OC CA.

Industria y Comercio
SUPERINTENDENCIA

SOLICITUD DE PATENTE DE INVENCION

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DATOS DEL SOLICITANTE

(71) Nombres y Apellidos o Razón Social: WARNER LAMBERT COMPANY

No. de Identificación:

Representante Legal (Personería Jurídica):

País de Domicilio: EE.UU

Departamento o Estado: New Jersey

Dirección: 201 Tabor Road

Ciudad: Morris Plains Teléfono:

(74) DATOS DEL APODERADO

Nombre: RODOLFO RODRIGUEZ MADRID

Dirección y Domicilio: Tranv. 6 No. 27-10 Pent-House

Ciudad: BOGOTA Teléfono: 3-417003

DATOS DEL INVENTOR

(72) Nombres del Inventor(es): BIRD,PAUL; ELLSWORTH,EDMUND LEE; NGUYEN,DAI QUOC; SANCHEZ,JOSEPH PETER; SHOWALTER, HOWARD DANIEL HOLLIS; SINGH,RAJESHWAR; STIER,MICHAEL ANDREW; TRAN,TUAN PHONG; WATSON,BRIAN MORGAN; YIP, JUDY.

Identificación: DE: CANADA; EE.UU; CANADA; EE.UU; EE.UU.; CANADA; EE.UU.; EE.UU; EE.UU.; CANADA.

Dirección: 11407-73 Avenue, Alberta T6G 0E2,Canadá; 6699 Kestrel Court,Michigan 48116,EE.UU; 4928-13 Avenue, Alberta T6L 6J9, Canadá; 22372 Antler Drive, Michigan 48050, EE.UU; 3578 Lamplighter Drive, Michigan 48103, EE.UU; 7927 22 Avenue, Alberta, T6K 1Z2, Canadá; 4886 Club Place, Michigan 48197, EE.UU; 43517 Argonne CT, Michigan 48188, EE.UU; 3816 Brian Place,Indiana 46033,EE.UU; 306, 4607-20 Avenue, Alberta,T6L 5W7,Canadá.

Ciudad: Edmonton; Brighton; Edmonton; Novi; Ann Arbor; Edmonton; Ypsilanti; Canton; Carmel; Edmonton. Teléfono:

TITULO DE PATENTE DE INVENCION

(54) Título de Invención: AGENTES ANTIBACTERIANOS DE 3-AMINOQUINAZOLIN-2,4-DIONAS

PRIORIDAD REIVINDICADA SI [X] NO [ ] TIPO DE PRIORIDAD ANDINA [X] UNIONISTA [ ]

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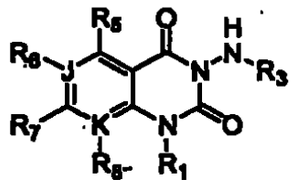
(51) CLASIFICACION INTERNACIONAL: A61K 31/498, 31/4025

RESUMEN CON EL OBJETO Y LA FINALIDAD DE PATENTE DE INVENCION

Las 3- aminoquinazolin-2,4-dionas tienen la fórmula



En donde:

R_1 y R_3 incluyen alquilo, alquenilo, alquinilo, cicloalquilo, arilo, heterocíclico y heteroarilo;

R_5, R_6 y R_8 incluyen H, alquilo, alcoxi, halo, NO_2, CN, NH_2, alquilo y dialquilamino;

R_7 es hidrógeno, alquilo, cicloalquilo, heterocíclico, heterocíclico fusionado, arilo y arilo fusionado;

J y K son C o N;

y Sales farmacéuticamente aceptables de ellos.

ANEXOS DE LA SOLICITUD

Certificado de Existencia y Representación Legal cuando el solicitante sea Persona Jurídica	[X]
Los poderes debidamente otorgados, o mención de su protocolización	[X]
Recibo de la tasa respectiva	[X]
Si se reivindica prioridad Andina:	
Copia de la primera solicitud	[ ]
Traducción Oficial	[ ]
Si se reivindica prioridad Unionista:	
Copia certificada de la primera solicitud:	[ ]
Nota: Debe presentarse dentor de los tres (3) meses, contados a partir de la fecha de radicación de la solicitud posterior	
Traducción Simple	[ ]
Capítulo Descriptivo	[ ]
Dibujos, planos necesarios	[X]
Capítulo reivindicado	[X]
Tarjeta archivo propietarios según formato	[X]
Tarjeta archivo temático según formato	[X]
Extracto para publicación según formato	[X]
Arte final 12x12 Cms	[X]
Otros Documentos	[X]

SOLICITO LA CONCESION DE PATENTE DE INVENCION Y DECLARO QUE LA INVENCION ES NUEVA Y DE MI PROPIEDAD

FIRMA

NOMBRE RODOLFO RODRIGUEZ MADRID **C.C.** 3'782.584 **T.P.No.** 52383

FUENTE NORMATIVA DE RECIPROCIDAD

Con fundamento jurídico en el artículo 12 de la Decisión 344 de la C.A.C y el artículo 4, literal f, del Decreto 117/94, en lo que hace referencia a la Fuente Normativa de reciprocidad se basa en:

a) – Artículo 4 del Convenio de París aprobado mediante Ley 178 de 1994 y declarado exequible por la Corte Constitucional en sentencia del 18 de Enero de 1996.

De conformidad con el artículo 12 de la Decisión 344 de C.A.C.; la prioridad debe reconocerse a las solicitudes de patente provenientes de un país que conceda un trato reciproco a solicitudes provenientes de los países miembros del Acuerdo de Cartagena.

Si por el artículo 4.A.1 del Convenio de París, los Estados Unidos debe reconocer el derecho de prioridad a solicitudes de patente provenientes de países del Acuerdo de Cartagena y miembros del Convenio de París; Colombia debe reconocer reciprocidad a una solicitud de Patente estadounidense presentada en Colombia según lo establecido en el artículo 12 de la Decisión 344 de la C.A.C.

De acuerdo a lo anterior las solicitudes de Patente de Invención procedentes de un país que conceda un trato reciproco, en este caso los Estados Unidos de América, pueden ser objeto del denominado derecho de Prioridad.

b).- .Cito además, como fuente normativa de reciprocidad, en lo referente a prioridad de patentes de Invención, el Acuerdo por el cual se establece la ORGANIZACIÓN MUNDIAL DE COMERCIO (OMC) suscrito en Marrakech (Marruecos) el 15 de abril de 1994, y sus acuerdos multilaterales anexos ADPIC (TRIP'S por sus siglas en Inglés). "Acuerdo Sobre los Aspectos de los Derechos de Propiedad Intelectual relacionados con el Comercio". Aprobado mediante la Ley 170 de 1994, declarado exequible mediante sentencia de la Corte Constitucional del 28 de Marzo de 1995, y cuyo canje de ratificación fue depositado el 31 de Marzo de 1995 para su entrada en vigencia el 30 de abril de 1995, en concordancia (La ley 170 de 1994) con el artículo 4 del Convenio de París.

El Artículo 2 ordinal 1 del Anexo 1c de ADPIC (TRIP'S), del Acuerdo, establece "Los miembros cumplirán los artículos 1 a 12 y el 19 del Convenio de París (1967)" por lo tanto deberá aplicarse entre Colombia y Estados Unidos de América como miembros de ADPIC (TRIP'S). Lo mencionado en el Artículo 4.A.1 del Convenio de París (uno de los artículos de obligatorio cumplimiento bajo ADPIC), donde se establece que la prioridad sobre la primera solicitud en el mundo será reconocida por los países miembros.

Quedando establecidas dos de las fuentes normativas de reciprocidad, respetuosamente le solicito a ese Despacho conceder para la solicitud de patente adjunta la fecha de prioridad reivindicada.

AGENTES ANTIBACTERIANOS DE 3-AMINOQUINAZOLIN-2,4-DIONAS

Campo de la invención

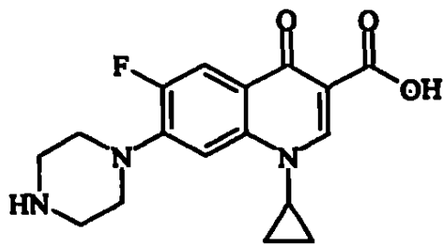
Esta invención se relaciona con 3-aminoquinazolin-2,4-dionas que tienen potente actividad antibacteriana in vitro y en vivo. Además, esta invención se relaciona con un método para inhibir tanto los mutantes de tipo silvestre como los resistentes a la quinolona de la girasa de ADN. Esta invención se relaciona con un método para tratar pacientes que tienen resistencia a los antibióticos y que necesitan el tratamiento de infecciones bacterianas.

ANTECEDENTES DE LA INVENCIÓN

La resistencia a los antibióticos es un problema mundial con un potencial catastrófico. Una Fuerza de Tareas de la Sociedad Estadounidense de Microbiología emitió recientemente un informe que define el problema de la resistencia y que busca nuevos agentes antibacterianos con estructuras o mecanismos novedosos para ofrecer alternativas para las opciones terapéuticas existentes (*Southern Med.J.* 1995;88:797).

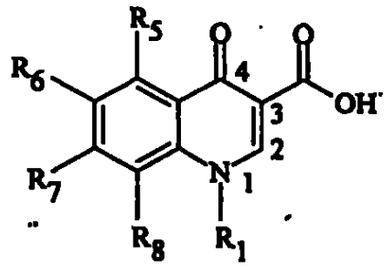
Las quinolonas son una clase de antibacterianos que se usan ampliamente en todo el mundo. Las quinolonas son inhibidores

potentes de las bacterias grampositivas y gramnegativas y pueden ser administradas por vía oral intravenosa. Las quinolonas se usan rutinariamente aún cuando tienen efectos colaterales (*J. Antimicrob. Chemother.*, 1994;33:685), y con frecuencia se ha observado una resistencia significativa (Gootz, *Medicinal Research*, 1996; Rev. 16:433). Una de las quinolonas usadas más ampliamente es la ciprofloxacina, que tiene la siguiente estructura química:



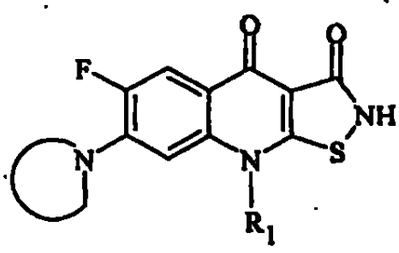
Las quinolonas tienen una relación entre la estructura y la actividad (SAR) distinguible definida por varios miles de análogos preparados durante los últimos 30 años (S.Mitsushashi, ed. *Progress in Drug Research*, 1992;38:11-147). En la SAR de las quinolonas (que se refiere a la fórmula siguiente que representa quinolonas sustituidas), está bien establecido que el grupo N_1, en combinación con el carboxilo de C_3 y el carbonilo de C_4, son esenciales para la actividad, y que todos los sustituyentes en C_2 desvían de la actividad (*J. Antimicob. Chemother.*, 1994;33:685 y Gootz, arriba, 1996).

También está bien establecido que R_6 es idealmente flúor, y que R_7 es un heterociclo que contiene nitrógeno. R_1 es idealmente un grupo alquilo pequeño, un cicloalquilo o un fenilo.



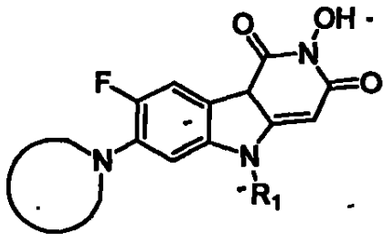
Las quinolonas inhiben el crecimiento bacteriano mediante la inhibición de la girasa de ADN y la topoisomerasa IV (Gootz, arriba, 1996). La interacción con la girasa parece depender de la relación de N_1/carbonilo de C_4/carboxilo de C_3.

Los intentos de diseñar imitaciones de quinolonas novedosas se han concentrado en la relación de N_1/carbonilo de C_4/carboxilo de C_3. Se han diseñado ciertos análogos de isotiazol triciclico para mantener la relación totalmente planar, y para hacer que el NH del anillo de isotiazol sea tan ácido como el grupo carboxilo de C_3 de la quinolina (Chu, *Drugs Exptl. Clin. Res.*, 1990;16:215).



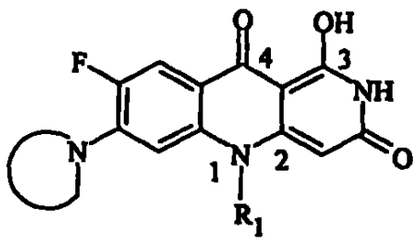
Aunque mantienen una excelente actividad antibacteriana, estos compuestos también muestran una actividad antitumor y de topoisomerasa de mamíferos (*Drugs of the Future*, 1992;17:1101). Estas actividades son indeseadas en un agente antibacteriano.

Varias publicaciones (Patente Estadounidense NO. 5.283.248; *J.Med. Chem.*, 1992;35:1358; *Antimicrob. Agents Chemother.*, 1995;39:163) revelan compuestos tricíclicos (tales como la estructura siguiente) que tienen actividad antibacteriana y actividad inhibidora de la girasa de ADN.



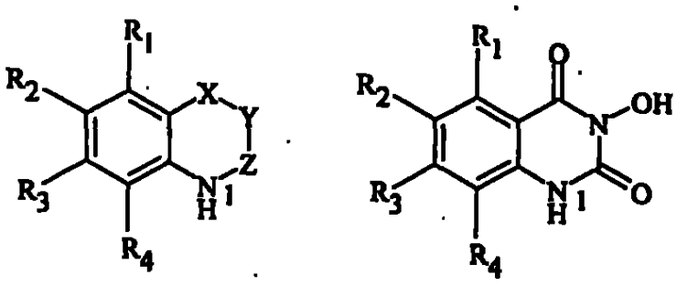
Para tales compuestos, la relación del N_1 al carbonilo de C_4 es sesgada. Los compuestos de este tipo son ineficaces contra bacterias que son resistentes a las quinolonas.

Otros análogos tricíclicos de la siguiente estructura se revelan como imitaciones de quinolinas (JP 4.091.090 3/92; Interscience Conference on Antimicrobial Agents and Chemotherapy 1991, Resumen 1494).



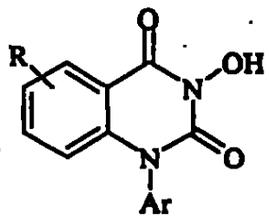
Si bien se mantiene la relación N_1-carbonilo de C_4 de la quinolina ideal, la región de C_2, donde la sustitución es indeseable, es parte de un sistema de anillo fusionado. Estos compuestos no son activos contra las bacterias resistentes a las quinolonas.

WO 96/04288 describe una serie de benzoheterociclos de las fórmulas



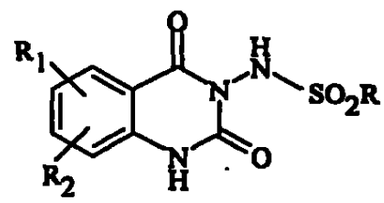
donde X, Y y Z son grupos receptadores y donantes de unión de hidrógeno. Entre los compuestos representados, están las N-hidroxi-quinazolin-2,4-dionas, donde R_1-R_4 pueden representar hidroxi, amino, nitro, una variedad de alquilos, ésteres y amidas. En todos los casos, el sustituyente en N_1 es hidrógeno. Ninguno de los sustituyentes R_1-R_4 son heterociclos que contienen nitrógeno. No se revela ninguna actividad antibacteriana para estos compuestos.

La Patente Estadounidense No. 5.155.110 describe N_1-aril-N-hidroxi-quinazolin-2,4-dionas de la fórmula



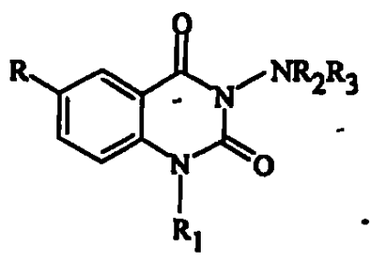
en donde R puede ser halo, ciano, hidroxi, alcoxi y amino sustituido. Los heterociclos de amino no están incluidos en R, y no se informa de ninguna actividad antibacteriana para tales compuestos.

Los compuestos enseñados en la Publicación Internacional No. WO 95/19346 como AMPA, NMDA y los antagonistas de receptor de quinasa tienen la fórmula:



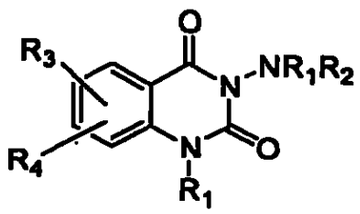
en donde los sustituyentes de R se definen como alquilo o fenilo, y R_1 y R_2 se definen como H, alquilo, alcoxi, alquenilo, halógeno, NO_2, NH_2 (no) sustituido, CN, etc. Nuevamente, no se revela ninguna actividad antibacteriana para estos compuestos.

Kornet y sus colaboradores (Kornet M.J. et al, *J. Heterocyl. Chem.*, 1984;21:1533-1535) revelaron compuestos anticonvulsivos que tienen la fórmula



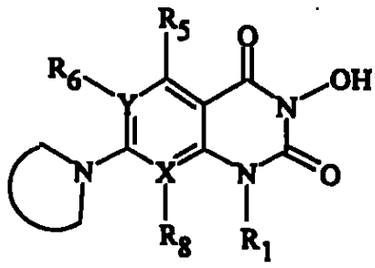
en donde R se define como H, Me, o Cl; R_1 y R_2 como H o Me; y R_3 como Me o t-butilo. Alternativamente, R_2 y R_3, junto con el átomo de nitrógeno al cual están unidos, pueden formar un anillo heterocíclico tal como piperidinilo, morfolinilo, etc. No se informa que estos compuestos tengan actividad antibacteriana.

Numerosas publicaciones enseñan compuestos que tienen actividades diurética y sedante y con la estructura genérica siguiente (ES 80/489674, JP 80/33323, BE 80/199792, FR 78/33438, JP 70/97932; Baronnet R., Callendret R., Blanchart L., Foussard-Blanpin O., Bretaudeau J., *Eur. J. Med.-Chim. Ther.*, 1983;18:241-247).



Éstos son compuestos en los cuales NR_1R_2 puede formar un heterociclo, o R_1 y R_2 independientemente pueden representar H o un alquilo pequeño, R_3 y R_4 pueden representar H, halógeno, sulfonamida, alquilo, o alcoxi. No se ha informado de ninguna actividad antibacteriana para estos compuestos.

La Publicación Internacional No. WO 99/21480 describe 3-hidroxi-quinazolin-2,4-dionas como agentes antibacterianos.



Los compuestos de este tipo son imitaciones de quinolonas en donde el ácido carboxílico exocíclico de la posición 3 de las quinolonas es reemplazado por un oxo en la posición 2 y un hidroxi en la posición N-3. Los compuestos de este tipo están diseñados para mantener una relación completamente planar y para hacer que el N-OH se mantenga ácido, como en la quinolona CO_2H (Chu, *Drugs Exptl. Clin. Res,* 1990;16:215). Estos compuestos inhiben la girasa de ADN y la topoisomerasa IV, y demuestran actividad antibacteriana in vitro. Sin embargo, tales compuestos no son efectivos contra las bacterias resistentes a las quinolonas.

Aún existe la necesidad de encontrar nuevos agentes antibacterianos que tengan la potencia de las quinolonas pero que sean activos contra las cepas bacterianas resistentes a las quinolonas. La presente invención proporciona tales

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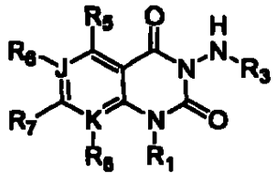
compuestos, que son caracterizados como 3-aminoquinazolin-2,4-dionas. Uno de los objetivos de esta invención es proporcionar estos nuevos compuestos, y un método para tratar infecciones bacterianas en mamíferos administrando estos compuestos.

RESUMEN DE LA INVENCIÓN

La presente invención proporciona 3-aminoquinazolin-2,4-dionas que tienen actividad antibacteriana. Los compuestos inhiben la girasa de ADN, pero no tienen resistencia cruzada con los mutantes de quinolonas que ya no son sensibles a los agentes tales como la ciprofloxacina.

La invención proporciona los compuestos de la Fórmula I



I

o una sal farmacéuticamente aceptable de ellos en donde:

R_1 y R_3 independientemente son H,

alquilo y alquilo sustituido de C_1-C_{12},

alquenilo y alquenilo sustituido de C_2-C_{12},

alquinilo y alquinilo sustituido de C_2-C_{12},

cicloalquilo y cicloalquilo sustituido de C_3-C_{12},

arilo y arilo sustituido,

heterocíclico y heterocíclico sustituido,

o heteroarilo y heteroarilo sustituido;

R_5, R_6 y R_8 independientemente son H,

$(O)_n$alquilo de C_1-C_{12}, y alquilo sustituido;

$(O)_n$alquenilo de C_2-C_{12} y alquenilo sustituido;

$(O)_n$alquinilo de C_2-C_{12} y alquinilo sustituido;

halo,

NO_2,

CN,

NR'R" en donde n es 0 o 1;

R' y R" independientemente son H,

alquilo y alquilo sustituido de C_1-C_{12},

alquenilo y alquenilo sustituido de C_2-C_{12},

alquinilo y alquinilo sustituido de C_2-C_{12},

CO-alquilo de C_1-C_{12} y alquilo sustituido,

o R' y R" tomados junto con el nitrógeno al cual están unidos forman un anillo de 3 a 7 miembros que contiene de 1 a 3 heteroátomos seleccionados de N, O y S, dicho anillo es no sustituido o sustituido con hasta 4 grupos sustituyentes;

R_1 y R_8 pueden ser tomados junto con los átomos a los cuales están unidos para formar un anillo cíclico que tiene de 1 a 3

heteroátomos seleccionados de N, O y S y optativamente sustituidos por R' y R";

R_7 es hidrógeno,

alquilo y alquilo sustituido de C_1-C_{12},

alquenilo y alquenilo sustituido de C_2-C_{12},

alquinilo y alquinilo sustituido de C_2-C_{12},

halo,

NO_2,

CN,

NR'R",

COOR',

arilo,

arilo fusionado,

heterocíclico,

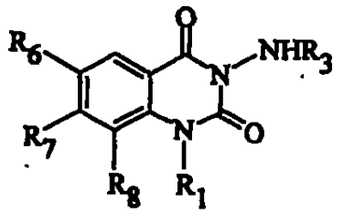
heterocíclico bicíclico, o

espiro heterocíclico en donde todos los grupos del anillo pueden ser sustituidos;

J y K independientemente son C o N, siempre que cuando J o K es N, R_6 o R_8 esté ausente en esa posición.

R_7 es denominado aquí como la "cadena lateral" del núcleo de la 3-aminoquinazolin-2,4-diona. La cadena lateral de R_7 puede ser cualquier grupo conocido en el arte de las quinolonas como un sustituyente adecuado en la posición 7 del anillo de la quinolona.

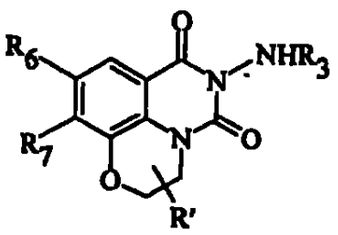
Los compuestos preferidos de eta invención tienen la Fórmula II



II

en donde R_1, R_3, R_6, R_7 y R_8 son lo definido anteriormente.

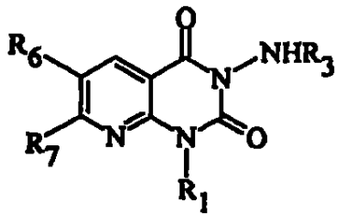
Otros compuestos preferidos tienen la Fórmula III



III

en donde R_3, R_6, R_7 y R' son lo definido anteriormente.

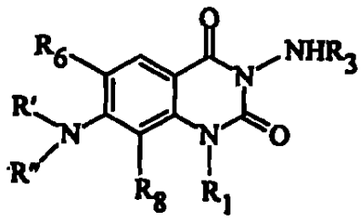
Otro grupo preferido son los compuestos que tienen la Fórmula IV



IV

en donde R_1, R_3, R_6 y R_7 son lo definido anteriormente.

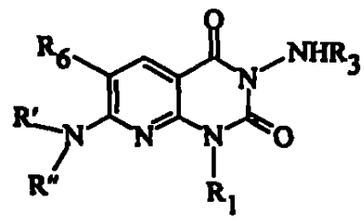
Los compuestos más preferidos de esta invención tienen la Fórmula V



V

en donde R_1, R_3, R_6, R_8, R′ y R″ son lo definido anteriormente. Una realización especialmente preferida son los compuestos de la Fórmula V en donde R′ y R″ son tomados junto con el nitrógeno al cual están unidos para completar el anillo que optativamente se sustituye con grupos tales como alquilo y alquilo sustituido, amino, alquilamino, dialquilamino, y aril amino.

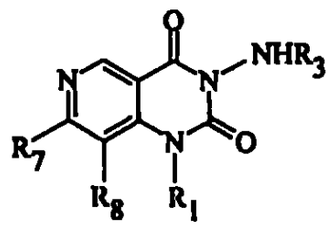
Otro grupo preferido son los compuestos que tienen la Fórmula VI



VI

en donde R_1, R_3, R_6, R′ y R″ son lo definido anteriormente.

Aún otro grupo preferido de los compuestos de la invención, son aquellos de la Fórmula VII



VII

en donde R_1, R_3, R_7 y R_8 son lo definido anteriormente.

Los compuestos especialmente preferidos provistos por la invención son:

3-Amino-7-(3-aminometilpirrolidin-1-il)-8-cloro-1-ciclopropil-6-fluoro-1H-quinazolin-2,4-diona;

3-Amino-8-cloro-1-ciclopropil-6-fluoro-7-piperazin-1-il-1H-quinazolin-2,4-diona;

3-Amino-7-[3-(aminometil)-3-metilpirrolidin-1-il]-8-cloro-1-ciclopropil-6-fluoro-1H-quinazolin-2,4-diona;

3-Amino-7-(6-amino-3-aza-biciclo[3.1.0]hex-3-il)-8-cloro-1-ciclopropil-6-fluoro-1H-quinazolin-2,4-diona;

3-Amino-7-((S)-3-N-metilaminopirrolidin-1-il)-8-cloro-1-ciclopropil-6-fluoro-1H-quinazolin-2,4-diona;

3-Amino-7-((S)-3-aminopirrolidin-1-il)-8-cloro-(2,4-difluoroanilino)-6-fluoro-1H-quinazolin-2,4-diona;

3-Amino-7-[(S)-3-aminopirrolidin-1-il]-1-ciclopropilamino-6,8-difluoro-1H-quinazolin-2,4-diona;

3-Amino-7-[(S)-3-aminopirrolidin-1-il]-1-ciclopropilamino-5,8-difluoro-1H-quinazolin-2,4-diona;

3-Amino-7-((S)-aminopirrolidin-1-il)-1-ciclopropil-5,6,8-trifluoro-1H-quinazolin-2,4-diona;

3-Amino-7-(3-aminopirrolidin-1-il)-8-cloro-1-ciclopropil-6-fluoro-1H-quinazolin-2,4-diona;

7-((S)-3-Aminopirrolidin-1-il)-1-ciclopropil-3,5-diamino-6,8-difluoro-1H-quinazolin-2,4-diona;

3-Amino-7-(3-hidroximetilpirrolidin-1-il)-8-cloro-1-ciclopropil-6-fluoro-1H-quinazolin-2,4-diona;

3-Amino-7-(3-aminoetilpirrolidin-1-il)-8-cloro-1-ciclopropil-6-fluoro-1H-quinazolin-2,4-diona;

3-Amino-7-((S)-7-amino-5-azaespiro[2.4]hept-5-il)-8-cloro-1-ciclopropil-6-fluoro-1H-quinazolin-2,4-diona;

3-Amino-7-[(R)-3-(1-amino-1-metiletil)pirrolidin-1-il]-8-cloro-1-ciclopropil-6-fluoro-1H-quinazolin-2,4-diona;

3-Amino-7-(3-aminometilpirrolidin-1-il)-1-ciclopropil-6-fluoro-1H-quinazolin-2,4-diona;

3-Amino-7-(pirrolidin-1-il)-8-cloro-1-ciclopropil-6-fluoro-1H-quinazolin-2,4-diona;

3-Amino-7-(3-aminopirrolidin-1-il)-8-cloro-6-fluoro-1-isopropil-1H-quinazolin-2,4-diona;

3-Amino-7-(3-aminopirrolidin-1-il)-1-sec-butil-8-cloro-6-fluoro-1H-quinazolin-2,4-diona;

3-Amino-7-[3-aminopirrolidin-1-il]-1-ciclopropil-6-fluoro-8-metoxi-1H-quinazolin-2,4-diona;

3-Amino-7-[3-aminopirrolidin-1-il]-8-cloro-1-ciclobutilamino-6-fluoro-1H-quinazolin-2,4-diona;

3-Amino-7-(3-aminopirrolidin-1-il)-1-ciclopropil-8-fluoro-1H-quinazolin-2,4-diona;

3-Amino-7-(3-aminopirrolidin-1-il)-6-cloro-1-ciclopropil-8-fluoro-1H-quinazolin-2,4-diona;

3-Amino-7-((S)-3-aminopirrolidin-1-il)-1-ciclopropilmetil-8-fluoro-1H-quinazolin-2,4-diona;

3-Amino-7-[(R)-3-(1-amino-1-metiletil)pirrolidin-1-il]-1-ciclopropilmetil-8-fluoro-1H-quinazolin-2,4-diona;

3-Amino-7-((S)-3-aminopirrolidin-1-il)-1-etil-8-fluoro-1H-quinazolin-2,4-diona;

3-Amino-1-etil-6-fluoro-7-[(R)-3-(1-amino-1-metiletil)-pirrolidin-1-il]-1H-quinazolin-2,4-diona;

3-Amino-7-((S)-3-aminopirrolidin-1-il)-1-ciclopropil-6-fluoro-1H-quinazolin-2,4-diona;

3-Amino-7-(3-aminopirrolidin-1-il)-1-ciclopropil-6-fluoro-8-metil-1H-quinazolin-2,4-diona;

3-Amino-7-(3-aminometilpirrolidin-1-il)-1-ciclopropil-6-fluoro-8-metil-1H-quinazolin-2,4-diona;

3-Amino-7-(3-aminopirrolidin-1-il)-1-ciclopropil-8-fluoro-6-metoxi-1H-quinazolin-2,4-diona;

3-Amino-7-(3-aminometilpirrolidin-1-il)-1-ciclopropil-6-fluoro-8-metoxi-1H-quinazolin-2,4-diona;

3-Amino-7-(3-aminopirrolidin-1-il)-1-ciclopropil-8-etoxi-6-fluoro-1H-quinazolin-2,4-diona;

3-Amino-7-(3-aminopirrolidin-1-il)-1-ciclopropil-6-fluoro-2,4-dioxo-1,2,3,4-tetrahidroquinazolin-8-carbonitrilo;

3-Amino-8-cloro-1-ciclopropil-6-fluoro-7-(3-[1,2,3-triazol]-1-il-pirrolidin-1-il)-1H-quinazolin-2,4-diona;

3-Amino-7-[(S)-3-((R)-1-aminoetil)pirrolidin-1-il]-1-ciclopropil-6-fluoro-8-metoxi-1H-quinazolin-2,4-diona;

3-Amino-7-[(S)-3-((S)-1-aminoetil)pirrolidin-1-il]-1-ciclopropil-6-fluoro-8-metoxi-1H-quinazolin-2,4-diona;

3-Amino-7-[(S)-3-((S)-1-aminoetil)pirrolidin-1-il]-1-ciclopropil-6-fluoro-8-metil-1H-quinazolin-2,4-diona;

3-Amino-7-[(S)-3-((S)-1-aminoetil)pirrolidin-1-il]-1-ciclopropil-6-fluoro-8-metil-1H-quinazolin-2,4-diona;

5-Amino-9-((S)-3-aminopirrolidin-1-il)-8-fluoro-3-metil-2,3-dihidro-1-oxa-3a,5-diazafenalen-4,6-diona;

5-Amino-9-[(R)-3-((S)-1-aminoetil)pirrolidin-1-il]-8-fluoro-3-metil-2,3-dihidro-1-oxa-3a,5-diazafenalen-4,6-diona;

2-Amino-8-((S)-3-aminopirrolidin-1-il)-9-fluoro-5-metil-6,7-dihidro-5H-pirido[3,2,1-ij]quinazolin-1,3-diona;

2-Amino-8-[(R)-3-((S)-1-aminoetil)pirrolidin-1-il]-9-fluoro-5-metil-6,7-dihidro-5H-pirido[3,2,1-ij]quinazolin-1,3-diona;

3-Amino-7-((S)-3-aminopirrolidin-1-il)-1-ciclopropil-6-fluoro-1H-pirido[2,3-d]pirimidin-2,4-diona;

3-Amino-7-(6-amino-3-azabiciclo[3.1.0]hex-3-il)-1-ciclopropil-6-fluoro-1H-pirido[2,3-d]pirimidin-2,4-diona;

3-Amino-7-(3-aminometil-3-metilpirrolidin-1-il)-1-ciclopropil-6-fluoro-1H-pirido[2,3-d]pirimidin-2,4-diona;

3-Amino-1-ciclopropil-6-fluoro-7-(octahidropirrolo[3,4-c]piridin-2-il)-1H-pirido[2,3-d]pirimidin-2,4-diona;

3-Amino-1-ciclopropil-6-fluoro-7-(octahidropirrolo[3,4-b]piridin-2-il)-1H-pirido[2,3-d]pirimidin-2,4-diona;

3-Amino-7-[(R)-3-(1-amino-1-metiletil)pirrolidin-1-il]-1-ciclopropil-6-fluoro-1H-pirido[2,3-d]pirimidin-2,4-diona;

3-Amino-7-(3-aminometilpiperidin-1-il)-1-ciclopropil-6-fluoro-1H-pirido[2,3-d]pirimidin-2,4-diona;

trans-3-Amino-7-(3-aminometil-4-trifluorometilpirrolidin-1-il)-1-ciclopropil-6-fluoro-1H-pirido[2,3-d]pirimidin-2,4-diona;

3-Amino-1-ciclopropil-6-fluoro-7-[(R)-3-((R)-1-metilamino-etil)pirrolidin-1-il]-1H-pirido[2,3-d]pirimidin-2,4-diona;

3-Amino-7-[(R)-3-((S)-1-aminoetil)pirrolidin-1-il]-1-ciclopropil-6-fluoro-1H-pirido[2,3-d]pirimidin-2,4-diona;

3-Amino-7-[3-(1-aminopropil)pirrolidin-1-il]-1-ciclopropil-6-fluoro-8-metil-1H-quinazolin-2,4-diona;

3-Amino-1-ciclopropil-6-fluoro-8-metil-7-[(R)-3-((S)-1-metilaminoetil)pirrolidin-1-il]-1H-quinazolin-2,4-diona;

3-Amino-7-[7-(1-aminoetil)-5-azaespiro[2.4]hept-5-il]-1-ciclopropil-6-fluoro-1H-quinazolin-2,4-diona;

Amida del ácido 1-(3-amino-8-cloro-1-ciclopropil-6-fluoro-2,4-dioxo-1,2,3,4-tetrahidroquinazolin-7-il)piperidin-3-carboxílico;

3-Amino-[7-trans-3-aminometil-4-trifluorometilpirrolidin-1-il]-8-cloro-1-ciclopropil-6-fluoro-1H-quinazolin-2,4-diona;

3-Amino-8-cloro-1-ciclopropil-6-fluoro-7-{3-[(2,2,2-trifluoro-etilamino)metil]pirrolidin-1-il}-1H-quinazolin-2,4-diona;

3-Amino-8-cloro-1-ciclopropil-6-fluoro-7-(5-metilhexahidro-pirrolo[3,4-c]pirrol-2-il)-1H-quinazolin-2,4-diona;

3-amino-8-cloro-1-ciclopropil-7-(2,7-diazaespiro[4.4]non-2-il)-6-fluoro-1H-quinazolin-2,4-diona;

3-Amino-7-(3-aminometil-3-bencilpirrolidin-1-il)-8-cloro-1-ciclopropil-6-fluoro-1H-quinazolin-2,4-diona;

3-Amino-7-[(R)-3-((S)-1-aminoetil)pirroldin-1-il]-8-cloro-1-ciclopropil-6-fluoro-1H-quinazolin-2,4-diona;

3-Amino-8-cloro-1-ciclopropil-6-fluoro-7-(3-hidroxiimino-pirrolidin-1-il)-1H-quinazolin-2,4-diona;

3-Amino-7-[trans-3-amino-4-trifluorometilpirrolidin-1-il]-8-cloro-1-ciclopropil-6-fluoro-1H-quinazolin-2,4-diona;

3-Amino-8-cloro-1-ciclopropil-6-fluoro-7-[(R)-3-(S)-1-metilaminoetil)pirrolidin-1-il]-1H-quinazolin-2,4-diona;

3-Amino-7-(trans-3-amino-4-fenilpirroldin-1-il)-8-cloro-1-ciclopropl-6-fluoro-1H-quinazolin-2,4-diona;

3-Amino-7-[trans-3-amino-4-(4-hidroxifenil)pirrolidin-1-il]-8-cloro-1-ciclopropil-6-fluoro-1H-quinazolin-2,4-diona;

N-[1-(3-Amino-8-cloro-1-ciclopropil-6-fluoro-2,4-dioxo-1,2,3,4-tetrahidroquinazolin-7-il)pirrolidin-3-ilmetil]metanosulfonamida;

3-Amino-7-(3-aminometilpiperidin-1-il)-8-cloro-1-ciclopropil-6-fluoro-1H-quinazolin-2,4-diona;

3-Amino-8-cloro-1-ciclopropil-6-fluoro-7-[3-(isopropilamino-metil)pirrolidin-1-il]-1H-quinazolin-2,4-diona;

3-Amino-7-(3-aminometilpirrolidin-1-il)-6,8-dicloro-1-ciclopropil-1H-quinazolin-2,4-diona;

N-[1-(3-Amino-8-cloro-1-ciclopropil-6-fluoro-2,4-dioxo-1,2,3,4-tetrahidroquinazolin-7-il)pirrolidin-3-ilmetil]metanosulfonamida;

3-Amino-7-[(R)-3-(S)-(1-aminoetil)pirrolidin-1-il]-1-ciclopropil-6-fluoro-8-metil-1H-quinazolin-2,4-diona;

3-Amino-7-[(R)-3-(1-amino-1-metiletil)pirrolidin-1-il]-1-ciclopropil-6-fluoro-8-metil-1H-quinazolin-2,4-diona;

3-Amino-7-[3-(1-aminoetil)-3-metoxipirrolidin-1-il]-1-ciclopropil-6-fluoro-8-metil-1H-quinazolin-2,4-diona;

3-Amino-7-[3-(1-aminoetil)-3-fluoropirrolidin-1-il]-1-ciclopropil-6-fluoro-8-metoxi-1H-quinazolin-2,4-diona;

3-Amino-7-(3-aminopirrolidin-1-il)-1-ciclopropil-6-fluoro-5-metil-1H-quinazolin-2,4-diona;

3-Amino-7-[(R)-3-(S)-(1-aminoetil)pirrolidin-1-il]-1-ciclopropil-6-fluoro-5-metil-1H-quinazolin-2,4-diona;

3-Amino-7-(3-aminometil-3-metoximetilpirrolidin-1-il)-1-ciclopropil-6-fluoro-8-metil-1H-quinazolin-2,4-diona;

3-Amino-7-(3-aminometil-3-fluorometilpirrolidin-1-il)-1-ciclopropil-6-fluoro-1H-quinazolin-2,4-diona;

3-Amino-7-(trans-3-aminometil-4-trifluorometilpirrolidin-1-il)-1-ciclopropil-6-fluoro-8-metoxi-1H-quinazolin-2,4-diona;

3-Amino-7-[3-(1-aminoetil)piperidin-1-il]-1-ciclopropil-6-fluoro-8-metoxi-1H-quinazolin-1,4-diona;

3-Amino-7-[3-(aminoetil)piperidin-1-il]-1-ciclopropil-6-fluoro-8-metil-1H-quinazolin-2,4-diona;

3-Amino-7-[4-(1-aminoetil)-3,3-dimetilpirrolidin-1-il]-1-ciclopropil-6-fluoro-8-metoxi-1H-quinazolin-2,4-diona;

3-Amino-7-[4-(1-aminoetil)-3,3-dimetilpirrolidin-1-il]-1-ciclopropil-6-fluoro-8-metil-1H-quinazolin-2,4-diona;

3-Amino-7-(3-amino-3-fenilpirrolidin-1-il)-1-ciclopropil-6-fluoro-8-metil-1H-quinazolin-2,4-diona;

3-Amino-7-[3-(1-aminoetil)-4-metilpirrolidin-1-il]-1-ciclopropil-6-fluoro-8-metil-1H-quinazolin-2,4-diona;

3-Amino-7-(3-aminoetil-3-fenilpirrolidin-1-il)-1-ciclopropil-6-fluoro-8-metil-1H-quinazolin-2,4-diona;

3-Amino-7-(7-aminometil-5-azaespiro[2,4]hept-5-il)-1-ciclopropil-6-fluoro-8-metil-1H-quinazolin-2,4-diona;

3-Amino-7-(7-aminometil-5-azaespiro[2,4]hept-5-il)-1-ciclopropil-6-fluoro-8-metoxi-1H-quinazolin-2,4-diona;

3-Amino-7-(3-aminometil-3-hidroxipirrolidin-1-il)-1-ciclopropil-6-fluoro-8-metoxi-1H-quinazolin-2,4-diona;

3-Amino-7-(3-aminometilpiperidin-1-il)-1-ciclopropil-6-fluoro-8-metil-1H-quinazolin-2,4-diona;

3-Amino-7-(3-amino-4-metoxipirrolidin-1-il)-1-ciclopropil-6-fluoro-8-metil-1H-quinazolin-2,4-diona;

3-Amino-7-(3-amino-4-metoxipirrolidin-1-il)-1-ciclopropil-6-fluoro-8-metoxi-1H-quinazolin-2,4-diona;

3-Amino-7-(3-amino-4-fluoropirrolidin-1-il)-1-ciclopropil-6-fluoro-8-metoxi-1H-quinazolin-2,4-diona;

3-Amino-7-(3-aminometil-3-metilpirrolidin-1-il)-1-ciclopropil-6-fluoro-8-metil-1H-quinazolin-2,4-diona;

3-Amino-7-[(R)-3-(-((S)-1-aminoetil)pirrolidin-1-il]-1-ciclopropil-8-etil-6-fluoro-1H-quinazolin-2,4-diona;

Trifluoroacetato del ácido 1-(3-amino-1-ciclopropil-6-fluoro-8-metoxi-2,4-dioxo-1,2,3,4-tetrahidroquinazolin-7-il)pirrolidin-3-carboxílico;

Trifluoroacetato del ácido 1-(3-amino-1-ciclopropil-6-fluoro-8-metil-2,4-dioxo-1,2,3,4-tetrahidroquinazolin-7-il)pirrolidin-3-carboxílico;

3-Amino-7-(1-aminometil-3-azabiciclo[3.1.0]hex-3-il)-1-ciclopropil-6-fluoro-8-metoxi-1H-quinazolin-2,4-diona;

3-Amino-7-(1-aminometil-3-azabiciclo[3.1.0]hex-3-il)-1-ciclopropil-6-fluoro-8-metil-1H-quinazolin-2,4-diona;

3-Amino-7-[(S)-3-((R)-1-aminoetil)pirrolidin-1-il]-1-ciclopropil-6-fluoro-8-metoxi-1H-quinazolin-2,4-diona;

3-Amino-7[(S)-3-((R)-1-aminoetil)pirrolidin-1-il]-1-ciclopropil-6-fluoro-8-metil-1H-quinazolin-2,4-diona;

3-Amino-1-ciclopropil-6-fluoro-8-metil-7-(octahidropirrolo[3,4-b]piridin-6-il)-1H-quinazolin-2,4-diona;

3-Amino-7-(trans-3-aminometil-4-metilpirrolidin-1-il)-8-cloro-1-ciclopropil-6-fluoro-1H-quinazolin-2,4-diona;

3-Amino-7-(trans-3-aminometil-4-metilpirrolidin-1-il)-1-ciclopropil-6-fluoro-8-metoxi-1H-quinazolin-2,4-diona;

3-Amino-7-(trans-3-aminometil-4-metilpirrolidin-1-il)-1-ciclopropil-6-fluoro-8-metil-1H-quinazolin-2,4-diona;

3-Amino-7-(trans-3-amino-4-metilpirolidin-1-il)-1-ciclopropil-6-fluoro-8-metoxi-1H-quinazolin-2,4-diona;

3-Amino-7-(3-aminometilmorfolin-1-il)-1-ciclopropil-6-fluoro-8-metoxi-1H-quinazolin-2,4-diona;

3-amino-7-(3-aminometilpiperidin-1-il)-1-ciclopropil-6-fluoro-8-metoxi-1H-quinazolin-2,4-diona;

3-Amino-7-[3-(1-aminometil)-4-metilpirrolidin-1-il]-1-ciclopropil-6-fluoro-8-metoxi-1H-quinazolin-2,4-diona;

3-Amino-7-(3-amino-3-fenilpirrolidin-1-il)-8-cloro-1-ciclopropil-6-fluoro-1H-quinazolin-2,4-diona;

3-Amino-7-(3-amino-3-metilpirrolidin-1-il)-1-ciclopropil-6-fluoro-8-metil-1H-quinazolin-2,4-diona;

3-Amino-1-ciclopropil-6-fluoro-8-metil-7-pirrolidin-1-il-1H-quinazolin-2,4-diona;

3-Amino-1-ciclopropil-6-fluoro-8-metoxi-7-pirrolidin-1-il-1H-quinazolin-2,4-diona;

3-Amino-1-ciclopropil-6-fluoro-7-[3-(1-hidroxi-1-metiletil)-pirrolidin-1-il]-8-metil-1H-quinazolin-2,4-diona;

3-Amino-1-ciclopropil-6-fluoro-7-[3-(1-hidroxi-1-metiletil)-pirrolidin-1-il]-8-metoxi-1H-quinazolin-2,4-diona;

3-Amino-1-ciclopropil-6-fluoro-5-metil-7-[(R)-3-((S)-1-metilaminoetil)pirrolidin-1-il]-1H-quinazolin-2,4-diona;

(S)-1-[(R)-1-(3-Amino-1-ciclopropil-7-[3-(1-etilaminoetil)pirrolidin-1-il]-6-fluoro-8-metoxi-1H-quinazolin-2,4-diona;

3-Amino-1-ciclopropil-7-[(R)-3-((S)-1-etilaminoetil)pirrolidin-1-il]-6-fluoro-8-metil-1H-quinazolin-2,4-diona;

3-Amino-7-(6-fluoro-1-metil-3-azabiciclo[3.2.0]hept-3-il)-1-ciclopropil-6-fluoro-8-metoxi-1H-quinazolin-2,4-diona;

3-Amino-7-(4-aminometilpiperidin-1-il)-1-ciclopropil-6-fluoro-8-metoxi-1H-quinazolin-2,4-diona;

3-Amino-7-(3-aminometilazetidin-1-il)-1-ciclopropil-6-fluoro-8-metoxi-1H-quinazolin-2,4-diona;

cis-3-Amino-7-(3-aminometil-4-fluoropirrolidin-1-il)-1-ciclopropil-6-fluoro-8-metoxi-1H-quinazolin-2,4-diona;

trans-3-Amino-7-(3-aminometil-4-fluoropirrolidin-1-il)-1-ciclopropil-6-fluoro-8-metoxi-1H-quinazolin-2,4-diona;

3-Amino-7-(1-amino-5-azaespiro[2.4]hept-5-il)-1-ciclopropil-6-fluoro-8-metoxi-1H-quinazolin-2,4-diona;

3-Amino-7-(3-aminometiloctahidroisoindol-2-il)-1-ciclopropil-6-fluoro-8-metoxi-1H-quinazolin-2,4-diona;

3-Amino-7-(3-aminometiloctahidroisoindol-2-il)-1-ciclopropil-6-fluoro-8-metil-1H-quinazolin-2,4-diona;

3-Amino-7-[(R)-3-((S)-1-aminoetilpirrolidin-1-il]-1-ciclopropil-6-fluoro-8-metoxi-1H-quinazolin-2,4-diona;

3-Amino-7-(6-amino-3-azabiciclo[3.1.0]hex-3-il)-1-ciclopropil-6-fluoro-8-metil-1H-quinazolin-2,4-diona;

3-Amino-7-[3-(1-amino-1-metiletil)pirrolidin-1-il]-1-ciclopropil-6-fluoro-8-metoxi-1H-quinazolin-2,4-diona;

3-Amino-1-ciclopropil-6-fluoro-7-[3-(isopropilaminometil)pirrolidin-1-il]-8-metoxi-1H-quinazolin-2,4-diona;

3-Amino-1-ciclopropil-6-fluoro-8-metoxi-7-[(4aS,7aS)-octahidropirrolo[3,4-b]piridin-6-il-1H-quinazolin-2,4-diona;

3-Amino-7-(3-amino-4-fluoropirrolidin-1-il)-1-ciclopropil-6-fluoro-8-metoxi-1H-quinazolin-2,4-diona;

3-Amino-7-(3-aminometil-3-metilopirrolidin-1-il)-1-ciclopropil-6-fluoro-8-metoxi-1H-quinazolin-2,4-diona;

3-Amino-7-(4-aminopiperidin-1-il)-1-ciclopropil-6-fluoro-8-metoxi-1H-quinazolin-2,4-diona;

3-Amino-7-(3-aminopiperidin-1-il)-1-ciclopropil-6-fluoro-8-metoxi-1H-quinazolin-2,4-diona;

3-Amino-1-ciclopropil-6-fluoro-8-metoxi-7-[(R)-3-((S)-1-metilaminoetil)pirrolidin-1-il]-1H-quinazolin-2,4-diona;

3-Amino-7-(3-aminoazetidin-1-il)-1-ciclopropil-6-fluoro-8-metoxi-1H-quinazolin-2,4-diona;

3-Amino-7-[(3R,4S)-3-((S)-1-aminoetil)-4-fluoropirrolidin-1-il]-1-ciclopropil-6-fluoro-8-metil-1H-quinazolin-2,4-diona;

3-Amino-7-[(3R,4S)-3-((S)-1-aminoetil)-4-fluoropirrolidin-1-il]-1-ciclopropil-6-fluoro-8-metil-1H-quinazolin-2,4-diona;

3-Amino-7-[(3R,4R)-3-(R)-1-aminoetil)-4-fluoropirrolidin-1-il]-1-ciclopropil-6-fluoro-8-metil-1H-quinazolin-2,4-diona;

3-Amino-7-[(3R,4R)-3-((R)-1-aminoetil)-4-fluoropirrolidin-1-il]-1-ciclopropil-8-metil-1H-quinazolin-2,4-diona;

3-Amino-7-[(3R,4S)-3-(-1-amino-1-metiletil)-4-fluoropirrolidin-1-il]-1-ciclopropil-6-fluoro-8-metil-1H-quinazolin-2,4-diona;

3-Amino-7-[(3R,4S)-3-(-1-amino-1-metiletil)-4-fluoropirrolidin-1-il]-1-ciclopropil-8-metil-1H-quinazolin-2,4-diona;

3-Amino-7-[(3R,4R)-3-(-1-amino-1-metiletil)-4-fluoropirrolidin-1-il]-1-ciclopropil-6-fluoro-8-metil-1H-quinazolin-2,4-diona;

3-Amino-7-[(3R,4R)-3-(-1-amino-1-metiletil)-4-fluoropirrolidin-1-il]-1-ciclopropil-8-metil-1H-quinazolin-2,4-diona;

3-Amino-7-[(3R,4S)-3-((R)-1-amino-2-metoxietil)-4-fluoropirrolidin-1-il]-1-ciclopropil-6-fluoro-8-metil-1H-quinazolin-2,4-diona;

3-Amino-7-[(3R,4S)-3-((R)-1-amino-2-metoxietil)-4-fluoropirrolidin-1-il]-1-ciclopropil-8-metil-1H-quinazolin-2,4-diona;

3-Amino-7-[(3R,4R)-3-((S)-1-amino-2-metoxietil)-4-fluoropirrolidin-1-il]-1-ciclopropil-6-fluoro-8-metil-1H-quinazolin-2,4-diona;

3-Amino-7-[(3R,4R)-3-((S)-1-amino-2-metoxietil)-4-fluoropirrolidin-1-il]-1-ciclopropil-8-metil-1H-quinazolin-2,4-diona;

3-Amino-7-[(3R,4S)-3-((R)-1-amino-2-metoxietil)-4-metilpirrolidin-1-il]-1-ciclopropil-6-fluoro-8-metil-1H-quinazolin-2,4-diona;

3-Amino-7-[(3R,4S)-3-((R)-1-amino-2-metoxietil)-4-metilpirrolidin-1-il]-1-ciclopropil-8-metil-1H-quinazolin-2,4-diona;

3-Amino-7-[(3R,4R)-3-((S)-1-amino-2-metoxietil)-4-metilpirrolidin-1-il]-1-ciclopropil-6-fluoro-8-metil-1H-quinazolin-2,4-diona;

3-Amino-7-[(3R,4R)-3-((S)-1-amino-2-metoxietil)-4-metilpirrolidin-1-il]-1-ciclopropil-8-metil-1H-quinazolin-2,4-diona;

3-Amino-7-[(R)-4-((R)-1-amino-2-metoxietil)-3,3-dimetilpirrolidin-1-il]-1-ciclopropil-6-fluoro-8-metil-1H-quinazolin-2,4-diona;

3-Amino-7-[(R)-4-((R)-1-amino-2-metoxietil)-3,3-dimetilpirrolidin-1-il]-1-ciclopropil-8-metil-1H-quinazolin-2,4-diona;

3-Amino-7-[(R)-4-((S)-1-amino-2-metoxietil)-3,3-dimetilpirrolidin-1-il]-1-ciclopropil-6-fluoro-8-metil-1H-quinazolin-2,4-diona;

3-Amino-7-[(R)-4-(S)-1-amino-2-metoxietil)-3,3-dimetilpirrolidin-1-il]-1-ciclopropil-8-metil-1H-quinazolin-2,4-diona;

3-Amino-7-[(R)-3-((R)-1-amino-2-fenoxietil)pirrolidin-1-il]-1-ciclopropil-6-fluoro-8-metil-1H-quinazolin-2,4-diona;

3-Amino-7-[(R)-3-((R)-1-amino-2-fenoxietil)pirrolidin-1-il]-1-ciclopropil-8-metil-1H-quinazolin-2,4-diona;

3-Amino-7-[(3R,4S)-3-((R)-1-amino-2-fenoxietil)-4-metilpirrolidin-1-il]-1-ciclopropil-6-fluoro-8-metil-1H-quinazolin-2,4-diona;

3-Amino-7-[(3R,4S)-3-((R)-1-amino-2-fenoxietil)-4-metilpirrolidin-1-il]-1-ciclopropil-8-metil-1H-quinazolin-2,4-diona;

3-Amino-7-[(3R,4S)-3-((R)-1-amino-2-fenoxietil)-4-fluoropirrolidin-1-il]-1-ciclopropil-6-fluoro-8-metil-1H-quinazolin-2,4-diona;

3-Amino-7-[(3R,4S)-3-((R)-1-amino-2-fenoxietil)-4-fluoropirrolidin-1-il]-1-ciclopropil-8-metil-1H-quinazolin-2,4-diona;

3-Amino-7-[(R)-3-((S)-1-amino-2-fenoxietil)pirrolidin-1-il]-1-ciclopropil-6-fluoro-8-metil-1H-quinazolin-2,4-diona;

3-Amino-7-[(R)-3-((S)-1-amino-2-fenoxietil)pirrolidin-1-il]-1-ciclopropil-8-metil-1H-quinazolin-2,4-diona;

3-Amino-7-[(3R,4S)-3-((S)-1-amino-2-fenoxietil)-4-metilpirrolidin-1-il]-1-ciclopropil-6-fluoro-8-metil-1H-quinazolin-2,4-diona;

3-Amino-7-[(3R,4S)-3-((S)-1-amino-2-fenoxietil)-4-metilpirrolidin-1-il]-1-ciclopropil-8-metil-1H-quinazolin-2,4-diona;

3-Amino-7-[(3R,4S)-3-((S)-1-amino-2-fenoxietil)-4-fluoropirrolidin-1-il]-1-ciclopropil-6-fluoro-8-metil-1H-quinazolin-2,4-diona;

3-Amino-7-[(3R,4S)-3-((S)-1-amino-2-fenoxietil)-4-fluoropirrolidin-1-il]-1-ciclopropil-8-metil-1H-quinazolin-2,4-diona;

3-Amino-7-[(R)-4-((R)-1-amino-2-fenoxietil)-3,3-dimetilpirrolidin-1-il]-1-ciclopropil-6-fluoro-8-metil-1H-quinazolin-2,4-diona;

3-Amino-7-[(R)-4-((R)-1-amino-2-fenoxietil)-3,3-dimetilpirrolidin-1-il]-1-ciclopropil-8-metil-1H-quinazolin-2,4-diona;

3-Amino-7-[(R)-4-((S)-1-amino-2-fenoxietil)-3,3-dimetilpirrolidin-1-il]-1-ciclopropil-6-fluoro-8-metil-1H-quinazolin-2,4-diona;

3-Amino-7-[(R)-4-((S)-1-amino-2-fenoxietil)-3,3-dimetilpirrolidin-1-il]-1-ciclopropil-8-metil-1H-quinazolin-2,4-diona;

3-Amino-7-[(R)-3-((S)-1-amino-2-etoxietil)pirrolidin-1-il]-1-ciclopropil-6-fluoro-8-metil-1H-quinazolin-2,4-diona;

3-Amino-7-[(R)-3-((S)-1-amino-2-etoxietil)pirrolidin-1-il]-1-ciclopropil-8-metil-1H-quinazolin-2,4-diona;

3-Amino-7-[(R)-3-((R)-1-amino-2-etoxietil)pirrolidin-1-il]-1-ciclopropil-6-fluoro-8-metil-1H-quinazolin-2,4-diona;

3-Amino-7-[(R)-3-((R)-1-amino-2-etoxietil)pirrolidin-1-il]-1-ciclopropil-8-metil-1H-quinazolin-2,4-diona;

3-Amino-7-[(3R,4S)-3-((R)-1-amino-2-etoxietil)-4-metilpirrolidin-1-il]-1-ciclopropil-6-fluoro-8-metil-1H-quinazolin-2,4-diona;

3-Amino-7-[(3R,4S)-3-((R)-1-amino-2-etoxietil)-4-metilpirrolidin-1-il]-1-ciclopropil-8-metil-1H-quinazolin-2,4-diona;

3-Amino-7-[(3R,4S)-3-((R)-1-amino-2-etoxietil)-4-fluoropirrolidin-1-il]-1-ciclopropil-6-fluoro-8-metil-1H-quinazolin-2,4-diona;

3-Amino-7-[(3R,4S)-3-((R)-1-amino-2-etoxietil)-4-fluoropirrolidin-1-il]-1-ciclopropil-8-metil-1H-quinazolin-2,4-diona;

3-Amino-7-[(R)-4-((R)-1-amino-2-etoxietil)-3,3-dimetilpirrolidìn-1-il]-1-ciclopropil-6-fluoro-8-metil-1H-quinazolin-2,4-diona;

3-Amino-7-[(R)-4-((R)-1-amino-2-etoxietil)-3,3-dimetilpirrolidin-1-il]-1-ciclopropil-8-metil-1H-quinazolin-2,4-diona;

3-Amino-7-[(3R,4R)-3-((S)-1-amino-2-etoxietil)-4-metilpirrolidin-1-il]-1-ciclopropil-6-fluoro-8-metil-1H-quinazolin-2,4-diona;

3-Amino-7-[(3R,4R)-3-((S)-1-amino-2-etoxietil)-4-metilpirrolidin-1-il]-1-ciclopropil-8-metil-1H-quinazolin-2,4-diona;

3-Amino-7-[(3R,4R)-3-((S)-1-amino-2-etoxietil)-4-fluoropirrolidin-1-il]-1-ciclopropil-6-fluoro-8-metil-1H-quinazolin-2,4-diona;

3-Amino-7-[(3R,4R)-3-((S)-1-amino-2-etoxietil)-4-fluoropirrolidin-1-il]-1-ciclopropil-8-metil-1H-quinazolin-2,4-diona;

3-Amino-7-[(R)-3-((S)-1-amino-3-metoxipropil)pirrolidin-1-il]-1-ciclopropil-6-fluoro-8-metil-1H-quinazolin-2,4-diona;

3-Amino-7-[(R)-3-((S)-1-amino-3-metoxipropil)pirrolidin-1-il]-1-ciclopropil-8-metil-1H-quinazolin-2,4-diona;

3-Amino-7-[(3R,4S)-3-((S)-1-amino-3-metoxipropil)-4-metilpirrolidin-1-il]-1-ciclopropil-6-fluoro-8-metil-1H-quinazolin-2,4-diona;

3-Amino-7-[(3R,4S)-3-((S)-1-amino-3-metoxipropil)-4-metilpirrolidin-1-il]-1-ciclopropil-8-metil-1H-quinazolin-2,4-diona;

3-Amino-7-[(3R,4S)-3-((S)-1-amino-3-metoxipropil)-4-fluoropirrolidin-1-il]-1-ciclopropil-6-fluoro-8-metil-1H-quinazolin-2,4-diona;

3-Amino-7-[(3R,4S)-3-((S)-1-amino-3-metoxipropil)-4-fluoropirrolidin-1-il]-1-ciclopropil-8-metil-1H-quinazolin-2,4-diona;

3-Amino-7-[(R)-3-((R)-1-amino-3-metoxipropil)pirrolidin-1-il]-1-ciclopropil-6-fluoro-8-metil-1H-quinazolin-2,4-diona;

3-Amino-7-[(R)-3-((R)-1-amino-3-metoxipropil)pirrolidin-1-il]-1-ciclopropil-8-metil-1H-quinazolin-2,4-diona;

3-Amino-7-[(3R,4R)-3-((R)-1-amino-3-metoxipropil)-4-metilpirrolidin-1-il]-1-ciclopropil-6-fluoro-8-metil-1H-quinazolin-2,4-diona;

3-Amino-7-[(3R,4R)-3-((R)-1-amino-3-metoxipropil)-4-metilpirrolidin-1-il]-1-ciclopropil-8-metil-1H-quinazolin-2,4-diona;

3-Amino-7-[(3R,4R)-3-((R)-1-amino-3-metoxipropil)-4-fluoropirrolidin-1-il]-1-ciclopropil-6-fluoro-8-metil-1H-quinazolin-2,4-diona;

3-Amino-7-[(3R,4R)-3-((R)-1-amino-3-metoxipropil)-4-fluoropirrolidin-1-il]-1-ciclopropil-8-metil-1H-quinazolin-2,4-diona;

{(R)-2-Amino-2-[(R)-1-(3-amino-1-ciclopropil-6-fluoro-8-metil-2,4-dioxo-1,2,3,4-tetrahidroquinazolin-7-il)pirrolidin-3-il]etil}urea;

{(R)-2-Amino-2-[(R)-1-(3-amino-1-ciclopropil-8-metil-2,4-dioxo-1,2,3,4-tetrahidroquinazolin-7-il)pirrolidin-3-il]etil}urea;

{(S)-2-Amino-2-[(R)-1-(3-amino-1-ciclopropil-6-fluoro-8-metil-2,4-dioxo-1,2,3,4-tetrahidroquinazolin-7-il)pirrolidin-3-il]etil}urea;

{(S)-2-Amino-2-[(R)-1-(3-amino-1-ciclopropil-8-metil-2,4-dioxo-1,2,3,4-tetrahidroquinazolin-7-il)pirrolidin-3-il]etil}urea;

{(R)-2-Amino-2-[(3R,4S)-1-(3-amino-1-ciclopropil-6-fluoro-8-metil-2,4-dioxo-1,2,3,4-tetrahidroquinazolin-7-il)-4-metilpirrolidin-3-il]etil}urea;

{(R)-2-Amino-2-[(3R,4S)-1-(3-amino-1-ciclopropil-8-metil-2,4-dioxo-1,2,3,4-tetrahidroquinazolin-7-il)-4-metilpirrolidin-3-il]etil}urea;

{(S)-2-Amino-2-[(3R,4R)-1-(3-amino-1-ciclopropil-6-fluoro-8-metil-2,4-dioxo-1,2,3,4-tetrahidroquinazolin-7-il)-4-metilpirrolidin-3-il]etil}urea;

{(S)-2-Amino-2-[(3R,4R)-1-(3-amino-1-ciclopropil-8-metil-2,4-dioxo-1,2,3,4-tetrahidroquinazolin-7-il)-4-metilpirrolidin-3-il]etil}urea;

{2-Amino-2-[(1-(3-amino-1-ciclopropil-6-fluoro-8-metil-2,4-dioxo-1,2,3,4-tetrahidroquinazolin-7-il)-4-fluoropirrolidin-3-il]etil}urea;

{2-Amino-2-[(1-(3-amino-1-ciclopropil-8-metil-2,4-dioxo-1,2,3,4-tetrahidroquinazolin-7-il)-4-fluoropirrolidin-3-il]etil}urea;

{2-Amino-2-[(1-(3-amino-1-ciclopropil-6-fluoro-8-metil-2,4-dioxo-1,2,3,4-tetrahidroquinazolin-7-il)-4,4-dimetilpirrolidin-3-il]etil}urea;

{2-Amino-2-[(1-(3-amino-1-ciclopropil-8-metil-2,4-dioxo-1,2,3,4-tetrahidroquinazolin-7-il)-4,4-dimetilpirrolidin-3-il]etil}urea;

3-Amino-7-[(3R,4S)-3-((S)-1-aminoetil)-4-fluoropirrolidin-1-il]-1-ciclopropil-6-fluoro-8-metoxi-1H-quinazolin-2,4-diona;

3-Amino-7-[(3R,4S)-3-((S)-1-aminoetil)-4-fluoropirrolidin-1-il]-1-ciclopropil-8-metoxi-1H-quinazolin-2,4-diona;

3-Amino-7-[(3R,4R)-3-((R)-1-aminoetil)-4-fluoropirrolidin-1-il]-1-ciclopropil-6-fluoro-8-metoxi-1H-quinazolin-2,4-diona;

3-Amino-7-[(3R,4R)-3-((R)-1-aminoetil)-4-fluoropirrolidin-1-il]-1-ciclopropil-8-metoxi-1H-quinazolin-2,4-diona;

3-Amino-7-[(3R,4S)-3-(-1-amino-1-metiletil)-4-fluoropirrolidin-1-il]-1-ciclopropil-6-fluoro-8-metoxi-1H-quinazolin-2,4-diona;

3-Amino-7-[(3R,4S)-3-(-1-amino1-metiletil)-4-fluoropirrolidin-1-il]-1-ciclopropil-8-metoxi-1H-quinazolin-2,4-diona;

3-Amino-7-[(3R,4R)-3-(-1-amino-1-metiletil)-4-fluoropirrolidin-1-il]-1-ciclopropil-6-fluoro-8-metoxi-1H-quinazolin-2,4-diona;

3-Amino-7-[(3R,4R)-3-(-1-amino-1-metiletil)-4-fluoropirrolidin-1-il]-1-ciclopropil-8-metoxi-1H-quinazolin-2,4-diona;

3-Amino-7-[(3R,4S)-3-((R)-1-amino-2-metoxietil)-4-fluoropirrolidin-1-il]-1-ciclopropil-6-fluoro-8-metoxi-1H-quinazolin-2,4-diona;

3-Amino-7-[(3R,4S)-3-((R)-1-amino-2-metoxietil)-4-fluoropirrolidin-1-il]-1-ciclopropil-8-metoxi-1H-quinazolin-2,4-diona;

3-Amino-7-[(3R,4R)-3-((S)-1-amino-2-metoxietil)-4-fluoropirrolidin-1-il]-1-ciclopropil-6-fluoro-8-metoxi-1H-quinazolin-2,4-diona;

3-Amino-7-[(3R,4R)-3-((S)-1-amino-2-metoxietil)-4-fluoropirrolidin-1-il]-1-ciclopropil-8-metoxi-1H-quinazolin-2,4-diona;

3-Amino-7-[(3R,4S)-3-((R)-1-amino-2-metoxietil)-4-metilpirrolidin-1-il]-1-ciclopropil-6-fluoro-8-metoxi-1H-quinazolin-2,4-diona;

3-Amino-7-[(3R,4S)-3-((R)-1-amino-2-metoxietil)-4-metilpirrolidin-1-il]-1-ciclopropil-8-metoxi-1H-quinazolin-2,4-diona;

3-Amino-7-[(3R,4R)-3-((S)-1-amino-2-metoxietil)-4-metilpirrolidin-1-il]-1-ciclopropil-6-fluoro-8-metoxi-1H-quinazolin-2,4-diona;

3-Amino-7-[(3R,4R)-3-((S)-1-amino-2-metoxietil)-4-metilpirrolidin-1-il]-1-ciclopropil-8-metoxi-1H-quinazolin-2,4-diona;

3-Amino-7-[(R)-4-((R)-1-amino-2-metoxietil)-3,3-dimetilpirrolidin-1-il]-1-ciclopropil-6-fluoro-8-metoxi-1H-quinazolin-2,4-diona;

3-Amino-7-[(R)-4-((R)-1-amino-2-metoxietil)-3,3-dimetilpirrolidin-1-il]-1-ciclopropil-8-metoxi-1H-quinazolin-2,4-diona;

3-Amino-7-[(R)-4-((S)-1-amino-2-metoxietil)-3,3-dimetilpirrolidin-1-il]-1-ciclopropil-6-fluoro-8-metoxi-1H-quinazolin-2,4-diona;

3-Amino-7-[(R)-4-((S)-1-amino-2-metoxietil)-3,3-dimetilpirrolidin-1-il]-1-ciclopropil-8-metoxi-1H-quinazolin-2,4-diona;

3-Amino-7-[(R)-3-((R)-1-amino-2-fenoxietil)pirrolidin-1-il]-1-ciclopropil-6-fluoro-8-metoxi-1H-quinazolin-2,4-diona;

3-Amino-7-[(R)-3-((R)-1-amino-2-fenoxietil)pirrolidin-1-il]-1-ciclopropil-8-metoxi-1H-quinazolin-2,4-diona;

3-Amino-7-[(3R,4S)-3-((R)-1-amino-2-fenoxietil)-4-metilpirrolidin-1-il]-1-ciclopropil-6-fluoro-8-metoxi-1H-quinazolin-2,4-diona;

3-Amino-7-[(3R,4S)-3-((R)-1-amino-2-fenoxietil)-4-metilpirrolidin-1-il]-1-ciclopropil-8-metoxi-1H-quinazolin-2,4-diona;

3-Amino-7-[(3R,4S)-3-((R)-1-amino-2-fenoxietil)-4-fluoropirrolidin-1-il]-1-ciclopropil-6-fluoro-8-metoxi-1H-quinazolin-2,4-diona;

3-Amino-7-[(3R,4S)-3-((R)-1-amino-2-fenoxietil)-4-fluoropirrolidin-1-il]-1-ciclopropil-8-metoxi-1H-quinazolin-2,4-diona;

3-Amino-7-[(R)-3-((S)-1-amino-2-fenoxietil)pirrolidin-1-il]-1-ciclopropil-6-fluoro-8-metoxi-1H-quinazolin-2,4-diona;

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3-Amino-7-[(R)-3-((S)-1-amino-2-fenoxietil)pirrolidin-1-il]-1-ciclopropil-8-metoxi-1H-quinazolin-2,4-diona;

3-Amino-7-[(3R,4S)-3-((S)-1-amino-2-fenoxietil)-4-metilpirrolidin-1-il]-1-ciclopropil-6-fluoro-8-metoxi-1H-quinazolin-2,4-diona;

3-Amino-7-[(3R,4S)-3-((S)-1-amino-2-fenoxietil)-4-metilpirrolidin-1-il]-1-ciclopropil-8-metoxi-1H-quinazolin-2,4-diona;

3-Amino-7-[(3R,4S)-3-((S)-1-amino-2-fenoxietil)-4-fluoropirrolidin-1-il]-1-ciclopropil-6-fluoro-8-metoxi-1H-quinazolin-2,4-diona;

3-Amino-7-[(3R,4S)-3-((S)-1-amino-2-fenoxietil)-4-fluoropirrolidin-1-il]-1-ciclopropil-8-metoxi-1H-quinazolin-2,4-diona;

3-Amino-7-[(R)-4-((R)-1-amino-2-fenoxietil)-3,3-dimetilpirrolidin-1-il]-1-ciclopropil-6-fluoro-8-metoxi-1H-quinazolin-2,4-diona;

3-Amino-7-[(R)-4-((R)-1-amino-2-fenoxietil)-3,3-dimetilpirrolidin-1-il]-1-ciclopropil-8-metoxi-1H-quinazolin-2,4-diona;

3-Amino-7-[(R)-4-((S)-1-amino-2-fenoxietil)-3,3-dimetilpirrolidin-1-il]-1-ciclopropil-6-fluoro-8-metoxi-1H-quinazolin-2,4-diona;

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3-Amino-7-[(R)-4-((S)-1-amino-2-fenoxietil)-3,3-dimetilpirrolidin-1-il]-1-ciclopropil-8-metoxi-1H-quinazolin-2,4-diona;

3-Amino-7-[(R)-4-((S)-1-amino-2-etoxietil)pirrolidin-1-il]-1-ciclopropil-6-fluoro-8-metoxi-1H-quinazolin-2,4-diona;

3-Amino-7-[(R)-4-((S)-1-amino-2-etoxietil)pirrolidin-1-il]-1-ciclopropil-8-metoxi-1H-quinazolin-2,4-diona;

3-Amino-7-[(R)-3-((R)-1-amino-2-etoxietil)pirrolidin-1-il]-1-ciclopropil-6-fluoro-8-metoxi-1H-quinazolin-2,4-diona;

3-Amino-7-[(R)-3-((R)-1-amino-2-etoxietil)pirrolidin-1-il]-1-ciclopropil-8-metoxi-1H-quinazolin-2,4-diona;

3-Amino-7-[(3R,4S)-3-((R)-1-amino-2-etoxietil)-4-metilpirrolidin-1-il]-1-ciclopropil-6-fluoro-8-metoxi-1H-quinazolin-2,4-diona;

3-Amino-7-[(3R,4S)-3-((R)-1-amino-2-etoxietil)-4-metilpirrolidin-1-il]-1-ciclopropil-8-metoxi-1H-quinazolin-2,4-diona;

3-Amino-7-[(3R,4S)-3-((R)-1-amino-2-etoxietil)-4-fluoropirrolidin-1-il]-1-ciclopropil-6-fluoro-8-metoxi-1H-quinazolin-2,4-diona;

3-Amino-7-[(3R,4S)-3-((R)-1-amino-2-etoxietil)-4-fluoropirrolidin-1-il]-1-ciclopropil-8-metoxi-1H-quinazolin-2,4-diona;

3-Amino-7-[(R)-4-((R)-1-amino-2-etoxietil)-3,3-dimetilpirrolidin-1-il]-1-ciclopropil-6-fluoro-8-metoxi-1H-quinazolin-2,4-diona;

3-Amino-7-[(R)-4-((R)-1-amino-2-etoxietil)-3,3-dimetilpirrolidin-1-il]-1-ciclopropil-8-metoxi-1H-quinazolin-2,4-diona;

3-Amino-7-[(3R,4R)-3-((S)-1-amino-2-etoxietil)-4-metilpirrolidin-1-il]-1-ciclopropil-6-fluoro-8-metoxi-1H-quinazolin-2,4-diona;

3-Amino-7-[(3R,4R)-3-((S)-1-amino-2-etoxietil)-4-metilpirrolidin-1-il]-1-ciclopropil-8-metoxi-1H-quinazolin-2,4-diona;

3-Amino-7-[(3R,4R)-3-((S)-1-amino-2-etoxietil)-4-fluoropirrolidin-1-il]-1-ciclopropil-6-fluoro-8-metoxi-1H-quinazolin-2,4-diona;

3-Amino-7-[(3R,4R)-3-((S)-1-amino-2-etoxietil)-4-fluoropirrolidin-1-il]-1-ciclopropil-8-metoxi-1H-quinazolin-2,4-diona;

3-Amino-7-[(R)-3-((S)-1-amino-3-metoxipropil)pirrolidin-1-il]-1-ciclopropil-6-fluoro-8-metoxi-1H-quinazolin-2,4-diona;

3-Amino-7-[(R)-3-((S)-1-amino-3-metoxipropil)pirrolidin-1-il]-1-ciclopropil-8-metoxi-1H-quinazolin-2,4-diona;

3-Amino-7-[(3R,4S)-3-((S)-1-amino-3-metoxipropil)-4-metilpirrolidin-1-il]-1-ciclopropil-6-fluoro-8-metoxi-1H-quinazolin-2,4-diona;

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3-Amino-7-[(3R,4S)-3-((S)-1-amino-3-metoxipropil)-4-metilpirrolidin-1-il]-1-ciclopropil-8-metoxi-1H-quinazolin-2,4-diona;

3-Amino-7-[(3R,4S)-3-((S)-1-amino-3-metoxipropil)-4-fluoropirrolidin-1-il]-1-ciclopropil-6-fluoro-8-metoxi-1H-quinazolin-2,4-diona;

3-Amino-7-[(3R,4S)-3-((S)-1-amino-3-metoxipropil)-4-fluoropirrolidin-1-il]-1-ciclopropil-8-metoxi-1H-quinazolin-2,4-diona;

3-Amino-7-[(R)-3-((R)-1-amino-3-metoxipropil)pirrolidin-1-il]-1-ciclopropil-6-fluoro-8-metoxi-1H-quinazolin-2,4-diona;

3-Amino-7-[(R)-3-((R)-1-amino-3-metoxipropil)pirrolidin-1-il]-1-ciclopropil-8-metoxi-1H-quinazolin-2,4-diona;

3-Amino-7-[(3R,4R)-3-((R)-1-amino-3-metoxipropil)-4-metilpirrolidin-1-il]-1-ciclopropil-6-fluoro-8-metoxi-1H-quinazolin-2,4-diona;

3-Amino-7-[(3R,4R)-3-((R)-1-amino-3-metoxipropil)-4-metilpirrolidin-1-il]-1-ciclopropil-8-metoxi-1H-quinazolin-2,4-diona;

3-Amino-7-[(3R,4R)-3-((R)-1-amino-3-metoxipropil)-4-fluoropirrolidin-1-il]-1-ciclopropil-6-fluoro-8-metoxi-1H-quinazolin-2,4-diona;

3-Amino-7-[(3R,4R)-3-((R)-1-amino-3-metoxipropil)-4-fluoropirrolidin-1-il]-1-ciclopropil-8-metoxi-1H-quinazolin-2,4-diona;

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{(R)-2-Amino-2-[(R)-1-(3-amino-1-ciclopropil-6-fluoro-8-metoxi-2,4-dioxo-1,2,3,4-tetrahidroquinazolin-7-il)pirrolidin-3-il]etil}urea;

{(R)-2-Amino-2-[(R)-1-(3-amino-1-ciclopropil-8-metoxi-2,4-dioxo-1,2,3,4-tetrahidroquinazolin-7-il)pirrolidin-3-il]etil}urea;

{(S)-2-Amino-2-[(R)-1-(3-amino-1-ciclopropil-6-fluoro-8-metoxi-2,4-dioxo-1,2,3,4-tetrahidroquinazolin-7-il)pirrolidin-3-il]etil}urea;

{(S)-2-Amino-2-[(R)-1-(3-amino-1-ciclopropil-8-metoxi-2,4-dioxo-1,2,3,4-tetrahidroquinazolin-7-il)pirrolidin-3-il]etil}urea;

{(R)-2-Amino-2-[(3R,4S)-1-(3-amino-1-ciclopropil-6-fluoro-8-metoxi-2,4-dioxo-1,2,3,4-tetrahidroquinazolin-7-il)-4-metilpirrolidin-3-il]etil}urea;

{(R)-2-Amino-2-[(3R,4S)-1-(3-amino-1-ciclopropil-8-metoxi-2,4-dioxo-1,2,3,4-tetrahidroquinazolin-7-il)-4-metilpirrolidin-3-il]etil}urea;

{(S)-2-Amino-2-[(3R,4R)-1-(3-amino-1-ciclopropil-6-fluoro-8-metoxi-2,4-dioxo-1,2,3,4-tetrahidroquinazolin-7-il)-4-metilpirrolidin-3-il]etil}urea;

{(S)-2-Amino-2-[(3R,4R)-1-(3-amino-1-ciclopropil-8-metoxi-2,4-dioxo-1,2,3,4-tetrahidroquinazolin-7-il)-4-metilpirrolidin-3-il]etil}urea;

{2-Amino-2-[(1-(3-amino-1-ciclopropil-6-fluoro-8-metoxi-2,4-dioxo-1,2,3,4-tetrahidroquinazolin-7-il)-4-fluoropirrolidin-3-il]etil}urea;

{2-Amino-2-[(1-(3-amino-1-ciclopropil-8-metoxi-2,4-dioxo-1,2,3,4-tetrahidroquinazolin-7-il)-4-fluoropirrolidin-3-il]etil}urea;

{2-Amino-2-[(1-(3-amino-1-ciclopropil-6-fluoro-8-metoxi-2,4-dioxo-1,2,3,4-tetrahidroquinazolin-7-il)-4,4-dimetilpirrolidin-3-il]etil}urea;

{2-Amino-2-[(1-(3-amino-1-ciclopropil-8-metoxi-2,4-dioxo-1,2,3,4-tetrahidroquinazolin-7-il)-4,4-dimetilpirrolidin-3-il]etil}urea;

3-Amino-7-[3-(1-aminoetil)-4-fluoropirrolidin-1-il]-1-ciclopropil-8-metil-1H-pirido[4,3-d]pirimidin-2,4-diona;

3-Amino-7-[3-(1-amino-1-metiletil)-4-fluoropirrolidin-1-il]-1-ciclopropil-8-metil-1H-pirido[4,3-d]pirimidin-2,4-diona;

3-Amino-7-[3-(1-amino-2-metoxietil)-4-fluoropirrolidin-1-il]-1-ciclopropil-8-metil-1H-pirido[4,3-d]pirimidin-2,4-diona;

3-Amino-7-[3-(1-amino-2-metoxietil)-4-metilpirrolidin-1-il]-1-ciclopropil-8-metil-1H-pirido[4,3-d]pirimidin-2,4-diona;

3-Amino-7-[4-(1-amino-2-metoxietil)-3,3-dimetilpirrolidin-1-il]-1-ciclopropil-8-metil-1H-pirido[4,3-d]pirimidin-2,4-diona;

3-Amino-7-[3-(1-amino-2-fenoxietil)-pirrolidin-1-il]-1-ciclopropil-8-metil-1H-pirido[4,3-d]pirimidin-2,4-diona;

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3-Amino-7-[3-(1-amino-2-fenoxietil)-4-metilpirrolidin-1-il]-1-ciclopropil-8-metil-1H-pirido[4,3-d]pirimidin-2,4-diona;

3-Amino-7-[3-(1-amino-2-fenoxietil)-4-fluoropirrolidin-1-il]-1-ciclopropil-8-metil-1H-pirido[4,3-d]pirimidin-2,4-diona;

3-Amino-7-[4-(1-amino-2-fenoxietil)-3,3-dimetilpirrolidin-1-il]-1-ciclopropil-8-metil-1H-pirido[4,3-d]pirimidin-2,4-diona;

3-Amino-7-[3-(1-amino-2-etoxietil)pirrolidin-1-il]-1-ciclopropil-8-metil-1H-pirido[4,3-d]pirimidin-2,4-diona;

3-Amino-7-[3-(1-amino-2-etoxietil)-4-metilpirrolidin-1-il]-1-ciclopropil-8-metil-1H-pirido[4,3-d]pirimidin-2,4-diona;

3-Amino-7-[3-(1-amino-2-etoxietil)-4-fluoropirrolidin-1-il]-1-ciclopropil-8-metil-1H-pirido[4,3-d]pirimidin-2,4-diona;

3-Amino-7-[3-(1-amino-2-etoxietil)-4,4-dimetilpirrolidin-1-il]-1-ciclopropil-8-metil-1H-pirido[4,3-d]pirimidin-2,4-diona;

3-Amino-7-[3-(1-amino-2-metoxipropil)pirrolidin-1-il]-1-ciclopropil-8-metil-1H-pirido[4,3-d]pirimidin-2,4-diona;

3-Amino-7-[3-(1-amino-2-metoxipropil)-4-metilpirrolidin-1-il]-1-ciclopropil-8-metil-1H-pirido[4,3-d]pirimidin-2,4-diona;

3-Amino-7-[3-(1-amino-2-metoxipropil)-4-fluoropirrolidin-1-il]-1-ciclopropil-8-metil-1H-pirido[4,3-d]pirimidin-2,4-diona;

(2-Amino-2-[1-(3-amino-1-ciclopropil-8-metil-2,4-dioxo-1,2,3,4-tetrahidropirido[4,3-d]pirimidin-7-il)pirrolidin-3-il]etilurea;

(2-Amino-2-[1-(3-amino-1-ciclopropil-8-metil-2,4-dioxo-1,2,3,4-tetrahidropirido[4,3-d]pirimidin-7-il)-4-metilpirrolidin-3-il]etilurea;

(2-Amino-2-[1-(3-amino-1-ciclopropil-8-metil-2,4-dioxo-1,2,3,4-tetrahidropirido[4,3-d]pirimidin-7-il)-4-fluoropirrolidin-3-il]etilurea;

(2-Amino-2-[1-(3-amino-1-ciclopropil-8-metil-2,4-dioxo-1,2,3,4-tetrahidropirido[4,3-d]pirimidin-7-il)-4,4-dimetilpirrolidin-3-il]etilurea;

3-Amino-7-[3-(1-aminoetil)-4-fluoropirrolidin-1-il]-1-ciclopropil-6-fluoro-8-metil-1H-pirido[3,2-d]pirimidin-2,4-diona;

3-Amino-7-[3-(1-aminoetil)-4-fluoropirrolidin-1-il]-1-ciclopropil-8-metil-1H-pirido[3,2-d]pirimidin-2,4-diona;

3-Amino-7-[3-(1-amino-1-metiletil)-4-fluoropirrolidin-1-il]-1-ciclopropil-6-fluoro-8-metil-1H-pirido[3,2-d]pirimidin-2,4-diona;

3-Amino-7-[3-(1-amino-1-metiletil)-4-fluoropirrolidin-1-il]-1-ciclopropil-8-metil-1H-pirido[3,2-d]pirimidin-2,4-diona;

3-Amino-7-[3-(1-amino-2-metoxietil)-4-fluoropirrolidin-1-il]-1-ciclopropil-6-fluoro-8-metil-1H-pirido[3,2-d]pirimidin-2,4-diona;

3-Amino-7-[3-(1-amino-2-metoxietil)-4-fluoropirrolidin-1-il]-1-ciclopropil-8-metil-1H-pirido[3,2-d]pirimidin-2,4-diona;

3-Amino-7-[3-(1-amino-2-metoxietil)-4-metilpirrolidin-1-il]-1-ciclopropil-6-fluoro-8-metil-1H-pirido[3,2-d]pirimidin-2,4-diona;

3-Amino-7-[3-(1-amino-2-metoxietil)-4-metilpirrolidin-1-il]-1-ciclopropil-8-metil-1H-pirido[3,2-d]pirimidin-2,4-diona;

3-Amino-7-[4-(1-amino-2-metoxietil)-3,3-dimetilpirrolidin-1-il]-1-ciclopropil-6-fluoro-8-metil-1H-pirido[3,2-d]pirimidin-2,4-diona;

3-Amino-7-[4-(1-amino-2-metoxietil)-3,3-dimetilpirrolidin-1-il]-1-ciclopropil-8-metil-1H-pirido[3,2-d]pirimidin-2,4-diona;

3-Amino-7-[3-(1-amino-2-fenoxietil)pirrolidin-1-il]-1-ciclopropil-6-fluoro-8-metil-1H-pirido[3,2-d]pirimidin-2,4-diona;

3-Amino-7-[3-(1-amino-2-fenoxietil)pirrolidin-1-il]-1-ciclopropil-8-metil-1H-pirido[3,2-d]pirimidin-2,4-diona;

3-Amino-7-[3-(1-amino-2-fenoxietil)-4-metilpirrolidin-1-il]-1-ciclopropil-6-fluoro-8-metil-1H-pirido[3,2-d]pirimidin-2,4-diona;

3-Amino-7-[3-(1-amino-2-fenoxietil)-4-metilpirrolidin-1-il]-1-ciclopropil-8-metil-1H-pirido[3,2-d]pirimidin-2,4-diona;

3-Amino-7-[3-(1-amino-2-fenoxietil)-4-fluoropirrolidin-1-il]-1-ciclopropil-6-fluoro-8-metil-1H-pirido[3,2-d]pirimidin-2,4-diona;

3-Amino-7-[3-(1-amino-2-fenoxietil)-4-fluoropirrolidin-1-il]-1-ciclopropil-8-metil-1H-pirido[3,2-d]pirimidin-2,4-diona;

3-Amino-7-[4-(1-amino-2-fenoxietil)-3,3-dimetilpirrolidin-1-il]-1-ciclopropil-6-fluoro-8-metil-1H-pirido[3,2-d]pirimidin-2,4-diona;

3-Amino-7-[4-(1-amino-2-fenoxietil)-3,3-dimetilpirrolidin-1-il]-1-ciclopropil-8-metil-1H-pirido[3,2-d]pirimidin-2,4-diona;

3-Amino-7-[3-(1-amino-2-etoxietil)pirrolidin-1-il]-1-ciclopropil-6-fluoro-8-metil-1H-pirido[3,2-d]pirimidin-2,4-diona;

3-Amino-7-[3-(1-amino-2-etoxietil)pirrolidin-1-il]-1-ciclopropil-8-metil-1H-pirido[3,2-d]pirimidin-2,4-diona;

3-Amino-7-[3-(1-amino-2-etoxietil)-4-metilpirrolidin-1-il]-1-ciclopropil-6-fluoro-8-metil-1H-pirido[3,2-d]pirimidin-2,4-diona;

3-Amino-7-[3-(1-amino-2-etoxietil)-4-metilpirrolidin-1-il]-1-ciclopropil-8-metil-1H-pirido[3,2-d]pirimidin-2,4-diona;

3-Amino-7-[3-(1-amino-2-etoxietil)-4-fluoropirrolidin-1-il]-1-ciclopropil-6-fluoro-8-metil-1H-pirido[3,2-d]pirimidin-2,4-diona;

3-Amino-7-[3-(1-amino-2-etoxietil)-4-fluoropirrolidin-1-il]-1-ciclopropil-8-metil-1H-pirido[3,2-d]pirimidin-2,4-diona;

3-Amino-7-[3-(1-amino-2-etoxietil)-4,4-dimetilpirrolidin-1-il]-1-ciclopropil-6-fluoro-8-metil-1H-pirido[3,2-d]pirimidin-2,4-diona;

3-Amino-7-[3-(1-amino-2-etoxietil)-4,4-dimetilpirrolidin-1-il]-1-ciclopropil-8-metil-1H-pirido[3,2-d]pirimidin-2,4-diona;

3-Amino-7-[3-(1-amino-2-metoxipropil)pirrolidin-1-il]-1-ciclopropil-6-fluoro-8-metil-1H-pirido[3,2-d]pirimidin-2,4-diona;

3-Amino-7-[3-(1-amino-2-metoxipropil)pirrolidin-1-il]-1-ciclopropil-8-metil-1H-pirido[3,2-d]pirimidin-2,4-diona;

3-Amino-7-[3-(1-amino-2-metoxipropil)-4-metilpirrolidin-1-il]-1-ciclopropil-6-fluoro-8-metil-1H-pirido[3,2-d]pirimidin-2,4-diona;

3-Amino-7-[3-(1-amino-2-metoxipropil)-4-metilpirrolidin-1-il]-1-ciclopropil-8-metil-1H-pirido[3,2-d]pirimidin-2,4-diona;

3-Amino-7-[3-(1-amino-2-metoxipropil)4-fluoropirrolidin-1-il]-1-ciclopropil-6-fluoro-8-metil-1H-pirido[3,2-d]pirimidin-2,4-diona;

3-Amino-7-[3-(1-amino-2-metoxipropil)-4-fluoropirrolidin-1-il]-1-ciclopropil-8-metil-1H-pirido[3,2-d]pirimidin-2,4-diona;

{2-Amino-2-[1-(3-amino-1-ciclopropil-6-fluoro-8-metil-2,4-dioxo-1,2,3,4-tetrahidropirido[3,2-d]pirimidin-7-il)pirrolidin-3-il]etilurea;

{2-Amino-2-[1-(3-amino-1-ciclopropil-8-metil-2,4-dioxo-1,2,3,4-tetrahidropirido[3,2-d]pirimidin-7-il)pirrolidin-3-il]etilurea;

{2-Amino-2-[1-(3-amino-1-ciclopropil-6-fluoro-8-metil-2,4-dioxo-1,2,3,4-tetrahidropirido[3,2-d]pirimidin-7-il)-4-metilpirrolidin-3-il]etilurea;

{2-Amino-2-[1-(3-amino-1-ciclopropil-8-metil-2,4-dioxo-1,2,3,4-tetrahidropirido[3,2-d]pirimidin-7-il)-4-metilpirrolidin-3-il]etilurea;

{2-Amino-2-[1-(3-amino-1-ciclopropil-6-fluoro-8-metil-2,4-dioxo-1,2,3,4-tetrahidropirido[3,2-d]pirimidin-7-il)-4-fluoropirrolidin-3-il]etilurea;

{2-Amino-2-[1-(3-amino-1-ciclopropil-8-metil-2,4-dioxo-1,2,3,4-tetrahidropirido[3,2-d]pirimidin-7-il)-4-fluoropirrolidin-3-il]etilurea;

{2-Amino-2-[1-(3-amino-1-ciclopropil-6-fluoro-8-metil-2,4-dioxo-1,2,3,4-tetrahidropirido[3,2-d]pirimidin-7-il)-4,4-dimetilpirrolidin-3-il]etilurea;

{2-Amino-2-[1-(3-amino-1-ciclopropil-8-metil-2,4-dioxo-1,2,3,4-tetrahidropirido[3,2-d]pirimidin-7-il)-4,4-dimetilpirrolidin-3-il]etilurea;

3-Amino-7-(3-aminometilfenil)-8-cloro-1-ciclopropil-6-fluoro-1H-quinazolin-2,4-diona;

3-Amino-7-(3-aminometilfenil)-8-metil-1-ciclopropil-6-fluoro-1H-quinazolin-2,4-diona;

3-Amino-7-(3-aminometilfenil)-8-metoxi-1-ciclopropil-6-fluoro-1H-quinazolin-2,4-diona;

3-Amino-7-(3-aminometilfenil)-8-cloro-1-ciclopropil-1H-quinazolin-2,4-diona;

3-Amino-7-(3-aminometilfenil)-8-metil-1-ciclopropil-1H-quinazolin-2,4-diona;

3-Amino-7-(3-aminometilfenil)-8-metoxi-1-ciclopropil-1H-quinazolin-2,4-diona;

3-Amino-7-(2-aminometiltiazol-4-il)-8-cloro-1-ciclopropil-6-fluoro-1H-quinazolin-2,4-diona;

3-Amino-7-(2-aminometiltiazol-4-il)-8-metil-1-ciclopropil-6-fluoro-1H-quinazolin-2,4-diona;

3-Amino-7-(2-aminometiltiazol-4-il)-8-metoxi-1-ciclopropil-6-fluoro-1H-quinazolin-2,4-diona;

3-Amino-7-(2-aminometiltiazol-4-il)-8-cloro-1-ciclopropil-1H-quinazolin-2,4-diona;

3-Amino-7-(2-aminometiltiazol-4-il)-8-metil-1-ciclopropil-1H-quinazolin-2,4-diona;

3-Amino-7-(2-aminometiltiazol-4-il)-8-metoxi-1-ciclopropil-1H-quinazolin-2,4-diona;

3-Amino-7-[2-(1-aminoetil)tiazol-4-il]-8-cloro-1-ciclopropil-6-fluoro-1H-quinazolin-2,4-diona;

3-Amino-7-[2-(1-aminoetil)tiazol-4-il]-8-metil-1-ciclopropil-6-fluoro-1H-quinazolin-2,4-diona;

3-Amino-7-[2-(1-aminoetil)tiazol-4-il]-8-metoxi-1-ciclopropil-6-fluoro-1H-quinazolin-2,4-diona;

3-Amino-7-[2-(1-aminoetil)tiazol-4-il]-8-cloro-1-ciclopropil-1H-quinazolin-2,4-diona;

3-Amino-7-[2-(1-aminoetil)tiazol-4-il]-8-metil-1-ciclopropil-1H-quinazolin-2,4-diona;

3-Amino-7-[2-(1-aminoetil)tiazol-4-il]-8-metoxi-1-ciclopropil-1H-quinazolin-2,4-diona;

3-Amino-7-(5-aminometiltiofen-3-il)-8-cloro-1-ciclopropil-6-fluoro-1H-quinazolin-2,4-diona;

3-Amino-7-(5-aminometiltiofen-3-il)-8-metil-1-ciclopropil-6-fluoro-1H-quinazolin-2,4-diona;

3-Amino-7-(5-aminometiltiofen-3-il)-8-metoxi-1-ciclopropil-6-fluoro-1H-quinazolin-2,4-diona;

3-Amino-7-(5-aminometiltiofen-3-il)-8-cloro-1-ciclopropil-1H-quinazolin-2,4-diona;

3-Amino-7-(5-aminometiltiofen-3-il)-8-metil-1-ciclopropil-1H-quinazolin-2,4-diona;

3-Amino-7-(5-aminometiltiofen-3-il)-8-metoxi-1-ciclopropil-1H-quinazolin-2,4-diona;

3-Amino-7-(4-aminometil-3,3-difluoropirrolidin-1-il)-8-cloro-1-ciclopropil-6-fluoro-1H-quinazolin-2,4-diona;

3-Amino-7-(4-aminometil-3,3-difluoropirrolidin-1-il)-8-metil-1-ciclopropil-6-fluoro-1H-quinazolin-2,4-diona;

3-Amino-7-(4-aminometil-3,3-difluoropirrolidin-1-il)-8-metoxi-1-ciclopropil-6-fluoro-1H-quinazolin-2,4-diona;

3-Amino-7-(4-aminometil-3,3-difluoropirrolidin-1-il)-8-cloro-1-ciclopropil-1H-quinazolin-2,4-diona;

3-Amino-7-(4-aminometil-3,3-difluoropirrolidin-1-il)-8-metil-1-ciclopropil-1H-quinazolin-2,4-diona;

3-Amino-7-(4-aminometil-3,3-difluoropirrolidin-1-il)-8-metoxi-1-ciclopropil-1H-quinazolin-2,4-diona;

3-Amino-7-(4-(1-aminoetil)-3,3-difluoropirrolidin-1-il)-8-cloro-1-ciclopropil-6-fluoro-1H-quinazolin-2,4-diona;

3-Amino-7-(4-(1-aminoetil)-3,3-difluoropirrolidin-1-il)-8-metil-1-ciclopropil-6-fluoro-1H-quinazolin-2,4-diona;

3-Amino-7-(4-(1-aminoetil)-3,3-difluoropirrolidin-1-il)-8-metoxi-1-ciclopropil-6-fluoro-1H-quinazolin-2,4-diona;

3-Amino-7-(4-(1-aminoetil)-3,3-difluoropirrolidin-1-il)-8-cloro-1-ciclopropil-1H-quinazolin-2,4-diona;

3-Amino-7-(4-(1-aminoetil)-3,3-difluoropirrolidin-1-il)-8-metil-1-ciclopropil-1H-quinazolin-2,4-diona;

3-Amino-7-(4-(1-aminoetil)-3,3-difluoropirrolidin-1-il)-8-metoxi-1-ciclopropil-1H-quinazolin-2,4-diona;

3-Amino-7-(4-(1-amino-1-metiletil)-3,3-difluoropirrolidin-1-il)-8-cloro-1-ciclopropil-6-fluoro-1H-quinazolin-2,4-diona;

3-Amino-7-(4-(1-amino-1-metiletil)-3,3-difluoropirrolidin-1-il)-8-metil-1-ciclopropil-6-fluoro-1H-quinazolin-2,4-diona;

3-Amino-7-(4-(1-amino-1-metiletil)-3,3-difluoropirrolidin-1-il)-8-metoxi-1-ciclopropil-6-fluoro-1H-quinazolin-2,4-diona;

3-Amino-7-(4-(1-amino-1-metiletil)-3,3-difluoropirrolidin-1-il)-8-cloro-1-ciclopropil-1H-quinazolin-2,4-diona;

3-Amino-7-(4-(1-amino-1-metiletil)-3,3-difluoropirrolidin-1-il)-8-metil-1-ciclopropil-1H-quinazolin-2,4-diona;

3-Amino-7-(4-(1-amino-1-metiletil)-3,3-difluoropirrolidin-1-il)-8-metoxi-1-ciclopropil-1H-quinazolin-2,4-diona;

3-Amino-7-(3-(1-aminoetil)pirrolidin-1-il)-1-ciclopropil-6-fluoro-5,8-dimetil-1H-quinazolin-2,4-diona;

3-Amino-7-(3-(1-aminoetil)pirrolidin-1-il)-1-ciclopropil-5,8-dimetil-1H-quinazolin-2,4-diona;

3-Amino-7-(3-(1-aminoetil)pirrolidin-1-il)-1-ciclopropil-6-fluoro-8-metoxi-5-metil-1H-quinazolin-2,4-diona;

3-Amino-7-(3-(1-aminoetil)pirrolidin-1-il)-1-ciclopropil-8-metoxi-5-metil-1H-quinazolin-2,4-diona;

3,8-Diamino-7-[3-(1-aminoetil)pirrolidin-1-il]-1-ciclopropil-6-fluoro-5-metil-1H-quinazolin-2,4-diona; y

3,8-Diamino-7-[3-(1-aminoetil)pirrolidin-1-il]-1-ciclopropil-5-metil-1H-quinazolin-2,4-diona.

Otra realización de la invención es una composición farmacéutica que comprende un compuesto de la Fórmula I junto con un excipiente, portador, o diluyente. Las composiciones preferidas tienen un compuesto de las Fórmulas II, III, IV, V, VI, o VII diluido con un excipiente, portador o diluyente.

Aún otra realización de la invención es un método para tratar infecciones bacterianas en mamíferos, que comprende administrar una cantidad efectiva antibacteriana de un compuesto de la Fórmula I. Los métodos preferidos comprenden

administrar un compuesto de las Fórmulas II, III, IV, V, VI, o VII.

Otra realización es un método para prevenir o eliminar el crecimiento bacteriano en superficies, que comprende aplicar a la superficie una cantidad efectiva antibacteriana de un compuesto de las Fórmulas I-VII.

DESCRIPCIÓN DETALLADA

Todas las referencias citadas aquí, incluidas las patentes, se incorporan aquí como referencia.

Los términos usados en esta memoria descriptiva y en las reivindicaciones anexas tienen los siguientes significados. El término "halo" significa cloro, bromo, flúor y yodo.

El término "alquilo" significa un radical de hidrocarburo recto o ramificado que tiene de 1 a 12 átomos de carbono e incluye, por ejemplo, metilo, etilo, n-propilo, isopropilo, n-butilo, sec-butilo, isobutilo, terc-butilo, n-pentilo, n-hexilo, n-heptilo, n-octilo, 2-isopropilheptilo, 3-n-butiloctilo, n-nonilo, n-decilo, undecilo, y dodecilo.

Los grupos alquilo preferidos son alquilo de C_1-C_6 tales como metilo, isopropilo, neopentilo, y 1-metilpentilo.

El término "alquenilo de C_2-C_{12}" significa un radical de hidrocarburo recto o ramificado que tiene de 1 a 3 uniones dobles. Los ejemplos incluyen etenilo, 2-propen-1-ilo, 1,3-butadien-1-ilo, 3-hexen-1-ilo, 5-octen-2-ilo, 2-isopropil-3,5-octadien-1-ilo, cis-3-hexen-1-ilo, y trans-2-hepten1-ilo. Los grupos alquenilo preferidos incluyen los alquenilos de C_2-C_6 tales como etenilo, 2-propen-1-ilo, 2-buten-1-ilo, y 3-penten-1-ilo.

El término "alquinilo de C_2-C_{12}" significa un radical de hidrocarburo recto o ramificado que tiene 1 a 3 uniones triples. Los ejemplos incluyen etinilo, propinilo, 3-butin-1-ilo, 4-hexin-1-ilo, 5-octin-3-ilo, 4,6-octadiin-1-ilo, 4-decin-1-ilo y 1,1-dimetil-5-decin-1-ilo. Los grupos alquinilo preferidos son los alquinilos de C_2-C_6 tales como etinilo, propinilo, 3-butin-1-ilo, y 5-hexin-1-ilo.

Los grupos alquilo alquenilo y alquinilo pueden ser sustituidos con 1 a 3 grupos seleccionados de halo, hidroxi, ciano, alcoxi de C_1-C_6, nitro, amino, alquilamino de C_1-C_6, dialquilamino de C_1-C_6, carboxi, alcoxicarbonilo de C_1-C_6, aminocarbonilo, halo, dihalo y trihalometilo, tiol,

alquilsulfanilo, alquilsulfinilo, y aminosulfonilo. Los ejemplos de grupos alquilo sustituido incluyen fluorometilo, tribromometilo, hidroximetilo, 3-metoxipropilo, 3-carboxipentilo, 3,5-dibromo-6-aminocarbonildecilo, y 4-etilsulfiniloctilo. Los ejemplos de grupos alquenilo sustituido incluyen 2-bromoetenilo, 1-amino-2-propen-1-ilo, 3-hiroxipent-2-en-1-ilo, 4-metoxicarbonil-hex-2-en-1-ilo, y 2-nitro-3-bromo-4-yodo-oct-5-en-1-ilo. Grupos alquinilo sustituido típicos incluyen 2-hidroxietinilo, 3-dimetilamino-hex-5-in-1-ilo, y 2-ciano-hept-3-in-1-ilo.

El término "cicloalquilo" significa un anillo de hidrocarburo que contiene de 3 a 12 átomos de carbono, por ejemplo, ciclopropilo, ciclobutilo, ciclopentilo, ciclohexilo, decalinilo, norpinanilo, y adamantilo. Cuando es posible, el grupo cicloalquilo puede contener uniones dobles, por ejemplo, 3-ciclohexen-1-ilo. El anillo de cicloalquilo puede ser no sustituido o sustituido por 1 a 3 sustituyentes seleccionados de alquilo, alcoxi, tioalcoxi, hyidroxi, tiol, nitro, halógeno, amino, alquil y dialquilamino, formilo, carboxilo, CN, -NH-CO-R', -CO-NHR', $-CO_2R'$, -COR', arilo o heteroarilo, en donde alquilo, arilo y heteroarilo son lo definido anteriormente. Los ejemplos de grupos cicloalquilo sustituido incluyen fluorociclopropilo, 2-yodociclobutilo, 2,3-

dimetilciclopentilo, 2,2-dimetoxiciclohexilo, y 3-fenilciclopentilo.

El término "heterocíclico" significa un sistema de anillo cíclico o bicíclico fusionado o policíclico que tiene de 3 a 12 átomos del anillo, donde 1 a 5 son heteroátomos seleccionados de N, O y S. Los grupos heterocíclicos pueden ser sustituidos con 1 a 3 de los sustituyentes enumerados anteriormente para los grupos cicloalquilo. Los ejemplos de grupos heterocíclicos incluyen éteres cíclicos (oxiranos) tales como óxido de etileno, tetrahidrofurano, dioxano, y éteres cíclicos sustituidos, en donde los sustituyentes son aquellos descriptos anteriormente para los grupos alquilo y cicloalquilo. Los éteres cíclicos sustituidos típicos incluyen óxido de propileno, feniloxirano (óxido de estireno), cis-2-buten-óxido (2,3-dimetiloxirano), 3-clorotetrahidrofurano, 2,6-dimetil-1,4-dioxano, y similares. Los heterociclos que contienen nitrógeno son grupos tales como pirrolidina, piperidina, piperazina, tetrahidrotriazina, tetrahidropirazol, y grupos sustituidos tales como 3-aminopirrolidina, 4-metilpiperazin-1-ilo, y similares. Los heterociclos que contienen azufre típicos incluyen tetrahidrotiofeno, dihidro-1,3-tiol-2-ilo, y hexahidrotiofen-4-ilo. Otros heterociclos empleados comúnmente incluyen dihidro-oxatiol-4-ilo, tetrahidro-oxazolilo, tetrahidro-oxadiazolilo, tertrahidro-

dioxazolilo, tetrahidro-oxatiazolilo, hexahidrotriazinilo, tetrahidro-oxazinilo, morfolinilo, tiomorfolinilo, tetrahidropirimidinilo, dioxolinilo, octahidrobenzofuranilo, octahidrobencimidazolilo, y octahidrobenzotiazolilo. Para los heterociclos que contienen azufre, los heterociclos con azufre oxidado que contienen grupos SO o SO_2 también están incluidos. Los ejemplos incluyen las formas de sulfóxido y sulfona del tetrahidrotiofeno.

El término "arilo" significa un anillo aromático cíclico o policíclico que tiene de 5 a 12 átomos de carbono, y que es no sustituido o sustituido con hasta 3 de los grupos sustituyentes citados anteriormente para alquilo, alquenilo y alquinilo. Los ejemplos de grupos arilo incluyen fenilo, 2,6-diclorofenilo, 3-metoxifenilo, naftilo, 4-tionaftilo, tetralinilo, antracinilo, fenantrenilo, benzonaftenilo, fluorenilo, 2-acetamidofluoren-9-ilo, y 4'-bromobifenilo.

El término "heteroarilo" significa un sistema de anillo cíclico o policíclico aromático que tiene de 1 a 4 heteroátomos seleccionados de N, O y S. Los grupos heteroarilo típicos incluyen 2- o 3-tienilo, 2- o 3-furanilo, 2- o 3-pirrolilo, 2-, 4-, o 5-imidazolilo, 3-, 4- o 5-pirazolilo, 2-, 4- o 5-tiazolilo, 3-, 4- o 5-isotiazolilo, 2-, 4- o 5-oxazolilo, 3-, 4- o 5-isoxazolilo, 3- o 5-1,2,4-triazolilo, 4- o 5-1,2,3-triazolilo, tetrazolilo, 2-, 3- o 4-piridinilo, 3-, 4- o 5-piridazinilo, 2-pirazinilo, 2-, 4- o 5-pirimidinilo,

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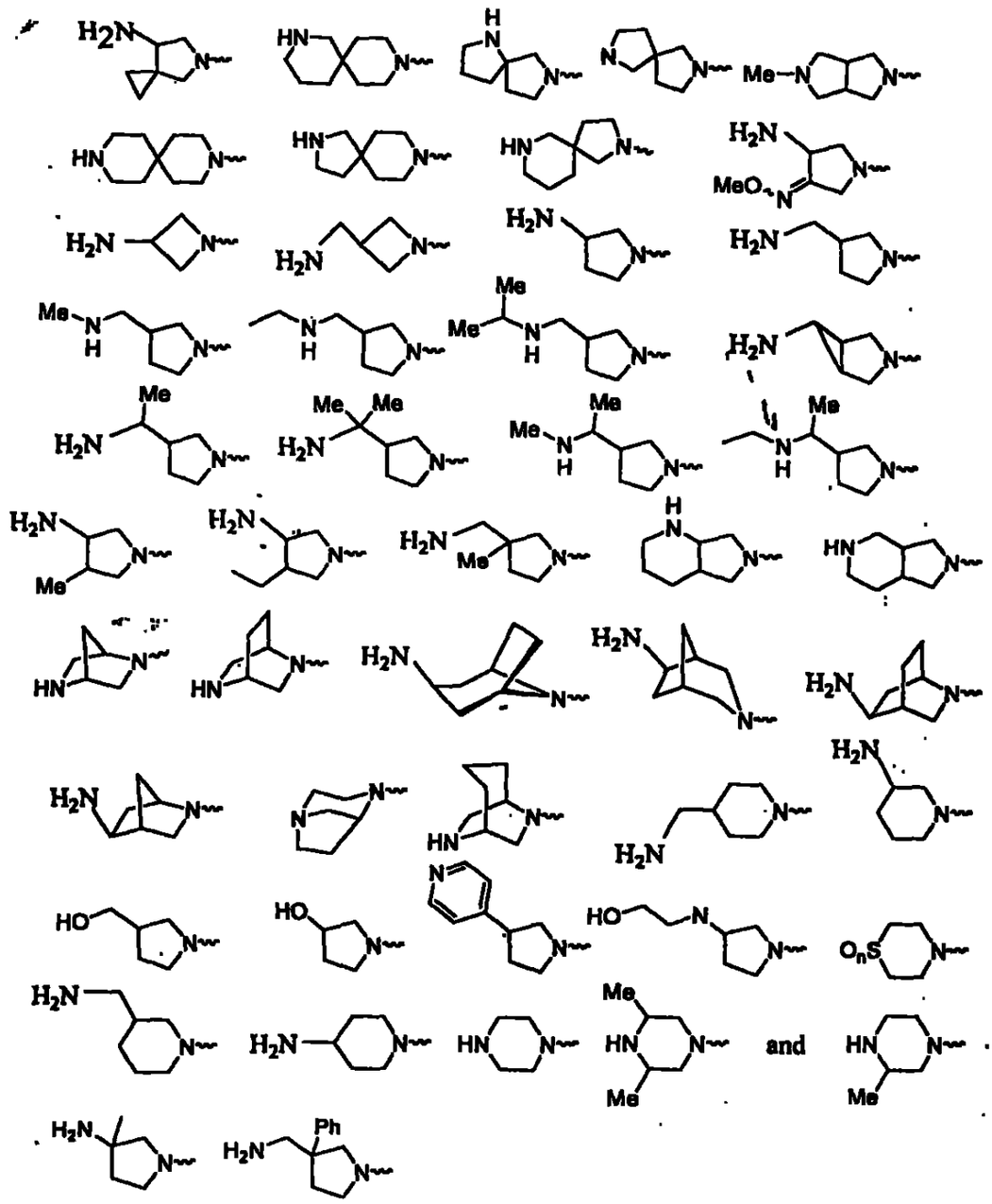
2-, 3-, 4-, 5-, 6-, 7-, u 8-quinolinilo, 1-, 3-, 4-, 5-, 6-, 7- u 8-isoquinolinilo, 2-, 3-, 4-, 5-, 6-, o 7-indolilo, 2-, 3-, 4-, 5-, 6-, o 7-benzo[b]tienilo, 2-, 4-, 5-, 6-, o 7-benzoxazolilo, 2-, 4-, 5-, 6-, o 7-bencimidazolilo, 2-, 4-, 5-, 6-, o 7-benzotiazolilo. Los grupos heteroarilo pueden ser no sustituidos o sustituidos por 1 a 3 sustituyentes seleccionados de aquellos descriptos anteriormente para alquilo, alquenilo, y alquinilo, por ejemplo, cianotienilo y formilpirrolilo.

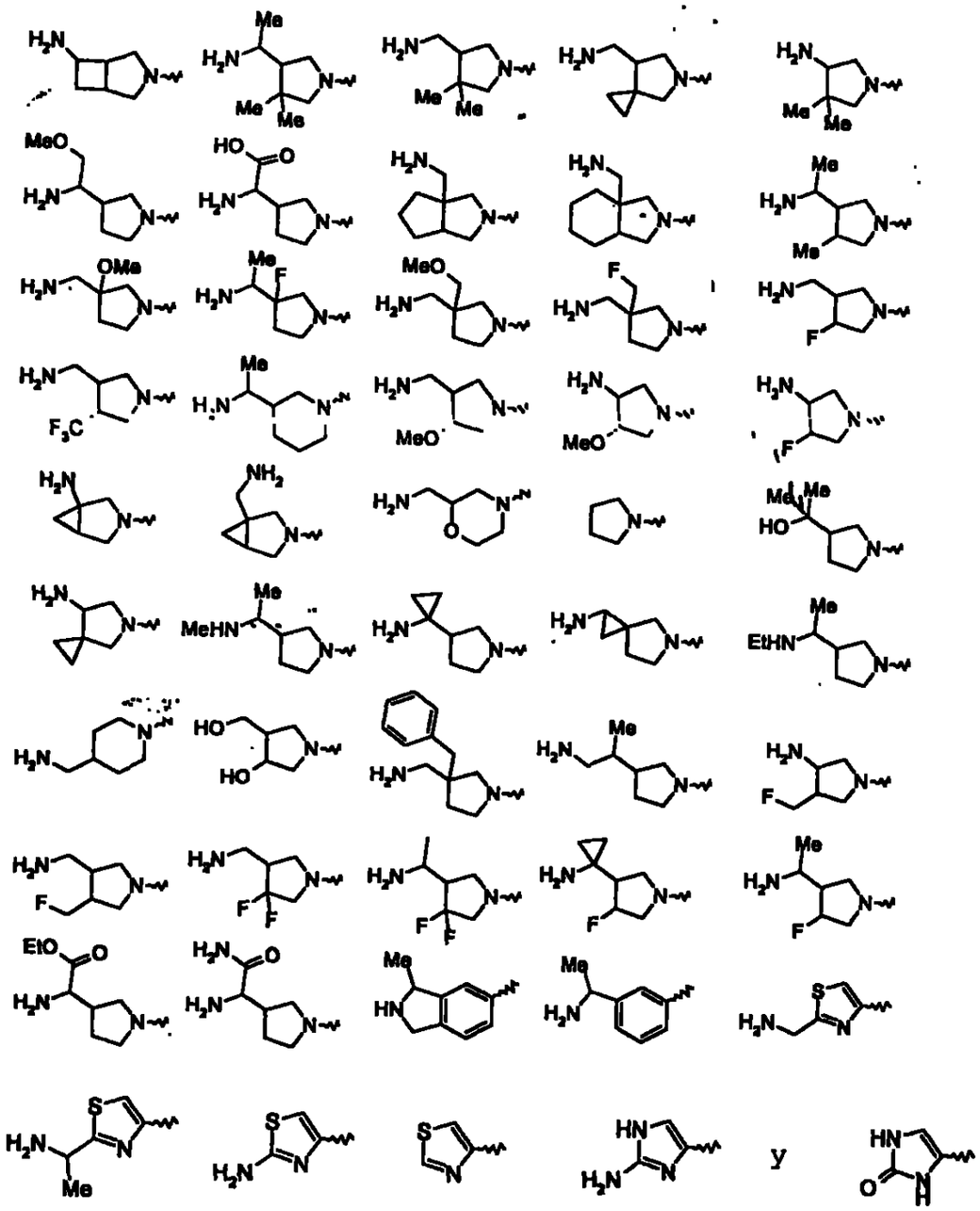
Los anillos heterocíclicos fusionados aromáticos preferidos de 8 a 10 átomos incluyen en forma no taxativa 2-, 3-, 4-, 5-, 6-, 7- u 8-quinolinilo, 1-, 3-, 4-, 5-, 6-, 7- u 8-isoquinolinilo, 2-, 3-, 4-, 5-, 6- o 7-indolilo, 2-, 3-, 4-, 5-, 6-, o 7-benzo[b]tienilo, 2-, 4-, 5-, 6- o 7-benzoxazolilo, 2-, 4-, 5-, 6- o 7-bencimidazolilo, 2-, 4-, 5-, 6- o 7-benzotiazolilo.

Los compuestos preferidos de la invención tienen la Fórmula I en donde R_7 es un grupo heterocíclico o heteroarilo tal como aquellos descriptos anteriormente. Tales grupos heterocíclicos o heteroarilo son denominados aquí genéricamente como "  ".

Otros ejemplos de heterociclos, heterociclos fusionados y grupos heteroarilo típicos que son preferidos como sustituyentes de R_7 se enumeran a continuación en la Tabla A.

Tabla A





Los grupos precedentes son especialmente preferidos como cadenas laterales de R_7 en el sistema de anillo de quinazolina. Los heterociclos y grupos heteroarilo tales como aquellos

representados anteriormente son conocidos en el arte de las quinolinas y son preferidos por los métodos de la bibliografía tales como *J. Med. Chem.*, 1992;35:1764; *J. Med. Chem.*, 1996;39:3070; *Synlett.*, 1996:1097; y *J. Med. Chem.*, 1986;29:445. Cualquiera de las aminas primarias o secundarias mostrada como sustituyentes en los grupos heteroarilo o heterocíclico pueden ser sustituidas por alquilo, tal como metilo, etilo, isopropilo y similares.

Algunos de los compuestos de la Fórmula I son capaces de formar sales de adición ácidas y/o básicas farmacéuticamente aceptables. La totalidad de estas formas están dentro del alcance de la presente invención y se preparan mediante métodos reconocidos del arte. Por ejemplo, una sal de adición ácida se prepara poniendo a la forma de base libre del compuesto de la invención en contacto con una cantidad suficiente del ácido deseado para producir la sal en la forma convencional. Las sales de adición ácidas farmacéuticamente aceptables de los compuestos de la Fórmula I incluyen sales derivadas de ácidos inorgánicos tales como ácido clorhídrico, nítrico, fosfórico, sulfúrico, bromhídrico, yodhídrico, fluorhídrico, fosforoso, y similares, así como las sales derivadas de ácidos orgánicos, tales como ácidos mono y dicarboxílicos alifáticos, ácidos alcanoicos fenil-sustituidos, ácidos hidroxi alcanoicos, ácidos alcanodioicos,

ácidos aromáticos, ácidos sulfónicos alifáticos y aromáticos, etc. Tales sales incluyen entonces sulfato, pirosulfato, bisulfato, sulfito, bisulfito, nitrato, fosfato, monohidrogenfosfato, dihidrogenfosfato, metafosfato, pirofosfato, acetato, trifluoroacetato, propionato, caprilato, isobutirato, oxalato, malonato, succinato, suberato, sebacato, fumarato, maleato, mandelato, benzoato, clorobenzoato, metilbenzoato, dinitrobenzoato, ftalato, bencensulfonato, toluensulfonato, fenilacetato, citrato, lactato, tartrato, metanosulfonato, y similares. También están contempladas las sales de aminoácidos tales como arginato y similares, así como gluconato y galacturonato. Todas estas sales se preparan fácilmente, por ejemplo, como lo describe Berge S.M. et al, "Sales Farmacéutica", *Journal of Pharmaceutical Science,* 1977;66:1-19.

Las sales de adición básicas farmacéuticamente aceptables se forman con metales o aminas, tales como metales alcalinos o alcalinotérreos o aminas orgánicas, cuando los compuestos de la Fórmula I tienen un grupo ácido tal como carboxi. Las sales de adición básicas de compuestos de la invención ácidos se preparan poniendo en contacto a la forma de ácido libre con una cantidad suficiente de la base deseada para producir la sal en la forma convencional. Las base tipicas incluyen hidróxido de sodio, óxido de calcio, dietilamina, piridina.

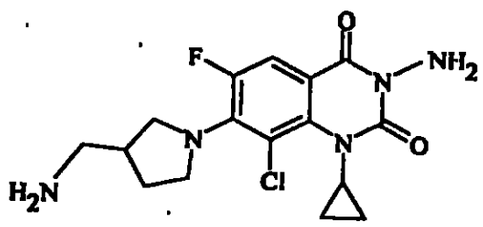
Los ejemplos de metales usados como cationes son sodio, potasio, magnesio, calcio y similares. Los ejemplos de aminas adecuadas son N,N'-dibenciletilendiamina, cloroprocaína, colina, dietanoamina, diciclohexilamina, etilendiamina, N-metilglucamina, y procaína (ver, por ejemplo, Berge S.M., arriba, 1977).

Ciertos compuestos de la presente invención pueden existir en formas no solvatadas así como formas solvatadas, que incluyen las formas hidratradas. En general, las formas solvatadas, que incluyen las formas hidratadas, son equivalentes a las formas no solvatadas y están contempladas dentro del alcance de la presente invención.

Ciertos compuestos de la presente invención poseen uno o más centros quirales. Cada centro puede existir en la configuración R o S. La presente invención incluye todas las formas diasteroméricas, enantioméricas y epiméricas, así como las mezclas apropiadas de ellas. Además, los compuestos de la presente invención pueden existir como isómeros geométricos. La presente invención incluye todos los cis, trans, sin, anti, entgegen (E) y zusammen (Z) isómeros, así como las mezclas de ellos.

Las estructuras de compuestos representativos de la invención se muestran en la Tabla 1:

TABLA 1



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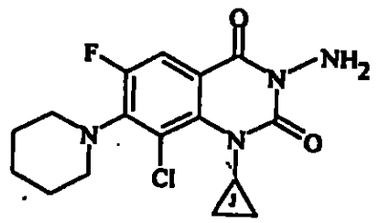

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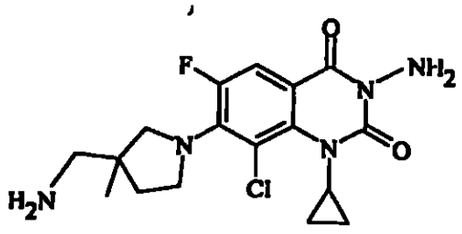

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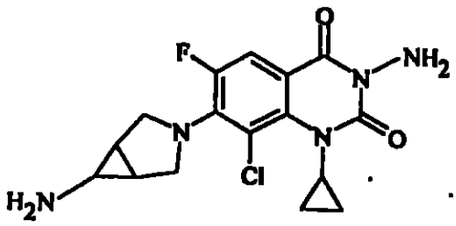

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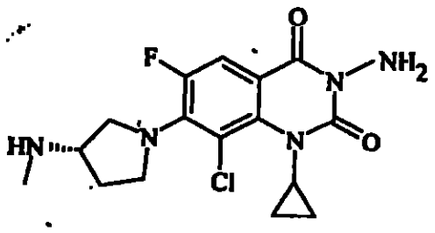

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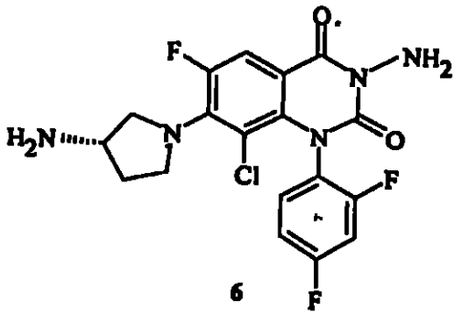

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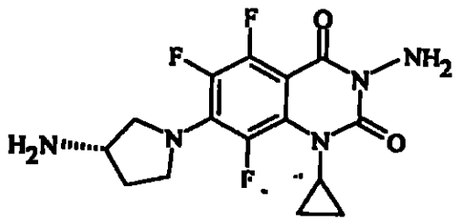

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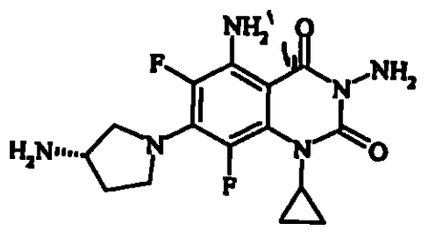

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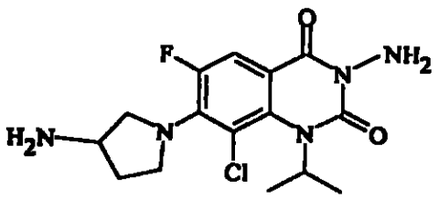

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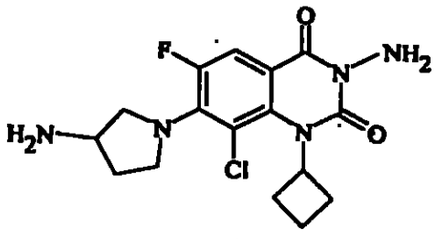

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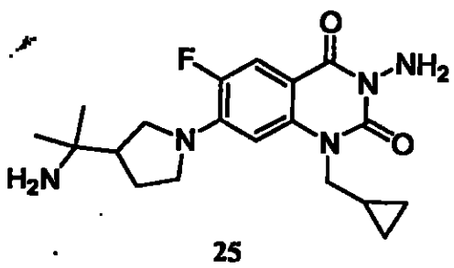

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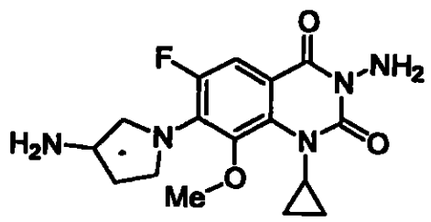

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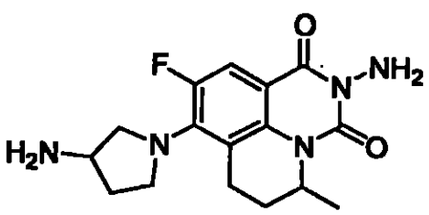

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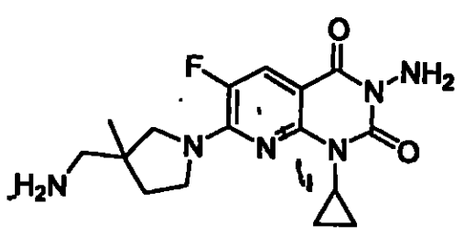

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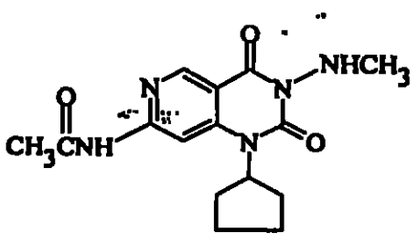

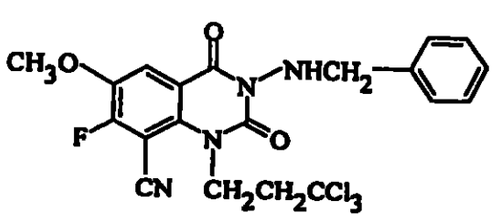

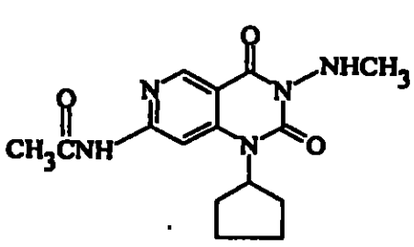

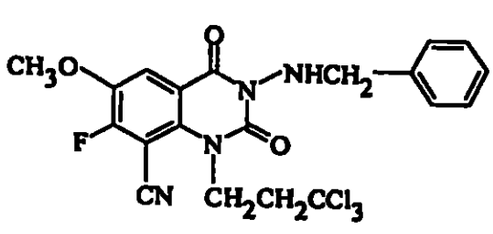

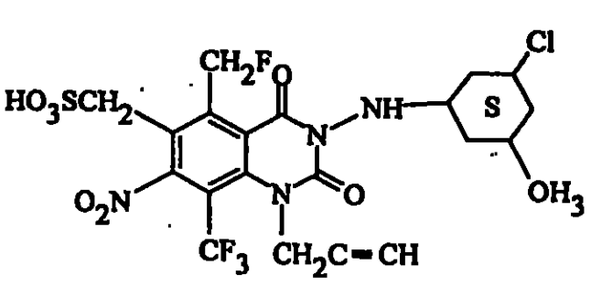

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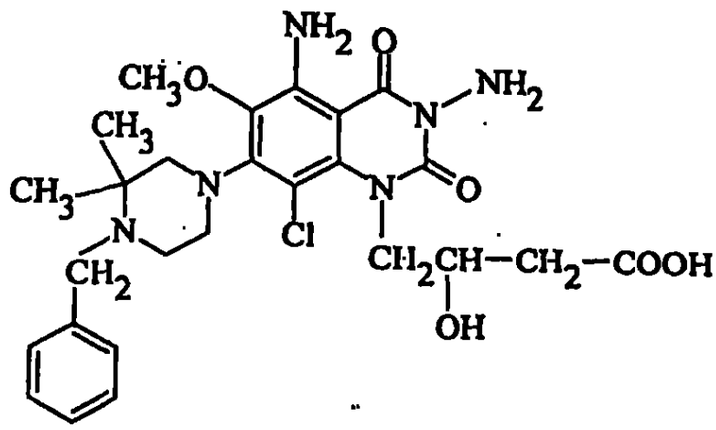


Los compuestos de la Fórmula I pueden prepararse utilizando una metodología de síntesis estándar conocida para los expertos en el arte de la química orgánica. Muchos de los compuestos tienen grupos funcionales reactivos que generalmente es necesario derivar con un grupo protector para impedir reacciones colaterales no deseadas. Por ejemplo, los grupos funcionales tales como alcoholes, grupos ácidos y aminas generalmente son protegidos mientras se realiza una reacción en un sitio diferente de la molécula, y luego el grupo protector es removido siguiendo la transformación química deseada. El uso de tales grupos protectores es estándar en la síntesis de la química orgánica, como se describe, por ejemplo en T.W. Green y P.G. Wuts, *Grupos Protectores en la Síntesis Orgánica*, 2ª edición, Ciudad de Nueva York: John Wiley & Sons, 1991. Por lo tanto, por

ejemplo, los grupos protectores tales como los siguientes pueden ser utilizados para proteger grupos amino, hidroxilo y otros grupos adecuados de reactividad relacionada: grupos acilo carboxílico, tales como formilo, acetilo, trifluoroacetilo; grupos alcoxicarbonilo, tales como etoxicarbonilo, t-butoxicarbonilo (BOC), β,β,β-tricloroetoxicarbonilo (TCEC), β-yodoetoxicarbonilo; grupos ariloxicarbonilo, tales como benciloxicarbonilo, p-metoxibenciloxicarbonilo, fenoxicarbonilo; grupos trialquil sililo, tales como trimetilsililo y t-butildimetilsililo (TBDMS); y grupos tales como tritilo, tetrahidropiranilo, viniloxicarbonilo, o-nitrofenilsulfenilo, difenilfosfinilo, p-toluensulfonilo, y bencilo pueden todos ser utilizados. El grupo protector puede ser removido, después de la finalización de la reacción sintética en cuestión, mediante procedimientos conocidos para los expertos en el arte. Por ejemplo, un grupo BOC puede ser removido mediante acidólisis, un grupo tritilo mediante acidólisis o hidrogenólisis, TBDMS mediante el tratamiento con iones de fluoruro, y TCEC mediante el tratamiento con zinc.

Las ilustraciones de preparaciones típicas de compuestos de la presente invención que tienen la Fórmula I se muestran en los Esquemas 1-22. Las cadenas laterales heterocíclicas y

aromáticas típicas definidas por R_7 en la Fórmula I se preparan como se describe en los Esquemas A1-A8. La totalidad de las 3-aminoquinazolin-2,4-dionas de la invención pueden prepararse a partir de materiales iniciales de ácido benzoico sustituido apropiadamente. Los grupos protectores (citados en los esquemas como "Pro") pueden usarse cuando sea apropiado en muchos de los esquemas. Aunque se indica específicamente en ciertos esquemas, el uso y elección apropiada de grupos protectores es conocido por los expertos en el arte, y no se limita a las ilustraciones específicas que se muestran a continuación. También se debe entender que tales grupos protectores no solamente sirven para proteger químicamente los sitios reactivos, sino que también mejoran la solubilidad o cambian de otro modo las propiedades físicas del compuesto de la invención subyacente. Numerosas reacciones tales como las oxidaciones y reducciones no se muestran en detalle en los esquemas pero pueden realizarse mediante métodos estándar conocidos para los expertos en el arte. En general, los materiales iniciales usados en los siguientes esquemas se obtienen de fuentes comerciales, o se preparan fácilmente mediante métodos estándar. Todos los artículos publicados, patentes, libros y similares citados se incorporan aquí como referencia.

Como se muestra en el Esquema 1, un ácido benzoico difluoro sustituido reacciona con cloruro de oxalilo o un reactivo acilante equivalente (tal como un anhídrido de ácido), y el haluro o anhídrido de ácido reacciona con un alcohol (ZOH) para dar el éster respectivo (Z es un alquilo de C_1-C_6 tal como metilo, etilo, isopropilo, etc.). El éster reacciona con una amina, por ejemplo, una amina heterocíclica, para producir el derivado fenilo 4-heterocíclico deseado. Alternativamente, también se pueden introducir carbociclos y arilos en esta posición 4 usando acoplamientos catalizados con paladio de carbociclos de estaño o boronato y arilos, con materiales iniciales que contienen Br, I o triflato en la posición 4 como se describe en Suzuki A., *Pure Appl. Chem.*, 1994;66(2):213-222 y Stille J.K., *Angew. Chem.*, 1986;98(6):504-519.

La reacción del ácido 2-fluoro benzoico con una amina primaria R_1NH_2 da el éster del ácido 2-amino benzoico correspondiente. El grupo éster se hidroliza rápidamente mediante la reacción con un ácido tal como ácido clorhídrico o una base tal como hidróxido de sodio para dar el ácido 2-amino benzoico polisustituido correspondiente. El ácido luego se acopla a una hidrazina protegida apropiadamente para proporcionar la amida correspondiente, que a su vez es ciclizada para generar la quinazolin-2,4-diona mediante el tratamiento con, por ejemplo, fosgeno. En este punto, el grupo protector puede ser removido

para dar la amina libre **A** de la Fórmula I, que puede representar un producto final de la invención, y que puede ser derivado, si desea, por ejemplo, mediante alquilación con R_3Cl.

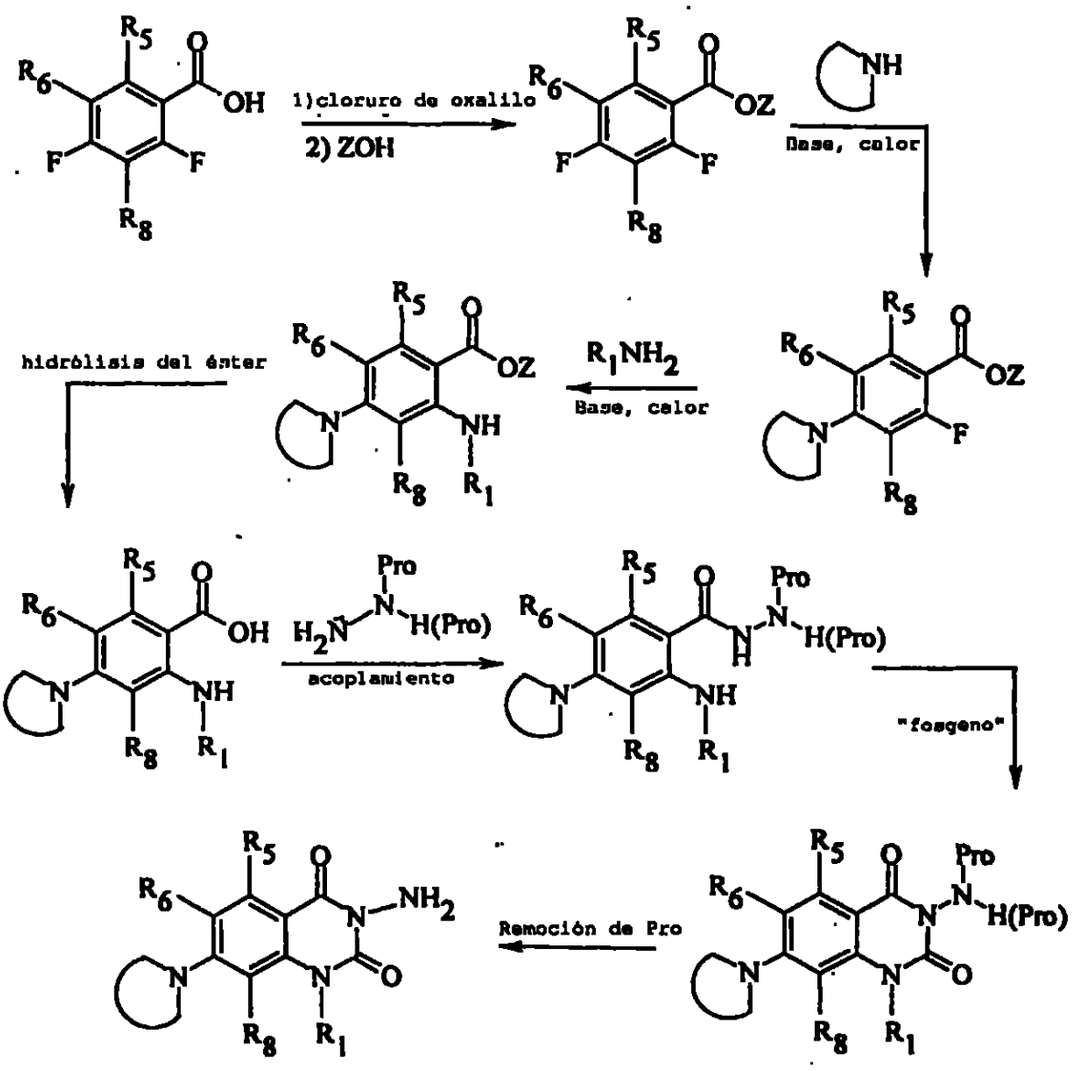
Alternativamente, la quinazolin-2,4-diona también puede ser metalizada a bajas temperaturas con bases tales como, por ejemplo, NaH, KH, y diisopropilamina de litio, y luego ser alquilada o acilada para proporcionar la amina N-protegida-mono-sustituida (R_3) correspondiente. El grupo protector (Pro) de la amina N-protegida-mono-sustituida es removido mediante métodos convencionales tales como hidrogenación, tratamiento con un ácido o base, o catálisis con un metal para dar el compuesto **C** de la invención.

Si R_5 es un grupo saliente tal como F, se activa hacia el desplazamiento con un nucleófilo HY-Pro' donde Y es N u O y Pro' es un grupo protector tal como trimetilsililo. Otros grupos de R_5 tales como cloro, bromo, o sulfonilo son también grupos salientes buenos. El desplazamiento generalmente se realiza en un solvente tal como etanol, DMSO, DMF, THF, y a una temperatura de 0°C a 120°C.

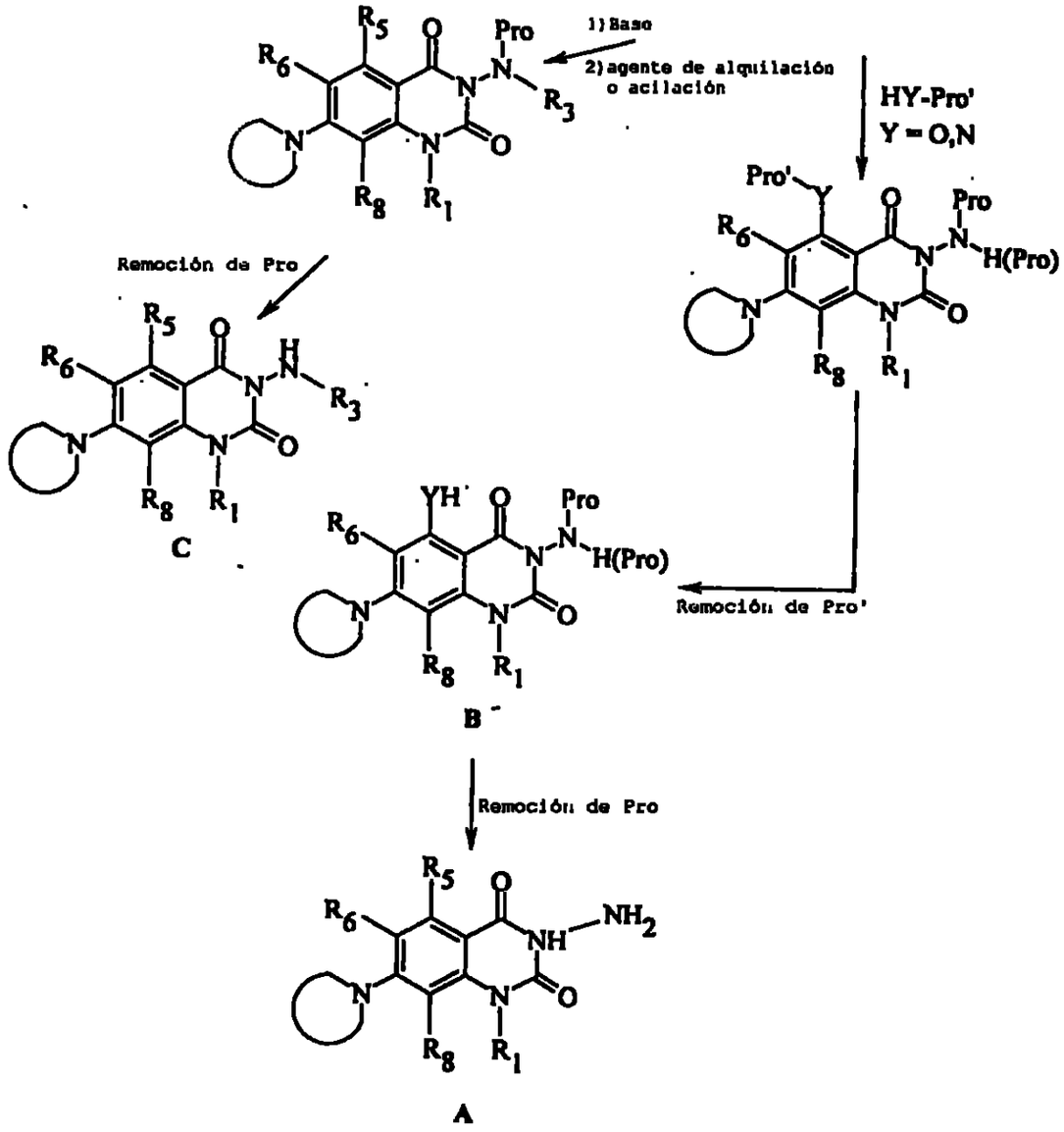
Los grupos protectores (Pro) pueden ser removidos selectivamente mediante hidrogenación, tratamiento con un ácido o base, catálisis con un metal, u otros de tales métodos

estándar. Cuando Pro es bencilo, el bencilo puede ser removido con Pd/C e hidrógeno. Un grupo carbamato de t-butilo puede ser removido por HCl alcohólico, TFA, o TFA en diclorometano, acetato de etilo o éter dietílico. Los carbamatos alílicos pueden ser removidos por $PhSiH_3$ y catalizador de Pd. Los solventes tales como alcohol, THF, alcohol/THF, alcohol/THF/DMF, éter dietílico, etc., generalmente se emplean en tales reacciones de rotura del grupo protector.

Esquema 1


1)cloruro de oxalilo
2) ZOH
Base, calor
hidrólisis del éster
R_1NH_2
Base, calor
acoplamiento
"fosgeno"
Remoción de Pro
A

Esquema 1 (cont.)



En el Esquema 2, se utiliza un ácido *orto*-aminobenzoico como el material inicial, y se alquila sobre el grupo amino. Por ejemplo, cuando R_1 es ciclopropilo, la alquilación se realiza de acuerdo con el método de Gillaspy (*Tetrahedron Letters*, 1995:7399) para proporcionar la ciclopropil amina. Cuando R_1 es

fenilo o fenilo sustituido, la amina respectiva se prepara desde el ácido *orto*-fluorobenzoico usando una base, tal como diisopropilamida de litio o Li-hexametil disilazida, y la aril amina apropiada (R_1NH_2). Cuando R_1 es un grupo alquilo, tal como t-butilo o isopropilo, el R_1 puede ser introducido mediante la reacción de la amina y el ácido orto halo benzoico con un catalizador de Cu tal como cobre, bronce o acetato cúprico en la presencia de una base tal como acetato de potasio, trietilamina o piridina.

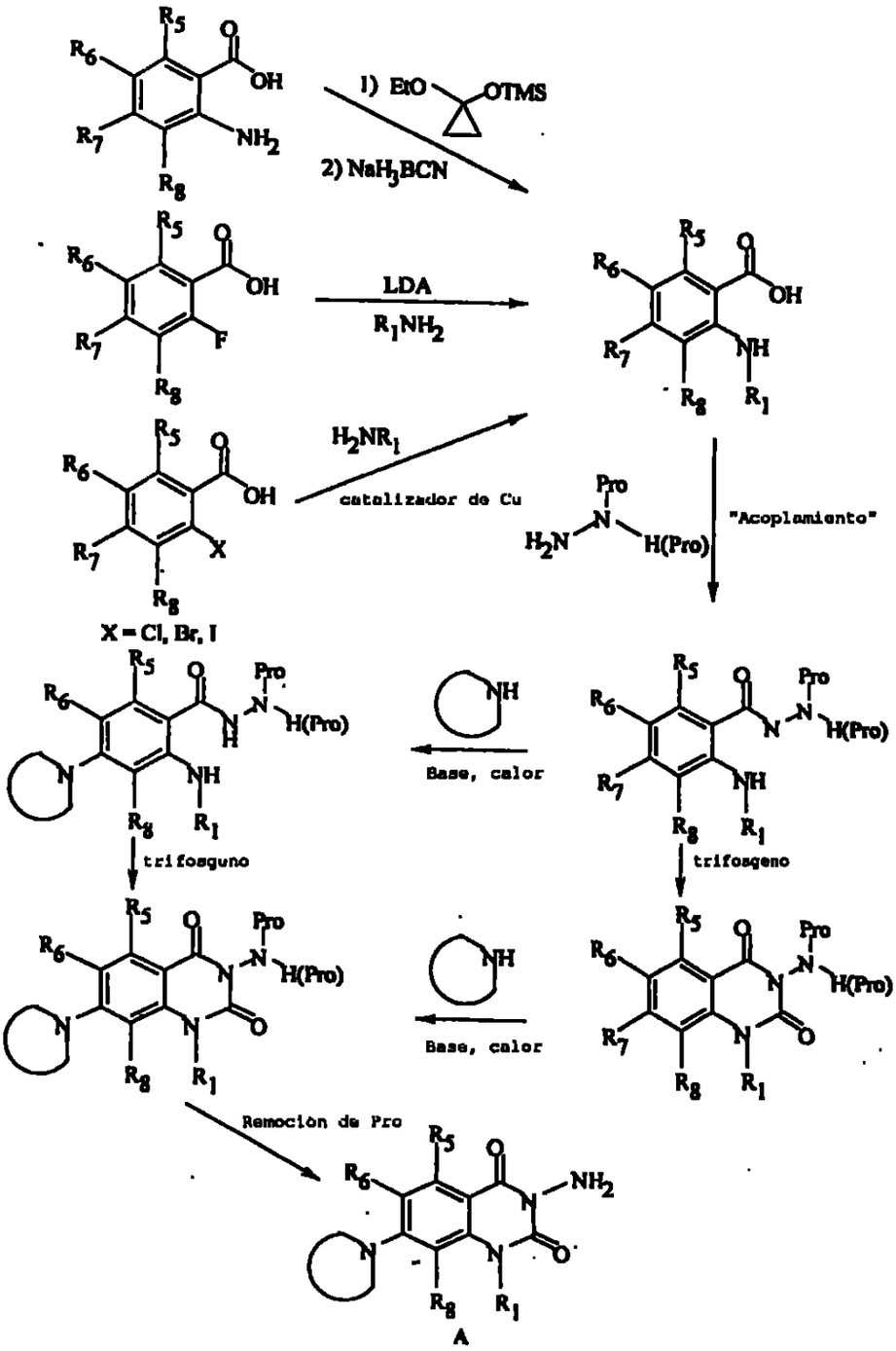
El ácido amino benzoico R_1-sustituido luego se acopla a una hidrazina protegida apropiadamente para proporcionar la benzamida correspondiente usando métodos descriptos en la bibliografía. La amida correspondiente puede reaccionar además, si R_7 es un grupo saliente tal como flúor, con diversas aminas heterocíclicas (ej. piperidina o pirrolidina) para formar el derivado benzamida 4-heterocíclica deseado. Alternativamente, también se pueden introducir carbociclos y arilos (ej., ciclobutilo o fenilo) en esta posición 4 usando acoplamientos catalizados con paladio de carbociclos de estaño y arilos, si el material inicial contiene un Br, I o triflato en la posición 4.

El derivado benzamida 4-sustituido luego es ciclizado para generar la quinazolin-2,4-diona mediante la reacción con

carbonildiimidazol (CDI), fosgeno, trifosgeno o similar en solventes etéreos tales como éter dietílico, hidrocarburos clorados tales como diclorometano, o hidrocarburos aromáticos tales como tolueno, en la presencia de una base tal como trietilamina o $NaHCO_3$.

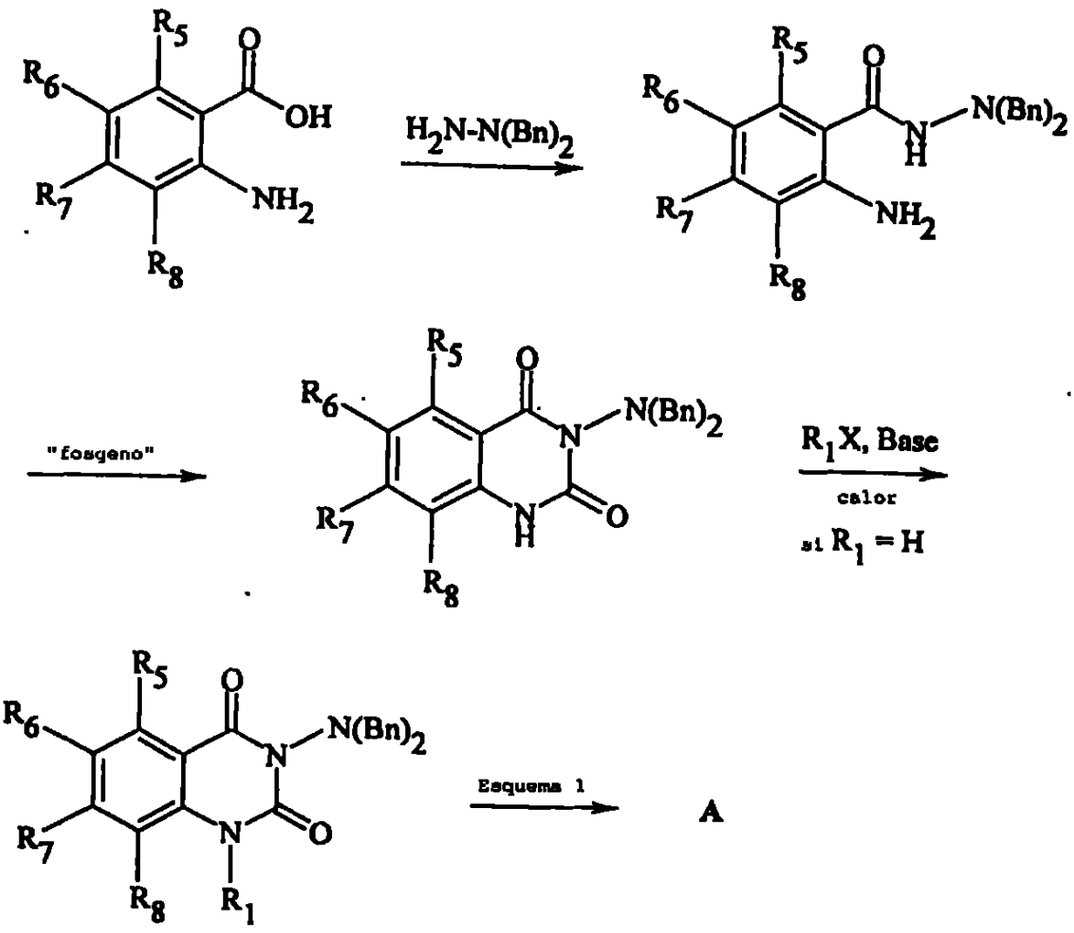
Alternativamente, la amida correspondiente primero es ciclizada y luego el grupo halo de R_7 es desplazado mediante la reacción con una amina carbocíclica  para dar el mismo producto. La desprotección mediante métodos convencionales proporciona el compuesto **A** de la invención.

Esquema 2


1) EtO OTMS
2) NaH3BCN
LDA
R1NH2
H2NR1
catalizador de Cu
"Acoplamiento"
X = Cl, Br, I
Base, calor
Base, calor
trifosguno
trifosgeno
Remoción de Pro
A

El Esquema 3 ilustra la alquilación en la posición 1 de una 3-aminoquinazolin-2,4-diona para proporcionar compuestos de la invención en donde R_1 es alquilo. Un ácido 2-aminobenzoico reacciona con una hidrazina N,N-diprotegida tal como dibencil hidrazina (H_2N-NBr_2) para proporcionar la amida N-protegida correspondiente. El intermedio puede entonces reaccionar con fosgeno o fosgeno/base en un solvente etéreo, o con un equivalente de fosgeno tal como trifosgeno en un hidrocarburo clorado tal como diclorometano, para dar la quinazolin-2,4-diona. La alquilación de la quinazolin-2,4-diona para proporcionar una quinolin-2,4-diona 1-alquilada se logra mediante la reacción con un haluro de alquilo como lo describe Bouzard, arriba, 1990. Típicamente, tales reacciones se realizan en THF, éter, DMSO, un alcanol, o DMF, y en la presencia de una base. Los haluros de alquilo típicos (R_1X donde X es halo) incluyen yoduro de etilo, bromuro de etilo, yoduro de ciclopropilo, bromuro de n-decilo, y similares. Las bases típicas incluyen hidruro de sodio, carbonato de potasio, y similares. La conversión de la quinazolin-2,4-diona 1-alquilada a otros compuestos de la invención (y la remoción de los grupos protectores tales como bencilo Bn) puede realizarse de acuerdo con el Esquema 1, por ejemplo, para dar los compuestos 1-alquil (R_1 = alquilo) 3-amino (NH_2) tales como **A**.

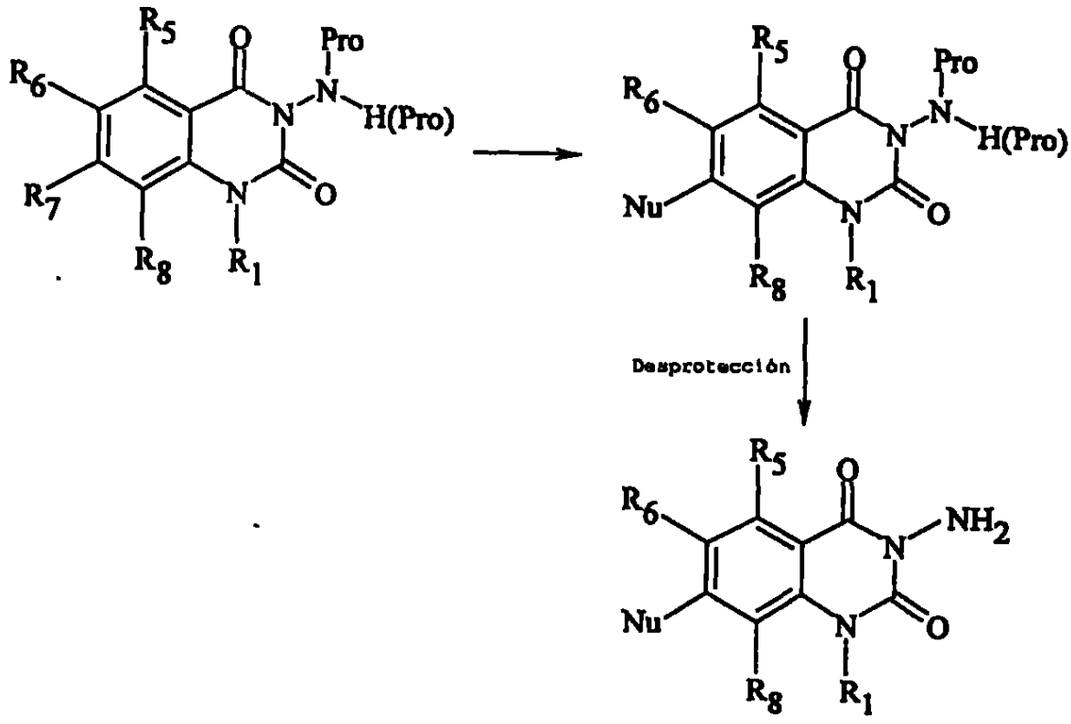
Esquema 3



El desplazamiento de los grupos salientes ubicados en la posición 7 de la quinazolina (ej, R_7 = halo) mostrado en los Esquemas 1 y 2 no se limita a heterociclos de nitrógeno. Otros nucleófilos (Nu) tales como CH_3O-, N_3-, R'R"NH, R'-NH_2, y R'S- (donde R' y R" son lo definido anteriormente) también desplazan un grupo saliente tal como F, Cl o NO_2 en la posición 7 como se muestra en el Esquema 4. Cuando el grupo saliente es

un triflato o un haluro superior, se pueden usar reactivos de organo estaño u organoboronatos con catalizadores de paladio para suministrar un nucleófilo de carbono. La metodología mostrada en el Esquema 4 sigue aquella de Stille et al, *Angew. Chem. Int. Ed. Eng.*, 1986;25:508 y es ejemplificadapor Mitchell (*Synthesis*, 1992:803).

Esquema 4



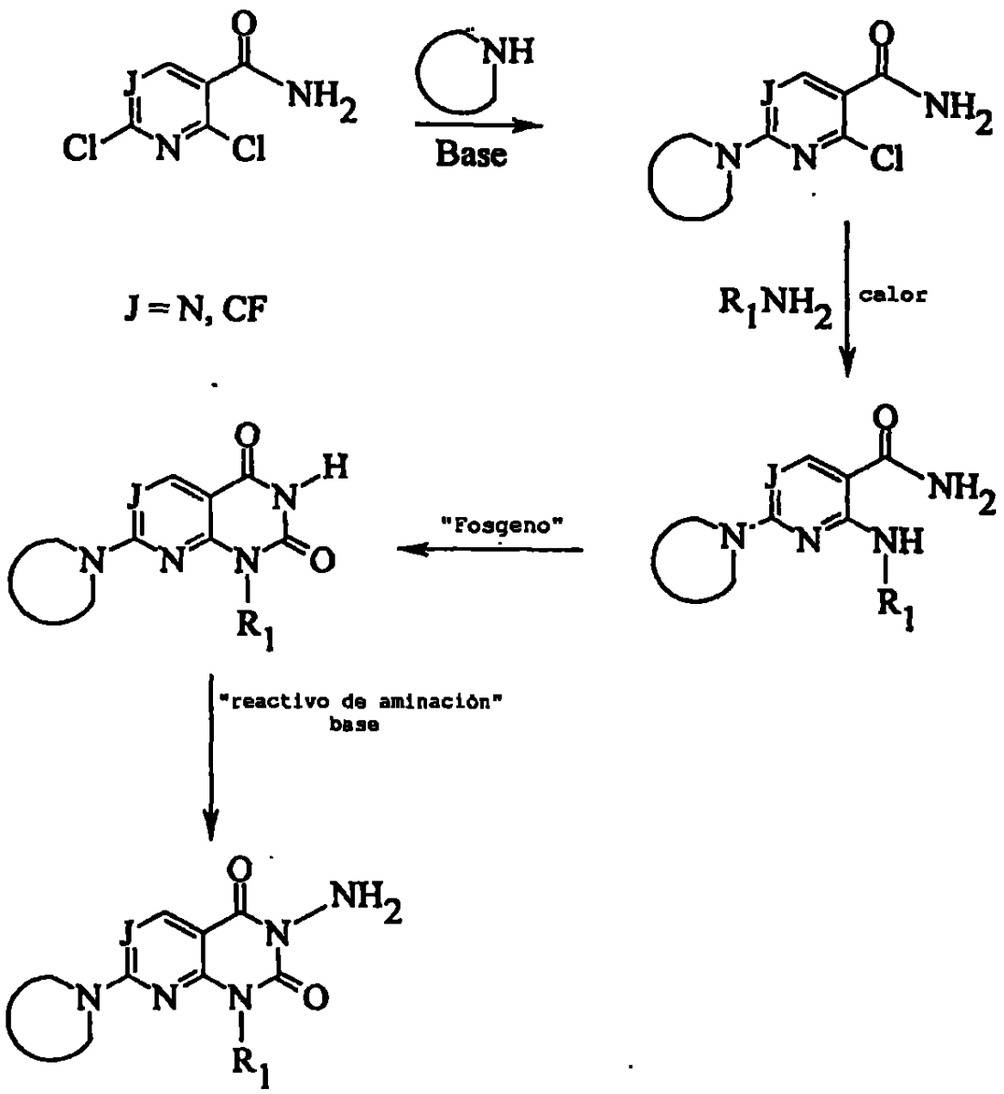
La totalidad de la química representada y descripta en los Esquemas 1 a 4 es aplicable para fabricar compuestos de la Fórmula I en donde J y K son ambos carbono, o donde uno o ambos J y K son N. Cuando J o K es nitrógeno, las reacciones de desplazamiento descriptas anteriormente son aún más fáciles que cuando J y K son carbono.

Los compuestos de a invención donde J y/o K de la Fórmula I son nitrógeno pueden prepararse mediante los Esquemas 1, 2, 3 y 4, o mediante vías que aprovechan la activación de los

grupos *orto* y *para* hacia el átomo de nitrógeno de J y/o K. Tales vías introducen sistemáticamente los grupos de R_7 y R_8 que se desee. Esta metodología también se aplica a los casos en la Fórmula I en que K-R_8 es C-H o C-F y J-R_6 es C-F. Tales sustituciones sistemáticas se ilustran en el Esquema 5. Por ejemplo, una piridin amida tiene grupos salientes tales cmo halo a ambos lados del nitrógeno. Tales grupos generalmente son cloro, pero flúor, alquiltiol, y sulfóxidos tales como los sulfóxidos de metilo son también buenos grupos salientes para tales compuestos. Estos grupos salientes pueden ser desplazados en secuencia en base a la reactividad. En el Esquema 5, donde J = N o J-R_6 = CF, el 4-cloro (*para* con respecto al grupo aminocarbonilo) es desplazado en forma preferencial (con respecto al grupo 2-cloro) usando una amina nucleófila tal como dietilamina, pirrolidina, metilpiperazina, y similares para dar el análogo amino sustituido correspondiente. Este análogo luego reacciona con R_1NH_2 para desplazar el segundo grupo saliente (ej, el grupo 2-cloro). La piridilamida 2,6-disustituida reacciona luego con CDI, fosgeno, u otros equivalentes de fosgeno para formar el producto de quinazolina ciclizada. La aminación en la posición 3 de NH se logra mediante la reacción con cualquier número de reactivos de aminación tales como amoniaco y N-alquilaminas, por ejemplo, como lo describe Kloetzer (*Sci. Pharm.*,

1984;52:46-50) para dar el compuesto de la invención correspondiente.

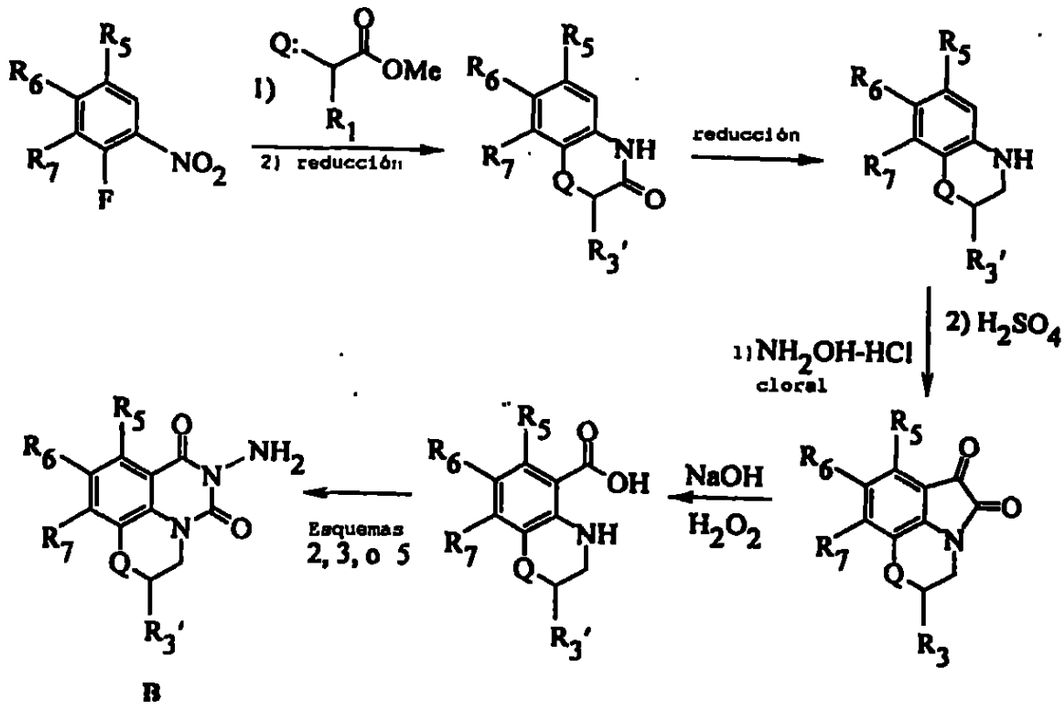
Esquema 5



Los compuestos tricíclicos (es decir, donde R_1 y R_8 en la Fórmula I se toman junto con los átomos a los cuales están unidos para formar un anillo) pueden prepararse de acuerdo con

los Esquemas 6 y 7. Los Esquemas 6 y 7 difieren en la introducción de las sustituciones de R_1 en las Estructuras **B** y **C** en donde $R_1 = R_{1'}$ y R_1 es lo definido anteriormente para las Fórmulas I y $R_{1'}$ es alquilo, alquenilo, alquinilo, arilo, cicloalquilo, heteroarilo, y similares. En el Esquema 6, el compuesto *orto*-fluoro nitro (también se pueden emplear otros grupos salientes tales como cloro, bromo y sulfonilo en lugar de fluoro) es desplazado por el éster sustituido α-nucleófilo (donde Q es un nucleófilo Nu tal como metilo o metoxi). El grupo nitro luego se reduce usando, por ejemplo, Ni de Raney, H_2 sobre Pd/C, o un metal activo en un ácido tal como hierro o estaño en HCl o ácido acético. La amina recién formada se cicla rápidamente con el éster (pueden emplearse otros análogos ácidos tales como tioésteres, amidas, y similares). El producto ciclado luego se reduce con agentes reductores de hidruro tales como $LiAlH_4$ y similares para producir el derivado de dihidroquinolina, que a su vez reacciona con hidrato de cloral y luego un ácido para formar el anillo de diona. El anillo diona luego se abre usando, por ejemplo, hidróxido de sodio y peróxido de hidrógeno para dar el ácido benzoico. El anillo de 3-aminoquinazolindiona luego se preparar usando la química descripta en los Esquemas 2, 3, o 5 para dar el compuesto de la invención **B**, donde $R_{3'}$ es alquilo, alquenilo, cicloalquilo, arilo y heteroarilo.

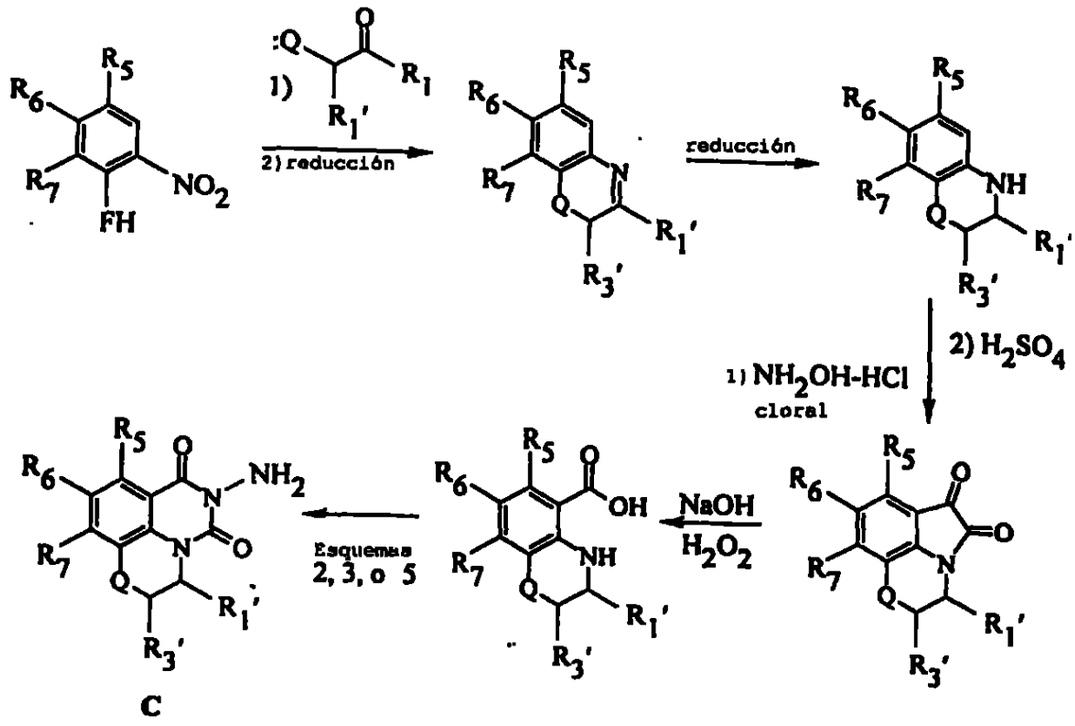
Esquema 6



En una serie similar de reacciones ilustradas en el Esquema 7, el compuesto *orto*-fluoro nitro reacciona con una cetona α-nucleófilo sustituida, y el producto resultante se reduce igualmente. En esta secuencia, la anilina resultante forma una imina cíclica, que se reduce más con H_2 en Pd/C o mediante agentes reductores de hidruro químico tales como borohidruro de sodio o cianoborohidruro de sodio para dar la dihidroquinolina. Tales aminaciones reductivas son conocidas en el arte y típicamente se realizan en THF, alcohol, agua, mezclas de alcoholes, o en mezclas de agua y DMF. Los pasos

restantes para producir **C** siguen aquellos del Esquema 6. Cuando el sustituyente de C-7 es un grupo saliente (ej., R_7 = halo), los compuestos **B** y **C** pueden reaccionar nuevamente con nucleófilos (tales como pirrolidina o piperidina) para dar compuestos de la Fórmula I como en los esquemas previos.

Esquema 7

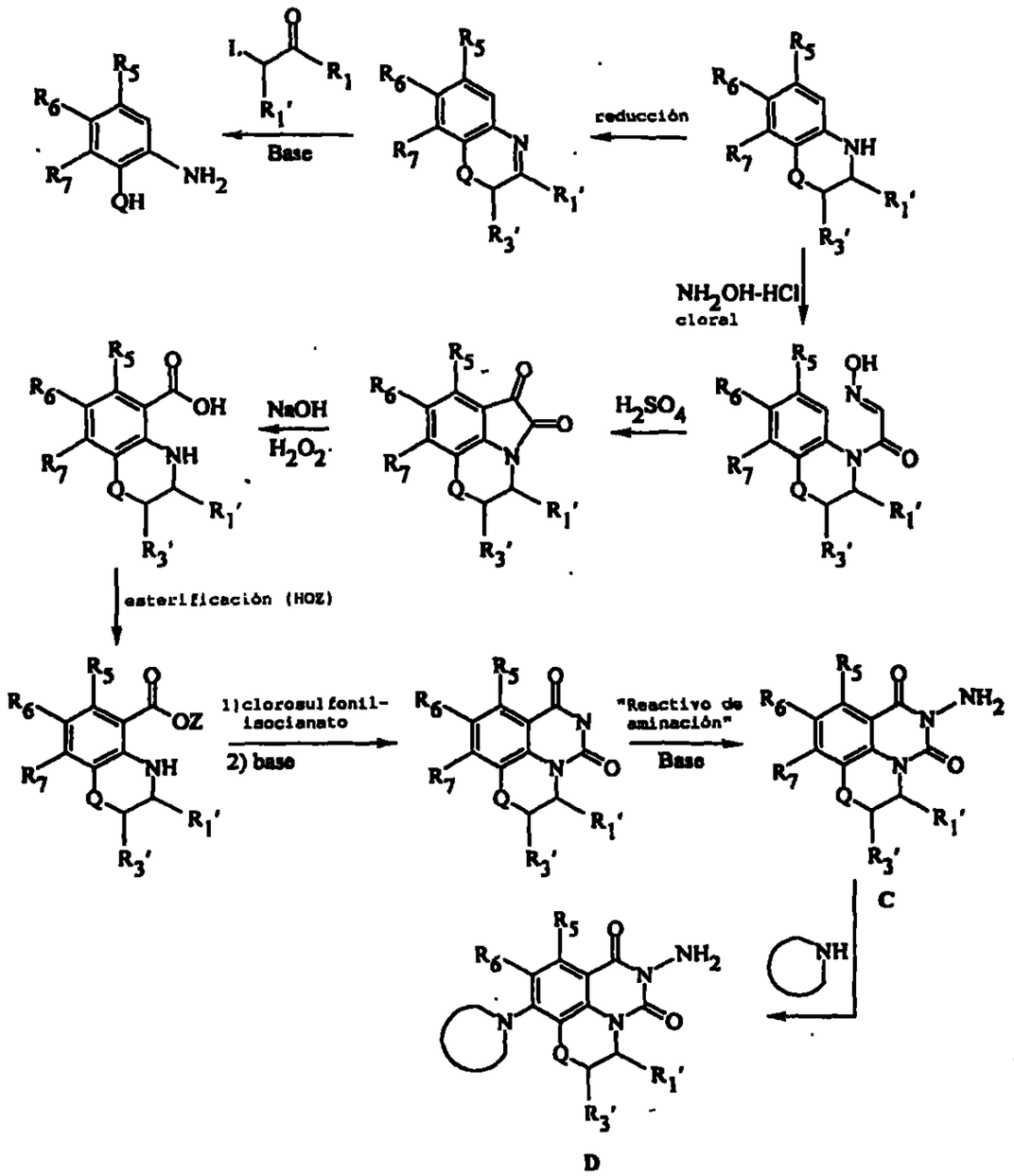


En el Esquema 8, los compuestos tricíclicos deseados como C se preparan en una forma ligeramente diferente. En este caso, el nucleófilo Q (tal como hidroximetilo) es unido al anillo de fenilo de la anilina inicial, y un grupo saliente L (tal como halo) es unido alfa al reactivo de cetona. El nucleófilo puede ser activado con bases tales como hidruro de sodio o hidruro de potasio, trietilamina o 1,8-diazabiciclo[5.4.0]-undec-7-eno (DBU), o carbonato de sodio, potasio, o cesio para desplazar el grupo saliente L. En esta secuencia, la anilina resultante forma una amina cíclica, que se reduce más con H_2 en Pd/C o por agentes químicos reductores de hidruro tales como borohidruro de sodio o cianoborohidruro de sodio para dar una

dihidroquinolina. Tales aminaciones reductivas son conocidas en el arte y típicamente se realizan en THF, alcohol, agua, mezclas de agua y alcohol, o en mezclas de agua y DMF. El intermedio de dihidroquinolina reacciona con hidrato cloral y luego un ácido para formar el anillo de diona. El anillo de diona luego se abre mediante la reacción con una base, por ejemplo hidróxido de sodio y peróxido de hidrógeno, para dar el ácido benzoico. El anillo de 3-aminoquinazolindiona luego se prepara formando primero un éster en el ácido benzoico como en el Esquema 2, luego mediante la reacción del éster del ácido benzoico con diclorosulfonilisocianato o similar a temperaturas de 0°C y menores, luego el tratamiento con una base tal como trietilamina o diisopropiletilamina. La aminación se puede realizar en la misma forma descripta en el Esquema 5 para proporcionar compuestos de la estructura C. Cuando R_7 es un grupo saliente tal como Cl o F, los compuestos de la invención de las estructuras B (en el Esquema 6) y D (en el Esquema 8) pueden prepararse acoplando a la cadena lateral de R_7, por ejemplo, diversas aminas heterocíclicas  para producir los derivados deseados. Alternativamente, también se pueden introducir carbociclos y arilos como las cadenas laterales de R_7 usando acoplamientos catalizados con paladio con carbociclos de estaño o boronato y arilos, por ejemplo, cuando R_7 es un Br, I o triflato.

92

Esquema 8

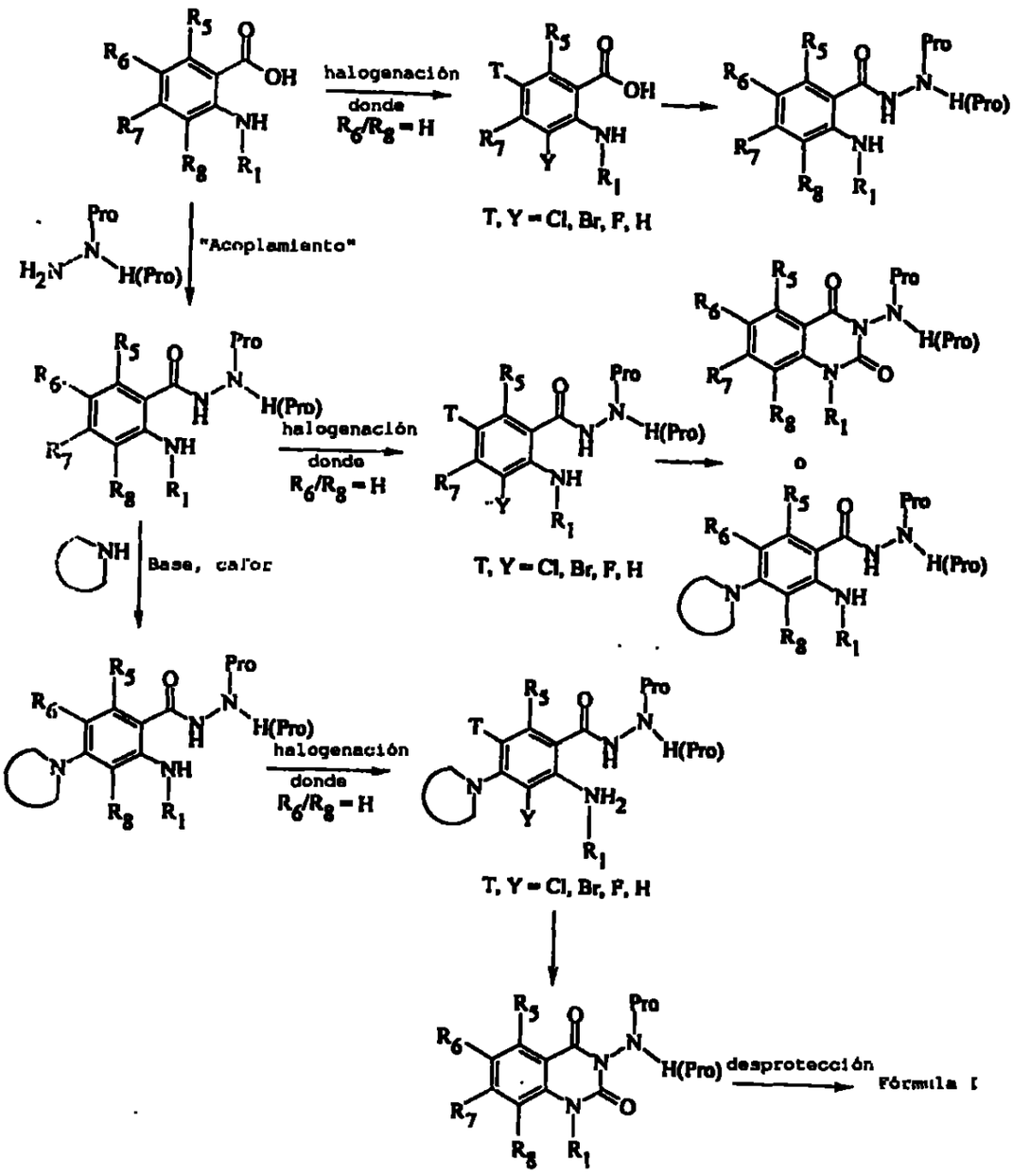

reducción
Base
NH2OH-HCl
cloral
NaOH
H2O2
H2SO4
esterificación (HOZ)
1)clorosulfonil-isocianato
2) base
"Reactivo de aminación"
Base
C
D

Debe hacerse notar a partir de los Esquemas 6, 7 y 8 que R_1, y R_3, forman centros quirales, dando *R* y *S* enantiómeros y diastereómeros. Tales enantiómeros y diastereómeros pueden ser separados, si se desea, en cualquier etapa por HPLC quiral, o por otras técnicas de resolución convencionales. La resolución del ácido benzoico precursor se puede lograr también mediante cristalización fraccionaria usando ácido mandélico, ácido tartárico, u otros agentes de rosolución que llevan ácidos ópticamente puros, quirales. Las amidas quirales también pueden prepararse desde ácidos benzoicos usando aminas quirales tales como alcanforsulfonamida, bencilamina, o similar. Los isómeros pueden luego ser separados y la amida quiral se puede hidrolizar como se desee.

El Esquema 9 ilustra la síntesis de compuestos de la Fórmula I en donde uno o ambos de R_6 y R_8 son halo a través de la halogenación. La halogenación se realiza en un ácido 2-aminobenzoico donde uno o ambos de R_6 y R_8 son hidrógeno. Si R_6 y R_8 en el ácido benzoico son H, entonces la halogenación puede lograrse en ambas posiciones en forma selectiva o simultánea. Por lo tanto, por ejemplo, la cloración en R_6 o R_8 se logra mediante la reacción del ácido benzoico con N-clorosuccinamida, t-butilhipoclorito, gas cloro, y similares. En forma similar, la bromación en R_6 y R_8 también se puede lograr mediante la reacción del ácido benzoico con Br_2, N-

bromosuccinamida, y similares. Tales halogenaciones son conocida en el arte. La halogenación proporciona el respectivo compuesto mono o dihalo. El ácido benzoico halogenado puede reaccionar como se muestra en los Esquemas 1 y 2 para proporcionar las quinazolin-2,4-dionas de la Fórmula I.

Esquema 9

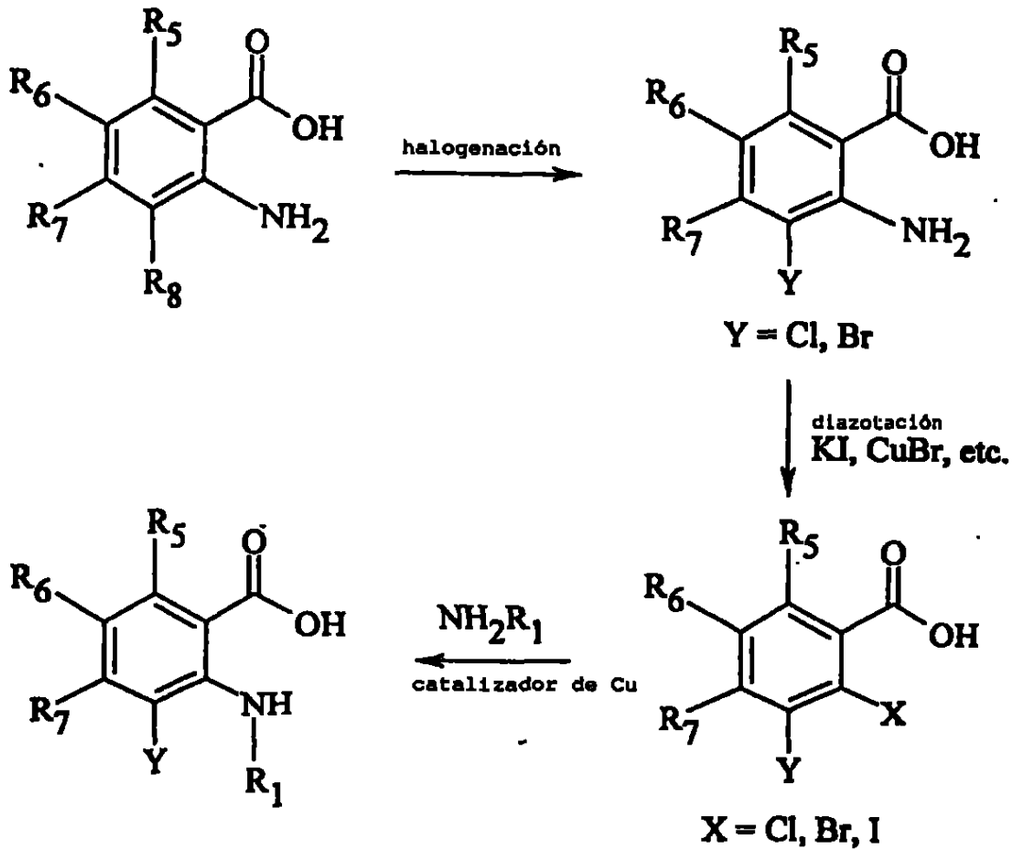


En el Esquema 10, los compuestos donde R_8 es H, se halogenan como se describe en el Esquema 9 para proporcionar el ácido 3-halo-2-aminobenzoico (Y = halo). Este intermedio puede luego

ser diazotado mediante la reacción del grupo 2-amino con nitrito de sodio o nitrito de t-butilo, que luego se convierte en el ácido 2-halobenzoico en la presencia de una sal de sodio, potasio, o cobre tal como yoduro de sodio, clouro de potasio y similares. El ácido 2,3-dihalobenzoico resultante (donde X e Y son ambos halo) luego es convertido en el ácido 3-halo-2-aminobenzoico mediante la reacción con una amina R_1NH_2 en la presencia de un catalizador de cobre. El ácido 3-halo-2-aminobenzoico es convertido en una amida y ciclado para dar la 8-halo-3-amino-quinazolin-2,4-diona correspondiente, como se ilustra en el Esquema 2.

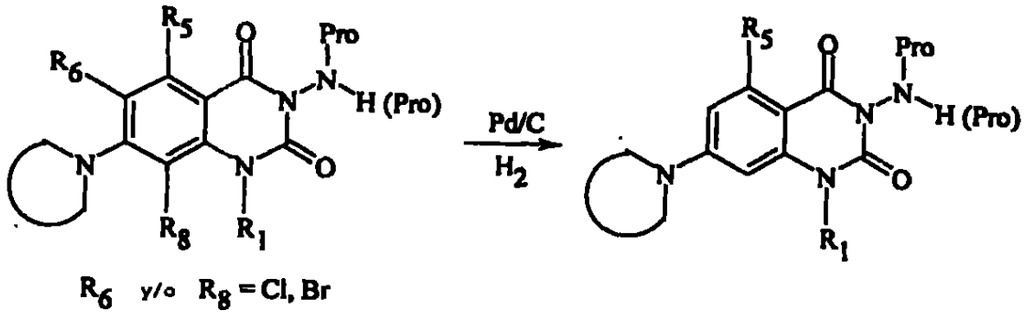
97

Esquema 10



Los compuestos de la Fórmula I donde R_6 y/o R_8 es halo tal como cloro o bromo, son deshalogenados rápidamente mediante la reacción con catalizadores de metales bajo presión de hidrógeno (Esquema 11). Los catalizadores adecuados incluyen las numerosas variaciones de Pd en carbono, níquel de Raney, u otros agentes que se sabe que efectúan tal deshalogenación.

Esquema 11

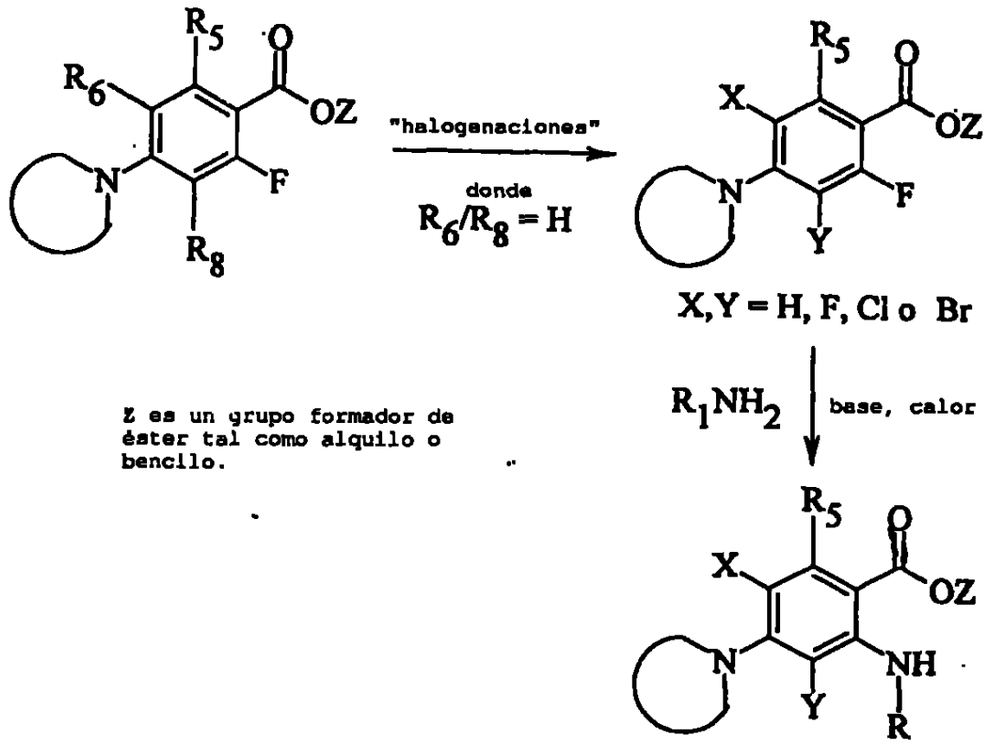


R_6 y/o R_8 = Cl, Br

Los compuestos de la Fórmula I donde R_6 y/o R_8 son hidrógeno pueden ser halogenados para dar el compuesto mono o dihalo (ej., R_6 o R_8 = Cl o Br). Los compuestos de la invención preferentemente se preparan halogenando primero un derivado de ácido benzoico, y luego ciclando el benzoato halogenado (Esquema 12). Si R_6 y R_8 son H, entonces la halogenación se puede realizar en ambas posiciones selectiva o simultáneamente. Las halogenaciones pueden realizarse como se describió anteriormente para el Esquema 10. El compuesto resultante luego es convertido en el ácido aminobenzoico 2-sustituido como se ilustra en el Esquema 1, que posteriormente se cicla y amina.

99

Esquema 12

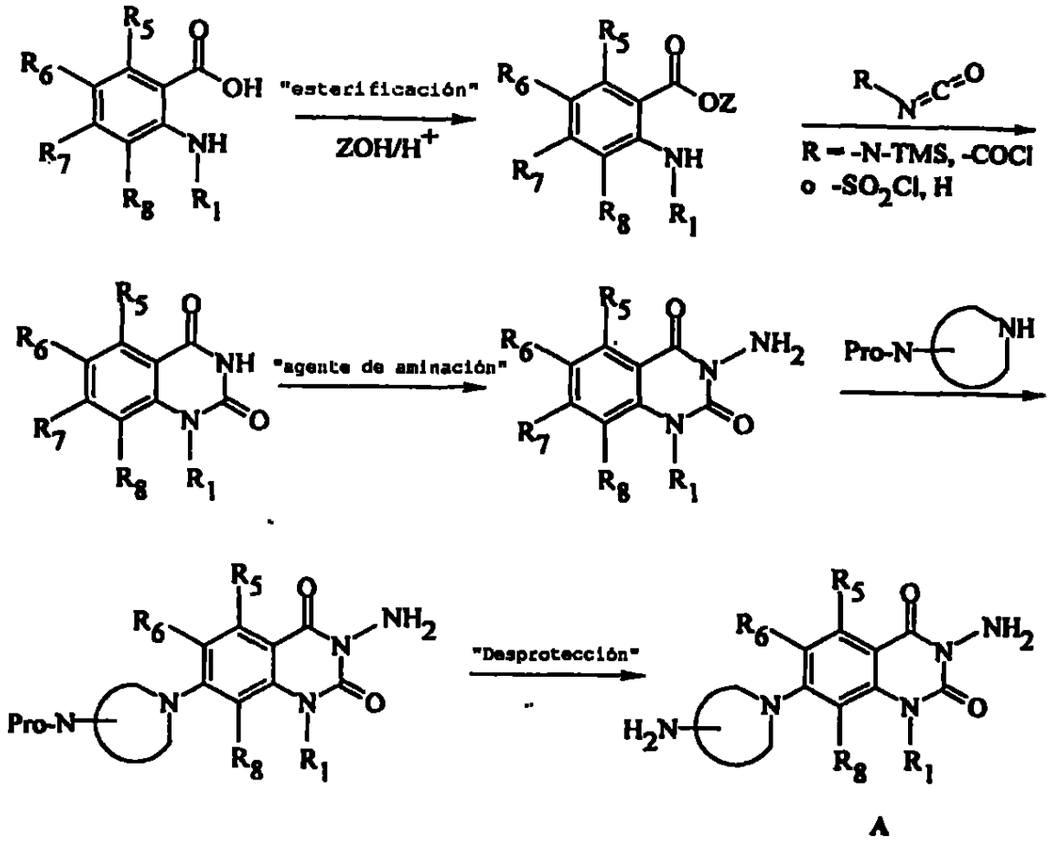


Los compuestos de la Fórmula I de la invención pueden prepararse también como se muestra en el Esquema 13. Los ácidos benzoicos sustituidos pueden convertirse en ésteres (donde Z es un grupo formador de éster tal como alquilo o bencilo) mediante numerosos métodos conocidos por los expertos en el arte. El éster reacciona con un isocianato tal como trimetilsililisocianato, clorosulfonil isocianato, luego mediante el tratamiento con una base tal como trietilamina, t-butóxido de sodio o similar, para proporcionar una quinazolin-

2,4-diona. La quinazolin-2,4-diona puede aminarse mediante la reacción con un agente de aminación tal como amoniaco como se describe en el Esquema 5 para generar la 3-aminoquinazolin-2,4-diona. Este compuesto puede reaccionar además, cuando R_7 es un grupo saliente tal como fluoro, con diversas aminas heterocíclicas. Nuevamente, también pueden introducirse carbociclos y arilos en R_7 si R_7 es un Br, I o triflato, usando acoplamientos catalizados con paladio de carbocicos de estaño o boronato y arilos. La remoción de cualquier grupo protector (Pro) por medios normales proporciona compuestos de la invención tales como **A**, como se describe en el Esquema 1.

101

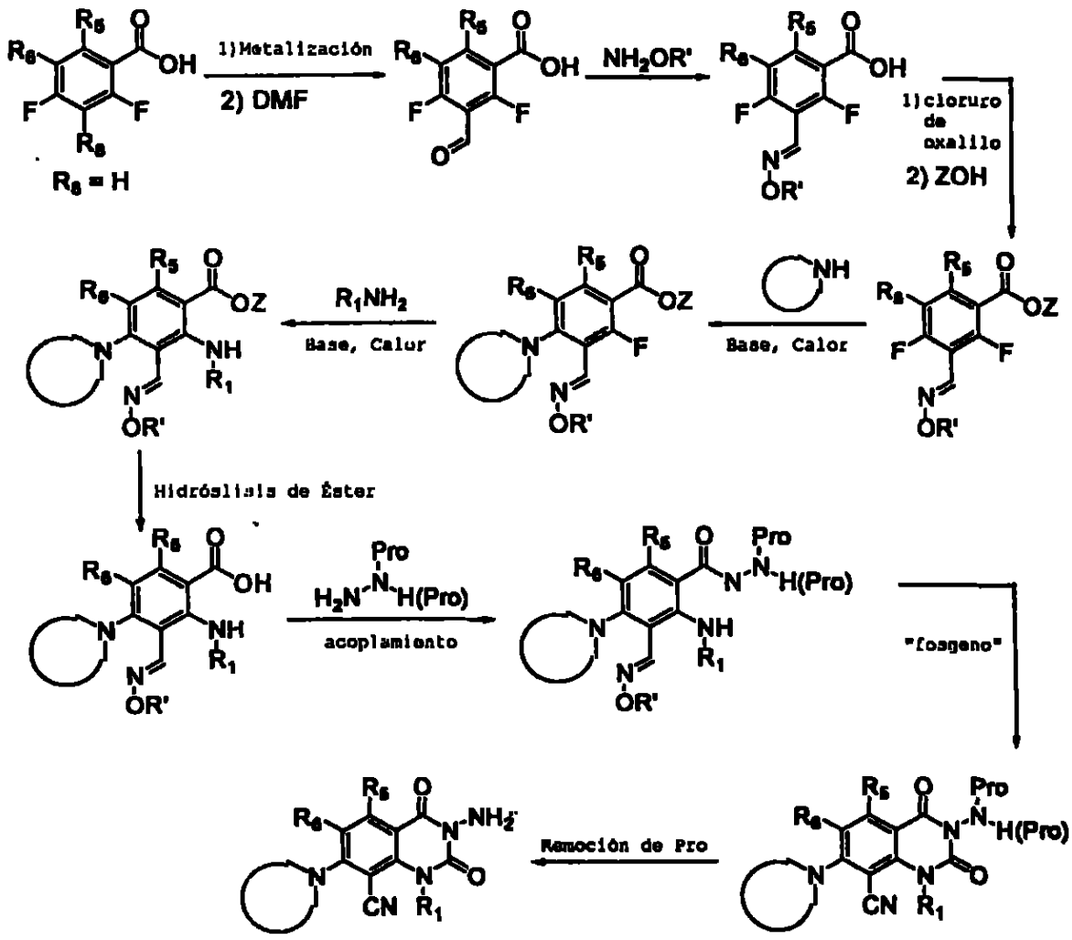
Esquema 13



Los compuestos de la Fórmula I de la invención que tienen un sustituyente de ciano pueden prepararse como se muestra en el Esquema 14. Por ejemplo, un ácido benzoico donde R_8 es hidrógeno puede metalizarse con una base fuerte tal como hexametildisilazano de litio o diisopropilamina de litio. El intermedio metalizado resultante puede luego ser enfriado con dimetilformamida o un equivalente para proporcionar un aldehído. El aldehído puede ser convertido en una oxima

mediante la reacción con una alcoxi amina (también pueden emplearse otros electrófilos tales como haluros de alquilo, amidas activadas, ésteres y fuentes de haluro tales como 1,2-dicloro-tetrafluoroetano, para proporcionar otros derivados de ácido benzoico que pueden usarse como se define en los Esquemas 1, 2, 13 y 15). La oxima es convertida en un grupo ciano en condiciones de ciclización requeridas para formar el sistema de anillo de quinazolindiona (ej., la reacción con fosgeno) como se describe en los Esquema 1, 12 y 13. La desprotección proporciona compuestos de la invención donde R_8 es -CN.

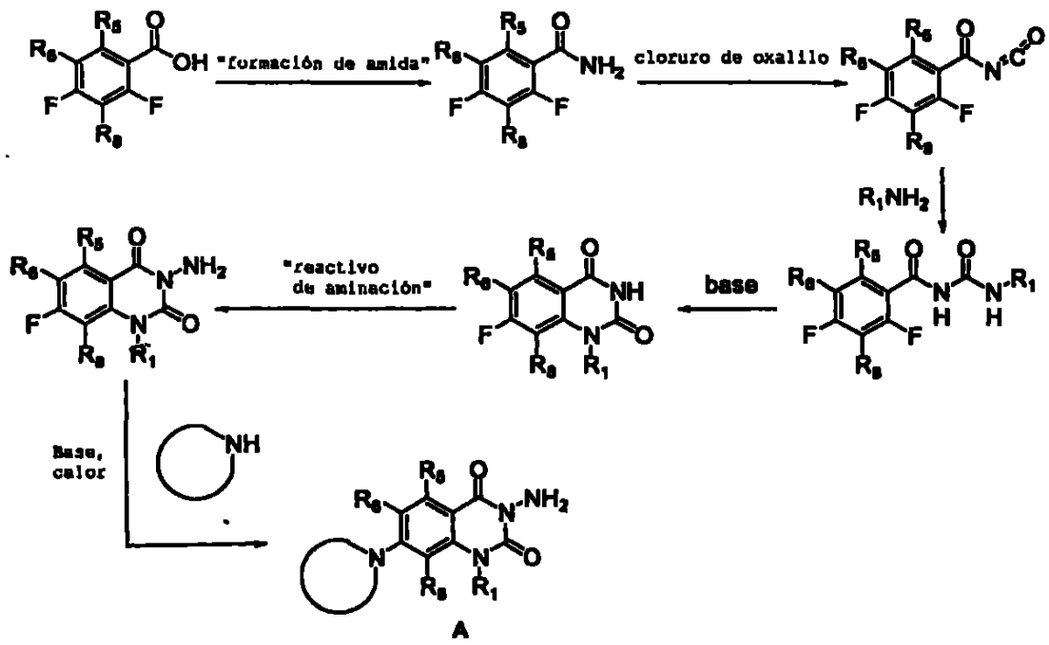
Esquema 14



Otra alternativa para preparar los compuestos de la invención se ilustra en el Esquema 15. Ácidos benzoicos sustituidos apropiadamente pueden ser convertidos en benzamidas mediante cualquier número de métodos descriptos anteriormente. Una benzamida puede entonces ser tratada con cloruro de oxalilo en un solvente clorado tal como diclorometano o un equivalente

para proporcionar un isocianato. El isocianato reacciona con una amina primaria sustituida para dar una urea benzoil sustituida. Este intermedio puede ser ciclado para formar un sistema de anillo de quinazolindiona mediante la reacción con hidruro de sodio, hexametildisilazano de potasio u otras bases nucleófilas, generalmente en un solvente tal como tetrahidrofurano (THF)/dimetilformamida, THF con 18-corona-6, THF/dioxano, THF/glima, THF/diglima, dimetoxietano/tolueno o un equivalente. La quinazolindiona puede entonces ser aminada mediante la reacción con cualquier número de reactivos de aminación descriptos por Kloetzer (*Sci. Pharm.*, 1984;52:46-50). El sistema de anillo de 3-aminoquinazolindiona resultante puede entonces ser acoplado rápidamente con una amina heterocíclica sustituida apropiadamente (tal como aquellas indicadas anteriormente en la Tabla A) mediante la reacción en la presencia de una base tal como una trietil amina, diisopropiletil amina, tetrametil guanidina, y similares en solventes tales como sulfóxido de dimetilo, dimetilformamida, dimetilacetamida, sulfolano o el equivalente. Cualquier grupo protector asociado con la cadena lateral de amina heterocíclica se remueve luego mediante métodos conocidos por los expertos en el arte para proporcionar compuestos de la invención que tienen la Estructura **A**.

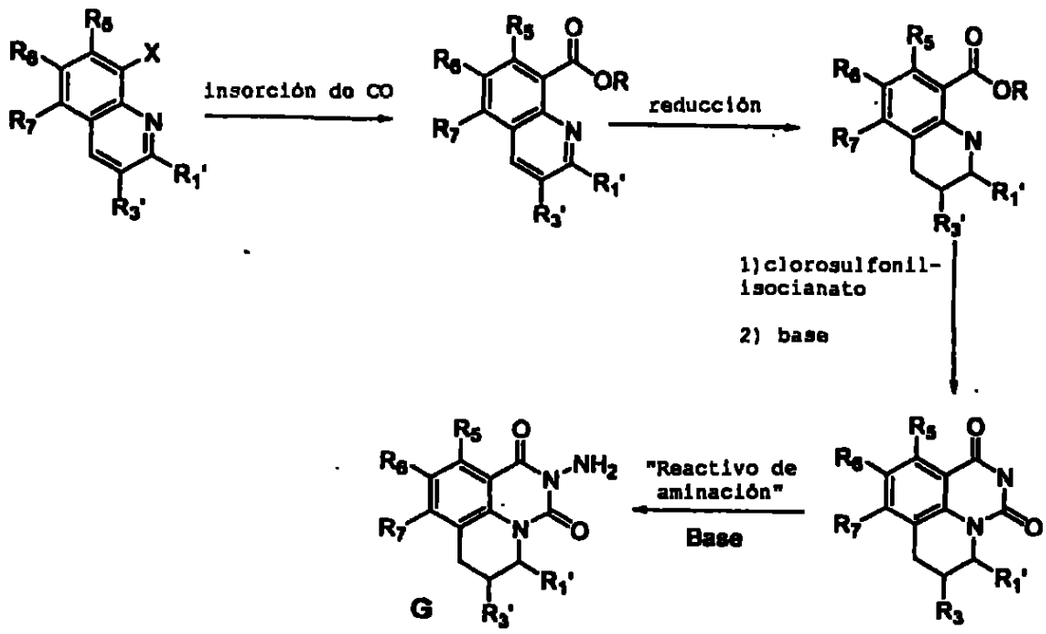
Esquema 15



Se pueden preparar compuestos tricíclicos (es decir donde R_1 y R_8, junto con los átomos a los cuales están unidos, forman un anillo carbocíclico en los compuestos de la invención de la Fórmula I) de acuerdo con el Esquema 16 donde la inserción de monóxido de carbono mediado por paladio en una quinolina (X = Br, I o triflato) en condiciones con buenos precedentes da origen a un éster. El anillo de quinolina puede luego ser hidrogenado para proporcionar una tetrahidroquinolina mediante condiciones de hidrogenación estándar. El resto del Esquema 16 sigue el Esquema 8 para proporcionar compuestos de la invención tales como G sustituidos con un sustituyente

desplazable en R_7 (ej., halo). Estos compuestos pueden además reaccionar con nucleófilos tales como aminas de la Tabla A para dar compuestos de la Fórmula I.

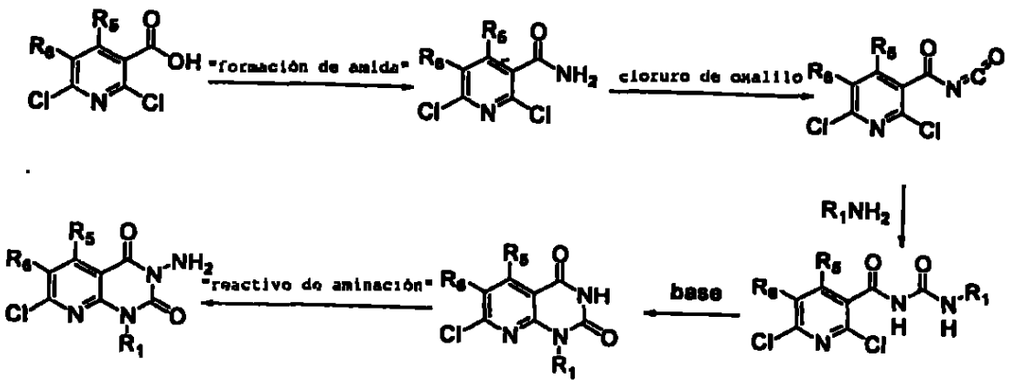
Esquema 16



Los compuestos de la Fórmula I donde K es N pueden prepararse por vías mostradas en los Esquemas 1, 2, 3, 4 y 6, o por vías tales como la ilustrada en el Esquema 17, que sigue estrechamente la química mostrada en el Esquema 15. Los grupos salientes (ej. halo) *orto* y *para* con respecto al grupo carbonilo del material inicial de piridilo están altamente activados. Los dos grupos salientes *orto* con respecto al

nitrógeno de piridina son generalmente cloro, pero flúor, alquiltiol, y los sulfóxidos tales como sulfóxido de metilo son también buenos grupos salientes para tales compuestos. El intermedio de urea se cicliza rápidamente hacia la 7-halo-quinazolindiona. La aminación en la posición 3 da un compuesto de la invención que es un importante intermedio debido al buen grupo saliente en la posición 7 (R_7 = halo), que es desplazado rápidamente mediante la reacción con una amina  .

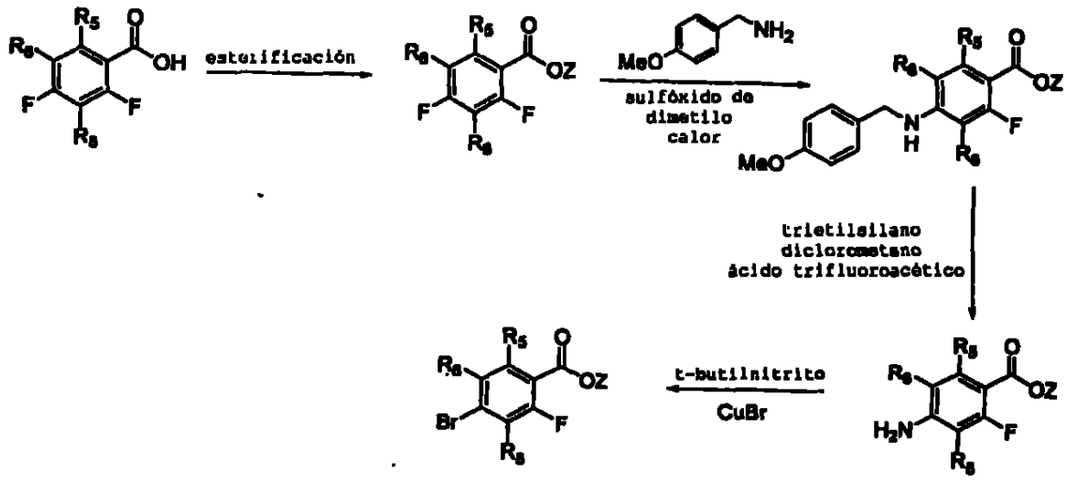
Esquema 17



El Esquema 18 ilustra la síntesis de materiales iniciales de ácido benzoico que tienen un bromo para R_7. Un ácido benzoico difluoro sustituido es convertido en un éster mediante la primera reacción con cloruro de oxalilo o un reactivo equivalente (que incluye anhídrido de ácido), y el haluro o anhídrido de ácido reacciona con un alcanol para lograr el éster respectivo (Z = metilo, etilo, isopropilo, etc.). El éster luego reacciona con 4-metoxibencilamina o un equivalente para producir el derivado de ácido benzoico 4-sustituido deseado. Este intermedio reacciona con trietilsilano y ácido trifluoroacético en un solvente clorado tal como diclorometano o un equivalente para proporcionar un derivado de anilina. Alternativamente, un experto en el arte también puede emplear la catálisis de metales de transición. La anilina resultante luego es sometida a diazotación y convertida en un bromuro

mediante el tratamiento con bromuro cuproso. El éster luego se hidroliza mediante métodos conocidos hacia el ácido benzoico deseado, que puede usarse como un material inicial como se ilustra en el Esquema 20 siguiente.

Esquema 18



En el Esquema 19, derivados de ácido 4-cloro-2-fluorobenzoico pueden ser clorados selectivamente con gas cloro en ácido clorosulfónico a una temperatura de 40°C-100°C.

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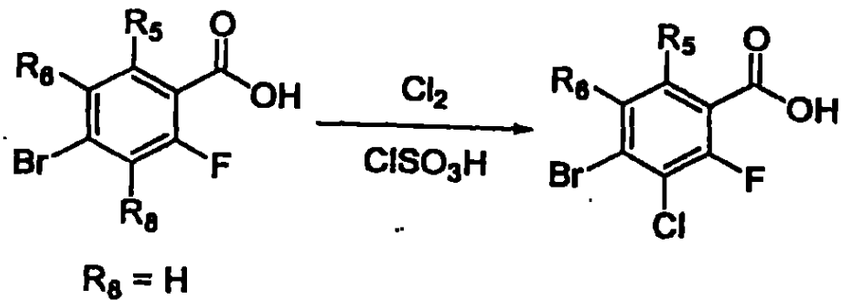
Esquema 19



$R_8 = H$

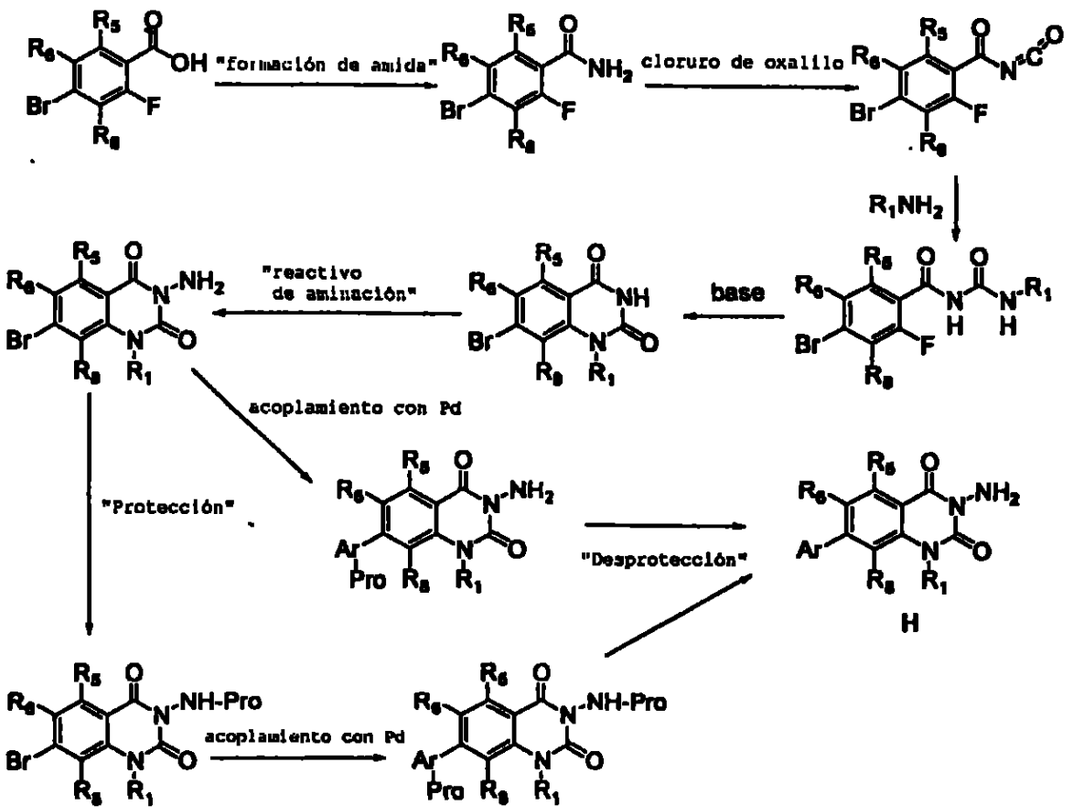
El Esquema 20 ilustra el uso de ácidos 4-bromobenzoicos como materiales iniciales para fabricar compuestos de la invención donde R_7 es arilo. Los ácidos 4-bromobenzoicos son convertidos en benzamidas mediante cualquier número de métodos conocidos en el arte. Una benzamida reacciona con cloruro de oxalilo en un solvente clorado tal como diclorometano o un equivalente para proporcionar un isocianato. El isocianato reacciona con una amina primaria sustituida para dar una urea benzoil sustituida. Este intermedio puede ser ciclado para formar un sistema de anillo de quinazolindiona mediante la reacción con hidruro de sodio, hexametildisilazano de potasio u otras bases no nucleófilas en tetrahidrofurano/dimetilformamida, tetrahidrofurano con 18-corona-6, tolueno/dioxano, tetrahidrofurano/glima, tetrahidrofurano/diglima, glima/tolueno, o un equivalente. La quinazolindiona puede entonces ser aminada con un número de reactivos de aminación

como se describe en el Esquema 15. El sistema de anillo de 3-aminoquinazolindiona puede entonces ser acoplado rápidamente con un estanano o derivado de ácido borónico de un arilo sustituido tal como fenilo o heterociclo aromático sustituido (Ar).

Alternativamente, la amina en la posición 3 puede ser protegida con un grupo protector tal como carbamato de terc-butilo o trifluoroacetamida. Los grupos protectores de estos tipos son conocidos en el arte. El sistema de anillo de aminoquinazolindiona 3-derivado puede entonces ser acoplado a través de la catálisis con paladio con un estanano aromático (Ar) o ácido borónico.

Cada una de las vías descriptas, al desproteger con los procedimientos estándar, proporciona los compuestos de la invención de la Fórmula I donde R_7 es arilo tal como fenilo o fenilo sustituido, o heteroarilo tal como piridilo o piridilo sustituido.

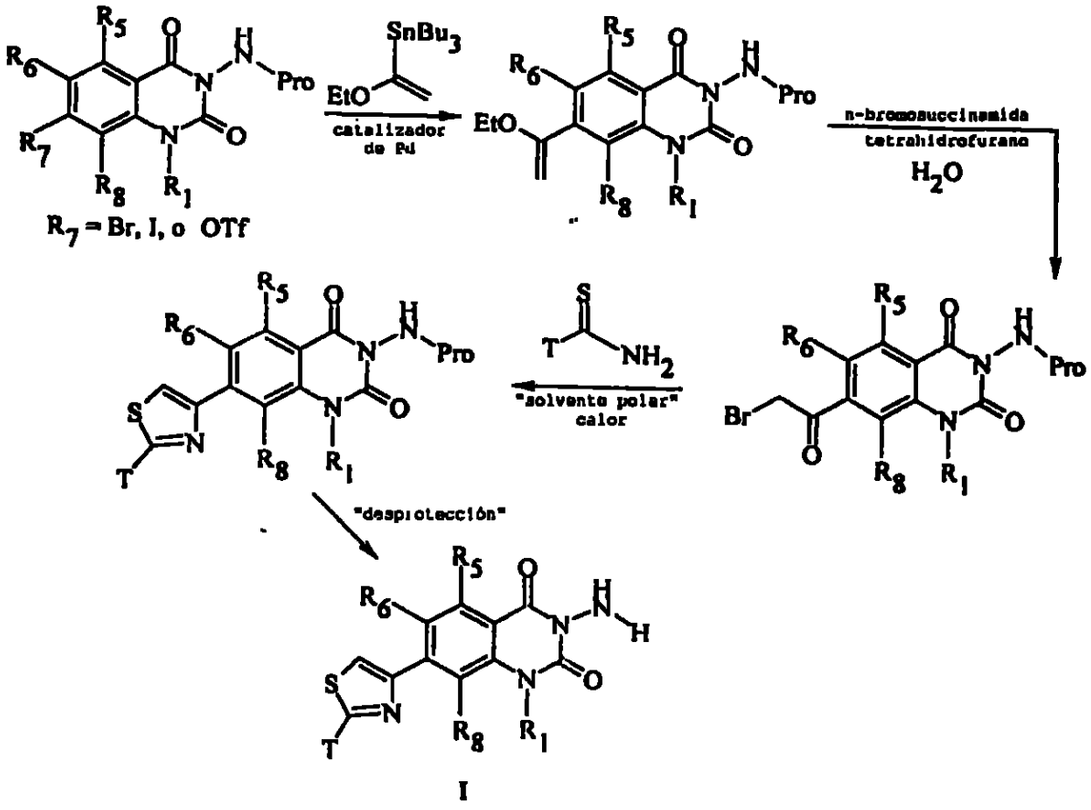
Esquema 20



Los compuestos de la Fórmula I donde R_7 es un grupo heteroarilo (tal como aquellos de la Tabla A) se preparan alternativamente como se ilustra en el Esquema 21, donde R_7 es un tiazol sustituido. Una 3-amino-7-bromoquinazolindiona 3-protegida del Esquema 20 reacciona con 1-tributil-etoxivinilestaño en la presencia de un catalizador de paladio. El aducto 7-sustituido resultante reacciona con un reactivo de bromación tal como n-bromosuccinamida y similares en tetrahidrofurano/H_2O para

proporcionar una α-bromocetona en la posición 7 de la quinazolindiona. La reacción de este intermedio con una tioamida (o tiourea) en un solvente polar tal como dimetil formamida, dimetilacetamida, o etanol, y a una temperatura elevada de 80°C a 120°C, realiza la ciclización para formar u grupo tiazolilo. La desproteccion mediante cualquier método conocido puede entonces aplicarse para proporcionar compuestos de la invención de la Fórmula I en donde R_7 es el heteroarilo, optativamente con T, que es H, alquilo, alquilo sustituido, NH_2, NH-alquilo y N-dialquilo.

Esquema 21



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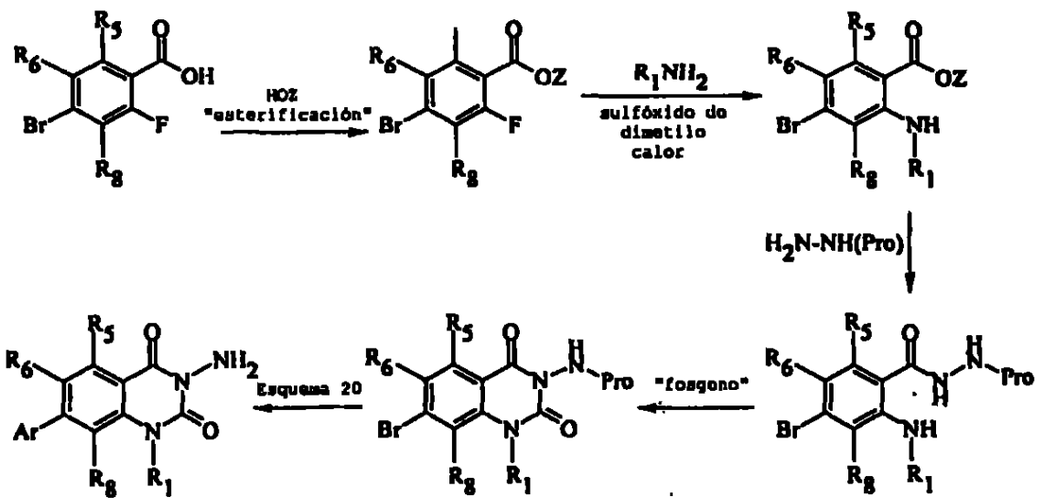
Alternativamente, los compuestos 7-aromáticos o aromáticos heterocíclicos de la Fórmula I se preparan como se muestra en el Esquema 22. Un ácido 4-bromo-2-fluorobenzoico (Esquemas 18 o 19) primero se esterifica (Z es alquilo o bencilo) y el éster reacciona con una amina primaria sustituida (R_1NH_2) en sulfóxido de dimetilo (DMSO) a temperatura elevada de 100°C para proporcionar un éster antranílico. La anilina resultante luego reacciona con una hidrazina protegida apropiadamente para proporcionar la amida correspondiente, por ejemplo como

se describe en el Esquema 1. La amido anilina resultante luego se cicliza mediante la reacción con un fosgeno, CDI, o similar para generar la quinazolin-2,4-diona. La ciclización típicamente se realiza en un solvente, tal como solventes etéreos, hidrocarburos clorados tales como cloroformo, o hidrocarburos aromáticos tales como tolueno, y en la presencia de una base tal como trietilamina o $NaHCO_3$. El sistema de anillo de quinazolin-2,4-diona luego se modifica nuevamente como se describe en el Esquema 20 para proporcionar el compuesto 7-arilo (Ar) de la Fórmula I deseado.

Esquema 22



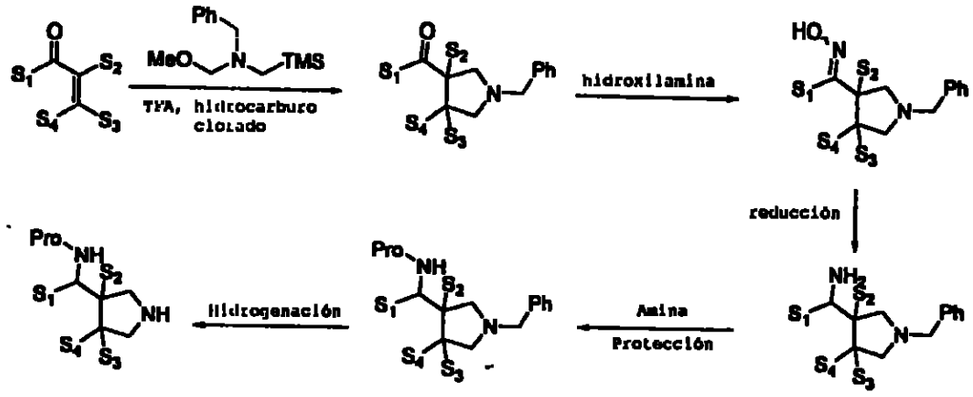
Como se indicó anteriormente, R_7 en la Fórmula I es citado como la "cadena lateral" del núcleo de la 3-aminoquinazolin-2,4-diona. Las cadenas laterales de R_7 son cualquiera de aquellas típicamente halladas en los antibióticos de quinolona. La mayor parte de los reactivos de la cadena lateral de R_7 que se requieren para fabricar los compuestos de la Fórmula I están rápidamente disponibles de fuentes comerciales. Las cadenas laterales de R_7 típicas se muestran en la Tabla A precedente.

La síntesis de las cadenas laterales de R_7 puede lograrse mediante métodos estándar, por ejemplo los mostrados en los siguientes esquemas o los hallados en la bibliografía. Los expertos en el arte pueden fabricar cualquiera de los materiales iniciales requeridos para preparar los compuestos de la invención, aunque la mayoría está disponible en fuentes comerciales. Los siguientes esquemas se proporcionan para ilustrar la síntesis de reactivos de cadenas laterales de R_7 típicos.

El Esquema A1 ilustra la síntesis de pirrolidinas típicas, que son cadenas laterales preferidas (R_7) para compuestos de la invención de la Fórmula I. En el Esquema A1, enonas activadas apropiadamente pueden pasar por [3+2]cicloadiciones en las condiciones descriptas por Tsuge et al (Recent advances in azomethine ylid chemistry. En: Advances in Heterocyclic

Chemistry [Katritsky A., ed.] San Diego: Academic Press, 231-349). Estas reacciones se realizan en un solvente de hidrocarburo clorado tal como diclorometano, cloroformo, o dicloroetano y similares, y en la presencia de un ácido catalítico tal como ácido trifluoroacético, para proporcionar pirrolidinas sustituidas (en donde S_1, S_2, S_3 y S_4 independientemente son alquilo, alquilo sustituido, arilo, amino, alquil y dialquilamino). Estos intermedios pueden entonces ser tratados con hidroxilamina o cualquier hidroxilamina O-alquilada o arilada en una variedad de condiciones conocidas por los expertos en el arte, para proporcionar pirrolidinas sustituidas oximadas. Las oximas se reducen a aminas con hidruro de litio y aluminio, hidruro de diisobutilaluminio, borano o mediante hidrogenación catalítica selectiva. Las aminas primarias resultantes pueden entonces ser protegidas usando numerosos métodos descriptos en "Grupos Protectores en Síntesis Orgánica" de Theodora Green (ver arriba). La pirrolidina bencílica puede entonces ser desprotegida mediante hidrogenación, y la pirrolidina resultante puede ser usada en la preparación de 3-aminoquinazolindionas amino sustituidas 7-cíclicas de la Fórmula I mostradas en los esquemas anteriores.

Esquema A1



En el Esquema A2, también pueden usarse enoatos (o nitrilos vinílogos) en [3+2]cicloadiciones para proporcionar pirrolidinas 3- y 4-sustituidas. La funcionalidad de éster (o nitrilo) puede entonces ser tratada directamente con reactivos de alquil litio a baja temperatura (0°C) en éter para proporcionar cetonas sustituidas con S_1, o el éster (Z es alquilo o bencilo) puede ser hidrolizado en condiciones generalmente empleadas por los conocedores del arte para proporcionar ácidos carboxílicos. Este intermedio puede entonces ser transformado en un cloruro de ácido con cloruro de oxalilo y dimetil formamida catalítica en solventes tales como diclorometano o cloroformo o en una amida activada (Singh J., Satyamurthi N., Aidhen I., Singh J., *Prakt. Chem.* [Weinheim, Ger.], 2000;342(4):340-347). Un cloruro de ácido puede ser convertido en una cetona usando reactivos de organocobre (Lipshutz B.H., Sengupta S., *Org. React.* [N.Y.],

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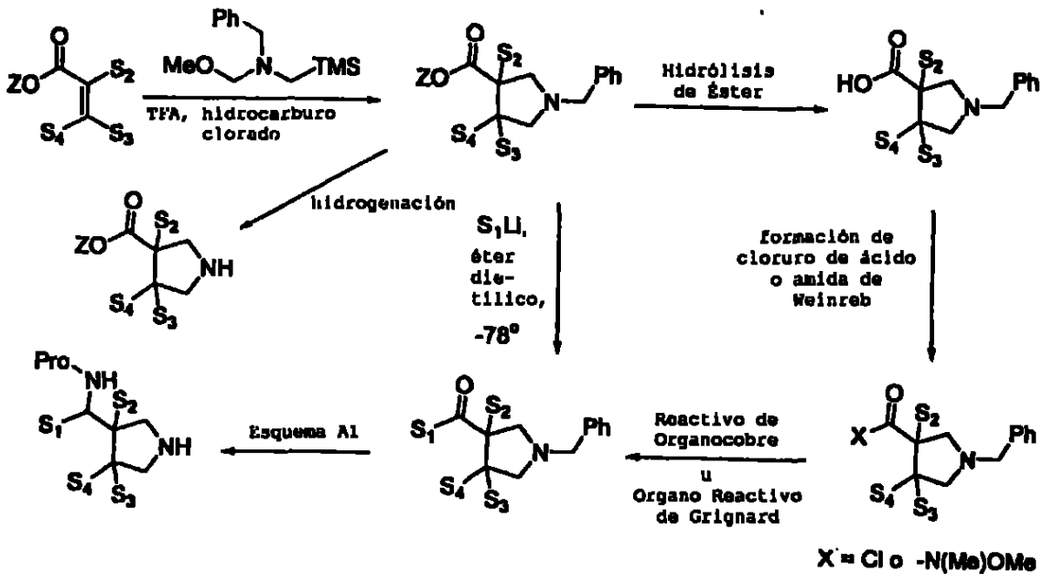
1992;41:135-631), y las amidas de Weinreb pueden ser convertidas en cetonas de acuerdo con los métodos descriptos por Weinreb (*Tetrahedron Lett.*, 1981;22(39):3815-3818) usando organo reactivos de Grignard. Las cetonas resultantes pueden ser convertidas en pirrolidinas (optativamente sustituidas con S_2, S_3 y S_4) como se describe en el Esquema A1. Como se indicó anteriormente, las pirrolidinas y pirrolidinas sustituidas son grupos de R_7 preferidos en la Fórmula I.

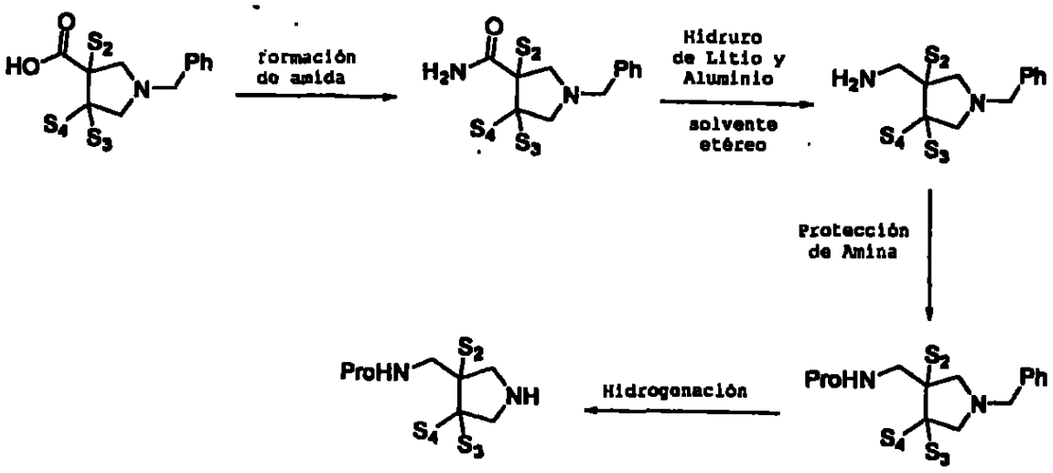
Esquema A2



En el Esquema A3, las pirrolidinas N-bencil sustituidas de ácido 3-carboxílico (Esquema A2) pueden ser convertidas enamidas mediante numerosos métodos conocidos por los expertos

en el arte de la síntesis orgánica. Las amidas pueden ser entonces tratadas con hidruro de litio y aluminio en un solvente etéreo tal como éter dietílico o tetrahidrofurano o similares para proporcionar aminas que pueden ser protegidas como se describe en el Esquema A1. La hidrogenación con catálisis de paladio proporcionar una pirrolidina sustituida apropiadamente (S_2, S_3, S_4 son independientemente alquilo, alquilo inferior, arilo, etc.).

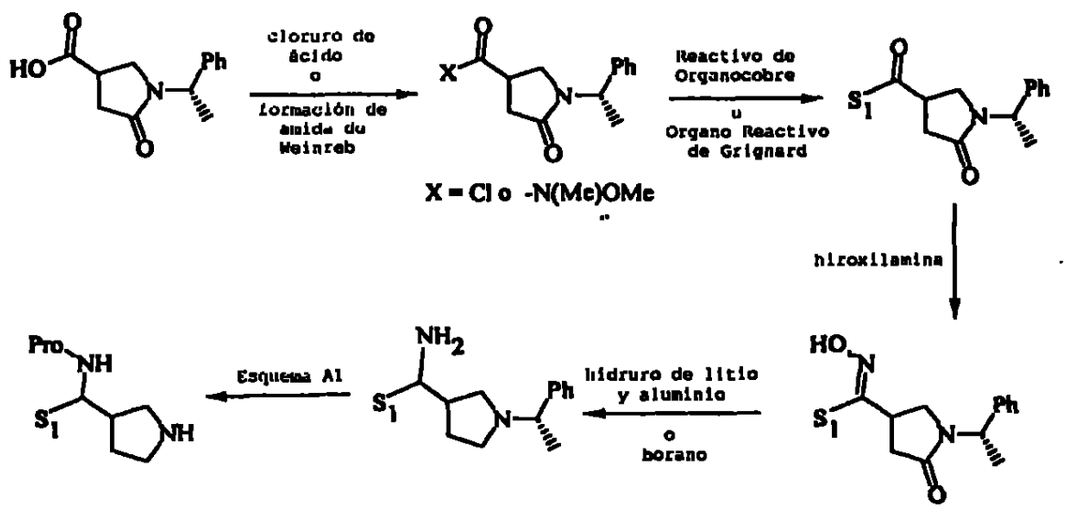
Esquema A3



En el Esquema A4, una 3-carboxipirrolidinona (Culbertson T.P., Domagala J.M., Nichols J.B., Priebe S., Skeean R.W., *J. Med. Chem.*, 1987;30(10):1711-1715) puede ser convertida en un cloruro de ácido o una amida de Weinreb en la misma forma definida en el Esquema A3. Los cloruro de ácidos reaccionan con un reactivo de organocobre o un organo reactivo de

Grignard (para una amida de Weinreb) para proporcionar una cetona que puede ser manipulada como se describe en el Esquema A1 para proporcionar una pirrolidina sustituida apropiadamente con una variedad de sustituciones en S_1 (alquilo, alquilo inferior, alquilo sustituido, arilo). El uso de S-metilbencilo (o R-metilbencilo) como un grupo protector para el nitrógeno de la pirrolidina permite la separación de enantiómeros y diastereómeros en cualquier paso en la secuencia de la reacción.

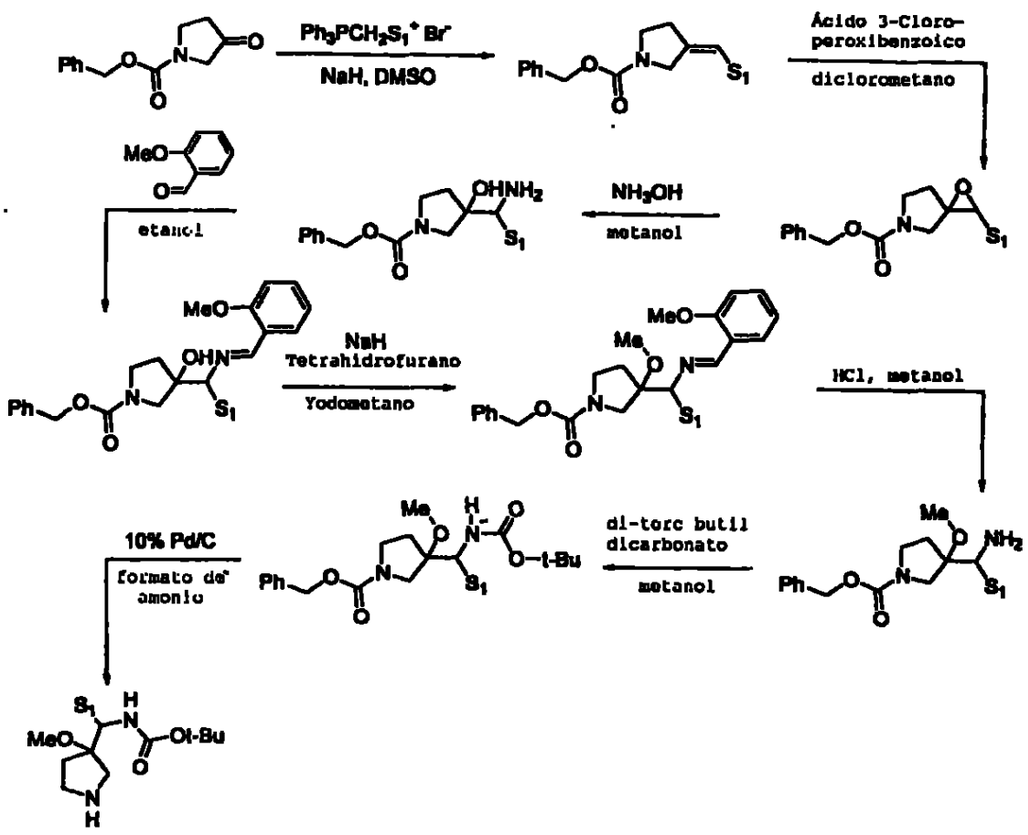
Esquema A4



En el Esquema A5, una 3-pirrolidinona carboxibencil protegida reacciona con una sal de Wittig en la presencia de hidruro de sodio o un equivalente en sulfóxido de dimetilo o cualquier solvente polar para dar una olefina. La olefina resultante es

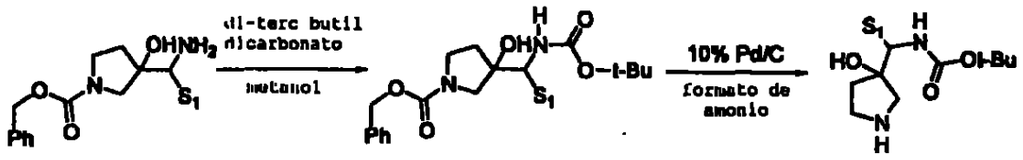
oxidada con ácido 3-cloroperoxibenzoico en diclorometano u otro hidrocarburo clorado adecuado para proporcionar un epóxido. El epóxido reacciona con hidróxido de amonio en metanol, etanol, dimetilformamida, dimetilacetamida o similar para generar un aminoalcohol. La metilación del grupo hidroxilo terciario puede entonces realizarse mediante la formación de una base de Schiff, seguida por la formación de un alcóxido con hidruro de sodio y el tratamiento con yodometano. La hidrólisis de la base de Schiff en condiciones estándar libera la amina. La reacción de la amina con di-terc-butildicarbonato en metanol, seguida por la hidrogenación a través de la catálisis con paladio proporciona cadenas laterales de R_7 (S_1 es alquilo, alquilo inferior, y arilo) que pueden usarse en la síntesis de compuestos de la Fórmula I.

Esquema A5



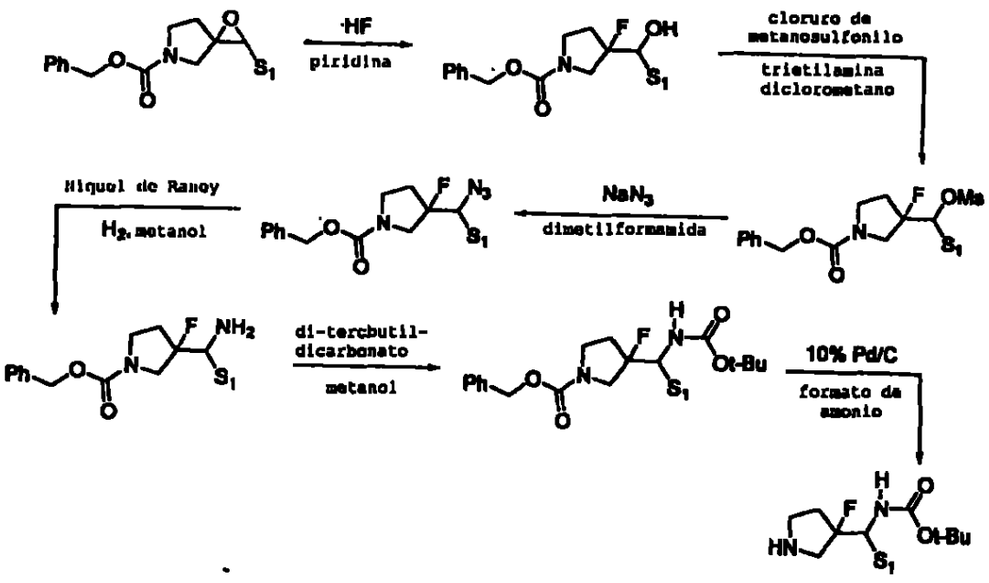
En el Esquema A6, el intermedio aminoalcohol descripto en el Esquema A5 reacciona con di-terc-butildicarbonato en metanol para producir el intermedio N-protegido. También se pueden utilizar otras estrategias de protección de aminas conocidas por los expertos en el arte. La hidrogenación bajo catálisis de paladio proporcionar cadenas laterales de R_7 de pirrolidina sustituida que se usan en la síntesis de los compuestos de la Fórmula I.

Esquema A6



En el Esquema A7, un intermedio de epóxido (Esquema A5) se abre selectivamente con ácido fluorhídrico en piridina, y el alcohol secundario resultante reacciona con cloruro de metanosulfonilo, o un reactivo de sulfonación equivalente, en diclorometano u otro hidrocarburo clorado y trietilamina. Otras bases apròpiadas incluyen diisopropiletilamina, piridina colidina, n-metilmorfolina, y similares. El mesilato es desplazado luego mediante la reacción con azida de sodio, y la azida se reduce con níquel de Raney bajo presión de hidrógeno en metanol. Tales transformaciones tienen buenos precedentes en el arte. La amina resultante reacciona luego con di-terc-butildicarbonato en metanol como se muestra en los Esquemas A4-A6 y el producto se hidrogena para proporcionar la cadena lateral de R_7 mostrada anteriormente.

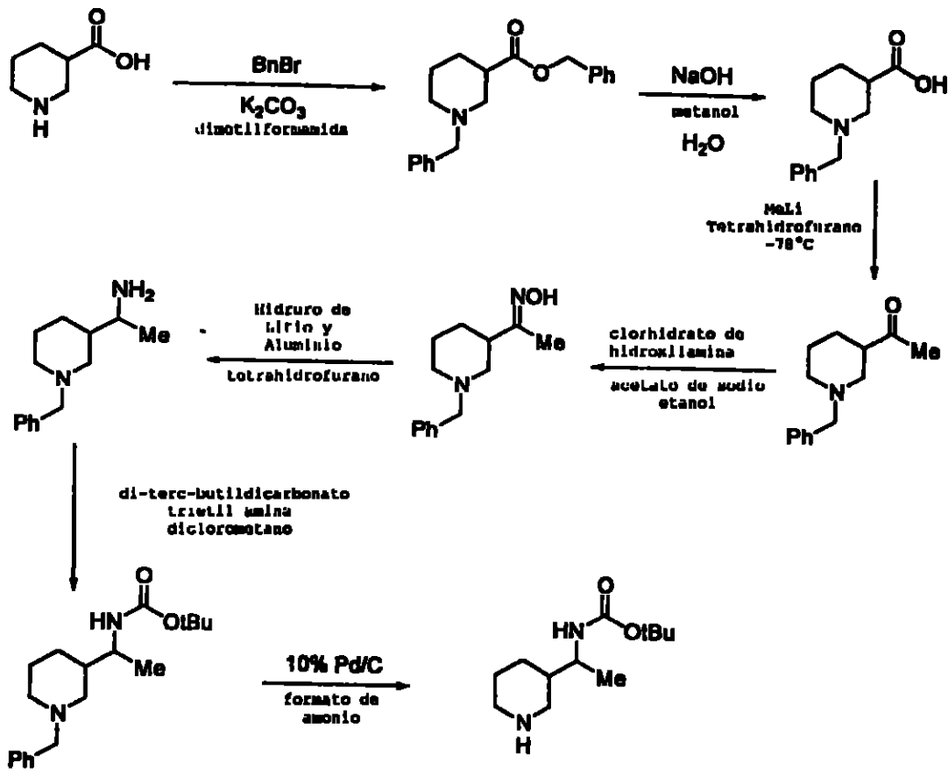
Esquema A7



La síntesis de piperidinas 3-sustituidas se demuestra en el Esquema A8. La esterificación y alquilación del ácido 3-piperidin carboxílico se logra simultáneamente mediante el tratamiento con un bromuro de bencilo en un solvente polar tal como dimetilformamida o sulfóxido de dimetilo y una base tal como carbonato de potasio (K_2CO_3) o un equivalente. El éster luego se hidroliza, y el ácido carboxílico resultante se convierte en una metil cetona mediante el tratamiento con metillitio a baja temperatura (0°C). Este intermedio luego se convierte en una oxima mediante numerosos métodos conocidos por los expertos en el arte. La oxima se reduce con hidruro de litio y aluminio en tetrahidrofurano para proporcionar una oxima. La amina reacciona con di-terc-butildicarbonato en

diclorometano y trietilamina como una base. Como se muestra en los Esquemas A4-A6, el producto luego se hidrogena para proporcionar la cadena lateral de R_7.

Esquema A8



Debe reconocerse a partir de los Esquemas A1-A8 que las sustituiciones en sistemas de anillos tales como un anillo de pirrolidina, piperazina, o piperidina forman centros quirales que dan R y S enantiómeros y diastereómeros. Tales enantiómeros o diastereómeros pueden ser separados, si se desea, por HPLC quiral en cualquier etapa. La resolución de cualquiera de los intermedios se puede realizar con técnicas

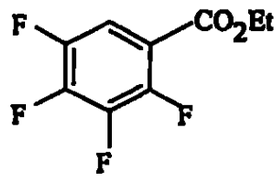
de cristalización fraccionada usando ácido mandélico, ácido tartárico, u otros agentes de resolución de ácido ópticamente puro, quiral. Las aminas bencílicas quirales pueden usarse en la preparación de materiales iniciales para los esquemas anteriores, y las amidas quirales pueden también prepararse usando ácidos quirales, tales como ácido mandélico y similares. Los isómeros pueden ser separados y la amina quiral puede ser hidrogenada, o la amida quiral puede ser hidrolizada.

La síntesis de compuestos de la Fórmula I de la invención se ilustra además con los siguientes ejemplos detallados. Los ejemplos no limitan el alcance o el espíritu de la invención a los procedimientos específicos descriptos. Los materiales iniciales y diversos intermedios utilizados en los siguientes ejemplos pueden obtenerse de fuentes comerciales, o se preparan rápidamente a partir de compuestos orgánicos disponibles comercialmente, usando métodos sintéticos conocidos.

EJEMPLO 1

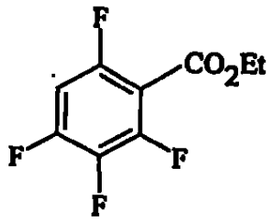
Síntesis de Benzoatos

(a) Etil éster del ácido 2,3,4,5-tetrafluorobenzoico



Una solución de ácido 2,3,4,5-tetrafluorobenzoico (4,68 g, 24,1 mmol) en diclorometano (50 ml) a 0°C es tratada con cloruro de oxalilo (11,5 ml, 132 mmol) seguido por N,N-dimetilformamida (4 gotas). La mezcla se agita a 0°C durante 5 minutos y luego a temperatura ambiente durante 1,5 hora. La mezcla se concentra hasta secarse y posteriormente se co-evapora desde benceno. El cloruro de ácido resultante se diluye con diclorometano (50 ml), se enfría a 0°C y se agrega etanol anhidro (15,0 ml, 256 mmol) gota a gota. La solución resultante se agita a temperatura ambiente durante 4,5 horas, luego se vierte en $NaHCO_3$ saturado y se extrae con cloroformo. Los extractos orgánicos combinados se lavan con solución salina, se secan sobre Na_2SO_4, se filtran y se concentran bajo vacío para lograr el compuesto del título (5,37 g). ^1H NMR ($CDCl_3$): δ 7,67-7,55 (m, 1H), 4,42 (q, 2H), 1,41 (t, 3H).

(b) Etil éster del ácido 2,3,4,6-tetrafluorobenzoico



Ácido 2,3,4,6-tetrafluorobenzoico (4,8 g, 24,7 mmol) en diclorometano (80 ml) se enfría a 0°C bajo una atmósfera de nitrógeno y es tratado con cloruro de oxalilo (11,2 ml, 128 mmol) seguido por N,N-dimetilformamida anhidra (2 gotas). La mezcla se calienta a temperatura ambiente y se agita durante 2 horas. La solución se co-evapora con benceno para dar un aceite que se recoge en diclorometano (80 ml), se enfría a 0°C bajo una atmósfera inerte, y se trata con etanol anhidro (15 ml, 258 mmol). Pasadas 5 horas a temperatura ambiente, la solución se vierte en $NaHCO_3$ saturado y se extrae con cloroformo. La fase orgánica se lava con solución salina, se seca sobre Na_2SO_4, se filtra y se concentra bajo vacío para proporcionar el compuesto del título (3,3 g). Este material se usa sin nueva purificación. ^1H NMR ($CDCl_3$): δ 6,93-6,75 (m, 1H), 4,42 (q, 2H), 1,39 (t, 3H).

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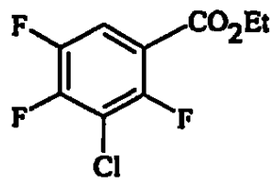
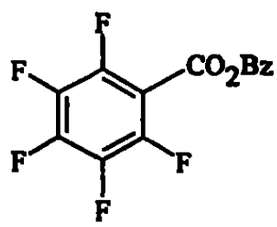
(c) Etil éster del ácido 3-cloro-2,4,5-trifluorobenzoico



A una solución de ácido 3-cloro-2,4,5-trifluorobenzoico (Ejemplo 20, 4,90 g, 23,3 mmol) en diclorometano (50 ml) se agrega cloruro de oxalilo (5,1 ml, 58,2 mmol) y N,N-dimetilformamida (1 gota). Pasados 45 minutos, la mezcla de la reacción se concentra en vacío. El residuo resultante se disuelve en diclorometano (50 ml) y se trata con etanol (10 ml, 172 mmol). A los 30 minutos, la mezcla de la reacción se diluye con diclorometano y se lava con $NaHCO_3$ saturado, agua y solución salina. La capa orgánica se seca sobre $MgSO_4$, se filtra y el filtrado se concentra para lograr el compuesto del título (5,59 g). ^1H NMR ($CDCl_3$): δ 7,76-7,68 (m, 1H), 4,40 (q, 2H), 1,39 (t, 3H).

(d) Bencil éster del ácido 2,3,4,5,6-pentafluorobenzoico



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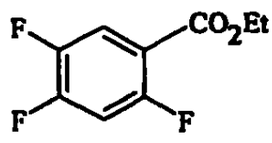
Una solución de ácido 2,3,4,5,6-pentafluorobenzoico (15,25 g, 71,9 mmol), 4-dimetilaminopiridina (4,4 g, 36,0 mmol) y alcohol bencílico (7,4 ml, 71,5 mmol) en diclorometano (150 ml) se enfría a 0°C bajo una atmósfera inerte. Se agrega clorhidrato de 1-[3-(dimetilamino)propil]-3-etil carbodiimida (16,7 g, 87,1 mmol) y la mezcla se agita a 0°C durante 2 horas. La mezcla se calienta a temperatura ambiente, se agita durante 24 horas y luego se vierte en solución salina. La mezcla se extrae con cloroformo y la fase orgánica se lava con $NaHCO_3$, se seca sobre Na_2SO_4, se filtra y se concentra bajo vacío para dar el compuesto del título como un sólido blanco (16,7 g). Este material se usa sin nueva purificación. ^1H NMR ($CDCl_3$): δ 7,49-7,27 (m, 5H), 5,40 (s, 2H).

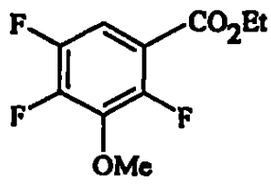
(e) Etil éster del ácido 2,4,5-trifluorobenzoico



A una solución de ácido 2,4,5-trifluorobenzoico (10,85 g, 61,6 mmol) en diclorometano (100 ml) se agrega cloruro de oxalilo (13,5 ml, 154 mmol) y N,N-dimetilformamida (1 gota). A los 45 minutos, la mezcla de la reacción se concentra bajo vacío. El residuo resultante se disuelve en diclorometano (100 ml) y a

esta solución se agrega etanol (18 ml, 310 mmol). A los 30 minutos, la mezcla de la reacción se diluye con diclorometano y se lava con $NaHCO_3$ saturado, agua y solución salina. La capa orgánica se seca sobre $MgSO_2$, se filtra y el filtrado se concentra para lograr el compuesto del título como un aceite (12,23 g). ^1H NMR ($CDCl_3$): δ 7,85-7,73 (m, 1H), 7,06-6,94 (m, 1H), 4,38 (q, 2H), 1,38 (t, 3H).

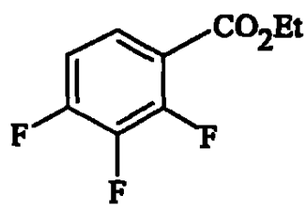
(f) Etil éster del ácido 2,4,5-trifluoro-3-metoxibenzoico



Una solución de ácido 2,4,5-trifluorobenzoico (2,513 g, 12,19 mmol) en diclorometano (50 ml) a 0°C es tratada con cloruro de oxalilo (5,4 ml, 61,9 mmol) seguido por N,N-dimetilformamida (4 gotas). La mezcla se agita a 0°C durante 5 minutos y luego a temperatura ambiente durante 2,5 horas. La mezcla se concentra hasta casi secarse y luego se co-evapora desde benceno. El cloruro de ácido resultante se diluye con diclorometano (50 ml), se enfría a 0°C, y luego se agrega etanol anhidro (7,30 ml, 124 mmol) gota a gota. La solución resultante se agita a temperatura ambiente durante 4,5 horas, se vierte en $NaHCO_3$ saturado, y se extrae con diclorometano.

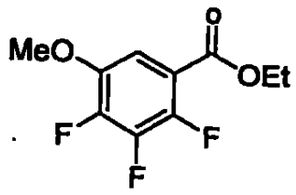
Los extractos orgánicos combinados se lavan con solución salina, se secan sobre Na_2SO_4, se filtran y se concentran bajo vacío para lograr el compuesto del título como un líquido de color amarillo claro (2,82 g). ^1H NMR ($CDCl_3$): δ 7,47 (ddd, 1H), 4,39 (q, 2H), 4,05 (s, 3H), 1,40 (t, 3H).

(g) Etil éster del ácido 2,3,4-trifluorobenzoico



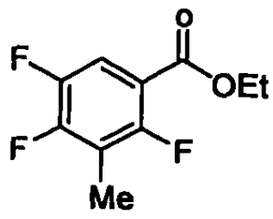
A una solución de ácido 2,3,4-trifluorobenzoico (10,85 g, 61,6 mmol) en diclorometano (100 ml) se agrega cloruro de oxalilo (13,5 ml, 154 mmol) y N,N-dimetilformamida (3 gotas). A los 45 minutos, la mezcla de la reacción se concentra bajo vacío. El residuo resultante se disuelve en diclorometano (100 ml) y a esta solución se agrega etanol (18 ml, 310 mmol). A los 30 minutos, la mezcla de la reacción se diluye con diclorometano y se lava con $NaHCO_3$, agua y solución salina. La capa orgánica se seca sobre $MgSO_4$, se filtra y el filtrado se concentra para lograr el compuesto del título como un aceite (12,23 g). ^1H NMR ($CDCl_3$): δ 7,93-7,67 (m, 1H), 7,09-6,96 (m, 1H), 4,39 (q, 2H), 1,40 (t, 3H).

(h) Etil éster del ácido 2,3,4-trifluoro-5-metoxibenzoico



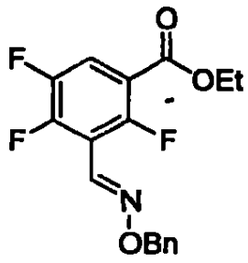
Una solución de ácido 2,3,4-trifluoro-5-metoxibenzoico (Hayashi et al, *Bull. Chem. Soc. Jap.*, 1972;45(9):2909-2914, 3,443 g, 16,7 mmol) en diclorometano (100 ml) a 0°C es tratada con cloruro de oxalilo (7 ml, 80 mmol) seguido por N,N-dimetilformamida (4 gotas). La mezcla se agita a temperatura ambiente durante 3,5 horas, se concentra hasta casi secarse, y se co-evapora con benceno. El cloruro de ácido luego se diluye con diclorometano, se enfría a 0°C, y se trata con etanol absoluto (10 ml, 170 mmol). La solución resultante se agita a temperatura ambiente durante 20 horas, se vierte en una solución de $NaHCO_3$ saturado y se extrae con diclorometano. Los extractos orgánicos se lavan con solución salina, se secan sobre Na_2SO_4, se filtran y se concentran bajo vacío para lograr el compuesto del título (3,785 g). ^1H NMR ($CDCl_3$): δ 7,36-7,29 (m, 1H), 4,42 (q, 2H), 3,93 (s, 2H), 1,44 (t, 3H).

(i) Etil éster del ácido 2,4,5-trifluoro-3-metoxibenzoico



Uns solución de ácido 3-metil-2,4,5-trifluorobenzoico (Shimizu T., Asai T., Kumai S., Jpn. Kokai Tokkyo Koho (1997) Solicitud Japonesa JP 95-219069, 4,3 g, 22,6 mmol) en diclorometano (100 ml) a 0°C es tratada con cloruro de oxalilo (4,2 g, 33 mmol) y luego con N,N-dimetilformamida (2 gotas). La mezcla se agita a temperatura ambiente durante 3 horas, se concentra y se seca en vacío. El cloruro de ácido se diluye con diclorometano, se enfría a 0°C, y se trata con etanol absoluto (10 ml, 170 mmol). La solución resultante se agita a temperatura ambiente durante 20 horas, se vierte en una solución de $NaHCO_3$ saturado y se extrae con diclorometano. Los extractos orgánicos se lavan con solución salina, se secan sobre Na_2SO_4, se filtran y se concentran bajo vacío para lograr el compuesto del título (3,8 g). ^1H NMR ($CDCl_3$): δ 7,67-7,26 (m, 1H), 4,44 (q, 2H), 2,27 (dd, 3H), 1,42 (t, 3H).

(j) Etil éster del ácido 3-(Benciloxiiminometil)-2,4,5-trifluorobenzoico



Ácido 2,4,5-trifluoro-3-formilbenzoico (Hiriuchi N., Yonezawa T., Chiba K., Yoshida H., Solicitud Internacional PCT [1999] WO 97-JP2918), (5,70 g, 27,9 mmol), trietilamina (11 ml, 78,9 mmol), clorhidrato de O-bencilhidroxilamina (4,47 g, 28,0 mmol) y tetrahidrofurano anhidro (150 ml) se agitan a temperatura ambiente durante 50 horas. La mezcla se vierte en solución salina y se ajusta el pH a 5,5-6,0 usando ácido clorhídrico 1,0 M. La mezcla se extrae con acetato de etilo. La fase orgánica se seca sobre Na_2SO_4, se filtra y se concentra en vacío para proporcionar ácido 3-(benciloxiiminometil)-2,4,5-trifluorobenzoico (8,63 g), que se usa sin nueva purificación. ^1H NMR ($CDCl_3$): δ 9,82-9,18 (bs, 1H), 8,24 (s, 1H), 7,94-7,68 (m, 1H), 7,55-7,23 (m, 5H), 5,23 (d, 2H). MS (EI, M-1) m/z 308.

El ácido 3-(benciloxiiminometil)-2,4,5-trifluorobenzoico (0,117 g, 0,378 mmol), 4-dimetilaminopiridina (0,023 g, 0,189 mmol), etanol anhidro (0,030 ml, 0,517 mmol) se mezclan en diclorometano (6 ml), se enfrían a 0°C y se tratan con

clorhidrato de 1-etil-3-(3-dimetilaminopropil)carbodiimida (0,082 g, 0,427 mmol). Después de estar 2 horas a 0°C y a temperatura ambiente durante 21 horas, los solventes se evaporan. El residuo se disuelve en cloroformo, se lava con $NaHCO_3$ saturado y solución salina, se seca sobre Na_2SO_4, se filtra y se concentra en vacío. La purificación mediante cromatografía (acetato de etilo/hexanos de 1:8) proporciona el compuesto del título (0,068 g). ^1H NMR ($CDCl_3$): δ 8,27 (s, 1H), 7,87-7,66 (m, 1H), 7,49-7,28 (m, 5H), 5,27 (s, 2H), 4,48-4,29 (q, 2H), 1,46-1,31 (t, 3H).

EJEMPLO 2

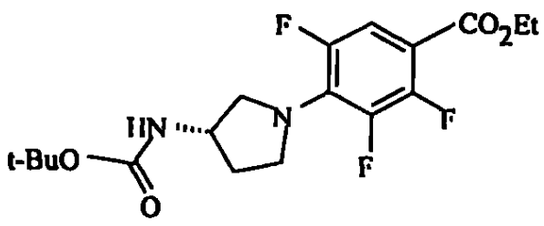
Síntesis de Benzoatos 4-Heterocíclicos

Procedimiento General

Una mezcla de éster del ácido benzoico 4-fluoro sustituido (1 eq.), pirrolidina sustituida (1,3-2,5 eq.) y trietilamina (2-10 eq.) en N,N-dimetilformamida o acetonitrilo se calienta a 50°C-100°C durante 15 a 60 horas. La solución luego se concentra hasta casi secarse, se vierte sobre una solución saturada de $NaHCO_3$ y se extrae con acetato de etilo. Los extractos orgánicos combinados se lavan con solución salina, se secan sobre Na_2SO_4, se filtran y se concentran en vacío. El residuo resultante se purifica mediante cromatografía de

columna (acetato de etilo/hexanos) para lograr ésteres de ácidos 4-pirrolidinil sustituidos.

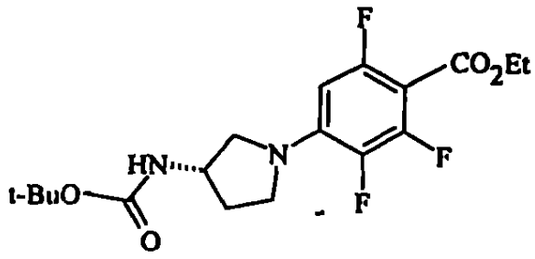
(a) Etil éster del ácido 4-[(S)-3-terc-butoxicarbonilaminopirrolidin-1-il]-2,3,5-trifluorobenzoico



Una solución de etil éster del ácido 2,3,4,5-tetrafluorobenzoico (Ejemplo 1a, 4,03 g, 18,1 mmol), terc-butil éster del ácido (S)-pirrolidin-3-ilcarbámico (4,02 g, 21,6 mmol) (Sánchez J.P., Domagala J.M., Heifetz C.L., Priebe S.R., Sesnie J.A., Trehan A.K., *J. Med. Chem.*, 1992;35(10):1764-1773), y trietilamina (18,0 ml, 129 mmol) en acetonitrilo (50 ml) se calienta a 50°C bajo una atmósfera de nitrógeno durante 4,5 horas. La solución amarilla se concentra en vacío y se vierte en una solución de $NaHCO_3$ saturado. La mezcla se extrae luego con clororformo, y los extractos orgánicos combinados se lavan con solución salina, se secan sobre Na_2SO_4, se filtran y se concentran en vacío. El residuo resultante luego se purifica mediante cromatografía de columna rápida (acetato de etilo:hexanos de 1:7) para lograr el compuesto del título (5,24 g). ^1H NMR ($CDCl_3$): δ 7,35 (ddd,

1H), 4,70-4,65 (bs, 1H), 4,42-4,20 (m, 3H), 3,90-3,62 (m, 3H), 3,58-3,42 (m, 1H), 2,28-2,03 (m, 1H), 1,99-1,80 (m, 1H), 1,46 (s, 9H), 1,37 (t, 3H).

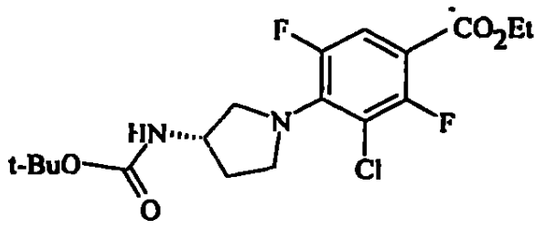
(b) Etil éster del ácido 4-[(S)-3-terc-butoxicarbonilaminopirrolidin1-1-il]-2,3,6-trifluorobenzoico



Una solución de etil éster del ácido 2,3,4,6-tetrafluorobenzoico (Ejemplo 1b, 5,1 g, 22,9 mmol), trietilamina (22 ml, 157 mmol) y terc-butil éster del ácido (S)-pirrolidin-3-ilcarbámico (5,2 g, 27,9 mmol) en acetonitrilo (60 ml) se agita a temperatura ambiente durante 64 horas. La mezcla se concentra en vacío y el residuo se disuelve en cloroformo, se lava con $NaHCO_3$ y luego con solución salina, se seca sobre Na_2SO_4, se filtra y se concentra bajo vacío para lograr un sólido. El sólido se purifica mediante cromatografía de columna (acetato de etilo/cloroformo/hexanos de 1:1:7) para lograr el compuesto del título (6,21 g). ^1H NMR ($CDCl_3$): δ 6,07 (ddd, 1H), 4,78-4,63 (bd, 1H), 4,49-4,22 (m,

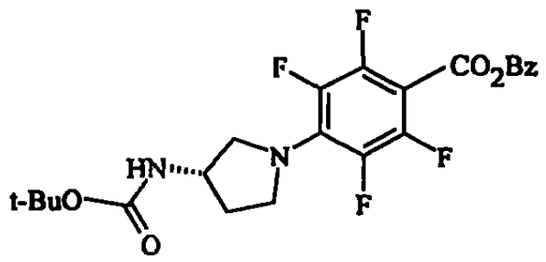
3H), 3,80-3,68 (m, 1H), 3,66-3,28 (m, 3H), 2,33-2,13 (m, 1H), 2,04-1,83 (m, 1H), 1,45 (s, 9H), 1,36 (t, 3H).

(c) Etil éster del ácido 4-[(S)-3-terc-butoxicarbonilaminopirrolidin-1-il]-3-cloro-2,5-difluorobenzoico



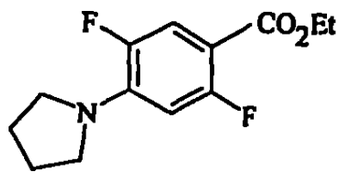
A una solución de etil éster del ácido 3-cloro-2,4,5-trifluorobenzoico (Ejemplo 1c, 5,50 g, 23,05 mmol) en acetonitrilo (25 ml) se agrega trietilamina (6,43 ml, 46,1 mmol) y terc-butil éster del ácido (S)-pirrolidin-3-ilcarbámico (4,72 g, 25,4 mmol). Depués de 48 horas, la mezcla se diluye con acetato de etilo y se lava con $NaHCO_3$ saturado, agua y solución salina. La capa orgánica se seca sobre $MgSO_4$, se filtra y el filtrado se concentra para lograr el compuesto del título (9,34 g). MS CI: m/z 405 (MH^+).

(d) Bencil éster del ácido 4-[(S)-3-(terc-butoxicarbonilamino)pirrolidin-1-il]-2,3,5,6-tetrafluorobenzoico



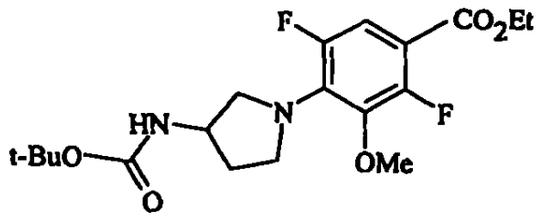
Una solución de bencil éster del ácido 2,3,4,5,6-pentafluorobenzoico (Ejemplo 1d, 8,05 g, 26,6 mmol), trietilamina (26 ml, 186 mmol) y terc-butil éster del ácido (S)-pirrolidin-3-il-carbámico (5,6 g, 30 mmol) en acetonitrilo (150 ml) se agita a temperatura ambiente durante 24 horas. El solvente se remueve bajo vacío y el residuo se disuelve en cloroformo, se lava con $NaHCO_3$ y luego solución salina, se seca sobre Na_2SO_4, se filtra y se concentra en vacío para lograr un sólido. El sólido luego se purifica mediante cromatografía de columna (acetato de etilo/cloroformo/hexanos de 1:1:6) para dar el compuesto del título como un sólido (7,92 g). ^1H NMR ($CDCl_3$): δ 7,48-7,30 (m, 5H), 5,35 (s, 2H), 4,77-4,50 (m, 1H), 4,37-4,19 (m, 1H), 4,01-3,63 (m, 3H), 3,59-3,46 (m, 1H), 2,29-2,09 (m, 1H), 2,01-1,82 (m, 1H), 1,45 (s, 9H).

(e) Etil éster del ácido 4-(pirrolidin-1-il)-2,5-difluorobenzoico



A una solución de etil éster del ácido 2,4,5-trifluorobenzoico (Ejemplo 1e, 4,32 g, 21,2 mmol) en acetonitrilo (25 ml) se agrega trietilamina (5,9 ml, 42,3 mmol) y pirrolidina (2,2 ml, 25,4 mmol). Después de 24 horas, la mezcla de la reacción se diluye con acetato de etilo y se lava con $NaHCO_3$ saturado, agua y solución salina. La capa orgánica se seca sobre $MgSO_4$, se filtra y el filtrado se concentra para lograr el compuesto del título como un aceite (5,25 g). MS CI: m/z 256 (MH^+).

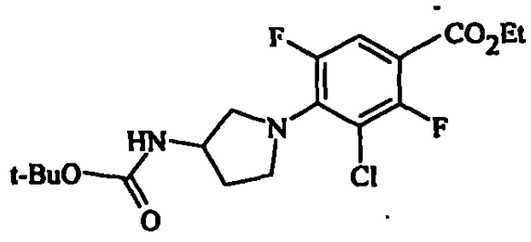
(f) Etil éster del ácido 4-[3-(terc-butoxicarbonilamino)pirrolidin-1-il]-2,5-difluoro-3-metoxibenzoico



Una solución de etil éster del ácido 2,4,5-trifluoro-3-metoxibenzoico (Ejemplo 1f, 2,821 g, 12,05 mmol), terc-butil éster del ácido pirrolidin-3-ilcarbámico (3,310 g, 17,77 mmol) y trietilamina (9,13 g, 12,6 ml, 90,23 mmol) en acetonitrilo

(50 ml) se calienta a 40°C bajo nitrógeno durante 2 días. La solución amarilla se concentra hasta casi secarse y se vierte en una solución de $NaHCO_3$ saturado y se extrae con diclorometano. Los extractos orgánicos combinados se lavan con solución salina, se secan sobre Na_2SO_4, se filtran y se concentran bajo vacío. El residuo resultante se purifica mediante cromatografía de columna rápida (acetato de etilo/hexanos de 1:7) para lograr el compuesto del título como un sólido amarillo (3,743 g). MS EI: m/z 401 (MH^+).

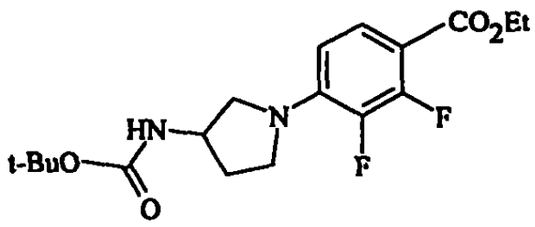
(g) Etil éster del ácido 4-[3-terc-butoxicarbonilaminopirrolidin-1-il]-3-cloro-2,5-difluorobenzoico



A una solución de etil éster del ácido 3-cloro-2,4,5-trifluorobenzoico (Ejemplo 1c, 5,50 g, 23,05 mmol) en acetonitrilo (25 ml) se agrega trietilamina (6,43 ml, 46,1 mmol) y terc-butil éster del ácido pirrolidin-3-ilcarbámico (4,72 g, 25,4 mmol). Después de 48 horas, la mezcla se diluye con acetato de etilo y se lava con $NaHCO_3$ saturado, agua y

solución salina. La capa orgánica se seca sobre $MgSO_4$, se filtra y el filtrado se concentra para lograr el compuesto del título (9,2 g). MS CI: m/z 405 (MH^+).

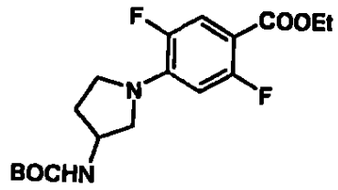
(b) Etil éster del ácido 4-[3-(terc-butoxicarbonilamino)pirrolidin-1-il]-2,3-difluorobenzoico



Una solución de etil éster del ácido 2,3,4-trifluorobenzoico (Ejemplo 1g, 3,70 g, 18,1 mmol), terc-butil éster del ácido pirrolidin-3-ilcarbámico (4,02 g, 21,6 mmol) y trietilamina (18,0 ml, 129 mmol) en acetonitrilo (50 ml) se calienta a 50°C bajo una atmósfera de nitrógeno durante 4,5 horas. La solución se concentra en vacío y se vierte en una solución de $NaHCO_3$ saturado. La mezcla se extrae luego con cloroformo y los extractos orgánicos combinados se lavan con solución salina, se secan con Na_2SO_4, se filtran y la mezcla se concentra en vacío. El residuo resultante se purifica luego mediante cromatografía de columna (acetato de etilo/hexanos de 1:7) para lograr el compuesto del título (4,70 g). ^1H NMR ($CDCl_3$): δ 7,59-7,49 (m, 1H), 6,35-6,26 (m, 1H), 4,88-4,84 (bd, 1H),

4,39-4,28 (m, 3H), 3,81-3,50 (m, 3H), 3,48-3,34 (m, 1H), 2,32-2,15 (m, 1H), 2,02-1,76 (m, 1H), 1,45 (s, 9H), 1,40 (t, 3H).

(i) Etil éster del ácido 4-(3-terc-butoxicarbonilaminopirrolidin-1-il)-2,5-difluorobenzoico



A una solución de etil éster del ácido 2,4,5-trifluorobenzoico (Ejemplo 1e, 14,8 g, 72,4 mmol) en acetonitrilo (225 ml) se agrega trietilamina (65 ml, 466 mmol) y terc-butil éster del ácido pirrolidin-3-ilcarbámico (16,07 g, 86,2 mmol). Después de 45 horas, la mezcla de la reacción se diluye con acetato de etilo y se lava con $NaHCO_3$ saturado, agua y solución salina. la capa orgánica se seca sobre $MgSO_4$, se filtra y el filtrado se concentra para lograr un aceite. El residuo resultante se purifica mediante cromatografía rápida (acetato de etilo/hexanos de 1:5) para lograr el compuesto del título. MS (ES, M+1) m/z 371, punto de fusión 98°C-100°C.

Los siguientes compuestos se sintetizan de acuerdo con los procedimientos generales descriptos en los Ejemplos 2a-i precedentes.

(k) Etil éster del ácido 4-(3-terc-butoxicarbonilaminopirrolidin-1-il)-2,5-difluoro-3-metilbenzoico (MS ES, MH^+) m/z 385) usando etil éster del ácido 2,4,5-trifluoro-3-metilbenzoico (Ejemplo 1i) y terc-butil éster del ácido pirrolidin-3-ilcarbámico.

(l) Etil éster del ácido 4-[3-(terc-butoxicarbonilaminometil)pirrolidin-1-il]-2,5-difluoro-3-metilbenzoico (MS ES, MH^+) m/z 399) usando etil éster del açido 2,4,5-trifluoro-3-metilbenzoico (Ejemplo 1i) y 3-(terc-butoxicarbonilaminometil)pirrolidina (Rogers D.H., Saunders J., Williams J.P., DE 19955794).

(m) Etil éster del ácido 4-(3-terc-butoxicarbonilaminopirrolidin-1-il)-2,3-difluoro-5-metoxibenzoico (MS ES, MH^+) m/z 401) usando etil éster del ácido 2,3,4-trifluoro-5-metoxibenzoico (Ejemplo 1h) y terc-butil éster del ácido pirrolidin-3-ilcarbámico.

(n) Etil éster del ácido 4-[3-(terc-butoxicarbonilaminometil)pirrolidin-1-il]-2,5-difluoro-3-

metoxibenzoico (MS ES, MH^+) m/z 415) usando etil éster del ácido 2,4,5-trifluoro-3-metoxibenzoico (Ejemplo 1f) y 3-(terc-butoxicarbonilaminometil)pirrolidina (Rogers D.H., Saunders J., Williams J.P., DE 19955794).

(o) Etil éster del ácido 4-(3-terc-butoxicarbonilaminopirrolidin-1-il)-3-etoxi-2,5-difluorobenzoico (^1H NMR (200 MHz, $CDCl_3$): δ 7,31 (dd, 1H), 4,71 (bs, 1H), 4,34-3,4 (m, 9H), 2,23-1,81 (m, 2H), 1,45 (s, 9H), 1,37 (t, 3H), 1,33 (t, 3H); ((MS ES, MH^+) m/z 415) usando etil éster deĭ ácido 3-etoxi-2,3-difluorobenzoico (Sánchez J.P., Gogliotti R.D., Domagala J.M., Gracheck S.J., Huband M.D., Sesnie J.A., Cohen M.A., Shapiro M.A., *J. Med. Chem.*, 1995;38(22):4478-4487) y terc-butil éster del ácido pirrolidin-3-ilcarbámico.

(p) Etil éster del ácido 3-(benciloxiiminometil)-4-(3-terc-butoxicarbonilaminopirrolidin-1-il)-2,5-difluorobenzoico (MS ES, MH^+) m/z 504) usando etil éster del ácido 3-(benciloxiiminometil)-2,4,5-trifluorobenzoico (Ejemplo 1j) y terc-butil éster del ácido pirrolidin-3-ilcarbámico.

(q) Etil éster del ácido 3-Cloro-2,5-difluoro-4-(3-[1,2,3]-triazol-1-ilpirrolidin-1-il)benzoico (^1H NMR (200 MHz, $CDCl_3$): δ 7,79 (s, 1H), 7,65 (s, 1H), 7,45-7,51 (m, 1H), 5,40-5,30 (m,

1H), 4,34-4,24 (q, 2H), 4,13-3,45 (m, 4H), 2,65-2,50 (m, 1H), 2,43-2,28 (m, 1H), 1,34-1,27 (t, 3H)) usando etil éster del ácido 3-cloro-2,4,5-trifluorobenzoico (Ejemplo 1c) y 1-pirrolidin-3-il-1H-[1,2,3]triazol (Singh R., Singh I.P., Thomas G., Singh M.P., Micetich R.G., Fahti-Afshar R., Doerksen T.R., Solicitud Internacional PCT, 1992, WO 9210492 A1).

EJEMPLO 3

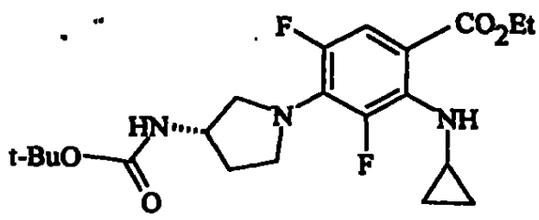
Síntesis de Amino Benzoatos 2-Sustituidos

Procedimiento Gèneral

Una solución de etil ésteres del ácido 4-(pirrolidin-1-il)-2-fluorobenzoico (Ejemplo 2) y ciclopropilamina (10-15 eq.) en sulfóxido de dimetilo y trietilamina (2-5 eq.) se calienta en un tubo de vidrio sellado durante 3 días a 140°C. Se sopla aire comprimido en la mezcla para remover la ciclopropilamina excedente. La solución resultante se concentra bajo vacío y se purifica mediante cromatografía de columna (acetato de etilo/hexanos) para lograr ésteres del ácido 4-(sustituido pirrolidin-1-il)-2-ciclopropilamino-benzoico.

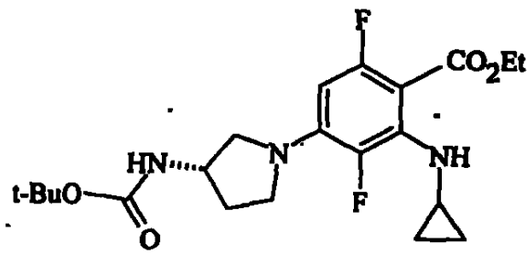
(a) Etil éster del ácido 4-[(S)-3-terc-butoxicarbonilaminopirrolidin-1-il]-2-ciclopropilamino-3,5-difluorobenzoico

149



Una solución de etil éster del ácido 4-[(S)-3-(terc-butoxicarbonilamino)pirrolidin-1-il]-2,3,5-trifluorobenzoico (Ejemplo 2a, 1,95 g, 5,01 mmol) y ciclopropilamina (14,0 ml, 201 mmol) en sulfóxido de dimetilo (5 ml) se calienta en un tubo de vidrio sellado durante 44,5 horas a 100°C. Se sopla aire comprimido en la solución negra para remover la ciclopropilamina excedente. La solución se concentra bajo alto vacío y se purifica mediante cromatografía de columna rápida (acetato de etilo/hexanos de 1:9) para lograr el compuesto del título (1,77 g). ^{1}H NMR ($CDCl_3$): δ 7,32 (dd, 1H), 4,81-4,67 (bs, 1H), 4,35-4,16 (m, 3H), 3,95-3,40 (m, 4H), 2,98-2,80 (m, 1H), 2,25-2,08 (m, 1H), 1,97-1,77 (m, 1H), 1,46 (s, 9H), 1,34 (t, 3H), 0,72-0,63 (m, 2H), 0,57-0,49 (m, 2H).

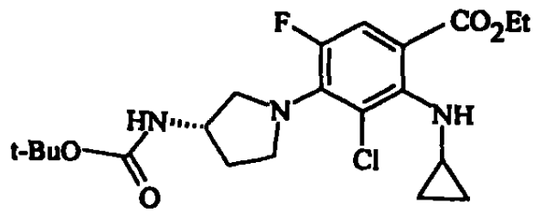
(b) Etil éster del ácido 4-[(S)-3-terc-butoxicarbonilaminopirrolidin-1-il]-2-ciclopropilamino-3,6-difluorobenzoico



Una solución de etil éster del ácido 4-[(S)-3-(terc-butoxicarbonilamino)pirrolidin-1-il]-2,3,6-trifluorobenzoico (Ejemplo 2b, 5,4 g, 13,9 mmol), ciclopropilamina (40 ml, 577 mmol) y sulfóxido de dimetilo (28 ml) en un tubo de vidrio sellado se calienta a 100°C durante 27 horas. La amina en exceso se remueve soplando aire comprimido antes de que la solución se concentre bajo alto vacío. El residuo se purifica entonces mediante cromatografía de columna (acetato de etilo/cloroformo/hexanos de 1:1:8) para lograr el compuesto del título (4,80 g). ^{1}H NMR ($CDCl_3$): δ 7,42 (bs, 1H), 5,69 (ddd, 1H), 4,76-4,61 (m, 1H), 4,37-4,19 (m, 3H), 3,81-3,66 (m, 1H), 3,65-3,43 (m, 2H), 3,39-3,28 (m, 1H), 2,98-2,82 (m, 1H), 2,30-2,09 (m, 1H), 1,98-1,82 (m, 1H), 1,45 (s, 9H), 1,34 (t, 3H), 0,72-0,68 (m, 2H), 0,67-0,44 (m, 2H).

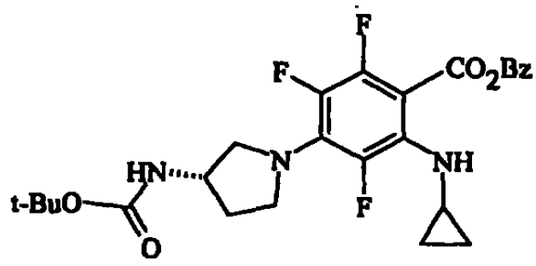
(c) Etil éster del ácido 4-[(S)-3-terc-butoxicarbonilaminopirrolidin-1-il]-3-cloro-2-ciclopropilamino-5-fluorobenzoico

151



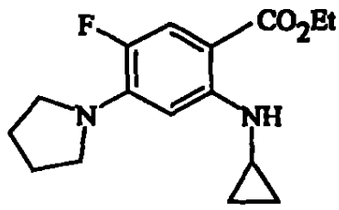
Una solución de etil éster del ácido 4-[(S)-3-(terc-butoxicarbonilamino)pirrolidin-1-il]-3-cloro-2,5-difluorobenzoico (Ejemplo 2c, 9,34 g, 23,1 mmol), ciclopropilamina (16 ml, 228 mmol) y sulfóxido de dimetilo (30 ml) se calienta en un tubo sellado a 110°C durante 3 días. Después de enfriar a temperatura ambiente la mezcla de la reacción se diluye con acetato de etilo y se lava con $NaHCO_3$ saturado, agua y solución salina. La capa orgánica se seca sobre $MgSO_4$, se filtra y el filtrado se concentra para lograr un residuo marrón. El residuo se purifica luego mediante cromatografía de columna (acetato de etilo/hexanos de 1:1) para lograr el compuesto del título (4,41 g). MS CI: m/z 442 (MH^+).

(d) Bencil éster del ácido 4-[(S)-3-terc-butoxicarbonilaminopirrolidin-1-il]-2-ciclopropilamino-3,5,6-trifluorobenzoico



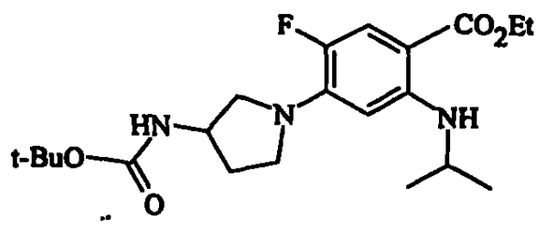
Una solución de bencil éster del ácido 4-[(S)-3-(terc-butoxicarbonilamino)pirrolidin-1-il]-2,3,5,6-tetrafluorobenzoico (Ejemplo 2d, 2,5 g, 5,3 mmol), ciclopropilamina (40 ml, 577 mmol) y sulfóxido de dimetilo (20 ml) en un tubo de vidrio sellado se calienta a 80°C durante 24 horas. La amina en exceso se remueve soplando aire comprimido y la solución luego se concentra bajo alto vacío. El residuo se purifica mediante cromatografía de columna (acetato de etilo/cloroformo/hexanos 1:1:7) para lograr el compuesto del título como un sólido (2,31 g). ^{1}H NMR ($CDCl_3$): δ 7,47-7,27 (m, 5H), 7,12 (bs, 1H), 5,30 (s, 2H), 4,78-4,62 (m, 1H), 4,35-4,17 (m, 1H), 3,96-3,56 (m, 3H), 3,54-3,39 (m, 1H), 2,91-2,73 (m, 1H), 2,24-2,02 (m, 1H), 1,96-1,77 (m, 1H), 1,45 (s, 9H), 0,69-0,56 (m, 2H), 0,53-0,40 (m, 2H).

(e) Etil éster del ácido 2-ciclopropilamino-5-fluoro-4-pirrolidin-1-ilbenzoico



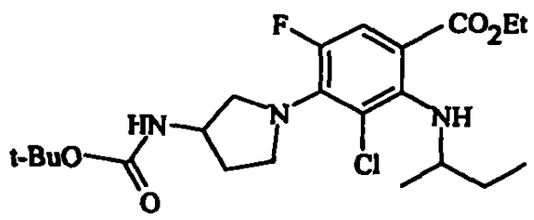
Etil éster del ácido 4-(pirrolidin-1-il)-2,5-difluorobenzoico (Ejemplo 2c, 5,25 g, 20,6 mmol) y ciclopropilamina (30 ml, 428 mmol) se agitan en sulfóxido de dimetilo (30 ml) a 110°C durante 3 días en un tubo sellado. Después de enfriar a temperatura ambiente, la mezcla de la reacción se diluye con acetato de etilo y se lava con $NaHCO_3$ saturado, agua y solución salina. La capa orgánica se seca sobre $MgSO_4$, se filtra y el filtrado se concentra para lograr un residuo marrón. El residuo se purifica mediante cromatografía de columna rápida (hexanos/diclorometano 1:9) para lograr el compuesto del título como un sólido (5,39 g). MS CI: m/z 293 (MH^+).

(f) Etil éster del ácido 4-[3-(terc-butoxicarbonilamino)pirrolidin-1-il]-5-fluoro-2-isopropilaminobenzoico



Etil éster del ácido 4-[3-(terc-butoxicarbonilamino)-pirrolidin-1-il]-2,5-difluorobenzoico (Ejemplo 2j, 5,4 g, 13,9 mmol), isopropilamina (40 ml, 469 mmol) y sulfóxido de dimetilo (25 ml) se calientan a 100°C durante 4 días en un tubo de vidrio sellado. La amina en exceso se remueve soplando aire comprimido. El residuo se filtra y se concentra bajo vacio para dar un aceite espeso. Purificación mediante cromatografía de columna (acetato de etilo/cloroformo/hexanos 1:1:7) para proporcionar el compuesto del título como un sólido (1,6 g). MS: m/z 410 (MH^+).

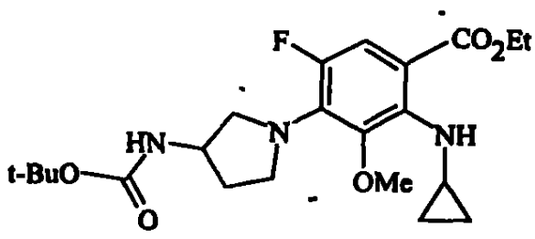
(g) Etil éster del ácido 4-[(S)-3-(terc-butoxicarbonilamino)pirrolidin-1-il]-2-sec-butilamino-3-cloro-5-fluorobenzoico



Etil éster del ácido 4-[(S)-3-(terc-butoxicarbonilamino)pirrolidin-1-il]-3-cloro-2,5-difluorobenzoico (Ejemplo 2c, 1,95 g, 4,81 mmol), sec-butilamina (30 ml, 296 mmol) y sulfóxido de dimetilo (20 ml) se calientan en un tubo de vidrio sellado a 110°C durante 24

horas. La mezcla de la reacción se evapora, y la purificación mediante cromatografía de columna (1:8, acetato de etilo/hexanos) proporciona el compuesto del título como un jarabe amarillo (3,69 g). MS EI: m/z 548 (MH^+).

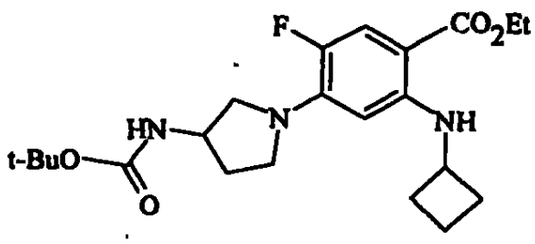
(b) Etil éster del ácido 4-[3-terc-butoxicarbonilaminopirrolidin-1-il]-2-ciclopropilamino-5-fluoro-3-metoxibenzoico



Una solución de etil éster del ácido 4-[3-(terc-butoxicarbonilamino)pirrolidin-1-il]-2,5-difluoro-3-metoxibenzoico (Ejemplo 2f, 3,087 g, 7,71 mmol) y ciclopropilamina (12,0 ml, 172 mmol) en sulfóxido de dimetilo (5 ml) se calienta en un tubo de vidrio sellado durante 3 días a 110°C. Se sopla aire comprimido en la solución negra para remover le ciclopropilamina en exceso. La solución se concentra bajo vacío y se purifica mediante cromatografía de columna rápida (acetato de etilo/hexanos 1:5) para lograr el compuesto del título como un sólido amarillo (0,875 g). ^1H NMR ($CDCl_3$): δ 7,33 (d, 1H), 7,15 (bs, 1H), 4,78-4,65 (m, 1H),

4,33-4,15 (m, 3H), 3,92-3,50 (m, 3H), 3,55 (s, 3H), 3,45-3,34 (m, 1H), 3,02-2,89 (m, 1H), 2,28-2,09 (m, 1H), 1,93-1,77 (m, 1H), 1,46 (s, 9H), 1,34 (t, 3H), 0,7-0,59 (m, 2H), 0,49-0,42 (m, 2H).

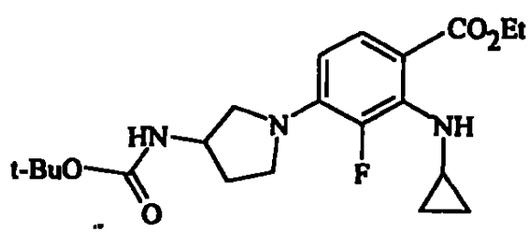
(i) Etil éster del ácido 4-[3-terc-butoxicarbonilaminopirrolidin-1-il]-2-ciclobutilamino-5-fluorobenzoico



Una solución de etil éster del ácido 4-[3-(terc-butoxicarbonilamino)pirrolidin-1-il]-2,5-difluorobenzoico (2j, 3,059 g, 8,26 mmol) y ciclobutilamina (15,0 ml, 175 mmol) en sulfóxido de dimetilo (20 ml) se calienta en un recipiente sellado durante 4 días a 110°C. Se sopla aire comprimido en la solución negra para remover la ciclobutilamina en exceso. La solución se concentra bajo vacío y se urifica mediante cromatografía de columna rápida (acetato de etilo/hexanos 1:5) para lograr el compuesto del título como un sólido amarillo (1,715 g). ^{1}H NMR ($CDCl_3$): δ 7,67 (bs, 1H), 7,48 (d, 1H), 5,54 (d, 1H), 4,77-4,64 (bs, 1H), 4,38-4,18 (m, 3H), 3,97-3,85 (m,

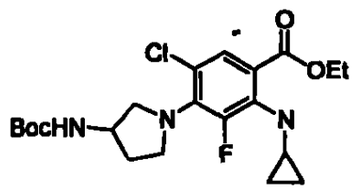
1H), 3,80-3,42 (m, 3H), 3,41-3,30 (m, 1H), 2,50-2,32 (m, 2H), 2,28-2,12 (m, 1H), 2,05-1,70 (m, 5H), 1,46 (s, 9H), 1,35 (t, 3H).

(j) Etil éster del ácido 4-[3-terc-butoxicarbonilaminopirrolidin-1-il]-2-ciclopropilamino-2-fluorobenzoico



Una solución de etil éster del ácido 4-[3-(terc-butoxicarbonilamino)pirrolidin-1-il]-2,3-difluorobenzoico (Ejemplo 2h, 1,85 g, 5,01 mmol) y ciclopropilamina (14,0 ml, 201 mmol) en N,N-dimetilacetamida (5 ml) se calienta en un tubo de vidrio sellado durante 48 horas a 100°C. La solución luego se concentra bajo alto vacío y se purifica mediante cromatografía de columna (acetato de etilo/hexanos 1:9) para lograr el compuesto del título (1,57 g). ^{1}H NMR ($CDCl_3$): δ 7,59 (bs, 1H), 7,57 (dd, 1H), 6,00 (dd, 1H), 4,82-4,68 (bd, 1H), 4,39-4,18 (m, 3H), 3,80-3,49 (m, 3H), 3,41-3,30 (m, 1H), 3,0-2,88 (m, 1H), 2,31-2,11 (m, 1H), 2,00-1,85 (m, 1H), 1,45 (s, 9H), 1,37 (t, 3H), 0,73-0,50 (m, 4H).

(k) Etil éster del ácido 4-[3-(terc-butoxicarbonilamino)pirrolidin-1-il]-5-cloro-2-ciclopopilamino-3-fluorobenzoico



Una solución de etil éster del ácido 4-[3-(terc-butoxicarbonilamino)pirrolidin-1-il]-5-cloro-2,3-difluorobenzoico (Ejemplo 21, 3,75 g, 9,3 mmol) y ciclopropilamina (14,0 ml, 201 mmol) en N,N-dimetilacetamida (5 ml) se calienta en un tubo de vidrio sellado durante 48 horas a 100°C. La solución luego se concentra bajo alto vacío y se purifica mediante cromatografía de columna (acetato de etilo/hexanos 1:9) para lograr el compuesto del título (2,0 g). ^{1}H NMR ($CDCl_3$): δ 7,64 (d, 1H), 7,56 (bs, 1H), 4,98-4,90 (bd, 1H), 4,40-4,20 (m, 3H), 3,78-3,63 (m, 4H), 2,97-2,83 (m, 1H), 2,35-2,21 (m, 1H), 1,93-1,81 (m, 1H), 1,46 (s, 9H), 1,38 (t, 3H), 0,75-0,61 (m, 2H), 0,57-0,50 (m, 2H).

Los siguientes compuestos se sintetizan de acuerdo con los procedimientos generales de los Ejemplos 3a-k descriptos anteriormente.

(l) Etil éster del ácido 4-(3-terc-butoxicarbonilaminopirroldin-1-il)-2-ciclopropilamino-5-fluoro-3-metilbenzoico ([MS ES, MH^+] m/z 422) usando etil éster del ácido 4-(3-terc-butoxicarbonilaminopirrolidin-1-il)-2,5-difluoro-3-metilbenzoico (Ejemplo 2k).

(m) Etil éster del ácido 4-[3-(terc-butoxicarbonilaminometil)pirroldin-1-il]-2-ciclopropilamino-5-fluoro-3-metilbenzoico ([MS ES, MH+1] m/z 436) usando etil éster del ácido 4-[3-(terc-butoxicarbonilaminometil)-pirrolidin-1-il]-2,5-difluoro-3-metilbenzoico (Ejemplo 2l).

(n) Etil éster del ácido 4-(3-terc-butoxicarbonilaminopirroldin-1-il)-2-ciclopropilamino-3-fluoro-5-metoxibenzoico ([MS ES, MH+1] m/z 439) usando etil éster del ácido 4-(3-terc-butoxicarbonilaminopirrolidin-1-il)-2,3-difluoro-5-metoxibenzoico (Ejemplo 2m).

(o) Etil éster del ácido 4-[3-(terc-butoxicarbonilaminometil)pirroldin-1-il)-2-ciclopropilamino-5-fluoro-3-metoxibenzoico ([MS ES, MH^+] m/z 453) usando etil éster del ácido 4-[3-(terc-butoxicarbonilaminometil)-pirrolidin-1-il)-2,5-difluoro-3-metoxibenzoico (Ejemplo 2n).

(p) Etil éster del ácido 4-(3-terc-butoxicarbonilaminopirroldin-1-il)-2-ciclopropilamino-3-etoxi-5-fluorobenzoico ([MS ES, MH^+] m/z 452) usando etil éster del ácido 4-(3-terc-butoxicarbonilaminopirrolidin-1-il)-3-etoxi-2,5-difluorobenzoico (Ejemplo 2o).

(q) Etil éster del ácido 3-(benciloxiiminometil)-4-(3-terc-butoxicarbonilaminopirrolidin-1-il)-2-ciclopropilamino-5-fluorobenzoico ([MS ES, MH^+] m/z 541) usando etil éster del ácido 3-(benciloxiiminometil)-4-(3-terc-butoxicarbonilaminopirrolidin-1-il)-2,5-difluorobenzoico (Ejemplo 2p).

(r) Etil éster del ácido 3-Cloro-2-ciclopropilamino-5-fluoro-4-(3-[1,2,3]-triazol-1-il-pirrolidin-1-il)benzoico (^1H NMR (200 MHz, $CDCl_3$): δ 8,00 (s, 1H), 7,73 (s, 1H), 7,52 (d, 1H), 7,19 (bs, 1H), 5,53-5,39 (m, 1H), 4,36-4,21 (q, 2H), 4,14-4,01 (m, 1H), 3,98-3,83 (m, 1H), 2,71-2,58 (m, 1H), 2,43-2,29 (m, 1H), 1,41-1,28 (t, 3H), 0,73-0,59 (m, 2H), 0,52-0,37 (m, 2H)) usando etil éster del ácido 3-cloro-2,5-difluoro-4-(3-[1,2,3]-triazol-1-il-pirrolidin-1-il)benzoico (Ejemplo 2q).

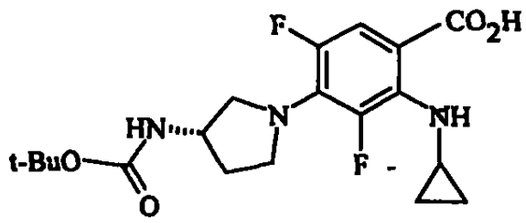
EJEMPLO 4

Hidrólisis de Ésteres

Procedimiento General

Una solución de éster del ácido 4-(sustituido-pirrolidin-1-il)-2-ciclopropilaminobenzoico (Ejemplo 3) e hidróxido de sodio acuoso (10-20 eq., 1,0 N) en tetrahidrofurano y metanol se calienta durante 16 a 24 horas a 70°C. La solución se enfría, se diluye con agua y se concentra parcialmente bajo vacío. La solución resultante se acidifica a pH 6 con ácido clorhídrico 1,0 N acuoso, luego el pH se ajusta a pH 7-8 con 5% de solución de $NaHCO_3$ y se extrae con acetato de etilo. Los extractos orgánicos combinados se secan sobre Na_2SO_4, se filtran y se concentran en vacío para lograr el ácido 4-(sustituido-pirrolidin-1-il)-2-ciclopropilaminobenzoico.

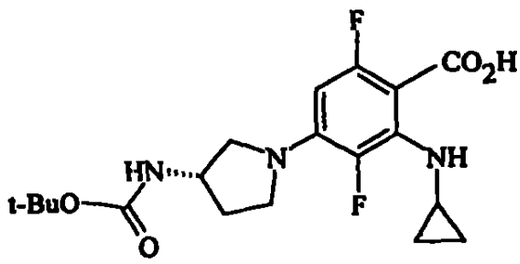
(a) Ácido 4-[(S)-3-terc-butoxicarbonilaminopirrolidin-1-il]-2-ciclopropilamino-3,5-difluorobenzoico



Una solución etil éster del ácido 4-[(S)-3-terc-butoxicarbonilamino)pirrolidin-1-il]-2-ciclopropilamino-3,5-difluorobenzoico (Ejemplo 3a, 40 g, 3,29 mmol) e hidróxido de sodio acuoso (1,33 N, 15,0 ml, 20,0 mmol) en tetrahidrofurano

(20 ml) y metanol (50 ml) se calienta durante 3 horas a 50°C. La solución se enfría, se diluye con agua, y se concentra parcialmente en vacío. La solución resultante se acidifica a pH 6 con ácido clorhídrico 1N acuoso y luego el pH se ajusta a pH 7-8 con 5% de $NaHCO_3$ y se extrae con cloroformo. Los extractos orgánicos combinados se secan sobre Na_2SO_4, se filtran y se concentran para dar el compuesto del título como un sólido amarillo pálido (1,31 g). ^1H NMR (DMSO-d_6): δ 12,65 (bs, 1H), 7,48 (bs, 1H), 7,27-7,14 (m, 2H), 4,08-3,92 (m, 1H).

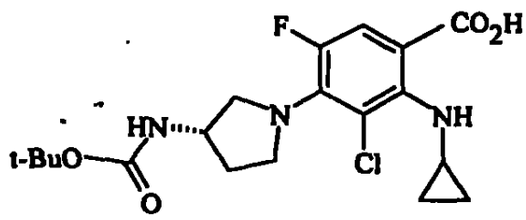
(b) Ácido 4-[(S)-3-terc-butoxicarbonilaminopirridin-1-il]-2-ciclopropilamino-3,6-difluorobenzoico



Una solución de etil éster del ácido 4-[(S)-3-terc-butoxicarbonilaminopirrolidin-1-il]-2-ciclopropilamino-3,6-difluorobenzoico (Ejemplo 3b, 1,45 g, 3,40 mmol) e hidróxido de sodio acuoso (1,33 N, 17,0 ml, 22,6 mmol) en tetrahidrofurano (20 ml) y metanol (50 ml) se calienta durante

21 horas a 50°C. La solución se enfría, se diluye con agua, y luego se concenra parcialmente en vacío. La solución resultante se acidifica a pH 6 con ácido clorhídrico 1N acuoso y luego el pH se ajusta a pH 7-8 con 5% de $NaHCO_3$ y se extrae con acetato de etilo tres veces. Los extractos orgánicos combinados se secan sobre Na_2SO_4, se filtran y se concentran bajo vacío para dar el compuesto del título como un sólido verde pálido (1,33 g). ^1H NMR (DMSO-d_6): δ 7,21 (bd, 1H), 5,83 (dd, 1H), 4,12-3,98 (m, 1H), 3,75-3,20 (m, 5H), 2,88-2,78 (m, 1H), 2,14-1,96 (m, 1H), 1,90-1,73 (m, 1H), 1,39 (s, 9H), 0,69-0,59 (m, 2H), 0,45-0,36 (m, 2H).

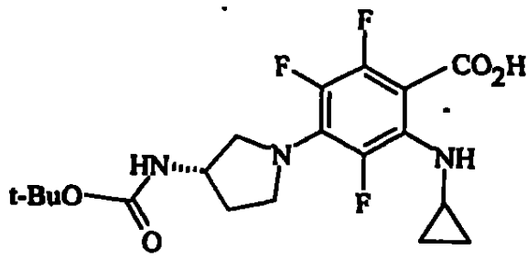
(c) Ácido 4-[(S)-3-terc-butoxicarbonilaminopirrolidin-1-il]-3-cloro-2-ciclopropilamino-5-fluoro-benzoico



A una solución de etil éster del ácido 4-[(S)-3-(terc-butoxicarbonilamino)pirrolidin-1-il]-3-cloro-2-ciclopropilamino-5-fluorobenzoico (Ejemplo 3c, 2,90 g, 6,56 mmol) en metanol (30 ml) y tetrahidrofurano (30 ml) se agrega una solución 1N de hidróxido de sodio (50 ml). La mezcla de la

reacción se agita a 80°C durante 20 horas, se enfría a temperatura ambiente y se diluye con acetato de etilo. La capa orgánica se lava con ácido clorhídrico 1N, agua y solución salina. La capa orgánica se secó sobre $MgSO_4$, se filtró y el filtrado se concentró para dar el compuesto del título como un sólido (2,74 g). MS CI: m/z 414 (MH^+).

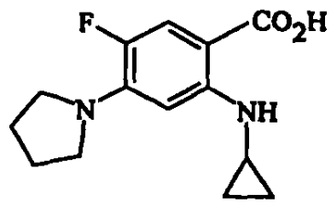
(d) Ácido 4-[(S)-3-terc-butoxicarbonilaminopirrolidin-1-il]-2-ciclopropilamino-3,5,6-trifluorobenzoico



Una solución de 4-[(S)-3-(terc-butoxicarbonilamino)pirrolidin-1-il]-2-ciclopropilamino-3,5,6-trifluorobenzoato (Ejemplo 3d, 3,68 g, 7,31 mmol), NaOH 1,0 M (75 ml), metanol (50 ml), y tetrahidrofurano (50 ml) se calienta a 50°C durante 24 horas. La mezcla se concentra parcialmente bajo vacío y luego se extrae con diclorometano. La fase acuosa es llevada a pH 7,5 usando HCl 1,0 M y es extraída con acetato de etilo. Los extractos orgánicos combinados se secan sobre Na_2SO_4, se filtran y se concentran bajo vacío para lograr el ácido 4-

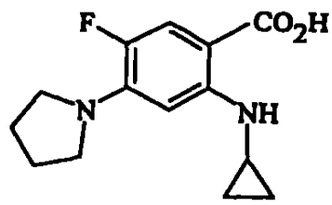
[(S)-3-terc-butoxicarbonilamino-pirridin-1-il]-2-ciclopropilamino-3,5,6-trifluorobenzoico como un sólido (2,9 g). Este material se usa sin nueva purificación. ^{1}H NMR (DMSO-d_6): δ 7,19 (bd, 1H), 4,12-3,95 (m, 1H), 3,83-3,52 (m, 3H), 3,48-3,33 (m, 1H), 2,83-2,69 (m, 1H), 2,10-1,94 (m, 1H), 1,89-1,72 (m, 1H), 1,49 (s, 9H), 0,70-0,56 (m, 2H), 0,44-0,33 (m, 2H).

(e) Ácido 2-ciclopropilamino-5-fluoro-4-pirrolidin-1-ilbenzoico



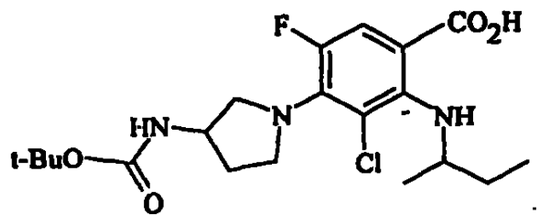
A una solución de etil éster del ácido 4-(pirrolidin-1-il)-2-ciclopropilamino-5-fluorobenzoico (Ejemplo 3e, 3,10 g, 10,4 mmol) en metanol (50 ml) y tetrahidrofurano (20 ml) se agrega una solución 1N de hidróxido de sodio (35 ml). La mezcla de la reacción se agita a 80°C durante 20 horas, se enfría a temperatura ambiente y se diluye con acetato de etilo. La capa orgánica se lava con ácido clorhídrico 1N, agua y solución salina. La capa orgánica se seca sobre $MgSO_4$, se filtra y el filtrado se concentra para lograr el compuesto del título como un sólido (2,74 g). MS CI: m/z 263 (M^+).

(f) Ácido 4-[3-terc-butoxicarbonilaminopirrolidin-1-il]-5-fluoro-2-isopropilaminobenzoico



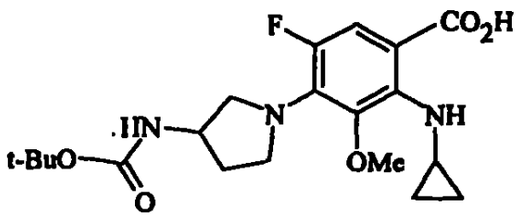
Una solución de etil éster del ácido 4-[3-(terc-butoxicarbonilamino)pirrolidin-1-il]-5-fluoro-2-isopropilaminobenzoico (Ejemplo 3f, 1,5 g, 3,40 mmol), hidróxido de sodio 1M acuoso (50 ml), tetrahidrofurano (40 ml), y metanol (40 ml) se calienta durante 25 horas a 70°C. La solución se enfría, se diluye con agua, y luego se concentra parcialmente. La solución resultante se acidifica a pH 7-8 con ácido clorhídrico 1,0 M acuoso y se extrae con acetato de etilo. Los extractos orgánicos combinados se secan sobre Na_2SO_4, se filtran y se concentran bajo vacío para dar el compuesto del título como un sólido (1,25 g). MS EI: m/z 380 (M^+).

(g) Ácido 4-[3-(terc-butoxicarbonilamino)pirrolidin-1-il]-2-sec-butilamino-3-cloro-5-fluorobenzoico



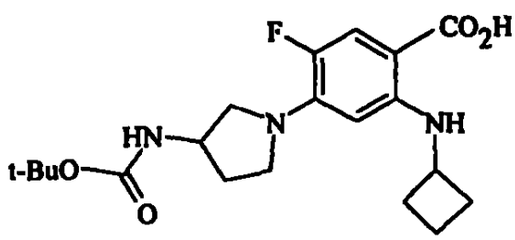
Una solución de etil éster del ácido 4-[3-terc-butoxicarbonilaminopirrolidin-1-il]-2-sec-butilamino-3-cloro-5-fluorobenzoico (Ejemplo 3g, 3,57 g, 7,79 mmol), hidróxido de sodio 1,0N (50 ml) y metanol (80 ml) se calienta a 80°C durante 16,5 horas. La mezcla se evapora parcialmente, se diluye con agua (150 ml) y el pH se ajusta a 7,0-8,0 usando ácido clorhídrico 1,0 M. La mezcla se extrae con acetato de etilo, se seca sobre Na_2SO_4 y se concentra bajo vacío para dar el compuesto del título como un sólido blancuzco (1,26 g) que se usa sin nueva purificación. MS EI: m/z 430 (M^+).

(h) Ácido 4-[3-terc-butoxicarbonilaminopirrolidin-1-il]-2-ciclopropilamino-5-fluoro-3-metoxibenzoico



Una solución de etil éster del ácido 4-[3-terc-butoxicarbonilaminopirrolidin-1-il]-2-ciclopropilamino-5-fluoro-3-metoxibenzoico (Ejemplo 3h, 0,173 g, 0,395 mmol) e hidróxido de sodio acuoso (1,33 N, 2,0 ml, 2,66 mmol) en tetrahidrofurano (10 ml) y metanol (30 ml) se calienta durante 22 horas a 70°C. La solución se enfria, se diluye con agua, y se concentra parcialmente bajo vacío. La solución resultante se acidifica a pH 6 con ácido clorhídrico 1N acuoso y luego el pH se ajusta a 7-8 con 5% de solución de $NaHCO_3$ y se extrae con acetato de etilo. Los extractos orgánicos combinados se secan sobre Na_2SO_4, se filtran y se concentran en vacío para lograr el compuesto del título como un sólido amarillo (0,160 g). ^1H NMR ($CDCl_3$): δ 7,46 (d, 1H), 4,80-4,69 (bs, 1H), 4,33-4,18 (m, 1H), 3,90-3,45 (m, 3H), 3,62 (s, 3H), 3,43-3,32 (m, 1H), 2,91-2,80 (m, 1H), 2,28-2,10 (m, 1H), 1,96-1,78 (m, 1H), 1,46 (s, 9H), 0,63-0,52 (m, 4H).

(i) Ácido 4-[3-terc-butoxicarbonilaminopirrolidin-1-il]-2-ciclobutilamino-5-fluorobenzoico



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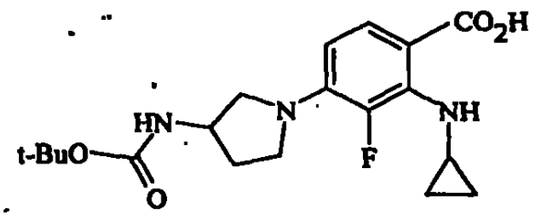
Una solución de etil éster del ácido 4-[3-terc-butoxicarbonilaminopirrolidin-1-il]-2-ciclobutilamino-5-fluorobenzoico (Ejemplo 3i, 1,51 g, 3,58 mmol) e hidróxido de sodio acuoso (1,33 N, 20,0 ml, 26,6 mmol) en tetrahidrofurano (15 ml) y metanol (40 ml) se refluye durante 19 horas. La solución se enfría, se diluye con agua y se concentra parcialmente bajo vacío. La solución resultante se acidifica a pH 6 con ácido clorhídrico 1,0 N acuoso y luego el pH se ajusta a pH 7-8 con 5% de solución de $NaHCO_3$ y se extrae con acetato de etilo. Los extractos orgánicos combinados se secan sobre Na_2SO_4, se filtran y se concentran bajo vacío para lograr el compuesto del título como un sólido amarillo (1,53 g). MS EI: m/z 394 (MH^+).

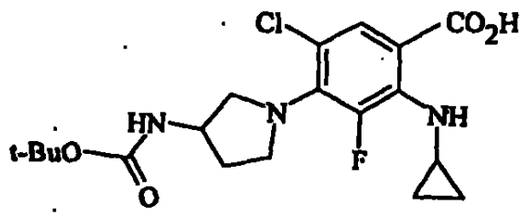
(j) Ácido 4-[3-(terc-butoxicarbonilamino)pirrolidin-1-il]-2-ciclopropilamino-3-fluorobenzoico



Una solución de etil éstre del ácido 4-[3-(terc-butoxicarbonilamino)pirrolidin-1-il]-2-ciclopropilamino-3-fluorobenzoico (Ejemplo 3j, 1,34 g, 3,29 mmol) e hidróxido de

sodio acuoso (2N, 20 ml) en tetrahidrofurano (20 ml) y metanol (20 ml) se refluye durante 1 hora. La solución se concentra parcialmente en vacío, luego se acidifica a pH 6 y se extrae con cloroformo. Los extractos orgánicos combinados se secan sobre Na_2SO_4, se filtran y se concentran para dar el compuesto del título (1,40 g). ^1H NMR ($CDCl_3$): δ 7,59 (dd, 1H), 6,06 (dd, 1H), 4,80-4,70 (bd, 1H), 4,38-4,22 (m, 1H), 3,79-3,50 (m, 3H), 3,47-3,35 (m, 1H), 2,98-2,87 (m, 1H), 2,30-2,14 (m, 1H), 1,97-1,84 (m, 1H), 1,46 (s, 9H), 0,69-0,54 (m, 4H).

(k) Ácido 4-[3-(terc-butoxicarbonilamino)pirrolidin-1-il]-5-cloro-2-ciclopropilamino-3-fluorobenzoico



Una solución de etil éster del ácido 4-[3-(terc-butoxicarbonilamino)pirrolidin-1-il]-5-cloro-2-ciclopropilamino-3-fluorobenzoico (Ejemplo 3k, 2,00, 4,50 mmol) e hidróxido de sodio acuoso (2,0 N, 20 ml) en tetrahidrofurano (20 ml) y metanol (20 ml) se refluye durante 1 hora. La solución se concentra parcialmente en vacío, se

acidifica a pH 6, y se extrae con cloroformo. Los extractos orgánicos combinados se secan sobre Na_2SO_4, se filtran y se concentran para dar el compuesto del título (1,70 g). ^1H NMR ($CDCl_3$): δ 7,71 (d, 1H), 4,91-4,82 (bd, 1H), 4,40-4,25 (m, 1H), 3,77-3,69 (m, 2H), 3,53-3,34 (m, 2H), 3,00-2,88 (m, 1H), 2,24-2,15 (m, 1H), 1,90-1,80 (m, 1H), 1,46 (s, 9H), 0,72-0,54 (m, 4H).

Los siguientes compuestos se sintetizan de acuerdo con los procedimientos generales de los Ejemplos 4a-k.

(l) Ácido 4-(3-terc-butoxicarbonilaminopirroldin-1-il)-2-ciclopropilamino-5-fluoro-3-metilbenzoico ([MS ES, MH^+] m/z 394) usando etil éster del ácido 4-(3-terc-butoxicarbonilaminopirrolidin-1-il)-2-ciclopropilamino-5-fluoro-3-metilbenzoico (Ejemplo 3l).

(m) Ácido 4-[3-(terc-butoxicarbonilaminometil)pirroldin-1-il]-2-ciclopropilamino-5-fluoro-3-metilbenzoico ([MS ES, MH+1] m/z 408) usando etil éster del ácido 4-[3-(terc-butoxicarbonilaminometil)-pirrolidin-1-il]-2-ciclopropilamino-5-fluoro-3-metilbenzoico (Ejemplo 3m).

(n) Ácido 4-(3-terc-butoxicarbonilaminopirroldin-1-il)-2-ciclopropilamino-3-fluoro-5-metoxibenzoico (^1H NMR (200 MHz,

$CDCl_3$): δ 12,50 (bs, 1H), 7,18-7,09 (m, 1H), 7,07 (d, 1H), 4,07-3,90 (m, 1H), 3,80-3,50 (m, 2H), 3,66 (s, 3H), 3,42-3,29 (m, 2H), 2,88-2,71 (m, 1H), 2,10-1,91 (m, 1H), 1,86-1,67 (m, 1H), 1,39 (s, 9H), 0,70-0,57 (m, 2H), 0,46-0,32 (m, 2H)) usando etil éster del ácido 4-(3-terc-butoxicarbonilaminopirrolidin-1-il)-2-ciclopropilamino-3-fluoro-5-metoxi-benzoico (Ejemplo 3n).

(o) Ácido 4-[3-(terc-butoxicarbonilaminometil)pirroldin-1-il)-2-ciclopropilamino-5-fluoro-3-metoxibenzoico ([MS ES, MH+1] m/z 424) usando etil éster del ácido 4-[3-(terc-butoxicarbonilaminometil)-pirrolidin-1-il)-2-ciclopropilamino-5-fluoro-3-metoxibenzoico (Ejemplo 3o).

(p) Ácido 4-(3-terc-butoxicarbonilaminopirroldin-1-il)-2-ciclopropilamino-3-etoxi-5-fluorobenzoico ([MS ES, MH^+] m/z 424) usando etil éster del ácido 4-(3-terc-butoxicarbonilaminopirrolidin-1-il)-3-etoxi-5-fluorobenzoico (Ejemplo 3p).

(q) Ácido 3-(benciloxiiminometil)-4-(3-terc-butoxicarbonilaminopirrolidin-1-il)-2-ciclopropilamino-5-fluorobenzoico ([MS ES, MH^+] m/z 513) usando etil éster del ácido 3-(benciloxiiminometil)-4-(3-terc-

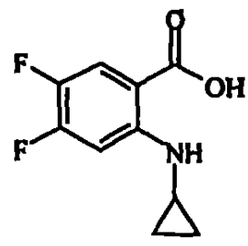
butoxicarbonilaminopirrolidin-1-il)-2-ciclopropilamino-5-fluorobenzoico (Ejemplo 3q).

(r) Ácido 3-Cloro-2-ciclopropilamino-5-fluoro-4-(3-[1,2,3]-triazol-1-il-pirrolidin-1-il)benzoico (^{1}H NMR (200 MHz, $CDCl_3$): δ 8,50 (bs, 1H), 8,03 (s, 1H), 7,72 (s, 1H), 7,60 (d, 1H), 5,54-5,39 (m, 1H), 4,13-3,97 (m, 1H), 3,92-3,85 (m, 1H), 3,68-3,63 (m, 1H), 3,54-3,42 (m, 1H), 3,10-3,00 (m, 1H), 2,78-2,60 (m, 1H), 2,39-2,33 (m, 1H), 0,70-0,58 (m, 2H), 0,58-0,46 (m, 2H)) usando etil éster del ácido 3-cloro-2-ciclopropilamino-5-fluoro-4-(3-[1,2,3]-triazol-1-il-pirrolidin-1-il)benzoico (Ejemplo 3r).

EJEMPLO 5

Síntesis de Ácidos Antranílicos N-Sustituidos

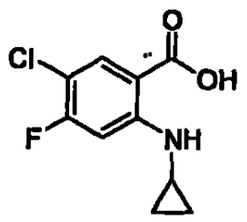
(a) Ácido 2-ciclopropilamino-4,5-difluorobenzoico



A una solución de ácido 4,5-difluorobenzoico (1,13 g, 6,53 mmol) en metanol anhidro (40 ml) se agrega tamiz molecular (3 Å), ácido acético (3,70 ml, 65,3 mmol) y [(1-

etoxiciclopropil)oxi]trimetilsilano (5,25 ml, 26,11 mmol). Después de 30 minutos, se agrega cianoborohidruro de sodio (2,08 g, 32,64 mmol) y la mezcla de la reacción se calienta a reflujo. Después de 16 horas, la reacción se enfría a temperatura ambiente, se filtra, se lava con metanol y el filtrado combinado se concentra bajo vacío para lograr un aceite viscoso. El aceite resultante se disuelve en acetato de etilo y se lava con ácido clorhídrico 1,0 M, agua y solución salina. La capa orgánica se seca sobre $MgSO_4$, se filtra y el filtrado se concentra bajo vacío para lograr un sólido beige (1,32 g). MS CI: m/z 212 (M^+).

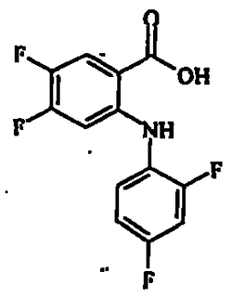
(b) Ácido 5-cloro-2-ciclopropilamino-4-fluorobenzoico



A una solución de ácido 4,5-difluoroantranílico (1,20 g, 6,37 mmol) en metanol anhidro (50 ml) se agregan tamices moleculares (3 Å), ácido acético (3,70 ml, 65,3 mmol) y [(1-etoxiciclopropil)oxi]trimetilsilano (5,12 ml, 25,5 mmol). Después de 30 minutos, se agrega cianoborohidruro de sodio (2,03 g, 31,9 mmol) y la mezcla de la reacción se calienta a reflujo. Después de 16 horas, la reacción se enfría a temperatura ambiente, se filtra, se lava con metanol y el

filtrado combinado se concentra bajo vacío para lograr un aceite viscoso. El aceite resultante se disuelve en acetato de etilo y se lava con ácido clorhídrico 1,0 M, agua y solución salina. La capa orgánica se seca sobre $MgSO_4$, se filtra y el filtrado se concentra bajo vacío para lograr un sólido castaño (1,78 g). MS CI: m/z 228 (M^+).

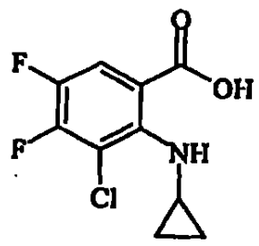
(c) Ácido 2-(2,4-difluoroanilino)-4,5-difluorobenzoico



Se genera diisopropilamida de litio a -5°C combinando diisopropilamina (7,2 ml, 51 mmol) y n-butillitio (33 ml, 53 mmol) en tetrahidrofurano anhidro (150 ml) bajo una atmósfera inerte. Después de 0,5 hora, la solución se enfría a -78°c y se agrega 2,4-difluoroanilina (3,46 ml, 34 mmol) y se agita durante 2 horas. Se agrega 2,4,5-trifluorobenzoico (3,0 g, 17 mmol) y luego se deja calentar la mezcla a temperatura ambiente durante 18 horas. Se agrega una solución saturada de cloruro de hidrógeno/dioxano (10 ml), y después de 1 hora, la mezcla se concentra en un sólido. El sólido se disuelve en

cloroformo y se lava con ácido clorhídrico 1,0 M, agua y solución salina. La solución se seca, se concentra en vacío, y se purifica mediante cromatografía de columna (acetato de etilo/hexanos 3:1) para dar ácido 2-(2,4-difluoroanilino)-4,5-difluorobenzoico como un sólido (2,18 g). ^{1}H NMR ($CDCl_3$): δ 8,95 (bs, 1H), 7,80-7,75 (m, 2H), 7,50-6,85 (m, 3H), 6,62-6,40 (m, 1H). MS EI: m/z 286 (M^+).

(d) Ácido 3-cloro-2-ciclopropilamino-4,5-difluorobenzoico



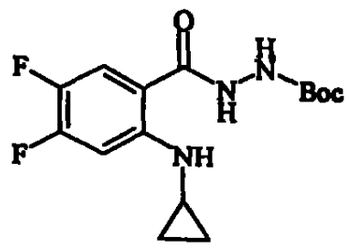
En un tubo sellado una mezcla de ácido 2-bromo-3-cloro-4,5-difluorobenzoico (Ejemplo 20, 7,96 g, 29,3 mmol), ciclopropil amina (4,20 ml, 58,7 mmol), acetato de potasio (5,77 g, 58,6 mmol), acetato cúprico monohidratado (0,50 g, 2,5 mmol) y trietilamina (4,9 ml, 35,19 mmol) en alcohol isopropílico se agita a 80°C. Después de 16 horas, la mezcla de la reacción se concentra bajo vacío, y el residuo resultante se disuelve en acetato de etilo. La capa orgánica se lava con ácido clorhídrico 1,0 M, agua y solución salina. La capa orgánica se seca sobre $MgSO_4$ y se filtra. El filtrado se concentra bajo

vacío y se purifica a través de cromatografía de columna rápida (5% de alcohol isopropílico/1% de ácido fórmico/94% de diclorometano) para lograr el compuesto del título (4,62 g). MS CI: m/z 248 (MH^+).

EJEMPLO 6

Síntesis de t-Butil ésteres hidrazincarboxílicos

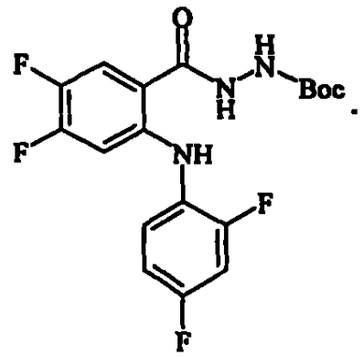
(a) terc-Butil éster del ácido (2-ciclopropilamino-4,5-difluorobenzoil)hidrazincarboxílico



A una solución de ácido 2-ciclopropilamino-4,5-difluorobenzoico (Ejemplo 5) (1,32 g, 6,19 mmol) y carbazato de terc-butilo (1,30 g, 9,75 mmol) en diclorometano (30 ml) se agrega 1-etil-3-(3-dimetilaminopropil)-carbodiimida (1,87 g, 9,75 mmol). Después de 16 horas, la mezcla de la reacción se diluye con diclorometano y se lava con $NaHCO_3$ saturado, agua y solución salina. La capa orgánica se seca sobre $MgSO_4$ y se filtra. El filtrado se concentra bajo vacío y se purifica mediante cromatografía de columna rápida (acetato de

etilo/hexanos 1:2) para lograr terc-butil éster del ácido N_2-(2-ciclopropilamino-4,5-difluorobenzoil)hidrazincarboxílico como un sólido (1,65 g). MS EI: m/z 328 (M^+).

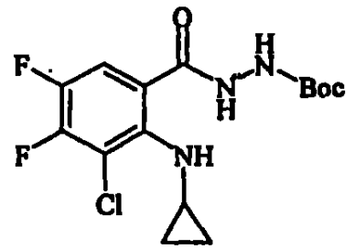
(b) terc-Butil éster del ácido [2-(2,4-difluoroanilino)-4,5-difluorobenzoil]hidrazincarboxílico



A una solución de ácido 2-(2,4-difluoroanilino)-4,5-difluorobenzoico (Ejemplo 5, 2,18 g, 7,6 mmol) y carbazato de terc-butilo (1,57 g, 11,8 mmol) en diclorometano (30 ml) se agrega 1-etil-3-(3-dimetilaminopropil)-carbodiimida (2,25 g, 11,77 mmol). Después de agitar durante 16 horas a temperatura ambiente, la mezcla de la reacción se diluye con diclorometano y luego se lava con $NaHCO_3$ saturado, agua y solución salina. La capa orgánica se seca sobre Na_2SO_4, se concentra bajo vacío y se purifica mediante cromatografía de columna (acetato de etilo/hexanos 1:3) para lograr el terc-butil éster del ácido

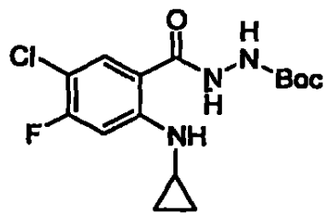
[2-(2,4-difluoroanilino)-4,5-difluorobenbenzoil]-hidrazincarboxílico como un sólido (2,20 g). MS EI: m/z 400 (M^+).

(c) terc-Butil éster del ácido (3-cloro-2-ciclopropilamino-4,5-difluorobenzoil)-hidrazincarboxílico



A una solución de ácido 3-cloro-2-ciclopropilamino-4,5-difluorobenzoico (Ejemplo 5d, 2,09 g, 8,45 mmol) en diclorometano (30 ml) se agrega carbazato de terc-butilo (1,67 g, 12,7 mmol) y 1-etil-3-(3-dimetilaminopropil)-carbodiimida (2,43 g, 12,7 mmol). Después de 16 horas, la mezcla de la reacción se diluye con diclorometano y luego se lava con $NaHCO_3$ saturado, agua y solución salina. La capa orgánica se seca sobre Na_2SO_4, se concentra bajo vacío y se purifica mediante cromatografía de columna (acetato de etilo/hexanos 1:2) para lograr el compuesto del título (1,93 g). MS EI: m/z 360 (M^+).

(d) terc-Butil éster del ácido (5-cloro-2-ciclopropilamino-4-fluorobenzoil)-hidrazincarboxílico



A una solución de ácido 5-cloro-2-ciclopropilamino-4-fluorobenzoico (Ejemplo 5, 1,48 g, 6,46 mmol) en diclorometano (50 ml) se agrega carbazato de terc-butilo (1,28 g, 9,69 mmol) y 1-etil-3-(3-dimetilaminopropil)-carbodiimida (1,86 g, 9,69 mmol). Después de 16 horas, la mezcla de la reacción se diluye con diclorometano y luego se lava con $NaHCO_3$ saturado, agua y solución salina. La capa orgánica se seca sobre Na_2SO_4, se concentra bajo vacío y se purifica mediante cromatografía de columna (acetato de etilo/hexanos 1:2) para lograr el terc-butil éster del ácido (3-cloro-2-ciclopropilamino-4,5-difluorobenzoil)hidrazincarboxílico como un sólido (1,04 g). MS EI: m/z 344 (M^+).

EJEMPLO 7

Síntesis de t-butil ésteres del ácido benzoilhidrazincarboxílico 4-heterocíclico

Procedimiento general A

Una solución de un terc-butil éster del ácido benzoilhidrazincarboxílico sustituido del Ejemplo 6 (donde R_7 = F), amina heterocíclica (2 eq.) y trietilamina (10 eq.) se agita en sulfóxido de dimetilo o N,N-dimetilformamida (6 ml) a 120°C en un tubo sellado durante 16 horas. Después de enfriar a temperatura ambiente, la mezcla de la reacción se diluye con acetato de etilo y se lava con $NaHCO_3$ saturado, agua y solución salina. La capa orgánica se seca sobre $MgSO_4$, se filtra y el filtrado se concentra para lograr un residuo marrón. La trituración con éter dietílico o la purificación mediante cromatografía de columna rápida (acetato de etilo/hexanos) da el producto.

Procedimiento General B

A una suspensión de un ácido benzoico del Ejemplo 4 (3,30 mmol) y carbazato de terc-butilo (1,5 eq.) en diclorometano anhidro se agrega clorhidrato de 1-[3-(dimetilamino)propil]-3-etilcarbodiimida (1,5 eq.). La mezcla se agita a temperatura ambiente durante 20 horas, se vierte en $NaHCO_3$ saturado y se extrae con diclorometano. Los extractos orgánicos combinados se lavan con solución salina, se secan sobre Na_2SO_4, se filtran y se concentran en vacío. La purificación mediante cromatografía de columna rápida (acetato de etilo/hexanos) logra los compuestos del título.

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Los siguientes compuestos se sintetizan de acuerdo con los Procedimientos Generales A o B precedentes:

(a) terc-Butil éster del ácido N'-{4-[3-(terc-butoxicarbonilaminometil)pirrolidin-1-il]-2-ciclopropilamino-5-fluorobenzoil}hidrazincarboxílico (MS CI: m/z 508 (MH^+)) usando terc-butil éster del ácido (2-ciclopropilamino-4,5-difluorobenzoil)-hidrazincarboxílico (Ejemplo 6a) y 3-(terc-butoxicabonilaminometil)pirrolidina (Método General A).

(b) terc-Butil éster del ácido N'-4-[4-(terc-butoxicarbonilpiperazin-1-il)-2-ciclopropilamino-5-fluorobenzoil]hidrazincarboxílico (MS CI: m/z 494 (MH^+)) usando terc-butil éster del ácido (2-ciclopropilamino-4,5-difluorobenzoil)-hidrazincarboxílico (Ejemplo 6a) y 4-terc-butoxicabonilpiperazina (Método General A).

(c) terc-Butil éster del ácido N'-{4-[3-(terc-butoxicarbonilaminometil)-3-metilpirrolidin-1-il]-2-ciclopropilamino-5-fluorobenzoil}hidrazincarboxílico (MS CI: m/z 522 (MH^+)) usando terc-butil éster del ácido (2-ciclopropilamino-4,5-difluorobenzoil)-hidrazincarboxílico (Ejemplo 6a) y 3-(terc-butoxicabonilaminometil)-3-metilpirrolidina (Sánchez J.P., Bridges A.J., Bucsh R., Domagala J.M., Gogliotti R.D., Hagen S.E., Heifetz C.L.,

Joannides E.T., Sesnie J.C., et al, *J. Med. Chem.*, 1992;35(2):361-367) (Método General A).

(d) terc-Butil éster del ácido N'-[4-(6-terc-butoxicarbonilamino-3-azabiciclo[3.1.0]hex-3-il)-2-ciclopropilamino-5-fluorobenzoil]hidrazincarboxílico (MS CI: m/z 506 (MH^+)) usando terc-butil éster del ácido (2-ciclopropilamino-4,5-difluorobenzoil)-hidrazincarboxílico (Ejemplo 6a) y terc-butil éster del ácido (3-azabiciclo[3.1.0]hex-6-il)carbámico (Brighty K.E., 1991, EP 413455) (Método General A).

(e) terc-Butil éster del ácido N'-{4-[(S)-3-(terc-butoxicarbonil-N-metilamino)pirrolidin-1-il]-2-ciclopropilamino-5-fluorobenzoil}hidrazincarboxílico (MS CI: m/z 508 (MH^+)) usando terc-butil éster del ácido (2-ciclopropilamino-4,5-difluorobenzoil)-hidrazincarboxílico (Ejemplo 6a) y (S)-3-(terc-butoxicabonil-N-metilamino) pirrolidina (Chu D.T., Li Q., Cooper C.S., Fung A.K.L., Lee C.M., Plattner J.J., Solicitud Internacional PCT 1995:255. WO 9510519) (Método General A).

(f) terc-Butil éster del ácido N'-{4-[(S)-3-(terc-butoxicarbonilamino)pirrolidin-1-il]-2-(2,4-difluoroanilino)-5-fluorobenzoil}hidrazincarboxílico (MS CI: m/z 566 (MH^+))

usando terc-butil éster del ácido [2-(2,4-difluoroanilino)-4,5-difluorobenzoil]-hidrazincarboxílico (Ejemplo 6b) y terc-butil éster del ácido (S)-pirrolidin-3-ilcarbámico (Método General A).

(g) terc-Butil éster del ácido N'-{4-[(S)-3-(terc-butoxicarbonilamino)-pirrolidin-1-il]-2-ciclopropilamino-3,5-difluorobenzoil}hidrazincarboxílico (MS CI: m/z 538 (MH^+)) usando ácido 4-[(S)-3-terc-butoxicarbonilaminopirrolidin-1-il]-2-ciclopropilamino-3,5-difluorobenzoico (Ejemplo 4a) (Método General B).

(h) terc-Butil éster del ácido N'-{4-[(S)-3-(terc-butoxicarbonilamino)-pirrolidin-1-il]-2-ciclopropilamino-3,6-difluorobenzoil}hidrazincarboxílico (^1H NMR ($CDCl_3$): δ 8,08 (bs, 2H), 6,50 (bs, 1H), 5,70 (dd, 1H), 4,76-4,68 (m, 1H), 4,37-4,23 (m, 1H), 3,78-3,68 (m, 1H), 3,65-3,42 (m, 2H), 3,40-3,30 (m, 1H), 2,96-2,83 (m, 1H), 2,28-2,14 (m, 1H), 2,00-1,84 (m, 1H), 1,49 (s, 9H), 1,46 (s, 9H), 0,68-0,61 (m, 2H), 0,58-0,48 (m, 2H)) usando ácido 4-[(S)-3-terc-butoxicarbonilaminopirrolidin-1-il]-2-ciclopropilamino-3,6-difluorobenzoico (Ejemplo 4b) (Método General B).

(i) terc-Butil éster del ácido N'-{4-[(S)-3-(terc-butoxicarbonilamino)-pirrolidin-1-il]-2-ciclopropilamino-

3,5,6-trifluorobenzoil}hidrazincarboxílico (^{1}H NMR ($CDCl_3$): δ 8,04 (bd, 1H), 7,55 (bs, 1H), 6,52 (bs, 1H), 4,79-4,67 (m, 1H), 4,37-4,19 (m, 1H), 3,97-3,55 (m, 3H), 3,53-3,40 (m, 1H), 2,90-2,75 (m, 1H), 2,29-2,06 (m, 1H), 1,96-1,75 (m, 1H), 1,49 (s, 9H), 1,46 (s, 9H), 0,69-0,57 (m, 2H), 0,54-0,43 (m, 2H)) usando ácido 4-[(S)-3-terc-butoxicarbonilaminopirrolidin-1-il]-2-ciclopropilamino-3,5,6-trifluorobenzoico (Ejemplo 4d) (Método General B).

(j) terc-Butil éster del ácido N'-{4-[(S)-3-(terc-butoxicarbonilamino)pirrolidin-1-il]-3-cloro-2-ciclopropilamino-5-fluorobenzoil}hidrazincarboxílico (MS CI: m/z 528 (MH^+)) usando ácido 4-[(S)-3-terc-butoxicarbonilaminopirrolidin-1-il]-3-cloro-2-ciclopropilamino-5-fluorobenzoico (Ejemplo 4c) (Método General B).

(k) terc-Butil éster del ácido N'-[(S)-4-(7-terc-butoxicarbonilamino-5-azaespiro[2.4]hept-5-il)-2-ciclopropilamino-5-fluorobenzoil]hidrazincarboxílico (MS CI: m/z 520 (MH^+)) usando terc-butil éster del ácido (2-ciclopropilamino-4,5-difluorobenzoil)-hidrazincarboxílico (Ejemplo 6a) y terc-butil éster del ácido (5-azaespiro[2,4]hept-7-il)carbámico (Método General A).

(l) terc-Butil éster del ácido N'-{4-[(R)-3-(1-terc-butoxicarbonilamino-1-metiletil)pirrolidin-1-il]-3-cloro-2-ciclopropilamino-5-fluorobenzoil}hidrazincarboxílico (MS CI: m/z 570 (MH^+)) usando terc-butil éster del ácido (3-cloro-2-ciclopropilamino-4,5-difluorobenzoil)-hidrazincarboxílico (Ejemplo 6c) y [(R)-3-(1-terc-butoxicarbonilamino-1-metiletil)pirrolidina (Fredij V., Lenoir E.A., III, Suto M.J., Zeller J.R., Wemple J., *Tetrahedron: Asymmetry*, 1994;5[7]:1131-1134) (Método General A).

(m) terc-Butil éster del ácido N'-[4-(pirrolidin-1-il)-2-ciclopropilamino-5-difluorobenzoil]hidrazincarboxílico (MS CI: m/z 379 (MH^+)) usando ácido 2-ciclopropilamino-5-fluoro-4-pirrolidin-1-ilbenzoico (Ejemplo 4e) (Método General B).

(n) terc-Butil éster del ácido N'-{4-[3-(terc-butoxicarbonilamino)-pirrolidin-1-il]-5-fluoro-2-isopropilaminobenzoil}hidrazincarboxílico (MS CI: m/z 496 (MH^+)) usando ácido 4-[3-terc-butoxicarbonilaminopirrolidin-1-il]-5-fluoro-2-isopropilaminobenzoico (Ejemplo 4f) (Método General B).

(o) terc-Butil éster del ácido N'-{4-[3-(terc-butoxicarbonilamino)pirrolidin-1-il]-2-sec-butilamino-3-cloro-5-fluorobenzoil}hidrazincarboxílico (MS CI: m/z 544 (MH^+))

usando ácido 4-[3-(terc-butoxicarbonilamino)pirrolidin-1-il]-2-secbutilamino-3-cloro-5-fluorobenzoico (Ejemplo 4g) (Método General B).

(p) terc-Butil éster del ácido N'-{4-[3-(terc-butoxicarbonilamino)pirrolidin-1-il]-2-ciclopropilamino-5-fluoro-3-metoxibenzoil}hidrazincarboxílico (MS CI: m/z 524 (MH^+)) usando ácido 4-[3-terc-butoxicarbonilamino-pirrolidin-1-il]-2-ciclopropilamino-5-fluoro-3-metoxibenzoico (Ejemplo 4b) (Método General B).

(q) terc-Butil éster del ácido N'-{4-[3-(terc-butoxicarbonilamino)pirrolidin-1-il]-2-ciclobutilamino-5-fluorobenzoil}hidrazincarboxílico (MS CI: m/z 394 (MH^+)) usando ácido 4-[3-terc-butoxicarbonilaminopirrolidin-1-il]-2-ciclobutilamino-5-fluorobenzoico (Ejemplo 4i) (Método General B).

(r) terc-Butil éster del ácido N'-{4-[3-(terc-butoxicarbonilamino)pirrolidin-1-il]-2-ciclopropilamino-3-fluorobenzoil}hidrazincarboxílico (MS CI: m/z 494 (MH^+)) usando ácido 4-[3-(terc-butoxicarbonilamino)pirrolidin-1-il]-2-ciclopropilamino-3-fluorobenzoico (Ejemplo 4j) (Método General B).

(s) terc-Butil éster del ácido N'-{4-[3-(terc-butoxicarbonilamino)pirrolidin-1-il]-2-ciclopropilamino-3-fluorobenzoil}hidrazincarboxílico (^{1}H NMR ($CDCl_3$): δ 8,77 (bs, 1H), 7,35 (d, 1H), 6,82 (bs, 1H), 6,55 (bs, 1H), 5,01-4,97 (m, 1H), 4,29 (bs, 1H), 3,74-3,57 (m, 2H), 3,41-3,24 (m, 2H), 2,84-2,75 (m, 1H), 2,33-2,16 (m, 1H), 1,92-1,72 (m, 1H), 1,47 (s, 9H), 0,69-0,62 (m, 2H), 0,60-0,50 (m, 2H)) usando ácido 4-[3-(terc-butoxicarbonilamino)pirrolidin-1-il]-5-cloro-2-ciclopropilamino-3-fluorobenzoico (Ejemplo 4k) (Método General B).

(t) terc-Butil éster del ácido N'-[4-(3-terc-butoxicarbonilaminopirrolidin-1-il)-2-ciclopropilamino-5-fluoro-3-metilbenzoil]hidrazincarboxílico ([MS ES, MH^+] m/z 508) usando ácido 4-(3-terc-butoxicarbonilaminopirrolidin-1-il)-2-ciclopropilamino-5-fluoro-3-metilbenzoico (Ejemplo 41) (Método General B).

(u) terc-Butil éster del ácido N'-{4-[3-(terc-butoxicarbonilaminometil)pirrolidin-1-il]-2-ciclopropilamino-5-fluoro-3-metilbenzoil}hidrazincarboxílico ([MS ES, MH^+] m/z 522) usando ácido 4-[3-(terc-butoxicarbonilaminometil)pirrolidin-1-il]-2-ciclopropilamino-5-fluoro-3-metilbenzoico (Ejemplo 4m) (Método General B).

(v) terc-Butil éster del ácido N'-[4-(3-terc-butoxicarbonilaminopirrolidin-1-il)-2-ciclopropilamino-3-fluoro-5-metoxibenzoil]hidrazincarboxílico ([MS ES, MH^+] m/z 525) usando ácido 4-(3-terc-butoxicarbonilaminopirrolidin-1-il)-2-ciclopropilamino-3-fluoro-5-metoxibenzoico (Ejemplo 4n) (Método General B).

(w) terc-Butil éster del ácido N'-{4-[3-(terc-butoxicarbonilaminometil)pirrolidin-1-il]-2-ciclopropilamino-5-fluoro-3-metoxibenzoil}hidrazincarboxílico ([MS ES, MH_2^{+2}] m/z 539) usando ácido 4-[3-(terc-butoxicarbonilaminometil)pirrolidin-1-il]-2-ciclopropilamino-5-fluoro-3-metoxibenzoico (Ejemplo 4o) (Método General B).

(x) terc-Butil éster del ácido N'-[3-(Benciloxiiminometil)-4-(3-terc-butoxicarbonilaminopirrolidin-1-il)-2-ciclopropilamino-5-fluorobenzoil]hidrazincarboxílico ([MS ES, MH^+] m/z 627) usando ácido 3-(benciloxiiminometil)-4-(3-terc-butoxicarbonilaminopirrolidin-1-il)-2-ciclopropilamino-5-fluorobenzoico (Ejemplo 4q) (Método General B).

(y) terc-Butil éster del ácido N'-[3-cloro-2-ciclopropilaino-5-fluoro-4-(3-[1,2,3-triazol]-1-il-pirrolidin-1-il)benzoil]hidrazincarboxílico (^1H NMR (200 MHz, $CDCl_3$): δ 9,90 (bs, 1H), 7,97 (s, 1H), 7,72 (s, 1H), 7,52 (d, 1H), 7,17 (bs,

1H), 5,51-5,41 (m, 1H), 4,59 (bs, 1H), 4,06-3,95 (m, 1H), 3,87-3,74 (m, 1H), 3,61-3,55 (m, 1H), 3,48-3,36 (m, 1H), 2,97-2,90 (m, 1H), 2,77-2,59 (m, 1H), 2,42-2,31 (m, 1H), 1,46 (s, 9H), 0,68-0,50 (m, 4H)ʃ usando ácido 3-cloro-2-ciclopropilamino-5-fluoro-4-(3-[1,2,3-triazol]-1-ilbenzoico (Ejemplo 4r) (Método General B).

(z) terc-Butil éster del ácido N-{1-{4-[3-(terc-butoxicarbonilaminometil)-piperidin-1-il]-2-ciclopropilamino-5-fluorofenil}metanoil)hidrazincarboxílico (MS CI: m/e 522 (MH+)) desde terc-butil éster del ácido piperidin-3-ilmetilcarbámico (Hilpert K., Ackermann J., Banner D.W., Gast A., Gubernator K., Hadvary P., Labler L., Mueller K., Schmid G., et al, *J. Med. Chem.*, 1994;37[23]:3889-3901) y terc-butil éster del ácido (2-ciclopropilamino-4,5-difluorobenzoil)hidrazincarboxílico (Ejemplo 6a) (Método General A).

(aa) terc-Butil éster del ácido N-[1-(4-{3-[(terc-butoxicarbonilisopropilamino)-metil]pirrolidin-1-il}-2-ciclopropilamino-5-fluorofenil)metanoil]-hidrazincarboxílico (MS CI: m/e 550 (MH+)) usando isopropilpirrolidin-3-ilmetilamina (Mich T.F., Culbertson T.P., US 4550103) y terc-butil éster del ácido (2-ciclopropilamino-4,5-difluorobenzoil-hidrazincarboxílico (Ejemplo 6a) (Método General B).

(bb) terc-Butil éster del ácido N'-(1-{4-[3-(terc-butoxicarbonilaminometil)pirrolidin-1-il]-5-cloro-2-ciclopropilaminofenil}metanoil)hidrazincarboxílico ([MS CI: m/e 524 [M^++1]) usando terc-butil éster del ácido (3-cloro-2-ciclopropilamino-4,5-difluorobenzoil)hidrazincarboxílico (Ejemplo 6c) y 3-(terc-butoxicarbonilaminometil)pirrolidina (Método General A).

(cc) terc-Butil éster del ácido N'-[4-(3-terc-butoxicarbonilaminopirrolidin-1-il)-2-ciclopropilamino-3-etoxi-5-fluorobenzoil]hidrazincarboxílico (MS ES: m/z 537) desde ácido (4-(3-terc-butoxicarbonilamino-pirrolidin-1-il)-2-ciclopropilamino-3-etoxi-5-fluorobenzoico (Ejemplo 4p) (Método General A).

EJEMPLO 8

Síntesis de terc-butil ésteres del ácido (2,4-dioxo-1,4-dihidro-2H-quinazolin-3-il)carbámico

Método General A

A una solución de terc-butil éster del ácido benzoilhidrazincarboxílico (del Ejemplo 7 (0,435 mmol) en tetrahidrofurano (15 ml) se agrega carbonato de potasio (0,300 g, 2,18 mmol) y trifosgeno (0,167 g, 0,566 mmol). La mezcla de

la reacción se refluye durante 90 minutos, se enfría a temperatura ambiente y se diluye con acetato de etilo. La capa orgánica se lava con agua y solución salina, luego se seca sobre $MgSO_4$ y se filtra. El filtrado se concentra bajo vacío y se purifica mediante cromatografía de columna rápida (acetato de etilo/hexanos) para lograr los compuestos del título.

Método General B

Una solución de terc-butil éster del ácido (2,4-dioxo-1,4-dihidro-2H-quinazolin-3-il)carbámico (tal como, por ejemplo, el Ejemplo 14), cadena lateral de pirrolidina (2 eq.), y trietilamina (10 eq.) se agita en sulfóxido de dimetilo o acetonitrilo (3 ml) a 80°C durante 48 horas. Después de enfriar a temperatura ambiente, la mezcla de la reacción se diluye con acetato de etilo y se lava con $NaHCO_3$, agua y solución salina. La capa orgánica se seca sobre $MgSO_4$, se filtra y se concentra. El residuo resultante se purifica mediante cromatografía de columna rápida (acetato de etilo/hexanos) para lograr los compuestos del título.

Método General C

A una solución de terc-butil éster del ácido (2,4-dioxo-1,4-dihidro-2H-quinazolin-3-il)carbámico C-6- y/o C-8-halogenado

en etanol y tetrahidrofurano, se agrega trietilamina y 20% de paladio sobre carbono. Se introduce hidrógeno en la mezcla de la reacción a alta presión durante varios días, luego la mezcla de la reacción se filtra a través de Celita, se lava con etanol y el filtrado combinado se concentra en vacío y se purifica mediante cromatografía de columna rápida (acetato de etilo/hexanos) para lograr los compuestos del título.

Método General D

Una suspensión de terc-butil éster del ácido benzoilhidrazincarboxílico (del Ejemplo 7) y trietilamina (10 eq.) se agita en tetrahidrofurano anhidro durante 5 minutos. Se agrega fosgeno (solución al 20% en tolueno, 2 eq.) en una porción a la suspensión. La mezcla de la reacción se calienta a 60°C durante 4,5 horas, se enfría a temperatura ambiente, se vierte en una solución de $NaHCO_3$ saturado y se extrae con cloroformo. Los extractos orgánicos combinados se lavan con agua, solución salina y luego se secan sobre Na_2SO_4, se filtran y se concentran bajo vacío. El residuo resultante se purifica mediante cromatografía de columna rápida (acetato de etilo/hexanos 1:1) para lograr los compuestos del título.

Método General E

Una pirrolidina sustituida apropiadamente (1,5-2 eq.), una 3-dibencilamino-6,7-difluoro-1-sustituido-1H-quinazolin-2,4-diona (Ejemplo 16) (1 eq.) y trietilamina (10 eq.) se combinan en acetonitrilo y se calientan a reflujo durante 72 horas. La solución se enfría, se concentra y se disuelve nuevamente en cloroformo. La solución orgánica se lava con ácido clorhídrico 1,0 N, $NaHCO_3$ saturado, y se seca sobre sulfato de magnesio. La solución se concentra para dar los compuestos del título.

Método General F

Una solución de terc-butil éster del ácido (2,4-dioxo-1,4-dihidro-2H-quinazolin-3-il)-carbámico (tal como, por ejemplo, el Ejemplo 14), cadena lateral de pirrolidina (2 eq.), y trietilamina (10 eq.) se agita en sulfóxido de dimetilo o acetonitrilo (3 ml) a 80°C durante 20 a 40 horas. Después de enfriar a temperatura ambiente, la mezcla de la reacción se diluye con acetato de etilo y se lava con $NaHCO_3$ saturado, agua, y solución salina. La capa orgánica se seca sobre $MgSO_4$, se filtra y se concentra. El residuo resultante se disuelve nuevamente en cloruro de metileno y luego se trata con di-terc-butil dicarbonato (2 eq.). Después de 1 hora, la mezcla de la reacción se concentra y el producto se purifica mediante cromatografía de columna rápida (acetato de etilo/hexanos) para lograr los compuestos del título.

Los siguientes compuestos se sintetizan de acuerdo con los Procedimientos Generales A-F del Ejemplo 8:

(a) terc-Butil éster del ácido {7-[3-(terc-butoxicarbonilaminometil)pirrolidin-1-il]-8-cloro-1-ciclopropil-6-fluoro-2,4-dioxo-1,4-dihidro-2H-quinazolin-3-il}-carbámico (MS CI: m/z 568 (MH+)) desde terc-butil éster del ácido N'-{4-[3-(terc-butoxicarbonilaminometil)pirrolidin-1-il]-3-cloro-2-ciclopropilamino-5-fluorobenzoil}hidrazincarboxílico (Ejemplo 18a) (Método General A).

(b) terc-Butil éster del ácido 7-[4-(terc-butoxicarbonilpiperazin-1-il)-8-cloro-1-ciclopropil-6-fluoro-2,4-dioxo-1,4-dihidro-2H-quinazolin-3-il]-carbámico (MS CI: m/z 554 (MH+)) desde terc-butil éster del ácido N'-4-[4-(terc-butoxicarbonilpiperazin-1-il)-3-cloro-2-ciclopropilamino-5-fluorobenzoil]hidrazincarboxílico (Ejemplo 18b) (Método General A).

(c) terc-Butil éster del ácido {7-[3-(terc-butoxicarbonilaminometil)-3-metilpirrolidin-1-il]-8-cloro-1-ciclopropil-6-fluoro-2,4-dioxo-1,4-dihidro-2H-quinazolin-3-il}-carbámico (MS CI: m/z 582 (MH+)) desde terc-butil éster del ácido N'-{4-[3-(terc-butoxicarbonilaminometil)-3-

metilpirrolidin-1-il]-3-cloro-2-ciclopropilamino-5-fluorobenzoil)hidrazincarboxílico (Ejemplo 18c) (Método General A).

(d) terc-Butil éster del ácido [7-(6-terc-butoxicarbonilamino-3-azabiciclo[3.1.0]hex-3-il)-8-cloro-1-ciclopropil-6-fluoro-2,4-dioxo-1,4-dihidro-2H-quinazolin-3-il]-carbámico (MS CI: m/z 566 (MH+)) desde terc-butil éster del ácido N'-[4-(6-terc-butoxicarbonilamino-3-azabiciclo[3.1.0]hex-3-il)-3-cloro-2-ciclopropilamino-5-fluorobenzoil]hidrazincarboxílico (Ejemplo 18d) (Método General A).

(e) terc-Butil éster del ácido {7-[(S)-3-(terc-butoxicarbonil-N-metilamino)pirrolidin-1-il]-8-cloro-1-ciclopropil-6-fluoro-2,4-dioxo-1,4-dihidro-2H-quinazolin-3-il}-carbámico (MS CI: m/z 568 (MH+)) desde terc-butil éster del ácido N'-{4-[(S)-3-(terc-butoxicarbonil-N-metilamino)pirrolidin-1-il]-3-cloro-2-ciclopropilamino-5-fluoro-benzoil}hidrazincarboxílico (Ejemplo 18e) (Método General A).

(f) terc-Butil éster del ácido {7-[(S)-3-(terc-butoxicarbonilamino)pirrolidin-1-il]-8-cloro-1-(2,4-difluoroanilino)-6-fluoro-1,4-dihidro-2,4-dioxo-2H-quinazolin-3-il}-carbámico (^{1}H NMR ($CDCl_3$): δ 7,45-7,38 (m, 1H), 6,97-6,81 (m, 1H), 6,73-6,66 (m, 1H), 6,54-6,42 (m, 1H), 4,90-4,81 (bs,

1H), 4,31-4,21 (bs, 1H), 3,86-3,36 (m, 4H), 2,32-2,04 (m, 1H), 1,96-1,84 (m, 1H), 1,61 (s, 9H), 1,45 (s, 9H)) desde terc-butil éster del ácido N'-{4-[(S)-3-(terc-butoxicarbonil-N-amino)pirrolidin-1-il]-3-cloro-2-(2,4-difluoroanilino)-5-fluorobenzoil}-hidrazincarboxílico (Ejemplo 18f) (Método General A).

(g) terc-Butil éster del ácido 7-[(S)-3-(terc-butoxicarbonilamino)pirrolidin-1-il]-1-ciclopropilamino-6,8-difluoro-1,4-dihidro-2,4-dioxo-2H-quinazolin-3-il}-carbámico (^{1}H NMR ($CDCl_3$): δ 7,54 (dd, 1H), 6,67 (bs, 1H), 4,79-4,68 (bs, 1H), 4,39-4,23 (m, 1H), 4,10-3,65 (m, 3H), 3,58-3,45 (m, 1H), 3,37-3,25 (m, 1H), 2,30-2,11 (m, 1H), 2,03-1,86 (m, 1H), 1,50 (s, 9H), 1,47 (s, 9H), 1,20-1,12 (m, 2H), 0,83-0,74 (bs, 2H)) desde terc-butil éster del ácido N'-{4-[(S)-3-(terc-butoxicarbonilamino)pirrolidin-1-il]-2-ciclopropilamino-3,5-difluorobenzoil}-hidrazincarboxílico (Ejemplo 5g) (Método General A).

(h) terc-Butil éster del ácido {7-[(S)-3-(terc-butoxicarbonilamino)pirrolidin-1-il]-1-ciclopropilamino-5,8-difluoro-1,4-dihidro-2,4-dioxo-2H-quinazolin-3-il}-carbámico (MS CI: m/z 538 (M^+)) desde terc-butil éster del ácido N'-{4-[(S)-3-(terc-butoxicarbonilamino)pirrolidin-1-il]-2-

ciclopropilamino-3,6-difluorobenzoil}hidrazincarboxílico (Ejemplo 15h) (Método General A).

(i) terc-Butil éster del ácido {7-[(S)-3-(terc-butoxicarbonilamino)pirrolidin-1-il]-1-ciclopropil-1,4-dihidro-2,4-dioxo-5,6,8-trifluoro-2H-quinazolin-3-il}-carbámico (MS CI: m/z 556 (MH^+)) desde terc-butil éster del ácido N'-{4-[(S)-3-(terc-butoxicarbonilamino)pirrolidin-1-il]-2-ciclopropilamino-3,5,6-trifluorobenzoil}hidrazincarboxílico (Ejemplo 5i) (Método General A).

(j) terc-Butil éster del ácido {7-[3-(terc-butoxicarbonilamino)pirrolidin-1-il]-8-cloro-1-ciclopropil-6-fluoro-2,4-dioxo-1,4-dihidro-2H-quinazolin-3-il}-carbámico (MS CI: m/z 552 (MH^+)) desde terc-butil éster del ácido N'-{4-[(S)-3-(terc-butoxicarbonilamino)pirrolidin-1-il]-3-cloro-2-ciclopropilamino-5-fluoro-benzoil}hidrazincarboxílico (Ejemplo 5j) (Método General A).

(k) terc-Butil éster del ácido [7-(3-hidroximetilpirrolidin-1-il)-8-cloro-1-ciclopropil-6-fluoro-2,4-dioxo-1,4-dihidro-2H-quinazolin-3-il]-carbámico (MS CI: m/z 467 (MH^+)) desde terc-butil éster del ácido (8-cloro-1-ciclopropil-6,7-difluoro-2,4-dioxo-1,4-dihidro-2H-quinazolin-3-il)carbámico (Ejemplo 14) y

3-hidroximetilpirrolidina (Roussi G., Zhang J., *Tetrahedron Lett.*, 1988;29(28):3481-3482) (Método General B).

(l) terc-Butil éster del ácido {7-[3-(terc-butoxicarbonilaminoetil)pirrolidin-1-il]-8-cloro-1-ciclopropil-6-fluoro-2,4-dioxo-1,4-dihidro-2H-quinazolin-3-il}-carbámico (MS CI: m/z 580 (MH^+)) desde terc-butil éster del ácido (8-cloro-1-ciclopropil-6,7-difluoro-2,4-dioxo-1,4-dihidro-2H-quinazolin-3-il)carbámico (Ejemplo 14) y 3-(terc-butoxicarbonilaminoetil)pirrolidina (Antonsson K.T., Bylund R.E., Gustafsson N.D., Nisson N.O.I. WO 9429336) (Método General B).

(m) terc-Butil éster del ácido [7-(7-terc-butoxicarbonilamino-5-azaespiro[2.4]hept-5-il)-8-cloro-1-ciclopropil-6-fluoro-2,4-dioxo-1,4-dihidro-2H-quinazolin-3-il]-carbámico (MS CI: m/z 580 (MH^+)) desde terc-butil éster del ácido N'-[(S)-4-(7-terc-butoxicarbonilamino-5-azaespiro[2.4]hept-5-il)-3-cloro-2-ciclopropilamino-5-fluorobenzoil]hidrazincarboxílico (Ejemplo 18g) (Método General A).

(n) terc-Butil éster del ácido {7-[(R)-3-(1-terc-butoxicarbonilamino-1-metiletil)pirrolidin-1-il]-8-cloro-1-ciclopropil-6-fluoro-2,4-dioxo-1,4-dihidro-2H-quinazolin-3-il}-carbámico (MS CI: m/z 596 (MH^+)) desde terc-butil éster del

ácido N'-{4-[(R)-3-(1-terc-butoxicarbonilamino-1-metiletil)pirrolidin-1-il]-3-cloro-2-ciclopropilamino-5-fluorobenzoil}hidrazincarboxílico (Ejemplo 71) (Método General A).

(o) terc-Butil éster del ácido {7-[3-(terc-butoxicarbonilaminometil)pirrolidin-1-il]-1-ciclopropil-6-fluoro-2,4-dioxo-1,4-dihidro-2H-quinazolin-3-il]-carbámico (MS CI: m/z 534 (MH^+)) desde terc-butil éster del ácido {7-[3-(terc-butoxicarbonilaminometil)pirrolidin-1-il]-8-cloro-1-ciclopropil-6-fluoro-2,4-dioxo-1,4-dihidro-2H-quinazolin-3-il}carbámico (Ejemplo 8a) (Método General C).

(p) terc-Butil éster del ácido [7-(pirrolidin-1-il)-8-cloro-1-ciclopropil-6-fluoro-2,4-dioxo-1,4-dihidro-2H-quinazolin-3-il]-carbámico (MS CI: m/z 437 (MH^+)) usando terc-butil éster del ácido N'-[4-(pirrolidin-1-il)-3-cloro-2-ciclopropilamino-5-fluorobenzoil]hidrazincarboxílico (Ejemplo 18h) (Método General A).

(q) terc-Butil éster del ácido {7-[3-(terc-butoxicarbonilamino)pirrolidin-1-il]-8-cloro-6-fluoro-1-isopropil-2,4-dioxo-1,4-dihidro-2H-quinazolin-3-il}-carbámico (MS CI: m/z 530 (M^+)) usando terc-butil éster del ácido N'-{4-[3-(terc-butoxicarbonilamino)pirrolidin-1-il)-3-cloro-5-

fluoro-2-isopropilaminobenzoil}-hidrazincarboxílico (Ejemplo 18i) (Método General A).

(r) terc-Butil éster del ácido {7-[3-(terc-butoxicarbonilamino)pirrolidin-1-il]-1-sec-butil-8-cloro-6-fluoro-2,4-dioxo-2H-quinazolin-3-il}-carbámico (MS CI: m/z 570 (MH^+)) usando terc-butil éster del ácido N'-{4-[3-(terc-butoxicarbonilamino)pirrolidin-1-il]-2-sec-butilamino-3-cloro-5-fluorobenzoil}hidrazincarboxílico (Ejemplo 7o) (Método General A).

(s) terc-Butil éster del ácido {7-[3-(terc-butoxicarbonilamino)pirrolidin-1-il]-1-ciclopropil-6-fluoro-2,4-dioxo-1,4-dihidro-2H-quinazolin-3-il}-carbámico (MS CI: m/z 550 (MH^+)) usando terc-butil éster del ácido N'-{4-[3-terc-butoxicarbonilamino)pirrolidin-1-il]-2-ciclopropilamino-5-fluoro-3-metoxibenzoil}hidrazincarboxílico (Ejemplo 7p) (Método General D).

(t) terc-Butil éster del ácido {7-[3-(terc-butoxicarbonilamino)pirrolidin-1-il]-8-cloro-1-ciclobutilamino-6-fluoro-2,4-dioxo-1,4-dihidro-2H-quinazolin-3-il}-carbámico (MS CI: m/z 568 (MH^+)) usando terc-butil éster del ácido N'-{4-[3-(terc-butoxicarbonilamino)pirrolidin-1-il]-

2-ciclobutilamino-5-fluorobenzoil}hidrazincarboxílico (Ejemplo 7q) (Método General A).

(u) terc-Butil éster del ácido {7-[3-(terc-butoxicarbonilamino)pirrolidin-1-il]-1-ciclopropil-8-fluoro-2,4-dioxo-1,4-dihidro-2H-quinazolin-3-il)-carbámico (MS CI: m/z 520 (MH^+)) usando terc-butil éster del ácido N'-{4-[3-terc-butoxicarbonilamino)pirrolidin-1-il]-2-ciclopropilamino-3-fluorobenzoil}hidrazincarboxílico (Ejemplo 7r) (Método General D).

(v) terc-Butil éster del ácido {7-[3-(terc-butoxicarbonilamino)pirrolidin-1-il]-6-cloro-1-ciclopropil-8-fluoro-2,4-dioxo-1,4-dihidro-2H-quinazolin-3-il}-carbámico (^1H NMR ($CDCl_3$): δ 7,36 (d, 1H), 6,64 (bs, 1H), 4,86-4,80 (bd, 1H), 4,31-4,25 (m, 1H), 3,81-3,66 (m, 2H), 3,51-3,31 (m, 2H), 3,02-2,97 (m, 1H), 2,32-2,22 (m, 1H), 1,95-1,85 (m, 1H), 1,63 (s, 9H), 1,46 (s, 9H), 0,77-0,73 (m, 2H), 0,63-0,57 (bs, 2H)) usando terc-butil éster del ácido N'-{4-[3-terc-butoxicarbonilamino)pirrolidin-1-il]-5-cloro-2-ciclopropilamino-3-fluorobenzoil}hidrazincarboxílico (Ejemplo 7s) (Método General D).

(w) terc-Butil éster del ácido [(S)-1-(1-ciclopropilmetil-3-dibencilamino-6-fluoro-2,4-dioxo-1,2,3,4-tetrahidroquinazolin-

7-il)pirrolidin-3-il]-carbámico (MS CI, m/z 614 (MH^+)) usando 3-dibencilamino-6,7-difluoro-1-ciclopropilmetil-1H-quinazolin-2,4-diona (Ejemplo 17a) y terc-butil éster del ácido (S)-pirrolidin-3-ilcarbámico (Método General E).

(x) terc-Butil éster del ácido {1-[(R)-1-(1-ciclopropilmetil-3-dibencilamino-6-fluoro-2,4-dioxo-1,2,3,4-tetrahidroquinazolin-7-il)pirrolidin-3-il]-1-ilmetil}-carbámico (MS CI, m/z 656 (MH^+)) usando 3-dibencilamino-6,7-difluoro-1-ciclopropilmetil-1H-quinazolin-2,4-diona (Ejemplo 17a) y terc-butil éster del ácido (R)-3-(1-terc-butoxicarbonilamino-1-metiletil)pirrolidina (Método General E).

(y) terc-Butil éster del ácido [(S)-1-(3-dibencilamino-1-etil-6-fluoro-2,4-dioxo-1,2,3,4-tetrahidroquinazolin-7-il)pirrolidin-3-il]-carbámico (punto de fusión 104°C-106°C, MS CI, m/z 588 (MH^+)) usando 3-dibencilamino-6,7-difluoro-1-etil-1H-quinazolin-2,4-diona (Ejemplo 17b) y terc-butil éster del ácido (S)-pirrolidin-3-ilcarbámico (Método General E).

(z) terc-Butil éster del ácido [(R)-1-(3-dibencilamino-1-etil-6-fluoro-2,4-dioxo-1,2,3,4-tetrahidroquinazolin-7-il)-1-metil-1-pirrolidin-3-iletil]-carbámico (MS CI, m/z 630 (MH^+)) usando 3-dibencilamino-6,7-difluoro-1-etil-1H-quinazolin-2,4-diona

(Ejemplo 17b) y terc-butil éster del ácido (R)-(1-terc-butoxicarbonilamino-1-metiletil)pirrolidina (Método General E).

(aa) terc-Butil éster del ácido [7-(3-terc-butoxicarbonilaminopirrolidin-1-il)-1-ciclopropil-6-fluoro-8-metil-2,4-dioxo-1,4-dihidro-2H-quinazolin-3-il)-carbámico ([MS ES, MH^+] m/z 534) usando terc-butil éster del ácido N'-[4-(3-terc-butoxicarbonilamino-pirrolidin-1-il)-2-ciclopropilamino-5-fluoro-3-metilbenzoil]-hidrazincarboxílico (Ejemplo 7t) (Método General D).

(bb) terc-Butil éster del ácido (7-[3-(terc-butoxicarbonilamino)pirrolidin-1-il]-1-ciclopropil-6-fluoro-8-metil-2,4-dioxo-1,4-dihidro-2H-quinazolin-3-il}-carbámico ([MS ES, MH^+] m/z 548)) usando terc-butil éster del ácido N'-(4-[3-(terc-butoxicarbonilaminometil)pirrolidin-1-il]-2-ciclopropilamino-5-fluoro-3-metilbenzoil}hidrazincarboxílico (Ejemplo 7u) (Método General D).

(cc) terc-Butil éster del ácido [7-(3-terc-butoxicarbonilaminopirrolidin-1-il)-1-ciclopropil-8-fluoro-6-metoxi-2,4-dioxo-1,4-dihidro-2H-quinazolin-3-il]-carbámico ([MS ES, MH_2^+] m/z 551) usando terc-butil éster del ácido N'-[4-(3-terc-butoxicarbonilaminopirrolidin-1-il)-2-

ciclopropilamino-3-fluoro-5-metoxibenzoil]hidrazincarboxílico (Ejemplo 7v) (Método General D).

(dd) terc-Butil éster del ácido {7-[3-(terc-butoxicarbonilamino)pirrolidin-1-il]-1-ciclopropil-6-fluoro-8-metoxi-2,4-dioxo-1,4-dihidro-2H-quinazolin-3-il}-carbámico ([MS ES, MH_2^{+2}] m/z 565) usando terc-butil éster del ácido N'-{4-[3-(terc-butoxicarbonilaminometil)pirrolidin-1-il]-2-ciclopropilamino-5-fluoro-3-metoxibenzoil}hidrazincarboxílico (Ejemplo 7w) (Método General D).

(ee) terc-Butil éster del ácido [7-(3-terc-butoxicarbonilaminopirrolidin-1-il)-1-ciclopropil-8-etoxi-6-fluoro-2,4-dioxo-1,4-dihidro-2H-quinazolin-3-il]carbámico ([MS ES, MH_2^{+2}] m/z 565) desde terc-butil éster del ácido N'-[4-(3-terc-butoxicarbonilaminopirrolidin-1-il)-2-ciclopropilamino-3-etoxi-5-fluorobenzoil]-hidrazincarboxílico (Ejemplo 7cc) (Método General A).

(ff) terc-Butil éster del ácido [7-(3-terc-butoxicarbonilaminopirrolidin-1-il)-8-ciano-1-ciclopropil-6-fluoro-2,4-dioxo-1,4-dihidro-2H-quinazolin-3-il]carbámico ([MS ES, MH^+] m/z 545) desde terc-butil éster del ácido N'-[3-benciloxiiminometil)-4-(3-terc-butoxicarbonilaminopirrolidin-

1-il)-2-ciclopropilamino-5-fluoro-benzoil]-hidrazincarboxílico (Ejemplo 7x) (Método General A).

(gg) terc-Butil éster del ácido [8-cloro-1-ciclopropil-6-fluoro-2,4-dioxo-7-(3-[1,2,3-triazol]-1-il-pirrolidin-1-il)-1,4-dihidro-2H-quinazolin-3-il]carbámico (^{1}H NMR (200 MHz, $CDCl_3$): δ 7,96 (s, 1H), 7,74 (s, 1H), 7,29 (d, 1H), 6,26 (bs, 1H), 5,51-5,39 (m, 1H), 4,17-4,07 (m, 1H), 3,99-3,88 (m, 1H), 3,71-3,66 (m, 1H), 3,57-3,45 (m, 1H), 3,15-3,05 (m, 1H), 2,74-2,60 (m, 1H), 2,40-2,32 (m, 1H), 1,64 (s, 9H), 0,76-0,49 (m, 4H)) desde terc-butil éster del ácido N'-[3-3-cloro-2-ciclopropilamino-5-fluoro-4-(3-[1,2,3-triazol0-1-il-pirrolidin-1-il)benzoil]hidrazincarboxílico (Ejemplo 7y) (Método General A).

(hh) terc-Butil éster del ácido [7-(3-carbamoilpiperidin-1-il)-8-cloro-1-ciclopropil-6-fluoro-2,4-dioxo-1,4-dihidro-2H-quinazolin-3-il]-carbámico (MS CI: m/z 496 (MH^+)) desde terc-butil éster del ácido (8-cloro-1-ciclopropil-6,7-difluoro-2,4-dioxo-1,4-dihidro-2H-quinazolin-3-il)carbámico (Ejemplo 14) y 3-carbamoil-piperidina (Método General B).

(ii) terc-Butil éster del ácido {7-[trans-3-(terc-butoxicarbonilaminometil)-4-trifluorometil-pirrolidin-1-il]-8-cloro-1-ciclopropil-6-fluoro-2,4-dioxo-1,4-dihidro-2H-

quinazolin-3-il}-carbámico (MS CI: m/z 635 (M^+)) desde terc-butil éster del ácido (8-cloro-1-ciclopropil-6,7-difluoro-2,4-dioxo-1,4-dihidro-2H-quinazolin-3-il)carbámico (Ejemplo 14) y trans-3-(terc-butoxicarbonilaminometil)-4-trifluorometilpirrolidina (Li Q., Tufano M., et al, *J. Med. Chem. Lett.*, 1998;8[15]:1953-1958) (Método General B).

(jj) terc-Butil éster del ácido 8-cloro-1-ciclopropil-6-fluoro-2,4-dioxo-7-{3-[(2,2,2-trifluoro-etilamino)metil]pirrolidin-1-il}-1,4-dihidro-2H-quinazolin-3-il)-carbámico (MS CI: m/z 548 (MH^+)) usando terc-butil éster del ácido (8-cloro-1-ciclopropil-6,7-difluoro-2,4-dioxo-1,4-dihidro-2H-quinazolin-3-il)carbámico (Ejemplo 14) y terc-butil éster del ácido {3-[(2,2,2-trifluoroetilamino)metil]pirrolidin-1-il}carbámico (Domagala J.M., Mich T.F., Sánchez J.P., US 5097032) (Método General B).

(kk) terc-Butil éster del ácido [8-cloro-1-ciclopropil-6-fluoro-7-(5-metilhexahidro-pirrolo[3,4-c]pirrol-2-il)-2,4-dioxo-1,4-dihidro-2H-quinazolin-3-il]-carbámico (MS CI: m/z 494 (MH^+)) usando terc-butil éster del ácido (8-cloro-1-ciclopropil-6,7-difluoro-2,4-dioxo-1,4-dihidro-2H-quinazolin-3-il)carbámico (Ejemplo 14) y 5-metiloctahidropirrolo[3,4-c]pirrol (Ohnmacht C.J., Jr., Draper C.W., Dedinas R.F.,

Loftus P., Wong J.J., *J. Heterocycl. Chem.*, 1983;20[2]:321-329) (Método General B).

(ll) terc-Butil éster del ácido [8-cloro-1-ciclopropil-7-(2,7-diazaespiro[4.4]non-2-il)-6-fluoro-2,4-dioxo-1,4-dihidro-2H-quinazolin-3-il]-carbámico (MS CI: m/z 494 (MH^+)) usando terc-butil éster del ácido (8-cloro-1-ciclopropil-6,7-difluoro-2,4-dioxo-1,4-dihidro-2H-quinazolin-3-il)carbámico (Ejemplo 14) y terc-butil éster del ácido (2,7-diaza-espiro[4.4]non-2-il)carbámico (Culbertson T.P., Sánchez J.P., Gambino L., Sesnie J.A., *J. Med. Chem.*, 1990;33[8]:2270-2275) (Método General B).

(mm) terc-Butil éster del ácido {7-[3-bencil-3-(terc-butoxicarbonilaminometil)pirrolidin-1-il]-8-cloro-1-ciclopropil-6-fluoro-2,4-dioxo-1,4-dihidro-2H-quinazolin-3-il}-carbámico (MS CI: m/z 658 (MH^+)) usando terc-butil éster del ácido (8-cloro-1-ciclopropil-6,7-difluoro-2,4-dioxo-1,4-dihidro-2H-quinazolin-3-il)carbámico (Ejemplo 14) y terc-butil éster del ácido (3-bencilpirrolidin-3-ilmetil)carbámico (Ejemplo A7o) (Método General B).

(nn) terc-Butil éster del ácido {7-[(R)-3-((S)-1-terc-butoxicarbonilaminoetil)pirrolidin-1-il]-8-cloro-1-ciclopropil-6-fluoro-2,4-dioxo-1,4-dihidro-2H-quinazolin-3-

il)-carbámico (MS CI: m/z 582 (MH^+)) desde terc-butil éster del ácido (8-cloro-1-ciclopropil-6,7-difluoro-2,4-dioxo-1,4-dihidro-2H-quinazolin-3-il)carbámico (Ejemplo 14) y terc-butil éster del ácido (R)-(S)-1-pirrolidin-3-iletil)carbámico (Johnson D.R., Szoteck D.L., Domagala J.M., Stickney T.M., Michel A., Kampf J.W., *J. Heterocycl. Chem.*, 1992;29[6]:1481-1488) (Método General B).

(oo) terc-Butil éster del ácido [8-cloro-1-ciclopropil-6-fluoro-7-(3-hidroxiiminopirrolidin-1-il)-2,4-dioxo-1,4-dihidro-2H-quinazolin-3-il]carbámico (MS CI: m/z 469 (MH^+)) usando terc-butil éster del ácido (8-cloro-1-ciclopropil-6,7-difluoro-2,4-dioxo-1,4-dihidro-2H-quinazolin-3-il)carbámico (Ejemplo 14) y oxima de pirrolidin-3-ona (Ejemplo A7) (Método General B).

(pp) terc-Butil éster del ácido [7-trans-(3-terc-butoxicarbonilamino-4-trifluorometilpirrolidin-1-il)-8-cloro-1-ciclopropil-6-fluoro-2,4-dioxo-1,4-dihidro-2H-quinazolin-3-il]-carbámico (MS CI: m/z 622 (MH^+)) desde terc-butil éster del ácido (8-cloro-1-ciclopropil-6,7-difluoro-2,4-dioxo-1,4-dihidro-2H-quinazolin-3-il)carbámico (Ejemplo 14) y terc-butil éster del ácido trans-(4-trifluorometilpirrolidin-3-il)carbámico (Fukui H., Shibata T., Naito T., Nakano J.,

Maejima T., Senda H., Iwatani W., et al, *Biorg. Med. Chem. Lett.*, 1998;8[20]:2833-2838) (Método General B).

(qq) terc-Butil éster del ácido (7-[(R)-3-(S)-1-(terc-butoxicarbonilmetilamino)etil]pirrolidin-1-il)-8-cloro-1-ciclopropil-6-fluoro-2,4-dioxo-1,4-dihidro-2H-quinazolin-3-il)-carbámico (MS CI: m/z 596 (MH^+)) desde terc-butil éster del ácido (8-cloro-1-ciclopropil-6,7-difluoro-2,4-dioxo-1,4-dihidro-2H-quinazolin-3-il)carbámico (Ejemplo 14) y (R)-3-((S)-1-(metilaminoetil)pirrolidina (*J. Het. Chem.*, 1992;29:1481) (Método General F).

(rr) terc-Butil éster del ácido trans-[7-((3-terc-butoxicarbonilamino-4-fenilpirrolidin-1-il)-8-cloro-1-ciclopropil-6-fluoro-2,4-dioxo-1,4-dihidro-2H-quinazolin-3-il]-carbámico (MS CI: m/z 630 (MH^+)) usando terc-butil éster del ácido (8-cloro-1-ciclopropil-6,7-difluoro-2,4-dioxo-1,4-dihidro-2H-quinazolin-3-il)carbámico (Ejemplo 14) y terc-butil éster del ácido trans-4-fenilpirrolidin-3-ilamino carbámico (Bucsh R.A., Domagala J.M., Laborde E., Sesnie J.C., *J. Med. Chem.*, 1993;36[26]:4139-4151) (Método General B).

(ss) terc-Butil éster del ácido trans-[7-[3-terc-butoxicarbonilamino-4-(4-hidroxifenil)-pirrolidin-1-il]-8-cloro-1-ciclopropil-6-fluoro-2,4-dioxo-1,4-dihidro-2H-

quinazolin-3-il)-carbámico (MS: m/z 646 (MH^+)) usando terc-butil éster del ácido (8-cloro-1-ciclopropil-6,7-difluoro-2,4-dioxo-1,4-dihidro-2H-quinazolin-3-il)carbámico (Ejemplo 14) y terc-butil éster del ácido trans-4-(4-hidroxifenil)-pirrolidin-3-ilamino carbámico (Bucsh R.A., Domagala J.M., Laborde E., Sesnie J.C., *J. Med. Chem.*, 1992;36[26]:4139-4151) (Procedimiento General B).

(tt) terc-Butil éster del ácido {7-[3-(terc-butoxicarbonilaminometil)piperidin-1-il]-8-cloro-1-ciclopropil-6-fluoro-2,4-dioxo-1,4-dihidro-2H-quinazolin-3-il}-carbámico (MS CI: m/z 580 (M^+)) usando terc-butil éster del ácido (8-cloro-1-ciclopropil-6,7-difluoro-2,4-dioxo-1,4-dihidro-2H-quinazolin-3-il)carbámico (Ejemplo 14) y terc-butil éster del ácido (piperidin-3-ilmetil)carbámico (Método General B).

(uu) terc-Butil éster del ácido (7-{3-[(terc-butoxicarbonilisopropilamino)metil]pirrolidin-1-il}-8-cloro-1-ciclopropil-6-fluoro-2,4-dioxo-1,4-dihidro-2H-quinazolin-3-il)-carbámico (MS CI: m/z 608 (M^+)) desde terc-butil éster del ácido (8-cloro-1-ciclopropil-6,7-difluoro-2,4-dioxo-1,4-dihidro-2H-quinazolin-3-il)carbámico (Ejemplo 14) y 3-(isopropilaminometil)pirrolidina (Domagala et al, *J. Med. Chem.*, 1994;3889-3901) (Método General F).

(vv) terc-Butil éster del ácido [7-[3-(terc-butoxicarbonilaminometil)pirrolidin-1-il]-6,8-dicloro-1-ciclopropil-2,4-dioxo-1,4-dihidro-2H-quinazolin-3-il}-carbámico (MS CI: m/z 584 (MH^+)) desde terc-butil éster del ácido (8-cloro-1-ciclopropil-6,7-difluoro-2,4-dioxo-1,4-dihidro-2H-quinazolin-3-il)carbámico (Ejemplo 14) y terc-butil éster del ácido (pirrolidin-3-ilmetil)carbámico (Método General B).

(ww) terc-Butil éster del ácido [7-(3-terc-butoxicarbonilamino-3-fenilpirrolidin-1-il]-8-cloro-1-ciclopropil-6-fluoro-2,4-dioxo-1,4-dihidro-2H-quinazolin-3-il]-carbámico (^1H NMR (200 MHz, $CDCl_3$): δ 7,68 (d, 1H), 7,50-7,29 (m, 5H), 6,72 (s, 1H), 5,24 (s, 1H), 4,18-3,85 (m, 3H), 3,78-3,52 (m, 2H), 2,70 (s, 1H), 2,58-2,39 (m, 1H), 1,62-0,62 (m, 22H)) desde terc-butil éster del ácido (8-cloro-1-ciclopropil-6,7-difluoro-2,4-dioxo-1,4-dihidro-2H-quinazolin-3-il)carbámico (Ejemplo 14) y terc-butil éster del ácido (3-fenilpirrolidin-3-il)carbámico (Ejemplo A30) usando el Método General B.

(xx) terc-Butil éster del ácido [7-[3-(terc-butoxicarbonilaminometil)-4-metilpirrolidin-1-il]-8-cloro-1-ciclopropil-6-fluoro-2,4-dioxo-1,4-dihidro-2H-quinazolin-3-il}-carbámico (MS ES: m/z 582 (MH^+)) desde terc-butil éster del

ácido (8-cloro-1-ciclopropil-6,7-difluoro-2,4-dioxo-1,4-dihidro-2H-quinazolin-3-il)carbámico (Ejemplo 14) y terc-butil éster del ácido trans-(4-metilpirrolidin-3-il)carbámico (Kuniyoshi M., Seigo S., Keiji H., Takayoshi I., Solicitud de Patente Europea, 1987, EP 208210) usando el procedimiento general F.

EJEMPLO 9

Desprotección de Quinazolin-2,4-dionas

Método General A

Se hace burbujear gas hidrógeno en éter dietílico (o diclorometano o dicloroetano) durante 15 minutos. La solución resultante se enfría a 0°C y se agrega a una solución de terc-butil éster del ácido 2,4-dioxo-1,4-dihidro-2H-quinazolin-3-il}carbámico (Ejemplo 6). La mezcla de la reacción se calienta lentamente a temperatura ambiente. Después de 30 horas, el precipitado se filtra, se lava con éter (o diclorometano o dicloroetano) y hexanos, y se seca bajo vacío para lograr la sal de clorhidrato de la amina desprotegida deseada, como un sólido.

Método General B

El compuesto se disuelve en ácido trifluoroacético y se agita a 0°C durante 3 a 8 horas. El ácido se remueve soplando aire comprimido sobre la solución o concentrado en vacío. El

residuo se co-evapora dos veces con etanol y se seca en vacío para dar la sal de trifluoroacetato del compuesto del título como un sólido.

Método General C

Un terc-butil éster del ácido 3-dibencilamino-6-fluoro-1-sustituido-2,4-dioxo-1,2,3,4-tetrahidro-quinazolin-7-il)pirrolidin-3-il]carbámico y 20% de Pd/C (cat.) se combinan en metanol y se agitan bajo 50 psi de hidrógeno durante 22,5 horas. La suspensión se filtra a través de Celita y se concentra. El residuo se purifica mediante cromatografía (SiO_2, $CHCl_3$) para dar un sólido. El sólido luego se disuelve en cloruro de metileno, se enfría a 0°C y se pasa gas de HCl a través de la solución durante 10 minutos. La suspensión se agita durante 2 horas y se concentra para dar el compuesto del título.

Método General D

Se hace burbujear gas de cloruro de hidrógeno a través de una solución del sustrato en éter dietílico, y la solución se agita durante 2 horas. El solvente se remueve bajo presión reducida para lograr el compuesto del título deseado como un sólido.

Método General E

Una solución del sustrato en etanol es tratada con una solución de etanol saturado con cloruro de hidrógeno gaseoso. La mezcla de la reacción se agita a temperatura ambiente durante 18 horas, y el solvente se remueve en vacío. El residuo se disuelve en agua, se filtra a través de una almohadilla de fibra de vidrio para aclararlo y se liofiliza. El residuo sólido se tritura con éter, se filtra, se lava con éter y se seca en vacío.

Método General F

Una solución de 3-amino-7-cloro-1-ciclopropil-6-fluoro-1H-pirido[2,3-d]pirimidin-2,4-diona (Ejemplo 24b), 1,2 eq. de cadena lateral de amina heterocíclica, y N,N-diisopropiletilamina/acetonitrilo 1:3 se calienta a 50°C durante 18 horas. La mezcla de la reacción se diluye con agua, se enfría a 0°C y el sólido se remueve mediante filtración, se lava con 50% de acetonitrilo acuoso, y se seca en vacío para dar un sólido que se disuelve en etanol y se trata con una solución de etanol saturado con cloruro de hidrógeno gaseoso. La mezcla luego se agita a temperatura ambiente durante 18 horas. El solvente se remueve en vacío y el residuo se tritura

con éter. El sólido se remueve por filtración, se lava con éter y se seca en vacío.

Los siguientes compuestos se sintetizan de acuerdo con los Procedimientos Generales A-F del Ejemplo 9:

(a) Clorhidrato la 3-amino-7-(3-aminometilpirrolidin-1-il)-8-cloro-1-ciclopropil-6-fluoro-1H-quinazolin-2,4-diona (**Compuesto 1**) (punto de fusión 153°C-155°C, MS CI: m/z 368 (MH^+)) desde terc-butil éster del ácido 7-[3-(terc-butoxicarbonilamino-metil)pirrolidin-1-il]-8-cloro-1-ciclopropil-6-fluoro-2,4-dioxo-1,4-dihidro-2H-quinazolin-3-il}carbámico (Ejemplo 8a) usando el Método General A.

(b) Clorhidrato la 3-amino-8-cloro-1-ciclopropil-6-fluoro-7-piperazin-1-il-1H-quinazolin-2,4-diona (**Compuesto 2**) (punto de fusión 156°C-159°C, MS CI: m/z 354 (MH^+)) desde terc-butil éster del ácido 7-[4-(terc-butoxicarbonilpiperazin-1-il)-8-cloro-1-ciclopropil-6-fluoro-2,4-dioxo-1,4-dihidro-2H-quinazolin-3-il}carbámico (Ejemplo 8b) usando el Método General A.

(c) Clorhidrato de 3-amino-7-[3-(aminometil)-3-metilpirrolidin-1-il]-8-cloro-1-ciclopropil-6-fluoro-1H-quinazolin-2,4-diona (**Compuesto 3**) (punto de fusión 166°C-

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168°C, MS CI: m/z 382 (MH^+)) desde terc-butil éster del ácido {7-[3-(terc-butoxicarbonilamino-metil)-3-metilpirrolidin-1-il]-8-cloro-1-ciclopropil-6-fluoro-2,4-dioxo-1,4-dihidro-2H-quinazolin-3-il}carbámico (Ejemplo 8c) usando el Método General A.

(d) Clorhidrato de 3-amino-7-(6-amino-3-aza-biciclo[3.1.0]hex-1-il)-8-cloro-1-ciclopropil-6-fluoro-1H-quinazolin-2,4-diona (**Compuesto 4**) (punto de fusión 111°C-114°C, MS CI: m/z 366 (MH^+)) desde terc-butil éster del ácido [7-(6-terc-butoxicarbonilamino-3-azabiciclo[3.1.0]hex-3-il)-8-cloro-1-ciclopropil-6-fluoro-2,4-dioxo-1,4-dihidro-2H-quinazolin-3-il}carbámico (Ejemplo 8d) usando el Método General A.

(e) Clorhidrato de 3-amino-7-((S)-3-N-metilaminopirrolidin-1-il)-8-cloro-1-ciclopropil-6-fluoro-1H-quinazolin-2,4-diona (**Compuesto 5**) (punto de fusión 1183°C-120°C, MS CI: m/z 368 (MH^+)) desde terc-butil éster del ácido {7-[(S)-3-(terc-butoxicarbonil-N-metilamino)pirrolidin-1-il]-8-cloro-1-ciclopropil-6-fluoro-2,4-dioxo-1,4-dihidro-2H-quinazolin-3-il}carbámico (Ejemplo 8e) usando el Método General A.

(f) Clorhidrato de 3-amino-7-((S)-3-aminometilpirrolidin-1-il)-8-cloro-1-(2,4-difluoroanilino)-6-fluoro-1H-quinazolin-

2,4-diona (**Compuesto 6**) (punto de fusión 184°C-186°C, MS CI: m/z 427 (MH^+)) desde terc-butil éster del ácido {7-[(S)-3-(terc-butoxicarbonilamino)pirrolidin-1-il]-8-cloro-1-(2,4-difluoroanilino)-6-fluoro-1,4-dihidro-2,4-dioxo-2H-quinazolin-3-il}carbámico (Ejemplo 8f) usando el Método General A.

(g) Clorhidrato de 3-amino-7-[(S)-3-aminopirrolidin-1-il]-1-ciclopropil-6,8-difluoro-1H-quinazolin-2,4-diona (**Compuesto 7**) (punto de fusión 288°C, MS EI: m/z 388 (M^+)) desde terc-butil éster del ácido 7-[(S)-3-(terc-butoxicarbonilamino)-pirrolidin-1-il}-1-ciclopropilamino-6,8-difluoro-1,4-dihidro-2,4-dioxo-2H-quinazolin-3-il}carbámico (Ejemplo 8g) usando el Método General A.

(h) Clorhidrato de 3-amino-7-[(S)-3-aminopirrolidin-1-il]-1-ciclopropilamino-5,8-difluoro-1H-quinazolin-2,4-diona (**Compuesto 8**) (punto de fusión 338°C, MS EI: m/z 338 (M^+)) desde terc-butil éster del ácido {7-[(S)-3-(terc-butoxicarbonilamino)-pirrolidin-1-il]-1-ciclopropilamino-5,8-difluoro-1,4-dihidro-2,4-dioxo-2H-quinazolin-3-il}carbámico (Ejemplo 8h) usando el Método General A.

(i) Clorhidrato de 3-amino-7-((S)-3-aminopirrolidin-1-il)-1-ciclopropil-5,6,8-trifluoro-1H-quinazolin-2,4-diona (**Compuesto 9**) (punto de fusión 271°C, MS CI: m/z 356 (MH^+)) desde terc-

butil éster del ácido {7-[(S)-3-(terc-butoxicarbonilamino)-pirrolidin-1-il]-1-ciclopropil-1,4-dihidro-2,4-dioxo-5,6,8-trifluoro-2H-quinazolin-3-il}carbámico (Ejemplo 8i) usando el Método General A.

(j) Clorhidrato de 3-amino-7-(3-aminopirrolidin-1-il)-8-cloro-1-ciclopropil-6-fluoro-1H-quinazolin-2,4-diona (**Compuesto 10**) (punto de fusión 134°C-136°C, MS CI: m/z 354 (MH^+)) desde terc-butil éster del ácido {7-[3-(terc-butoxicarbonilamino)-pirrolidin-1-il]-8-cloro-1-ciclopropil-6-fluoro-2,4-dioxo-1,4-dihidro-2H-quinazolin-3-il}carbámico (Ejemplo 8a) usando el Método General A.

(k) Clorhidrato de 7-((S)-3-aminopirrolidin-1-il)-1-ciclopropil-3,5-diamino-6,8-difluoro-1H-quinazolin-2,4-diona (**Compuesto 11**) (punto de fusión 215°C-218°C, MS EI: m/z 352 (M^+)) desde terc-butil éster del ácido {5-amino-7-[(S)-3-(terc-butoxicarbonilamino)pirrolidin-1-il]-1-ciclopropil-6,8-difluoro-1,4-dihidro-2,4-dioxo-2H-quinazolin-3-il}carbámico (Ejemplo 12) usando el Método General A.

(l) Clorhidrato de 3-amino-7-(3-hidroximetilpirrolidin-1-il)-8-cloro-1-ciclopropil-6-fluoro-1H-quinazolin-2,4-diona (**Compuesto 12**) (punto de fusión 78°C-80°C, MS CI: m/z 369 (MH^+)) desde terc-butil éster del ácido [7-(3-

hidroximetilpirrolidin-1-il)-8-cloro-1-ciclopropil-6-fluoro-2,4-dioxo-1,4-dihidro-2H-quinazolin-3-il]carbámico (Ejemplo 8k) usando el Método General A.

(m) Clorhidrato de 3-amino-7-(3-aminoetilpirrolidin-1-il)-8-cloro-1-ciclopropil-6-fluoro-1H-quinazolin-2,4-diona (**Compuesto 13**) (punto de fusión 158°C-160°C, MS CI: m/z 382 (MH^+)) desde terc-butil éster del ácido {7-[3-(terc-butoxicarbonilamino-etil)pirrolidin-1-il]-8-cloro-1-ciclopropil-6-fluoro-2,4-dioxo-1,4-dihidro-2H-quinazolin-3-il}carbámico (Ejemplo 81) usando el Método General A.

(n) Clorhidrato de 3-amino-7-((S)-7-amino-5-azaespiro[2.4]hept-5-il)-8-cloro-1-ciclopropil-6-fluoro-1H-quinazolin-2,4-diona (**Compuesto 14**) (punto de fusión 177°C-179°C, MS CI: m/z 380 (MH^+)) desde terc-butil éster del ácido [7-(7-terc-butoxicarbonilamino-5-azaespiro[2.4]hept-5-il)-8-cloro-1-ciclopropil-6-fluoro-2,4-dioxo-1,4-dihidro-2H-quinazolin-3-il]carbámico (Ejemplo 8m) usando el Método General A.

(o) Clorhidrato de 3-amino-7-[(R)-3-(1-amino-1-metiletil)pirrolidin-1-il]-8-cloro-1-ciclopropil-6-fluoro-1H-quinazolin-2,4-diona (**Compuesto 15**) (punto de fusión 117°C-120°C, MS CI: m/z 396 (MH^+)) desde terc-butil éster del ácido

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{7-[((R)-3-terc-butoxicarbonilamino-1-metiletil)pirrolidin-1-il]-8-cloro-1-ciclopropil-6-fluoro-2,4-dioxo-1,4-dihidro-2H-quinazolin-3-il}carbámico (Ejemplo 8n) usando el Método General A.

(p) Clorhidrato de 3-amino-7-(3-aminometilpirrolidin-1-il)-1-ciclopropil-6-fluoro-1H-quinazolin-2,4-diona (**Compuesto 16**) (punto de fusión 170°C-172°C, MS CI: m/z 334 (MH^+)) desde terc-butil éster del ácido {7-[3-(terc-butoxicarbonilamino-metil)pirrolidin-1-il]-1-ciclopropil-6-fluoro-2,4-dioxo-1,4-dihidro-2H-quinazolin-3-il}carbámico (Ejemplo 8o) usando el Método General A.

(q) Clorhidrato de 3-amino-7-(pirrolidin-1-il)-8-cloro-1-ciclopropil-6-fluoro-1H-quinazolin-2,4-diona (**Compuesto 17**) (punto de fusión 96°C-98°C, MS CI: m/z 339 (MH^+)) desde terc-butil éster del ácido [7-(pirrolidin-1-il)-8-cloro-1-ciclopropil-6-fluoro-2,4-dioxo-1,4-dihidro-2H-quinazolin-3-il]carbámico (Ejemplo 8p) usando el Método General A.

(r) Trifluoroacetato de 3-amino-7-(3-aminopirrolidin-1-il)-8-cloro-6-fluoro-1H-quinazolin-2,4-diona (**Compuesto 18**) (punto de fusión 151°C, MS EI: m/z 356 (MH^+)) desde terc-butil éster del ácido {7-[3-(terc-butoxicarbonilamino)-pirrolidin-1-il}-8-

cloro-6-fluoro-1-isopropil-2,4-dioxo-6-fluoro-2H-quinazolin-3-il}carbámico (Ejemplo 8q) usando el Método General B.

(s) Trifluoroacetato de 3-amino-7-(3-aminopirrolidin-1-il)-1-sec-butil-8-cloro-6-fluoro-1H-quinazolin-2,4-diona (**Compuesto 19**) (punto de fusión 115°C) desde terc-butil éster del ácido {7-[3-(terc-butoxicarbonilamino)pirrolidin-1-il]-1-sec-butil-8-cloro-6-fluoro-2,4-dioxo-2H-quinazolin-3-il}carbámico (Ejemplo 8r) usando el Método General B.

(t) Clorhidrato de 3-amino-7-[3-aminopirrolidin-1-il]-1-ciclopropil-6-fluoro-8-metoxi-1H-quinazolin-2,4-diona (**Compuesto 20**) (punto de fusión 216°C-218°C, MS EI: m/z 350 (MH^+)) desde terc-butil éster del ácido {7-[3-(terc-butoxicarbonilamino)-pirrolidin-1-il]-1-ciclopropil-6-fluoro-8-metoxi-2,4-dioxo-1,4-dihidro-2H-quinazolin-3-il}carbámico (Ejemplo 8s) usando el Método General A.

(u) Clorhidrato de 3-amino-7-[3-aminopirrolidin-1-il]-8-cloro-1-ciclobutilamino-6-fluoro-1H-quinazolin-2,4-diona (**Compuesto 21**) (punto de fusión 205°C-208°C, MS EI: m/z 368 (MH^+)) desde terc-butil éster del ácido {7-[3-(terc-butoxicarbonilamino)pirrolidin-1-il}-8-cloro-1-ciclobutilamino-6-fluoro-2,4-dioxo-1,4-dihidro-2H-quinazolin-3-il}carbámico (Ejemplo 8t) usando el Método General A.

(y) Clorhidrato de 3-amino-7-[(S)-3-(1-amino-1-metiletil)pirrolidin-1-il]-1-ciclopropilmetil-8-fluoro-1H-quinazolin-2,4-diona (**Compuesto 25**) (punto de fusión >250°C, MS CI: m/z 376 (MH^+)) desde terc-butil éster del ácido {1-[(R)-1-(ciclopropilmetil-3-dibencilamino-6-fluoro-2,4-dioxo-1,2,3,4-tetrahidroquinazolin-7-il)pirrolidin-3-il]-1-metiletil}carbámico (Ejemplo 8x) usando el Método General C.

(z) Clorhidrato de 3-amino-7-((S)-3-aminopirrolidin-1-il)-1-etil-8-fluoro-1H-quinazolin-2,4-diona (**Compuesto 26**) (punto de fusión 248°C-251°C, MS CI: m/z 308 (MH^+)) desde terc-butil éster del ácido [(S)-1-(3-dibencilamino-1-etil-6-fluoro-2,4-dioxo-1,2,3,4-tetrahidroquinazolin-7-il)pirrolidin-3-il]carbámico (Ejemplo 8y) usando el Método General C.

(aa) Clorhidrato de 3-amino-1-etil-6-fluoro-7-[(R)-3-(1-amino-1-metiletil)-pirrolidin-1-il]-1H-quinazolin-2,4-diona (**Compuesto 27**) (punto de fusión >250°C, MS CI: m/z 350 (MH^+)) desde terc-butil éster del ácido [(R)-1-(3-dibencilamino-1-etil-6-fluoro-2,4-dioxo-1,2,3,4-tetrahidroquinazolin-7-il)-1-metil-1-pirrolidin-3-iletil]carbámico (Ejemplo 8z) usando el Método General C.

(bb) Clorhidrato de 3-amino-7-((S)-3-aminopirrolidin-1-il)-1-ciclopropil-6-fluoro-1H-quinazolin-2,4-diona (**Compuesto 28**)

(v) Trifluoroacetato de 3-amino-7-(3-aminopirrolidin-1-il)-1-ciclopropil-8-fluoro-1H-quinazolin-2,4-diona (**Compuesto 22**) (punto de fusión 210°C-212°C, MS EI: m/z 320 (MH^+)) desde terc-butil éster del ácido {7-[3-(terc-butoxicarbonilamino)-pirrolidin-1-il]-1-ciclopropil-8-fluoro-2,4-dioxo-1,4-dihidro-2H-quinazolin-3-il}carbámico (Ejemplo 8u) usando el Método General A.

(w) Trifluoroacetato de 3-amino-7-(3-aminopirrolidin-1-il]-6-cloro-1-ciclopropil-8-fluoro-1H-quinazolin-2,4-diona (**Compuesto 23**) (punto de fusión 135°C-137°C, MS EI: m/z 354 (MH^+)) desde terc-butil éster del ácido {7-[3-(terc-butoxicarbonilamino)-pirrolidin-1-il]-6-cloro-1-ciclopropil-8-fluoro-2,4-dioxo-1,4-dihidro-2H-quinazolin-3-il}carbámico (Ejemplo 8v) usando el Método General B.

(x) Clorhidrato de 3-amino-7-((S)-3-aminopirrolidin-1-il)-1-ciclopropilmetil-8-fluoro-1H-quinazolin-2,4-diona (**Compuesto 24**) (punto de fusión >250°C, MS CI: m/z 334 (MH^+)) desde terc-butil éster del ácido [(S)-1-(1-ciclopropilmetil)-3-dibencilamino-6-fluoro-2,4-dioxo-1,2,3,4-tetrahidroquinazolin-7-il)pirrolidin-3-il]carbámico (Ejemplo 8w) usando el Método General C.

(punto de fusión >250°C, MS CI: m/z 320 (MH^+)) desde 3-amino-{7-[(S)-3-(terc-butoxicarbonilamino)pirrolidin-1-il]-1-ciclopropil-6-fluoro-1H-quinazolin-2,4-diona (Ejemplo 25) usando el Método General A.

(cc) Trifluoroacetato de 3-amino-7-(3-aminopirrolidin-1-il)-1-ciclopropil-6-fluoro-8-metil-1H-quinazolin-2,4-diona (**Compuesto 29**) (punto de fusión 110°C-112°C, MS ES, MH^+ m/z 334) desde terc-butil éster del ácido [7-(3-terc-butoxocarbonilamino-pirrolidin-1-il)-1-ciclopropil-6-fluoro-8-metil-2,4-dioxo-1,4-dihidro-2H-quinazolin-3-il]carbámico (Ejemplo 8aa) usando el Método General B.

(dd) Trifluoroacetato de 3-amino-7-(3-aminometilpirrolidin-1-il)-1-ciclopropil-6-fluoro-8-metil-1H-quinazolin-2,4-diona (**Compuesto 30**) (punto de fusión 82°C-84°C, MS ES, m/z 348 (MH^+)) desde terc-butil éster del ácido {7-[3-(terc-butoxocarbonilaminometil)-pirrolidin-1-il]-1-ciclopropil-6-fluoro-8-metil-2,4-dioxo-1,4-dihidro-2H-quinazolin-3-il}carbámico (Ejemplo 8bb) usando el Método General B.

(ee) Clorhidrato de 3-amino-7-(3-aminopirrolidin-1-il)-1-ciclopropil-8-fluoro-6-metoxi-1H-quinazolin-2,4-diona (**Compuesto 31**) (punto de fusión 208°C-210°C, MS ES, m/z 350 (MH^+)) desde terc-butil éster del ácido [7-(3-terc-

butoxocarbonilamino-pirrolidin-1-il)-1-ciclopropil-8-fluoro-6-metoxi-2,4-dioxo-1,4-dihidro-2H-quinazolin-3-il]carbámico (Ejemplo 8cc) usando el Método General A.

(ff) Clorhidrato de 3-amino-7-(3-aminometilpirrolidin-1-il)-1-ciclopropil-6-fluoro-8-metoxi-1H-quinazolin-2,4-diona (**Compuesto 32**) (punto de fusión 180°C-182°C, MS ES, m/z 364 (MH^+)) desde terc-butil éster del ácido {7-[3-terc-butoxocarbonilaminometil)pirrolidin-1-il]-1-ciclopropil-6-fluoro-8-metoxi-2,4-dioxo-1,4-dihidro-2H-quinazolin-3-il}carbámico (Ejemplo 8dd) usando el Método General A.

(gg) Clorhidrato de 3-amino-7-(3-aminopirrolidin-1-il)-1-ciclopropil-8-etoxi-6-fluoro-1H-quinazolin-2,4-diona (**Compuesto 33**) (punto de fusión 220°C, MS ES, m/z 364 (MH^+)) desde terc-butil éster del ácido [7-(3-terc-butoxocarbonilamino-pirrolidin-1-il)-1-ciclopropil-8-etoxi-6-fluoro-2,4-dioxo-1,4-dihidro-2H-quinazolin-3-il]carbámico (Ejemplo 8ee) usando el Método General A.

(hh) Clorhidrato de 3-amino-7-(3-aminopirrolidin-1-il)-1-ciclopropil-6-fluoro-2,4-dioxo-1,2,3,4-tetrahidroquinazolin-8-carbonitrilo (**Compuesto 34**) (punto de fusión 277°C, MS ES, m/z 345 (MH^+)) desde terc-butil éster del ácido [7-(3-terc-butoxocarbonilaminopirrolidin-1-il)-8-ciano-1-ciclopropil-6-

fluoro-2,4-dioxo-1,4-dihidro-2H-quinazolin-3-il]carbámico (Ejemplo 8ff) usando el Método General A.

(ii) Trifluoroacetato de 3-amino-8-cloro-1-ciclopropil-6-fluoro-7-(3-[1,2,3-triazol]-1-il-pirrolidin-1-il)-1H-quinazolin-2,4-diona (**Compuesto 35**) (punto de fusión 145°C-147°C, MS ES, m/z 406 (MH^+)) desde terc-butil éster del ácido [8-cloro-1-ciclopropil-6-fluoro-2,4-dioxo-7-(3-[1,2,3-triazol]-1-il-pirrolidin-1-il)-1,4-dihidro-2H-quinazolin-3-il]carbámico (Ejemplo 8gg) usando el Método General B.

(jj) Clorhidrato de 3-amino-7-[(S)-3-((R)-1-aminoetil)pirrolidin-1-il]-1-ciclopropil-6-fluoro-8-metoxi-1H-quinazolin-2,4-diona (**Compuesto 36**) (punto de fusión 215°C-217°C) desde terc-butil éster del ácido {(R)-1-[(S)-1-(3-amino-1-ciclopropil-6-fluoro-8-metoxi-2,4-dioxo-1,2,3,4-tetrahidroquinazolin-7-il)pirrolidin-3-il]etil}-carbámico (Ejemplo 28a) usando el Método General E.

(kk) Clorhidrato de 3-amino-7-[(S)-3-((S)-1-aminoetil)pirrolidin-1-il]-1-ciclopropil-6-fluoro-8-metoxi-1H-quinazolin-2,4-diona (**Compuesto 37**) (punto de fusión 221°C-223°C) desde terc-butil éster del ácido {(S)-1-[(S)-1-(3-amino-1-ciclopropil-6-fluoro-8-metoxi-2,4-dioxo-1,2,3,4-

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tetrahidroquinazolin-7-il)pirrolidin-3-il]etil)-carbámico (Ejemplo 28b) usando el Método General A.

(ll) Clorhidrato de 3-amino-7-[(S)-3-((R)-1-aminoetil)pirrolidin-1-il]-1-ciclopropil-6-fluoro-8-metil-1H-quinazolin-2,4-diona (**Compuesto 38**) (punto de fusión 197°C-199°C) desde terc-butil éster del ácido {(R)-1-[(S)-1-(3-amino-1-ciclopropil-6-fluoro-8-metil-2,4-dioxo-1,2,3,4-tetrahidroquinazolin-7-il)pirrolidin-3-il]etil}-carbámico (Ejemplo 28c) usando el Método General E.

(mm) Clorhidrato de 3-amino-7-[(S)-3-((S)-1-aminoetil)pirrolidin-1-il]-1-ciclopropil-6-fluoro-8-metil-1H-quinazolin-2,4-diona (**Compuesto 39**) (punto de fusión 192°C-194°C) desde terc-butil éster del ácido {(S)-1-[(S)-1-(3-amino-1-ciclopropil-6-fluoro-8-metil-2,4-dioxo-1,2,3,4-tetrahidroquinazolin-7-il)pirrolidin-3-il]etil}-carbámico (Ejemplo 28d) usando el Método General E.

(nn) Clorhidrato de 5-amino-9-((S)-3-aminopirrolidin-1-il)-8-fluoro-3-metil-2,3-dihidro-1-oxa-3a,5-diazafenalen-4,6-diona (**Compuesto 40**) (punto de fusión 202°C-204°C) desde terc-butil éster del ácido [(S)-1-(5-amino-8-fluoro-3-metil-4,6-dioxo-2,3,5,6-tetrahidro-4H-1-oxa-3a,5-diazafenalen-9-il)pirrolidin-3-il]carbámico (Ejemplo 28c) usando el Método General E.

(oo) Clorhidrato de 5-amino-9-[(R)-3-((S)-1-aminoetil)pirrolidin-1-il]-8-fluoro-3-metil-2,3-dihidro-1-oxa-3a,5-diazafenalen-4,6-diona (**Compuesto 41**) (punto de fusión 192°C-194°C) desde terc-butil éster del ácido {(S)-1-[(R)-1-(5-amino-8-fluoro-3-metil-4,6-dioxo-2,3,5,6-tetrahidro-4H-1-oxa-3a,5-diazafenalen-9-il)pirrolidin-3-il]etil}carbámico (Ejemplo 28f) usando el Método General E.

(pp) Clorhidrato de 2-amino-8-((S)-3-aminopirrolidin-1-il)-9-fluoro-5-metil-6,7-dihidro-5H-pirido[3,2,1-ij]quinazolin-1,3-diona (**Compuesto 42**) (punto de fusión 202°C-204°C) desde terc-butil éster del ácido [(S)-1-(2-amino-9-fluoro-5-metil-1,3-dioxo-2,3,6,7-tetrahidro-1H,5H-pirido[3,2,1-ij]quinazolin-8-il)pirrolidin-3-il]carbámico (Ejemplo 28g) usando el Método General E.

(qq) Clorhidrato de 2-amino-8-[(R)-3-((S)-1-aminoetil)pirrolidin-1-il]-9-fluoro-5-metil-6,7-dihidro-5H-pirido[3,2,1-ij]quinazolin-1,3-diona (**Compuesto 43**) (punto de fusión 197°C-199°C) desde terc-butil éster del ácido {(R)-3-[(S)-1-(2-amino-9-fluoro-5-metil-1,3-dioxo-2,3,6,7-tetrahidro-1H,5H-pirido[3,2,1-ij]quinazolin-8-il)pirrolidin-3-il]etil}carbámico (Ejemplo 28h) usando el Método General E.

(rr) Clorhidrato de 3-amino-7-((S)-3-aminopirrolidin-1-il)-1-ciclopropil-6-fluoro-1H-pirido[2,3-d]pirimidin-2,4-diona (**Compuesto 44**) (punto de fusión 213°C-215°C) desde terc-butil éster del ácido [1-(3-amino-1-ciclopropil-6-fluoro-2,4-dioxo-1,2,3,4-tetrahidro-pirido[2,3-d]pirimidin-7-il)pirrolidin-3-il]carbámico (Ejemplo 28i) usando el Método General E.

(ss) Clorhidrato de 3-amino-7-(6-amino-3-azabiciclo[3.1.0]hex-3-il)-1-ciclopropil-6-fluoro-1H-pirido[2,3-d]pirimidin-2,4-diona (**Compuesto 45**) (punto de fusión 268°C-270°C) desde 3-amino-7-cloro-1-ciclopropil-6-fluoro-1H-pirido[2,3-d]pirimidin-2,4-diona (Ejemplo 24b) y terc-butil éster del ácido 3-azabiciclo[3.1.0]hex-6-ilcarbámico usando el Método General F.

(tt) Clorhidrato de 3-amino-7-(3-aminoetil-3-metilpirrolidin-1-il)-1-ciclopropil-6-fluoro-1H-pirido[2,3-d]pirimidin-2,4-diona (**Compuesto 46**) (punto de fusión 187°C-189°C) desde 3-amino-7-cloro-1-ciclopropil-6-fluoro-1H-pirido[2,3-d]pirimidin-2,4-diona (Ejemplo 24b) y terc-butil éster del ácido [1-metil-(3-metilpirrolidin-3-il)]metilcarbámico (*J. Med. Chem.*, 1992;361-367) usando el Método General F.

(uu) Clorhidrato de 3-amino-1-ciclopropil-6-fluoro-7-(octahidropirrolo[3,4-c]piridin-2-il)-1H-pirido[2,3-

d]pirimidin-2,4-diona (**Compuesto 47**) (punto de fusión 200°C-203°C) desde 3-amino-7-cloro-1-ciclopropil-6-fluoro-1H-pirido[2,3-d]pirimidin-2,4-diona (Ejemplo 24b) y terc-butil éster del ácido (3aS,7aR)-octahidropirrolo[3,4-c]piridin-5-carboxílico (Ejemplo A27) usando el Método General F.

(vv) Clorhidrato de 3-amino-1-ciclopropil-6-fluoro-7-(octahidropirrolo[3,4-b]piridin-2-il)-1H-pirido[2,3-d]pirimidin-2,4-diona (**Compuesto 48**) (punto de fusión 200°C-202°C) desde 3-amino-7-cloro-1-ciclopropil-6-fluoro-1H-pirido[2,3-d]pirimidin-2,4-diona (Ejemplo 24b) y terc-butil éster del ácido octahidropirrolo[3,4-b]piridin-5-carboxílico usando el Método General F.

(ww) Clorhidrato de 3-amino-7-[(R)-3-(1-amino-1-metiletil)pirrolidin-1-il]-1-ciclopropil-6-fluoro-1H-pirido[2,3-d]pirimidin-2,4-diona (**Compuesto 49**) (punto de fusión >260°C) desde 3-amino-7-cloro-1-ciclopropil-6-fluoro-1H-pirido[2,3-d]pirimidin-2,4-diona (Ejemplo 24b) y (R)-3-(1-amino-1-metiletil)-pirrolidina usando el Método General F.

(xx) Clorhidrato de 3-amino-7-(3-aminometilpiperidin-1-il)-1-ciclopropil-6-fluoro-1H-pirido[2,3-d]pirimidin-2,4-diona (**Compuesto 50**) (punto de fusión 152°C-154°C) desde 3-amino-7-cloro-1-ciclopropil-6-fluoro-1H-pirido[2,3-d]pirimidin-2,4-

diona (Ejemplo 24b) y terc-butil éster del ácido (3-aminometilpiperidin-1-il)carbámico (Hilpert K. et al, *J. Med. Chem.*, 1994;37[23]:3889-3901) usando el Método General F.

(yy) Clorhidrato de trans-3-amino-7-(3-aminometil-4-trifluorometilpirrolidin-1-il)-1-ciclopropil-6-fluoro-1H-pirido[2,3-d]pirimidin-2,4-diona (**Compuesto 51**) (punto de fusión 214°C-216°C) desde 3-amino-7-cloro-1-ciclopropil-6-fluoro-1H-pirido[2,3-d]pirimidin-2,4-diona (Ejemplo 24b) y 3-aminometil-4-trifluorometilpirrolidina (Li Q., Wang W., Berst K.B., Clairborne A., Hasvold L., Raye K. Tufano M. et al, *Bioorg. Med. Chem. Lett.*, 1998;8:1953-1958) usando el Método General F.

(zz) Clorhidrato de 3-amino-1-ciclopropil-6-fluoro-7-[(R)-1-metilamino-etil)pirrolidin-1-il]-1H-pirido[2,3-d]pirimidin-2,4-diona (**Compuesto 52**) (punto de fusión 137°C-139°C) desde 3-amino-7-cloro-1-ciclopropil-6-fluoro-1H-pirido[2,3-d]pirimidin-2,4-diona (Ejemplo 24b) y terc-butil éster del ácido (R)-3-((R)-1-metilaminoetil)pirrolidina usando el Método General F.

(aaa) Clorhidrato de 3-amino-7-[(R)-3-((S)-1-aminoetil)pirrolidin-1-il]-1-ciclopropil-6-fluoro-1H-pirido[2,3-d]pirimidin-2,4-diona (**Compuesto 53**) (punto de

fusión >260°C) desde terc-butil éster del ácido {(S)-1-[(R)-1-(3-amino-1-ciclopropil-6-fluoro-2,4-dioxo-1,2,3,4-tetrahidropirido[2,3-d]pirimidin-7-il)pirrolidin-3-il]etil}-carbámico (Ejemplo 28j) usando el Método General E.

(bbb) Clorhidrato de 3-amino-7-[(1-aminopropil)pirrolidin-1-il]-1-ciclopropil-6-fluoro-8-metil-1H-quinazolin-2,4-diona (**Compuesto 54**) (MS CI: m/z 376 (MH^+) desde terc-butil éster del ácido {1-[1-(3-amino-1-ciclopropil-6-fluoro-8-metil-2,4-dioxo-1,2,3,4-tetrahidroquinazolin-7-il)pirrolidin-3-il]propil}-carbámico (Ejemplo 28ooo) usando el Método General E.

(ccc) Clorhidrato de 3-amino-1-ciclopropil-6-fluoro-8-metil-7-[(R))-3-((S)-1-metilaminoetil)pirrolidin-1-il]-1H-quinazolin-2,4-diona (**Compuesto 55**) (punto de fusión 153°C-155°C) desde terc-butil éster del ácido {(S)-1-[(R)-1-(3-amino-1-ciclopropil-6-fluoro-8-metil-2,4-dioxo-1,2,3,4-tetrahidroquinazolin-7-il)pirrolidin-3-il]etil}metilcarbámico (Ejemplo 28ppp) usando el Método General E.

(ddd) Clorhidrato de 3-amino-7-[7-(1-aminoetil)-5-azaespiro[2.4]hept-5-il]-1-ciclopropil-6-fluoro-8-metil-1H-quinazolin-2,4-diona (**Compuesto 56**) (punto de fusión 178°C-180°C, MS CI: m/z 388 (MH^+)) desde terc-butil éster del ácido {1-[5-(3-amino-1-ciclopropil-6-fluoro-8-metil-2,4-dioxo-

1,2,3,4-tetrahidroquinazolin-7-il)5-azaespiro[2.4]hept-7-il]etil}-carbámico (Ejemplo 28qqq) usando el Método General E.

(eee) Amida de ácido 1-(3-amino-8-cloro-1-ciclopropil-6-fluoro-2,4-dioxo-1,2,3,4-tetrahidroquinazolin-7-il)piperidin-3-carboxílico (**Compuesto 58**) (punto de fusión 141°C-144°C, MS CI: m/z 396 (MH^+)) desde terc-butil éster del ácido [7-(3-carbamoilpiperidin-1-il)-8-cloro-1-ciclopropil-6-fluoro-2,4-dioxo-1,4-dihidro-2H-quinazolin-3-il]carbámico (Ejemplo 8hh) usando el Método General A.

(fff) Clorhidrato de 3-amino-7-[trans-3-aminometilpirrolidin-1-il]-8-cloro-1-ciclopropil-6-fluoro-1H-quinazolin-2,4-diona (**Compuesto 59**) (punto de fusión 171°C-173°C, MS CI: m/z 436 (MH^+)) desde terc-butil éster del ácido {7-[trans-3-(terc-butoxicarbonilaminometil)-4-trifluorometilpirrolidin-1-il]-8-cloro-1-ciclopropil-6-fluoro-2,4-dioxo-1,4-dihidro-2H-quinazolin-3-il}carbámico (Ejemplo 8i) usando el Método General E.

(ggg) Clorhidrato de 3-amino-8-cloro-1-ciclopropil-6-fluoro-7-{3-[(2,2,2-trifluoro-etilamino)metil]pirrolidin-1-il}-1H-quinazolin-2,4-diona (**Compuesto 60**) (punto de fusión 163°C-164°C, MS CI: m/z 450 (MH^+)) desde terc-butil éster del ácido 8-cloro-1-ciclopropil-6-fluoro-2,4-dioxo-7-{3-[(2,2,2-

trifluoroetilamino)metil]-pirrolidin-3-il}-1,4-dihidro-2H-quinazolin-3-il)carbámico (Ejemplo 8jj) usando el Método General E.

(hhh) Clorhidrato de 3-amino-8-cloro-1-ciclopropil-6-fluoro-7-(5-metilhexahidro-pirrolo[3,4-c]pirrol-2-il)-1H-quinazolin-2,4-diona (**Compuesto 61**) (punto de fusión 133°C-135°C, MS CI: m/z 394 (MH^+)) desde terc-butil éster del ácido [8-cloro-1-ciclopropil-6-fluoro-7-(5-metilhexahidropirrolo[3,4-c]pirrol-2-il)-2,4-dioxo-1,4-dihidro-2H-quinazolin-3-il]carbámico (Ejemplo 8kk) usando el Método General E.

(iii) Clorhidrato de 3-amino-8-cloro-1-ciclopropil-7-(2,7-diazaespiro[4.4]non-2-il)-6-fluoro-1H-quinazolin-2,4-diona (**Compuesto 62**) (punto de fusión 147°C-149°C, MS CI: m/z 394 (MH^+)) desde terc-butil éster del ácido [8-cloro-1-ciclopropil-7-(2,7-diazaespiro[4.4]non-2-il)-6-fluoro-2,4-dioxo-1,4-dihidro-2H-quinazolin-3-il)carbámico (Ejemplo 8ll) usando el Método General E.

(jjj) Clorhidrato de 3-amino-7-(3-aminometil-3-bencilpirrolidin-1-il)-8-cloro-1-ciclopropil-6-fluoro-1H-quinazolin-2,4-diona (**Compuesto 63**) (punto de fusión 148°C-150°C, MS CI: m/z 458 (MH^+)) desde terc-butil éster del ácido {7-[3-bencil-3-(3-terc-butoxicarbonilaminometil)pirrolidin-1-

il]-8-cloro-1-ciclopropil-6-fluoro-2,4-dioxo-1,4-dihidro-2H-quinazolin-3-il)carbámico (Ejemplo 8mm) usando el Método General E.

(kkk) Clorhidrato de 3-amino-7-[(R)-3-((S(-1-aminoetil)pirrolidin-1-il]-8-cloro-1-ciclopropil-6-fluoro-1H-quinazolin-2,4-diona (**Compuesto 64**) (punto de fusión 164°C-166°C, MS CI: m/z 382 (MH^+)) desde terc-butil éster del ácido {7-[(R)-3-((S)-1-terc-butoxicarbonilaminoetil)pirrolidin-1-il]-8-cloro-1-ciclopropil-6-fluoro-2,4-dioxo-1,4-dihidro-2H-quinazolin-3-il}carbámico (Ejemplo 8nn) usando el Método General E.

(lll) Clorhidrato de 3-amino-8-cloro-1-ciclopropil-6-fluoro-7-(3-hidroxiimino-pirrolidin-1-il)-1H-quinazolin-2,4-diona (**Compuesto 65**) (punto de fusión 147°C-149°C, MS CI: m/z 368 (MH^+)) desde terc-butil éster del ácido [8-cloro-1-ciclopropil-6-fluoro-7-(3-hidroxiimino-pirrolidin-1-il)-2,4-dioxo-1,4-dihidro-2H-quinazolin-3-il]carbámico (Ejemplo 8oo) usando el Método General E.

(mmm) Clorhidrato de 3-amino-7-[trans-3-amino--4-trifluorometilpirrolidin-1-il]-8-cloro-1-ciclopropil-6-fluoro-1H-quinazolin-2,4-diona (**Compuesto 66**) (punto de fusión 181°C-183°C, MS CI: m/z 422 (MH^+)) desde terc-butil éster del ácido

[7-(trans-3-terc-butoxicarbonilamino-4-trifluorometilpirrolidin-1-il)-8-cloro-1-ciclopropil-6-fluoro-2,4-dioxo-1,4-dihidro-2H-quinazolin-3-il]carbámico (Ejemplo 8pp) usando el Método General E.

(nnn) Clorhidrato de 3-amino-8-cloro-1-ciclopropil-6-fluoro-7-[(R)-3-(S)-1-metilaminoetil)pirrolidin-1-il]-1H-quinazolin-2,4-diona (**Compuesto 67**) (punto de fusión 122°C-124°C, MS CI: m/z 396 (MH^+)) desde terc-butil éster del ácido (7-[(R)-3-(S)-1-(terc-butoxicarbonilmetilamino)etil]pirrolidin-1-il)-8-cloro-1-ciclopropil-6-fluoro-2,4-dioxo-1,4-dihidro-2H-quinazolin-3-il)carbámico (Ejemplo 8qq) usando el Método General E.

(ooo) Clorhidrato de 3-amino-7-(trans-3-amino-4-fenilpirrolidin-1-il)-8-cloro-1-ciclopropil-6-fluoro-1H-quinazolin-2,4-diona (**Compuesto 68**) (punto de fusión 174°C-175°C, MS CI: m/z 430 (MH^+)) desde terc-butil éster del ácido [7-(trans-3-terc-butoxicarbonilamino-4-fenilpirrolidin-1-il)-8-cloro-1-ciclopropil-6-fluoro-2,4-dioxo-1,4-dihidro-2H-quinazolin-3-il]carbámico (Ejemplo 8rr) usando el Método General E.

(ppp) Clorhidrato de 3-amino-7-[trans-3-amino-4-(4-hidroxifenil)pirrolidin-1-il]-8-cloro-1-ciclopropil-6-fluoro-

1H-quinazolin-2,4-diona (**Compuesto 69**) (punto de fusión >200°C, MS CI: m/z 446 (MH^+)) desde terc-butil éster del ácido 7-[trans-3-terc-butoxicarbonilamino-4-(4-hidroxifenil)pirrolidin-1-il]-8-cloro-1-ciclopropil-6-fluoro-2,4-dioxo-1,4-dihidro-2H-quinazolin-3-il)carbámico (Ejemplo 8ss) usando el Método General E.

(qqq) Clorhidrato de N-[1-(3-Amino-8-cloro-1-ciclopropil-6-fluoro-2,4-dioxo-1,2,3,4-tetrahidroquinazolin-7-il)pirrolidin-3-ilmetil]metanosulfonamida (**Compuesto 70**) (punto de fusión 109°C-112°C, MS-CI: m/z 446 (MH^+)) desde terc-butil éster del ácido {8-cloro-1-ciclopropil-6-fluoro-7-[3-(metanosulfonilaminometil)-pirrolidin-1-il]-2,4-dioxo-1,4-dihidro-2H-quinazolin-3-il}carbámico (Ejemplo 36) usando el Método General E.

(rrr) Clorhidrato de 3-amino-7-(3-aminometilpiperidin-1-il)-8-cloro-1-ciclopropil-6-fluoro-1H-quinazolin-2,4-diona (**Compuesto 71**) (punto de fusión 131°C-133°C, MS CI: m/z 382 (MH^+)) desde terc-butil éster del ácido {7-[3-(terc-butoxicarbonilaminometil)piperidin-1-il]-8-cloro-1-ciclopropil-6-fluoro-2,4-dioxo-1,4-dihidro-2H-quinazolin-3-il}carbámico (Ejemplo 8tt) usando el Método General E.

(sss) Clorhidrato de 3-amino-8-cloro-1-ciclopropil-6-fluoro-7-[3-(isopropilamino-metil)pirrolidin-1-il]-1H-quinazolin-2,4-diona (**Compuesto 72**) (punto de fusión 125°C-127°C, MS CI: m/z 410 (MH^+)) desde terc-butil éster del ácido (7-{3-[(terc-butoxicarbonil-isopropilamino)metil]pirrolidin-1-il}-8-cloro-1-ciclopropil-6-fluoro-2,4-dioxo-1,4-dihidro-2H-quinazolin-3-il)carbámico (Ejemplo 8uu) usando el Método General E.

(ttt) Clorhidrato de 3-amino-7-(3-aminometilpirrolidin-1-il)-6,8-dicloro-1-ciclopropil-2,4-diona (**Compuesto 73**) (punto de fusión 147°C-149°C, MS CI: m/z 384 (MH^+)) desde terc-butil éster del ácido {7-[3-(terc-butoxicarbonilaminometil)-pirrolidin-1-il]-6,8-dicloro-1-ciclopropil-2,4-dioxo-1,4-dihidro-2H-quinazolin-3-il}carbámico usando el Método General E.

(uuu) N-[1-(3-Amino-8-cloro-1-ciclopropil-6-fluoro-2,4-dioxo-1,2,3,4-tetrahidroquinazolin-7-il)pirrolidin-3-ilmetil]metanosulfonamida (**Compuesto 74**) (punto de fusión 109°C-112°C, MS CI: m/z 446 (MH^+)) desde terc-butil éster del ácido {8-cloro-1-ciclopropil-6-fluoro-7-[3-(metanosulfonilaminometil)pirrolidin-1-il]-2,4-dioxo-1,4-dihidro-2H-quinazolin-3-il}carbámico (Ejemplo 36) usando el Método General E.

(vvv) Clorhidrato de 3-amino-7-[(R)-3-(S)-(1-aminoetil)pirrolidin-1-il]-1-ciclopropil-6-fluoro-8-metil-1H-quinazolin-2,4-diona (**Compuesto 75**) (punto de fusión 194°C-196°C, ^{1}H NMR (200 MHz, DMSO-d_6): δ 8,25 (bs, 3H), 7,47 (d, 1H), 4,68 (bs, 3H), 3,59-3,23 (m, 7H), 2,49 (s, 3H), 2,02-1,92 (m, 1H), 1,80-1,60 (m, 1H), 1,30 (d, 3H), 1,13-1,08 (m, 2H), 0,62-0,50 (m, 1H); MS ES: m/z 362 (MH^+)) desde terc-butil éster del ácido {1-[1-[(R)-3-(S)-(3-amino-1-ciclopropil-6-fluoro-8-metil-2,4-dioxo-1,2,3,4-tetrahidroquinazolin-7-il)pirrolidin-3-il]etil}carbámico (Ejemplo 28k) usando el Método General A.

(www) Clorhidrato de 3-amino-7-[(R)-3-(1-amino-1-metiletil)pirrolidin-1-il]-1-ciclopropil-6-fluoro-8-metil-1H-quinazolin-2,4-diona (**Compuesto 76**) (punto de fusión 200°C-202°C, MS CI: m/z 376 (MH^+)) desde terc-butil éster del ácido {1-[(R)-1-(3-amino-1-ciclopropil-6-fluoro-8-metil-2,4-dioxo-1,2,3,4-tetrahidroquinazolin-7-il)pirrolidin-3-il]-1-metiletil}carbámico (Ejemplo 28l) usando el Método General A.

(xxx) Clorhidrato de 3-amino-7-[3-(1-aminoetil)-3-metoxipirrolidin-1-il]-1-ciclopropil-6-fluoro-8-metil-1H-quinazolin-2,4-diona (**Compuesto 77**) (punto de fusión 190°C-192°C, ^{1}H NMR (200 MHz, DMSO-d_6): δ 8,07 (bs, 3H), 7,49 (d, 1H), 3,89-3,10 (m, 12H), 2,42 (s, 3H), 2,39-2,08 (m, 2H), 1,29

(d, 3H), 1,07-1,03 (m, 2H), 0,62-0,50 (m, 2H); MS ES: m/z 392 (MH^+)) desde terc-butil éster del ácido (1-[1-(3-amino-1-ciclopropil-6-fluoro-8-metil-2,4-dioxo-1,2,3,4-tetrahidroquinazolin-7-il)-3-metoxipirrolidin-3-il]etil}carbámico (Ejemplo 28m) usando el Método General A.

(yyy) Clorhidrato de 3-amino-7-[3-(1-aminoetil)-3-fluoropirrolidin-1-il]-1-ciclopropil-6-fluoro-8-metoxi-1H-quinazolin-2,4-diona (**Compuesto 78**) (punto de fusión 190°C-192°C, MS ES: m/z 396 (MH^+)) desde terc-butil éster del ácido (1-[1-(3-amino-1-ciclopropil-6-fluoro-8-metoxi-2,4-dioxo-1,2,3,4-tetrahidroquinazolin-7-il)-3-fluoropirrolidin-3-il]etil}carbámico (Ejemplo 28o) usando el Método General A.

(zzz) Clorhidrato de 3-amino-7-(3-aminopirrolidin-1-il)-1-ciclopropil-6-fluoro-5-metil-1H-quinazolin-2,4-diona (**Compuesto 79**) (punto de fusión 238°C-240°C, MS ES: m/z 334 (MH^+)) desde terc-butil éster del ácido [1-(3-amino-1-ciclopropil-6-fluoro-5-metil-2,4-dioxo-1,2,3,4-tetrahidroquinazolin-7-il)pirrolidin-3-il]carbámico (Ejemplo 28p) usando el Método General A.

(aaaa) Clorhidrato de 3-amino-7-[(R)-3-(S)-(1-aminoetil)pirrolidin-1-il]-1-ciclopropil-6-fluoro-5-metil-1H-quinazolin-2,4-diona (**Compuesto 80**) (punto de fusión 245°C-

247°C, MS ES: m/z 362 (MH^+)) desde terc-butil éster del ácido [1-(S)-[1-(R)-(3-amino-1-ciclopropil-6-fluoro-5-metil-2,4-dioxo-1,2,3,4-tetrahidroquinazolin-7-il)pirrolidin-3-il]etil]carbámico (Ejemplo 28q) usando el Método General A.

(bbbb) Clorhidrato de 3-amino-7-(3-aminoetil)-3-metoximetilpirrolidin-1-il)-1-ciclopropil-6-fluoro-8-metil-1H-quinazolin-2,4-diona (**Compuesto 81**) (punto de fusión 172°C-177°C, MS ES: m/z 392 (MH^+)) desde terc-butil éster del ácido [1-(3-amino-1-ciclopropil-6-fluoro-8-metil-2,4-dioxo-1,2,3,4-tetrahidroquinazolin-7-il)-3-metoximetilpirrolidin-3-ilmetil]carbámico (Ejemplo 28r) usando el Método General A.

(cccc) Clorhidrato de 3-amino-7-(3-aminometil)-3-fluorometilpirrolidin-1-il)-1-ciclopropil-6-fluoro-1H-quinazolin-2,4-diona (**Compuesto 82**) (punto de fusión 160°C-163°C, MS ES: m/z 380 (MH^+)) desde terc-butil éster del ácido [1-(3-amino-1-ciclopropil-6-fluoro-8-metil-2,4-dioxo-1,2,3,4-tetrahidroquinazolin-7-il)-3-fluorometilpirrolidin-3-ilmetil]carbámico (Ejemplo 28s) usando el Método General A.

(dddd) Clorhidrato de 3-amino-7-(trans-3-aminometil-4-trifluorometilpirrolidin-1-il)-1-ciclopropil-6-fluoro-8-metoxi-1H-quinazolin-2,4-diona (**Compuesto 84**) (punto de fusión 205°C-207°C, MS ES: m/z 432 (MH^+)) desde terc-butil éster del

ácido [trans-(3-amino-1-ciclopropil-6-fluoro-8-metoxi-2,4-dioxo-1,2,3,4-tetrahidroquinazolin-7-il)-4-trifluorometilpirrolidin-3-ilmetil]carbámico (Ejemplo 28t) usando el Método General A.

(eeee) Clorhidrato de 3-amino-7-[3-(1-aminoetil)piperidin-1-il]-1-ciclopropil-6-fluoro-8-metoxi-1H-quinazolin-2,4-diona (**Compuesto 84**) (punto de fusión 198°C, MS ES: m/z 392 (MH^+)) desde terc-butil éster del ácido {1-[1-(3-amino-1-ciclopropil-6-fluoro-8-metoxi-2,4-dioxo-1,2,3,4-tetrahidroquinazolin-7-il)-piperidin-3-il]etil}carbámico (Ejemplo 28u) usando el Método General A.

(ffff) Clorhidrato de 3-amino-7-[3-(aminoetil)-piperidin-1-il]-1-ciclopropil-6-fluoro-8-metil-1H-quinazolin-2,4-diona (**Compuesto 85**) (punto de fusión 200°C, ^1H NMR (200 MHz, DMSO-d_6): δ 8,25 (bs, 3H), 7,52 (d, 1H), 6,36 (bs, 3H), 3,54-2,80 (m, 6H), 2,48 (s, 3H), 2,02-1,15 (m, 8H), 1,02-0,50 (m, 4H); MS ES: m/z 376 (MH^+)) desde terc-butil éster del ácido {1-[1-(3-amino-1-ciclopropil-6-fluoro-8-metil-2,4-dioxo-1,2,3,4-tetrahidroquinazolin-7-il)piperidin-3-il]etil}carbámico (Ejemplo 28v) usando el Método General A.

(gggg) Clorhidrato de 3-amino-7-[4-(1-aminoetil-3,3-dimetilpirrolidin-1-il]-1-ciclopropil-6-fluoro-8-metoxi-1H-

quinazolin-2,4-diona (**Compuesto 86**) (punto de fusión 230°C, MS ES: m/z 406 (MH^+)) desde terc-butil éster del ácido {1-[1-(3-amino-1-ciclopropil-6-fluoro-8-metoxi-2,4-dioxo-1,2,3,4-tetrahidroquinazolin-7-il)-4,4-dimetilpirrolidin-3-il]etil}carbámico (Ejemplo 28w) usando el Método General A.

(hhhh) Clorhidrato de 3-amino-7-[4-(1-aminoetil-3,3-dimetilpirrolidin-1-il]-1-ciclopropil-6-fluoro-8-metil-1H-quinazolin-2,4-diona (**Compuesto 87**) (punto de fusión 246°C, MS ES: m/z 390 (MH^+)) desde terc-butil éster del ácido {1-[1-(3-amino-1-ciclopropil-6-fluoro-8-metil-2,4-dioxo-1,2,3,4-tetrahidroquinazolin-7-il)-4,4-dimetilpirrolidin-3-il]etil}carbámico (Ejemplo 28x) usando el Método General A.

(iiii) Clorhidrato de 3-amino-7-(3-amino-3-fenilpirrolidin-1-il)-1-ciclopropil-6-fluoro-8-metil-1H-quinazolin-2,4-diona (**Compuesto 88**) (punto de fusión 236°C, MS ES: m/z 410 (MH^+)) desde terc-butil éster del ácido [1-(3-amino-1-ciclopropil-6-fluoro-8-metil-2,4-dioxo-1,2,3,4-tetrahidroquinazolin-7-il)-3-fenilpirrolidin-3-il]carbámico (Ejemplo 28z) usando el Método General A.

(jjjj) Clorhidrato de 3-amino-7-[3-(1-aminoetil-4-metilpirrolidin-1-il]-1-ciclopropil-6-fluoro-8-metil-1H-quinazolin-2,4-diona (**Compuesto 89**) (punto de fusión 240°C, MS

ES: m/z 376 (MH^+)) desde terc-butil éster del ácido {1-[1-(3-amino-1-ciclopropil-6-fluoro-8-metil-2,4-dioxo-1,2,3,4-tetrahidroquinazolin-7-il)-4-metilpirrolidin-3-il]etil}carbámico (Ejemplo 28y) usando el Método General A.

(kkkk) Clorhidrato de 3-amino-7-(3-aminometil-3-fenilpirrolidin-1-il)-1-ciclopropil-6-fluoro-8-metil-1H-quinazolin-2,4-diona (**Compuesto 90**) (punto de fusión 227°C-231°C, MS ES: m/z 424 (MH^+)) desde terc-butil éster del ácido [1-(3-amino-1-ciclopropil-6-fluoro-8-metil-2,4-dioxo-1,2,3,4-tetrahidroquinazolin-7-il)-3-fenilpirrolidin-3-ilmetil]carbámico (Ejemplo 28aa) usando el Método General A.

(llll) Clorhidrato de 3-amino-7-(7-aminometil-5-azaespiro[2,4]hept-5-il)-1-ciclopropil-6-fluoro-8-metil-1H-quinazolin-2,4-diona (**Compuesto 91**) (punto de fusión 167°C, MS ES: m/z 374 (MH^+)) desde terc-butil éster del ácido [5-(3-amino-1-ciclopropil-6-fluoro-8-metil-2,4-dioxo-1,2,3,4-tetrahidroquinazolin-7-il)-5-azaespiro[2.4]hept-7-ilmetil]carbámico (Ejemplo 28bb) usando el Método General A.

(mmmm) Clorhidrato de 3-amino-7-(7-aminometil-5-azaespiro[2,4]hept-5-il)-1-ciclopropil-6-fluoro-8-metoxi-1H-quinazolin-2,4-diona (**Compuesto 92**) (punto de fusión 178°C, MS ES: m/z 390 (MH^+)) desde terc-butil éster del ácido [5-(3-

amino-1-ciclopropil-6-fluoro-8-metoxi-2,4-dioxo-1,2,3,4-tetrahidroquinazolin-7-il)-5-azaespiro[2.4]hept-7-ilmetil]carbámico (Ejemplo 28cc) usando el Método General A.

(nnnn) Clorhidrato de 3-amino-7-(3-aminometil-3-hidroxipirrolidin-1-il)-1-ciclopropil-6-fluoro-8-metoxi-1H-quinazolin-2,4-diona (**Compuesto 93**) (punto de fusión 202°C, MS ES: m/z 380(MH^+)) desde terc-butil éster del ácido [1-(3-amino-1-ciclopropil-6-fluoro-8-metoxi-2,4-dioxo-1,2,3,4-tetrahidroquinazolin-7-il)-3-hidroxipirrolidin-3-ilmetil]carbámico (Ejemplo 28dd) usando el Método General A.

(oooo) Clorhidrato de 3-amino-7-(3-aminometilpiperidin-1-il)-1-ciclopropil-6-fluoro-8-metil-1H-quinazolin-2,4-diona (**Compuesto 95**) (punto de fusión 219°C-221°C, MS ES: m/z 362 (MH^+)) desde terc-butil éster del ácido [1-(3-amino-1-ciclopropil-6-fluoro-8-metil-2,4-dioxo-1,2,3,4-tetrahidroquinazolin-7-il)-piperidin-3-ilmetil]carbámico (Ejemplo 28ee) usando el Método General A.

(pppp) Clorhidrato de 3-amino-7-(3-aminometil-4-metoxipirrolidin-1-il)-1-ciclopropil-6-fluoro-8-metil-1H-quinazolin-2,4-diona (**Compuesto 96**) (punto de fusión >250°C, MS ES: m/z 364 (MH^+)) desde terc-butil éster del ácido [1-(3-amino-1-ciclopropil-6-fluoro-8-metil-2,4-dioxo-1,2,3,4-

tetrahidroquinazolin-7-il)-4-metoxipirrolidin-3-il]carbámico (Ejemplo 28ff) usando el Método General A.

(qqqq) Clorhidrato de 3-amino-7-(3-amino-4-metoxipirrolidin-1-il)-1-ciclopropil-6-fluoro-8-metoxi-1H-quinazolin-2,4-diona (**Compuesto 97**) (punto de fusión >250°C, MS ES: m/z 380 (MH^+)) desde terc-butil éster del ácido [1-(3-amino-1-ciclopropil-6-fluoro-8-metoxi-2,4-dioxo-1,2,3,4-tetrahidroquinazolin-7-il)-4-metoxipirrolidin-3-il]carbámico (Ejemplo 28gg) usando el Método General A.

(rrrr) Clorhidrato de 3-amino-7-(3-amino-4-fluoropirrolidin-1-il)-1-ciclopropil-6-fluoro-8-metoxi-1H-quinazolin-2,4-diona (**Compuesto 98**) (punto de fusión >250°C, MS ES: m/z 368 (MH^+)) desde terc-butil éster del ácido [1-(3-amino-1-ciclopropil-6-fluoro-8-metoxi-2,4-dioxo-1,2,3,4-tetrahidroquinazolin-7-il)-4-fluoropirrolidin-3-il]carbámico (Ejemplo 28hh) usando el Método General A.

(ssss) Clorhidrato de 3-amino-7-(3-aminometil-3-metilpirrolidin-1-il)-1-ciclopropil-6-fluoro-8-metil-1H-quinazolin-2,4-diona (**Compuesto 99**) (punto de fusión 210°C, MS ES: m/z 362 (MH^+)) desde terc-butil éster del ácido [1-(3-amino-1-ciclopropil-6-fluoro-8-metil-2,4-dioxo-1,2,3,4-

tetrahidroquinazolin-7-il)-3-metilpirrolidin-3-ilmetil]carbámico (Ejemplo 28ii) usando el Método General A.

(tttt) Clorhidrato de 3-amino-7-[(R)-3-(-((S)-1-aminoetil)pirrolidin-1-il]-1-ciclopropil-8-etil-6-fluoro-1H-quinazolin-2,4-diona (**Compuesto 100**) (punto de fusión 155°C-157°C, MS ES: m/z 376 (MH^+)) desde terc-butil éster del ácido ((S)-1-[(R)-1-(3-amino-1-ciclopropil-8-etil-6-fluoro-2,4-dioxo-1,2,3,4-tetrahidroquinazolin-7-il)pirrolidin-3-il]etil)carbámico (Ejemplo 28jj) usando el Método General A.

(uuuu) Trifluoroacetato de ácido 1-(3-amino-1-ciclopropil-6-fluoro-8-metoxi-2,4-dioxo-1,2,3,4-tetrahidroquinazolin-7-il)pirrolidin-3-carboxílico (**Compuesto 101**) (punto de fusión 252°C (descomp.), MS ES: m/z 379 (MH^+)) desde terc-butil éster del ácido 1-(3-amino-1-ciclopropil-6-fluoro-8-metoxi-2,4-dioxo-1,2,3,4-tetrahidroquinazolin-7-il)pirrolidin-3-carboxílico (Ejemplo 28kk) usando el Método General B.

(vvvv) Trifluoroacetato de ácido 1-(3-amino-1-ciclopropil-6-fluoro-8-metil-2,4-dioxo-1,2,3,4-tetrahidroquinazolin-7-il)pirrolidin-3-carboxílico (**Compuesto 101**) (punto de fusión 226°C (descomp.), MS ES: m/z 363 (MH^+)) desde terc-butil éster del ácido 1-(3-amino-1-ciclopropil-6-fluoro-8-metil-2,4-dioxo-

1,2,3,4-tetrahidroquinazolin-7-il)pirrolidin-3-carboxílico (Ejemplo 28ll) usando el Método General A.

(wwww) Clorhidrato de 3-amino-7-(1-aminometil-3-azabiciclo[3.1.0]hex-3-il)-1-ciclopropil-6-fluoro-8-metoxi-1H-quinazolin-2,4-diona (**Compuesto 103**) (punto de fusión 183°C-185°C, MS ES: m/z 376 (MH^+)) desde terc-butil éster del ácido [3-(3-amino-1-ciclopropil-6-fluoro-8-metoxi-2,4-dioxo-1,2,3,4-tetrahidroquinazolin-7-il)-3-azabiciclo[3.1.0]hex-1-ilmetil]carbámico (Ejemplo 28mm) usando el Método General A.

(xxxx) Clorhidrato de 3-amino-7-(1-aminometil-3-azabiciclo[3.1.0]hex-3-il)-1-ciclopropil-6-fluoro-8-metil-1H-quinazolin-2,4-diona (**Compuesto 104**) (punto de fusión 189°C-194°C, MS ES: m/z 360 (MH^+)) desde terc-butil éster del ácido [3-(3-amino-1-ciclopropil-6-fluoro-8-metil-2,4-dioxo-1,2,3,4-tetrahidroquinazolin-7-il)-3-azabiciclo[3.1.0]hex-1-ilmetil]carbámico (Ejemplo 28nn) usando el Método General A.

(yyyy) Clorhidrato de 3-amino-7-[(S)-3-((R)-1-aminoetil)pirrolidin-1-il]-1-ciclopropil-6-fluoro-8-metoxi-1H-quinazolin-2,4-diona (**Compuesto 105**) (punto de fusión 175°C-179°C, MS ES: m/z 378 (MH^+)) desde terc-bútil éster del ácido {(R)-1-[(S)-1-(3-amino-1-ciclopropil-6-fluoro-8-metoxi-2,4-

dioxo-1,2,3,4-tetrahidroquinazolin-7-il)pirrolidin-3-il]etil)carbámico (Ejemplo 28oo) usando el Método General A.

(zzzz) Clorhidrato de 3-amino-7-[(S)-3-((R)-1-aminoetil)pirrolidin-1-il]-1-ciclopropil-6-fluoro-8-metil-1H-quinazolin-2,4-diona (**Compuesto 106**) (punto de fusión 172°C-176°C, MS ES: m/z 362 (MH^+)) desde terc-butil éster del ácido {(R)-1-[(S)-1-(3-amino-1-ciclopropil-6-fluoro-8-metoxi-2,4-dioxo-1,2,3,4-tetrahidroquinazolin-7-il)pirrolidin-3-il]etil}carbámico (Ejemplo 28pp) usando el Método General A.

(aaaaa) Clorhidrato de 3-amino-1-ciclopropil-6-fluoro-8-metil-7-(octahidropirrolo[3,4-b]piridin-6-il)-1H-quinazolin-2,4-diona (**Compuesto 107**) (punto de fusión 220°C, MS ES: m/z 374 (MH^+)) desde terc-butil éster del ácido 6-(3-amino-1-ciclopropil-6-fluoro-8-metil-2,4-dioxo-1,2,3,4-tetrahidroquinazolin-7-il)octahidropirrolo[3,4-b]piridin-1-carboxílico (Ejemplo 28qq) usando el Método General A.

(bbbbb) Clorhidrato de 3-amino-7-(trans-3-aminometil-4-metilpirrolidin-1-il)-8-cloro-1-ciclopropil-6-fluoro-1H-quinazolin-2,4-diona (**Compuesto 108**) (punto de fusión 215°C-217°C, MS ES: m/z 382 (MH^+)) desde terc-butil éster del ácido {7-[trans-3-(terc-butoxicarbonil-aminometil)-4-metilpirrolidin-1-il]-8-cloro-1-ciclopropil-6-fluoro-2,4-

dioxo-1,4-dihidro-2H-quinazolin-3-il}carbámico (**Compuesto 109**) (Ejemplo 8xx) usando el Método General A.

(ccccc) Clorhidrato de 3-amino-7-(trans-3-aminometil-4-metilpirrolidin-1-il)-1-ciclopropil-6-fluoro-8-metoxi-1H-quinazolin-2,4-diona (**Compuesto 110**) (punto de fusión 189°C, MS ES: m/z 378 (MH^+)) desde terc-butil éster del ácido [trans-1-(3-amino-1-ciclopropil-6-fluoro-8-metoxi-2,4-dioxo-1,2,3,4-tetrahidroquinazolin-7-il)-4-metilpirrolidin-3-ilmetil]carbámico (Ejemplo 28rr) usando el Método General A.

(ddddd) Clorhidrato de 3-amino-7-(trans-3-aminometil-4-metilpirrolidin-1-il)-1-ciclopropil-6-fluoro-8-metil-1H-quinazolin-2,4-diona (**Compuesto 111**) (punto de fusión 220°C, MS ES: m/z 362 (MH^+)) desde terc-butil éster del ácido [trans-1-(3-amino-1-ciclopropil-6-fluoro-8-metil-2,4-dioxo-1,2,3,4-tetrahidroquinazolin-7-il)-4-metilpirrolidin-3-ilmetil]carbámico (Ejemplo 28ss) usando el Método General A.

(eeeee) Clorhidrato de 3-amino-7-(trans-3-amino-4-metilpirrolidin-1-il)-1-ciclopropil-6-fluoro-8-metoxi-1H-quinazolin-2,4-diona (**Compuesto 112**) (punto de fusión 209°C, MS ES: m/z 364 (MH^+)) desde terc-butil éster del ácido [trans-1-(3-amino-1-ciclopropil-6-fluoro-8-metoxi-2,4-dioxo-1,2,3,4-

tetrahidroquinazolin-7-il)-4-metilpirrolidin-3-il]carbámico (Ejemplo 28tt) usando el Método General A.

(fffff) Clorhidrato de 3-amino-7-(3-aminometilmorfolin-1-il)-1-ciclopropil-6-fluoro-8-metoxi-1H-quinazolin-2,4-diona (**Compuesto 113**) (punto de fusión 195°C, MS ES: m/z 380 (MH^+)) desde terc-butil éster del ácido [4-(3-amino-1-ciclopropil-6-fluoro-8-metoxi-2,4-dioxo-1,2,3,4-tetrahidroquinazolin-7-il)-morfolin-2-ilmetil]carbámico (Ejemplo 28uu) usando el Método General A.

(ggggg) Clorhidrato de 3-amino-7-(3-aminometilpiperidin-1-il)-1-ciclopropil-6-fluoro-8-metoxi-1H-quinazolin-2,4-diona (**Compuesto 114**) (punto de fusión 201°C, MS ES: m/z 378 (MH^+)) desde terc-butil éster del ácido [1-(3-amino-1-ciclopropil-6-fluoro-8-metoxi-2,4-dioxo-1,2,3,4-tetrahidroquinazolin-7-il)piperidin-3-ilmetil]-carbámico (Ejemplo 28vv) usando el Método General A.

(hhhhh) Clorhidrato de 3-amino-7-[3-(1-aminoetil)-4-metilpirrolidin-1-il]-1-ciclopropil-6-fluoro-8-metoxi-1H-quinazolin-2,4-diona (**Compuesto 115**) (punto de fusión 204,5°C, MS ES: m/z 392 (MH^+)) desde terc-butil éster del ácido (1-[1-(3-amino-1-ciclopropil-6-fluoro-8-metoxi-2,4-dioxo-1,2,3,4-

tetrahidroquinazolin-7-il)-4-metilpirrolidin-3-il]etil}carbámico (Ejemplo 28ww) usando el Método General A.

(iiiii) Clorhidrato de 3-amino-7-(3-amino-3-fenilpirrolidin-1-il)-8-cloro-1-ciclopropil-6-fluoro-1H-quinazolin-2,4-diona (**Compuesto 116**) (punto de fusión 198°C-200°C, MS ES: m/z 430 (MH^+)) desde terc-butil éster del ácido [7-(3-terc-butoxicarbonilamino-3-fenilpirrolidin-1-il)-8-cloro-1-ciclopropil-6-fluoro-2,4-dioxo-1,4-dihidro-2H-quinazolin-3-il]carbámico (Ejemplo 6ww) usando el Método General A.

(jjjjj) Clorhidrato de 3-amino-7-(3-amino-3-metilpirrolidin-1-il)-1-ciclopropil-6-fluoro-8-metil-1H-quinazolin-2,4-diona (**Compuesto 117**) (punto de fusión 237°C-240°C, MS ES: m/z 348 (MH^+)) desde terc-butil éster del ácido [1-(1-ciclopropil-6-fluoro-8-metil-2,4-dioxo-1,2,3,4-tetrahidroquinazolin-7-il)-3-metilpirrolidin-3-il]carbámico (Ejemplo 28xx) usando el Método General A.

(kkkkk) Clorhidrato de 3-amino-1-ciclopropil-6-fluoro-8-metil-7-pirrolidin-1-il-1H-quinazolin-2,4-diona (**Compuesto 118**) (punto de fusión 178°C-180°C, MS ES: m/z 319 (MH^+)) desde 3-amino-1-ciclopropil-6-fluoro-8-metil-7-pirrolidin-1-il-1H-quinazolin-2,4-diona (Ejemplo 28yy) usando el Método General A.

(llllll) Clorhidrato de 3-amino-1-ciclopropil-6-fluoro-8-metoxi-7-pirrolidin-1-il-1H-quinazolin-2,4-diona (**Compuesto 119**) (punto de fusión 92°C-94°C, MS ES: m/z 335 (MH^+)) desde 3-amino-1-ciclopropil-6-fluoro-8-metoxi-7-pirrolidin-1-il-1H-quinazolin-2,4-diona (Ejemplo 28zz) usando el Método General A.

(mmmmm) Clorhidrato de 3-amino-1-ciclopropil-6-fluoro-7-[3-(1-hidroxi-1-metiletil)pirrolidin-1-il]-8-metil-1H-quinazolin-2,4-diona (**Compuesto 120**) (punto de fusión 116°C-120°C, MS ES: m/z 377 (MH^+)) desde 3-amino-1-ciclopropil-6-fluoro-7-[3-(1-hidroxi-1-metiletil)pirrolidin-1-il]-8-metil-1H-quinazolin-2,4-diona (Ejemplo 28aaa) usando el Método General E.

(nnnnn) Clorhidrato de 3-amino-1-ciclopropil-6-fluoro-7-[3-(1-hidroxi-1-metiletil)pirrolidin-1-il]-8-metoxi-1H-quinazolin-2,4-diona (**Compuesto 121**) (punto de fusión 134°C (descomp.), MS ES: m/z 393 (MH^+)) desde 3-amino-1-ciclopropil-6-fluoro-7-[3-(1-hidroxi-1-metiletil)pirrolidin-1-il]-8-metoxi-1H-quinazolin-2,4-diona (Ejemplo 28bbb) usando el Método General E.

(ooooo) Clorhidrato de 3-amino-1-ciclopropil-6-fluoro-5-metil-7-[(R)-3-((S)-1-metilaminoetil)pirrolidin-1-il]-1H-quinazolin-

2,4-diona (**Compuesto 122**) (punto de fusión 182°C-185°C, MS ES: m/z 376 (MH^+)) desde ((S)-1-[(R)-3-amino-1-ciclopropil-6-fluoro-5-metil-7-[(R)-3-((S)-1-metilaminoetil)pirrolidin-1-il]-1H-quinazolin-2,4-diona (Ejemplo 28ccc) usando el Método General E.

(ppppp) Clorhidrato de (S)-1-[(R)-1-(3-amino-1-ciclopropil-7-[3-(1-etilaminoetil)pirrolidin-1-il)-6-fluoro-8-metoxi-1H-quinazolin-2,4-diona (**Compuesto 123**) (punto de fusión 185°C-190°C, MS ES: m/z 406 (MH^+)) desde (S)-1-[(R)-1-(3-amino-1-ciclopropil-7-[3-(1-etilaminoetil)pirrolidin-1-il)-6-fluoro-8-metoxi-1H-quinazolin-2,4-diona (Ejemplo 28ddd) usando el Método General E.

(qqqqq) Clorhidrato de 3-amino-1-ciclopropil-7-[(R)-3-((S)-1-etilaminoetil)pirrolidin-1-il]-6-fluoro-8-metil-1H-quinazolin-2,4-diona (**Compuesto 124**) (punto de fusión 210°C-215°C, MS ES: m/z 390 (MH^+)) desde 3-amino-1-ciclopropil-7-[(R)-3-((S)-1-etilaminoetil)pirrolidin-1-il]-6-fluoro-8-metil-1H-quinazolin-2,4-diona (Ejemplo 28eee) usando el Método General E.

(rrrrr) Clorhidrato de 3-amino-7-(6-amino-3-azabiciclo[3.2.0]hept-3-il)-1-ciclopropil-6-fluoro-8-metoxi-1H-quinazolin-2,4-diona (**Compuesto 125**) (punto de fusión

>190°C, MS ES: m/z 390 (MH^+)) desde 3-amino-7-(6-amino-1-metil-3-azabiciclo[3.2.0]hept-3-il)-1-ciclopropil-6-fluoro-8-metoxi-1H-quinazolin-2,4-diona (Ejemplo 28fff) usando el Método General E.

(sssss) Clorhidrato de 3-amino-7-(4-aminometilpiperidin-1-il)-1-ciclopropil-6-fluoro-8-metoxi-1H-quinazolin-2,4-diona **(Compuesto 126)** (punto de fusión 201°C, MS ES: m/z 378 (MH^+)) desde 3-amino-7-(4-aminometilpiperidin-1-il)-1-ciclopropil-6-fluoro-8-metoxi-1H-quinazolin-2,4-diona (Ejemplo 28hhh) usando el Método General E.

(ttttt) Clorhidrato de 3-amino-7-(3-aminometilazetidin-1-il)-1-ciclopropil-6-fluoro-8-metoxi-1H-quinazolin-2,4-diona **(Compuesto 127)** (MS ES: m/z 350 (MH^+)) desde 3-amino-7-(3-aminometilazetidin-1-il)-1-ciclopropil-6-fluoro-8-metoxi-1H-quinazolin-2,4-diona (Ejemplo 28ggg) usando el Método General E.

(uuuuu) Clorhidrato de cis-3-amino-7-(3-aminometil-4-fluoropirrolidin-1-il)-1-ciclopropil-6-fluoro-8-metoxi-1H-quinazolin-2,4-diona **(Compuesto 128)** (punto de fusión 169°C-179°C, MS ES: m/z 382 (MH^+)) desde terc-butil éster del ácido cis-[1-(3-amino-1-ciclopropil-6-fluoro-8-metoxi-2,4-dioxo-

1,2,3,4-tetrahidroquinazolin-7-il)-4-fluoropirrolidin-3-ilmetil]carbámico (Ejemplo 28iii) usando el Método General A.

(vvvvv) Clorhidrato de trans-3-amino-7-(3-aminometil-4-fluoropirrolidin-1-il)-1-ciclopropil-6-fluoro-8-metoxi-1H-quinazolin-2,4-diona (**Compuesto 129**) (punto de fusión 144°C-147°C, MS ES: m/z 382 (MH^+)) desde terc-butil éster del ácido trans-[1-(3-amino-1-ciclopropil-6-fluoro-8-metoxi-2,4-dioxo-1,2,3,4-tetrahidroquinazolin-7-il)-4-fluoropirrolidin-3-ilmetil]carbámico (Ejemplo 28jjj) usando el Método General A.

(wwwww) Clorhidrato de 3-amino-7-(1-amino-5-azaespiro[2.4]hept-5-il)-1-ciclopropil-6-fluoro-8-metoxi-1H-quinazolin-2,4-diona (**Compuesto 130**) (punto de fusión >250°C, MS APCI: m/z 376 (MH^+)) desde terc-butil éster del ácido [1-(3-amino-1-ciclopropil-6-fluoro-8-metoxi-2,4-dioxo-1,2,3,4-tetrahidroquinazolin-7-il)-(1-amino-5-azaespiro[2.4]hept-5-il)]carbámico (Ejemplo 28kkk) usando el Método General A.

(xxxxx) Clorhidrato de 3-amino-7-(3a-aminometiloctahidroisoindol-2-il)-1-ciclopropil-6-fluoro-8-metoxi-1H-quinazolin-2,4-diona (**Compuesto 131**) (punto de fusión >250°C, MS APCI: m/z 418 (MH^+)) desde terc-butil éster del ácido 1-(3-amino-1-ciclopropil-6-fluoro-8-metoxi-2,4-dioxo-1,2,3,4-tetrahidroquinazolin-7-il)-3-

aminometiloctahidroisoindol-2-il]carbámico (Ejemplo 28lll) usando el Método General A.

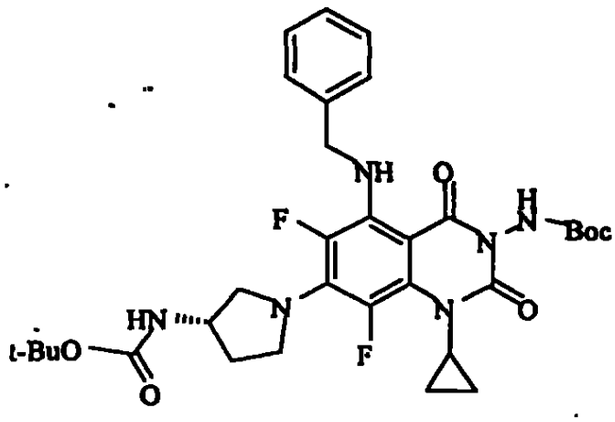
(yyyyy) Clorhidrato de 3-amino-7-(3a-aminometiloctahidroisoindol-2-il)-1-ciclopropil-6-fluoro-8-metil-1H-quinazolin-2,4-diona (**Compuesto 132**) (punto de fusión >250°C, MS APCI: m/z 402 (MH^+)) desde terc-butil éster del ácido 1-(3-amino-1-ciclopropil-6-fluoro-8-metil-2,4-dioxo-1,2,3,4-tetrahidroquinazolin-7-il)-3-aminometiloctahidroisoindol-2-il]carbámico (Ejemplo 28mmm) usando el Método General A.

(zzzzz) Clorhidrato de 3-amino-7-[(R)-3-((S)-1-aminoetilpirrolidin-1-il]-1-ciclopropil-6-fluoro-8-metoxi-1H-quinazolin-2,4-diona (**Compuesto 133**) (punto de fusión 228°C-230°C, MS APCI: m/z 378 (MH^+)) desde terc-butil éster del ácido ((S)-1-[(R)-1-(3-amino-1-ciclopropil-6-fluoro-8-metoxi-2,4-dioxo-1,2,3,4-tetrahidroquinazolin-7-il)pirrolidin-3-il]etil)carbámico (Ejemplo 28nnn) usando el Método General E.

(aaaaaa) Clorhidrato de 3-amino-7-(6-aminom-3-azabiciclo[3.1.0]hex-3-il)-1-ciclopropil-6-fluoro-8-metil-1H-quinazolin-2,4-diona (**Compuesto 134**) (punto de fusión 180°C-182°C, MS ES: m/z 346 (MH^+)) desde terc-butil éster del ácido [3-(3-amino-1-ciclopropil-6-fluoro-8-metil-2,4-dioxo-1,2,3,4-tetrahidroquinazolin-7-il)-3-azabiciclo[3.1.0]hex-6-il]carbámico (Ejemplo 28n) usando el Método General A.

EJEMPLO 10

Síntesis del terc-butil éster del ácido {7-[(S)-3-(terc-butoxicarbonilamino)pirrolidin-1-il]-5-bencilamino-1-ciclopropil-6,8-difluoro-1,4-dihidro-2,4-dioxo-2H-quinazolin-3-il}carbámico

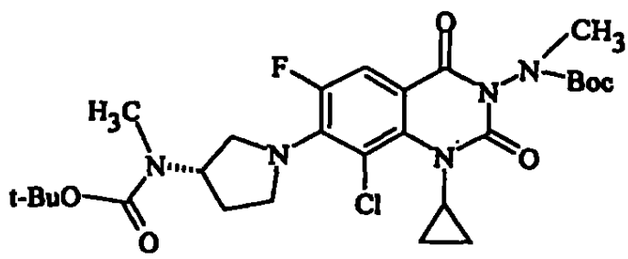


Una solución del terc-butil éster del ácido {7-[(S)-3-(terc-butoxicarbonilamino)pirrolidin-1-il]-1-ciclopropil-1,4-dihidro-2,4-dioxo-5,6,8-trifluoro-2H-quinazolin-3-il}carbámico del Ejemplo 8 (0,51 g, 0,914 mmol), trietilamina (1,3 ml, 9,3 mmol) y bencilamina (0,50 ml, 4,6 mmol) en sulfóxido de dimetilo (7,5 ml) se calienta a 100°C durante 16 horas en un tubo sellado. La mezcla se concentra bajo alto vacío y el residuo se purifica mediante cromatografía de columna (acetato de etilo/hexanos 1:2) para lograr el terc-butil éster del ácido {7-[(S)-3-(terc-butoxicarbonilamino)pirrolidin-1-il]-5-bencilamino-1-ciclopropil-6,8-difluoro-1,4-dihidro-2,4-dioxo-2H-quinazolin-3-il}carbámico como un sólido (0,51 g). ^{1}H NMR ($CDCl_3$): δ 8,50 (bs, 1H), 7,37-7,18 (m, 5H), 6,56 (bs, 1H),

4,76-4,62 (bd, 1H), 4,59-4,48 (m, 2H), 4,34-4,18 (m, 1H), 3,93-3,49 (m, 3H), 3,48-3,20 (m, 2H), 2,24-2,04 (m, 1H), 1,96-1,74 (m, 1H), 1,49 (s, 9H), 1,46 (s, 9H), 1,13-1,00 (m, 2H), 0,75-0,61 (m, 2H).

EJEMPLO 11

Síntesis del terc-butil éster del ácido {7-[(S)-3-(terc-butoxicarbonil-N-metilamino)pirrolidin-1-il]-8-cloro-1-ciclopropil-6-fluoro-2,4-dioxo-1,4-dihidro-2H-quinazolin-3-il}-metilcarbámico

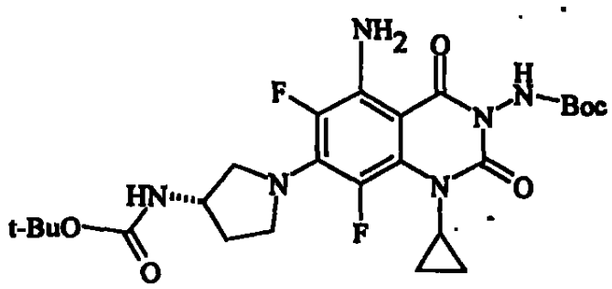


A una solución del terc-butil éster del ácido {7-[(S)-3-(terc-butoxicarbonil-N-metilamino)pirrolidin-1-il]-8-cloro-1-ciclopropil-6-fluoro-2,4-dioxo-1,4-dihidro-2H-quinazolin-3-il}carbámico del Ejemplo 8 (0,238 g, 0,421 mmol), en N,N-dimetilformamida (5 ml) a -78°C bajo una atmósfera de nitrógeno, se agrega hidruro de sodio (60% de dispersión en aceite mineral, 0,025 g, 0,631 mmol). Después de 30 minutos se agrega yodometano (0,052 ml, 0,842 mmol) y la mezcla se

calienta a temperatura ambiente. Después de una hora, la mezcla de la reacción se diluye con acetato de etilo y se lava con solución de cloruro de amonio saturado, agua y solución salina. La capa orgánica se seca sobre $MgSO_4$, se filtra y el filtrado se concentra. El residuo resultante se purifica mediante cromatografía de columna rápida (acetato de etilo/hexanos 1:1) para lograr el compuesto del título (0,118 g). ^1H NMR ($CDCl_3$): δ 7,63 (dd, 1H), 4,78 (bs, 1H), 3,87-3,45 (m, 6H), 2,62-2,44 (m, 6H), 2,31-2,12 (m, 2H), 1,49-1,47 (m, 18H), 1,23-1,07 (m, 2H), 0,75-0,53 (m, 2H). MS CI: m/z 582 (MH^+).

EJEMPLO 12

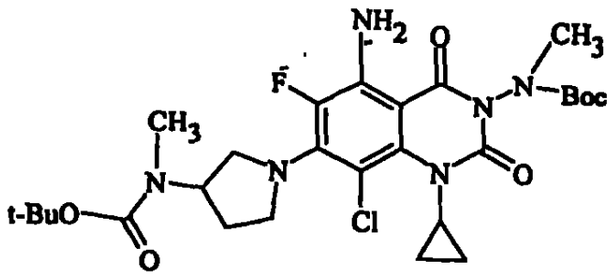
Síntesis del terc-butil éster del ácido {5-amino-7-[(S)-3-(terc-butoxicarbonilamino)pirrolidin-1-il]-1-ciclopropil-6,8-difluoro-1,4-dihidro-2,4-dioxo-2H-quinazolin-3-il}carbámico



El terc-butil éster del ácido {7-[(S)-3-(terc-butoxicarbonilamino)pirrolidin-1-il]-5-bencilamino-1-ciclopropil-6,8-difluoro-1,4-dihidro-2,4-dioxo-2H-quinazolin-3-il}carbámico del Ejemplo 10 (0,435 g, 0,676 mmol) en tetrahidrofurano (20 ml) se hidrogena a temperatura ambiente y a presión atmosférica sobre 20% de hidróxido de paladio sobre carbono (0,114 g) durante 27 horas. La mezcla se filtra a través de Celita, el sólido se lava con cloroformo, y los filtrados combinados se concentran bajo vacío. La purificación mediante cromatografía de columna (acetato de etilo/hexanos 2:3) da el terc-butil éster del ácido {5-amino-7-[(S)-3-(terc-butoxicarbonilamino)pirrolidin-1-il]-1-ciclopropil-6,8-difluoro-1,4-dihidro-2,4-dioxo-2H-quinazolin-3-il}carbámico como un sólido (0,284 g). ^{1}H NMR ($CDCl_3$): δ 6,61 (bs, 1H), 5,94 (bs, 2H), 4,82-4,69 (bd, 1H), 4,40-4,21 (m, 1H), 4,00-3,59 (m, 3H), 3,55-3,41 (m, 1H), 3,35-3,21 (m, 1H), 2,32-2,08 (m, 1H), 2,01-1,80 (m, 1H), 1,50 (s, 9H), 1,46 (s, 9H), 1,17-1,01 (m, 2H), 0,77-0,63 (m, 2H).

EJEMPLO 13

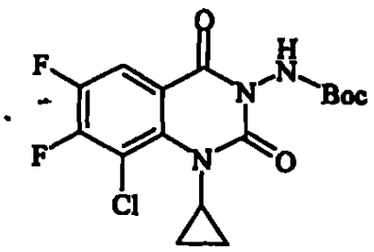
Síntesis de la 8-Cloro-1-ciclopropil-6-fluoro-3-metilamino-7-[(S)-3-metilaminopirrolidin-1-il]-1H-quinazolin-2,4-diona



Se hace burbujear gas cloruro de hidrógeno en éter dietílico (30 ml) durante 15 minutos. La solución resultante se enfría a 0°C y se agrega al terc-butil éster del ácido {7-[(S)-3-(terc-butoxicarbonilmetilamino)pirrolidin-1-il]-8-cloro-1-ciclopropil-6-fluoro-2,4-dioxo-1,4-dihidro-2H-quinazolin-3-il}metil-carbámico del Ejemplo 11 (0,118 g, 0,202 mmol). La mezcla de la reacción se calienta lentamente a temperatura ambiente. Después de 30 horas, el precipitado se filtra, se lava con éter y hexanos, y se seca bajo vacío para lograr la sal de clorhidrato del compuesto del título como un sólido (0,0632 g, punto de fusión 77°C-79°C). MS CI: m/z 382 (MH^+).

EJEMPLO 14

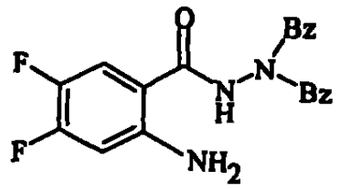
Síntesis del terc-butil éster del ácido (8-cloro-1-ciclopropil-6,7-difluoro-2,4-dioxo-1,4-dihidro-2H-quinazolin-3-il)carbámico



A una solución del terc-butil éster del ácido (3-cloro-2-ciclopropilamino-4,5-difluorobenzoil)-hidrazincarboxílico (Ejemplo 6c) (1,93 g, 5,34 mmol) en tetrahidrofurano (50 ml) se agrega carbonato de potasio (3,69 g, 26,7 mmol) y trifosgeno (2,06 g, 6,95 mmol). La mezcla de la reacción se refluye durante 90 minutos, se enfría a temperatura ambiente, y se diluye con acetato de etilo. La capa orgánica se lava con agua y solución salina, luego se seca sobre $MgSO_4$ y se filtra. El filtrado se concentra bajo vacio y se purifica mediante cromatografía de columna rápida (acetato de etilo/hexanos 1:2) para lograr el compuesto del título (1,27 g). MS EI: m/z 386 (M^+).

EJEMPLO 15

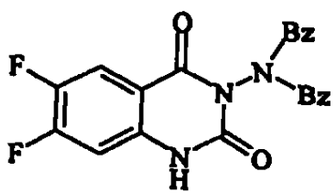
Síntesis de la 2,2-dibencilhidrazida del ácido 2-amino-4,5-difluorobenzoico



Ácido 4,5-difluoroantranílico (4,73 g, 27,3 mmol) y N,N-dibencilhidrazina (8,69 g, 42 mmol) se combinan en 200 ml de cloruro de metileno. Luego se se agrega clorhidrato de 1-etil-3-(3-dimetilaminopropil)carbodiimida (EDAC) (7,85 g, 41 mmol) a esta solución, y la mezcla se agita durante 18 horas a 25°C. La solución se lava cn $NaHCO_3$ saturado, solución salina y se seca sobre sulfato de magnesio. La solución se concentra para dar 15,8 g de un aceite oscuro y se purifica mediante cromatografía (SiO_2, $CHCl_3$) para dar 3,4 g del compuesto del título como un sólido. MS CI: m/z 368 (MH^+).

EJEMPLO 16

Síntesis de la 3-Dibencilamino-6,7-difluoro-1H-quinazolin-2,4-diona

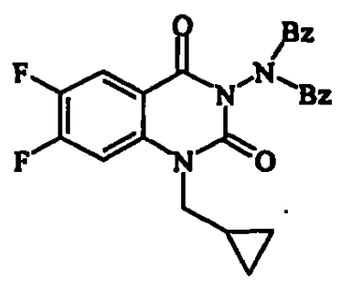


La 2,2-dibencilhidrazida del ácido 2-amino-4,5-difluorobenzoico (Ejemplo 15) (0,81 g, 2,2 mmol) y trifosgeno (0,33 g, 1,1 mmol) se combinan en 100 ml de cloruro de metileno y se agita a 25°C durante 20 horas. La solución se vierte en 200 ml de $NaHCO_3$ saturado, las capas se separan, y la capa acuosa se lava tres veces con acetato de etilo. Las capas orgánicas combinadas se secan sobre sulfato de magnesio y luego se concentran para dar 0,86 g del compuesto del título como un sólido. MS CI: m/z 394 (MH^+).

EJEMPLO 17

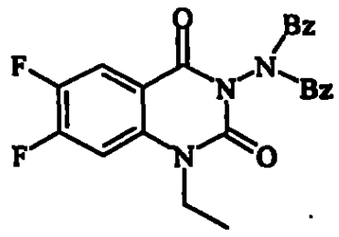
Síntesis de la 3-Dibencilamino-6,7-difluoro-1-sustituido-1H-quinazolin-2,4-diona

(a) 3-Dibencilamino-6,7-difluoro-1-ciclopropilmetil-1H-quinazolin-2,4-diona



Una solución de la 3-dibencilamino-6,7-difluoro-1H-quinazolin-2,4-diona (Ejemplo 16) (0,43 g, 1,1 mmol) en 10 ml de N,N-dimetilformamida se agrega a una suspensión de hidruro de sodio (0,05 g, 1,3 mmol) en 10 ml de N,N-dimetilformamida y se agita durante 30 minutos. Se agrega bromometilciclopropano (0,16 ml, 1,6 mmol) y la mezcla se agita a 25°C durante 18 horas. La reacción se extingue con 1 ml de agua y se concentra en vacío. El residuo se disuelve en cloroformo, se lava con agua, solución salina y se seca sobre sulfato de magnesio. La solución se concentra y se purifica mediante cromatografía (SiO_2, $CHCl_3$) para dar 0,33 g del compuesto del título como un sólido. MS CI: m/z 448 (MH^+).

(b) 3-Dibencilamino-6,7-difluoro-1-etil-1H-quinazolin-2,4-diona



Una solución de la 3-dibencilamino-6,7-difluoro-1H-quinazolin-2,4-diona (Ejemplo 16) (0,43 g, 1,1 mmol) en 10 ml de N,N-dimetilformamida se agrega a una suspensión de hidruro de sodio (0,05 g, 1,3 mmol) en 10 ml de N,N-dimetilformamida y se agita durante 30 minutos. Se agrega yoduro de etilo (0,13 ml, 1,6 mmol) y la mezcla se agita a 25°C durante 18 horas. La reacción se extingue con 1 ml de agua y se concentra en vacío. El residuo se disuelve en cloroformo, se lava con agua, solución salina y se seca sobre sulfato de magnesio. La solución se concentra y se purifica mediante cromatografía (SiO_2, $CHCl_3$) para dar 0,34 g del compuesto del título como un sólido, punto de fusión 133°C-135°C, MS CI: m/z 422 (MH^+).

EJEMPLO 18

Cloración

Método General de Cloración

A una solución de un terc-butil éster del ácido benzoilhidrazincarboxílico (Ejemplo 7) en ácido acético (5 ml) se agrega N-clorosuccinimida (1,2 eq.). Después de 1 hora, la mezcla de la reacción se diluye con acetato de etilo y se lava

con $NaHCO_3$ saturado, agua y solución salina. La capa orgánica se seca sobre $MgSO_4$ y se filtra. El filtrado se concentra bajo vacío y se purifica mediante cromatografía de columna rápida (acetato de etilo/hexanos) para lograr el terc-butil éster del ácido cloro-benzoilhidrazincarboxílico correspondiente.

Los siguientes compuestos se sintetizan de acuerdo con el Método General de Cloración precedente:

(a) terc-Butil éster del ácido N'-{4-[3-(terc-butoxicarbonilaminometil)pirrolidin-1-il]-3-cloro-2-ciclopropilamino-5-fluorobenzoil)hidrazincarboxílico (MS CI: m/z 542 (MH^+)) desde terc-butil éster del ácido N'-{4-[3-(terc-butoxicarbonilamino-metil)pirrolidin-1-il]-2-ciclopropilamino-5-fluorobenzoil}-hidrazincarboxílico (Ejemplo 7a).

(b) terc-Butil éster del ácido N'-4-[4-(terc-butoxicarbonilpiperazin-1-il)-3-cloro-2-ciclopropilamino-5-fluorobenzoil]hidrazincarboxílico (MS CI: m/z 528 (MH^+)) desde terc-butil éster del ácido N'-4-[4-(terc-butoxicarbonilpiperazin-1-il)-2-ciclopropilamino-5-fluorobenzoil]hidrazincarboxílico (Ejemplo 7b).

(c) terc-Butil éster del ácido N'-{4-[3-(terc-butoxicarbonilaminometil)-3-metilpirrolidin-1-il]-3-cloro-2-

ciclopropilamino-5-fluorobenzoil}hidrazincarboxílico (MS CI: m/z 556 (MH^+)) desde terc-butil éster del ácido N'-{4-[3-(terc-butoxicarbonilaminometil)-3-metilpirrolidin-1-il]-2-ciclopropilamino-5-fluorobenzoil}hidrazincarboxílico (Ejemplo 7c).

(d) terc-Butil éster del ácido N'-[4-(6-terc-butoxicarbonilamino-3-azabiciclo[3.1.0]hex-3-il)-3-cloro-2-ciclopropilamino-5-fluorobenzoil]hidrazincarboxílico (MS CI: m/z 540 (MH^+)) desde terc-butil éster del ácido N'-[4-(6-terc-butoxicarbonilamino-3-azabiciclo[3.1.0]hex-3-il)-2-ciclopropilamino-5-fluorobenzoil]-hidrazincarboxílico (Ejemplo 7d).

(e) terc-Butil éster del ácido N'-{4-[(S)-3-(terc-butoxicarbonil-N-metilamino)pirrolidin-1-il]-3-cloro-2-ciclopropilamino-5-fluorobenzoil}hidrazincarboxílico (MS CI: m/z 542 (MH^+)) desde terc-butil éster del ácido N'-{4-[(S)-3-(terc-butoxicarbonil-N-metilamino)pirrolidin-1-il]-2-ciclopropilamino-5-fluorobenzoil}-hidrazincarboxílico (Ejemplo 7e).

(f) terc-Butil éster del ácido N'-{4-[(S)-3-(terc-butoxicarbonil-N-amino)pirrolidin-1-il]-3-cloro-2-(2,4-difluoroanilino)-5-fluorobenzoil}hidrazincarboxílico ($CDCl_3$): δ

9,70 (bs, 1H), 7,76 (d, 1H), 6,93-6,82 (m, 1H), 6,70-6,62 (m, 2H), 6,48-6,34 (m, 2H), 4,91-4,87 (bs, 1H), 4,29-4,20 (m, 1H), 3,78-3,60 (m, 2H), 3,50-3,28 (m, 2H), 2,33-2,20 (m, 1H), 1,94-1,66 (m, 1H), 1,44 (s, 9H), 1,42 (s, 9H), (MS CI: m/z 601 (MH^+)) desde terc-butil éster del ácido N'-[4-[(S)-3-(terc-butoxicarbonilamino)pirrolidin-1-il]-2-(2,4-difluoroanilino)-5-fluorobenzoil)-hidrazincarboxílico (Ejemplo 7f).

(g) terc-Butil éster del ácido N'-[4-((S)-7-terc-butoxicarbonilamino-5-azaespiro[2.4]hept-5-il)-3-cloro-2-ciclopropilamino-5-fluorobenzoil]hidrazincarboxílico (MS CI: m/z 554 (MH^+)) desde terc-butil éster del ácido N'-[(S)-4-(7-terc-butoxicarbonil-5-azaespiro[2.4]hept)-2-ciclopropilamino-5-fluorobenzoil]hidrazincarboxílico (Ejemplo 7k).

(h) terc-Butil éster del ácido N'-[4-(pirrolidin-1-il)-3-cloro-2-ciclopropilamino-5-fluorobenzoil]hidrazincarboxílico (MS CI: m/z 413 (MH^+)) desde terc-butil éster del ácido N'-[4-(pirrolidin-1-il)-2-ciclopropilamino-5-fluorobenzoil]-hidrazincarboxílico (Ejemplo 7m).

(i) terc-Butil éster del ácido N'-[4-[3-(terc-butoxicarbonilamino)pirrolidin-1-il]-3-cloro-5-fluoro-2-isopropilaminobenzoil)hidrazincarboxílico (MS CI: m/z 530 (MH^+)) desde terc-butil éster del ácido N'-[4-[3-(terc-

butoxicarbonilamino)pirrolidin-1-il]-5-fluoro-2-isopropilaminobenzoil}hidrazincarboxílico (Ejemplo 7n).

(j) terc-Butil éster del ácido N'-{4-[3-(terc-butoxicarbonilamino)pirrolidin-1-il]-2-ciclobutilamino-3-cloro-5-fluorobenzoil}hidrazincarboxílico (MS CI: m/z 542 (MH^+)) desde terc-butil éster del ácido N'-{4-[3-(terc-butoxicarbonilamino)-pirrolidin-1-il]-2-ciclobutilamino-5-fluorobenzoil}hidrazincarboxílico (Ejemplo 7q).

(k) terc-Butil éster del ácido N'-(1-{4-[3-(terc-butoxicarbonilamino-metil)piperidin-1-il]-3-cloro-2-ciclopropilamino-5-fluorofenil}metanoil)hidrazincarboxílico (MS CI: m/z 556 (MH^+)) desde terc-butil éster del ácido N'-(1-{4-[3-(terc-butoxicarbonilaminometil)piperidin-1-il]-2-ciclopropilamino-5-fluorofenil}metanoil)hidrazincarboxílico (Ejemplo 7z).

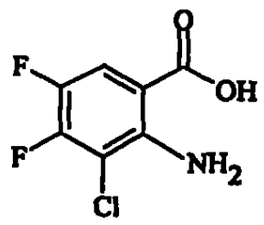
(l) terc-Butil éster del ácido N'-[1-(4-{3-[(terc-butoxicarbonilisopropilamino)metil]-pirrolidin-1-il}-3-cloro-2-ciclopropilamino-5-fluorofenil)metanoil]hidrazincarboxílico (MS CI: m/z 584 (MH^+)) desde terc-butil éster del ácido N'-[1-(4-{3-[(terc-butoxicarbonilisopropilamino)metil]pirrolidin-1-il}-2-ciclopropilamino-5-fluorofenil)metanoil]hidrazincarboxílico (Ejemplo 7aa).

(m) terc-Butil éster del ácido N'-(1-{4-[3-(terc-butoxicarbonilaminometil)pirrolidin-1-il]-3,5-dicloro-2-ciclopropilaminofenil}metanoil)hidrazincarboxílico (MS CI: m/z 558 (MH^+)) desde terc-butil éster del ácido N'-(1-{4-[3-(terc-butoxicarbonilamino-metil)pirrolidin-1-il]-5-cloro-2-ciclopropilaminofenil}metanoil)-hidrazincarboxílico (Ejemplo 7bb).

EJEMPLO 19

Cloración de Ácidos Benzoicos Sustituidos

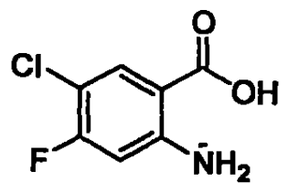
(a) Síntesis del ácido 3-cloro-4,5-difluoroantranílico



A una solución de ácido 4,5-difluoroantranílico (2,45 g, 14,2 mmol) en diclorometano (25 ml) se agrega ácido acético (10 ml) y terc-butil éster del ácido hipocloroso (1,75 ml, 15,6 mmol). Después de 2 horas, la mezcla de la reacción se diluye con acetato de etilo y se lava con agua y solución salina. La capa orgánica se seca sobre $MgSO_4$, se filtra y se concentra. El residuo resultante se purifica mediante cromatografía de

columna rápida (5% de alcohol isopropílico/1% de ácido fórmico/94% de diclorometano) para lograr el ácido 3-cloro-4,5-difluoroantranílco como un aceite (2,97 g). MS CI: m/z 206 (M^+).

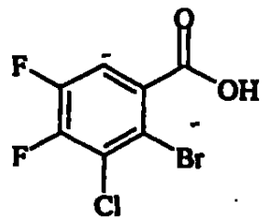
(b) Ácido 5-cloro-4-fluoroantranílico



A una solución de ácido 4-fluoroantranílico (0,882 g, 5,69 mmol) en cloruro de metileno (50 ml) y ácido acético (10 ml) se agrega una solución de terc-butil hipoclorito (0,71 ml, 6,25 mmol) en diclorometano (1 ml) gota a gota durante 1 minuto. Después de 90 minutos, la mezcla de la reacción se lava con agua y solución salina. La capa orgánica se seca sobre $MgSO_4$, se filtra y el filtrado se concentra para lograr el ácido 5-cloro-4-fluoroantranílco (1,20 g). MS CI: m/z 188 (M^+).

EJEMPLO 20

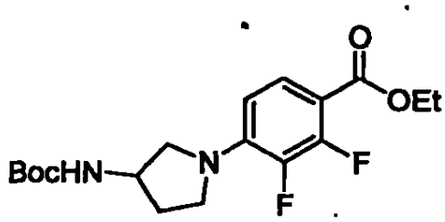
Síntesis del ácido 2-bromo-3-cloro-4,5-difluorobenzoico



Una solución de bromuro cuproso (10,96 g, 49,2 mmol) en acetonitrilo (100 ml) se enfría a 0°C y luego se agregan terc-butil nitrito (7,31 ml, 61,5 mmol) y ácido 3-cloro-4,5-difluoroantranílico (Ejemplo 19) (8,51 g, 41,0 mmol). La mezcla se calienta lentamente a temperatura ambiente y después de 20 horas el solvente se remueve bajo vacío. El residuo resultante se disuelve en acetato de etilo y se lava con ácido clorhídrico 1,0 M, agua y solución salina. La capa orgánica se seca sobre $MgSO_4$ y se filtra. El filtrado se concentra bajo vacío y se purifica mediante cromatografía de columna rápida (5% de alcohol isopropílico/1% de ácido fórmico/94% de diclorometano) para lograr el ácido 2-bromo-3-cloro-4,5-difluorobenzoico como un sólido (7,96 g). MS CI: m/z 271 (MH^+).

EJEMPLO 21

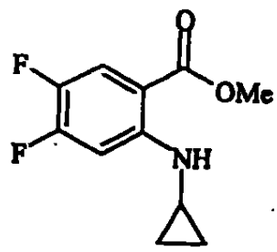
Síntesis del etil éster del ácido 4-[3-(terc-butoxicarbonilamino)pirrolidin-1-il]-2,3-difluorobenzoico



A una solución del etil éster del acido 4-[3-(terc-butoxicarbonilamino)pirrolidin-1-il]-2,3-difluorobenzoico (Ejemplo 2h) (3,50 g, 9,50 mmol) en diclorometano (80 ml) se agrega ácido acético (8 ml) y terc-butil hipoclorito (1,75 ml, 15,6 mmol). Después de 20 minutos, la mezcla de la reacción se diluye con acetato de etilo y se lava con agua y solución salina. La capa orgánica se seca sobre sulfato de sodio, se filtra y el filtrado se concentra. El residuo resultante se purifica mediante cromatografía de columna (acetato de etilo/hexanos 1:4) para lograr el compuesto del título (3,75 g) como un aceite. ^{1}H NMR ($CDCl_3$): δ 7,69 (dd, 1H), 4,85-4,76 (bd, 1H), 4,50-4,20 (m, 3H), 3,90-3,74 (m, 2H), 3,62-3,36 (m, 2H), 2,40-2,20 (m, 1H), 1,91-1,84 (m, 1H), 1,45 (s, 9H), 1,40 (s, 9H).

EJEMPLO 22

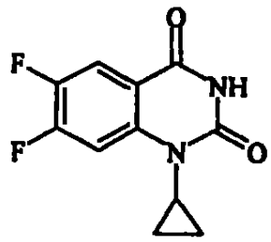
Síntesis del metil éster del ácido 2-ciclopropilamino-4,5-difluorobenzoico



A una solución de ácido 2-ciclopropilamino-4,5-difluorobenzoico (Ejemplo 5a) (6,0 g, 28,1 mmol), diclorometano (100 ml) y metanol (20 ml), se agrega (trimetilsilil)diazometano (solución 2,9 M en hexano) gota a gota hasta que cesa la evolución de gas. La solución se agita a temperatura ambiente durante 0,5 hora y se agrega 88% de ácido fórmico gota a gota hasta que cesa la evolución de gas. Se agrega agua, y la solución se extrae con diclorometano, se seca sobre $MgSO_4$, se filtra y el solvente se remueve bajo presión reducida. El residuo se purifica mediante cromatografía de columna de gel de sílice usando hexano/EtOAc (9:1) como el eluyente para lograr 5,4 g del compuesto del título como un aceite claro. MS CI: m/z 228 (MH^+).

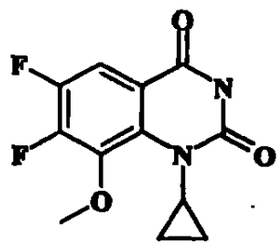
EJEMPLO 23

(a) Síntesis de la 1-Ciclopropil-6,7-difluoro-1H-quinazolin-2,4-diona



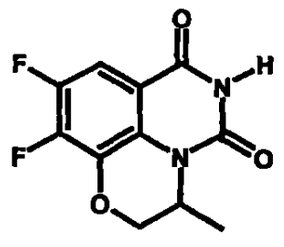
A una solución de etil éster del ácido 2-ciclopropilamino-4,5-difluorobenzoico (Ejemplo 22) (5,0 g, 22,0 mmol) diclorometano seco (120 ml) bajo una atmósfera de N_2, se agrega isocianato de clorosulfanilo (3,11 g, 22 mmol). La solución reacciona a temperatura ambiente durante 4 horas, el solvente se remueve bajo presión reducida. El residuo se enfría a -20°C y se agrega una solución salina fría (100 ml) con tampón de $NaHCO_3$. La solución se calienta a temperatura ambiente durante 1 hora. El volumen se reduce en la mitad con una corriente de aire, y el sólido se recoge mediante filtración. El sólido seco se agrega a una solución de trietilamina (5 ml) en THF (250 ml) y se refluye toda la noche. La reacción se enfría, el solvente se remueve bajo presión reducida, se disuelve en agua (100 ml), y se acidifica a pH 1-2 con ácido clorhídrico 1,0 M. El precipitado resultante se recoge mediante filtración para lograr 2,0 g del compuesto del título. MS CI: m/z 239 (MH^+).

(b) 1-Ciclopropil-6,7-difluoro-8-metoxi-1H-quinazolin-2,4-diona



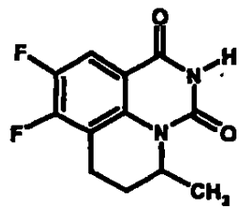
Una solución de 1-ciclopropil-3-(3-metoxi-2,4,5-trifluorobenzoil)urea (Ejemplo 27b, 0,94 g, 3,26 mmol) en tetrahidrofurano (20 ml) y N,N-dimetilformamida (5 ml) se trata con hidruro de sodio (0,275 g, 6,8 mmol, 60% en una dispersión de aceite mineral) y se calienta a reflujo durante 16 horas. La mezcla se enfría, se trata con NH_4Cl saturado y se extrae con diclorometano. La capa orgánica se lava luego con solución salina, se seca sobre Na_2SO_4 y se concentra bajo presión reducida. La cromatografía de columna rápida (acetato de etilo/hexanos 1:3) logra el compuesto del título. MS (EI, M+1) m/z 269.

(c) Síntesis de la 8,9-Difluoro-3-metil-2,3-dihidro-1-oxa-3a,5-diaza-fenalen-4,6-diona



Una solución de 1,5 g (6,2 mmol) de metil éster del ácido 7,8-difluoro-3-metil-3,4-dihidro-2H-1,4-benzoxazin-5-carboxílico (Ejemplo 32a) en 25 ml de diclorometano se enfría a -20°C y se trata gota a gota con 0,92 g (6,5 mmol) de isocianato de clorosulfonilo. La reacción se agita a temperatura ambiente durante 18 horas y el solvente se remueve en vacío. El residuo se trata con una solución de bicarbonato de sodio saturado y se extrae con diclorometano. La capa orgánica se seca ($MgSO_4$), se filtra y se concentra en vacío. El residuo se disuelve en 50 ml de tetrahidrofurano; y la solución resultante se trata con 5,0 g (5,0 mmol) de trietilamina. Después de calentar a reflujo durante 4 horas, el solvente se remueve en vacío, y el residuo se tritura con 5 ml de diclorometano/acetato de etilo (80:20). El material insoluble se remueve mediante filtración, se lava con la mezcla de solventes precedente (2 ml) para dar 0,25 g del compuesto del título, punto de fusión 259°C-261°C. El filtrado es sometido a cromatografía sobre gel de sílice en grado rápido (230-400 malla) eluyendo con diclorometano/acetato de etilo (80:20) para dar 0,38 g del material inicial. Al continuar eluyendo se obtiene 0,2 g adicionales del compuesto del título. ^1H NMR (400 MHz, $CDCl_3$): δ 11,78 (s, 1H), 7,50 (m, 1H), 4,68 (s, 1H), 4,52 (d, 1H), 4,17 (d, 1H), 1,23 (d, 3H).

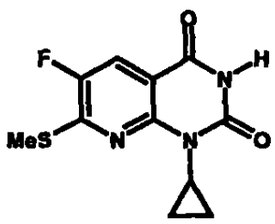
(d) Síntesis de la 8,9-Difluoro-5-metil-6,7-dihidro-5H-pirido[3,2,1-ij]quinazolin-1,3-diona



Una solución de 1,07 g (4,4 mmol) de metil éster del ácido 5,6-difluoro-2-metil-1,2,3,4-tetrahidro-quinazolin-8-carboxílico (Ejemplo 32) en 25 ml de diclorometano se enfría a -20°C y se trata gota a gota con 0,85 g (6,0 mmol) de isocianato de clorosulfonilo. La reacción se agita a -20°C durante 1 hora, se trata con 1,0 g (12 mmol) de acetato de sodio sólido y el solvente se remueve en vacío. El residuo se enfría en un baño de hielo y tritura con una solución saturada de acetato de sodio en solución salina. El precipitado se remueve por filtración, se lava con la solución de acetato de sodio y se seca en vacío. El precipitado seco se lava con éter para remover el material inicial y se seca en vacío. El sólido seco se suspende en 40 ml de tetrahidrofurano seco, se enfría a 5°C y se trata por porciones con 1,2 g (12 mmol) de terc-butóxido de sodio. Después de completar el agregado, la mezcla de la reacción se agita a 5°C durante 30 minutos, se remueve el baño y la reacción se agita a temperatura ambiente durante 1 hora. El solvente se remueve en vacío; el residuo se disuelve en agua, se enfría a 5°C y se acidifica con ácido

fórmico. El precipitado resultante se remueve por filtración, se lava con agua y se seca en vacio para lograr 0,8 g del compuesto del título, punto de fusión 212°C-214°C.

(e) 1-Ciclopropil-6-fluoro-7-metilsulfanil-1H-pirido[2,3-d]pirimidin-2,4-diona



Una solución de 4,1 g (15,2 mmol) de etil 2-ciclopropilamino-5-fluoro-6-metilsulfanilnicotinato (Ejemplo 34) en 125 ml de diclorometano se enfría a -20°C y se trata gota a gota con 5,24 g (37 mmol) de isocianato de clorosulfonilo. La reacción se agita a -20°C durante 3 horas y se la deja llegar a la temperatura ambiente durante toda la noche. La mezcla se enfría nuevamente a -20°C y se trata con 6,8 g (80 mmol) de acetato de sodio sólido. Después de agitar durante 1 hora sin enfriar, el solvente se remueve en vacio sin calentar. El residuo se tritura con una solución saturada de acetato de sodio en solución salina y se extrae con acetato de etilo (3 x 75 ml). Las capas orgánicas combinadas se secan ($MgSO_4$), se filtran y se evaporan en vacio. El residuo se suspende en 100 ml de tetrahidrofurano y se trata con 3,6 g (32 mmol) de terc-butóxido de sodio sólido y se agita a temperatura ambiente

durante 36 horas. El solvente se remueve en vacío, el residuo se tritura con 100 ml de ácido fórmico 0,1 M y se extrae con acetato de etilo (3 x 100 ml). Las capas orgánicas combinadas se lavan con agua, se secan ($MgSO_4$), se filtran y se evaporan en vacío para dar un residuo que es sometido a cromatografía sobre gel de sílice en grado rápido (230-400 malla eluyendo con diclorometano para dar 0,75 g del compuesto del título, punto de fusión 220°C-222°C.

Procedimiento General A

Hidruro de sodio (3 eq., 60% de dispersión en aceite mineral) se agrega por porciones a una solución de 1-ciclopropil-3-benzoilurea (Ejemplo 27) en tetrahidrofurano/N,N-dimetilformamida 20:1 a -25°C. La mezcla se agita a temperatura ambiente durante 30 minutos, luego se refluye toda la noche. Se vierte en agua helada, y la solución se acidifica con 10% de ácido clorhídrico y se extrae con acetato de etilo. El extracto se lava con solución salina, se seca y se concentra. El residuo se purifica mediante cromatografía de columna de gel de sílice (acetato de etilo/hexanos) para lograr 1-ciclopropil-6,7-difluoro-1H-quinazolin-2,4-dionas 8-sustituidas.

Los siguientes compuestos se sintetizan de acuerdo con el Procedimiento General A del Ejemplo 23:

(e) 1-Ciclopropil-6,7-difluoro-8-metil-1H-quinazolin-2,4-diona (^{1}H NMR (200 MHz, $CDCl_3$): δ 8,61 (bs, 1H), 7,83 (dd, 1H), 3,37-3,35 (m, 1H), 2,60 (dd, 3H), 1,31-1,12 (m, 2H), 0,71-0,63 (m, 2H)), desde 1-ciclopropil-3-(2,4,5-trifluoro-3-metilbenzoil)urea (Ejemplo 27c).

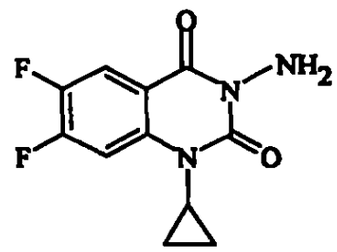
(f) 1-Ciclopropil-6,7-difluoro-5-metil-1H-quinazolin-2,4-diona (^{1}H NMR (200 MHz, $CDCl_3$): δ 8,37 (bs, 1H), 7,96 (dd, 1H), 2,81-2,74 (m, 1H), 2,61 (d, 3H), 1,26-1,14 (m, 2H), 0,81-0,73 (m, 2H)), desde 1-ciclopropil-3-(3,4,6-trifluoro-2-metilbenzoil)urea (Ejemplo 27d).

(g) 1-Ciclopropil-6,7-difluoro-8-etil-1H-quinazolin-2,4-diona (^{1}H NMR (200 MHz, $CDCl_3$): δ 9,41 (bs, 1H), 7,86-7,77 (m, 1H), 3,40-3,20 (m, 3H), 1,30-1,10 (m, 5H), 0,75-0,67 (m, 2H)), desde 1-ciclopropil-3-(3-etil-2,4,5-trifluorobenzoil)urea (Ejemplo 27e).

(i) 7-Cloro-1-ciclopropil-6-fluoro-1H-pirido[2,3-d]pirimidin-2,4-diona (punto de fusión 214°C-216°C) desde 1-ciclopropil-3-(2,6-dicloro-5-fluoro-piridin-3-carbonil)urea (Ejemplo 27a).

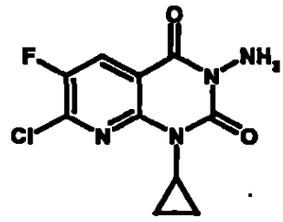
EJEMPLO 24

(a) Síntesis de la 3-Amino-1-ciclopropil-6,7-difluoro-1H-quinazolin-2,4-diona



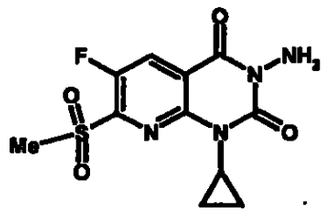
A una solución de 1-ciclópropil-6,7-difluoro-1H-quinazolin-2,4-diona (Ejemplo 23a, 2,0 g, 8,92 mmol) en dioxano (7,5 ml) y dimetilformamida (7,5 ml) se agrega NaH (60% de dispersión en aceite, 428 mg, 10,7 mmol). La solución se calienta a 60°C durante 10 minutos y se enfría a temperatura ambiente. A la solución enfriada se agrega O-(2,4-dinitrofenil)hidroxilamina (1,77 g, 8,92 mmol) y la solución se calienta a 80°C durante 30 minutos. La solución roja resultante se enfría a temperatura ambiente, se vierte sobre hielo picado y se extrae con EtOAc. Las capas orgánicas combinadas se secan sobre $MgSO_4$, se filtran y el solvente se remueve bajo presión reducida. El sólido resultante se tritura con Et_2O y se seca con aire para lograr 1,44 g del compuesto del título. MS CI: m/z 254 (MH^+).

(b) 3-Amino-7-cloro-1-ciclopropil-6-fluoro-1H-pirido[2,3-d]pirimidin-2,4-diona



Una solución de 0,83 g (15 mmol) de 7-cloro-1-ciclopropil-6-fluoro-1H-pirido[2,3-d]pirimidin-2,4-diona (Ejemplo 23i) en 50 ml de dimetilformamida-dioxano (1:1) se enfría a 0°C y se trata por porciones con 0,8 g (20 mmol) de 60% de hidruro de sodio/aceite mineral. La reacción se agita a temperatura ambiente durante 30 minutos, se enfría nuevamente a 0°C y se agregan 3,2 g (16 mmol) de 2,4-dinitrofenilhidroxilamina toda de una vez. Después de agitar a temperatura ambiente toda la noche, el dioxano se remueve en vacío y el residuo se diluye a 300 ml con hielo y agua y se agita a 5°C durante 1 hora. El precipitado se remueve mediante filtración, se lava con agua, éter y se seca en vacío para dar 2,65 g del compuesto del título, punto de fusión 192°C-194°C. Se puede aislar una segunda cosecha (0,6 g) evaporando el filtrado y triturando el residuo con éter de petróleo.

(c) Ácido 3-amino-1-ciclopropil-6-fluoro-2,4-dioxo-1,2,3,4-tetrahidro-pirido[2,3-d]pirimidin-7-tiosulfónico



Una solución de 0,47 g (1,57 mmol) de ácido 1-ciclopropil-6-fluoro-2,4-dioxo-1,2,3,4-tetrahidro-pirid[2,3-d]pirimidin-7-tiosulfónico (Ejemplo 35) en 20 ml de dimetilformamida/dioxano (1:1) se trata por porciones con 0,08 g (2,0 mmol) de 60% de hidruro de sodio/aceite mineral. La reacción se agita a temperatura ambiente durante 1 hora y se agregan 0,32 g (1,6 mmol) de 2,4-dinitrofenilhidroxilamina toda de una vez. Después de agitar a temperatura ambiente toda la noche, el dioxano se remueve en vacío y el residuo se diluye a 100 ml con hielo y agua y se agita a 5°C durante 1 hora. La solución acuosa se extrae con acetato de etilo (3 x 50 ml) y las capas orgánicas combinadas se lavan con agua, se secan ($MgSO_4$), se filtran y se evaporan en vacío para dar 0,4 g del compuesto del título, punto de fusión 167°C-169°C.

Procedimiento General A (Ejemplo 24)

A una solución de 1-ciclopropil-6,7-difluoro-1H-quinazolin-2,4-diona (Ejemplo 23) en 1:1 tetrahidrofurano seco o dioxano y N,N-dimetilformamida seca se agrega en porciones hidruro de sodio (1,1 eq., 60% de dispersión en aceite mineral) a

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temperatura ambiente. Después de agitar a 50°C durante 20 a 30 minutos, la solución resultante se enfría a temperatura ambiente y se agrega 1,4-dinitrofenilhidroxilamina (4 eq.). La mezcla se calienta de 60°C a 80°C durante 30 minutos, se enfría, y el dioxano se remueve a presión reducida. El residuo se vierte en agua helada y se extrae con acetato de etilo. Las capas orgánicas se combinan, se lavan con solución salina, se secan con Na_2SO_4 y se concentran en vacío. El residuo se purifica mediante cromatografía de columna rápida (acetato de etilo/hexanos) para lograr una 3-amino-1-ciclopropil-6,7-difluoro-1H-quinazolin-2,4-diona.

Los compuestos se sintetizan de acuerdo con el Procedimiento General A del Ejemplo 24:

(d) 3-Amino-1-ciclopropil-6,7-difluoro-8-metoxi-1H-quinazolin-2,4-diona (MS EI: m/z 284 (MH^+) desde 1-ciclopropil-6,7-difluoro-8-metoxi-1H-quinazolin-2,4-diona (Ejemplo 23b).

(e) 3-Amino-1-ciclopropil-6,7-difluoro-8-metil-1H-quinazolin-2,4-diona (^1H NMR (200 MHz, $CDCl_3$): δ 7,86 (dd, 1H), 5,20 (bs, 2H), 3,48-3,38 (m, 1H), 2,61 (dd, 3H), 1,29-1,17 (m, 2H), 0,73-0,62 (m, 2H)), desde 1-ciclopropil-6,7-difluoro-8-metil-1H-quinazolin-2,4-diona (Ejemplo 23e).

(f) 3-Amino-1-ciclopropil-6,7-difluoro-5-metil-1H-quinazolin-2,4-diona (^{1}H NMR (200 MHz, $CDCl_3$): δ 7,45 (dd, 1H), 5,28 (bs, 2H), 2,94-2,83 (m, 1H), 2,77 (d, 3H), 1,41-1,31 (m, 2H), 0,98-0,93 (m, 2H)), desde 1-ciclopropil-6,7-difluoro-5-metil-1H-quinazolin-2,4-diona (Ejemplo 23f).

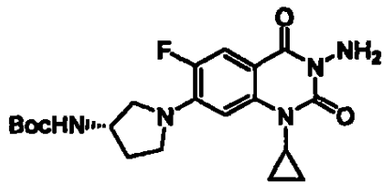
(g) 3-Amino-1-ciclopropil-6,7-difluoro-8-etil-1H-quinazolin-2,4-diona (^{1}H NMR (200 MHz, $CDCl_3$): δ 7,84-7,75 (m, 1H), 5,37 (bs, 2H), 3,50-3,40 (m, 3H), 3,37-3,21 (m, 2H), 1,29-1,15 (m, 5H), 0,75-0,66 (m, 2H)), desde 1-ciclopropil-6,7-difluoro-8-etil-1H-quinazolin-2,4-diona (Ejemplo 23g).

(h) 5-Amino-8,9-difluoro-3-metil-2,3-dihidro-1-oxa-3a,5-diaza-fenalen-4,6-diona (punto de fusión 171°C-173°C), desde 8,9-difluoro-3-metil-2,3-dihidro-1-oxa-3a,5-diaza-fenalen-4,6-diona (Ejemplo 23c).

(i) 2-Amino-8,9-difluoro-5-metil-6,7-dihidro-5H-pirido[3,2,1-ij]quinazolin-1,3-diona (punto de fusión 140°C-142°C, ^{1}H NMR (400 MHz, $CDCl_3$): δ 7,90 (m, 1H), 5,30 (bs, 2H), 5,07 (m, 1H), 3,08 (m, 3H), 2,85 (m, 1H), 2,15 (m, 1H), 1,95 (m, 1H), 1,31 (d, 3H)), desde 8,9-difluoro-5-metil-6,7-dihidro-5H-pirido[3,2,1-ij]quinazolin-1,3-diona (Ejemplo 23d).

EJEMPLO 25

Síntesis de la 3-Amino-7-[(S)-3-(terc-butoxicarbonilamino)-pirrolidin-1-il]-1-ciclopropil-6-fluoro-1H-quinazolin-2,4-diona



A una solución de 3-amino-1-ciclopropil-6,7-difluoro-1H-quinazolin-2,4-diona (Ejemplo 24a) (50,0 mg, 0,20 mmol) y trietilamina (74 mg, 0,74 mmol) en acetonitrilo (3 ml) se agrega terc-butil éster del ácido (S)-pirrolidin-3-il-carbámico (74 mg, 0,40 mmol). La solución se refluye durante 18 horas, el solvente se remueve bajo presión reducida y el residuo se tritura con agua. El sólido se recoge mediante filtración y se seca al aire para lograr 74 mg del compuesto del título. MS CI: m/z 420 (MH^+).

EJEMPLO 26

Síntesis de Benzamidas

Procedimiento General A

Una solución de un ácido benzoico sustituido apropiadamente, cloruro de oxalilo (1,5 eq.) y diclorometano se trata con N,N-dimetilformamida (2 gotas), la solución se agita a temperatura

ambiente durante 2 horas. La mezcla se concentra bajo presión reducida, y el residuo se disuelve en THF seca y se agrega lentamente a una solución de amonio en éter dietílico a -70°C. La mezcla luego se deja calentar a temperatura ambiente y se agita durante 30 minutos. La mezcla se filtra y el sólido resultante se disuelve en acetato de etilo, se lava con agua y se seca sobre Na_2SO_4. El solvente luego se concentra en vacío para proporcionar la amida deseada.

Los siguientes compuestos se sintetizan de acuerdo con el método del Procedimiento General A precedente:

(a) 3,4,6-Trifluoro-2-metilbenzamida (^{1}H NMR (200 MHz, $CDCl_3$): δ 6,89-6,77 (m, 1H), 6,41 (bs, 1H), 5,95 (m, 1H), 2,39 (d, 3H)) desde ácido 3,4,6-trifluorobenzoico (Hagen S. et al, *Heterocycl. Chem.*, 1990;27[6]:1609-1616).

(b) 3-Etil-2,4,5-trifluorolbenzamida (^{1}H NMR (200 MHz, $CDCl_3$): δ 7,78-7,60 (m, 1H), 6,61 (bs, 1H), 2,67 (q, 2H), 1,15 (t, 3H)) desde ácido 3-etil-2,4,5-trifluorobenzoico (Takemura, Solicitud de Patente Internacional PCT, 1996, WO 9623782).

EJEMPLO 27

Síntesis de Ureas 1-ciclopropil-3-benzoil sustituidas

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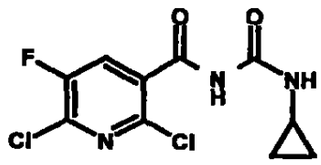
(a) 1-Ciclopropil-3-(2,6-dicloro-5-fluoro-piridin-3-carbonil)urea



Una solución de 5,8 g (27,8 mmol) de 2,6-dicloro-5-fluoronicotinamida (*Chem. Pharm. Bull.*, 1987;35:2280) en 60 ml de diclorometano se trata gota a gota con 5,1 g (40 mmol) de cloruro de oxalilo, y la mezcla de la reacción se calienta a reflujo durante 18 horas. El solvente se remueve en vacío, y el residuo se disuelve en 50 ml de diclorometano, que también se remueve en vacío. El residuo se disuelve en 50 ml de diclorometano, se enfría a -20°C y se trata gota a gota con 2,28 g (40 mmol) de ciclopropilamina. La mezcla de la reacción se agita de -20°C a -10° durante ½ hora, luego se la deja llegar a la temperatura ambiente durante 2 horas. El solvente se remueve en vacío y el residuo se tritura con 25 ml de diclorometano, que también se remueve en vacío para dar 8,0 g del compuesto del título, punto de fusión 171°C-173°C.

Procedimiento General A

A una solución de benzamida sustituida (Ejemplo 26) en 1,2-diclorometano se agrega cloruro de oxalilo (1,5 eq.) y la

mezcla se refluye durante 16 horas. El solvente luego se remueve bajo presión reducida para obtener un isocianato crudo. El isocianato luego se recoge en dioxano, se enfría a 0°C y se trata con ciclopropilamina (1,5 eq.) en dioxano. La mezcla luego se calienta a temperatura ambiente y se agita durante 3 horas. La mezcla luego se concentra bajo presión reducida, se disuelve en acetato de etilo, se lava con agua, se seca sobre Na_2SO_4 y se evapora bajo presión reducida. El residuo resultante se purifica mediante cromatografía de columna rápida (acetato de etilo/hexanos) para lograr la 1-ciclopropil-3-benzoil urea.

Los siguientes compuestos se sintetizan de acuerdo con el método del Procedimiento General A precedente:

(b) 1-Ciclopropil-3-(2,4,5-trifluoro-3-metoxi-benzoil)urea (MS ES (MH^+): m/z 289) desde 2,4,5-trifluoro-3-metoxibenzamida (Masuzawa K. Suzue S., Hirai K., Ishizaki T., Solicitud de Patente Europea, 1987, EP 230295).

(c) 1-Ciclopropil-3-(2,4,5-trifluoro-3-metilbenzoil)urea (^1H NMR (200 MHz, $CDCl_3$): δ 8,69 (d, 1H), 8,48 (bs, 1H), 7,75-7,62 (m, 1H), 2,83-2,71 (m, 1H), 2,30 (dd, 3H), 0,87-0,78 (m, 2H), 0,67-0,59 (m, 2H)) desde 2,4,5-trifluoro-3-metilbenzamida

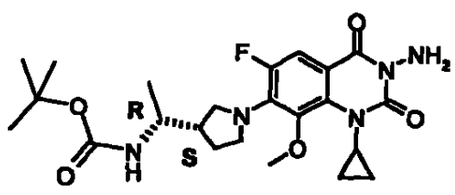
(Masuzawa K. Suzue S., Hirai K., Ishizaki T., Solicitud de Patente Europea, 1987, EP 237955).

(d) 1-Ciclopropil-3-(3,4,6-trifluoro-2-metilbenzoil)urea (^{1}H NMR (200 MHz, $CDCl_3$): δ 8,99 (bs, 1H), 8,37 (bs, 1H), 6,93-6,80 (m, 1H), 2,74-2,65 (m, 1H), 2,35 (d, 3H), 0,84-0,71 (m, 2H), 0,66-0,58 (m, 2H)) desde 3,4,6-trifluoro-2-metilbenzamida (Ejemplo 26a).

(e) 1-Ciclopropil-3-(3-etil-2,4,5-trifluorobenzoil)urea (^{1}H NMR (200 MHz, $CDCl_3$): δ 8,76-8,69 (bd, 1H), 8,50 (bs, 1H), 7,76-7,63 (m, 1H), 2,84-2,72 (m, 3H), 1,27-1,20 (m, 3H), 0,91-0,81 (m, 2H), 0,71-0,61 (m, 2H)) desde 3-etil-2,4,5-trifluorobenzamida (Ejemplo 26b).

EJEMPLO 28

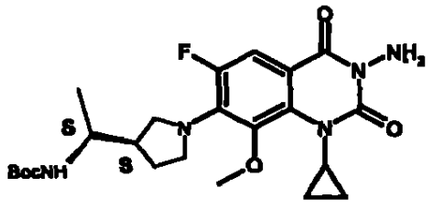
(a) Síntesis del terc-butil éster del ácido [(R)-1-[(S)-1-(3-amino-1-ciclopropil-6-fluoro-8-metoxi-2,4-dioxo-1,2,3,4-tetrahidroquinazolin-7-il)pirrolidin-3-il]etil)-carbámico



Una solución de 0,57 g (2,0 mmol) de 3-amino-1-ciclopropil-6,7-difluoro-8-metoxi-1H-quinazolin-2,4-diona (Ejemplo 24d),

0,64 g (3,0 mmol) de terc-butil éster del ácido ((S)-(R)-1-pirrolidin-3-iletil)carbámico (*J. Het. Chem.*, 1992;29:1481), 0,81 g (8,0 mmol) de trietilamina y 10 ml de sulfóxido de dimetilo se calienta a 110°C durante 4 horas. La mezcla de la reacción se enfría a temperatura ambiente, se vierte en 150 ml de hielo y agua, y se extrae con acetato de etilo (2 x 125 ml). Las capas orgánicas combinadas se lavan con agua, se secan ($MgSO_4$), se filtran y se evaporan en vacío para dar 1,1 g de producto crudo. La cromatografía sobre gel de sílice en grado rápido (230-400 malla) eluyendo con diclorometano/etanol (9:1) proporciona 0,92 g del compuesto del título, punto de fusión 96°C-98°C.

(b) Síntesis del terc-butil éster del ácido {(S)-10[(S)-1-(3-Amino-1-ciclopropil-6-fluoro-8-metoxi-2,4-dioxo-1,2,3,4-tetrahidroquinazolin-7-il-pirrolidin-3-il]etil}-carbámico



Una solución de 0,57 g (2,0 mmol) de 3-amino-1-ciclopropil-6,7-difluoro-8-metoxi-1H-quinazolin-2,4-diona (Ejemplo 24d), 0,64 g (3,0 mmol) de terc-butil éster del ácido ((S)-(S)-1-pirrolidin-3-iletil)carbámico (*J. Het. Chem.*, 1992;29:1481),

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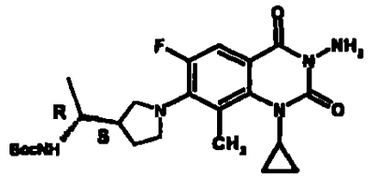
0,81 g (8,0 mmol) de trietilamina y 10 ml de sulfóxido de dimetilo se calienta a 110°C durante 4 horas. La mezcla de la reacción se enfría a temperatura ambiente, se vierte en 150 ml de hielo y agua, y se extrae con acetato de etilo (2 x 125 ml). Las capas orgánicas combinadas se lavan con agua, se secan ($MgSO_4$), se filtran y se evaporan en vacío para dar 1,08 g de producto crudo. La cromatografía sobre gel de sílice en grado rápido (230-400 malla) eluyendo con diclorometano/etanol (9:1) proporciona 0,9 g del compuesto del título, punto de fusión 87°C-89°C.

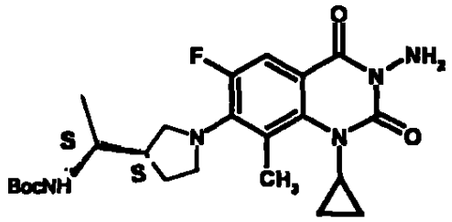
(c) Síntesis del terc-butil éster del ácido [(R)-1-[(S)-1-(3-amino-1-ciclopropil-6-fluoro-8-metil-2,4-dioxo-1,2,3,4-tetrahidro-quinazolin-7-il)-pirrolidin-3-il]-etil)-carbámico



Una solución de 0,5 g (1,9 mmol) de 3-amino-1-ciclopropil-6,7-difluoro-8-metil-1H-quinazolin-2,4-diona (Ejemplo 24e), 0,64 g (3,0 mmol) de terc-butil éster del ácido ((S)-(R)-1-pirrolidin-3-iletil)carbámico, 0,81 g (8,0 mmol) de trietilamina y 10 ml de sulfóxido de dimetilo se calienta a

110°C durante 4 horas. Después de que la cromatografía de capa delgada muestra una reacción incompleta, se agregan 0,43 g (2,0 mmol) adicionales de derivado de pirrolidina y 0,81 g (8,0 mmol) trietilamina y la reacción se calienta a 120°C durante 18 horas. La mezcla de la reacción se enfría a temperatura ambiente, se vierte en 200 ml de hielo y agua, y se extrae con acetato de etilo (2 x 125 ml). Las capas orgánicas combinadas se lavan con agua, se secan ($MgSO_4$), se filtran y se evaporan en vacío para dar 1,1 g de producto crudo. La cromatografía sobre gel de sílice en grado rápido (230-400 malla) eluyendo con acetato de etilo proporciona 0,4 g del compuesto del título, punto de fusión 86°C-88°C.

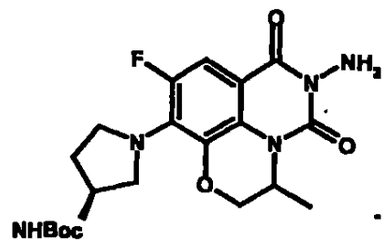
(d) Síntesis del terc-butil éster del ácido {(S)-1-[(S)-1-(3-amino-1-ciclopropil-6-fluoro-8-metil-2,4-dioxo-1,2,3,4-tetrahidroquinazolin-7-il)pirrolidin-3-il]etil}-carbámico



Una solución de 0,5 g (1,9 mmol) de 3-amino-1-ciclopropil-6,7-difluoro-8-metil-1H-quinazolin-2,4-diona (Ejemplo 24e), 0,64 g (3,0 mmol) de terc-butil éster del ácido ((S)-(S)-1-pirrolidin-3-iletil)carbámico, 0,81 g (8,0 mmol) de

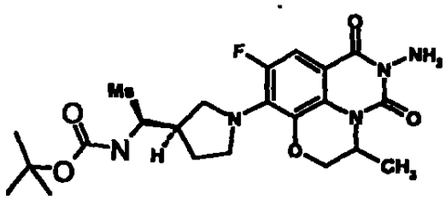
trietilamina y 10 ml de sulfóxido de dimetilo se calienta a 110°C durante 4 horas. Después de que la cromatografía de capa delgada muestra una reacción incompleta, se agregan 0,43 g (2,0 mmol) adicionales de derivado de pirrolidina y 0,81 g (8,0 mmol) de trietilamina y la reacción se calienta a 120°c durante 18 horas. La mezcla de la reacción se enfría a temperatura ambiente, se vierte en 200 ml de hielo y agua, y se extrae con acetato de etilo (2 x 125 ml). Las capas orgánicas combinadas se lavan con agua, se secan ($MgSO_4$), se filtran y se evaporan en vacío para dar 1,3 g de producto crudo. La cromatografía sobre gel de sílice en grado rápido (230-400 malla) eluyendo con 400 ml diclorometano/acetato de etilo (8:2), 600 ml de (6:4) y 1 L de (4:6) proporciona 0,46 g del compuesto del título, punto de fusión 84°C-86°C.

(e) Síntesis del terc-butil éster del ácido [(S)-1-(5-amino-8-fluoro-3-metil-4,6-dioxo-2,3,5,6-tetrahidro-4H-1-oxa-3a,5-diazafenalen-9-il)pirrolidin-3-il]carbámico



Una solución de 0,2 g (0,75 mmol) de 5-amino-8,9-difluoro-3-metil-2,3-dihidro-1-oxa-3a,5-diazafenalen-4,6-diona (Ejemplo 24h), 0,58 g (2,0 mmol) de terc-butil éster del ácido (S)-3-pirrolidinilcarbámico (*J. Med. Chem.*, 1992;35:1764), 0,5 g (0,5 mmol) de trietilamina y 20 ml de acetonitrilo se calienta a reflujo durante 18 horas. El solvente se remueve en vacío y el residuo se particiona entre diclorometano-agua. La capa orgánica se lava con agua, se seca ($MgSO_4$), y se concentra en vacío. El residuo es sometido a cromatografía sobre gel de sílice en grado rápido (230-400 malla) eluyendo con diclorometano/etanol (95:5) para dar 0,34 g del compuesto del título, punto de fusión 114°C-116°C.

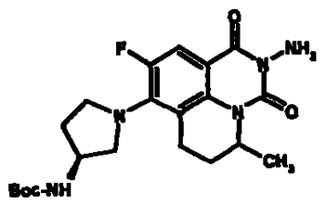
(f) terc-Butil éster del ácido {(S)-1-[(R)-1-(5-amino-3-metil-4,6-dioxo-2,3,5,6-tetrahidro-4H-1-oxa-3a,5-diazafenalen-9-il)pirrolidin-3-il]etil}carbámico



Una solución de 0,11 g (0,41 mmol) de 5-amino-8,9-difluoro-3-metil-2,3-dihidro-1-oxa-3a,5-diazafenalen-4,6-diona (Ejemplo 24h), 0,26 g (1,3 mmol) de terc-butil éster del ácido ((R)-(S)-1-pirrolidin-3-iletil)carbámico (*J. Het. Chem.*,

1992;29:1481), 0,25 g (2,5 mmol) de trietilamina y 10 ml de acetonitrilo se calienta a reflujo durante 18 horas. El solvente se remueve en vacío y el residuo se particiona entre acetato de etilo/agua. La capa orgánica se lava con agua, se seca ($MgSO_4$), y se concentra en vacío. El residuo es sometido a cromatografía sobre gel de sílice en grado rápido (230-400 malla) eluyendo con diclorometano/etanol (95:5) para dar 0,14 g del compuesto del título, ^1H NMR (400 MHz, $CDCl_3$): δ 7,43 (d, 1H), 5,24 (bs, 2H), 4,82 (m, 1H), 4,56 (m, 1H), 4,33 (d, 1H), 3,99 (m, 1H), 3,86 (m, 1H), 3,73 (m, 1H), 3,59 (m, 2H), 2,18 (m, 1H), 3,01 (m, 1H), 1,67 (m, 1H), 1,44 (s, 9H), 1,40 (m, 3H), 1,25 (m, 1H) 1,20 (d, 3H).

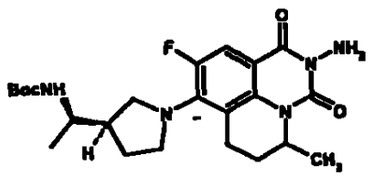
(g) terc-Butil éster del ácido [(S)-1-(2-amino-9-fluoro-5-metil-1,3-dioxo-2,3,6,7-tetrahidro-1H,5H-pirido[3,2,1-ij]quinazolin-8-il)pirrolidin-3-il]-carbámico



Una solución de 0,12 g (0,45 mmol) de 5-amino-8,9-difluoro-5-metil-6,7-dihidro-5H-pirido[3,2,1-ij]quinazolin-1,3-diona (Ejemplo 24i), 0,34 g (1,8 mmol) de terc-butil éster del ácido (S)-3-pirrolidinilcarbámico (*J. Med. Chem.*, 1992;35:1764), 0,2

g (2,0 mmol) de trietilamina y 7 ml de sulfóxido de dimetilo se calienta a 110°C durante 18 horas. La reacción se enfría a temperatura ambiente, se diluye con 80 ml de hielo y agua y se agita a 5°C durante 1 hora. El precipitado resultante se remueve mediante filtración, se lava con agua y se seca en vacío. El sólido es sometido a cromatografía sobre gel de sílice en grado rápido (230-400 malla) eluyendo con diclorometano/etanol (9:1) para dar 0,14 g del compuesto del título, punto de fusión 98°C-100°C.

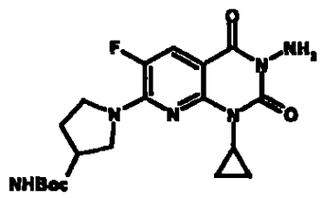
(h) terc-Butil éster del ácido ((R)-3-[(S)-1-(2-amino-9-fluoro-5-metil-1,3-dioxo-2,3,6,7-tetrahidro-1H,5H-pirido[3,2,1-ij]quinazolin-8-il)pirrolidin-3-il]etilcarbámico



Una solución de 0,12 g (0,45 mmol) de 5-amino-8,9-difluoro-5-metil-6,7-dihidro-5H-pirido[3,2,1-ij]quinazolin-1,3-diona (Ejemplo 24i), 0,39 g (1,8 mmol) de terc-butil éster del ácido ((R)-(S)-1-pirrolidin-3-iletil)carbámico (*J. Het. Chem.*, 1992;29:1481), en 5 ml de sulfóxido de dimetilo se calienta a 110°C durante 18 horas. La reacción se enfría a temperatura ambiente, se diluye con 80 ml de hielo y agua y se agita a 5°C

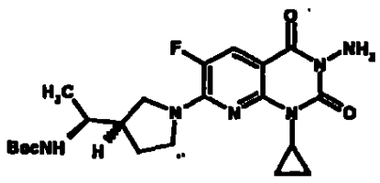
durante 1 hora. El precipitado resultante se remueve mediante filtración, se lava con agua y se seca en vacío. El sólido es sometido a cromatografía sobre gel de sílice en grado rápido (230-400 malla) eluyendo con diclorometano/etanol (9:1) para dar 0,13 g del compuesto del título, punto de fusión 93°C-95°C.

(i) terc-Butil éster del ácido [1-(3-amino-1-ciclopropil-6-fluoro-2,4-dioxo-1,2,3,4-tetrahidro-pirido[2,3-d]pirimidin-7-il)pirrolidin-3-il]carbámico



Una solución de 0,11 g (0,4 mmol) de 3-amino-7-cloro-1-ciclopropil-6-fluoro-1H-pirido[2,3-d]pirimidin-2,4-diona (Ejemplo 24b), 0,105 g (0,56 mmol) de terc-butil éster del ácido (S)-3-pirrolidinilcarbámico (*J. Med. Chem.*, 1992;35:1764), 1,2 ml de N,N-diisopropiletilamina y 3 ml de acetonitrilo se calienta a 50°C durante 18 horas. La mezcla de la reacción se diluye con 9 ml de agua y se enfría a 0°C y el sólido se remueve mediante filtración, se lava con 50% de acetonitrilo acuoso y se seca en vacío para dar 0,14 g del compuesto del título, punto de fusión 108°C-110°C.

(j) terc-Butil éster del ácido {(S)-1-[(R)-1-(3-amino-1-ciclopropil-6-fluoro-1,2,3,4-tetrahidropirido[2,3-d]pirimidin-7-il)pirrolidin-3-il]etil}-carbámico



Una solución de 0,12 g (0,38 mmol) de ácido 3-amino-1-ciclopropil-6-fluoro-2,4-dioxo-1,2,3,4-tetrahidro-pirido[2,3-d]pirimidin-7-tiosulfónico (Ejemplo 24c), en 10 ml de acetonitrilo se trata con 0,24 g (1,14 mmol) de terc-butil éster del ácido ((R)-(S)-1-pirrolidin-3-iletil)carbámico (*J. Het. Chem.*, 1992;29:1481), 0,25 g (2,5 mmol) de trietilamina y se agita a temperatura ambiente durante 18 horas, luego a 50°C durante 1 hora. El solvente se remueve en vacío y el residuo se particiona entre acetato de etilo (50 ml) y agua (25 ml). La capa orgánica se lava con agua, se seca ($MgSO_4$), se filtra y se evapora en vacío para dar 0,28 g. La cromatografía de columna (2 x 12 cm) de gel de sílice en grado rápido (230-400 malla) eluyendo con diclorometano/etanol (95:5) proporciona 0,1 g del compuesto del título, punto de fusión 175°C-177°C.

Procedimiento General A

Una solución del Ejemplo 24, 1-2,5 eq. de la cadena lateral de amina heterocíclica y 3-3,5 eq. de 1,8-diazabiciclo-5,4,0-undecen-7-eno (DBU) o trietilamina se agita en sulfóxido de dimetilo (1 ml) a 130°C durante 48 horas. Después de enfriar a temperatura ambiente, la mezcla de la reacción se diluye con acetato de etilo y se lava con $NaHCO_3$ saturado, agua y solución salina. La capa orgánica se seca sobre $MgSO_4$, se filtra y el filtrado se concentra. El residuo resultante se purifica mediante cromatografía de columna rápida (isopropanol/diclorometano) para lograr el producto.

Procedimiento General B

Una solución del Ejemplo 24 y la cadena lateral de diamina heterocíclica (1,5-3,0 eq.) se agita en sulfóxido de dimetilo a 130°C durante 3 horas. Después de enfriar a temperatura ambiente, la mezcla de la reacción se diluye con acetato de etilo y se lava con $NaHCO_3$ saturado, agua y solución salina. La capa orgánica se seca sobre $MgSO_4$, se filtra y el filtrado se concentra. El residuo resultante se disuelve nuevamente en diclorometano y mientras se agita, se agrega di-terc-butil dicarbonato (0,41 g, 1,87 mmol). Después de 1 hora, la mezcla de la reacción se concentra y el producto se purifica mediante cromatografía de columna rápida (EtOAc/hexanos 1:1) para lograr el producto.

Procedimiento General C

Una solución del Ejemplo 24, la cadena lateral de diamina heterocíclica (1,5-3,0 eq.) y tetrametil guanidina (1-5,0 eq.) se agita en sulfóxido de dimetilo a 80°C-130°C durante 36 a 24 horas. Después de enfriar a temperatura ambiente, la mezcla de la reacción se diluye con agua y NH_4Cl. El sólido se lava con agua y se seca para dar el producto crudo. El producto se purifica mediante cromatografía de columna rápida (SiO_2) usando ($CHCl_3$/MeOH o acetato de etilo/hexanos) para lograr el producto.

Los siguientes compuestos se sintetizan de acuerdo con los Procedimientos Generales A, B, y C del Ejemplo 28:

(k) terc-Butil éster del ácido {1-[(R)-1-((S)-3-amino-1-ciclopropil-6-fluoro-8-metil-2,4-dioxo-1,2,3,4-tetrahidroquinazolin-7-il)pirrolidin-3-il]etil}carbámico (MS ES: m/z 462 (MH^+)) desde 3-amino-1-ciclopropil-6,7-difluoro-8-metil-1H-quinazolin-2,4-diona (Ejemplo 24e) y terc-butil éster del ácido (R)-((S)-1-pirrolidin-3-il)etilcarbámico (Kimura Y., Atarashi S., Takahashi M., Hayakkawa I., *Chem. Pharm. Bull.*, 1994;42:1442) usando el Método General A.

(l) terc-Butil éster del ácido {1-[(S)-1-(3-amino-1-ciclopropil-6-fluoro-8-metil-2,4-dioxo-1,2,3,4-tetrahidroquinazolin-7-il)pirrolidin-3-il]-1-metiletil}carbámico (MS ES: m/z 476 (MH^+)) desde 3-amino-1-ciclopropil-6,7-difluoro-8-metil-1H-quinazolin-2,4-diona (Ejemplo 24e) y terc-butil éster del ácido [(S)-(pirrolidin-3-il)-1-metiletil]carbámico usando el Método General A.

(m) terc-Butil éster del ácido {1-[1-(3-amino-1-ciclopropil-6-fluoro-8-metil-2,4-dioxo-1,2,3,4-tetrahidroquinazolin-7-il)-3-metoxipirrolidin-3-il]etil}carbámico (MS ES: m/z 492 (MH^+)) desde 3-amino-1-ciclopropil-6,7-difluoro-8-metil-1H-quinazolin-2,4-diona (Ejemplo 24e) y terc-butil éster del ácido [1-(3-metoxipirrolidin-3-il)etil]carbámico (Ejemplo A5b) usando el Método General A.

(n) terc-Butil éster del ácido [3-(3-amino-1-ciclopropil-6-fluoro-8-metil-2,4-dioxo-1,2,3,4-tetrahidroquinazolin-7-il)-3-azabiciclo[3.1.0]hex-6-il]carbámico (MS ES: m/z 446 (MH^+)) desde 3-amino-1-ciclopropil-6,7-difluoro-8-metil-1H-quinazolin-2,4-diona (Ejemplo 24e) y terc-butil éster del ácido 3-azabiciclo[3.1.0]hex-6-ilcarbámico (Brighty K.E., 1991, EP 413455) usando el Método General A.

(o) terc-Butil éster del ácido {1-[1-(3-amino-1-ciclopropil-6-fluoro-8-metoxi-2,4-dioxo-1,2,3,4-tetrahidroquinazolin-7-il)-3-fluoropirrolidin-3-il]etil}carbámico (MS ES: m/z 496 (MH^+)) desde 3-amino-1-ciclopropil-6,7-difluoro-8-metoxi-1H-quinazolin-2,4-diona (Ejemplo 24d) y terc-butil éster del ácido (4-fluoropirrolidin-3-il)etilcarbámico (Ejemplo A5c) usando el Método General A.

(p) terc-Butil éster del ácido [1-(3-amino-1-ciclopropil-6-fluoro-5-metil-2,4-dioxo-1,2,3,4-tetrahidroquinazolin-7-il)pirrolidin-3-il]carbámico (MS ES: m/z 434 (MH^+)) desde 3-amino-1-ciclopropil-6,7-difluoro-5-metil-1H-quinazolin-2,4-diona (Ejemplo 24f) y terc-butil éster del ácido (pirrolidin-3-il)carbámico usando el Método General A.

(q) terc-Butil éster del ácido {1-(R)-[1-(S)-(3-amino-1-ciclopropil-6-fluoro-5-metil-2,4-dioxo-1,2,3,4-tetrahidroquinazolin-7-il)pirrolidin-3-il]etil}carbámico (MS ES: m/z 462 (MH^+)) desde 3-amino-1-ciclopropil-6,7-difluoro-5-metil-1H-quinazolin-2,4-diona (Ejemplo 24f) y ((R)-((S)-1-pirrolidin-3-il-etil)amina usando el Método General A.

(r) terc-Butil éster del ácido [1-(3-amino-1-ciclopropil-6-fluoro-8-metil-2,4-dioxo-1,2,3,4-tetrahidroquinazolin-7-il)-3-metoximetilpirrolidin-3-ilmetil]carbámico (MS ES: m/z 493

(MH^+)) desde 3-amino-1-ciclopropil-6,7-difluoro-8-metil-1H-quinazolin-2,4-diona (Ejemplo 24e) y terc-butil éster del ácido (3-metoximetilpirrolidin-3-ilmetil)carbámico (Ejemplo A5d) usando el Método General A.

(s) terc-Butil éster del ácido [1-(3-amino-1-ciclopropil-6-fluoro-8-metil-2,4-dioxo-1,2,3,4-tetrahidroquinazolin-7-il)-3-fluorometilpirrolidin-3-ilmetil]carbámico (^1H NMR (200 MHz, $CDCl_3$): δ 7,60 (d, 1H), 5,18 (bs, 2H), 4,97 (bs, 1H), 4,61-4,10 (m, 4H), 3,72-3,19 (m, 5H), 2,46 (s, 3H), 2,00-1,71 (m, 2H), 1,45 (s, 9H), 1,21-1,10 (m, 2H), 0,68-0,56 (m, 2H)) desde 3-amino-1-ciclopropil-6,7-difluoro-8-metil-1H-quinazolin-2,4-diona (Ejemplo 24e) y terc-butil éster del ácido 1-(3-fluorometilpirrolidin-3-ilmetil)carbámico (Li Q., Wang W., Berst K.B., Clairborne A., Hasvold L., Raye K., Tufano M., et al, *Bioorg. Med. Chem. Lett.*, 1998;8:1953-1958) usando el Método General A.

(t) terc-Butil éster del ácido [trans-(3-amino-1-ciclopropil-6-fluoro-8-metoxi-2,4-dioxo-1,2,3,4-tetrahidroquinazolin-7-il)-4-trifluorometilpirrolidin-3-ilmetil]carbámico (^1H NMR (200 MHz, $CDCl_3$): δ 7,56 (d, 1H), 5,17 (bs, 2H), 4,75 (bs, 1H), 3,97-3,68 (m, 3H), 3,57 (s, 3H), 3,51-3,13 (m, 4H), 2,98-2,60 (m, 2H), 1,45 (s, 9H), 1,20-1,08 (m, 2H), 0,71-0,55 (m, 2H))

desde 3-amino-1-ciclopropil-6,7-difluoro-8-metoxi-1H-quinazolin-2,4-diona (Ejemplo 24d) y terc-butil éster del ácido [trans-(4-trifluorometilpirrolidin-3-ilmetil)carbámico (Li Q., Wang W., Berst K.B., Clairborne A., Hasvold L., Raye K., Tufano M., et al, *Bioorg. Med. Chem. Lett.*, 1998;8:1953-1958) usando el Método General A.

(u) terc-Butil éster del ácido {1-[1-(3-amino-1-ciclopropil-6-fluoro-8-metoxi-2,4-dioxo-1,2,3,4-tetrahidroquinazolin-7-il)-piperidin-3-il]etil}carbámico (MS (ES, M+1)m/z 492 (MH^+)) desde 3-amino-1-ciclopropil-6,7-difluoro-8-metoxi-1H-quinazolin-2,4-diona (Ejemplo 24d) y terc-butil éster del ácido (1-piperidin-3-iletil)carbámico (Ejemplo A5e) usando el Método General A.

(v) terc-Butil éster del ácido {1-[1-(3-amino-1-ciclopropil-6-fluoro-8-metil-2,4-dioxo-1,2,3,4-tetrahidroquinazolin-7-il)piperidin-3-il]etil}carbámico (MS ES: m/z 476 (MH^+)) desde 3-amino-1-ciclopropil-6,7-difluoro-8-metil-1H-quinazolin-2,4-diona (Ejemplo 24e) y terc-butil éster del ácido (1-piperidin-3-il)etilcarbámico (Ejemplo A5e) usando el Método General A.

(w) terc-Butil éster del ácido {1-[1-(3-amino-1-ciclopropil-6-fluoro-8-metoxi-2,4-dioxo-1,2,3,4-tetrahidroquinazolin-7-il)-4,4-dimetilpirrolidin-3-il]etil}carbámico (MS ES: m/z 506 (MH^+)) desde 3-amino-1-ciclopropil-6,7-difluoro-8-metoxi-1H-

quinazolin-2,4-diona (Ejemplo 24d) y terc-butil éster del ácido [1-(4,4-dimetilpirrolidin-3-il)etil]carbámico (Ejemplo A5f) usando el Método General A.

(x) terc-Butil éster del ácido {1-[1-(3-amino-1-ciclopropil-6-fluoro-8-metil-2,4-dioxo-1,2,3,4-tetrahidroquinazolin-7-il)-4,4-dimetilpirrolidin-3-il]etil}carbámico (MS ES: m/z 490 (MH^+)) desde 3-amino-1-ciclopropil-6,7-difluoro-8-metil-1H-quinazolin-2,4-diona (Ejemplo 24e) y terc-butil éster del ácido [1-(4,4-dimetilpirrolidin-3-il)etil]carbámico (Ejemplo A5f) usando el Método General A.

(y) terc-Butil éster del ácido {1-[1-(3-amino-1-ciclopropil-6-fluoro-8-metil-2,4-dioxo-1,2,3,4-tetrahidroquinazolin-7-il)-4-metilpirrolidin-3-il]etil}carbámico (MS ES: m/z 476 (MH^+)) desde 3-amino-1-ciclopropil-6,7-difluoro-8-metil-1H-quinazolin-2,4-diona (Ejemplo 24e) y terc-butil éster del ácido [1-(4-metilpirrolidin-3-il)etil]carbámico (Ejemplo A5g) usando el Método General A.

(z) terc-Butil éster del ácido [1-(3-amino-1-ciclopropil-6-fluoro-8-metil-2,4-dioxo-1,2,3,4-tetrahidroquinazolin-7-il)-3-fenilpirrolidin-3-il]carbámico (^1H NMR (200 MHz, $CDCl_3$): δ 7,61 (d, 1H), 7,50-7,12 (m, 5H), 5,19 (bs, 2H), 4,07-3,70 (m, 3H), 3,62-3,34 (m, 2H), 2,68-2,52 (m, 1H), 2,45 (s, 3H), 1,68 (m,

2H), 1,50-0,95 (m, 11H), 0,62 (m, 2H)) desde 3-amino-1-ciclopropil-6,7-difluoro-8-metil-1H-quinazolin-2,4-diona (Ejemplo 24e) y terc-butil éster del ácido (3-fenilpirrolidin-3-il)carbámico (Ejemplo A30) usando el Método General A.

(aa) terc-Butil éster del ácido [1-(3-amino-1-ciclopropil-6-fluoro-8-metil-2,4-dioxo-1,2,3,4-tetrahidroquinazolin-7-il)-3-fenilpirrolidin-3-ilmetil]carbámico (^{1}H NMR (200 MHz, $CDCl_3$): δ 7,68 (d, 1H), 7,50-7,29 (m, 5H), 6,72 (s, 1H), 5,24 (s, 2H), 4,18-3,85 (m, 3H), 3,78-3,52 (m, 2H), 2,70 (s, 1H), 2,58-2,39 (m, 4H), 1,62-0,62 (m, 15H)) desde 3-amino-1-ciclopropil-6,7-difluoro-8-metil-1H-quinazolin-2,4-diona (Ejemplo 24e) y terc-butil éster del ácido (3-fenilpirrolidin-3-ilmetil)carbámico (Ejemplo A5p) usando el Método General A.

(bb) terc-Butil éster del ácido [5-(3-amino-1-ciclopropil-6-fluoro-8-metil-2,4-dioxo-1,2,3,4-tetrahidroquinazolin-7-il)-5-azaespiro[2.4]hept-7-ilmetil]carbámico (MS ES: m/z 474 (MH^+)) desde 3-amino-1-ciclopropil-6,7-difluoro-8-metil-1H-quinazolin-2,4-diona (Ejemplo 24e) y terc-butil éster del ácido (5-azaespiro[2,4]hept-7-ilmetil)carbámico (Ejemplo A5h) usando el Método General A.

(cc) terc-Butil éster del ácido [5-(3-amino-1-ciclopropil-6-fluoro-8-metoxi-2,4-dioxo-1,2,3,4-tetrahidroquinazolin-7-il)-

5-azaespiro[2.4]hept-7-ilmetil]carbámico (MS ES: m/z 490 (MH^+)) desde 3-amino-1-ciclopropil-6,7-difluoro-8-metoxi-1H-quinazolin-2,4-diona (Ejemplo 24e) y terc-butil éster del ácido (5-azaespiro[2,4]hept-7-ilmetil)carbámico (Ejemplo A5h) usando el Método General A.

(dd) terc-Butil éster del ácido [1-(3-amino-1-ciclopropil-6-fluoro-8-metoxi-2,4-dioxo-1,2,3,4-tetrahidroquinazolin-7-il)-3-hidroxipirrolidin-3-ilmetil]carbámico (MS ES: m/z 480 (MH^+)) desde 3-amino-1-ciclopropil-6,7-difluoro-8-metoxi-1H-quinazolin-2,4-diona (Ejemplo 24d) y terc-butil éster del ácido (3-hidroxipirrolidin-3-ilmetil)carbámico (Ejemplo A5i) usando el Método General A.

(ee) terc-Butil éster del ácido [1-(3-amino-1-ciclopropil-6-fluoro-8-metil-2,4-dioxo-1,2,3,4-tetrahidroquinazolin-7-il)piperidin-3-ilmetil]carbámico (REF) (MS ES: m/z 462 (MH^+)) desde 3-amino-1-ciclopropil-6,7-difluoro-8-metil-1H-quinazolin-2,4-diona (Ejemplo 24e) y terc-butil éster del ácido (piperidin-3-ilmetil)carbámico (Hilpert K., Ackermann J., Banner D.W., Gast A., Gubernator K., Hadvary P., Labler L. et al, *J. Med. Chem.*, 1994;37[23]:3889-3901) usando el Método General A.

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(ff) terc-Butil éster del ácido [1-(3-amino-1-ciclopropil-6-fluoro-8-metil-2,4-dioxo-1,2,3,4-tetrahidroquinazolin-7-il)-4-metoxipirrolidin-3-il]carbámico (^{1}H NMR (200 MHz, $CDCl_3$): δ 7,60-7,54 (d, 1H), 5,16 (s, 2H), 4,82 (s, 1H), 4,20-3,85 (m, 5H), 3,42 (s, 3H), 3,23 (t, 2H), 2,41 (s, 3H), 1,47 (s, 9H), 1,18-1,10 (m, 2H), 0,61 (s, 2H)) desde 3-amino-1-ciclopropil-6,7-difluoro-8-metil-1H-quinazolin-2,4-diona (Ejemplo 24e) y terc-butil éster del ácido 4-(metoxipirrolidin-3-il)carbámico (Li Q., Cooper C.S., Anthony K.L., Lee C.M., Plattner J.J., Ma Z., Wang W., 1996, WO 9639407) usando el Método General A.

(gg) terc-Butil éster del ácido [1-(3-amino-1-ciclopropil-6-fluoro-8-metoxi-2,4-dioxo-1,2,3,4-tetrahidroquinazolin-7-il)-4-metoxipirrolidin-3-il]carbámico (^{1}H NMR (200 MHz, $CDCl_3$): δ 7,21 (d, 1H), 5,23-5,14 (m, 3H), 4,33-3,22 (m, 13H), 1,40 (s, 9H), 1,18 (m, 2H), 0,60 (s, 2H)) desde 3-amino-1-ciclopropil-6,7-difluoro-8-metoxi-1H-quinazolin-2,4-diona (Ejemplo 24d) y terc-butil éster del ácido 4-(metoxipirrolidin-3-il)carbámico (Li Q., Cooper C.S., Anthony K.L., Lee C.M., Plattner J.J., Ma Z., Wang W., 1996, WO 9639407) usando el Método General A.

(hh) terc-Butil éster del ácido [1-(3-amino-1-ciclopropil-6-fluoro-8-metoxi-2,4-dioxo-1,2,3,4-tetrahidroquinazolin-7-il)-4-fluoropirrolidin-3-il]carbámico (^{1}H NMR (200 MHz, $CDCl_3$): δ

7,40-7,34 (d, 1H), 5,30-4,80 (m, 3H), 4,50-3,10 (m, 10H), 1,47 (s, 9H), 1,30-0,50 (m, 4H)) desde 3-amino-1-ciclopropil-6,7-difluoro-8-metoxi-1H-quinazolin-2,4-diona (Ejemplo 24d) y terc-butil éster del ácido 4-(fluoropirrolidin-3-il)carbámico (Li Q., Wang W., Berst K.B., Clairborne A., Hasvold L., Raye K., Tufano M., et al, *Bioorg. Chem. & Med. Chem. Lett.*, 1998;8:1953-1958) usando el Método General A.

(ii) terc-Butil éster del ácido [1-(3-amino-1-ciclopropil-6-fluoro-8-metil-2,4-dioxo-1,2,3,4-tetrahidroquinazolin-7-il)-3-metilpirrolidin-3-ilmetil]carbámico (MS ES: m/z 462 (MH^+)) desde 3-amino-1-ciclopropil-6,7-difluoro-8-metil-1H-quinazolin-2,4-diona (Ejemplo 24e) y terc-butil éster del ácido (3-metilpirrolidin-3-ilmetil)carbámico (*J. Med. Chem.*, 1992:361-367) usando el Método General A.

(jj) terc-Butil éster del ácido {(S)-1-[(R)-1-(3-amino-1-ciclopropil-8-etil-6-fluoro-2,4-dioxo-1,2,3,4-tetrahidroquinazolin-7-il)pirrolidin-3-il]etil}carbámico (MS ES: m/z 476 (MH^+)) desde 3-amino-1-ciclopropil-8-etil-6,7-difluoro-1H-quinazolin-2,4-diona (Ejemplo 24g) y terc-butil éster del ácido ((R)-[(R)-1-pirrolidin-3-il-etil)etil]carbámico usando el Método General A.

(kk) terc-Butil éster del ácido 1-(3-amino-1-ciclopropil-6-fluoro-8-metoxi-2,4-dioxo-1,2,3,4-tetrahidroquinazolin-7-il)-pirrolidin-3-carboxílico (^{1}H NMR (200 MHz, $CDCl_3$): δ 7,51 (d, 1H), 5,15 (s, 2H), 3,88-3,58 (m, 4H); 3,50 (s, 3H), 3,42-3,30 (m, 1H), 3,14-3,02 (m, 1H), 2,25-2,17 (m, 2H), 1,48 (s, 9H), 1,14-1,05 (m, 2H), 0,68-0,61 (m, 2H)) desde 3-amino-1-ciclopropil-6,7-difluoro-8-metoxi-1H-quinazolin-2,4-diona (Ejemplo 24d) y terc-butil éster del ácido pirrolidin-3-carboxílico (Hayakawa I., Tanaka Y., EP 101829) usando el Método General A.

(ll) terc-Butil éster del ácido 1-(3-amino-1-ciclopropil-6-fluoro-8-metil-2,4-dioxo-1,2,3,4-tetrahidroquinazolin-7-il)-pirrolidin-3-carboxílico (^{1}H NMR (200 MHz, $CDCl_3$): δ 7,61 (d, 1H), 5,16 (s, 2H), 3,70-3,40 (m, 5H), 3,17-3,03 (m, 1H), 2,43 (s, 3H), 2,29-2,19 (m, 2H), 1,47 (s, 9H), 1,22-1,12 (m, 2H), 0,67-0,57 (m, 2H)) desde 3-amino-1-ciclopropil-6,7-difluoro-8-metil-1H-quinazolin-2,4-diona (Ejemplo 24e) y terc-butil éster del ácido pirrolidin-3-carboxílico (Hayakawa I., Tanaka Y., EP 101829) usando el Método General A.

(mm) terc-Butil éster del ácido [3-(3-amino-1-ciclopropil-6-fluoro-8-metoxi-2,4-dioxo-1,2,3,4-tetrahidroquinazolin-7-il)-3-azabiciclo[3.1.0]hex-1-ilmetil]carbámico (^{1}H NMR (200 MHz,

$CDCl_3$): δ 7,53 (d, 1H), 5,31 (bs, 2H), 4,73 (bs, 1H), 3,82-3,01 (m, 11H), 1,45 (s, 9H), 1,42-1,34 (m, 1H), 1,14-1,10 (m, 3H), 0,71-0,63 (m, 2H)) desde 3-amino-1-ciclopropil-6,7-difluoro-8-metoxi-1H-quinazolin-2,4-diona (Ejemplo 24d) y terc-butil éster del ácido (3-azabiciclo[3.1.0]hex-1-ilmetil)carbámico (Ejemplo A5j) usando el Método General A.

(nn) terc-Butil éster del ácido [3-(3-amino-1-ciclopropil-6-fluoro-8-metil-2,4-dioxo-1,2,3,4-tetrahidroquinazolin-7-il)-3-azabiciclo[3.1.0]hex-1-ilmetil]carbámico (MS ES: m/z 460 (MH^+)) desde 3-amino-1-ciclopropil-6,7-difluoro-8-metil-1H-quinazolin-2,4-diona (Ejemplo 24e) y terc-butil éster del ácido (3-azabiciclo[3.1.0]hex-1-ilmetil)carbámico (Ejemplo A5j) usando el Método General A.

(oo) terc-Butil éster del ácido {(R)-1-[(S)-1-(3-amino-1-ciclopropil-6-fluoro-8-metoxi-2,4-dioxo-1,2,3,4-tetrahidroquinazolin-7-il)pirrolidin-3-il]etil}carbámico (MS ES: m/z 478 (MH^+)) desde 3-amino-1-ciclopropil-6,7-difluoro-8-metoxi-1H-quinazolin-2,4-diona (Ejemplo 24d) y terc-butil éster del ácido (R)-1-((S)-1-pirrolidin-3-il)etil)carbámico (Schroeder M.C., Kiely J.S., Johnson D.R., Szotek D.L., Domagala J.M., Stickney T.M., Kampf J.W., *J. Heterocyclic Chem.*, 1992:29:1481) usando el Método General A.

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(pp) terc-Butil éster del ácido {(R)-1-[(S)-1-(3-amino-1-ciclopropil-6-fluoro-8-metoxi-2,4-dioxo-1,2,3,4-tetrahidroquinazolin-7-il)pirrolidin-3-il]etil}carbámico (^{1}H NMR (200 MHz, $CDCl_3$): δ 7,51-7,44 (d, 1H), 5,17 (bs, 2H), 4,62 (bs, 0,5H), 4,58 (bs, 0,5H), 3,79-3,74 (m, 3H), 3,61-3,53 (m, 2H), 3,49 (s, 3H), 3,41-3,32 (m, 1H), 2,22-2,06 (m, 2H), 1,87-1,67 (m, 1H), 1,46 (s, 9H), 1,23-1,19 (d, 3H), 1,08-1,02 (m, 2H), 0,76-0,62 (m, 2H)). (MS ES: m/z 462) desde 3-amino-1-ciclopropil-6,7-difluoro-8-metoxi-1H-quinazolin-2,4-diona (Ejemplo 24d) y terc-butil éster del ácido (R)-1-((S)-1-pirrolidin-3-il)etil)carbámico usando el Método General A.

(qq) terc-Butil éster del ácido 6-(3-amino-1-ciclopropil-6-fluoro-8-metil-2,4-dioxo-1,2,3,4-tetrahidroquinazolin-7-il)-octahidropirrolo[3,4-b]piridin-1-carboxílico (^{1}H NMR (200 MHz, $CDCl_3$): δ 7,61-7,55 (d, 1H), 5,16 (bs, 2H), 4,52 (bs, 0,5H), 4,48 (bs, 0,5H), 4,95-3,38 (m, 6H), 2,40 (s, 3H), 2,36-1,83 (m, 3H), 1,46 (s, 9H), 1,21-1,17 (m, 5H), 0,65-0,57 (m, 2H)) desde 3-amino-1-ciclopropil-6,7-difluoro-8-metil-1H-quinazolin-2,4-diona (Ejemplo 24e) y terc-butil éster del ácido octahidropirrolo[3,4-b]piridin-3-carboxílico usando el Método General A.

(rr) terc-Butil éster del ácido [(trans)-1-(3-amino-1-ciclopropil-6-fluoro-8-metoxi-2,4-dioxo-1,2,3,4-tetrahidroquinazolin-7-il)-4-metilpirrolidin-3-ilmetil]carbámico (MS ES: m/z 478 (MH^+)) desde 3-amino-1-ciclopropil-6,7-difluoro-8-metoxi-1H-quinazolin-2,4-diona (Ejemplo 24d) y terc-butil éster del ácido (trans-4-metilpirrolidin-3-ilmetil)carbámico (Kuniyoshi M., Seigo S., Keiji H., Takayoshi I., Solicitud de Patente Europea EP 208210, 1987) usando el Método General A.

(ss) terc-Butil éster del ácido [1-(3-amino-1-ciclopropil-6-fluoro-8-metil-2,4-dioxo-1,2,3,4-tetrahidroquinazolin-7-il)-4-metilpirrolidin-3-ilmetil]carbámico (MS ES: m/z 462 (MH^+)) desde 3-amino-1-ciclopropil-6,7-difluoro-8-metil-1H-quinazolin-2,4-diona (Ejemplo 24e) y terc-butil éster del ácido (4-metilpirrolidin-3-ilmetil)carbámico (Kuniyoshi M., Seigo S., Keiji H., Takayoshi I., Solicitud de Patente Europea EP 208210, 1987) usando el Método General A.

(tt) terc-Butil éster del ácido [1-(3-amino-1-ciclopropil-6-fluoro-8-metoxi-2,4-dioxo-1,2,3,4-tetrahidroquinazolin-7-il)-4-metilpirrolidin-3-il]carbámico (MS ES: m/z 464 (MH^+)) desde 3-amino-1-ciclopropil-6,7-difluoro-8-metoxi-1H-quinazolin-2,4-diona (Ejemplo 24d) y terc-butil éster del ácido (4-metilpirrolidin-3-il)carbámico (Di Cesare P., Bouzard D.,

Essiz M., Jacquet J.P., Ledoussai B., Kiechet J.R., Remuzon P. et al, *J. Med. Chem.*, 1992;35:4205) usando el Método General A.

(uu) terc-Butil éster del ácido [1-(3-amino-1-ciclopropil-6-fluoro-8-metoxi-2,4-dioxo-1,2,3,4-tetrahidroquinazolin-7-il)-morfolin-3-ilmetil]carbámico (MS ES: m/z 480 (MH^+)) desde 3-amino-1-ciclopropil-6,7-difluoro-8-metoxi-1H-quinazolin-2,4-diona (Ejemplo 24d) y terc-butil éster del ácido 1-(morfolin-3-ilmetil)carbámico (Araki K., Kuroda T., Uemori S., Moriguchi A., Ikeda Y., Hirayama F., Yokoyama Y. et al, *J. Med. Chem.*, 1993;36:1356) usando el Método General A.

(vv) terc-Butil éster del ácido [1-(3-amino-1-ciclopropil-6-fluoro-8-metoxi-2,4-dioxo-1,2,3,4-tetrahidroquinazolin-7-il)-piperidin-3-ilmetil]carbámico (MS ES: m/z 478 (MH^+)) desde 3-amino-1-ciclopropil-6,7-difluoro-8-metoxi-1H-quinazolin-2,4-diona (Ejemplo 24d) y terc-butil éster del ácido 1-piperidin-3-ilmetilcarbámico (Hilpert K. et al, *J. Med. Chem.*, 1994;37(23):3889-3901) usando el Método General A.

(ww) terc-Butil éster del ácido (1-[1-(3-amino-1-ciclopropil-6-fluoro-8-metoxi-2,4-dioxo-1,2,3,4-tetrahidroquinazolin-7-il)-4-metilpirrolidin-3-il]etil)carbámico (MS ES: m/z 464 (MH^+)) desde 3-amino-1-ciclopropil-6,7-difluoro-8-metoxi-1H-

quinazolin-2,4-diona (Ejemplo 24d) y terc-butil éster del ácido [1-(4-metilpirrolidin-3-il)etil]carbámico (A5g) usando el Método General A.

(xx) terc-Butil éster del ácido [1-(1-ciclopropil-6-fluoro-8-metil-2,4-dioxo-1,2,3,4-tetrahidroquinazolin-7-il)-3-metilpirrolidin-3-ilmetil]carbámico (^{1}H NMR (200 MHz, $CDCl_3$): δ 7,61 (d, 1H), 5,15 (s, 2H), 4,74 (s, 1H), 3,71-3,37 (m, 6H), 2,45-2,20 (m, 4H), 1,45 (s, 12H), 1,21-1,08 (m, 2H), 0,61 (d, 2H)) desde 3-amino-1-ciclopropil-6,7-difluoro-8-metil-1H-quinazolin-2,4-diona (Ejemplo 24e) y terc-butil éster del ácido 3-metilpirrolidin-3-ilcarbámico (Yoshida T., Yamamoto Y., Orita H., Kakiuchi M., Takahashi Y., Itakura M., Kado N., et al, *Chem. Pharm. Bull.*, 1996;44[7]:1376-1386) usando el Método General A.

(yy) 3-Amino-1-ciclopropil-6-fluoro-8-metil-7-pirrolidin-1-il-1H-quinazolin-2,4-diona (^{1}H NMR (200 MHz, $CDCl_3$): δ 7,61-7,54 (d, 1H), 5,15 (bs, 2H), 3,51-3,40 (m, 5H), 2,39 (s, 3H), 2,01-1,95 (m, 4H), 1,21-1,11 (m, 2H), 0,67-0,62 (m, 2H)) desde 3-amino-1-ciclopropil-6,7-difluoro-8-metil-1H-quinazolin-2,4-diona (Ejemplo 24e) y pirrolidina usando el Método General A.

(zz) 3-Amino-1-ciclopropil-6-fluoro-8-metoxi-7-pirrolidin-1-il-1H-quinazolin-2,4-diona (^{1}H NMR (200 MHz, $CDCl_3$): δ 7,49-7,42 (d, 1H), 5,13 (bs, 2H), 3,66-3,54 (m, 5H), 3,50 (s, 3H), 3,42-3,31 (m, 1H), 2,02-1,92 (m, 4H), 1,17-1,07 (m, 2H), 0,69-0,61 (m, 2H)) desde 3-amino-1-ciclopropil-6,7-difluoro-8-metoxi-1H-quinazolin-2,4-diona (Ejemplo 24d) y pirrolidina usando el Método General A.

(aaa) 3-Amino-1-ciclopropil-6-fluoro-7-[3-(1-hidroxietil-1-metil)-pirrolidin-1-il]-8-metil-1H-quinazolin-2,4-diona (^{1}H NMR (200 MHz, $CDCl_3$): δ 7,59 (d, 1H), 5,15 (bs, 2H), 3,68-3,53 (m, 2H), 3,44-3,31 (m, 3H), 2,42 (s, 3H), 2,00-1,82 (m, 2H), 1,58 (s, 1H), 1,28 (s, 6H), 1,20-1,10 (m, 2H), 1,00-0,80 (m, 1H), 0,66-0,60 (m, 2H)) desde 3-amino-1-ciclopropil-6,7-difluoro-8-metil-1H-quinazolin-2,4-diona (Ejemplo 24e) y 1-metil-1-pirrolidin-3-il-etanol (Ejemplo A5n) usando el Método General A.

(bbb) 3-Amino-1-ciclopropil-6-fluoro-7-[3-(1-hidroxi-1-metiletil)-pirrolidin-1-il]-8-metoxi-1H-quinazolin-2,4-diona (^{1}H NMR (200 MHz, $CDCl_3$): δ 7,50 (d, 1H), 5,14 (bs, 2H), 3,86-3,70 (m, 2H), 3,49 (s, 3H), 3,60-3,30 (m, 3H), 2,40-2,22 (m, 1H), 2,00-1,80 (m, 2H), 1,30 (s, 6H), 1,09-0,85 (m, 2H), 0,75-0,57 (m, 2H)) desde 3-amino-1-ciclopropil-6,7-difluoro-8-

metoxi-1H-quinazolin-2,4-diona (Ejemplo 24d) y 1-metil-1-pirrolidin-3-il-etanol (Ejemplo A5n) usando el Método General A.

(ccc) 1-[(R)-1-(3-(S)-Amino-1-ciclopropil-6-fluoro-5-metil-7-[3-(1-metilaminoetil)pirrolidin-1-il]-1H-quinazolin-2,4-diona (MS ES: m/z 376 (MH^+)) desde 3-amino-1-ciclopropil-6,7-difluoro-5-metil-1H-quinazolin-2,4-diona (Ejemplo 24e) y metil-((R)-((S)-1-pirrolidin-3-il)etil)amina usando el Método General A.

(ddd) 1-[(R)-1-(3-(S)-Amino-1-ciclopropil-7-[3-(1-etilaminoetil)pirrolidin-1-il]-6-fluoro-8-metoxi-1H-quinazolin-2,4-diona (MS ES: m/z 406 (MH^+)) desde 3-amino-1-ciclopropil-6,7-difluoro-8-metoxi-1H-quinazolin-2,4-diona (Ejemplo 24d) y etil-((R)-((S)-1-pirrolidin-3-il)etil)amina (Domagala J.M., Hagen S.E., Joannides T., Kiely J.S., Laborde E., Schroeder M.C., Sesnie J.A., et al, *J. Med. Chem.*, 1993;36[7]:871-882) usando el Método General A.

(eee) 3-Amino-1-ciclopropil-7-[(R)-3-((S)-1-etilaminoetil)-pirrolidin-1-il]-6-fluoro-8-metil-1H-quinazolin-2,4-diona (MS ES: m/z 390 (MH^+)) desde 3-amino-1-ciclopropil-6,7-difluoro-8-metil-1H-quinazolin-2,4-diona (Ejemplo 24e) y etil-((R)-((S)-1-pirrolidin-3-il)etil)amina usando el Método General A.

(fff) 3-Amino-7-(6-amino-1-metil-3-azabiciclo[3.2.0]hept-3-il)-1-ciclopropil-6-fluoro-8-metoxi-1H-quinazolin-2,4-diona (MS ES: m/z 390 (MH^+)) desde 3-amino-1-ciclopropil-6,7-difluoro-8-metoxi-1H-quinazolin-2,4-diona (Ejemplo 24d) y 1-metil-3-azabiciclo[3.2.0]hept-6-ilamina (Kim C.S., Kim J.W., Lee J.M., Youn Y.S., Shin Y.J., Lee K.H., Kim J.H. WO 94/15933) usando el Método General A.

(ggg) 3-Amino-7-(3-aminometilazetidin-1-il)-1-ciclopropil-6-fluoro-8-metoxi-1H-quinazolin-2,4-diona (MS ES: m/z 350 (MH^+)) desde 3-amino-1-ciclopropil-6,7-difluoro-8-metoxi-1H-quinazolin-2,4-diona (Ejemplo 24d) y azetidin-3-ilmetilamina (Okada T., Ezumi K., Yamakawa M., Sato H., Tsuji T., Tsushima T., Motokawa K., Komatsu Y., *Chem. Pharm. Bull.*, 1993;41:126-131) usando el Método General A.

(hhh) 3-Amino-7-(4-aminometilpiperidin-1-il)-1-ciclopropil-6-fluoro-8-metoxi-1H-quinazolin-2,4-diona (MS ES: m/z 378 (MH^+)) desde 3-amino-1-ciclopropil-6,7-difluoro-8-metoxi-1H-quinazolin-2,4-diona (Ejemplo 24d) y piperidin-4-ilmetilamina usando el Método General A.

(iii) terc-Butil éster del ácido [(cis)-1-(3-Amino-1-ciclopropil-6-fluoro-8-metoxi-2,4-dioxo-1,2,3,4-tetrahidroquinazolin-7-il)-4-fluoropirrolidin-3-

ilmetil]carbámico (MS ES: m/z 482 (MH^+)) desde 3-amino-1-ciclopropil-6,7-difluoro-8-metoxi-1H-quinazolin-2,4-diona (Ejemplo 24d) y terc-butil éster del ácido (cis-4-fluoropirrolidin-3-ilmetil)carbámico [A5k] usando el Método General A.

(jjj) terc-Butil éster del ácido [(trans)-1-(3-Amino-1-ciclopropil-6-fluoro-8-metoxi-2,4-dioxo-1,2,3,4-tetrahidroquinazolin-7-il)-4-fluoropirrolidin-3-ilmetil]carbámico (MS ES: m/z 482 (MH^+)) desde 3-amino-1-ciclopropil-6,7-difluoro-8-metoxi-1H-quinazolin-2,4-diona (Ejemplo 24d) y terc-butil éster del ácido (trans-4-metilpirrolidin-3-ilmetil)carbámico [A5l] usando el Método General A.

(kkk) terc-Butil éster del ácido [1-(3-Amino-1-ciclopropil-6-fluoro-8-metoxi-2,4-dioxo-1,2,3,4-tetrahidroquinazolin-7-il)-(1-amino-5-azaespiro[2.4]hept-5-il)]carbámico (MS APCI: m/z 476 (MH^+)) desde 3-amino-1-ciclopropil-6,7-difluoro-8-metoxi-1H-quinazolin-2,4-diona (Ejemplo 24d) y terc-butil éster del ácido 1-amino-5-azaespiro[2.4]hept-5-il-carbámico (Li Q., Chu D.T.W., Clairborne A., Cooper C.S., Lee C.M., Raye K., Berst K.B., et al, *J. Med. Chem.*, 1996;39[16]:3070-3088) usando el Método General C.

(lll) terc-Butil éster del ácido [1-(3-Amino-7-(3a-aminometiloctahidroisoindol-2-il)-1-ciclopropil-6-fluoro-8-metoxi-2,4-dioxo-1,2,3,4-tetrahidroquinazolin-7-il)-(1-amino-5-azaespiro[2.4]hept-5-il]carbámico (MS APCI: m/z 518 (MH^+)) desde 3-amino-1-ciclopropil-6,7-difluoro-8-metoxi-1H-quinazolin-2,4-diona (Ejemplo 24d) y terc-butil éster del ácido (3a-aminometiloctahidro-isoindol-2-il)carbámico (Ma Z., Chu D.T.W., Cooper C.S., Li Q., Fung A.K.L., Wang S., Shen L.L., et al, *J. Med. Chem.*, 1999;42(20):4202-4213) usando el Método General C.

(mmm) 3-Amino-7-(3a-aminometiloctahidroisoindol-2-il)-1-ciclopropil-6-fluoro-8-metil-1H-quinazolin-2,4-diona (MS APCI: m/z 502 (MH^+)) desde 3-amino-1-ciclopropil-6,7-difluoro-8-metil-1H-quinazolin-2,4-diona (Ejemplo 24e) y terc-butil éster del ácido 3a-aminometiloctahidroisoindol-2-ilcarbámico (Ma Z., Chu D.T.W., Cooper C.S., Li Q., Fung A.K.L., Wang S., Shen L.L., et al, *J. Med. Chem.*, 1999;42(20):4202-4213) usando el Método General C.

(nnn) terc-Butil éster del ácido ((S)-1-[(R)-1-(3-Amino-1-ciclopropil-6-fluoro-8-metoxi-2,4-dioxo-1,2,3,4-tetrahidroquinazolin-7-il)pirrolidin-3-il]etil)carbámico (MS APCI: m/z 476 (MH^+)) desde 3-amino-1-ciclopropil-6,7-difluoro-8-metoxi-1H-quinazolin-2,4-diona (Ejemplo 24d) y terc-butil

éster del ácido ((R)-(S)-1-pirrolidin-3-il)etilcarbámico (*J. Het. Chem.*, 1992;29:1481) usando el Método General C.

(ooo) terc-Butil éster del ácido {1-[1-(3-Amino-1-ciclopropil-6-fluoro-8-metil-2,4-dioxo-1,2,3,4-tetrahidroquinazolin-7-il)-pirrolidin-3-il]-propil}carbámico (MS: m/z 476 (MH^+)) desde 3-amino-1-ciclopropil-6,7-difluoro-8-metil-1H-quinazolin-2,4-diona (Ejemplo 24e) y terc-butil éster del ácido (1-pirrolidin-3-il-propil)-carbámico (Kimura Y., Atarashi S., Takahashi M., Hayakkawa I., *Chem. Pharm. Bull.*, 1994;42:1442) usando el Método General A.

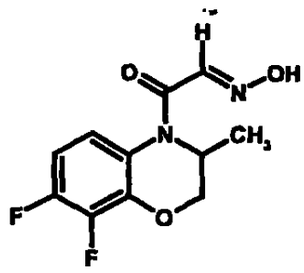
(ppp) terc-Butil éster del ácido {(S)-1-[(R)-1-(3-Amino-1-ciclopropil-6-fluoro-8-metil-2,4-dioxo-1,2,3,4-tetrahidroquinazolin-7-il)pirrolidin-3-il]etil}-metil-carbámico (MS: m/z 476 (MH^+)) desde 3-amino-1-ciclopropil-6,7-difluoro-8-metil-1H-quinazolin-2,4-diona (Ejemplo 24e) y metil-(R)-((S)-1-pirrolidin-3-il)etilamina (Plummer J.S., Emery L.A., Stier M.A., Suto M.J., *Tetrahedron Lett.*, 1993;34(47):7529-7532) usando el Método General A.

(qqq) terc-Butil éster del ácido {1-[5-(3-amino-1-ciclopropil-6-fluoro-8-metil-2,4-dioxo-1,2,3,4-tetrahidroquinazolin-7-il)-5-aza-espiro[2.4]hept-7-il]etil}carbámico (MS CI: m/z 488 (MH^+)) desde 3-amino-1-ciclopropil-6,7-difluoro-8-metil-1H-

quinazolin-2,4-diona (Ejemplo 24e) y terc-butil éster del ácido [1-(5-aza-espiro[2.4]hept-7-il)etil]carbámico (Ejemplo A5a) usando el Método General A.

EJEMPLO 29

Oxima del (7,8-difluoro-3-metil-2,3-dihidro-1,4-benzoxazin-4-il)-oxoacetaldehído

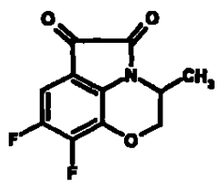


Una solución de 8,27 g (50 mmol) de hidrato cloral en 125 ml de agua se trata con 112,8 g (0,35 mmol) de sulfato de sodio decahidratado. La mezcla se agita y se trata con una solución de clorhidrato de 7,8-difluoro-3-metil-3,4-dihidro-2H-benz[1,4]oxazina (*Chem. Pharm. Bull,* 1984;32:4907) (preparado disolviendo 8,26 g (44,6 mmol) de la base libre en 50 mmol de ácido clorhídrico concentrado en 70 ml de 50% de etanol acuoso). La reacción se agita y se agrega una solución de 9,8 g (140 mmol) de clorhidrato de hidroxilamina en 50 ml de agua. Después de calentar de 75°C a 80°C durante 3 horas, la reacción se agita a temperatura ambiente toda la noche. El precipitado resultante se remueve mediante filtración, se lava

con agua, y la masa de filtro húmedo se disuelve en diclorometano. La solución orgánica se lava con agua, se seca ($MgSO_4$), se decolora con carbón, se filtra y se concentra en vacío para dar 10,5 g del compuesto del título, punto de fusión 188°C-190°C.

EJEMPLO 30

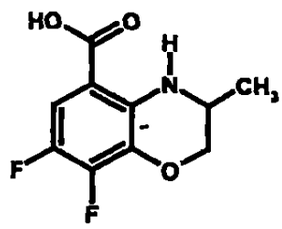
Síntesis de la 6,7-difluoro-3-metil-3,4-dihidro-5-oxa-2ª-aza-acenaftilen-1,2-diona



Una solución de 45 ml de 98% de ácido sulfúrico en 18 ml de auga se calienta de 50°C a 60°C y se trata por porciones durante 30 minutos con 10,5 g (41 mmol) de oxima de (7,8-difluoro-3-metil-2,3-dihidro-1,4-benzoxazin-4-il)oxoacetaldehído (Ejemplo 29). Después de que se completa el agregado, la reacción se calienta a 80°C durante 15 minutos y se vierte en 200 ml de hielo y agua. La mezcla se agita hasta que el hielo se funde y el sólido se remueve por filtración, se lava con agua y la masa de filtro húmedo se disuelve en diclorometano. La solución orgánica se lava con agua (2 x 200 ml), se seca ($MgSO_4$), se filtra y se concentra en vacío dando 7,1 g del compuesto del título, punto de fusión 169°-171°C.

EJEMPLO 31

Síntesis del ácido 7,8-difluoro-3-metil-3,4-dihidro-2H-1,4-benzoxazin-5-carboxílico

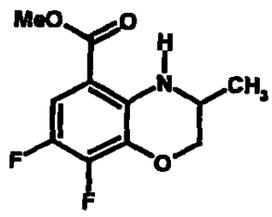


Una suspensión de 6,9 g (28,8 mmol) de 6,7-difluoro-3-metil-3,4-dihidro-5-oxa-2a-aza-acenaftilen-1,2-diona (Ejemplo 30) en 250 ml de 4,5% de hidróxido de sodio acuoso se trata gota a gota con 16,4 ml de 30% de peróxido de hidrógeno durante 1 hora. La reacción se filtra para remover restos de material insoluble y el filtrado se acidifica a pH 4,5 con ácido acético. Después de enfriar a 5°C, el precipitado se remueve por filtración, se lava con agua y se seca en vacío para dar 5,5 g del compuesto del título, punto de fusión 200°C-202°C.

EJEMPLO 32

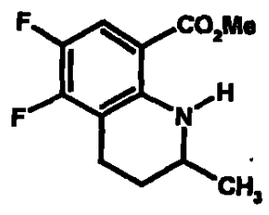
Síntesis de Ésteres Antranílicos

(a) Metil éster del ácido 7,8-difluoro-3-metil-3,4-dihidro-2H-1,4-benzoxazin-5-carboxílico



Una solución de 2,1 g (9,1 mmol) de ácido 7,8-difluoro-3-metil-3,4-dihidro-2H-1,4-benzoxazin-5-carboxílico (Ejemplo 31) en 50 ml de metanol se enfría nuevamente a 0°C y se resatura con gas cloruro de hidrógeno. Después de agitar otras 24 horas a temperatura ambiente, el solvente se remueve en vacío y el residuo se particiona entre diclorometano/5% de bicarbonato de sodio acuoso (200 ml : 100 ml). La capa orgánica se separa, se lava con 5% de bicarbonato de sodio acuoso, se seca ($MgSO_4$), se filtra y se concentra en vacío, para lograr 1,9 g del compuesto del título. ^1H NMR (400 MHz, $CDCl_3$): δ 7,27 (bs, 1H), 7,24 (m, 1H), 4,26 (m, 1H), 3,82 (s, 3H), 3,75 (m, 1H), 3,62 (m, 1H), 1,22 (d, 3H).

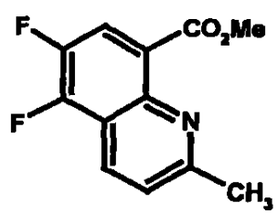
(b) Síntesis del metil éster del ácido 5,6-difluoro-2-metil-1,2,3,4-tetrahidro-quinolin-8-carboxílico



Una solución de 8,0 g (33,7 mmol) de metil éster del ácido 5,6-difluoro-2-metilquinolin-8-carboxílico (Ejemplo 33) en 100 ml de ácido acético glacial se trata con 2,15 g de platino sobre carbono (0,8 g de catalizador activo + 62,8% de agua) y luego se agita en una atmósfera de hidrógeno a temperaturas de 24°C a 29°C y a presiones de 23,9 psi a 46,6 psi durante 3 horas. El catalizador se remueve por filtración y el solvente se remueve en vacío a 50°C. El residuo se tritura con agua (50 ml) y se extrae con diclorometano (2 x 200 ml). Las capas orgánica combinadas se agitan con 5% de solución de bicarbonato de sodio, se lavan con agua, se secan ($MgSO_4$), se filtran y se evaporan en vacío. El residuo es sometido a cromatografía sobre gel de sílice en grado rápido (230-400 malla) eluyendo con diclorometano para dar 5,6 g del compuesto del título como un aceite amarillo claro. ^1H NMR (400 MHz, $CDCl_3$): δ 7,66 (bs, 1H), 7,49 (m, 1H), 3,82 (s, 3H), 3,46 (m, 1H), 2,88 (m, 1H), 1,97 (m, 1H), 1,27 (d, 3H).

EJEMPLO 33

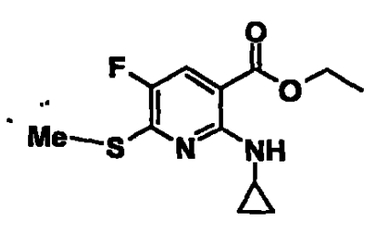
Síntesis del metil éster del ácido 5,6-difluoro-2-metilquinolin-8-carboxílico



En un reactor de acero inoxidable, una solución de 9,53 g (36,9 mmol) de 8-bromo-5,6-difluoro-2-metilquinolina (*Chem. Pharm. Bull.*, 1996;44:642), 6,8 g (67,6 mmol) de trietilamina, 0,67 g (3,0 mmol) de acetato de paladio (II), 1,28 g (3,1 mmol) de 1,3-bis(difenil-fosfino)propano en 90 ml de dimetilformamida y 65 ml de metanol recibe flujo de gas nitrógeno y se presuriza a 550 psi con monóxido de carbono. La reacción se balancea y se calienta a 75°c durante 24 horas, se enfría a temperatura ambiente y se evapora en vacío. El residuo se tritura con agua (50 ml) y se extrae con diclorometano (2 x 200 ml). Las capas orgánicas combinadas se lavan con agua (2 x 50 ml), se secan ($MgSO_4$), se filtran y se evaporan en vacío. El residuo es sometido a cromatografía sobre gel de sílice en grado rápido (230-400 malla) eluyendo con diclorometano (200 ml), luego con diclorometano/acetato de etilo (90:10) para dar 8,0 g del compuesto del título, punto de fusión 99°C-101°C.

EJEMPLO 34

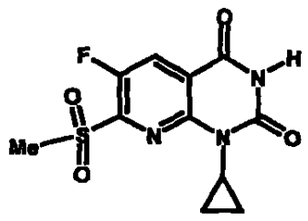
Síntesis del etil éster del ácido 2-ciclopropilamino-5-fluoro-6-metilsulfanilnicotínico



Una solución de 8,7 g (34,8 mmol) de etil éster del ácido 2-cloro-5-fluoro-6-metilsulfanilnicotínico (*J. Med. Chem.*, 1993;36:2676) y 5,7 g (100 mmol) de ciclopropilamina en 100 ml de acetonitrilo se calienta a reflujo durante 18 horas. Después de que la TLC muestra la presencia de material inicial sin reaccionar, se agregan 4,12 g (72 mmol) de ciclopropilamina y la mezcla de la reacción se refluye durante 48 horas. El solvente se remueve en vacío y el residuo se particiona entre diclorometano (250 ml) y agua (100 ml). La capa orgánica se lava con agua, se seca ($MgSO_4$), se filtra y se concentra en vacío. El residuo es sometido a cromatografía sobre gel de sílice en grado rápido (230-400 malla) eluyendo con diclorometano para dar 6,5 g del compuesto del título, punto de fusión 67°C-69°C.

EJEMPLO 35

Síntesis del ácido 1-Ciclopropil-6-fluoro-2,4-dioxo-1,2,3,4-tetrahidropirido[2,3-d]pirimidin-7-tiosulfónico

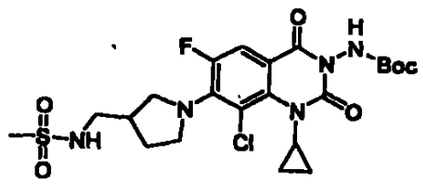


Una solución de 0,65 g (2,4 mmol) de 1-ciclopropil-6-fluoro-7-metilsulfanil-1H-pirido[2,3-d]pirimidin-2,4-diona (Ejemplo

23e) en 20 ml de ácido fórmico se trata con 1,83 g (19,5 mmol) de peróxido de urea-hidrógeno y la mezcla de la reacción se agita a temperatura ambiente toda la noche. El precipitado resultante se remueve por filtración, se lava con agua, acetato de etilo y se seca en vacío para dar 0,63 g del compuesto del título, punto de fusión 300°C-302°C.

EJEMPLO 36

Síntesis del terc-butil éster del ácido {8-cloro-1-ciclopropil-6-fluoro-7-[3-(metanosulfonilamino-metil)pirrolidin-1-il]-2,4-dioxo-1,4-dihidro-2H-quinazolin-3-il}carbámico



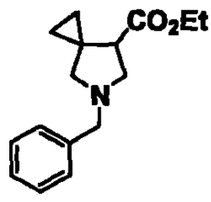
A una solución de terc-butil éster del ácido (8-cloro-1-ciclopropil-6,7-dihidro-2,4-dioxo-1,4-dihidro-2H-quinazolin-3-il)carbámico (Ejemplo 14, 0,37 g, 0,97 mmol) en acetonitrilo (20 ml) se agrega pirrolidin-3-il-metilamina (0,115 g, 1,16 mmol) y trietilamina (2,7 ml, 19,3 mmol). Después de refluir durante 20 horas, la mezcla de la reacción se enfría a temperatura ambiente y se diluye con acetato de etilo. La capa orgánica se lava con bicarbonato de sodio saturado, agua y solución salina. La capa orgánica se seca sobre $MgSO_4$, se

filtra y el filtrado se concentra. El residuo resultante se disuelve nuevamente en cloruro de metileno (10 ml) a 0°C y mientras se agita, se agrega trietilamina (0,33 ml, 2,34 mmol) y cloruro de metanosulfonilo (0,072 ml, 0,94 mmol). Después de 2 horas, la mezcla de la reacción se diluye con acetato de etilo y se lava con bicarbonato de sodio saturado, agua y solución salina. La capa orgánica se seca sobre $MgSO_4$, se filtra y el filtrado se concentra y el producto se purifica por cromatografía de columna rápida (EtOAc/hexanos 1:1) para lograr terc-butil éster del ácido {8-cloro-1-ciclopropil-6-fluoro-7-[3-(metanosulfonilaminometil)pirrolidin-1-il]-2,4-dioxo-1,4-dihidro-2H-quinazolin-3-il}carbámico (0,043 g). MS CI: m/e 446 ((MH^+)-Boc).

Síntesis de Cadenas Laterales de Aminas

EJEMPLO A1

(a) Etil éster del ácido 5-bencil-5-azaespiro[2,4]heptan-1-il-carboxílico

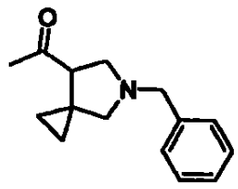


Una solución de etil éster del ácido ciclopropiliden acético (192 g, 1520 mmol [Salaun J. Bennani F., Compain J.C., Fadel

A., Ollivier J.J., *Org. Chem.*, 1980;45(21):4129-3415]) y N-(metoximetil)-N-(trimetilsililmetil)-bencilamina (572 g, 2410 mmol [Gerlach K., Hoffmann H.M.R., Wartchow R.J., *Chem. Soc.*, Perkin Trans. 11, 1998(22):3867-3872]) en diclorometano (5,5 L) se trató con una solución de ácido trifluoroacético 1,0N en diclorometano (80 ml) y la reacción se agitó a temperatura ambiente durante 30 minutos. El solvente se evaporó a presión reducida y el producto se purificó por destilación de Kugelrohr (277 g). MS CI: m/z 260 (MH^+).

EJEMPLO A2

(a) Síntesis de 1-(5-Bencil-5-azaespiro[2.4]hept-7-il)etanona

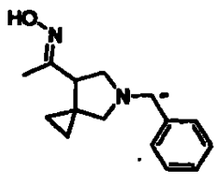


Una solución (-78°C) de etil éster del ácido 5-bencil-5-azaespiro[2.4]heptano-7-carboxílico (Ejemplo A1a, 8,15 g, 31,4 mmol) en éter dietílico (200 ml) bajo una atmósfera de nitrógeno se trata con metillitio (1,4 M en éter dietílico, 22,4 ml, 31,4 mmol) durante un período de 10 minutos. Después de 1 hora, la mezcla de la reacción se calienta a -10°C y se enfría con cloruro de amonio acuoso saturado. La mezcla se

vierte en un embudo separador y la capa orgánica se lava con cloruro de amonio acuoso saturado, agua y solución salina. La capa orgánica se seca luego con $MgSO_4$, se filtra y el filtrado se concentra. El residuo resultante se purifica por cromatografía de columna rápida (1% de trietilamina/7% de isopropanol/92% de CH_2Cl_2 para lograr el compuesto del título (3,93 g). MS CI: m/z 230 (MH^+).

EJEMPLO A3

(a) Síntesis de la oxima de 1-(5-bencil-5-azaespiro[2.4]hept-7-il)etanona



1-(5-Bencil-5-azaespiro[2.4]hept-7-il)etanona (Ejemplo A2a, 3,93 g, 17,1 mmol) y clorhidrato de hidroxilamina (1,78 g, 25,7 mmol) se agitan en piridina (10 ml) a 90°C. Después de 20 horas, la mezcla de la reacción se diluye con acetato de etilo y la capa orgánica se lava con $NaHCO_3$ saturado, agua y solución salina. La capa orgánica se seca con $MgSO_4$, se filtra y el filtrado se concentra para lograr la oxima de 1-(5-bencil-5-azaespiro[2.4-hept-7-il)etanona como un aceite (3,07 g). MSCI: m/z 245 (MH^+).

Método General A

Una solución de sustrato, clorhidrato de hidroxilamina (1,2 eq.), acetato de sodio (0,9 eq.) en etanol se agita a temperatura ambiente durante 2 horas. El solvente se remueve en vacío y el residuo se particiona entre acetato de etilo y solución de cloruro de sodio saturado. La parte acuosa se extrae nuevamente con acetato de etilo y los extractos combinados se secan sobre Na_2SO_4, se filtran y se concentran bajo vacío para lograr el compuesto del título.

Los siguientes compuestos se preparan de acuerdo con el Método General A.

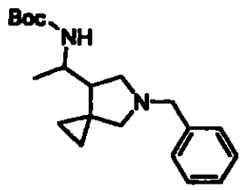
(b) Oxima de 1-(bencilpiperidin-3-il)etanona (^{1}H NMR (200 MHz, $CDCl_3$): δ 7,48-7,28 (m, 5H), 3,92-3,68 (m, 2H), 3,28-3,10 (m, 4H), 2,8-2,62 (m, 2H), 2,38-1,72 (m, 3H), 1,3-1,18 (m, 3H)) desde 1-(bencilpiperidin-3-il)etanona (Ejemplo A23).

(c) Oxima de 1-(1-bencil-4,4-dimetilpirrolidin-3-il)etanona (^{1}H NMR (200 MHz, $CDCl_3$): δ 7,68-7,30 (m, 5H), 6,50-5,80 (bs, 1H), 3,80-2,38 (m, 6H), 1,90 (s, 3H), 1,38-0,96 (m, 7H)) desde 1-(1-bencil-4,4-dimetilpirrolidin-3-il)etanona (Ejemplo A18b).

(d) Oxima de 1-(1-bencil-4-metilpirrolidin-3-il)etanona (^{1}H NMR (200 MHz, $CDCl_3$): δ 7,41-7,15 (m, 5H), 3,78-3,44 (m, 3H), 2,98-2,80 (m, 1H), 2,75-2,39 (m, 3H), 2,35-2,08 (m, 2H), 1,90 (m, 3H), 1,18-0,95 (m, 3H)) desde 1-(1-bencil-4-metilpirrolidin-3-il)etanona (Ejemplo A23b).

EJEMPLO A4

(a) Síntesis del terc-butil éster del ácido 1-(5-bencil-5-azaespiro[2,4]hept-7-il)-etil]carbámico



A una solución de oxima de 1-(5-bencil-5-azaespiro[2,4]hept-7-il)etanona (Ejemplo A3a, 2,90 g, 11,9 mmol) en metanol (100 ml), se agrega níquel de Raney (2 g). Se introduce hidrógeno en la mezcla de la reacción a alta presión (48 psi) durante 20 horas y la mezcla de la reacción se filtra a través de celita, se lava con metanol, y los filtrados combinados se concentran en vacío. El residuo resultante se disuelve nuevamente en diclorometano (25 ml) y se trata con di-terc-butil dicarbonato (3,24 g, 14,9 mmol). Después de 1 hora, la mezcla se concentra y el producto se purifica por cromatografía de columna rápida (1% de trietilamina/7% de isopropanol/92% de diclorometano)

para lograr el terc-butil éster del ácido 1-(5-bencil-5-azaespiro[2,4]hept-7-il)-etil]carbámico (1,47 g). MS CI: m/z 331 (MH^+).

Método General A

Di-terc-butil dicarbonato (0,69 g, 0,3 mmol) se agrega a una solución de amina en metanol (4 ml) a 0°C. Después de agitar a temperatura ambiente durante 2 horas, la mezcla se concentra y el residuo se purifica por cromatografía (SiO_2, acetato de etilo/hexanos) para lograr los ésteres carbámicos del título.

Método General B

Una solución helada de sustrato en metanol y agua 2:1 se trata con di-terc-butil dicarbonato (1,25 eq.). La solución resultante se agita a temperatura ambiente durante 18 horas y se extrae con diclorometano. Los extractos orgánicos se lavan con solución salina, se secan sobre Na_2SO_4, se filtran y se concentran bajo vacío. El residuo se purifica por cromatografía de columna (acetato de etilo/hexanos) para lograr los compuestos del título.

Método General C

A una solución de sustrato en diclorometano se agrega di-terc-butil dicarbonato (2 eq.) y trietilamina (2 eq.). La mezcla resultante se agita a temperatura ambiente durante 18 horas y se diluye con agua. El extracto orgánico se lava con agua, solución salina y se seca sobre Na_2SO_4, se filtra y se concentra en vacío. El residuo luego se purifica por cromatografía de columna para lograr el compuesto del título.

Los Ejemplos A4b-A4m se preparan de acuerdo con los Métodos Generales A, B y C.

(b) Bencil éster del ácido 3-(1-terc-butoxicarbonilaminoetil)-3-metoxipirrolidin-1-carboxílico (^{1}H NMR (200 MHz, $CDCl_3$): δ 7,37-7,29 (m, 5H), 5,13 (bs, 1H), 3,91-3,22 (m, 8H), 2,03-1,75 (m, 2H), 1,43 (s, 9H), 1,16-1,11 (m, 3H)) desde bencil éster del ácido 3-(1-aminoetil)-3-metoxipirrolidin-1-carboxílico (Ejemplo A13a) usando el Método General A.

(c) Bencil éster del ácido 3-(1-terc-butoxicarbonilaminoetil)-3-fluoropirrolidin-1-carboxílico (^{1}H NMR (200 MHz, $CDCl_3$): δ 7,35 (s, 5H), 5,13 (s, 2H), 4,79 (d, 1H), 3,97-3,26 (m, 5H), 2,17-1,75 (m, 2H), 1,44 (s, 9H), 1,24 (d, 3H)) desde bencil éster del ácido 3-(1-aminoetil)-3-fluoropirrolidin-1-carboxílico (Ejemplo A13b) usando el Método General A.

(d) terc-Butil éster del ácido (1-bencil-3-metoximetilpirrolidin-3-ilmetil)carbámico (^{1}H NMR (200 MHz, $CDCl_3$): δ 7,35-7,17 (m, 5H), 5,78 (bs, 1H), 3,56 (s, 2H), 3,32 (s, 3H), 3,27 (s, 2H), 3,21-3,12 (m, 2H), 2,71-2,62 (m, 1H), 2,54-2,30 (m, 3H), 1,78-1,54 (m, 2H), 1,46 (s, 9H)) desde (1-bencil-3-metoximetilpirrolidin-3-il)metilamina (Ejemplo A13c) usando el Método General B.

(e) terc-Butil éster del ácido [1-(1-bencilpiperidin-3-il)etil]carbámico (^{1}H NMR (200 MHz, $CDCl_3$): δ 7,3 (s, 5H), 4,46-4,30 (m, 4H), 3,62-3,42 (m, 4H), 2,94-2,62 (m, 3H), 2,0-1,0 (m, 8H), 1,44 (s, 9H)) desde 1-(1-bencilpiperidin-3-il)etilamina (Ejemplo A13d) usando el Método General C.

(f) terc-Butil éster del ácido [1-(1-bencil-4,4-dimetilpirrolidin-3-il)etil]carbámico (^{1}H NMR (200 MHz, $CDCl_3$): **Isómero-1**: δ 7,36-7,22 (m, 5H), 3,82-3,38 (m, 2H), 2,98-1,78 (m, 5H), 1,52-1,0 (m, 19H); **Isómero-2**: δ 7,35-7,25 (m, 5H), 4,35-4,18 (m, 1H), 3,70-3,45 (m, 2H), 2,90-1,54 (m, 6H), 1,43 (s, 9H), 1,18-0,92 (m, 9H)) desde 1-(1-bencil-4,4-dimetilpirrolidin-3-il)etilamina (Ejemplo A13e) usando el Método General C.

(g) terc-Butil éster del ácido [1-(1-bencil-4-metilpirrolidin-3-il)etil]carbámico (^{1}H NMR (200 MHz, $CDCl_3$): δ 7,38-7,13 (m, 5H), 3,71-3,32 (m, 4H), 3,08-1,53 (m, 6H), 1,52-1,31 (m, 9H), 1,14-0,94 (m, 6H). MS ES: m/z 319 (MH^+)) desde 1-(1-bencil-4-metilpirrolidin-3-il)etilamina (Ejemplo A13f) usando el Método General C.

(h) terc-Butil éster del ácido (5-bencil-5-azaespiro[2,4]hept-7-ilmetil)carbámico (MS ES: m/z 317 (MH^+)) desde 1-(5-bencil-5-azaespiro[2,4]hept-7-il)metilamina (Ejemplo A13g) usando el Método General C.

(i) terc-Butil éster del ácido (1-bencil-3-hidroxipirrolidin-3-ilmetil)carbámico (MS ES: m/z 307 (MH^+)) desde 3-aminometil-1-bencilpirrolidin-3-ol (Grohe K., Schriewer M., Haller I., Metzger K., Endermann R., Zeiler H., EP 0326916) usando el Método General C.

(j) terc-Butil éster del ácido [3-(1-feniletil)-3-azabiciclo[3.1.0]hex-1-ilmetilcarbámico (MS ES: m/z 317 (MH^+)) desde 1-[3-(1-feniletil)-3-azabiciclo[3.1.0]hex-1-il]metilamina (Ejemplo A13h) usando el Método General C.

(k) terc-Butil éster del ácido (1,3-dibencilpirrolidin-3-ilmetil)carbámico (MS ES: m/z 381 (MH^+)) desde 1-(1,3-

dibencilpirrolidin-3-il)metilamina (Ejemplo A13i) usando el Método General C.

(l) terc-Butil éster del ácido (1-bencil-4-fluoropirrolidin-3-iletil)carbámico (^{1}H NMR (200 MHz, $CDCl_3$): δ 7,30 (s, 5H), 5,04 (m, 1H), 4,77 (m, 1H), 3,63 (s, 2H), 3,20 (t, 2H), 2,86-3,00 (m, 2H), 2,76 (d, 1H), 2,20-2,60 (m, 2H), 1,45 (s, 9H)) desde (1-bencil-4-fluoropirrolidin-3-il)metilamina (Bouzard D., Di Cesare P., Essiz M., Jacquet J.P., Kiechel J.P., Remuzon P., Weber A., et al, *J. Med. Chem.*, 1990;33:1344-1352) usando el Método General C.

(m) terc-Butil éster del ácido cis-(1-bencil-4-fluoropirrolidin-3-ilmetil)carbámico (^{1}H NMR (200 MHz, $CDCl_3$): δ 7,30 (s, 5H), 5,04 (m, 1H), 4,77 (m, 1H), 3,63 (s, 2H), 3,20 (t, 2H), 2,00-2,86 (m, 2H), 2,76 (d, 1H), 2,60-2,20 (m, 2H), 1,45 (s, 9H)) desde cis-(1-bencil-4-fluoro-pirrolidin-3-il)metilamina (Matsumoto J., Nakano J., Chiba K., Minamida A., Nishimura Y., Jpn. Kokai Tokkyo Koho, 1987; 11 páginas, JP 62072660, A2 19870403) usando el Método General C.

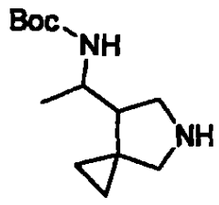
(n) terc-Butil éster del ácido trans-(1-bencil-4-fluoropirrolidin-3-ilmetilcarbámico (^{1}H NMR (200 MHz, $CDCl_3$): δ 7,30 (s, 5H), 5,25 (m, 1H), 4,77 (m, 1H), 3,85 (s, 2H), 3,55

(t, 2H), 3,40-2,40 (m, 5H), 1,47 (s, 9H)) desde trans-(1-bencil-4-fluoropirrolidin-3-il)metilamina (Matsumoto J., Nakano J., Chiba K., Minamida A., Nishimura Y., Jpn. Kokai Tokkyo Koho, 1987; 11 páginas, JP 62072660, A2 19870403) usando el Método General C.

(o) terc-Butil éster del ácido (1-bencil-3-fenilpirrolidin-3-ilmetil)carbámico (MS ES: m/z 367 (MH^+)) desde éster de (1-bencil-3-fenilpirrolidin-3-il)metilamina (Hagen S., Domagala J.M., Heifetz C.L., Sánchez J.P., Solomon M., *J. Med. Chem.*, 199;33:849-854) usando el Método General C.

EJEMPLO A5

(a) Síntesis del terc-butil éster del ácido [1-(5-azaespiro[2.4]hept-7-il)etil]carbámico



Una solución de berc-butil éster del ácido [1-(5-bencil-5-azaespiro[2.4]hept-7-il)etil]carbámico (Ejemplo A4a, 1,47 g) en metanol (30 ml) en un agitador de Parr se trata con 10% de paladio sobre carbono (0,5 g) y se introduce hidrógeno (50 psi) durante 24 horas. La mezcla de la reacción se filtra a través de celita, se lava con metanol, y el filtrado combinado

se concentra en vacío para lograr el compuesto del título. MS CI: m/z 241 (MH^+).

Método General A

A una solución de sustrato en metanol se agrega formato de amonio (5 eq.) y 10% de paladio sobre carbón (0,75 eq. en peso volumen). Después de estar 2 horas a reflujo, la mezcla de la reacción se enfría, se diluye con diclorometano y se filtra. El filtrado se concentra para lograr el compuesto del título.

Los Ejemplos A5b-A5o se preparan usando el Método General A.

(b) terc-Butil éster del ácido [1-(3-metoxipirrolidin-3-il)etil]carbámico (^1H NMR (200 MHz, $CDCl_3$): δ 5,30 (bs, 1H), 5,03 (dd, 1H), 3,92 (bs, 1H), 3,28-2,82 (m, 7H), 1,97-1,72 (m, 2H), 1,44 (s, 9H), 1,19-1,14 (m, 3H)) desde bencil éster del ácido 3-(1-terc-butoxicarbonilaminoetil)-3-metoxipirrolidin-1-carboxílico (Ejemplo A4b) usando el Método A.

(c) terc-Butil éster del ácido [1-(3-fluoropirrolidin-3-il)etil]carbámico (^1H NMR (200 MHz, $CDCl_3$): δ 4,89 (d, 1H), 3,95-3,61 (m, 1H), 3,21-2,70 (m, 4H), 2,11-1,53 (m, 1H), 1,44 (s, 9H), 1,26 (d, 3H)) desde bencil éster del ácido 3-(1-terc-

butoxicarbonilaminoetil)-3-fluoropirrolidin-1-carboxílico (Ejemplo A4c) usando el Método A.

(d) terc-Butil éster del ácido (3-metoximetilpirrolidin-3-ilmetil)carbámico (^{1}H NMR (200 MHz, $CDCl_3$): δ 5,25 (bs, 1H), 3,35 (s, 3H), 3,30 (s, 2H), 3,27-3,15 (m, 2H), 3,09-2,94 (m, 2H), 2,78 (s, 2H), 1,68-1,56 (m, 2H), 1,45 (s, 9H). (MS ES: m/z 245 (MH^+)) desde terc-butil éster del ácido (1-bencil-3-metoximetilpirrolidin-3-ilmetil)carbámico (Ejemplo A4d) usando el Método A.

(e) terc-Butil éster del ácido (1-piperidin-3-iletil)carbámico (^{1}H NMR (200 MHz, $CDCl_3$): δ 4,52-4,32 (m, 1H), 3,68-3,18 (m, 4H), 2,74-2,42 (m, 1H), 2,02-1,2 (m, 5H), 1,44 (s, 9H), 1,30-1,04 (m, 3H)) desde terc-butil éster del ácido [1-(1-bencilpiperiidin-3-il)etil]carbámico (Ejemplo A4e) usando el Método A.

(f) terc-Butil éster del ácido [1-(4,4-dimetilpirrolidin-3-il)etil]carbámico (^{1}H NMR (200 MHz, $CDCl_3$): δ 6,28-5,85 (bs, 1H), 4,75 (d, 1H), 3,92-1,80 (m, 6H), 1,43 (s, 9H), 1,30-1,0 (9H)) desde terc-butil éster del ácido [1-(1-bencil-4,4-dimetilpirrolidin-3-il)etil]carbámico (Ejemplo A4f).

(g) terc-Butil éster del ácido [1-(4-metilpirrolidin-3-il)etil]carbámico (^{1}H NMR (200 MHz, $CDCl_3$): δ 4,88-4,40 (m, 1H), 4,02-3,38 (m, 4H), 3,25-2,75 (m, 2H), 2,46-1,88 (m, 2H), 1,44 (s, 9H), 1,31-1,04 (9H)) desde terc-butil éster del ácido [1-(1-bencil-4-metilpirrolidin-3-il)etil]carbámico (Ejemplo A4g).

(h) terc-Butil éster del ácido (5-azaespiro[2,4]hept-7-ilmetil)carbámico (MS ES: m/z 227 (MH^+)) desde terc-butil éster del ácido (5-bencil-5-azaespiro[2,4]hept-7-ilmetil)carbámico (Ejemplo A4h).

(i) terc-Butil éster del ácido (3-hidroxipirrolidin-3-ilmetil)carbámico (MS ES: m/z 217 (MH^+)) desde terc-butil éster del ácido (1-bencil-3-hidroxipirrolidin-3-ilmetil)carbámico (Ejemplo A4i).

(j) terc-Butil éster del ácido (3-azabiciclo[3.1.0]hex-1-ilmetil)carbámico (MS ES: m/z 213 (MH^+)) desde terc-butil éster del ácido [3-(1-feniletil)-3-azabiciclo[3.1.0]hex-1-ilmetilcarbámico (Ejemplo A4j).

(k) terc-Butil éster del ácido cis-(4-fluoropirrolidin-3-ilmetil)carbámico (^{1}H NMR (200 MHz, $CDCl_3$): δ 5,60-5,00 (m,

4H), 3,60-3,10 (m, 4H), 3,00 (t, 1H), 2,75-1,30 (m, 1H), 1,44 (s, 9H)) desde terc-butil éster del ácido cis-(1-bencil-4-fluoropirrolidin-3-ilmetil)carbámico (Ejemplo A41).

(l) terc-Butil éster del ácido trans-(4-fluoropirrolidin-3-ilmetil)carbámico (^{1}H NMR (200 MHz, $CDCl_3$): δ 6,60-5,70 (m, 2H), 5,25 (bs, 0,5H), 4,98 (bs, 0,5H), 3,70-2,90 (m, 5H), 2,90-2,50 (m, 1H), 1,44 (s, 9H)) desde terc-butil éster del ácido trans-(1-bencil-4-fluoropirrolidin-3-ilmetil)carbámico (Ejemplo A4m).

(m) 3-Hidroxi4-hidroximetilpirrolidina (^{1}H NMR (200 MHz, DMSO-d_6): δ 5,50-4,30 (bs, 3H), 4,30-1,50 (m, 8H)) usando 1-bencil-3-hidroxi-4-hidroximetilpirrolidina (Jaeger E., Biel J.H., *J. Org. Chem.*, 1965;30:740-744).

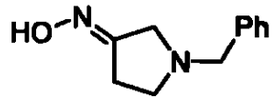
(n) 1-Metil-1-pirrolidin-3-il-etanol (MS ES: m/z 130 (MH^+)) desde 2-(1-bencilpirrolidin-3-il)propan-2-ol (Ejemplo A25).

(o) terc-Butil éster del ácido (3-bencilpirrolidin-3-ilmetil)carbámico (punto de fusión 183°C-185°C) desde terc-butil éster del ácido (1,3-dibencilpirrolidin-3-ilmetil)carbámico (Ejemplo A4K).

(p) terc-Butil éster del ácido (3-fenilpirrolidin-3-ilmetil)carbámico (MS APCI: m/z 277 (MH^+)) desde terc-butil éster del ácido (1-bencil-3-fenilpirrolidin-3-ilmetil)carbámico (Ejemplo A4o).

EJEMPLO A6

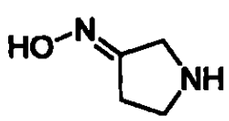
Síntesis de oxima de 1-Bencilpirrolidin-3-ona



A una solución de 1-bencilpirrolidin-3-ona (1,0 g, 5,71 mmol) en piridina (5 ml) se agrega clorhidrato de hidroxilamina (0,59 g, 8,57 mmol). Después de agitar a 90°C durante 5 horas, la mezcla de la reacción se diluye con acetato de etilo y se lava con bicarbonato de sodio saturado, agua y solución salina. La capa orgánica se seca sobre $MgSO_4$, se filtra y el filtrado se concentra para lograr la oxima de 1-bencilpirrolidin-3-ona (1,11 g) como un aceite. MS CI: m/z 191 (MH^+).

EJEMPLO A7

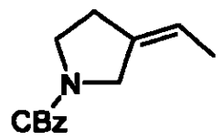
Síntesis de oxima de pirrolidin-3-ona



En un agitador de Parr, oxima de 1-bencilpirrolidin-3-ona (1,5 g) en metanol (20 ml) se trata con 20% de paladio sobre carbono (0,5 g) bajo presión de hidrógeno (50 psi) durante 24 horas. La mezcla luego se filtra a través de Celita, se lava con metanol, y el filtrado combinado se concentra en vacio para lograr el compuesto del título como un aceite (1,2 g). MS CI: m/e 101 (M^++1).

EJEMPLO A8

Síntesis del bencil éster del ácido 3-etilidenpirrolidin-1-carboxílico

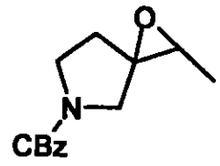


Bajo una atmósfera inerte, hidruro de sodio (0,160 g, 7 mmol) y bromuro de etiltrifenilfosfonio (2 g, 5,4 mmol) se mezclan en sulfóxido de dimetilo (10 ml) y se agitan durante 40 minutos. Se agrega bencil éster de ácido 3-oxopirrolidin-1-carboxílico (1,18 g, 5,4 mmol (*J. Med. Chem.*, 1992;35:1392)) en sulfóxido de dimetilo seco (5 ml) a la reacción y la mezcla se agita a 70°C durante 3 horas. La reacción se enfría, se diluye con agua fría y se extrae con acetato de etilo. La fase orgánica se lava con solución salina, se seca sobre Na_2SO_4 y se evapora. El residuo se purifica por cromatografía de columna (hexanos/acetato de etilo 65:35) para lograr el compuesto del

título (0,650 g) como un aceite viscoso. ^{1}H NMR (200 MHz, $CDCl_3$): δ 7,37-7,28 (m, 5H), 5,40-5,32 (m, 1H), 5,15 (s, 2H), 3,97 (bs, 2H), 3,60-3,44 (m, 2H), 2,49 (bs, 2H), 1,65-1,60 (m, 3H).

EJEMPLO A9

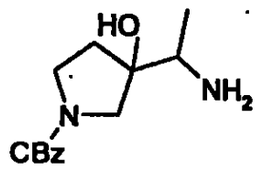
Síntesis del bencil éster del ácido 2-metil-1-oxa-5-azaespiro[2,4]heptano-5-carboxílico



Una solución de bencil éster del ácido 3-etilidenpirrolidin-1-carboxílico (Ejemplo A8, 0,65 g, 2,8 mmol) y ácido 3-cloroperoxibenzoico (0,86 g, 5 mmol) en diclorometano (15 ml) se agita a temperatura ambiente durante 3 horas. El perácido excedente se descompone agregando 10% de sulfito de sodio. La capa orgánica se lava con 5% de solución de bicarbonato de sodio, se seca sobre Na_2SO_4 y se evapora. El residuo se purifica por cromatografía de columna (hexanos/acetato de etilo 1:1) para lograr el compuesto del título (0,310 g). ^{1}H NMR (200 MHz, $CDCl_3$): δ 7,36-7,26 (m, 5H), 5,14 (s, 2H), 3,73-3,55 (m, 3H), 3,34 (d, 1H), 3,20-3,13 (m, 1H), 2,26-2,11 (m, 1H), 1,90-1,62 (m, 1H), 1,33 (d, 3H).

EJEMPLO A10

Síntesis de bencil éster del ácido 3-(1-aminoetil)-3-hidroxipirrolidin-1-carboxílico



Una solución de bencil éster del ácido 2-metil-1-oxa-5-azaespiro[2,4]heptano-5-carboxílico (Ejemplo A9, 0,31 g, 1,25 mmol) en metanol (10 ml) e hidróxido de amonio (7 ml) se calienta en un tubo sellado a 100°C durante 16 horas. Después de enfriar, la mezcla de la reacción se disuelve en acetato de etilo, se lava con agua, se seca sobre Na_2SO_4 y se evapora para lograr el compuesto del título (0,340 g). ^1H NMR (200 MHz, $CDCl_3$): δ 7,33-7,26 (m, 5H), 5,28 (bs, 2H), 5,07 (s, 2H), 3,56-3,16 (m, 5H), 2,03-1,76 (m, 2H), 1,15 (d, 3H).

EJEMPLO A11

Síntesis del bencil éster del ácido 3-hidroxi-3-(1-[(2-hidroxibenciliden)amino]etil)pirrolidin-1-carboxílico

Una solución de bencil éster del ácido 3-(1-aminoetil)-3-hidroxipirrolidin-1-carboxílico (Ejemplo A10, 0,34 g, 0,93 mmol) y salicilaldehído (0,147 g, 1,2 mmol) en etanol seco (5 ml) se refluye durante 5 horas. Después de la evaporación del

solvente, el residuo se purifica por cromatografía de columna (acetato de etilo/hexanos/hidróxido de amonio 30:70:0,01) para lograr el compuesto del título (0,12 g). ^{1}H NMR (200 MHz, $CDCl_3$): δ 8,39 (s, 1H), 7,41-7,25 (m, 7H), 6,97-6,85 (m, 2H), 5,09 (s, 2H), 3,65-3,34 (m, 5H), 2,01-1,87 (m, 2H), 1,37-1,32 (m, 3H).

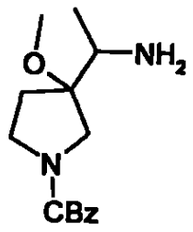
EJEMPLO A12

Síntesis del bencil éster del ácido 3-metoxi-3-{1-[(2-metoxibenciliden)amino]etil}pirrolidin-1-carboxílico

A una solución agitada de bencil éster del ácido 3-hidroxi-3-{1-[(2-hidroxibenciliden)amino]-etil}pirrolidin-1-carboxílico (Ejemplo A11, 0,120 g, 0,33 mmol) en tetrahidrofurano (5 ml) a 0°C se agregan 0,024 g (1 mmol) de hidruro de sodio. La mezcla se agita a temperatura ambiente durante 2 horas y se agrega yoduro de metilo (3 ml) y se continúa agitando toda la noche. Después de la evaporación, se agrega acetato de etilo y agua al residuo. La capa orgánica se evapora, se seca sobre Na_2SO_4 y se concentra para lograr el compuesto del título (0,125 g). ^{1}H NMR (200 MHz, $CDCl_3$): δ 8,70 (s, 1H), 7,95 (d, 1H), 7,41-7,32 (m, 6H), 7,01-6,88 (m, 2H), 5,09 (s, 2H), 3,86 (s, 3H), 3,72-3,22 (m, 8H), 2,33-1,73 (m, 2H), 1,27-1,24 (m, 3H).

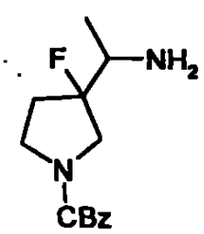
EJEMPLO A13

(a) Síntesis del bencil éster del ácido 1-(3-aminoetil)-3-metoxipirrolidin-1-carboxílico



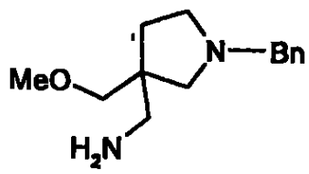
Una solución de bencil éster del ácido 3-metoxi-3-{1-[(2-metoxibenciliden)amino]etil-pirrolidin-1-carboxílico (Ejemplo A12, 0,120 g, 0,3 mmol) en cloruro de hidrógeno 3 M en metanol (1 ml) se calienta a 40°C toda la noche. La reacción se basifica, se extrae con acetato de etilo y la capa orgánica se seca sobre Na_2SO_4. Después de la concentración, el residuo se purifica por cromatografía de columna (metanol/diclorometano 20:80) para lograr el compuesto del título (0,060 g). ^1H NMR (200 MHz, $CDCl_3$): δ 7,38-7,29 (m, 5H), 5,12 (s, 2H), 3,64-3,19 (m, 8H), 2,47 (bs, 2H), 2,07-1,80 (m, 2H), 1,16-1,10 (m, 3H).

(b) Bencil éster del ácido 3-(1-aminoetil)-3-fluoropirrolidin-1-carboxílico



Una solución de bencil éster del ácido 3-(1-azidoetil)-3-fluoropirrolidin-1-carboxílico (Ejemplo A16, 0,16 g, 0,5 mmol) en metanol (10 ml) se trata con níquel Raney (100 mg, peso húmedo) y se agita en una atmósfera de hidrógeno a temperatura ambiente y a 55 psi durante 17 horas. El catalizador se remueve por filtración a través de Celita, y el solvente se remueve en vacío para lograr el compuesto del título (0,12 g). ^{1}H NMR (200 MHz, $CDCl_3$): δ 7,30 (s, 5H), 5,12 (s, 2H), 3,84-3,22 (m, 5H), 2,23-1,79 (m, 4H), 1,20 (d, 3H).

(c) 1-(1-Bencil-3-metoximetilpirrolidin-3-il)metilamina



Hidrato de hidrazina (solución al 85% en agua, 0,372 g, 6,32 mmol) se agrega a una solución de 2-(1-bencil-3-metoximetilpirrolidin-3-ilmetil)isoindol-1,3-diona (Ejemplo A20, 1,581 g, 4,34 mmol) en etanol (50 ml). La mezcla resultante se refluye durante 4,5 horas, se enfría y se acidifica con ácido clorhídrico concentrado. El precipitado se remueve por filtración y el filtrado se concentra en vacío. El residuo se disuelve en etanol/agua (2:1) y el material insoluble se remueve por filtración. El filtrado se basifica a pH 10 con una solución de hidróxido de sodio 1N y se extrae

con diclorometano. Los extractos orgánicos combinados se secan sobre Na_2SO_4, se filtran y se concentran bajo vacío para lograr el compuesto del título (0,910 g). ^1H NMR (200 MHz, $CDCl_3$): δ 7,41-7,15 (m, 5H), 3,57 (s, 2H), 3,33 (s, 3H), 3,30 (s, 2H), 2,71 (s, 2H), 2,64-2,51 (m, 2H), 2,42-2,24 (m, 2H), 1,68-1,52 (m, 2H), 1,38-1,10 (m, 2H).

Método General A

Hidruro de litio y aluminio (2 eq.) se agregan lentamente a una solución de una oxima, nitrilo o derivado de amida en tetrahidrofurano seco. Después de completar el agregado, la mezcla se refluye durante 2 a 6 horas, se enfría en un baño de hielo y se enfría con una solución de sulfato de sodio saturado. El sólido se remueve por filtración y el filtrado se concentra en vacío para lograr el compuesto del título.

Los ejemplos A13d-i se preparan de acuerdo con el Método General A.

(d) 1-(1-Bencilpiperidin-3-il)etilamina (^1H NMR (200 MHz, DMSO-d_6): δ 7,38-7,18 (m, 5H), 3,52-3,22 (m, 2H), 2,82-2,58 (m, 3H), 1,92-0,75 (m, 10H)) desde oxima de 1-(1-bencilpiperidin-3-il)etanona (Ejemplo A3b).

(e) Oxima de 1-(1-Bencil-4,4-dimetilpirrolidin-3-il)etanona (^{1}H NMR (200 MHz, $CDCl_3$): δ 7,36-7,22 (m, 5H), 3,66-3,42 (m, 2H), 2,94-2,10 (m, 5H), 1,32-0,88 (m, 10H)) desde oxima de 1-(1-bencil-4,4-dimetilpirrolidin-3-il)etanona (Ejemplo A3c).

(f) 1-(1-Bencil-4-metilpirrolidin-3-il)etilamina (^{1}H NMR (200 MHz, $CDCl_3$): δ 7,38-7,11 (m, 5H), 3,63-3,12 (m, 2H), 2,78-2,27 (m, 5H), 2,23-1,18 (m, 4H), 1,10-0,78 (m, 6H)) desde oxima de 1-(1-bencil-4-metilpirrolidin-3-il)etanona (Ejemplo A3d).

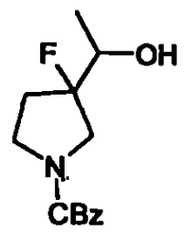
(g) 1-(5-Bencil-5-azaespiro[2,4]hept-7-il)metilamina (^{1}H NMR (200 MHz, $CDCl_3$): δ 7,36-7,21 (m, 5H), 3,68-3,53 (m, 2H), 3,1 (dd, 1H), 2,61-2,38 (m, 5H), 2,1-1,92 (m, 1H), 1,29 (bs, 2H), 0,72-0,32 (m, 4H)) desde amida del ácido 5-bencil-5-azaespiro[2,4]heptano-7-carboxílico (Ejemplo A24).

(h) 1-[3-(1-Feniletil)-3-azabiciclo[3.1.0]hex-1-il]metilamina (MS ES: m/z 317 (MH^+)) desde 3-(1-feniletil)-3-azabiciclo[3.1.0]hexano-1-carbonitrilo (Takemura M., Kimura Y., Kawakami K., EP 0807630).

(i) 1,3-Dibencil-3-pirrolidinmetanamina (MS EI: m/z 281 (MH^+) desde 1,3-dibencil-3-pirrolidin carboxamida (Ejemplo A29).

EJEMPLO A14

Síntesis del bencil éster del ácido 3-fluoro-3-(1-hidroxietil)pirrolidin-1-carboxílico



Una solución de 0,247 g (1 mmol) de bencil éster del ácido 2-mtil-1-oxa-5-azaespiro[2,4]-heptano-5-carboxílico (Ejemplo A9) en diclorometano (3 ml se agrega a un matraz de polipropileno que contiene 0,5 ml de fluoruro de hidrógeno-piridina a -40°C. Se deja que la reacción llegue a la temperatura ambiente y se continúa agitando durante 3 horas. La mezcla de la reacción se vierte en una solución de hidróxido de amonio helado (30 ml) y se extrae con diclorometano. La capa orgánica se seca, se filtra y se concentra para lograr el compuesto del título (0,267 g). ^{1}H NMR (200 MHz, $CDCl_3$): δ 7,35 (s, 5H), 5,13 (s, 2H), 3,96-3,34 (m, 5H), 2,20-1,98 (m, 3H), 1,33-1,26 (m, 3H).

EJEMPLO A15

Síntesis del bencil éster del ácido 3-fluoro-3-(1-metanosulfoniloxietil)pirrolidin-1-carboxílico

A una solución a -10°C de bencil éster del ácido 3-fluoro-3-(1-hidroxietil)pirrolidin-1-carboxílico (Ejemplo A14, 0,267 g, 1,00 mmol), trietilamina (0,4 g, 4 mmol) y diclorometano (10 ml), se agrega cloruro de metanosulfonilo (0,229 g, 2,00 mmol). La mezcla se agita a temperatura ambiente durante 2 horas y se concentra en vacío. El residuo se particiona entre acetato de etilo y agua. La capa orgánica se seca sobre Na_2SO_4 y se concentra para lograr el compuesto del título (0,330 g). ^1H NMR (200 MHz, $CDCl_3$): δ 7,36 (s, 5H), 5,14 (s, 2H), 4,99-4,81 (m, 1H), 3,76-3,37 (m, 4H), 3,06 (s, 3H), 2,25-1,96 (m, 2H), 1,52-1,47 (m, 3H).

EJEMPLO A16

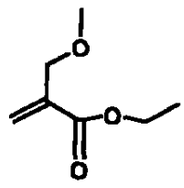
Síntesis del bencil éster del ácido 3-(1-Azidoetil)-3-fluoropirrolidin-1-carboxílico

A una solución de bencil éster del ácido 3-fluoro-3-(1-metanosulfoniloxietil)pirrolidin-1-carboxílico (Ejemplo A15, 0,25 g, 0,72 mmol) en N,N-dimetilformamida (5 ml) se agrega azida de sodio (0,13 g, 2 mmol). La mezcla de la reacción se calienta a 120°C toda la noche. La mezcla se diluye con agua y se extrae con acetato de etilo. Los extractos se lavan con solución salina, se secan sobre Na_2SO_4 y se concentran para lograr el compuesto del título (0,160 g). ^1H NMR (200 MHz,

$CDCl_3$): δ 7,28 (s, 5H), 5,08 (s, 2H), 3,80-3,25 (m, 5H), 2,13-1,75 (m, 2H), 1,40 (d, 3H).

EJEMPLO A17

Síntesis del etil éster del ácido 2-metoximetilacrílico



Una solución de etil α-(bromometil)acrilato (0,99 g, 5,1 mmol [Villieras J., Rambaud M., *Síntesis*, 1982:924-926]) en metanol (10 ml) se agrega a una solución helada de metóxido de sodio (0,33 g, 6,1 mmol) en metanol (50 ml). La suspensión se refluye durante 21 horas, se enfría, se diluye con agua y se extrae con diclorometano. Los extractos orgánicos se secan sobre Na_2SO_4, se filtran y se concentran bajo vacío. El residuo resultante se purifica por cromatografía de columna rápida (acetato de etilo/hexanos 1:5) para lograr el compuesto del título (0,211 g). ^1H NMR (200 MHz, $CDCl_3$): δ 6,33-6,26 (m, 1H), 5,88-5,80 (m, 1H), 4,23 (q, 2H), 4,19-4,10 (m, 2H), 3,41 (s, 3H), 1,31 (t, 3H).

EJEMPLO A18

Método General A

Una solución de sustrato y N-(metoximetil)-N-(trimetilsililmetil)bencilamina (1,3 eq.) en diclorometano a 0°C se trata con ácido trifluoroacético (0,07 eq.). La mezcla se agita a temperatura ambiente durante 3 horas, se diluye con diclorometano y se lava sucesivamente con solución de $NaHCO_3$ saturado y solución salina. Los extractos orgánicos se secan sobre Na_2SO_4, se filtran, y se concentran bajo vacío para lograr los compuestos del título.

Los siguientes ejemplos (Ejemplo A18a-e) se preparan de acuerdo con el Método General A.

(a) Etil éster del ácido 1-bencil-3-metoximetilpirrolidin-3-carboxílico (^{1}H NMR (200 MHz, $CDCl_3$): δ 7,45-7,16 (m, 5H), 3,78-3,67 (m, 2H), 3,55 (s, 2H), 3,31 (s, 3H), 3,11-2,92 (m, 1H), 2,89-2,49 (m, 2H), 2,42-2,21 (m, 2H), 1,99-1,78 (m, 1H), 1,26 (t, 3H)) desde etil éster del ácido 2-metoximetilacrílico. (Ejemplo A17).

(b) 1-(1-Bencil-4,4-dimetilpirrolidin-3-il)etanona (^{1}H NMR (200 MHz, $CDCl_3$): δ 7,36-7,22 (m, 5H), 3,60 (d, 2H), 3,05-2,20 (m,

5H), 2,15 (s, 3H), 1,30 (s, 3H), 0,96 (s, 3H)) desde óxido de mesitilo.

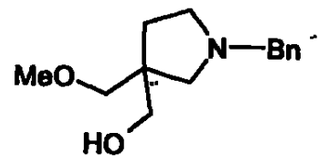
(c) Etil éster del ácido 1-bencil-4-metilpirrolidin-3-carboxílico (^{1}H NMR (200 MHz, $CDCl_3$): δ 7,44-7,13 (m, 5H), 4,21-4,04 (q, 1H), 3,71-3,49 (m, 3H), 2,94-2,71 (m, 3H), 2,61-2,41 (m, 2H), 2,28-2,04 (m, 1H), 1,32-1,18 (t, 3H), 1,16-1,04 (d, 3H). MS ES: m/z 248 (MH^+)) desde crotonato de etilo.

(d) terc-Butil éster del ácido pirrolidin-3-carboxílico (MS ES: m/z 172 (MH^+)) desde terc-butilacrilato.

(e) Ácido etil 1,3-dibencil-3-pirrolidincarboxílico (MS ES: m/z 324 (MH^+)) desde ácido etil-2-fenilmetilacrílico (Vassiliou S., Mucha A., Cuniasse P., Georgiadis D., Lucet-Levannier K., Beau F., Kannan R. et al, *J. Med. Chem.*, 1999;42(14):2610-2620).

EJEMPLO A19

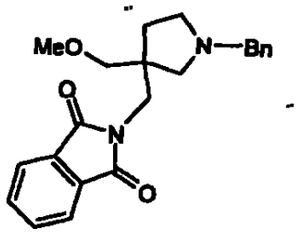
Síntesis de (1-Bencil-3-metoximetilpirrolidin-3-il)metanol



Una solución de etil éster del ácido 1-bencil-3-metoximetilpirrolidin-3-carboxílico (Ejemplo A18a, 2,30 g, 8,3 mmol) en tetrahidrofurano anhidro (10 ml) se agrega gota a gota a una suspensión helada de hidruro de litio y aluminio (0,821 g, 22 mmol) en tetrahdidrofurano (50 ml). La mezcla resutante se agita a temperatura ambiente durante 18 horas, se enfría agregando gota a gota hidróxido de sodio 1N y agua. Los sólidos se remueven por filtración, se suspenden nuevamente en tetrahidrofurano caliente y se filtran. Los filtrados combinados se concentran en vacío y el residuo se particiona entre diclorometano y agua. Los extractos orgánicos se secan sobre Na_2SO_4, se filtran y se concentran bajo vacío para lograr el compuesto del título (1,71 g). ^1H NMR (200 MHz, $CDCl_3$): δ 7,41-7,17 (m, 5H), 3,84-3,43 (m, 4H), 3,34 (s, 2H), 3,32 (s, 3H), 2,85-2,60 (m, 2H), 2,54-2,14 (m, 3H), 1,98-1,50 (m, 2H).

EJEMPLO A20

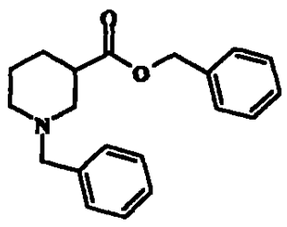
2-(1-Bencil-3-metoximetilpirrolidin-3-ilmetil)isoindol-1,3-diona



Una solución de (1-bencil-3-metoximetilpirrolidin-3-il)metanol (Ejemplo A19, 1,71 g, 7,27 mmol), trifenilfosfina (2,16 g, 8,22 mmol), ftalimida (1,14 g, 7,73 mmol) y tetrahidrofurano anhidro se enfría a 0°C y se trata con dietil azodicarboxilato (1,62 g, 9,31 mmol). La mezcla resultante se agita a temperatura ambiente durante 18 horas y se concentra bajo vacío. El residuo se purifica por cromatografía de columna rápida (acetato de etilo/hexanos 1:5) para lograr el compuesto del título, (0,58 g) como un sólido. ^{1}H NMR (200 MHz, $CDCl_3$): δ 7,91-7,80 (m, 2H), 7,78-7,66 (m, 2H), 7,39-7,11 (m, 5H), 3,95-3,72 (m, 2H), 3,65-3,40 (m, 2H), 3,31 (s, 2H), 3,27 (s, 3H), 2,72-2,34 (m, 4H), 2,02-1,82 (m, 1H), 1,76-1,56 (m, 1H). MS ES: m/z 365 (MH^+).

EJEMPLO A21

Síntesis del bencil éster del ácido 1-bencilpiperidin-3-carboxílico

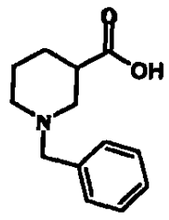


A una solución de ácido nipecótico (8,0 g, 61,9 mmol) en N,N-dimetilformamida (80 ml) se agrega bromuro de bencilo (31,8 g, 186 mmol) y carbonato de potasio (42,8 g, 310 mmol). La mezcla

se calienta a 70°C durante 18 horas y se diluye con acetato de etilo . y agua. El extracto orgánico se lava con ácido clorhídrico 1,0 M, agua y solución salina, se seca sobre Na_2SO_4, se filtra y se concentra en vacío. El residuo se purifica por cromatografía de columna (acetato de etilo/hexanos 1:7) para lograr el compuesto del título (8,6 g). ^1H NMR (200 MHz, DMSO-d_6): δ 7,27-7,42 (m, 10H), 5,07 (s, 2H), 3,45 (s, 2H), 2,88-2,49 (m, 3H), 2,32-1,32 (m, 6H).

EJEMPLO A22

Síntesis del ácido 1-bencilpiperidin-3-carboxílico



A una solución de 3,0 g (9,7 mmol) de bencil éster del ácido 1-bencilpiperidin-3-carboxílico (Ejemplo A21) en metanol (20 ml) se agrega hidróxido de sodio 1N (20 ml), y la reacción se agita a temperatura ambiente durante 18 horas. El metanol se remueve en vacío y la solución acuosa básica se acidifica a pH 4 con ácido clorhídrico 1,0 M. Después de lavar con acetato de etilo, la capa ácida acuosa se liofiliza. El sólido se suspende en metanol (10 ml), se agita durante 10 minutos y se filtra. El filtrado se evapora en vacío para lograr el

compuesto del título. ^{1}H NMR (200 MHz, DMSO-d_6): δ 7,38-7,23 (m, 5H), 3,58 (s, 2H), 2,98-2,40 (m, 3H), 2,30-1,25 (m, 6H).

EJEMPLO A23

Método General A

Se agrega metil litio (1,1 eq.) gota a gota a una solución a -70°C de sustrato en tetrahidrofurano (15 ml). La mezcla resultante se agita a -70°C durante 1 hora, y luego se calienta a temperatura ambiente durante 18 horas. La reacción se diluye con agua helada y el éter y la capa orgánica se separan. La capa acuosa se extrae con éter y los extractos combinados se secan con Na_2SO_4 y se concentran en vacío para lograr el compuesto del título.

Los siguientes compuestos se preparan de acuerdo con el procedimiento general A.

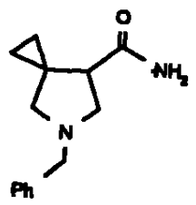
(a) 1-(1-Bencilpiperidin-3-il)etanona (^{1}H NMR (200 MHz, DMSO-d_6): δ 7,38-7,22 (m, 5H), 3,45 (s, 2H), 2,85-2,48 (m, 3H), 2,05 (s, 3H), 2,16-1,06 (m, 6H)) desde ácido 1-bencilpiperidin-3-carboxílico (Ejemplo A22).

(b) 1-(1-Bencil-4-metilpirrolidin-3-il)etanona (^{1}H NMR (200 MHz, $CDCl_3$): δ 7,42-7,18 (m, 5H), 3,71-3,45 (m, 3H), 2,89-2,33

(m, 5H), 2,16 (s, 3H), 2,12 (d, 3H)) desde etil éster del ácido 1-bencil-4-metilpirrolidin-3-carboxílico (Ejemplo A18c).

EJEMPLO A24

Síntesis de la amida de ácido 5-bencil-5-azaespiro[2,4]heptano-7-carboxílico



La amida del ácido 5-bencil-5-azaespiro[2,4]heptano-7-carboxílico (3,32 g) se prepara desde el ácido 5-bencil-5-azaespiro[2,4]heptano-7-carboxílico (Ejemplo A28b, 5,0 g, 21,64 mmol) en diclorometano mediante la conversión al cloruro de ácido usando cloruro de oxalilo (5,0 ml, 65 mmol) y N,N-dimetilformamida (3 gotas. Se deja que la mezcla se agite durante 2 horas, luego que se concentre en vacío. El residuo se disuelve nuevamente en diclorometano y la mezcla se concentra nuevamente en vacio. El residuo se disuelve nuevamente en éter y se trata con una solución de amoníaco en éter. Después de 1 hora, la mezcla se concentra en vacío para proporcionar el compuesto del título. ^{1}H NMR (200 MHz, $CDCl_3$): δ 7,6 (bs, 1H), 7,38-7,23 (m, 5H), 5,42 (bs, 1H), 3,75-3,57 (m, 2H), 3,19 (d, 1H), 2,83-2,64 (m, 2H), 2,4 (d, 2H), 0,96-0,58 (m, 4H).

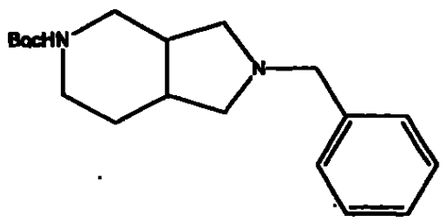
EJEMPLO A25

Síntesis del 2(1-Bencilpirrolidin-3-il)propan-2-ol

A una solución a 5°C de etil éster del ácido 1-bencilpirrolidin-3-carboxílico (0,467 g, 2,0 mmol) en tetrahidrofurano (25 ml) se agrega una solución etérea de bromuro de metilmagnesio (3,3 ml, 10 mmol). La mezcla de la reacción se agita a temperatura ambiente durante 2 horas, se enfría a 0°C y se agrega cloruro de amonio acuoso saturado (10 ml) y luego agua (10 ml). La mezcla se extrae con acetato de etilo (2 x 100 ml) y los extractos orgánicos combinados se lavan con solución salina, se secan sobre Na_2SO_4, se filtran y se concentran bajo vacío para lograr el compuesto del título (0,43 g). ^1H NMR (200 MHz, $CDCl_3$): δ 7,30-7,22 (m, 5H), 3,59 (s, 2H), 3,0 (bs, 1H), 2,80-2,66 (m, 2H), 2,48-2,30 (m, 2H), 2,20-2,05 (m, 1H), 1,94-1,80 (m, 2H), 1,19 (s, 3H), 1,16 (s, 3H).

EJEMPLO A26

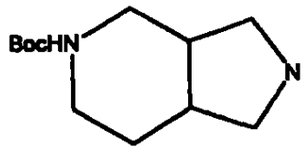
Síntesis del terc-butil éster del ácido 2-benciloctahidropirrolo[3,4-c]piridin-5-carboxílico



2-Benciloctahidropirrolo[3,4-c]piridina (21,6 g, 100 mmol [Himmer T., Petersen U., Bremm K.-D., Endermann R., Stegermann M., Wetzstein H-G., 1995, US 5578604] se disuelve en 1.000 ml de diclorometano que contiene trietilamina (16,7 ml, 120 mmol). Luego se agrega di-t-butildicarbonato (22,6 g, 120 mmol) y la mezcla se agita a temperatura ambiente durante 18 horas. La capa orgánica se lava con $NaHCO_3$ saturado, solución salina, se seca y se concentra para proporcionar 30 g del compuesto del título como un aceite; MS EI+: 318 (MH^+).

EJEMPLO A27

Síntesis del terc-butil éster del ácido octahidropirrolo[3,4-c]piridin-5-carboxílico

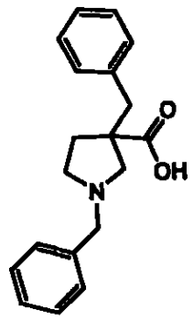


El terc-butil éster del ácido 2-benciloctahidropirrolo[3,4-c]piridin-5-carboxílico (Ejemplo A26, 24,98 g, 78,8 mmol) en 400 ml de metanol se trata con 2,5 g de 20% de Pd/C y se agita durante 20,5 horas bajo 50 PSI de hidrógeno. La solución se

filtra y se concentra para lograr 17,8 g del compuesto del título como un sólido. MS APCI: m/z 228 (MH^+).

EJEMPLO A28

(a) Síntesis del ácido 1,3-dibencilpirrolidin-3-carboxílico

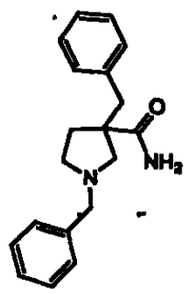


A una solución de etil éster del ácido 1,3-dibencilpirrolidin-3-carboxílico (Ejemplo A18e, 13,1 g, 41 mmol) en 250 ml de metanol se agrega NaOH 2N (46 ml, 92 mmol) y la reacción se calienta a reflujo durante 24 horas. La solución se enfría, se concentra, se disuelve nuevamente en agua y se extrae con éter. El pH de la capa acuosa se ajusta a 7 y el sólido precipitado se recoge, para dar 9,3 g del compuesto del título. MS EI+: m/z 296 (MH^+), punto de fusión 209°C-210°C.

(b) Ácido 2-bencil-5-azaespiro[2,4]heptano-7-carboxílico (MS ES: m/z 232) desde 5-bencil-7-etoxicarbonil-5-azaespiro[2,4]heptano (A1) usando el método del Ejemplo A28a.

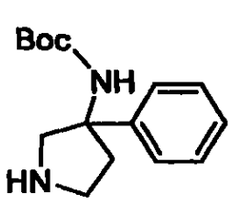
EJEMPLO A29

Síntesis de amida de ácido 1,3-dibencilpirrolidin-3-carboxílico



Una mezcla de ácido 1,3-dibencilpirrolidin-3-carboxílico (Ejemplo A28, 4,0 g, 13,5 mmol), 1,1'-carbonildiimidazol (2,42 g, 14,9 mmol) y trietilamina (2,08 ml, 14,9 mmol) en tetrahidrofurano (100 ml) se calienta a reflujo durante 1,5 horas. La solución se enfría, se vierte en NH_4OH (300 ml) y se agita durante 18 horas. La mezcla se extrae con cloroformo, la capa orgánica se lava con agua, se seca y se concentra para lograr 4,13 g del compuesto del título como un aceite; MS EI+: m/z 295 (MH^+).

EJEMPLO A30



terc-Butil éster del ácido (1-bencil-3-fenilpirrolidin-3-il)carboxílico (Hagen S.E., Domagala J.M., Heifetz C.L., Sánchez J.P., Solomon M., *J. Med. Chem.*, 1990;33(2):849-854) (2,79 g, 7,9 mmol) en 100 ml de metanol se trata con 1,0 g de 20% de Pd/C y se agita durante 17 horas bajo 50 psi de hidrógeno. La solución se filtra y se concentra para lograr 2,07 g del compuesto del título como una espuma; MS EI+: m/z 263 (MH^+).

Los compuestos de la presente invención son potentes inhibidores del crecimiento bacteriano en animales y en superficies, y también son inhibidores de enzimas bacterianas. Los compuestos de la invención han sido evaluados en numerosos ensayos in vitro y en vivo estándar usados rutinariamente en el arte antibacteriano para medir la actividad antibacteriana de los compuestos en ensayo.

Ensayo Antibacteriano

Los compuestos de la presente invención se ensayan contra un surtido de organismos gramnegativos y grampositivos usando técnicas de microtitulación estándar (Cohen et al, *Antimicrob. Agents Chemother.*, 1985;28:766; Heifetz et al, *Antimicrob. Agents Chemother.*, 1974;6:124). Los resultados de la evaluación de 3-aminoquinazolin-2,4-dionas de la Fórmula I

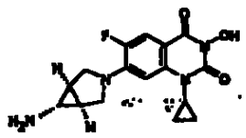
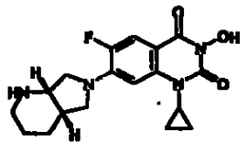
representativas se muestran en la Tabla 2 y se comparan con dos 3-hidroxiquinazolin-2,4-dionas.

Ensayo de la Girasa de ADN

Los efectos de lso compuestos de la invención sobre la actividad de la girasa de ADN se determinan en el ensayo de inhibición de superenrollado, siguiendo las condiciones de reacción recomendadas por el proveedor de la enzima (Lucent, Ltd., Leicester, UK). Las reacciones se realizan en tampón G (35 mM de Tris-HCl (pH 7,5), 24 mM de KCl, 4 mM de $MgCl_2$, 2 mM de DTT, 1,8 mM de espermidina, 1 mM de ATP, 0,1 mg/ml de albúmina de suero bovino). Plásmido pBR322 relajado (0,25 µg, Lucent, Ltd., Leicester, UK) reacciona con 1 U de girasa *E. coli* (Lucent, Ltd., Leicester, UK) en la ausencia o presencia de compuestos en ensayo, durante 30 minutos a 37°C. Las reacciones son detenidas agregando SDS y proteinasa K a las respectivas concentraciones finales de 1% y 0,5 mg/ml. Después de estar otros 30 minutos a 37°C, se agrega un décimo del volumen de 10X de tampón de carga (0,3% de azul de bromofenol, 36% de Ficoll, 10 mM de Na_2HPO_4) y las reacciones se cargan en geles de agarosa y son sometidos a electroforesis. La concentración de compuestos de la Fórmula I de la invención representativos que inhiben el 50% de la actividad de

superenrollado de la girasa de ADN se da como un IC_{50} y se registra en la Tabla 2.

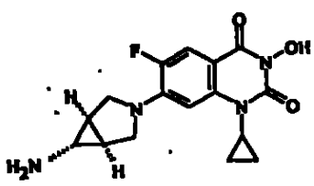
TABLA 2. Actividades Antibacteriana y de girasa *E. coli*

Número o Estructura del Compuesto	Concentraciones Inhibidoras Mínimas µg/ml						Girasa *E.Coli*
	Gramnegativas			Grampositivas			IC_{50} (µM)
	E.coli MC4100	*E.coli* B90	*E.coli* Tol C	*E. faecalis* RB1	*S. aureus* 29213	*S. pyogenes* C203	
1	2,0	1,0	0,25	1,0	0,5	0,13	1,0
2	16,0	4,0	2,0	>64	>64	>64	26,0
7	2,0	0,5	0,25	8,0	8,0	4,0	1,3
9	2,0	1,0	0,5	32,0	16,0	16,0	3,0
11	2,0	0,5	0,25	8,0	8,0	4,0	11,0
12	16,0	0,25	0,13	4,0	2,0	8,0	2,1
14	4,0	0,25	0,5	8,0	8,0	4,0	2,4
	1,0	0,25	0,25	4,0	4,0	2,0	0,9
	8,0	2,0	1,0	64,0	32,0	32,0	5,0

La actividad en vivo de los compuestos de la invención se evalúa de acuerdo con el procedimiento de Miller et al, *Proc. Soc. Exp. Biol. Med.*, 1944;57:261. La dosis protectora mediana

(PD_{50}) se determina en ratones a los que se dan inyecciones sistémicas letales. Dos 3-aminoquinazolin-2,4-dionas son comparadas con una 3-hidroxiquinazolin-2,4-diona, y los resultados se presentan en la Tabla 3. Los resultados establecen la inesperada superioridad de los compuestos de la invención de 3-amino comparados con análogos 3-hidroxi similares.

TABLA 3. Dosis Protectora Mediana En Vivo (PD_{50}) en Ratones

Número o Estructura del Compuesto	Organismo	PD50 (mg/kg)
1	S. pyogenes	12
10	*E. coli*	72
	*S. pyogenes*	>100

Ensayo de Antibacterianos con Resistencia Cruzada

Los compuestos de la presente invención se ensayan contra un surtido de organismos *E. coli* y *S. aureus* resistentes a la ciprofloxacina descriptos abajo usando técnicas de microtitulación estándar (Cohen, et al, *Antimicrob. Agents Chemother.*, 1985;28:766; Heifetz, et al, *Antimicrob. Agents*

Chemother., 1974;6:124). Los resultados de la evaluación se muestran en la Tabla 4 y se comparan con dos 3-hidroxiquinazolin-2,4-dionas.

Organismos *E. coli* y *S. aureus*

E. coli JL4: *E. coli* W3110 + Tol C- (cepa deficiente de bomba Tol C con antecedente de *E. coli* W3110)

E. coli LLM-1: Isógeno a *E. coli* JL4 con mutación D87G (ácido aspártico a glicina en la posición 87) en la QRDR (región de determinación de resistencia a quinolina)

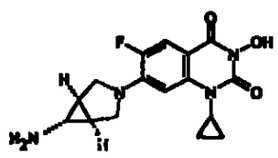
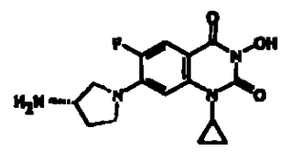
S. aureus UC-76: Cepa de laboratorio sensible típica (tipo salvaje)

S. aureus 2552: Isógeno a *S. aureus* UC-76, con bomba norA regulada hacia arriba

S. aureus 2554: Isógeno a *S. aureus* 2552, con mutación de punto en la posición 80 de la subunidad *grlA*

S. aureus 2558: Isógeno a *S. aureus* 2554, con mutación de punto en la posición 84 de la subunidad *gyrA*

TABLA 4. Actividades Antibacterianas contra Cepas Resistentes a la Ciprofloxacina

Número o Estructura del Compuesto	Concentraciones Inhibidoras Mínimas µg/ml					
	E.coli JL4	*E.coli* LLM1	*S.aureus* UC-76	*S.aureus* 2552	*S.aureus* 2554	*S.aureus* 2558
1	0,13	0,5	0,13	1	1	1
3	0,5	1	1	2	2	4
12	0,06	0,25	1	1	1	2
	0,25	4	4	32	32	>64
	0,5	2	4	>64	>64	>64

Las imitaciones de quinolona provistos por esta invención muestran actividad gramnegativa y grampositiva. Los compuestos también muestran inhibición de la actividad/girasa de ADN bacteriana. Los compuestos demuestran una actividad protectora en vivo en ratones y no son altamente citotóxicos para las células de mamíferos, indicando así una selectividad para las bacterias. Los compuestos de la Fórmula I son entonces útiles

para tratar y prevenir la enfermedad y el crecimiento bacteriano en animales y superficies. Los compuestos pueden aplicarse a superficies de madera y de metal, por ejemplo, para eliminar el crecimiento bacteriano. Los compuestos pueden administrarse a animales tales como humanos, caballos, perros, ovejas, y ganado para prevenir y tratar infecciones bacterianas.

Los compuestos de la presente invención pueden prepararse y administrarse en una amplia variedad de formas de dosificación oral y parenteral para la administración conveniente a los animales. Por lo tanto, los compuestos de la presente invención pueden administrarse por inyección, es decir, en forma intravenosa, intramuscular, intracutánea, subcutánea, intraduodenal, o intraperitoneal. También los compuestos de la presente invención pueden administrarse por inhalación, por ejemplo, intranasal. Además, los compuestos de la presente invención pueden administrarse en forma transdérmica. Será obvio para los expertos en el arte que las siguientes formas de dosificación pueden comprender como el componente activo, un compuesto de la Fórmula I o una sal farmacéuticamnte aceptable del compuesto de la Fórmula I correspondiente. Las formulaciones típicamente comprenden del 1% al 95% en peso del compuesto activo de la invención. Los compuestos pueden disolverse o suspenderse en líquidos, tales como etanol, y

aplicarse a superficies de madera o de metal para prevenir y/o eliminar el crecimiento bacteriano.

Para preparar composiciones farmacéuticas a partir de los compuestos de la presente invención, los portadores farmacéuticamnte aceptables pueden ser sólidos o líquidos. Las preparaciones en forma sólida incluyen polvos, tabletas, cápsulas, supositorios, y gránulos dispersables. Un portador sólido puede ser una o más sustancias que también pueden actuar como diluyentes, agentes saborizantes, ligantes, conservantes, agentes desintegradores de tabletas, o un material encapsulante.

En los polvos, el portador es un sólido finamente dividido que se mezcla con el componente activo finamente dividido.

En las tabletas, el componente activo se mezcla con el portador que tiene las propiedades ligantes necesarias en proporciones adecuadas y se compacta en la forma y tamaño deseados.

Los polvos y tabletas preferentemente contienen del 5% al 70% del compuesto activo. Los portadores adecuados son carbonato de magnesio, estearato de magnesio, talco, azúcar, lactosa, pectina, dextrina, almidón, gelatina, tragacanto,

metilcelulosa, carboximetilcelulosa de sodio, una cera de bajo punto de fusión, manteca de cacao, y similares. El término "preparación" incluye la formulación del compuesto activo con un material encapsulante como un portador que proporcionar una cápsula en la cual el componente activo con o sin otros portadores, está rodeado por un portador, que por lo tanto está en asociación con él. En forma similar, están incluidas las tabletas. Las tabletas, polvos, cápsulas pueden usarse como formas de dosificación sólidas adecuadas para la administración oral.

Para preparar supositorios, una cera de bajo punto de fusión, tal como una mezcla de glicéridos de ácidos grasos o manteca de cacao, se funde primero y el componente activo se dispersa homogéneamente en ella, por ejemplo agitando. La mezcla homogénea fundida luego se vierte en moldes de tamaño conveniente, se la deja enfriar y por lo tanto solidificar.

Las preparaciones en forma líquida incluyen soluciones, suspensiones, y emulsiones, por ejemplo, soluciones en agua o propilenglicol. Para la inyección parenteral, se pueden formular preparaciones líquidas en solución en polietilenglicol acuoso.

Las soluciones acuosas adecuadas para el uso oral pueden prepararse disolviendo el componente activo en agua y agregando agentes colorantes, saborizantes, estabilizadores y espesantes adeduados según se desee.

Las suspensiones acuosas adecuadas para uso oral pueden hacerse dispersando el componente activo finamente dividido en agua con un material viscoso, tal como gomas naturales o sintéticas, resinas, metilcelulosa, carboximetilcelulosa de sodio, y otros agentes de suspensión conocidos.

También están incluidas las preparaciones en forma sólida que han de ser convertidas, poco antes de ser usadas, en preparaciones en forma líquida para administración oral. Tales formas líquidas incluyen soluciones, suspensiones, y emulsiones. Estas preparaciones pueden contener, además del componente activo, colorantes, saborizantes, estabilizadores, tampones, edulcorantes artificiales y naturales, dispersantes, espesantes, agentes solubilizantes, y similares.

La preparación farmacéutica está preferentemente en forma de dosificación unitaria. En tal forma la preparación se divide en dosis unitarias que contienen cantidades apropiadas del componente activo. La forma de dosificación unitaria puede ser una preparación empaquetada, el paquete contiene cantidades

discretas de la preparación, tales como tabletas, cápsulas, y polvos empaquetados en tubos o ampollas. También la forma de dosificación unitaria puede ser la propia cápsula o tableta, o puede ser el número apropiado de éstas en forma empaquetada.

La cantidad del compuesto de la invención de una preparación de dosis unitaria puede variarse o ajustarse de 0,1 mg a 100 mg, preferentemente de 0,5 mg a 100 mg, de acuerdo con la aplicación particular y la potencia del componente activo determinada por el médico. La composición puede contener también, si se desea, otros agentes terapéuticos compatibles.

En el uso terapéutico como agentes para el tratamiento de infecciones causadas por bacterias, los compuestos utilizados en el método farmacéutico de esta invención se administran en la dosificación inicial de 0,01 mg a 500 mg/kg diarios. Se prefiere una gama de dosificación diaria de 0,01 mg a 100 mg/kg. Las dosificaciones, sin embargo, pueden variarse según los requerimientos del paciente, la gravedad de la condición que se está tratando, y el compuesto particular que se está empleando. La determinación de la dosificación correcta para una situación particular está dentro de la pericia médica. Generalmente, el tratamiento se inicia con dosis más pequeñas que son menores que la dosis óptima del compuesto. Luego, la dosis se aumenta en pequeños incrementos hasta que se logra el

efecto óptimo según las circunstancias. Por conveniencia, la dosificación diaria total puede dividirse y administrarse en porciones durante el día, si así se desea.

Los siguientes ejemplos adicionales ilustran formulaciones típicas para su uso de acuerdo con la invención.

EJEMPLO 37

1. Formulación de Tabletas

Ingrediente	Cantidad (mg)
Compuesto No. 10	50
Almidón de maíz (mezcla)	15
Almidón de maíz (pasta)	5
Lactosa	50
Estearato de calcio	2
Fosfato de dicalcio	28
	150

El compuesto 10 se mezcla hasta lograr uniformidad con la mezcla de almidón de maíz, lactosa, y fosfato de dicalcio. La pasta de almidón de maíz se prepara como una pasta acuosa al 10% y se mezcla hasta lograr uniformidad con la otra mezcla. La granulación húmeda se pasa a través de un tamiz de malla 8 estándar. Los gránulos húmedos se secan y luego se mezclan hasta lograr uniformidad con el estearato de calcio y se

prensan en una tableta. Tales tabletas se administran en forma oral a pacientes que sufren infecciones bacterianas a razón de una a cuatro veces por día.

2. Formulación de Cápsulas

Ingredientes	Cantidad (mg)
Compuesto No. 25	120
Lactosa USP	150
Almidón	100
Estearato de magnesio	5
	150

Los ingredientes se mezclan hasta lograr uniformidad y se empaquetan en una cápsula de gelatina blanda. Las cápsulas se administran a razón de una a dos por día a un paciente infectado con bacterias resistentes a antibióticos de quinolona disponibles comercialmente.

3. Preparación Líquida

Ingrediente	Cantidad
Compuesto No. 18	500 mg
Agua	1.000 mg

El compuesto se disuelve en agua y la solución se asperja sobre superficies de madera y en instalaciones de duchas para controlar y eliminar el crecimiento bacteriano.

La invención y la forma y proceso para fabricarla y usarla, son conocidas en el arte en términos completos, claros, concisos y precisos que permiten a cualquier persona conocedora del arte a quien corresponda, fabricarla y usarla. Se ha de entender que se han descripto realizaciones preferidas de la presente invención y que se pueden hacer modificaciones en ella sin apartarse del espíritu o alcance de la presente invención que se expone en las reivindicaciones. Para señalar particularmente y reivindicar en forma distinguible el objeto considerado como la invención, las siguientes reivindicaciones concluyen esta memoria descriptiva.

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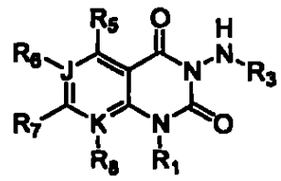
REIVINDICACIONES

Habiendo descripto y determinado la naturaleza y alcance de la presente invención y la manera en que la misma ha de ser llevada a la práctica, se declara que lo que reivindica como invención y de propiedad exclusiva es:

1. Un compuesto de la Fórmula I



I

o una sal farmacéuticamente aceptable de ellos en donde:

R_1 y R_3 independientemente son H,

alquilo y alquilo sustituido de C_1-C_{12},

alquenilo y alquenilo sustituido de C_2-C_{12},

alquinilo y alquinilo sustituido de C_2-C_{12},

cicloalquilo y cicloalquilo sustituido de C_3-C_{12},

arilo y arilo sustituido,

heterocíclico y heterocíclico sustituido,

o heteroarilo y heteroarilo sustituido;

R_5, R_6 y R_8 independientemente son H,

$(O)_n$alquilo de C_1-C_{12}, y alquilo sustituido;

$(O)_n$alquenilo de C_2-C_{12} y alquenilo sustituido;

$(O)_n$alquinilo de C_2-C_{12} y alquinilo sustituido;

en donde n es 0 o 1,

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halo,

NO_2,

CN,

NR'R";

R' y R" independientemente son H,

alquilo y alquilo sustituido de C_1-C_{12},

alquenilo y alquenilo sustituido de C_2-C_{12},

alquinilo y alquinilo sustituido de C_2-C_{12},

CO-alquilo de C_1-C_{12} y alquilo sustituido,

o R' y R" tomados junto con el nitrógeno al cual están unidos forman un anillo de 3 a 7 miembros que contiene de 1 a 3 heteroátomos seleccionados de N, O y S, dicho anillo es no sustituido o sustituido con hasta 4 grupos sustituyentes;

R_1 y R_8 pueden ser tomados junto con los átomos a los cuales están unidos para formar un anillo cíclico que tiene de 1 a 3 heteroátomos seleccionados de N, O y S y optativamente sustituidos por R' y R";

R_7 es hidrógeno,

alquilo y alquilo sustituido de C_1-C_{12},

alquenilo y alquenilo sustituido de C_2-C_{12},

alquinilo y alquinilo sustituido de C_2-C_{12},

halo,

NO_2,

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CN,

NR'R",

COOR',

arilo,

arilo fusionado,

heterocíclico,

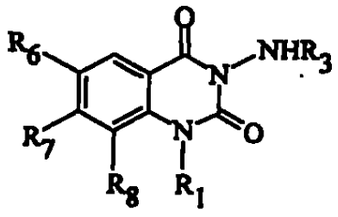
heterocíclico bicíclico, o

espiro heterocíclico

en donde todos los grupos del anillo pueden ser sustituidos; y

J y K independientemente son C o N, siempre que cuando J o K es N, R_6 o R_8 esté ausente en esa posición.

2. Un compuesto de la Fórmula II



II

o una sal farmacéuticamente aceptable de ellos,

en donde:

R_1 y R_3 independientemente son H,

alquilo y alquilo sustituido de C_1-C_{12},

alquenilo y alquenilo sustituido de C_2-C_{12},

alquinilo y alquinilo sustituido de C_2-C_{12},

cicloalquilo y cicloalquilo sustituido de C_3-C_{12},

arilo y arilo sustituido,

heterocíclico y heterocíclico sustituido,

o heteroarilo y heteroarilo sustituido;

R_6 y R_8 independientemente son H,

$(O)_n$alquilo de C_1-C_{12}, y alquilo sustituido;

$(O)_n$alquenilo de C_2-C_{12} y alquenilo sustituido;

$(O)_n$alquinilo de C_2-C_{12} y alquinilo sustituido;

en donde n es 0 o 1,

halo,

NO_2,

CN,

NR'R";

R_7 es hidrógeno,

alquilo y alquilo sustituido de C_1-C_{12},

alquenilo y alquenilo sustituido de C_2-C_{12},

alquinilo y alquinilo sustituido de C_2-C_{12},

halo,

NO_2,

CN,

NR'R",

COOR',

arilo,

arilo fusionado,

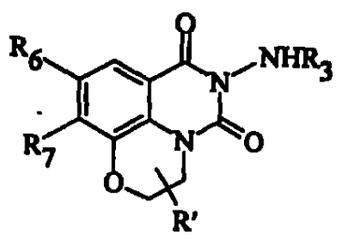
heterocíclico,

heterocíclico bicíclico, o

espiro heterocíclico

en donde todos los grupos del anillo pueden ser sustituidos.

3. Un compuesto de la Fórmula III



III

en donde

R_3 es H,

alquilo y alquilo sustituido de C_1-C_{12},

alquenilo y alquenilo sustituido de C_2-C_{12},

alquinilo y alquinilo sustituido de C_2-C_{12},

cicloalquilo y cicloalquilo sustituido de C_3-C_{12},

arilo y arilo sustituido,

heterociclico y heterociclico sustituido,

o heteroarilo y heteroarilo sustituido;

R_6 es H,

$(O)_n$alquilo de C_1-C_{12}, y alquilo sustituido;

$(O)_n$alquenilo de C_2-C_{12} y alquenilo sustituido;

$(O)_n$alquinilo de C_2-C_{12} y alquinilo sustituido;

en donde n es 0 o 1,

halo,

NO_2,

CN,

393
392

NR'R";

R_7 es hidrógeno,

alquilo y alquilo sustituido de C_1-C_{12},

alquenilo y alquenilo sustituido de C_2-C_{12},

alquinilo y alquinilo sustituido de C_2-C_{12},

halo,

NO_2,

CN,

NR'R",

COOR',

arilo,

arilo fusionado,

heterocíclico,

heterocíclico biciclico, o

espiro heterocíclico

en donde todos los grupos del anillo pueden ser sustituidos; y

R' es H,

alquilo y alquilo sustituido de C_1-C_{12},

alquenilo y alquenilo sustituido de C_2-C_{12},

alquinilo y alquinilo sustituido de C_2-C_{12},

CO-alquilo de C_1-C_{12} y alquilo sustituido.

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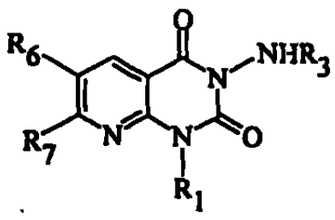
(4) Un compuesto de la Fórmula IV



IV

o una sal farmacéuticamente aceptable de ellos,

en donde:

R_1 y R_3 independientemente son H,

alquilo y alquilo sustituido de C_1-C_{12},

alquenilo y alquenilo sustituido de C_2-C_{12},

alquinilo y alquinilo sustituido de C_2-C_{12},

cicloalquilo y cicloalquilo sustituido de C_3-C_{12},

arilo y arilo sustituido,

heterocíclico y heterocíclico sustituido,

o heteroarilo y heteroarilo sustituido;

R_6 es H,

$(O)_n$alquilo de C_1-C_{12}, y alquilo sustituido;

$(O)_n$alquenilo de C_2-C_{12} y alquenilo sustituido;

$(O)_n$alquinilo de C_2-C_{12} y alquinilo sustituido;

en donde n es 0 o 1,

halo,

NO_2,

CN,

NR'R";

395
394

R_7 es hidrógeno,

alquilo y alquilo sustituido de C_1-C_{12},

alquenilo y alquenilo sustituido de C_2-C_{12},

alquinilo y alquinilo sustituido de C_2-C_{12},

halo,

NO_2,

CN,

NR'R",

COOR',

arilo,

arilo fusionado;

heterocíclico,

heterocíclico bicíclico, o

espiro heterocíclico

en donde todos los grupos del anillo pueden ser sustituidos;

R' y R" independientemente son H,

alquilo y alquilo sustituido de C_1-C_{12},

alquenilo y alquenilo sustituido de C_2-C_{12},

alquinilo y alquinilo sustituido de C_2-C_{12},

CO-alquilo de C_1-C_{12} y alquilo sustituido,

o R' y R" tomados junto con el nitrógeno al cual están unidos forman un anillo de 3 a 7 miembros que contiene de 1 a 3 heteroátomos seleccionados de N, O y S, dicho anillo es no sustituido o sustituido con hasta 4 grupos sustituyentes.

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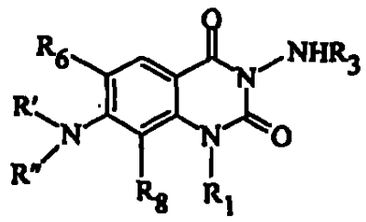
9. Un compuesto de la la Fórmula V



V

o una sal farmacéuticamente aceptable de ellos,

en donde:

R_1 y R_3 independientemente son H,

alquilo y alquilo sustituido de C_1-C_{12},

alquenilo y alquenilo sustituido de C_2-C_{12},

alquinilo y alqùinilo sustituido de C_2-C_{12},

cicloalquilo y cicloalquilo sustituido de C_3-C_{12},

arilo y arilo sustituido,

heterocíclico y heterocíclico sustituido,

o heteroarilo y heteroarilo sustituido;

R_6 y R_8 independientemente son H,

$(O)_n$alquilo de C_1-C_{12}, y alquilo sustituido;

$(O)_n$alquenilo de C_2-C_{12} y alquenilo sustituido;

$(O)_n$alquinilo de C_2-C_{12} y alquinilo sustituido;

en donde n es 0 o 1,

halo,

NO_2,

CN,

NR'R";

R' y R" independientemente son H,

397
396

alquilo y alquilo sustituido de C_1-C_{12},

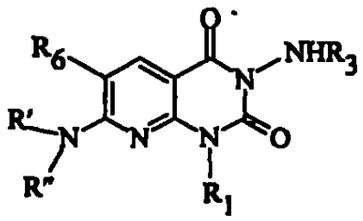
alquenilo y alquenilo sustituido de C_2-C_{12},

alquinilo y alquinilo sustituido de C_2-C_{12},

CO-alquilo de C_1-C_{12} y alquilo sustituido,

o R' y R" tomados junto con el nitrógeno al cual están unidos forman un anillo de 3 a 7 miembros que contiene de 1 a 3 heteroátomos seleccionados de N, O y S, dicho anillo es no sustituido o sustituido con hasta 4 grupos sustituyentes.

6. Un compuesto de la Fórmula VI



VI

o una sal farmacéuticamente aceptable de ellos,

en donde:

R_1 y R_3 independientemente son H,

alquilo y alquilo sustituido de C_1-C_{12},

alquenilo y alquenilo sustituido de C_2-C_{12},

alquinilo y alquinilo sustituido de C_2-C_{12},

cicloalquilo y cicloalquilo sustituido de C_3-C_{12},

arilo y arilo sustituido,

heterocíclico y heterocíclico sustituido,

o heteroarilo y heteroarilo sustituido;

R_6 es H,

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3918

$(O)_n$alquilo de C_1-C_{12}, y alquilo sustituido;

$(O)_n$alquenilo de C_2-C_{12} y alquenilo sustituido;

$(O)_n$alquinilo de C_2-C_{12} y alquinilo sustituido;

en donde n es 0 o 1,

halo,

NO_2,

CN,

NR'R";

R' y R" independientemente son H,

alquilo y alquilo sustituido de C_1-C_{12},

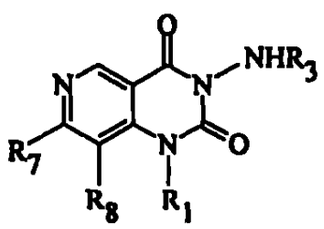
alquenilo y alquenilo sustituido de C_2-C_{12},

alquinilo y alquinilo sustituido de C_2-C_{12},

CO-alquilo de C_1-C_{12} y alquilo sustituido,

o R' y R" tomados junto con el nitrógeno al cual están unidos forman un anillo de 3 a 7 miembros que contiene de 1 a 3 heteroátomos seleccionados de N, O y S, dicho anillo es no sustituido o sustituido con hasta 4 grupos sustituyentes.

7. Un compuesto de la Fórmula VII



VII

398
399

o una sal farmacéuticamente aceptable de ellos,

en donde:

R_1 y R_3 independientemente son H,

alquilo y alquilo sustituido de C_1-C_{12},

alquenilo y alquenilo sustituido de C_2-C_{12},

alquinilo y alquinilo sustituido de C_2-C_{12},

cicloalquilo y cicloalquilo sustituido de C_3-C_{12},

arilo y arilo sustituido,

heterocíclico y heterocíclico sustituido,

o heteroarilo y heteroarilo sustituido;

R_7 es hidrógeno,

alquilo y alquilo sustituido de C_1-C_{12},

alquenilo y alquenilo sustituido de C_2-C_{12},

alquinilo y alquinilo sustituido de C_2-C_{12},

halo,

NO_2,

CN,

NR'R",

COOR',

arilo,

arilo fusionado,

heterocíclico,

heterocíclico biciclico, o

espiro heterocíclico

en donde todos los grupos del anillo pueden ser sustituidos; y

R_8 es H,

$(O)_n$alquilo de C_1-C_{12}, y alquilo sustituido;

$(O)_n$alquenilo de C_2-C_{12} y alquenilo sustituido;

$(O)_n$alquinilo de C_2-C_{12} y alquinilo sustituido;

en donde n es 0 o 1,

halo,

NO_2,

CN,

NR'R";

en donde R' y R" independientemente son H,

alquilo y alquilo sustituido de C_1-C_{12},

alquenilo y alquenilo sustituido de C_2-C_{12},

alquinilo y alquinilo sustituido de C_2-C_{12},

CO-alquilo de C_1-C_{12} y alquilo sustituido,

o R' y R" tomados junto con el nitrógeno al cual están unidos forman un anillo de 3 a 7 miembros que contiene de 1 a 3 heteroátomos seleccionados de N, O y S, dicho anillo es no sustituido o sustituido con hasta 4 grupos sustituyentes;

R_1 y R_8 pueden ser tomados junto con los átomos a los cuales están unidos para formar un anillo cíclico que tiene de 1 a 3 heteroátomos seleccionados de N, O y S y optativamente sustituidos por R' y R";

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401

R_7 es hidrógeno,

alquilo y alquilo sustituido de C_1-C_{12},

alquenilo y alquenilo sustituido de C_2-C_{12},

alquinilo y alquinilo sustituido de C_2-C_{12},

halo,

NO_2,

CN,

NR'R",

COOR',

arilo,

arilo fusionado,

heterocíclico,

heterocíclico bicíclico, o

espiro heterocíclico

en donde todos los grupos del anillo pueden ser sustituidos; y

J y K independientemente son C o N, siempre que cuando J o K es N, R_6 o R_8 esté ausente en esa posición.

8. Un compuesto de la reivindicación 1, caracterizado porque R_7 se selecciona de:

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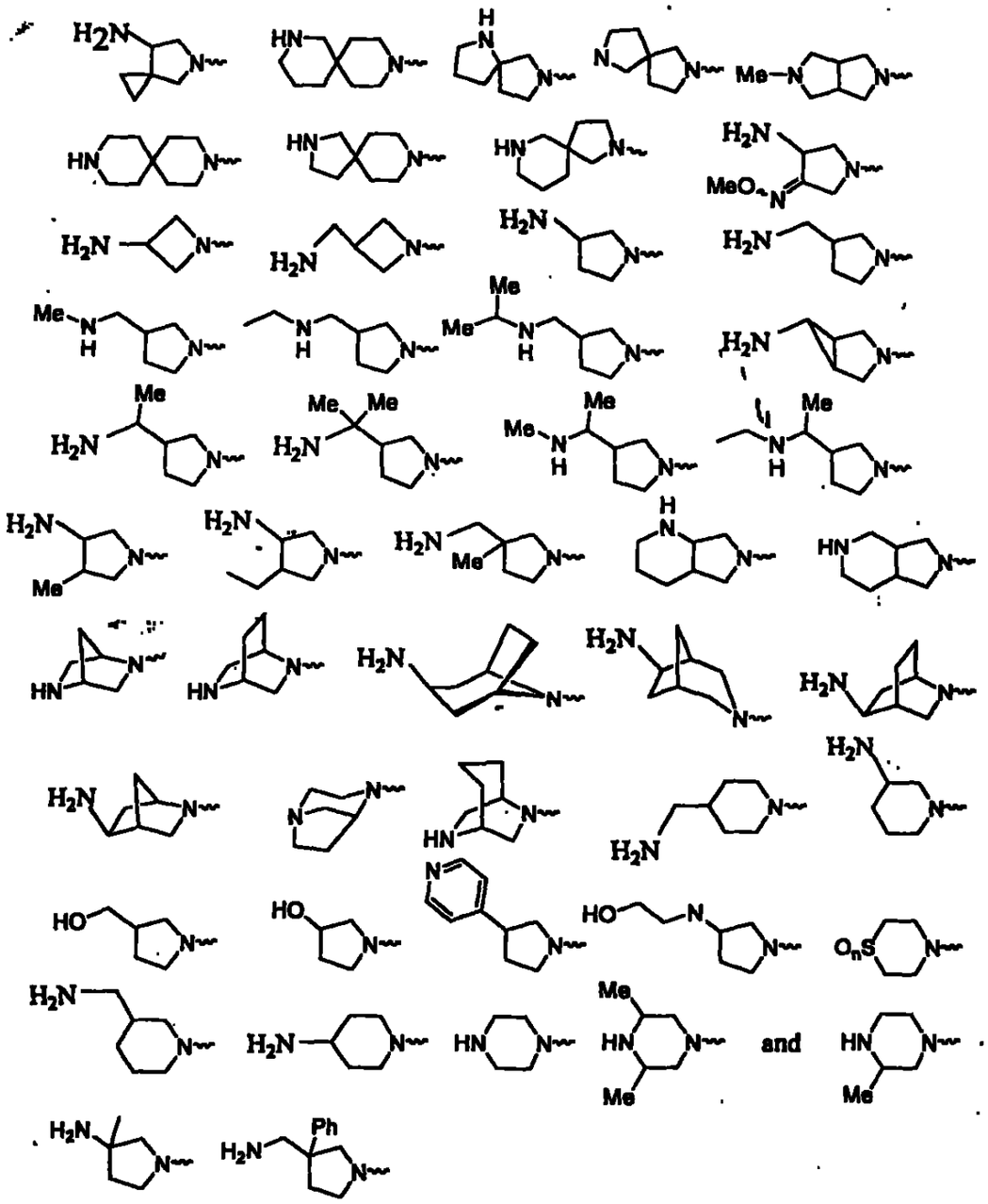
402



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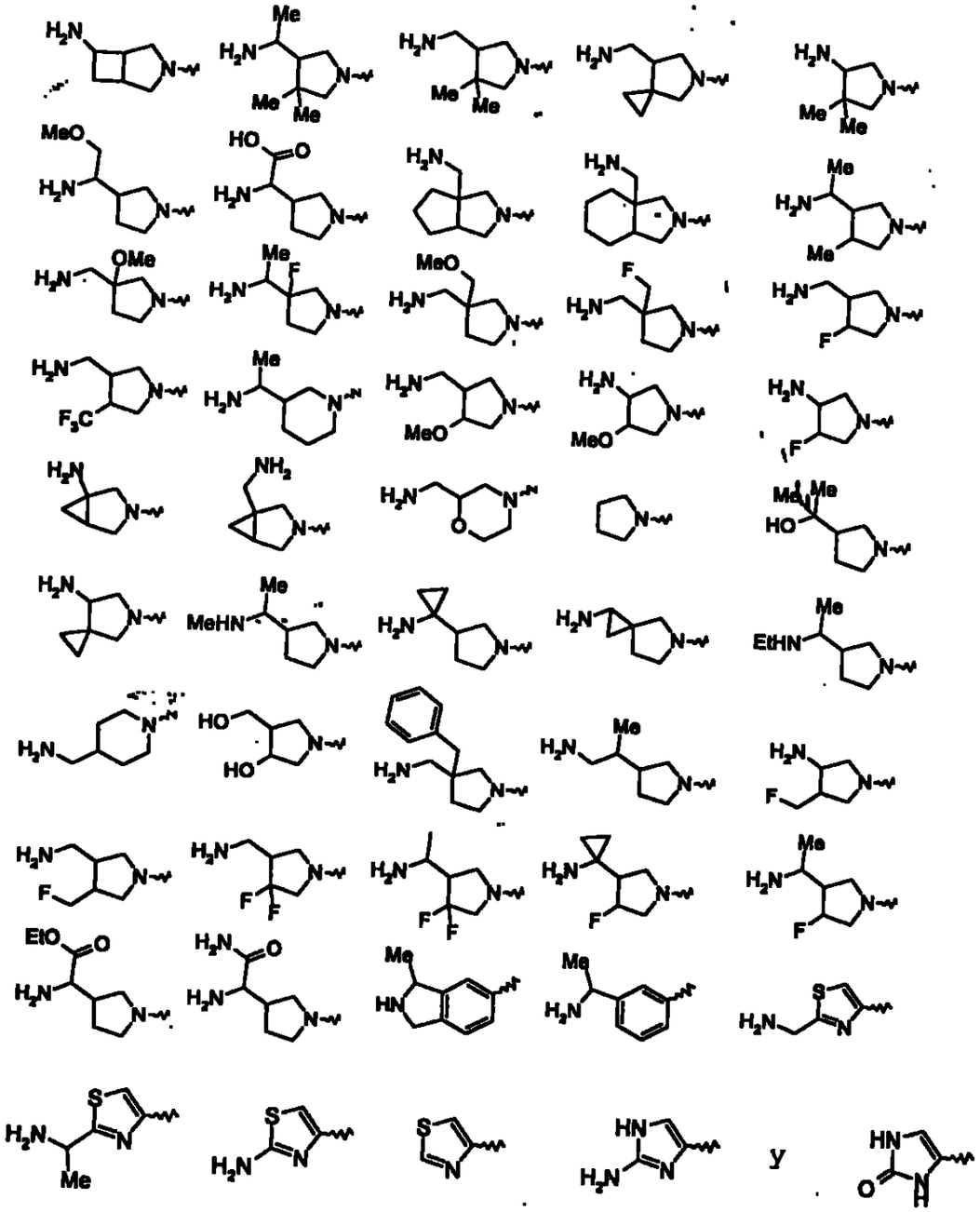

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404

9. Un compuesto de la reivindicació 8, caracterizado porque R_7 es pirrolidinilo, pirrolidinilo sustituido, piperazinilo, piperazinilo sustituido, piperidinilo o piperidinilo sustituido.

10. Un compuesto seleccionado de:

3-Amino-7-(3-aminometilpirrolidin-1-il)-8-cloro-1-ciclopropil-6-fluoro-1H-quinazolin-2,4-diona;

3-Amino-8-cloro-1-ciclopropil-6-fluoro-7-piperazin-1-il-1H-quinazolin-2,4-diona;

3-Amino-7-[3-(aminometil)-3-metilpirrolidin-1-il]-8-cloro-1-ciclopropil-6-fluoro-1H-quinazolin-2,4-diona;

3-Amino-7-(6-amino-3-aza-biciclo[3.1.0]hex-3-il)-8-cloro-1-ciclopropil-6-fluoro-1H-quinazolin-2,4-diona;

3-Amino-7-((S)-3-N-metilaminopirrolidin-1-il)-8-cloro-1-ciclopropil-6-fluoro-1H-quinazolin-2,4-diona;

3-Amino-7-((S)-3-aminopirrolidin-1-il)-8-cloro-(2,4-difluoroanilino)-6-fluoro-1H-quinazolin-2,4-diona;

3-Amino-7-[(S)-3-aminopirrolidin-1-il]-1-ciclopropilamino-6,8-difluoro-1H-quinazolin-2,4-diona;

3-Amino-7-[(S)-3-aminopirrolidin-1-il]-1-ciclopropilamino-5,8-difluoro-1H-quinazolin-2,4-diona;

3-Amino-7-((S)-3-aminopirrolidin-1-il)-1-ciclopropil-5,6,8-trifluoro-1H-quinazolin-2,4-diona;

3-Amino-7-(3-aminopirrolidin-1-il)-8-cloro-1-ciclopropil-6-fluoro-1H-quinazolin-2,4-diona;

7-((S)-3-Aminopirrolidin-1-il)-1-ciclopropil-3,5-diamino-6,8-difluoro-1H-quinazolin-2,4-diona;

3-Amino-7-(3-hidroximetilpirrolidin-1-il)-8-cloro-1-ciclopropil-6-fluoro-1H-quinazolin-2,4-diona;

3-Amino-7-(3-aminoetilpirrolidin-1-il)-8-cloro-1-ciclopropil-6-fluoro-1H-quinazolin-2,4-diona;

3-Amino-7-((S)-7-amino-5-azaespiro[2.4]hept-5-il)-8-cloro-1-ciclopropil-6-fluoro-1H-quinazolin-2,4-diona;

3-Amino-7-[(R)-3-(1-amino-1-metiletil)pirrolidin-1-il]-8-cloro-1-ciclopropil-6-fluoro-1H-quinazolin-2,4-diona;

3-Amino-7-(3-aminometilpirrolidin-1-il)-1-ciclopropil-6-fluoro-1H-quinazolin-2,4-diona;

3-Amino-7-(pirrolidin-1-il)-8-cloro-1-ciclopropil-6-fluoro-1H-quinazolin-2,4-diona;

3-Amino-7-(3-aminopirrolidin-1-il)-8-cloro-6-fluoro-1-isopropil-1H-quinazolin-2,4-diona;

3-Amino-7-(3-aminopirrolidin-1-il)-1-sec-butil-8-cloro-6-fluoro-1H-quinazolin-2,4-diona;

3-Amino-7-[3-aminopirrolidin-1-il]-1-ciclopropil-6-fluoro-8-metoxi-1H-quinazolin-2,4-diona;

3-Amino-7-[3-aminopirrolidin-1-il]-8-cloro-1-ciclobutilamino-6-fluoro-1H-quinazolin-2,4-diona;

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3-Amino-7-(3-aminopirrolidin-1-il)-1-ciclopropil-8-fluoro-1H-quinazolin-2,4-diona;

3-Amino-7-(3-aminopirrolidin-1-il)-6-cloro-1-ciclopropil-8-fluoro-1H-quinazolin-2,4-diona;

3-Amino-7-((S)-3-aminopirrolidin-1-il)-1-ciclopropilmetil-8-fluoro-1H-quinazolin-2,4-diona;

3-Amino-7-[(R)-3-(1-amino-1-metiletil)pirrolidin-1-il]-1-ciclopropilmetil-8-fluoro-1H-quinazolin-2,4-diona;

3-Amino-7-((S)-3-aminopirrolidin-1-il)-1-etil-8-fluoro-1H-quinazolin-2,4-diona;

3-Amino-1-etil-6-fluoro-7-[(R)-3-(1-amino-1-metiletil)-pirrolidin-1-il]-1H-quinazolin-2,4-diona;

3-Amino-7-((S)-3-aminopirrolidin-1-il)-1-ciclopropil-6-fluoro-1H-quinazolin-2,4-diona;

3-Amino-7-(3-aminopirrolidin-1-il)-1-ciclopropil-6-fluoro-8-metil-1H-quinazolin-2,4-diona;

3-Amino-7-(3-aminometilpirrolidin-1-il)-1-ciclopropil-6-fluoro-8-metil-1H-quinazolin-2,4-diona;

3-Amino-7-(3-aminopirrolidin-1-il)-1-ciclopropil-8-fluoro-6-metoxi-1H-quinazolin-2,4-diona;

3-Amino-7-(3-aminometilpirrolidin-1-il)-1-ciclopropil-6-fluoro-8-metoxi-1H-quinazolin-2,4-diona;

3-Amino-7-(3-aminopirrolidin-1-il)-1-ciclopropil-8-etoxi-6-fluoro-1H-quinazolin-2,4-diona;

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3-Amino-7-(3-aminopirrolidin-1-il)-1-ciclopropil-6-fluoro-2,4-dioxo-1,2,3,4-tetrahidroquinazolin-8-carbonitrilo;

3-Amino-8-cloro-1-ciclopropil-6-fluoro-7-(3-[1,2,3-triazol]-1-il-pirrolidin-1-il)-1H-quinazolin-2,4-diona;

3-Amino-7-[(S)-3-((R)-1-aminoetil)pirrolidin-1-il]-1-ciclopropil-6-fluoro-8-metoxi-1H-quinazolin-2,4-diona;

3-Amino-7-[(S)-3-((S)-1-aminoetil)pirrolidin-1-il]-1-ciclopropil-6-fluoro-8-metoxi-1H-quinazolin-2,4-diona;

3-Amino-7-[(S)-3-((S)-1-aminoetil)pirrolidin-1-il]-1-ciclopropil-6-fluoro-8-metil-1H-quinazolin-2,4-diona;

3-Amino-7-[(S)-3-((S)-1-aminoetil)pirrolidin-1-il]-1-ciclopropil-6-fluoro-8-metil-1H-quinazolin-2,4-diona;

5-Amino-9-((S)-3-aminopirrolidin-1-il)-8-fluoro-3-metil-2,3-dihidro-1-oxa-3a,5-diazafenalen-4,6-diona;

5-Amino-9-[(R)-3-((S)-1-aminoetil)pirrolidin-1-il]-8-fluoro-3-metil-2,3-dihidro-1-oxa-3a,5-diazafenalen-4,6-diona;

2-Amino-8-((S)-3-aminopirrolidin-1-il)-9-fluoro-5-metil-6,7-dihidro-5H-pirido[3,2,1-ij]quinazolin-1,3-diona;

2-Amino-8-[(R)-3-((S)-1-aminoetil)pirrolidin-1-il]-9-fluoro-5-metil-6,7-dihidro-5H-pirido[3,2,1-ij]quinazolin-1,3-diona;

3-Amino-7-((S)-3-aminopirrolidin-1-il)-1-ciclopropil-6-fluoro-1H-pirido[2,3-d]pirimidin-2,4-diona;

3-Amino-7-(6-amino-3-azabiciclo[3.1.0]hex-3-il)-1-ciclopropil-6-fluoro-1H-pirido[2,3-d]pirimidin-2,4-diona;

3-Amino-7-(3-aminoetil-3-metilpirrolidin-1-il)-1-ciclopropil-6-fluoro-1H-pirido[2,3-d]pirimidin-2,4-diona;

3-Amino-1-ciclopropil-6-fluoro-7-(octahidropirrolo[3,4-c]piridin-2-il)-1H-pirido[2,3-d]pirimidin-2,4-diona;

3-Amino-1-ciclopropil-6-fluoro-7-(octahidropirrolo[3,4-b]piridin-2-il)-1H-pirido[2,3-d]pirimidin-2,4-diona;

3-Amino-7-[(R)-3-(1-amino-1-metiletil)pirrolidin-1-il]-1-ciclopropil-6-fluoro-1H-pirido[2,3-d]pirimidin-2,4-diona;

3-Amino-7-(3-aminometilpiperidin-1-il)-1-ciclopropil-6-fluoro-1H-pirido[2,3-d]pirimidin-2,4-diona;

trans-3-Amino-7-(3-aminometil-4-trifluorometilpirrolidin-1-il)-1-ciclopropil-6-fluoro-1H-pirido[2,3-d]pirimidin-2,4-diona;

3-Amino-1-ciclopropil-6-fluoro-7-[(R)-3-((R)-1-metilaminoetil)pirrolidin-1-il]-1H-pirido[2,3-d]pirimidin-2,4-diona;

3-Amino-7-[(R)-3-((S)-1-aminoetil)pirrolidin-1-il]-1-ciclopropil-6-fluoro-1H-pirido[2,3-d]pirimidin-2,4-diona;

3-Amino-7-[3-(1-aminopropil)pirrolidin-1-il]-1-ciclopropil-6-fluoro-8-metil-1H-quinazolin-2,4-diona;

3-Amino-1-ciclopropil-6-fluoro-8-metil-7-[(R)-3-((S)-1-metilaminoetil)pirrolidin-1-il]-1H-quinazolin-2,4-diona;

3-Amino-7-[7-(1-aminoetil)-5-azaespiro[2.4]hept-5-il]-1-ciclopropil-6-fluoro-1H-quinazolin-2,4-diona;

Amida del ácido 1-(3-amino-8-cloro-1-ciclopropil-6-fluoro-2,4-dioxo-1,2,3,4-tetrahidroquinazolin-7-il)piperidin-3-carboxílico;

3-Amino-[7-trans-3-aminometil-4-trifluorometilpirrolidin-1-il]-8-cloro-1-ciclopropil-6-fluoro-1H-quinazolin-2,4-diona;

3-Amino-8-cloro-1-ciclopropil-6-fluoro-7-{3-[(2,2,2-trifluoro-etilamino)metil]pirrolidin-1-il}-1H-quinazolin-2,4-diona;

3-Amino-8-cloro-1-ciclopropil-6-fluoro-7-(5-metilhexahidro-pirrolo[3,4-c]pirrol-2-il)-1H-quinazolin-2,4-diona;

3-amino-8-cloro-1-ciclopropil-7-(2,7-diazaespiro[4.4]non-2-il)-6-fluoro-1H-quinazolin-2,4-diona;

3-Amino-7-(3-aminoetil-3-bencilpirrolidin-1-il)-8-cloro-1-ciclopropil-6-fluoro-1H-quinazolin-2,4-diona;

3-Amino-7-[(R)-3-((S)-1-aminoetil)pirroldin-1-il]-8-cloro-1-ciclopropil-6-fluoro-1H-quinazolin-2,4-diona;

3-Amino-8-cloro-1-ciclopropil-6-fluoro-7-(3-hidroxiimino-pirrolidin-1-il)-1H-quinazolin-2,4-diona;

3-Amino-7-[trans-3-amino-4-trifluorometilpirrolidin-1-il]-8-cloro-1-ciclopropil-6-fluoro-1H-quinazolin-2,4-diona;

3-Amino-8-cloro-1-ciclopropil-6-fluoro-7-[(R)-3-(S)-1-metilaminoetil)pirrolidin-1-il]-1H-quinazolin-2,4-diona;

3-Amino-7-(trans-3-amino-4-fenilpirrolidin-1-il)-8-cloro-1-ciclopropil-6-fluoro-1H-quinazolin-2,4-diona;

3-Amino-7-[trans-3-amino-4-(4-hidroxifenil)pirrolidin-1-il]-8-cloro-1-ciclopropil-6-fluoro-1H-quinazolin-2,4-diona;

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N-[1-(3-Amino-8-cloro-1-ciclopropil-6-fluoro-2,4-dioxo-1,2,3,4-tetrahidroquinazolin-7-il)pirrolidin-3-ilmetil]metanosulfonamida;

3-Amino-7-(3-aminometilpiperidin-1-il)-8-cloro-1-ciclopropil-6-fluoro-1H-quinazolin-2,4-diona;

3-Amino-8-cloro-1-ciclopropil-6-fluoro-7-[3-(isopropilamino-metil)pirrolidin-1-il]-1H-quinazolin-2,4-diona;

3-Amino-7-(3-aminometilpirrolidin-1-il)-6,8-dicloro-1-ciclopropil-1H-quinazolin-2,4-diona;

N-[1-(3-Amino-8-cloro-1-ciclopropil-6-fluoro-2,4-dioxo-1,2,3,4-tetrahidroquinazolin-7-il)pirrolidin-3-ilmetil]metanoslfonamida;

3-Amino-7-[(R)-3-(S)-(1-aminoetil)pirrolidin-1-il]-1-ciclopropil-6-fluoro-8-metil-1H-quinazolin-2,4-diona;

3-Amino-7-[(R)-3-(1-amino-1-metiletil)pirrolidin-1-il]-1-ciclopropil-6-fluoro-8-metil-1H-quinazolin-2,4-diona;

3-Amino-7-[3-(1-aminoetil)-3-metoxipirrolidin-1-il]-1-ciclopropil-6-fluoro-8-metil-1H-quinazolin-2,4-diona;

3-Amino-7-[3-(1-aminoetil)-3-fluoropirrolidin-1-il]-1-ciclopropil-6-fluoro-8-metoxi-1H-quinazolin-2,4-diona;

3-Amino-7-(3-aminopirrolidin-1-il)-1-ciclopropil-6-fluoro-5-metil-1H-quinazolin-2,4-diona;

3-Amino-7-[(R)-3-(S)-(1-aminoetil)pirrolidin-1-il]-1-ciclopropil-6-fluoro-5-metil-1H-quinazolin-2,4-diona;

3-Amino-7-(3-aminometil-3-metoximetilpirrolidin-1-il)-1-ciclopropil-6-fluoro-8-metil-1H-quinazolin-2,4-diona;

3-Amino-7-(3-aminometil-3-fluorometilpirrolidin-1-il)-1-ciclopropil-6-fluoro-1H-quinazolin-2,4-diona;

3-Amino-7-(trans-3-aminometil-4-trifluorometilpirrolidin-1-il)-1-ciclopropil-6-fluoro-8-metoxi-1H-quinazolin-2,4-diona;

3-Amino-7-[3-(1-aminometil)piperidin-1-il]-1-ciclopropil-6-fluoro-8-metoxi-1H-quinazolin-1,4-diona;

3-Amino-7-[3-(aminoetil)piperidin-1-il]-1-ciclopropil-6-fluoro-8-metil-1H-quinazolin-2,4-diona;

3-Amino-7-[4-(1-aminoetil)-3,3-dimetilpirrolidin-1-il]-1-ciclopropil-6-fluoro-8-metoxi-1H-quinazolin-2,4-diona;

3-Amino-7-[4-(1-aminoetil)-3,3-dimetilpirrolidin-1-il]-1-ciclopropil-6-fluoro-8-metil-1H-quinazolin-2,4-diona;

3-Amino-7-(3-amino-3-fenilpirrolidin-1-il)-1-ciclopropil-6-fluoro-8-metil-1H-quinazolin-2,4-diona;

3-Amino-7-[3-(1-aminoetil)-4-metilpirrolidin-1-il]-1-ciclopropil-6-fluoro-8-metil-1H-quinazolin-2,4-diona;

3-Amino-7-(3-aminometil-3-fenilpirrolidin-1-il)-1-ciclopropil-6-fluoro-8-metil-1H-quinazolin-2,4-diona;

3-Amino-7-(7-aminometil-5-azaespiro[2,4]hept-5-il)-1-ciclopropil-6-fluoro-8-metil-1H-quinazolin-2,4-diona;

3-Amino-7-(7-aminometil-5-azaespiro[2,4]hept-5-il)-1-ciclopropil-6-fluoro-8-metoxi-1H-quinazolin-2,4-diona;

3-Amino-7-(3-aminometil-3-hidroxipirrolidin-1-il)-1-ciclopropil-6-fluoro-8-metoxi-1H-quinazolin-2,4-diona;

3-Amino-7-(3-aminometilpiperidin-1-il)-1-ciclopropil-6-fluoro-8-metil-1H-quinazolin-2,4-diona;

3-Amino-7-(3-amino-4-metoxipirrolidin-1-il)-1-ciclopropil-6-fluoro-8-metil-1H-quinazolin-2,4-diona;

3-Amino-7-(3-amino-4-metoxipirrolidin-1-il)-1-ciclopropil-6-fluoro-8-metoxi-1H-quinazolin-2,4-diona;

3-Amino-7-(3-amino-4-fluoropirrolidin-1-il)-1-ciclopropil-6-fluoro-8-metoxi-1H-quinazolin-2,4-diona;

3-Amino-7-(3-aminometil-3-metilpirrolidin-1-il)-1-ciclopropil-6-fluoro-8-metil-1H-quinazolin-2,4-diona;

3-Amino-7-[(R)-3-(-((S)-1-aminoetil)pirrolidin-1-il]-1-ciclopropil-8-etil-6-fluoro-1H-quinazolin-2,4-diona;

Trifluoroacetato del ácido 1-(3-amino-1-ciclopropil-6-fluoro-8-metoxi-2,4-dioxo-1,2,3,4-tetrahidroquinazolin-7-il)pirrolidin-3-carboxílico;

Trifluoroacetato del ácido 1-(3-amino-1-ciclopropil-6-fluoro-8-metil-2,4-dioxo-1,2,3,4-tetrahidroquinazolin-7-il)pirrolidin-3-carboxílico;

3-Amino-7-(1-aminometil-3-azabiciclo[3.1.0]hex-3-il)-1-ciclopropil-6-fluoro-8-metoxi-1H-quinazolin-2,4-diona;

3-Amino-7-(1-aminometil-3-azabiciclo[3.1.0]hex-3-il)-1-ciclopropil-6-fluoro-8-metil-1H-quinazolin-2,4-diona;

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3-Amino-7-[(S)-3-((R)-1-aminoetil)pirrolidin-1-il]-1-ciclopropil-6-fluoro-8-metoxi-1H-quinazolin-2,4-diona;

3-Amino-7[(S)-3-((R)-1-aminoetil)pirrolidin-1-il]-1-ciclopropil-6-fluoro-8-metil-1H-quinazolin-2,4-diona;

3-Amino-1-ciclopropil-6-fluoro-8-metil-7-(octahidropirrolo[3,4-b]piridin-6-il)-1H-quinazolin-2,4-diona;

3-Amino-7-(trans-3-aminometil-4-metilpirrolidin-1-il)-8-cloro-1-ciclopropil-6-fluoro-1H-quinazolin-2,4-diona;

3-Amino-7-(trans-3-aminometil-4-metilpirrolidin-1-il)-1-ciclopropil-6-fluoro-8-metoxi-1H-quinazolin-2,4-diona;

3-Amino-7-(trans-3-aminometil-4-metilpirrolidin-1-il)-1-ciclopropil-6-fluoro-8-metil-1H-quinazolin-2,4-diona;

3-Amino-7-(trans-3-amino-4-metilpirolidin-1-il)-1-ciclopropil-6-fluoro-8-metoxi-1H-quinazolin-2,4-diona;

3-Amino-7-(3-aminometilmorfolin-1-il)-1-ciclopropil-6-fluoro-8-metoxi-1H-quinazolin-2,4-diona;

3-amino-7-(3-aminometilpiperidin-1-il)-1-ciclopropil-6-fluoro-8-metoxi-1H-quinazolin-2,4-diona;

3-Amino-7-[3-(1-aminoetil)-4-metilpirrolidin-1-il]-1-ciclopropil-6-fluoro-8-metoxi-1H-quinazolin-2,4-diona;

3-Amino-7-(3-amino-3-fenilpirrolidin-1-il)-8-cloro-1-ciclopropil-6-fluoro-1H-quinazolin-2,4-diona;

3-Amino-7-(3-amino-3-metilpirrolidin-1-il)-1-ciclopropil-6-fluoro-8-metil-1H-quinazolin-2,4-diona;

3-Amino-1-ciclopropil-6-fluoro-8-metil-7-pirrolidin-1-il-1H-quinazolin-2,4-diona;

3-Amino-1-ciclopropil-6-fluoro-8-metoxi-7-pirrolidin-1-il-1H-quinazolin-2,4-diona;

3-Amino-1-ciclopropil-6-fluoro-7-[3-(1-hidroxi-1-metiletil)-pirrolidin-1-il]-8-metil-1H-quinazolin-2,4-diona;

3-Amino-1-ciclopropil-6-fluoro-7-[3-(1-hidroxi-1-metiletil)-pirrolidin-1-il]-8-metoxi-1H-quinazolin-2,4-diona;

3-Amino-1-ciclopropil-6-fluoro-5-metil-7-[(R)-3-((S)-1-metilaminoetil)pirrolidin-1-il]-1H-quinazolin-2,4-diona;

(S)-1-[(R)-1-(3-Amino-1-ciclopropil-7-[3-(1-etilaminoetil)pirrolidin-1-il]-6-fluoro-8-metoxi-1H-quinazolin-2,4-diona;

3-Amino-1-ciclopropil-7-[(R)-3-((S)-1-etilaminoetil)pirrolidin-1-il]-6-fluoro-8-metil-1H-quinazolin-2,4-diona;

3-Amino-7-(6-amino-1-metil-3-azabiciclo[3.2.0]hept-3-il)-1-ciclopropil-6-fluoro-8-metoxi-1H-quinazolin-2,4-diona;

3-Amino-7-(4-aminometilpiperidin-1-il)-1-ciclopropil-6-fluoro-8-metoxi-1H-quinazolin-2,4-diona;

3-Amino-7-(3-aminometilazetidin-1-il)-1-ciclopropil-6-fluoro-8-metoxi-1H-quinazolin-2,4-diona;

cis-3-Amino-7-(3-aminometil-4-fluoropirrolidin-1-il)-1-ciclopropil-6-fluoro-8-metoxi-1H-quinazolin-2,4-diona;

trans-3-Amino-7-(3-aminometil-4-fluoropirrolidin-1-il)-1-ciclopropil-6-fluoro-8-metoxi-1H-quinazolin-2,4-diona;

3-Amino-7-(1-amino-5-azaespiro[2.4]hept-5-il)-1-ciclopropil-6-fluoro-8-metoxi-1H-quinazolin-2,4-diona;

3-Amino-7-(3-aminometiloctahidroisoindol-2-il)-1-ciclopropil-6-fluoro-8-metoxi-1H-quinazolin-2,4-diona;

3-Amino-7-(3-aminometiloctahidroisoindol-2-il)-1-ciclopropil-6-fluoro-8-metil-1H-quinazolin-2,4-diona;

3-Amino-7-[(R)-3-((S)-1-aminoetilpirrolidin-1-il]-1-ciclopropil-6-fluoro-8-metoxi-1H-quinazolin-2,4-diona;

3-Amino-7-(6-amino-3-azabiciclo[3.1.0]hex-3-il)-1-ciclopropil-6-fluoro-8-metil-1H-quinazolin-2,4-diona;

3-Amino-7-[3-(1-amino-1-metiletil)pirrolidin-1-il]-1-ciclopropil-6-fluoro-8-metoxi-1H-quinazolin-2,4-diona;

3-Amino-1-ciclopropil-6-fluoro-7-[3-(isopropilaminometil)pirrolidin-1-il]-8-metoxi-1H-quinazolin-2,4-diona;

3-Amino-1-ciclopropil-6-fluoro-8-metoxi-7-[(4aS,7aS)-octahidropirrolo[3,4-b]piridin-6-il-1H-quinazolin-2,4-diona;

3-Amino-7-(3-amino-4-fluorometilpirrolidin-1-il)-1-ciclopropil-6-fluoro-8-metoxi-1H-quinazolin-2,4-diona;

3-Amino-7-(3-aminometil-3-metilopirrolidin-1-il)-1-ciclopropil-6-fluoro-8-metoxi-1H-quinazolin-2,4-diona;

3-Amino-7-(4-aminopiperidin-1-il)-1-ciclopropil-6-fluoro-8-metoxi-1H-quinazolin-2,4-diona;

3-Amino-7-(3-aminopiperidin-1-il)-1-ciclopropil-6-fluoro-8-metoxi-1H-quinazolin-2,4-diona;

3-Amino-1-ciclopropil-6-fluoro-8-metoxi-7-[(R)-3-((S)-1-metilaminoetil)pirrolidin-1-il]-1H-quinazolin-2,4-diona;

3-Amino-7-(3-aminoazetidin-1-il)-1-ciclopropil-6-fluoro-8-metoxi-1H-quinazolin-2,4-diona;

3-Amino-7-[(3R,4S)-3-((S)-1-aminoetil)-4-fluoropirrolidin-1-il]-1-ciclopropil-6-fluoro-8-metil-1H-quinazolin-2,4-diona;

3-Amino-7-[(3R,4S)-3-((S)-1-aminoetil)-4-fluoropirrolidin-1-il]-1-ciclopropil-6-fluoro-8-metil-1H-quinazolin-2,4-diona;

3-Amino-7-[(3R,4R)-3-(R)-1-aminoetil)-4-fluoropirrolidin-1-il]-1-ciclopropil-6-fluoro-8-metil-1H-quinazolin-2,4-diona;

3-Amino-7-[(3R,4R)-3-((R)-1-aminoetil)-4-fluoropirrolidin-1-il]-1-ciclopropil-8-metil-1H-quinazolin-2,4-diona;

3-Amino-7-[(3R,4S)-3-(-1-amino-1-metiletil)-4-fluoropirrolidin-1-il]-1-ciclopropil-6-fluoro-8-metil-1H-quinazolin-2,4-diona;

3-Amino-7-[(3R,4S)-3-(-1-amino-1-metiletil)-4-fluoropirrolidin-1-il]-1-ciclopropil-8-metil-1H-quinazolin-2,4-diona;

3-Amino-7-[(3R,4R)-3-(-1-amino-1-metiletil)-4-fluoropirrolidin-1-il]-1-ciclopropil-6-fluoro-8-metil-1H-quinazolin-2,4-diona;

3-Amino-7-[(3R,4R)-3-(-1-amino-1-metiletil)-4-fluoropirrolidin-1-il]-1-ciclopropil-8-metil-1H-quinazolin-2,4-diona;

3-Amino-7-[(3R,4S)-3-((R)-1-amino-2-metoxietil)-4-fluoropirrolidin-1-il]-1-ciclopropil-6-fluoro-8-metil-1H-quinazolin-2,4-diona;

3-Amino-7-[(3R,4S)-3-((R)-1-amino-2-metoxietil)-4-fluoropirrolidin-1-il]-1-ciclopropil-8-metil-1H-quinazolin-2,4-diona;

3-Amino-7-[(3R,4R)-3-((S)-1-amino-2-metoxietil)-4-fluoropirrolidin-1-il]-1-ciclopropil-6-fluoro-8-metil-1H-quinazolin-2,4-diona;

3-Amino-7-[(3R,4R)-3-((S)-1-amino-2-metoxietil)-4-fluoropirrolidin-1-il]-1-ciclopropil-8-metil-1H-quinazolin-2,4-diona;

3-Amino-7-[(3R,4S)-3-((R)-1-amino-2-metoxietil)-4-metilpirrolidin-1-il]-1-ciclopropil-6-fluoro-8-metil-1H-quinazolin-2,4-diona;

3-Amino-7-[(3R,4S)-3-((R)-1-amino-2-metoxietil)-4-metilpirrolidin-1-il]-1-ciclopropil-8-metil-1H-quinazolin-2,4-diona;

3-Amino-7-[(3R,4R)-3-((S)-1-amino-2-metoxietil)-4-metilpirrolidin-1-il]-1-ciclopropil-6-fluoro-8-metil-1H-quinazolin-2,4-diona;

3-Amino-7-[(3R,4R)-3-((S)-1-amino-2-metoxietil)-4-metilpirrolidin-1-il]-1-ciclopropil-8-metil-1H-quinazolin-2,4-diona;

3-Amino-7-[(R)-4-((R)-1-amino-2-metoxietil)-3,3-dimetilpirrolidin-1-il]-1-ciclopropil-6-fluoro-8-metil-1H-quinazolin-2,4-diona;

3-Amino-7-[(R)-4-((R)-1-amino-2-metoxietil)-3,3-dimetilpirrolidin-1-il]-1-ciclopropil-8-metil-1H-quinazolin-2,4-diona;

3-Amino-7-[(R)-4-((S)-1-amino-2-metoxietil)-3,3-dimetilpirrolidin-1-il]-1-ciclopropil-6-fluoro-8-metil-1H-quinazolin-2,4-diona;

3-Amino-7-[(R)-4-(S)-1-amino-2-metoxietil)-3,3-dimetilpirrolidin-1-il]-1-ciclopropil-8-metil-1H-quinazolin-2,4-diona;

3-Amino-7-[(R)-3-((R)-1-amino-2-fenoxietil)pirrolidin-1-il]-1-ciclopropil-6-fluoro-8-metil-1H-quinazolin-2,4-diona;

3-Amino-7-[(R)-3-((R)-1-amino-2-fenoxietil)pirrolidin-1-il]-1-ciclopropil-8-metil-1H-quinazolin-2,4-diona;

3-Amino-7-[(3R,4S)-3-((R)-1-amino-2-fenoxietil)-4-metilpirrolidin-1-il]-1-ciclopropil-6-fluoro-8-metil-1H-quinazolin-2,4-diona;

3-Amino-7-[(3R,4S)-3-((R)-1-amino-2-fenoxietil)-4-metilpirrolidin-1-il]-1-ciclopropil-8-metil-1H-quinazolin-2,4-diona;

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3-Amino-7-[(3R,4S)-3-((R)-1-amino-2-fenoxietil)-4-fluoropirrolidin-1-il]-1-ciclopropil-6-fluoro-8-metil-1H-quinazolin-2,4-diona;

3-Amino-7-[(3R,4S)-3-((R)-1-amino-2-fenoxietil)-4-fluoropirrolidin-1-il]-1-ciclopropil-8-metil-1H-quinazolin-2,4-diona;

3-Amino-7-[(R)-3-((S)-1-amino-2-fenoxietil)pirrolidin-1-il]-1-ciclopropil-6-fluoro-8-metil-1H-quinazolin-2,4-diona;

3-Amino-7-[(R)-3-((S)-1-amino-2-fenoxietil)pirrolidin-1-il]-1-ciclopropil-8-metil-1H-quinazolin-2,4-diona;

3-Amino-7-[(3R,4S)-3-((S)-1-amino-2-fenoxietil)-4-metilpirrolidin-1-il]-1-ciclopropil-6-fluoro-8-metil-1H-quinazolin-2,4-diona;

3-Amino-7-[(3R,4S)-3-((S)-1-amino-2-fenoxietil)-4-metilpirrolidin-1-il]-1-ciclopropil-8-metil-1H-quinazolin-2,4-diona;

3-Amino-7-[(3R,4S)-3-((S)-1-amino-2-fenoxietil)-4-fluoropirrolidin-1-il]-1-ciclopropil-6-fluoro-8-metil-1H-quinazolin-2,4-diona;

3-Amino-7-[(3R,4S)-3-((S)-1-amino-2-fenoxietil)-4-fluoropirrolidin-1-il]-1-ciclopropil-8-metil-1H-quinazolin-2,4-diona;

3-Amino-7-[(R)-4-((R)-1-amino-2-fenoxietil)-3,3-dimetilpirrolidin-1-il]-1-ciclopropil-6-fluoro-8-metil-1H-quinazolin-2,4-diona;

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3-Amino-7-[(R)-4-((R)-1-amino-2-fenoxietil)-3,3-dimetilpirrolidin-1-il]-1-ciclopropil-8-metil-1H-quinazolin-2,4-diona;

3-Amino-7-[(R)-4-((S)-1-amino-2-fenoxietil)-3,3-dimetilpirrolidin-1-il]-1-ciclopropil-6-fluoro-8-metil-1H-quinazolin-2,4-diona;

3-Amino-7-[(R)-4-((S)-1-amino-2-fenoxietil)-3,3-dimetilpirrolidin-1-il]-1-ciclopropil-8-metil-1H-quinazolin-2,4-diona;

3-Amino-7-[(R)-3-((S)-1-amino-2-etoxietil)pirrolidin-1-il]-1-ciclopropil-6-fluoro-8-metil-1H-quinazolin-2,4-diona;

3-Amino-7-[(R)-3-((S)-1-amino-2-etoxietil)pirrolidin-1-il]-1-ciclopropil-8-metil-1H-quinazolin-2,4-diona;

3-Amino-7-[(R)-3-((R)-1-amino-2-etoxietil)pirrolidin-1-il]-1-ciclopropil-6-fluoro-8-metil-1H-quinazolin-2,4-diona;

3-Amino-7-[(R)-3-((R)-1-amino-2-etoxietil)pirrolidin-1-il]-1-ciclopropil-8-metil-1H-quinazolin-2,4-diona;

3-Amino-7-[(3R,4S)-3-((R)-1-amino-2-etoxietil)-4-metilpirrolidin-1-il]-1-ciclopropil-6-fluoro-8-metil-1H-quinazolin-2,4-diona;

3-Amino-7-[(3R,4S)-3-((R)-1-amino-2-etoxietil)-4-metilpirrolidin-1-il]-1-ciclopropil-8-metil-1H-quinazolin-2,4-diona;

3-Amino-7-[(3R,4S)-3-((R)-1-amino-2-etoxietil)-4-fluoropirrolidin-1-il]-1-ciclopropil-6-fluoro-8-metil-1H-quinazolin-2,4-diona;

3-Amino-7-[(3R,4S)-3-((R)-1-amino-2-etoxietil)-4-fluoropirrolidin-1-il]-1-ciclopropil-8-metil-1H-quinazolin-2,4-diona;

3-Amino-7-[(R)-4-((R)-1-amino-2-etoxietil)-3,3-dimetilpirrolidin-1-il]-1-ciclopropil-6-fluoro-8-metil-1H-quinazolin-2,4-diona;

3-Amino-7-[(R)-4-((R)-1-amino-2-etoxietil)-3,3-dimetilpirrolidin-1-il]-1-ciclopropil-8-metil-1H-quinazolin-2,4-diona;

3-Amino-7-[(3R,4R)-3-((S)-1-amino-2-etoxietil)-4-metilpirrolidin-1-il]-1-ciclopropil-6-fluoro-8-metil-1H-quinazolin-2,4-diona;

3-Amino-7-[(3R,4R)-3-((S)-1-amino-2-etoxietil)-4-metilpirrolidin-1-il]-1-ciclopropil-8-metil-1H-quinazolin-2,4-diona;

3-Amino-7-[(3R,4R)-3-((S)-1-amino-2-etoxietil)-4-fluoropirrolidin-1-il]-1-ciclopropil-6-fluoro-8-metil-1H-quinazolin-2,4-diona;

3-Amino-7-[(3R,4R)-3-((S)-1-amino-2-etoxietil)-4-fluoropirrolidin-1-il]-1-ciclopropil-8-metil-1H-quinazolin-2,4-diona;

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3-Amino-7-[(R)-3-((S)-1-amino-3-metoxipropil)pirrolidin-1-il]-1-ciclopropil-6-fluoro-8-metil-1H-quinazolin-2,4-diona;

3-Amino-7-[(R)-3-((S)-1-amino-3-metoxipropil)pirrolidin-1-il]-1-ciclopropil-8-metil-1H-quinazolin-2,4-diona;

3-Amino-7-[(3R,4S)-3-((S)-1-amino-3-metoxipropil)-4-metilpirrolidin-1-il]-1-ciclopropil-6-fluoro-8-metil-1H-quinazolin-2,4-diona;

3-Amino-7-[(3R,4S)-3-((S)-1-amino-3-metoxipropil)-4-metilpirrolidin-1-il]-1-ciclopropil-8-metil-1H-quinazolin-2,4-diona;

3-Amino-7-[(3R,4S)-3-((S)-1-amino-3-metoxipropil)-4-fluoropirrolidin-1-il]-1-ciclopropil-6-fluoro-8-metil-1H-quinazolin-2,4-diona;

3-Amino-7-[(3R,4S)-3-((S)-1-amino-3-metoxipropil)-4-fluoropirrolidin-1-il]-1-ciclopropil-8-metil-1H-quinazolin-2,4-diona;

3-Amino-7-[(R)-3-((R)-1-amino-3-metoxipropil)pirrolidin-1-il]-1-ciclopropil-6-fluoro-8-metil-1H-quinazolin-2,4-diona;

3-Amino-7-[(R)-3-((R)-1-amino-3-metoxipropil)pirrolidin-1-il]-1-ciclopropil-8-metil-1H-quinazolin-2,4-diona;

3-Amino-7-[(3R,4R)-3-((R)-1-amino-3-metoxipropil)-4-metilpirrolidin-1-il]-1-ciclopropil-6-fluoro-8-metil-1H-quinazolin-2,4-diona;

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3-Amino-7-[(3R,4R)-3-((R)-1-amino-3-metoxipropil)-4-metilpirrolidin-1-il]-1-ciclopropil-8-metil-1H-quinazolin-2,4-diona;

3-Amino-7-[(3R,4R)-3-((R)-1-amino-3-metoxipropil)-4-fluoropirrolidin-1-il]-1-ciclopropil-6-fluoro-8-metil-1H-quinazolin-2,4-diona;

3-Amino-7-[(3R,4R)-3-((R)-1-amino-3-metoxipropil)-4-fluoropirrolidin-1-il]-1-ciclopropil-8-metil-1H-quinazolin-2,4-diona;

{(R)-2-Amino-2-[(R)-1-(3-amino-1-ciclopropil-6-fluoro-8-metil-2,4-dioxo-1,2,3,4-tetrahidroquinazolin-7-il)pirrolidin-3-il]etil}urea;

{(R)-2-Amino-2-[(R)-1-(3-amino-1-ciclopropil-8-metil-2,4-dioxo-1,2,3,4-tetrahidroquinazolin-7-il)pirrolidin-3-il]etil}urea;

{(S)-2-Amino-2-[(R)-1-(3-amino-1-ciclopropil-6-fluoro-8-metil-2,4-dioxo-1,2,3,4-tetrahidroquinazolin-7-il)pirrolidin-3-il]etil}urea;

{(S)-2-Amino-2-[(R)-1-(3-amino-1-ciclopropil-8-metil-2,4-dioxo-1,2,3,4-tetrahidroquinazolin-7-il)pirrolidin-3-il]etil}urea;

{(R)-2-Amino-2-[(3R,4S)-1-(3-amino-1-ciclopropil-6-fluoro-8-metil-2,4-dioxo-1,2,3,4-tetrahidroquinazolin-7-il)-4-metilpirrolidin-3-il]etil}urea;

{(R)-2-Amino-2-[(3R,4S)-1-(3-amino-1-ciclopropil-8-metil-2,4-dioxo-1,2,3,4-tetrahidroquinazolin-7-il)-4-metilpirrolidin-3-il]etil}urea;

{(S)-2-Amino-2-[(3R,4R)-1-(3-amino-1-ciclopropil-6-fluoro-8-metil-2,4-dioxo-1,2,3,4-tetrahidroquinazolin-7-il)-4-metilpirrolidin-3-il]etil}urea;

{(S)-2-Amino-2-[(3R,4R)-1-(3-amino-1-ciclopropil-8-metil-2,4-dioxo-1,2,3,4-tetrahidroquinazolin-7-il)-4-metilpirrolidin-3-il]etil}urea;

{2-Amino-2-[(1-(3-amino-1-ciclopropil-6-fluoro-8-metil-2,4-dioxo-1,2,3,4-tetrahidroquinazolin-7-il)-4-fluoropirrolidin-3-il]etil}urea;

{2-Amino-2-[(1-(3-amino-1-ciclopropil-8-metil-2,4-dioxo-1,2,3,4-tetrahidroquinazolin-7-il)-4-fluoropirrolidin-3-il]etil}urea;

{2-Amino-2-[(1-(3-amino-1-ciclopropil-6-fluoro-8-metil-2,4-dioxo-1,2,3,4-tetrahidroquinazolin-7-il)-4,4-dimetilpirrolidin-3-il]etil}urea;

{2-Amino-2-[(1-(3-amino-1-ciclopropil-8-metil-2,4-dioxo-1,2,3,4-tetrahidroquinazolin-7-il)-4,4-dimetilpirrolidin-3-il]etil}urea;

3-Amino-7-[(3R,4S)-3-((S)-1-aminoetil)-4-fluoropirrolidin-1-il]-1-ciclopropil-6-fluoro-8-metoxi-1H-quinazolin-2,4-diona;

3-Amino-7-[(3R,4S)-3-((S)-1-aminoetil)-4-fluoropirrolidin-1-il]-1-ciclopropil-8-metoxi-1H-quinazolin-2,4-diona;

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3-Amino-7-[(3R,4R)-3-((R)-1-aminoetil)-4-fluoropirrolidin-1-il]-1-ciclopropil-6-fluoro-8-metoxi-1H-quinazolin-2,4-diona;

3-Amino-7-[(3R,4R)-3-((R)-1-aminoetil)-4-fluoropirrolidin-1-il]-1-ciclopropil-8-metoxi-1H-quinazolin-2,4-diona;

3-Amino-7-[(3R,4S)-3-(-1-amino-1-metiletil)-4-fluoropirrolidin-1-il]-1-ciclopropil-6-fluoro-8-metoxi-1H-quinazolin-2,4-diona;

3-Amino-7-[(3R,4S)-3-(-1-amino-1-metiletil)-4-fluoropirrolidin-1-il]-1-ciclopropil-8-metoxi-1H-quinazolin-2,4-diona;

3-Amino-7-[(3R,4R)-3-(-1-amino-1-metiletil)-4-fluoropirrolidin-1-il]-1-ciclopropil-6-fluoro-8-metoxi-1H-quinazolin-2,4-diona;

3-Amino-7-[(3R,4R)-3-(-1-amino-1-metiletil)-4-fluoropirrolidin-1-il]-1-ciclopropil-8-metoxi-1H-quinazolin-2,4-diona;

3-Amino-7-[(3R,4S)-3-((R)-1-amino-2-metoxietil)-4-fluoropirrolidin-1-il]-1-ciclopropil-6-fluoro-8-metoxi-1H-quinazolin-2,4-diona;

3-Amino-7-[(3R,4S)-3-((R)-1-amino-2-metoxietil)-4-fluoropirrolidin-1-il]-1-ciclopropil-8-metoxi-1H-quinazolin-2,4-diona;

3-Amino-7-[(3R,4R)-3-((S)-1-amino-2-metoxietil)-4-fluoropirrolidin-1-il]-1-ciclopropil-6-fluoro-8-metoxi-1H-quinazolin-2,4-diona;

3-Amino-7-[(3R,4R)-3-((S)-1-amino-2-metoxietil)-4-fluoropirrolidin-1-il]-1-ciclopropil-8-metoxi-1H-quinazolin-2,4-diona;

3-Amino-7-[(3R,4S)-3-((R)-1-amino-2-metoxietil)-4-metilpirrolidin-1-il]-1-ciclopropil-6-fluoro-8-metoxi-1H-quinazolin-2,4-diona;

3-Amino-7-[(3R,4S)-3-((R)-1-amino-2-metoxietil)-4-metilpirrolidin-1-il]-1-ciclopropil-8-metoxi-1H-quinazolin-2,4-diona;

3-Amino-7-[(3R,4R)-3-((S)-1-amino-2-metoxietil)-4-metilpirrolidin-1-il]-1-ciclopropil-6-fluoro-8-metoxi-1H-quinazolin-2,4-diona;

3-Amino-7-[(3R,4R)-3-((S)-1-amino-2-metoxietil)-4-metilpirrolidin-1-il]-1-ciclopropil-8-metoxi-1H-quinazolin-2,4-diona;

3-Amino-7-[(R)-4-((R)-1-amino-2-metoxietil)-3,3-dimetilpirrolidin-1-il]-1-ciclopropil-6-fluoro-8-metoxi-1H-quinazolin-2,4-diona;

3-Amino-7-[(R)-4-((R)-1-amino-2-metoxietil)-3,3-dimetilpirrolidin-1-il]-1-ciclopropil-8-metoxi-1H-quinazolin-2,4-diona;

3-Amino-7-[(R)-4-((S)-1-amino-2-metoxietil)-3,3-dimetilpirrolidin-1-il]-1-ciclopropil-6-fluoro-8-metoxi-1H-quinazolin-2,4-diona;

3-Amino-7-[(R)-4-((S)-1-amino-2-metoxietil)-3,3-dimetilpirrolidin-1-il]-1-ciclopropil-8-metoxi-1H-quinazolin-2,4-diona;

3-Amino-7-[(R)-3-((R)-1-amino-2-fenoxietil)pirrolidin-1-il]-1-ciclopropil-6-fluoro-8-metoxi-1H-quinazolin-2,4-diona;

3-Amino-7-[(R)-3-((R)-1-amino-2-fenoxietil)pirrolidin-1-il]-1-ciclopropil-8-metoxi-1H-quinazolin-2,4-diona;

3-Amino-7-[(3R,4S)-3-((R)-1-amino-2-fenoxietil)-4-metilpirrolidin-1-il]-1-ciclopropil-6-fluoro-8-metoxi-1H-quinazolin-2,4-diona;

3-Amino-7-[(3R,4S)-3-((R)-1-amino-2-fenoxietil)-4-metilpirrolidin-1-il]-1-ciclopropil-8-metoxi-1H-quinazolin-2,4-diona;

3-Amino-7-[(3R,4S)-3-((R)-1-amino-2-fenoxietil)-4-fluoropirrolidin-1-il]-1-ciclopropil-6-fluoro-8-metoxi-1H-quinazolin-2,4-diona;

3-Amino-7-[(3R,4S)-3-((R)-1-amino-2-fenoxietil)-4-fluoropirrolidin-1-il]-1-ciclopropil-8-metoxi-1H-quinazolin-2,4-diona;

3-Amino-7-[(R)-3-((S)-1-amino-2-fenoxietil)pirrolidin-1-il]-1-ciclopropil-6-fluoro-8-metoxi-1H-quinazolin-2,4-diona;

3-Amino-7-[(R)-3-((S)-1-amino-2-fenoxietil)pirrolidin-1-il]-1-ciclopropil-8-metoxi-1H-quinazolin-2,4-diona;

3-Amino-7-[(3R,4S)-3-((S)-1-amino-2-fenoxietil)-4-metilpirrolidin-1-il]-1-ciclopropil-6-fluoro-8-metoxi-1H-quinazolin-2,4-diona;

3-Amino-7-[(3R,4S)-3-((S)-1-amino-2-fenoxietil)-4-metilpirrolidin-1-il]-1-ciclopropil-8-metoxi-1H-quinazolin-2,4-diona;

3-Amino-7-[(3R,4S)-3-((S)-1-amino-2-fenoxietil)-4-fluoropirrolidin-1-il]-1-ciclopropil-6-fluoro-8-metoxi-1H-quinazolin-2,4-diona;

3-Amino-7-[(3R,4S)-3-((S)-1-amino-2-fenoxietil)-4-fluoropirrolidin-1-il]-1-ciclopropil-8-metoxi-1H-quinazolin-2,4-diona;

3-Amino-7-[(R)-4-((R)-1-amino-2-fenoxietil)-3,3-dimetilpirrolidin-1-il]-1-ciclopropil-6-fluoro-8-metoxi-1H-quinazolin-2,4-diona;

3-Amino-7-[(R)-4-((R)-1-amino-2-fenoxietil)-3,3-dimetilpirrolidin-1-il]-1-ciclopropil-8-metoxi-1H-quinazolin-2,4-diona;

3-Amino-7-[(R)-4-((S)-1-amino-2-fenoxietil)-3,3-dimetilpirrolidin-1-il]-1-ciclopropil-6-fluoro-8-metoxi-1H-quinazolin-2,4-diona;

3-Amino-7-[(R)-4-((S)-1-amino-2-fenoxietil)-3,3-dimetilpirrolidin-1-il]-1-ciclopropil-8-metoxi-1H-quinazolin-2,4-diona;

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3-Amino-7-[(R)-4-((S)-1-amino-2-etoxietil)pirrolidin-1-il]-1-ciclopropil-6-fluoro-8-metoxi-1H-quinazolin-2,4-diona;

3-Amino-7-[(R)-4-((S)-1-amino-2-etoxietil)pirrolidin-1-il]-1-ciclopropil-8-metoxi-1H-quinazolin-2,4-diona;

3-Amino-7-[(R)-3-((R)-1-amino-2-etoxietil)pirrolidin-1-il]-1-ciclopropil-6-fluoro-8-metoxi-1H-quinazolin-2,4-diona;

3-Amino-7-[(R)-3-((R)-1-amino-2-etoxietil)pirrolidin-1-il]-1-ciclopropil-8-metoxi-1H-quinazolin-2,4-diona;

3-Amino-7-[(3R,4S)-3-((R)-1-amino-2-etoxietil)-4-metilpirrolidin-1-il]-1-ciclopropil-6-fluoro-8-metoxi-1H-quinazolin-2,4-diona;

3-Amino-7-[(3R,4S)-3-((R)-1-amino-2-etoxietil)-4-metilpirrolidin-1-il]-1-ciclopropil-8-metoxi-1H-quinazolin-2,4-diona;

3-Amino-7-[(3R,4S)-3-((R)-1-amino-2-etoxietil)-4-fluoropirrolidin-1-il]-1-ciclopropil-6-fluoro-8-metoxi-1H-quinazolin-2,4-diona;

3-Amino-7-[(3R,4S)-3-((R)-1-amino-2-etoxietil)-4-fluoropirrolidin-1-il]-1-ciclopropil-8-metoxi-1H-quinazolin-2,4-diona;

3-Amino-7-[(R)-4-((R)-1-amino-2-etoxietil)-3,3-dimetilpirrolidin-1-il]-1-ciclopropil-6-fluoro-8-metoxi-1H-quinazolin-2,4-diona;

3-Amino-7-[(R)-4-((R)-1-amino-2-etoxietil)-3,3-dimetilpirrolidin-1-il]-1-ciclopropil-8-metoxi-1H-quinazolin-2,4-diona;

3-Amino-7-[(3R,4R)-3-((S)-1-amino-2-etoxietil)-4-metilpirrolidin-1-il]-1-ciclopropil-6-fluoro-8-metoxi-1H-quinazolin-2,4-diona;

3-Amino-7-[(3R,4R)-3-((S)-1-amino-2-etoxietil)-4-metilpirrolidin-1-il]-1-ciclopropil-8-metoxi-1H-quinazolin-2,4-diona;

3-Amino-7-[(3R,4R)-3-((S)-1-amino-2-etoxietil)-4-fluoropirrolidin-1-il]-1-ciclopropil-6-fluoro-8-metoxi-1H-quinazolin-2,4-diona;

3-Amino-7-[(3R,4R)-3-((S)-1-amino-2-etoxietil)-4-fluoropirrolidin-1-il]-1-ciclopropil-8-metoxi-1H-quinazolin-2,4-diona;

3-Amino-7-[(R)-3-((S)-1-amino-3-metoxipropil)pirrolidin-1-il]-1-ciclopropil-6-fluoro-8-metoxi-1H-quinazolin-2,4-diona;

3-Amino-7-[(R)-3-((S)-1-amino-3-metoxipropil)pirrolidin-1-il]-1-ciclopropil-8-metoxi-1H-quinazolin-2,4-diona;

3-Amino-7-[(3R,4S)-3-((S)-1-amino-3-metoxipropil)-4-metilpirrolidin-1-il]-1-ciclopropil-6-fluoro-8-metoxi-1H-quinazolin-2,4-diona;

3-Amino-7-[(3R,4S)-3-((S)-1-amino-3-metoxipropil)-4-metilpirrolidin-1-il]-1-ciclopropil-8-metoxi-1H-quinazolin-2,4-diona;

3-Amino-7-[(3R,4S)-3-((S)-1-amino-3-metoxipropil)-4-fluoropirrolidin-1-il]-1-ciclopropil-6-fluoro-8-metoxi-1H-quinazolin-2,4-diona;

3-Amino-7-[(3R,4S)-3-((S)-1-amino-3-metoxipropil)-4-fluoropirrolidin-1-il]-1-ciclopropil-8-metoxi-1H-quinazolin-2,4-diona;

3-Amino-7-[(R)-3-((R)-1-amino-3-metoxipropil)pirrolidin-1-il]-1-ciclopropil-6-fluoro-8-metoxi-1H-quinazolin-2,4-diona;

3-Amino-7-[(R)-3-((R)-1-amino-3-metoxipropil)pirrolidin-1-il]-1-ciclopropil-8-metoxi-1H-quinazolin-2,4-diona;

3-Amino-7-[(3R,4R)-3-((R)-1-amino-3-metoxipropil)-4-metilpirrolidin-1-il]-1-ciclopropil-6-fluoro-8-metoxi-1H-quinazolin-2,4-diona;

3-Amino-7-[(3R,4R)-3-((R)-1-amino-3-metoxipropil)-4-metilpirrolidin-1-il]-1-ciclopropil-8-metoxi-1H-quinazolin-2,4-diona;

3-Amino-7-[(3R,4R)-3-((R)-1-amino-3-metoxipropil)-4-fluoropirrolidin-1-il]-1-ciclopropil-6-fluoro-8-metoxi-1H-quinazolin-2,4-diona;

3-Amino-7-[(3R,4R)-3-((R)-1-amino-3-metoxipropil)-4-fluoropirrolidin-1-il]-1-ciclopropil-8-metoxi-1H-quinazolin-2,4-diona;

{(R)-2-Amino-2-[(R)-1-(3-amino-1-ciclopropil-6-fluoro-8-metoxi-2,4-dioxo-1,2,3,4-tetrahidroquinazolin-7-il)pirrolidin-3-il]etil}urea;

{(R)-2-Amino-2-[(R)-1-(3-amino-1-ciclopropil-8-metoxi-2,4-dioxo-1,2,3,4-tetrahidroquinazolin-7-il)pirrolidin-3-il]etil}urea;

{(S)-2-Amino-2-[(R)-1-(3-amino-1-ciclopropil-6-fluoro-8-metoxi-2,4-dioxo-1,2,3,4-tetrahidroquinazolin-7-il)pirrolidin-3-il]etil}urea;

{(S)-2-Amino-2-[(R)-1-(3-amino-1-ciclopropil-8-metoxi-2,4-dioxo-1,2,3,4-tetrahidroquinazolin-7-il)pirrolidin-3-il]etil}urea;

{(R)-2-Amino-2-[(3R,4S)-1-(3-amino-1-ciclopropil-6-fluoro-8-metoxi-2,4-dioxo-1,2,3,4-tetrahidroquinazolin-7-il)-4-metilpirrolidin-3-il]etil}urea;

{(R)-2-Amino-2-[(3R,4S)-1-(3-amino-1-ciclopropil-8-metoxi-2,4-dioxo-1,2,3,4-tetrahidroquinazolin-7-il)-4-metilpirrolidin-3-il]etil}urea;

{(S)-2-Amino-2-[(3R,4R)-1-(3-amino-1-ciclopropil-6-fluoro-8-metoxi-2,4-dioxo-1,2,3,4-tetrahidroquinazolin-7-il)-4-metilpirrolidin-3-il]etil}urea;

{(S)-2-Amino-2-[(3R,4R)-1-(3-amino-1-ciclopropil-8-metoxi-2,4-dioxo-1,2,3,4-tetrahidroquinazolin-7-il)-4-metilpirrolidin-3-il]etil}urea;

{2-Amino-2-[(1-(3-amino-1-ciclopropil-6-fluoro-8-metoxi-2,4-dioxo-1,2,3,4-tetrahidroquinazolin-7-il)-4-fluoropirrolidin-3-il]etil}urea;

{2-Amino-2-[(1-(3-amino-1-ciclopropil-8-metoxi-2,4-dioxo-1,2,3,4-tetrahidroquinazolin-7-il)-4-fluoropirrolidin-3-il]etil}urea;

{2-Amino-2-[(1-(3-amino-1-ciclopropil-6-fluoro-8-metoxi-2,4-dioxo-1,2,3,4-tetrahidroquinazolin-7-il)-4,4-dimetilpirrolidin-3-il]etil}urea;

{2-Amino-2-[(1-(3-amino-1-ciclopropil-8-metoxi-2,4-dioxo-1,2,3,4-tetrahidroquinazolin-7-il)-4,4-dimetilpirrolidin-3-il]etil}urea;

3-Amino-7-[3-(1-aminoetil)-4-fluoropirrolidin-1-il]-1-ciclopropil-8-metil-1H-pirido[4,3-d]pirimidin-2,4-diona;

3-Amino-7-[3-(1-amino-1-metiletil)-4-fluoropirrolidin-1-il]-1-ciclopropil-8-metil-1H-pirido[4,3-d]pirimidin-2,4-diona;

3-Amino-7-[3-(1-amino-2-metoxietil)-4-fluoropirrolidin-1-il]-1-ciclopropil-8-metil-1H-pirido[4,3-d]pirimidin-2,4-diona;

3-Amino-7-[3-(1-amino-2-metoxietil)-4-metilpirrolidin-1-il]-1-ciclopropil-8-metil-1H-pirido[4,3-d]pirimidin-2,4-diona;

3-Amino-7-[4-(1-amino-2-metoxietil)-3,3-dimetilpirrolidin-1-il]-1-ciclopropil-8-metil-1H-pirido[4,3-d]pirimidin-2,4-diona;

3-Amino-7-[3-(1-amino-2-fenoxietil)-pirrolidin-1-il]-1-ciclopropil-8-metil-1H-pirido[4,3-d]pirimidin-2,4-diona;

3-Amino-7-[3-(1-amino-2-fenoxietil)-4-metilpirrolidin-1-il]-1-ciclopropil-8-metil-1H-pirido[4,3-d]pirimidin-2,4-diona;

3-Amino-7-[3-(1-amino-2-fenoxietil)-4-fluoropirrolidin-1-il]-1-ciclopropil-8-metil-1H-pirido[4,3-d]pirimidin-2,4-diona;

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3-Amino-7-[4-(1-amino-2-fenoxietil)-3,3-dimetilpirrolidin-1-il]-1-ciclopropil-8-metil-1H-pirido[4,3-d]pirimidin-2,4-diona;

3-Amino-7-[3-(1-amino-2-etoxietil)pirrolidin-1-il]-1-ciclopropil-8-metil-1H-pirido[4,3-d]pirimidin-2,4-diona;

3-Amino-7-[3-(1-amino-2-etoxietil)-4-metilpirrolidin-1-il]-1-ciclopropil-8-metil-1H-pirido[4,3-d]pirimidin-2,4-diona;

3-Amino-7-[3-(1-amino-2-etoxietil)-4-fluoropirrolidin-1-il]-1-ciclopropil-8-metil-1H-pirido[4,3-d]pirimidin-2,4-diona;

3-Amino-7-[3-(1-amino-2-etoxietil)-4,4-dimetilpirrolidin-1-il]-1-ciclopropil-8-metil-1H-pirido[4,3-d]pirimidin-2,4-diona;

3-Amino-7-[3-(1-amino-2-metoxipropil)pirrolidin-1-il]-1-ciclopropil-8-metil-1H-pirido[4,3-d]pirimidin-2,4-diona;

3-Amino-7-[3-(1-amino-2-metoxipropil)-4-metilpirrolidin-1-il]-1-ciclopropil-8-metil-1H-pirido[4,3-d]pirimidin-2,4-diona;

3-Amino-7-[3-(1-amino-2-metoxipropil)-4-fluoropirrolidin-1-il]-1-ciclopropil-8-metil-1H-pirido[4,3-d]pirimidin-2,4-diona;

{2-Amino-2-[1-(3-amino-1-ciclopropil-8-metil-2,4-dioxo-1,2,3,4-tetrahidropirido[4,3-d]pirimidin-7-il)pirrolidin-3-il]etilurea;

{2-Amino-2-[1-(3-amino-1-ciclopropil-8-metil-2,4-dioxo-1,2,3,4-tetrahidropirido[4,3-d]pirimidin-7-il)-4-metilpirrolidin-3-il]etilurea;

{2-Amino-2-[1-(3-amino-1-ciclopropil-8-metil-2,4-dioxo-1,2,3,4-tetrahidropirido[4,3-d]pirimidin-7-il)-4-fluoropirrolidin-3-il]etilurea;

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(2-Amino-2-[1-(3-amino-1-ciclopropil-8-metil-2,4-dioxo-1,2,3,4-tetrahidropirido[4,3-d]pirimidin-7-il)-4,4-dimetilpirrolidin-3-il]etilurea;

3-Amino-7-[3-(1-aminoetil)-4-fluoropirrolidin-1-il]-1-ciclopropil-6-fluoro-8-metil-1H-pirido[3,2-d]pirimidin-2,4-diona;

3-Amino-7-[3-(1-aminoetil)-4-fluoropirrolidin-1-il]-1-ciclopropil-8-metil-1H-pirido[3,2-d]pirimidin-2,4-diona;

3-Amino-7-[3-(1-amino-1-metiletil)-4-fluoropirrolidin-1-il]-1-ciclopropil-6-fluoro-8-metil-1H-pirido[3,2-d]pirimidin-2,4-diona;

3-Amino-7-[3-(1-amino-1-metiletil)-4-fluoropirrolidin-1-il]-1-ciclopropil-8-metil-1H-pirido[3,2-d]pirimidin-2,4-diona;

3-Amino-7-[3-(1-amino-2-metoxietil)-4-fluoropirrolidin-1-il]-1-ciclopropil-6-fluoro-8-metil-1H-pirido[3,2-d]pirimidin-2,4-diona;

3-Amino-7-[3-(1-amino-2-metoxietil)-4-fluoropirrolidin-1-il]-1-ciclopropil-8-metil-1H-pirido[3,2-d]pirimidin-2,4-diona;

3-Amino-7-[3-(1-amino-2-metoxietil)-4-metilpirrolidin-1-il]-1-ciclopropil-6-fluoro-8-metil-1H-pirido[3,2-d]pirimidin-2,4-diona;

3-Amino-7-[3-(1-amino-2-metoxietil)-4-metilpirrolidin-1-il]-1-ciclopropil-8-metil-1H-pirido[3,2-d]pirimidin-2,4-diona;

3-Amino-7-[4-(1-amino-2-metoxietil)-3,3-dimetilpirrolidin-1-il]-1-ciclopropil-6-fluoro-8-metil-1H-pirido[3,2-d]pirimidin-2,4-diona;

3-Amino-7-[4-(1-amino-2-metoxietil)-3,3-dimetilpirrolidin-1-il]-1-ciclopropil-8-metil-1H-pirido[3,2-d]pirimidin-2,4-diona;

3-Amino-7-[3-(1-amino-2-fenoxietil)pirrolidin-1-il]-1-ciclopropil-6-fluoro-8-metil-1H-pirido[3,2-d]pirimidin-2,4-diona;

3-Amino-7-[3-(1-amino-2-fenoxietil)pirrolidin-1-il]-1-ciclopropil-8-metil-1H-pirido[3,2-d]pirimidin-2,4-diona;

3-Amino-7-[3-(1-amino-2-fenoxietil)-4-metilpirrolidin-1-il]-1-ciclopropil-6-fluoro-8-metil-1H-pirido[3,2-d]pirimidin-2,4-diona;

3-Amino-7-[3-(1-amino-2-fenoxietil)-4-metilpirrolidin-1-il]-1-ciclopropil-8-metil-1H-pirido[3,2-d]pirimidin-2,4-diona;

3-Amino-7-[3-(1-amino-2-fenoxietil)-4-fluoropirrolidin-1-il]-1-ciclopropil-6-fluoro-8-metil-1H-pirido[3,2-d]pirimidin-2,4-diona;

3-Amino-7-[3-(1-amino-2-fenoxietil)-4-fluoropirrolidin-1-il]-1-ciclopropil-8-metil-1H-pirido[3,2-d]pirimidin-2,4-diona;

3-Amino-7-[4-(1-amino-2-fenoxietil)-3,3-dimetilpirrolidin-1-il]-1-ciclopropil-6-fluoro-8-metil-1H-pirido[3,2-d]pirimidin-2,4-diona;

3-Amino-7-[4-(1-amino-2-fenoxietil)-3,3-dimetilpirrolidin-1-il]-1-ciclopropil-8-metil-1H-pirido[3,2-d]pirimidin-2,4-diona;

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3-Amino-7-[3-(1-amino-2-etoxietil)pirrolidin-1-il]-1-ciclopropil-6-fluoro-8-metil-1H-pirido[3,2-d]pirimidin-2,4-diona;

3-Amino-7-[3-(1-amino-2-etoxietil)pirrolidin-1-il]-1-ciclopropil-8-metil-1H-pirido[3,2-d]pirimidin-2,4-diona;

3-Amino-7-[3-(1-amino-2-etoxietil)-4-metilpirrolidin-1-il]-1-ciclopropil-6-fluoro-8-metil-1H-pirido[3,2-d]pirimidin-2,4-diona;

3-Amino-7-[3-(1-amino-2-etoxietil)-4-metilpirrolidin-1-il]-1-ciclopropil-8-metil-1H-pirido[3,2-d]pirimidin-2,4-diona;

3-Amino-7-[3-(1-amino-2-etoxietil)-4-fluoropirrolidin-1-il]-1-ciclopropil-6-fluoro-8-metil-1H-pirido[3,2-d]pirimidin-2,4-diona;

3-Amino-7-[3-(1-amino-2-etoxietil)-4-fluoropirrolidin-1-il]-1-ciclopropil-8-metil-1H-pirido[3,2-d]pirimidin-2,4-diona;

3-Amino-7-[3-(1-amino-2-etoxietil)-4,4-dimetilpirrolidin-1-il]-1-ciclopropil-6-fluoro-8-metil-1H-pirido[3,2-d]pirimidin-2,4-diona;

3-Amino-7-[3-(1-amino-2-etoxietil)-4,4-dimetilpirrolidin-1-il]-1-ciclopropil-8-metil-1H-pirido[3,2-d]pirimidin-2,4-diona;

3-Amino-7-[3-(1-amino-2-metoxipropil)pirrolidin-1-il]-1-ciclopropil-6-fluoro-8-metil-1H-pirido[3,2-d]pirimidin-2,4-diona;

3-Amino-7-[3-(1-amino-2-metoxipropil)pirrolidin-1-il]-1-ciclopropil-8-metil-1H-pirido[3,2-d]pirimidin-2,4-diona;

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3-Amino-7-[3-(1-amino-2-metoxipropil)-4-metilpirrolidin-1-il]-1-ciclopropil-6-fluoro-8-metil-1H-pirido[3,2-d]pirimidin-2,4-diona;

3-Amino-7-[3-(1-amino-2-metoxipropil)-4-metilpirrolidin-1-il]-1-ciclopropil-8-metil-1H-pirido[3,2-d]pirimidin-2,4-diona;

3-Amino-7-[3-(1-amino-2-metoxipropil)-4-fluoropirrolidin-1-il]-1-ciclopropil-6-fluoro-8-metil-1H-pirido[3,2-d]pirimidin-2,4-diona;

3-Amino-7-[3-(1-amino-2-metoxipropil)-4-fluoropirrolidin-1-il]-1-ciclopropil-8-metil-1H-pirido[3,2-d]pirimidin-2,4-diona;

{2-Amino-2-[1-(3-amino-1-ciclopropil-6-fluoro-8-metil-2,4-dioxo-1,2,3,4-tetrahidropirido[3,2-d]pirimidin-7-il)pirrolidin-3-il]etilurea;

{2-Amino-2-[1-(3-amino-1-ciclopropil-8-metil-2,4-dioxo-1,2,3,4-tetrahidropirido[3,2-d]pirimidin-7-il)pirrolidin-3-il]etilurea;

{2-Amino-2-[1-(3-amino-1-ciclopropil-6-fluoro-8-metil-2,4-dioxo-1,2,3,4-tetrahidropirido[3,2-d]pirimidin-7-il)-4-metilpirrolidin-3-il]etilurea;

{2-Amino-2-[1-(3-amino-1-ciclopropil-8-metil-2,4-dioxo-1,2,3,4-tetrahidropirido[3,2-d]pirimidin-7-il)-4-metilpirrolidin-3-il]etilurea;

{2-Amino-2-[1-(3-amino-1-ciclopropil-6-fluoro-8-metil-2,4-dioxo-1,2,3,4-tetrahidropirido[3,2-d]pirimidin-7-il)-4-fluoropirrolidin-3-il]etilurea;

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{2-Amino-2-[1-(3-amino-1-ciclopropil-8-metil-2,4-dioxo-1,2,3,4-tetrahidropirido[3,2-d]pirimidin-7-il)-4-fluoropirrolidin-3-il]etilurea;

{2-Amino-2-[1-(3-amino-1-ciclopropil-6-fluoro-8-metil-2,4-dioxo-1,2,3,4-tetrahidropirido[3,2-d]pirimidin-7-il)-4,4-dimetilpirrolidin-3-il]etilurea;

{2-Amino-2-[1-(3-amino-1-ciclopropil-8-metil-2,4-dioxo-1,2,3,4-tetrahidropirido[3,2-d]pirimidin-7-il)-4,4-dimetilpirrolidin-3-il]etilurea;

3-Amino-7-(3-aminometilfenil)-8-cloro-1-ciclopropil-6-fluoro-1H-quinazolin-2,4-diona;

3-Amino-7-(3-aminometilfenil)-8-metil-1-ciclopropil-6-fluoro-1H-quinazolin-2,4-diona;

3-Amino-7-(3-aminometilfenil)-8-metoxi-1-ciclopropil-6-fluoro-1H-quinazolin-2,4-diona;

3-Amino-7-(3-aminometilfenil)-8-cloro-1-ciclopropil-1H-quinazolin-2,4-diona;

3-Amino-7-(3-aminometilfenil)-8-metil-1-ciclopropil-1H-quinazolin-2,4-diona;

3-Amino-7-(3-aminometilfenil)-8-metoxi-1-ciclopropil-1H-quinazolin-2,4-diona;

3-Amino-7-(2-aminometiltiazol-4-il)-8-cloro-1-ciclopropil-6-fluoro-1H-quinazolin-2,4-diona;

3-Amino-7-(2-aminometiltiazol-4-il)-8-metil-1-ciclopropil-6-fluoro-1H-quinazolin-2,4-diona;

3-Amino-7-(2-aminometiltiazol-4-il)-8-metoxi-1-ciclopropil-6-fluoro-1H-quinazolin-2,4-diona;

3-Amino-7-(2-aminometiltiazol-4-il)-8-cloro-1-ciclopropil-1H-quinazolin-2,4-diona;

3-Amino-7-(2-aminometiltiazol-4-il)-8-metil-1-ciclopropil-1H-quinazolin-2,4-diona;

3-Amino-7-(2-aminometiltiazol-4-il)-8-metoxi-1-ciclopropil-1H-quinazolin-2,4-diona;

3-Amino-7-[2-(1-aminoetil)tiazol-4-il]-8-cloro-1-ciclopropil-6-fluoro-1H-quinazolin-2,4-diona;

3-Amino-7-[2-(1-aminoetil)tiazol-4-il]-8-metil-1-ciclopropil-6-fluoro-1H-quinazolin-2,4-diona;

3-Amino-7-[2-(1-aminoetil)tiazol-4-il]-8-metoxi-1-ciclopropil-6-fluoro-1H-quinazolin-2,4-diona;

3-Amino-7-[2-(1-aminoetil)tiazol-4-il]-8-cloro-1-ciclopropil-1H-quinazolin-2,4-diona;

3-Amino-7-[2-(1-aminoetil)tiazol-4-il]-8-metil-1-ciclopropil-1H-quinazolin-2,4-diona;

3-Amino-7-[2-(1-aminoetil)tiazol-4-il]-8-metoxi-1-ciclopropil-1H-quinazolin-2,4-diona;

3-Amino-7-(5-aminometiltiofen-3-il)-8-cloro-1-ciclopropil-6-fluoro-1H-quinazolin-2,4-diona;

3-Amino-7-(5-aminometiltiofen-3-il)-8-metil-1-ciclopropil-6-fluoro-1H-quinazolin-2,4-diona;

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3-Amino-7-(5-aminometiltiofen-3-il)-8-metoxi-1-ciclopropil-6-fluoro-1H-quinazolin-2,4-diona;

3-Amino-7-(5-aminometiltiofen-3-il)-8-cloro-1-ciclopropil-1H-quinazolin-2,4-diona;

3-Amino-7-(5-aminometiltiofen-3-il)-8-metil-1-ciclopropil-1H-quinazolin-2,4-diona;

3-Amino-7-(5-aminometiltiofen-3-il)-8-metoxi-1-ciclopropil-1H-quinazolin-2,4-diona;

3-Amino-7-(4-aminometil-3,3-difluoropirrolidin-1-il)-8-cloro-1-ciclopropil-6-fluoro-1H-quinazolin-2,4-diona;

3-Amino-7-(4-aminometil-3,3-difluoropirrolidin-1-il)-8-metil-1-ciclopropil-6-fluoro-1H-quinazolin-2,4-diona;

3-Amino-7-(4-aminometil-3,3-difluoropirrolidin-1-il)-8-metoxi-1-ciclopropil-6-fluoro-1H-quinazolin-2,4-diona;

3-Amino-7-(4-aminometil-3,3-difluoropirrolidin-1-il)-8-cloro-1-ciclopropil-1H-quinazolin-2,4-diona;

3-Amino-7-(4-aminometil-3,3-difluoropirrolidin-1-il)-8-metil-1-ciclopropil-1H-quinazolin-2,4-diona;

3-Amino-7-(4-aminometil-3,3-difluoropirrolidin-1-il)-8-metoxi-1-ciclopropil-1H-quinazolin-2,4-diona;

3-Amino-7-(4-(1-aminoetil)-3,3-difluoropirrolidin-1-il)-8-cloro-1-ciclopropil-6-fluoro-1H-quinazolin-2,4-diona;

3-Amino-7-(4-(1-aminoetil)-3,3-difluoropirrolidin-1-il)-8-metil-1-ciclopropil-6-fluoro-1H-quinazolin-2,4-diona;

3-Amino-7-(4-(1-aminoetil)-3,3-difluoropirrolidin-1-il)-8-metoxi-1-ciclopropil-6-fluoro-1H-quinazolin-2,4-diona;

3-Amino-7-(4-(1-aminoetil)-3,3-difluoropirrolidin-1-il)-8-cloro-1-ciclopropil-1H-quinazolin-2,4-diona;

3-Amino-7-(4-(1-aminoetil)-3,3-difluoropirrolidin-1-il)-8-metil-1-ciclopropil-1H-quinazolin-2,4-diona;

3-Amino-7-(4-(1-aminoetil)-3,3-difluoropirrolidin-1-il)-8-metoxi-1-ciclopropil-1H-quinazolin-2,4-diona;

3-Amino-7-(4-(1-amino-1-metiletil)-3,3-difluoropirrolidin-1-il)-8-cloro-1-ciclopropil-6-fluoro-1H-quinazolin-2,4-diona;

3-Amino-7-(4-(1-amino-1-metiletil)-3,3-difluoropirrolidin-1-il)-8-metil-1-ciclopropil-6-fluoro-1H-quinazolin-2,4-diona;

3-Amino-7-(4-(1-amino-1-metiletil)-3,3-difluoropirrolidin-1-il)-8-metoxi-1-ciclopropil-6-fluoro-1H-quinazolin-2,4-diona;

3-Amino-7-(4-(1-amino-1-metiletil)-3,3-difluoropirrolidin-1-il)-8-cloro-1-ciclopropil-1H-quinazolin-2,4-diona;

3-Amino-7-(4-(1-amino-1-metiletil)-3,3-difluoropirrolidin-1-il)-8-metil-1-ciclopropil-1H-quinazolin-2,4-diona;

3-Amino-7-(4-(1-amino-1-metiletil)-3,3-difluoropirrolidin-1-il)-8-metoxi-1-ciclopropil-1H-quinazolin-2,4-diona;

3-Amino-7-(3-(1-aminoetil)pirrolidin-1-il)-1-ciclopropil-6-fluoro-5,8-dimetil-1H-quinazolin-2,4-diona;

3-Amino-7-(3-(1-aminoetil)pirrolidin-1-il)-1-ciclopropil-5,8-dimetil-1H-quinazolin-2,4-diona;

3-Amino-7-(3-(1-aminoetil)pirrolidin-1-il)-1-ciclopropil-6-fluoro-8-metoxi-5-metil-1H-quinazolin-2,4-diona;

3-Amino-7-(3-(1-aminoetil)pirrolidin-1-il)-1-ciclopropil-8-metoxi-5-metil-1H-quinazolin-2,4-diona;

3,8-Diamino-7-[3-(1-aminoetil)pirrolidin-1-il]-1-ciclopropil-6-fluoro-5-metil-1H-quinazolin-2,4-diona; y

3,8-Diamino-7-[3-(1-aminoetil)pirrolidin-1-il]-1-ciclopropil-5-metil-1H-quinazolin-2,4-diona.

11. Una composición farmacéutica, caracterizada porque comprende un compuesto de la reivindicación 1 mezclado con un portador, diluyente o excipiente.

12. Una composición farmacéutica, caracterizada porque comprende un compuesto de la reivindicación 2 mezclado con un portador, diluyente o excipiente.

13. Una composición farmacéutica, caracterizada porque comprende un compuesto de la reivindicación 3 mezclado con un portador, diluyente o excipiente.

14. Una composición farmacéutica, caracterizada porque comprende un compuesto de la reivindicación 4 mezclado con un portador, diluyente o excipiente.

15. Una composición farmacéutica, caracterizada porque comprende un compuesto de la reivindicación 5 mezclado con un portador, diluyente o excipiente.

16. Una composición farmacéutica, caracterizada porque comprende un compuesto de la reivindicación 6 mezclado con un portador, diluyente o excipiente.

17. Una composición farmacéutica, caracterizada porque comprende un compuesto de la reivindicación 7 mezclado con un portador, diluyente o excipiente.

18. Una composición farmacéutica, caracterizada porque comprende un compuesto de la reivindicación 10 mezclado con un portador, diluyente o excipiente.

19. Un método para tratar una infección bacteriana en un mamífero, caracterizado porque comprende administrar al mamífero una cantidad efectiva antibacteriana de un compuesto de la reivindicación 1.

20. Un método para tratar una infección bacteriana en un mamífero, caracterizado porque comprende administrar al mamífero una cantidad efectiva antibacteriana de un compuesto de la reivindicación 2.

21. Un método para tratar una infección bacteriana en un mamífero, caracterizado porque comprende administrar al mamífero una cantidad efectiva antibacteriana de un compuesto de la reivindicación 3.

22. Un método para tratar una infección bacteriana en un mamífero, caracterizado porque comprende administrar al mamífero una cantidad efectiva antibacteriana de un compuesto de la reivindicación 4.

23. Un método para tratar una infección bacteriana en un mamífero, caracterizado porque comprende administrar al mamífero una cantidad efectiva antibacteriana de un compuesto de la reivindicación 5.

24. Un método para tratar una infección bacteriana en un mamífero, caracterizado porque comprende administrar al mamífero una cantidad efectiva antibacteriana de un compuesto de la reivindicación 6.

25. Un método para tratar una infección bacteriana en un mamífero, caracterizado porque comprende administrar al mamífero una cantidad efectiva antibacteriana de un compuesto de la reivindicación 7.

26. Un método para tratar una infección bacteriana en un mamífero, caracterizado porque comprende administrar al mamífero una cantidad efectiva antibacteriana de un compuesto de la reivindicación 10.

27. Un método para inhibir un mutante de tipo silvestre de la girasa de ADN en un mamífero, caracterizado porque comprende administrar al mamífero una cantidad efectiva de un compuesto de la reivindicación 1.

28. Un método para inhibir un mutante de girasa de ADN resistente a la quinolona en un mamífero, caracterizado porque comprende administrar al mamífero una cantidad efectiva de un compuesto de la reivindicación 1.

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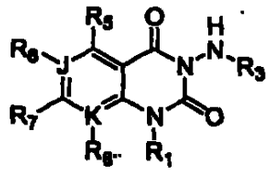
RESUMEN DE LA INVENCIÓN

Las 3-aminoquinazolin-2,4-dionas tienen la fórmula



en donde:

R_1 y R_3 incluyen alquilo, alquenilo, alquinilo, cicloalquilo, arilo, heterocíclico y heteroarilo;

R_5, R_6, y R_8 incluyen H, alquilo, alcoxi, halo, NO_2, CN, NH_2, alquil y dialquilamino;

R_7 es hidrógeno, alquilo, cicloalquilo, heterocíclico, heterocíclico fusionado, arilo y arilo fusionado;

J y K son C o N;

y sales farmacéuticamente aceptables de ellos.

3-AMINOQUINAZOLIN-2,4-DIONE ANTIBACTERIAL AGENTS

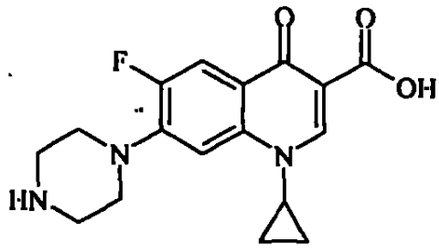
Field of the Invention

This invention relates to 3-aminoquinazolin-2,4-diones that have potent in vitro and in vivo antibacterial activity. In addition, this invention relates to a method of inhibiting both wild-type and quinolone resistant mutants of DNA gyrase. This invention further relates to a method of treating patients having antibiotic resistance and in need of treatment for bacterial infections.

BACKGROUND OF THE INVENTION

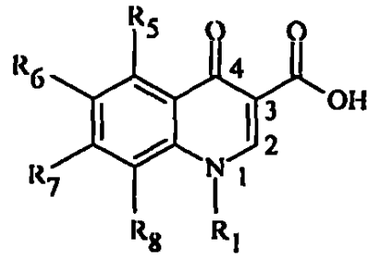
Antibiotic resistance is a worldwide problem with catastrophic potential. The American Society of Microbiology Task Force recently issued a report defining the resistance problem and calling for new antibacterial agents with novel structures or mechanisms to offer alternatives to existing therapeutic choices (*Southern Med. J.*, 1995;88:797).

The quinolones are a class of antibacterials that are widely used throughout the world. The quinolones are potent inhibitors of gram positive and gram negative bacteria, and may be administered orally or intravenously. The quinolones are routinely used even though they have side effects (*J. Antimicrob. Chemother.*, 1994;33:685), and significant resistance has been frequently noted (Gootz, *Medicinal Research*, 1996;Rev. 16:433). One of the most widely used quinolones is ciprofloxacin, which has the following chemical structure:



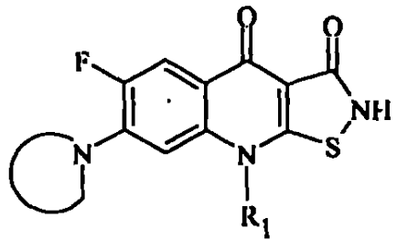
The quinolones have a distinct structure activity relationship (SAR) which is defined by several thousands of analogs prepared over the last 30 years

(S. Mitsuhashi, ed. *Progress in Drug Research*, 1992;38:11-147). In the quinolone SAR (referring to the formula below representing substituted quinolones), it is well-established that the N_1 group, in combination with the C_3-carboxyl and the C_4-carbonyl, are essential for activity, and that any substituents at C_2 detract from activity (*J. Antimicrob. Chemother.*, 1994;33:685 and Gootz, supra., 1996). It is also well-established that R_6 is ideally fluorine, and that R_7 is a nitrogen containing heterocycle. R_1 is ideally a small alkyl, a cycloalkyl, or a phenyl group.



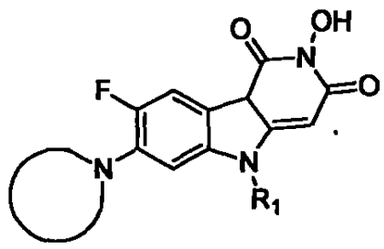
The quinolones inhibit bacterial growth by inhibition of DNA gyrase and topoisomerase IV (Gootz, supra., 1996). The gyrase interaction appears to rely on the N_1/C_4-carbonyl/C_3-carboxyl relationship.

Attempts to design novel quinolone mimics have focused on the N_1/C_4-carbonyl/C_3-carboxyl relationship. Certain tricyclic isothiazole analogs were designed to keep an all-planar relationship, and to have the NH of the isothiazole ring be as acidic as the quinolone C_3-carboxyl group (Chu, *Drugs Exptl. Clin. Res.*, 1990;16:215).



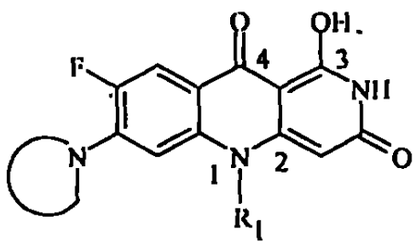
While maintaining excellent antibacterial activity, these compounds also show antitumor and mammalian topoisomerase activity (*Drugs of the Future*, 1992;17:1101). These activities are undesired in an antibacterial agent.

Several publications (US Patent No. 5,283,248; *J. Med. Chem.*, 1992;35:1358; *Antimicrob. Agents Chemother.*, 1995;39:163) disclose tricyclic compounds (such as the structure below) having antibacterial activity and DNA gyrase inhibiting activity.



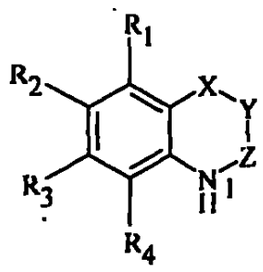
For such compounds, the relationship of the N_1 to the C_4-carbonyl is skewed. Compounds of this type are ineffective against bacteria that are quinolone resistant.

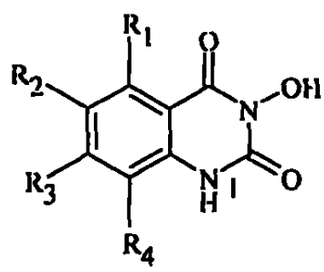
Other tricyclic analogs of the following structure are disclosed as quinolone mimics (JP 4,091,090.3/92; Interscience Conference on Antimicrobial Agents and Chemotherapy 1991, Abstract 1494).



While the ideal quinolone N_1-C_4-carbonyl relationship is maintained, the C_2 region, where substitution is undesirable, is part of a fused-ringed system. These compounds are not active against quinolone resistant bacteria.

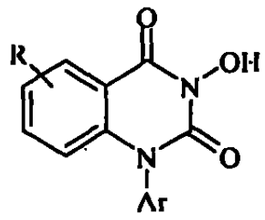
WO 96/04288 describes a series of benzoheterocycles of the formulas





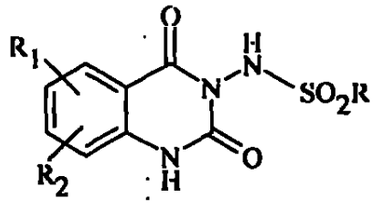
where X, Y, and Z are hydrogen bond acceptor and donator groups. Among the compounds depicted are N-hydroxy-quinazoline-2,4-diones, where R_1-R_4 can represent hydroxy, amino, nitro, a variety of alkyls, esters, and amides. In all cases, the substituent on N_1 is hydrogen. None of the substituents R_1-R_4 are nitrogen containing heterocycles. No antibacterial activity is disclosed for these compounds.

United States Patent No. 5,155,110 describes N_1-aryl-N-hydroxy-quinazoline-2,4-diones of the formula



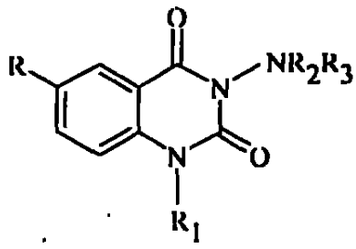
where R may be halo, cyano, hydroxy, alkoxy, and substituted amino. Amino heterocycles are not included in R, and no antibacterial activity is reported for such compounds.

Compounds taught in International Publication No. WO 95/19346 as AMPA, NMDA, and kinase receptor antagonists have the formula



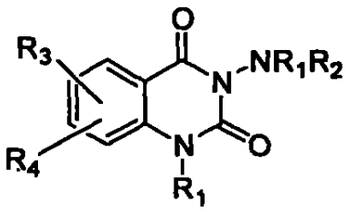
where R substituents are defined as alkyl or phenyl, and R_1 and R_2 are defined as H, alkyl, alkoxy, alkenyl, halogen, NO_2, (un)substituted NH_2, CN, etc. Again, no antibacterial activity is disclosed for these compounds.

Kornet and coworkers (Kornet M.J. et al., *J. Heterocyl. Chem.*, 1984;21:1533-1535) disclosed anticonvulsant compounds having the formula



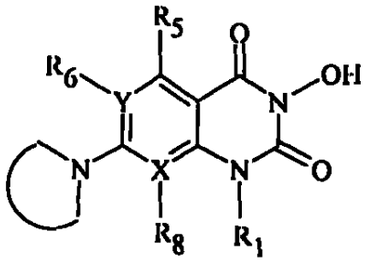
where R is defined as H, Me, or Cl; R_1 and R_2 as H or Me; and R_3 as Me or t-butyl. Alternatively, R_2 and R_3, together with the nitrogen atom to which they are attached, can form a heterocyclic ring such as piperidinyl, morpholinyl, etc. These compounds are not reported to have antibacterial activity.

A number of publications teach compounds having diuretic and sedative activities and with the generic structure as follows (ES 80/489675, JP 80/33323, BE 80/199792, FR 78/33438, JP 70/97932; Baronnet R., Callendret R., Blanchard L., Foussard-Blanpin O., Bretaudeau J., *Eur. J. Med.-Chim. Ther.*, 1983;18:241-247).



These are compounds in which NR_1R_2 can form a heterocycle, or R_1 and R_2 independently can represent H or a small alkyl. R_3 and R_4 can represent H, halogen, sulphonamide, alkyl, or alkoxy. No antibacterial activity is reported for these compounds.

International Publication No. WO 99/21840 describes 3-hydroxy-quinazoline-2,4-diones as antibacterial agents.



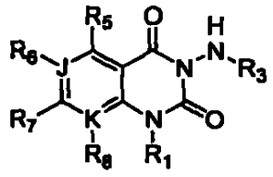
Compounds of this type are quinolone mimics where the 3-position exocyclic carboxylic acid of the quinolones is replaced by an oxo at the 2-position and a hydroxy at the N-3-position. Compounds of this type are designed to keep an all-planar relationship and to have the N-OH remain acidic, as in the quinolone CO_2H (Chu, *Drugs Exptl. Clin. Res.*, 1990;16:215). These compounds inhibit DNA gyrase and topoisomerase IV, and demonstrate antibacterial activity in vitro. However, such compounds are not effective against quinolone resistant bacteria.

The need continues to find new antibacterial agents that have the potency of the quinolones, but which are active against quinolone resistant bacterial strains. The present invention provides such compounds, which are characterized as 3-aminoquinazolin-2,4-diones. An object of this invention is to provide these new compounds, and a method for treating bacterial infections in mammals by administering these compounds.

SUMMARY OF THE INVENTION

The present invention provides 3-aminoquinazolin-2,4-diones having antibacterial activity. The compounds inhibit DNA gyrase, but are not cross-resistant with quinolone mutants that are no longer sensitive to agents such as ciprofloxacin.

The invention provides compounds of Formula I



I

or a pharmaceutically acceptable salt thereof wherein:

R_1 and R_3 independently are H,

C_1-C_{12} alkyl and substituted alkyl,

C_2-C_{12} alkenyl and substituted alkenyl,

C_2-C_{12} alkynyl and substituted alkynyl,

C_3-C_{12} cycloalkyl and substituted cycloalkyl,

aryl and substituted aryl,

heterocyclic and substituted heterocyclic,

or heteroaryl and substituted heteroaryl;

R_5, R_6, and R_8 independently are H,

$(O)_nC_1$-C_{12} alkyl, and substituted alkyl;

$(O)_nC_2$-C_{12} alkenyl, and substituted alkenyl;

$(O)_nC_2$-C_{12} alkynyl, and substituted alkynyl;

halo,

NO_2,

CN,

NR'R'' wherein n is 0 or 1;

R' and R'' independently are H,

C_1-C_{12} alkyl and substituted alkyl,

C_2-C_{12} alkenyl and substituted alkenyl,

C_2-C_{12} alkynyl and substituted alkynyl,

CO-C_1-C_{12} alkyl and substituted alkyl,

or R' and R'' taken together with the nitrogen to which they are attached form a 3- to 7-membered ring containing from 1 to 3 heteroatoms selected from N, O, and S, said ring being unsubstituted or substituted with up to 4 substituent groups;

R_1 and R_8 can be taken together with the atoms to which they are attached to form a cyclic ring having from 1 to 3 heteroatoms selected from N, O, and S, and optionally substituted by R' and R'';

R_7 is hydrogen,

C_1-C_{12} alkyl and substituted alkyl,

C_2-C_{12} alkenyl and substituted alkenyl,

C_2-C_{12} alkynyl and substituted alkynyl,

halo,

NO_2,

CN,

NR'R",

COOR',

aryl,

fused aryl,

heterocyclic,

fused heterocyclic,

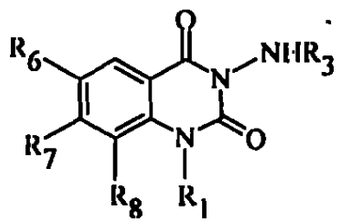
bicyclic heterocyclic, or

spiro heterocyclic wherein all ring groups can be substituted;

J and K independently are C or N, provided that when J or K is N, R_6 or R_8 is absent at that position.

R_7 is referred to herein as the "side chain" of the 3-aminoquinazolin-2,4-dione nucleus. The R_7 side chain can be any group known in the quinolone art as a suitable substituent at the 7-position of the quinolone ring.

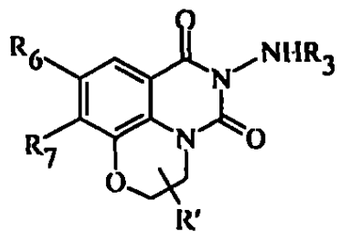
Preferred compounds of this invention have Formula II



II

wherein R_1, R_3, R_6, R_7, and R_8 are as defined above.

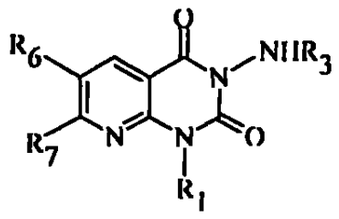
Further preferred compounds have Formula III



III

wherein R_3, R_6, R_7, and R' are as defined above.

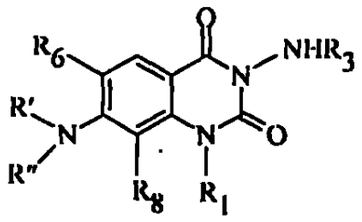
Another preferred group of compounds have Formula IV



IV

wherein R_1, R_3, R_6, and R_7 are as defined above.

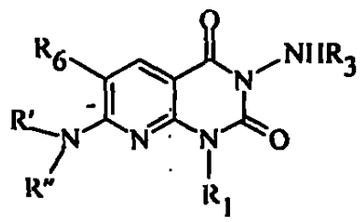
The most preferred compounds of this invention have Formula V



V

wherein R_1, R_3, R_6, R8, R', and R" are as defined above. An especially preferred embodiment are compounds of Formula V wherein R' and R" are taken together with the nitrogen to which they are attached to complete a ring which is optionally substituted with groups such as alkyl and substituted alkyl, and amino, alkylamino, dialkylamino, and aryl amino.

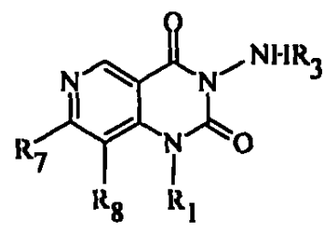
A further preferred group of compounds have Formula VI



VI

wherein R_1, R_3, R_6, R', and R" are as defined above.

Still another preferred group of invention compounds are those of Formula VII



VII

wherein R_1, R_3, R_7, and R_8 are as defined above.

Especially preferred compounds provided by the invention are:

3-Amino-7-(3-aminomethylpyrrolidin-1-yl)-8-chloro-1-cyclopropyl-6-fluoro-1*H*-quinazoline-2,4-dione;

3-Amino-8-chloro-1-cyclopropyl-6-fluoro-7-piperazin-1-yl-1*H*-quinazoline-2,4-dione;

3-Amino-7-[3-(aminomethyl)-3-methylpyrrolidin-1-yl]-8-chloro-1-cyclopropyl-6-fluoro-1*H*-quinazoline-2,4-dione;

3-Amino-7-(6-amino-3-aza-bicyclo[3.1.0]hex-3-yl)-8-chloro-1-cyclopropyl-6-fluoro-1*H*-quinazolin-2,4-dione;

3-Amino-7-((S)-3-N-methylaminopyrrolidin-1-yl)-8-chloro-1-cyclopropyl-6-fluoro-1*H*-quinazoline-2,4-dione;

3-Amino-7-((S)-3-aminopyrrolidin-1-yl)-8-chloro-1-(2,4-difluoroanilino)-6-fluoro-1*H*-quinazoline-2,4-dione;

3-Amino-7-[(S)-3-aminopyrrolidin-1-yl]-1-cyclopropylamino-6,8-difluoro-1H-quinazoline-2,4-dione;

3-Amino-7-[(S)-3-aminopyrrolidin-1-yl]-1-cyclopropylamino-5,8-difluoro-1*H*-quinazoline-2,4-dione;

3-Amino-7-((S)-3-aminopyrrolidin-1-yl)-1-cyclopropyl-5,6,8-trifluoro-1*H*-quinazoline-2,4-dione;

3-Amino-7-(3-aminopyrrolidin-1-yl)-8-chloro-1-cyclopropyl-6-fluoro-1*H*-quinazoline-2,4-dione;

7-((S)-3-Aminopyrrolidin-1-yl)-1-cyclopropyl-3,5-diamino-6,8-difluoro-1*H*-quinazoline-2,4-dione;

3-Amino-7-(3-hydroxymethylpyrrolidin-1-yl)-8-chloro-1-cyclopropyl-6-fluoro-1*H*-quinazoline-2,4-dione;

3-Amino-7-(3-aminoethylpyrrolidin-1-yl)-8-chloro-1-cyclopropyl-6-fluoro-1*H*-quinazoline-2,4-dione;

3-Amino-7-((S)-7-amino-5-azaspiro[2.4]hept-5-yl)-8-chloro-1-cyclopropyl-6-fluoro-1*H*-quinazoline-2,4-dione;

3-Amino-7-[(R)-3-(1-amino-1-methylethyl)pyrrolidin-1-yl]-8-chloro-1-cyclopropyl-6-fluoro-1*H*-quinazoline-2,4-dione;

3-Amino-7-(3-aminomethylpyrrolidin-1-yl)-1-cyclopropyl-6-fluoro-1*H*-quinazoline-2,4-dione;

3-Amino-7-(pyrrolidin-1-yl)-8-chloro-1-cyclopropyl-6-fluoro-1*H*-quinazoline-2,4-dione;

3-Amino-7-(3-aminopyrrolidin-1-yl)-8-chloro-6-fluoro-1-isopropyl-1*H*-quinazoline-2,4-dione;

3-Amino-7-(3-aminopyrrolin-1-yl)-1-*sec*-butyl-8-chloro-6-fluoro-1*H*-quinazoline-2,4-dione;

3-Amino-7-[3-aminopyrrolidin-1-yl]-1-cyclopropyl-6-fluoro-8-methoxy-1*H*-quinazoline-2,4-dione;

3-Amino-7-[3-aminopyrrolidin-1-yl]-8-chloro-1-cyclobutylamino-6-fluoro-1*H*-quinazoline-2,4-dione;

3-Amino-7-(3-aminopyrrolidin-1-yl)-1-cyclopropyl-8-fluoro-1*H*-quinazoline-2,4-dione;

3-Amino-7-(3-aminopyrrolidin-1-yl)-6-chloro-1-cyclopropyl-8-fluoro-1*H*-quinazoline-2,4-dione;

3-Amino-7-((S)-3-aminopyrrolidin-1-yl)-1-cyclopropylmethyl-8-fluoro-1*H*-quinazoline-2,4-dione;

3-Amino-7-[(R)-3-(1-amino-1-methylethyl)pyrrolidin-1-yl]-1-cyclopropylmethyl-8-fluoro-1*H*-quinazoline-2,4-dione;

3-Amino-7-((S)-3-aminopyrrolidin-1-yl)-1-ethyl-8-fluoro-1*H*-quinazoline-2,4-dione;

3-Amino-1-ethyl-6-fluoro-7-[(R)-3-(1-amino-1-methylethyl)-pyrrolidin-1-yl]-1H-quinazoline-2,4-dione;

3-Amino-7-((S)-3-aminopyrrolidin-1-yl)-1-cyclopropyl-6-fluoro-1*H*-quinazoline-2,4-dione;

3-Amino-7-(3-aminopyrrolidin-1-yl)-1-cyclopropyl-6-fluoro-8-methyl-1H-quinazoline-2,4-dione;

3-Amino-7-(3-aminomethylpyrrolidin-1-yl)-1-cyclopropyl-6-fluoro-8-methyl-1H-quinazoline-2,4-dione;

3-Amino-7-(3-aminopyrrolidin-1-yl)-1-cyclopropyl-8-fluoro-6-methoxy-1H-quinazoline-2,4-dione;

3-Amino-7-(3-aminomethylpyrrolidin-1-yl)-1-cyclopropyl-6-fluoro-8-methoxy-1H-quinazoline-2,4-dione;

3-Amino-7-(3-aminopyrrolidin-1-yl)-1-cyclopropyl-8-ethoxy-6-fluoro-1H-quinazoline-2,4-dione;

3-Amino-7-(3-aminopyrrolidin-1-yl)-1-cyclopropyl-6-fluoro-2,4-dioxo-1,2,3,4-tetrahydroquinazoline-8-carbonitrile;

3-Amino-8-chloro-1-cyclopropyl-6-fluoro-7-(3-[1,2,3-triazol]-1-yl-pyrrolidin-1-yl)-1H-quinazoline-2,4-dione;

3-Amino-7-[(S)-3-((R)-1-aminoethyl)pyrrolidin-1-yl]-1-cyclopropyl-6-fluoro-8-methoxy-1H-quinazoline-2,4-dione;

3-Amino-7-[(S)-3-((S)-1-aminoethyl)pyrrolidin-1-yl]-1-cyclopropyl-6-fluoro-8-methoxy-1H-quinazoline-2,4-dione;

3-Amino-7-[(S)-3-((R)-1-aminoethyl)pyrrolidin-1-yl]-1-cyclopropyl-6-fluoro-8-methyl-1H-quinazoline-2,4-dione;

3-Amino-7-[(S)-3-((S)-1-aminoethyl)pyrrolidin-1-yl]-1-cyclopropyl-6-fluoro-8-methyl-1H-quinazoline-2,4-dione;

5-Amino-9-((S)-3-aminopyrrolidin-1-yl)-8-fluoro-3-methyl-2,3-dihydro-1-oxa-3a,5-diazaphenalene-4,6-dione;

5-Amino-9-[(R)-3-((S)-1-aminoethyl)pyrrolidin-1-yl]-8-fluoro-3-methyl-2,3-dihydro-1-oxa-3a,5-diazaphenalene-4,6-dione;

2-Amino-8-((S)-3-aminopyrrolidin-1-yl)-9-fluoro-5-methyl-6,7-dihydro-5H-pyrido[3.2,1-ij]quinazoline-1,3-dione,;

2-Amino-8-[(R)-3-((S)-1-aminoethyl)pyrrolidin-1-yl]-9-fluoro-5-methyl-6,7-dihydro-5H-pyrido[3,2,1-ij]quinazoline-1,3-dione;

3-Amino-7-((S)-3-aminopyrrolidin-1-yl)-1-cyclopropyl-6-fluoro-1H-pyrido[2,3-d]pyrimidine-2,4-dione;

3-Amino-7-(6-amino-3-azabicyclo[3.1.0]hex-3-yl)-1-cyclopropyl-6-fluoro-1H-pyrido[2,3-d]pyrimidine-2,4-dione,;

3-Amino-7-(3-aminomethyl-3-methylpyrrolidin-1-yl)-1-cyclopropyl-6-fluoro-1H-pyrido[2,3-d]pyrimidine-2,4-dione,;

3-Amino-1-cyclopropyl-6-fluoro-7-(octahydropyrrolo[3,4-c]pyridin-2-yl)-1H-pyrido[2,3-d]pyrimidine-2,4-dione;

3-Amino-1-cyclopropyl-6-fluoro-7-(octahydropyrrolo[3,4-b]pyridin-2-yl)-1H-pyrido[2,3-d]pyrimidine-2,4-dione;

3-Amino-7-[(R)-3-(1-amino-1-methylethyl)pyrrolidin-1-yl]-1-cyclopropyl-6-fluoro-1H-pyrido[2,3-d]pyrimidine-2,4-dione;

3-Amino-7-(3-aminomethylpiperidin-1-yl)-1-cyclopropyl-6-fluoro-1H-pyrido[2,3-d]pyrimidine-2,4-dione;

trans-3-Amino-7-(3-aminomethyl-4-trifluoromethylpyrrolidin-1-yl)-1-cyclopropyl-6-fluoro-1H-pyrido[2,3-d]pyrimidine-2,4-dione;

3-Amino-1-cyclopropyl-6-fluoro-7-[(R)-3-((R)-1-methylaminoethyl)pyrrolidin-1-yl]-1H-pyrido[2,3-d]pyrimidine-2,4-dione;

3-Amino-7-[(R)-3-((S)-1-aminoethyl)pyrrolidin-1-yl]-1-cyclopropyl-6-fluoro-1H-pyrido[2,3-d]pyrimidine-2,4-dione;

3-Amino-7-[3-(1-aminopropyl)pyrrolidin-1-yl]-1-cyclopropyl-6-fluoro-8-methyl-1*H*-quinazoline-2,4-dione;

3-Amino-1-cyclopropyl-6-fluoro-8-methyl-7-[(R)-3-((S)-1-methylaminoethyl)pyrrolidin-1-yl]-1*H*-quinazoline-2,4-dione;

3-Amino-7-[7-(1-aminoethyl)-5-azaspiro[2.4]hept-5-yl]-1-cyclopropyl-6-fluoro-8-methyl-1*H*-quinazoline-2,4-dione;

1-(3-Amino-8-chloro-1-cyclopropyl-6-fluoro-2,4-dioxo-1,2,3,4-tetrahydroquinazolin-7-yl)piperidine-3-carboxylic acid amide;

3-Amino-[7-trans-3-aminomethyl-4-trifluoromethylpyrrolidin-1-yl]-8-chloro-1-cyclopropyl-6-fluoro-1*H*-quinazoline-2,4-dione;

3-Amino-8-chloro-1-cyclopropyl-6-fluoro-7-{3-[(2,2,2-trifluoroethylamino)methyl]pyrrolidin-1-yl}-1*H*-quinazoline-2,4-dione;

3-Amino-8-chloro-1-cyclopropyl-6-fluoro-7-(5-methylhexahydropyrrolo[3,4-*c*]pyrrol-2-yl)-1*H*-quinazoline-2,4-dione;

3-Amino-8-chloro-1-cyclopropyl-7-(2,7-diazaspiro[4.4]non-2-yl)-6-fluoro-1*H*-quinazoline-2,4-dione;

3-Amino-7-(3-aminomethyl-3-benzylpyrrolidin-1-yl)-8-chloro-1-cyclopropyl-6-fluoro-1*H*-quinazoline-2,4-dione;

3-Amino-7-[(R)-3-((S)-1-aminoethyl)pyrrolidin-1-yl]-8-chloro-1-cyclopropyl-6-fluoro-1H-quinazoline-2,4-dione;

3-Amino-8-chloro-1-cyclopropyl-6-fluoro-7-(3-hydroxyimino-pyrrolidin-1-yl)-1*H*-quinazoline-2,4-dione;

3-Amino-7-[trans-3-amino-4-trifluoromethylpyrrolidin-1-yl]-8-chloro-1-cyclopropyl-6-fluoro-1H-quinazoline-2,4-dione;

3-Amino-8-chloro-1-cyclopropyl-6-fluoro-7-[(R)-3-(S)-1-methylaminoethyl)pyrrolidin-1-yl]-1*H*-quinazoline-2,4-dione;

3-Amino-7-(trans-3-amino-4-phenylpyrrolidin-1-yl)-8-chloro-1-cyclopropyl-6-fluoro-1*H*-quinazoline-2,4-dione;

3-Amino-7-[trans-3-amino-4-(4-hydroxyphenyl)pyrrolidin-1-yl]-8-chloro-1-cyclopropyl-6-fluoro-1*H*-quinazoline-2,4-dione;

N-[1-(3-Amino-8-chloro-1-cyclopropyl-6-fluoro-2,4-dioxo-1,2,3,4-tetrahydroquinazolin-7-yl)pyrrolidin-3-ylmethyl]methanesulfonamide;

3-Amino-7-(3-aminomethylpiperidin-1-yl)-8-chloro-1-cyclopropyl-6-fluoro-1H-quinazoline-2,4-dione;

3-Amino-8-chloro-1-cyclopropyl-6-fluoro-7-[3-(isopropylamino-methyl)pyrrolidin-1-yl]-1*H*-quinazoline-2,4-dione;

3-Amino-7-(3-aminomethylpyrrolidin-1-yl)-6,8-dichloro-1-cyclopropyl-1*H*-quinazoline-2,4-dione;

N-[1-(3-Amino-8-chloro-1-cyclopropyl-6-fluoro-2,4-dioxo-1,2,3,4-tetrahydroquinazolin-7-yl)pyrrolidin-3-ylmethyl]methanesulfonamide;

3-Amino-7-[(R)-3-(S)-(1-aminoethyl)pyrrolidin-1-yl]-1-cyclopropyl-6-fluoro-8-methyl-1H-quinazoline-2,4-dione;

3-Amino-7-[(R)-3-(1-amino-1-methylethyl)pyrrolidin-1-yl]-1-cyclopropyl-6-fluoro-8-methyl-1H-quinazoline-2,4-dione;

3-Amino-7-[3-(1-aminoethyl)-3-methoxypyrrolidin-1-yl]-1-cyclopropyl-6-fluoro-8-methyl-1H-quinazoline-2,4-dione;

3-Amino-7-[3-(1-aminoethyl)-3-fluoropyrrolidin-1-yl]-1-cyclopropyl-6-fluoro-8-methoxy-1H-quinazoline-2,4-dione;

3-Amino-7-(3-aminopyrrolidin-1-yl)-1-cyclopropyl-6-fluoro-5-methyl-1H-quinazoline-2,4-dione;

3-Amino-7-[(R)-3-(S)-(1-aminoethyl)pyrrolidin-1-yl]-1-cyclopropyl-6-fluoro-5-methyl-1H-quinazoline-2,4-dione;

3-Amino-7-(3-aminomethyl-3-methoxymethylpyrrolidin-1-yl)-1-cyclopropyl-6-fluoro-8-methyl-1H-quinazoline-2,4-dione;

3-Amino-7-(3-aminomethyl-3-fluoromethylpyrrolidin-1-yl)-1-cyclopropyl-6-fluoro-1H-quinazoline-2,4-dione;

3-Amino-7-(trans-3-aminomethyl-4-trifluoromethylpyrrolidin-1-yl)-1-cyclopropyl-6-fluoro-8-methoxy-1H-quinazoline-2,4-dione;

3-Amino-7-[3-(1-aminoethyl)piperidin-1-yl]-1-cyclopropyl-6-fluoro-8-methoxy-1H-quinazoline-2,4-dione;

3-Amino-7-[3-(aminoethyl)piperidin-1-yl]-1-cyclopropyl-6-fluoro-8-methyl-1H-quinazoline-2,4-dione;

3-Amino-7-[4-(1-aminoethyl)-3,3-dimethylpyrrolidin-1-yl]-1-cyclopropyl-6-fluoro-8-methoxy-1H-quinazoline-2,4-dione;

3-Amino-7-[4-(1-aminoethyl)-3,3-dimethylpyrrolidin-1-yl]-1-cyclopropyl-6-fluoro-8-methyl-1H-quinazoline-2,4-dione;

3-Amino-7-(3-amino-3-phenylpyrrolidin-1-yl)-1-cyclopropyl-6-fluoro-8-methyl-1H-quinazoline-2,4-dione;

3-Amino-7-[3-(1-aminoethyl)-4-methylpyrrolidin-1-yl]-1-cyclopropyl-6-fluoro-8-methyl-1H-quinazoline-2,4-dione;

3-Amino-7-(3-aminomethyl-3-phenylpyrrolidin-1-yl)-1-cyclopropyl-6-fluoro-8-methyl-1H-quinazoline-2,4-dione;

3-Amino-7-(7-aminomethyl-5-azaspiro[2,4]hept-5-yl)-1-cyclopropyl-6-fluoro-8-methyl-1H-quinazoline-2,4-dione;

3-Amino-7-(7-aminomethyl-5-azaspiro[2,4]hept-5-yl)-1-cyclopropyl-6-fluoro-8-methoxy-1H-quinazoline-2,4-dione;

3-Amino-7-(3-aminomethyl-3-hydroxypyrrolidin-1-yl)-1-cyclopropyl-6-fluoro-8-methoxy-1H-quinazoline-2,4-dione;

3-Amino-7-(3-aminomethylpiperidin-1-yl)-1-cyclopropyl-6-fluoro-8-methyl-1H-quinazoline-2,4-dione;

3-Amino-7-(3-amino-4-methoxypyrrolidin-1-yl)-1-cyclopropyl-6-fluoro-8-methyl-1H-quinazoline-2,4-dione;

3-Amino-7-(3-amino-4-methoxypyrrolidin-1-yl)-1-cyclopropyl-6-fluoro-8-methoxy-1H-quinazoline-2,4-dione;

3-Amino-7-(3-amino-4-fluoropyrrolidin-1-yl)-1-cyclopropyl-6-fluoro-8-methoxy-1H-quinazoline-2,4-dione;

3-Amino-7-(3-aminomethyl-3-methylpyrrolidin-1-yl)-1-cyclopropyl-6-fluoro-8-methyl-1H-quinazoline-2,4-dione;

3-Amino-7-[(R)-3 (-((S)-1-aminoethyl)pyrrolidin-1-yl]-1-cyclopropyl-8-ethyl-6-fluoro-1H-quinazoline-2,4-dione;

1-(3-Amino-1-cyclopropyl-6-fluoro-8-methoxy-2,4-dioxo-1,2,3,4-tetrahydroquinazolin-7-yl)pyrrolidine-3-carboxylic acid trifluoroacetate;

1-(3-Amino-1-cyclopropyl-6-fluoro-8-methyl-2,4-dioxo-1,2,3,4-tetrahydroquinazolin-7-yl)pyrrolidine-3-carboxylic acid trifluoroacetate;

3-Amino-7-(1-aminomethyl-3-azabicyclo[3.1.0]hex-3-yl)-1-cyclopropyl-6-fluoro-8-methoxy-1H-quinazoline-2,4-dione;

3-Amino-7-(1-aminomethyl-3-azabicyclo[3.1.0]hex-3-yl)-1-cyclopropyl-6-fluoro-8-methyl-1H-quinazoline-2,4-dione;

3-Amino-7-[(S)-3-((R)-1-aminoethyl)pyrrolidin-1-yl]-1-cyclopropyl-6-fluoro-8-methoxy-1H-quinazoline-2,4-dione;

3-Amino-7-[(S)-3-((R)-1-aminoethyl)pyrrolidin-1-yl]-1-cyclopropyl-6-fluoro-8-methyl-1H-quinazoline-2,4-dione;

3-Amino-1-cyclopropyl-6-fluoro-8-methyl-7-(octahydropyrrolo [3,4-b]pyridin-6-yl)-1H-quinazoline-2,4-dione;

3-Amino-7-(trans-3-aminomethyl-4-methylpyrrolidin-1-yl)-8-chloro-1-cyclopropyl-6-fluoro-1H-quinazoline-2,4-dione;

3-Amino-7-(trans-3-aminomethyl-4-methylpyrrolidin-1-yl)-1-cyclopropyl-6-fluoro-8-methoxy-1H-quinazoline-2,4-dione;

3-Amino-7-(trans-3-aminomethyl-4-methylpyrrolidin-1-yl)-1-cyclopropyl-6-fluoro-8-methyl-1H-quinazoline-2,4-dione;

3-Amino-7-(trans-3-amino-4-methylpyrrolidin-1-yl)-1-cyclopropyl-6-fluoro-8-methoxy-1H-quinazoline-2,4-dione;

3-Amino-7-(3-aminomethylmorpholin-1-yl)-1-cyclopropyl-6-fluoro-8-methoxy-1H-quinazoline-2,4-dione;

3-Amino-7-(3-aminomethylpiperidin-1-yl)-1-cyclopropyl-6-fluoro-8-methoxy-1H-quinazoline-2,4-dione;

3-Amino-7-[3-(1-aminoethyl)-4-methylpyrrolidin-1-yl]-1-cyclopropyl-6-fluoro-8-methoxy-1H-quinazoline-2,4-dione;

3-Amino-7-(3-amino-3-phenylpyrrolidin-1-yl)-8-chloro-1-cyclopropyl-6-fluoro-1H-quinazoline-2,4-dione;

3-Amino-7-(3-amino-3-methylpyrrolidin-1-yl)-1-cyclopropyl-6-fluoro-8-methyl-1H-quinazoline-2,4-dione;

3-Amino-1-cyclopropyl-6-fluoro-8-methyl-7-pyrrolidin-1yl-1H-quinazoline-2,4-dione;

3-Amino-1-cyclopropyl-6-fluoro-8-methoxy-7-pyrrolidin-1yl-1H-quinazoline-2,4-dione;

3-Amino-1-cyclopropyl-6-fluoro-7-[3-(1-hydroxy-1-methylethyl)-pyrrolidin-1-yl]-8-methyl-1H-quinazoline-2,4-dione;

3-Amino-1-cyclopropyl-6-fluoro-7-[3-(1-hydroxy-1-methylethyl)-pyrrolidin-1-yl]-8-methoxy-1H-quinazoline-2,4-dione;

3-Amino-1-cyclopropyl-6-fluoro-5-methyl-7-[(R)-3-((S)-1-methylaminoethyl)pyrrolidin-1-yl]-1H-quinazoline-2,4-dione;

(S)-1-[(R)-1-(3-Amino-1-cyclopropyl-7-[3-(1-ethylaminoethyl)pyrrolidin-1-yl)-6-fluoro-8-methoxy-1H-quinazoline-2,4-dione;

3-Amino-1-cyclopropyl-7-[(R)-3-((S)-1-ethylaminoethyl)pyrrolidin-1-yl]-6-fluoro-8-methyl-1H-quinazoline-2,4-dione;

3-Amino-7-(6-amino-1-methyl-3-azabicyclo[3.2.0]hept-3-yl)-1-cyclopropyl-6-fluoro-8-methoxy-1H-quinazoline-2,4-dione;

3-Amino-7-(4-aminomethylpiperidin-1-yl)-1-cyclopropyl-6-fluoro-8-methoxy-1H-quinazoline-2,4-dione;

3-Amino-7-(3-aminomethylazetidin-1-yl)-1-cyclopropyl-6-fluoro-8-methoxy-1H-quinazoline-2,4-dione;

cis-3-Amino-7-(3-aminomethyl-4-fluoropyrrolidin-1-yl)-1-cyclopropyl-6-fluoro-8-methoxy-1H-quinazoline-2,4-dione;

trans-3-Amino-7-(3-aminomethyl-4-fluoropyrrolidin-1-yl)-1-cyclopropyl-6-fluoro-8-methoxy-1H-quinazoline-2,4-dione;

3-Amino-7-(1-amino-5-azaspiro[2.4]hept-5-yl)-1-cyclopropyl-6-fluoro-8-methoxy-1H-quinazoline-2,4-dione;

3-Amino-7-(3-aminomethyloctahydroisoindol-2-yl)-1-cyclopropyl-6-fluoro-8-methoxy-1H-quinazoline-2,4-dione;

3-Amino-7-(3-aminomethyloctahydroisoindol-2-yl)-1-cyclopropyl-6-fluoro-8-methyl-1H-quinazoline-2,4-dione;

3-Amino-7-[(R)-3-((S)-1-aminoethylpyrrolidin-1-yl]-1-cyclopropyl-6-fluoro-8-methoxy-1H-quinazoline-2,4-dione;

3-Amino-7-(6-amino-3-azabicyclo[3.1.0]hex-3-yl)-1-cyclopropyl-6-fluoro-8-methyl-1H-quinazoline-2,4-dione;

3-Amino-7-[3-(1-amino-1-methylethyl)pyrrolidin-1-yl]-1-cyclopropyl-6-fluoro-8-methoxy-1*H*-quinazoline-2,4-dione;

3-Amino-1-cyclopropyl-6-fluoro-7-[3-(isopropylaminomethyl) pyrrolidin-1-yl]-8-methoxy-1*H*-quinazoline-2,4-dione;

3-Amino-1-cyclopropyl-6-fluoro-8-methoxy-7-[(4aS,7aS)-octahydropyrrolo[3,4-b]pyridin-6-yl-1*H*-quinazoline-2,4-dione;

3-Amino-7-(3-amino-4-fluoromethylpyrrolidin-1-yl)-1-cyclopropyl-6-fluoro-8-methoxy-1*H*-quinazoline-2,4-dione;

3-Amino-7-(3-aminomethyl-3-methylpyrrolidin-1-yl)-1-cyclopropyl-6-fluoro-8-methoxy-1*H*-quinazoline-2,4-dione;

3-Amino-7-(4-aminopiperidin-1-yl)-1-cyclopropyl-6-fluoro-8-methoxy-1*H*-quinazoline-2,4-dione;

3-Amino-7-(3-aminopiperidin-1-yl)-1-cyclopropyl-6-fluoro-8-methoxy-1*H*-quinazoline-2,4-dione;

3-Amino-1-cyclopropyl-6-fluoro-8-methoxy-7-[(R)-3-((S)-1-methylaminoethyl)pyrrolidin-1-yl]-1*H*-quinazoline-2,4-dione;

3-Amino-7-(3-aminoazetidin-1-yl)-1-cyclopropyl-6-fluoro-8-methoxy-1*H*-quinazoline-2,4-dione;

3-Amino-7-[(3R,4S)-3-((S)-1-aminoethyl)-4-fluoropyrrolidin-1-yl]-1-cyclopropyl-6-fluoro-8-methyl-1H-quinazoline-2,4-dione;

3-Amino-7-[(3R,4S)-3-((S)-1-aminoethyl)-4-fluoropyrrolidin-1-yl]-1-cyclopropyl-8-methyl-1H-quinazoline-2,4-dione;

3-Amino-7-[(3R,4R)-3-(R)-1-aminoethyl)-4-fluoropyrrolidin-1-yl]-1-cyclopropyl-6-fluoro-8-methyl-1H-quinazoline-2,4-dione;

3-Amino-7-[(3R,4R)-3-((R)-1-aminoethyl)-4-fluoropyrrolidin-1-yl]-1-cyclopropyl-8-methyl-1H-quinazoline-2,4-dione;

3-Amino-7-[(3R,4S)-3-(-1-amino-1-methylethyl)-4-fluoropyrrolidin-1-yl]-1-cyclopropyl-6-fluoro-8-methyl-1H-quinazoline-2,4-dione;

3-Amino-7-[(3R,4S)-3-(-1-amino-1-methylethyl)-4-fluoropyrrolidin-1-yl]-1-cyclopropyl-8-methyl-1H-quinazoline-2,4-dione;

3-Amino-7-[(3R,4R)-3-(-1-amino-1-methylethyl)-4-fluoropyrrolidin-1-yl]-1-cyclopropyl-6-fluoro-8-methyl-1H-quinazoline-2,4-dione;

3-Amino-7-[(3R,4R)-3-(-1-amino-1-methylethyl)-4-fluoropyrrolidin-1-yl]-1-cyclopropyl-8-methyl-1H-quinazoline-2,4-dione;

3-Amino-7-[(3R,4S)-3-((R)-1-amino-2-methoxyethyl)-4-fluoropyrrolidin-1-yl]-1-cyclopropyl-6-fluoro-8-methyl-1H-quinazoline-2,4-dione;

3-Amino-7-[(3R,4S)-3-((R)-1-amino-2-methoxyethyl)-4-fluoropyrrolidin-1-yl]-1-cyclopropyl-8-methyl-1H-quinazoline-2,4-dione;

3-Amino-7-[(3R,4R)-3-((S)-1-amino-2-methoxyethyl)-4-fluoropyrrolidin-1-yl]-1-cyclopropyl-6-fluoro-8-methyl-1H-quinazoline-2,4-dione;

3-Amino-7-[(3R,4R)-3-((S)-1-amino-2-methoxyethyl)-4-fluoropyrrolidin-1-yl]-1-cyclopropyl-8-methyl-1H-quinazoline-2,4-dione;

3-Amino-7-[(3R,4S)-3-((R)-1-amino-2-methoxyethyl)-4-methylpyrrolidin-1-yl]-1-cyclopropyl-6-fluoro-8-methyl-1H-quinazoline-2,4-dione;

3-Amino-7-[(3R,4S)-3-((R)-1-amino-2-methoxyethyl)-4-methylpyrrolidin-1-yl]-1-cyclopropyl-8-methyl-1H-quinazoline-2,4-dione;

3-Amino-7-[(3R,4R)-3-((S)-1-amino-2-methoxyethyl)-4-methylpyrrolidin-1-yl]-1-cyclopropyl-6-fluoro-8-methyl-1H-quinazoline-2,4-dione;

3-Amino-7-[(3R,4R)-3-((S)-1-amino-2-methoxyethyl)-4-methylpyrrolidin-1-yl]-1-cyclopropyl-8-methyl-1H-quinazoline-2,4-dione;

3-Amino-7-[(R)-4-((R)-1-amino-2-methoxyethyl)-3,3-dimethylpyrrolidin-1-yl]-1-cyclopropyl-6-fluoro-8-methyl-1H-quinazoline-2,4-dione;

3-Amino-7-[(R)-4-(R)-1-amino-2-methoxyethyl)-3,3-dimethylpyrrolidin-1-yl]-1-cyclopropyl-8-methyl-1H-quinazoline-2,4-dione;

3-Amino-7-[(R)-4-((S)-1-amino-2-methoxyethyl)-3,3-dimethylpyrrolidin-1-yl]-1-cyclopropyl-6-fluoro-8-methyl-1H-quinazoline-2,4-dione;

3-Amino-7-[(R)-4-(S)-1-amino-2-methoxyethyl)-3,3-dimethylpyrrolidin-1-yl]-1-cyclopropyl-8-methyl-1H-quinazoline-2,4-dione;

3-Amino-7-[(R)-3-((R)-1-amino-2-phenoxyethyl)pyrrolidin-1-yl]-1-cyclopropyl-6-fluoro-8-methyl-1H-quinazoline-2,4-dione;

3-Amino-7-[(R)-3-(R)-1-amino-2-phenoxyethyl)pyrrolidin-1-yl]-1-cyclopropyl-8-methyl-1H-quinazoline-2,4-dione;

3-Amino-7-[(3R,4S)-3-((R)-1-amino-2-phenoxyethyl)-4-methylpyrrolidin-1-yl]-1-cyclopropyl-6-fluoro-8-methyl-1H-quinazoline-2,4-dione;

3-Amino-7-[(3R,4S)-3-((R)-1-amino-2-phenoxyethyl)-4-methylpyrrolidin-1-yl]-1-cyclopropyl-8-methyl-1H-quinazoline-2,4-dione;

3-Amino-7-[(3R,4S)-3-((R)-1-amino-2-phenoxyethyl)-4-fluoropyrrolidin-1-yl]-1-cyclopropyl-6-fluoro-8-methyl-1H-quinazoline-2,4-dione;

3-Amino-7-[(3R,4S)-3-((R)-1-amino-2-phenoxyethyl)-4-fluoropyrrolidin-1-yl]-1-cyclopropyl-8-methyl-1H-quinazoline-2,4-dione;

3-Amino-7-[(R)-3-((S)-1-amino-2-phenoxyethyl)pyrrolidin-1-yl]-1-cyclopropyl-6-fluoro-8-methyl-1H-quinazoline-2,4-dione;

3-Amino-7-[(R)-3-((S)-1-amino-2-phenoxyethyl)pyrrolidin-1-yl]-1-cyclopropyl-8-methyl-1H-quinazoline-2,4-dione;

3-Amino-7-[(3R,4S)-3-((S)-1-amino-2-phenoxyethyl)-4-methylpyrrolidin-1-yl]-1-cyclopropyl-6-fluoro-8-methyl-1H-quinazoline-2,4-dione;

3-Amino-7-[(3R,4S)-3-((S)-1-amino-2-phenoxyethyl)-4-methylpyrrolidin-1-yl]-1-cyclopropyl-8-methyl-1H-quinazoline-2,4-dione;

3-Amino-7-[(3R,4S)-3-((S)-1-amino-2-phenoxyethyl)-4-fluoropyrrolidin-1-yl]-1-cyclopropyl-6-fluoro-8-methyl-1H-quinazoline-2,4-dione;

3-Amino-7-[(3R,4S)-3-((S)-1-amino-2-phenoxyethyl)-4-fluoropyrrolidin-1-yl]-1-cyclopropyl-8-methyl-1H-quinazoline-2,4-dione;

3-Amino-7-[(R)-4-((R)-1-amino-2-phenoxyethyl)-3,3-dimethylpyrrolidin-1-yl]-1-cyclopropyl-6-fluoro-8-methyl-1H-quinazoline-2,4-dione;

3-Amino-7-[(R)-4-((R)-1-amino-2-phenoxyethyl)-3,3-dimethylpyrrolidin-1-yl]-1-cyclopropyl-8-methyl-1H-quinazoline-2,4-dione;

3-Amino-7-[(R)-4-((S)-1-amino-2-phenoxyethyl)-3,3-dimethylpyrrolidin-1-yl]-1-cyclopropyl-6-fluoro-8-methyl-1H-quinazoline-2,4-dione;

3-Amino-7-[(R)-4-((S)-1-amino-2-phenoxyethyl)-3,3-dimethylpyrrolidin-1-yl]-1-cyclopropyl-8-methyl-1H-quinazoline-2,4-dione;

3-Amino-7-[(R)-3-((S)-1-amino-2-ethoxyethyl)pyrrolidin-1-yl]-1-cyclopropyl-6-fluoro-8-methyl-1H-quinazoline-2,4-dione;

3-Amino-7-[(R)-3-((S)-1-amino-2-ethoxyethyl)pyrrolidin-1-yl]-1-cyclopropyl-8-methyl-1H-quinazoline-2,4-dione;

3-Amino-7-[(R)-3-((R)-1-amino-2-ethoxyethyl)pyrrolidin-1-yl]-1-cyclopropyl-6-fluoro-8-methyl-1H-quinazoline-2,4-dione;

3-Amino-7-[(R)-3-((R)-1-amino-2-ethoxyethyl)pyrrolidin-1-yl]-1-cyclopropyl-8-methyl-1H-quinazoline-2,4-dione;

3-Amino-7-[(3R,4S)-3-((R)-1-amino-2-ethoxyethyl)-4-methylpyrrolidin-1-yl]-1-cyclopropyl-6-fluoro-8-methyl-1H-quinazoline-2,4-dione;

3-Amino-7-[(3R,4S)-3-((R)-1-amino-2-ethoxyethyl)-4-methylpyrrolidin-1-yl]-1-cyclopropyl-8-methyl-1H-quinazoline-2,4-dione;

3-Amino-7-[(3R,4S)-3-((R)-1-amino-2-ethoxyethyl)-4-fluoropyrrolidin-1-yl]-1-cyclopropyl-6-fluoro-8-methyl-1H-quinazoline-2,4-dione;

3-Amino-7-[(3R,4S)-3-((R)-1-amino-2-ethoxyethyl)-4-fluoropyrrolidin-1-yl]-1-cyclopropyl-8-methyl-1H-quinazoline-2,4-dione;

3-Amino-7-[(R)-4-((R)-1-amino-2-ethoxyethyl)-3,3-dimethylpyrrolidin-1-yl]-1-cyclopropyl-6-fluoro-8-methyl-1H-quinazoline-2,4-dione;

3-Amino-7-[(R)-4-((R)-1-amino-2-ethoxyethyl)-3,3-dimethylpyrrolidin-1-yl]-1-cyclopropyl-8-methyl-1H-quinazoline-2,4-dione;

3-Amino-7-[(3R,4R)-3-((S)-1-amino-2-ethoxyethyl)-4-methylpyrrolidin-1-yl]-1-cyclopropyl-6-fluoro-8-methyl-1H-quinazoline-2,4-dione;

3-Amino-7-[(3R,4R)-3-((S)-1-amino-2-ethoxyethyl)-4-methylpyrrolidin-1-yl]-1-cyclopropyl-8-methyl-1H-quinazoline-2,4-dione;

3-Amino-7-[(3R,4R)-3-((S)-1-amino-2-ethoxyethyl)-4-fluoropyrrolidin-1-yl]-1-cyclopropyl-6-fluoro-8-methyl-1H-quinazoline-2,4-dione;

3-Amino-7-[(3R,4R)-3-((S)-1-amino-2-ethoxyethyl)-4-fluoropyrrolidin-1-yl]-1-cyclopropyl-8-methyl-1H-quinazoline-2,4-dione;

3-Amino-7-[(R)-3-((S)-1-amino-3-methoxypropyl)pyrrolidin-1-yl]-1-cyclopropyl-6-fluoro-8-methyl-1H-quinazoline-2,4-dione;

3-Amino-7-[(R)-3-((S)-1-amino-3-methoxypropyl)pyrrolidin-1-yl]-1-cyclopropyl-8-methyl-1H-quinazoline-2,4-dione;

3-Amino-7-[(3R,4S)-3-((S)-1-amino-3-methoxypropyl)-4-methylpyrrolidin-1-yl]-1-cyclopropyl-6-fluoro-8-methyl-1H-quinazoline-2,4-dione;

3-Amino-7-[(3R,4S)-3-((S)-1-amino-3-methoxypropyl)-4-methylpyrrolidin-1-yl]-1-cyclopropyl-8-methyl-1H-quinazoline-2,4-dione;

3-Amino-7-[(3R,4S)-3-((S)-1-amino-3-methoxypropyl)-4-fluoropyrrolidin-1-yl]-1-cyclopropyl-6-fluoro-8-methyl-1H-quinazoline-2,4-dione;

3-Amino-7-[(3R,4S)-3-((S)-1-amino-3-methoxypropyl)-4-fluoropyrrolidin-1-yl]-1-cyclopropyl-8-methyl-1H-quinazoline-2,4-dione;

3-Amino-7-[(R)-3-((R)-1-amino-3-methoxypropyl)pyrrolidin-1-yl]-1-cyclopropyl-6-fluoro-8-methyl-1H-quinazoline-2,4-dione;

3-Amino-7-[(R)-3-((R)-1-amino-3-methoxypropyl)pyrrolidin-1-yl]-1-cyclopropyl-8-methyl-1H-quinazoline-2,4-dione;

3-Amino-7-[(3R,4R)-3-((R)-1-amino-3-methoxypropyl)-4-methylpyrrolidin-1-yl]-1-cyclopropyl-6-fluoro-8-methyl-1H-quinazoline-2,4-dione;

3-Amino-7-[(3R,4R)-3-((R)-1-amino-3-methoxypropyl)-4-methylpyrrolidin-1-yl]-1-cyclopropyl-8-methyl-1H-quinazoline-2,4-dione;

3-Amino-7-[(3R,4R)-3-((R)-1-amino-3-methoxypropyl)-4-fluoropyrrolidin-1-yl]-1-cyclopropyl-6-fluoro-8-methyl-1H-quinazoline-2,4-dione;

3-Amino-7-[(3R,4R)-3-((R)-1-amino-3-methoxypropyl)-4-fluoropyrrolidin-1-yl]-1-cyclopropyl-8-methyl-1H-quinazoline-2,4-dione;

{(R)-2-Amino-2-[(R)-1-(3-amino-1-cyclopropyl-6-fluoro-8-methyl-2,4-dioxo-1,2,3,4-tetrahydroquinazolin-7-yl)pyrrolidin-3-yl]ethyl}urea;

{(R)-2-Amino-2-[(R)-1-(3-amino-1-cyclopropyl-8-methyl-2,4-dioxo-1,2,3,4-tetrahydroquinazolin-7-yl)pyrrolidin-3-yl]ethyl}urea;

{(S)-2-Amino-2-[(R)-1-(3-amino-1-cyclopropyl-6-fluoro-8-methyl-2,4-dioxo-1,2,3,4-tetrahydroquinazolin-7-yl)pyrrolidin-3-yl]ethyl}urea;

{(S)-2-Amino-2-[(R)-1-(3-amino-1-cyclopropyl-8-methyl-2,4-dioxo-1,2,3,4-tetrahydroquinazolin-7-yl)pyrrolidin-3-yl]ethyl}urea;

{(R)-2-Amino-2-[(3R,4S)-1-(3-amino-1-cyclopropyl-6-fluoro-8-methyl-2,4-dioxo-1,2,3,4-tetrahydroquinazolin-7-yl)-4-methylpyrrolidin-3-yl]ethyl}urea;

{(R)-2-Amino-2-[(3R,4S)-1-(3-amino-1-cyclopropyl-8-methyl-2,4-dioxo-1,2,3,4-tetrahydroquinazolin-7-yl)-4-methylpyrrolidin-3-yl]ethyl}urea;

{(S)-2-Amino-2-[(3R,4R)-1-(3-amino-1-cyclopropyl-6-fluoro-8-methyl-2,4-dioxo-1,2,3,4-tetrahydroquinazolin-7-yl)-4-methylpyrrolidin-3-yl]ethyl}urea;

{(S)-2-Amino-2-[(3R,4R)-1-(3-amino-1-cyclopropyl-8-methyl-2,4-dioxo-1,2,3,4-tetrahydroquinazolin-7-yl)-4-methylpyrrolidin-3-yl]ethyl}urea;

{2-Amino-2-[(1-(3-amino-1-cyclopropyl-6-fluoro-8-methyl-2,4-dioxo-1,2,3,4-tetrahydroquinazolin-7-yl)-4-fluoropyrrolidin-3-yl]ethyl}urea;

{2-Amino-2-[(1-(3-amino-1-cyclopropyl-8-methyl-2,4-dioxo-1,2,3,4-tetrahydroquinazolin-7-yl)-4-fluoropyrrolidin-3-yl]ethyl}urea;

{2-Amino-2-[(1-(3-amino-1-cyclopropyl-6-fluoro-8-methyl-2,4-dioxo-1,2,3,4-tetrahydroquinazolin-7-yl)-4,4-dimethylpyrrolidin-3-yl]ethyl}urea;

{2-Amino-2-[(1-(3-amino-1-cyclopropyl-8-methyl-2,4-dioxo-1,2,3,4-tetrahydroquinazolin-7-yl)-4,4-dimethylpyrrolidin-3-yl]ethyl}urea;

3-Amino-7-[(3R,4S)-3-((S)-1-aminoethyl)-4-fluoropyrrolidin-1-yl]-1-cyclopropyl-6-fluoro-8-methoxy-1H-quinazoline-2,4-dione;

3-Amino-7-[(3R,4S)-3-((S)-1-aminoethyl)-4-fluoropyrrolidin-1-yl]-1-cyclopropyl-8-methoxy-1H-quinazoline-2,4-dione;

3-Amino-7-[(3R,4R)-3-(R)-1-aminoethyl)-4-fluoropyrrolidin-1-yl]-1-cyclopropyl-6-fluoro-8-methoxy-1H-quinazoline-2,4-dione;

3-Amino-7-[(3R,4R)-3-((R)-1-aminoethyl)-4-fluoropyrrolidin-1-yl]-1-cyclopropyl-8-methoxy-1H-quinazoline-2,4-dione;

3-Amino-7-[(3R,4S)-3-(-1-amino-1-methylethyl)-4-fluoropyrrolidin-1-yl]-1-cyclopropyl-6-fluoro-8-methoxy-1H-quinazoline-2,4-dione;

3-Amino-7-[(3R,4S)-3-(-1-amino-1-methylethyl)-4-fluoropyrrolidin-1-yl]-1-cyclopropyl-8-methoxy-1H-quinazoline-2,4-dione;

3-Amino-7-[(3R,4R)-3-(-1-amino-1-methylethyl)-4-fluoropyrrolidin-1-yl]-1-cyclopropyl-6-fluoro-8-methoxy-1H-quinazoline-2,4-dione;

3-Amino-7-[(3R,4R)-3-(-1-amino-1-methylethyl)-4-fluoropyrrolidin-1-yl]-1-cyclopropyl-8-methoxy-1H-quinazoline-2,4-dione;

3-Amino-7-[(3R,4S)-3-((R)-1-amino-2-methoxyethyl)-4-fluoropyrrolidin-1-yl]-1-cyclopropyl-6-fluoro-8-methoxy-1H-quinazoline-2,4-dione;

3-Amino-7-[(3R,4S)-3-((R)-1-amino-2-methoxyethyl)-4-fluoropyrrolidin-1-yl]-1-cyclopropyl-8-methoxy-1H-quinazoline-2,4-dione;

3-Amino-7-[(3R,4R)-3-((S)-1-amino-2-methoxyethyl)-4-fluoropyrrolidin-1-yl]-1-cyclopropyl-6-fluoro-8-methoxy-1H-quinazoline-2,4-dione;

3-Amino-7-[(3R,4R)-3-((S)-1-amino-2-methoxyethyl)-4-fluoropyrrolidin-1-yl]-1-cyclopropyl-8-methoxy-1H-quinazoline-2,4-dione;

3-Amino-7-[(3R,4S)-3-((R)-1-amino-2-methoxyethyl)-4-methylpyrrolidin-1-yl]-1-cyclopropyl-6-fluoro-8-methoxy-1H-quinazoline-2,4-dione;

3-Amino-7-[(3R,4S)-3-((R)-1-amino-2-methoxyethyl)-4-methylpyrrolidin-1-yl]-1-cyclopropyl-8-methoxy-1H-quinazoline-2,4-dione;

3-Amino-7-[(3R,4R)-3-((S)-1-amino-2-methoxyethyl)-4-methylpyrrolidin-1-yl]-1-cyclopropyl-6-fluoro-8-methoxy-1H-quinazoline-2,4-dione;

3-Amino-7-[(3R,4R)-3-((S)-1-amino-2-methoxyethyl)-4-methylpyrrolidin-1-yl]-1-cyclopropyl-8-methoxy-1H-quinazoline-2,4-dione;

3-Amino-7-[(R)-4-((R)-1-amino-2-methoxyethyl)-3,3-dimethylpyrrolidin-1-yl]-1-cyclopropyl-6-fluoro-8-methoxy-1H-quinazoline-2,4-dione;

3-Amino-7-[(R)-4-(R)-1-amino-2-methoxyethyl)-3,3-dimethylpyrrolidin-1-yl]-1-cyclopropyl-8-methoxy-1H-quinazoline-2,4-dione;

3-Amino-7-[(R)-4-((S)-1-amino-2-methoxyethyl)-3,3-dimethylpyrrolidin-1-yl]-1-cyclopropyl-6-fluoro-8-methoxy-1H-quinazoline-2,4-dione;

3-Amino-7-[(R)-4-(S)-1-amino-2-methoxyethyl)-3,3-dimethylpyrrolidin-1-yl]-1-cyclopropyl-8-methoxy-1H-quinazoline-2,4-dione;

3-Amino-7-[(R)-3-((R)-1-amino-2-phenoxyethyl)pyrrolidin-1-yl]-1-cyclopropyl-6-fluoro-8-methoxy-1H-quinazoline-2,4-dione;

3-Amino-7-[(R)-3-(R)-1-amino-2-phenoxyethyl)pyrrolidin-1-yl]-1-cyclopropyl-8-methoxy-1H-quinazoline-2,4-dione;

3-Amino-7-[(3R,4S)-3-((R)-1-amino-2-phenoxyethyl)-4-methylpyrrolidin-1-yl]-1-cyclopropyl-6-fluoro-8-methoxy-1H-quinazoline-2,4-dione;

3-Amino-7-[(3R,4S)-3-((R)-1-amino-2-phenoxyethyl)-4-methylpyrrolidin-1-yl]-1-cyclopropyl-8-methoxy-1H-quinazoline-2,4-dione;

3-Amino-7-[(3R,4S)-3-((R)-1-amino-2-phenoxyethyl)-4-fluoropyrrolidin-1-yl]-1-cyclopropyl-6-fluoro-8-methoxy-1H-quinazoline-2,4-dione;

3-Amino-7-[(3R,4S)-3-((R)-1-amino-2-phenoxyethyl)-4-fluoropyrrolidin-1-yl]-1-cyclopropyl-8-methoxy-1H-quinazoline-2,4-dione;

3-Amino-7-[(R)-3-((S)-1-amino-2-phenoxyethyl)pyrrolidin-1-yl]-1-cyclopropyl-6-fluoro-8-methoxy-1H-quinazoline-2,4-dione;

3-Amino-7-[(R)-3-((S)-1-amino-2-phenoxyethyl)pyrrolidin-1-yl]-1-cyclopropyl-8-methoxy-1H-quinazoline-2,4-dione;

3-Amino-7-[(3R,4S)-3-((S)-1-amino-2-phenoxyethyl)-4-methylpyrrolidin-1-yl]-1-cyclopropyl-6-fluoro-8-methoxy-1H-quinazoline-2,4-dione;

3-Amino-7-[(3R,4S)-3-((S)-1-amino-2-phenoxyethyl)-4-methylpyrrolidin-1-yl]-1-cyclopropyl-8-methoxy-1H-quinazoline-2,4-dione;

3-Amino-7-[(3R,4S)-3-((S)-1-amino-2-phenoxyethyl)-4-fluoropyrrolidin-1-yl]-1-cyclopropyl-6-fluoro-8-methoxy-1H-quinazoline-2,4-dione;

3-Amino-7-[(3R,4S)-3-((S)-1-amino-2-phenoxyethyl)-4-fluoropyrrolidin-1-yl]-1-cyclopropyl-8-methoxy-1H-quinazoline-2,4-dione;

3-Amino-7-[(R)-4-((R)-1-amino-2-phenoxyethyl)-3,3-dimethylpyrrolidin-1-yl]-1-cyclopropyl-6-fluoro-8-methooxy-1H-quinazoline-2,4-dione;

3-Amino-7-[(R)-4-((R)-1-amino-2-phenoxyethyl)-3,3-dimethylpyrrolidin-1-yl]-1-cyclopropyl-8-methoxy-1H-quinazoline-2,4-dione;

3-Amino-7-[(R)-4-((S)-1-amino-2-phenoxyethyl)-3,3-dimethylpyrrolidin-1-yl]-1-cyclopropyl-6-fluoro-8-methoxy-1H-quinazoline-2,4-dione;

3-Amino-7-[(R)-4-((S)-1-amino-2-phenoxyethyl)-3,3-dimethylpyrrolidin-1-yl]-1-cyclopropyl-8-methoxy-1H-quinazoline-2,4-dione;

3-Amino-7-[(R)-3-((S)-1-amino-2-ethoxyethyl)pyrrolidin-1-yl]-1-cyclopropyl-6-fluoro-8-methoxy-1H-quinazoline-2,4-dione;

3-Amino-7-[(R)-3-((S)-1-amino-2-ethoxyethyl)pyrrolidin-1-yl]-1-cyclopropyl-8-methoxy-1H-quinazoline-2,4-dione;

3-Amino-7-[(R)-3-((R)-1-amino-2-ethoxyethyl)pyrrolidin-1-yl]-1-cyclopropyl-6-fluoro-8-methoxy-1H-quinazoline-2,4-dione;

3-Amino-7-[(R)-3-((R)-1-amino-2-ethoxyethyl)pyrrolidin-1-yl]-1-cyclopropyl-8-methoxy-1H-quinazoline-2,4-dione;

3-Amino-7-[(3R,4S)-3-((R)-1-amino-2-ethoxyethyl)-4-methylpyrrolidin-1-yl]-1-cyclopropyl-6-fluoro-8-methoxy-1H-quinazoline-2,4-dione;

3-Amino-7-[(3R,4S)-3-((R)-1-amino-2-ethoxyethyl)-4-methylpyrrolidin-1-yl]-1-cyclopropyl-8-methoxy-1H-quinazoline-2,4-dione;

3-Amino-7-[(3R,4S)-3-((R)-1-amino-2-ethoxyethyl)-4-fluoropyrrolidin-1-yl]-1-cyclopropyl-6-fluoro-8-methoxy-1H-quinazoline-2,4-dione;

3-Amino-7-[(3R,4S)-3-((R)-1-amino-2-ethoxyethyl)-4-fluoropyrrolidin-1-yl]-1-cyclopropyl-8-methoxy-1H-quinazoline-2,4-dione;

3-Amino-7-[(R)-4-((R)-1-amino-2-ethoxyethyl)-3,3-dimethylpyrrolidin-1-yl]-1-cyclopropyl-6-fluoro-8-methoxy-1H-quinazoline-2,4-dione;

3-Amino-7-[(R)-4-((R)-1-amino-2-ethoxyethyl)-3,3-dimethylpyrrolidin-1-yl]-1-cyclopropyl-8-methooxy-1H-quinazoline-2,4-dione;

3-Amino-7-[(3R,4R)-3-((S)-1-amino-2-ethoxyethyl)-4-methylpyrrolidin-1-yl]-1-cyclopropyl-6-fluoro-8-methoxy-1H-quinazoline-2,4-dione;

3-Amino-7-[(3R,4R)-3-((S)-1-amino-2-ethoxyethyl)-4-methylpyrrolidin-1-yl]-1-cyclopropyl-8-methoxy-1H-quinazoline-2,4-dione;

3-Amino-7-[(3R,4R)-3-((S)-1-amino-2-ethoxyethyl)-4-fluoropyrrolidin-1-yl]-1-cyclopropyl-6-fluoro-8-methoxy-1H-quinazoline-2,4-dione;

3-Amino-7-[(3R,4R)-3-((S)-1-amino-2-ethoxyethyl)-4-fluoropyrrolidin-1-yl]-1-cyclopropyl-8-methoxy-1H-quinazoline-2,4-dione;

3-Amino-7-[(R)-3-((S)-1-amino-3-methoxypropyl)pyrrolidin-1-yl]-1-cyclopropyl-6-fluoro-8-methoxy-1H-quinazoline-2,4-dione;

3-Amino-7-[(R)-3-((S)-1-amino-3-methoxypropyl)pyrrolidin-1-yl]-1-cyclopropyl-8-methoxy-1H-quinazoline-2,4-dione;

3-Amino-7-[(3R,4S)-3-((S)-1-amino-3-methoxypropyl)-4-methylpyrrolidin-1-yl]-1-cyclopropyl-6-fluoro-8-methoxy-1H-quinazoline-2,4-dione;

3-Amino-7-[(3R,4S)-3-((S)-1-amino-3-methoxypropyl)-4-methylpyrrolidin-1-yl]-1-cyclopropyl-8-methoxy-1H-quinazoline-2,4-dione;

3-Amino-7-[(3R,4S)-3-((S)-1-amino-3-methoxypropyl)-4-fluoropyrrolidin-1-yl]-1-cyclopropyl-6-fluoro-8-methoxy-1H-quinazoline-2,4-dione;

3-Amino-7-[(3R,4S)-3-((S)-1-amino-3-methoxypropyl)-4-fluoropyrrolidin-1-yl]-1-cyclopropyl-8-methoxy-1H-quinazoline-2,4-dione;

3-Amino-7-[(R)-3-((R)-1-amino-3-methoxypropyl)pyrrolidin-1-yl]-1-cyclopropyl-6-fluoro-8-methoxy-1H-quinazoline-2,4-dione;

3-Amino-7-[(R)-3-((R)-1-amino-3-methoxypropyl)pyrrolidin-1-yl]-1-cyclopropyl-8-methoxy-1H-quinazoline-2,4-dione;

3-Amino-7-[(3R,4R)-3-((R)-1-amino-3-methoxypropyl)-4-methylpyrrolidin-1-yl]-1-cyclopropyl-6-fluoro-8-methoxy-1H-quinazoline-2,4-dione;

3-Amino-7-[(3R,4R)-3-((R)-1-amino-3-methoxypropyl)-4-methylpyrrolidin-1-yl]-1-cyclopropyl-8-methoxy-1H-quinazoline-2,4-dione;

3-Amino-7-[(3R,4R)-3-((R)-1-amino-3-methoxypropyl)-4-fluoropyrrolidin-1-yl]-1-cyclopropyl-6-fluoro-8-methoxy-1H-quinazoline-2,4-dione;

-Amino-7-[(3R,4R)-3-((R)-1-amino-3-methoxypropyl)-4-fluoropyrrolidin-1-yl]-1-cyclopropyl-8-methoxy-1H-quinazoline-2,4-dione;

{(R)-2-Amino-2-[(R)-1-(3-amino-1-cyclopropyl-6-fluoro-8-methoxy-2,4-dioxo-1,2,3,4-tetrahydroquinazolin-7-yl)pyrrolidin-3-yl]ethyl}urea;

{(R)-2-Amino-2-[(R)-1-(3-amino-1-cyclopropyl-8-methoxy-2,4-dioxo-1,2,3,4-tetrahydroquinazolin-7-yl)pyrrolidin-3-yl]ethyl}urea;

{(S)-2-Amino-2-[(R)-1-(3-amino-1-cyclopropyl-6-fluoro-8-methoxy-2,4-dioxo-1,2,3,4-tetrahydroquinazolin-7-yl)pyrrolidin-3-yl]ethyl}urea;

{(S)-2-Amino-2-[(R)-1-(3-amino-1-cyclopropyl-8-methoxy-2,4-dioxo-1,2,3,4-tetrahydroquinazolin-7-yl)pyrrolidin-3-yl]ethyl}urea;

{(R)-2-Amino-2-[(3R,4S)-1-(3-amino-1-cyclopropyl-6-fluoro-8-methoxy-2,4-dioxo-1,2,3,4-tetrahydroquinazolin-7-yl)-4-methylpyrrolidin-3-yl]ethyl}urea;

{(R)-2-Amino-2-[(3R,4S)-1-(3-amino-1-cyclopropyl-8-methoxy-2,4-dioxo-1,2,3,4-tetrahydroquinazolin-7-yl)-4-methylpyrrolidin-3-yl]ethyl}urea;

{(S)-2-Amino-2-[(3R,4R)-1-(3-amino-1-cyclopropyl-6-fluoro-8-methoxy-2,4-dioxo-1,2,3,4-tetrahydroquinazolin-7-yl)-4-methylpyrrolidin-3-yl]ethyl}urea;

{(S)-2-Amino-2-[(3R,4R)-1-(3-amino-1-cyclopropyl-8-methoxy-2,4-dioxo-1,2,3,4-tetrahydroquinazolin-7-yl)-4-methylpyrrolidin-3-yl]ethyl}urea;

{2-Amino-2-[(1-(3-amino-1-cyclopropyl-6-fluoro-8-methoxy-2,4-dioxo-1,2,3,4-tetrahydroquinazolin-7-yl)-4-fluoropyrrolidin-3-yl]ethyl}urea;

{2-Amino-2-[(1-(3-amino-1-cyclopropyl-8-methoxy-2,4-dioxo-1,2,3,4-tetrahydroquinazolin-7-yl)-4-fluoropyrrolidin-3-yl]ethyl}urea;

{2-Amino-2-[(1-(3-amino-1-cyclopropyl-6-fluoro-8-methoxy-2,4-dioxo-1,2,3,4-tetrahydroquinazolin-7-yl)-4,4-dimethylpyrrolidin-3-yl]ethyl}urea;

{2-Amino-2-[(1-(3-amino-1-cyclopropyl-8-methoxy-2,4-dioxo-1,2,3,4-tetrahydroquinazolin-7-yl)-4,4-dimethylpyrrolidin-3-yl]ethyl}urea;

3-Amino-7-[3-(1-aminoethyl)-4-fluoropyrrolidin-1-yl]-1-cyclopropyl-8-methyl-1H-pyrido[4,3-d]pyrimidine-2,4-dione;

3-Amino-7-[3-(1-amino-1-methylethyl)-4-fluoropyrrolidin-1-yl]-1-cyclopropyl-8-methyl-1H-pyrido[4,3-d]pyrimidine-2,4-dione;

3-Amino-7-[3-(1-amino-2-methoxyethyl)-4-fluoropyrrolidin-1-yl]-1-cyclopropyl-8-methyl-1H-pyrido[4,3-d]pyrimidine-2,4-dione;

3-Amino-7-[3-(1-amino-2-methoxyethyl)-4-methylpyrrolidin-1-yl]-1-cyclopropyl-8-methyl-1H-pyrido[4,3-d]pyrimidine-2,4-dione;

3-Amino-7-[4-(1-amino-2-methoxyethyl)-3,3-dimethylpyrrolidin-1-yl]-1-cyclopropyl-8-methyl-1H-pyrido[4,3-d]pyrimidine-2,4-dione;

3-Amino-7-[3-(1-amino-2-phenoxyethyl)-pyrrolidin-1-yl]-1-cyclopropyl-8-methyl-1H-pyrido[4,3-d]pyrimidine-2,4-dione;

3-Amino-7-[3-(1-amino-2-phenoxyethyl)-4-methylpyrrolidin-1-yl]-1-cyclopropyl-8-methyl-1H-pyrido[4,3-d]pyrimidine-2,4-dione;

3-Amino-7-[3-(1-amino-2-phenoxyethyl)-4-fluoropyrrolidin-1-yl]-1-cyclopropyl-8-methyl-1H-pyrido[4,3-d]pyrimidine-2,4-dione;

3-Amino-7-[4-(1-amino-2-phenoxyethyl)-3,3-dimethylpyrrolidin-1-yl]-1-cyclopropyl-8-methyl-1H-pyrido[4,3-d]pyrimidine-2,4-dione;

3-Amino-7-[3-(1-amino-2-ethoxyethyl)pyrrolidin-1-yl]-1-cyclopropyl-8-methyl-1H-pyrido[4,3-d]pyrimidine-2,4-dione;

3-Amino-7-[3-(1-amino-2-ethoxyethyl)-4-methylpyrrolidin-1-yl]-1-cyclopropyl-8-methyl-1H-pyrido[4,3-d]pyrimidine-2,4-dione;

3-Amino-7-[3-(1-amino-2-ethoxyethyl)-4-fluoropyrrolidin-1-yl]-1-cyclopropyl-8-methyl-1H-pyrido[4,3-d]pyrimidine-2,4-dione;

3-Amino-7-[3-(1-amino-2-ethoxyethyl)-4,4-dimethylpyrrolidin-1-yl]-1-cyclopropyl-8-methyl-1H-pyrido[4,3-d]pyrimidine-2,4-dione;

3-Amino-7-[3-(1-amino-2-methoxypropyl)pyrrolidin-1-yl]-1-cyclopropyl-8-methyl-1H-pyrido[4,3-d]pyrimidine-2,4-dione;

3-Amino-7-[3-(1-amino-2-methoxypropyl)-4-methylpyrrolidin-1-yl]-1-cyclopropyl-8-methyl-1H-pyrido[4,3-d]pyrimidine-2,4-dione;

3-Amino-7-[3-(1-amino-2-methoxypropyl)-4-fluoropyrrolidin-1-yl]-1-cyclopropyl-8-methyl-1H-pyrido[4,3-d]pyrimidine-2,4-dione;

{2-Amino-2-[1-(3-amino-1-cyclopropyl-8-methyl-2,4-dioxo-1,2,3,4-tetrahydropyrido[4,3-d]pyrimidin-7-yl)pyrrolidin-3-yl]ethylurea;

{2-Amino-2-[1-(3-amino-1-cyclopropyl-8-methyl-2,4-dioxo-1,2,3,4-tetrahydropyrido[4,3-d]pyrimidin-7-yl)-4-methylpyrrolidin-3-yl]ethylurea;

{2-Amino-2-[1-(3-amino-1-cyclopropyl-8-methyl-2,4-dioxo-1,2,3,4-tetrahydropyrido[4,3-d]pyrimidin-7-yl)-4-fluoropyrrolidin-3-yl]ethylurea;

{2-Amino-2-[1-(3-amino-1-cyclopropyl-8-methyl-2,4-dioxo-1,2,3,4-tetrahydropyrido[4,3-d]pyrimidin-7-yl)-4,4-dimethylpyrrolidin-3-yl]ethylurea;

3-Amino-7-[3-(1-aminoethyl)-4-fluoropyrrolidin-1-yl]-1-cyclopropyl-6-fluoro-8-methyl-1H-pyrido[3,2-d]pyrimidine-2,4-dione;

3-Amino-7-[3-(1-aminoethyl)-4-fluoropyrrolidin-1-yl]-1-cyclopropyl-8-methyl-1H-pyrido[3,2-d]pyrimidine-2,4-dione;

3-Amino-7-[3-(1-amino-1-methylethyl)-4-fluoropyrrolidin-1-yl]-1-cyclopropyl-6-fluoro-8-methyl-1H-pyrido[3,2-d]pyrimidine-2,4-dione;

3-Amino-7-[3-(1-amino-1-methylethyl)-4-fluoropyrrolidin-1-yl]-1-cyclopropyl-8-methyl-1H-pyrido[3,2-d]pyrimidine-2,4-dione;

3-Amino-7-[3-(1-amino-2-methoxyethyl)-4-fluoropyrrolidin-1-yl]-1-cyclopropyl-6-fluoro-8-methyl-1H-pyrido[3,2-d]pyrimidine-2,4-dione;

3-Amino-7-[3-(1-amino-2-methoxyethyl)-4-fluoropyrrolidin-1-yl]-1-cyclopropyl-8-methyl-1H-pyrido[3,2-d]pyrimidine-2,4-dione;

3-Amino-7-[3-(1-amino-2-methoxyethyl)-4-methylpyrrolidin-1-yl]-1-cyclopropyl-6-fluoro-8-methyl-1H-pyrido[3,2-d]pyrimidine-2,4-dione;

3-Amino-7-[3-(1-amino-2-methoxyethyl)-4-methylpyrrolidin-1-yl]-1-cyclopropyl-8-methyl-1H-pyrido[3,2-d]pyrimidine-2,4-dione;

3-Amino-7-[4-(1-amino-2-methoxyethyl)-3,3-dimethylpyrrolidin-1-yl]-1-cyclopropyl-6-fluoro-8-methyl-1H-pyrido[3,2-d]pyrimidine-2,4-dione;

3-Amino-7-[4-(1-amino-2-methoxyethyl)-3,3-dimethylpyrrolidin-1-yl]-1-cyclopropyl-8-methyl-1H-pyrido[3,2-d]pyrimidine-2,4-dione;

3-Amino-7-[3-(1-amino-2-phenoxyethyl)pyrrolidin-1-yl]-1-cyclopropyl-6-fluoro-8-methyl-1H-pyrido[3,2-d]pyrimidine-2,4-dione;

3-Amino-7-[3-(1-amino-2-phenoxyethyl)pyrrolidin-1-yl]-1-cyclopropyl-8-methyl-1H-pyrido[3,2-d]pyrimidine-2,4-dione;

3-Amino-7-[3-(1-amino-2-phenoxyethyl)-4-methylpyrrolidin-1-yl]-1-cyclopropyl-6-fluoro-8-methyl-1H-pyrido[3,2-d]pyrimidine-2,4-dione;

3-Amino-7-[3-(1-amino-2-phenoxyethyl)-4-methylpyrrolidin-1-yl]-1-cyclopropyl-8-methyl-1H-pyrido[3,2-d]pyrimidine-2,4-dione;

3-Amino-7-[3-(1-amino-2-phenoxyethyl)-4-fluoropyrrolidin-1-yl]-1-cyclopropyl-6-fluoro-8-methyl-1H-pyrido[3,2-d]pyrimidine-2,4-dione;

3-Amino-7-[3-(1-amino-2-phenoxyethyl)-4-fluoropyrrolidin-1-yl]-1-cyclopropyl-8-methyl-1H-pyrido[3,2-d]pyrimidine-2,4-dione;

3-Amino-7-[4-(1-amino-2-phenoxyethyl)-3,3-dimethylpyrrolidin-1-yl]-1-cyclopropyl-6-fluoro-8-methyl-1H-pyrido[3,2-d]pyrimidine-2,4-dione;

3-Amino-7-[4-(1-amino-2-phenoxyethyl)-3,3-dimethylpyrrolidin-1-yl]-1-cyclopropyl-8-methyl-1H-pyrido[3,2-d]pyrimidine-2,4-dione;

3-Amino-7-[3-(1-amino-2-ethoxyethyl)pyrrolidin-1-yl]-1-cyclopropyl-6-fluoro-8-methyl-1H-pyrido[3,2-d]pyrimidine-2,4-dione;

3-Amino-7-[3-(1-amino-2-ethoxyethyl)pyrrolidin-1-yl]-1-cyclopropyl-8-methyl-1H-pyrido[3,2-d]pyrimidine-2,4-dione;

3-Amino-7-[3-(1-amino-2-ethoxyethyl)-4-methylpyrrolidin-1-yl]-1-cyclopropyl-6-fluoro-8-methyl-1H-pyrido[3,2-d]pyrimidine-2,4-dione;

3-Amino-7-[3-(1-amino-2-ethoxyethyl)-4-methylpyrrolidin-1-yl]-1-cyclopropyl-8-methyl-1H-pyrido[3,2-d]pyrimidine-2,4-dione;

3-Amino-7-[3-(1-amino-2-ethoxyethyl)-4-fluoropyrrolidin-1-yl]-1-cyclopropyl-6-fluoro-8-methyl-1H-pyrido[3,2-d]pyrimidine-2,4-dione;

3-Amino-7-[3-(1-amino-2-ethoxyethyl)-4-fluoropyrrolidin-1-yl]-1-cyclopropyl-8-methyl-1H-pyrido[3,2-d]pyrimidine-2,4-dione;

3-Amino-7-[3-(1-amino-2-ethoxyethyl)-4,4-dimethylpyrrolidin-1-yl]-1-cyclopropyl-6-fluoro-8-methyl-1H-pyrido[3,2-d]pyrimidine-2,4-dione;

3-Amino-7-[3-(1-amino-2-ethoxyethyl)-4,4-dimethylpyrrolidin-1-yl]-1-cyclopropyl-8-methyl-1H-pyrido[3,2-d]pyrimidine-2,4-dione;

3-Amino-7-[3-(1-amino-2-methoxypropyl)pyrrolidin-1-yl]-1-cyclopropyl-6-fluoro-8-methyl-1H-pyrido[3,2-d]pyrimidine-2,4-dione;

3-Amino-7-[3-(1-amino-2-methoxypropyl)pyrrolidin-1-yl]-1-cyclopropyl-8-methyl-1H-pyrido[3,2-d]pyrimidine-2,4-dione;

3-Amino-7-[3-(1-amino-2-methoxypropyl)-4-methylpyrrolidin-1-yl]-1-cyclopropyl-6-fluoro-8-methyl-1H-pyrido[3,2-d]pyrimidine-2,4-dione;

3-Amino-7-[3-(1-amino-2-methoxypropyl)-4-methylpyrrolidin-1-yl]-1-cyclopropyl-8-methyl-1H-pyrido[3,2-d]pyrimidine-2,4-dione;

3-Amino-7-[3-(1-amino-2-methoxypropyl)-4-fluoropyrrolidin-1-yl]-1-cyclopropyl-6-fluoro-8-methyl-1H-pyrido[3,2-d]pyrimidine-2,4-dione;

3-Amino-7-[3-(1-amino-2-methoxypropyl)-4-fluoropyrrolidin-1-yl]-1-cyclopropyl-8-methyl-1H-pyrido[3,2-d]pyrimidine-2,4-dione;

{2-Amino-2-[1-(3-amino-1-cyclopropyl-6-fluoro-8-methyl-2,4-dioxo-1,2,3,4-tetrahydropyrido[3,2-d]pyrimidin-7-yl)pyrrolidin-3-yl]ethylurea;

{2-Amino-2-[1-(3-amino-1-cyclopropyl-8-methyl-2,4-dioxo-1,2,3,4-tetrahydropyrido[3,2-d]pyrimidin-7-yl)pyrrolidin-3-yl]ethylurea;

{2-Amino-2-[1-(3-amino-1-cyclopropyl-6-fluoro-8-methyl-2,4-dioxo-1,2,3,4-tetrahydropyrido[3,2-d]pyrimidin-7-yl)-4-methylpyrrolidin-3-yl]ethylurea;

{2-Amino-2-[1-(3-amino-1-cyclopropyl-8-methyl-2,4-dioxo-1,2,3,4-tetrahydropyrido[3,2-d]pyrimidin-7-yl)-4-methylpyrrolidin-3-yl]ethylurea;

{2-Amino-2-[1-(3-amino-1-cyclopropyl-6-fluoro-8-methyl-2,4-dioxo-1,2,3,4-tetrahydropyrido[3,2-d]pyrimidin-7-yl)-4-fluoropyrrolidin-3-yl]ethylurea;

{2-Amino-2-[1-(3-amino-1-cyclopropyl-8-methyl-2,4-dioxo-1,2,3,4-tetrahydropyrido[3,2-d]pyrimidin-7-yl)-4-fluoropyrrolidin-3-yl]ethylurea;

{2-Amino-2-[1-(3-amino-1-cyclopropyl-6-fluoro-8-methyl-2,4-dioxo-1,2,3,4-tetrahydropyrido[3,2-d]pyrimidin-7-yl)-4,4-dimethylpyrrolidin-3-yl]ethylurea;

{2-Amino-2-[1-(3-amino-1-cyclopropyl-8-methyl-2,4-dioxo-1,2,3,4-tetrahydropyrido[3,2-d]pyrimidin-7-yl)-4,4-dimethylpyrrolidin-3-yl]ethylurea;

3-Amino-7-(3-aminomethylphenyl)-8-chloro-1-cyclopropyl-6-fluoro-1H-quinazoline-2,4-dione;

3-Amino-7-(3-aminomethylphenyl)-8-methyl-1-cyclopropyl-6-fluoro-1H-quinazoline-2,4-dione;

3-Amino-7-(3-aminomethylphenyl)-8-methoxy-1-cyclopropyl-6-fluoro-1H-quinazoline-2,4-dione;

3-Amino-7-(3-aminomethylphenyl)-8-chloro-1-cyclopropyl-1H-quinazoline-2,4-dione;

3-Amino-7-(3-aminomethylphenyl)-8-methyl-1-cyclopropyl-1H-quinazoline-2,4-dione;

3-Amino-7-(3-aminomethylphenyl)-8-methoxy-1-cyclopropyl-1H-quinazoline-2,4-dione;

3-Amino-7-(2-aminomethylthiazol-4-yl)-8-chloro-1-cyclopropyl-6-fluoro-1H-quinazoline-2,4-dione;

3-Amino-7-(2-aminomethylthiazol-4-yl)-8-methyl-1-cyclopropyl-6-fluoro-1H-quinazoline-2,4-dione;

3-Amino-7-(2-aminomethylthiazol-4-yl)-8-methoxy-1-cyclopropyl-6-fluoro-1H-quinazoline-2,4-dione;

3-Amino-7-(2-aminomethylthiazol-4-yl)-8-chloro-1-cyclopropyl-1H-quinazoline-2,4-dione;

3-Amino-7-(2-aminomethylthiazol-4-yl)-8-methyl-1-cyclopropyl-1H-quinazoline-2,4-dione;

3-Amino-7-(2-aminomethylthiazol-4-yl)-8-methoxy-1-cyclopropyl-1H-quinazoline-2,4-dione;

3-Amino-7-[2-(1-aminoethyl)thiazol-4-yl)-8-chloro-1-cyclopropyl-6-fluoro-1H-quinazoline-2,4-dione;

3-Amino-7-[2-(1-aminoethyl)thiazol-4-yl)-8-methyl-1-cyclopropyl-6-fluoro-1H-quinazoline-2,4-dione;

3-Amino-7-[2-(1-aminoethyl)thiazol-4-yl)-8-methoxy-1-cyclopropyl-6-fluoro-1H-quinazoline-2,4-dione;

3-Amino-7-[2-(1-aminoethyl)thiazol-4-yl)-8-chloro-1-cyclopropyl-1H-quinazoline-2,4-dione;

3-Amino-7-[2-(1-aminoethyl)thiazol-4-yl)-8-methyl-1-cyclopropyl-1H-quinazoline-2,4-dione;

3-Amino-7-[2-(1-aminoethyl)thiazol-4-yl)-8-methoxy-1-cyclopropyl-1H-quinazoline-2,4-dione;

3-Amino-7-(5-aminomethylthiophen-3-yl)-8-chloro-1-cyclopropyl-6-fluoro-1H-quinazoline-2,4-dione;

3-Amino-7-(5-aminomethylthiophen-3-yl)-8-methyl-1-cyclopropyl-6-fluoro-1H-quinazoline-2,4-dione;

3-Amino-7-(5-aminomethylthiophen-3-yl)-8-methoxy-1-cyclopropyl-6-fluoro-1H-quinazoline-2,4-dione;

3-Amino-7-(5-aminomethylthiophen-3-yl)-8-chloro-1-cyclopropyl-1H-quinazoline-2,4-dione;

3-Amino-7-(5-aminomethylthiophen-3-yl)-8-methyl-1-cyclopropyl-1H-quinazoline-2,4-dione;

3-Amino-7-(5-aminomethylthiophen-3-yl)-8-methoxy-1-cyclopropyl-1H-quinazoline-2,4-dione;

3-Amino-7-(4-aminomethyl-3,3-difluoropyrrolidin-1-yl)-8-chloro-1-cyclopropyl-6-fluoro-1H-quinazoline-2,4-dione;

3-Amino-7-(4-aminomethyl-3,3-difluoropyrrolidin-1-yl)-8-methyl-1-cyclopropyl-6-fluoro-1H-quinazoline-2,4-dione;

3-Amino-7-(4-aminomethyl-3,3-difluoropyrrolidin-1-yl)-8-methoxy-1-cyclopropyl-6-fluoro-1H-quinazoline-2,4-dione;

3-Amino-7-(4-aminomethyl-3,3-difluoropyrrolidin-1-yl)-8-chloro-1-cyclopropyl-1H-quinazoline-2,4-dione;

3-Amino-7-(4-aminomethyl-3,3-difluoropyrrolidin-1-yl)-8-methyl-1-cyclopropyl-1H-quinazoline-2,4-dione

3-Amino-7-(4-aminomethyl-3,3-difluoropyrrolidin-1-yl)-8-methoxy-1-cyclopropyl-1H-quinazoline-2,4-dione;

3-Amino-7-(4-(1-aminoethyl)-3,3-difluoropyrrolidin-1-yl)-8-chloro-1-cyclopropyl-6-fluoro-1H-quinazoline-2,4-dione;

3-Amino-7-(4-(1-aminoethyl)-3,3-difluoropyrrolidin-1-yl)-8-methyl-1-cyclopropyl-6-fluoro-1H-quinazoline-2,4-dione;

3-Amino-7-(4-(1-aminoethyl)-3,3-difluoropyrrolidin-1-yl)-8-methoxy-1-cyclopropyl-6-fluoro-1H-quinazoline-2,4-dione;

3-Amino-7-(4-(1-aminoethyl)-3,3-difluoropyrrolidin-1-yl)-8-chloro-1-cyclopropyl-1H-quinazoline-2,4-dione;

3-Amino-7-(4-(1-aminoethyl)-3,3-difluoropyrrolidin-1-yl)-8-methyl-1-cyclopropyl-1H-quinazoline-2,4-dione;

3-Amino-7-(4-(1-aminoethyl)-3,3-difluoropyrrolidin-1-yl)-8-methoxy-1-cyclopropyl-1H-quinazoline-2,4-dione;

3-Amino-7-(4-(1-amino-1-methylethyl)-3,3-difluoropyrrolidin-1-yl)-8-chloro-1-cyclopropyl-6-fluoro-1H-quinazoline-2,4-dione;

3-Amino-7-(4-(1-amino-1-methylethyl)-3,3-difluoropyrrolidin-1-yl)-8-methyl-1-cyclopropyl-6-fluoro-1H-quinazoline-2,4-dione;

3-Amino-7-(4-(1-amino-1-methylethyl)-3,3-difluoropyrrolidin-1-yl)-8-methoxy-1-cyclopropyl-6-fluoro-1H-quinazoline-2,4-dione;

3-Amino-7-(4-(1-amino-1-methylethyl)-3,3-difluoropyrrolidin-1-yl)-8-chloro-1-cyclopropyl-1H-quinazoline-2,4-dione;

3-Amino-7-(4-(1-amino-1-methylethyl)-3,3-difluoropyrrolidin-1-yl)-8-methyl-1-cyclopropyl-1H-quinazoline-2,4-dione;

3-Amino-7-(4-(1-amino-1-methylethyl)-3,3-difluoropyrrolidin-1-yl)-8-methoxy-1-cyclopropyl-1H-quinazoline-2,4-dione;

3-Amino-7-(3-(1-aminoethyl)pyrrolidin-1-yl)-1-cyclopropyl-6-fluoro-5,8-dimethyl-1H-quinazoline-2,4-dione;

3-Amino-7-(3-(1-aminoethyl)pyrrolidin-1-yl)-1-cyclopropyl-5,8-dimethyl-1H-quinazoline-2,4-dione;

3-Amino-7-(3-(1-aminoethyl)pyrrolidin-1-yl)-1-cyclopropyl-6-fluoro-8-methoxy-5-methyl-1H-quinazoline-2,4-dione;

3-Amino-7-(3-(1-aminoethyl)pyrrolidin-1-yl)-1-cyclopropyl-8-methoxy-5-methyl-1H-quinazoline-2,4-dione;

3,8-Diamino-7-[3-(1-aminoethyl)pyrrolidin-1-yl]-1-cyclopropyl-6-fluoro-5-methyl-1H-quinazoline-2,4-dione; and

3,8-Diamino-7-[3-(1-aminoethyl)pyrrolidin-1-yl]-1-cyclopropyl-5-methyl-1H-quinazoline-2,4-dione.

A further embodiment of the invention is a pharmaceutical composition comprising a compound of Formula I together with an excipient, carrier, or diluent. Preferred compositions will have a compound of Formulas II, III, IV, V, VI, or VII mixed with an excipient, carrier, or diluent.

Still another embodiment of the invention is a method of treating bacterial infections in mammals comprising administering an antibacterial effective amount of a compound of Formula I. Preferred methods comprise administering a compound of Formulas II, III, IV, V, VI, or VII.

Another embodiment is a method of preventing or eliminating bacterial growth on surfaces comprising applying to the surface an antibacterially effective amount of a compound of Formulas I-VII.

DETAILED DESCRIPTION

All references cited herein, including patents, are incorporated herein by reference.

The terms used in this specification and the appended claims have the following meanings. The term "halo" means chloro, bromo, fluoro, and iodo.

The term "alkyl" means a straight or branched hydrocarbon radical having from 1 to 12 carbon atoms and includes, for example, methyl, ethyl, n-propyl, isopropyl, n-butyl, sec-butyl, isobutyl, tert-butyl, n-pentyl, n-hexyl, n-heptyl, n-octyl, 2-isopropylheptyl, 3-n-butyloctyl, n-nonyl, n-decyl, undecyl, and dodecyl.

Preferred alkyl groups are C_1-C_6 alkyl such as methyl, isopropyl, neopentyl, and 1-methylpentyl.

The term "C_2-C_{12} alkenyl" means a straight or branched hydrocarbon radical having from 1 to 3 double bonds. Examples include ethenyl, 2-propen-1-yl, 1,3-butadien-1-yl, 3-hexen-1-yl, 5-octen-2-yl, 2-isopropyl-3,5-octadien-1-yl, cis-3-hexen-1-yl, and trans-2-hepten-1-yl. Preferred alkenyl groups include C_2-C_6 alkenyls such as ethenyl, 2-propen-1-yl, 2-buten-1-yl, and 3-penten-1-yl.

The term "C_2-C_{12} alkynyl" means a straight or branched hydrocarbon radical having from 1 to 3 triple-bonds. Examples include ethynyl, propynyl, 3-butyn-1-yl, 4-hexyn-1-yl, 5-octyn-3-yl, 4,6-octadiyn-1-yl, 4-decyn-1-yl, and 1,1-dimethyl-5-decyn-1-yl. Preferred alkynyl groups are C_2-C_6 alkynyls such as ethynyl, propynyl, 3-butyn-1-yl, and 5-hexyn-1-yl.

The alkyl, alkenyl, and alkynyl groups can be substituted with 1 to 3 groups selected from halo, hydroxy, cyano, C_1-C_6 alkoxy, nitro, amino, C_1-C_6 alkylamino, di-C_1-C_6 alkylamino, carboxy, C_1-C_6 alkoxycarbonyl, aminocarbonyl, halo-dihalo and trihalomethyl, thiol, alkylsulfanyl, alkylsulfinyl, and aminosulfonyl. Examples of substituted alkyl groups include fluoromethyl, tribromomethyl, hydroxymethyl, 3-methoxypropyl, 3-carboxypentyl, 3,5-dibromo-6-aminocarbonyldecyl, and 4-ethylsulfinyloctyl. Examples of substituted alkenyl groups include 2-bromoethenyl, 1-amino-2-propen-1-yl, 3-hydroxypent-2-en-1-yl, 4-methoxycarbonyl-hex-2-en-1-yl, and 2-nitro-3-bromo-4-iodo-oct-5-en-1-yl. Typical substituted alkynyl groups include 2-hydroxyethynyl, 3-dimethylamino-hex-5-yn-1-yl, and 2-cyano-hept-3-yn-1-yl.

The term "cycloalkyl" means a hydrocarbon ring which contains from 3 to 12 carbon atoms, for example, cyclopropyl, cyclobutyl, cyclopentyl, cyclohexyl, decalinyl, norpinanyl, and adamantyl. Where possible, the cycloalkyl group may contain double bonds, for example, 3-cyclohexen-1-yl. The cycloalkyl ring may be unsubstituted or substituted by 1 to 3 substituents selected from alkyl, alkoxy, thioalkoxy, hydroxy, thiol, nitro, halogen, amino, alkyl and dialkylamino, formyl, carboxyl, CN, -NH-CO-R', -CO-NHR'-, -CO_2R', -COR', aryl, or heteroaryl, wherein alkyl, aryl, and heteroaryl are as defined herein. Examples of substituted cycloalkyl groups include fluorocyclopropyl, 2-iodocyclobutyl, 2,3-dimethylcyclopentyl, 2,2-dimethoxycyclohexyl, and 3-phenylcyclopentyl.

The term "heterocyclic" means a cyclic or fused bicyclic or polycyclic ring system having from 3 to 12 ring atoms, with from 1 to 5 being heteroatoms selected from N, O, and S. The heterocyclic groups can be substituted with 1 to 3 of the substituents listed above for the cycloalkyl groups. Examples of heterocyclic groups include cyclic ethers (oxiranes) such as ethyleneoxide, tetrahydrofuran, dioxane, and substituted cyclic ethers, wherein the substituents are those described above for the alkyl and cycloalkyl groups. Typical substituted cyclic ethers include propyleneoxide, phenyloxirane (styrene oxide), cis-2-butene-oxide (2,3-dimethyloxirane), 3-chlorotetrahydrofuran, 2,6-dimethyl-1,4-dioxane, and the like. Heterocycles containing nitrogen are groups such as pyrrolidine, piperidine, piperazine, tetrahydrotriazine, tetrahydropyrazole, and substituted groups such as 3-aminopyrrolidine, 4-methylpiperazin-1-yl, and the like. Typical sulfur containing heterocycles include tetrahydrothiophene, dihydro-1,3-dithiol-2-yl, and hexahydrothiepin-4-yl. Other commonly employed heterocycles include dihydro-oxathiol-4-yl, tetrahydro-oxazolyl, tetrahydro-oxadiazolyl, tetrahydro-dioxazolyl, tetrahydro-oxathiazolyl, hexahydrotriazinyl, tetrahydro-oxazinyl, morpholinyl, thiomorpholinyl, tetrahydropyrimidinyl, dioxolinyl, octahydrobenzofuranyl, octahydrobenzimidazolyl, and octahydrobenzothiazolyl. For heterocycles containing sulfur, the oxidized sulfur heterocycles containing SO or SO_2 groups are also included. Examples include the sulfoxide and sulfone forms of tetrahydrothiophene.

The term "aryl" means a cyclic or polycyclic aromatic ring having from 5 to 12 carbon atoms, and being unsubstituted or substituted with up to 3 of the substituent groups recited above for alkyl, alkenyl, and alkynyl. Examples of aryl groups include phenyl, 2,6-dichlorophenyl, 3-methoxyphenyl, naphthyl, 4-thionaphthyl, tetralinyl, anthracinyl, phenanthrenyl, benzonaphthenyl, fluorenyl, 2-acetamidofluoren-9-yl, and 4'-bromobiphenyl.

The term "heteroaryl" means an aromatic cyclic or polycyclic ring system having from 1 to 4 heteroatoms selected from N, O, and S. Typical heteroaryl groups include 2- or 3-thienyl, 2- or 3-furanyl, 2- or 3-pyrrolyl, 2-, 4-, or 5-imidazolyl, 3-, 4-, or 5-pyrazolyl, 2-, 4-, or 5-thiazolyl, 3-, 4-, or 5-isothiazolyl, 2-, 4-, or 5-oxazolyl, 3-, 4-, or 5-isoxazolyl, 3- or 5-1,2,4-triazolyl, 4- or

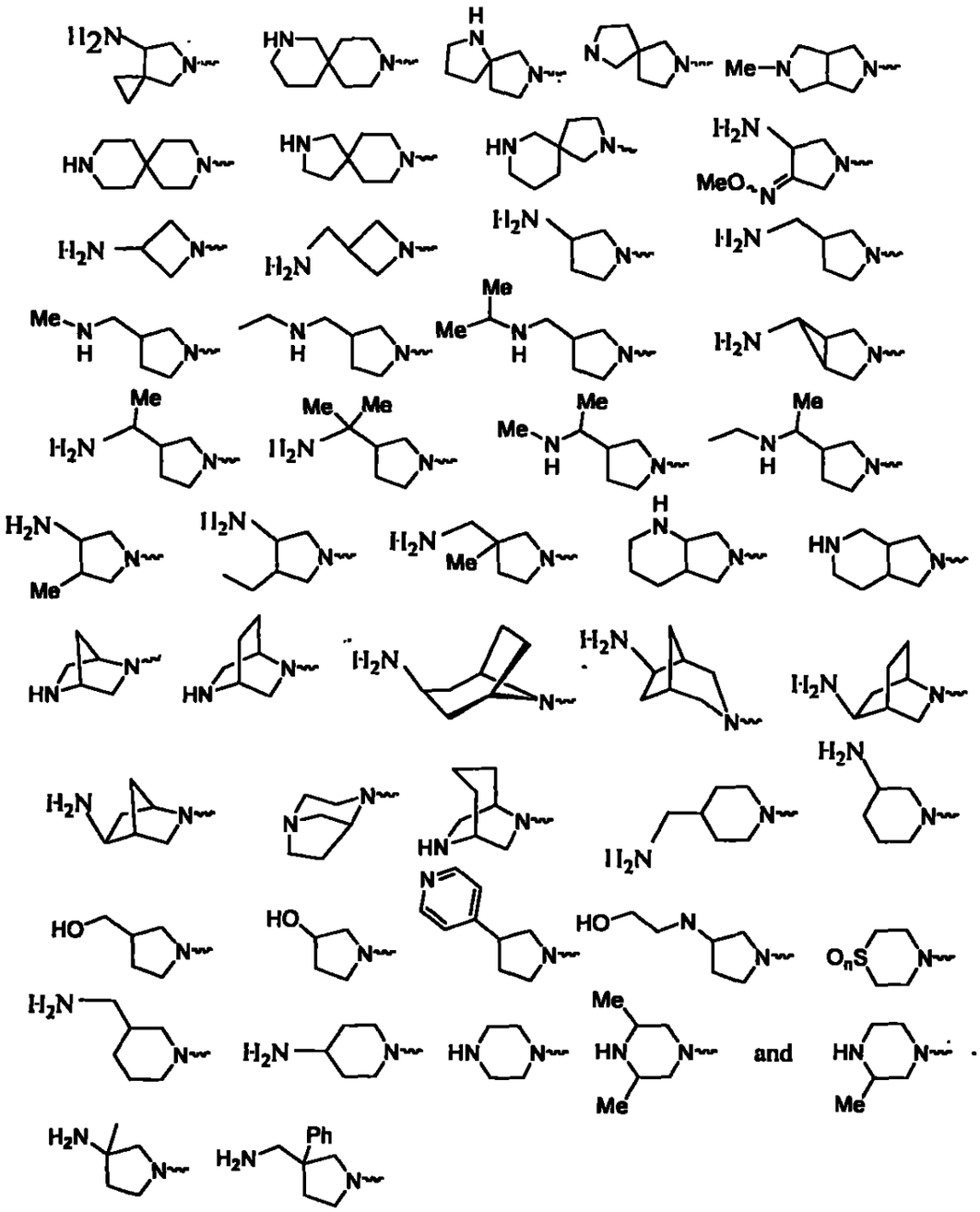
5-1,2,3-triazolyl, tetrazolyl, 2-, 3-, or 4-pyridinyl, 3-, 4-, or 5-pyridazinyl, 2-pyrazinyl, 2-, 4-, or 5-pyrimidinyl, 2-, 3-, 4-, 5-, 6-, 7-, or 8-quinolinyl, 1-, 3-, 4-, 5-, 6-, 7-, or 8-isoquinolinyl, 2-, 3-, 4-, 5-, 6-, or 7-indolyl, 2-, 3-, 4-, 5-, 6-, or 7-benzo[b]thienyl, 2-, 4-, 5-, 6-, or 7-benzoxazolyl, 2-, 4-, 5-, 6-, or 7-benzimidazolyl, 2-, 4-, 5-, 6-, or 7-benzothiazolyl. The heteroaryl groups may be unsubstituted or substituted by 1 to 3 substituents selected from those described above for alkyl, alkenyl, and alkynyl, for example, cyanothienyl and formylpyrrolyl.

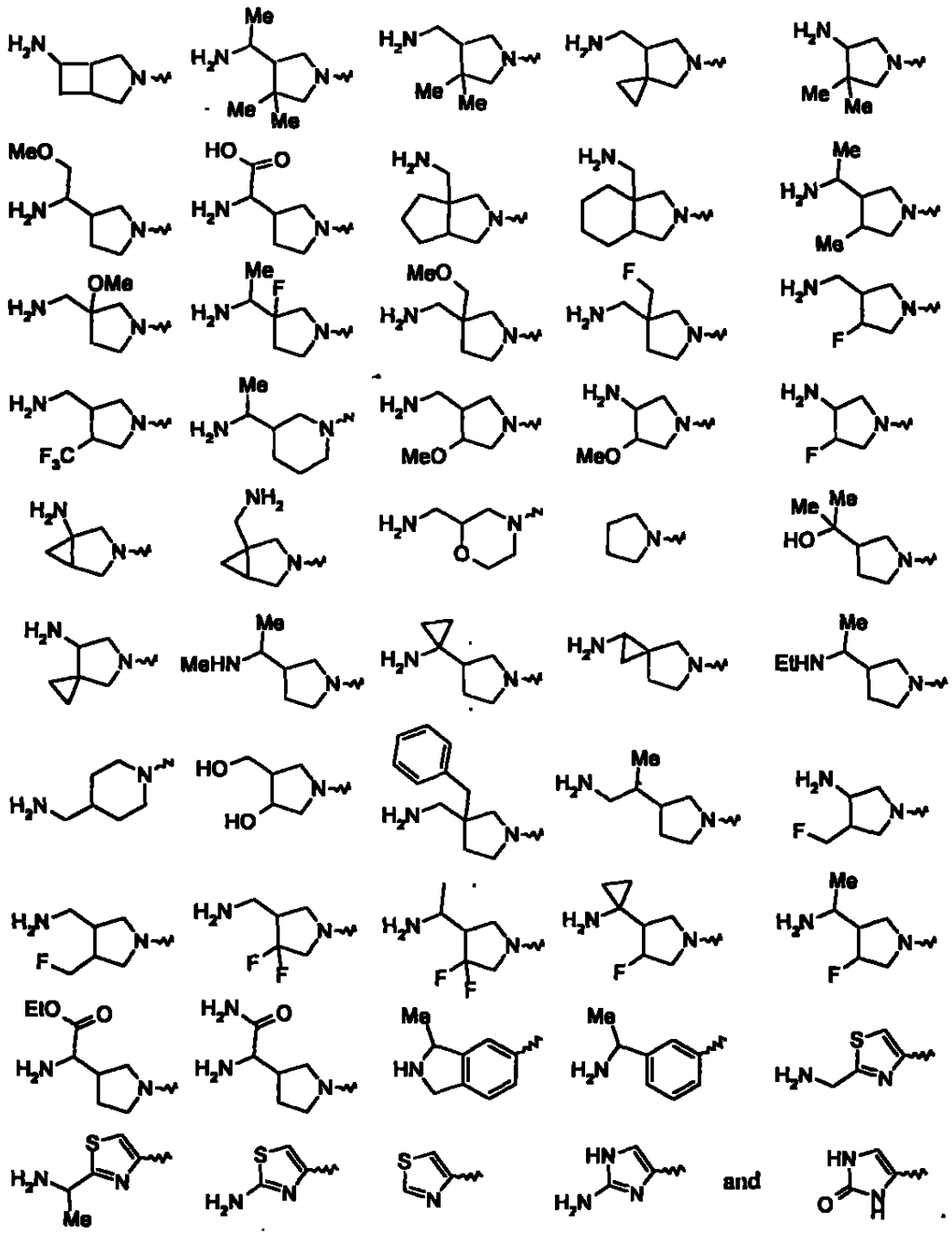
Preferred aromatic fused heterocyclic rings of from 8 to 10 atoms include but are not limited to 2-, 3-, 4-, 5-, 6-, 7-, or 8-quinolinyl, 1-, 3-, 4-, 5-, 6-, 7-, or 8-isoquinolinyl, 2-, 3-, 4-, 5-, 6-, or 7-indolyl, 2-, 3-, 4-, 5-, 6-, or 7-benzo[b]thienyl, 2-, 4-, 5-, 6-, or 7-benzoxazolyl, 2-, 4-, 5-, 6-, or 7-benzimidazolyl, 2-, 4-, 5-, 6-, or 7-benzothiazolyl.

Preferred compounds of the invention have Formula I wherein R_7 is a heterocyclic or heteroaryl group such as those described above. Such heterocyclic and heteroaryl groups will be referred to herein generically as "  ".

Further examples of typical heterocycles, fused heterocycles, and heteroaryl groups that are preferred as R_7 substituents are listed below in Table A.

Table A





The foregoing groups are especially preferred as R7 side chains on the quinazoline ring system. The heterocycles and heteroaryl groups such as those depicted above are known in the quinolone art and are prepared by literature methods such as *J. Med. Chem.*, 1992;35:1764; *J. Med. Chem.*, 1996;39:3070; *Synlett.*,1996:1097; and *J. Med. Chem.*, 1986;29:445. Any of the primary or

secondary amines shown as substituents on the heteroaryl or heterocyclic groups may be substituted by alkyl, such as methyl, ethyl, isopropyl, and the like.

Some of the compounds of Formula I are capable of forming pharmaceutically acceptable acid addition and/or base salts. All of these forms are within the scope of the present invention and are prepared by art recognized methods. For example, an acid addition salt is prepared by contacting the free base form of the invention compound with a sufficient amount of the desired acid to produce the salt in the conventional manner. Pharmaceutically acceptable acid addition salts of the compounds of Formula I include salts derived from inorganic acids such as hydrochloric, nitric, phosphoric, sulfuric, hydrobromic, hydriodic, hydrofluoric, phosphorous, and the like, as well as the salts derived from organic acids, such as aliphatic mono- and dicarboxylic acids, phenyl-substituted alkanoic acids, hydroxy alkanoic acids, alkanedioic acids, aromatic acids, aliphatic and aromatic sulfonic acids, etc. Such salts thus include sulfate, pyrosulfate, bisulfate, sulfite, bisulfite, nitrate, phosphate, monohydrogenphosphate, dihydrogenphosphate, metaphosphate, pyrophosphate, acetate, trifluoroacetate, propionate, caprylate, isobutyrate, oxalate, malonate, succinate suberate, sebacate, fumarate, maleate, mandelate, benzoate, chlorobenzoate, methylbenzoate, dinitrobenzoate, phthalate, benzensulfonate, toluenesulfonate, phenylacetate, citrate, lactate, tartrate, methanesulfonate, and the like. Also contemplated are salts of amino acids such as arginate and the like, as well as gluconate and galacturonate. All such salts are readily prepared, for example as described by Berge S.M. et al., "Pharmaceutical Salts," *Journal of Pharmaceutical Science*, 1977;66:1-19.

Pharmaceutically acceptable base addition salts are formed with metals or amines, such as alkali and alkaline earth metals or organic amines, when compounds of Formula I have an acidic group such as carboxy. The base addition salts of acidic invention compounds are prepared by contacting the free acid form with a sufficient amount of the desired base to produce the salt in the conventional manner. Typical bases include sodium hydroxide, calcium oxide, diethylamine, and pyridine. Examples of metals used as cations are sodium, potassium, magnesium, calcium, and the like. Examples of suitable amines are

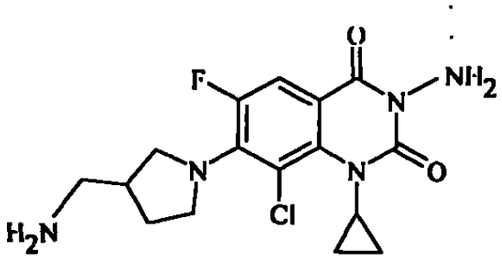
N,N'-dibenzylethylenediamine, chloroprocaine, choline, diethanolamine, dicyclohexylamine, ethylenediamine, N-methylglucamine, and procaine (see, for example, Berge S.M., supra., 1977).

Certain of the compounds of the present invention can exist in unsolvated forms as well as solvated forms, including hydrated forms. In general, the solvated forms, including hydrated forms, are equivalent to unsolvated forms and are intended to be encompassed within the scope of the present invention.

Certain of the compounds of the present invention possess one or more chiral centers. Each center may exist in the R or S configuration. The present invention includes all diastereomeric, enantiomeric, and epimeric forms, as well as the appropriate mixtures thereof. Additionally, the compounds of the present invention may exist as geometric isomers. The present invention includes all cis, trans, syn, anti, entgegen (E), and zusammen (Z) isomers, as well as the mixtures thereof.

Structures of representative compounds of the invention are shown below in Table 1.

TABLE 1



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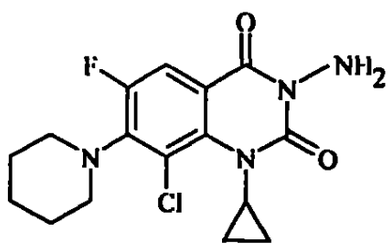

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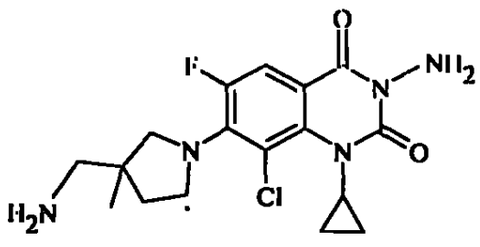

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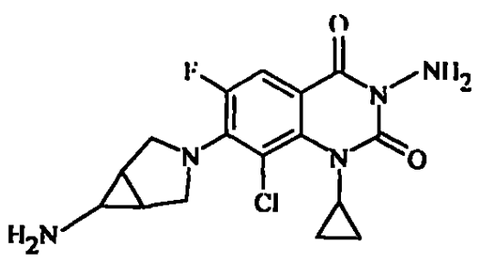

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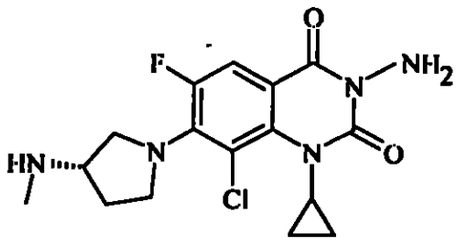

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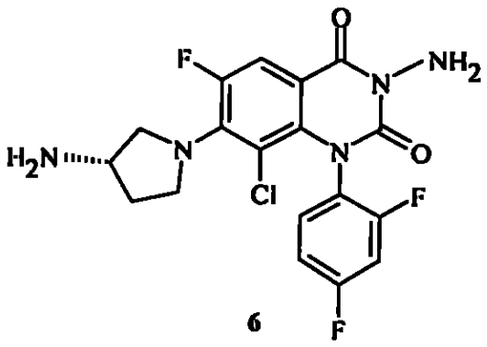

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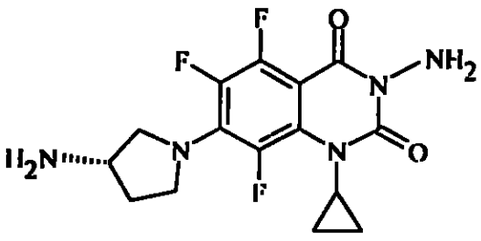

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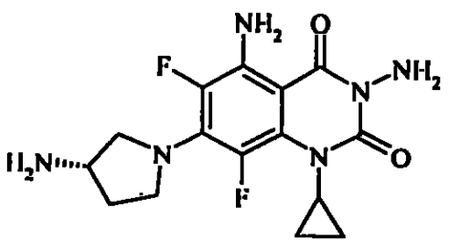

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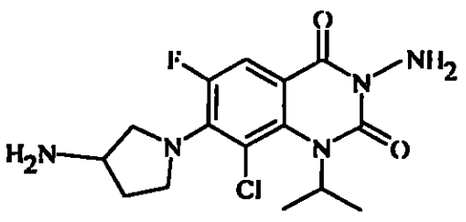

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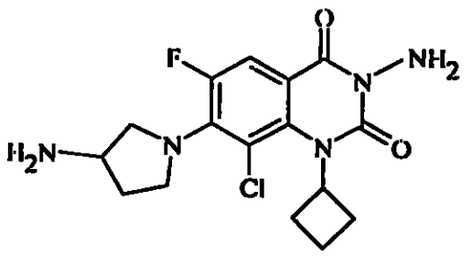

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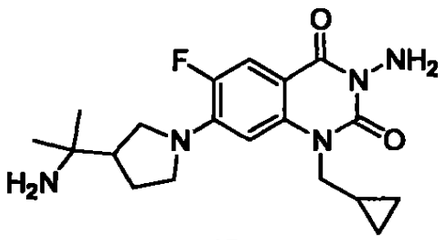

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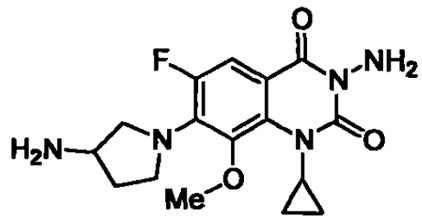

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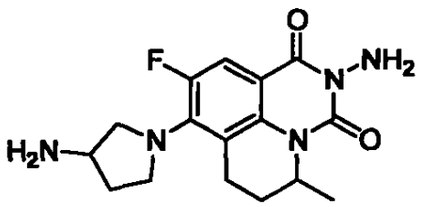

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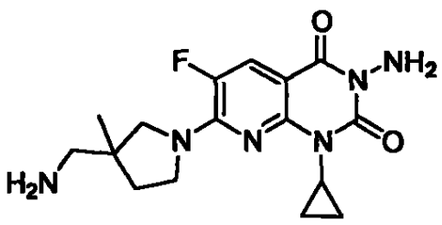

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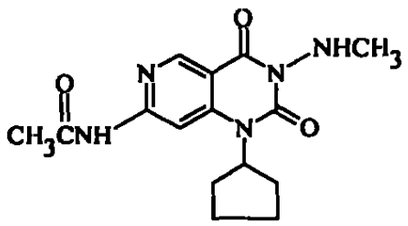

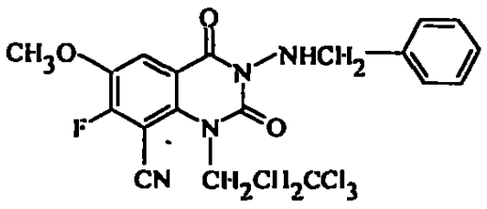

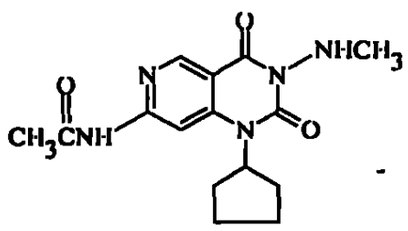

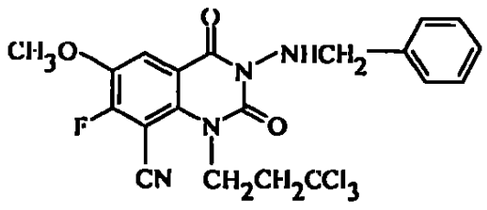

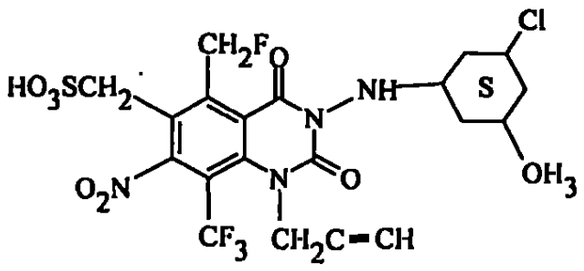

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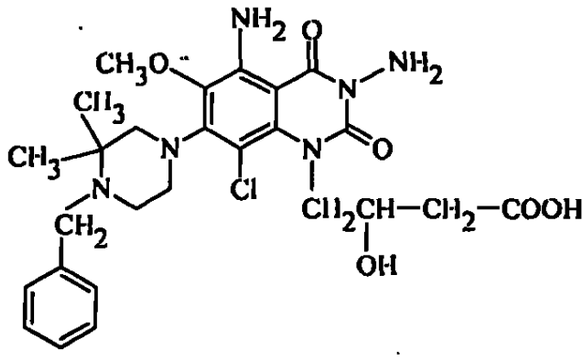


The compounds of Formula I can be prepared utilizing standard synthetic methodology well-known to those skilled in the art of organic chemistry. Many of the compounds have reactive functional groups that generally need to be derivatized with a protecting group in order to avoid unwanted side reactions. For example, functional groups such as alcohols, acid groups, and amines generally are protected while a reaction is carried out at a different site in the molecule, and then the protecting group is subsequently removed following the desired chemical transformation. The use of such protecting groups is standard in organic chemistry synthesis, as described, for example, in T.W. Green and P.G. Wuts, *Protective Groups in Organic Synthesis*, 2nd edition, New York City: John Wiley & Sons, 1991. Thus, for example, protecting groups such as the following may be utilized to protect suitable amino, hydroxyl, and other groups of related reactivity: carboxylic acyl groups, such as formyl, acetyl, trifluoroacetyl; alkoxycarbonyl groups, such as ethoxycarbonyl, *t*-butoxycarbonyl (BOC), β,β,β-trichloroethoxycarbonyl (TCEC), β-iodoethoxycarbonyl; aryloxycarbonyl groups, such as benzyloxycarbonyl, *p*-methoxybenzyloxycarbonyl, phenoxycarbonyl; trialkyl silyl groups, such as trimethylsilyl and *t*-butyldimethylsilyl (TBDMS); and groups such as trityl, tetrahydropyranyl, vinyloxycarbonyl, *o*-nitrophenylsulfenyl, diphenylphosphinyl, *p*-toluenesulfonyl, and benzyl may all be utilized. The protecting group may be removed, after completion of the synthetic reaction of interest, by procedures known to those skilled in the art. For example, a BOC group may be removed by acidolysis, a trityl group by acidolysis or

hydrogenolysis, TBDMS by treatment with fluoride ions, and TCEC by treatment with zinc.

Illustrations of typical preparations of compounds of the present invention having Formula I are shown in Schemes 1-22. Typical heterocyclic and aromatic side chains defined by R_7 in Formula I are prepared as described in Schemes A1-A8. All of the 3-aminoquinazoline-2,4-diones of the invention may be prepared from appropriately substituted benzoic acid starting materials. Protecting groups (referred to in the schemes as "Pro") may be used when appropriate throughout many of the schemes. Although specifically noted in certain schemes, the appropriate use and choice of protecting groups is well-known by those skilled in the art, and is not limited to the specific illustrations shown below. It should also be understood that such protecting groups not only serve to protect chemically reactive sites, but also to enhance solubility or otherwise change physical properties of the underlying invention compound. A number of general reactions such as oxidations and reductions are not shown in detail in the schemes, but can be carried out by standard methods well-known to those skilled in the art. In general, the starting materials used in the following schemes are obtained from commercial sources, or are readily prepared by standard methods. All cited published articles, patents, books, and the like are incorporated herein by reference.

As shown in Scheme 1, a difluoro substituted benzoic acid is reacted with oxalyl chloride or an equivalent acylating reagent (such as an acid anhydride), and the acid halide or anhydride is reacted with an alcohol (ZOH) to afford the respective ester (Z is C_1-C_6 alkyl such as methyl, ethyl, isopropyl, etc.). The ester is reacted with an amine, for example, a heterocyclic amine, to produce the desired 4-heterocyclic phenyl derivative. Alternatively, carbocycles and aryls may also be introduced at this 4-position using palladium catalyzed couplings of tin or boronate carbocycles and aryls, with starting materials containing a Br, I, or triflate at the 4-position as described by Suzuki A., *Pure Appl. Chem.*, 1994;66(2):213-222 and Stille J.K., *Angew. Chem.* 1986;98(6):504-519.

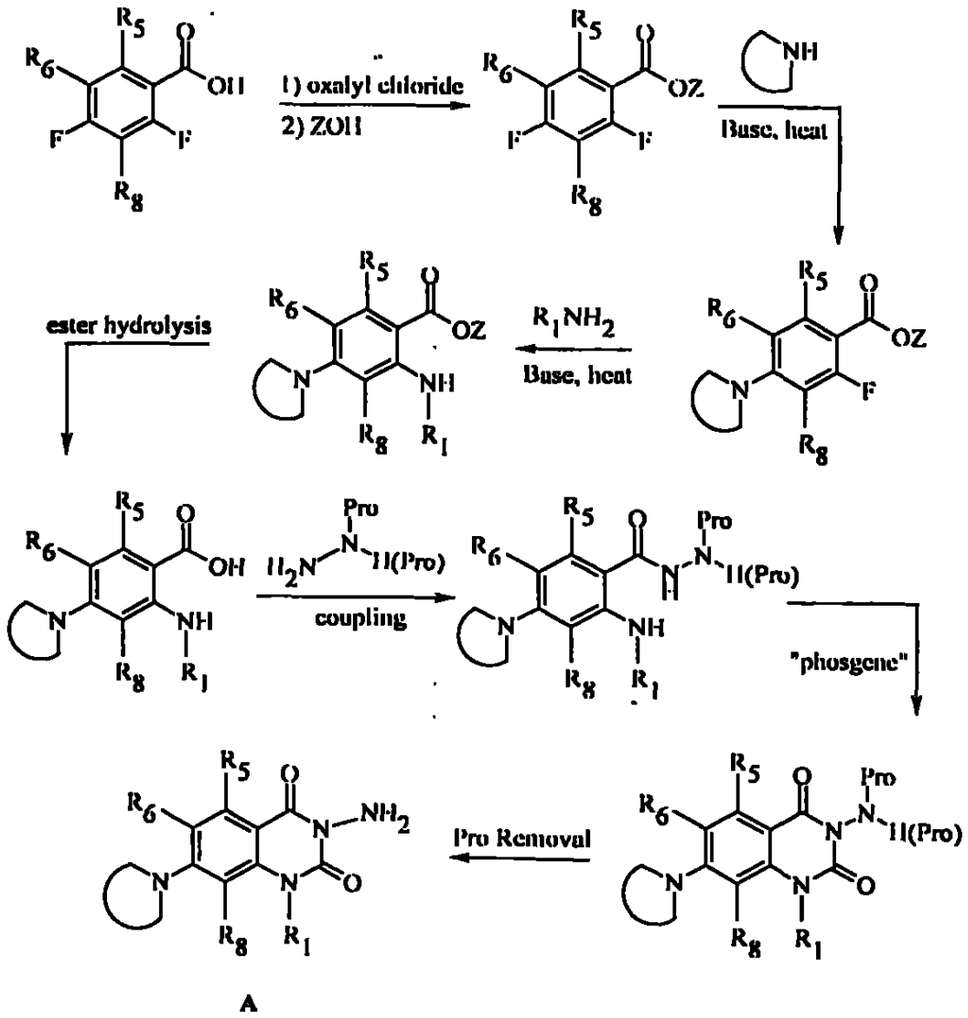
Reaction of the 2-fluoro benzoic acid analog with a primary amine R_1NH_2 affords the corresponding 2-amino benzoic acid ester. The ester group is readily hydrolyzed by reaction with an acid such as hydrochloric acid or a base such as sodium hydroxide to give the corresponding polysubstituted 2-amino benzoic acid. The acid is then coupled to an appropriately protected hydrazine to provide the corresponding amide, which in turn is cyclized to generate the quinazoline-2,4-dione by treatment with, for example, phosgene. At this point, the protecting group may be removed to give the free amine A of Formula I, which can represent a final product of the invention, and which can be further derivatized, if desired, for instance by alkylation with R_3Cl.

Alternatively, the quinazoline-2,4-dione may also be metallated at low temperatures with bases such as, for example, NaH, KH, and lithium diisopropylamine, and then alkylated or acylated to provide the corresponding N-protected-mono-substituted (R_3) amine. The protecting group (Pro) of the N-protected-mono-substituted amine is removed by conventional methods such as hydrogenation, treatment with acid or base, or metal catalysis to afford invention compound C.

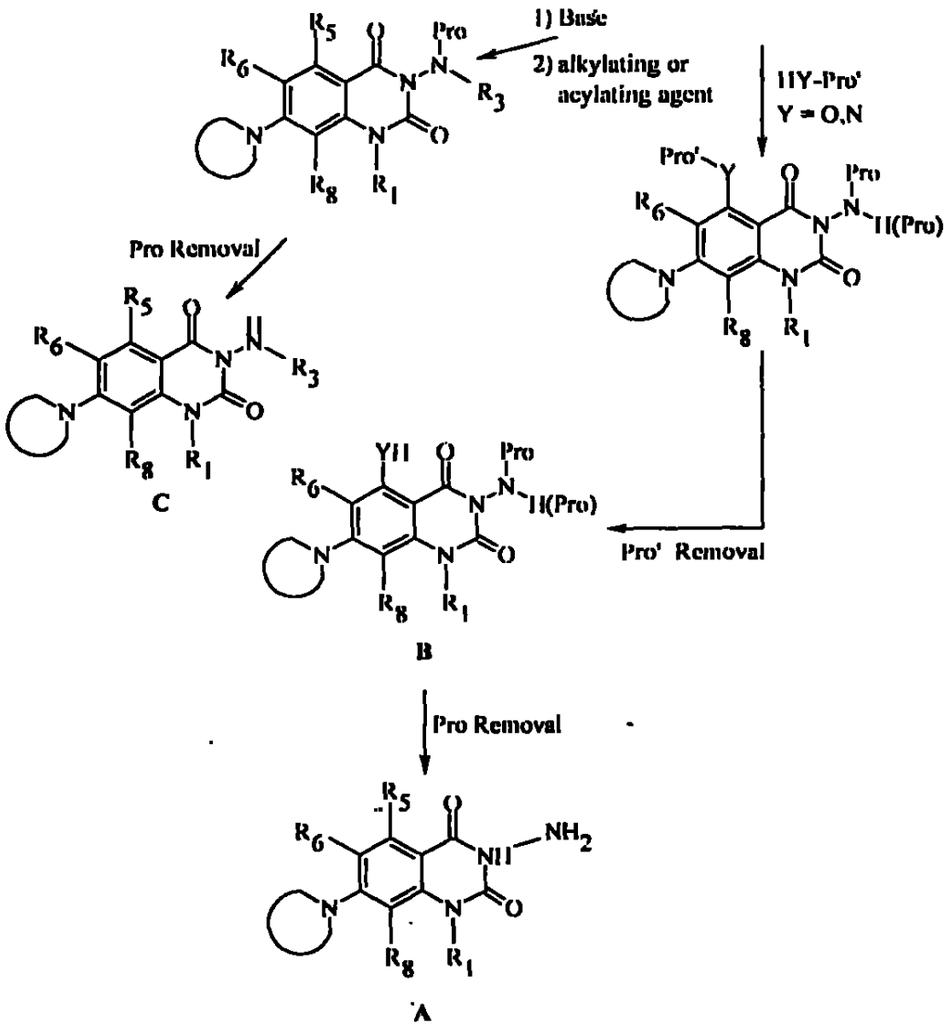
If R_5 is a leaving group such as F, it is activated towards displacement with a nucleophile HY-Pro' where Y is N or O and Pro' is a protecting group such as trimethylsilyl. Other R_5 groups such as chlorine, bromine, or sulfonyl are also good leaving groups. The displacement generally is carried out in a solvent such as ethanol, DMSO, DMF, THF, and at a temperature of about 0°C to 120°C.

The protecting groups (Pro) may be selectively removed by hydrogenation, acid or base treatment, metal catalysis, or such other standard methods. When Pro is benzyl, the benzyl may be removed with Pd/C and hydrogen. A t-butyl carbamate group may be removed by alcoholic HCl, TFA, or TFA in dichloromethane, ethyl acetate or diethyl ether. Allylic carbamates may be removed by $PhSiH_3$ and Pd catalyst. Solvents such as alcohol, THF, alcohol/THF, alcohol/THF/DMF, diethyl ether, etc. are generally employed in such protecting group cleavage reactions.

Scheme 1


1) oxalyl chloride
2) ZOH
Base, heat
R_1NH_2
Base, heat
ester hydrolysis
coupling
"phosgene"
Pro Removal
A

Scheme 1 (cont)



In Scheme 2, an *ortho*-aminobenzoic acid is utilized as the starting material, and is alkylated on the amino group. For example, when R_1 is cyclopropyl, the alkylation is carried out according to the method of Gillaspy (*Tetrahedon Letters*, 1995:7399) to provide the cyclopropyl amine. When R_1 is phenyl or substituted phenyl, the respective amine is prepared from the *ortho*-fluorobenzoic acid using a base, such as, lithium diisopropylamide or Li-hexamethyl disilazide, and the appropriate aryl amine (R_1NH_2). When R_1 is any alkyl group, such as t-butyl or isopropyl, the R_1 can be introduced by reacting

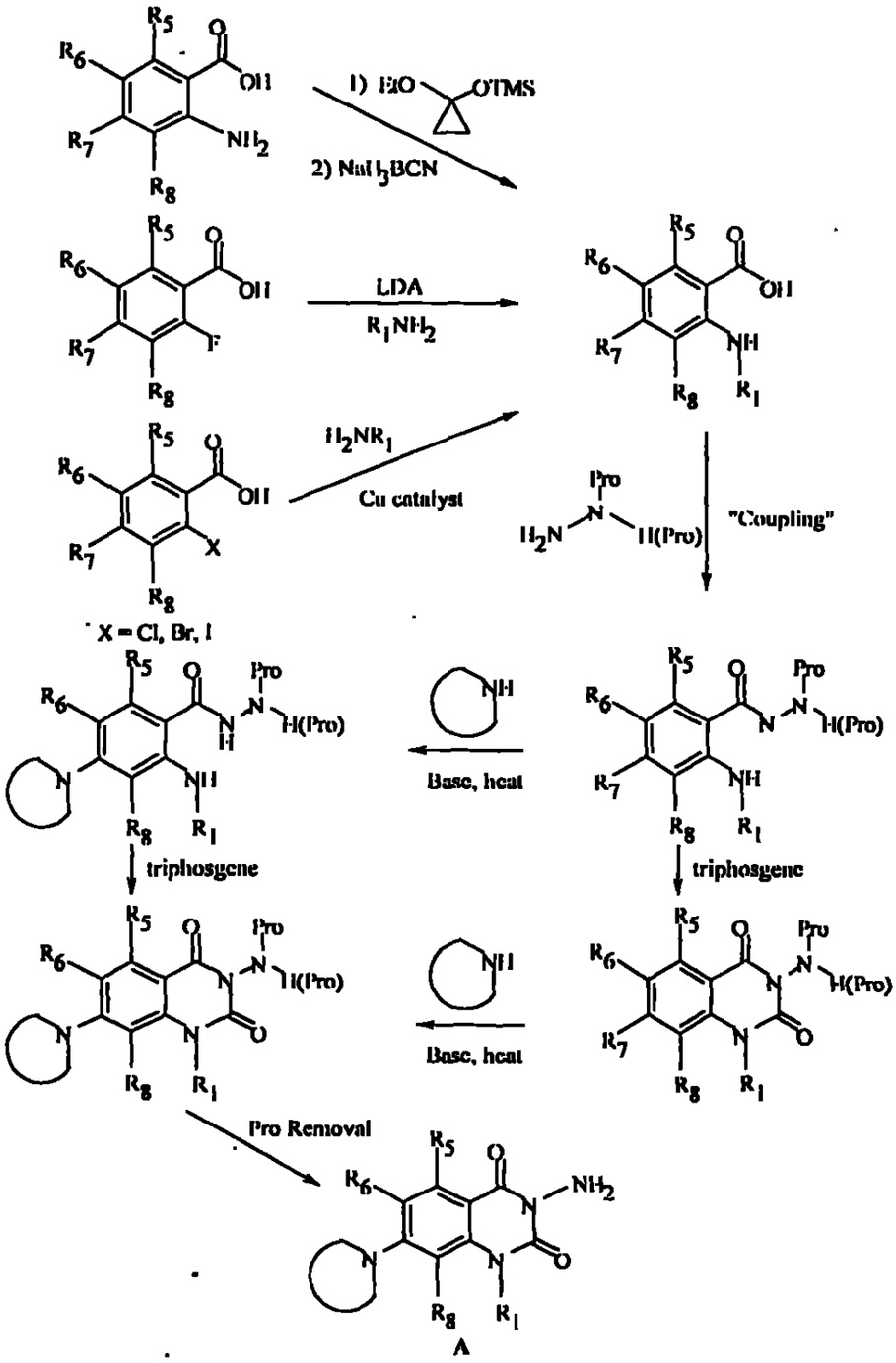
the amine and ortho halo benzoic acid with a Cu catalyst such as copper, bronze, or cupric acetate in the presence of a base such as potassium acetate, triethylamine, or pyridine.

The resulting R_1-substituted amino benzoic acid is then coupled to an appropriately protected hydrazine to provide the corresponding benzamide using methods described in the literature. The corresponding amide can be further reacted, if R_7 is a leaving group such as fluoro, with various heterocyclic amines (e.g., piperidine or pyrrolidine) to form the desired 4-heterocyclic benzamide derivative. Alternatively, carbocycles and aryls (e.g., cyclobutyl or phenyl) may also be introduced at this 4-position using palladium catalyzed couplings of tin or boronate carbocycles and aryls, if the starting material contains a Br, I, or triflate at the 4-position.

The 4-substituted benzamide derivative is then cyclized to generate the quinazoline-2,4-dione by reaction with carbonyldiimidazole (CDI), phosgene, triphosgene or the like in ethereal solvents such as diethyl ether, chlorinated hydrocarbons such as dichloromethane, or aromatic hydrocarbons such as toluene, in the presence of a base such as triethylamine or $NaHCO_3$.

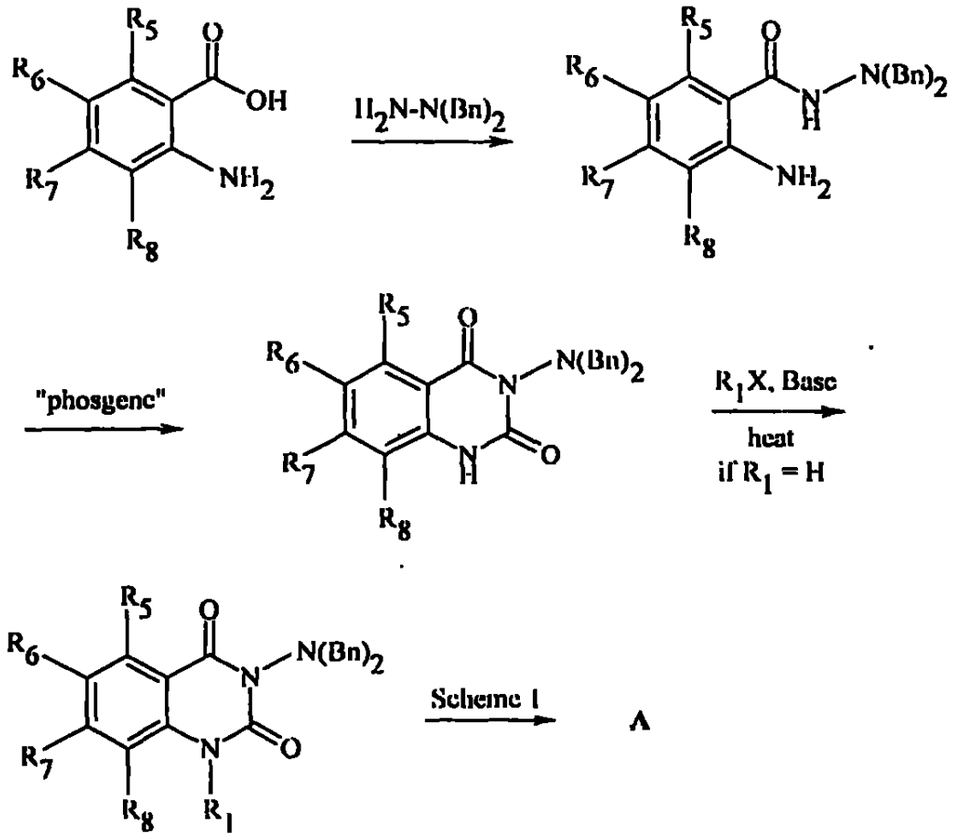
Alternatively, the corresponding amide is first cyclized and then the R_7 halo group is displaced by reaction with a carbocyclic amine  to afford the same product. Deprotection by conventional methods provides the invention compound A.

Scheme 2


1) EtO OTMS
2) NaH3BCN
LDA
R1NH2
H2NR1
Cu catalyst
"Coupling"
X = Cl, Br, I
Base, heat
triphosgene
Pro Removal
A

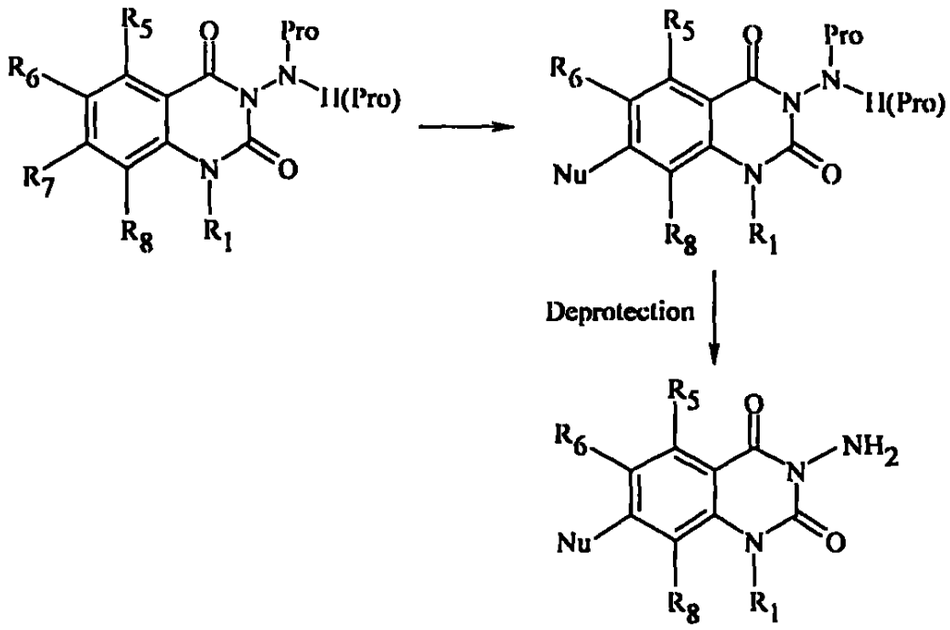
Scheme 3 illustrates alkylation at the 1-position of a 3-aminoquinazolin-2,4-dione to provide invention compounds wherein R_1 is alkyl. A 2-aminobenzoic acid is reacted with an N,N-diprotected hydrazine such as dibenzyl hydrazine (H_2N-NBn_2) to provide the corresponding N-protected amide. This intermediate can then be reacted with phosgene or phosgene/base in an ethereal solvent, or with a phosgene equivalent such as triphosgene in a chlorinated hydrocarbon such as dichloromethane, to give the quinazoline-2,4-dione. The alkylation of the quinazoline-2,4-dione to provide a 1-alkylated-quinazoline-2,4-dione is accomplished by reaction with an alkyl halide as described by Bouzard, supra., 1990. Typically, such reactions are carried out in THF, ether, DMSO, an alkanol, or DMF, and in the presence of a base. Typical alkyl halides (R_1X where X is halo) include ethyl iodide, ethyl bromide, cyclopropyl iodide, n-decyl bromide, and the like. Typical bases include sodium hydride, potassium carbonate, and the like. Conversion of the 1-alkylated-quinazoline-2,4-dione to other invention compounds (and removal of protecting groups such as benzyl Bn) can be carried out according to Scheme 1, for example, to give the corresponding 1-alkyl (R_1 = alkyl) 3-amino (NH_2)compounds such as A.

Scheme 3



Displacement of leaving groups located at the 7-position of the quinazolin (e.g., R_7 = halo) as shown in Schemes 1 and 2 is not limited to nitrogen heterocycles. Other nucleophiles (Nu) such as CH_3O-, N_3-, R'R"NH, R'-NH_2, and R'S- (where R' and R" are defined above) also displace a leaving group such as F, Cl, or NO_2 at the 7-position as shown in Scheme 4. When the leaving group is a triflate or higher halide, organo tin reagents or organoboronates may be used with palladium catalysts to deliver a carbon nucleophile. The methodology shown in Scheme 4 follows that of Stille et al., *Angew. Chem. Int. Ed. Eng.*, 1986;25:508 and is exemplified by Mitchell (*Synthesis*, 1992:803).

Scheme 4

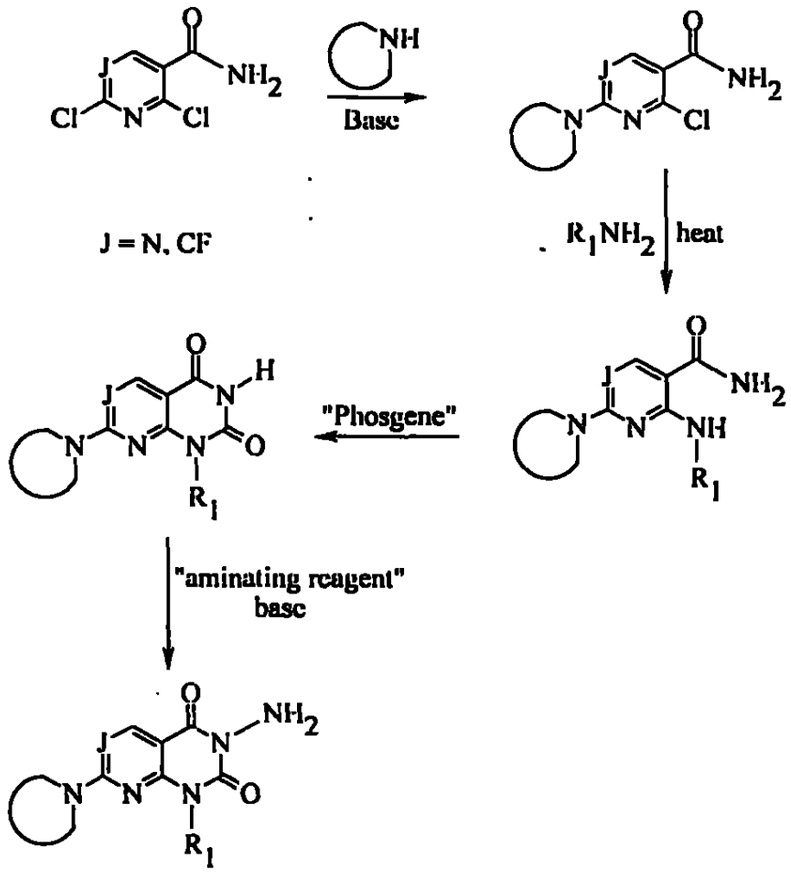


All of the chemistry depicted and described in Schemes 1 to 4 is applicable to make compounds of Formula I wherein J and K both are carbon, or where one or both of J and K are N. When either J or K is nitrogen, the displacement reactions described above is even more facile than when J and K are carbon.

Compounds of the invention where J and/or K of Formula I are nitrogen may be prepared by the Schemes 1, 2, 3, and 4, or by routes which take advantage of the activation of leaving groups *ortho* and *para* to the J and/or K nitrogen atom. Such routes will systematically introduce R_7 and R_1 groups as desired. This methodology also applies to cases in Formula I where K-R_8 is C-H or C-F and J-R_6 is C-F. Such systematic substitutions are illustrated in Scheme 5. For example, a pyridine amide has leaving groups such as halo on both sides of the nitrogen. Such groups are generally chlorine, but fluorine, alkylthiol, and sulfoxides such as methyl sulfoxides are also good leaving groups for such compounds. These leaving groups may be sequentially displaced based on reactivity. In Scheme 5, where J = N or J-R_6 = CF, the 4-chloro (para to the aminocarbonyl group) is displaced preferentially (relative to the 2-chloro group)

using a nucleophilic amine such as diethylamine, pyrrolidine, methylpiperazine, and the like to give the corresponding amino substituted analog. This analog is then reacted with R_1NH_2 to displace the second leaving group (e.g., the 2-chloro group). The resulting 2,6-disubstituted-pyridylamide is then reacted with CDI, phosgene, or other phosgene equivalents to form the cyclized quinazoline product. Amination at the 3-position NH is achieved by reaction with any number of aminating reagents such as ammonia and N-alkylamines, for example, as described by Kloetzer (*Sci. Pharm.*, 1984;52:46-50) to give the corresponding invention compound.

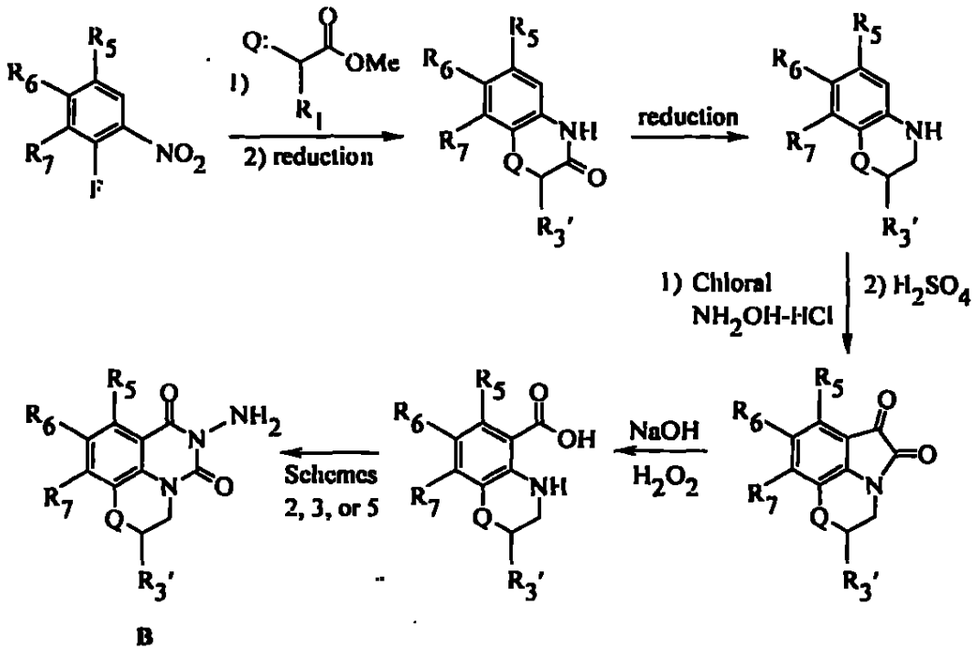
Scheme 5



Tricyclic compounds (i.e., where R_1 and R_8 in Formula I are taken together with the atoms to which they are attached to form a ring) can be prepared

according to Schemes 6 and 7. Schemes 6 and 7 differ in the introduction of the R_1 substitutions in Structures B and C wherein $R_1 = R_{1'}$ and R_1 is as defined above for Formula I and $R_{1'}$ is alkyl, alkenyl, alkynyl, aryl, cycloalkyl, heteroaryl, and the like. In Scheme 6, the *ortho*-fluoro nitro compound (other leaving groups such as chlorine, bromine, and sulfonyl may also be employed in place of fluoro) is displaced by the α-nucleophile substituted ester (where Q is a nucleophile Nu such as methyl or methoxy). The nitro group is then reduced using, for example, Raney Ni, H_2 over Pd/C, or an active metal in acid such as iron or tin in HCl or acetic acid. The newly formed amine readily cyclizes with the ester (other acid analogs may be employed such as thioesters, amides, and the like). The cyclized product is then reduced with hydride reducing agents such as $LiAlH_4$ and the like to produce the dihydroquinoline derivative, which in turn is reacted with chloral hydrate and then an acid to form the dione ring. The dione ring is subsequently opened using, for example, sodium hydroxide and hydrogen peroxide to give the benzoic acid. The 3-aminoquinazolinedione ring is then prepared using the chemistry described in Schemes 2, 3, or 5 to give the invention compound B, where R_3' is alkyl, alkenyl, cycloalkyl, aryl, and heteroaryl.

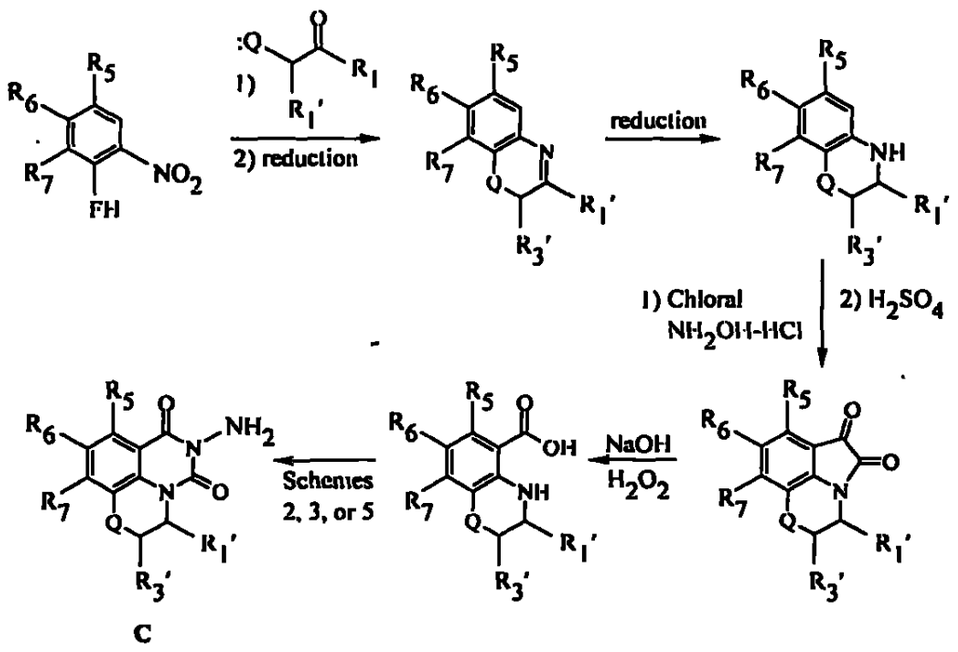
Scheme 6



B

In a similar series of reactions depicted in Scheme 7, the *ortho*-fluoro nitro compound is reacted with an α-nucleophile substituted ketone, and the resulting product is likewise reduced. In this sequence, the resulting aniline forms a cyclic imine, which is further reduced with H_2 on Pd/C or by chemical hydride reducing agents such as sodium borohydride or sodium cyanoborohydride to give the dihydroquinoline. Such reductive aminations are well-known in the art and are typically performed in THF, alcohol, water alcohol mixtures, or in water DMF mixtures. The remaining steps to produce C follow those of Scheme 6. When the C-7 substituent is a leaving group (e.g., R_7 = halo), compounds B and C may be further reacted with nucleophiles (such as pyrrolidine or piperidine) to give compounds of Formula I as in the previous schemes.

Scheme 7

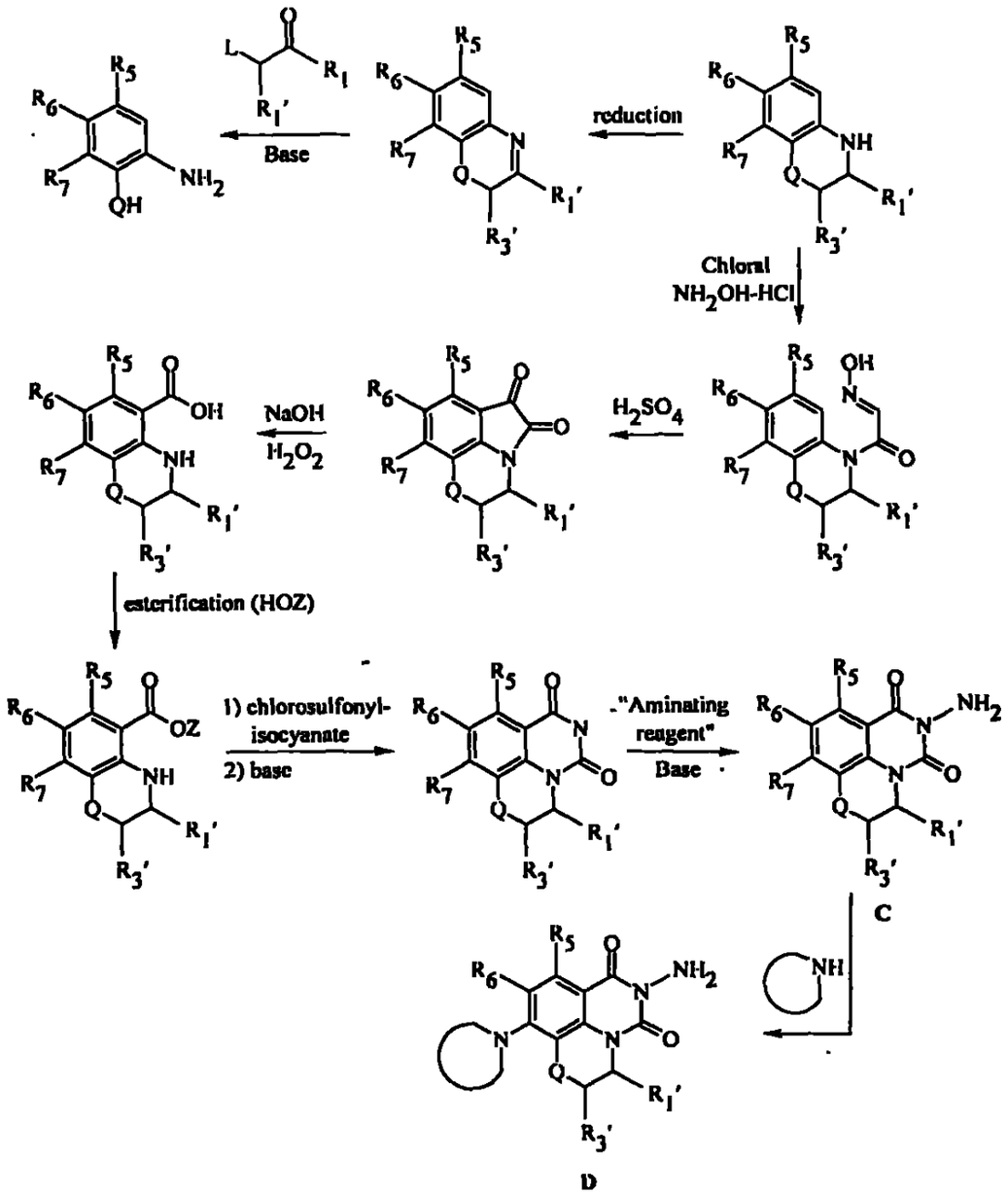


C

In Scheme 8, the target tricylic compounds as C are prepared in a slightly different manner. In this case, the nucleophile Q (such as hydroxymethyl) is attached to the phenyl ring of the starting aniline, and a leaving group L (such as halo) is attached alpha to the ketone reactant. The nucleophile may be activated with bases such as sodium hydride or potassium hydride, triethylamine or 1,8-diazabicyclo[5.4.0]-undec-7-ene (DBU), or sodium, potassium, or cesium carbonate to displace the leaving group L. In this sequence, the resulting aniline forms a cyclic imine, which is further reduced with H_2 on Pd/C or by chemical hydride reducing agents such as sodium borohydride or sodium cyanoborohydride to give a dihydroquinoline. Such reductive aminations are well-known in the art and are typically performed in THF, alcohol, water alcohol mixtures, or in water DMF mixtures. The dihydroquinoline intermediate is reacted with chloral hydrate, and then an acid to form the dione ring. The dione ring is subsequently opened by reaction with a base, for example sodium hydroxide and hydrogen peroxide, to give the benzoic acid. The 3-aminoquinazolindione ring is then prepared by first forming an ester on the benzoic acid as in Scheme 2, followed by reaction of the

benzoic acid ester with chlorosulfonylisocyanate or the like at temperatures of 0°C and below, followed by treatment with a base such as triethylamine or diisopropylethylamine. Amination can then be carried out in the same manner as described in Scheme 5 to provide compounds of structure C. When R_7 is a leaving group such as Cl or F, the invention compounds of structures B (in Scheme 6) and D (in Scheme 8) can be prepared by coupling to the R_7 side chain, e.g., various heterocyclic amines  to produce the desired derivatives. Alternatively, carbocycles and aryls may also be introduced as R_7 side chains using palladium catalyzed couplings with tin or bornate carbocycles and aryls, for example when R_7 is a Br, I, or triflate.

Scheme 8

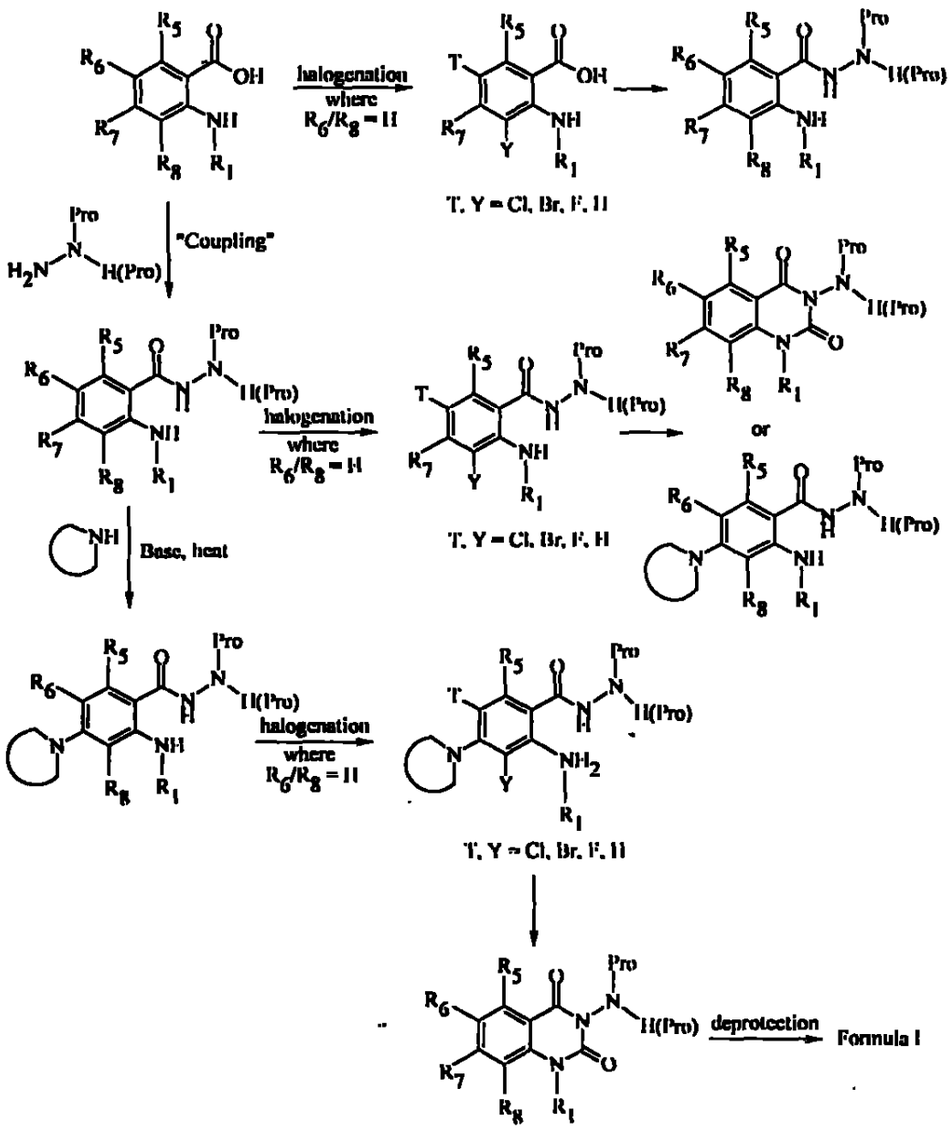


It should be noted from Schemes 6, 7, and 8 that R_1' and R_3' will form chiral centers, giving *R* and *S* enantiomers and diastereomers. Such enantiomers or diastereomers may be separated, if desired, at any stage by chiral HPLC, or by other conventional resolution techniques. Resolution of the precursor benzoic acid

may also be accomplished by fractional crystallization using mandelic acid, tartaric acid, or other chiral, optically pure acid bearing resolving agents. Chiral amides may also be prepared from the benzoic acids using chiral amines such as camphorsulfonamide, benzylamine, or the like. The isomers can then be separated and the chiral amide hydrolyzed as desired.

Scheme 9 illustrates synthesis of compounds of Formula I wherein one or both of R_6 and R_8 are halo via halogenation. The halogenation is carried out on a 2-aminobenzoic acid where one or both of R_6 and R_8 is hydrogen. If both R_6 and R_8 in the benzoic acid are H, then halogenation can be accomplished at both positions selectively or simultaneously. Thus, for example, chlorination at R_6 or R_8 is achieved by reaction of the benzoic acid with N-chlorosuccinamide, *t*-butylhypochlorite, chlorine gas, and the like. Similarly, bromination at R_6 and R_8 can also be accomplished by reaction of the benzoic acid with Br_2, N-bromosuccinimide, and the like. Such halogenations are well-known in the art. Halogenation provides the respective mono- or dihalo compound. The halogenated benzoic acid can be further reacted as shown in Schemes 1 and 2 to provide the quinazoline-2,4-diones of Formula I.

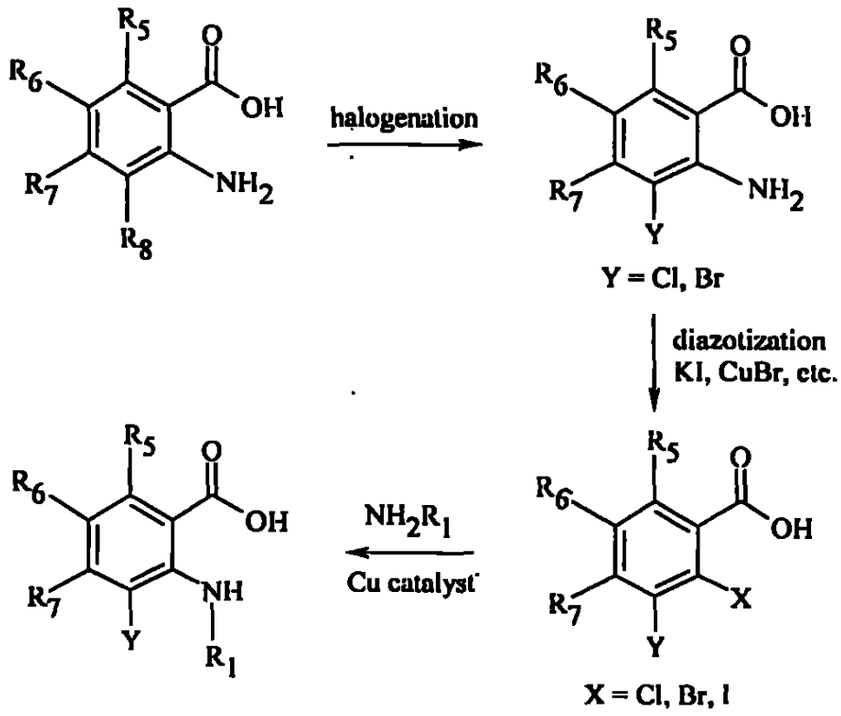
Scheme 9



In Scheme 10, compounds where R_8 is H are halogenated as described in Scheme 9 to provide the corresponding 3-halo-2-aminobenzoic acid (Y = halo). This intermediate can then be diazotized by reaction of the 2-amino group with sodium nitrite or t-butyl nitrite, which is then converted to a 2-halobenzoic acid in the presence of an appropriate sodium, potassium, or copper salt such as sodium iodide, potassium chloride, and the like. The resulting 2,3-dihalobenzoic acid

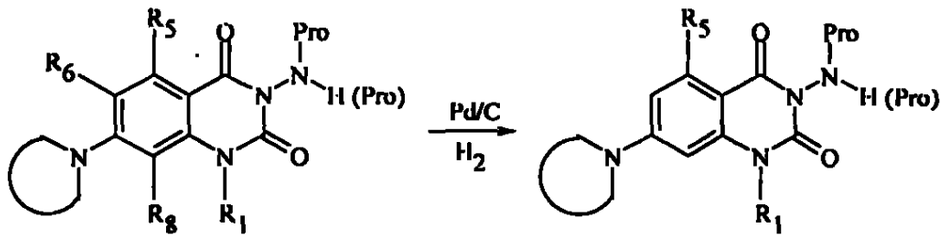
(where X and Y both are halo) is then converted to the 3-halo-2-aminobenzoic acid by reaction with an amine R_1NH_2 in the presence of a copper catalyst. The 3-halo-2-aminobenzoic acid is converted to an amide and cyclized to the corresponding 8-halo-3-amino-quinazolin-2,4-dione, as illustrated in Scheme 2.

Scheme 10



Compounds of Formula I wherein R_6 and/or R_8 is halo such as chloro or bromo are readily dehalogenated by reaction with metal catalysts under hydrogen pressure (Scheme 11). Suitable catalysts include the many variations of Pd on carbon, Raney nickel, or other reagents that are well-known to effect such dehalogenation.

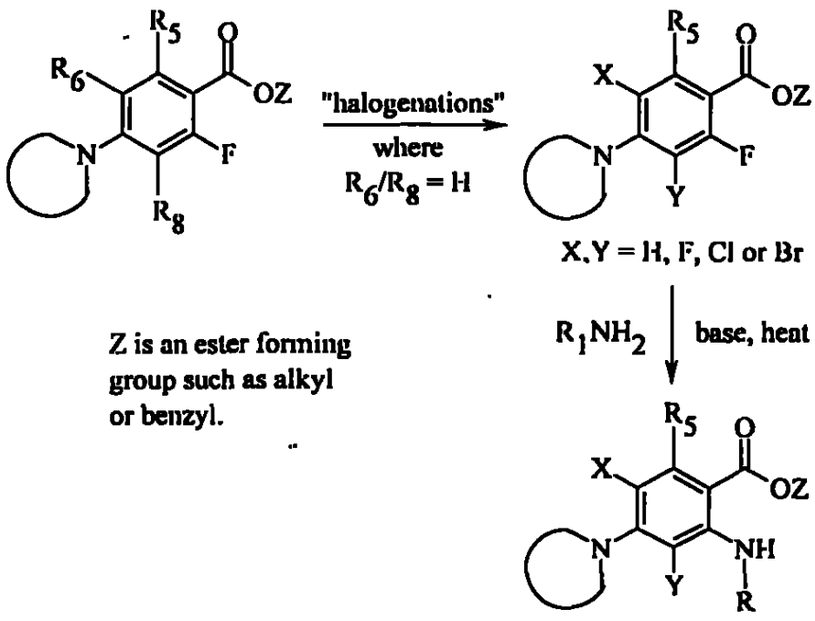
Scheme 11



R_6 and/or R_8 = Cl, Br

Compounds of Formula I wherein R_6 and/or R_8 are hydrogen can be halogenated to give the mono- or dihalo compound (e.g., R_6 or R_8 = Cl or Br). The invention compounds are preferably prepared by first halogenating a benzoic acid derivative, and then cyclizing the halogenated benzoate (Scheme 12). If both R_6 and R_8 are H, then halogenation can be accomplished at both positions selectively or simultaneously. Halogenations can be carried out as described above for Scheme 10. The resulting compound is then converted to the 2-substituted-aminobenzoic acid as depicted in Scheme 1, which is subsequently cyclized and aminated.

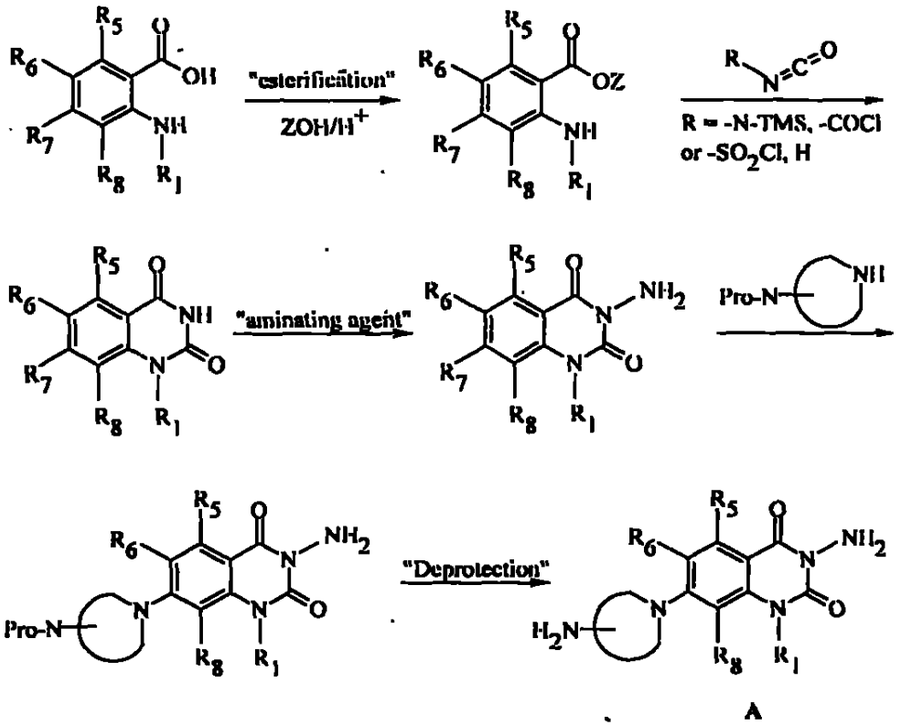
Scheme 12



Z is an ester forming group such as alkyl or benzyl.

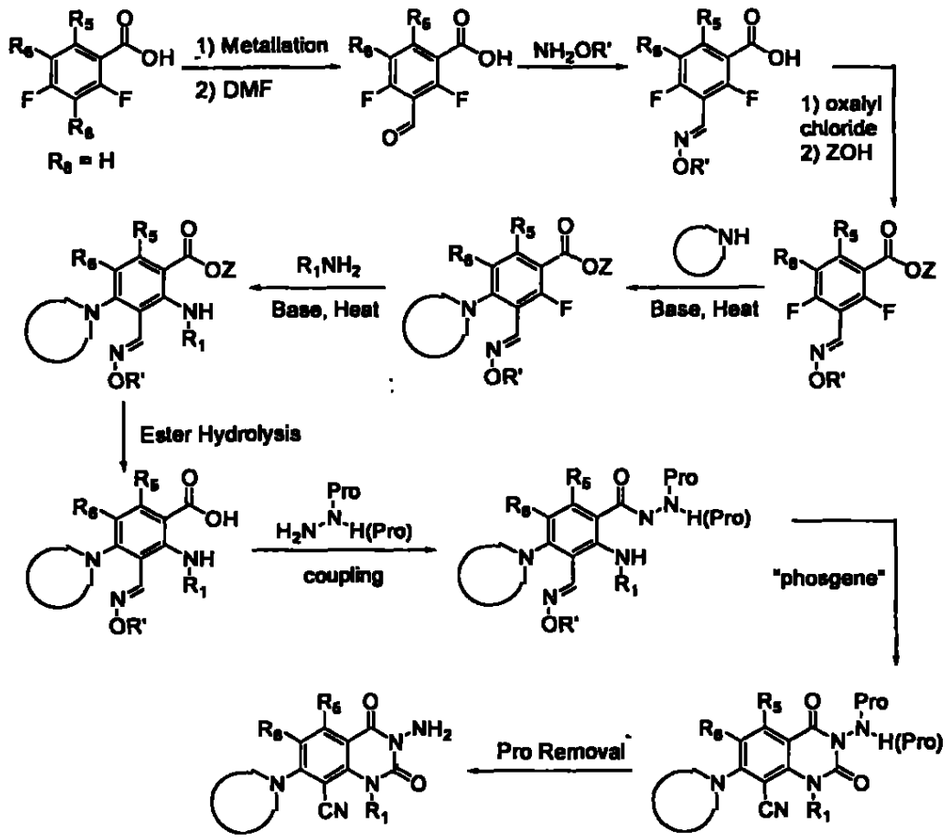
Invention compounds of Formula I can also be prepared as shown in Scheme 13. Substituted benzoic acids can be converted into esters (where Z is an ester forming group such as alkyl or benzyl) by a number of methods known by those skilled in the art. The ester is reacted with an isocyanate such as trimethylsilylisocyanate, chlorosulfanyl isocyanate, and chlorocarbonyl isocyanate, followed by treatment with a base such as triethylamine, sodium t-butoxide or the like, to provide a quinazoline-2,4-dione. The quinazoline-2,4-dione can be aminated by reaction with an aminating agent such as ammonia as described in Scheme 5 to generate the corresponding 3-aminoquinazoline-2,4-dione. This compound may be further reacted, when R_7 is a leaving group such as fluoro, with various heterocyclic amines. Again, carbocycles and aryls may also be introduced at R_7 if R_7 is a Br, I, or triflate, using palladium catalyzed couplings of tin or boronate carbocycles and aryls. Removal of any protecting groups (Pro) by normal means provides invention compounds such as A, as described above in Scheme 1.

Scheme 13



Invention compounds of Formula I having a cyano substituent can be prepared as shown in Scheme 14. For example, a benzoic acid wherein R_8 is hydrogen can be metallated with a strong base such as lithium hexamethyldisilazane or lithium diisopropylamine. The resulting metallated intermediate can then be quenched with dimethylformamide or an equivalent to provide an aldehyde. The aldehyde can be converted to an oxime by reaction with an alkoxy amine (other electrophiles such as alkyl halides, activated amides, esters and halide sources such as 1,2-dichloro-tetrafluoroethane may also be employed to provide other benzoic acid derivatives that can be used as defined in Schemes 1, 2, 13, and 15). The oxime is converted into a cyano group under the cyclization conditions required to form the quinazolinedione ring system (e.g., reaction with phosgene) as described in Schemes 1, 12, and 13. Deprotection provides invention compounds where R_8 is -CN.

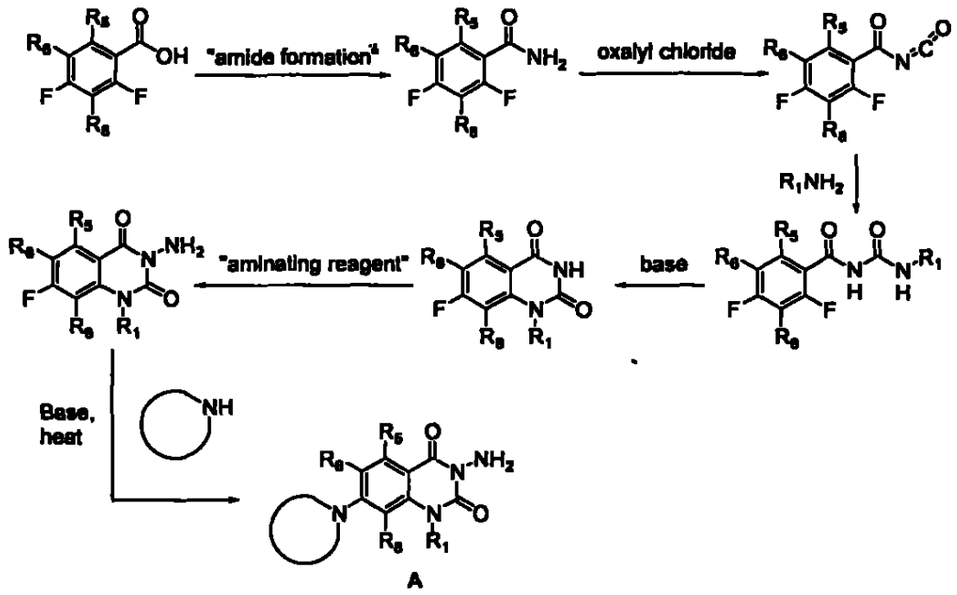
Scheme 14



Another alternative for preparing invention compounds is illustrated in Scheme 15. Appropriately substituted benzoic acids can be converted into benzamides by any number of methods as described above. A benzamide can then be treated with oxalyl chloride in a chlorinated solvent such as dichloroethane or an equivalent to provide an isocyanate. The isocyanate is reacted with a substituted primary amine to give a benzoyl substituted urea. This intermediate can be cyclized to form a quinazolinedione ring system by reaction with sodium hydride, potassium hexamethyldisilazane or other non-nucleophilic bases, generally in a solvent such as tetrahydrofuran (THF)/dimethylformamide, THF with 18-crown-6, THF/dioxane, THF/glyme, THF/diglyme, dimethoxyethane/ toluene or an equivalent. The quinazolinedione can then be aminated by reaction with any number of aminating reagents as described by Kloetzer (*Sci. Pharm.*, 1984;52:46-50). The resulting 3-aminoquinazolinedione ring system can then be

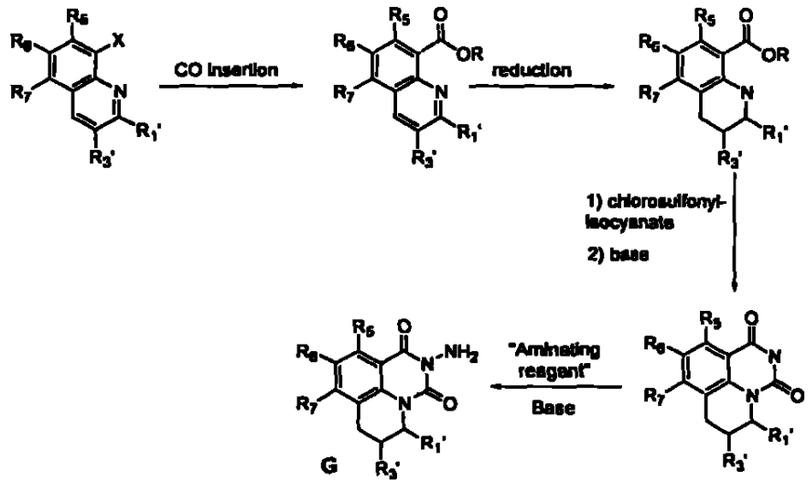
readily coupled with an appropriately substituted heterocyclic amine (such as those noted above in Table A) by reaction in the presence of a base such as triethyl amine, diisopropylethyl amine, tetramethyl guanidine, and the like in solvents such as dimethyl sulfoxide, dimethylformamide, dimethylacetamide, sulfolane or the equivalent. Any protecting group associated with the heterocyclic amine side chain is then removed by methods known to those skilled in the art to provide invention compounds having Structure A.

Scheme 15



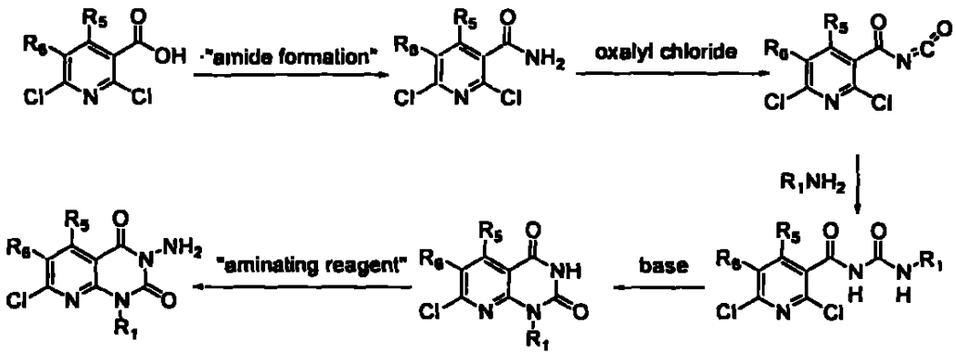
Tricyclic compounds (i.e., where R_1 and Rg, together with the atoms to which they are attached, form a carbocyclic ring in invention compounds of Formula I) can be prepared according to Scheme 16 where a palladium mediated carbon monoxide insertion on a quinoline (X = Br, I, or triflate) under well-precedented conditions gives rise to an ester. The quinoline ring can then be hydrogenated to provide a tetrahydroquinoline by standard hydrogenation conditions. The remainder of Scheme 16 follows that of Scheme 8 to provide invention compounds such as G, substituted with a displaceable substituent at R_7 (e.g., halo). These compounds may be further reacted with nucleophiles such as amines from Table A to give compounds of Formula I.

Scheme 16



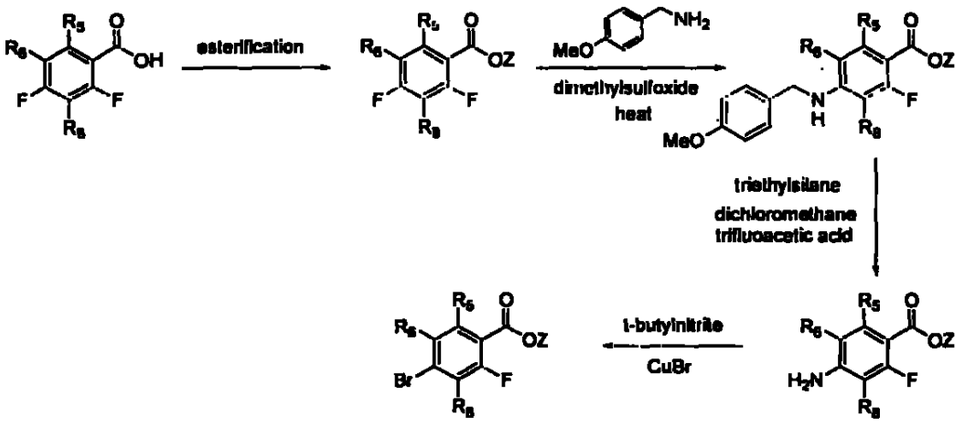
Compounds of Formula I where K is N may be prepared by the routes shown in Schemes 1, 2, 3, 4, and 6, or by routes such as the one illustrated in Scheme 17, which follows closely the chemistry shown in Scheme 15. The leaving groups (e.g. halo) *ortho* and *para* to the carboxyl group of the pyridyl starting material are highly activated. The two leaving groups ortho to the pyridine nitrogen are generally chlorine, but fluorine, alkylthiol, and sulfoxides such as methylsulfoxide are also good leaving groups for such compounds. The urea intermediate readily cyclizes to the 7-halo-quinazolinedione. Amination at the 3-position gives an invention compound that is an important intermediate due to the good leaving group at the 7-position (R_7 = halo), which is readily displaced by reaction with an amine .

Scheme 17



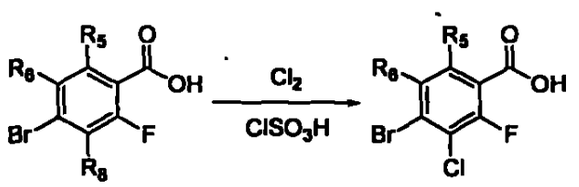
Scheme 18 illustrates the synthesis of benzoic acid starting materials that have a bromo for R7. A difluoro substituted benzoic acid is converted to an ester by first reaction with oxalyl chloride or an equivalent reagent (including acid anhydride), and the acid halide or anhydride is reacted with an alkanol to afford the respective ester (Z=methyl, ethyl, isopropyl, etc.). The ester is then reacted with 4-methoxybenzylamine or an equivalent to produce the desired 4-substituted benzoic acid derivative. This intermediate is reacted with triethylsilane and trifluoroacetic acid in a chlorinated solvent such as dichloromethane or an equivalent to provide an aniline derivative. Alternatively, one skilled in the art might also employ transition metal catalysis. The resulting aniline is then subjected to diazotization and converted to a bromide by treatment with cuprous bromide. The ester is then hydrolyzed by well-known methods to the desired benzoic acid, which can be used as a starting material as illustrated in Scheme 20 below.

Scheme 18



In Scheme 19, 4-bromo-2-fluorobenzoic acid derivatives can be selectively chlorinated by treatment with chlorine gas in chlorosulfonic acid at a temperature of 40°C-100°C.

Scheme 19



R_8 = H

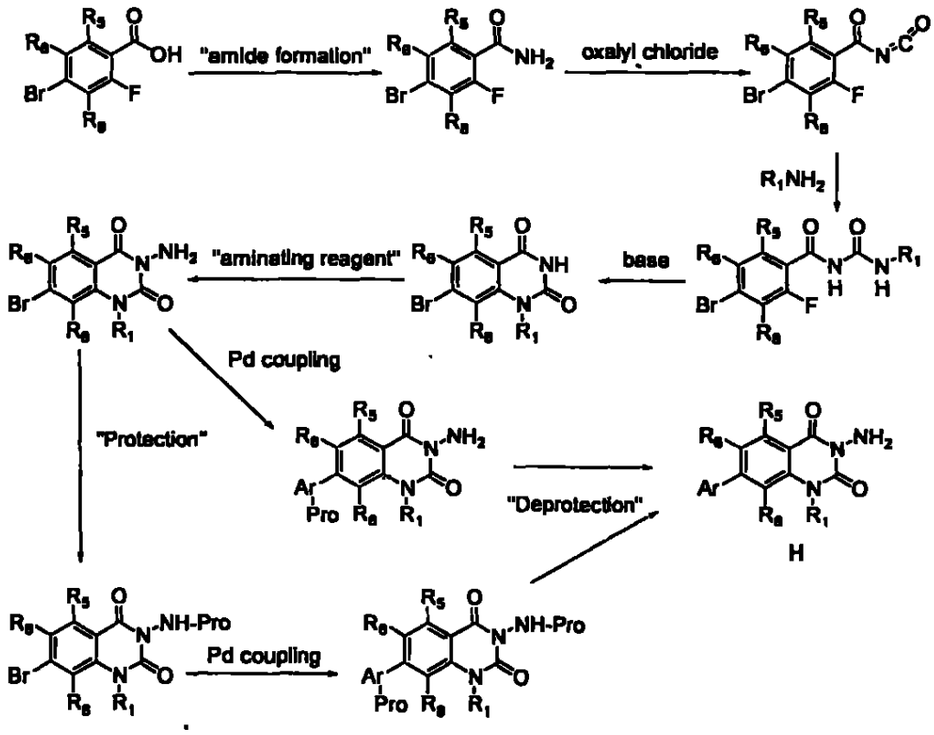
Scheme 20 illustrates use of 4-bromobenzoic acids as starting materials to make invention compounds wherein R7 is aryl. The 4-bromobenzoic acids are converted into benzamides by any number of methods known in the art. A benzamide is reacted with oxalyl chloride in a chlorinated solvent such as dichloroethane or an equivalent to provide an isocyanate. The isocyanate is reacted with a substituted primary amine to give a benzoyl substituted urea. This intermediate can be cyclized to form a quinazolinedione ring system by reaction with sodium hydride, potassium hexamethyldisilazane or other non-nucleophilic bases in tetrahydrofuran/dimethylformamide, tetrahydrofuran with 18-crown-6, toluene/dioxane, tetrahydrofuran/glyme, tetrahydrofuran/diglyme, glyme/toluene

or an equivalent. The quinazolinedione can then be aminated with a number of aminating reagents as described in Scheme 15. The resulting 3-aminoquinazolinedione ring system can then be readily coupled with a stannane or boronic acid derivative of a substituted aryl such as phenyl or substituted aromatic heterocycle (Ar).

Alternatively, the 3-position amine can be protected with a protecting group such as a tert-butyl carbamate or trifluoroacetamide. Protecting groups of these types are well known in the art. The 3-derivatized aminoquinazolinedione ring system can then be coupled via palladium catalysis with an aromatic (Ar) stannane or boronic acid.

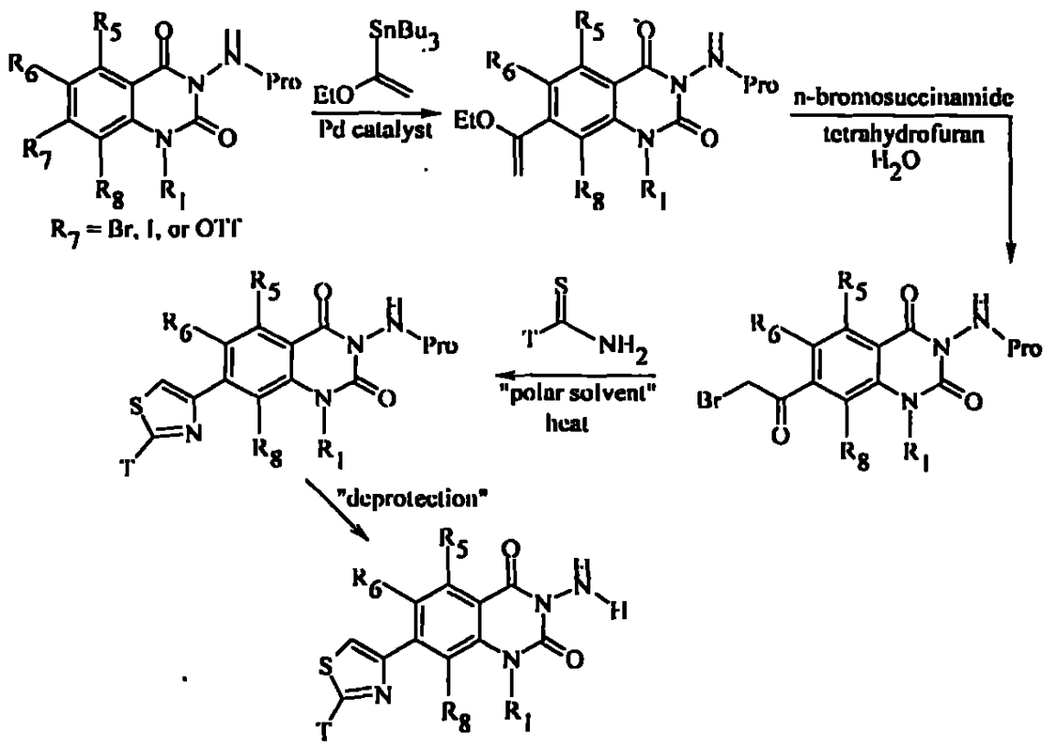
Each of the outlined routes, upon deprotection by standard procedures, provides invention compounds of Formula I where R_7 is aryl such as phenyl or substituted phenyl, or heteroaryl such as pyridyl or substituted pyridyl.

Scheme 20



Compounds of Formula I wherein R_7 is a heteroaryl group (such as those in Table A) are alternatively prepared as illustrated in Scheme 21, where R_7 is a substituted thiazole. A 3-protected 3-amino-7-bromoquinazolinedione from Scheme 20 is reacted with 1-tributyl-ethoxyvinyltin in the presence of a palladium catalyst. The resulting 7-substituted adduct is reacted with a brominating reagent such as n-bromosuccinimide and the like in tetrahydrofuran/H_2O to provide an α-bromoketone at the quinazolinedione 7-position. Reaction of this intermediate with a thioamide (or thiourea) in a polar solvent such as dimethyl formamide, dimethylacetamide, or ethanol, and at an elevated temperature of about 80°C to 120°C, effects cyclization to form a thiazolyl group. Deprotection by known methods can then be applied to provide invention compounds of Formula I wherein R_7 is the heteroaryl, optionally substituted with T, which is H, alkyl, substituted alkyl, NH_2, NH-alkyl and N-dialkyl.

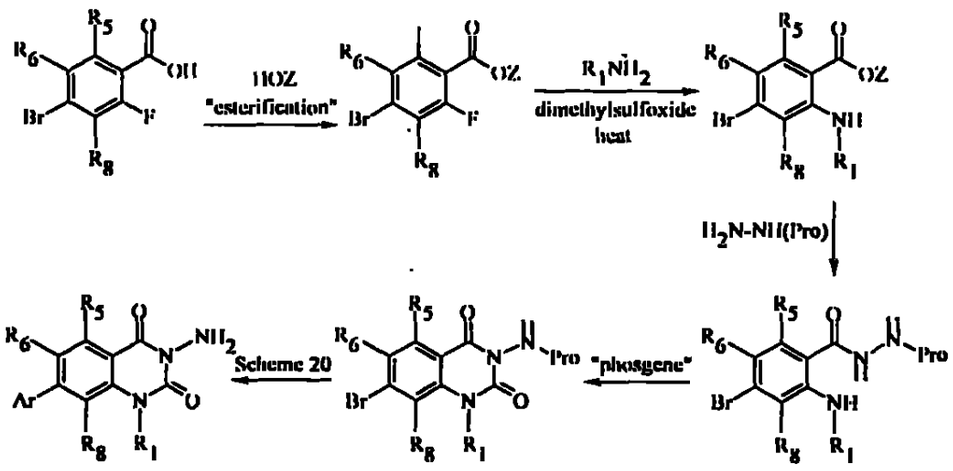
Scheme 21



I

Alternatively, 7-aromatic or heterocyclic aromatic compounds of Formula I are prepared as shown in Scheme 22. A 4-bromo-2-fluorobenzoic acid (Schemes 18 or 19) is first esterified (Z is alkyl or benzyl), and the ester is reacted with a substituted primary amine (R_1NH_2) in dimethylsulfoxide (DMSO) at elevated temperature of about 100°C to provide an anthranilic ester. The resulting aniline is then reacted with an appropriately protected hydrazine to provide the corresponding amide, for example as described in Scheme 1. The resulting amido aniline is then cyclized by reaction with phosgene, CDI, or the like to generate the quinazoline-2,4-dione. The cyclization typically is carried out in a solvent, such as ethereal solvents, chlorinated hydrocarbons such as chloroform, or aromatic hydrocarbons such as toluene, and in the presence of a base such as triethylamine or $NaHCO_3$. The quinazolin-2,4-dione ring system is then further modified as described in Scheme 20 to provide the desired 7-aryl (Ar) compound of Formula I.

Scheme 22

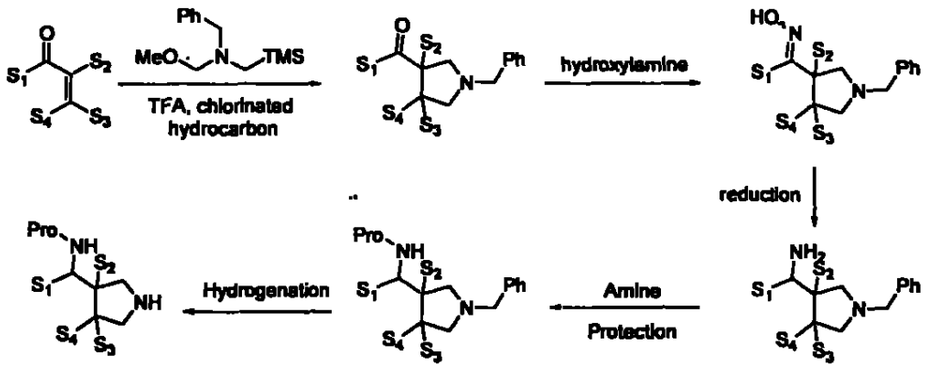


As noted above, R_7 in Formula I is referred to as the "side chain" of the 3-aminoquinazolin-2,4-dione nucleus. The R_7 side chains are any of those typically found on the quinolone antibiotics. Most of the R_7 side chain reactants that are required to make the Formula I compounds are readily available from commercial sources. Typical R_7 side chains are shown in Table A above.

The synthesis of the R_7 side chains can be accomplished by standard synthetic methods, for example as shown in the following schemes or as found in the literature. Those of ordinary skill in the art will be able to make any of the starting materials required to prepare the invention compounds, although most are available from commercial sources. The following schemes are provided to illustrate the synthesis of typical R_7 side chain reactants.

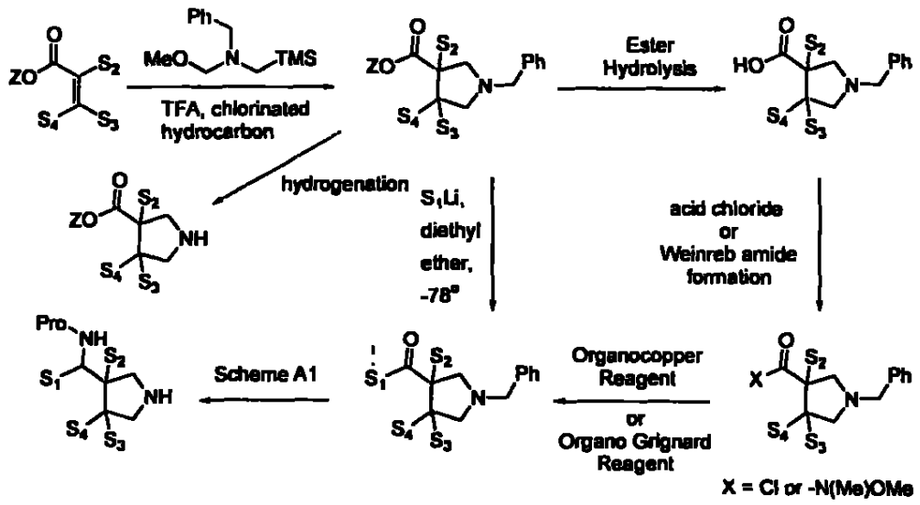
Scheme A1 illustrates the synthesis of typical pyrrolidines, which are preferred side chains (R_7) for invention compounds of Formula I. In Scheme A1, appropriately activated enones can undergo [3+2]cycloadditions under the conditions described by Tsuge et al. (Recent advances in azomethine ylid chemistry. In: Advances in Heterocyclic Chemistry [Katritsky A., ed.] San Diego: Academic Press, 231-349). These reactions are carried out in a chlorinated hydrocarbon solvent such as dichloromethane, chloroform, or dichloroethane and the like, and in the presence of a catalytic acid such as trifluoacetic acid, to provide substituted pyrrolidines (wherein S_1, S_2, S_3, and S_4 independently are alkyl, substituted alkyl, aryl, amino, alkyl and dialkylamino). These intermediates can then be treated with hydroxylamine or any O-alkylated or arylated hydroxylamine under a variety of conditions known to those skilled in the art to provide oximated substituted pyrrolidines. The oximes are reduced to amines with lithium aluminum hydride, diisobutylaluminum hydride, borane, or by selective catalytic hydrogenation. The resulting primary amines can then be protected using a number of methods as described in "Protecting Groups in Organic Synthesis" by Theodora Green (supra). The benzylic pyrrolidine can then be deprotected by hydrogenation, and the resulting pyrrolidine used in the preparation of 7-cyclic amino substituted 3-aminoquinazolinediones of Formula I as shown in the schemes above.

Scheme A1



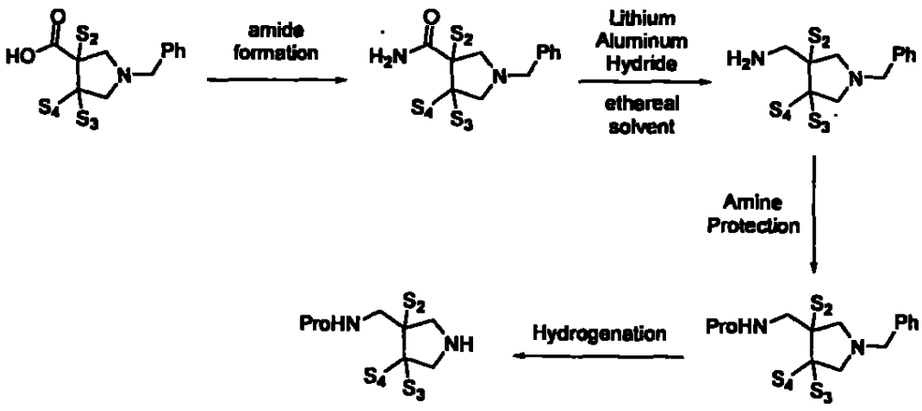
In Scheme A2, enoates (or vinylogous nitriles) may also be used in [3+2]cycloadditions to provide 3- and 4-substituted pyrrolidines. The ester (or nitrile) functionality can then be treated directly with alkyl lithium reagents at low temperature (0°C) in ether to provide S_1 substituted ketones, or the ester (Z is alkyl or benzyl) can be hydrolyzed under conditions usually employed by those skilled in the art to provide carboxylic acids. This intermediate can then be transformed into an acid chloride with oxalyl chloride and catalytic dimethyl formamide in solvents such as dichloromethane or chloroform or into an activated amide (Singh J., Satyamurthi N., Aidhen I., Singh J., *Prakt. Chem.* [Weinheim, Ger.], 2000;342(4):340-347). An acid chloride can be converted into a ketone using organocopper reagents (Lipshutz B.H., Sengupta S., *Org. React.* [N.Y.], 1992;41:135-631), and Weinreb amides can be converted into ketones according to the methods described by Weinreb (*Tetrahedron Lett.*, 1981;22(39):3815-3818) using organo Grignard reagents. The resulting ketones can then be converted into pyrrolidines (optionally substituted with S_2, S_3, and S_4) as described in Scheme A1. As noted above, pyrrolidines and substituted pyrrolidines are preferred R_7 groups in Formula I.

Scheme A2



In Scheme A3, 3-carboxylic acid N-benzyl substituted pyrrolidines (Scheme A2) can be converted into amides by a number of methods well-known to those who practice the art of organic synthesis. The amides can then be treated with lithium aluminum hydride in an ethereal solvent such as diethyl ether or tetrahydrofuran or the like to provide amines that can be protected as described in Scheme A1. Hydrogenation with palladium catalysis provides an appropriately substituted pyrrolidine (S_2, S_3, S_4 are independently alkyl, lower alkyl, aryl, etc.).

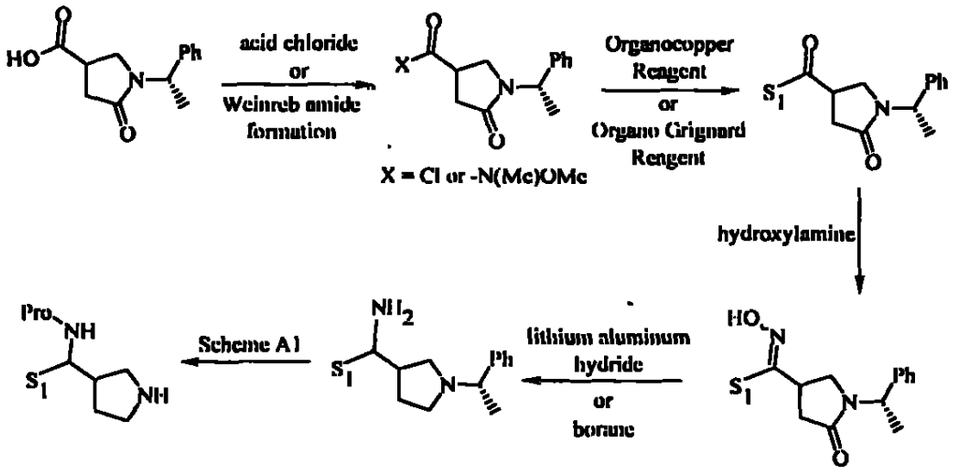
Scheme A3



In Scheme A4, a 3-carboxypyrrolidinone (Culbertson T.P., Domagala J.M., Nichols J.B., Pricbe S., Skeean R.W., *J. Med. Chem.*,

1987;30(10):1711-1715) can be converted into an acid chloride or Weinreb amide in the same fashion as that defined in Scheme A3. The acid chlorides are reacted with an organocopper reagent or an organo Grignard reagent (for a Weinreb amide) to provide a ketone that can be manipulated as described in Scheme A1 to provide an appropriately substituted pyrrolidine with a variety of substitutions at S_1 (alkyl, lower alkyl, substituted alkyl, aryl). The use of S-methylbenzyl (or R-methylbenzyl) as a protecting group for the pyrrolidine nitrogen allows for the separation of enantiomers and diastereomers at any step in the reaction sequence.

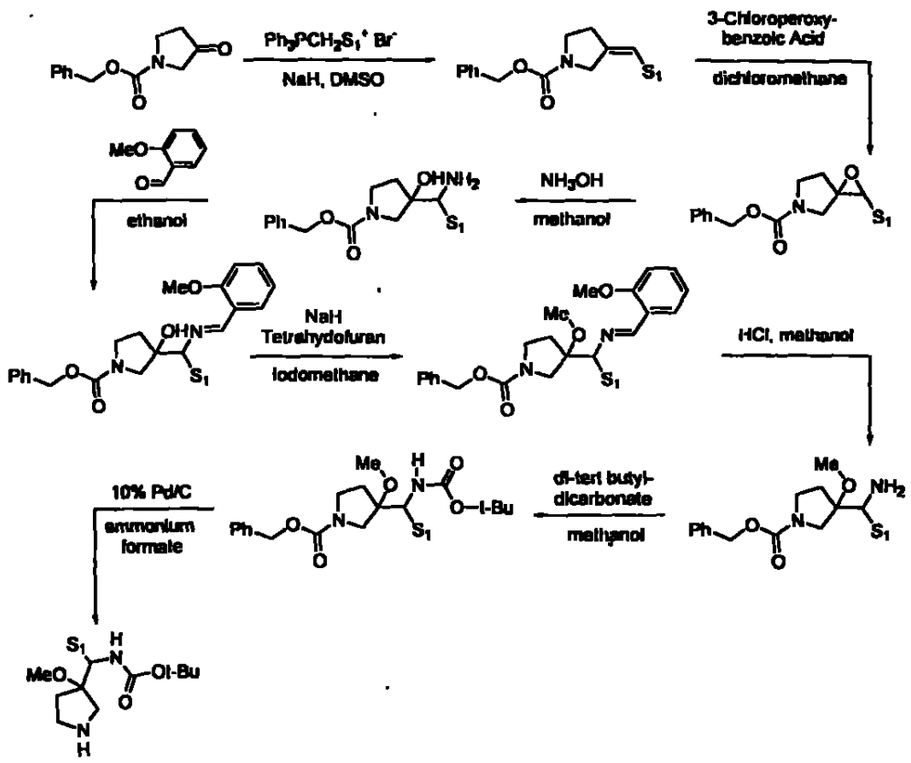
Scheme A4



In Scheme A5, carboxybenzyl protected 3-pyrrolidinone is reacted with a Wittig salt in the presence of sodium hydride or an equivalent in dimethylsulfoxide or any polar aprotic solvent to give an olefin. The resulting olefin is oxidized with 3-chloroperoxybenzoic acid in dichloromethane or other suitable chlorinated hydrocarbon to provide an epoxide. The epoxide is reacted with ammonium hydroxide in methanol, ethanol, dimethylformamide, dimethylacetamide or the like to generate an aminoalcohol. Methylation of the tertiary hydroxyl group can then be carried out by formation of a Schiff-base, followed by alkoxide formation with sodium hydride and treatment with iodomethane. Hydrolysis of the Schiff-base under standard conditions liberates the amine. Reaction of the amine with di-*tert*-butyldicarbonate in methanol, followed

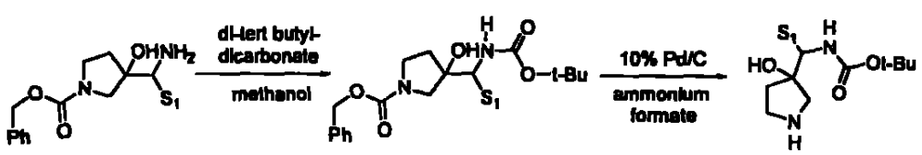
by hydrogenation via palladium catalysis provides R7 side chains (S_1 is alkyl, lower alkyl, and aryl) that can be used in the synthesis of compounds of Formula I.

Scheme A5



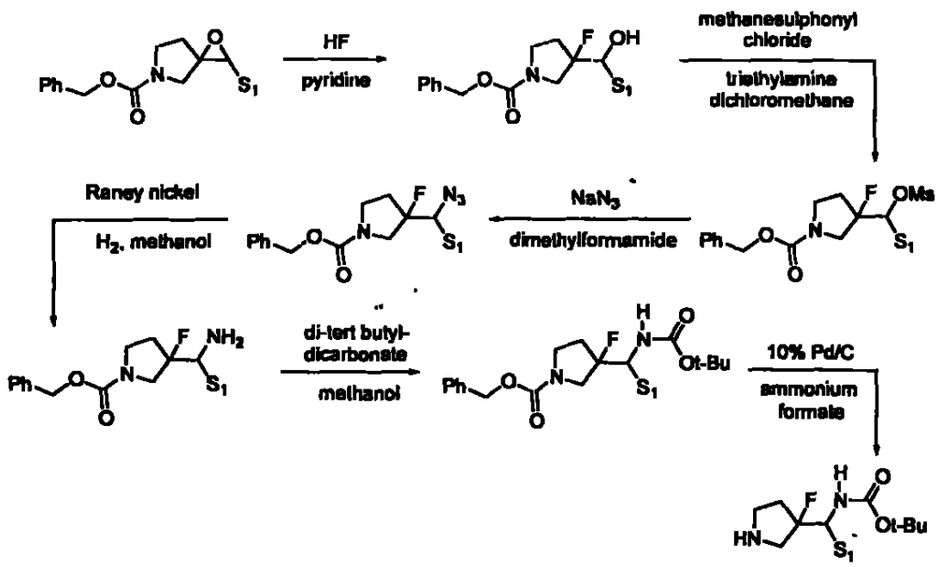
In Scheme A6, the aminoalcohol intermediate described in Scheme A5 is reacted with di-*tert*-butyldicarbonate in methanol to produce the N-protected intermediate. Other amine protection strategies familiar to those skilled in the art can also be utilized. Hydrogenation under palladium catalysis provides substituted pyrrolidine R7 side chains that are used in the synthesis of compounds of Formula I.

Scheme A6



In Scheme A7, an epoxide intermediate (Scheme A5) is selectively opened with hydrofluoric acid in pyridine, and the resulting secondary alcohol is reacted with methanesulfonylchloride, or an equivalent sulfonating reagent, in dichloromethane or another chlorinated hydrocarbon and triethylamine. Other appropriate bases include diisopropylethylamine, pyridine, collidine, *n*-methylmorpholine, and the like. The mesylate is then displaced by reaction with sodium azide, and the azide is reduced with Raney nickel under hydrogen pressure in methanol. Such transformations are well-precedented in the art. The resulting amine is then treated with di-tert-butyldicarbonate in methanol as shown in Schemes A4-A6, and the product is hydrogenated to provide the R_7 side chain as shown above.

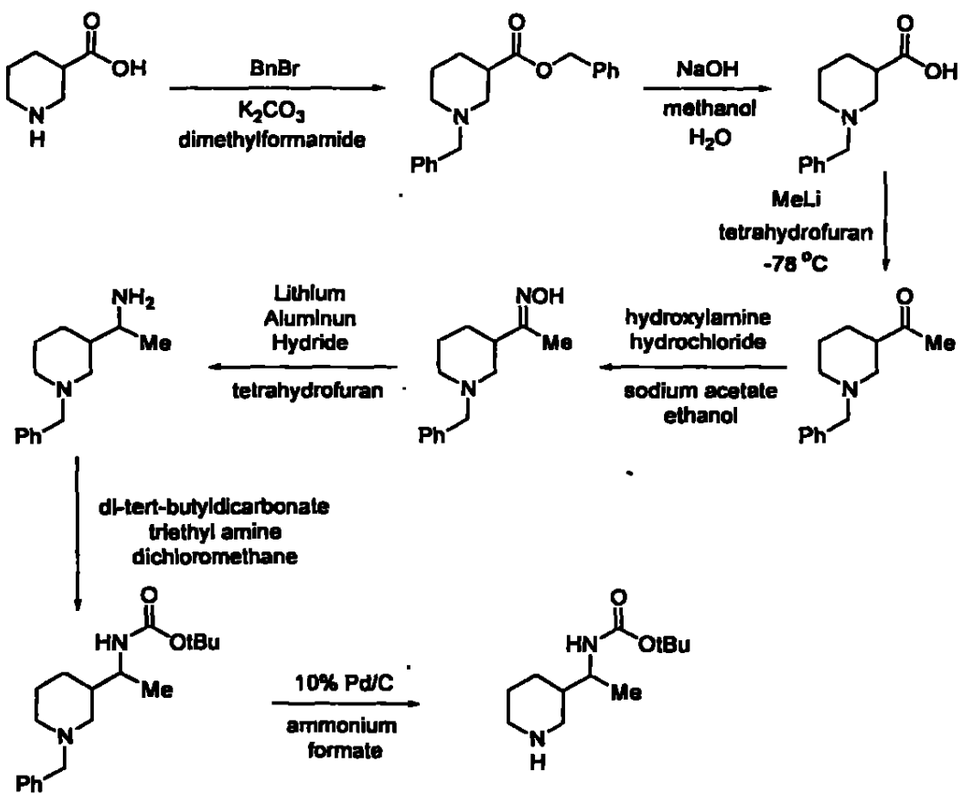
Scheme A7



The synthesis of 3-substituted piperidines is demonstrated in Scheme A8. Esterification and alkylation of 3-piperidine carboxylic acid is simultaneously accomplished by treatment with a benzylbromide in a polar solvent such as dimethylformamide or dimethylsulfoxide and a base such as potassium carbonate (K_2CO_3) or an equivalent. The ester is then hydrolyzed, and the resulting carboxylic acid is converted to a methyl ketone by treatment with methyllithium at low temperature (0°C). This intermediate is then converted to an oxime by a

number of methods known by those skilled in the art. The oxime is reduced with lithium aluminum hydride in tetrahydrofuran to provide an amine. The amine is reacted with di-*tert*-butyldicarbonate in dichloromethane and triethylamine as a base. As shown in Schemes A4-A6, the product is then hydrogenated to provide the R_7 side chain.

Scheme A8



It should be recognized from Schemes A1-A8 that substitutions on ring systems such as a pyrrolidine, piperazine, or piperidine ring will form chiral centers giving *R* and *S* enantiomers and diastereomers. Such enantiomers or diastereomers may be separated, if desired, by chiral HPLC at any stage. Resolution of any of the intermediates may be performed with techniques of fractional crystallization using mandelic acid, tartaric acid, or other chiral, optically pure acid resolving agents. Chiral benzylic amines can be used in the preparation of starting materials for the above schemes, and chiral amides may

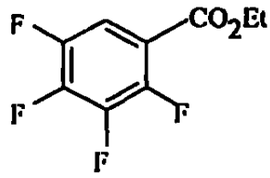
also be prepared using chiral acids, such as mandelic acid and the like. The isomers can then be separated and the chiral amine can be hydrogenated, or the chiral amide can be hydrolyzed.

The synthesis of invention compounds of Formula I is further illustrated by the following detailed examples. The examples are not to be construed as limiting the invention in scope or spirit to the specific procedures described. The starting materials and various intermediates utilized in the following examples may be obtained from commercial sources, or are readily prepared from commercially available organic compounds, using well-known synthetic methods.

EXAMPLE 1

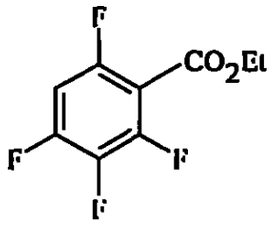
Synthesis of Benzoates

(a) 2,3,4,5-Tetrafluorobenzoic acid ethyl ester



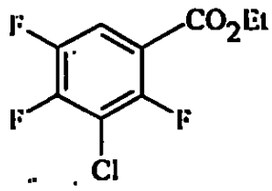
A solution of 2,3,4,5-tetrafluorobenzoic acid (4.68 g, 24.1 mmol) in dichloromethane (50 mL) at 0°C is treated with oxalyl chloride (11.5 mL, 132 mmol) followed by *N,N*-dimethylformamide (4 drops). The mixture is stirred at 0°C for 5 minutes and then at room temperature for 1.5 hours. The mixture is concentrated to dryness and subsequently co-evaporated from benzene. The resulting acid chloride is diluted with dichloromethane (50 mL), cooled to 0°C, and anhydrous ethanol (15.0 mL, 256 mmol) is added dropwise. The resulting solution is stirred at room temperature for 4.5 hours, then poured into saturated $NaHCO_3$ and extracted with chloroform. The combined organic extracts are washed with brine, dried over Na_2SO_4, filtered, and concentrated under vacuum to afford the title compound (5.37 g). ^1H NMR ($CDCl_3$): δ 7.67–7.55 (m, 1H), 4.42 (q, 2H), 1.41 (t, 3H).

(b) 2,3,4,6-Tetrafluorobenzoic acid ethyl ester



2,3,4,6-Tetrafluorobenzoic acid (4.8 g, 24.7 mmol) in dichloromethane (80 mL) is cooled to 0°C under a nitrogen atmosphere and treated with oxalyl chloride (11.2 mL, 128 mmol) followed by anhydrous *N,N*-dimethylformamide (2 drops). The mixture is warmed to room temperature and stirred for 2 hours. The solution is co-evaporated with benzene to yield an oil that is taken up in dichloromethane (80 mL), cooled to 0°C under an inert atmosphere, and treated with anhydrous ethanol (15 mL, 258 mmol). After 5 hours at room temperature, the solution is poured into saturated $NaHCO_3$ and extracted with chloroform. The organic phase is washed with brine, dried over Na_2SO_4, filtered, and concentrated under vacuum to provide the title compound (3.3 g). This material is used without further purification. ^1H NMR ($CDCl_3$): δ 6.93-6.75 (m, 1H), 4.42 (q, 2H), 1.39 (t, 3H).

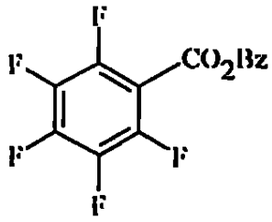
(c) 3-Chloro-2,4,5-trifluorobenzoic acid ethyl ester



To a solution of 3-chloro-2,4,5-trifluorobenzoic acid (Example 20, 4.90 g, 23.3 mmol) in dichloromethane (50 mL) is added oxalyl chloride (5.1 mL, 58.2 mmol) and *N,N*-dimethylformamide (1 drop). After 45 minutes, the reaction mixture is concentrated under vacuum. The resulting residue is dissolved in dichloromethane (50 mL) and treated with ethanol (10 mL, 172 mmol). After 30 minutes, the reaction mixture is diluted with dichloromethane and washed with saturated $NaHCO_3$, water, and brine. The organic layer is dried over $MgSO_4$,

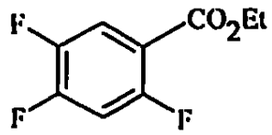
filtered, and the filtrate is concentrated to afford the title compound (5.59 g). ^{1}H NMR ($CDCl_3$): δ 7.76-7.68 (m, 1 H), 4.40 (q, 2 H), 1.39 (t, 3 H).

(d) 2,3,4,5,6-Pentafluorobenzoic acid benzyl ester



A solution of 2,3,4,5,6-pentafluorobenzoic acid (15.25 g, 71.9 mmol), 4-dimethylaminopyridine (4.4 g, 36.0 mmol) and benzyl alcohol (7.4 mL, 71.5 mmol) in dichloromethane (150 mL) is cooled to 0°C under an inert atmosphere. 1-[3-(Dimethylamino)propyl]-3-ethyl carbodiimide hydrochloride (16.7 g, 87.1 mmol) is added and the mixture stirred at 0°C for 2 hours. The mixture is warmed to ambient temperature, stirred for 24 hours, and then poured into brine. The mixture is extracted with chloroform and the organic phase washed with $NaHCO_3$, dried over Na_2SO_4, filtered and concentrated under vacuum to yield the title compound as a white solid (16.7 g). This material is used without further purification. ^{1}H NMR ($CDCl_3$): δ 7.49-7.27 (m, 5 H), 5.40 (s, 2 H).

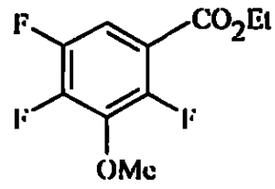
(e) 2,4,5-Trifluorobenzoic acid ethyl ester



To a solution of 2,4,5-trifluorobenzoic acid (10.85 g, 61.6 mmol) in dichloromethane (100 mL) is added oxalyl chloride (13.5 mL, 154 mmol) and *N,N*-dimethylformamide (1 drop). After 45 minutes, the reaction mixture is concentrated under vacuum. The resulting residue is dissolved in dichloromethane (100 mL), and to this solution is added ethanol (18 mL, 310 mmol). After 30 minutes, the reaction mixture is diluted with dichloromethane and washed with saturated $NaHCO_3$, water, and brine. The organic layer is dried over $MgSO_4$, filtered, and the filtrate is concentrated to afford the title compound as an oil

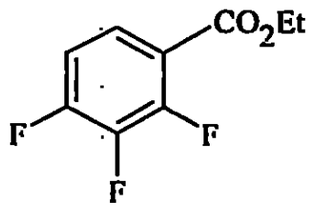
(12.23 g). ^{1}H NMR ($CDCl_3$): δ 7.85-7.73 (m, 1 H), 7.06-6.94 (m, 1 H), 4.38 (q, 2 H), 1.38 (t, 3 H).

(f) 2,4,5-Trifluoro-3-methoxybenzoic acid ethyl ester



A solution of 2,4,5-trifluoro-3-methoxybenzoic acid (2.513 g, 12.19 mmol) in dichloromethane (50 mL) at 0°C is treated with oxalyl chloride (5.4 mL, 61.9 mmol) followed by *N,N*-dimethylformamide (4 drops). The mixture is stirred at 0°C for 5 minutes and then at room temperature for 2.5 hours. The mixture is concentrated to near dryness and then co-evaporated from benzene. The resulting acid chloride is diluted with dichloromethane (50 mL), cooled to 0°C, and then anhydrous ethanol (7.30 mL, 124 mmol) is added dropwise. The resulting solution is stirred at room temperature for 4.5 hours, poured into saturated $NaHCO_3$ solution, and extracted with dichloromethane. The combined organic extracts are washed with brine, dried over Na_2SO_4, filtered, and concentrated under vacuum to afford the title compound as a light yellow liquid (2.82 g). ^{1}H NMR ($CDCl_3$): δ 7.47 (ddd, 1 H), 4.39 (q, 2 H), 4.05 (s, 3 H), 1.40 (t, 3 H).

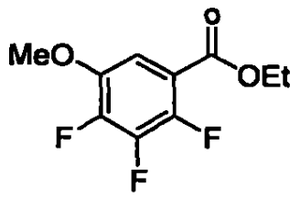
(g) 2,3,4-Trifluorobenzoic acid ethyl ester



To a solution of 2,3,4-trifluorobenzoic acid (10.85 g, 61.6 mmol) in dichloromethane (100 mL) is added oxalyl chloride (13.5 mL, 154 mmol) and N,N-dimethylformamide (3 drops). After 45 minutes, the reaction mixture is concentrated under vacuum. The resulting residue is dissolved in dichloromethane

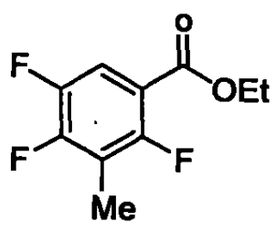
(100 mL) and to this solution is added ethanol (18 mL, 310 mmol). After 30 minutes, the reaction mixture is diluted with dichloromethane and washed with saturated $NaHCO_3$, water, and brine. The organic layer is dried over $MgSO_4$, filtered, and the filtrate is concentrated to afford the title compound as an oil (12.23 g). ^1H NMR ($CDCl_3$): δ 7.93-7.67 (m, 1 H), 7.09-6.96 (m, 1 H), 4.39 (q, 2 H), 1.40 (t, 3 H).

(h) 2,3,4-Trifluoro-5-methoxybenzoic acid ethyl ester



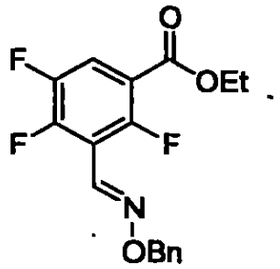
A solution of 2,3,4-trifluoro-5-methoxybenzoic acid (Hayashi et al., *Bull. Chem. Soc. Jap.*, 1972;45(9):2909-2914, 3.443 g, 16.7 mmol) in dichloromethane (100 mL) at 0°C is treated with oxalyl chloride (7 mL, 80 mmol) followed by *N,N*-dimethylformamide (4 drops). The mixture is stirred at room temperature for 3.5 hours, concentrated to near dryness, and co-evaporated with benzene. The acid chloride is then diluted with dichloromethane, cooled to 0°C, and treated with absolute ethanol (10 mL, 170 mmol). The resulting solution is stirred at room temperature for 20 hours, poured into saturated $NaHCO_3$ solution, and extracted with dichloromethane. The organic extracts are washed with brine, dried over Na_2SO_4, filtered, and concentrated under vacuum to afford the title compound (3.785 g). ^1H NMR (200 MHz, $CDCl_3$): δ 7.36-7.29 (m, 1H), 4.42 (q, 2H), 3.93 (s, 3H), 1.44 (t, 3H).

(i) 2,4,5-Trifluoro-3-methylbenzoic acid ethyl ester



A solution of 3-methyl-2,4,5-trifluorobenzoic acid (Shimizu T., Asai T., Kumai S., Jpn. Kokai Tokkyo Koho (1997) Japanese Appl. JP 95-219069, 4.3 g, 22.6 mmol) in dichloromethane (100 mL) at 0°C is treated with oxalyl chloride (4.2 g, 33 mmol) followed by *N,N*-dimethylformamide (2 drops). The mixture is stirred at room temperature for 3 hours, concentrated and dried in vacuo. The acid chloride is diluted with dichloromethane, cooled to 0°C, and treated with absolute ethanol (10 mL, 170 mmol). The resulting solution is stirred at room temperature for 20 hours, poured into saturated $NaHCO_3$ solution and extracted with dichloromethane. The organic extracts are washed with brine, dried over Na_2SO_4, filtered, and concentrated under vacuum to afford the title compound (3.8 g). ^1H NMR (200 MHz, $CDCl_3$): δ 7.67-7.26 (m, 1H), 4.44 (q, 2H), 2.27 (dd, 3H), 1.42 (t, 3H).

(j) 3-(Benzyloxyiminomethyl)-2,4,5-trifluorobenzoic acid ethyl ester



2,4,5-Trifluoro-3-formylbenzoic acid (Horiuchi N., Yonezawa T., Chiba K., Yoshida H., PCT Int.Appl. [1999] WO 97-JP2918), (5.70 g, 27.9 mmol), triethylamine (11 mL, 78.9 mmol), O-benzylhydroxylamine hydrochloride (4.47 g, 28.0 mmol) and anhydrous tetrahydrofuran (150 mL) are stirred at room temperature for 50 hours. The mixture is poured into brine and the pH adjusted to 5.5-6.0 using 1.0 M hydrochloric acid. The mixture is extracted with ethyl acetate. The organic phase is dried over Na_2SO_4, filtered, and concentrated in vacuo to provide 3-(benzyloxyiminomethyl)-2,4,5-trifluorobenzoic acid (8.63 g), which is used without further purification. ^1H NMR (200 MHz, $CDCl_3$): δ 9.82-9.18 (bs, 1H), 8.24 (s, 1H), 7.94-7.68 (m, 1H), 7.55-7.23 (m, 5H), 5.23 (d, 2H). MS (EI, M-1) m/z 308.

3-(Benzyloxyiminomethyl)-2,4,5-trifluorobenzoic acid (0.117 g, 0.378 mmol), 4-dimethylaminopyridine (0.023 g, 0.189 mmol), anhydrous ethanol (0.030 mL, 0.517 mmol) are mixed in dichloromethane (6 mL), cooled to 0°C, and treated with 1-ethyl-3-(3-dimethylaminopropyl)carbodiimide hydrochloride (0.082 g, 0.427 mmol). After 2 hours at 0°C and room temperature for 21 hours, the solvents are evaporated. The residue is dissolved in chloroform, washed with saturated $NaHCO_3$ and brine, dried over Na_2SO_4, filtered, and concentrated in vacuo. Purification by chromatography (1:8 ethyl acetate/hexanes) provided the title compound (0.068 g). ^1H NMR (200 MHz, $CDCl_3$): δ 8.27 (s, 1H), 7.87-7.66 (m, 1H), 7.49-7.28 (m, 5H), 5.27 (s, 2H), 4.48-4.29 (q, 2H), 1.46-1.31 (t, 3H).

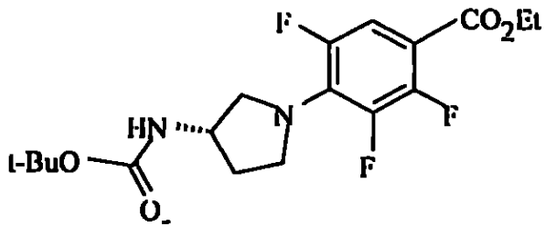
EXAMPLE 2

Synthesis of 4-Heterocyclic Benzoates

General Procedure

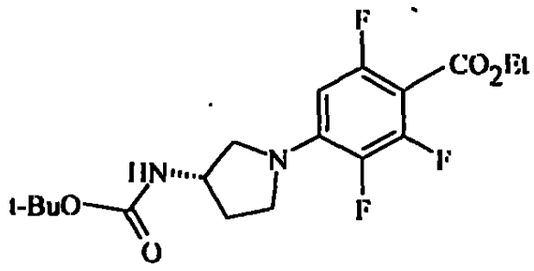
A mixture of 4-fluoro substituted benzoic acid ester (1 eq.), substituted pyrrolidine (1.3-2.5 eq.), and triethylamine (2-10 eq.) in *N,N*-dimethylacetamide or acetonitrile is heated to 50°C-100°C for 15 to 60 hours. The solution is then concentrated to near dryness, poured into saturated $NaHCO_3$ solution, and extracted with ethyl acetate. The combined organic extracts are washed with brine, dried over Na_2SO_4, filtered, and concentrated in vacuo. The resulting residue is purified by column chromatography (ethyl acetate/hexanes) to afford 4-pyrrolidinyl substituted benzoic acid esters.

(a) 4-[(S)-3-tert-Butoxycarbonylaminopyrrolidin-1-yl]-2,3,5-trifluorobenzoic acid ethyl ester



A solution of 2,3,4,5-tetrafluorobenzoic acid ethyl ester (Example 1a, 4.03 g, 18.1 mmol), (S)-pyrrolidin-3-ylcarbamic acid *tert*-butyl ester (4.02 g, 21.6 mmol) (Sanchez J.P., Domagala J.M., Heifetz C.L., Priebe S.R., Sesnie J.A., Trehan A.K., *J. Med. Chem.*, 1992;35(10):1764-1773), and triethylamine (18.0 mL, 129 mmol) in acetonitrile (50 mL) is heated at 50°C under a nitrogen atmosphere for 4.5 hours. The yellow solution is concentrated in vacuo and poured into a saturated $NaHCO_3$ solution. The mixture is then extracted with chloroform, and the combined organic extracts are washed with brine, dried with Na_2SO_4, filtered, and concentrated in vacuo. The resulting residue is then purified by flash column chromatography (1:7 ethyl acetate/hexanes) to afford the title compound (5.24 g). ^1H NMR ($CDCl_3$): δ 7.35 (ddd, 1H), 4.70-4.65 (bs, 1H), 4.42-4.20 (m, 3H), 3.90-3.62 (m, 3H), 3.58-3.42 (m, 1H), 2.28-2.03 (m, 1H), 1.99-1.80 (m, 1H), 1.46 (s, 9H), 1.37 (t, 3H).

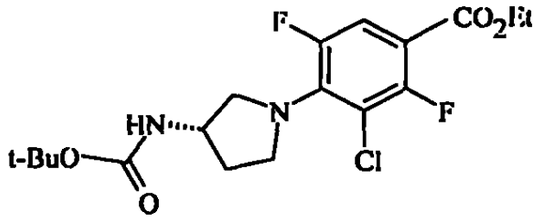
(b) 4-[(S)-3-tert-Butoxycarbonylaminopyrrolidin-1-yl]-2,3,6-trifluorobenzoic acid ethyl ester



A solution of 2,3,4,6-tetrafluorobenzoic acid ethyl ester (Example 1b, 5.1 g, 22.9 mmol), triethylamine (22 mL, 157 mmol), and (S)-pyrrolidin-3-ylcarbamic acid tert-butyl ester (5.2 g, 27.9 mmol) in acetonitrile (60 mL) is stirred at room temperature for 64 hours. The mixture is concentrated in vacuo and the residue dissolved in chloroform, washed with $NaHCO_3$ and then brine, dried over Na_2SO_4, filtered, and concentrated under vacuum to afford a solid. The solid is purified by column chromatography (1:1:7 ethyl acetate/chloroform/hexanes) to afford the title compound (6.21 g). ^1H NMR ($CDCl_3$): δ 6.07 (ddd, 1H),

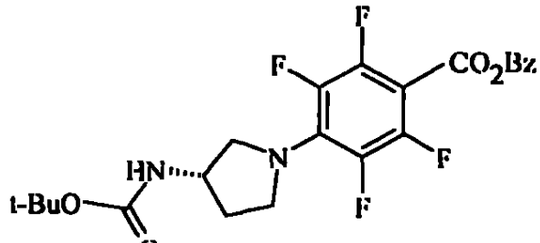
4.78-4.63 (bd, 1H), 4.49-4.22 (m, 3H), 3.80-3.68 (m, 1H), 3.66-3.28 (m, 3H), 2.33-2.13 (m, 1H), 2.04-1.83 (m, 1H), 1.45 (s, 9H), 1.36 (t, 3H).

(c) ***4-[(S)-3-tert-Butoxycarbonylaminopyrrolidin-1-yl]-3-chloro-2,5-difluorobenzoic acid ethyl ester***



To a solution of 3-chloro-2,4,5-trifluorobenzoic acid ethyl ester (Example 1c, 5.50 g, 23.05 mmol) in acetonitrile (25 mL) is added triethylamine (6.43 mL, 46.1 mmol) and (S)-pyrrolidin-3-ylcarbamic acid *tert*-butyl ester (4.72 g, 25.4 mmol). After 48 hours, the mixture is diluted with ethyl acetate and washed with saturated $NaHCO_3$, water, and brine. The organic layer is dried over $MgSO_4$, filtered, and the filtrate is concentrated to afford the title compound (9.34 g). MS CI: *m/z* 405 (MH^+).

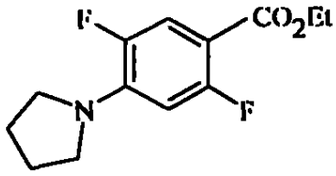
(d) ***4-[(S)-3-(tert-Butoxycarbonylamino)pyrrolidin-1-yl]-2,3,5,6-tetrafluorobenzoic acid benzyl ester***



A solution of 2,3,4,5,6-pentafluorobenzoic acid benzyl ester (Example 1d, 8.05 g, 26.6 mmol), triethylamine (26 mL, 186 mmol), and (S)-pyrrolidin-3-yl-carbamic acid *tert*-butyl ester (5.6 g, 30 mmol) in acetonitrile (150 mL) is stirred at room temperature for 24 hours. The solvent is removed under vacuum and the residue dissolved in chloroform, washed with $NaHCO_3$ and then brine, dried over Na_2SO_4, filtered, and concentrated in vacuo to afford a solid. The solid is then purified by column chromatography (1:1:6 ethyl acetate/chloroform/hexanes) to

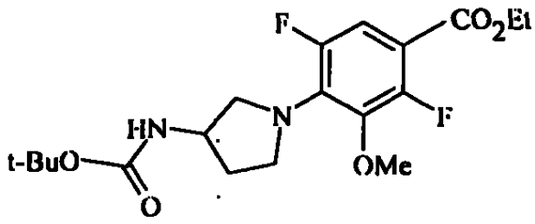
yield the title compound as a solid (7.92 g). ^{1}H NMR ($CDCl_3$): δ 7.48-7.30 (m, 5H), 5.35 (s, 2H), 4.77-4.50 (m, 1H), 4.37-4.19 (m, 1H), 4.01-3.63 (m, 3H), 3.59-3.46 (m, 1H), 2.29-2.09 (m, 1H), 2.01-1.82 (m, 1H), 1.45 (s, 9H).

(e) 4-(Pyrrolidin-1-yl)-2,5-difluorobenzoic acid ethyl ester



To a solution of 2,4,5-trifluorobenzoic acid ethyl ester (Example 1e, 4.32 g, 21.2 mmol) in acetonitrile (25 mL) is added triethylamine (5.9 mL, 42.3 mmol) and pyrrolidine (2.2 mL, 25.4 mmol). After 24 hours, the reaction mixture is diluted with ethyl acetate and washed with saturated $NaHCO_3$, water, and brine. The organic layer is dried over $MgSO_4$, filtered, and the filtrate is concentrated to afford the title compound as an oil (5.25 g). MS CI: *m/z* 256 (MH^+).

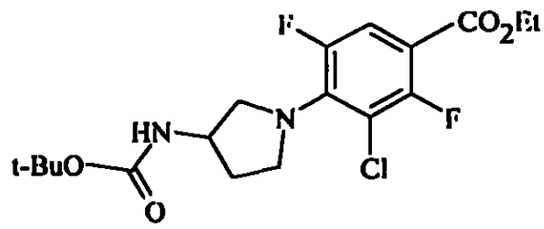
(f) 4-[3-(tert-Butoxycarbonylamino)pyrrolidin-1-yl]-2,5-difluoro-3-methoxybenzoic acid ethyl ester



A solution of 2,4,5-trifluoro-3-methoxybenzoic acid ethyl ester (Example 1f, 2.821 g, 12.05 mmol), pyrrolidin-3-ylcarbamic acid *tert*-butyl ester (3.310 g, 17.77 mmol), and triethylamine (9.13 g, 12.6 mL, 90.23 mmol) in acetonitrile (50 mL) is heated at 40°C under nitrogen for 2 days. The yellow solution is concentrated to near dryness and poured into saturated $NaHCO_3$ solution and extracted with dichloromethane. The combined organic extracts are washed with brine, dried over Na_2SO_4, filtered, and concentrated under vacuum. The resulting residue is purified by flash column chromatography

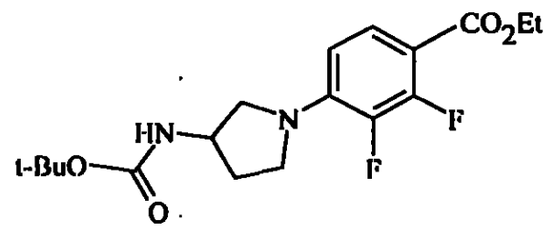
(1:7 ethyl acetate/hexanes) to afford the title compound as a yellow solid (3.743 g). MS EI: *m/z* 401 (MH^+).

(g) 4-[3-tert-Butoxycarbonylaminopyrrolidin-1-yl]-3-chloro-2,5-difluorobenzoic acid ethyl ester



To a solution of 3-chloro-2,4,5-trifluorobenzoic acid ethyl ester (Example 1c, 5.50 g, 23.05 mmol) in acetonitrile (25 mL) is added triethylamine (6.43 mL, 46.1 mmol) and pyrrolidin-3-ylcarbamic acid *tert*-butyl ester (4.72 g, 25.4 mmol). After 48 hours, the mixture is diluted with ethyl acetate and washed with saturated $NaHCO_3$, water, and brine. The organic layer is dried over $MgSO_4$, filtered, and the filtrate is concentrated to afford the title compound (9.2 g). MS CI: *m/z* 405 (MH^+).

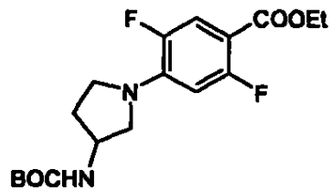
(h) 4-[3-(tert-Butoxycarbonylamino)pyrrolidin-1-yl]-2,3-difluorobenzoic acid ethyl ester



A solution of 2,3,4-trifluorobenzoic acid ethyl ester (Example 1g, 3.70 g, 18.1 mmol), pyrrolidin-3-ylcarbamic acid *tert*-butyl ester (4.02 g, 21.6 mmol), and triethylamine (18.0 mL, 129 mmol) in acetonitrile (50 mL) is heated at 50°C under nitrogen atmosphere for 4.5 hours. The solution is concentrated in vacuo and poured into a saturated $NaHCO_3$ solution. The mixture is then extracted with chloroform, and the combined organic extracts are washed with brine, dried with Na_2SO_4, filtered, and the mixture concentrated in vacuo. The resulting residue is

then purified by column chromatography (1:7 ethyl acetate/hexanes) to afford the title compound (4.70 g). ^{1}H NMR ($CDCl_3$): δ 7.59-7.49 (m, 1H), 6.35-6.26 (m, 1H), 4.88-4.84 (bd, 1H), 4.39-4.28 (m, 3H), 3.81-3.50 (m, 3H), 3.48-3.34 (m, 1H), 2.32-2.15 (m, 1H), 2.02-1.76 (m, 1H), 1.45 (s, 9H), 1.40 (t, 3H).

(i) ***4-(3-tert-Butoxycarbonylaminopyrrolidin-1-yl)-2,5-difluorobenzoic acid ethyl ester***



To a solution of 2,4,5-trifluorobenzoic acid ethyl ester (Example 1c, 14.8 g, 72.4 mmol) in acetonitrile (225 mL) is added triethylamine (65 mL, 466 mmol) and pyrrolidin-3-ylcarbamic acid tert-butyl ester (16.07 g, 86.2 mmol). After 45 hours, the reaction mixture is diluted with ethyl acetate and washed with saturated $NaHCO_3$, water, and brine. The organic layer is dried over $MgSO_4$, filtered, and the filtrate is concentrated to afford an oil. The resulting residue is purified by flash chromatography (1:5 ethyl acetate/hexanes) to afford the title compound. MS (ES, M+1) m/z 371, mp 98-100°C.

The following compounds are synthesized according to general procedures described in Examples 2a-i above.

(k) 4-(3-*tert*-Butoxycarbonylaminopyrrolidin-1-yl)-2,5-difluoro-3-methylbenzoic acid ethyl ester (MS ES, MH^+) m/z 385) using 2,4,5-trifluoro-3-methylbenzoic acid ethyl ester (Example 1i) and pyrrolidin-3-ylcarbamic acid *tert*-butyl ester.

(l) 4-[3-(*tert*-Butoxycarbonylaminomethyl)pyrrolidin-1-yl]-2,5-difluoro-3-methylbenzoic acid ethyl ester (MS ES, MH^+) m/z 399) using 2,4,5-trifluoro-3-methylbenzoic acid ethyl ester (Example 1i) and 3-(*tert*-butoxycarbonylaminomethyl)pyrrolidine (Rogers D.H., Saunders J., Williams J.P., DE 19955794).

(m) 4-(3-*tert*-Butoxycarbonylaminopyrrolidin-1-yl)-2,3-difluoro-5-methoxybenzoic acid ethyl ester (MS ES, MH^+) m/z 401) using 2,3,4-trifluoro-5-methoxybenzoic acid ethyl ester (Example 1h) and pyrrolidin-3-ylcarbamic acid *tert*-butyl ester.

(n) 4-[3-(*tert*-Butoxycarbonylaminomethyl)pyrrolidin-1-yl]-2,5-difluoro-3-methoxybenzoic acid ethyl ester (MS ES, MH^+) m/z 415) using 2,4,5-trifluoro-3-methoxybenzoic acid ethyl ester (Example 1l) and 3-(*tert*-butoxycarbonylaminomethyl)pyrrolidine (Rogers D.H., Saunders J., Williams J.P., DE 19955794).

(o) 4-(3-*tert*-Butoxycarbonylaminopyrrolidin-1-yl)-3-ethoxy-2,5-difluorobenzoic acid ethyl ester. (^1H NMR (200 MHz, $CDCl_3$): δ 7.31 (dd, 1H), 4.71 (bs, 1H), 4.34-3.4 (m, 9H), 2.23-1.81 (m, 2H), 1.45 (s, 9H), 1.37 (t, 3H), 1.33 (t, 3H); ((MS ES, MH^+) m/z 415.) using 3-ethoxy-2,5-difluorobenzoic acid ethyl ester (Sanchez J.P., Gogliotti R.D., Domagala J.M., Gracheck S.J., Huband M.D., Sesnie J.A., Cohen M.A., Shapiro M.A., *J. Med. Chem.*, 1995;38(22):4478-4487) and pyrrolidin-3-ylcarbamic acid *tert*-butyl ester.

(p) 3-(Benzyloxyiminomethyl)-4-(3-*tert*-butoxycarbonylaminopyrrolidin-1-yl)-2,5-difluorobenzoic acid ethyl ester (MS ES, MH^+) m/z 504) using 3-(benzyloxyiminomethyl)-2,4,5-trifluorobenzoic acid ethyl ester (Example 1j) and pyrrolidin-3-ylcarbamic acid *tert*-butyl ester.

(q) 3-Chloro-2,5-difluoro-4-(3-[1,2,3]-triazol-1-ylpyrrolidin-1-yl)benzoic acid ethyl ester (^1H NMR (200 MHz, $CDCl_3$): δ 7.79 (s, 1H), 7.65 (s, 1H), 7.41-7.51 (m, 1H), 5.40–5.30 (m, 1H), 4.34–4.24 (q, 2H), 4.13–3.45 (m, 4H), 2.65–2.50 (m, 1H), 2.43–2.28 (m, 1H), 1.34–1.27 (t, 3H)) using 3-chloro-2,4,5-trifluorobenzoic acid ethyl ester (Example 1c) and 1-pyrrolidin-3-yl-1H-[1,2,3]triazole (Singh R., Singh I.P., Thomas G., Singh M.P., Micetich R.G., Fahti-Afshar R., Doerksen T.R., PCT Int. Appl., 1992, WO 9210492 A1).

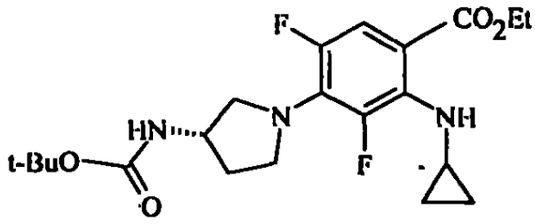
EXAMPLE 3

Synthesis of 2-Substituted-Amino Benzoates

General Procedure

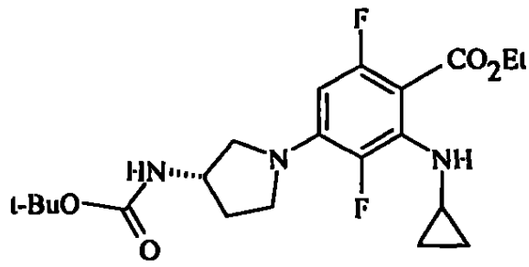
A solution of 4-(pyrrolidin-1-yl)-2-fluorobenzoic acid ethyl esters (Example 2) and cyclopropylamine (10-15 eq.) in dimethyl sulfoxide and triethylamine (2-5 eq.) is heated in a sealed glass tube for 3 days at 140°C. Compressed air is blown into the mixture to remove excess cyclopropylamine. The resulting solution is concentrated under vacuum and purified by column chromatography (ethyl acetate/hexanes) to afford 4-(substituted pyrrolidin-1-yl)-2-cyclopropylamino-benzoic acid esters.

(a) 4-[(S)-3-tert-Butoxycarbonylaminopyrrolidin-1-yl]-2-cyclopropylamino-3,5-difluorobenzoic acid ethyl ester



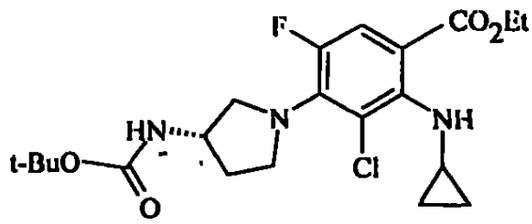
A solution of 4-[(S)-3-(*tert*-butoxycarbonylamino)pyrrolidin-1-yl]-2,3,5-trifluorobenzoic acid ethyl ester (Example 2a, 1.95 g, 5.01 mmol) and cyclopropylamine (14.0 mL, 201 mmol) in dimethyl sulfoxide (5 mL) is heated in a sealed glass tube for 44.5 hours at 100°C. Compressed air is blown into the black solution to remove excess cyclopropylamine. The solution is concentrated under high vacuum and purified by flash column chromatography (1:9 ethyl acetate/hexanes) to afford the title compound (1.77 g). ^{1}H NMR ($CDCl_3$): δ 7.32 (dd, 1H), 4.81-4.67 (bs, 1H), 4.35-4.16 (m, 3H), 3.95-3.40 (m, 4H), 2.92-2.80 (m, 1H), 2.25-2.08 (m, 1H), 1.97-1.77 (m, 1H), 1.46 (s, 9H), 1.34 (t, 3H), 0.72-0.63 (m, 2H), 0.57-0.49 (m, 2H).

(b) ***4-[(S)-3-tert-Butoxycarbonylaminopyrrolidin-1-yl]-2-cyclopropylamino-3,6-difluorobenzoic acid ethyl ester***



A solution of 4-[(S)-3-(*tert*-butoxycarbonylamino)pyrrolidin-1-yl]-2,3,6-trifluorobenzoic acid ethyl ester (Example 2b, 5.4 g, 13.9 mmol), cyclopropylamine (40 mL, 577 mmol), and dimethyl sulfoxide (28 mL) in a sealed glass tube is heated at 100°C for 27 hours. The excess amine is removed by blowing in compressed air before the solution is concentrated under high vacuum. The residue is then purified by column chromatography (1:1:8 ethyl acetate/ chloroform/hexanes) to afford the title compound (4.80 g). ^{1}H NMR ($CDCl_3$): δ 7.42 (bs, 1H), 5.69 (ddd, 1H), 4.76-4.61 (m, 1H), 4.37-4.19 (m, 3H), 3.81-3.66 (m, 1H), 3.65-3.43 (m, 2H), 3.39-3.28 (m, 1H), 2.98-2.82 (m, 1H), 2.30-2.09 (m, 1H), 1.98-1.82 (m, 1H), 1.45 (s, 9H), 1.34 (t, 3H), 0.72-0.68 (m, 2H), 0.67-0.44 (m, 2H).

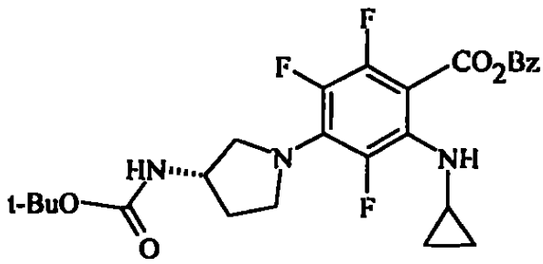
(c) ***4-[(S)-3-tert-Butoxycarbonylaminopyrrolidin-1-yl]-3-chloro-2-cyclopropylamino-5-fluorobenzoic acid ethyl ester***



A solution of 4-[(S)-3-(*tert*-butoxycarbonylamino)pyrrolidin-1-yl]-3-chloro-2,5-difluorobenzoic acid ethyl ester (Example 2c, 9.34 g, 23.1 mmol), cyclopropylamine (16 mL, 228 mmol), and dimethyl sulfoxide (30 mL) is heated in a sealed tube at 110°C for 3 days. After cooling to room temperature, the reaction mixture is diluted with ethyl acetate and washed with saturated $NaHCO_3$,

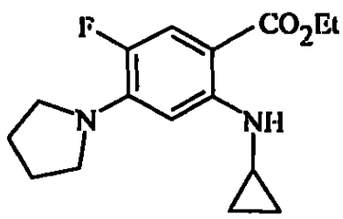
water, and brine. The organic layer is dried over $MgSO_4$, filtered, and the filtrate is concentrated to afford a brown residue. The residue is then purified via flash column chromatography (1:1 ethyl acetate/hexanes) to afford the title compound (4.41 g). MS CI: *m/z* 442 (MH^+).

(d) ***4-[(S)-3-tert-Butoxycarbonylaminopyrrolidin-1-yl]-2-cyclopropylamino-3,5,6-trifluorobenzoic acid benzyl ester***



A solution of 4-[(S)-3-(*tert*-butoxycarbonylamino)pyrrolidin-1-yl]-2,3,5,6-tetrafluorobenzoic acid benzyl ester (Example 2d, 2.5 g, 5.3 mmol), cyclopropylamine (40 mL, 577 mmol), and dimethyl sulfoxide (20 mL) in a sealed glass tube is heated at 80°C for 24 hours. The excess amine is removed by blowing in compressed air, and the solution is then concentrated under high vacuum. The residue is purified by column chromatography (1:1:7 ethyl acetate/ chloroform/hexanes) to afford the title compound as a solid (2.31 g). ^1H NMR ($CDCl_3$): δ 7.47-7.27 (m, 5H), 7.12 (bs, 1H), 5.30 (s, 2H), 4.78-4.62 (m, 1H), 4.35-4.17 (m, 1H), 3.96-3.56 (m, 3H), 3.54-3.39 (m, 1H), 2.91-2.73 (m, 1H), 2.24-2.02 (m, 1H), 1.96-1.77 (m, 1H), 1.45 (s, 9H), 0.69-0.56 (m, 2H), 0.53-0.40 (m, 2H).

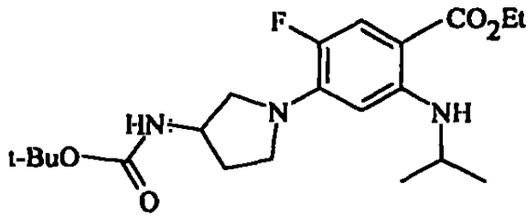
(e) ***2-Cyclopropylamino-5-fluoro-4-pyrrolindin-1-ylbenzoic acid ethyl ester***



4-(Pyrrolidin-1-yl)-2,5-difluorobenzoic acid ethyl ester (Example 2c, 5.25 g, 20.6 mmol) and cyclopropylamine (30 mL, 428 mmol) are stirred in

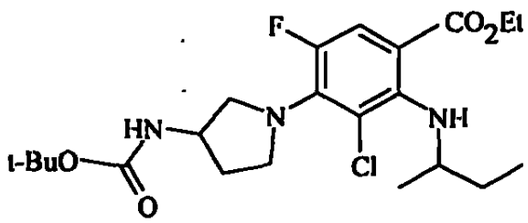
dimethyl sulfoxide (30 mL) at 110°C for 3 days in a sealed tube. After cooling to room temperature, the reaction mixture is diluted with ethyl acetate and washed with saturated $NaHCO_3$, water, and brine. The organic layer is dried over $MgSO_4$, filtered, and the filtrate concentrated to afford a brown residue. The residue is purified via flash column chromatography (1:9 hexanes/dichloromethane) to afford the title compound as a solid (5.39 g). MS CI: *m/z* 293 (MH^+).

(f) 4-[3-(tert-Butoxycarbonylamino)pyrrolidin-1-yl]-5-fluoro-2-isopropylaminobenzoic acid ethyl ester



4-[3-(*tert*-Butoxycarbonylamino)-pyrrolidin-1-yl]-2,5-difluorobenzoic acid ethyl ester (Example 2j, 5.4 g, 13.9 mmol), isopropylamine (40 mL, 469 mmol), and dimethyl sulfoxide (25 mL) are heated at 100°C for 4 days in a sealed glass tube. The excess amine is removed by blowing in compressed air. The residue is filtered and concentrated under vacuum to a thick oil. Purification by column chromatography (1:1:7 ethyl acetate/chloroform/hexanes) to provide the title compound as a solid (1.6 g). MS: *m/z* 410 (MH^+).

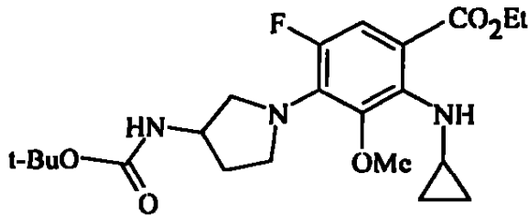
(g) 4-[(S)-3-(tert-butoxycarbonylamino)pyrrolidin-1-yl]-2-sec-butylamino-3-chloro-5-fluorobenzoic acid ethyl ester



4-[(S)-3-(*tert*-Butoxycarbonylamino)pyrrolidin-1-yl]-3-chloro-2,5-difluorobenzoic acid ethyl ester (Example 2c, 1.95 g, 4.81 mmol), *sec*-butylamine (30 mL, 296 mmol), and dimethyl sulfoxide (20 mL) are heated in a sealed glass tube at 110°C for 24 hours. The reaction mixture is evaporated, and purification

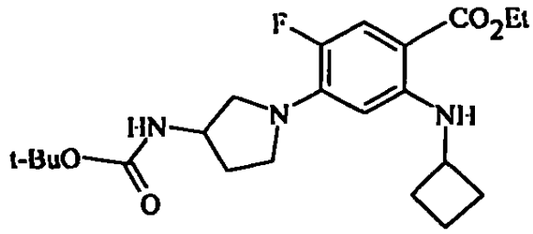
by column chromatography (1:8, ethyl acetate/hexanes) provides the title compound as a yellow syrup (3.69 g). MS EI: *m/z* 458 (MH^+).

(h) 4-[3-tert-butoxycarbonylamino)pyrrolidin-1-yl]-2-cyclopropylamino-5-fluoro-3-methoxybenzoic acid ethyl ester



A solution of 4-[3-(*tert*-butoxycarbonylamino)pyrrolidin-1-yl]-2,5-difluoro-3-methoxybenzoic acid ethyl ester (Example 2f, 3.087 g, 7.71 mmol) and cyclopropylamine (12.0 mL, 172 mmol) in dimethyl sulfoxide (5 mL) is heated in a sealed glass tube for 3 days at 110°C. Compressed air is blown into the black solution to remove excess cyclopropylamine. The solution is concentrated under vacuum and purified by flash column chromatography (1:5 ethyl acetate/hexanes) to afford the title compound as a yellow solid (0.875 g). ^1H NMR ($CDCl_3$): δ 7.33 (d, 1H), 7.15 (bs, 1H), 4.78-4.65 (m, 1H), 4.33-4.15 (m, 3H), 3.92-3.50 (m, 3H), 3.55 (s, 3H), 3.45-3.34 (m, 1H), 3.02-2.89 (m, 1H), 2.28-2.09 (m, 1H), 1.93-1.77 (m, 1H), 1.46 (s, 9H), 1.34 (t, 3H), 0.7-0.59 (m, 2H), 0.49-0.42 (m, 2H).

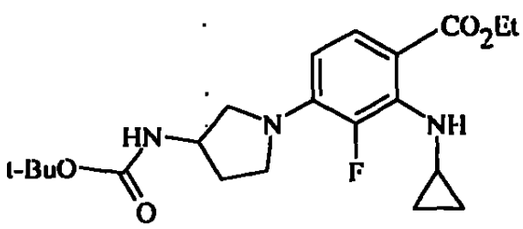
(i) 4-[3-tert-Butoxycarbonylamino)pyrrolidin-1-yl]-2-cyclobutylamino-5-fluorobenzoic acid ethyl ester



A solution of 4-[3-(*tert*-butoxycarbonylamino)pyrrolidin-1-yl]-2,5-difluorobenzoic acid ethyl ester (2j, 3.059 g, 8.26 mmol) and cyclobutylamine (15.0 mL, 175 mmol) in dimethyl sulfoxide (20 mL) is heated in a sealed vessel for 4 days at 110°C. Compressed air is blown into the black solution to remove

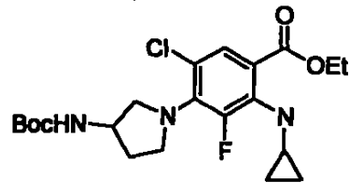
excess cyclobutylamine. The solution is concentrated under vacuum and purified by flash column chromatography (1:5 ethyl acetate/hexanes) to afford the title compound as a yellow solid (1.715 g). ^{1}H NMR ($CDCl_3$): δ 7.67 (bs, 1H), 7.48 (d, 1H), 5.54 (d, 1H), 4.77-4.64 (bs, 1H), 4.38-4.18 (m, 3H), 3.97-3.85 (m, 1H), 3.80-3.42 (m, 3H), 3.41-3.30 (m, 1H), 2.50-2.32 (m, 2H), 2.28-2.12 (m, 1H), 2.05-1.70 (m, 5H), 1.46 (s, 9H), 1.35 (t, 3H).

(j) 4-[3-(tert-Butoxycarbonylamino)pyrrolidin-1-yl]-2-cyclopropylamino-3-fluorobenzoic acid ethyl ester



A solution of 4-[3-(*tert*-butoxycarbonylamino)pyrrolidin-1-yl]-2,3-difluorobenzoic acid ethyl ester (Example 2h, 1.85 g, 5.01 mmol) and cyclopropylamine (14.0 mL, 201 mmol) in *N,N*-dimethylacetamide (5 mL) is heated in a sealed glass tube for 48 hours at 100°C. The solution is then concentrated under high vacuum and purified by column chromatography (1:9 ethyl acetate/hexanes) to afford the title compound (1.57 g). ^{1}H NMR ($CDCl_3$): δ 7.59 (bs, 1H), 7.57 (dd, 1H), 6.00 (dd, 1H), 4.82-4.68 (bd, 1H), 4.39-4.18 (m, 3H), 3.80-3.49 (m, 3H), 3.41-3.30 (m, 1H), 3.00-2.88 (m, 1H), 2.31-2.11 (m, 1H), 2.00-1.85 (m, 1H), 1.45 (s, 9H), 1.37 (t, 3H), 0.73-0.50 (m, 4H).

(k) 4-[3-(tert-Butoxycarbonylamino)pyrrolidin-1-yl]-5-chloro-2-cyclopropylamino-3-fluorobenzoic acid ethyl ester



A solution of 4-[3-(*tert*-butoxycarbonylamino)pyrrolidin-1-yl]-5-chloro-2,3-difluorobenzoic acid ethyl ester (Example 21, 3.75 g, 9.3 mmol) and cyclopropylamine (14.0 mL, 201 mmol) in *N,N*-dimethylacetamide (5 mL) is heated in a sealed glass tube for 48 hours at 100°C. The solution is then concentrated under high vacuum and purified by column chromatography (1:9 ethyl acetate/hexanes) to afford the title compound (2.0 g). ^{1}H NMR ($CDCl_3$): δ 7.64 (d, 1H), 7.56 (bs, 1H), 4.98-4.90 (bd, 1H), 4.40-4.20 (m, 3H), 3.78-3.63 (m, 4H), 2.97-2.83 (m, 1H), 2.35-2.21 (m, 1H), 1.93-1.81 (m, 1H), 1.46 (s, 9H), 1.38 (t, 3H), 0.75-0.61 (m, 2H), 0.57-0.50 (m, 2H).

The following compounds are synthesized according to general procedures Examples 3a-k described above.

(l) 4-(3-*tert*-Butoxycarbonylaminopyrrolidin-1-yl)-2-cyclopropylamino-5-fluoro-3-methylbenzoic acid ethyl ester ([MS ES, MH^+] m/z 422) using 4-(3-*tert*-butoxycarbonylaminopyrrolidin-1-yl)-2,5-difluoro-3-methyl-benzoic acid ethyl ester (Example 2k).

(m) 4-[3-(*tert*-Butoxycarbonylaminomethyl)pyrrolidin-1-yl]-2-cyclopropylamino-5-fluoro-3-methylbenzoic acid ethyl ester. ([MS ES, M+1] m/z 436) using 4-[3-(*tert*-butoxycarbonylaminomethyl)-pyrrolidin-1-yl]-2,5-difluoro-3-methylbenzoic acid ethyl ester (Example 2l).

(n) 4-(3-*tert*-Butoxycarbonylaminopyrrolidin-1-yl)-2-cyclopropylamino-3-fluoro-5-methoxybenzoic acid ethyl ester. ([MS ES, M+1] m/z 439) using 4-(3-*tert*-butoxycarbonylaminopyrrolidin-1-yl)-2,3-difluoro-5-methoxybenzoic acid ethyl ester (Example 2m).

(o) 4-[3-(*tert*-Butoxycarbonylaminomethyl)pyrrolidin-1-yl]-2-cyclopropylamino-5-fluoro-3-methoxybenzoic acid ethyl ester ([MS ES, MH^+] m/z 453) using 4-[3-(*tert*-butoxycarbonylaminomethyl)-pyrrolidin-1-yl]-2,5-difluoro-3-methoxybenzoic acid ethyl ester (Example 2n)

(p) 4-(3-*tert*-Butoxycarbonylaminopyrrolidin-1-yl)-2-cyclopropylamino-3-ethoxy-5-fluorobenzoic acid ethyl ester ([MS ES, MH^+]

m/z 452). using 4-(3-*tert*-butoxycarbonylaminopyrrolidin-1-yl)-3-ethoxy-2,5-difluorobenzoic acid ethyl ester (Example 2o).

(q) 3-(Benzyloxyiminomethyl)-4-(3-*tert*-butoxycarbonylaminopyrrolidin-1-yl)-2-cyclopropylamino-5-fluorobenzoic acid ethyl ([MS ES, MH^+] m/z 541) using 3-(benzyloxyiminomethyl)-4-(3-*tert*-butoxycarbonylaminopyrrolidin-1-yl)-2,5-difluorobenzoic acid ethyl ester (Example 2p).

(r) 3-Chloro-2-cyclopropylamino-5-fluoro-4-(3-[1,2,3]-triazol-1-yl-pyrrolidin-1-yl)benzoic acid ethyl ester (^1H NMR (200 MHz, $CDCl_3$): δ 8.00 (s, 1H), 7.73 (s, 1H), 7.52 (d, 1H), 7.19 (bs, 1H), 5.53-5.39 (m, 1H), 4.36-4.21 (q, 2H), 4.14-4.01 (m, 1H), 3.98-3.83 (m, 1H), 2.71-2.58 (m, 1H), 2.43-2.29 (m, 1H), 1.41-1.28 (t, 3H), 0.73-0.59 (m, 2H), 0.52-0.37 (m, 2H)) using 3-chloro-2,5-difluoro-4-(3-[1,2,3]-triazol-1-yl-pyrrolidin-1-yl)benzoic acid ethyl ester (Example 2q)

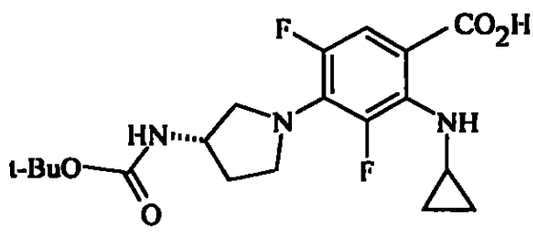
EXAMPLE 4

Ester Hydrolysis

General Procedure

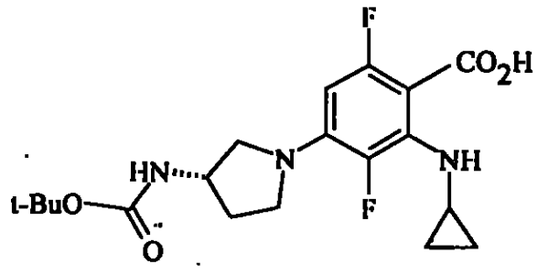
A solution of 4-(substituted-pyrrolidin-1-yl)-2-cyclopropylaminobenzoic acid ester (Example 3) and aqueous sodium hydroxide (10-20 eq., 1.0N) in tetrahydrofuran and methanol is heated for 16 to 24 hours at 70°C. The solution is cooled, diluted with water, and partially concentrated under vacuum. The resulting solution is acidified to pH 6 with aqueous 1.0*N* hydrochloric acid, then the pH is adjusted to pH 7-8 with 5% $NaHCO_3$ solution and extracted with ethyl acetate. The combined organic extracts are dried over Na_2SO_4, filtered, and concentrated in vacuo to afford 4-(substituted-pyrrolidin-1-yl)-2-cyclopropylaminobenzoic acid.

(a) 4-[(S)-3-tert-Butoxycarbonylaminopyrrolidin-1-yl]-2-cyclopropylamino-3,5-difluorobenzoic acid



A solution of 4-[(S)-3-*tert*-butoxycarbonylamino)pyrrolidin-1-yl]-2-cyclopropylamino-3,5-difluorobenzoic acid ethyl ester (Example 3a, 1.40 g, 3.29 mmol) and aqueous sodium hydroxide (1.33 *N*, 15.0 mL, 20.0 mmol) in tetrahydrofuran (20 mL) and methanol (50 mL) is heated for 3 hours at 50°C. The solution is cooled, diluted with water, and partially concentrated in vacuo. The resulting solution is acidified to pH 6 with aqueous 1*N* hydrochloric acid, and then the pH is adjusted to pH 7-8 with 5% $NaHCO_3$ and extracted with chloroform. The combined organic extracts are dried over Na_2SO_4, filtered, and concentrated to give the title compound as a pale yellow solid (1.31 g). ^1H NMR (DMSO-d_6): δ 12.65 (bs, 1H), 7.48 (bs, 1H), 7.27-7.14 (m, 2H), 4.08-3.92 (m, 1H), 3.85-3.45 (m, 3H), 3.45-3.29 (m, 1H), 2.86-2.74 (m, 1H), 2.10-1.91 (m, 1H), 1.89-1.72 (m, 1H), 1.39 (s, 9H), 0.71-0.60 (m, 2H), 0.47-0.38 (m, 2H).

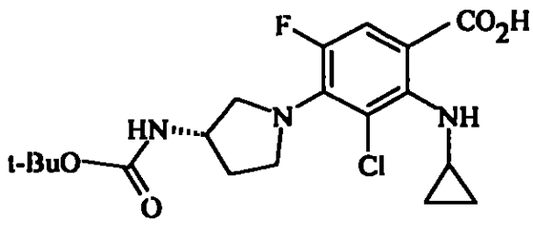
(b) 4-[(S)-3-tert-Butoxycarbonylaminopyrridin-1-yl]-2-cyclopropylamino-3,6-difluorobenzoic acid



A solution of 4-[(S)-3-*tert*-butoxycarbonylamino)pyrrolidin-1-yl]-2-cyclopropylamino-3,6-difluorobenzoic acid ethyl ester (Example 3b, 1.45 g, 3.40 mmol) and aqueous sodium hydroxide (1.33*N*, 17.0 mL, 22.6 mmol) in tetrahydrofuran (20 mL) and methanol (50 mL) is heated for 21 hours at 50°C.

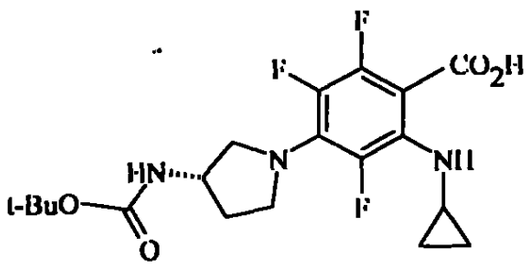
The solution is cooled, diluted with water, and then partially concentrated in vacuo. The resulting solution is acidified to pH 6 with aqueous 1*N* hydrochloric acid, and then the pH is adjusted to pH 7-8 with 5% $NaHCO_3$ and extracted with ethyl acetate three times. The combined organic extracts are dried over Na_2SO_4, filtered, and concentrated under vacuum to give the title compound as a pale green solid (1.33 g). ^{1}H NMR (DMSO-d_6): δ 7.21 (bd, 1H), 5.83 (dd, 1H), 4.12-3.98 (m, 1H), 3.75-3.20 (m, 5H), 2.88-2.78 (m, 1H), 2.14-1.96 (m, 1H), 1.90-1.73 (m, 1H), 1.39 (s, 9H), 0.69-0.59 (m, 2H), 0.45-0.36 (m, 2H).

*(c) **4-[(S)-3-tert-Butoxycarbonylaminopyrrolidin-1-yl]-3-chloro-2-cyclopropylamino-5-fluoro-benzoic acid***



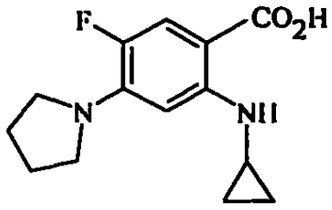
To a solution of 4-[(S)-3-(*tert*-butoxycarbonylamino)pyrrolidin-1-yl]-3-chloro-2-cyclopropylamino-5-fluorobenzoic acid ethyl ester (Example 3c, 2.90 g, 6.56 mmol) in methanol (30 mL) and tetrahydrofuran (30 mL) is added a 1*N* solution of sodium hydroxide (50 mL). The reaction mixture is stirred at 80°C for 20 hours, cooled to room temperature, and diluted with ethyl acetate. The organic layer is washed with 1*N* hydrochloric acid, water, and brine. The organic layer is dried over $MgSO_4$, filtered, and filtrate concentrated to the title compound as a solid (2.74 g). MS CI: *m/z* 414 (MH^+).

(d) ***4-[(S)-3-tert-Butoxycarbonylaminopyrrolidin-1-yl]-2-cyclopropylamino-3,5,6-trifluorobenzoic acid***



A solution of benzyl 4-[(S)-3-(*tert*-butoxycarbonylamino)pyrrolidin-1-yl]-2-cyclopropylamino-3,5,6-trifluorobenzoate (Example 3d, 3.68 g, 7.31 mmol), 1.0 M NaOH (75 mL), methanol (50 mL), and tetrahydrofuran (50 mL) is heated at 50°C for 24 hours. The mixture is partially concentrated under vacuum and then extracted with dichloromethane. The aqueous phase is brought to pH 7.5 using 1.0 M HCl and extracted with ethyl acetate. The combined ethyl acetate extracts are dried over Na_2SO_4, filtered, and concentrated under vacuum to afford 4-[(S)-3-*tert*-butoxycarbonylamino-pyrridin-1-yl]-2-cyclopropylamino-3,5,6-trifluoro-benzoic acid as a solid (2.9 g). This material is used without further purification. ^{1}H NMR (DMSO-d_6): δ 7.19 (bd, 1H), 4.12-3.95 (m, 1H), 3.83-3.52 (m, 3H), 3.48-3.33 (m, 1H), 2.83-2.69 (m, 1H), 2.10-1.94 (m, 1H), 1.89-1.72 (m, 1H), 1.49 (s, 9H), 0.70-0.56 (m, 2H), 0.44-0.33 (m, 2H).

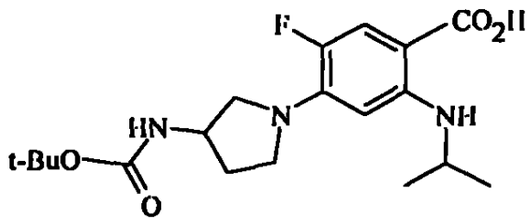
(e) ***2-Cyclopropylamino-5-fluoro-4-pyrrolidin-1-ylbenzoic acid***



To a solution of 4-(pyrrolidin-1-yl)-2-cyclopropylamino-5-fluorobenzoic acid ethyl ester (Example 3e, 3.10 g, 10.4 mmol) in methanol (50 mL) and tetrahydrofuran (20 mL) is added 1*N* solution of sodium hydroxide (35 mL). The reaction mixture is stirred at 80°C for 20 hours, cooled to room temperature, and diluted with ethyl acetate. The organic layer is washed with 1*N* hydrochloric acid,

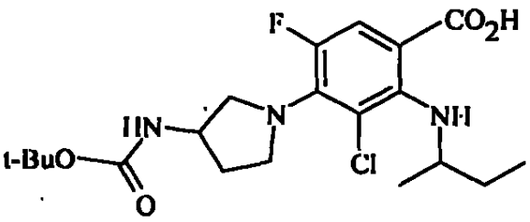
water, and brine. The organic layer is dried over $MgSO_4$, filtered, and the filtrate concentrated to afford the title compound as a solid (2.47 g). MS CI: *m/z* 263 (M^+).

(f) ***4-[3-tert-Butoxycarbonylamino)pyrrolidin-1-yl]-5-fluoro-2-isopropylaminobenzoic acid***



A solution of 4-[3-(*tert*-butoxycarbonylamino)pyrrolidin-1-yl]-5-fluoro-2-isopropylaminobenzoic acid ethyl ester (Example 3f, 1.5 g, 3.40 mmol), aqueous 1 M sodium hydroxide (50 mL), tetrahydrofuran (40 mL), and methanol (40 mL) are heated for 25 hours at 70°C. The solution is cooled, diluted with water, and then partially concentrated. The resulting solution is acidified to pH 7-8 with aqueous 1.0 M hydrochloric acid and extracted with ethyl acetate. The combined organic extracts are dried over Na_2SO_4, filtered, and concentrated under vacuum to give the title compound as a solid (1.25 g). MS EI: *m/z* 380 (M^+).

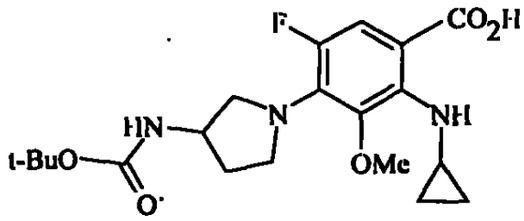
(g) ***4-[3-(tert-Butoxycarbonylamino)pyrrolidin-1-yl]-2-sec-butylamino-3-chloro-5-fluorobenzoic acid***



A solution of 4-[3-*tert*-butoxycarbonylamino)pyrrolidin-1-yl]-2-*sec*-butylamino-3-chloro-5-fluorobenzoic acid ethyl ester (Example 3g, 3.57 g, 7.79 mmol), 1.0N sodium hydroxide (50 mL), and methanol (80 mL) are heated at 80°C for 16.5 hours. The mixture is partially evaporated, diluted with water (150 mL), and the pH adjusted to 7.0-8.0 using 1.0 M hydrochloric acid. The

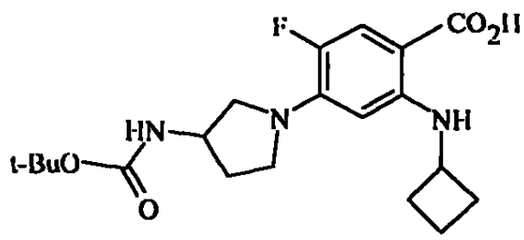
mixture is extracted with ethyl acetate, dried over Na_2SO_4, and concentrated under vacuum to give the title compound as an off-white solid (3.26 g) which is used without further purification. MS EI: *m/z* 430 (M^+).

(h) 4-[3-tert-Butoxycarbonylamino)pyrrolidin-1-yl]-2-cyclopropylamino-5-fluoro-3-methoxybenzoic acid



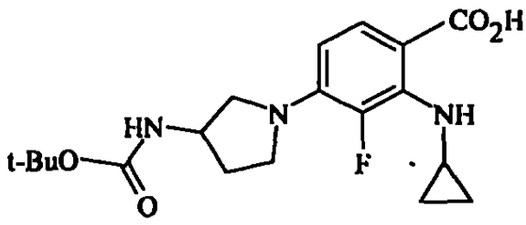
A solution of 4-[3-*tert*-butoxycarbonylamino)pyrrolidin-1-yl]-2-cyclopropylamino-5-fluoro-3-methoxybenzoic acid ethyl ester (Example 3h, 0.173 g, 0.395 mmol) and aqueous sodium hydroxide (1.33*N*, 2.0 mL, 2.66 mmol) in tetrahydrofuran (10 mL) and methanol (30 mL) is heated for 22 hours at 70°C. The solution is cooled, diluted with water, and partially concentrated under vacuum. The resulting solution is acidified to pH 6 with aqueous 1*N* hydrochloric acid, and then the pH is adjusted to pH 7-8 with 5% $NaHCO_3$ solution and extracted with ethyl acetate. The combined organic extracts are dried over Na_2SO_4, filtered, and concentrated in vacuo to afford the title compound as a yellow solid (0.160 g). ^1H NMR ($CDCl_3$): δ 7.46 (d, 1H), 4.80-4.69 (bs, 1H), 4.33-4.18 (m, 1H), 3.90-3.45 (m, 3H), 3.62 (s, 3H), 3.43-3.32 (m, 1H), 2.91-2.80 (m, 1H), 2.28-2.10 (m, 1H), 1.96-1.78 (m, 1H), 1.46 (s, 9H), 0.63-0.52 (m, 4H).

(i) 4-[3-tert-Butoxycarbonylamino)pyrrolidin-1-yl]-2-cyclobutylamino-5-fluorobenzoic acid



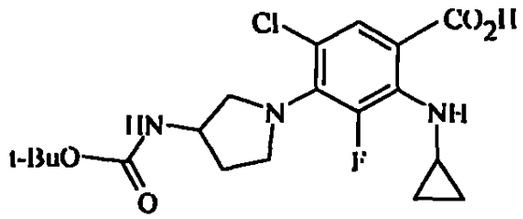
A solution of 4-[3-*tert*-butoxycarbonylamino)pyrrolidin-1-yl]-2-cyclobutylamino-5-fluorobenzoic acid ethyl ester (Example 3i, 1.51 g, 3.58 mmol) and aqueous sodium hydroxide (1.33*N*, 20.0 mL, 26.6 mmol) in tetrahydrofuran (15 mL) and methanol (40 mL) is refluxed for 19 hours. The solution is cooled, diluted with water, and partially concentrated under vacuum. The resulting solution is acidified to pH 6 with aqueous 1.0*N* hydrochloric acid, and then the pH is adjusted to pH 7-8 with 5% $NaHCO_3$ solution and extracted with ethyl acetate. The combined organic extracts are dried over Na_2SO_4, filtered, and concentrated under vacuum to afford the title compound as a yellow solid (1.353 g). MS EI: *m/z* 394 (MH^+).

(j) 4-[3-(tert-Butoxycarbonylamino)pyrrolidin-1-yl]-2-cyclopropylamino-3-fluorobenzoic acid



A solution of 4-[3-(*tert*-butoxycarbonylamino)pyrrolidin-1-yl]-2-cyclopropylamino-3-fluorobenzoic acid ethyl ester (Example 3j, 1.34 g, 3.29 mmol) and aqueous sodium hydroxide (2N, 20 mL) in tetrahydrofuran (20 mL) and methanol (20 mL) is refluxed for 1 hour. The solution is partially concentrated in vacuo, then acidified to pH 6 and extracted with chloroform. The combined organic extracts are dried over Na_2SO_4, filtered, and concentrated to give the title compound (1.40 g). ^1H NMR ($CDCl_3$): δ 7.59 (dd, 1H), 6.06 (dd, 1H), 4.80-4.70 (bd, 1H), 4.38-4.22 (m, 1H), 3.79-3.50 (m, 3H), 3.47-3.35 (m, 1H), 2.98-2.87 (m, 1H), 2.30-2.14 (m, 1H), 1.97-1.84 (m, 1H), 1.46 (s, 9H), 0.69-0.54 (m, 4H).

(k) 4-[3-(tert-Butoxycarbonylamino)pyrrolidin-1-yl]-5-chloro-2-cyclopropylamino-3-fluorobenzoic acid



A solution of 4-[3-(*tert*-butoxycarbonylamino)pyrrolidin-1-yl]-5-chloro-2-cyclopropylamino-3-fluorobenzoic acid ethyl ester (Example 3k, 2.00 g, 4.50 mmol) and aqueous sodium hydroxide (2.0N, 20 mL) in tetrahydrofuran (20 mL), and methanol (20 mL) is refluxed for 1 hour. The solution is partially concentrated in vacuo, acidified to pH 6, and extracted with chloroform. The combined organic extracts are dried over Na_2SO_4, filtered, and concentrated to give the title compound (1.70 g). ^1H NMR ($CDCl_3$): δ 7.71 (d, 1H), 4.91-4.82 (bd, 1H), 4.40-4.25 (m, 1H), 3.77-3.69 (m, 2H), 3.53-3.34 (m, 2H), 3.00-2.88 (m, 1H), 2.24-2.15 (m, 1H), 1.90-1.80 (m, 1H), 1.46 (s, 9H), 0.72-0.54 (m, 4H).

The following compounds are synthesized according to general procedures of Examples 4a-k.

(l) 4-(3-*tert*-Butoxycarbonylaminopyrrolidin-1-yl)-2-cyclopropylamino-5-fluoro-3-methylbenzoic acid ([MS ES, MH^+] m/z 394.) using 4-(3-*tert*-butoxycarbonylaminopyrrolidin-1-yl)-2-cyclopropylamino-5-fluoro-3-methylbenzoic acid ethyl ester (Example 3l).

(m) 4-[3-(*tert*-Butoxycarbonylaminomethyl)pyrrolidin-1-yl]-2-cyclopropylamino-5-fluoro-3-methylbenzoic acid ([MS ES, M+1] m/z 408) using 4-[3-(*tert*-butoxycarbonylaminomethyl)pyrrolidin-1-yl]-2-cyclopropylamino-5-fluoro-3-methylbenzoic acid ethyl ester (Example 3m).

(n) 4-(3-*tert*-Butoxycarbonylaminopyrrolidin-1-yl)-2-cyclopropylamino-3-fluoro-5-methoxybenzoic acid (^1H NMR (200 MHz, $CDCl_3$): δ 12.50 (bs, 1H), 7.18-7.09 (m, 1H), 7.07 (d, 1H), 4.07-3.90 (m, 1H),

3.80-3.50 (m, 2H), 3.66 (s, 3H), 3.42-3.29 (m, 2H), 2.88-2.71 (m, 1H), 2.10-1.91 (m, 1H), 1.86-1.67 (m, 1H), 1.39 (s, 9H), 0.70-0.57 (m, 2H), 0.46-0.32 (m, 2H)) using 4-(3-*tert*-butoxycarbonylaminopyrrolidin-1-yl)-2-cyclopropylamino-3-fluoro-5-methoxy-benzoic acid ethyl ester (Example 3n).

(o) 4-[3-(*tert*-Butoxycarbonylaminomethyl)pyrrolidin-1-yl]-2-cyclopropylamino-5-fluoro-3-methoxybenzoic acid. ([MS ES, M+1] m/z 424) using 4-[3-(*tert*-butoxycarbonylaminomethyl)pyrrolidin-1-yl]-2-cyclopropylamino-5-fluoro-3-methoxybenzoic acid ethyl ester (Example 3o)

(p) 4-(3-*tert*-Butoxycarbonylaminopyrrolidin-1-yl)-2-cyclopropylamino-3-ethoxy-5-fluorobenzoic acid ([MS ES, MH^+] m/z 424) using 4-(3-*tert*-butoxycarbonylaminopyrrolidin-1-yl)-2-cyclopropylamino-3-ethoxy-5-fluorobenzoic acid ethyl ester (Example 3p).

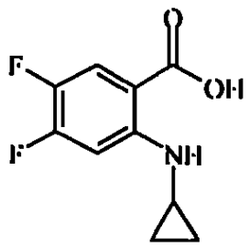
(q) 3-(Benzyloxyiminomethyl)-4-(3-*tert*-butoxycarbonylaminopyrrolidin-1-yl)-2-cyclopropylamino-5-fluorobenzoic acid (MS ES: m/z 513 (MH+]) using 3-(benzyloxyiminomethyl)-4-(3-*tert*-butoxycarbonylamino-pyrrolidin-1-yl)-2-cyclopropylamino-5-fluorobenzoic acid ethyl ester (Example 3q)

(r) 3-Chloro-2-cyclopropylamino-5-fluoro-4-(3-[1,2,3-triazol]-1-yl-pyrrolidin-1-yl)benzoic acid (^{1}H NMR (200 MHz, $CDCl_3$): δ 8.50 (bs, 1H), 8.03 (s, 1 H), 7.72 (s, 1H), 7.60 (d, 1H), 7, 5.54-5.39 (m, 1H), 4.13-3.97 (m, 1H), 3.92-3.85 (m, 1H), 3.68-3.63 (m, 1H), 3.54-3.42 (m, 1H), 3.10-3.00 (m, 1H), 2.78-2.60 (m, 1H), 2.39-2.33 (m, 1H), 0.70-0.58 (m, 2H), 0.58-0.46 (m, 2H)) using 3-chloro-2-cyclopropylamino-5-fluoro-4-(3-[1,2,3-triazol]-1-yl-pyrrolidin-1-yl)benzoic acid ethyl ester (Example 3r).

EXAMPLE 5

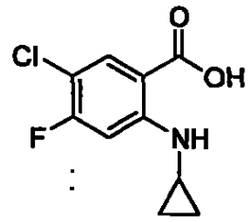
Synthesis of N-Substituted Anthranilic Acids

(a) 2-Cyclopropylamino-4,5-difluorobenzoic acid



To a solution of 4,5-difluoroanthranilic acid (1.13 g, 6.53 mmol) in anhydrous methanol (40 mL) is added molecular sieves (3 Å), acetic acid (3.70 mL, 65.3 mmol) and [(1-ethoxycyclopropyl)oxy]trimethylsilane (5.25 mL, 26.11 mmol). After 30 minutes, sodium cyanoborohydride (2.08 g, 32.64 mmol) is added, and the reaction mixture is heated to reflux. After 16 hours, the reaction is cooled to room temperature, filtered, washed with methanol, and the combined filtrate concentrated under vacuum to afford a viscous oil. The resulting oil is dissolved in ethyl acetate and washed with 1.0 M hydrochloric acid, water, and brine. The organic layer is dried over $MgSO_4$, filtered, and the filtrate is concentrated under vacuum to afford as a beige solid (1.32 g). MS CI: *m/z* 212 (M^+).

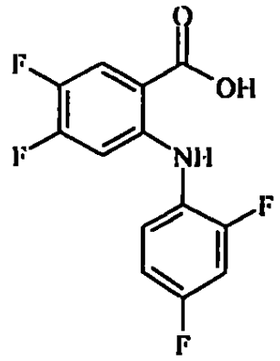
(b) 5-Chloro-2-cyclopropylamino-4-fluorobenzoic acid.



To a solution of 4,5-difluoroanthranilic acid (1.20 g, 6.37 mmol) in anhydrous methanol (50 mL) is added molecular sieves (3 Å), acetic acid (3.70 mL, 65.3 mmol), and [(1-ethoxycyclopropyl)oxy]trimethylsilane (5.12 mL, 25.5 mmol). After 30 minutes, sodium cyanoborohydride (2.03 g, 31.9 mmol) is added, and the reaction mixture is heated to reflux. After 16 hours, the reaction is cooled to room temperature, filtered, washed with methanol, and the combined filtrate concentrated under vacuum to afford a viscous oil. The resulting oil is dissolved in ethyl acetate and washed with 1.0 M hydrochloric acid, water, and brine. The organic layer is dried over $MgSO_4$, filtered, and the filtrate is

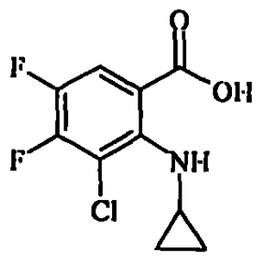
concentrated under vacuum to afford as a beige solid (1.78 g). MS CI: *m/e* 228 (M^+).

(c) 2-(2,4-Difluoroanilino)-4,5-difluorobenzoic acid



Lithium diisopropylamide is generated at -5°C by combining diisopropylamine (7.2 mL, 51 mmol) and n-butyllithium (33 mL, 53mmol) in anhydrous tetrahydrofuran (150 mL) under an inert atmosphere. After 0.5 hour, the solution is cooled to -78°C and 2,4-difluoroaniline (3.46 mL, 34 mmol) is added and stirred for 2 hours. 2,4,5-Trifluorobenzoic acid (3.0 g, 17 mmol) is added, and the mixture is subsequently allowed to warm to room temperature over 18 hours. A saturated solution of hydrogen chloride/dioxane (10 mL) is added, and after 1 hour, the mixture is concentrated to a solid. The solid is dissolved in chloroform and washed with 1.0 M hydrochloric acid, water, and brine. The solution is dried, concentrated in vacuo, and purified by column chromatography (3:1 ethyl acetate/hexanes) to give 2-(2,4-difluoroanilino)-4,5-difluorobenzoic acid as a solid (2.18 g). ^{1}H NMR ($CDCl_3$): δ 8.95 (bs, 1H), 7.80-7.75 (m, 2H), 7.50-6.85 (m, 3H), 6.62-6.40 (m, 1H). MS EI: *m/z* 286 (M^+).

(d) 3-Chloro-2-cyclopropylamino-4,5-difluorobenzoic acid

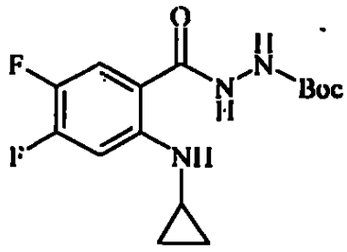


In a sealed tube a mixture of 2-bromo-3-chloro-4,5-difluorobenzoic acid (Example 20, 7.96 g, 29.3 mmol), cyclopropyl amine (4.20 mL, 58.7 mmol), potassium acetate (5.77 g, 58.6 mmol), cupric acetate monohydrate (0.50 g, 2.5 mmol), and triethylamine (4.9 mL, 35.19 mmol) in isopropyl alcohol is stirred at 80°C. After 16 hours, the reaction mixture is concentrated under vacuum, and the resulting residue is dissolved in ethyl acetate. The organic layer is washed with 1.0 M hydrochloric acid, water, and brine. The organic layer is dried over $MgSO_4$ and filtered. The filtrate is concentrated under vacuum and purified via flash column chromatography (5% isopropyl alcohol/1% formic acid/94% dichloromethane) to afford the title compound (4.62 g). MS CI: *m/z* 248 (MH^+).

EXAMPLE 6

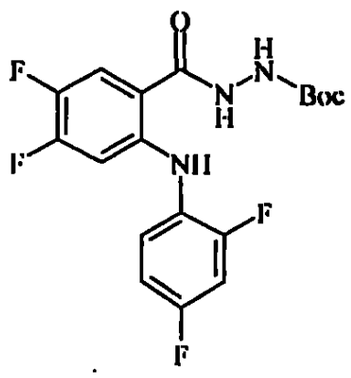
Synthesis of Hydrazinecarboxylic t-Butyl Esters

(a) (2-Cyclopropylamino-4,5-difluorobenzoyl)hydrazinecarboxylic acid tert-butyl ester



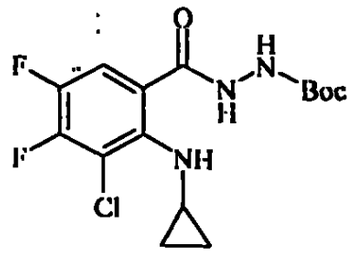
To a solution of 2-cyclopropylamino-4,5-difluorobenzoic acid (Example 5) (1.32 g, 6.19 mmol) and *tert*-butyl carbazate (1.30 g, 9.75 mmol) in dichloromethane (30 mL) is added 1-ethyl-3-(3-dimethylaminopropyl)-carbodiimide (1.87 g, 9.75 mmol). After 16 hours, the reaction mixture is diluted with dichloromethane and washed with saturated $NaHCO_3$, water, and brine. The organic layer is dried over $MgSO_4$ and filtered. The filtrate is concentrated under vacuum and purified via flash column chromatography (1:2 ethyl acetate/hexanes) to afford N_2-(2-cyclopropylamino-4,5-difluorobenzoyl)hydrazinecarboxylic acid *tert*-butyl ester as a solid (1.65 g). MS EI: *m/z* 328 (M^+).

(b) ***[2-(2,4-Difluoroanilino)-4,5-difluorobenzoyl]hydrazinecarboxylic acid tert-butyl ester***



To a solution of 2-(2,4-difluoroanilino)-4,5-difluorobenzoic acid (Example 5, 2.18 g, 7.6 mmol) and *tert*-butyl carbazate (1.57 g, 11.8 mmol) in dichloromethane (30 mL) is added 1-ethyl-3-(3-dimethylaminopropyl)-carbodiimide (2.25 g, 11.77 mmol). After stirring for 16 hours at room temperature, the reaction mixture is diluted with dichloromethane and then washed with saturated $NaHCO_3$, water, and brine. The organic layer is dried over Na_2SO_4, concentrated under vacuum, and purified via column chromatography (1:3 ethyl acetate/hexanes) to afford [2-(2,4-difluoroanilino)-4,5-difluorobenzoyl]-hydrazinecarboxylic acid *tert*-butyl ester as a solid (2.20 g). MS EI: *m/z* 400 (M^+).

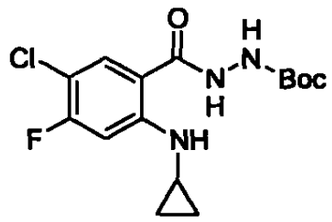
(c) ***(3-Chloro-2-cyclopropylamino-4,5-difluorobenzoyl)-hydrazinecarboxylic acid tert-butyl ester***



To a solution of 3-chloro-2-cyclopropylamino-4,5-difluorobenzoic acid (Example 5d, 2.09 g, 8.45 mmol) in dichloromethane (30 mL) is added *tert*-butyl carbazate (1.67 g, 12.7 mmol) and 1-ethyl-3-(3-dimethylaminopropyl)-carbodiimide (2.43 g, 12.7 mmol). After 16 hours, the reaction mixture is diluted

with dichloromethane and washed with saturated $NaHCO_3$, water, and brine. The organic layer is dried over $MgSO_4$ and filtered. The filtrate is concentrated under vacuum and purified via flash column chromatography (1:2 ethyl acetate/hexanes) to afford the title compound (1.93 g). MS EI: *m/z* 360 ($M^{+\cdot}$).

(d) ***(5-Chloro-2-cyclopropylamino-4-fluorobenzoyl)-hydrazinecarboxylic acid tert-butyl ester***



To a solution of 5-chloro-2-cyclopropylamino-4-fluorobenzoic acid (Example 5, 1.48 g, 6.46 mmol) in dichloromethane (50 mL) is added *tert*-butyl carbazate (1.28 g, 9.69 mmol) and 1-ethyl-3-(3-dimethylaminopropyl)carbodiimide (1.86 g, 9.69 mmol). After 16 hours, the reaction mixture is diluted with dichloromethane and washed with saturated $NaHCO_3$, water, and brine. The organic layer is dried over $MgSO_4$ and filtered. The filtrate is concentrated under vacuum and purified via flash column chromatography (1:2 ethyl acetate/hexanes) to afford (3-chloro-2-cyclopropylamino-4,5-difluorobenzoyl)hydrazinecarboxylic acid *tert*-butyl ester as a solid (1.04g). MS CI: *m/e* 344 (M^{+}+1).

EXAMPLE 7

Synthesis of 4-Heterocyclic-benzoylhydrazinecarboxylic acid t-butyl esters

General Procedure A

A solution of a substituted benzoylhydrazinecarboxylic acid *tert*-butyl ester from Example 6 (where R_7 = F), heterocyclic amine (2 eq.), and triethylamine (10 eq.) is stirred in dimethyl sulfoxide or *N,N*-dimethylformamide (6 mL) at 120°C in a sealed tube for 16 hours. After cooling to room temperature, the reaction mixture is diluted with ethyl acetate and washed with saturated $NaHCO_3$, water, and brine. The organic layer is dried over $MgSO_4$, filtered, and

the filtrate concentrated to afford a brown residue. Trituration with diethyl ether or purification via flash column chromatography (ethyl acetate/hexanes) yields the product.

General Procedure B

To a suspension of a benzoic acid of Example 4 (3.30 mmol) and *tert*-butyl carbazate (1.5 eq.) in anhydrous dichloromethane is added 1-[3-(dimethylamino)propyl]-3-ethylcarbodiimide hydrochloride (1.5 eq.). The mixture is stirred at room temperature for 20 hours, poured into saturated $NaHCO_3$, and extracted with dichloromethane. The combined organic extracts are washed with brine, dried over Na_2SO_4, filtered, and concentrated in vacuo. Purification by flash column chromatography (ethyl acetate/hexanes) afford the title compounds.

The following compounds are synthesized according to General Procedures A or B above:

(a) *N'*-{4-[3-(*tert*-Butoxycarbonylaminomethyl)pyrrolidin-1-yl]-2-cyclopropylamino-5-fluorobenzoyl}hydrazinecarboxylic acid *tert*-butyl ester (MS CI: *m/z* 508 (MH^+)) using (2-cyclopropylamino-4,5-difluorobenzoyl)-hydrazinecarboxylic acid *tert*-butyl ester (Example 6a) and 3-(*tert*-butoxycarbonylaminomethyl)pyrrolidine (General Method A).

(b) *N'*-4-[4-(*tert*-Butoxycarbonylpiperazin-1-yl)-2-cyclopropylamino-5-fluorobenzoyl]hydrazinecarboxylic acid *tert*-butyl ester (MS CI: *m/z* 494 (MH+)) using (2-cyclopropylamino-4,5-difluorobenzoyl)-hydrazinecarboxylic acid *tert*-butyl ester (Example 6a) and 4-*tert*-butoxycarbonylpiperazine (General Method A).

(c) *N'*-{4-[3-(*tert*-Butoxycarbonylaminomethyl)-3-methylpyrrolidin-1-yl]-2-cyclopropylamino-5-fluorobenzoyl}hydrazinecarboxylic acid *tert*-butyl ester (MS CI: *m/z* 522 (MH^+)) using (2-cyclopropylamino-4,5-difluorobenzoyl)-hydrazinecarboxylic acid *tert*-butyl ester (Example 6a) and 3-(*tert*-butoxycarbonylaminomethyl)-3-methylpyrrolidine (Sanchez J.P., Bridges A.J., Buesh R., Domagala J.M., Gogliotti R.D., Hagen S.E., Heifetz C.L.,

Jounnides E.T., Sesnie J.C., et al. *J. Med. Chem.*, 1992;35(2):361-367) (General Method A).

(d) *N'*-[4-(6-*tert*-Butoxycarbonylamino-3-azabicyclo[3.1.0]hex-3-yl)-2-cyclopropylamino-5-fluorobenzoyl]hydrazinecarboxylic acid *tert*-butyl ester (MS CI: *m/z* 506 (MH^+)) using (2-cyclopropylamino-4,5-difluorobenzoyl)-hydrazinecarboxylic acid *tert*-butyl ester (Example 6a) and (3-azabicyclo[3.1.0]hex-6-yl)carbamic acid tert-butyl ester (Brighty K.E., 1991, EP 413455] (General Method A).

(e) *N'*-{4-[(S)-3-(*tert*-Butoxycarbonyl-N-methylamino)pyrrolidin-1-yl]-2-cyclopropylamino-5-fluorobenzoyl}hydrazinecarboxylic acid *tert*-butyl ester (MS CI: *m/z* 508 (MH^+)) using (2-cyclopropylamino-4,5-difluorobenzoyl)-hydrazinecarboxylic acid *tert*-butyl ester (Example 6a) and (S)-3-(*tert*-butoxycarbonyl-*N*-methylamino)pyrrolidine (Chu D.T., Li Q., Cooper C.S., Fung A.K.L., Lee C.M., Plattner J.J.; PCT Int. Appl., 1995:255. WO 9510519) (General Method A).

(f) *N'*-{4-[(S)-3-(*tert*-Butoxycarbonylamino)pyrrolidin-1-yl]-2-(2,4-difluoroanilino)-5-fluorobenzoyl}hydrazinecarboxylic acid *tert*-butyl ester (MS CI: *m/z* 566 (MH^+)) using [2-(2,4-difluoroanilino)-4,5-difluorobenzoyl]-hydrazinecarboxylic acid *tert*-butyl ester (Example 6b) and (S)-pyrrolidin-3-ylcarbamic acid tert-butyl ester (General Method A).

(g) *N'*-{4-[(S)-3-*tert*-Butoxycarbonylamino)pyrrolidin-1-yl]-2-cyclopropylamino-3,5-difluorobenzoyl}hydrazinecarboxylic acid *tert*-butyl ester MS CI: *m/z* 538 (MH^+) using 4-[(S)-3-*tert*-butoxycarbonylaminopyrrolidin-1-yl]-2-cyclopropylamino-3,5-difluorobenzoic (Example 4a) (General Method B).

(h) *N'*-{4-[(S)-3-*tert*-Butoxycarbonylamino)pyrrolidin-1-yl]-2-cyclopropylamino-3,6-difluorobenzoyl}hydrazinecarboxylic acid *tert*-butyl ester (^1H NMR ($CDCl_3$): δ 8.08 (bs, 2H), 6.50 (bs, 1H), 5.70 (dd, 1H), 4.76-4.68 (m, 1H), 4.37-4.23 (m, 1H), 3.78-3.68 (m, 1H), 3.65-3.42 (m, 2H), 3.40-3.30 (m, 1H), 2.96-2.83 (m, 1H), 2.28-2.14 (m, 1H), 2.00-1.84 (m, 1H), 1.49 (s, 9H), 1.46 (s, 9H), 0.68-0.61 (m, 2H), 0.58-0.48 (m, 2H)) using 4-[(S)-3-*tert*-

butoxycarbonylaminopyrrolidin-1-yl]-2-cyclopropylamino-3,6-difluorobenzoic acid (Example 4b) (General Method B).

(i) *N'*-{4-[(S)-3-(*tert*-Butoxycarbonylamino)pyrrolidin-1-yl]-2-cyclopropylamino-3,5,6-trifluorobenzoyl}hydrazine carboxylic acid *tert*-butyl ester (^{1}H NMR ($CDCl_3$): δ 8.04 (bd, 1H), 7.55 (bs, 1H), 6.52 (bs, 1H), 4.79-4.67 (m, 1H), 4.37-4.19 (m, 1H), 3.97-3.55 (m, 3H), 3.53-3.40 (m, 1H), 2.90-2.75 (m, 1H), 2.29-2.06 (m, 1H), 1.96-1.75 (m, 1H), 1.49 (s, 9H), 1.46 (s, 9H), 0.69-0.57 (m, 2H), 0.54-0.43 (m, 2H)) using 4-[(S)-3-*tert*-butoxycarbonylaminopyrrolidin-1-yl]-2-cyclopropylamino-3,5,6-trifluorobenzoic acid (Example 4d) (General Method B).

(j) *N'*-{4-[(S)-3-(*tert*-Butoxycarbonylamino)pyrrolidin-1-yl]-3-chloro-2-cyclopropylamino-5-fluorobenzoyl}hydrazinecarboxylic *tert*-butyl ester (MS CI: *m/z* 528 (MH+)) using 4-[(S)-3-*tert*-butoxycarbonylaminopyrrolidin-1-yl]-3-chloro-2-cyclopropylamino-5-fluorobenzoic acid (Example 4c) (General Method B).

(k) *N'*-[(S)-4-(7-*tert*-Butoxycarbonylamino-5-azaspiro[2.4]hept-5-yl)-2-cyclopropylamino-5-fluorobenzoyl]hydrazinecarboxylic acid *tert*-butyl ester (MS CI: *m/z* 520 (MH^+)) using (2-cyclopropylamino-4,5-difluorobenzoyl)-hydrazinecarboxylic acid *tert*-butyl ester (Example 6a) and (5-azaspiro[2,4]hept-7-yl)carbamic acid tert-butyl ester (General Method A).

(l) *N'*-{4-[(*R*)-3-(1-*tert*-Butoxycarbonylamino-1-methylethyl)pyrrolidin-1-yl]-3-chloro-2-cyclopropylamino-5-fluorobenzoyl}hydrazinecarboxylic acid *tert*-butyl ester (MS CI: *m/z* 570 (MH+)) using (3-chloro-2-cyclopropylamino-4,5-difluorobenzoyl)-hydrazinecarboxylic acid *tert*-butyl ester (Example 6c) and [(*R*)-3-(1-*tert*-butoxycarbonylamino-1-methylethyl)pyrrolidine (Fedij V., Lenoir E.A., III, Suto M.J., Zeller J.R., Wemple J., *Tetrahedron: Asymmetry*, 1994;5[7]:1131-1134) (General Method A).

(m) *N'*-[4-(Pyrrolidin-1-yl)-2-cyclopropylamino-5-fluorobenzoyl]-hydrazinecarboxylic *tert*-butyl ester (MS CI: *m/z* 379 (MH^+)) using

2-cyclopropylamino-5-fluoro-4-pyrrolidin-1-ylbenzoic acid (Example 4e) (General Method B).

(n) *N'*-{4-[3-(*tert*-Butoxycarbonylamino)pyrrolidin-1-yl]-5-fluoro-2-isopropylaminobenzoyl}hydrazine carboxylic acid *tert*-butyl ester (MS EI: *m/z* 496 (MH^+)) using 4-[3-*tert*-butoxycarbonylamino)pyrrolidin-1-yl]-5-fluoro-2-isopropylaminobenzoic acid (Example 4f) (General Method B).

(o) *N'*-{4-[3-(*tert*-Butoxycarbonylamino)pyrrolidin-1-yl]-2-*sec*-butylamino-3-chloro-5-fluorobenzoyl}hydrazinecarboxylic acid *tert*-butyl ester (MS EI: *m/z* 544 (MH^+)) using 4-[3-(*tert*-butoxycarbonylamino)pyrrolidin-1-yl]-2-*sec*-butylamino-3-chloro-5-fluorobenzoic acid (Example 4g) (General Method B).

(p) *N'*-{4-[3-*tert*-Butoxycarbonylamino)pyrrolidin-1-yl]-2-cyclopropylamino-5-fluoro-3-methoxybenzoyl}hydrazinecarboxylic acid *tert*-butyl ester (MS EI: *m/z* 524 (MH^+)) using 4-[3-*tert*-butoxycarbonylamino)-pyrrolidin-1-yl]-2-cyclopropylamino-5-fluoro-3-methoxybenzoic acid (Example 4h) (General Method B).

(q) *N'*-{4-[3-(*tert*-Butoxycarbonylamino)pyrrolidin-1-yl]-2-cyclobutylamino-5-fluorobenzoyl}hydrazinecarboxylic acid *tert*-butyl ester (MS EI: *m/z* 394 (M^+)) using 4-[3-*tert*-butoxycarbonylamino)pyrrolidin-1-yl]-2-cyclobutylamino-5-fluorobenzoic acid (Example 4i) (General Method B).

(r) *N'*-{4-[3-(*tert*-Butoxycarbonylamino)pyrrolidin-1-yl]-2-cyclopropylamino-3-fluorobenzoyl}hydrazinecarboxylic acid tert-butyl ester (MS EI: *m/z* 494 (MH^+)) using 4-[3-(*tert*-butoxycarbonylamino)pyrrolidin-1-yl]-2-cyclopropylamino-3-fluorobenzoic acid (Example 4j) (General Method B).

(s) *N'*-{4-[3-(*tert*-Butoxycarbonylamino)pyrrolidin-1-yl]-5-chloro-2-cyclopropylamino-3-fluorobenzoyl}hydrazinecarboxylic acid tert-butyl ester (^1H NMR ($CDCl_3$): δ 8.77 (bs, 1H), 7.35 (d, 1H), 6.82 (bs, 1H), 6.55 (bs, 1H), 5.01-4.97 (m, 1H), 4.29 (bs, 1H), 3.74-3.57 (m, 2H), 3.41-3.24 (m, 2H), 2.84-2.75 (m, 1H), 2.33-2.16 (m, 1H), 1.92-1.72 (m, 1H), 1.47 (s, 9H), 1.45 (s, 9H), 0.69-0.62 (m, 2H), 0.60-0.50 (m, 2H)) using 4-[3-(*tert*-

butoxycarbonylamino)pyrrolidin-1-yl]-5-chloro-2-cyclopropylamino-3-fluorobenzoic acid (Example 4k) (General Method B).

(t) *N'*-[4-(3-*tert*-Butoxycarbonylaminopyrrolidin-1-yl)-2-cyclopropylamino-5-fluoro-3-methylbenzoyl]hydrazinecarboxylic acid *tert*-butyl ester ([MS ES, MH^+] m/z 508) using 4-(3-*tert*-butoxycarbonylaminopyrrolidin-1-yl)-2-cyclopropylamino-5-fluoro-3-methylbenzoic acid (Example 4l) (General Method B).

(u) N'-{4-[3-(*tert*-Butoxycarbonylaminomethyl)pyrrolidin-1-yl]-2-cyclopropylamino-5-fluoro-3-methylbenzoyl}hydrazinecarboxylic acid tert-butyl ester ([MS ES, MH^+] m/z 522) using 4-[3-(*tert*-butoxycarbonylaminomethyl)-pyrrolidin-1-yl]-2-cyclopropylamino-5-fluoro-3-methylbenzoic acid (Example 4m) (General Method B).

(v) *N'*-[4-(3-*tert*-Butoxycarbonylaminopyrrolidin-1-yl)-2-cyclopropylamino-3-fluoro-5-methoxybenzoyl]hydrazinecarboxylic acid *tert*-butyl ester. ([MS ES, MH^+] m/z 525) using 4-(3-*tert*-butoxycarbonylamino-pyrrolidin-1-yl)-2-cyclopropylamino-3-fluoro-5-methoxybenzoic acid (Example 4n) (General Method B).

(w) *N'*-{4-[3-(*tert*-Butoxycarbonylaminomethyl)pyrrolidin-1-yl]-2-cyclopropylamino-5-fluoro-3-methoxybenzoyl}hydrazinecarboxylic acid *tert*-butyl ester ([MS ES, MH_2^{+2}] m/z 539) using 4-[3-(tert-butoxycarbonylamino-methyl)pyrrolidin-1-yl]-2-cyclopropylamino-5-fluoro-3-methoxybenzoic acid (Example 4o) (General Method B).

(x) *N'*-[3-(Benzyloxyiminomethyl)-4-(3-*tert*-butoxycarbonylamino-pyrrolidin-1-yl)-2-cyclopropylamino-5-fluorobenzoyl]hydrazinecarboxylic acid *tert*-butyl ester. ([MS ES, MH^+] m/z 627) using 3-(benzyloxyiminomethyl)-4-(3-*tert*-butoxycarbonylaminopyrrolidin-1-yl)-2-cyclopropylamino-5-fluorobenzoic acid (Example 4q) (General Method B)

(y) *N'*-[3-Chloro-2-cyclopropylamino-5-fluoro-4-(3-[1,2,3-triazol]-1-yl-pyrrolidin-1-yl)benzoyl]hydrazinecarboxylic acid *tert*-butyl ester (^1H NMR (200 MHz, $CDCl_3$): δ 9.90 (bs, 1H), 7.97 (s, 1H), 7.72 (s, 1H, 7.52 (d, 1H), 7.17

(bs, 1H), 5.51-5.41 (m, 1H), 4.59 (bs, 1H), 4.06-3.95 (m, 1H), 3.87-3.74 (m, 1H), 3.61-3.55 (m, 1H), 3.48-3.36 (m, 1H), 2.97-2.90 (m, 1H), 2.77-2.59 (m, 1H) 2.42-2.31 (m, 1H), 1.46 (s, 9H), 0.68-0.50 (m, 4H)) using 3-chloro-2-cyclopropylamino-5-fluoro-4-(3-[1,2,3-triazol]-1-ylpyrrolidin-1-yl)benzoic acid (Example 4r) (General Method B).

(z) *N*-(1-{4-[3-(*tert*-Butoxycarbonylaminomethyl)-piperidin-1-yl]-2-cyclopropylamino-5-fluorophenyl}methanoyl)hydrazinecarboxylic acid *tert*-butyl ester (MS CI: *m/e* 522 (MH+)) from piperidin-3-ylmethylcarbamic acid *tert*-butyl ester (Hilpert K., Ackermann J., Banner D.W., Gast A., Gubernator K., Hadvary P., Labler L., Mueller K., Schmid G., et al., *J. Med. Chem.*, 1994;37[23]:3889-3901) and (2-Cyclopropylamino-4,5-difluorobenzoyl)-hydrazinecarboxylic acid *tert*-butyl ester (Example 6a) (General Method A).

(aa) *N*-[1-(4-{3-[(*tert*-Butoxycarbonylisopropylamino)-methyl]pyrrolidin-1-yl}-2-cyclopropylamino-5-fluorophenyl)methanoyl]-hydrazinecarboxylic acid *tert*-butyl ester (MS CI: *m/e* 550 (MH+)) using isopropylpyrrolidin-3-ylmethylamine (Mich T.F., Culbertson T.P., US 4550103) and (2-cyclopropylamino-4,5-difluorobenzoyl)-hydrazinecarboxylic acid *tert*-butyl ester (Example 6a) (General Method B).

(bb) *N'*-(1-{4-[3-(*tert*-Butoxycarbonylaminomethyl)pyrrolidin-1-yl]-5-chloro-2-cyclopropylaminophenyl}methanoyl)hydrazinecarboxylic acid *tert*-butyl ester (MS CI: *m/e* 524 [M^++1]) using (3-chloro-2-cyclopropylamino-4,5-difluorobenzoyl)hydrazinecarboxylic acid *tert*-butyl ester (Example 6c) and 3-(*tert*-butoxycarbonylaminomethyl)pyrrolidine (General Method A).

(cc) *N'*-[4-(3-*tert*-Butoxycarbonylaminopyrrolidin-1-yl)-2-cyclopropylamino-3-ethoxy-5-fluorobenzoyl]hydrazinecarboxylic acid *tert*-butyl ester (MS ES: m/z 537 (MH^+)) from (4-(3-*tert*-butoxycarbonylamino-pyrrolidin-1-yl)-2-cyclopropylamino-3-ethoxy-5-fluorobenzoic acid (Example 4p) (General Method A).

EXAMPLE 8

Synthesis of (2,4-dioxo-1,4-dihydro-2H-quinazolin-3-yl)carbamic acid tert-butyl esters

General Method A

To a solution of a benzoylhydrazinecarboxylic acid *tert*-butyl ester (from Example 7 (0.435 mmol) in tetrahydrofuran (15 mL) is added potassium carbonate (0.300 g, 2.18 mol) and triphosgene (0.167 g, 0.566 mmol). The reaction mixture is refluxed for 90 minutes, cooled to room temperature, and diluted with ethyl acetate. The organic layer is washed with water and brine, then dried over $MgSO_4$, and filtered. The filtrate is concentrated under vacuum and purified by flash column chromatography (ethyl acetate/hexanes) to afford the title compounds.

General Method B

A solution of (2,4-dioxo-1,4-dihydro-2H-quinazolin-3-yl)carbamic acid *tert*-butyl ester (such as, for example, Example 14), pyrrolidine side chain (2 eq.), and triethylamine (10 eq.) are stirred in dimethyl sulfoxide or acetonitrile (3 mL) at 80°C for 48 hours. After cooling to room temperature, the reaction mixture is diluted with ethyl acetate and washed with saturated $NaHCO_3$, water, and brine. The organic layer is dried over $MgSO_4$, filtered, and concentrated. The resulting residue is purified via flash column chromatography (ethyl acetate/hexanes) to afford the title compounds

General Method C

To a solution of a C-6- and/or C-8-halogenated-(2,4-dioxo-1,4-dihydro-2H-quinazolin-3-yl)carbamic acid tert-butyl ester in ethanol and tetrahydrofuran is added triethylamine and 20% palladium on carbon. Hydrogen is introduced to the reaction mixture at high pressure for several days, then the reaction mixture is filtered through Celite, washed with ethanol, and the combined filtrate concentrated in vacuo and purified via flash column chromatography (ethyl acetate/hexanes) to afford the title compounds.

General Method D

A suspension of benzoylhydrazinecarboxylic acid *tert*-butyl ester (from Example 7) and triethylamine (10 eq.) are stirred in anhydrous tetrahydrofuran for 5 minutes. Phosgene (20% solution in toluene, 2 eq.) is added in one portion to the suspension. The reaction mixture is heated at 60°C for 4.5 hours, cooled to room temperature, poured into saturated $NaHCO_3$ solution, and extracted with chloroform. The combined organic extracts are washed with water, brine, and then dried over Na_2SO_4, filtered, and concentrated under vacuum. The resulting residue is purified by flash column chromatography (1:1 ethyl acetate/hexanes) to afford the title compounds.

General Method E

An appropriately substituted pyrrolidine (1.5-2 eq.), a 3-dibenzylamino-6, 7-difluoro-1-substituted-1H-quinazoline-2,4-dione (Example 16) (1 eq.), and triethylamine (10 eq.) are combined in acetonitrile and heated to reflux for 72 hours. The solution is cooled, concentrated, and re-dissolved in chloroform. The organic solution is washed with 1.0 N hydrochloric acid, saturated $NaHCO_3$, brine, and dried over magnesium sulfate. The solution is concentrated to give the title compounds.

General Method F

A solution of (2,4-dioxo-1,4-dihydro-2H-quinazolin-3-yl)carbamic acid *tert*-butyl ester (such as, for example, Example 14), pyrrolidine side chain (2 eq.), and triethylamine (10 eq.) are stirred in dimethyl sulfoxide or acetonitrile (3 mL) at 80°C for 20 to 40 hours. After cooling to room temperature, the reaction mixture is diluted with ethyl acetate and washed with saturated $NaHCO_3$, water, and brine. The organic layer is dried over $MgSO_4$, filtered, and concentrated. The resulting residue is redissolved in methylene chloride and then treated with di-*tert*-butyl dicarbonate (2 eq). After 1 hour, the reaction mixture is concentrated and the product purified via flash column chromatography (ethylacetate/hexanes) to afford the title compounds.

The following compounds are synthesized according to General Procedures A-F of Example 8:

(a) {7-[3-(*tert*-Butoxycarbonylaminomethyl)pyrrolidin-1-yl]-8-chloro-1-cyclopropyl-6-fluoro-2,4-dioxo-1,4-dihydro-2*H*-quinazolin-3-yl}carbamic acid *tert*-butyl ester (MS Cl: *m/z* 568 (MH+)) from *N'*-{4-[3-(*tert*-butoxycarbonylaminomethyl)pyrrolidin-1-yl]-3-chloro-2-cyclopropylamino-5-fluorobenzoyl}hydrazinecarboxylic acid *tert*-butyl ester (Example 18a) (General Method A)

(b) 7-[4-(*tert*-Butoxycarbonylpiperazin-1-yl)-8-chloro-1-cyclopropyl-6-fluoro-2,4-dioxo-1,4-dihydro-2*H*-quinazolin-3-yl]carbamic acid *tert*-butyl ester (MS Cl: *m/z* 554 (MH+)) from *N'*-4-[4-(*tert*-butoxycarbonylpiperazin-1-yl)-3-chloro-2-cyclopropylamino-5-fluorobenzoyl]hydrazinecarboxylic acid *tert*-butyl ester (Example 18b) (General Method A).

(c) {7-[3-(*tert*-Butoxycarbonylaminomethyl)-3-methylpyrrolidin-1-yl]-8-chloro-1-cyclopropyl-6-fluoro-2,4-dioxo-1,4-dihydro-2*H*-quinazolin-3-yl}carbamic acid *tert*-butyl ester (MS Cl: *m/z* 582 (MH+)) from *N'*-{4-[3-(*tert*-butoxycarbonylaminomethyl)-3-methylpyrrolidin-1-yl]-3-chloro-2-cyclopropylamino-5-fluorobenzoyl}hydrazinecarboxylic acid *tert*-butyl ester (Example 18c) (General Method A).

(d) [7-(6-*tert*-Butoxycarbonylamino-3-azabicyclo[3.1.0]hex-3-yl)-8-chloro-1-cyclopropyl-6-fluoro-2,4-dioxo-1,4-dihydro-2*H*-quinazolin-3-yl]-carbamic acid *tert*-butyl ester (MS Cl: *m/z* 566 (MH^+)) from *N'*-[4-(6-tert-Butoxycarbonylamino-3-azabicyclo[3.1.0]hex-3-yl)-3-chloro-2-cyclopropylamino-5-fluorobenzoyl]hydrazinecarboxylic acid tert-butyl ester (Example 18d) (General Method A).

(e) {7-[(S)-3-(*tert*-Butoxycarbonyl-N-methylamino)pyrrolidin-1-yl]-8-chloro-1-cyclopropyl-6-fluoro-2,4-dioxo-1,4-dihydro-2*H*-quinazolin-3-yl}-carbamic acid *tert*-butyl ester (MS Cl: *m/z* 568 (MH^+)) from *N'*-{4-[(S)-3-(*tert*-butoxycarbonyl-N-methylamino)pyrrolidin-1-yl]-3-chloro-2-cyclopropylamino-5-fluoro-benzoyl}hydrazinecarboxylic acid *tert*-butyl ester (Example 18e) (General Method A).

(f) {7-[(S)-3-(*tert*-Butoxycarbonylamino)pyrrolidin-1-yl]-8-chloro-1-(2,4-difluoroanilino)-6-fluoro-1,4-dihydro-2,4-dioxo-2*H*-quinazolin-3-yl}-carbamic acid *tert*-butyl ester (^{1}H NMR ($CDCl_3$): δ 7.45-7.38 (m, 1H), 6.97-6.81 (m, 1H), 6.73-6.66 (m, 1H), 6.54-6.42 (m, 1H), 4.90-4.81 (bs, 1H), 4.31-4.21 (bs, 1H), 3.86-3.36 (m, 4H), 2.32-2.04 (m, 1H), 1.96-1.84 (m, 1H), 1.61 (s, 9H), 1.45 (s, 9H)) from *N'*-{4-[(S)-3-(*tert*-butoxycarbonyl-N-amino)-pyrrolidin-1-yl]-3-chloro-2-(2,4-difluoroanilino)-5-fluorobenzoyl}-hydrazinecarboxylic acid *tert*-butyl ester (Example 18f) (General Method A).

(g) 7-[(S)-3-(*tert*-Butoxycarbonylamino)pyrrolidin-1-yl]-1-cyclopropylamino-6,8-difluoro-1,4-dihydro-2,4-dioxo-2*H*-quinazolin-3-yl}-carbamic acid *tert*-butyl ester (^{1}H NMR ($CDCl_3$): δ 7.54 (dd, 1H), 6.67 (bs, 1H), 4.79-4.68 (bs, 1H), 4.39-4.23 (m, 1H), 4.10-3.65 (m, 3H), 3.58-3.45 (m, 1H), 3.37-3.25 (m, 1H), 2.30-2.11 (m, 1H), 2.03-1.86 (m, 1H), 1.50 (s, 9H), 1.47 (s, 9H), 1.20-1.12 (m, 2H), 0.83-0.74 (bs, 2H)) from *N'*-{4-[(S)-3-*tert*-butoxycarbonylamino)pyrrolidin-1-yl]-2-cyclopropylamino-3,5-difluorobenzoyl}-hydrazinecarboxylic acid *tert*-butyl ester (Example 5g) (General Method A).

(h) {7-[(S)-3-(*tert*-Butoxycarbonylamino)pyrrolidin-1-yl]-1-cyclopropylamino-5,8-difluoro-1,4-dihydro-2,4-dioxo-2*H*-quinazolin-3-yl}-carbamic acid *tert*-butyl ester (MS CI: *m/z* 538 (M^+)) from *N'*-{4-[(S)-3-*tert*-butoxycarbonylamino)pyrrolidin-1-yl]-2-cyclopropylamino-3,6-difluorobenzoyl}-hydrazinecarboxylic acid *tert*-butyl ester (Example 5h) (General Method A).

(i) {7-[(S)-3-(*tert*-Butoxycarbonylamino)pyrrolidin-1-yl]-1-cyclopropyl-1,4-dihydro-2,4-dioxo-5,6,8-trifluoro-2*H*-quinazolin-3-yl}-carbamic acid *tert*-butyl ester (MS CI: *m/z* 556 (MH^+)) from *N'*-{4-[(S)-3-(*tert*-butoxycarbonylamino)pyrrolidin-1-yl]-2-cyclopropylamino-3,5,6-trifluorobenzoyl}hydrazine carboxylic acid *tert*-butyl ester (Example 5i) (General Method A)

(j) {7-[3-(*tert*-Butoxycarbonylamino)pyrrolidin-1-yl]-8-chloro-1-cyclopropyl-6-fluoro-2,4-dioxo-1,4-dihydro-2*H*-quinazolin-3-yl}carbamic acid *tert*-butyl ester (MS CI: *m/z* 552 (MH^+)) from *N'*-{4-[(S)-3-(*tert*-

butoxycarbonylamino)pyrrolidin-1-yl]-3-chloro-2-cyclopropylamino-5-fluorobenzoyl}hydrazinecarboxylic *tert*-butyl ester (Example 5j) (General Method A).

(k) [7-(3-Hydroxymethylpyrrolidin-1-yl)-8-chloro-1-cyclopropyl-6-fluoro-2,4-dioxo-1,4-dihydro-2*H*-quinazolin-3-yl]carbamic acid tert-butyl ester (MS CI: *m/z* 467 (MH^+)) from (8-chloro-1-cyclopropyl-6,7-difluoro-2,4-dioxo-1,4-dihydro-2H-quinazolin-3-yl)carbamic acid tert-butyl ester (Example 14) and 3-Hydroxymethylpyrrolidine (Roussi G., Zhang J., *Tetrahedron Lett.*, 1988;29(28):3481-3482) (General Method B).

(l) {7-[3-(*tert*-Butoxycarbonylaminoethyl)pyrrolidin-1-yl]-8-chloro-1-cyclopropyl-6-fluoro-2,4-dioxo-1,4-dihydro-2*H*-quinazolin-3-yl}carbamic acid *tert*-butyl ester (MS CI: *m/z* 580 (MH^+)) from (8-chloro-1-cyclopropyl-6,7-difluoro-2,4-dioxo-1,4-dihydro-2H-quinazolin-3-yl)carbamic acid tert-butyl ester (Example 14) and 3-(*tert*-butoxycarbonylaminoethyl)pyrrolidine (Antonsson K.T., Bylund R.E., Gustafsson N.D., Nilsson N.O.I. WO 9429336) (General Method B).

(m) [7-(7-*tert*-Butoxycarbonylamino-5-azaspiro[2.4]hept-5-yl)-8-chloro-1-cyclopropyl-6-fluoro-2,4-dioxo-1,4-dihydro-2*H*-quinazolin-3-yl]-carbamic acid *tert*-butyl ester (MS CI: *m/z* 580 (MH^+)) from *N'*-[(S)-4-(7-*tert*-butoxycarbonylamino-5-azaspiro[2.4]hept-5-yl)-3-chloro-2-cyclopropylamino-5-fluorobenzoyl]hydrazinecarboxylic acid *tert*-butyl ester (Example 18g) (General Method A).

(n) {7-[(R)-3-(1-*tert*-Butoxycarbonylamino-1-methylethyl)pyrrolidin-1-yl]-8-chloro-1-cyclopropyl-6-fluoro-2,4-dioxo-1,4-dihydro-2*H*-quinazolin-3-yl}carbamic acid *tert*-butyl ester (MS CI: *m/z* 596 (MH^+) from *N'*-{4-[(*R*)-3-(1-*tert*-butoxycarbonylamino-1-methylethyl)pyrrolidin-1-yl]-3-chloro-2-cyclopropylamino-5-fluorobenzoyl}hydrazinecarboxylic acid *tert*-butyl ester (Example 7l) (General Method A).

(o) {7-[3-(*tert*-Butoxycarbonylaminomethyl)pyrrolidin-1-yl]-1-cyclopropyl-6-fluoro-2,4-dioxo-1,4-dihydro-2*H*-quinazolin-3-yl}carbamic acid *tert*-butyl ester (MS CI: *m/z* 534 (MH^+)) from {7-[3-(*tert*-butoxycarbonylaminomethyl)pyrrolidin-1-yl]-8-chloro-1-cyclopropyl-6-

fluoro-2,4-dioxo-1,4-dihydro-2*H*-quinazolin-3-yl}carbamic acid *tert*-butyl ester (Example 8a) (General Method C).

(p) [7-(Pyrrolidin-1-yl)-8-chloro-1-cyclopropyl-6-fluoro-2,4-dioxo-1,4-dihydro-2*H*-quinazolin-3-yl]carbamic acid *tert*-butyl ester (MS CI: *m/z* 437 (MH^+)) using *N'*-[4-(Pyrrolidin-1-yl)-3-chloro-2-cyclopropylamino-5-fluorobenzoyl]hydrazinecarboxylic *tert*-butyl ester (Example 18h) (General Method A).

(q) {7-[3-(*tert*-Butoxycarbonylamino)pyrrolidin-1-yl]-8-chloro-6-fluoro-1-isopropyl-2,4-dioxo-6-fluoro-2*H*-quinazolin-3-yl}carbamic acid *tert*-butyl ester. (MS EI: *m/z* 530 (M^+)) using *N'*-{4-[3-(*tert*-butoxycarbonylamino)-pyrrolidin-1-yl)-3-chloro-5-fluoro-2-isopropylaminobenzoyl}-hydrazinecarboxylic acid tert-butyl ester (Example 18i) (General Method A).

(r) {7-[3-(*tert*-Butoxycarbonylamino)pyrrolidin-1-yl]-1-*sec*-butyl-8-chloro-6-fluoro-2,4-dioxo-2*H*-quinazolin-3-yl}carbamic acid *tert*-butyl ester (MS EI: *m/z* 570 (MH^+)) using *N'*-{4-[3-(*tert*-butoxycarbonylamino)pyrrolidin-1-yl]-2-*sec*-butylamino-3-chloro-5-fluorobenzoyl}hydrazinecarboxylic acid *tert*-butyl ester (Example 7o) (General Method A).

(s) {7-[3-(*tert*-Butoxycarbonylamino)pyrrolidin-1-yl]-1-cyclopropyl-6-fluoro-8-methoxy-2,4-dioxo-1,4-dihydro-2*H*-quinazolin-3-yl}carbamic acid *tert*-butyl ester (MS EI: *m/z* 550 (MH^+)) using *N'*-{4-[3-*tert*-butoxycarbonylamino)pyrrolidin-1-yl]-2-cyclopropylamino-5-fluoro-3-methoxybenzoyl}hydrazinecarboxylic acid *tert*-butyl ester (Example 7p) (General Method D).

(t) {7-[3-(*tert*-Butoxycarbonylamino)pyrrolidin-1-yl]-8-chloro-1-cyclobutylamino-6-fluoro-2,4-dioxo-1,4-dihydro-2*H*-quinazolin-3-yl}carbamic acid *tert*-butyl ester (MS EI: *m/z* 568 (MH^+)) using *N'*-{4-[3-(*tert*-butoxycarbonylamino)pyrrolidin-1-yl]-2-cyclobutylamino-5-fluorobenzoyl}-hydrazinecarboxylic acid *tert*-butyl ester (Example 7q) (General Method A).

(u) {7-[3-(*tert*-Butoxycarbonylamino)pyrrolidin-1-yl]-1-cyclopropyl-8-fluoro-2,4-dioxo-1,4-dihydro-2*H*-quinazolin-3-yl}carbamic acid *tert*-butyl ester (MS EI: *m/z* 520 (MH^+)) using *N'*-{4-[3-(*tert*-butoxycarbonylamino)pyrrolidin-

1-yl]-2-cyclopropylamino-3-fluorobenzoyl}hydrazinecarboxylic acid tert-butyl ester (Example 7r) (General Method D).

(v) {7-[3-(*tert*-Butoxycarbonylamino)pyrrolidin-1-yl]-6-chloro-1-cyclopropyl-8-fluoro-2,4-dioxo-1,4-dihydro-2*H*-quinazolin-3-yl}carbamic acid *tert*-butyl ester (^{1}H NMR ($CDCl_3$): δ 7.36 (d, 1H), 6.64 (bs, 1H), 4.86-4.80 (bd, 1H), 4.31-4.25 (m, 1H), 3.81-3.66 (m, 2H), 3.51-3.31 (m, 2H), 3.02-2.97 (m, 1H), 2.32-2.22 (m, 1H), 1.95-1.85 (m, 1H), 1.63 (s, 9H), 1.46 (s, 9H), 0.77-0.73 (m, 2H), 0.63-0.57 (bs, 2H)) using *N'*-{4-[3-(*tert*-butoxycarbonylamino)pyrrolidin-1-yl]-5-chloro-2-cyclopropylamino-3-fluorobenzoyl}hydrazinecarboxylic acid tert-butyl ester (Example 7s) (General Method D).

(w) [(S)-1-(1-Cyclopropylmethyl-3-dibenzylamino-6-fluoro-2,4-dioxo-1,2,3,4-tetrahydroquinazolin-7-yl)pyrrolidin-3-yl]carbamic acid tert-butyl ester (MS CI, *m/z* 614 (MH^+)) using 3-dibenzylamino-6,7-difluoro-1-cyclopropylmethyl-1H-quinazoline-2,4-dione (Example 17a) and (S)-pyrrolidin-3-ylcarbamic acid tert-butyl ester (General Method E).

(x) {1-[(R)-1-(Cyclopropylmethyl-3-dibenzylamino-6-fluoro-2,4-dioxo-1,2,3,4-tetrahydroquinazolin-7-yl)pyrrolidin-3-yl]-1-methylethyl}-carbamic acid tert-butyl ester (MS CI: *m/z* 656 (MH^+)) using 3-dibenzylamino-6,7-difluoro-1-cyclopropylmethyl-1H-quinazoline-2,4-dione (Example 17a) and (*R*)-3-(1-*tert*-butoxycarbonylamino-1-methylethyl)pyrrolidine (General Method E).

(y) [(S)-1-(3-Dibenzylamino-1-ethyl-6-fluoro-2,4-dioxo-1,2,3,4-tetrahydroquinazolin-7-yl)pyrrolidin-3-yl]carbamic acid *tert*-butyl ester (mp 104-106°C, MS CI: *m/z* 588 (MH^+)) using 3-dibenzylamino-6,7-difluoro-1-ethyl-1H-quinazoline-2,4-dione (Example 17b) and (S)-pyrrolidin-3-ylcarbamic acid *tert*-butyl ester (General Method E).

(z) [(R)-1-(3-Dibenzylamino-1-ethyl-6-fluoro-2,4-dioxo-1,2,3,4-tetrahydro-quinazolin-7-yl)-1-methyl-1-pyrrolidin-3-ylethyl]carbamic acid *tert*-butyl ester (MS CI: *m/z* 630 (MH^+)) using 3-dibenzylamino-6,7-difluoro-1-ethyl-1H-quinazoline-2,4-dione (Example 17b) and (R)-(1-*tert*-butoxycarbonylamino-1-methylethyl)pyrrolidine (General Method E).

(aa) [7-(3-*tert*-Butoxycarbonylaminopyrrolidin-1-yl)-1-cyclopropyl-6-fluoro-8-methyl-2,4-dioxo-1,4-dihydro-2H-quinazolin-3-yl]carbamic acid *tert*-butyl ester ([MS ES, MH^+] m/z 534) using *N'*-[4-(3-*tert*-butoxycarbonylamino-pyrrolidin-1-yl)-2-cyclopropylamino-5-fluoro-3-methylbenzoyl]-hydrazinecarboxylic acid *tert*-butyl ester (Example 7t) (General Method D).

(bb) {7-[3-(*tert*-Butoxycarbonylaminomethyl)pyrrolidin-1-yl]-1-cyclopropyl-6-fluoro-8-methyl-2,4-dioxo-1,4-dihydro-2H-quinazolin-3-yl}-carbamic acid *tert*-butyl ester (MS ES, MH^+) m/z 548)) using *N'*-{4-[3-(*tert*-butoxycarbonylaminomethyl)pyrrolidin-1-yl]-2-cyclopropylamino-5-fluoro-3-methylbenzoyl}hydrazinecarboxylic acid *tert*-butyl ester (Example 7u) (General Method D.

(cc) [7-(3-*tert*-Butoxycarbonylaminopyrrolidin-1-yl)-1-cyclopropyl-8-fluoro-6-methoxy-2,4-dioxo-1,4-dihydro-2H-quinazolin-3-yl]carbamic acid *tert*-butyl ester ([MS ES, MH_2^+] m/z 551) using *N'*-[4-(3-*tert*-butoxycarbonylamino-pyrrolidin-1-yl)-2-cyclopropylamino-3-fluoro-5-methoxybenzoyl]-hydrazinecarboxylic acid *tert*-butyl ester (Example 7v) (General Method D).

(dd) {7-[3-(*tert*-Butoxycarbonylaminomethyl)pyrrolidin-1-yl]-1-cyclopropyl-6-fluoro-8-methoxy-2,4-dioxo-1,4-dihydro-2H-quinazolin-3-yl}-carbamic acid *tert*-butyl ester ([MS ES, MH_2^{+2}] m/z 565) using *N'*-{4-[3-(*tert*-butoxycarbonylaminomethyl)pyrrolidin-1-yl]-2-cyclopropylamino-5-fluoro-3-methoxybenzoyl}hydrazinecarboxylic acid *tert*-butyl ester (Example 7w) (General Method D).

(ee) [7-(3-*tert*-Butoxycarbonylaminopyrrolidin-1-yl)-1-cyclopropyl-8-ethoxy-6-fluoro-2,4-dioxo-1,4-dihydro-2H-quinazolin-3-yl]carbamic acid tert-butyl ester ([MS ES, MH_2^{+2}] m/z 565) from *N'*-[4-(3-*tert*-butoxycarbonylamino-pyrrolidin-1-yl)-2-cyclopropylamino-3-ethoxy-5-fluorobenzoyl]-hydrazinecarboxylic acid tert-butyl ester (Example 7ee) (General Method A).

(ff) [7-(3-*tert*-Butoxycarbonylaminopyrrolidin-1-yl)-8-cyano-1-cyclopropyl-6-fluoro-2,4-dioxo-1,4-dihydro-2H-quinazolin-3-yl]carbamic acid *tert*-butyl ester ([MS ES, MH^+] m/z 545) from *N'*-[3-(benzyloxyiminomethyl)-4-

(3-*tert*-butoxycarbonylaminopyrrolidin-1-yl)-2-cyclopropylamino-5-fluoro-benzoyl]hydrazinecarboxylic acid *tert*-butyl ester (Example 7x) (General Method A).

(gg) [8-Chloro-1-cyclopropyl-6-fluoro-2,4-dioxo-7-(3-[1,2,3-triazol]-1-yl-pyrrolidin-1-yl)-1,4-dihydro-2H-quinazolin-3-yl]carbamic acid *tert*-butyl ester (^{1}H NMR (200 MHz, $CDCl_3$): δ 7.96 (s, 1H), 7.74 (s, 1H), 7.29 (d, 1H), 6.26 (bs, 1H), 5.51-5.39 (m, 1H), 4.17-4.07 (m, 1H), 3.99-3.88 (m, 1H), 3.71-3.66 (m, 1H), 3.57-3.45 (m, 1H), 3.15-3.05 (m, 1H), 2.74-2.60 (m, 1H), 2.44-2.32 (m, 1H), 1.64 (s, 9H), 0.76-0.49 (m, 4H)) from N'-[3-chloro-2-cyclopropylamino-5-fluoro-4-(3-[1,2,3-triazol]-1-yl-pyrrolidin-1-yl)benzoyl]hydrazinecarboxylic acid *tert*-butyl ester (Example 7y) (General Method A).

(hh) [7-(3-Carbamoylpiperidin-1-yl)-8-chloro-1-cyclopropyl-6-fluoro-2,4-dioxo-1,4-dihydro-2*H*-quinazolin-3-yl]carbamic acid *tert*-butyl ester (MS CI: *m/z* 496 (MH^+)) from (8-chloro-1-cyclopropyl-6,7-difluoro-2,4-dioxo-1,4-dihydro-2H-quinazolin-3-yl)carbamic acid *tert*-butyl ester (Example 14) and 3-carbamoyl-piperidine (General Method B).

(ii) {7-[(trans-3-(*tert*-Butoxycarbonylaminomethyl)-4-trifluoromethyl-pyrrolidin-1-yl]-8-chloro-1-cyclopropyl-6-fluoro-2,4-dioxo-1,4-dihydro-2*H*-quinazolin-3-yl}carbamic acid *tert*-butyl ester (MS CI: *m/z* 635 (M^+)) from (8-chloro-1-cyclopropyl-6,7-difluoro-2,4-dioxo-1,4-dihydro-2H-quinazolin-3-yl)-carbamic acid tert-butyl ester (Example 14) and trans-3-(*tert*-butoxycarbonylaminomethyl)-4-trifluoromethylpyrrolidine (Li Q., Wang W., Berst K.B., Claiborne A., Hasvold L., Raye K., Tufano M., et al., *J. Med. Chem. Lett.*, 1998;8[15]:1953-1958) (General Method B).

(jj) 8-Chloro-1-cyclopropyl-6-fluoro-2,4-dioxo-7-{3-[(2,2,2-trifluoro-ethylamino)methyl]pyrrolidin-1-yl}-1,4-dihydro-2*H*-quinazolin-3-yl)carbamic acid *tert*-butyl ester (MS CI: *m/z* 548 (M^+)) using (8-chloro-1-cyclopropyl-6,7-difluoro-2,4-dioxo-1,4-dihydro-2H-quinazolin-3-yl)carbamic acid tert-butyl ester (Example 14) and {3-[(2,2,2-trifluoroethylamino)methyl]pyrrolidin-1-yl}carbamic acid *tert*-butyl ester (Domagala J.M., Mich T.F., Sanchez J.P. US 5097032) (General Method B).

(kk) [8-Chloro-1-cyclopropyl-6-fluoro-7-(5-methylhexahydro-pyrrolo[3,4-*c*]pyrrol-2-yl)-2,4-dioxo-1,4-dihydro-2*H*-quinazolin-3-yl]carbamic acid *tert*-butyl ester (MS CI: *m/z* 494 (MH^+)) using (8-chloro-1-cyclopropyl-6,7-difluoro-2,4-dioxo-1,4-dihydro-2H-quinazolin-3-yl)carbamic acid *tert*-butyl ester (Example 14) and 5-methyloctahydropyrrolo[3,4-*c*]pyrrole (Ohnmacht C.J. Jr., Draper C.W., Dedinas R.F., Loftus P., Wong J.J., *J. Heterocycl. Chem.*, 1983;20[2]:321-329) (General Method B).

(ll) [8-Chloro-1-cyclopropyl-7-(2,7-diazaspiro[4.4]non-2-yl)-6-fluoro-2,4-dioxo-1,4-dihydro-2*H*-quinazolin-3-yl]carbamic acid *tert*-butyl ester (MS CI: *m/z* 494 (MH^+)) from (8-chloro-1-cyclopropyl-6,7-difluoro-2,4-dioxo-1,4-dihydro-2H-quinazolin-3-yl)carbamic acid *tert*-butyl ester (Example 14) and (2,7-diaza-spiro[4.4]non-2-yl)carbamic acid *tert*-butyl ester (Culbertson T.P., Sanchez J.P., Gambino L., Sesnie J.A., *J. Med. Chem.*, .1990;33(8):2270-2275) (General Method B).

(mm) (7-[3-Benzyl-3-(*tert*-butoxycarbonylaminomethyl)pyrrolidin-1-yl]-8-chloro-1-cyclopropyl-6-fluoro-2,4-dioxo-1,4-dihydro-2*H*-quinazolin-3-yl}-carbamic acid tert-butyl ester (MS CI: *m/z* 658 (MH^+)) using (8-chloro-1-cyclopropyl-6,7-difluoro-2,4-dioxo-1,4-dihydro-2H-quinazolin-3-yl)carbamic acid *tert*-butyl ester (Example 14) and (3-benzylpyrrolidin-3-ylmethyl)carbamic acid *tert*-butyl ester (Example A7o) (General Method B).

(nn) {7-[(R)-3-((S)-1-*tert*-Butoxycarbonylaminoethyl)pyrrolidin-1-yl]-8-chloro-1-cyclopropyl-6-fluoro-2,4-dioxo-1,4-dihydro-2*H*-quinazolin-3-yl}-carbamic acid *tert*-butyl ester ((MS CI: *m/z* 582 (MH^+)) from (8-chloro-1-cyclopropyl-6,7-difluoro-2,4-dioxo-1,4-dihydro-2H-quinazolin-3-yl)carbamic acid tert-butyl ester (Example 14) and (R)-(S)-1-pyrrolidin-3-ylethyl)carbamic acid *tert*-butyl ester (Johnson D.R., Szoteck D.L., Domagala J.M., Stickney T.M., Michel A., Kampf J.W., *J. Heterocycl. Chem.*, 1992;29[6]:1481-1488) (General Method B).

(oo) [8-Chloro-1-cyclopropyl-6-fluoro-7-(3-hydroxyiminopyrrolidin-yl)-2,4-dioxo-1,4-dihydro-2*H*-quinazolin-3-yl]carbamic acid *tert*-butyl ester (MS CI: *m/z* 469 (MH^+)) from (8-chloro-1-cyclopropyl-6,7-difluoro-2,4-dioxo-

1,4-dihydro-2H-quinazolin-3-yl)carbamic acid *tert*-butyl ester (Example 14) and pyrrolidin-3-one oxime (Example A7) (General Method B).

(pp) [7-trans-(3-*tert*-Butoxycarbonylamino-4-trifluoromethylpyrrolidin-1-yl)-8-chloro-1-cyclopropyl-6-fluoro-2,4-dioxo-1,4-dihydro-2*H*-quinazolin-3-yl]-carbamic acid *tert*-butyl ester (MS Cl: *m/z* 622 (MH^+)) from (8-chloro-1-cyclopropyl-6,7-difluoro-2,4-dioxo-1,4-dihydro-2H-quinazolin-3-yl)carbamic acid *tert*-butyl ester (Example 14) and trans-(4-trifluoromethylpyrrolidin-3-yl)carbamic acid *tert*-butyl ester (Fukui H., Shibata T., Naito T. Nakano J., Maejima T., Senda H., Iwatani W., et al., *Bioorg. Med. Chem. Lett.*, 1998;8[20]:2833-2838) (General Method B).

(qq) (7-{(R)-3-(S)-1-(*tert*-Butoxycarbonylmethylamino) ethyl] pyrrolidin-1-yl}-8-chloro-1-cyclopropyl-6-fluoro-2,4-dioxo-1,4-dihydro-2*H*-quinazolin-3-yl)carbamic acid *tert*-butyl ester (MS Cl: *m/z* 596 (MH^+)) from (8-chloro-1-cyclopropyl-6,7-difluoro-2,4-dioxo-1,4-dihydro-2H-quinazolin-3-yl)carbamic acid *tert*-butyl ester (Example 14) and (R)-3-((S)-1-methylaminoethyl)pyrrolidine (*J. Het. Chem.*, 1992;29:1481) (General Method F).

(rr) trans-[7-((3-*tert*-Butoxycarbonylamino-4-phenylpyrrolidin-1-yl)-8-chloro-1-cyclopropyl-6-fluoro-2,4-dioxo-1,4-dihydro-2*H*-quinazolin-3-yl]carbamic acid *tert*-butyl ester (MS Cl: *m/z* 630 (MH^+)) using (8-chloro-1-cyclopropyl-6,7-difluoro-2,4-dioxo-1,4-dihydro-2*H*-quinazolin-3-yl)carbamic acid *tert*-butyl ester (Example 14) and trans-4-phenylpyrrolidin-3-ylamine carbamic acid *tert*-butyl ester (Bucsh R.A., Domagala J.M., Laborde E., Sesnie J.C., *J. Med. Chem.*, 1993;36[26]:4139-1451) (General Method B).

(ss) trans-{7-[3-*tert*-Butoxycarbonylamino-4-(4-hydroxyphenyl)-pyrrolidin-1-yl]-8-chloro-1-cyclopropyl-6-fluoro-2,4-dioxo-1,4-dihydro-2*H*-quinazolin-3-yl}-carbamic acid *tert*-butyl ester (MS: *m/z* 646 (MH^+)) using (8-chloro-1-cyclopropyl-6,7-difluoro-2,4-dioxo-1,4-dihydro-2*H*-quinazolin-3-yl)carbamic acid *tert*-butyl ester (Example 14) and trans-4-(4-hydroxyphenyl)-pyrrolidin-3-ylamine carbamic acid *tert*-butyl ester (Bucsh R.A., Domagala J.M., Laborde E., Sesnie J.C., *J. Med. Chem.*, 1993;36[26]:4139-4151) (General Procedure B).

(tt) {7-[3-(*tert*-Butoxycarbonylaminomethyl)piperidin-1-yl]-8-chloro-1-cyclopropyl-6-fluoro-2,4-dioxo-1,4-dihydro-2*H*-quinazolin-3-yl}carbamic acid *tert*-butyl ester (MS Cl: *m/z* 580 (M^+)) using (8-chloro-1-cyclopropyl-6,7-difluoro-2,4-dioxo-1,4-dihydro-2H-quinazolin-3-yl)carbamic acid *tert*-butyl ester (Example 14) and (piperidin-3-ylmethyl)carbamic acid *tert*-butyl ester (General Method B).

(uu) (7-{3-[(*tert*-Butoxycarbonylisopropylamino)methyl]pyrrolidin-1-yl}-8-chloro-1-cyclopropyl-6-fluoro-2,4-dioxo-1,4-dihydro-2H-quinazolin-3-yl)-carbamic acid *tert*-butyl ester (MS Cl: m/z 608 (M^+)) from (8-chloro-1-cyclopropyl-6,7-difluoro-2,4-dioxo-1,4-dihydro-2H-quinazolin-3-yl)carbamic acid *tert*-butyl ester (Example 14) and 3-(isopropylaminomethyl)pyrrolidine (Domagala et al., *J. Med. Chem.*, 1994;3889-3901) (General Method F).

(vv) {7-[3-(*tert*-Butoxycarbonylaminomethyl)pyrrolidin-1-yl]-6,8-dichloro-1-cyclopropyl-2,4-dioxo-1,4-dihydro-2*H*-quinazolin-3-yl}carbamic acid *tert*- butyl ester (MS Cl: *m/z* 584 (MH^+)) from (8-chloro-1-cyclopropyl-6,7-difluoro-2,4-dioxo-1,4-dihydro-2H-quinazolin-3-yl)carbamic acid *tert*-butyl ester (Example 14) and (pyrrolidine-3-ylmethyl)carbamic acid *tert*-butyl ester (General Method B).

(ww) [7-(3-*tert*-Butoxycarbonylamino-3-phenylpyrrolidin-1-yl)-8-chloro-1-cyclopropyl-6-fluoro-2,4-dioxo-1,4-dihydro-2H-quinazolin-3-yl]carbamic acid *tert*-butyl ester (^{1}H NMR (200 MHz, $CDCl_3$) δ 7.68 (d, 1H), 7.50-7.29 (m, 5H), 6.72 (s, 1H), 5.24 (s, 1H), 4.18-3.85 (m, 3H), 3.78-3.52 (m, 2H), 2.70 (s, 1H), 2.58-2.39 (m, 1H), 1.62-0.62 (m, 22H)) from (8-chloro-1-cyclopropyl-6,7-difluoro-2,4-dioxo-1,4-dihydro-2H-quinazolin-3-yl)carbamic acid *tert*-butyl ester (Example 14) and (3-phenylpyrrolidin-3-yl)carbamic acid *tert*-butyl ester (Example A30) using General Method B.

(xx) {7-[3-(*tert*-Butoxycarbonylaminomethyl)-4-methylpyrrolidin-1-yl]-8-chloro-1-cyclopropyl-6-fluoro-2,4-dioxo-1,4-dihydro-2H-quinazolin-3-yl}carbamic acid *tert*-butyl ester (MS ES: m/z 582 (MH^+)) from (8-chloro-1-cyclopropyl-6,7-difluoro-2,4-dioxo-1,4-dihydro-2H-quinazolin-3-yl)carbamic acid *tert*-butyl ester (Example 14) and trans-(4-methylpyrrolidin-3-yl)carbamic acid

tert-butyl ester (Kuniyoshi M., Seigo S., Keiji H., Takayoshi I., Eur. Pat. Appl., 1987, EP 208210) using general procedure F.

EXAMPLE 9

Deprotection of Quinazolin-2,4-diones

General Method A

Hydrogen chloride gas is bubbled into diethyl ether (or dichloromethane or dichloroethane for 15 minutes. The resulting solution is then cooled to 0°C and added to a solution of a 2,4-dioxo-1,4-dihydro-2*H*-quinazolin-3-yl}carbamic acid *tert*-butyl ester (Example 6), The reaction mixture is slowly warmed to room temperature. After 30 hours, the precipitate is filtered, washed with ether (or dichloromethane or dichloroethane) and hexanes, and dried under vacuum to afford the hydrochloride salt of the desired deprotected amine as a solid.

General Method B

A compound is dissolved in trifluoroacetic acid and stirred at 0°C for 3 to 8 hours. The acid is removed by blowing compressed air over the solution or concentrate in vacuo. The residue is twice co-evaporated with ethanol and dried in vacuo to yield the trifluoroacetate salt of the title compound as a solid.

General Method C

A 3-dibenzylamino-6-fluoro-1-substituted-2,4-dioxo-1,2,3,4-tetrahydro-quinazolin-7-yl)pyrrolidin-3-yl]carbamic acid tert-butyl ester and 20% Pd/C (cat.) are combined in methanol and shaken under 50 psi of hydrogen for 22.5 hours. The suspension is filtered through Celite and concentrated. The residue is purified via chromatography (SiO_2, $CHCl_3$) to give a solid. The solid is then dissolved in methylene chloride, cooled to 0°C, and HCl gas is passed through the solution for 10 minutes. The suspension is stirred for 2 hours and concentrated to give the title compound.

General Method D

Hydrogen chloride gas is bubbled through a solution of substrate in diethyl ether, and the solution stirred for 2 hours. The solvent is removed under reduced pressure to afford the desired title compound as a solid.

General Method E

A solution of substrate in ethanol is treated with a solution of ethanol saturated with gaseous hydrogen chloride. The reaction mixture is stirred at room temperature for 18 hours, and the solvent is removed in vacuo. The residue is dissolved in water, filtered through a fiber glass pad to clarify, and lyophilized. The solid residue is triturated with ether, filtered, washed with ether and dried in vacuo.

General Method F

A solution of 3-amino-7-chloro-1-cyclopropyl-6-fluoro-1H-pyrido[2,3-d]pyrimidine-2,4-dione (Example 24b), 1.2 eq. of heterocyclic amine side chain, and 1:3 *N,N*-diisopropylethylamine/acetonitrile is heated at 50°C for 18 hours. The reaction mixture is diluted with water, cooled to 0°C, and the solid is removed by filtration, washed with 50% aqueous acetonitrile, and dried in vacuo to give a solid that is dissolved in ethanol and treated with a solution of ethanol saturated with gaseous hydrogen chloride. The mixture is then stirred at room temperature for 18 hours. The solvent is removed in vacuo and the residue is triturated with ether. The solid is removed by filtration, washed with ether and dried in vacuo.

The following compounds are synthesized according to General Procedures A-F of Example 9:

(a) 3-Amino-7-(3-aminomethylpyrrolidin-1-yl)-8-chloro-1-cyclopropyl-6-fluoro-1*H*-quinazoline-2,4-dione hydrochloride (**Compound 1**) (mp 153-155°C, MS Cl: *m/z* 368 (MH^+)) from 7-[3-(*tert*-butoxycarbonylamino-methyl)pyrrolidin-1-yl]-8-chloro-1-cyclopropyl-6-fluoro-2,4-dioxo-1,4-dihydro-2*H*-quinazolin-3-yl}carbamic acid *tert*-butyl ester (Example 8a) using General Method A.

(b) 3-Amino-8-chloro-1-cyclopropyl-6-fluoro-7-piperazin-1-yl-1*H*-quinazoline-2,4-dione hydrochloride (**Compound 2**) (mp 156-159°C, MS CI: *m/z* 354 (MH^+)) from 7-[4-(*tert*-butoxycarbonylpiperazin-1-yl)-8-chloro-1-cyclopropyl-6-fluoro-2,4-dioxo-1,4-dihydro-2*H*-quinazolin-3-yl]carbamic acid *tert*-butyl ester (Example 8b) using General Method A.

(c) 3-Amino-7-[3-(aminomethyl)-3-methylpyrrolidin-1-yl]-8-chloro-1-cyclopropyl-6-fluoro-1*H*-quinazoline-2,4-dione hydrochloride (**Compound 3**) (mp 166-168°C, MS CI: *m/z* 382 (MH^+)) from {7-[3-(*tert*-butoxycarbonylaminomethyl)-3-methylpyrrolidin-1-yl]-8-chloro-1-cyclopropyl-6-fluoro-2,4-dioxo-1,4-dihydro-2*H*-quinazolin-3-yl}carbamic acid *tert*-butyl ester (Example 8c) using General Method A.

(d) 3-Amino-7-(6-amino-3-aza-bicyclo[3.1.0]hex-3-yl)-8-chloro-1-cyclopropyl-6-fluoro-1*H*-quinazolin-2,4-dione hydrochloride (**Compound 4**) (mp 111-114°C, MS CI: *m/z* 366 (MH^+)) from [7-(6-*tert*-butoxycarbonylamino-3-azabicyclo[3.1.0]hex-3-yl)-8-chloro-1-cyclopropyl-6-fluoro-2,4-dioxo-1,4-dihydro-2*H*-quinazolin-3-yl]carbamic acid *tert*-butyl ester (Example 8d) using General Method A.

(e) 3-Amino-7-((S)-3-N-methylaminopyrrolidin-1-yl)-8-chloro-1-cyclopropyl-6-fluoro-1*H*-quinazoline-2,4-dione hydrochloride (**Compound 5**) (mp 118-120°C, MS CI: *m/z* 368 (MH^+)) from {7-[(S)-3-(*tert*-butoxycarbonyl-N-methylamino)pyrrolidin-1-yl]-8-chloro-1-cyclopropyl-6-fluoro-2,4-dioxo-1,4-dihydro-2*H*-quinazolin-3-yl}carbamic acid *tert*-butyl ester (Example 8e) using General Method A.

(f) 3-Amino-7-((S)-3-aminopyrrolidin-1-yl)-8-chloro-1-(2,4-difluoroanilino)-6-fluoro-1*H*-quinazoline-2,4-dione hydrochloride (**Compound 6**) (mp 184-186°C, MS CI: *m/z* 427(MH^+)) from {7-[(S)-3-(*tert*-butoxycarbonylamino)pyrrolidin-1-yl]-8-chloro-1-(2,4-difluoroanilino)-6-fluoro-1,4-dihydro-2,4-dioxo-2*H*-quinazolin-3-yl}carbamic acid *tert*-butyl ester (Example 8f) using General Method A.

(g) 3-Amino-7-[(S)-3-aminopyrrolidin-1-yl]-1-cyclopropylamino-6,8-difluoro-1H-quinazoline-2,4-dione hydrochloride (**Compound 7**) (mp 288°C

(dec.), MS EI: *m/z* 338 (M^+)) from 7-[(S)-3-(*tert*-butoxycarbonylamino)-pyrrolidin-1-yl]-1-cyclopropylamino-6,8-difluoro-1,4-dihydro-2,4-dioxo-2H-quinazolin-3-yl}carbamic acid *tert*-butyl ester (Example 8g) using General Method A.

(h) 3-Amino-7-[(S)-3-aminopyrrolidin-1-yl]-1-cyclopropylamino-5,8-difluoro-1*H*-quinazoline-2,4-dione hydrochloride (**Compound 8**) (mp 338°C (dec), MS EI: *m/z* 338 (M^+)) from {7-[(S)-3-(*tert*-butoxycarbonylamino)-pyrrolidin-1-yl]-1-cyclopropylamino-5,8-difluoro-1,4-dihydro-2,4-dioxo-2*H*-quinazolin-3-yl}carbamic acid *tert*-butyl ester (Example 8h) using General Method A

(i) 3-Amino-7-((S)-3-aminopyrrolidin-1-yl)-1-cyclopropyl-5,6,8-trifluoro-1*H*-quinazoline-2,4-dione hydrochloride (**Compound 9**) (mp 271°C (dec.), MS CI: *m/z* 356 (MH^+)) from {7-[(S)-3-(*tert*-butoxycarbonylamino)-pyrrolidin-1-yl]-1-cyclopropyl-1,4-dihydro-2,4-dioxo-5,6,8-trifluoro-2*H*-quinazolin-3-yl}-carbamic acid *tert*-butyl ester (Example 8i) using General Method A.

(j) 3-Amino-7-(3-aminopyrrolidin-1-yl)-8-chloro-1-cyclopropyl-6-fluoro-1*H*-quinazoline-2,4-dione hydrochloride (**Compound 10**) (mp 134-136°C, MS CI: *m/z* 354 (MH^+)) from {7-[3-(*tert*-butoxycarbonylamino)-pyrrolidin-1-yl]-8-chloro-1-cyclopropyl-6-fluoro-2,4-dioxo-1,4-dihydro-2*H*-quinazolin-3-yl}carbamic acid *tert*-butyl ester (Example 8a) using General Method A.

(k) 7-((S)-3-Aminopyrrolidin-1-yl)-1-cyclopropyl-3,5-diamino-6,8-difluoro-1*H*-quinazoline-2,4-dione hydrochloride (**Compound 11**) (mp 215-218°C (dec.), MS EI: 352 (M^+)) from {5-amino-7-[(S)-3-(*tert*-butoxycarbonylamino)pyrrolidin-1-yl]-1-cyclopropyl-6,8-difluoro-1,4-dihydro-2,4-dioxo-2H-quinazolin-3-yl}carbamic acid *tert*-butyl ester (Example 12) using Method A.

(l) 3-Amino-7-(3-hydroxymethylpyrrolidin-1-yl)-8-chloro-1-cyclopropyl-6-fluoro-1*H*-quinazoline-2,4-dione hydrochloride (**Compound 12**) (mp 78-80°C, MS CI: *m/z* 369 (MH^+)) from [7-(3-hydroxymethylpyrrolidin-1-yl)-

8-chloro-1-cyclopropyl-6-fluoro-2,4-dioxo-1,4-dihydro-2*H*-quinazolin-3-yl]carbamic acid tert-butyl ester (Example 8k) using Method A.

(m) 3-Amino-7-(3-aminoethylpyrrolidin-1-yl)-8-chloro-1-cyclopropyl-6-fluoro-1*H*-quinazoline-2,4-dione hydrochloride (**Compound 13**) (mp 158-160°C, MS CI: *m/z* 382 (MH^+)) from {7-[3-(*tert*-butoxycarbonylamino-ethyl)pyrrolidin-1-yl]-8-chloro-1-cyclopropyl-6-fluoro-2,4-dioxo-1,4-dihydro-2*H*-quinazolin-3-yl}carbamic acid *tert*-butyl ester (Example 8l) using Method A.

(n) 3-Amino-7-((S)-7-amino-5-azaspiro[2.4]hept-5-yl)-8-chloro-1-cyclopropyl-6-fluoro-1*H*-quinazoline-2,4-dione hydrochloride (**Compound 14**) (mp 177-179°C, MS CI: *m/z* 380 (MH^+) from [7-(7-*tert*-butoxycarbonylamino-5-azaspiro[2.4]hept-5-yl)-8-chloro-1-cyclopropyl-6-fluoro-2,4-dioxo-1,4-dihydro-2*H*-quinazolin-3-yl]carbamic acid *tert*-butyl ester (Example 8m) using General Method A.

(o) 3-Amino-7-[(R)-3-(1-amino-1-methylethyl)pyrrolidin-1-yl]-8-chloro-1-cyclopropyl-6-fluoro-1*H*-quinazoline-2,4-dione hydrochloride (**Compound 15**) (mp 117-120°C, MS CI: *m/z* 396 (MH^+)) from {7-[(R)-3-(1-*tert*-butoxycarbonylamino-1-methylethyl)pyrrolidin-1-yl]-8-chloro-1-cyclopropyl-6-fluoro-2,4-dioxo-1,4-dihydro-2*H*-quinazolin-3-yl}carbamic acid *tert*-butyl ester (Example 8n) using General Method A.

(p) 3-Amino-7-(3-aminomethylpyrrolidin-1-yl)-1-cyclopropyl-6-fluoro-1*H*-quinazoline-2,4-dione hydrochloride (**Compound 16**) (mp 170-172°C, MS CI: *m/z* 334 (MH^+)) from {7-[3-(*tert*-butoxycarbonylamino-methyl)pyrrolidin-1-yl]-1-cyclopropyl-6-fluoro-2,4-dioxo-1,4-dihydro-2*H*-quinazolin-3-yl}carbamic acid *tert*-butyl ester (Example 8o) using General Method A.

(q) 3-Amino-7-(pyrrolidin-1-yl)-8-chloro-1-cyclopropyl-6-fluoro-1*H*-quinazoline-2,4-dione hydrochloride (**Compound 17**) (mp 96-98°C, MS CI: *m/z* 339 (MH^+)) from [7-(pyrrolidin-1-yl)-8-chloro-1-cyclopropyl-6-fluoro-2,4-dioxo-1,4-dihydro-2*H*-quinazolin-3-yl]carbamic acid *tert*-butyl ester (Example 8p) using General Method A.

(r) 3-Amino-7-(3-aminopyrrolidin-1-yl)-8-chloro-6-fluoro-1-isopropyl-1*H*-quinazoline-2,4-dione trifluoroacetate (**Compound 18**) (mp 151°C, MS El: *m/z* 356 (MH^+)) from {7-[3-(*tert*-butoxycarbonylamino)-pyrrolidin-1-yl]-8-chloro-6-fluoro-1-isopropyl-2,4-dioxo-6-fluoro-2*H*-quinazolin-3-yl}carbamic acid *tert*-butyl ester (Example 8q) using General Method B.

(s) 3-Amino-7-(3-aminopyrrolin-1-yl)-1-*sec*-butyl-8-chloro-6-fluoro-1*H*-quinazoline-2,4-dione trifluoroacetate (**Compound 19**) (mp 115°C) from {7-[3-(*tert*-butoxycarbonylamino)pyrrolidin-1-yl]-1-*sec*-butyl-8-chloro-6-fluoro-2,4-dioxo-2*H*-quinazolin-3-yl}carbamic acid *tert*-butyl ester (Example 8r) using General Method B.

(t) 3-Amino-7-[3-aminopyrrolidin-1-yl]-1-cyclopropyl-6-fluoro-8-methoxy-1*H*-quinazoline-2,4-dione hydrochloride (**Compound 20**) (mp 216-218°C, MS El: *m/z* 350 (MH^+)) from {7-[3-(*tert*-butoxycarbonylamino)-pyrrolidin-1-yl]-1-cyclopropyl-6-fluoro-8-methoxy-2,4-dioxo-1,4-dihydro-2*H*-quinazolin-3-yl}carbamic acid *tert*-butyl ester (Example 8s) using Method A.

(u) 3-Amino-7-[3-aminopyrrolidin-1-yl]-8-chloro-1-cyclobutylamino-6-fluoro-1*H*-quinazoline-2,4-dione hydrochloride (**Compound 21**) (mp 205-208°C (dec.), MS El: *m/z* 368 (MH^+)) from {7-[3-(*tert*-butoxycarbonylamino)pyrrolidin-1-yl]-8-chloro-1-cyclobutylamino-6-fluoro-2,4-dioxo-1,4-dihydro-2*H*-quinazolin-3-yl}carbamic acid *tert*-butyl ester (Example 8t) using General Method A.

(v) 3-Amino-7-(3-aminopyrrolidin-1-yl)-1-cyclopropyl-8-fluoro-1*H*-quinazoline-2,4-dione trifluoroacetate (**Compound 22**) (mp 210-212°C, MS El: *m/z* 320 (MH^+)) from {7-[3-(*tert*-butoxycarbonylamino)pyrrolidin-1-yl]-1-cyclopropyl-8-fluoro-2,4-dioxo-1,4-dihydro-2*H*-quinazolin-3-yl}carbamic acid *tert*-butyl ester (Example 8u) using Method A.

(w) 3-Amino-7-(3-aminopyrrolidin-1-yl)-6-chloro-1-cyclopropyl-8-fluoro-1*H*-quinazoline-2,4-dione trifluoroacetate (**Compound 23**) (mp 135-137°C, MS El: *m/z* 354 (MH^+)) from {7-[3-(*tert*-butoxycarbonylamino)-pyrrolidin-1-yl]-6-chloro-1-cyclopropyl-8-fluoro-2,4-dioxo-1,4-dihydro-2*H*-

quinazolin-3-yl}carbamic acid *tert*-butyl ester (Example 8v) using General Method B.

(x) 3-Amino-7-((S)-3-aminopyrrolidin-1-yl)-1-cyclopropylmethyl-8-fluoro-1*H*-quinazoline-2,4-dione hydrochloride (**Compound 24**) (mp >250°C, MS CI: m/z 334 (MH^+)) from [(S)-1-(1-cyclopropylmethyl-3-dibenzylamino-6-fluoro-2,4-dioxo-1,2,3,4-tetrahydroquinazolin-7-yl)pyrrolidin-3-yl]carbamic acid tert-butyl ester (Example 8w) using General Method C.

(y) 3-Amino-7-[(R)-3-(1-amino-1-methylethyl)pyrrolidin-1-yl]-1-cyclopropylmethyl-8-fluoro-1*H*-quinazoline-2,4-dione hydrochloride (**Compound 25**) (mp >250°C, MS CI: *m/z* 376 (MH^+)) from {1-[(R)-1-(cyclopropylmethyl-3-dibenzylamino-6-fluoro-2,4-dioxo-1,2,3,4-tetrahydroquinazolin-7-yl)pyrrolidin-3-yl]-1-methylethyl}carbamic acid tert-butyl ester (Example 8x) using General Method C.

(z) 3-Amino-7-((S)-3-aminopyrrolidin-1-yl)-1-ethyl-8-fluoro-1*H*-quinazoline-2,4-dione hydrochloride (**Compound 26**) (mp 248-251°C, MS CI: m/z 308 (MH^+)) from [(S)-1-(3-dibenzylamino-1-ethyl-6-fluoro-2,4-dioxo-1,2,3,4-tetrahydroquinazolin-7-yl)pyrrolidin-3-yl]-carbamic acid tert-butyl ester (Example 8y) using General Method C.

(aa) 3-Amino-1-ethyl-6-fluoro-7-[(R)-3-(1-amino-1-methylethyl)-pyrrolidin-1-yl]-1H-quinazoline-2,4-dione hydrochloride (**Compound 27**) (mp >250°C, MS CI: *m/z* 350 (MH^+)) from [(R)-1-(3-dibenzylamino-1-ethyl-6-fluoro-2,4-dioxo-1,2,3,4-tetrahydroquinazolin-7-yl)-1-methyl-1-pyrrolidin-3-ylethyl]carbamic acid tert-butyl ester (Example 8z) using Method C.

(bb) 3-Amino-7-((S)-3-aminopyrrolidin-1-yl)-1-cyclopropyl-6-fluoro-1*H*-quinazoline-2,4-dione hydrochloride (**Compound 28**) (mp >250°C, MS CI: *m/z* 320 (MH^+)) from 3-amino-{7-[(S)-3-(tert-butoxycarbonylamino)pyrrolidin-1-yl]-1-cyclopropyl-6-fluoro-1H-quinazoline-2,4-dione (Example 25) using General Method A.

(cc) 3-Amino-7-(3-aminopyrrolidin-1-yl)-1-cyclopropyl-6-fluoro-8-methyl-1H-quinazoline-2,4-dione trifluoroacetate (**Compound 29**) (mp 110-112°C, MS ES, MH^+) m/z 334) from [7-(3-tert-butoxycarbonylamino-

pyrrolidin-1-yl)-1-cyclopropyl-6-fluoro-8-methyl-2,4-dioxo-1,4-dihydro-2H-quinazolin-3-yl]carbamic acid *tert*-butyl ester (Example 8aa) using General Method B.

(dd) 3-Amino-7-(3-aminomethylpyrrolidin-1-yl)-1-cyclopropyl-6-fluoro-8-methyl-1H-quinazoline-2,4-dione trifluoroacetate (**Compound 30**) (mp 82-84°C, MS ES, m/z 348 (MH^+)) from {7-[3-(tert-butoxycarbonylaminomethyl)-pyrrolidin-1-yl]-1-cyclopropyl-6-fluoro-8-methyl-2,4-dioxo-1,4-dihydro-2H-quinazolin-3-yl} carbamic acid tert-butyl ester (Example 8bb) using General Method B.

(ee) 3-Amino-7-(3-aminopyrrolidin-1-yl)-1-cyclopropyl-8-fluoro-6-methoxy-1H-quinazoline-2,4-dione hydrochloride (**Compound 31**) (mp 208-210°C, MS ES, m/z 350(MH^+)) from [7-(3-tert-butoxycarbonylamino-pyrrolidin-1-yl)-1-cyclopropyl-8-fluoro-6-methoxy-2,4-dioxo-1,4-dihydro-2H-quinazolin-3-yl]carbamic acid *tert*-butyl ester (Example 8cc) using General Method A.

(ff) 3-Amino-7-(3-aminomethylpyrrolidin-1-yl)-1-cyclopropyl-6-fluoro-8-methoxy-1H-quinazoline-2,4-dione hydrochloride (**Compound 32**) (mp 180-182°C, MS ES, m/z 364 (MH^+)) from {7-[3-(*tert*-butoxycarbonylaminomethyl)pyrrolidin-1-yl]-1-cyclopropyl-6-fluoro-8-methoxy-2,4-dioxo-1,4-dihydro-2H-quinazolin-3-yl}-carbamic acid *tert*-butyl ester (Example 8dd) using General Method A.

(gg) 3-Amino-7-(3-aminopyrrolidin-1-yl)-1-cyclopropyl-8-ethoxy-6-fluoro-1H-quinazoline-2,4-dione hydrochloride (**Compound 33**) (mp 220°C, MS ES, m/z 364 (MH^+)) from [7-(3-*tert*-butoxycarbonylaminopyrrolidin-1-yl)-1-cyclopropyl-8-ethoxy-6-fluoro-2,4-dioxo-1,4-dihydro-2H-quinazolin-3-yl]carbamic acid tert-butyl ester (Example 8ee) using General Method A.

(hh) 3-Amino-7-(3-aminopyrrolidin-1-yl)-1-cyclopropyl-6-fluoro-2,4-dioxo-1,2,3,4-tetrahydroquinazoline-8-carbonitrile hydrochloride (**Compound 34**) (mp 277°C, MS ES, m/z 345 (MH^+)) from [7-(3-*tert*-butoxycarbonylaminopyrrolidin-1-yl)-8-cyano-1-cyclopropyl-6-fluoro-2,4-dioxo-

1,4-dihydro-2H-quinazolin-3-yl]carbamic acid tert-butyl ester (Example 8ff) using General Method A.

(ii) 3-Amino-8-chloro-1-cyclopropyl-6-fluoro-7-(3-[1,2,3-triazol]-1-yl-pyrrolidin-1-yl)-1H-quinazoline-2,4-dione trifluoroacetate (**Compound 35**) (mp 145-147°C, MS ES, m/z 406 (MH+)) from [8-chloro-1-cyclopropyl-6-fluoro-2,4-dioxo-7-(3-[1,2,3-triazol]-1-yl-pyrrolidin-1-yl)-1,4-dihydro-2H-quinazolin-3-yl]carbamic acid *tert*-butyl ester (Example 8gg) using General Method B.

(jj) 3-Amino-7-[(S)-3-((R)-1-aminoethyl)pyrrolidin-1-yl]-1-cyclopropyl-6-fluoro-8-methoxy-1H-quinazoline-2,4-dione hydrochloride (**Compound 36**), (mp 215-217°C) from {(R)-1-[(S)-1-(3-amino-1-cyclopropyl-6-fluoro-8-methoxy-2,4-dioxo-1,2,3,4-tetrahydroquinazolin-7-yl)pyrrolidin-3-yl]ethyl}-carbamic acid *tert*-butyl ester (Example 28a) using General Method E.

(kk) 3-Amino-7-[(S)-3-((S)-1-aminoethyl)pyrrolidin-1-yl]-1-cyclopropyl-6-fluoro-8-methoxy-1H-quinazoline-2,4-dione hydrochloride (**Compound 37**) (mp 221-223°C) from {(S)-1-[(S)-1-(3-amino-1-cyclopropyl-6-fluoro-8-methoxy-2,4-dioxo-1,2,3,4-tetrahydroquinazolin-7-yl)pyrrolidin-3-yl]ethyl}-carbamic acid *tert*-butyl ester (Example 28b) using General Method A.

(ll) 3-Amino-7-[(S)-3-((R)-1-aminoethyl)pyrrolidin-1-yl]-1-cyclopropyl-6-fluoro-8-methyl-1H-quinazoline-2,4-dione hydrochloride (**Compound 38**) (mp 197-199°C) from {(R)-1-[(S)-1-(3-amino-1-cyclopropyl-6-fluoro-8-methyl-2,4-dioxo-1,2,3,4-tetrahydroquinazolin-7-yl)pyrrolidin-3-yl]ethyl}carbamic acid *tert*-butyl ester (Example 28c) using General Method E.

(mm) 3-Amino-7-[(S)-3-((S)-1-aminoethyl)pyrrolidin-1-yl]-1-cyclopropyl-6-fluoro-8-methyl-1H-quinazoline-2,4-dione hydrochloride (**Compound 39**) (mp 192-194°C) from {(S)-1-[(S)-1-(3-amino-1-cyclopropyl-6-fluoro-8-methyl-2,4-dioxo-1,2,3,4-tetrahydroquinazolin-7-yl)pyrrolidin-3-yl]-ethyl}carbamic acid *tert*-butyl ester (Example 28d) using General Method E.

(nn) 5-Amino-9-((S)-3-aminopyrrolidin-1-yl)-8-fluoro-3-methyl-2,3-dihydro-1-oxa-3a,5-diazaphenalene-4,6-dione hydrochloride (**Compound 40**) (mp 202-204°C) from [(S)-1-(5-amino-8-fluoro-3-methyl-4,6-dioxo-2,3,5,6-

tetrahydro-4H-1-oxa-3a,5-diazaphenalen-9-yl)pyrrolidin-3-yl]carbamic acid tert-butyl ester (Example 28e) using General Method E.

(oo) 5-Amino-9-[(R)-3-((S)-1-aminoethyl)pyrrolidin-1-yl]-8-fluoro-3-methyl-2,3-dihydro-1-oxa-3a,5-diazaphenalene-4,6-dione hydrochloride (**Compound 41**) (mp 192-194°C) from {(S)-1-[(R)-1-(5-amino-8-fluoro-3-methyl-4,6-dioxo-2,3,5,6-tetrahydro-4H-1-oxa-3a,5-diazaphenalen-9-yl)-pyrrolidin-3-yl]ethyl}carbamic acid *tert*-butyl ester (Example 28f) using General Method E.

(pp) 2-Amino-8-((S)-3-aminopyrrolidin-1-yl)-9-fluoro-5-methyl-6,7-dihydro-5H-pyrido[3,2,1-ij]quinazoline-1,3-dione, hydrochloride (**Compound 42**) (mp 202-204°C) from [(S)-1-(2-amino-9-fluoro-5-methyl-1,3-dioxo-2,3,6,7-tetrahydro-1H,5H-pyrido[3,2,1-ij]quinazolin-8-yl)pyrrolidin-3-yl]carbamic acid *tert*-butyl ester (Example 28g) using General Method E.

(qq) 2-Amino-8-[(R)-3-((S)-1-aminoethyl)pyrrolidin-1-yl]-9-fluoro-5-methyl-6,7-dihydro-5H-pyrido[3,2,1-ij]quinazoline-1,3-dione hydrochloride (**Compound 43**) (mp 197-199°C) from {(R)-3-[(S)-1-(2-amino-9-fluoro-5-methyl-1,3-dioxo-2,3,6,7-tetrahydro-1H,5H-pyrido[3,2,1-ij]quinazolin-8-yl)-pyrrolidin-3-yl}ethyl]carbamic acid *tert*-butyl ester (Example 28h) using General Method E.

(rr) 3-Amino-7-((S)-3-aminopyrrolidin-1-yl)-1-cyclopropyl-6-fluoro-1H-pyrido[2,3-d]pyrimidine-2,4-dione hydrochloride (**Compound 44**) (mp 213-215°C) from [1-(3-Amino-1-cyclopropyl-6-fluoro-2,4-dioxo-1,2,3,4-tetrahydro-pyrido[2,3-d]pyrimidin-7-yl)pyrrolidin-3-yl]carbamic acid *tert*-butyl ester (Example 28i) using General Method E.

(ss) 3-Amino-7-(6-amino-3-azabicyclo[3.1.0]hex-3-yl)-1-cyclopropyl-6-fluoro-1H-pyrido[2,3-d]pyrimidine-2,4-dione, hydrochloride (**Compound 45**) (mp 268-270°C) from 3-amino-7-chloro-1-cyclopropyl-6-fluoro-1H-pyrido[2,3-d]pyrimidine-2,4-dione (Example 24b) and 3-azabicyclo[3.1.0]hex-6-ylcarbamic acid tert-butyl ester using General Method F.

(tt) 3-Amino-7-(3-aminomethyl-3-methylpyrrolidin-1-yl)-1-cyclopropyl-6-fluoro-1H-pyrido[2,3-d]pyrimidine-2,4-dione, hydrochloride

(**Compound 46**) (mp 187-189°C) from 3-amino-7-chloro-1-cyclopropyl-6-fluoro-1H-pyrido[2,3-d]pyrimidine-2,4-dione (Example 24b) and [1-methyl-(3-methylpyrrolidin-3-yl)]methylcarbamic acid *tert*-butyl ester (*J. Med. Chem.*, 1992;361-367) using General Method F.

(uu) 3-Amino-1-cyclopropyl-6-fluoro-7-(octahydropyrrolo[3,4-c]pyridin-2-yl)-1H-pyrido[2,3-d]pyrimidine-2,4-dione hydrochloride (**Compound 47**) (mp 200-203°C) from 3-amino-7-chloro-1-cyclopropyl-6-fluoro-1H-pyrido[2,3-d]pyrimidine-2,4-dione (Example 24b) and (3aS,7aR)-octahydropyrrolo[3,4-c]pyridine-5-carboxylic acid tert-butyl ester (Example A27) using General Method F.

(vv) 3-Amino-1-cyclopropyl-6-fluoro-7-(octahydropyrrolo[3,4-b]pyridin-2-yl)-1H-pyrido[2,3-d]pyrimidine-2,4-dione hydrochloride (**Compound 48**) (mp 200-202°C) from 3-amino-7-chloro-1-cyclopropyl-6-fluoro-1H-pyrido[2,3-d]pyrimidine-2,4-dione (Example 24b) and octahydropyrrolo[3,4-b]pyridine-5-carboxylic acid *tert*-butyl ester using General Method F.

(ww) 3-Amino-7-[(R)-3-(1-amino-1-methylethyl)pyrrolidin-1-yl]-1-cyclopropyl-6-fluoro-1H-pyrido[2,3-d]pyrimidine-2,4-dione hydrochloride (**Compound 49**) (mp >260°C) from 3-amino-7-chloro-1-cyclopropyl-6-fluoro-1H-pyrido[2,3-d]pyrimidine-2,4-dione (Example 24b) and (R)-3-(1-amino-1-methylethyl)-pyrrolidine using General Method F.

(xx) 3-Amino-7-(3-aminomethylpiperidin-1-yl)-1-cyclopropyl-6-fluoro-1H-pyrido[2,3-d]pyrimidine-2,4-dione, dihydrochloride(**Compound 50**) (mp 152-154°C) from 3-amino-7-chloro-1-cyclopropyl-6-fluoro-1H-pyrido[2,3-d]pyrimidine-2,4-dione (Example 24b) and (3-aminomethylpiperidin-1-yl)carbamic acid tert-butyl ester (Hilpert K. et al., *J. Med. Chem.*, 1994;37[23]:3889-3901) using General Method F.

(yy) trans-3-Amino-7-(3-aminomethyl-4-trifluoromethylpyrrolidin-1-yl)-1-cyclopropyl-6-fluoro-1H-pyrido[2,3-d]pyrimidine-2,4-dione hydrochloride (**Compound 51**) (mp 214-216°C) from 3-amino-7-chloro-1-cyclopropyl-6-fluoro-1H-pyrido[2,3-d]pyrimidine-2,4-dione (Example 24b) and 3-aminomethyl-4-trifluoromethylpyrrolidine (Li Q., Wang W., Berst K.B., Claiborne A.,

Hasvold L., Raye K., Tufano M., et al., *Bioorg. Med. Chem. Lett.*, 1998;8:1953-1958) using General Method F.

(zz) 3-Amino-1-cyclopropyl-6-fluoro-7-[(R)-3-((R)-1-methylamino-ethyl)pyrrolidin-1-yl]-1H-pyrido[2,3-d]pyrimidine-2,4-dione hydrochloride (**Compound 52**) (mp 137-139°C) from 3-amino-7-chloro-1-cyclopropyl-6-fluoro-1H-pyrido[2,3-d]pyrimidine-2,4-dione (Example 24b) and (R)-3-((R)-1-methylaminoethyl)pyrrolidine using General Method F.

(aaa) 3-Amino-7-[(R)-3-((S)-1-aminoethyl)pyrrolidin-1-yl]-1-cyclopropyl-6-fluoro-1H-pyrido[2,3-d]pyrimidine-2,4-dione hydrochloride (**Compound 53**) (mp >260°C) from {(S)-1-[(R)-1-(3-amino-1-cyclopropyl-6-fluoro-2,4-dioxo-1,2,3,4-tetrahydropyrido[2,3-d]pyrimidin-7-yl)pyrrolidin-3-yl]-ethyl}carbamic acid *tert*-butyl ester (Example 28j) using General Method E.

(bbb) 3-Amino-7-[3-(1-aminopropyl)pyrrolidin-1-yl]-1-cyclopropyl-6-fluoro-8-methyl-1*H*-quinazoline-2,4-dione hydrochloride (**Compound 54**) (MS CI: *m/z* 376 (MH^+)) from {1-[1-(3-amino-1-cyclopropyl-6-fluoro-8-methyl-2,4-dioxo-1,2,3,4-tetrahydroquinazolin-7-yl)pyrrolidin-3-yl]propyl}carbamic acid *tert*-butyl ester (Example 28ooo) using General Method E.

(ccc) 3-Amino-1-cyclopropyl-6-fluoro-8-methyl-7-[(R)-3-((S)-1-methylaminoethyl)pyrrolidin-1-yl]-1*H*-quinazoline-2,4-dione hydrochloride (**Compound 55**) (mp 153-5°C) from {(S)-1-[(R)-1-(3-Amino-1-cyclopropyl-6-fluoro-8-methyl-2,4-dioxo-1,2,3,4-tetrahydroquinazolin-7-yl)pyrrolidin-3-yl]-ethyl}methylcarbamic acid *tert*-butyl ester (Example 28ppp) using General Method E.

(ddd) 3-Amino-7-[7-(1-aminoethyl)-5-azaspiro[2.4]hept-5-yl]-1-cyclopropyl-6-fluoro-8-methyl-1*H*-quinazoline-2,4-dione hydrochloride (**Compound 56**) (mp 178-80°C, MS CI: *m/z* 388 (MH^+)) from {1-[5-(3-amino-1-cyclopropyl-6-fluoro-8-methyl-2,4-dioxo-1,2,3,4-tetrahydroquinazolin-7-yl)-5-aza-spiro[2.4]hept-7-yl]-ethyl}carbamic acid *tert*-butyl ester (Example 28qqq) using General Method E.

(eee) 1-(3-Amino-8-chloro-1-cyclopropyl-6-fluoro-2,4-dioxo-1,2,3,4-tetrahydroquinazolin-7-yl)piperidine-3-carboxylic acid amide (**Compound 58**)

(mp 141-144°C, MS CI: *m/z* 396 (MH^+)) from [7-(3-carbamoylpiperidin-1-yl)-8-chloro-1-cyclopropyl-6-fluoro-2,4-dioxo-1,4-dihydro-2*H*-quinazolin-3-yl]-carbamic acid *tert*-butyl ester using General Method A (Example 8hh).

(lll) 3-Amino-[7-trans-3-aminomethyl-4-trifluoromethylpyrrolidin-1-yl]-8-chloro-1-cyclopropyl-6-fluoro-1*H*-quinazoline-2,4-dione hydrochloride (**Compound 59**) (mp 171-173°C, MS CI: *m/z* 436 (MH^+)) from {7-[trans-3-(*tert*-butoxycarbonylaminomethyl)-4-trifluoromethylpyrrolidin-1-yl]-8-chloro-1-cyclopropyl-6-fluoro-2,4-dioxo-1,4-dihydro-2*H*-quinazolin-3-yl}carbamic acid *tert*-butyl ester (Example 8ii) using General Method E.

(ggg) 3-Amino-8-chloro-1-cyclopropyl-6-fluoro-7-{3-[(2,2,2-trifluoro-ethylamino)methyl]pyrrolidin-1-yl}-1*H*-quinazoline-2,4-dione hydrochloride (**Compound 60**) (mp 163-164°C, MS CI: *m/z* 450 (MH^+)) from 8-chloro-1-cyclopropyl-6-fluoro-2,4-dioxo-7-{3-[(2,2,2-trifluoroethylamino)methyl]-pyrrolidin-1-yl}-1,4-dihydro-2*H*-quinazolin-3-yl)carbamic acid *tert*-butyl ester (Example 8jj) using General Method E.

(hhh) 3-Amino-8-chloro-1-cyclopropyl-6-fluoro-7-(5-methylhexahydro-pyrrolo[3,4-*c*]pyrrol-2-yl)-1*H*-quinazoline-2,4-dione hydrochloride (**Compound 61**) (mp 133-1355°C, MS CI: *m/z* 394 (MH^+)) from [8-chloro-1-cyclopropyl-6-fluoro-7-(5-methylhexahydropyrrolo[3,4-*c*]pyrrol-2-yl)-2,4-dioxo-1,4-dihydro-2*H*-quinazolin-3-yl]carbamic acid *tert*-butyl ester (Example 8kk) using General Method E.

(iii) 3-Amino-8-chloro-1-cyclopropyl-7-(2,7-diazaspiro[4.4]non-2-yl)-6-fluoro-1*H*-quinazoline-2,4-dione (**Compound 62**) (mp 147-149°C, MS CI: *m/z* 394 (MH^+)) from [8-chloro-1-cyclopropyl-7-(2,7-diazaspiro[4.4]non-2-yl)-6-fluoro-2,4-dioxo-1,4-dihydro-2*H*-quinazolin-3-yl]carbamic acid *tert*-butyl ester (Example 8ll) using General Method E.

(jjj) 3-Amino-7-(3-aminomethyl-3-benzylpyrrolidin-1-yl)-8-chloro-1-cyclopropyl-6-fluoro-1*H*-quinazoline-2,4-dione hydrochloride (**Compound 63**) (mp 148-150°C, MS CI: *m/z* 458 (MH^+)) from (7-[3-benzyl-3-(*tert*-butoxycarbonylaminomethyl)pyrrolidin-1-yl]-8-chloro-1-cyclopropyl-6-fluoro-

2,4-dioxo-1,4-dihydro-2*H*-quinazolin-3-yl}carbamic acid *tert*-butyl ester (Example 8mm) using General Method E.

(kkk) 3-Amino-7-[(R)-3-((S)-1-aminoethyl)pyrrolidin-1-yl]-8-chloro-1-cyclopropyl-6-fluoro-1*H*-quinazoline-2,4-dione hydrochloride (**Compound 64**) (mp 164-166°C, MS CI: *m/z* 382 (MH^+)) from {7-[(R)-3-((S)-1-*tert*-butoxycarbonylaminoethyl)pyrrolidin-1-yl]-8-chloro-1-cyclopropyl-6-fluoro-2,4-dioxo-1,4-dihydro-2*H*-quinazolin-3-yl}carbamic acid *tert*-butyl ester (Example 8nn) using General Method E.

(lll) 3-Amino-8-chloro-1-cyclopropyl-6-fluoro-7-(3-hydroxyimino-pyrrolidin-1-yl)-1*H*-quinazoline-2,4-dione (**Compound 65**) (mp 147-9°C, MS CI: *m/z* 368 (MH^+)) from) [8-chloro-1-cyclopropyl-6-fluoro-7-(3-hydroxyimino-pyrrolidin-yl)-2,4-dioxo-1,4-dihydro-2*H*-quinazolin-3-yl]carbamic acid *tert*-butyl ester (Example 8oo) using General Method E.

(mmm) 3-Amino-7-[trans-3-amino-4-trifluoromethylpyrrolidin-1-yl]-8-chloro-1-cyclopropyl-6-fluoro-1*H*-quinazoline-2,4-dione hydrochloride (**Compound 66**) (mp 181-183°C, MS CI: *m/z* 422 (MH^+)) from [7-(trans-3-*tert*-butoxycarbonylamino-4-trifluoromethylpyrrolidin-1-yl)-8-chloro-1-cyclopropyl-6-fluoro-2,4-dioxo-1,4-dihydro-2*H*-quinazolin-3-yl]carbamic acid *tert*-butyl ester (Example 8pp) using General Method E.

(nnn) 3-Amino-8-chloro-1-cyclopropyl-6-fluoro-7-[(R)-3-(S)-1-methylaminoethyl)pyrrolidin-1-yl]-1*H*-quinazoline-2,4-dione hydrochloride (**Compound 67**) (mp 122-124°C, MS CI: *m/z* 396 (MH^+)) from (7-{(R)-3-(S)-1-(*tert*-butoxycarbonylmethylamino)ethyl]pyrrolidin-1-yl}-8-chloro-1-cyclopropyl-6-fluoro-2,4-dioxo-1,4-dihydro-2*H*-quinazolin-3-yl)carbamic acid *tert*-butyl ester (Example 8qq) using General Method E.

(ooo) 3-Amino-7-(trans-3-amino-4-phenylpyrrolidin-1-yl)-8-chloro-1-cyclopropyl-6-fluoro-1*H*-quinazoline-2,4-dione hydrochloride (**Compound 68**) (mp 174-175°C, MS CI: *m/z* 430 (MH^+)) from [7-(trans-3-*tert*-butoxycarbonylamino-4-phenylpyrrolidin-1-yl)-8-chloro-1-cyclopropyl-6-fluoro-2,4-dioxo-1,4-dihydro-2*H*-quinazolin-3-yl]carbamic acid *tert*-butyl ester (Example 8rr) using General Method E.

(ppp) 3-Amino-7-[trans-3-amino-4-(4-hydroxyphenyl)pyrrolidin-1-yl]-8-chloro-1-cyclopropyl-6-fluoro-1*H*-quinazoline-2,4-dione hydrochloride (**Compound 69**) (mp >200°C, MS CI: *m/z* 446 (MH^+)) using 7-[trans-3-*tert*-butoxycarbonylamino-4-(4-hydroxyphenyl)pyrrolidin-1-yl]-8-chloro-1-cyclopropyl-6-fluoro-2,4-dioxo-1,4-dihydro-2*H*-quinazolin-3-yl}carbamic acid *tert*-butyl ester (Example 8ss) and General Method E.

(qqq) *N*-[1-(3-Amino-8-chloro-1-cyclopropyl-6-fluoro-2,4-dioxo-1,2,3,4-tetrahydroquinazolin-7-yl)pyrrolidin-3-ylmethyl]methanesulfonamide hydrochloride (**Compound 70**) (mp 109-112°C, MS CI: *m/e* 446 (MH^+)) from {8-chloro-1-cyclopropyl-6-fluoro-7-[3-(methanesulfonylaminomethyl)-pyrrolidin-1-yl]-2,4-dioxo-1,4-dihydro-2H-quinazolin-3-yl}carbamic acid *tert*-butyl ester (Example 36) using General Method E.

(rrr) 3-Amino-7-(3-aminomethylpiperidin-1-yl)-8-chloro-1-cyclopropyl-6-fluoro-1H-quinazoline-2,4-dione hydrochloride (**Compound 71**) (mp 131-133°C, MS CI: *m/z* 382 (MH^+)) from {7-[3-(*tert*-butoxycarbonylaminomethyl)piperidin-1-yl]-8-chloro-1-cyclopropyl-6-fluoro-2,4-dioxo-1,4-dihydro-2*H*-quinazolin-3-yl}carbamic acid *tert*-butyl ester (Example 8tt) using General Method E.

(sss) 3-Amino-8-chloro-1-cyclopropyl-6-fluoro-7-[3-(isopropylamino-methyl)pyrrolidin-1-yl]-1*H*-quinazoline-2,4-dione hydrochloride (**Compound 72**) (mp 125-127°C, MS CI: *m/z* 410 (MH^+)) from (7-{3-[(*tert*-butoxycarbonyl-isopropylamino)methyl]pyrrolidin-1-yl}-8-chloro-1-cyclopropyl-6-fluoro-2,4-dioxo-1,4-dihydro-2H-quinazolin-3-yl)carbamic acid *tert*-butyl ester (Example 8uu) using General Method E.

(ttt) 3-Amino-7-(3-aminomethylpyrrolidin-1-yl)-6,8-dichloro-1-cyclopropyl-1*H*-quinazoline-2,4-dione hydrochloride (**Compound 73**) (mp 147-149°C, MS CI: *m/z* 384 (MH^+)) from {7-[3-(*tert*-butoxycarbonylaminomethyl)-pyrrolidin-1-yl]-6,8-dichloro-1-cyclopropyl-2,4-dioxo-1,4-dihydro-2*H*-quinazolin-3-yl}carbamic acid *tert*- butyl ester using General Method E.

(uuu) *N*-[1-(3-Amino-8-chloro-1-cyclopropyl-6-fluoro-2,4-dioxo-1,2,3,4-tetrahydroquinazolin-7-yl)pyrrolidin-3-ylmethyl]methanesulfonamide (**Compound 74**) (mp 109-112°C, MS CI: *m/z* 446 (MH^+)) from {8-chloro-1-cyclopropyl-6-fluoro-7-[3-(methanesulfonylaminomethyl)pyrrolidin-1-yl]-2,4-dioxo-1,4-dihydro-2H-quinazolin-3-yl}carbamic acid *tert*-butyl ester (Example 36) using General Method E.

(vvv) 3-Amino-7-[(R)-3-(S)-(1-aminoethyl)pyrrolidin-1-yl]-1-cyclopropyl-6-fluoro-8-methyl-1H-quinazoline-2,4-dione hydrochloride (**Compound 75**) (mp 194-196°C, ^1H NMR (200 MHz, DMSO-d_6): δ 8.25 (bs, 3H), 7.47 (d, 1H), 4.68 (bs, 3H), 3.59-3.23 (m, 7H), 2.49 (s, 3H), 2.02-1.92 (m, 1H), 1.80-1.60 (m, 1H), 1.30 (d, 3H), 1.12-1.08 (m, 2H), 0.62-0.50 (m, 2H); MS ES: m/z 362 (MH^+)) from {1-[1-[(R)-3-(S)-(3-amino-1-cyclopropyl-6-fluoro-8-methyl-2,4-dioxo-1,2,3,4-tetrahydroquinazolin-7-yl)pyrrolidin-3-yl]ethyl}carbamic acid *tert*-butyl ester (Example 28k) using General Method A.

(www) 3-Amino-7-[(R)-3-(1-amino-1-methylethyl)pyrrolidin-1-yl]-1-cyclopropyl-6-fluoro-8-methyl-1H-quinazoline-2,4-dione hydrochloride (**Compound 76**) (mp 200-202°C, MS ES: m/z 376 (MH^+)) from {1-[(R)-1-(3-amino-1-cyclopropyl-6-fluoro-8-methyl-2,4-dioxo-1,2,3,4-tetrahydroquinazolin-7-yl)pyrrolidin-3-yl]-1-methylethyl}carbamic acid *tert*-butyl ester (Example 28l) using Method A.

(xxx) 3-Amino-7-[3-(1-aminoethyl)-3-methoxypyrrolidin-1-yl]-1-cyclopropyl-6-fluoro-8-methyl-1H-quinazoline-2,4-dione hydrochloride (**Compound 77**) (mp 190-192°C, ^1H NMR (200 MHz, DMSO-d_6): δ 8.07 (bs, 3H), 7.49 (d, 1H), 3.89-3.10 (m, 12H), 2.42 (s, 3H), 2.39-2.08 (m, 2H), 1.29 (d, 3H), 1.07-1.03 (m, 2H), 0.62-0.52 (m, 2H); MS ES: m/z 392 (MH^+)) from {1-[1-(3-amino-1-cyclopropyl-6-fluoro-8-methyl-2,4-dioxo-1,2,3,4-tetrahydroquinazolin-7-yl)-3-methoxypyrrolidin-3-yl]ethyl}carbamic acid *tert*-butyl ester (Example 28m) using General Method A.

(yyy) 3-Amino-7-[3-(1-aminoethyl)-3-fluoropyrrolidin-1-yl]-1-cyclopropyl-6-fluoro-8-methoxy-1H-quinazoline-2,4-dione hydrochloride

(**Compound 78**) (mp 190-192°C, MS ES: m/z 396 (MH^+)) from {1-[1-(3-amino-1-cyclopropyl-6-fluoro-8-methoxy-2,4-dioxo-1,2,3,4-tetrahydroquinazolin-7-yl)-3-fluoropyrrolidin-3-yl]ethyl}carbamic acid *tert*-butyl ester (Example 28o) using General Method A.

(*zzz*) 3-Amino-7-(3-aminopyrrolidin-1-yl)-1-cyclopropyl-6-fluoro-5-methyl-1H-quinazoline-2,4-dione hydrochloride (**Compound 79**) (mp 238-240°C, MS ES: m/z 334 (MH^+)) from [1-(3-amino-1-cyclopropyl-6-fluoro-5-methyl-2,4-dioxo-1,2,3,4-tetrahydroquinazolin-7-yl)pyrrolidin-3-yl]carbamic acid *tert*-butyl ester (Example 28p) using General Method A.

(aaaa) 3-Amino-7-[(R)-3-(S)-(1-aminoethyl)pyrrolidin-1-yl]-1-cyclopropyl-6-fluoro-5-methyl-1H-quinazoline-2,4-dione hydrochloride (**Compound 80**) (mp 245-247°C, MS ES: m/z 362 (MH^+)) from {1-(S)-[1-(R)-(3-amino-1-cyclopropyl-6-fluoro-5-methyl-2,4-dioxo-1,2,3,4-tetrahydroquinazolin-7-yl)pyrrolidin-3-yl]ethyl}carbamic acid *tert*-butyl ester (Example 28q) using General Method A.

(bbbb) 3-Amino-7-(3-aminomethyl-3-methoxymethylpyrrolidin-1-yl)-1-cyclopropyl-6-fluoro-8-methyl-1H-quinazoline-2,4-dione hydrochloride (**Compound 81**) (mp 172-177°C, MS ES: m/z 392 (MH^+)) from [1-(3-amino-1-cyclopropyl-6-fluoro-8-methyl-2,4-dioxo-1,2,3,4-tetrahydroquinazolin-7-yl)-3-methoxymethylpyrrolidin-3-ylmethyl]carbamic acid *tert*-butyl ester (Example 28r) using General Method A.

(cccc) 3-Amino-7-(3-aminomethyl-3-fluoromethylpyrrolidin-1-yl)-1-cyclopropyl-6-fluoro-1H-quinazoline-2,4-dione hydrochloride (**Compound 82**) (mp 160-163°C, MS ES: m/z 380 (MH^+)) from [1-(3-amino-1-cyclopropyl-6-fluoro-8-methyl-2,4-dioxo-1,2,3,4-tetrahydroquinazolin-7-yl)-3-fluoromethylpyrrolidin-3-ylmethyl]carbamic acid *tert*-butyl ester (Example 28s) using General Method A.

(dddd) 3-Amino-7-(trans-3-aminomethyl-4-trifluoromethylpyrrolidin-1-yl)-1-cyclopropyl-6-fluoro-8-methoxy-1H-quinazoline-2,4-dione hydrochloride (**Compound 83**) (mp 205-207°C, MS ES: m/z 432 (MH^+)) from [trans-(3-amino-1-cyclopropyl-6-fluoro-8-methoxy-2,4-dioxo-1,2,3,4-tetrahydroquinazolin-7-yl)-

4-trifluoromethylpyrrolidin-3-ylmethyl]carbamic acid *tert*-butyl ester (Example 28t) using General Method A.

(eeee) 3-Amino-7-[3-(1-aminoethyl)piperidin-1-yl]-1-cyclopropyl-6-fluoro-8-methoxy-1H-quinazoline-2,4-dione hydrochloride (**Compound 84**) (mp 198°C, MS ES: m/z 392 (MH^+)) from {1-[1-(3-amino-1-cyclopropyl-6-fluoro-8-methoxy-2,4-dioxo-1,2,3,4-tetrahydroquinazolin-7-yl)piperidin-3-yl]ethyl}carbamic acid *tert*-butyl ester (Example 28u) using General Method A.

(ffff) 3-Amino-7-[3-(aminoethyl)piperidin-1-yl]-1-cyclopropyl-6-fluoro-8-methyl-1H-quinazoline-2,4-dione hydrochloride (**Compound 85**) (mp 200°C, ^1H NMR (200 MHz, DMSO-d_6): δ 8.25 (bs, 3H), 7.52 (d, 1H), 6.36 (bs, 3H), 3.54-2.80 (m, 6H), 2.48 (s, 3H), 2.02-1.15 (m, 8H), 1.02-0.50 (m, 4H); MS ES: m/z 376(MH+)) from {1-[1-(3-amino-1-cyclopropyl-6-fluoro-8-methyl-2,4-dioxo-1,2,3,4-tetrahydroquinazolin-7-yl)piperidin-3-yl]ethyl}carbamic acid *tert*-butyl ester (Example 28v) using General Method A.

(gggg) 3-Amino-7-[4-(1-aminoethyl)-3,3-dimethylpyrrolidin-1-yl]-1-cyclopropyl-6-fluoro-8-methoxy-1H-quinazoline-2,4-dione hydrochloride (**Compound 86**) (mp 230°C, MS ES: m/z 406 (MH^+)) from {1-[1-(3-amino-1-cyclopropyl-6-fluoro-8-methoxy-2,4-dioxo-1,2,3,4-tetrahydroquinazolin-7-yl)-4,4-dimethylpyrrolidin-3-yl]ethyl}carbamic acid *tert*-butyl ester (Example 28w) using General Method A.

(hhhh) 3-Amino-7-[4-(1-aminoethyl)-3,3-dimethylpyrrolidin-1-yl]-1-cyclopropyl-6-fluoro-8-methyl-1H-quinazoline-2,4-dione hydrochloride (**Compound 87**) (mp 246°C, MS ES: m/z 390 (MH^+)) from {1-[1-(3-amino-1-cyclopropyl-6-fluoro-8-methyl-2,4-dioxo-1,2,3,4-tetrahydroquinazolin-7-yl)-4,4-dimethylpyrrolidin-3-yl]ethyl}carbamic acid *tert*-butyl ester (Example 28x) using General Method A.

(iiii) 3-Amino-7-(3-amino-3-phenylpyrrolidin-1-yl)-1-cyclopropyl-6-fluoro-8-methyl-1H-quinazoline-2,4-dione hydrochloride (**Compound 88**) (mp 236°C, MS ES: m/z 410 (MH^+)) from [1-(3-amino-1-cyclopropyl-6-fluoro-8-methyl-2,4-dioxo-1,2,3,4-tetrahydroquinazolin-7-yl)-3-phenylpyrrolidin-3-yl]carbamic acid *tert*-butyl ester (Example 28z) using General Method A.

(jjjj) 3-Amino-7-[3-(1-aminoethyl)-4-methylpyrrolidin-1-yl]-1-cyclopropyl-6-fluoro-8-methyl-1H-quinazoline-2,4-dione hydrochloride (**Compound 89**) (mp 240°C, MS ES: m/z 376 (MH^+)) from {1-[1-(3-amino-1-cyclopropyl-6-fluoro-8-methyl-2,4-dioxo-1,2,3,4-tetrahydroquinazolin-7-yl)-4-methylpyrrolidin-3-yl]ethyl}carbamic acid *tert*-butyl ester (Example 28y) using General Method A.

(kkkk) 3-Amino-7-(3-aminomethyl-3-phenylpyrrolidin-1-yl)-1-cyclopropyl-6-fluoro-8-methyl-1H-quinazoline-2,4-dione hydrochloride (**Compound 90**) (mp 227-231°C, MS ES: m/z 424 (MH^+)) from [1-(3-amino-1-cyclopropyl-6-fluoro-8-methyl-2,4-dioxo-1,2,3,4-tetrahydroquinazolin-7-yl)3-phenylpyrrolidin-3-ylmethyl]carbamic acid *tert*-butyl ester (Example 28aa) using General Method A.

(llll) 3-Amino-7-(7-aminomethyl-5-azaspiro[2,4]hept-5-yl)-1-cyclopropyl-6-fluoro-8-methyl-1H-quinazoline-2,4-dione hydrochloride (**Compound 91**) (mp 167°C, MS ES: m/z 374 (MH^+)) from [5-(3-amino-1-cyclopropyl-6-fluoro-8-methyl-2,4-dioxo-1,2,3,4-tetrahydroquinazolin-7-yl)-5-azaspiro[2.4]hept-7-ylmethyl]carbamic acid tert-butyl ester (Example 28bb) using General Method A.

(mmmm) 3-Amino-7-(7-aminomethyl-5-azaspiro[2,4]hept-5-yl)-1-cyclopropyl-6-fluoro-8-methoxy-1H-quinazoline-2,4-dione hydrochloride (**Compound 92**) (mp 178°C, MS ES: m/z 390 (MH^+)) from [5-(3-amino-1-cyclopropyl-6-fluoro-8-methoxy-2,4-dioxo-1,2,3,4-tetrahydroquinazolin-7-yl)-5-azaspiro[2.4]hept-7-ylmethyl]carbamic acid *tert*-butyl ester (Example 28cc) using General Method A.

(nnnn) 3-Amino-7-(3-aminomethyl-3-hydroxypyrrolidin-1-yl)-1-cyclopropyl-6-fluoro-8-methoxy-1H-quinazoline-2,4-dione hydrochloride (**Compound 93**) (mp 202°C, MS ES: m/z 380 (MH^+)) from [1-(3-amino-1-cyclopropyl-6-fluoro-8-methoxy-2,4-dioxo-1,2,3,4-tetrahydroquinazolin-7-yl)-3-hydroxypyrrolidin-3-ylmethyl]carbamic acid *tert*-butyl ester (Example 28dd) using General Method A.

(oooo) 3-Amino-7-(3-aminomethylpiperidin-1-yl)-1-cyclopropyl-6-fluoro-8-methyl-1H-quinazoline-2,4-dione hydrochloride (**Compound 95**) (mp 219-221°C, MS ES: m/z 362 (MH^+)) from [1-(3-amino-1-cyclopropyl-6-fluoro-8-methyl-2,4-dioxo-1,2,3,4-tetrahydroquinazolin-7-yl)piperidin-3-ylmethyl]carbamic acid *tert*-butyl ester (Example 28ee) using General Method A.

(pppp) 3-Amino-7-(3-amino-4-methoxypyrrolidin-1-yl)-1-cyclopropyl-6-fluoro-8-methyl-1H-quinazoline-2,4-dione hydrochloride (**Compound 96**) (mp >250°C, MS ES: m/z 364 (MH^+)) from [1-(3-amino-1-cyclopropyl-6-fluoro-8-methyl-2,4-dioxo-1,2,3,4-tetrahydroquinazolin-7-yl)-4-methoxypyrrolidin-3-yl] carbamic acid *tert*-butyl ester (Example 28ff) using General Method A.

(qqqq) 3-Amino-7-(3-amino-4-methoxypyrrolidin-1-yl)-1-cyclopropyl-6-fluoro-8-methoxy-1H-quinazoline-2,4-dione hydrochloride (**Compound 97**) (mp >250°C, MS ES: m/z 380 (MH^+)) from [1-(3-amino-1-cyclopropyl-6-fluoro-8-methoxy-2,4-dioxo-1,2,3,4-tetrahydroquinazolin-7-yl)-4-methoxypyrrolidin-3-yl]carbamic acid tert-butyl ester (Example 28gg) using General Method A.

(rrrr) 3-Amino-7-(3-amino-4-fluoropyrrolidin-1-yl)-1-cyclopropyl-6-fluoro-8-methoxy-1H-quinazoline-2,4-dione hydrochloride (**Compound 98**) (mp >250°C, MS ES: m/z 368 (MH^+)) from [1-(3-amino-1-cyclopropyl-6-fluoro-8-methoxy-2,4-dioxo-1,2,3,4-tetrahydroquinazolin-7-yl)-4-fluoropyrrolidin-3-yl]carbamic acid *tert*-butyl ester (Example 28hh) using General Method A.

(ssss) 3-Amino-7-(3-aminomethyl-3-methylpyrrolidin-1-yl)-1-cyclopropyl-6-fluoro-8-methyl-1H-quinazoline-2,4-dione hydrochloride (**Compound 99**) (mp 210°C, MS ES: m/z 362 (MH^+)) from [1-(3-amino-1-cyclopropyl-6-fluoro-8-methyl-2,4-dioxo-1,2,3,4-tetrahydroquinazolin-7-yl)-3-methylpyrrolidin-3-ylmethyl]carbamic acid *tert*-butyl ester (Example 28ii) using General Method A.

(tttt) 3-Amino-7-[(R)-3 (-((S)-1-aminoethyl)pyrrolidin-1-yl]-1-cyclopropyl-8-ethyl-6-fluoro-1H-quinazoline-2,4-dione hydrochloride (**Compound 100**) (mp 155-157°C, MS ES: m/z 376 (MH^+)) from {(S)-1-[(R)-1-(3-amino-1-cyclopropyl-8-ethyl-6-fluoro-2,4-dioxo-1,2,3,4-tetrahydroquinazolin-

7-yl)pyrrolidin-3-yl]ethyl}carbamic acid *tert*-butyl ester (Example 28jj) using General Method A.

(uuuu) 1-(3-Amino-1-cyclopropyl-6-fluoro-8-methoxy-2,4-dioxo-1,2,3,4-tetrahydroquinazolin-7-yl)pyrrolidine-3-carboxylic acid trifluoroacetate (**Compound 101**) (mp 252°C (decomp), MS ES: m/z 379 (MH^+)) from 1-(3-amino-1-cyclopropyl-6-fluoro-8-methoxy-2,4-dioxo-1,2,3,4-tetrahydroquinazolin-7-yl)pyrrolidine-3-carboxylic acid *tert*-butyl ester (Example 28kk) using General Method B.

(vvvv) 1-(3-Amino-1-cyclopropyl-6-fluoro-8-methyl-2,4-dioxo-1,2,3,4-tetrahydroquinazolin-7-yl)pyrrolidine-3-carboxylic acid trifluoroacetate (**Compound 102**) (mp 226°C (decomp), MS ES: m/z 363 (MH+)) from 1-(3-amino-1-cyclopropyl-6-fluoro-8-methyl-2,4-dioxo-1,2,3,4-tetrahydroquinazolin-7-yl)pyrrolidine-3-carboxylic acid *tert*-butyl ester (Example 28ll) using General Method A.

(wwww) 3-Amino-7-(1-aminomethyl-3-azabicyclo[3.1.0]hex-3-yl)-1-cyclopropyl-6-fluoro-8-methoxy-1H-quinazoline-2,4-dione hydrochloride (**Compound 103**) (mp 183-185°C, MS ES: m/z 376 MH^+)) from [3-(3-amino-1-cyclopropyl-6-fluoro-8-methoxy-2,4-dioxo-1,2,3,4-tetrahydroquinazolin-7-yl)-3-azabicyclo[3.1.0]hex-1-ylmethyl]yl]carbamic acid *tert*-butyl ester (Example 28mm) using General Method A.

(xxxx) 3-Amino-7-(1-aminomethyl-3-azabicyclo[3.1.0]hex-3-yl)-1-cyclopropyl-6-fluoro-8-methyl-1H-quinazoline-2,4-dione hydrochloride (**Compound 104**) (mp 189-194°C, MS ES: m/z 360 (MH^+)) from [3-(3-amino-1-cyclopropyl-6-fluoro-8-methyl-2,4-dioxo-1,2,3,4-tetrahydroquinazolin-7-yl)-3-azabicyclo[3.1.0]hex-1-ylmethyl]yl]carbamic acid *tert*-butyl ester (Example 28nn) using General Method A.

(yyyy) 3-Amino-7-[(S)-3-((R)-1-aminoethyl)pyrrolidin-1-yl]-1-cyclopropyl-6-fluoro-8-methoxy-1H-quinazoline-2,4-dione hydrochloride (**Compound 105**) (mp 175-179°C, MS ES: m/z 378 (MH^+)) from {(R)-1-[(S)-1-(3-amino-1-cyclopropyl-6-fluoro-8-methoxy-2,4-dioxo-1,2,3,4-

tetrahydroquinazolin-7-yl)pyrrolidin-3-yl]ethyl}carbamic acid *tert*-butyl ester (Example 28oo) using General Method A.

(zzzz) 3-Amino-7-[(S)-3-((R)-1-aminoethyl)pyrrolidin-1-yl]-1-cyclopropyl-6-fluoro-8-methyl-1H-quinazoline-2,4-dione hydrochloride (**Compound 106**) (mp 172-176°C, MS (ES: m/z 362 (MH^+)) from {(R)-1-[(S)-1-(3-amino-1-cyclopropyl-6-fluoro-8-methoxy-2,4-dioxo-1,2,3,4-tetrahydroquinazolin-7-yl)pyrrolidin-3-yl]ethyl}carbamic acid *tert*-butyl ester (Example 28pp) using General Method A.

(aaaaa) 3-Amino-1-cyclopropyl-6-fluoro-8-methyl-7-(octahydropyrrolo [3,4-b]pyridin-6-yl)-1H-quinazoline-2,4-dione hydrochloride (**Compound 107**) (mp 220°C, MS ES: m/z 374 (MH^+)) from 6-(3-amino-1-cyclopropyl-6-fluoro-8-methyl-2,4-dioxo-1,2,3,4-tetrahydroquinazolin-7-yl)octahydropyrrolo[3,4-b]pyridine-1-carboxylic acid *tert*-butyl ester (Example 28qq) using General Method A.

(bbbbb) 3-Amino-7-(trans-3-aminomethyl-4-methylpyrrolidin-1-yl)-8-chloro-1-cyclopropyl-6-fluoro-1H-quinazoline-2,4-dione hydrochloride (**Compound 108**) (mp 215-217°C, MS ES: m/z 382 (MH+)) from {7-[trans-3-(tert-butoxycarbonyl-aminomethyl)-4-methylpyrrolidin-1-yl]-8-chloro-1-cyclopropyl-6-fluoro-2,4-dioxo-1,4-dihydro-2H-quinazolin-3-yl}carbamic acid *tert*-butyl ester (**Compound 109**) (Example 8xx) using General Method A.

(ccccc) 3-Amino-7-(trans-3-aminomethyl-4-methylpyrrolidin-1-yl)-1-cyclopropyl-6-fluoro-8-methoxy-1H-quinazoline-2,4-dione hydrochloride (**Compound 110**) (mp 189°C, MS ES: m/z 378 (MH+)) from [trans-1-(3-amino-1-cyclopropyl-6-fluoro-8-methoxy-2,4-dioxo-1,2,3,4-tetrahydroquinazolin-7-yl)-4-methylpyrrolidin-3-ylmethyl]carbamic acid *tert*-butyl ester (Example 28rr) using General Method A.

(ddddd) 3-Amino-7-(trans-3-aminomethyl-4-methylpyrrolidin-1-yl)-1-cyclopropyl-6-fluoro-8-methyl-1H-quinazoline-2,4-dione hydrochloride (**Compound 111**) (mp 220°C, MS ES: m/z 362 (MH^+)) from [trans-1-(3-amino-1-cyclopropyl-6-fluoro-8-methyl-2,4-dioxo-1,2,3,4-tetrahydroquinazolin-7-yl)-4-

methylpyrrolidin-3-ylmethyl]carbamic acid *tert*-butyl ester (Example 28ss) using General Method A.

(eeeee) 3-Amino-7-(trans-3-amino-4-methylpyrrolidin-1-yl)-1-cyclopropyl-6-fluoro-8-methoxy-1H-quinazoline-2,4-dione hydrochloride (**Compound 112**) (mp 209°C, MS ES: m/z 364 (MH^+)) from [trans-1-(3-amino-1-cyclopropyl-6-fluoro-8-methoxy-2,4-dioxo-1,2,3,4-tetrahydroquinazolin-7-yl)-4-methylpyrrolidin-3-yl]carbamic acid tert-butyl ester (Example 28tt) using General Method A.

(fffff) 3-Amino-7-(3-aminomethylmorpholin-1-yl)-1-cyclopropyl-6-fluoro-8-methoxy-1H-quinazoline-2,4-dione hydrochloride (**Compound 113**) (mp 195°C, MS ES: m/z 380 (MH^+)) from [4-(3-amino-1-cyclopropyl-6-fluoro-8-methoxy-2,4-dioxo-1,2,3,4-tetrahydroquinazolin-7-yl)morpholin-2-ylmethyl]carbamic acid *tert*-butyl ester (Example 28uu) using General Method A.

(ggggg) 3-Amino-7-(3-aminomethylpiperidin-1-yl)-1-cyclopropyl-6-fluoro-8-methoxy-1H-quinazoline-2,4-dione hydrochloride (**Compound 114**) (mp 201°C, MS ES: m/z 378 (MH^+)) from [1-(3-amino-1-cyclopropyl-6-fluoro-8-methoxy-2,4-dioxo-1,2,3,4-tetrahydroquinazolin-7-yl)piperidin-3-ylmethyl]-carbamic acid *tert*-butyl ester (Example 28vv) using General Method A.

(hhhhh) 3-Amino-7-[3-(1-aminoethyl)-4-methylpyrrolidin-1-yl]-1-cyclopropyl-6-fluoro-8-methoxy-1H-quinazoline-2,4-dione hydrochloride (**Compound 115**) (mp 204.5°C, MS ES: m/z 392 (MH^+)) from {1-[1-(3-amino-1-cyclopropyl-6-fluoro-8-methoxy-2,4-dioxo-1,2,3,4-tetrahydroquinazolin-7-yl)-4-methylpyrrolidin-3-yl]ethyl}carbamic acid tert-butyl ester (Example 28ww) using General Method A.

(iiiii) 3-Amino-7-(3-amino-3-phenylpyrrolidin-1-yl)-8-chloro-1-cyclopropyl-6-fluoro-1H-quinazoline-2,4-dione hydrochloride (**Compound 116**) (mp 198-200°C, MS ES: m/z 430 (MH^+)) from [7-(3-*tert*-butoxycarbonylamino-3-phenylpyrrolidin-1-yl)-8-chloro-1-cyclopropyl-6-fluoro-2,4-dioxo-1,4-dihydro-2H-quinazolin-3-yl]carbamic acid *tert*-butyl ester (Example 6ww) using General Method A.

(iiiii) 3-Amino-7-(3-amino-3-methylpyrrolidin-1-yl)-1-cyclopropyl-6-fluoro-8-methyl-1H-quinazoline-2,4-dione hydrochloride (**Compound 117**) (mp 237-240°C, MS ES: m/z 348 (MH^+)) from [1-(1-cyclopropyl-6-fluoro-8-methyl-2,4-dioxo-1,2,3,4-tetrahydroquinazolin-7-yl)-3-methylpyrrolidin-3-yl]]carbamic acid *tert*-butyl ester (Example 28xx) using General Method A.

(kkkkk) 3-Amino-1-cyclopropyl-6-fluoro-8-methyl-7-pyrrolidin-1yl-1H-quinazoline-2,4-dione hydrochloride (**Compound 118**) (mp 178-180°C, MS ES: m/z 319 (MH^+)) from 3-amino-1-cyclopropyl-6-fluoro-8-methyl-7-pyrrolidin-1-yl-1H-quinazoline-2,4-dione (Example 28yy) using General Method A.

(lllll) 3-Amino-1-cyclopropyl-6-fluoro-8-methoxy-7-pyrrolidin-1yl-1H-quinazoline-2,4-dione hydrochloride (**Compound 119**) (mp 92-94°C, MS ES: m/z 335 (MH^+)) from 3-amino-1-cyclopropyl-6-fluoro-8-methoxy-7-pyrrolidin-1-yl-1H-quinazoline-2,4-dione (Example 28zz) using General Method A.

(mmmmm) 3-Amino-1-cyclopropyl-6-fluoro-7-[3-(1-hydroxy-1-methylethyl)pyrrolidin-1-yl]-8-methyl-1H-quinazoline-2,4-dione hydrochloride (**Compound 120**) (mp 116-120°C, MS ES: m/z 377 (MH^+)) from 3-amino-1-cyclopropyl-6-fluoro-7-[3-(1-hydroxy-1-methylethyl) pyrrolidin-1-yl]-8-methyl-1H-quinazoline-2,4-dione (Example 28aaa) using General Method E.

(nnnnn) 3-Amino-1-cyclopropyl-6-fluoro-7-[3-(1-hydroxy-1-methylethyl) pyrrolidin-1-yl]-8-methoxy-1H-quinazoline-2,4-dione hydrochloride (**Compound 121**) (mp 134°C (decomp), MS ES: m/z 393 (MH^+)) from 3-amino-1-cyclopropyl-6-fluoro-7-[3-(1-hydroxy-1-methylethyl) pyrrolidin-1-yl]-8-methoxy-1H-quinazoline-2,4-dione (Example 28bbb) using General Method E.

(ooooo) 3-Amino-1-cyclopropyl-6-fluoro-5-methyl-7-[(R)-3-((S)-1-methylaminoethyl)pyrrolidin-1-yl]-1H-quinazoline-2,4-dione hydrochloride (**Compound 122**) (mp 182-185°C, MS ES: m/z 376 (MH^+)) from {(S)-1-[(R)- 3-amino-1-cyclopropyl-6-fluoro-5-methyl-7-[(R)-3-((S)-1-methylaminoethyl)pyrrolidin-1-yl]-1H-quinazoline-2,4-dione (Example 28ccc) using General Method E.

(ppppp) (S)-1-[(R)-1-(3-Amino-1-cyclopropyl-7-[3-(1-ethylaminoethyl)pyrrolidin-1-yl)-6-fluoro-8-methoxy-1H-quinazoline-2,4-dione

hydrochloride (**Compound 123**) (mp 185-190°C, MS ES: m/z 406 (MH+)) from (S)-1-[(R)-1-(3-amino-1-cyclopropyl-7-[3-(1-ethylaminoethyl)pyrrolidin-1-yl)-6-fluoro-8-methoxy-1H-quinazoline-2,4-dione (Example 28ddd) using General Method E.

(qqqqq) 3-Amino-1-cyclopropyl-7-[(R)-3-((S)-1-ethylaminoethyl)pyrrolidin-1-yl]-6-fluoro-8-methyl-1H-quinazoline-2,4-dione hydrochloride (**Compound 124**) (mp 210-215°C, MS ES: m/z 390 (MH^+)) from 3-amino-1-cyclopropyl-7-[(R)-3-((S)-1-ethylaminoethyl)pyrrolidin-1-yl]-6-fluoro-8-methyl-1H-quinazoline-2,4-dione (Example 28eee) using General Method E.

(rrrrr) 3-Amino-7-(6-amino-1-methyl-3-azabicyclo[3.2.0]hept-3-yl)-1-cyclopropyl-6-fluoro-8-methoxy-1H-quinazoline-2,4-dione hydrochloride (**Compound 125**) (mp >190°C, MS ES: m/z 390 (MH^+)) from 3-amino-7-(6-amino-1-methyl-3-azabicyclo[3.2.0]hept-3-yl)-1-cyclopropyl-6-fluoro-8-methoxy-1H-quinazoline-2,4-dione (Example 28fff) using General Method E.

(sssss) 3-Amino-7-(4-aminomethylpiperidin-1-yl)-1-cyclopropyl-6-fluoro-8-methoxy-1H-quinazoline-2,4-dione hydrochloride (**Compound 126**) (mp 201°C, MS ES: m/z 378 (MH+)) from 3-amino-7-(4-aminomethylpiperidin-1-yl)-1-cyclopropyl-6-fluoro-8-methoxy-1H-quinazoline-2,4-dione (Example 28hhh) using General Method E.

(ttttt) 3-Amino-7-(3-aminomethylazetidin-1-yl)-1-cyclopropyl-6-fluoro-8-methoxy-1H-quinazoline-2,4-dione hydrochloride (**Compound 127**) (MS ES: m/z 350 (MH^+)) from 3-amino-7-(3-aminomethylazetidin-1-yl)-1-cyclopropyl-6-fluoro-8-methoxy-1H-quinazoline-2,4-dione (Example 28ggg) using General Method E.

(uuuuu) cis-3-Amino-7-(3-aminomethyl-4-fluoropyrrolidin-1-yl)-1-cyclopropyl-6-fluoro-8-methoxy-1H-quinazoline-2,4-dione hydrochloride (**Compound 128**) (mp 169-179°C, MS ES: m/z 382 (MH+)) from cis-[1-(3-amino-1-cyclopropyl-6-fluoro-8-methoxy-2,4-dioxo-1,2,3,4-tetrahydroquinazolin-7-yl)-4-fluoropyrrolidin-3-ylmethyl]carbamic acid *tert*-butyl ester (Example 28iii) using General Method A.

(vvvvv) trans-3-Amino-7-(3-aminomethyl-4-fluoropyrrolidin-1-yl)-1-cyclopropyl-6-fluoro-8-methoxy-1H-quinazoline-2,4-dione hydrochloride (**Compound 129**) (mp 144-147°C, MS ES: m/z 382 (MH^+)) from trans-[1-(3-amino-1-cyclopropyl-6-fluoro-8-methoxy-2,4-dioxo-1,2,3,4-tetrahydroquinazolin-7-yl)-4-fluoropyrrolidin-3-ylmethyl]carbamic acid *tert*-butyl ester (Example 28jjj) using General Method A.

(wwwww) 3-Amino-7-(1-amino-5-azaspiro[2.4]hept-5-yl)-1-cyclopropyl-6-fluoro-8-methoxy-1H-quinazoline-2,4-dione hydrochloride (**Compound 130**) (mp >250°C, MS APCI: m/z 376 (MH+)) from [1-(3-amino-1-cyclopropyl-6-fluoro-8-methoxy-2,4-dioxo-1,2,3,4-tetrahydroquinazolin-7-yl)- (1-amino-5-azaspiro[2.4]hept-5-yl)]carbamic acid tert-butyl ester (Example 28kkk) using General Method A.

(xxxxx) 3-Amino-7-(3a-aminomethyloctahydroisoindol-2-yl)-1-cyclopropyl-6-fluoro-8-methoxy-1H-quinazoline-2,4-dione hydrochloride (**Compound 131**) (mp >250°C, MS APCI: m/z 418 (MH+)) from 1-(3-amino-1-cyclopropyl-6-fluoro-8-methoxy-2,4-dioxo-1,2,3,4-tetrahydroquinazolin-7-yl)- 3-aminomethyloctahydroisoindol-2-yl]carbamic acid *tert*-butyl ester (Example 28lll) using General Method A

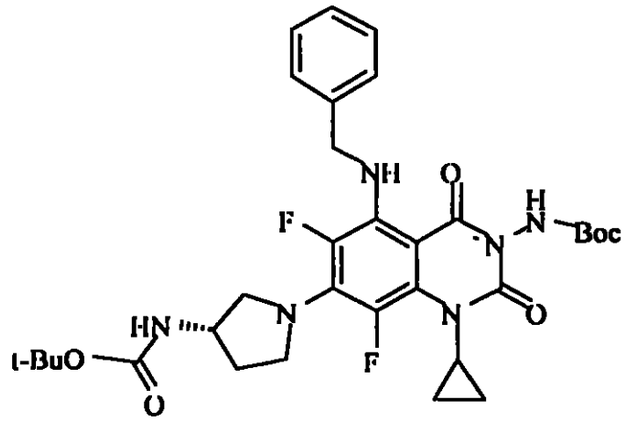
(yyyyy) 3-Amino-7-(3a-aminomethyloctahydroisoindol-2-yl)-1-cyclopropyl-6-fluoro-8-methyl-1H-quinazoline-2,4-dione hydrochloride (**Compound 132**) (mp >250°C, MS APCI: m/z 402 (MH^+)) from 1-(3-amino-1-cyclopropyl-6-fluoro-8-methyl-2,4-dioxo-1,2,3,4-tetrahydroquinazolin-7-yl)- 3-aminomethyloctahydroisoindol-2-yl]carbamic acid *tert*-butyl ester (Example 28mmm) using General Method A

(zzzzz) 3-Amino-7-[(R)-3-((S)-1-aminoethylpyrrolidin-1-yl]-1-cyclopropyl-6-fluoro-8-methoxy-1H-quinazoline-2,4-dione hydrochloride (**Compound 133**) (mp 228-230°C, MS APCI: m/z 378 (MH^+)) from {(S)-1-[(R)-1-(3-amino-1-cyclopropyl-6-fluoro-8-methoxy-2,4-dioxo-1,2,3,4-tetrahydroquinazolin-7-yl)pyrrolidin-3-yl]ethyl}carbamic acid *tert*-butyl ester (Example 28nnn) using General Method E

(aaaaaa) 3-Amino-7-(6-amino-3-azabicyclo[3.1.0]hex-3-yl)-1-cyclopropyl-6-fluoro-8-methyl-1H-quinazoline-2,4-dione hydrochloride (**Compound 134**) (mp 180-182°C, MS ES: m/z 346(MH^+)) from [3-(3-amino-1-cyclopropyl-6-fluoro-8-methyl-2,4-dioxo-1,2,3,4-tetrahydroquinazolin-7-yl)-3-azabicyclo[3.1.0]hex-6-yl]carbamic acid tert-butyl ester (Example 28n) using General Method A.

EXAMPLE 10

Synthesis of {7-[(S)-3-(tert-butoxycarbonylamino)pyrrolidin-1-yl]-5-benzylamino-1-cyclopropyl-6,8-difluoro-1,4-dihydro-2,4-dioxo-2H-quinazolin-3-yl}carbamic acid tert-butyl ester

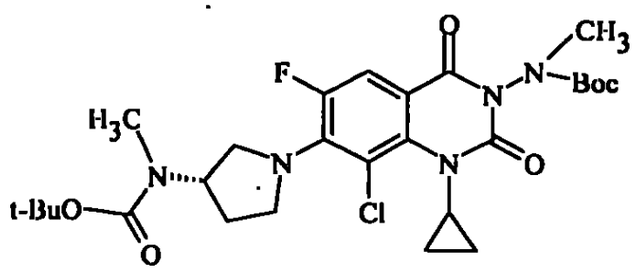


A solution of {7-[(S)-3-(*tert*-butoxycarbonylamino)pyrrolidin-1-yl]-1-cyclopropyl-1,4-dihydro-2,4-dioxo-5,6,8-trifluoro-2H-quinazolin-3-yl}carbamic acid *tert*-butyl ester from Example 8 (0.51 g, 0.914 mmol), triethylamine (1.3 mL, 9.3 mmol), and benzylamine (0.50 mL, 4.6 mmol) in dimethyl sulfoxide (7.5 mL) is heated at 100°C for 16 hours in a sealed glass tube. The mixture is concentrated under high vacuum and the residue purified by column chromatography (1:2 ethyl acetate/hexanes) to afford {7-[(S)-3-(*tert*-butoxycarbonylamino)pyrrolidin-1-yl]-5-benzylamino-1-cyclopropyl-6,8-difluoro-1,4-dihydro-2,4-dioxo-2H-quinazolin-3-yl}carbamic acid *tert*-butyl ester as a solid (0.51 g). ^1H NMR ($CDCl_3$): δ 8.50 (bs, 1H), 7.37-7.18 (m, 5H), 6.56 (bs, 1H), 4.76-4.62 (bd, 1H), 4.59-4.48 (m, 2H), 4.34-4.18 (m, 1H), 3.93-3.49 (m, 3H), 3.48-3.20 (m, 2H), 2.24-2.04 (m, 1H),

1.96-1.74 (m, 1H), 1.49 (s, 9H), 1.46 (s, 9H), 1.13-1.00 (m, 2H), 0.75-0.61 (m, 2H).

EXAMPLE 11

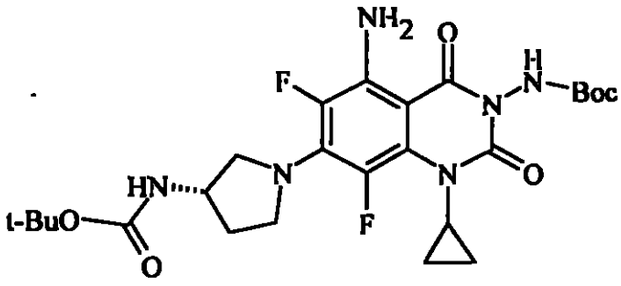
Synthesis of {7-[(S)-3-(tert-Butoxycarbonyl-N-methylamino)pyrrolidin-1-yl]-8-chloro-1-cyclopropyl-6-fluoro-2,4-dioxo-1,4-dihydro-2H-quinazolin-3-yl}-methylcarbamic acid tert-butyl ester



To a solution of {7-[(S)-3-(*tert*-butoxycarbonyl-N-methylamino)-pyrrolidin-1-yl]-8-chloro-1-cyclopropyl-6-fluoro-2,4-dioxo-1,4-dihydro-2H-quinazolin-3-yl}carbamic acid *tert*-butyl ester from Example 8 (0.238 g, 0.421 mmol) in *N,N*-dimethylformamide (5 mL) at -78°C under nitrogen atmosphere is added sodium hydride (60% dispersion in mineral oil, 0.025 g, 0.631 mmol). After 30 minutes, iodomethane (0.052 mL, 0.842 mmol) is added, and the reaction mixture is warmed to room temperature. After 1 hour, the reaction mixture is diluted with ethyl acetate and washed with saturated ammonium chloride solution, water, and brine. The organic layer is dried over $MgSO_4$, filtered, and the filtrate concentrated. The resulting residue is purified by flash column chromatography (1:1 ethyl acetate/hexanes) to afford the title compound (0.118 g). ^1H NMR ($CDCl_3$): δ 7.63 (dd, 1 H), 4.78 (bs, 1 H), 3.87-3.45 (m, 6 H), 2.62-2.44 (m, 6 H), 2.31-2.12 (m, 2 H), 1.49-1.47 (m, 18 H), 1.23-1.07 (m, 2 H), 0.75-0.53 (m, 2H). MS CI: *m/z* 582 (MH^+).

EXAMPLE 12

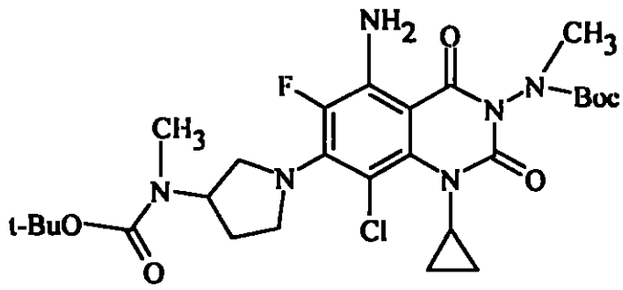
Synthesis of {5-Amino-7-[(S)-3-(tert-butoxycarbonylamino)pyrrolidin-1-yl]-1-cyclopropyl-6,8-difluoro-1,4-dihydro-2,4-dioxo-2H-quinazolin-3-yl}carbamic acid tert-butyl ester



{7-[(S)-3-(*tert*-Butoxycarbonylamino)pyrrolidin-1-yl]-5-benzylamino-1-cyclopropyl-6,8-difluoro-1,4-dihydro-2,4-dioxo-2H-quinazolin-3-yl}carbamic acid *tert*-butyl ester from Example 10 (0.435 g, 0.676 mmol) in tetrahydrofuran (20 mL) is hydrogenated at room temperature and atmospheric pressure over 20% palladium hydroxide on carbon (0.114 g) for 27 hours. The mixture is filtered through Celite, the solid is washed with chloroform, and the combined filtrates concentrated under vacuum. Purification by column chromatography (2:3 ethyl acetate/hexanes) gives {5-amino-7-[(S)-3-(*tert*-butoxycarbonylamino)pyrrolidin-1-yl]-1-cyclopropyl-6,8-difluoro-1,4-dihydro-2,4-dioxo-2H-quinazolin-3-yl}-carbamic acid *tert*-butyl ester as a solid (0.284 g). ^{1}H NMR ($CDCl_3$): δ 6.61 (bs, 1H), 5.94 (bs, 2H), 4.82-4.69 (bd, 1H), 4.40-4.21 (m, 1H), 4.00-3.59 (m, 3H), 3.55-3.41 (m, 1H), 3.35-3.21 (m, 1H), 2.32-2.08 (m, 1H), 2.01-1.80 (m, 1H), 1.50 (s, 9H), 1.46 (s, 9H), 1.17-1.01 (m, 2H), 0.77-0.63 (m, 2H).

EXAMPLE 13

Synthesis of 8-Chloro-1-cyclopropyl-6-fluoro-3-methylamino-7-[(S)-3-methylaminopyrrolidin-1-yl]-1H-quinazoline-2,4-dione

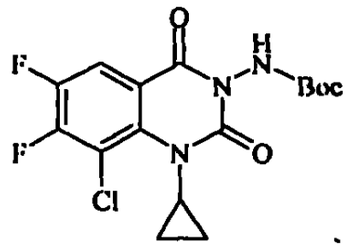


Hydrogen chloride gas is bubbled into diethyl ether (30 mL) for 15 minutes. The resulting solution is then cooled to 0°C and added to {7-[(S)-

3-(*tert*-butoxycarbonylmethylamino)pyrrolidin-1-yl]-8-chloro-1-cyclopropyl-6-fluoro-2,4-dioxo-1,4-dihydro-2*H*-quinazolin-3-yl}methyl-carbamic acid *tert*-butyl ester from Example 11 (0.118 g, 0.202 mmol). The reaction mixture is slowly warmed to room temperature. After 30 hours, the precipitate is filtered, washed with ether and hexanes, and dried under vacuum to afford the hydrochloride salt of the title compound as a solid (0.0632 g, mp 77-79°C). MS CI: *m/z* 382 (MH^+).

EXAMPLE 14

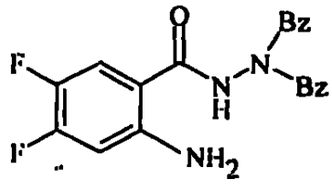
Synthesis of (8-Chloro-1-cyclopropyl-6,7-difluoro-2,4-dioxo-1,4-dihydro-2H-quinazolin-3-yl)carbamic acid tert-butyl ester



To a solution of (3-chloro-2-cyclopropylamino-4,5-difluorobenzoyl)-hydrazinecarboxylic acid *tert*-butyl ester (Example 6c) (1.93 g, 5.34 mmol) in tetrahydrofuran (50 mL) is added potassium carbonate (3.69 g, 26.7 mol) and triphosgene (2.06 g, 6.95 mmol). The reaction mixture is refluxed for 90 minutes, cooled to room temperature, and diluted with ethyl acetate. The organic layer is washed with water and brine, then dried over $MgSO_4$ and filtered. The filtrate is concentrated under vacuum and purified via flash column chromatography (1:2 ethyl acetate/hexanes) to afford the title compound (1.27 g). MS EI: *m/z* 386 (M^+).

EXAMPLE 15

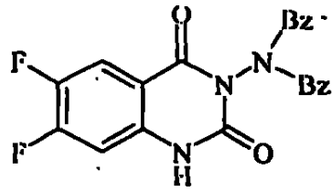
Synthesis of 2-Amino-4, 5-difluorobenzoic acid, 2,2-dibenzylhydrazide



4,5-Difluoroanthranilic acid (4.73 g, 27.3 mmol) and N,N-dibenzylhydrazine (8.69 g, 42 mmol) are combined in 200 mL of methylene chloride. 1-ethyl-3-(3-dimethylaminopropyl)carbodiimide hydrochloride (EDAC) (7.85 g, 41 mmol) is then added to this solution, and the mixture is stirred for 18 hours at 25°C. The solution is washed with saturated $NaHCO_3$, brine, and dried over magnesium sulfate. The solution is concentrated to give 15.8 g of a dark oil and purified via chromatography (SiO_2, $CHCl_3$) to give 3.4 g of the title compound as a solid. MS Cl: *m/z* 368 (MH^+).

EXAMPLE 16

Synthesis of 3-Dibenzylamino-6, 7-difluoro-1H-quinazoline-2, 4-dione

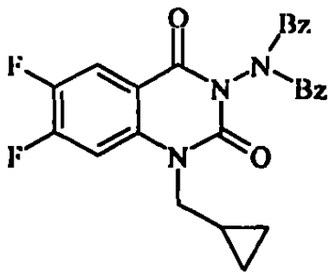


2-Amino-4,5-difluorobenzoic acid, 2,2-dibenzylhydrazide (Example 15) (0.81 g, 2.2 mmol) and triphosgene (0.33 g, 1.1 mmol) are combined in 100 mL of methylene chloride and stirred at 25°C for 20 hours. The solution is poured into 200 mL of saturated $NaHCO_3$, the layers are separated, and the aqueous layer is washed three times with ethyl acetate. The combined organic layers are dried over magnesium sulfate and then concentrated to give 0.86 g of the title compound as a solid. MS Cl: *m/z* 394 (MH^+).

EXAMPLE 17

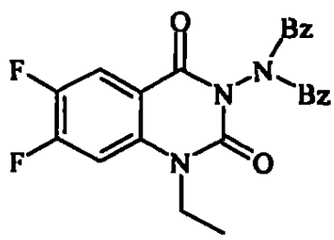
Synthesis of 3-Dibenzylamino-6,7-difluoro-1-substituted-1H-quinazoline-2,4-dione

(a) 3-Dibenzylamino-6,7-difluoro-1-cyclopropylmethyl-1H-quinazoline-2,4-dione



A solution of 3-dibenzylamino-6,7-difluoro-1H-quinazoline-2,4-dione (Example 16) (0.43 g, 1.1 mmol) in 10 mL of *N,N*-dimethylformamide is added to a suspension of sodium hydride (0.05 g, 1.3 mmol) in 10 mL of *N,N*-dimethylformamide and stirred for 30 minutes. Bromomethylcyclopropane (0.16 mL, 1.6 mmol) is added, and the mixture is stirred at 25°C for 18 hours. The reaction is quenched with 1 mL of water and concentrated in vacuo. The residue is dissolved in chloroform, washed with water, brine, and dried over magnesium sulfate. The solution is concentrated and purified via chromatography (SiO_2, $CHCl_3$) to give 0.33 g of the title compound as a solid. MS CI: *m/z* 448 (MH^+).

(b) 3-Dibenzylamino-6,7-difluoro-1-ethyl-1H-quinazoline-2,4-dione



A solution of 3-dibenzylamino-6,7-difluoro-1H-quinazoline-2,4-dione (Example 16) (0.43 g, 1.1 mmol) in 10 mL of *N,N*-dimethylformamide is added to a suspension of sodium hydride (0.05 g, 1.3 mmol) in 10 mL of *N,N*-dimethylformamide and stirred for 30 minutes. Ethyl iodide (0.13 mL, 1.6 mmol)

is added, and the mixture is stirred at 25°C for 18 hours. The reaction is quenched with 1 mL of water and concentrated in vacuo. The residue is dissolved in chloroform, washed with water, brine, and dried over magnesium sulfate. The solution is concentrated and purified via chromatography (SiO_2, $CHCl_3$) to give 0.34 g of the title compound as a solid, mp 133-135°C, MS CI, *m/z* 422 (MH^+).

EXAMPLE 18

Chlorination

General Chlorination Method

To a solution of a benzoylhydrazinecarboxylic acid *tert*-butyl ester (Example 7) in acetic acid (5 mL) is added *N*-chlorosuccinimide (1.2 eq.). After 1 hour, the reaction mixture is diluted with ethyl acetate and washed with saturated $NaHCO_3$, water, and brine. The organic layer is dried over $MgSO_4$ and filtered. The filtrate is concentrated under vacuum and purified via flash column chromatography (ethyl acetate/hexanes) to afford the corresponding chloro-benzoylhydrazinecarboxylic acid *tert*-butyl ester.

The following compounds are synthesized according to the General Chlorination Method above:

(a) *N'*-{4-[3-(*tert*-Butoxycarbonylaminomethyl)pyrrolidin-1-yl]-3-chloro-2-cyclopropylamino-5-fluorobenzoyl}hydrazinecarboxylic acid *tert*-butyl ester (MS CI: *m/z* 542 (MH^+)) from *N'*-{4-[3-(*tert*-butoxycarbonylamino-methyl)pyrrolidin-1-yl]-2-cyclopropylamino-5-fluorobenzoyl}-hydrazinecarboxylic acid *tert*-butyl ester (Example 7a).

(b) *N'*-4-[4-(*tert*-Butoxycarbonylpiperazin-1-yl)-3-chloro-2-cyclopropylamino-5-fluorobenzoyl]hydrazinecarboxylic acid *tert*-butyl ester (MS CI: *m/z* 528 (MH^+)) from *N'*-4-[4-(*tert*-butoxycarbonylpiperazin-1-yl)-2-cyclopropylamino-5-fluorobenzoyl]hydrazinecarboxylic acid *tert*-butyl ester (Example 7b).

(c) *N'*-{4-[3-(*tert*-Butoxycarbonylaminomethyl)-3-methylpyrrolidin-1-yl]-3-chloro-2-cyclopropylamino-5-fluorobenzoyl}hydrazinecarboxylic acid

tert-butyl ester (MS CI: *m/z* 556 (MH^+)) from *N'*-{4-[3-(*tert*-butoxycarbonylaminomethyl)-3-methylpyrrolidin-1-yl]-2-cyclopropylamino-5-fluorobenzoyl}hydrazinecarboxylic acid *tert*-butyl ester (Example 7c).

(d) *N'*-[4-(6-*tert*-Butoxycarbonylamino-3-azabicyclo[3.1.0]hex-3-yl)-3-chloro-2-cyclopropylamino-5-fluorobenzoyl]hydrazinecarboxylic acid *tert*-butyl ester (MS CI: *m/z* 540 (MH^+)) from *N'*-[4-(6-*tert*-butoxycarbonylamino-3-aza-bicyclo[3.1.0]hex-3-yl)-2-cyclopropylamino-5-fluorobenzoyl]-hydrazinecarboxylic acid *tert*-butyl ester (Example 7d).

(e) *N'*-{4-[(S)-3-(*tert*-Butoxycarbonyl-N-methylamino)pyrrolidin-1-yl]-3-chloro-2-cyclopropylamino-5-fluorobenzoyl}hydrazinecarboxylic acid *tert*-butyl ester (MS CI: *m/z* 542 (MH^+)) from *N'*-{4-[(S)-3-(*tert*-butoxycarbonyl-N-methylamino)pyrrolidin-1-yl]-2-cyclopropylamino-5-fluorobenzoyl}-hydrazinecarboxylic acid *tert*-butyl ester (Example 7e).

(f) *N'*-{4-[(S)-3-(*tert*-Butoxycarbonyl-N-amino)pyrrolidin-1-yl]-3-chloro-2-(2,4-difluoroanilino)-5-fluorobenzoyl}hydrazinecarboxylic acid *tert*-butyl ester ($CDCl_3$): δ 9.70 (bs, 1H), 7.76 (d, 1H), 6.93-6.82 (m, 1H), 6.70-6.62 (m, 2H), 6.48-6.34 (m, 2H), 4.91-4.87 (bs, 1H), 4.29-4.20 (m, 1H), 3.78-3.60 (m, 2H), 3.50-3.28 (m, 2H), 2.33-2.20 (m, 1H), 1.94-1.66 (m, 1H), 1.44 (s, 9H), 1.42 (s, 9H), (MS CI: *m/z* 601(MH^+)) from *N'*-{4-[(S)-3-(*tert*-butoxycarbonylamino)pyrrolidin-1-yl]-2-(2,4-difluoroanilino)-5-fluorobenzoyl}-hydrazinecarboxylic acid *tert*-butyl ester (Example 7f).

(g) *N'*-[4-((S)-7-*tert*-Butoxycarbonylamino-5-azaspiro[2.4]hept-5-yl)-3-chloro-2-cyclopropylamino-5-fluorobenzoyl]hydrazinecarboxylic acid *tert*-butyl ester (MS CI: 554 (MH^+)) from *N'*-[(S)-4-(7-*tert*-butoxycarbonylamino-5-aza-spiro[2.4]hept-5-yl)-2-cyclopropylamino-5-fluorobenzoyl]hydrazinecarboxylic acid *tert*-butyl ester (Example 7k).

(h) *N'*-[4-(Pyrrolidin-1-yl)-3-chloro-2-cyclopropylamino-5-fluoro-benzoyl]hydrazinecarboxylic *tert*-butyl ester (MS CI: *m/z* 413 (MH^+)) from *N'*-[4-(pyrrolidin-1-yl)-2-cyclopropylamino-5-fluorobenzoyl]hydrazinecarboxylic *tert*-butyl ester (Example 7m).

(i) *N'*-{4-[3-(*tert*-Butoxycarbonylamino)pyrrolidin-1-yl)-3-chloro-5-fluoro-2-isopropylaminobenzoyl}hydrazinecarboxylic acid tert-butyl ester (MS: *m/z* 530 (MH^+)) from *N'*-{4-[3-(*tert*-butoxycarbonylamino)pyrrolidin-1-yl]-5-fluoro-2-isopropylaminobenzoyl}hydrazine carboxylic acid *tert*-butyl ester (Example 7n).

(j) *N'*-{4-[3-(*tert*-Butoxycarbonylamino)pyrrolidin-1-yl]-2-cyclobutylamino-3-chloro-5-fluorobenzoyl}hydrazinecarboxylic acid *tert*-butyl ester (MS EI: *m/e* 542 (MH^+)) from *N'*-{4-[3-(*tert*-butoxycarbonylamino)-pyrrolidin-1-yl]-2-cyclobutylamino-5-fluorobenzoyl}hydrazinecarboxylic acid *tert*-butyl ester (Example 7q).

(k) *N'*-(1-{4-[3-(*tert*-Butoxycarbonylamino-methyl)piperidin-1-yl]-3-chloro-2-cyclopropylamino-5-fluorophenyl}methanoyl)hydrazinecarboxylic acid *tert*-butyl ester (MS Cl: *m/e* 556 (MH^+)) from *N'*-(1-{4-[3-(*tert*-butoxycarbonylaminomethyl)piperidin-1-yl]-2-cyclopropylamino-5-fluoro-phenyl}methanoyl)hydrazinecarboxylic acid *tert*-butyl ester (Example 7z).

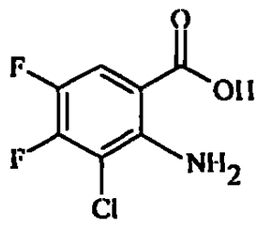
(l) *N'*-[1-(4-{3-[(*tert*-Butoxycarbonylisopropylamino)methyl]-pyrrolidin-1-yl}-3-chloro-2-cyclopropylamino-5-fluorophenyl)methanoyl]-hydrazine-carboxylic acid *tert*-butyl ester (MS Cl: *m/e* 584 (MH^+)) from *N'*-[1-(4-{3-[(*tert*-butoxycarbonylisopropylamino)methyl]pyrrolidin-1-yl}-2-cyclopropylamino-5-fluorophenyl)methanoyl]hydrazinecarboxylic acid *tert*-butyl ester (Example 7aa).

(m) *N'*-(1-{4-[3-(*tert*-Butoxycarbonylaminomethyl)pyrrolidin-1-yl]-3,5-dichloro-2-cyclopropylaminophenyl}methanoyl)hydrazinecarboxylic acid *tert*-butyl ester (MS Cl: *m/e* 558 (MH^+)) from *N'*-(1-{4-[3-(*tert*-butoxycarbonylamino-methyl)pyrrolidin-1-yl]-5-chloro-2-cyclopropylaminophenyl}methanoyl)-hydrazinecarboxylic acid *tert*-butyl ester (Example 7bb).

EXAMPLE 19

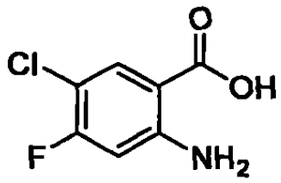
Chlorination of Substituted Benzoic Acids

(a) Synthesis of 3-Chloro-4,5-difluoroanthranilic acid



To a solution of 4,5-difluoroanthranilic acid (2.45 g, 14.2 mmol) in dichloromethane (25 mL) is added acetic acid (10 mL) and hypochlorous acid *tert*-butyl ester (1.75 mL, 15.6 mmol). After 2 hours, the reaction mixture is diluted with ethyl acetate and washed with water and brine. The organic layer is dried over $MgSO_4$, filtered, and concentrated. The resulting residue is purified via flash column chromatography (5% isopropyl alcohol/1% formic acid/94% dichloromethane) to afford 3-chloro-4,5-difluoroanthranilic acid as an oil (2.97 g). MS CI: *m/z* 206 (M^+).

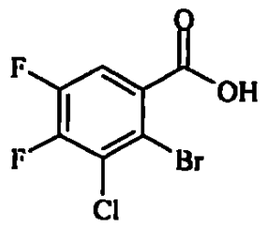
(b) 5-Chloro-4-fluoroanthranilic acid



To a solution of 4-fluoroanthranilic acid (0.882 g, 5.69 mmol) in methylene chloride (50 mL) and acetic acid (10 mL) is added *tert*-butyl hypochlorite (0.71 mL, 6.25 mmol) solution in dichloromethane (1 mL) dropwise over 1 minute. After 90 minutes, the reaction mixture is washed with water and brine. The organic layer is dried over $MgSO_4$, filtered, and the filtrate concentrated to afford 5-chloro-4-fluoroanthranilic acid (1.20 g). MS CI: *m/e* 188 (M^+).

EXAMPLE 20

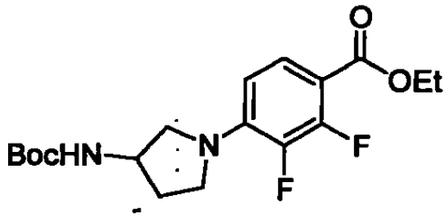
Synthesis of 2-Bromo-3-chloro-4,5-difluorobenzoic acid



A solution of cuprous bromide (10.96 g, 49.2 mmol)) in acetonitrile (100 mL) is cooled to 0°C and then *tert*-butyl nitrite (7.31 mL. 61.5 mmol) and 3-chloro-4,5-difluoroanthranilic acid (Example 19) (8.51 g, 41.0 mmol) are added. The mixture is slowly warmed to room temperature, and after 20 hours, the solvent is removed under vacuum. The resulting residue is dissolved in ethyl acetate and washed with 1.0 M hydrochloric acid, water, and brine. The organic layer is dried over $MgSO_4$ and filtered. The filtrate is concentrated under vacuum and purified via flash column chromatography (5% isopropyl alcohol/1% formic acid/94% dichloromethane) to afford 2-bromo-3-chloro-4,5-difluorobenzoic acid as a solid (7.96 g). MS Cl: *m/z* 271 (MH^+).

EXAMPLE 21

Synthesis of 4-[3-(tert-butoxycarbonylamino)pyrrolidin-1-yl]-2,3-difluorobenzoic acid ethyl ester

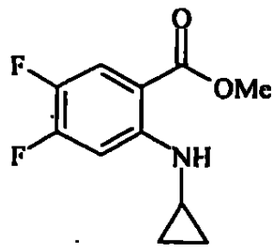


To a solution of 4-[3-(*tert*-butoxycarbonylamino)pyrrolidin-1-yl]-2,3-difluorobenzoic acid ethyl ester (Example 2h) (3.50 g, 9.50 mmol) in dichloromethane (80 mL) is added acetic acid (8 mL) and *tert*-butyl hypochlorite (1.75 mL, 15.6 mmol). After 20 minutes, the reaction mixture is diluted with ethyl acetate and washed with water and brine. The organic layer is dried over sodium

sulfate, filtered, and the filtrate concentrated. The resulting residue is purified by column chromatography (1:4 ethyl acetate/hexanes) to afford the title compound (3.75 g) as an oil. ^{1}H NMR ($CDCl_3$): δ 7.69 (dd, 1H), 4.85-4.76 (bd, 1H), 4.50-4.20 (m, 3H), 3.90-3.74 (m, 2H), 3.62-3.36 (m, 2H), 2.40-2.20 (m, 1H), 1.91-1.84 (m, 1H), 1.45 (s, 9H), 1.40 (s, 9H).

EXAMPLE 22

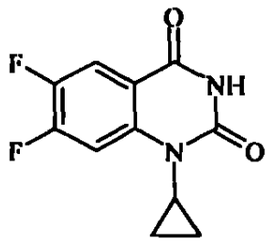
Synthesis of 2-cyclopropylamino-4,5-difluorobenzoic acid methyl ester



To a solution of 2-cyclopropylamino-4,5-difluorobenzoic acid (Example 5a) (6.0 g, 28.1 mmol), dichloromethane (100 mL), and methanol (20 mL) is added (trimethylsilyl)diazomethane (2.9 M solution in hexane) dropwise until the evolution of gas stops. The solution is stirred at room temperature for 0.5 hour and 88% formic acid is added dropwise until the evolution of gas again stops. Water is added, and the solution is extracted with dichloromethane, dried over $MgSO_4$, filtered, and the solvent removed under reduced pressure. The residue is purified by silica gel column chromatography using hexane/EtOAc (9:1) as the eluent to afford a 5.4 g of the title compound as a clear oil. MS CI: *m/z* 228 (MH^+).

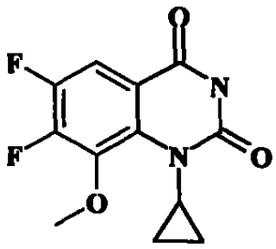
EXAMPLE 23

(a) Synthesis of 1-Cyclopropyl-6,7-difluoro-1H-quinazoline-2,4-dione



To a solution of 2-cyclopropylamino-4,5-difluorobenzoic acid ethyl ester (Example 22) (5.0 g, 22.0 mmol) in dry dichloromethane (120 mL) under a N_2 atmosphere is added chlorosulfanyl isocyanate (3.11 g, 22 mmol). The solution is reacted at room temperature for 4 hours, and the solvent is removed under reduced pressure. The residue is cooled to -20°C, and a cold brine solution (100 mL) buffered with $NaHCO_3$ is added. The solution is warmed to room temperature for 1 hour. The volume is reduced by half with a stream of air, and the solid is collected by filtration. The dry solid is added to a solution of triethylamine (5 mL) in THF (250 mL) and refluxed overnight. The reaction is cooled, the solvent removed under reduced pressure, dissolved in water (100 mL), and acidified to pH 1-2 with 1.0 M hydrochloric acid. The resulting precipitate is collected via filtration to afford 2.0 g of the title compound. MS CI: *m/z* 239 (MH^+).

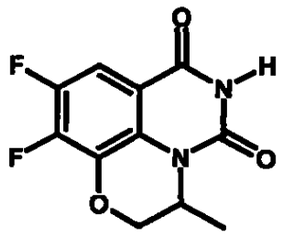
(b) 1-Cyclopropyl-6,7-difluoro-8-methoxy-1H-quinazoline-2,4-dione



A solution of 1-cyclopropyl-3-(3-methoxy-2,4,5-trifluorobenzoyl)urea (Example 27b, 0.94 g, 3.26 mmol) in tetrahydrofuran (20 mL) and *N,N*-dimethylformamide (5 mL) is treated with sodium hydride (0.275 g, 6.8 mmol, 60% in mineral oil dispersion) and heated at reflux for 16 hours. The mixture is cooled, treated with saturated NH_4Cl and extracted with dichloromethane. The

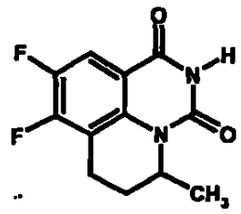
organic layer is then washed with brine, dried over Na_2SO_4 and concentrated under reduced pressure. Flash column chromatography (1:3 ethyl acetate/hexanes) afforded the title compound. MS (EI, M+1) m/z 269.

(c) Synthesis of 8,9-Difluoro-3-methyl-2,3-dihydro-1-oxa-3a,5-diaza-phenalene-4,6-dione



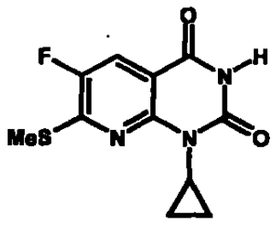
A solution of 1.5 g (6.2 mmol) of 7,8-difluoro-3-methyl-3,4-dihydro-2H-1,4-benzoxazine-5-carboxylic acid methyl ester (Example 32a) in 25 mL of dichloromethane is cooled to -20°C and treated dropwise with 0.92 g (6.5 mmol) of chlorosulfonyl isocyanate. The reaction is stirred at room temperature for 18 hours and the solvent removed in vacuo. The residue is treated with a saturated sodium bicarbonate solution and extracted with dichloromethane. The organic layer is dried ($MgSO_4$), filtered, and concentrated in vacuo. The residue is dissolved in 50 mL of tetrahydrofuran, and the resulting solution is treated with 5.0 g (5.0 mmol) of triethylamine. After heating at reflux for 4 hours, the solvent is removed in vacuo, and the residue is triturated with 5 mL of dichloromethane/ethyl acetate (80:20). The insoluble material is removed by filtration, washed with the above solvent mixture (2 mL) to give 0.25 g of the title compound, mp 259-261°C. The filtrate is chromatographed over flash grade silica gel (230-400 mesh) eluting with dichloromethane/ethyl acetate (80:20) to give 0.38 g of starting material. Continued elution afforded an additional 0.2 g of the title compound. ^1H NMR (400 MHz, $CDCl_3$): 11.78 (s, 1H), 7.50 (m, 1H), 4.68 (m, 1H), 4.52 (d, 1H), 4.17 (d, 1H), 1.23 (d, 3H).

(d) Synthesis of 8,9-Difluoro-5-methyl-6,7-dihydro-5H-pyrido[3,2,1-ij]quinazoline-1,3-dione



A solution of 1.07 g (4.4 mmol) of 5,6-difluoro-2-methyl-1,2,3,4-tetrahydro-quinoline-8-carboxylic acid methyl ester (Example 32) in 25 mL of dichloromethane is cooled to -20°C and treated dropwise with 0.85 g (6.0 mmol) of chlorosulfonyl isocyanate. The reaction is stirred at -20°C for 1 hour, treated with 1.0 g (12 mmol) of solid sodium acetate, and the solvent is removed in vacuo. The residue is cooled in an ice bath and triturated with a saturated solution of sodium acetate in brine. The precipitate is removed by filtration, washed with the sodium acetate solution and dried in vacuo. The dried precipitate is washed with ether to remove starting material and dried in vacuo. The dried solid is suspended in 40 mL of dry tetrahydrofuran, cooled to 5°C and treated portionwise with 1.2 g (12 mmol) of sodium tert-butoxide. After the addition is complete, the reaction mixture is stirred at 5°C for 30 minutes, the bath is removed, and the reaction is stirred to room temperature over 1 hour. The solvent is removed in vacuo; the residue is dissolved in water, cooled to 5°C and acidified with formic acid. The resulting precipitate is removed by filtration, washed with water and dried in vacuo affording 0.8 g of the title compound, mp 212-214°C.

(e) 1-Cyclopropyl-6-fluoro-7-methylsulfanyl-1H-pyrido[2,3-d]pyrimidine-2,4-dione



A solution of 4.1 g (15.2 mmol) of ethyl 2-cyclopropylamino-5-fluoro-6-methylsulfanylnicotinate (Example 34) in 125 mL of dichloromethane is cooled to -20°C and treated dropwise with 5.24 g (37 mmol) of chlorosulfonyl isocyanate. The reaction is stirred at -20°C for 3 hours and allowed to come to room temperature overnight. The mixture is recooled to -20°C and treated with 6.8 g (80 mmol) of solid sodium acetate. After stirring for 1 hour without cooling, the solvent is removed in vacuo without heating. The residue is triturated with a saturated solution of sodium acetate in brine and extracted with ethyl acetate (3 × 75 mL). The combined organic layers are dried ($MgSO_4$), filtered and evaporated in vacuo. The residue is suspended in 100 mL of tetrahydrofuran and treated with 3.6 g (32 mmol) of solid sodium tert-butoxide and stirred at room temperature for 36 hours. The solvent is removed in vacuo, the residue triturated with 100 mL of 0.1 M formic acid and extracted with ethyl acetate (3 × 100 mL). The combined organic layers are washed with water, dried ($MgSO_4$), filtered and evaporated in vacuo to give a residue which is chromatographed over flash grade silica gel (230-400 mesh) eluting with dichloromethane to give 0.75 g of the title compound, mp 220-222°C.

General Procedure A

Sodium hydride (3 eq., 60% mineral oil dispersion) is added portionwise to a solution of 1-cyclopropyl-3-benzoylurea (Example 27) in 20:1 tetrahydrofuran/ *N,N*-dimethylformamide at -25°C. The mixture is stirred at room temperature for 30 minutes, then refluxed overnight. It is poured into ice water, and the solution is acidified with 10% hydrochloric acid and extracted with ethyl acetate. The extract is washed with brine, dried, and concentrated. The residue is purified by silica gel column chromatography (ethyl acetate/hexanes) to afford 8-substituted 1-cyclopropyl-6,7-difluoro-1H-quinazoline-2,4-diones.

The following compounds are synthesized according to General Procedure A of Example 23:

(e) 1-Cyclopropyl-6,7-difluoro-8-methyl-1H-quinazoline-2,4-dione (^1H NMR (200 MHz, $CDCl_3$): δ 8.61 (bs, 1H), 7.83 (dd, 1H), 3.37-3.35 (m, 1H),

2.60 (dd, 3H), 1.31-1.12 (m, 2H), 0.71-0.63 (m, 2H) from 1-cyclopropyl-3-(2,4,5-trifluoro-3-methylbenzoyl)urea (Example 27c).

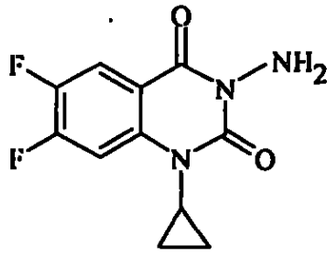
(f) 1-Cyclopropyl-6,7-difluoro-5-methyl-1H-quinazoline-2,4-dione (^{1}H NMR (200 MHz, $CDCl_3$): δ 8.37 (bs, 1H), 7.96 (dd, 1H), 2.81-2.74 (m, 1H), 2.61 (d, 3H), 1.26-1.14 (m, 2H), 0.81-0.73 (m, 2H)) from 1-cyclopropyl-3-(3,4,6-trifluoro-2-methylbenzoyl)urea (Example 27d).

(g) 1-cyclopropyl-6,7-difluoro-8-ethyl-1H-quinazoline-2,4-dione (^{1}H NMR (200 MHz, $CDCl_3$): δ 9.41 (bs, 1H), 7.86-7.77 (m, 1H), 3.40-3.20 (m, 3H), 1.30-1.10 (m, 5H), 0.75-0.67 (m, 2H)) from 1-cyclopropyl-3-(3-ethyl-2,4,5-trifluorobenzoylurea (Example 27e).

(i) 7-Chloro-1-cyclopropyl-6-fluoro-1H-pyrido[2,3-d]pyrimidine-2,4-dione (mp 214-216°C) from 1-cyclopropyl-3-(2,6-dichloro-5-fluoro-pyridine-3-carbonyl)urea (Example 27a).

EXAMPLE 24

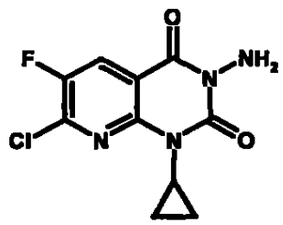
(a) Synthesis of 3-Amino-1-cyclopropyl-6,7-difluoro-1H-quinazoline-2,4-dione



To a solution of 1-cyclopropyl-6,7-difluoro-1*H*-quinazoline-2,4-dione (Example 23a, 2.0 g, 8.92 mmol) in dioxane (7.5 mL) and dimethylformamide (7.5 mL) is added NaH (60% dispersion in oil, 428 mg, 10.7 mmol). The solution is heated to 60°C for 10 minutes and cooled to room temperature. To the cooled solution is added O-(2,4-dinitrophenyl)hydroxylamine (1.77 g, 8.92 mmol), and the solution is heated to 80°C for 30 minutes. The resulting red solution is cooled to room temperature, poured over crushed ice, and extracted with EtOAc. The combined organic layers are dried over $MgSO_4$, filtered, and the solvent removed

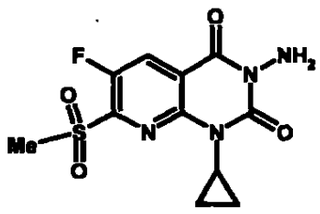
under reduced pressure. The resulting solid is triturated with Et_2O and air dried to afford 1.44 g of the title compound. MS CI: m/z 254 (MH^+).

(b) 3-Amino-7-chloro-1-cyclopropyl-6-fluoro-1H-pyrido[2,3-d]pyrimidine-2,4-dione



A solution of 3.83 g (15 mmol) of 7-chloro-1-cyclopropyl-6-fluoro-1H-pyrido[2,3-d]pyrimidine-2,4-dione (Example 23i) in 50 mL of dimethylformamide-dioxane (1:1) is cooled to 0°C and treated portionwise with 0.8 g (20 mmol) of 60% sodium hydride/mineral oil. The reaction is stirred to room temperature for 30 minutes, re-cooled to 0°C and 3.2 g (16 mmol) of 2,4-dinitrophenylhydroxylamine is added all at once. After stirring at room temperature overnight, the dioxane is removed in vacuo and the residue is diluted to 300 mL with ice and water and stirred at 5°C for 1 hour. The precipitate is removed by filtration, washed with water, ether and dried in vacuo to give 2.65 g of the title compound, mp 192-194°C. A second crop, (0.6 g) could be isolated by evaporating the filtrate and triturating the residue with petroleum ether.

(c) 3-Amino-1-cyclopropyl-6-fluoro-2,4-dioxo-1,2,3,4-tetrahydro-pyrido[2,3-d]pyrimidine-7-thiosulfonic acid



A solution of 0.47 g (1.57 mmol) of 1-cyclopropyl-6-fluoro-2,4-dioxo-1,2,3,4-tetrahydro-pyrido[2,3-d]pyrimidine-7-thiosulfonic acid (Example 35) in 20 mL of dimethylformamide/dioxane (1:1) is treated portionwise with 0.08 g (2.0 mmol) of 60% sodium hydride/mineral oil. The reaction is stirred at room

temperature for 1 hour and 0.32 g (1.6 mmol) of 2,4-dinitrophenylhydroxylamine is added all at once. After stirring at room temperature overnight, the dioxane is removed in vacuo and the residue is diluted to 100 mL with ice and water and stirred at 5°C for 1 hour. The aqueous solution is extracted with ethyl acetate (3 x 50 mL) with the combined organic layers being washed with water, dried ($MgSO_4$), filtered and evaporated in vacuo to give 0.4 g of the title compound, mp 167-169°C.

General Procedure A (Example 24)

To a solution of a 1-cyclopropyl-6,7-difluoro-1H-quinazoline-2,4-dione (Example 23) in 1:1 dry tetrahydrofuran or dioxane and dry *N,N*-dimethylformamide is added portionwise sodium hydride (1.1 eq., 60% mineral oil dispersion) at room temperature. After stirring at 50°C for 20 to 30 minutes, the resulting solution is cooled to room temperature and 2,4-dinitrophenylhydroxylamine (4 eq.) is added. The mixture is heated at 60°C to 80°C for 30 minutes, cooled, and the dioxane removed reduced pressure. The residue is poured into ice water and extracted with ethyl acetate. The organic layers are combined, washed with brine, dried with Na_2SO_4, and concentrated in vacuo. The residue is purified by flash column chromatography (ethyl acetate/hexanes) to afford a 3-amino-1-cyclopropyl-6,7-difluoro-1H-quinazoline-2,4-dione.

The compounds are synthesized according to General Procedure A of Example 24:

(d) 3-Amino-1-cyclopropyl-6,7-difluoro-8-methoxy-1H-quinazoline-2,4-dione (MS EI: m/z 284 (MH^+)) from 1-cyclopropyl-6,7-difluoro-8-methoxy-1H-quinazoline-2,4-dione (Example 23b).

(e) 3-Amino-1-cyclopropyl-6,7-difluoro-8-methyl-1H-quinazoline-2,4-dione (^1H NMR (200 MHz, $CDCl_3$): δ 7.86 (dd, 1H), 5.20 (bs, 2H), 3.48-3.38 (m, 1H), 2.61 (dd, 3H), 1.29-1.17 (m, 2H), 0.73-0.62 (m, 2H)) from 1-cyclopropyl-6,7-difluoro-8-methyl-1H-quinazoline-2,4-dione (Example 23e).

(f) 3-Amino-1-cyclopropyl-6,7-difluoro-5-methyl-1H-quinazoline-2,4-dione (^{1}H NMR (200 MHz, $CDCl_3$): δ 7.45 (dd, 1H), 5.28 (bs, 2H), 2.94-2.83 (m, 1H), 2.77 (d, 3H), 1.41-1.31 (m, 2H), 0.98-0.93 (m, 2H)) from 1-cyclopropyl-6,7-difluoro-5-methyl-1H-quinazoline-2,4-dione (Example 23f).

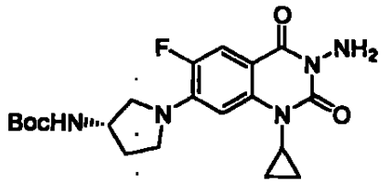
(g) 3-Amino-1-cyclopropyl-6,7-difluoro-8-ethyl-1H-quinazoline-2,4-dione (^{1}H NMR (200 MHz, $CDCl_3$): δ 7.84-7.75 (t, 1H), 5.37 (bs, 2H), 3.50-3.40 (m, 1H), 3.37-3.21 (m, 2H), 1.29-1.15 (m, 5H), 0.75-0.66 (m, 2H)) from 1-cyclopropyl-6,7-difluoro-8-ethyl-1H-quinazoline-2,4-dione (Example 23g).

(h) 5-Amino-8,9-difluoro-3-methyl-2,3-dihydro-1-oxa-3a,5-diaza-phenalene-4,6-dione (mp 171-173°C) from 8,9-difluoro-3-methyl-2,3-dihydro-1-oxa-3a,5-diaza-phenalene-4,6-dione (Example 23c).

(i) 2-Amino-8,9-difluoro-5-methyl-6,7-dihydro-5H-pyrido[3,2,1-ij]quinazoline-1,3-dione, mp 140-142°C, ^{1}H NMR (400 MHz, $CDCl_3$): 7.90 (m, 1H), 5.30 (bs, 2H), 5.07 (m, 1H), 3.08 (m, 1H), 2.85 (m, 1H), 2.15 (m, 1H), 1.95 (m, 1H), 1.31 (d, 3H)) from 8,9-difluoro-5-methyl-6,7-dihydro-5H-pyrido[3,2,1-ij]quinazoline-1,3-dione (Example 23d).

EXAMPLE 25

Synthesis of {3-Amino-7-[(S)-3-(tert-butoxycarbonylamino)pyrrolidin-1-yl]-1-cyclopropyl-6-fluoro-1H-quinazoline-2,4-dione



To a solution of 3-amino-1-cyclopropyl-6,7-difluoro-1*H*-quinazoline-2,4-dione (Example 24a) (50.0 mg, 0.20 mmol) and triethylamine (74 mg, 0.74 mmol) in acetonitrile (3 mL) is added (S)-pyrrolidin-3-yl carbamic acid *tert*-butyl ester (74 mg, 0.40 mmol). The solution is refluxed for 18 hours, the solvent is removed under reduced pressure, and the residue triturated with water. The solid is collected by filtration and air dried to afford 74 mg of the title compound. MS CI: *m/z* 420 (MH^+).

EXAMPLE 26

Synthesis of Benzamides

General Procedure A

A solution of an appropriately substituted benzoic acid, oxalyl chloride (1.5 eq.), and dichloromethane is treated with *N,N*-dimethylformamide (2 drops), the solution is stirred at room temperature for 2 hours. The mixture is concentrated under reduced pressure, and the residue is dissolved in dry THF and slowly added to a solution of ammonia in diethyl ether at -70°C. The mixture is then allowed to warm to ambient temperature and stirred for 30 minutes. The mixture is then filtered and the resulting solid dissolved in ethyl acetate, washed with water, and dried over Na_2SO_4. The solvent is then concentrated in vacuo to provide the desired amide.

The following compounds are synthesized according to the General Procedure A method above:

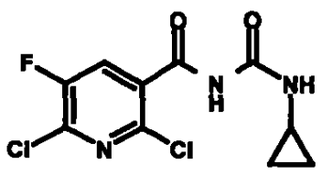
(a) 3,4,6-Trifluoro-2-methylbenzamide. (^{1}H NMR (200 MHz, $CDCl_3$): δ 6.89-6.77 (m, 1H), 6.41 (bs, 1H), 5.95 (bs, 1H), 2.39 (d, 3H)) from 3,4,6-trifluorobenzoic acid (Hagen S. et al., *Heterocycl. Chem.*, 1990;27[6]:1609-1616).

(b) 3-Ethyl-2,4,5-trifluorobenzamide, (^{1}H NMR (200 MHz, $CDCl_3$): δ 7.78–7.60 (m, 1H), 6.61 (bs, 2H), 2.67 (q, 2H), 1.15 (t, 3H)) from 3-ethyl-2,4,5-trifluorobenzoic acid (Takemura, PCT Int. Appl., 1996, WO 9623782).

EXAMPLE 27

Synthesis of 1-cyclopropyl-3-benzoyl substituted ureas.

(a) 1-Cyclopropyl-3-(2,6-dichloro-5-fluoro-pyridine-3-carbonyl)urea



A solution of 5.8 g (27.8 mmol) of 2,6-dichloro-5-fluoronicotinamide (*Chem. Pharm. Bull.*, 1987;35:2280) in 60 mL of dichloromethane is treated dropwise with 5.1 g (40 mmol) of oxalyl chloride, and the reaction mixture is heated at reflux for 18 hours. The solvent is removed in vacuo, and the residue is dissolved in 50 mL of dichloromethane, which is also removed in vacuo. The residue is dissolved in 50 mL of dichloromethane, cooled to -20°C and treated dropwise with 2.28 g (40 mmol) of cyclopropylamine. The reaction mixture is stirred at -20° to -10°C for ½ hour, then allowed to come to room temperature over 2 hours. The solvent is removed in vacuo and the residue is triturated with 25 mL of dichloromethane, which is also removed in vacuo to give 8.0 g of the title compound, mp 171-173°C.

General Procedure A

To a solution of substituted benzamide (Example 26) in 1,2-dichloroethane is added oxalyl chloride (1.5 eq.) and the mixture refluxed for 16 hours. The solvent is then removed under reduced pressure to obtain a crude isocyanate. The isocyanate is then taken up into dioxane, cooled to 0°C and treated with cyclopropylamine (1.5 eq.) in dioxane. The mixture is then warmed to ambient temperature and stirred for 3 hours. The mixture is then concentrated under reduced pressure, dissolved in ethyl acetate, washed with water, dried over Na_2SO_4 and evaporated under reduced pressure. The resulting residue is then purified by flash column chromatography (ethyl acetate/hexanes) to afford the 1-cyclopropyl-3-benzoyl urea.

The following compounds are synthesized according to the General Procedure A method above:

(b) 1-Cyclopropyl-3-(2,4,5-trifluoro-3-methoxy-benzoyl)urea (MS ES (MH^+): m/z 289) from 2,4,5-trifluoro-3-methoxybenzamide (Masuzawa K., Suzue S., Hirai K., Ishizaki T., Eur. Pat. Appl., 1987, EP 230295).

(c) 1-Cyclopropyl-3-(2,4,5-trifluoro-3-methylbenzoyl)urea (^1H NMR (200 MHz, $CDCl_3$): δ 8.69 (d, 1H), 8.48 (bs, 1H), 7.75-7.62 (m, 1H), 2.83-2.71 (m, 1H), 2.30 (dd, 3H), 0.87-0.78 (m, 2H), 0.67-0.59 (m, 2H)) from 2,4,5-

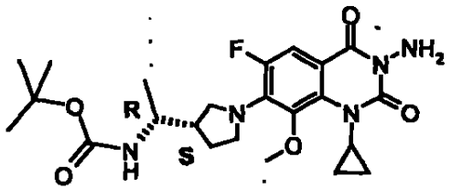
trifluoro-3-methylbenzamide (Masuzawa K., Suzue S., Hirai K., Ishizaki T., Eur. Pat. Appl., 1987, EP 237955).

(d) 1-Cyclopropyl-3-(3,4,6-trifluoro-2-methylbenzoyl)urea (^{1}H NMR (200 MHz, $CDCl_3$): δ 8.99 (bs, 1H), 8.37 (bs, 1H), 6.93-6.80 (m, 1H), 2.74-2.65 (m, 1H), 2.35 (d, 3H), 0.84-0.71 (m, 2H), 0.66-0.58 (m, 2H)) from 3,4,6-trifluoro-2-methylbenzamide (Example 26a).

(e) 1-Cyclopropyl-3-(3-ethyl-2,4,5-trifluorobenzoyl)urea (^{1}H NMR (200 MHz, $CDCl_3$): δ 8.76-8.69 (bd, 1H), 8.50 (bs, 1H), 7.76-7.63 (m, 1H), 2.84-2.72 (m, 3H), 1.27-1.20 (m, 3H), 0.91-0.81 (m, 2H), 0.71-0.61 (m, 2H)) from 3-ethyl-2,4,5-trifluorobenzamide (Example 26b).

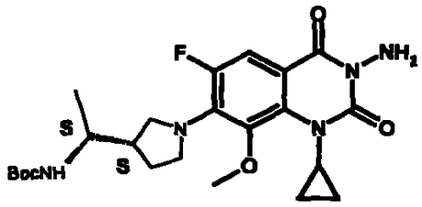
EXAMPLE 28

(a) Synthesis of {(R)-1-[(S)-1-(3-Amino-1-cyclopropyl-6-fluoro-8-methoxy-2,4-dioxo-1,2,3,4-tetrahydroquinazolin-7-yl)pyrrolidin-3-yl]ethyl}-carbamic acid tert-butyl ester



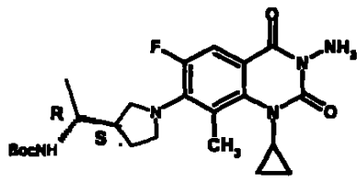
A solution of 0.57 g (2.0 mmol) of 3-amino-1-cyclopropyl-6,7-difluoro-8-methoxy-1H-quinazoline-2,4-dione (Example 24d), 0.64 g (3.0 mmol) of ((S)-(R)-1-pyrrolidin-3-ylethyl)carbamic acid *tert*-butyl ester (*J. Het. Chem.*, 1992;29:1481), 0.81 g (8.0 mmol) of triethylamine and 10 mL of dimethyl sulfoxide is heated at 110°C for 4 hours. The reaction mixture is cooled to room temperature, poured into 150 mL of ice and water, and extracted with ethyl acetate (2 × 125 mL). The combined organic layers are washed with water, dried ($MgSO_4$), filtered and evaporated in vacuo to give 1.1 g of crude product. Chromatography on flash grade silica gel (230-400 mesh) eluting with dichloromethane/ethanol (9:1) provided 0.92 g of the title compound, mp 96-98°C.

(b) Synthesis of {(S)-1-[(S)-1-(3-Amino-1-cyclopropyl-6-fluoro-8-methoxy-2,4-dioxo-1,2,3,4-tetrahydroquinazolin-7-yl-pyrrolidin-3-yl]ethyl}-carbamic acid tert-butyl ester



A solution of 0.57 g (2.0 mmol) of 3-amino-1-cyclopropyl-6,7-difluoro-8-methoxy-1H-quinazoline-2,4-dione (Example 24d), 0.64 g (3.0 mmol) of ((S)-(S)-1-pyrrolidin-3-ylethyl)carbamic acid *tert*-butyl ester (*J. Het. Chem.*, 1992;29:1481), 0.81 g (8.0 mmol) of triethylamine, and 10 mL of dimethyl sulfoxide is heated at 110°C for 4 hours. The reaction mixture is cooled to room temperature, poured into 150 mL of ice and water and extracted with ethyl acetate (2 x 125 mL). The combined organic layers are washed with water, dried ($MgSO_4$), filtered and evaporated in vacuo to give 1.08 g of crude product. Chromatography on flash grade silica gel (230-400 mesh) eluting with dichloromethane/ethanol (9:1) provided 0.9 g of the title compound, mp 87-89°C.

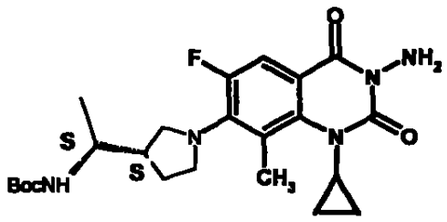
(c) Synthesis of {(R)-1-[(S)-1-(3-Amino-1-cyclopropyl-6-fluoro-8-methyl-2,4-dioxo-1,2,3,4-tetrahydro-quinazolin-7-yl)-pyrrolidin-3-yl]-ethyl}-carbamic acid tert-butyl ester



A solution of 0.5 g (1.9 mmol) of 3-amino-1-cyclopropyl-6,7-difluoro-8-methyl-1H-quinazoline-2,4-dione (Example 24c), 0.64 g (3.0 mmol) of ((S)-(R)-1-pyrrolidin-3-ylethyl)carbamic acid *tert*-butyl ester, 0.81 g (8.0 mmol) of triethylamine and 10 mL of dimethyl sulfoxide is heated at 110°C for 24 hours. After thin layer chromatography showed incomplete reaction, an additional 0.43 g (2.0 mmol) of pyrrolidine derivative and 0.81 g (8.0 mmol) of triethylamine are

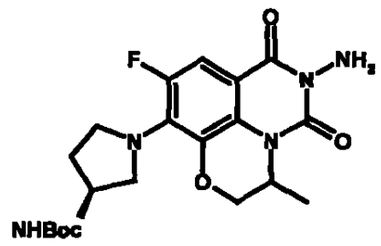
added and the reaction is heated at 120°C for 18 hours. The reaction mixture is cooled to room temperature, poured into 200 mL of ice and water and extracted with ethyl acetate (2 × 125 mL). The combined organic layers are washed with water, dried ($MgSO_4$), filtered and evaporated in vacuo to give 1.1 g of crude product. Chromatography on flash grade silica gel (230-400 mesh) eluting with ethyl acetate provided 0.4 g of the title compound, mp 86-88°C.

(d) Synthesis of {(S)-1-[(S)-1-(3-Amino-1-cyclopropyl-6-fluoro-8-methyl-2,4-diaxo-1,2,3,4-tetrahydroquinazolin-7-yl)pyrrolidin-3-yl]ethyl}-carbamic acid tert-butyl ester



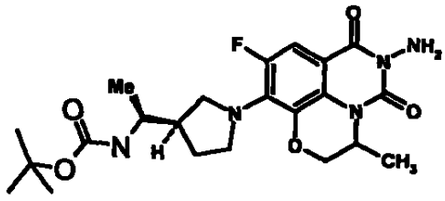
A solution of 0.5 g (1.9 mmol) of 3-amino-1-cyclopropyl-6,7-difluoro-8-methyl-1H-quinazoline-2,4-dione (Example 24e), 0.64 g (3.0 mmol) of ((S)-(S)-1-pyrrolidin-3-ylethyl)carbamic acid *tert*-butyl ester, 0.81 g (8.0 mmol) of triethylamine and 10 mL of dimethyl sulfoxide is heated at 110°C for 24 hours. After thin layer chromatography showed incomplete reaction, an additional 0.43 g (2.0 mmol) of pyrrolidine derivative and 0.81 g (8.0 mmol) of triethylamine are added and the reaction is heated at 120°C for 18 hours. The reaction mixture is cooled to room temperature, poured into 200 mL of ice and water and extracted with ethyl acetate (2 × 125 mL). The combined organic layers are washed with water, dried ($MgSO_4$), filtered and evaporated in vacuo to give 1.3 g of crude product. Chromatography on flash grade silica gel (230-400 mesh) eluting with 400 mL of dichloromethane/ethyl acetate (8:2), 600 mL of (6:4) and 1 L of (4:6) provided 0.46 g of the title compound, mp 84-86°C.

(e) Synthesis of [(S)-1-(5-Amino-8-fluoro-3-methyl-4,6-diaxo-2,3,5,6-tetrahydro-4H-1-oxa-3a,5-diazaphenalen-9-yl)pyrrolidin-3-yl]carbamic acid tert-butyl ester



A solution of 0.2 g (0.75 mmol) of 5-amino-8,9-difluoro-3-methyl-2,3-dihydro-1-oxa-3a,5-diazaphenalene-4,6-dione (Example 24h), 0.58 g (2.0 mmol) of (S)-3-pyrrolidinylcarbamic acid *tert*-butyl ester (*J. Med. Chem.*, 1992;35:1764), 0.5 g (0.5 mmol) of triethylamine and 20 mL of acetonitrile is heated at reflux for 18 hours. The solvent is removed in vacuo and the residue is partitioned between dichloromethane-water. The organic layer is washed with water, dried ($MgSO_4$) and concentrated in vacuo. The residue is chromatographed over flash grade silica gel (230-400 mesh) eluting with dichloromethane/ ethanol (95:5) to give 0.34 g of the title compound, mp 114-116°C.

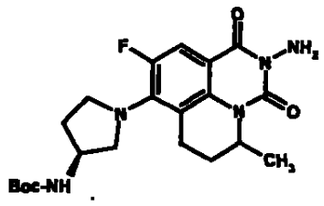
(f) {(S)-1-[(R)-1-(5-Amino-8-fluoro-3-methyl-4,6-dioxo-2,3,5,6-tetrahydro-4H-1-oxa-3a,5-diazaphenalen-9-yl)pyrrolidin-3-yl]ethyl}carbamic acid tert-butyl ester



A solution of 0.11 g (0.41 mmol) of 5-amino-8,9-difluoro-3-methyl-2,3-dihydro-1-oxa-3a,5-diazaphenalene-4,6-dione (Example 24h), 0.26 g (1.3 mmol) of ((R)-(S)-1-pyrrolidin-3-ylethyl)carbamic acid *tert*-butyl ester (*J. Het. Chem.*, 1992;29:1481), 0.25 g (2.5 mmol) of triethylamine and 10 mL of acetonitrile is heated at reflux for 18 hours. The solvent is removed in vacuo and the residue is partitioned between ethyl acetate/water. The organic layer is washed with water, dried ($MgSO_4$) and concentrated in vacuo. The residue is chromatographed over flash grade silica gel (230-400 mesh) eluting with dichloromethane/ethanol (95:5) to give 0.14 g of the title compound. ^1H NMR (400 MHz, $CDCl_3$): 7.43 (d, 1H),

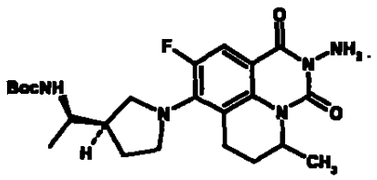
5.24 (bs, 2H), 4.82 (m, 1H), 4.56 (m, 1H), 4.33 (d, 1H), 3.99 (m, 1H), 3.86 (m, 1H), 3.73 (m, 1H), 3.59 (m, 2H), 2.18 (m, 1H), 3.01 (m, 1H), 1.67 (m, 1H), 1.44 (s, 9H), 1.40 (m, 3H), 1.25 (m, 1H), 1.20 (d, 3H).

(g) ***[(S)-1-(2-Amino-9-fluoro-5-methyl-1,3-dioxo-2,3,6,7-tetrahydro-1H,5H-pyrido[3,2,1-ij]quinazolin-8-yl) pyrrolidin-3-yl]carbamic acid tert-butyl ester***



A solution of 0.12 g (0.45 mmol) of 5-amino-8,9-difluoro-5-methyl-6,7-dihydro-5H-pyrido[3,2,1-ij]quinazoline-1,3-dione (Example 24i), 0.34 g (1.8 mmol) of (S)-3-pyrrolidinylcarbamic acid *tert*-butyl ester (*J. Med. Chem.*, 1992;35:1764), 0.2 g (2.0 mmol) of triethylamine and 7 mL of dimethyl sulfoxide is heated at 110°C for 18 hours. The reaction is cooled to room temperature, diluted with 80 mL of ice and water and stirred at 5°C for 1 hour. The resulting precipitate is removed by filtration, washed with water and dried in vacuo. The solid is chromatographed over flash grade silica gel (230-400 mesh) eluting with dichloromethane/ethanol (9:1) to give 0.14 g of the title compound, mp 98-100°C.

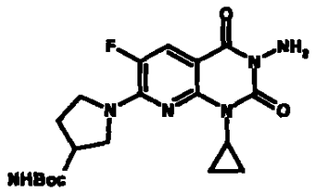
(h) ***{(R)-3-[(S)-1-(2-Amino-9-fluoro-5-methyl-1,3-dioxo-2,3,6,7-tetrahydro-1H,5H-pyrido[3,2,1-ij]quinazolin-8-yl)pyrrolidin-3-yl}ethylcarbamic acid tert-butyl ester***



A solution of 0.12 g (0.45 mmol) of 5-amino-8,9-difluoro-5-methyl-6,7-dihydro-5H-pyrido[3,2,1-ij]quinazoline-1,3-dione (Example 24i), 0.39 g (1.8 mmol) of ((R)-(S)-1-pyrrolidin-3-ylethyl)carbamic acid *tert*-butyl ester (*J. Het. Chem.*, 1992;29:1481), in 5 mL of dimethyl sulfoxide is heated at 110°C for

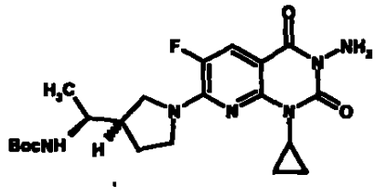
18 hours. The reaction is cooled to room temperature, diluted with 80 mL of ice and water and stirred at 5°C for 1 hour. The resulting precipitate is removed by filtration, washed with water and dried in vacuo. The solid is chromatographed over flash grade silica gel (230-400 mesh) eluting with dichloromethane/ethanol (9:1) to give 0.13 g of the title compound, mp 93-95°C.

(i) [1-(3-Amino-1-cyclopropyl-6-fluoro-2,4-dioxo-1,2,3,4-tetrahydro-pyrido[2,3-d]pyrimidin-7-yl)pyrrolidin-3-yl]carbamic acid tert-butyl ester



A solution of 0.11 g (0.4 mmol) of 3-amino-7-chloro-1-cyclopropyl-6-fluoro-1H-pyrido[2,3-d]pyrimidine-2,4-dione (Example 24b), 0.105 g (0.56 mmol) of (S)-3-pyrrolidinylcarbamic acid tert-butyl ester (*J. Med. Chem.*, 1992;35:1764), 1.2 mL of N, N-diisopropylethylamine and 3 mL of acetonitrile is heated at 50°C for 18 hours. The reaction mixture is diluted with 9 mL of water, cooled to 0°C and the solid is removed by filtration, washed with 50% aqueous acetonitrile and dried in vacuo to give 0.14 g of the title compound, mp 108-110°C.

(j) {(S)-1-[(R)-1-(3-Amino-1-cyclopropyl-6-fluoro-2,4-dioxo-1,2,3,4-tetrahydropyrido[2,3-d]pyrimidin-7-yl)pyrrolidin-3-yl]ethyl}-carbamic acid tert-butyl ester



A solution of 0.12 g (0.38 mmol) of 3-amino-1-cyclopropyl-6-fluoro-2,4-dioxo-1,2,3,4-tetrahydro-pyrido[2,3-d]pyrimidine-7-thiosulfonic acid (Compound 24c) in 10 mL of acetonitrile is treated with 0.24 g (1.14 mmol) of ((R)-(S)-1-pyrrolidin-3-ylethyl)carbamic acid tert-butyl ester (*J. Het. Chem.*,

1992;29:1481), 0.25 g (2.5 mmol) of triethylamine and stirred at room temperature for 18 hours then 50°C for 1 hour. The solvent is removed in vacuo and the residue is partitioned between ethyl acetate (50 mL) and water (25 mL). The organic layer is washed with water, dried ($MgSO_4$), filtered and evaporated in vacuo to give 0.28 g. Chromatography on flash grade silica gel (230-400 mesh) column (2 × 12 cm) eluting with dichloromethane/ethanol (95:5) provided 0.1 g of the title compound, mp 175-177°C.

General Procedure A

A solution of Example 24, 1-2.5 eq of heterocyclic amine side chain, and 3-3.5 eq. 1,8-diazabicyclo-5,4,0-undecen-7-ene (DBU) or triethylamine are stirred in dimethyl sulfoxide (1 mL) at 130°C for 3 to 48 hours. After cooling to room temperature, the reaction mixture is diluted with ethyl acetate and washed with saturated $NaHCO_3$, water, and brine. The organic layer is dried over $MgSO_4$, filtered, and the filtrate concentrated. The resulting residue is purified via flash column chromatography (isopropanol/dichloromethane) to afford the product.

General Procedure B

A solution of Example 24 and heterocyclic diamine side chain (1.5-3.0 eq.) is stirred in dimethyl sulfoxide at 130°C for 3 hours. After cooling to room temperature the reaction mixture is diluted with ethyl acetate and washed with saturated $NaHCO_3$, water, and brine. The organic layer is dried over $MgSO_4$, filtered, and the filtrate concentrated. The resulting residue is redissolved in dichloromethane and while stirring, di-*tert*-butyl dicarbonate (0.41 g, 1.87 mmol) is added. After 1 hour, the reaction mixture is concentrated and the product is purified via flash column chromatography (1:1 EtOAc/hexanes) to afford the product.

General procedure C

A solution of Example 24, heterocyclic diamine side chain (1.5-3.0 eq.) and tetramethyl guanidine (1-5.0 eq.) is stirred in dimethyl sulfoxide at (80°C-130°C) for 36 to 24 hours. After cooling to room temperature the reaction mixture is diluted with water and saturated NH_4Cl. The solid is washed with

water and dried to give the crude solid. The product is purified via flash column chromatography (SiO_2) using ($CHCl_3$/MeOH or ethyl acetate/hexanes) to afford the product.

The following compounds are synthesized according to the General Procedures A, B, and C of Example 28:

(k) {1-[(R)-1-((S)-3-Amino-1-cyclopropyl-6-fluoro-8-methyl-2,4-dioxo-1,2,3,4-tetrahydroquinazolin-7-yl)pyrrolidin-3-yl]ethyl}carbamic acid *tert*-butyl ester (MS ES: m/z 462 (MH+)) from 3-amino-1-cyclopropyl-6,7-difluoro-8-methyl-1H-quinazoline-2,4-dione (Example 24e) and (R)-((S)-1-pyrrolidin-3-yl)ethylcarbamic acid *tert*-butyl ester (Kimura Y., Atarashi S., Takahashi M., Hayakkawa I., *Chem. Pharm. Bull.*, 1994;42:1442) using General Method A.

(l) {1-[(S)-1-(3-Amino-1-cyclopropyl-6-fluoro-8-methyl-2,4-dioxo-1,2,3,4-tetrahydroquinazolin-7-yl)pyrrolidin-3-yl]-1-methylethyl}carbamic acid tert-butyl ester (MS ES: m/z 476 (MH^+)) from 3-amino-1-cyclopropyl-6,7-difluoro-8-methyl-1H-quinazoline-2,4-dione (Example 24e) and [(S)-(pyrrolidin-3-yl)-1-methylethyl]carbamic acid *tert*-butyl ester using General Method A.

(m) {1-[1-(3-Amino-1-cyclopropyl-6-fluoro-8-methyl-2,4-dioxo-1,2,3,4-tetrahydroquinazolin-7-yl)-3-methoxypyrrolidin-3-yl]ethyl}carbamic acid *tert*-butyl ester (MS ES: m/z 492 (MH^+)) from 3-amino-1-cyclopropyl-6,7-difluoro-8-methyl-1H-quinazoline-2,4-dione (Example 24e) and [1-(3-methoxypyrrolidin-3-yl)ethyl]carbamic acid *tert*-butyl ester (Example A5b) using General Method A.

(n) [3-(3-Amino-1-cyclopropyl-6-fluoro-8-methyl-2,4-dioxo-1,2,3,4-tetrahydroquinazolin-7-yl)-3-azabicyclo[3.1.0]hex-6-yl]carbamic acid tert-butyl ester (MS ES: m/z 446 (MH^+)) from 3-amino-1-cyclopropyl-6,7-difluoro-8-methyl-1H-quinazoline-2,4-dione (Example 24e) and 3-azabicyclo[3.1.0]hex-6-ylcarbamic acid tert-butyl ester (Brighty K.E., 1991, EP 413455) using General Method A.

(o) {1-[1-(3-Amino-1-cyclopropyl-6-fluoro-8-methoxy-2,4-dioxo-1,2,3,4-tetrahydroquinazolin-7-yl)-3-fluoropyrrolidin-3-yl]ethyl}carbamic acid

tert-butyl ester (MS ES: m/z 496 (MH^+)) from 3-amino-1-cyclopropyl-6,7-difluoro-8-methoxy-1H-quinazoline-2,4-dione (Example 24d) and (4-fluoro-pyrrolidin-3-yl)ethylcarbamic acid tert-butyl ester (Example A5c) using General Method A.

(p) [1-(3-Amino-1-cyclopropyl-6-fluoro-5-methyl-2,4-dioxo-1,2,3,4-tetrahydroquinazolin-7-yl)pyrrolidin-3-yl]carbamic acid tert-butyl ester (MS ES: m/z 434 (MH^+)) from 3-amino-1-cyclopropyl-6,7-difluoro-5-methyl-1H-quinazoline-2,4-dione (Example 24f) and (pyrrolidin-3-yl)carbamic acid tert-butyl ester using General Method A.

(q) {1-(R)-[1-(S)-(3-Amino-1-cyclopropyl-6-fluoro-5-methyl-2,4-dioxo-1,2,3,4-tetrahydroquinazolin-7-yl)pyrrolidin-3-yl]ethyl}carbamic acid *tert*-butyl ester (MS ES:m/z 462 (MH+)) from 3-amino-1-cyclopropyl-6,7-difluoro-5-methyl-1H-quinazoline-2,4-dione (Example 24f) and ((R)-((S)-1-pyrrolidin-3-yl-ethyl)amine using General Method A.

(r) [1-(3-Amino-1-cyclopropyl-6-fluoro-8-methyl-2,4-dioxo-1,2,3,4-tetrahydroquinazolin-7-yl)-3-methoxymethylpyrrolidin-3-ylmethyl]carbamic acid tert-butyl ester (MS ES: m/z 493 (MH^+)) from 3-amino-1-cyclopropyl-6,7-difluoro-8-methyl-1H-quinazoline-2,4-dione (Example 24e) and (3-methoxymethylpyrrolidin-3-ylmethyl)carbamic acid *tert*-butyl ester (Example A5d) using General Method A.

(s) [1-(3-Amino-1-cyclopropyl-6-fluoro-8-methyl-2,4-dioxo-1,2,3,4-tetrahydroquinazolin-7-yl)-3-fluoromethylpyrrolidin-3-ylmethyl]carbamic acid tert-butyl ester (^1H NMR (200 MHz, $CDCl_3$): δ 7.60 (d, 1H), 5.18 (bs, 1H), 4.97 (bs, 2H), 4.61-4.10 (m, 4H), 3.72-3.19 (m, 5H), 2.46 (s, 3H), 2.00-1.71 (m, 2H), 1.45 (s, 9H), 1.21-1.10 (m, 2H), 0.68-0.56 (m, 2H)) from 3-amino-1-cyclopropyl-6,7-difluoro-8-methyl-1H-quinazoline-2,4-dione (Example 24e) and 1-(3-fluoromethylpyrrolidin-3-ylmethyl]carbamic acid tert-butyl ester (Li Q., Wang W., Berst K.B., Claiborne A., Hasvold L., Raye K., Tufano M., et al., *Bioorg. Med. Chem. Lett.*, 1998;8:1953-1958) using General Method A.

(t) [trans-(3-Amino-1-cyclopropyl-6-fluoro-8-methoxy-2,4-dioxo-1,2,3,4-tetrahydroquinazolin-7-yl)-4-trifluoromethylpyrrolidin-3-

ylmethyl]carbamic acid tert-butyl ester (^{1}H NMR (200 MHz, $CDCl_3$): δ 7.56 (d, 1H), 5.17 (s, 2H), 4.75 (bs, 1H), 3.97-3.68 (m, 3H), 3.57 (s, 3H), 3.51-3.13 (m, 4H), 2.98-2.60 (m, 2H), 1.45 (s, 9H), 1.20-1.08 (m, 2H), 0.71-0.55 (m, 2H)) from 3-amino-1-cyclopropyl-6,7-difluoro-8-methoxy-1H-quinazoline-2,4-dione (Example 24d) and [trans-(4-trifluoromethylpyrrolidin-3-ylmethyl]carbamic acid *tert*-butyl ester (Li Q., Wang W., Berst K.B., Claiborne A., Hasvold L., Raye K., Tufano M., et al., *Bioorg. Med. Chem. Lett.*, 1998;8:1953-1958) using General Method A.

(u) {1-[1-(3-Amino-1-cyclopropyl-6-fluoro-8-methoxy-2,4-dioxo-1,2,3,4-tetrahydroquinazolin-7-yl)piperidin-3-yl]ethyl}carbamic acid *tert*-butyl ester (MS (ES, M+1) m/z 492 (MH^+)) from 3-amino-1-cyclopropyl-6,7-difluoro-8-methoxy-1H-quinazoline-2,4-dione (Example 24d) and (1-piperidin-3-ylethyl)carbamic acid *tert*-butyl ester (Example A5e) using General Method A.

(v) {1-[1-(3-Amino-1-cyclopropyl-6-fluoro-8-methyl-2,4-dioxo-1,2,3,4-tetrahydroquinazolin-7-yl)piperidin-3-yl]ethyl}carbamic acid *tert*-butyl ester (MS ES: m/z 476 (MH^+)) from 3-amino-1-cyclopropyl-6,7-difluoro-8-methyl-1H-quinazoline-2,4-dione (Example 24e) and 1-(piperidin-3-yl)ethylcarbamic acid *tert*-butyl ester (Example A5e) using General Method A.

(w) {1-[1-(3-Amino-1-cyclopropyl-6-fluoro-8-methoxy-2,4-dioxo-1,2,3,4-tetrahydroquinazolin-7-yl)-4,4-dimethylpyrrolidin-3-yl]ethyl}carbamic acid *tert*-butyl ester (MS ES: m/z 506 (MH^+)) from 3-amino-1-cyclopropyl-6,7-difluoro-8-methoxy-1H-quinazoline-2,4-dione (Example 24d) and [1-(4,4-dimethylpyrrolidin-3-yl)ethyl]carbamic acid *tert*-butyl ester (Example A5f) using General Method A.

(x) {1-[1-(3-Amino-1-cyclopropyl-6-fluoro-8-methyl-2,4-dioxo-1,2,3,4-tetrahydroquinazolin-7-yl)-4,4-dimethylpyrrolidin-3-yl]ethyl}carbamic acid *tert*-butyl ester (MS ES: m/z 490 (MH^+)) from 3-amino-1-cyclopropyl-6,7-difluoro-8-methyl-1H-quinazoline-2,4-dione (Example 24e) and [1-(4,4-dimethylpyrrolidin -3-yl)ethyl]carbamic acid *tert*-butyl ester (Example A5f) using General Method A.

(y) {1-[1-(3-Amino-1-cyclopropyl-6-fluoro-8-methyl-2,4-dioxo-1,2,3,4-tetrahydroquinazolin-7-yl)-4-methylpyrrolidin-3-yl]ethyl}carbamic acid tert-butyl ester (MS ES: m/z 476 (MH^+)) from 3-amino-1-cyclopropyl-6,7-difluoro-8-methyl-1H-quinazoline-2,4-dione (Example 24e) and [1-(4-methylpyrrolidin-3-yl)ethyl]carbamic acid tert-butyl ester (Example A5g) using General Method A.

(z) [1-(3-Amino-1-cyclopropyl-6-fluoro-8-methyl-2,4-dioxo-1,2,3,4-tetrahydroquinazolin-7-yl)-3-phenylpyrrolidin-3-yl]carbamic acid *tert*-butyl ester (^1H NMR (200 MHz, $CDCl_3$): δ 7.61 (d, 1H), 7.50-7.12 (m, 5H), 5.19 (bs, 2H), 4.07-3.70 (m, 3H), 3.62-3.34 (m, 2H), 2.68-2.52 (m, 1H), 2.45 (s, 3H), 1.68 (m, 2H), 1.50-0.95 (m, 11H), 0.62 (m, 2H)) from 3-amino-1-cyclopropyl-6,7-difluoro-8-methyl-1H-quinazoline-2,4-dione (Example 24e) and (3-phenylpyrrolidin-3-yl)carbamic acid *tert*-butyl ester (Example A30) (using General Method A).

(aa) [1-(3-Amino-1-cyclopropyl-6-fluoro-8-methyl-2,4-dioxo-1,2,3,4-tetrahydroquinazolin-7-yl)-3-phenylpyrrolidin-3-ylmethyl]carbamic acid *tert*-butyl ester (^1H NMR (200 MHz, $CDCl_3$): δ 7.68 (d, 1H), 7.50-7.29 (m, 5H), 6.72 (s, 1H), 5.24 (s, 2H), 4.18-3.85 (m, 3H), 3.78-3.52 (m, 2H), 2.70 (s, 1H), 2.58-2.39 (m, 4H), 1.62-0.62 (m, 15H) from 3-amino-1-cyclopropyl-6,7-difluoro-8-methyl-1H-quinazoline-2,4-dione (Example 24e) and (3-phenylpyrrolidin-3-ylmethyl)carbamic acid *tert*-butyl ester (Example A5p) using General Method A.

(bb) [5-(3-Amino-1-cyclopropyl-6-fluoro-8-methyl-2,4-dioxo-1,2,3,4-tetrahydroquinazolin-7-yl)-5-azaspiro[2.4]hept-7-ylmethyl]carbamic acid *tert*-butyl ester (MS ES: *m/z* 474 (MH^+)) from 3-amino-1-cyclopropyl-6,7-difluoro-8-methyl-1H-quinazoline-2,4-dione (Example 24e) and (5-azaspiro[2,4]hept-7-ylmethyl)carbamic acid *tert*-butyl ester (Example A5h) using General Method A.

(cc) [5-(3-Amino-1-cyclopropyl-6-fluoro-8-methoxy-2,4-dioxo-1,2,3,4-tetrahydroquinazolin-7-yl)-5-azaspiro[2.4]hept-7-ylmethyl]carbamic acid *tert*-butyl ester (MS ES: m/z 490 (MH^+)) from 3-amino-1-cyclopropyl-6,7-difluoro-8-methoxy-1H-quinazoline-2,4-dione (Example 24d) and 5-azaspiro[2,4]hept-7-ylmethyl)carbamic acid *tert*-butyl ester (Example A5h) using General Method A.

(dd) [1-(3-Amino-1-cyclopropyl-6-fluoro-8-methoxy-2,4-dioxo-1,2,3,4-tetrahydroquinazolin-7-yl)-3-hydroxypyrrolidin-3-ylmethyl]carbamic acid *tert*-butyl ester (MS ES: m/z 480 (MH^+)) from 3-amino-1-cyclopropyl-6,7-difluoro-8-methoxy-1H-quinazoline-2,4-dione (Example 24d) and (3-hydroxypyrrolidin-3-ylmethyl)carbamic acid *tert*-butyl ester (Example A5i) using General Method A.

(ee) [1-(3-Amino-1-cyclopropyl-6-fluoro-8-methyl-2,4-dioxo-1,2,3,4-tetrahydroquinazolin-7-yl)piperidin-3-ylmethyl]carbamic acid *tert*-butyl ester (**REF**) (MS ES: m/z 462 (MH+)) from 3-amino-1-cyclopropyl-6,7-difluoro-8-methyl-1H-quinazoline-2,4-dione (Example 24e) and (piperidin-3-ylmethyl]carbamic acid *tert*-butyl ester (Hilpert K., Ackermann J., Banner D.W., Gast A., Gubernator K., Hadvary P., Labler L., et al., *J. Med. Chem.*, 1994;37[23]:3889-3901) using General Method A.

(ff) [1-(3-Amino-1-cyclopropyl-6-fluoro-8-methyl-2,4-dioxo-1,2,3,4-tetrahydroquinazolin-7-yl)-4-methoxypyrrolidin-3-yl]carbamic acid *tert*-butyl ester (^1H NMR (200 MHz, $CDCl_3$): δ 7.60-7.54 (d, 1H), 5.16 (s, 2H), 4.82 (s, 1H), 4.20-3.85 (m, 5H), 3.42 (s, 3H), 3.23 (t, 2H), 2.41 (s, 3H), 1.47 (s, 9H), 1.18-1.10 (m, 2H), 0.61 (s, 2H)) from 3-amino-1-cyclopropyl-6,7-difluoro-8-methyl-1H-quinazoline-2,4-dione (Example 24e) and 4-(methoxypyrrolidin-3-yl)carbamic acid *tert*-butyl ester (Li Q., Cooper C.S., Anthony K.L., Lee C.M., Plattner J.J., Ma Z., Wang W., 1996, WO 9639407) using Method A.

(gg) [1-(3-Amino-1-cyclopropyl-6-fluoro-8-methoxy-2,4-dioxo-1,2,3,4-tetrahydroquinazolin-7-yl)-4-methoxypyrrolidin-3-yl]carbamic acid *tert*-butyl ester (^1H NMR (200 MHz, $CDCl_3$): δ 7.21 (d, 1H), 5.23-5.14 (m, 3H), 4.33-3.22 (m, 13H), 1.40 (s, 9H), 1.18 (m, 2H), 0.60 (s, 2H)) from 3-amino-1-cyclopropyl-6,7-difluoro-8-methoxy-1H-quinazoline-2,4-dione (Example 24d) and 4-(methoxypyrrolidin-3-yl)carbamic acid *tert*-butyl ester (Li Q., Cooper C.S., Anthony K.L., Lee C.M., Plattner J.J., Ma Z., Wang W., 1996, WO 9639407) using Method A.

(hh) [1-(3-Amino-1-cyclopropyl-6-fluoro-8-methoxy-2,4-dioxo-1,2,3,4-tetrahydroquinazolin-7-yl)-4-fluoropyrrolidin-3-yl]carbamic acid *tert*-butyl ester (^1H NMR (200 MHz, DMSO-d_6): δ 7.40-7.34 (d, 1H), 5.30-4.80 (m, 3H) 4.50-

3.10 (m, 10H), 1.47 (s, 9H), 1.30-0.50 (m, 4H)) from 3-amino-1-cyclopropyl-6,7-difluoro-8-methoxy-1H-quinazoline-2,4-dione (Example 24d) and 4-(fluoropyrrolidin-3-yl)carbamic acid *tert*-butyl ester (Li Q., Wang W., Berst K.B., Claiborne A., Hasvold L., Raye K., Tufano M., et al., *Bioorg. & Med. Chem. Lett.*, 1998;8:1953-1958) using General Method A.

(ii) [1-(3-Amino-1-cyclopropyl-6-fluoro-8-methyl-2,4-dioxo-1,2,3,4-tetrahydroquinazolin-7-yl)-3-methylpyrrolidin-3-ylmethyl]carbamic acid *tert*-butyl ester (MS ES: m/z 462 (MH^+)) from 3-amino-1-cyclopropyl-6,7-difluoro-8-methyl-1H-quinazoline-2,4-dione (Example 24e) and (3-methylpyrrolidin-3-ylmethyl)carbamic acid *tert*-butyl ester (*J. Med. Chem*, 1992:361-367) using General Method A.

(jj) {(S)-1-[(R)-1-(3-Amino-1-cyclopropyl-8-ethyl-6-fluoro-2,4-dioxo-1,2,3,4-tetrahydroquinazolin-7-yl)pyrrolidin-3-yl]ethyl}carbamic acid *tert*-butyl ester (MS ES: m/z 476 (MH^+)) from 3-amino-1-cyclopropyl-8-ethyl-6,7-difluoro-1H-quinazoline-2,4-dione (Example 24g) and ((R)-[(S)-1-pyrrolidin-3-yl-ethyl)ethyl]carbamic acid *tert*-butyl ester using General Method A.

(kk) 1-(3-Amino-1-cyclopropyl-6-fluoro-8-methoxy-2,4-dioxo-1,2,3,4-tetrahydroquinazolin-7-yl)pyrrolidine-3-carboxylic acid *tert*-butyl ester (^1H NMR (200 MHz, $CDCl_3$): δ 7.51 (d, 1H), 5.15 (s, 2H), 3.88-3.58 (m, 4H), 3.50 (s, 3H), 3.42-3.30 (m, 1H), 3.14-3.02 (m, 1H), 2.25-2.17 (m, 2H), 1.48 (s, 9H), 1.14-1.05 (m, 2H), 0.68-0.61 (m, 2H)) from 3-amino-1-cyclopropyl-6,7-difluoro-8-methoxy-1H-quinazoline-2,4-dione (Example 24d) and pyrrolidine-3-carboxylic acid *tert*-butyl ester (Hayakawa I., Tanaka Y., EP 101829) using General Method A.

(ll) 1-(3-Amino-1-cyclopropyl-6-fluoro-8-methyl-2,4-dioxo-1,2,3,4-tetrahydroquinazolin-7-yl)pyrrolidine-3-carboxylic acid *tert*-butyl ester (^1H NMR (200 MHz, $CDCl_3$): δ 7.61 (d, 1H), 5.16 (s, 2H), 3.70-3.40 (m, 5H), 3.17-3.03 (m, 1H), 2.43 (s, 3H), 2.29-2.19 (m, 2H), 1.47 (s, 9H), 1.22-1.12 (m, 2H), 0.67-0.57 (m, 2H)) from 3-amino-1-cyclopropyl-6,7-difluoro-8-methyl-1H-quinazoline-2,4-dione (Example 24e) and pyrrolidine-3-carboxylic acid *tert*-butyl ester (Hayakawa I., Tanaka Y., EP 101829) using General Method A.

(mm) [3-(3-Amino-1-cyclopropyl-6-fluoro-8-methoxy-2,4-dioxo-1,2,3,4-tetrahydroquinazolin-7-yl)-3-azabicyclo[3.1.0]hex-1-ylmethyl]yl]carbamic acid *tert*-butyl ester (^{1}H NMR (200 MHz, $CDCl_3$): δ 7.53 (d, 1H), 5.31 (bs, 2H), 4.73 (bs, 1H), 3.82-3.01 (m, 11H), 1.45 (s, 9H), 1.42-1.34 (m, 1H), 1.14-1.10 (m, 3H), 0.71-0.63 (m, 2H)), from 3-amino-1-cyclopropyl-6,7-difluoro-8-methoxy-1H-quinazoline-2,4-dione (Example 24d) and (3-azabicyclo[3.1.0]hex-1-ylmethyl)carbamic acid *tert*-butyl ester (Example A5j) using General Method A.

(nn) [3-(3-Amino-1-cyclopropyl-6-fluoro-8-methyl-2,4-dioxo-1,2,3,4-tetrahydroquinazolin-7-yl)-3-azabicyclo[3.1.0]hex-1-ylmethyl]yl]carbamic acid *tert*-butyl ester (MS ES: m/z 460) from 3-amino-1-cyclopropyl-6,7-difluoro-8-methyl-1H-quinazoline-2,4-dione (Example 24e) and (3-azabicyclo[3.1.0]hex-1-ylmethyl)carbamic acid *tert*-butyl ester (Example A5j) using General Method A.

(oo) {(R)-1-[(S)-1-(3-Amino-1-cyclopropyl-6-fluoro-8-methoxy-2,4-dioxo-1,2,3,4-tetrahydroquinazolin-7-yl)pyrrolidin-3-yl]ethyl}carbamic acid *tert*-butyl ester (MS ES: m/z 478 (MH^+)) from 3-amino-1-cyclopropyl-6,7-difluoro-8-methoxy-1H-quinazoline-2,4-dione (Example 24d) and (R)-1-((S)-pyrrolidine-3-yl)ethyl)carbamic acid *tert*-butyl ester (Schroeder M.C., Kiely J.S., Johnson D.R., Szotek D.L., Domagala J.M., Stickney T.M., Kampf J.W., *J. Heterocyclic Chem.*, 1992;29:1481) using General Method A.

(pp) {(R)-1-[(S)-1-(3-Amino-1-cyclopropyl-6-fluoro-8-methoxy-2,4-dioxo-1,2,3,4-tetrahydroquinazolin-7-yl)pyrrolidin-3-yl]ethyl}carbamic acid tert-butyl ester ^{1}H NMR (200 MHz, $CDCl_3$): δ 7.51-7.44 (d, 1H), 5.17 (bs, 2H), 4.62 (bs, 0.5H), 4.58 (bs, 0.5H), 3.79-3.74 (m, 3H), 3.61-3.53 (m, 2H), 3.49 (s, 3H), 3.41-3.32 (m, 1H), 2.22-2.06 (m, 2H), 1.87-1.67 (m, 1H), 1.46 (s, 9H),1.23-1.19 (d, 3H), 1.08-1.02 (m, 2H) 0.76-0.62 (m, 2H).(MS ES: m/z 462) from 3-amino-1-cyclopropyl-6,7-difluoro-8-methoxy-1H-quinazoline-2,4-dione (Example 24d) and (R)-1-((S)-pyrrolidine-3-yl)ethyl)carbamic acid *tert*-butyl ester using General Method A.

(qq) 6-(3-Amino-1-cyclopropyl-6-fluoro-8-methyl-2,4-dioxo-1,2,3,4-tetrahydroquinazolin-7-yl)octahydropyrrolo[3,4-b]pyridine-1-carboxylic acid *tert*-butyl ester (^{1}H NMR (200 MHz, $CDCl_3$): δ 7.61-7.55 (d, 1H), 5.16 (bs, 2H), 4.52

(bs, 0.5H), 4.48 (bs, 0.5H), 4.95-3.38 (m, 6H), 2.40 (s, 3H), 2.36-1.83(m, 3H),1.46 (s, 9H), 1.21-1.17 (m, 5H), 0.65-0.57 (m, 2H), from 3-amino-1-cyclopropyl-6,7-difluoro-8-methyl-1H-quinazoline-2,4-dione (Example 24e) and octahydropyrrolo[3,4-b]pyridine-5-carboxylic acid *tert*-butyl ester using General Method A.

(rr) [(trans)-1-(3-Amino-1-cyclopropyl-6-fluoro-8-methoxy-2,4-dioxo-1,2,3,4-tetrahydroquinazolin-7-yl)-4-methylpyrrolidin-3-ylmethyl]carbamic acid *tert*-butyl ester (MS ES: m/z 478 (MH^+)) from 3-amino-1-cyclopropyl-6,7-difluoro-8-methoxy-1H-quinazoline-2,4-dione (Example 24d) and (trans-4-methylpyrrolidin-3-ylmethyl)carbamic acid *tert*-butyl ester (Kuniyoshi M., Seigo S., Keiji H., Takayoshi I., Eur. Pat. Appl. EP 208210, 1987) using General Method A.

(ss) [1-(3-Amino-1-cyclopropyl-6-fluoro-8-methyl-2,4-dioxo-1,2,3,4-tetrahydroquinazolin-7-yl)-4-methylpyrrolidin-3-ylmethyl]carbamic acid tert-butyl ester (MS ES: m/z 462 (MH+)) from 3-amino-1-cyclopropyl-6,7-difluoro-8-methyl-1H-quinazoline-2,4-dione (Example 24e) and (4-methylpyrrolidin-3-ylmethyl)carbamic acid tert-butyl ester (Kuniyoshi M., Seigo S., Keiji H., Takayoshi I., Eur. Pat. Appl. EP 208210, 1987) using General Method A.

(tt) [1-(3-Amino-1-cyclopropyl-6-fluoro-8-methoxy-2,4-dioxo-1,2,3,4-tetrahydroquinazolin-7-yl)-4-methylpyrrolidin-3-yl]carbamic acid *tert*-butyl ester (MS ES: m/z 464 (MH^+)) from 3-amino-1-cyclopropyl-6,7-difluoro-8-methoxy-1H-quinazoline-2,4-dione (Example 24d) and (4-methylpyrrolidin-3-yl)carbamic acid *tert*-butyl ester (Di Cesare P., Bouzard D., Essiz M., Jacquet J.P., Ledoussai B., Kiechet J.R., Remuzon P. et al., *J. Med. Chem.*, 1992,35:4205) using General Method A.

(uu) [1-(3-Amino-1-cyclopropyl-6-fluoro-8-methoxy-2,4-dioxo-1,2,3,4-tetrahydroquinazolin-7-yl)morpholin-3-ylmethyl]carbamic acid *tert*-butyl ester (MS ES: m/z 480 (MH^+)) from 3-amino-1-cyclopropyl-6,7-difluoro-8-methoxy-1H-quinazoline-2,4-dione (Example 24d) and 1-(morpholin-3-ylmethyl)carbamic acid *tert*-butyl ester (Araki K., Kuroda T., Uemori S., Moriguchi A., Ikeda Y.,

Hirayama F., Yokoyama Y. et al., *J. Med. Chem.*, 1993,36:1356) using General Method A.

(vv) [1-(3-Amino-1-cyclopropyl-6-fluoro-8-methoxy-2,4-dioxo-1,2,3,4-tetrahydroquinazolin-7-yl)piperidin-3-ylmethyl]carbamic acid tert-butyl ester (MS ES: m/z 478 (MH^+)) from 3-amino-1-cyclopropyl-6,7-difluoro-8-methoxy-1H-quinazoline-2,4-dione (Example 24d) and 1-piperidin-3-ylmethylcarbamic acid tert-butyl ester (Hilpert K., et al., *J. Med. Chem.*, 1994;37(23):3889-3901) using General Method A.

(ww) {1-[1-(3-Amino-1-cyclopropyl-6-fluoro-8-methoxy-2,4-dioxo-1,2,3,4-tetrahydroquinazolin-7-yl)-4-methylpyrrolidin-3-yl]ethyl}carbamic acid *tert*-butyl ester (MS ES: m/z 492 (MH^+)) from 3-amino-1-cyclopropyl-6,7-difluoro-8-methoxy-1H-quinazoline-2,4-dione (Example 24d) and [1-(4-methylpyrrolidin -3-yl)ethyl]carbamic acid *tert*-butyl ester (A5g) using General Method A.

(xx) [1-(1-Cyclopropyl-6-fluoro-8-methyl-2,4-dioxo-1,2,3,4-tetrahydroquinazolin-7-yl)-3-methylpyrrolidin-3-yl]]carbamic acid *tert*-butyl ester (^1H NMR (200 MHz, $CDCl_3$): δ 7.61 (d, 1H), 5.15 (s, 2H), 4.74 (s, 1H), 3.71-3.37 (m, 6H), 2.45-2.20 (m, 4H), 1.45 (s, 12H), 1.21-1.08 (m, 2H), 0.61 (d, 2H)) from 3-amino-1-cyclopropyl-6,7-difluoro-8-methyl-1H-quinazoline-2,4-dione (Example 24e) and 3-methylpyrrolidin-3-ylcarbamic acid *tert*-butyl ester (Yoshida T., Yamamoto Y., Orita H., Kakiuchi M., Takahashi Y., Itakura M., Kudo N. et al., *Chem. Pharm. Bull.*, 1996;44[7]:1376-1386) using General Method A

(yy) 3-Amino-1-cyclopropyl-6-fluoro-8-methyl-7-pyrrolidin-1-yl-1H-quinazoline-2,4-dione (^1H NMR (200MHz, $CDCl_3$): δ 7.61-7.54 (d, 1H), 5.15 (bs, 2H), 3.51-3.40 (m, 5H), 2.39 (s, 3H), 2.01-1.95 (m, 4H), 1.21-1.11 (m, 2H), 0.67-0.62 (m, 2H)) from 3-amino-1-cyclopropyl-6,7-difluoro-8-methyl-1H-quinazoline-2,4-dione (Example 24e) and pyrrolidine using General Method A.

(zz) 3-Amino-1-cyclopropyl-6-fluoro-8-methoxy-7-pyrrolidin-1-yl-1H-quinazoline-2,4-dione (^1H NMR (200MHz, $CDCl_3$): δ 7.49–7.42 (d, 1H), 5.13 (bs, 2H), 3.66–3.54 (m, 4H), 3.50 (s, 3H), 3.42–3.31 (m, 1H), 2.02–1.92 (m, 4H),

1.17–1.07 (m, 2H), 0.69–0.61 (m, 2H)) from 3-amino-1-cyclopropyl-6,7-difluoro-8-methoxy-1H-quinazoline-2,4-dione (Example 24d) and pyrrolidine using General Method A.

(aaa) 3-Amino-1-cyclopropyl-6-fluoro-7-[3-(1-hydroxyethyl-1-methyl)-pyrrolidin-1-yl]-8-methyl-1H-quinazoline-2,4-dione (^{1}H NMR (200 MHz, $CDCl_3$): δ 7.59 (d, 1H), 5.15 (s, 2H), 3.68-3.53 (m, 2H), 3.44-3.31 (m, 3H), 2.42 (s, 3H), 2.00-1.82 (m, 2H), 1.58 (s, 1H), 1.28 (s, 6H), 1.20-1.10 (m, 2H), 1.00-0.80 (m, 1H), 0.66-0.60 (m, 2H)) from 3-amino-1-cyclopropyl-6,7-difluoro-8-methyl-1H-quinazoline-2,4-dione (Example 24e) and 1-methyl-1-pyrrolidin-3-yl-ethanol (Example A5n) using General Method A.

(bbb) 3-Amino-1-cyclopropyl-6-fluoro-7-[3-(1-hydroxy-1-methylethyl)-pyrrolidin-1-yl]-8-methoxy-1H-quinazoline-2,4-dione (^{1}H NMR (200 MHz, $CDCl_3$): δ 7.50 (d, 1H), 5.14 (s, 2H), 3.86-3.70 (m, 2H), 3.49 (s, 3H), 3.60-3.30 (m, 3H), 2.40-2.22 (m, 1H), 2.00-1.80 (m, 2H), 1.30 (s, 6H), 1.09-0.85 (m, 2H), 0.75-0.57 (m, 2H)) from 3-amino-1-cyclopropyl-6,7-difluoro-8-methoxy-1H-quinazoline-2,4-dione (Example 24d) and 1-methyl-1-pyrrolidin-3-yl-ethanol (Example A5n) using General Method A.

(ccc) 1-[(R)-1-(3-(S)-Amino-1-cyclopropyl-6-fluoro-5-methyl-7-[3-(1-methylaminoethyl)pyrrolidin-1-yl]-1H-quinazoline-2,4-dione (MS ES: m/z 376 (MH^+)) from 3-amino-1-cyclopropyl-6,7-difluoro-5-methyl-1H-quinazoline-2,4-dione (Example 24e) and methyl-((R)-((S)-1-pyrrolidin-3-yl)ethyl)amine using General Method A.

(ddd) 1-[(R)-1-(3-(S)-Amino-1-cyclopropyl-7-[3-(1-ethylaminoethyl)-pyrrolidin-1-yl)-6-fluoro-8-methoxy-1H-quinazoline-2,4-dione (MS ES: m/z 406 (MH^+)) from 3-amino-1-cyclopropyl-6,7-difluoro-8-methoxy-1H-quinazoline-2,4-dione (Example 24d) and ethyl-((R)-((S)-1-pyrrolidin-3-yl)ethyl)amine (Domagala J.M., Hagen S.E., Joannides T., Kiely J.S., Laborde E., Schroeder M.C., Sesnie J.A., et al., *J. Med. Chem.*, 1993;36[7]:871-882) using General Methqd A.

(eee) 3-Amino-1-cyclopropyl-7-[(R)-3-((S)-1-ethylaminoethyl)-pyrrolidin-1-yl]-6-fluoro-8-methyl-1H-quinazoline-2,4-dione (MS ES: m/z 390

(MH$^+$)) from 3-amino-1-cyclopropyl-6,7-difluoro-8-methyl-1H-quinazoline-2,4-dione (Example 24c) and ethyl-((R)-((S)-1-pyrrolidin-3-yl)ethyl)amine using General Method A.

(fff) 3-Amino-7-(6-amino-1-methyl-3-azabicyclo[3.2.0]hept-3-yl)-1-cyclopropyl-6-fluoro-8-methoxy-1H-quinazoline-2,4-dione (MS ES: m/z 390 (MH$^+$)) from 3-amino-1-cyclopropyl-6,7-difluoro-8-methoxy-1H-quinazoline-2,4-dione (Example 24d) and 1-methyl-3-azabicyclo[3.2.0]hept-6-ylamine (Kim C.S., Kim J.W., Lee J.M., Youn Y.S., Shin Y.J., Lee K.H., Kim J.H. WO 94/15933) using General Method A.

(ggg) 3-Amino-7-(3-aminomethylazetidin-1-yl)-1-cyclopropyl-6-fluoro-8-methoxy-1H-quinazoline-2,4-dione (MS ES: m/z 350 (MH$^+$)) from 3-amino-1-cyclopropyl-6,7-difluoro-8-methoxy-1H-quinazoline-2,4-dione (Example 24d) and azetidin-3-ylmethylamine (Okada T., Ezumi K., Yamakawa M., Sato H., Tsuji T., Tsushima T., Motokawa K., Komatsu Y., *Chem. Pharm. Bull.*, 1993;41:126-131) using General Method A.

(hhh) 3-Amino-7-(4-aminomethylpiperidin-1-yl)-1-cyclopropyl-6-fluoro-8-methoxy-1H-quinazoline-2,4-dione (MS ES: m/z 378 (MH$^+$)) from 3-amino-1-cyclopropyl-6,7-difluoro-8-methoxy-1H-quinazoline-2,4-dione (Example 24d) and piperidin-4-ylmethylamine using General Method A.

(iii) [(cis)-1-(3-Amino-1-cyclopropyl-6-fluoro-8-methoxy-2,4-dioxo-1,2,3,4-tetrahydroquinazolin-7-yl)-4-fluoropyrrolidin-3-ylmethyl]carbamic acid *tert*-butyl ester (MS ES: m/z 482 (MH$^+$)) from 3-amino-1-cyclopropyl-6,7-difluoro-8-methoxy-1H-quinazoline-2,4-dione (Example 24d) and (cis-4-fluoropyrrolidin-3-ylmethyl)carbamic acid *tert*-butyl ester [A5k)] using General Method A.

(jjj) [(trans)-1-(3-Amino-1-cyclopropyl-6-fluoro-8-methoxy-2,4-dioxo-1,2,3,4-tetrahydroquinazolin-7-yl)-4-fluoropyrrolidin-3-ylmethyl]carbamic acid *tert*-butyl ester (MS ES: m/z 482 (MH$^+$)) from 3-amino-1-cyclopropyl-6,7-difluoro-8-methoxy-1H-quinazoline-2,4-dione (Example 24d) and (trans-4-methylpyrrolidin-3-ylmethyl)carbamic acid *tert*-butyl ester [A5l] using General Method A.

(kkk) [1-(3-amino-1-cyclopropyl-6-fluoro-8-methoxy-2,4-dioxo-1,2,3,4-tetrahydroquinazolin-7-yl)-(1-amino-5-azaspiro[2.4]hept-5-yl)]carbamic acid *tert*-butyl ester (MS APCI: m/z 476 (MH^+)) from 3-amino-1-cyclopropyl-6,7-difluoro-8-methoxy-1H-quinazoline-2,4-dione (Example 14d) and 1-amino-5-aza-spiro[2.4]hept-5-yl)]carbamic acid *tert*-butyl ester (Li Q., Chu D.T.W., Claiborne A., Cooper C.S., Lee C.M., Raye K., Berst K.B., et al., *J. Med. Chem.*, 1996;39[16]:3070-3088) using General Method C.

(lll) [1-(3-Amino-7-(3a-aminomethyloctahydroisoindol-2-yl)-1-cyclopropyl-6-fluoro-8-methoxy-2,4-dioxo-1,2,3,4-tetrahydroquinazolin-7-yl]carbamic acid *tert*-butyl ester (MS APCI: m/z 518 (MH^+)) from 3-amino-1-cyclopropyl-6,7-difluoro-8-methoxy-1H-quinazoline-2,4-dione (Example 24d) and (3a-aminomethyloctahydro-isoindol-2-yl)carbamic acid *tert*-butyl ester (Ma Z., Chu D.T.W., Cooper C.S., Li Q., Fung A.K.L., Wang S., Shen L.L., et al., *J. Med. Chem.*, 1999;42(20):4202-4213) using General Method C.

(mmm) 3-Amino-7-(3a-aminomethyloctahydroisoindol-2-yl)-1-cyclopropyl-6-fluoro-8-methyl-1H-quinazoline-2,4-dione (MS APCI: m/z 502 (MH^+)) from 3-amino-1-cyclopropyl-6,7-difluoro-8-methyl-1H-quinazoline-2,4-dione (Example 24c) and 3a-aminomethyloctahydroisoindol-2-ylcarbamic acid-tert-butyl ester (Ma Z., Chu D.T.W., Cooper C.S., Li Q., Fung A.K.L., Wang S., Shen L.L., et al., *J. Med. Chem.*, 1999;42(20);4202-4213) using General Method C.

(nnn) {(S)-1-[(R)-1-(3-amino-1-cyclopropyl-6-fluoro-8-methoxy-2,4-dioxo-1,2,3,4-tetrahydroquinazolin-7-yl)pyrrolidin-3-yl]ethyl}carbamic acid *tert*-butyl ester (MS APCI: m/z 476 (MH^+)) from 3-amino-1-cyclopropyl-6,7-difluoro-8-methoxy-1H-quinazoline-2,4-dione (Example 14d) and ((R)-(S)-1-pyrrolidin-3-yl)ethylcarbamic acid *tert*-butyl ester (*J. Het. Chem.*, 1992;29:1481) using General Method C.

(ooo) {1-[1-(3-Amino-1-cyclopropyl-6-fluoro-8-methyl-2,4-dioxo-1,2,3,4-tetrahydro-quinazolin-7-yl)-pyrrolidin-3-yl]-propyl}-carbamic acid *tert*-butyl ester (MS: *m/e* 476 (MH^+)) from 3-amino-1-cyclopropyl-6,7-difluoro-8-methyl-1H-quinazoline-2,4-dione (Example 24e) and (1-pyrrolidin-3-yl-propyl)-

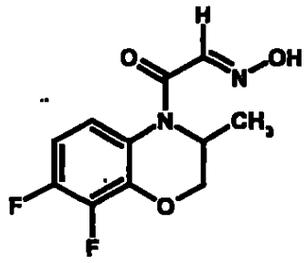
carbamic acid *tert*-butyl ester (Kimura Y., Atarashi S., Takahashi M., Hayakkawa I., *Chem. Pharm. Bull.*, 1994;42:1442) using General Method A.

(ppp) {(S)-1-[(R)-1-(3-Amino-1-cyclopropyl-6-fluoro-8-methyl-2,4-dioxo-1,2,3,4-tetrahydro-quinazolin-7-yl)pyrrolidin-3-yl]-ethyl}-methyl-carbamic acid dimethylethyl ester (MS: *m/e* 476 (MH^+)) from 3-amino-1-cyclopropyl-6,7-difluoro-8-methyl-1H-quinazoline-2,4-dione (Example 24e) and methyl-(R)-((S)-1-pyrrolidin-3-yl)ethylamine (Plummer J.S., Emery L.A., Stier M.A., Suto M.J., *Tetrahedron Lett.*, 1993;34(47):7529-7532) using General Method A.

(qqq) {1-[5-(3-Amino-1-cyclopropyl-6-fluoro-8-methyl-2,4-dioxo-1,2,3,4-tetrahydroquinazolin-7-yl)-5-aza-spiro[2.4]hept-7-yl]ethyl}carbamic acid *tert*-butyl ester (MS CI: *m/e* 488 (MH^+)) from 3-amino-1-cyclopropyl-6,7-difluoro-8-methyl-1H-quinazoline-2,4-dione (Example 24e) and [1-(5-aza-spiro[2.4]hept-7-yl)ethyl]carbamic acid tert-butyl ester (Example A5a) using General Method A.

EXAMPLE 29

(7,8-Difluoro-3-methyl-2,3-dihydro-1,4-benzoxazin-4-yl)-oxoacetaldehyde oxime

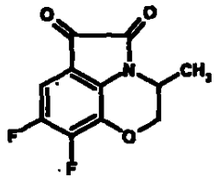


A solution of 8.27 g (50 mmol) of chloral hydrate in 125 mL of water is treated with 112.8 g (0.35 mmol) of sodium sulfate decahydrate. The mixture is stirred and treated with a solution of 7,8-difluoro-3-methyl-3,4-dihydro-2H-benz[1,4]oxazine (*Chem. Pharm. Bull.*, 1984;32:4907) hydrochloride (prepared by dissolving 8.26 g (44.6 mmol) of the free base in 50 mmol of concentrated hydrochloric acid in 70 mL of 50% aqueous ethanol). The reaction is stirred and a solution of 9.8 g (140 mmol) of hydroxylamine hydrochloride in 50 mL of water is added. After heating at 75 to 80°C for 3 hours, the reaction is stirred at room

temperature overnight. The resulting precipitate is removed by filtration, washed with water, and the wet filter cake is dissolved in dichloromethane. The organic solution is washed with water, dried ($MgSO_4$), decolorized with charcoal, filtered and concentrated in vacuo to give 10.5 g of the title compound, mp 188-190°C.

EXAMPLE 30

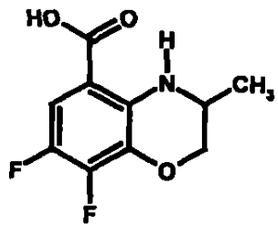
Synthesis of 6,7-Difluoro-3-methyl-3,4-dihydro-5-oxa-2a-aza-acenaphthylene-1,2-dione



A solution of 45 mL of 98% sulfuric acid in 18 mL of water is heated to 50°C to 60°C and treated portionwise over 30 minutes with 10.5 g (41 mmol) of (7,8-difluoro-3-methyl-2,3-dihydro-1,4-benzoxazin-4-yl)oxoacetaldehyde oxime (Example 29). After the addition is complete, the reaction is heated to 80°C for 15 minutes and poured onto 200 mL of ice and water. The mixture is stirred until the ice melts and the solid is removed by filtration, washed with water and the wet filter cake is dissolved in dichloromethane. The organic solution is washed with water (2 × 200 mL), dried ($MgSO_4$), filtered and concentrated in vacuo affording 7.1 g of the title compound, mp 169-171°C.

EXAMPLE 31

Synthesis of 7,8-Difluoro-3-methyl-3,4-dihydro-2H-1,4-benzoxazine-5-carboxylic acid

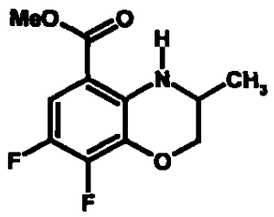


A suspension of 6.9 g (28.8 mmol) of 6,7-difluoro-3-methyl-3,4-dihydro-5-oxa-2a-aza-acenaphthylene-1,2-dione (Example 30) in 250 mL of 4.5% aqueous sodium hydroxide is treated dropwise with 16.4 mL of 30% hydrogen peroxide over 1 hour. The reaction is filtered to remove a trace of insoluble material and the filtrate is acidified to pH 4.5 with acetic acid. After cooling to 5°C, the precipitate is removed by filtration, washed with water and dried in vacuo to give 5.5 g of the title compound, mp 200-202°C.

EXAMPLE 32

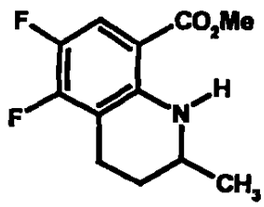
Synthesis of Anthranilic Esters

(a) 7,8-Difluoro-3-methyl-3,4-dihydro-2H-1,4-benzoxazine-5-carboxylic acid methyl ester



A solution of 2.1 g (9.1 mmol) of 7,8-difluoro-3-methyl-3,4-dihydro-2H-1,4-benzoxazine-5-carboxylic acid (Example 31) in 50 mL of methanol is cooled to 0°C and saturated with hydrogen chloride gas. The reaction is stirred at room temperature for 18 hours, recooled to 0°C and resaturated with hydrogen chloride gas. After stirring an additional 24 hours at room temperature, the solvent is removed in vacuo and the residue is partitioned between dichloromethane/5% aqueous sodium bicarbonate (200:100 mL). The organic layer is separated, washed with 5% aqueous sodium bicarbonate, water, dried (MgSO4), filtered, and concentrated in vacuo affording 1.9 g of the title compound. ^{1}H NMR (400 MHz, $CDCl_3$): 7.27 (bs, 1H), 7.24 (m, 1H), 4.26 (m, 1H), 3.82 (s, 3H), 3.75 (m, 1H), 3.62 (m, 1H), 1.22 (d, 3H).

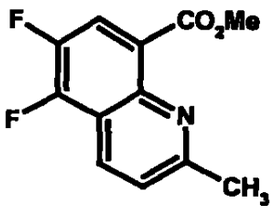
(b) Synthesis of 5,6-Difluoro-2-methyl-1,2,3,4-tetrahydro-quinoline-8-carboxylic acid methyl ester



A solution of 8.0 g (33.7 mmol) of 5,6-difluoro-2-methylquinoline-8-carboxylic acid methyl ester (Example 33) in 100 mL of glacial acetic acid is treated with 2.15 g of platinum on carbon (0.8 g of active catalyst + 62.8% water) and then shaken in a hydrogen atmosphere at temperatures of 24°C to 29°C and pressures of 23.9 to 46.6 psi for 3 hours. The catalyst is removed by filtration and the solvent is removed in vacuo at 50°C. The residue is triturated with water (50 mL) and extracted with dichloromethane (2 x 200 mL). The combined organic layers are stirred with 5% sodium bicarbonate solution, washed with water, dried ($MgSO_4$), filtered and evaporated in vacuo. The residue is chromatographed over flash grade silica gel (230-400 mesh) eluting with dichloromethane to give 5.6 g of the title compound as a light yellow oil. ^1H NMR (400 MHz, $CDCl_3$): 7.66 (bs, 1H), 7.49 (m, 1H), 3.82 (s, 3H), 3.46 (m, 1H), 2.88 (m, 1H), 2.67 (m, 1H), 1.97 (m, 1H), 1.27 (d, 3H).

EXAMPLE 33

Synthesis of 5,6-Difluoro-2-methylquinoline-8-carboxylic acid methyl ester

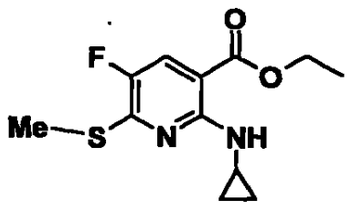


In a stainless steel reactor, a solution of 9.53 g (36.9 mmol) of 8-bromo-5,6-difluoro-2-methylquinoline (*Chem. Pharm. Bull.*, 1996;44:642), 6.8 g (67.6 mmol) of triethylamine, 0.67 g (3.0 mmol) of palladium (II) acetate, 1.28 g (3.1 mmol) of 1,3-bis(diphenyl-phosphino)propane in 90 mL of dimethylformamide and 65 mL of methanol is flushed with nitrogen gas and pressurized to 550 psi with carbon monoxide. The reaction is rocked and heated to

75°C for 24 hours, cooled to room temperature and evaporated in vacuo. The residue is triturated with water (50 mL) and extracted with dichloromethane (2 × 200 mL). The combined organic layers are washed with water (2 × 50 mL), dried ($MgSO_4$), filtered and evaporated in vacuo. The residue is chromatographed over flash grade silica gel (230-400 mesh) eluting with dichloromethane (200 mL), then dichloromethane/ethyl acetate (90:10) to give 8.0 g of the title compound, mp 99-101°C.

EXAMPLE 34

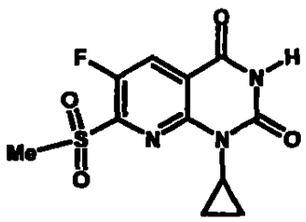
Synthesis of 2-cyclopropylamino-5-fluoro-6-methylsulfanylnicotinic acid ethyl ester



A solution of 8.7 g (34.8 mmol) of 2-chloro-5-fluoro-6-methylsulfanylnicotinic acid ethyl ester (*J. Med. Chem.*, 1993;36:2676) and 5.7 g (100 mmol) of cyclopropylamine in 100 mL of acetonitrile is heated at reflux for 18 hours. After TLC showed the presence of unreacted starting material, 4.12 g (72 mmol) of cyclopropylamine is added and the reaction mixture is refluxed for 48 hours. The solvent is removed in vacuo and the residue is partitioned between dichloromethane (250 mL) and water (100 mL). The organic layer is washed with water, dried ($MgSO_4$), filtered, and concentrated in vacuo. The residue is chromatographed over flash grade silica gel (230-400 mesh) eluting with dichloromethane to give 6.5 g of the title compound, mp 67-69°C.

EXAMPLE 35

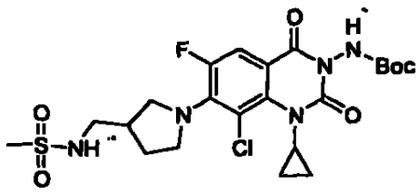
Synthesis of 1-Cyclopropyl-6-fluoro-2,4-dioxo-1,2,3,4-tetrahydropyrido[2,3-d]pyrimidine-7-thiosulfonic acid



A solution of 0.65 g (2.4 mmol) of 1-cyclopropyl-6-fluoro-7-methylsulfanyl-1H-pyrido[2,3-d]pyrimidine-2,4-dione (Example 23e) in 20 mL of formic acid is treated with 1.83 g (19.5 mmol) of urea-hydrogen peroxide and the reaction mixture is stirred at room temperature overnight. The resulting precipitate is removed by filtration, washed with water, ethyl acetate and dried in vacuo to give 0.63 g of the title compound, mp 300-302°C.

EXAMPLE 36

Synthesis of {8-Chloro-1-cyclopropyl-6-fluoro-7-[3-(methanesulfonylamino-methyl)pyrrolidin-1-yl]-2,4-dioxo-1,4-dihydro-2H-quinazolin-3-yl}carbamic acid tert-butyl ester



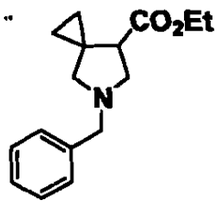
A solution of (8-chloro-1-cyclopropyl-6,7-difluoro-2,4-dioxo-1,4-dihydro-2*H*-quinazolin-3-yl)carbamic acid *tert*-butyl ester (Example 14, 0.37 g, 0.97 mmol) in acetonitrile (20 mL) is added pyrrolidin-3-yl-methylamine (0.115 g, 1.16 mmol) and triethylamine (2.7 mL, 19.3 mmol). After refluxing for 20 hours, the reaction mixture is cooled to room temperature and diluted with ethyl acetate. The organic layer is washed with saturated sodium bicarbonate, water, and brine. The organic layer is dried over $MgSO_4$, filtered, and the filtrate concentrated. The resulting residue is redissolved in methylene chloride (10 mL) at 0°C and while stirring, triethylamine (0.33 mL, 2.34 mmol) and methanesulfonyl chloride (0.072 mL, 0.94 mmol) is added. After 2 hours, the reaction mixture is diluted with ethyl acetate and washed with saturated sodium

bicarbonate, water, and brine. The organic layer is dried over $MgSO_4$, filtered, and the filtrate concentrated and the product is purified via flash column chromatography (1:1 EtOAc/hexanes) to afford {8-chloro-1-cyclopropyl-6-fluoro-7-[3-(methanesulfonylaminomethyl)pyrrolidin-1-yl]-2,4-dioxo-1,4-dihydro-2*H*-quinazolin-3-yl}carbamic acid *tert*-butyl ester (0.043 g). MS CI: *m/e* 446 ((MH^+)-Boc).

Amine Side Chain Synthesis

EXAMPLE A1

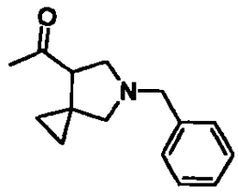
(a) 5-Benzyl-5-azaspiro[2,4]heptan-1-carboxylic acid ethyl ester



A solution of cyclopropylidene acetic acid ethyl ester (192 g, 1520 mmol [Salaun J., Bennani F., Compain J.C., Fadel A., Ollivier J.J., *Org. Chem.*, 1980;45(21):4129-3415]) and N-(methoxymethyl)-N-(trimethylsilylmethyl)-benzylamine (572 g, 2410 mmol [Gerlach K., Hoffmann H.M.R., Wartchow R.J., *Chem. Soc.*, Perkin Trans. 11, 1998(22):3867-3872]) in dichloromethane (5.5 L) was treated with a solution of 1.0N trifluoroacetic acid in dichloromethane (80 mL) and the reaction is stirred at ambient temperature for 30 minutes. The solvent is then evaporated at reduced pressure and the product purified by Kugelrohr distillation (277 g). MS CI: m/z 260 (MH^+).

EXAMPLE A2

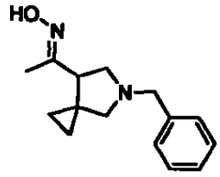
(a) Synthesis of 1-(5-Benzyl-5-azaspiro[2.4]hept-7-yl)ethanone



A solution (-78°C) of 5-benzyl-5-azaspiro[2.4]heptane-7-carboxylic acid ethyl ester (Example A1a, 8.15 g, 31.4 mmol) in diethyl ether (200 mL) under a nitrogen atmosphere is treated with methyllithium (1.4 *M* in diethyl ether, 22.4 mL, 31.4 mmol) over a period of 10 minutes. After 1 hour, reaction mixture is warmed to -10°C and quenched with saturated aqueous ammonium chloride. The mixture is poured into a separatory funnel and the organic layer is washed with saturated aqueous ammonium chloride, water, and brine. The organic layer is then dried with $MgSO_4$, filtered, and the filtrate concentrated. The resulting residue is purified via flash column chromatography (1% triethylamine/7% isopropanol/92% CH_2Cl_2) to afford the title compound (3.93 g). MS CI: *m/z* 230 (MH^+).

EXAMPLE A3

(a) Synthesis of 1-(5-Benzyl-5-azaspiro[2.4]hept-7-yl)ethanone oxime



1-(5-benzyl-5-azaspiro[2.4]hept-7-yl)ethanone (Example A2a, 3.93 g, 17.1 mmol) and hydroxylamine hydrochloride (1.78 g, 25.7 mmol) are stirred in pyridine (10 mL) at 90°C. After 20 hours, the reaction mixture is diluted with ethyl acetate and the organic layer is washed with saturated $NaHCO_3$, water, and brine. The organic layer is dried with $MgSO_4$, filtered, and the filtrate concentrated to afford 1-(5-benzyl-5-azaspiro[2.4]hept-7-yl)ethanone oxime as an oil (3.07 g). MSCI: *m/z* 245 (MH^+).

General Method A

A solution of substrate, hydroxylamine hydrochloride (1.2 eq.), sodium acetate (0.9 eq.) in ethanol is stirred at room temperature for 2 hours. The solvent is removed in vacuo and the residue is partitioned between ethyl acetate and saturated sodium chloride solution. The aqueous is re-extracted with ethyl acetate

and the combined extracts are dried over Na_2SO_4, filtered and concentrated under vacuum to afford the title compound.

The compounds below were prepared according to General Method A.

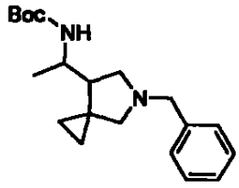
(b) 1-(1-Benzylpiperidin-3-yl)ethanone oxime (^{1}H NMR (200 MHz, $CDCl_3$): δ 7.48-7.28 (m, 5H), 3.92-3.68 (m, 2H), 3.28-3.0 (m, 4H), 2.88-2.62 (m, 2H), 2.38-1.72 (m, 3H), 1.3-1.18 (m, 3H)) from 1-(1-benzylpiperidin-3-yl)ethanone (Example A23).

(c) 1-(1-Benzyl-4,4-dimethylpyrrolidin-3-yl)ethanone oxime (^{1}H NMR (200 MHz, $CDCl_3$): δ 7.68-7.30 (m, 5H), 6.60-5.80 (bs, 1H), 3.80-2.38 (m, 6H), 1.90 (s, 3H), 1.38-0.96 (m, 7H)) from 1-(1-benzyl-4,4-dimethylpyrrolidin-3-yl)ethanone (Example A18b).

(d) 1-(1-Benzyl-4-methylpyrrolidin-3-yl)ethanone oxime (^{1}H NMR (200 MHz, $CDCl_3$): δ 7.41-7.15 (m, 5H), 3.78-3.44 (m, 3H), 2.98-2.80 (m, 1H), 2.75-2.39 (m, 3H), 2.35-2.08 (m, 2H), 1.90 (m, 3H), 1.18-0.95 (m, 3H)) from 1-(1-benzyl-4-methylpyrrolidin-3-yl)ethanone (Example A23b).

EXAMPLE A4

(a) Synthesis of 1-(5-Benzyl-5-azaspiro[2.4]hept-7-yl)-ethyl]carbamic acid tert-butyl ester



To a solution of 1-(5-benzyl-5-azaspiro[2.4]hept-7-yl)ethanone oxime (Example A3a, 2.90 g, 11.9 mmol) in methanol (100 mL) is added Raney-Nickel (2 g). Hydrogen is introduced to the reaction mixture at high pressure (48 psi) for 20 hours and the reaction mixture is filtered through celite, washed with methanol, and the combined filtrates concentrated in vacuo. The resulting residue is redissolved in dichloromethane (25 mL) and treated with di-*tert*-butyl dicarbonate (3.24 g, 14.9 mmol). After 1 hour, the mixture is concentrated and the product purified via flash column chromatography (1% triethylamine/7% isopropanol/92%

dichloromethane) to afford [1-(5-benzyl-5-azaspiro[2.4]hept-7-yl)-ethyl]carbamic acid *tert*-butyl ester (1.47 g). MS CI: *m/z* 331 (MH^+).

General Method A

Di-*tert*-butyl dicarbonate (0.69 g, 0.3 mmol) is added to a solution of amine in methanol (4 mL) at 0°C. After stirring at room temperature for 2 hours, the mixture is concentrated and the residue is purified by chromatography (SiO_2, ethyl acetate/hexanes) to afford the title carbamic esters.

General Method B

An ice-cold solution of substrate in 2:1 methanol and water is treated with di-*tert*-butyl dicarbonate (1.25 eq.). The resulting solution is stirred at room temperature for 18 hours and extracted with dichloromethane. The organic extracts are washed with brine, dried over Na_2SO_4, filtered and concentrated under vacuum. The residue is purified by flash column chromatography (ethyl acetate/hexanes) to afford the title compounds.

General Method C

To a solution of substrate in dichloromethane is added di-*tert*-butyl dicarbonate (2 eq.) and triethylamine (2 eq.). The resulting mixture is stirred at room temperature for 18 hours and diluted with water. The organic extract is washed with water, brine, dried over Na_2SO_4, filtered and concentrated in vacuo. The residue is then purified by column chromatography to afford the title compound.

Examples A4b-A4m are prepared according to General Methods A, B, and C.

(b) 3-(1-*tert*-Butoxycarbonylaminoethyl)-3-methoxypyrrolidine-1-carboxylic acid benzyl ester (^1H NMR (200 MHz, $CDCl_3$): δ 7.37-7.29 (m, 5H), 5.13 (s, 2H), 4.70 (bs, 1H), 3.91-3.22 (m, 8H), 2.03-1.75 (m, 2H), 1.43 (s, 9H), 1.16-1.11 (m, 3H)) from 3-(1-aminoethyl)-3-methoxypyrrolidine-1-carboxylic acid benzyl ester (Example A13a) using General Method A.

(c) 3-(1-*tert*-Butoxycarbonylaminoethyl)- 3-fluoropyrrolidine-1-carboxylic acid benzyl ester (^1H NMR (200 MHz, $CDCl_3$): δ 7.35 (s, 5H), 5.13 (s,

2H), 4.79 (d, 1H), 3.97-3.26 (m, 5H), 2.17-1.75 (m, 2H), 1.44 (s, 9H), 1.24 (d, 3H)) from 3-(1-aminoethyl)-3-fluoropyrrolidine-1-carboxylic acid benzyl ester (Example A13b) using General Method A.

(d) (1-Benzyl-3-methoxymethylpyrrolidin-3-ylmethyl)carbamic acid *tert*-butyl ester (^{1}H NMR (200 MHz, $CDCl_3$): δ 7.35-7.17 (m, 5H), 5.78 (bs, 1H), 3.56 (s, 2H), 3.32 (s, 3H), 3.27 (s, 2H), 3.21-3.12 (m, 2H), 2.71-2.62 (m, 1H), 2.54-2.30 (m, 3H), 1.78-1.54 (m, 2H), 1.46 (s, 9H)) from (1-benzyl-3-methoxymethylpyrrolidin-3-yl)methylamine (Example A13c) using General Method B.

(e) [1-(1-Benzylpiperidin-3-yl)ethyl]carbamic acid *tert*-butyl ester (^{1}H NMR (200 MHz, $CDCl_3$): δ 7.3 (s, 5H), 4.46-4.30 (m, 1H), 3.62-3.42 (m, 4H), 2.94-2.62 (m, 3H), 2.0-1.0 (m, 8H), 1.44 (s, 9H)) from 1-(1-benzylpiperidin-3-yl)ethylamine (Example A13d) using General Method C.

(f) [1-(1-Benzyl-4,4-dimethylpyrrolidin-3-yl)ethyl]carbamic acid *tert*-butyl ester (^{1}H NMR (200 MHz, $CDCl_3$): **Isomer-1**: δ 7.36-7.22 (m, 5H), 3.82-3.38 (m, 2H), 2.98-1.78 (m, 5H), 1.52-1.0 (m, 19H); **Isomer-2**: δ 7.35-7.25 (m, 5H), 4.35-4.18 (m, 1H), 3.70-3.45 (m, 2H), 2.90-1.54 (m, 6H), 1.43 (s, 9H), 1.18-0.92 (m, 9H)) from 1-(1-Benzyl-4,4-dimethylpyrrolidin-3-yl)ethylamine (Example A13e) using General Method C.

(g) [1-(1-Benzyl-4-methylpyrrolidin-3-yl)ethyl]carbamic acid *tert*-butyl ester (^{1}H NMR (200 MHz, $CDCl_3$): δ 7.38-7.13 (m, 5H), 3.71-3.32 (m, 4H), 3.08-1.53 (m, 6H), 1.52-1.31 (m, 9H), 1.14-0.94 (m, 6H). MS ES: *m/z* 319 (MH^+)) from 1-(1-benzyl-4-methylpyrrolidin-3-yl)ethylamine (Example A13f) using General Method C.

(h) (5-Benzyl-5-azaspiro[2,4]hept-7-ylmethyl)carbamic acid *tert*-butyl ester (MS ES: *m/z* 317 (MH^+)) from 1-(5-benzyl-5-azaspiro[2,4]hept-7-yl)methylamine (Example A13g) using General Method C.

(i) (1-Benzyl-3-hydroxypyrrolidin-3-ylmethyl)carbamic acid *tert*-butyl ester (MS ES: *m/z* 307 (MH^+)) from 3-aminomethyl-1-benzylpyrrolidin-3-ol

(Grohe K., Schriewer M., Haller I., Metzger K., Endermann R., Zeiler H., EP 0326916) using General Method C.

(j) [3-(1-Phenylethyl)-3-azabicyclo[3.1.0]hex-1-ylmethylcarbamic acid *tert*-butyl ester (MS ES: m/z 317 (MH^+)) from 1-[3-(1-phenylethyl)-3-azabicyclo[3.1.0]hex-1-yl]methylamine (Example A13h) using General Method C.

(k) (1,3-Dibenzylpyrrolidin-3-ylmethyl)carbamic acid tert-butyl ester (MS EI+: m/z 381 (MH^+)) using 1-(1,3-dibenzylpyrrolidin-3-yl)methylamine (Example A13i) using General Method C.

(l) (1-Benzyl-4-fluoropyrrolidin-3-ylmethyl)carbamic acid tert-butyl ester (^1H NMR (200 MHz, $CDCl_3$): δ 7.30 (s, 5H), 5.04 (m, 1H), 5.04(m, 1H), 4.77 (m, 1H), 3.63 (s, 2H), 3.20 (t, 2H), 2.86-3.00 (m, 2H), 2.76 (d, 1H), 2.20-2.60 (m, 2H), 1.45 (s, 9H)) from (1-benzyl-4-fluoropyrrolidin-3yl)methylamine (Bouzard D., Di Cesare P., Essiz M., Jacquet J.P., Kicchel J.R., Remuzon P., Weber A., et al., *J. Med. Chem.*, 1990;33:1344-1352) using General Method C.

(m) cis-(1-Benzyl-4-fluoropyrrolidin-3-ylmethyl)carbamic acid *tert*-butyl ester (^1H NMR (200 MHz, $CDCl_3$): δ 7.30 (s, 5H), 5.04 (m, 1H), 4.77 (m, 1H), 3.63 (s, 2H), 3.20 (t, 2H), 3.00-2.86 (m, 2H), 2.76 (d, 1H), 2.60–2.20 (m, 2H), 1.45 (s, 9H)) from cis-(1-benzyl-4-fluoro-pyrrolidin-3-yl)methylamine (Matsumoto J., Nakano J., Chiba K., Minamida A., Nishimura Y., Jpn. Kokai Tokkyo Koho, 1987;11 pp., JP 62072660, A2 19870403) using General Method C.

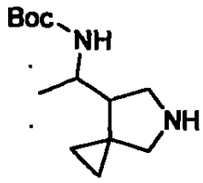
(n) trans-(1-Benzyl-4-fluoropyrrolidin-3-ylmethylcarbamic acid tert-butyl ester (^1H NMR (200 MHz, $CDCl_3$): δ 7.30 (s, 5H), 5.25 (m, 1H), 4.77 (m, 1H), 3.85 (s, 2H), 3.55 (t, 2H), 3.40–2.40 (m, 5H), 1.47 (s, 9H) from trans-(1-benzyl-4-fluoropyrrolidin-3-yl)methylamine (Matsumoto J., Nakano J., Chiba K., Minamida A., Nishimura Y., Jpn. Kokai Tokkyo Koho, 1987;11 pp., JP 62072660, A2 19870403) using General Method C.

(o) (1-Benzyl-3-phenylpyrrolidine-3-ylmethyl)carbamic acid tert-butyl ester (MS ES: m/z 367 (MH^+)) from (1-benzyl-3-phenylpyrrolidine-3-

yl)methylamine ester (Hagen S., Domagala J.M., Heifetz C.L., Sanchez J.P., Solomon M., *J. Med. Chem.*, 1990;33:849-854) using General Method C.

EXAMPLE A5

(a) Synthesis of [1-(5-Azaspiro[2.4]hept-7-yl)ethyl]carbamic acid tert-butyl ester



A solution of [1-(5-benzyl-5-azaspiro[2.4]hept-7-yl)ethyl]carbamic acid *tert*-butyl ester (Example A4a, 1.47 g) in methanol (30 mL) in a Parr shaker is treated with 10% palladium on carbon (0.5 g) and hydrogen introduced (50 psi) for 24 hours. The reaction mixture is filtered through celite, washed with methanol, and the combined filtrate concentrated in vacuo to afford the title compound. MS CI: *m/z* 241 (MH^+).

General Method A

To a solution of substrate in methanol is added ammonium formate (5 eq.) and 10% palladium on charcoal (0.75 wt. vol. eq.). After 2 hours at reflux, the reaction mixture is cooled, diluted with dichloromethane and filtered. The filtrate is concentrated to afford the title compound.

Examples A5b-A5o are prepared using General Method A.

(b) [1-(3-Methoxypyrrolidin-3-yl)ethyl]carbamic acid *tert*-butyl ester (^{1}H NMR (200 MHz, $CDCl_3$): δ 5.30 (bs, 1H), 5.03 (dd, 1H), 3.92 (bs, 1H), 3.28-2.82 (m, 7H), 1.97-1.72 (m, 2H), 1.44 (s, 9H), 1.19-1.14 (m, 3H)) from 3-(1-*tert*-butoxycarbonylaminoethyl)-3-methoxypyrrolidine-1-carboxylic acid benzyl ester (Example A4b) using General Method A.

(c) [1-(3-Fluoropyrrolidin-3-yl)ethyl]carbamic acid *tert*-butyl ester (^{1}H NMR (200.MHz, $CDCl_3$): δ 4.89 (d, 1H), 3.95-3.61 (m, 1H), 3.21-2.70 (m, 4H), 2.11-1.53 (m, 1H), 1.44 (s, 9H), 1.26 (d, 3H)) from 3-(1-*tert*-

butoxycarbonylaminoethyl)-3-fluoropyrrolidine-1-carboxylic acid benzyl ester (Example A4e) using General Method A.

(d) (3-Methoxymethylpyrrolidin-3-ylmethyl)carbamic acid *tert*-butyl ester (^{1}H NMR (200 MHz, $CDCl_3$): δ 5.25 (bs, 1H), 3.35 (s, 3H), 3.30 (s, 2H), 3.27-3.15 (m, 2H), 3.09-2.94 (m, 2H), 2.78 (s, 2H), 1.68-1.56 (m, 2H), 1.45 (s, 9H). (MS ES: m/z 245 (MH^+)) from (1-benzyl-3-methoxymethylpyrrolidin-3-ylmethyl)carbamic acid *tert*-butyl ester (Example A4d) using General Method A.

(e) (1-Piperidin-3-ylethyl)carbamic acid *tert*-butyl ester (^{1}H NMR (200 MHz, $CDCl_3$): δ 4.52-4.32 (m, 1H), 3.68-3.18 (m, 4H), 2.74-2.42 (m, 1H), 2.02-1.2 (m, 5H), 1.44 (s, 9H), 1.30-1.04 (m, 3H)) from [1-(1-benzylpiperidin-3-yl)ethyl]carbamic acid *tert*-butyl ester (Example A4e) using General Method A.

(f) [1-(4,4-Dimethylpyrrolidin-3-yl)ethyl]carbamic acid *tert*-butyl ester (^{1}H NMR (200 MHz, $CDCl_3$): 6.28-5.85 (bs, 1H), 4.75 (d, 1H), 3.92-1.80 (m, 6H), 1.43 (s, 9H), 1.30-1.0 (9H)) from [1-(1-benzyl-4,4-dimethylpyrrolidin-3-yl)ethyl]carbamic acid *tert*-butyl ester (Example A4f).

(g) [1-(4-Methylpyrrolidin-3-yl)ethyl]carbamic acid *tert*-butyl ester (^{1}H NMR (200 MHz, $CDCl_3$): δ 4.88-4.40 (m, 1H), 4.02-3.38 (m, 4H), 3.25-2.75 (m, 2H), 2.46-1.88 (m, 2H), 1.44 (s, 9H), 1.31-1.04 (m, 6H)) from [1-(1-benzyl-4-methylpyrrolidin-3-yl)ethyl]carbamic acid *tert*-butyl ester (Example A4g).

(h) (5-Azaspiro[2,4]hept-7-ylmethyl)carbamic acid *tert*-butyl ester (MS ES: *m/z* 227 (MH^+)) from (5-benzyl-5-azaspiro[2,4]hept-7-ylmethyl)carbamic acid *tert*-butyl ester (Example A4h).

(i) (3-Hydroxypyrrolidin-3-ylmethyl)carbamic acid *tert*-butyl ester (MS ES: *m/z* 217 (MH^+)) using (1-benzyl-3-hydroxypyrrolidin-3-ylmethyl)carbamic acid *tert*-butyl ester (Example A4i).

(j) (3-Azabicyclo[3.1.0]hex-1-ylmethyl)carbamic acid *tert*-butyl ester (MS ES: m/z 213 (MH^+)) using [3-(1-phenylethyl)-3-azabicyclo[3.1.0]hex-1-ylmethylcarbamic acid *tert*-butyl ester (Example A4j).

(k) cis-(4-Fluoropyrrolidin-3-ylmethyl)carbamic acid *tert*-butyl ester (^{1}H NMR (200 MHz, $CDCl_3$): δ 5.60-5.00 (m, 4H), 3.60-3.10 (m, 4H), 3.00 (t,

111), 2.75-2.30 (m, 1H), 1.44 (s, 9H)) using cis-(1-benzyl-4-fluoropyrrolidin-3-ylmethyl)carbamic acid *tert*-butyl ester (Example A4l).

(l) trans-(4-Fluoropyrrolidin-3-ylmethyl)carbamic acid *tert*-butyl ester (^{1}H NMR (200 MHz, $CDCl_3$): δ 6.60-5.70 (m, 2H), 5.25 (bs, 0.5H), 4.98 (bs, 0.5H), 3.70-2.90 (m, 5H) 2.90-2.50 (m, 1H), 1.44 (s, 9H)) using trans-(1-benzyl-4-fluoropyrrolidin-3-ylmethyl)carbamic acid *tert*-butyl ester (Example A4m).

(m) 3-Hydroxy-4-hydroxymethylpyrrolidine (^{1}H NMR (200 MHz, DMSO-d_6): δ 5.50-4.30 (bs, 3H), 4.30-1.50 (m, 8H)) using 1-benzyl-3-hydroxy-4-hydroxymethylpyrrolidine (Jaeger E., Biel J.H., *J. Org. Chem.*, 1965;30:740–744).

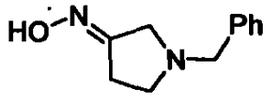
(n) 1-Methyl-1-pyrrolidin-3-yl-ethanol (MS ES: m/z 130 (MH^+)) from 2-(1-benzylpyrrolidin-3-yl)propan-2-ol (Example A25).

(o) (3-benzylpyrrolidin-3-ylmethyl)carbamic acid *tert*-butyl ester (mp 183-185°C) from (1,3-dibenzylpyrrolidin-3-ylmethyl)carbamic acid *tert*-butyl ester (Example A4K).

(p) A5p (3-Phenylpyrrolidine-3-ylmethyl)carbamic acid tert-butyl ester (MS APCI: m/z 277 (MH^+)) from (1-benzyl-3-phenylpyrrolidine-3-ylmethyl)carbamic acid tert-butyl ester (Example A4o).

EXAMPLE A6

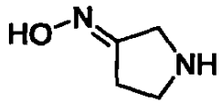
Synthesis of 1-Benzylpyrrolidin-3-one oxime



To a solution of 1-benzylpyrrolidin-3-one (1.0 g, 5.71 mmol) in pyridine (5 mL) is added hydroxylamine hydrochloride (0.59 g, 8.57 mmol). After stirring at 90°C for 5 hours, the reaction mixture is diluted with ethyl acetate and washed with saturated sodium bicarbonate, water, and brine. The organic layer is dried over $MgSO_4$, filtered, and filtrate concentrated to afford 1-benzylpyrrolidin-3-one oxime (1.11 g) as an oil. MS CI: *m/z* 191 (MH^+).

EXAMPLE A7

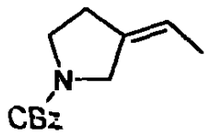
Synthesis of Pyrrolidin-3-one oxime



In a Parr shaker, 1-benzylpyrrolidin-3-one oxime (1.5 g) in methanol (20 mL) is treated with 20% palladium on carbon (0.5 g) under Hydrogen pressure (50 psi) for 24 hours. The mixture is then filtered through Celite, washed with methanol, and the combined filtrate concentrated in vacuo to afford the title compound as an oil (1.2 g). MS CI: *m/e* 101 (M^++1).

EXAMPLE A8

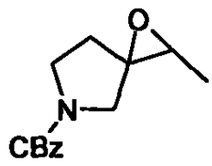
Synthesis of 3-Ethylidenepyrrolidine-1-carboxylic acid benzyl ester



Under an inert atmosphere, sodium-hydride (0.160 g, 7 mmol) and ethyltriphenylphosphonium bromide (2 g, 5.4 mmol) are mixed in dry dimethyl sulfoxide (10 mL) and stirred for 40 minutes. 3-Oxopyrrolidine-1-carboxylic acid benzyl ester (1.18 g, 5.4 mmol (*J. Med. Chem.*, 1992;35:1392)) in dry dimethyl sulfoxide (5 mL) is added to the reaction and the mixture is stirred at 70°C for 3 hours. The reaction is cooled, diluted with cold water and extracted with ethyl acetate. The organic phase is washed with brine, dried over Na_2SO_4 and evaporated. The residue is purified by column chromatography (65:35 hexanes/ethyl acetate) to afford the title compound (0.650 g) as a viscous oil. ^{1}H NMR (200 MHz, $CDCl_3$): δ 7.37-7.28 (m, 5H), 5.40-5.32 (m, 1H), 5.15 (s, 2H), 3.97 (bs, 2H), 3.60-3.44 (m, 2H), 2.49 (bs, 2H), 1.65-1.60 (m, 3H).

EXAMPLE A9

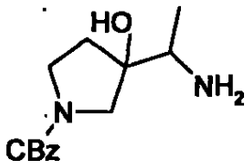
Synthesis of 2-Methyl-1-oxa-5-azaspiro[2,4]heptane-5-carboxylic acid benzyl ester



A solution of 3-ethylidenepyrrolidine-1-carboxylic acid benzyl ester (Example A8, 0.65 g, 2.8 mmol) and 3-chloroperoxybenzoic acid (0.86 g, 5 mmol) in dichloromethane (15 mL) is stirred at room temperature for 3 hours. The excess peracid is decomposed by the addition of 10% sodium sulfite. The organic layer is washed with 5% sodium bicarbonate solution, dried over Na_2SO_4 and evaporated. The residue is purified by column chromatography (1:1 hexanes/ethyl acetate) to afford the title compound (0.310 g). ^1H NMR (200 MHz, $CDCl_3$): δ 7.36-7.26 (m, 5H), 5.14 (s, 2H), 3.73-3.55 (m, 3H), 3.34 (d, 1H), 3.20-3.13 (m, 1H), 2.26-2.11 (m, 1H), 1.90-1.62 (m, 1H), 1.33 (d, 3H).

EXAMPLE A10

Synthesis of 3-(1-Aminoethyl)-3-hydroxypyrrolidine-1-carboxylic acid benzyl ester



A solution of 2-methyl-1-oxa-5-azaspiro[2.4]heptane-5-carboxylic acid benzyl ester (Example A9, 0.31 g, 1.25 mmol) in methanol (10 mL) and ammonium hydroxide (7 mL) is heated in a sealed tube at 100°C for 16 hours. After cooling, the reaction mixture is dissolved ethyl acetate, washed with water, dried over Na_2SO_4 and evaporated to afford the title compound (0.340 g).

^1H NMR (200 MHz, $CDCl_3$): δ 7.33-7.26 (m, 5H), 5.28 (bs, 2H), 5.07(s, 2H), 3.56-3.16(m, 5H), 2.03-1.76 (m, 2H), 1.15 (d, 3H).

EXAMPLE A11

Synthesis of 3-Hydroxy-3-{1-[(2-hydroxybenzylidene)amino]ethyl}pyrrolidine-1-carboxylic acid benzyl ester

A solution of 3-(1-aminoethyl)-3-hydroxypyrrolidine-1-carboxylic acid benzyl ester (Example A10, 0.34 g, 0.93 mmol) and salicylaldehyde (0.147 g, 1.2 mmol) in dry ethanol (5 mL) is refluxed for 3 hours. After evaporation of the solvent, the residue is purified by column chromatography (30:70:0.01 ethyl acetate/hexanes/ammonium hydroxide) to afford the title compound (0.12 g). ^{1}H NMR (200 MHz, $CDCl_3$): δ 8.39 (s, 1H), 7.41-7.25 (m, 7H), 6.97-6.85 (m, 2H), 5.09 (s, 2H), 3.65-3.34 (m, 5H), 2.01-1.87 (m, 2H), 1.37-1.32 (m, 3H).

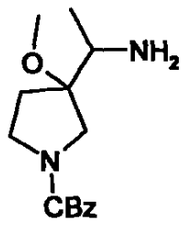
EXAMPLE A12

Synthesis of 3-Methoxy-3-{1-[(2-methoxybenzylidene)amino]ethyl}pyrrolidine-1-carboxylic acid benzyl ester.

To a stirred solution of 3-hydroxy-3-{1-[(2-hydroxybenzylidene)amino]-ethyl}pyrrolidine -1-carboxylic acid benzyl ester (Example A11, 0.120 g, 0.33 mmol) in tetrahydrofuran (5 mL) at 0°C is added 0.024 g (1 mmol) of sodium hydride. The mixture is stirred at room temperature for 2 hours and methyl iodide (3 mL) is added and stirring was continued overnight. After evaporation, ethyl acetate and water are added to the residue. The organic layer is separated, dried over Na_2SO_4 and concentrated to afford the title compound (0.125 g). ^{1}H NMR (200 MHz, $CDCl_3$): δ 8.70 (s, 1H), 7.95 (d, 1H), 7.41-7.32 (m, 6H), 7.01-6.88 (m, 2H), 5.09 (s, 2H), 3.86 (s, 3H), 3.72-3.22 (m, 8H), 2.33-1.73 (m, 2H), 1.27-1.24 (m, 3H).

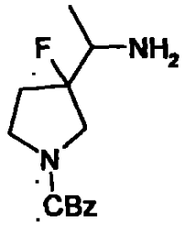
EXAMPLE A13

(a) Synthesis of 3-(1-Aminoethyl)-3-methoxypyrrolidine-1-carboxylic acid benzyl ester



A solution of 3-methoxy-3-{1-[(2-methoxybenzylidene)amino]ethyl-pyrrolidine-1-carboxylic acid benzyl ester (Example A12, 0.120 g, 0.3 mmol) in 3 M hydrogen chloride in methanol (1 mL) is heated at 40°C overnight. The reaction is basified, extracted with ethyl acetate and the organic layer is dried over Na_2SO_4. After concentration, the residue is purified by column chromatography (20:80 methanol/dichloromethane) to afford the title compound (0.060 g). ^1H NMR (200 MHz, $CDCl_3$): δ 7.38-7.29 (m, 5H), 5.12 (s, 2H), 3.64-3.19 (m, 8H), 2.47 (bs, 2H), 2.07-1.80 (m, 2H), 1.16-1.10 (m, 3H).

(b) 3-(1-Aminoethyl)-3-fluoropyrrolidine-1-carboxylic acid benzyl ester



A solution of 3-(1-azidoethyl)-3-fluoropyrrolidine-1-carboxylic acid benzyl ester (Example A16, 0.16 g, 0.5 mmol) in methanol (10 mL) is treated with Raney nickel (100 mg, wet weight) and shaken in a hydrogen atmosphere at room temperature and at 55 psi for 17 hours. The catalyst is removed by filtration through Celite, and the solvent is removed in vacuo to afford the title compound (0.12 g). ^1H NMR (200 MHz, $CDCl_3$): δ 7.30 (s, 5H), 5.12 (s, 2H), 3.84-3.22 (m, 5H), 2.23-1.79 (m, 4H), 1.20 (d, 3H).

(c) 1-(1-Benzyl-3-methoxymethylpyrrolidin-3-yl)methylamine

(f) 1-(1-Benzyl-4-methylpyrrolidin-3-yl)ethylamine (^{1}H NMR (200 MHz, $CDCl_3$): δ 7.38-7.11 (m, 5H), 3.63-3.12 (m, 2H), 2.78-2.27 (m, 5H), 2.23-1.18 (m, 4H), 1.10-0.78 (m, 6H)) from 1-(1-benzyl-4-methylpyrrolidin-3-yl)ethanone oxime (Example A3d).

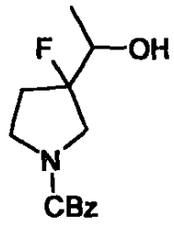
(g) 1-(5-Benzyl-5-azaspiro[2,4]hept-7-yl)methylamine (^{1}H NMR ($CDCl_3$): δ 7.36-7.21 (m, 5H), 3.68-3.53 (m, 2H), 3.1 (dd, 1H), 2.61-2.38 (m, 5H), 2.1-1.92 (m, 1H), 1.29 (bs, 2H), 0.72-0.32 (m, 4H)) from 5-benzyl-5-azaspiro[2,4]heptane-7-carboxylic acid amide (Example A24).

(h) 1-[3-(1-Phenylethyl)-3-azabicyclo[3.1.0]hex-1-yl]methylamine (MS ES: m/z 217 (MH^+)) from 3-(1-phenylethyl)-3-azabicyclo[3.1.0]hexane-1-carbonitrile (Takemura M., Kimura Y., Kawakami K., EP 0807630).

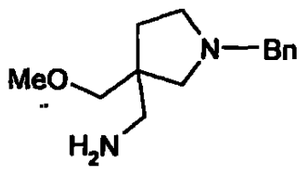
(i) 1,3-Dibenzyl-3-pyrrolidinemethanamine (MS EI: m/z 281 (MH^+)) from 1,3-dibenzyl-3-pyrrolidine carboxamide (Example A29).

EXAMPLE A14

Synthesis of 3-Fluoro-3-(1-hydroxyethyl)pyrrolidine-1-carboxylic acid benzyl ester



A solution of 0.247 g, (1 mmol) of 2-methyl-1-oxa-5-azaspiro[2,4]-heptane-5-carboxylic acid benzyl ester (Example A9) in dichloromethane (3 mL) is added to a polypropylene flask containing 0.5 mL of hydrogen fluoride-pyridine at -40°C. The reaction is allowed to come to room temperature and stirring is continued for 3 hours. The reaction mixture is poured into an aqueous ice-cold ammonium hydroxide solution (30 mL) and extracted with dichloromethane. The organic layer is dried, filtered and concentrated to afford the title compound



Hydrazine hydrate (85% solution in water, 0.372 g, 6.32 mmol) is added to a solution of 2-(1-benzyl-3-methoxymethylpyrrolidin-3-ylmethyl)isoindole-1,3-dione (Example A20, 1.581 g, 4.34 mmol) in ethanol (50 mL). The resulting mixture is refluxed for 4.5 hours, cooled and acidified with concentrated hydrochloric acid. The precipitate is removed by filtration and the filtrate is concentrated in vacuo. The residue is dissolved in ethanol/water (2:1) and the insoluble material is removed by filtration. The filtrate is basified to pH 10 with 1N sodium hydroxide solution and extracted with dichloromethane. The combined organic extracts are dried over Na_2SO_4, filtered and concentrated under vacuum to afford the title compound (0.910 g). ^{1}H NMR (200 MHz, $CDCl_3$): δ 7.41-7.15 (m, 5H), 3.57 (s, 2H), 3.33 (s, 3H), 3.30 (s, 2H), 2.71 (s, 2H), 2.64-2.51 (m, 2H), 2.42-2.24 (m, 2H), 1.68-1.52 (m, 2H), 1.38-1.10 (m, 2H).

General Method A

Lithium aluminium hydride (2 eq.) is slowly added to a solution of oxime, nitrile, or amide derivative in dry tetrahydrofuran. After the addition is complete, the mixture is refluxed for 2 to 6 hours, cooled in an ice bath and quenched with saturated sodium sulfate solution. The solid is removed by filtration and the filtrate is concentrated in vacuo to afford the title compound.

Examples A13d-i are prepared according to General Method A.

(d) 1-(1-Benzylpiperidin-3-yl)ethylamine (^{1}H NMR (200 MHz, DMSO-d_6): δ 7.38-7.18 (m, 5H), 3.52-3.22 (m, 2H), 2.82-2.58 (m, 3H), 1.92-0.75 (m, 10H)) from 1-(1-benzylpiperidin-3-yl)ethanone oxime (Example A3b).

(e) 1-(1-Benzyl-4,4-dimethylpyrrolidin-3-yl)ethylamine (^{1}H NMR (200 MHz, $CDCl_3$): δ 7.36-7.22 (m, 5H), 3.66-3.42 (m, 2H), 2.94-2.10 (m, 5H), 1.32-0.88 (m, 10H)) from 1-(1-benzyl-4,4-dimethylpyrrolidin-3-yl)ethanone oxime (Example A3c).

(f) 1-(1-Benzyl-4-methylpyrrolidin-3-yl)ethylamine (^{1}H NMR (200 MHz, $CDCl_3$): δ 7.38-7.11 (m, 5H), 3.63-3.12 (m, 2H), 2.78-2.27 (m, 5H), 2.23-1.18 (m, 4H), 1.10-0.78 (m, 6H)) from 1-(1-benzyl-4-methylpyrrolidin-3-yl)ethanone oxime (Example A3d).

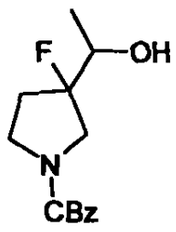
(g) 1-(5-Benzyl-5-azaspiro[2,4]hept-7-yl)methylamine (^{1}H NMR ($CDCl_3$): δ 7.36-7.21 (m, 5H), 3.68-3.53 (m, 2H), 3.1 (dd, 1H), 2.61-2.38 (m, 5H), 2.1-1.92 (m, 1H), 1.29 (bs, 2H), 0.72-0.32 (m, 4H)) from 5-benzyl-5-azaspiro[2,4]heptane-7-carboxylic acid amide (Example A24).

(h) 1-[3-(1-Phenylethyl)-3-azabicyclo[3.1.0]hex-1-yl]methylamine (MS ES: m/z 217 (MH^+)) from 3-(1-phenylethyl)-3-azabicyclo[3.1.0]hexane-1-carbonitrile (Takemura M., Kimura Y., Kawakami K., EP 0807630).

(i) 1,3-Dibenzyl-3-pyrrolidinemethanamine (MS EI: m/z 281 (MH^+)) from 1,3-dibenzyl-3-pyrrolidine carboxamide (Example A29).

EXAMPLE A14

Synthesis of 3-Fluoro-3-(1-hydroxyethyl)pyrrolidine-1-carboxylic acid benzyl ester



A solution of 0.247 g, (1 mmol) of 2-methyl-1-oxa-5-azaspiro[2,4]-heptane-5-carboxylic acid benzyl ester (Example A9) in dichloromethane (3 mL) is added to a polypropylene flask containing 0.5 mL of hydrogen fluoride-pyridine at -40°C. The reaction is allowed to come to room temperature and stirring is continued for 3 hours. The reaction mixture is poured into an aqueous ice-cold ammonium hydroxide solution (30 mL) and extracted with dichloromethane. The organic layer is dried, filtered and concentrated to afford the title compound

(0.267 g). ^{1}H NMR (200 MHz, $CDCl_3$): δ 7.35 (s, 5H), 5.13 (s, 2H), 3.96-3.34 (m, 5H), 2.20-1.98 (m, 3H), 1.33-1.26 (m, 3H).

EXAMPLE A15

Synthesis of 3-Fluoro-3-(1-methanesulfonyloxyethyl)pyrrolidine-1-carboxylic acid benzyl ester

To a -10°C solution of 3-fluoro-3-(1-hydroxyethyl)pyrrolidine-1-carboxylic acid benzyl ester (Example A14, 0.267 g, 1.00 mmol), triethylamine (0.4 g, 4 mmol) and dichloromethane (10 mL) is added methanesulfonyl chloride (0.229 g, 2.00 mmol). The mixture is stirred at room temperature for 2 hours and concentrated in vacuo. The residue is partitioned between ethyl acetate and water. The organic layer is dried over Na_2SO_4 and concentrated to afford the title compound (0.330 g). ^{1}H NMR (200 MHz, $CDCl_3$): δ 7.36 (s, 5H), 5.14 (s, 2H), 4.99-4.81 (m, 1H), 3.76-3.37 (m, 4H), 3.06 (s, 3H), 2.25-1.96 (m, 2H), 1.52-1.47 (m, 3H).

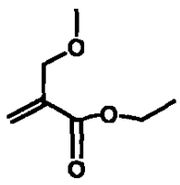
EXAMPLE A16

Synthesis of 3-(1-Azidoethyl)- 3-fluoropyrrolidine-1-carboxylic acid benzyl ester

To a solution of 3-fluoro-3-(1-methanesulfonyloxyethyl)pyrrolidine-1-carboxylic acid benzyl ester (Example A15, 0.25 g, 0.72 mmol) in *N,N*-dimethylformamide (5 mL) is added sodium azide (0.13 g, 2 mmol). The reaction mixture is heated at 120°C overnight. The mixture is diluted with water and extracted with ethyl acetate. The extracts are washed with brine, dried over Na_2SO_4 and concentrated to afford the title compound (0.160 g). ^{1}H NMR (200 MHz, $CDCl_3$): δ 7.28 (s, 5H), 5.08 (s, 2H), 3.80-3.25 (m, 5H), 2.13-1.75 (m, 2H), 1.40 (d, 3H).

Example A17

Synthesis of 2-Methoxymethylacrylic acid ethyl ester



A solution of ethyl α-(bromomethyl)acrylate (0.99 g, 5.1 mmol [Villieras J., Rambaud M., *Synthesis*, 1982:924-926]) in methanol (10 mL) is added to an ice-cold solution of sodium methoxide (0.33 g, 6.1 mmol) in methanol (50 mL). The suspension is refluxed for 21 hours, cooled, diluted with water and extracted with dichloromethane. The organic extracts are dried over Na_2SO_4, filtered and concentrated under vacuum. The resulting residue is purified by flash column chromatography (1:5 ethyl acetate/hexanes) to afford the title compound (0.211 g). ^1H NMR (200 MHz, $CDCl_3$): δ 6.33-6.26 (m, 1H), 5.88-5.80 (m, 1H), 4.23 (q, 2H), 4.19-4.10 (m, 2H), 3.41 (s, 3H), 1.31 (t, 3H).

EXAMPLE A18

General Method A

A solution of substrate and *N*-(methoxymethyl)-*N*-(trimethylsilylmethyl)benzylamine (1.3 eq.) in dichloromethane at 0°C is treated with trifluoroacetic acid (0.07 eq). The mixture is stirred at room temperature for 3 hours, diluted with dichloromethane and washed successively with a saturated $NaHCO_3$ solution and brine. The organic extracts are dried over Na_2SO_4, filtered, and concentrated under vacuum to afford the title compounds.

The examples below (Example A18a-e) were prepared according to General Method A.

(a) 1-Benzyl-3-methoxymethylpyrrolidine-3-carboxylic acid ethyl ester (^1H NMR (200 MHz, $CDCl_3$): δ 7.45-7.16 (m, 5H), 4.19 (q, 2H), 3.78-3.67 (m, 2H), 3.55 (s, 2H), 3.31 (s, 3H), 3.11-2.92 (m, 1H), 2.89-2.49 (m, 2H), 2.42-2.21 (m, 2H), 1.99-1.78 (m, 1H), 1.26 (t, 3H)) from 2-methoxymethylacrylic acid ethyl ester (Example A17).

(b) 1-(1-Benzyl-4,4-dimethylpyrrolidin-3-yl)ethanone (^{1}H NMR (200 MHz, $CDCl_3$): δ 7.36-7.22 (m, 5H), 3.60 (d, 2H), 3.05-2.20 (m, 5H), 2.15 (s, 3H), 1.30 (s, 3H), 0.96 (s, 3H)) from mesityl oxide.

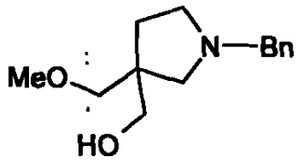
(c) 1-Benzyl-4-methylpyrrolidine-3-carboxylic acid ethyl ester (^{1}H NMR (200 MHz, $CDCl_3$): δ 7.44-7.13 (m, 5H), 4.21-4.04 (q, 1H), 3.71-3.49 (m, 3H), 2.94-2.71 (m, 3H), 2.61-2.41 (m, 2H), 2.28-2.04 (m, 1H), 1.32-1.18 (t, 3H), 1.16-1.04 (d, 3H). MS ES: m/z 248 (MH^+)) from ethyl crotonate.

(d) Pyrrolidine-3-carboxylic acid *tert*-butyl ester (MS ES: *m/z* 172 (MH^+)) from *tert*-butylacrylate.

(e) Ethyl 1,3-dibenzyl-3-pyrrolidinecarboxylic acid (MS EI+: m/z 324 (MH^+)) from ethyl-2-phenylmethylacrylic acid (Vassiliou S., Mucha A., Cuniasse P., Georgiadis D., Lucet-Levannier K., Beau F., Kannan R, et al., *J. Med. Chem.*, 1999;42(14):2610-2620).

EXAMPLE A19

Synthesis of (1-Benzyl-3-methoxymethylpyrrolidin-3-yl)methanol

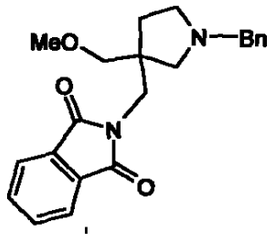


A solution of 1-benzyl-3-methoxymethylpyrrolidine-3-carboxylic acid ethyl ester (Example A18a, 2.30 g, 8.3 mmol) in anhydrous tetrahydrofuran (10 mL) is added dropwise to an ice-cold suspension of lithium aluminum hydride (0.821 g, 22 mmol) in tetrahydrofuran (50 mL). The resulting mixture is stirred at room temperature for 18 hours, cooled and quenched by the sequential dropwise addition of 1N sodium hydroxide and water. The solids are removed by filtration, re-suspended in hot tetrahydrofuran and filtered. The combined filtrates are concentrated in vacuo and the residue is partitioned between dichloromethane and water. The organic extracts are dried over Na_2SO_4, filtered and concentrated under vacuum to afford the title compound (1.71 g). ^{1}H NMR (200 MHz,

$CDCl_3$): δ 7.41-7.17 (m, 5H), 3.84-3.43 (m, 4H), 3.34 (s, 2H), 3.32 (s, 3H), 2.85-2.60 (m, 2H), 2.54-2.14 (m, 3H), 1.98-1.50 (m, 2H).

EXAMPLE A20

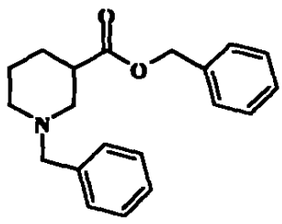
2-(1-Benzyl-3-methoxymethylpyrrolidin-3-ylmethyl)isoindole-1,3-dione



A solution of (1-benzyl-3-methoxymethylpyrrolidin-3-yl)methanol (Example A19, 1.71 g, 7.27 mmol), triphenylphosphine (2.16 g, 8.22 mmol), phthalimide (1.14 g, 7.73 mmol), and anhydrous tetrahydrofuran is cooled to 0°C and treated with diethyl azodicarboxylate (1.62 g, 9.31 mmol). The resulting mixture is stirred at room temperature for 18 hours and concentrated under vacuum. The residue is purified by flash column chromatography (1:5 ethyl acetate/hexanes) to afford the title compound, (0.58 g) as a solid. ^1H NMR (200 MHz, $CDCl_3$): δ 7.91-7.80 (m, 2H), 7.78-7.66 (m, 2H), 7.39-7.11 (m, 5H), 3.95-3.72 (m, 2H), 3.65-3.40 (m, 2H), 3.31 (s, 2H), 3.27 (s, 3H), 2.72-2.34 (m, 4H), 2.02-1.82 (m, 1H), 1.76-1.56 (m, 1H). MS ES: m/z 365 (MH^+).

EXAMPLE A21

Synthesis of 1-Benzylpiperidine-3-carboxylic acid benzyl ester

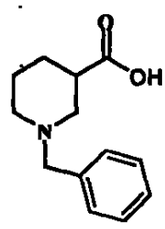


To a solution added of nipecotic acid (8.0 g, 61.9 mmol) in *N,N*-dimethylformamide (80 mL) is benzyl bromide (31.8 g, 186 mmol) and potassium carbonate (42.8 g, 310 mmol). The mixture is heated at 70°C for 18 hours and

diluted with ethyl acetate and water. The organic extract is washed with 1.0 M hydrochloric acid, water and brine, dried over Na_2SO_4, filtered and concentrated in vacuo. The residue is purified by column chromatography (1:7 ethyl acetate/hexanes) to afford the title compound (8.6 g). ^{1}H NMR (200 MHz, DMSO-d_6): δ 7.27-7.42 (m, 10H), 5.07 (s, 2H), 3.45 (s, 2H), 2.88-2.49 (m, 3H), 2.32-1.32 (m, 6H).

EXAMPLE A22

Synthesis of 1-Benzylpiperidine-3-carboxylic acid



To a solution 3.0 g (9.7 mmol) of 1-benzylpiperidine-3-carboxylic acid benzyl ester (Example A21) in methanol (20 mL) was added 1N sodium hydroxide (20 mL), and the reaction is stirred at room temperature for 18 hours. The methanol is removed in vacuo and the basic aqueous solution is acidified to pH 4 with 1.0 M hydrochloric acid. After washing with ethyl acetate, the aqueous acid layer is lyophilized. The solid is suspended in methanol (10 mL), stirred for 10 minutes and filtered. The filtrate is evaporated in vacuo to afford the title compound (2.0 g). ^{1}H NMR (200 MHz, DMSO-d_6): δ 7.38-7.23 (m, 5H), 3.58 (s, 2H), 2.98-2.40 (m, 3H), 2.30-1.25 (m, 6H).

EXAMPLE A23

General procedure A

Methyl lithium (1.1 eq.) is added dropwise to a -70°C solution of substrate in tetrahydrofuran (15 mL). The resulting mixture is stirred at -70°C for 1 hour, and then warmed to room temperature for 18 hours. The reaction is diluted with ice water and ether and the organic layer is separated. The aqueous layer is

extracted with ether and the combined extracts are dried with Na_2SO_4 and concentrated in vacuo to afford the title compound.

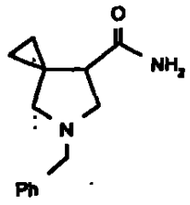
The following compounds are prepared according to general procedure A.

(a) 1-(1-Benzylpiperidin-3-yl)ethanone (^{1}H NMR (200 MHz, DMSO-d_6): δ 7.38-7.22 (m, 5H), 3.45 (s, 2H), 2.85-2.48 (m, 3H), 2.05 (s, 3H), 2.16-1.06 (m, 6H)) from 1-benzylpiperidine-3-carboxylic acid (Example A22).

(b) 1-(1-Benzyl-4-methylpyrrolidin-3-yl)ethanone (^{1}H NMR (200 MHz, $CDCl_3$): δ 7.42-7.18 (m, 5H), 3.71-3.45 (m, 3H), 2.89-2.33 (m, 5H), 2.16 (s, 3H), 1.12 (d, 3H)) from 1-benzyl-4-methylpyrrolidine-3-carboxylic acid ethyl ester (Example A18c).

EXAMPLE A24

Synthesis of 5-Benzyl-5-azaspiro[2,4]heptane-7-carboxylic acid amide



5-Benzyl-5-azaspiro[2,4]heptane-7-carboxylic acid amide (3.32 g) is prepared from 5-benzyl-5-azaspiro[2,4]heptane-7-carboxylic acid (Example A28b, 5.0 g, 21.64 mmol) in dichloromethane by conversion to the acid chloride using oxalyl chloride (5.0 mL, 65 mmol) and *N,N*-dimethylformamide (3 drops). The mixture is allowed to stir for 2 hours then concentrate in vacuo. The residue is redissolved in dichloromethane and the mixture is again concentrated in vacuo. The residue is dissolved in ether and treated with a solution of ammonia in ether. After 1 hour, the mixture is concentrated in vacuo to provide the title compound. ^{1}H NMR ($CDCl_3$): δ 7.6 (bs, 1H), 7.38-7.23 (m, 5H), 5.42 (bs, 1H), 3.75-3.57 (m, 2H), 3.19 (d, 1H), 2.83-2.64 (m, 2H), 2.4 (d, 2H), 0.96-0.58 (m, 4H).

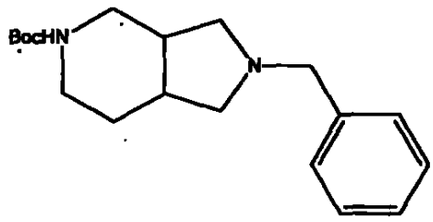
EXAMPLE A25

Synthesis of 2(1-Benzylpyrrolidin-3-yl)propan-2-ol

To a 5°C solution of 1-benzylpyrrolidine-3-carboxylic acid ethyl ester (0.467 g, 2.0 mmol) in tetrahydrofuran (25 mL) is added an etherial solution of methylmagnesium bromide (3.3 mL, 10 mmol). The reaction mixture is stirred at room temperature for 2 hours, cooled to 0°C and saturated aqueous ammonium chloride (10 mL) is added followed by water (10 mL). The mixture is extracted with ethyl acetate (2 × 100 mL) and the combined organic extracts are washed with brine, dried over Na_2SO_4, filtered and concentrated under vacuum to afford the title compound (0.43 g). ^1H NMR (200 MHz, $CDCl_3$): δ 7.30-7.22 (m, 5H), 3.59 (s, 2H), 3.0 (bs, 1H), 2.80-2.66 (m, 2H), 2.48-2.30 (m, 2H), 2.20-2.05 (m, 1H), 1.94-1.80 (m, 2H), 1.19 (s, 3H), 1.16 (s, 3H).

EXAMPLE A26

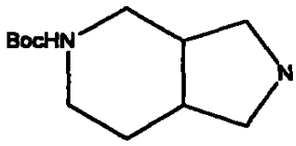
Synthesis of 2-Benzyloctahydropyrrolo[3,4-c]pyridine-5-carboxylic acid tert-butyl ester



2-Benzyloctahydropyrrolo[3,4-c]pyridine (21.6 g, 100 mmol [Himmler T., Petersen U., Bremm K-D., Endermann R., Stegemann M., Wetzstein H-G., 1995, US 5578604] is dissolved in 1000 mL of dichloromethane containing triethylamine (16.7 mL, 120 mmol). Then di-t-butyldicarbonate (22.6 g, 120 mmol) is added and the mixture is stirred at room temperature for 18 hours. The organic layer is washed with saturated $NaHCO_3$, brine, dried, and concentrated to provide 30 g of the title compound as an oil; MS EI+: 318 (MH^+).

EXAMPLE A27

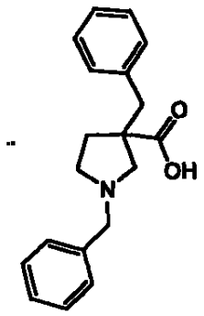
Synthesis of octahydropyrrolo[3,4-c]pyridine-5-carboxylic acid tert-butyl ester



2-Benzyloctahydropyrrolo[3,4-c]pyridine-5-carboxylic acid *tert*-butyl ester (Example A26, 24.98 g, 78.8 mmol) in 400 mL of methanol is treated with 2.5 g of 20% Pd/C and shaken for 20.5 hours under 50 PSI of hydrogen. The solution is filtered and concentrated to afford 17.8 g of the title compound as a solid. MS APCI: m/z 228 (MH^+).

EXAMPLE A28

(a) Synthesis of 1,3-Dibenzylpyrrolidine-3-carboxylic acid

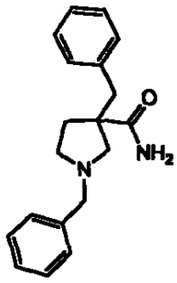


To a solution of 1,3-dibenzylpyrrolidine-3-carboxylic acid ethyl ester (Example A18e, 13.1 g, 41 mmol) in 250 mL of methanol is added 2N NaOH (46 mL, 92 mmol) and the reaction is heated to reflux for 24 hours. The solution is cooled, concentrated, redissolved in water and extracted with ether. The pH of the aqueous layer is adjusted to 7 and the precipitated solid is collected, to give 9.3 g of the title compound, MS EI+: m/z 296 (MH^+), mp 209-210°C.

(b) 5-Benzyl-5-azaspiro[2,4]heptane-7-carboxylic acid (MS ES: m/z 232) from 5-benzyl-7-ethoxycarbonyl-5-azaspiro[2,4]heptane (A1) using the method of Example A28a

EXAMPLE A29

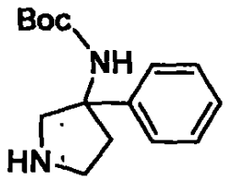
Synthesis of 1,3-Dibenzylpyrrolidine-3-carboxylic acid amide



A mixture of 1,3-dibenzylpyrrolidine-3-carboxylic acid (Example A28, 4.0 g, 13.5 mmol), 1,1'-carbonyldiimidazole (2.42 g, 14.9 mmol), and triethylamine (2.08 mL, 14.9 mmol) in tetrahydrofuran (100 mL) is heated at reflux for 1.5 hours. The solution is cooled, poured into NH_4OH (300 mL), and stirred for 18 hours. The mixture is extracted with chloroform, the organic layer is washed with water, dried, and concentrated to afford 4.13 g of the title compound as an oil; MS El+: m/z 295 (MH^+).

EXAMPLE A30

Synthesis of (3-Phenylpyrrolidin-3-yl)carbamic acid tert-butyl ester



(1-Benzyl-3-phenylpyrrolidin-3-yl)carbamic acid tert-butyl ester (Hagen S.E., Domagala J.M., Heifetz C.L., Sanchez J.P., Solomon M., *J. Med. Chem.*, 1990;33(2):849-854) (2.79 g, 7.9 mmol) in 100 mL of methanol is treated with 1.0 g of 20% Pd/C and shaken for 17 hours under 50 psi of hydrogen. The solution is filtered and concentrated to afford 2.07 g of the title compound as a foam; MS El+: m/z 263 (MH^+).

The compounds of the present invention are potent inhibitors of bacterial growth both in animals and on surfaces, and also are inhibitors of bacterial enzymes. The invention compounds have been evaluated in a number of standard

in vitro and in vivo assays routinely used by those in the antibacterial art to measure antibacterial activity of test compounds.

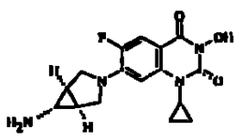
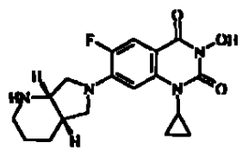
Antibacterial Assay

The compounds of the present invention are tested against an assortment of Gram negative and Gram positive organisms using standard microtitration techniques (Cohen et al., *Antimicrob. Agents Chemother.*, 1985;28:766; Heifetz et al., *Antimicrob. Agents Chemother.*, 1974;6:124). The results of the evaluation of representative 3-aminoquinazolin-2,4-diones of Formula I are shown in Table 2 and compared to two 3-hydroxyquinazolin-2,4-diones.

DNA Gyrase Assay

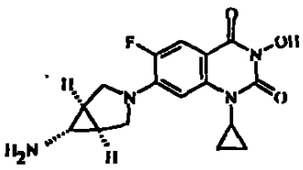
The effects of invention compounds on the activity of DNA gyrase is determined in the supercoiling inhibition assay, following reaction conditions recommended by the enzyme supplier (Lucent, Ltd., Leicester, UK). Reactions are performed in buffer G (35 mM Tris-HCl (pH 7.5), 24 mM KCl, 4 mM $MgCl_2$, 2 mM DTT, 1.8 mM spermidine, 1 mM ATP, 0.1 mg/mL bovine serum albumin). Relaxed plasmid pBR322 (0.25 µg, Lucent, Ltd., Leicester, UK) is reacted with 1 U *E. coli* gyrase (Lucent, Ltd., Leicester, UK), in the absence or presence of test compounds, for 30 minutes at 37°C. Reactions are stopped by the addition of SDS and proteinase K to respective final concentrations of 1% and 0.5 mg/mL. After an additional 30 minutes at 37°C, one-tenth volume of 10X loading buffer (0.3% bromophenol blue, 16% Ficoll, 10 mM Na_2HPO_4) is added, and reactions are loaded onto agarose gels and electrophoresed. The concentration of representative invention compounds of Formula I inhibiting 50% of the supercoiling activity of DNA gyrase is given as an IC_{50} and recorded in Table 2.

TABLE 2. Antibacterial and *E. coli* gyrase Activities

Compound Number or Structure	Minimum Inhibitory Concentrations µg/mL						*E. coli* gyrase
	Gram Negatives			Gram Positives			
	E. coli MC4100	*E. coli* B90	*E. coli* Tol C	*E. faecalis* RB1	*S. aureus* 29213	*S. pyogenes* C203	IC_{50} (µM)
1	2.0	1.0	0.25	1.0	0.5	0.13	1.0
2	16.0	4.0	2.0	>64	>64	>64	26.0
7	2.0	0.5	0.25	8.0	8.0	4.0	1.3
9	2.0	1.0	0.5	32.0	16.0	16.0	3.0
11	2.0	0.5	0.25	8.0	8.0	4.0	11.0
12	16.0	0.25	0.13	4.0	2.0	8.0	2.1
14	4.0	0.25	0.5	8.0	8.0	4.0	2.4
	1.0	0.25	0.25	4.0	4.0	2.0	0.9
	8.0	2.0	1.0	64.0	32.0	32.0	5.0

The in vivo activity of invention compounds is evaluated according to the procedure of Miller et al., *Proc. Soc. Exp. Biol. Med.*, 1944;57:261. The median protective dose (PD_{50}) is determined in mice given lethal systemic infections. Two 3-aminoquinazolin-2,4-diones of the invention are compared to a 3-hydroxyquinazolin-2,3-dione, and the results are presented in Table 3. The results establish the unexpected superiority of the 3-amino invention compounds compared to similar 3-hydroxy analogs.

TABLE 3. In Vivo Median Protective Dose (PD_{50}) in Mice

Compound Number or Structure	Organism	PD50 (mg/kg)
1	S. pyogenes	12
10	*E. coli*	72
	*S. pyogenes*	>100

Cross Resistance Antibacterial Assay

The compounds of the present invention are tested against an assortment of ciprofloxacin resistant *E. coli* and *S. aureus* organisms described below using standard microtitration techniques (Cohen, et al., *Antimicrob. Agents Chemother.*, 1985;28:766; Heifetz, et al., *Antimicrob. Agents Chemother.*, 1974;6:124). The results of the evaluation are shown in Table 4 and compared to two 3-hydroxyquinazolin-2,4-diones.

E. coli and *S. aureus* organisms:

E. coli JL4: *E. coli* W3110 + Tol C⁻ (Tol C pump deficient strain with *E. coli* W3110 background)

E. coli LLM-1: Isogenic to *E. coli* JL4 with a D87G mutation (aspartic acid to glycine at position 87) in the QRDR (quinolone resistance determining region)

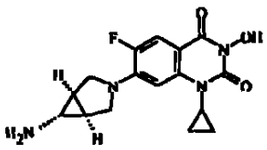
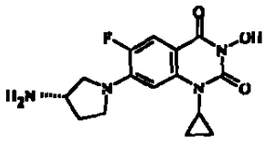
S. aureus UC-76: Typical sensitive laboratory strain (Wild type)

S. aureus 2552: Isogenic to *S. aureus* UC-76, with upregulated norA pump

S. aureus 2554: Isogenic to *S. aureus* 2552, with point mutation at position 80 of *grlA*.subunit

S. aureus 2558: Isogenic to *S. aureus 2554*, with point mutation at position 84 of *gyrA* subunit

TABLE 4. Antibacterial Activities Against Ciprofloxacin Resistant Strains

Compound Number or Structure	Minimum Inhibitory Concentrations µg/mL					
	E.coli JL4	*E. coli* LLM1	*S. aureus* UC-76	*S. aureus* 2552	*S. aureus* 2554	*S. aureus* 2558
1	0.13	0.5	0.13	1	1	1
3	0.5	1	1	2	2	4
12	0.06	0.25	1	1	1	2
	0.25	4	4	32	32	>64
	0.5	2	4	>64	>64	>64

The quinolone mimics provided by this invention display Gram-negative and Gram-positive activity. The compounds also show inhibition of bacterial DNA gyrase/activity. The compounds demonstrate in vivo protective activity in mice and are not highly cytotoxic to mammalian cells, thus indicating selectivity for bacteria. The compounds of Formula I are thus useful for treating and preventing bacterial disease and growth in both animals and on surfaces. The compounds can be applied to wood and metal surfaces, for instance, to eliminate bacterial growth. The compounds can be administered to animals such as humans, horses, dogs, sheep, and cattle to prevent and treat bacterial infections.

The compounds of the present invention can be prepared and administered in a wide variety of oral and parenteral dosage forms for convenient administration to animals. Thus, the compounds of the present invention can be administered by injection, that is, intravenously, intramuscularly, intracutaneously, subcutaneously, intraduodenally, or intraperitoneally. Also, the compounds of the present invention can be administered by inhalation, for example, intranasally. Additionally, the compounds of the present invention can be administered transdermally. It will be obvious to those skilled in the art that the

following dosage forms may comprise as the active component, either a compound of Formula I or a corresponding pharmaceutically acceptable salt of a compound of Formula I. The formulations typically will comprise from about 1 to about 95 percent by weight of the active invention compound. The compounds can be dissolved or suspended in liquids, such as ethanol, and applied to wood or metal surfaces to prevent and/or kill bacterial growth.

For preparing pharmaceutical compositions from the compounds of the present invention, pharmaceutically acceptable carriers can be either solid or liquid. Solid form preparations include powders, tablets, pills, capsules, cachets, suppositories, and dispersible granules. A solid carrier can be one or more substances which may also act as diluents, flavoring agents, binders, preservatives, tablet disintegrating agents, or an encapsulating material.

In powders, the carrier is a finely divided solid which is in a mixture with the finely divided active component.

In tablets, the active component is mixed with the carrier having the necessary binding properties in suitable proportions and compacted in the shape and size desired.

The powders and tablets preferably contain from five or ten to about seventy percent of the active compound. Suitable carriers are magnesium carbonate, magnesium stearate, talc, sugar, lactose, pectin, dextrin, starch, gelatin, tragacanth, methylcellulose, sodium carboxymethylcellulose, a low melting wax, cocoa butter, and the like. The term "preparation" is intended to include the formulation of the active compound with encapsulating material as a carrier providing a capsule in which the active component with or without other carriers, is surrounded by a carrier, which is thus in association with it. Similarly, cachets and lozenges are included. Tablets, powders, capsules, pills, cachets, and lozenges can be used as solid dosage forms suitable for oral administration.

For preparing suppositories, a low melting wax, such as a mixture of fatty acid glycerides or cocoa butter, is first melted and the active component is dispersed homogeneously therein, as by stirring. The molten homogenous mixture is then poured into convenient sized molds, allowed to cool, and thereby to solidify.

Liquid form preparations include solutions, suspensions, and emulsions, for example, water or water propylene glycol solutions. For parenteral injection liquid preparations can be formulated in solution in aqueous polyethylene glycol solution.

Aqueous solutions suitable for oral use can be prepared by dissolving the active component in water and adding suitable colorants, flavors, stabilizing, and thickening agents as desired.

Aqueous suspensions suitable for oral use can be made by dispersing the finely divided active component in water with viscous material, such as natural or, synthetic gums, resins, methylcellulose, sodium carboxymethylcellulose, and other well-known suspending agents.

Also included are solid form preparations which are intended to be converted, shortly before use, to liquid form preparations for oral administration. Such liquid forms include solutions, suspensions, and emulsions. These preparations may contain, in addition to the active component, colorants, flavors, stabilizers, buffers, artificial and natural sweeteners, dispersants, thickeners, solubilizing agents, and the like.

The pharmaceutical preparation is preferably in unit dosage form. In such form the preparation is divided into unit doses containing appropriate quantities of the active component. The unit dosage form can be a packaged preparation, the package containing discrete quantities of preparation, such as packeted tablets, capsules, and powders in vials or ampoules. Also, the unit dosage form can be a capsule, tablet, cachet, or lozenge itself, or it can be the appropriate number of any of these in packaged form.

The quantity of invention compound in a unit dose preparation may be varied or adjusted from 0.1 mg to 100 mg, preferably from 0.5 mg to 100 mg, according to the particular application and the potency of the active component as determined by a skilled physician. The composition can, if desired, also contain other compatible therapeutic agents.

In therapeutic use as agents for the treatment of infections caused by a bacteria, the compounds utilized in the pharmaceutical method of this invention are administered at the initial dosage of about 0.01 mg to about 500 mg/kg daily.

A daily dose range of about 0.01 mg to about 100 mg/kg is preferred. The dosages, however, may be varied depending upon the requirements of the patient, the severity of the condition being treated, and the particular compound being employed. Determination of the proper dosage for a particular situation is within the skill of the medical art. Generally, treatment is initiated with smaller dosages which are less than the optimum dose of the compound. Thereafter, the dosage is increased by small increments until the optimum effect under the circumstances is reached. For convenience, the total daily dosage may be divided and administered in portions during the day, if desired.

The following additional examples illustrate typical formulations for use according to the invention.

EXAMPLE 37

1. Tablet Formulation

Ingredient	Amount (mg)
Compound No. 10	50
Cornstarch (mix)	15
Cornstarch (paste)	5
Lactose	50
Calcium stearate	2
Dicalcium phosphate	28
	150

Compound 10 is blended to uniformity with the cornstarch mix, lactose, and dicalcium phosphate. The cornstarch paste is prepared as a 10% aqueous paste, and it is blended to uniformity with the other mixture. The wet granulation is passed through a standard 8-mesh screen. The wet granules are dried and then blended to uniformity with the calcium stearate and pressed into a tablet. Such tablets are administered orally to patients suffering from bacterial infections at the rate of from one to about four times a day.

2. Capsule Formulation

Ingredients	Amount (mg)
Compound No. 25	120
Lactose USP	150
Starch	100
Magnesium stearate	5
	150

The ingredients are blended to uniformity and packed into a soft gelatin capsule. The capsules are administered at the rate of one to two per day to a patient infected with bacteria resistant to commercially available quinolone antibiotics.

3. Liquid Preparation

Ingredient	Amount
Compound No. 18	500 mg
Water	1000 mL

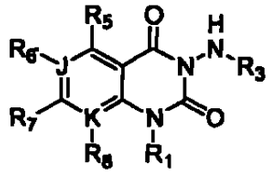
The compound is dissolved in water, and the solution is sprayed onto wood surfaces and in shower stalls to control and eliminate bacterial growth.

The invention and the manner and process of making and using it, are now described in such full, clear, concise and exact terms as to enable any person skilled in the art to which it pertains, to make and use the same. It is to be understood that the foregoing describes preferred embodiments of the present invention and that modifications may be made therein without departing from the spirit or scope of the present invention as set forth in the claims. To particularly point out and distinctly claim the subject matter regarded as invention, the following claims conclude this specification.

CLAIMS

What is claimed is:

1. A compound of Formula I



I

or a pharmaceutically acceptable salt thereof wherein:

R_1 and R_3 independently are H,

C_1-C_{12} alkyl and substituted alkyl,

C_2-C_{12} alkenyl and substituted alkenyl,

C_2-C_{12} alkynyl and substituted alkynyl,

C_3-C_{12} cycloalkyl and substituted cycloalkyl,

aryl and substituted aryl,

heterocyclic and substituted heterocyclic,

or heteroaryl and substituted heteroaryl;

R_5, R_6, and R_8 independently are H,

$(O)_nC_1$-C_{12} alkyl and substituted alkyl,

$(O)_nC_2$-C_{12} alkenyl and substituted alkenyl,

$(O)_nC_2$-C_{12} alkynyl and substituted alkynel,

wherein n is 0 or 1,

halo,

NO_2,

CN,

NR'R";

R' and R" independently are H,

C_1-C_{12} alkyl and substituted alkyl,

C_2-C_{12} alkenyl and substituted alkenyl,

C_2-C_{12} alkynyl and substituted alkynyl,

CO-C_1-C_{12} alkyl and substituted alkyl,

or R' and R'' taken together with the nitrogen to which they are attached form a 3- to 7-membered ring containing from 1 to 3 heteroatoms selected from N, O, and S, said ring being unsubstituted or substituted with up to 4 substituent groups;

R_1 and R_8 can be taken together with the atoms to which they are attached to form a cyclic ring having from 1 to 3 heteroatoms selected from N, O, and S, and optionally substituted by R' and R'';

R_7 is hydrogen,

C_1-C_{12} alkyl and substituted alkyl,

C_2-C_{12} alkenyl and substituted alkenyl,

C_2-C_{12} alkynyl and substituted alkynyl,

halo,

NO_2,

CN,

NR'R'',

COOR',

aryl,

fused aryl,

heterocyclic,

fused heterocyclic,

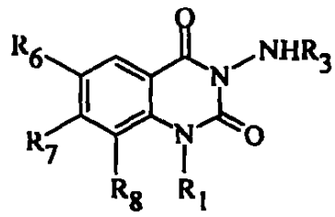
bicyclic heterocyclic, or

spiro heterocyclic,

wherein all ring groups can be substituted; and

J and K independently are C or N, provided that when J or K is N, R_6 or R_8 is absent at that position.

2. A compound of Formula II



II

or a pharmaceutically acceptable salt thereof,

wherein:

R_1 and R_3 independently are H,

C_1-C_{12} alkyl and substituted alkyl,

C_2-C_{12} alkenyl and substituted alkenyl,

C_2-C_{12} alkynyl and substituted alkynyl,

C_3-C_{12} cycloalkyl and substituted cycloalkyl,

aryl and substituted aryl,

heterocyclic and substituted heterocyclic,

or heteroaryl and substituted heteroaryl;

R_6 and R_8 independently are H,

$(O)_nC_1$-C_{12} alkyl and substituted alkyl,

$(O)_nC_2$-C_{12} alkenyl and substituted alkenyl

$(O)_nC_2$-C_{12} alkynyl and substituted alkynyl,

wherein n is 0 or 1,

halo,

NO_2,

CN,

NR'R";

R_7 is hydrogen,

C_1-C_{12} alkyl and substituted alkyl,

C_2-C_{12} alkenyl and substituted alkenyl,

C_2-C_{12} alkynyl and substituted alkynyl,

halo,

NO_2.

CN,

NR'R",

COOR'.

aryl,

fused aryl,

heterocyclic,

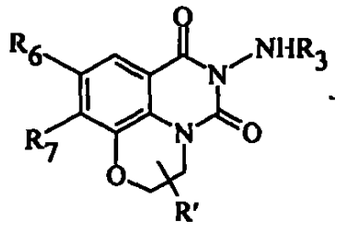
fused heterocyclic,

bicyclic heterocyclic, or

spiro heterocyclic,

wherein all ring groups can be substituted.

3. A compound of Formula III



III

wherein

R_3 is H,

C_1-C_{12} alkyl and substituted alkyl,

C_2-C_{12} alkenyl and substituted alkenyl,

C_2-C_{12} alkynyl and substituted alkynyl,

C_3-C_{12} cycloalkyl and substituted cycloalkyl,

aryl and substituted aryl,

heterocyclic and substituted heterocyclic,

or heteroaryl and substituted heteroaryl;

R_6 is H,

$(O)_nC_1$-C_{12} alkyl and substituted alkyl,

$(O)_nC_2$-C_{12} alkenyl and substituted alkenyl,

$(O)_nC_2$-C_{12} alkynyl and substituted alkynyl,

wherein n is 0 or 1,

halo,

NO_2,

CN,

NR'R";

R_7 is hydrogen,

C_1-C_{12} alkyl and substituted alkyl,

C_2-C_{12} alkenyl and substituted alkenyl,

C_2-C_{12} alkynyl and substituted alkynyl,

halo,

NO_2,

CN,

NR'R",

COOR',

aryl,

fused aryl,

heterocyclic,

fused heterocyclic,

bicyclic heterocyclic, or

spiro heterocyclic,

wherein all ring groups can be substituted; and

R' is H,

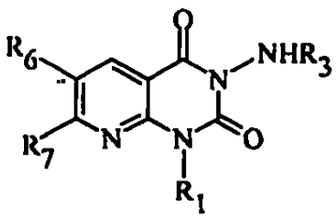
C_1-C_{12} alkyl and substituted alkyl,

C_2-C_{12} alkenyl and substituted alkenyl,

C_2-C_{12} alkynyl and substituted alkynyl, or

CO-C_1-C_{12} alkyl and substituted alkyl.

4. A compound of Formula IV



IV

or a pharmaceutically acceptable salt thereof.

wherein:

R_1 and R_3 independently are H,

C_1-C_{12} alkyl and substituted alkyl,

C_2-C_{12} alkenyl and substituted alkenyl,

C_2-C_{12} alkynyl and substituted alkynyl,

C_3-C_{12} cycloalkyl and substituted cycloalkyl,

aryl and substituted aryl,

heterocyclic and substituted heterocyclic,

or heteroaryl and substituted heteroaryl;

R_6 is H,

$(O)_nC_1$-C_{12} alkyl and substituted alkyl,

$(O)_nC_2$-C_{12} alkenyl and substituted alkenyl,

$(O)_nC_2$-C_{12} alkynyl and substituted alkynyl,

wherein n is 0 or 1,

halo,

NO_2,

CN,

NR'R";

R_7 is hydrogen,

C_1-C_{12} alkyl and substituted alkyl,

C_2-C_{12} alkenyl and substituted alkenyl,

C_2-C_{12} alkynyl and substituted alkynyl,

halo,

NO_2,

CN,

NR'R",

COOR',

aryl,

fused aryl,

heterocyclic,

fused heterocyclic,

bicyclic heterocyclic, or

spiro heterocyclic,

wherein all ring groups can be substituted.

R' and R" independently are H,

C_1-C_{12} alkyl and substituted alkyl,

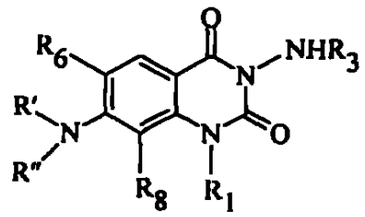
C_2-C_{12} alkenyl and substituted alkenyl,

C_2-C_{12} alkynyl and substituted alkynyl,

CO-C_1-C_{12} alkyl and substituted alkyl,

or R' and R" taken together with the nitrogen to which they are attached form a 3- to 7-membered ring containing from 1 to 3 heteroatoms selected from N, O, and S, said ring being unsubstituted or substituted with up to 4 substituent groups.

5. A compound of Formula V



V

or a pharmaceutically acceptable salt thereof,

wherein:

R_1 and R_3 independently are H,

C_1-C_{12} alkyl and substituted alkyl,

C_2-C_{12} alkenyl and substituted alkenyl,

C_2-C_{12} alkynyl and substituted alkynyl,

C_3-C_{12} cycloalkyl and substituted cycloalkyl,

aryl and substituted aryl,

heterocyclic and substituted heterocyclic,

or heteroaryl and substituted heteroaryl;

R_6 and R_8 independently are H,

$(O)_nC_1$-C_{12} alkyl and substituted alkyl,

$(O)_nC_2$-C_{12} alkenyl and substituted alkenyl,

$(O)_nC_2$-C_{12} alkynyl and substituted alkynyl,

wherein n is 0 or 1,

halo,

NO_2,

CN,

NR'R";

R' and R" independently are H,

C_1-C_{12} alkyl and substituted alkyl,

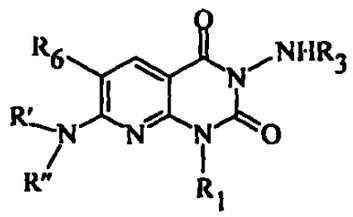
C_2-C_{12} alkenyl and substituted alkenyl,

C_2-C_{12} alkynyl and substituted alkynyl,

CO-C_1-C_{12} alkyl and substituted alkyl,

or R' and R" taken together with the nitrogen to which they are attached form a 3- to 7-membered ring containing from 1 to 3 heteroatoms selected from N, O, and S, said ring being unsubstituted or substituted with up to 4 substituent groups.

6. A compound of Formula VI



VI

or a pharmaceutically acceptable salt thereof,

wherein:

R_1 and R_3 independently are H,

C_1-C_{12} alkyl and substituted alkyl,

C_2-C_{12} alkenyl and substituted alkenyl,

C_2-C_{12} alkynyl and substituted alkynyl,

C_3-C_{12} cycloalkyl and substituted cycloalkyl,

aryl and substituted aryl,

heterocyclic and substituted heterocyclic,

or heteroaryl and substituted heteroaryl;

R_6 is H,

$(O)_nC_1$-C_{12} alkyl and substituted alkyl,

$(O)_nC_2$-C_{12} alkenyl and substituted alkenyl,

$(O)_nC_2$-C_{12} alkynyl and substituted alkynyl,

wherein n is 0 or 1,

halo,

NO_2,

CN,

NR'R";

R' and R" independently are H,

C_1-C_{12} alkyl and substituted alkyl,

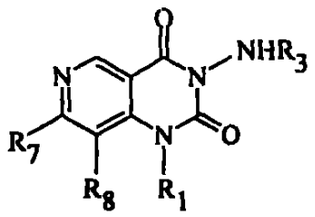
C_2-C_{12} alkenyl and substituted alkenyl,

C_2-C_{12} alkynyl and substituted alkynyl,

CO-C_1-C_{12} alkyl and substituted alkyl,

or R′ and R″ taken together with the nitrogen to which they are attached form a 3- to 7-membered ring containing from 1 to 3 heteroatoms selected from N, O, and S, said ring being unsubstituted or substituted with up to 4 substituent groups.

7. A compound of Formula VII



VII

or a pharmaceutically acceptable salt thereof,

wherein:

R_1 and R_3 independently are H,

C_1-C_{12} alkyl and substituted alkyl,

C_2-C_{12} alkenyl and substituted alkenyl,

C_2-C_{12} alkynyl and substituted alkynyl,

C_3-C_{12} cycloalkyl and substituted cycloalkyl,

aryl and substituted aryl,

heterocyclic and substituted heterocyclic,

or heteroaryl and substituted heteroaryl;

R_7 is hydrogen,

C_1-C_{12} alkyl and substituted alkyl,

C_2-C_{12} alkenyl and substituted alkenyl,

C_2-C_{12} alkynyl and substituted alkynyl,

halo,

NO_2,

CN,

NR′R″,

COOR′,

aryl,

fused aryl,

heterocyclic,

fused heterocyclic,

bicyclic heterocyclic, or

spiro heterocyclic,

wherein all ring groups can be substituted; and

R_8 is H,

$(O)_nC_1$-C_{12} alkyl and substituted alkyl,

$(O)_nC_2$-C_{12} alkenyl and substituted alkenyl,

$(O)_nC_2$-C_{12} alkynyl and substituted alkynyl,

wherein n is 0 or 1,

halo,

NO_2,

CN,

NR'R";

wherein R' and R" independently are H,

C_1-C_{12} alkyl and substituted alkyl,

C_2-C_{12} alkenyl and substituted alkenyl,

C_2-C_{12} alkynyl and substituted alkynyl,

CO-C_1-C_{12} alkyl and substituted alkyl,

or R' and R" taken together with the nitrogen to which they are attached form a 3- to 7-membered ring containing from 1 to 3 heteroatoms selected from N, O, and S, said ring being unsubstituted or substituted with up to 4 substituent groups;

R_1 and R_8 can be taken together with the atoms to which they are attached to form a cyclic ring having from 1 to 3 heteroatoms selected from N, O, and S, and optionally substituted by R' and R";

R_7 is hydrogen,

C_1-C_{12} alkyl and substituted alkyl,

C_2-C_{12} alkenyl and substituted alkenyl,

C_2-C_{12} alkynyl and substituted alkynyl,

halo,

NO_2,

CN,

NR'R",

COOR',

aryl,

fused aryl,

heterocyclic,

fused heterocyclic,

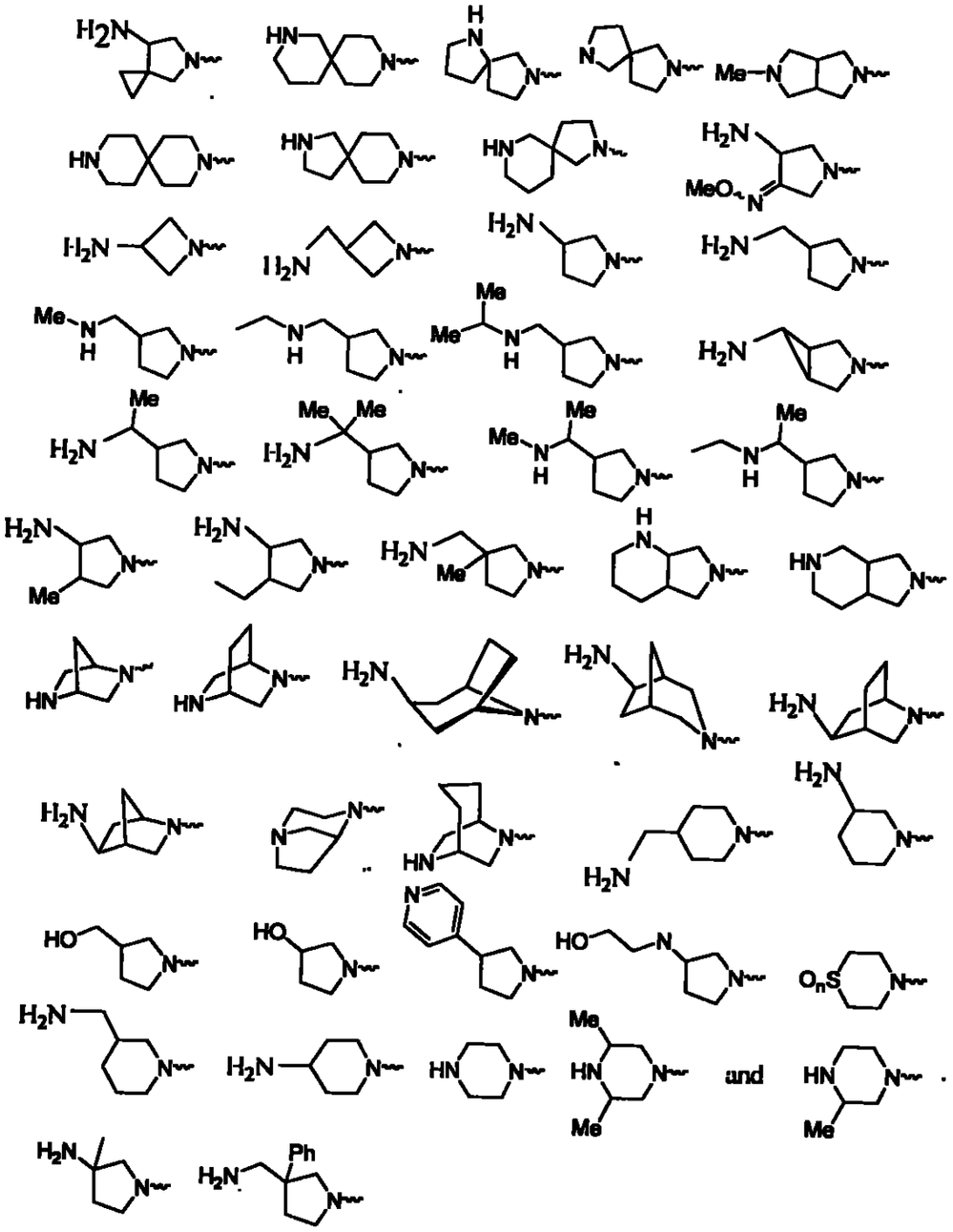
bicyclic heterocyclic, or

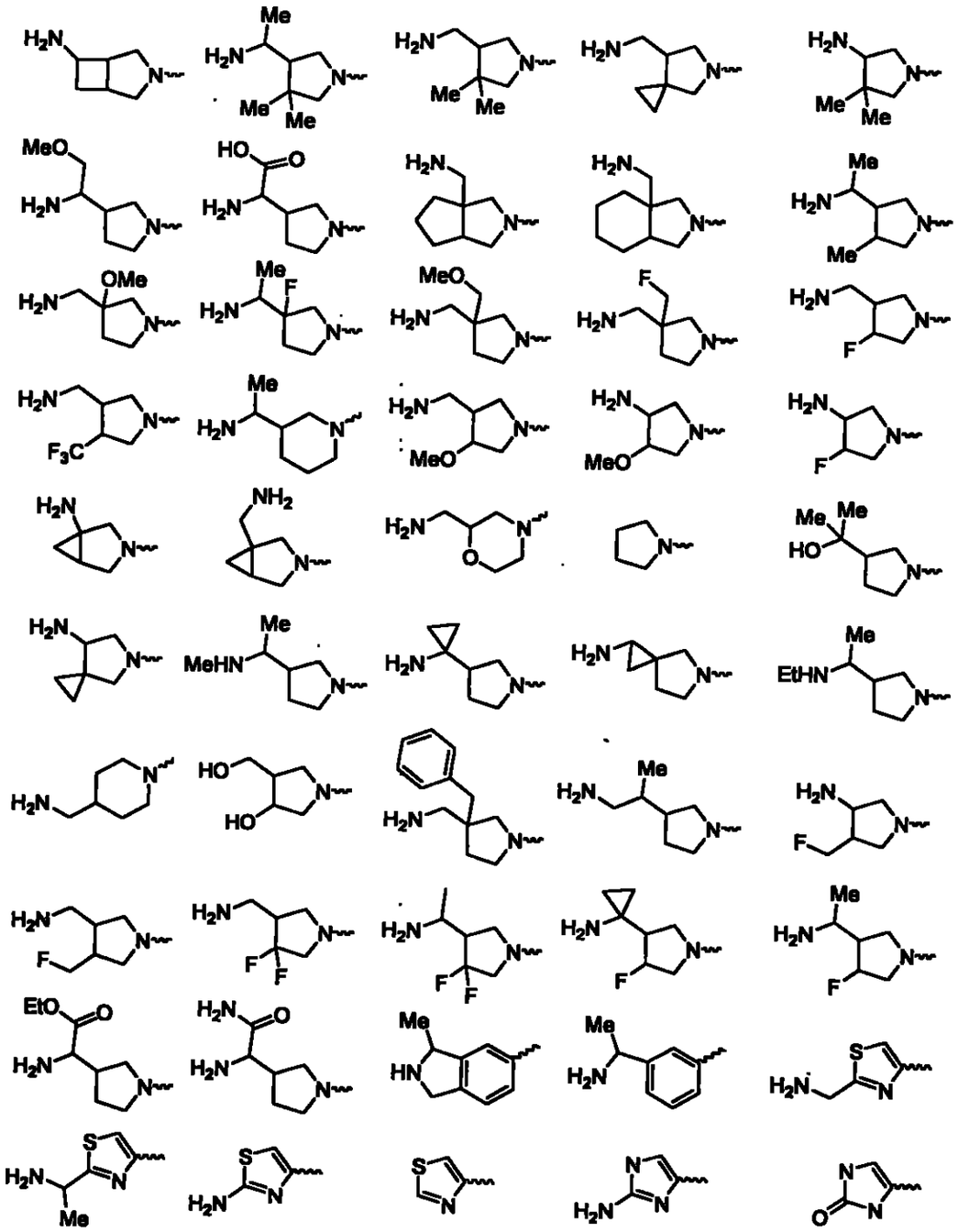
spiro heterocyclic,

wherein all ring groups can be substituted; and

J and K independently are C or N, provided that when J or K is N, R_6 or R_8 is absent at that position.

8. A compound of Claim 1 wherein R_7 is selected from:


and



9. A compound of Claim 8 whercin R_7 is pyrrolidinyl, substituted pyrrolidinyl, piperazinyl, substituted piperazinyl, piperidinyl or substituted piperidinyl.

10. A compound selected from:

3-Amino-7-(3-aminomethylpyrrolidin-1-yl)-8-chloro-1-cyclopropyl-6-fluoro-1*H*-quinazoline-2,4-dione;

3-Amino-8-chloro-1-cyclopropyl-6-fluoro-7-piperazin-1-yl-1*H*-quinazoline-2,4-dione;

3-Amino-7-[3-(aminomethyl)-3-methylpyrrolidin-1-yl]-8-chloro-1-cyclopropyl-6-fluoro-1*H*-quinazoline-2,4-dione;

3-Amino-7-(6-amino-3-aza-bicyclo[3.1.0]hex-3-yl)-8-chloro-1-cyclopropyl-6-fluoro-1*H*-quinazolin-2,4-dione;

3-Amino-7-((S)-3-N-methylaminopyrrolidin-1-yl)-8-chloro-1-cyclopropyl-6-fluoro-1*H*-quinazoline-2,4-dione;

3-Amino-7-((S)-3-aminopyrrolidin-1-yl)-8-chloro-1-(2,4-difluoroanilino)-6-fluoro-1*H*-quinazoline-2,4-dione;

3-Amino-7-[(S)-3-aminopyrrolidin-1-yl]-1-cyclopropylamino-6,8-difluoro-1H-quinazoline-2,4-dione;

3-Amino-7-[(S)-3-aminopyrrolidin-1-yl]-1-cyclopropylamino-5,8-difluoro-1*H*-quinazoline-2,4-dione;

3-Amino-7-((S)-3-aminopyrrolidin-1-yl)-1-cyclopropyl-5,6,8-trifluoro-1*H*-quinazoline-2,4-dione;

3-Amino-7-(3-aminopyrrolidin-1-yl)-8-chloro-1-cyclopropyl-6-fluoro-1*H*-quinazoline-2,4-dione;

7-((S)-3-Aminopyrrolidin-1-yl)-1-cyclopropyl-3,5-diamino-6,8-difluoro-1*H*-quinazoline-2,4-dione;

3-Amino-7-(3-hydroxymethylpyrrolidin-1-yl)-8-chloro-1-cyclopropyl-6-fluoro-1*H*-quinazoline-2,4-dione;

3-Amino-7-(3-aminoethylpyrrolidin-1-yl)-8-chloro-1-cyclopropyl-6-fluoro-1*H*-quinazoline-2,4-dione;

3-Amino-7-((S)-7-amino-5-azaspiro[2.4]hept-5-yl)-8-chloro-1-cyclopropyl-6-fluoro-1*H*-quinazoline-2,4-dione;

3-Amino-7-[(R)-3-(1-amino-1-methylethyl)pyrrolidin-1-yl]-8-chloro-1-cyclopropyl-6-fluoro-1*H*-quinazoline-2,4-dione;

3-Amino-7-(3-aminomethylpyrrolidin-1-yl)-1-cyclopropyl-6-fluoro-1*H*-quinazoline-2,4-dione;

3-Amino-7-(pyrrolidin-1-yl)-8-chloro-1-cyclopropyl-6-fluoro-1*H*-quinazoline-2,4-dione;

3-Amino-7-(3-aminopyrrolidin-1-yl)-8-chloro-6-fluoro-1-isopropyl-1*H*-quinazoline-2,4-dione;

3-Amino-7-(3-aminopyrrolin-1-yl)-1-*sec*-butyl-8-chloro-6-fluoro-1*H*-quinazoline-2,4-dione;

3-Amino-7-[3-aminopyrrolidin-1-yl]-1-cyclopropyl-6-fluoro-8-methoxy-1*H*-quinazoline-2,4-dione;

3-Amino-7-[3-aminopyrrolidin-1-yl]-8-chloro-1-cyclobutylamino-6-fluoro-1*H*-quinazoline-2,4-dione;

3-Amino-7-(3-aminopyrrolidin-1-yl)-1-cyclopropyl-8-fluoro-1*H*-quinazoline-2,4-dione;

3-Amino-7-(3-aminopyrrolidin-1-yl)-6-chloro-1-cyclopropyl-8-fluoro-1*H*-quinazoline-2,4-dione;

3-Amino-7-((S)-3-aminopyrrolidin-1-yl)-1-cyclopropylmethyl-8-fluoro-1*H*-quinazoline-2,4-dione;

3-Amino-7-[(R)-3-(1-amino-1-methylethyl)pyrrolidin-1-yl]-1-cyclopropylmethyl-8-fluoro-1*H*-quinazoline-2,4-dione;

3-Amino-7-((S)-3-aminopyrrolidin-1-yl)-1-ethyl-8-fluoro-1*H*-quinazoline-2,4-dione;

3-Amino-1-ethyl-6-fluoro-7-[(R)-3-(1-amino-1-methylethyl)-pyrrolidin-1-yl]-1H-quinazoline-2,4-dione;

3-Amino-7-((S)-3-aminopyrrolidin-1-yl)-1-cyclopropyl-6-fluoro-1*H*-quinazoline-2,4-dione;

3-Amino-7-(3-aminopyrrolidin-1-yl)-1-cyclopropyl-6-fluoro-8-methyl-1H-quinazoline-2,4-dione;

3-Amino-7-(3-aminomethylpyrrolidin-1-yl)-1-cyclopropyl-6-fluoro-8-methyl-1H-quinazoline-2,4-dione;

3-Amino-7-(3-aminopyrrolidin-1-yl)-1-cyclopropyl-8-fluoro-6-methoxy-1H-quinazoline-2,4-dione;

3-Amino-7-(3-aminomethylpyrrolidin-1-yl)-1-cyclopropyl-6-fluoro-8-methoxy-1H-quinazoline-2,4-dione;

3-Amino-7-(3-aminopyrrolidin-1-yl)-1-cyclopropyl-8-ethoxy-6-fluoro-1H-quinazoline-2,4-dione;

3-Amino-7-(3-aminopyrrolidin-1-yl)-1-cyclopropyl-6-fluoro-2,4-dioxo-1,2,3,4-tetrahydroquinazoline-8-carbonitrile;

3-Amino-8-chloro-1-cyclopropyl-6-fluoro-7-(3-[1,2,3-triazol]-1-yl-pyrrolidin-1-yl)-1H-quinazoline-2,4-dione;

3-Amino-7-[(S)-3-((R)-1-aminoethyl)pyrrolidin-1-yl]-1-cyclopropyl-6-fluoro-8-methoxy-1H-quinazoline-2,4-dione;

3-Amino-7-[(S)-3-((S)-1-aminoethyl)pyrrolidin-1-yl]-1-cyclopropyl-6-fluoro-8-methoxy-1H-quinazoline-2,4-dione;

3-Amino-7-[(S)-3-((R)-1-aminoethyl)pyrrolidin-1-yl]-1-cyclopropyl-6-fluoro-8-methyl-1H-quinazoline-2,4-dione;

3-Amino-7-[(S)-3-((S)-1-aminoethyl)pyrrolidin-1-yl]-1-cyclopropyl-6-fluoro-8-methyl-1H-quinazoline-2,4-dione;

5-Amino-9-((S)-3-aminopyrrolidin-1-yl)-8-fluoro-3-methyl-2,3-dihydro-1-oxa-3a,5-diazaphenalene-4,6-dione;

5-Amino-9-[(R)-3-((S)-1-aminoethyl)pyrrolidin-1-yl]-8-fluoro-3-methyl-2,3-dihydro-1-oxa-3a,5-diazaphenalene-4,6-dione;

2-Amino-8-((S)-3-aminopyrrolidin-1-yl)-9-fluoro-5-methyl-6,7-dihydro-5H-pyrido[3,2,1-ij]quinazoline-1,3-dione,;

2-Amino-8-[(R)-3-((S)-1-aminoethyl)pyrrolidin-1-yl]-9-fluoro-5-methyl-6,7-dihydro-5H-pyrido[3,2,1-ij]quinazoline-1,3-dione;

3-Amino-7-((S)-3-aminopyrrolidin-1-yl)-1-cyclopropyl-6-fluoro-1H-pyrido[2,3-d]pyrimidine-2,4-dione;

3-Amino-7-(6-amino-3-azabicyclo[3.1.0]hex-3-yl)-1-cyclopropyl-6-fluoro-1H-pyrido[2,3-d]pyrimidine-2,4-dione,;

3-Amino-7-(3-aminomethyl-3-methylpyrrolidin-1-yl)-1-cyclopropyl-6-fluoro-1H-pyrido[2,3-d]pyrimidine-2,4-dione,;

3-Amino-1-cyclopropyl-6-fluoro-7-(octahydropyrrolo[3,4-c]pyridin-2-yl)-1H-pyrido[2,3-d]pyrimidine-2,4-dione;

3-Amino-1-cyclopropyl-6-fluoro-7-(octahydropyrrolo[3,4-b]pyridin-2-yl)-1H-pyrido[2,3-d]pyrimidine-2,4-dione;

3-Amino-7-[(R)-3-(1-amino-1-methylethyl)pyrrolidin-1-yl]-1-cyclopropyl-6-fluoro-1H-pyrido[2,3-d]pyrimidine-2,4-dione;

3-Amino-7-(3-aminomethylpiperidin-1-yl)-1-cyclopropyl-6-fluoro-1H-pyrido[2,3-d]pyrimidine-2,4-dione;

trans-3-Amino-7-(3-aminomethyl-4-trifluoromethylpyrrolidin-1-yl)-1-cyclopropyl-6-fluoro-1H-pyrido[2,3-d]pyrimidine-2,4-dione;

3-Amino-1-cyclopropyl-6-fluoro-7-[(R)-3-((R)-1-methylaminoethyl)pyrrolidin-1-yl]-1H-pyrido[2,3-d]pyrimidine-2,4-dione;

3-Amino-7-[(R)-3-((S)-1-aminoethyl)pyrrolidin-1-yl]-1-cyclopropyl-6-fluoro-1H-pyrido[2,3-d]pyrimidine-2,4-dione;

3-Amino-7-[3-(1-aminopropyl)pyrrolidin-1-yl]-1-cyclopropyl-6-fluoro-8-methyl-1*H*-quinazoline-2,4-dione;

3-Amino-1-cyclopropyl-6-fluoro-8-methyl-7-[(R)-3-((S)-1-methylaminoethyl)pyrrolidin-1-yl]-1*H*-quinazoline-2,4-dione;

3-Amino-7-[7-(1-aminoethyl)-5-azaspiro[2.4]hept-5-yl]-1-cyclopropyl-6-fluoro-8-methyl-1*H*-quinazoline-2,4-dione;

1-(3-Amino-8-chloro-1-cyclopropyl-6-fluoro-2,4-dioxo-1,2,3,4-tetrahydroquinazolin-7-yl)piperidine-3-carboxylic acid amide;

3-Amino-[7-trans-3-aminomethyl-4-trifluoromethylpyrrolidin-1-yl]-8-chloro-1-cyclopropyl-6-fluoro-1*H*-quinazoline-2,4-dione;

3-Amino-8-chloro-1-cyclopropyl-6-fluoro-7-{3-[(2,2,2-trifluoroethylamino)methyl]pyrrolidin-1-yl}-1*H*-quinazoline-2,4-dione;

3-Amino-8-chloro-1-cyclopropyl-6-fluoro-7-(5-methylhexahydropyrrolo[3,4-*c*]pyrrol-2-yl)-1*H*-quinazoline-2,4-dione;

3-Amino-8-chloro-1-cyclopropyl-7-(2,7-diazaspiro[4.4]non-2-yl)-6-fluoro-1*H*-quinazoline-2,4-dione;

3-Amino-7-(3-aminomethyl-3-benzylpyrrolidin-1-yl)-8-chloro-1-cyclopropyl-6-fluoro-1*H*-quinazoline-2,4-dione;

3-Amino-7-[(R)-3-((S)-1-aminoethyl)pyrrolidin-1-yl]-8-chloro-1-cyclopropyl-6-fluoro-1H-quinazoline-2,4-dione;

3-Amino-8-chloro-1-cyclopropyl-6-fluoro-7-(3-hydroxyimino-pyrrolidin-1-yl)-1*H*-quinazoline-2,4-dione;

3-Amino-7-[trans-3-amino-4-trifluoromethylpyrrolidin-1-yl]-8-chloro-1-cyclopropyl-6-fluoro-1H-quinazoline-2,4-dione;

3-Amino-8-chloro-1-cyclopropyl-6-fluoro-7-[(R)-3-(S)-1-methylaminoethyl)pyrrolidin-1-yl]-1*H*-quinazoline-2,4-dione;

3-Amino-7-(trans-3-amino-4-phenylpyrrolidin-1-yl)-8-chloro-1-cyclopropyl-6-fluoro-1*H*-quinazoline-2,4-dione;

3-Amino-7-[trans-3-amino-4-(4-hydroxyphenyl)pyrrolidin-1-yl]-8-chloro-1-cyclopropyl-6-fluoro-1*H*-quinazoline-2,4-dione;

N-[1-(3-Amino-8-chloro-1-cyclopropyl-6-fluoro-2,4-dioxo-1,2,3,4-tetrahydroquinazolin-7-yl)pyrrolidin-3-ylmethyl]methanesulfonamide;

3-Amino-7-(3-aminomethylpiperidin-1-yl)-8-chloro-1-cyclopropyl-6-fluoro-1H-quinazoline-2,4-dione;

3-Amino-8-chloro-1-cyclopropyl-6-fluoro-7-[3-(isopropylamino-methyl)pyrrolidin-1-yl]-1*H*-quinazoline-2,4-dione;

3-Amino-7-(3-aminomethylpyrrolidin-1-yl)-6,8-dichloro-1-cyclopropyl-1*H*-quinazoline-2,4-dione;

N-[1-(3-Amino-8-chloro-1-cyclopropyl-6-fluoro-2,4-dioxo-1,2,3,4-tetrahydroquinazolin-7-yl)pyrrolidin-3-ylmethyl]methanesulfonamide;

3-Amino-7-[(R)-3-(S)-(1-aminoethyl)pyrrolidin-1-yl]-1-cyclopropyl-6-fluoro-8-methyl-1H-quinazoline-2,4-dione;

3-Amino-7-[(R)-3-(1-amino-1-methylethyl)pyrrolidin-1-yl]-1-cyclopropyl-6-fluoro-8-methyl-1H-quinazoline-2,4-dione;

3-Amino-7-[3-(1-aminoethyl)-3-methoxypyrrolidin-1-yl]-1-cyclopropyl-6-fluoro-8-methyl-1H-quinazoline-2,4-dione;

3-Amino-7-[3-(1-aminoethyl)-3-fluoropyrrolidin-1-yl]-1-cyclopropyl-6-fluoro-8-methoxy-1H-quinazoline-2,4-dione;

3-Amino-7-(3-aminopyrrolidin-1-yl)-1-cyclopropyl-6-fluoro-5-methyl-1H-quinazoline-2,4-dione;

3-Amino-7-[(R)-3-(S)-(1-aminoethyl)pyrrolidin-1-yl]-1-cyclopropyl-6-fluoro-5-methyl-1H-quinazoline-2,4-dione;

3-Amino-7-(3-aminomethyl-3-methoxymethylpyrrolidin-1-yl)-1-cyclopropyl-6-fluoro-8-methyl-1H-quinazoline-2,4-dione;

3-Amino-7-(3-aminomethyl-3-fluoromethylpyrrolidin-1-yl)-1-cyclopropyl-6-fluoro-1H-quinazoline-2,4-dione;

3-Amino-7-(trans-3-aminomethyl-4-trifluoromethylpyrrolidin-1-yl)-1-cyclopropyl-6-fluoro-8-methoxy-1H-quinazoline-2,4-dione;

3-Amino-7-[3-(1-aminoethyl)piperidin-1-yl]-1-cyclopropyl-6-fluoro-8-methoxy-1H-quinazoline-2,4-dione;

3-Amino-7-[3-(aminoethyl)piperidin-1-yl]-1-cyclopropyl-6-fluoro-8-methyl-1H-quinazoline-2,4-dione;

3-Amino-7-[4-(1-aminoethyl)-3,3-dimethylpyrrolidin-1-yl]-1-cyclopropyl-6-fluoro-8-methoxy-1H-quinazoline-2,4-dione;

3-Amino-7-[4-(1-aminoethyl)-3,3-dimethylpyrrolidin-1-yl]-1-cyclopropyl-6-fluoro-8-methyl-1H-quinazoline-2,4-dione;

3-Amino-7-(3-amino-3-phenylpyrrolidin-1-yl)-1-cyclopropyl-6-fluoro-8-methyl-1H-quinazoline-2,4-dione;

3-Amino-7-[3-(1-aminoethyl)-4-methylpyrrolidin-1-yl]-1-cyclopropyl-6-fluoro-8-methyl-1H-quinazoline-2,4-dione;

3-Amino-7-(3-aminomethyl-3-phenylpyrrolidin-1-yl)-1-cyclopropyl-6-fluoro-8-methyl-1H-quinazoline-2,4-dione;

3-Amino-7-(7-aminomethyl-5-azaspiro[2,4]hept-5-yl)-1-cyclopropyl-6-fluoro-8-methyl-1H-quinazoline-2,4-dione;

3-Amino-7-(7-aminomethyl-5-azaspiro[2,4]hept-5-yl)-1-cyclopropyl-6-fluoro-8-methoxy-1H-quinazoline-2,4-dione;

3-Amino-7-(3-aminomethyl-3-hydroxypyrrolidin-1-yl)-1-cyclopropyl-6-fluoro-8-methoxy-1H-quinazoline-2,4-dione;

3-Amino-7-(3-aminomethylpiperidin-1-yl)-1-cyclopropyl-6-fluoro-8-methyl-1H-quinazoline-2,4-dione;

3-Amino-7-(3-amino-4-methoxypyrrolidin-1-yl)-1-cyclopropyl-6-fluoro-8-methyl-1H-quinazoline-2,4-dione;

3-Amino-7-(3-amino-4-methoxypyrrolidin-1-yl)-1-cyclopropyl-6-fluoro-8-methoxy-1H-quinazoline-2,4-dione;

3-Amino-7-(3-amino-4-fluoropyrrolidin-1-yl)-1-cyclopropyl-6-fluoro-8-methoxy-1H-quinazoline-2,4-dione;

3-Amino-7-(3-aminomethyl-3-methylpyrrolidin-1-yl)-1-cyclopropyl-6-fluoro-8-methyl-1H-quinazoline-2,4-dione;

3-Amino-7-[(R)-3 (-((S)-1-aminoethyl)pyrrolidin-1-yl]-1-cyclopropyl-8-ethyl-6-fluoro-1H-quinazoline-2,4-dione;

1-(3-Amino-1-cyclopropyl-6-fluoro-8-methoxy-2,4-dioxo-1,2,3,4-tetrahydroquinazolin-7-yl)pyrrolidine-3-carboxylic acid trifluoroacetate;

1-(3-Amino-1-cyclopropyl-6-fluoro-8-methyl-2,4-dioxo-1,2,3,4-tetrahydroquinazolin-7-yl)pyrrolidine-3-carboxylic acid trifluoroacetate;

3-Amino-7-(1-aminomethyl-3-azabicyclo[3.1.0]hex-3-yl)-1-cyclopropyl-6-fluoro-8-methoxy-1H-quinazoline-2,4-dione;

3-Amino-7-(1-aminomethyl-3-azabicyclo[3.1.0]hex-3-yl)-1-cyclopropyl-6-fluoro-8-methyl-1H-quinazoline-2,4-dione;

3-Amino-7-[(S)-3-((R)-1-aminoethyl)pyrrolidin-1-yl]-1-cyclopropyl-6-fluoro-8-methoxy-1H-quinazoline-2,4-dione;

3-Amino-7-[(S)-3-((R)-1-aminoethyl)pyrrolidin-1-yl]-1-cyclopropyl-6-fluoro-8-methyl-1H-quinazoline-2,4-dione;

3-Amino-1-cyclopropyl-6-fluoro-8-methyl-7-(octahydropyrrolo[3,4-b]pyridin-6-yl)-1H-quinazoline-2,4-dione;

3-Amino-7-(trans-3-aminomethyl-4-methylpyrrolidin-1-yl)-8-chloro-1-cyclopropyl-6-fluoro-1H-quinazoline-2,4-dione;

3-Amino-7-(trans-3-aminomethyl-4-methylpyrrolidin-1-yl)-1-cyclopropyl-6-fluoro-8-methoxy-1H-quinazoline-2,4-dione;

3-Amino-7-(trans-3-aminomethyl-4-methylpyrrolidin-1-yl)-1-cyclopropyl-6-fluoro-8-methyl-1H-quinazoline-2,4-dione;

3-Amino-7-(trans-3-amino-4-methylpyrrolidin-1-yl)-1-cyclopropyl-6-fluoro-8-methoxy-1H-quinazoline-2,4-dione;

3-Amino-7-(3-aminomethylmorpholin-1-yl)-1-cyclopropyl-6-fluoro-8-methoxy-1H-quinazoline-2,4-dione;

3-Amino-7-(3-aminomethylpiperidin-1-yl)-1-cyclopropyl-6-fluoro-8-methoxy-1H-quinazoline-2,4-dione;

3-Amino-7-[3-(1-aminoethyl)-4-methylpyrrolidin-1-yl]-1-cyclopropyl-6-fluoro-8-methoxy-1H-quinazoline-2,4-dione;

3-Amino-7-(3-amino-3-phenylpyrrolidin-1-yl)-8-chloro-1-cyclopropyl-6-fluoro-1H-quinazoline-2,4-dione;

3-Amino-7-(3-amino-3-methylpyrrolidin-1-yl)-1-cyclopropyl-6-fluoro-8-methyl-1H-quinazoline-2,4-dione;

3-Amino-1-cyclopropyl-6-fluoro-8-methyl-7-pyrrolidin-1yl-1H-quinazoline-2,4-dione;

3-Amino-1-cyclopropyl-6-fluoro-8-methoxy-7-pyrrolidin-1yl-1H-quinazoline-2,4-dione;

3-Amino-1-cyclopropyl-6-fluoro-7-[3-(1-hydroxy-1-methylethyl)-pyrrolidin-1-yl]-8-methyl-1H-quinazoline-2,4-dione;

3-Amino-1-cyclopropyl-6-fluoro-7-[3-(1-hydroxy-1-methylethyl)-pyrrolidin-1-yl]-8-methoxy-1H-quinazoline-2,4-dione;

3-Amino-1-cyclopropyl-6-fluoro-5-methyl-7-[(R)-3-((S)-1-methylaminoethyl)pyrrolidin-1-yl]-1H-quinazoline-2,4-dione;

(S)-1-[(R)-1-(3-Amino-1-cyclopropyl-7-[3-(1-ethylaminoethyl)pyrrolidin-1-yl)-6-fluoro-8-methoxy-1H-quinazoline-2,4-dione;

3-Amino-1-cyclopropyl-7-[(R)-3-((S)-1-ethylaminoethyl)pyrrolidin-1-yl]-6-fluoro-8-methyl-1H-quinazoline-2,4-dione;

3-Amino-7-(6-amino-1-methyl-3-azabicyclo[3.2.0]hept-3-yl)-1-cyclopropyl-6-fluoro-8-methoxy-1H-quinazoline-2,4-dione;

3-Amino-7-(4-aminomethylpiperidin-1-yl)-1-cyclopropyl-6-fluoro-8-methoxy-1H-quinazoline-2,4-dione;

3-Amino-7-(3-aminomethylazetidin-1-yl)-1-cyclopropyl-6-fluoro-8-methoxy-1H-quinazoline-2,4-dione;

cis-3-Amino-7-(3-aminomethyl-4-fluoropyrrolidin-1-yl)-1-cyclopropyl-6-fluoro-8-methoxy-1H-quinazoline-2,4-dione;

trans-3-Amino-7-(3-aminomethyl-4-fluoropyrrolidin-1-yl)-1-cyclopropyl-6-fluoro-8-methoxy-1H-quinazoline-2,4-dione;

3-Amino-7-(1-amino-5-azaspiro[2.4]hept-5-yl)-1-cyclopropyl-6-fluoro-8-methoxy-1H-quinazoline-2,4-dione;

3-Amino-7-(3-aminomethyloctahydroisoindol-2-yl)-1-cyclopropyl-6-fluoro-8-methoxy-1H-quinazoline-2,4-dione;

3-Amino-7-(3-aminomethyloctahydroisoindol-2-yl)-1-cyclopropyl-6-fluoro-8-methyl-1H-quinazoline-2,4-dione;

3-Amino-7-[(R)-3-((S)-1-aminoethylpyrrolidin-1-yl]-1-cyclopropyl-6-fluoro-8-methoxy-1H-quinazoline-2,4-dione;

3-Amino-7-(6-amino-3-azabicyclo[3.1.0]hex-3-yl)-1-cyclopropyl-6-fluoro-8-methyl-1H-quinazoline-2,4-dione;

3-Amino-7-[3-(1-amino-1-methylethyl)pyrrolidin-1-yl]-1-cyclopropyl-6-fluoro-8-methoxy-1*H*-quinazoline-2,4-dione;

3-Amino-1-cyclopropyl-6-fluoro-7-[3-(isopropylaminomethyl) pyrrolidin-1-yl]-8-methoxy-1*H*-quinazoline-2,4-dione;

3-Amino-1-cyclopropyl-6-fluoro-8-methoxy-7-[(4aS,7aS)-octahydropyrrolo[3,4-b]pyridin-6-yl-1*H*-quinazoline-2,4-dione;

3-Amino-7-(3-amino-4-fluoromethylpyrrolidin-1-yl)-1-cyclopropyl-6-fluoro-8-methoxy-1*H*-quinazoline-2,4-dione;

3-Amino-7-(3-aminomethyl-3-methylpyrrolidin-1-yl)-1-cyclopropyl-6-fluoro-8-methoxy-1*H*-quinazoline-2,4-dione;

3-Amino-7-(4-aminopiperidin-1-yl)-1-cyclopropyl-6-fluoro-8-methoxy-1*H*-quinazoline-2,4-dione;

3-Amino-7-(3-aminopiperidin-1-yl)-1-cyclopropyl-6-fluoro-8-methoxy-1*H*-quinazoline-2,4-dione;

3-Amino-1-cyclopropyl-6-fluoro-8-methoxy-7-[(R)-3-((S)-1-methylaminoethyl)pyrrolidin-1-yl]-1*H*-quinazoline-2,4-dione;

3-Amino-7-(3-aminoazetidin-1-yl)-1-cyclopropyl-6-fluoro-8-methoxy-1*H*-quinazoline-2,4-dione;

3-Amino-7-[(3R,4S)-3-((S)-1-aminoethyl)-4-fluoropyrrolidin-1-yl]-1-cyclopropyl-6-fluoro-8-methyl-1H-quinazoline-2,4-dione;

3-Amino-7-[(3R,4S)-3-((S)-1-aminoethyl)-4-fluoropyrrolidin-1-yl]-1-cyclopropyl-8-methyl-1H-quinazoline-2,4-dione;

3-Amino-7-[(3R,4R)-3-(R)-1-aminoethyl)-4-fluoropyrrolidin-1-yl]-1-cyclopropyl-6-fluoro-8-methyl-1H-quinazoline-2,4-dione;

3-Amino-7-[(3R,4R)-3-((R)-1-aminoethyl)-4-fluoropyrrolidin-1-yl]-1-cyclopropyl-8-methyl-1H-quinazoline-2,4-dione;

3-Amino-7-[(3R,4S)-3-(-1-amino-1-methylethyl)-4-fluoropyrrolidin-1-yl]-1-cyclopropyl-6-fluoro-8-methyl-1H-quinazoline-2,4-dione;

3-Amino-7-[(3R,4S)-3-(-1-amino-1-methylethyl)-4-fluoropyrrolidin-1-yl]-1-cyclopropyl-8-methyl-1H-quinazoline-2,4-dione;

3-Amino-7-[(3R,4R)-3-(-1-amino-1-methylethyl)-4-fluoropyrrolidin-1-yl]-1-cyclopropyl-6-fluoro-8-methyl-1H-quinazoline-2,4-dione;

3-Amino-7-[(3R,4R)-3-(-1-amino-1-methylethyl)-4-fluoropyrrolidin-1-yl]-1-cyclopropyl-8-methyl-1H-quinazoline-2,4-dione;

3-Amino-7-[(3R,4S)-3-((R)-1-amino-2-methoxyethyl)-4-fluoropyrrolidin-1-yl]-1-cyclopropyl-6-fluoro-8-methyl-1H-quinazoline-2,4-dione;

3-Amino-7-[(3R,4S)-3-((R)-1-amino-2-methoxyethyl)-4-fluoropyrrolidin-1-yl]-1-cyclopropyl-8-methyl-1H-quinazoline-2,4-dione;

3-Amino-7-[(3R,4R)-3-((S)-1-amino-2-methoxyethyl)-4-fluoropyrrolidin-1-yl]-1-cyclopropyl-6-fluoro-8-methyl-1H-quinazoline-2,4-dione;

3-Amino-7-[(3R,4R)-3-((S)-1-amino-2-methoxyethyl)-4-fluoropyrrolidin-1-yl]-1-cyclopropyl-8-methyl-1H-quinazoline-2,4-dione;

3-Amino-7-[(3R,4S)-3-((R)-1-amino-2-methoxyethyl)-4-methylpyrrolidin-1-yl]-1-cyclopropyl-6-fluoro-8-methyl-1H-quinazoline-2,4-dione;

3-Amino-7-[(3R,4S)-3-((R)-1-amino-2-methoxyethyl)-4-methylpyrrolidin-1-yl]-1-cyclopropyl-8-methyl-1H-quinazoline-2,4-dione;

3-Amino-7-[(3R,4R)-3-((S)-1-amino-2-methoxyethyl)-4-methylpyrrolidin-1-yl]-1-cyclopropyl-6-fluoro-8-methyl-1H-quinazoline-2,4-dione;

3-Amino-7-[(3R,4R)-3-((S)-1-amino-2-methoxyethyl)-4-methylpyrrolidin-1-yl]-1-cyclopropyl-8-methyl-1H-quinazoline-2,4-dione;

3-Amino-7-[(R)-4-((R)-1-amino-2-methoxyethyl)-3,3-dimethylpyrrolidin-1-yl]-1-cyclopropyl-6-fluoro-8-methyl-1H-quinazoline-2,4-dione;

3-Amino-7-[(R)-4-(R)-1-amino-2-methoxyethyl)-3,3-dimethylpyrrolidin-1-yl]-1-cyclopropyl-8-methyl-1H-quinazoline-2,4-dione;

3-Amino-7-[(R)-4-((S)-1-amino-2-methoxyethyl)-3,3-dimethylpyrrolidin-1-yl]-1-cyclopropyl-6-fluoro-8-methyl-1H-quinazoline-2,4-dione;

3-Amino-7-[(R)-4-(S)-1-amino-2-methoxyethyl)-3,3-dimethylpyrrolidin-1-yl]-1-cyclopropyl-8-methyl-1H-quinazoline-2,4-dione;

3-Amino-7-[(R)-3-((R)-1-amino-2-phenoxyethyl)pyrrolidin-1-yl]-1-cyclopropyl-6-fluoro-8-methyl-1H-quinazoline-2,4-dione;

3-Amino-7-[(R)-3-(R)-1-amino-2-phenoxyethyl)pyrrolidin-1-yl]-1-cyclopropyl-8-methyl-1H-quinazoline-2,4-dione;

3-Amino-7-[(3R,4S)-3-((R)-1-amino-2-phenoxyethyl)-4-methylpyrrolidin-1-yl]-1-cyclopropyl-6-fluoro-8-methyl-1H-quinazoline-2,4-dione;

3-Amino-7-[(3R,4S)-3-((R)-1-amino-2-phenoxyethyl)-4-methylpyrrolidin-1-yl]-1-cyclopropyl-8-methyl-1H-quinazoline-2,4-dione;

3-Amino-7-[(3R,4S)-3-((R)-1-amino-2-phenoxyethyl)-4-fluoropyrrolidin-1-yl]-1-cyclopropyl-6-fluoro-8-methyl-1H-quinazoline-2,4-dione;

3-Amino-7-[(3R,4S)-3-((R)-1-amino-2-phenoxyethyl)-4-fluoropyrrolidin-1-yl]-1-cyclopropyl-8-methyl-1H-quinazoline-2,4-dione;

3-Amino-7-[(R)-3-((S)-1-amino-2-phenoxyethyl)pyrrolidin-1-yl]-1-cyclopropyl-6-fluoro-8-methyl-1H-quinazoline-2,4-dione;

3-Amino-7-[(R)-3-((S)-1-amino-2-phenoxyethyl)pyrrolidin-1-yl]-1-cyclopropyl-8-methyl-1H-quinazoline-2,4-dione;

3-Amino-7-[(3R,4S)-3-((S)-1-amino-2-phenoxyethyl)-4-methylpyrrolidin-1-yl]-1-cyclopropyl-6-fluoro-8-methyl-1H-quinazoline-2,4-dione;

3-Amino-7-[(3R,4S)-3-((S)-1-amino-2-phenoxyethyl)-4-methylpyrrolidin-1-yl]-1-cyclopropyl-8-methyl-1H-quinazoline-2,4-dione;

3-Amino-7-[(3R,4S)-3-((S)-1-amino-2-phenoxyethyl)-4-fluoropyrrolidin-1-yl]-1-cyclopropyl-6-fluoro-8-methyl-1H-quinazoline-2,4-dione;

3-Amino-7-[(3R,4S)-3-((S)-1-amino-2-phenoxyethyl)-4-fluoropyrrolidin-1-yl]-1-cyclopropyl-8-methyl-1H-quinazoline-2,4-dione;

3-Amino-7-[(R)-4-((R)-1-amino-2-phenoxyethyl)-3,3-dimethylpyrrolidin-1-yl]-1-cyclopropyl-6-fluoro-8-methyl-1H-quinazoline-2,4-dione;

3-Amino-7-[(R)-4-((R)-1-amino-2-phenoxyethyl)-3,3-dimethylpyrrolidin-1-yl]-1-cyclopropyl-8-methyl-1H-quinazoline-2,4-dione;

3-Amino-7-[(R)-4-((S)-1-amino-2-phenoxyethyl)-3,3-dimethylpyrrolidin-1-yl]-1-cyclopropyl-6-fluoro-8-methyl-1H-quinazoline-2,4-dione;

3-Amino-7-[(R)-4-((S)-1-amino-2-phenoxyethyl)-3,3-dimethylpyrrolidin-1-yl]-1-cyclopropyl-8-methyl-1H-quinazoline-2,4-dione;

3-Amino-7-[(R)-3-((S)-1-amino-2-ethoxyethyl)pyrrolidin-1-yl]-1-cyclopropyl-6-fluoro-8-methyl-1H-quinazoline-2,4-dione;

3-Amino-7-[(R)-3-((S)-1-amino-2-ethoxyethyl)pyrrolidin-1-yl]-1-cyclopropyl-8-methyl-1H-quinazoline-2,4-dione;

3-Amino-7-[(R)-3-((R)-1-amino-2-ethoxyethyl)pyrrolidin-1-yl]-1-cyclopropyl-6-fluoro-8-methyl-1H-quinazoline-2,4-dione;

3-Amino-7-[(R)-3-((R)-1-amino-2-ethoxyethyl)pyrrolidin-1-yl]-1-cyclopropyl-8-methyl-1H-quinazoline-2,4-dione;

3-Amino-7-[(3R,4S)-3-((R)-1-amino-2-ethoxyethyl)-4-methylpyrrolidin-1-yl]-1-cyclopropyl-6-fluoro-8-methyl-1H-quinazoline-2,4-dione;

3-Amino-7-[(3R,4S)-3-((R)-1-amino-2-ethoxyethyl)-4-methylpyrrolidin-1-yl]-1-cyclopropyl-8-methyl-1H-quinazoline-2,4-dione;

3-Amino-7-[(3R,4S)-3-((R)-1-amino-2-ethoxyethyl)-4-fluoropyrrolidin-1-yl]-1-cyclopropyl-6-fluoro-8-methyl-1H-quinazoline-2,4-dione;

3-Amino-7-[(3R,4S)-3-((R)-1-amino-2-ethoxyethyl)-4-fluoropyrrolidin-1-yl]-1-cyclopropyl-8-methyl-1H-quinazoline-2,4-dione;

3-Amino-7-[(R)-4-((R)-1-amino-2-ethoxyethyl)-3,3-dimethylpyrrolidin-1-yl]-1-cyclopropyl-6-fluoro-8-methyl-1H-quinazoline-2,4-dione;

3-Amino-7-[(R)-4-((R)-1-amino-2-ethoxyethyl)-3,3-dimethylpyrrolidin-1-yl]-1-cyclopropyl-8-methyl-1H-quinazoline-2,4-dione;

3-Amino-7-[(3R,4R)-3-((S)-1-amino-2-ethoxyethyl)-4-methylpyrrolidin-1-yl]-1-cyclopropyl-6-fluoro-8-methyl-1H-quinazoline-2,4-dione;

3-Amino-7-[(3R,4R)-3-((S)-1-amino-2-ethoxyethyl)-4-methylpyrrolidin-1-yl]-1-cyclopropyl-8-methyl-1H-quinazoline-2,4-dione;

3-Amino-7-[(3R,4R)-3-((S)-1-amino-2-ethoxyethyl)-4-fluoropyrrolidin-1-yl]-1-cyclopropyl-6-fluoro-8-methyl-1H-quinazoline-2,4-dione;

3-Amino-7-[(3R,4R)-3-((S)-1-amino-2-ethoxyethyl)-4-fluoropyrrolidin-1-yl]-1-cyclopropyl-8-methyl-1H-quinazoline-2,4-dione;

3-Amino-7-[(R)-3-((S)-1-amino-3-methoxypropyl)pyrrolidin-1-yl]-1-cyclopropyl-6-fluoro-8-methyl-1H-quinazoline-2,4-dione;

3-Amino-7-[(R)-3-((S)-1-amino-3-methoxypropyl)pyrrolidin-1-yl]-1-cyclopropyl-8-methyl-1H-quinazoline-2,4-dione;

3-Amino-7-[(3R,4S)-3-((S)-1-amino-3-methoxypropyl)-4-methylpyrrolidin-1-yl]-1-cyclopropyl-6-fluoro-8-methyl-1H-quinazoline-2,4-dione;

3-Amino-7-[(3R,4S)-3-((S)-1-amino-3-methoxypropyl)-4-methylpyrrolidin-1-yl]-1-cyclopropyl-8-methyl-1H-quinazoline-2,4-dione;

3-Amino-7-[(3R,4S)-3-((S)-1-amino-3-methoxypropyl)-4-fluoropyrrolidin-1-yl]-1-cyclopropyl-6-fluoro-8-methyl-1H-quinazoline-2,4-dione;

3-Amino-7-[(3R,4S)-3-((S)-1-amino-3-methoxypropyl)-4-fluoropyrrolidin-1-yl]-1-cyclopropyl-8-methyl-1H-quinazoline-2,4-dione;

3-Amino-7-[(R)-3-((R)-1-amino-3-methoxypropyl)pyrrolidin-1-yl]-1-cyclopropyl-6-fluoro-8-methyl-1H-quinazoline-2,4-dione;

3-Amino-7-[(R)-3-((R)-1-amino-3-methoxypropyl)pyrrolidin-1-yl]-1-cyclopropyl-8-methyl-1H-quinazoline-2,4-dione;

3-Amino-7-[(3R,4R)-3-((R)-1-amino-3-methoxypropyl)-4-methylpyrrolidin-1-yl]-1-cyclopropyl-6-fluoro-8-methyl-1H-quinazoline-2,4-dione;

3-Amino-7-[(3R,4R)-3-((R)-1-amino-3-methoxypropyl)-4-methylpyrrolidin-1-yl]-1-cyclopropyl-8-methyl-1H-quinazoline-2,4-dione;

3-Amino-7-[(3R,4R)-3-((R)-1-amino-3-methoxypropyl)-4-fluoropyrrolidin-1-yl]-1-cyclopropyl-6-fluoro-8-methyl-1H-quinazoline-2,4-dione;

3-Amino-7-[(3R,4R)-3-((R)-1-amino-3-methoxypropyl)-4-fluoropyrrolidin-1-yl]-1-cyclopropyl-8-methyl-1H-quinazoline-2,4-dione;

{(R)-2-Amino-2-[(R)-1-(3-amino-1-cyclopropyl-6-fluoro-8-methyl-2,4-dioxo-1,2,3,4-tetrahydroquinazolin-7-yl)pyrrolidin-3-yl]ethyl}urea;

{(R)-2-Amino-2-[(R)-1-(3-amino-1-cyclopropyl-8-methyl-2,4-dioxo-1,2,3,4-tetrahydroquinazolin-7-yl)pyrrolidin-3-yl]ethyl}urea;

{(S)-2-Amino-2-[(R)-1-(3-amino-1-cyclopropyl-6-fluoro-8-methyl-2,4-dioxo-1,2,3,4-tetrahydroquinazolin-7-yl)pyrrolidin-3-yl]ethyl}urea;

{(S)-2-Amino-2-[(R)-1-(3-amino-1-cyclopropyl-8-methyl-2,4-dioxo-1,2,3,4-tetrahydroquinazolin-7-yl)pyrrolidin-3-yl]ethyl}urea;

{(R)-2-Amino-2-[(3R,4S)-1-(3-amino-1-cyclopropyl-6-fluoro-8-methyl-2,4-dioxo-1,2,3,4-tetrahydroquinazolin-7-yl)-4-methylpyrrolidin-3-yl]ethyl}urea;

{(R)-2-Amino-2-[(3R,4S)-1-(3-amino-1-cyclopropyl-8-methyl-2,4-dioxo-1,2,3,4-tetrahydroquinazolin-7-yl)-4-methylpyrrolidin-3-yl]ethyl}urea;

{(S)-2-Amino-2-[(3R,4R)-1-(3-amino-1-cyclopropyl-6-fluoro-8-methyl-2,4-dioxo-1,2,3,4-tetrahydroquinazolin-7-yl)-4-methylpyrrolidin-3-yl]ethyl}urea;

{(S)-2-Amino-2-[(3R,4R)-1-(3-amino-1-cyclopropyl-8-methyl-2,4-dioxo-1,2,3,4-tetrahydroquinazolin-7-yl)-4-methylpyrrolidin-3-yl]ethyl}urea;

{2-Amino-2-[(1-(3-amino-1-cyclopropyl-6-fluoro-8-methyl-2,4-dioxo-1,2,3,4-tetrahydroquinazolin-7-yl)-4-fluoropyrrolidin-3-yl]ethyl}urea;

{2-Amino-2-[(1-(3-amino-1-cyclopropyl-8-methyl-2,4-dioxo-1,2,3,4-tetrahydroquinazolin-7-yl)-4-fluoropyrrolidin-3-yl]ethyl}urea;

{2-Amino-2-[(1-(3-amino-1-cyclopropyl-6-fluoro-8-methyl-2,4-dioxo-1,2,3,4-tetrahydroquinazolin-7-yl)-4,4-dimethylpyrrolidin-3-yl]ethyl}urea;

{2-Amino-2-[(1-(3-amino-1-cyclopropyl-8-methyl-2,4-dioxo-1,2,3,4-tetrahydroquinazolin-7-yl)-4,4-dimethylpyrrolidin-3-yl]ethyl}urea;

3-Amino-7-[(3R,4S)-3-((S)-1-aminoethyl)-4-fluoropyrrolidin-1-yl]-1-cyclopropyl-6-fluoro-8-methoxy-1H-quinazoline-2,4-dione;

3-Amino-7-[(3R,4S)-3-((S)-1-aminoethyl)-4-fluoropyrrolidin-1-yl]-1-cyclopropyl-8-methoxy-1H-quinazoline-2,4-dione;

3-Amino-7-[(3R,4R)-3-(R)-1-aminoethyl)-4-fluoropyrrolidin-1-yl]-1-cyclopropyl-6-fluoro-8-methoxy-1H-quinazoline-2,4-dione;

3-Amino-7-[(3R,4R)-3-((R)-1-aminoethyl)-4-fluoropyrrolidin-1-yl]-1-cyclopropyl-8-methoxy-1H-quinazoline-2,4-dione;

3-Amino-7-[(3R,4S)-3-(-1-amino-1-methylethyl)-4-fluoropyrrolidin-1-yl]-1-cyclopropyl-6-fluoro-8-methoxy-1H-quinazoline-2,4-dione;

3-Amino-7-[(3R,4S)-3-(-1-amino-1-methylethyl)-4-fluoropyrrolidin-1-yl]-1-cyclopropyl-8-methoxy-1H-quinazoline-2,4-dione;

3-Amino-7-[(3R,4R)-3-(-1-amino-1-methylethyl)-4-fluoropyrrolidin-1-yl]-1-cyclopropyl-6-fluoro-8-methoxy-1H-quinazoline-2,4-dione;

3-Amino-7-[(3R,4R)-3-(-1-amino-1-methylethyl)-4-fluoropyrrolidin-1-yl]-1-cyclopropyl-8-methoxy-1H-quinazoline-2,4-dione;

3-Amino-7-[(3R,4S)-3-((R)-1-amino-2-methoxyethyl)-4-fluoropyrrolidin-1-yl]-1-cyclopropyl-6-fluoro-8-methoxy-1H-quinazoline-2,4-dione;

3-Amino-7-[(3R,4S)-3-((R)-1-amino-2-methoxyethyl)-4-fluoropyrrolidin-1-yl]-1-cyclopropyl-8-methoxy-1H-quinazoline-2,4-dione;

3-Amino-7-[(3R,4R)-3-((S)-1-amino-2-methoxyethyl)-4-fluoropyrrolidin-1-yl]-1-cyclopropyl-6-fluoro-8-methoxy-1H-quinazoline-2,4-dione;

3-Amino-7-[(3R,4R)-3-((S)-1-amino-2-methoxyethyl)-4-fluoropyrrolidin-1-yl]-1-cyclopropyl-8-methoxy-1H-quinazoline-2,4-dione;

3-Amino-7-[(3R,4S)-3-((R)-1-amino-2-methoxyethyl)-4-methylpyrrolidin-1-yl]-1-cyclopropyl-6-fluoro-8-methoxy-1H-quinazoline-2,4-dione;

3-Amino-7-[(3R,4S)-3-((R)-1-amino-2-methoxyethyl)-4-methylpyrrolidin-1-yl]-1-cyclopropyl-8-methoxy-1H-quinazoline-2,4-dione;

3-Amino-7-[(3R,4R)-3-((S)-1-amino-2-methoxyethyl)-4-methylpyrrolidin-1-yl]-1-cyclopropyl-6-fluoro-8-methoxy-1H-quinazoline-2,4-dione;

3-Amino-7-[(3R,4R)-3-((S)-1-amino-2-methoxyethyl)-4-methylpyrrolidin-1-yl]-1-cyclopropyl-8-methoxy-1H-quinazoline-2,4-dione;

3-Amino-7-[(R)-4-((R)-1-amino-2-methoxyethyl)-3,3-dimethylpyrrolidin-1-yl]-1-cyclopropyl-6-fluoro-8-methoxy-1H-quinazoline-2,4-dione;

3-Amino-7-[(R)-4-(R)-1-amino-2-methoxyethyl)-3,3-dimethylpyrrolidin-1-yl]-1-cyclopropyl-8-methoxy-1H-quinazoline-2,4-dione;

3-Amino-7-[(R)-4-((S)-1-amino-2-methoxyethyl)-3,3-dimethylpyrrolidin-1-yl]-1-cyclopropyl-6-fluoro-8-methoxy-1H-quinazoline-2,4-dione;

3-Amino-7-[(R)-4-(S)-1-amino-2-methoxyethyl)-3,3-dimethylpyrrolidin-1-yl]-1-cyclopropyl-8-methoxy-1H-quinazoline-2,4-dione;

3-Amino-7-[(R)-3-((R)-1-amino-2-phenoxyethyl)pyrrolidin-1-yl]-1-cyclopropyl-6-fluoro-8-methoxy-1H-quinazoline-2,4-dione;

3-Amino-7-[(R)-3-(R)-1-amino-2-phenoxyethyl)pyrrolidin-1-yl]-1-cyclopropyl-8-methoxy-1H-quinazoline-2,4-dione;

3-Amino-7-[(3R,4S)-3-((R)-1-amino-2-phenoxyethyl)-4-methylpyrrolidin-1-yl]-1-cyclopropyl-6-fluoro-8-methoxy-1H-quinazoline-2,4-dione;

3-Amino-7-[(3R,4S)-3-((R)-1-amino-2-phenoxyethyl)-4-methylpyrrolidin-1-yl]-1-cyclopropyl-8-methoxy-1H-quinazoline-2,4-dione;

3-Amino-7-[(3R,4S)-3-((R)-1-amino-2-phenoxyethyl)-4-fluoropyrrolidin-1-yl]-1-cyclopropyl-6-fluoro-8-methoxy-1H-quinazoline-2,4-dione;

3-Amino-7-[(3R,4S)-3-((R)-1-amino-2-phenoxyethyl)-4-fluoropyrrolidin-1-yl]-1-cyclopropyl-8-methoxy-1H-quinazoline-2,4-dione;

3-Amino-7-[(R)-3-((S)-1-amino-2-phenoxyethyl)pyrrolidin-1-yl]-1-cyclopropyl-6-fluoro-8-methoxy-1H-quinazoline-2,4-dione;

3-Amino-7-[(R)-3-((S)-1-amino-2-phenoxyethyl)pyrrolidin-1-yl]-1-cyclopropyl-8-methoxy-1H-quinazoline-2,4-dione;

3-Amino-7-[(3R,4S)-3-((S)-1-amino-2-phenoxyethyl)-4-methylpyrrolidin-1-yl]-1-cyclopropyl-6-fluoro-8-methoxy-1H-quinazoline-2,4-dione;

3-Amino-7-[(3R,4S)-3-((S)-1-amino-2-phenoxyethyl)-4-methylpyrrolidin-1-yl]-1-cyclopropyl-8-methoxy-1H-quinazoline-2,4-dione;

3-Amino-7-[(3R,4S)-3-((S)-1-amino-2-phenoxyethyl)-4-fluoropyrrolidin-1-yl]-1-cyclopropyl-6-fluoro-8-methoxy-1H-quinazoline-2,4-dione;

3-Amino-7-[(3R,4S)-3-((S)-1-amino-2-phenoxyethyl)-4-fluoropyrrolidin-1-yl]-1-cyclopropyl-8-methoxy-1H-quinazoline-2,4-dione;

3-Amino-7-[(R)-4-((R)-1-amino-2-phenoxyethyl)-3,3-dimethylpyrrolidin-1-yl]-1-cyclopropyl-6-fluoro-8-methooxy-1H-quinazoline-2,4-dione;

3-Amino-7-[(R)-4-((R)-1-amino-2-phenoxyethyl)-3,3-dimethylpyrrolidin-1-yl]-1-cyclopropyl-8-methoxy-1H-quinazoline-2,4-dione;

3-Amino-7-[(R)-4-((S)-1-amino-2-phenoxyethyl)-3,3-dimethylpyrrolidin-1-yl]-1-cyclopropyl-6-fluoro-8-methoxy-1H-quinazoline-2,4-dione;

3-Amino-7-[(R)-4-((S)-1-amino-2-phenoxyethyl)-3,3-dimethylpyrrolidin-1-yl]-1-cyclopropyl-8-methoxy-1H-quinazoline-2,4-dione;

3-Amino-7-[(R)-3-((S)-1-amino-2-ethoxyethyl)pyrrolidin-1-yl]-1-cyclopropyl-6-fluoro-8-methoxy-1H-quinazoline-2,4-dione;

3-Amino-7-[(R)-3-((S)-1-amino-2-ethoxyethyl)pyrrolidin-1-yl]-1-cyclopropyl-8-methoxy-1H-quinazoline-2,4-dione;

3-Amino-7-[(R)-3-((R)-1-amino-2-ethoxyethyl)pyrrolidin-1-yl]-1-cyclopropyl-6-fluoro-8-methoxy-1H-quinazoline-2,4-dione;

3-Amino-7-[(R)-3-((R)-1-amino-2-ethoxyethyl)pyrrolidin-1-yl]-1-cyclopropyl-8-methoxy-1H-quinazoline-2,4-dione;

3-Amino-7-[(3R,4S)-3-((R)-1-amino-2-ethoxyethyl)-4-methylpyrrolidin-1-yl]-1-cyclopropyl-6-fluoro-8-methoxy-1H-quinazoline-2,4-dione;

3-Amino-7-[(3R,4S)-3-((R)-1-amino-2-ethoxyethyl)-4-methylpyrrolidin-1-yl]-1-cyclopropyl-8-methoxy-1H-quinazoline-2,4-dione;

3-Amino-7-[(3R,4S)-3-((R)-1-amino-2-ethoxyethyl)-4-fluoropyrrolidin-1-yl]-1-cyclopropyl-6-fluoro-8-methoxy-1H-quinazoline-2,4-dione;

3-Amino-7-[(3R,4S)-3-((R)-1-amino-2-ethoxyethyl)-4-fluoropyrrolidin-1-yl]-1-cyclopropyl-8-methoxy-1H-quinazoline-2,4-dione;

3-Amino-7-[(R)-4-((R)-1-amino-2-ethoxyethyl)-3,3-dimethylpyrrolidin-1-yl]-1-cyclopropyl-6-fluoro-8-methoxy-1H-quinazoline-2,4-dione;

3-Amino-7-[(R)-4-((R)-1-amino-2-ethoxyethyl)-3,3-dimethylpyrrolidin-1-yl]-1-cyclopropyl-8-methooxy-1H-quinazoline-2,4-dione;

3-Amino-7-[(3R,4R)-3-((S)-1-amino-2-ethoxyethyl)-4-methylpyrrolidin-1-yl]-1-cyclopropyl-6-fluoro-8-methoxy-1H-quinazoline-2,4-dione;

3-Amino-7-[(3R,4R)-3-((S)-1-amino-2-ethoxyethyl)-4-methylpyrrolidin-1-yl]-1-cyclopropyl-8-methoxy-1H-quinazoline-2,4-dione;

3-Amino-7-[(3R,4R)-3-((S)-1-amino-2-ethoxyethyl)-4-fluoropyrrolidin-1-yl]-1-cyclopropyl-6-fluoro-8-methoxy-1H-quinazoline-2,4-dione;

3-Amino-7-[(3R,4R)-3-((S)-1-amino-2-ethoxyethyl)-4-fluoropyrrolidin-1-yl]-1-cyclopropyl-8-methoxy-1H-quinazoline-2,4-dione;

3-Amino-7-[(R)-3-((S)-1-amino-3-methoxypropyl)pyrrolidin-1-yl]-1-cyclopropyl-6-fluoro-8-methoxy-1H-quinazoline-2,4-dione;

3-Amino-7-[(R)-3-((S)-1-amino-3-methoxypropyl)pyrrolidin-1-yl]-1-cyclopropyl-8-methoxy-1H-quinazoline-2,4-dione;

3-Amino-7-[(3R,4S)-3-((S)-1-amino-3-methoxypropyl)-4-methylpyrrolidin-1-yl]-1-cyclopropyl-6-fluoro-8-methoxy-1H-quinazoline-2,4-dione;

3-Amino-7-[(3R,4S)-3-((S)-1-amino-3-methoxypropyl)-4-methylpyrrolidin-1-yl]-1-cyclopropyl-8-methoxy-1H-quinazoline-2,4-dione;

3-Amino-7-[(3R,4S)-3-((S)-1-amino-3-methoxypropyl)-4-fluoropyrrolidin-1-yl]-1-cyclopropyl-6-fluoro-8-methoxy-1H-quinazoline-2,4-dione;

3-Amino-7-[(3R,4S)-3-((S)-1-amino-3-methoxypropyl)-4-fluoropyrrolidin-1-yl]-1-cyclopropyl-8-methoxy-1H-quinazoline-2,4-dione;

3-Amino-7-[(R)-3-((R)-1-amino-3-methoxypropyl)pyrrolidin-1-yl]-1-cyclopropyl-6-fluoro-8-methoxy-1H-quinazoline-2,4-dione;

3-Amino-7-[(R)-3-((R)-1-amino-3-methoxypropyl)pyrrolidin-1-yl]-1-cyclopropyl-8-methoxy-1H-quinazoline-2,4-dione;

3-Amino-7-[(3R,4R)-3-((R)-1-amino-3-methoxypropyl)-4-methylpyrrolidin-1-yl]-1-cyclopropyl-6-fluoro-8-methoxy-1H-quinazoline-2,4-dione;

3-Amino-7-[(3R,4R)-3-((R)-1-amino-3-methoxypropyl)-4-methylpyrrolidin-1-yl]-1-cyclopropyl-8-methoxy-1H-quinazoline-2,4-dione;

3-Amino-7-[(3R,4R)-3-((R)-1-amino-3-methoxypropyl)-4-fluoropyrrolidin-1-yl]-1-cyclopropyl-6-fluoro-8-methoxy-1H-quinazoline-2,4-dione;

-Amino-7-[(3R,4R)-3-((R)-1-amino-3-methoxypropyl)-4-fluoropyrrolidin-1-yl]-1-cyclopropyl-8-methoxy-1H-quinazoline-2,4-dione;

{(R)-2-Amino-2-[(R)-1-(3-amino-1-cyclopropyl-6-fluoro-8-methoxy-2,4-dioxo-1,2,3,4-tetrahydroquinazolin-7-yl)pyrrolidin-3-yl]ethyl}urea;

{(R)-2-Amino-2-[(R)-1-(3-amino-1-cyclopropyl-8-methoxy-2,4-dioxo-1,2,3,4-tetrahydroquinazolin-7-yl)pyrrolidin-3-yl]ethyl}urea;

{(S)-2-Amino-2-[(R)-1-(3-amino-1-cyclopropyl-6-fluoro-8-methoxy-2,4-dioxo-1,2,3,4-tetrahydroquinazolin-7-yl)pyrrolidin-3-yl]ethyl}urea;

{(S)-2-Amino-2-[(R)-1-(3-amino-1-cyclopropyl-8-methoxy-2,4-dioxo-1,2,3,4-tetrahydroquinazolin-7-yl)pyrrolidin-3-yl]ethyl}urea;

{(R)-2-Amino-2-[(3R,4S)-1-(3-amino-1-cyclopropyl-6-fluoro-8-methoxy-2,4-dioxo-1,2,3,4-tetrahydroquinazolin-7-yl)-4-methylpyrrolidin-3-yl]ethyl}urea;

{(R)-2-Amino-2-[(3R,4S)-1-(3-amino-1-cyclopropyl-8-methoxy-2,4-dioxo-1,2,3,4-tetrahydroquinazolin-7-yl)-4-methylpyrrolidin-3-yl]ethyl}urea;

{(S)-2-Amino-2-[(3R,4R)-1-(3-amino-1-cyclopropyl-6-fluoro-8-methoxy-2,4-dioxo-1,2,3,4-tetrahydroquinazolin-7-yl)-4-methylpyrrolidin-3-yl]ethyl}urea;

{(S)-2-Amino-2-[(3R,4R)-1-(3-amino-1-cyclopropyl-8-methoxy-2,4-dioxo-1,2,3,4-tetrahydroquinazolin-7-yl)-4-methylpyrrolidin-3-yl]ethyl}urea;

{2-Amino-2-[(1-(3-amino-1-cyclopropyl-6-fluoro-8-methoxy-2,4-dioxo-1,2,3,4-tetrahydroquinazolin-7-yl)-4-fluoropyrrolidin-3-yl]ethyl}urea;

{2-Amino-2-[(1-(3-amino-1-cyclopropyl-8-methoxy-2,4-dioxo-1,2,3,4-tetrahydroquinazolin-7-yl)-4-fluoropyrrolidin-3-yl]ethyl}urea;

{2-Amino-2-[(1-(3-amino-1-cyclopropyl-6-fluoro-8-methoxy-2,4-dioxo-1,2,3,4-tetrahydroquinazolin-7-yl)-4,4-dimethylpyrrolidin-3-yl]ethyl}urea;

{2-Amino-2-[(1-(3-amino-1-cyclopropyl-8-methoxy-2,4-dioxo-1,2,3,4-tetrahydroquinazolin-7-yl)-4,4-dimethylpyrrolidin-3-yl]ethyl}urea;

3-Amino-7-[3-(1-aminoethyl)-4-fluoropyrrolidin-1-yl]-1-cyclopropyl-8-methyl-1H-pyrido[4,3-d]pyrimidine-2,4-dione;

3-Amino-7-[3-(1-amino-1-methylethyl)-4-fluoropyrrolidin-1-yl]-1-cyclopropyl-8-methyl-1H-pyrido[4,3-d]pyrimidine-2,4-dione;

3-Amino-7-[3-(1-amino-2-methoxyethyl)-4-fluoropyrrolidin-1-yl]-1-cyclopropyl-8-methyl-1H-pyrido[4,3-d]pyrimidine-2,4-dione;

3-Amino-7-[3-(1-amino-2-methoxyethyl)-4-methylpyrrolidin-1-yl]-1-cyclopropyl-8-methyl-1H-pyrido[4,3-d]pyrimidine-2,4-dione;

3-Amino-7-[4-(1-amino-2-methoxyethyl)-3,3-dimethylpyrrolidin-1-yl]-1-cyclopropyl-8-methyl-1H-pyrido[4,3-d]pyrimidine-2,4-dione;

3-Amino-7-[3-(1-amino-2-phenoxyethyl)-pyrrolidin-1-yl]-1-cyclopropyl-8-methyl-1H-pyrido[4,3-d]pyrimidine-2,4-dione;

3-Amino-7-[3-(1-amino-2-phenoxyethyl)-4-methylpyrrolidin-1-yl]-1-cyclopropyl-8-methyl-1H-pyrido[4,3-d]pyrimidine-2,4-dione;

3-Amino-7-[3-(1-amino-2-phenoxyethyl)-4-fluoropyrrolidin-1-yl]-1-cyclopropyl-8-methyl-1H-pyrido[4,3-d]pyrimidine-2,4-dione;

3-Amino-7-[4-(1-amino-2-phenoxyethyl)-3,3-dimethylpyrrolidin-1-yl]-1-cyclopropyl-8-methyl-1H-pyrido[4,3-d]pyrimidine-2,4-dione;

3-Amino-7-[3-(1-amino-2-ethoxyethyl)pyrrolidin-1-yl]-1-cyclopropyl-8-methyl-1H-pyrido[4,3-d]pyrimidine-2,4-dione;

3-Amino-7-[3-(1-amino-2-ethoxyethyl)-4-methylpyrrolidin-1-yl]-1-cyclopropyl-8-methyl-1H-pyrido[4,3-d]pyrimidine-2,4-dione;

3-Amino-7-[3-(1-amino-2-ethoxyethyl)-4-fluoropyrrolidin-1-yl]-1-cyclopropyl-8-methyl-1H-pyrido[4,3-d]pyrimidine-2,4-dione;

3-Amino-7-[3-(1-amino-2-ethoxyethyl)-4,4-dimethylpyrrolidin-1-yl]-1-cyclopropyl-8-methyl-1H-pyrido[4,3-d]pyrimidine-2,4-dione;

3-Amino-7-[3-(1-amino-2-methoxypropyl)pyrrolidin-1-yl]-1-cyclopropyl-8-methyl-1H-pyrido[4,3-d]pyrimidine-2,4-dione;

3-Amino-7-[3-(1-amino-2-methoxypropyl)-4-methylpyrrolidin-1-yl]-1-cyclopropyl-8-methyl-1H-pyrido[4,3-d]pyrimidine-2,4-dione;

3-Amino-7-[3-(1-amino-2-methoxypropyl)-4-fluoropyrrolidin-1-yl]-1-cyclopropyl-8-methyl-1H-pyrido[4,3-d]pyrimidine-2,4-dione;

{2-Amino-2-[1-(3-amino-1-cyclopropyl-8-methyl-2,4-dioxo-1,2,3,4-tetrahydropyrido[4,3-d]pyrimidin-7-yl)pyrrolidin-3-yl]ethylurea;

{2-Amino-2-[1-(3-amino-1-cyclopropyl-8-methyl-2,4-dioxo-1,2,3,4-tetrahydropyrido[4,3-d]pyrimidin-7-yl)-4-methylpyrrolidin-3-yl]ethylurea;

{2-Amino-2-[1-(3-amino-1-cyclopropyl-8-methyl-2,4-dioxo-1,2,3,4-tetrahydropyrido[4,3-d]pyrimidin-7-yl)-4-fluoropyrrolidin-3-yl]ethylurea;

{2-Amino-2-[1-(3-amino-1-cyclopropyl-8-methyl-2,4-dioxo-1,2,3,4-tetrahydropyrido[4,3-d]pyrimidin-7-yl)-4,4-dimethylpyrrolidin-3-yl]ethylurea;

3-Amino-7-[3-(1-aminoethyl)-4-fluoropyrrolidin-1-yl]-1-cyclopropyl-6-fluoro-8-methyl-1H-pyrido[3,2-d]pyrimidine-2,4-dione;

3-Amino-7-[3-(1-aminoethyl)-4-fluoropyrrolidin-1-yl]-1-cyclopropyl-8-methyl-1H-pyrido[3,2-d]pyrimidine-2,4-dione;

3-Amino-7-[3-(1-amino-1-methylethyl)-4-fluoropyrrolidin-1-yl]-1-cyclopropyl-6-fluoro-8-methyl-1H-pyrido[3,2-d]pyrimidine-2,4-dione;

3-Amino-7-[3-(1-amino-1-methylethyl)-4-fluoropyrrolidin-1-yl]-1-cyclopropyl-8-methyl-1H-pyrido[3,2-d]pyrimidine-2,4-dione;

3-Amino-7-[3-(1-amino-2-methoxyethyl)-4-fluoropyrrolidin-1-yl]-1-cyclopropyl-6-fluoro-8-methyl-1H-pyrido[3,2-d]pyrimidine-2,4-dione;

3-Amino-7-[3-(1-amino-2-methoxyethyl)-4-fluoropyrrolidin-1-yl]-1-cyclopropyl-8-methyl-1H-pyrido[3,2-d]pyrimidine-2,4-dione;

3-Amino-7-[3-(1-amino-2-methoxyethyl)-4-methylpyrrolidin-1-yl]-1-cyclopropyl-6-fluoro-8-methyl-1H-pyrido[3,2-d]pyrimidine-2,4-dione;

3-Amino-7-[3-(1-amino-2-methoxyethyl)-4-methylpyrrolidin-1-yl]-1-cyclopropyl-8-methyl-1H-pyrido[3,2-d]pyrimidine-2,4-dione;

3-Amino-7-[4-(1-amino-2-methoxyethyl)-3,3-dimethylpyrrolidin-1-yl]-1-cyclopropyl-6-fluoro-8-methyl-1H-pyrido[3,2-d]pyrimidine-2,4-dione;

3-Amino-7-[4-(1-amino-2-methoxyethyl)-3,3-dimethylpyrrolidin-1-yl]-1-cyclopropyl-8-methyl-1H-pyrido[3,2-d]pyrimidine-2,4-dione;

3-Amino-7-[3-(1-amino-2-phenoxyethyl)pyrrolidin-1-yl]-1-cyclopropyl-6-fluoro-8-methyl-1H-pyrido[3,2-d]pyrimidine-2,4-dione;

3-Amino-7-[3-(1-amino-2-phenoxyethyl)pyrrolidin-1-yl]-1-cyclopropyl-8-methyl-1H-pyrido[3,2-d]pyrimidine-2,4-dione;

3-Amino-7-[3-(1-amino-2-phenoxyethyl)-4-methylpyrrolidin-1-yl]-1-cyclopropyl-6-fluoro-8-methyl-1H-pyrido[3,2-d]pyrimidine-2,4-dione;

3-Amino-7-[3-(1-amino-2-phenoxyethyl)-4-methylpyrrolidin-1-yl]-1-cyclopropyl-8-methyl-1H-pyrido[3,2-d]pyrimidine-2,4-dione;

3-Amino-7-[3-(1-amino-2-phenoxyethyl)-4-fluoropyrrolidin-1-yl]-1-cyclopropyl-6-fluoro-8-methyl-1H-pyrido[3,2-d]pyrimidine-2,4-dione;

3-Amino-7-[3-(1-amino-2-phenoxyethyl)-4-fluoropyrrolidin-1-yl]-1-cyclopropyl-8-methyl-1H-pyrido[3,2-d]pyrimidine-2,4-dione;

3-Amino-7-[4-(1-amino-2-phenoxyethyl)-3,3-dimethylpyrrolidin-1-yl]-1-cyclopropyl-6-fluoro-8-methyl-1H-pyrido[3,2-d]pyrimidine-2,4-dione;

3-Amino-7-[4-(1-amino-2-phenoxyethyl)-3,3-dimethylpyrrolidin-1-yl]-1-cyclopropyl-8-methyl-1H-pyrido[3,2-d]pyrimidine-2,4-dione;

3-Amino-7-[3-(1-amino-2-ethoxyethyl)pyrrolidin-1-yl]-1-cyclopropyl-6-fluoro-8-methyl-1H-pyrido[3,2-d]pyrimidine-2,4-dione;

3-Amino-7-[3-(1-amino-2-ethoxyethyl)pyrrolidin-1-yl]-1-cyclopropyl-8-methyl-1H-pyrido[3,2-d]pyrimidine-2,4-dione;

3-Amino-7-[3-(1-amino-2-ethoxyethyl)-4-methylpyrrolidin-1-yl]-1-cyclopropyl-6-fluoro-8-methyl-1H-pyrido[3,2-d]pyrimidine-2,4-dione;

3-Amino-7-[3-(1-amino-2-ethoxyethyl)-4-methylpyrrolidin-1-yl]-1-cyclopropyl-8-methyl-1H-pyrido[3,2-d]pyrimidine-2,4-dione;

3-Amino-7-[3-(1-amino-2-ethoxyethyl)-4-fluoropyrrolidin-1-yl]-1-cyclopropyl-6-fluoro-8-methyl-1H-pyrido[3,2-d]pyrimidine-2,4-dione;

3-Amino-7-[3-(1-amino-2-ethoxyethyl)-4-fluoropyrrolidin-1-yl]-1-cyclopropyl-8-methyl-1H-pyrido[3,2-d]pyrimidine-2,4-dione;

3-Amino-7-[3-(1-amino-2-ethoxyethyl)-4,4-dimethylpyrrolidin-1-yl]-1-cyclopropyl-6-fluoro-8-methyl-1H-pyrido[3,2-d]pyrimidine-2,4-dione;

3-Amino-7-[3-(1-amino-2-ethoxyethyl)-4,4-dimethylpyrrolidin-1-yl]-1-cyclopropyl-8-methyl-1H-pyrido[3,2-d]pyrimidine-2,4-dione;

3-Amino-7-[3-(1-amino-2-methoxypropyl)pyrrolidin-1-yl]-1-cyclopropyl-6-fluoro-8-methyl-1H-pyrido[3,2-d]pyrimidine-2,4-dione;

3-Amino-7-[3-(1-amino-2-methoxypropyl)pyrrolidin-1-yl]-1-cyclopropyl-8-methyl-1H-pyrido[3,2-d]pyrimidine-2,4-dione;

3-Amino-7-[3-(1-amino-2-methoxypropyl)-4-methylpyrrolidin-1-yl]-1-cyclopropyl-6-fluoro-8-methyl-1H-pyrido[3,2-d]pyrimidine-2,4-dione;

3-Amino-7-[3-(1-amino-2-methoxypropyl)-4-methylpyrrolidin-1-yl]-1-cyclopropyl-8-methyl-1H-pyrido[3,2-d]pyrimidine-2,4-dione;

3-Amino-7-[3-(1-amino-2-methoxypropyl)-4-fluoropyrrolidin-1-yl]-1-cyclopropyl-6-fluoro-8-methyl-1H-pyrido[3,2-d]pyrimidine-2,4-dione;

3-Amino-7-[3-(1-amino-2-methoxypropyl)-4-fluoropyrrolidin-1-yl]-1-cyclopropyl-8-methyl-1H-pyrido[3,2-d]pyrimidine-2,4-dione;

{2-Amino-2-[1-(3-amino-1-cyclopropyl-6-fluoro-8-methyl-2,4-dioxo-1,2,3,4-tetrahydropyrido[3,2-d]pyrimidin-7-yl)pyrrolidin-3-yl]ethylurea;

{2-Amino-2-[1-(3-amino-1-cyclopropyl-8-methyl-2,4-dioxo-1,2,3,4-tetrahydropyrido[3,2-d]pyrimidin-7-yl)pyrrolidin-3-yl]ethylurea;

{2-Amino-2-[1-(3-amino-1-cyclopropyl-6-fluoro-8-methyl-2,4-dioxo-1,2,3,4-tetrahydropyrido[3,2-d]pyrimidin-7-yl)-4-methylpyrrolidin-3-yl]ethylurea;

{2-Amino-2-[1-(3-amino-1-cyclopropyl-8-methyl-2,4-dioxo-1,2,3,4-tetrahydropyrido[3,2-d]pyrimidin-7-yl)-4-methylpyrrolidin-3-yl]ethylurea;

{2-Amino-2-[1-(3-amino-1-cyclopropyl-6-fluoro-8-methyl-2,4-dioxo-1,2,3,4-tetrahydropyrido[3,2-d]pyrimidin-7-yl)-4-fluoropyrrolidin-3-yl]ethylurea;

{2-Amino-2-[1-(3-amino-1-cyclopropyl-8-methyl-2,4-dioxo-1,2,3,4-tetrahydropyrido[3,2-d]pyrimidin-7-yl)-4-fluoropyrrolidin-3-yl]ethylurea;

{2-Amino-2-[1-(3-amino-1-cyclopropyl-6-fluoro-8-methyl-2,4-dioxo-1,2,3,4-tetrahydropyrido[3,2-d]pyrimidin-7-yl)-4,4-dimethylpyrrolidin-3-yl]ethylurea;

{2-Amino-2-[1-(3-amino-1-cyclopropyl-8-methyl-2,4-dioxo-1,2,3,4-tetrahydropyrido[3,2-d]pyrimidin-7-yl)-4,4-dimethylpyrrolidin-3-yl]ethylurea;

3-Amino-7-(3-aminomethylphenyl)-8-chloro-1-cyclopropyl-6-fluoro-1H-quinazoline-2,4-dione;

3-Amino-7-(3-aminomethylphenyl)-8-methyl-1-cyclopropyl-6-fluoro-1H-quinazoline-2,4-dione;

3-Amino-7-(3-aminomethylphenyl)-8-methoxy-1-cyclopropyl-6-fluoro-1H-quinazoline-2,4-dione;

3-Amino-7-(3-aminomethylphenyl)-8-chloro-1-cyclopropyl-1H-quinazoline-2,4-dione;

3-Amino-7-(3-aminomethylphenyl)-8-methyl-1-cyclopropyl-1H-quinazoline-2,4-dione;

3-Amino-7-(3-aminomethylphenyl)-8-methoxy-1-cyclopropyl-1H-quinazoline-2,4-dione;

3-Amino-7-(2-aminomethylthiazol-4-yl)-8-chloro-1-cyclopropyl-6-fluoro-1H-quinazoline-2,4-dione;

3-Amino-7-(2-aminomethylthiazol-4-yl)-8-methyl-1-cyclopropyl-6-fluoro-1H-quinazoline-2,4-dione;

3-Amino-7-(2-aminomethylthiazol-4-yl)-8-methoxy-1-cyclopropyl-6-fluoro-1H-quinazoline-2,4-dione;

3-Amino-7-(2-aminomethylthiazol-4-yl)-8-chloro-1-cyclopropyl-1H-quinazoline-2,4-dione;

3-Amino-7-(2-aminomethylthiazol-4-yl)-8-methyl-1-cyclopropyl-1H-quinazoline-2,4-dione;

3-Amino-7-(2-aminomethylthiazol-4-yl)-8-methoxy-1-cyclopropyl-1H-quinazoline-2,4-dione;

3-Amino-7-[2-(1-aminoethyl)thiazol-4-yl)-8-chloro-1-cyclopropyl-6-fluoro-1H-quinazoline-2,4-dione;

3-Amino-7-[2-(1-aminoethyl)thiazol-4-yl)-8-methyl-1-cyclopropyl-6-fluoro-1H-quinazoline-2,4-dione;

3-Amino-7-[2-(1-aminoethyl)thiazol-4-yl)-8-methoxy-1-cyclopropyl-6-fluoro-1H-quinazoline-2,4-dione;

3-Amino-7-[2-(1-aminoethyl)thiazol-4-yl)-8-chloro-1-cyclopropyl-1H-quinazoline-2,4-dione;

3-Amino-7-[2-(1-aminoethyl)thiazol-4-yl)-8-methyl-1-cyclopropyl-1H-quinazoline-2,4-dione;

3-Amino-7-[2-(1-aminoethyl)thiazol-4-yl)-8-methoxy-1-cyclopropyl-1H-quinazoline-2,4-dione;

3-Amino-7-(5-aminomethylthiophen-3-yl)-8-chloro-1-cyclopropyl-6-fluoro-1H-quinazoline-2,4-dione;

3-Amino-7-(5-aminomethylthiophen-3-yl)-8-methyl-1-cyclopropyl-6-fluoro-1H-quinazoline-2,4-dione;

3-Amino-7-(5-aminomethylthiophen-3-yl)-8-methoxy-1-cyclopropyl-6-fluoro-1H-quinazoline-2,4-dione;

3-Amino-7-(5-aminomethylthiophen-3-yl)-8-chloro-1-cyclopropyl-1H-quinazoline-2,4-dione;

3-Amino-7-(5-aminomethylthiophen-3-yl)-8-methyl-1-cyclopropyl-1H-quinazoline-2,4-dione;

3-Amino-7-(5-aminomethylthiophen-3-yl)-8-methoxy-1-cyclopropyl-1H-quinazoline-2,4-dione;

3-Amino-7-(4-aminomethyl-3,3-difluoropyrrolidin-1-yl)-8-chloro-1-cyclopropyl-6-fluoro-1H-quinazoline-2,4-dione;

3-Amino-7-(4-aminomethyl-3,3-difluoropyrrolidin-1-yl)-8-methyl-1-cyclopropyl-6-fluoro-1H-quinazoline-2,4-dione;

3-Amino-7-(4-aminomethyl-3,3-difluoropyrrolidin-1-yl)-8-methoxy-1-cyclopropyl-6-fluoro-1H-quinazoline-2,4-dione;

3-Amino-7-(4-aminomethyl-3,3-difluoropyrrolidin-1-yl)-8-chloro-1-cyclopropyl-1H-quinazoline-2,4-dione;

3-Amino-7-(4-aminomethyl-3,3-difluoropyrrolidin-1-yl)-8-methyl-1-cyclopropyl-1H-quinazoline-2,4-dione

3-Amino-7-(4-aminomethyl-3,3-difluoropyrrolidin-1-yl)-8-methoxy-1-cyclopropyl-1H-quinazoline-2,4-dione;

3-Amino-7-(4-(1-aminoethyl)-3,3-difluoropyrrolidin-1-yl)-8-chloro-1-cyclopropyl-6-fluoro-1H-quinazoline-2,4-dione;

3-Amino-7-(4-(1-aminoethyl)-3,3-difluoropyrrolidin-1-yl)-8-methyl-1-cyclopropyl-6-fluoro-1H-quinazoline-2,4-dione;

3-Amino-7-(4-(1-aminoethyl)-3,3-difluoropyrrolidin-1-yl)-8-methoxy-1-cyclopropyl-6-fluoro-1H-quinazoline-2,4-dione;

3-Amino-7-(4-(1-aminoethyl)-3,3-difluoropyrrolidin-1-yl)-8-chloro-1-cyclopropyl-1H-quinazoline-2,4-dione;

3-Amino-7-(4-(1-aminoethyl)-3,3-difluoropyrrolidin-1-yl)-8-methyl-1-cyclopropyl-1H-quinazoline-2,4-dione;

3-Amino-7-(4-(1-aminoethyl)-3,3-difluoropyrrolidin-1-yl)-8-methoxy-1-cyclopropyl-1H-quinazoline-2,4-dione;

3-Amino-7-(4-(1-amino-1-methylethyl)-3,3-difluoropyrrolidin-1-yl)-8-chloro-1-cyclopropyl-6-fluoro-1H-quinazoline-2,4-dione;

3-Amino-7-(4-(1-amino-1-methylethyl)-3,3-difluoropyrrolidin-1-yl)-8-methyl-1-cyclopropyl-6-fluoro-1H-quinazoline-2,4-dione;

3-Amino-7-(4-(1-amino-1-methylethyl)-3,3-difluoropyrrolidin-1-yl)-8-methoxy-1-cyclopropyl-6-fluoro-1H-quinazoline-2,4-dione;

3-Amino-7-(4-(1-amino-1-methylethyl)-3,3-difluoropyrrolidin-1-yl)-8-chloro-1-cyclopropyl-1H-quinazoline-2,4-dione;

3-Amino-7-(4-(1-amino-1-methylethyl)-3,3-difluoropyrrolidin-1-yl)-8-methyl-1-cyclopropyl-1H-quinazoline-2,4-dione;

3-Amino-7-(4-(1-amino-1-methylethyl)-3,3-difluoropyrrolidin-1-yl)-8-methoxy-1-cyclopropyl-1H-quinazoline-2,4-dione;

3-Amino-7-(3-(1-aminoethyl)pyrrolidin-1-yl)-1-cyclopropyl-6-fluoro-5,8-dimethyl-1H-quinazoline-2,4-dione;

3-Amino-7-(3-(1-aminoethyl)pyrrolidin-1-yl)-1-cyclopropyl-5,8-dimethyl-1H-quinazoline-2,4-dione;

3-Amino-7-(3-(1-aminoethyl)pyrrolidin-1-yl)-1-cyclopropyl-6-fluoro-8-methoxy-5-methyl-1H-quinazoline-2,4-dione;

3-Amino-7-(3-(1-aminoethyl)pyrrolidin-1-yl)-1-cyclopropyl-8-methoxy-5-methyl-1H-quinazoline-2,4-dione;

3,8-Diamino-7-[3-(1-aminoethyl)pyrrolidin-1-yl]-1-cyclopropyl-6-fluoro-5-methyl-1H-quinazoline-2,4-dione; and

3,8-Diamino-7-[3-(1-aminoethyl)pyrrolidin-1-yl]-1-cyclopropyl-5-methyl-1H-quinazoline-2,4-dione.

11. A pharmaceutical composition comprising a compound of Claim 1 admixed with a carrier, diluent, or excipient.

12. A pharmaceutical composition comprising a compound of Claim 2 admixed with a carrier, diluent, or excipient.

13. A pharmaceutical composition comprising a compound of Claim 3 admixed with a carrier, diluent, or excipient.

14. A pharmaceutical composition comprising a compound of Claim 4 admixed with a carrier, diluent, or excipient.

15. A pharmaceutical composition comprising a compound of Claim 5 admixed with a carrier, diluent, or excipient.

16. A pharmaceutical composition comprising a compound of Claim 6 admixed with a carrier, diluent, or excipient.

17. A pharmaceutical composition comprising a compound of Claim 7 admixed with a carrier, diluent, or excipient.

18. A pharmaceutical composition comprising a compound of Claim 10 admixed with a carrier, diluent, or excipient.

19. A method of treating a bacterial infection in a mammal comprising administering to the mammal an antibacterial effective amount of a compound of Claim 1.

20. A method of treating a bacterial infection in a mammal comprising administering to the mammal an antibacterial effective amount of a compound of Claim 2.

21. A method of treating a bacterial infection in a mammal comprising administering to the mammal an antibacterial effective amount of a compound of Claim 3.

22. A method of treating a bacterial infection in a mammal comprising administering to the mammal an antibacterial effective amount of a compound of Claim 4.

23. A method of treating a bacterial infection in a mammal comprising administering to the mammal an antibacterial effective amount of a compound of Claim 5.

24. A method of treating a bacterial infection in a mammal comprising administering to the mammal an antibacterial effective amount of a compound of Claim 6.

25. A method of treating a bacterial infection in a mammal comprising administering to the mammal an antibacterial effective amount of a compound of Claim 7.

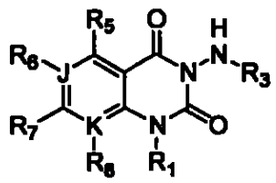
26. A method of treating a bacterial infection in a mammal comprising administering to the mammal an antibacterial effective amount of a compound of Claim 10.

27. A method of inhibiting a wild-type mutant of DNA gyrase in a mammal comprising administering to the mammal an effective amount of a compound of Claim 1.

28. A method of inhibiting a quinolone resistant mutant of DNA gyrase in a mammal comprising administering to the mammal an effective amount of a compound of Claim 1.

ABSTRACT

Antibacterial 3-aminoquinazolin-2,4-diones have the formula



wherein:

R_1 and R_3 include alkyl, alkenyl, alkynyl, cycloalkyl, aryl, heterocyclic, and heteroaryl;

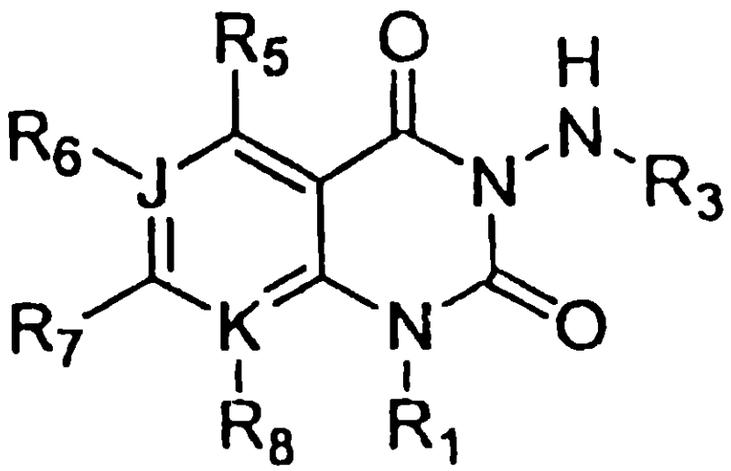
R_5, R_6, and R_8 include H, alkyl, alkoxy, halo, NO_2, CN, NH_2, alkyl and dialkylamino;

R_7 is hydrogen, alkyl, cycloalkyl, heterocyclic, fused heterocyclic, aryl and fused aryl;

J and K are C or N;

and pharmaceutically acceptable salts thereof.

NOTA: SE RETIRAN FOLIOS 731 Y 732. EXTRAVIO PARA PUBLICACIÓN Y 735. MITRE FINAL 12 X 12. 2020 26/IX/2021. LOS FOLIOS 733 Y 734 SON TARJETAS.


R5
O
H
N
R6
J
N
R3
R7
K
N
O
R8
R1

RC 733737

Industria y Comercio

SUPERINTENDENCIA

NIT : 899176087 2

737

2001-01-22

RECIBO OFICIAL DE CAJA : 2,664
FECHA : ENERO 22 DE 2001

***** C O N S I G N A C I O N *****

DEPOSITANTE	TIPO PAGO	BANCO	SUCURSAL	CUENTA	No. PAGO	Vr. PAGO
JUAN D. CEBALLEROS	CONSIGNACION	BANCO POPULAR	BOGOTA	050-00110 6	3047711	612,000.00

***** C O N C E P T O *****

CANT.	SECTISTICO	CONCEPTO	TOTAL CONCEPTO
1	50005-01-01 SOLICITUDES	1 TRAMITES DE SOL. DE PATENTE DE IN	600,000.00
		TOTAL : $	600,000.00

SON: SEISCIENTOS OCHO MIL PESOS

RESPONSABLE : _____

RECIBO DE CAJA APLICADO AL EXPEDIENTE No. _____

Carrera 13 No. 27-00 Pisos 5, 7 y 10
Conmutador: 382 0840
Fax: 350 5220
e-mail: info@sic.gov.co
www.sic.gov.co
Bogotá, D.C., Colombia

Industria y Comercio
SUPERINTENDENCIA

REQUISITOS MINIMOS PARA ADMISION A TRAMITE

PATENTE DE INVENCIÓN [ ] **MODELO DE UTILIDAD [ ]**

- Indicación de que se solicita la concesión de una patente [ ]
- Datos de identificación del solicitante o de la persona que presenta la solicitud [ ]
- Descripción de la invención [ ]
- Dibujos de ser estos pertinentes [ ]
- Comprobante de Pago de las tasas establecidas [ ]

COMPLETA [ ] INCOMPLETA [ ]

DISEÑO INDUSTRIAL [ ]

- Indicación de que se solicita el registro de Diseño Industrial [ ]
- Datos de identificación del solicitante o de la persona que presenta la solicitud. [ ]
- Representación gráfica y fotográfica del Diseño Industrial o muestra del material que incorpora el diseño . [ ]
- Comprobante de pago de las tasas establecidas. [ ]

COMPLETA [ ] INCOMPLETA [ ]

ESQUEMA DE TRAZADO [ ]

- Indicación de que se solicita el registro de un Esquema de trazado. [ ]
- Datos de identificación del solicitante o de la persona que presenta la solicitud. [ ]
- Representación gráfica del esquema de trazado [ ]
- Comprobante de pago de las tasas establecidas. [ ]

COMPLETA [ ] INCOMPLETA [ ]

Firma Responsable

Fecha:

Carrera 13 No. 27-00 Piso 5 y 10
Conmutador: 334 12 21-2-3-4
Fax: 281 31 25 e-mail: info@sic.gov.co
Santa Fe de Bogotá D.C. - Colombia

735

Industria y Comercio
SUPERINTENDENCIA

INFORME DE PROTOCOLO

Expediente 01-4183

Fecha: 27 de Marzo del 2001 .

Se certifica que:

Desde fecha 22 de octubre de 1997 ,
del folio 94.235 al folio 94.238 del
libro de Protocolo N° 323 , obra el
documento N° 17.877 conferido por
WARNER-LAMBERT COMPANY
domiciliado(a) en Morris Plains, New Jersey,
E.U.A.

al doctor DANIEL GOYTIA , quien a su vez
sustituye a "RODRIGUEZ Y ASOCIADOS" Y/O
RODOLFO RODRIGUEZ MADRID Y/O CARLOS JULIO
BUITRAGO GARZON Y/O MARINA RODRIUEZ MADRID

OBSERVACIONES: En el libro se encuentra protocolizada la la sustitución, pero no el poder concedido al abogado DANIEL GOYTIA por la sociedad arriba mencionada. Tampoco consta dentro del mismo la existencia y representanción legal de la sociedad. (8 de Agosto del 2000).

Carrera 13 No. 27-00 Pisos 5, 7 y 10
Conmutador: 382 0840
Fax: 382 2695
E-mail: info@sic.gov.co
Bogotá, D.C., Colombia