

SUPERINTENDENCIA DE INDUSTRIA Y COMERCIO	
RAD: 13-2653- -4	FECHA: 2013-12-13 17:32:58
DEP: 2020 DIRECCION DE NUEVAS CREACIONES	EVE: 378 FASE NACIONAL INCLUIDO CAPITULO I
TRA: 11 PCT-PATENTE DE INVENCION CAPITULOS I Y II	FOLIOS: 26
ACT: 519 PRESENTACION	

DIRECCIÓN DE NUEVAS CREACIONES

2020
Bogotá, D.C.,

Abogado(a)/Señor(a)
LUZ CLEMENCIA DE PAEZ

Asunto: Radicación: 13-2653- -4
 Trámite: 11
 Evento: 378
 Actuación: 519
 Oficio: 23098
 Folios: 26

Patente de Invención	X			Patente de Modelo de Utilidad	
Vía Nacional					
Vía PCT (Fase Nacional)	X	Capítulo I	X	Capítulo II	
No. Solicitud Internacional	PCT/GB2011/000862				
Fecha de Presentación Internacional	08/06/2011				

1. Documentos estudiados

Descripción:	Radicado N°13-002653-00000-0000	Enero 8 de 2013
Reivindicaciones	Radicado N°13-002653-00000-0000	Enero 8 de 2013
Prioridad:	GB 1009603.0	Junio 8 de 2010

2. Análisis de la Prioridad

Se acepta la reivindicación de Prioridad porque esta solicitud fue presentada dentro del plazo establecido (Art. 9 D 486) y su contenido técnico corresponde con el de la prioridad reivindicada.

3. Objeto de la invención

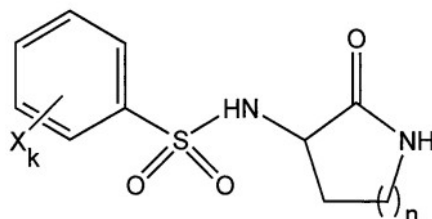
De acuerdo con lo establecido en el numeral 1.2.2.2 del Capítulo Primero del Título 10 de la Circular Única para efectos del examen de patentabilidad, se tendrá en cuenta la tasa pagada por el solicitante al momento de comenzar el examen para las reivindicaciones adicionales; esto es que cuando la solicitud contenga más de diez (10) reivindicaciones y no se haya pagado la tasa complementaria, sólo se estudiarán las cubiertas por la tasa pagada.

Por lo tanto, el capítulo reivindicatorio presente en el Radicado N°13–002653–00000–0000 está compuesto por 20 reivindicaciones será estudiado en su totalidad, porque se incluye el pago por las reivindicaciones adicionales 11 a 20, de acuerdo con el recibo presente en la página 89 del Radicado N°13–002653–00000–0000.

Título de la solicitud: “Agentes anti inflamatorios”

El problema planteado en esta solicitud consiste en la obtención de compuestos alternativos con actividad antiinflamatoria.

Para resolver este problema técnico, la solicitud en estudio plantea la obtención de compuestos derivados de 3 – aminolactama bencenosulfonilo sustituida, con actividad antiinflamatoria.



El objeto de la presente Solicitud se relaciona con la Clasificación Internacional de Patentes (CIP): A61K31/45; A61P29/00; C07D211/76; C07D223/10.

4. Excepción a la Patentabilidad (Art 20 D 486, literal d)

El objeto de las reivindicaciones 18 y 19 no es patentable, de acuerdo con el artículo citado.

5. Reivindicaciones relativas al uso o a un segundo uso (Arts. 14 y 21 D 486)

El uso de las reivindicaciones 3, 4, 8, 9, 11 a 17 y 20 no es patentable, de acuerdo con el artículo 14.

6. De la Solicitud de la Patente

Título

El título de la presente solicitud se considera muy general y ambiguo, porque al mencionar “agentes antiinflamatorios” se define el objeto de la invención por su actividad más no por su conformación. Además, dentro del mismo se incluye una cantidad indefinida de compuestos los cuales no hacen parte del objeto de la presente invención. Se observa que los compuestos de la presente invención son derivados de N – (2 – oxo azepin – 3 – il) bencenosulfonamida y derivados de N –

(2 – oxo piperidin – 3 – il) bencenosulfonamida. Se solicita modificar el título de la presente invención de acuerdo con las observaciones anteriores.

Reivindicaciones (Art 30 D 486, Art 22 PCT)

Las reivindicación 1 no es clara ni concisa, porque se mencionan sustituyentes de manera muy general e indefinida tales como “alquilo, haloalquilo, hidroxialquilo, alcoxi, aminoalquilo, aminodialquilo, halógeno”, los cuales pueden ser cualquier sustituyente posible, de tal manera que a partir de los sustituyentes planteados, se obtiene una cantidad indefinida de posibles compuestos, de tal manera que se incrementa la complejidad de la presenta solicitud y por lo tanto, no es posible definir de forma certera el verdadero alcance de lo que se desea proteger. Por lo tanto, se solicita realizar una restricción muchísimo más razonable de los sustituyentes de la presente invención, de tal forma que a partir de estos se obtengan los compuestos sintetizados, probados y que representan la solución al problema técnico planteado dentro de la presente invención. Se solicita mencionar específicamente los sustituyentes empleados (por ejemplo, en vez de mencionar alquilo, mencionar si es metil, etil, isopropil, butil dodecil, 2, 5, 9 – trimetiltetradecanoil, etc...). Es cierto que un inventor esta en el pleno derecho de proteger su invención en la extensión que desee siempre y cuando se conserve un único concepto inventivo, sin embargo, el artículo 30 de la Decisión 486 determina que las reivindicaciones que definen una invención deben ser claras, concisas y estar plenamente detalladas en el capítulo descriptivo. Se sugiere al solicitante realizar dicha restricción, de acuerdo a lo que se muestra en la siguiente tabla:

Sustituyente	Soportado en la descripción
X	F, CF ₃ , CH ₃ , CH ₂ CH ₃ , CH ₂ CH ₂ CH ₃ , C(CH ₃) ₃ , (CH ₂) ₅ CH ₃ , (CH ₂) ₇ CH ₃
k	1, 2
n	2, 3

Adicionalmente, cuando se mencionan las condiciones de los sustituyentes C1 a C5, la explicación es confusa y por lo tanto no es clara. Por lo tanto, se solicita mencionar las sustituyentes para cada uno de los sustituyentes C1 a C5 y se sugiere modificar el sustituyente X_k por C1, C2, C3, C4 y C5 en los carbonos correspondientes para entender con más claridad las salvedades planteadas en la reivindicación 1. También se solicita eliminar la expresión “para uso en el tratamiento de un trastorno inflamatorio”, ya que el uso no se considera como material susceptible de patentabilidad.

De igual manera, se solicita eliminar la expresión “para uso en el tratamiento de un trastorno inflamatorio” de la reivindicación 2, ya que el uso no se considera como material susceptible de patentabilidad.

Para la reivindicación 20, la cual se afecta por uso, no es clara la mención del término “biblioteca”, porque este término no es claro desde el punto de vista

técnico de la invención y además no hace parte del concepto inventivo de las reivindicaciones 1 a 19, por lo cual se recomienda eliminar esta reivindicación.

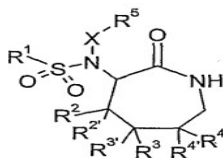
6. Determinación del Estado de la Técnica

El Estado de la Técnica se determinó con base en la fecha de presentación de la solicitud de la cual se invoca prioridad, es decir, el 8 de junio de 2010.

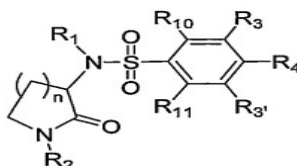
Consultadas las fuentes de información con que se cuenta, se encontró los siguientes documentos que anticipan el objeto de esta solicitud.

Item	Documento	Título	Fecha de Publicación
D1	WO2006005486	"Sulfonamide derivatives"	Enero 19 de 2006
D2	WO2005042489	"N – substituted benzene sulfonamides"	Mayo 12 de 2005
D3	WO2004033455	"Succinate salts of heterocyclic DPP-IV inhibitors"	Abril 22 de 2004
D4	US5527777	"Peptide compounds, in particular LHRH antagonists"	Junio 18 de 1996
D5	<i>Bioorganic & Medicinal Chemistry Letters</i> . 2008. 18; 1511 – 1519	"Substituted 2 – oxo – azepane derivatives are potents orally active γ – secretasa inhibitors"	Noviembre 5 de 2007
D6	<i>Bioorganic & Medicinal Chemistry Letters</i> . 2007. 17; 5790 – 5796	"Amino – caprolactams derivatives as γ – secretasa inhibitors"	Agosto 26 de 2007
D7	<i>Journal of Organic Chemistry</i> . 1991. 56; 452 – 454	"Synthesis of Secondary Amines by Rhodium Catalyzed Hydrogenation of Nitriles"	1991

El documento D1¹ divulga compuestos derivados de 2 – oxo azepin – 3 – il sulfonamida, como inhibidores de gamma secretasa, para el tratamiento de la enfermedad de Alzheimer



El documento D2² divulga compuestos derivados de bencenosulfonamida, como inhibidores del liberador de péptido beta amiloide, para el tratamiento de trastornos cognitivos



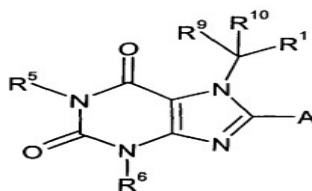
El documento D3³ divulga compuestos sal succinato de imidazo [4,5-d] piperidina, como inhibidores de DPP-IV, para el tratamiento de la diabetes tipo II

¹[http://worldwide.espacenet.com/publicationDetails/originalDocument?](http://worldwide.espacenet.com/publicationDetails/originalDocument?CC=WO&NR=2006005486A1&KC=A1&FT=D&ND=3&date=20060119&DB=worldwide.espacenet.com&locale=es_LP)

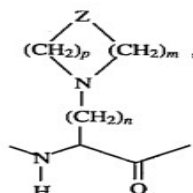
[CC=WO&NR=2006005486A1&KC=A1&FT=D&ND=3&date=20060119&DB=worldwide.espacenet.com&locale=es_LP](http://worldwide.espacenet.com/publicationDetails/originalDocument?CC=WO&NR=2006005486A1&KC=A1&FT=D&ND=3&date=20060119&DB=worldwide.espacenet.com&locale=es_LP)

²[http://worldwide.espacenet.com/publicationDetails/originalDocument?](http://worldwide.espacenet.com/publicationDetails/originalDocument?CC=WO&NR=2005042489A1&KC=A1&FT=D&ND=3&date=20050512&DB=worldwide.espacenet.com&locale=es_LP)

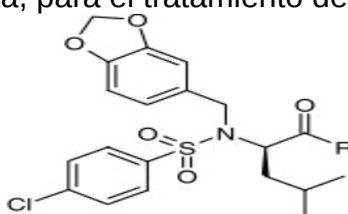
[CC=WO&NR=2005042489A1&KC=A1&FT=D&ND=3&date=20050512&DB=worldwide.espacenet.com&locale=es_LP](http://worldwide.espacenet.com/publicationDetails/originalDocument?CC=WO&NR=2005042489A1&KC=A1&FT=D&ND=3&date=20050512&DB=worldwide.espacenet.com&locale=es_LP)



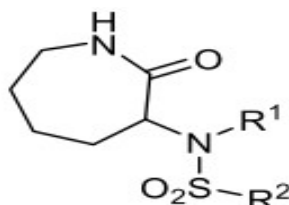
El documento D4⁴ divulga compuestos peptídicos como inhibidores de LHRH como regulador estrogénico



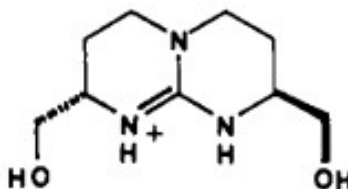
El documento D5⁵ divulga compuestos derivados de 2 – oxo azepano como inhibidores de gama secretasa, para el tratamiento de la enfermedad de Alzheimer



El documento D6⁶ divulga compuestos derivados de 2 – oxo azepan benceno sulfonamida como inhibidores de gama secretasa, para el tratamiento de la enfermedad de Alzheimer



El documento D7⁷ divulga la síntesis de compuestos de guanidina a partir de L o D Asparagina



3http://worldwide.espacenet.com/publicationDetails/originalDocument?CC=WO&NR=2004033455A2&KC=A2&FT=D&ND=3&date=20040422&DB=worldwide.espacenet.com&locale=es_LP

4http://worldwide.espacenet.com/publicationDetails/originalDocument?CC=US&NR=5527777A&KC=A&FT=D&ND=3&date=19960618&DB=worldwide.espacenet.com&locale=es_LP

5<http://www.sciencedirect.com/science/article/pii/S0960894X07012565>

6<http://www.sciencedirect.com/science/article/pii/S0960894X07010037>

7<http://pubs.acs.org/doi/abs/10.1021/jo00001a088>

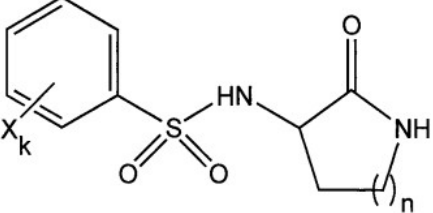
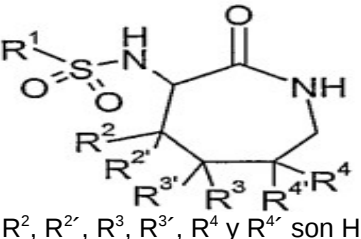
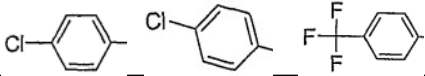
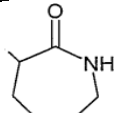
7. Examen de Patentabilidad.

Novedad (Art 16 D 486)

La reivindicación 1 divulga un compuesto de fórmula general I o una sal farmacéuticamente aceptable, caracterizado por la estructura, donde... (Página 66 del radicado N°13-02653-00000-0000).

.

Comparación de las características técnicas **esenciales**, con las del Estado de la Técnica:

Solicitud	D1
Compuesto de la fórmula I 	Compuesto de la Fórmula IV 
X _k , donde X es halógeno, haloalquilo k es 1	R1 es 
n es 3 para obtener el anillo de 2 – oxo azepina	

Las características técnicas esenciales de los compuestos de la fórmula I de acuerdo con la reivindicación 1, se han divulgado previamente en D1 (D1: Página 12, compuesto IV; páginas 18 a 32, sustituyentes de R¹), en donde se muestran los compuestos derivados de N – (2 – oxo azepin – 3 – il) – 4 – halo/haloalquil bencenosulfonamida, como intermediarios para la síntesis de compuestos de la fórmula I inhibidores de gama secretasa para el tratamiento de la enfermedad de Alzheimer, con las características técnicas esenciales descritas en la tabla anterior.

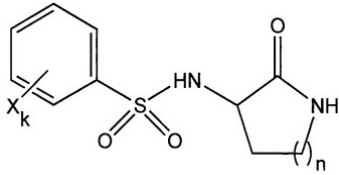
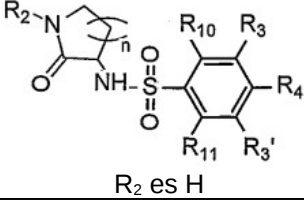
En consecuencia, la reivindicación 1, de acuerdo a lo divulgado en D1, carece de Novedad.

Las reivindicaciones 2, 6, 7 y 10 dependientes de la reivindicación 1, no divulgan características adicionales que otorguen novedad a los compuestos de la reivindicación 1. Por lo tanto, estas reivindicaciones también carecen de Novedad.

La reivindicación 1 divulga un compuesto de fórmula general I o una sal

farmacéuticamente aceptable, caracterizado por la estructura, donde... (Página 66 del radicado N°13–02653–00000–0000).

Comparación de las características técnicas **esenciales**, con las del Estado de la Técnica:

Solicitud	D2
Compuesto de la fórmula I 	Compuesto 9.0 
n es 1, 2 o 3	n es 1, 2 o 3
X _k , donde X es H, halógeno, alquilo, alcoxi, haloalquilo, alquilamino, dialquilamino k es 1 a 5	R ₃ es H, halógeno, alquilo C1-6, alcoxi C1-6, haloalquilo C1-6; R ₄ es H, halógeno, alquilo C1-6, alcoxi C1-6, NHR', NR'R'' (R' y R'' son H o alquilo C1-6); R ₃ ' es H o halógeno; R ₁₀ y R ₁₁ son H o F

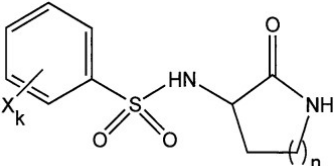
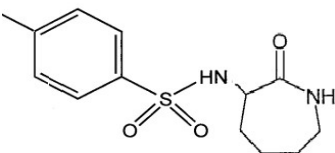
Las características técnicas esenciales de los compuestos de la fórmula I de acuerdo con la reivindicación 1, se han divulgado previamente en D2 (D2: Página 12, líneas 22 – 26 y 33; página 13, línea 5; página 91, esquema 3, compuesto 9.0), en donde se muestran compuestos derivados de 2 – oxo pirrolidin/piperidin/azepin – 3 – il bencenosulfonamida como intermediarios para la síntesis de los compuestos de Fórmula I como inhibidores del liberador de péptido beta amiloide para el tratamiento de trastornos cognitivos, con las características técnicas esenciales descritas en la tabla anterior.

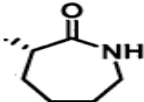
En consecuencia, la reivindicación 1, de acuerdo a lo divulgado en D2, carece de Novedad.

Las reivindicaciones 2, 5 a 7 y 10, dependientes de la reivindicación 1, no divulgan características adicionales que otorguen novedad a los compuestos de la reivindicación 1. Por lo tanto, estas reivindicaciones también carecen de Novedad.

La reivindicación 1 divulga un compuesto de fórmula general I o una sal farmacéuticamente aceptable, caracterizado por la estructura, donde... (Página 66 del radicado N°13–02653–00000–0000).

Comparación de las características técnicas **esenciales**, con las del Estado de la Técnica:

Solicitud	D3
Compuesto de la fórmula I 	Compuesto 6A 

n es 3 para obtener el anillo de 2 – oxo azepina	
X _k , es alquilo, k es 1	Metil en la posición 4 del grupo benceno sulfonamida

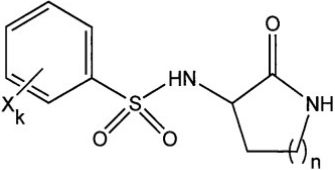
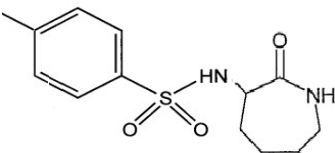
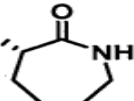
Las características técnicas esenciales de los compuestos de la fórmula XI de acuerdo con la reivindicación 12, se han divulgado previamente en D3 (D3: Página 42, línea 19, compuesto 6A), en donde se muestra el compuesto N – (2 – oxo azepan – 3 – il) – 4 – metil bencenosulfonamida, como intermediario en la síntesis del compuesto 8 – (3 – aminoazepan – 1 – il) – 7 – bencil – 1, 3 – dimetil – 3, 7 – dihidropurina – 2, 6 – diona inhibidores de DPP-IV, para el tratamiento de la diabetes tipo II, con las características técnicas esenciales descritas en la tabla anterior.

En consecuencia, la reivindicación 1, de acuerdo a lo divulgado en D3, carece de Novedad.

Las reivindicaciones 2, 5 y 7, dependientes de la reivindicación 1, no divulgan características adicionales que otorguen novedad a los compuestos de la reivindicación 1. Por lo tanto, estas reivindicaciones también carecen de Novedad.

La reivindicación 1 divulga un compuesto de fórmula general I o una sal farmacéuticamente aceptable, caracterizado por la estructura, donde... (Página 66 del radicado N°13–02653–00000–0000).

Comparación de las características técnicas **esenciales**, con las del Estado de la Técnica:

Solicitud	D4
Compuesto de la fórmula I 	Ejemplo 16 
n es 3 para obtener el anillo de 2 – oxo azepina	
X _k , es alquilo, k es 1	Metil en la posición 4 del grupo benceno sulfonamida

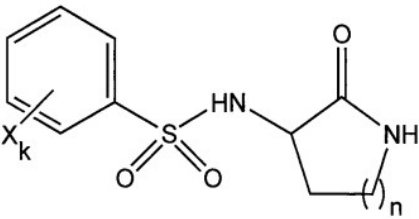
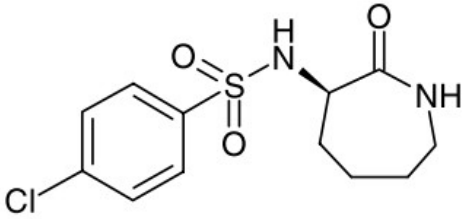
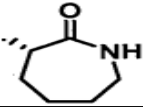
Las características técnicas esenciales de los compuestos de la fórmula XI de acuerdo con la reivindicación 12, se han divulgado previamente en D4 (D4: Columna 18, líneas 1 y 2), en donde se muestra el compuesto 3 – tosilamidohexahidro – 2 – azepinona, como intermediario en la síntesis de compuestos peptídicos como inhibidores de LHRH como regulador estrogénico para el tratamiento de la diabetes tipo II, con las características técnicas esenciales descritas en la tabla anterior.

En consecuencia, la reivindicación 1, de acuerdo a lo divulgado en D3, carece de Novedad.

Las reivindicaciones 2, 5 y 7, dependientes de la reivindicación 1, no divulgan características adicionales que otorguen novedad a los compuestos de la reivindicación 1. Por lo tanto, estas reivindicaciones también carecen de Novedad.

La reivindicación 1 divulga un compuesto de fórmula general I o una sal farmacéuticamente aceptable, caracterizado por la estructura, donde... (Página 66 del radicado N°13-02653-00000-0000).

Comparación de las características técnicas **esenciales**, con las del Estado de la Técnica:

Solicitud	D5
Compuesto de la fórmula I 	Compuesto 36 
n es 3 para obtener el anillo de 2 – oxo azepina	
X_k, donde X es halógeno; k es 1	Cloro en posición 4 del grupo benceno sulfonamida

Las características técnicas esenciales de los compuestos de la fórmula XI de acuerdo con la reivindicación 12, se han divulgado previamente en D5 (D5: Página 306, compuesto 36) en donde se muestra el compuesto N – (2 – oxo azepin – 3 – il) – 4 – cloro bencenosulfonamida, como intermediarios para la síntesis de compuestos inhibidores de gama secretasa para el tratamiento de la enfermedad de Alzheimer, con las características técnicas esenciales descritas en la tabla anterior.

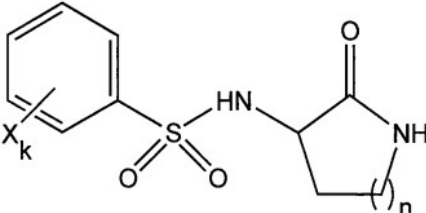
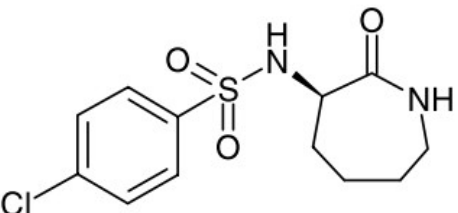
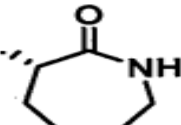
En consecuencia, la reivindicación 1, de acuerdo a lo divulgado en D5, carece de Novedad.

Las reivindicaciones 2, 5 y 7, dependientes de la reivindicación 1, no divulgan características adicionales que otorguen novedad a los compuestos de la reivindicación 1. Por lo tanto, estas reivindicaciones también carecen de Novedad.

La reivindicación 1 divulga un compuesto de fórmula general I o una sal farmacéuticamente aceptable, caracterizado por la estructura, donde... (Página 66

del radicado N°13–02653–00000–0000).

Comparación de las características técnicas **esenciales**, con las del Estado de la Técnica:

Solicitud	D6
Compuesto de la fórmula I 	Compuesto 6 
n es 3 para obtener el anillo de 2 – oxo azepina	
X _k , donde X es halógeno; k es 1	Cloro en posición 4 del grupo benceno sulfonamida

Las características técnicas esenciales de los compuestos de la fórmula XI de acuerdo con la reivindicación 12, se han divulgado previamente en D6 (D6: Página 5791, compuesto 6) en donde se muestra el compuesto N – (2 – oxo azepin – 3 – il) – 4 – cloro bencenosulfonamida, como intermediarios para la síntesis de compuestos inhibidores de gama secretasa para el tratamiento de la enfermedad de Alzheimer, con las características técnicas esenciales descritas en la tabla anterior.

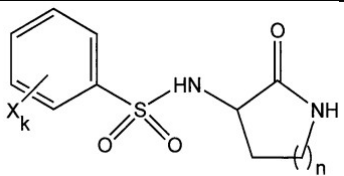
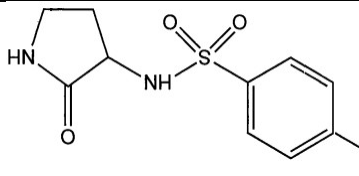
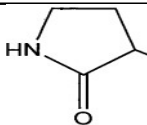
En consecuencia, la reivindicación 1, de acuerdo a lo divulgado en D6, carece de Novedad.

Las reivindicaciones 2, 5 y 7, dependientes de la reivindicación 1, no divulgan características adicionales que otorguen novedad a los compuestos de la reivindicación 1. Por lo tanto, estas reivindicaciones también carecen de Novedad.

La reivindicación 1 divulga un compuesto de fórmula general I o una sal farmacéuticamente aceptable, caracterizado por la estructura, donde... (Página 66 del radicado N°13–02653–00000–0000).

Comparación de las características técnicas **esenciales**, con las del Estado de la Técnica:

Solicitud	D7
Compuesto de la fórmula I	Amina del ejemplo 9

	
n es 1 para obtener el anillo de 2 – oxo pirrolidina	
X _k , donde X es halógeno, alquilo, amino; k es 0, 1, 2	Grupo benzamida opcionalmente sustituido por halógeno, alquilo o amino

Las características técnicas esenciales de los compuestos de la fórmula XI de acuerdo con la reivindicación 12, se han divulgado previamente en D7 () en donde se muestra el compuesto N – (2 – oxo pirrolidin – 3 – il) – 4 – metil bencenosulfonamida, como intermediario en síntesis de nuevos compuestos, con las características técnicas esenciales descritas en la tabla anterior.

En consecuencia, la reivindicación 1, de acuerdo a lo divulgado en D7, carece de Novedad.

Las reivindicaciones 2, 5 y 7, dependientes de la reivindicación 1, no divulgan características adicionales que otorguen novedad a los compuestos de la reivindicación 1. Por lo tanto, estas reivindicaciones también carecen de Novedad.

8. Conclusión

Los requisitos de Patentabilidad de esta solicitud se ven afectados de la siguiente manera:

Item	Documento	Reivindicaciones	Requisitos que afecta
D1	WO2006005486	1, 2, 6, 7 y 10	Novedad
D2	WO2005042489	1, 2, 6, 7 y 10	Novedad
D3	WO2004033455	1, 2, 5 y 7	Novedad
D4	US5527777	1, 2 y 5 a 7	Novedad
D5	<i>Bioorganic & Medicinal Chemistry Letters</i> . 2008 . 18; 1511 – 1519	1, 2, 5 y 7	Novedad
D6	<i>Bioorganic & Medicinal Chemistry Letters</i> . 2007 . 17; 5790 – 5796	1, 2, 5 y 7	Novedad
D7	<i>Journal of Organic Chemistry</i> . 1991 . 56; 452 – 454	1, 2, 5 y 7	Novedad

En cumplimiento del artículo 45 de la Decisión 486 de la Comisión de la Comunidad Andina, se le indica que debe dar respuesta dentro del término de sesenta (60) días contados a partir del día siguiente de la fecha de notificación de la presente comunicación. En caso de no dar respuesta al presente requerimiento, o si a pesar de la respuesta subsistieran los impedimentos para la concesión, se denegará la patente.

Se invita al solicitante se sirva indicar, si así lo considera, su renuncia al término faltante de sesenta (60) días para dar respuesta a este requerimiento y presentarla por escrito.

Finalmente, se le recuerda al solicitante que si como respuesta a este requerimiento llegara a modificar el capítulo reivindicatorio y éste contenga más de diez (10) reivindicaciones, no pagará la tasa de modificación voluntaria pero sí la correspondiente al pago por reivindicación adicional.

Notifíquese el presente oficio conforme a lo dispuesto en el numeral 5.2, literal e), del capítulo quinto del título primero de la Circular Única No. 10 de 2001.



JOSÉ LUIS SALAZAR LÓPEZ
Director de Nuevas Creaciones (c)

El anterior requerimiento fue notificado por fijación en lista, de fecha 2013-12-17

Elaboró: Dayron Alexander Ramirez Reyes
Revisó: Gloria Jacqueline Alfonso Roza

Substituted 2-oxo-azepane derivatives are potent, orally active γ -secretase inhibitors

Eric A. Kitas,^{a,*} Guido Galley,^a Roland Jakob-Roetne,^a Alexander Flohr,^a Wolfgang Wostl,^a Harald Mauser,^a André M. Alker,^b Christian Czech,^c Laurence Ozmen,^c Pascale David-Pierson,^d Dieter Reinhardt^c and Helmut Jacobsen^c

^aPharma Division, Discovery Chemistry, F. Hoffmann-La Roche Ltd, CH-4070 Basel, Switzerland

^bPharma Division, Molecular Structure Research, F. Hoffmann-La Roche Ltd, CH-4070 Basel, Switzerland

^cPharma Division, Preclinical CNS Research, F. Hoffmann-La Roche Ltd, CH-4070 Basel, Switzerland

^dPharma Division, Safety Technical Services, F. Hoffmann-La Roche Ltd, CH-4070 Basel, Switzerland

Received 21 September 2007; revised 18 October 2007; accepted 22 October 2007

Available online 5 November 2007

Abstract—A hydroxamic acid screening hit **1** was elaborated to 5,5-dimethyl-2-oxoazepane derivatives exhibiting low nanomolar inhibition of γ -secretase, a key proteolytic enzyme involved in Alzheimer's disease. Early ADME data showed a high metabolic clearance for the geminal dimethyl analogs which could be overcome by replacement with the bioisosteric geminal difluoro group. Synthesis and structure–activity relationship are discussed and in vivo active compounds are presented.
© 2007 Elsevier Ltd. All rights reserved.

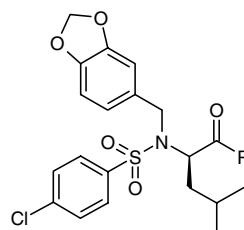
Alzheimer's disease (AD) is characterized by the deposition in the brain of amyloid in extracellular plaques and intracellular neurofibrillary tangles. The amyloid plaques are composed of A β peptides (mainly 40- and 42-amino-acid length) which originate from β -amyloid precursor protein (APP) by a series of proteolytic cleavage steps involving enzymes β -secretase and γ -secretase. Whereas β -secretase is a typical aspartyl protease, γ -secretase proteolytic activity consists of several proteins including the presenilins, nicastrin, aph1, and pen-2.¹ Among the known substrates of γ -secretase are the APP and the proteins of the Notch receptor family.^{2,3} According to the amyloid hypothesis of AD, the production and deposition of A β is the ultimate cause of the disease.

In our program to identify potent and selective inhibitors of γ -secretase, a micromolar screening hit **1** was identified from our proprietary compound library. Hydroxamic acid **1** was elaborated to the primary amide **2**, a nanomolar inhibitor of amyloid synthesis as determined by our cellular A β lowering assay (Table 1).⁴

Keywords: Alzheimer's disease; Amyloid A β lowering; γ -Secretase; Proteolytic activity; Metabolism; In vivo.

* Corresponding author. Tel.: +41 61 688 76 18; fax: +41 61 688 64 59; e-mail: eric_a.kitas@roche.com

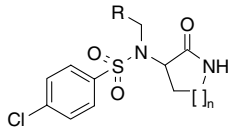
Table 1. HTS hit **1** and representative early modifications



Compound	R	A β lowering IC ₅₀ (μ M)
1	NHOH	2.6
2	NH ₂	0.008

The poor physicochemical properties (e.g., compound **2**: solubility <1 μ g/ml; log *D* > 3; low PAMPA permeability⁵) and relatively high clearance (e.g., compound **2**: human/mouse 34/282 μ l/min/mg protein) observed for primary amides in this class led us to consider ring constrained structures (Table 2). Cyclic lactams **3–6** were prepared, thus fusing the vectors corresponding to the isobutyl and amide groups in **2**. The azepinone (*n* = 3) ring size was found to be optimal in this series with sulfonamide **5** having a modest inhibition of IC₅₀ 0.40 μ M.⁶

Alternatives to the piperonyl northern vector were examined and phenyl ring substitutions (Me, OMe

Table 2. Lactam derivatives 3–16


Compound	<i>n</i>	R	Aβ lowering IC ₅₀ (μM)
3	1		>20
4	2		14
5	3		0.40
6	4		9
7	3		0.32
8	3		0.23
9 [R isomer]	3		0.17
10 [S isomer]	3		17
11	3		0.15
12 [R isomer]	3		0.08
13	3		0.17
14	3		2
15 [R isomer]	3		0.14
16	3		0.9

OCF₃, Cl, F, data not shown) indicated that larger para-substituents were tolerated (**12–15**) and inhibitory activities could be improved by further addition of F to the phenyl ring (**8–11**). The preferred *R*-stereochemistry was established by preparing compounds **9** and **10** starting from (*R*)-3-amino-azepan-2-one and (*S*)-3-amino-azepan-2-one, respectively. Furthermore, phenyl to pyridyl replacement such as in compound **16** maintained sub-micromolar affinity for γ-secretase. Minimal variations to the aryl western vector were attempted as

para-chlorophenyl was a well-established pharmacophore in sulfonamide or sulfone classes of γ-secretase inhibitors.⁷ Nevertheless, some variations will be discussed later (vide infra, Table 4).

Next we considered the SAR at the azepinone ring in an attempt to improve the modest inhibition seen so far. *N*-Methyl substitution of the lactam gave inactive compounds (data not shown).

An overlay of lactam **12** with the most potent acyclic analog **2** (Fig. 1) shows the high similarity of both classes. Interestingly, the structural comparison suggests that the lactams do not occupy all available space (indicated by the cyan sphere). Thus, additional substitution in 4- or 5-position was considered for improving binding affinity.

Indeed the introduction of an isopropyl- or CF₃-substituent (Table 3, compounds **17** and **18**) in position 5 led

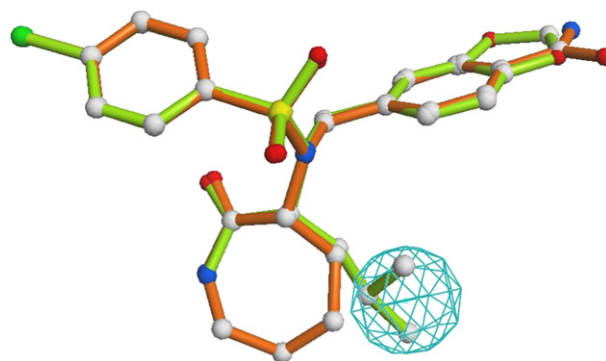
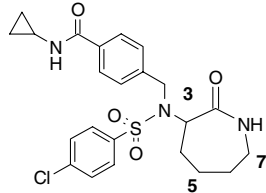


Figure 1. Overlay of acyclic HTS derivative **2** and lactam **12**. The X-ray structure⁸ of **15** of the lactam series was taken as reference for a flexible alignment of **2** using the program Moloc (Gerber, P.; www.moloc.ch, 2007). For clarity the propionic acid side chain was replaced by a primary amide leading to compound **12**.

Table 3. Substituted 2-oxoazepane derivatives


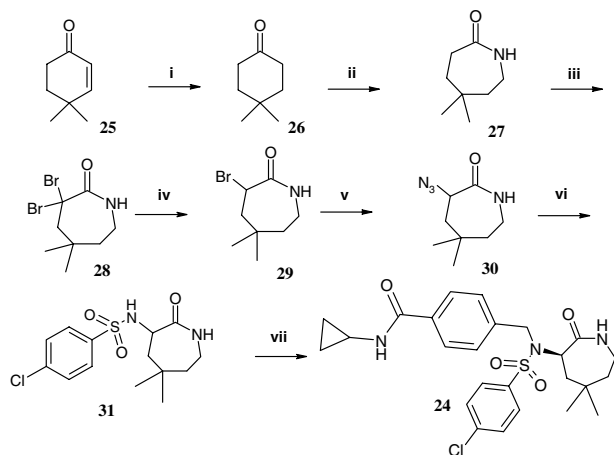
Compound	Lactam subst.	Aβ lowering IC ₅₀ (μM)	Cl (human/mouse microsomes) ^a
17	5- <i>i</i> -Pr[Rac]	0.04	51/203
18	5-CF ₃ [Rac]	0.02	19/39
19	5- <i>t</i> -Bu[Rac]	0.12	93/110
20	5,5-Me ₂	0.006	45/191
21	7,7-Me ₂	>20	—
22	6,6-Me ₂	3.5	—
23	4,4-Me ₂	0.39	—
24 [R isomer]	5,5-Me ₂	0.015	36/655
32 [R isomer]	5,5-F ₂	0.004	1.9/2.2
33 [R isomer]	6,6-F ₂	0.30	0.0/5.4

^a Microsomal clearance (μl/min/mg protein).

to stronger inhibition of γ -secretase activity compared to the corresponding unsubstituted derivative **13**. This effect was less pronounced for the larger *t*-butyl derivative **19**. A very potent compound could be obtained with geminal dimethyl substitution **20** and also simplified the structure by the removal of one chiral center. Starting from **20** as the least complex structure, a 'gem.dimethyl walk' around the caprolactam (compounds **20–23**) showed that optimal substitution was in fact the 5-position.

The synthesis of **24** (the active *R*-isomer of **20**) is described in Scheme 1 and began with the hydrogenation of α,β -unsaturated cyclohexenone **25** to yield **26** which was subjected to a Beckmann rearrangement using hydroxylamine-*o*-sulfonic acid in formic acid.⁹ Selective dibromination in position 3 of the azepinone followed by monodebromination under hydrogenolytic conditions afforded **30**.¹⁰ Sodium azide displacement of Br and reduction of azide to amine was followed by preparation of sulfonamide **31** as a mixture of 1:1 enantiomers which were separated by chiral chromatography. Further derivatization with 4-chloromethyl-*N*-cyclopropylbenzamide under basic conditions gave compound **24**. The active isomer was tentatively assigned with the *R*-configuration by comparing A β lowering activities of the enantiomer pair **9** and **10**.

With the first potent γ -secretase inhibitors in hand, we initiated early ADME profiling. Human/mouse microsomal clearance was relatively high for 5-alkyl substituted derivatives **17**, **19**, **20**, when compared to **18**, suggesting that alkyl substituents were labile to microsomal oxidation. Our attempts at blocking this liability led us to the surprising result that the 5,5-difluoro and 6,6-difluoro analogs yielded highly bioavailable inhibitors **32** and **33**, respectively, with **32** matching the



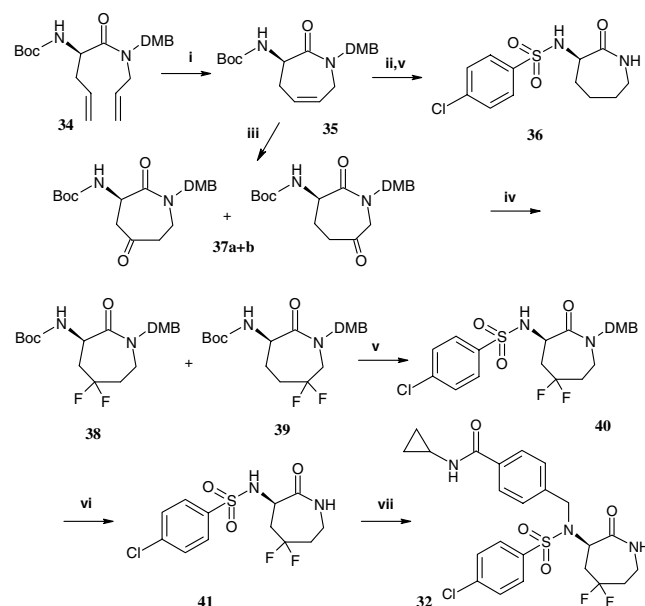
Scheme 1. Reagents and conditions: (i) H₂, Pd–C in EtOH, 95%; (ii) hydroxylamine-*o*-sulfonic acid in formic acid, reflux, 2 h, 55%; (iii) PCl₅, ZnCl₂, Br₂ 4 h, 67 %; (iv) H₂ Pd–C, NaOAc in AcOH, 71%; (v) NaN₃ in DMSO, 80 °C, 1.5 h, 21%; (vi) H₂ Pd–C then 4-chlorobenzenesulfonyl chloride, DIEA, 1.5 h 67%; (vii) chiral separation on Chiralpak AD 20% isopropanol, 80% heptane, then 4-chloromethyl-*N*-cyclopropylbenzamide, K₂CO₃ KI, 65 °C 2.5 h, 31%.¹¹

potency of the chiral 5,5-dimethyl analog **24** in the A β lowering assay (Table 3).

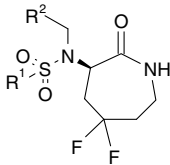
The synthesis of fluoro ring-substituted 3-amino-azepan-2-ones is described in Scheme 2. (*R*)-*N* Boc-allylglycine was coupled to allyl-(2,4-dimethoxybenzyl)amine to yield the bis-allyl intermediate **34**.¹² Ring closure metathesis reaction preferably using the 2nd generation Grubb's catalyst (0.1 equiv) proceeded efficiently without the need for high dilution affording **35** in 80% yield. The chiral integrity of the cyclization product was assessed by its further reaction to yield known compound **36** where respective optical rotations could be compared,¹³ confirming the mildness of the olefin metathesis conditions. Alkene **35** was oxidized to the 5,6-oxo regioisomers using a palladium complex in a saturated oxygen environment.

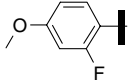
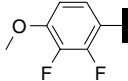
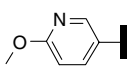
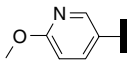
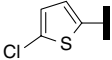
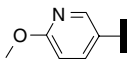
The regioisomeric mixture **37a,b** was used directly in the further transformation to geminal difluorinated compounds using DAST (3 equiv) in a modest 45% overall yield and following silica gel chromatography the preferred isomer **38** was isolated in a 22% yield. In a straightforward manner, further homologation of **38** yielded the potent inhibitor **32**.¹⁴

Compound **32** was profiled in vivo in a transgenic mouse model for inhibition of γ -secretase activity¹⁵ and was found to be inactive after 3 $\times$ 20 mg/kg po and ip administration. We attributed this finding to possible low brain penetration due to the presence of two amides in its structure. We therefore went back to methoxyaryl northern substituents that we already



Scheme 2. Reagents and conditions: (i) Grubb's II cat., reflux, 1.5 h, MeCl₂, [0.03 M] 80%; (ii) H₂ Pd–C, EtOH then TFA; (iii) O₂, PdCl₂CuCl, DMF/water, 50 °C, 2 d, 72%; (iv) DAST, MeCl₂, 5 h, 45% overall; (v) separation from **39** then HCl/1,4-dioxane, 2 h then 4-chlorobenzenesulfonyl chloride, DIEA in MeCl₂, 2 h, 60%; (vi) TFA/triethylsilane/water, 3 d, 40%; (vii) 4-chloromethyl-*N*-cyclopropylbenzamide, K₂CO₃, KI in DMF 65 °C, 1.5 h.

Table 4. 5,5-Difluoro-substituted 2-oxoazepane derivatives


Compound	R ¹	R ²	Aβ lowering IC ₅₀ (μM)	Cl (human/mouse microsomes) ^a
42	pCl-Ph		0.02	13/105
43	pCl-Ph		0.002	19/121
44	pCl-Ph		0.03	9/72
45	CF ₃ (CH ₂) ₂		0.15	—
46			0.11	—

^a Microsomal clearance (μl/min/mg protein).

found active with the non-fluorinated caprolactams (vide supra, Table 2). The methoxyphenyl derivative **42** was less potent than **32** but inhibitory activity could be further improved by addition of another fluorine (Table 4). In fact, compounds **43** and **44** were found to be active in vivo at a minimal effective dose (MED) of 20 mg/kg po. This relatively high dose may be explained by the low brain exposure (typically brain/plasma ratio <0.1) determined from the in vivo experiments.¹⁶

A few examples at replacing the *para*-chlorophenyl moiety were prepared and trifluoropropyl **45** and the 5-chlorothiophene **46** derivatives were identified as potential alternatives.

In conclusion, we have identified a series of 5,5-difluoro-substituted 2-oxoazepane derivatives which are potent inhibitors of γ-secretase. Difluoro-substitution was found to be a key factor to ensure both potency and metabolic stability of the compounds. Further variation of substituents yielded compounds **43** and **44** which were orally active in a transgenic mouse model for AD. Low brain exposure possibly related to observed P-glycoprotein interactions for representative compounds,¹⁷ is a remaining issue that needs to be addressed for this otherwise attractive series.

Acknowledgments

The excellent technical assistance of Patrick Studer, Betty Hennequin, Annick Goergler, Roman Hutter, Peter Weber, Joseph Wuhrlin, Daniel Zimmerli, Fabienne Goepfert, Patrick Biry, Remy Wybrecht, Marie Elise

Brun, Vittorio Bona, Christophe Schweitzer, and Markus Haenggi is gratefully acknowledged.

Supplementary data

Supplementary data associated with this article can be found, in the online version, at doi:10.1016/j.bmcl.2007.10.074.

References and notes

- Hardy, J.; Selkoe, D. J. *Science* **2002**, 297, 353.
- (a) Radtke, R. et al. *Nat. Immunol.* **2004**, 5, 247; (b) Radtke, F.; Clevers, H. *Science* **2005**, 307, 1904.
- Shih, Ie-Ming; Wang, Tian-Li *Cancer Res.* **2007**, 67, 1879.
- Description of Aβ lowering assay: HEK293 cells which express a human βAPP cDNA were treated for 16–18 h with compound. The supernatant was harvested and the Aβ 40 peptide concentrations were determined. Ninety-six well ELISA plates (e.g., Nunc MaxiSorb) were coated with monoclonal antibody which specifically recognizes the C-terminal end of Aβ40 (Brockhaus et al., *NeuroReport* **1998**, 9, 1481). After blocking of non-specific binding sites with, e.g., 1% BSA and washing, the culture supernatants were added in suitable dilutions together with a horseradish peroxidase-coupled Aβ-detection antibody (e.g., antibody 4G8, Senetek, Maryland Heights, MO) and incubated for 5–7 h. Subsequently the wells of the microtiter plate were washed extensively with Tris-buffered saline containing 0.05% Tween 20 and the assay was developed with tetramethylbenzidine/H₂O₂ in citric acid buffer. After stopping the reaction with one volume 1 N H₂SO₄ the reaction was measured in an ELISA reader at 450 nm wavelength. In repeated measurements the stan-

- dard deviation for the calculated IC_{50} was 30%. Measured data were also in agreement with cell-free-assay data obtained for selected compounds according to the procedure by Li (*Proc. Natl. Acad. Sci. U.S.A.* **2000**, 97, 6138).
- For a description of the PAMPA (parallel artificial membrane permeability assay) model, a prediction assay for oral absorption Kansy, M.; Fischer, H.; Kratzat, K.; Senner, F.; Wagner, B.; Parrilla, I. *Helv. Chim. Acta* **2000**, 447.
 - Other recent publications on *N*-(oxoazepanyl) benzene-sulfonamides and related derivatives as γ -secretase inhibitors for treating Alzheimer's disease: Neitzel, M.; Dapfen, M. S.; Marugg, J. WO Patent WO2005042489, 2005; Parker, M. F.; Bronson, J. J.; Barten, D. M. et al. *Bioorg. Med. Chem. Lett.* **2007**, 17, 5790.
 - (a) Further literature exemplifying the sulfonamide and sulfone classes of γ -secretase inhibitors: Smith, D. W. WO Patent WO2000050391, 2000; (b) Pineiro J. L.; Churcher I.; Dinnell K. et al. WO patent WO2002081435, 2002; (c) Parker M. F.; McElhone K. E.; Mate R. A. et al. WO patent WO20-03053912, 2003; (d) Josien H. B. WO patent WO2003013527, 2003; (e) Churcher, I.; Harrison, T.; Kerrad, S. et al. WO patent WO2004031137, 2004; (f) Brands K. M.; Davies A. J.; Oakley P. J. et al. WO2004013090, 2004; (g) Churcher, I.; Behr, D.; Best, J. D., et al. *Bioorg. Med. Chem. Lett.* **2006**, 16, 280; (h) Asberom, T.; Zhao, Z.; Bara, T. A. *Bioorg. Med. Chem. Lett.* **2007**, 17, 511.
 - Full crystallographic data for compound **15** have been deposited with the Cambridge Crystallographic Data Center (CCDC Reference No. 661530). Copies of the data can be obtained free of charge via the internet at <http://www.ccdc.cam.ac.uk>.
 - Olah, G. A.; Fung, A. P. *Synthesis* **1979**, 537.
 - Shirota, F.; Nagasawa, H. T.; Elberling, J. A. *J. Med. Chem.* **1977**, 20, 1623.
 - For detailed experimental conditions, see: Galley, G.; Jakob-Roetne, R.; Kitas, E. A. WO Patent WO2006005486, 2006.
 - Analogous RCM in synthesis of 3-aminoazocan-2-one derivatives Creighton, C. J.; Leo, G. C.; Du, Y.; Reitz, A. B. *Bioorg. Med. Chem.* **2004**, 12, 4375.
 - Compound **36** $[\alpha]_D -130.6^\circ$ ($c = 0.64$, $CHCl_3$) was also prepared using commercial (*R*)-3-amino-azepan-2-one: $[\alpha]_D -130.9^\circ$ ($c = 0.89$, $CHCl_3$).
 - For detailed experimental conditions, see: Flohr, A.; Galley, G.; Jakob-Roetne, R.; Kitas, E. A.; Wostl, W. US Patent US20070037789, 2007.
 - Compounds were profiled in vivo in the PS2APP transgenic mouse which expresses the human APPsw cDNA and a human FAD presenilin 2 cDNA. See also (a) Richards, J. G.; Higgins, G. A.; Quagazzal, A. M.; Ozmen, L.; Kew, J. N.; Bohrmann, B.; Malherbe, P.; Brockhaus, M.; Loetscher, H.; Czech, C.; Huber, G.; Bluethmann, ; Jacobsen, H.; Kemp, J. A. *J. Neurosci.* **2003**, 23, 8989; (b) Inhibition of γ -secretase was assessed by accumulation of its substrate, the C-terminal fragment (CTF β) of APP released by the previous β -secretase cleavage. The accumulation of CTF β in total brain was quantified by Western blot (see reference above Richards et al. for details). Compounds were first tested at 20 mg/kg for efficacy followed by a dose-response with 0.5–3–10–30 mg/kg, three animals per dose. The well-characterized γ -secretase inhibitor LY411575 was used as reference compound. The CTF β band was quantified by Chemo-luminescence and normalized to an endogenous control protein band. In the PS2APP transgenic mouse the expression of the human APP transgene is driven by a neuron-specific form of the Thyl promoter. The peripheral level of APP and the plasma level of A β peptide are too low to allow a meaningful determination of γ -secretase inhibition; The use of CTF β accumulation as a sensitive marker for γ -secretase inhibition has been described by others (c) Zhao, Guojun; Cui, Mei-Zhen; Mao, Guozhang; Dong, Yunzhou; Tan, Jianxin; Sun, Longsheng; Xu1, Xuemin *J. Biol. Chem.* **2005**, 280, 37689; (d) Walsh, D. M.; Fadeeva, J. V.; LaVoie, M. J.; Paliga, K.; Eggert, S.; Kimberly, W. T.; Wasco, W.; Selkoe, D. J. *Biochemistry* **2003**, 42, 6664; (e) De Strooper, B.; Saftig, P.; Craesserts, K.; Vanderstichele, H.; Guhde, G.; Annaert, W.; Von Figura, K.; Van Leuven, F. *Nature* **1998**, 391, 387.
 - Compound **44** was dosed at 20 mg/kg po and the brain/plasma ratio was determined at 2 h: plasma conc. = 1046 g/ml, brain conc. = 60 ng/g; $b/p = 0.06$; $N = 3$.
 - The permeability and the P-gp substrate properties of **44** were assessed by a bi-directional transport assay in an epithelial cell monolayer system, using LLC-PK1 cells exogenously expressing human P-glycoprotein (P-gp), MDR1. A high passive permeability of around 280 nm/s was estimated based on the observed apical to basolateral and reverse permeabilities in the different experiments where active transport was inhibited. Directional transport (at a concentration of 1 μ M) was observed in cells expressing the human MDR1 transporter with an export permeability ratio of 2.2, while in presence of an inhibitor (Elacridar, 5 μ M) this transport was fully inhibited (export ratio = 1). These results indicate that **44** is a substrate for human MDR1 P-glycoprotein.

Amino-caprolactam derivatives as γ -secretase inhibitors

Michael F. Parker,^{a,*} Joanne J. Bronson,^a Donna M. Barten,^b Jason A. Corsa,^b Wengsheng Du,^b Kevin M. Felsenstein,^{b,†} Valerie L. Guss,^b Darcy Izzarelli,^b Alice Loo,^b Kate E. McElhone,^{a,‡} Larry R. Marcin,^a Ramesh Padmanabha,^b Roger Pak,^b Craig T. Polson,^b Jeremy H. Toyn,^b Sam Varma,^b Jian Wang,^c Victoria Wong,^b Ming Zheng^d and Susan B. Roberts^b

^aDepartment of Discovery Chemistry, Bristol-Myers Squibb Research and Development,
5 Research Parkway, Wallingford, CT 06492, USA

^bDepartment of Neuroscience Biology, Bristol-Myers Squibb Research and Development,
5 Research Parkway, Wallingford, CT 06492, USA

^cDepartment of Bioanalytical Research, Bristol-Myers Squibb Research and Development, Rt. 206, Lawrenceville, NJ 08543, USA

^dDepartment of Drug Metabolism and Pharmacokinetics, Bristol-Myers Squibb Research and Development,
5 Research Parkway, Wallingford, CT 06492, USA

Received 24 July 2007; revised 20 August 2007; accepted 23 August 2007
Available online 26 August 2007

Abstract—A series of amino-caprolactam sulfonamides were developed from a screening hit. Compounds with good in vitro and in vivo γ -secretase activity are reported.

© 2007 Elsevier Ltd. All rights reserved.

Alzheimer's disease (AD) is a progressive, neurodegenerative disorder characterized by memory impairment and cognitive dysfunction.¹ AD is characterized pathologically by the accumulation of senile (neuritic) plaques, neurofibrillary tangles, amyloid deposition in neural tissues and vessels, synaptic loss, and neuronal death.^{2a,b} AD is the most common form of dementia and now represents the third leading cause of death after cardiovascular disorders and cancer.³ Evidence suggests the accumulation of β -amyloid peptides (A β) is responsible for the neuronal toxicity that is associated with AD.⁴ A β peptides are generated by sequential proteolytic cleavage of a 695–770 amino acid precursor protein (APP)⁵ by the action of β - and γ -secretases.

We have been interested in identification of compounds that inhibit the production of β -amyloid peptide (β -AP) from β -amyloid precursor protein (β -APP), since such agents may be useful for the treatment or prevention of Alzheimer's disease. A cell-based assay measuring A β production⁶ from membranes isolated from cells expressing β -APP⁷ was performed on our internal compound collection and the caprolactam sulfonamide derivative **1**^{8,9} (Fig. 1) was found to be a promising inhibitor of γ -secretase (IC₅₀ = 120 nM). Herein we report the SAR within this series of caprolactam γ -secretase inhibitors.

Starting from commercially available D- or L-lysine **2**, amino caprolactam **3** was conveniently made by ring closure of the trimethylsilyl amino ester¹⁰ as shown in

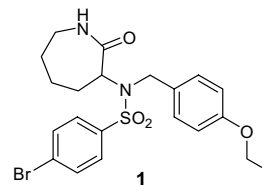


Figure 1.

Keywords: γ -Secretase inhibitors; Alzheimer's disease; N-Benzyl amino caprolactams.

* Corresponding author. Tel.: +1 203 677 6466; fax: +1 203 677 7702; e-mail: parkerm@BMS.com

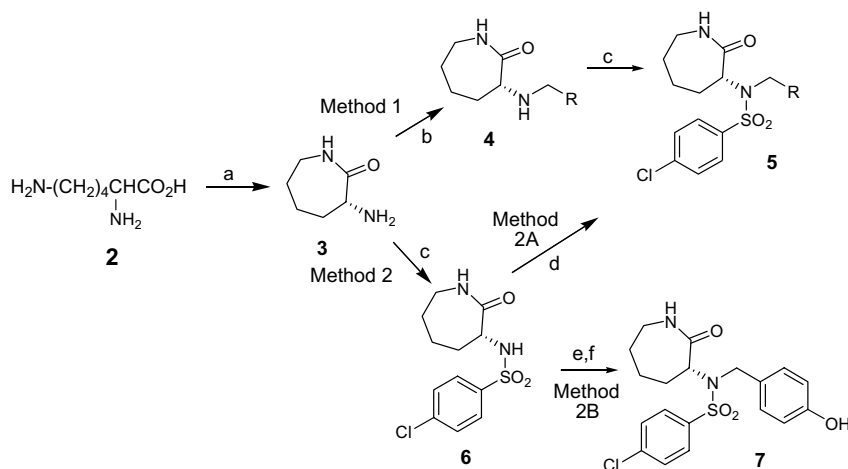
[†] Present address: Johnson & Johnson PRD, Spring House, PA 19477, USA.

[‡] Present address: Johnson & Johnson Pharmaceutical Research & Development, La Jolla, CA 92121, USA.

Scheme 1. This synthetically useful chiral amine underwent reductive amination by treatment with an aldehyde and sodium cyanoborohydride in methanol to provide intermediate **4**. The resulting secondary amines were treated with a variety of sulfonyl chlorides to produce the desired analog **5** shown in **Scheme 1**. Alternatively the chiral amino caprolactam **3** could first be sulfonylated to afford intermediate **6**. The resulting secondary sulfonamides could be preferentially alkylated with an array of alkyl or benzyl halides in DMF with K_2CO_3 (method 2A). In the preparation of the 4-hydroxybenzyl benzenesulfonamide analog **7**, synthesis via method 1 or method 2A was unsuccessful because of decomposition of the benzylic halide under the usual reaction conditions. The alkylation of the sulfonamide was accom-

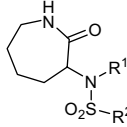
plished instead by a standard Mitsunobu reaction on the sulfonamide caprolactam **6** with the differentially protected ether alcohol, 4-(*tert*-butyldimethylsilyloxy) benzyl alcohol. The crude product of this reaction was then deprotected with tetrabutyl ammonium fluoride in THF, to yield the desired phenol **7**.

Optimization of the 4-bromosulfonamide caprolactam screening lead first focused on determination of whether the enantiomers had differential potency. Comparison of the enantiomers **8** and **9** clearly showed the R-isomer, which was derived from D-lysine, to be significantly, and as with **9**, exceptionally more potent.¹² Likewise, with the enantiomer pair **10** and **11**, the R-isomer **11** was >300× more potent (**Table 1**).



Scheme 1. General synthesis of *N*-benzyl-*N*-benzenesulfonamide derivatives. Reagents: (a) hexamethyldisilazane, chlorotrimethylsilane, xylene, 95%; (b) alkyl aldehyde or benzaldehyde, $ZnCl_2$, $NaCNBH_4$, MeOH, 40–80%; (c) 4-chlorobenzenesulfonyl chloride, Et_3N , CH_2Cl_2 , 92%; (d) alkyl or benzyl halide, K_2CO_3 , DMF, 30–88%; (e) triphenylphosphine, 4-(*tert*-butyldimethylsilyloxy) benzyl alcohol, diethylazodicarboxylate, THF, 58%; (f) TBAF, THF, 72%.

Table 1. Inhibitory activities of caprolactam enantiomers

					
Ex. #	R ¹	R ²	Method	Isomer	Aβ40 IC ₅₀ (nM) ^a
1			2A	D/L	120
8			2A	S	3400
9			2A	R	13
10			1	S	3200
11			1	R	9.7

^a Values are means of four experiments, with 12 drug concentrations in each exp.; intra-assay variance <10%.⁶

We next probed the effect of the lactam ring size¹¹ on potency. As exemplified by compounds **12**, **13**, and **14** in Figure 2, both the 5- and 6-membered lactams were significantly less potent than the corresponding over the 7-membered ring **14**. As a result of these findings, subsequent analogs were focused on the caprolactam core (Fig. 2).

Modification of the aryl moiety attached to the sulfonamide sulfur atom was also undertaken. As shown in Table 2, the 4-chlorobenzenesulfonamide (e.g., **16** and **21**) was optimal for potency. Introduction of a heteroaryl sulfonamide, as in the thiophene analog **17**, led to a 50-fold loss in potency. Substitution of the 4-chloro by fluorine (e.g., **15** and **20**) or removal of the chlorine as in **19** resulted in a modest decrease in potency. Substitu-

tion with an alkyl group as in **18** was quite detrimental to potency.

Our strategy was then to examine the nature of the substituents at R¹ on the sulfonamide nitrogen while keeping 4-chlorophenylsulfonamide constant. Compounds shown in Table 3 result from examination of various benzylic substituents, while compounds in Table 4 illustrate a variety of non-benzylic groups. As shown in Table 3, *para*-substitution on the benzyl side chain generally improved potency when compared to the unsubstituted ring system **22**. Strongly electron-donating *para*-substituents conferred the greatest potency, as seen with the methoxyphenyl analog **23** (IC₅₀ = 2.8 nM) and the phenol **7** (IC₅₀ = 5.0 nM). While electron-rich systems were generally more potent (e.g., aniline **25**,

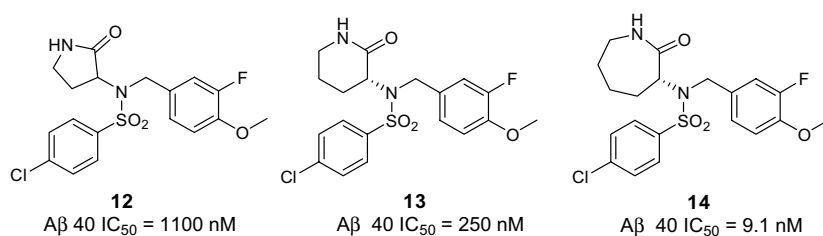
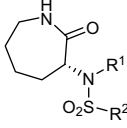
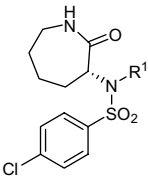


Figure 2.

Table 2. Modification of the aryl sulfonamide moiety

				
Ex. #	R ¹	R ²	Method	Aβ40 (IC ₅₀ nM) ^a
9			2A	13
15			1	57
16			2A	9.0
17			1	830
18			1	7700
19			1	180
20			1	25
21			1	21

^a Values are means of four experiments, with 12 drug concentrations in each exp.; intra-assay variance <10%.

Table 3. Inhibitory activities of R^1 benzylic substituents


Ex. #	R^1	Method	A β 40 (IC ₅₀ nM) ^a
22		1	65
23		1	2.8
7		2B	5.0
24		2A	13
25		1	11
26		2A	76
27		2A	18
28		2A	45
29		2A	33
30		2A	12
31		2A	25
32		2A	41
21		1	21
14		1	9.1
11		1	9.7
33		2A	15

Table 3 (continued)

Ex. #	R^1	Method	A β 40 (IC ₅₀ nM) ^a
34		2A	93
35		2A	29
36		2A	64
37		2A	60
38		2A	820
39		2A	660
40		2A	130
41		2A	550
42		2A	130
43		2A	67
44		1	460
45		1	120
46		1	340
47		1	27
48		2B	690
49		2B	4500

^a Values are means of four experiments, with 12 drug concentrations in each exp.; intra-assay variance <10%.

IC_{50} = 11 nM; *tert*-butylphenyl **24**, IC_{50} = 12 nM), electron-withdrawing groups such as CF_3SO_2 (**28**, IC_{50} = 25 nM) and CN (**32**, IC_{50} = 41 nM) were also tolerated. Combination of a *para*-OR group with a *meta*-substituent was also acceptable as seen with

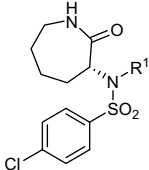
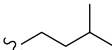
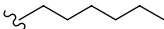
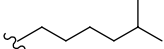
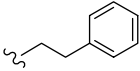
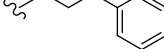
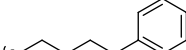
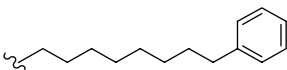
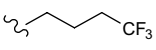
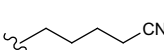
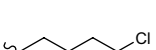
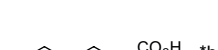
the 3-fluoro-4-methoxy phenyl analog **14** (IC_{50} = 9.1 nM) and the methylenedioxyphenyl derivative **11** (IC_{50} = 9.7 nM). By comparison, single *meta*-substitution of the benzylic group was generally less favored than *para*-substitution as illustrated by comparison of **23/34**, **32/36**, and **21/37**. *Ortho*-substitution was significantly disfavored as seen with compounds **38** and **39**. Disubstituted benzyl groups lacking *para*-substituents (e.g., **40–43**) were also less potent.

In order to improve solubility, we examined a series of pyridylmethyl side chains. The 3-pyridyl analog **45** was more potent than the 2-pyridyl **44** and the 4-pyridyl **46** isomers. Attenuating the pK_a of the pyridyl ring by adding a 4-chloro substitution as in **47** had a positive effect on binding. With the exception of **47**, the pyridyl series was significantly less potent than the simple methoxy- or methylenedioxy phenyl compounds. Finally, branching at the benzylic position was examined. Addition of an α -methyl group, as shown in examples **48** and **49**, resulted in a significant loss of potency.

Analogues with alkyl side chains on the sulfonamide nitrogen were also examined (Table 4). Elimination of the aryl ring had a negative impact on the potency in this series. Interestingly, we found that substantial length was required to impart even modest activity in the simple alkyl series, as shown with compounds **50–53**. In the case of the phenyl alkyl derivatives, extending chain length also improved potency, with the phenylpropyl derivative **55** being the most potent in the series. However, further extension of the phenyl derivative chain length led to a decrease in potency. Capping the terminus of the alkyl side chain with functional groups such as CF_3 , CN, Cl or CO_2H (**58–61**, respectively) did not improve potency to the level of benzylic substituents, although the trifluoromethylpropyl derivative **60** had better potency than the simple propyl derivative **50**. Even the best compound in the alkyl series was still 10-fold less active than in the benzyl series.

To further assess the caprolactam series, the methoxyphenyl (**23**) and the dimethylaniline (**25**) were evaluated *in vivo*¹³ for the reduction of brain concentrations of A β . The compounds were selected for further study based on their potency in the A β 40 *in vitro* assay.⁶ Transgenic mice (Tg2576 mice,¹⁴ 3–6 months of age) were treated by oral gavage with test compounds at a dose of 200 μ mol/kg. The effects of **23** and **25** on A β in brain and plasma concentrations and relative compound concentrations at 3 h post dose are shown in Table 5. Both compounds **23** and **25** are highly protein bound (>97%) but were found to diminish brain and plasma concentrations of A β as measured by a standard ELISA for A β 40.⁶ Compound concentrations were analyzed by LC–MS–MS method. Although **23** is ~4-

Table 4. Inhibitory activities of R^1 alkyl substituents

			
Ex. #	R^1	Method	A β 40 (IC_{50} nM) ^a
50		2A	1400
51		1	620
52		2A	110
53		2A	85
54		2A	1100
55		2A	67
56		2A	470
57		2A	1000
58		2A	330
59		2A	180
60		2B	150
61	 ^{*b}	2B	3900

^a Values are means of four experiments, with 12 drug concentrations in each exp.; intra-assay variance <10%.

^b Synthesized from the bromo ester, followed by saponification to yield the acid **61**.

Table 5. *In vivo* efficacy of potent caprolactam sulfonamides

Ex. #	A β 40 IC_{50} (nM)	A β 42 IC_{50} (nM)	% inhibition brain ¹³ (concn)	% inhibition plasma ¹³ (concn)	B/P ratio
23	2.8	2.4	49% (2200 nM)	47% (280 nM)	7
25	11	7.8	52% (4200 nM)	61% (1600 nM)	2.8

fold more potent than the aniline **25**, **25** has higher relative brain and plasma exposures. This may explain why the in vivo potencies of these compounds are comparable.

In summary, potent γ -secretase inhibitors emerged from SAR studies and optimization of an initial amino caprolactam screening hit. The most potent compounds to emerge from this study were the 4-methoxy benzyl compound **23** and the *N,N*-dimethyl analog **25**. These compounds were approximately 50-fold more potent than the original screening hit and markedly reduced the concentration of A β in the brain and plasma in transgenic Tg2576 mice. However, **23** and **25** were also found to be nanomolar inhibitors of the human CYP450 isoforms 3A4 and 2C19. Further investigations are focused on the removal of these liabilities from this and similar sulfonamide series.

References and notes

- Scheff, S. W.; Price, D. A.; Schmitt, F. A.; Mufson, E. J. *Neurobiol. Aging* **2006**, 27, 1372.
- (a) Clark, C. M.; Karlawish, J. H. *Ann. Intern. Med.* **2003**, 138, 400; (b) Hardy, J.; Higgins, G. A. *Science* **1992**, 256, 184.
- Nguyen, J.; Yamani, A.; Kiso, Y. *Curr. Pharm. Des.* **2006**, 12, 4295.
- Walsh, D. M.; Klyubin, I.; Fadeeva, J. V.; Cullen, W. K.; Anwyl, R.; Wolfe, S.; Rowan, M. J.; Delkow, D. J. *Nature* **2002**, 416, 535.
- Selkow, D. J.; Podlisny, M. B.; Joachim, C. I.; Vickers, E. A.; Lee, G.; Fritz, L. C.; Itersdorf, T. *Proc. Natl. Acad. Sci. U.S.A.* **1988**, 85, 7341.
- H4 cells stably transfected with APP751 containing the Swedish mutation (H4 APP751 SWE clone 8.20, developed at BMS) were maintained in log phase through twice weekly passage at a 1:20 split. For IC₅₀ determinations, 1.5×10^4 cells/well in DMEM containing 0.0125% BSA (Sigma A8412) were plated directly into 384-well compound plates (Costar 3709) containing 0.1 μ l serially diluted compound in DMSO. Following incubation for 19 h in 5% CO₂ at 37 °C, plates were briefly centrifuged (1000 rpm, 5 min). A 10 μ l aliquot from each well was transferred to a second assay plate (Costar 3709) for A β 1–40 measurements. Antibody cocktails were freshly prepared by dilution into 40 mM Tris–HCl (pH 7.4) with 0.2% BSA and added to assay plates. For the A β 40 measurements, antibodies specific for the A β 40 neoepitope (TSD, developed at BMS; conjugated to the Wallac reagent (Perkin-Elmer)) and 26D6 as described above were mixed and 20 μ l of the mixture was added to the 10 μ l aliquots which had been removed previously from the cell plate yielding a final concentration of 1.6 ng/well TSD and 17.5 ng/well 26D6. Assay plates containing antibodies were sealed with aluminum foil and incubated overnight at 4 °C. Signal was determined using a Viewlux counter (Perkin-Elmer) and IC₅₀ values determined using curve fitting in CurveMaster (Excel-Fit based data analysis package). Also, see Smith, D. W.; Munoz, B.; Srinivasan, K.; Bergstrom, C. P.; Chaturvedula, P. V.; Deshpande, M. S.; Keavy, D. J.; Lau, W. Y.; Parker, M. F.; Sloan, C. P.; Wallace, O. B.; Wang, H. H. WO 0050391.
- Roberts, S. B.; Hendrick, J. P.; Vinitzky, A.; Lewis, M.; Smith, D. W.; Pak, R. Isolation of functionally active γ -secretase presenilin 1 complex and fluorescence assay for γ -secretase activity and inhibitors. US 2004, 0121411 A1.
- Purchased from ComGenex Corporation as part of a collection of sulfonamides.
- Recently disclosed in a patent, Martin, N.; preparation of *N*-substituted heterocyclic sulfonamides for treating cognitive disorders. US 2006/0270657A1.
- Pellegata, R.; Pinza, G.; Pifferi, G. *Synthesis* **1978**, 614.
- The 3-amino-2-piperidone was synthesized from D-ornithine following the method of Pellegata (9). The 3-amino-2-pyrrolidinone was purchased from Ramidus AB.
- Possible clarifications for the 10-fold increase in activity include but are not limited to: antagonism or partial agonist activity by the inactive enantiomer, chiral ligand regulated enzyme activity, allosteric binding by one of the enantiomers or even relative error in the binding assay. These hypothetical explanations are being explored further.
- Determination of A β , full length APP, and APP carboxy-terminal fragments, brain tissues was performed following the procedure as described previously. Barten, D. M.; Guss, V. L.; Corsa, J. A.; Loo, A.; Hansel, S. B.; Zheng, B.; Munoz, K.; Srinivasan, K.; Wang, B.; Roberson, B. J.; Polson, C. T.; Wang, J.; Roberts, S. B.; Hendrick, J. P.; Anderson, J. J.; Loy, J. K.; Denton, R.; Verdoorn, T. A.; Smith, D. W.; Felsenstein, K. M. *J. Pharmacol. Exp. Ther.* **2005**, 312, 635.
- Hsiao, K.; Chapman, P.; Nilsen, S.; Eckman, C.; Havigaya, Y.; Younkin, S.; Yang, F.; Cole, G. *Science* **1996**, 274, 99.

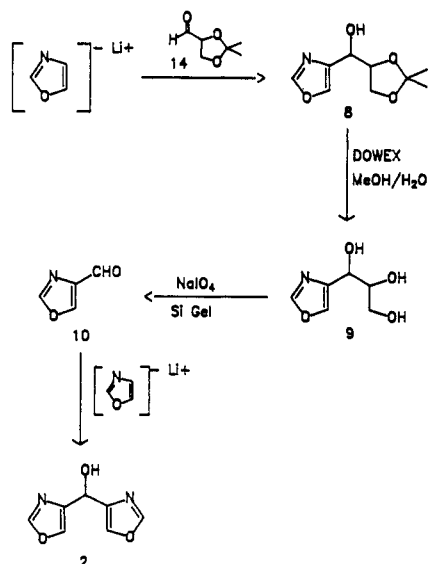


Figure 4. Symmetrical bis(oxazolyl)methanol 2.

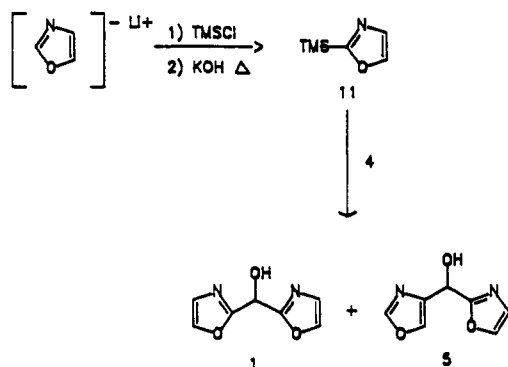


Figure 5. Bis(oxazolyl)methanols 1 and 5.

stereoisomers. Hydrolysis of the acetonide group is accomplished using Dowex 50 in moist methanol to give a quantitative yield of triol 9. Oxidative cleavage of 9 using a heterogeneous reagent formed by adsorption of aqueous NaIO_4 onto silica gel affords 1,3-oxazole-4-carboxaldehyde (10) as a solid in 70% yield after chromatography. Treatment of 10 with 1.3 equiv of lithiooxazole gives 2 in 62% isolated yield.

A low-yielding preparation of 1 is shown in Figure 5. Excess 2-(trimethylsilyl)-1,3-oxazole (11) and 1,3-oxazole-2-carboxaldehyde (4) are heated neat at 70 °C for 90 min to afford a mixture of 1 and 5 (ca. 1:1, 21% combined yield), which are separable by chromatography. In this sense 2-(trimethylsilyl)-1,3-oxazole behaves as both 2- and 4-lithiooxazole synthons with aldehydes. This is in contrast with literature precedents for thiazole and substituted oxazoles where reaction of 2-TMS derivatives with aldehydes give high-yielding and regioselective reactions, affording only 2-substituted products.^{2,4,6}

In summary, the equilibrium between 2-lithiooxazole and the ring-opened lithium enolate provides the basis for the ambident nucleophilicity observed for "lithiooxazole". Highly reactive, oxophilic electrophiles such as TMS-Cl and D_2O react at oxygen, aldehydes react at the 4-position, and most other weaker electrophiles either react at the 2-position or do not react. In all instances high regioselectivity is observed, i.e. mixtures of 0-, 2- and 4-substituted products are typically not found. The unusual preference for 4-substitution seen with aldehydes appears to be related to their low oxophilicity and their ability to react at lower temperatures. The fact that traces of the 2-sub-

stituted product, 13b, are seen when benzaldehyde is allowed to react with lithiooxazole at room temperature is supportive of this regioselectivity hypothesis. By reacting 2-(trimethylsilyl)-1,3-oxazole with aldehydes it is possible to alter the regioselectivity of addition, affording low yields of both 4- and 2-substituted products. The isomeric bis(oxazolyl)methanols, 1, 2 and 5, may be prepared from "lithiooxazole" by three different strategies.

Registry No. 1, 130551-89-2; 2, 130551-90-5; 4, 65373-52-6; 5, 130551-91-6; 6, 130551-92-7; 7a, 130551-93-8; 8 (isomer 1), 130551-94-9; 8 (isomer 2), 130551-95-0; 9, 130551-96-1; 10, 118994-84-6; 11, 120629-79-0; 12, 130551-97-2; 13a, 130551-98-3; 13b, 130552-00-0; 14, 5736-03-8; 15, 67245-00-5; 16, 130551-99-4; BuCHO, 110-62-3; PhCHO, 100-52-7; PhCOPh, 119-61-9; HCO_2Et , 109-94-4; TMS-Cl, 75-77-4; BuI, 542-69-8; PhCH_2Br , 100-39-0; $(\text{EtO})_2\text{CO}$, 105-58-8; HCONMe_2 , 68-12-2; oxazole, 288-42-6.

Supplementary Material Available: Experimental details for representative reactions, spectral data, analytical data, and ^1H NMR spectra of new compounds (25 pages). Ordering information is given on any current masthead page.

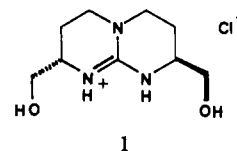
Synthesis of Secondary Amines by Rhodium Catalyzed Hydrogenation of Nitriles

Amalia Galán,[†] Javier de Mendoza,^{*,†} Pilar Prados,[†] Javier Rojo,[†] and Antonio M. Echavarren^{*,†}

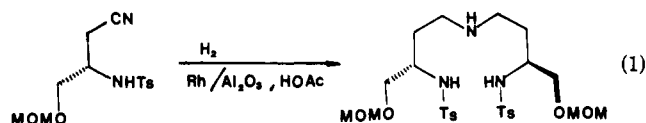
Departamento de Química, C-I, Universidad Autónoma de Madrid, Cantoblanco, 28049-Madrid, Spain, and Instituto de Química Orgánica, CSIC, Juan de la Cierva 3, 28006-Madrid, Spain

Received May 1, 1990

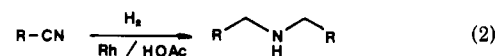
We recently reported the preparation of the first example of a C_2 symmetric, chiral guanidine 1 and its enantiomer starting from L- or D-asparagine, respectively.¹ These chiral guanidines complex aromatic carboxylate anions² and phosphate containing guests.^{3,4} The high



efficiency of the reported syntheses relied on the one-step assemblage of a protected triamine dimer by a rhodium-catalyzed hydrogenation of nitrile 2 (eq 1).



As part of a broader program aimed at developing chiral anion receptors based on guanidine subunits, we examined the generality of this secondary amine synthesis for the preparation of the key synthetic intermediates (eq 2).

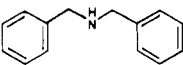
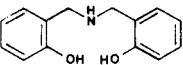
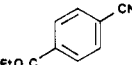
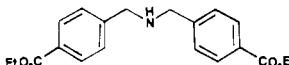
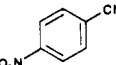
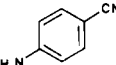
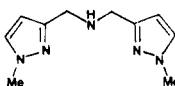
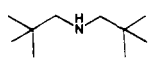
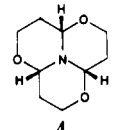
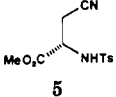
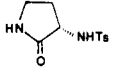
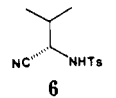
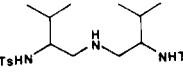


The catalytic hydrogenation of nitriles is usually complicated by the formation of mixtures of primary, secondary, and tertiary amines.⁵ The composition of the reduction products depends markedly on the nature of the

[†] Universidad Autónoma de Madrid.

^{*} Instituto de Química Orgánica, CSIC.

Table I^a

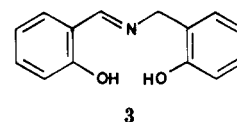
entry	nitrile	amine	yield, %
1			85
2			83
3			72
4			95
5			79 ^b
6			80 ^c
7	$\text{CH}_3(\text{CH}_2)_{16}\text{CN}$	$\text{CH}_3(\text{CH}_2)_{17}\text{NH}-(\text{CH}_2)_{17}\text{CH}_3$	78 ^c
8	$\text{HO}-\text{CH}_2\text{CH}_2\text{CN}$		70
9			76
10 ^d			70

^a Unless otherwise stated, 5% Rh on alumina was used in the reduction. ^b Characterized as the *N*-acetyl derivative. ^c Isolated as the hydrochloride. ^d The hydrogenation was performed over 5% Rh on carbon catalyst.

metal catalysts, on the reaction temperature and hydrogen pressure, and on the nitrile structure.⁵ For the conversion of nitriles into primary amines under mild conditions (room temperature, 2–3 atm of hydrogen), the use of rhodium catalysts in the presence of ammonia in alcoholic solvents has been recommended.^{6,7} In the absence of ammonia, the catalytic hydrogenation has been reported to lead instead to mixtures, with secondary amines as the major products.^{5–7} In our hands such a procedure proved to be unreliable, and complex mixtures of amines were obtained when methanol or ethanol was used as solvent. In this paper we report that the preparation of secondary amines from nitriles can be carried out with rhodium

catalysts in acetic acid under ambient conditions in good yields.

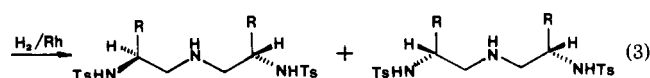
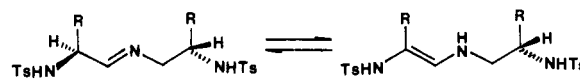
The results of the catalytic hydrogenation of nitriles with rhodium on alumina or carbon are summarized in Table I. The reaction appears to be general. Aromatic (entries 1–3), heteroaromatic (entry 5), and aliphatic nitriles (entries 6, 7, and 10) are readily hydrogenated to secondary amines under 1 atm of hydrogen at room temperature in glacial acetic acid for 20–30 h. Presumably the acidic solvent promotes the condensation of the primary amines with the aldimines leading to the desired secondary amines. In one instance (entry 2) the intermediate imine 3 could be isolated as a byproduct. None of the tertiary amines were detected (however, see below), although small amounts of primary amines were observed in some instances in the crude reaction mixtures. These byproducts were minimized by increasing the nitrile concentration.^{5b}



The hydrogenation tolerates OH, CO₂Et, and NHTs functional groups (entries 2, 3, and 10) and does not seem to be sensitive to steric hindrance in the α-position of the nitrile (entries 6 and 10). However, not unexpectedly, an aromatic nitro group is reduced in high yield under the reaction conditions (entry 4).

Surprisingly, while the reduction of 2-hydroxybenzonitrile proceeded uneventfully (entry 2), the aliphatic analogue, 3-hydroxypropanenitrile, affords the interesting tertiary amine 4 as a single isomer (entry 8), as a result of the trimerization of the intermediate primary imine. The structure was assigned on the basis of its 300-MHz ¹H NMR spectrum, which showed coupling constants between the C-2, C-3, and C-4 protons as expected for a tetrahydro[1,3]oxazine ring in the chair conformation.⁸ Furthermore, the ¹³C NMR spectrum showed only three carbon resonances of the C₃ symmetric amine. Consistently with the assigned trans-fused structure, with a syn arrangement of the three oxygens and the nitrogen lone electron pair, protonation with trifluoroacetic acid yields a stable ammonium salt. To the best of our knowledge, 4 constitutes the first member of this heterocyclic ring system. The formation of a secondary amine was also prevented by formation of a lactam in the reduction of the β-cyanoalanine derivative 5 (entry 9).

The catalytic hydrogenation of optically pure nitrile 6, obtained in four steps from L-valine, was also examined. In this case, the intermediate imine 7, formed in the hydrogenation of 6, could exist in equilibrium with the enamine 8, yielding, after hydrogenation, a mixture of (*R,S*)-9 and its *meso* isomer 10 (eq 3). Alternatively, complete



racemization could take place at the primary imine stage

(1) Echavarren, A.; Galán, A.; de Mendoza, J.; Salmerón, A.; Lehn, J.-M. *Helv. Chim. Acta* 1988, 71, 685.

(2) Echavarren, A.; Galán, A.; Lehn, J.-M.; de Mendoza, J. *J. Am. Chem. Soc.* 1989, 111, 4994.

(3) Deslongchamps, G.; Galán, A.; de Mendoza, J.; Rebek, J., Jr., manuscript in preparation.

(4) Schmidtchen, F. P. *Tetrahedron Lett.* 1989, 30, 4493.

(5) For reviews on the catalytic hydrogenation of nitriles, see: (a) Cerveny, L., Ed. *Catalytic Hydrogenation. In Studies in Surface Science and Catalysis*; Elsevier: Amsterdam, 1986; Vol. 27, Chapter 4. (b) Rylander, P. *Catalytic Hydrogenation in Organic Syntheses*; Academic: New York, 1979; Chapter 8. (c) Freifelder, M. *Catalytic Hydrogenation in Organic Synthesis. Procedures and Commentary*; Wiley-Interscience: New York, 1978; Chapter 6.

(6) Freifelder, M. *J. Am. Chem. Soc.* 1960, 82, 2386.

(7) Reduction of 3-indoleacetonitrile in the absence of ammonia was reported to yield predominantly the secondary amine, contaminated with some tryptamine (yield not stated). In other examples the yield of secondary amine ranged from 10 to 20%, in reactions run in the presence of ammonia.⁶

(8) Crabb, T. A.; Hall, M. J. *J. Chem. Soc., Perkin Trans. 2* 1973, 1379.

leading to racemic **9** and *meso*-**10** by an analogous process. In the event, the catalytic hydrogenation of **6** proceeded smoothly over Rh on carbon, which gave more reproducible results, furnishing an inseparable mixture of **9** and **10** (entry 10). Although variable optical rotations were obtained, analysis of the ^1H NMR spectrum after the addition of the chiral shift reagent (+)-Eu(tfc) $_3$ gave rise to a similar splitting of the *N*-tosyl methyl resonances to that shown with the secondary amines derived from racemic nitrile (*rac*-**6**), prepared from *rac*-valine. The ratio between the *d*, *l* and *meso* secondary amines was estimated to be approximately 1:1 by integration of the NH protons of the corresponding *N*-acetyl derivatives in a ^1H NMR spectrum measured at 50 °C in (CD $_3$) $_2$ SO. At lower temperatures or in deuteriochloroform solutions the spectra were complicated by the presence of several rotamers. Similarly, the presence of amide rotamers precluded any accurate determination of the diastereoisomeric excess based on the analysis of the ^1H or ^{19}F NMR spectra of the derived Mosher amides.¹⁰

In summary, the catalytic hydrogenation of nitriles to secondary amines under ambient conditions has been described. This synthetic method could be particularly useful for the rapid assemblage of functionalized subunits in the preparation of macrocyclic structures.

Experimental Section

General Procedure for the Catalytic Hydrogenation of Nitriles. A mixture of nitrile (0.35 mmol) in glacial acetic acid (3 mL) and 5% rhodium on alumina (400 mg) was stirred at 23 °C under 1 atm of H $_2$ for 24–30 h. The progress of the reaction was monitored by TLC. The resulting suspension was filtered through Celite, and the filtrate was partitioned between dichloromethane and saturated aqueous sodium bicarbonate solution. In entries 6 and 7 the crude secondary amine was treated with 1 M HCl in methanol at 23 °C for 1 h, followed by evaporation of the solvent to give the amine hydrochloride. Isolated yields of pure amines are shown in Table I.

Acknowledgment. This work was supported by the "Comisión Asesora de Investigación Científica y Técnica" (CAICYT, Grant 84-0410). We gratefully acknowledge Prof. J. Elguero for a gift of 3-cyano-1-methylpyrazole and A. Salmerón for some hydrogenation experiments.

Supplementary Material Available: Experimental details and spectroscopic data for (S)- and (R,S)-*N*-tosylvaline, *N*-tosylvalinamide, and the compounds in Table I and ^1H NMR and COSY spectra for amine **4** (9 pages). Ordering information is given on any current masthead page.

(9) (+)-Eu(tfc) $_3$ = europium(III) tris[3-(trifluoromethylhydroxymethylene)-(+)-camphorato].

(10) Dale, J. A.; Dull, D. L.; Mosher, H. S. *J. Org. Chem.* 1969, 34, 2543.

Synthesis of Castasterone and Formal Synthesis of Brassinolide from Stigmasterol via a Selenosulfonation Approach

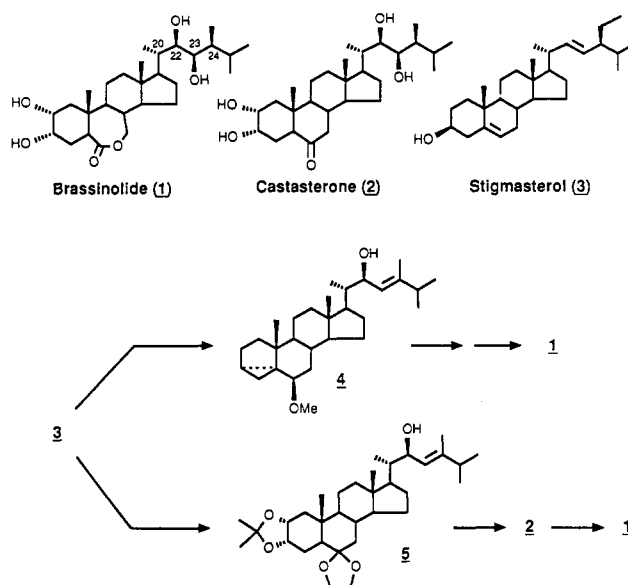
Thomas G. Back* and M. Vijaya Krishna

Department of Chemistry, University of Calgary, Calgary, Alberta, Canada T2N 1N4

Received May 14, 1990

Brassinolide (**1**) is a steroidal plant growth-promoter that was first isolated by Grove and co-workers¹ from *Brassica*

Scheme I



napus L. pollen in 1979. Its low abundance in natural sources and intriguing structure have made it the target of several syntheses.^{2,3} The unusual B-ring lactone and the four contiguous chiral centers at C-20, C-22, C-23, and C-24, including the vicinal diol at C-22 and C-23, are structural features that require special attention. Certain related sterols such as castasterone (**2**) exhibit similar activity,⁴ and their syntheses are also of interest.^{3c,f,k}

We recently reported the preparation of the allylic alcohol **4** from stigmasterol (**3**)⁵ using selenosulfonation methodology.⁶ Alcohol **4** has also been prepared by other methods^{3a,n} and is a useful intermediate for the elaboration of brassinosterol side chains. We now report the selenosulfonation-based preparation of the more highly elaborated intermediate **5**, which provides more direct access

(1) Grove, M. D.; Spencer, G. F.; Rohwedder, W. K.; Mandava, N.; Worley, J. F.; Warthen, J. D., Jr.; Steffens, G. L.; Flippen-Anderson, J. L.; Cook, J. C., Jr. *Nature (London)* 1979, 281, 216.

(2) For reviews of brassinosteroids, see: (a) Chen, S. C. *Chem. Can.* 1983, 35 (September), 13. (b) Singh, H.; Bhardwaj, T. R. *Indian J. Chem., Sect. B* 1986, 25B, 989.

(3) For previous syntheses of brassinolide, see: (a) Fung, S.; Siddall, J. B. *J. Am. Chem. Soc.* 1980, 102, 6580. (b) Ishiguro, M.; Takatsuto, S.; Morisaki, M.; Ikekawa, N. *J. Chem. Soc., Chem. Commun.* 1980, 962. (c) Takatsuto, S.; Yazawa, N.; Ishiguro, M.; Morisaki, M.; Ikekawa, N. *J. Chem. Soc., Perkin Trans. 1* 1984, 139. (d) Mori, K.; Sakakibara, M.; Ichikawa, Y.; Ueda, H.; Okada, K.; Umemura, T.; Yabuta, G.; Kuwahara, S.; Kondo, M.; Minobe, M.; Sogabe, A. *Tetrahedron* 1982, 38, 2099. (e) Sakakibara, M.; Okada, K.; Ichikawa, Y.; Mori, K. *Heterocycles* 1982, 17, 301. (f) Mori, K.; Sakakibara, M.; Okada, K. *Tetrahedron* 1984, 40, 1767. (g) Sakakibara, M.; Mori, K. *Agric. Biol. Chem.* 1983, 47, 663. (h) Thompson, M. J.; Mandava, N. B.; Meudt, W. J.; Lusby, W. R.; Spaulding, D. W. *Steroids* 1981, 38, 567. (i) Donaubauer, J. R.; Greaves, A. M.; McMorris, T. C. *J. Org. Chem.* 1984, 49, 2833. (j) Kametani, T.; Katoh, T.; Tsubuki, M.; Honda, T. *J. Am. Chem. Soc.* 1986, 108, 7055. (k) Kametani, T.; Katoh, T.; Fujio, J.; Nogiwa, I.; Tsubuki, M.; Honda, T. *J. Org. Chem.* 1988, 53, 1982. (l) Kametani, T.; Kigawa, M.; Tsubuki, M.; Honda, T. *J. Chem. Soc., Perkin Trans. 1* 1988, 1503. (m) Wei-Shan, Z.; Jiang, B.; Pan, X. *J. Chem. Soc., Chem. Commun.* 1989, 612. (n) Anastasia, M.; Allevi, P.; Ciuffreda, P.; Fiecchi, A.; Scala, A. *J. Org. Chem.* 1984, 49, 4297. (o) Anastasia, M.; Ciuffreda, P.; Fiecchi, A. *J. Chem. Soc., Perkin Trans. 1* 1983, 379.

(4) (a) Takatsuto, S.; Yazawa, N.; Ikekawa, N.; Takematsu, T.; Takeuchi, Y.; Koguchi, M. *Phytochem.* 1983, 22, 2437. (b) Thompson, M. J.; Meudt, W. J.; Mandava, N. B.; Dutky, S. R.; Lusby, W. R.; Spaulding, D. W. *Steroids* 1982, 39, 89.

(5) Back, T. G.; Brunner, K.; Krishna, M. V.; Lai, E. K. Y. *Can. J. Chem.* 1989, 67, 1032.

(6) (a) Back, T. G. In *Organoselenium Chemistry*; Liotta, D., Ed.; Wiley: New York, 1987; Chapter 7, pp 347–354. (b) Back, T. G. In *The Chemistry of Organic Selenium and Tellurium Compounds*; Patai, S., Ed.; Wiley: Chichester, 1987; Volume 2, Chapter 3, pp 136–138.