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Act: 400 OPOS/OBSERVER Folios: 120

FORMULARIO ÚNICO DE OPOSICIÓN

①

OPOSICIÓN A

- | | |
|--|--|
| ☒ Patente de Invención | ☒ Marca Colectiva |
| ☒ Patente de Modelo de Utilidad | ☒ Marca de Certificación |
| ☒ Diseño Industrial | ☒ Lema Comercial |
| ☒ Esquema de Trazado para Circuitos Integrados | |
| ☒ Marcas de Productos o Servicios | |

②

Número del expediente: 08-035238

Solicitante: AVENTIS PHARMACEUTICALS INC

**SOLICITUD
PUBLICADA**

Apoderado: MILIO FERRERO

Título de la nueva creación o denominación del signo: SAL DE DIHIDROGENO
FOSFATO DE UN ANTAGONISTA DEL RECEPTOR DE PROSTAGLANDINA D2

Gaceta: 604

③ **OPOSICIÓN PRESENTADA POR:**

SOLICITANTE	Nombre: <u>PROCAPS S.A.</u> Dirección: <u>CAJETA 80 No. 78b-201</u> Nacionalidad o Domicilio: <u>COLOMBIA</u> Lugar de Constitución: <u>BARRANQUILLA</u> Teléfono: <u>371 99 00</u> Fax: <u>373 08 18</u> E-mail:	IDENTIFICACIÓN C.C. ☐ NIT ☒ C.E. ☐ Otro ☐ Cual Número: <u>890.106.527-5</u>
REPRESENTANTE O APODERADO	Nombre: <u>CIELO ANGELA PEÑA RODRIGUEZ</u> Dirección: <u>CARRERA 13 No. 119-95</u> Teléfono: <u>(571)213 12 13</u> Fax: <u>(571)612 19 79</u> E-mail: <u>negocios@optimum-co.com</u>	IDENTIFICACIÓN C.C. ☒ NIT ☐ C.E. ☐ Otro ☐ Cual Número: <u>51.940.252</u> TP <u>82701</u>

④ **FUNDAMENTOS DE LA OPOSICIÓN**

Art 14, 16, 18, 20 y 30 de la Decisión 486 de la CAN

Causal: No cumple con los requisitos de patentabilidad.

Signo opositor:

Justificación:

La presente solicitud no cumple con los requisitos de patentabilidad dado que lo
revelado, ya se encontraba en el estado de la técnica o es posible derivarlo de la
misma tal y como se demostrara en el capítulo "Fundamento de Hechos".

⑤ Comprobante de pago No. _____

Fecha _____

⑥ ANEXOS

- ☒ Comprobante de pago de la tasa.
- ☒ Poderes, si fuere el caso.
- ☒ Pruebas de los fundamentos de la oposicion.
- ☐ Documentos que acrediten el legitimo interés, si fuere el caso.
- ☒ Documento que acredita la existencia y representación legal de las partes, cuando sean personas jurídicas.

⑦

NOMBRE CIELO ANGELA PEÑA

FIRMA

C.C. 51.940.252

TP. 82701



Derecho de la Competencia, Propiedad
Industrial y Comercio Exterior

Señora Jefe,

DIVISIÓN DE NUEVAS CREACIONES

Superintendencia de Industria y Comercio

E. S. D.

Referencia : Expediente N° 08 035238
Asunto : Oposición a la solicitud de patente de Invención titulada
"SAL DE HIDROGENO FOSFATO DE UN
ANTAGONISTA DEL RECEPTOR DE
PROSTAGLANDINA D2"
Solicitante : AVENTIS PHARMACEUTICALS INC
Opositora : PROCAPS S.A.

Publicada en la ~~Gaceta~~ de la Propiedad Industrial
N° 604 del 29 de Mayo de 2009

Yo, **CIELO ANGELA PEÑA RODRIGUEZ**, abogada en ejercicio, identificada como aparece al pie de su firma, con tarjeta profesional No. **82701** del Consejo Superior de la Judicatura, en mi condición de apoderada de la sociedad **PROCAPS S.A.** conformada bajo las leyes de la República de Colombia y domiciliada en la ciudad de Barranquilla, Colombia, atentamente manifiesto que estando dentro del término de ley y por orden expresa de mi representada, presento oposición a la concesión del registro de la Patente de Invención titulada "SAL DE HIDROGENO FOSFATO DE UN ANTAGONISTA DEL RECEPTOR DE PROSTAGLANDINA D2", cuyo titular es **AVENTIS PHARMACEUTICALS INC.**, y pido a Usted declarar fundada esta oposición y en consecuencia negar el registro de la patente solicitada.

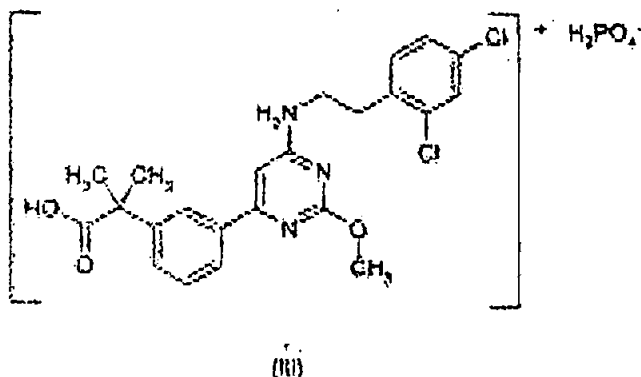
1. INTERÉS PARA ACTUAR ✓

Conforme a lo dispuesto en el artículo 42 de la Decisión 486 de 2000 de la CAN, estando dentro del término estipulado por la ley, manifiesto el legítimo interés de nuestra representada para oponerse al registro de la patente de la referencia, atendiendo a que la solicitud pretendida no cumple con los requisitos dispuestos en la ley como se analizará más adelante y de ser concedida afectaría directamente la comercialización de algunos productos de mi representada, que contienen, en particular un antagonista del receptor de prostaglandina D2. Por lo tanto, solicito respetuosamente a ese Despacho se sirva tener en cuenta la presente oposición dentro del trámite administrativo que se surte en esta Superintendencia.

2. FUNDAMENTOS DE HECHOS

2.1. La solicitud objeto de la presente fue presentada el 8 de abril de 2008 reivindicando prioridad bajo la solicitud US20050726290P del 2005-10-13; y fue publicada en Colombia, en la Gaceta de la Propiedad Industrial N° 604 del 29 de Mayo de 2009, cuya publicación internacional corresponde a la WO2007047378 del 2007-04-26.

2.2. La solicitud colombiana 08 035238 objeto de la presente oposición, se refiere a un compuesto de Fórmula (III):



en una forma cristalina y una composición farmacéutica que comprende una cantidad farmacéuticamente eficaz del compuesto de la fórmula I, en mezcla con un vehículo farmacéuticamente aceptable; así como un método para tratar una enfermedad alérgica, mastocitosis sistémica, un trastorno acompañado por activación sistémica de mastocitos, choque anafiláctico, broncoconstricción, bronquitis, urticaria, eczema, enfermedades acompañadas por picor, inflamación, enfermedades pulmonares obstructivas crónicas, lesión de reperusión isquémica, accidente cerebrovascular, artritis reumatoide crónica, pleuresía, o colitis ulcerosa, en un paciente que lo necesita, que comprende administrar al paciente una cantidad farmacéuticamente eficaz del compuesto.

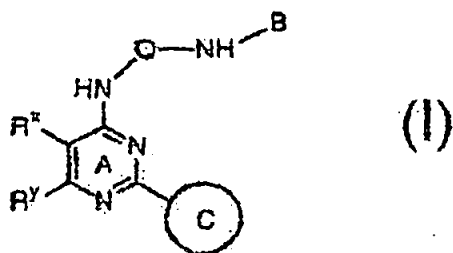
2.3. En primera instancia, se debe advertir que las reivindicaciones se refieren a un método de tratamiento y no sólo a la composición farmacológica o a un método de fabricación mediante la cual se obtenga un producto tangible y según la legislación, decisión 486 de la Comunidad Andina de Naciones, Artículo 14.- "Los Países Miembros otorgarán patentes para las invenciones, sean de producto o de procedimiento (...)", los usos no están contemplados como patentables; y, Artículo 20.- "No serán patentables (...) d) los métodos terapéuticos o quirúrgicos para el tratamiento humano o animal, así como los métodos de diagnóstico aplicados a los seres humanos o a animales".

Solo serán patentables los productos o procedimientos. Por lo tanto a luz de la norma, dicha materia referente al uso y a un método de tratamiento no sería patentable.

2.4. Ahora bien, con base en el artículo 14 de la Decisión 486 de la CAN consagra lo siguiente: *"Los países miembros otorgarán patentes para las invenciones, sean de producto o procedimiento, en todos los campos de la tecnología, siempre que sean nuevas, tengan nivel inventivo y sean susceptibles de aplicación industrial"*. Así las cosas, las invenciones objeto de patente deben ser nuevas y tener nivel inventivo. Bien, pues antes de la fecha de prioridad de esta solicitud se encuentran los siguientes documentos que afecta la patentabilidad de la presente solicitud:

- D1: WO03049739 publicada el 19 de junio de 2003.

2.5. Ahora bien, además que el presente se refiere a un uso y a un método de tratamiento que no es patentable a la luz de la norma en Colombia, su uso y aplicación, es posible derivarlo de manera evidente del estado de la técnica, particularmente a partir del documento D1, que en la descripción proporciona un compuesto de fórmula (I):



2.6. o un derivado farmacéuticamente aceptable como compuestos inhibidores de la proteína kinasa, en particular inhibidores de proteína kinases GSK-3, donde dicho compuesto revela una similar propiedad farmacéutica, contra la alergia y/o la inflamación, particularmente a partir de las reivindicaciones 29 y 30, la página 22



hasta la página 17, línea 2. Por lo tanto, este documento objeto de oposición a la luz del documento D1 carece evidentemente de ALTURA O NIVEL INVENTIVO, dado que cualquier persona versada en la materia puede llegar de manera evidente, combinando la materia revelada aquí en la anterioridad D1 con su conocimiento medio sobre la materia, para llegar a conformar un compuesto de la fórmula I, en mezcla con un vehículo farmacéuticamente aceptable; así como un método para tratar una enfermedad alérgica y/o inflamación entre otros.

2.7. En consecuencia y de acuerdo a lo descrito anteriormente, se deriva que la solicitud colombiana 08 035238 no puede pretender un monopolio por patente toda vez que lo que pretende no cumple con dos de los tres requisitos necesarios para su protección.

2.8. Que por consiguiente, respecto a la solicitud pretendida se tiene que:

2.8.1. **CARENCIA DE ALTURA INVENTIVA.** Según la Decisión 486 de la Comunidad Andina de Naciones, Artículo 18.- *"Se considerará que una invención tiene nivel inventivo, si para una persona del oficio normalmente versada en la materia técnica correspondiente, esa invención no hubiese resultado obvia ni se hubiese derivado de manera evidente del estado de la técnica."* A la fecha de prioridad, 13 de octubre de 2005, a partir del documento D2 en combinación con D1, puede llegar de manera evidente a un compuesto de la fórmula I, en mezcla con un vehículo farmacéuticamente aceptable; así como un método para tratar una enfermedad alérgica y/o inflamación entre otros, sobre el cual busca protección en el capítulo reivindicatorio.

2.8.2. **CARENCIA DE APLICACIÓN INDUSTRIAL** La Decisión 486 de la CAN consagra en su artículo 14 lo siguiente: *"Los países miembros otorgarán patentes*



para las invenciones, sean de producto o procedimiento, en todos los campos de la tecnología, siempre que sean nuevas, tengan nivel inventivo y sean susceptibles de aplicación industrial". La presente solicitud carece de aplicación Industrial ya que como se demostró anteriormente, algunas cláusulas reclaman el método terapéutico y estos no son aplicables industrialmente porque primero no se obtiene un producto o proceso; y segundo no es reproducible o repetible a escala industrial. Por lo tanto, el objeto de la presente invención referido a los usos y métodos terapéuticos, no cumplen con el requisito de la aplicación industrial.

2.9. Dado lo anterior, es posible deducir que la solicitud y lo reivindicado no es objeto de patentabilidad pues es contrario a lo que dicta la Decisión 486 de la Comunidad Andina de Naciones, Artículo 14.- *"Los Países Miembros otorgarán patentes para las invenciones, sean de producto o de procedimiento, en todos los campos de la tecnología, siempre que sean nuevas, tengan nivel inventivo y sean susceptibles de aplicación industrial."* La solicitud pretendida no cumple con dos de los tres requisitos de patentabilidad.

2.10. Por todo lo anterior, atentamente solicito a usted que se sirva declarar fundada la presente oposición y negar el registro Patente de invención denominada **"SAL DE HIDROGENO FOSFATO DE UN ANTAGONISTA DEL RECEPTOR DE PROSTAGLANDINA D2 "**, cuyo titular es **AVENTIS PHARMACEUTICALS INC**, solicitud Colombiana que apareció publicada en la Gaceta de la Propiedad Industrial N° 604 del 29 de Mayo de 2009.

3. PRUEBAS



De conformidad con lo dispuesto por las normas vigentes, solicito a usted tener como prueba en este asunto los siguientes:

- D1: WO03049739 publicada el 19 de junio de 2003.

4. FUNDAMENTO DE DERECHO

Fundamento esta observación en las normas legales siguientes:

- 4.1. Numeral 1 del artículo 586 del Código de Comercio.
- 4.2. Artículo 42 de la Decisión 486 de la Comisión del Acuerdo de Cartagena.
- 4.3. En las demás normas concordantes.

5. ANEXOS

Para los efectos correspondientes anexo al presente escrito los siguientes documentos:

1. Poder para actuar en el presente.
 2. Documento que acredita al representante legal de PROCAPS S.A.
 3. Recibo de caja del respectivo pago de tasa.
 4. Copias de los documentos:
- D1: WO03049739 publicada el 19 de junio de 2003.



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Derecho de la Competencia, Propiedad
Industrial y Comercio Exterior

6. NOTIFICACIONES

Para efectos de notificaciones que por disposición del artículo 50 del Decreto 01 de 1984 debe hacer su Despacho, informo que mi representada y la suscrita recibiremos notificaciones en la Secretaría de su Despacho o en mis oficinas situadas en la Carrera 13 N° 119-95, Of. 104 de esta ciudad de Bogotá.

Señor Superintendente,

CIELO ANGELA PEÑA RODRIGUEZ

C.C. 51'940.252 de Bogotá

T.P.A. 82701 del C.S. de la J.



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CAMARA DE COMERCIO
DE BARRANQUILLA
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CERTIFICADO DE EXISTENCIA Y REPRESENTACION LEGAL O DE INSCRIPCION DE DOCUMENTOS.

PROCAPS S.A.

NIT: 890.106.527-5

EL SUSCRITO SECRETARIO DE LA CAMARA DE COMERCIO DE BARRANQUILLA, CON FUNDAMENTO EN LAS INSCRIPCIONES DEL REGISTRO MERCANTIL:

C E R T I F I C A

Que por Escritura Pública No. 1,190 del 22 de Julio de 1976, otorgada en la Notaria Tercera de Barranquilla, inscrito(as) en esta Cámara de Comercio el 28 de Julio de 1976 bajo el No. 6,070 del libro respectivo, fue constituida la sociedad limitada denominada "PRODUCTORA DE CAPSULAS DE GELATINAS LIMITADA PROCAPS LIMITADA".

C E R T I F I C A

Que por Escritura Pública No. 1,307 del 28 de Junio de 1979, otorgada en la Notaria Tercera de Barranquilla, inscrito(as) en esta Cámara de Comercio el 23 de Julio de 1979 bajo el No. 10,039 del libro respectivo, la sociedad antes mencionada se transformo en sociedad anonima bajo la denominacion social de "PRODUCTORA DE CAPSULAS DE GELATINA S.A." PROCAPS S.A.

C E R T I F I C A

Que por Escritura Pública No. 3,810 del 31 de Dic/bre de 1980, otorgada en la Notaria Primera de Barranquilla, inscrito(as) en esta Cámara de Comercio el 30 de Enero de 1981 bajo el No. 12,705 del libro respectivo, la sociedad antes mencionada se transformo en sociedad de responsabilidad limitada bajo al razon social de "PRODUCTORA DE CAPSULAS DE GELATINA LIMITADA PROCAPS LIMITADA".

C E R T I F I C A

Que por Escritura Pública No. 3,755 del 10 de Nov/bre de 1983, otorgada en la Notaria Unica de Soledad, inscrito(as) en esta Cámara de Comercio el 22 de Nov/bre de 1983 bajo el No. 17,922 del libro respectivo, la sociedad antes mencionada se transformo en sociedad anonima bajo la denominacion social de "PRODUCTORA DE CAPSULAS DE GELATINA S.A." PROCAPS S.A.

C E R T I F I C A

Que por Escritura Pública No. 3,615 del 06 de Dic/bre de 1996, otorgada en la Notaria 2a. de Barranquilla, inscrito(as) en esta Cámara de Comercio el 20 de Dic/bre de 1996 bajo el No. 67,218 del

CERTIFICADO DE EXISTENCIA Y REPRESENTACION LEGAL O DE INSCRIPCION DE DOCUMENTOS.

PROCAPS S.A.-----
NIT 890.106.527-5.

Libro respectivo, la sociedad antes mencionada-----
cambio de razon social, por la denominacion LABORATORIOS PROCAPS S.A.

C E R T I F I C A

Que por Escritura Pública No. 3,775 del 18 de Dic/bre de 1996,
otorgada en la Notaria 2a de Barranquilla, inscrito(as) en esta
Cámara de Comercio, el 23 de Enero de 1997 bajo el No. 67,704 del
libro respectivo, la sociedad antes mencionada-----
cambio de razon social, por la denominacion PROCAPS S.A. -----

C E R T I F I C A

Que dicha sociedad ha sido reformada por las siguientes escrituras
y/o documentos privados:

Numero	aaaa/mm/dd	Notaria	No	Insc o Reg	aaaa/mm/dd
39	1979/01/18	Notaria 3a. de Barranquilla.	9,452		1979/01/24
992	1981/04/30	Notaria 1a. de Barranquilla	13,112		1981/05/06
1,464	1982/08/27	Notaria Unica de Soledad	15,533		1982/09/08
2,744	1983/08/18	Notaria Unica de Soledad	17,416		1983/08/26
3,826	1984/07/16	Notaria Unica de Soledad	19,554		1984/07/27
3,835	1985/08/26	Notaria Unica de Soledad	22,230		1985/09/04
2,260	1986/09/10	Notaria Unica de Soledad	24,995		1986/09/15
1,849	1989/07/11	Notaria 2a. de Barranquilla	33,909		1989/07/13
444	1990/02/21	Notaria 2a. de Barranquilla	36,101		1990/03/16
3,090	1991/12/17	Notaria 2a. de Barranquilla	43,993		1992/01/28
269	1993/02/01	Notaria 2a. de Barranquilla	48,428		1993/02/16
2,342	1993/07/28	Notaria 2a. de Barranquilla	50,582		1993/08/10
3,652	1993/11/09	Notaria 2a. de Barranquilla	51,798		1993/11/22
3,615	1996/12/06	Notaria 2a. de Barranquilla	67,218		1996/12/20
89	1997/01/16	Notaria 2a. de Barranquilla	67,704		1997/01/23
2,070	1997/07/17	Notaria 2a. de Barranquilla	70,627		1997/07/31
2,281	1997/08/04	Notaria 2a. de Barranquilla	70,813		1997/08/14
765	1999/04/22	Notaria 3a. de Barranquilla	80,628		1999/04/23
459	2001/02/21	Notaria 2a. de Barranquilla	91,502		2001/02/23
2,608	2001/10/05	Notaria 2a. de Barranquilla	95,771		2001/11/08
1,730	2004/07/29	Notaria 2. de Barranquilla	112,999		2004/08/26
416	2005/03/03	Notaria 2. de Barranquilla	116,364		2005/03/10
1,613	2005/07/28	Notaria 2. de Barranquilla	119,322		2005/08/18
710	2009/05/05	Notaria 3 a. de Barranquilla	150,130		2009/06/30
1,054	2009/06/25	Notaria 3 a. de Barranquilla	150,130		2009/06/30

C E R T I F I C A

Que de acuerdo con la(s) escritura(s) arriba citada(s), la sociedad
se rige por las siguientes disposiciones:

DENOMINACION O RAZON SOCIAL:

PROCAPS S.A.

SIGLA: PROCAPS.

DOMICILIO PRINCIPAL: Barranquilla.

NIT No: 890.106.527-5.

MATRICULA MERCANTIL: 24.802.



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CERTIFICADO DE EXISTENCIA Y REPRESENTACION LEGAL O DE INSCRIPCION DE DOCUMENTOS.

PROCAPS S.A.

NIT: 890.106.527-5

CERTIFICA

Dirección para notificaciones judiciales:

CL 80 No 78 B - 201

De la ciudad de Barranquilla.

CERTIFICA

DURACION: El término de duración de la sociedad se fijó hasta el 18 de Agosto de 2073.

CERTIFICA

OBJETO SOCIAL: El objeto principal de la sociedad sera: a) La fabricación, importación y comercialización de alimentos procesados y suplementos dietarios. b) La fabricación de capsulas y otros productos similares a partir de materiales tales como gelatinas u otros de distinta naturaleza, que puedan ser utilizados como envases o recipientes de productos y sustancias quimicas, farmaceuticas, alimenticias y cosmeticas, para uso y consumo humano y veterinario. c) La investigación, desarrollo y fabricación de toda clase de productos y sustancias quimicas, farmaceuticas, alimenticias y cosmeticas para uso y consumo humano, animal y vegetal. d) La compra y venta de materias primas, insumos y productos intermedios necesarios para los procesos de fabricación de sustancias quimicas, farmaceuticas, alimenticias y cosmeticas, asi como la comercialización interna y externa de los productos terminados. e) La compra, venta, importación, exportación y distribución de toda clase de elementos instrumentales y equipos medicos, quirurgicos, odontologicos y hospitalarios para la salud humana y animal. f) La compra, venta, exportación, fabricación, importación, distribución de dulces, confites, galletas y todo tipo de golosinas o alimentos para el consumo humano. g) Actuar como representante o agente de personas naturales y juridicas, nacionales y extranjeras en la realización de operaciones o transacciones relacionadas con la industria farmaceutica y en especial con cualquiera de las actividades descritas en los literales a), b), c), d) y e) antes descritos. h) Prestar los servicios de asesorias y consultoria en las areas administrativas, de mercadeo, analisis clinico, asistencia tecnica, investigación, costos y producción, exportaciones, importaciones, ventas, relacionadas con iguales o similares actividades a las que constituyen el objeto de PROCAPS S.A., asi como los de publicidad y promoción de productos quimicos, alimenticios, cosmeticos y

***** CONTINUA *****

CERTIFICADO DE EXISTENCIA Y REPRESENTACION LEGAL O DE INSCRIPCION DE DOCUMENTOS.

PROCAPS S.A.-----
NIT 890.106.527-5.

farmaceuticos para uso humano, animal o industrial. Adquirir, operar, administrar y explotar, a cualquier titulo, empresa o establecimientos dedicados a la investigacion, desarrollo, fabricacion o comercializacion de productos quimicos, farmaceuticos, alimenticios, hospitalarios o cosmeticos. En desarrollo de su objeto principal, la sociedad podra tomar interes social como accionista, socio o fundador de empresas que tengan igual o similar objeto, comprar, vender, importar y exportar maquinarias, insumos y repuestos requeridos para el desarrollo de sus actividades; tomar dinero en prestamo, financiar y garantizar las operaciones comerciales que celebre con terceros relativas a su objeto; celebrar y ejecutar todo tipo de actos y contratos necesarios para desarrollar sus operaciones; girar, aceptar, otorgar y protestar todo tipo de titulos valores e instrumentos negociables, comprar, vender y constituir gravámenes sobre bienes muebles e inmuebles, designar representantes apoderados en el pais y en el exterior y, en general, realizar cualquier acto o negocio que sea necesario o conveniente para el desarrollo de su objeto social y para la mejor proteccion de sus intereses corporativos o la de sus socios. La sociedad podra garantizar el cumplimiento de sus obligaciones adquiridas por terceros o por sus socios, para lo cual podra inclusive constituir gravámenes reales sobre sus bienes de cualquier naturaleza.

C E R T I F I C A		
CAPITAL	Nro Acciones	Valor Acción
Autorizado		
\$*****2,000,000,000	*****2,000,000	*****1,000
Suscrito		
\$*****1,229,071,000	*****1,229,071	*****1,000
Pagado		
\$*****1,229,071,000	*****1,229,071	*****1,000

C E R T I F I C A

ADMINISTRACION: La direccion y administracion de la sociedad corresponde a la Asamblea General de Accionistas, a la Junta Directiva, al Presidente, al Vicepresidente y a un Gerente General. Corresponde a la Junta Directiva las siguientes funciones y atribuciones entre otras: Autorizar cualquier acto o contrato cuya cuantia sea superior al equivalente en pesos Colombianos a doscientos cincuenta mil dolares de los Estados Unidos de America (US\$250,000), liquidados a la tasa de cambio representativa del mercado vigente el dia en que se surta la transaccion. Cuando se trate de operaciones en virtud de las cuales la sociedad garantice obligaciones de terceros o de los socios, se requerira que la operacion sea aprobada con el voto de por lo menos 2/3 partes de los integrantes de la Junta Directiva. La sociedad tendra un Presidente, quien ejercera la representacion legal de la sociedad y tendra las siguientes atribuciones entre otras: Ejecutar las decisiones de la Asamblea General de Accionistas y de la Junta Directiva. Ejercer la Representacion Legal de la sociedad en todos los actos y contratos que se

***** C O N T I N U A *****



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requieran para el desarrollo del objeto social, de conformidad con lo previsto en las leyes y en los presentes estatutos. Constituir apoderados judiciales y extrajudiciales, recibir notificaciones, absolver interrogatorios de parte, confesar obligaciones de la sociedad, transigir, desistir y allanar a la sociedad en cualquier asunto judicial. Aprobar y celebrar en nombre de la sociedad todo acto o contrato cuya cuantía sea igual o inferior al equivalente en pesos colombianos a doscientos cincuenta mil dolares de los Estados Unidos de America (US\$250.000), liquidados a la tasa de cambio representativa del mercado vigente el día en que se surta la transacción o celebración del acto. Las demás funciones que le correspondan como Representante Legal por disposición de la ley, de estos estatutos o de la Junta Directiva. El Presidente tendrá un suplente, designado por la Junta Directiva, quien reemplazara al Presidente en sus faltas temporales, absolutas o meramente accidentales, con entidades facultades y sin que sea necesario para ello acreditar la ausencia del principal. La sociedad tendrá un Vicepresidente designado por la Junta Directiva, quien también ejercerá la representación legal de la sociedad, pudiendo ejercerla conjunta o separadamente con el Presidente. El vicepresidente tendrá las siguientes facultades entre otras Ejecutar dentro de su competencia las decisiones de la Asamblea General de Accionistas, de la Junta Directiva y del Presidente. Ejercer la representación legal de la sociedad en todos los actos y contratos que se requieran para el desarrollo del objeto social, de conformidad con lo previsto en las leyes y en los presentes estatutos. Constituir apoderados judiciales y extrajudiciales, recibir notificaciones, absolver interrogatorios de parte, confesar obligaciones de la sociedad, transigir, desistir y allanar a la sociedad en cualquier asunto judicial. Aprobar y celebrar en nombre de la sociedad todo acto o contrato cuya cuantía sea igual o inferior al equivalente en pesos colombianos a ciento cincuenta mil dolares de los Estados Unidos de America (US\$150.000), liquidados a la tasa de cambio representativa del mercado vigente el día en que se surta la aprobación o celebración del acto, siempre que no se trate de enajenar bienes inmuebles o cualquier otro activo fijo de la sociedad, inclusive de naturaleza muebles, acciones, cuotas o partes de intereses inversiones y todo tipo de derechos de la sociedad, o de constituir gravámenes sobre cualquiera de los anteriores, facultades que radican exclusiva y privativamente en cabeza del Presidente. Las demás funciones que le corresponda como Representante legal por disposición de la ley, de estos estatutos o de la Junta Directiva. El Vicepresidente tendrá (1) suplente, designado por la Junta Directiva, quien lo reemplazara conjunta o separadamente en sus faltas temporales, absolutas o meramente accidentales, con idénticas facultades y sin que sea necesario para

***** CONTINUA *****

CERTIFICADO DE EXISTENCIA Y REPRESENTACION LEGAL O DE INSCRIPCION DE DOCUMENTOS.

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ello acreditar la ausencia del principal. La sociedad tendrá un (1) Gerente General, con su respectivo Suplente, designados por la Junta Directiva. El Suplente reemplazara al Gerente General, en sus faltas temporales, absolutas o meramente accidentales, quien junto con el gerente general, llevarán la representación legal de la sociedad, con idénticas facultades, pudiéndolas ejercer conjunta o separadamente con el Presidente y Vicepresidente, con idénticas facultades que el Gerente General y sin que sea necesario para ello acreditar la ausencia del titular. El Gerente General tendrá las siguientes facultades entre otras: Ejercer la representación legal de la sociedad en todos los actos y contratos que se requieran para el desarrollo del objeto social, de conformidad con lo previsto en las leyes y en los presentes estatutos. Aprobar y celebrar en nombre de la sociedad todo acto o contrato cuya cuantía sea igual o inferior al equivalente en pesos Colombianos a Cincuenta Mil dolares de los Estados Unidos de America (US\$50.000), liquidados a la tasa de cambio representativa del mercado vigente el día en que se surta la aprobación o celebración del acto, siempre que no se trate de enajenar a cualquier título bienes inmuebles o cualquier otro activo fijo de la sociedad, inclusive de naturaleza mueble, acciones, cuotas o partes de interés, inversiones y todo tipo de derechos de la sociedad, o de constituir gravámenes sobre cualquiera de las anteriores facultades que radican exclusiva y privativamente en cabeza del Presidente.

C E R T I F I C A

Que según Acta No. 116 del 27 de Junio de 1997 correspondiente a la Asamblea de Accionistas en Barranquilla, de la sociedad:
PROCAPS S.A.-----

cuya parte pertinente se inscribió en esta Cámara de Comercio, el 15 de Agosto de 1997 bajo el No. 70,838 del libro respectivo, y según Acta No. 127 del 22 de Marzo de 2000 correspondiente a la Asamblea de Accionistas en Barranquilla, de la sociedad:
PROCAPS S.A.-----

cuya parte pertinente se inscribió en esta Cámara de Comercio, el 29 de Mayo de 2000 bajo el No. 87,250 del libro respectivo, fueron hechos los siguientes nombramientos:

CLASE: JUNTA DIRECTIVA

Principales

1. Miński Gontovnik Ruben
2. Miński Gontovnik Meyer
3. Miński Gontovnik Jose

CC.*****7,463,982

CC.*****7,461,324

CC.*****8,671,834

Suplentes

1. Minski Zirberblum Elliot
2. Minski Deitel Daniel
3. Minski Sharon

CC.*****72,219,541

PA.*990,212,082,805

C E R T I F I C A

***** C O N T I N U A *****



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CAMARA DE COMERCIO
DE BARRANQUILLA
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CERTIFICADO DE EXISTENCIA Y REPRESENTACION LEGAL O DE INSCRIPCION DE DOCUMENTOS.

PROCAPS S.A.

NIT: 890.106.527-5

Que según Acta No. 116 del 27 de Junio de 1997 correspondiente a la Asamblea de Accionistas en Barranquilla, de la sociedad: PROCAPS S.A. cuya parte pertinente se inscribió en esta Cámara de Comercio, el 15 de Agosto de 1997 bajo el No. 70,838 del libro respectivo, fueron hechos los siguientes nombramientos:

Cargo/Nombre	Identificación
Presidente. Minski Gontovnik Ruben	CC.*****7,463,982
Suplente del Presidente Minski Minski Abraham	CC.*****802,575
Vicepresidente Minski Gontovnik Meyer	CC.*****7,461,324
Suplente del vicepresidente Minski Gontovnik Jose	CC.*****8,671,834

CERTIFICA

Que según Acta No. 11 del 01 de Febrero de 2001 correspondiente a la Junta Directiva en Barranquilla, de la sociedad: PROCAPS S.A. cuya parte pertinente se inscribió en esta Cámara de Comercio, el 12 de Febrero de 2001 bajo el No. 91,273 del libro respectivo, fueron hechos los siguientes nombramientos:

Cargo/Nombre	Identificación
Gerente General. Uribe Ochoa Guillermo Luis	CC.*****70,073,754

CERTIFICA

Que según Acta No. 406 del 02 de Sep/bre de 2004 correspondiente a la Junta Directiva en Barranquilla, de la sociedad: PROCAPS S.A. cuya parte pertinente se inscribió en esta Cámara de Comercio, el 09 de Sep/bre de 2004 bajo el No. 113,263 del libro respectivo, fueron hechos los siguientes nombramientos:

Cargo/Nombre	Identificación
Suplente del Gerente Tanaka Tatekawa Walter	CC.*****16,251,923

CERTIFICA

Que según Acta No. 124 del 29 de Marzo de 1999 correspondiente a la Asamblea de Accionistas en Barranquilla, de la sociedad: PROCAPS S.A. cuya parte pertinente se inscribió en esta Cámara de Comercio, el 04 de Agosto de 1999 bajo el No. 82,226 del libro respectivo, fueron hechos los siguientes nombramientos:

Cargo/Nombre	Identificación
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CERTIFICADO DE EXISTENCIA Y REPRESENTACION LEGAL O DE INSCRIPCION DE DOCUMENTOS.

PROCAPS S.A. -
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Revisor Fiscal Ppal.
Vargas Pertuz Ana Isabel

CC.*****32,696,645

C E R T I F I C A

Que según Acta No. 151 del 31 de Marzo de 2009 correspondiente a la Asamblea de Accionistas en Barranquilla, de la sociedad: PROCAPS S.A. cuya parte pertinente se inscribió en esta Cámara de Comercio, el 30 de Julio de 2009 bajo el No. 151,129 del libro respectivo, fueron hechos los siguientes nombramientos:

Cargo/Nombre
Suplente del Revisor Fiscal.
Duarte Diaz David

Identificación

CC.*****73,115,965

C E R T I F I C A

Que por Escritura Pública No. 2,784 del 07 de Dic/bre de 2007, otorgada en la Notaria 2 a. de Barranquilla cuya parte pertinente se inscribió en esta Cámara de Comercio, el 20 de Dic/bre de 2007 bajo el No. 3,492 del libro respectivo,

y las inscripciones 3.492-1, 3.493, 3.494, 3.495, 3.496, 3.497, 3.498, 3.499, 3.500, 3.501, 3.502, 3.503, 3.504, 3.505, 3.506, 3.507. Consta que RUBEN MINSKI GONTOVNIK, C.C. No. 2,463.982, obrando como Presidente y Representante Legal de la sociedad C.I.

NATURMEGA S.A. que obrando en su condición de Presidente y Representante Legal de la sociedad PROCAPS S.A. el presidente debidamente facultado por los Estatutos Sociales y por el Maximo Organó Social, otorga los siguientes poderes: Otorgar poder general, amplio y suficiente a los doctores JOSEFINA DEL CARMEN MIELES BUELVAS CC.No.33.138.497; a MARCELA CARVAJALINO PAGANO

CC.No.22.579.748; CRISTINA VIOLI FRANCESCHINI CC.No.22.463.716, con las facultades que se transcriben a continuación: a.- Para que representen a la sociedad PROCAPS S.A. ante todo tipo de

autoridades administrativas y jurisdiccionales, en asuntos de naturaleza civil, laboral, comercial, penal, aduanera, cambiaria, tributaria, policiva, administrativa y fiscal. b.- Contestar y

presentar demandas, requerimientos, recursos, pedir y aportar pruebas, recibir, notificarse, ejercer la acción de tutela, tramitar incidente de desacato, comparecer en los procesos que

cursen contra la sociedad, allanarse en nombre de la sociedad en los asuntos que sean necesarios, transigir, desistir, sustituir, renunciar y reasumir el poder. c.- La facultad expresa de

conciliar, por tanto pueden llegar a acuerdos conciliatorios, transaccionales, judiciales o extrajudiciales o extrajudiciales, cualquiera que sea su cuantía, para lo cual las apoderadas deben

aportar la autorización simple y escrita del Representante legal de la sociedad. d.- Podrán presentar solicitudes de devolución y/o compensación de impuestos, ventas y rentas, recibir los pagos por las devoluciones y adelantar todo trámite o proceso administrativo

ante la DIAN, de tal forma que en ningún momento quede sin representación legal de la sociedad. PODERES ESPECIALES: a.- Se confiere poder especial, amplio y suficiente a las personas que se

determinan seguidamente que conforman el grupo A y B, para, para



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CAMARA DE COMERCIO
DE BARRANQUILLA
12*****

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que conjuntamente suscriban contratos de suministros de mercancías y servicios con entidades oficiales, hasta la suma de OCHOCIENTOS MIL DOLARES DE LOS ESTADOS UNIDOS DE AMERICA (US800.000.00), liquidados a la tasa representativa del mercado vigente en el día que se realice la respectiva transacción. Grupo A. WALTER NANAKA TATEKAWA CC.No.16.251.923, CLAUDIA TANGARIFE CASTILLO CC.No.41.660.293, CARMEN ALICIA FLOREZ CC.No.22.434.044, IVAN VILLAREAL CAMACHO CC.No.91.201.749, CARMEN ALICIA HERRERA DIAZGRANADOS CC.No.22.377.540, DAVID ANTONIO CHARRIS GIRALDO CC.No.19.341.274, RICARDO DORADO HURTADO CC.No.79.715.772, JAIME FORERO LLINAS CC.No.19.300.593. b.- Sé confiere poder especial amplio y suficiente al señor WILLIAM ALBERTO BARROS CERRA CC.No.8.715.941, para que en nombre y representación de PROCAPS S.A., suscriban declaraciones cambiarias, aduaneras y tributarias a que este obligada la sociedad, en el giro normal de sus negocios y operaciones sociales, por tanto quedan facultados para firmarlas, como también los demás documentos relacionados con ellas, notificarse, aportar y solicitar las pruebas que sean necesarias. c.- Otorgar poder especial amplio y suficiente al señor MARLON TATIS PAREDES CC.No.72.176.874 y al señor WILLIAM ALBERTO BARROS CERRA CC.No.8.715.941, para que en nombre y representación de PROCAPS S.A., suscriban las declaraciones, reportes y cualquier documento relacionado con los tramites o registros de Comercio Exterior y o cualquier entidad del Estado que haga sus veces: d) Otorgar poder especial amplio y suficiente a la doctora CARMEN ALICIA HERRERA DIAZGRANADOS, CC.No.22.377.540 y al doctor WALTER TANAKA TATEKAWA CC.No.16.251.923, para que en nombre y representación de PROCAPS S.A., endosen los títulos valores de la sociedad hasta por la suma de UN MIL MILLONES DE PESOS (1.000.000.000.00) M.L. CUARTO: El representante legal de la sociedad PROCAPS S.A., doctor RUBEN MINSKI GONTOVNIK, manifiesta que la presente reforma fue aprobada por la Asamblea General Extraordinaria de Accionista de PROCAPS S.A., con observancia de las disposiciones legales y estatutarias.

C E R T I F I C A

Que por Escritura Pública No. 1.933 del 16 de Sep/bre de 2008, otorgada en la Notaria 2 a. de Barranquilla cuya parte pertinente se inscribió en esta Cámara de Comercio, el 06 de Octubre de 2008 bajo el No. 3,748 del libro respectivo, Consta que el señor RUBEN MINSKI GONTOVNIK, C.C. No. 7.463.982, que comparece en su condición de Presidente y Representante Legal de la Sociedad PROCAPS S.A., confiere por medio de este instrumento, publico Poder especial Amplio y Suficiente a la doctora MILENA

***** C O N T I N U A *****

CERTIFICADO DE EXISTENCIA Y REPRESENTACION LEGAL O DE INSCRIPCION DE DOCUMENTOS

PROCAPS S.A.
NIT: 890.106.527-5.

ESCAFFI PARDO, C.C. No. 32.758.420, para que en nombre y representación de PROCAPS S.A., suscriba declaraciones cambiarias, aduaneras y tributarias a que este obligada la sociedad en el giro normal de sus negocios y operaciones sociales, por tanto queda facultada para firmar, como tambien los demás documentos relacionados con ellas, notificarse, aportar y solicitar las pruebas que sean necesarias.

C E R T I F I C A

Que en esta Cámara de Comercio no aparecen inscripciones posteriores de documentos referentes a reforma, disolución, liquidación o nombramientos de representantes legales de la expresada sociedad.

C E R T I F I C A

Que su última Renovación fue el: 27 de Marzo de 2009.

La información sobre embargos de establecimiento se suministra en Certificados de Matrícula, la de contratos sujetos a registro, en Certificados Especiales.

C E R T I F I C A

Que los actos de registro aquí certificados quedan en firme cinco días hábiles después de la correspondiente inscripción, siempre que, dentro de dicho término, no sean objeto de los recursos de reposición ante esta entidad y/o de apelación para ante la Superintendencia de Industria y Comercio.

m. bayas



PODER ESPECIAL

Yo, **WALTER TANAKA TATEKAWA**, mayor de edad y vecino de la ciudad de Barranquilla (Colombia), identificado como aparece al pie de mi firma, quien en el presente documento actúa en calidad de Representante Legal de la sociedad **PROCAPS S.A.** sociedad legalmente constituida y domiciliada en la ciudad de Barranquilla (Colombia), por el presente documento otorgo a la doctora **CIELO ANGELA PEÑA RODRIGUEZ**, abogada en ejercicio, identificada como aparece al pie de su firma, con tarjeta profesional No. 82701 del C.S. de la J., poder especial, amplio y suficiente, para formular oposiciones u observaciones a la solicitud de patente No. 08 035.238, titulada "**SAL DE HIDROGENO FOSFATO DE UN ANTAGONISTA DEL RECEPTOR DE PROSTAGLANDINA D2**", cuyo titular es **AVENTIS PHARMACEUTICALS INC.**, publicada en la gaceta No. 604 del 29 de mayo de 2009.

Nuestro apoderado queda facultado, de manera expresa, para realizar todo tipo de actos necesarios para llevar a cabo el trámite de la oposición, incluyendo, sin limitación, preparar y presentar solicitudes, hacer declaraciones, pagar tasas, contribuciones e impuestos, recabar los títulos o certificados. Asimismo quedan autorizados para impugnar administrativa y judicialmente todo lo que fuere resuelto en el expediente a que se hace expresa referencia en el presente poder, con todas las facultades generales y específicas que fuera requerido para ella.

De la misma manera, además de las facultades que le confiere la naturaleza del presente mandato, se encuentran facultados para recibir, desistir, transigir, sustituir, y reasumir el presente poder, incoar acciones, interponer recursos y demás facultades conferidas por la ley.

Dado y Firmado en Barranquilla (Colombia) a los 19 días del mes de Agosto de 2009.

PROCAPS S.A.

C.C. N° 16'251.923

NIT: 890.106.527-5

Representante Legal

Acepto:

CIELO ANGELA PEÑA RODRIGUEZ

C.C. 51'940.252 de Bogotá

T.P.A. 82701 del C.S. de la J.

NOTARIA TERCERA DEL CIRCULO DE BARRANQUILLA
ALFONSO LUIS AVILA FADUL
DILIGENCIA DE PRESENTACION PERSONAL Y
RECONOCIMIENTO

El suscrito Notario certifica que este escrito fue presentado
personalmente por:

WALTER TANAKA TATEKAWA

Identificado con: 116.251983 de PAUMARA

Quien declaró que su contenido es cierto y que lo firmó puesta en
tes por.

[Firma]

21 AGO. 2005 MA

NOTARIO TERCERO DE BARRANQUILLA

NOTARIA TERCERA DEL CIRCULO
DE BARRANQUILLA
ALFONSO LUIS AVILA FADUL
NOTARIO

17

SUPERINTENDENCIA DE INDUSTRIA Y COMERCIO



No. 08-035238-00003-0000

Fecha: 2009-08-28 17:31:52 Dep: 2020 NULCREACION
Tra: 11 PATENTE/II Cve: 378 FASE NACIONAL
Art: 401 OPOSICION/OBSERVILR Folios: 120

SUPERINTENDENCIA DE INDUSTRIA Y COMERCIO

NIT : 869176089-2

RECIBO OFICIAL DE CAJA : 09 - 63,988
FECHA : AGOSTO 28 DE 2009

***** CONSIGNACION *****

DEPOSITANTE	TIPO PAGO	BANCO	CUENTA	No. PAGO	FECHA PGO	Vr. PAGO
LAB. PROCAPS	CONSIGNACION	BANCO DE BOGOTA	062754397	127575825	10/09/2009	574,000.00

***** CONCEPTO *****

CANT.	RENTISTICO	CONCEPTO	TOTAL CONCEPTO
1	50005-01-04	PRESENTACION DE OBSERVACIONES	
		12 MARCAS Y LEHAS COMERCIALES	287,000.00
		TOTAL :	287,000.00

SON: DOSCIENTOS OCHENTA Y SIETE MIL PESOS

RESPONSABLE : _____

RECIBO DE CAJA APLICADO AL EXPEDIENTE No. _____

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(12) INTERNATIONAL APPLICATION PUBLISHED UNDER THE PATENT COOPERATION TREATY (PCT)

(19) World Intellectual Property Organization
International Bureau



(43) International Publication Date
19 June 2003 (19.06.2003)

PCT

(10) International Publication Number
WO 03/049739 A1

(51) International Patent Classification: A61K 31/506,
C07D 239/04, A61P 35/00, C07D 401/12, 403/12, 405/14,
409/14, 417/12, 413/12, 409/12, 401A01, 409/04, 495/04,
471A04, 475/00

(74) Agent: SHAIR, Karoline, K., M.; Vertex Pharmaceuti-
cals, Inc., 130 Waverly Street, Cambridge, MA 02139 (US).

(21) International Application Number: PCT/US02/39190

(22) International Filing Date: 9 December 2002 (09.12.2002)

(25) Filing Language: English

(26) Publication Language: English

(30) Priority Data:
60/338,857 7 December 2001 (07.12.2001) US

(81) Designated States (national): AE, AG, AL, AM, AT, AU,
AZ, BA, BB, BG, BR, BY, BZ, CA, CH, CN, CO, CR, CU,
CZ, DE, DK, DM, DZ, EC, EE, ES, FI, GB, GD, GE, GH,
GM, HR, HU, ID, IL, IN, IS, JP, KG, KP, KR, KZ, LC,
LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW,
MX, MZ, NO, NZ, OM, PH, PL, PT, RO, RU, SD, SE, SG,
SK, SI, TJ, TM, TN, TR, TT, TZ, UA, UG, US, UZ, VN,
YU, ZA, ZM, ZW.

(84) Designated States (regional): ARIPO patent (GH, GM,
KE, LS, MW, MZ, SD, SL, SZ, TZ, UG, ZM, ZW),
Eurasian patent (AM, AZ, BY, KG, KZ, MD, RU, TJ, TM),
European patent (AT, BE, BG, CH, CY, CZ, DE, DK, EE,
ES, FI, FR, GB, GR, IT, LT, LU, MC, NL, PT, SE, SI, SK,
TR), OAPI patent (BF, BJ, CF, CG, CI, CM, GA, GN, GQ,
GW, ML, MR, NE, SN, TD, TG).

(71) Applicant (for all designated States except US): VER-
TEX PHARMACEUTICALS, INC. [US/US]; 130 Wa-
verly Street, Cambridge, MA 02139 (US).

(72) Inventors; and

(75) Inventors/Applicants (for US only): CHOQUETTE,
Deborah [US/US]; 17 Blakely Road, Medford, MA 02155
(US); DAVIES, Robert, J. [GB/US]; 65 Orient Avenue,
Arlington, MA 02474 (US); WANNAMAKER, Marion,
W. [US/US]; 375 Harvard Road, Stow, MA 01775 (US).

Published:

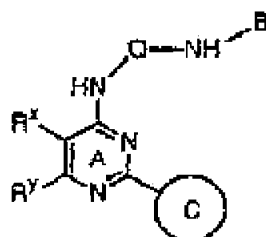
— with international search report

For two-letter codes and other abbreviations, refer to the "Guid-
ance Notes on Codes and Abbreviations" appearing at the begin-
ning of each regular issue of the PCT Gazette.



WO 03/049739 A1

(54) Title: PYRIMIDINE-BASED COMPOUNDS USEFUL AS GSK-3 INHIBITORS



(I)

(57) Abstract: The present invention provides a compound of formula (I), or a pharmaceutically acceptable derivative thereof. These compounds are inhibitors of protein kinases, particularly inhibitors of GSK-3 mammalian protein kinases. The invention also provides pharmaceutically acceptable compositions comprising the compounds of the invention and methods of utilizing these compounds and compositions in the treatment of various protein kinase mediated disorders, such as diabetes, cancer, stroke and Alzheimer's disease.

PYRIMIDINE-BASED COMPOUNDS USEFUL AS GSK-3 INHIBITORS

CROSS REFERENCE TO RELATED APPLICATIONS

[0001] The present application claims priority under 35 U.S.C. § 119(e) to U.S. Provisional Application number 60/338,857, filed December 7, 2001, entitled "Pyrimidine-Based Compounds Useful as GSK-3 Inhibitors", the entire contents of which are hereby incorporated by reference.

FIELD OF THE INVENTION

[0002] The present invention is in the field of medicinal chemistry and relates to compounds that are protein kinase inhibitors, compositions containing such compounds and methods of use. More particularly, this invention relates to compounds that are inhibitors of Glycogen synthase kinase-3 (GSK-3). The invention also relates to methods of treating diseases associated with the protein kinase GSK-3, such as diabetes, cancer, stroke, and Alzheimer's disease.

BACKGROUND OF THE INVENTION

[0003] The search for new therapeutic agents has been greatly aided in recent years by better understanding of the structure of enzymes and other biomolecules associated with target diseases. One important class of enzymes that has been the subject of extensive study is the protein kinases.

[0004] Protein kinases mediate intracellular signal transduction. They do this by effecting a phosphoryl transfer from a nucleoside triphosphate to a protein acceptor that is involved in a signaling pathway. There are a number of kinases and pathways through which extracellular and other stimuli cause a variety of cellular responses to occur inside the cell. Examples of such stimuli include environmental and chemical stress signals (e.g. osmotic shock, heat shock, ultraviolet radiation, bacterial endotoxin, H₂O₂), cytokines (e.g. interleukin-1 (IL-1) and tumor necrosis factor α (TNF- α)), and growth factors (e.g. granulocyte macrophage-colony-stimulating factor (GM-CSF), and fibroblast growth factor (FGF)). An extracellular stimulus may effect one or more cellular responses related to cell growth, migration, differentiation, secretion of hormones, activation of transcription factors,

muscle contraction, glucose metabolism, control of protein synthesis and regulation of cell cycle.

[0005] Many diseases are associated with abnormal cellular responses triggered by protein kinase-mediated events. These diseases include autoimmune diseases, inflammatory diseases, neurological and neurodegenerative diseases, cancer, cardiovascular diseases, allergies and asthma, Alzheimer's disease and hormone-related diseases. Accordingly, there has been a substantial effort in medicinal chemistry to find protein kinase inhibitors that are effective as therapeutic agents.

[0006] Glycogen synthase kinase-3 (GSK-3) is a serine/threonine protein kinase comprised of α and β isoforms that are each encoded by distinct genes [Coghlan et al., *Chemistry & Biology*, **7**, 793-803 (2000); and Kim and Kimmel, *Curr. Opinion Genetics Dev.*, **10**, 508-514 (2000)]. GSK-3 has been implicated in various diseases including diabetes, Alzheimer's disease, CNS disorders such as manic depressive disorder and neurodegenerative diseases, and cardiomyocyte hypertrophy [WO 99/65897; WO 00/38675; and Haq et al., *J. Cell Biol.* (2000) **151**, 117-130]. These diseases may be caused by, or result in, the abnormal operation of certain cell signaling pathways in which GSK-3 plays a role. GSK-3 has been found to phosphorylate and modulate the activity of a number of regulatory proteins. These proteins include glycogen synthase, which is the rate limiting enzyme necessary for glycogen synthesis, the microtubule associated protein Tau, the gene transcription factor β -catenin, the translation initiation factor eIF2B, as well as ATP citrate lyase, axin, heat shock factor-1, c-Jun, c-myc, c-myb, CREB, and CEPB α . These diverse protein targets implicate GSK-3 in many aspects of cellular metabolism, proliferation, differentiation and development.

[0007] In a GSK-3 mediated pathway that is relevant for the treatment of type II diabetes, insulin-induced signaling leads to cellular glucose uptake and glycogen synthesis. Along this pathway, GSK-3 is a negative regulator of the insulin-induced signal. Normally, the presence of insulin causes inhibition of GSK-3 mediated phosphorylation and deactivation of glycogen synthase. The inhibition of GSK-3 leads to increased glycogen synthesis and glucose uptake [Klein et al., *PNAS*, **93**, 8455-8459 (1996); Cross et al., *Biochem. J.*, **303**, 21-26 (1994); Cohen, *Biochem. Soc. Trans.*, **21**, 555-567 (1993); and Massillon et al., *Biochem J.* **299**, 123-128 (1994)]. However, in a diabetic patient, where the insulin response is impaired, glycogen synthesis and glucose uptake fail to increase despite the presence of relatively high blood levels of insulin. This leads to abnormally

high blood levels of glucose with acute and long term effects that may ultimately result in cardiovascular disease, renal failure and blindness. In such patients, the normal insulin-induced inhibition of GSK-3 fails to occur. It has also been reported that in patients with type II diabetes, GSK-3 is overexpressed [WO 00/38675]. Therapeutic inhibitors of GSK-3 are therefore potentially useful for treating diabetic patients suffering from an impaired response to insulin.

[0008] GSK-3 activity has also been associated with Alzheimer's disease. This disease is characterized by the well-known β -amyloid peptide and the formation of intracellular neurofibrillary tangles. The neurofibrillary tangles contain hyperphosphorylated Tau protein, in which Tau is phosphorylated on abnormal sites. GSK-3 has been shown to phosphorylate these abnormal sites in cell and animal models. Furthermore, inhibition of GSK-3 has been shown to prevent hyperphosphorylation of Tau in cells [Lovestone et al., *Current Biology* 4, 1077-86 (1994); and Brownlee et al., *Neuroreport* 8, 3251-55 (1997)]. Therefore, it is believed that GSK-3 activity may promote generation of the neurofibrillary tangles and the progression of Alzheimer's disease.

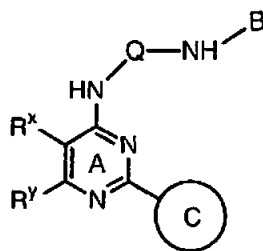
[0009] Another substrate of GSK-3 is β -catenin which is degraded after phosphorylation by GSK-3. Reduced levels of β -catenin have been reported in schizophrenic patients and have also been associated with other diseases related to increase in neuronal cell death [Zhong et al., *Nature*, 395, 698-702 (1998); Takashima et al., *PNAS*, 90, 7789-93 (1993); and Pei et al., *J. Neuropathol. Exp*, 56, 70-78 (1997)].

[0010] GSK-3 activity has also been associated with stroke [Wang et al., *Brain Res*, 859, 381-5 (2000); Sasaki et al., *Neurol Res*, 23, 588-92 (2001); Hashimoto et al., *J. Biol. Chem*, 277, 32985-32991 (2002)].

[0011] Considering the lack of currently available treatment options for the majority of the conditions associated with GSK-3 and other protein kinases, there is still a great need for new therapeutic agents that inhibit these protein targets.

SUMMARY OF THE INVENTION

[0012] The present invention addresses this need by providing compounds and pharmaceutical compositions thereof that are effective as protein kinase inhibitors, particularly as inhibitors of GSK-3. These compounds have the general formula I:



I

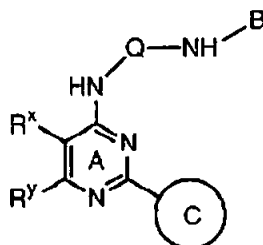
or a pharmaceutically acceptable derivative or prodrug thereof, wherein B, Q, Ring C, R^x , and R^y are as defined below.

[0013] In another embodiment, the invention provides pharmaceutical compositions comprising a GSK-3 inhibitor of this invention. These compositions may be utilized in methods for treating or preventing a variety of GSK-3 mediated conditions, such as neurodegenerative disorders, diabetes, Alzheimer's disease, Huntington's Disease, Parkinson's Disease, AIDS-associated dementia, amyotrophic lateral sclerosis (ALS, Lou Gehrig's Disease), multiple sclerosis (MS), schizophrenia, cardiomyocyte hypertrophy, reperfusion/ ischemia, baldness, and stroke.

[0014] The compositions of this invention are also useful in methods for enhancing glycogen synthesis and/or lowering blood levels of glucose and therefore are especially useful for diabetic patients. These compositions are also useful in methods for inhibiting the production of hyperphosphorylated Tau protein, which is useful in halting or slowing the progression of Alzheimer's disease. Another embodiment of this invention relates to a method for inhibiting the phosphorylation of β -catenin, which is useful for treating schizophrenia.

DESCRIPTION OF THE INVENTION

[0015] It has now been found that compounds of this invention and pharmaceutical compositions thereof are effective as protein kinase inhibitors, particularly as inhibitors of GSK-3. These compounds have the general formula I:



I

- or a pharmaceutically acceptable derivative or prodrug thereof, wherein:
- B is an optionally substituted 5-6 membered monocyclic or 8-10 membered bicyclic aromatic ring, wherein said monocyclic or bicyclic ring has 0-4 heteroatoms selected from oxygen, sulfur or nitrogen;
- Q is a C₁₋₄ alkylidene chain, wherein each methylene unit of said Q is substituted by R² and R^{2'}, and up to two non-adjacent methylene units of said Q are optionally and independently replaced by -SO₂ or -C(=O);
- Ring C is selected from a phenyl, thienyl, pyridinyl, pyrimidinyl, pyridazinyl, pyrazinyl, or 1,2,4-triazinyl ring, wherein said Ring C optionally has one or two ortho substituents independently selected from -R¹, any substitutable carbon position on Ring C is independently substituted by -R⁵, or two adjacent substituents on Ring C are optionally taken together with their intervening atoms to form a fused, unsaturated or partially unsaturated, 5-6 membered ring having 0-3 heteroatoms selected from oxygen, sulfur or nitrogen, said fused ring being optionally substituted by halo, oxo, or -R⁸;
- R¹ is selected from -halo, -CN, -NO₂, T-V-R⁶, phenyl, 5-6 membered heteroaryl ring, 5-6 membered heterocyclyl ring, or C₁₋₆ aliphatic group, said phenyl, heteroaryl, and heterocyclyl rings each optionally substituted by up to three groups independently selected from halo, oxo, or -R⁸, said C₁₋₆ aliphatic group optionally substituted with halo, cyano, nitro, or oxygen, or R¹ and an adjacent substituent taken together with their intervening atoms form said ring fused to Ring C;
- each R² is independently selected from H, -OH, C₁₋₁₀ aliphatic; (C₁₋₁₀ aliphatic)-NH-(C₁₋₁₀ aliphatic); -O-(C₁₋₁₀ aliphatic); -NH₂, -NH(C₁₋₁₀ aliphatic), -N(C₁₋₁₀ aliphatic)₂, -C(=O)R, aryl, or heteroaryl, wherein said aliphatic, aryl, or heteroaryl is optionally substituted;
- R is selected from an optionally substituted group selected from C₁₋₁₀ aliphatic, aryl, aralkyl, heteroaryl, or heteroaralkyl;
- each R^{2'} is independently selected from H or an optionally substituted C₁₋₁₀ aliphatic group;
- R^X and R^Y are independently selected from T-R³, or R^X and R^Y are taken together with their intervening atoms to form a fused, partially saturated or aromatic, 5-8 membered ring having 0-3 ring heteroatoms selected from oxygen, sulfur, or nitrogen, wherein any substitutable carbon on said fused ring formed by R^X and R^Y is substituted by oxo or T-R³, and any substitutable nitrogen on said ring formed by R^X and R^Y is substituted by R⁴;

T is a valence bond or a C₁₋₄ alkylidene chain;

R³ is selected from -R', -halo, -OR', -C(=O)R', -CO₂R', -COCOR', -COCH₂COR', -NO₂, -CN, -S(O)R', -S(O)₂R', -SR', -N(R⁴)₂, -CON(R⁷)₂, -SO₂N(R⁷)₂, -OC(=O)R', -N(R⁷)COR', -N(R⁷)CO₂(optionally substituted C₁₋₆ aliphatic), -N(R⁴)N(R⁴)₂, -C=NN(R⁴)₂, -C=N-OR', -N(R⁷)CON(R⁷)₂, -N(R⁷)SO₂N(R⁷)₂, -N(R⁴)SO₂R', or -OC(=O)N(R⁷)₂;

each R' is independently selected from hydrogen or an optionally substituted group selected from C₁₋₆ aliphatic, C₆₋₁₀ aryl, a heteroaryl ring having 5-10 ring atoms, or a heterocyclyl ring having 5-10 ring atoms;

each R⁴ is independently selected from -R⁷, -COR⁷, -CO₂(C₁₋₆ aliphatic), -CON(R⁷)₂, -SO₂R⁷, or two R⁴ on the same nitrogen are taken together to form a 5-8 membered heterocyclyl or heteroaryl ring;

each R⁵ is independently selected from -R', halo, -OR', -C(=O)R', -CO₂R', -COCOR', -NO₂, -CN, -S(O)R', -SO₂R', -SR', -N(R⁴)₂, -CON(R⁴)₂, -SO₂N(R⁴)₂, -OC(=O)R', -N(R⁴)COR', -N(R⁴)CO₂(optionally substituted C₁₋₆ aliphatic), -N(R⁴)N(R⁴)₂, -C=NN(R⁴)₂, -C=N-OR', -N(R⁴)CON(R⁴)₂, -N(R⁴)SO₂N(R⁴)₂, -N(R⁴)SO₂R', or -OC(=O)N(R⁴)₂, or R⁵ and an adjacent substituent taken together with their intervening atoms form said ring fused to Ring C;

V is -O-, -S-, -SO-, -SO₂-, -N(R⁶)SO₂-, -SO₂N(R⁶)-, -N(R⁶)-, -CO-, -CO₂-, -N(R⁶)CO-, -N(R⁶)C(O)O-, -N(R⁶)CON(R⁶)-, -N(R⁶)SO₂N(R⁶)-, -N(R⁶)N(R⁶)-, -C(O)N(R⁶)-, -OC(O)N(R⁶)-, -C(R⁶)₂O-, -C(R⁶)₂S-, -C(R⁶)₂SO-, -C(R⁶)₂SO₂-, -C(R⁶)₂SO₂N(R⁶)-, -C(R⁶)₂N(R⁶)-, -C(R⁶)₂N(R⁶)C(O)-, -C(R⁶)₂N(R⁶)C(O)O-, -C(R⁶)=NN(R⁶)-, -C(R⁶)=N-O-, -C(R⁶)₂N(R⁶)N(R⁶)-, -C(R⁶)₂N(R⁶)SO₂N(R⁶)-, or -C(R⁶)₂N(R⁶)CON(R⁶)-;

each R⁶ is independently selected from hydrogen or an optionally substituted C₁₋₄ aliphatic group, or two R⁶ groups on the same nitrogen atom are taken together with the nitrogen atom to form a 5-6 membered heterocyclyl or heteroaryl ring;

each R⁷ is independently selected from hydrogen or an optionally substituted C₁₋₆ aliphatic group, or two R⁷ on the same nitrogen are taken together with the nitrogen to form a 5-8 membered heterocyclyl or heteroaryl ring; and

each R⁸ is independently selected from an optionally substituted C₁₋₄ aliphatic group, -OR⁶, -SR⁶, -COR⁶, -SO₂R⁶, -N(R⁶)₂, -N(R⁶)N(R⁶)₂, -CN, -NO₂, -CON(R⁶)₂, or -CO₂R⁶.

[0016] As used herein, the following definitions shall apply unless otherwise indicated.

[0017] The phrase "optionally substituted" is used interchangeably with the phrase "substituted or unsubstituted." Unless otherwise indicated, an optionally substituted group may have a substituent at each substitutable position of the group, and each substitution is independent of the other.

[0018] The term "aliphatic" or "aliphatic group", as used herein, means a straight-chain or branched, substituted or unsubstituted C₁-C₈ hydrocarbon chain that is completely saturated or that contains one or more units of unsaturation, or a monocyclic C₃-C₈ hydrocarbon or bicyclic C₈-C₁₂ hydrocarbon that is completely saturated or that contains one or more units of unsaturation, but which is not aromatic (also referred to herein as "carbocycle" "cycloaliphatic" or "cycloalkyl"), that has a single point of attachment to the rest of the molecule wherein any individual ring in said bicyclic ring system has 3-7 members. For example, suitable aliphatic groups include, but are not limited to, linear or branched, substituted or unsubstituted alkyl, alkenyl, alkynyl groups and hybrids thereof such as (cycloalkyl)alkyl, (cycloalkenyl)alkyl or (cycloalkyl)alkenyl.

[0019] The terms "alkyl", "alkoxy", "hydroxyalkyl", "alkoxyalkyl", and "alkoxycarbonyl", used alone or as part of a larger moiety include both straight and branched chains containing one to twelve carbon atoms. The terms "alkenyl" and "alkynyl" used alone or as part of a larger moiety shall include both straight and branched chains containing two to twelve carbon atoms.

[0020] The term "heteroatom" means nitrogen, oxygen, or sulfur and includes any oxidized form of nitrogen and sulfur, and the quaternized form of any basic nitrogen. Also the term "nitrogen" includes a substitutable nitrogen of a heterocyclic ring. As an example, in a saturated or partially unsaturated ring having 0-3 heteroatoms selected from oxygen, sulfur or nitrogen, the nitrogen may be N (as in 3,4-dihydro-2H-pyrrolyl), NH (as in pyrrolidinyl) or NR⁺ (as in N-substituted pyrrolidinyl).

[0021] The term "unsaturated", as used herein, means that a moiety has one or more units of unsaturation, and includes aryl rings.

[0022] The term "aryl" used alone or as part of a larger moiety as in "aralkyl", "aralkoxy", or "aryloxyalkyl", refers to monocyclic, bicyclic and tricyclic ring systems having a total of five to fourteen ring members, wherein at least one ring in the system is aromatic and wherein each ring in the system contains 3 to 7 ring members. The term "aryl" may be used interchangeably with the term "aryl ring". The term "aryl" also refers to heteroaryl ring systems as defined hereinbelow.

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[0023] The term "heterocycle", "heterocyclyl", "heterocycloaliphatic", or "heterocyclic" as used herein means non-aromatic, monocyclic, bicyclic or tricyclic ring systems having five to fourteen ring members in which one or more ring members is a heteroatom, wherein each ring in the system contains 3 to 7 ring members.

[0024] The term "heteroaryl", used alone or as part of a larger moiety as in "heteroaralkyl" or "heteroarylalkoxy", refers to monocyclic, bicyclic and tricyclic ring systems having a total of five to fourteen ring members, wherein at least one ring in the system is aromatic, at least one ring in the system contains one or more heteroatoms, and wherein each ring in the system contains 3 to 7 ring members. The term "heteroaryl" may be used interchangeably with the term "heteroaryl ring" or the term "heteroaromatic".

[0025] An aryl (including aralkyl, aralkoxy, aryloxyalkyl and the like) or heteroaryl (including heteroaralkyl and heteroarylalkoxy and the like) group may contain one or more substituents. Suitable substituents on the unsaturated carbon atom of an aryl, heteroaryl, aralkyl, or heteroaralkyl group are selected from halogen, $-R^o$, $-OR^o$, $-SR^o$, 1,2-methylenedioxy, 1,2-ethylenedioxy, phenyl (Ph) optionally substituted with R^o , $-O(Ph)$ optionally substituted with R^o , $-CH_2(Ph)$ optionally substituted with R^o , $-CH_2CH_2(Ph)$, optionally substituted with R^o , $-NO_2$, $-CN$, $-N(R^o)_2$, $-NR^oC(O)R^o$, $-NR^oC(O)N(R^o)_2$, $-NR^oCO_2R^o$, $-NR^oNR^oC(O)R^o$, $-NR^oNR^oC(O)N(R^o)_2$, $-NR^oNR^oCO_2R^o$, $-C(O)C(O)R^o$, $-C(O)CH_2C(O)R^o$, $-CO_2R^o$, $-C(O)R^o$, $-C(O)N(R^o)_2$, $-OC(O)N(R^o)_2$, $-S(O)_2R^o$, $-SO_2N(R^o)_2$, $-S(O)R^o$, $-NR^oSO_2N(R^o)_2$, $-NR^oSO_2R^o$, $-C(=S)N(R^o)_2$, $-C(=NH)-N(R^o)_2$, or $-(CH_2)_qNHC(O)R^o$ wherein q is 0-2, and wherein each R^o is independently selected from hydrogen, optionally substituted C_{1-6} aliphatic, an unsubstituted 5-6 membered heteroaryl or heterocyclic ring, phenyl, $-O(Ph)$, or $-CH_2(Ph)$, or wherein two occurrences of R^o , on the same substituent or different substituents, taken together, form a 5-8-membered heterocyclyl or heteroaryl ring having 1-3 heteroatoms independently selected from nitrogen, oxygen, or sulfur. Optional substituents on the aliphatic group of R^o are selected from NH_2 , $NH(C_{1-4} \text{ aliphatic})$, $N(C_{1-4} \text{ aliphatic})_2$, halogen, C_{1-4} aliphatic, OH , $O(C_{1-4} \text{ aliphatic})$, NO_2 , CN , CO_2H , $CO_2(C_{1-4} \text{ aliphatic})$, $O(\text{halo } C_{1-4} \text{ aliphatic})$, or halo C_{1-4} aliphatic.

[0026] An aliphatic group or a non-aromatic heterocyclic ring may contain one or more substituents. Suitable substituents on the saturated carbon of an aliphatic group or of a non-aromatic heterocyclic ring are selected from those listed above for the unsaturated carbon of

an aryl or heteroaryl group and the following: $=O$, $=S$, $=NNHR^*$, $=NN(R^*)_2$, $=NNHC(O)R^*$, $=NNHCO_2(\text{alkyl})$, $=NNHSO_2(\text{alkyl})$, or $=NR^*$, where each R^* is independently selected from hydrogen or an optionally substituted C_{1-6} aliphatic. Optional substituents on the aliphatic group of R^* are selected from NH_2 , $NH(C_{1-4} \text{ aliphatic})$, $N(C_{1-4} \text{ aliphatic})_2$, halogen, C_{1-4} aliphatic, OH , $O(C_{1-4} \text{ aliphatic})$, NO_2 , CN , CO_2H , $CO_2(C_{1-4} \text{ aliphatic})$, $O(\text{halo } C_{1-4} \text{ aliphatic})$, or $\text{halo}(C_{1-4} \text{ aliphatic})$.

[0027] Optional substituents on the nitrogen of a non-aromatic heterocyclic ring are selected from $-R^+$, $-N(R^+)_2$, $-C(O)R^+$, $-CO_2R^+$, $-C(O)C(O)R^+$, $-C(O)CH_2C(O)R^+$, $-SO_2R^+$, $-SO_2N(R^+)_2$, $-C(=S)N(R^+)_2$, $-C(=NH)-N(R^+)_2$, or $-NR^+SO_2R^+$; wherein R^+ is hydrogen, an optionally substituted C_{1-6} aliphatic, optionally substituted phenyl, optionally substituted $-O(\text{Ph})$, optionally substituted $-CH_2(\text{Ph})$, optionally substituted $-CH_2CH_2(\text{Ph})$, or an unsubstituted 5-6 membered heteroaryl or heterocyclic ring, or wherein two occurrences of R^+ , on the same substituent or different substituents, taken together, form a 5-8-membered heterocyclyl or heteroaryl ring having 1-3 heteroatoms independently selected from nitrogen, oxygen, or sulfur. Optional substituents on the aliphatic group or the phenyl ring of R^+ are selected from NH_2 , $NH(C_{1-4} \text{ aliphatic})$, $N(C_{1-4} \text{ aliphatic})_2$, halogen, C_{1-4} aliphatic, OH , $O(C_{1-4} \text{ aliphatic})$, NO_2 , CN , CO_2H , $CO_2(C_{1-4} \text{ aliphatic})$, $O(\text{halo } C_{1-4} \text{ aliphatic})$, or $\text{halo}(C_{1-4} \text{ aliphatic})$.

[0028] The term "alkylidene chain" refers to a straight or branched carbon chain that may be fully saturated or have one or more units of unsaturation and has two points of attachment to the rest of the molecule.

[0029] A combination of substituents or variables is permissible only if such a combination results in a stable or chemically feasible compound. A stable compound or chemically feasible compound is one that is not substantially altered when kept at a temperature of 40°C or less, in the absence of moisture or other chemically reactive conditions, for at least a week.

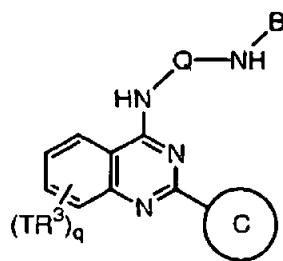
[0030] It will be apparent to one skilled in the art that certain compounds of this invention may exist in tautomeric forms, all such tautomeric forms of the compounds being within the scope of the invention.

[0031] Unless otherwise stated, structures depicted herein are also meant to include all stereochemical forms of the structure; i.e., the R and S configurations for each asymmetric center. Therefore, single stereochemical isomers as well as enantiomeric and diastereomeric mixtures of the present compounds are within the scope of the invention.

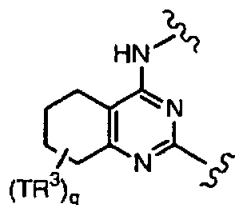
Unless otherwise stated, structures depicted herein are also meant to include compounds that differ only in the presence of one or more isotopically enriched atoms. For example, compounds having the present structures except for the replacement of a hydrogen by a deuterium or tritium, or the replacement of a carbon by a ^{13}C - or ^{14}C -enriched carbon are within the scope of this invention. Such compounds are useful, for example, as analytical tools or probes in biological assays.

[0032] *II. Description of Certain Exemplary Compounds:*

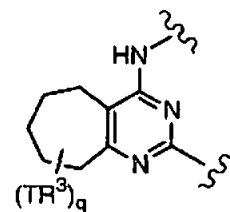
[0033] As described generally above, compounds of formula I include both monocyclic and bicyclic pyrimidine systems. For example, in certain embodiments, R^{X} and R^{Y} may be taken together to form a fused ring, providing a bicyclic ring system. Preferred $\text{R}^{\text{X}}/\text{R}^{\text{Y}}$ rings include a 5-, 6-, 7-, or 8-membered partially saturated or aromatic ring having 0-2 heteroatoms, wherein said $\text{R}^{\text{X}}/\text{R}^{\text{Y}}$ ring is optionally substituted with oxo or one or more occurrences of TR^3 or R^4 . Examples of certain preferred pyrimidine ring A systems of formula I are the mono- and bicyclic ring A systems shown below, wherein B, Q, TR^3 , R^4 and ring C are as defined generally above and herein, and q is 0-4.



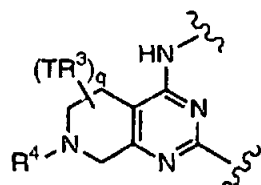
I-A



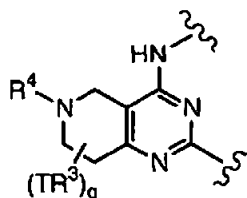
I-B



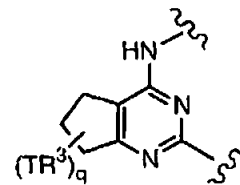
I-C



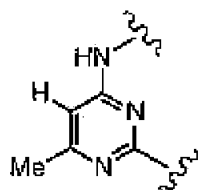
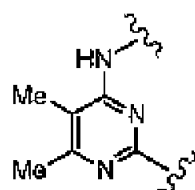
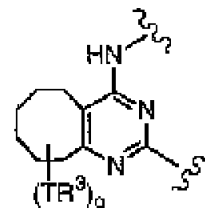
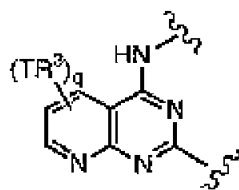
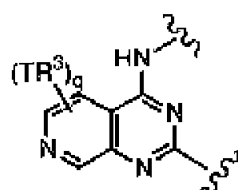
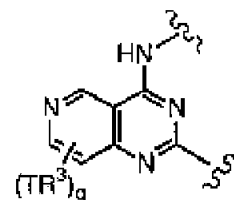
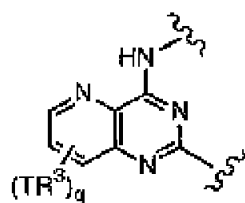
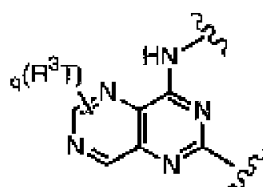
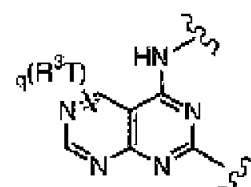
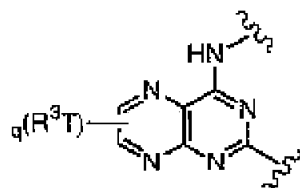
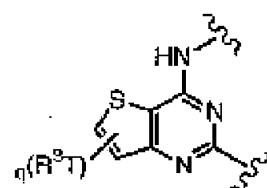
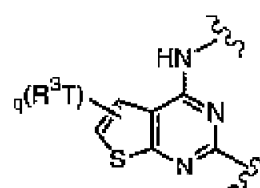
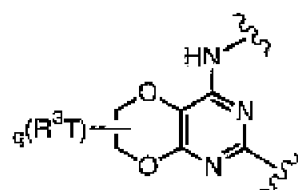
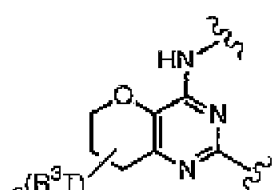
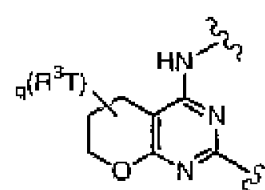
I-D

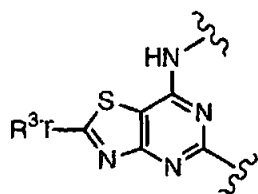


I-E

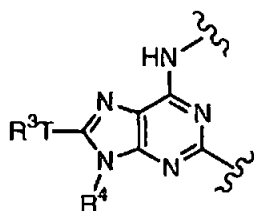


I-F

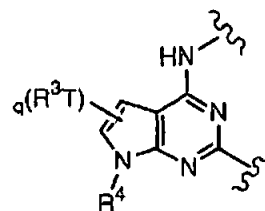
**I-G****I-H****I-I****I-J****I-K****I-L****I-M****I-N****I-O****I-P****I-Q****I-R****I-S****I-T****I-U**



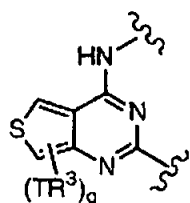
I-V



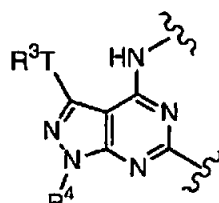
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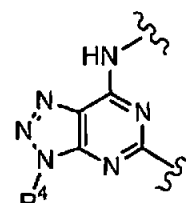
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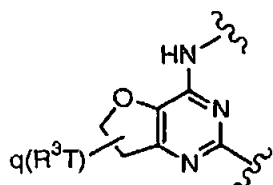
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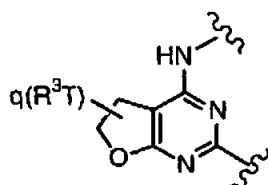
I-Z



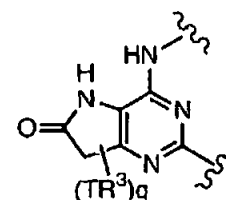
I-AA



I-BB



I-CC



I-DD

[0034] Preferred bicyclic Ring A systems include I-A, I-B, I-C, I-D, I-E, I-F, I-G, I-H, I-I, I-J, I-K, I-L, and I-M, more preferably I-A, I-B, I-C, I-F, and I-H, and most preferably I-A, I-B, and I-H.

[0035] As described generally above, the bicyclic pyrimidine ring system formed when R^X and R^Y are taken together may optionally be substituted with one or more occurrences of $T-R^3$ on any substitutable carbon atom, and with R^4 on any substitutable nitrogen atom. Exemplary $T-R^3$ substituents include $-R'$, halo, $-OR'$, $-C(=O)R'$, $-CO_2R'$, $-COCOR'$, $-NO_2$, $-CN$, $-S(O)R'$, $-SO_2R'$, $-SR'$, $-N(R^4)_2$, $-CON(R^4)_2$, $-SO_2N(R^4)_2$, $-OC(=O)R'$, $-N(R^4)COR'$, $-N(R^4)CO_2$ (optionally substituted C_{1-6} aliphatic), $-N(R^4)N(R^4)_2$, $-C=NN(R^4)_2$, $-C=N-OR'$, $-N(R^4)CON(R^4)_2$, $-N(R^4)SO_2N(R^4)_2$, $-N(R^4)SO_2R'$, or $-OC(=O)N(R^4)_2$. Exemplary R^4 substituents include $-R^7$, $-COR^7$, $-CO_2(C_{1-6}$ aliphatic), $-CON(R^7)_2$, or $-SO_2R^7$, or two R^4 on the same nitrogen are taken together to form a 5-8 membered heterocyclcyl or heteroaryl ring, and R' and R^7 are as defined herein. Preferred R^X/R^Y ring substituents include $-halo$, $-R'$, $-OR'$, $-COR'$, $-CO_2R'$, $-CON(R^4)_2$, $-CN$, or $-N(R^4)_2$ wherein R' is H or an optionally substituted C_{1-6} aliphatic group.

[0036] In certain other exemplary embodiments, compounds of formula I have a monocyclic pyrimidine ring system which is substituted by R^X and R^Y . Preferred R^X groups include hydrogen, alkyl- or dialkylamino, acetamido, or a C_{1-4} aliphatic group such as methyl, ethyl, cyclopropyl, isopropyl or t-butyl. Preferred R^Y groups include T- R^3 wherein T is a valence bond or a methylene, and R^3 is $-R'$, $-N(R^4)_2$, or $-OR'$. When R^3 is $-R'$ or $-OR'$, a preferred R' is an optionally substituted group selected from C_{1-6} aliphatic, phenyl, or a 5-6 membered heteroaryl or heterocyclyl ring. Examples of preferred R^Y include 2-pyridyl, 4-pyridyl, piperidiny, methyl, ethyl, cyclopropyl, isopropyl, t-butyl, alkyl- or dialkylamino, acetamido, optionally substituted phenyl such as phenyl or halo-substituted phenyl, and methoxymethyl.

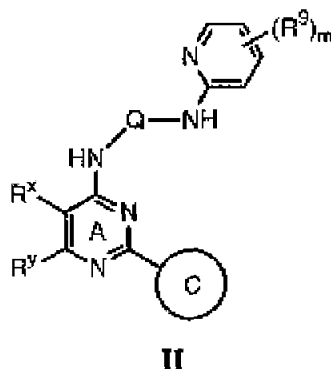
[0037] As described generally above, Q is a C_{1-4} alkylidene chain, wherein each methylene unit of said Q is substituted by R^2 and $R^{2'}$, and up to two non-adjacent methylene units of said Q are optionally and independently replaced by $-SO_2$ or $-C(=O)$. Preferred R^2 and $R^{2'}$ groups include H, alkyl, haloalkyl, heterocycloaminoalkyl, alkylaminoalkyl, and alkyl, wherein all alkyl moieties have 1-10 carbon atoms and are unsubstituted unless otherwise indicated. More preferably, each of R^2 and $R^{2'}$ is hydrogen. In certain preferred embodiments, Q is $-CH_2CH_2-$, $-CH_2CH_2CH_2-$, or $-CH_2CH_2CH_2CH_2-$, $-SO_2CH_2-$, $-CH_2SO_2-$, $-(C=O)CH_2-$, or $-CH_2(C=O)-$. In more preferred embodiments, Q is $-CH_2CH_2-$, $-CH_2CH_2CH_2-$, or $-CH_2CH_2CH_2CH_2-$, $-SO_2CH_2-$, or $-CH_2SO_2-$. In most preferred embodiments, Q is $-CH_2CH_2-$, $-CH_2CH_2CH_2-$, or $-CH_2CH_2CH_2CH_2-$.

[0038] In certain embodiments, B is an optionally substituted carbocyclic aryl having 5-10 carbon ring atoms. In certain other embodiments, B is an optionally substituted heteroaryl having 5-10 carbon ring atoms and one or more ring heteroatoms. Preferred B groups include pyridyl, pyrimidinyl, thiazolyl, indolyl, imidazolyl, oxadiazolyl, tetrazolyl, pyrazinyl, triazolyl, thienyl, furanyl, quinolinyl, purinyl, naphthyl, benzothiazolyl, benzopyridyl, benzimidazolyl, indazolyl, isothiazolyl, pyrazolyl, pyridazinyl, isoxazolyl, phenyl, benzothiophenyl, and pyridothiophenyl, all of which may be substituted with at least one and no more than three substituents. Exemplary substituents are independently selected from, without limitation, nitro, amino, cyano, halo, thioamido, amidino, oxamidino, alkoxyamidino, imidino, guanidino, sulfonamido, carboxyl, formyl, alkyl, haloalkyl, alkoxy, haloalkoxy, alkoxyalkyl, alkylaminoalkoxy, alkylcarbonyl, aralkylcarbonyl, heteroaralkylcarbonyl, alkylthio, aminoalkyl, cyanoalkyl, hydroxy, alkoxycarbonyl, aryl,

32

aralkyl, heteroaryl, and heteroaralkyl, wherein all alkyl moieties have 1-10 carbon atoms and are unsubstituted unless otherwise indicated.

[0039] In other preferred embodiments, B is optionally substituted 2-pyridyl and compounds have the general formula II:



wherein m is 0-4, and each occurrence of R^9 is independently selected from H, nitro, amino, cyano, halo, thioamido, amidino, oxamidino, alkoxyamidino, imidino, guanidino, sulfonamido, carboxyl, formyl, alkyl, haloalkyl, alkoxy, haloalkoxy, alkoxyalkyl, alkylaminoalkoxy, alkylcarbonyl, aralkylcarbonyl, heteroaralkylcarbonyl, alkylthio, aryl, aralkyl, heteroaryl, and heteroaralkyl, wherein all alkyl moieties have 1-10 carbon atoms and are unsubstituted unless otherwise indicated. In preferred embodiments, m is 0, 1, or 2. In more preferred embodiments, m is 1 or 2. Most preferred R^9 substituents include hydrogen, C_{1-4} alkyl, nitro, amino, cyano, cyanomethyl, trifluoromethyl, hydroxy, and methoxy.

[0040] In other preferred embodiments, B is indazolyl, pyrazolyl, or thiazolyl optionally substituted with one or more independent occurrences of R^9 . Preferred R^9 substituents on indazolyl, pyrazolyl, or thiazolyl include hydrogen, C_{1-4} alkyl, nitro, amino, cyano, cyanomethyl, trifluoromethyl, hydroxy, and methoxy.

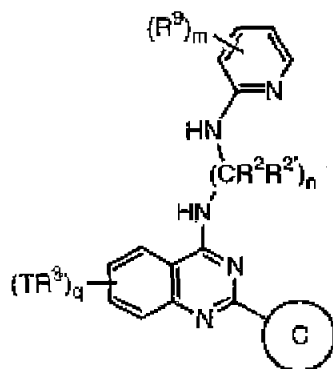
[0041] Preferred formula I Ring C groups are phenyl and pyridinyl. When two adjacent substituents on Ring C are taken together to form a fused ring, Ring C is contained in a bicyclic ring system. Preferred fused rings include a benzo or pyrido ring. Such rings preferably are fused at ortho and meta positions of Ring C. Examples of preferred bicyclic Ring C systems include naphthyl, quinolinyl, isoquinolinyl and benzodioxolyl.

[0042] Preferably, Ring C groups have one to two ortho substituents independently selected from R^1 . An ortho position on Ring C is defined relative to the position where the pyrimidine ring is attached. Preferred R^1 groups include -halo, an optionally substituted C_{1-}

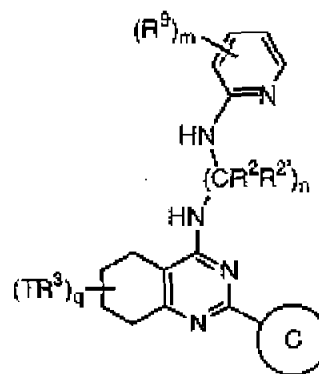
$_6$ aliphatic group, phenyl, $-\text{COR}^6$, $-\text{OR}^6$, $-\text{CN}$, $-\text{SO}_2\text{R}^6$, $-\text{SO}_2\text{NH}_2$, $-\text{N}(\text{R}^6)_2$, $-\text{CO}_2\text{R}^6$, $-\text{CONH}_2$, $-\text{NHCOR}^6$, $-\text{OC}(\text{O})\text{NH}_2$, or $-\text{NHSO}_2\text{R}^6$. When R^1 is an optionally substituted C_{1-6} aliphatic group, the most preferred optional substituents are halogen. Examples of preferred R^1 groups include $-\text{CF}_3$, $-\text{Cl}$, $-\text{F}$, $-\text{CN}$, $-\text{COCH}_3$, $-\text{OCH}_3$, $-\text{OH}$, $-\text{CH}_2\text{CH}_3$, $-\text{OCH}_2\text{CH}_3$, $-\text{CH}_3$, $-\text{CF}_2\text{CH}_3$, cyclohexyl, t-butyl, isopropyl, cyclopropyl, $-\text{C}\equiv\text{CH}$, $-\text{C}\equiv\text{C}-\text{CH}_3$, $-\text{SO}_2\text{CH}_3$, $-\text{SO}_2\text{NH}_2$, $-\text{N}(\text{CH}_3)_2$, $-\text{CO}_2\text{CH}_3$, $-\text{CONH}_2$, $-\text{NHCOCCH}_3$, $-\text{OC}(\text{O})\text{NH}_2$, $-\text{NHSO}_2\text{CH}_3$, and $-\text{OCF}_3$.

[0043] On Ring C of formula I, preferred R^5 substituents, when present, include -halo, -CN, $-\text{NO}_2$, $-\text{N}(\text{R}^4)_2$, optionally substituted C_{1-6} aliphatic group, $-\text{OR}^1$, $-\text{C}(\text{O})\text{R}^1$, $-\text{CO}_2\text{R}^1$, $-\text{CONH}(\text{R}^4)$, $-\text{N}(\text{R}^4)\text{COR}^1$, $-\text{SO}_2\text{N}(\text{R}^4)_2$, and $-\text{N}(\text{R}^4)\text{SO}_2\text{R}^1$. More preferred R^5 substituents include $-\text{Cl}$, $-\text{F}$, $-\text{CN}$, $-\text{CF}_3$, $-\text{NH}_2$, $-\text{NH}(\text{C}_{1-4} \text{ aliphatic})$, $-\text{N}(\text{C}_{1-4} \text{ aliphatic})_2$, $-\text{O}(\text{C}_{1-4} \text{ aliphatic})$, $\text{C}_{1-4} \text{ aliphatic}$, and $-\text{CO}_2(\text{C}_{1-4} \text{ aliphatic})$. Examples of such preferred R^5 substituents include $-\text{Cl}$, $-\text{F}$, $-\text{CN}$, $-\text{CF}_3$, $-\text{NH}_2$, $-\text{NHMe}$, $-\text{NMe}_2$, $-\text{OEt}$, methyl, ethyl, cyclopropyl, isopropyl, t-butyl, and $-\text{CO}_2\text{Et}$.

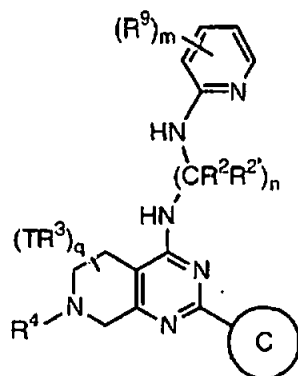
[0044] More preferred ring systems of formula I are the following, which may be substituted as described above, wherein B is pyridyl and R^X and R^Y are each methyl, or R^X and R^Y are taken together with the pyrimidine ring to form a quinazoline, tetrahydroquinazoline, or tetrahydropyridopyrimidine ring:



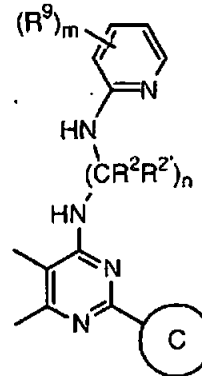
I-A-a



I-B-a



I-D-a



I-H-a

[0045] Particularly preferred are those compounds of formula I-A-a, I-B-a, I-D-a, or I-H-a, wherein ring C is a phenyl ring and R^1 is halo, methyl, cyano, OMe, OH, or trifluoromethyl.

[0046] Preferred formula I compounds include those compounds where one or more of, or each of, B, ring C, R^X , R^Y , or R^1 is defined such that:

(a) B is an optionally substituted 5-6 membered monocyclic or 8-10 membered bicyclic aromatic ring, wherein said monocyclic or bicyclic ring has 1-4 heteroatoms selected from oxygen, sulfur or nitrogen;

(b) Ring C is a phenyl or pyridinyl ring having one or two ortho substituents independently selected from $-R^1$, wherein Ring C is further substituted by $-R^5$ and wherein when Ring C and two adjacent substituents thereon form a bicyclic ring system, the bicyclic ring system is selected from a naphthyl, quinolinyl or isoquinolinyl ring;

(c) R^X is hydrogen or C_{1-4} aliphatic and R^Y is $T-R^3$, or R^X and R^Y are taken together with their intervening atoms to form an optionally substituted 5-7 membered partially saturated or aromatic ring having 0-2 ring nitrogens; and

(d) R^1 is -halo, an optionally substituted C_{1-6} aliphatic group, phenyl, $-COR^6$, $-OR^6$, $-CN$, $-SO_2R^6$, $-SO_2NH_2$, $-N(R^6)_2$, $-CO_2R^6$, $-CONH_2$, $-NHCOR^6$, $-OC(O)NH_2$, or $-NHSO_2R^6$.

[0047] Other preferred formula I compounds include those compounds where one or more of, or each of, B, R^2 , ring C, R^X , R^Y , R^1 , or R^5 is defined such that:

(a) B is an optionally substituted group selected from pyridyl, pyrimidinyl, thiazolyl, indolyl, imidazolyl, oxadiazolyl, tetrazolyl, pyrazinyl, triazolyl, thienyl, furanyl, quinolinyl, purinyl, naphthyl, benzothiazolyl, benzopyridyl, benzimidazolyl, indazolyl,

isothiazolyl, pyrazolyl, pyridazinyl, isoxazolyl, phenyl, benzothiophenyl, or pyridothiophenyl;

(b) R^2 is H, alkyl, haloalkyl, heterocycloaminoalkyl, alkylaminoalkyl, and alkyl, wherein all alkyl moieties have 1-10 carbon atoms are unsubstituted;

(c) Ring C is a phenyl or pyridinyl ring having one or two ortho substituents independently selected from $-R^1$, wherein Ring C is further substituted by $-R^5$ and wherein when Ring C and two adjacent substituents thereon form a bicyclic ring system, the bicyclic ring system is a naphthyl ring;

(d) R^X is hydrogen or methyl and R^Y is $-R'$, $N(R^4)_2$, or $-OR'$, or R^X and R^Y are taken together with their intervening atoms to form a 5-7 membered partially saturated or aromatic carbocyclic ring optionally substituted with $-R'$, halo, $-OR'$, $-C(=O)R'$, $-CO_2R'$, $-COCOR'$, $-NO_2$, $-CN$, $-S(O)R'$, $-SO_2R'$, $-SR'$, $-N(R^4)_2$, $-CON(R^4)_2$, $-SO_2N(R^4)_2$, $-OC(=O)R'$, $-N(R^4)COR'$, $-N(R^4)CO_2$ (optionally substituted C_{1-6} aliphatic), $-N(R^4)N(R^4)_2$, $-C=NN(R^4)_2$, $-C=N-OR'$, $-N(R^4)CON(R^4)_2$, $-N(R^4)SO_2N(R^4)_2$, $-N(R^4)SO_2R'$, or $-OC(=O)N(R^4)_2$;

(e) R^1 is $-halo$, a C_{1-6} haloaliphatic group, a C_{1-6} aliphatic group, phenyl, OMe, OH, or $-CN$; and

(f) each R^5 is independently selected from $-halo$, $-CN$, $-NO_2$, $-N(R^4)_2$, optionally substituted C_{1-6} aliphatic group, $-OR'$, $-C(O)R'$, $-CO_2R'$, $-CONH(R^4)$, $-N(R^4)COR'$, $-SO_2N(R^4)_2$, or $-N(R^4)SO_2R'$.

[0048] Still other preferred formula I compounds include those compounds where one or more of, or each of, B, R^2 , ring C, R^X , R^Y , R^1 , or R^5 is defined such that:

(a) B is an optionally substituted pyridyl group optionally substituted by 0, 1, or 2 occurrences of R^9 , wherein each occurrence of R^9 is independently hydrogen, C_{1-4} alkyl, nitro, amino, cyano, cyanomethyl, trifluoromethyl, hydroxy, and methoxy;

(b) R^2 is H, alkyl, haloalkyl, heterocycloaminoalkyl, alkylaminoalkyl, and alkyl, wherein all alkyl moieties have 1-10 carbon atoms are unsubstituted;

(c) Ring C is a phenyl or pyridinyl ring having one or two ortho substituents independently selected from $-R^1$, wherein Ring C is further substituted by $-R^5$ and wherein when Ring C and two adjacent substituents thereon form a bicyclic ring system, the bicyclic ring system is a naphthyl ring;

(d) R^X is hydrogen or methyl and R^Y is $-R'$, $N(R^4)_2$, or $-OR'$, or R^X and R^Y are taken together with their intervening atoms to form a 5-7 membered partially saturated or aromatic ring having 1-2 nitrogen ring atoms optionally substituted with $-R'$, halo, $-OR'$, $-C(=O)R'$, $-CO_2R'$, $-COCOR'$, $-NO_2$, $-CN$, $-S(O)R'$, $-SO_2R'$, $-SR'$, $-N(R^4)_2$, $-CON(R^4)_2$, $-SO_2N(R^4)_2$, $-OC(=O)R'$, $-N(R^4)COR'$, $-N(R^4)CO_2$ (optionally substituted C_{1-6} aliphatic), $-N(R^4)N(R^4)_2$, $-C=NN(R^4)_2$, $-C=N-OR'$, $-N(R^4)CON(R^4)_2$, $-N(R^4)SO_2N(R^4)_2$, $-N(R^4)SO_2R'$, or $-OC(=O)N(R^4)_2$;

(e) R^1 is $-\text{halo}$, a C_{1-6} haloaliphatic group, a C_{1-6} aliphatic group, phenyl, OMe, OH, or $-CN$; and

(f) each R^5 is independently selected from $-\text{halo}$, $-CN$, $-NO_2$, $-N(R^4)_2$, optionally substituted C_{1-6} aliphatic group, $-OR'$, $-C(O)R'$, $-CO_2R'$, $-CONH(R^4)$, $-N(R^4)COR'$, $-SO_2N(R^4)_2$, or $-N(R^4)SO_2R'$.

[0049] Even more preferred formula I compounds include those compounds where one or more of, or each of, B, R^2 , ring C, R^X , R^Y , R^1 , or R^5 is defined such that:

(a) B is an optionally substituted pyridyl group optionally substituted with 2 independent occurrences of R^9 , wherein each occurrence of R^9 is independently hydrogen, C_{1-4} alkyl, nitro, amino, cyano, cyanomethyl, trifluoromethyl, hydroxy, and methoxy;

(b) each R^2 and $R^{2'}$ is H;

(c) Ring C is a phenyl ring having one or two ortho substituents independently selected from $-R^1$, wherein Ring C is further substituted by $-R^5$;

(d) R^X is hydrogen or methyl and R^Y is methyl, methoxymethyl, ethyl, cyclopropyl, isopropyl, t-butyl, alkyl- or an optionally substituted group selected from 2-pyridyl, 4-pyridyl, piperidinyl, or phenyl, or R^X and R^Y are taken together with their intervening atoms to form an optionally substituted benzo ring or partially saturated 6-membered carbocyclic ring;

(e) R^1 is $-\text{halo}$, a C_{1-4} aliphatic group optionally substituted with halogen, OMe, OH, or $-CN$; and

(f) each R^5 is independently selected from $-Cl$, $-F$, $-CN$, $-CF_3$, $-NH_2$, $-NH(C_{1-4}$ aliphatic), $-N(C_{1-4}$ aliphatic) $_2$, $-O(C_{1-4}$ aliphatic), optionally substituted C_{1-4} aliphatic, and $-CO_2(C_{1-4}$ aliphatic).

[0050] Representative compounds of formula I are shown below in Table 1.

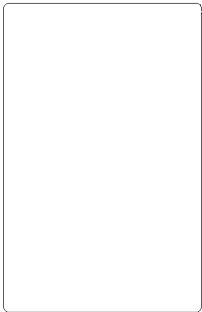
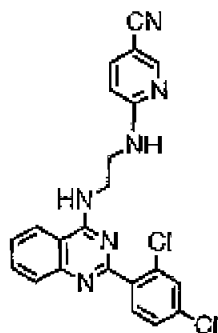
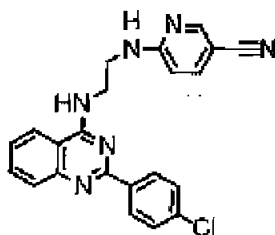


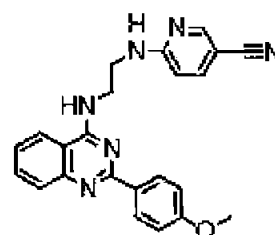
Table 1



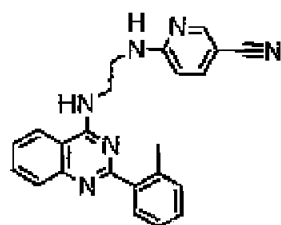
I-1



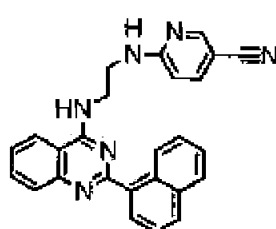
I-2



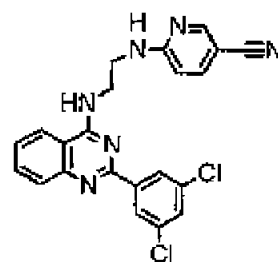
I-3



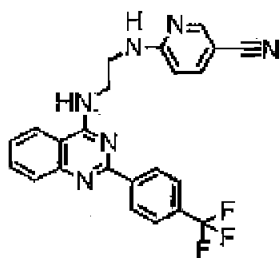
I-4



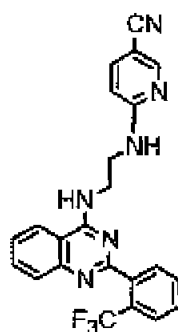
I-5



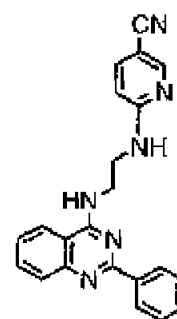
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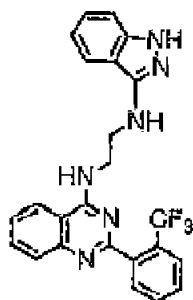
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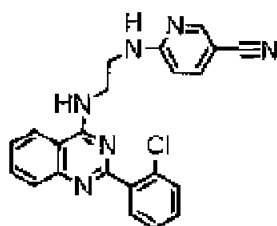
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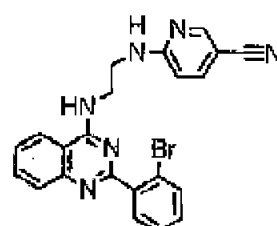
I-9



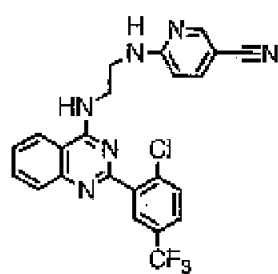
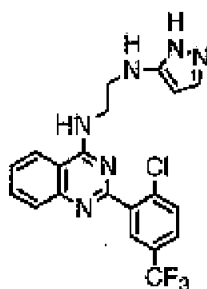
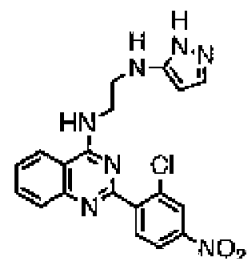
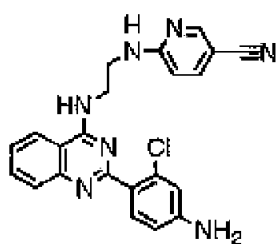
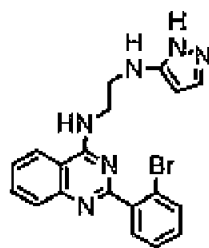
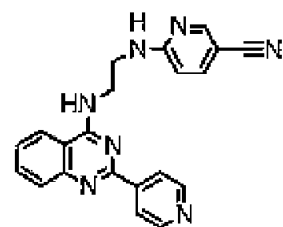
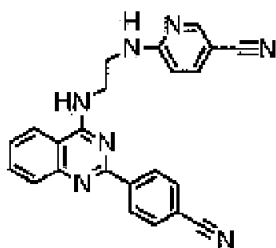
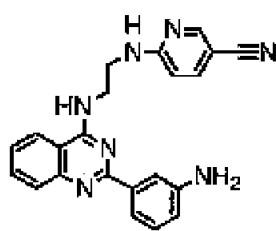
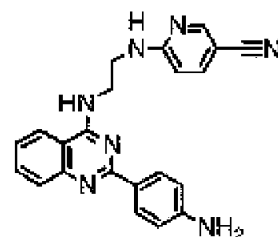
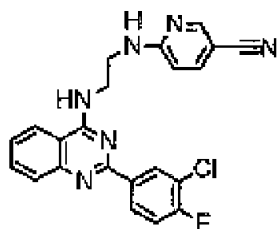
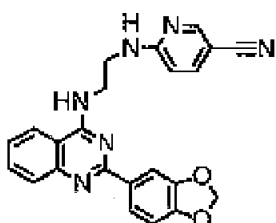
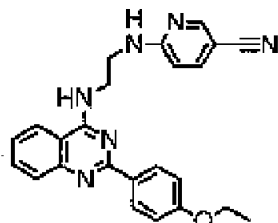
I-10

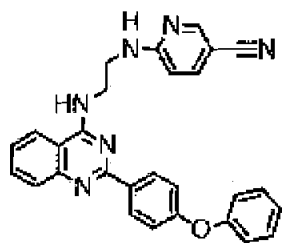


I-11

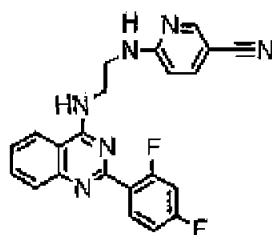


I-12

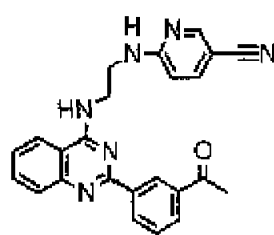
**I-13****I-14****I-15****I-16****I-17****I-18****I-19****I-20****I-21****I-22****I-23****I-24**



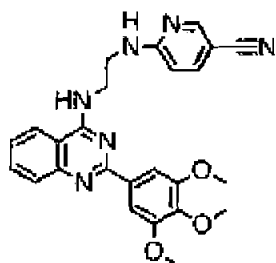
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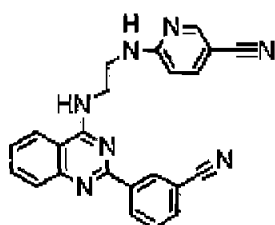
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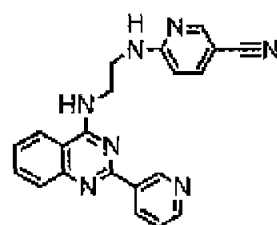
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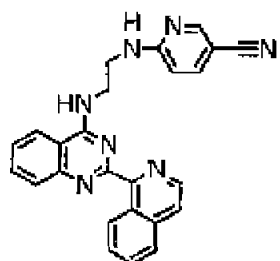
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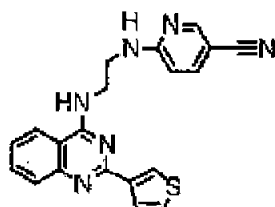
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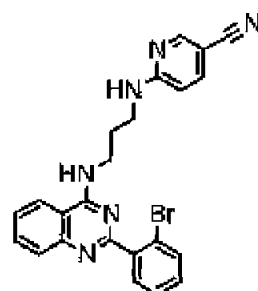
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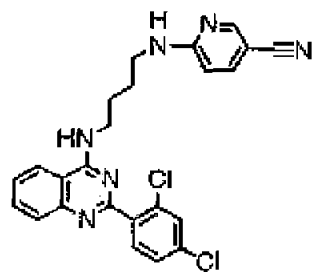
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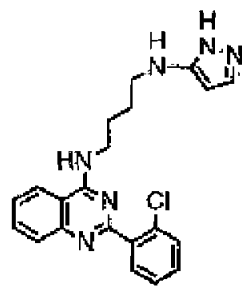
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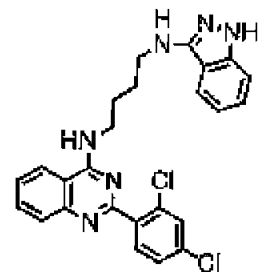
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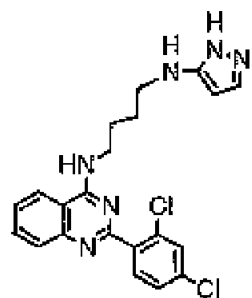
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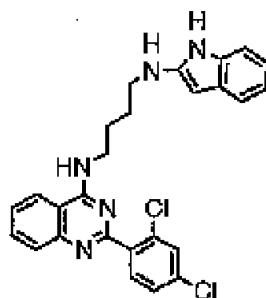
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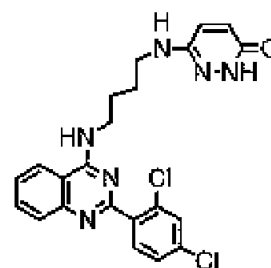
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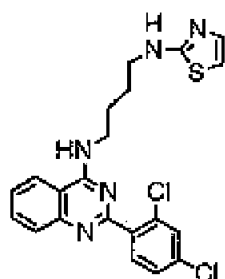
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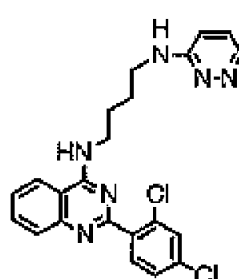
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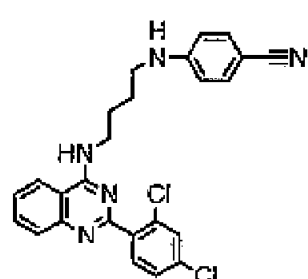
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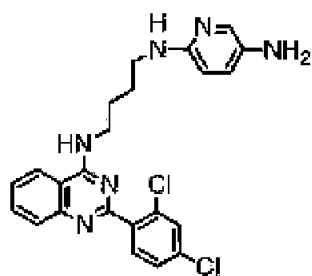
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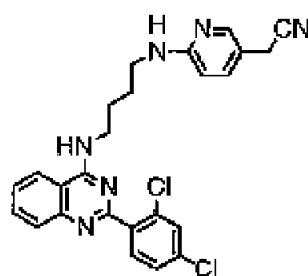
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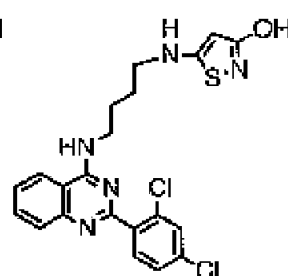
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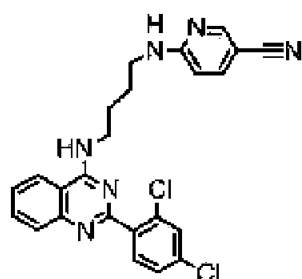
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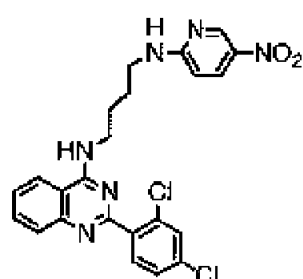
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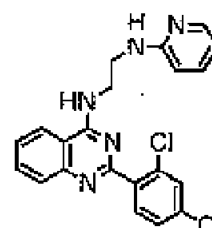
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I-46

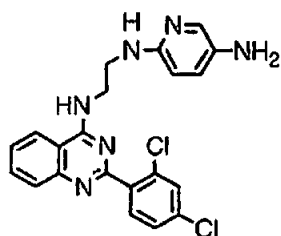


I-47

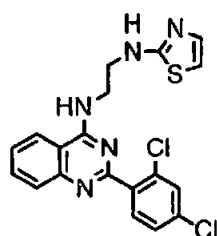


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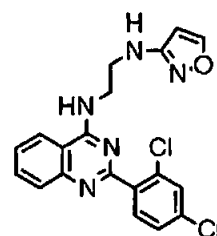
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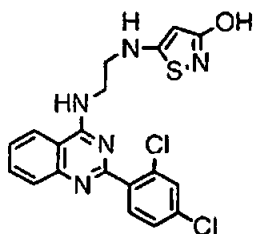
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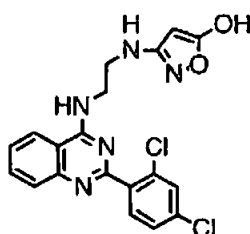
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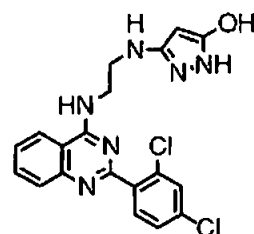
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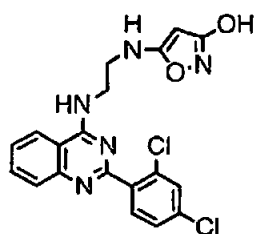
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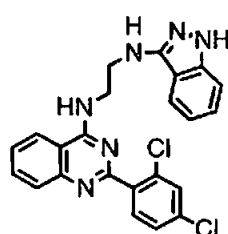
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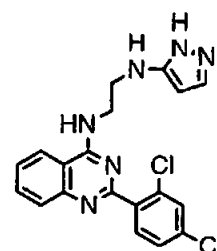
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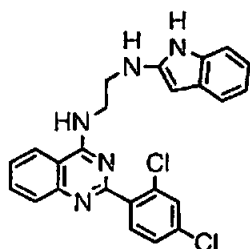
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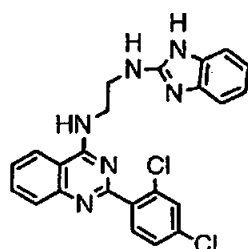
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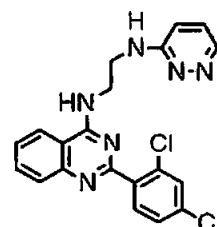
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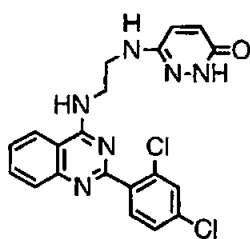
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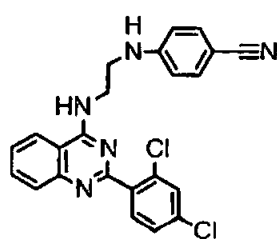
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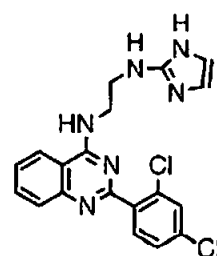
I-60



I-61

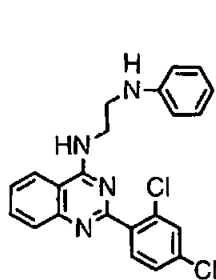


I-62

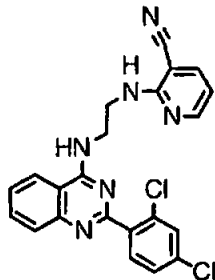


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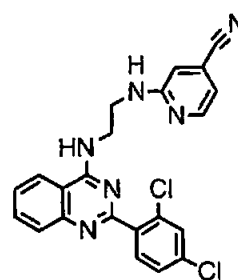
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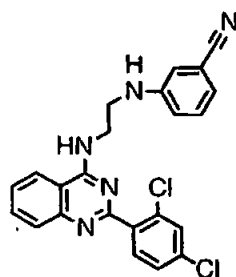
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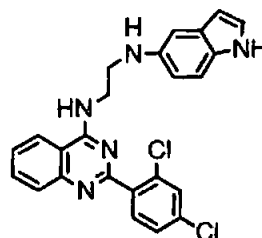
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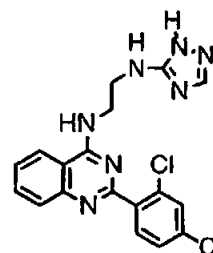
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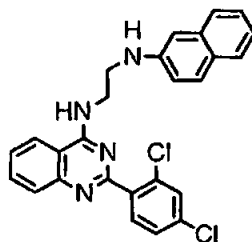
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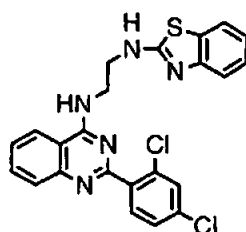
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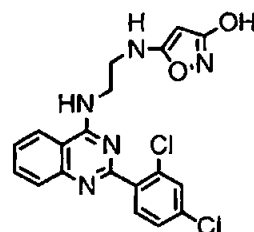
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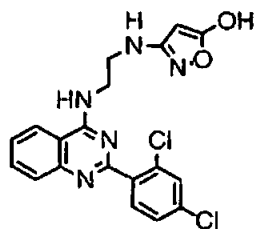
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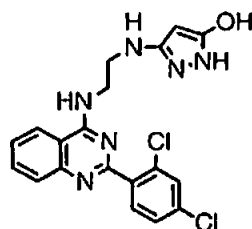
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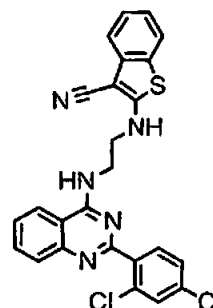
I-72



I-73

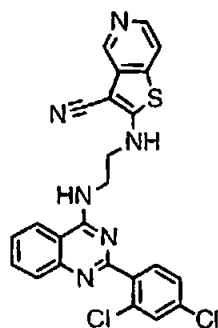


I-74

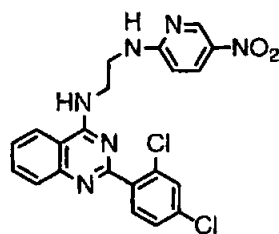


I-75

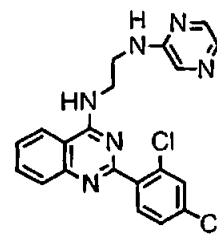
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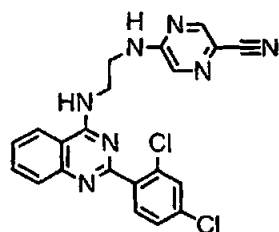
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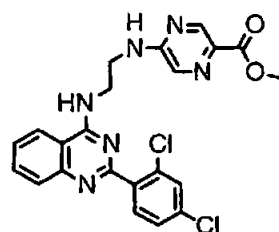
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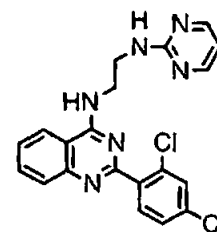
I-78



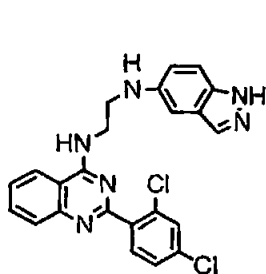
I-79



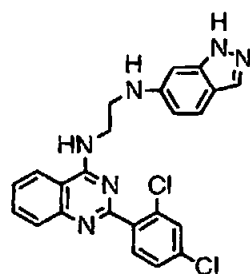
I-80



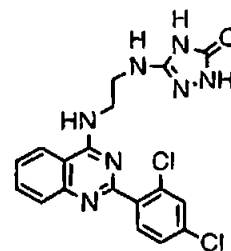
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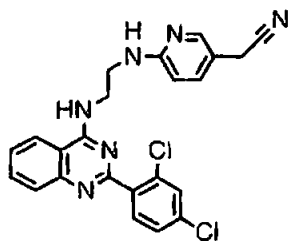
I-82



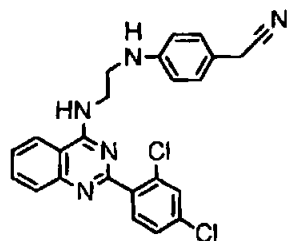
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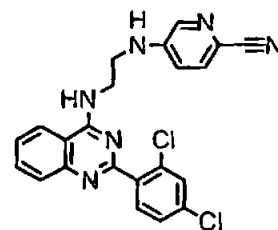
I-84



I-85

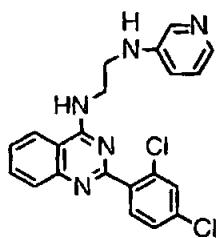


I-86

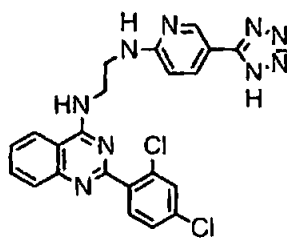


I-87

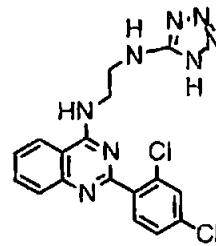
48



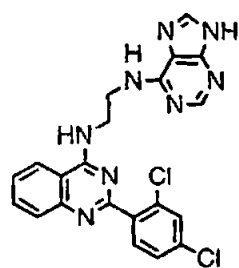
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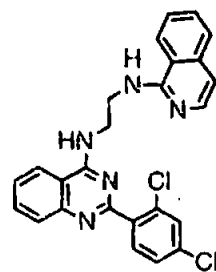
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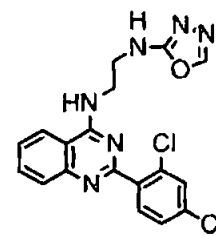
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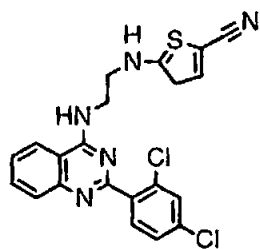
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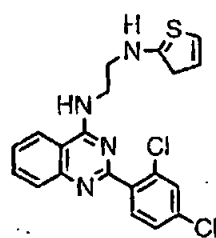
I-92



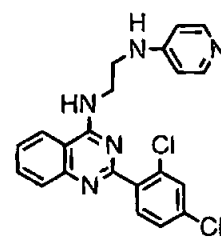
I-93



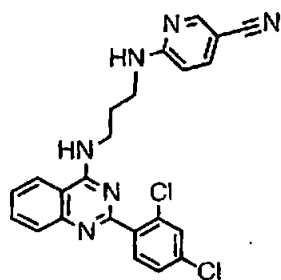
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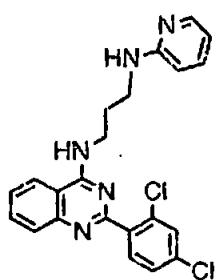
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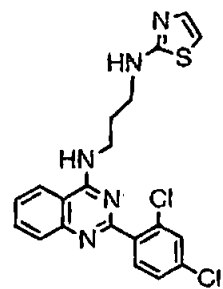
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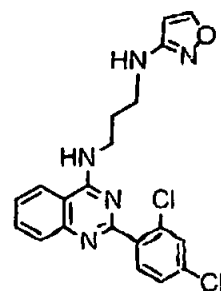
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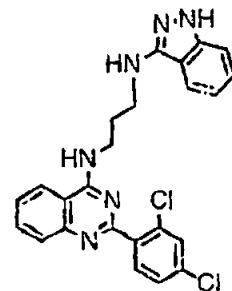
I-98



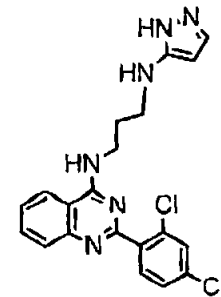
I-99



I-100

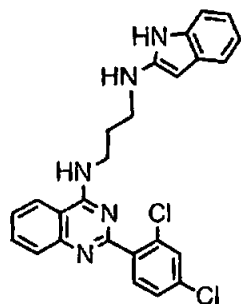


I-101

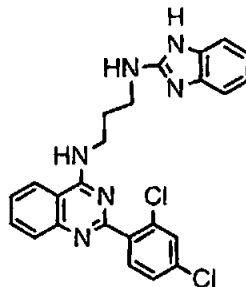


I-102

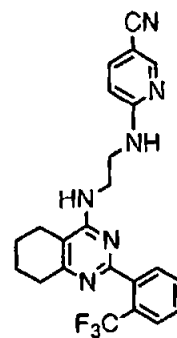
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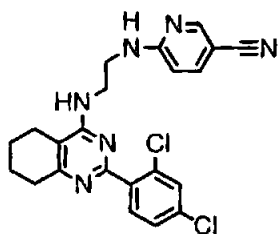
I-103



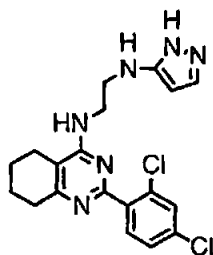
I-104



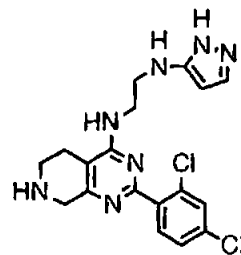
I-105



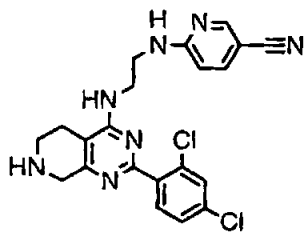
I-106



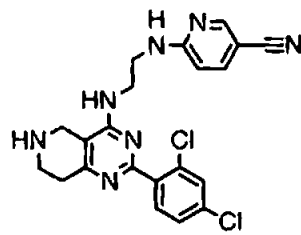
I-107



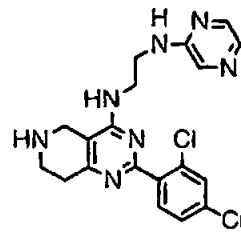
I-108



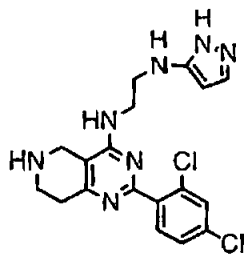
I-109



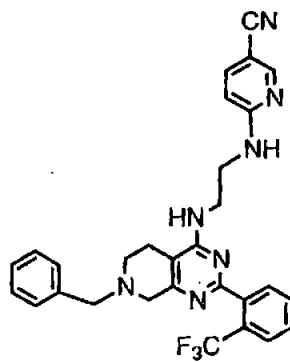
I-110



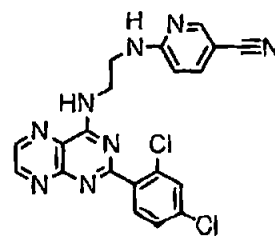
I-111



I-112

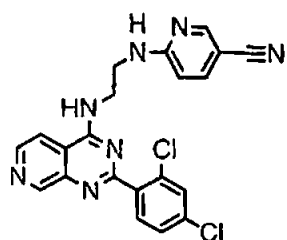


I-113

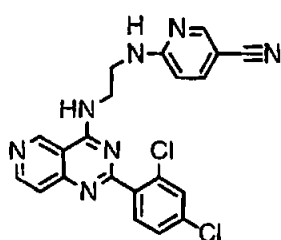


I-114

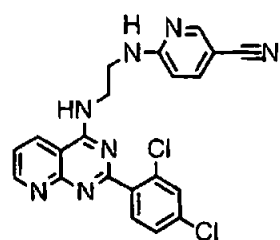
47



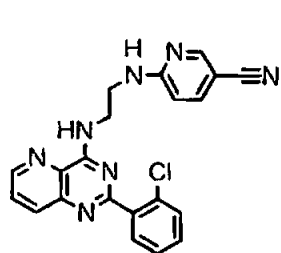
I-115



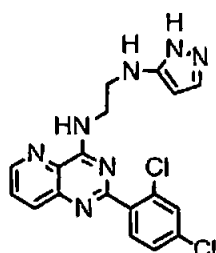
I-116



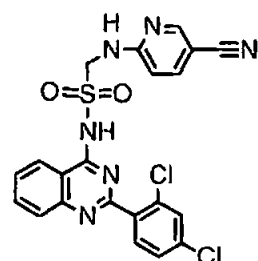
I-117



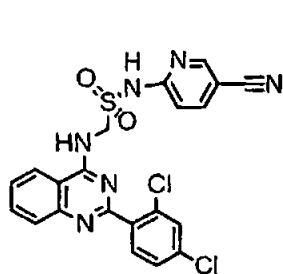
I-118



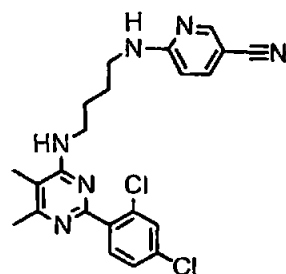
I-119



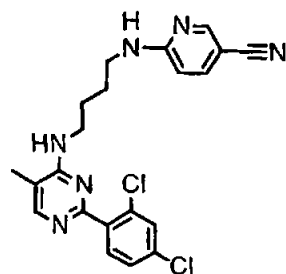
I-120



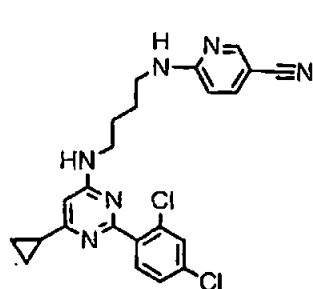
I-121



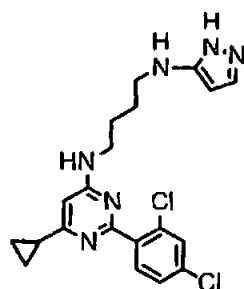
I-122



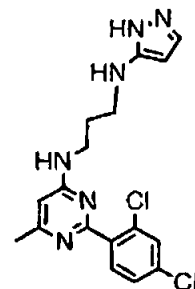
I-123



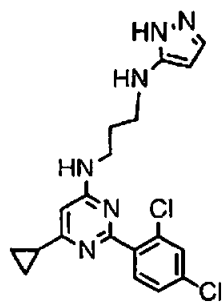
I-124



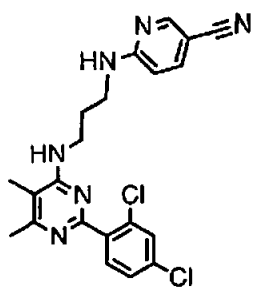
I-125



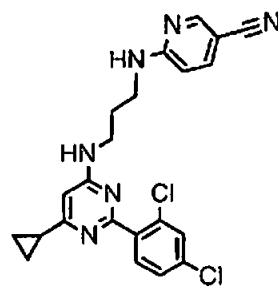
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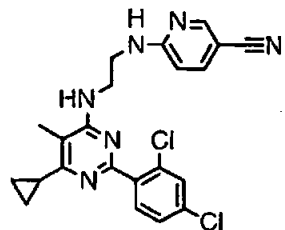
I-127



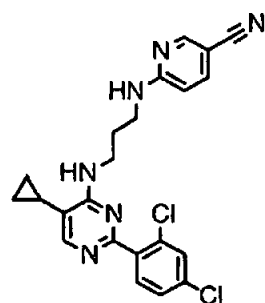
I-128



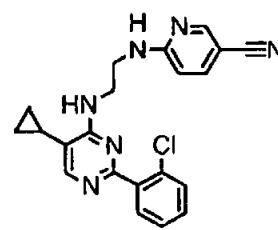
I-129



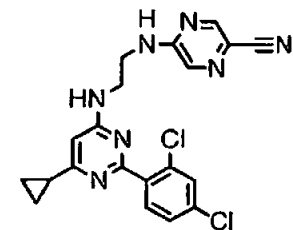
I-130



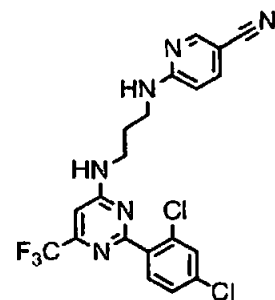
I-131



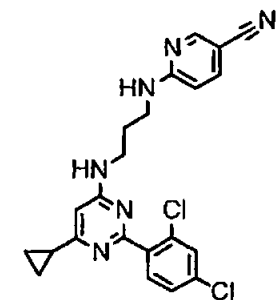
I-132



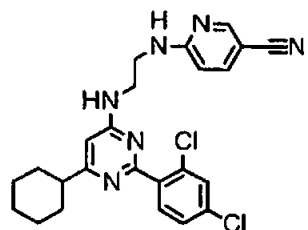
I-133



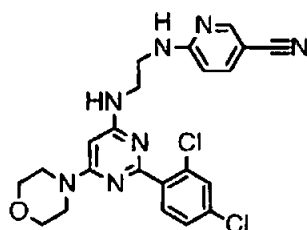
I-134



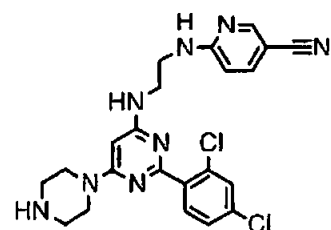
I-135



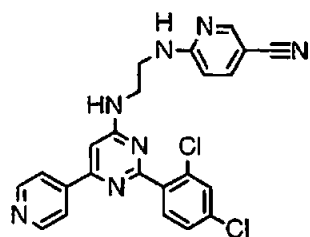
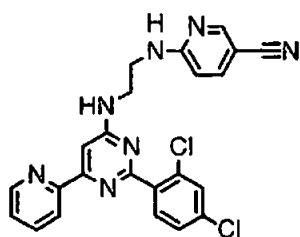
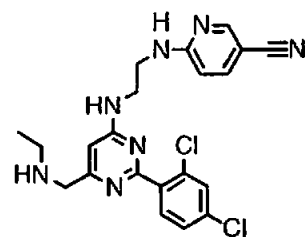
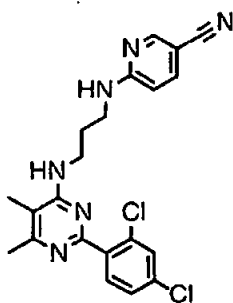
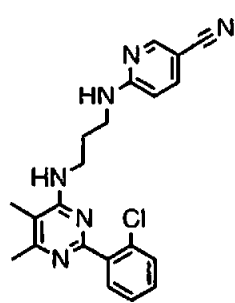
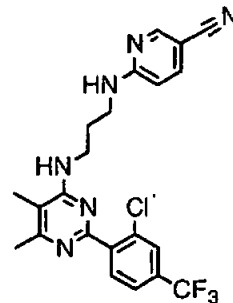
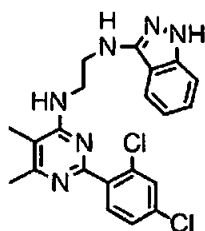
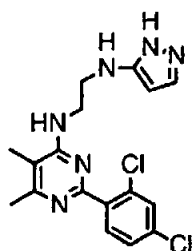
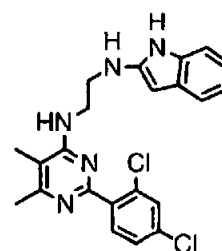
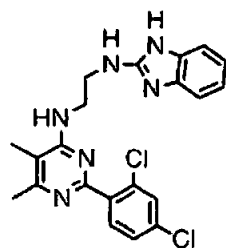
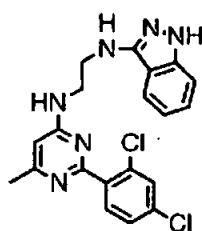
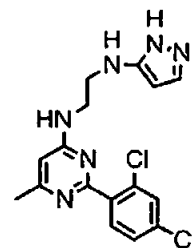
I-136

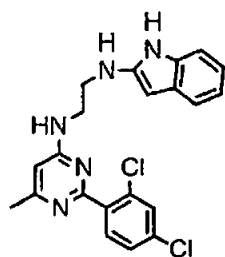


I-137

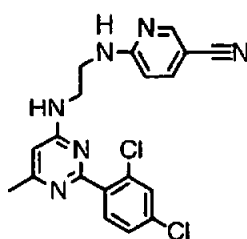


I-138

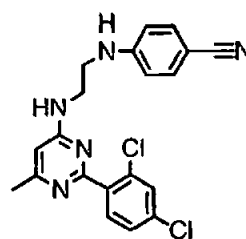
**I-139****I-140****I-141****I-142****I-143****I-144****I-145****I-146****I-147****I-148****I-149****I-150**



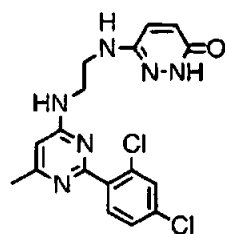
I-151



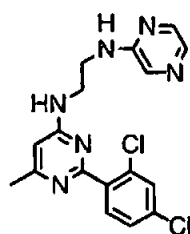
I-152



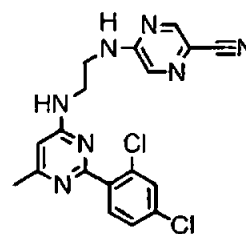
I-153



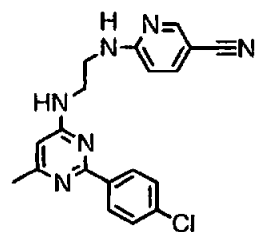
I-154



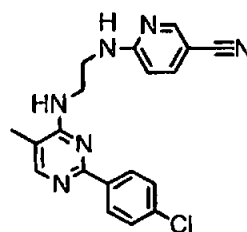
I-155



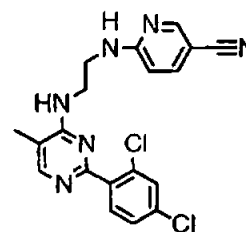
I-156



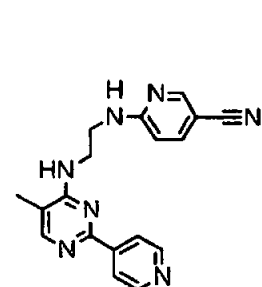
I-157



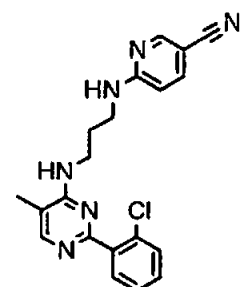
I-158



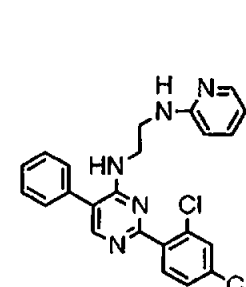
I-159



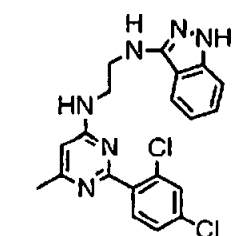
I-160



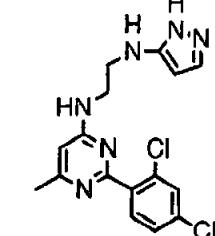
I-161



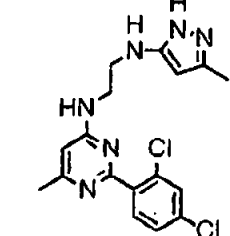
I-162



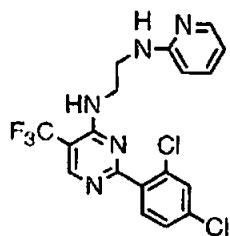
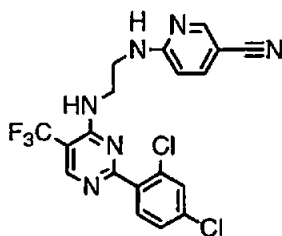
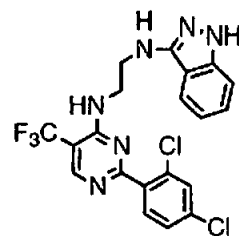
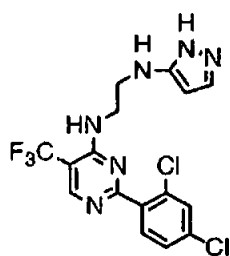
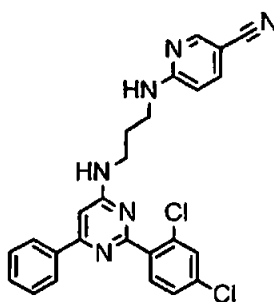
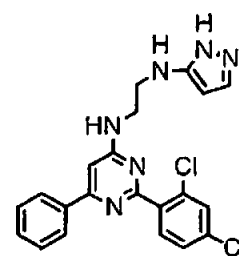
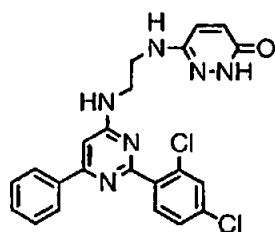
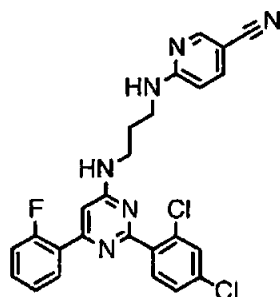
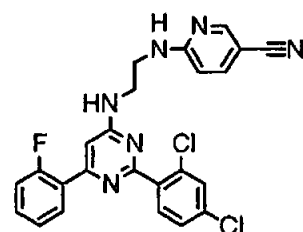
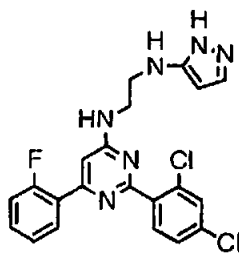
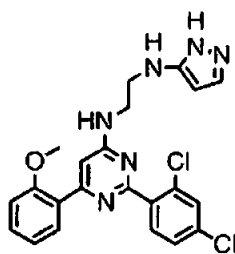
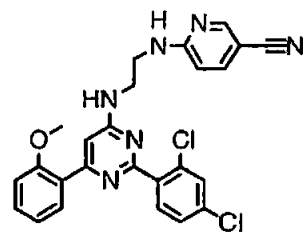
I-163

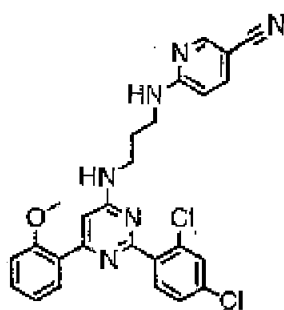
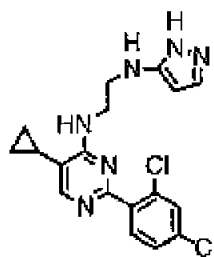
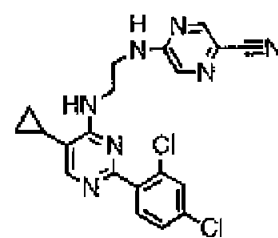
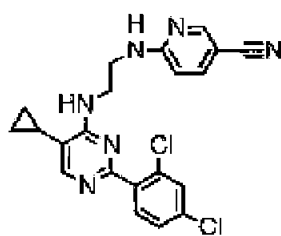
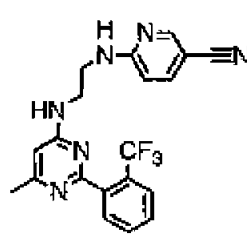
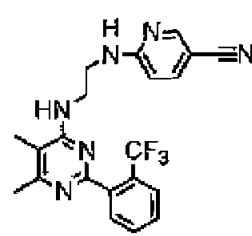
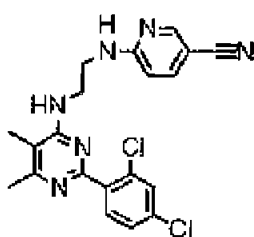
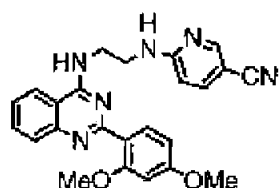
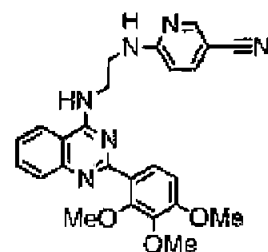
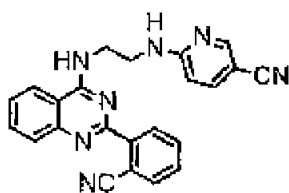
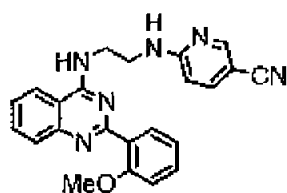
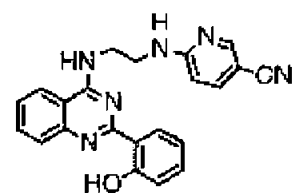


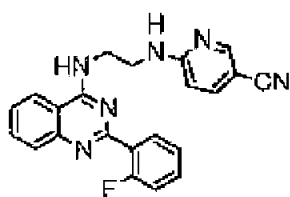
I-164



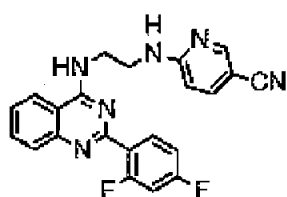
I-165

**I-166****I-167****I-168****I-169****I-170****I-171****I-172****I-173****I-174****I-175****I-176****I-177**

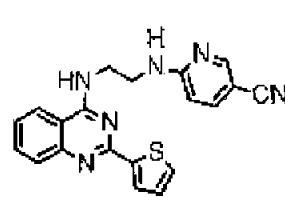
**I-178****I-179****I-180****I-181****I-182****I-183****I-184****I-185****I-186****I-187****I-188****I-189**



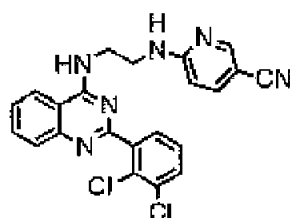
I-190



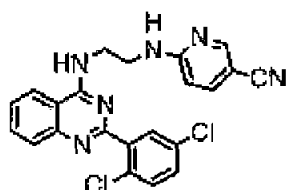
I-191



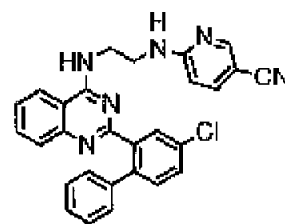
I-192



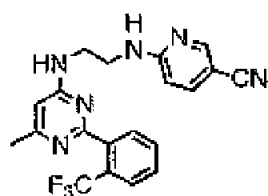
I-193



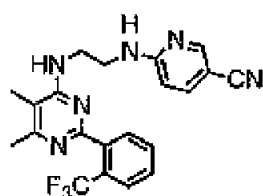
I-194



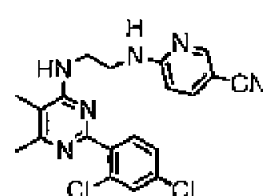
I-195



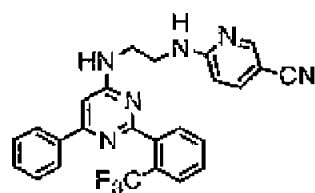
I-196



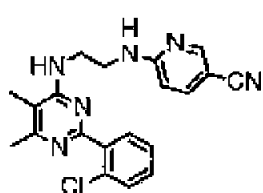
I-197



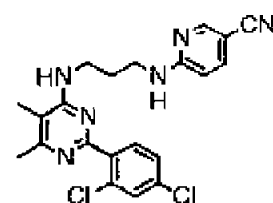
I-198



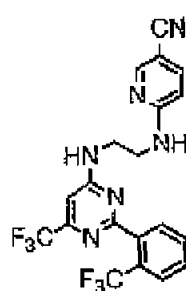
I-199



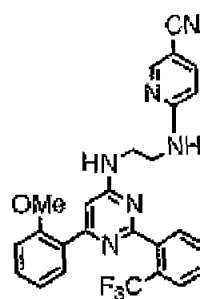
I-200



I-201



I-202



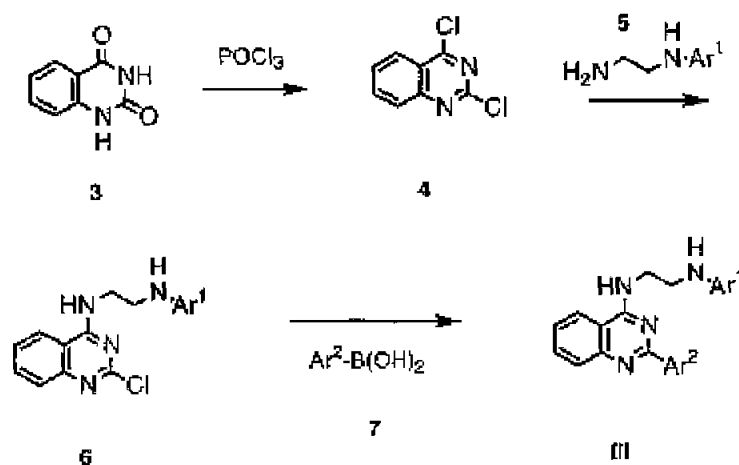
I-203

[0051] *III. General Synthetic Methodology:*

[0052] The compounds of this invention may be prepared in general by methods known to those skilled in the art for analogous compounds, as illustrated by the general scheme below, and the preparative examples that follow.

[0053] Although certain exemplary embodiments are depicted and described above and herein, it will be appreciated that a compounds of the invention can be prepared according to the methods described generally above using appropriate starting materials.

[0054] Scheme I



[0055] Scheme I shows a general approach for making compounds of formula III. In Scheme I, Ar¹ is a synthetic equivalent of B in formula I and Ar² is a synthetic equivalent of Ring C in formula I. Preparation of the dichloropyrimidine 4 may be achieved in a manner similar to that described in *Chem. Pharm. Bull.*, 30, 3121-3124 (1982). The chlorine in position 4 of intermediate 4 may be replaced by a diamine 5 to provide intermediate 6 in a manner similar to that described in *J. Med. Chem.*, 38, 3547-3557 (1995). The diamine 5 may be either commercially available, readily synthesized via methods known in the art

such as those described in WO 99/65897 (Chiron), or provided by methods disclosed in the synthetic examples. Although an example where Q is $-\text{CH}_2\text{CH}_2-$ is depicted above, it will be appreciated that additional compounds where Q is described generally for formula I can also be prepared according to the methods cited above. Ring C is then introduced using a boronic ester 7 under palladium catalysis [see *Tetrahedron*, **48**, 8117-8126 (1992)]. This method is illustrated by the following procedure.

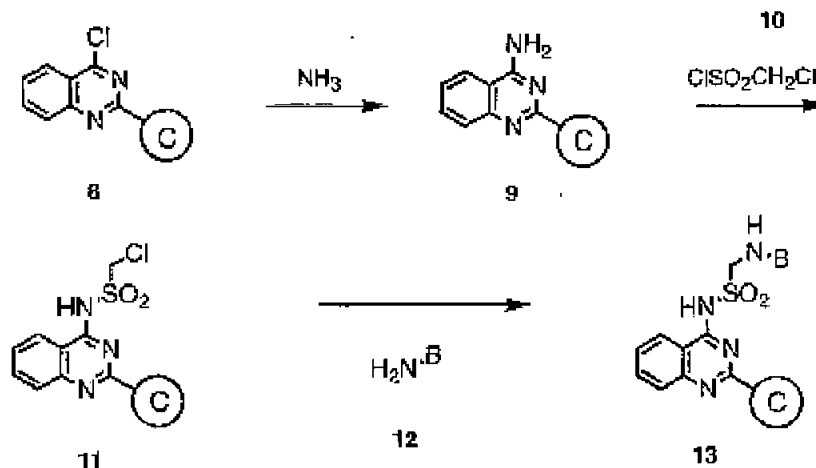
[0056] A suspension of 1*H*-quinazoline-2,4-dione 3 (10.0 g, 61.7 mmol) in POCl_3 (60 mL, 644 mmol) and *N,N*-dimethylaniline (8 mL, 63.1 mmol) is heated under reflux for 2 h. Excess POCl_3 is evaporated under vacuum, the residue is poured into ice, and the precipitate is collected by filtration. The crude solid 2,4-dichloroquinazoline product 4 may be used without further purification.

[0057] To a solution of 2,4-dichloro-quinazoline 4 (3.3 g, 16.6 mmol) in anhydrous ethanol (150 mL) is added a diamine 5 (32.9 mmol). The mixture is stirred at room temperature for 4 hours, and the resulting precipitate is collected by filtration, washed with ethanol, and dried under vacuum to afford intermediate 6.

[0058] To a solution of intermediate 6 (0.19 mmol) in DMF (1.0 mL) is added the desired boronic acid 7 (0.38 mmol), 2M Na_2CO_3 (0.96 mmol), and tri-*t*-butylphosphine (0.19 mmol). Under nitrogen, $\text{PdCl}_2(\text{dppf})$ (0.011 mmol) is added in one portion. The reaction mixture is then heated at 80°C for 5 to 10 hours, cooled to room temperature, and poured into water (2 mL). The resulting precipitate is collected by filtration, washed with water, and purified by HPLC.

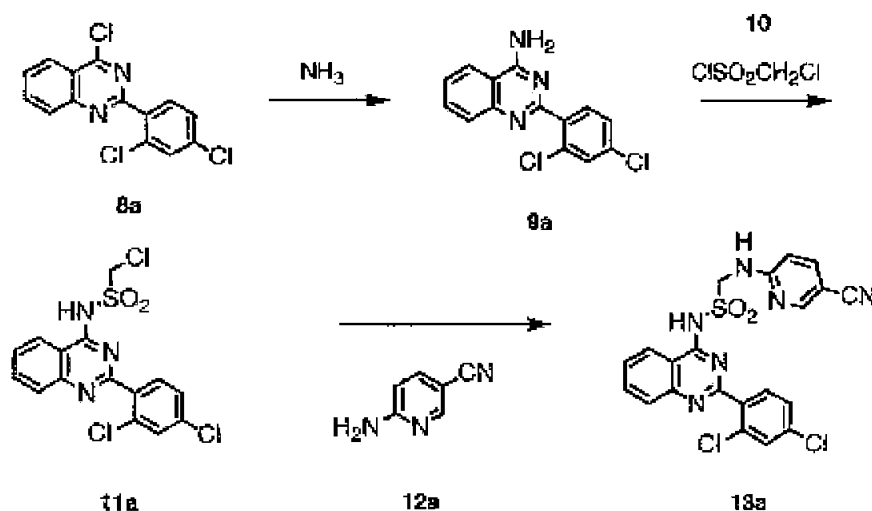
[0059] Compounds where one methylene unit of Q is replaced by SO_2 can be prepared according to the general methods depicted in Schemes 2, 3, 4 and 5 below. Scheme 2 illustrates a general method for the preparation of compounds of formula 13. Although compounds where Ring A is quinazolinyl are depicted below, it will be appreciated that compounds of general formula I (for example compounds having other ring systems as described generally herein) can also be prepared according to these methods.

[0060] **Scheme 2**



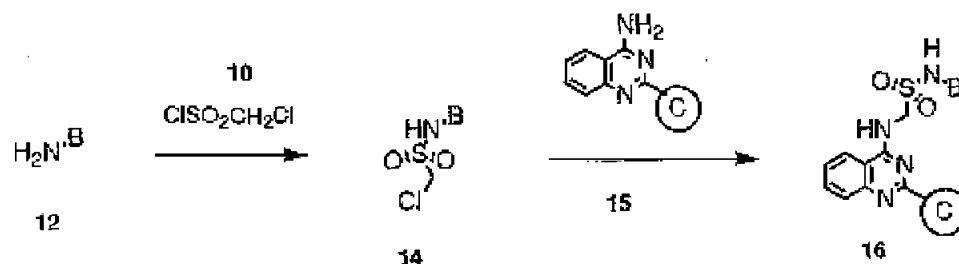
[0061] Scheme 3 depicts the preparation of certain exemplary compounds where ring C is a substituted phenyl moiety, and B is a substituted pyridyl moiety.

[0062] Scheme 3



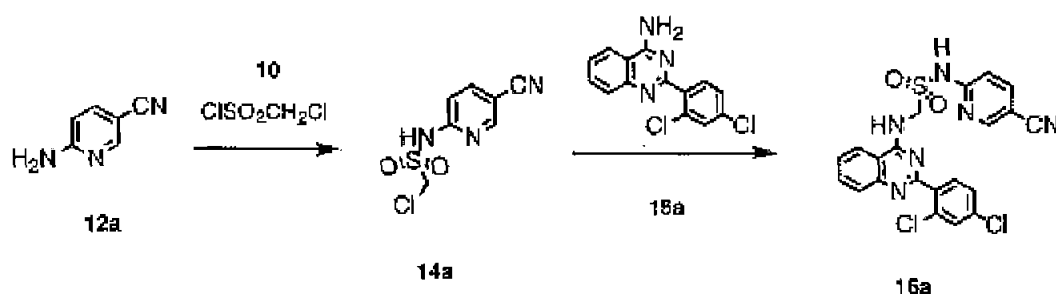
[0063] Scheme 4 illustrates a general method for the preparation of compounds of formula 16. Although compounds where Ring A is quinazolinyl are depicted below, it will be appreciated that compounds of general formula I (for example compounds having other ring systems as described generally herein) can also be prepared according to these methods.

[0064] Scheme 4



[0065] Scheme 5 depicts the preparation of certain exemplary compounds where ring C is a substituted phenyl moiety, and B is a substituted pyridyl moiety.

[0066] Scheme 5



[0067] One having ordinary skill in the art may synthesize other compounds of this invention following the teachings of the specification using reagents that are readily synthesized or commercially available.

[0068] *IV. Uses of Compounds of the Invention:*

[0069] The activity of a compound utilized in this invention as an inhibitor of GSK-3 kinase may be assayed *in vitro*, *in vivo* or in a cell line according to methods known in the art. *In vitro* assays include assays that determine inhibition of either the phosphorylation activity or ATPase activity of activated GSK-3. Alternate *in vitro* assays quantitate the ability of the inhibitor to bind to GSK-3. Inhibitor binding may be measured by radiolabelling the inhibitor prior to binding, isolating the inhibitor/GSK-3 complex and determining the amount of radiolabel bound. Alternatively, inhibitor binding may be determined by running a competition experiment where new inhibitors are incubated with GSK-3 bound to known radioligands. Detailed conditions for assaying a compound utilized in this invention as an inhibitor of GSK-3 kinase are set forth in the Examples below.

[0070] According to another embodiment, the invention provides a composition comprising a compound of this invention or a pharmaceutically acceptable derivative thereof and a pharmaceutically acceptable carrier, adjuvant, or vehicle. Preferably, the amount of compound in the compositions of this invention is such that is therapeutically

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effective, and most preferably effective to detectably inhibit a protein kinase, particularly GSK-3 kinase, in a biological sample or in a patient. Preferably the composition of this invention is formulated for administration to a patient in need of such composition. Most preferably, the composition of this invention is formulated for oral administration to a patient.

[0071] The term "patient", as used herein, means an animal, preferably a mammal, and most preferably a human.

[0072] The term "pharmaceutically acceptable carrier, adjuvant, or vehicle" refers to a non-toxic carrier, adjuvant, or vehicle that does not destroy the pharmacological activity of the compound with which it is formulated. Pharmaceutically acceptable carriers, adjuvants or vehicles that may be used in the compositions of this invention include, but are not limited to, ion exchangers, alumina, aluminum stearate, lecithin, serum proteins, such as human serum albumin, buffer substances such as phosphates, glycine, sorbic acid, potassium sorbate, partial glyceride mixtures of saturated vegetable fatty acids, water, salts or electrolytes, such as protamine sulfate, disodium hydrogen phosphate, potassium hydrogen phosphate, sodium chloride, zinc salts, colloidal silica, magnesium trisilicate, polyvinyl pyrrolidone, cellulose-based substances, polyethylene glycol, sodium carboxymethylcellulose, polyacrylates, waxes, polyethylene-polyoxypropylene-block polymers, polyethylene glycol and wool fat.

[0073] The term "detectably inhibit", as used herein means a measurable change in GSK-3 activity between a sample comprising said composition and a GSK-3 kinase and an equivalent sample comprising GSK-3 kinase in the absence of said composition.

[0074] Pharmaceutically acceptable salts of the compounds of this invention include those derived from pharmaceutically acceptable inorganic and organic acids and bases. Examples of suitable acid salts include acetate, adipate, alginate, aspartate, benzoate, benzenesulfonate, bisulfate, butyrate, citrate, camphorate, camphorsulfonate, cyclopentanepropionate, digluconate, dodecylsulfate, ethanesulfonate, formate, fumarate, glucoheptanoate, glycerophosphate, glycolate, hemisulfate, heptanoate, hexanoate, hydrochloride, hydrobromide, hydroiodide, 2-hydroxyethanesulfonate, lactate, malate, malonate, methanesulfonate, 2-naphthalenesulfonate, nicotinate, nitrate, oxalate, palmoate, pectinate, persulfate, 3-phenylpropionate, phosphate, picrate, pivalate, propionate, salicylate, succinate, sulfate, tartrate, thiocyanate, tosylate and undecanoate. Other acids, such as oxalic, while not in themselves pharmaceutically acceptable, may be employed in

the preparation of salts useful as intermediates in obtaining the compounds of the invention and their pharmaceutically acceptable acid addition salts.

[0075] Salts derived from appropriate bases include alkali metal (e.g., sodium and potassium), alkaline earth metal (e.g., magnesium), ammonium and $N^+(C_{1-4} \text{ alkyl})_4$ salts. This invention also envisions the quaternization of any basic nitrogen-containing groups of the compounds disclosed herein. Water or oil-soluble or dispersible products may be obtained by such quaternization.

[0076] The compositions of the present invention may be administered orally, parenterally, by inhalation spray, topically, rectally, nasally, buccally, vaginally or via an implanted reservoir. The term "parenteral" as used herein includes subcutaneous, intravenous, intramuscular, intra-articular, intra-synovial, intrasternal, intrathecal, intrahepatic, intralesional and intracranial injection or infusion techniques. Preferably, the compositions are administered orally, intraperitoneally or intravenously. Sterile injectable forms of the compositions of this invention may be aqueous or oleaginous suspension. These suspensions may be formulated according to techniques known in the art using suitable dispersing or wetting agents and suspending agents. The sterile injectable preparation may also be a sterile injectable solution or suspension in a non-toxic parenterally-acceptable diluent or solvent, for example as a solution in 1,3-butanediol. Among the acceptable vehicles and solvents that may be employed are water, Ringer's solution and isotonic sodium chloride solution. In addition, sterile, fixed oils are conventionally employed as a solvent or suspending medium.

[0077] For this purpose, any bland fixed oil may be employed including synthetic mono- or di-glycerides. Fatty acids, such as oleic acid and its glyceride derivatives are useful in the preparation of injectables, as are natural pharmaceutically-acceptable oils, such as olive oil or castor oil, especially in their polyoxyethylated versions. These oil solutions or suspensions may also contain a long-chain alcohol diluent or dispersant, such as carboxymethyl cellulose or similar dispersing agents that are commonly used in the formulation of pharmaceutically acceptable dosage forms including emulsions and suspensions. Other commonly used surfactants, such as Tweens, Spans and other emulsifying agents or bioavailability enhancers which are commonly used in the manufacture of pharmaceutically acceptable solid, liquid, or other dosage forms may also be used for the purposes of formulation.

[0078] The pharmaceutically acceptable compositions of this invention may be orally administered in any orally acceptable dosage form including, but not limited to, capsules, tablets, aqueous suspensions or solutions. In the case of tablets for oral use, carriers commonly used include lactose and corn starch. Lubricating agents, such as magnesium stearate, are also typically added. For oral administration in a capsule form, useful diluents include lactose and dried cornstarch. When aqueous suspensions are required for oral use, the active ingredient is combined with emulsifying and suspending agents. If desired, certain sweetening, flavoring or coloring agents may also be added.

[0079] Alternatively, the pharmaceutically acceptable compositions of this invention may be administered in the form of suppositories for rectal administration. These can be prepared by mixing the agent with a suitable non-irritating excipient that is solid at room temperature but liquid at rectal temperature and therefore will melt in the rectum to release the drug. Such materials include cocoa butter, beeswax and polyethylene glycols.

[0080] The pharmaceutically acceptable compositions of this invention may also be administered topically, especially when the target of treatment includes areas or organs readily accessible by topical application, including diseases of the eye, the skin, or the lower intestinal tract. Suitable topical formulations are readily prepared for each of these areas or organs.

[0081] Topical application for the lower intestinal tract can be effected in a rectal suppository formulation (see above) or in a suitable enema formulation. Topically-transdermal patches may also be used.

[0082] For topical applications, the pharmaceutically acceptable compositions may be formulated in a suitable ointment containing the active component suspended or dissolved in one or more carriers. Carriers for topical administration of the compounds of this invention include, but are not limited to, mineral oil, liquid petrolatum, white petrolatum, propylene glycol, polyoxyethylene, polyoxypropylene compound, emulsifying wax and water. Alternatively, the pharmaceutically acceptable compositions can be formulated in a suitable lotion or cream containing the active components suspended or dissolved in one or more pharmaceutically acceptable carriers. Suitable carriers include, but are not limited to, mineral oil, sorbitan monostearate, polysorbate 60, cetyl esters wax, cetyl alcohol, 2-octyldodecanol, benzyl alcohol and water.

[0083] For ophthalmic use, the pharmaceutically acceptable compositions may be formulated as micronized suspensions in isotonic, pH adjusted sterile saline, or, preferably,

as solutions in isotonic, pH adjusted sterile saline, either with or without a preservative such as benzylalkonium chloride. Alternatively, for ophthalmic uses, the pharmaceutically acceptable compositions may be formulated in an ointment such as petrolatum.

[0084] The pharmaceutically acceptable compositions of this invention may also be administered by nasal aerosol or inhalation. Such compositions are prepared according to techniques well-known in the art of pharmaceutical formulation and may be prepared as solutions in saline, employing benzyl alcohol or other suitable preservatives, absorption promoters to enhance bioavailability, fluorocarbons, and/or other conventional solubilizing or dispersing agents.

[0085] Most preferably, the pharmaceutically acceptable compositions of this invention are formulated for oral administration.

[0086] The amount of the compounds of the present invention that may be combined with the carrier materials to produce a composition in a single dosage form will vary depending upon the host treated, the particular mode of administration. Preferably, the compositions should be formulated so that a dosage of between 0.01-100 mg/kg body weight/day of the inhibitor can be administered to a patient receiving these compositions.

[0087] It should also be understood that a specific dosage and treatment regimen for any particular patient will depend upon a variety of factors, including the activity of the specific compound employed, the age, body weight, general health, sex, diet, time of administration, rate of excretion, drug combination, and the judgment of the treating physician and the severity of the particular disease being treated. The amount of a compound of the present invention in the composition will also depend upon the particular compound in the composition.

[0088] Depending upon the particular condition, or disease, to be treated or prevented, additional therapeutic agents, which are normally administered to treat or prevent that condition, may also be present in the compositions of this invention. As used herein, additional therapeutic agents that are normally administered to treat or prevent a particular disease, or condition, are known as "appropriate for the disease, or condition, being treated".

[0089] For example, chemotherapeutic agents or other anti-proliferative agents may be combined with the compounds of this invention to treat proliferative diseases and cancer. Examples of known chemotherapeutic agents include, but are not limited to, Gleevec™, adriamycin, dexamethasone, vincristine, cyclophosphamide, fluorouracil, topotecan, taxol, interferons, and platinum derivatives.

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[0090] Other examples of agents the inhibitors of this invention may also be combined with include, without limitation: treatments for Alzheimer's Disease such as Aricept[®] and Exelon[®]; treatments for Parkinson's Disease such as L-DOPA/carbidopa, entacapone, ropinrole, pramipexole, bromocriptine, pergolide, trihexephendyl, and amantadine; agents for treating Multiple Sclerosis (MS) such as beta interferon (e.g., Avonex[®] and Rebif[®]), Copaxone[®], and mitoxantrone; treatments for asthma such as albuterol and Singulair[®]; agents for treating schizophrenia such as zyprexa, risperdal, seroquel, and haloperidol; anti-inflammatory agents such as corticosteroids, TNF blockers, IL-1 RA, azathioprine, cyclophosphamide, and sulfasalazine; immunomodulatory and immunosuppressive agents such as cyclosporin, tacrolimus, rapamycin, mycophenolate mofetil, interferons, corticosteroids, cyclophosphamide, azathioprine, and sulfasalazine; neurotrophic factors such as acetylcholinesterase inhibitors, MAO inhibitors, interferons, anti-convulsants, ion channel blockers, riluzole, and anti-Parkinsonian agents; agents for treating cardiovascular disease such as beta-blockers, ACE inhibitors, diuretics, nitrates, calcium channel blockers, and statins; agents for treating liver disease such as corticosteroids, cholestyramine, interferons, and anti-viral agents; agents for treating blood disorders such as corticosteroids, anti-leukemic agents, and growth factors; agents for treating immunodeficiency disorders such as gamma globulin; and agents for treating diabetes such as insulin or insulin analogues, in injectable or inhalation form, glitazones, alpha glucosidase inhibitors, biguanides, insulin sensitizers, and sulfonyl ureas.

[0091] The amount of additional therapeutic agent present in the compositions of this invention will be no more than the amount that would normally be administered in a composition comprising that therapeutic agent as the only active agent. Preferably the amount of additional therapeutic agent in the presently disclosed compositions will range from about 50% to 100% of the amount normally present in a composition comprising that agent as the only therapeutically active agent.

[0092] In an alternate embodiment, the methods of this invention that utilize compositions that do not contain an additional therapeutic agent, comprise the additional step of separately administering to said patient an additional therapeutic agent. When these additional therapeutic agents are administered separately they may be administered to the patient prior to, sequentially with or following administration of the compositions of this invention.

[0093] According to another embodiment, the invention relates to a method of inhibiting GSK-3 kinase activity in a biological sample comprising the step of contacting said biological sample with a compound of this invention, or a composition comprising said compound.

[0094] The term "biological sample", as used herein, includes, without limitation, cell cultures or extracts thereof; biopsied material obtained from a mammal or extracts thereof; and blood, saliva, urine, feces, semen, tears, or other body fluids or extracts thereof.

[0095] Inhibition of GSK-3 kinase activity in a biological sample is useful for a variety of purposes that are known to one of skill in the art. Examples of such purposes include, but are not limited to, blood transfusion, organ-transplantation, biological specimen storage, and biological assays.

[0096] According to another embodiment, the invention provides a method for treating or lessening the severity of a GSK-3-mediated disease or condition in a patient comprising the step of administering to said patient a composition according to the present invention.

[0097] The term "GSK-3-mediated disease" as used herein, means any disease or other deleterious condition or disease in which GSK-3 is known to play a role. Such diseases or conditions include, without limitation, autoimmune diseases, inflammatory diseases, metabolic, neurological and neurodegenerative diseases, cardiovascular diseases, allergy, asthma, diabetes, Alzheimer's disease, Huntington's disease, Parkinson's disease, AIDS-associated dementia, amyotrophic lateral sclerosis (ALS, Lou Gehrig's disease), multiple sclerosis (MS), schizophrenia, cardiomyocyte hypertrophy, reperfusion/ischemia, stroke, and baldness.

[0098] According to a preferred embodiment, the method of the present invention relates to treating or lessening the severity of stroke.

[0099] According to another preferred embodiment, the method of the present invention relates to treating or lessening the severity of a neurodegenerative or neurological disorder.

[00100] In other embodiments, the invention relates to a method of enhancing glycogen synthesis and/or lowering blood levels of glucose in a patient in need thereof, comprising administering to said patient a therapeutically effective amount of a composition comprising a compound of formula I. This method is especially useful for diabetic patients.

[00101] In yet another embodiment, the invention relates to a method of inhibiting the production of hyperphosphorylated Tau protein in a patient in need thereof, comprising administering to said patient a therapeutically effective amount of a composition comprising

a compound of formula I. This method is especially useful in halting or slowing the progression of Alzheimer's disease.

[00102] In still another embodiment, the invention relates to a method of inhibiting the phosphorylation of β -catenin in a patient in need thereof, comprising administering to said patient a therapeutically effective amount of a composition comprising a compound of formula I. This method is especially useful for treating schizophrenia.

[00103] The compounds of this invention or pharmaceutically acceptable compositions thereof may also be incorporated into compositions for coating an implantable medical device, such as prostheses, artificial valves, vascular grafts, stents and catheters. Vascular stents, for example, have been used to overcome restenosis (re-narrowing of the vessel wall after injury). However, patients using stents or other implantable devices risk clot formation or platelet activation. These unwanted effects may be prevented or mitigated by pre-coating the device with a pharmaceutically acceptable composition comprising a kinase inhibitor. Suitable coatings and the general preparation of coated implantable devices are described in US Patents 6,099,562; 5,886,026; and 5,304,121. The coatings are typically biocompatible polymeric materials such as a hydrogel polymer, polymethyldisiloxane, polycaprolactone, polyethylene glycol, polylactic acid, ethylene vinyl acetate, and mixtures thereof. The coatings may optionally be further covered by a suitable topcoat of fluorosilicone, polysaccharides, polyethylene glycol, phospholipids or combinations thereof to impart controlled release characteristics in the composition. Implantable devices coated with a compound of this invention are another embodiment of the present invention.

[00104] In order that the invention described herein may be more fully understood, the following examples are set forth. It should be understood that these examples are for illustrative purposes only and are not to be construed as limiting this invention in any manner.

SYNTHETIC EXAMPLES

[00105] The following HPLC methods were used in the analysis of the compounds as specified in the Synthetic Examples set forth below.

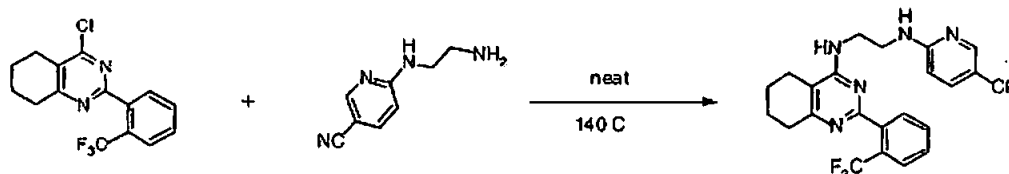
[00106] HPLC conditions

[00107] A) LC-MS: Column: Waters (YMC) ODS-AQ 2.0x50mm, S5, 120Å.

Gradient: 90% water (0.2% Formic acid), 10% acetonitrile (containing 0.1% Formic acid) to 10% water (0.1% formic acid), 90% acetonitrile (containing 0.1% formic acid) over 5.0 min, hold for 0. min and return to initial conditions. Total run time 7.0 min. Flow rate: 1.0 mL/min

[00108] HPLC: Column: C18, 3 μ m, 2.1 X 50 mm, "Lighting" by Jones Chromatography. Gradient: 100% water (containing 1% acetonitrile, 0.1% TFA) to 100% acetonitrile (containing 0.1% TFA) over 4.0 min, hold at 100% acetonitrile for 1.4 min and return to initial conditions. Total run time 7.0

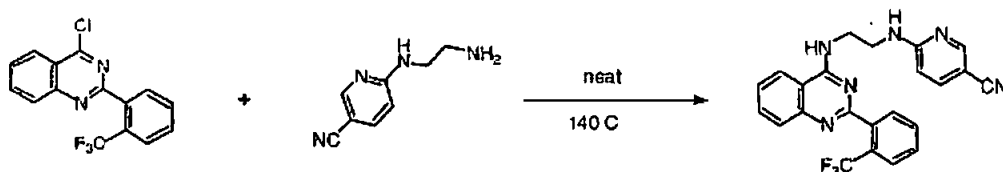
[00109] Example 1 **6-{2-[2-(2-Trifluoromethyl-phenyl)-5,6,7,8-tetrahydro-quinazolin-4-ylamino]-ethylamino}-nicotinonitrile (Compound I-105)**



[00110] A mixture of 4-chloro-2-(2-trifluoromethyl-phenyl)-5,6,7,8-tetrahydroquinazoline and 6-(2-amino-ethylamino)-nicotinonitrile (prepared according to the method described by Nuss *et al*, WO 99/65997) was dissolved in ethanol (2 mL). The solvent was removed under a stream of nitrogen gas and the residue was heated at 140°C for 18 hours. Purification was achieved by silica gel chromatography (1:1 hexane/ethyl acetate, 1:2 hexane/ethyl acetate) to yield the title compound as a white solid (35 mg, 50%).

[00111] ^1H NMR (500 MHz, d_6 -DMSO, ppm) δ 8.35 (s, 1H), 7.8 (d, 1H), 7.73-7.65 (m, 2H), 7.65-7.6 (m, 2H), 5.7 (br s, 1H), 6.9 (br s, 1H), 6.57-6.47 (m, 1H), 3.58-3.52 (m, 2H), 3.52-3.42 (m, 2H), 2.64-2.58 (m, 2H), 2.4-2.34 (m, 2H), and 1.83-1.75 (m, 4H); LC-MS (ES+) m/e = 439.18 (M+H); R_t = 2.06 min

[00112] Example 2 **6-{2-[2-(2-Trifluoromethyl-phenyl)-quinazolin-4-ylamino]-ethylamino}-nicotinonitrile (Compound I-8)**

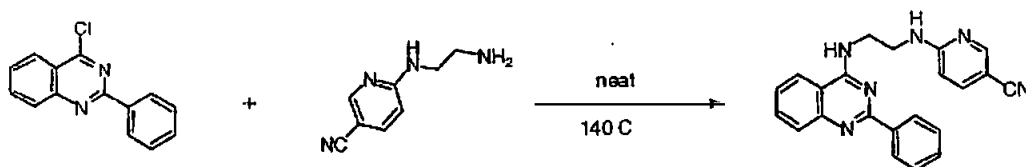


[00113] This compound was prepared in an analogous manner as described in Example 1 using 4-chloro-2-(2-trifluoromethyl-phenyl)-quinazoline. Purification was achieved by silica gel chromatography (1:1 hexane/ethyl acetate, 1:2 hexane/ethyl acetate) to yield the title compound (34 mg, 49%).

[00114] ^1H NMR (500 MHz, d_6 -DMSO, ppm) δ 8.58 (br s, 1H), 8.37 (s, 1H), 8.28 (d, 1H), 7.85-7.74 (m, 6H), 7.7-7.66 (m, 1H), 7.6-7.55 (m, 2H), 6.53 (br s, 1H), 3.77-3.72 (m, 2H), 3.65-3.57 (m, 2H); LC-MS (ES+) m/e = 435.09

(M+H); R_t = 2.09 min.

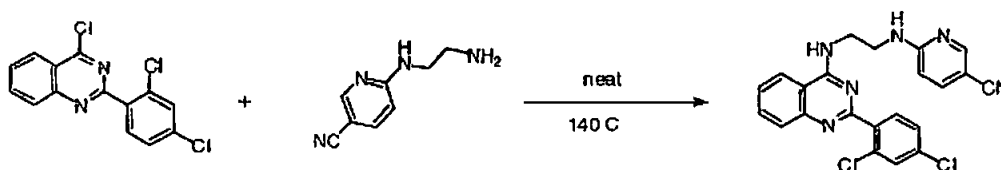
[00115] Example 3 **6-[2-(2-Phenyl-quinazolin-4-ylamino)-ethylamino]-nicotinonitrile (Compound I-9)**



[00116] This compound was prepared in an analogous manner as described in Example 1 using 4-chloro-2-phenyl-quinazoline. Purification was achieved by silica gel chromatography (2:1 hexane/ethyl acetate, 1:1 hexane/ethyl acetate) to yield the title compound as a white solid (37 mg, 49%).

[00117] ^1H NMR (500 MHz, d_6 -DMSO, ppm) δ 8.52-8.4 (m, 4H), 8.23 (d, 1H), 7.88-7.82 (m, 1H), 7.78-7.71 (m, 2H), 7.66-7.6 (m, 1H), 7.52-7.43 (m, 4H), 6.58-6.49 (m, 1H), 3.9-3.84 (m, 2H), 3.83-3.65 (m, 2H); LC-MS (ES+) m/e = 367.08 (M+H); R_t = 1.91 min.

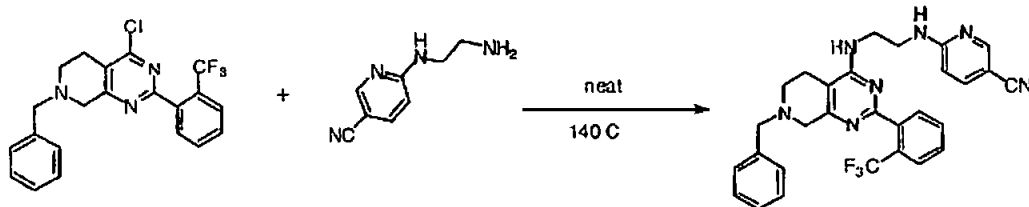
[00118] Example 4 **6-[2-[2-(2,4-Dichloro-phenyl)-quinazolin-4-ylamino]-ethylamino]-nicotinonitrile (Compound I-1)**



[00119] This compound was prepared in an analogous manner as described in Example 1 using 4-chloro-2-(2,4-dichloro-phenyl)-quinazoline and 6-(2-amino-ethylamino)-nicotinonitrile. Purification was achieved by silica gel chromatography (2:1 hexane/ethyl acetate, 1:1 hexane/ethyl acetate) to yield the title compound as a white solid (36 mg, 51%).

[00120] ^1H NMR (500 MHz, d_6 -DMSO, ppm) δ 8.64-8.56 (m, 1H), 8.37 (s, 1H), 8.31-8.24 (m, 1H), 7.84-7.69 (m, 5H), 7.62-7.50 (m, 3H), 6.59-6.48 (m, 1H), 3.80-3.70 (m, 2H), 3.72-3.59 (m, 2H); LC-MS (ES+) m/e = 434.96 (M+H); R_t = 2.18 min.

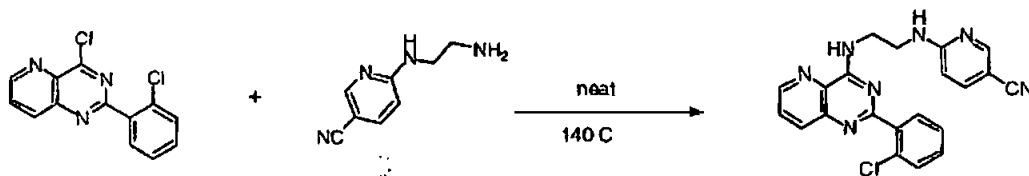
[00121] Example 5 **6-[2-[7-Benzyl-2-(2-trifluoromethyl-phenyl)-5,6,7,8-tetrahydropyrido[3,4-d]pyrimidin-4-ylamino]-ethylamino]-nicotinonitrile (Compound I-113)**



[00122] This compound was prepared in an analogous manner as described in Example 1 using 7-benzyl-4-chloro-2-(2-(trifluoromethyl)-phenyl)-5,6,7,8-tetrahydropyrido[3,4-*d*]pyrimidine and 6-(2-amino-ethylamino)-nicotinonitrile. Purification was achieved by silica gel chromatography (1:3 hexane/ethyl acetate, 1:4 hexane/ethyl acetate) to yield the title compound as a yellow foam (76 mg, 58%).

[00123] ^1H NMR (500 MHz, CDCl_3 , ppm) δ 8.30 (s, 1H), 7.75 (d, 1H), 7.69-7.65 (m, 1H), 7.62 (t, 1H), 7.60-7.52 (m, 1H), 7.43-7.27 (m, 6H), 6.11-5.98 (m, 2H), 5.33 (br s, 1H), 3.84-3.73 (m, 4H), 3.66-3.57 (m, 4H), 2.92-2.82 (m, 2H), 2.53-2.42 (m, 2H); LC-MS (ES+) $m/e = 530.05$ (M+H); $R_t = 2.29$ min.

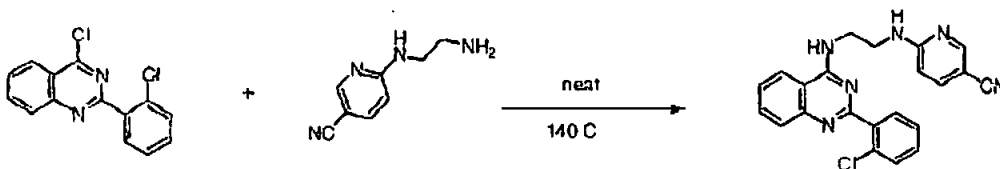
[00124] **Example 6** 6-{2-[2-(2-Chloro-phenyl)-pyrido[3,2-*d*]pyrimidin-4-ylamino]-ethylamino}-nicotinonitrile (Compound I-118)



[00125] This compound was prepared in an analogous manner as described in Example 1 using 4-chloro-2-(2-chloro-phenyl)-pyrido[3,2-*d*]pyrimidine and 6-(2-amino-ethylamino)-nicotinonitrile. Purification was achieved by silica gel chromatography (1:1 hexane/ethyl acetate, 1:2 hexane/ethyl acetate, 1:4 hexane/ethyl acetate) to yield the title compound as a white solid (36 mg, 49%).

[00126] ^1H NMR (500 MHz, d_6 -DMSO, ppm) δ 8.89-8.80 (m, 2H), 8.34 (s, 1H), 8.15 (d, 1H), 7.90-7.82 (m, 1H), 7.80-7.73 (m, 1H), 7.64 (d, 1H), 7.59-7.51 (m, 2H), 7.50-7.40 (m, 2H), 6.59-6.42 (br m, 1H), 3.80-3.75 (m, 2H), 3.70-3.58 (m, 2H); LC-

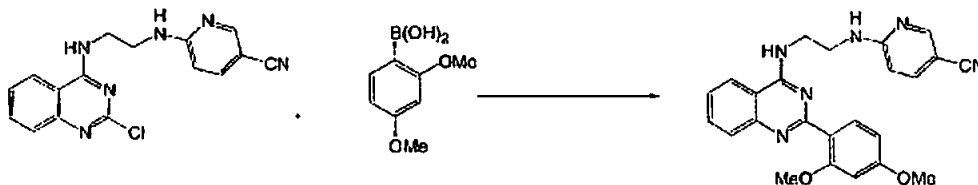
[00127] **Example 7** 6-{2-[2-(2-Chloro-phenyl)-quinazolin-4-ylamino]-ethylamino}-nicotinonitrile (Compound I-11)



[00128] This compound was prepared in an analogous manner as described in Example 1 using 4-chloro-2-(2-chloro-phenyl)-quinazoline. Purification was achieved by silica gel chromatography (1:1 hexane/ethyl acetate, 1:2 hexane/ethyl acetate) to yield the title compound as a white solid (47 mg, 64%).

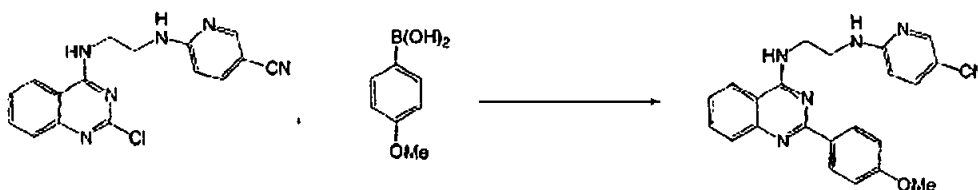
[00129] ¹H NMR (500 MHz, d₆-DMSO, ppm) δ8.60-8.55 (m, 1H), 8.39 (s, 1H), 8.26 (d, 1H), 7.84-7.78 (m, 2H), 7.76 (d, 1H), 7.71-7.69 (m, 1H), 7.65-7.52 (m, 3H), 7.50-7.42 (m, 2H), 6.61-6.46 (m, 1H), 3.77-3.59 (m, 4H); LC-MS (ES+) m/e= 401.03 (M+H); R_t= 1.89 min.

[00130] Example 8 6-{2-[2-(2,4-Dimethoxy-phenyl)-quinazolin-4-ylamino]-ethylamino}-nicotinonitrile (Compound I-185)



[00131] A mixture of 6-[2-(2-Chloro-quinazolin-4-ylamino)-ethylamino]-nicotinonitrile (65mg, 0.2 mmol), 2,4-dimethoxyphenylboronic acid (55mg, 0.3 mmol), tetrakis(triphenylphosphine)palladium (2mg) and aqueous saturated NaHCO₃ (0.5 ml) in 1,2-dimethoxyethane (3 ml) was stirred at 110°C under nitrogen for 14 h. The reaction mixture was concentrated. The residue was dissolved in a mixture of DMSO and MeOH and purified by reverse-phase HPLC. The title compound was obtained as a white solid (76 mg, 69%). ¹H NMR (500 MHz, DMSO(d₆)): δ13.20 (s, 1H), 10.20 (m, 1H), 8.38 (d, 2H), 8.00 (m, 2H), 7.82 (m, 1H), 7.78 (d, 2H), 7.72 (t, 1H), 6.80 (s, 1H), 6.70 (d, 1H), 3.90 (m, 7H), 3.83 (s, 3H). FIA-MS: (ES-) m/e= 425.3 (M-H), (ES+) m/e= 427.2 (M+H).

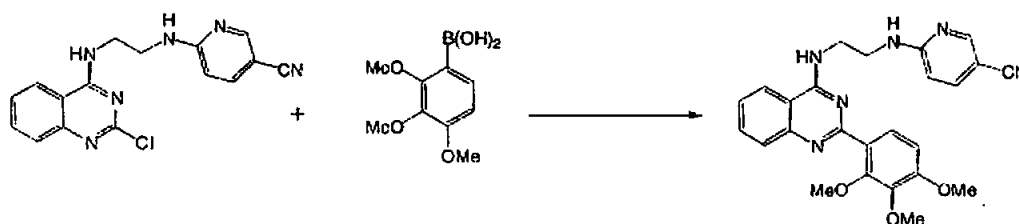
[00132] Example 9 6-{2-[2-(4-Methoxy-phenyl)-quinazolin-4-ylamino]-ethylamino}-nicotinonitrile (compound I-3)



[00133] This compound was prepared in an analogous manner as described in Example 8 using 4-methoxyphenylboronic acid. Purification was achieved on silica gel, eluting with 40-50% EtOAc in hexanes to give the title compound as a white solid (18.5mg, 30%).

[00134] ^1H NMR (500 MHz, d_6 -DMSO, ppm) δ 8.57-8.33 (m, 5H), 8.18 (d, 1H), 7.92-7.78 (m, 1H), 7.77-7.58 (m, 3H), 7.51-7.37 (m, 1H), 7.01 (d, 2H), 6.59-6.40 (m, 1H), 3.90-3.80 (m, 5H), 3.75-3.62 (m, 2H). LC-MS (ES+) m/e = 397.06 (M+H), (ES-) 395.11 (M-H); R_t = 2.10 min.

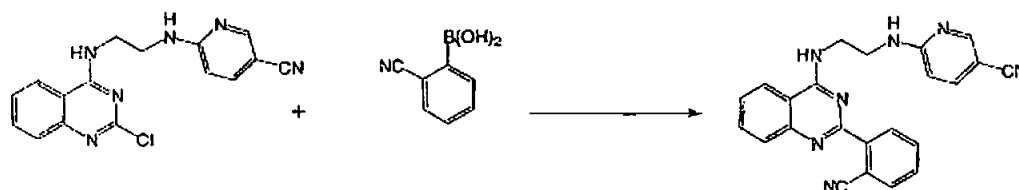
[00135] Example 10 6-{2-[2-(2,3,4-Trimethoxy-phenyl)-quinazolin-4-ylamino]-ethylamino}-nicotinonitrile (Compound I-186)



[00136] This compound was prepared in an analogous manner to described in Example 8 using 2,3,4-trimethoxyphenyl boronic acid. Purification was achieved on silica gel, eluting with 50-60% EtOAc in hexanes to give the title compound as a white solid (13mg, 18%).

[00137] ^1H NMR (500 MHz, d_6 -DMSO, ppm) δ 8.39 (br s, 2H), 8.29-8.16 (m, 1H), 7.87-7.65 (m, 3H), 7.64-7.55 (m, 1H), 7.54-7.45 (m, 1H), 7.39 (d, 1H), 6.87 (d, 1H), 6.61-6.39 (br, 1H), 3.85 (d, 6H), 3.78 (s, 5H), 3.69-3.56 (m, 2H). LC-MS (ES+) m/e = 457.3 (M+H); R_t = 2.36 min.

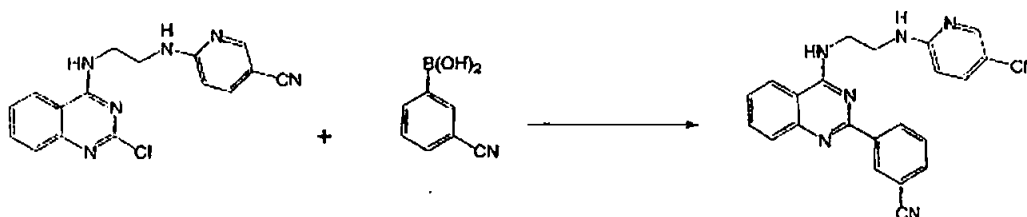
[00138] Example 11 6-{2-[2-(2-Cyano-phenyl)-quinazolin-4-ylamino]-ethylamino}-nicotinonitrile (Compound I-187)



[00139] This compound was prepared in an analogous manner to Example 8 using 2-cyano-phenylboronic acid. Purification was achieved purified by reverse-phase HPLC

[00140] ^1H NMR (500 MHz, $\text{DMSO}(d_6)$): δ 9.7 (m, 1H), 8.38 (d, 2H), 8.00 (m, 2H), 7.82 (m, 1H), 7.78 (d, 2H), 7.72 (t, 1H), 6.80 (s, 1H), 6.70 (d, 1H), 4.04 (m, 2H), 3.65 (m, 2H). FIA-MS: (ES+) m/e = 392.3 (M+H).

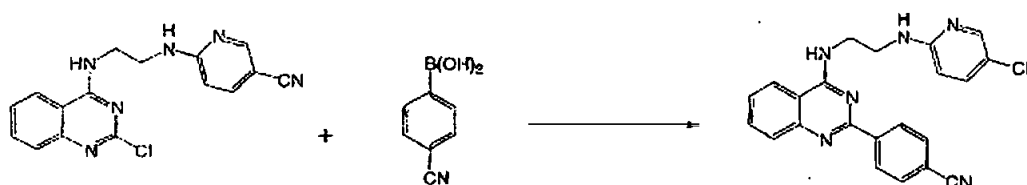
[00141] Example 12 6-{2-[2-(3-Cyano-phenyl)-quinazolin-4-ylamino]-ethylamino}-nicotinonitrile (compound I-29)



[00142] This compound was prepared in an analogous manner to Example 8 using 3-cyano-phenylboronic acid. Purification was achieved purified by reverse-phase HPLC

[00143] ^1H NMR (500 MHz, $\text{DMSO}(d_6)$): δ 10.02 (m, 1H), 8.65 (s, 1H), 8.50 (d, 1H), 8.42 (m, 2H), 8.19 (d, 1H), 8.05 (t, 1H), 7.95 (d, 1H), 7.80 (m, 2H), 7.77 (t, 1H), 7.50 (br.s, 1H), 6.40 (br.s, 1H), 4.05 (m, 2H), 3.75 (m, 2H). FIA-MS: (ES+) m/e = 392.3 (M+H), (ES-) m/e = 504.1 (M + TFA).

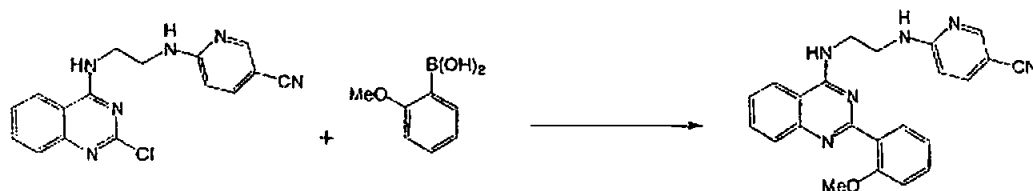
[00144] Example 13 6-{2-[2-(4-Cyano-phenyl)-quinazolin-4-ylamino]-ethylamino}-nicotinonitrile (compound I-19)



[00145] This compound was prepared in an analogous manner to Example 8 using 4-cyano-phenylboronic acid. Purification was achieved purified by reverse-phase HPLC

[00146] ^1H NMR (500 MHz, $\text{DMSO}(d_6)$): δ 9.7 (m, 1H), 8.38 (m, 4H), 8.05 (d, 2H), 7.95 (t, 1H), 7.87 (d, 1H), 7.80 (m, 1H), 7.70 (m, 1H), 7.50 (m, 1H), 6.40 (m, 1H), 4.00 (m, 2H), 3.75 (m, 2H). FIA-MS: (ES+) m/e = 392.2 (M+H), (ES-) m/e = 504.1 (M + TFA).

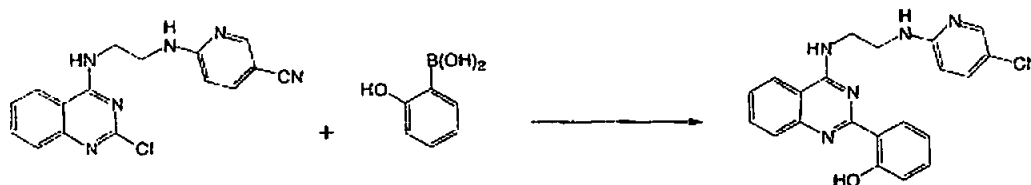
[00147] Example 14 6-{2-[2-(2-Methoxy-phenyl)-quinazolin-4-ylamino]-ethylamino}-nicotinonitrile (Compound I-188)



[00148] This compound was prepared in an analogous manner to Example 8 using 2-methoxy-phenylboronic acid. Purification was achieved purified by reverse-phase HPLC

^1H NMR (500 MHz, $\text{DMSO}(d_6)$): δ 13.80 (s, 1H), 10.30 (t, 1H), 8.48 (d, 1H), 8.32 (s, 1H), 8.06 (t, 1H), 7.93 (d, 1H), 7.76 (m, 2H), 7.68 (m, 2H), 7.50 (d, 1H), 7.29 (d, 1H), 7.10 (t, 1H), 6.40 (br.s, 1H), 4.05 (m, 2H), 4.00 (s, 3H), 3.75 (m, 2H). FIA-MS: (ES+) m/e = 397.3 (M+H), (ES-) m/e = 395.2 (M-H).

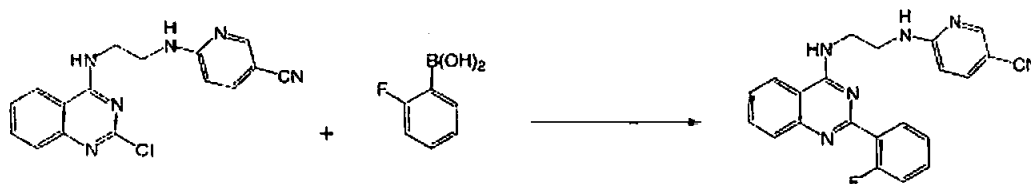
[00149] Example 15 6-{2-[2-(2-Hydroxy-phenyl)-quinazolin-4-ylamino]-ethylamino}-nicotinonitrile (Compound I-189)



[00150] This compound was prepared in an analogous manner to Example 8 using 2-hydroxy-phenylboronic acid. Purification was achieved purified by reverse-phase HPLC

^1H NMR (500 MHz, $\text{DMSO}(d_6)$): δ 14.80 (s, 1H), 8.85 (t, 1H), 8.48 (s, 1H), 8.35 (d, 1H), 8.27 (d, 1H), 7.85 (m, 2H), 7.80 (d, 1H), 7.67 (m, 1H), 7.60 (t, 1H), 7.36 (t, 1H), 6.92 (m, 2H), 6.58 (m, 1H), 3.90 (m, 2H), 3.73 (m, 2H). FIA-MS: (ES+) m/e = 383.2 (M+H), (ES-) m/e = 381.2 (M-H).

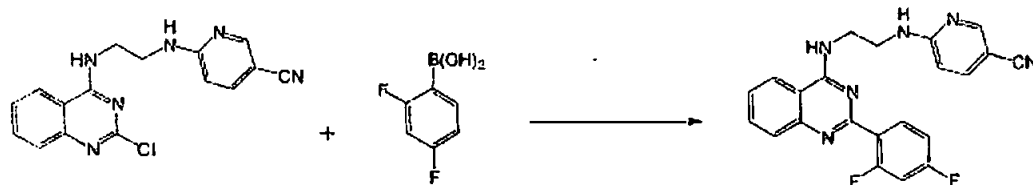
[00151] Example 16 6-{2-[2-(2-Fluoro-phenyl)-quinazolin-4-ylamino]-ethylamino}-nicotinonitrile (Compound I-190)



[00152] This compound was prepared in an analogous manner to Example 8 using 2-fluoro-phenylboronic acid. Purification was achieved purified by reverse-phase HPLC

[00153] ^1H NMR (500 MHz, $\text{DMSO}(d_6)$): δ 10.40 (s, 1H), 8.47 (d, 1H), 8.33 (s, 1H), 8.10 (t, 1H), 7.94 (d, 1H), 7.80 (m, 4H), 7.50 (m, 2H), 7.42 (t, 1H), 6.50 (m, 1H), 4.00 (m, 2H), 3.73 (m, 2H). FIA-MS: (ES+) m/e = 385.2 (M+H), (ES-) m/e = 383.2 (M-H).

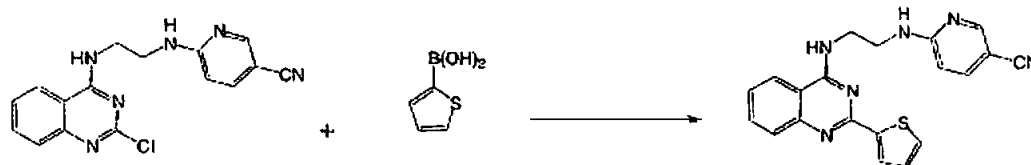
[00154]. Example 17 6-[2-[2-(2,4-Difluoro-phenyl)-quinazolin-4-ylamino]-ethylamino]-nicotinonitrile (Compound I-191)



[00155] This compound was prepared in an analogous manner to Example 8 using 2,4-difluoro-phenylboronic acid. Purification was achieved purified by reverse-phase HPLC

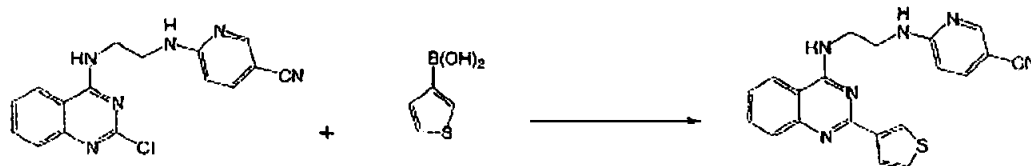
[00156] ^1H NMR (500 MHz, $\text{DMSO}(d_6)$): δ 10.30 (s, 1H), 8.43 (d, 1H), 8.30 (s, 1H), 8.10 (t, 1H), 7.90 (m, 2H), 7.75 (m, 2H), 7.55 (td, 1H), 7.48 (m, 1H), 7.33 (td, 1H), 6.45 (m, 1H), 4.00 (m, 2H), 3.71 (m, 2H). FIA-MS: (ES+) m/e = 403.2 (M+H), (ES-) m/e = 515.1 (M+TFA).

[00157] Example 18 6-[2-(2-Thiophen-2-yl-quinazolin-4-ylamino)-ethylamino]-nicotinonitrile (Compound I-192)



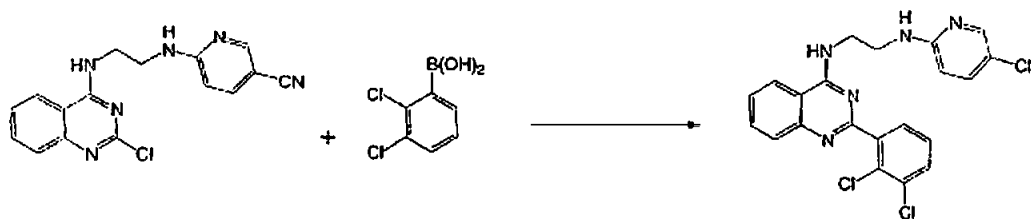
[00158] ^1H NMR (500 MHz, $\text{DMSO}(d_6)$): δ 10.18 (s, 1H), 8.45 (m, 2H), 8.10 (d, 1H), 8.10 (t, 1H), 8.05 (t, 1H), 7.90 (d, 1H), 7.88 (br.s, 1H), 7.72 (t, 1H), 7.71 (br.s, 1H), 7.37 (d, 1H), 6.50 (br.s, 1H), 4.00 (m, 2H), 3.75 (m, 2H). FIA-MS: (ES+) m/e = 373.2 (M+H), (ES-) m/e = 485.1 (M+TFA).

[00159] Example 19 6-[2-(2-Thiophen-3-yl-quinazolin-4-ylamino)-ethylamino]-nicotinonitrile (compound I-32)



[00160] ^1H NMR (500 MHz, $\text{DMSO}(d_6)$): δ 10.17 (s, 1H), 8.73 (s, 1H), 8.40 (m, 2H), 8.05 (t, 1H), 7.93 (d, 1H), 7.85 (m, 2H), 7.80 (d, 1H), 7.70 (t, 1H), 7.58 (br.s, 1H), 6.50 (br.s, 1H), 4.07 (m, 2H), 3.75 (m, 2H). FIA-MS: (ES+) m/e = 373.2 (M+H), (ES-) m/e = 485.1 (M+TFA).

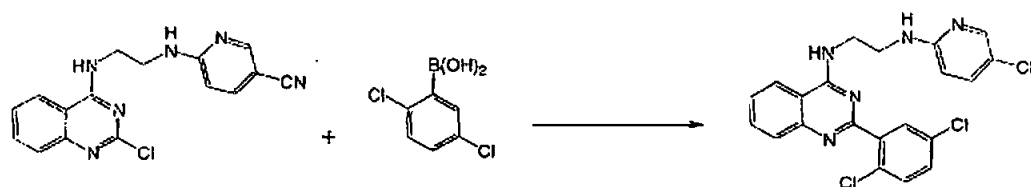
[00161] Example 20 6-{2-[2-(2,3-Dichloro-phenyl)-quinazolin-4-ylamino]-ethylamino}-nicotinonitrile (Compound I-193)



[00162] This compound was prepared in an analogous manner to Example 8 using 2,3-dichloro-phenylboronic acid. Purification was achieved purified by reverse-phase HPLC.

[00163] ^1H NMR (500 MHz, $\text{DMSO}(d_6)$): δ 10.37 (s, 1H), 8.48 (s, 1H), 8.30 (d, 1H), 8.08 (t, 1H), 7.97 (d, 1H), 7.80 (m, 2H), 7.78 (m, 1H), 7.70 (d, 1H), 7.58 (t, 1H), 7.50 (dd, 1H), 6.43 (br.s, 1H), 3.97 (m, 2H), 3.68 (m, 2H). FIA-MS: (ES+) m/e = 435.0 (M+H), (ES-) m/e = 547.0 (M+TFA).

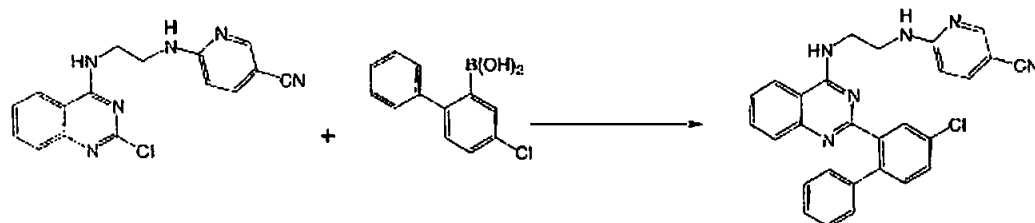
[00164] Example 21 6-{2-[2-(2,5-Dichloro-phenyl)-quinazolin-4-ylamino]-ethylamino}-nicotinonitrile (Compound I-194)



[00165] This compound was prepared in an analogous manner to Example 8 using 2,5-dichloro-phenylboronic acid. Purification was achieved purified by reverse-phase HPLC.

[00166] ^1H NMR (500 MHz, $\text{DMSO}(d_6)$): δ 10.35 (s, 1H), 8.52 (d, 1H), 8.30 (d, 1H), 8.10 (t, 1H), 7.97 (d, 1H), 7.82 (m, 3H), 7.78 (m, 1H), 7.70 (s, 1H), 7.48 (d, 1H), 6.43 (br.s, 1H), 3.92 (m, 2H), 3.60 (m, 2H). FIA-MS: (ES+) m/e = 435.0 (M+H), (ES-) m/e = 547.0 (M+TFA).

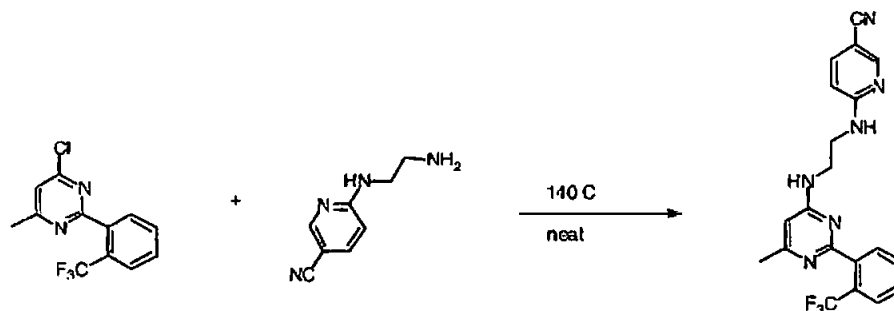
[00167] Example 22 6-{2-[2-(4-Chloro-biphenyl-2-yl)-quinazolin-4-ylamino]-ethylamino}-nicotinonitrile (Compound I-195)



[00168] This compound was prepared in an analogous manner to Example 8 using 4-chlorobiphenylboronic acid. Purification was achieved purified by reverse-phase HPL

[00169] ^1H NMR (500 MHz, $\text{DMSO}(d_6)$): δ 10.20 (s, 1H), 8.39 (d, 1H), 8.30 (s, 1H), 8.05 (t, 1H), 7.85 (d, 1H), 7.78 (m, 3H), 7.70 (t, 1H), 7.65 (d, 1H), 7.55 (dd, 1H), 7.30 (m, 5H), 6.45 (d, 1H), 3.45 (m, 2H), 3.33 (m, 2H). FIA-MS: (ES+) m/e = 443.2 (M+H), (ES-) m/e = 441.2 (M-H), 477.2 (M+TFA).

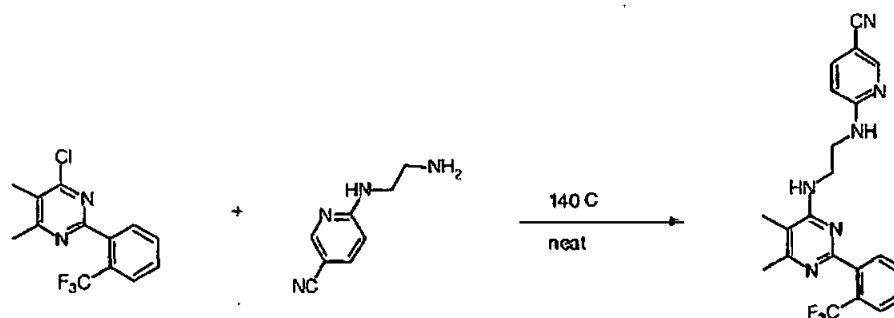
[00170] Example 23 6-{2-[6-Methyl-2-(2-trifluoromethyl-phenyl)-pyrimidin-4-ylamino]-ethylamino}-nicotinonitrile (Compound I-196)



[00171] This compound was prepared in an analogous manner as described in Example 1 using 4-chloro-6-methyl-2-(2-trifluoromethyl-phenyl)-pyrimidine. Purification was achieved by silica gel chromatography (1:1 ethyl acetate/ hexane, 3:1 ethyl acetate/hexane, 4:1 ethyl acetate/hexane, 6:1 ethyl acetate/hexane) to yield the title compound (50 mg, 69%).

[00172] ^1H NMR (500 MHz, d_6 -DMSO, ppm) δ 2.25 (s, 3H), 3.4-3.52 (br m, 4H), 6.30 (br s, 1H), 6.50-6.56 (m, 1H), 7.50-7.60 (m, 1H), 7.62-7.68 (m, 3H), 7.69-7.77 (m, 2H), 7.80-7.82 (m, 1H), 8.40 (br s, 1H); LC-MS (ES+) m/e = 399.13 (M+H); R_t = 1.90 min.

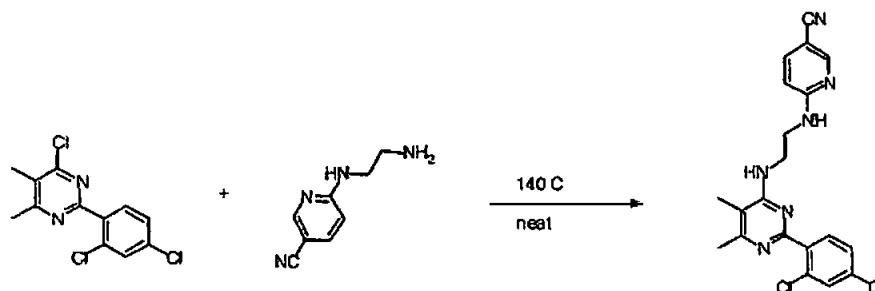
[00173] Example 24 6-{2-[5,6-Dimethyl-2-(2-trifluoromethyl-phenyl)-pyrimidin-4-ylamino]-ethylamino}-nicotinonitrile (Compound I-197)



[00174] This compound was prepared in an analogous manner as described in Example 1 using 4-chloro-5,6-dimethyl-2-(2-(trifluoromethyl)-phenyl)-pyrimidine. Purification was achieved by silica gel chromatography (1:1 ethyl acetate/ hexane, 2:1 ethyl acetate/hexane) to yield the title compound (43 mg, 60%).

[00175] ^1H NMR (500 MHz, d_6 -DMSO, ppm) δ 2.25 (s, 3H), 2.30 (s, 3H), 3.45-3.59 (m, 4H), 6.50 (br s, 1H), 6.94 (br s, 1H), 7.52-7.60 (m, 1H), 7.60-7.66 (m, 2H), 7.69-7.75 (m, 2H), 7.78-7.84 (m, 1H), 8.36 (s, 1H); LC-MS (ES+) m/e = 413.12 (M+H); R_t = 1.90 min.

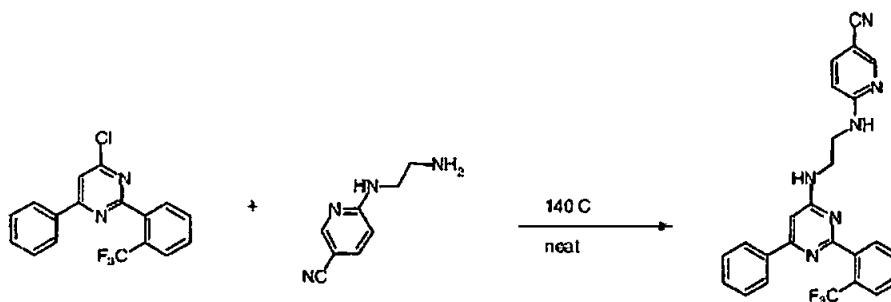
[00176] Example 25 6-{2-[2-(2,4-Dichloro-phenyl)-5,6-dimethyl-pyrimidin-4-ylamino]-ethylamino}-nicotinonitrile (Compound I-198)



[00177] This compound was prepared in an analogous manner as described in Example 1 using 4-chloro-2-(2,4-dichloro-phenyl)-5,6-dimethyl-pyrimidine. Purification was achieved by silica gel chromatography (1:1 ethyl acetate/ hexane, 2:1 ethyl acetate/hexane) to yield the title compound (31 mg, 43%).

[00178] ^1H NMR (500 MHz, d_6 -DMSO, ppm) δ 2.02 (s, 3H), 2.30 (s, 3H), 3.48-3.56 (m, 4H), 6.50 (br s, 1H), 7.00 (br s, 1H), 7.47 (d, 1H), 7.55-7.60 (m, 1H), 7.61-7.69 (m, 2H), 7.70-7.75 (m, 1H), 8.35 (s, 1H); LC-MS (ES+) m/e = 413.00 (M+H); R_t = 1.95 min.

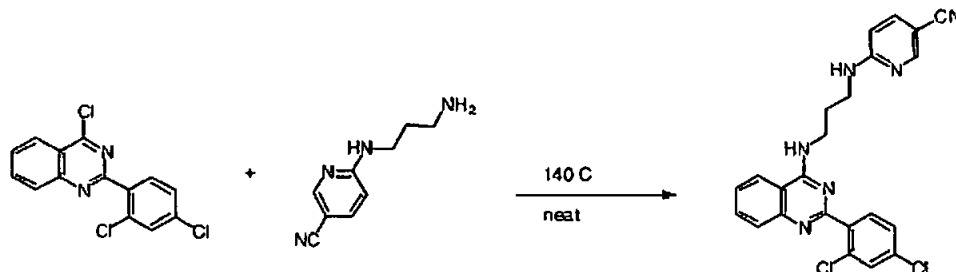
[00179] Example 26 6-{2-[6-Phenyl-2-(2-(trifluoromethyl)-phenyl)-pyrimidin-4-ylamino]-ethylamino}-nicotinonitrile (Compound I-199)



[00180] This compound was prepared in an analogous manner as described in Example 1 using 4-chloro-6-phenyl-2-(2-(trifluoromethyl)phenyl)-pyrimidine. Purification was achieved by silica gel chromatography (1:1 ethyl acetate/ hexane, 2:1 ethyl acetate/hexane) to yield the title compound (48 mg, 70%).

[00181] ^1H NMR (500 MHz, d_6 -DMSO, ppm) δ 3.45 (m, 4H), 6.50-6.58 (m, 1H), 6.92-7.00 (m, 1H), 7.44-7.52 (m, 3H), 7.55-7.62 (m, 1H), 7.65-7.70 (m, 1H), 7.70-7.80 (m, 4H), 7.82-7.87 (m, 1H), 7.98-8.05 (m, 2H), 8.35-8.42 (m, 1H); LC-MS (ES+) m/e = 461.07 (M+H); R_t = 3.33 min.

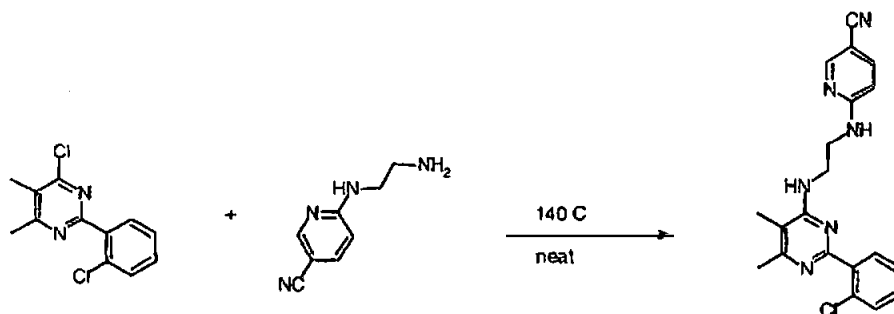
[00182] Example 27 6-{3-[2-(2,4-Dichloro-phenyl)-quinazolin-4-ylamino]-propylamino}-nicotinonitrile (Compound I-97)



[00183] This compound was prepared in an analogous manner as described in Example 1 using 4-chloro-2-(2,4-dichloro-phenyl)-quinazoline and 6-(3-amino-propylamino)-nicotinonitrile, (which was prepared in a similar fashion to 6-(2-amino-ethylamino)-nicotinonitrile). Purification was achieved by silica gel chromatography (1:1 ethyl acetate/ hexane, 2:1 ethyl acetate/hexane) to yield the title compound (50 mg, 57%).

[00184] ^1H NMR (500 MHz, d_6 -DMSO, ppm) δ 1.91-2.0 (m, 2H), 3.37-3.45 (m, 2H), 3.60-3.70 (m, 2H), 6.47 (d, 1H), 7.50-7.54 (m, 1H), 7.54-7.60 (m, 1H), 7.60-7.65 (m, 2H), 7.68-7.70 (m, 1H), 7.72-7.85 (m, 3H), 8.28 (d, 1H), 8.35 (s, 1H), 8.42-8.52 (m, 1H); LC-MS (ES+) m/e = 448.94 (M+H); R_t = 2.31 min.

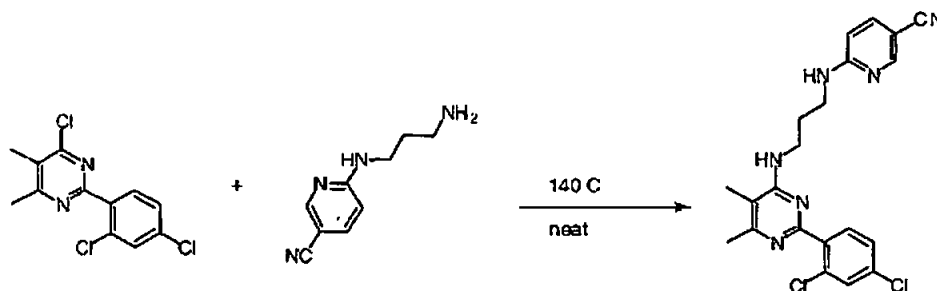
[00185] Example 28 6-{2-[2-(2-Chloro-phenyl)-5,6-dimethyl-pyrimidin-4-ylamino]-ethylamino}-nicotinonitrile (Compound I-143)



[00186] This compound was prepared in an analogous manner as described in Example 1 using 4-chloro-2-(2-chloro-phenyl)-5,6-dimethyl-pyrimidine. Purification was achieved by silica gel chromatography (2:1 ethyl acetate/ hexane, 4:1 ethyl acetate/hexane) to yield the title compound (46 mg, 61%).

[00187] ^1H NMR (500 MHz, d_6 -DMSO, ppm) δ 2.02 (s, 3H), 2.31 (s, 3H), 3.46-3.65 (m, 4H), 6.47-6.60 (m, 1H), 6.92-7.04 (m, 1H), 7.36-7.45 (m, 2H), 7.48-7.52 (m, 1H), 7.54-7.68 (m, 2H), 7.70-7.80 (m, 1H), 8.34-8.42 (m, 1H); LC-MS (ES+) m/e = 379.02 (M+H); R_t = 1.72 min.

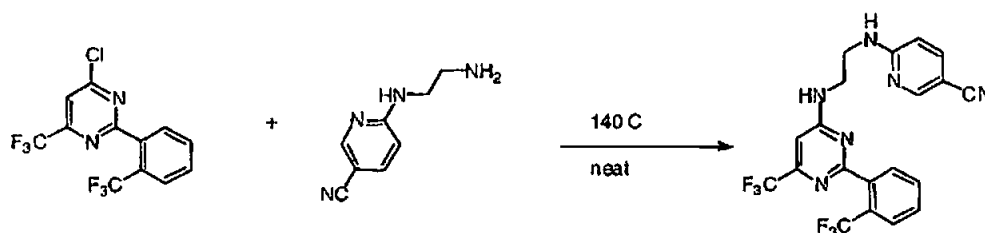
[00188] Example 29 6-{3-[2-(2,4-Dichloro-phenyl)-5,6-dimethyl-pyrimidin-4-ylamino]-propylamino}-nicotinonitrile (Compound I-142)



[00189] This compound was prepared in an analogous manner as described in Example 1 using 4-chloro-2-(2,4-dichloro-phenyl)-5,6-dimethyl-pyrimidine and 6-(3-amino-propylamino)-nicotinonitrile, (which was prepared in a similar fashion to 6-(2-amino-ethylamino)-nicotinonitrile). Purification was achieved by silica gel chromatography (1:1 ethyl acetate/ hexane, 2:1 ethyl acetate/hexane) to yield the title compound (32 mg, 43%).

[00190] ^1H NMR (500 MHz, d_6 -DMSO, ppm) δ 1.79-1.86 (m, 2H), 2.01 (s, 3H), 2.30 (s, 3H), 3.30-3.40 (m, 2H), 3.41-3.50 (m, 2H), 6.46 (d, 1H), 6.83-6.92 (m, 1H), 7.42-7.50 (m, 1H), 7.56-7.70 (m, 4H), 8.31 (s, 1H); LC-MS (ES+) m/e = 426.98 (M+H); R_t = 2.07 min.

[00191] Example 30 6-{2-[6-Trifluoromethyl-2-(2-trifluoromethyl-phenyl)-pyrimidin-4-ylamino]-ethylamino}-nicotinonitrile (Compound I-202)

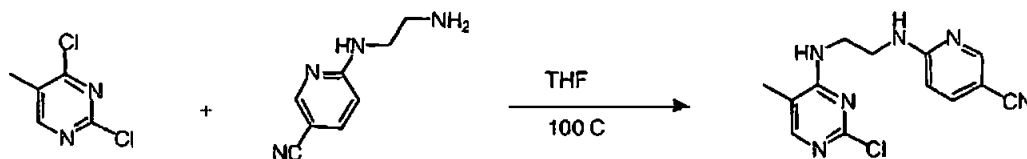


[00192] This compound was prepared in an analogous manner as described in Example 1 using 4-chloro-6-trifluoromethyl-2-(2-trifluoromethyl-phenyl)-pyrimidine. Purification was achieved by silica gel chromatography (1:1 ethyl acetate/ hexane, 3:1 ethyl acetate/hexane) to yield the title compound (18 mg, 26%).

[00193] ^1H NMR (500 MHz, d_6 -DMSO, ppm) δ 3.46-3.55 (m, 2H), 3.56-3.64 (m, 2H), 6.47-6.53 (m, 1H), 6.88 (s, 1H), 7.58 (d, 1H), 7.66-7.81 (m, 4H), 7.82-7.90 (m, 1H), 8.32-8.41 (m, 2H); LC-MS (ES+) m/e = 453.04 (M+H); R_t = 3.86 min.

[00194] Example 31 6-{2-[2-(4-Chloro-phenyl)-5-methyl-pyrimidin-4-ylamino]-ethylamino}-nicotinonitrile (Compound I-158)

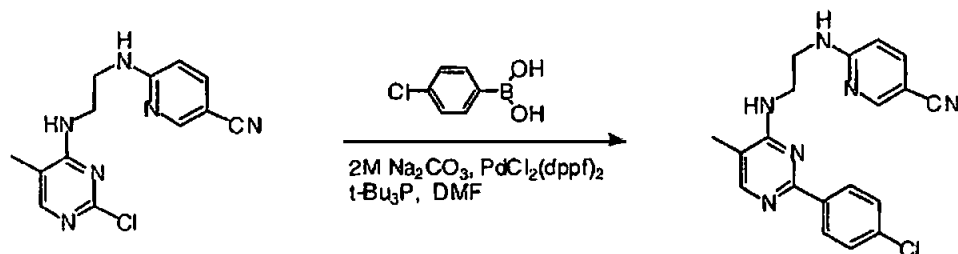
[00195] **Step A.** 6-[2-(2-Chloro-5-methyl-pyrimidin-4-ylamino)-ethylamino]-nicotinonitrile



[00196] A mixture of 2,4-Dichloro-5-methyl-pyrimidine (250 mg, 1.53 mmol) and 6-(2-amino-ethylamino)-nicotinonitrile (373 mg, 2.30 mmol, prepared according to the method described by Nuss *et al*, WO 99/65997) was dissolved in tetrahydrofuran (10 mL). The reaction mixture was heated at 100 C for 2 days. Purification was achieved by silica gel chromatography (1:3 hexane/ethyl acetate, 1:4 hexane/ethyl acetate, 1:6 hexane/ethyl acetate) to yield the title compound as a white solid (154 mg, 35%).

[00197] ^1H NMR (500 MHz, d_6 -DMSO, ppm) δ 1.94 (s, 3H), 3.45-3.61 (m, 4H), 6.48-6.68 (m, 1H), 7.40-7.45 (m, 1H), 7.61-7.78 (m, 2H), 7.80 (s, 1H), 8.40 (s, 1H); LC-MS (ES+) m/e = 288.98 (M+H); R_t = 2.09 min.

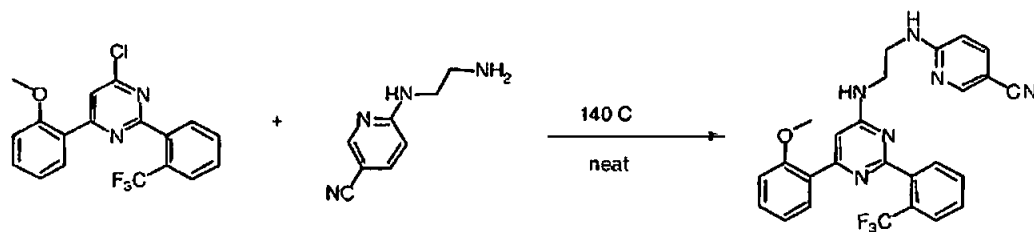
[00198] **Step B.** 6-{2-[2-(4-Chloro-phenyl)-5-methyl-pyrimidin-4-ylamino]-ethylamino}-nicotinonitrile



[00199] 6-[2-(2-Chloro-5-methyl-pyrimidin-4-ylamino)-ethylamino]-nicotinonitrile (50 mg, 0.174 mmol) was dissolved in *N,N*-dimethylformamide (2 mL) under an argon atmosphere. 4-chlorophenylboronic acid (41 mg, 0.260 mmol), 2M aqueous sodium carbonate (435 μ L, 0.870 mmol), 1,1'-bis(diphenylphosphino)ferrocene-palladium (II) dichloride (8 mg, 0.01 mmol), and tri-*t*-butylphosphine (43 μ L, 0.174 mmol) were added and the reaction mixture was heated at 80°C for 16 hours. The mixture was diluted with dichloromethane then washed with water (1x) and brine (1x). The organic layer was dried over magnesium sulfate and concentrated in vacuo. Purification was achieved by preparative HPLC (20% to 60% 0.1% trifluoroacetic acid in acetonitrile over 10 minutes) to yield the title compound as a white solid (10.2 mg, 16%).

[00200] ^1H NMR (500 MHz, d_6 -DMSO, ppm) δ 2.12 (s, 3H), 3.50-3.70 (m, 2H), 3.78-3.91 (m, 2H), 6.35-6.52 (m, 1H), 7.50-7.61 (m, 1H), 7.66 (d, 2H), 7.75-7.87 (m, 1H), 8.08 (d, 2H), 8.16 (s, 1H), 8.35-8.48 (m, 1H), 8.60-8.70 (m, 1H); LC-MS (ES+) m/e = 364.95 (M+H); R_t = 2.25 min.

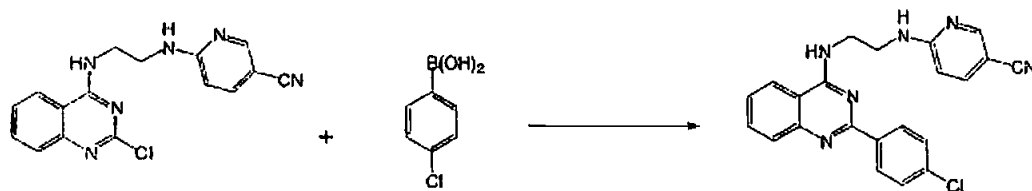
[00201] Example 32 6-[2-[6-(2-Methoxy-phenyl)-2-(2-trifluoromethyl-phenyl)-pyrimidin-4-ylamino]-ethylamino]-nicotinonitrile (Compound I-203)



[00202] This compound was prepared in an analogous manner as described in Example 1 using 4-chloro-6-(2-methoxy-phenyl)-2-(2-trifluoromethyl-phenyl)-pyrimidine. Purification was achieved by preparative HPLC (20% to 60% 0.1% trifluoroacetic acid in acetonitrile over 10 minutes) to yield the title compound (28.4 mg, 42%).

[00203] ^1H NMR (500 MHz, d_6 -DMSO, ppm) δ 3.45-3.65 (m, 4H), 3.87 (s, 3H), 6.50-6.55 (m, 1H), 7.02-7.14 (m, 2H), 7.18-7.25 (m, 1H), 7.48-7.65 (m, 2H), 7.72-7.97 (m, 6H), 8.32 (s, 1H); LC-MS (ES+) m/e = 491.18 (M+H); R_t = 2.56 min.

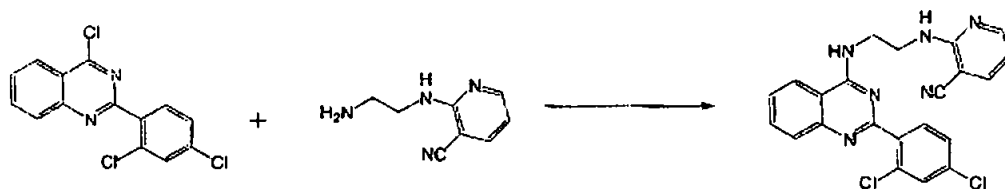
[00204] Example 33 6-{2-[2-(2,4-Difluoro-phenyl)-quinazolin-4-ylamino]-ethylamino}-nicotinonitrile (Compound I-2)



[00205] This compound was prepared in an analogous manner to Example 8 using 4-chloro-phenylboronic acid. Purification was achieved purified by reverse-phase HPL

[00206] ^1H NMR (500 MHz, $\text{DMSO}(d_6)$): δ 8.52-8.37 (m, 2H), 8.32-8.20 (m, 2H), 8.30 (s, 1H), 8.11-7.39 (m, 8H), 6.53-6.34 (m, 1H), 4.09-3.95 (m, 2H), 3.80-3.65 (m, 2H). LC-MS (ES+) $m/e = 401.10$ (M+H); $R_t = 2.20$ min

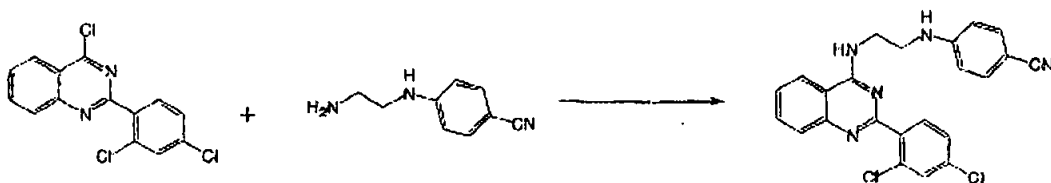
[00207] Example 34 2-{2-[2-(2,4-Dichloro-phenyl)-quinazolin-4-ylamino]-ethylamino}-nicotinonitrile (Compound I-65)



[00208] This compound was prepared in an analogous manner to Example 1 using 2-(2-amino-ethylamino)nicotinonitrile (prepared from 6-chloro pyridine-2-carbonitrile according to the method described by Nuss *et al*, WO 99/65997). Isolated as a white solid (3.0mg, 2%).

[00209] ^1H NMR (500 MHz, $\text{DMSO}(d_6)$): δ 10.30-10.10 (1H, bs), 8.45 (1H, m), 8.17 (1H, m), 8.10-8.05 (1H, m), 7.90-7.70 (6H, m), 7.35 (1H, m), 6.55 (1H, m), 4.0-7.90 (2H, m), 3.80-3.70 (2H, m). HPLC $R_t = 3.10$ min.; FIA (M+H) 434.9, (M-H) 432.6;

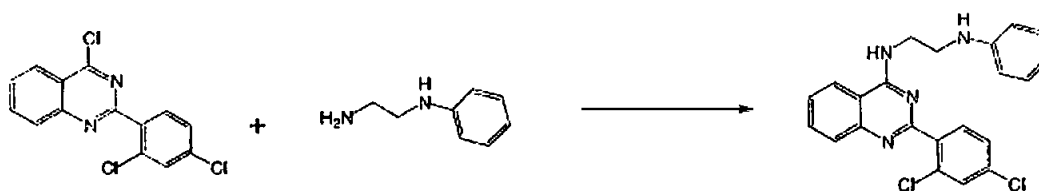
[00210] Example 35 4-{2-[2-(2,4-Dichloro-phenyl)-quinazolin-4-ylamino]-ethylamino}-benzonitrile (Compound I-62)



[00211] This compound was prepared in an analogous manner to Example 1 using 4-(2-amino-ethylamino)-benzonitrile (prepared from 4-fluorobenzonitrile according to the method described by Nuss *et al*, WO 99/65997). Isolated as a white solid (23.6mg, 28%.

[00212] ^1H NMR (500 MHz, $\text{DMSO}-d_6$: δ 10.20-10.00 (1H, bs), 8.40 (1H, m), 8.00 (1H, m), 8.0-7.60 (6H, m), 7.20 (2H, m), 6.60 (2H, m), 3.80-3.70 (2H, m), 3.45-3.35 (2H, m). HPLC R_t = 3.23 min.; FIA (M+H) m/e = 434.0, (M-H) m/e = 431.7

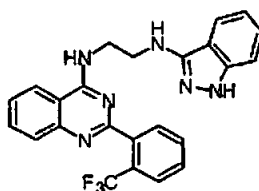
[00213] Example 36 ***N*-[2-(2,4-Dichloro-phenyl)-quinazolin-4-yl]-*N'*-phenyl-ethane-1,2-diamine (Compound I-64)**



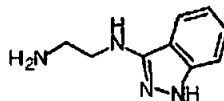
[00214] This compound was prepared in an analogous manner to Example 1 using *N*-phenylethylenediamine. Isolated as a white solid (49.9mg, 28%)

[00215] ^1H NMR (500 MHz, $\text{DMSO}-d_6$: δ 10.40-10.25 (1H, bs), 8.45 (1H, m), 8.05 (1H, m), 7.92 (1H, s), 8.85-7.60 (4H, m), 6.90 (2H, m), 6.60 (2H, m), 6.45 (1H, m), 3.85-3.75 (2H, m), 3.40-3.30 (2H, m). HPLC R_t = 3.22 min; FIA (M+H) m/e = 409.0, (M-H) m/e = 407.0

[00216] Example 37 ***N*-(1*H*-Indazol-3-yl)-*N'*-[2-(2-trifluoromethyl-phenyl)-quinazolin-4-yl]-ethane-1,2-diamine, trifluoro-acetic acid salt (Compound I-10)**



[00217] ***N*1-(1*H*-Indazol-3-yl)-ethane-1,2-diamine**



[00218] A mixture of 3-aminoindazole (0.40 g, 3 mmol) and 2-bromoethylamine hydrobromide (0.62 g, 3 mmol) in ethanol (15 mL) was sealed in a pressure tube and heated at 160-170°C for 2 days. The crude mixture was partitioned between aqueous sodium

bicarbonate and 1:9 methanol:ethyl acetate. The organic layer was dried over sodium sulfate and the solvent was then evaporated. Purification by flash chromatography (SiO₂) eluted with 0.2:2:8 ammonium hydroxide:methanol:dichloromethane provided N1-(1H-indazol-3-yl)-ethane-1,2-diamine and 1-(2-aminoethyl)-1H-indazol-3-ylamine, both containing impurities.

[00219] N1-(1H-Indazol-3-yl)-ethane-1,2-diamine was isolated (52.5 mg, 10% yield, 74.7% purity by HPLC) as a colorless film. $R_f=0.05$ (SiO₂, 1:9 methanol: dichloromethane); ¹H-NMR (500 MHz, CD₃OD, ppm) δ 7.65 (d, J=7.3 Hz, 1H), 7.27 (m, 2H), 6.96 (dt, J=1.0, 7.2 Hz, 1H), 3.48 (t, J=6.5 Hz, 2H), 3.01 (t, J=6.0 Hz, 2H) (+ impurity peaks); MS (LC/MS) 177.01 (M+H); HPLC $R_t=1.100$ min.

[00220] 1-(2-Aminoethyl)-1H-indazol-3-ylamine was isolated (57.1 mg, 11% yield) as a colorless film. $R_f=0.16$ (SiO₂, 1:9 methanol:dichloromethane); ¹H-NMR (500 MHz, CD₃OD, ppm) δ 7.56 (d, J=7.4 Hz, 1H), 7.23 (d, J=8.8 Hz, 1H), 7.14 (t, J=7.6 Hz, 1H), 6.75 (t, J=7.5 Hz, 1H), 4.19 (t, J=6.3 Hz, 2H), 3.08 (t, J=6.3 Hz, 2H) (+ impurity peaks); MS (LC/MS) 177.01 (M+H); HPLC $R_t=0.500$ min.

[00221] A mixture of 4-chloro-2-(2-trifluoromethyl-phenyl)-quinazoline (0.05 g, 0.16 mmol) and N1-(1H-indazol-3-yl)-ethane-1,2-diamine (0.03 g, 0.16 mmol) in dimethylformamide (2 mL) was heated at 120-125°C for 2 h. After cooling, the reaction mixture was poured into water (30 mL) and was treated with saturated bicarbonate (10 mL). The resulting precipitate was filtered off and was then washed with water. Purification by preparative HPLC (Gilson) provided the title compound (3% yield) as a yellow film.

[00222] ¹H-NMR (500 MHz, d₆-DMSO, ppm) δ 11.6 (s, 1H), 8.48 (d, J=7.8 Hz, 1H), 7.97 (m, 2H), 7.81 (m, 6H), 7.63 (d, J=8.0 Hz, 1H), 7.25 (d, J=2.5 Hz, 1H), 6.89 (m, 1H), 3.93 (t, J=5.8 Hz, 2H), 3.61 (t, J=6.1 Hz, 2H); MS (LC/MS) 449.14 (M+H); HPLC $R_t=2.677$ min.

[00223] EXAMPLE 12 - BIOLOGICAL TESTING

[00224] The activity of the compounds as protein kinase inhibitors is assayed *in vitro*, *in vivo* or in a cell line. *In vitro* assays include assays that determine inhibition of either the phosphorylation activity or ATPase activity of the activated protein kinase. Alternate *in vitro* assays quantitate the ability of the inhibitor to bind to the protein kinase. Inhibitor binding may be measured by radiolabelling the inhibitor prior to binding, isolating the inhibitor/protein kinase complex and determining the amount of radiolabel bound.

Alternatively, inhibitor binding may be determined by running a competition experiment where new inhibitors are incubated with the protein kinase bound to known radioligands.

[00225] K_i DETERMINATION FOR THE INHIBITION OF GSK-3

[00226] Compounds were screened for their ability to inhibit GSK-3 β (AA 1-420) activity using a standard coupled enzyme system [Fox et al. *Protein Sci.* 7, 2249 (1998)]. Reactions were carried out in a solution containing 100 mM HEPES (pH 7.5), 10 mM MgCl₂, 25 mM NaCl, 300 μ M NADH, 1 mM DTT and 1.5% DMSO. Final substrate concentrations in the assay were 20 μ M ATP (Sigma Chemicals, St Louis, MO) and 300 μ M peptide (American Peptide, Sunnyvale, CA). Reactions were carried out at 30 °C and 20 nM GSK-3 β . Final concentrations of the components of the coupled enzyme system were 2.5 mM phosphoenolpyruvate, 300 μ M NADH, 30 μ g/ml pyruvate kinase and 10 μ g/ml lactate dehydrogenase.

[00227] An assay stock buffer solution was prepared containing all of the reagents listed above with the exception of ATP and the test compound of interest. The assay stock buffer solution (175 μ l) was incubated in a 96 well plate with 5 μ l of the test compound of interest at final concentrations spanning 0.002 μ M to 30 μ M at 30 °C for 10 min. Typically, a 12 point titration was conducted by preparing serial dilutions (from 10 mM compound stocks) with DMSO of the test compounds in daughter plates. The reaction was initiated by the addition of 20 μ l of ATP (final concentration 20 μ M). Rates of reaction were obtained using a Molecular Devices Spectramax plate reader (Sunnyvale, CA) over 10 min at 30 °C. The K_i values were determined from the rate data as a function of inhibitor concentration.

[00228] The following compounds were shown to have K_i values less than 0.1 μ M for GSK-3: compounds I-1, I-2, I-8, I-9, I-11, I-19, I-62, I-118, I-183, I-188, I-189, I-190, I-191, I-195, I-197, I-198, and I-200.

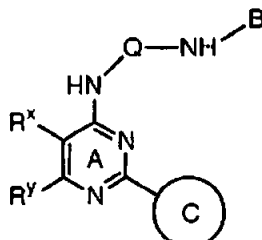
[00229] The following compounds were shown to have K_i values between 0.1 and 1.0 μ M for GSK-3: compounds I-3, I-10, I-29, I-32, I-105, I-113, I-158, I-182, I-187, I-192, I-193, I-194, I-196, I-199, I-202, and I-203.

[00230] While we have hereinbefore presented a number of embodiments of this invention, it is apparent that our basic construction can be altered to provide other embodiments that utilize the compounds and methods of this invention. Therefore, it will be appreciated that the scope of this invention is to be defined by the appended claims rather than by the specific embodiments that have been represented by way of example.

8A

CLAIMS

1. A compound of formula I:



I

- or a pharmaceutically acceptable derivative or prodrug thereof, wherein:
- B is an optionally substituted 5-6 membered monocyclic or 8-10 membered bicyclic aromatic ring, wherein said monocyclic or bicyclic ring has 0-4 heteroatoms selected from oxygen, sulfur or nitrogen;
- Q is a C_{1-4} alkylidene chain, wherein each methylene unit of said Q is substituted by R^2 and $R^{2'}$, and up to two non-adjacent methylene units of said Q are optionally and independently replaced by $-SO_2$ or $-C(=O)$;
- Ring C is selected from a phenyl, thienyl, pyridinyl, pyrimidinyl, pyridazinyl, pyrazinyl, or 1,2,4-triazinyl ring, wherein said Ring C optionally has one or two ortho substituents independently selected from $-R^1$, any substitutable carbon position on Ring C is independently substituted by $-R^5$, or two adjacent substituents on Ring C are optionally taken together with their intervening atoms to form a fused, unsaturated or partially unsaturated, 5-6 membered ring having 0-3 heteroatoms selected from oxygen, sulfur or nitrogen, said fused ring being optionally substituted by halo, oxo, or $-R^8$;
- R^1 is selected from $-halo$, $-CN$, $-NO_2$, $T-V-R^6$, phenyl, 5-6 membered heteroaryl ring, 5-6 membered heterocyclyl ring, or C_{1-6} aliphatic group, said phenyl, heteroaryl, and heterocyclyl rings each optionally substituted by up to three groups independently selected from halo, oxo, or $-R^8$, said C_{1-6} aliphatic group optionally substituted with halo, cyano, nitro, or oxygen, or R^1 and an adjacent substituent taken together with their intervening atoms form said ring fused to Ring C;
- each R^2 is independently selected from H, $-OH$, C_{1-10} aliphatic; $(C_{1-10} \text{ aliphatic})-NH-(C_{1-10} \text{ aliphatic})$; $-O-(C_{1-10} \text{ aliphatic})$; $-NH_2$, $-NH(C_{1-10} \text{ aliphatic})$, $-N(C_{1-10} \text{ aliphatic})_2$, $-C(=O)R$, aryl, or heteroaryl, wherein said aliphatic, aryl, or heteroaryl is optionally substituted;

R is selected from an optionally substituted group selected from C₁₋₁₀ aliphatic, aryl, aralkyl, heteroaryl, or heteroaralkyl;

each R² is independently selected from H or an optionally substituted C₁₋₁₀ aliphatic group;

R^X and R^Y are independently selected from T-R³, or R^X and R^Y are taken together with their intervening atoms to form a fused, partially saturated or aromatic, 5-8 membered ring having 0-3 ring heteroatoms selected from oxygen, sulfur, or nitrogen, wherein any substitutable carbon on said fused ring formed by R^X and R^Y is substituted by oxo or T-R³, and any substitutable nitrogen on said ring formed by R^X and R^Y is substituted by R⁴;

T is a valence bond or a C₁₋₄ alkylidene chain;

R³ is selected from -R', -halo, -OR', -C(=O)R', -CO₂R', -COCOR', -COCH₂COR', -NO₂, -CN, -S(O)R', -S(O)₂R', -SR', -N(R⁴)₂, -CON(R⁷)₂, -SO₂N(R⁷)₂, -OC(=O)R', -N(R⁷)COR', -N(R⁷)CO₂(optionally substituted C₁₋₆ aliphatic), -N(R⁴)N(R⁴)₂, -C=NN(R⁴)₂, -C=N-OR', -N(R⁷)CON(R⁷)₂, -N(R⁷)SO₂N(R⁷)₂, -N(R⁴)SO₂R', or -OC(=O)N(R⁷)₂;

each R' is independently selected from hydrogen or an optionally substituted group selected from C₁₋₆ aliphatic, C₆₋₁₀ aryl, a heteroaryl ring having 5-10 ring atoms, or a heterocyclyl ring having 5-10 ring atoms;

each R⁴ is independently selected from -R⁷, -COR⁷, -CO₂(C₁₋₆ aliphatic), -CON(R⁷)₂, or -SO₂R⁷, or two R⁴ on the same nitrogen are taken together to form a 5-8 membered heterocyclyl or heteroaryl ring;

each R⁵ is independently selected from -R', halo, -OR', -C(=O)R', -CO₂R', -COCOR', -NO₂, -CN, -S(O)R', -SO₂R', -SR', -N(R⁴)₂, -CON(R⁴)₂, -SO₂N(R⁴)₂, -OC(=O)R', -N(R⁴)COR', -N(R⁴)CO₂(optionally substituted C₁₋₆ aliphatic), -N(R⁴)N(R⁴)₂, -C=NN(R⁴)₂, -C=N-OR', -N(R⁴)CON(R⁴)₂, -N(R⁴)SO₂N(R⁴)₂, -N(R⁴)SO₂R', or -OC(=O)N(R⁴)₂, or R⁵ and an adjacent substituent taken together with their intervening atoms form said ring fused to Ring C;

V is -O-, -S-, -SO-, -SO₂-, -N(R⁶)SO₂-, -SO₂N(R⁶)-, -N(R⁶)-, -CO-, -CO₂-, -N(R⁶)CO-, -N(R⁶)C(O)O-, -N(R⁶)CON(R⁶)-, -N(R⁶)SO₂N(R⁶)-, -N(R⁶)N(R⁶)-, -C(O)N(R⁶)-, -OC(O)N(R⁶)-, -C(R⁶)₂O-, -C(R⁶)₂S-, -C(R⁶)₂SO-, -C(R⁶)₂SO₂-, -C(R⁶)₂SO₂N(R⁶)-, -C(R⁶)₂N(R⁶)-, -C(R⁶)₂N(R⁶)C(O)-, -C(R⁶)₂N(R⁶)C(O)O-, -C(R⁶)=NN(R⁶)-, -C(R⁶)=N-O-, -C(R⁶)₂N(R⁶)N(R⁶)-, -C(R⁶)₂N(R⁶)SO₂N(R⁶)-, or -C(R⁶)₂N(R⁶)CON(R⁶)-;

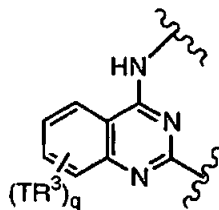
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each R^6 is independently selected from hydrogen or an optionally substituted C_{1-4} aliphatic group, or two R^6 groups on the same nitrogen atom are taken together with the nitrogen atom to form a 5-6 membered heterocyclyl or heteroaryl ring;

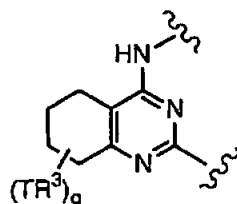
each R^7 is independently selected from hydrogen or an optionally substituted C_{1-6} aliphatic group, or two R^7 on the same nitrogen are taken together with the nitrogen to form a 5-8 membered heterocyclyl or heteroaryl ring; and

each R^8 is independently selected from an optionally substituted C_{1-4} aliphatic group, $-OR^6$, $-SR^6$, $-COR^6$, $-SO_2R^6$, $-N(R^6)_2$, $-N(R^6)N(R^6)_2$, $-CN$, $-NO_2$, $-CON(R^6)_2$, or $-CO_2R^6$.

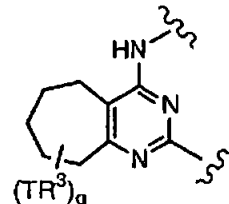
2. The compound according to claim 1, wherein ring A is selected from one of:



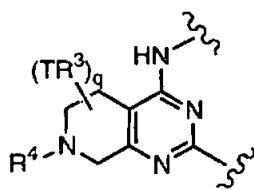
I-A



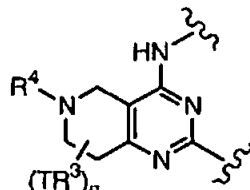
I-B



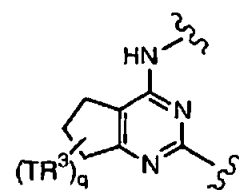
I-C



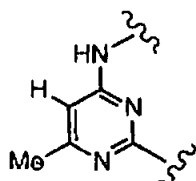
I-D



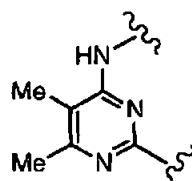
I-E



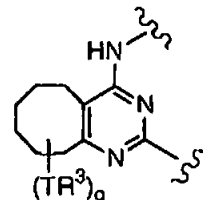
I-F



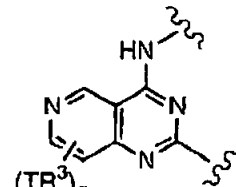
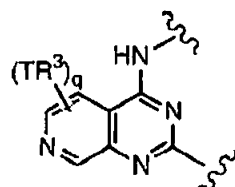
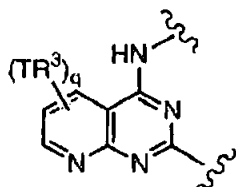
I-G



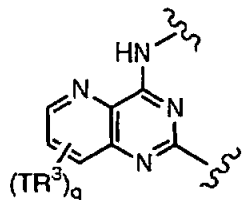
I-H



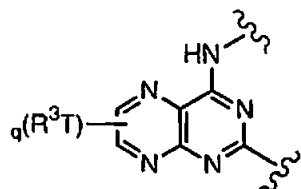
I-I



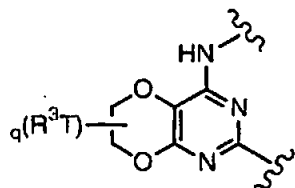
I-J



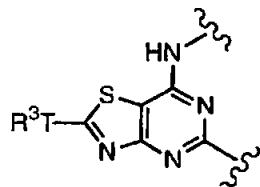
I-M



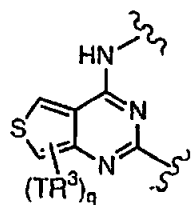
I-P



I-S

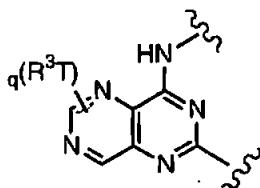


I-V

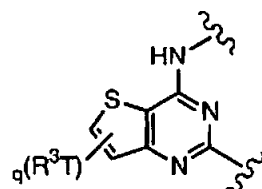


I-Y

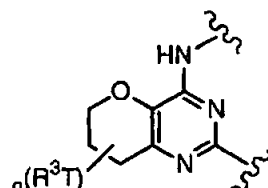
I-K



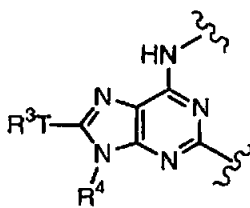
I-N



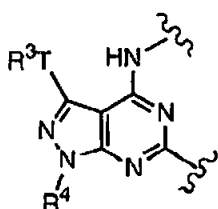
I-Q



I-T

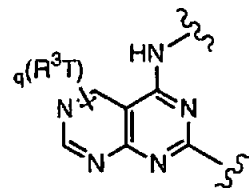


I-W

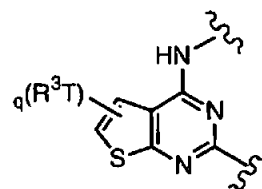


I-Z

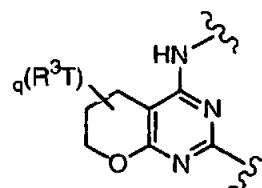
I-L



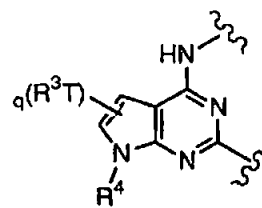
I-O



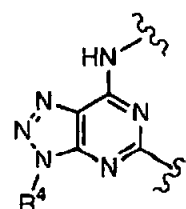
I-R



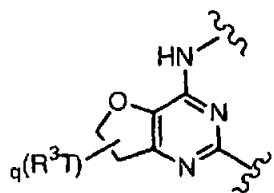
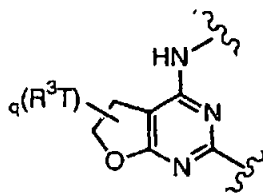
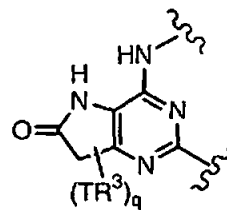
I-U



I-X



I-AA

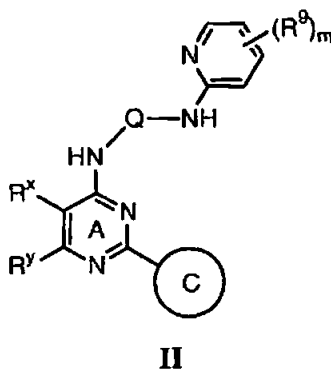
**I-BB****I-CC****I-DD**

3. The compound of claim 2, wherein Ring A is selected from one of **I-A**, **I-B**, **I-C**, **I-D**, **I-E**, **I-F**, **I-G**, **I-H**, **I-I**, **I-J**, **I-K**, **I-L**, or **I-M**.
4. The compound of claim 2, wherein Ring A is selected from one of **I-A**, **I-B**, **I-C**, **I-F**, or **I-H**.
5. The compound of claim 2, wherein q is 0-4, and $T-R^3$ substituents are selected from $-R'$, halo, $-OR'$, $-C(=O)R'$, $-CO_2R'$, $-COCOR'$, $-NO_2$, $-CN$, $-S(O)R'$, $-SO_2R'$, $-SR'$, $-N(R^4)_2$, $-CON(R^4)_2$, $-SO_2N(R^4)_2$, $-OC(=O)R'$, $-N(R^4)COR'$, $-N(R^4)CO_2$ (optionally substituted C_{1-6} aliphatic), $-N(R^4)N(R^4)_2$, $-C=NN(R^4)_2$, $-C=N-OR'$, $-N(R^4)CON(R^4)_2$, $-N(R^4)SO_2N(R^4)_2$, $-N(R^4)SO_2R'$, or $-OC(=O)N(R^4)_2$. Exemplary R^4 substituents include $-R^7$, $-COR^7$, $-CO_2(C_{1-6}$ aliphatic), $-CON(R^7)_2$, or $-SO_2R^7$, or two R^4 on the same nitrogen are taken together to form a 5-8 membered heterocyclyl or heteroaryl ring.
6. The compound of claim 1, wherein compounds of formula **I** have a monocyclic pyrimidine ring system which is substituted by R^X and R^Y , wherein R^X groups include hydrogen, alkyl- or dialkylamino, acetamido, or a C_{1-4} aliphatic group such as methyl, ethyl, cyclopropyl, isopropyl or t-butyl, and R^Y groups include $T-R^3$ wherein T is a valence bond or a methylene, and R^3 is $-R'$, $-N(R^4)_2$, or $-OR'$.
7. The compound of claim 1, wherein Q is $-CH_2CH_2-$, $-CH_2CH_2CH_2-$, or $-CH_2CH_2CH_2CH_2-$, $-SO_2CH_2-$, $-CH_2SO_2-$, $-(C=O)CH_2-$, or $-CH_2(C=O)-$.
8. The compound of claim 1, wherein B groups are selected from optionally substituted pyridyl, pyrimidinyl, thiazolyl, indolyl, imidazolyl, oxadiazolyl, tetrazolyl, pyrazinyl, triazolyl, thienyl, furanyl, quinoliny, purinyl, naphthyl, benzothiazolyl, benzopyridyl,

benzimidazolyl, indazolyl, isothiazolyl, pyrazolyl, pyridazinyl, isoxazolyl, phenyl, benzothiophenyl, or pyridothiophenyl.

9. The compound of claim 8, wherein substituents for B groups are each independently selected from nitro, amino, cyano, halo, thioamido, amidino, oxamidino, alkoxyamidino, imidino, guanidino, sulfonamido, carboxyl, formyl, alkyl, haloalkyl, alkoxy, haloalkoxy, alkoxyalkyl, alkylaminoalkoxy, alkylcarbonyl, aralkylcarbonyl, heteroaralkylcarbonyl, alkylthio, aminoalkyl, cyanoalkyl, hydroxy, alkoxycarbonyl, aryl, aralkyl, heteroaryl, or heteroaralkyl.

10. The compound of claim 1, wherein B is optionally substituted 2-pyridyl and compounds have the general formula II:



wherein m is 0-4, and each occurrence of R^9 is independently selected from H, nitro, amino, cyano, halo, thioamido, amidino, oxamidino, alkoxyamidino, imidino, guanidino, sulfonamido, carboxyl, formyl, alkyl, haloalkyl, alkoxy, haloalkoxy, alkoxyalkyl, alkylaminoalkoxy, alkylcarbonyl, aralkylcarbonyl, heteroaralkylcarbonyl, alkylthio, aryl, aralkyl, heteroaryl, or heteroaralkyl.

11. The compound of claim 10, wherein R^9 substituents are selected from hydrogen, C_{1-4} alkyl, nitro, amino, cyano, cyanomethyl, trifluoromethyl, hydroxy, or methoxy.

12. The compound of claim 1, wherein B is indazolyl, pyrazolyl, or thiazolyl optionally substituted with one or more independent occurrences of R^9 , wherein R^9 substituents are

selected from hydrogen, C₁₋₄alkyl, nitro, amino, cyano, cyanomethyl, trifluoromethyl, hydroxy, or methoxy.

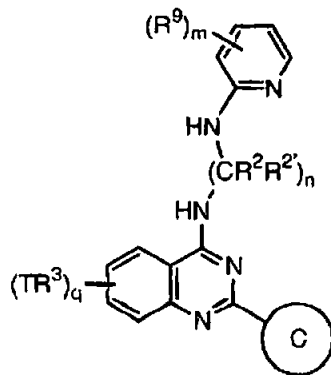
13. The compound of claim 1, wherein Ring C is optionally substituted phenyl or pyridinyl.

14. The compound of claim 1, wherein ring C is optionally substituted naphthyl, quinolinyl, isoquinolinyl or benzodioxolyl.

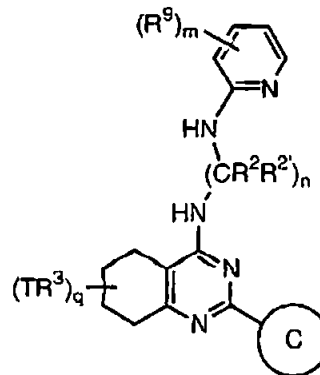
15. The compound of claim 13 or 14, wherein optional substituents on Ring C are selected from R¹ or R⁵, wherein each occurrence of R¹ is independently selected from -halo, an optionally substituted C₁₋₆ aliphatic group, phenyl, -COR⁶, -OR⁶, -CN, -SO₂R⁶, -SO₂NH₂, -N(R⁶)₂, -CO₂R⁶, -CONH₂, -NHCOR⁶, -OC(O)NH₂, or -NHSO₂R⁶; and each occurrence of R⁵ is selected from -halo, -CN, -NO₂, -N(R⁴)₂, optionally substituted C₁₋₆ aliphatic group, -OR', -C(O)R', -CO₂R', -CONH(R⁴), -N(R⁴)COR', -SO₂N(R⁴)₂, or -N(R⁴)SO₂R'.

16. The compound of claim 15, wherein R¹ groups are selected from -CF₃, -Cl, -F, -CN, -COCH₃, -OCH₃, -OH, -CH₂CH₃, -OCH₂CH₃, -CH₃, -CF₂CH₃, cyclohexyl, t-butyl, isopropyl, cyclopropyl, -C≡CH, -C≡C-CH₃, -SO₂CH₃, -SO₂NH₂, -N(CH₃)₂, -CO₂CH₃, -CONH₂, -NHCOCH₃, -OC(O)NH₂, -NHSO₂CH₃, or -OCF₃; and R⁵ groups are selected from -Cl, -F, -CN, -CF₃, -NH₂, -NH(C₁₋₄ aliphatic), -N(C₁₋₄ aliphatic)₂, -O(C₁₋₄ aliphatic), C₁₋₄ aliphatic, or -CO₂(C₁₋₄ aliphatic).

17. The compound of claim 1, having one of the formulas:

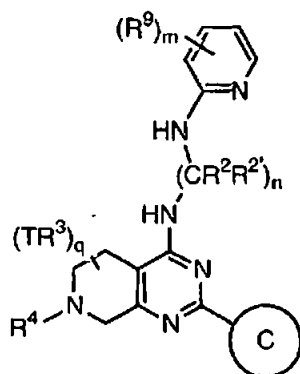


I-A-a

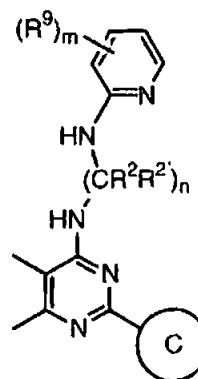


I-B-a

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I-D-a



I-H-a

wherein q is 0-4, and $T-R^3$ substituents are selected from $-R'$, halo, $-OR'$, $-C(=O)R'$, $-CO_2R'$, $-COCOR'$, $-NO_2$, $-CN$, $-S(O)R'$, $-SO_2R'$, $-SR'$, $-N(R^4)_2$, $-CON(R^4)_2$, $-SO_2N(R^4)_2$, $-OC(=O)R'$, $-N(R^4)COR'$, $-N(R^4)CO_2$ (optionally substituted C_{1-6} aliphatic), $-N(R^4)N(R^4)_2$, $-C=NN(R^4)_2$, $-C=N-OR'$, $-N(R^4)CON(R^4)_2$, $-N(R^4)SO_2N(R^4)_2$, $-N(R^4)SO_2R'$, or $-OC(=O)N(R^4)_2$; and wherein m is 0-4, and each occurrence of R^9 is independently selected from H, nitro, amino, cyano, halo, thioamido, amidino, oxamidino, alkoxyamidino, imidino, guanidino, sulfonamido, carboxyl, formyl, alkyl, haloalkyl, alkoxy, haloalkoxy, alkoxyalkyl, alkylaminoalkoxy, alkylcarbonyl, aralkylcarbonyl, heteroaralkylcarbonyl, alkylthio, aryl, aralkyl, heteroaryl, or heteroaralkyl.

18. The compound of claim 17, wherein ring C is a phenyl ring and R^1 is halo, methyl, cyano, OMe, OH, or trifluoromethyl.

19. The compound of claim 1, wherein one or more of, or each of, B, ring C, R^X , R^Y , or R^1 is defined such that:

(a) B is an optionally substituted 5-6 membered monocyclic or 8-10 membered bicyclic aromatic ring, wherein said monocyclic or bicyclic ring has 1-4 heteroatoms selected from oxygen, sulfur or nitrogen;

(b) Ring C is a phenyl or pyridinyl ring having one or two ortho substituents independently selected from $-R^1$, wherein Ring C is further substituted by $-R^5$ and wherein when Ring C and two adjacent substituents thereon form a bicyclic ring system, the bicyclic ring system is selected from a naphthyl, quinolinyl or isoquinolinyl ring;

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(c) R^X is hydrogen or C_{1-4} aliphatic and R^Y is $T-R^3$, or R^X and R^Y are taken together with their intervening atoms to form an optionally substituted 5-7 membered partially saturated or aromatic ring having 0-2 ring nitrogens; and

(d) R^1 is -halo, an optionally substituted C_{1-6} aliphatic group, phenyl, $-COR^6$, $-OR^6$, $-CN$, $-SO_2R^6$, $-SO_2NH_2$, $-N(R^6)_2$, $-CO_2R^6$, $-CONH_2$, $-NHCOR^6$, $-OC(O)NH_2$, or $-NHOSO_2R^6$.

20. The compound of claim 1, wherein one or more of, or each of, B, R^2 , ring C, R^X , R^Y , R^1 , or R^5 is defined such that:

(a) B is an optionally substituted group selected from pyridyl, pyrimidinyl, thiazolyl, indolyl, imidazolyl, oxadiazolyl, tetrazolyl, pyrazinyl, triazolyl, thienyl, furanyl, quinolinyl, purinyl, naphthyl, benzothiazolyl, benzopyridyl, benzimidazolyl, indazolyl, isothiazolyl, pyrazolyl, pyridazinyl, isoxazolyl, phenyl, benzothiophenyl, or pyridothiophenyl;

(b) R^2 is H, alkyl, haloalkyl, heterocycloaminoalkyl, alkylaminoalkyl, and alkyl, wherein all alkyl moieties have 1-10 carbon atoms are unsubstituted;

(c) Ring C is a phenyl or pyridinyl ring having one or two ortho substituents independently selected from $-R^1$, wherein Ring C is further substituted by $-R^5$ and wherein when Ring C and two adjacent substituents thereon form a bicyclic ring system, the bicyclic ring system is a naphthyl ring;

(d) R^X is hydrogen or methyl and R^Y is $-R'$, $N(R^4)_2$, or $-OR'$, or R^X and R^Y are taken together with their intervening atoms to form a 5-7 membered partially saturated or aromatic carbocyclic ring optionally substituted with $-R'$, halo, $-OR'$, $-C(=O)R'$, $-CO_2R'$, $-COCOR'$, $-NO_2$, $-CN$, $-S(O)R'$, $-SO_2R'$, $-SR'$, $-N(R^4)_2$, $-CON(R^4)_2$, $-SO_2N(R^4)_2$, $-OC(=O)R'$, $-N(R^4)COR'$, $-N(R^4)CO_2$ (optionally substituted C_{1-6} aliphatic), $-N(R^4)N(R^4)_2$, $-C=NN(R^4)_2$, $-C=N-OR'$, $-N(R^4)CON(R^4)_2$, $-N(R^4)SO_2N(R^4)_2$, $-N(R^4)SO_2R'$, or $-OC(=O)N(R^4)_2$;

(e) R^1 is -halo, a C_{1-6} haloaliphatic group, a C_{1-6} aliphatic group, phenyl, OMe, OH, or $-CN$; and

(f) each R^5 is independently selected from -halo, $-CN$, $-NO_2$, $-N(R^4)_2$, optionally substituted C_{1-6} aliphatic group, $-OR'$, $-C(O)R'$, $-CO_2R'$, $-CONH(R^4)$, $-N(R^4)COR'$, $-SO_2N(R^4)_2$, or $-N(R^4)SO_2R'$.

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21. The compound of claim 1, wherein one or more of, or each of, B, R², ring C, R^X, R^Y, R¹, or R⁵ is defined such that:

(a) B is an optionally substituted pyridyl group optionally substituted by 0, 1, or 2 occurrences of R⁹, wherein each occurrence of R⁹ is independently hydrogen, C₁₋₄alkyl, nitro, amino, cyano, cyanomethyl, trifluoromethyl, hydroxy, and methoxy;

(b) R² is H, alkyl, haloalkyl, heterocycloaminoalkyl, alkylaminoalkyl, and alkyl, wherein all alkyl moieties have 1-10 carbon atoms are unsubstituted;

(c) Ring C is a phenyl or pyridinyl ring having one or two ortho substituents independently selected from -R¹, wherein Ring C is further substituted by -R⁵ and wherein when Ring C and two adjacent substituents thereon form a bicyclic ring system, the bicyclic ring system is a naphthyl ring;

(d) R^X is hydrogen or methyl and R^Y is -R', N(R⁴)₂, or -OR', or R^X and R^Y are taken together with their intervening atoms to form a 5-7 membered partially saturated or aromatic ring having 1-2 nitrogen ring atoms optionally substituted with -R', halo, -OR', -C(=O)R', -CO₂R', -COCOR', -NO₂, -CN, -S(O)R', -SO₂R', -SR', -N(R⁴)₂, -CON(R⁴)₂, -SO₂N(R⁴)₂, -OC(=O)R', -N(R⁴)COR', -N(R⁴)CO₂(optionally substituted C₁₋₆ aliphatic), -N(R⁴)N(R⁴)₂, -C=NN(R⁴)₂, -C=N-OR', -N(R⁴)CON(R⁴)₂, -N(R⁴)SO₂N(R⁴)₂, -N(R⁴)SO₂R', or -OC(=O)N(R⁴)₂;

(e) R¹ is -halo, a C₁₋₆ haloaliphatic group, a C₁₋₆ aliphatic group, phenyl, OMe, OH, or -CN; and

(f) each R⁵ is independently selected from -halo, -CN, -NO₂, -N(R⁴)₂, optionally substituted C₁₋₆ aliphatic group, -OR', -C(O)R', -CO₂R', -CONH(R⁴), -N(R⁴)COR', -SO₂N(R⁴)₂, or -N(R⁴)SO₂R'.

22. The compound of claim 1, wherein one or more of, or each of, B, R², ring C, R^X, R^Y, R¹, or R⁵ is defined such that:

(a) B is an optionally substituted pyridyl group optionally substituted with 2 independent occurrences of R⁹, wherein each occurrence of R⁹ is independently hydrogen, C₁₋₄alkyl, nitro, amino, cyano, cyanomethyl, trifluoromethyl, hydroxy, and methoxy;

(b) each R² and R^{2'} is H;

(c) Ring C is a phenyl ring having one or two ortho substituents independently selected from -R¹, wherein Ring C is further substituted by -R⁵;

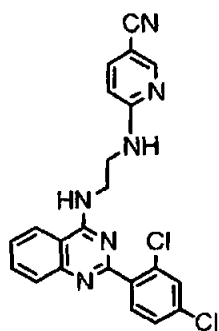
94

(d) R^X is hydrogen or methyl and R^Y is methyl, methoxymethyl, ethyl, cyclopropyl, isopropyl, t-butyl, alkyl- or an optionally substituted group selected from 2-pyridyl, 4-pyridyl, piperidinyl, or phenyl, or R^X and R^Y are taken together with their intervening atoms to form an optionally substituted benzo ring or partially saturated 6-membered carbocyclic ring;

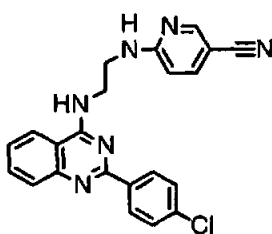
(e) R^1 is -halo, a C_{1-4} aliphatic group optionally substituted with halogen, OMe, OH, or -CN; and

(f) each R^5 is independently selected from -Cl, -F, -CN, -CF₃, -NH₂, -NH(C_{1-4} aliphatic), -N(C_{1-4} aliphatic)₂, -O(C_{1-4} aliphatic), optionally substituted C_{1-4} aliphatic, and -CO₂(C_{1-4} aliphatic).

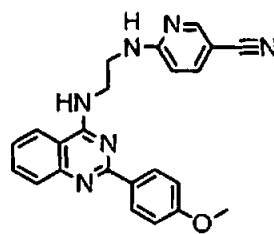
23. The compound of claim 1, selected from one of the compounds:



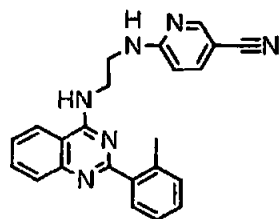
I-1



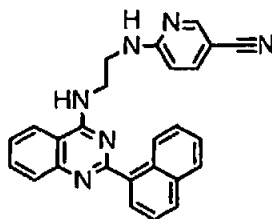
I-2



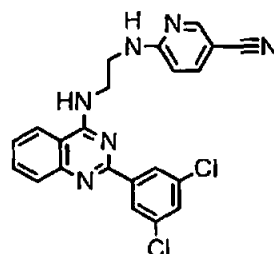
I-3



I-4

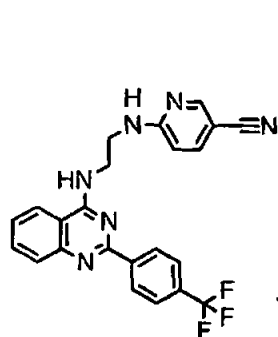


I-5

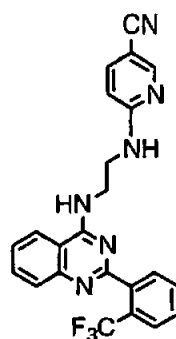


I-6

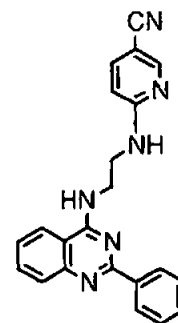
ar



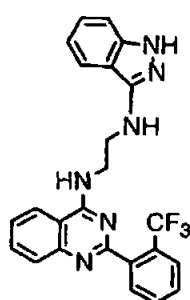
I-7



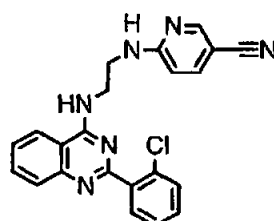
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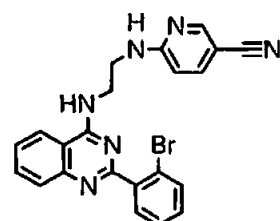
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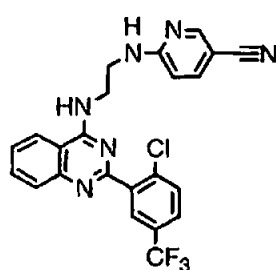
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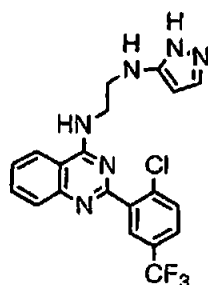
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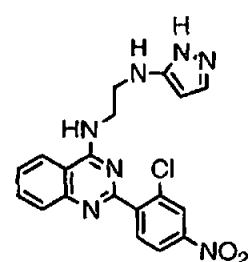
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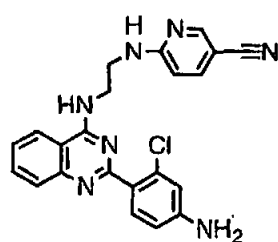
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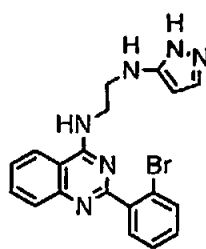
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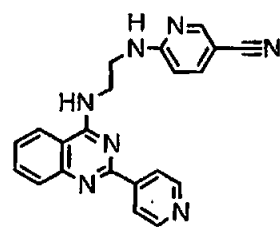
I-15



I-16

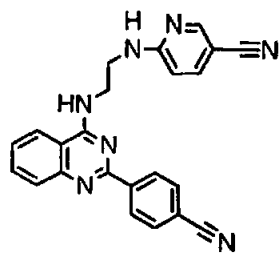


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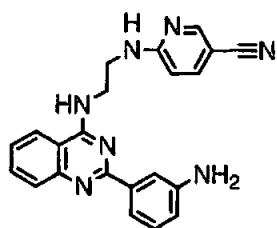


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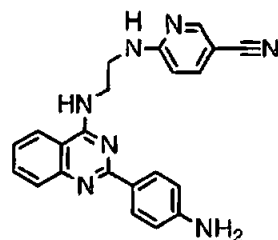
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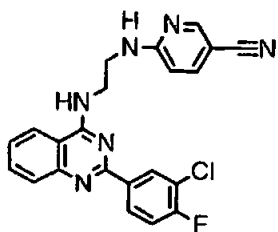
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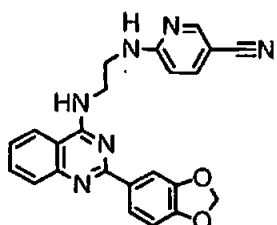
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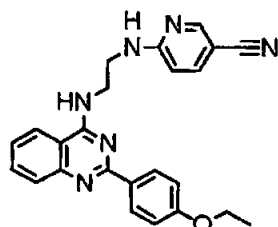
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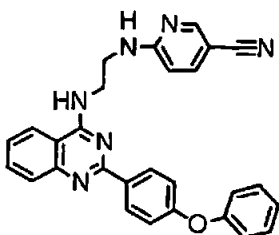
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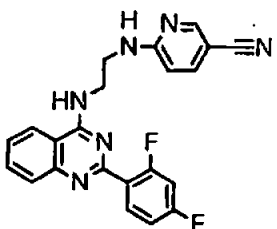
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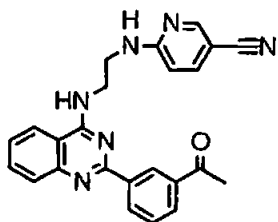
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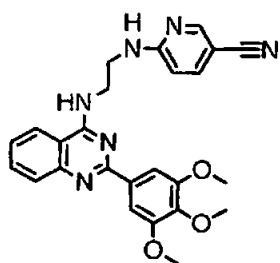
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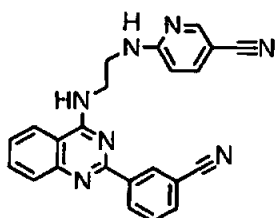
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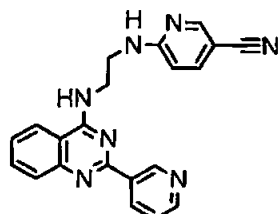
I-27



I-28

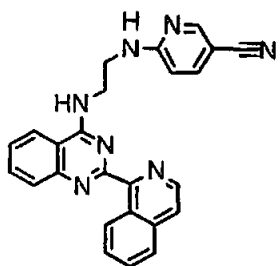


I-29

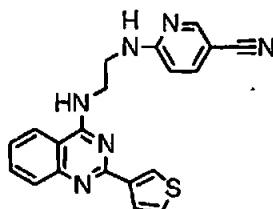


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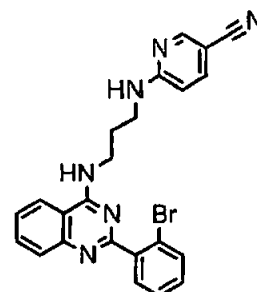
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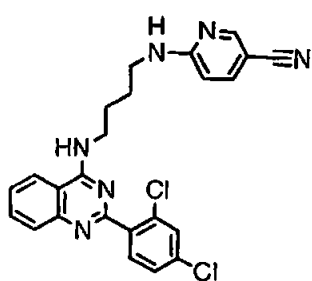
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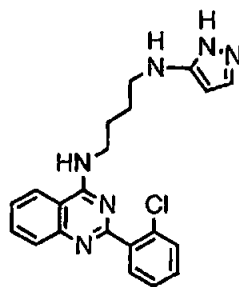
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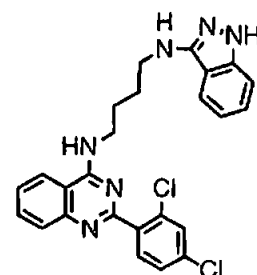
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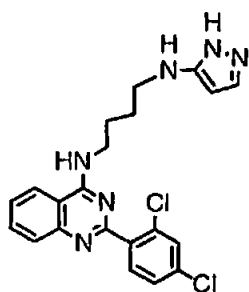
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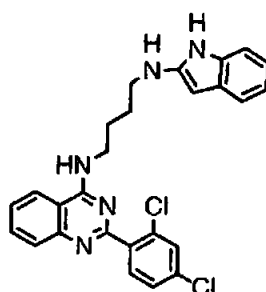
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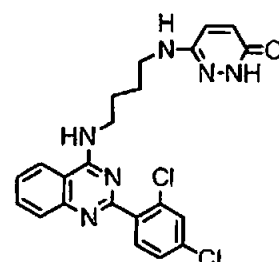
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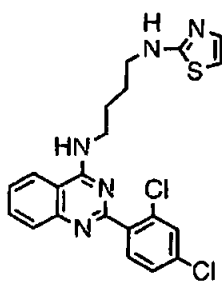
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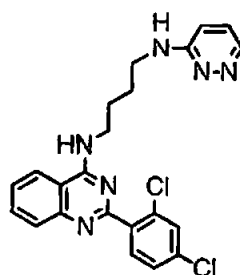
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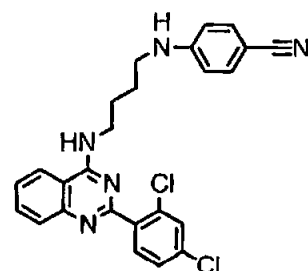
I-39



I-40

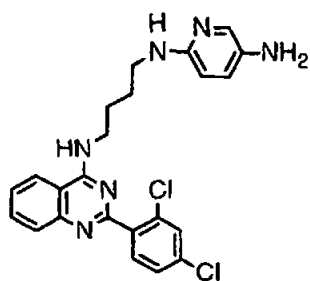


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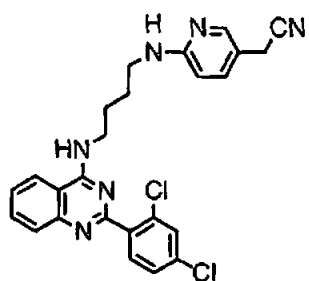


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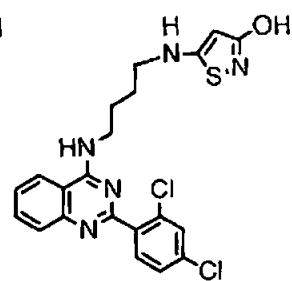
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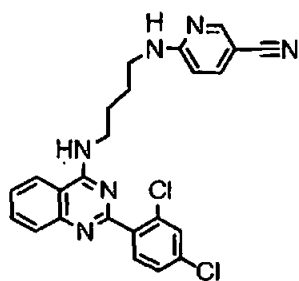
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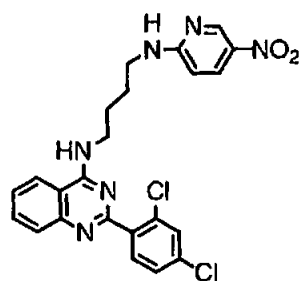
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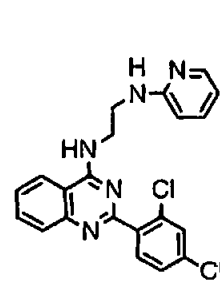
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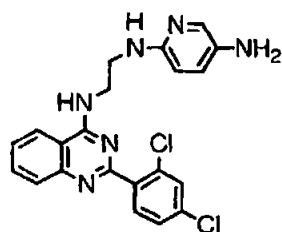
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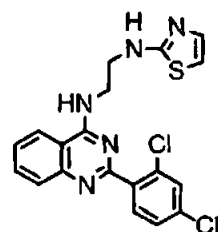
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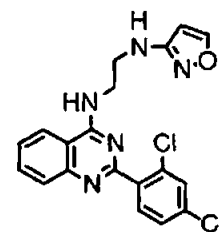
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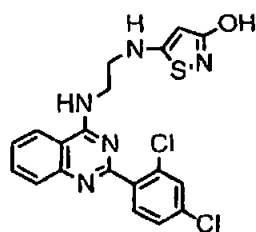
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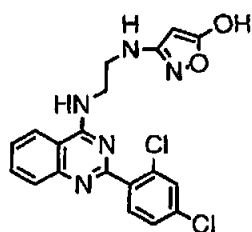
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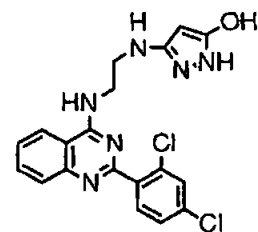
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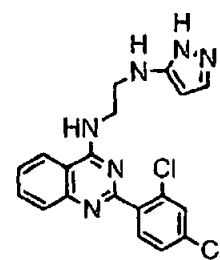
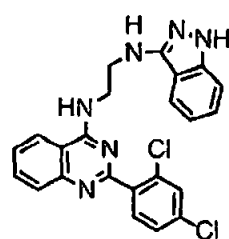
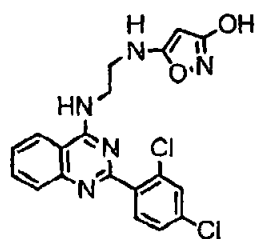
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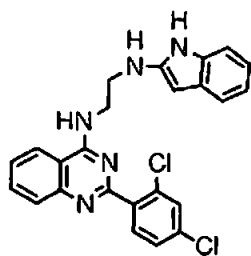
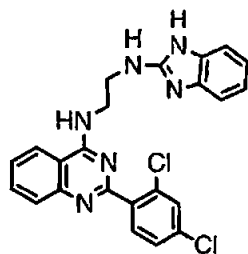
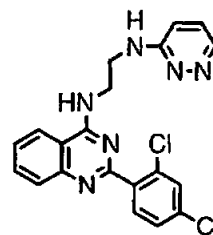
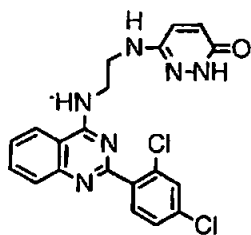
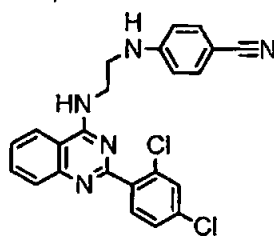
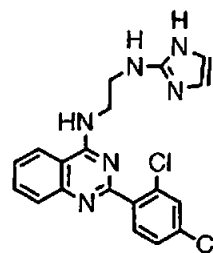
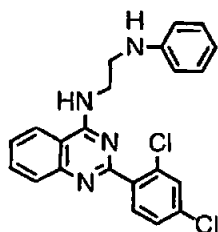
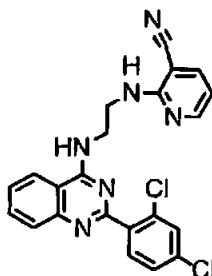
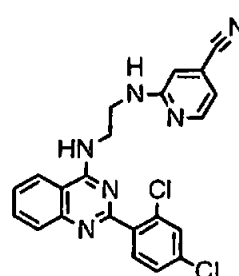
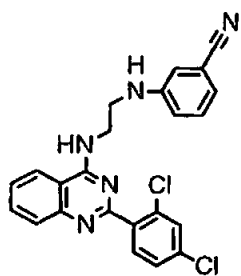
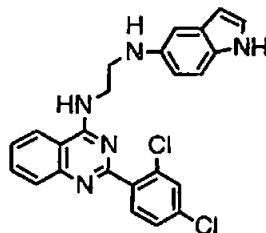
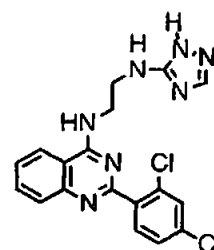
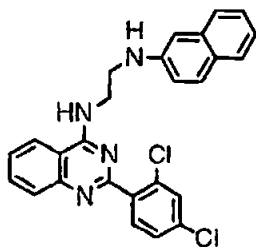
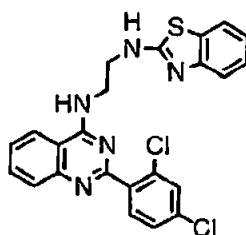
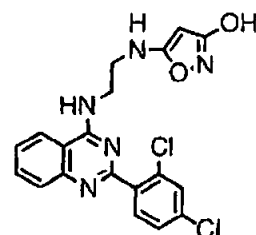


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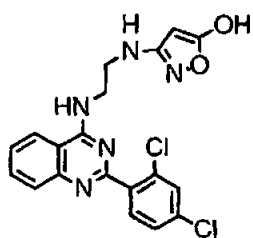
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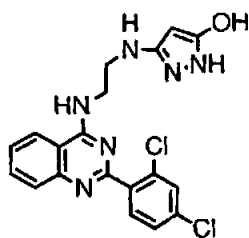
I-55**I-56****I-57****I-58****I-59****I-60****I-61****I-62****I-63****I-64****I-65****I-66****I-67****I-68****I-69**

100

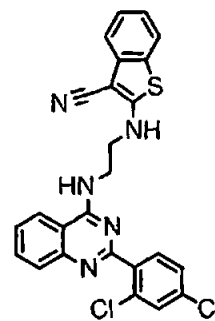
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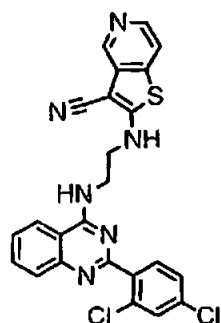
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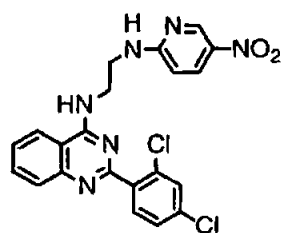
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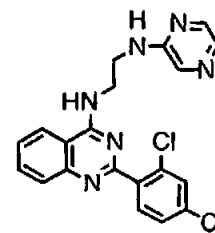
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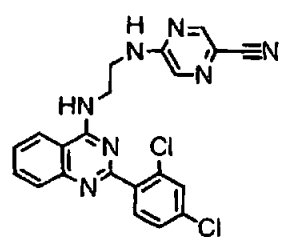
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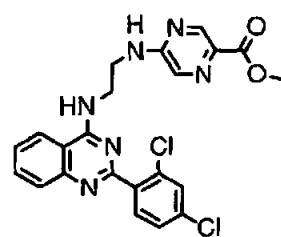
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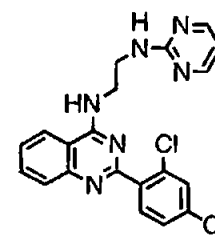
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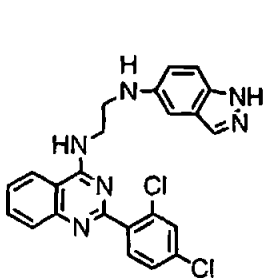
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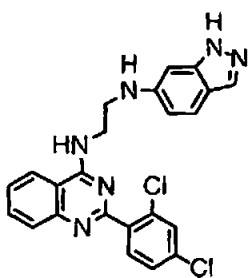
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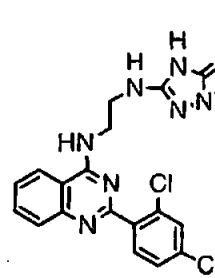
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I-80



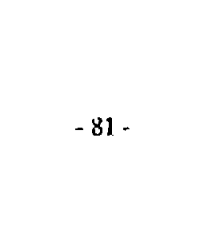
I-81



I-82



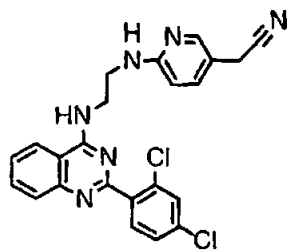
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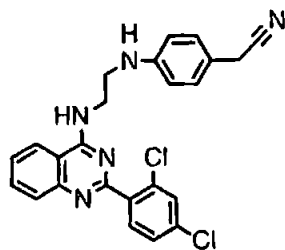
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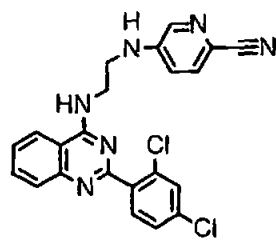
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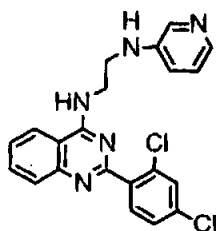
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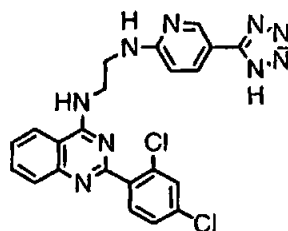
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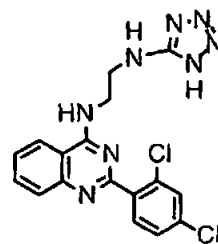
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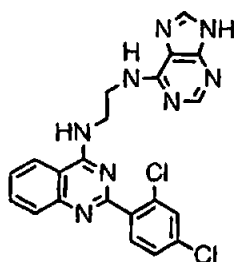
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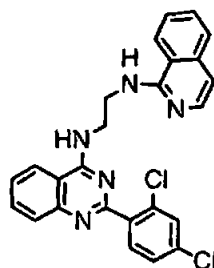
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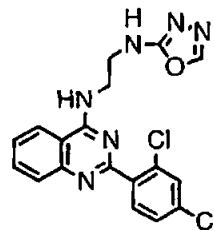
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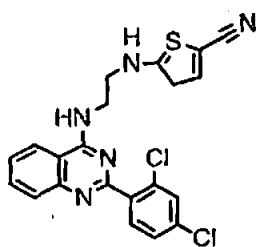
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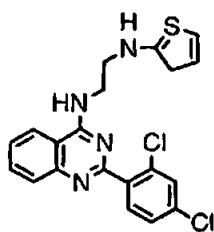
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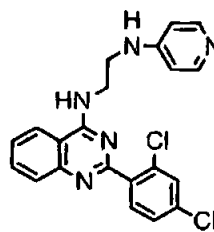
I-93



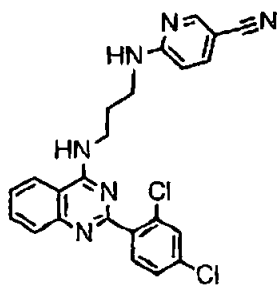
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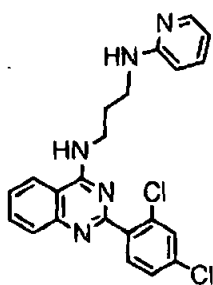
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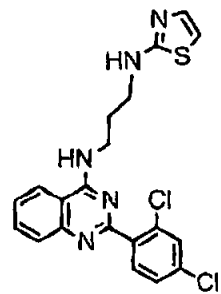
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I-97

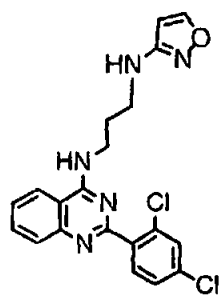


I-98

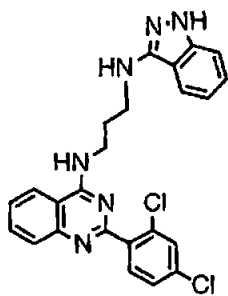


I-99

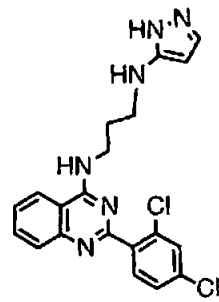
102



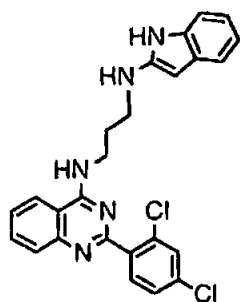
I-100



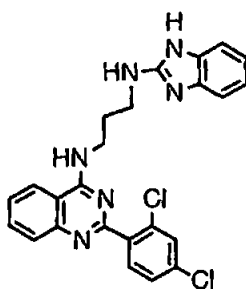
I-101



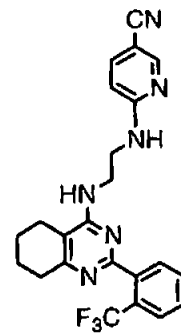
I-102



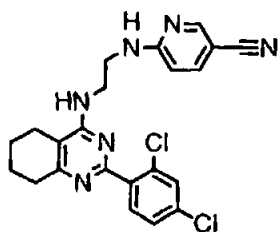
I-103



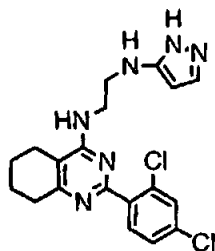
I-104



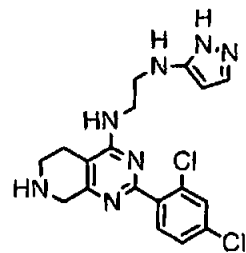
I-105



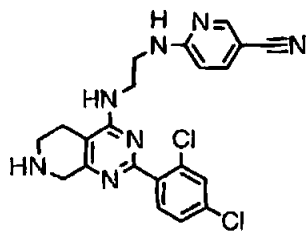
I-106



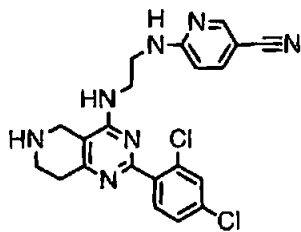
I-107



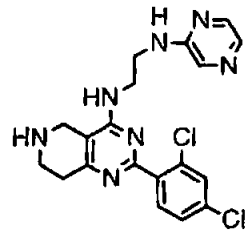
I-108



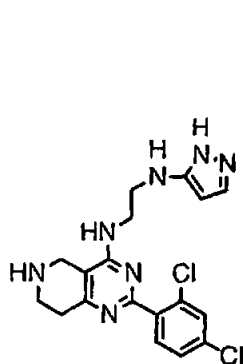
I-109



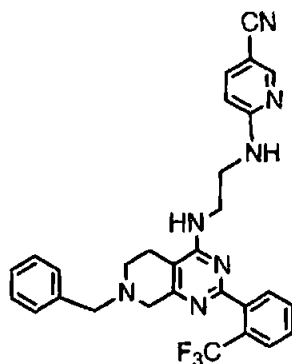
I-110



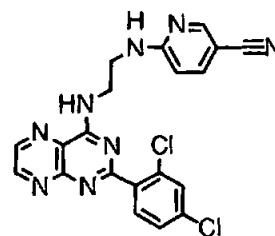
I-111



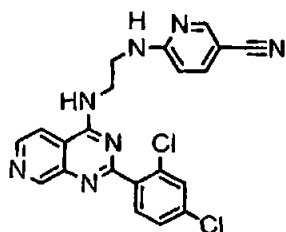
I-112



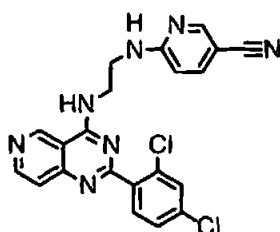
I-113



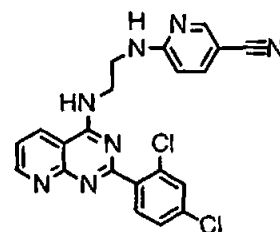
I-114



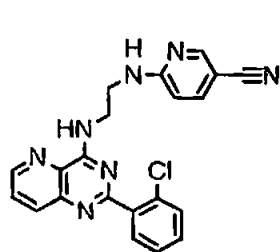
I-115



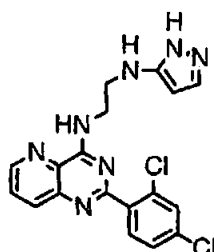
I-116



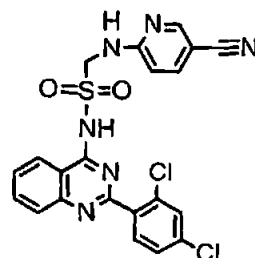
I-117



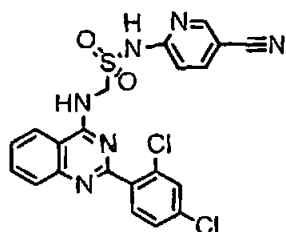
I-118



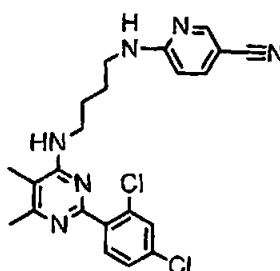
I-119



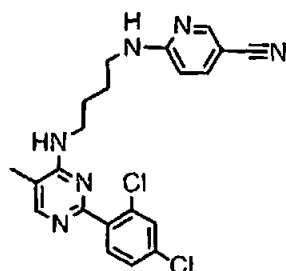
I-120



I-121

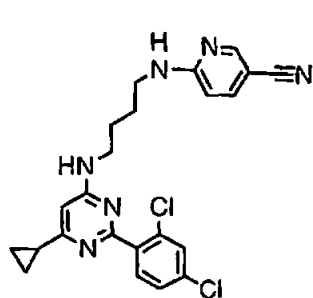


I-122

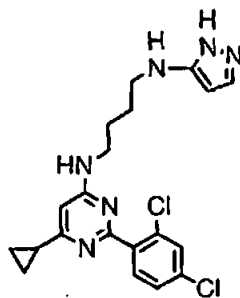


I-123

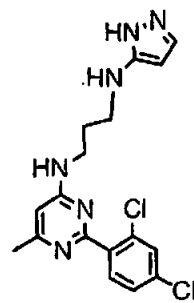
104



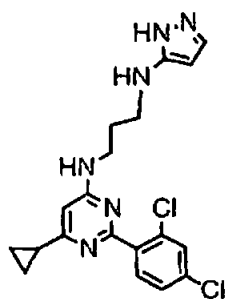
I-124



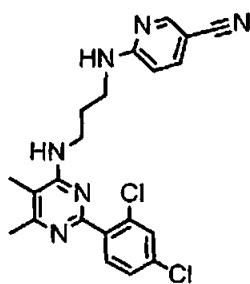
I-125



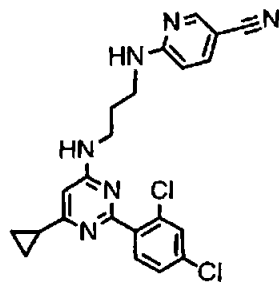
I-126



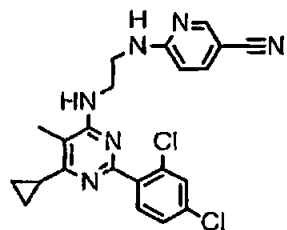
I-127



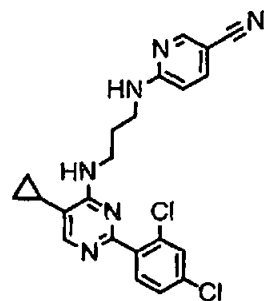
I-128



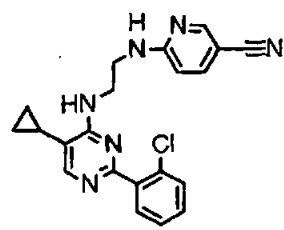
I-129



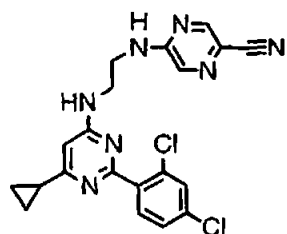
I-130



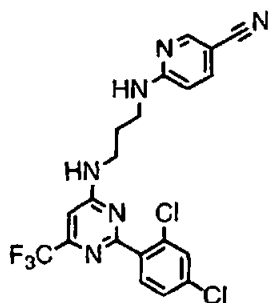
I-131



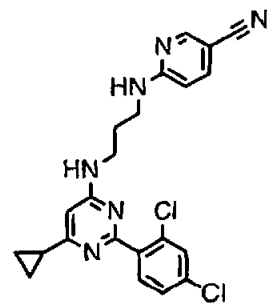
I-132



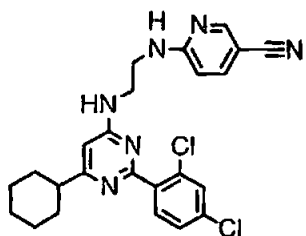
I-133



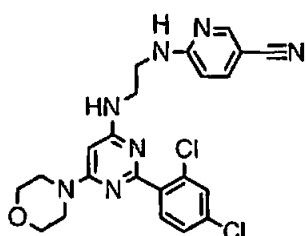
I-134



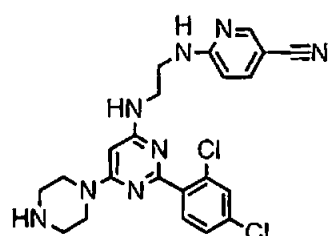
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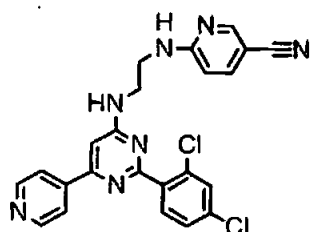
I-136



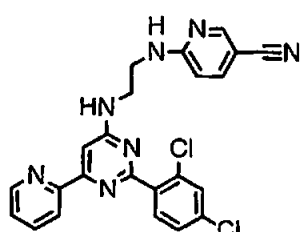
I-137



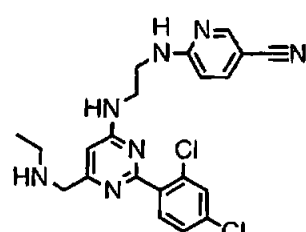
I-138



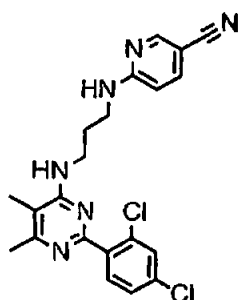
I-139



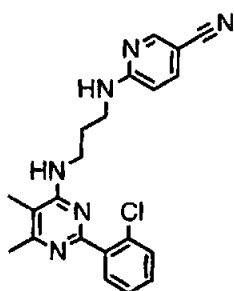
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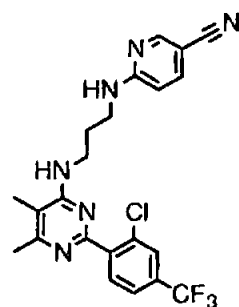
I-141



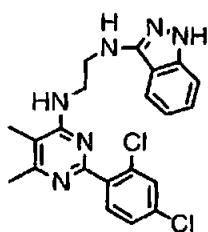
I-142



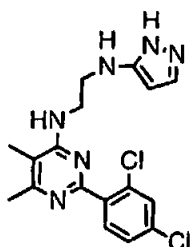
I-143



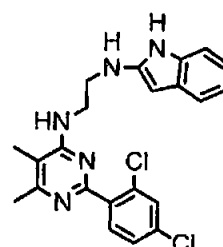
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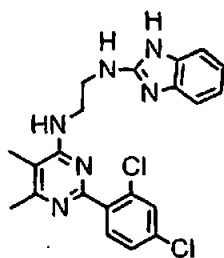
I-145



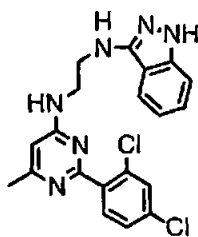
I-146



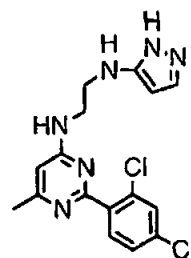
I-147



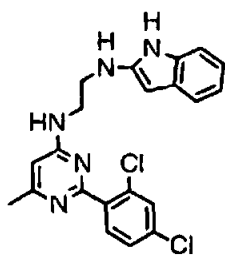
I-148



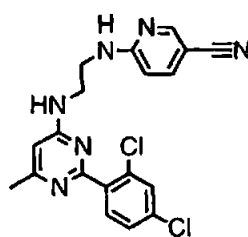
I-149



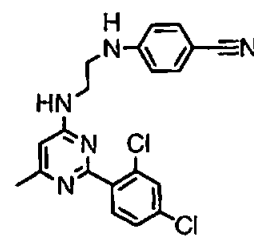
I-150



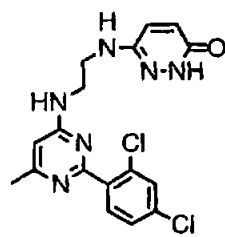
I-151



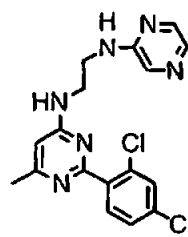
I-152



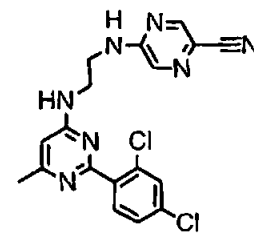
I-153



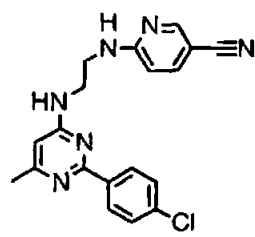
I-154



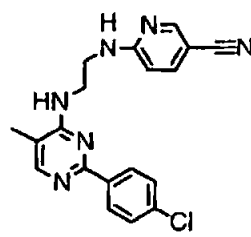
I-155



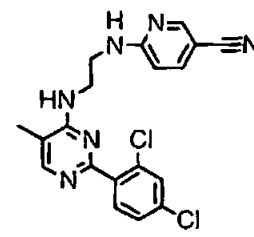
I-156



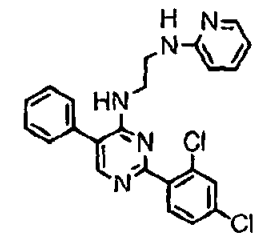
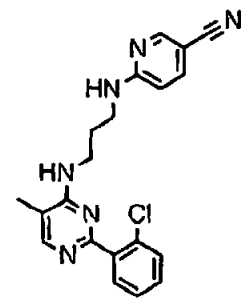
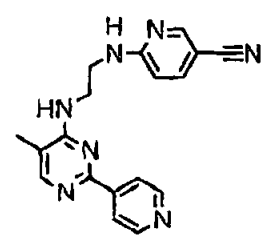
I-157



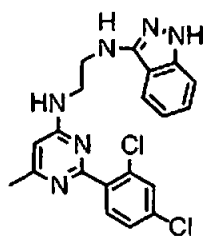
I-158



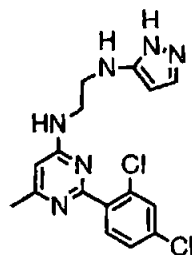
I-159



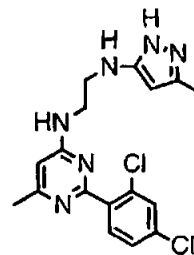
I-160



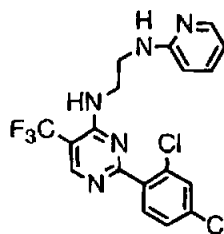
I-161



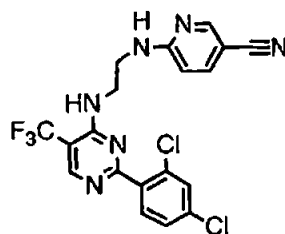
I-162



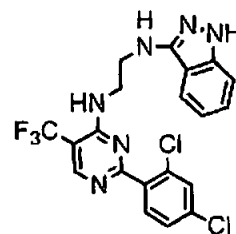
I-163



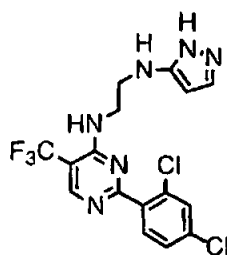
I-164



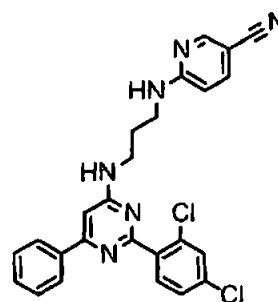
I-165



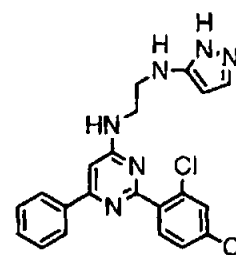
I-166



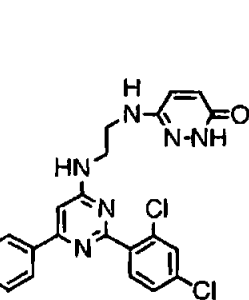
I-167



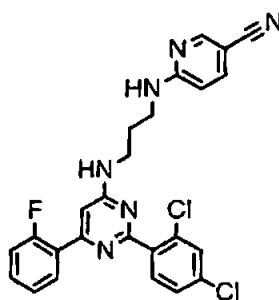
I-168



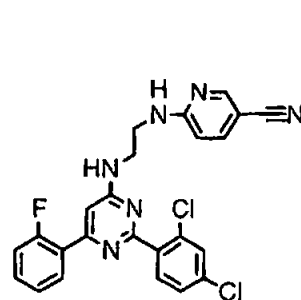
I-169



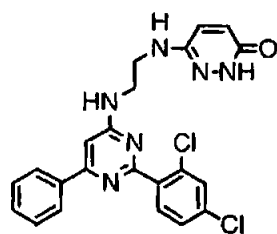
I-170



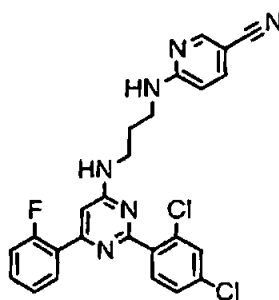
I-171



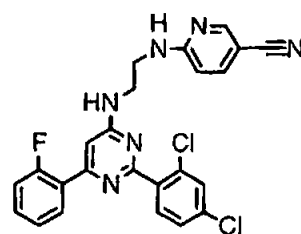
I-172

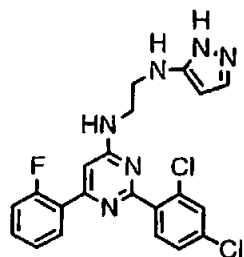


I-173

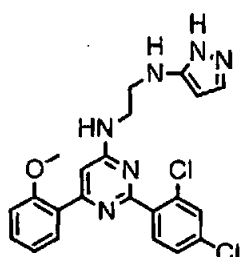


I-174

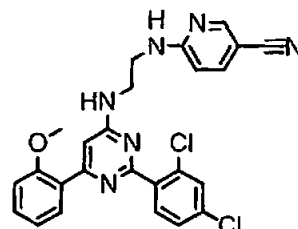




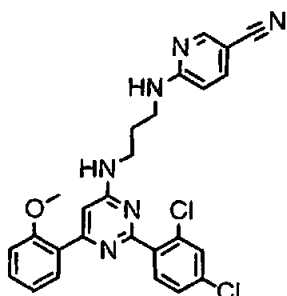
I-175



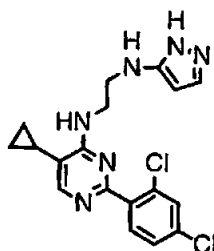
I-176



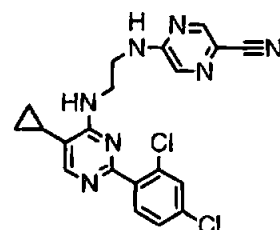
I-177



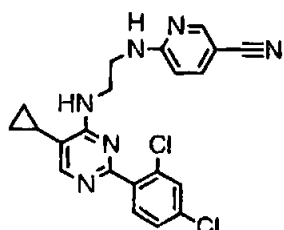
I-178



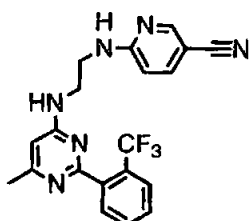
I-179



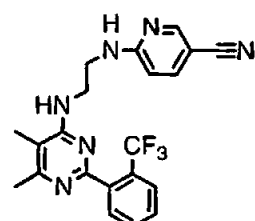
I-180



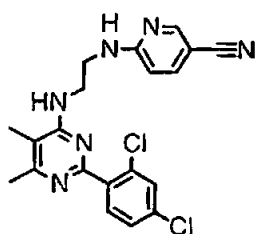
I-181



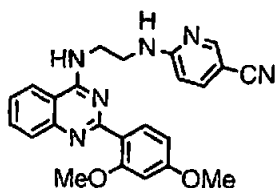
I-182



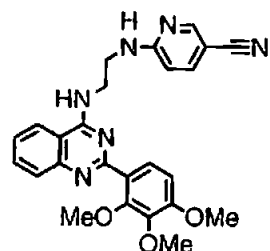
I-183



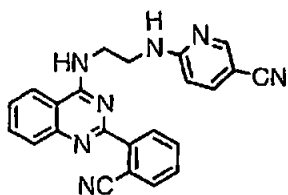
I-184



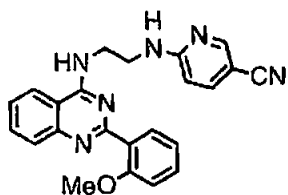
I-185



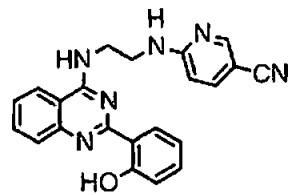
I-186



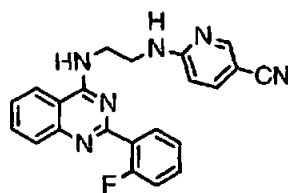
I-187



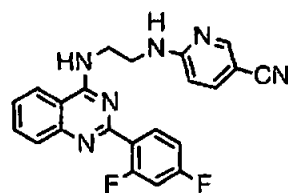
I-188



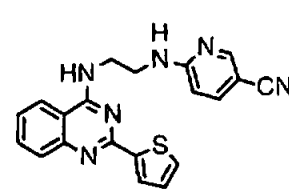
I-189



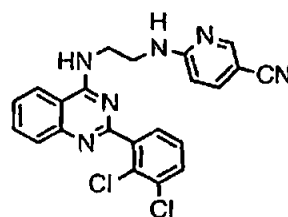
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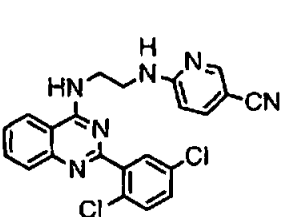
I-191



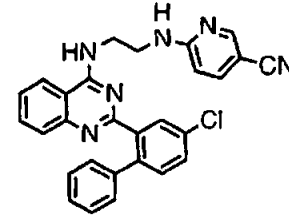
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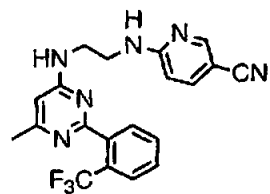
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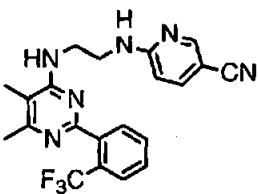
I-194



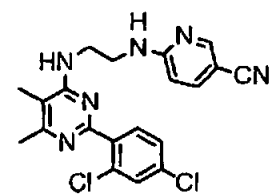
I-195



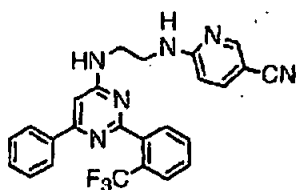
I-196



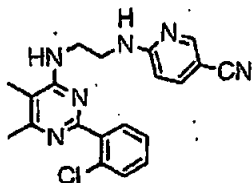
I-197



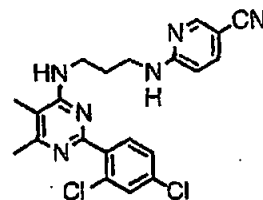
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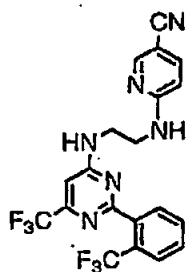
I-199



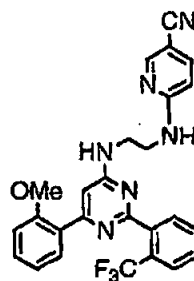
I-200



I-201



I-202



I-203

24. A composition comprising a compound of claim 1, and a pharmaceutically acceptable carrier, adjuvant, or vehicle.
25. A composition comprising a therapeutically effective amount of a compound of claim 1, and a pharmaceutically acceptable carrier, adjuvant, or vehicle.
26. The composition of claim 25, wherein the therapeutically effective amount is an amount capable of inhibiting GSK-3 activity.
27. The composition of claim 24, further comprising one of more additional therapeutic agents.
28. A method of inhibiting GSK-3 kinase activity in a biological sample, comprising the step of contacting said biological sample with:
 - a) a composition according to claim 25; or
 - b) a compound according to claim 1.

29. A method of treating or lessening the severity of an autoimmune disease, an inflammatory disease, a metabolic disorder, a neurological or neurodegenerative disorder, or a cardiovascular disease in a patient, comprising the step of administering to said patient:

- a) a composition according to claim 25; or
- b) a compound according to claim 1.

30. The method of claim 29, wherein the disease is selected from allergy, asthma, diabetes, Alzheimer's disease, Huntington's disease, Parkinson's disease, AIDS-associated dementia, amyotrophic lateral sclerosis (AML, Lou Gehrig's disease), multiple sclerosis (MS), schizophrenia, cardiomyocyte hypertrophy, reperfusion/ischemia, stroke, or baldness.

31. The method of claim 29, wherein the disease is stroke.

32. The method of claim 29, wherein the disease is a neurological or neurodegenerative disorder.

33. The method of claim 29, comprising the additional step of administering to said patient an additional therapeutic agent selected from a treatment for Alzheimer's Disease, a treatment for Parkinson's Disease, an agent for treating Multiple Sclerosis (MS), a treatment for asthma, an anti-inflammatory agent, an immunomodulatory or immunosuppressive agent, a neurotrophic factor, an agent for treating stroke, an agent for treating cardiovascular disease, or an agent for treating diabetes, wherein:

- said additional therapeutic agent is appropriate for the disease being treated; and
- said additional therapeutic agent is administered together with said composition as a single dosage form or separately from said composition as part of a multiple dosage form.

34. A method of treating or lessening the severity of a GSK-3-mediated disease or condition in a patient, comprising the step of administering to said patient:

- a) a composition according to claim 25; or
- b) a compound according to claim 1.

35. The method of claim 34, wherein said GSK-3-mediated disease is selected from an autoimmune disease, an inflammatory disease, a metabolic disorder, a neurological or neurodegenerative disorder, or a cardiovascular disease.

36. The method of claim 34, wherein said GSK-3-mediated disease is selected from allergy, asthma, diabetes, Alzheimer's disease, Huntington's disease, Parkinson's disease, AIDS-associated dementia, amyotrophic lateral sclerosis (ALS, Lou Gehrig's disease), multiple sclerosis (MS), schizophrenia, cardiomyocyte hypertrophy, reperfusion/ischemia, stroke, or baldness.

37. The method of claim 34, wherein said GSK-3-mediated disease is stroke.

38. The method of claim 34, wherein said GSK-3-mediated disease is a neurological or neurodegenerative disorder.

39. The method of claim 34, comprising the additional step of administering to said patient an additional therapeutic agent selected from a treatment for Alzheimer's Disease, a treatment for Parkinson's Disease, an agent for treating Multiple Sclerosis (MS), a treatment for asthma, an anti-inflammatory agent, an immunomodulatory or immunosuppressive agent, a neurotrophic factor, an agent for treating stroke, an agent for treating cardiovascular disease, or an agent for treating diabetes, wherein:

said additional therapeutic agent is appropriate for the disease being treated; and
said additional therapeutic agent is administered together with said composition as a single dosage form or separately from said composition as part of a multiple dosage form.

INTERNATIONAL SEARCH REPORT

International Application No
PCT/US 02/39190

A. CLASSIFICATION OF SUBJECT MATTER

IPC 7 A61K31/506 C07D239/94 A61P35/00 C07D401/12 C07D403/12
C07D405/14 C07D409/14 C07D417/12 C07D413/12 C07D409/12
C07D401/04 C07D409/04 C07D495/04 C07D471/04 C07D475/00

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)

IPC 7 C07D A61K A61P

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)

CHEM ABS Data, WPI Data, BEILSTEIN Data, EPO-Internal

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
P, X	WO 02 053557 A (WELLER THOMAS ;BOLLI MARTIN (CH); BOSS CHRISTOPH (CH); FISCHLI WAL) 11 July 2002 (2002-07-11) claims 1,14 page 49 -page 50 page 65 -page 72 page 108 -page 109 page 122 -page 123 page 185 -page 188 --- -/--	1-27, 29-39



Further documents are listed in the continuation of box C.



Patent family members are listed in annex.

* Special categories of cited documents:

- *A* document defining the general state of the art which is not considered to be of particular relevance
- *E* earlier document but published on or after the international filing date
- *L* document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)
- *O* document referring to an oral disclosure, use, exhibition or other means
- *P* document published prior to the international filing date but later than the priority date claimed

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- *X* document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone
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- *F* document member of the same patent family

Date of the actual completion of the international search

28 February 2003

Date of mailing of the international search report

14/03/2003

Name and mailing address of the ISA

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INTERNATIONAL SEARCH REPORT

International Application No.

PCT/US 02/39190

A. CLASSIFICATION OF SUBJECT MATTER
IPC 7 A61K31/519

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
P, X	DATABASE CHEMCATS 'Online! CHEMICAL ABSTRACTS SERVICES COLUMBUS, OHIO, US; XP002232960 order numbers: RDR03878; RDR03879; RDR03877; RDR03876; RDR03874; RDR03871; RDR03870; RH 02109 & "Maybridge HTS" 11 November 2002 (2002-11-11) , MAYBRIDGE PLC , TINAGEL, CORNWALL, PL34 OHW UNITED KINGDOM	1-27
P, Y	WO 02 22605 A (KNEGTEL RONALD ;BEBBINGTON DAVID (GB); CHARRIER JEAN DAMIEN (GB);) 21 March 2002 (2002-03-21) claims	1-39



Further documents are listed in the continuation of box C.



Patent family members are listed in annex.

* Special categories of cited documents:

- *A* document defining the general state of the art which is not considered to be of particular relevance
- *E* earlier document but published on or after the international filing date
- *L* document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)
- *O* document referring to an oral disclosure, use, exhibition or other means
- *P* document published prior to the international filing date but later than the priority date claimed

- *T* later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention
- *X* document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone
- *Y* document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art.
- *8* document member of the same patent family

Date of the actual completion of the international search

28 February 2003

Date of mailing of the international search report

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INTERNATIONAL SEARCH REPORT

International Application No

PCT/US 02/39190

C.(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT

Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
Y	WO 99 65897 A (RAMURTHY SAVITHRY ;CHIRON CORP (US); GOFF DANE (US); NUSS JOHN M () 23 December 1999 (1999-12-23) claims examples	1-39
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X	EP 0 826 673 A (DAINIPPON PHARMACEUTICAL CO) 4 March 1998 (1998-03-04) claims 1,18-23 examples 63,204	1-27, 29-39
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X	US 3 506 665 A (SANTILLI ARTHUR A ET AL) 14 April 1970 (1970-04-14) claims 1,5,9	1-27
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INTERNATIONAL SEARCH REPORT

International Application No.

PCT/US 02/39190

C.(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT

Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	DATABASE CA 'Online! CHEMICAL ABSTRACTS SERVICE, COLUMBUS, OHIO, US; KOMKOV, A. V. ET AL: "5-Acetyl-6-amino-4-(methylthio)-2-phenylp yrimidine and its use in the synthesis of functionalized pyrido'2,3-d!pyrimidines and pyrimido'4,5-d!pyrimidines" retrieved from STN Database accession no. 124:117226 XP002232961 abstract & IZVESTIYA AKADEMII NAUK, SERIYA KHIMICHESKAYA (1995), (7), 1324-8 , -----	1-27

INTERNATIONAL SEARCH REPORT

International application No.
PCT/US 02/39190

Box I Observations where certain claims were found unsearchable (Continuation of item 1 of first sheet)

This International Search Report has not been established in respect of certain claims under Article 17(2)(a) for the following reasons:

1. ☒ Claims Nos.:
because they relate to subject matter not required to be searched by this Authority, namely:

Although claims 28-39 are directed to a method of treatment of the human/animal body, the search has been carried out and based on the alleged effects of the compound/composition.
2. ☒ Claims Nos.: 1-39 (in part)
because they relate to parts of the International Application that do not comply with the prescribed requirements to such an extent that no meaningful International Search can be carried out, specifically:
see FURTHER INFORMATION sheet PCT/ISA/210
3. ☐ Claims Nos.:
because they are dependent claims and are not drafted in accordance with the second and third sentences of Rule 6.4(a).

Box II Observations where unity of invention is lacking (Continuation of item 2 of first sheet)

This International Searching Authority found multiple inventions in this International application, as follows:

1. ☐ As all required additional search fees were timely paid by the applicant, this International Search Report covers all searchable claims.
2. ☐ As all searchable claims could be searched without effort justifying an additional fee, this Authority did not invite payment of any additional fee.
3. ☐ As only some of the required additional search fees were timely paid by the applicant, this International Search Report covers only those claims for which fees were paid, specifically claims Nos.:
4. ☐ No required additional search fees were timely paid by the applicant. Consequently, this International Search Report is restricted to the invention first mentioned in the claims; it is covered by claims Nos.:

Remark on Protest

- ☐ The additional search fees were accompanied by the applicant's protest.
- ☐ No protest accompanied the payment of additional search fees.

FURTHER INFORMATION CONTINUED FROM PCT/ISA/ 210

Continuation of Box I.2

Claims Nos.: 1-39 (in part)

The claims are partly directed to "pharmaceutically acceptable derivatives or prodrugs" of structurally defined compounds. Since there is no further explanation in the description which derivatives (in terms of structural features) are meant to be covered by such a definition, unclarity (Art. 6 PCT) arises to such an extent as to make a meaningful search impossible. The search has been restricted to compounds structurally defined in the claims.

The applicant's attention is drawn to the fact that claims, or parts of claims, relating to inventions in respect of which no international search report has been established need not be the subject of an international preliminary examination (Rule 66.1(e) PCT). The applicant is advised that the EPO policy when acting as an International Preliminary Examining Authority is normally not to carry out a preliminary examination on matter which has not been searched. This is the case irrespective of whether or not the claims are amended following receipt of the search report or during any Chapter II procedure.

INTERNATIONAL SEARCH REPORT

Information on patent family members

International Application No

PCT/US 02/39190

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INTERNATIONAL SEARCH REPORT

Information on patent family members

International Application No

PCT/US 02/39190

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