidazol-5-yl)-4-biphenylyl)-1H-imidazol-2-yl)-1-pyrrolidinyl)carbonyl)-2-methylpropyl)acetamide;

methyl ((1R)-2-oxo-1-phenyl-2-((2S)-2-(5-(4'-(2-((2S)-1-(phenylacetyl)-2-pyrrolidinyl)-1H-imidazol-5-yl)-4-biphenylyl)-1H-imidazol-2-yl)-1-pyrrolidinyl)ethyl)carbamate;

benzyl tert-butyl (2S,2'S)-2,2'-(4,4'-biphenyldiylbis(1H-imidazole-5,2-diyl))di(1-pyrrolidinecarboxylate);

tert-butyl (2S)-2-(5-(4'-(2-((2S)-2-pyrrolidinyl)-1H-imidazol-5-yl)-4-biphenylyl)-1H-imidazol-2-yl)-1-pyrrolidinecarboxylate;

tert-butyl (2S)-2-(5-(4'-(2-((2S)-1-((2R)-2-((methoxycarbonyl)amino)-2-phenylacetyl)-2-pyrrolidinyl)-1H-imidazol-5-yl)-4-biphenylyl)-1H-imidazol-2-yl)-1-pyrrolidinecarboxylate;

methyl ((1R)-2-oxo-1-phenyl-2-((2S)-2-(5-(4'-(2-((2S)-2-pyrrolidinyl)-1H-imidazol-5-yl)-4-biphenylyl)-1H-imidazol-2-yl)-1-pyrrolidinyl)ethyl)carbamate;

(1R)-N,N-dimethyl-2-oxo-1-phenyl-2-((2S)-2-(5-(4'-(2-((2S)-1-((2R)-2-phenyl-2-(1-piperidinyl)acetyl)-2-pyrrolidinyl)-1H-imidazol-5-yl)-4-biphenylyl)-1H-imidazol-2-yl)-1-pyrrolidinyl)ethanamine;

1-((1R)-2-oxo-1-phenyl-2-((2S)-2-(5-(4'-(2-((2S)-1-((2R)-tetrahydro-2-furanylcarbonyl)-2-pyrrolidinyl)-1H-imidazol-5-yl)-4-biphenylyl)-1H-imidazol-2-yl)-1-pyrrolidinyl)ethyl)piperidine;

methyl ((1R)-1-(2-chlorophenyl)-2-oxo-2-((2S)-2-(5-(4'-(2-((2S)-1-((2R)-2-phenyl-2-(1-piperidinyl)acetyl)-2-pyrrolidinyl)-1H-imidazol-5-yl)-4-biphenylyl)-1H-imidazol-2-yl)-1-pyrrolidinyl)ethyl)carbamate;

(1R)-1-(2-chlorophenyl)-N,N-dimethyl-2-oxo-2-((2S)-2-(5-(4'-(2-((2S)-1-((2R)-2-phenyl-2-(1-piperidinyl)acetyl)-2-pyrrolidinyl)-1H-imidazol-5-yl)-4-biphenylyl)-1H-imidazol-2-yl)-1-pyrrolidinyl)ethanamine;

(1R)-1-(2-fluorophenyl)-N,N-dimethyl-2-oxo-2-((2S)-2-(5-(4'-(2-((2S)-1-((2R)-2-phenyl-2-(1-piperidinyl)acetyl)-2-pyrrolidinyl)-1H-imidazol-5-yl)-4-biphenylyl)-1H-imidazol-2-yl)-1-pyrrolidinyl)ethanamine;

(1R)-N,N-dimethyl-2-oxo-1-phenyl-2-((2S)-2-(5-(4'-(2-((2S)-1-((2R)-2-phenyl-2-(1-piperidinyl)acetyl)-2-pyrrolidinyl)-1H-imidazol-5-yl)-4-biphenylyl)-1H-imidazol-2-yl)-1-pyrrolidinyl)ethanamine;

1-((1R)-2-oxo-1-phenyl-2-((2S)-2-(5-(4'-(2-((2S)-1-((2R)-tetrahydro-2-furanylcarbonyl)-2-pyrrolidinyl)-1H-imidazol-5-yl)-4-biphenylyl)-1H-imidazol-2-yl)-1-pyrrolidinyl)ethyl)piperidine;

methyl ((1R)-1-(2-chlorophenyl)-2-oxo-2-((2S)-2-(5-(4'-(2-((2S)-1-((2R)-2-phenyl-2-(1-piperidinyl)acetyl)-2-pyrrolidinyl)-1H-imidazol-5-yl)-4-biphenylyl)-1H-imidazol-2-yl)-1-pyrrolidinyl)ethyl)carbamate;

(1R)-1-(2-chlorophenyl)-N,N-dimethyl-2-oxo-2-((2S)-2-(5-(4'-(2-((2S)-1-((2R)-2-phenyl-2-(1-piperidinyl)acetyl)-2-pyrrolidinyl)-1H-imidazol-5-yl)-4-biphenylyl)-1H-imidazol-2-yl)-1-pyrrolidinyl)ethanamine;

(1R)-1-(2-fluorophenyl)-N,N-dimethyl-2-oxo-2-((2S)-2-(5-(4'-(2-((2S)-1-((2R)-2-phenyl-2-(1-piperidinyl)acetyl)-2-pyrrolidinyl)-1H-imidazol-5-yl)-4-biphenylyl)-1H-imidazol-2-yl)-1-pyrrolidinyl)ethanamine;

methyl ((1R)-2-((2S)-2-(5-(4'-(2-((2S)-1-((4-methyl-1-piperazinyl)carbonyl)-2-pyrrolidinyl)-1H-imidazol-5-yl)-4-biphenylyl)-1H-imidazol-2-yl)-1-pyrrolidinyl)-2-oxo-1-phenylethyl)carbamate;

methyl ((1R)-2-((2S)-2-(5-(4'-(2-((2S)-1-glycyl-2-pyrrolidinyl)-1H-imidazol-5-yl)-4-biphenylyl)-1H-imidazol-2-yl)-1-pyrrolidinyl)-2-oxo-1-phenylethyl)carbamate;

methyl ((1R)-2-((2S)-2-(5-(4'-(2-((2S)-1-(N-(tert-butoxycarbonyl)glycyl)-2-pyrrolidinyl)-1H-imidazol-5-yl)-4-biphenylyl)-1H-imidazol-2-yl)-1-pyrrolidinyl)-2-oxo-1-phenylethyl)carbamate;

methyl ((1S)-2-((2S)-2-(5-(4'-(2-((2S)-1-((2R)-2-(diethylamino)-2-phenylacetyl)-2-pyrrolidinyl)-1H-imidazol-5-yl)-4-biphenylyl)-1H-imidazol-2-yl)-1-pyrrolidinyl)-1-methyl-2-oxoethyl)carbamate;

methyl ((1R)-2-((2S)-2-(5-(4'-(2-((2S)-1-acetyl-2-pyrrolidinyl)-1H-imidazol-5-yl)-4-biphenylyl)-1H-imidazol-2-yl)-1-pyrrolidinyl)-2-oxo-1-phenylethyl)carbamate;

methyl ((1R)-2-oxo-1-phenyl-2-((2S)-2-(5-(4'-(2-((2S)-1-propionyl-2-pyrrolidinyl)-1H-imidazol-5-yl)-4-biphenylyl)-1H-imidazol-2-yl)-1-pyrrolidinyl)ethyl)carbamate;

methyl ((1R)-2-((2S)-2-(5-(4'-(2-((2S)-1-(cyclopropylcarbonyl)-2-pyrrolidinyl)-1H-imidazol-5-yl)-4-biphenylyl)-1H-imidazol-2-yl)-1-pyrrolidinyl)-2-oxo-1-phenylethyl)carbamate;

methyl ((1R)-2-((2S)-2-(5-(4'-(2-((2S)-1-(cyclopropylacetyl)-2-pyrrolidinyl)-1H-imidazol-5-yl)-4-biphenylyl)-1H-imidazol-2-yl)-1-pyrrolidinyl)-2-oxo-1-phenylethyl)carbamate;

methyl ((1R)-2-((2S)-2-(5-(4'-(2-((2S)-1-((2R)-2-hydroxypropanoyl)-2-pyrrolidinyl)-1H-imidazol-5-yl)-4-biphenylyl)-1H-imidazol-2-yl)-1-pyrrolidinyl)-2-oxo-1-phenylethyl)carbamate;

methyl ((1R)-2-oxo-1-phenyl-2-((2S)-2-(5-(4'-(2-((2S)-1-((2R)-tetrahydro-2-furanylcarbonyl)-2-pyrrolidinyl)-1H-imidazol-5-yl)-4-biphenylyl)-1H-imidazol-2-yl)-1-pyrrolidinyl)ethyl)carbamate;

methyl ((1R)-2-((2S)-2-(5-(4'-(2-((2S)-1-(N,N-dimethylglycyl)-2-pyrrolidinyl)-1H-imidazol-5-yl)-4-biphenylyl)-1H-imidazol-2-yl)-1-pyrrolidinyl)-2-oxo-1-phenylethyl)carbamate;

methyl ((1R)-2-((2S)-2-(5-(4'-(2-((2S)-1-((2S)-2-(dimethylamino)-2-phenylacetyl)-2-pyrrolidinyl)-1H-imidazol-5-yl)-4-biphenylyl)-1H-imidazol-2-yl)-1-pyrrolidinyl)-2-oxo-1-phenylethyl)carbamate;

methyl ((1R)-2-((2S)-2-(5-(4'-(2-((2S)-1-(4-morpholinylacetyl)-2-pyrrolidinyl)-1H-imidazol-5-yl)-4-biphenylyl)-1H-imidazol-2-yl)-1-pyrrolidinyl)-2-oxo-1-phenylethyl)carbamate;

methyl (2-((2S)-2-(5-(4'-(2-((2S)-1-((2R)-2-((methoxycarbonyl)amino)-2-phenylacetyl)-2-pyrrolidinyl)-1H-imidazol-5-yl)-4-biphenylyl)-1H-imidazol-2-yl)-1-pyrrolidinyl)-2-oxocthyl)carbamatc;

methyl ((1R)-2-((2S)-2-(5-(4'-(2-((2S)-1-(N-acetylglycyl)-2-pyrrolidinyl)-1H-imidazol-5-yl)-4-biphenylyl)-1H-imidazol-2-yl)-1-pyrrolidinyl)-2-oxo-1-phenylethyl)carbamate;

mcthyl ((1R)-2-((2S)-2-(5-(4'-(2-((2S)-1-((2R)-2-(dimcthylamino)-2-phcnylacctyl)-2-pyrrolidinyl)-1H-imidazol-5-yl)-4-biphenylyl)-1H-imidazol-2-yl)-1-pyrrolidinyl)-2-oxo-1-phenylethyl)carbamate;

methyl ((1R)-2-((2S)-2-(5-(4'-(2-((2S)-1-((2R)-2-hydroxy-2-phenylacetyl)-2-pyrrolidinyl)-1H-imidazol-5-yl)-4-biphenylyl)-1H-imidazol-2-yl)-1-pyrrolidinyl)-2-oxo-1-phenylethyl)carbamate;

methyl ((1R)-2-((2S)-2-(5-(4'-(2-((2S)-1-((1-methyl-4-piperidinyl)carbonyl)-2-pyrrolidinyl)-1H-imidazol-5-yl)-4-biphenylyl)-1H-imidazol-2-yl)-1-pyrrolidinyl)-2-oxo-1-phenylethyl)carbamate;

methyl ((1R)-2-oxo-1-phenyl-2-((2S)-2-(5-(4'-(2-((2S)-1-(tetrahydro-2H-pyran-4-ylcarbonyl)-2-pyrrolidinyl)-1H-imidazol-5-yl)-4-biphenylyl)-1H-imidazol-2-yl)-1-pyrrolidinyl)ethyl)carbamate;

methyl ((1R)-2-oxo-1-phenyl-2-((2S)-2-(5-(4'-(2-((2S)-1-(2-pyridinylacetyl)-2-pyrrolidinyl)-1H-imidazol-5-yl)-4-biphenylyl)-1H-imidazol-2-yl)-1-pyrrolidinyl)ethyl)carbamate;

methyl ((1R)-2-oxo-1-phenyl-2-((2S)-2-(5-(4'-(2-((2S)-1-(3-pyridinylacetyl)-2-pyrrolidinyl)-1H-imidazol-5-yl)-4-biphenylyl)-1H-imidazol-2-yl)-1-pyrrolidinyl)ethyl)carbamate;

methyl ((1R)-2-oxo-1-phenyl-2-((2S)-2-(5-(4'-(2-((2S)-1-(4-pyridinylacetyl)-2-pyrrolidinyl)-1H-imidazol-5-yl)-4-biphenylyl)-1H-imidazol-2-yl)-1-pyrrolidinyl)ethyl)carbamate;

methyl ((1R)-2-((2S)-2-(5-(4'-(2-((2S)-1-((1-methyl-1H-imidazol-5-yl)carbonyl)-2-pyrrolidinyl)-1H-imidazol-5-yl)-4-biphenylyl)-1H-imidazol-2-yl)-1-pyrrolidinyl)-2-oxo-1-phenylethyl)carbamate;

methyl ((1R)-2-((2S)-2-(5-(4'-(2-((2S)-1-(dimethylcarbamoyl)-2-pyrrolidinyl)-1H-imidazol-5-yl)-4-biphenylyl)-1H-imidazol-2-yl)-1-pyrrolidinyl)-2-oxo-1-phenylethyl)carbamate;

methyl ((1R)-2-((2S)-2-(5-(4'-(2-((2S)-1-(1-methyl-D-prolyl)-2-pyrrolidinyl)-1H-imidazol-5-yl)-4-biphenylyl)-1H-imidazol-2-yl)-1-pyrrolidinyl)-2-oxo-1-phenylethyl)carbamate;

methyl ((1R)-2-((2S)-2-(5-(4'-(2-((2S)-1-(1-methyl-L-prolyl)-2-pyrrolidinyl)-1H-imidazol-5-yl)-4-biphenylyl)-1H-imidazol-2-yl)-1-pyrrolidinyl)-2-oxo-1-phenylethyl)carbamate;

methyl ((1R)-2-((2S)-2-(5-(4'-(2-((2S)-1-(N-acetyl-D-alanyl)-2-pyrrolidinyl)-1H-imidazol-5-yl)-4-biphenylyl)-1H-imidazol-2-yl)-1-pyrrolidinyl)-2-oxo-1-phenylethyl)carbamate;

methyl ((1R)-2-((2S)-2-(5-(4'-(2-((2S)-1-(N-acetyl-L-alanyl)-2-pyrrolidinyl)-1H-imidazol-5-yl)-4-biphenylyl)-1H-imidazol-2-yl)-1-pyrrolidinyl)-2-oxo-1-phenylethyl)carbamate;

methyl ((1R)-2-((2S)-2-(5-(4'-(2-((2S)-1-(methoxyacetyl)-2-pyrrolidinyl)-1H-imidazol-5-yl)-4-biphenylyl)-1H-imidazol-2-yl)-1-pyrrolidinyl)-2-oxo-1-phenylethyl)carbamate;

methyl ((1R)-2-((2S)-2-(5-(4'-(2-((2S)-1-((2R)-2-hydroxybutanoyl)-2-pyrrolidinyl)-1H-imidazol-5-yl)-4-biphenylyl)-1H-imidazol-2-yl)-1-pyrrolidinyl)-2-oxo-1-phenylethyl)carbamate;

methyl ((1R)-2-((2S)-2-(5-(4'-(2-((2S)-1-((4-methyl-1-piperazinyl)acetyl)-2-pyrrolidinyl)-1H-imidazol-5-yl)-4-biphenylyl)-1H-imidazol-2-yl)-1-pyrrolidinyl)-2-oxo-1-phenylethyl)carbamate;

methyl ((1R)-2-oxo-1-phenyl-2-((2S)-2-(5-(4'-(2-((2S)-1-(1-pyrrolidinylacetyl)-2-pyrrolidinyl)-1H-imidazol-5-yl)-4-biphenylyl)-1H-imidazol-2-yl)-1-pyrrolidinyl)ethyl)carbamate;

methyl ((1R)-2-oxo-1-phenyl-2-((2S)-2-(5-(4'-(2-((2S)-1-((2S)-tetrahydro-2-furanylcarbonyl)-2-pyrrolidinyl)-1H-imidazol-5-yl)-4-biphenylyl)-1H-imidazol-2-yl)-1-pyrrolidinyl)ethyl)carbamate;

methyl ((1R)-2-((2S)-2-(5-(4'-(2-((2S)-1-((1-hydroxycyclopropyl)carbonyl)-2-pyrrolidinyl)-1H-imidazol-5-yl)-4-biphenylyl)-1H-imidazol-2-yl)-1-pyrrolidinyl)-2-oxo-1-phenylethyl)carbamate;

methyl ((1R)-2-((2S)-2-(5-(4'-(2-((2S)-1-(1H-imidazol-5-ylacetyl)-2-pyrrolidinyl)-1H-imidazol-5-yl)-4-biphenylyl)-1H-imidazol-2-yl)-1-pyrrolidinyl)-2-oxo-1-phenylethyl)carbamate;

methyl ((1R)-2-((2S)-2-(5-(4'-(2-((2S)-1-((1-methyl-1H-imidazol-4-yl)acetyl)-2-pyrrolidinyl)-1H-imidazol-5-yl)-4-biphenylyl)-1H-imidazol-2-yl)-1-pyrrolidinyl)-2-oxo-1-phenylethyl)carbamate;

methyl ((1R)-2-((2S)-2-(5-(4'-(2-((2S)-1-(1H-imidazol-2-ylcarbonyl)-2-pyrrolidinyl)-1H-imidazol-5-yl)-4-biphenylyl)-1H-imidazol-2-yl)-1-pyrrolidinyl)-2-oxo-1-phenylethyl)carbamate;

methyl ((1R)-2-((2S)-2-(5-(4'-(2-((2S)-1-((4-hydroxy-1-piperidinyl)(phenyl)acetyl)-2-pyrrolidinyl)-1H-imidazol-5-yl)-4-biphenylyl)-1H-imidazol-2-yl)-1-pyrrolidinyl)-2-oxo-1-phenylethyl)carbamate;

methyl ((1R)-2-oxo-1-phenyl-2-((2S)-2-(5-(4'-(2-((2S)-1-(1H-tetrazol-5-ylacetyl)-2-pyrrolidinyl)-1H-imidazol-5-yl)-4-biphenylyl)-1H-imidazol-2-yl)-1-pyrrolidinyl)ethyl)carbamate;

methyl ((1R)-2-oxo-1-phenyl-2-((2S)-2-(5-(4'-(2-((2S)-1-(2-pyridinylcarbonyl)-2-pyrrolidinyl)-1H-imidazol-5-yl)-4-biphenylyl)-1H-imidazol-2-yl)-1-pyrrolidinyl)ethyl)carbamate;

methyl ((1R)-2-oxo-1-phenyl-2-((2S)-2-(5-(4'-(2-((2S)-1-(3-pyridinylcarbonyl)-2-pyrrolidinyl)-1H-imidazol-5-yl)-4-biphenylyl)-1H-imidazol-2-yl)-1-pyrrolidinyl)ethyl)carbamate;

methyl ((1R)-2-((2S)-2-(5-(4'-(2-((2S)-1-isonicotinoyl-2-pyrrolidinyl)-1H-imidazol-5-yl)-4-biphenylyl)-1H-imidazol-2-yl)-1-pyrrolidinyl)-2-oxo-1-phenylethyl)carbamate;

methyl ((1R)-2-((2S)-2-(5-(4'-(2-((2S)-1-((4R)-4-fluoro-1-methyl-L-prolyl)-2-pyrrolidinyl)-1H-imidazol-5-yl)-4-biphenylyl)-1H-imidazol-2-yl)-1-pyrrolidinyl)-2-oxo-1-phenylethyl)carbamate;

methyl ((1R)-2-((2S)-2-(5-(4'-(2-((2S)-1-(1,3-oxazol-2-ylcarbonyl)-2-pyrrolidinyl)-1H-imidazol-5-yl)-4-biphenylyl)-1H-imidazol-2-yl)-1-pyrrolidinyl)-2-oxo-1-phenylethyl)carbamate;

methyl ((1R)-2-((2S)-2-(5-(4'-(2-((2S)-1-(1,3-oxazol-5-ylcarbonyl)-2-pyrrolidinyl)-1H-imidazol-5-yl)-4-biphenylyl)-1H-imidazol-2-yl)-1-pyrrolidinyl)-2-oxo-1-phenylethyl)carbamate;

methyl ((1R)-2-((2S)-2-(5-(4'-(2-((2S)-1-((dimethylamino)(oxo)acetyl)-2-pyrrolidinyl)-1H-imidazol-5-yl)-4-biphenylyl)-1H-imidazol-2-yl)-1-pyrrolidinyl)-2-oxo-1-phenylethyl)carbamate;

methyl ((1R)-2-oxo-1-phenyl-2-((2S)-2-(5-(4'-(2-((2S)-1-(tetrahydro-3-furanylcarbonyl)-2-pyrrolidinyl)-1H-imidazol-5-yl)-4-biphenylyl)-1H-imidazol-2-yl)-1-pyrrolidinyl)ethyl)carbamate;

methyl ((1R)-2-((2S)-2-(5-(4'-(2-((2S)-1-(N-(methoxycarbonyl)-L-alanyl)-2-pyrrolidinyl)-1H-imidazol-5-yl)-4-biphenylyl)-1H-imidazol-2-yl)-1-pyrrolidinyl)-2-oxo-1-phenylethyl)carbamate;

methyl ((1R)-2-((2S)-2-(5-(4'-(2-((2S)-1-(N,N-dimethyl-L-alanyl)-2-pyrrolidinyl)-1H-imidazol-5-yl)-4-biphenylyl)-1H-imidazol-2-yl)-1-pyrrolidinyl)-2-oxo-1-phenylethyl)carbamate;

methyl (2S)-2-(5-(4'-(2-((2S)-1-((2R)-2-((methoxycarbonyl)amino)-2-phenylacetyl)-2-pyrrolidinyl)-1H-imidazol-5-yl)-4-biphenylyl)-1H-imidazol-2-yl)-1-pyrrolidinecarboxylate;

methyl ((1R)-2-((2S)-2-(5-(4'-(2-((2S)-1-(4-morpholinylcarbonyl)-2-pyrrolidinyl)-1H-imidazol-5-yl)-4-biphenylyl)-1H-imidazol-2-yl)-1-pyrrolidinyl)-2-oxo-1-phenylethyl)carbamate;

methyl ((1R)-2-((2S)-2-(5-(4'-(2-((2S)-1-((4S)-4-fluoro-L-prolyl)-2-pyrrolidinyl)-1H-imidazol-5-yl)-4-biphenylyl)-1H-imidazol-2-yl)-1-pyrrolidinyl)-2-oxo-1-phenylethyl)carbamate;

methyl ((1R)-2-oxo-1-phenyl-2-((2S)-2-(5-(4'-(2-((2S)-1-L-prolyl-2-pyrrolidinyl)-1H-imidazol-5-yl)-4-biphenylyl)-1H-imidazol-2-yl)-1-pyrrolidinyl)ethyl)carbamate;

methyl ((1R)-2-((2S)-2-(5-(4'-(2-((2S)-1-(4,4-difluoro-L-prolyl)-2-pyrrolidinyl)-1H-imidazol-5-yl)-4-biphenylyl)-1H-imidazol-2-yl)-1-pyrrolidinyl)-2-oxo-1-phenylethyl)carbamate;

methyl ((1R)-2-((2S)-2-(5-(4'-(2-((2S)-1-((4R)-4-fluoro-L-prolyl)-2-pyrrolidinyl)-1H-imidazol-5-yl)-4-biphenylyl)-1H-imidazol-2-yl)-1-pyrrolidinyl)-2-oxo-1-phenylethyl)carbamate;

methyl ((1R)-2-((2S)-2-(5-(4'-(2-((2S)-1-((1S,3S,5S)-2-azabicyclo[3.1.0]hex-3-ylcarbonyl)-2-pyrrolidinyl)-1H-imidazol-5-yl)-4-biphenylyl)-1H-imidazol-2-yl)-1-pyrrolidinyl)-2-oxo-1-phenylethyl)carbamate;

methyl ((1R)-2-((2S)-2-(5-(4'-(2-((2S)-1-L-alanyl-2-pyrrolidinyl)-1H-imidazol-5-yl)-4-biphenylyl)-1H-imidazol-2-yl)-1-pyrrolidinyl)-2-oxo-1-phenylethyl)carbamate;

methyl ((1R)-2-oxo-1-phenyl-2-((2S)-2-(5-(4'-(2-((2S)-1-((2R)-2-phenyl-2-(1-piperidinyl)acetyl)-2-pyrrolidinyl)-1H-imidazol-5-yl)-4-biphenylyl)-1H-imidazol-2-yl)-1-pyrrolidinyl)ethyl)carbamate;

methyl ((1R)-2-((2S)-2-(5-(4'-(2-((2S)-1-((2S)-2-(2-fluorophenyl)-2-hydroxypropanoyl)-2-pyrrolidinyl)-1H-imidazol-5-yl)-4-biphenylyl)-1H-imidazol-2-yl)-1-pyrrolidinyl)-2-oxo-1-phenylethyl)carbamate;

methyl ((1R)-2-oxo-2-((2S)-2-(5-(4'-(2-((2S)-1-(5-oxo-D-prolyl)-2-pyrrolidinyl)-1H-imidazol-5-yl)-4-biphenylyl)-1H-imidazol-2-yl)-1-pyrrolidinyl)-1-phenylethyl)carbamate;

methyl ((1R)-2-((2S)-2-(5-(4'-(2-((2S)-1-((2R)-2-(4-hydroxy-4-methyl-1-piperidinyl)-2-phenylacetyl)-2-pyrrolidinyl)-1H-imidazol-5-yl)-4-biphenylyl)-1H-imidazol-2-yl)-1-pyrrolidinyl)-2-oxo-1-phenylethyl)carbamate;

tert-butyl (4R)-4-(((2S)-2-(5-(4'-(2-((2S)-1-((2R)-2-((methoxycarbonyl)amino)-2-phenylacetyl)-2-pyrrolidinyl)-1H-imidazol-5-yl)-4-biphenylyl)-1H-imidazol-2-yl)-1-pyrrolidinyl)carbonyl)-1,3-thiazolidine-3-carboxylate;

methyl ((1R)-2-((2S)-2-(5-(4'-(2-((2S)-1-((1-((tert-butoxycarbonyl)amino)cyclopentyl)carbonyl)-2-pyrrolidinyl)-1H-imidazol-5-yl)-4-biphenylyl)-1H-imidazol-2-yl)-1-pyrrolidinyl)-2-oxo-1-phenylethyl)carbamate;

methyl ((1R)-2-((2S)-2-(5-(4'-(2-((2S)-1-(N-benzoylglycyl)-2-pyrrolidinyl)-1H-imidazol-5-yl)-4-biphenylyl)-1H-imidazol-2-yl)-1-pyrrolidinyl)-2-oxo-1-phenylethyl)carbamate;

methyl ((1R)-2-((2S)-2-(5-(4'-(2-((2S)-1-(4-(4-methyl-1-piperazinyl)benzoyl)-2-pyrrolidinyl)-1H-imidazol-5-yl)-4-biphenylyl)-1H-imidazol-2-yl)-1-pyrrolidinyl)-2-oxo-1-phenylethyl)carbamate;

methyl ((1R)-2-oxo-1-phenyl-2-((2S)-2-(5-(4'-(2-((2S)-1-((5-phenyl-2-thienyl)carbonyl)-2-pyrrolidinyl)-1H-imidazol-5-yl)-4-biphenylyl)-1H-imidazol-2-yl)-1-pyrrolidinyl)ethyl)carbamate;

methyl ((1R)-2-oxo-1-phenyl-2-((2S)-2-(5-(4'-(2-((2S)-1-((4-phenyl-1,2,3-thiadiazol-5-yl)carbonyl)-2-pyrrolidinyl)-1H-imidazol-5-yl)-4-biphenylyl)-1H-imidazol-2-yl)-1-pyrrolidinyl)ethyl)carbamate;

methyl ((1R)-2-oxo-1-phenyl-2-((2S)-2-(5-(4'-(2-((2S)-1-((2-phenyl-1,3-thiazol-4-yl)carbonyl)-2-pyrrolidinyl)-1H-imidazol-5-yl)-4-biphenylyl)-1H-imidazol-2-yl)-1-pyrrolidinyl)ethyl)carbamate;

tert-butyl 4-(((2S)-2-(5-(4'-(2-((2S)-1-((2R)-2-((methoxycarbonyl)amino)-2-phenylacetyl)-2-pyrrolidinyl)-1H-imidazol-5-yl)-4-biphenylyl)-1H-imidazol-2-yl)-1-pyrrolidinyl)carbonyl)-4-methyl-1-piperidinecarboxylate;

methyl ((1R)-2-((2S)-2-(5-(4'-(2-((2S)-1-(4-(dimethylamino)butanoyl)-2-pyrrolidinyl)-1H-imidazol-5-yl)-4-biphenylyl)-1H-imidazol-2-yl)-1-pyrrolidinyl)-2-oxo-1-phenylethyl)carbamate;

methyl ((1R)-2-((2S)-2-(5-(4'-(2-((2S)-1-((3-hydroxyphenyl)acetyl)-2-pyrrolidinyl)-1H-imidazol-5-yl)-4-biphenylyl)-1H-imidazol-2-yl)-1-pyrrolidinyl)-2-oxo-1-phenylethyl)carbamate;

methyl ((1R)-2-((2S)-2-(5-(4'-(2-((2S)-1-(N,N-dimethyl-beta-alanyl)-2-pyrrolidinyl)-1H-imidazol-5-yl)-4-biphenylyl)-1H-imidazol-2-yl)-1-pyrrolidinyl)-2-oxo-1-phenylethyl)carbamate;

methyl ((1R)-2-((2S)-2-(5-(4'-(2-((2S)-1-(4-(hydroxymethyl)benzoyl)-2-pyrrolidinyl)-1H-imidazol-5-yl)-4-biphenylyl)-1H-imidazol-2-yl)-1-pyrrolidinyl)-2-oxo-1-phenylethyl)carbamate;

methyl ((1R)-2-((2S)-2-(5-(4'-(2-((2S)-1-(((3R)-1-benzyl-3-pyrrolidinyl)carbonyl)-2-pyrrolidinyl)-1H-imidazol-5-yl)-4-biphenylyl)-1H-imidazol-2-yl)-1-pyrrolidinyl)-2-oxo-1-phenylethyl)carbamate;

tert-butyl (2S)-2-(2-((2S)-2-(5-(4'-(2-((2S)-1-((2R)-2-((methoxycarbonyl)amino)-2-phenylacetyl)-2-pyrrolidinyl)-1H-imidazol-5-yl)-4-biphenylyl)-1H-imidazol-2-yl)-1-pyrrolidinyl)-2-oxoethyl)-1-pyrrolidinecarboxylate;

methyl ((1R)-2-((2S)-2-(5-(4'-(2-((2S)-1-((5-methyl-1H-pyrazol-3-yl)acetyl)-2-pyrrolidinyl)-1H-imidazol-5-yl)-4-biphenylyl)-1H-imidazol-2-yl)-1-pyrrolidinyl)-2-oxo-1-phenylethyl)carbamate;

methyl ((1R)-2-((2S)-2-(5-(4'-(2-((2S)-1-(((3S)-7-hydroxy-1,2,3,4-tetrahydro-3-isoquinolinyl)carbonyl)-2-pyrrolidinyl)-1H-imidazol-5-yl)-4-biphenylyl)-1H-imidazol-2-yl)-1-pyrrolidinyl)-2-oxo-1-phenylethyl)carbamate;

tert-butyl (2R)-2-(((2S)-2-(5-(4'-(2-((2S)-1-((2R)-2-((methoxycarbonyl)amino)-2-phenylacetyl)-2-pyrrolidinyl)-1H-imidazol-5-yl)-4-biphenylyl)-1H-imidazol-2-yl)-1-pyrrolidinyl)carbonyl)-1-piperidinecarboxylate;

methyl ((1R)-2-oxo-1-phenyl-2-((2S)-2-(5-(4'-(2-((2S)-1-((5-phenyl-4-isoxazolyl)carbonyl)-2-pyrrolidinyl)-1H-imidazol-5-yl)-4-biphenylyl)-1H-imidazol-2-yl)-1-pyrrolidinyl)ethyl)carbamate;

methyl ((1R)-2-((2S)-2-(5-(4'-(2-((2S)-1-(((1R,3S)-3-((tert-butoxycarbonyl)amino)cyclopentyl)carbonyl)-2-pyrrolidinyl)-1H-imidazol-5-yl)-4-biphenylyl)-1H-imidazol-2-yl)-1-pyrrolidinyl)-2-oxo-1-phenylethyl)carbamate;

methyl ((1R)-2-oxo-1-phenyl-2-((2S)-2-(5-(4'-(2-((2S)-1-(3-(1-piperidinyl)propanoyl)-2-pyrrolidinyl)-1H-imidazol-5-yl)-4-biphenylyl)-1H-imidazol-2-yl)-1-pyrrolidinyl)ethyl)carbamate;

methyl ((1R)-2-((2S)-2-(5-(4'-(2-((2S)-1-(2-benzoylbenzoyl)-2-pyrrolidinyl)-1H-imidazol-5-yl)-4-biphenylyl)-1H-imidazol-2-yl)-1-pyrrolidinyl)-2-oxo-1-phenylethyl)carbamate;

methyl ((1R)-2-((2S)-2-(5-(4'-(2-((2S)-1-((2-methoxyphenoxy)acetyl)-2-pyrrolidinyl)-1H-imidazol-5-yl)-4-biphenylyl)-1H-imidazol-2-yl)-1-pyrrolidinyl)-2-oxo-1-phenylethyl)carbamate;

tert-butyl 3-(((2S)-2-(5-(4'-(2-((2S)-1-((2R)-2-((methoxycarbonyl)amino)-2-phenylacetyl)-2-pyrrolidinyl)-1H-imidazol-5-yl)-4-biphenylyl)-1H-imidazol-2-yl)-1-pyrrolidinyl)carbonyl)-1-azetidinecarboxylate;

methyl ((1R)-2-((2S)-2-(5-(4'-(2-((2S)-1-(((3S)-1-benzyl-3-pyrrolidinyl)carbonyl)-2-pyrrolidinyl)-1H-imidazol-5-yl)-4-biphenylyl)-1H-imidazol-2-yl)-1-pyrrolidinyl)-2-oxo-1-phenylethyl)carbamate;

methyl ((1R)-2-oxo-1-phenyl-2-((2S)-2-(5-(4'-(2-((2S)-1-(3-(1-pyrrolidinyl)benzoyl)-2-pyrrolidinyl)-1H-imidazol-5-yl)-4-biphenylyl)-1H-imidazol-2-yl)-1-pyrrolidinyl)ethyl)carbamate;

methyl ((1R)-2-((2S)-2-(5-(4'-(2-((2S)-1-(2-((tert-butoxycarbonyl)amino)benzoyl)-2-pyrrolidinyl)-1H-imidazol-5-yl)-4-biphenylyl)-1H-imidazol-2-yl)-1-pyrrolidinyl)-2-oxo-1-phenylethyl)carbamate;

tert-butyl (3R)-3-(((2S)-2-(5-(4'-(2-((2S)-1-((2R)-2-((methoxycarbonyl)amino)-2-phenylacetyl)-2-pyrrolidinyl)-1H-imidazol-5-yl)-4-biphenylyl)-1H-imidazol-2-yl)-1-pyrrolidinyl)carbonyl)-1-piperidinecarboxylate;

methyl ((1R)-2-oxo-1-phenyl-2-((2S)-2-(5-(4'-(2-((2S)-1-((1-(trifluoromethyl)cyclopropyl)carbonyl)-2-pyrrolidinyl)-1H-imidazol-5-yl)-4-biphenylyl)-1H-imidazol-2-yl)-1-pyrrolidinyl)ethyl)carbamate;

methyl ((1R)-2-((2S)-2-(5-(4'-(2-((2S)-1-(4-(dimethylamino)benzoyl)-2-pyrrolidinyl)-1H-imidazol-5-yl)-4-biphenylyl)-1H-imidazol-2-yl)-1-pyrrolidinyl)-2-oxo-1-phenylethyl)carbamate;

methyl ((1R)-2-((2S)-2-(5-(4'-(2-((2S)-1-(3-benzoylbenzoyl)-2-pyrrolidinyl)-1H-imidazol-5-yl)-4-biphenylyl)-1H-imidazol-2-yl)-1-pyrrolidinyl)-2-oxo-1-phenylethyl)carbamate;

methyl ((1R)-2-((2S)-2-(5-(4'-(2-((2S)-1-((cis-4-((tert-butoxycarbonyl)amino)cyclohexyl)carbonyl)-2-pyrrolidinyl)-1H-imidazol-5-yl)-4-biphenylyl)-1H-imidazol-2-yl)-1-pyrrolidinyl)-2-oxo-1-phenylethyl)carbamate;

tert-butyl 4-(((2S)-2-(5-(4'-(2-((2S)-1-((2R)-2-((methoxycarbonyl)amino)-2-phenylacetyl)-2-pyrrolidinyl)-1H-imidazol-5-yl)-4-biphenylyl)-1H-imidazol-2-yl)-1-pyrrolidinyl)carbonyl)-1-piperidinecarboxylate;

methyl ((1R)-2-((2S)-2-(5-(4'-(2-((2S)-1-((cis-4-((tert-butoxycarbonyl)amino)cyclohexyl)carbonyl)-2-pyrrolidinyl)-1H-imidazol-5-yl)-4-biphenylyl)-1H-imidazol-2-yl)-1-pyrrolidinyl)-2-oxo-1-phenylethyl)carbamate;

methyl ((1R)-2-((2S)-2-(5-(4'-(2-((2S)-1-(diphenylacetyl)-2-pyrrolidinyl)-1H-imidazol-5-yl)-4-biphenylyl)-1H-imidazol-2-yl)-1-pyrrolidinyl)-2-oxo-1-phenylethyl)carbamate;

methyl ((1R)-2-oxo-2-((2S)-2-(5-(4'-(2-((2S)-1-(4-oxopentanoyl)-2-pyrrolidinyl)-1H-imidazol-5-yl)-4-biphenylyl)-1H-imidazol-2-yl)-1-pyrrolidinyl)-1-phenylethyl)carbamate;

methyl ((1R)-2-((2S)-2-(5-(4'-(2-((2S)-1-(2-fluorobenzoyl)-2-pyrrolidinyl)-1H-imidazol-5-yl)-4-biphenylyl)-1H-imidazol-2-yl)-1-pyrrolidinyl)-2-oxo-1-phenylethyl)carbamate;

methyl ((1R)-2-((2S)-2-(5-(4'-(2-((2S)-1-(2-biphenylylcarbonyl)-2-pyrrolidinyl)-1H-imidazol-5-yl)-4-biphenylyl)-1H-imidazol-2-yl)-1-pyrrolidinyl)-2-oxo-1-phenylethyl)carbamate;

methyl ((1R)-2-((2S)-2-(5-(4'-(2-((2S)-1-(2-benzylbenzoyl)-2-pyrrolidinyl)-1H-imidazol-5-yl)-4-biphenylyl)-1H-imidazol-2-yl)-1-pyrrolidinyl)-2-oxo-1-phenylethyl)carbamate;

methyl ((1R)-2-((2S)-2-(5-(4'-(2-((2S)-1-((2E)-3-(4-(dimethylamino)phenyl)-2-propenoyl)-2-pyrrolidinyl)-1H-imidazol-5-yl)-4-biphenylyl)-1H-imidazol-2-yl)-1-pyrrolidinyl)-2-oxo-1-phenylethyl)carbamate;

methyl ((1R)-2-oxo-1-phenyl-2-((2S)-2-(5-(4'-(2-((2S)-1-(1,3-thiazol-4-ylcarbonyl)-2-pyrrolidinyl)-1H-imidazol-5-yl)-4-biphenylyl)-1H-imidazol-2-yl)-1-pyrrolidinyl)ethyl)carbamate;

methyl ((1R)-2-((2S)-2-(5-(4'-(2-((2S)-1-((((1R,2S,5R)-2-isopropyl-5-methylcyclohexyl)oxy)acetyl)-2-pyrrolidinyl)-1H-imidazol-5-yl)-4-biphenylyl)-1H-imidazol-2-yl)-1-pyrrolidinyl)-2-oxo-1-phenylethyl)carbamate;

methyl ((1R)-2-((2S)-2-(5-(4'-(2-((2S)-1-((dimethylamino)(2-thienyl)acetyl)-2-pyrrolidinyl)-1H-imidazol-5-yl)-4-biphenylyl)-1H-imidazol-2-yl)-1-pyrrolidinyl)-2-oxo-1-phenylethyl)carbamate;

methyl ((1R)-2-((2S)-2-(5-(4'-(2-((2S)-1-((dimethylamino)(3-thienyl)acetyl)-2-pyrrolidinyl)-1H-imidazol-5-yl)-4-biphenylyl)-1H-imidazol-2-yl)-1-pyrrolidinyl)-2-oxo-1-phenylethyl)carbamate;

methyl ((1R)-2-((2S)-2-(5-(4'-(2-((2S)-1-((dimethylamino)(2-methyl-1,3-thiazol-4-yl)acetyl)-2-pyrrolidinyl)-1H-imidazol-5-yl)-4-biphenylyl)-1H-imidazol-2-yl)-1-pyrrolidinyl)-2-oxo-1-phenylethyl)carbamate;

methyl ((1R)-2-((2S)-2-(5-(4'-(2-((2S)-1-(1,2-benzisoxazol-3-yl(dimethylamino)acetyl)-2-pyrrolidinyl)-1H-imidazol-5-yl)-4-biphenylyl)-1H-imidazol-2-yl)-1-pyrrolidinyl)-2-oxo-1-phenylethyl)carbamate;

methyl ((1R)-2-((2S)-2-(5-(4'-(2-((2S)-1-(1-benzothiophen-3-yl(dimethylamino)acetyl)-2-pyrrolidinyl)-1H-imidazol-5-yl)-4-biphenylyl)-1H-imidazol-2-yl)-1-pyrrolidinyl)-2-oxo-1-phenylethyl)carbamate;

methyl ((1R)-2-((2S)-2-(5-(4'-(2-((2S)-1-((dimethylamino)(1-naphthyl)acetyl)-2-pyrrolidinyl)-1H-imidazol-5-yl)-4-biphenylyl)-1H-imidazol-2-yl)-1-pyrrolidinyl)-2-oxo-1-phenylethyl)carbamate;

methyl ((1R)-2-((2S)-2-(5-(4'-(2-((2S)-1-((dimethylamino)(3-quinolinyl)acetyl)-2-pyrrolidinyl)-1H-imidazol-5-yl)-4-biphenylyl)-1H-imidazol-2-yl)-1-pyrrolidinyl)-2-oxo-1-phenylethyl)carbamate;

methyl ((1R)-2-((2S)-2-(5-(4'-(2-((2S)-1-((dimethylamino)(2-methyl-1,3-benzothiazol-5-yl)acetyl)-2-pyrrolidinyl)-1H-imidazol-5-yl)-4-biphenylyl)-1H-imidazol-2-yl)-1-pyrrolidinyl)-2-oxo-1-phenylethyl)carbamate;

methyl ((1R)-2-((2S)-2-(5-(4'-(2-((2S)-1-((dimethylamino)(3-(trifluoromethyl)phenyl)acetyl)-2-pyrrolidinyl)-1H-imidazol-5-yl)-4-biphenylyl)-1H-imidazol-2-yl)-1-pyrrolidinyl)-2-oxo-1-phenylethyl)carbamate;

methyl ((1R)-2-((2S)-2-(5-(4'-(2-((2S)-1-((dimethylamino)(2-(trifluoromethyl)phenyl)acetyl)-2-pyrrolidinyl)-1H-imidazol-5-yl)-4-biphenylyl)-1H-imidazol-2-yl)-1-pyrrolidinyl)-2-oxo-1-phenylethyl)carbamate;

methyl ((1R)-2-((2S)-2-(5-(4'-(2-((2S)-1-((2-chlorophenyl)(dimethylamino)acetyl)-2-pyrrolidinyl)-1H-imidazol-5-yl)-4-biphenylyl)-1H-imidazol-2-yl)-1-pyrrolidinyl)-2-oxo-1-phenylethyl)carbamate;

methyl ((1R)-2-((2S)-2-(5-(4'-(2-((2S)-1-((3-chlorophenyl)(dimethylamino)acetyl)-2-pyrrolidinyl)-1H-imidazol-5-yl)-4-biphenylyl)-1H-imidazol-2-yl)-1-pyrrolidinyl)-2-oxo-1-phenylethyl)carbamate;

methyl ((1R)-2-((2S)-2-(5-(4'-(2-((2S)-1-((4-chlorophenyl)(dimethylamino)acetyl)-2-pyrrolidinyl)-1H-imidazol-5-yl)-4-biphenylyl)-1H-imidazol-2-yl)-1-pyrrolidinyl)-2-oxo-1-phenylethyl)carbamate;

methyl ((1R)-2-((2S)-2-(5-(4'-(2-((2S)-1-((dimethylamino)(2-fluorophenyl)acetyl)-2-pyrrolidinyl)-1H-imidazol-5-yl)-4-biphenylyl)-1H-imidazol-2-yl)-1-pyrrolidinyl)-2-oxo-1-phenylethyl)carbamate;

methyl ((1R)-2-((2S)-2-(5-(4'-(2-((2S)-1-((dimethylamino)(3-fluorophenyl)acetyl)-2-pyrrolidinyl)-1H-imidazol-5-yl)-4-biphenylyl)-1H-imidazol-2-yl)-1-pyrrolidinyl)-2-oxo-1-phenylethyl)carbamate;

methyl ((1R)-2-((2S)-2-(5-(4'-(2-((2S)-1-((dimethylamino)(2-pyridinyl)acetyl)-2-pyrrolidinyl)-1H-imidazol-5-yl)-4-biphenylyl)-1H-imidazol-2-yl)-1-pyrrolidinyl)-2-oxo-1-phenylethyl)carbamate;

methyl ((1R)-2-((2S)-2-(4-(4'-(2-((2S)-1-((dimethylamino)(3-pyridinyl)acetyl)-2-pyrrolidinyl)-1H-imidazol-5-yl)-4-biphenylyl)-1H-imidazol-2-yl)-1-pyrrolidinyl)-2-oxo-1-phenylethyl)carbamate;

methyl ((1R)-2-((2S)-2-(5-(4'-(2-((2S)-1-((4-methoxyphenyl)acetyl)-2-pyrrolidinyl)-1H-imidazol-5-yl)-4-biphenylyl)-1H-imidazol-2-yl)-1-pyrrolidinyl)-2-oxo-1-phenylethyl)carbamate;

methyl ((1R)-2-((2S)-2-(5-(4'-(2-((2S)-1-((3-methoxyphenyl)acetyl)-2-pyrrolidinyl)-1H-imidazol-5-yl)-4-biphenylyl)-1H-imidazol-2-yl)-1-pyrrolidinyl)-2-oxo-1-phenylethyl)carbamate;

methyl ((1R)-2-((2S)-2-(5-(4'-(2-((2S)-1-((2-methoxyphenyl)acetyl)-2-pyrrolidinyl)-1H-imidazol-5-yl)-4-biphenylyl)-1H-imidazol-2-yl)-1-pyrrolidinyl)-2-oxo-1-phenylethyl)carbamate;

methyl ((1R)-2-((2S)-2-(5-(4'-(2-((2S)-1-((2-chlorophenyl)acetyl)-2-pyrrolidinyl)-1H-imidazol-5-yl)-4-biphenylyl)-1H-imidazol-2-yl)-1-pyrrolidinyl)-2-oxo-1-phenylethyl)carbamate;

methyl ((1R)-2-((2S)-2-(5-(4'-(2-((2S)-1-((3-chlorophenyl)acetyl)-2-pyrrolidinyl)-1H-imidazol-5-yl)-4-biphenylyl)-1H-imidazol-2-yl)-1-pyrrolidinyl)-2-oxo-1-phenylethyl)carbamate;

methyl ((1R)-2-((2S)-2-(5-(4'-(2-((2S)-1-((4-chlorophenyl)acetyl)-2-pyrrolidinyl)-1H-imidazol-5-yl)-4-biphenylyl)-1H-imidazol-2-yl)-1-pyrrolidinyl)-2-oxo-1-phenylethyl)carbamate;

methyl ((1R)-2-((2S)-2-(5-(4'-(2-((2S)-1-((2-methylphenyl)acetyl)-2-pyrrolidinyl)-1H-imidazol-5-yl)-4-biphenylyl)-1H-imidazol-2-yl)-1-pyrrolidinyl)-2-oxo-1-phenylethyl)carbamate;

methyl ((1R)-2-((2S)-2-(5-(4'-(2-((2S)-1-((4-methylphenyl)acetyl)-2-pyrrolidinyl)-1H-imidazol-5-yl)-4-biphenylyl)-1H-imidazol-2-yl)-1-pyrrolidinyl)-2-oxo-1-phenylethyl)carbamate;

methyl ((1R)-2-((2S)-2-(5-(4'-(2-((2S)-1-((3-methylphenyl)acetyl)-2-pyrrolidinyl)-1H-imidazol-5-yl)-4-biphenylyl)-1H-imidazol-2-yl)-1-pyrrolidinyl)-2-oxo-1-phenylethyl)carbamate;

methyl ((1R)-2-((2S)-2-(5-(4'-(2-((2S)-1-((2-methyl-1,3-thiazol-4-yl)acetyl)-2-pyrrolidinyl)-1H-imidazol-5-yl)-4-biphenylyl)-1H-imidazol-2-yl)-1-pyrrolidinyl)-2-oxo-1-phenylethyl)carbamate;

methyl ((1R)-2-oxo-1-phenyl-2-((2S)-2-(5-(4'-(2-((2S)-1-(3-thienylacetyl)-2-pyrrolidinyl)-1H-imidazol-5-yl)-4-biphenylyl)-1H-imidazol-2-yl)-1-pyrrolidinyl)ethyl)carbamate;

methyl ((1R)-2-((2S)-2-(5-(4'-(2-((2S)-1-((3-methyl-5-isoxazolyl)acetyl)-2-pyrrolidinyl)-1H-imidazol-5-yl)-4-biphenylyl)-1H-imidazol-2-yl)-1-pyrrolidinyl)-2-oxo-1-phenylethyl)carbamate;

methyl ((1R)-2-((2S)-2-(5-(4'-(2-((2S)-1-(cyclohexylacetyl)-2-pyrrolidinyl)-1H-imidazol-5-yl)-4-biphenylyl)-1H-imidazol-2-yl)-1-pyrrolidinyl)-2-oxo-1-phenylethyl)carbamate;

methyl ((1R)-2-oxo-1-phenyl-2-((2S)-2-(5-(4'-(2-((2S)-1-((2R)-2-phenylpropanoyl)-2-pyrrolidinyl)-1H-imidazol-5-yl)-4-biphenylyl)-1H-imidazol-2-yl)-1-pyrrolidinyl)ethyl)carbamate;

methyl ((1R)-2-oxo-1-phenyl-2-((2S)-2-(5-(4'-(2-((2S)-1-((1-phenylcyclopropyl)carbonyl)-2-pyrrolidinyl)-1H-imidazol-5-yl)-4-biphenylyl)-1H-imidazol-2-yl)-1-pyrrolidinyl)ethyl)carbamate;

methyl ((1R)-2-((2S)-2-(5-(4'-(2-((2S)-1-((1-(4-chlorophenyl)cyclopropyl)carbonyl)-2-pyrrolidinyl)-1H-imidazol-5-yl)-4-biphenylyl)-1H-imidazol-2-yl)-1-pyrrolidinyl)-2-oxo-1-phenylethyl)carbamate;

methyl ((1R)-2-((2S)-2-(5-(4'-(2-((2S)-1-(2-(4-chlorophenyl)-2-methylpropanoyl)-2-pyrrolidinyl)-1H-imidazol-5-yl)-4-biphenylyl)-1H-imidazol-2-yl)-1-pyrrolidinyl)-2-oxo-1-phenylethyl)carbamate;

methyl ((1R)-2-((2S)-2-(5-(4'-(2-((2S)-1-((2R)-2-methoxy-2-phenylacetyl)-2-pyrrolidinyl)-1H-imidazol-5-yl)-4-biphenylyl)-1H-imidazol-2-yl)-1-pyrrolidinyl)-2-oxo-1-phenylethyl)carbamate;

methyl ((1R)-2-oxo-1-phenyl-2-((2S)-2-(5-(4'-(2-((2S)-1-((2S)-3,3,3-trifluoro-2-methoxy-2-phenylpropanoyl)-2-pyrrolidinyl)-1H-imidazol-5-yl)-4-biphenylyl)-1H-imidazol-2-yl)-1-pyrrolidinyl)ethyl)carbamate;

(1R)-2-((2S)-2-(5-(4'-(2-((2S)-1-((2R)-2-((methoxycarbonyl)amino)-2-phenylacetyl)-2-pyrrolidinyl)-1H-imidazol-5-yl)-4-biphenylyl)-1H-imidazol-2-yl)-1-pyrrolidinyl)-2-oxo-1-phenylethyl acetate;

(1S)-2-((2S)-2-(5-(4'-(2-((2S)-1-((2R)-2-((methoxycarbonyl)amino)-2-phenylacetyl)-2-pyrrolidinyl)-1H-imidazol-5-yl)-4-biphenylyl)-1H-imidazol-2-yl)-1-pyrrolidinyl)-2-oxo-1-phenylethyl acetate;

methyl ((1R)-2-((2S)-2-(5-(4'-(2-((2S)-1-((2-(4-morpholinylmethyl)phenyl)acetyl)-2-pyrrolidinyl)-1H-imidazol-5-yl)-4-biphenylyl)-1H-imidazol-2-yl)-1-pyrrolidinyl)-2-oxo-1-phenylethyl)carbamate;

methyl ((1R)-2-oxo-1-phenyl-2-((2S)-2-(5-(4'-(2-((2S)-1-((2-(1-piperidinylmethyl)phenyl)acetyl)-2-pyrrolidinyl)-1H-imidazol-5-yl)-4-biphenylyl)-1H-imidazol-2-yl)-1-pyrrolidinyl)ethyl)carbamate;

methyl ((1R)-2-oxo-1-phenyl-2-((2S)-2-(5-(4'-(2-((2S)-1-((2-(1-pyrrolidinylmethyl)phenyl)acetyl)-2-pyrrolidinyl)-1H-imidazol-5-yl)-4-biphenylyl)-1H-imidazol-2-yl)-1-pyrrolidinyl)ethyl)carbamate;

methyl ((1R)-2-((2S)-2-(5-(4'-(2-((2S)-1-((2-((dimethylamino)methyl)phenyl)acetyl)-2-pyrrolidinyl)-1H-imidazol-5-yl)-4-biphenylyl)-1H-imidazol-2-yl)-1-pyrrolidinyl)-2-oxo-1-phenylethyl)carbamate;

(1R)-N,N-dimethyl-2-oxo-1-phenyl-2-((2S)-2-(5-(4'-(2-((2S)-1-(3-pyridinylacetyl)-2-pyrrolidinyl)-1H-imidazol-5-yl)-4-biphenylyl)-1H-imidazol-2-yl)-1-pyrrolidinyl)ethanamine;

(1R)-N,N-dimethyl-2-oxo-1-phenyl-2-((2S)-2-(5-(4'-(2-((2S)-1-((2R)-tetrahydro-2-furanylcarbonyl)-2-pyrrolidinyl)-1H-imidazol-5-yl)-4-biphenylyl)-1H-imidazol-2-yl)-1-pyrrolidinyl)ethanamine;

(1R)-N,N-dimethyl-2-oxo-1-phenyl-2-((2S)-2-(5-(4'-(2-((2S)-1-((2S)-tetrahydro-2-furanylcarbonyl)-2-pyrrolidinyl)-1H-imidazol-5-yl)-4-biphenylyl)-1H-imidazol-2-yl)-1-pyrrolidinyl)ethanamine;

(1R)-N,N-dimethyl-2-((2S)-2-(5-(4'-(2-((2S)-1-((1-methyl-1H-imidazol-4-yl)acetyl)-2-pyrrolidinyl)-1H-imidazol-5-yl)-4-biphenylyl)-1H-imidazol-2-yl)-1-pyrrolidinyl)-2-oxo-1-phenylethanamine;

(1R)-N,N-dimethyl-2-((2S)-2-(5-(4'-(2-((2S)-1-((2R)-2-(4-morpholinyl)-2-phenylacetyl)-2-pyrrolidinyl)-1H-imidazol-5-yl)-4-biphenylyl)-1H-imidazol-2-yl)-1-pyrrolidinyl)-2-oxo-1-phenylethanamine;

(1R)-N,N-dimethyl-2-oxo-1-phenyl-2-((2S)-2-(5-(4'-(2-((2S)-1-((2R)-2-phenyl-2-(1-pyrrolidinyl)acetyl)-2-pyrrolidinyl)-1H-imidazol-5-yl)-4-biphenylyl)-1H-imidazol-2-yl)-1-pyrrolidinyl)ethanamine;

methyl (2-((2S)-2-(5-(4'-(2-((2S)-1-((2R)-2-(dimethylamino)-2-phenylacetyl)-2-pyrrolidinyl)-1H-imidazol-5-yl)-4-biphenylyl)-1H-imidazol-2-yl)-1-pyrrolidinyl)-2-oxoethyl)carbamate;

methyl ((1S)-2-((2S)-2-(5-(4'-(2-((2S)-1-((2R)-2-(dimethylamino)-2-phenylacetyl)-2-pyrrolidinyl)-1H-imidazol-5-yl)-4-biphenylyl)-1H-imidazol-2-yl)-1-pyrrolidinyl)-1-methyl-2-oxoethyl)carbamate;

(1R)-N,N-dimethyl-2-((2S)-2-(5-(4'-(2-((2S)-1-(4-morpholinylcarbonyl)-2-pyrrolidinyl)-1H-imidazol-5-yl)-4-biphenylyl)-1H-imidazol-2-yl)-1-pyrrolidinyl)-2-oxo-1-phenylethanamine;

(1R)-N,N-dimethyl-2-oxo-1-phenyl-2-((2S)-2-(5-(4'-(2-((2S)-1-(1-pyrrolidinylcarbonyl)-2-pyrrolidinyl)-1H-imidazol-5-yl)-4-biphenylyl)-1H-imidazol-2-yl)-1-pyrrolidinyl)ethanamine;

(2S)-1-((2S)-2-(5-(4'-(2-((2S)-1-((2R)-2-(dimethylamino)-2-phenylacetyl)-2-pyrrolidinyl)-1H-imidazol-5-yl)-4-biphenylyl)-1H-imidazol-2-yl)-1-pyrrolidinyl)-2-(2-fluorophenyl)-1-oxo-2-propanol;

(5R)-5-(((2S)-2-(5-(4'-(2-((2S)-1-((2R)-2-(dimethylamino)-2-phenylacetyl)-2-pyrrolidinyl)-1H-imidazol-5-yl)-4-biphenylyl)-1H-imidazol-2-yl)-1-pyrrolidinyl)carbonyl)-2-pyrrolidinone;

1-((1R)-2-((2S)-2-(5-(4'-(2-((2S)-1-((2R)-2-(dimethylamino)-2-phenylacetyl)-2-pyrrolidinyl)-1H-imidazol-5-yl)-4-biphenylyl)-1H-imidazol-2-yl)-1-pyrrolidinyl)-2-oxo-1-phenylethyl)-4-methyl-4-piperidinol;

tert-butyl (4R)-4-(((2S)-2-(5-(4'-(2-((2S)-1-((2R)-2-(dimethylamino)-2-phenylacetyl)-2-pyrrolidinyl)-1H-imidazol-5-yl)-4-biphenylyl)-1H-imidazol-2-yl)-1-pyrrolidinyl)carbonyl)-1,3-thiazolidine-3-carboxylate;

tert-butyl (1-(((2S)-2-(5-(4'-(2-((2S)-1-((2R)-2-(dimethylamino)-2-phenylacetyl)-2-pyrrolidinyl)-1H-imidazol-5-yl)-4-biphenylyl)-1H-imidazol-2-yl)-1-pyrrolidinyl)carbonyl)cyclopentyl)carbamate;

N-(2-((2S)-2-(5-(4'-(2-((2S)-1-((2R)-2-(dimethylamino)-2-phenylacetyl)-2-pyrrolidinyl)-1H-imidazol-5-yl)-4-biphenylyl)-1H-imidazol-2-yl)-1-pyrrolidinyl)-2-oxoethyl)benzamide;

(1R)-N,N-dimethyl-2-((2S)-2-(5-(4'-(2-((2S)-1-(4-(4-methyl-1-piperazinyl)benzoyl)-2-pyrrolidinyl)-1H-imidazol-5-yl)-4-biphenylyl)-1H-imidazol-2-yl)-1-pyrrolidinyl)-2-oxo-1-phenylethanamine;

(1R)-N,N-dimethyl-2-oxo-1-phenyl-2-((2S)-2-(5-(4'-(2-((2S)-1-((5-phenyl-2-thienyl)carbonyl)-2-pyrrolidinyl)-1H-imidazol-5-yl)-4-biphenylyl)-1H-imidazol-2-yl)-1-pyrrolidinyl)ethanamine;

(1R)-N,N-dimethyl-2-((2S)-2-(5-(4'-(2-((2S)-1-(4-(4-morpholinyl)benzoyl)-2-pyrrolidinyl)-1H-imidazol-5-yl)-4-biphenylyl)-1H-imidazol-2-yl)-1-pyrrolidinyl)-2-oxo-1-phenylethanamine;

(1R)-N,N-dimethyl-2-oxo-1-phenyl-2-((2S)-2-(5-(4'-(2-((2S)-1-((4-phenyl-1,2,3-thiadiazol-5-yl)carbonyl)-2-pyrrolidinyl)-1H-imidazol-5-yl)-4-biphenylyl)-1H-imidazol-2-yl)-1-pyrrolidinyl)ethanamine;

(1R)-N,N-dimethyl-2-oxo-1-phenyl-2-((2S)-2-(5-(4'-(2-((2S)-1-((2-phenyl-1,3-thiazol-4-yl)carbonyl)-2-pyrrolidinyl)-1H-imidazol-5-yl)-4-biphenylyl)-1H-imidazol-2-yl)-1-pyrrolidinyl)ethanamine;

tert-butyl 4-(((2S)-2-(5-(4'-(2-((2S)-1-((2R)-2-(dimethylamino)-2-phenylacetyl)-2-pyrrolidinyl)-1H-imidazol-5-yl)-4-biphenylyl)-1H-imidazol-2-yl)-1-pyrrolidinyl)carbonyl)-4-methyl-1-piperidinecarboxylate;

3-(2-((2S)-2-(5-(4'-(2-((2S)-1-((2R)-2-(dimethylamino)-2-phenylacetyl)-2-pyrrolidinyl)-1H-imidazol-5-yl)-4-biphenylyl)-1H-imidazol-2-yl)-1-pyrrolidinyl)-2-oxoethyl)phenol;

3-((2S)-2-(5-(4'-(2-((2S)-1-((2R)-2-(dimethylamino)-2-phenylacetyl)-2-pyrrolidinyl)-1H-imidazol-5-yl)-4-biphenylyl)-1H-imidazol-2-yl)-1-pyrrolidinyl)-N,N-dimethyl-3-oxo-1-propanamine;

(4-(((2S)-2-(5-(4'-(2-((2S)-1-((2R)-2-(dimethylamino)-2-phenylacetyl)-2-pyrrolidinyl)-1H-imidazol-5-yl)-4-biphenylyl)-1H-imidazol-2-yl)-1-pyrrolidinyl)carbonyl)phenyl)methanol;

(1R)-2-((2S)-2-(5-(4'-(2-((2S)-1-(1H-indol-3-ylcarbonyl)-2-pyrrolidinyl)-1H-imidazol-5-yl)-4-biphenylyl)-1H-imidazol-2-yl)-1-pyrrolidinyl)-N,N-dimethyl-2-oxo-1-phenylethanamine;

(1R)-2-((2S)-2-(5-(4'-(2-((2S)-1-(((3R)-1-benzyl-3-pyrrolidinyl)carbonyl)-2-pyrrolidinyl)-1H-imidazol-5-yl)-4-biphenylyl)-1H-imidazol-2-yl)-1-pyrrolidinyl)-N,N-dimethyl-2-oxo-1-phenylethanamine;

tert-butyl (2S)-2-(2-((2S)-2-(5-(4'-(2-((2S)-1-((2R)-2-(dimethylamino)-2-phenylacetyl)-2-pyrrolidinyl)-1H-imidazol-5-yl)-4-biphenylyl)-1H-imidazol-2-yl)-1-pyrrolidinyl)-2-oxoethyl)-1-pyrrolidinecarboxylate;

(1R)-N,N-dimethyl-2-((2S)-2-(5-(4'-(2-((2S)-1-((5-methyl-1H-pyrazol-3-yl)acetyl)-2-pyrrolidinyl)-1H-imidazol-5-yl)-4-biphenylyl)-1H-imidazol-2-yl)-1-pyrrolidinyl)-2-oxo-1-phenylethanamine;

tert-butyl (2R)-2-(((2S)-2-(5-(4'-(2-((2S)-1-((2R)-2-(dimethylamino)-2-phenylacetyl)-2-pyrrolidinyl)-1H-imidazol-5-yl)-4-biphenylyl)-1H-imidazol-2-yl)-1-pyrrolidinyl)carbonyl)-1-piperidinecarboxylate;

tert-butyl ((1S,3R)-3-(((2S)-2-(5-(4'-(2-((2S)-1-((2R)-2-(dimethylamino)-2-phenylacetyl)-2-pyrrolidinyl)-1H-imidazol-5-yl)-4-biphenylyl)-1H-imidazol-2-yl)-1-pyrrolidinyl)carbonyl)cyclopentyl)carbamate;

(1R)-N,N-dimethyl-2-oxo-1-phenyl-2-((2S)-2-(5-(4'-(2-((2S)-1-(3-(1-piperidinyl)propanoyl)-2-pyrrolidinyl)-1H-imidazol-5-yl)-4-biphenylyl)-1H-imidazol-2-yl)-1-pyrrolidinyl)ethanamine;

(2-(((2S)-2-(5-(4'-(2-((2S)-1-((2R)-2-(dimethylamino)-2-phenylacetyl)-2-pyrrolidinyl)-1H-imidazol-5-yl)-4-biphenylyl)-1H-imidazol-2-yl)-1-pyrrolidinyl)carbonyl)phenyl)(phenyl)methanone;

(1R)-2-((2S)-2-(5-(4'-(2-((2S)-1-((2-methoxyphenoxy)acetyl)-2-pyrrolidinyl)-1H-imidazol-5-yl)-4-biphenylyl)-1H-imidazol-2-yl)-1-pyrrolidinyl)-N,N-dimethyl-2-oxo-1-phenylethanamine;

tert-butyl 3-(((2S)-2-(5-(4'-(2-((2S)-1-((2R)-2-(dimethylamino)-2-phenylacetyl)-2-pyrrolidinyl)-1H-imidazol-5-yl)-4-biphenylyl)-1H-imidazol-2-yl)-1-pyrrolidinyl)carbonyl)-1-azetidinecarboxylate;

(1R)-2-((2S)-2-(5-(4'-(2-((2S)-1-(((3S)-1-benzyl-3-pyrrolidinyl)carbonyl)-2-pyrrolidinyl)-1H-imidazol-5-yl)-4-biphenylyl)-1H-imidazol-2-yl)-1-pyrrolidinyl)-N,N-dimethyl-2-oxo-1-phenylethanamine;

(1R)-N,N-dimethyl-2-oxo-1-phenyl-2-((2S)-2-(5-(4'-(2-((2S)-1-(3-(1-pyrrolidinyl)benzoyl)-2-pyrrolidinyl)-1H-imidazol-5-yl)-4-biphenylyl)-1H-imidazol-2-yl)-1-pyrrolidinyl)ethanamine;

tert-butyl (2-(((2S)-2-(5-(4'-(2-((2S)-1-((2R)-2-(dimethylamino)-2-phenylacetyl)-2-pyrrolidinyl)-1H-imidazol-5-yl)-4-biphenylyl)-1H-imidazol-2-yl)-1-pyrrolidinyl)carbonyl)phenyl)carbamate;

tert-butyl (3R)-3-(((2S)-2-(5-(4'-(2-((2S)-1-((2R)-2-(dimethylamino)-2-phenylacetyl)-2-pyrrolidinyl)-1H-imidazol-5-yl)-4-biphenylyl)-1H-imidazol-2-yl)-1-pyrrolidinyl)carbonyl)-1-piperidinecarboxylate;

(1R)-N,N-dimethyl-2-oxo-1-phenyl-2-((2S)-2-(5-(4'-(2-((2S)-1-((1-(trifluoromethyl)cyclopropyl)carbonyl)-2-pyrrolidinyl)-1H-imidazol-5-yl)-4-biphenylyl)-1H-imidazol-2-yl)-1-pyrrolidinyl)ethanamine;

4-(((2S)-2-(5-(4'-(2-((2S)-1-((2R)-2-(dimethylamino)-2-phenylacetyl)-2-pyrrolidinyl)-1H-imidazol-5-yl)-4-biphenylyl)-1H-imidazol-2-yl)-1-pyrrolidinyl)carbonyl)-N,N-dimethylaniline;

(3-(((2S)-2-(5-(4'-(2-((2S)-1-((2R)-2-(dimethylamino)-2-phenylacetyl)-2-pyrrolidinyl)-1H-imidazol-5-yl)-4-biphenylyl)-1H-imidazol-2-yl)-1-pyrrolidinyl)carbonyl)phenyl)(phenyl)methanone;

tert-butyl (cis-4-(((2S)-2-(5-(4'-(2-((2S)-1-((2R)-2-(dimethylamino)-2-phenylacetyl)-2-pyrrolidinyl)-1H-imidazol-5-yl)-4-biphenylyl)-1H-imidazol-2-yl)-1-pyrrolidinyl)carbonyl)cyclohexyl)carbamate;

'tert-butyl 4-(((2S)-2-(5-(4'-(2-((2S)-1-((2R)-2-(dimethylamino)-2-phenylacetyl)-2-pyrrolidinyl)-1H-imidazol-5-yl)-4-biphenylyl)-1H-imidazol-2-yl)-1-pyrrolidinyl)carbonyl)-1-piperidinecarboxylate;

tert-butyl (cis-4-(((2S)-2-(5-(4'-(2-((2S)-1-((2R)-2-(dimethylamino)-2-phenylacetyl)-2-pyrrolidinyl)-1H-imidazol-5-yl)-4-biphenylyl)-1H-imidazol-2-yl)-1-pyrrolidinyl)carbonyl)cyclohexyl)carbamate;

(1R)-2-((2S)-2-(5-(4'-(2-((2S)-1-(diphenylacetyl)-2-pyrrolidinyl)-1H-imidazol-5-yl)-4-biphenylyl)-1H-imidazol-2-yl)-1-pyrrolidinyl)-N,N-dimethyl-2-oxo-1-phenylethanamine;

5-((2S)-2-(5-(4'-(2-((2S)-1-((2R)-2-(dimethylamino)-2-phenylacetyl)-2-pyrrolidinyl)-1H-imidazol-5-yl)-4-biphenylyl)-1H-imidazol-2-yl)-1-pyrrolidinyl)-5-oxo-2-pentanone;

(1R)-2-((2S)-2-(5-(4'-(2-((2S)-1-(2-fluorobenzoyl)-2-pyrrolidinyl)-1H-imidazol-5-yl)-4-biphenylyl)-1H-imidazol-2-yl)-1-pyrrolidinyl)-N,N-dimethyl-2-oxo-1-phenylethanamine;

(1R)-2-((2S)-2-(5-(4'-(2-((2S)-1-(2-biphenylylcarbonyl)-2-pyrrolidinyl)-1H-imidazol-5-yl)-4-biphenylyl)-1H-imidazol-2-yl)-1-pyrrolidinyl)-N,N-dimethyl-2-oxo-1-phenylethanamine;

(1R)-2-((2S)-2-(5-(4'-(2-((2S)-1-(2-benzylbenzoyl)-2-pyrrolidinyl)-1H-imidazol-5-yl)-4-biphenylyl)-1H-imidazol-2-yl)-1-pyrrolidinyl)-N,N-dimethyl-2-oxo-1-phenylethanamine;

4-((1E)-3-((2S)-2-(5-(4'-(2-((2S)-1-((2R)-2-(dimethylamino)-2-phenylacetyl)-2-pyrrolidinyl)-1H-imidazol-5-yl)-4-biphenylyl)-1H-imidazol-2-yl)-1-pyrrolidinyl)-3-oxo-1-propen-1-yl)-N,N-dimethylaniline;

(1R)-N,N-dimethyl-2-oxo-1-phenyl-2-((2S)-2-(5-(4'-(2-((2S)-1-(1,3-thiazol-4-ylcarbonyl)-2-pyrrolidinyl)-1H-imidazol-5-yl)-4-biphenylyl)-1H-imidazol-2-yl)-1-pyrrolidinyl)ethanamine;

(1R)-2-((2S)-2-(5-(4'-(2-((2S)-1-((((1R,2S,5R)-2-isopropyl-5-methylcyclohexyl)oxy)acetyl)-2-pyrrolidinyl)-1H-imidazol-5-yl)-4-biphenylyl)-1H-imidazol-2-yl)-1-pyrrolidinyl)-N,N-dimethyl-2-oxo-1-phenylethanamine;

1-(6-chloro-3-pyridinyl)-2-((2S)-2-(5-(4'-(2-((2S)-1-((2R)-2-(dimethylamino)-2-phenylacetyl)-2-pyrrolidinyl)-1H-imidazol-5-yl)-4-biphenylyl)-1H-imidazol-2-yl)-1-pyrrolidinyl)-N,N-dimethyl-2-oxoethanamine;

2-((2S)-2-(5-(4'-(2-((2S)-1-((2R)-2-(dimethylamino)-2-phenylacetyl)-2-pyrrolidinyl)-1H-imidazol-5-yl)-4-biphenylyl)-1H-imidazol-2-yl)-1-pyrrolidinyl)-N,N-dimethyl-2-oxo-1-(3-pyridinyl)ethanamine;

2-((2S)-2-(5-(4'-(2-((2S)-1-((2R)-2-(dimethylamino)-2-phenylacetyl)-2-pyrrolidinyl)-1H-imidazol-5-yl)-4-biphenylyl)-1H-imidazol-2-yl)-1-pyrrolidinyl)-N,N-dimethyl-2-oxo-1-(2-pyridinyl)ethanamine;

(1R)-N,N-dimethyl-2-oxo-1-phenyl-2-((2S)-2-(5-(4'-(2-((2S)-1-(2-thienylacetyl)-2-pyrrolidinyl)-1H-imidazol-5-yl)-4-biphenylyl)-1H-imidazol-2-yl)-1-pyrrolidinyl)ethanamine;

(1R)-N,N-dimethyl-2-oxo-1-phenyl-2-((2S)-2-(5-(4'-(2-((2S)-1-(3-thienylacetyl)-2-pyrrolidinyl)-1H-imidazol-5-yl)-4-biphenylyl)-1H-imidazol-2-yl)-1-pyrrolidinyl)ethanamine;

(1R)-N,N-dimethyl-2-((2S)-2-(5-(4'-(2-((2S)-1-(1-naphthylacetyl)-2-pyrrolidinyl)-1H-imidazol-5-yl)-4-biphenylyl)-1H-imidazol-2-yl)-1-pyrrolidinyl)-2-oxo-1-phenylethanamine;

(1R)-2-((2S)-2-(5-(4'-(2-((2S)-1-(1H-imidazol-5-ylacetyl)-2-pyrrolidinyl)-1H-imidazol-5-yl)-4-biphenylyl)-1H-imidazol-2-yl)-1-pyrrolidinyl)-N,N-dimethyl-2-oxo-1-phenylethanamine;

(1R)-2-((2S)-2-(5-(4'-(2-((2S)-1-((2-fluorophenyl)acetyl)-2-pyrrolidinyl)-1H-imidazol-5-yl)-4-biphenylyl)-1H-imidazol-2-yl)-1-pyrrolidinyl)-N,N-dimethyl-2-oxo-1-phenylethanamine;

(1R)-2-((2S)-2-(5-(4'-(2-((2S)-1-((3-fluorophenyl)acetyl)-2-pyrrolidinyl)-1H-imidazol-5-yl)-4-biphenylyl)-1H-imidazol-2-yl)-1-pyrrolidinyl)-N,N-dimethyl-2-oxo-1-phenylethanamine;

(1R)-2-((2S)-2-(5-(4'-(2-((2S)-1-((4-fluorophenyl)acetyl)-2-pyrrolidinyl)-1H-imidazol-5-yl)-4-biphenylyl)-1H-imidazol-2-yl)-1-pyrrolidinyl)-N,N-dimethyl-2-oxo-1-phenylethanamine;

(1R)-2-((2S)-2-(5-(4'-(2-((2S)-1-(1-benzothiophen-3-ylacetyl)-2-pyrrolidinyl)-1H-imidazol-5-yl)-4-biphenylyl)-1H-imidazol-2-yl)-1-pyrrolidinyl)-N,N-dimethyl-2-oxo-1-phenylethanamine;

(1R)-2-((2S)-2-(5-(4'-(2-((2S)-1-(1,2-benzisoxazol-3-ylacetyl)-2-pyrrolidinyl)-1H-imidazol-5-yl)-4-biphenylyl)-1H-imidazol-2-yl)-1-pyrrolidinyl)-N,N-dimethyl-2-oxo-1-phenylethanamine;

(1R)-2-((2S)-2-(5-(4'-(2-((2S)-1-(1H-indol-3-ylacetyl)-2-pyrrolidinyl)-1H-imidazol-5-yl)-4-biphenylyl)-1H-imidazol-2-yl)-1-pyrrolidinyl)-N,N-dimethyl-2-oxo-1-phenylethanamine;

2-((2S)-1-((2R)-2-phenyl-2-(1-pyrrolidinyl)acetyl)-2-pyrrolidinyl)-5-(4'-(2-((2S)-1-((2S)-tetrahydro-2-furanylcarbonyl)-2-pyrrolidinyl)-1H-imidazol-5-yl)-4-biphenylyl)-1H-imidazole;

4-((1R)-2-oxo-1-phenyl-2-((2S)-2-(5-(4'-(2-((2S)-1-((2R)-2-phenyl-2-(1-pyrrolidinyl)acetyl)-2-pyrrolidinyl)-1H-imidazol-5-yl)-4-biphenylyl)-1H-imidazol-2-yl)-1-pyrrolidinyl)ethyl)morpholine;

1-(2-oxo-1-phenyl-2-((2S)-2-(5-(4'-(2-((2S)-1-((2R)-2-phenyl-2-(1-pyrrolidinyl)acetyl)-2-pyrrolidinyl)-1H-imidazol-5-yl)-4-biphenylyl)-1H-imidazol-2-yl)-1-pyrrolidinyl)ethyl)-4-piperidinol;

1-methyl-4-(2-oxo-1-phenyl-2-((2S)-2-(5-(4'-(2-((2S)-1-((2R)-2-phenyl-2-(1-pyrrolidinyl)acetyl)-2-pyrrolidinyl)-1H-imidazol-5-yl)-4-biphenylyl)-1H-imidazol-2-yl)-1-pyrrolidinyl)ethyl)piperazine;

(1R)-N,N-diethyl-2-oxo-1-phenyl-2-((2S)-2-(5-(4'-(2-((2S)-1-((2R)-2-phenyl-2-(1-pyrrolidinyl)acetyl)-2-pyrrolidinyl)-1H-imidazol-5-yl)-4-biphenylyl)-1H-imidazol-2-yl)-1-pyrrolidinyl)ethanamine;

methyl ((1R)-2-oxo-1-phenyl-2-((2S)-2-(5-(4'-(2-((2S)-1-((2R)-2-phenyl-2-(1-pyrrolidinyl)acetyl)-2-pyrrolidinyl)-1H-imidazol-5-yl)-4-biphenylyl)-1H-imidazol-2-yl)-1-pyrrolidinyl)ethyl)carbamate;

methyl ((1S)-1-methyl-2-oxo-2-((2S)-2-(5-(4'-(2-((2S)-1-((2R)-2-phenyl-2-(1-pyrrolidinyl)acetyl)-2-pyrrolidinyl)-1H-imidazol-5-yl)-4-biphenylyl)-1H-imidazol-2-yl)-1-pyrrolidinyl)ethyl)carbamate;

methyl (2-oxo-2-((2S)-2-(5-(4'-(2-((2S)-1-((2R)-2-phenyl-2-(1-pyrrolidinyl)acetyl)-2-pyrrolidinyl)-1H-imidazol-5-yl)-4-biphenylyl)-1H-imidazol-2-yl)-1-pyrrolidinyl)ethyl)carbamate;

(2S)-N,N-dimethyl-1-oxo-1-((2S)-2-(5-(4'-(2-((2S)-1-((2R)-2-phenyl-2-(1-pyrrolidinyl)acetyl)-2-pyrrolidinyl)-1H-imidazol-5-yl)-4-biphenylyl)-1H-imidazol-2-yl)-1-pyrrolidinyl)-2-propanamine;

1-(2-oxo-1-phenyl-2-((2S)-2-(5-(4'-(2-((2S)-1-((2R)-tetrahydro-2-furanylcarbonyl)-2-pyrrolidinyl)-1H-imidazol-4-yl)-4-biphenylyl)-1H-imidazol-2-yl)-1-pyrrolidinyl)ethyl)-4-phenylpiperidine;

1-(2-oxo-1-phenyl-2-((2S)-2-(5-(4'-(2-((2S)-1-((2R)-tetrahydro-2-furanylcarbonyl)-2-pyrrolidinyl)-1H-imidazol-4-yl)-4-biphenylyl)-1H-imidazol-2-yl)-1-pyrrolidinyl)ethyl)-4-phenylpiperidine;

1-methyl-4-(2-oxo-1-phenyl-2-((2S)-2-(5-(4'-(2-((2S)-1-((2R)-tetrahydro-2-furanylcarbonyl)-2-pyrrolidinyl)-1H-imidazol-4-yl)-4-biphenylyl)-1H-imidazol-2-yl)-1-pyrrolidinyl)ethyl)piperazine;

1-methyl-4-(2-oxo-1-phenyl-2-((2S)-2-(5-(4'-(2-((2S)-1-((2R)-tetrahydro-2-furanylcarbonyl)-2-pyrrolidinyl)-1H-imidazol-4-yl)-4-biphenylyl)-1H-imidazol-2-yl)-1-pyrrolidinyl)ethyl)piperazine;

benzyl 4-(2-oxo-1-phenyl-2-((2S)-2-(5-(4'-(2-((2S)-1-((2R)-tetrahydro-2-furanylcarbonyl)-2-pyrrolidinyl)-1H-imidazol-4-yl)-4-biphenylyl)-1H-imidazol-2-yl)-1-pyrrolidinyl)ethyl)-1-piperazinecarboxylate;

benzyl 4-(2-oxo-1-phenyl-2-((2S)-2-(5-(4'-(2-((2S)-1-((2R)-tetrahydro-2-furanylcarbonyl)-2-pyrrolidinyl)-1H-imidazol-4-yl)-4-biphenylyl)-1H-imidazol-2-yl)-1-pyrrolidinyl)ethyl)-1-piperazinecarboxylate;

1-(2-oxo-1-phenyl-2-((2S)-2-(5-(4'-(2-((2S)-1-((2R)-tetrahydro-2-furanylcarbonyl)-2-pyrrolidinyl)-1H-imidazol-4-yl)-4-biphenylyl)-1H-imidazol-2-yl)-1-pyrrolidinyl)ethyl)piperazine;

4-(2-oxo-1-phenyl-2-((2S)-2-(5-(4'-(2-((2S)-1-((2R)-tetrahydro-2-furanylcarbonyl)-2-pyrrolidinyl)-1H-imidazol-4-yl)-4-biphenylyl)-1H-imidazol-2-yl)-1-pyrrolidinyl)ethyl)-2-piperazinone;

1-methyl-3-((1R)-2-oxo-1-phenyl-2-((2S)-2-(4-(4'-(2-((2S)-1-((2R)-tetrahydro-2-furanylcarbonyl)-2-pyrrolidinyl)-1H-imidazol-4-yl)-4-biphenylyl)-1H-imidazol-2-yl)-1-pyrrolidinyl)ethyl)urea;

1-ethyl-3-((1R)-2-oxo-1-phenyl-2-((2S)-2-(4-(4'-(2-((2S)-1-((2R)-tetrahydro-2-furanylcarbonyl)-2-pyrrolidinyl)-1H-imidazol-4-yl)-4-biphenylyl)-1H-imidazol-2-yl)-1-pyrrolidinyl)ethyl)urea;

1-cyclopentyl-3-((1R)-2-oxo-1-phenyl-2-((2S)-2-(4-(4'-(2-((2S)-1-((2R)-tetrahydro-2-furanylcarbonyl)-2-pyrrolidinyl)-1H-imidazol-4-yl)-4-biphenylyl)-1H-imidazol-2-yl)-1-pyrrolidinyl)ethyl)urea;

1,1-dimethyl-3-((1R)-2-oxo-1-phenyl-2-((2S)-2-(4-(4'-(2-((2S)-1-((2R)-tetrahydro-2-furanylcarbonyl)-2-pyrrolidinyl)-1H-imidazol-4-yl)-4-biphenylyl)-1H-imidazol-2-yl)-1-pyrrolidinyl)ethyl)urea;

1-methyl-4-(2-oxo-1-phenyl-2-((2S)-2-(5-(4'-(2-((2S)-1-((2S)-tetrahydro-2-furanylcarbonyl)-2-pyrrolidinyl)-1H-imidazol-5-yl)-4-biphenylyl)-1H-imidazol-2-yl)-1-pyrrolidinyl)ethyl)piperazine;

4-((1R)-2-oxo-1-phenyl-2-((2S)-2-(5-(4'-(2-((2S)-1-((2S)-tetrahydro-2-furanylcarbonyl)-2-pyrrolidinyl)-1H-imidazol-5-yl)-4-biphenylyl)-1H-imidazol-2-yl)-1-pyrrolidinyl)ethyl)morpholine;

(1R)-N,N-diethyl-2-oxo-1-phenyl-2-((2S)-2-(5-(4'-(2-((2S)-1-((2S)-tetrahydro-2-furanylcarbonyl)-2-pyrrolidinyl)-1H-imidazol-5-yl)-4-biphenylyl)-1H-imidazol-2-yl)-1-pyrrolidinyl)ethanamine;

(1R)-N-ethyl-N-methyl-2-oxo-1-phenyl-2-((2S)-2-(5-(4'-(2-((2S)-1-((2S)-tetrahydro-2-furanylcarbonyl)-2-pyrrolidinyl)-1H-imidazol-5-yl)-4-biphenylyl)-1H-imidazol-2-yl)-1-pyrrolidinyl)ethanamine;

(1S)-2-oxo-1-phenyl-2-((2S)-2-(5-(4'-(2-((2S)-1-((2R)-2-phenyl-2-(1-piperidinyl)acetyl)-2-pyrrolidinyl)-1H-imidazol-5-yl)-4-biphenylyl)-1H-imidazol-2-yl)-1-pyrrolidinyl)ethyl acetate;

4-methyl-1-((1R)-2-oxo-1-phenyl-2-((2S)-2-(5-(4'-(2-((2S)-1-((2R)-2-phenyl-2-(1-piperidinyl)acetyl)-2-pyrrolidinyl)-1H-imidazol-5-yl)-4-biphenylyl)-1H-imidazol-2-yl)-1-pyrrolidinyl)ethyl)-4-piperidinol;

1-((1R)-2-((2S)-2-(5-(4'-(2-((2S)-1-(2-fluorobenzoyl)-2-pyrrolidinyl)-1H-imidazol-5-yl)-4-biphenylyl)-1H-imidazol-2-yl)-1-pyrrolidinyl)-2-oxo-1-phenylethyl)piperidine;

N,N-dimethyl-4-(((2S)-2-(5-(4'-(2-((2S)-1-((2R)-2-phenyl-2-(1-piperidinyl)acetyl)-2-pyrrolidinyl)-1H-imidazol-5-yl)-4-biphenylyl)-1H-imidazol-2-yl)-1-pyrrolidinyl)carbonyl)aniline;

5-oxo-5-((2S)-2-(5-(4'-(2-((2S)-1-((2R)-2-phenyl-2-(1-piperidinyl)acetyl)-2-pyrrolidinyl)-1H-imidazol-5-yl)-4-biphenylyl)-1H-imidazol-2-yl)-1-pyrrolidinyl)-2-pentanone;

1-((1R)-2-((2S)-2-(5-(4'-(2-((2S)-1-(diphenylacetyl)-2-pyrrolidinyl)-1H-imidazol-5-yl)-4-biphenylyl)-1H-imidazol-2-yl)-1-pyrrolidinyl)-2-oxo-1-phenylethyl)piperidine;

1-(3-oxo-3-((2S)-2-(5-(4'-(2-((2S)-1-((2R)-2-phenyl-2-(1-piperidinyl)acetyl)-2-pyrrolidinyl)-1H-imidazol-5-yl)-4-biphenylyl)-1H-imidazol-2-yl)-1-pyrrolidinyl)propyl)piperidine;

1-((1R)-2-((2S)-2-(5-(4'-(2-((2S)-1-((2-methoxyphenoxy)acetyl)-2-pyrrolidinyl)-1H-imidazol-5-yl)-4-biphenylyl)-1H-imidazol-2-yl)-1-pyrrolidinyl)-2-oxo-1-phenylethyl)piperidine;

tert-butyl 4-(((2S)-2-(5-(4'-(2-((2S)-1-((2R)-2-phenyl-2-(1-piperidinyl)acetyl)-2-pyrrolidinyl)-1H-imidazol-5-yl)-4-biphenylyl)-1H-imidazol-2-yl)-1-pyrrolidinyl)carbonyl)-1-piperidinecarboxylate;

4-(4-(((2S)-2-(5-(4'-(2-((2S)-1-((2R)-2-phenyl-2-(1-piperidinyl)acetyl)-2-pyrrolidinyl)-1H-imidazol-5-yl)-4-biphenylyl)-1H-imidazol-2-yl)-1-pyrrolidinyl)carbonyl)phenyl)morpholine;

1-((1R)-2-oxo-1-phenyl-2-((2S)-2-(5-(4'-(2-((2S)-1-(1,3-thiazol-4-ylcarbonyl)-2-pyrrolidinyl)-1H-imidazol-5-yl)-4-biphenylyl)-1H-imidazol-2-yl)-1-pyrrolidinyl)ethyl)piperidine;

tert-butyl 3-(((2S)-2-(5-(4'-(2-((2S)-1-((2R)-2-phenyl-2-(1-piperidinyl)acetyl)-2-pyrrolidinyl)-1H-imidazol-5-yl)-4-biphenylyl)-1H-imidazol-2-yl)-1-pyrrolidinyl)carbonyl)-1-azetidinecarboxylate;

tert-butyl (cis-4-(((2S)-2-(5-(4'-(2-((2S)-1-((2R)-2-phenyl-2-(1-piperidinyl)acetyl)-2-pyrrolidinyl)-1H-imidazol-5-yl)-4-biphenylyl)-1H-imidazol-2-yl)-1-pyrrolidinyl)carbonyl)cyclohexyl)carbamate;

tert-butyl 4-methyl-4-(((2S)-2-(5-(4'-(2-((2S)-1-((2R)-2-phenyl-2-(1-piperidinyl)acetyl)-2-pyrrolidinyl)-1H-imidazol-5-yl)-4-biphenylyl)-1H-imidazol-2-yl)-1-pyrrolidinyl)carbonyl)-1-piperidinecarboxylate;

1-((1R)-2-oxo-1-phenyl-2-((2S)-2-(5-(4'-(2-((2S)-1-((1-(trifluoromethyl)cyclopropyl)carbonyl)-2-pyrrolidinyl)-1H-imidazol-5-yl)-4-biphenylyl)-1H-imidazol-2-yl)-1-pyrrolidinyl)ethyl)piperidine;

1-((1R)-2-((2S)-2-(5-(4'-(2-((2S)-1-((5-methyl-1H-pyrazol-3-yl)acetyl)-2-pyrrolidinyl)-1H-imidazol-5-yl)-4-biphenylyl)-1H-imidazol-2-yl)-1-pyrrolidinyl)-2-oxo-1-phenylethyl)piperidine;

1-((1R)-2-((2S)-2-(5-(4'-(2-((2S)-1-(((3R)-1-benzyl-3-pyrrolidinyl)carbonyl)-2-pyrrolidinyl)-1H-imidazol-5-yl)-4-biphenylyl)-1H-imidazol-2-yl)-1-pyrrolidinyl)-2-oxo-1-phenylethyl)piperidine;

1-((1R)-2-((2S)-2-(5-(4'-(2-((2S)-1-(((3S)-1-benzyl-3-pyrrolidinyl)carbonyl)-2-pyrrolidinyl)-1H-imidazol-5-yl)-4-biphenylyl)-1H-imidazol-2-yl)-1-pyrrolidinyl)-2-oxo-1-phenylethyl)piperidine;

1-((1R)-2-((2S)-2-(5-(4'-(2-((2S)-1-((2R)-2-methoxy-2-phenylacetyl)-2-pyrrolidinyl)-1H-imidazol-5-yl)-4-biphenylyl)-1H-imidazol-2-yl)-1-pyrrolidinyl)-2-oxo-1-phenylethyl)piperidine;

1-((1R)-2-((2S)-2-(5-(4'-(2-((2S)-1-((2S)-2-methoxy-2-phenylacetyl)-2-pyrrolidinyl)-1H-imidazol-5-yl)-4-biphenylyl)-1H-imidazol-2-yl)-1-pyrrolidinyl)-2-oxo-1-phenylethyl)piperidine;

(1R)-2-oxo-1-phenyl-2-((2S)-2-(5-(4'-(2-((2S)-1-((2R)-2-phenyl-2-(1-piperidinyl)acetyl)-2-pyrrolidinyl)-1H-imidazol-5-yl)-4-biphenylyl)-1H-imidazol-2-yl)-1-pyrrolidinyl)ethyl acetate;

1-((1R)-2-oxo-1-phenyl-2-((2S)-2-(5-(4'-(2-((2S)-1-((1-phenylcyclopropyl)carbonyl)-2-pyrrolidinyl)-1H-imidazol-5-yl)-4-biphenylyl)-1H-imidazol-2-yl)-1-pyrrolidinyl)ethyl)piperidine;

N,N-dimethyl-1-(2-(2-oxo-2-((2S)-2-(5-(4'-(2-((2S)-1-((2R)-2-phenyl-2-(1-piperidinyl)acetyl)-2-pyrrolidinyl)-1H-imidazol-5-yl)-4-biphenylyl)-1H-imidazol-2-yl)-1-pyrrolidinyl)ethyl)phenyl)methanamine;

1-((1R)-2-((2S)-2-(5-(4'-(2-((2S)-1-((3-methyl-5-isoxazolyl)acetyl)-2-pyrrolidinyl)-1H-imidazol-5-yl)-4-biphenylyl)-1H-imidazol-2-yl)-1-pyrrolidinyl)-2-oxo-1-phenylethyl)piperidine;

1-((1R)-2-((2S)-2-(5-(4'-(2-((2S)-1-((2-methyl-1,3-thiazol-4-yl)acetyl)-2-pyrrolidinyl)-1H-imidazol-5-yl)-4-biphenylyl)-1H-imidazol-2-yl)-1-pyrrolidinyl)-2-oxo-1-phenylethyl)piperidine;

4-(2-(2-oxo-2-((2S)-2-(5-(4'-(2-((2S)-1-((2R)-2-phenyl-2-(1-piperidinyl)acetyl)-2-pyrrolidinyl)-1H-imidazol-5-yl)-4-biphenylyl)-1H-imidazol-2-yl)-1-pyrrolidinyl)ethyl)benzyl)morpholine;

1-((1R)-2-oxo-1-phenyl-2-((2S)-2-(5-(4'-(2-((2S)-1-((2-(1-pyrrolidinylmethyl)phenyl)acetyl)-2-pyrrolidinyl)-1H-imidazol-5-yl)-4-biphenylyl)-1H-imidazol-2-yl)-1-pyrrolidinyl)ethyl)piperidine;

1-((1R)-2-((2S)-2-(5-(4'-(2-((2S)-1-((2-fluorophenyl)acetyl)-2-pyrrolidinyl)-1H-imidazol-5-yl)-4-biphenylyl)-1H-imidazol-2-yl)-1-pyrrolidinyl)-2-oxo-1-phenylethyl)piperidine;

1-((1R)-2-((2S)-2-(5-(4'-(2-((2S)-1-acetyl-2-pyrrolidinyl)-1H-imidazol-5-yl)-4-biphenylyl)-1H-imidazol-2-yl)-1-pyrrolidinyl)-2-oxo-1-phenylethyl)piperidine;

1-((1R)-2-oxo-1-phenyl-2-((2S)-2-(5-(4'-(2-((2S)-1-(2-thienylacetyl)-2-pyrrolidinyl)-1H-imidazol-5-yl)-4-biphenylyl)-1H-imidazol-2-yl)-1-pyrrolidinyl)ethyl)piperidine;

(1R)-2-((2S)-2-(5-(4'-(2-((2S)-1-((2R)-2-(dimethylamino)-2-(2-fluorophenyl)acetyl)-2-pyrrolidinyl)-1H-imidazol-5-yl)-4-biphenylyl)-1H-imidazol-2-yl)-1-pyrrolidinyl)-N,N-dimethyl-2-oxo-1-phenylethanamine;

(1R)-1-(2-fluorophenyl)-2-((2S)-2-(5-(4'-(2-((2S)-1-((2R)-2-methoxy-2-phenylacetyl)-2-pyrrolidinyl)-1H-imidazol-5-yl)-4-biphenylyl)-1H-imidazol-2-yl)-1-pyrrolidinyl)-N,N-dimethyl-2-oxoethanamine;

(1R)-2-((2S)-2-(5-(4'-(2-((2S)-1-((2R)-2-(dimethylamino)-2-(2-fluorophenyl)acetyl)-2-pyrrolidinyl)-1H-imidazol-5-yl)-4-biphenylyl)-1H-imidazol-2-yl)-1-pyrrolidinyl)-2-oxo-1-phenylethyl acetate;

(1R)-1-(2-fluorophenyl)-N,N-dimethyl-2-oxo-2-((2S)-2-(5-(4'-(2-((2S)-1-((1-phenylcyclopropyl)carbonyl)-2-pyrrolidinyl)-1H-imidazol-5-yl)-4-biphenylyl)-1H-imidazol-2-yl)-1-pyrrolidinyl)ethanamine;

(1R)-1-(2-chlorophenyl)-2-((2S)-2-(5-(4'-(2-((2S)-1-((2R)-2-(dimethylamino)-2-phenylacetyl)-2-pyrrolidinyl)-1H-imidazol-5-yl)-4-biphenylyl)-1H-imidazol-2-yl)-1-pyrrolidinyl)-N,N-dimethyl-2-oxoethanamine;

methyl ((1R)-2-((2S)-2-(5-(4'-(2-((2S)-1-((2R)-2-(2-chlorophenyl)-2-(dimethylamino)acetyl)-2-pyrrolidinyl)-1H-imidazol-5-yl)-4-biphenylyl)-1H-imidazol-2-yl)-1-pyrrolidinyl)-2-oxo-1-phenylethyl)carbamate;

(1R)-1-(2-chlorophenyl)-2-((2S)-2-(5-(4'-(2-((2S)-1-((2R)-2-methoxy-2-phenylacetyl)-2-pyrrolidinyl)-1H-imidazol-5-yl)-4-biphenylyl)-1H-imidazol-2-yl)-1-pyrrolidinyl)-N,N-dimethyl-2-oxoethanamine;

(1R)-1-(2-chlorophenyl)-N,N-dimethyl-2-oxo-2-((2S)-2-(5-(4'-(2-((2S)-1-((2R)-tetrahydro-2-furanylcarbonyl)-2-pyrrolidinyl)-1H-imidazol-5-yl)-4-biphenylyl)-1H-imidazol-2-yl)-1-pyrrolidinyl)ethanamine;

methyl ((1R)-1-(2-chlorophenyl)-2-oxo-2-((2S)-2-(5-(4'-(2-((2S)-1-((2R)-tetrahydro-2-furanylcarbonyl)-2-pyrrolidinyl)-1H-imidazol-5-yl)-4-biphenylyl)-1H-imidazol-2-yl)-1-pyrrolidinyl)ethyl)carbamate;

methyl ((1R)-1-(2-chlorophenyl)-2-((2S)-2-(5-(4'-(2-((2S)-1-((2R)-2-(dimethylamino)-2-phenylacetyl)-2-pyrrolidinyl)-1H-imidazol-5-yl)-4-biphenylyl)-1H-imidazol-2-yl)-1-pyrrolidinyl)-2-oxoethyl)carbamate;

methyl ((1R)-2-((2S)-2-(5-(4'-(2-((2S)-1-((2R)-2-(2-chlorophenyl)-2-((methoxycarbonyl)amino)acetyl)-2-pyrrolidinyl)-1H-imidazol-5-yl)-4-biphenylyl)-1H-imidazol-2-yl)-1-pyrrolidinyl)-2-oxo-1-phenylethyl)carbamate;

methyl ((1R)-1-(2-chlorophenyl)-2-((2S)-2-(5-(4'-(2-((2S)-1-((2R)-2-(4-hydroxy-4-methyl-1-piperidinyl)-2-phenylacetyl)-2-pyrrolidinyl)-1H-imidazol-5-yl)-4-biphenylyl)-1H-imidazol-2-yl)-1-pyrrolidinyl)-2-oxoethyl)carbamate;

methyl ((1R)-1-(2-chlorophenyl)-2-((2S)-2-(5-(4'-(2-((2S)-1-((2R)-2-methoxy-2-phenylacetyl)-2-pyrrolidinyl)-1H-imidazol-5-yl)-4-biphenylyl)-1H-imidazol-2-yl)-1-pyrrolidinyl)-2-oxocthyl)carbamatc;

methyl ((1R)-1-(2-chlorophenyl)-2-((2S)-2-(5-(4'-(2-((2S)-1-((2R)-2-(2-chlorophenyl)-2-(dimethylamino)acetyl)-2-pyrrolidinyl)-1H-imidazol-5-yl)-4-biphenylyl)-1H-imidazol-2-yl)-1-pyrrolidinyl)-2-oxoethyl)carbamate;

mcthyl ((1R)-2-((2S)-2-(5-(4'-(2-((2S)-1-(cthylcarbamoyl)-2-pyrrolidinyl)-1H-imidazol-5-yl)-4-biphenylyl)-1H-imidazol-2-yl)-1-pyrrolidinyl)-2-oxo-1-phenylethyl)carbamate;

dibenzyl (2S,2'S)-2,2'-(4,4'-biphenyldiylbis(1H-imidazole-5,2-diyl))di(1-pyrrolidinecarboxylate);

benzyl (2S)-2-(5-(4'-(2-((2S)-2-pyrrolidinyl)-1H-imidazol-5-yl)-4-biphenylyl)-1H-imidazol-2-yl)-1-pyrrolidinecarboxylate;

(2R)-N-((1R)-2-oxo-1-phenyl-2-((2S)-2-(5-(4'-(2-((2S)-1-((2S)-tetrahydro-2-furanylcarbonyl)-2-pyrrolidinyl)-1H-imidazol-5-yl)-4-biphenylyl)-1H-imidazol-2-yl)-1-pyrrolidinyl)ethyl)tetrahydro-2-furancarboxamide;

(1R)-2-oxo-1-phenyl-2-((2S)-2-(5-(4'-(2-((2S)-1-((2S)-tetrahydro-2-furanylcarbonyl)-2-pyrrolidinyl)-1H-imidazol-5-yl)-4-biphenylyl)-1H-imidazol-2-yl)-1-pyrrolidinyl)ethanamine;

(2R)-N-((1R)-2-oxo-1-phenyl-2-((2S)-2-(5-(4'-(2-((2S)-1-((2S)-tetrahydro-2-furanylcarbonyl)-2-pyrrolidinyl)-1H-imidazol-5-yl)-4-biphenylyl)-1H-imidazol-2-yl)-1-pyrrolidinyl)ethyl)tetrahydro-2-furancarboxamide;

N-((1R)-2-oxo-1-phenyl-2-((2S)-2-(5-(4'-(2-((2S)-1-((2S)-tetrahydro-2-furanylcarbonyl)-2-pyrrolidinyl)-1H-imidazol-5-yl)-4-biphenylyl)-1H-imidazol-2-yl)-1-pyrrolidinyl)ethyl)-4-morpholinecarboxamide;

(2S)-N-((1R)-2-oxo-1-phenyl-2-((2S)-2-(5-(4'-(2-((2S)-1-((2S)-tetrahydro-2-furanylcarbonyl)-2-pyrrolidinyl)-1H-imidazol-5-yl)-4-biphenylyl)-1H-imidazol-2-yl)-1-pyrrolidinyl)ethyl)tetrahydro-2-furancarboxamide;

1-methyl-N-((1R)-2-oxo-1-phenyl-2-((2S)-2-(5-(4'-(2-((2S)-1-((2S)-tetrahydro-2-furanylcarbonyl)-2-pyrrolidinyl)-1H-imidazol-5-yl)-4-biphenylyl)-1H-imidazol-2-yl)-1-pyrrolidinyl)ethyl)-L-prolinamide;

1-methyl-N-((1R)-2-oxo-1-phenyl-2-((2S)-2-(5-(4'-(2-((2S)-1-((2S)-tetrahydro-2-furanylcarbonyl)-2-pyrrolidinyl)-1H-imidazol-5-yl)-4-biphenylyl)-1H-imidazol-2-yl)-1-pyrrolidinyl)ethyl)-4-piperidinecarboxamide;

N-((1R)-2-oxo-1-phenyl-2-((2S)-2-(5-(4'-(2-((2S)-1-((2S)-tetrahydro-2-furanylcarbonyl)-2-pyrrolidinyl)-1H-imidazol-5-yl)-4-biphenylyl)-1H-imidazol-2-yl)-1-pyrrolidinyl)ethyl)tetrahydro-2H-pyran-4-carboxamide;

(4R)-4-fluoro-1-methyl-N-((1R)-2-oxo-1-phenyl-2-((2S)-2-(5-(4'-(2-((2S)-1-((2S)-tetrahydro-2-furanylcarbonyl)-2-pyrrolidinyl)-1H-imidazol-5-yl)-4-biphenylyl)-1H-imidazol-2-yl)-1-pyrrolidinyl)ethyl)-L-prolinamide;

4-methyl-N-((1R)-2-oxo-1-phenyl-2-((2S)-2-(5-(4'-(2-((2S)-1-((2S)-tetrahydro-2-furanylcarbonyl)-2-pyrrolidinyl)-1H-imidazol-5-yl)-4-biphenylyl)-1H-imidazol-2-yl)-1-pyrrolidinyl)ethyl)-1-piperazinecarboxamide;

N-((1R)-2-oxo-1-phenyl-2-((2S)-2-(5-(4'-(2-((2S)-1-((2R)-tetrahydro-2-furanylcarbonyl)-2-pyrrolidinyl)-1H-imidazol-5-yl)-4-biphenylyl)-1H-imidazol-2-yl)-1-pyrrolidinyl)ethyl)acetamide;

(2R)-N-((1R)-2-oxo-1-phenyl-2-((2S)-2-(5-(4'-(2-((2S)-1-((2R)-tetrahydro-2-furanylcarbonyl)-2-pyrrolidinyl)-1H-imidazol-5-yl)-4-biphenylyl)-1H-imidazol-2-yl)-1-pyrrolidinyl)ethyl)tetrahydro-2-furancarboxamide;

N-((1R)-2-oxo-1-phenyl-2-((2S)-2-(5-(4'-(2-((2S)-1-((2R)-tetrahydro-2-furanylcarbonyl)-2-pyrrolidinyl)-1H-imidazol-5-yl)-4-biphenylyl)-1H-imidazol-2-yl)-1-pyrrolidinyl)ethyl)-4-morpholinecarboxamide;

1-methyl-N-((1R)-2-oxo-1-phenyl-2-((2S)-2-(5-(4'-(2-((2S)-1-((2R)-tetrahydro-2-furanylcarbonyl)-2-pyrrolidinyl)-1H-imidazol-4-yl)-4-biphenylyl)-1H-imidazol-2-yl)-1-pyrrolidinyl)ethyl)-1H-imidazole-5-carboxamide;

1-methyl-N-((1R)-2-oxo-1-phenyl-2-((2S)-2-(5-(4'-(2-((2S)-1-((2R)-tetrahydro-2-furanylcarbonyl)-2-pyrrolidinyl)-1H-imidazol-4-yl)-4-biphenylyl)-1H-imidazol-2-yl)-1-pyrrolidinyl)ethyl)-L-prolinamide;

N-((1R)-2-oxo-1-phenyl-2-((2S)-2-(5-(4'-(2-((2S)-1-((2R)-tetrahydro-2-furanylcarbonyl)-2-pyrrolidinyl)-1H-imidazol-4-yl)-4-biphenylyl)-1H-imidazol-2-yl)-1-pyrrolidinyl)ethyl)-2-(3-pyridinyl)acetamide;

N^2,N^2-dimethyl-N-((1R)-2-oxo-1-phenyl-2-((2S)-2-(5-(4'-(2-((2S)-1-((2R)-tetrahydro-2-furanylcarbonyl)-2-pyrrolidinyl)-1H-imidazol-4-yl)-4-biphenylyl)-1H-imidazol-2-yl)-1-pyrrolidinyl)ethyl)glycinamide;

1-((1R)-2-oxo-1-phenyl-2-((2S)-2-(5-(4'-(2-((2S)-1-((2R)-tetrahydro-2-furanylcarbonyl)-2-pyrrolidinyl)-1H-imidazol-4-yl)-4-biphenylyl)-1H-imidazol-2-yl)-1-pyrrolidinyl)ethyl)-3-(3-pyridinyl)urea;

(1R,1'R)-2,2'-((2,2'-dimethyl-4,4'-biphenyldiyl)bis(1H-imidazole-5,2-diyl(2S)-2,1-pyrrolidinediyl))bis(N,N-dimethyl-2-oxo-1-phenylethanamine);

dimethyl ((2,2'-dimethyl-4,4'-biphenyldiyl)bis(1H-imidazole-5,2-diyl(2S)-2,1-pyrrolidinediyl((1R)-2-oxo-1-phenyl-2,1-ethanediyl)))biscarbamate;

(1R,1'R)-2,2'-((2-methyl-4,4'-biphenyldiyl)bis(1H-imidazole-5,2-diyl(2S)-2,1-pyrrolidinediyl))bis(N,N-dimethyl-2-oxo-1-phenylethanamine);

dimethyl ((2-methyl-4,4'-biphenyldiyl)bis(1H-imidazole-5,2-diyl(2S)-2,1-pyrrolidinediyl((1R)-2-oxo-1-phenyl-2,1-ethanediyl)))biscarbamate;

(1R,1'R)-2,2'-((2-methyl-4,4'-biphenyldiyl)bis(1H-imidazole-5,2-diyl(2S)-2,1-pyrrolidinediyl))bis(2-oxo-1-phenylethanol);

methyl ((1R)-2-((2S)-2-(5-(4'-(2-((2S)-1-((2R)-2-(dimethylamino)-2-phenylacetyl)-2-pyrrolidinyl)-1H-imidazol-5-yl)-2'-methyl-4-biphenylyl)-1H-imidazol-2-yl)-1-pyrrolidinyl)-2-oxo-1-phenylethyl)carbamate;

methyl ((1R)-2-((2S)-2-(5-(2'-methyl-4'-(2-((2S)-1-(3-pyridinylacetyl)-2-pyrrolidinyl)-1H-imidazol-5-yl)-4-biphenylyl)-1H-imidazol-2-yl)-1-pyrrolidinyl)-2-oxo-1-phenylethyl)carbamate;

methyl ((1R)-2-((2S)-2-(5-(2'-methyl-4'-(2-((2S)-1-((2S)-tetrahydro-2-furanylcarbonyl)-2-pyrrolidinyl)-1H-imidazol-5-yl)-4-biphenylyl)-1H-imidazol-2-yl)-1-pyrrolidinyl)-2-oxo-1-phenylethyl)carbamate;

methyl ((1R)-2-((2S)-2-(5-(4'-(2-((2S)-1-((2R)-2-(dimethylamino)-2-phenylacetyl)-2-pyrrolidinyl)-1H-imidazol-5-yl)-2,2'-dimethyl-4-biphenylyl)-1H-imidazol-2-yl)-1-pyrrolidinyl)-2-oxo-1-phenylethyl)carbamate;

(1R,1'R)-2,2'-((2-(trifluoromethyl)-4,4'-biphenyldiyl)bis(1H-imidazole-5,2-diyl(2S)-2,1-pyrrolidinediyl))bis(N,N-dimethyl-2-oxo-1-phenylethanamine);

(1R,1'R)-2,2'-((2-(trifluoromethyl)-4,4'-biphenyldiyl)bis(1H-imidazole-5,2-diyl(2S)-2,1-pyrrolidinediyl))bis(N,N-dimethyl-2-oxo-1-phenylethanamine);

5,5'-(2-(trifluoromethyl)-4,4'-biphenyldiyl)bis(2-((2S)-1-((2R)-2-phenyl-2-(1-pyrrolidinyl)acetyl)-2-pyrrolidinyl)-1H-imidazole);

(1R,1'R)-2,2'-(4,4'-biphenyldiylbis(1H-imidazole-5,2-diyl(4R)-1,3-thiazolidine-4,3-diyl))bis(N,N-dimethyl-2-oxo-1-phenylethanamine);

dimethyl (4,4'-biphenyldiylbis(1H-imidazole-5,2-diyl(4R)-1,3-thiazolidine-4,3-diyl((1R)-2-oxo-1-phenyl-2,1-ethanediyl)))biscarbamate;
(4R,4'R)-4,4'-(4,4'-biphenyldiylbis(1H-imidazole-5,2-diyl))bis(3-((2R)-tetrahydro-2-furanylcarbonyl)-1,3-thiazolidine);
(1R,1'R)-2,2'-(4,4'-biphenyldiylbis((1-methyl-1H-imidazole-4,2-diyl)(2S)-2,1-pyrrolidinediyl))bis(N,N-dimethyl-2-oxo-1-phenylethanamine);
(1S,1'S)-2,2'-(4,4'-biphenyldiylbis(1H-imidazole-5,2-diyl(2S)-2,1-pyrrolidinediyl))bis(1-cyclohexyl-2-oxoethanol);
(2S,2'S)-1,1'-(4,4'-biphenyldiylbis(1H-imidazole-5,2-diyl(2S)-2,1-pyrrolidinediyl))bis(4-methyl-1-oxo-2-pentanol);
(2S,2'S)-1,1'-(4,4'-biphenyldiylbis(1H-imidazole-5,2-diyl(2S)-2,1-pyrrolidinediyl))bis(3-methyl-1-oxo-2-butanol);
3-buten-1-yl ((1S)-1-(((2S)-2-(5-(4'-(2-((2S)-1-((2S)-2-(((3-buten-1-yloxy)carbonyl)amino)-3-methylbutanoyl)-2-pyrrolidinyl)-1H-imidazol-5-yl)-4-biphenylyl)-1H-imidazol-2-yl)-1-pyrrolidinyl)carbonyl)-2-methylpropyl)carbamate;
methyl ((1S)-2-methyl-1-(((2S)-2-(5-(4'-(2-((2S)-1-(N-methylglycyl)-2-pyrrolidinyl)-1H-imidazol-5-yl)-4-biphenylyl)-1H-imidazol-2-yl)-1-pyrrolidinyl)carbonyl)propyl)carbamate;
(2S,2'S)-1,1'-(4,4'-biphenyldiylbis(1H-imidazole-5,2-diyl(2S)-2,1-pyrrolidinediyl))bis(N-methyl-1-oxo-2-propanamine);
(4S,4'S)-4,4'-(4,4'-biphenyldiylbis(1H-imidazole-5,2-diyl(2S)-2,1-pyrrolidinediylcarbonyl))bis(1,3-oxazinan-2-one);
methyl ((1S)-2-((2S)-2-(5-(4'-(2-((2S)-1-((2R)-2-(diethylamino)-2-phenylacetyl)-2-pyrrolidinyl)-1H-imidazol-5-yl)-4-biphenylyl)-1H-imidazol-2-yl)-1-pyrrolidinyl)-2-oxo-1-(tetrahydro-2H-pyran-4-yl)ethyl)carbamate;
methyl ((1S)-1-(((2S)-2-(5-(4'-(2-((2S)-1-(N-ethylglycyl)-2-pyrrolidinyl)-1H-imidazol-5-yl)-4-biphenylyl)-1H-imidazol-2-yl)-1-pyrrolidinyl)carbonyl)-2-methylpropyl)carbamate;
methyl ((1S)-1-(((2S)-2-(5-(4'-(2-((2S)-1-(N-benzylglycyl)-2-pyrrolidinyl)-1H-imidazol-5-yl)-4-biphenylyl)-1H-imidazol-2-yl)-1-pyrrolidinyl)carbonyl)-2-methylpropyl)carbamate;

methyl ((1S)-1-(((2S)-2-(5-(4'-(2-((2S)-1-(N-isobutylglycyl)-2-pyrrolidinyl)-1H-imidazol-5-yl)-4-biphenylyl)-1H-imidazol-2-yl)-1-pyrrolidinyl)carbonyl)-2-methylpropyl)carbamate;

methyl ((1S)-1-(((2S)-2-(5-(4'-(2-((2S)-1-(N-sec-butylglycyl)-2-pyrrolidinyl)-1H-imidazol-5-yl)-4-biphenylyl)-1H-imidazol-2-yl)-1-pyrrolidinyl)carbonyl)-2-methylpropyl)carbamate;

methyl ((1S)-1-(((2S)-2-(5-(4'-(2-((2S)-1-(N-isopropylglycyl)-2-pyrrolidinyl)-1H-imidazol-5-yl)-4-biphenylyl)-1H-imidazol-2-yl)-1-pyrrolidinyl)carbonyl)-2-methylpropyl)carbamate;

methyl ((1S)-1-(((2S)-2-(5-(4'-(2-((2S)-1-(N,N-diisopropylglycyl)-2-pyrrolidinyl)-1H-imidazol-5-yl)-4-biphenylyl)-1H-imidazol-2-yl)-1-pyrrolidinyl)carbonyl)-2-methylpropyl)carbamate;

methyl ((1S)-1-(((2S)-2-(5-(4'-(2-((2S)-1-((2R)-2-((methoxycarbonyl)amino)-2-(3-oxetanyl)acetyl)-2-pyrrolidinyl)-1H-imidazol-5-yl)-4-biphenylyl)-1H-imidazol-2-yl)-1-pyrrolidinyl)carbonyl)-2-methylpropyl)carbamate;

methyl ((1S)-1-(((2S)-2-(5-(4'-(2-((2S)-1-((2S)-2-((methoxycarbonyl)amino)-2-(3-oxetanyl)acetyl)-2-pyrrolidinyl)-1H-imidazol-5-yl)-4-biphenylyl)-1H-imidazol-2-yl)-1-pyrrolidinyl)carbonyl)-2-methylpropyl)carbamate;

methyl ((1S)-1-(((2S)-2-(5-(4'-(2-((2S)-1-((2S)-2-((methoxycarbonyl)amino)-3-methylbutanoyl)-2-pyrrolidinyl)-1H-imidazol-5-yl)-4-biphenylyl)-1H-imidazol-2-yl)-2-methyl-1-pyrrolidinyl)carbonyl)-2-methylpropyl)carbamate;

methyl ((1S,2R)-2-methoxy-1-(((2S)-2-(5-(4'-(2-((2S)-1-(N-(methoxycarbonyl)-O-methyl-L-threonyl)-2-pyrrolidinyl)-1H-imidazol-5-yl)-4-biphenylyl)-1H-imidazol-2-yl)-2-methyl-1-pyrrolidinyl)carbonyl)propyl)carbamate;

methyl ((1R)-2-((2R)-2-(5-(4'-(2-((2S,5R)-1-((2R)-2-((methoxycarbonyl)amino)-2-phenylacetyl)-5-phenyl-2-pyrrolidinyl)-1H-imidazol-5-yl)-4-biphenylyl)-1H-imidazol-2-yl)-1-pyrrolidinyl)-2-oxo-1-phenylethyl)carbamate;

rel-(1R)-2-((2S)-2-(4-(4'-(2-((2S)-1-((2R)-2-(dimethylamino)-2-phenylacetyl)octahydro-1H-indol-2-yl)-1H-imidazol-5-yl)-4-biphenylyl)-1H-imidazol-2-yl)-1-pyrrolidinyl)-N,N-dimethyl-2-oxo-1-phenylethanamine;

methyl rel-((1R)-2-((2S)-2-(4-(4'-(2-((2S)-1-((2R)-2-((methoxycarbonyl)amino)-2-phenylacetyl)octahydro-1H-indol-2-yl)-1H-imidazol-5-yl)-4-biphenylyl)-1H-imidazol-2-yl)-1-pyrrolidinyl)-2-oxo-1-phenylethyl)carbamate;

(1R)-N-ethyl-2-((2S)-2-(4-(4'-(2-((2S)-1-((2R)-2-(ethylamino)-2-phenylacetyl)-2-pyrrolidinyl)-1H-imidazol-5-yl)-4-biphenylyl)-1H-imidazol-2-yl)-1-pyrrolidinyl)-2-oxo-1-phenylethanamine;

(1R)-N-methyl-2-((2S)-2-(4-(4'-(2-((2S)-1-((2R)-2-(methylamino)-2-phenylacetyl)-2-pyrrolidinyl)-1H-imidazol-5-yl)-4-biphenylyl)-1H-imidazol-2-yl)-1-pyrrolidinyl)-2-oxo-1-phenylethanamine;

N-((1R)-2-oxo-1-phenyl-2-((2S)-2-(4-(4'-(2-((2S)-1-((2R)-2-phenyl-2-(propylamino)acetyl)-2-pyrrolidinyl)-1H-imidazol-5-yl)-4-biphenylyl)-1H-imidazol-2-yl)-1-pyrrolidinyl)ethyl)-1-propanamine;

N-((1R)-2-((2S)-2-(4-(4'-(2-((2S)-1-((2R)-2-(butylamino)-2-phenylacetyl)-2-pyrrolidinyl)-1H-imidazol-5-yl)-4-biphenylyl)-1H-imidazol-2-yl)-1-pyrrolidinyl)-2-oxo-1-phenylethyl)-1-butanamine;

ethyl ((1S)-1-(((2S)-2-(4-(4'-(2-((2S)-1-((2S)-2-((ethoxycarbonyl)amino)-3-methylbutanoyl)-2-pyrrolidinyl)-1H-imidazol-4-yl)-4-biphenylyl)-1H-imidazol-2-yl)-1-pyrrolidinyl)carbonyl)-2-methylpropyl)carbamate;

propyl ((1S)-1-methyl-2-oxo-2-((2S)-2-(4-(4'-(2-((2S)-1-(N-(propoxycarbonyl)-L-alanyl)-2-pyrrolidinyl)-1H-imidazol-5-yl)-4-biphenylyl)-1H-imidazol-2-yl)-1-pyrrolidinyl)ethyl)carbamate;

butyl ((1S)-2-((2S)-2-(4-(4'-(2-((2S)-1-(N-(butoxycarbonyl)-L-alanyl)-2-pyrrolidinyl)-1H-imidazol-5-yl)-4-biphenylyl)-1H-imidazol-2-yl)-1-pyrrolidinyl)-1-methyl-2-oxoethyl)carbamate;

(2S)-2-hydroxy-N-((1S)-2-((2S)-2-(5-(4'-(2-((2S)-1-(N-((2S)-2-hydroxy-3-methylbutanoyl)-L-alanyl)-2-pyrrolidinyl)-1H-imidazol-4-yl)-4-biphenylyl)-1H-imidazol-2-yl)-1-pyrrolidinyl)-1-methyl-2-oxoethyl)-3-methylbutanamide;

ethyl ((1S)-1-(((2S)-2-(4-(4'-(2-((2S)-1-((2S)-2-((ethoxycarbonyl)amino)-3-methylbutanoyl)-2-pyrrolidinyl)-1H-imidazol-4-yl)-4-biphenylyl)-1H-imidazol-2-yl)-1-pyrrolidinyl)carbonyl)-2-methylpropyl)carbamate;

isopropyl ((1S)-1-(((2S)-2-(4-(4'-(2-((2S)-1-((2S)-2-((isopropoxycarbonyl)amino)-3-methylbutanoyl)-2-pyrrolidinyl)-1H-imidazol-4-yl)-4-biphenylyl)-1H-imidazol-2-yl)-1-pyrrolidinyl)carbonyl)-2-methylpropyl)carbamate;

(2S)-1-((2S)-2-(4-(4'-(2-((2S)-1-((2S)-2-hydroxypropanoyl)-2-pyrrolidinyl)-1H-imidazol-5-yl)-4-biphenylyl)-1H-imidazol-2-yl)-1-pyrrolidinyl)-1-oxo-2-propanol;

tert-butyl ((1S)-1-(((2S)-2-(5-(4'-(2-((2S)-1-((2S)-2-((tert-butoxycarbonyl)(methyl)amino)-4-methylpentanoyl)-2-pyrrolidinyl)-1H-imidazol-4-yl)-4-biphenylyl)-1H-imidazol-2-yl)-1-pyrrolidinyl)carbonyl)-3-methylbutyl)methylcarbamate;

tert-butyl ((1S)-1-(((2S)-2-(5-(4'-(2-((2S)-1-((2S)-2-((tert-butoxycarbonyl)(methyl)amino)-3-methylpentanoyl)-2-pyrrolidinyl)-1H-imidazol-4-yl)-4-biphenylyl)-1H-imidazol-2-yl)-1-pyrrolidinyl)carbonyl)-2-methylbutyl)methylcarbamate;

tert-butyl ((1S)-1-(((2S)-2-(5-(4'-(2-((2S)-1-((2S)-2-((tert-butoxycarbonyl)(methyl)amino)-3-methylbutanoyl)-2-pyrrolidinyl)-1H-imidazol-4-yl)-4-biphenylyl)-1H-imidazol-2-yl)-1-pyrrolidinyl)carbonyl)-2-methylpropyl)methylcarbamate;

tert-butyl ((1S,2R)-1-(((2S)-2-(4-(4'-(2-((2S)-1-(N-(tert-butoxycarbonyl)-N-methyl-L-alloisoleucyl)-2-pyrrolidinyl)-1H-imidazol-5-yl)-4-biphenylyl)-1H-imidazol-2-yl)-1-pyrrolidinyl)carbonyl)-2-methylbutyl)methylcarbamate;

(2S)-N,4-dimethyl-1-((2S)-2-(4-(4'-(2-((2S)-1-((2S)-4-methyl-2-(methylamino)pentanoyl)-2-pyrrolidinyl)-1H-imidazol-5-yl)-4-biphenylyl)-1H-imidazol-2-yl)-1-pyrrolidinyl)-1-oxo-2-pentanamine;

(2S)-N,3-dimethyl-1-((2S)-2-(4-(4'-(2-((2S)-1-((2S)-3-methyl-2-(methylamino)pentanoyl)-2-pyrrolidinyl)-1H-imidazol-5-yl)-4-biphenylyl)-1H-imidazol-2-yl)-1-pyrrolidinyl)-1-oxo-2-pentanamine;

(2S)-N,3-dimethyl-1-((2S)-2-(4-(4'-(2-((2S)-1-((2S)-3-methyl-2-(methylamino)butanoyl)-2-pyrrolidinyl)-1H-imidazol-5-yl)-4-biphenylyl)-1H-imidazol-2-yl)-1-pyrrolidinyl)-1-oxo-2-butanamine;

(2S,3R)-N,3-dimethyl-1-((2S)-2-(4-(4'-(2-((2S)-1-((2S,3R)-3-methyl-2-(methylamino)pentanoyl)-2-pyrrolidinyl)-1H-imidazol-5-yl)-4-biphenylyl)-1H-imidazol-2-yl)-1-pyrrolidinyl)-1-oxo-2-pentanamine;

methyl ((1S)-1-(((2S)-2-(4-(4'-(2-((2S)-1-((2S)-2-((methoxycarbonyl)amino)-2,3-dimethylbutanoyl)-2-pyrrolidinyl)-1H-imidazol-5-yl)-4-biphenylyl)-1H-imidazol-2-yl)-1-pyrrolidinyl)carbonyl)-1,2-dimethylpropyl)carbamate;

methyl ((1S)-2-((2S)-2-(4-(4'-(2-((2S)-1-((2S)-2-((methoxycarbonyl)amino)-2-(tetrahydro-2H-pyran-4-yl)acetyl)-2-pyrrolidinyl)-1H-imidazol-5-yl)-4-biphenylyl)-

1H-imidazol-2-yl)-1-pyrrolidinyl)-2-oxo-1-(tetrahydro-2H-pyran-4-yl)ethyl)carbamate;

methyl (2-((2S)-2-(4-(4'-(2-((2S)-1-(((methoxycarbonyl)amino)(tetrahydro-2H-pyran-4-yl)acetyl)-2-pyrrolidinyl)-1H-imidazol-5-yl)-4-biphenylyl)-1H-imidazol-2-yl)-1-pyrrolidinyl)-2-oxo-1-(tetrahydro-2H-pyran-4-yl)ethyl)carbamate;

methyl ((1S)-2-((2S)-2-(4-(4'-(2-((2S)-1-((2R)-2-(ethylamino)-2-phenylacetyl)-2-pyrrolidinyl)-1H-imidazol-5-yl)-4-biphenylyl)-1H-imidazol-2-yl)-1-pyrrolidinyl)-1-methyl-2-oxoethyl)carbamate;

methyl ((1S)-1-(((2S)-2-(5-(4'-(2-((2S)-1-((2R)-2-(diethylamino)-2-phenylacetyl)-2-pyrrolidinyl)-1H-imidazol-4-yl)-4-biphenylyl)-1H-imidazol-2-yl)-1-pyrrolidinyl)carbonyl)-1,2-dimethylpropyl)carbamate;

methyl ((1S)-2-methyl-1-(((2S)-2-(4-(4'-(2-((2S)-1-(N-(tetrahydro-2H-pyran-4-yl)-L-alanyl)-2-pyrrolidinyl)-1H-imidazol-4-yl)-4-biphenylyl)-1H-imidazol-2-yl)-1-pyrrolidinyl)carbonyl)propyl)carbamate;

methyl ((1S)-2-methyl-1-(((2S)-2-(4-(4'-(2-((2S)-1-(N-(tetrahydro-2H-pyran-4-yl)-L-valyl)-2-pyrrolidinyl)-1H-imidazol-4-yl)-4-biphenylyl)-1H-imidazol-2-yl)-1-pyrrolidinyl)carbonyl)propyl)carbamate;

methyl ((1S)-2-methyl-1-(((2S)-2-(4-(4'-(2-((2S)-1-(N-(tetrahydro-2H-pyran-4-yl)glycyl)-2-pyrrolidinyl)-1H-imidazol-4-yl)-4-biphenylyl)-1H-imidazol-2-yl)-1-pyrrolidinyl)carbonyl)propyl)carbamate;

methyl ((1S)-2-methyl-1-(((2S)-2-(4-(4'-(2-((2S)-1-(N-(tetrahydro-2H-pyran-4-yl)-D-valyl)-2-pyrrolidinyl)-1H-imidazol-4-yl)-4-biphenylyl)-1H-imidazol-2-yl)-1-pyrrolidinyl)carbonyl)propyl)carbamate;

methyl ((1S)-2-methyl-1-(((2S)-2-(4-(4'-(2-((2S)-1-(N-(tetrahydro-2H-pyran-4-yl)-D-alanyl)-2-pyrrolidinyl)-1H-imidazol-4-yl)-4-biphenylyl)-1H-imidazol-2-yl)-1-pyrrolidinyl)carbonyl)propyl)carbamate;

(3S)-tetrahydro-3-furanyl ((1S)-1-(((2S)-2-(4-(4'-(2-((2S)-1-(N-(methoxycarbonyl)-L-valyl)-2-pyrrolidinyl)-1H-imidazol-4-yl)-4-biphenylyl)-1H-imidazol-2-yl)-1-pyrrolidinyl)carbonyl)-2-methylpropyl)carbamate;

tetrahydro-2H-pyran-4-yl ((1S)-1-(((2S)-2-(4-(4'-(2-((2S)-1-(N-(methoxycarbonyl)-L-valyl)-2-pyrrolidinyl)-1H-imidazol-4-yl)-4-biphenylyl)-1H-imidazol-2-yl)-1-pyrrolidinyl)carbonyl)-2-methylpropyl)carbamate;

(3R)-tetrahydro-3-furanyl ((1S)-1-(((2S)-2-(4-(4'-(2-((2S)-1-(N-(methoxycarbonyl)-L-valyl)-2-pyrrolidinyl)-1H-imidazol-4-yl)-4-biphenylyl)-1H-imidazol-2-yl)-1-pyrrolidinyl)carbonyl)-2-methylpropyl)carbamate;

methyl ((1S)-1-(((2S)-2-(4-(4'-(2-((2S)-1-((2R)-2-((methoxycarbonyl)amino)-2-(tetrahydro-2H-pyran-4-yl)acetyl)-2-pyrrolidinyl)-1H-imidazol-5-yl)-4-biphenylyl)-1H-imidazol-2-yl)-1-pyrrolidinyl)carbonyl)-2-methylpropyl)carbamate;

methyl ((1S)-1-(((2S)-2-(4-(4'-(2-((2S)-1-((2S)-2-((methoxycarbonyl)amino)-2-(tetrahydro-2H-pyran-4-yl)acetyl)-2-pyrrolidinyl)-1H-imidazol-5-yl)-4-biphenylyl)-1H-imidazol-2-yl)-1-pyrrolidinyl)carbonyl)-2-methylpropyl)carbamate;

N-((1S)-1-(((2S)-2-(4-(4'-(2-((2S)-1-((2S)-2-acetamido-3-methylbutanoyl)-2-pyrrolidinyl)-1H-imidazol-4-yl)-4-biphenylyl)-1H-imidazol-2-yl)-1-pyrrolidinyl)carbonyl)-2-methylpropyl)acetamide;

N-((1S)-2-methyl-1-(((2S)-2-(4-(4'-(2-((2S)-1-((2S)-3-methyl-2-(propionylamino)butanoyl)-2-pyrrolidinyl)-1H-imidazol-4-yl)-4-biphenylyl)-1H-imidazol-2-yl)-1-pyrrolidinyl)carbonyl)propyl)propanamide;

2-methoxy-N-((1S)-1-(((2S)-2-(4-(4'-(2-((2S)-1-((2S)-2-((methoxyacetyl)amino)-3-methylbutanoyl)-2-pyrrolidinyl)-1H-imidazol-4-yl)-4-biphenylyl)-1H-imidazol-2-yl)-1-pyrrolidinyl)carbonyl)-2-methylpropyl)acetamide;

1-methyl-3-((1S)-2-methyl-1-(((2S)-2-(4-(4'-(2-((2S)-1-(N-(methylcarbamoyl)-L-valyl)-2-pyrrolidinyl)-1H-imidazol-4-yl)-4-biphenylyl)-1H-imidazol-2-yl)-1-pyrrolidinyl)carbonyl)propyl)urea;

1-ethyl-3-((1S)-1-(((2S)-2-(4-(4'-(2-((2S)-1-((2S)-2-((ethylcarbamoyl)amino)-3-methylbutanoyl)-2-pyrrolidinyl)-1H-imidazol-4-yl)-4-biphenylyl)-1H-imidazol-2-yl)-1-pyrrolidinyl)carbonyl)-2-methylpropyl)urea;

N-((1S)-2-methyl-1-(((2S)-2-(4-(4'-(2-((2S)-1-((2S)-3-methyl-2-((methylsulfonyl)amino)butanoyl)-2-pyrrolidinyl)-1H-imidazol-4-yl)-4-biphenylyl)-1H-imidazol-2-yl)-1-pyrrolidinyl)carbonyl)propyl)methanesulfonamide;

N-((1S)-1-(((2S)-2-(4-(4'-(2-((2S)-1-((2S)-2-((ethylsulfonyl)amino)-3-methylbutanoyl)-2-pyrrolidinyl)-1H-imidazol-4-yl)-4-biphenylyl)-1H-imidazol-2-yl)-1-pyrrolidinyl)carbonyl)-2-methylpropyl)ethanesulfonamide;

N-((1S)-1-(((2S)-2-(4-(4'-(2-((2S)-1-((2S)-2-((cyclopropylsulfonyl)amino)-3-methylbutanoyl)-2-pyrrolidinyl)-1H-imidazol-4-yl)-4-biphenylyl)-1H-imidazol-2-yl)-1-pyrrolidinyl)carbonyl)-2-methylpropyl)cyclopropanesulfonamide;

N-((1S)-1-methyl-2-((2S)-2-(5-(4'-(2-((2S)-1-(N-(methylsulfonyl)-L-alanyl)-2-pyrrolidinyl)-1H-imidazol-4-yl)-4-biphenylyl)-1H-imidazol-2-yl)-1-pyrrolidinyl)-2-oxoethyl)methanesulfonamide;

methyl ((1S)-2-methyl-1-(((2S)-2-(5-(4'-(2-((2S)-1-(N-2-pyrimidinyl-L-valyl)-2-pyrrolidinyl)-1H-imidazol-5-yl)-4-biphenylyl)-1H-imidazol-2-yl)-1-pyrrolidinyl)carbonyl)propyl)carbamate;

methyl ((1S)-1-methyl-2-oxo-2-((2S)-2-(5-(4'-(2-((2S)-1-(N-2-pyrimidinyl-L-valyl)-2-pyrrolidinyl)-1H-imidazol-5-yl)-4-biphenylyl)-1H-imidazol-2-yl)-1-pyrrolidinyl)ethyl)carbamate;

methyl ((1R)-2-oxo-1-phenyl-2-((2S)-2-(5-(4'-(2-((2S)-1-(N-2-pyrimidinyl-L-valyl)-2-pyrrolidinyl)-1H-imidazol-5-yl)-4-biphenylyl)-1H-imidazol-2-yl)-1-pyrrolidinyl)ethyl)carbamate;

N-((1S)-1-(((2S)-2-(5-(4'-(2-((2S)-1-((2R)-2-(diethylamino)-2-phenylacetyl)-2-pyrrolidinyl)-1H-imidazol-5-yl)-4-biphenylyl)-1H-imidazol-2-yl)-1-pyrrolidinyl)carbonyl)-2-methylpropyl)-2-pyrimidinamine;

methyl ((1S)-2-methyl-1-(((2S)-2-(5-(4'-(2-((2S)-1-(N-(1-methyl-4,5-dihydro-1H-imidazol-2-yl)-L-valyl)-2-pyrrolidinyl)-1H-imidazol-5-yl)-4-biphenylyl)-1H-imidazol-2-yl)-1-pyrrolidinyl)carbonyl)propyl)carbamate;

methyl ((1S)-1-(((2S)-2-(5-(4'-(2-((2S)-1-(N-(4,5-dihydro-1H-imidazol-2-yl)-L-valyl)-2-pyrrolidinyl)-1H-imidazol-5-yl)-4-biphenylyl)-1H-imidazol-2-yl)-1-pyrrolidinyl)carbonyl)-2-methylpropyl)carbamate;

methyl ((1S)-2-((2S)-2-(5-(4'-(2-((2S)-1-(N-(4,5-dihydro-1H-imidazol-2-yl)-L-valyl)-2-pyrrolidinyl)-1H-imidazol-5-yl)-4-biphenylyl)-1H-imidazol-2-yl)-1-pyrrolidinyl)-1-methyl-2-oxoethyl)carbamate;

N-((1S)-1-(((2S)-2-(5-(4'-(2-((2S)-1-((2R)-2-(diethylamino)-2-phenylacetyl)-2-pyrrolidinyl)-1H-imidazol-5-yl)-4-biphenylyl)-1H-imidazol-2-yl)-1-pyrrolidinyl)carbonyl)-2-methylpropyl)-4,5-dihydro-1H-imidazol-2-amine;

methyl ((1R)-2-oxo-1-phenyl-2-((2S)-2-(5-(4'-(2-((2S)-1-(N-2-pyrimidinyl-D-valyl)-2-pyrrolidinyl)-1H-imidazol-5-yl)-4-biphenylyl)-1H-imidazol-2-yl)-1-pyrrolidinyl)ethyl)carbamate;

methyl ((1S)-2-methyl-1-(((2S)-2-(5-(4'-(2-((2S)-1-(N-2-pyrimidinyl-D-valyl)-2-pyrrolidinyl)-1H-imidazol-5-yl)-4-biphenylyl)-1H-imidazol-2-yl)-1-pyrrolidinyl)carbonyl)propyl)carbamate;

methyl ((1S)-1-methyl-2-oxo-2-((2S)-2-(5-(4'-(2-((2S)-1-(N-2-pyrimidinyl-D-valyl)-2-pyrrolidinyl)-1H-imidazol-5-yl)-4-biphenylyl)-1H-imidazol-2-yl)-1-pyrrolidinyl)ethyl)carbamate;

N-((1R)-1-(((2S)-2-(5-(4'-(2-((2S)-1-((2R)-2-(diethylamino)-2-phenylacetyl)-2-pyrrolidinyl)-1H-imidazol-5-yl)-4-biphenylyl)-1H-imidazol-2-yl)-1-pyrrolidinyl)carbonyl)-2-methylpropyl)-2-pyrimidinamine;

methyl ((1S)-2-methyl-1-(((2S)-2-(5-(4'-(2-((2S)-1-(N-(1-methyl-4,5-dihydro-1H-imidazol-2-yl)-D-valyl)-2-pyrrolidinyl)-1H-imidazol-5-yl)-4-biphenylyl)-1H-imidazol-2-yl)-1-pyrrolidinyl)carbonyl)propyl)carbamate;

methyl ((1S)-1-(((2S)-2-(5-(4'-(2-((2S)-1-(N-(4,5-dihydro-1H-imidazol-2-yl)-D-valyl)-2-pyrrolidinyl)-1H-imidazol-5-yl)-4-biphenylyl)-1H-imidazol-2-yl)-1-pyrrolidinyl)carbonyl)-2-methylpropyl)carbamate;

methyl ((1S)-1-cyclopropyl-2-((2S)-2-(5-(4'-(2-((2S)-1-(N-(4,5-dihydro-1H-imidazol-2-yl)-D-valyl)-2-pyrrolidinyl)-1H-imidazol-5-yl)-4-biphenylyl)-1H-imidazol-2-yl)-1-pyrrolidinyl)-2-oxoethyl)carbamate;

N-((1R)-1-(((2S)-2-(5-(4'-(2-((2S)-1-((2R)-2-(diethylamino)-2-phenylacetyl)-2-pyrrolidinyl)-1H-imidazol-5-yl)-4-biphenylyl)-1H-imidazol-2-yl)-1-pyrrolidinyl)carbonyl)-2-methylpropyl)-4,5-dihydro-1H-imidazol-2-amine;

methyl ((1S)-1-(((2S)-2-(5-(4'-(2-((2S)-1-(N-(5-amino-1-methyl-1H-1,2,4-triazol-3-yl)-L-valyl)-2-pyrrolidinyl)-1H-imidazol-5-yl)-4-biphenylyl)-1H-imidazol-2-yl)-1-pyrrolidinyl)carbonyl)-2-methylpropyl)carbamate;

methyl ((1S)-1-(((2S)-2-(5-(4'-(2-((2S)-1-(N-(4,5-dihydro-1,3-thiazol-2-yl)-L-valyl)-2-pyrrolidinyl)-1H-imidazol-5-yl)-4-biphenylyl)-1H-imidazol-2-yl)-1-pyrrolidinyl)carbonyl)-2-methylpropyl)carbamate;

methyl ((1S)-2-methyl-1-(((2S)-2-(5-(4'-(2-((2S)-1-(N-4-pyrimidinyl-L-valyl)-2-pyrrolidinyl)-1H-imidazol-5-yl)-4-biphenylyl)-1H-imidazol-2-yl)-1-pyrrolidinyl)carbonyl)propyl)carbamate;

methyl ((1S)-1-(((2S)-2-(5-(4'-(2-((2S)-1-(N-(5-amino-1,2,4-oxadiazol-3-yl)-L-valyl)-2-pyrrolidinyl)-1H-imidazol-5-yl)-4-biphenylyl)-1H-imidazol-2-yl)-1-pyrrolidinyl)carbonyl)-2-methylpropyl)carbamate;

methyl ((1S)-1-(((2S)-2-(5-(4'-(2-((2S)-1-(N-(cyano(dimethyl)carbamimidoyl)-L-valyl)-2-pyrrolidinyl)-1H-imidazol-5-yl)-4-biphenylyl)-1H-imidazol-2-yl)-1-pyrrolidinyl)carbonyl)-2-methylpropyl)carbamate;

methyl ((1S)-2-methyl-1-(((2S)-2-(5-(4'-(2-((2S)-1-(N-3-pyridinyl-L-valyl)-2-pyrrolidinyl)-1H-imidazol-5-yl)-4-biphenylyl)-1H-imidazol-2-yl)-1-pyrrolidinyl)carbonyl)propyl)carbamate;

methyl ((1S)-1-methyl-2-oxo-2-((2S)-2-(5-(4'-(2-((2S)-1-(N-3-pyridinyl-L-valyl)-2-pyrrolidinyl)-1H-imidazol-5-yl)-4-biphenylyl)-1H-imidazol-2-yl)-1-pyrrolidinyl)ethyl)carbamate;

methyl ((1S,2R)-2-methoxy-1-(((2S)-2-(5-(4'-(2-((2S)-1-(N-3-pyridinyl-L-valyl)-2-pyrrolidinyl)-1H-imidazol-5-yl)-4-biphenylyl)-1H-imidazol-2-yl)-1-pyrrolidinyl)carbonyl)propyl)carbamate;

N-((1S)-1-(((2S)-2-(5-(4'-(2-((2S)-1-((2R)-2-(diethylamino)-2-phenylacetyl)-2-pyrrolidinyl)-1H-imidazol-5-yl)-4-biphenylyl)-1H-imidazol-2-yl)-1-pyrrolidinyl)carbonyl)-2-methylpropyl)-3-pyridinamine;

methyl ((1S)-2-methyl-1-(((2S)-2-(5-(4'-(2-((2S)-1-(N-5-pyrimidinyl-L-valyl)-2-pyrrolidinyl)-1H-imidazol-5-yl)-4-biphenylyl)-1H-imidazol-2-yl)-1-pyrrolidinyl)carbonyl)propyl)carbamate;

methyl ((1S)-2-((2S)-2-(5-(4'-(2-((2S)-1-((2R)-2-(diethylamino)-2-phenylacetyl)-2-pyrrolidinyl)-1H-imidazol-5-yl)-4-biphenylyl)-1H-imidazol-2-yl)-1-pyrrolidinyl)-2-oxo-1-(1H-1,2,3-triazol-4-ylmethyl)ethyl)carbamate;

methyl ((1S)-2-((2S)-2-(5-(4'-(2-((2S)-1-(N-(methoxycarbonyl)-L-alanyl)-2-pyrrolidinyl)-1H-imidazol-5-yl)-4-biphenylyl)-1H-imidazol-2-yl)-1-pyrrolidinyl)-2-oxo-1-(1H-1,2,3-triazol-4-ylmethyl)ethyl)carbamate;

methyl ((1S)-1-(((2S)-2-(5-(4'-(2-((2S)-1-((2S)-2-((methoxycarbonyl)amino)-3-(1H-1,2,3-triazol-4-yl)propanoyl)-2-pyrrolidinyl)-1H-imidazol-5-yl)-4-biphenylyl)-1H-imidazol-2-yl)-1-pyrrolidinyl)carbonyl)-2-methylpropyl)carbamate;

methyl ((1S)-2-((2S)-2-(5-(4'-(2-((2S)-1-((2S,3R)-3-methoxy-2-((methoxycarbonyl)amino)butanoyl)-2-pyrrolidinyl)-1H-imidazol-5-yl)-4-biphenylyl)-1H-imidazol-2-yl)-1-pyrrolidinyl)-2-oxo-1-(1H-1,2,3-triazol-4-ylmethyl)ethyl)carbamate;

methyl ((1S)-2-((2S)-2-(5-(4'-(2-((2S)-1-((2R)-2-(diethylamino)-2-phenylacetyl)-2-pyrrolidinyl)-1H-imidazol-5-yl)-4-biphenylyl)-1H-imidazol-2-yl)-1-pyrrolidinyl)-2-oxo-1-(1H-pyrazol-1-ylmethyl)ethyl)carbamate;

methyl ((1S)-2-((2S)-2-(5-(4'-(2-((2S)-1-(N-(methoxycarbonyl)-L-alanyl)-2-pyrrolidinyl)-1H-imidazol-5-yl)-4-biphenylyl)-1H-imidazol-2-yl)-1-pyrrolidinyl)-2-oxo-1-(1H-pyrazol-1-ylmethyl)ethyl)carbamate;

methyl ((1S)-1-(((2S)-2-(5-(4'-(2-((2S)-1-((2S)-2-((methoxycarbonyl)amino)-3-(1H-pyrazol-1-yl)propanoyl)-2-pyrrolidinyl)-1H-imidazol-5-yl)-4-biphenylyl)-1H-imidazol-2-yl)-1-pyrrolidinyl)carbonyl)-2-methylpropyl)carbamate;

methyl ((1S)-2-((2S)-2-(5-(4'-(2-((2S)-1-(N-(methoxycarbonyl)-O-methyl-L-threonyl)-2-pyrrolidinyl)-1H-imidazol-5-yl)-4-biphenylyl)-1H-imidazol-2-yl)-1-pyrrolidinyl)-2-oxo-1-(1H-pyrazol-1-ylmethyl)ethyl)carbamate;

methyl ((1S)-2-((2S)-2-(5-(4'-(2-((2S)-1-((2R)-2-(diethylamino)-2-phenylacetyl)-2-pyrrolidinyl)-1H-imidazol-5-yl)-4-biphenylyl)-1H-imidazol-2-yl)-1-pyrrolidinyl)-1-((1-methyl-1H-imidazol-4-yl)methyl)-2-oxoethyl)carbamate;

methyl ((1S)-2-((2S)-2-(5-(4'-(2-((2S)-1-(N-(methoxycarbonyl)-L-alanyl)-2-pyrrolidinyl)-1H-imidazol-5-yl)-4-biphenylyl)-1H-imidazol-2-yl)-1-pyrrolidinyl)-1-((1-methyl-1H-imidazol-4-yl)methyl)-2-oxoethyl)carbamate;

methyl ((1S)-1-(((2S)-2-(5-(4'-(2-((2S)-1-((2S)-2-((methoxycarbonyl)amino)-3-(1-methyl-1H-imidazol-4-yl)propanoyl)-2-pyrrolidinyl)-1H-imidazol-5-yl)-4-biphenylyl)-1H-imidazol-2-yl)-1-pyrrolidinyl)carbonyl)-2-methylpropyl)carbamate;

methyl ((1S)-2-((2S)-2-(5-(4'-(2-((2S)-1-((2S,3R)-3-methoxy-2-((methoxycarbonyl)amino)butanoyl)-2-pyrrolidinyl)-1H-imidazol-5-yl)-4-biphenylyl)-1H-imidazol-2-yl)-1-pyrrolidinyl)-1-((1-methyl-1H-imidazol-4-yl)methyl)-2-oxoethyl)carbamate;

methyl ((1S)-2-((2S)-2-(5-(4'-(2-((2S)-1-((2R)-2-(diethylamino)-2-phenylacetyl)-2-pyrrolidinyl)-1H-imidazol-5-yl)-4-biphenylyl)-1H-imidazol-2-yl)-1-pyrrolidinyl)-1-((1-methyl-1H-imidazol-5-yl)methyl)-2-oxoethyl)carbamate;

methyl ((1S)-2-((2S)-2-(5-(4'-(2-((2S)-1-(N-(methoxycarbonyl)-L-alanyl)-2-pyrrolidinyl)-1H-imidazol-5-yl)-4-biphenylyl)-1H-imidazol-2-yl)-1-pyrrolidinyl)-1-((1-methyl-1H-imidazol-5-yl)methyl)-2-oxoethyl)carbamate;

methyl ((1S)-1-(((2S)-2-(5-(4'-(2-((2S)-1-((2S)-2-((methoxycarbonyl)amino)-3-(1-methyl-1H-imidazol-5-yl)propanoyl)-2-pyrrolidinyl)-1H-imidazol-5-yl)-4-biphenylyl)-1H-imidazol-2-yl)-1-pyrrolidinyl)carbonyl)-2-methylpropyl)carbamate;

methyl ((1S)-2-((2S)-2-(5-(4'-(2-((2S)-1-((2S,3R)-3-methoxy-2-((methoxycarbonyl)amino)butanoyl)-2-pyrrolidinyl)-1H-imidazol-5-yl)-4-

biphenylyl)-1H-imidazol-2-yl)-1-pyrrolidinyl)-1-((1-methyl-1H-imidazol-5-yl)methyl)-2-oxoethyl)carbamate;

methyl ((1S)-1-methyl-2-oxo-2-((2S)-2-(5-(4'-(2-((2S)-1-(((2S)-4-oxo-2-azetidinyl)carbonyl)-2-pyrrolidinyl)-1H-imidazol-5-yl)-4-biphenylyl)-1H-imidazol-2-yl)-1-pyrrolidinyl)ethyl)carbamate;

methyl (2S)-2-(((2S)-2-(5-(4'-(2-((2S)-1-(N-(methoxycarbonyl)-L-alanyl)-2-pyrrolidinyl)-1H-imidazol-5-yl)-4-biphenylyl)-1H-imidazol-2-yl)-1-pyrrolidinyl)carbonyl)-1-azetidinecarboxylate;

methyl (2S)-2-(((2S)-2-(5-(4'-(2-((2S)-1-((2R)-2-(diethylamino)-2-phenylacetyl)-2-pyrrolidinyl)-1H-imidazol-5-yl)-4-biphenylyl)-1H-imidazol-2-yl)-1-pyrrolidinyl)carbonyl)-1-azetidinecarboxylate;

methyl ((1S)-3-((2S)-2-(5-(4'-(2-((2S)-1-((2R)-2-(diethylamino)-2-phenylacetyl)-2-pyrrolidinyl)-1H-imidazol-5-yl)-4-biphenylyl)-1H-imidazol-2-yl)-1-pyrrolidinyl)-1-methyl-3-oxopropyl)carbamate;

methyl ((1R)-3-((2S)-2-(5-(4'-(2-((2S)-1-((2R)-2-(diethylamino)-2-phenylacetyl)-2-pyrrolidinyl)-1H-imidazol-5-yl)-4-biphenylyl)-1H-imidazol-2-yl)-1-pyrrolidinyl)-1-isopropyl-3-oxopropyl)carbamate;

methyl ((1S)-1-benzyl-3-((2S)-2-(5-(4'-(2-((2S)-1-((2R)-2-(diethylamino)-2-phenylacetyl)-2-pyrrolidinyl)-1H-imidazol-5-yl)-4-biphenylyl)-1H-imidazol-2-yl)-1-pyrrolidinyl)-3-oxopropyl)carbamate;

methyl ((1R)-3-((2S)-2-(5-(4'-(2-((2S)-1-((2R)-2-(diethylamino)-2-phenylacetyl)-2-pyrrolidinyl)-1H-imidazol-5-yl)-4-biphenylyl)-1H-imidazol-2-yl)-1-pyrrolidinyl)-3-oxo-1-(2-thienylmethyl)propyl)carbamate;

methyl ((1R)-3-((2S)-2-(5-(4'-(2-((2S)-1-((2R)-2-(diethylamino)-2-phenylacetyl)-2-pyrrolidinyl)-1H-imidazol-5-yl)-4-biphenylyl)-1H-imidazol-2-yl)-1-pyrrolidinyl)-3-oxo-1-(3-thienylmethyl)propyl)carbamate;

methyl ((1S)-3-((2S)-2-(5-(4'-(2-((2S)-1-((2R)-2-(diethylamino)-2-phenylacetyl)-2-pyrrolidinyl)-1H-imidazol-5-yl)-4-biphenylyl)-1H-imidazol-2-yl)-1-pyrrolidinyl)-3-oxo-1-(2-thienylmethyl)propyl)carbamate;

methyl ((1S,3R)-3-(((2S)-2-(5-(4'-(2-((2S)-1-((2R)-2-(diethylamino)-2-phenylacetyl)-2-pyrrolidinyl)-1H-imidazol-5-yl)-4-biphenylyl)-1H-imidazol-2-yl)-1-pyrrolidinyl)carbonyl)cyclopentyl)carbamate;

methyl ((1R)-1-benzyl-3-((2S)-2-(5-(4'-(2-((2S)-1-((2R)-2-(diethylamino)-2-phenylacetyl)-2-pyrrolidinyl)-1H-imidazol-5-yl)-4-biphenylyl)-1H-imidazol-2-yl)-1-pyrrolidinyl)-3-oxopropyl)carbamate;

methyl ((1R)-3-((2S)-2-(5-(4'-(2-((2S)-1-((2R)-2-(diethylamino)-2-phenylacetyl)-2-pyrrolidinyl)-1H-imidazol-5-yl)-4-biphenylyl)-1H-imidazol-2-yl)-1-pyrrolidinyl)-1-(2-fluorobenzyl)-3-oxopropyl)carbamate;

methyl ((1R,3S)-3-(((2S)-2-(5-(4'-(2-((2S)-1-((2R)-2-(diethylamino)-2-phenylacetyl)-2-pyrrolidinyl)-1H-imidazol-5-yl)-4-biphenylyl)-1H-imidazol-2-yl)-1-pyrrolidinyl)carbonyl)cyclopentyl)carbamate;

methyl ((1S)-1-(((2S)-2-(5-(4'-(2-((2S)-1-(((1R,3S)-3-((methoxycarbonyl)amino)cyclopentyl)carbonyl)-2-pyrrolidinyl)-1H-imidazol-5-yl)-4-biphenylyl)-1H-imidazol-2-yl)-1-pyrrolidinyl)carbonyl)-2-methylpropyl)carbamate;

methyl ((1S)-1-(((2S)-2-(5-(4'-(2-((2S)-1-(((1S,3R)-3-((methoxycarbonyl)amino)cyclopentyl)carbonyl)-2-pyrrolidinyl)-1H-imidazol-5-yl)-4-biphenylyl)-1H-imidazol-2-yl)-1-pyrrolidinyl)carbonyl)-2-methylpropyl)carbamate;

methyl ((1R)-2-((2S)-2-(5-(4'-(2-((2S)-1-(((1R,3S)-3-((methoxycarbonyl)amino)cyclopentyl)carbonyl)-2-pyrrolidinyl)-1H-imidazol-5-yl)-4-biphenylyl)-1H-imidazol-2-yl)-1-pyrrolidinyl)-2-oxo-1-phenylethyl)carbamate;

methyl ((1R)-2-((2S)-2-(5-(4'-(2-((2S)-1-(((1S,3R)-3-((methoxycarbonyl)amino)cyclopentyl)carbonyl)-2-pyrrolidinyl)-1H-imidazol-5-yl)-4-biphenylyl)-1H-imidazol-2-yl)-1-pyrrolidinyl)-2-oxo-1-phenylethyl)carbamate;

methyl ((1S)-1-(((2S)-2-(5-(4'-(2-((2S)-1-((2S)-2-((methoxycarbonyl)amino)-3-(2-pyridinyl)propanoyl)-2-pyrrolidinyl)-1H-imidazol-5-yl)-4-biphenylyl)-1H-imidazol-2-yl)-1-pyrrolidinyl)carbonyl)-2-methylpropyl)carbamate;

methyl ((1S)-2-((2S)-2-(5-(4'-(2-((2S)-1-(N-(methoxycarbonyl)-L-alanyl)-2-pyrrolidinyl)-1H-imidazol-5-yl)-4-biphenylyl)-1H-imidazol-2-yl)-1-pyrrolidinyl)-2-oxo-1-(2-pyridinylmethyl)ethyl)carbamate;

methyl ((1S)-2-((2S)-2-(5-(4'-(2-((2S)-1-((2S,3R)-3-methoxy-2-((methoxycarbonyl)amino)butanoyl)-2-pyrrolidinyl)-1H-imidazol-5-yl)-4-biphenylyl)-1H-imidazol-2-yl)-1-pyrrolidinyl)-2-oxo-1-(2-pyridinylmethyl)ethyl)carbamate;

methyl ((1S)-2-((2S)-2-(5-(4'-(2-((2S)-1-((2R)-2-(diethylamino)-2-phenylacetyl)-2-pyrrolidinyl)-1H-imidazol-5-yl)-4-biphenylyl)-1H-imidazol-2-yl)-1-pyrrolidinyl)-2-oxo-1-(2-pyridinylmethyl)ethyl)carbamate;

methyl ((1S)-1-(((2S)-2-(5-(4'-(2-((2S)-1-((cis-4-((methoxycarbonyl)amino)cyclohexyl)carbonyl)-2-pyrrolidinyl)-1H-imidazol-5-yl)-4-biphenylyl)-1H-imidazol-2-yl)-1-pyrrolidinyl)carbonyl)-2-methylpropyl)carbamate;

methyl ((1S)-1-(((2S)-2-(5-(4'-(2-((2S)-1-((trans-4-((methoxycarbonyl)amino)cyclohexyl)carbonyl)-2-pyrrolidinyl)-1H-imidazol-5-yl)-4-biphenylyl)-1H-imidazol-2-yl)-1-pyrrolidinyl)carbonyl)-2-methylpropyl)carbamate;

methyl ((1S)-1-(((2S)-2-(5-(4'-(2-((2S)-1-((cis-4-(diethylamino)cyclohexyl)carbonyl)-2-pyrrolidinyl)-1H-imidazol-5-yl)-4-biphenylyl)-1H-imidazol-2-yl)-1-pyrrolidinyl)carbonyl)-2-methylpropyl)carbamate;

methyl ((1S,2R)-1-(((2S)-2-(5-(4'-(2-((2S)-1-((cis-4-(diethylamino)cyclohexyl)carbonyl)-2-pyrrolidinyl)-1H-imidazol-5-yl)-4-biphenylyl)-1H-imidazol-2-yl)-1-pyrrolidinyl)carbonyl)-2-methoxypropyl)carbamate;

cis-4-(((2S)-2-(5-(4'-(2-((2S)-1-((2R)-2-(diethylamino)-2-phenylacetyl)-2-pyrrolidinyl)-1H-imidazol-5-yl)-4-biphenylyl)-1H-imidazol-2-yl)-1-pyrrolidinyl)carbonyl)-N,N-diethylcyclohexanamine;

methyl ((1S)-2-((2S)-2-(5-(4'-(2-((2S)-1-((cis-4-(diethylamino)cyclohexyl)carbonyl)-2-pyrrolidinyl)-1H-imidazol-5-yl)-4-biphenylyl)-1H-imidazol-2-yl)-1-pyrrolidinyl)-1-methyl-2-oxoethyl)carbamate;

methyl ((1S)-1-((1-benzyl-1H-imidazol-4-yl)methyl)-2-((2S)-2-(5-(4'-(2-((2S)-1-((2S,3R)-3-methoxy-2-((methoxycarbonyl)amino)butanoyl)-2-pyrrolidinyl)-1H-imidazol-5-yl)-4-biphenylyl)-1H-imidazol-2-yl)-1-pyrrolidinyl)-2-oxoethyl)carbamate;

methyl ((1S)-1-(((2S)-2-(5-(4'-(2-((2S)-1-((2S)-3-(1-benzyl-1H-imidazol-4-yl)-2-((methoxycarbonyl)amino)propanoyl)-2-pyrrolidinyl)-1H-imidazol-5-yl)-4-biphenylyl)-1H-imidazol-2-yl)-1-pyrrolidinyl)carbonyl)-2-methylpropyl)carbamate;

methyl ((1S)-2-((2S)-2-(5-(4'-(2-((2S)-1-((2S)-3-(1-benzyl-1H-imidazol-4-yl)-2-((methoxycarbonyl)amino)propanoyl)-2-pyrrolidinyl)-1H-imidazol-5-yl)-4-biphenylyl)-1H-imidazol-2-yl)-1-pyrrolidinyl)-1-methyl-2-oxoethyl)carbamate;

methyl ((1S)-2-((2S)-2-(5-(4'-(2-((2S)-1-((2S,3R)-3-methoxy-2-((methoxycarbonyl)amino)butanoyl)-2-pyrrolidinyl)-1H-imidazol-5-yl)-4-biphenylyl)-1H-imidazol-2-yl)-1-pyrrolidinyl)-2-oxo-1-(1,3-thiazol-4-ylmethyl)ethyl)carbamate;

methyl ((1S)-1-(((2S)-2-(5-(4'-(2-((2S)-1-((2S)-2-((methoxycarbonyl)amino)-3-(1,3-thiazol-4-yl)propanoyl)-2-pyrrolidinyl)-1H-imidazol-5-yl)-4-biphenylyl)-1H-imidazol-2-yl)-1-pyrrolidinyl)carbonyl)-2-methylpropyl)carbamate;

methyl ((1S)-2-((2S)-2-(5-(4'-(2-((2S)-1-((2R)-2-(diethylamino)-2-phenylacetyl)-2-pyrrolidinyl)-1H-imidazol-5-yl)-4-biphenylyl)-1H-imidazol-2-yl)-1-pyrrolidinyl)-2-oxo-1-(1,3-thiazol-4-ylmethyl)ethyl)carbamate;

methyl ((1S)-2-((2S)-2-(5-(4'-(2-((2S)-1-(N-(methoxycarbonyl)-L-alanyl)-2-pyrrolidinyl)-1H-imidazol-5-yl)-4-biphenylyl)-1H-imidazol-2-yl)-1-pyrrolidinyl)-2-oxo-1-(1,3-thiazol-4-ylmethyl)ethyl)carbamate;

methyl ((1S)-2-((2S)-2-(5-(4'-(2-((2S)-1-((2S,3R)-3-methoxy-2-((methoxycarbonyl)amino)butanoyl)-2-pyrrolidinyl)-1H-imidazol-5-yl)-4-biphenylyl)-1H-imidazol-2-yl)-1-pyrrolidinyl)-2-oxo-1-(3-pyridinylmethyl)ethyl)carbamate;

methyl ((1S)-2-((2S)-2-(5-(4'-(2-((2S)-1-((2S)-2-((methoxycarbonyl)amino)-3-methylbutanoyl)-2-pyrrolidinyl)-1H-imidazol-5-yl)-4-biphenylyl)-1H-imidazol-2-yl)-1-pyrrolidinyl)-2-oxo-1-(3-pyridinylmethyl)ethyl)carbamate;

methyl ((1S)-2-((2S)-2-(5-(4'-(2-((2S)-1-((2R)-2-(diethylamino)-2-phenylacetyl)-2-pyrrolidinyl)-1H-imidazol-5-yl)-4-biphenylyl)-1H-imidazol-2-yl)-1-pyrrolidinyl)-2-oxo-1-(3-pyridinylmethyl)ethyl)carbamate;

methyl ((1S)-2-((2S)-2-(5-(4'-(2-((2S)-1-(N-(methoxycarbonyl)-L-alanyl)-2-pyrrolidinyl)-1H-imidazol-5-yl)-4-biphenylyl)-1H-imidazol-2-yl)-1-pyrrolidinyl)-2-oxo-1-(3-pyridinylmethyl)ethyl)carbamate;

methyl ((1R,3S)-3-(((2S)-2-(5-(4'-(2-((2S)-1-((2S)-3-methoxy-2-((methoxycarbonyl)amino)butanoyl)-2-pyrrolidinyl)-1H-imidazol-5-yl)-4-biphenylyl)-1H-imidazol-2-yl)-1-pyrrolidinyl)carbonyl)cyclopentyl)carbamate;

methyl ((1S)-2-((2S)-2-(5-(4'-(2-((2S)-1-((2S,3R)-3-methoxy-2-((methoxycarbonyl)amino)butanoyl)-2-pyrrolidinyl)-1H-imidazol-5-yl)-4-biphenylyl)-1H-imidazol-2-yl)-1-pyrrolidinyl)-2-oxo-1-(4-pyridinylmethyl)ethyl)carbamate;

methyl ((1S)-2-((2S)-2-(5-(4'-(2-((2S)-1-((2S)-2-((methoxycarbonyl)amino)-3-methylbutanoyl)-2-pyrrolidinyl)-1H-imidazol-5-yl)-4-biphenylyl)-1H-imidazol-2-yl)-1-pyrrolidinyl)-2-oxo-1-(4-pyridinylmethyl)ethyl)carbamate;

methyl ((1S)-2-((2S)-2-(5-(4'-(2-((2S)-1-((2R)-2-(diethylamino)-2-phenylacetyl)-2-pyrrolidinyl)-1H-imidazol-5-yl)-4-biphenylyl)-1H-imidazol-2-yl)-1-pyrrolidinyl)-2-oxo-1-(4-pyridinylmethyl)ethyl)carbamate;

methyl ((1S)-2-((2S)-2-(5-(4'-(2-((2S)-1-(N-(methoxycarbonyl)-L-alanyl)-2-pyrrolidinyl)-1H-imidazol-5-yl)-4-biphenylyl)-1H-imidazol-2-yl)-1-pyrrolidinyl)-2-oxo-1-(4-pyridinylmethyl)ethyl)carbamate;

methyl ((1S)-1-(((2S)-2-(5-(4'-(2-((2S)-1-(O-(hydroxy(methoxy)phosphoryl)-N-(methoxycarbonyl)-L-tyrosyl)-2-pyrrolidinyl)-1H-imidazol-5-yl)-4-biphenylyl)-1H-imidazol-2-yl)-1-pyrrolidinyl)carbonyl)-2-methylpropyl)carbamate;

methyl ((1S,2R)-1-(((2S)-2-(5-(4'-(2-((2S)-1-(O-(hydroxy(methoxy)phosphoryl)-N-(methoxycarbonyl)-L-tyrosyl)-2-pyrrolidinyl)-1H-imidazol-5-yl)-4-biphenylyl)-1H-imidazol-2-yl)-1-pyrrolidinyl)carbonyl)-2-methoxypropyl)carbamate;

methyl ((1S)-1-(((2S)-2-(5-(4'-(2-((2S)-1-(((1S,2R)-2-((methoxycarbonyl)amino)cyclohexyl)carbonyl)-2-pyrrolidinyl)-1H-imidazol-5-yl)-4-biphenylyl)-1H-imidazol-2-yl)-1-pyrrolidinyl)carbonyl)-2-methylpropyl)carbamate;

methyl ((1R,2S)-2-(((2S)-2-(5-(4'-(2-((2S)-1-((2R)-2-(diethylamino)-2-phenylacetyl)-2-pyrrolidinyl)-1H-imidazol-5-yl)-4-biphenylyl)-1H-imidazol-2-yl)-1-pyrrolidinyl)carbonyl)cyclohexyl)carbamate;

methyl ((1R)-2-((2S)-2-(5-(4'-(2-((2S)-1-(((1S,2R)-2-((methoxycarbonyl)amino)cyclohexyl)carbonyl)-2-pyrrolidinyl)-1H-imidazol-5-yl)-4-biphenylyl)-1H-imidazol-2-yl)-1-pyrrolidinyl)-2-oxo-1-phenylethyl)carbamate;

methyl ((1R,2S)-2-(((2S)-2-(5-(4'-(2-((2S)-1-(N-(methoxycarbonyl)-L-alanyl)-2-pyrrolidinyl)-1H-imidazol-5-yl)-4-biphenylyl)-1H-imidazol-2-yl)-1-pyrrolidinyl)carbonyl)cyclohexyl)carbamate;

methyl ((1R,2S)-2-(((2S)-2-(5-(4'-(2-((2S)-1-((cis-4-(diethylamino)cyclohexyl)carbonyl)-2-pyrrolidinyl)-1H-imidazol-5-yl)-4-biphenylyl)-1H-imidazol-2-yl)-1-pyrrolidinyl)carbonyl)cyclohexyl)carbamate;

methyl ((1R,2S)-2-(((2S)-2-(5-(4'-(2-((2S)-1-((2R)-2-acetamido-2-phenylacetyl)-2-pyrrolidinyl)-1H-imidazol-5-yl)-4-biphenylyl)-1H-imidazol-2-yl)-1-pyrrolidinyl)carbonyl)cyclohexyl)carbamate;

methyl ((1S)-1-(((2S)-2-(5-(4'-(2-((2S)-1-((2S)-3-(1H-indol-3-yl)-2-((methoxycarbonyl)amino)propanoyl)-2-pyrrolidinyl)-1H-imidazol-5-yl)-4-biphenylyl)-1H-imidazol-2-yl)-1-pyrrolidinyl)carbonyl)-2-methylpropyl)carbamate;

methyl ((1S)-1-(1H-indol-3-ylmethyl)-2-((2S)-2-(5-(4'-(2-((2S)-1-((2S,3R)-3-methoxy-2-((methoxycarbonyl)amino)butanoyl)-2-pyrrolidinyl)-1H-imidazol-5-yl)-4-biphenylyl)-1H-imidazol-2-yl)-1-pyrrolidinyl)-2-oxoethyl)carbamate;

methyl ((1S)-2-((2S)-2-(5-(4'-(2-((2S)-1-((2R)-2-(diethylamino)-2-phenylacetyl)-2-pyrrolidinyl)-1H-imidazol-5-yl)-4-biphenylyl)-1H-imidazol-2-yl)-1-pyrrolidinyl)-1-(1H-indol-3-ylmethyl)-2-oxoethyl)carbamate;

methyl ((1S)-2-((2S)-2-(5-(4'-(2-((2S)-1-((2S)-3-(1H-indol-3-yl)-2-((methoxycarbonyl)amino)propanoyl)-2-pyrrolidinyl)-1H-imidazol-5-yl)-4-biphenylyl)-1H-imidazol-2-yl)-1-pyrrolidinyl)-1-methyl-2-oxoethyl)carbamate;

methyl ((1S)-1-(4-(aminomethyl)benzyl)-2-((2S)-2-(5-(4'-(2-((2S)-1-((2S)-2-((methoxycarbonyl)amino)-3-methylbutanoyl)-2-pyrrolidinyl)-1H-imidazol-5-yl)-4-biphenylyl)-1H-imidazol-2-yl)-1-pyrrolidinyl)-2-oxoethyl)carbamate;

methyl ((1S)-1-(((2S)-2-(5-(4'-(2-((2S)-1-(O-benzyl-N-(methoxycarbonyl)-L-tyrosyl)-2-pyrrolidinyl)-1H-imidazol-5-yl)-4-biphenylyl)-1H-imidazol-2-yl)-1-pyrrolidinyl)carbonyl)-2-methylpropyl)carbamate;

methyl ((1S,2R)-1-(((2S)-2-(5-(4'-(2-((2S)-1-(O-benzyl-N-(methoxycarbonyl)-L-tyrosyl)-2-pyrrolidinyl)-1H-imidazol-5-yl)-4-biphenylyl)-1H-imidazol-2-yl)-1-pyrrolidinyl)carbonyl)-2-methoxypropyl)carbamate;

methyl ((1S)-1-(4-(benzyloxy)benzyl)-2-((2S)-2-(5-(4'-(2-((2S)-1-((2R)-2-(diethylamino)-2-phenylacetyl)-2-pyrrolidinyl)-1H-imidazol-5-yl)-4-biphenylyl)-1H-imidazol-2-yl)-1-pyrrolidinyl)-2-oxoethyl)carbamate;

methyl ((1S)-1-(4-(benzyloxy)benzyl)-2-((2S)-2-(5-(4'-(2-((2S)-1-(N-(methoxycarbonyl)-L-alanyl)-2-pyrrolidinyl)-1H-imidazol-5-yl)-4-biphenylyl)-1H-imidazol-2-yl)-1-pyrrolidinyl)-2-oxoethyl)carbamate;

methyl ((1R,2R)-2-(((2S)-2-(5-(4'-(2-((2S)-1-(N-(methoxycarbonyl)-L-alanyl)-2-pyrrolidinyl)-1H-imidazol-5-yl)-4-biphenylyl)-1H-imidazol-2-yl)-1-pyrrolidinyl)carbonyl)cyclopentyl)carbamate;

methyl ((1R,2R)-2-(((2S)-2-(5-(4'-(2-((2S)-1-((2R)-2-(diethylamino)-2-phenylacetyl)-2-pyrrolidinyl)-1H-imidazol-5-yl)-4-biphenylyl)-1H-imidazol-2-yl)-1-pyrrolidinyl)carbonyl)cyclopentyl)carbamate;

methyl ((1R)-2-((2S)-2-(5-(4'-(2-((2S)-1-(((1R,2R)-2-((methoxycarbonyl)amino)cyclopentyl)carbonyl)-2-pyrrolidinyl)-1H-imidazol-5-yl)-4-biphenylyl)-1H-imidazol-2-yl)-1-pyrrolidinyl)-2-oxo-1-phenylethyl)carbamate;

methyl ((1S)-1-(4-hydroxybenzyl)-2-((2S)-2-(5-(4'-(2-((2S)-1-((2S)-2-((methoxycarbonyl)amino)-3-methylbutanoyl)-2-pyrrolidinyl)-1H-imidazol-5-yl)-4-biphenylyl)-1H-imidazol-2-yl)-1-pyrrolidinyl)-2-oxoethyl)carbamate;

methyl ((1S)-2-((2S)-2-(5-(4'-(2-((2S)-1-((2R)-2-(diethylamino)-2-phenylacetyl)-2-pyrrolidinyl)-1H-imidazol-5-yl)-4-biphenylyl)-1H-imidazol-2-yl)-1-pyrrolidinyl)-1-(4-hydroxybenzyl)-2-oxoethyl)carbamate;

methyl ((1S)-1-(4-hydroxybenzyl)-2-((2S)-2-(5-(4'-(2-((2S)-1-(N-(methoxycarbonyl)-L-alanyl)-2-pyrrolidinyl)-1H-imidazol-5-yl)-4-biphenylyl)-1H-imidazol-2-yl)-1-pyrrolidinyl)-2-oxoethyl)carbamate;

methyl ((1S)-1-(4-(acetamidomethyl)benzyl)-2-((2S)-2-(5-(4'-(2-((2S)-1-((2S)-2-((methoxycarbonyl)amino)-3-methylbutanoyl)-2-pyrrolidinyl)-1H-imidazol-5-yl)-4-biphenylyl)-1H-imidazol-2-yl)-1-pyrrolidinyl)-2-oxoethyl)carbamate;

methyl ((1S)-1-(4-(((ethylcarbamoyl)amino)methyl)benzyl)-2-((2S)-2-(5-(4'-(2-((2S)-1-((2S)-2-((methoxycarbonyl)amino)-3-methylbutanoyl)-2-pyrrolidinyl)-1H-imidazol-5-yl)-4-biphenylyl)-1H-imidazol-2-yl)-1-pyrrolidinyl)-2-oxoethyl)carbamate;

methyl ((1S,2S)-2-(((2S)-2-(5-(4'-(2-((2S)-1-((2R)-2-(diethylamino)-2-phenylacetyl)-2-pyrrolidinyl)-1H-imidazol-5-yl)-4-biphenylyl)-1H-imidazol-2-yl)-1-pyrrolidinyl)carbonyl)cyclopentyl)carbamate;

methyl ((1R)-2-((2S)-2-(5-(4'-(2-((2S)-1-(((1S,2S)-2-((methoxycarbonyl)amino)cyclopentyl)carbonyl)-2-pyrrolidinyl)-1H-imidazol-5-yl)-4-biphenylyl)-1H-imidazol-2-yl)-1-pyrrolidinyl)-2-oxo-1-phenylethyl)carbamate;

methyl ((1S,2S)-2-(((2S)-2-(5-(4'-(2-((2S)-1-(N-(methoxycarbonyl)-L-alanyl)-2-pyrrolidinyl)-1H-imidazol-5-yl)-4-biphenylyl)-1H-imidazol-2-yl)-1-pyrrolidinyl)carbonyl)cyclopentyl)carbamate;

methyl ((1S)-1-(((2S)-2-(5-(4'-(2-((2S)-1-(N-(methoxycarbonyl)-O-methyl-L-homoseryl)-2-pyrrolidinyl)-1H-imidazol-5-yl)-4-biphenylyl)-1H-imidazol-2-yl)-1-pyrrolidinyl)carbonyl)-2-methylpropyl)carbamate;

methyl ((1S)-3-methoxy-1-(((2S)-2-(5-(4'-(2-((2S)-1-(N-(methoxycarbonyl)-L-alanyl)-2-pyrrolidinyl)-1H-imidazol-5-yl)-4-biphenylyl)-1H-imidazol-2-yl)-1-pyrrolidinyl)carbonyl)propyl)carbamate;

methyl ((1S,2R)-2-methoxy-1-(((2S)-2-(5-(4'-(2-((2S)-1-(N-(methoxycarbonyl)-O-methyl-L-homoseryl)-2-pyrrolidinyl)-1H-imidazol-5-yl)-4-biphenylyl)-1H-imidazol-2-yl)-1-pyrrolidinyl)carbonyl)propyl)carbamate;

methyl ((1S,2S)-2-(((2S)-2-(5-(4'-(2-((2S)-1-(N-(methoxycarbonyl)-O-methyl-L-homoseryl)-2-pyrrolidinyl)-1H-imidazol-5-yl)-4-biphenylyl)-1H-imidazol-2-yl)-1-pyrrolidinyl)carbonyl)cyclopentyl)carbamate;

methyl ((1S)-2-((2S)-2-(5-(4'-(2-((2S)-1-((2S)-2-((methoxycarbonyl)amino)-3-(1H-1,2,3-triazol-4-yl)propanoyl)-2-pyrrolidinyl)-1H-imidazol-5-yl)-4-biphenylyl)-1H-imidazol-2-yl)-1-pyrrolidinyl)-2-oxo-1-(1H-1,2,3-triazol-4-ylmethyl)ethyl)carbamate;

dimethyl (4,4'-biphenyldiylbis(1H-imidazole-5,2-diyl(2S)-2,1-pyrrolidinediyl((2S)-4-oxo-4,2-butanediyl)))biscarbamate;

dimethyl (4,4'-biphenyldiylbis(1H-imidazole-5,2-diyl(2S)-2,1-pyrrolidinediyl((3R)-4-methyl-1-oxo-1,3-pentanediyl)))biscarbamate;

methyl ((1R)-3-((2S)-2-(5-(4'-(2-(1-((3R)-3-((methoxycarbonyl)amino)-3-phenylpropanoyl)-2-pyrrolidinyl)-1H-imidazol-5-yl)-4-biphenylyl)-1H-imidazol-2-yl)-1-pyrrolidinyl)-3-oxo-1-phenylpropyl)carbamate;

methyl ((1S)-3-((2S)-2-(5-(4'-(2-(1-((3S)-3-((methoxycarbonyl)amino)-3-phenylpropanoyl)-2-pyrrolidinyl)-1H-imidazol-5-yl)-4-biphenylyl)-1H-imidazol-2-yl)-1-pyrrolidinyl)-3-oxo-1-phenylpropyl)carbamate;

methyl ((1S)-2-((2S)-2-(5-(4'-(2-((2S)-1-((2S)-2-((methoxycarbonyl)amino)-3-(2-pyridinyl)propanoyl)-2-pyrrolidinyl)-1H-imidazol-5-yl)-4-biphenylyl)-1H-imidazol-2-yl)-1-pyrrolidinyl)-2-oxo-1-(2-pyridinylmethyl)ethyl)carbamate;

methyl ((1S)-2-((2S)-2-(5-(4'-(2-((2S)-1-((2S)-3-(1H-imidazol-4-yl)-2-((methoxycarbonyl)amino)propanoyl)-2-pyrrolidinyl)-1H-imidazol-5-yl)-4-biphenylyl)-1H-imidazol-2-yl)-1-pyrrolidinyl)-1-(1H-imidazol-4-ylmethyl)-2-oxoethyl)carbamate;

(6S,6'S)-6,6'-(4,4'-biphenyldiylbis(1H-imidazole-5,2-diyl(2S)-2,1-pyrrolidinediylcarbonyl))didihydro-2,4(1H,3H)-pyrimidinedione;
(4S,5R,4'S,5'R)-4,4'-(4,4'-biphenyldiylbis(1H-imidazole-5,2-diyl(2S)-2,1-pyrrolidinediylcarbonyl))bis(5-methyl-1,3-oxazolidin-2-one);
N-(3-((2S)-2-(5-(4'-(2-((2S)-1-(3-acetamidopropanoyl)-2-pyrrolidinyl)-1H-imidazol-5-yl)-4-biphenylyl)-1H-imidazol-2-yl)-1-pyrrolidinyl)-3-oxopropyl)acetamide;
dimethyl (4,4'-biphenyldiylbis(1H-imidazole-5,2-diyl(2S)-2,1-pyrrolidinediyl((3R)-1-oxo-5-phenyl-1,3-pentanediyl)))biscarbamate;
dimethyl (4,4'-biphenyldiylbis(1H-imidazole-5,2-diyl(2S)-2,1-pyrrolidinediyl((2R)-4-oxo-1-(2-thienyl)-4,2-butanediyl)))biscarbamate;
dimethyl (4,4'-biphenyldiylbis(1H-imidazole-5,2-diyl(2S)-2,1-pyrrolidinediyl((2R)-4-oxo-1-(3-thienyl)-4,2-butanediyl)))biscarbamate;
dimethyl (4,4'-biphenyldiylbis(1H-imidazole-5,2-diyl(2S)-2,1-pyrrolidinediyl((2S)-4-oxo-1-(2-thienyl)-4,2-butanediyl)))biscarbamate;
dimethyl (4,4'-biphenyldiylbis(1H-imidazole-5,2-diyl(2S)-2,1-pyrrolidinediylcarbonyl(1R,2R)-2,1-cyclohexanediyl))biscarbamate;
di-tert-butyl (4,4'-biphenyldiylbis(1H-imidazole-5,2-diyl(2S)-2,1-pyrrolidinediyl((2S)-4-(dimethylamino)-1-oxo-1,2-butanediyl)))biscarbamate;
dimethyl (4,4'-biphenyldiylbis(1H-imidazole-5,2-diyl(2S)-2,1-pyrrolidinediylcarbonyl(1R,2S)-2,1-cyclohexanediyl))biscarbamate;
(3S,3'S)-4,4'-(4,4'-biphenyldiylbis(1H-imidazole-5,2-diyl(2S)-2,1-pyrrolidinediyl))bis(N~1~,N~1~-dimethyl-4-oxo-1,3-butanediamine);
dimethyl (4,4'-biphenyldiylbis(1H-imidazole-5,2-diyl(2S)-2,1-pyrrolidinediyl((2R)-4-oxo-1-phenyl-4,2-butanediyl)))biscarbamate;
dimethyl (4,4'-biphenyldiylbis(1H-imidazole-5,2-diyl(2S)-2,1-pyrrolidinediylcarbonyl(1R,3S)-3,1-cyclopentanediyl))biscarbamate;
methyl ((1R)-1-benzyl-2-((2S)-2-(5-(4'-(2-((2S)-1-((2R)-2-((methoxycarbonyl)amino)-3-phenylpropanoyl)-2-pyrrolidinyl)-1H-imidazol-5-yl)-4-biphenylyl)-1H-imidazol-2-yl)-1-pyrrolidinyl)-2-oxoethyl)carbamate;
dimethyl (4,4'-biphenyldiylbis(1H-imidazole-5,2-diyl(2S)-2,1-pyrrolidinediyl((2S)-4-(dimethylamino)-1-oxo-1,2-butanediyl)))biscarbamate;
(2R,2'R)-1,1'-(4,4'-biphenyldiylbis(1H-imidazole-5,2-diyl(2S)-2,1-pyrrolidinediyl))bis(N,N-dimethyl-1-oxo-3-phenyl-2-propanamine);

methyl ((1S)-1-benzyl-2-((2S)-2-(5-(4'-(2-((2S)-1-((2S)-2-((methoxycarbonyl)amino)-3-phenylpropanoyl)-2-pyrrolidinyl)-1H-imidazol-5-yl)-4-biphenylyl)-1H-imidazol-2-yl)-1-pyrrolidinyl)-2-oxoethyl)carbamate;

dimethyl (4,4'-biphenyldiylbis(1H-imidazole-5,2-diyl(2S)-2,1-pyrrolidinediylcarbonyl(1R,3S)-3,1-cyclopentanediyl))biscarbamate;

dimethyl (4,4'-biphenyldiylbis(1H-imidazole-5,2-diyl(2S)-2,1-pyrrolidinediylcarbonylcis-4,1-cyclohexanediyl))biscarbamate;

dimethyl (4,4'-biphenyldiylbis(1H-imidazole-5,2-diyl(2S)-2,1-pyrrolidinediylcarbonyltrans-4,1-cyclohexanediyl))biscarbamate;

({cis)-4,4'-(4,4'-biphenyldiylbis(1H-imidazole-5,2-diyl(2S)-2,1-pyrrolidinediylcarbonyl))bis(N,N-diethylcyclohexanamine);

methyl ((1S)-2-((2S)-2-(5-(4'-(2-((2S)-1-((2S)-2-((methoxycarbonyl)amino)-3-(1,3-thiazol-4-yl)propanoyl)-2-pyrrolidinyl)-1H-imidazol-5-yl)-4-biphenylyl)-1H-imidazol-2-yl)-1-pyrrolidinyl)-2-oxo-1-(1,3-thiazol-4-ylmethyl)ethyl)carbamate;

methyl ((1S)-2-((2S)-2-(5-(4'-(2-((2S)-1-((2S)-3-(1-benzyl-1H-imidazol-4-yl)-2-((methoxycarbonyl)amino)propanoyl)-2-pyrrolidinyl)-1H-imidazol-5-yl)-4-biphenylyl)-1H-imidazol-2-yl)-1-pyrrolidinyl)-1-((1-benzyl-1H-imidazol-4-yl)methyl)-2-oxoethyl)carbamate;

dimethyl (4,4'-biphenyldiylbis(1H-imidazole-5,2-diyl(2S)-2,1-pyrrolidinediylcarbonyl(1S,2S)-2,1-cyclopentanediyl))biscarbamate;

methyl ((1S)-3-methoxy-1-(((2S)-2-(5-(4'-(2-((2S)-1-(N-(methoxycarbonyl)-O-methyl-L-homoseryl)-2-pyrrolidinyl)-1H-imidazol-5-yl)-4-biphenylyl)-1H-imidazol-2-yl)-1-pyrrolidinyl)carbonyl)propyl)carbamate;

methyl ((1S)-2-((2S,4R)-4-fluoro-2-(5-(4'-(2-((2S,4R)-4-fluoro-1-(N-(methoxycarbonyl)-L-alanyl)-2-pyrrolidinyl)-1H-imidazol-5-yl)-4-biphenylyl)-1H-imidazol-2-yl)-1-pyrrolidinyl)-1-methyl-2-oxoethyl)carbamate;

methyl ((1S)-2-((2S,4R)-4-hydroxy-2-(5-(4'-(2-((2S,4R)-4-hydroxy-1-(N-(methoxycarbonyl)-L-alanyl)-2-pyrrolidinyl)-1H-imidazol-5-yl)-4-biphenylyl)-1H-imidazol-2-yl)-1-pyrrolidinyl)-1-methyl-2-oxoethyl)carbamate;

methyl ((1S)-1-(((2S,4R)-4-hydroxy-2-(5-(4'-(2-((2S,4R)-4-hydroxy-1-((2S)-2-((methoxycarbonyl)amino)-3-methylbutanoyl)-2-pyrrolidinyl)-1H-imidazol-5-yl)-4-biphenylyl)-1H-imidazol-2-yl)-1-pyrrolidinyl)carbonyl)-2-methylpropyl)carbamate;

dimethyl (4,4'-biphenyldiylbis(1H-imidazole-5,2-diyl((2S,4R)-4-hydroxy-2,1-pyrrolidinediyl)((1S)-1-cyclopropyl-2-oxo-2,1-ethanediyl)))biscarbamate;

(3S,5S,3'S,5'S)-5,5'-(4,4'-biphenyldiylbis(1H-imidazole-5,2-diyl))bis(1-((2R)-2-(diethylamino)-2-phenylacetyl)-3-pyrrolidinol);

methyl ((1S)-2-((2S,4S)-4-hydroxy-2-(5-(4'-(2-((2S,4S)-4-hydroxy-1-(N-(methoxycarbonyl)-L-alanyl)-2-pyrrolidinyl)-1H-imidazol-5-yl)-4-biphenylyl)-1H-imidazol-2-yl)-1-pyrrolidinyl)-1-methyl-2-oxoethyl)carbamate;

methyl ((1S)-1-(((2S,4S)-4-hydroxy-2-(5-(4'-(2-((2S,4S)-4-hydroxy-1-((2S)-2-((methoxycarbonyl)amino)-3-methylbutanoyl)-2-pyrrolidinyl)-1H-imidazol-5-yl)-4-biphenylyl)-1H-imidazol-2-yl)-1-pyrrolidinyl)carbonyl)-2-methylpropyl)carbamate;

methyl ((1S)-1-(((2S,4S)-4-fluoro-2-(5-(4'-(2-((2S,4S)-4-fluoro-1-((2S)-2-((methoxycarbonyl)amino)-3-methylbutanoyl)-2-pyrrolidinyl)-1H-imidazol-5-yl)-4-biphenylyl)-1H-imidazol-2-yl)-1-pyrrolidinyl)carbonyl)-2-methylpropyl)carbamate;

methyl ((1S)-1-(((2S,4R)-4-fluoro-2-(5-(4'-(2-((2S,4R)-4-fluoro-1-((2S)-2-((methoxycarbonyl)amino)-4-methylpentanoyl)-2-pyrrolidinyl)-1H-imidazol-5-yl)-4-biphenylyl)-1H-imidazol-2-yl)-1-pyrrolidinyl)carbonyl)-3-methylbutyl)carbamate;

methyl ((1S)-2-((2S,4S)-4-fluoro-2-(5-(4'-(2-((2S,4S)-4-fluoro-1-(N-(methoxycarbonyl)-L-alanyl)-2-pyrrolidinyl)-1H-imidazol-5-yl)-4-biphenylyl)-1H-imidazol-2-yl)-1-pyrrolidinyl)-1-methyl-2-oxoethyl)carbamate;

methyl ((1S)-2-((2S,4S)-2-(5-(4'-(2-((2S,4S)-1-((2R)-2-(diethylamino)-2-phenylacetyl)-4-fluoro-2-pyrrolidinyl)-1H-imidazol-5-yl)-4-biphenylyl)-1H-imidazol-2-yl)-4-fluoro-1-pyrrolidinyl)-1-methyl-2-oxoethyl)carbamate;

methyl ((1S)-1-(((2S,4S)-2-(5-(4'-(2-((2S,4S)-1-((2R)-2-(diethylamino)-2-phenylacetyl)-4-fluoro-2-pyrrolidinyl)-1H-imidazol-5-yl)-4-biphenylyl)-1H-imidazol-2-yl)-4-fluoro-1-pyrrolidinyl)carbonyl)-2-methylpropyl)carbamate;

methyl ((1S)-1-(((2S,4R)-4-fluoro-2-(5-(4'-(2-((2S,4R)-4-fluoro-1-((2S)-2-((methoxycarbonyl)amino)-3-methylbutanoyl)-2-pyrrolidinyl)-1H-imidazol-5-yl)-4-biphenylyl)-1H-imidazol-2-yl)-1-pyrrolidinyl)carbonyl)-2-methylpropyl)carbamate;

(1R,1'R)-2,2'-(4,4'-biphenyldiylbis(1H-imidazole-5,2-diyl((2S,4R)-4-fluoro-2,1-pyrrolidinediyl)))bis(N,N-diethyl-2-oxo-1-phenylethanamine);

3-((1S)-1-(((2S)-2-(4-(4'-(2-((2S)-1-((2S)-2-((dimethylcarbamoyl)amino)-3-methylbutanoyl)-2-pyrrolidinyl)-1H-imidazol-4-yl)-4-biphenylyl)-1H-imidazol-2-yl)-1-pyrrolidinyl)carbonyl)-2-methylpropyl)-1,1-dimethylurea;

3-((1S)-2-((2S)-2-(4-(4'-(2-((2S)-1-(N-(dimethylcarbamoyl)-L-alanyl)-2-pyrrolidinyl)-1H-imidazol-4-yl)-4-biphenylyl)-1H-imidazol-2-yl)-1-pyrrolidinyl)-1-methyl-2-oxoethyl)-1,1-dimethylurea;

2-fluoroethyl ((1S)-1-(((2S)-2-(4-(4'-(2-((2S)-1-((2S)-2-(((2-fluoroethoxy)carbonyl)amino)-3-methylbutanoyl)-2-pyrrolidinyl)-1H-imidazol-4-yl)-4-biphenylyl)-1H-imidazol-2-yl)-1-pyrrolidinyl)carbonyl)-2-methylpropyl)carbamate;

methyl ((1S)-2-ethyl-1-(((2S)-2-(4-(4'-(2-((2S)-1-((2S)-3-ethyl-2-((methoxycarbonyl)amino)pentanoyl)-2-pyrrolidinyl)-1H-imidazol-4-yl)-4-biphenylyl)-1H-imidazol-2-yl)-1-pyrrolidinyl)carbonyl)butyl)carbamate;

1,1'-(4,4'-biphenyldiylbis(1H-imidazole-4,2-diyl(2S)-2,1-pyrrolidinediyl((2S)-3-methyl-1-oxo-1,2-butanediyl)))ditetrahydro-2(1H)-pyrimidinone;

methyl ((1S)-1-(((2S)-2-(4-(4'-(2-((2S)-1-((2S)-2-((methoxycarbonyl)amino)-4-methylpentanoyl)-2-pyrrolidinyl)-1H-imidazol-4-yl)-4-biphenylyl)-1H-imidazol-2-yl)-1-pyrrolidinyl)carbonyl)-3-methylbutyl)carbamate;

methyl ((1S)-1-(((2S)-2-(4-(4'-(2-((2S)-4,4-difluoro-1-((2S)-2-((methoxycarbonyl)amino)-3-methylbutanoyl)-2-pyrrolidinyl)-1H-imidazol-4-yl)-4-biphenylyl)-1H-imidazol-2-yl)-4,4-difluoro-1-pyrrolidinyl)carbonyl)-2-methylpropyl)carbamate;

(1R,1'R)-2,2'-(4,4'-biphenyldiylbis(1H-imidazole-4,2-diyl((2S)-4,4-difluoro-2,1-pyrrolidinediyl)))bis(N,N-dimethyl-2-oxo-1-phenylethanamine);

(1R,1'R)-2,2'-(4,4'-biphenyldiylbis(1H-imidazole-4,2-diyl((2S)-4,4-difluoro-2,1-pyrrolidinediyl)))bis(N,N-diethyl-2-oxo-1-phenylethanamine);

methyl ((1S,2R)-1-(((2S)-2-(4-(4'-(2-((2S)-4,4-difluoro-1-(N-(methoxycarbonyl)-O-methyl-L-threonyl)-2-pyrrolidinyl)-1H-imidazol-4-yl)-4-biphenylyl)-1H-imidazol-2-yl)-4,4-difluoro-1-pyrrolidinyl)carbonyl)-2-methoxypropyl)carbamate;

methyl ((1S)-2-((2S)-2-(4-(4'-(2-((2S)-4,4-difluoro-1-(N-(methoxycarbonyl)-L-alanyl)-2-pyrrolidinyl)-1H-imidazol-4-yl)-4-biphenylyl)-1H-imidazol-2-yl)-4,4-difluoro-1-pyrrolidinyl)-1-methyl-2-oxoethyl)carbamate;

methyl ((1S)-1-(((2S)-2-(4-(4'-(2-((2S)-4,4-difluoro-1-((2S)-2-((methoxycarbonyl)amino)-3-methylbutanoyl)-2-pyrrolidinyl)-1H-imidazol-4-yl)-4-biphenylyl)-1H-imidazol-2-yl)-1-pyrrolidinyl)carbonyl)-2-methylpropyl)carbamate;

rac-(1R)-2-((2S)-2-(4-(4'-(2-((2S)-1-((2R)-2-(diethylamino)-2-phenylacetyl)-4,4-difluoro-2-pyrrolidinyl)-1H-imidazol-4-yl)-4-biphenylyl)-1H-imidazol-2-yl)-1-pyrrolidinyl)-N,N-diethyl-2-oxo-1-phenylethanamine;

methyl ((1S)-1-(((2R,3S)-3-hydroxy-2-(4-(4'-(2-((2S)-1-((2S)-2-((methoxycarbonyl)amino)-3-methylbutanoyl)-2-pyrrolidinyl)-1H-imidazol-4-yl)-4-biphenylyl)-1H-imidazol-2-yl)-1-pyrrolidinyl)carbonyl)-2-methylpropyl)carbamate;

methyl ((1S)-2-((2S)-2-(4-(4'-(2-((2R,3S)-3-hydroxy-1-(N-(methoxycarbonyl)-L-alanyl)-2-pyrrolidinyl)-1H-imidazol-4-yl)-4-biphenylyl)-1H-imidazol-2-yl)-1-pyrrolidinyl)-1-methyl-2-oxoethyl)carbamate;

methyl ((1S)-1-(((2R)-3-hydroxy-2-(4-(4'-(2-((2S)-1-((2S)-2-((methoxycarbonyl)amino)-3-methylbutanoyl)-2-pyrrolidinyl)-1H-imidazol-4-yl)-4-biphenylyl)-1H-imidazol-2-yl)-1-pyrrolidinyl)carbonyl)-2-methylpropyl)carbamate;

methyl 2-((2S)-1-(tert-butoxycarbonyl)-2-pyrrolidinyl)-5-(4'-(2-((2S)-1-(tert-butoxycarbonyl)-2-pyrrolidinyl)-1H-imidazol-5-yl)-4-biphenylyl)-1H-imidazole-4-carboxylate;

ethyl 2-((2S)-1-(tert-butoxycarbonyl)-2-pyrrolidinyl)-5-(4'-(2-((2S)-1-(tert-butoxycarbonyl)-2-pyrrolidinyl)-1H-imidazol-5-yl)-4-biphenylyl)-1H-imidazole-4-carboxylate;

benzyl 2-((2S)-1-(tert-butoxycarbonyl)-2-pyrrolidinyl)-5-(4'-(2-((2S)-1-(tert-butoxycarbonyl)-2-pyrrolidinyl)-1H-imidazol-5-yl)-4-biphenylyl)-1H-imidazole-4-carboxylate;

tert-butyl (2S)-2-(5-(4'-(2-((2S)-1-(tert-butoxycarbonyl)-2-pyrrolidinyl)-1H-imidazol-5-yl)-4-biphenylyl)-4-(methylcarbamoyl)-1H-imidazol-2-yl)-1-pyrrolidinecarboxylate;

methyl 2-((2S)-1-((2R)-2-((methoxycarbonyl)amino)-2-phenylacetyl)-2-pyrrolidinyl)-5-(4'-(2-((2S)-1-((2R)-2-((methoxycarbonyl)amino)-2-phenylacetyl)-2-pyrrolidinyl)-1H-imidazol-5-yl)-4-biphenylyl)-1H-imidazole-4-carboxylate;

methyl 2-((2S)-1-((2R)-2-(dimethylamino)-2-phenylacetyl)-2-pyrrolidinyl)-5-(4'-(2-((2S)-1-((2R)-2-(dimethylamino)-2-phenylacetyl)-2-pyrrolidinyl)-1H-imidazol-5-yl)-4-biphenylyl)-1H-imidazole-4-carboxylate;

methyl 2-((2S)-1-((2R)-2-phenyl-2-(1-piperidinyl)acetyl)-2-pyrrolidinyl)-5-(4'-(2-((2S)-1-((2R)-2-phenyl-2-(1-piperidinyl)acetyl)-2-pyrrolidinyl)-1H-imidazol-5-yl)-4-biphenylyl)-1H-imidazole-4-carboxylate;

ethyl 2-((2S)-1-((2R)-2-((methoxycarbonyl)amino)-2-phenylacetyl)-2-pyrrolidinyl)-5-(4'-(2-((2S)-1-((2R)-2-((methoxycarbonyl)amino)-2-phenylacetyl)-2-pyrrolidinyl)-1H-imidazol-5-yl)-4-biphenylyl)-1H-imidazole-4-carboxylate;

ethyl 2-((2S)-1-((2R)-2-(dimethylamino)-2-phenylacetyl)-2-pyrrolidinyl)-5-(4'-(2-((2S)-1-((2R)-2-(dimethylamino)-2-phenylacetyl)-2-pyrrolidinyl)-1H-imidazol-5-yl)-4-biphenylyl)-1H-imidazole-4-carboxylate;

benzyl 2-((2S)-1-((2R)-2-((methoxycarbonyl)amino)-2-phenylacetyl)-2-pyrrolidinyl)-5-(4'-(2-((2S)-1-((2R)-2-((methoxycarbonyl)amino)-2-phenylacetyl)-2-pyrrolidinyl)-1H-imidazol-5-yl)-4-biphenylyl)-1H-imidazole-4-carboxylate;

benzyl 2-((2S)-1-((2R)-2-(dimethylamino)-2-phenylacetyl)-2-pyrrolidinyl)-5-(4'-(2-((2S)-1-((2R)-2-(dimethylamino)-2-phenylacetyl)-2-pyrrolidinyl)-1H-imidazol-5-yl)-4-biphenylyl)-1H-imidazole-4-carboxylate;

benzyl 2-((2S)-1-((2R)-2-phenyl-2-(1-piperidinyl)acetyl)-2-pyrrolidinyl)-5-(4'-(2-((2S)-1-((2R)-2-phenyl-2-(1-piperidinyl)acetyl)-2-pyrrolidinyl)-1H-imidazol-5-yl)-4-biphenylyl)-1H-imidazole-4-carboxylate;

benzyl 2-((2S)-1-(N-(methoxycarbonyl)-L-alanyl)-2-pyrrolidinyl)-5-(4'-(2-((2S)-1-(N-(methoxycarbonyl)-L-alanyl)-2-pyrrolidinyl)-1H-imidazol-5-yl)-4-biphenylyl)-1H-imidazole-4-carboxylate;

methyl ((1R)-2-((2S)-2-(5-(4'-(2-((2S)-1-((2R)-2-((methoxycarbonyl)amino)-2-phenylacetyl)-2-pyrrolidinyl)-1H-imidazol-5-yl)-4-biphenylyl)-4-(methylcarbamoyl)-1H-imidazol-2-yl)-1-pyrrolidinyl)-2-oxo-1-phenylethyl)carbamate;

2-((2S)-1-((2R)-2-(dimethylamino)-2-phenylacetyl)-2-pyrrolidinyl)-5-(4'-(2-((2S)-1-((2R)-2-(dimethylamino)-2-phenylacetyl)-2-pyrrolidinyl)-1H-imidazol-5-yl)-4-biphenylyl)-N-methyl-1H-imidazole-4-carboxamide;

N-methyl-2-((2S)-1-((2R)-2-phenyl-2-(1-piperidinyl)acetyl)-2-pyrrolidinyl)-5-(4'-(2-((2S)-1-((2R)-2-phenyl-2-(1-piperidinyl)acetyl)-2-pyrrolidinyl)-1H-imidazol-5-yl)-4-biphenylyl)-1H-imidazole-4-carboxamide;

methyl ((1S)-2-((2S)-2-(5-(4'-(2-((2S)-1-(N-(methoxycarbonyl)-L-alanyl)-2-pyrrolidinyl)-4-(methylcarbamoyl)-1H-imidazol-5-yl)-4-biphenylyl)-1H-imidazol-2-yl)-1-pyrrolidinyl)-1-methyl-2-oxoethyl)carbamate;

methyl ((1R)-2-((2S)-2-(4-carbamoyl-5-(4'-(2-((2S)-1-((2R)-2-((methoxycarbonyl)amino)-2-phenylacetyl)-2-pyrrolidinyl)-1H-imidazol-5-yl)-4-biphenylyl)-1H-imidazol-2-yl)-1-pyrrolidinyl)-2-oxo-1-phenylethyl)carbamate;

2-((2S)-1-((2R)-2-((methoxycarbonyl)amino)-2-phenylacetyl)-2-pyrrolidinyl)-5-(4'-(2-((2S)-1-((2R)-2-((methoxycarbonyl)amino)-2-phenylacetyl)-2-pyrrolidinyl)-1H-imidazol-5-yl)-4-biphenylyl)-1H-imidazole-4-carboxylic acid;

2-((2S)-1-((2R)-2-phenyl-2-(1-piperidinyl)acetyl)-2-pyrrolidinyl)-5-(4'-(2-((2S)-1-((2R)-2-phenyl-2-(1-piperidinyl)acetyl)-2-pyrrolidinyl)-1H-imidazol-5-yl)-4-biphenylyl)-1H-imidazole-4-carboxylic acid;

tert-butyl (2S)-2-(5-(4'-(2-((2S)-1-(tert-butoxycarbonyl)-2-pyrrolidinyl)-1H-imidazol-5-yl)-4-biphenylyl)-4-(trifluoromethyl)-1H-imidazol-2-yl)-1-pyrrolidinecarboxylate;

tert-butyl (2S)-2-(5-(4'-(2-((2S)-1-((benzyloxy)carbonyl)-2-pyrrolidinyl)-1H-imidazol-5-yl)-4-biphenylyl)-4-(trifluoromethyl)-1H-imidazol-2-yl)-1-pyrrolidinecarboxylate;

methyl ((1R)-2-((2S)-2-(5-(4'-(2-((2S)-1-((2R)-2-((methoxycarbonyl)amino)-2-phenylacetyl)-2-pyrrolidinyl)-1H-imidazol-5-yl)-4-biphenylyl)-4-(trifluoromethyl)-1H-imidazol-2-yl)-1-pyrrolidinyl)-2-oxo-1-phenylethyl)carbamate;

methyl ((1S)-2-((2S)-2-(5-(4'-(2-((2S)-1-(N-(methoxycarbonyl)-L-alanyl)-2-pyrrolidinyl)-4-(trifluoromethyl)-1H-imidazol-5-yl)-4-biphenylyl)-1H-imidazol-2-yl)-1-pyrrolidinyl)-1-methyl-2-oxoethyl)carbamate;

methyl ((1S)-1-(((2S)-2-(5-(4'-(2-((2S)-1-((2S)-2-((methoxycarbonyl)amino)-3-methylbutanoyl)-2-pyrrolidinyl)-1H-imidazol-5-yl)-4-biphenylyl)-4-(trifluoromethyl)-1H-imidazol-2-yl)-1-pyrrolidinyl)carbonyl)-2-methylpropyl)carbamate;

(1R)-2-((2S)-2-(5-(4'-(2-((2S)-1-((2R)-2-(diethylamino)-2-phenylacetyl)-2-pyrrolidinyl)-1H-imidazol-5-yl)-4-biphenylyl)-4-(trifluoromethyl)-1H-imidazol-2-yl)-1-pyrrolidinyl)-N,N-diethyl-2-oxo-1-phenylethanamine;

methyl ((1S)-1-cyclopropyl-2-((2S)-2-(5-(4'-(2-((2S)-1-((2S)-2-cyclopropyl-2-((methoxycarbonyl)amino)acetyl)-2-pyrrolidinyl)-1H-imidazol-5-yl)-4-biphenylyl)-4-(trifluoromethyl)-1H-imidazol-2-yl)-1-pyrrolidinyl)-2-oxoethyl)carbamate;

methyl ((1S,2R)-2-methoxy-1-(((2S)-2-(5-(4'-(2-((2S)-1-(N-(methoxycarbonyl)-O-methyl-L-threonyl)-2-pyrrolidinyl)-4-(trifluoromethyl)-1H-imidazol-5-yl)-4-biphenylyl)-1H-imidazol-2-yl)-1-pyrrolidinyl)carbonyl)propyl)carbamate;

benzyl (2S)-2-(5-(4'-(2-((2S)-1-(N-(methoxycarbonyl)-L-alanyl)-2-pyrrolidinyl)-4-(trifluoromethyl)-1H-imidazol-5-yl)-4-biphenylyl)-1H-imidazol-2-yl)-1-pyrrolidinecarboxylate;

methyl ((1S)-2-((2S)-2-(5-(4'-(2-((2S)-1-((2R)-2-(diethylamino)-2-phenylacetyl)-2-pyrrolidinyl)-1H-imidazol-5-yl)-4-biphenylyl)-4-(trifluoromethyl)-1H-imidazol-2-yl)-1-pyrrolidinyl)-1-methyl-2-oxoethyl)carbamate;

tert-butyl (2S)-2-(4-(4'-(2-((2S)-1-(tert-butoxycarbonyl)-2-pyrrolidinyl)-1H-imidazol-5-yl)-4-methoxy-3-biphenylyl)-1H-imidazol-2-yl)-1-pyrrolidinecarboxylate;

di-tert-butyl (2S,2'S)-2,2'-((3-fluoro-4,4'-biphenyldiyl)bis(1H-imidazole-4,2-diyl))di(1-pyrrolidinecarboxylate);

tert-butyl (2S)-2-(4-(4'-(2-((2S)-1-(tert-butoxycarbonyl)-2-pyrrolidinyl)-1H-imidazol-5-yl)-2,5-difluoro-4-biphenylyl)-1H-imidazol-2-yl)-1-pyrrolidinecarboxylate;

di-tert-butyl (2S,2'S)-2,2'-((3,3'-difluoro-4,4'-biphenyldiyl)bis(1H-imidazole-5,2-diyl))di(1-pyrrolidinecarboxylate);

tert-butyl (2S)-2-(4-(4'-(2-((2S)-1-((benzyloxy)carbonyl)-2-pyrrolidinyl)-1H-imidazol-5-yl)-3-fluoro-4-biphenylyl)-1H-imidazol-2-yl)-1-pyrrolidinecarboxylate;

tert-butyl (2S)-2-(4-(4'-(2-((2S)-1-((benzyloxy)carbonyl)-2-pyrrolidinyl)-1H-imidazol-5-yl)-3,3'-difluoro-4-biphenylyl)-1H-imidazol-2-yl)-1-pyrrolidinecarboxylate;

tert-butyl (2S)-2-(5-(3-fluoro-4'-(2-((2S)-1-((2R)-2-((methoxycarbonyl)amino)-2-phenylacetyl)-2-pyrrolidinyl)-1H-imidazol-5-yl)-4-biphenylyl)-1H-imidazol-2-yl)-1-pyrrolidinecarboxylate;

tert-butyl (2S)-2-(5-(4'-(2-((2S)-1-((2R)-2-(diethylamino)-2-phenylacetyl)-2-pyrrolidinyl)-1H-imidazol-5-yl)-3-fluoro-4-biphenylyl)-1H-imidazol-2-yl)-1-pyrrolidinecarboxylate;

tert-butyl (2S)-2-(5-(3-fluoro-4'-(2-((2S)-1-(N-(methoxycarbonyl)-L-valyl)-2-pyrrolidinyl)-1H-imidazol-5-yl)-4-biphenylyl)-1H-imidazol-2-yl)-1-pyrrolidinecarboxylate;

tert-butyl (2S)-2-(5-(3,3'-difluoro-4'-(2-((2S)-1-((2R)-2-((methoxycarbonyl)amino)-2-phenylacetyl)-2-pyrrolidinyl)-1H-imidazol-5-yl)-4-biphenylyl)-1H-imidazol-2-yl)-1-pyrrolidinecarboxylate;

tert-butyl (2S)-2-(5-(3,3'-difluoro-4'-(2-((2S)-1-(N-(methoxycarbonyl)-L-valyl)-2-pyrrolidinyl)-1H-imidazol-5-yl)-4-biphenylyl)-1H-imidazol-2-yl)-1-pyrrolidinecarboxylate;

tert-butyl (2S)-2-(5-(3-fluoro-4'-(2-((2S)-2-pyrrolidinyl)-1H-imidazol-5-yl)-4-biphenylyl)-1H-imidazol-2-yl)-1-pyrrolidinecarboxylate triacetate;

tert-butyl (2S)-2-(5-(3,3'-difluoro-4'-(2-((2S)-2-pyrrolidinyl)-1H-imidazol-5-yl)-4-biphenylyl)-1H-imidazol-2-yl)-1-pyrrolidinecarboxylate;

methyl ((1R)-2-((2S)-2-(5-(3'-fluoro-4'-(2-((2S)-2-pyrrolidinyl)-1H-imidazol-5-yl)-4-biphenylyl)-1H-imidazol-2-yl)-1-pyrrolidinyl)-2-oxo-1-phenylethyl)carbamate;

methyl ((1S)-1-(((2S)-2-(5-(3'-fluoro-4'-(2-((2S)-2-pyrrolidinyl)-1H-imidazol-5-yl)-4-biphenylyl)-1H-imidazol-2-yl)-1-pyrrolidinyl)carbonyl)-2-methylpropyl)carbamate;

(1R)-N,N-diethyl-2-((2S)-2-(5-(3'-fluoro-4'-(2-((2S)-2-pyrrolidinyl)-1H-imidazol-5-yl)-4-biphenylyl)-1H-imidazol-2-yl)-1-pyrrolidinyl)-2-oxo-1-phenylethanamine;

methyl ((1S)-1-(((2S)-2-(5-(3,3'-difluoro-4'-(2-((2S)-2-pyrrolidinyl)-1H-imidazol-5-yl)-4-biphenylyl)-1H-imidazol-2-yl)-1-pyrrolidinyl)carbonyl)-2-methylpropyl)carbamate;

methyl ((1R)-2-((2S)-2-(5-(3,3'-difluoro-4'-(2-((2S)-2-pyrrolidinyl)-1H-imidazol-5-yl)-4-biphenylyl)-1H-imidazol-2-yl)-1-pyrrolidinyl)-2-oxo-1-phenylethyl)carbamate;

5,5'-(4-methoxy-3,4'-biphenyldiyl)bis(2-((2S)-2-pyrrolidinyl)-1H-imidazole);

5,5'-(3-fluoro-4,4'-biphenyldiyl)bis(2-((2S)-2-pyrrolidinyl)-1H-imidazole) tetraacetate;

5,5'-(2,5-difluoro-4,4'-biphenyldiyl)bis(2-((2S)-2-pyrrolidinyl)-1H-imidazole);

(1R,1'R)-2,2'-((4-methoxy-3,4'-biphenyldiyl)bis(1H-imidazole-5,2-diyl(2S)-2,1-pyrrolidinediyl))bis(N,N-dimethyl-2-oxo-1-phenylethanamine);

dimethyl ((4-methoxy-3,4'-biphenyldiyl)bis(1H-imidazole-5,2-diyl(2S)-2,1-pyrrolidinediyl((1R)-2-oxo-1-phenyl-2,1-ethanediyl)))biscarbamate;

methyl ((1S)-1-(((2S)-2-(5-(4'-(2-((2S)-1-((2R)-2-(diethylamino)-2-phenylacetyl)-2-pyrrolidinyl)-1H-imidazol-5-yl)-3-fluoro-4-biphenylyl)-1H-imidazol-2-yl)-1-pyrrolidinyl)carbonyl)-2-methylpropyl)carbamate;

methyl ((1S)-2-((2S)-2-(5-(4'-(2-((2S)-1-((2R)-2-(diethylamino)-2-phenylacetyl)-2-pyrrolidinyl)-1H-imidazol-5-yl)-3-fluoro-4-biphenylyl)-1H-imidazol-2-yl)-1-pyrrolidinyl)-1-methyl-2-oxoethyl)carbamate;

methyl ((1R)-2-((2S)-2-(5-(4'-(2-((2S)-1-((2R)-2-(diethylamino)-2-phenylacetyl)-2-pyrrolidinyl)-1H-imidazol-5-yl)-3-fluoro-4-biphenylyl)-1H-imidazol-2-yl)-1-pyrrolidinyl)-2-oxo-1-phenylethyl)carbamate;

methyl ((1R)-2-((2S)-2-(5-(3'-fluoro-4'-(2-((2S)-1-(N-(methoxycarbonyl)-L-alanyl)-2-pyrrolidinyl)-1H-imidazol-5-yl)-4-biphenylyl)-1H-imidazol-2-yl)-1-pyrrolidinyl)-2-oxo-1-phenylethyl)carbamate;

methyl ((1R)-2-((2S)-2-(5-(4'-(2-((2S)-1-((2R)-2-(diethylamino)-2-phenylacetyl)-2-pyrrolidinyl)-1H-imidazol-5-yl)-3'-fluoro-4-biphenylyl)-1H-imidazol-2-yl)-1-pyrrolidinyl)-2-oxo-1-phenylethyl)carbamate;

methyl ((1S)-1-(((2S)-2-(5-(3'-fluoro-4'-(2-((2S)-1-((2S)-2-((methoxycarbonyl)amino)-3-methylbutanoyl)-2-pyrrolidinyl)-1H-imidazol-5-yl)-4-biphenylyl)-1H-imidazol-2-yl)-1-pyrrolidinyl)carbonyl)-2-methylpropyl)carbamate;

methyl ((1S)-1-(((2S)-2-(5-(3'-fluoro-4'-(2-((2S)-1-(N-(methoxycarbonyl)-L-alanyl)-2-pyrrolidinyl)-1H-imidazol-5-yl)-4-biphenylyl)-1H-imidazol-2-yl)-1-pyrrolidinyl)carbonyl)-2-methylpropyl)carbamate;

methyl ((1S,2R)-1-(((2S)-2-(5-(3-fluoro-4'-(2-((2S)-1-(N-(methoxycarbonyl)-L-valyl)-2-pyrrolidinyl)-1H-imidazol-5-yl)-4-biphenylyl)-1H-imidazol-2-yl)-1-pyrrolidinyl)carbonyl)-2-methoxypropyl)carbamate;

methyl ((1S)-1-(((2S)-2-(5-(4'-(2-((2S)-1-(N,N-diethyl-D-alanyl)-2-pyrrolidinyl)-1H-imidazol-5-yl)-3'-fluoro-4-biphenylyl)-1H-imidazol-2-yl)-1-pyrrolidinyl)carbonyl)-2-methylpropyl)carbamate;

methyl ((1S)-1-(((2S)-2-(5-(4'-(2-((2S)-1-((2R)-2-(diethylamino)-2-phenylacetyl)-2-pyrrolidinyl)-1H-imidazol-5-yl)-3'-fluoro-4-biphenylyl)-1H-imidazol-2-yl)-1-pyrrolidinyl)carbonyl)-2-methylpropyl)carbamate;

methyl ((1S)-2-((2S)-2-(5-(3'-fluoro-4'-(2-((2S)-1-(N-(methoxycarbonyl)-L-alanyl)-2-pyrrolidinyl)-1H-imidazol-5-yl)-4-biphenylyl)-1H-imidazol-2-yl)-1-pyrrolidinyl)-1-methyl-2-oxoethyl)carbamate;

dimethyl ((3-fluoro-4,4'-biphenyldiyl)bis(1H-imidazole-5,2-diyl(2S)-2,1-pyrrolidinediyl((1R)-2-oxo-1-phenyl-2,1-ethanediyl)))biscarbamate;

(1R,1'R)-2,2'-((3-fluoro-4,4'-biphenyldiyl)bis(1H-imidazole-5,2-diyl(2S)-2,1-pyrrolidinediyl))bis(N,N-diethyl-2-oxo-1-phenylethanamine);

methyl ((1R)-2-((2S)-2-(5-(4'-(2-((2S)-1-(N,N-diethyl-D-alanyl)-2-pyrrolidinyl)-1H-imidazol-5-yl)-3'-fluoro-4-biphenylyl)-1H-imidazol-2-yl)-1-pyrrolidinyl)-2-oxo-1-phenylethyl)carbamate;

methyl ((1S)-1-cyclopropyl-2-((2S)-2-(5-(4'-(2-((2S)-1-((2R)-2-(diethylamino)-2-phenylacetyl)-2-pyrrolidinyl)-1H-imidazol-5-yl)-3-fluoro-4-biphenylyl)-1H-imidazol-2-yl)-1-pyrrolidinyl)-2-oxoethyl)carbamate;

methyl ((1S)-1-cyclopropyl-2-((2S)-2-(5-(3-fluoro-4'-(2-((2S)-1-(N-(methoxycarbonyl)-L-valyl)-2-pyrrolidinyl)-1H-imidazol-5-yl)-4-biphenylyl)-1H-imidazol-2-yl)-1-pyrrolidinyl)-2-oxoethyl)carbamate;

methyl ((1R)-2-((2S)-2-(5-(4'-(2-((2S)-1-(N,N-diethyl-D-alanyl)-2-pyrrolidinyl)-1H-imidazol-5-yl)-3'-fluoro-4-biphenylyl)-1H-imidazol-2-yl)-1-pyrrolidinyl)-2-oxo-1-phenylethyl)carbamate;

methyl ((1S)-2-((2S)-2-(5-(2',5'-difluoro-4'-(2-((2S)-1-(N-(methoxycarbonyl)-L-alanyl)-2-pyrrolidinyl)-1H-imidazol-5-yl)-4-biphenylyl)-1H-imidazol-2-yl)-1-pyrrolidinyl)-1-methyl-2-oxoethyl)carbamate;

dimethyl ((2,5-difluoro-4,4'-biphenyldiyl)bis(1H-imidazole-5,2-diyl(2S)-2,1-pyrrolidinediyl((1R)-2-oxo-1-phenyl-2,1-ethanediyl)))biscarbamate;

(1R,1'R)-2,2'-((2,5-difluoro-4,4'-biphenyldiyl)bis(1H-imidazole-5,2-diyl(2S)-2,1-pyrrolidinediyl))bis(N,N-diethyl-2-oxo-1-phenylethanamine);

methyl ((1S)-1-cyclopropyl-2-((2S)-2-(5-(3,3'-difluoro-4'-(2-((2S)-1-(N-(methoxycarbonyl)-L-valyl)-2-pyrrolidinyl)-1H-imidazol-5-yl)-4-biphenylyl)-1H-imidazol-2-yl)-1-pyrrolidinyl)-2-oxoethyl)carbamate;

methyl ((1S,2R)-1-(((2S)-2-(5-(3,3'-difluoro-4'-(2-((2S)-1-(N-(methoxycarbonyl)-L-valyl)-2-pyrrolidinyl)-1H-imidazol-5-yl)-4-biphenylyl)-1H-imidazol-2-yl)-1-pyrrolidinyl)carbonyl)-2-methoxypropyl)carbamate;

methyl ((1S)-1-(((2S)-2-(5-(3,3'-difluoro-4'-(2-((2S)-1-(N-(methoxycarbonyl)-L-alanyl)-2-pyrrolidinyl)-1H-imidazol-5-yl)-4-biphenylyl)-1H-imidazol-2-yl)-1-pyrrolidinyl)carbonyl)-2-methylpropyl)carbamate;

methyl ((1S)-1-(((2S)-2-(5-(3,3'-difluoro-4'-(2-((2S)-1-((2S)-2-((methoxycarbonyl)amino)-3-methylbutanoyl)-2-pyrrolidinyl)-1H-imidazol-5-yl)-4-biphenylyl)-1H-imidazol-2-yl)-1-pyrrolidinyl)carbonyl)-2-methylpropyl)carbamate;

methyl ((1S)-1-(((2S)-2-(5-(4'-(2-((2S)-1-(N,N-diethyl-D-alanyl)-2-pyrrolidinyl)-1H-imidazol-5-yl)-3,3'-difluoro-4-biphenylyl)-1H-imidazol-2-yl)-1-pyrrolidinyl)carbonyl)-2-methylpropyl)carbamate;

methyl ((1S)-1-(((2S)-2-(5-(3,3'-difluoro-4'-(2-((2S)-1-((2R)-2-((methoxycarbonyl)amino)-2-phenylacetyl)-2-pyrrolidinyl)-1H-imidazol-5-yl)-4-biphenylyl)-1H-imidazol-2-yl)-1-pyrrolidinyl)carbonyl)-2-methylpropyl)carbamate;
methyl ((1S)-2-((2S)-2-(5-(3,3'-difluoro-4'-(2-((2S)-1-(N-(methoxycarbonyl)-L-alanyl)-2-pyrrolidinyl)-1H-imidazol-5-yl)-4-biphenylyl)-1H-imidazol-2-yl)-1-pyrrolidinyl)-1-methyl-2-oxoethyl)carbamate;
methyl ((1R)-2-((2S)-2-(5-(3,3'-difluoro-4'-(2-((2S)-1-(N-(methoxycarbonyl)-L-alanyl)-2-pyrrolidinyl)-1H-imidazol-5-yl)-4-biphenylyl)-1H-imidazol-2-yl)-1-pyrrolidinyl)-2-oxo-1-phenylethyl)carbamate;
methyl ((1R)-2-((2S)-2-(5-(4'-(2-((2S)-1-(N,N-diethyl-D-alanyl)-2-pyrrolidinyl)-1H-imidazol-5-yl)-3,3'-difluoro-4-biphenylyl)-1H-imidazol-2-yl)-1-pyrrolidinyl)-2-oxo-1-phenylethyl)carbamate;
methyl ((1R)-2-((2S)-2-(5-(4'-(2-((2S)-1-((2R)-2-(diethylamino)-2-phenylacetyl)-2-pyrrolidinyl)-1H-imidazol-5-yl)-3,3'-difluoro-4-biphenylyl)-1H-imidazol-2-yl)-1-pyrrolidinyl)-2-oxo-1-phenylethyl)carbamate;
methyl ((1S,2R)-1-(((2S)-2-(5-(3,3'-difluoro-4'-(2-((2S)-1-((2R)-2-((methoxycarbonyl)amino)-2-phenylacetyl)-2-pyrrolidinyl)-1H-imidazol-5-yl)-4-biphenylyl)-1H-imidazol-2-yl)-1-pyrrolidinyl)carbonyl)-2-methoxypropyl)carbamate bis(trifluoroacetate);
methyl ((1S)-1-cyclopropyl-2-((2S)-2-(5-(3,3'-difluoro-4'-(2-((2S)-1-((2R)-2-((methoxycarbonyl)amino)-2-phenylacetyl)-2-pyrrolidinyl)-1H-imidazol-5-yl)-4-biphenylyl)-1H-imidazol-2-yl)-1-pyrrolidinyl)-2-oxoethyl)carbamate;
7,7'-(4,4'-biphenyldiylbis(1H-imidazole-5,2-diyl(2S)-2,1-pyrrolidinediyl(2-oxo-1-phenyl-2,1-ethanediyl)))bis(7-azabicyclo[2.2.1]heptane);
7,7'-(4,4'-biphenyldiylbis(1H-imidazole-5,2-diyl(2S)-2,1-pyrrolidinediyl(2-oxo-1-phenyl-2,1-ethanediyl)))bis(7-azabicyclo[2.2.1]heptane);
N,N'-(4,4'-biphenyldiylbis(1H-imidazole-5,2-diyl(2S)-2,1-pyrrolidinediyl((1R)-2-oxo-1-phenyl-2,1-ethanediyl)))bis(N-ethylcyclopropanamine);
ethyl ((1R)-2-((2S)-2-(5-(4'-(2-((2S)-1-(N-(ethoxycarbonyl)-D-alanyl)-2-pyrrolidinyl)-1H-imidazol-5-yl)-4-biphenylyl)-1H-imidazol-2-yl)-1-pyrrolidinyl)-1-methyl-2-oxoethyl)carbamate;

ethyl ((1S)-2-((2S)-2-(5-(4'-(2-((2S)-1-(N-(ethoxycarbonyl)-L-alanyl)-2-pyrrolidinyl)-1H-imidazol-5-yl)-4-biphenylyl)-1H-imidazol-2-yl)-1-pyrrolidinyl)-1-methyl-2-oxoethyl)carbamate;

dimethyl (4,4'-biphenyldiylbis(1H-imidazole-5,2-diyl(2S)-2,1-pyrrolidinediylcarbonyl-1,1-cyclopropanediyl))biscarbamate;

methyl (2-((2S)-2-(5-(4'-(2-((2S)-1-(2-((methoxycarbonyl)amino)-2-methylpropanoyl)-2-pyrrolidinyl)-1H-imidazol-5-yl)-4-biphenylyl)-1H-imidazol-2-yl)-1-pyrrolidinyl)-1,1-dimethyl-2-oxoethyl)carbamate;

(2R,2'R)-1,1'-(4,4'-biphenyldiylbis(1H-imidazole-5,2-diyl(2S)-2,1-pyrrolidinediyl))bis(N,N-dimethyl-1-oxo-2-propanamine);

(2R,2'R)-1,1'-(4,4'-biphenyldiylbis(1H-imidazole-5,2-diyl(2S)-2,1-pyrrolidinediyl))bis(N,N-diethyl-1-oxo-2-propanamine);

(2R,2'R)-1,1'-(4,4'-biphenyldiylbis(1H-imidazole-5,2-diyl(2S)-2,1-pyrrolidinediyl))bis(N,N-diethyl-3-methyl-1-oxo-2-butanamine);

methyl ((1S)-1-(((2S)-2-(5-(4'-(2-((2S)-1-((2S)-2-((methoxycarbonyl)(methyl)amino)-3-methylbutanoyl)-2-pyrrolidinyl)-1H-imidazol-5-yl)-4-biphenylyl)-1H-imidazol-2-yl)-1-pyrrolidinyl)carbonyl)-2-methylpropyl)methylcarbamate;

dimethyl (4,4'-biphenyldiylbis(1H-imidazole-5,2-diyl(2S)-2,1-pyrrolidinediyl((1S)-2-oxo-1-phenyl-2,1-ethanediyl)))biscarbamate;

N,N'-(4,4'-biphenyldiylbis(1H-imidazole-5,2-diyl(2S)-2,1-pyrrolidinediyl((2R)-1-oxo-1,2-propanediyl)))bis(N-propyl-1-propanamine);

methyl ((1S)-2-hydroxy-1-(((2S)-2-(5-(4'-(2-((2S)-1-((2S)-3-hydroxy-2-((methoxycarbonyl)amino)-3-methylbutanoyl)-2-pyrrolidinyl)-1H-imidazol-5-yl)-4-biphenylyl)-1H-imidazol-2-yl)-1-pyrrolidinyl)carbonyl)-2-methylpropyl)carbamate;

methyl ((1S,2R)-2-hydroxy-1-(((2S)-2-(5-(4'-(2-((2S)-1-((2S,3R)-3-hydroxy-2-((methoxycarbonyl)amino)butanoyl)-2-pyrrolidinyl)-1H-imidazol-5-yl)-4-biphenylyl)-1H-imidazol-2-yl)-1-pyrrolidinyl)carbonyl)propyl)carbamate;

methyl ((1S,2S)-2-hydroxy-1-(((2S)-2-(5-(4'-(2-((2S)-1-((2S,3S)-3-hydroxy-2-((methoxycarbonyl)amino)butanoyl)-2-pyrrolidinyl)-1H-imidazol-5-yl)-4-biphenylyl)-1H-imidazol-2-yl)-1-pyrrolidinyl)carbonyl)propyl)carbamate;

methyl ((1S)-2-((2S)-2-(5-(4'-(2-((2S)-1-(N-(methoxycarbonyl)-L-alanyl)-2-pyrrolidinyl)-1H-imidazol-5-yl)-4-biphenylyl)-1H-imidazol-2-yl)-1-pyrrolidinyl)-1-methyl-2-oxoethyl)carbamate;

methyl ((1R)-2-((2S)-2-(5-(4'-(2-((2S)-1-(N-(methoxycarbonyl)-D-alanyl)-2-pyrrolidinyl)-1H-imidazol-5-yl)-4-biphenylyl)-1H-imidazol-2-yl)-1-pyrrolidinyl)-1-methyl-2-oxoethyl)carbamate;

(2S,2'S)-1,1'-(4,4'-biphenyldiylbis(1H-imidazole-5,2-diyl(2S)-2,1-pyrrolidinediyl))bis(N,N-dimethyl-1-oxo-2-propanamine);

dimethyl (4,4'-biphenyldiylbis(1H-imidazole-5,2-diyl(2S)-2,1-pyrrolidinediyl((2R)-1-oxo-1,2-butanediyl)))biscarbamate;

dimethyl (4,4'-biphenyldiylbis(1H-imidazole-5,2-diyl(2S)-2,1-pyrrolidinediyl((2S)-1-oxo-1,2-butanediyl)))biscarbamate;

dimethyl (4,4'-biphenyldiylbis(1H-imidazole-5,2-diyl(2S)-2,1-pyrrolidinediyl((1R)-1-cyclopropyl-2-oxo-2,1-ethanediyl)))biscarbamate;

dimethyl (4,4'-biphenyldiylbis(1H-imidazole-5,2-diyl(2S)-2,1-pyrrolidinediyl((1S)-1-cyclopropyl-2-oxo-2,1-ethanediyl)))biscarbamate;

methyl ((1S)-1-(((2S)-2-(5-(4'-(2-((2S)-1-((2S)-2-((methoxycarbonyl)amino)-3,3-dimethylbutanoyl)-2-pyrrolidinyl)-1H-imidazol-5-yl)-4-biphenylyl)-1H-imidazol-2-yl)-1-pyrrolidinyl)carbonyl)-2,2-dimethylpropyl)carbamate;

dimethyl (4,4'-biphenyldiylbis(1H-imidazole-5,2-diyl(2S)-2,1-pyrrolidinediyl((4S)-5-oxo-1-pentene-5,4-diyl)))biscarbamate;

methyl ((1S)-2-((2S)-2-(5-(4'-(2-((2S)-1-(N-(methoxycarbonyl)-O-methyl-L-seryl)-2-pyrrolidinyl)-1H-imidazol-5-yl)-4-biphenylyl)-1H-imidazol-2-yl)-1-pyrrolidinyl)-1-(methoxymethyl)-2-oxoethyl)carbamate;

methyl ((1S)-1-(((2S)-2-(5-(4'-(2-((2S)-1-((2S)-2-((methoxycarbonyl)amino)pentanoyl)-2-pyrrolidinyl)-1H-imidazol-5-yl)-4-biphenylyl)-1H-imidazol-2-yl)-1-pyrrolidinyl)carbonyl)butyl)carbamate;

methyl ((1S)-1-(((2R)-2-(5-(4'-(2-((2R)-1-((2S)-2-((methoxycarbonyl)amino)-3-methylbutanoyl)-2-pyrrolidinyl)-1H-imidazol-5-yl)-4-biphenylyl)-1H-imidazol-2-yl)-1-pyrrolidinyl)carbonyl)-2-methylpropyl)carbamate;

methyl ((1S)-1-(((2S)-2-(5-(4'-(2-((2R)-1-((2S)-2-((methoxycarbonyl)amino)-3-methylbutanoyl)-2-pyrrolidinyl)-1H-imidazol-5-yl)-4-biphenylyl)-1H-imidazol-2-yl)-1-pyrrolidinyl)carbonyl)-2-methylpropyl)carbamate;

dimethyl (4,4'-biphenyldiylbis(1H-imidazole-5,2-diyl(2R)-2,1-pyrrolidinediyl((1R)-1-cyclopropyl-2-oxo-2,1-ethanediyl)))biscarbamate;

ethyl ((1R)-2-((2S)-2-(5-(4'-(2-((2S)-1-((2R)-2-(diethylamino)-2-phenylacetyl)-2-pyrrolidinyl)-1H-imidazol-5-yl)-4-biphenylyl)-1H-imidazol-2-yl)-1-pyrrolidinyl)-1-methyl-2-oxoethyl)carbamate;

ethyl ((1S)-2-((2S)-2-(5-(4'-(2-((2S)-1-((2R)-2-(diethylamino)-2-phenylacetyl)-2-pyrrolidinyl)-1H-imidazol-5-yl)-4-biphenylyl)-1H-imidazol-2-yl)-1-pyrrolidinyl)-1-methyl-2-oxoethyl)carbamate;

(5S)-5-(((2S)-2-(5-(4'-(2-((2S)-1-((2R)-2-(diethylamino)-2-phenylacetyl)-2-pyrrolidinyl)-1H-imidazol-5-yl)-4-biphenylyl)-1H-imidazol-2-yl)-1-pyrrolidinyl)carbonyl)-2-pyrrolidinone;

methyl (1-(((2S)-2-(5-(4'-(2-((2S)-1-((2R)-2-(diethylamino)-2-phenylacetyl)-2-pyrrolidinyl)-1H-imidazol-5-yl)-4-biphenylyl)-1H-imidazol-2-yl)-1-pyrrolidinyl)carbonyl)cyclopropyl)carbamate;

methyl (2-((2S)-2-(5-(4'-(2-((2S)-1-((2R)-2-(diethylamino)-2-phenylacetyl)-2-pyrrolidinyl)-1H-imidazol-5-yl)-4-biphenylyl)-1H-imidazol-2-yl)-1-pyrrolidinyl)-1,1-dimethyl-2-oxoethyl)carbamate;

(2R)-1-((2S)-2-(5-(4'-(2-((2S)-1-((2R)-2-(diethylamino)-2-phenylacetyl)-2-pyrrolidinyl)-1H-imidazol-5-yl)-4-biphenylyl)-1H-imidazol-2-yl)-1-pyrrolidinyl)-N,N-diethyl-1-oxo-2-propanamine;

(2S)-1-((2S)-2-(5-(4'-(2-((2S)-1-((2R)-2-(diethylamino)-2-phenylacetyl)-2-pyrrolidinyl)-1H-imidazol-5-yl)-4-biphenylyl)-1H-imidazol-2-yl)-1-pyrrolidinyl)-N,N-diethyl-1-oxo-2-propanamine;

(1R)-N,N-diethyl-2-((2S)-2-(5-(4'-(2-((2S)-1-(1,3-oxazol-2-ylcarbonyl)-2-pyrrolidinyl)-1H-imidazol-5-yl)-4-biphenylyl)-1H-imidazol-2-yl)-1-pyrrolidinyl)-2-oxo-1-phenylethanamine;

(1R)-N,N-diethyl-2-oxo-1-phenyl-2-((2S)-2-(5-(4'-(2-((2S)-1-(3-pyridinylcarbonyl)-2-pyrrolidinyl)-1H-imidazol-5-yl)-4-biphenylyl)-1H-imidazol-2-yl)-1-pyrrolidinyl)ethanamine;

(2R)-1-((2S)-2-(5-(4'-(2-((2S)-1-((2R)-2-(diethylamino)-2-phenylacetyl)-2-pyrrolidinyl)-1H-imidazol-5-yl)-4-biphenylyl)-1H-imidazol-2-yl)-1-pyrrolidinyl)-1-oxo-2-propanol;

(2S)-1-((2S)-2-(5-(4'-(2-((2S)-1-((2R)-2-(diethylamino)-2-phenylacetyl)-2-pyrrolidinyl)-1H-imidazol-5-yl)-4-biphenylyl)-1H-imidazol-2-yl)-1-pyrrolidinyl)-1-oxo-2-propanol;

methyl (1-(((2S)-2-(5-(4'-(2-((2S)-1-((2R)-2-(diethylamino)-2-phenylacetyl)-2-pyrrolidinyl)-1H-imidazol-5-yl)-4-biphenylyl)-1H-imidazol-2-yl)-1-pyrrolidinyl)carbonyl)cyclobutyl)carbamate;

methyl (1-(((2S)-2-(5-(4'-(2-((2S)-1-((2R)-2-(diethylamino)-2-phenylacetyl)-2-pyrrolidinyl)-1H-imidazol-5-yl)-4-biphenylyl)-1H-imidazol-2-yl)-1-pyrrolidinyl)carbonyl)cyclopentyl)carbamate;

N-((1S)-2-((2S)-2-(5-(4'-(2-((2S)-1-((2R)-2-(diethylamino)-2-phenylacetyl)-2-pyrrolidinyl)-1H-imidazol-5-yl)-4-biphenylyl)-1H-imidazol-2-yl)-1-pyrrolidinyl)-1-methyl-2-oxoethyl)-N-propyl-1-propanamine;

(4S)-4-(((2S)-2-(5-(4'-(2-((2S)-1-((2R)-2-(diethylamino)-2-phenylacetyl)-2-pyrrolidinyl)-1H-imidazol-5-yl)-4-biphenylyl)-1H-imidazol-2-yl)-1-pyrrolidinyl)carbonyl)-1,3-oxazolidin-2-one;

(2R)-1-((2S)-2-(5-(4'-(2-((2S)-1-((2R)-2-(diethylamino)-2-phenylacetyl)-2-pyrrolidinyl)-1H-imidazol-5-yl)-4-biphenylyl)-1H-imidazol-2-yl)-1-pyrrolidinyl)-N,N-diethyl-3-methyl-1-oxo-2-butanamine;

N-((1R)-2-((2S)-2-(5-(4'-(2-((2S)-1-((2R)-2-(diethylamino)-2-phenylacetyl)-2-pyrrolidinyl)-1H-imidazol-5-yl)-4-biphenylyl)-1H-imidazol-2-yl)-1-pyrrolidinyl)-1-methyl-2-oxoethyl)-N-propyl-1-propanamine;

methyl ((1R)-2-((2S)-2-(5-(4'-(2-((2S)-1-((2R)-2-(diethylamino)-2-phenylacetyl)-2-pyrrolidinyl)-1H-imidazol-5-yl)-4-biphenylyl)-1H-imidazol-2-yl)-1-pyrrolidinyl)-2-oxo-1-phenylethyl)carbamate;

(1R)-N,N-diethyl-2-((2S)-2-(5-(4'-(2-((2S)-1-((2R)-2-(4-morpholinyl)-2-phenylacetyl)-2-pyrrolidinyl)-1H-imidazol-5-yl)-4-biphenylyl)-1H-imidazol-2-yl)-1-pyrrolidinyl)-2-oxo-1-phenylethanamine;

methyl ((1S)-2-((2S)-2-(5-(4'-(2-((2S)-1-((2R)-2-(diethylamino)-2-phenylacetyl)-2-pyrrolidinyl)-1H-imidazol-5-yl)-4-biphenylyl)-1H-imidazol-2-yl)-1-pyrrolidinyl)-1-methyl-2-oxoethyl)carbamate;

methyl (2-((2S)-2-(5-(4'-(2-((2S)-1-((2R)-2-(diethylamino)-2-phenylacetyl)-2-pyrrolidinyl)-1H-imidazol-5-yl)-4-biphenylyl)-1H-imidazol-2-yl)-1-pyrrolidinyl)-2-oxoethyl)carbamate;

(1R)-N,N-diethyl-2-((2S)-2-(5-(4'-(2-((2S)-1-(4-morpholinylcarbonyl)-2-pyrrolidinyl)-1H-imidazol-5-yl)-4-biphenylyl)-1H-imidazol-2-yl)-1-pyrrolidinyl)-2-oxo-1-phenylethanamine;

(1R)-2-((2S)-2-(5-(4'-(2-((2S)-1-((2R)-2-(diethylamino)-2-phenylacetyl)-2-pyrrolidinyl)-1H-imidazol-5-yl)-4-biphenylyl)-1H-imidazol-2-yl)-1-pyrrolidinyl)-N,N-dimethyl-2-oxo-1-phenylethanamine;

methyl ((1R)-2-((2S)-2-(5-(4'-(2-((2S)-1-((2R)-2-(diethylamino)-2-phenylacetyl)-2-pyrrolidinyl)-1H-imidazol-5-yl)-4-biphenylyl)-1H-imidazol-2-yl)-1-pyrrolidinyl)-1-methyl-2-oxoethyl)carbamate;

methyl ((1R)-1-(((2S)-2-(5-(4'-(2-((2S)-1-((2R)-2-(diethylamino)-2-phenylacetyl)-2-pyrrolidinyl)-1H-imidazol-5-yl)-4-biphenylyl)-1H-imidazol-2-yl)-1-pyrrolidinyl)carbonyl)propyl)carbamate;

methyl ((1S)-1-(((2S)-2-(5-(4'-(2-((2S)-1-((2R)-2-(diethylamino)-2-phenylacetyl)-2-pyrrolidinyl)-1H-imidazol-5-yl)-4-biphenylyl)-1H-imidazol-2-yl)-1-pyrrolidinyl)carbonyl)propyl)carbamate;

methyl ((1R)-1-cyclopropyl-2-((2S)-2-(5-(4'-(2-((2S)-1-((2R)-2-(diethylamino)-2-phenylacetyl)-2-pyrrolidinyl)-1H-imidazol-5-yl)-4-biphenylyl)-1H-imidazol-2-yl)-1-pyrrolidinyl)-2-oxoethyl)carbamate;

methyl ((1S)-1-cyclopropyl-2-((2S)-2-(5-(4'-(2-((2S)-1-((2R)-2-(diethylamino)-2-phenylacetyl)-2-pyrrolidinyl)-1H-imidazol-5-yl)-4-biphenylyl)-1H-imidazol-2-yl)-1-pyrrolidinyl)-2-oxoethyl)carbamate;

methyl ((1S)-1-(((2S)-2-(5-(4'-(2-((2S)-1-((2R)-2-(diethylamino)-2-phenylacetyl)-2-pyrrolidinyl)-1H-imidazol-5-yl)-4-biphenylyl)-1H-imidazol-2-yl)-1-pyrrolidinyl)carbonyl)-2-methylpropyl)carbamate;

methyl ((1S)-1-(((2S)-2-(5-(4'-(2-((2S)-1-((2R)-2-(diethylamino)-2-phenylacetyl)-2-pyrrolidinyl)-1H-imidazol-5-yl)-4-biphenylyl)-1H-imidazol-2-yl)-1-pyrrolidinyl)carbonyl)-2,2-dimethylpropyl)carbamate;

methyl ((1S)-1-(((2S)-2-(5-(4'-(2-((2S)-1-((2R)-2-(diethylamino)-2-phenylacetyl)-2-pyrrolidinyl)-1H-imidazol-5-yl)-4-biphenylyl)-1H-imidazol-2-yl)-1-pyrrolidinyl)carbonyl)-3-buten-1-yl)carbamate;

methyl ((1S)-2-((2S)-2-(5-(4'-(2-((2S)-1-((2R)-2-(diethylamino)-2-phenylacetyl)-2-pyrrolidinyl)-1H-imidazol-5-yl)-4-biphenylyl)-1H-imidazol-2-yl)-1-pyrrolidinyl)-1-(methoxymethyl)-2-oxoethyl)carbamate;

methyl ((1S)-1-(((2S)-2-(5-(4'-(2-((2S)-1-((2R)-2-(diethylamino)-2-phenylacetyl)-2-pyrrolidinyl)-1H-imidazol-5-yl)-4-biphenylyl)-1H-imidazol-2-yl)-1-pyrrolidinyl)carbonyl)butyl)carbamate;

methyl ((1R)-2-((2S)-2-(5-(4'-(2-((2S)-1-(N,N-diethyl-D-alanyl)-2-pyrrolidinyl)-1H-imidazol-5-yl)-4-biphenylyl)-1H-imidazol-2-yl)-1-pyrrolidinyl)-2-oxo-1-phenylethyl)carbamate;

methyl ((1R)-2-((2S)-2-(5-(4'-(2-((2S)-1-(N,N-dipropyl-D-alanyl)-2-pyrrolidinyl)-1H-imidazol-5-yl)-4-biphenylyl)-1H-imidazol-2-yl)-1-pyrrolidinyl)-2-oxo-1-phenylethyl)carbamate;

methyl ((1R)-2-((2S)-2-(5-(4'-(2-((2S)-1-(1H-imidazol-5-ylcarbonyl)-2-pyrrolidinyl)-1H-imidazol-5-yl)-4-biphenylyl)-1H-imidazol-2-yl)-1-pyrrolidinyl)-2-oxo-1-phenylethyl)carbamate;

M66a: methyl ((1R)-2-((2S)-2-(5-(4'-(2-((2S)-1-(4-(diethylamino)-2-((methoxycarbonyl)amino)butanoyl)-2-pyrrolidinyl)-1H-imidazol-5-yl)-4-biphenylyl)-1H-imidazol-2-yl)-1-pyrrolidinyl)-2-oxo-1-phenylethyl)carbamate;

methyl ((1R)-2-((2S)-2-(5-(4'-(2-((2S)-1-((2R)-2-(diethylamino)butanoyl)-2-pyrrolidinyl)-1H-imidazol-5-yl)-4-biphenylyl)-1H-imidazol-2-yl)-1-pyrrolidinyl)-2-oxo-1-phenylethyl)carbamate;

methyl ((1S)-1-(((2S)-2-(5-(4'-(2-((2S)-1-(4-(diethylamino)-2-((methoxycarbonyl)amino)butanoyl)-2-pyrrolidinyl)-1H-imidazol-5-yl)-4-biphenylyl)-1H-imidazol-2-yl)-1-pyrrolidinyl)carbonyl)-2-methylpropyl)carbamate;

methyl ((1S)-1-(((2S)-2-(5-(4'-(2-((2S)-1-((2S)-2-((methoxycarbonyl)amino)-3-methylbutanoyl)-2-pyrrolidinyl)-1H-imidazol-5-yl)-4-biphenylyl)-1H-imidazol-2-yl)-1-pyrrolidinyl)carbonyl)-3-(4-morpholinyl)propyl)carbamate;

methyl ((1S)-1-(((2S)-2-(5-(4'-(2-((2S)-1-(N,N-diethyl-L-alanyl)-2-pyrrolidinyl)-1H-imidazol-5-yl)-4-biphenylyl)-1H-imidazol-2-yl)-1-pyrrolidinyl)carbonyl)-2-methylpropyl)carbamate;

methyl ((1S)-1-(((2S)-2-(5-(4'-(2-((2S)-1-(N,N-diethyl-D-alanyl)-2-pyrrolidinyl)-1H-imidazol-5-yl)-4-biphenylyl)-1H-imidazol-2-yl)-1-pyrrolidinyl)carbonyl)-2-methylpropyl)carbamate;

methyl ((1S)-2-((2S)-2-(5-(4'-(2-((2S)-1-(N-(methoxycarbonyl)-L-valyl)-2-pyrrolidinyl)-1H-imidazol-5-yl)-4-biphenylyl)-1H-imidazol-2-yl)-1-pyrrolidinyl)-1-(methoxymethyl)-2-oxoethyl)carbamate;

methyl ((1S)-1-(((2S)-2-(5-(4'-(2-((2S)-1-((2S)-2-((methoxycarbonyl)amino)-3,3-dimethylbutanoyl)-2-pyrrolidinyl)-1H-imidazol-5-yl)-4-biphenylyl)-1H-imidazol-2-yl)-1-pyrrolidinyl)carbonyl)-2-methylpropyl)carbamate;

methyl (2-((2S)-2-(5-(4'-(2-((2S)-1-((2S)-2-((methoxycarbonyl)amino)-3-methylbutanoyl)-2-pyrrolidinyl)-1H-imidazol-5-yl)-4-biphenylyl)-1H-imidazol-2-yl)-1-pyrrolidinyl)-2-oxoethyl)carbamate;

methyl ((1S)-1-(((2S)-2-(5-(4'-(2-((2S)-1-((2S)-2-((methoxycarbonyl)amino)butanoyl)-2-pyrrolidinyl)-1H-imidazol-5-yl)-4-biphenylyl)-1H-imidazol-2-yl)-1-pyrrolidinyl)carbonyl)-2-methylpropyl)carbamate;

methyl ((1S)-1-(((2S)-2-(5-(4'-(2-((2S)-1-((2S)-2-((methoxycarbonyl)amino)-3-methylbutanoyl)-2-pyrrolidinyl)-1H-imidazol-5-yl)-4-biphenylyl)-1H-imidazol-2-yl)-1-pyrrolidinyl)carbonyl)butyl)carbamate;

methyl ((1S)-1-(((2S)-2-(5-(4'-(2-((2S)-1-((2S)-2-((methoxycarbonyl)amino)-3-methylbutanoyl)-2-pyrrolidinyl)-1H-imidazol-5-yl)-4-biphenylyl)-1H-imidazol-2-yl)-1-pyrrolidinyl)carbonyl)-3-buten-1-yl)carbamate;

methyl ((1S)-1-(((2S)-2-(5-(4'-(2-((2S)-1-((2S)-2-cyclopropyl-2-((methoxycarbonyl)amino)acetyl)-2-pyrrolidinyl)-1H-imidazol-5-yl)-4-biphenylyl)-1H-imidazol-2-yl)-1-pyrrolidinyl)carbonyl)-2-methylpropyl)carbamate;

methyl ((1S)-1-(((2S)-2-(5-(4'-(2-((2S)-1-((2R)-2-(ethyl(methyl)amino)-2-phenylacetyl)-2-pyrrolidinyl)-1H-imidazol-5-yl)-4-biphenylyl)-1H-imidazol-2-yl)-1-pyrrolidinyl)carbonyl)-2-methylpropyl)carbamate;

methyl ((1S)-1-(((2S)-2-(5-(4'-(2-((2S)-1-(N,N-diethyl-D-valyl)-2-pyrrolidinyl)-1H-imidazol-5-yl)-4-biphenylyl)-1H-imidazol-2-yl)-1-pyrrolidinyl)carbonyl)-2-methylpropyl)carbamate;

methyl ((1S)-1-(((2S)-2-(5-(4'-(2-((2S)-1-((2R)-2-((methoxycarbonyl)amino)-2-phenylacetyl)-2-pyrrolidinyl)-1H-imidazol-5-yl)-4-biphenylyl)-1H-imidazol-2-yl)-1-pyrrolidinyl)carbonyl)-2-methylpropyl)carbamate;

methyl ((1S)-2-methyl-1-(((2S)-2-(5-(4'-(2-((2S)-1-(3-methylbutanoyl)-2-pyrrolidinyl)-1H-imidazol-5-yl)-4-biphenylyl)-1H-imidazol-2-yl)-1-pyrrolidinyl)carbonyl)propyl)carbamate;

methyl ((1S)-2-methyl-1-(((2S)-2-(5-(4'-(2-((2S)-1-((4-methyl-1-piperazinyl)carbonyl)-2-pyrrolidinyl)-1H-imidazol-5-yl)-4-biphenylyl)-1H-imidazol-2-yl)-1-pyrrolidinyl)carbonyl)propyl)carbamate;

methyl ((1S)-1-(((2S)-2-(5-(4'-(2-((2S)-1-(N,N-dipropyl-D-alanyl)-2-pyrrolidinyl)-1H-imidazol-5-yl)-4-biphenylyl)-1H-imidazol-2-yl)-1-pyrrolidinyl)carbonyl)-2-methylpropyl)carbamate;

methyl ((1S)-1-(((2S)-2-(5-(4'-(2-((2S)-1-(N,N-dipropyl-L-alanyl)-2-pyrrolidinyl)-1H-imidazol-5-yl)-4-biphenylyl)-1H-imidazol-2-yl)-1-pyrrolidinyl)carbonyl)-2-methylpropyl)carbamate;

methyl ((1S)-1-(((2S)-2-(5-(4'-(2-((2S)-1-((2R)-2-(diethylamino)butanoyl)-2-pyrrolidinyl)-1H-imidazol-5-yl)-4-biphenylyl)-1H-imidazol-2-yl)-1-pyrrolidinyl)carbonyl)-2-methylpropyl)carbamate;

methyl ((1S)-1-(((2S)-2-(5-(4'-(2-((2S)-1-((2S)-2-(diethylamino)butanoyl)-2-pyrrolidinyl)-1H-imidazol-5-yl)-4-biphenylyl)-1H-imidazol-2-yl)-1-pyrrolidinyl)carbonyl)-2-methylpropyl)carbamate;

methyl ((1S)-1-(((2S)-2-(5-(4'-(2-((2S)-1-(1H-imidazol-4-ylcarbonyl)-2-pyrrolidinyl)-1H-imidazol-5-yl)-4-biphenylyl)-1H-imidazol-2-yl)-1-pyrrolidinyl)carbonyl)-2-methylpropyl)carbamate;

methyl ((1S)-1-(((2S)-2-(5-(4'-(2-((2S)-1-(N,N-diethyl-O-methyl-L-seryl)-2-pyrrolidinyl)-1H-imidazol-5-yl)-4-biphenylyl)-1H-imidazol-2-yl)-1-pyrrolidinyl)carbonyl)-2-methylpropyl)carbamate;

methyl ((1S)-1-(((2S)-2-(5-(4'-(2-((2S)-1-(N^2,N^2-diethyl-D-asparaginyl)-2-pyrrolidinyl)-1H-imidazol-5-yl)-4-biphenylyl)-1H-imidazol-2-yl)-1-pyrrolidinyl)carbonyl)-2-methylpropyl)carbamate;

methyl ((1S)-1-(((2S)-2-(5-(4'-(2-((2R)-1-((2R)-2-((methoxycarbonyl)amino)-3-methylbutanoyl)-2-pyrrolidinyl)-1H-imidazol-5-yl)-4-biphenylyl)-1H-imidazol-2-yl)-1-pyrrolidinyl)carbonyl)-2-methylpropyl)carbamate;

methyl ((1S)-1-(((2S)-2-(5-(4'-(2-((2S)-1-(N,N-diethyl-O-methyl-D-seryl)-2-pyrrolidinyl)-1H-imidazol-5-yl)-4-biphenylyl)-1H-imidazol-2-yl)-1-pyrrolidinyl)carbonyl)-2-methylpropyl)carbamate;

methyl ((1S)-1-(((2S)-2-(5-(4'-(2-((2S)-1-(N,N-diethyl-3-methyl-D-valyl)-2-pyrrolidinyl)-1H-imidazol-5-yl)-4-biphenylyl)-1H-imidazol-2-yl)-1-pyrrolidinyl)carbonyl)-2-methylpropyl)carbamate;

methyl ((1S)-3-amino-1-(((2S)-2-(5-(4'-(2-((2S)-1-((2S)-2-((methoxycarbonyl)amino)-3-methylbutanoyl)-2-pyrrolidinyl)-1H-imidazol-5-yl)-4-biphenylyl)-1H-imidazol-2-yl)-1-pyrrolidinyl)carbonyl)-3-oxopropyl)carbamate ;

methyl ((1S)-1-methyl-2-((2S)-2-(5-(4'-(2-((2S)-1-(1,3-oxazol-2-ylcarbonyl)-2-pyrrolidinyl)-1H-imidazol-5-yl)-4-biphenylyl)-1H-imidazol-2-yl)-1-pyrrolidinyl)-2-oxocthyl)carbamatc;

methyl ((1S)-1-cyclopropyl-2-((2S)-2-(5-(4'-(2-((2S)-1-(N-(methoxycarbonyl)-L-alanyl)-2-pyrrolidinyl)-1H-imidazol-5-yl)-4-biphenylyl)-1H-imidazol-2-yl)-1-pyrrolidinyl)-2-oxoethyl)carbamate;

mcthyl ((1S)-1-(((2S)-2-(5-(4'-(2-((2S)-1-((2S)-2-((methoxycarbonyl)amino)propanoyl)-2-pyrrolidinyl)-1H-imidazol-5-yl)-4-biphenylyl)-1H-imidazol-2-yl)-1-pyrrolidinyl)carbonyl)butyl)carbamate;

methyl ((1S)-1-(((2S)-2-(5-(4'-(2-((2S)-1-(N-(methoxycarbonyl)-L-alanyl)-2-pyrrolidinyl)-1H-imidazol-5-yl)-4-biphenylyl)-1H-imidazol-2-yl)-1-pyrrolidinyl)carbonyl)-2,2-dimethylpropyl)carbamate;

methyl ((1S)-2-((2S)-2-(5-(4'-(2-((2S)-1-(N,N-diethyl-D-alanyl)-2-pyrrolidinyl)-1H-imidazol-5-yl)-4-biphenylyl)-1H-imidazol-2-yl)-1-pyrrolidinyl)-1-methyl-2-oxoethyl)carbamate;

methyl ((1S)-2-((2S)-2-(5-(4'-(2-((2S)-1-(7-azabicyclo[2.2.1]hept-7-yl(phenyl)acetyl)-2-pyrrolidinyl)-1H-imidazol-5-yl)-4-biphenylyl)-1H-imidazol-2-yl)-1-pyrrolidinyl)-1-methyl-2-oxoethyl)carbamate;

methyl ((1S)-2-((2S)-2-(5-(4'-(2-((2S)-1-((2R)-2-hydroxy-2-phenylacetyl)-2-pyrrolidinyl)-1H-imidazol-5-yl)-4-biphenylyl)-1H-imidazol-2-yl)-1-pyrrolidinyl)-1-methyl-2-oxoethyl)carbamate;

methyl ((1S)-2-((2S)-2-(5-(4'-(2-((2S)-1-((2R)-2-(ethyl(methyl)amino)-2-phenylacetyl)-2-pyrrolidinyl)-1H-imidazol-5-yl)-4-biphenylyl)-1H-imidazol-2-yl)-1-pyrrolidinyl)-1-methyl-2-oxoethyl)carbamate;

methyl ((1S)-2-((2S)-2-(5-(4'-(2-((2S)-1-(N-(methoxycarbonyl)-L-alanyl)-2-pyrrolidinyl)-1H-imidazol-5-yl)-4-biphenylyl)-1H-imidazol-2-yl)-1-pyrrolidinyl)-1-(methoxymethyl)-2-oxoethyl)carbamate;

methyl ((1S)-2-((2S)-2-(5-(4'-(2-((2S)-1-(N,N-diethyl-D-valyl)-2-pyrrolidinyl)-1H-imidazol-5-yl)-4-biphenylyl)-1H-imidazol-2-yl)-1-pyrrolidinyl)-1-methyl-2-oxoethyl)carbamate;

methyl ((1S)-2-((2S)-2-(5-(4'-(2-((2S)-1-(N,N-dipropyl-D-alanyl)-2-pyrrolidinyl)-1H-imidazol-5-yl)-4-biphenylyl)-1H-imidazol-2-yl)-1-pyrrolidinyl)-1-methyl-2-oxoethyl)carbamate;

methyl ((1S)-2-((2S)-2-(5-(4'-(2-((2S)-1-(N,N-dipropyl-L-alanyl)-2-pyrrolidinyl)-1H-imidazol-5-yl)-4-biphenylyl)-1H-imidazol-2-yl)-1-pyrrolidinyl)-1-methyl-2-oxoethyl)carbamate;

methyl ((1S)-1-(((2S)-2-(5-(4'-(2-((2S)-1-(3-hydroxy-L-valyl)-2-pyrrolidinyl)-1H-imidazol-5-yl)-4-biphenylyl)-1H-imidazol-2-yl)-1-pyrrolidinyl)carbonyl)-2-methylpropyl)carbamate;

methyl ((1S)-1-(((2S)-2-(5-(4'-(2-((2S)-1-((2S)-3-hydroxy-2-((methoxycarbonyl)amino)-3-methylbutanoyl)-2-pyrrolidinyl)-1H-imidazol-5-yl)-4-biphenylyl)-1H-imidazol-2-yl)-1-pyrrolidinyl)carbonyl)-2-methylpropyl)carbamate;

methyl ((1S)-1-(((2S)-2-(5-(4'-(2-((2S)-1-((2S,3R)-4-hydroxy-2-((methoxycarbonyl)amino)-3-methylbutanoyl)-2-pyrrolidinyl)-1H-imidazol-5-yl)-4-biphenylyl)-1H-imidazol-2-yl)-1-pyrrolidinyl)carbonyl)-2-methylpropyl)carbamate;

methyl ((1S)-1-(((2S)-2-(5-(4'-(2-((2S)-1-((2S,3S)-4-hydroxy-2-((methoxycarbonyl)amino)-3-methylbutanoyl)-2-pyrrolidinyl)-1H-imidazol-5-yl)-4-biphenylyl)-1H-imidazol-2-yl)-1-pyrrolidinyl)carbonyl)-2-methylpropyl)carbamate;

methyl ((1S)-2-methyl-1-(((2S)-2-(5-(4'-(2-((2S)-1-L-valyl-2-pyrrolidinyl)-1H-imidazol-5-yl)-4-biphenylyl)-1H-imidazol-2-yl)-1-pyrrolidinyl)carbonyl)propyl)carbamate;

benzyl (3S)-3-((methoxycarbonyl)amino)-4-((2S)-2-(5-(4'-(2-((2S)-1-(N-(methoxycarbonyl)-L-valyl)-2-pyrrolidinyl)-1H-imidazol-5-yl)-4-biphenylyl)-1H-imidazol-2-yl)-1-pyrrolidinyl)-4-oxobutanoate;

methyl (3S)-3-((methoxycarbonyl)amino)-4-((2S)-2-(5-(4'-(2-((2S)-1-(N-(methoxycarbonyl)-L-valyl)-2-pyrrolidinyl)-1H-imidazol-5-yl)-4-biphenylyl)-1H-imidazol-2-yl)-1-pyrrolidinyl)-4-oxobutanoate;

(3S)-3-((methoxycarbonyl)amino)-4-((2S)-2-(5-(4'-(2-((2S)-1-(N-(methoxycarbonyl)-L-valyl)-2-pyrrolidinyl)-1H-imidazol-5-yl)-4-biphenylyl)-1H-imidazol-2-yl)-1-pyrrolidinyl)-4-oxobutanoic acid;

methyl ((1S)-1-(((2S)-2-(5-(4'-(2-((2S)-1-((2S)-2-((methoxycarbonyl)amino)-4-(4-methyl-1-piperazinyl)-4-oxobutanoyl)-2-pyrrolidinyl)-1H-imidazol-5-yl)-4-biphenylyl)-1H-imidazol-2-yl)-1-pyrrolidinyl)carbonyl)-2-methylpropyl)carbamate;

methyl ((1S)-3-(dimethylamino)-1-(((2S)-2-(5-(4'-(2-((2S)-1-((2S)-2-((methoxycarbonyl)amino)-3-methylbutanoyl)-2-pyrrolidinyl)-1H-imidazol-5-yl)-4-biphenylyl)-1H-imidazol-2-yl)-1-pyrrolidinyl)carbonyl)-3-oxopropyl)carbamate;

4,4'-bis(2-((2S)-1-(N-(methoxycarbonyl)-L-valyl)-2-pyrrolidinyl)-1H-imidazol-5-yl)-2-biphenylcarboxylic acid;

4,4'-bis(2-((2S)-1-((2R)-2-cyclopropyl-2-((methoxycarbonyl)amino)acetyl)-2-pyrrolidinyl)-1H-imidazol-5-yl)-2-biphenylcarboxylic acid;

4,4'-bis(2-((2S)-1-((2S)-2-cyclopropyl-2-((methoxycarbonyl)amino)acetyl)-2-pyrrolidinyl)-1H-imidazol-5-yl)-2-biphenylcarboxylic acid;

4,4'-bis(2-((2S)-1-((2R)-2-((methoxycarbonyl)amino)-2-phenylacetyl)-2-pyrrolidinyl)-1H-imidazol-5-yl)-2-biphenylcarboxylic acid;

methyl ((1S)-1-(((2S)-2-(5-(2'-carbamoyl-4'-(2-((2S)-1-((2S)-2-((methoxycarbonyl)amino)-3-methylbutanoyl)-2-pyrrolidinyl)-1H-imidazol-5-yl)-4-biphenylyl)-1H-imidazol-2-yl)-1-pyrrolidinyl)carbonyl)-2-methylpropyl)carbamate;

methyl ((1S)-1-(((2S)-2-(5-(2-(hydroxymethyl)-4'-(2-((2S)-1-((2S)-2-((methoxycarbonyl)amino)-3-methylbutanoyl)-2-pyrrolidinyl)-1H-imidazol-5-yl)-4-biphenylyl)-1H-imidazol-2-yl)-1-pyrrolidinyl)carbonyl)-2-methylpropyl)carbamate;

methyl ((1S)-1-(((2S)-2-(5-(2-((dimethylamino)methyl)-4'-(2-((2S)-1-((2S)-2-((methoxycarbonyl)amino)-3-methylbutanoyl)-2-pyrrolidinyl)-1H-imidazol-5-yl)-4-biphenylyl)-1H-imidazol-2-yl)-1-pyrrolidinyl)carbonyl)-2-methylpropyl)carbamate;

dimethyl ((2-((dimethylamino)methyl)-4,4'-biphenyldiyl)bis(1H-imidazole-5,2-diyl(2S)-2,1-pyrrolidinediyl((1R)-2-oxo-1-phenyl-2,1-ethanediyl)))biscarbamate;

methyl ((1S)-1-(((1S,3S,5S)-3-(5-(4'-(2-((1S,3S,5S)-2-((2S)-2-((methoxycarbonyl)amino)-3-methylbutanoyl)-2-azabicyclo[3.1.0]hex-3-yl)-1H-imidazol-5-yl)-4-biphenylyl)-1H-imidazol-2-yl)-2-azabicyclo[3.1.0]hex-2-yl)carbonyl)-2-methylpropyl)carbamate;

methyl ((1R)-1-(((1S,3S,5S)-3-(5-(4'-(2-((1S,3S,5S)-2-((2R)-2-((methoxycarbonyl)amino)-3-methylbutanoyl)-2-azabicyclo[3.1.0]hex-3-yl)-1H-imidazol-5-yl)-4-biphenylyl)-1H-imidazol-2-yl)-2-azabicyclo[3.1.0]hex-2-yl)carbonyl)-2-methylpropyl)carbamate;

dimethyl (4,4'-biphenyldiylbis(1H-imidazole-5,2-diyl(1S,3S,5S)-2-azabicyclo[3.1.0]hexane-3,2-diyl((1R)-2-oxo-1-phenyl-2,1-ethanediyl)))biscarbamate;

methyl ((1S)-2-hydroxy-1-(((1S,3S,5S)-3-(5-(4'-(2-((1S,3S,5S)-2-((2S)-3-hydroxy-2-((methoxycarbonyl)amino)-3-methylbutanoyl)-2-azabicyclo[3.1.0]hex-3-yl)-1H-

imidazol-5-yl)-4-biphenylyl)-1H-imidazol-2-yl)-2-azabicyclo[3.1.0]hex-2-yl)carbonyl)-2-methylpropyl)carbamate;

dimethyl (4,4'-biphenyldiylbis(1H-imidazole-5,2-diyl(1S,3S,5S)-2-azabicyclo[3.1.0]hexane-3,2-diyl((2S)-1-oxo-1,2-butanediyl)))biscarbamate;

dimethyl (4,4'-biphenyldiylbis(1H-imidazole-5,2-diyl(1S,3S,5S)-2-azabicyclo[3.1.0]hexane-3,2-diyl((1S)-1-cyclopropyl-2-oxo-2,1-ethanediyl)))biscarbamate;

methyl ((1S)-1-(((1S,3S,5S)-3-(5-(4'-(2-((1S,3S,5S)-2-((2S)-2-((methoxycarbonyl)amino)-3,3-dimethylbutanoyl)-2-azabicyclo[3.1.0]hex-3-yl)-1H-imidazol-5-yl)-4-biphenylyl)-1H-imidazol-2-yl)-2-azabicyclo[3.1.0]hex-2-yl)carbonyl)-2,2-dimethylpropyl)carbamate;

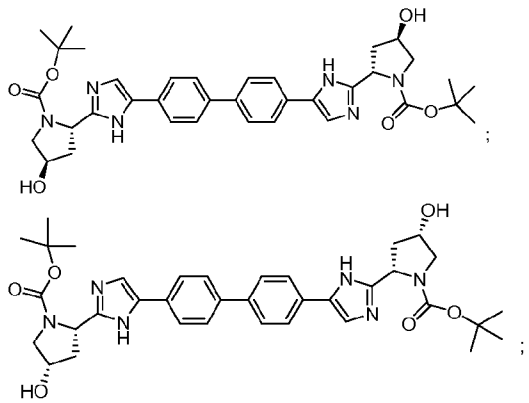
methyl (2-((1S,3S,5S)-3-(5-(4'-(2-((1S,3S,5S)-2-(((methoxycarbonyl)amino)acetyl)-2-azabicyclo[3.1.0]hex-3-yl)-1H-imidazol-5-yl)-4-biphenylyl)-1H-imidazol-2-yl)-2-azabicyclo[3.1.0]hex-2-yl)-2-oxoethyl)carbamate;

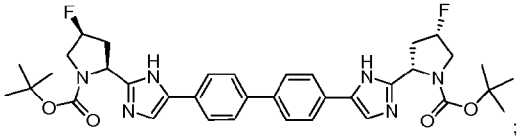
methyl ((1S)-2-((1S,3S,5S)-3-(5-(4'-(2-((1S,3S,5S)-2-(N-(methoxycarbonyl)-L-alanyl)-2-azabicyclo[3.1.0]hex-3-yl)-1H-imidazol-5-yl)-4-biphenylyl)-1H-imidazol-2-yl)-2-azabicyclo[3.1.0]hex-2-yl)-1-methyl-2-oxoethyl)carbamate; and

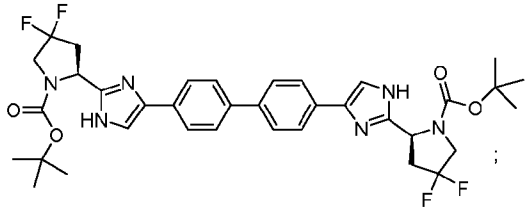
methyl ((1S)-1-(((1R,3R,5R)-3-(5-(4'-(2-((1R,3R,5R)-2-((2S)-2-((methoxycarbonyl)amino)-3-methylbutanoyl)-2-azabicyclo[3.1.0]hex-3-yl)-1H-imidazol-5-yl)-4-biphenylyl)-1H-imidazol-2-yl)-2-azabicyclo[3.1.0]hex-2-yl)carbonyl)-2-methylpropyl)carbamate;

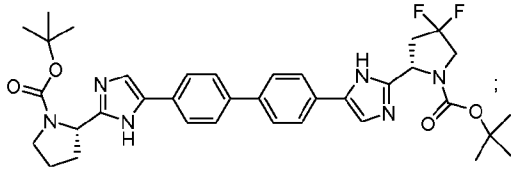
or a pharmaceutically acceptable salt thereof.

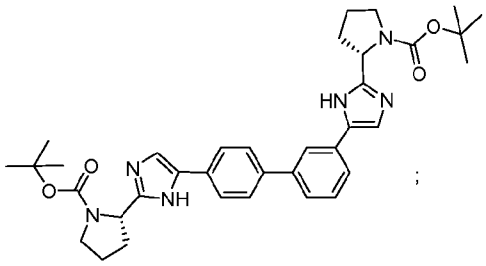
20. A compound selected from

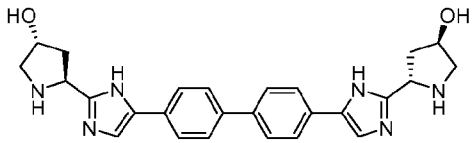


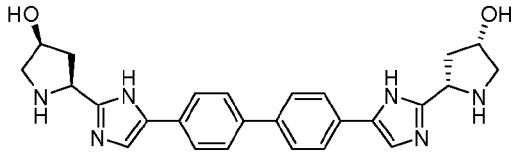

;

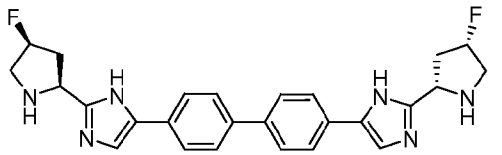

;

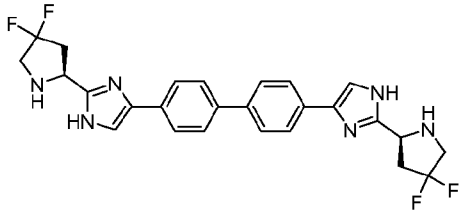

;

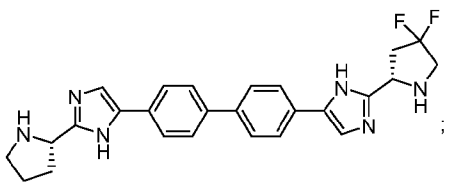

;

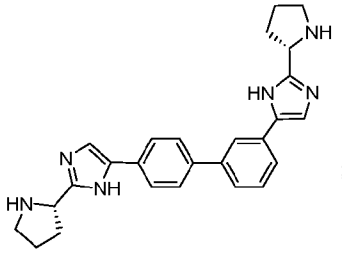

;

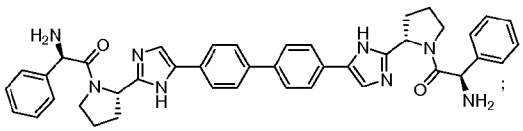

;

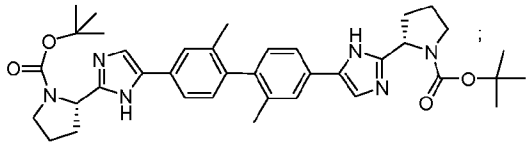

;

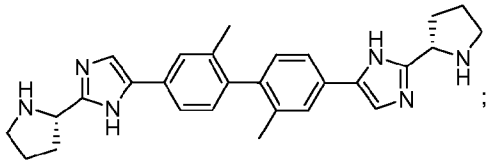

;

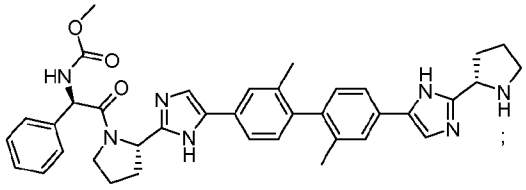

;

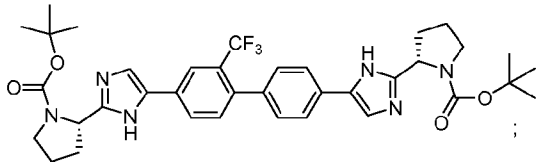

;

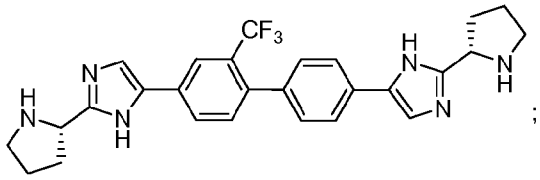

;

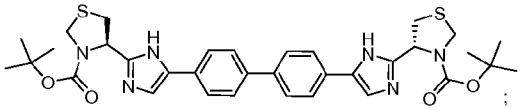

;

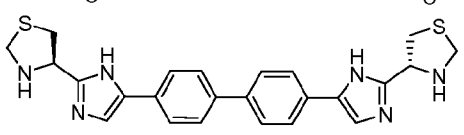

;

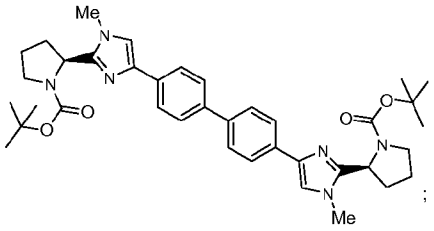

;

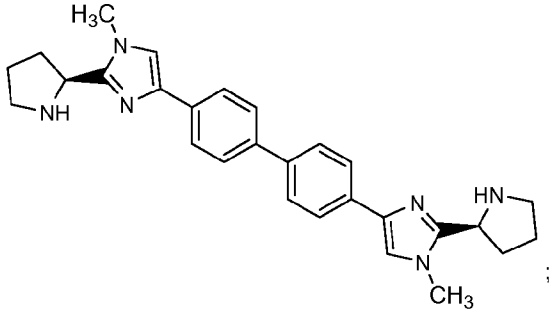

;

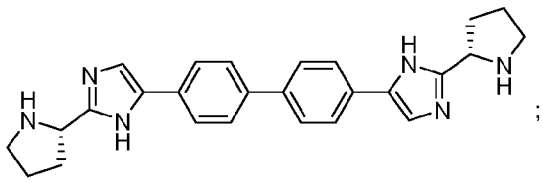

;

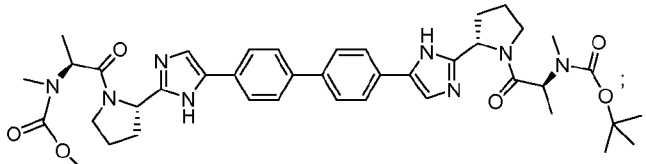

;

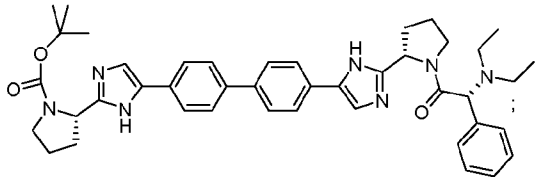

;

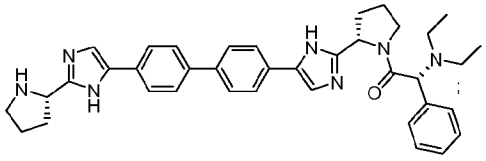

;

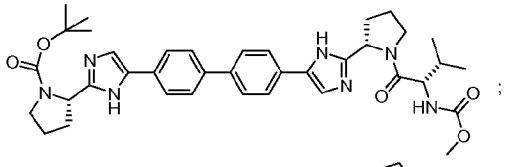

;

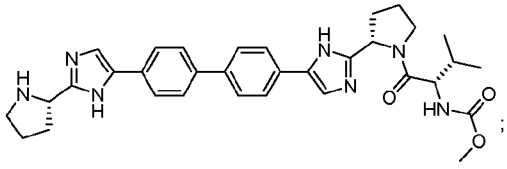

;

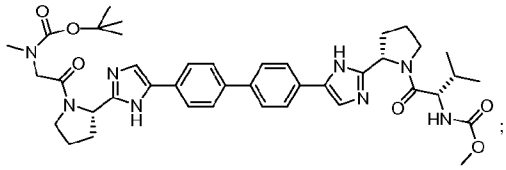

;

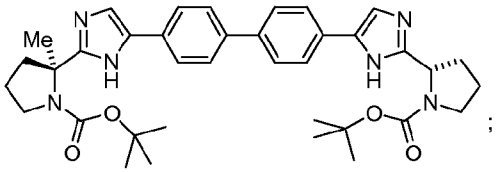

;

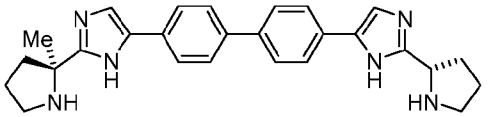

;

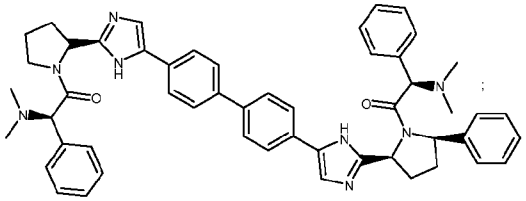

;

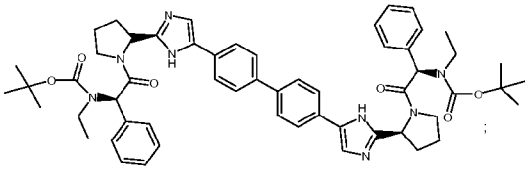

;

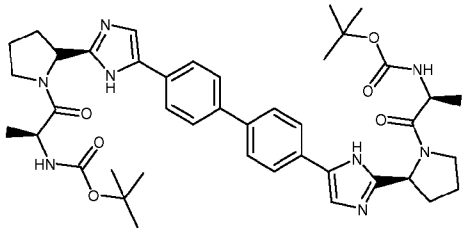

;

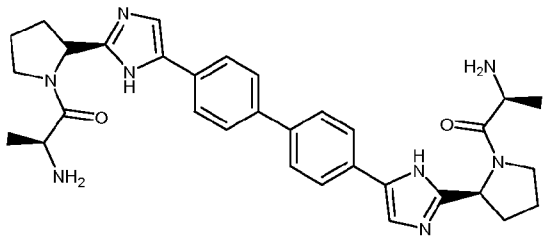

;

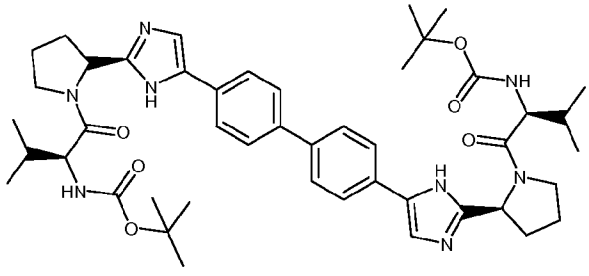

;

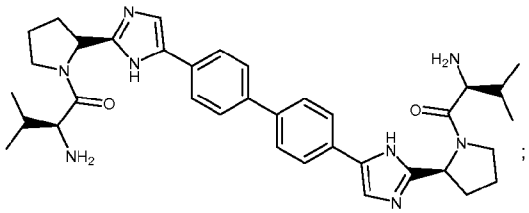

;

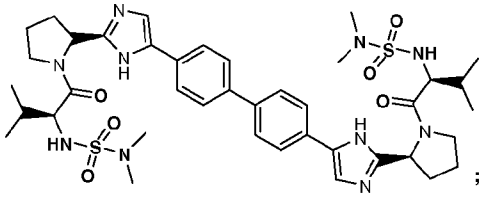

;

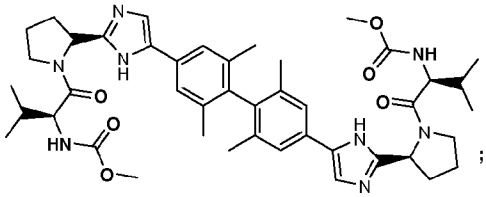

;

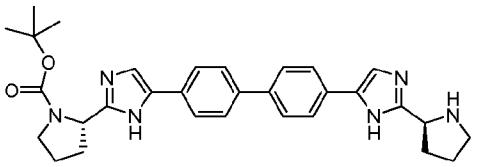

;

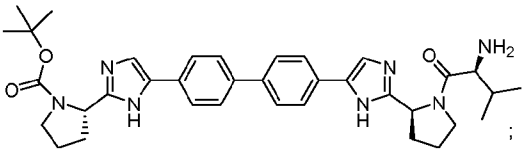

;

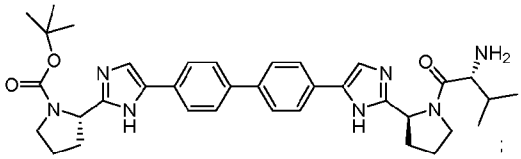

;

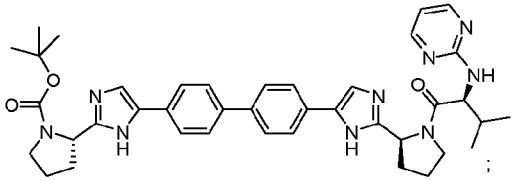

;

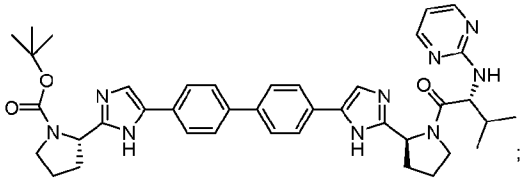

;

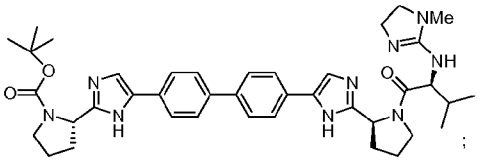

;

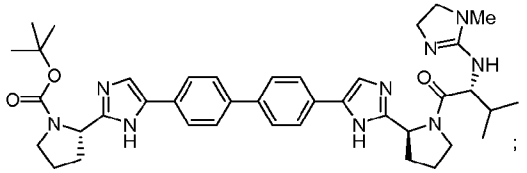

;

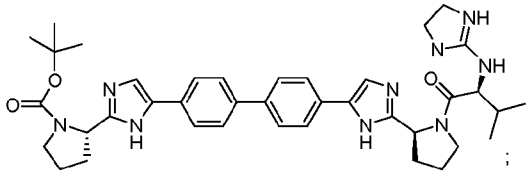

;

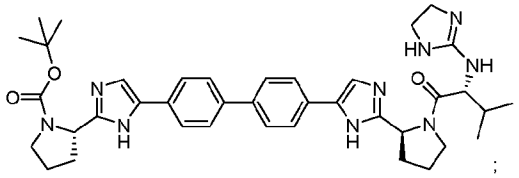

;

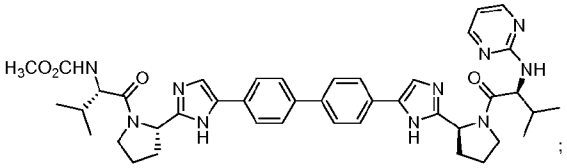

;

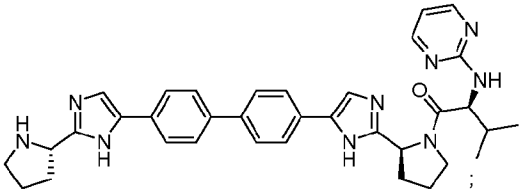

;

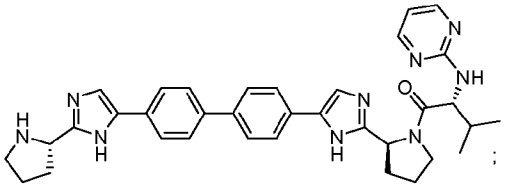

;

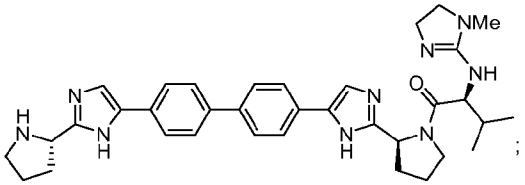

;

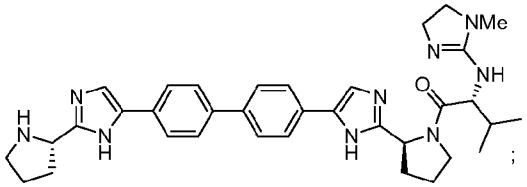

;

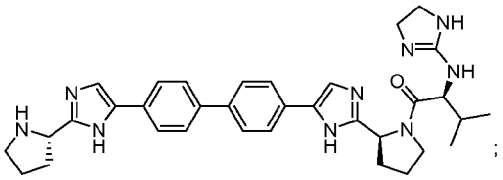

;

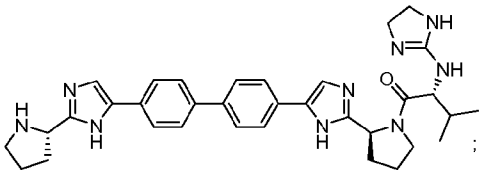

;

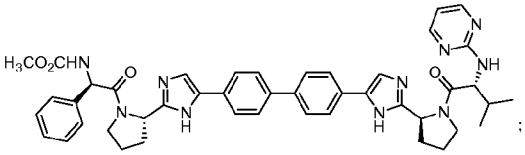

;

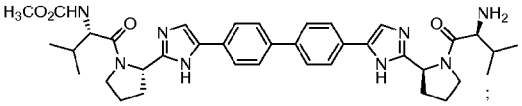

;

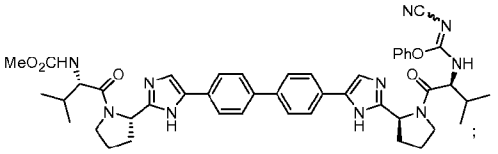

;

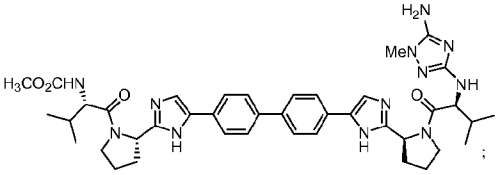

;

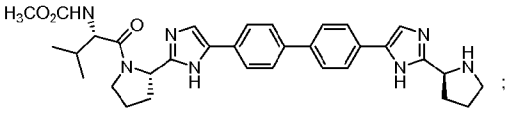

;

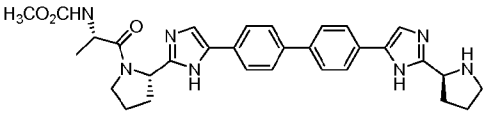

;

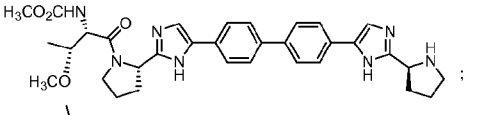

;

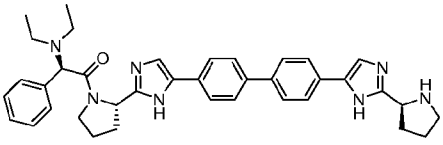

;

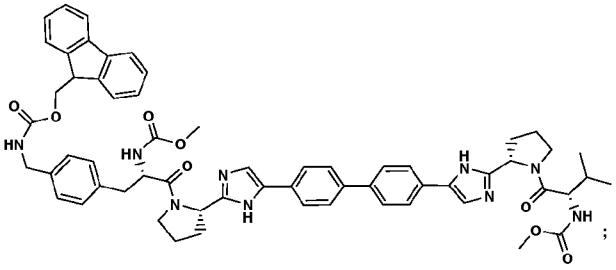

;

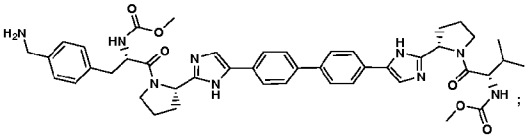

;

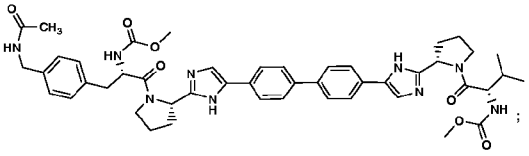

;

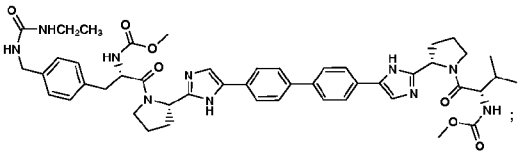

;

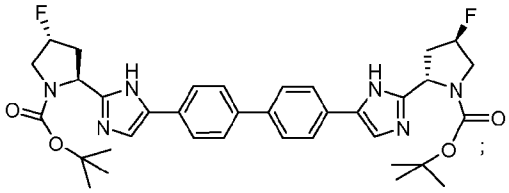

;

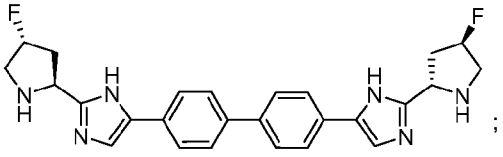


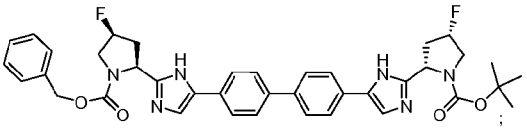


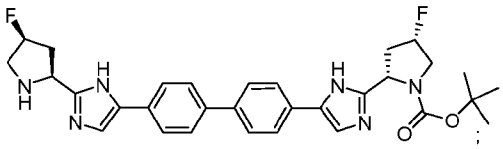


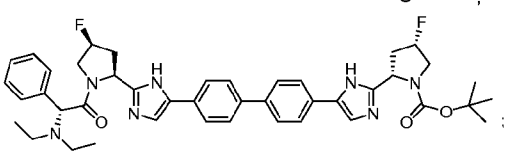


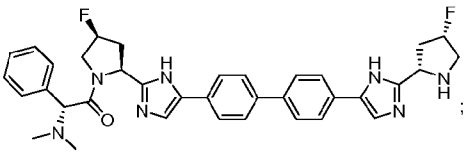


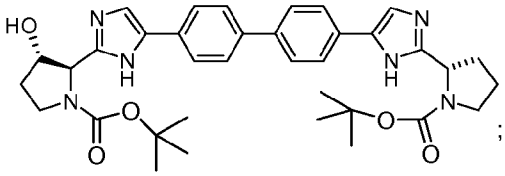


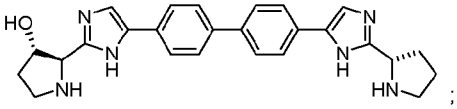


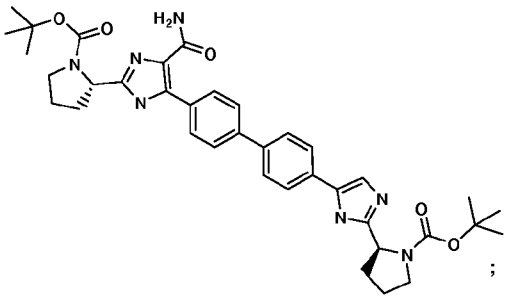


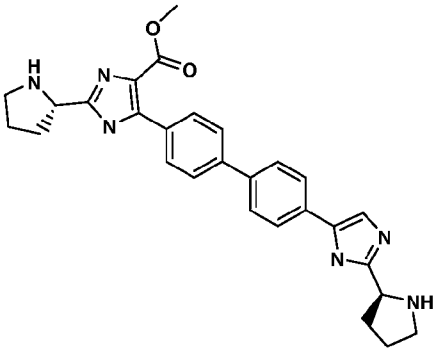


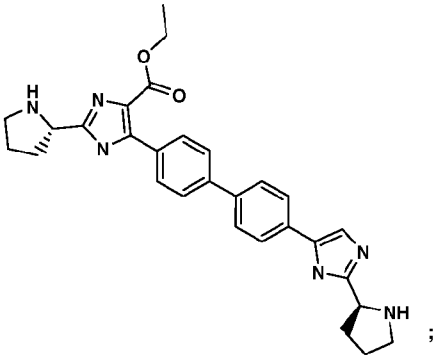


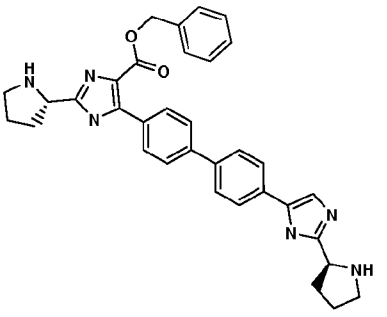

;

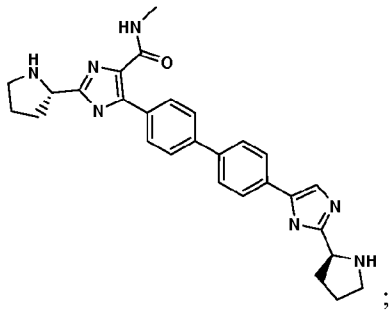

;

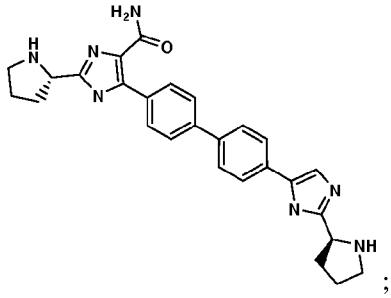

;

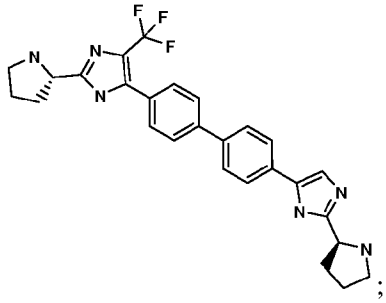

;

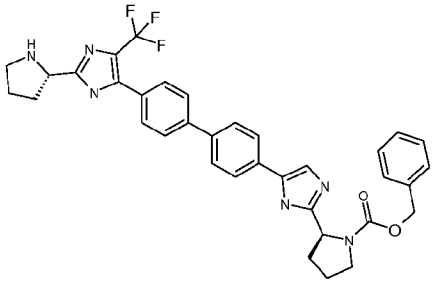

;

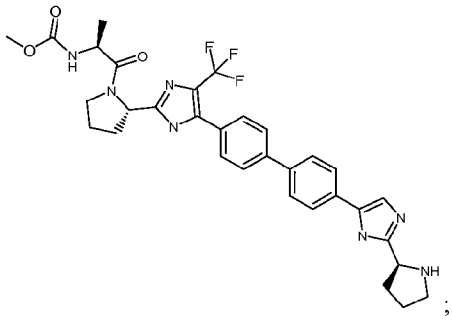

;

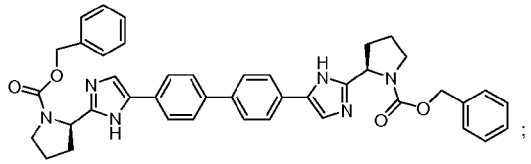

;

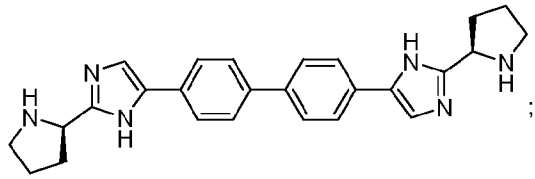

;

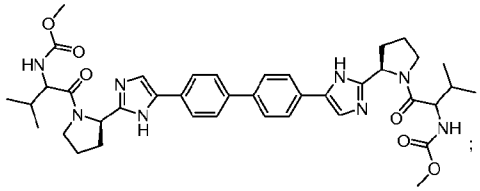

;

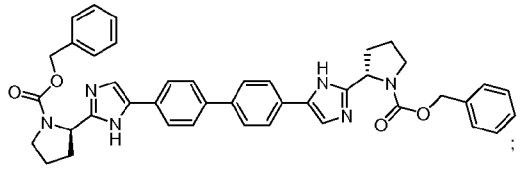

;

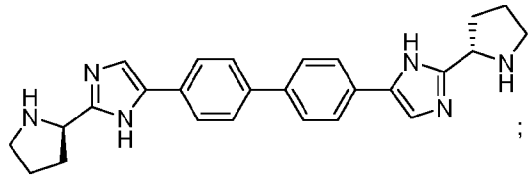

;

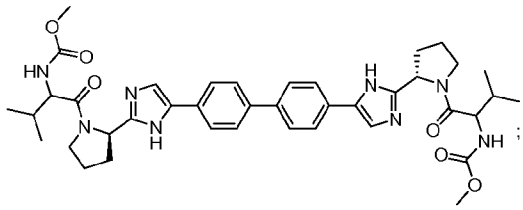
 ;

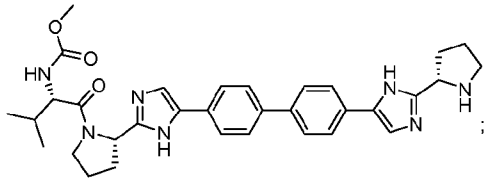
 ;

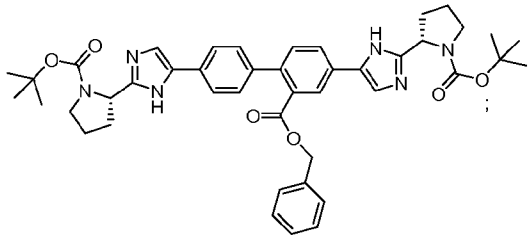
 ;

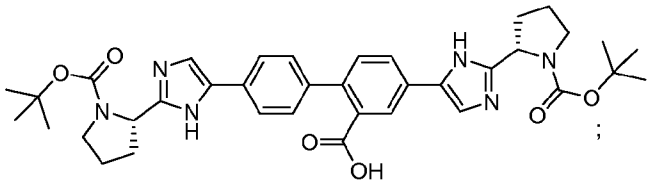
 ;

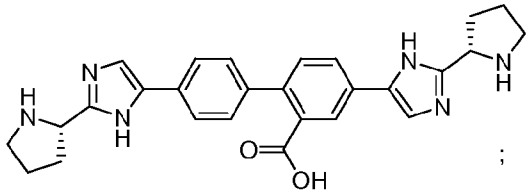
 ;

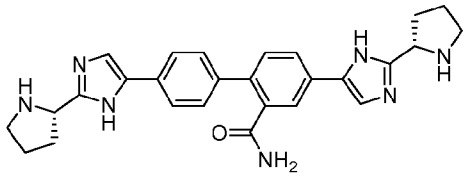
 ;

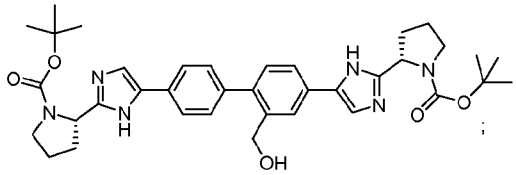
 ;

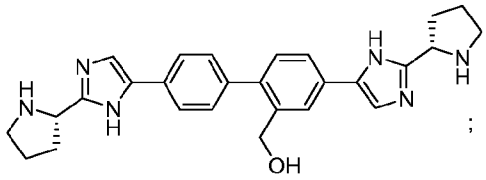
 ;

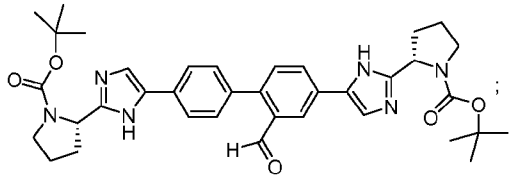

;

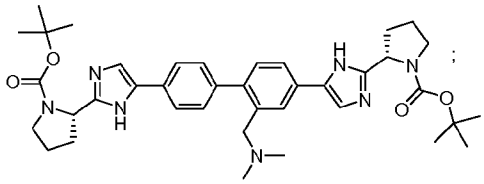

;

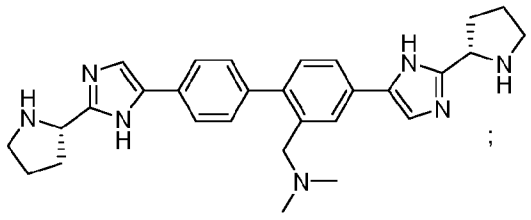

;

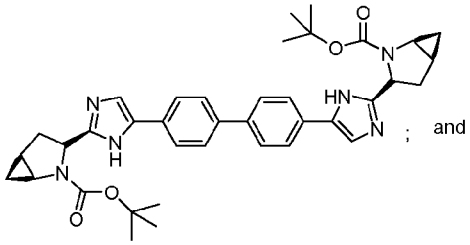

;

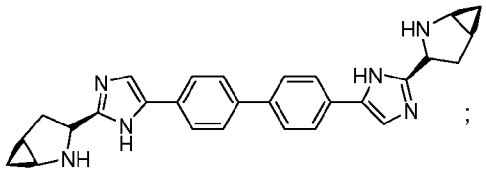

;


;


;


;


; and


;

or a pharmaceutically acceptable salt thereof.

21. A compound selected from

methyl ((1S)-1-(((2S)-2-(5-(4'-(2-((2S)-1-((2S)-2-((methoxycarbonyl)amino)-3-methylbutanoyl)-2-pyrrolidinyl)-1H-imidazol-5-yl)-4-biphenylyl)-1H-imidazol-2-yl)-1-pyrrolidinyl)carbonyl)-2-methylpropyl)carbamate;

(1R,1'R)-2,2'-(4,4'-biphenyldiylbis(1H-imidazole-5,2-diyl(2S)-2,1-pyrrolidinediyl))bis(N,N-dimethyl-2-oxo-1-phenylethanamine);

methyl ((1S)-2-((2S)-2-(5-(4'-(2-((2S)-1-((2R)-2-(diethylamino)-2-phenylacetyl)-2-pyrrolidinyl)-1H-imidazol-5-yl)-4-biphenylyl)-1H-imidazol-2-yl)-1-pyrrolidinyl)-1-methyl-2-oxoethyl)carbamate;

methyl ((1S)-1-(((2S)-2-(4-(4'-(2-((2S)-4,4-difluoro-1-((2S)-2-((methoxycarbonyl)amino)-3-methylbutanoyl)-2-pyrrolidinyl)-1H-imidazol-4-yl)-4-biphenylyl)-1H-imidazol-2-yl)-4,4-difluoro-1-pyrrolidinyl)carbonyl)-2-methylpropyl)carbamate;

methyl ((1S)-1-(((1R,3R,5R)-3-(5-(4'-(2-((1R,3R,5R)-2-((2S)-2-((methoxycarbonyl)amino)-3-methylbutanoyl)-2-azabicyclo[3.1.0]hex-3-yl)-1H-imidazol-5-yl)-4-biphenylyl)-1H-imidazol-2-yl)-2-azabicyclo[3.1.0]hex-2-yl)carbonyl)-2-methylpropyl)carbamate;

methyl ((1R)-2-oxo-1-phenyl-2-((2S)-2-(5-(4'-(2-((2S)-1-((2R)-tetrahydro-2-furanylcarbonyl)-2-pyrrolidinyl)-1H-imidazol-5-yl)-4-biphenylyl)-1H-imidazol-2-yl)-1-pyrrolidinyl)ethyl)carbamate;

methyl ((1S)-2-methyl-1-(((2S)-2-(5-(4'-(2-((2S)-1-(N-2-pyrimidinyl-D-valyl)-2-pyrrolidinyl)-1H-imidazol-5-yl)-4-biphenylyl)-1H-imidazol-2-yl)-1-pyrrolidinyl)carbonyl)propyl)carbamate;
methyl ((1R)-2-((2S)-2-(5-(4'-(2-((2S)-1-((2R)-2-(dimethylamino)-2-phenylacetyl)-2-pyrrolidinyl)-1H-imidazol-5-yl)-4-biphenylyl)-1H-imidazol-2-yl)-1-pyrrolidinyl)-2-oxo-1-phenylethyl)carbamate;
dimethyl (4,4'-biphenyldiylbis(1H-imidazole-5,2-diyl(2S)-2,1-pyrrolidinediyl((1R)-2-oxo-1-phenyl-2,1-ethanediyl)))biscarbamate;
(1R)-N,N-dimethyl-2-oxo-1-phenyl-2-((2S)-2-(5-(4'-(2-((2S)-1-((2R)-tetrahydro-2-furanylcarbonyl)-2-pyrrolidinyl)-1H-imidazol-5-yl)-4-biphenylyl)-1H-imidazol-2-yl)-1-pyrrolidinyl)ethanamine;
methyl ((1S)-2-((2S)-2-(5-(4'-(2-((2S)-1-(N-(methoxycarbonyl)-L-alanyl)-2-pyrrolidinyl)-1H-imidazol-5-yl)-4-biphenylyl)-1H-imidazol-2-yl)-1-pyrrolidinyl)-1-methyl-2-oxoethyl)carbamate; and
methyl ((1S)-1-(((2S)-2-(5-(4'-(2-((2S)-1-((2S)-2-((methoxycarbonyl)amino)-3,3-dimethylbutanoyl)-2-pyrrolidinyl)-1H-imidazol-5-yl)-4-biphenylyl)-1H-imidazol-2-yl)-1-pyrrolidinyl)carbonyl)-2,2-dimethylpropyl)carbamate;
or a pharmaceutically acceptable salt thereof.

22. A pharmaceutically acceptable salt of a compound of claim 21, wherein the salt is a dihydrochloride salt.

23. A compound which is methyl ((1S)-1-(((2S)-2-(5-(4'-(2-((2S)-1-((2S)-2-((methoxycarbonyl)amino)-3-methylbutanoyl)-2-pyrrolidinyl)-1H-imidazol-5-yl)-4-biphenylyl)-1H-imidazol-2-yl)-1-pyrrolidinyl)carbonyl)-2-methylpropyl)carbamate; or a pharmaceutically acceptable salt thereof.

24. A compound which is (1R,1'R)-2,2'-(4,4'-biphenyldiylbis(1H-imidazole-5,2-diyl(2S)-2,1-pyrrolidinediyl))bis(N,N-dimethyl-2-oxo-1-phenylethanamine); or a pharmaceutically acceptable salt thereof.

25. A compound which is methyl ((1S)-2-((2S)-2-(5-(4'-(2-((2S)-1-((2R)-2-(diethylamino)-2-phenylacetyl)-2-pyrrolidinyl)-1H-imidazol-5-yl)-4-biphenylyl)-1H-

imidazol-2-yl)-1-pyrrolidinyl)-1-methyl-2-oxoethyl)carbamate; or a pharmaceutically acceptable salt thereof.

26. A compound which is methyl ((1S)-1-(((2S)-2-(4-(4'-(2-((2S)-4,4-difluoro-1-((2S)-2-((methoxycarbonyl)amino)-3-methylbutanoyl)-2-pyrrolidinyl)-1H-imidazol-4-yl)-4-biphenylyl)-1H-imidazol-2-yl)-4,4-difluoro-1-pyrrolidinyl)carbonyl)-2-methylpropyl)carbamate; or a pharmaceutically acceptable salt thereof.

27. A compound which is methyl ((1S)-1-(((1R,3R,5R)-3-(5-(4'-(2-((1R,3R,5R)-2-((2S)-2-((methoxycarbonyl)amino)-3-methylbutanoyl)-2-azabicyclo[3.1.0]hex-3-yl)-1H-imidazol-5-yl)-4-biphenylyl)-1H-imidazol-2-yl)-2-azabicyclo[3.1.0]hex-2-yl)carbonyl)-2-methylpropyl)carbamate; or a pharmaceutically acceptable salt thereof.

28. A compound which is methyl ((1R)-2-oxo-1-phenyl-2-((2S)-2-(5-(4'-(2-((2S)-1-((2R)-tetrahydro-2-furanylcarbonyl)-2-pyrrolidinyl)-1H-imidazol-5-yl)-4-biphenylyl)-1H-imidazol-2-yl)-1-pyrrolidinyl)ethyl)carbamate; or a pharmaceutically acceptable salt thereof.

29. A compound which is methyl ((1S)-2-methyl-1-(((2S)-2-(5-(4'-(2-((2S)-1-(N-2-pyrimidinyl-D-valyl)-2-pyrrolidinyl)-1H-imidazol-5-yl)-4-biphenylyl)-1H-imidazol-2-yl)-1-pyrrolidinyl)carbonyl)propyl)carbamate; or a pharmaceutically acceptable salt thereof.

30. A compound which is methyl ((1R)-2-((2S)-2-(5-(4'-(2-((2S)-1-((2R)-2-(dimethylamino)-2-phenylacetyl)-2-pyrrolidinyl)-1H-imidazol-5-yl)-4-biphenylyl)-1H-imidazol-2-yl)-1-pyrrolidinyl)-2-oxo-1-phenylethyl)carbamate; or a pharmaceutically acceptable salt thereof.

31. A compound which is dimethyl (4,4'-biphenyldiylbis(1H-imidazole-5,2-diyl(2S)-2,1-pyrrolidinediyl((1R)-2-oxo-1-phenyl-2,1-ethanediyl)))biscarbamate; or a pharmaceutically acceptable salt thereof.

32. A compound which is (1R)-N,N-dimethyl-2-oxo-1-phenyl-2-((2S)-2-(5-(4'-(2-((2S)-1-((2R)-tetrahydro-2-furanylcarbonyl)-2-pyrrolidinyl)-1H-imidazol-5-yl)-4-biphenylyl)-1H-imidazol-2-yl)-1-pyrrolidinyl)ethanamine; or a pharmaceutically acceptable salt thereof.

33. A compound which is methyl ((1S)-2-((2S)-2-(5-(4'-(2-((2S)-1-(N-(methoxycarbonyl)-L-alanyl)-2-pyrrolidinyl)-1H-imidazol-5-yl)-4-biphenylyl)-1H-imidazol-2-yl)-1-pyrrolidinyl)-1-methyl-2-oxoethyl)carbamate; or a pharmaceutically acceptable salt thereof.

34. A compound which is methyl ((1S)-1-(((2S)-2-(5-(4'-(2-((2S)-1-((2S)-2-((methoxycarbonyl)amino)-3,3-dimethylbutanoyl)-2-pyrrolidinyl)-1H-imidazol-5-yl)-4-biphenylyl)-1H-imidazol-2-yl)-1-pyrrolidinyl)carbonyl)-2,2-dimethylpropyl)carbamate; or a pharmaceutically acceptable salt thereof.

35. A composition comprising a compound of claim 1, or a pharmaceutically acceptable salt thereof, and a pharmaceutically acceptable carrier.

36. The composition of claim 35 further comprising one or two additional compounds having anti-HCV activity.

37. The composition of claim 36 wherein at least one of the additional compounds is an interferon or a ribavirin.

38. The composition of claim 37 wherein the interferon is selected from interferon alpha 2B, pegylated interferon alpha, consensus interferon, interferon alpha 2A, and lymphoblastiod interferon tau.

39. The composition of claim 36 wherein at least one of the additional compounds is selected from interleukin 2, interleukin 6, interleukin 12, a compound that enhances the development of a type 1 helper T cell response, interfering RNA, anti-sense RNA, Imiqimod, ribavirin, an inosine 5'-monophospate dehydrogenase inhibitor, amantadine, and rimantadine.

40. The composition of claim 36 wherein at least one of the additional compounds is effective to inhibit the function of a target selected from HCV metalloprotease, HCV serine protease, HCV polymerase, HCV helicase, HCV NS4B protein, HCV entry, HCV assembly, HCV egress, HCV NS5A protein, and IMPDH for the treatment of an HCV infection.

41. A method of treating an HCV infection in a patient, comprising administering to the patient a therapeutically effective amount of a compound of claim 1, or a pharmaceutically acceptable salt thereof.

42. The method of claim 41 further comprising administering one or two additional compounds having anti-HCV activity prior to, after or simultaneously with the compound of claim 1, or a pharmaceutically acceptable salt thereof.

43. The method of claim 42 wherein at least one of the additional compounds is an interferon or a ribavirin.

44. The method of claim 43 wherein the interferon is selected from interferon alpha 2B, pegylated interferon alpha, consensus interferon, interferon alpha 2A, and lymphoblastiod interferon tau.

45. The method of claim 42 wherein at least one of the additional compounds is selected from interleukin 2, interleukin 6, interleukin 12, a compound that enhances the development of a type 1 helper T cell response, interfering RNA, anti-sense RNA, Imiqimod, ribavirin, an inosine 5'-monophospate dehydrogenase inhibitor, amantadine, and rimantadine.

46. The method of claim 42 wherein at least one of the additional compounds is effective to inhibit the function of a target selected from HCV metalloprotease, HCV serine protease, HCV polymerase, HCV helicase, HCV NS4B portein, HCV entry, HCV assembly, HCV egress, HCV NS5A protein, and IMPDH for the treatment of an HCV infection.

ABSTRACT

The present disclosure relates to compounds, compositions and methods for the treatment of hepatitis C virus (HCV) infection. Also disclosed are pharmaceutical compositions containing such compounds and methods for using these compounds in the treatment of HCV infection.

Electronic Acknowledgement Receipt

EFS ID:	2059409
Application Number:	11835462
International Application Number:	
Confirmation Number:	1473
Title of Invention:	Hepatitis C Virus Inhibitors
First Named Inventor/Applicant Name:	Carol Bachand
Customer Number:	23914
Filer:	Pamela A. Mingo/Annamarie Bodisch
Filer Authorized By:	Pamela A. Mingo
Attorney Docket Number:	10889 NP
Receipt Date:	08-AUG-2007
Filing Date:	
Time Stamp:	09:53:37
Application Type:	Utility under 35 USC 111(a)

Payment information:

Submitted with Payment	yes
Payment was successfully received in RAM	$7550
RAM confirmation Number	4122
Deposit Account	193880
The Director of the USPTO is hereby authorized to charge indicated fees and credit any overpayment as follows: Charge any Additional Fees required under 37 C.F.R. Section 1.16 and 1.17	

File Listing:

Document Number	Document Description	File Name	File Size(Bytes) /Message Digest	Multi Part /.zip	Pages (if appl.)
1	Application Data Sheet	10889USNP_ADS_08082007.pdf	243102 1084de13aa47971924e2ff87f267c727aed403ad	no	8
Warnings:					
Information:					
This is not an USPTO supplied ADS fillable form					
2		10889USNP_APP_08082007.pdf	4155119 f64fa0df7647c697363f76f9d4b8dc2a8b9f6609	yes	732

Multipart Description/PDF files in .zip description

Document Description	Start	End
Specification	1	634
Claims	635	731
Abstract	732	732

Warnings:					
Information:					
3	Fee Worksheet (PTO-06)	fee-info.pdf	8656 1b2df3ce9f166938e657f17f7a31e3e60bc197ed	no	2
Warnings:					
Information:					
		Total Files Size (in bytes):	4406877		

This Acknowledgement Receipt evidences receipt on the noted date by the USPTO of the indicated documents, characterized by the applicant, and including page counts, where applicable. It serves as evidence of receipt similar to a Post Card, as described in MPEP 503.

New Applications Under 35 U.S.C. 111
If a new application is being filed and the application includes the necessary components for a filing date (see 37 CFR 1.53(b)-(d) and MPEP 506), a Filing Receipt (37 CFR 1.54) will be issued in due course and the date shown on this Acknowledgement Receipt will establish the filing date of the application.

National Stage of an International Application under 35 U.S.C. 371
If a timely submission to enter the national stage of an international application is compliant with the conditions of 35 U.S.C. 371 and other applicable requirements a Form PCT/DO/EO/903 indicating acceptance of the application as a national stage submission under 35 U.S.C. 371 will be issued in addition to the Filing Receipt, in due course.

New International Application Filed with the USPTO as a Receiving Office
If a new international application is being filed and the international application includes the necessary components for an international filing date (see PCT Article 11 and MPEP 1810), a Notification of the International Application Number and of the International Filing Date (Form PCT/RO/105) will be issued in due course, subject to prescriptions concerning national security, and the date shown on this Acknowledgement Receipt will establish the international filing date of the application.