Industria y Comercio

SUPERINTENDENCIA

QT

SUPERINTENDENCIA DE INDUSTRIA Y COMERCIO
INVENTARIO

Delegatura de Propiedad Industrial
División de Nuevas Creaciones

PCT

SOLICITUD

PATENTE DE INVENCIÓN

21. **EXPEDIENTE No.** 10-580

54. **TÍTULO** Antagonistas no básicos del receptor de la hormona concentradora de melanina 1 y procedimientos

51. **CLASIFICACIÓN INTERNACIONAL**

71. **SOLICITANTE** Bristol-Myers Squibb Company

DOMICILIO Princeton, New Jersey, Estados Unidos

74. **APODERADO** Alvaro Correa Ordoñez

22. **BOGOTÁ, D.C.,** Enero 5 de 2.010

(FORMA P-10)

IV, Titulo, Cap I ó II
Fr 06-02-2010
No Cedular

PETITORIO

Industria y Comercio
SUPERINTENDENCIA

SUPERINTENDENCIA DE INDUSTRIA Y COMERCIO
No. 10-000580- -00000-0000
Fecha: 2010-01-05 16:23:40 Dep: 2020 DIR.NUEVASCR
Tra. 11 PATENTEIYII Eve: 378 FASENACIONALI
Act. 411 PRESENTACION Folios: 343

FORMULARIO ÚNICO DE SOLICITUD DE PATENTE
PCT
ENTRADA EN FASE NACIONAL

(1) SOLICITUD DE :

[X] Patente de Invención [ ] Patente de Modelo de Utilidad
[X] Capítulo I. [ ] Capítulo II.

(2) SOLICITANTE (71)

Nombre: **BRISTOL-MYERS SQUIBB COMPANY**
Dirección: Route 206 and Province Line Road Princeton, New Jersey 08543-4000 (US)
Nacionalidad o Domicilio: Estados Unidos de América
Lugar de Constitución: Estados Unidos de América
Teléfono: Fax:
E-Mail

IDENTIFICACION
C.C. [ ] NIT [ ]
C.E. [ ] Otro [ ]
Cual
Número

(3) REPRESENTANTE O APODERADO

Nombre: ALVARO CORREA ORDOÑEZ
Dirección: Avenida 82 No. 10-62 Piso 6
Teléfono: 6341500 Fax: 3762211
E-Mail: office.bogota@bakernet.com

IDENTIFICACION
C.C. [X] NIT [ ]
C.E. [ ] Otro [ ]
Cual
Número 79.143.366 Usaquén TP 20281

(4) INVENTOR (ES) (72)

Nombre: STEIN, Philip, D.; BISAHA, Sharon, N.; AHMAD, Saleem; NGU, Khehyong; WASHBURN, William, N.
Dirección: 3 Harbourton Ridge Drive, Pennington, New Jersey 08534, US; 38 Buttonwood Street, Lambertville, New Jersey 08530, US; c/o Bristol–Myers Squibb Company, Route 206 and Province Line Road Princeton, New Jersey 08543, US; c/o Bristol–Myers Squibb Company, Route 206 and Province Line Road Princeton, New Jersey 08543, US; c/o Bristol–Myers Squibb Company, 311 Pennington-Rocky Hill Road, Pennington, New Jersey 08534, US
Nacionalidad o Domicilio: Estados Unidos de América (Respectivamente)

(5) PCT (85)

Solicitud Internacional No. PCT/US2008/069361 Fecha 07-07-2009
Publicación Internacional No. WO 2009/009501 Fecha 15-01-2009

(6) Título (54) ANTAGONISTAS NO BASICOS DEL RECEPTOR DE LA HORMONA CONCENTRADORA DE MELANINA 1 Y PROCEDIMIENTOS

(7) Clasificación Internacional (51) C07D 241/18 , C07D 401/12

(8) Prioridad SI [X] NO [ ]

(33) País de Origen	(32) Fecha	(31) Número de Solicitud
US	06-07-2007	60/948,213
US	18-06-2008	12/141,228

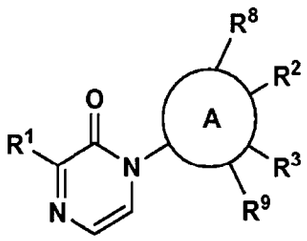
(9) Comprobante de pago No. EN HOJA ANEXA **Fecha** Enero 04, 2010

Instrucciones para el diligenciamiento del presente formulario, ver reverso de esta página

(10) **ANEXOS**

- [X] Comprobante de pago de la tasa de presentación de la solicitud
- [X] Documento que acredita la existencia y representación legal cuando el solicitante sea persona jurídica
- [X] Poderes, si fuere el caso Ver radicado No. 08 129.339 - Poder General BMS
- [ ] Documento de cesión del inventor al solicitante o a su causante
- [ ] Declaraciones
- [X] Copia de la solicitud internacional. (Resumen, descripción, reivindicaciones, dibujos)
- [X] Traducción de la solicitud internacional al castellano. (Resumen, descripción, reivindicaciones, dibujos)
- [X] Copia del examen preliminar internacional efectuado por la Autoridad Internacional de Examen preliminar (IPEA)
- [ ] Traducción del examen preliminar internacional efectuado por la IPEA
- [ ] De ser el caso, copia del contrato de acceso
- [ ] De ser el caso, documento que acredite la licencia o autorización de uso de conocimientos tradicionales de las comunidades indígenas
- [ ] De ser el caso, certificado de depósito del material biológico
- [X] Arte final 12 x 12
- [ ] De ser el caso, información sobre otras solicitudes de patente o títulos obtenidos en el extranjero por el mismo titular o su causante, relacionadas parcial o totalmente con la invención de esta solicitud
- [X] De ser el caso, modificaciones efectuadas a la solicitud internacional.
- [X] Otros: Extractos

(11) **FIGURA CARATERISTICA**



(I)

(12) Solicito la concesión de la patente,

NOMBRE: ALVARO CORREA ORDOÑEZ

FIRMA:

C.C. 79.143.366 de Usaquén T.P. 20.281

Instrucciones para la presentación de los anexos, ver reverso de esta página

9

2009/015

SUPERINTENDENCIA DE INDUSTRIA Y COMERCIO

NIT : 800176089-2

SUPERINTENDENCIA DE INDUSTRIA Y COMERCIO
No. 10-000580- -00000-0000
Fecha 2010-01-05 16:23:40 Dep. 2020 DIR.NUEVASCR
Tra. 11 PATENTEIYII Eve. 378 FASENACIONALI
Act. 411 PRESENTACION Folios: 343

RECIBO OFICIAL DE CAJA : 09 - 80,592
FECHA : OCTUBRE 26 DE 2009

***** C O N S I G N A C I O N *****

DEPOSITANTE	TIPO PAGO	BANCO	CUENTA	No. PAGO	FECHA PGO	Vr. PAGO
BAKER & MCKENZIE	CONSIGNACION	BANCO DE BOGOTA	062754387	121953904	26/10/2009	5[illegible],821,000.00

***** C O N C E P T O *****

CANT.	RENTISTICO	CONCEPTO		TOTAL CONCEPTO
1	50005-01-01 SOLICITUDES	85	EXAMEN DE PATENTABILIDAD DE INVEN	452,000.00
			TOTAL : $	452,000.00

SON: CUATROCIENTOS CINCUENTA Y DOS MIL PESOS

RESPONSABLE: _____

RECIBO DE CAJA APLICADO AL EXPEDIENTE No._____

10

2009/016

SUPERINTENDENCIA DE INDUSTRIA Y COMERCIO

NIT : 800176089-2

SUPERINTENDENCIA DE INDUSTRIA Y COMERCIO
No. 10-000580- -00000-0000
Fecha 2010-01-05 16:23:40 Dep 2020 DIR NUEVASCR
Tra 11 PATENTEIY!! Eve 378 FASENACIONALI
Act 411 PRESENTACION Folios: 343

RECIBO OFICIAL DE CAJA : 09 - 88,791
FECHA : NOVIEMBRE 25 DE 2009

***** C O N S I G N A C I O N *****

DEPOSITANTE	TIPO PAGO	BANCO	CUENTA	No. PAGO	FECHA PGO	Vr. PAGO
BAKER & MCKENZIE	CONSIGNACION	BANCO DE BOGOTA	062754387	53918196	25/11/2009	70,018,300.00

***** C O N C E P T O *****

CANT.	RENTISTICO	CONCEPTO	TOTAL CONCEPTO
1	50005-01-08 PRORROGA DE TERMINOS	31 PRORROGA DE TERMINOS	81,000.00
		TOTAL : $	81,000.00

SON: OCHENTA Y UNO MIL PESOS

RESPONSABLE : _____

RECIBO DE CAJA APLICADO AL EXPEDIENTE No._____

2009/016

SUPERINTENDENCIA DE INDUSTRIA Y COMERCIO

NIT : 800176089-2

CERTIFICACION DE EXCEDENTE : 09 - 88,718
FECHA : NOVIEMBRE 25 DE 2009

SUPERINTENDENCIA DE INDUSTRIA Y COMERCIO
No. 10-000580- -00000-0000
Fecha: 2010-01-05 16:23:40 Dep: 2020 DIR NULVASCR
Tra: 11 PATENTEIYII Eve: 378 FASENACIONALI
Act: 411 PRESENTACION Folios: 343

***** C O N S I G N A C I O N *****

DEPOSITANTE	TIPO PAGO	BANCO	CUENTA	No. PAGO	FECHA PGO	Vr. PAGO
BAKER & MCKENZIE	CONSIGNACION	BANCO DE BOGOTA	062754387	53918196	25/11/2009	70,018,300.00

***** C O N C E P T O *****

CANT.	RENTISTICO	CONCEPTO	TOTAL CONCEPTO
1	50005-01-09 OTROS SERVICIOS DE PROPIEDAD I	99 OTROS SERVCIOS ADMINISTRATIVOS	7,000.00
		TOTAL : $	7,000.00

N: SIETE MIL PESOS

RESPONSABLE : _____

RECIBO DE CAJA APLICADO AL EXPEDIENTE NO. _____

ESTA CERTIFICACION DE EXCEDENTE DE PAGO SOLO PODRA SER UTILIZADA COMO PARTE DE LA CANCELACION DE UNA TARIFA VIGENTE Y NO PODRA SER SUSTITUIDA POR NINGUN RECIBO.

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SUPERINTENDENCIA DE INDUSTRIA Y COMERCIO

NIT : 800176089-2

SUPERINTENDENCIA DE INDUSTRIA Y COMERCIO
No. 10-000580- -00000-0000
Fecha: 2010-01-05 16:23:40 Dep: 2020 DIR.NUEVASCR
Tra: 11 PATENTEIYII Eve: 378 FASLNACIONALI
Act: 411 PRESENTACION Folios: 343

RECIBO OFICIAL DE CAJA : 09 - 80,361
FECHA : OCTUBRE 26 DE 2009

***** C O N S I G N A C I O N *****

DEPOSITANTE	TIPO PAGO	BANCO	CUENTA	No. PAGO	FECHA PGO	Vr. PAGO
BAKER & MCKENZIE	CONSIGNACION	BANCO DE BOGOTA	062754387	121953904	26/10/2009	54,821,000.00

***** C O N C E P T O *****

CANT.	RENTISTICO	CONCEPTO	TOTAL CONCEPTO
1	50005-01-09 OTROS SERVICIOS DE PROPIEDAD I	21 CERTIFICACIONES	12,000.00
		TOTAL : $	12,000.00

SON: DOCE MIL PESOS

RESPONSABLE : _____

RECIBO DE CAJA APLICADO AL EXPEDIENTE No._____

13

2009 / 0 . .

SUPERINTENDENCIA DE INDUSTRIA Y COMERCIO

NIT : 800176089-

SUPERINTENDENCIA DE INDUSTRIA Y COMERCIO
No. 10-000580- -00000-0000
Fecha: 2010-01-05 16:23:40 Dep: 2020 DIR.NUEVASOR
Tra: 11 PATENTEIYII Eve: 378 FASENACIONALI
Act: 411 PRESENTACION Folios: 343

CERTIFICACION DE EXCEDENTE : 09 - 88,649
FECHA : NOVIEMBRE 25 DE 2009

***** C O N S I G N A C I O N *****

DEPOSITANTE	TIPO PAGO	BANCO	CUENTA	No. PAGO	FECHA PGO	Vr. PAGO
BAKER & MCKENZIE	CONSIGNACION	BANCO DE BOGOTA	062754387	53918196	25/11/2009	70,018,300.00

***** C O N C E P T O *****

CANT.	RENTISTICO	CONCEPTO	TOTAL CONCEPTO
1	50005-01-09 OTROS SERVICIOS DE PROPIEDAD I	99 OTROS SERVCIOS ADMINISTRATIVOS	2,000.00
		TOTAL : $	2,000.00

SON: DOS MIL PESOS

RESPONSABLE : _____

RECIBO DE CAJA APLICADO AL EXPEDIENTE No._____

ESTA CERTIFICACION DE EXCEDENTE DE PAGO SOLO PODRA SER UTILIZADA COMO PARTE DE LA CANCELACION DE UNA TARIFA VIGENTE Y NO PODRA SER SUSTITUIDA POR NINGUN RECIBO.

2009/016 84

SUPERINTENDENCIA DE INDUSTRIA Y COMERCIO

NIT : 800176089-2

SUPERINTENDENCIA DE INDUSTRIA Y COMERCIO
No. 10-000580- -00000-0000
Fecha 2010-01-05 16:23:40 Dep 2020 DIR NUEVASCR
Tra 11 PATENTEIYII Lve 378 FASENACIONALI
Act 411 PRESENTACION Folios 343

CERTIFICACION DE EXCEDENTE : 09 - 88,684
FECHA : NOVIEMBRE 25 DE 2009

***** C O N S I G N A C I O N *****

DEPOSITANTE	TIPO PAGO	BANCO	CUENTA	No. PAGO	FECHA PGO	Vr. PAGO
BAKER & MCKENZIE	CONSIGNACION	BANCO DE BOGOTA	062754387	53918196	25/11/2009	70,018,300.00

***** C O N C E P T O *****

CANT.	RENTISTICO	CONCEPTO	TOTAL CONCEPTO
1	50005-01-09 OTROS SERVICIOS DE PROPIEDAD I	99 OTROS SERVCIOS ADMINISTRATIVOS	4,000.00
		TOTAL : $	4,000.00

SON: CUATRO MIL PESOS

RESPONSABLE : _____

RECIBO DE CAJA APLICADO AL EXPEDIENTE No._____

ESTA CERTIFICACION DE EXCEDENTE DE PAGO SOLO PODRA SER UTILIZADA COMO PARTE DE LA CANCELACION DE UNA TARIFA VIGENTE Y NO PODRA SER SUSTITUIDA POR NINGUN RECIBO.

2009/014

SUPERINTENDENCIA DE INDUSTRIA Y COMERCIO

NIT : 800176089-2

SUPERINTENDENCIA DE INDUSTRIA Y COMERCIO
No. 10-000580- -00000-0000
Fecha 2010-01-05 16:23:40 Dep 2020 DIR NUEVASCR
Tra 11 PATENTEIYII Lve 378 FASENACIONALI
Act 411 PRESENTACION Folios: 343

CERTIFICACION DE EXCEDENTE : 09 - 72,802
FECHA : SEPTIEMBRE 28 DE 2009

***** C O N S I G N A C I O N *****

DEPOSITANTE	TIPO PAGO	BANCO	CUENTA	No. PAGO	FECHA PGO	Vr. PAGO
BAKER & MCKENZIE	CONSIGNACION	BANCO DE BOGOTA	062754387	45078143	28/09/2009	97,587,500.00

***** C O N C E P T O *****

CANT.	RENTISTICO	CONCEPTO	TOTAL CONCEPTO
1	50005-01-09 OTROS SERVICIOS DE PROPIEDAD I	99 OTROS SERVCIOS ADMINISTRATIVOS	32,000.00
		TOTAL : $	32,000.00

SON: TREINTA Y DOS MIL PESOS

RESPONSABLE : _____

RECIBO DE CAJA APLICADO AL EXPEDIENTE No._____

ESTA CERTIFICACION DE EXCEDENTE DE PAGO SOLO PODRA SER UTILIZADA COMO PARTE DE LA CANCELACION DE UNA TARIFA VIGENTE Y NO PODRA SER SUSTITUIDA POR NINGUN RECIBO.

SUPERINTENDENCIA DE INDUSTRIA Y COMERCIO

2009/014

NIT : 800176089-2

CERTIFICACION DE EXCEDENTE : 09 - 72,803
FECHA : SEPTIEMBRE 28 DE 2009

SUPERINTENDENCIA DE INDUSTRIA Y COMERCIO
No. 10-000580- -00000-0000
Fecha: 2010-01-05 16:23:40 Dep: 2020 DIR.NUEVASCR
Tra: 11 PATENTLIYII Lve: 378 FASENACIONALI
Act: 411 PRESENTACION Folios: 343

***** C O N S I G N A C I O N *****

DEPOSITANTE	TIPO PAGO	BANCO	CUENTA	No. PAGO	FECHA PGO	Vr. PAGO
BAKER & MCKENZIE	CONSIGNACION	BANCO DE BOGOTA	062754387	45078143	28/09/2009	97,587,500.00

***** C O N C E P T O *****

CANT.	RENTISTICO	CONCEPTO	TOTAL CONCEPTO
1	50005-01-09 OTROS SERVICIOS DE PROPIEDAD I	99 OTROS SERVCIOS ADMINISTRATIVOS	32,000.00
		TOTAL : $	32,000.00

SON: TREINTA Y DOS MIL PESOS

RESPONSABLE : _____

RECIBO DE CAJA APLICADO AL EXPEDIENTE No._____

ESTA CERTIFICACION DE EXCEDENTE DE PAGO SOLO PODRA SER UTILIZADA COMO PARTE DE LA CANCELACION DE UNA TARIFA VIGENTE Y NO PODRA SER SUSTITUIDA POR NINGUN RECIBO.

2009/016

16

SUPERINTENDENCIA DE INDUSTRIA Y COMERCIO

NIT : 800176089-2

SUPERINTENDENCIA DE INDUSTRIA Y COMERCIO
No. 10-000580- -00000-0000
Fecha 2010-01-05 16:23:40 Dep: 2020 DIR.NUEVASCR
Tra: 11 PATENTEIYII Eve: 378 FASENACIONALI
Act: 411 PRESENTACION Folios: 343

RECIBO OFICIAL DE CAJA : 09 - 88,855
FECHA : NOVIEMBRE 25 DE 2009

***** C O N S I G N A C I O N *****

DEPOSITANTE	TIPO PAGO	BANCO	CUENTA	No. PAGO	FECHA PGO	Vr. PAGO
BAKER & MCKENZIE	CONSIGNACION	BANCO DE BOGOTA	062754387	53918196	25/11/2009	70,018,300.00

***** C O N C E P T O *****

CANT.	RENTISTICO	CONCEPTO		TOTAL CONCEPTO
1	50005-01-01 SOLICITUDES	85	EXAMEN DE PATENTABILIDAD DE INVEN	452,000.00
			TOTAL : $	452,000.00

SON: CUATROCIENTOS CINCUENTA Y DOS MIL PESOS

RESPONSABLE : _____

RECIBO DE CAJA APLICADO AL EXPEDIENTE No._____

Industria y Comercio

SUPERINTENDENCIA

SUPERINTENDENCIA DE INDUSTRIA Y COMERCIO
DIVISION DE NUEVAS CREACIONES
TARJETA ARCHIVO PROPIETARIOS

PATENTE DE INVENCION ____ PCT X MODELO DE UTILIDAD ____ DISEÑO INDUSTRIAL ____

(21) N° de solicitud: (22) Fecha de solicitud:

(51) Clasificación Internacional : C07D 241/18 , C07D 401/12

(71)Solicitante(s) **BRISTOL-MYERS SQUIBB COMPANY**

(72) Inventor(es) STEIN, Philip, D.; BISAHA, Sharon, N.; AHMAD, Saleem; NGU, Khehyong; WASHBURN, William, N.

(74) Apoderado: ALVARO CORREA ORDOÑEZ

(30) Prioridad	(31) *No. Prioridad*	32) *Fecha*	(33) *País*
	60/948,213	06-07-2007	US
	12/141,228	18-06-2008	US

(85) Fecha inicio fase nacional: 06-02-2010

(86) Datos relativos a la presentación de la solicitud PCT
Fecha de presentación de la solicitud: 07-07-2009
No. de solicitud PCT/US2008/069361

(87) Publicación internacional
Fecha: 15-01-2009
N° publicación: WO 2009/009501

(54) Titulo: ANTAGONISTAS NO BASICOS DEL RECEPTOR DE LA HORMONA CONCENTRADORA DE MELANINA 1 Y PROCEDIMIENTOS

Industria y Comercio
SUPERINTENDENCIA

SUPERINTENDENCIA DE INDUSTRIA Y COMERCIO
DIVISION DE NUEVAS CREACIONES
TARJETA ARCHIVO TEMATICO

PATENTE DE INVENCION ____ PCT _X_ MODELO DE UTILIDAD ____ DISEÑO INDUSTRIAL ___

(21) N° de solicitud: (22) Fecha de solicitud:

(51) Clasificación Internacional : C07D 241/18 , C07D 401/12

(71)Solicitante(s) **BRISTOL-MYERS SQUIBB COMPANY**

(72) Inventor(es) STEIN, Philip, D.; BISAHA, Sharon, N.; AHMAD, Saleem; NGU, Khehyong; WASHBURN, William, N.

(74) Apoderado: ALVARO CORREA ORDOÑEZ

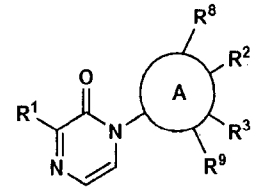
(30) Prioridad

(31) *No. Prioridad*	32) *Fecha*	(33) *País*
60/948,213	06-07-2007	US
12/141,228	18-06-2008	US

(85) Fecha límite inicio fase nacional: 06-02-2010

(86) Datos relativos a la presentación de la solic. PCT
Fecha de presentación de la solicitud: 07-07-2009
No. de solicitud PCT/US2008/069361

(87) Publicación internacional:
Fecha: 15-01-2009
No. Publicación : WO 2009/009501

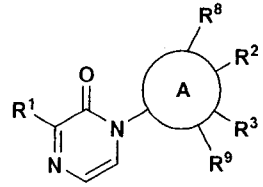


(I)

(54) Titulo:

ANTAGONISTAS NO BASICOS DEL RECEPTOR DE LA HORMONA CONCENTRADORA DE MELANINA 1 Y PROCEDIMIENTOS

(57) Resumen: La presente solicitud proporciona compuestos, incluyendo todos los estereoisómeros, solvatos, profármacos y formas farmacéuticamente aceptables de los mismos de acuerdo con la Fórmula I



I

CONTINUA AL RESPALDO ...

en la que  , R^1, R^2, R^3, R^8, y R^9 se definen en la presente memoria.

Además, la presente solicitud proporciona composiciones farmacéuticas que contienen al menos un compuesto de acuerdo con la Fórmula I y opcionalmente al menos un agente terapéutico adicional. Finalmente, la presente solicitud proporciona procedimientos para tratar a un paciente que padece de una enfermedad o trastorno modulado por MCHR-1 tal como, por ejemplo, obesidad, diabetes, depresión o ansiedad, mediante la administración de una dosis terapéuticamente eficaz de un compuesto de acuerdo con la Fórmula I.

Industria y Comercio
SUPERINTENDENCIA

SUPERINTENDENCIA DE INDUSTRIA Y COMERCIO
DIVISION DE NUEVAS CREACIONES
EXTRACTO PARA PUBLICACIÓN
SOLICITUD DE PATENTE DE INVENCIÓN PCT

(21) N° de solicitud:

22) Fecha de solicitud:

(30) Prioridad

(31) No.	32) Fecha	(33) País
60/948,213	06-07-2007	US
12/141,228	18-06-2008	US

(51) Int Cl: C07D 241/18 , C07D 401/12

(71)Solicitante(s) **BRISTOL-MYERS SQUIBB COMPANY**

(72) Inventor(es) STEIN, Philip, D.; BISAHA, Sharon, N.; AHMAD, Saleem; NGU, Khehyong; WASHBURN, William, N.

(74) Apoderado: **ALVARO CORREA ORDOÑEZ**

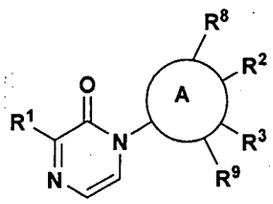
(85) Fecha limite inicio fase nacional: 06-02-2010

(86) Datos relativos a la presentación de la solicitud PCT
Fecha de presentación de la solicitud: 07-07-2009
No. de solicitud PCT/US2008/069361

(87) Publicación internacional
Fecha: 15-01-2009
N° publicación: WO 2009/009501

(54) Titulo: ANTAGONISTAS NO BASICOS DEL RECEPTOR DE LA HORMONA CONCENTRADORA DE MELANINA 1 Y PROCEDIMIENTOS

Reivindicación(es): 1. Un compuesto de Fórmula I o una sal farmacéuticamente aceptable del mismo

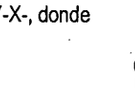


I

donde

(A) es un anillo fenileno o un anillo heteroarilo que contiene uno o dos átomos de nitrógeno o un átomo de oxígeno;

R^1 es Z-Y-X-, donde

X es O, S,  ;

Y es un enlace, un cicloalquilo de 3 a 6 miembros o una cadena alquilo; y

Z es arilo o heteroarilo;

R^2 es -E-G-$(J)_m$, donde m es un número entero de 1 a 3;

E es O, S o un enlace;

G es alquilo inferior, fenilalquilo, cicloalquilo, cicloalquilalquilo, alquilcicloalquilo, cicloalcoxi, alquilcicloalcoxi o cicloalcoxialquilo, y

cada J es independientemente hidrógeno, hidroxilo, CN, $-SO_2R^7$, $-SR^7$, $-SOR^7$, alquilo inferior, alcoxi inferior, CF_3, CF_3O-, $-COOR^5$ o $-CONR^{5a}R^6$, donde cada uno de R^{5a} y R^6 se selecciona independientemente entre el grupo constituido por H, alquilo C_{1-3} y cicloalquilo, o R^{5a} y R^6 tomados juntos pueden ser propanodiilo, butanodiilo o pentanodiilo con el átomo de N al que están unidos para formar una amina cíclica de 4, 5 ó 6 miembros que puede estar opcionalmente sustituida;

R^5 es H, alquilo C_{1-6} o cicloalquilo;

R^7 es alquilo inferior; y

R^3 es alquilo C_{1-6}, cicloalquilo, alcoxi C_{1-6}, halógeno, hidrógeno, -S-alquilo C_{1-6}, CN, CF_3O o CF_3;

y donde R^2 y R^3 pueden tomarse juntos para formar un anillo de 5 a 7 miembros que está saturado o parcialmente insaturado y puede incluir opcionalmente un heteroátomo E que es O o 0, 1 ó 2 átomos de N, donde el anillo está sustituido con uno o dos grupos -O-G-$(J)_m$, donde al menos un J es OH, y que puede estar opcionalmente sustituido con otros sustituyentes como los indicados para "alquilo" o "heteroarilo";

con la condición de que cuando (A) es un grupo fenileno, E-G y R^3 no sean grupos alcoxi inferior no sustituidos iguales, y cuando G es alquilo inferior y J es H, R^3 no sea hidrógeno; y

cada uno de R^8 y R^9 es independientemente hidrógeno, halógeno o alquilo inferior;
incluyendo ésteres de los mismos, profármacos de los mismos, solvatos de los mismos y todos los estereoisómeros de los mismos.

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(71) Applicant *(for all designated States except US)*: **BRISTOL-MYERS SQUIBB COMPANY** [US/US]; Route 206 and Province Line Road, Princeton, New Jersey 08543-4000 (US).

(72) Inventors; and
(75) Inventors/Applicants *(for US only)*: **STEIN, Philip, D.** [US/US]; 3 Harbourton Ridge Drive, Pennington, New Jersey 08534 (US). **BISAHA, Sharon, N.** [US/US]; 38 Buttonwood Street, Lambertville, New Jersey 08530 (US). **AHMAD, Saleem** [US/US]; c/o Bristol-Myers Squibb Company, Route 206 and Province Line Road, Princeton, New Jersey 08543 (US). **NGU, Khehyong** [US/US]; c/o Bristol-Myers Squibb Company, Route 206 and Province Line Road, Princeton, New Jersey 08543 (US). **WASHBURN, William, N.** [US/US]; c/o Bristol-Myers Squibb Company, 311 Pennington-Rocky Hill Road, Pennington, New Jersey 08534 (US).

(74) Agents: **RODNEY, Burton** et al.; Bristol-Myers Squibb Company, P.O. Box 4000, Princeton, New Jersey 08543-4000 (US).

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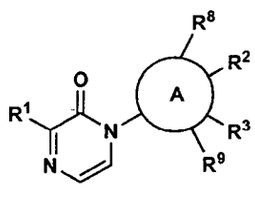
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(54) Title: NON-BASIC MELANIN CONCENTRATING HORMONE RECEPTOR-1 ANTAGONISTS AND METHODS



(I)

(57) Abstract: The present application provides compounds, including all stereoisomers, solvates, prodrugs and pharmaceutically acceptable forms thereof according to Formula I, wherein, R1, R2, R3, R8, and R9 are defined herein. Additionally, the present application provides pharmaceutical compositions containing at least one compound according to Formula I and optionally at least one additional therapeutic agent. Finally, the present application provides methods for treating a patient suffering from an MCHR-1 modulated disease or disorder such as, for example, obesity, diabetes, depression or anxiety by administration of a therapeutically effective dose of a compound according to Formula I.

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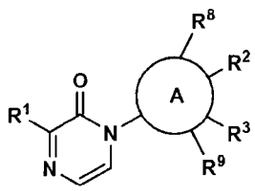
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(54) Title: NON-BASIC MELANIN CONCENTRATING HORMONE RECEPTOR-1 ANTAGONISTS AND METHODS



(I)

(57) Abstract: The present application provides compounds, including all stereoisomers, solvates, prodrugs and pharmaceutically acceptable forms thereof according to Formula I, wherein, R1, R2, R3, R8, and R9 are defined herein. Additionally, the present application provides pharmaceutical compositions containing at least one compound according to Formula I and optionally at least one additional therapeutic agent. Finally, the present application provides methods for treating a patient suffering from an MCHR-1 modulated disease or disorder such as, for example, obesity, diabetes, depression or anxiety by administration of a therapeutically effective dose of a compound according to Formula I.

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NON-BASIC MELANIN CONCENTRATING HORMONE RECEPTOR-1 ANTAGONISTS AND METHODS

FIELD OF THE INVENTION

[0001] The present invention relates to non-basic melanin concentrating hormone receptor-1 (MCHR1) antagonists, pharmaceutical compositions containing MCHR1 antagonists and methods of treating diabetes, obesity and related diseases employing such MCHR1 antagonists.

BACKGROUND OF THE INVENTION

[0002] Several lines of pharmacological and genetic evidence support the role of Melanin Concentrating Hormone Receptor-1 (hereafter "MCHR1") as a modulator of food intake and body weight. Central administration of melanin concentrating hormone (MCH) increases food intake and body weight both in rats and in mice. Chronic ICV infusion of MCH causes increased food intake and ultimately obesity in mice, while infusion of an MCH peptide antagonist blocks MCH-induced food intake and results in weight loss and decreased feeding in diet-induced obese mice.

[0003] The expression of both the MCH peptide and receptor are modulated by nutritional status. MCH mRNA is upregulated both in hyperphagic obese mice (ob/ob), and fasted animals. Targeted disruption of the gene for MCH peptide results in hypophagia and leanness. Disruption of the MCHR1 gene causes leanness, altered metabolism, and hyperlocomotion accompanied by mild hyperphagia. Conversely, over-expression of MCH peptide results in hyperphagia, obesity and diabetes. Small molecule MCHR1 antagonists have been shown to cause weight loss in rodent weight and feeding models after both oral and intraperitoneal administration; *Eur. J. Pharmacol.*, 438:129-135 (2002), *Nat. Med.*, 8:825-830 (2002), *Eur. J. Pharmacol.*, 497:41-47 (2004).

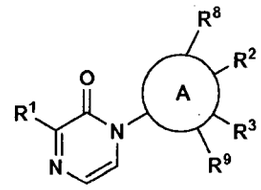
[0004] Numerous non-peptide MCHR1 antagonists have been disclosed. The scope of the genus for each reflects a common perception regarding the criteria required for ligand recognition as MCHR1 agonists. A recent review of MCHR1 patent disclosures emphasized the commonality of these structures by the following description; "Ubiquitous throughout the MCH patent literature are molecules

consisting of a central scaffold to which linkers to an aryl or heteroaryl group and a basic amino functionality are attached." (Kowalski, T.J. et al., *Expert Opin. Investig. Drugs*, 13:1113-1122 (2004)). Pharmacophore models of these geni consistently envision a presumed prerequisite electrostatic interaction between a basic amine center of the antagonist ligand and aspartic acid 123 of the receptor which presumably is envisaged to emulate the mandatory interaction between arginine 14 of MCH peptide agonists with aspartic acid 123 of the MCHR1 receptor. (Ulven, T., *J. Med. Chem.*, 48:5684-5697 (2005)) However, incorporation of this basic amine in a MCHR1 antagonist increases substantially the probability of binding to off-target ion-channels and biogenic amine receptors.

[0005] In accordance with the present invention, there is provided a series of novel high affinity selective MCHR1 antagonists for which binding affinity is not dependent upon inclusion of a basic amine functionality that is common to most of the disclosed MCHR antagonists. As a consequence, the absence of the basic center greatly reduces the probability of off-target interactions such as binding to other biogenic amine receptors as well as binding to ion channels such as the HERG receptor in the heart. The reduction/abolition of affinity for the HERG receptor is especially important since ligand occupancy is associated with initiation of fatal arrhythmias.

SUMMARY OF THE INVENTION

[0006] In one embodiment of the present invention, a compound of the Formula I or a pharmaceutically acceptable salt thereof is provided



I

wherein

(A) is a phenylene ring or a heteroaryl ring which is a monocyclic ring or a bicyclic ring which contains one or two nitrogen atoms or one oxygen atom;

R^1 is Z-Y-X-; wherein

X is O, S, , or  ;

Y is a bond, a 3- to 6-membered cycloalkyl, or an alkyl chain; and

Z is aryl such as phenyl and naphthyl, or heteroaryl such as pyridinyl, pyridimidinyl, pyrazinyl, benzimidazolyl, benzothiazolyl, benzoxazolyl, or other "heteroaryl";

R^2 is -E-G-$(J)_m$, with m being an integer from 1 to 3;

E is O, S, or a bond;

G is lower alkyl, phenylalkyl, cycloalkyl, cycloalkylalkyl, alkylcycloalkyl, cycloalkoxy, alkylcycloalkoxy, or cycloalkoxyalkyl;

each J is independently hydrogen, hydroxyl, CN, $-SO_2R^7$, $-SR^7$, $-SOR^7$, lower alkyl, lower alkoxy, CF_3, CF_3O-, $-COOR^5$ (wherein R^5 is H, C_{1-3} alkyl, or cycloalkyl), or $-CO-NR^{5a}R^6$ wherein R^{5a} and R^6 are each independently selected from H, C_{1-3} alkyl, or cycloalkyl, or R^{5a} and R^6 taken together can be propanediyl, butanediyl or pentanediyl to form with the N atom to which they are attached a 4-, 5- or 6-membered cyclic amine, such as azetidinyl, pyrrolidinyl, piperidinyl, morpholinyl, or piperazinyl, optionally substituted with substituents as set out for "heterocyclo";

R^7 is lower alkyl;

R^3 is C_{1-6} alkyl, cycloalkyl ,C_{1-6} alkoxy, halogen, hydrogen, -S-C_{1-6} alkyl, CN, CF_3O, or CF_3;

and wherein R^2 and R^3 can be taken together to form a 5- to 7-membered ring which is saturated, unsaturated, or partially unsaturated and may include an E heteroatom, which is O, or 0, 1 or 2 N atoms, which ring is substituted with one or two of -O-G-$(J)_m$ groups, wherein at least one J is OH, and optionally other substituents as set out for "alkyl", "aryl", or "heteroaryl", such as alkyl and/or OH;

with the proviso that where is a phenylene ring, E-G and R^3 are not identical unsubstituted lower alkoxy groups, and when G is lower alkyl and J is H, R^3 is not hydrogen; and

R^8 and R^9 are each independently hydrogen, halogen, or lower alkyl;

including esters thereof, prodrugs thereof, solvates thereof, and all stereoisomers thereof.

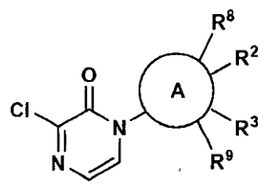
[0007] Any of the foregoing Z moieties may either be unsubstituted or substituted with 1, 2 or 3 of amino, halo, C_{1-6} alkyl, C_{1-3} alkylamino, di-C_{1-3} alkylamino, C_{1-3} alkoxy, C_{1-3} thioalkyl, C_{1-3} trifluoroalkoxy, trifluoromethyl, cycloalkyl, cycloalkoxy, or heteroaryl such as pyridyl or substituted with any of the substituents as set out for "aryl", "heteroaryl", or "alkyl".

[0008] Examples of substituents for the J group in the form of a cyclic amine include but are not limited to lower alkyl, lower alkoxy, OH, CF_3, or CF_3O, or other substituents as set out for "alkyl" and "heteroaryl".

[0009] In a further aspect of the invention, there is provided a pharmaceutical composition which contains a therapeutically effective amount of the compound of the invention Formula I as defined above, in association with a pharmaceutically acceptable carrier or diluent.

[0010] There is also provided a method for the treatment of diabetes, obesity and other related conditions involving the MCHR1 in a mammal (such as a human, dog or cat) in need thereof, which includes the steps of administering to the mammal a therapeutically effective amount of the compound of Formula I of the invention as defined above.

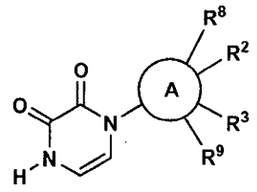
[0011] The invention also sets forth one or more methods for making the compound of Formula I of the invention. In one embodiment, there is provided a process for the preparation of the compound of Formula I of the invention, wherein the compound **a**



a

is reacted with the alkali metal salt of Z-Y-X^1H (**b**) (X^1 = O or S), preferably Z-$(CH_2)_n$-X^1H (n = 0, 1, 2 or 3).

[0012] In another embodiment of the invention, there is provided a process for the preparation of the compound of Formula I of the invention, wherein the compound **c**



c

is reacted with Z-Y-X^1H (**b**), preferably Z-$(CH_2)_n$-X^1H (n = 0, 1, 2 or 3), and preferably in the presence of an activating agent.

[0013] The present invention is directed to these, as well as other important ends, hereinafter described.

DETAILED DESCRIPTION OF THE INVENTION

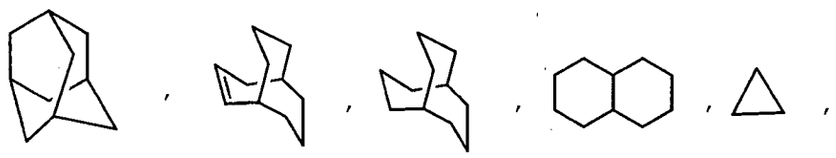
[0014] The present application provides compounds, including all stereoisomers, solvates, prodrugs and pharmaceutically acceptable forms thereof according to Formula I. Additionally, the present application provides pharmaceutical compositions containing at least one compound according to Formula I of the invention alone and optionally at least one additional therapeutic agent. Finally, the present application provides methods for treating a patient suffering from an MCHR-1 modulated disease or disorder such as, for example, obesity, diabetes, depression or anxiety by administration of a therapeutically effective dose of a compound according to Formula I of the invention as defined above.

DEFINITIONS

[0015] Unless otherwise indicated, the term "lower alkyl" as may be employed herein alone or as part of another group includes both straight and branched chain hydrocarbons containing 1 to 8 carbons, and the terms "alkyl", "alk", "alkyl chain", "alkylene", or "alkylene chain" as may be employed herein alone or as part of another group includes both straight and branched chain hydrocarbons containing 1 to 20 carbons, preferably 1 to 10 carbons, more preferably 1 to 8 carbons, in the normal chain, such as methyl, ethyl, propyl, isopropyl, butyl, *t*-butyl, isobutyl, pentyl, hexyl, isohexyl, heptyl, 4,4-dimethylpentyl, octyl, 2,2,4-trimethylpentyl, nonyl, decyl,

undecyl, dodecyl, the various branched chain isomers thereof, and the like as well as such groups including 2 free bonds and thus are linking groups, namely "alkylene", as well as such groups including 1 to 4 substituents such as halo, for example F, Br, Cl or I or CF_3, alkyl, alkoxy, aryl, aryloxy, aryl(aryl) or diaryl, arylalkyl, arylalkyloxy, alkenyl, alkynyl, cycloalkyl, cycloalkenyl, cycloalkylalkyl, cycloalkylalkyloxy, hydroxy, hydroxyalkyl, acyl, alkanoyl, heteroaryl, heteroaryloxy, cycloheteroalkyl, arylheteroaryl, arylalkoxycarbonyl, heteroarylalkyl, heteroarylalkoxy, aryloxyalkyl, aryloxyaryl, alkylamido, alkanoylamino, arylcarbonylamino, nitro, cyano, thiol, haloalkyl, trihaloalkyl and/or alkylthio.

[0016] Unless otherwise indicated, the term "cycloalkyl" or "lower cycloalkyl" as may be employed herein alone or as part of another group includes saturated or partially unsaturated (containing 1 or 2 double bonds) cyclic hydrocarbon groups containing 1 to 3 rings, any one of which may optionally be a spiro substituted cycloalkyl, including monocycloalkyl, bicycloalkyl and tricycloalkyl, containing a total of 3 to 20 carbons forming the rings, preferably 3 to 10 carbons, forming the ring and which may be fused to 1 or 2 aromatic rings as described for aryl, which include cyclopropyl, cyclobutyl, cyclopentyl, cyclohexyl, cycloheptyl, cyclooctyl, cyclodecyl and cyclododecyl, cyclohexenyl,

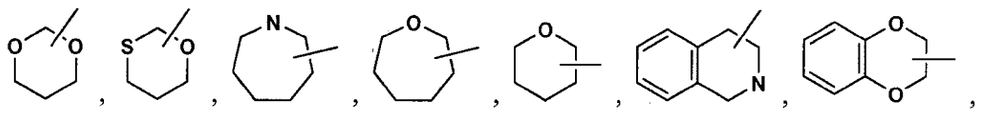


as well as such groups including 2 free bonds and thus are linking groups, any of which groups may be optionally substituted with 1 to 4 substituents such as halogen, alkyl, alkoxy, hydroxy, aryl, aryloxy, arylalkyl, cycloalkyl, alkylamido, alkanoylamino, oxo, acyl, arylcarbonylamino, nitro, cyano, thiol and/or alkylthio and/or any of the substituents set for "alkyl".

[0017] Unless otherwise indicated, the term "cycloalkoxy" or "lower cycloalkoxy" as employed herein alone or as part of another group, represents a 4-, 5- or 6-membered saturated ring containing an oxygen in the ring and includes  ,  , and  , as well as such groups including 2 free bonds and thus are

linking groups, and which may be optionally substituted with 1 or two of any of the substituents as set out for cycloalkyl.

[0018] The term "heterocyclo", "heterocycle", "heterocyclyl", "heterocyclic" or "cycloheteroalkyl" ring, as may be used herein, represents an unsubstituted or substituted stable 4- to 7-membered monocyclic ring system which may be saturated or unsaturated, preferably saturated or partially unsaturated, and which consists of carbon atoms, with one to four heteroatoms selected from nitrogen, oxygen or sulfur, and wherein the nitrogen and sulfur heteroatoms may optionally be oxidized, and the nitrogen heteroatom may optionally be quaternized, and including any bicyclic group in which the heterocyclic ring is fused to a benzene ring. The heterocyclic ring may be attached at any heteroatom or carbon atom which results in the creation of a stable structure. Examples of such heterocyclic groups include, but is not limited to, piperidinyl, piperazinyl, oxopiperazinyl, oxopiperidinyl, oxopyrrolidinyl, oxoazepinyl, azepinyl, pyrrolyl, pyrrolidinyl, furanyl, thienyl, pyrazolyl, pyrazolidinyl, imidazolyl, imidazolinyl, imidazolidinyl, pyridyl, pyrazinyl, pyrimidinyl, pyridazinyl, oxazolyl, oxazolidinyl, isooxazolyl, isoxazolidinyl, morpholinyl, thiazolyl, thiazolidinyl, isothiazolyl, thiadiazolyl, tetrahydropyranyl, thiamorpholinyl, thiamorpholinyl sulfoxide, thiamorpholinyl sulfone, oxadiazolyl,



, and other heterocycles described in Katritzky, A.R. et al., eds., *Comprehensive Heterocyclic Chemistry: The Structure, Reactions, Synthesis and Uses of Heterocyclic Compounds*, Pergamon Press, New York, NY, publ. (1984); and Katritzky, A.R. et al., eds., *Comprehensive Heterocyclic Chemistry II: A Review of the Literature 1982-1995*, Elsevier Science, Inc., Tarrytown, NY, publ. (1996); and references therein, as well as such groups including 2 free bonds and thus are linking groups, as well as such groups optionally substituted with 1 to 3 of F, Br, Cl or I or CF_3, alkyl, alkoxy, aryl, aryloxy, aryl(aryl) or diaryl, arylalkyl, arylalkyloxy, alkenyl, alkynyl, cycloalkyl, cycloalkenyl,

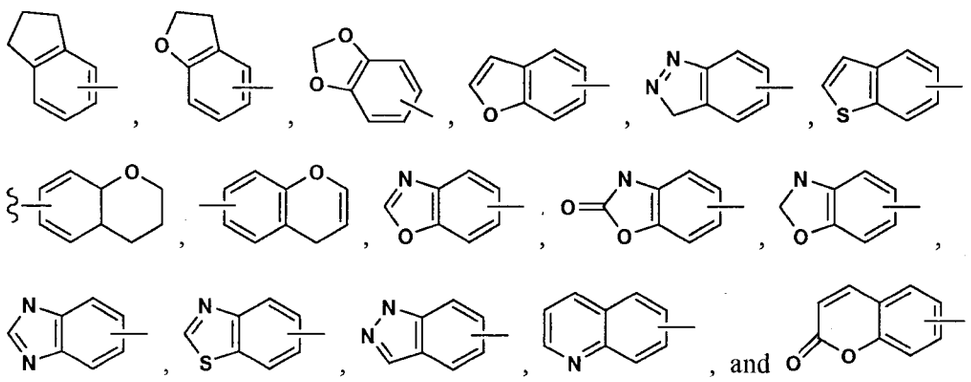
cycloalkylalkyl, cycloalkylalkyloxy, hydroxy, hydroxyalkyl, acyl, alkanoyl, heteroaryl, heteroaryloxy, cycloheteroalkyl, arylheteroaryl, arylalkoxycarbonyl, heteroarylalkyl, heteroarylalkoxy, aryloxyalkyl, aryloxyaryl, alkylamido, alkanoylamino, arylcarbonylamino, nitro, cyano, thiol, haloalkyl, trihaloalkyl, and/or alkylthio.

[0019] The term "alkanoyl" as may be used herein alone or as part of another group refers to alkyl linked to a carbonyl group.

[0020] The term "halogen" or "halo" as may be used herein alone or as part of another group refers to chlorine, bromine, fluorine, and iodine, with chlorine or fluorine being preferred.

[0021] The term "metal ion" refers to alkali metal ions such as sodium, potassium or lithium and alkaline earth metal ions such as magnesium and calcium, as well as zinc and aluminum.

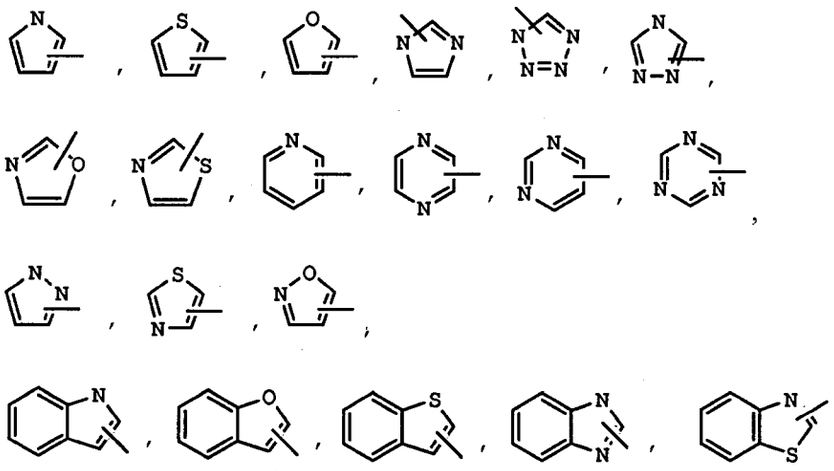
[0022] Unless otherwise indicated, the term "aryl" or "Aryl" as may be employed herein alone or as part of another group refers to monocyclic and bicyclic aromatic groups containing 6 to 10 carbons in the ring portion (such as phenyl or naphthyl including l-naphthyl and 2-naphthyl) and may optionally include one to three additional rings fused to a carbocyclic ring or a heterocyclic ring (such as aryl, cycloalkyl, heteroaryl or cycloheteroalkyl rings), for example

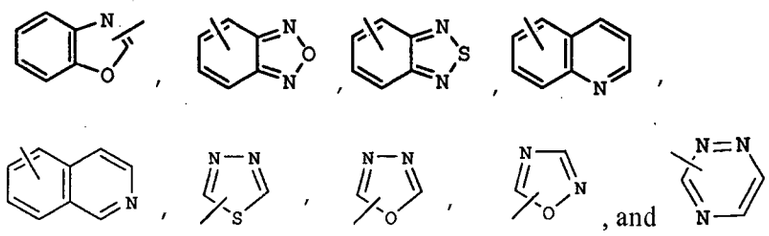


and as well as such groups including 2 free bonds and thus are linking groups, and may be optionally substituted through available carbon atoms with 1, 2, or 3 groups selected from hydrogen, halo, haloalkyl, alkyl, haloalkyl, alkoxy, haloalkoxy, alkenyl, trifluoromethyl, trifluoromethoxy, alkynyl, cycloalkyl-alkyl, cycloheteroalkyl, cycloheteroalkylalkyl, aryl, heteroaryl, arylalkyl, aryloxy, aryloxyalkyl, arylalkoxy,

alkoxycarbonyl, arylcarbonyl, arylalkenyl, aminocarbonylaryl, arylthio, arylsulfinyl, arylazo, heteroarylalkyl, heteroarylalkenyl, heteroarylheteroaryl, heteroaryloxy, hydroxy, nitro, cyano, thiol, alkylthio, arylthio, heteroarylthio, arylthioalkyl, alkoxyarylthio, alkylcarbonyl, arylcarbonyl, alkylaminocarbonyl, arylaminocarbonyl, alkoxycarbonyl, aminocarbonyl, alkylcarbonyloxy, arylcarbonyloxy, alkylcarbonylamino, arylcarbonylamino, arylsulfinyl, arylsulfinylalkyl, arylsulfonylamino and arylsulfonaminocarbonyl and/or any of the substituents for "alkyl" set out herein.

[0023] Unless otherwise indicated, the term "heteroaryl" as may be used herein alone or as part of another group refers to a 5- or 6-membered aromatic ring which includes 1, 2, 3 or 4 hetero atoms such as nitrogen, oxygen or sulfur. Such rings may be fused to an aryl, cycloalkyl, heteroaryl or heterocyclyl and include possible N-oxides as described in Katritzky, A.R. et al., eds., *Comprehensive Heterocyclic Chemistry: The Structure, Reactions, Synthesis and Uses of Heterocyclic Compounds*, Pergamon Press, New York, NY, publ. (1984); and Katritzky, A.R. et al., eds., *Comprehensive Heterocyclic Chemistry II: A Review of the Literature 1982-1995*, Elsevier Science, Inc., Tarrytown, NY, publ. (1996); and references therein as well as such groups including 2 free bonds and thus are linking groups. Further, "heteroaryl", as defined herein, may optionally be substituted with one or more substituents such as the substituents included above for "alkyl" and/or "aryl". Examples of heteroaryl groups include the following:





and the like.

[0024] Unless otherwise indicated, the term "lower alkoxy", "alkoxy", "aryloxy" or "aralkoxy" as may be employed herein alone or as part of another group includes any of the above alkyl, aralkyl or aryl groups linked to an oxygen atom.

[0025] Unless otherwise indicated, the term "lower alkylthio", alkylthio", "arylthio" or "aralkylthio" as may be employed herein alone or as part of another group includes any of the above alkyl, aralkyl or aryl groups linked to a sulfur atom.

[0026] The term "polyhaloalkyl" as may be used herein refers to an "alkyl" group as defined above which includes from 2 to 9, preferably from 2 to 5, halo substituents, such as F or Cl, preferably F, such as CF_3CH_2, CF_3 or $CF_3CF_2CH_2$.

[0027] The term "polyhaloalkyloxy" as may be used herein refers to an "alkoxy" or "alkyloxy" group as defined above which includes from 2 to 9, preferably from 2 to 5, halo substituents, such as F or Cl, preferably F, such as CF_3CH_2O, CF_3O or $CF_3CF_2CH_2O$.

[0028] Unless otherwise indicated, the term "alkenyl" as used herein alone or as part of another group refers to straight or branched chain radicals of 2 to 20 carbons, preferably 2 to 12 carbons, and more preferably 1 to 8 carbons in the normal chain, which include one to six double bonds in the normal chain, such as vinyl, 2-propenyl, 3-butenyl, 2-butenyl, 4-pentenyl, 3-pentenyl, 2-hexenyl, 3-hexenyl, 2-heptenyl, 3-heptenyl, 4-heptenyl, 3-octenyl, 3-nonenyl, 4-decenyl, 3-undecenyl, 4-dodecenyl, 4,8,12-tetradecatrienyl, and the like. Optionally, said alkenyl group may be substituted with one or substituents, such as those substituents disclosed for alkyl.

[0029] Unless otherwise indicated, the term "alkynyl" as used herein alone or as part of another group refers to straight or branched chain radicals of 2 to 20 carbons, preferably 2 to 12 carbons and more preferably 2 to 8 carbons in the normal chain, which include one triple bond in the normal chain, such as 2-propynyl, 3-butynyl, 2-

butynyl, 4-pentynyl, 3-pentynyl, 2-hexynyl, 3-hexynyl, 2-heptynyl, 3-heptynyl, 4-heptynyl, 3-octynyl, 3-nonynyl, 4-decynyl,3-undecynyl, 4-dodecynyl and the like. Optionally, said alkynyl group may be substituted with one or substituents, such as those substituents disclosed for alkyl.

[0030] The term "cycloalkenyl" as employed herein alone or as part of another group refers to partially unsaturated cyclic hydrocarbons containing 3 to 12 carbons, preferably 5 to 10 carbons and 1 or 2 double bonds. Exemplary cycloalkenyl groups include cyclobutenyl, cyclopentenyl, cyclohexenyl, cycloheptenyl, cyclooctenyl, cyclohexadienyl, and cycloheptadienyl. Optionally, said cycloalkenyl group may be substituted with one or substituents, such as those substituents disclosed for alkyl.

[0031] The term "bicycloalkyl" as employed herein alone or as part of another group includes saturated bicyclic ring groups such as, without limitation, [3.3.0]bicyclooctane, [4.3.0]bicyclononane, [4.4.0]bicyclodecane (decalin), [2.2.2]bicyclooctane, and so forth.

[0032] The term "polycycloalkyl" as employed herein alone or as part of another group includes two or more cycloalkyl ring systems, as defined herein, wherein at least one carbon atom is a part of at least two separately identifiable ring systems. The polycycloalkyl group may contain bridging between two carbon atoms, for example, bicyclo[1.1.0]butyl, bicyclo[3.2.1]octyl, bicyclo[5.2.0]nonyl, tricycl[2.2.1.0.sup.1]heptyl, norbornyl and pinanyl. The polycycloalkyl group may contain one or more fused ring systems, for example, decalinyl (radical from decalin) and perhydroanthracenyl. The polycycloalkyl group may contain a spiro union, in which a single atom is the only common member of two rings, for example, spiro[3.4]octyl, spiro[3.3]heptyl and spiro[4.5]decyl.

[0033] The term "acyl" as employed herein by itself or part of another group, as defined herein, refers to an organic radical linked to a carbonyl $\left(\overset{O}{\overset{\|}{C}}\right)$ group; examples of acyl groups include a substituent group attached to a carbonyl, such as alkanoyl, alkenoyl, aroyl, aralkanoyl, heteroaryl, cycloalkanoyl, cycloheteroalkanoyl and the like.

[0034] "Optional" or "optionally" means that the subsequently described event or circumstance may or may not occur, and that the description includes, without

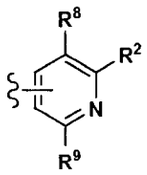
limitation, instances where said event or circumstance occurs and instances in which it does not. For example, optionally substituted alkyl means that alkyl may or may not be substituted by those groups enumerated in the definition of substituted alkyl.

[0035] "Substituted," as used herein, whether express or implied and whether preceded by "optionally" or not, means that any one or more hydrogen on the designated atom (C, N, etc.) is replaced with a selection from the indicated group, provided that the designated atom's normal valency is not exceeded, and that the substitution results in a stable compound. For instance, when a CH_2 is substituted by a keto substituent (=O), then 2 hydrogens on the atom are replaced. Combinations of substituents and/or variables are permissible only if such combinations result in stable compounds. Further, when more than one position in a given structure may be substituted with a substituent selected from a specified group, the substituents may be either the same or different at every position.

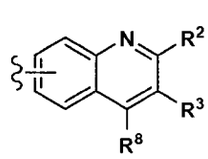
[0036] The designation "〰" or "§—" attached to a ring or other group refers to a free bond or linking group.

SPECIFIC EMBODIMENTS

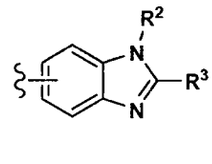
[0037] The (A) group may be phenylene or a heteroaryl which is monocyclic or bicyclic and includes rings such as



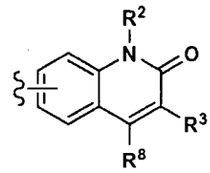
(pyridinyl) ,



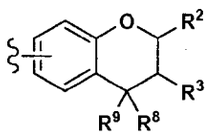
(quinolinyl) ,



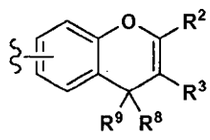
(benzimidazolyl) ,



(quinolin-2(1H)-one) ,

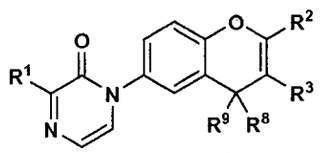


(chromanyl) , or



(chromenyl) , with phenylene and pyridinyl being preferred.

[0038] The Formula I compound of the invention may have the structure



IG

[0039] In the compound of Formula I of the invention, it is desired that

(A) is phenylene or pyridinyl;

X is O or S; and/or

Y is a bond or an alkylene chain of 1, 2 or 3 atoms; and/or

Z is phenyl; or

Z is a heteroaryl such as pyridinyl or benzothiazole; and/or

R^2 is E-G-J; and/or

E is O or S; and/or

G is a lower alkyl or alkylcycloalkyl; and/or

J is H, OH, SO_2R^7, lower alkyl, lower alkoxy, or CF_3, more preferably OH; and/or

R^3 is C_{1-6} alkyl, C_{1-6} alkoxy, H, or halo; and/or

R^8 and R^9 are independently H or CH_3; and/or

wherein R^2 and R^3 can be taken together to form a 5- to 7-membered ring which is saturated, unsaturated, or partially unsaturated and may include an E heteroatom, which is O, or 0, 1 or 2 N atoms, which ring is substituted with one or two of -O-G-$(J)_m$ groups, wherein at least one J is OH and optionally other substituents as set out for "alkyl", "aryl", or "heteroaryl", such as alkyl and/or OH.

[0040] The above groups may be substituted as indicated herein.

[0041] Examples of the various groups of the compounds of Formula I of the invention are set out below:

(A) is phenylene or pyridinyl;

Z is

(1) aryl, such as phenyl or naphthyl, each of which is optionally substituted with:

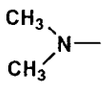
a) halogen such as Cl, Br or F,

b) alkyl such as CH_3, C_2H_5 or *i*-C_3H_7,

c) alkoxy such as CH_3O,

d) polyhaloalkyl such as CF_3,

e) polyhaloalkoxy such as CF_3O,

f) amino, alkylamino or dialkylamino such as  ,

g) alkylthio such as CH_3S,

h) OH,

i) esters such as -$COOCH_3$, or

j) aryl such as phenyl,

(2) monocyclic heteroaryl such as

a) pyridinyl,

b) pyrazinyl, or

c) pyrimidinyl,

each of a), b) or c) being optionally substituted with alkyl such as methyl, polyhaloalkyl such as trifluoromethyl, halogen such as Cl or F, or alkoxy such as CH_3O;

(3) benzothiazole optionally substituted with halo such as F, Cl, alkoxy such as CH_3O,

(4) benzoxazole optionally substituted with halo such as Cl,

(5) benzimidazole,

(6) thiazole optionally substituted with aryl such as phenyl, and alkyl such as *t*-C_4H_9,

(7) indanyl,

(8) quinolinyl optionally substituted with CF_3, or

(9) imidazolidinyl; and/or

Y is a bond or alkylene such as methylene, or ethylene or propylene; and/or

X is S, O, SO, or SO_2; and/or

J is

(1) H,

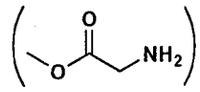
(2) -CO-$NR^{5a}R^6$ where R^{5a} and R^6 together with the N to which they are attached form a pyrrolidinyl ring,

(3) OH,

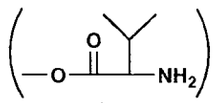
(4) COOH,

(5) COOalkyl such as $COOCH_3$,

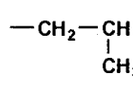
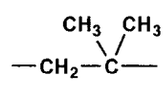
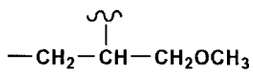
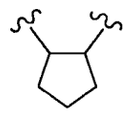
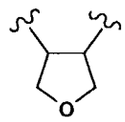
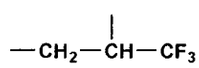
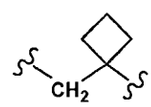
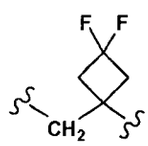
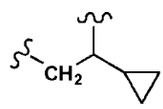
(6) SO_2R^7 such as $SO_2C_2H_5$, or

(7) prodrug esters such as glycine  , phosphate

PO_4 ( and the corresponding Na salt thereof), and valine

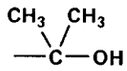
 ; and/or

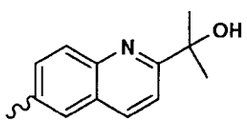
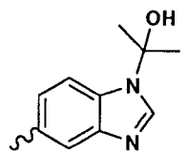
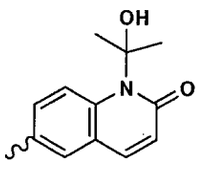
m is 1 or 2; and/or

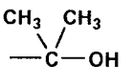
G is CH_2, $(CH_2)_2$, $(CH_2)_3$,  ,  ,  ,  , cycloalkyl such as , cycloalkoxy such as  ,  , or alkylcycloalkyl such as  ,  and  ; and/or

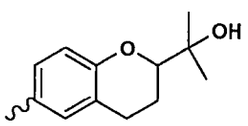
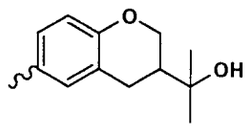
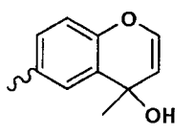
E is O; and/or

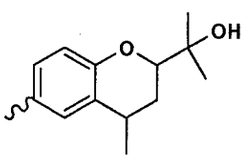
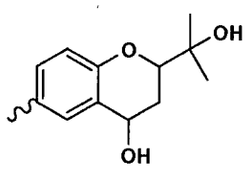
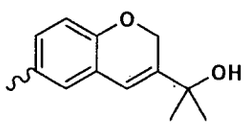
R^3 is H, alkoxy such as CH_3O, hydroxyalkyl such as $HOCH_2CH_2$-, alkyl such as CH_3 or C_2H_5, halo such as F or Cl, CN, or hydroxyalkoxy such as $HOCH_2CH_2O$-; and/or

R^2 and R^3 can be optionally taken together to form a 5- or 6-membered unsaturated or aromatic ring containing one or two N atoms, which ring is optionally substituted with hydroxyalkyl such as  , for example

 ,  and  ,

or where R^2 and R^3 can be optionally taken together to form a 6-membered saturated, unsaturated or partially unsaturated O-containing ring, which ring is optionally substituted with hydroxyalkyl such as  , alkyl such as CH_3 and OH, for example

 ,  ,  ,

 ,  , and  ; and/or

R^8 is H, halo such as F and Cl, or alkyl such as methyl; and/or

R^9 is H.

[0042] In a further embodiment of the compound of Formula I of the invention, X = O and  is phenylene or pyridinyl. In another embodiment, X = S and  is phenylene.

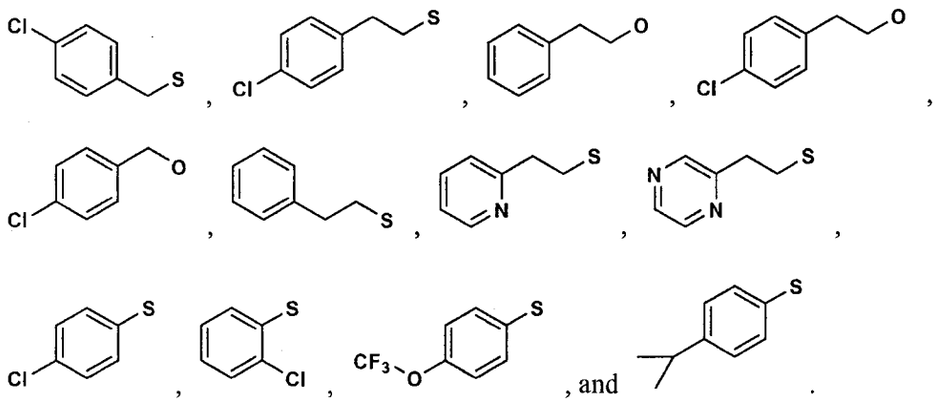
[0043] In a further embodiment in Formula I of the invention, Y is a bond. Also in a further embodiment, Y is methylene, ethylene or propylene. In addition, the alkyl chain or alkyl moiety in Y may be attached to the ortho-position of Z to generate a bicyclic moiety. In this embodiment, the bicyclic moiety is preferably 1-indanyl or 2-indanyl when Z is phenyl.

[0044] In a further embodiment, Z is selected from phenyl, naphthyl, pyridinyl, pyrazinyl, benzimidazolyl, benzothiazolyl, and benzoxazolyl, preferably phenyl and pyridinyl.

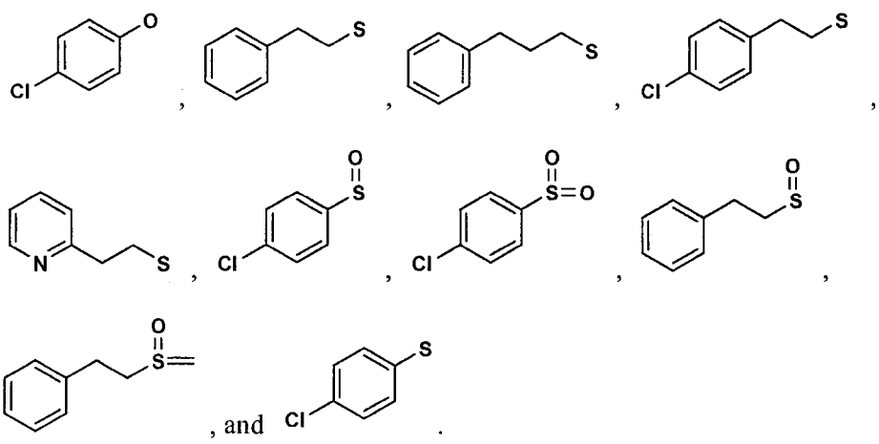
[0045] Furthermore, in the embodiment wherein R^5 and R^6 taken together form a 4-, 5- or 6-membered cyclic amine, it is preferred that this component be selected from the group consisting of azetidinyl, pyrrolidinyl, piperidinyl, morpholinyl, and piperazinyl.

[0046] Also preferred is the embodiment wherein R^3 is C_1-C_6 alkoxy. Especially preferred is the embodiment wherein R^3 is C_1-C_3 alkoxy or C_1-C_3 alkyl. Even more preferably, R^3 is methoxy or methyl.

[0047] In one embodiment of the invention, R^1 may be selected from the group consisting of:

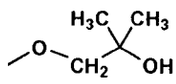
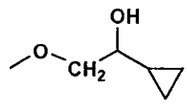


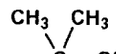
[0048] It is also desirable that in Formula I, R^2 is -O-2-hydroxy-propane, R^3 is methoxy, and R^1 is selected from the group consisting of:

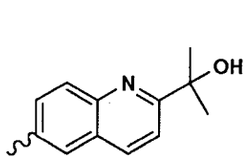
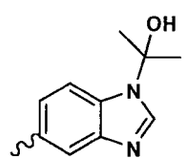
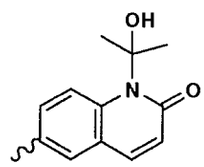


[0049] In another embodiment of the invention, it is desirable that

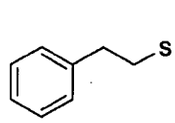
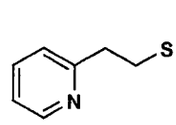
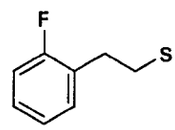
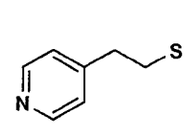
(A) is phenylene;

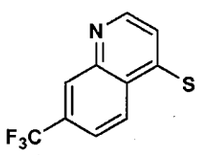
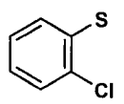
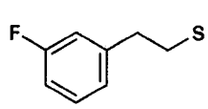
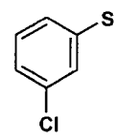
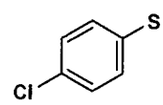
R^2 is  or  ; or

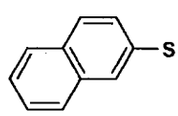
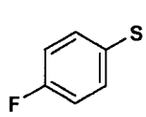
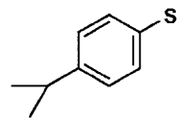
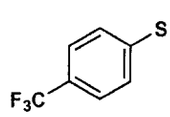
R^2 and R^3 can be optionally taken together to form a 5- or 6-membered unsaturated or aromatic ring containing one or two N atoms, which ring is optionally substituted with hydroxyalkyl such as  , for example

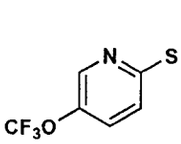
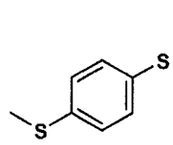
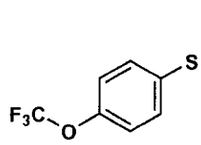
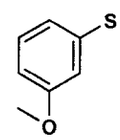
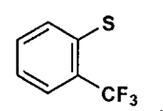
 ,  and  ; and

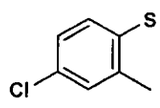
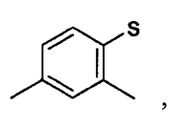
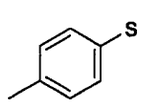
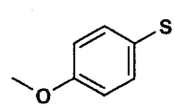
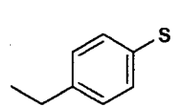
R^3 is methoxy or methyl, and R^1 is selected from the group consisting of:

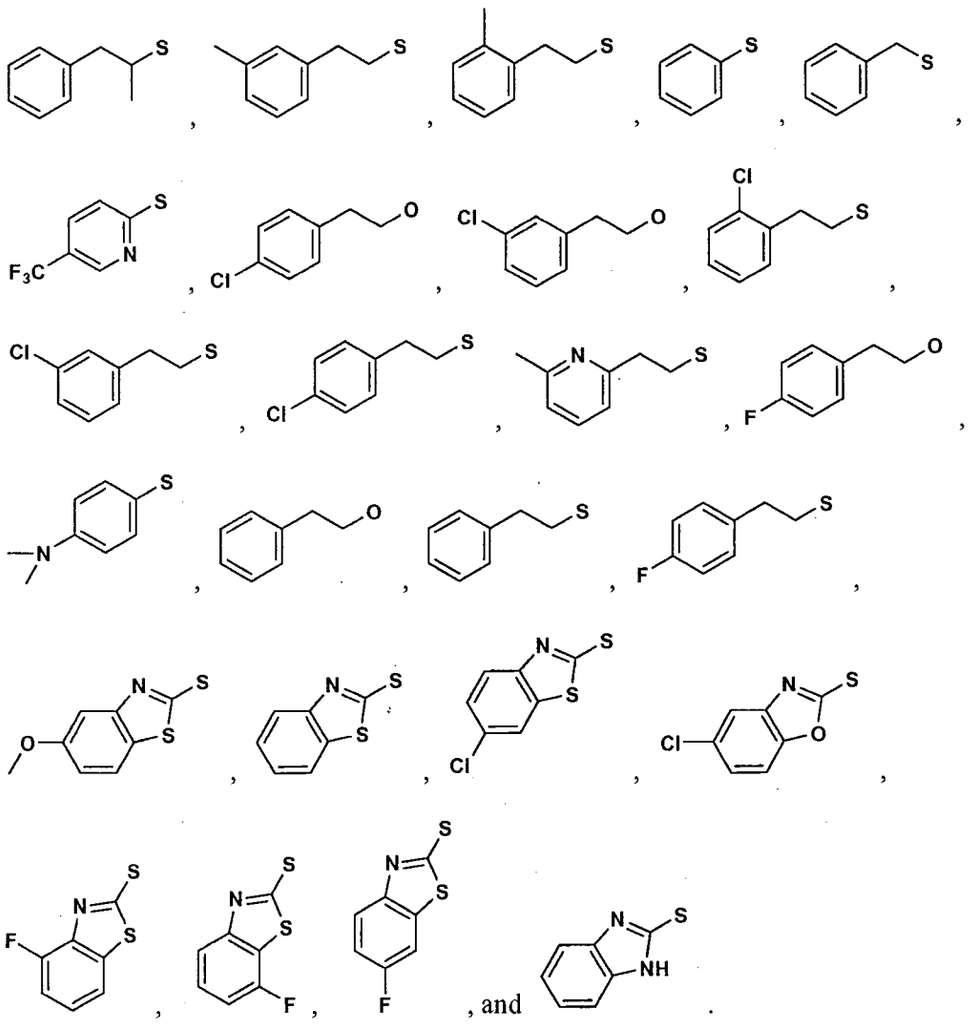
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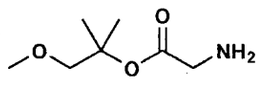
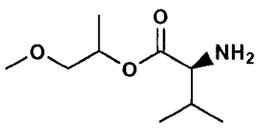
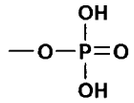
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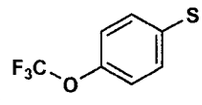
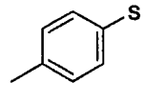
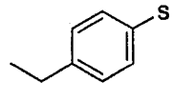
 ,  ,  ,  ,  ,



[0050] Also desired is the prodrug embodiment, hereinafter described, wherein in Formula I,

R^2 is E-G-hydroxyl-$^{Pro\text{-}Drug}$ or more preferably  ,  , and  ;

R^3 is methoxy; and

R^1 is selected from  ,  , and  .

[0051] Also desired are compounds of Formula I wherein


is phenylene;

R^1 is Z-Y-X- wherein

X is S,

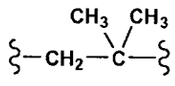
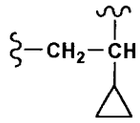
Y is an alkyl chain of 1 to 3 carbons or a bond,

Z is heteroaryl or phenyl,

each of which Z is optionally substituted with CF_3, CF_3O, or halo;

R^2 is -E-G-J wherein

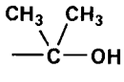
E is O,

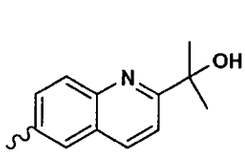
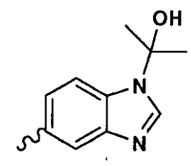
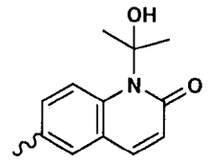
G is lower alkyl such as  or alkylcycloalkyl such as  , and

J is OH;

R^3 is H, alkoxy such as CH_3O, or alkyl such as CH_3;

R^8 and R^9 are independently H or CH_3; and

R^2 and R^3 can be optionally taken together to form a 5- or 6-membered unsaturated or aromatic ring containing one or two N atoms, which ring is optionally substituted with hydroxyalkyl such as  , for example

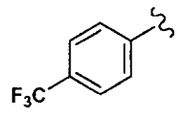
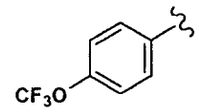
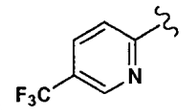
 ,  and  .

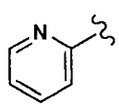
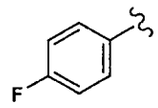
[0052] In still more preferred compounds of Formula I,

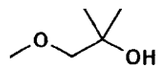
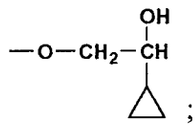

is phenylene;

X is S;

Y is a bond or $(CH_2)_2$;

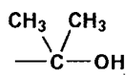
Z is  ,  ,  ,  ,

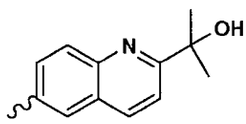
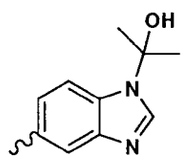
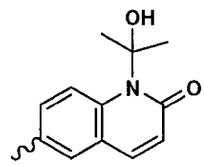
 , or  ;

E-G-J is  or  ;

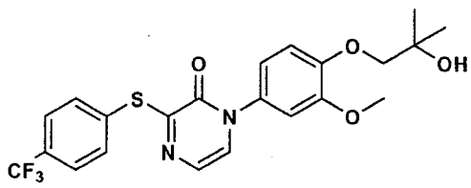
R^3 is CH_3O or CH_3;

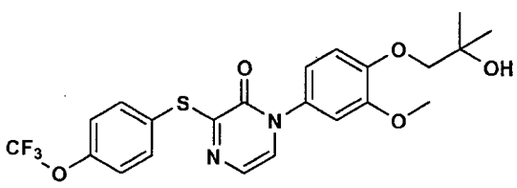
R^8 and R^9 are each H; and

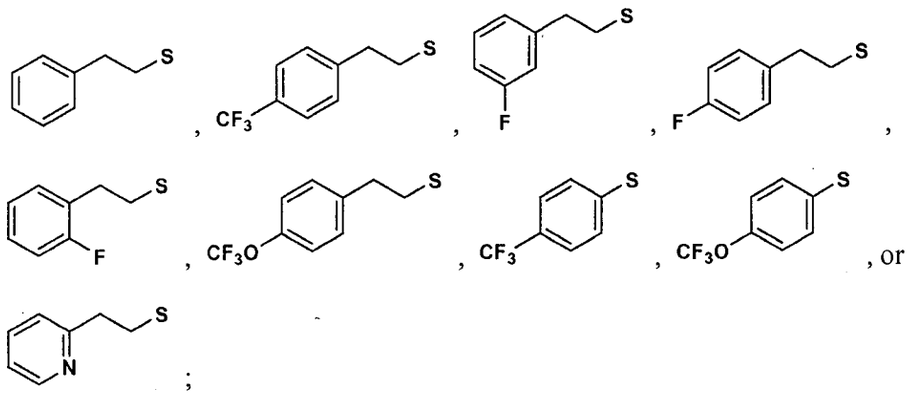
R^2 and R^3 can be optionally taken together to form a 5- or 6-membered unsaturated or aromatic ring containing one or two N atoms, which ring is optionally substituted with hydroxyalkyl such as  , for example

 ,  and  .

[0053] Some preferred compounds of the invention include the following:

 ,

 ,



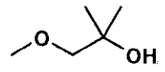
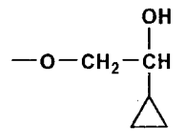
;

R^2 is -E-G-J wherein

E is O,

G is lower alkyl or alkylcycloalkyl, and

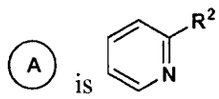
J is OH,

for example, R^2 is  or  ;

R^3 is alkoxy such as CH_3O, alkyl such as CH_3, or halo such as Cl; and

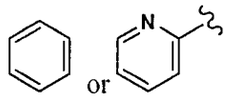
R^8 and R^9 are independently H or CH_3.

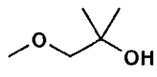
[0055] In still more desired compounds of Formula I,

 ;

X is S;

Y is a bond or $(CH_2)_2$;

Z is  ;

E-G-J is  ; and

R^3 is CH_3, H or Cl.

METHODS OF PREPARATION

[0056] The compounds of Formula I according to the various embodiments herein described can be prepared as shown in the following non-limiting reaction schemes and description thereof, as well as relevant published literature procedures that may be used by one skilled in the art.

[0057] Scheme 1 below portrays a generalized reaction sequence for the synthesis of compounds of Formula I.

[0058] Compounds of Formula I, for which R^1 is Z-Y-O or Z-Y-S and R^2 does not contain a tertiary alcohol, can be prepared by condensation of compounds of Formula II in a solvent such as THF with alkali metal salts such as Na^+ or K^+ of compounds of Formula III. The alkali salts of compounds of Formula III had been previously prepared by addition of compounds of Formula III to a stirred dispersion of NaH or KH in a solvent such as THF under an inert atmosphere of N_2 or Ar. Compounds of Formula II can be prepared by treatment of compounds of Formula IV with thionyl chloride in a solvent such as DMF. Compounds of Formula III are commercially available or may be readily prepared by one skilled in the arts.

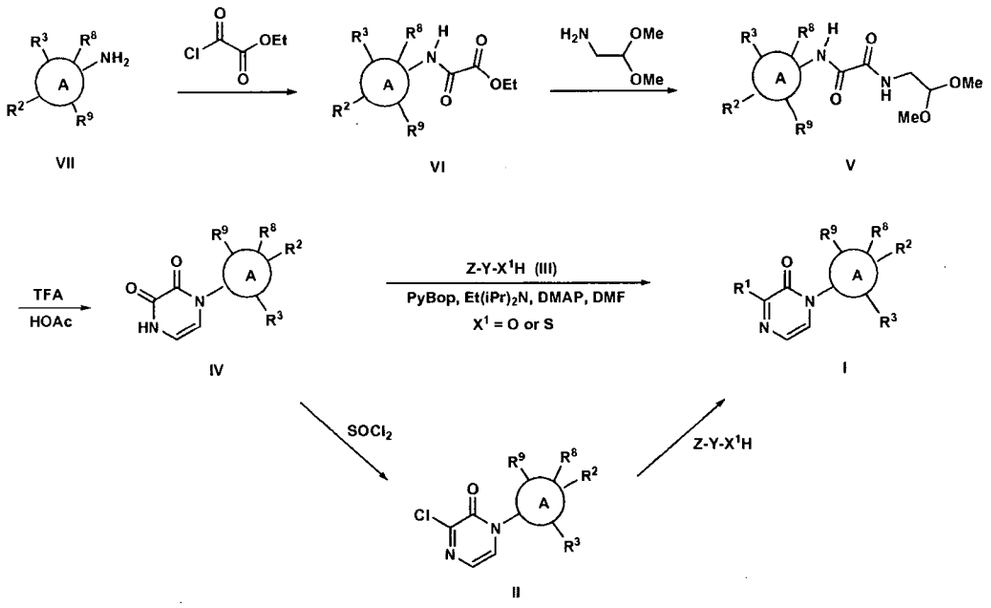
[0059] Alternatively, a general synthesis of compounds of Formula I, for which R^1 is Z-Y-O, Z-Y-S or Z-Y-NR^4H, entails condensation of compounds of Formula IV with compounds of Formula III by stirring these components in a solvent such as DMF containing benzotriazo-1-yl-oxy-trispyrrolidinophosphonium hexafluoroborate (PyBOP) as an activating agent, DMAP and a hindered amine such as Et(*i*Pr)$_2$N. Other activating agents may be utilized by the skilled artisan.

[0060] Compounds of Formula IV can be prepared by heating compounds of Formula V to 120-150°C in microwave in a 1:1.1 mixture of HOAc/TFA. Compounds of Formula V can be prepared by stirring compounds of Formula VI with 2,2-dimethoxyethylamine in a solvent such as EtOAc. Compounds of Formula VI can be prepared by treatment of compounds of Formula VII with ethyl oxalyl chloride in a mixture of EtOAC and water containing a weak base such as potassium carbonate. Compounds of Formula VII are either commercially available or can be prepared as described in USSN 11/586,255.

[0061] Compounds of Formula I for which R^1 is Z-Y-SO or Z-Y-SO_2 can be prepared by treatment of compounds of Formula I where R^1 is Z-Y-S with one or two

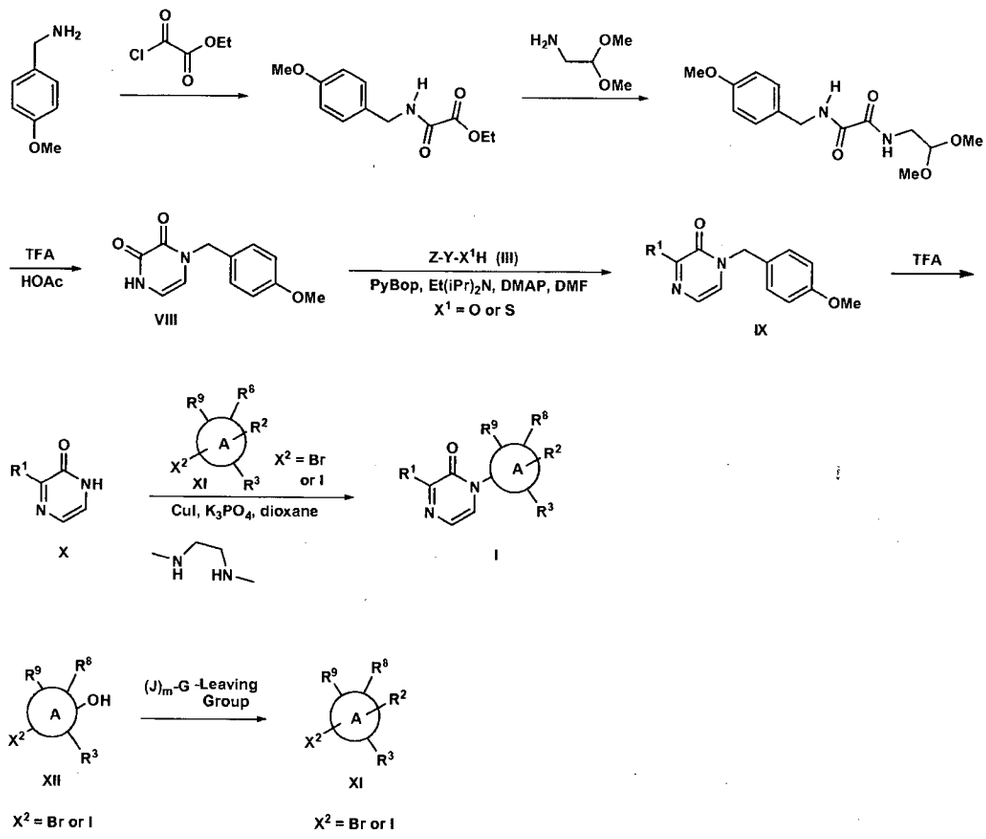
equivalents of an oxidant such as *m*-chloroperbenzoic acid in a solvent such as CH_2Cl_2.

Scheme 1



[0062] Alternatively compounds of formula I can be prepared as outlined in Scheme 2. by Cu catalyzed arylation of compounds of formula X by heating X with aryl halides or iodides of formula XI in a solvent such as dioxane containing a cuprous salt such as cuprous iodide along with potassium tribasic phosphate and a chelating agent such as N-methyl, N'-methyl ethylene diamine. Compounds of formula X can be prepared by heating compounds of formula IX in TFA. Compounds of formula IX can be prepared by condensation of compound of Formula VIII with compounds of Formula III by stirring these components in a solvent such as DMF containing benzotriazo-1-yl-oxy-trispyrrolidinophosphonium hexafluoroborate (PyBOP) as an activating agent, DMAP and a hindered amine such as $Et(iPr)_2N$. Compound of formula VIII is readily obtained from p-methoxybenzyl amine utilizing the chemistry described in Scheme 1. Aryl halides of formula XI are readily prepared by one skilled in the arts by alkylation of the corresponding commercially available halogenated phenol.

Scheme 2

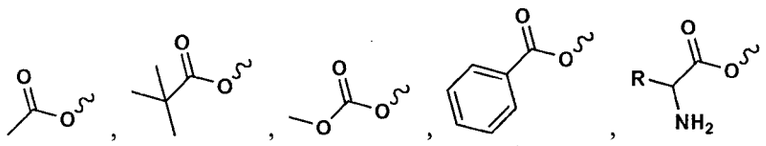


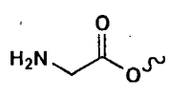
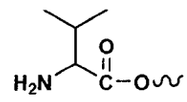
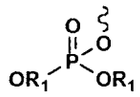
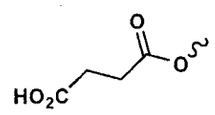
[0063] Other methods of preparing the compounds of Formula I are within the scope of the invention as well.

PRODRUGS, SALTS, ESTERS AND STEREOISOMERS

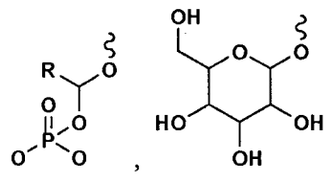
[0064] The compounds of the invention also include "prodrugs". The term "prodrug" as used herein encompasses both the term "prodrug esters" and the term "prodrug ethers". The term "prodrug esters" as employed herein includes esters and carbonates formed by reacting one or more hydroxyls of compounds of Formula I with either alkyl, alkoxy, or aryl substituted acylating agents or phosphorylating agent employing procedures known to those skilled in the art to generate acetates, pivalates, methylcarbonates, benzoates, amino acid esters, phosphates, half acid esters such as malonates, succinates or glutarates, and the like. In certain embodiments, amino acid esters may be especially preferred.

[0065] Examples of such prodrug esters include



(R = H or isopropyl or other alkyl group) (for example,  and ),  (where R_1 is H or an alkali metal such as Na), that is  .

[0066] The term "prodrug ethers" include both phosphate acetals and O-glucosides. Representative examples of such prodrug ethers include



[0067] The compounds of Formula I can also be present as salts, which are further within the scope of this invention. Pharmaceutically acceptable (i.e., non-toxic, physiologically acceptable) salts are preferred. If the compounds of Formula I have, for example, at least one basic center, they can form acid addition salts. These are formed, for example, with strong inorganic acids, such as mineral acids, for example sulfuric acid, phosphoric acid (phosphate ester) or a hydrohalic acid, with organic carboxylic acids, such as alkanecarboxylic acids of 1 to 4 carbon atoms, for example acetic acid, which are unsubstituted or substituted, for example, by halogen as chloroacetic acid, such as saturated or unsaturated dicarboxylic acids, for example oxalic, malonic, succinic, maleic, fumaric, phthalic or terephthalic acid, such as hydroxycarboxylic acids, for example ascorbic, glycolic, lactic, malic, tartaric or citric acid, such as amino acids, (for example aspartic acid, glutamic acid, glycine, valine, lysine, or arginine), or benzoic acid, or with organic sulfonic acids, such as (C_1-C_4) alkyl or arylsulfonic acids which are unsubstituted or substituted, for example by halogen, for example methyl- or p-toluene- sulfonic acid. Corresponding acid addition salts can also be formed having, if desired, an additionally present basic

center. The compounds of Formula I having at least one acid group (for example COOH) can also form salts with bases. Suitable salts with bases are, for example, metal salts, such as alkali metal or alkaline earth metal salts, for example sodium, potassium or magnesium salts, or salts with ammonia or an organic amine, such as morpholine, thiomorpholine, piperidine, pyrrolidine, a mono, di or tri-lower alkylamine, for example ethyl, *tert*-butyl, diethyl, diisopropyl, triethyl, tributyl or dimethyl-propylamine, or a mono, di or trihydroxy lower alkylamine, for example mono, di or triethanolamine. Corresponding internal salts may furthermore be formed. Salts which are unsuitable for pharmaceutical uses but which can be employed, for example, for the isolation or purification of free compounds of Formula I or their pharmaceutically acceptable salts, are also included.

[0068] Preferred salts of the compounds of Formula I which contain a basic group include monohydrochloride, hydrogensulfate, methanesulfonate, phosphate, nitrate or acetate.

[0069] Preferred salts of the compounds of Formula I which contain an acid group include sodium, potassium and magnesium salts and pharmaceutically acceptable organic amines.

[0070] All stereoisomers of the compounds of the invention are contemplated, either in admixture or in pure or substantially pure form. The compounds of the present application can have asymmetric centers at any of the carbon atoms including any one of the R substituents. Consequently, compounds of Formula I can exist in enantiomeric or diastereomeric forms or in mixtures thereof. The processes for preparation can utilize racemates, enantiomers or diastereomers as starting materials. When diastereomeric or enantiomeric products are prepared, they can be separated by conventional methods for example, chromatographic or fractional crystallization.

UTILITY

[0071] The compounds of the present application can be administered to mammals, preferably humans, for the treatment of a variety of conditions and disorders, including, but not limited to metabolic and eating disorders as well as conditions associated with metabolic disorders (e.g., obesity, diabetes, arteriosclerosis, hypertension, polycystic ovary disease, cardiovascular disease,

osteoarthritis, dermatological disorders, impaired glucose hemostasis, insulin resistance, hypercholesterolemia, hypertriglyceridemia, choletithiasis, dislipidemic conditions, bulimia nervosa and compulsive eating disorders); sleep disorders; and psychiatric disorders, such as depression, anxiety, schizophrenia, substance abuse, cognition-enhancement and Parkinson's disease.

[0072] The compounds described in the present application could be used to enhance the effects of cognition-enhancing agents, such as acetylcholinesterase inhibitors (e.g., tacrine), muscarinic receptor-1 agonists (e.g., milameline), nicotinic agonists, glutamic acid receptor (AMPA and NMDA) modulators, and nootropic agents (e.g., piracetam, levetiracetam). Examples of suitable therapies for treatment of Alzheimer's disease and cognitive disorders for use in combination with the compounds of the present application include donepezil, tacrine, revastigraine, 5HT6, gamma secretase inhibitors, beta secretase inhibitors, SK channel blockers, Maxi-K blockers, and KCNQs blockers.

[0073] The compounds described in the present application could be used to enhance the effects of agents used in the treatment of Parkinson's Disease. Examples of agents used to treat Parkinson's Disease include: levadopa with or without a COMT inhibitor, antiglutamatergic drugs (amantadine, riluzole), alpha-2 adrenergic antagonists such as idazoxan, opiate antagonists, such as naltrexone, other dopamine agonists or transporter modulators, such as ropinirole, or pramipexole or neurotrophic factors such as glial derived neurotrophic factor (GDNF).

PHARMACEUTICAL COMBINATIONS

[0074] The present application includes within its scope pharmaceutical compositions comprising, as an active ingredient, a therapeutically effective amount of at least one of the compounds of Formula I, alone or in combination with a pharmaceutical carrier or diluent. Optionally, compounds of the present application can be used alone, in combination with other suitable therapeutic agents useful in the treatment of the aforementioned disorders including: anti-obesity agents; anti-diabetic agents, appetite suppressants; cholesterol/lipid-lowering agents, HDL-raising agents, cognition enhancing agents, agents used to treat neurodegeneration, agents used to treat respiratory conditions, agents used to treat bowel disorders, anti-inflammatory

agents; anti-anxiety agents; anti-depressants; anti-hypertensive agents; cardiac glycosides; and anti-tumor agents.

[0075] Such other therapeutic agent(s) may be administered prior to, simultaneously with, or following the administration of the melanin-concentrating hormone receptor (MCHR) antagonists in accordance with the application.

[0076] Examples of suitable anti-obesity agents for use in combination with the compounds of the present application include melanocortin receptor (MC4R) agonists, cannabinoid receptor modulators, growth hormone secretagogue receptor (GHSR) antagonists, galanin receptor modulators, orexin antagonists, CCK agonists, GLP-1 agonists, and other Pre-proglucagon-derived peptides; NPY1 or NPY5 antagonist, NPY2 and NPY4 modulators, corticotropin releasing factor agonists, histamine receptor-3 (H3) modulators, aP2 inhibitors, PPAR gamma modulators, PPAR delta modulators, acetyl-CoA carboxylase (ACC) inhibitors, 11-β-HSD-1 inhibitors, adinopectin receptor modulators; beta 3 adrenergic agonists, such as AJ9677 (Takeda/Dainippon), L750355 (Merck), or CP331648 (Pfizer) or other known beta 3 agonists as disclosed in U.S. Patent Nos. 5,541,204, 5,770,615, 5,491,134, 5,776,983 and 5,488,064, a thyroid receptor beta modulator, such as a thyroid receptor ligand as disclosed in WO 97/21993 (U. Cal SF), WO 99/00353 (KaroBio) and WO 00/039077 (KaroBio), a lipase inhibitor, such as orlistat or ATL-962 (Alizyme), serotonin receptor agonists, (e.g., BVT-933 (Biovitrum)), monoamine reuptake inhibitors or releasing agents, such as fenfluramine, dexfenfluramine, fluvoxamine, fluoxetine, paroxetine, sertraline, chlorphentermine, cloforex, clortermine, picilorex, sibutramine, dexamphetamine, phentermine, phenylpropanolamine or mazindol, anorectic agents such as topiramate (Johnson & Johnson), CNTF (ciliary neurotrophic factor) /Axokine® (Regeneron), BDNF (brain-derived neurotrophic factor), leptin and leptin receptor modulators, or cannabinoid-1 receptor antagonists, such as SR-141716 (Sanofi) or SLV-319 (Solvay).

[0077] Examples of suitable anti-diabetic agents for use in combination with the compounds of the present application include: insulin secretagogues or insulin sensitizers, which may include biguanides, sulfonyl ureas, glucosidase inhibitors, aldose reductase inhibitors, PPAR γ agonists such as thiazolidinediones, PPAR α agonists (such as fibric acid derivatives), PPAR δ antagonists or agonists, PPAR α/γ

dual agonists, 11-β-HSD-1 inhibitors, dipeptidyl peptidase IV (DP4) inhibitors including saxagliptin, SGLT2 inhibitors including dapagliflozin and serglifozin, glycogen phosphorylase inhibitors, and/or meglitinides, as well as insulin, and/or glucagon-like peptide-1 (GLP-1), GLP-1 agonist, incretin modulators, AMP kinase activators, glucocortical antagonists, fructose bis 1,6-phosphatase inhibitors, glucokinase inhibitors and/or a PTP-1B inhibitor (protein tyrosine phosphatase-1B inhibitor).

[0078] The antidiabetic agent may be an oral antihyperglycemic agent preferably a biguanide such as metformin or phenformin or salts thereof, preferably metformin HCl. Where the antidiabetic agent is a biguanide, the compounds of the present application will be employed in a weight ratio to biguanide within the range from about 0.001:1 to about 10:1, preferably from about 0.01:1 to about 5:1.

[0079] The antidiabetic agent may also preferably be a sulfonyl urea such as glyburide (also known as glibenclamide), glimepiride (disclosed in U.S. Patent No. 4,379,785), glipizide, gliclazide or chlorpropamide, other known sulfonylureas or other antihyperglycemic agents which act on the ATP-dependent channel of the beta-cells, with glyburide and glipizide being preferred, which may be administered in the same or in separate oral dosage forms. The oral antidiabetic agent may also be a glucosidase inhibitor such as acarbose (disclosed in U.S. Patent No. 4,904,769) or miglitol (disclosed in U.S. Patent No. 4,639,436), which may be administered in the same or in a separate oral dosage forms.

[0080] The compounds of the present application may be employed in combination with a PPAR γ agonist such as a thiazolidinedione oral anti-diabetic agent or other insulin sensitizers (which has an insulin sensitivity effect in NIDDM patients) such as rosiglitazone (SKB), pioglitazone (Takeda), Mitsubishi's MCC-555 (disclosed in U.S. Patent No. 5,594,016), Glaxo-Wellcome's GL-262570, englitazone (CP-68722, Pfizer) or darglitazone (CP-86325, Pfizer, isaglitazone (MIT/J&J), JTT-501 (JPNT/P&U), L-895645 (Merck), R-119702 (Sankyo/WL), NN-2344 (Dr. Reddy/NN), or YM-440 (Yamanouchi), preferably rosiglitazone and pioglitazone.

[0081] The compounds of the present application may also be employed with a PPARα/γ dual agonist such as MK-767/KRP-297 (Merck/Kyorin; as described in Yajima, K. et al., *Am. J. Physiol. Endocrinol. Metab.*, 284:E966-E971 (2003)), AZ-

242 (tesaglitazar; Astra-Zeneca; as described in Ljung, B. et al., *J. Lipid Res.*, 43:1855-1863 (2002)); muraglitazar; or the compounds described in U.S. Patent No. 6,414,002.

[0082] The compounds of the present invention may be employed in combination with anti-hyperlipidemia agents, or agents used to treat arteriosclerosis. An example of an hypolipidemic agent would be an HMG CoA reductase inhibitor which includes, but is not limited to, mevastatin and related compounds as disclosed in U.S. Patent No. 3,983,140, lovastatin (mevinolin) and related compounds as disclosed in U.S. Patent No. 4,231,938, pravastatin and related compounds such as disclosed in U.S. Patent No. 4,346,227, simvastatin and related compounds as disclosed in U.S. Patent Nos. 4,448,784 and 4,450,171. Other HMG CoA reductase inhibitors which may be employed herein include, but are not limited to, fluvastatin, disclosed in U.S. Patent No. 5,354,772, cerivastatin disclosed in U.S. Patent Nos. 5,006,530 and 5,177,080, atorvastatin disclosed in U.S. Patent Nos. 4,681,893, 5,273,995, 5,385,929 and 5,686,104, pitavastatin (Nissan/Sankyo's nisvastatin (NK-104) or itavastatin), disclosed in U.S. Patent No. 5,011,930, Shionogi-Astra/Zeneca rosuvastatin (visastatin (ZD-4522)) disclosed in U.S. Patent No. 5,260,440, and related statin compounds disclosed in U.S. Patent No. 5,753,675, pyrazole analogs of mevalonolactone derivatives as disclosed in U.S. Patent No. 4,613,610, indene analogs of mevalonolactone derivatives as disclosed in PCT application WO 86/03488, 6-[2-(substituted-pyrrol-1-yl)-alkyl)pyran-2-ones and derivatives thereof as disclosed in U.S. Patent No. 4,647,576, Searle's SC-45355 (a 3-substituted pentanedioic acid derivative) dichloroacetate, imidazole analogs of mevalonolactone as disclosed in PCT application WO 86/07054, 3-carboxy-2-hydroxy-propane-phosphonic acid derivatives as disclosed in French Patent No. 2,596,393, 2,3-disubstituted pyrrole, furan and thiophene derivatives as disclosed in European Patent Application No. 0221025, naphthyl analogs of mevalonolactone as disclosed in U.S. Patent No. 4,686,237, octahydronaphthalenes such as disclosed in U.S. Patent No. 4,499,289, keto analogs of mevinolin (lovastatin) as disclosed in European Patent Application No.0142146 A2, and quinoline and pyridine derivatives disclosed in U.S. Patent Nos. 5,506,219 and 5,691,322. In addition, phosphinic acid compounds useful

in inhibiting HMG CoA reductase suitable for use herein are disclosed in GB 2205837.

[0083] The squalene synthetase inhibitors suitable for use herein include, but are not limited to, α-phosphono-sulfonates disclosed in U.S. Patent No. 5,712,396, those disclosed by Biller, et al., *J. Med. Chem.*, 31:1869-1871 (1998) including isoprenoid (phosphinyl-methyl)phosphonates as well as other known squalene synthetase inhibitors, for example, as disclosed in U.S. Patent Nos. 4,871,721 and 4,924,024 and in Biller, S.A. et al., *Current Pharmaceutical Design*, 2:1-40 (1996).

[0084] In addition, other squalene synthetase inhibitors suitable for use herein include the terpenoid pyrophosphates disclosed by Ortiz de Montellano, P. et al., *J. Med. Chem.*, 20:243-249 (1977), the farnesyl diphosphate analog A and presqualene pyrophosphate (PSQ-PP) analogs as disclosed by Corey et al., *J. Am. Chem. Soc.*, 98:1291-1293 (1976), phosphinylphosphonates reported by McClard, R.W. et al., *J. Am. Chem. Soc.*, 109:5544 (1987) and cyclopropanes reported by Capson, T.L., Ph.D., dissertation, June, 1987, Dept. Med. Chem., U. of Utah, Abstract, Table of Contents, pp. 16, 17, 40-43, 48-51, Summary.

[0085] Other hypolipidemic agents suitable for use herein include, but are not limited to, fibric acid derivatives, such as fenofibrate, gemfibrozil, clofibrate, bezafibrate, ciprofibrate, clinofibrate and the like, probucol, and related compounds as disclosed in U.S. Patent No. 3,674,836, probucol and gemfibrozil being preferred, bile acid sequestrants such as cholestyramine, colestipol and DEAE-Sephadex (SECHOLEX, POLICEXIDE) and cholestagel (Sankyo/Geltex), as well as lipostabil (Rhone-Poulenc), Eisai E-5050 (an N-substituted ethanolamine derivative), imanixil (HOE-402), tetrahydrolipstatin (THL), istigmastanylphosphorylcholine (SPC, Roche), aminocyclodextrin (Tanabe Seiyoku), Ajinomoto AJ-814 (azulene derivative), melinamide (Sumitomo), Sandoz 58-035, American Cyanamid CL-277,082 and CL-283,546 (disubstituted urea derivatives), nicotinic acid (niacin), acipimox, acifran, neomycin, p-aminosalicylic acid, aspirin, poly(diallylmethylamine) derivatives such as disclosed in U.S. Patent No. 4,759,923, quaternary amine poly(diallyldimethylammonium chloride) and ionenes such as disclosed in U.S. Patent No. 4,027,009, and other known serum cholesterol lowering agents.

[0086] The other hypolipidemic agent may be an ACAT inhibitor (which also has anti-atherosclerosis activity) such as disclosed in, *Drugs of the Future*, 24:9-15 (1999), (Avasimibe); Nicolosi et al., "The ACAT inhibitor, Cl-1011 is effective in the prevention and regression of aortic fatty streak area in hamsters", *Atherosclerosis* (Shannon, Irel.), 137(1):77-85 (1998); Ghiselli, G., "The pharmacological profile of FCE 27677: a novel ACAT inhibitor with potent hypolipidemic activity mediated by selective suppression of the hepatic secretion of ApoB100-containing lipoprotein", *Cardiovasc. Drug Rev.*, 16(1):16-30 (1998); Smith, C. et al., "RP 73163: a bioavailable alkylsulfinyl-diphenylimidazole ACAT inhibitor", *Bioorg. Med. Chem. Lett.*, 6(1):47-50 (1996); Krause, B.R. et al., Chapter 6: "ACAT Inhibitors: Physiologic Mechanisms for Hypolipidemic and Anti-Atherosclerotic Activities in Experimental Animals", *Inflammation: Mediators and Pathways*, CRC Press, Inc., publ., Ruffolo, Jr., R.R. et al., eds., pp. 173-198 (1995); Sliskovic et al., "ACAT inhibitors: potential anti-atherosclerotic agents", *Curr. Med. Chem.*, 1(3):204-225 (1994); Stout et al., "Inhibitors of acyl-CoA:cholesterol O-acyl transferase (ACAT) as hypocholesterolemic agents. 6. The first water-soluble ACAT inhibitor with lipid-regulating activity. Inhibitors of acyl-CoA:cholesterol acyltransferase (ACAT). 7. Development of a series of substituted N-phenyl-N'-[(1-phenylcyclopentyl)-methyl]ureas with enhanced hypocholesterolemic activity", *Chemtracts: Org. Chem.*, 8(6):359-362 (1995), or TS-962 (Taisho Pharmaceutical Co. Ltd), as well as F-1394, CS-505, F-12511, HL-004, K-10085 and YIC-C8-434.

[0087] The hypolipidemic agent may be an upregulator of LDL receptor activity such as MD-700 (Taisho Pharmaceutical Co. Ltd) and LY295427 (Eli Lilly). The hypolipidemic agent may be a cholesterol absorption inhibitor preferably Schering-Plough's SCH48461 (ezetimibe) as well as those disclosed in *Atherosclerosis*, 115:45-63 (1995) and *J. Med. Chem.*, 41:973 (1998).

[0088] The other lipid agent or lipid-modulating agent may be a cholesteryl transfer protein inhibitor (CETP) such as Pfizer's CP-529,414 as well as those disclosed in WO/0038722 and in EP 818448 (Bayer) and EP 992496, and Pharmacia's SC-744 and SC-795, as well as CETi-1 and JTT-705.

[0089] The hypolipidemic agent may be an ileal Na^+/bile acid co-transporter inhibitor such as disclosed in *Drugs of the Future*, 24:425-430 (1999). The ATP

citrate lyase inhibitor which may be employed in the combination of the application may include, for example, those disclosed in U.S. Patent No. 5,447,954.

[0090] The other lipid agent also includes a phytoestrogen compound such as disclosed in WO 00/30665 including isolated soy bean protein, soy protein concentrate or soy flour as well as an isoflavone such as genistein, daidzein, glycitein or equol, or phytosterols, phytostanol or tocotrienol as disclosed in WO 2000/015201; a beta-lactam cholesterol absorption inhibitor such as disclosed in EP 675714; an HDL upregulator such as an LXR agonist, a PPAR α-agonist and/or an FXR agonist; an LDL catabolism promoter such as disclosed in EP 1022272; a sodium-proton exchange inhibitor such as disclosed in DE 19622222; an LDL-receptor inducer or a steroidal glycoside such as disclosed in U.S. Patent No. 5,698,527 and GB 2304106; an anti-oxidant such as beta-carotene, ascorbic acid, α-tocopherol or retinol as disclosed in WO 94/15592 as well as Vitamin C and an antihomocysteine agent such as folic acid, a folate, Vitamin B6, Vitamin B12 and Vitamin E; isoniazid as disclosed in WO 97/35576; a cholesterol absorption inhibitor, an HMG-CoA synthase inhibitor, or a lanosterol demethylase inhibitor as disclosed in WO 97/48701; a PPAR δ agonist for treating dyslipidemia; or a sterol regulating element binding protein-I (SREBP-1) as disclosed in WO 2000/050574, for example, a sphingolipid, such as ceramide, or neutral sphingomyelenase (N-SMase) or fragment thereof. Preferred hypolipidemic agents are pravastatin, lovastatin, simvastatin, atorvastatin, fluvastatin, pitavastatin and rosuvastatin, as well as niacin and/or cholestagel.

[0091] The compounds of the present invention may also be employed in combination with anti-hypertensive agents. Examples of suitable anti-hypertensive agents for use in combination with the compounds of the present application include beta adrenergic blockers, calcium channel blockers (L-type and/or T-type; e.g., diltiazem, verapamil, nifedipine, amlodipine and mybefradil), diuretics (e.g., chlorothiazide, hydrochlorothiazide, flumethiazide, hydroflumethiazide, bendroflumethiazide, methylchlorothiazide, trichloromethiazide, polythiazide, benzthiazide, ethacrynic acid tricrynafen, chlorthalidone, furosemide, musolimine, bumetanide, triamtrenene, amiloride, spironolactone), renin inhibitors, ACE inhibitors (e.g., captopril, zofenopril, fosinopril, enalapril, ceranopril, cilazopril, delapril, pentopril, quinapril, ramipril, lisinopril), AT-1 receptor antagonists (e.g., losartan,

irbesartan, valsartan), ET receptor antagonists (e.g., sitaxsentan, atrsentan and compounds disclosed in U.S. Patent Nos. 5,612,359 and 6,043,265), Dual ET/AII antagonist (e.g., compounds disclosed in WO 00/01389), neutral endopeptidase (NEP) inhibitors, vasopepsidase inhibitors (dual NEP-ACE inhibitors) (e.g., omapatrilat and gemopatrilat), and nitrates.

[0092] MCHR1 antagonists could also be useful in treating other diseases associated with obesity, including sleep disorders. Therefore, the compounds described in the present application could be used in combination with therapeutics for treating sleep disorders. Examples of suitable therapies for treatment of sleeping disorders for use in combination with the compounds of the present application include melatonin analogs, melatonin receptor antagonists, ML 1 B agonists, GABA receptor modulators; NMDA receptor modulators, histamine-3 (H3) receptor modulators, dopamine agonists and orexin receptor modulators.

[0093] MCHR1 antagonists may reduce or ameliorate substance abuse or addictive disorders. Therefore, combination of cannabinoid receptor modulators with agents used to treat addictive disorders may reduce the dose requirement or improve the efficacy of current addictive disorder therapeutics. Examples of agents used to treat substance abuse or addictive disorders are: selective serotonin reuptake inhibitors (SSRI), methadone, buprenorphine, nicotine and bupropion.

[0094] MCHR1 antagonists may reduce anxiety or depression; therefore, the compounds described in this application may be used in combination with anti-anxiety agents or antidepressants. Examples of suitable anti-anxiety agents for use in combination with the compounds of the present application include benzodiazepines (e.g., diazepam, lorazepam, oxazepam, alprazolam, chlordiazepoxide, clonazepam, chlorazepate, halazepam and prazepam), 5HT1A receptor agonists (e.g., buspirone, flesinoxan, gepirone and ipsapirone), and corticotropin releasing factor (CRF) antagonists.

[0095] Examples of suitable classes of anti-depressants for use in combination with the compounds of the present application include norepinephrine reuptake inhibitors (tertiary and secondary amine tricyclics), selective serotonin reuptake inhibitors (SSRIs) (fluoxetine, fluvoxamine, paroxetine and sertraline), monoamine oxidase inhibitors (MAOIs) (isocarboxazid, phenelzine, tranylcypromine, selegiline),

reversible inhibitors of monoamine oxidase (RIMAs) (moclobemide), serotonin and norepinephrine reuptake inhibitors (SNRIs) (venlafaxine), corticotropin releasing factor (CRF) receptor antagonists, alpha-adrenoreceptor antagonists, and atypical antidepressants (bupropion, lithium, nefazodone, trazodone and viloxazine).

[0096] The combination of a conventional antipsychotic drug with a MCHR1 antagonist could also enhance symptom reduction in the treatment of psychosis or mania. Further, such a combination could enable rapid symptom reduction, reducing the need for chronic treatment with antipsychotic agents. Such a combination could also reduce the effective antipsychotic dose requirement, resulting in reduced probability of developing the motor dysfunction typical of chronic antipsychotic treatment.

[0097] Examples of suitable antipsychotic agents for use in combination with the compounds of the present application include the phenothiazine (chlorpromazine, mesoridazine, thioridazine, acetophenazine, fluphenazine, perphenazine and trifluoperazine), thioxanthine (chlorprothixene, thiothixene), heterocyclic dibenzazepine (clozapine, olanzepine and aripiprazole), butyrophenone (haloperidol), diphenylbutylpiperidine (pimozide) and indolone (molindolone) classes of antipsychotic agents. Other antipsychotic agents with potential therapeutic value in combination with the compounds in the present application include loxapine, sulpiride and risperidone.

[0098] Combination of the compounds in the present application with conventional antipsychotic drugs could also provide an enhanced therapeutic effect for the treatment of schizophrenic disorders, as described above for manic disorders. As used here, schizophrenic disorders include paranoid, disorganized, catatonic, undifferentiated and residual schizophrenia, schizophreniform disorder, schizoaffective disorder, delusional disorder, brief psychotic disorder and psychotic disorder not specified. Examples of suitable antipsychotic drugs for combination with the compounds in the present application include the antipsychotics mentioned above, as well as dopamine receptor antagonists, muscarinic receptor agonists, 5HT2A receptor antagonists and 5HT2A/dopamine receptor antagonists or partial agonists (e.g., olanzepine, aripiprazole, risperidone, ziprasidone).

DOSAGE FORMS

[0099] The compounds of the present invention can be administered in oral dosage form The dosage form for said pharmaceutical composition includes such oral dosage forms as granules, powders, tablets, capsules, syrups, emulsions, suspensions, etc. and such non-oral dosage forms as injections (e.g., subcutaneous, intravenous, intramuscular and intraperitoneal injections), drip infusions, external application forms (e.g., nasal spray preparations, transdermal preparations, ointments, etc.), and suppositories (e.g., rectal and vaginal suppositories).

[00100] These dosage forms can be manufactured by the per se known technique conventionally used in pharmaceutical procedures. The specific manufacturing procedures are as follows.

[00101] To manufacture an oral dosage form, an excipient (e.g., lactose, sucrose, starch, mannitol, etc.), a disintegrator (e.g., calcium carbonate, carboxymethylcellulose calcium, etc.), a binder (e.g., α-starch, gum arabic, carboxymethylcellulose, polyvinylpyrrolidone, hydroxypropylcellulose, etc.), and a lubricant (e.g., talc, magnesium stearate, polyethylene glycol 6000, etc.), for instance, are added to the active component or components and the resulting composition is compressed. Where necessary, the compressed product is coated, by the per se known technique, for masking the taste or for enteric dissolution or sustained release. The coating material that can be used includes, for instance, ethylcellulose, hydroxymethylcellulose, polyoxyethylene glycol, cellulose acetate phthalate, hydroxypropylmethylcellulose phthalate, and Eudragit (Rohm & Haas, Germany, methacrylic-acrylic copolymer).

[00102] Injections can be manufactured typically by the following procedure. The active component or components are dissolved, suspended or emulsified in an aqueous vehicle (e.g., distilled water, physiological saline, Ringer's solution, etc.) or an oily vehicle (e.g., vegetable oil such as olive oil, sesame oil, cottonseed oil, corn oil, etc. or propylene glycol) together with a dispersant, e.g., Tween 80 (Atlas Powder, U.S.A.), HCO 60 (Nikko Chemicals), polyethylene glycol, carboxymethylcellulose, sodium alginate, etc.), a preservative (e.g., methyl p-hydroxybenzoate, propyl p-hydroxybenzoate, benzyl alcohol, chlorobutanol, phenol, etc.), an isotonizing agent (e.g., sodium chloride, glycerol, sorbitol, glucose, inverted

sugar, etc.) and other additives. If desired, a solubilizer (e.g., sodium salicylate, sodium acetate, etc.), a stabilizer (e.g., human serum albumin), a soothing agent (e.g., benzalkonium chloride, procaine hydrochloride, etc.) and other additives can also be added.

[00103] A dosage form for external application can be manufactured by processing the active component or components into a solid, semi-solid or liquid composition. To manufacture a solid composition, for instance, the active component or components, either as they are or in admixture with an excipient (e.g., lactose, mannitol, starch, microcrystalline cellulose, sucrose, etc.), a thickener (e.g., natural gums, cellulose derivatives, acrylic polymers, etc.), etc., are processed into powders. The liquid composition can be manufactured in substantially the same manner as the injections mentioned above. The semi-solid composition is preferably provided in a hydrous or oily gel form or an ointment form. These compositions may optionally contain a pH control agent (e.g., carbonic acid, phosphoric acid, citric acid, hydrochloric acid, sodium hydroxide, etc.), and a preservative (e.g., p-hydroxybenzoic acid esters, chlorobutanol, benzalkonium chloride, etc.), among other additives.

[00104] Suppositories can be manufactured by processing the active component or components into an oily or aqueous composition, whether solid, semi-solid or liquid. The oleaginous base that can be used includes, for instance, higher fatty acid glycerides [e.g., cacao butter, Witepsols (Dinamit-Nobel), etc.], medium-chain fatty acids [e.g., Migriols (Dinamit-Nobel), etc.], vegetable oils (e.g., sesame oil, soybean oil, cotton-seed oil, etc.), etc. The water-soluble base includes, for instance, polyethylene glycols propylene glycol, etc. The hydrophilic base includes, for instance, natural gums, cellulose derivatives, vinyl polymers, and acrylic polymers, etc.

DOSAGES

[00105] The dosage of the pharmaceutical composition of the present invention may be appropriately determined with reference to the dosages recommended for the respective active components and can be selected appropriately according to the recipient, the recipient's age and body weight, current clinical status, administration

time, dosage form, method of administration, and combination of the active components, among other factors. For example, the dosage of the compound of Formula I of the invention for a human adult can be selected from the clinical oral dose range of 0.01 to 30 mg/kg body weight (preferably 0.05 to 10 mg/kg body weight, more preferably 0.05 to 5 mg/kg body weight) or the clinical parenteral dose range of 0.005 to 10 mg/kg body weight (preferably 0.01 to 10 mg/kg body weight, more preferably 0.01 to 1 mg/kg body weight) or 1 to 1000 mg/day. The other active component or components having different modes of action for use in combination can also be used in dose ranges selected by referring to the respective recommended clinical dose ranges. Administration is generally carried out in a single dose/day or in divided doses, for example, 2 to 4 times a day.

ABBREVIATIONS

[00106] The following abbreviations may be employed herein:

Ph = phenyl

Bn = benzyl

t-Bu = tertiary butyl

Me = methyl

Et = ethyl

TMS = trimethylsilyl

TBS = *tert*-butyldimethylsilyl

Et_2O = diethyl ether

EtOAc = ethyl acetate

MeOH = methanol

EtOH = ethanol

i-PrOH = isopropanol

HOAc or AcOH = acetic acid

i-Pr_2NEt = diisopropylethylamine

Et_3N = triethylamine

DMAP = 4-dimethylaminopyridine

$NaBH_4$ = sodium borohydride

n-BuLi = n-butyllithium

Pd/C = palladium on carbon

KOH = potassium hydroxide

NaOH = sodium hydroxide

LiOH = lithium hydroxide

K_2CO_3 = potassium carbonate

$NaHCO_3$ = sodium bicarbonate

Ar = argon

N_2 = nitrogen

min = minute(s)

h or hr = hour(s)

L = liter

mL = milliliter

μL = microliter

g = gram(s)

mg = milligram(s)

mol = moles

mmol = millimole(s)

meq = milliequivalent

RT = room temperature

sat or sat'd = saturated

aq. = aqueous

TLC = thin layer chromatography

HPLC = high performance liquid chromatography

LC/MS = high performance liquid chromatography/mass spectrometry

MS or Mass Spec = mass spectrometry

NMR = nuclear magnetic resonance

mp = melting point

EXAMPLES

[00107] The following examples are provided to illustrate various preferred embodiments of the invention, and should not be construed as limiting the scope thereof.

GENERAL EXPERIMENTAL INFORMATION SECTION

[00108] In the following examples, nomenclature conforms to either IUPAC or CAS guidelines; was generated using (or is consistent with) the Autonom® module (version 2.1) distributed with ChemDraw Ultra 6.0®; or are taken from vendor literature.

brine = saturated aqueous sodium chloride

DIC = diisopropylcarbodiimide

DMF = N,N-dimethylformamide

HOBT = Hydroxybenzotriazole

PyBOP = benzotriazo-1-yl-oxy-trispyrrolidinophosphonium hexafluoroborate

TFA = trifluoroacetic acid

THF = tetrahydrofuranyl

WSC = 1-[3-(dimethylamino)propyl]-3-ethylcarbodiimide hydrochloride

Analytical Chromatography Methods

[00109] HPLC: column:

Method 1: Phenom-Luna (ODS) S-5, 4.6 mm x 50 mm; flow-5.0 mL/min.; detection at 220 nm; solvent- A = 10% methanol/water + 0.2% phosphoric acid, B = 90% methanol/water + 0.2% phosphoric acid; gradient-linear, 0% B to 100% B over 4 min and 100% B for 1 min.

Method 2: YMC Combiscreen S-5, 4.6 mm x 50 mm; flow-4.0 mL/min.; detection at 220 nm; solvent- A = 10% methanol/water + 0.2% phosphoric acid, B = 90% methanol/water + 0.2% phosphoric acid; gradient-linear, 0% B to 100% B over 4 min and 100% B for 1 min.

LC MS: column-Phen-Luna (S5 ODS column) 4.6 mm x 30 mm; detection at 220 nm; flow-4 mL/min; solvent- A = 10% methanol/water + 0.1% TFA, B = 90% methanol/water + 0.1% TFA; linear gradient, 0% B to 100% B over 2 min and 100% B for 1 min.

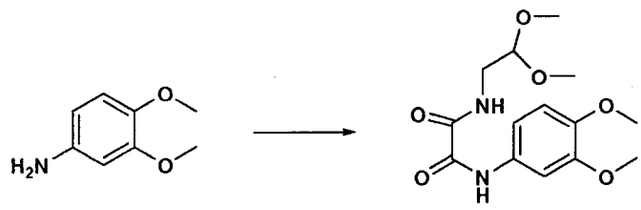
Preparative HPLC Chromatography Method

[00110] Phenomenex Luna C18, S5, 21 x 100 mm; flow-20 mL/min, detection at 220 nm; solvent- A = 10% methanol/water + 0.1% TFA, B = 90% methanol/water + 0.1% TFA; gradient-linear, 10% B to 90% B over 20 min.

General Experimental Procedures for Preparation of 3-(Arylthio)-1-(aryl)pyrazin-2(1H)-one

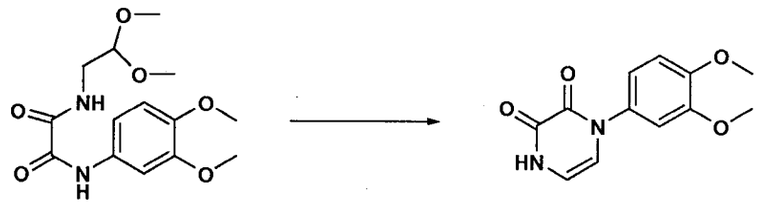
Preparation of 1-Aryl pyrazine-2,3(1H,4H)-dione

Part A



[00111] Ethyl oxalyl chloride (7.8 g, 6.8 mL, 57 mmol) was added to a mixture of 3,4-dimethoxyaniline (4.4 g, 29 mmol) and K_2CO_3 (14 g, 140 mmol) in EtOAc (44 mL) and water (12 mL) at 0°C. After stirring at 0°C for 10 min, water (18 mL) was added; whereupon the mixture was transferred to a separatory funnel and extracted with EtOAc (2 x 40 mL). The combined EtOAc were filtered through Na_2SO_4 and evaporated to about 30 mL. After addition of 2,2-dimethoxyethylamine (3.8 g, 3.9 mL, 36 mmol), the reaction was stirred at ambient temperature overnight. The resultant white solid was filtered and then washed with hexane to afford N1-(2,2-dimethoxyethyl)-N2-(3,4-dimethoxyphenyl)oxalamide as a light purple-grey solid (6.3 g, 71% yield). HPLC 33% 2.47 min and 63% at 2.79 min. LC MS 1.37 min (M+1 = 281 and 335). H-NMR ($CDCl_3$) 9.15 (broad s, 1H), 7.76 (broad s, 1H), 7.41 (d, J = 2.4 Hz, 1H), 7.06 (dd, J = 2.4, 8.7 Hz, 1H), 6.85 (d, J = 8.7 Hz, 1H), 4.45 (t, J = 5.5 Hz, 1H), 3.90 (s, 3H), 3.88 (s, 3H), 3.52 (t, J = 5.5 Hz, 2H), 3.42 (s, 6 H).

Part B

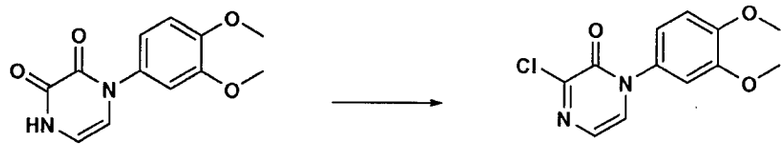


[00112] After addition of trifluoroacetic acid (0.12 mL, 1.7 mmol) to a mixture of the aryl oxalamide prepared in Part A (0.50 g, 1.6 mmol) in acetic acid (1.0 mL), the resulting solution was heated to 125°C for 20 min using a microwave. Following evaporation of the solvent, the residue was triturated with EtOAc to afford 1-(3,4-dimethoxyphenyl)pyrazine-2,3(1H,4H)-dione as a white solid (1.1 g, 92% yield). HPLC 1.83 min. LC MS 1.20 min (M+1 = 249). H-NMR (CD_3OD) 7.06 (m, 2H), 6.97 (m, 1H), 6.56 (d, J = 5.7 Hz, 1H), 6.45 (d, J = 5.7 Hz, 1H), 3.89 (s, 3H), 3.85 (s, 3H).

Preparation of Desired Substituted 3-thio-1-aryl-pyrazin-2(1H)-one

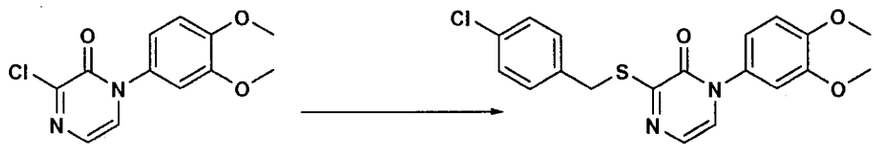
Method 1

Part C



[00113] Thionyl chloride (0.28 g, 0.17 mL, 2.4 mmol) was slowly added to a stirred solution of the 1-aryl pyrazine-2,3(1H,4H)-dione prepared in Part B (0.54 g, 2.2 mmol) in EtOAc (0.88 mL) and DMF (0.44 mL) at 45°C. After stirring at 55 to 60°C for 2 h, the reaction was transferred to a separatory funnel, diluted with EtOAc and 2N $KHCO_3$ and extracted with EtOAc (2 x). The combined organic layers were washed with 2N $KHCO_3$ and water; whereupon, the combined aqueous layers were extracted with CH_2Cl_2. All of the organic layers were combined prior to drying over $MgSO_4$ to afford 3-chloro-1-(3,4-dimethoxyphenyl)pyrazin-2(1H)-one (0.34 g, 59% yield). HPLC 2.33 min. LC MS 1.00 min (M+1 = 267/269). The chloropyrazinone was used in the subsequent steps without further purification.

Part D



[00114] 4-Chlorobenzylmercaptan (71 mg, 0.059 mL, 0.45 mmol) was added to a stirred THF (1.0 mL) suspension of sodium hydride (60% oil dispersion, 18 mg, 0.45 mmol), that had been previously washed with hexane 3x. The reaction was stirred at ambient temperature for 20 min until it became a solid mass; whereupon, the chloropyrazinone prepared in Part C (100 mg, 0.38 mmol) in THF (5 mL) was added resulting in gas evolution. After stirring at ambient temperature for 40 min, the reaction was diluted with CH_2Cl_2/H_2O, extracted with CH_2Cl_2 (2 x) and dried over $MgSO_4$ to afford 220 mg of crude product after evaporation of the solvent. The desired was purified by chromatography on silica gel (12 g) employing gradient elution (0 - 100% EtOAc/hexane over 12 min) to elute the desired 3-(4-chlorobenzylthio)-1-(3,4-dimethoxyphenyl)pyrazin-2(1H)-one (130 mg, 89% yield).

Method 2

[00115] A solution of the 1-aryl pyrazine-2,3(1H,4H)-dione prepared in Part B (67 mg, 0.27 mmol), diisopropylethyl amine (0.15 mL, 0.81 mmol), pyBOP (0.23 g, 0.46 mmol), and dimethylaminopyridine (13 mg) in DMF (1.2 mL) was stirred at ambient temperature for 15 min. After addition of 2-pyridylethyl mercaptan (28 mg, 0.40 mmol), the reaction was stirred at ambient temperature for 2.5 h prior to quenching by addition of H_2O and extraction with EtOAc. The EtOAc extracts were washed with water (2 x), brine, dried over $MgSO_4$ and concentrated to yield 204 mg of crude product. Chromatography on silica employing a gradient elution with hexane/EtOAc afforded the desired product 1-(3,4-dimethoxyphenyl)-3-(2-(pyrazin-2-yl)ethylthio)pyrazin-2(1H)-one (17 mg, 17% yield).

Method 2a

[00116] The same procedure was employed as that described in Method 2 except that the reaction was run for 18 hr.

Method 3

[00117] Following preparation of the oxalamide as described in Part A, ring closure can be effected by prolonged thermal heating in TFA/HOAc at 78°C for 1d. In the case of 3-methoxy-4-(2-(pyrrolidin-1-yl)ethoxy)aniline which contained a basic amine, the reaction was brought to pH 6 to 7 with saturated $NaHCO_3$ and then evaporated *in vacuo*. The residue was absorbed on silica gel and purified by flash chromatography (5 to 15% 2N NH_3 in $MeOH/CH_2Cl_2$) to afford the desired 1-aryl pyrazine-2,3(1H,4H)-dione in 36% yield. This material was subsequently converted to final product following the procedure described in Method 2.

Method 4

[00118] If the oxalamide as described in Part A contained a primary or secondary alcohol, prolonged thermal heating in TFA/HOAc at 78°C for 1 day not only effected ring closure but also converted the alcohol moiety to an acetate. The resulting 1-aryl pyrazine-2,3(1H,4H)-dione was converted to the desired 3-thio substituted-1-arylpyrazin-2-one employing Method 1. Following workup and purification as described in Method 1, the acetylated product was converted to the desired 3-thio substituted-1-arylpyrazin-2-one (19 mg, 0.041 mmol) bearing a free hydroxyl by dissolution in MeOH (1.0 mL) and H_2O (0.1 mL) and stirring at ambient temperature for 1h after addition of potassium carbonate (30 mg). The reaction was then diluted with CH_2Cl_2/H_2O prior to extraction with CH_2Cl_2 (2 x). After drying the combined organic layers over $MgSO_4$, concentration afforded the desired final product (16 mg, 93% yield).

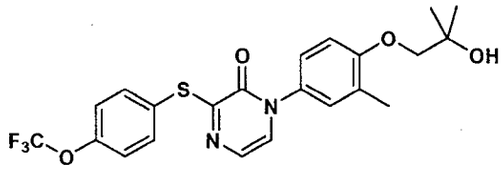
Method 5

[00119] For weakly nucleophilic thiols more forcing conditions were required effect PyBOP mediated conversion of the 1-aryl pyrazine-2,3(1H,4H)-dione to a 3-thio substituted-1-arylpyrazin-2-ones. Accordingly, a DMF solution (0.4 mL) containing the 1-aryl pyrazine-2,3(1H,4H)-dione prepared in Part B (92 mg, 0.30 mmol), PyBOP (0.27 g, 0.53 mmol) and diisopropylethylamine (0.16 mL, 0.9 mmol) was stirred for 3 h before addition of a DMF solution prepared by stirring 5-methoxybenzo[d]thiazole-2-thiol (296 mg, 1.502 mmol) with NaH (60.1 mg, 1.502

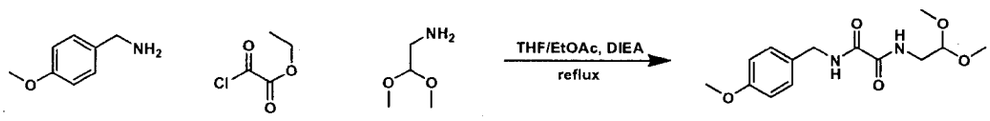
mmol, rinsed with hexane 2x) in DMF (0.2 mL) at ambient temperature for 10 min. After stirring at ambient temperature for 7 days, the reaction mixture was diluted with EtOAc and washed sequentially with water (2 x) and brine prior to drying over $MgSO_4$. After evaporation of the solvent, CH_2Cl_2 (10 mL) was added to the 0.30 g of crude product. Filtration to remove any residual solids followed by evaporation of the filtrate afforded 0.10 g crude product. Final purification required flash chromatography on 12 g silica gel using gradient elution (0 to 100% EtOAc/CH_2Cl_2) followed by preparatory HPLC (YMC S5 ODS 20x100 mm, 20 mL/min, 30 to 100% B in A over 10 min, .Solvent A = 10% MeOH/H_2O - 0.1% TFA, Solvent B = 90% MeOH/H_2O - 0.1% TFA) to afford pure desired product (6.3 mg, 4% yield).

Method 6

General Experimental Procedures for Preparation of 1-(4-(2-Hydroxy-2-methylpropoxy)-3-methylphenyl)-3-(4-(trifluoromethoxy)phenylthio)pyrazin-2(1H)-one



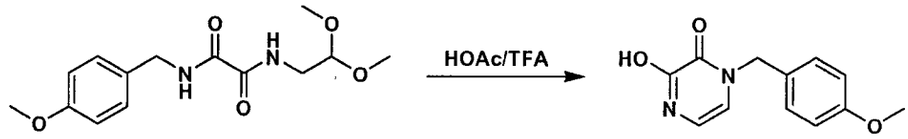
Part A. N1-(2,2-Dimethoxyethyl)-N2-(4-methoxybenzyl)oxalamide



[00120] To a mixture of (4-methoxyphenyl)methanamine (9.90 g, 72.2 mmol) in THF (40 mL) was slowly added ethyl 2-chloro-2-oxoacetate (10.84 g, 79 mmol). After stirring the reaction at RT for 15 min, a solution of 2,2-dimethoxyethanamine (9.10 g, 87 mmol) and N,N-diisopropylethylamine (37.8 mL, 217 mmol) in EtOAc (40.0 mL) was added. The reaction was heated at reflux for 18 hours; whereupon, after cooling to RT, saturated $NaHCO_3$ (50 ml) was added and the mixture extracted with EtOAc (50 ml). The EtOAc layer was dried over Na_2SO_4 and concentrated. The crude product was purified by silica gel chromatography employing a solvent gradient (CH_2Cl_2 to 5 % MeOH/ CH_2Cl_2) to elute N1-(2,2-dimethoxyethyl)-N2-(4-

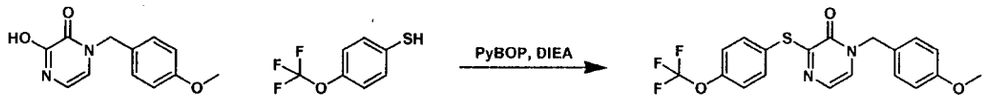
methoxybenzyl)oxalamide (7.50 g, 25.3 mmol, 35.1 % yield) as white solid. 1H NMR (400 MHz, chloroform-d) δ ppm 9.07 (1 H, s), 7.69 (1 H, t, J=5.65 Hz), 7.59 (1 H, d, J=8.78 Hz), 6.74 (1 H, d, J=8.78 Hz), 4.46 (1 H, t, J=5.40 Hz), 3.79 (2 H, s), 3.53 (2 H, t), 3.44 (6 H, s), 2.23 (6 H, d, J=5.27 Hz), 1.37 (6 H, s).

Part B. 3-Hydroxy-1-(4-methoxybenzyl)pyrazin-2(1H)-one



[00121] A solution of N1-(2,2-dimethoxyethyl)-N2-(4-methoxybenzyl)oxalamide (7.5 g, 25.3 mmol) and TFA (2.340 mL, 30.4 mmol) in AcOH (160 mL) was stirred at 135°C in a seal tube for 1.5 hours. After cooling to RT and removal of the volatiles under vacuum, ethyl ether (150 ml) and sat. aq. $NaHCO_3$ solution (150 ml) were added. The resulting precipitate was collected by filtration, washed with H_2O (50 ml) and ether (50 ml) prior to drying under high vacuum to yield 3-hydroxy-1-(4-methoxybenzyl)pyrazin-2(1H)-one (5.30 g, 21.68 mmol, 86 % yield) as brown solid. 1H NMR (400 MHz, DMSO-d_6) δ ppm 11.17 (1 H, br. s.), 7.18 (2 H, d), 6.81 (2 H, d), 6.46 (1 H, d, *J*=5.77 Hz), 6.23 (1 H, br. s.), 4.74 (2 H, s), 3.24 (1 H, s).

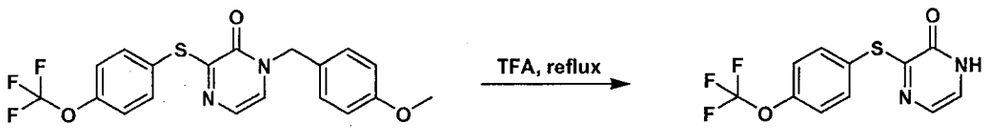
Part C. 1-(4-Methoxybenzyl)-3-(4-(trifluoromethoxy)phenylthio)pyrazin-2(1H)-one



[00122] A mixture of 3-hydroxy-1-(4-methoxybenzyl)pyrazin-2(1H)-one (2.0 g, 8.61 mmol), PyBOP (7.84 g, 15.07 mmol) and N,N-diisopropylethylamine (4.51 mL, 25.8 mmol) in DMF (40 mL) was stirred at RT under N_2 for 3 hours whereupon 4-(trifluoromethoxy)benzenethiol (2.007 g, 10.33 mmol) was added. After having stirred for 18 additional hours, the reaction was diluted with saturated aq. $NaHCO_3$ (65 ml) and was then extracted with EtOAc (60 ml). The EtOAc layer was dried over Na_2SO_4 and concentrated. The crude product was purified by silica gel chromatography employing a solvent gradient (hexane to 75 % EtOAc/hexane) to elute 1-(4-methoxybenzyl)-3-(4-(trifluoromethoxy)phenylthio)pyrazin-2(1H)-one

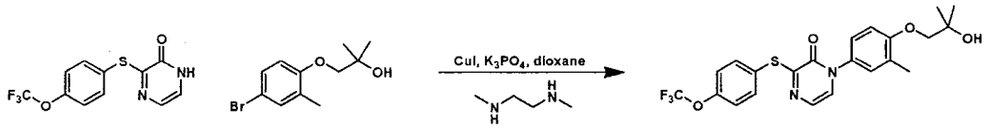
(2.76 g, 6.42 mmol, 74.6 % yield) as white solid. 1H NMR (400 MHz, chloroform-d) δ ppm 7.58 (2 H, d, *J*=8.78 Hz), 7.21 - 7.35 (4 H, m), 7.02 (1 H, d, *J*=4.52 Hz), 6.90 (2 H, d, *J*=8.78 Hz), 6.85 (1 H, d, *J*=4.27 Hz), 5.03 (2 H, s), 3.81 (3 H, s).

Part D. 3-(4-(Trifluoromethoxy)phenylthio)pyrazin-2(1H)-one



[00123] A solution of 1-(4-methoxybenzyl)-3-(4-(trifluoromethoxy)phenylthio)-pyrazin-2(1H)-one (2.76 g, 6.76 mmol) in TFA (25 mL) was stirred at reflux for 2 days. Since LC-MS analysis revealed that 28 % SM remained, the reaction was stirred for 7 days. After removal of the TFA under vacuum, the crude product was purified by silica gel chromatography employing a solvent gradient (hexane to 100 % EtOAc to elute 3-(4-(trifluoromethoxy)phenylthio)pyrazin-2(1H)-one (1.60 g, 5.27 mmol, 78 % yield) as off-white solid. 1H NMR (400 MHz, chloroform-d) δ ppm 7.61 (2 H, d, J=9.03 Hz), 7.29 (2 H, d, J=7.78 Hz), 7.24 (1 H, d, J=4.02 Hz), 7.07 (1 H, d).

Part E. 1-(4-(2-Hydroxy-2-methylpropoxy)-3-methylphenyl)-3-(4-(trifluoromethoxy)phenylthio)pyrazin-2(1H)-one

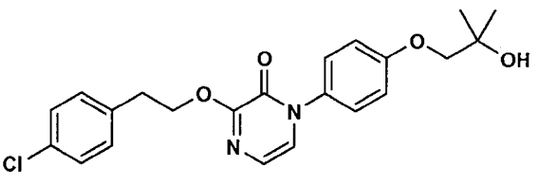


[00124] A mixture of 3-(4-(trifluoromethoxy)phenylthio)pyrazin-2(1H)-one (100 mg, 0.347 mmol), 1-(4-bromo-2-methylphenoxy)-2-methylpropan-2-ol (90 mg, 0.347 mmol), N1,N2-dimethylethane-1,2-diamine (92 mg, 1.041 mmol), copper(I) iodide (19.82 mg, 0.104 mmol) and K_3PO_4 (221 mg, 1.041 mmol) in dioxane (1.0 mL) was stirred at 115°C in a sealed tube for 2 hours. After removal of the precipitate by filtration, the filtrate was concentrated. The crude product was purified by silica gel chromatography employing a solvent gradient (hexane to 100 % EtOAc) to elute 1-(4-(2-hydroxy-2-methylpropoxy)-3-methylphenyl)-3-(4-(trifluoromethoxy)phenylthio)-pyrazin-2(1H)-one (18.65 mg, 0.040 mmol, 11.52 % yield) as off-white solid. 1H NMR (500 MHz, methanol-d_3) δ ppm 7.62 - 7.68 (2 H,

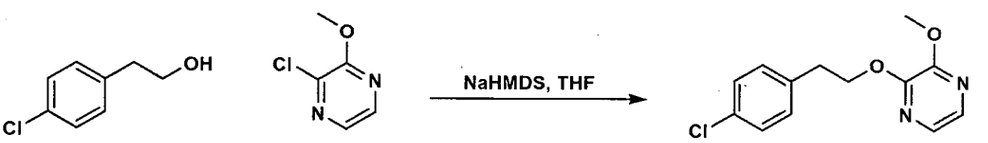
m), 7.37 (2 H, d, *J*=7.97 Hz), 7.21 - 7.28 (3 H, m), 7.16 (1 H, d, *J*=4.40 Hz), 7.02 (1 H, d, *J*=8.25 Hz), 3.84 (2 H, s), 2.31 (3 H, s), 1.36 (6 H, s).

Method 7

General Experimental Procedures for Preparation of 3-(4-Chlorophenethoxy)-1-(4-(2-hydroxy-2-methylpropoxy)phenyl)pyrazin-2(1H)-one

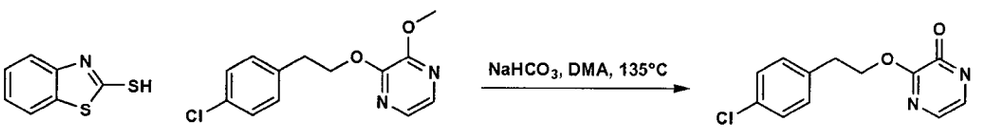


Part A. 2-(4-Chlorophenethoxy)-3-methoxypyrazine



[00125] To a mixture of 2-(4-chlorophenyl)ethanol (1.246 g, 7.96 mmol) in THF was added 1.0 M sodium bis(trimethylsilyl)amide in THF (6.92 mL, 6.92 mmol). After stirring at RT under nitrogen for 18 hours, the reaction was diluted with a solution of saturated $NaHCO_3$ (65 ml) and extracted with EtOAc 720 ml). The ethyl acetate layer was dried over Na_2SO_4 and concentrated. The crude product was purified by silica gel chromatography employing a solvent gradient (hexane to 30 % ethyl acetate) to elute 2-(4-chlorophenethoxy)-3-methoxypyrazine (1.25 g, 4.72 mmol, 68.3 % yield) as clear oil. 1H NMR (500 MHz, $CDCl_3$) δ ppm 7.61 - 7.64 (1 H, m), 7.59 - 7.61 (1 H, m), 7.26 - 7.30 (2 H, m), 7.20 - 7.24 (2 H, m), 7.15 (1 H, d, *J*=8.52 Hz), 4.49 - 4.63 (2 H, m), 4.02 (3 H, s), 3.12 (2 H, t, *J*=7.29 Hz).

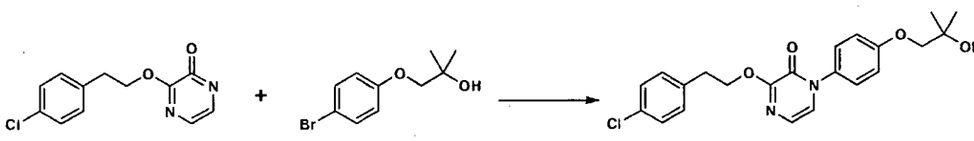
Part B. 3-(4-Chlorophenethoxy)pyrazin-2(1H)-one



[00126] A mixture of benzo[d]thiazole-2-thiol (1.264 g, 7.56 mmol), 2-(4-chlorophenethoxy)-3-methoxypyrazine (1.00 g, 3.78 mmol) and $NaHCO_3$ (1.587 g, 18.89 mmol) in DMA (10 mL) was stirred at 135°C for 6 hours. After cooling to RT,

the mixture was diluted with a solution of saturated $NaHCO_3$ (55 ml) and was then extracted with EtOAc (60 ml). The EtOAc layer was dried over Na_2SO_4 and concentrated. The crude product was purified by silica gel chromatography employing a solvent gradient (hexane to 100 % EtOAc) to elute 3-(4-chlorophenethoxy)pyrazin-2(1H)-one (477 mg, 1.808 mmol, 47.9 % yield) as off-white solid. 1H NMR (400 MHz, chloroform-d) δ ppm 7.27 - 7.31 (2 H, m), 7.19 - 7.25 (2 H, m), 6.95 (1 H, d, J=4.27 Hz), 6.89 (1 H, d, J=4.52 Hz), 4.54 (2 H, t, J=7.53 Hz), 3.14 (2 H, t, J=7.40 Hz).

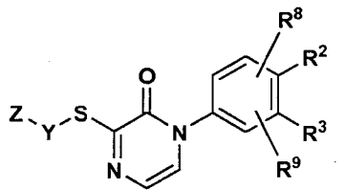
Part C. 3-(4-Chlorophenethoxy)-1-(4-(2-hydroxy-2-methylpropoxy)phenyl)pyrazin-2(1H)-one

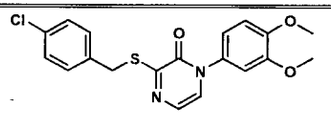
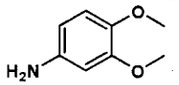
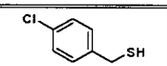
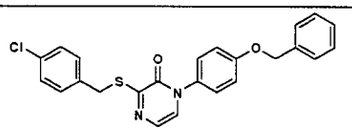
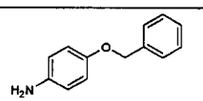
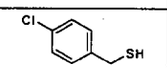
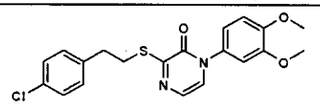
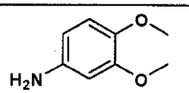
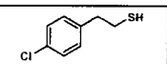
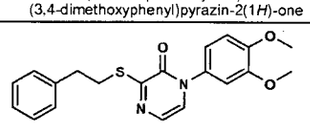
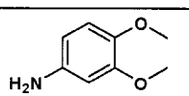
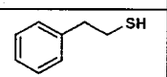


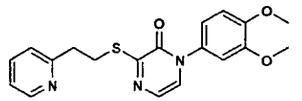
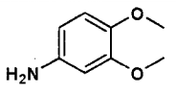
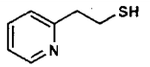
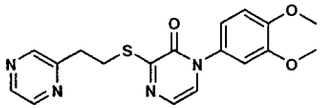
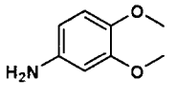
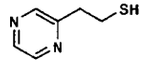
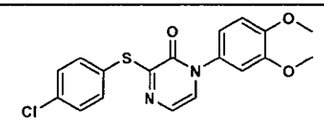
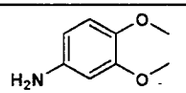
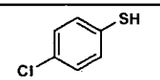
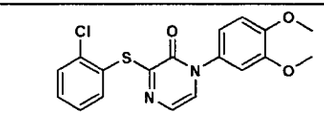
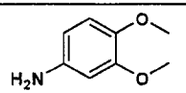
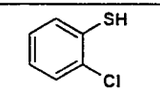
[00127] A mixture of 3-(4-chlorophenethoxy)pyrazin-2(1H)-one (25 mg, 0.100 mmol), K_3PO_4 (63.5 mg, 0.299 mmol), copper (1) iodide (18.99 mg, 0.100 mmol), 1-(4-bromophenoxy)-2-methylpropan-2-ol and N,N'-dimethylethylenediamine (0.032 mL, 0.299 mmol) in dioxane (1.0 mL) was stirred at 110 °C for 60 min. After removal of the precipitate by filtration, the filtrate was concentrated. The crude product was purified by silica gel chromatography employing a solvent gradient (CH_2Cl_2 to 10 % MeOH/ CH_2Cl_2) to elute 3-(4-chlorophenethoxy)-1-(4-(2-hydroxy-2-methylpropoxy)phenyl)pyrazin-2(1H)-one (31.82 mg, 0.073 mmol, 73.1 % yield) as white solid. 1H NMR (500 MHz, chloroform-d) δ ppm 7.32 (2 H, d), 7.23 - 7.29 (4 H, m), 7.02 (2 H, d), 6.84 (2 H, s), 4.51 (2 H, t, *J*=7.29 Hz), 3.83 (2 H, s), 3.13 (2 H, t, *J*=7.15 Hz), 1.36 (6 H, s).

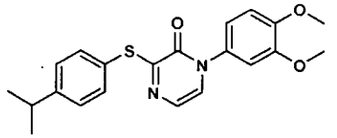
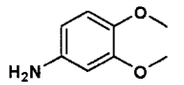
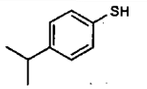
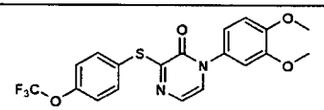
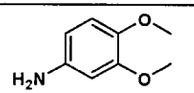
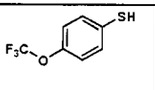
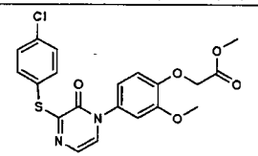
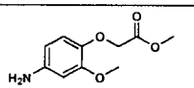
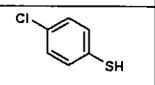
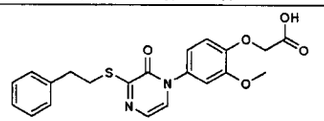
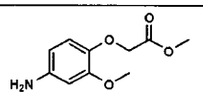
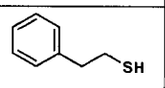
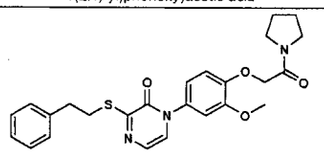
TABLE 1

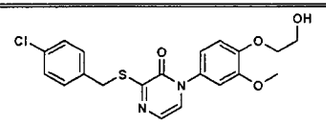
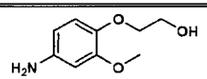
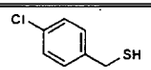
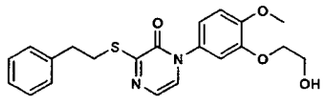
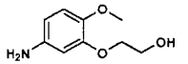
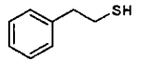
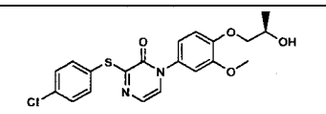
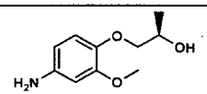
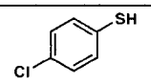
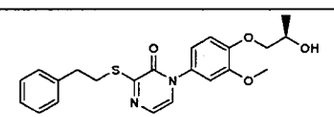
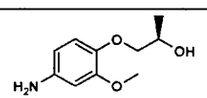
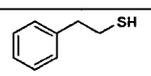
3-Thio substituted-1-arylpyrazin-2(1H)-ones

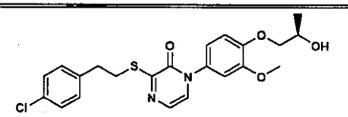
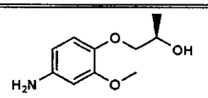
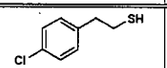
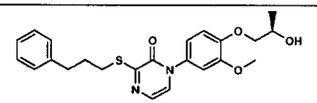
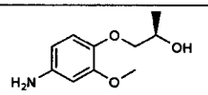
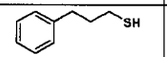
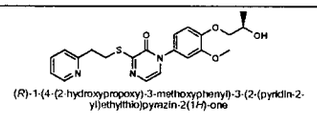
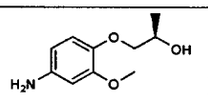
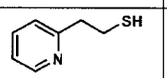
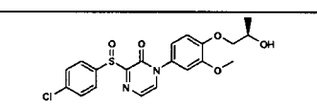


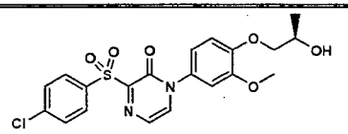
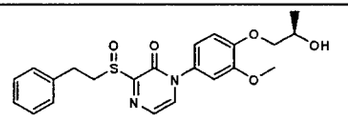
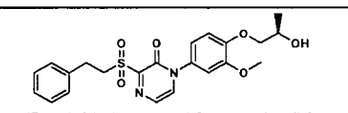
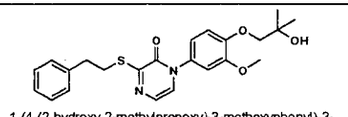
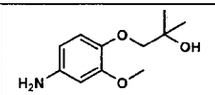
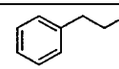
Ex. No.	Structure	Aniline/Bromide Component	Thiol Component	Method	Yield (%)	HPLC (Min) Method 1	LC-MS (M+H)	H-NMR Data ($CDCl_3$)
1	 3-(4-chlorobenzylthio)-1-(3,4-dimethoxyphenyl)pyrazin-2(1*H*)-one			1	50	4.09	389/391	7.36 (d, J = 8.4 Hz, 2H), 7.26 (d, J = 8.4 Hz, 2H), 7.41 (d, J = 2.4 Hz, 1H), 7.25 (d, J = 4.6 Hz, 1H), 6.98 (d, J = 4.6 Hz, 1H), 6.94 (d, J = 2.2 Hz, 1H), 6.91 (d, J = 8.5 Hz, 1H), 6.88 (dd, J = 2.2 and 8.5 Hz, 1H), 4.28 (s, 2H), 3.91 (s, 3H), 3.87 (s, 3H).
2	 1-(4-(benzyloxy)phenyl)-3-(4-chlorobenzylthio)pyrazin-2(1*H*)-one			1		4.60	435/437	7.44-7.24 (m, 12H), 7.05 (d, J = 8.9 Hz, 2H), 6.96 (d, J = 4.5 Hz, 1H), 5.09 (s, 2H), 4.27 (s, 2H).
3	 3-(4-chlorophenethylthio)-1-(3,4-dimethoxyphenyl)pyrazin-2(1*H*)-one			1	9	4.23	403/405	7.27 (m, 6H), 6.93 (m, 3H), 3.92 (s, 3H), 3.89 (s, 3H), 3.30 (t, J = 7.3 Hz, 2H), 2.98 (t, J = 7.3 Hz, 2H)
4	 1-(3,4-dimethoxyphenyl)-3-(phenethylthio)pyrazin-2(1*H*)-one			1	68	4.01	369	7.28 (m, 6H), 6.92 (m, 4H), 3.91 (s, 3H), 3.88 (s, 3H), 3.32 (dd, J = 2.2 and 7.5 Hz, 2H), 3.02 (dd, J = 2.2 and 7.5 Hz, 2H)

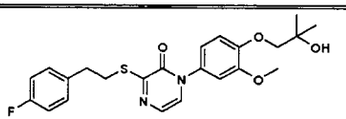
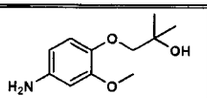
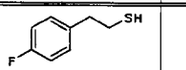
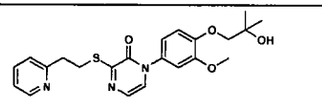
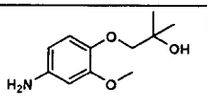
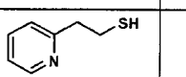
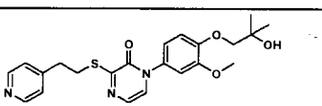
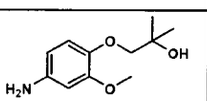
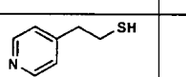
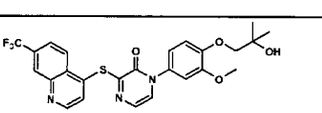
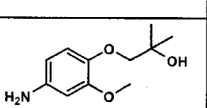
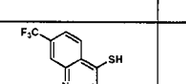
Ex. No.	Structure	Aniline/Bromide Component	Thiol Component	Method	Yield (%)	HPLC (Min) Method 1	LC-MS (M+H)	H-NMR Data ($CDCl_3$)
5	 1-(3,4-dimethoxyphenyl)-3-(2-(pyridin-2-yl)ethylthio)pyrazin-2(1*H*)-one			2	11	2.36	370	CD_3OD) 8.35 (dd, J = 1.0 and 4.5 Hz, 1H), 7.65 (m, 1H), 7.27 (d, J = 7.8 Hz, 1H), 7.23 (d, J = 4.3 Hz, 1H), 7.16 (m, 1H), 7.11 (d, J = 4.3 Hz, 1H), 6.93 (d, J = 2.3 Hz, 1H), 6.92 (d, J = 8.5 Hz, 1H), 6.82 (dd, J = 2.3 and 8.5 Hz, 1H), 3.74 (s, 3H), 3.69 (s, 3H), 3.33 (t, J = 7.1 Hz, 2H), 3.06 (t, J = 7.1 Hz, 2H).
6	 1-(3,4-dimethoxyphenyl)-3-(2-(pyrazin-2-yl)ethylthio)pyrazin-2(1*H*)-one			2	37	3.01	371	8.45 (s, 1H), 8.44 (d, J = 3.0 Hz, 1H), 8.33 (d, J = 3.0 Hz, 1H), 7.22 (d, J = 4.5 Hz, 1H), 7.12 (d, J = 4.5 Hz, 1H), 6.94 (d, J = 2.4 Hz, 1H), 6.93 (d, J = 8.5 Hz, 1H), 6.83 (dd, J = 2.4 and 8.5 Hz, 1H), 3.74 (s, 3H), 3.71 (s, 3H), 3.39 (t, J = 7.2 Hz, 2H), 3.13 (t, J = 7.2 Hz, 2H)
7	 3-(4-chlorophenylthio)-1-(3,4-dimethoxyphenyl)pyrazin-2(1*H*)-one			2	9	3.87	375/377	7.52 (d, J = 8.5 Hz, 2H), 7.42 (d, J = 8.5 Hz, 2H), 7.13 (d, J = 4.5 Hz, 1H), 6.97 (d, J = 4.5 Hz, 1H), 6.95 (m, 1H), 6.92 (m, 2H), 3.93 (s, 3H), 3.89 (s, 3H).
8	 3-(2-chlorophenylthio)-1-(3,4-dimethoxyphenyl)pyrazin-2(1*H*)-one			2	23	3.59	375/377	7.67 (dd, J = 1.7 and 7.6 Hz, 1H), 7.57 (dd, J = 1.3 and 8.0 Hz, 1H), 7.43 (dd, J = 1.7 and 7.6 Hz, 1H), 7.35 Hz (dd, J = 1.3 and 7.5 Hz, 1H), 7.12 (d, J = 4.4 Hz, 1H), 7.00 (d, J = 1.6 Hz, 1H), 6.98 (d, J = 4.4 Hz, 1H), 6.95 (m, 2H), 3.93 (s, 3H), 3.91(s, 3H).

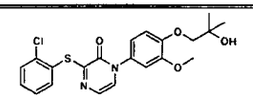
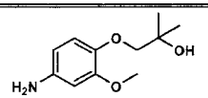
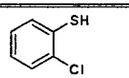
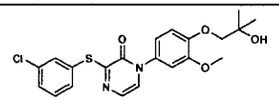
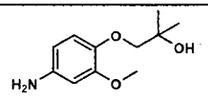
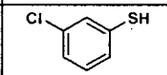
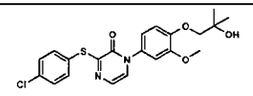
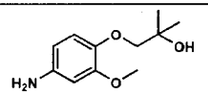
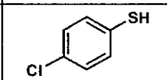
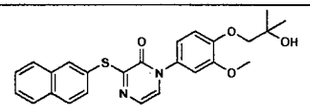
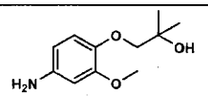
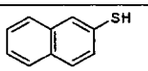
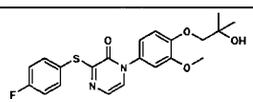
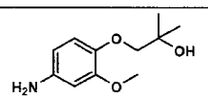
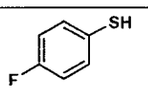
Ex. No.	Structure	Aniline/Bromide Component	Thiol Component	Method	Yield (%)	HPLC (Min) Method 1	LC-MS (M+H)	H-NMR Data ($CDCl_3$)
9	 1-(3,4-dimethoxyphenyl)-3-(4-isopropylphenylthio)-pyrazin-2(1*H*)-one			2	70	4.13	383	7.51 (d, J = 8.2 Hz, 2H), 7.32 (d, J= 8.2 Hz, 2H), 7.13 (d, J = 4.5 Hz, 1H), 6.99 (m, 1H), 6.96 (d, J = 4.5 Hz, 1H), 6.91 (m, 2H), 3.92 (s, 3H), 3.90 (s, 3H), 2.96 (sept, J = 7.7 Hz, 1H), 1.28 (d, J = 7.7 Hz, 6H).
10	 1-(3,4-dimethoxyphenyl)-3-(4-trifluoro-methoxyphenylthio)-pyrazin-2(1*H*)-one			2	60	4.02	425	7.61 (d, J = 8.5 Hz, 2H), 7.29 (d, J = 8.5 Hz, 2H), 7.13 (d, J = 4.4 Hz, 1H), 7.00 (d, J = 4.4 Hz, 1H), 6.96 (m, 1H), 6.92 (m, 2H), 3.93 (s, 3H), 3.90 (s, 3H)
11	 methyl 2-(4-(3-(4-chlorophenylthio)-2-oxopyrazin-1(2*H*)-yl)-2-methoxyphenoxy)acetate			1	2.5	3.94	433/435	7.36 (m, 2H), 7.28 (m, 3H), 6.96 (m, 3H), 6.87 (m, 1H), 4.72 (s, 3H), 4.28 (s, 2H), 3.87 (s, 3H).
12	 2-(2-methoxy-4-(2-oxo-3-(phenethylthio)pyrazin-1(2*H*)-yl)phenoxy)acetic acid			1	8		413	9.45 (broad s, 1H), 7.39 (m, 1H), 7.28 (m, 5H), 6.98 (m, 2H), 6.87 (m, 2H), 4.73 (s, 2H), 3.85 (s, 3H), 3.34 (t, J = 8.2 Hz, 2H), 3.01 (t, J = 8.2 Hz, 2H)
13	 1-(3-methoxy-4-(2-oxo-2-(pyrrolidin-1-yl)ethoxy)-phenyl)-3-(phenethylthio)pyrazin-2(1*H*)-one			WSC, HOBT mediated coupling of Ex 15	27	3.95	466	7.30 (m, 6H), 7.05 (d, J = 7.5 Hz, 1H), 7.01 (d, J = 1.6 Hz, 1H), 6.96 (d, J = 6.6 Hz, 1H) 6.84 (dd, J = 1.6 and 7.5 Hz, 1H), 4.72 (s, 2H), 3.87 (s, 3H), 3.55 (m, 4H), 3.32 (t, J = 7.4 Hz, 2H), 3.02 (t, J = 7.4 Hz, 2H), 1.97 (m, 2H), 1.86 (m, 2H).

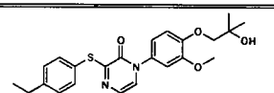
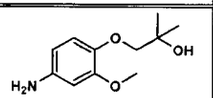
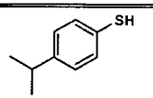
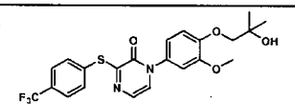
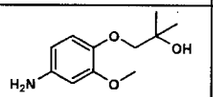
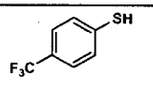
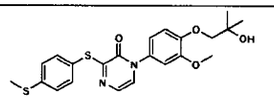
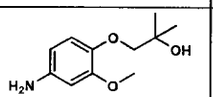
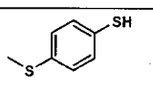
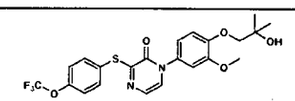
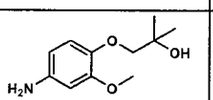
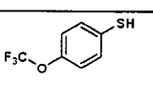
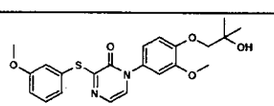
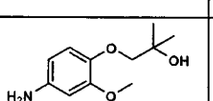
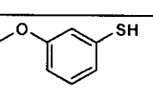
Ex. No.	Structure	Aniline/Bromide Component	Thiol Component	Method	Yield (%)	HPLC (Min) Method 1	LC-MS (M+H)	H-NMR Data ($CDCl_3$)
14	 3-(4-chlorobenzylthio)-1-(4-(2-hydroxyethoxy)-3-methoxyphenyl)pyrazin-2(1*H*)-one			4	3.9	3.96	419/421	7.36 (m, 2H), 7.26 (m, 3H), 6.97 (m, 3H), 6.87 (m, 1H), 4.28 (s, 2H), 4.15 (t, J = 4.2 Hz, 2H), 3.98 (t, J = 4.2 Hz, 2H), 3.85 (s, 3H).
15	 1-(3-(2-hydroxyethoxy)-4-methoxyphenyl)-3-(phenethylthio)pyrazin-2(1*H*)-one			2 Method 4 for ester hydrolysis	2	3.86	399	(CD_3OD) 7.41 (d, J = 4.3 Hz, 1H), 7.31 (m, 4H), 7.26 (d, J = 4.3 Hz, 1H), 7.20 (m, 1H), 7.10 (d, J = 8.6 Hz, 1H), 7.12 (d, J = 2.4 Hz, 1H), 7.00 (dd, J = 2.4 and 8.6 Hz, 1H), 4.09 (t, J = 4.7 Hz, 2H), 3.92 (s, 3H), 3.90 (t, J = 4.7 Hz, 2H), 3.33 (dd, J = 6.0 and 8.0 Hz, 2H), 3.00 (dd, J = 6.0 and 8.0 Hz, 2H).
16	 (*R*)-3-(4-chlorophenylthio)-1-(4-(2-hydroxypropoxy)-3-methoxyphenyl)pyrazin-2(1*H*)-one			4	12	3.93	419/421	7.51 (d, J = 8.5 Hz, 2H), 7.42 (d, J = 8.5 Hz, 2H), 7.13 (d, J = 4.5 Hz, 1H), 6.99 (m, 3H), 6.90 (dd, J = 1.8 and 5.9 Hz, 1H), 4.22 (m, 1H), 4.04 (dd, J = 3.0 and 9.5 Hz, 1H), 3.87 (s, 3H), 3.84 (dd, J = 1.2 and 9.5 Hz, 1H), 2.77 (broad s, 1H), 1.28 (d, J = 6.4 Hz, 3H).
17	 (*R*)-1-(4-(2-hydroxypropoxy)-3-methoxyphenyl)-3-(phenethylthio)pyrazin-2(1*H*)-one			4		4.06	413	7.27 (m, 6H), 6.97 (m, 3H), 6.89 (dd, J = 2.2 and 8.4 Hz, 1H), 4.23 (m, 1H), 4.03 (dd, J = 3.0 and 9.6 Hz, 1H), 3.86 (s, 3H), 3.84 (dd, J = 1.0 and 9.6 Hz, 1H), 3.32 (t, J = 5.4 Hz, 2H), 3.02 (t, J = 5.4 Hz, 2H), 2.83 (broad s, 1H), 1.27 (d, J = 6.4 Hz, 3H).

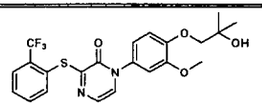
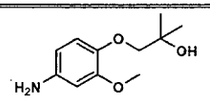
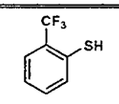
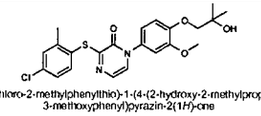
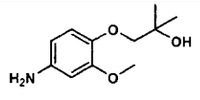
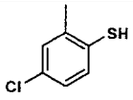
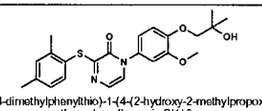
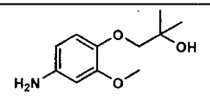
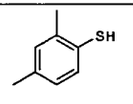
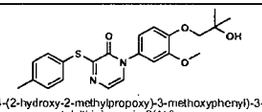
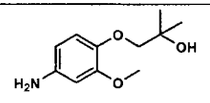
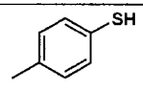
Ex. No.	Structure	Aniline/Bromide Component	Thiol Component	Method	Yield (%)	HPLC (Min) Method 1	LC-MS (M+H)	H-NMR Data ($CDCl_3$)
18	 (*R*)-3-(4-chlorophenethylthio)-1-(4-(2-hydroxypropoxy)-3-methoxyphenyl)pyrazin-2(1*H*)-one			4		4.20	447/449	7.27 (m, 5H), 6.98 (m, 3H), 6.89 (dd, J = 2.4 and 8.5 Hz, 1H), 4.23 (m, 1H), 4.02 (dd, J = 3.0 and 9.6 Hz, 1H), 3.86 (s, 3H), 3.83 (dd, J = 1.0 and 9.6 Hz, 1H), 3.30 (t, J = 7.3 Hz, 2H), 2.98 (t, J = 7.3 Hz, 2H), 2.81 (broad s, 1H), 1.27 (d, J = 6.3 Hz, 3H).
19	 (*R*)-1-(4-(2-hydroxypropoxy)-3-methoxyphenyl)-3-(3-phenylpropylthio)pyrazin-2(1*H*)-one			4		4.13	427	7.23 (m, 6H), 6.98 (m, 2H), 6.97 (d, J = 4.6 Hz, 1H), 6.95 (dd, J = 2.2 and 8.4 Hz, 1H), 4.23 (m, 1H), 4.07 (dd, J = 3.0 and 9.6 Hz, 1H), 3.87 (s, 3H), 3.84 (dd, J = 1.0 and 9.6 Hz, 1H), 3.12 (m, 2H), 2.81 (m, 2H), 2.67 (broad s, 1H), 2.07 (m, 2H), 1.27 (d, J = 6.5 Hz, 3H).
20	 (*R*)-1-(4-(2-hydroxypropoxy)-3-methoxyphenyl)-3-(2-(pyridin-2-yl)ethylthio)pyrazin-2(1*H*)-one			4		2.45	414	8.57 (d, J = 4.4 Hz, 1H), 7.62 (dd, J = 1.6 and 6.5 Hz, 1H), 7.27 (m, 2H), 7.15 (dd, J = 1.2 and 5.5 Hz, 1H), 6.96 (m, 3H), 6.88 (dd, J = 2.4 and 8.5 Hz, 1H), 4.22 (m, 1H), 4.02 (dd, J = 3.0 and 9.5 Hz, 1H), 3.85 (s, 3H), 3.86 (dd, J = 1.0 and 9.6 Hz, 1H), 3.50 (t, J = 6.8 Hz, 2H), 3.22 (t, J = 6.8 Hz, 2H), 2.98 (broad s, 1H), 1.27 (d, J = 8.6 Hz, 3H).
21	 3-(4-chlorophenylsulfinyl)-1-(4-((*R*)-2-hydroxypropoxy)-3-methoxyphenyl)pyrazin-2(1*H*)-one			MCPBA oxidation of Ex 19	57	3.18	435/437	7.90 (d, J = 8.6 Hz, 2H), 7.65 (d, J = 4.2 Hz, 1H), 7.44 (d, J = 8.6 Hz, 2H), 7.35 (d, J = 4.2 Hz, 1H), 6.97 (d, J = 8.5 Hz, 1H), 6.87 (d, J = 2.1 Hz, 1H), 6.84 (dd, J = 2.1 and 8.5 Hz, 1H), 4.23 (m, 1H), 4.01 (dd, J = 2.9 and 9.4 Hz, 1H), 3.85 (s, 3H), 3.83 (dd, J = 1.1 and 9.4 Hz, 1H) 1.27 (d, J = 6.4 Hz, 3H).

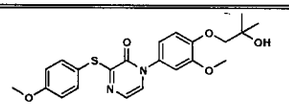
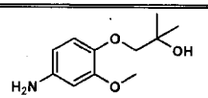
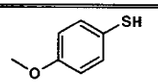
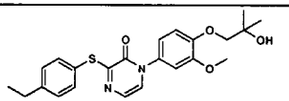
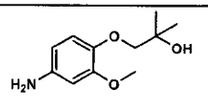
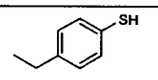
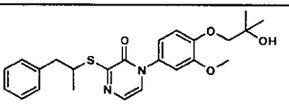
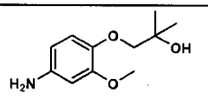
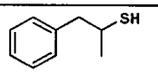
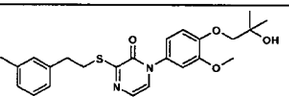
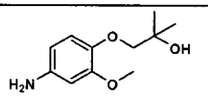
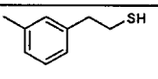
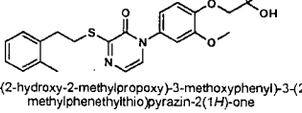
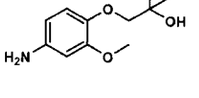
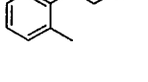
Ex. No.	Structure	Aniline/Bromide Component	Thiol Component	Method	Yield (%)	HPLC (Min) Method 1	LC-MS (M+H)	H-NMR Data ($CDCl_3$)
22	 (*R*)-3-(4-chlorophenylsulfonyl)-1-(4-(2-hydroxy-propoxy)-3-methoxyphenyl)pyrazin-2(1*H*)-one			MCPBA oxidation of Ex 19	10	3.18	451/453	8.12 (d, J = 8.6 Hz, 2H), 7.60 (d, J = 6.1 Hz, 1H), 7.51 (d, J = 6.1 Hz, 1H), 7.50 (d, J = 8.6 Hz, 2H), 6.96 (d, J = 8.6 Hz, 1H), 6.90 (d, J = 2.4 Hz, 1H), 6.84 (dd, J = 2.4 and 8.6 Hz, 1H), 4.23 (m, 1H), 4.01 (dd, J = 3.0 and 9.5 Hz, 1H), 3.86 (s, 3H), 3.84 (dd, J = 1.2 and 9.5 Hz, 1H) 1.28 (d, J = 6.0 Hz, 3H).
23	 1-(4-((*R*)-2-hydroxypropoxy)-3-methoxyphenyl)-3-(phenethylsulfinyl)pyrazin-2(1*H*)-one			MCPBA oxidation of Ex 20	17	2.96	445	7.52 (d, J = 4.1 Hz, 1H), 7.40 (d, J = 4.1 Hz, 1H), 7.20 (m, 5H), 7.00(d, J = 8.6 Hz, 1H), 6.90 (d, J = 2.5 Hz, 1H), 6.81 (dd, J = 2.5 and 8.6 Hz, 1H) 4.25 (m, 1H), 4.05 (dd, J = 3.1 and 9.5 Hz, 1H), 3.88 (s, 3H), 3.86 (m, 3H), 3.20 (t, H = 7.8 Hz, 2H), 1.29 (d, J = 6.2 Hz, 3H).
24	 (*R*)-1-(4-(2-hydroxypropoxy)-3-methoxyphenyl)-3-(phenethylsulfonyl)pyrazin-2(1*H*)-one			MCPBA oxidation of Ex 20	61	3.02	429	7.65 (d, J = 6.2 Hz, 1H), 7.30 (d, J = 6.2 Hz, 1H), 7.20 (m, 5H), 6.99 (d, J = 8.4 Hz, 1H), 6.85 (d, J = 1.0 Hz, 1H), 6.84 (dd, J = 1.0 and 8.4 Hz, 1H) 4.25 (m, 1H), 4.02 (dd, J = 2.9 and 9.6 Hz, 1H), 3.87 (s, 3H), 3.85 (dd, J = 1.2 and 9.6 Hz, 1H), 3.61 (m, 2H), 3.53 (m, 1H), 3.17 (m, 2H), 1.28 (d, J = 6.8 Hz, 3H).
25	 1-(4-(2-hydroxy-2-methylpropoxy)-3-methoxyphenyl)-3-(phenethylthio)pyrazin-2(1*H*)-one			2a	33	4.11	427	7.28 (m, 7H), 6.97 (d, J = 2.3 Hz, 1H), 6.97 (d, J = 8.5 Hz, 1H), 6.88 (dd, J = 2.3, 8.5 Hz, 1H), 3.86 (s, 5H), 3.33 (dd, J = 7.6 and 8.8 Hz, 2H), 3.02 (dd, J = 5.9 and 8.8 Hz, 2H), 1.36 (s, 6H).

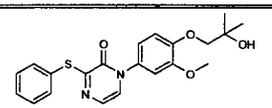
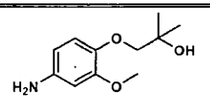
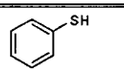
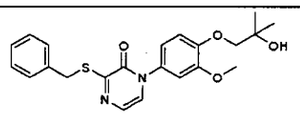
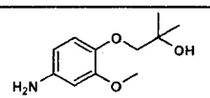
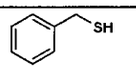
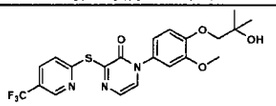
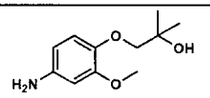
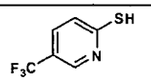
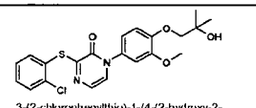
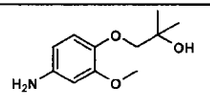
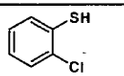
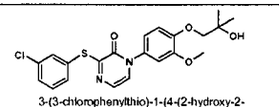
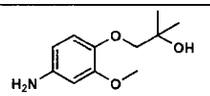
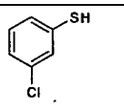
Ex. No.	Structure	Aniline/Bromide Component	Thiol Component	Method	Yield (%)	HPLC (Min) Method 1	LC-MS (M+H)	H-NMR Data ($CDCl_3$)
26	 3-(4-fluorophenethylthio)-1-(4-(2-hydroxy-2-methylpropoxy)-3-methoxyphenyl)pyrazin-2(1*H*)-one			2a	10	3.8	445	7.25 (d, J = 4.4 Hz, 1H), 7.17 (m, 2H), 6.94 (m, 5 H), 6.84 (dd, J = 2.2 and 8.5 Hz, 1H), 3.82 (s, 3H), 3.77 (s, 2H), 3.23 (t, J = 7.4 Hz, 2H), 2.91 (t, J = 7.4 Hz, 2H), 1.27 (s, 6H)
27	 1-(4-(2-hydroxy-2-methylpropoxy)-3-methoxyphenyl)-3-(2-(pyridin-2-yl)ethylthio)pyrazin-2(1*H*)-one			2a	29	2.67	428	8.57 (d, J = 4.2 Hz, 1H), 7.62 (dd, J = 5.9 and 7.6 Hz, 1H), 7.27 (m, 2H), 7.15 (m, 1H), 6.97 (m, 3H), 6.88 (dd, J = 2.3, 8.4 Hz, 1H), 3.85 (s, 5H), 3.50 (t, J = 7.2 Hz, 2H), 3.22 (t, J = 7.2 Hz, 2H), 1.36 (s, 6H).
28	 1-(4-(2-hydroxy-2-methylpropoxy)-3-methoxyphenyl)-3-(2-(pyridin-4-yl)ethylthio)pyrazin-2(1*H*)-one			2a	31	2.74	428	8.68 (d, J = 6.1 Hz, 2H), 7.97 (d, J = 6.1 Hz, 2H), 7.29 (d, J = 5.4 Hz, 1H), 7.21 (d, J = 5.4 Hz, 1H), 7.00 (d, J = 2.0 Hz, 1H), 6.98 (d, J = 8.8 Hz, 1H), 6.86 (dd, J = 2.0 and 8.8 Hz, 1H), 3.77 (s, 3H), 3.75 (s, 2H), 3.42 (t, J = 7.2 Hz, 2H), 3.30 (t, J = 7.2 Hz, 2H), 1.24 (s, 6H).
29	 1-(4-(2-hydroxy-2-methylpropoxy)-3-methoxyphenyl)-3-(7-(trifluoromethyl)quinolin-4-ylthio)pyrazin-2(1*H*)-one			2a	12	4.02	518	8.94 (d, J = 4.5 Hz, 1H), 8.36 (d, J = 8.8 Hz, 1H), 8.32 (s, 1H), 7.92 (d, J = 4.5 Hz, 1H), 7.74 (dd, J = 1.5 and 8.9 Hz, 1H), 7.21 (d, J = 4.4 Hz, 1H), 7.06 (d, J = 2.3 Hz, 1H), 7.00 (d, J = 8.6 Hz, 1H), 6.92 (dd, J = 2.3 and 8.6 Hz, 1H), 6.90 (d, J = 4.4 Hz, 1H), 3.79 (s, 3H), 3.75 (s, 2H), 1.24 (s, 6H).

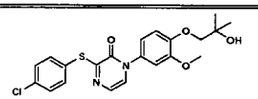
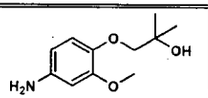
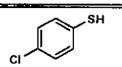
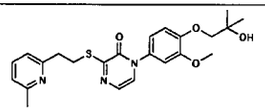
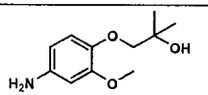
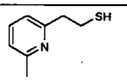
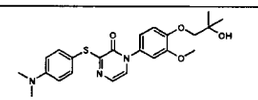
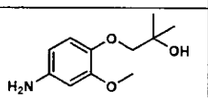
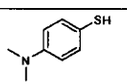
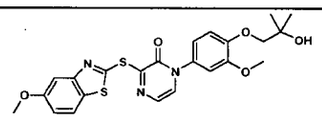
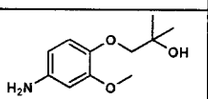
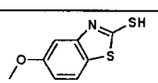
Ex. No.	Structure	Aniline/Bromide Component	Thiol Component	Method	Yield (%)	HPLC (Min) Method 1	LC-MS (M+H)	H-NMR Data ($CDCl_3$)
30	 3-(2-chlorophenylthio)-1-(4-(2-hydroxy-2-methylpropoxy)-3-methoxyphenyl)pyrazin-2(1*H*)-one			2a	50	3.76	433/435	7.67 (dd, J = 1.4 and 7.5 Hz, 1H), 7.56 (dd, J = 1.2 and 8.0 Hz, 1H), 7.42 (dt, J = 1.4 and 7.5 Hz, 1H), 7.36 (dt, J = 1.2 and 7.5 Hz, 1H), 7.11 (d, J = 4.5 Hz, 1H), 7.01 (d, J = 2.3 Hz, 1H), 6.96 (d, J = 8.4 Hz, 1H), 6.93 (d, J = 4.5 Hz, 1H), 6.90 (dd, J = 2.3 and 8.4 Hz, 1H), 3.87 (s, 3H), 3.86 (s, 2H), 2.72 (broad s, 1H), 1.36 (s, 6H).
31	 3-(3-chlorophenylthio)-1-(4-(2-hydroxy-2-methylpropoxy)-3-methoxyphenyl)pyrazin-2(1*H*)-one			2a	62	3.98	433/435	7.59 (d, J = 1.7 Hz, 1H), 7.48 (m, 1H), 7.41 (m, 2H), 7.14 (d, J = 4.5 Hz, 1H), 7.00 (m, 3H), 6.90 (dd, J = 2.4 and 8.5 Hz, 1H), 3.87 (s, 3H), 3.86 (s, 2H), 2.71 (broad s, 1H), 1.36 (s, 6H).
32	 3-(4-chlorophenylthio)-1-(4-(2-hydroxy-2-methylpropoxy)-3-methoxyphenyl)pyrazin-2(1*H*)-one			2a	58	4.00	433/435	7.52 (dd, J = 1.9 and 6.7 Hz, 2H), 7.43 (dd, J = 1.9 and 6.7 Hz, 2H), 7.13 (d, J = 4.4 Hz, 1H), 6.99 (d, J = 2.3 Hz, 1H), 6.98 (d, J = 4.4 Hz, 1H), 6.96 (d, J = 8.4 Hz, 1H), 6.90 (dd, J = 2.3 and 8.4 Hz, 1H), 3.87 (s, 3H), 3.86 (s, 2H), 2.70 (broad s, 1H), 1.36 (s, 6H).
33	 1-(4-(2-hydroxy-2-methylpropoxy)-3-methoxyphenyl)-3-(naphthalen-2-ylthio)pyrazin-2(1*H*)-one			2a	70	4.11	449	8.12 (s, 1H), 7.88 (m, 3H), 7.61 (dd, J = 1.4 and 8.6 Hz, 1H), 7.53 (m, 2H), 7.09 (d, J = 4.5 Hz, 1H), 7.02 (d, J = 2.3 Hz, 1H), 6.98 (d, J = 8.5 Hz, 1H), 6.96 (d, J = 4.5 Hz, 1H), 6.91 (dd, J = 2.3 and 8.5 Hz, 1H), 3.88 (s, 3H), 3.87 (s, 2H), 2.75 (broad s, 1H), 1.37 (s, 6H).
34	 3-(4-fluorophenylthio)-1-(4-(2-hydroxy-2-methylpropoxy)-3-methoxyphenyl)pyrazin-2(1*H*)-one			2a	34	3.72	417	7.56 (m, 2H), 7.12 (m, 3H), 6.98 (m, 3H), 6.89 (m, 1H), 386 (s, 5H), 1.36 (s, 6H).

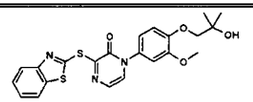
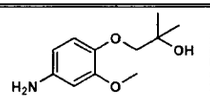
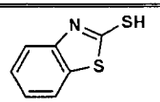
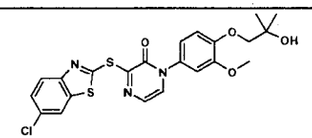
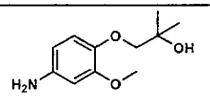
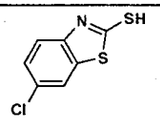
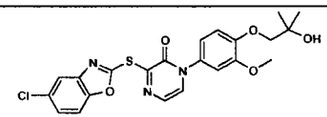
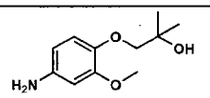
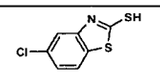
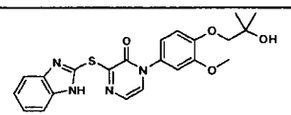
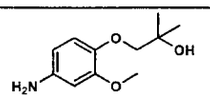
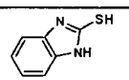
Ex. No.	Structure	Aniline/Bromide Component	Thiol Component	Method	Yield (%)	HPLC (Min) Method 1	LC-MS (M+H)	H-NMR Data ($CDCl_3$)
35	 1-(4-(2-hydroxy-2-methylpropoxy)-3-methoxyphenyl)-3-(4-isopropylphenylthio)pyrazin-2(1*H*)-one			2a	39	4.24	441	7.50 (d, J= 8.2 Hz, 2H), 7.32 (d, J = 8.2 Hz, 2H), 7.15 (d, J = 4.5 Hz, 1H), 7.02 (d, J = 2.3 Hz, 1H), 6.97 (d, J = 4.5 Hz, 1H), 6.96 (d, J = 8.5 Hz, 1H), 6.92 (dd, J = 2.3 and 8.5 Hz, 1H), 3.90 (s, 3H), 3.85 (s, 2H), 2.98 (m, 1H), 2.85 (broad s, 1H), 1.35 (s, 6H), 1.24 (d, J = 6.8 Hz, 6H).
36	 1-(4-(2-hydroxy-2-methylpropoxy)-3-methoxyphenyl)-3-(4-(trifluoromethyl)phenylthio)pyrazin-2(1*H*)-one			2a	16	4.10	467	7.64 (d, J = 9.0 Hz, 2H), 7.62 (d, J = 9.0 Hz, 2H), 7.18 (d, J = 4.5 Hz, 1H), 7.04 (d, J = 4.5 Hz, 1H), 7.00 (d, J = 2.2 Hz, 1H), 6.98 (d, J = 8.5 Hz, 1H), 6.86 (dd, J = 2.2 and 8.5 Hz, 1H), 3.75 (s, 3H), 3.73 (s, 2H), 1.22 (s, 6H).
37	 1-(4-(2-hydroxy-2-methylpropoxy)-3-methoxyphenyl)-3-(4-(methylthio)phenylthio)pyrazin-2(1*H*)-one			2a	50	3.96	445	7.48 (d, J = 8.4 Hz, 2H), 7.30 (d, J = 8.4 Hz, 2H), 7.28 (d, J = 4.5 Hz, 1H), 7.12 (d, J = 4.5 Hz, 1H), 6.99 (d, J = 8.5 Hz, 1H), 6.96 (d, J = 2.4 Hz, 1H), 6.89 (dd, J = 2.4 and 8.5 Hz, 1H), 3.86 (s, 5H), 2.51 (s, 3H), 1.35 (s, 6H).
38	 1-(4-(2-hydroxy-2-methylpropoxy)-3-methoxyphenyl)-3-(4-(trifluoromethoxy)phenylthio)pyrazin-2(1*H*)-one			2a	52	4.15	483	7.62 (d, J = 8.6 Hz, 2H), 7.30 (d, J = 8.6 Hz, 2H), 7.16 (d, J = 4.4 Hz, 1H), 7.06 (d, J = 4.4 Hz, 1H), 7.00 (d, J = 8.5 Hz, 1H), 6.98 (d, J = 2.3 Hz, 1H), 6.93 (dd, J = 2.3 and 8.5 Hz, 1H), 3.91 (s, 3H), 3.86 (s, 2H), 1.36 (s, 6H).
39	 1-(4-(2-hydroxy-2-methylpropoxy)-3-methoxyphenyl)-3-(3-methoxyphenylthio)pyrazin-2(1*H*)-one			2a	60	3.72	429	7.37 (t, J = 8.0 Hz, 1H), 7.18 (d, J = 8.0 Hz, 1H), 7.14 (m, 2H), 6.98 (m, 4H), 6.90 (m, 1H), 3.86 (s, 5H), 3.77 (s, 3H), 1.36 (s, 6H).

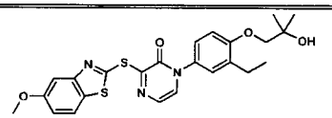
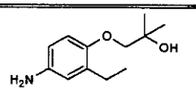
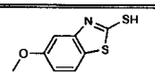
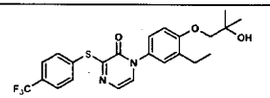
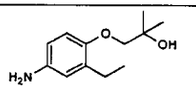
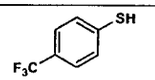
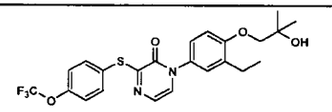
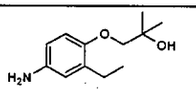
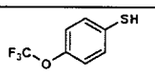
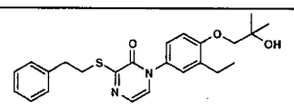
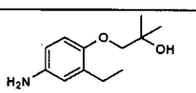
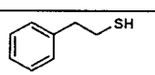
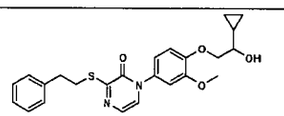
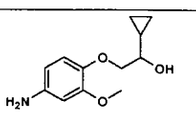
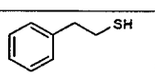
Ex. No.	Structure	Aniline/Bromide Component	Thiol Component	Method	Yield (%)	HPLC (Min) Method 1	LC-MS (M+H)	H-NMR Data ($CDCl_3$)
40	 1-(4-(2-hydroxy-2-methylpropoxy)-3-methoxyphenyl)-3-(2-(trifluoromethyl)phenylthio)pyrazin-2(1*H*)-one			2a	49	3.88	467	7.84 (d, J = 7.5 Hz, 1H), 7.71 (d, J = 7.5 Hz, 1H), 7.62 (t, J = 7.5 Hz, 1H), 7.60 (t, J = 7.5 Hz, 1H), 7.05 (d, J = 4.4 Hz, 1H), 7.01 (d, J = 2.4 Hz, 1H), 6.98 (d, J = 8.5 Hz, 1H), 6.97 (d, J = 4.4 Hz, 1H), 6.90 (dd, J = 2.4 and 8.5 Hz, 1H), 3.88 (s, 3H), 3.86 (s, 2H), 1.36 (s, 6H).
41	 3-(4-chloro-2-methylphenylthio)-1-(4-(2-hydroxy-2-methylpropoxy)-3-methoxyphenyl)pyrazin-2(1*H*)-one			2a	50	4.20	447/449	7.48 (d, J = 8.4 Hz, 1H), 7.36 (d, J = 2.0 Hz, 1H), 7.24 (dd, J = 2.0 and 8.4 Hz, 1H), 7.10 (d, J = 4.5 Hz, 1H), 7.00 (d, J = 2.4 Hz, 1H), 6.98 (d, J = 8.5 Hz, 1H), 6.96 (d, J = 4.5 Hz, 1H), 6.90 (dd, J = 2.4 and 8.5 Hz, 1H), 3.88 (s, 3H), 3.87 (s, 2H), 2.40 (s, 3H), 1.38 (s, 6H).
42	 3-(2,4-dimethylphenylthio)-1-(4-(2-hydroxy-2-methylpropoxy)-3-methoxyphenyl)pyrazin-2(1*H*)-one			2a	60	4.04	427	7.44 (d, J = 7.9 Hz, 1H), 7.19 (s, 1H), 7.11 (d, J = 4.5 Hz, 1H), 7.08 (d, J = 7.9 Hz, 1H), 7.01 (d, J = 2.3 Hz, 1H), 6.97 (d, J = 8.6 Hz, 1H), 6.93 (d, J = 4.5 Hz, 1H), 6.90 (dd, J = 2.3 and 8.6 Hz, 1H), 3.87 (s, 3H), 3.86 (s, 2H), 2.39 (s, 3H), 2.37 (s, 3H), 1.36 (s, 6H).
43	 1-(4-(2-hydroxy-2-methylpropoxy)-3-methoxyphenyl)-3-(*p*-tolylthio)pyrazin-2(1*H*)-one			2a	60	3.87	413	7.46 (d, J = 8.0 Hz, 2H), 7.27 (d, J = 8.0 Hz, 2H), 7.15 (d, J = 4.4 Hz, 1H), 7.01 (d, J = 2.3 Hz, 1H), 6.97 (d, J = 8.5 Hz, 1H), 6.96 (d, J = 4.4 Hz, 1H), 6.92 (dd, J = 2.3 and 8.5 Hz, 1H), 3.91 (s, 3H), 3.85 (s, 2H), 2.40 (s, 3H), 1.35 (s, 6H).

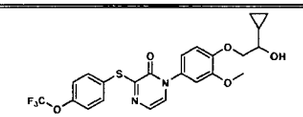
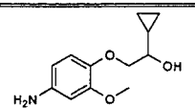
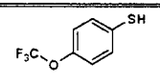
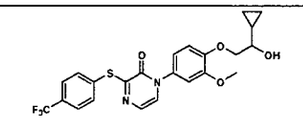
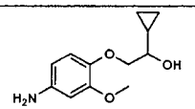
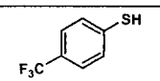
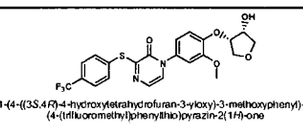
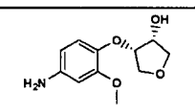
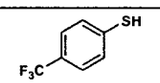
Ex. No.	Structure	Aniline/Bromide Component	Thiol Component	Method	Yield (%)	HPLC (Min) Method 1	LC-MS (M+H)	H-NMR Data ($CDCl_3$)
44	 1-(4-(2-hydroxy-2-methylpropoxy)-3-methoxyphenyl)-3-(4-methoxyphenylthio)pyrazin-2(1*H*)-one			2a	39	3.71	429	7.48 (d, J = 8.7 Hz, 2H), 7.14 (d, J = 4.5 Hz, 1H), 7.00 (d, J = 2.3 Hz, 1H), 6.99 (d, J = 8.0 Hz, 2H), 6.97 (d, J = 4.5 Hz, 1H), 6.97 (d, J = 8.5 Hz, 1H), 6.92 (dd, J = 2.3 and 8.5 Hz, 1), 3.89 (s, 3H), 3.85 (s, 5H), 1.35 (s, 6H).
45	 3-(4-ethylphenylthio)-1-(4-(2-hydroxy-2-methylpropoxy)-3-methoxyphenyl)pyrazin-2(1*H*)-one			2a	64	4.05	427	7.45 (d, J = 8.3 Hz, 2H), 7.25 (d, J = 8.3 Hz, 2H), 7.11 (d, J = 3.9 Hz, 1H), 6.97 (d, J = 2.2 Hz, 1H), 6.93 (d, J = 8.2 Hz, 1H), 6.92 (d, J = 3.9 Hz, 1H), 6.87 (dd, J = 2.2 and 8.2 Hz, 1H), 3.86 (s, 3H), 3.81 (s, 2H), 2.66 (q, J =5.5 Hz, 2H), 1.31 (s, 6H), 1.22 (t, J = 5.5 Hz, 3H).
46	 1-(4-(2-hydroxy-2-methylpropoxy)-3-methoxyphenyl)-3-(1-phenylpropan-2-ylthio)pyrazin-2(1*H*)-one			2a	29	4.25	441	7.27 (m, 5H), 7.20 (m, 1H), 6.92 (m, 3H), 6.85 (dd, J = 2.2, 8.0 Hz, 1H), 3.97 (m, 1H), 3.84 (s, 3H), 3.81 (s, 2H), 3.16 (dd, J = 2.0 and 8.0 Hz, 1H), 2.74 (dd, J = 5.0 and 8.0 Hz, 1H), 1.33 (s, 6H), 1.32 (d, J = 9.3 Hz, 3H).
47	 1-(4-(2-hydroxy-2-methylpropoxy)-3-methoxyphenyl)-3-(3-methylphenethylthio)pyrazin-2(1*H*)-one			2a	59	4.31	441	7.30 (m, 1H), 7.21 (m, 1H), 7.11 (m, 1H), 7.05 (m, 1H), 6.97 (m, 4H), 6.89 (m, 1H), 3.87 (s, 3H), 3.84 (s, 2H), 3.31 (dd, J = 6.0 and 8.3 Hz, 2H), 2.98 (t, J = 8.3 Hz, 2H), 2.35 (s, 3H), 1.35 (s, 6H)
48	 1-(4-(2-hydroxy-2-methylpropoxy)-3-methoxyphenyl)-3-(2-methylphenethylthio)pyrazin-2(1*H*)-one			2a	88	4.30	441	7.26 (d, J = 4.4 Hz, 1H), 7.19 (d, J = 7.2 Hz, 1H), 7.10 (m, 3H), 6.95 (m, 3H), 6.84 (dd, J = 2.2 and 8.2 Hz, 1H), 3.83 (s, 3H), 3.79 (s, 2H), 3.22 (dd, J = 5.7 and 8.5 Hz, 2H), 2.96 (dd, J = 5.5 and 8.5 Hz, 2H), 2.34 (s, 3H), 1.29 (s, 6H).

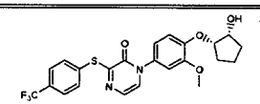
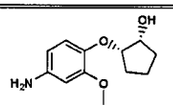
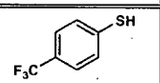
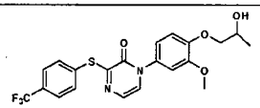
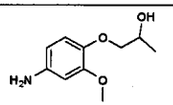
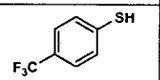
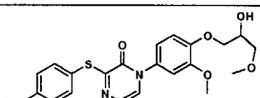
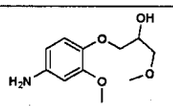
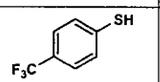
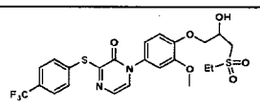
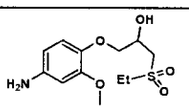
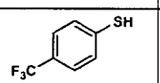
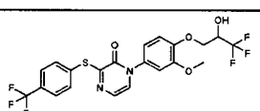
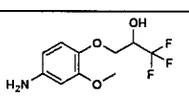
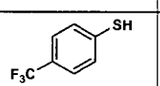
Ex. No.	Structure	Aniline/Bromide Component	Thiol Component	Method	Yield (%)	HPLC (Min) Method 1	LC-MS (M+H)	H-NMR Data ($CDCl_3$)
49	 1-(4-(2-hydroxy-2-methylpropoxy)-3-methoxyphenyl)-3-(phenylthio)pyrazin-2(1*H*)-one			2a	51	3.62	399	7.52 (m, 2H), 7.39 (m, 3H), 7.05 (d, J = 4.4 Hz, 1H), 6.92 (d, J = 2.4 Hz, 1H), 6.90 (d, J = 8.4 Hz, 1H), 6.89 (d, J = 4.4 Hz, 1H), 6.83 (dd, J = 2.4 and 8.4 Hz, 1H), 3.80 (s, 3H), 3.79 (s, 2H), 1.29 (s, 6H).
50	 3-(benzylthio)-1-(4-(2-hydroxy-2-methylpropoxy)-3-methoxyphenyl)pyrazin-2(1*H*)-one			2a	51	3.95	413	7.43 (d, J = 7.1 Hz, 2H), 7.30 (m, 4H), 6.96 (m, 3H), 6.88 (dd, J = 2.4 and 8.5 Hz, 1H), 4.33 (s, 2H), 3.87 (s, 3H), 3.84 (s, 2H), 1.35 (s, 6H).
51	 1-(4-(2-hydroxy-2-methylpropoxy)-3-methoxyphenyl)-3-(5-(trifluoromethyl)pyridin-2-ylthio)pyrazin-2(1*H*)-one			2a	6	3.63	468	8.89 (s, 1H), 8.17 (d, J = 7.2 Hz, 1H), 8.10 (d, J = 7.2 Hz, 1H), 7.45 (d, J = 4.4 Hz, 1H), 7.30 (d, J = 4.4 Hz, 1H), 7.15 (d, J = 2.4 Hz, 1H), 7.12 (d, J = 8.6 Hz, 1H), 7.01 (dd, J = 2.4 and 8.6 Hz, 1H), 3.91 (s, 3H), 3.87 (s, 2H), 1.35 (s, 6H).
52	 3-(2-chlorophenylthio)-1-(4-(2-hydroxy-2-methylpropoxy)-3-methoxyphenyl)pyrazin-2(1*H*)-one			2a	50	4.02	433/435	7.67 (dd, J = 1.4 and 7.5 Hz, 1H), 7.56 (dd, J = 1.2 and 8.0 Hz, 1H), 7.42 (dt, J = 1.4 and 7.5 Hz, 1H), 7.36 (dt, J = 1.2 and 7.5 Hz, 1H), 7.11 (d, J = 4.5 Hz, 1H), 7.01 (d, J = 2.3 Hz, 1H), 6.96 (d, J = 8.4 Hz, 1H), 6.93 (d, J = 4.5 Hz, 1H), 6.90 (dd, J = 2.3 and 8.4 Hz, 1H), 3.87 (s, 3H), 3.86 (s, 2H), 2.72 (broad s, 1H), 1.36 (s, 6H).
53	 3-(3-chlorophenylthio)-1-(4-(2-hydroxy-2-methylpropoxy)-3-methoxyphenyl)pyrazin-2(1*H*)-one			2a	62	3.76	433/435	7.59 (d, J = 1.7 Hz, 1H), 7.48 (m, 1H), 7.41 (m, 2H), 7.14 (d, J = 4.5 Hz, 1H), 7.00 (m, 3H), 6.90 (dd, J = 2.4 and 8.5 Hz, 1H), 3.87 (s, 3H), 3.86 (s, 2H), 2.71 (broad s, 1H), 1.36 (s, 6H).

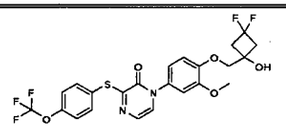
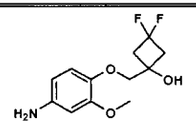
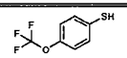
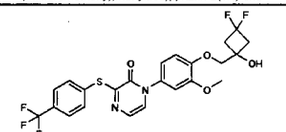
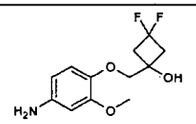
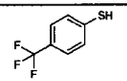
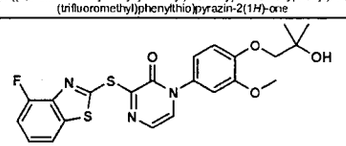
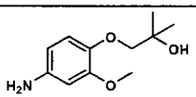
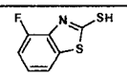
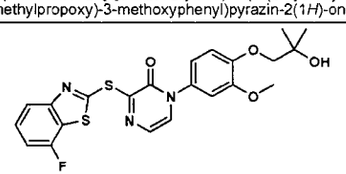
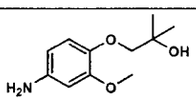
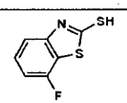
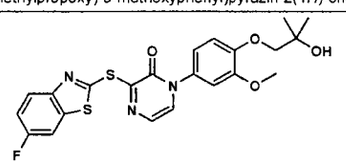
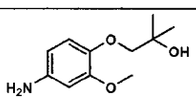
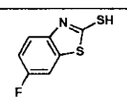
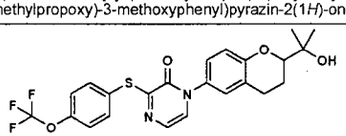
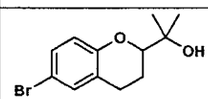
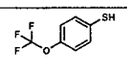
Ex. No.	Structure	Aniline/Bromide Component	Thiol Component	Method	Yield (%)	HPLC (Min) Method 1	LC-MS (M+H)	H-NMR Data ($CDCl_3$)
54	 3-(4-chlorophenylthio)-1-(4-(2-hydroxy-2-methylpropoxy)-3-methoxyphenyl)pyrazin-2(1*H*)-one			2a	58	3.98	433/435	7.52 (dd, J = 1.9 and 6.7 Hz, 2H), 7.43 (dd, J = 1.9 and 6.7 Hz, 2H), 7.13 (d, J = 4.4 Hz, 1H), 6.99 (d, J = 2.3 Hz, 1H), 6.98 (d, J = 4.4 Hz, 1H), 6.96 (d, J = 8.4 Hz, 1H), 6.90 (dd, J = 2.3 and 8.4 Hz, 1H), 3.87 (s, 3H), 3.86 (s, 2H), 2.70 (broad s, 1H), 1.36 (s, 6H).
55	 1-(4-(2-hydroxy-2-methylpropoxy)-3-methoxyphenyl)-3-(2-(6-methylpyridin-2-yl)ethylthio)pyrazin-2(1*H*)-one			2a	50%	2.74	442	7.67 (t, J = 7.7 Hz, 1H), 7.38 (d, J = 4.4 Hz, 1H), 7.25 (d, J = 4.4 Hz, 1H), 7.16 (m, 2H), 7.10 (d, J = 2.4 Hz, 1H), 7.08 (d, J = 8.6 Hz, 1H), 6.95 (dd, J = 2.4 and 8.6 Hz, 1H), 3.89 (s, 3H), 3.86 (s, 2H), 3.45 (t, J = 7.1 Hz, 2H), 3.15 (t, J = 7.1 Hz, 2H), 2.53 (s, 3H), 1.34 (s, 6H).
56	 3-(4-(dimethylamino)phenylthio)-1-(4-(2-hydroxy-2-methylpropoxy)-3-methoxyphenyl)pyrazin-2(1*H*)-one			2a	44%	3.03	442	7.40 (d, J = 8.9 Hz, 2H), 7.13 (d, J = 4.8 Hz, 1H), 7.00 (d, J = 2.3 Hz, 1H), 6.97 (d, J = 8.5 Hz, 1H), 6.92 (d, J = 4.8 Hz, 1H), 6.90 (dd, J = 2.3 and 8.5 Hz, 1H), 6.76 (d, J = 8.9 Hz, 2H), 3.87 (s, 3H), 3.86 (s, 2H), 3.01 (s, 6H), 1.36 (s, 6H).
57	 1-(4-(2-hydroxy-2-methylpropoxy)-3-methoxyphenyl)-3-(5-methoxybenzo[*d*]thiazol-2-ylthio)pyrazin-2(1*H*)-one			5	3	3.68	486	7.77 (d, J = 8.8 Hz, 1H), 7.57 (d, J = 2.5 Hz, 1H), 7.37 (d, J = 4.4 Hz, 1H), 7.14 (d, J = 4.4 Hz, 1H), 7.08 (dd, J = 2.5, 8.8 Hz, 1H, 7.02 (m, 2H), 6.93 (dd, J = 2.5, 8.5 Hz, 1H), 3.92 (s, 3H), 3.90 (s, 2H), 1.39 (s, 6H).

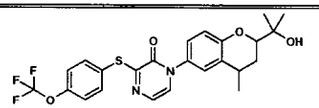
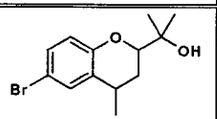
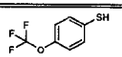
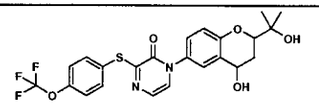
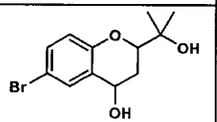
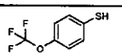
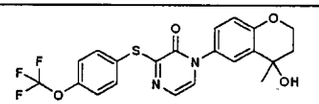
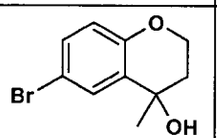
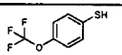
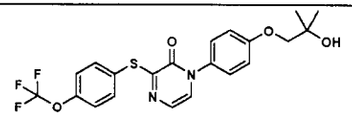
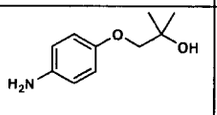
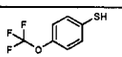
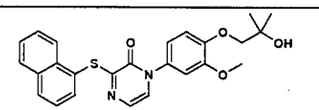
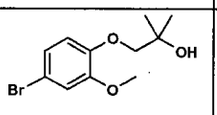
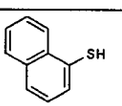
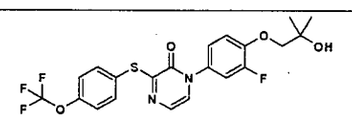
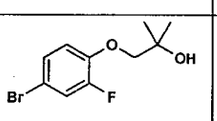
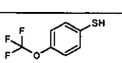
Ex. No.	Structure	Aniline/Bromide Component	Thiol Component	Method	Yield (%)	HPLC (Min) Method 1	LC-MS (M+H)	H-NMR Data ($CDCl_3$)
58	 3-(benzo[*d*]thiazol-2-ylthio)-1-(4-(2-hydroxy-2-methylpropoxy)-3-methoxyphenyl)pyrazin-2(1*H*)-one			5		3.64	456	7.93 (d, J = 8.3 Hz, 1H), 7.87 (d, J = 8.1 Hz, 1H), 7.43 (t, J = 8.2 Hz, 1H), 7.35 (m, 3H), 7.07 (d, J = 2.3 Hz, 1H), 7.01 (d, J = 8.6 Hz, 1H), 6.93 (dd, J = 2.3 and 8.5 Hz, 1H), 3.79 (s, 3H), 3.76 (s, 2H), 1.24 (s, 6H).
59	 3-(6-chlorobenzo[*d*]thiazol-2-ylthio)-1-(4-(2-hydroxy-2-methylpropoxy)-3-methoxyphenyl)pyrazin-2(1*H*)-one			5		3.99	490/492	7.87 (d, J = 8.6 Hz, 1H), 7.79 (d, J = 2.0 Hz, 1H), 7.38 (dd, J = 2.0 and 8.6 Hz, 1H), 7.30 (d, J = 4.4 Hz, 1H), 7.08 (d, J = 4.4 Hz, 1H), 6.92 (d, J = 2.5 Hz, 1H), 6.91 (d, J = 8.6 Hz, 1H), 6.85 (dd, J = 2.5 and 8.6 Hz, 1H), 3.80 (s, 5H), 1.30 (s, 6H).
60	 3-(5-chlorobenzo[*d*]oxazol-2-ylthio)-1-(4-(2-hydroxy-2-methylpropoxy)-3-methoxyphenyl)pyrazin-2(1*H*)-one			5		3.67	474/476	7.71 (d, J = 2.0, 1H), 7.45 (d, J = 8.7 Hz, 1H), 7.32 (dd, J = 2.0 and 8.7 Hz, 1H), 7.11 (d, J = 4.4 Hz, 1H), 7.04 (d, J = 4.4 Hz, 1H), 6.91 (d, J = 8.6 Hz, 1H), 6.90 (d, J = 2.4 Hz, 1H), 6.84 (dd, J = 2.4 and 8.6 Hz, 1H), 3.81 (s, 3H), 3.79 (s, 2H), 1.29 (s, 6H).
61	 3-(1*H*-benzo[*d*]imidazol-2-ylthio)-1-(4-(2-hydroxy-2-methylpropoxy)-3-methoxyphenyl)pyrazin-2(1*H*)-one			5		2.68	439	7.71 (dd, J = 3.1 and 6.2 Hz, 2H), 7.49 (dd, J = 3.1 and 6.2 Hz, 2H), 7.43 (d, J = 4.4 Hz, 1H), 7.22 (d, J = 4.4 Hz, 1H), 7.04 (d, J = 2.5 Hz, 1H), 7.01 (d, J = 8.5 Hz, 1H), 6.91 (dd, J = 2.4 and 8.5 Hz, 1H), 3.79 (s, 3H), 3.75 (s, 2H), 1.24 (s, 6H).

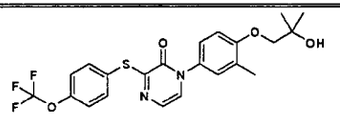
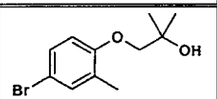
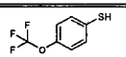
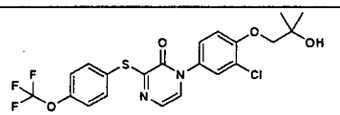
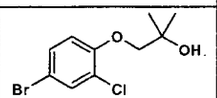
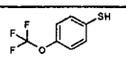
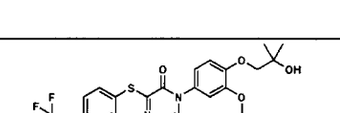
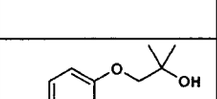
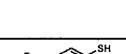
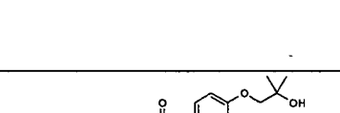
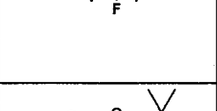
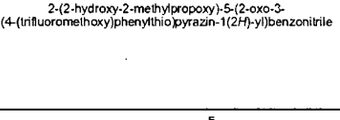
Ex. No.	Structure	Aniline/Bromide Component	Thiol Component	Method	Yield (%)	HPLC (Min) Method 1	LC-MS (M+H)	H-NMR Data ($CDCl_3$)
62	 1-(3-ethyl-4-(2-hydroxy-2-methylpropoxy)phenyl)-3-(5-methoxybenzo[*d*]thiazol-2-ylthio)pyrazin-2(1*H*)-one			5		4.11	484	7.68 (d, J = 8.8 Hz, 1H), 7.46 (d, J = 2.4 Hz, 1H), 7.27 (d, J = 4.4 Hz, 1H), 7.16 (m, 2H), 7.04 (d, J = 4.4 Hz, 1H), 7.00 (dd, J = 2.5 and 8.7 Hz, 1H), 6.85 (d, J = 9.4 Hz, 1H), 3.82 (s, 3H), 3.78 (s, 2H), 2.65 (q, J = 7.5 Hz, 2H), 1.32 (s, 6H), 1.15 (t, J = 7.5 Hz, 3H).
63	 1-(3-ethyl-4-(2-hydroxy-2-methylpropoxy)phenyl)-3-(4-(trifluoromethyl)phenylthio)pyrazin-2(1*H*)-one			2a		4.05	465	7.64 (d, J = 8.5 Hz, 2H), 7.62 (d, J = 8.5 Hz, 2H), 7.15 (m, 2H) 7.04 (d, J = 4.4 Hz, 1H), 6.93 (d, J = 4.4 Hz, 1H), 6.84 (d, J = 9.2 Hz, 1H), 3.77 (s, 2H), 2.63 (q, J = 7.5 Hz, 2H), 1.30 (s, 6H), 1.17 (t, J = 7.5 Hz, 3H)
64	 1-(3-ethyl-4-(2-hydroxy-2-methylpropoxy)phenyl)-3-(4-(trifluoromethoxy)phenylthio)pyrazin-2(1*H*)-one			2a		4.15	481	7.43 (d, J = 8.8 Hz, 2H), 7.31 (d, J = 8.8 Hz, 2H), 7.24 (d, J = 2.4 Hz, 1H), 7.22 (d, J = 8.5 Hz, 1H), 7.14 (d, J = 4.4 Hz, 1H), 7.00 (d, J = 4.4 Hz, 1H), 6.94 (dd, J = 2.4, 8.5 Hz, 1H), 3.86 (s, 2H), 2.74 (q, J = 7.5 Hz, 2H), 1.41 (s, 6H), 1.26 (t, J = 7.5 Hz, 3H).
65	 1-(3-ethyl-4-(2-hydroxy-2-methylpropoxy)phenyl)-3-(phenethylthio)pyrazin-2(1*H*)-one			2a		4.08 Method 2	425	7.10 (m, 8H), 6.84 (d, J = 4.4 Hz, 1H), 6.76 (d, J = 8.5 Hz, 1H), 3.70 (s, 2H), 3.21 (m, 2H), 2.90 (m, 2H), 2.59 (q, J = 7.4 Hz, 2H), 1.26 (s, 6H), 1.12 (t, J = 7.4 Hz, 3H)
66	 1-(4-(2-cyclopropyl-2-hydroxyethoxy)-3-methoxyphenyl)-3-(phenethylthio)pyrazin-2(1*H*)-one			2a		3.81	439	7.23 (m, 5H), 7.14 (m, 1H), 6.92 (m, 3H), 6.83 (dd, J = 2.4, 8.6 Hz), 4.08 (dd, J = 2.6, 9.7 Hz, 1H), 3.93 (t, J = 8.2 Hz, 1H), 3.80 (s, 3H), 3.25 (m, 3H), 2.94 (m, 2H), 0.88 (m, 1H), 0.57 (m, 1H), 0.51 (m, 1H), 0.36 (m, 1H), 0.22 (m, 1H)

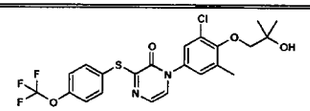
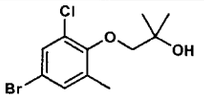
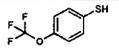
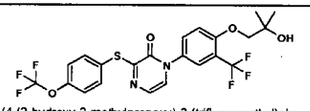
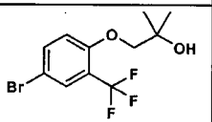
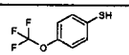
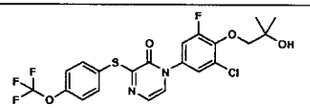
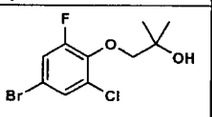
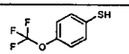
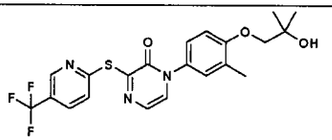
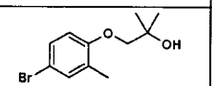
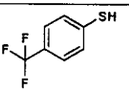
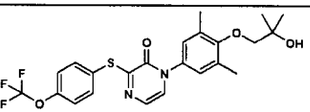
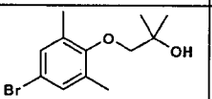
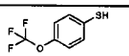
Ex. No.	Structure	Aniline/Bromide Component	Thiol Component	Method	Yield (%)	HPLC (Min) Method 1	LC-MS (M+H)	H-NMR Data ($CDCl_3$)
67	 1-(4-(2-cyclopropyl-2-hydroxyethoxy)-3-methoxyphenyl)-3-(4-(trifluoromethoxy)phenylthio)pyrazin-2(1*H*)-one			2a		3.87	495	7.54 (d, J = 8.8 Hz, 2H), 7.21 (d, J = 8.8 Hz, 2H), 7.05 (d, J = 4.4 Hz, 1H), 6.93 (d, J = 8.5 Hz, 1H), 6.92 (d, J = 2.4 Hz, 1H), 6.91 (d, J = 4.4 Hz, 1H), 6.84 (dd, J = 2.4, 8.5 Hz, 1H) 4.13 (dd, J = 2.8, 9.7 Hz, 1H), 3.96 (dd, J = 1.3, 8.2 Hz, 1H), 3.79 (s, 3H), 3.29 (dt, J = 2.5, 9.8 Hz, 1H), 0.93 (m, 1H), 0.57 (m, 1H), 0.51 (m, 1H), 0.41 (m, 1H), 0.25 (m, 1H)
68	 1-(4-(2-cyclopropyl-2-hydroxyethoxy)-3-methoxyphenyl)-3-(4-(trifluoromethyl)phenylthio)pyrazin-2(1*H*)-one			2a		3.74 Method 2	479	7.66 (d, J = 8.5 Hz, 2H), 7.64 (d, J = 8.5 Hz, 2H), 7.51 (d, J = 4.4 Hz, 1H), 7.09 (d, J = 4.4 Hz, 1H), 7.00 (d, J = 8.2 Hz, 1H), 6.98 (d, J = 2.2 Hz, 1H), 6.89 (dd, J = 2.2, 8.2 Hz, 1H), 4.22 (dd, J = 2.2, 9.3 Hz, 1H), 3.96 (dd, J = 1.1, 9.4 Hz, 1H), 3.84 (s, 3H), 3.27 (dt, J = 2.5, 9.8 Hz, 1H), 0.93 (m, 1H), 0.57 (m, 1H), 0.51 (m, 1H), 0.41 (m, 1H), 0.25 (m, 1H)
69	 1-(4-((3*S*,4*R*)-4-hydroxytetrahydrofuran-3-yloxy)-3-methoxyphenyl)-3-(4-(trifluoromethyl)phenylthio)pyrazin-2(1*H*)-one			2a		3.59 Method 2	481	7.64 (m, 4H), 7.06 (d, J = 4.4 Hz, 1H), 6.98 (d, J = 2.8 Hz, 1H), 6.95 (d, J = 9.7 Hz, 1H), 6.93 (d, J = 4.4 Hz, 1H), 6.86 (dd, J = 2.8 and 9.7 Hz, 1H), 4.63 (m, 1H), 4.34 (m, 1H), 4.09 (m, 1H), 3.97 (m, 2H), 3.83 (s, 3H), 3.78 (m, 1H), 3.07 (d, J = 6.4 Hz, 1H).

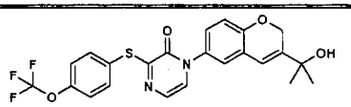
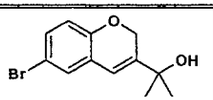
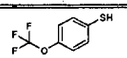
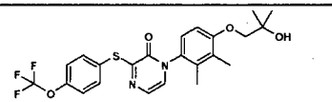
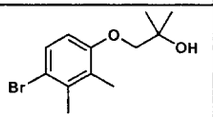
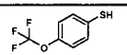
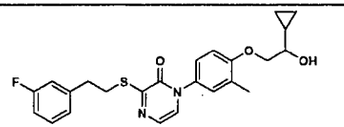
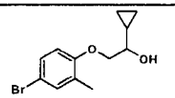
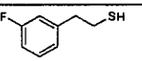
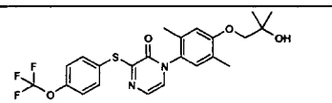
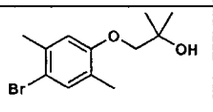
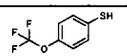
Ex. No.	Structure	Aniline/Bromide Component	Thiol Component	Method	Yield (%)	HPLC (Min) Method 1	LC-MS (M+H)	H-NMR Data ($CDCl_3$)
70	 1-(4-((1S,2R)-2-hydroxycyclopentyloxy)-3-methoxyphenyl)-3-(4-(trifluoromethyl)phenylthio)pyrazin-2(1*H*)-one			2a		3.87 Method 2	479	7.62 (m, 4 H), 7.05 (d, J = 4.5 Hz, 1H), 6.95 (d, J = 8.5 Hz, 1H), 6.93 (d, J = 4.5 Hz, 1H), 6.92 (d, J = 2.4 Hz, 1H), 6.83 (dd, J = 2.4 and 8.5 Hz, 1H), 4.42 (m, 1H), 4.13 (m, 1H), 3.75 (s, 3H), 3.04 (m, 1H), 1.99 (m, 1H), 1.70 to 1.90 (m, 4H), 1.52 (m, 1H).
71	 1-(4-(2-hydroxypropoxy)-3-methoxyphenyl)-3-(4-(trifluoromethyl)phenylthio)pyrazin-2(1*H*)-one			2a		3.74 Method 2	453	7.85 (d, J = 8.4 Hz, 2H), 7.80 (d, J = 8.4 Hz, 2H), 7.48 (d, J = 4.4 Hz, 1H), 7.16 (d, J = 4.4 Hz, 1H), 7.15 (d, J = 2.4 Hz, 1H), 7.10 (d, J = 8.6 Hz, 1H), 7.01 (dd, J = 2.4, 8.6 Hz, 1H), 3.97 (m, 1H), 3.90 (m, 1H), 3.81 (m, 1H), 3.78 (s, 3H), 1.16 (d, 3H)
72	 1-(4-(2-hydroxy-3-methoxypropoxy)-3-methoxyphenyl)-3-(4-(trifluoromethyl)phenylthio)pyrazin-2(1*H*)-one			2a		3.72 Method 2	483	7.64 (m, 4H), 7.06 (d, J = 4.5 Hz, 1H), 6.96 (d, J = 8.5 Hz, 1H), 6.94 (d, J = 4.5 Hz, 1H), 6.92 (d, J = 2.5 Hz, 1H), 6.84 (dd, J = 2.5, 8.5 Hz, 1H), 4.04 (m, 2H), 3.81 (s, 3H), 3.50 (m, 2H), 3.36 (s, 3H)
73	 1-(4-(3-(ethylsulfonyl)-2-hydroxypropoxy)-3-methoxyphenyl)-3-(4-(trifluoromethyl)phenylthio)pyrazin-2(1*H*)-one			2a		3.62 Method 2	545	7.63 (m, 4H), 7.06 (d, J = 4.4 Hz, 2H), 6.94 (d, J = 4.4 Hz, 1H), 6.92 (d, J = 2.0 Hz, 1H), 6.90 (d, J = 8.5 Hz, 1H), 6.83 (dd, J = 2.0 and 8.5 Hz, 1H), 4.54 (m, 1H), 4.02 (d, J = 5.4 Hz, 2H), 3.78 (s, 3H), 3.62 (m, 1 H), 3.0 to 3.40 (m, 3H), 1.86 (m, 1 H), 1.38 (t, J = 7.4 Hz, 3H).
74	 1-(3-methoxy-4-(3,3,3-trifluoro-2-hydroxypropoxy)phenyl)-3-(4-(trifluoromethyl)phenylthio)pyrazin-2(1*H*)-one			2a			507	3.90 (s, 3 H), 4.14 - 4.22 (m, 1 H), 4.32 (dd, *J*=10.45, 3.65 Hz, 1 H), 4.36 - 4.47 (m, 1 H), 7.03 (dd, *J*=8.56, 2.27 Hz, 1 H), 7.14 - 7.22 (m, 3 H), 7.34 (d, *J*=4.28 Hz, 1 H), 7.74 - 7.83 (m, 4 H)

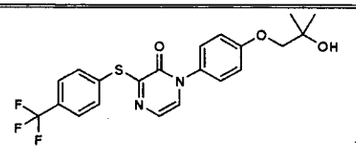
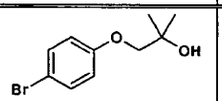
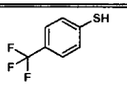
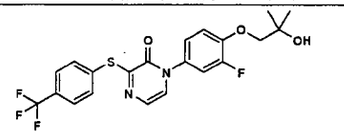
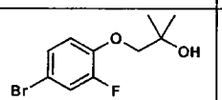
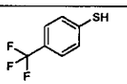
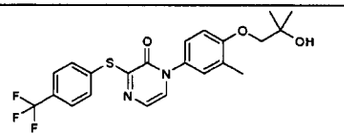
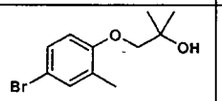
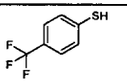
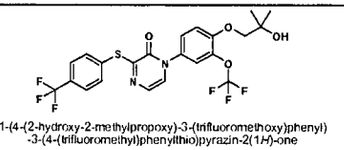
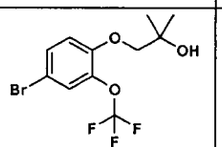
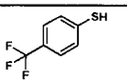
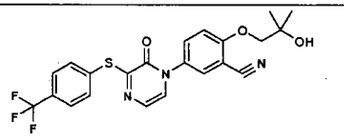
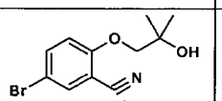
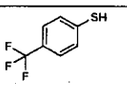
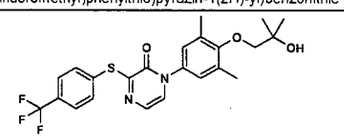
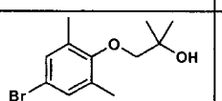
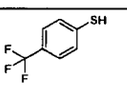
Ex. No.	Structure	Aniline/Bromide Component	Thiol Component	Method	Yield (%)	HPLC (Min) Method 1	LC-MS (M+H)	H-NMR Data ($CDCl_3$)
75	 1-(4-((3,3-difluoro-1-hydroxycyclobutyl)methoxy)-3-methoxyphenyl)-3-(4-(trifluoromethoxy)phenylthio)pyrazin-2(1*H*)-one			2a			531	^{1}H NMR (400 MHz, MeOD) δ ppm 7.69(d, 2H), 7.38(d, 2H), 7.33(d, 1H), 7.18(m, 3H), 7.03(d, 1H), 4.09(s, 2H), 3.91(s, 3H), 2.93(m, 2H), 2.66(m, 2H).
76	 1-(4-((3,3-difluoro-1-hydroxycyclobutyl)methoxy)-3-methoxyphenyl)-3-(4-(trifluoromethyl)phenylthio)pyrazin-2(1*H*)-one			2a			515	^{1}H NMR (400 MHz, MeOD) δ ppm 7.78(s, 4H), 7.34(s, 1H), 7.19(m, 3H), 7.03(d, 1H), 4.09(s, 2H), 3.90(s, 3H), 2.93_m, 2H), 2.66(m, 2H).
77	 3-(4-fluorobenzo[*d*]thiazol-2-ylthio)-1-(4-(2-hydroxy-2-methylpropoxy)-3-methoxyphenyl)pyrazin-2(1*H*)-one			2a			474	^{1}H NMR (400 MHz, MeOD) δ ppm 7.78(d, 1H), 7.53(m, 3H), 7.30(m, 1H), 7.20(s, 1H), 7.12(m, 1H), 7.06(d, 1H), 3.91(s, 3H), 3.88(s, 2H), 1.36(s, 6H).
78	 3-(7-fluorobenzo[*d*]thiazol-2-ylthio)-1-(4-(2-hydroxy-2-methylpropoxy)-3-methoxyphenyl)pyrazin-2(1*H*)-one			2a			474	^{1}H NMR (400 MHz, MeOD) δ ppm 7.85(d, 1H), 7.53(m, 3H), 7.21(m, 4H), 3.91(s, 3H), 3.88(s, 2H), 1.36(s, 6H).
79	 3-(6-fluorobenzo[*d*]thiazol-2-ylthio)-1-(4-(2-hydroxy-2-methylpropoxy)-3-methoxyphenyl)pyrazin-2(1*H*)-one			2a			474	^{1}H NMR (400 MHz, MeOD) δ ppm 7.97(d, 1H), 7.85(d, 1H), 7.53(d, 2H), 7.35(t, 1H), 7.21(s, 1H), 7.16(m, 1H), 7.07(m, 1H), 3.91(s, 3H), 3.88(s, 2H), 1.36(s, 6H).
80	 1-(2-(2-hydroxypropan-2-yl)chroman-6-yl)-3-(4-(trifluoromethoxy)phenylthio)pyrazin-2(1*H*)-one			6			479	^{1}H NMR (400 MHz, MeOD) δ ppm 7.68(d, 2H), 7.40(d, 2H), 7.28(s, 1H), 7.17(m, 3H), 6.97(d, 1H), 3.82(s, 1H), 2.96(m, 2H), 2.24(m, 1H), 2.81(m, 1H), 1.33(s, 6H).

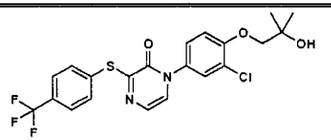
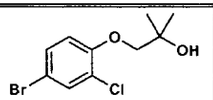
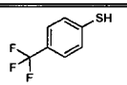
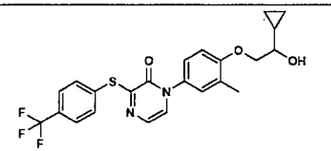
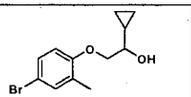
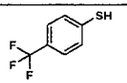
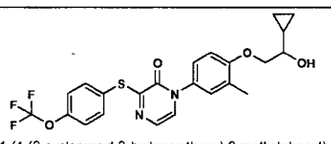
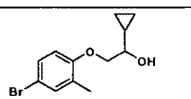
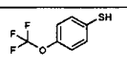
Ex. No.	Structure	Aniline/Bromide Component	Thiol Component	Method	Yield (%)	HPLC (Min) Method 1	LC-MS (M+H)	H-NMR Data ($CDCl_3$)
81	 1-(2-(2-hydroxypropan-2-yl)-4-methylchroman-6-yl)-3-(4-(trifluoromethoxy)phenylthio)pyrazin-2(1*H*)-one			6			491	^{1}H NMR (400 MHz, MeOD) δ ppm 7.69(d, 2H), 7.40(d, 2H), 7.28(m, 2H), 7.20(m, 2H), 6.91(d, 1H), 5.79(s, 1H), 4.70(s, 1H), 2.08(s, 2H), 1.31(d, 6H).
82	 1-(4-hydroxy-2-(2-hydroxypropan-2-yl)chroman-6-yl)-3-(4-(trifluoromethoxy)phenylthio)pyrazin-2(1*H*)-one			6			495	^{1}H NMR (400 MHz, $CDCl_3$) δ ppm 7.61(d, 2H), 7.59(s, 1H), 7.28(m, 2H), 7.14(m, 2H), 6.99(s, 1H), 6.92(d, 1H), 4.87(t, 1H), 4.00(d, 1H), 2.36(m, 1H), 1.84(q, 1H), 1.38(d, 6H).
83	 1-(4-hydroxy-4-methylchroman-6-yl)-3-(4-(trifluoromethoxy)phenylthio)pyrazin-2(1*H*)-one			6			433 (M+H-H_2O)	^{1}H NMR (400 MHz, MeOD) δ ppm 7.70(d, 2H), 7.61(s, 1H), 7.43(d, 2H), 7.28(m, 2H), 7.20(s, 1H), 6.95(d, 1H), 4.35(m,2H), 2.12(br-s, 2H), 1.62(s, 3H).
84	 1-(4-(2-hydroxy-2-methylpropoxy)phenyl)-3-(4-(trifluoromethoxy)phenylthio)pyrazin-2(1*H*)-one			6			453	1H NMR (500 MHz, chloroform-d) δ ppm 7.62 (2 H, d, *J*=8.80 Hz), 7.36 (2 H, d, *J*=8.80 Hz), 7.29 (2 H, d, *J*=7.97 Hz), 7.13 (1 H, d, *J*=4.67 Hz), 7.04 (2 H, d, *J*=8.80 Hz), 6.98 (1 H, d, *J*=4.40 Hz), 3.84 (2 H, s), 1.37 (6 H, s).
85	 1-(4-(2-hydroxy-2-methylpropoxy)-3-methoxyphenyl)-3-(naphthalen-1-ylthio)pyrazin-2(1*H*)-one			6			449	1H NMR (500 MHz, chloroform-d) δ ppm 8.31 (1 H, dd, *J*=6.19, 3.44 Hz), 8.00 (1 H, d, *J*=8.25 Hz), 7.85 - 7.95 (2 H, m), 7.51 - 7.56 (3 H, m), 7.04 (1 H, d, *J*=2.20 Hz), 6.97 - 7.02 (1 H, m), 6.89 - 6.96 (3 H, m), 3.90 (3 H, s), 3.88 (2 H, s), 1.37 (6 H, s).
86	 1-(3-fluoro-4-(2-hydroxy-2-methylpropoxy)phenyl)-3-(4-(trifluoromethoxy)phenylthio)pyrazin-2(1*H*)-one			6			471	1H NMR (500 MHz, methanol-d_3) δ ppm 7.62 - 7.68 (2 H, m), 7.34 - 7.39 (3 H, m), 7.21 - 7.29 (3 H, m), 7.15 (1 H, d, *J*=4.40 Hz), 3.91 (2 H, s), 1.34 (6 H, s).

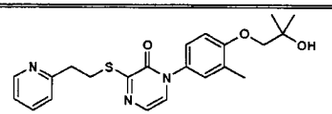
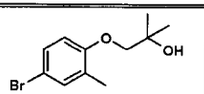
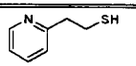
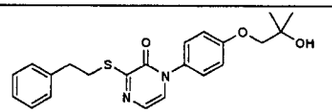
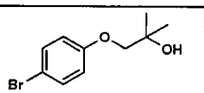
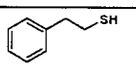
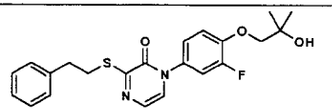
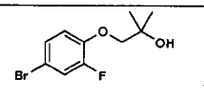
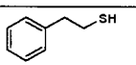
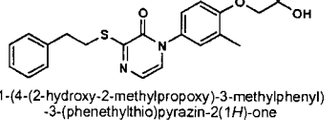
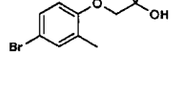
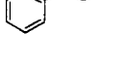
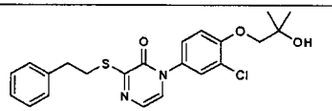
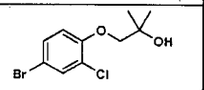
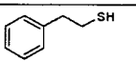
Ex. No.	Structure	Aniline/Bromide Component	Thiol Component	Method	Yield (%)	HPLC (Min) Method 1	LC-MS (M+H)	H-NMR Data ($CDCl_3$)
87	 1-(4-(2-hydroxy-2-methylpropoxy)-3-methylphenyl) -3-(4-(trifluoromethoxy)phenylthio)pyrazin-2(1*H*)-one			6			467	1H NMR (500 MHz, methanol-d_3) δ ppm 7.62 - 7.69 (2 H, m), 7.36 (2 H, d, *J*=7.97 Hz), 7.21 - 7.28 (3 H, m), 7.15 (1 H, d, *J*=4.40 Hz), 7.02 (1 H, d, *J*=8.52 Hz), 3.84 (2 H, s), 2.31 (3 H, s), 1.36 (6 H, s).
88	 1-(3-chloro-4-(2-hydroxy-2-methylpropoxy)phenyl) -3-(4-(trifluoromethoxy)phenylthio)pyrazin-2(1*H*)-one			6			487	1H NMR (500 MHz, methanol-d_3) δ ppm 7.65 (2 H, d, *J*=8.80 Hz), 7.59 (1 H, d, *J*=2.75 Hz), 7.33 - 7.41 (3 H, m), 7.27 (1 H, d, *J*=4.40 Hz), 7.22 (1 H, d, *J*=8.80 Hz), 7.15 (1 H, d, *J*=4.40 Hz), 3.91 (2 H, s), 1.37 (6 H, s)
89	 1-(4-(2-hydroxy-2-methylpropoxy)-3-(trifluoromethoxy)phenyl) -3-(4-(trifluoromethoxy)phenylthio)pyrazin-2(1*H*)-one			6			537	1H NMR (500 MHz, methanol-d_3) δ ppm 7.66 (2 H, d), 7.52 - 7.56 (1 H, m), 7.46 (1 H, dd, *J*=8.94, 2.61 Hz), 7.37 (2 H, d, *J*=7.97 Hz), 7.33 (1 H, d, *J*=8.80 Hz), 7.29 (1 H, d, *J*=4.40 Hz), 7.16 (1 H, d, *J*=4.67 Hz), 3.91 (2 H, s), 1.34 (6 H, s).
90	 2-(2-hydroxy-2-methylpropoxy)-5-(2-oxo-3- (4-(trifluoromethoxy)phenylthio)pyrazin-1(2*H*)-yl)benzonitrile			6			478	1H NMR (500 MHz, methanol-d_3) δ ppm 7.85 (1 H, d, *J*=2.75 Hz), 7.74 (1 H, dd, *J*=8.94, 2.61 Hz), 7.65 (2 H, d), 7.33 - 7.39 (3 H, m), 7.29 (1 H, d, *J*=4.67 Hz), 7.16 (1 H, d, *J*=4.40 Hz), 4.01 (2 H, s), 1.38 (6 H, s).
91	 1-(3,5-difluoro-4-(2-hydroxy-2-methylpropoxy)phenyl)-3-(4- (trifluoromethoxy)phenylthio)pyrazin-2(1*H*)-one			6			489	1H NMR (500 MHz, methanol-d_3) δ ppm 7.65 (2 H, d, *J*=8.80 Hz), 7.37 (2 H, d, *J*=7.97 Hz), 7.24 - 7.32 (3 H, m), 7.15 (1 H, d, *J*=4.40 Hz), 4.00 (2 H, s), 1.33 (6 H, s).

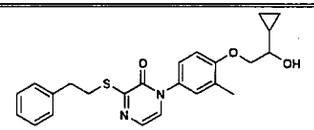
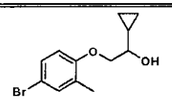
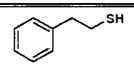
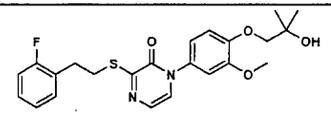
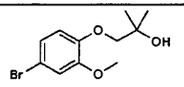
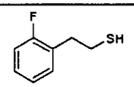
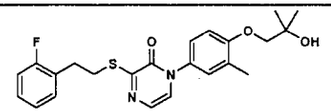
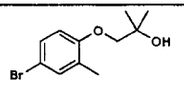
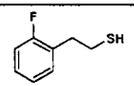
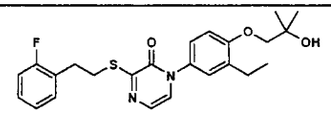
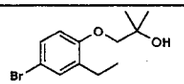
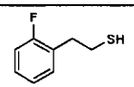
Ex. No.	Structure	Aniline/Bromide Component	Thiol Component	Method	Yield (%)	HPLC (Min) Method 1	LC-MS (M+H)	H-NMR Data ($CDCl_3$)
92	 1-(3-chloro-4-(2-hydroxy-2-methylpropoxy)-5-methylphenyl) -3-(4-(trifluoromethoxy)phenylthio)pyrazin-2(1*H*)-one			6			501	1H NMR (500 MHz, methanol-d_3) δ ppm 7.65 (2 H, d, *J*=8.80 Hz), 7.45 (1 H, d, *J*=2.75 Hz), 7.37 (2 H, d, *J*=7.97 Hz), 7.30 (1 H, d, *J*=1.92 Hz), 7.27 (1 H, d, *J*=4.40 Hz), 7.15 (1 H, d, *J*=4.67 Hz), 3.78 (2 H, s), 2.40 (3 H, s), 1.39 (6 H, s).
93	 1-(4-(2-hydroxy-2-methylpropoxy)-3-(trifluoromethyl)phenyl) -3-(4-(trifluoromethoxy)phenylthio)pyrazin-2(1*H*)-one			6			521	1H NMR (500 MHz, methanol-d_3) δ ppm 7.77 (1 H, d, *J*=2.47 Hz), 7.62 - 7.71 (3 H, m), 7.35 (3 H, dd, *J*=14.57, 8.52 Hz), 7.30 (1 H, d, *J*=4.40 Hz), 7.17 (1 H, d, *J*=4.40 Hz), 3.94 (2 H, s), 1.35 (6 H, s).
94	 1-(3-chloro-5-fluoro-4-(2-hydroxy-2-methylpropoxy)phenyl) -3-(4-(trifluoromethoxy)phenylthio)pyrazin-2(1*H*)-one			6			505	1H NMR (500 MHz, methanol-d_3) δ ppm 7.65 (2 H, d), 7.46 - 7.51 (1 H, m), 7.42 (1 H, dd, *J*=11.27, 2.47 Hz), 7.37 (2 H, d, *J*=7.97 Hz), 7.28 (1 H, d, *J*=4.40 Hz), 7.15 (1 H, d, *J*=4.40 Hz), 3.98 (2 H, s), 1.37 (6 H, s).
95	 1-(4-(2-hydroxy-2-methylpropoxy)-3-methylphenyl) -3-(5-(trifluoromethoxy)pyridin-2-ylthio)pyrazin-2(1*H*)-one			6			452	1H NMR (500 MHz, chloroform-d) δ ppm 8.88 (1 H, s), 7.89 - 7.99 (2 H, m), 7.16 - 7.24 (3 H, m), 7.07 (1 H, d, *J*=4.40 Hz), 6.90 (1 H, d, *J*=8.52 Hz), 3.84 (2 H, s), 2.30 (3 H, s), 1.39 (6 H, s)
96	 1-(4-(2-hydroxy-2-methylpropoxy)-3,5-dimethylphenyl) -3-(4-(trifluoromethoxy)phenylthio)pyrazin-2(1*H*)-one			6			481	1H NMR (400 MHz, chloroform-d) δ ppm 7.62 (2 H, d, *J*=8.78 Hz), 7.29 (2 H, d, *J*=8.03 Hz), 7.11 (1 H, d, *J*=4.52 Hz), 7.08 (2 H, s), 6.96 (1 H, d, *J*=4.52 Hz), 3.64 (2 H, s), 2.33 (6 H, s), 1.39 (6 H, s).

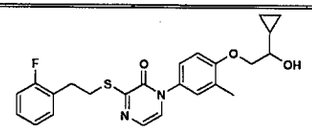
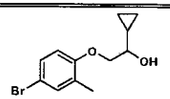
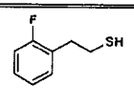
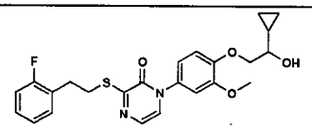
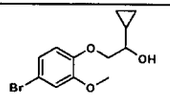
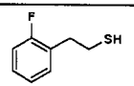
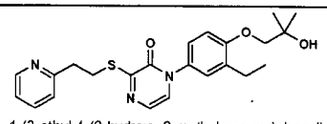
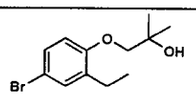
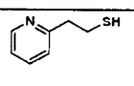
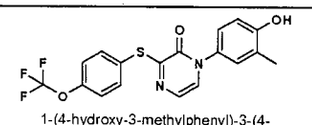
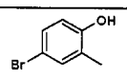
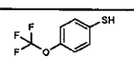
Ex. No.	Structure	Aniline/Bromide Component	Thiol Component	Method	Yield (%)	HPLC (Min) Method 1	LC-MS (M+H)	H-NMR Data ($CDCl_3$)
97	 1-(3-(2-hydroxypropan-2-yl)-2*H*-chromen-6-yl)-3-(4-(trifluoromethoxy)phenylthio)pyrazin-2(1*H*)-one			6			477	1H NMR (400 MHz, MeOD) δ ppm 7.68(d, 2H), 7.39(d, 2H), 7.28(d, 1H), 7.18(m, 3H), 6.93(d,1H), 6.49(s, 1H), 1.42(s, 6H).
98	 1-(4-(2-hydroxy-2-methylpropoxy)-2,3-dimethylphenyl)-3-(4-(trifluoromethoxy)phenylthio)pyrazin-2(1*H*)-one			6			481	1H NMR (400 MHz, MeOD) δ ppm 7.69 (2 H, d), 7.39 (2 H, d, *J*=8.03 Hz), 7.18 (2 H, dd), 7.08 (1 H, d, *J*=8.53 Hz), 6.93 (1 H, d, *J*=8.78 Hz), 3.84 (2 H, s), 2.30 (3 H, s), 2.02 (3 H, s), 1.38 (6 H, s).
99	 1-(4-(2-cyclopropyl-2-hydroxyethoxy)-3-methylphenyl)-3-(3-fluorophenethylthio)pyrazin-2(1*H*)-one			6			441	1H NMR (500 MHz, chloroform-d) δ ppm 7.23 - 7.31 (2 H, m), 7.16 - 7.23 (2 H, m), 7.07 (1 H, d, *J*=7.42 Hz), 6.98 - 7.04 (1 H, m), 6.88 - 6.98 (3 H, m), 4.14 (1 H, dd, *J*=9.35, 3.30 Hz), 4.04 (1 H, dd, *J*=9.35, 7.15 Hz), 3.26 - 3.40 (3 H, m), 2.97 - 3.06 (2 H, m), 2.27 (3 H, s), 0.99 - 1.10 (1 H, m), 0.55 - 0.68 (2 H, m), 0.43 - 0.51 (1 H, m), 0.30 - 0.38 (1 H, m)
100	 1-(4-(2-hydroxy-2-methylpropoxy)-2,5-dimethylphenyl)-3-(4-(trifluoromethoxy)phenylthio)pyrazin-2(1*H*)-one			6			481	1H NMR (400 MHz, chloroform-d) δ ppm 7.63 (2 H, dd, *J*=8.78, 2.26 Hz), 7.30 (2 H, d, *J*=7.78 Hz), 7.11 (1 H, dd, *J*=4.27, 2.26 Hz), 6.98 (1 H, s), 6.84 (1 H, dd, *J*=4.52, 2.26 Hz), 6.76 (1 H, s), 3.84 (2 H, br. s.), 2.24 (3 H, s), 2.14 (3 H, s), 1.39 (6 H, d, *J*=2.26 Hz).

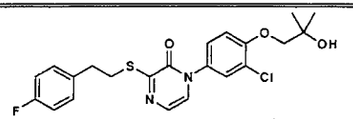
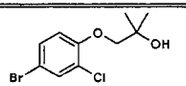
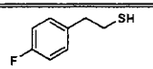
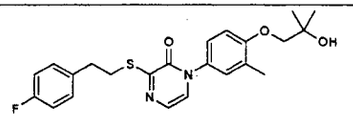
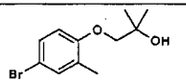
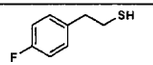
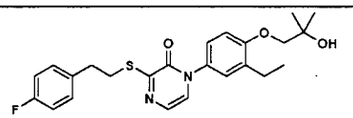
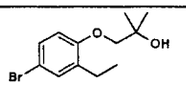
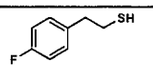
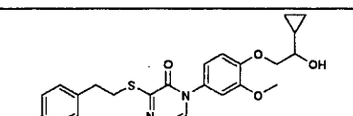
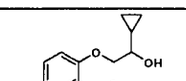
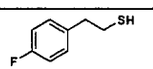
Ex. No.	Structure	Aniline/Bromide Component	Thiol Component	Method	Yield (%)	HPLC (Min) Method 1	LC-MS (M+H)	H-NMR Data ($CDCl_3$)
101	 1-(4-(2-hydroxy-2-methylpropoxy)phenyl)-3-(4-(trifluoromethyl)phenylthio)pyrazin-2(1*H*)-one			6			437	1H NMR (500 MHz, chloroform-d) δ ppm 7.71 (4 H, m), 7.36 (2 H, d, *J*=8.80 Hz), 7.13 (1 H, d, *J*=4.40 Hz), 7.04 (2 H, d, *J*=9.35 Hz), 7.00 (1 H, d, *J*=4.40 Hz), 3.84 (2 H, s), 1.37 (6 H, s).
102	 1-(3-fluoro-4-(2-hydroxy-2-methylpropoxy)phenyl)-3-(4-(trifluoromethyl)phenylthio)pyrazin-2(1*H*)-one			6			455	1H NMR (500 MHz, chloroform-d) δ ppm 7.71 (4 H, m), 7.26 (1 H, dd, *J*=11.00, 2.75 Hz), 7.11 – 7.19 (2 H, m), 7.05 – 7.11 (1 H, m), 6.98 (1 H, d, *J*=4.95 Hz), 3.91 (2 H, s), 1.38 (6 H, s)
103	 1-(4-(2-hydroxy-2-methylpropoxy)-3-methylphenyl)-3-(4-(trifluoromethyl)phenylthio)pyrazin-2(1*H*)-one			6			451	1H NMR (500 MHz, chloroform-d) δ ppm 7.67 – 7.75 (4 H, m), 7.18 – 7.25 (2 H, m), 7.12 (1 H, d, *J*=4.40 Hz), 6.99 (1 H, d, *J*=4.40 Hz), 6.91 (1 H, d, *J*=8.25 Hz), 3.85 (2 H, s), 2.31 (3 H, s), 1.39 (6 H, s)
104	 1-(4-(2-hydroxy-2-methylpropoxy)-3-(trifluoromethoxy)phenyl)-3-(4-(trifluoromethyl)phenylthio)pyrazin-2(1*H*)-one			6			521	1H NMR (500 MHz, chloroform-d) δ ppm 7.66 - 7.78 (4 H, m), 7.35 - 7.42 (2 H, m), 7.08 - 7.17 (2 H, m), 6.99 (1 H, d, *J*=4.40 Hz), 3.90 (2 H, s), 1.38 (6 H, s)
105	 2-(2-hydroxy-2-methylpropoxy)-5-(2-oxo-3-(4-(trifluoromethyl)phenylthio)pyrazin-1(2*H*)-yl)benzonitrile			6			462	1H NMR (500 MHz, chloroform-d) δ ppm 7.60 - 7.78 (6 H, m), 7.09 - 7.17 (2 H, m), 6.95 (1 H, d, *J*=4.40 Hz), 3.97 (2 H, s), 1.43 (6 H, s)
106	 1-(4-(2-hydroxy-2-methylpropoxy)-3,5-dimethylphenyl)-3-(4-(trifluoromethyl)phenylthio)pyrazin-2(1*H*)-one			6			465	1H NMR (500 MHz, chloroform-d) δ ppm 7.71 (4 H, d, *J*=6.05 Hz), 7.07 - 7.14 (3 H, m), 6.98 (1 H, d, *J*=4.40 Hz), 3.64 (2 H, s), 2.33 (6 H, s), 1.40 (6 H, s)

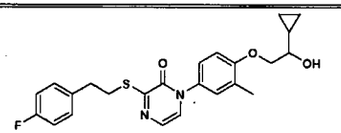
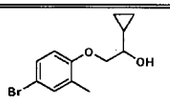
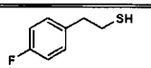
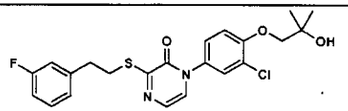
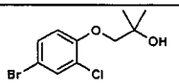
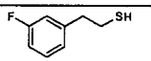
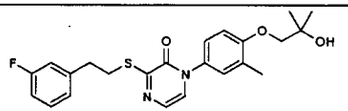
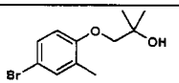
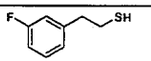
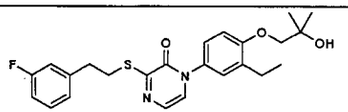
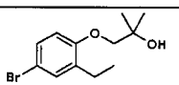
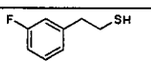
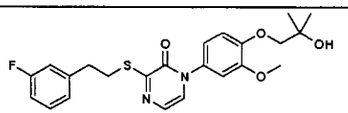
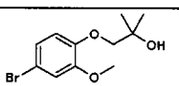
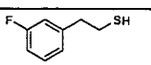
Ex. No.	Structure	Aniline/Bromide Component	Thiol Component	Method	Yield (%)	HPLC (Min) Method 1	LC-MS (M+H)	H-NMR Data ($CDCl_3$)
107	 1-(3-chloro-4-(2-hydroxy-2-methylpropoxy)phenyl) -3-(4-(trifluoromethyl)phenylthio)pyrazin-2(1*H*)-one			6			471	1H NMR (500 MHz, chloroform-d) δ ppm 7.67 - 7.74 (4 H, m), 7.50 (1 H, d, *J*=2.47 Hz), 7.32 (1 H, dd, *J*=8.80, 2.47 Hz), 7.13 (1 H, d, *J*=4.67 Hz), 7.03 (1 H, d, *J*=8.80 Hz), 6.97 (1 H, d, *J*=4.40 Hz), 3.91 (2 H, s), 1.40 (6 H, s)
108	 1-(4-(2-cyclopropyl-2-hydroxyethoxy)-3-methylphenyl) -3-(4-(trifluoromethyl)phenylthio)pyrazin-2(1*H*)-one			6			463	1H NMR (500 MHz, chloroform-d) δ ppm 7.64 - 7.77 (4 H, m), 7.19 - 7.24 (2 H, m), 7.12 (1 H, d, *J*=4.40 Hz), 7.00 (1 H, d, *J*=4.40 Hz), 6.94 (1 H, d, *J*=8.80 Hz), 4.16 (1 H, dd, *J*=9.35, 3.30 Hz), 4.06 (1 H, dd, *J*=9.35, 7.15 Hz), 3.31 - 3.42 (1 H, m), 2.29 (3 H, s), 0.99 - 1.11 (1 H, m), 0.55 - 0.71 (2 H, m), 0.43 - 0.52 (1 H, m), 0.29 - 0.41 (1 H, m)
109	 1-(4-(2-cyclopropyl-2-hydroxyethoxy)-3-methylphenyl) -3-(4-(trifluoromethoxy)phenylthio)pyrazin-2(1*H*)-one			6			479	1H NMR (500 MHz, chloroform-d) δ ppm 7.61 (2 H, d), 7.29 (2 H, d, *J*=7.97 Hz), 7.19 - 7.24 (2 H, m), 7.11 (1 H, d, *J*=4.67 Hz), 6.98 (1 H, d, *J*=4.40 Hz), 6.94 (1 H, d, *J*=8.52 Hz), 4.15 (1 H, dd, *J*=9.35, 3.30 Hz), 4.05 (1 H, dd, *J*=9.35, 7.15 Hz), 3.30 - 3.42 (1 H, m), 2.28 (3 H, s), 0.99 - 1.11 (1 H, m), 0.55 - 0.70 (2 H, m), 0.42 - 0.52 (1 H, m), 0.30 - 0.39 (1 H, m)

Ex. No.	Structure	Aniline/Bromide Component	Thiol Component	Method	Yield (%)	HPLC (Min) Method 1	LC-MS (M+H)	H-NMR Data ($CDCl_3$)
110	 1-(4-(2-hydroxy-2-methylpropoxy)-3-methylphenyl) -3-(2-(pyridin-2-yl)ethylthio)pyrazin-2(1*H*)-one			6			412	1H NMR (400 MHz, MeOD) δ ppm 8.67 (1 H, d), 8.48 (1 H, td, *J*=7.91, 1.51 Hz), 8.02 (1 H, d, *J*=8.28 Hz), 7.81 - 7.95 (1 H, m), 7.07 - 7.29 (4 H, m), 6.93 (1 H, d, *J*=8.78 Hz), 3.76 (2 H, s), 3.35 - 3.57 (4 H, m), 2.22 (3 H, s), 1.27 (6 H, s)
111	 1-(4-(2-hydroxy-2-methylpropoxy)phenyl) -3-(phenethylthio)pyrazin-2(1*H*)-one			6			397	1H NMR (500 MHz, methanol-d_3) δ ppm 7.32 - 7.40 (3 H, m), 7.25 - 7.29 (4 H, m), 7.16 - 7.23 (2 H, m), 7.08 (2 H, d, *J*=8.80 Hz), 3.83 (2 H, s), 3.31 (2 H, s), 2.89 - 3.03 (2 H, m), 1.32 (6 H, s)
112	 1-(3-fluoro-4-(2-hydroxy-2-methylpropoxy) phenyl)-3-(phenethylthio)pyrazin-2(1*H*)-one			6			415	1H NMR (500 MHz, methanol-d_3) δ ppm 7.12 - 7.46 (10 H, m), 3.90 (1 H, s), 3.21 - 3.42 (2 H, m), 2.90 - 3.03 (2 H, m), 1.33 (6 H, s)
113	 1-(4-(2-hydroxy-2-methylpropoxy)-3-methylphenyl) -3-(phenethylthio)pyrazin-2(1*H*)-one			6			411	1H NMR (500 MHz, methanol-d_3) δ ppm 7.38 (1 H, d, *J*=4.40 Hz), 7.25 - 7.32 (4 H, m), 7.16 - 7.24 (4 H, m), 7.00 (1 H, d, *J*=8.25 Hz), 3.83 (1 H, s), 3.24 - 3.39 (2 H, m), 2.90 - 3.05 (2 H, m), 2.29 (3 H, s), 1.35 (6 H, s)
114	 1-(3-chloro-4-(2-hydroxy-2-methylpropoxy) phenyl)-3-(phenethylthio)pyrazin-2(1*H*)-one			6			431	1H NMR (500 MHz, methanol-d_3) δ ppm 7.56 (1 H, d, *J*=2.20 Hz), 7.33 - 7.42 (2 H, m), 7.17 - 7.31 (7 H, m), 3.90 (2 H, s), 3.23 - 3.42 (2 H, m), 2.89 - 3.08 (2 H, m), 1.36 (6 H, s)

Ex. No.	Structure	Aniline/Bromide Component	Thiol Component	Method	Yield (%)	HPLC (Min) Method 1	LC-MS (M+H)	H-NMR Data ($CDCl_3$)
115	 1-(4-(2-cyclopropyl-2-hydroxyethoxy)-3-methylphenyl) -3-(phenethylthio)pyrazin-2(1*H*)-one			6			423	1H NMR (500 MHz, methanol-d_3) δ ppm 7.37 (1 H, d, *J*=4.40 Hz), 7.25 - 7.32 (4 H, m), 7.16 - 7.23 (4 H, m), 7.03 (1 H, d, *J*=9.35 Hz), 3.99 - 4.17 (2 H, m), 3.25 - 3.39 (3 H, m), 2.91 - 3.04 (2 H, m), 2.28 (3 H, s), 0.98 - 1.11 (1 H, m), 0.51 - 0.61 (2 H, m), 0.29 - 0.47 (2 H, m)
116	 3-(2-fluorophenethylthio)-1-(4-(2-hydroxy-2-methylpropoxy) -3-methoxyphenyl)pyrazin-2(1*H*)-one			6			445	1H NMR (500 MHz, methanol-d_3) δ ppm 7.30 - 7.39 (2 H, m), 7.20 - 7.27 (2 H, m), 7.01 - 7.13 (4 H, m), 6.95 (1 H, dd, *J*=8.52, 2.47 Hz), 3.86 (2 H, s), 3.24 - 3.39 (2 H, m), 2.97 - 3.11 (2 H, m), 1.32 (6 H, s)
117	 3-(2-fluorophenethylthio)-1-(4-(2-hydroxy-2-methyl propoxy)-3-methylphenyl)pyrazin-2(1*H*)-one			6			429	1H NMR (500 MHz, methanol-d_3) δ ppm 7.29 - 7.38 (2 H, m), 7.17 - 7.26 (4 H, m), 6.97 - 7.13 (3 H, m), 3.83 (2 H, s), 3.28 - 3.36 (2 H, m), 3.04 (2 H, t, *J*=7.42 Hz), 2.29 (3 H, s), 1.35 (6 H, s)
118	 1-(3-ethyl-4-(2-hydroxy-2-methylpropoxy)phenyl) -3-(2-fluorophenethylthio)pyrazin-2(1*H*)-one			6			443	1H NMR (400 MHz, chloroform-d) δ ppm 7.16 - 7.35 (5 H, m), 6.86 - 7.13 (4 H, m), 3.84 (2 H, s), 3.26 - 3.41 (2 H, m), 3.07 (2 H, t, *J*=7.65 Hz), 2.71 (2 H, q, *J*=7.53 Hz), 1.32 - 1.47 (6 H, m), 1.23 (3 H, t, *J*=7.65 Hz)

Ex. No.	Structure	Aniline/Bromide Component	Thiol Component	Method	Yield (%)	HPLC (Min) Method 1	LC-MS (M+H)	H-NMR Data ($CDCl_3$)
119	 1-(4-(2-cyclopropyl-2-hydroxyethoxy)-3-methylphenyl) -3-(2-fluorophenethylthio)pyrazin-2(1*H*)-one			6			441	1H NMR (500 MHz, methanol-d_3) δ ppm 7.28 - 7.37 (2 H, m), 7.16 - 7.26 (4 H, m), 6.99 - 7.12 (3 H, m), 3.95 - 4.18 (2 H, m), 3.22 - 3.42 (3 H, m), 3.04 (2 H, t, *J*=7.42 Hz), 2.27 (3 H, s), 0.97 - 1.13 (1 H, m), 0.46 - 0.63 (2 H, m), 0.29 - 0.46 (2 H, m)
120	 1-(4-(2-cyclopropyl-2-hydroxyethoxy)-3-methoxyphenyl) -3-(2-fluorophenethylthio)pyrazin-2(1*H*)-one			6			457	1H NMR (500 MHz, methanol-d_3) δ ppm 7.20 - 7.30 (2 H, m), 7.11 - 7.18 (2 H, m), 6.92 - 7.04 (4 H, m), 6.86 (1 H, dd, *J*=8.52, 2.47 Hz), 3.85 - 4.12 (2 H, m), 3.76 (3 H, s), 3.16 - 3.31 (3 H, m), 2.87 - 3.03 (2 H, m), 0.82 - 1.00 (1 H, m), 0.38 - 0.54 (2 H, m), 0.18 - 0.37 (2 H, m)
121	 1-(3-ethyl-4-(2-hydroxy-2-methylpropoxy)phenyl) -3-(2-(pyridin-2-yl)ethylthio)pyrazin-2(1*H*)-one			6			426	1H NMR (400 MHz, MeOD) δ ppm 8.29 (1 H, d, *J*=4.02 Hz), 7.60 (1 H, td, *J*=7.65, 1.76 Hz), 7.16 - 7.26 (2 H, m), 6.98 - 7.14 (4 H, m), 6.85 (1 H, d, *J*=9.03 Hz), 3.66 (2 H, s), 3.29 (2 H, t, *J*=7.28 Hz), 3.02 (2 H, t, *J*=7.40 Hz), 2.56 (2 H, q, *J*=7.53 Hz), 1.18 (6 H, s), 1.05 (3 H, t, *J*=7.53 Hz)
122	 1-(4-hydroxy-3-methylphenyl)-3-(4-(trifluoromethoxy)phenylthio)pyrazin-2(1*H*)-one			6			395	1H NMR (400 MHz, chloroform-d) δ ppm 7.62 (2 H, d, *J*=8.78 Hz), 7.30 (2 H, d, *J*=8.03 Hz), 7.16 (1 H, d, *J*=4.52 Hz), 7.10 (1 H, d, *J*=2.01 Hz), 6.91 - 7.05 (2 H, m), 6.70 (1 H, d, *J*=8.53 Hz), 6.22 (1 H, s), 2.21 (3 H, s)

Ex. No.	Structure	Aniline/Bromide Component	Thiol Component	Method	Yield (%)	HPLC (Min) Method 1	LC-MS (M+H)	H-NMR Data ($CDCl_3$)
123	 1-(3-chloro-4-(2-hydroxy-2-methylpropoxy)phenyl) -3-(4-fluorophenethylthio)pyrazin-2(1*H*)-one			6			449	1H NMR (500 MHz, chloroform-d) δ ppm 7.47 (1 H, d, *J*=2.47 Hz), 7.21 - 7.32 (4 H, m), 6.97 - 7.04 (3 H, m), 6.93 (1 H, d, *J*=4.67 Hz), 3.89 (2 H, s), 3.30 (2 H, t, *J*=7.70 Hz), 2.98 (2 H, t, *J*=7.84 Hz), 1.40 (6 H, s)
124	 3-(4-fluorophenethylthio)-1-(4-(2-hydroxy-2-methyl propoxy)-3-methylphenyl)pyrazin-2(1*H*)-one			6			429	1H NMR (500 MHz, chloroform-d) δ ppm 7.22 - 7.29 (3 H, m), 7.16 - 7.22 (2 H, m), 6.99 (2 H, t, *J*=8.66 Hz), 6.95 (1 H, d, *J*=4.40 Hz), 6.88 (1 H, d, *J*=8.52 Hz), 3.84 (2 H, s), 3.21 - 3.36 (2 H, m), 2.90 - 3.08 (2 H, m), 2.29 (3 H, s), 1.38 (6 H, s)
125	 1-(3-ethyl-4-(2-hydroxy-2-methylpropoxy) phenyl)-3-(4-fluorophenethylthio)pyrazin-2(1*H*)-one			6			443	1H NMR (500 MHz, chloroform-d) δ ppm 7.22 - 7.29 (3 H, m), 7.17 - 7.22 (2 H, m), 6.94 - 7.03 (3 H, m), 6.90 (1 H, d, *J*=8.25 Hz), 3.84 (2 H, s), 3.25 - 3.35 (2 H, m), 2.92 - 3.05 (2 H, m), 2.71 (2 H, q), 1.39 (6 H, s), 1.23 (3 H, t, *J*=7.56 Hz)
126	 1-(4-(2-cyclopropyl-2-hydroxyethoxy)-3-methoxyphenyl) -3-(4-fluorophenethylthio)pyrazin-2(1*H*)-one			6			457	1H NMR (500 MHz, chloroform-d) δ ppm 7.23 - 7.28 (2 H, m), 6.95 - 7.03 (6 H, m), 6.90 (1 H, dd, *J*=8.52, 2.20 Hz), 4.20 (1 H, dd, *J*=9.62, 2.75 Hz), 4.03 (1 H, dd, *J*=9.62, 8.25 Hz), 3.86 (3 H, s), 3.26 - 3.40 (3 H, m), 2.93 - 3.06 (2 H, m), 0.89 - 1.04 (1 H, m), 0.52 - 0.66 (2 H, m), 0.41 - 0.49 (1 H, m), 0.27 - 0.36 (1 H, m)

Ex. No.	Structure	Aniline/Bromide Component	Thiol Component	Method	Yield (%)	HPLC (Min) Method 1	LC-MS (M+H)	H-NMR Data ($CDCl_3$)
127	 1-(4-(2-cydopropyl-2-hydroxyethoxy)-3-methylphenyl) -3-(4-fluorophenethylthio)pyrazin-2(1*H*)-one			6			441	1H NMR (500 MHz, chloroform-d) δ ppm 7.22 - 7.28 (3 H, m), 7.16 - 7.22 (2 H, m), 6.90 - 7.03 (4 H, m), 4.14 (1 H, dd, *J*=9.35, 3.30 Hz), 4.04 (1 H, dd, *J*=9.35, 7.15 Hz), 3.24 - 3.41 (3 H, m), 2.93 - 3.05 (2 H, m), 2.27 (3 H, s), 0.99 - 1.09 (1 H, m), 0.55 - 0.70 (2 H, m), 0.43 - 0.51 (1 H, m), 0.29 - 0.39 (1 H, m)
128	 1-(3-chloro-4-(2-hydroxy-2-methylpropoxy) phenyl)-3-(3-fluorophenethylthio)pyrazin-2(1*H*)-one			6			449	1H NMR (500 MHz, chloroform-d) δ ppm 7.47 (1 H, d, *J*=2.75 Hz), 7.21 - 7.34 (3 H, m), 6.88 - 7.10 (5 H, m), 3.89 (2 H, s), 3.27 - 3.37 (2 H, m), 2.97 - 3.06 (2 H, m), 1.40 (6 H, s)
129	 3-(3-fluorophenethylthio)-1-(4-(2-hydroxy-2-methyl propoxy)-3-methylphenyl)pyrazin-2(1*H*)-one			6			429	1H NMR (500 MHz, chloroform-d) δ ppm 7.23 - 7.31 (3 H, m), 7.16 - 7.22 (2 H, m), 6.86 - 7.09 (4 H, m), 3.84 (2 H, s), 3.27 - 3.35 (2 H, m), 2.96 - 3.05 (2 H, m), 2.29 (3 H, s), 1.38 (6 H, s)
130	 1-(3-ethyl-4-(2-hydroxy-2-methylpropoxy) phenyl)-3-(3-fluorophenethylthio)pyrazin-2(1*H*)-one			6			443	1H NMR (500 MHz, chloroform-d) δ ppm 7.24 - 7.30 (2 H, m), 7.17 - 7.22 (2 H, m), 6.86 - 7.11 (5 H, m), 3.84 (2 H, s), 3.24 - 3.38 (2 H, m), 2.96 - 3.08 (2 H, m), 2.71 (2 H, q, *J*=7.70 Hz), 1.38 (6 H, s), 1.23 (3 H, t, *J*=7.56 Hz)
131	 3-(3-fluorophenethylthio)-1-(4-(2-hydroxy-2-methyl propoxy)-3-methoxyphenyl)pyrazin-2(1*H*)-one			6			445	1H NMR (500 MHz, chloroform-d) δ ppm 7.20 - 7.38 (2 H, m), 6.83 - 7.14 (7 H, m), 3.86 (5 H, s), 3.23 - 3.40 (2 H, m), 2.93 - 3.10 (2 H, m), 1.36 (6 H, s)

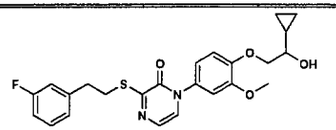
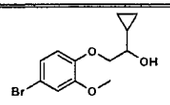
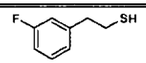
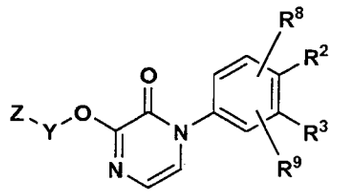
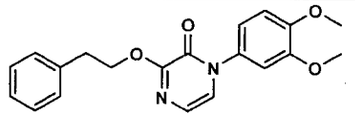
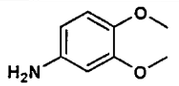
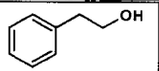
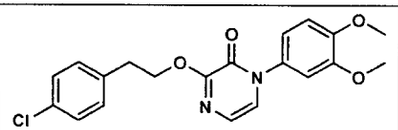
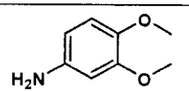
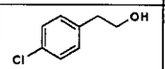
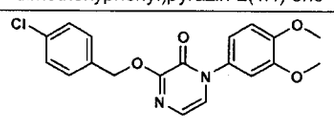
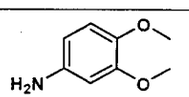
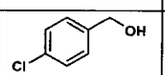
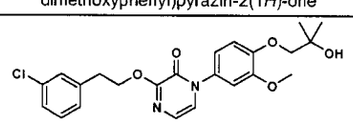
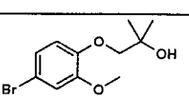
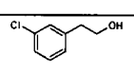
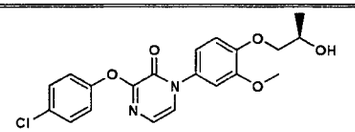
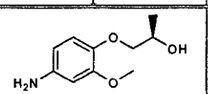
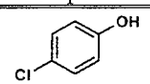
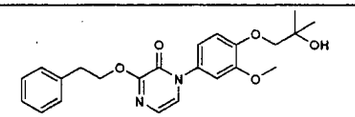
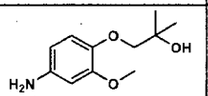
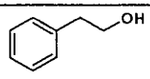
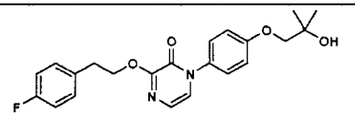
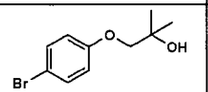
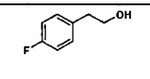
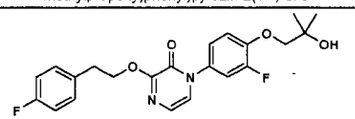
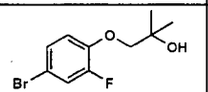
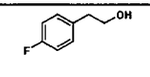
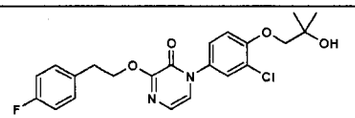
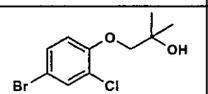
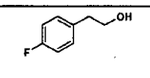
Ex. No.	Structure	Aniline/Bromide Component	Thiol Component	Method	Yield (%)	HPLC (Min) Method 1	LC-MS (M+H)	H-NMR Data ($CDCl_3$)
132	 1-(4-(2-cyclopropyl-2-hydroxyethoxy)-3-methoxyphenyl) -3-(3-fluorophenethylthio)pyrazin-2(1*H*)-one			6			457	1H NMR (500 MHz, chloroform-d) δ ppm 7.24 - 7.31 (2 H, m), 7.07 (1 H, d, *J*=7.42 Hz), 6.96 - 7.04 (4 H, m), 6.87 - 6.96 (2 H, m), 4.20 (1 H, dd, *J*=9.62, 2.75 Hz), 4.03 (1 H, dd, *J*=9.90, 8.25 Hz), 3.86 (5 H, s), 3.26 - 3.43 (3 H, m), 2.96 - 3.06 (2 H, m), 0.91 - 1.03 (1 H, m), 0.52 - 0.68 (2 H, m), 0.41 - 0.50 (1 H, m), 0.26 - 0.35 (1 H, m)

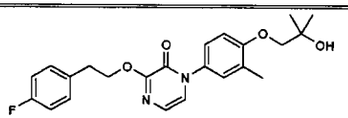
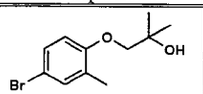
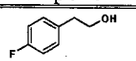
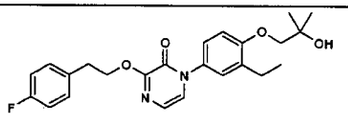
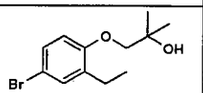
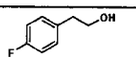
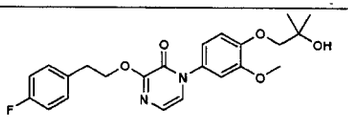
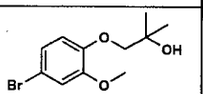
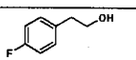
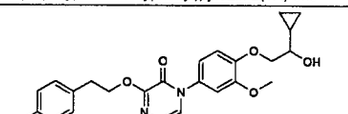
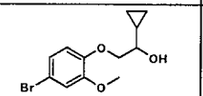
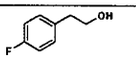
TABLE 2

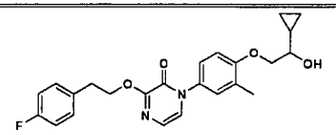
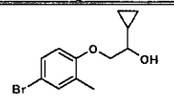
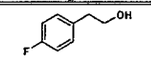
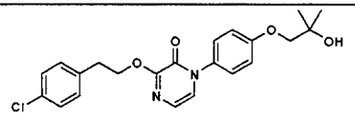
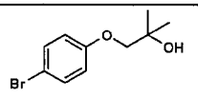
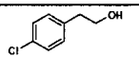
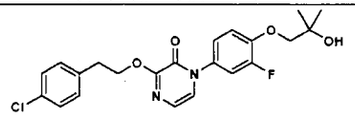
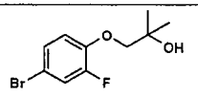
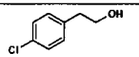
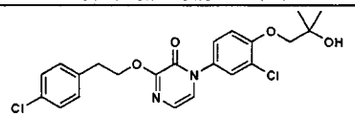
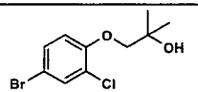
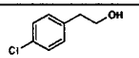
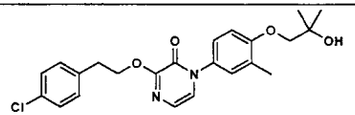
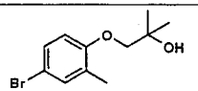
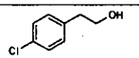
3-Oxa substituted-1-arylpyrazin-2(1H)-ones

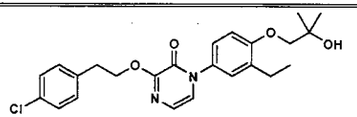
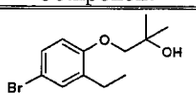
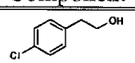
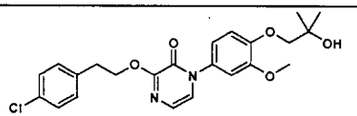
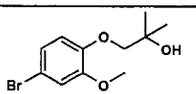
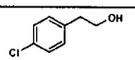
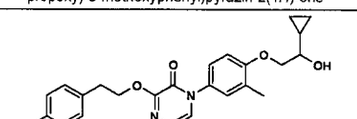
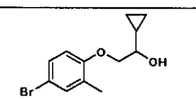
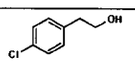
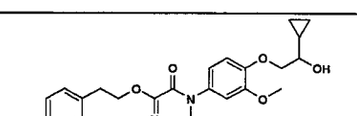
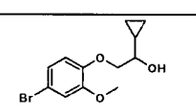
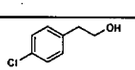


Ex. No.	Structure	Aniline/Bromide Component	Alcohol Component	Method	Yield (%)	HPLC	LC-MS	HNMR Data ($CDCl_3$)
133	 1-(3,4-dimethoxyphenyl)-3-phenethoxypyrazin-2(1*H*)-one			1	18	3.71	353	7.27 (m, 5H), 6.93 (m, 5H), 4.55 (t, J = 7.5 Hz, 2H), 3.92 (s, 3H), 3.89 (s, 3H), 3.17 (t, J = 7.5 Hz, 2H).
134	 3-(4-chlorophenethoxy)-1-(3,4-dimethoxyphenyl)pyrazin-2(1*H*)-one			1	26	3.96	387/389	7.25 (m, 4H), 6.92 (m, 5H), 4.52 (t, J = 7.2 Hz, 2H), 3.92 (s, 3H), 3.89 (s, 3H), 3.12 (t, J = 7.2 Hz, 2H).
135	 3-(4-chlorobenzyloxy)-1-(3,4-dimethoxyphenyl)pyrazin-2(1*H*)-one			1	68	3.83	373/375	7.37 (d, J = 8.4 Hz, 2H), 7.25 (d, J = 8.4 Hz, 2H), 6.60 (m, 5H), 5.32 (s, 2H), 3.84 (s, 3H), 3.80 (s, 3H)
136	 3-(3-chlorophenethoxy)-1-(4-(2-hydroxy-2-methyl propoxy)-3-methoxyphenyl)pyrazin-2(1*H*)-one			7			445	1H NMR (500 MHz, chloroform-d) δ ppm 7.30 (1 H, s), 7.22 (3 H, d, *J*=4.95 Hz), 6.94 - 7.00 (2 H, m), 6.83 - 6.91 (3 H, m), 4.54 (2 H, t, *J*=7.42 Hz), 3.86 (5 H, s), 3.15 (2 H, t, *J*=7.42 Hz), 1.36 (6 H, s)

Ex. No.	Structure	Aniline/Bromide Component	Alcohol Component	Method	Yield (%)	HPLC	LC-MS	HNMR Data ($CDCl_3$)
137	 (*R*)-3-(4-chlorophenoxy)-1-(4-(2-hydroxypropoxy)-3-methoxyphenyl)pyrazin-2(1*H*)-one			4		3.59	403/405	7.42 (d, J = 8.9 Hz, 2H), 7.18 (d, J = 8.9 Hz, 2H), 7.02 (m, 2H), 6.80(d, J = 4.6 Hz, 1H), 6.93 (dd, J = 2.2 and 8.4 Hz, 1H), 6.81 (d, J = 4.6 Hz, 1H) 4.25 (m, 1H), 4.05 (dd, J = 3.0 and 9.6 Hz, 1H), 3.88 (s, 3H), 3.86 (dd, J = 1.0 and 9.6 Hz, 1H), 2.73 (broad s, 1H), 1.27 (d, J = 4.3 Hz, 3H).
138	 1-(4-(2-hydroxy-2-methylpropoxy)-3-methoxyphenyl)-3-phenethoxypyrazin-2(1*H*)-one			1	5	3.86	411	7.32 (m, 5H), 7.23 (m, 1H), 6.96 (m, 2H), 6.87 (m, 2H), 4.55 (t, J = 2.0 Hz, 2H), 3.86 (s, 5H), 3.18 (t, J = 2.0 Hz, 2H), 1.35 (s, 6H).
139	 3-(4-fluorophenethoxy)-1-(4-(2-hydroxy-2-methylpropoxy)phenyl)pyrazin-2(1*H*)-one			7			399	1H NMR (500 MHz, chloroform-d) δ ppm 7.23 - 7.38 (4 H, m), 6.95 - 7.05 (4 H, m), 6.84 (2 H, s), 4.51 (2 H, t, *J*=7.29 Hz), 3.83 (2 H, s), 3.14 (2 H, s), 1.36 (6 H, s)
140	 1-(3-fluoro-4-(2-hydroxy-2-methylpropoxy)phenyl) -3-(4-fluorophenethoxy)pyrazin-2(1*H*)-one			7			417	1H NMR (500 MHz, chloroform-d) δ ppm 7.25 - 7.30 (2 H, m), 7.21 (1 H, dd, *J*=11.00, 2.47 Hz), 6.96 - 7.15 (4 H, m), 6.75 - 6.90 (2 H, m), 4.51 (2 H, t, *J*=7.29 Hz), 3.89 (2 H, s), 3.13 (2 H, t, *J*=7.15 Hz), 1.38 (6 H, s)
141	 1-(3-chloro-4-(2-hydroxy-2-methylpropoxy)phenyl) -3-(4-fluorophenethoxy)pyrazin-2(1*H*)-one			7			433	1H NMR (500 MHz, chloroform-d) δ ppm 7.45 (1 H, d, *J*=2.75 Hz), 7.22 - 7.35 (3 H, m), 6.94 - 7.07 (3 H, m), 6.75 - 6.88 (2 H, m), 4.51 (2 H, t, *J*=7.15 Hz), 3.89 (2 H, s), 3.13 (2 H, t, *J*=7.15 Hz), 1.40 (6 H, s)

Ex. No.	Structure	Aniline/Bromide Component	Alcohol Component	Method	Yield (%)	HPLC	LC-MS	HNMR Data ($CDCl_3$)
142	 3-(4-fluorophenethoxy)-1-(4-(2-hydroxy-2-methyl propoxy)-3-methylphenyl)pyrazin-2(1*H*)-one			7			413	1H NMR (500 MHz, chloroform-d) δ ppm 7.24 - 7.31 (2 H, m), 7.15 - 7.21 (2 H, m), 6.99 (2 H, t, *J*=8.66 Hz), 6.89 (1 H, d, *J*=7.97 Hz), 6.83 (2 H, s), 4.50 (2 H, t, *J*=7.29 Hz), 3.84 (2 H, s), 3.13 (2 H, t, *J*=7.29 Hz), 2.29 (3 H, s), 1.38 (6 H, s)
143	 1-(3-ethyl-4-(2-hydroxy-2-methylpropoxy) phenyl)-3-(4-fluorophenethoxy)pyrazin-2(1*H*)-one			7			427	1H NMR (500 MHz, chloroform-d) δ ppm 7.24 - 7.31 (2 H, m), 7.16 - 7.21 (2 H, m), 6.99 (2 H, t, *J*=8.66 Hz), 6.90 (1 H, d, *J*=9.35 Hz), 6.82 - 6.86 (2 H, m), 4.51 (2 H, t, *J*=7.29 Hz), 3.84 (2 H, s), 3.14 (2 H, t, *J*=7.29 Hz), 2.71 (2 H, q), 1.39 (6 H, s), 1.24 (3 H, t, *J*=7.56 Hz)
144	 3-(4-fluorophenethoxy)-1-(4-(2-hydroxy-2-methyl propoxy)-3-methoxyphenyl)pyrazin-2(1*H*)-one			7			429	1H NMR (500 MHz, chloroform-d) δ ppm 7.23 - 7.32 (2 H, m), 6.94 - 7.03 (4 H, m), 6.82 - 6.90 (3 H, m), 4.51 (2 H, t, *J*=7.29 Hz), 3.85 (5 H, s), 3.14 (2 H, t, *J*=7.29 Hz), 1.36 (6 H, s)
145	 1-(4-(2-cyclopropyl-2-hydroxyethoxy)-3-methoxyphenyl) -3-(4-fluorophenethoxy)pyrazin-2(1*H*)-one			7			441	1H NMR (500 MHz, chloroform-d) δ ppm 7.24 - 7.32 (2 H, m), 6.95 - 7.04 (4 H, m), 6.83 - 6.91 (3 H, m), 4.51 (2 H, t, *J*=7.29 Hz), 4.20 (1 H, dd, *J*=9.76, 2.89 Hz), 4.03 (1 H, dd, *J*=9.90, 8.25 Hz), 3.31 - 3.43 (1 H, m), 3.14 (2 H, t, *J*=7.29 Hz), 0.90 - 1.05 (1 H, m), 0.52 - 0.68 (2 H, m), 0.41 - 0.49 (1 H, m), 0.26 - 0.35 (1 H, m)

Ex. No.	Structure	Aniline/Bromide Component	Alcohol Component	Method	Yield (%)	HPLC	LC-MS	HNMR Data ($CDCl_3$)
146	 1-(4-(2-cyclopropyl-2-hydroxyethoxy)-3-methylphenyl) -3-(4-fluorophenethoxy)pyrazin-2(1*H*)-one			7			425	1H NMR (500 MHz, chloroform-d) δ ppm 7.25 - 7.31 (2 H, m), 7.16 - 7.20 (2 H, m), 6.95 - 7.02 (2 H, m), 6.90 - 6.94 (1 H, m), 6.81 - 6.86 (2 H, m), 4.50 (2 H, t, *J*=7.29 Hz), 4.14 (1 H, dd, *J*=9.35, 3.30 Hz), 4.04 (1 H, dd, *J*=9.35, 7.15 Hz), 3.36 (1 H, dt, *J*=8.45, 3.61 Hz), 3.13 (2 H, t, *J*=7.15 Hz), 2.27 (3 H, s), 0.99 - 1.09 (1 H, m), 0.55 - 0.70 (2 H, m), 0.43 - 0.51 (1 H, m), 0.30 - 0.39 (1 H, m)
147	 3-(4-chlorophenethoxy)-1-(4-(2-hydroxy-2-methylpropoxy)phenyl)pyrazin-2(1*H*)-one			7			415	1H NMR (500 MHz, chloroform-d) δ ppm 7.32 (2 H, d), 7.23 - 7.29 (4 H, m), 7.02 (2 H, d), 6.84 (2 H, s), 4.51 (2 H, t, *J*=7.29 Hz), 3.83 (2 H, s), 3.13 (2 H, t, *J*=7.15 Hz), 1.36 (6 H, s)
148	 3-(4-chlorophenethoxy)-1-(3-fluoro-4-(2-hydroxy-2-methylpropoxy)phenyl)pyrazin-2(1*H*)-one			7			433	1H NMR (500 MHz, chloroform-d) δ ppm 7.18 - 7.31 (5 H, m), 7.03 - 7.15 (2 H, m), 6.75 - 6.89 (2 H, m), 4.51 (2 H, t, *J*=7.15 Hz), 3.89 (2 H, s), 3.13 (2 H, t, *J*=7.15 Hz), 1.38 (6 H, s)
149	 1-(3-chloro-4-(2-hydroxy-2-methylpropoxy)phenyl) -3-(4-chlorophenethoxy)pyrazin-2(1*H*)-one			7			449	1H NMR (500 MHz, chloroform-d) δ ppm 7.45 (1 H, d, *J*=2.75 Hz), 7.22 - 7.32 (5 H, m), 7.00 (1 H, d, *J*=8.80 Hz), 6.77 - 6.90 (2 H, m), 4.51 (2 H, t, *J*=7.29 Hz), 3.89 (2 H, s), 3.13 (2 H, t, *J*=7.15 Hz), 1.40 (6 H, s)
150	 3-(4-chlorophenethoxy)-1-(4-(2-hydroxy-2-methyl propoxy)-3-methylphenyl)pyrazin-2(1*H*)-one			7			429	1H NMR (500 MHz, chloroform-d) δ ppm 7.23 - 7.30 (4 H, m), 7.14 - 7.20 (2 H, m), 6.88 (1 H, d, *J*=8.25 Hz), 6.83 (2 H, s), 4.51 (2 H, t, *J*=7.15 Hz), 3.84 (2 H, s), 3.13 (2 H, t, *J*=7.15 Hz), 2.29 (3 H, s), 1.38 (6 H, s)

Ex. No.	Structure	Aniline/Bromide Component	Alcohol Component	Method	Yield (%)	HPLC	LC-MS	HNMR Data ($CDCl_3$)
151	 3-(4-chlorophenethoxy)-1-(3-ethyl-4-(2-hydroxy-2-methylpropoxy)phenyl)pyrazin-2(1*H*)-one			7			443	1H NMR (500 MHz, chloroform-d) δ ppm 7.23 - 7.29 (4 H, m), 7.16 - 7.21 (2 H, m), 6.90 (1 H, d, *J*=9.35 Hz), 6.84 (2 H, q, *J*=4.49 Hz), 4.51 (2 H, t, *J*=7.29 Hz), 3.84 (2 H, s), 3.13 (2 H, t, *J*=7.29 Hz), 2.71 (2 H, q, *J*=7.51 Hz), 1.39 (6 H, s), 1.23 (3 H, t, *J*=7.56 Hz)
152	 3-(4-chlorophenethoxy)-1-(4-(2-hydroxy-2-methylpropoxy)-3-methoxyphenyl)pyrazin-2(1*H*)-one			7			445	1H NMR (500 MHz, chloroform-d) δ ppm 7.18 - 7.33 (4 H, m), 6.93 - 7.04 (2 H, m), 6.79 - 6.91 (3 H, m), 4.51 (2 H, t, *J*=7.15 Hz), 3.85 (5 H, s), 3.14 (2 H, t, *J*=7.29 Hz), 1.36 (6 H, s)
153	 3-(4-chlorophenethoxy)-1-(4-(2-cyclopropyl-2-hydroxyethoxy)-3-methylphenyl)pyrazin-2(1*H*)-one			7			441	1H NMR (500 MHz, chloroform-d) δ ppm 7.23 - 7.29 (4 H, m), 7.16 - 7.20 (2 H, m), 6.92 (1 H, d), 6.80 - 6.85 (2 H, m), 4.51 (2 H, t, *J*=7.29 Hz), 4.14 (1 H, dd, *J*=9.35, 3.57 Hz), 4.04 (1 H, dd, *J*=9.35, 7.15 Hz), 3.31 - 3.42 (1 H, m), 3.13 (2 H, t, *J*=7.29 Hz), 2.27 (3 H, s), 0.97 - 1.11 (1 H, m), 0.55 - 0.70 (2 H, m), 0.42 - 0.51 (1 H, m), 0.30 - 0.40 (1 H, m)
154	 3-(4-chlorophenethoxy)-1-(4-(2-cyclopropyl-2-hydroxyethoxy)-3-methoxyphenyl)pyrazin-2(1*H*)-one			7			457	1H NMR (500 MHz, chloroform-d) δ ppm 7.23 - 7.29 (4 H, m), 7.01 (1 H, d, *J*=8.80 Hz), 6.97 (1 H, d, *J*=2.47 Hz), 6.82 - 6.91 (3 H, m), 4.51 (2 H, t, *J*=7.15 Hz), 4.20 (1 H, dd, *J*=9.76, 2.89 Hz), 4.03 (1 H, dd, *J*=9.62, 8.25 Hz), 3.86 (3 H, s), 3.30 - 3.41 (1 H, m), 3.14 (2 H, t, *J*=7.15 Hz), 0.89 - 1.04 (1 H, m), 0.52 - 0.68 (2 H, m), 0.42 - 0.50 (1 H, m), 0.25 - 0.37 (1 H, m)

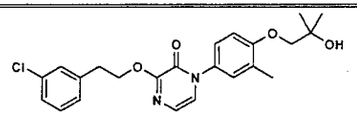
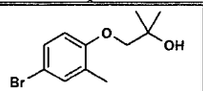
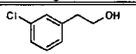
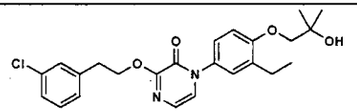
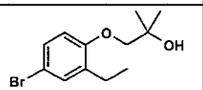
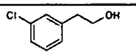
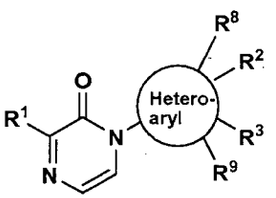
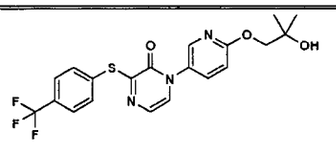
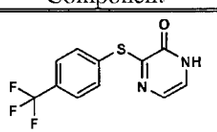
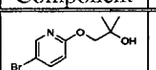
Ex. No.	Structure	Aniline/Bromide Component	Alcohol Component	Method	Yield (%)	HPLC	LC-MS	HNMR Data ($CDCl_3$)
155	 3-(3-chlorophenethoxy)-1-(4-(2-hydroxy-2-methyl propoxy)-3-methylphenyl)pyrazin-2(1*H*)-one			7			429	1H NMR (500 MHz, chloroform-d) δ ppm 7.30 (1 H, s), 7.16 - 7.25 (5 H, m), 6.89 (1 H, d, *J*=8.52 Hz), 6.83 (2 H, s), 4.53 (2 H, t, *J*=7.42 Hz), 3.84 (2 H, s), 3.14 (2 H, t, *J*=7.29 Hz), 2.29 (3 H, s), 1.38 (6 H, s)
156	 3-(3-chlorophenethoxy)-1-(3-ethyl-4-(2-hydroxy-2 -methylpropoxy)phenyl)pyrazin-2(1*H*)-one			7			443	1H NMR (500 MHz, chloroform-d) δ ppm 7.30 (1 H, s), 7.16 - 7.25 (5 H, m), 6.90 (1 H, d, *J*=9.35 Hz), 6.82 - 6.87 (2 H, m), 4.53 (2 H, t, *J*=7.42 Hz), 3.84 (2 H, s), 3.15 (2 H, t, *J*=7.29 Hz), 2.65 - 2.76 (2 H, m), 1.38 (6 H, s), 1.24 (3 H, t, *J*=7.56 Hz)

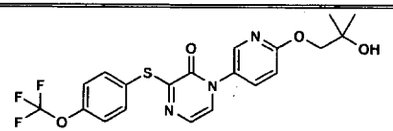
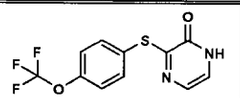
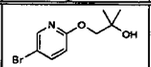
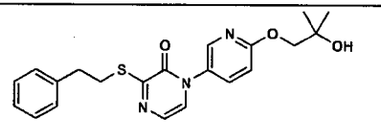
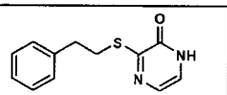
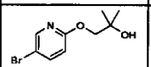
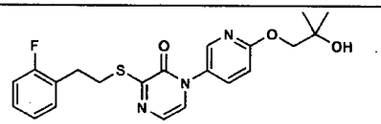
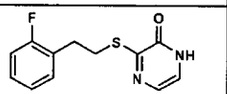
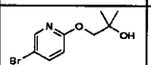
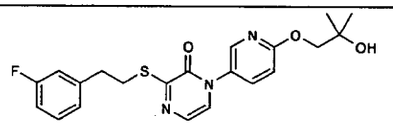
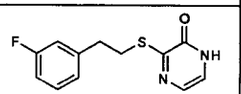
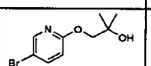
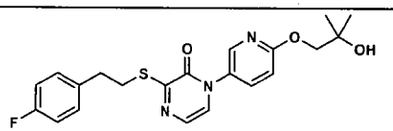
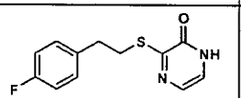
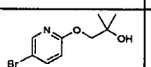
TABLE 3

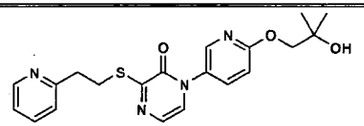
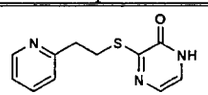
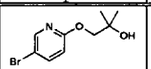
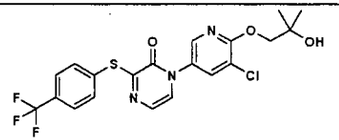
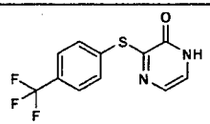
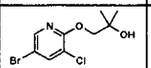
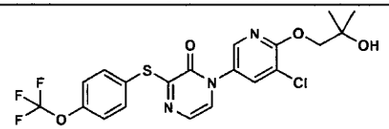
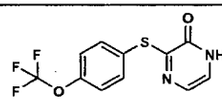
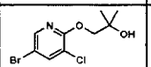
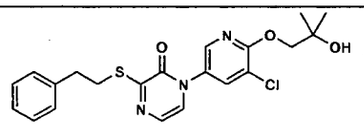
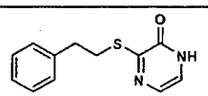
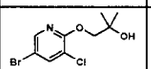
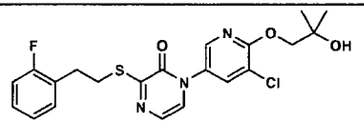
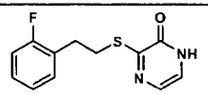
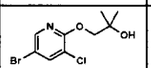
3-Substituted-1-heteroarylpyrazin-2(1H)-ones

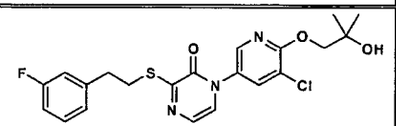
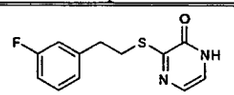
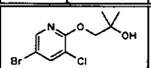
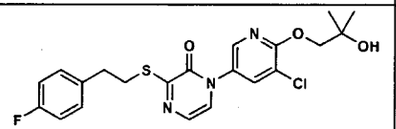
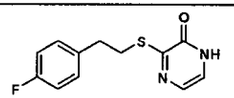
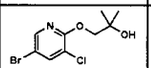
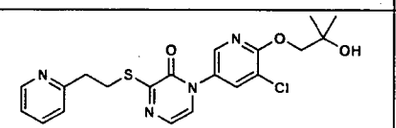
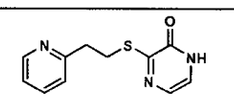
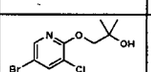
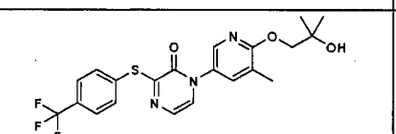
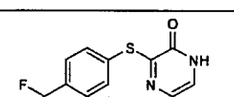
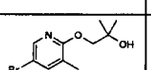


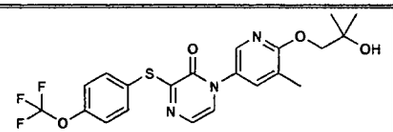
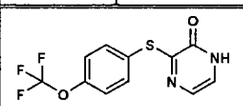
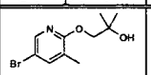
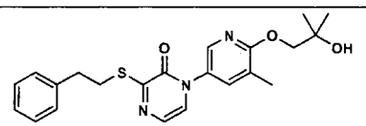
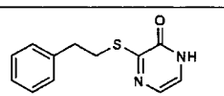
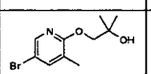
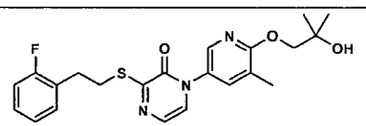
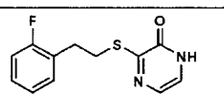
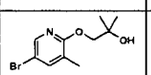
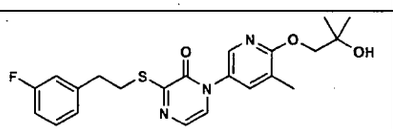
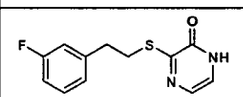
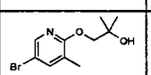
Ex. No.	Structure	Aniline/Bromide Component	Alcohol Component	Method	Yield (%)	HPLC	LC-MS	HNMR Data ($CDCl_3$)
157	 1-(6-(2-hydroxy-2-methylpropoxy)pyridin-3-yl) -3-(4-(trifluoromethyl)phenylthio)pyrazin-2(1*H*)-one			8			438	1H NMR (500 MHz, methanol-d_3) δ ppm 8.41 (1 H, d, *J*=2.47 Hz), 8.09 (1 H, dd, *J*=9.07, 2.75 Hz), 7.72 - 7.79 (4 H, m), 7.35 (1 H, d, *J*=4.40 Hz), 7.24 (1 H, d, *J*=9.07 Hz), 7.19 (1 H, d, *J*=4.67 Hz), 4.25 (2 H, s), 1.33 (6 H, s).

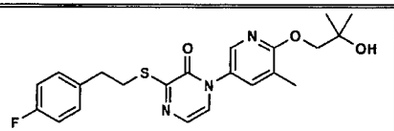
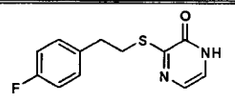
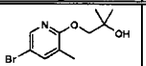
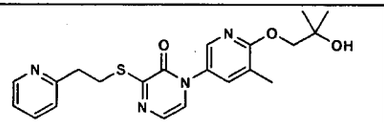
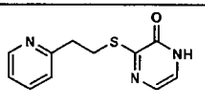
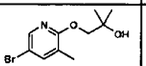
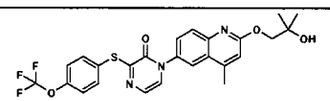
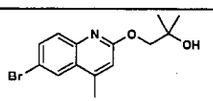
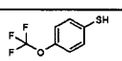
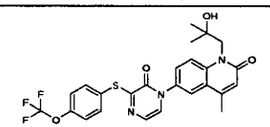
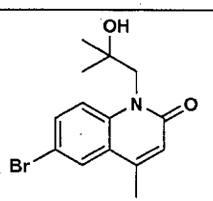
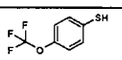
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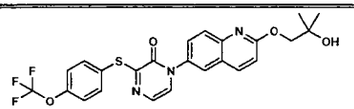
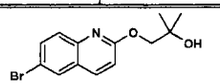
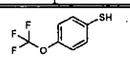
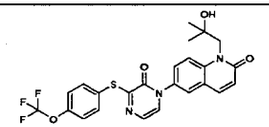
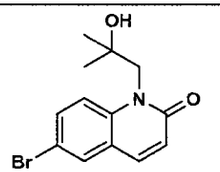
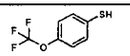
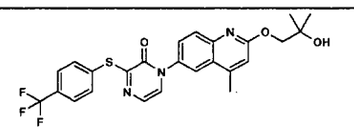
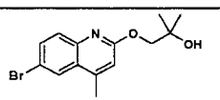
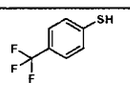
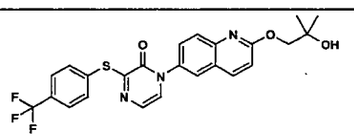
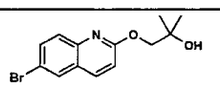
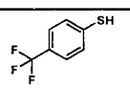
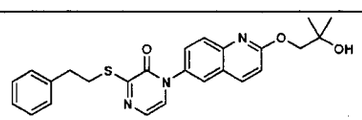
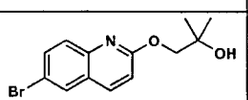
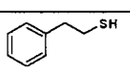
Ex. No.	Structure	Aniline/Bromide Component	Alcohol Component	Method	Yield (%)	HPLC	LC-MS	HNMR Data ($CDCl_3$)
158	 1-(6-(2-hydroxy-2-methylpropoxy)pyridin-3-yl)-3-(4-(trifluoromethoxy)phenylthio)pyrazin-2(1*H*)-one			8			454	1H NMR (500 MHz, methanol-d_3) δ ppm 8.25 (1 H, d, *J*=2.47 Hz), 7.84 (1 H, dd, *J*=8.80, 2.75 Hz), 7.63 - 7.69 (2 H, m), 7.37 (2 H, d, *J*=7.97 Hz), 7.31 (1 H, d, *J*=4.40 Hz), 7.17 (1 H, d, *J*=4.67 Hz), 7.00 (1 H, d, *J*=8.80 Hz), 4.19 (2 H, s), 1.31 (6 H, s)
159	 1-(6-(2-hydroxy-2-methylpropoxy)pyridin-3-yl)-3-(phenethylthio)pyrazin-2(1*H*)-one			8			398	1H NMR (400 MHz, methanol-d_3) δ ppm 8.23 (1 H, d, *J*=2.64 Hz), 7.80 (1 H, dd, *J*=8.90, 2.75 Hz), 7.39 (1 H, d, *J*=4.39 Hz), 7.15 - 7.33 (6 H, m), 6.98 (1 H, d, *J*=8.79 Hz), 4.18 (2 H, s), 3.30 - 3.38 (2 H, m), 2.91 - 3.08 (2 H, m), 1.31 (6 H, s)
160	 3-(2-fluorophenethylthio)-1-(6-(2-hydroxy-2-methylpropoxy)pyridin-3-yl)pyrazin-2(1*H*)-one			8			416	1H NMR (400 MHz, methanol-d_3) δ ppm 8.22 (1 H, d, *J*=2.64 Hz), 7.80 (1 H, dd, *J*=8.90, 2.75 Hz), 7.37 (1 H, d, *J*=4.61 Hz), 7.28 - 7.35 (1 H, m), 7.17 - 7.28 (2 H, m), 6.88 - 7.16 (3 H, m), 4.18 (1 H, s), 3.25 - 3.43 (2 H, m), 3.04 (2 H, t, *J*=7.47 Hz), 1.30 (6 H, s)
161	 3-(3-fluorophenethylthio)-1-(6-(2-hydroxy-2-methylpropoxy)pyridin-3-yl)pyrazin-2(1*H*)-one			8			416	1H NMR (400 MHz, methanol-d_3) δ ppm 8.23 (1 H, d, *J*=2.64 Hz), 7.80 (1 H, dd, *J*=8.90, 2.75 Hz), 7.40 (1 H, d, *J*=4.61 Hz), 7.23 - 7.34 (2 H, m), 6.89 - 7.14 (4 H, m), 4.18 (1 H, s), 3.29 - 3.40 (2 H, m), 2.95 - 3.06 (2 H, m), 1.30 (6 H, s)
162	 3-(4-fluorophenethylthio)-1-(6-(2-hydroxy-2-methylpropoxy)pyridin-3-yl)pyrazin-2(1*H*)-one			8			416	1H NMR (400 MHz, methanol-d_3) δ ppm 8.15 (1 H, d, *J*=2.42 Hz), 7.73 (1 H, dd, *J*=8.90, 2.75 Hz), 7.31 (1 H, d, *J*=4.39 Hz), 7.15 - 7.26 (3 H, m), 6.85 - 7.00 (3 H, m), 4.10 (2 H, s), 3.22 - 3.29 (2 H, m), 2.89 (2 H, t, *J*=7.58 Hz), 1.23 (6 H, s)

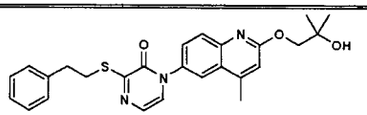
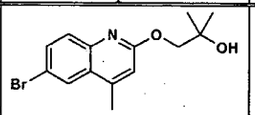
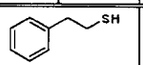
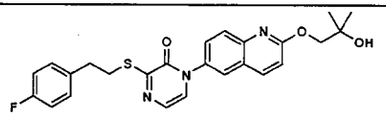
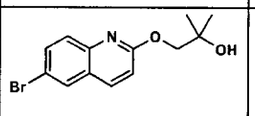
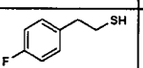
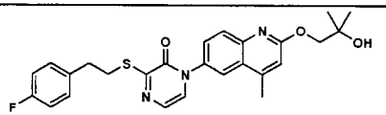
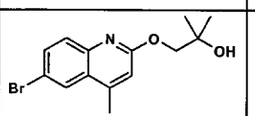
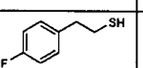
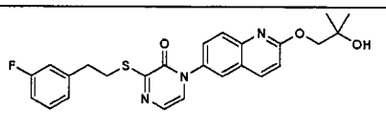
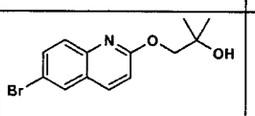
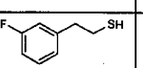
Ex. No.	Structure	Aniline/Bromide Component	Alcohol Component	Method	Yield (%)	HPLC	LC-MS	HNMR Data ($CDCl_3$)
163	 1-(6-(2-hydroxy-2-methylpropoxy)pyridin-3-yl) -3-(2-(pyridin-2-yl)ethylthio)pyrazin-2(1*H*)-one			8			399	1H NMR (400 MHz, methanol-d_3) δ ppm 8.40 - 8.54 (1 H, m), 8.22 (1 H, d, *J*=2.20 Hz), 7.72 - 7.86 (2 H, m), 7.35 - 7.44 (2 H, m), 7.23 - 7.32 (2 H, m), 6.98 (1 H, d, *J*=9.01 Hz), 4.18 (2 H, s), 3.47 (2 H, t, *J*=7.36 Hz), 3.19 (2 H, t, *J*=7.36 Hz), 1.30 (6 H, s)
164	 1-(5-chloro-6-(2-hydroxy-2-methylpropoxy)pyridin -3-yl)-3-(4-(trifluoromethyl)phenylthio)pyrazin-2(1*H*)-one			8			472	1H NMR (500 MHz, chloroform-d) δ ppm 8.11 (1 H, d, *J*=2.47 Hz), 7.89 (1 H, d, *J*=2.47 Hz), 7.71 (4 H, s), 7.16 (1 H, d, *J*=4.40 Hz), 6.95 (1 H, d, *J*=4.40 Hz), 4.30 (2 H, s), 1.38 (6 H, s)
165	 1-(5-chloro-6-(2-hydroxy-2-methylpropoxy)pyridin-3-yl) -3-(4-(trifluoromethoxy)phenylthio)pyrazin-2(1*H*)-one			8			488	1H NMR (500 MHz, chloroform-d) δ ppm 8.10 (1 H, d, *J*=2.47 Hz), 7.88 (1 H, d, *J*=2.47 Hz), 7.61 (2 H, d, *J*=8.80 Hz), 7.30 (2 H, d, *J*=7.97 Hz), 7.16 (1 H, d, *J*=4.67 Hz), 6.94 (1 H, d, *J*=4.40 Hz), 4.30 (2 H, s), 1.38 (6 H, s)
166	 1-(5-chloro-6-(2-hydroxy-2-methylpropoxy) pyridin-3-yl)-3-(phenethylthio)pyrazin-2(1*H*)-one			8			432	1H NMR (400 MHz, chloroform-d) δ ppm 8.09 (1 H, d, *J*=2.42 Hz), 7.86 (1 H, d, *J*=2.64 Hz), 7.21 - 7.37 (6 H, m), 6.91 (1 H, d, *J*=4.39 Hz), 4.29 (2 H, s), 3.28 - 3.43 (2 H, m), 2.94 - 3.09 (2 H, m), 1.37 (6 H, s)
167	 1-(5-chloro-6-(2-hydroxy-2-methylpropoxy)pyridin-3-yl)-3-(2-fluorophenethylthio)pyrazin-2(1*H*)-one			8			450	1H NMR (400 MHz, chloroform-d) δ ppm 8.08 (1 H, d, *J*=2.42 Hz), 7.86 (1 H, d, *J*=2.42 Hz), 7.16 - 7.33 (3 H, m), 6.98 - 7.13 (2 H, m), 6.90 (1 H, d, *J*=4.61 Hz), 4.29 (2 H, s), 3.29 - 3.41 (2 H, m), 3.07 (2 H, t, *J*=7.69 Hz), 1.37 (6 H, s)

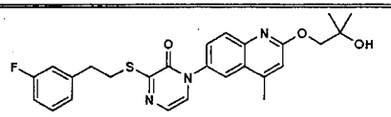
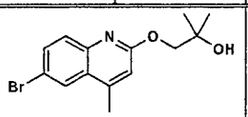
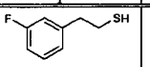
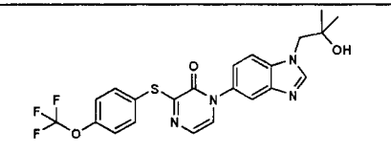
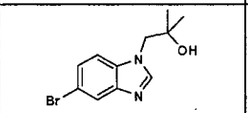
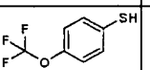
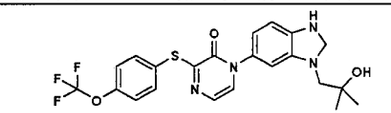
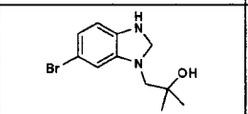
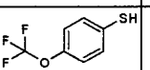
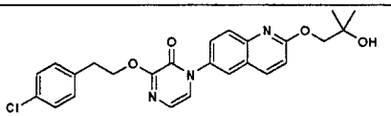
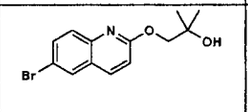
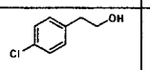
Ex. No.	Structure	Aniline/Bromide Component	Alcohol Component	Method	Yield (%)	HPLC	LC-MS	HNMR Data ($CDCl_3$)
168	 1-(5-chloro-6-(2-hydroxy-2-methylpropoxy) pyridin-3-yl)-3-(3-fluorophenethylthio)pyrazin-2(1*H*)-on			8			450	1H NMR (500 MHz, chloroform-d) δ ppm 8.09 (1 H, d, *J*=2.20 Hz), 7.86 (1 H, d, *J*=2.47 Hz), 7.26 - 7.34 (2 H, m), 7.06 (1 H, d, *J*=7.70 Hz), 6.98 - 7.03 (1 H, m), 6.89 - 6.97 (2 H, m), 4.29 (2 H, s), 3.27 - 3.40 (2 H, m), 2.94 - 3.10 (2 H, m), 1.37 (6 H, s)
168	 1-(5-chloro-6-(2-hydroxy-2-methylpropoxy)pyridin-3-yl) -3-(4-fluorophenethylthio)pyrazin-2(1*H*)-one			8			450	1H NMR (500 MHz, chloroform-d) δ ppm 8.08 (1 H, d, *J*=2.47 Hz), 7.86 (1 H, d, *J*=2.47 Hz), 7.30 (1 H, d, *J*=4.40 Hz), 7.21 - 7.25 (2 H, m), 7.00 (2 H, t, *J*=8.66 Hz), 6.91 (1 H, d, *J*=4.67 Hz), 4.29 (2 H, s), 3.23 - 3.39 (2 H, m), 2.91 - 3.05 (2 H, m), 1.37 (6 H, s)
169	 1-(5-chloro-6-(2-hydroxy-2-methylpropoxy)pyridin -3-yl)-3-(2-(pyridin-2-yl)ethylthio)pyrazin-2(1*H*)-one			8			433	1H NMR (500 MHz, chloroform-d) δ ppm 8.57 (1 H, d, *J*=3.85 Hz), 8.08 (1 H, d, *J*=2.47 Hz), 7.85 (1 H, d, *J*=2.47 Hz), 7.63 (1 H, td, *J*=7.63, 1.79 Hz), 7.31 (1 H, d, *J*=4.67 Hz), 7.24 (1 H, d, *J*=7.70 Hz), 7.11 - 7.18 (1 H, m), 6.90 (1 H, d, *J*=4.40 Hz), 4.29 (2 H, s), 3.45 - 3.59 (2 H, m), 3.22 (2 H, t, *J*=7.42 Hz), 1.37 (6 H, s)
170	 1-(6-(2-hydroxy-2-methylpropoxy)-5-methylpyridin-3-yl)-3-(4-(trifluoromethyl)phenylthio)pyrazin-2(1*H*)-one			8			452	1H NMR (500 MHz, chloroform-d) δ ppm 8.00 (1 H, d, *J*=2.75 Hz), 7.67 - 7.76 (4 H, m), 7.60 (1 H, d, *J*=1.92 Hz), 7.14 (1 H, d, *J*=4.40 Hz), 6.96 (1 H, d, *J*=4.40 Hz), 4.28 (2 H, s), 2.30 (3 H, s), 1.36 (6 H, s)

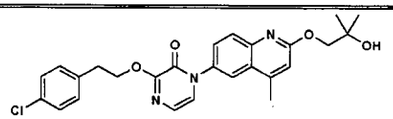
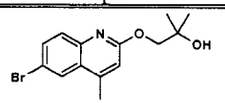
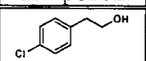
Ex. No.	Structure	Aniline/Bromide Component	Alcohol Component	Method	Yield (%)	HPLC	LC-MS	HNMR Data ($CDCl_3$)
171	 1-(6-(2-hydroxy-2-methylpropoxy)-5-methylpyridin-3-yl -3-(4-(trifluoromethoxy)phenylthio)pyrazin-2(1*H*)-one			8			468	1H NMR (500 MHz, chloroform-d) δ ppm 8.00 (1 H, d, *J*=2.75 Hz), 7.57 - 7.65 (3 H, m), 7.29 (2 H, d, *J*=7.97 Hz), 7.14 (1 H, d, *J*=4.40 Hz), 6.94 (1 H, d, *J*=4.40 Hz), 4.28 (2 H, s), 2.29 (3 H, s), 1.35 (6 H, s)
172	 1-(6-(2-hydroxy-2-methylpropoxy)-5-methylpyridin -3-yl)-3-(phenethylthio)pyrazin-2(1*H*)-one			8			412	1H NMR (500 MHz, chloroform-d) δ ppm 7.98 (1 H, d, *J*=2.20 Hz), 7.58 (1 H, d, *J*=1.65 Hz), 7.27 - 7.36 (5 H, m), 7.21 - 7.25 (1 H, m), 6.91 (1 H, d, *J*=4.40 Hz), 4.27 (2 H, s), 3.27 - 3.40 (2 H, m), 2.95 - 3.11 (2 H, m), 2.28 (3 H, s), 1.35 (6 H, s)
173	 3-(2-fluorophenethylthio)-1-(6-(2-hydroxy-2-methyl propoxy)-5-methylpyridin-3-yl)pyrazin-2(1*H*)-one			8			430	1H NMR (500 MHz, chloroform-d) δ ppm 7.98 (1 H, d, *J*=2.75 Hz), 7.58 (1 H, d, *J*=1.92 Hz), 7.27 - 7.33 (2 H, m), 7.18 - 7.24 (1 H, m), 7.00 - 7.12 (2 H, m), 6.91 (1 H, d, *J*=4.40 Hz), 4.27 (2 H, s), 3.29 - 3.41 (2 H, m), 3.07 (2 H, t, *J*=7.70 Hz), 2.28 (3 H, s), 1.35 (6 H, s)
174	 3-(3-fluorophenethylthio)-1-(6-(2-hydroxy-2-methyl propoxy)-5-methylpyridin-3-yl)pyrazin-2(1*H*)-one			8			430	1H NMR (500 MHz, chloroform-d) δ ppm 7.98 (1 H, d, *J*=2.47 Hz), 7.58 (1 H, d, *J*=1.92 Hz), 7.27 - 7.32 (1 H, m), 7.26 (1 H, d, *J*=7.70 Hz), 7.06 (1 H, d, *J*=7.70 Hz), 6.98 - 7.04 (1 H, m), 6.89 - 7.95 (2 H, m), 4.27 (2 H, s), 3.25 - 3.38 (2 H, m), 2.94 - 3.08 (2 H, m), 2.28 (3 H, s), 1.35 (6 H, s)

Ex. No.	Structure	Aniline/Bromide Component	Alcohol Component	Method	Yield (%)	HPLC	LC-MS	HNMR Data ($CDCl_3$)
175	 3-(4-fluorophenethylthio)-1-(6-(2-hydroxy-2-methyl propoxy)-5-methylpyridin-3-yl)pyrazin-2(1*H*)-one			8			430	1H NMR (500 MHz, chloroform-d) δ ppm 7.98 (1 H, d, *J*=2.75 Hz), 7.58 (1 H, d, *J*=1.92 Hz), 7.28 (1 H, d, *J*=4.67 Hz), 7.21 - 7.25 (2 H, m), 7.00 (2 H, t, *J*=8.66 Hz), 6.91 (1 H, d, *J*=4.40 Hz), 4.27 (2 H, s), 3.22 - 3.38 (2 H, m), 2.92 - 3.07 (2 H, m), 2.28 (3 H, s), 1.35 (6 H, s)
176	 1-(6-(2-hydroxy-2-methylpropoxy)-5-methylpyridin -3-yl)-3-(2-(pyridin-2-yl)ethylthio)pyrazin-2(1*H*)-one			8			413	1H NMR (500 MHz, chloroform-d) δ ppm 8.57 (1 H, d, *J*=3.85 Hz), 7.97 (1 H, d, *J*=2.20 Hz), 7.62 (1 H, td, *J*=7.63, 1.79 Hz), 7.57 (1 H, d, *J*=1.92 Hz), 7.29 (1 H, d, *J*=4.40 Hz), 7.24 (1 H, d, *J*=7.97 Hz), 7.15 (1 H, dd, *J*=6.60, 4.95 Hz), 6.90 (1 H, d, *J*=4.67 Hz), 4.27 (2 H, s), 3.51 (2 H, t, *J*=7.42 Hz), 3.22 (2 H, t, *J*=7.42 Hz), 2.27 (3 H, s), 1.35 (6 H, s)
177	 1-(2-(2-hydroxy-2-methylpropoxy)-4-methylquinolin-6-yl)-3-(4-(trifluoromethoxy)phenylthio)pyrazin-2(1*H*)-one			6			518	1H NMR (500 MHz, methanol-d_3) d ppm 8.08 (1 H, d, *J*=2.47 Hz), 7.93 (1 H, d, *J*=8.80 Hz), 7.65 - 7.74 (3 H, m), 7.43 (1 H, d, *J*=4.67 Hz), 7.38 (2 H, d, *J*=7.97 Hz), 7.22 (1 H, d, *J*=4.40 Hz), 6.98 (1 H, d, *J*=1.10 Hz), 4.31 (2 H, s), 2.66 (3 H, d, *J*=1.10 Hz), 1.34 (6 H, s)
178	 1-(2-hydroxy-2-methylpropyl)-4-methyl-6-(2-oxo-3-(4-(trifluoromethoxy)phenylthio)pyrazin-1(2*H*)-yl)quinolin-2(1*H*)-one			6			518	1H NMR (500 MHz, methanol-d_3) δ ppm 8.09 (1 H, d, *J*=9.35 Hz), 7.96 (1 H, d, *J*=2.47 Hz), 7.64 - 7.75 (3 H, m), 7.29 - 7.49 (3 H, m), 7.21 (1 H, d, *J*=4.40 Hz), 6.69 (1 H, s), 4.38 - 4.58 (2 H, m), 2.54 (3 H, s), 1.28 (6 H, s)

Ex. No.	Structure	Aniline/Bromide Component	Alcohol Component	Method	Yield (%)	HPLC	LC-MS	HNMR Data ($CDCl_3$)
179	 1-(2-(2-hydroxy-2-methylpropoxy)quinolin-6-yl)-3-(4-(trifluoromethoxy)phenylthio)pyrazin-2(1*H*)-one			6			504	1H NMR (500 MHz, methanol-d_3) δ ppm 8.21 (1 H, d, *J*=8.80 Hz), 7.90 - 7.98 (2 H, m), 7.73 (1 H, dd, *J*=8.80, 2.47 Hz), 7.67 (2 H, d), 7.35 - 7.42 (3 H, m), 7.21 (1 H, d, *J*=4.40 Hz), 7.11 (1 H, d, *J*=9.07 Hz), 4.34 (2 H, s), 1.35 (6 H, s).
180	 1-(2-hydroxy-2-methylpropyl)-6-(2-oxo-3-(4-(trifluoromethoxy)phenylthio)pyrazin-1(2*H*)-yl)quinolin-2(1*H*)-one			6			504	1H NMR (500 MHz, methanol-d_3) δ ppm 8.08 (1 H, d, *J*=9.35 Hz), 7.97 (1 H, d, *J*=9.35 Hz), 7.84 (1 H, d, *J*=2.47 Hz), 7.63 - 7.73 (3 H, m), 7.31 - 7.42 (3 H, m), 7.20 (1 H, d, *J*=4.40 Hz), 6.78 (1 H, d, *J*=9.35 Hz), 4.50 (2 H, br. s.), 1.29 (6 H, s).
181	 1-(2-(2-hydroxy-2-methylpropoxy)-4-methylquinolin-6-yl)-3-(4-(trifluoromethyl)phenylthio)pyrazin-2(1*H*)-one			6			502	1H NMR (400 MHz, chloroform-d) δ ppm 7.89 - 8.00 (2 H, m), 7.68 - 7.79 (4 H, m), 7.64 (1 H, dd, *J*=8.79, 2.42 Hz), 7.19 (1 H, d, *J*=4.39 Hz), 7.11 (1 H, d, *J*=4.39 Hz), 6.92 (1 H, d, *J*=0.88 Hz), 4.41 (2 H, s), 2.64 (3 H, s), 1.36 (6 H, s)
182	 1-(2-(2-hydroxy-2-methylpropoxy)quinolin-6-yl)-3-(4-(trifluoromethyl)phenylthio)pyrazin-2(1*H*)-one			6			488	1H NMR (400 MHz, chloroform-d) δ ppm 8.06 (1 H, d, *J*=8.79 Hz), 7.94 (1 H, d, *J*=9.01 Hz), 7.85 (1 H, d, *J*=2.42 Hz), 7.64 - 7.78 (5 H, m), 7.18 (1 H, d, *J*=4.61 Hz), 7.11 (1 H, d, *J*=4.39 Hz), 7.06 (1 H, d, *J*=9.01 Hz), 4.43 (2 H, s), 1.38 (6 H, s)
183	 1-(2-(2-hydroxy-2-methylpropoxy)quinolin-6-yl)-3-(phenethylthio)pyrazin-2(1*H*)-one			6			448	1H NMR (400 MHz, chloroform-d) δ ppm 8.04 (1 H, d, *J*=8.78 Hz), 7.92 (1 H, d, *J*=9.04 Hz), 7.83 (1 H, d, *J*=2.51 Hz), 7.65 (1 H, dd, *J*=8.91, 2.38 Hz), 7.28 - 7.36 (5 H, m), 7.20 - 7.28 (1 H, m), 7.02 - 7.09 (2 H, m), 4.42 (2 H, s), 3.28 - 3.44 (2 H, m), 2.93 - 3.12 (2 H, m), 1.37 (6 H, s)

Ex. No.	Structure	Aniline/Bromide Component	Alcohol Component	Method	Yield (%)	HPLC	LC-MS	HNMR Data ($CDCl_3$)
184	 1-(2-(2-hydroxy-2-methylpropoxy)-4-methylquinolin-6-yl)-3-(phenethylthio)pyrazin-2(1*H*)-one			6			462	1H NMR (400 MHz, chloroform-d) δ ppm 7.88 - 7.98 (2 H, m), 7.62 (1 H, dd, *J*=8.91, 2.38 Hz), 7.20 - 7.37 (6 H, m), 7.07 (1 H, d, *J*=4.27 Hz), 6.90 (1 H, s), 4.40 (2 H, s), 3.30 - 3.39 (2 H, m), 2.98 - 3.12 (2 H, m), 2.63 (3 H, s), 1.35 (6 H, s)
185	 3-(4-fluorophenethylthio)-1-(2-(2-hydroxy-2-methylpropoxy)quinolin-6-yl)pyrazin-2(1*H*)-one			6			466	1H NMR (500 MHz, chloroform-d) δ ppm 8.04 (1 H, d, *J*=8.80 Hz), 7.92 (1 H, d, *J*=9.07 Hz), 7.83 (1 H, d, *J*=2.20 Hz), 7.65 (1 H, dd, *J*=8.94, 2.34 Hz), 7.32 (1 H, d, *J*=4.40 Hz), 7.23 - 7.30 (2 H, m), 6.92 - 7.12 (4 H, m), 4.42 (2 H, s), 3.43 - 3.57 (2 H, m), 3.25 - 3.33 (2 H, m), 2.91 - 3.08 (2 H, m), 1.37 (6 H, s)
186	 3-(4-fluorophenethylthio)-1-(2-(2-hydroxy-2-methyl propoxy)-4-methylquinolin-6-yl)pyrazin-2(1*H*)-one			6			480	1H NMR (500 MHz, chloroform-d) δ ppm 7.88 - 7.97 (2 H, m), 7.62 (1 H, dd, *J*=8.80, 2.47 Hz), 7.33 (1 H, d, *J*=4.40 Hz), 7.23 - 7.29 (2 H, m), 7.07 (1 H, d, *J*=4.40 Hz), 7.01 (2 H, t, *J*=8.66 Hz), 6.90 (1 H, s), 4.40 (2 H, s), 3.27 - 3.38 (2 H, m), 2.95 - 3.08 (2 H, m), 2.63 (3 H, s), 1.35 (6 H, s)
187	 3-(3-fluorophenethylthio)-1-(2-(2-hydroxy-2-methylpropoxy)quinolin-6-yl)pyrazin-2(1*H*)-one			6			466	1H NMR (500 MHz, chloroform-d) δ ppm 8.04 (1 H, d, *J*=8.80 Hz), 7.92 (1 H, d, *J*=9.07 Hz), 7.83 (1 H, d, *J*=2.47 Hz), 7.65 (1 H, dd, *J*=8.80, 2.47 Hz), 7.34 (1 H, d, *J*=4.40 Hz), 7.27 - 7.31 (1 H, m), 6.99 - 7.10 (4 H, m), 6.89 - 6.97 (1 H, m), 4.42 (2 H, s), 3.30 - 3.38 (2 H, m), 2.98 - 3.08 (2 H, m), 1.37 (6 H, s)

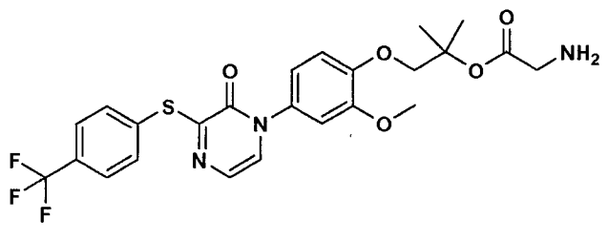
Ex. No.	Structure	Aniline/Bromide Component	Alcohol Component	Method	Yield (%)	HPLC	LC-MS	HNMR Data ($CDCl_3$)
188	 3-(3-fluorophenethylthio)-1-(2-(2-hydroxy-2-methyl propoxy)-4-methylquinolin-6-yl)pyrazin-2(1*H*)-one			6			480	1H NMR (500 MHz, chloroform-d) δ ppm 7.95 (1 H, d, *J*=2.20 Hz), 7.91 (1 H, d, *J*=8.80 Hz), 7.62 (1 H, dd, *J*=8.94, 2.34 Hz), 7.34 (1 H, d, *J*=4.67 Hz), 7.28 (1 H, dd, *J*=7.97, 1.92 Hz), 7.00 - 7.10 (3 H, m), 6.89 - 6.97 (2 H, m), 4.40 (2 H, s), 3.28 - 3.41 (2 H, m), 2.97 - 3.10 (2 H, m), 2.63 (3 H, s), 1.35 (6 H, s)
189	 1-(1-(2-hydroxy-2-methylpropyl)-1*H*-benzo[*d*]imidazol -5-yl)-3-(4-(trifluoromethoxy)phenylthio)pyrazin-2(1*H*)-one			6			477	1H NMR (500 MHz, methanol-d_3) δ ppm 8.28 (1 H, s), 7.70 - 7.80 (2 H, m), 7.55 - 7.61 (2 H, m), 7.25 - 7.32 (4 H, m), 7.11 (1 H, d, *J*=4.40 Hz), 4.19 (2 H, s), 1.14 (6 H, s)
190	 1-(3-(2-hydroxy-2-methylpropyl)-2,3-dihydro-1*H*-benzo[*d*]imi -5-yl)-3-(4-(trifluoromethoxy)phenylthio)pyrazin-2(1*H*)-on			6			477	1H NMR (500 MHz, methanol-d_3) δ ppm 8.30 (1 H, s), 7.76 - 7.85 (2 H, m), 7.65 - 7.71 (2 H, m), 7.34 - 7.42 (3 H, m), 7.20 (1 H, d, *J*=4.40 Hz), 4.29 (2 H, s), 1.24 (6 H, s)
191	 3-(4-chlorophenethoxy)-1-(2-(2-hydroxy-2-methyl propoxy)quinolin-6-yl)pyrazin-2(1*H*)-one			7			466	1H NMR (500 MHz, chloroform-d) δ ppm 8.04 (1 H, d, *J*=8.80 Hz), 7.92 (1 H, d, *J*=8.80 Hz), 7.80 (1 H, d, *J*=2.47 Hz), 7.64 (1 H, dd, *J*=8.94, 2.34 Hz), 7.23 - 7.30 (4 H, m), 7.04 (1 H, d, *J*=8.80 Hz), 6.95 (1 H, d, *J*=4.67 Hz), 6.90 (1 H, d, *J*=4.67 Hz), 4.54 (2 H, t, *J*=7.15 Hz), 4.42 (2 H, s), 3.15 (2 H, t, *J*=7.29 Hz), 1.37 (6 H, s)

Ex. No.	Structure	Aniline/Bromide Component	Alcohol Component	Method	Yield (%)	HPLC	LC-MS	HNMR Data ($CDCl_3$)
192	 3-(4-chlorophenethoxy)-1-(2-(2-hydroxy-2-methyl propoxy)-4-methylquinolin-6-yl)pyrazin-2(1*H*)-one			7			480	1H NMR (500 MHz, chloroform-d) δ ppm 7.88 - 7.95 (2 H, m), 7.61 (1 H, dd, *J*=8.80, 2.47 Hz), 7.27 - 7.30 (4 H, m), 6.96 (1 H, d, *J*=4.67 Hz), 6.90 (2 H, d, *J*=4.67 Hz), 4.54 (2 H, t, *J*=7.15 Hz), 4.40 (2 H, s), 3.15 (2 H, t, *J*=7.15 Hz), 2.62 (3 H, s), 1.35 (6 H, s)

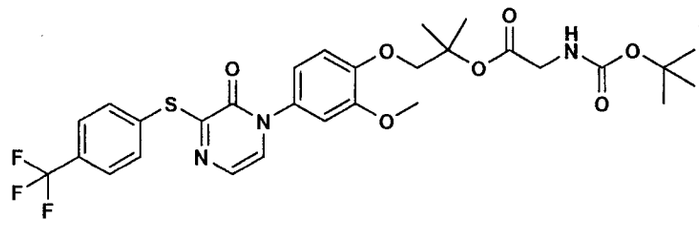
[00128] Prodrugs were prepared of selected secondary and tertiary alcohols to improve solubility and exposure. Standard conditions, employed to generate amino acid esters of all but the glycine ester of the tertiary alcohols, are exemplified in Example 193. Preparation of the glycine ester of the tertiary alcohols is exemplified in Example 202. Preparation of a phosphate ester prodrug is exemplified by Example 204.

EXAMPLE 193

1-(2-Methoxy-4-(2-oxo-3-(4-(trifluoromethyl)phenylthio)pyrazin-1(2H)-yl)phenoxy)-2-methylpropan-2-yl 2-aminoacetate



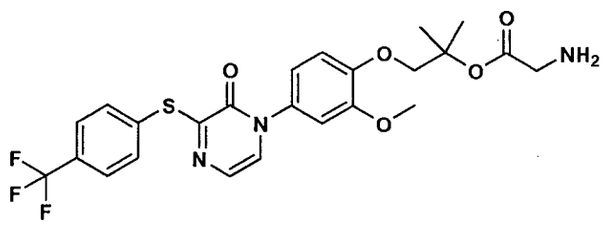
Part A. 1-(2-Methoxy-4-(2-oxo-3-(4-(trifluoromethyl)phenylthio)pyrazin-1(2H)-yl)phenoxy)-2-methylpropan-2-yl 2-(*tert*-butoxycarbonylamino)acetate



[00129] To a stirred suspension of the alcohol prepared in Example 36 (3.0 g, 6.4 mmol), 4-pyrrolidinopyridine (0.95 g, 6.4 mmol) and BOC-glycine (3.4 g, 19 mmol) in CH_2Cl_2 (60 mL) at 42 °C was added *N,N'*-diisopropylcarbodiimide 3.0 mL, 19 mmol) over 3.5 h. After stirring at reflux for 2.5 h, HPLC analysis showed 25% alcohol still remained. More BOC-glycine (3.4 g, 19 mmol) was added followed by additional *N,N'*-diisopropylcarbodiimide (3.0 mL, 19 mmol) which was slowly added over 3.5 h; whereupon, HPLC analysis showed < 5% alcohol remained. The reaction was allowed to cool to RT prior to addition of hydrazine monohydrate (18 mL, 370 mmol). After stirring for 5 minutes, the reaction mixture was cooled to 0 °C and

filtered. The filtrates were sequentially washed with cold 1*M* HCl (3x20 mL) and cold 2% $NaHCO_3$ (3x20 mL) prior to drying over $MgSO_4$ and concentrating under vacuum to afford 5.6 g of crude product. Chromatography (silica gel 230-400 mesh, gradient elution: 0 to 60% EtOAc/hexane over 47 min) of the residue afforded the desired ester (3.9 g, 88% yield). HPLC 4.42 min. LC MS (M+1 = 624), H-NMR ($CDCl_3$) 7.72 (m, 4H), 7.12 (d, J = 4.4 Hz, 1H), 7.02 (d, J = 4.4 Hz, 1H), 7.00 (d, J = 8.3 Hz, 1H), 6.99 (d, J = 2.5 Hz, 1H), 6.90 (dd, J = 2.5 and 8.3 Hz, 1H), 4.21 (s, 2H), 3.87 (s, 3H), 3.78 (m, 2H), 1.61 (s, 6H), 1.45 (s, 9H).

Part B. 1-(2-Methoxy-4-(2-oxo-3-(4-(trifluoromethyl)phenylthio)pyrazin-1(2H)-yl)phenoxy)-2-methylpropan-2-yl 2-aminoacetate



[00130] The BOC'd glycinate ester described in Part A (3.9 g, 6.2 mmol) was treated with 1:2 TFA/ CH_2Cl_2 (145 mL) at RT for 25 min. After removal of the volatiles under vacuum, the residual TFA was removed by co-evaporation with CH_2Cl_2 (3x8 mL) and drying under vacuum for 20 min. Following dissolution in CH_2Cl_2 (70 mL), the solution was washed with cold 5% $NaHCO_3$ (3x30 mL) dried over $MgSO_4$ and concentrated to yield 3.3 g of crude product. Purification by flash chromatography (120 g silica gel, 0 to 5% MeOH/CH_2Cl_2 over 24 min) afforded the desired free amine (2.5 g, 77% yield).). HPLC 3.72 min. LC MS 2.18 min (M+1 = 524), H-NMR ($CDCl_3$) 7.75 (d, J = 8.7 Hz, 2H), 7.72 (d, J = 8.7 Hz, 2H), 7.14 (d, J = 4.4 Hz, 1H), 7.02 (d, J = 4.4 Hz, 1H), 7.00 (d, J = 8.5 Hz, 1H), 6.99 (d, J = 2.4 Hz, 1H), 6.92 (dd, J = 2.4 and 8.5 Hz, 1H), 4.24 (s, 2H), 3.89 (s, 3H), 3.36 (m, 2H), 1.63 (s, 6H), 1.54 (broad s, 2H).

EXAMPLES 194 TO 201

[00131] Examples 194 to 201 were prepared in a similar manner to Example 193 using the appropriate alcohol and BOC glycine followed by TFA removal of the BOC group.

TABLE 4

Glycine Prodrug Esters

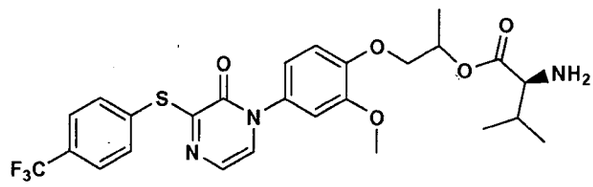
Example No.	Glycine ester of Example No.	HPLC (Met1)	LC MS	^{1}H-NMR ($CDCl_3$)
194	38	3.86	540	7.55 (d, J = 9.3 Hz, 2H), 7.27 (d, J = 9.3 Hz, 2H), 7.18 (d, J = 4.4 Hz, 1H), 7.06 (d, J = 4.4 Hz, 1H), 7.01 (d, J = 2.2 Hz, 1H), 6.99 (d, J = 8.2 Hz, 1H), 6.86 (dd, J = 2.2 and 8.2 Hz, 1H), 4.15 (s, 2H), 3.76 (s, 3H), 3.17 (s, 2H), 1.50 (s, 6H).
195	32	3.59	470	7.47 (d, J = 8.7 Hz, 2H), 7.27 (d, J = 8.7 Hz, 2H), 7.11 (d, J = 4.4 Hz, 1H), 6.98 (d, J = 2.3 Hz, 1H), 6.97 (d, J = 8.5 Hz, 1H), 6.95 (d, J = 4.4 Hz, 1H), 6.88 (dd, J = 2.3 and 8.5 Hz, 1H), 4.20 (s, 2H), 3.86 (s, 3H), 3.33 (s, 2H), 2.40 (s, 3H), 1.50 (s, 6H).
196	50	3.78	484	7.34 (d, J = 8.3 Hz, 2H), 7.22 (d, J = 8.3 Hz, 2H), 7.05 (d, J = 4.4 Hz, 1H), 6.92 (d, J = 2.2 Hz, 1H), 6.90 (d, J = 8.2 Hz, 1H), 6.87 (d, J = 4.4 Hz, 1H), 6.83 (dd, J = 2.2 and 8.2 Hz, 1H), 4.14 (s, 2H), 3.79 (s, 3H), 3.27 (s, 2H), 2.63 (q, H = 7.7 Hz, 2H), 1.54 (s, 6H), 1.19 (t, J = 7.7 Hz, 3H).
197	65		482	7.25-7.09 (m, 8H), 6.87 (d, J = 4.4 Hz, 1H), 6.80 (d, J = 9.4 Hz, 1H), 4.09 (s, 2H), 3.30 (2, 2H), 3.23 (dd, J = 7.2, 9.8 Hz, 2H), 2.94 (dd, J = 7.2 and 8.2 Hz, 2H), 2.58 (q, J = 7.6 Hz, 2H), 1.55 (s, 6H), 1.13 (t, J = 7.6 Hz, 3H).
198	87		524	1H NMR (400 MHz, chloroform-d) δ ppm 8.40 (2 H, br. s.), 7.59 (2 H, d, *J*=8.78 Hz), 7.28 (2 H, d, *J*=8.03 Hz), 7.09 - 7.23 (3 H, m), 6.97 (2 H, d, *J*=4.27 Hz), 4.22 (2 H, br. s.), 3.79 (2 H, br. s.), 2.27 (3 H, s), 1.62 (6 H, s)
199	88		544	1H NMR (500 MHz, methanol-d_3) δ ppm 7.65 (2 H, d, *J*=9.07 Hz), 7.61 (1 H, d, *J*=2.47 Hz), 7.34 - 7.43 (3 H, m), 7.23 - 7.29 (2 H, m), 7.16 (1 H, d, *J*=4.40 Hz), 4.38 (2 H, s), 3.75 (2 H, s), 1.68 (6 H, s)
200	123		486	1H NMR (500 MHz, methanol-d_3) δ ppm 7.38 (1 H, d, *J*=4.40 Hz), 7.29 (2 H, dd, *J*=8.52, 5.50 Hz), 7.19 - 7.25 (3 H, m), 6.98 - 7.05 (3 H, m), 4.29 (2 H, s), 3.74 (2 H, s), 3.31 - 3.35 (2 H, m), 2.98 (2 H, t, *J*=7.56 Hz), 2.28 (3 H, s), 1.67 (6 H, s)

Example No.	Glycine ester of Example No.	HPLC (Met1)	LC MS	^{1}H-NMR ($CDCl_3$)
201	113		468	1H NMR (500 MHz, methanol-d_3) δ ppm 7.39 (1 H, d, *J*=4.40 Hz), 7.25 - 7.31 (4 H, m), 7.17 - 7.25 (4 H, m), 7.03 (1 H, d, *J*=8.25 Hz), 4.28 (2 H, s), 3.74 (2 H, s), 3.24 - 3.39 (2 H, m), 2.91 - 3.04 (2 H, m), 2.28 (3 H, s), 1.67 (6 H, s)

[00132] If desired the amino acid prodrug esters may be converted to the corresponding HCl salt. For example, the HCl salt of Example 197 was prepared by dissolving the compound (0.655 mg, 1.36mmoles) in CH_2Cl_2 (10 mL) and MeOH (1 mL) and cooling to -30°C. 1N HCl in ether (2.3 mL, 1.7 eq) was added with stirring. Evaporation *in vacuo* afforded the desired salt. (0.71 g). LC MS was identical to the free base. H-NMR (CD_3OD) 7.30 (d, J = 4.4 Hz, 1H), 7.20 (m, 4H), 7.13 (m, 4H), 6.93 (d, J = 8.5 Hz, 1H), 4.19 (s, 2H), 3.64 (s, 2H), 3.23 (dd, J = 7.4, 15.4 Hz, 2H), 2.90 (dd, J = 8.0 and 15.4 Hz, 2H), 2.62 (q, J = 7.5 Hz, 2H), 1.59 (s, 6H), 1.14 (t, J = 7.5 Hz, 3H).

EXAMPLE 202

1-(2-Methoxy-4-(2-oxo-3-(4-(trifluoromethyl)phenylthio)pyrazin-1(2H)-yl)phenoxy)propan-2-yl 2-amino-3-methylbutanoate



[00133] To a stirred mixture of the alcohol described in Example 71 (0.882 g, 1.949 mmol), 4- dimethylaminopyridine (0.714 g, 5.85 mmol) and N-(*t*-butoxycarbonyl)-L-valine (1.271 g, 5.85 mmol) in 18 mL of CH_2Cl_2 at rt was added WSC (1.121 g, 5.85 mmol). After stirring at ambient temperature for 30 min, the reaction mixture was transferred to a separatory funnel, washed with cold 5% H_2SO_4 (3x), 5% Na_2CO_3 (2x), and water and dried over $MgSO_4$. Evaporation of the solvent afforded 1.03 g of crude product as the BOC amine. The crude product was dissolved in a 1:2 mixture of TFA/CH_2Cl_2 (18 mL). After stirring for 15 min the solvent was evaporated *in vacuo*. The residue was transferred to a separatory funnel with CH_2Cl_2,

washed with cold 5% Na_2CO_3 (2x), and dried over $MgSO_4$ to afford crude 790 mg of product after evaporation of the solvent. The product was purified by flash chromatography (80 g silica gel, gradient elution: 1 to 8 % MeOH/CH_2Cl_2 over 24 min) to afforded the desired valine ester as a free base (0.69 g, 64% yield).

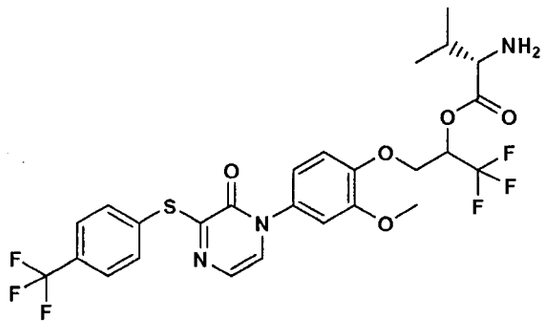
[00134] HPLC (Method 1) 3.84 min. LC MS 2.26 min (M+1 = 552), H-NMR ($CDCl_3$) 7.74 (d, J = 8.7 Hz, 2H), 7.72 (d, J = 8.7 Hz, 2H), 7.13 (d, J = 4.4 Hz, 1H), 7.02 (d, J = 4.4 Hz, 1H), 7.00 (d, J = 8.5 Hz, 1H), 6.99 (d, J = 2.4 Hz, 1H), 6.91 (dd, J = 2.4 and 8.5 Hz, 1H), 5.34 (m, 1H), 4.12 (m, 2H), 3.86 (d, 3H), 3.30 (t, J = 5.2 Hz, 1H), 2.05 (m, 1H), 1.40 (d, J = 6.4 Hz), 0.98 (m, 3H), 0.92 (m, 3H).

[00135] The HCl salt of Example 176 was prepared by dissolving the compound in CH_2Cl_2 (9 mL). After cooling the solution to -30°C, 1N HCl in ether (2.85 mL, 1.7 eq) was added with stirring. The yellow precipitate was collected and dried to afford the HCl salt (0.74 g).

[00136] LC MS was identical to the free base. H-NMR ($CDCl_3$) 7.74 (d, J = 8.7 Hz, 2H), 7.79 (m, 4H), 7.33 (d, J = 4.4 Hz, 1H), 7.18 (d, J = 8.5 Hz, 1H), 7.15 (d, J = 2.4 Hz, 1H), 7.02 (dd, J = 2.4 and 8.5 Hz, 1H), 5.51 (m, 1H), 4.24 (m, 2H), 3.86 (d, 3H), 3.33 (s, 1H), 2.30 (m, 1H), 1.41 (d, J = 6.4 Hz), 1.12 (m, 6H).

EXAMPLE 203

(2S)-1,1,1-Trifluoro-3-(2-methoxy-4-(2-oxo-3-(4-(trifluoromethyl)phenylthio)pyrazin-1(2H)-yl)phenoxy)propan-2-yl 2-amino-3-methylbutanoate



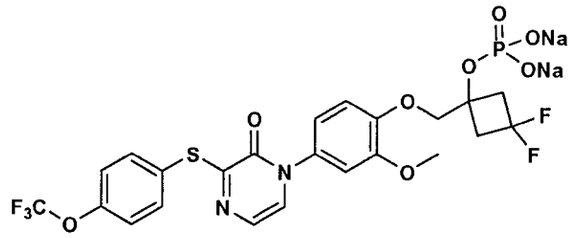
[00137] In an analogous fashion to that described in Example 202, the valine ester of the alcohol described in Example 74 was prepared.

[00138] LC MS at t = 2.35 min. (m+1 = 606) Phenomenex S5 C18 4.6X30 mm column/water-MeOH-TFA 90:10:0.1 to 10:90:0.1 gradient over 2 min at 5 mL/min with 1 min hold at the end of the gradient.

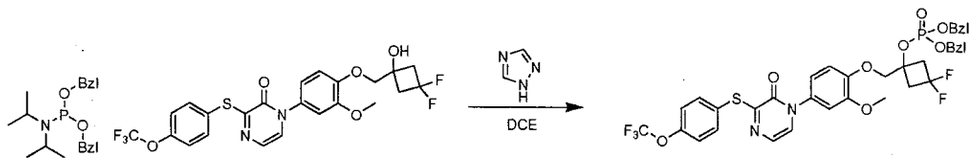
[00139] ^{1}H NMR (500 MHz, $CDCl_3$) δ ppm 0.97 (dd, *J*=35.13, 6.92 Hz, 6 H), 1.97 - 2.20 (m, 1 H), 3.42 (d, *J*=4.78 Hz, 1 H), 3.86 (s, 4 H), 4.26 - 4.36 (m, 1 H), 4.44 (dd, *J*=11.08, 3.53 Hz, 1 H), 5.73 - 5.87 (m, 1 H), 6.91 (dd, *J*=8.56, 2.27 Hz, 1 H), 6.97 - 7.06 (m, 2 H), 7.13 (d, *J*=4.53 Hz, 1 H), 7.58 (s, 1 H), 7.66 - 7.77 (m, 4 H).

EXAMPLE 204

Sodium 3,3-difluoro-1-((2-methoxy-4-(2-oxo-3-(4-(trifluoromethoxy)-phenylthio)pyrazin-1(2H)-yl)phenoxy)methyl)cyclobutyl phosphate



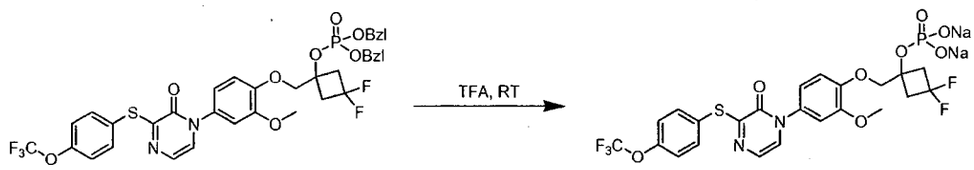
Part A. Dibenzyl 3,3-difluoro-1-((2-methoxy-4-(2-oxo-3-(4-(trifluoromethoxy)phenylthio)pyrazin-1(2H)-yl)phenoxy)methyl)cyclobutyl phosphate



[00140] To a mixture of dibenzyl diisopropylphosphoramidite (135 mg, 0.390 mmol), 1-(4-((3,3-difluoro-1-hydroxycyclobutyl)methoxy)-3-methoxyphenyl)-3-(4-(trifluoromethoxy)phenylthio)pyrazin-2(1H)-one (Example 75) (69 mg, 0.130 mmol) and 1H-1,2,4-triazole (27.0 mg, 0.390 mmol) in DCE (20 mL) was stirred at reflux for 6 hours. The mixture was cooled to RT. 30 % hydrogen peroxide in water (10 ml) was slowly added and the mixture was stirred at RT for 30 min. The mixture was diluted with a solution of aqueous 10 % sodium thiosulfate (40 ml) and was extracted with DCM (50 ml). The DCM layer was dried over sodium sulfate and concentrated.

The crude product was purified by ISCO silica gel Column (40 g) and the product was eluted with hexane to 100 % ethyl acetate in 10 min. Yield dibenzyl 3,3-difluoro-1-((2-methoxy-4-(2-oxo-3-(4-(trifluoromethoxy)phenylthio)pyrazin-1(2H)-yl)phenoxy)methyl)cyclobutyl phosphate (79 mg, 0.100 mmol, 77 % yield) as off-white solid. 1H NMR (400 MHz, chloroform-d) δ ppm 7.57 - 7.66 (2 H, m), 7.27 - 7.39 (12 H, m), 7.13 (1 H, d, J=4.53 Hz), 6.81 - 7.00 (4 H, m), 4.97 - 5.14 (4 H, m), 4.29 (2 H, s), 3.75 (3 H, s), 2.93 - 3.20 (4 H, m).

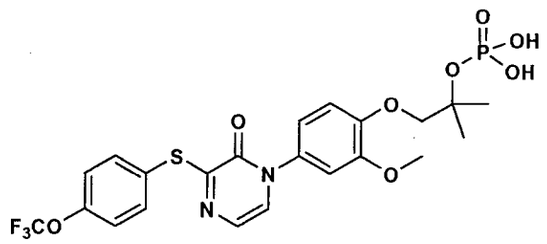
Part B. Sodium 3,3-difluoro-1-((2-methoxy-4-(2-oxo-3-(4-(trifluoromethoxy)phenylthio)pyrazin-1(2H)-yl)phenoxy)methyl)cyclobutyl phosphate



[00141] To a solution of dibenzyl 3,3-difluoro-1-((2-methoxy-4-(2-oxo-3-(4-(trifluoromethoxy)phenylthio)pyrazin-1(2H)-yl)phenoxy)methyl)cyclobutyl phosphate (79 mg, 0.100 mmol) in TFA (2 mL) was stirred at RT for 3.5 hours. The mixture was concentrated. The crude product was purified by prep-HPLC (Phenomenex, Luna 5 micron 25 x 250 mm, flow rate = 30 ml/min., gradient = 20% A to 100%B in 10 min., A =90%H2O/10% MeOH/0.1% TFA, B = 10%H2O/90% MeOH/0.1% TFA). Yield 46 mg, 0.075 mmol. as yellow gum. The yellow gum in ACN (2 ml) was added 0.5 N aqueous sodium bicarbonate (302 µl, 0.151 mmol.), the mixture was diluted with water (5 ml). The solution was then lyopholized. Yield sodium 3,3-difluoro-1-((2-methoxy-4-(2-oxo-3-(4-(trifluoromethoxy)phenylthio)pyrazin-1(2H)-yl)phenoxy)methyl)cyclobutyl phosphate (51.08 mg, 0.078 mmol, 78 % yield) as off-white powder. MS (M+H=611). 1H NMR (400 MHz, MeOD) δ ppm 7.54 - 7.63 (2 H, m), 7.19 - 7.33 (3 H, m), 7.02 - 7.17 (3 H, m), 6.91 (1 H, dd, J=8.44, 2.39 Hz), 4.28 (2 H, s), 3.80 (3 H, s), 3.13 - 3.32 (2 H, m), 2.75 - 2.90 (2 H, m).

EXAMPLE 205

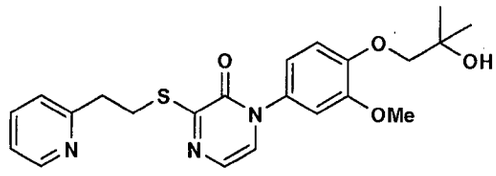
Sodium 1-(2-methoxy-4-(2-oxo-3-(4-(trifluoromethoxy)phenylthio)pyrazin-1(2H)-yl)phenoxy)-2-methylpropan-2-yl phosphate



[00142] In an analogous fashion to that described in Example 204, the phosphate prodrug of the alcohol described in Example 38 was prepared. MS (M-H=561). 1H NMR (400 MHz, MeOD) δ ppm 7.57 (2 H, d, J=8.56 Hz), 7.28 (2 H, d, J=8.31 Hz), 7.20 (1 H, d, J=4.28 Hz), 6.97 - 7.12 (3 H, m), 6.88 (1 H, dd, J=8.56, 2.27 Hz), 4.00 (2 H, s), 3.78 (3 H, s), 1.48 (6 H, s).

[00143] The following experimental descriptions exemplify the preparation of specific compounds as set out in Examples 27, 95, 110, 113, and 124.

EXAMPLE 27

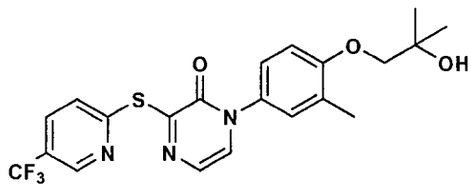


1-(4-(2-Hydroxy-2-methylpropoxy)-3-methoxyphenyl)-3-(2-(pyridin-2-yl)-ethylthio)pyrazin-2(1H)-one

[00144] Following the procedures described in parts A-D of example 134, 2-methoxy-4-nitrophenol was converted to 1-(4-(2-hydroxy-2-methylpropoxy)-3-methoxyphenyl)pyrazine-2,3(1H,4H)-dione. A solution of 1-(4-(2-hydroxy-2-methylpropoxy)-3-methoxyphenyl)pyrazine-2,3(1H,4H)-dione prepared in Part ? (2.28 g, 7.44 mmol), $EtN(iPr)_2$ (3.9 mL, 22.3 mmol), PyBOP (6.78 g, 13.0 mmol) in DMF (35 mL) was stirred at ambient temperature for 1.5 h. After addition of 2-pyridylethyl mercaptan (1.24 g, 8.93 mmol), the reaction was stirred at ambient temperature. After stirring overnight the reaction mixture was partially concentrated

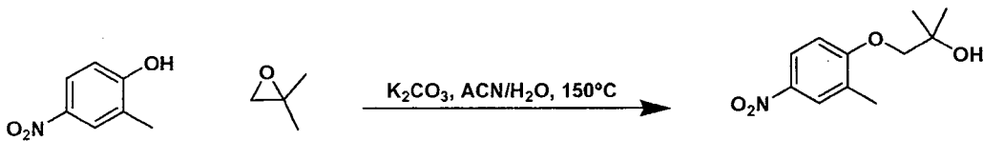
under reduced pressure, quenching by addition of aq. $NaHCO_3$ and extracted with EtOAc. The EtOAc extracts were washed with brine, dried over $MgSO_4$ and concentrated. Chromatography on silica employing a gradient elution with 2.5-10% methanol/methylene chloride, followed by chromatography on silica eluting with EtOAc, and trituration with EtOAc/Hexanes afforded the desired product 1-(4-(2-hydroxy-2-methylpropoxy)-3-methoxyphenyl)-3-(2-(pyridin-2-yl)ethylthio)pyrazin-2(1H)-one (2.15g, 68% yield).

EXAMPLE 95



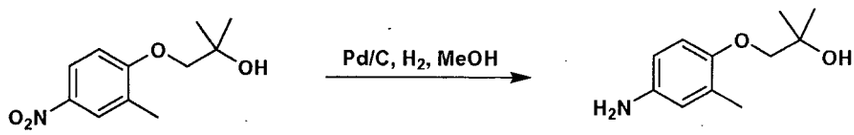
1-(4-(2-Hydroxy-2-methylpropoxy)-3-methylphenyl)-3-(5-(trifluoromethyl)pyridin-2-ylthio)pyrazin-2(1H)-one

Part A. 2-Methyl-1-(2-methyl-4-nitrophenoxy)propan-2-ol



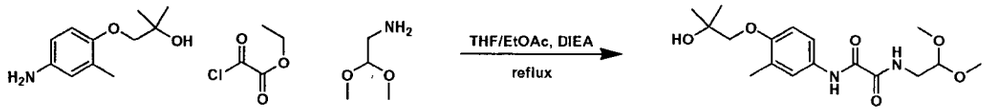
[00145] A mixture of 2-methyl-4-nitrophenol (5.50 g, 35.9 mmol), 2,2-dimethyloxirane (7.77 g, 108 mmol), K_2CO_3 (4.96 g, 35.9 mmol) and NaH_2PO_4 (4.31 g, 35.9 mmol) in MeCN (50 mL) and H_2O (8.82 mL) was stirred at 140°C in a steel bomb for 6 hours. After cooling to RT, the reaction was diluted with aq. saturated $NaHCO_3$ (80 ml) prior to extraction with EtOAc (100 ml). The EtOAc layer was dried over Na_2SO_4 and concentrated. The crude product was purified by silica gel chromatography employing a solvent gradient (hexane to 60 % ethyl acetate) to elute 2-methyl-1-(2-methyl-4-nitrophenoxy)propan-2-ol (7.3 g, 32.4 mmol, 90 % yield) as yellow oil. MS (M+1 = 226). 1H NMR (500 MHz, chloroform-d) δ ppm 8.00 - 8.15 (2 H, m), 6.86 (1 H, d, *J*=8.80 Hz), 3.90 (2 H, s), 2.33 (3 H, s), 1.40 (6 H, s).

Part B. 1-(4-Amino-2-methylphenoxy)-2-methylpropan-2-ol



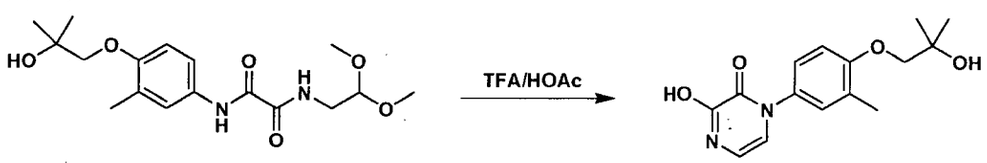
[00146] A mixture of 2-methyl-1-(2-methyl-4-nitrophenoxy)propan-2-ol (7.30 g, 32.4 mmol) and 10 % Pd/C (0.345 g, 3.24 mmol) in MeOH (150 mL) was hydrogenated at 1 atm of H_2 for 18 hours. After removal of the Pd/C by filtration, the solution was concentrated to yield 1-(4-amino-2-methylphenoxy)-2-methylpropan-2-ol (6.10 g, 29.7 mmol, 92 % yield) as clear gum which was carried forward without further purification.

Part C. N1-(2,2-Dimethoxyethyl)-N2-(4-(2-hydroxy-2-methylpropoxy)-3-methylphenyl)oxalamide



[00147] Slow addition of a solution of ethyl 2-chloro-2-oxoacetate (4.69 g, 34.4 mmol) in THF (30 ml) to a solution of 1-(4-amino-2-methylphenoxy)-2-methylpropan-2-ol (6.10 g, 31.2 mmol) in THF (100 mL) resulted in formation of a precipitate as the reaction stirred at RT for 30 min. At which time a solution of Et_3N (13.06 mL, 94 mmol) and 2,2-dimethoxyethanamine (3.94 g, 37.5 mmol) in EtOAc (100 mL) was added prior to heating the mixture at reflux for 25 hours. After cooling and concentration under vacuum, the residue, following dilution with CH_2Cl_2, was extracted with aqueous 0.5 N HCl (2 x 150 ml). The CH_2Cl_2 layer was dried over sodium sulfate and concentrated to yield N1-(2,2-dimethoxyethyl)-N2-(4-(2-hydroxy-2-methylpropoxy)-3-methylphenyl)-oxalamide (11.40 g, 30.6 mmol, 98 % yield) as white solid which was carried forward without further purification.

Part D. 3-Hydroxy-1-(4-(2-hydroxy-2-methylpropoxy)-3-methylphenyl)pyrazin-2(1H)-one



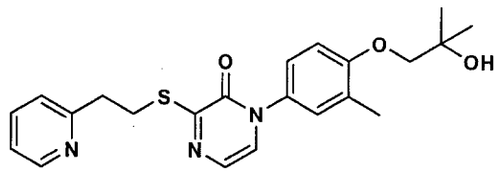
[00148] A solution of N1-(2,2-dimethoxyethyl)-N2-(4-(2-hydroxy-2-methylpropoxy)-3-methylphenyl)oxalamide (11.4 g, 32.2 mmol) and TFA (2.97 mL, 38.6 mmol) in AcOH (120 mL) was stirred at 135°C in a seal tube for 60 min. After cooling and concentration under vacuum, addition of CH_2Cl_2 (300 ml) produced a precipitate which was collected by filtration and was washed with CH_2Cl_2 (150 ml) to yield 3-hydroxy-1-(4-(2-hydroxy-2-methylpropoxy)-3-methylphenyl)pyrazin-2(1H)-one (7.19 g, 23.53 mmol, 73.1 % yield) as brown solid. MS (M+1 = 226). 1H NMR (500 MHz, methanol-d_3) δ ppm 7.13 - 7.26 (2 H, m), 6.98 (1 H, d, *J*=8.52 Hz), 6.50 (1 H, d, *J*=5.77 Hz), 6.41 (1 H, d, *J*=6.05 Hz), 3.82 (2 H, s), 2.29 (3 H, s), 1.35 (6 H, s).

Part E. 1-(4-(2-Hydroxy-2-methylpropoxy)-3-methylphenyl)-3-(5-(trifluoromethyl)-pyridin-2-ylthio)pyrazin-2(1H)-one

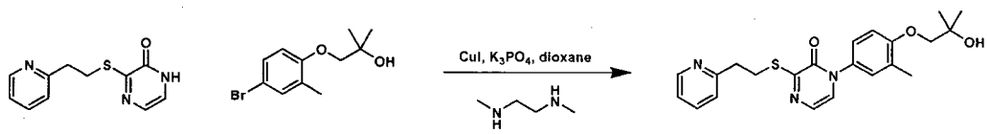


[00149] A mixture of 3-hydroxy-1-(4-(2-hydroxy-2-methylpropoxy)-3-methylphenyl)pyrazin-2(1H)-one (100 mg, 0.344 mmol), PyBOP (314 mg, 0.603 mmol) and EtN(iPr)$_2$ (0.180 mL, 1.033 mmol) in DMF (6 mL) was stirred at RT for 3 hours prior to addition of 5-(trifluoromethyl)pyridine-2-thiol (74.1 mg, 0.413 mmol). After stirring for 3 days, The reaction was diluted with aq. saturated $NaHCO_3$ (15 ml) prior to extraction with EtOAc (20 ml). The EtOAc layer was dried over Na_2SO_4 and concentrated. The crude product was purified by prep-HPLC (Phenomenex, Luna 5 micron 30 x 250 mm, flow rate = 30 ml/min., gradient = 20% A to 100%B in 30 min., A =90%H_2O/10% MeOH/0.1% TFA, B = 10%H_2O/90% MeOH/0.1% TFA). After concentration, the residue in EtOAc (30 ml) was converted to the free base by washing with aq. saturated $NaHCO_3$ (30 ml). The EtOAc layer was dried over Na_2SO_4 and concentrated. To yield 1-(4-(2-hydroxy-2-methylpropoxy)-3-methylphenyl)-3-(5-(trifluoromethyl)pyridin-2-ylthio)pyrazin-2(1H)-one (22.76 mg, 14%) as off-white solid. MS (M+1 = 452). 1H NMR (500 MHz, chloroform-d) δ ppm 8.88 (1 H, s), 7.89 - 7.99 (2 H, m), 7.16 - 7.24 (3 H, m), 7.07 (1 H, d, *J*=4.40 Hz), 6.90 (1 H, d, *J*=8.52 Hz), 3.84 (2 H, s), 2.30 (3 H, s), 1.39 (6 H, s).

EXAMPLE 110

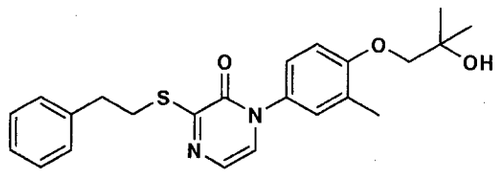


1-(4-(2-Hydroxy-2-methylpropoxy)-3-methylphenyl)-3-(2-(pyridin-2-yl)ethylthio)pyrazin-2(1H)-one



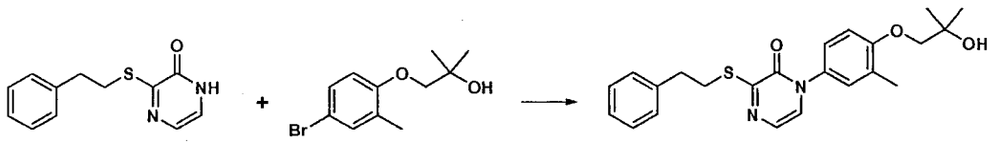
[00150] A mixture of 3-(2-(pyridin-2-yl)ethylthio)pyrazin-2(1H)-one (100 mg, 0.429 mmol), which was prepared by the procedure described in Method 7 except for substitution of 2-(2-pyridylethylthiol) for 2-(4-chlorophenethanol), 1-(4-bromo-2-methylphenoxy)-2-methylpropan-2-ol (133 mg, 0.514 mmol), N1,N2-dimethylethane-1,2-diamine (113 mg, 1.286 mmol), K_3PO_4 (0.106 mL, 1.286 mmol) and copper(1) iodide (82 mg, 0.429 mmol) in dioxane (1.0 mL) was stirred at 115°C for 90 min. The reaction mixture, after cooling to RT, was filtered and the filtrate was concentrated. The crude product was purified by silica gel chromatography employing a solvent gradient (hexane to 100 % ethyl acetate) to yield 1-(4-(2-hydroxy-2-methylpropoxy)-3-methylphenyl)-3-(2-(pyridin-2-yl)ethylthio)pyrazin-2(1H)-one (140 mg, 0.340 mmol, 79 % yield) as white solid. MS (M+H 412). 1H NMR (400 MHz, MeOD) δ ppm 8.67 (1 H, d), 8.48 (1 H, td, *J*=7.91, 1.51 Hz), 8.02 (1 H, d, *J*=8.28 Hz), 7.81 - 7.95 (1 H, m), 7.07 - 7.29 (4 H, m), 6.93 (1 H, d, *J*=8.78 Hz), 3.76 (2 H, s), 3.35 - 3.57 (4 H, m), 2.22 (3 H, s), 1.27 (6 H, s).

EXAMPLE 113



1-(4-(2-Hydroxy-2-methylpropoxy)-3-methylphenyl)-3-(phenethylthio)pyrazin-

2(1H)-one



[00151] A mixture of 3-(phenethylthio)pyrazin-2(1H)-one (25 mg, 0.108 mmol), which was prepared by the procedure described in Method 7 except for substitution of 2-phenethylthiol for 2-(4-chlorophenethanol), 1-(4-bromo-2-methylphenoxy)-2-methylpropan-2-ol (33.5 mg, 0.129 mmol), copper iodide (20.50 mg, 0.108 mmol), K_3PO_4 (70 mg, 0.323 mmol) and N,N'-dimethylethylenediamine (28.5 mg, 0.323 mmol) in dioxane (1.0 ml) was stirred at 115°C for 2 hours. The reaction mixture, after cooling to RT, was filtered and the filtrate was concentrated. The crude product was purified by silica gel chromatography employing a solvent gradient (hexane to 100 % ethyl acetate) to elute to yield 1-(4-(2-hydroxy-2-methylpropoxy)-3-methylphenyl)-3-(phenethylthio)-pyrazin-2(1H)-one (26.74 mg, 0.062 mmol, 57.5 % yield) as off-white solid. MS (M+1 = 411). 1H NMR (500 MHz, methanol-d_3) δ ppm 7.38 (1 H, d, *J*=4.40 Hz), 7.25 - 7.32 (4 H, m), 7.16 - 7.24 (4 H, m), 7.00 (1 H, d, *J*=8.25 Hz), 3.83 (1 H, s), 3.24 - 3.39 (2 H, m), 2.90 - 3.05 (2 H, m), 2.29 (3 H, s), 1.35 (6 H, s).

RADIOLIGAND BINDING ASSAY FOR ASSESSMENT OF MCHR1 ACTIVITY

Assay and Biological Evaluation

[00152] Compounds of Formula I were initially characterized in an *in vitro* binding assay to determine their Ki or ability to antagonize binding of a peptide agonist to the human melanin concentrating hormone receptor (MCHR1).

Radioligand Binding Assay for Assessment of MCHR1 Activity

[00153] Membranes from stably transfected HEK-293 cells expressing a mutated (E4Q, A5T) hMCHR1 receptor were prepared by dounce homogenization and differential centrifugation. Binding experiments were carried out with 0.5 -1.0 ug of membrane protein incubated in a total of 0.2 ml in 25 mM HEPES (pH 7.4) with 10 mM $MgCl_2$, 2 mM EGTA, and 0.1% BSA (Binding Buffer) for 90 min. For

competition binding assays, reactions were carried out in the presence of with 0.06 - 0.1 nM [Phe^{13}, [^{125}I]Tyr^{19}]-MCH and increasing concentrations of unlabeled test molecules. Reactions were terminated by rapid vacuum filtration over 96 well-GFC Unifilter plates pre-coated with 0.075 ml binding buffer containing 1% BSA, and washed 3 times with 0.4 ml of Phospho-buffered Saline (pH 7.4) containing 0.01% TX-100. Filters were dried; 0.05 ml microscint 20 was added to each well and radioactivity was subsequently quantified by scintillation counting on a TopCount™ microplate scintillation counter (Packard). Inhibitory constants were determined by nonlinear least squares analysis using a four parameter logistic equation.

Biological Data

[00154] The following representative *in vitro* biological data was measured in a binding assay for the compounds from the Examples herein above:

Example	Ki (nM)
113	8
124	9
65	10
110	17
125	17
131	18
38	20
181	21
67	28
36	33
95	41
155	45
69	49
71	62
27	63
151	64
141	78
172	85
59	125
170	132
10	141
46	232
178	290
3	576
169	1294

Example	Ki (nM)
39	1580
157	1730
49	3043
19	3127
28	3153
40	3218
50	4664

EVALUATION OF PRODRUGS

[00155] The relative ability of the prodrug to enhance exposure (bioavailability) was assessed in an eight hour PK study using cannulated Sprague Dawley (CD, Charles River Breeding Laboratory) rats. The compounds (parent and prodrug esters) were administered p.o. at 2.0 ml/kg as a suspension in 0.5% methyl cellulose, 0.1% Tween 80 in water at 10 mg/kg p.o. Blood samples were taken at 1, 2, 4 and 8 hr. After determination of parent concentration, an AUC was calculated for the eight hour study.

Assessment of *In Vivo* MCHR1 Activity

[00156] Male Sprague Dawley (CD, Charles River Breeding Laboratory) rats weighing approximately 240 grams were placed in individual plastic cages with AlphaDri bedding. The room was maintained at 72 °F and 50% humidity, and a 12/12 light dark cycle with lights out at 1600 hours. The rats were conditioned for 5 days prior to the start of the study to having a choice of foods. A normal chow (Harlan Teklad, 2018) that contains 18% protein, 5% fat and 73% carbohydrate and a high fat high sugar diet (Research Diets (D2327) that contains 20% protein, 40% fat and 40% carbohydrate where the carbohydrate is entirely sucrose and the fat is soybean and coconut oil. Studies have revealed that rats exhibit a high preference for the high fat/high sucrose diet (80% preference). Body weight and consumption of both kinds of food as well as water intake were measured daily. Water was available ad lib throughout the study. Food consumption is presented as daily caloric consumption which is the sum of grams of chow multiplied by the Kcal per gram (3.5) plus grams of high fat high sugar multiplied by Kcal per gram (4.59).

[00157] Baseline body weight was measured prior to drug treatment on day 0 of the study. Baseline food consumption was the average of the 3 days prior to the first drug treatment. Drug was administered daily p.o. at 2.0 ml/kg at 1500 hours beginning on day 0 and continuing daily through day 4 as a suspension in 0.5% methyl cellulose, 0.1% Tween 80 in water at 3.0, 10 and 30 mg/kg p.o. All data were evaluated using ANOVA and Fishers PLSD statistics.

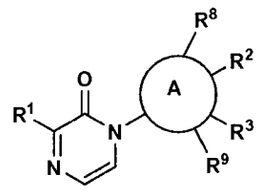
Biological Data

Example	Dose (mg/kg)	Weight Reduction versus Vehicle
193	3	0.7%
	10	2.1%
	30	3.4%
194	3	0.9%
	10	2.7%
	30	7.4%
202	30	2.2%
27	45	4.1%
113	45	4.2%

[00158] While the invention has been described according to several embodiments, various modifications thereto, in addition to those described herein, may become apparent to those skilled in the art from the foregoing description. Such modifications are also intended to fall within the scope of the appended claims.

WHAT IS CLAIMED IS:

1. A compound of Formula I or a pharmaceutically acceptable salt thereof

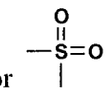


I

wherein

(A) is a phenylene ring or a heteroaryl ring which contains one or two nitrogen atoms or one oxygen atom;

R^1 is Z-Y-X-, wherein

X is O, S,  , or  ;

Y is a bond, a 3- to 6-membered cycloalkyl, an alkyl chain; and

Z is aryl or heteroaryl;

R^2 is -E-G-$(J)_m$, with m being an integer from 1 to 3;

E is O, S or a bond;

G is lower alkyl, phenylalkyl, cycloalkyl, cycloalkylalkyl, alkylcycloalkyl, cycloalkoxy, alkylcycloalkoxy, or cycloalkoxyalkyl, and

each J is independently hydrogen, hydroxyl, CN, $-SO_2R^7$, $-SR^7$, $-SOR^7$, lower alkyl, lower alkoxy, CF_3, CF_3O-, $-COOR^5$, or $-CO-NR^{5a}R^6$, wherein R^{5a} and R^6 are each independently selected from the group consisting of H, C_{1-3} alkyl, and cycloalkyl, or R^{5a} and R^6 taken together can be propanediyl, butanediyl or pentanediyl with the N atom to which they are attached to form a 4-, 5- or 6-membered cyclic amine which may be optionally substituted;

R^5 is H, C_{1-6} alkyl, or cycloalkyl;

R^7 is lower alkyl; and

R^3 is C_{1-6} alkyl, cycloalkyl ,C_{1-6} alkoxy, halogen, hydrogen, -S-C_{1-6} alkyl, CN, CF_3O, or CF_3;

and wherein R^2 and R^3 can be taken together to form a 5- to 7-membered ring which is saturated or partially unsaturated and may optionally include an E heteroatom which is O or 0, 1 or 2 N atoms, which ring is substituted with one or two -O-G-$(J)_m$ groups wherein at least one J is OH, and which may optionally be substituted with other substituents as set out for "alkyl" or "heteroaryl";

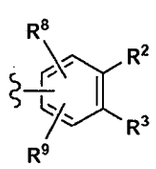
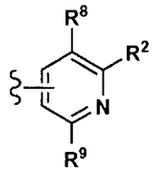
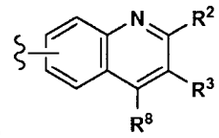
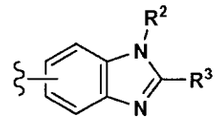
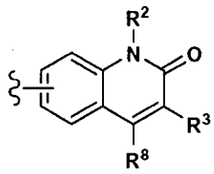
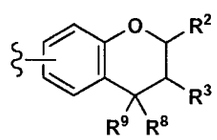
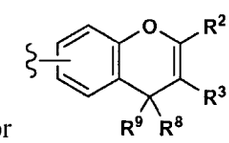
with the proviso that where (A) is a phenylene group, E-G and R^3 are not identical unsubstituted lower alkoxy groups, and when G is lower alkyl and J is H, R^3 is not hydrogen; and

R^8 and R^9 are each independently hydrogen, halogen, or lower alkyl;

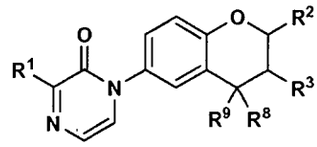
including esters thereof, prodrugs thereof, solvates thereof, and all stereoisomers thereof.

2. The compound as defined in Claim 1 wherein (A) is a phenylene or wherein (A) is a monocyclic or bicyclic heteroaryl ring.

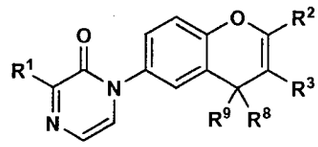
3. The compound as defined in Claim 1 wherein (A) is

4. The compound as defined in Claim 1 wherein (A) is



IF , or



IG ,

or a pharmaceutically acceptable salt thereof or prodrug of any of the above.

6. The compound as defined in Claim 4 wherein

X is O or S; and/or

R^1 is Z-Y-X,

wherein Y is a bond or an alkylene chain of 1 to 3 atoms; and/or

wherein Z is phenyl or aryl;

wherein Z is heteroaryl; and/or

wherein R^2 is -E-G-J; and/or

wherein E is O or S; and/or

wherein G is an alkylene chain or alkylcycloalkyl; and/or

wherein J is H, OH, SO_2R^7, lower alkyl, lower alkoxy, or CF_3; and/or

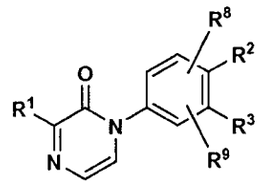
R^3 is C_{1-6} alkyl, C_{1-6} alkoxy, H, or halo; and or

R^8 is H or alkyl; and/or

R^9 is H; and or

R^2 and R^3 may optionally be taken together to form a 5- to 7-membered ring which is saturated, unsaturated or partially unsaturated, and may include an O atom or 1 or 2 N atoms, which ring is substituted with one or two -O-G-$(J)_m$ groups wherein at least one J is OH, and which may be optionally substituted with other substituents as set out for "alkyl" or "heteroaryl".

7. The compound as defined in Claim 1 or a pharmaceutically acceptable salt thereof



IA

8. The compound as defined in Claim 7 wherein

R^1 is Z-Y-X;

X is S; and/or

Y is a bond or alkylene chain; and/or

Z is phenyl or pyridyl; and/or

E is O; and/or

G is an alkylene chain or alkylcycloalkyl; and/or

J is H or OH; and/or

R^3 is H, alkoxy, alkyl, or halo; and/or

R^8 is H or CH_3; and/or

R^9 is H;

wherein R^2 and R^3 may be taken together to form a 5- to 7-membered ring which is saturated, unsaturated or partially unsaturated, and may include an O atom or 1 or 2 N atoms, which ring is substituted with 1 or 2 -O-G-$(J)_m$ groups wherein at least one J is OH, and which may be further optionally substituted with alkyl and/or OH.

9. The compound as defined in Claim 1 wherein

Z is aryl or heteroaryl, with any of the foregoing Z moieties either unsubstituted or substituted with 1, 2 or 3 of amino, halo, C_{1-6} alkyl, C_{1-3} alkylamino, di-C_{1-3} alkylamino, C_{1-3} alkoxy, C_{1-3} thioalkyl, C_{1-3} trifluoroalkoxy, trifluoromethyl, cycloalkyl, cycloalkoxy, or heteroaryl; and or

J is hydrogen, hydroxyl, CN, $-SO_2R^7$, $-SR^7$, $-SOR^7$, lower alkyl, lower alkoxy, CF_3, CF_3O-, $-COOR^5$, or $-CO-NR^{5a}R^6$, wherein R^{5a} and R^6 are each independently selected from the group consisting of H, C_{1-3} alkyl, and cycloalkyl, or R^{5a} and R^6 taken together can be propanediyl, butanediyl or pentanediyl with the N atom to

which they are attached to form a 4-, 5- or 6-membered cyclic amine optionally substituted with lower alkyl, lower alkoxy, hydroxyl, CF_3, or CF_3O.

10. The compound of Claim 1 wherein:

Z is

(1) aryl, which is optionally substituted with:
  a) halogen,
  b) alkyl,
  c) alkoxy,
  d) polyhaloalkyl,
  e) polyhaloalkoxy,
  f) amino, alkylamino or dialkylamino,
  g) alkylthio,
  h) OH,
  i) an ester, or
  j) aryl,

(2) heteroaryl which is:
  a) pyridinyl,
  b) pyrazinyl, or
  c) pyrimidinyl,

each of a), b) or c) being optionally substituted with alkyl, polyhaloalkyl, alkoxy, or halogen,

(3) benzothiazole optionally substituted with halo or alkoxy,

(4) benzoxazole optionally substituted with halo,

(5) benzimidazole,

(6) thiazole optionally substituted with aryl or alkyl,

(7) indanyl,

(8) quinolinyl optionally substituted with CF_3, or

(9) imidazolidinyl; and/or

Y is a bond or alkylene; and/or

X is S, O, SO, or SO_2; and/or

J is

(1) H,

(2) -CO-NR^{5a}R^{6} wherein R^{5a} and R^{6} together with the N to which they are attached form a pyrrolidinyl ring,

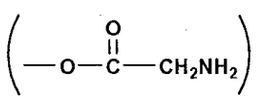
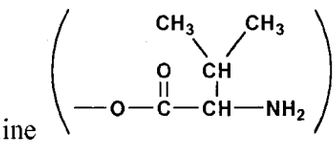
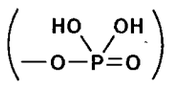
(3) OH,

(4) COOH,

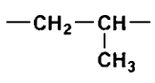
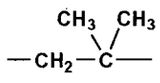
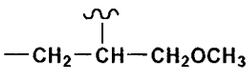
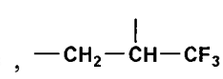
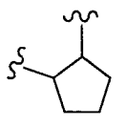
(5) COOalkyl,

(6) SO_2R^7, or

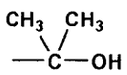
(7) prodrug esters which are selected from glycine

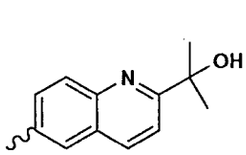
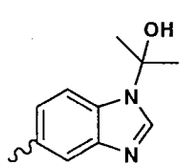
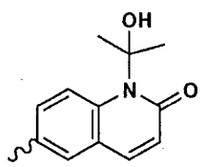
 , valine  , and phosphate  ; and/or

m is 1 or 2; and/or

G is a bond or CH_2, $(CH_2)_2$, $(CH_2)_3$,  ,  ,  ,  , cycloalkyl which is  , or cycloalkoxy which is  ;

E is O; and/or

wherein R^2 and R^3 can be optionally taken together to form a 5- or 6-membered unsaturated or aromatic ring containing one or two N atoms, which ring is optionally substituted with hydroxyalkyl which is  , and is

 ,  and  ,

and wherein R^2 and R^3 can optionally be taken together to form a 6-membered saturated or partially unsaturated O-containing ring, which ring is optionally substituted with hydroxyalkyl, alkyl, and/or OH; and/or

R^3 is H, alkoxy, hydroxyalkyl, alkyl, halo, or hydroxyalkoxy; and/or

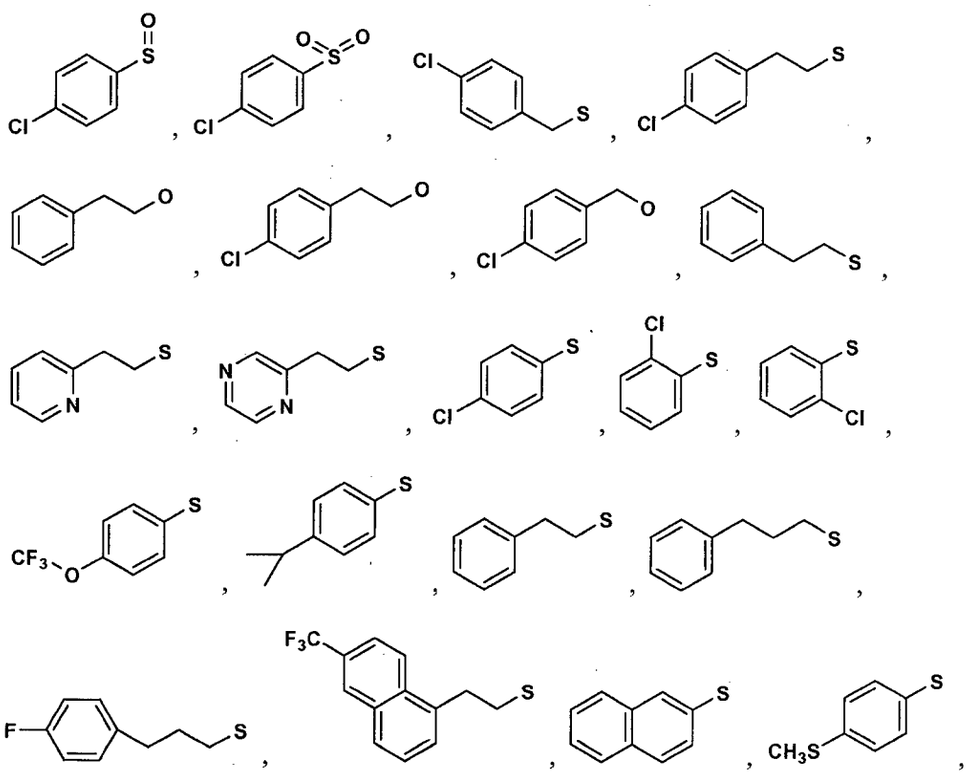
R^8 is H, halo or alkyl; and/or

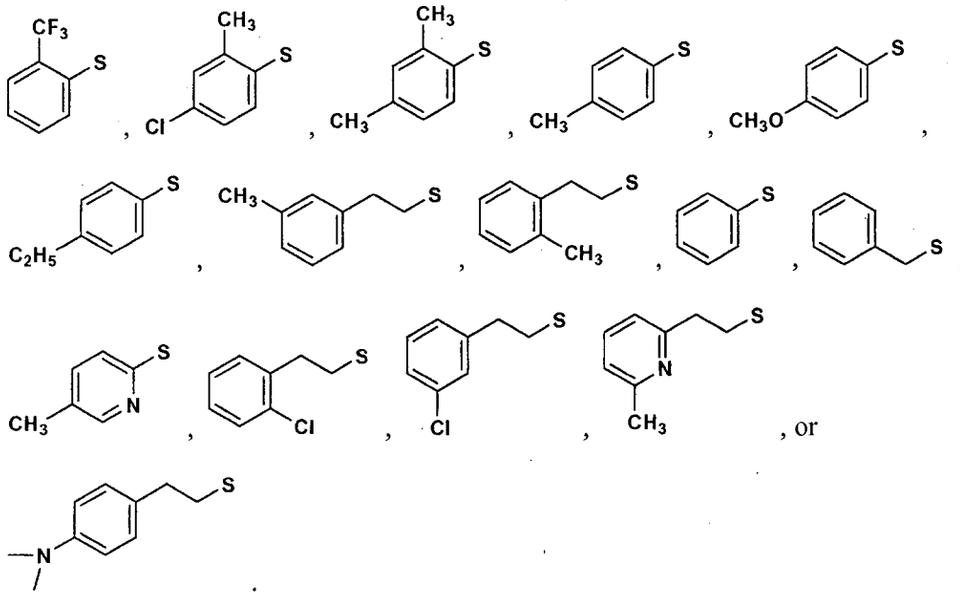
R^9 is H.

11. The compound of Claim 7, wherein Z is selected from the group consisting of phenyl, naphthyl, pyridinyl, pyrimidinyl, pyrazinyl, benzimidazolyl, and benzoxazolyl.

12. The compound of Claim 7, wherein R^3 is C_1-C_6 alkoxy or C_{1-6} alkyl.

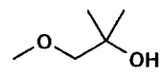
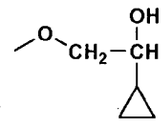
13. The compound of Claim 7, wherein R^1 is selected from the group consisting of:





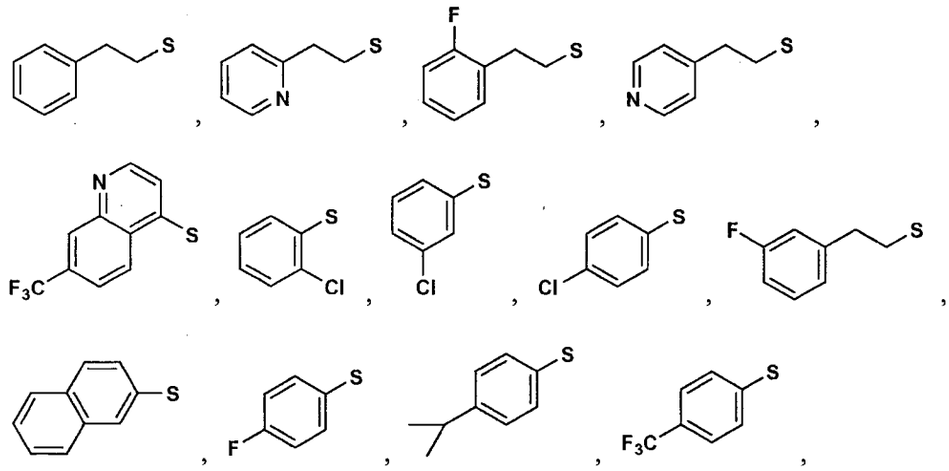
14. The compound of Claim 7 wherein

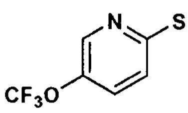
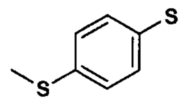
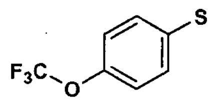
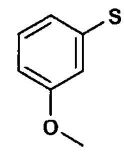
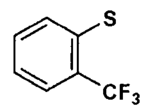
(A) is a phenylene; and/or

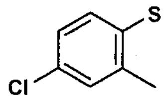
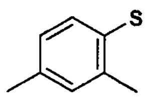
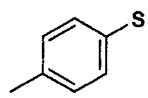
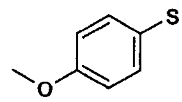
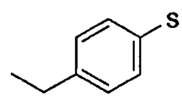
R^2 is  or  ; and/or

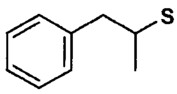
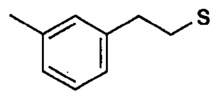
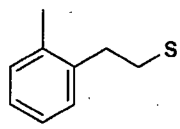
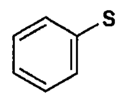
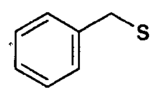
R^3 is methoxy or methyl;

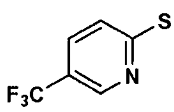
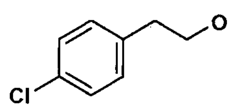
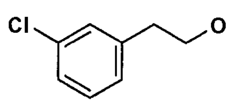
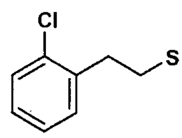
R^1 is selected from the group consisting of:

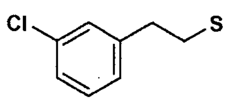
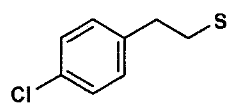
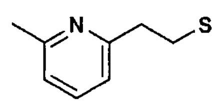
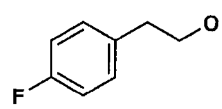


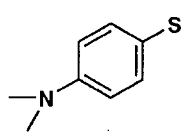
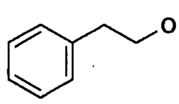
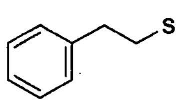
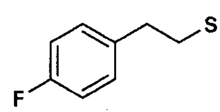
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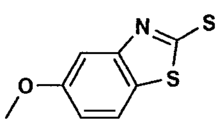
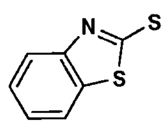
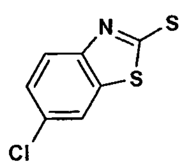
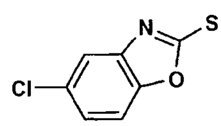
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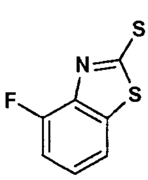
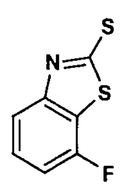
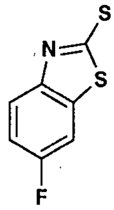
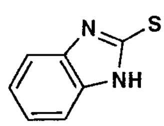
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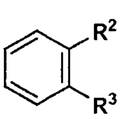
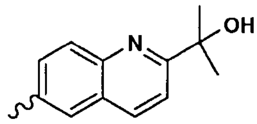
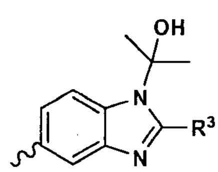
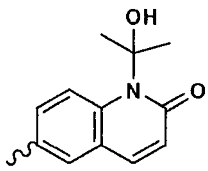
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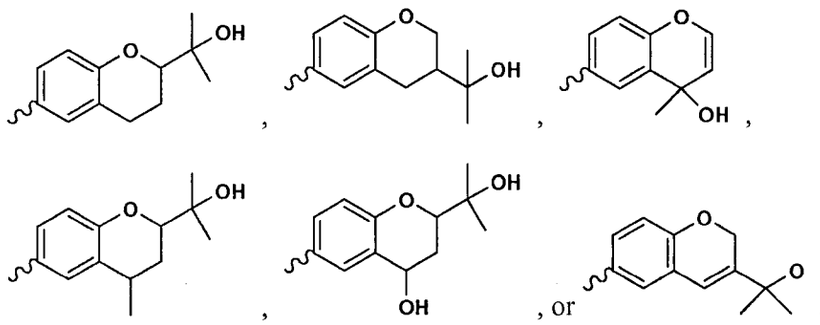
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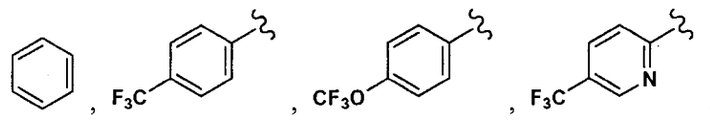
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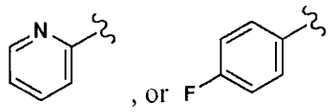


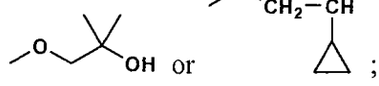
15. The compound as defined in Claim 7 wherein

X is S;

Y is a bond or $(CH_2)_2$;

Z is 



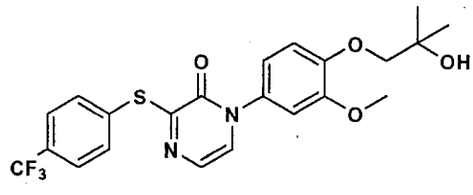
E-G-J is 

R^3 is CH_3O or CH_3;

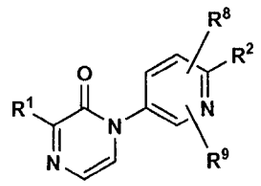
R^8 is H; and

R^9 is H.

16. The compound as defined in Claim 1 having the following formula:



18. A compound of Formula IB or a pharmaceutically acceptable salt thereof having the structure



IB

19. The compound as defined in Claim 18 wherein

R^1 is Z-Y-X- wherein

X is S,

Y is an alkyl chain of 1 to 3 carbons or a bond,

Z is heteroaryl or phenyl,

each of which Z is optionally substituted with CF_3, CF_3O, or halo;

R^2 is -E-G-J wherein

E is O,

G is lower alkyl or alkylcycloalkyl, and

J is OH;

R^3 is alkoxy, alkyl or halo;

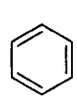
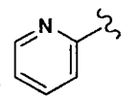
R^8 is H or alkyl; and

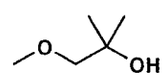
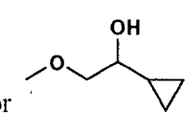
R^9 is H.

20. The compound as defined in Claim 18 wherein

X is S;

Y is a bond or $(CH_2)_2$;

Z is  or  ;

R^2 is E-G-J which is  or  ;

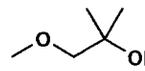
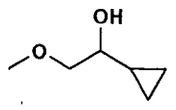
R^3 is H, Cl, CH_3, or CH_3O; and

R^8 and R^9 are each H.

21. The compound of Claim 1 wherein

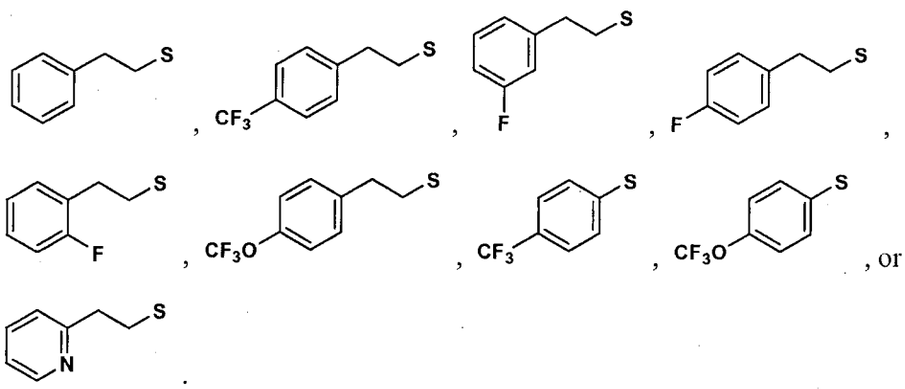


is a heteroaryl ring;

R^2 is  or  ;

R^3 is methoxy, Cl, H, or methyl; and

R^1 is selected from the group consisting of:



22. A pharmaceutical composition comprising a therapeutically effective amount of a compound as defined in Claim 1, alone or in combination with at least one additional therapeutic agent, in association with a pharmaceutically acceptable carrier or diluent.

23. A pharmaceutical combination comprising:
at least one compound according to Claim 1, and
at least one additional therapeutic agent.

24. The combination as defined in Claim 23 wherein the additional therapeutic agent is an acetyl-cholinesterase inhibitor, a muscarinic receptor-1 agonist, a nicotinic agonist, a glutamic acid receptor (AMPA and NMDA) modulator, a nootropic agent, an agent for Alzheimer's disease, an agent for treatment of Parkinson's disease, anti-hyperlipidemia agent, an anti-obesity agent; anti-diabetic agent, appetite suppressant; cholesterol/lipid-lowering agent, HDL-raising agent,

cognition enhancing agent, an agent used to treat neurodegeneration, an agent used to treat respiratory conditions, an agent used to treat bowel disorders, an anti-inflammatory agent; anti-anxiety agent; an anti-depressant; an anti-hypertensive agent; an anti-sleep disorder agent; a cardiac glycoside; or an anti-tumor agent.

25. The combination as defined in Claim 24 wherein the anti-obesity agent is a melanocortin receptor (MC4R) agonist, a cannabinoid receptor modulator, a growth hormone secretagogue receptor (GHSR) antagonist, a galanin receptor modulator, an orexin antagonist, a CCK agonist, a GLP-1 agonist, a Pre-proglucagon-derived peptides; an NPY1 or NPY5 antagonist, an NPY2 or NPY4 modulator, a corticotropin releasing factor agonist, a histamine receptor-3 (H3) modulator, an aP2 inhibitor, a PPAR gamma modulator, a PPAR delta modulator, an acetyl-CoA carboxylase (ACC) inhibitor, an 11-β-HSD-1 inhibitor, an adinopectin receptor modulator; a beta 3 adrenergic agonist, a thyroid receptor beta modulator, a lipase inhibitor, a serotonin receptor agonist, a monoamine reuptake inhibitor or releasing agent, an anorectic agent, a CNTF (ciliary neurotrophic factor), a BDNF (brain-derived neurotrophic factor), a leptin and leptin receptor modulator, or a cannabinoid-1 receptor antagonist, and the antidiabetic agent is an insulin secretagogue or insulin sensitizer, which is a biguanide, a sulfonyl urea, a glucosidase inhibitor, an aldose reductase inhibitor, a PPAR γ agonist, a PPAR α agonist, a PPAR δ antagonist or agonist, a PPAR α/γ dual agonist, an11-β-HSD-1 inhibitor, a dipeptidyl peptidase IV (DP4) inhibitor, a SGLT2 inhibitor, a glycogen phosphorylase inhibitor, a meglitinide, a glucagon-like peptide-1 (GLP-1), a GLP-1 agonist, and/or a PTP-1B inhibitor (protein tyrosine phosphatase-1B inhibitor), and wherein the additional therapeutic agent is an anti-hyperlipidemia agent, or agent used to treat arteriosclerosis, which is an HMG CoA reductase inhibitor, a squalene synthetase inhibitor, a fibric acid derivative, aspirin, a bile acid sequestrant, an ACAT inhibitor, an upregulator of LDL receptor activity, a cholesterol absorption inhibitor, a cholesteryl transfer protein (CETP) inhibitor, an ileal Na+/bile acid cotransporter inhibitor, a phytoestrogen, a beta-lactam cholesterol absorption inhibitor, an HDL upregulator, a PPAR α-agonist and/or an FXR agonist; an LDL catabolism promoter such, a sodium-proton exchange inhibitor, an LDL-receptor inducer or a steroidal

glycoside, an anti-oxidant, or an antihomocysteine agent, isoniazid, an HMG-CoA synthase inhibitor, or a lanosterol demethylase inhibitor, a PPAR δ agonist, or a sterol regulating element binding protein-I (SREBP-1), and the anti-hypertensive agent, which is a beta adrenergic blocker, a calcium channel blocker (L-type and/or T-type), a diuretic, a renin inhibitor, an ACE inhibitor, an AT-1 receptor antagonist, an ET receptor antagonist, a Dual ET/AII antagonist, a neutral endopeptidase (NEP) inhibitor, a vasopeptidase inhibitor (dual NEP-ACE inhibitor) or a nitrate; the sleep disorder agent is a melatonin analog, a melatonin receptor antagonist, an ML 1 B agonist, a GABA receptor modulator, an NMDA receptor modulator, a histamine-3 (H3) receptor modulator, a dopamine agonist or an orexin receptor modulator; an agent for treating substance abuse or, addictive disorders which is a cannabinoid receptor modulator, a selective serotonin reuptake inhibitor (SSRI), methadone, buprenorphine, nicotine or bupropion; the anti-anxiety agents or antidepressants, which is a benzodiazepine, a 5HT1A receptor agonist, or a corticotropin releasing factor (CRF) antagonist; or a norepinephrine reuptake inhibitor (tertiary and secondary amine tricyclics), a selective serotonin reuptake inhibitor (SSRI), a monoamine oxidase inhibitor (MAOI), a reversible inhibitor of monoamine oxidase (RIMA), a serotonin and norepinephrine reuptake inhibitor (SNRI), a corticotropin releasing factor (CRF) receptor antagonist, an alpha-adrenoreceptor antagonist, or an atypical antidepressant.

26. A method for treating obesity, diabetes, arteriosclerosis, hypertension, polycystic ovary disease, cardiovascular disease, osteoarthritis, dermatological disorders, impaired glucose hemostasis, insulin resistance, hypercholesterolemia, hypertriglyceridemia, choletithiasis, dyslipidemia, bulimia nervosa and compulsive eating disorders; sleep disorders; and psychiatric disorders, depression, anxiety, schizophrenia, substance abuse, cognition-enhancement or Parkinson's disease, which comprises administering to a patient in need of treatment, a compound as defined in Claim 1.

27. The method as defined in Claim 26 for treating obesity or Type II diabetes.

28. A method of treating Type II diabetes, which comprises administering to a patient in need of treatment a compound as defined in Claim 1.

29. Use of a compound as defined in Claim 1 in the manufacture of a medicament for the treatment of diabetes.

30. Use of a compound as defined in Claim 1 in the manufacture of a medicament for treatment of diabetes, in which such treatment comprises a combination with another therapeutic agent, for concurrent or sequential use, in any order.

31. Combination of a compound as defined in Claim 1 and another therapeutic agent as a medicament for the treatment of diabetes.

ANTAGONISTAS NO BÁSICOS DEL RECEPTOR DE LA HORMONA CONCENTRADORA DE MELANINA 1 Y PROCEDIMIENTOS

CAMPO DE LA INVENCIÓN

La presente invención se refiere a nuevos antagonistas no básicos del receptor de la hormona concentradora de melanina 1 (MCHR1), a composiciones farmacéuticas que contienen antagonistas del MCHR1 y a procedimientos para tratar la diabetes, la obesidad y enfermedades relacionadas que emplean dichos antagonistas del MCHR1.

ANTECEDENTES DE LA INVENCIÓN

Varias líneas de pruebas farmacológicas y genéticas confirman el papel del receptor de la hormona concentradora de melanina 1 (en lo sucesivo, "MCHR1") como un modulador de la ingesta de alimentos y del peso corporal. La administración central de la hormona concentradora de melanina (MCH) aumenta la ingesta de alimentos y el peso corporal tanto en ratas como en ratones. La infusión ICV crónica de MCH provoca una ingesta de alimentos aumentada y, en última instancia, obesidad en ratones, mientras que la infusión de un antagonista peptídico de MCH bloquea la ingesta de alimentos inducida por MCH y da como resultado una pérdida de peso y una alimentación disminuida en ratones obesos inducidos por la dieta.

La expresión tanto del péptido como del receptor de MCH está modulada por el estado nutricional. El ARNm de MCH está regulado positivamente tanto en el ratones obesos hiperfágicos (ob/ob) como en animales en ayunas. La interrupción dirigida del gen para el péptido

MCH da como resultado hipofagia y delgadez. La alteración del gen de MCHR1 causa delgadez, metabolismo alterado e hiperlocomoción acompañada de una hiperfagia moderada. Por el contrario, la sobreexpresión del péptido MCH da cómo resultado hiperfagia, obesidad y diabetes. Se ha demostrado que pequeñas moléculas antagonistas de MCHR1 provocan una pérdida de peso en modelos roedores de peso y alimentación después de la administración tanto por vía oral como intraperitoneal; Eur. J. Pharmacol., 438: 129-135, (2002), *Nat. Med.,* 8: 825-830 (2002), *Eur. J. Pharmacol.,* 497: 41-47 (2004).

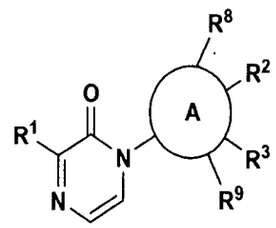
Se han descrito numerosos antagonistas no peptídicos de MCHR1. El alcance del género para cada uno refleja una percepción común con respecto a los criterios necesarios para el reconocimiento de ligandos como agonistas de MCHR1. Una recapitulación reciente de descripciones de patentes de MCHR1 enfatizaba las características en común entre estas estructuras mediante la descripción siguiente; "Por toda la bibliografía de patentes de MCH se encuentran moléculas que consisten en un armazón central al que están unidos engarces a un grupo arilo o heteroarilo y una funcionalidad amino básica" (Kowalski, T. J. *Expert Opin. Investig. Drugs* 13: 1113-1122 (2004)). Los modelos de farmacóforos de estos géneros prevén sistemáticamente una interacción electrostática como supuesto requisito indispensable entre un centro amino básico del ligando antagonista y el ácido aspártico 123 del receptor, que presumiblemnte está previsto para emular la interacción obligatoria entre la arginina 14 de los agonistas peptídicos de MCH con el ácido aspártico 123 del receptor MCHR1. (Ulven T., *J. Med. Chem.*

2005: 48, 5684-5697 (2005)). Sin embargo, la incorporación de esta amina básica en un antagonista de MCHR1 aumenta sustancialmente la probabilidad de unión a canales iónicos ajenos a la diana y receptores de aminas biógenas.

De acuerdo con la presente invención, se proporciona una serie de nuevos antagonistas selectivos de MCHR1 de gran afinidad para los que la afinidad de unión no depende de la inclusión de una funcionalidad amina básica que es común a la mayoría de los antagonistas de MCHR descritos. Como consecuencia, la ausencia de centro básico reduce enormemente la probabilidad de interacciones ajenas a la diana, tal como la unión a otros receptores de aminas biógenas, así como la unión a canales iónicos tales como el receptor de HERG en el corazón. La reducción o supresión de la afinidad por el receptor de HERG es especialmente importante puesto que la ocupación de ligando está asociada con el inicio de arritmias mortales.

SUMARIO DE LA INVENCIÓN

En una realización de la presente invención invención se proporciona un compuesto de la Fórmula I, o una sal farmacéuticamente aceptable del mismo:

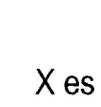
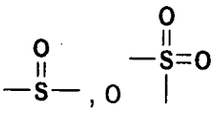


I

en la que

(A) es un anillo fenileno o un anillo heteroarilo que es un anillo monocíclico o un anillo bicíclico que contiene uno o dos átomos de nitrógeno o un átomo de oxígeno;

R^1 es Z-Y-X-, donde

X es O, S,  , o  ;

Y es un enlace, un cicloalquilo de 3 a 6 miembros o una cadena alquilo; y

Z es arilo tal como fenilo y naftilo, o heteroarilo tal como piridinilo, piridimidinilo, pirazinilo, bencimidazolilo, benzotiazolilo, benzoxazolilo, u otro "heteroarilo";

R^2 es -E-G-$(J)_m$, donde m es un número entero de 1 a 3;

E es O, S o un enlace;

G es alquilo inferior, fenilalquilo, cicloalquilo, cicloalquilalquilo, alquilcicloalquilo, cicloalcoxi, alquilcicloalcoxi o cicloalcoxialquilo;

cada J es independientemente hidrógeno, hidroxilo, CN, $-SO_2R^7$, $-SR^7$, $-SOR^7$, alquilo inferior, alcoxi inferior, CF_3, CF_3O-, $-COOR^5$ (donde R^5 es H, alquilo C_{1-3} o cicloalquilo), o $-CO-NR^{5a}R^6$ donde cada uno de R^{5a} y R^6 se selecciona independientemente entre H, alquilo C_{1-3} o cicloalquilo, o R^{5a} y R^6 tomados juntos pueden ser propanodiilo, butanodiilo o pentanodiilo para formar con el átomo de N al que están unidos una amina cíclica de 4, 5 ó 6 miembros, tal como azetidinilo, pirrolidinilo, piperidinilo, morfolinilo o piperazinilo, opcionalmente sustituido con sustituyentes como los indicados para "heterociclo";

R^7 es alquilo inferior;

R^3 es alquilo C_{1-6}, cicloalquilo, alcoxi C_{1-6}, halógeno, hidrógeno, -S-alquilo C_{1-6}, CN, CF_3O o CF_3;

y donde R^2 y R^3 pueden tomarse juntos para formar un anillo de 5 a 7 miembros que está saturado, insaturado o parcialmente insaturado y puede incluir un heteroátomo E, que es O, o 0, 1 ó 2 átomos de N, donde el anillo está sustituido con uno o dos de los grupos $-O-G-(J)_m$, donde al menos un J es OH, y opcionalmente otros sustituyentes como los indicados para "alquilo", "arilo" o "heteroarilo", tal como alquilo y/o OH;

con la condición de que cuando (A) es un anillo fenileno, E-G y R^3 no sean grupos alcoxi inferior sin sustituir iguales, y cuando G es alquilo inferior y J es H, R^3 no sea hidrógeno; y

cada uno de R^8 y R^9 es independientemente hidrógeno, halógeno o alquilo inferior;

incluyendo ésteres de los mismos, profármacos de los mismos, solvatos de los mismos y todos los estereoisómeros de los mismos.

Cualquiera de los restos Z anteriores puede estar sin sustituir o sustituido con 1, 2 ó 3 de amino, halo, alquilo C_{1-6}, alquilamino C_{1-3}, di-alquilamino C_{1-3}, alcoxi C_{1-3}, tioalquilo C_{1-3}, trifluoroalcoxi C_{1-3}, trifluorometilo, cicloalquilo, cicloalcoxi o heteroarilo tal como piridilo o sustituido con cualquiera de los sustituyentes indicados para "arilo", "heteroarilo" o "alquilo".

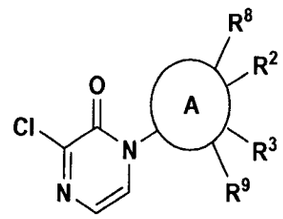
Los ejemplos de sustituyentes para el grupo J como una amina cíclica incluyen, pero sin limitación, alquilo inferior, alcoxi inferior, OH, CF_3 o CF_3O, u otros sustituyentes como los indicados para "alquilo" y "heteroarilo".

En un aspecto más de la invención, se proporciona una composición

farmacéutica que contiene una cantidad terapéuticamente eficaz del compuesto de Fórmula I de la invención como se ha definido anteriormente, junto con un vehículo o diluyente farmacéuticamente aceptable.

También se proporciona un procedimiento para el tratamiento de la diabetes, la obesidad y otras afecciones relacionadas que implican el MCHR1 en un mamífero (tal como un ser humano, perro o gato) que lo necesita, que incluye las etapas de administrar al mamífero una cantidad terapéuticamente eficaz del compuesto de Fórmula I de la invención como se ha definido anteriormente.

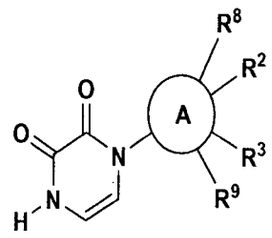
La invención también se refiere a uno o más procedimientos para preparar el compuesto de Fórmula I de la invención. En una realización, se proporciona un procedimiento para la preparación del compuesto de Fórmula I de la invención, en el que el compuesto **a**



a

se hace reaccionar con la sal de metal alcalino de Z-Y-X^1H (**b**) (X^1 = O o S), preferiblemente Z-$(CH_2)_n$-X^1H (n = 0, 1, 2 ó 3).

En otra realización de la invención, se proporciona un procedimiento para la preparación del compuesto de Fórmula I de la invención, en el que el compuesto **c**



c

se hace reaccionar con Z-Y-X^1H, preferiblemente Z-$(CH_2)_n$-X^1H (n = 0, 1, 2 ó 3) y preferiblemente en presencia de un agente de activación.

La presente invención se refiere a estos, así como a otros fines importantes, que se describirán en lo sucesivo en la presente memoria.

DESCRIPCIÓN DETALLADA DE LA INVENCIÓN

La presente solicitud proporciona compuestos, incluyendo todos los estereoisómeros, solvatos, profármacos y formas farmacéuticamente aceptables de los mismos de acuerdo con la Fórmula I. Además, la presente solicitud proporciona composiciones farmacéuticas que contienen al menos un compuesto de acuerdo con la Fórmula I de la invención solo y opcionalmente al menos un agente terapéutico adicional. Finalmente, la presente solicitud proporciona procedimientos para tratar a un paciente que padece una enfermedad o trastorno modulado por MCHR-1 tal como, por ejemplo, obesidad, diabetes, depresión o ansiedad mediante la administración de una dosis terapéuticamente eficaz de un compuesto de acuerdo con la Fórmula I.

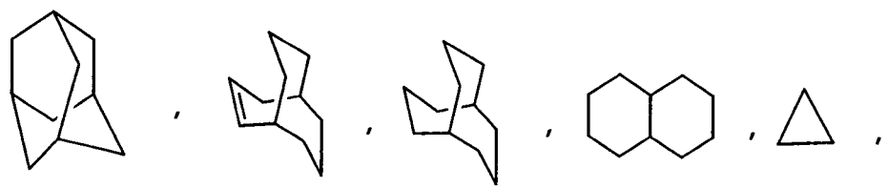
Definiciones

A menos que se indique otra cosa, el término "alquilo inferior", como puede emplearse en la presente memoria, solo o como parte de otro

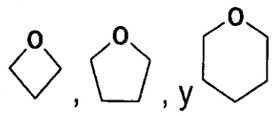
grupo, incluye hidrocarburos de cadena lineal y ramificada que contienen de 1 a 8 carbonos, y los términos “alquilo", “alq”, "cadena alquilo", "alquileno" o "cadena alquileno" como pueden emplearse en la presente memoria, solos o como parte de otro grupo, incluyen hidrocarburos de cadena lineal y ramificada que contienen de 1 a 20 carbonos, preferiblemente de 1 a 10 carbonos, más preferiblemente de 1 a 8 carbonos, en la cadena normal, tal como metilo, etilo, propilo, isopropilo, butilo, *t*-butilo, isobutilo, pentilo, hexilo, isohexilo, heptilo, 4,4-dimetilpentilo, octilo, 2,2,4-trimetilpentilo, nonilo, decilo, undecilo, dodecilo, los diversos isómeros de cadena ramificada de los mismos y similares, así como dichos grupos que incluyen 2 enlaces libres y por lo tanto son grupos de unión, concretamente "alquileno", así como dichos grupos que incluyen de 1 a 4 sustituyentes, tales como halo, por ejemplo F, Br, Cl, I o CF_3, alquilo, alcoxi, arilo, ariloxi, aril(arilo) o diarilo, arilalquilo, arilalquiloxi, alquenilo, alquinilo, cicloalquilo, cicloalquenilo, cicloalquilalquilo, cicloalquilalquiloxi, hidroxi, hidroxialquilo, acilo, alcanoílo, heteroarilo, heteroariloxi, cicloheteroalquilo, arilheteroarilo, arilalcoxicarbonilo, heteroarilalquilo, heteroarilalcoxi, ariloxialquilo, ariloxiarilo, alquilamido, alcanoilamino, arilcarbonilamino, nitro, ciano, tiol, haloalquilo, trihaloalquilo y/o alquiltio.

A menos que se indique otra cosa, el término “cicloalquilo" o "cicloalquilo inferior" como puede emplearse en la presente memoria, solo o como parte de otro grupo, incluye grupos de hidrocarburo cíclicos, saturados o parcialmente insaturados (que contienen 1 ó 2 dobles enlaces), que contienen de 1 a 3 anillos, pudiendo ser cualquiera de ellos

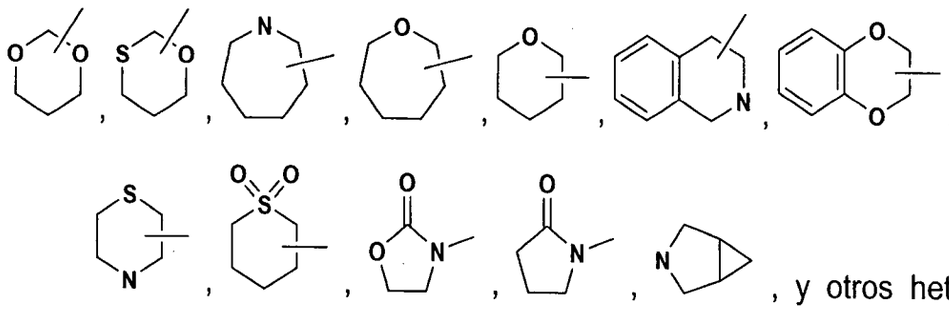
opcionalmente un cicloalquilo espiro sustituido, incluyendo monocicloalquilo, bicicloalquilo y tricicloalquilo, que contienen un total de 3 a 20 carbonos formando los anillos, preferiblemente de 3 a 10 carbonos, formando el anillo y que pueden estar condensados con 1 ó 2 anillos aromáticos como se describe para arilo, incluyendo ciclopropilo, ciclobutilo, ciclopentilo, ciclohexilo, cicloheptilo, ciclooctilo, ciclodecilo y ciclododecilo, ciclohexenilo,



así como dichos grupos que incluyen 2 enlaces libres y por lo tanto son grupos de unión, donde cualquiera de los grupos puede estar opcionalmente sustituido con 1 a 4 sustituyentes, tales como halógeno, alquilo, alcoxi, hidroxi, arilo, ariloxi, arilalquilo, cicloalquilo, alquilamido, alcanoilamino, oxo, acilo, arilcarbonilamino, nitro, ciano, tiol y/o alquiltio y/o cualquiera de los sustituyentes indicados para "alquilo".

A menos que se indique otra cosa, el término "cicloalcoxi" o "cicloalcoxi inferior" como se emplea en la presente memoria, solo o como parte de otro grupo, representa un anillo saturado de 4, 5 ó 6 miembros que contiene un oxígeno en el anillo e incluye  , así como dichos grupos que incluyen 2 enlaces libres y por lo tanto son grupos de unión, y que puede estar opcionalmente sustituido con 1 o dos de cualquiera de los sustituyentes que se han indicado para cicloalquilo.

El término "heterociclo", "heterociclo", "heterociclilo", "heterocíclico" o anillo "cicloheteroalquilo", como puede usarse en la presente memoria, representa un sistema de anillos monocíclicos, de 4 a 7 miembros, estable, sin sustituir o sustituido, que puede estar saturado o insaturado, preferiblemente saturado o parcialmente insaturado, y que consta de átomos de carbono, con uno a cuatro heteroátomos seleccionados entre nitrógeno, oxígeno o azufre, y donde los heteroátomos de nitrógeno y azufre pueden estar opcionalmente oxidados, y el heteroátomo de nitrógeno puede estar opcionalmente cuaternizado, e incluyendo cualquier grupo bicíclico en el que el anillo heterocíclico está condensado con un anillo de benceno. El anillo heterocíclico puede estar unido a cualquier heteroátomo o átomo de carbono que dé como resultado la creación de una estructura estable. Los ejemplos de tales grupos heterocíclicos incluyen, pero sin limitación, piperidinilo, piperazinilo, oxopiperazinilo, oxopiperidinilo, oxopirrolidinilo, oxoazepinilo, azepinilo, pirrolilo, pirrolidinilo, furanilo, tienilo, pirazolilo, pirazolidinilo, imidazolilo, imidazolinilo, imidazolidinilo, piridilo, pirazinilo, pirimidinilo, piridazinilo, oxazolilo, oxazolidinilo, isooxazolilo, isoxazolidinilo, morfolinilo, tiazolilo, tiazolidinilo, isotiazolilo, tiadiazolilo, tetrahidropiranilo, tiamorfolinilo, tiamorfolinil sulfóxido, tiamorfolinil sulfona, oxadiazolilo,



, y otros heterociclos descritos en Katritzky, A. R. y col., eds., *Comprehensive Heterociclic*

Chemistry: The Structure, Reactions, Synthesis and Uses of Heterociclic Compounds, Pergamon Press, Nueva York, NY, publ. (1984); y Katritzky, A. R. y col., eds., *Comprehensive Heterociclic Chemistry II: A Review of the Literature 1982-1995*, Elsevier Science, Inc., Tarrytown, NY, publ. (1996); y referencias citadas en estos documentos, así como dichos grupos que incluyen 2 enlaces libres y por lo tanto son grupos de unió, así como dichos grupos opcionalmente sustituidos con 1 a 3 de F, Br, Cl o I o CF_3, alquilo, alcoxi, arilo, ariloxi, aril(arilo) o diarilo, arilalquilo, arilalquiloxi, alquenilo, alquinilo, cicloalquilo, cicloalquenilo, cicloalquilalquilo, cicloalquilalquiloxi, hidroxi, hidroxialquilo, acilo, alcanoílo, heteroarilo, heteroariloxi, cicloheteroalquilo, arilheteroarilo, arilalcoxicarbonilo, heteroarilalquilo, heteroarilalcoxi, ariloxialquilo, ariloxiarilo, alquilamido, alcanoilamino, arilcarbonilamino, nitro, ciano, tiol, haloalquilo, trihaloalquilo y/o alquiltio.

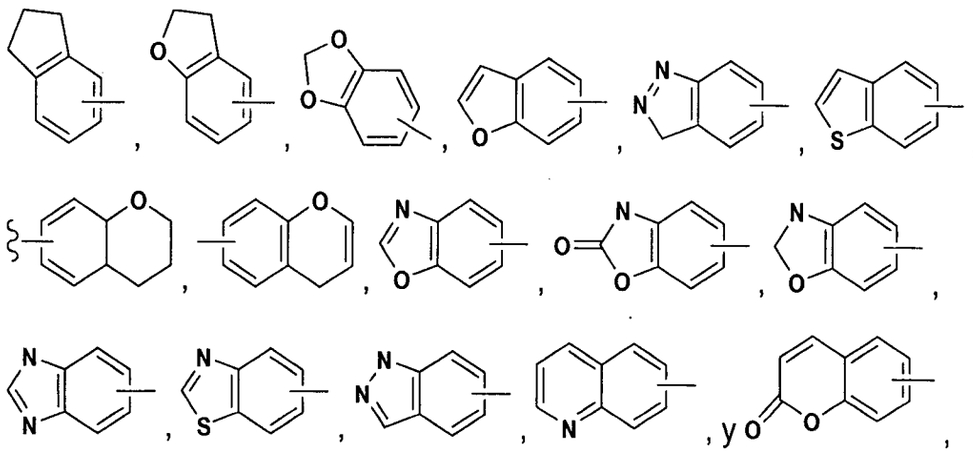
El término "alcanoílo", como puede usarse en la presente memoria, solo o como parte de otro grupo, se refiere a alquilo unido a un grupo carbonilo.

El término "halógeno" o "halo", como puede usarse en la presente memoria, solo o como parte de otro grupo, se refiere a cloro, bromo, flúor y yodo, preferiblemente cloro o flúor.

El término "ión metálico" se refiere a iones de metales alcalinos tales como sodio, potasio o litio, y a iones de metales alcalinotérreos, tales como magnesio y calcio, así como cinc y aluminio.

A menos que se indique otra cosa, el término "arilo" o "aril", como puede emplearse en la presente memoria, solo o como parte de otro grupo, se refiere

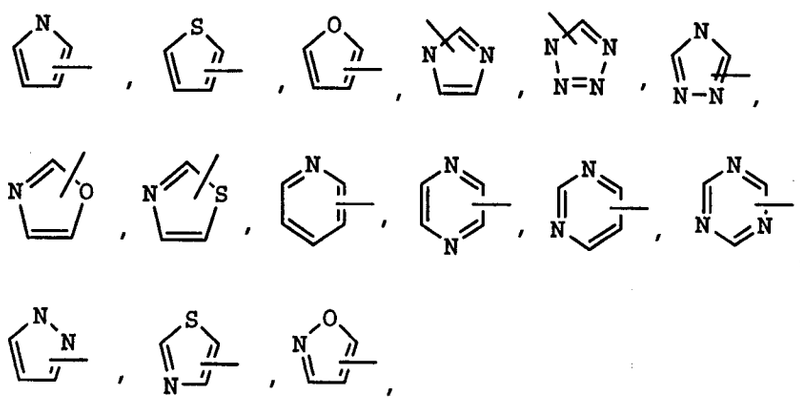
a grupos aromáticos, monocíclicos y bicíclicos, que contienen de 6 a 10 carbonos en la porción del anillo (tal como fenilo o naftilo, incluyendo l-naftilo y 2-naftilo) y pueden incluir opcionalmente de uno a tres anillos adicionales condensados con un anillo carbocíclico o un anillo heterocíclico (tal como anillos arilo, cicloalquilo, heteroarilo o cicloheteroalquilo), por ejemplo

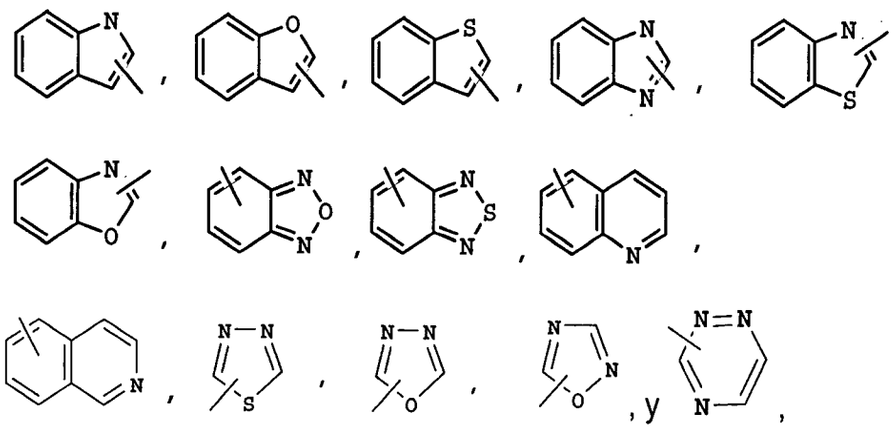


y así como dichos grupos que incluyen 2 enlaces libres y por lo tanto son grupos de unión, y pueden estar opcionalmente sustituidos a través de átomos de carbono disponibles con 1, 2 ó 3 grupos seleccionados entre hidrógeno, halo, haloalquilo, alquilo, haloalquilo, alcoxi, haloalcoxi, alquenilo, trifluorometilo, trifluorometoxi, alquinilo, cicloalquil-alquilo, cicloheteroalquilo, cicloheteroalquilalquilo, arilo, heteroarilo, arilalquilo, ariloxi, ariloxialquilo, arilalcoxi, alcoxicarbonilo, arilcarbonilo, arilalquenilo, aminocarbonilarilo, ariltio, arilsulfinilo, arilazo, heteroarilalquilo, heteroarilalquenilo, heteroarilheteroarilo, heteroariloxi, hidroxi, nitro, ciano, tiol, alquiltio, ariltio, heteroariltio, ariltioalquilo, alcoxiariltio, alquilcarbonilo, arilcarbonilo, alquilaminocarbonilo, arilaminocarbonilo, alcoxicarbonilo, aminocarbonilo, alquilcarboniloxi, arilcarboniloxi, alquilcarbonilamino, arilcarbonilamino, arilsulfinilo,

arilsulfinilalquilo, arilsulfonilamino y arilsulfonaminocarbonilo y/o cualquiera de los sustituyentes indicados para alquilo en la presente memoria.

A menos que se indique otra cosa, el término "heteroarilo", como puede usarse en la presente memoria, solo o como parte de otro grupo, se refiere a un anillo aromático de 5 ó 6 miembros, que incluye 1, 2, 3 ó 4 heteroátomos, tales como nitrógeno, oxígeno o azufre. Dichos anillos pueden estar condensados con un arilo, cicloalquilo, heteroarilo o heterociclilo e incluyen posibles N-óxidos, como se describe en Katritzky, A. R. y col., eds. *Comprehensive Heterociclic Chemistry: The Structure, Reactions, Synthesis and Uses of Heterociclic Compounds*, Pergamon Press, Nueva York, NY, publ. (1984); y Katritzky, A. R., y col., eds. *Comprehensive Heterociclic Chemistry II: A Review of the Literature 1982-1995*, Elsevier Science, Inc., Tarrytown, NY, publ. (1996); y referencias citadas en estos documentos, así como dichos grupos que incluyen 2 enlaces libres y por lo tanto son grupos de unión. Además, "heteroarilo", como se define en la presente memoria, puede estar opcionalmente sustituido con uno o más sustituyentes, tales como los sustituyentes incluidos anteriormente para "alquilo" y/o "arilo". Los ejemplos de grupos heteroarilo incluyen los siguientes:





y similares.

A menos que se indique otra cosa, el término "alcoxi inferior", "alcoxi", "ariloxi" o "aralcoxi", como puede emplearse en la presente memoria, solo o como parte de otro grupo, incluye cualquiera de los grupos alquilo, aralquilo o arilo anteriores, unido a un átomo de oxígeno.

A menos que se indique otra cosa, el término "alquiltio inferior", alquiltio", "ariltio" o "aralquiltio", como puede emplearse en la presente memoria, solo o como parte de otro grupo, incluye cualquiera de los grupos alquilo, aralquilo o arilo anteriores, unido a un átomo de azufre.

El término "polihaloalquilo", como puede usarse en la presente memoria, se refiere a un grupo "alquilo", como se ha definido anteriormente, que incluye de 2 a 9, preferiblemente de 2 a 5, sustituyentes halo, tales como F o Cl, preferiblemente F, tal como CF_3CH_2, CF_3 o $CF_3CF_2CH_2$.

El término "polihaloalquiloxi", como puede usarse en la presente memoria, se refiere a un grupo "alcoxi" o "alquiloxi", como se ha definido anteriormente, que incluye de 2 a 9, preferiblemente de 2 a 5, sustituyentes halo, tales como F o Cl, preferiblemente F, tal como CF_3CH_2O, CF_3O o $CF_3CF_2CH_2O$.

A menos que se indique otra cosa, el término "alcoxi inferior", "alcoxi", "ariloxi" o "aralcoxi" como puede emplearse en la presente memoria, solo o como parte de otro grupo, incluye cualquiera de los grupos alquilo, aralquilo o arilo anteriores unido a un átomo de oxígeno.

A menos que se indique otra cosa, el término "alquiltio inferior", alquiltio", "ariltio" o "aralquiltio" como puede emplearse en la presente memoria, solo o como parte de otro grupo, incluye cualquiera de los grupos alquilo, aralquilo o arilo anteriores unido a un átomo de azufre.

El término "polihaloalquilo", como puede usarse en la presente memoria, se refiere a un grupo "alquilo", como se ha definido anteriormente que incluye de 2 a 9, preferiblemente de 2 a 5, sustituyentes halo, tales como F o Cl, preferiblemente F, tales como CF_3CH_2, CF_3 o $CF_3CF_2CH_2$.

El término "polihaloalquiloxi", como puede usarse en la presente memoria, se refiere a un grupo "alcoxi" o "alquiloxi", como se ha definido anteriormente que incluye de 2 a 9, preferiblemente de 2 a 5, sustituyentes halo, tales como F o Cl, preferiblemente F, tales como CF_3CH_2O, CF_3O o $CF_3CF_2CH_2O$.

A menos que se indique otra cosa, el término "alquenilo", como se usa en la presente memoria, solo o como parte de otro grupo, se refiere a radicales de cadena lineal o ramificada de 2 a 20 carbonos, preferiblemente de 2 a 12 carbonos, y más preferiblemente de 1 a 8 carbonos en la cadena normal, que incluyen de uno a seis dobles enlaces en la cadena normal, tales como vinilo, 2-propenilo, 3-butenilo, 2-butenilo, 4-pentenilo, 3-pentenilo, 2-hexenilo, 3-hexenilo, 2-heptenilo, 3-heptenilo, 4-heptenilo, 3-octenilo, 3-nonenilo, 4-decenilo, 3-undecenilo, 4-dodecenilo, 4,8,12-tetradecatrienilo y similares.

Opcionalmente, dicho grupo alquenilo puede estar sustituido con uno o sustituyentes, tales como los sustituyentes descritos para alquilo.

A menos que se indique otra cosa, el término "alquinilo", como se usa en la presente memoria, solo o como parte de otro grupo, se refiere a radicales de cadena lineal o ramificada de 2 a 20 carbonos, preferiblemente de 2 a 12 carbonos y más preferiblemente de 2 a 8 carbonos en la cadena normal, que incluyen un triple enlace en la cadena normal, tales como 2-propinilo, 3-butinilo, 2-butinilo, 4-pentinilo, 3-pentinilo, 2-hexinilo, 3-hexinilo, 2-heptinilo, 3-heptinilo, 4-heptinilo, 3-octinilo, 3-noninilo, 4-decinilo,3-undecinilo, 4-dodecinilo y similares. Opcionalmente, dicho grupo alquinilo puede estar sustituido con uno o sustituyentes, tales como los sustituyentes descritos para alquilo.

El término "cicloalquenilo", como se emplea en la presente memoria, solo o como parte de otro grupo, se refiere a hidrocarburos cíclicos parcialmente insaturados que contienen de 3 a 12 carbonos, preferiblemente de 5 a 10 carbonos y 1 ó 2 dobles enlaces. Los grupos cicloalquenilo ejemplares incluyen ciclobutenilo, ciclopentenilo, ciclohexenilo, cicloheptenilo, ciclooctenilo, ciclohexadienilo y cicloheptadienilo. Opcionalmente, dicho grupo cicloalquenilo puede estar sustituido con uno o sustituyentes, tales como los sustituyentes descritos para alquilo.

El término "biciclоalquilo", como se emplea en la presente memoria, solo o como parte de otro grupo, incluye grupos de anillo bicíclico saturado tales como, pero sin limitación, [3.3.0]biciclooctano, [4.3.0]biciclononano, [4.4.0]biciclodecano (decalina), [2.2.2]biciclooctano, y así sucesivamente.

El término "policicloalquilo", como se emplea en la presente memoria, solo o como parte de otro grupo, incluye dos o más sistemas de anillos

cicloalquilo, como se han definido en la presente memoria, donde al menos un átomo de carbono es una parte de al menos dos sistemas de anillo identificables por separado. El grupo policicloalquilo puede contener una unión entre dos átomos de carbono, por ejemplo, biciclo[1.1.0]butilo, biciclo[3.2.1]octilo, biciclo[5.2.0]nonilo, triciclo[2.2.1,0^1]heptilo, norbornilo y pinanilo. El grupo policicloalquilo puede contener uno o más sistemas de anillos condensados, por ejemplo, decalinilo (radical de decalina) y perhidroantracenilo. El grupo policicloalquilo puede contener una unión espiro, donde un solo átomo es el único miembro común de dos anillos, por ejemplo, espiro[3.4]octilo, espiro[3.3]heptilo y espiro[4.5]decilo.

El término "acilo", como se emplea en la presente memoria, por sí mismo o como parte de otro grupo, como se ha definido en la presente memoria, se refiere a un radical orgánico unido a un grupo carbonilo $\left(\begin{matrix}O\\ \|\\ C\end{matrix}\right)$; los ejemplos de grupos acilo incluyen un grupo sustituyente unido a un carbonilo, tal como alcanoílo, alquenoílo, aroílo, aralcanoílo, heteroarilo, cicloalcanoílo, cicloheteroalcanoilo y similares.

"Opcional" u "opcionalmente" significa que el evento o circunstancia descrita posteriormente puede producirse o no, y que la descripción incluye, pero sin limitación, casos en los que dicho evento o circunstancia se produce y casos en los que no. Por ejemplo, alquilo opcionalmente sustituido significa que el alquilo puede estar o no estar sustituido con los grupos enumerados en la definición de alquilo sustituido.

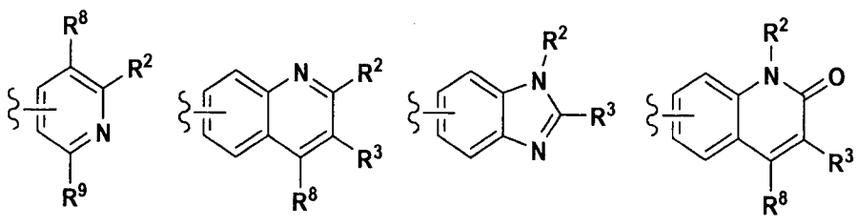
"Sustituido," como se usa en la presente memoria, de forma expresa o implicada y si está precedido por "opcionalmente" o no, significa que uno cualquiera o más hidrógenos del átomo designado (C, N, etc.) se reemplazan

por una selección del grupo indicado, con la condición de que no se supere la valencia normal del átomo designado, y que la sustitución dé como resultado un compuesto estable. Por ejemplo, cuando un CH_2 está sustituido con un sustituyente ceto (=O), entonces se reemplazan 2 hidrógenos del átomo. Las combinaciones de sustituyentes y/o variables se permiten únicamente si dichas combinaciones dan como resultado compuestos estables. Además, cuando más de una posición de una estructura dada puede estar sustituida con un sustituyente seleccionado entre un grupo especificado, los sustituyentes pueden ser iguales o diferentes en cada posición.

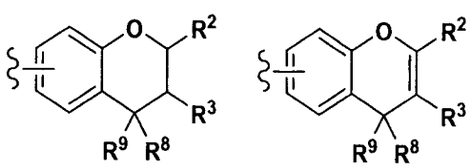
La designación " ∿ " o " ⌇— " unida a un anillo o a otro grupo se refiere a un enlace libre o grupo de unión.

REALIZACIONES ESPECÍFICAS

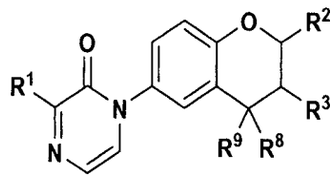
El grupo (A) puede ser un fenileno o un heteroarilo que es monocíclico o bicíclico e incluye anillos tales como



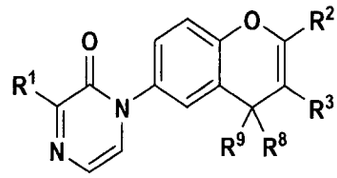
(piridinilo) , **(quinolinilo)** , **(bencimidazolilo)** , **(quinolin-2(1H)-ona)** ,



(cromanilo) o **(cromenilo)** , donde se prefieren fenileno y piridinilo.



IF , o



IG .

En el compuesto de Fórmula I de la invención, se desea que

(A) sea fenileno o piridinilo;

X sea O o S; y/o

Y sea un enlace o una cadena alquileno de 1, 2 ó 3 átomos; y/o

Z sea fenilo; o

Z sea un heteroarilo, tal como piridinilo o benzotiazol; y/o

R^2 sea E-G-J; y/o

E sea O o S; y/o

G sea un alquilo inferior o alquilcicloalquilo; y/o

J sea H, OH, SO_2R^7, alquilo inferior, alcoxi inferior o CF_3, más preferiblemente OH; y/o

R^3 sea alquilo C_{1-6}, alcoxi C_{1-6}, H o halo; y/o

R^8 y R^9 sean independientemente H o CH_3; y/o

donde R^2 y R^3 pueden tomarse juntos para formar un anillo de 5 a 7 miembros que está saturado, insaturado o parcialmente insaturado, y puede incluir un heteroátomo E, que es O, o 0, 1 ó 2 átomos de N,

donde el anillo está sustituido con uno o dos de los grupos -O-G-$(J)_m$, donde la menos un J es OH y opcionalmente otros sustituyentes como los indicados para "alquilo", "arilo" o "heteroarilo", tales como alquilo y/u OH.

Los grupos anteriores pueden estar sustituidos como se indica en la presente memoria.

Los ejemplos de los diversos grupos de los compuestos de Fórmula I de la invención se indican a continuación:

(A) es fenileno o piridinilo;

Z es

(1) arilo, tal como fenilo o naftilo, estando cada uno de ellos opcionalmente sustituido con:

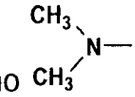
a) halógeno, tal como Cl, Br o F,

b) alquilo, tal como CH_3, C_2H_5 o *i*-C_3H_7,

c) alcoxi, tal como CH_3O,

d) polihaloalquilo, tal como CF_3,

e) polihaloalcoxi, tal como CF_3O,

f) amino, alquilamino o dialquilamino, tal como  ,

g) alquiltio, tal como CH_3S,

h) OH,

i) ésteres, tales como -$COOCH_3$, o

j) arilo, tal como fenilo,

(2) heteroarilo monocíclico, tal como

a) piridinilo,

b) pirazinilo, o

c) pirimidinilo,

estando cada uno de a), a) o c) opcionalmente sustituido con alquilo, tal como metilo, polihaloalquilo, tal como trifluorometilo, halógeno, tal como Cl o F, o alcoxi, tal como CH_3O;

(3) benzotiazol opcionalmente sustituido con halo, tal como F, Cl, alcoxi, tal como CH_3O,

(4) benzoxazol opcionalmente sustituido con halo, tal como Cl,

(5) bencimidazol,

(6) tiazol opcionalmente sustituido con arilo, tal como fenilo, y alquilo, tal como *t*-C_4H_9,

(7) indanilo,

(8) quinolinilo opcionalmente sustituido con CF_3, o

(9) imidazolidinilo; y/o

Y es un enlace o alquileno, tal como metileno, o etileno o propileno; y/o

X es S, O, SO o SO_2; y/o

J es

(1) H,

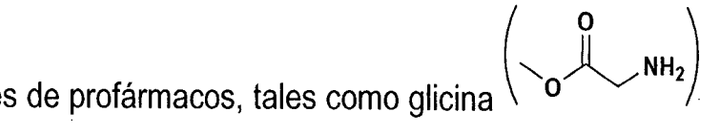
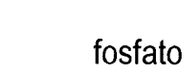
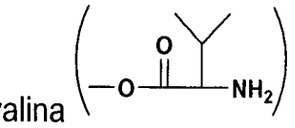
(2) -CO-$NR^{5a}R^6$ donde R^{5a} y R^6 junto con el N al que están unidos forman un anillo pirrolidinilo,

(3) OH,

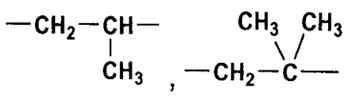
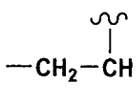
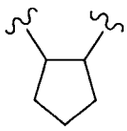
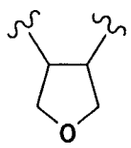
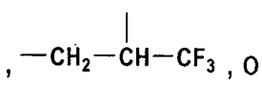
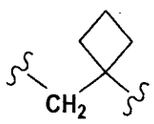
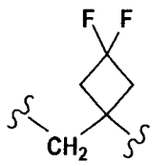
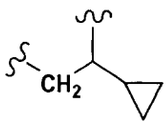
(4) COOH,

(5) COO-alquilo, tal como $COOCH_3$,

(6) SO_2R^7, tal como $SO_2C_2H_5$, o

(7) ésteres de profármacos, tales como glicina  ,
fosfato PO_4 ( y la sal de Na correspondiente de los mismos), y valina  ; y/o

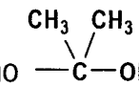
m es 1 ó 2; y/o

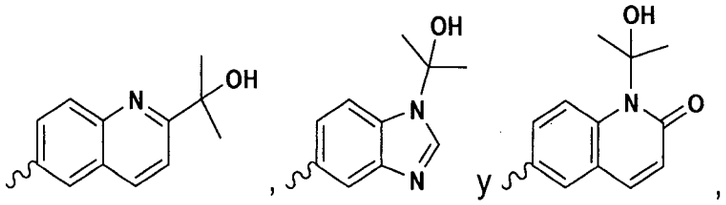
G es CH_2, $(CH_2)_2$, $(CH_2)_3$,  ,
 , cicloalquilo, tal como  , cicloalcoxi, tal como
 ,  , o alquilcicloalquilo, tal como  ,
 y  ; y/o

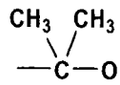
E es O; y/o

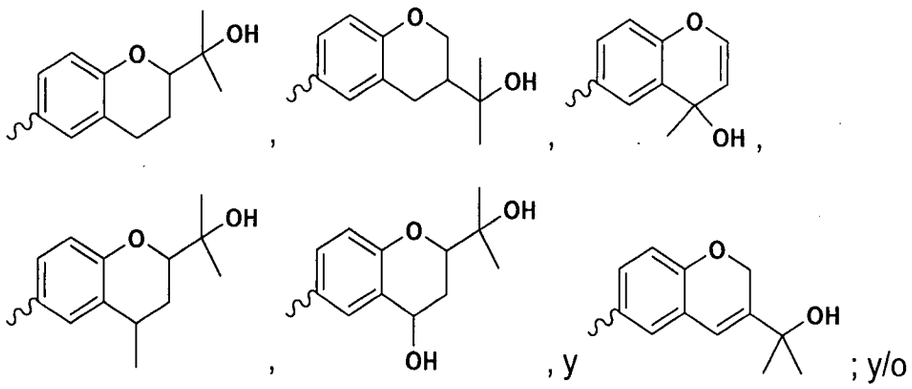
R^3 es H, alcoxi, tal como CH_3O, hidroxialquilo, tal como $HOCH_2CH_2$-, alquilo, tal como CH_3 o C_2H_5, halo, tal como F o Cl, CN, o hidroxialcoxi, tal como $HOCH_2CH_2O$-; y/o

R^2 y R^3 pueden tomarse opcionalmente juntos para formar un anillo insaturado o aromático, de 5 ó 6 miembros, que contiene uno o dos

átomos de N, donde el anillo está opcionalmente sustituido con hidroxialquilo, tal como  , por ejemplo



o donde R^2 y R^3 pueden tomarse opcionalmente juntos para formar un anillo que contiene O, saturado, insaturado o parcialmente insaturado, de 6 miembros, donde el anillo está opcionalmente sustituido con hidroxialquilo, tal como  , alquilo, tal como CH_3 y OH, por ejemplo



R^8 es H, halo, tal como F y Cl, o alquilo, tal como metilo; y/o

R^9 es H.

En una realización más del compuesto de Fórmula I de la invención, X = O y  es fenileno o piridinilo. En otra realización, X = S y  es fenileno.

En una realización más en la Fórmula I de la invención, Y es un enlace. Además, en una realización adicional, Y es metileno, etileno o propileno.

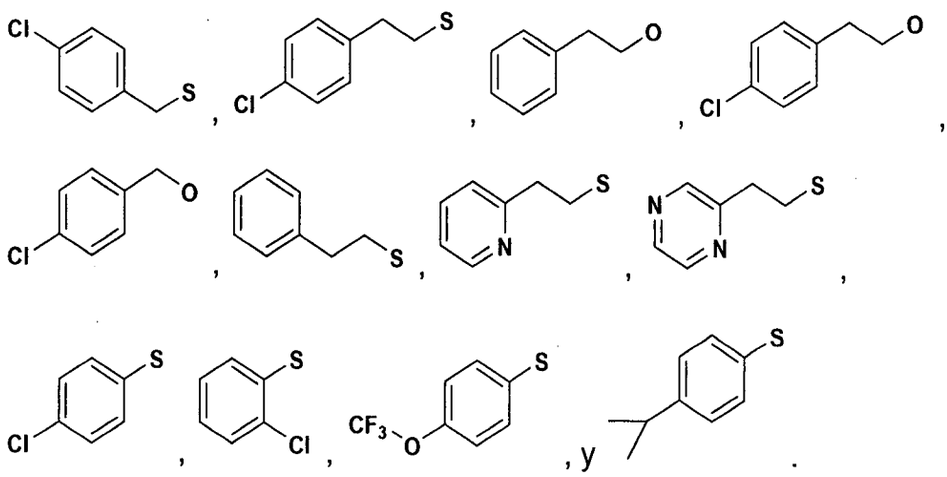
Además, la cadena alquilo o el resto alquilo de Y puede unirse a la posición *orto* de Z para generar un resto bicíclico. En esta realización, el resto bicíclico es preferiblemente 1-indanilo o 2-indanilo cuando Z es fenilo.

En una realización más, Z se selecciona entre fenilo, naftilo, piridinilo, pirazinilo, bencimidazolilo, benzotiazolilo y benzoxazolilo, preferiblemente fenilo y piridinilo.

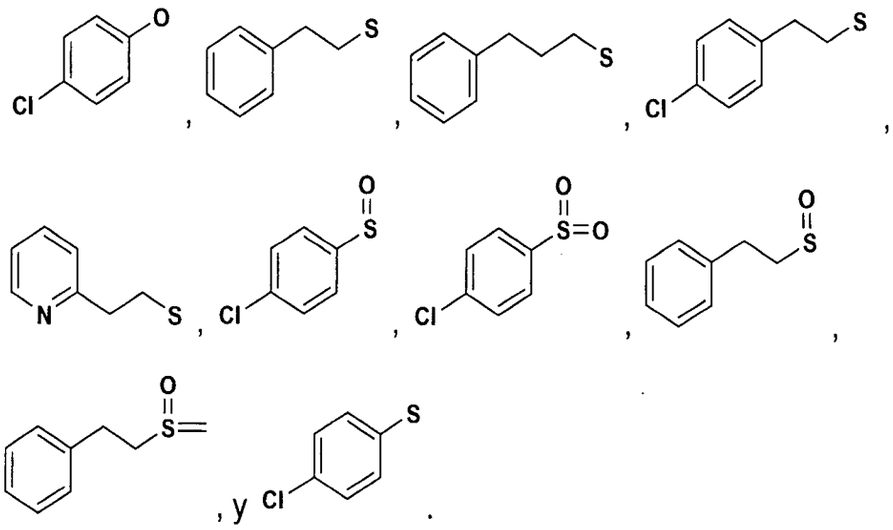
Además, en la realización en la que R^5 y R^6 tomados juntos forman una amina cíclica de 4, 5 ó 6 miembros, se prefiere que este componente se selecciona entre el grupo constituido por azetidinilo, pirrolidinilo, piperidinilo, morfolinilo y piperazinilo.

También se prefiere la realización en la que R^3 es alcoxi C_1-C_6. Se prefiere especialmente la realización en la que R^3 es alcoxi C_1-C_3 o alquilo C_1-C_3. Aún más preferiblemente, R^3 es metoxi o metilo.

En una realización de la invención, R^1 puede seleccionarse entre el grupo constituido por:

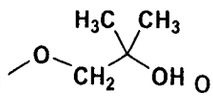
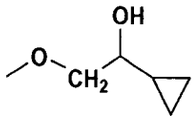


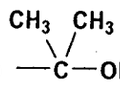
También es deseable que en la Fórmula I, R^2 sea O-2-hidroxi-propano, R^3 sea metoxi, y R^1 se seleccione entre el grupo constituido por:

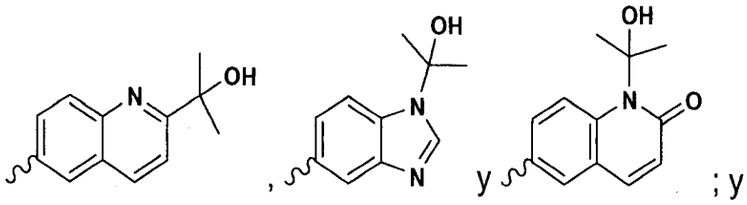


En otra realización de la invención, es deseable que

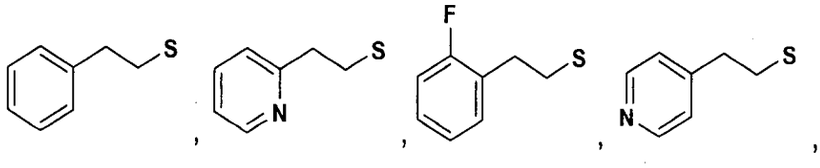
(A) sea fenileno;

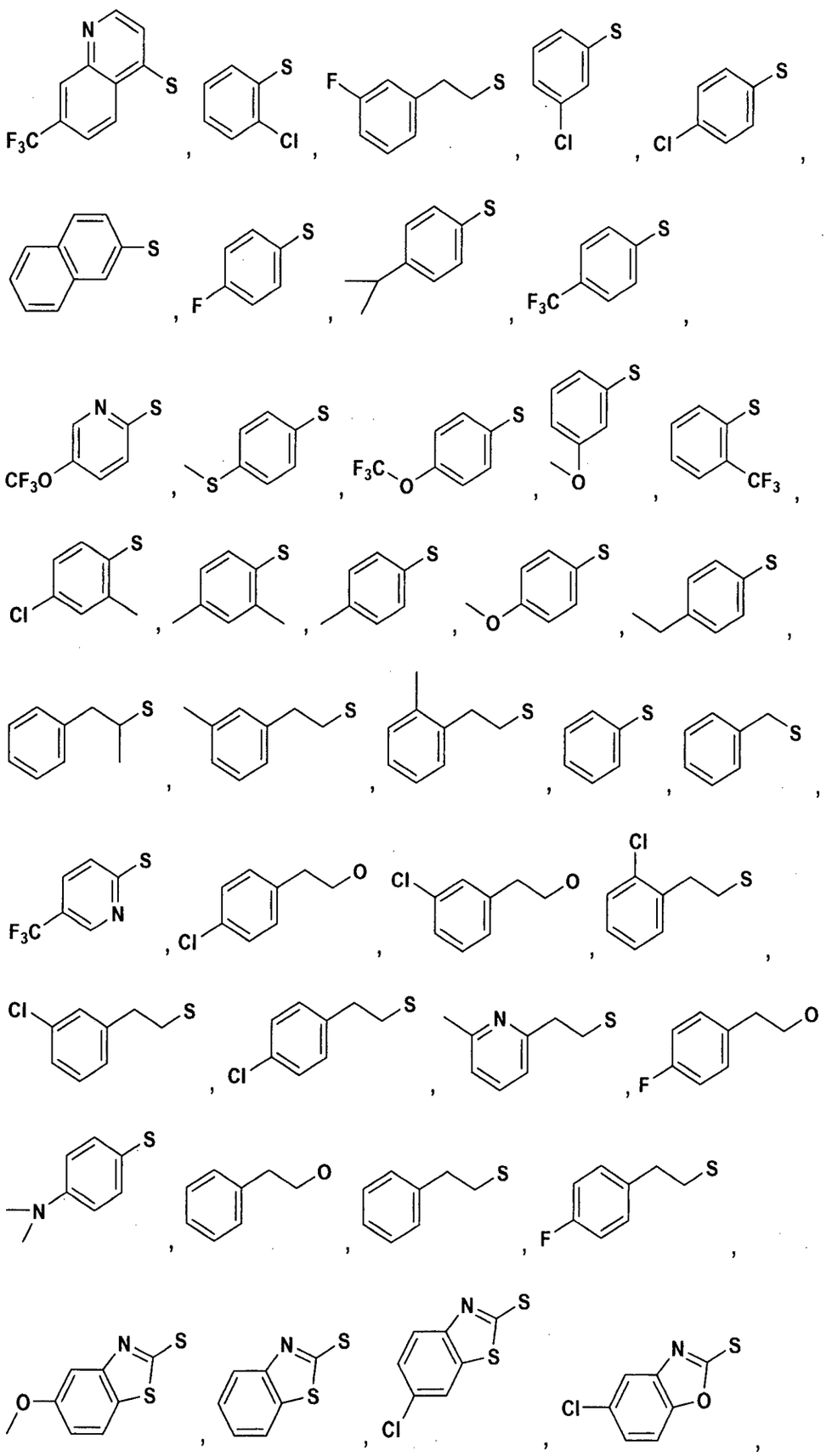
R^2 sea  o  ; o

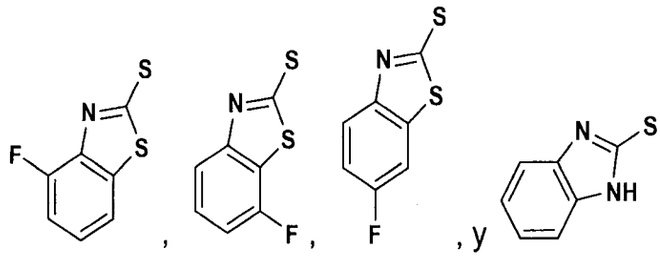
R^2 y R^3 puedan tomarse opcionalmente juntos para formar un anillo insaturado o aromático, de 5 ó 6 miembros, que contiene uno o dos átomos de N, donde el anillo está opcionalmente sustituido con hidroxialquilo, tal como  , por ejemplo

 ; y

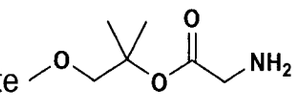
R^3 sea metoxi o metilo, y R^1 se seleccione entre el grupo constituido por:

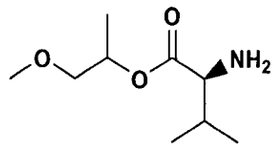
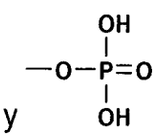




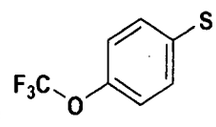
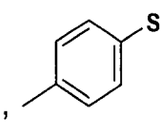
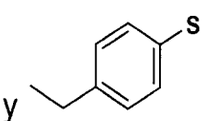


También se desea la realización del profármaco, que se describe a continuación en la presente memoria, donde en la Fórmula I,

R^2 es E-G-hidroxil-$^{Pro\text{-}Fármaco}$ o más preferiblemente  ,

 , y  ;

R^3 es metoxi; y

R^1 se selecciona entre  ,  , y  .

También se desean compuestos de Fórmula I en la que

 es fenileno;

R^1 es Z-Y-X- donde

X es S,

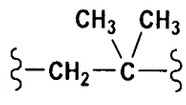
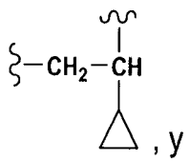
Y es una cadena alquilo de 1 a 3 carbonos o un enlace,

Z es heteroarilo o fenilo,

cada uno de Z está opcionalmente sustituido con CF_3, CF_3O o halo;

R^2 es -E-G-J donde

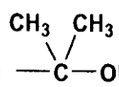
E es O,

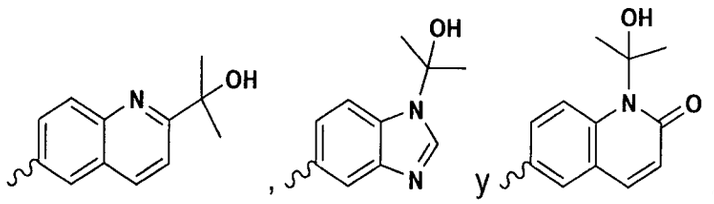
G es alquilo inferior, tal como  o alquilcicloalquilo, tal como  , y

J es OH;

R^3 es H, alcoxi, tal como CH_3O, o alquilo, tal como CH_3;

R^8 y R^9 son independientemente H o CH_3; y

R^2 y R^3 pueden tomarse opcionalmente juntos para formar un anillo insaturado o aromático, de 5 ó 6 miembros, que contiene uno o dos átomos de N, donde el anillo está opcionalmente sustituido con hidroxialquilo, tal como  , por ejemplo

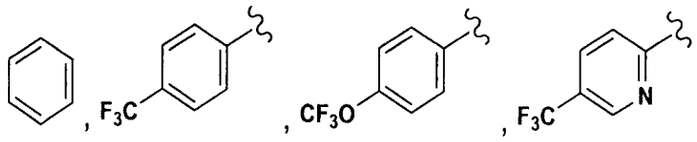


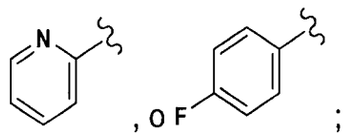
En compuestos aún más preferidos de Fórmula I,

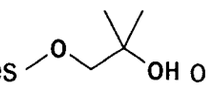
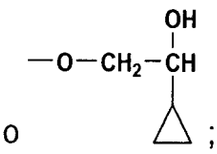
 es fenileno;

X es S;

Y es un enlace o $(CH_2)_2$;

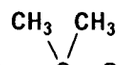
Z es 

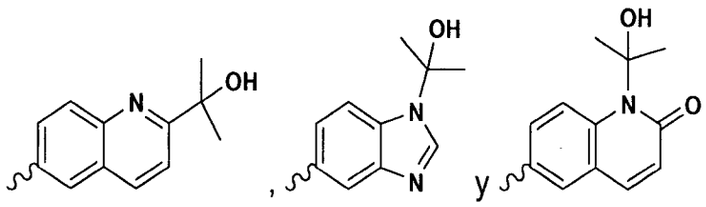


E-G-J es  o  ;

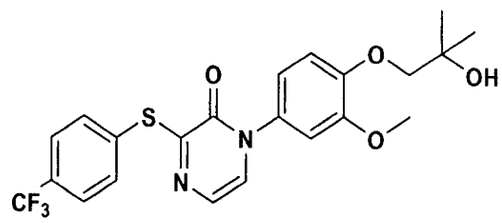
R^3 es CH_3O o CH_3;

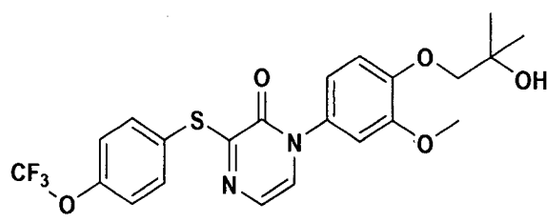
cada uno de R^8 y R^9 es H; y

R^2 y R^3 pueden tomarse opcionalmente juntos para formar un anillo insaturado o aromático, de 5 ó 6 miembros, que contiene uno o dos átomos de N, donde el anillo está opcionalmente sustituido con hidroxialquilo, tal como  , por ejemplo



Algunos compuestos preferidos de la invención incluyen los siguientes:



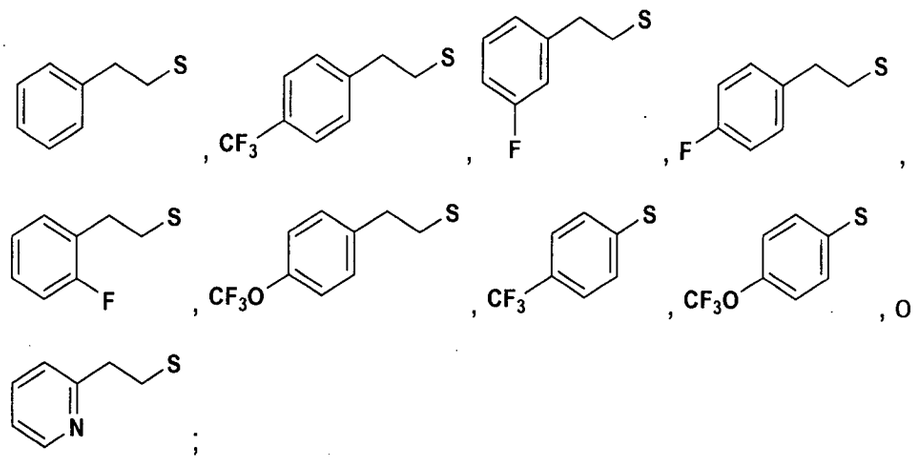


Y es una cadena alquilo de 1 a 3 carbonos, tal como $(CH_2)_2$ o un enlace,

Z es heteroarilo, tal como 2-piridilo o fenilo,

cada uno de Z está opcionalmente sustituido con CF_3, CF_3O o halo, tal como F,

de manera que R^1 pueda seleccionarse entre:



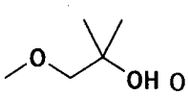
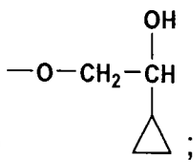
;

R^2 es -E-G-J donde

E es O,

G es alquilo inferior o alquilcicloalquilo, y

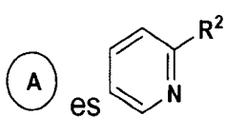
J es OH,

por ejemplo, R^2 es  o  ;

R^3 es alcoxi, tal como CH_3O, alquilo, tal como CH_3, o halo, tal como Cl; y

R^8 y R^9 son independientemente H o CH_3,

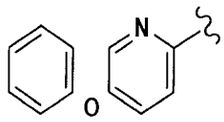
En compuestos aún más deseados de Fórmula I,

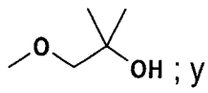


;

X es S;

Y es un enlace o $(CH_2)_2$;

Z es  ;

E-G-J es  ; y

R^3 es CH_3, H o Cl.

PROCEDIMIENTOS DE PREPARACIÓN

Los compuestos de Fórmula I de acuerdo con las diversas de la presente memoria pueden prepararse como se muestra en los siguientes esquemas de reacción no limitantes y en la descripción de los mismos, así como en los procedimientos bibliográficos publicados pertinentes que pueden usarse por un especialistas en la técnica.

El Esquema 1 que se muestra a continuación representa una secuencia de reacción generalizada para la síntesis de compuestos de Fórmula I.

Los compuestos de Fórmula I, para la que R^1 es Z-Y-O o Z-Y-S y R^2 no contiene un alcohol terciario, pueden prepararse por condensación de compuestos de Fórmula II en un disolvente, tal como THF, con sales de metales alcalinos, tales como Na^+ o K^+ de compuestos de Fórmula III. Las sales alcalinas de los compuestos de Fórmula III se han preparado previamente mediante la adición de compuestos de Fórmula III a una dispersión agitada de NaH o KH en un disolvente, tal como THF, en una atmósfera inerte de N_2 o Ar. Los compuestos de Fórmula II pueden prepararse por tratamiento de compuestos de Fórmula IV con cloruro de tionilo en un disolvente, tal como DMF. Los compuestos de Fórmula III

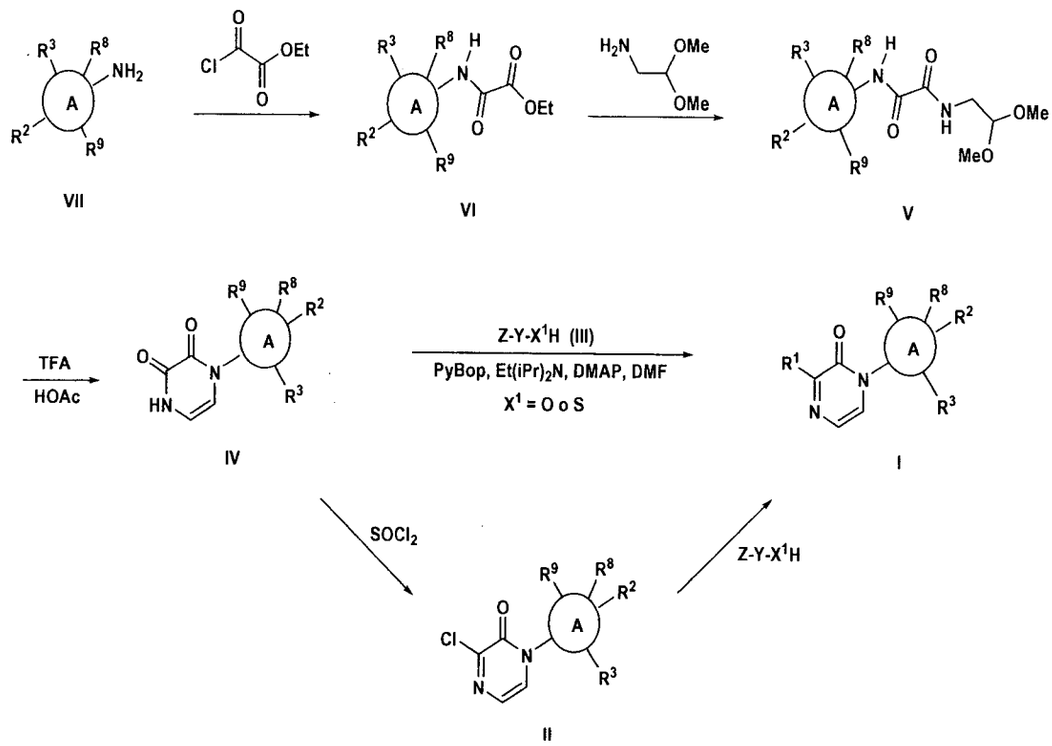
están disponibles en el mercado o pueden prepararse fácilmente por los especialistas en la técnica.

Como alternativa, una síntesis general de compuestos de Fórmula I para la que R^1 es Z-Y-O, Z-Y-S o Z-Y-NR^4H, implica condensación de compuestos de Fórmula IV con compuestos de Fórmula III con agitación de estos componentes en un disolvente, tal como DMF, que contiene hexafluoroborato de benzotriazo-1-il-oxi-trispirrolidinofosfonio (PyBOP) como agente de activación, DMAP y una amina impedida, tal como Et(*i*Pr)$_2$N. Pueden usarse otros agentes de activación por el especialista.

Los compuestos de Fórmula IV pueden prepararse por calentamiento de compuestos de Fórmula V a 120 – 150°C en el microondas en una mezcla 1:1,1 de HOAc/TFA. Los compuestos de Fórmula V pueden prepararse por agitación de compuestos de Fórmula VI con 2,2-dimetoxietilamina en un disolvente, tal como EtOAc. Los compuestos de Fórmula VI pueden prepararse por tratamiento de compuestos de Fórmula VII con cloruro de etiloxalilo en una mezcla de EtOAc y agua que contiene una base débil, tal como carbonato potásico. Los compuestos de Fórmula VII están disponibles en el mercado o pueden prepararse como se describe en el documento USSN 11/586.255.

Los compuestos de Fórmula I para la que R^1 es Z-Y-SO o Z-Y-SO_2 pueden prepararse por tratamiento de compuestos de Fórmula I en la que R^1 es Z$(CH_2)_n$S con uno o dos equivalentes de un oxidante, tal como ácido *m*-cloroperbenzoico, en un disolvente tal como CH_2Cl_2.

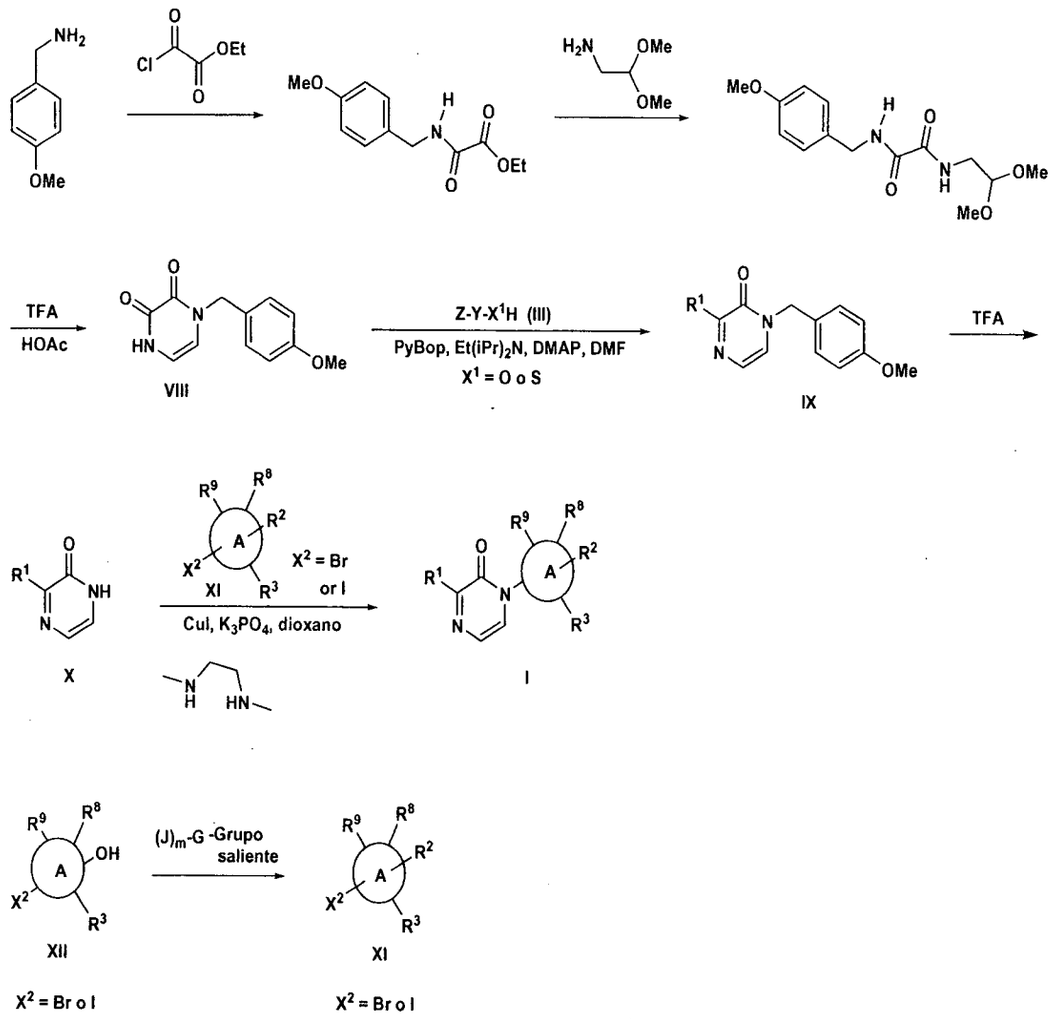
Esquema 1



Como alternativa, pueden prepararse compuestos de fórmula I como se indica en el Esquema 2, por arilación catalizada con Cu de compuestos de fórmula X con calentamiento de X con haluros o yoduros de arilo de fórmula XI en un disolvente, tal como dioxano que contiene una sal de cobre, tal como yoduro de cobre, junto con fosfato potásico tribásico y un agente quelante, tal como *N*-metil, *N'*-metil etilendiamina. Los compuestos de fórmula X pueden prepararse por calentamiento de compuestos de fórmula IX en TFA. Los compuestos de fórmula IX pueden prepararse por condensación del compuesto de Fórmula VIII con compuestos de Fórmula III con agitación de estos componentes en un disolvente, tal como DMF que contiene hexafluoroborato de benzotriazo-1-il-oxi-trispirrolidinofosfonio (PyBOP) como un agente de activación, DMAP y una amina impedida, tal como Et(*i*Pr)$_2$N. El compuesto de fórmula VIII se obtiene fácilmente a partir de *p*-metoxibencilamina utilizando la química descrita en el Esquema 1. Los haluros de arilo de fórmula XI se

preparan fácilmente por un especialista en la técnica por alquilación del fenol halogenado correspondiente disponible en el mercado.

Esquema 2



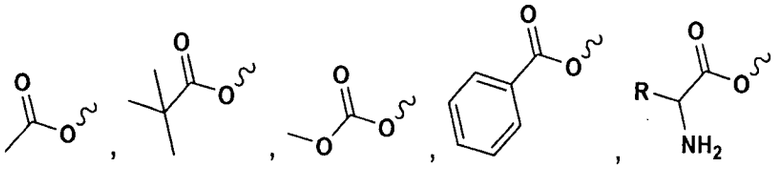
Otros procedimientos para preparar los compuestos de Fórmula I también están dentro del alcance de la invención.

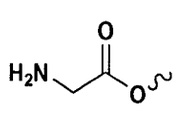
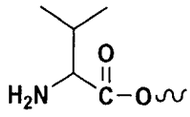
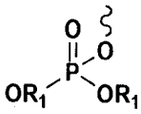
PROFÁRMACOS, SALES, ÉSTERES Y ESTEREOISÓMEROS

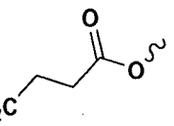
Los compuestos de la invención también incluyen "profármacos". El término "profármaco", como se usa en la presente memoria, incluye el

término "ésteres de profármaco" y el término "éteres de profármaco". El término "ésteres de profármaco", como se emplea en la presente memoria, incluye ésteres y carbonatos formados haciendo reaccionar uno o más hidroxilos de compuestos de Fórmula I con agentes acilantes o agentes fosforilantes sustituidos con alquilo, alcoxi o arilo sustituido que emplean procedimientos conocidos por los especialistas en la técnica para generar acetatos, pivalatos, metilcarbonatos, benzoatos, ésteres de aminoácidos, fosfatos, ésteres semiácidos, tales como malonatos, succinatos o glutaratos, y similares. En ciertas realizaciones, pueden preferirse especialmente ésteres de aminoácidos.

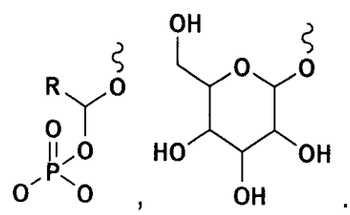
Los ejemplos de tales ésteres de profármaco incluyen



(R = H o isopropilo u otro grupo alquilo) (por ejemplo,  y ), 

(donde R_1 es H o un metal alcalino, tal como Na), es decir,  .

El término "éteres de profármacos" incluye fosfato acetales y O-glucósidos. Los ejemplos representativos de tales éteres de profármaco incluyen



Los compuestos de Fórmula I también pueden estar presentes en forma

de sales, que también están dentro del alcance de esta invención. Se prefieren sales farmacéuticamente aceptables (es decir, no tóxicas y fisiológicamente aceptables). Si los compuestos de Fórmula I tienen, por ejemplo, al menos un centro básico, pueden formar sales de adición de ácidos. Éstas se forman, por ejemplo, con ácidos inorgánicos fuertes, tales como ácidos minerales, por ejemplo ácido sulfúrico, ácido fosfórico (éster fosfato) o un ácido hidrohálico, con ácidos carboxílicos orgánicos, tales como ácidos alcanocarboxílicos de 1 a 4 átomos de carbono, por ejemplo ácido acético, que están sin sustituir o sustituidos, por ejemplo, con halógeno, tales como ácido cloroacético, tales como ácidos dicarboxílicos saturados o insaturados, por ejemplo, ácido oxálico, malónico, succínico, maleico, fumárico, ftálico o tereftálico, tales como ácidos hidroxicarboxílicos, por ejemplo, ácido ascórbico, glicólico, láctico, málico, tartárico o cítrico, tales como aminoácidos, (por ejemplo, ácido aspártico, ácido glutámico, glicina, valina, lisina o arginina), o ácido benzoico, o con ácidos sulfónicos orgánicos, tales como ácidos alquil (C_1-C_4) o arilsulfónicos que están sin sustituir o sustituidos, por ejemplo con halógeno, por ejemplo, ácido metil- o *p*-tolueno-sulfónico. También pueden formarse sales de adición de ácidos correspondientes de forma que tengan, si se desea, un centro básico adicionalmente presente. Los compuestos de Fórmula I que tienen al menos un grupo ácido (por ejemplo COOH) también pueden formar sales con bases. Son sales con bases adecuadas, por ejemplo, sales de metales, tales como sales de metales alcalinos o alcalinotérreos, por ejemplo, sales de sodio, potasio o magnesio, o sales con amoniaco o con una amina orgánica, tal como morfolina, tiomorfolina, piperidina, pirrolidina, una mono, di o tri-alquilamina inferior, por ejemplo etil, *terc*-butil, dietil, diisopropil, trietil, tributil o dimetil-propilamina, o

una mono, di o trihidroxialquilamina inferior, por ejemplo mono, di o trietanolamina. También pueden formarse adicionalmente sales internas correspondientes. También se incluyen sales que son inadecuadas para usos farmacéuticos pero que pueden emplearse, por ejemplo, para el aislamiento o purificación de compuestos libres de Fórmula I o de sus sales farmacéuticamente aceptables.

Las sales preferidas de los compuestos de Fórmula I que contienen un grupo básico incluyen monoclorhidrato, hidrogenosulfato, metanosulfonato, fosfato, nitrato o acetato.

Las sales preferidas de los compuestos de Fórmula I que contienen un grupo ácido incluyen sales de sodio, potasio y magnesio y aminas orgánicas farmacéuticamente aceptables.

Se incluyen todos los estereoisómeros de los compuestos de la invención, en mezcla o en forma pura o sustancialmente pura. Los compuestos de la presente solicitud pueden tener centros asimétricos en cualquiera de los átomos de carbono, incluyendo uno cualquiera de los sustituyentes R. Por consiguiente, los compuestos de Fórmula I pueden existir en formas enantioméricas o diastereoméricas o en mezclas de las mismas. Los procesos para la preparación pueden utilizar racematos, enantiómeros o diastereómeros como materiales de partida. Cuando se preparan productos diastereoméricos o enantioméricos, éstos pueden separarse por procedimientos convencionales, por ejemplo, procedimientos cromatográficos o cristalización fraccionada.

UTILIDAD

Los compuestos de la presente solicitud pueden administrarse a

mamíferos, preferiblemente humanos, para el tratamiento de una diversidad de afecciones y trastornos incluyendo, pero sin limitación, trastornos metabólicos y de la alimentación, así como afecciones asociadas con trastornos metabólicos (por ejemplo, obesidad, diabetes, arterioesclerosis, hipertensión, enfermedad ovárica poliquística, enfermedad cardiovascular, osteoartritis, trastornos dermatológicos, hemostasia de la glucosa alterada, resistencia a la insulina, hipercolesterolemia, hipertrigliceridemia, colelitiasis, afecciones dislipidémicas, bulimia nerviosa y trastornos compulsivos de la alimentación); trastornos del sueño; y trastornos psiquiátricos, tales como depresión, ansiedad, esquizofrenia, abuso de sustancias, potenciación de la cognición y enfermedad de Parkinson.

Los compuestos descritos en la presente solicitud podrían usarse para potenciar los efectos de agentes potenciadores de la cognición, tales como inhibidores de la acetilcolinesterasa (por ejemplo, tacrina), agonistas del receptor muscarínico 1 (por ejemplo, milamelina), agonistas nicotínicos, moduladores del receptor del ácido glutámico (AMPA y NMDA) y agentes nootrópicos (por ejemplo, piracetam, levetiracetam). Los ejemplos de terapias adecuadas para el tratamiento de la enfermedad de Alzheimer y de trastornos cognitivos para el uso junto con los compuestos de la presente solicitud incluyen donepezilo, tacrina, revastigraína, 5HT6, inhibidores de la gamma secretasa, inhibidores de la beta secretasa, bloqueantes de los canales SK, bloqueantes de Maxi-K y bloqueantes de KCNQ.

Los compuestos descritos en la presente solicitud podrían usarse para potenciar los efectos de agentes usados en el tratamiento de la enfermedad de Parkinson. Los ejemplos de agentes usados para tratar la enfermedad de

Parkinson incluyen: levadopa con o sin un inhibidor de COMT, fármacos antiglutamatérgicos (amantadina, riluzol), antagonistas alfa-2 adrenérgicos tales como idazoxano, antagonistas de opiáceos, tales como naltrexona, otros agonistas de la dopamina o moduladores del transporte, tales como ropinirol o pramipexol o factores neurotróficos tales como factor neurotrófico derivado de la glía (GDNF).

COMBINACIONES FARMACÉUTICAS

La presente solicitud incluye dentro de su alcance composiciones farmacéuticas que comprenden, como ingrediente activo, una cantidad terapéuticamente eficaz de al menos uno de los compuestos de Fórmula I, solo o junto con un vehículo o diluyente farmacéutico. Opcionalmente, los compuestos de la presente solicitud pueden usarse solos, junto con otros agentes terapéuticos útiles en el tratamiento de los trastornos mencionados anteriormente, incluyendo: agentes antiobesidad; agentes antidiabéticos, supresores del apetito; agentes que disminuyen el colesterol o los lípidos, agentes que aumentan el HDL, agentes potenciadores de la cognición, agentes usados para tratar la neurodegeneración, agentes usados para tratar afecciones respiratorias, agentes usados para tratar enfermedades del intestino, agentes antiinflamatorios; agentes antiansiedad; antidepresivos; agentes antihipertensores; glucósidos cardiacos; y agentes antitumorales.

Dichos otros agentes terapéuticos pueden administrarse antes de, simultáneamente con o después de la administración de los antagonistas del receptor de la hormona concentradora de melanina (MCHR), de acuerdo con la solicitud.

Los ejemplos de agentes antiobesidad adecuados para el uso junto con los compuestos de la presente solicitud incluyen agonistas del receptor de la melanocortina (MC4R), moduladores del receptor de canabinoides, antagonistas del receptor secretagogo de la hormona de crecimiento (GHSR), moduladores del receptor de la galanina, antagonistas de orexina, antagonistas de CCK, agonistas de GLP-1 y otros péptidos derivados del preproglucagón; antagonistas de NPY1 o NPY5, moduladores de NPY2 y NPY4, agonistas del factor liberador de corticotropina, moduladores del receptor de histamina 3 (H3), inhibidores de aP2, moduladores de PPAR gamma, moduladores de PPAR delta, inhibidores de la acetil-CoA carboxilasa (ACC), inhibidores de la 11-β-HSD-1, moduladores del receptor de adinopectina; agonistas beta 3 adrenérgicos tales como AJ9677 (Takeda/Dainippon), L750355 (Merck) o CP331648 (Pfizer) u otros agonistas beta 3 conocidos, como se describen en las Patentes de Estados Unidos Nº 5.541.204, 5.770.615, 5.491.134, 5.776.983 y 5.488.064, un modulador del receptor tiroideo beta, tal como un ligando del receptor tiroideo, como se describe en los documentos WO 97/21993 (U. Cal SF), WO 99/00353 (KaroBio) y WO 00/039077 (KaroBio), un inhibidor de la lipasa, tal como orlistat o ATL-962 (Alizyme), agonistas del receptor de la serotonina (por ejemplo, BVT-933 (Biovitrum)), agentes inhibidores de la recaptación o liberadores de monoaminas, tales como fenfluramina, dexfenfluramina, fluvoxamina, fluoxetina, paroxetina, sertralina, clorfentermina, cloforex, clortermina, picilorex, sibutramina, dexamfetamina, fentermina, fenilpropanolamina o mazindol, agentes anoréxigenos tales como topiramato (Johnson & Johnson), CNTF (factor neurotrófico ciliar)/Axokine® (Regeneron), BDNF (factor neurotrófico derivado del cerebro), moduladores de leptina y del

receptor de leptina o antagonistas del receptor canabinoide 1, tales como SR-141716 (Sanofi) o SLV-319 (Solvay).

Los ejemplos de agentes antidiabéticos adecuados para el uso junto con los compuestos de la presente solicitud incluyen: secretagogos de insulina o sensibilizadores a la insulina, que pueden incluir biguanidas, sulfonil ureas, inhibidores de la glucosidasa, inhibidores de la aldosa reductasa, agonistas de PPAR γ, tales como tiazolidinodionas, agonistas de PPAR α (tales como derivados del ácido fíbrico), antagonistas o agonistas de PPAR δ, agonistas dobles de PPAR α y γ, inhibidores de la 11-β-HSD-1, inhibidores de la dipeptidil peptidasa IV (DP4), incluyendo saxagliptina, inhibidores de SGLT2, incluyendo dapagliflozina y serglifozina, inhibidores de la glucógeno fosforilasa y/o meglitinidas, así como insulina y/o péptido 1 de tipo glucagón (GLP-1), agonista de GLP-1, moduladores de la incretina, activadores de la AMP quinasa, antagonistas glucocorticoides, inhibidores de la fructosa bis 1,6-fosfatasa, inhibidores de glucoquinasa y/o un inhibidor de PTP-1B (inhibidor de la proteína tirosina fosfatasa-1B).

El agente antidiabético puede ser un agente antihiperglucémico, preferiblemente una biguanida tal como metformina o fenformina o sales de las mismas, preferiblemente metformina HCl. Cuando el agente antidiabético es una biguanida, los compuestos de la presente solicitud se emplearán en una proporción en peso con respecto a la biguanida dentro del intervalo de aproximadamente 0,001:1 a aproximadamente 10:1, preferiblemente de aproximadamente 0,01:1 a aproximadamente 5:1.

El agente antidiabético también puede ser, preferiblemente, una sulfonil urea tal como gliburida (también conocida como glibenclamida), glimepirida

(descrita en la Patente de Estados Unidos Nº 4.379.785), glipizida, gliclazida o clorpropamida, otras sulfonilureas conocidas u otros agentes antihiperglucémicos que actúen sobre el canal dependiente de ATP de las células beta, prefiriéndose gliburida y glipizida, que pueden administrase en la misma o en formas farmacéuticas orales independientes. El agente antidiabético oral también puede ser un inhibidor de la glucosidasa, tal como ascarbosa (descrita en la Patente de Estados Unidos Nº 4.904.769) o miglitol (descrito en la Patente de Estados Unidos Nº 4.639.436), que puede administrarse en la misma o en formas farmacéuticas orales independientes.

Los compuestos de la presente solicitud pueden emplearse junto con un agonista de PPAR γ, tal como un agente antidiabético oral de tiazolidinodiona u otros sensibilizadores a la insulina (que tienen un efecto de sensibilidad a la insulina en pacientes de NIDDM), tales como rosiglitazona (SKB), pioglitazona (Takeda), MCC-555 de Mitsubishi (descrito en la Patente de Estados Unidos Nº 5.594.016), GL-262570 de Glaxo-Wellcome, englitazona (CP-68722, Pfizer) o darglitazona (CP-86325, Pfizer), isaglitazona (MIT/J&J), JTT-501 (JPNT/P&U), L-895645 (Merck), R-119702 (Sankyo/WL), NN-2344 (Dr. Reddy/NN) o YM-440 (Yamanouchi), preferiblemente rosiglitazona y pioglitazona.

Los compuestos de la presente solicitud también pueden emplearse con un agonista doble de PPAR α y γ, tal como MK-767/KRP-297 (Merck/Kyorin; como se describe en Yajima K., y col., *Am. J. Physiol. Endocrinol. Metab.*, 284: E966-E971 (2003)), AZ-242 (tesaglitazar; Astra-Zeneca; como se describe en Ljung B., y col., *J. Lipid Res.*, 43, 1855-1863 (2002)); muraglitazar; o los compuestos descritos en la Patente de Estados Unidos Nº 6.414.002.

Los compuestos de la presente invención pueden emplearse junto con

agentes antihiperlipidémicos o agentes usados para tratar la arterioesclerosis. Un ejemplo de un agente hipolipidémico sería un inhibidor de la HMG CoA reductasa que incluye, pero sin limitación, mevastatina y compuestos relacionados, como se describen en la Patente de Estados Unidos Nº 3.983.140, lovastatina (mevinolina) y compuestos relacionados, como se describen en la Patente de Estados Unidos Nº 4.231.938, pravastatina y compuestos relacionados, como se describen en la Patente de Estados Unidos Nº 4.346.227, simvastatina y compuestos relacionados, como se describen en las Patentes de Estados Unidos Nº 4.448.784 y 4.450.171. Otros inhidores de la HMG CoA reductasa que pueden emplearse en este documento incluyen, pero sin limitación, fluvastatina, que se describe en la Patente de Estados Unidos Nº 5.354.772, cerivastatina, que se describe en las Patentes de Estados Unidos Nº 5.006.530 y 5.177.080, atorvastatina, que se describe en las Patentes de Estados Unidos Nº 4.681.893, 5.273.995, 5.385.929 y 5.686.104, pitavastatina (nisvastatina (NK-104) o itavastatina de Nissan/Sankyo), que se describe en la Patente de Estados Unidos Nº 5.011.930, rosuvastatina de Shionogi-Astra/Zeneca (visastatina (ZD-4522)), que se describe en la Patente de Estados Unidos Nº 5.260.440, y compuestos de estatina relacionados que se describen en la Patente de Estados Unidos Nº 5.753.675, análogos del pirazol de derivados de mevalonolactona, como se describen en la Patente de Estados Unidos Nº 4.613.610, análogos del indeno de derivados de mevalonolactona, como se describe en la solicitud PCT WO 86/03488, 6-[2-(pirrol-1-il-sustituido)-alquil)piran-2-onas y derivados de las mismas, como se describen en la Patente de Estados Unidos Nº 4.647.576, dicloroacetato de SC-45355 de Searle (un derivado del ácido pentanodioico sustituido en posición 3),

análogos del imidazol de mevalonolactona, como se describen en la solicitud PCT WO 86/07054, derivados del ácido 3-carboxi-2-hidroxi-propano-fosfónico, como se describen en la Patente Francesa Nº 2.596.393, derivados de pirrol, furano y tiofeno disustituidos en las posiciones 2 y 3, como se describen en la Solicitud de Patente Europea Nº 0221025, análogos del naftilo de mevalonolactona, como se describen en la Patente de Estados Unidos Nº 4.686.237, octahidronaftalenos, tales como los que se describen en la Patente de Estados Unidos Nº 4.499.289, ceto-análogos de mevinolina (lovastatina), como se describen en la solicitud de Patente Europea Nº 0142146 A2, y derivados de quinolina y piridina descritos en las Patentes de Estados Unidos Nº 5.506.219 y 5.691.322. Además, en el documento GB 2205837 se describen compuestos del ácido fosfínico útiles en la inhibición de la HMG CoA reductasa adecuados para el uso en este documento.

Los inhibidores de la escualeno sintetasa adecuados para el uso en este documento incluyen, pero sin limitación, α-fosfono-sulfonatos descritos en la Patente de Estados Unidos Nº 5.712.396, los descritos por Biller, y col., *J. Med. Chem.*, 31, 1869-1871 (1998), incluyendo (fosfinil-metil)fosfonatos de isoprenoides así como otros inhibidores de la escualeno sintetasa conocidos, por ejemplo, como se describen en las Patentes de Estados Unidos Nº 4.871.721 y 4.924.024 y en Biller, S. A., y col., *Current Pharmaceutical Design*, 2: 1-40 (1996).

Además, otros inhibidores de la escualeno sintetasa adecuados para el uso en este documento incluyen los pirofosfatos de terpenoides descritos por Ortiz de Montellano, P. y col., *J. Med. Chem.*, 20: 243-249 (1977), el análogo A del difosfato de farnesilo y análogos del pirofosfato de preescualeno (PSQ-PP),

como se describen por Corey y col., *J. Am. Chem. Soc.*, 98: 1291-1293 (1976), fosfinilfosfonatos descritos por McClard, R. W. y col., *J. Am. Chem. Soc.*, 109: 5544 (1987) y ciclopropanos descritos por Capson, T. L., tesis doctoral, junio de 1987, Dept. Med. Chem. U de Utah, Resumen, Tabla de contenidos, págs. 16, 17, 40-43, 48-51, Sumario.

Otros agentes hipolipidémicos adecuados para el uso en este documento incluyen, pero sin limitación, derivados del ácido fíbrico, tales como fenofibrato, gemfibrozilo, clofibrato, bezafibrato, ciprofibrato, clinofibrato y similares, probucol y compuestos relacionados, como se describen en la Patente de Estados Unidos Nº 3.674.836, prefiriéndose probucol y gemfibrozil, secuestrantes de ácidos biliares, tales como colestiramina, colestipol y DEAE-Sephadex (SECHOLEX, POLICEXIDE) y colestagel (Sankyo/Geltex), así como lipostabilo (Rhone-Poulenc), Eisai E-5050 (un derivado N-sustituido de etanolamina), imanixilo (HOE-402), tetrahidrolipstatina (THL), istigmastanilfosforilcolina (SPC, Roche), aminociclodextrina (Tanabe Seiyoku), Ajinomoto AJ-814 (derivado del azuleno), melinamida (Sumitomo), Sandoz 58-035, American Cyanamid CL-277.082 y CL-283.546 (derivados disustituidos de la urea), ácido nicotínico (niacina), acipimox, acifran, neomicina, ácido p-aminosalicílico, aspirina, derivados de poli(dialilmetilamina), tales como los que se describen en la Patente de Estados Unidos Nº 4.759.923, poli(cloruro de dialildimetilamonio) de amina cuaternaria e iononas, tales como las que se describen en la Patente de Estados Unidos Nº 4.027.009, y otros agentes conocidos que disminuyen el colesterol en suero.

El otro agente hipolipidémico puede ser un inhibidor de ACAT (que también tiene actividad antiaterosclerótica), tal como se describe en *Drugs of*

the Future, 24: 9-15 (1999), (Avasimibe); Nicolosi y col., "The ACAT inhibitor, CI-1011 is effective in the prevention and regression of aortic fatty streak area in hamsters", *Atherosclerosis* (Shannon, Irel), 137(1): 77-85 (1998); Ghiselli, G., "The pharmacological profile of FCE 27677: a novel ACAT inhibitor with potent hypolipidemic activity mediated by selective suppression of the hepatic secretion of ApoB100-containing lipoprotein", *Cardiovasc. Drug Rev.*, 16(1): 16-30 (1998); Smith, C., y col., "RP 73163: a bioavailable alkylsulfinyl-diphenylimidazole ACAT inhibitor", *Bioorg. Med. Chem. Lett*, 6(1): 47-50 (1996); Krause, B.R. y col., Capítulo 6: "ACAT Inhibitors: Physiologic Mechanisms for Hypolipidemic and Anti-Atherosclerotic Activities in Experimental Animals", *Inflammation: Mediators and pathways,* CRC Press, Inc., publ., Ruffolo, Jr., R.R. y col., ed., págs. 173-198 (1995); Sliskovic y col., "ACAT inhibitors: potential anti-atherosclerotic agents", *Curr. Med. Chem.*, 1(3): 204-25 (1994); Stout y col., "Inhibitors of acil-CoA: cholesterol O-acyl transferase (ACAT) as hypocholesterolemic agents. 6. The first water-soluble ACAT inhibitor with lipid-regulating activity. Inhibitors of acyl-CoA: cholesterol acyltransferase (ACAT). 7, Development of a series of substituted N-phenyl-N'-[(1-phenylcyclopentyl)-methyl]ureas with enhanced hypocholesterolemic activity", *Chemtracts: Org. Chem.*, 8(6): 359-362 (1995), o TS-962 (Taisho Pharmaceutical Co. Ltd), así como F-1394, CS-505, F-12511, HL-004, K-10085 y YIC-C8-434.

El agente hipolipidémico puede ser un regulador positivo de la actividad del receptor de LDL, tal como MD-700 (Taisho Pharmaceutical Co. Ltd) y LY295427 (Eli Lilly). El agente hipolipidémico puede ser un inhibidor de la absorción de colesterol, preferiblemente SCH48461 de Schering-Plough (ezetimiba), así como los descritos en *Atherosclerosis,* 115: 45-63 (1995) y *J.*

Med. Chem. 41: 973 (1998).

El otro agente lipídico o agente modulador de lípidos puede ser un inhibidor de la proteína de transferencia de colesterilo (CETP), tal como CP-529.414 de Pfizer, así como los descritos en los documentos WO/0038722 y en EP 818448 (Bayer) y EP 992496 y SC-744 y SC-795 de Pharmacia, así como CETi-1 y JTT-705.

El agente hipolipidémico puede ser un inhibidor del cotransportador ileal de Na^+ y ácidos biliares, tal como se describe en Drugs of the Future, 24: 425-430 (1999). El inhibidor de la ATP citrato liasa que puede emplearse junto con la solicitud puede incluir, por ejemplo, los descritos en la Patente de Estados Unidos Nº 5.447.954.

El otro agente lipídico también incluye un compuesto fitoestrogénico, tal como se describe en el documento WO 00/30665, incluyendo proteína de semilla de soja aislada, concentrado de proteína de soja o harina de soja, así como una isoflavona tal como genisteína, daidzeína, gliciteína o ecuol, o fitoesteroles, fitoestanol o tocotrienol, como se describen en el documento WO 2000/015201; un inhibidor beta lactámico de la absorción del colesterol, tal como se describe en el documento EP 675714; un regulador positivo de HDL, tal como un agonista de LXR, un agonista de PPAR α y/o un agonista de FXR; un promotor del catabolismo de LDL, tal como se describe en el documento EP 1022272; un inhibidor del intercambio de sodio y protones, tal como se describe en el documento DE 19622222; un inductor del receptor de LDL o un glucósido esteroideo, tal como se describen en la Patente de Estados Unidos Nº 5.698.527 y en el documento GB 2304106; un antioxidante, tal como beta-caroteno, ácido ascórbico, α-tocoferol o retinol, como se describen en el

documento WO 94/15592, así como Vitamina C y un agente antihomocisteína, tal como ácido fólico, un folato, Vitamina B6, Vitamina B12 y Vitamina E; isoniazida como se describe en el documento WO 97/35576; un inhibidor de la absorción de colesterol, un inhibidor de la HMG-CoA sintasa o un inhibidor de la lanosterol demetilasa, como se describe en el documento WO 97/48701; un agonista de PPAR δ para tratar la dislipidemia; o una proteína de unión a elementos de regulación por esteroles I (SREBP-1), como se describe en el documento WO 2000/050574, por ejemplo, un esfingolípido, tal como ceramida, o esfingomielinasa neutra (N-SMase) o un fragmento de la misma. Son agentes hipolipidémicos preferidos pravastatina, lovastatina, simvastatina, atorvastatina, fluvastatina, pitavastatina y rosuvastatina, así como niacina y/o colestagel.

Los compuestos de la presente invención también pueden emplearse junto con agentes antihipertensores. Los ejemplos de agentes antihipertensores adecuados para el uso junto con los compuestos de la presente solicitud incluyen bloqueantes beta adrenérgicos, bloqueantes de los canales de calcio (de tipo L y/o de tipo T; por ejemplo, diltiazem, verapamilo, nifedipino, amlodipino y mibefradilo), diuréticos (por ejemplo, clorotiazida, hidroclorotiazida, flumetiazida, hidroflumetiazida, bendroflumetiazida, metilclorotiazida, triclorometiazida, politiazida, benzotiazida, tricrinafeno del ácido etacrínico, clortalidona, furosemida, musolimina, bumetanida, triamtreneno, amilorida, espironolactona), inhibidores de renina, inhibidores de ACE (por ejemplo, captopril, zofenopril, fosinopril, enalapril, ceranopril, cilazopril, delapril, pentopril, quinapril, ramipril, lisinopril), antagonistas del receptor de AT-1 (por ejemplo, losartan, irbesartan, valsartan), antagonistas del receptor ET (por ejemplo, sitaxsentan, atrsentan y compuestos descritos en la

Patente de Estados Unidos Nº 5.612.359 y 6.043.265), antagonista doble de ET/AII (por ejemplo, compuestos descritos en el documento WO 00/01389), inhibidores de la endopeptidasa neutra (NEP), inhibidores de la vasopepsidasa (inhibidores dobles de NEP-ACE) (por ejemplo, omapatrilat y gemopatrilat) y nitratos.

Los antagonistas de MCHR1 también podrían ser útiles en el tratamiento de otras enfermedades asociadas con la obesidad, incluyendo trastornos del sueño. Por lo tanto, los compuestos descritos en la presente solicitud podrían usarse junto con agentes terapéuticos para tratar trastornos del sueño. Los ejemplos de terapias adecuadas para el tratamiento de trastornos del sueño para el uso junto con los compuestos de la presente solicitud incluyen análogos de la melatonina, antagonistas del receptor de melatonina, agonistas de ML 1 B, moduladores del receptor GABA; moduladores del receptor de NMDA, moduladores del receptor de histamina-3 (H3), agonistas de dopamina y moduladores del receptor de orexina.

Los antagonistas de MCHR1 pueden reducir o aliviar trastornos adictivos o de abuso de sustancias. Por lo tanto, la combinación de moduladores del receptor de canabinoides con agentes usados para tratar trastornos adictivos puede reducir el requerimiento de dosis o mejorar la eficacia de los agentes terapéuticos de trastornos adictivos actuales. Son ejemplos de agentes usados para tratar trastornos adictivos o de abuso de sustancias: inhibidores selectivos de la recaptación de serotonina (SSRI), metadona, buprenorfina, nicotina y bupropión.

Los antagonistas de MCHR1 pueden reducir la ansiedad o la depresión; por lo tanto, los compuestos descritos en esta solicitud pueden usarse junto

con agentes antiansiedad o antidepresivos. Los ejemplos de agentes antiansiedad adecuados para el uso junto con los compuestos de la presente solicitud incluyen benzodiazepinas (por ejemplo, diazepam, lorazepam, oxazepam, alprazolam, clordiazepóxido, clonazepam, clorazepato, halazepam y prazepam), agonistas del receptor de 5HT1A (por ejemplo, buspirona, flesinoxan, gepirona e ipsapirona) y antagonistas del factor de liberación de corticotropina (CRF).

Los ejemplos de clases adecuadas de antidepresivos para el uso junto con los compuestos de la presente solicitud incluyen inhibidores de la recaptación de norepinefrina (aminas tricíclicas terciarias y secundarias), inhibidores selectivos de la recaptación de serotonina (SSRI) (fluoxetina, fluvoxamina, paroxetina y sertralina), inhibidores de la monoamino oxidasa (MAOI) (isocarboxazid, fenelzina, tranilcipromina, selegilina), inhibidores reversibles de la monoamino oxidasa (RIMA) (moclobemida), inhibidores de la recaptación de serotonina y norepinefrina (SNRI) (venlafaxina), antagonistas del receptor del factor de liberación de corticotropina (CRF), antagonistas de alfa-adrenorreceptores y antidepresivos atípicos (bupropión, litio, nefazodona, trazodona y viloxazina).

La combinación de un fármaco antipsicótico convencional con un antagonista de MCHR1 también podría potenciar la reducción de síntomas en el tratamiento de psicosis o manías. Además, dicha combinación podría permitir una reducción rápida de los síntomas y reducir la necesidad de tratamiento crónico con agentes antipsicóticos. Dicha combinación podría reducir también el requerimiento de dosis de antipsicóticos eficaz, dando como resultado una probabilidad reducida de desarrollar la disfunción motora típica del tratamiento

antipsicótico crónico.

Los ejemplos de agentes antipsicóticos adecuados para usar junto con los compuestos de la presente solicitud incluyen las clases de agentes antipsicóticos fenotiazina (clorpromazina, mesoridazina, tioridazina, acetofenazina, flufenazina, perfenazina y trifluoperazina), tioxantina (clorprotixeno, tiotixeno), dibenzazepina heterocíclica (clozapina, olanzepina y aripiprazol), butirofenona (haloperidol), difenilbutilpiperidina (pimozida) e indolona (molindolona). Otros agentes antipsicóticos con un valor terapéutico potencial junto con los compuestos de la presente solicitud incluyen loxapina, sulpirida y risperidona.

La combinación de los compuestos de la presente solicitud con fármacos antipsicóticos convencionales también podría proporcionar un efecto terapéutico potenciado para el tratamiento de trastornos esquizofrénicos, como se ha descrito anteriormente para trastornos maníacos. Como se usan en este documento, los trastornos esquizofrénicos incluyen esquizofrenia paranoide, desorganizada, catatónica, indiferenciada y residual, trastorno esquizofreniforme, trastorno esquizoafectivo, trastorno delirante, trastorno psicótico breve y trastorno psicótico no especificado. Los ejemplos de fármacos antipsicóticos adecuados para la combinación con los compuestos de la presente solicitud incluyen los antipsicóticos mencionados anteriormente, así como antagonistas del receptor de dopamina, antagonistas de receptores muscarínicos, antagonistas del receptor de 5HT2A y antagonistas del receptor de 5HT2A/dopamina o agonistas parciales (por ejemplo, olanzepina, aripiprazol, risperidona, ziprasidona).

FORMAS DE DOSIFICACIÓN

Los compuestos de la presente invención pueden administrarse en forma de dosificación oral. La forma de dosificación oral para dicha composición farmacéutica incluye formas de dosificación oral tales como gránulos, polvos, comprimidos, cápsulas, jarabes, emulsiones, suspensiones, etc., y formas de dosificación no oral tales como inyecciones (por ejemplo, inyecciones subcutáneas, intravenosas, intramusculares e intraperitoneales), infusiones de goteo, formas de aplicación externa (por ejemplo, preparaciones de pulverización nasal, preparaciones transdérmicas, pomadas, etc.) y supositorios (por ejemplo, supositorios rectales y vaginales).

Estas formas de dosificación pueden fabricarse por la técnica conocida *per se* usada convencionalmente en procedimientos farmacéuticos. Los procedimientos de fabricación específicos son los siguientes.

Para fabricar una forma de dosificación oral, se añaden un excipiente (por ejemplo, lactosa, sacarosa, almidón, manitol, etc.), un disgregante (por ejemplo, carbonato cálcico, carboximetilcelulosa cálcica, etc.), un aglutinante (por ejemplo, α-almidón, goma arábiga, carboximetilcelulosa, polivinilpirrolidona, hidroxipropilcelulosa, etc.) y un lubricante (por ejemplo, talco, estearato de magnesio, polietilenglicol 6000, etc.), por ejemplo, a un componente o componentes activos y la composición resultante se comprime. Cuando es necesario, el producto comprimido se recubre, por la técnica conocida *per se*, para enmascarar el sabor o para proporcionar una disolución entérica o liberación sostenida. El material de recubrimiento que puede usarse incluye, por ejemplo, etilcelulosa, hidroximetilcelulosa, polioxietilenglicol,

acetato ftalato de celulosa, ftalato de hidroxipropilmetilcelulosa y Eudragit (Rohm & Haas, Alemania, copolímero metacrílico-acrílico).

Pueden fabricarse inyecciones típicamente por el siguiente procedimiento. El componente o componentes activos se disuelven, suspenden o emulsionan en un vehículo acuoso (por ejemplo, agua destilada, solución salina fisiológica, solución de Ringer, etc.) o en un vehículo oleoso (por ejemplo, aceite vegetal, tal como aceite de oliva, aceite de sésamo, aceite de semilla de algodón, aceite de maíz, etc. o propilenglicol) junto con un dispersante, por ejemplo, Tween 80 (Atlas Powder, Estados Unidos), HCO 60 (Nikko Chemicals), polietilenglicol, carboximetilcelulosa, alginato sódico, etc.), un conservante (por ejemplo, *p*-hidroxibenzoato de metilo, *p*-hidroxibenzoato de propilo, alcohol bencílico, clorobutanol, fenol, etc.), un agente isotonizante (por ejemplo, cloruro sódico, glicerol, sorbitol, glucosa, azúcar invertido, etc.) y otros aditivos. Si se desea, también pueden añadirse un solubilizante (por ejemplo, salicilato sódico, acetato sódico, etc.), un estabilizante (por ejemplo, albúmina de suero humano), un agente balsámico (por ejemplo, cloruro de benzalconio, clorhidrato de procaína, etc.) y otros aditivos.

Una forma de dosificación para aplicación externa puede fabricarse procesando el componente o componentes activos en una composición sólida, semisólida o líquida. Para fabricar una composición sólida, por ejemplo, el componente o componentes activos, tal como estén o mezclados con un excipiente (por ejemplo, lactosa, manitol, almidón, celulosa microcristalina, sacarosa, etc.), un espesante (por ejemplo, gomas naturales, derivados de celulosa, polímeros acrílicos, etc.), etc., se procesan en polvos. La composición líquida puede fabricarse sustancialmente de la misma manera que las

inyecciones mencionadas anteriormente. La composición semisólida se proporciona preferiblemente en forma de un hidrogel o gel oleoso o en forma de una pomada. Estas composiciones pueden contener opcionalmente un agente de control del pH (por ejemplo, ácido carbónico, ácido fosfórico, ácido cítrico, ácido clorhídrico, hidróxido sódico, etc.) y un conservante (por ejemplo, ésteres del ácido *p*-hidroxibenzoico, clorobutanol, cloruro de benzalconio, etc.), entre otros aditivos.

Pueden fabricarse supositorios procesando el componente o componentes activos en una composición oleosa o acuosa, ya sea en estado sólido, semisólido o líquido. La base oleaginosa que puede usarse incluye, por ejemplo, glicéridos de ácidos grasos superiores [por ejemplo, manteca de cacao, Witepsols (Dinamit-Nobel), etc.], ácidos grasos de cadena media [por ejemplo, Migriols (Dinamit-Nobel), etc.], aceites vegetales (por ejemplo, aceite de sésamo, aceite de semilla de soja, aceite de semilla de algodón, etc.), etc. La base soluble en agua incluye, por ejemplo, polietilenglicoles, propilenglicol, etc. La base hidrófila incluye, por ejemplo, gomas naturales, derivados de celulosa, polímeros de vinilo y polímeros acrílicos, etc.

DOSIFICACIONES

Las dosificaciones de la composición farmacéutica de la presente invención pueden determinarse apropiadamente con referencia a las dosificaciones recomendadas para los componentes activos respectivos, y pueden seleccionarse apropiadamente de acuerdo con el receptor, la edad y el peso corporal del receptor, estado clínico actual, tiempo de administración, forma de dosificación, procedimiento de administración y combinación de

componentes activos, entre otros factores. Por ejemplo, la dosificación del compuesto de Fórmula I de la invención para un ser humano adulto puede seleccionarse entre el intervalo de dosificación clínica oral de 0,01 a 30 mg/kg de peso corporal (preferiblemente de 0,05 a 10 mg/kg de peso corporal, más preferiblemente de 0,05 a 5 mg/kg de peso corporal) o el intervalo de dosificación clínica parenteral de 0,005 a 10 mg/kg de peso corporal (preferiblemente de 0,01 a 10 mg/kg de peso corporal, más preferiblemente de 0,01 a 1 mg/kg de peso corporal) o de 1 a 1000 mg/día. El otro componente o componentes activos que tienen modos de acción diferentes para uso en la combinación también pueden usarse en los intervalos de dosificación seleccionados haciendo referencia a los intervalos de dosificación clínica recomendados respectivos. La administración se realiza generalmente en una sola dosis/día o en dosis divididas, por ejemplo, de 2 a 4 veces al día.

ABREVIATURAS

En la presente memoria pueden emplearse las siguientes abreviaturas:

Ph = fenilo

Bn = bencilo

t-Bu = butilo terciario

Me = metilo

Et = etilo

TMS = trimetilsililo

TBS = *terc*-butildimetilsililo

Et_2O = éter dietílico

EtOAc = acetato de etilo

MeOH = metanol

EtOH = etanol

i-PrOH = isopropanol

HOAc o AcOH = ácido acético

i-Pr_2NEt = diisopropiletilamina

Et_3N = trietilamina

DMAP = 4-dimetilaminopiridina

$NaBH_4$ = borohidruro sódico

n-BuLi = *n*-butillitio

Pd/C = paladio sobre carbono

KOH = hidróxido potásico

NaOH = hidróxido sódico

LiOH = hidróxido de litio

K_2CO_3 = carbonato potásico

$NaHCO_3$ = bicarbonato sódico

Ar = argón

N_2 = nitrógeno

min = minuto(s)

h = hora(s)

L = litro

ml = mililitro

µl = microlitro

g = gramo(s)

mg = miligramo(s)

mol = moles

mmol = milimol(es)

mequiv. = miliequivalentes

TA = temperatura ambiente

sat. = saturado

ac. = acuoso

TLC = cromatografía de capa fina

HPLC = cromatografía líquida de alta resolución

CL/EM = cromatografía líquida de alta resolución/espectrometría de masas

EM o Espec. de Masas = espectrometría de masas

RMN = resonancia magnética nuclear

p.f. = punto de fusión

EJEMPLOS

Los siguientes ejemplos se proporcionan para ilustrar diversas realizaciones preferidas de la invención, y no deben interpretarse como limitación del alcance de la misma.

SECCIÓN DE INFORMACIÓN EXPERIMENTAL GENERAL

En los siguientes ejemplos, la nomenclatura está sometida a las directrices de la IUPAC o CAS; y se generó usando (o es coherente con) el módulo Autonom® (versión 2.1) distribuido con ChemDraw Ultra 6,0®; o se tomó de la bibliografía del vendedor.

salmuera = cloruro sódico acuoso saturado

DIC = diisopropilcarbodiimida

DMF = *N,N*-dimetilformamida

HOBT = Hidroxibenzotriazol

PyBOP = hexafluoroborato de benzotriazo-1-il-oxi-trispirrolidinofosfonio

TFA = ácido trifluoroacético

THF = tetrahidrofuranilo

WSC = hidrocloruro de 1-[3-(dimetilamino)propil]-3-etilcarbodiimida

Procedimientos de cromatografía analíticos

HPLC: columna:

Procedimiento 1: Phenom-Luna (ODS) S-5, 4,6 mm x 50 mm; flujo - 5,0 ml/min.; detección a 220 nm; disolvente - A = metanol al 10%/agua + ácido fosfórico al 0,2%, B = metanol al 90%/agua + ácido fosfórico al 0,2%; gradiente - lineal, de 0% de B a 100% de B durante 4 min y 100% de B durante 1 min.

Procedimiento 2: YMC Combiscreen S-5, 4,6 mm x 50 mm; flujo - 4,0 ml/min.; detección a 220 nm; disolvente - A = metanol al 10%/agua + ácido fosfórico al 0,2%, B = metanol al 90%/agua + ácido fosfórico al 0,2%; gradiente - lineal, de 0% de B a 100% de B durante 4 min y 100% de B durante 1 min.

CL EM: columna - Phen-Luna (columna S5 ODS) 4,6 mm x 30 mm; detección a 220 nm; flujo - 4 ml/min; disolvente - A = metanol al 10%/agua + TFA al 0,1%, B = metanol al 90%/agua + TFA al 0,1%; gradiente lineal, de 0% de B a 100% de B durante 2 min y 100% de B durante 1 min.

Procedimiento de Cromatografía HPLC Preparativa

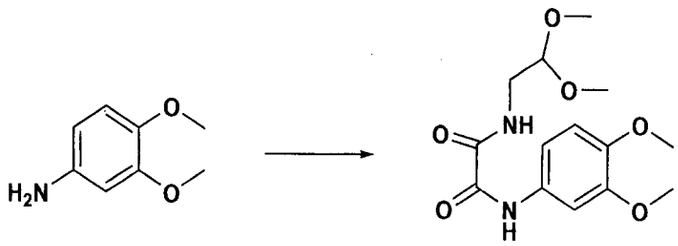
Phenomenex Luna C18, S5, 21 x 100 mm; flujo - 20 ml/min, detección a 220 nm; disolvente - A = metanol al 10%/agua + TFA al 0,1%, B = metanol al

90%/agua + TFA al 0,1%; gradiente - lineal, de 10% de B a 90% B durante 20 min.

Procedimientos Experimentales Generales para la Preparación de 3-(Ariltio-1-(aril)pirazin-2(1*H*)-ona

Preparación de 1-aril-pirazina-2,3(1H,4H)-diona

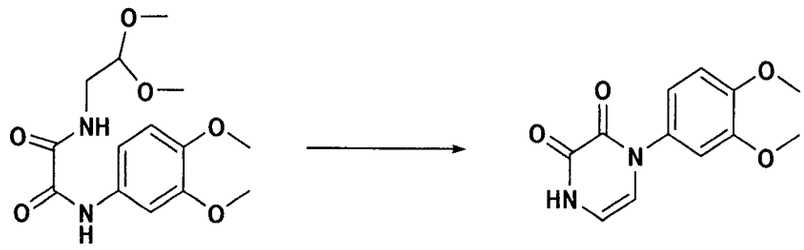
Parte A



Se añadió cloruro de etiloxalilo (7,8 g, 6,8 ml, 57 mmol) a una mezcla de 3,4-dimetoxianilina (4,4 g, 29 mmol) y K_2CO_3 (14 g, 140 mmol) en EtOAc (44 ml) y agua (12 ml) a 0°C. Después de agitar a 0°C durante 10 min, se añadió agua (18 ml); después de lo cual la mezcla se transfirió a un embudo de decantación y se extrajo con EtOAc (2 x 40 ml). Los extractos de EtOAc combinados se filtraron a través de Na_2SO_4 y se evaporaron hasta alcanzar un volumen de aproximadamente 30 ml. Después de la adición de 2,2-dimetoxietilamina (3,8 g, 3,9 ml, 36 mmol), la reacción se agitó a temperatura ambiente durante una noche. El sólido de color blanco resultante se filtró y después se lavó con hexano, proporcionando *N1*-(2,2-dimetoxietil)-N2-(3,4-dimetoxifenil)oxalamida en forma de un sólido de color púrpura-gris claro (6,3 g, rendimiento del 71%). HPLC 33% a 2,47 min y 63% a 2,79 min. CL EM 1,37 min (M+1 = 281 y 335). RMN H ($CDCl_3$) 9,15 (s ancho, 1H), 7,76 (s ancho, 1H), 7,41 (d, *J* = 2,4 Hz,

1H), 7,06 (dd, *J* = 2,4, 8,7 Hz, 1H), 6,85 (d, *J* = 8,7 Hz, 1H), 4,45 (t, *J* = 5,5 Hz, 1H), 3,90 (s, 3H), 3,88 (s, 3H), 3,52 (t, *J* = 5,5 Hz, 2H), 3,42 (s, 6 H).

Parte B

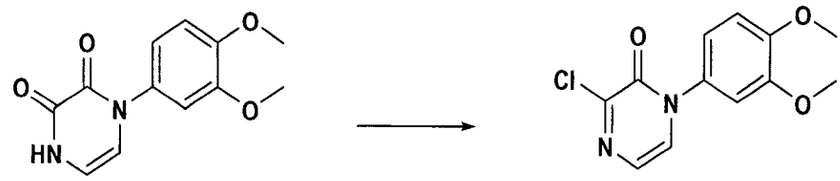


Después de la adición de ácido trifluoroacético (0,12 ml, 1,7 mmol) a una mezcla de la ariloxalamida preparada en la Parte A (0,50 g, 1,6 mmol) en ácido acético (1,0 ml), la solución resultante se calentó a 125°C durante 20 min usando un microondas. Después de la evaporación del disolvente, el residuo se trituró con EtOAc, proporcionando 1-(3,4-dimetoxifenil)pirazina-2,3(1*H*,4*H*)-diona en forma de un sólido de color blanco (1,1 g, rendimiento del 92%). HPLC 1,83 min. CL EM 1,20 min (M+1 = 249). RMN H (CD_3OD) 7,06 (m, 2H), 6,97 (m, 1H), 6,56 (d, *J* = 5,7 Hz, 1H), 6,45 (d, *J* = 5,7 Hz, 1H), 3,89 (s, 3H), 3,85 (s, 3H).

Preparación de la 3-tio-1-aril-pirazin-2(1*H*)-ona sustituida deseada

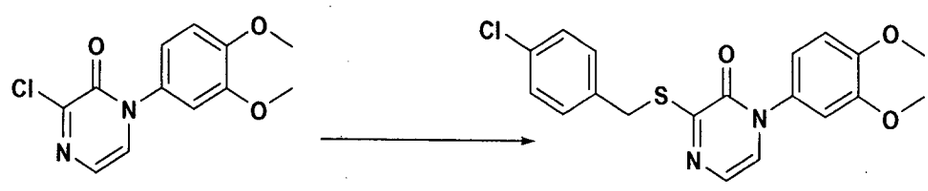
Procedimiento 1

Parte C



Se añadió lentamente cloruro de tionilo (0,28 g, 0,17 ml, 2,4 mmol) a una solución agitada de la 1-aril-pirazina-2,3(1*H*,4*H*)-diona preparada en la Parte B (0,54 g, 2,2 mmol) en EtOAc (0,88 ml) y DMF (0,44 ml) a 45ºC. Después de agitar de 55 a 60ºC durante 2 h, la reacción se transfirió a un embudo de decantación, se diluyó con EtOAc y $KHCO_3$ 2 N y se extrajo con EtOAc (2 veces). Las fases orgánicas combinadas se lavaron con $KHCO_3$ 2 N y agua; después de ello, las fases acuosas combinadas se extrajeron con CH_2Cl_2. Todas las fases orgánicas se combinaron antes del secado sobre $MgSO_4$, proporcionando 3-cloro-1-(3,4-dimetoxifenil)pirazin-2(1*H*)-ona (0,34 g, rendimiento del 59%). HPLC 2,33 min. CL EM 1,00 min (M+1 = 267/269). La cloropirazinona se usó en las etapas posteriores sin purificación adicional.

Parte D



Se añadió 4-clorobencilmercaptano (71 mg, 0,059 ml, 0,45 mmol) a una suspensión agitada en THF (1,0 ml) de hidruro sódico (dispersión en aceite al 60%, 18 mg, 0,45 mmol), que se había lavado previamente 3 veces con hexano. La reacción se agitó a temperatura ambiente durante 20 min hasta que se convirtió en una masa sólida; después de ello, se añadió la cloropirazinona

preparada en la Parte C (100 mg, 0,38 mmol) en THF (5 ml), dando como resultado desprendimiento de gas. Después de agitar a temperatura ambiente durante 40 min, la reacción se diluyó con CH_2Cl_2/H_2O, se extrajo con CH_2Cl_2 (2 veces) y se secó sobre $MgSO_4$, proporcionando 220 mg de producto en bruto después de la evaporación del disolvente. El producto deseado se purificó por cromatografía sobre gel de sílice (12 g) empleando un gradiente de elución (EtOAc al 0 - 100%/hexano durante 12 min) para eluir la 3-(4-clorobenciltio-1-(3,4-dimetoxifenil)pirazin-2(1*H*)-ona deseada (130 mg, rendimiento del 89%).

Procedimiento 2

Una solución de la 1-aril-pirazina-2,3(1*H*,4*H*)-diona preparada en la Parte B (67 mg, 0,27 mmol), diisopropiletilamina (0,15 ml, 0,81 mmol), PyBOP (0,23 g, 0,46 mmol) y dimetilaminopiridina (13 mg) en DMF (1,2 ml) se agitó a temperatura ambiente durante 15 min. Después de la adición de 2-piridiletilmercaptano (28 mg, 0,40 mmol), la reacción se agitó a temperatura ambiente durante 2,5 h antes de inactivarse mediante la adición de H_2O y extracción con EtOAc. Los extractos de EtOAc se lavaron con agua (2 veces) y salmuera, se secaron sobre $MgSO_4$ y se concentraron, produciendo 204 mg del producto en bruto. La cromatografía sobre sílice empleando un gradiente de elución con hexano/EtOAc proporcionó el producto deseado 1-(3,4-dimetoxifenil)-3-(2-(pirazin-2-il)etiltio)pirazin-2(1*H*)-ona (17 mg, rendimiento del 17%).

Procedimiento 2a

Se empleó el mismo procedimiento que se ha descrito en el

Procedimiento 2 con la excepción de que la reacción se realizó durante 18 h.

Procedimiento 3

Después de la preparación de la oxalamida como se ha descrito en la Parte A, puede realizarse el cierre del anillo por calentamiento térmico prolongado en TFA/HOAc a 78ºC durante día. En el caso de la 3-metoxi-4-(2-(pirrolidin-1-il)etoxi)anilina que contenía una amina básica, la reacción se llevó a un valor de pH de 6 a 7 con $NaHCO_3$ saturado y después se evaporó al vacío. El residuo se absorbió sobre gel de sílice y se purificó por cromatografía ultrarrápida (NH_3 2 N del 5 al 15% en $MeOH/CH_2Cl_2$), proporcionando la 1-aril-pirazina-2,3(1*H*,4*H*)-diona deseada con un rendimiento del 36%. Este material se convirtió posteriormente en el producto final siguiendo el procedimiento descrito en el Procedimiento 2.

Procedimiento 4

Si la oxalamida que se ha descrito en la Parte A contenía un alcohol primario o secundario, el calentamiento térmico prolongado en TFA/HOAc a 78ºC durante 1 día no sólo produjo el cierre del anillo sino que además convirtió el resto alcohólico en un acetato. La 1-aril-pirazina-2,3(1*H*,4*H*)-diona resultante se convirtió en la 3-tio sustituido-1-arilpirazin-2-ona deseada empleando el Procedimiento 1. Después del tratamiento y la purificación como se han descrito en el Procedimiento 1, el producto acetilado se convirtió en la 3-tio sustituido-1-arilpirazin-2-ona deseada (19 mg, 0,041 mmol) que tenía un hidroxilo libre por disolución en MeOH (1,0 ml) y H_2O (0,1 ml) y agitación a temperatura ambiente durante 1 h después de la adición de carbonato potásico

(30 mg). Después, la reacción se diluyó con CH_2Cl_2/H_2O antes de la extracción con CH_2Cl_2 (2 veces). Después de secar las fases orgánicas combinadas sobre $MgSO_4$, la concentración proporcionó el producto final deseado (16 mg, rendimiento del 93%).

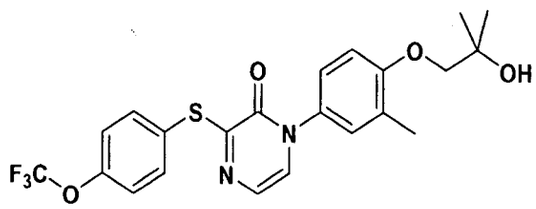
Procedimiento 5

Para tioles débilmente nucleófilos se requirieron condiciones más fuertes para realizar la conversión mediada por PyBOP de la 1-aril-pirazina-2,3(1*H*,4*H*)-diona en 3-tio sustituido-1-arilpirazin-2-onas. Por consiguiente, se agitó una solución en DMF (0,4 ml) que contenía la 1-aril-pirazina-2,3(1*H*,4*H*)-diona preparada en la Parte B (92 mg, 0,30 mmol), PyBOP (0,27 g, 0,53 mmol) y diisopropiletilamina (0,16 ml, 0,9 mmol) durante 3 h antes de la adición de una solución de DMF preparada por agitación de 5-metoxibenzo[d]tiazol-2-tiol (296 mg, 1,502 mmol) con NaH (60,1 mg, 1,502 mmol, se aclaró 2 veces con hexano) en DMF (0,2 ml) a temperatura ambiente durante 10 min. Después de agitar a temperatura ambiente durante 7 días, la mezcla de reacción se diluyó con EtOAc y se lavó secuencialmente con agua (2 veces) y salmuera antes de secarse sobre $MgSO_4$. Después de la evaporación del disolvente, se añadió CH_2Cl_2 (10 ml) a 0,30 g de producto en bruto. La filtración para retirar cualquier sólido residual seguido de evaporación del filtrado proporcionó 0,10 g del producto en bruto. La purificación final requirió cromatografía ultrarrápida sobre 12 g de gel de sílice usando un gradiente de elución (EtOAc del 0 al 100%/CH_2Cl_2) seguido de HPLC preparativa (YMC S5 ODS 20 x 100 mm, 20 ml/min, del 30 a 100% de B en A durante 10 min. Disolvente A = MeOH al 10%/H2O - TFA al 0,1%, Disolvente B = MeOH al 90%/H2O - TFA al 0,1%),

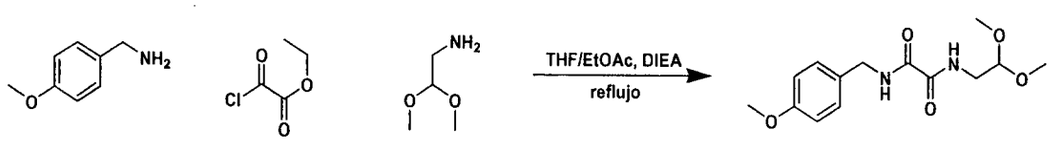
proporcionando el producto puro deseado (6,3 mg, rendimiento del 4%).

Procedimiento 6

Procedimientos Experimentales Generales para la Preparación de 1-(4-(2-Hidroxi-2-metilpropoxi)-3-metilfenil)-3-(4-(trifluorometoxi)feniltio)pirazin-2(1*H*)-ona



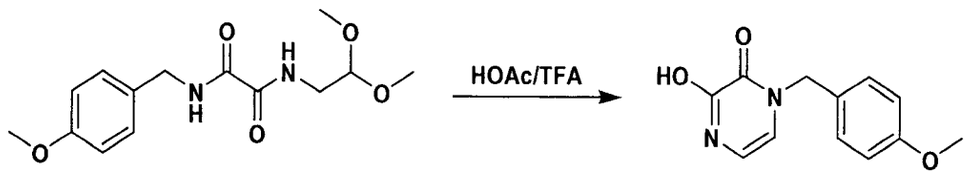
Parte A. *N*1-(2,2-Dimetoxietil)-*N*2-(4-metoxibencil)oxalamida



A una mezcla de (4-metoxifenil)metanamina (9,90 g, 72,2 mmol) en THF (40 ml) se le añadió lentamente 2-cloro-2-oxoacetato de etilo (10,84 g, 79 mmol). Después de agitar la reacción a TA durante 15 min, se añadió una solución de 2,2-dimetoxietanamina (9,10 g, 87 mmol) y *N,N*-diisopropiletilamina (37,8 ml, 217 mmol) en EtOAc (40,0 ml). La reacción se calentó a reflujo durante 18 horas; después de lo cual, tras la refrigeración a TA, se añadió $NaHCO_3$ saturado (50 ml) y la mezcla se extrajo con EtOAc (50 ml). La fase de EtOAc se secó sobre Na_2SO_4 y se concentró. El producto en bruto se purificó por cromatografía sobre gel de sílice empleando un gradiente disolvente (de CH_2Cl_2 a MeOH al 5%/CH_2Cl_2) para eluir la *N*1-(2,2-dimetoxietil)-*N*2-(4-metoxibencil)oxalamida (7,50 g, 25,3 mmol, rendimiento del 35,1%) en forma de un sólido de color blanco. RMN ^1H (400 MHz, cloroformo-d) δ ppm 9,07 (1 H, s), 7,69 (1 H, t, J = 5,65 Hz), 7,59 (1 H, d, J = 8,78 Hz), 6,74 (1 H, d, J = 8,78

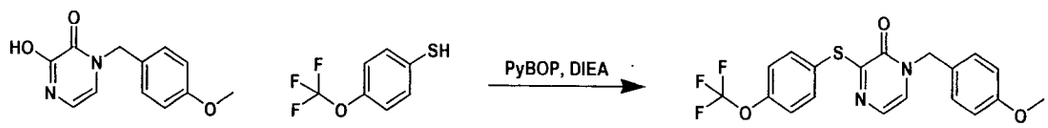
Hz), 4,46 (1 H, t, J = 5,40 Hz), 3,79 (2 H, s), 3,53 (2 H, t), 3,44 (6 H, s), 2,23 (6 H, d, J = 5,27 Hz), 1,37 (6 H, s).

Parte B. 3-Hidroxi-1-(4-metoxibencil)pirazin-2(1*H*)-ona



Una solución de *N*1-(2,2-dimetoxietil)-N2-(4-metoxibencil)oxalamida (7,5 g, 25,3 mmol) y TFA (2,340 ml, 30,4 mmol) en AcOH (160 ml) se agitó a 135ºC en un tubo cerrado herméticamente durante 1,5 horas. Después de enfriar a TA y de retirar los volátiles al vacío, se añadieron éter etílico (150 ml) y una solución ac. sat. de $NaHCO_3$ (150 ml). El precipitado resultante se recogió por filtración, se lavó con H_2O (50 ml) y éter (50 ml) antes del secado a alto vacío para producir 3-hidroxi-1-(4-metoxibencil)pirazin-2(1*H*)-ona (5,30 g, 21,68 mmol, rendimiento del 86%) en forma de un sólido de color pardo. RMN ^1H (400 MHz, DMSO-d_6) δ ppm 11,17 (1 H, s a), 7,18 (2 H, d), 6,81 (2 H, d), 6,46 (1 H, d, J = 5,77 Hz), 6,23 (1 H, s a), 4,74 (2 H, s), 3,24 (1 H, s).

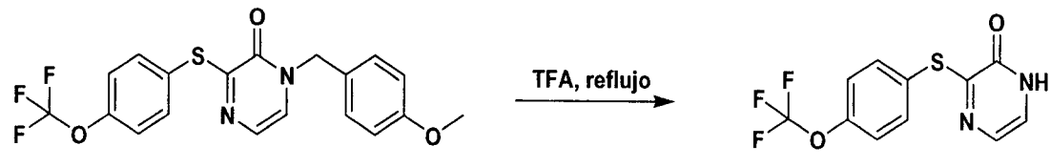
Parte C. 1-(4-Metoxibencil)-3-(4-(trifluorometoxi)feniltio)pirazin-2(1*H*)-ona



Una mezcla de 3-hidroxi-1-(4-metoxibencil)pirazin-2(1*H*)-ona (2,0 g, 8,61 mmol), PyBOP (7,84 g, 15,07 mmol) y *N,N*-diisopropiletilamina (4,51 ml, 25,8 mmol) en DMF (40 ml) se agitó a TA en atmósfera de N_2 durante 3 horas, después de lo cual se añadió 4-(trifluorometoxi)bencenotiol (2,007 g, 10,33 mmol). Después de agitar durante 18 horas más, la reacción se diluyó con

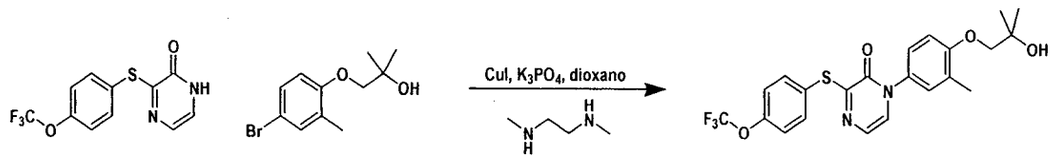
$NaHCO_3$ ac. saturado (65 ml) y después se extrajo con EtOAc (60 ml). La fase de EtOAc se secó sobre Na_2SO_4 y se concentró. El producto en bruto se purificó por cromatografía sobre gel de sílice empleando un gradiente disolvente (de hexano a EtOAc al 75%/hexano) para eluir 1-(4-metoxibencil)-3-(4-(trifluorometoxi)feniltio)pirazin-2(1*H*)-ona (2,76 g, 6,42 mmol, rendimiento del 74,6%) en forma de un sólido de color blanco. RMN ^{1}H (400 MHz, cloroformo-d) δ ppm 7,58 (2 H, d, J = 8,78 Hz), 7,21 - 7,35 (4 H, m), 7,02 (1 H, d, J = 4,52 Hz), 6,90 (2 H, d, J = 8,78 Hz), 6,85 (1 H, d, J = 4,27 Hz), 5,03 (2 H, s), 3,81 (3 H, s).

Parte D. 3-(4-(Trifluorometoxi)feniltio)pirazin-2(1*H*)-ona



Una solución de 1-(4-metoxibencil)-3-(4-(trifluorometoxi)feniltio)-pirazin-2(1*H*)-ona (2,76 g, 6,76 mmol) en TFA (25 ml) se agitó a la temperatura de reflujo durante 2 días. Como el análisis por CL-EM reveló que aún quedaba un 28% de MP, la reacción se agitó durante 7 días. Después de la retirada del TFA al vacío, el producto en bruto se purificó por cromatografía sobre gel de sílice empleando un gradiente disolvente (de hexano a EtOAc al 100%) para eluir la 3-(4-(trifluorometoxi)feniltio)pirazin-2(1*H*)-ona (1,60 g, 5,27 mmol, rendimiento del 78%) en forma de un sólido de color blanquecino. RMN ^{1}H (400 MHz, cloroformo-d) δ ppm 7,61 (2 H, d, J = 9,03 Hz), 7,29 (2 H, d, J = 7,78 Hz), 7,24 (1 H, d, J = 4,02 Hz), 7,07 (1 H, d).

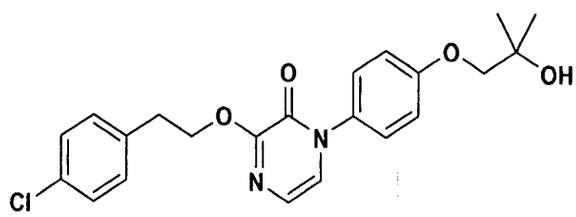
Parte E. 1-(4-(2-Hidroxi-2-metilpropoxi)-3-metilfenil)-3-(4-(trifluorometoxi)feniltio)pirazin-2(1*H*)-ona



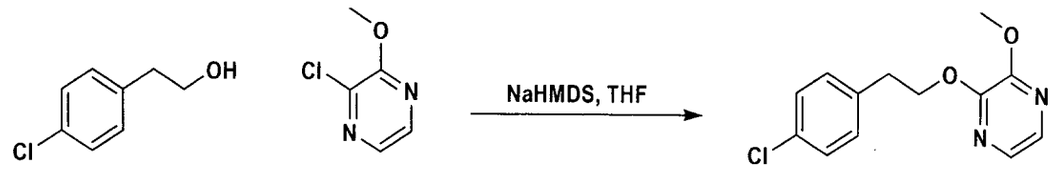
Una mezcla de 3-(4-(trifluorometoxi)feniltio)pirazin-2(1*H*)-ona (100 mg, 0,347 mmol), 1-(4-bromo-2-metilfenoxi)-2-metilpropan-2-ol (90 mg, 0,347 mmol), *N*1,*N*2-dimetiletano-1,2-diamina (92 mg, 1,041 mmol), yoduro de cobre (I) (19,82 mg, 0,104 mmol) y K_3PO_4 (221 mg, 1,041 mmol) en dioxano (1,0 ml) se agitó a 115°C en un tubo cerrado herméticamente durante 2 horas. Después de la retirada del precipitado por filtración, el filtrado se concentró. El producto en bruto se purificó por cromatografía sobre gel de sílice empleando un gradiente disolvente (de hexano a EtOAc al 100%) para eluir la 1-(4-(2-hidroxi-2-metilpropoxi)-3-metilfenil)-3-(4-(trifluorometoxi)feniltio)-pirazin-2(1*H*)-ona (18,65 mg, 0,040 mmol, rendimiento del 11,52%) en forma de un sólido de color blanquecino. RMN ^{1}H (500 MHz, metanol-d_3) δ ppm 7,62 - 7,68 (2 H, m), 7,37 (2 H, d, J = 7,97 Hz), 7,21 - 7,28 (3 H, m), 7,16 (1 H, d, J = 4,40 Hz), 7,02 (1 H, d, J = 8,25 Hz), 3,84 (2 H, s), 2,31 (3 H, s), 1,36 (6 H, s).

Procedimiento 7

Procedimientos Experimentales Generales para la Preparación de 3-(4-Clorofenetoxi)-1-(4-(2-hidroxi-2-metilpropoxi)fenil)pirazin-2(1*H*)-ona

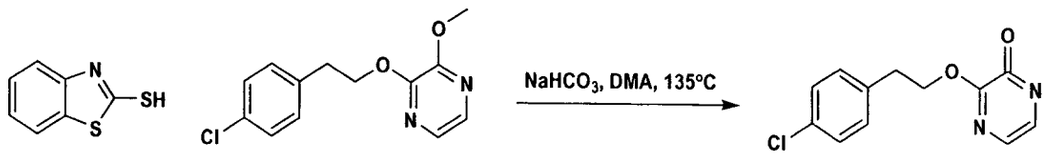


Parte A. 2-(4-Clorofenetoxi)-3-metoxipirazina



A una mezcla de 2-(4-clorofenil)etanol (1,246 g, 7,96 mmol) en THF se le añadió *bis*(trimetilsilil)amida sódica 1,0 M en THF (6,92 ml, 6,92 mmol). Después de agitar a TA en atmósfera de nitrógeno durante 18 horas, la reacción se diluyó con una solución de $NaHCO_3$ saturado (65 ml) y se extrajo con EtOAc 720 ml). La fase de acetato de etilo se secó sobre Na_2SO_4 y se concentró. El producto en bruto se purificó por cromatografía sobre gel de sílice empleando un gradiente disolvente (de hexano a 30% acetato de etilo) para eluir la 2-(4-clorofenetoxi)-3-metoxipirazina (1,25 g, 4,72 mmol, rendimiento del 68,3%) en forma de un aceite transparente. RMN ^1H (500 MHz, $CDCl_3$) δ ppm 7,61 - 7,64 (1 H, m), 7,59 - 7,61 (1 H, m), 7,26 - 7,30 (2 H, m), 7,20 - 7,24 (2 H, m), 7,15 (1 H, d, J = 8,52 Hz), 4,49 - 4,63 (2 H, m), 4,02 (3 H, s), 3,12 (2 H, t, J = 7,29 Hz).

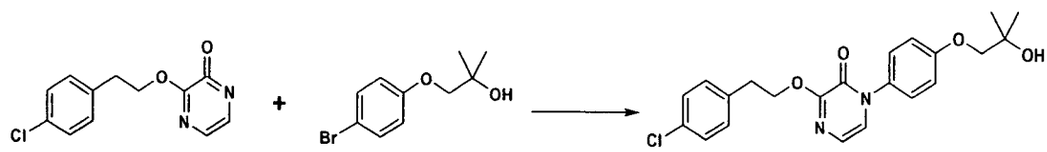
Parte B. 3-(4-Clorofenetoxi)pirazin-2(1*H*)-ona



Una mezcla de benzo[d]tiazol-2-tiol (1,264 g, 7,56 mmol), 2-(4-clorofenetoxi)-3-metoxipirazina (1,00 g, 3,78 mmol) y $NaHCO_3$ (1,587 g, 18,89 mmol) en DMA (10 ml) se agitó a 135°C durante 6 horas. Después de enfriar a TA, la mezcla se diluyó con una solución de $NaHCO_3$ saturado (55 ml) y después se extrajo con EtOAc (60 ml). La fase de EtOAc se secó sobre Na_2SO_4 y se concentró. El producto en bruto se purificó por cromatografía

sobre gel de sílice empleando un gradiente disolvente (de hexano a EtOAc al 100%) para eluir la 3-(4-clorofenetoxi)pirazin-2(1*H*)-ona (477 mg, 1,808 mmol, rendimiento del 47,9%) en forma de un sólido de color blanquecino. RMN ^{1}H (400 MHz, cloroformo-d) δ ppm 7,27 - 7,31 (2 H, m), 7,19 - 7,25 (2 H, m), 6,95 (1 H, d, J = 4,27 Hz), 6,89 (1 H, d, J = 4,52 Hz), 4,54 (2 H, t, J = 7,53 Hz), 3,14 (2 H, t, J = 7,40 Hz).

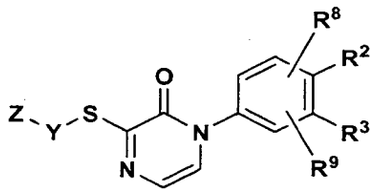
Parte C. 3-(4-Clorofenetoxi)-1-(4-(2-hidroxi-2-metilpropoxi)fenil)pirazin-2(1*H*)-ona

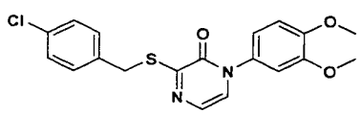
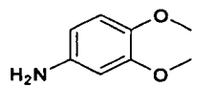
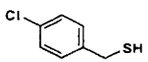
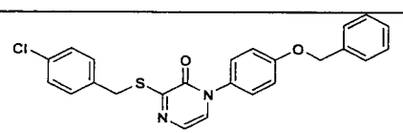
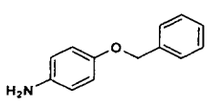
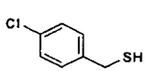
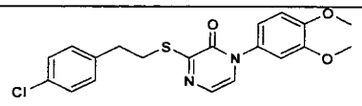
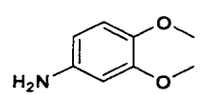
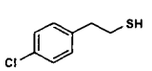


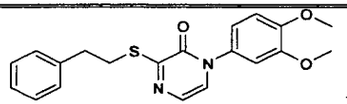
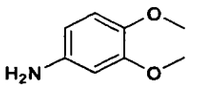
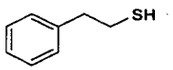
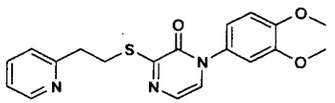
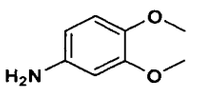
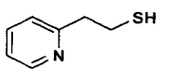
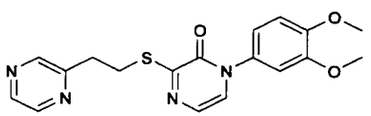
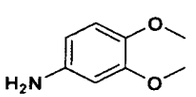
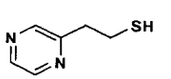
Una mezcla de 3-(4-clorofenetoxi)pirazin-2(1*H*)-ona (25 mg, 0,100 mmol), K_3PO_4 (63,5 mg, 0,299 mmol), yoduro de cobre (I) (18,99 mg, 0,100 mmol), 1-(4-bromofenoxi)-2-metilpropan-2-ol y *N,N'*-dimetiletilendiamina (0,032 ml, 0,299 mmol) en dioxano (1,0 ml) se agitó a 110°C durante 60 min. Después de la retirada del precipitado por filtración, el filtrado se concentró. El producto en bruto se purificó por cromatografía sobre gel de sílice empleando un gradiente disolvente (de CH_2Cl_2 a MeOH al 10%/CH_2Cl_2) para eluir la 3-(4-clorofenetoxi)-1-(4-(2-hidroxi-2-metilpropoxi)fenil)pirazin-2(1*H*)-ona (31,82 mg, 0,073 mmol, rendimiento del 73,1%) en forma de un sólido de color blanco. RMN ^{1}H (500 MHz, cloroformo-d) δ ppm 7,32 (2 H, d), 7,23 - 7,29 (4 H, m), 7,02 (2 H, d), 6,84 (2 H, s), 4,51 (2 H, t, J = 7,29 Hz), 3,83 (2 H, s), 3,13 (2 H, t, J = 7,15 Hz), 1,36 (6 H, s).

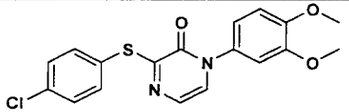
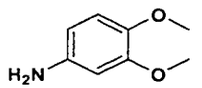
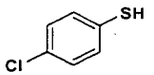
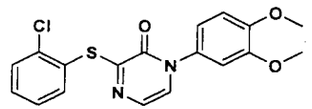
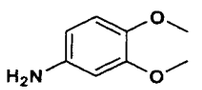
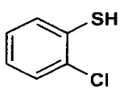
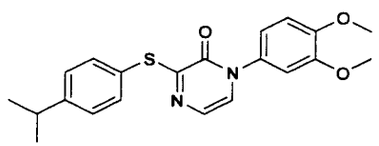
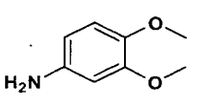
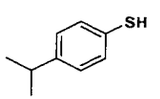
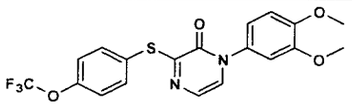
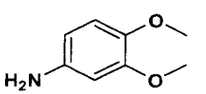
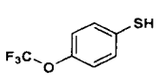
TABLA 1

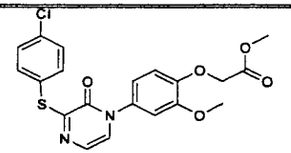
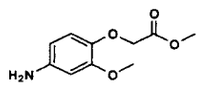
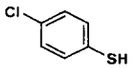
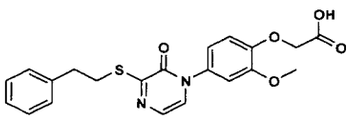
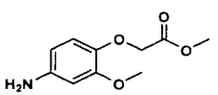
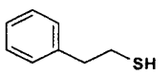
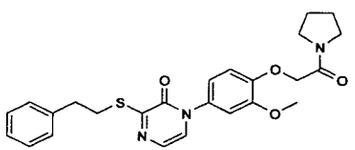
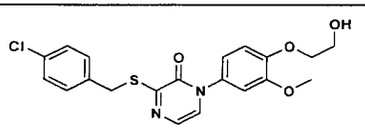
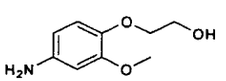
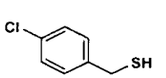
1-Arilpirazin-2(1*H*)-onas 3-tio-sustituidas

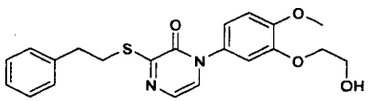
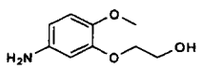
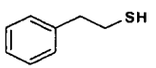
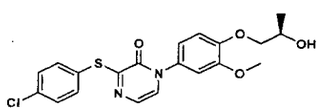
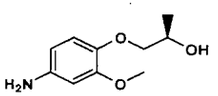
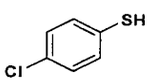
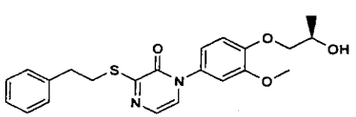
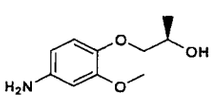
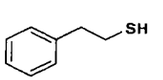


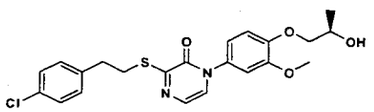
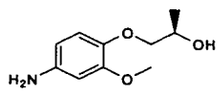
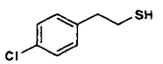
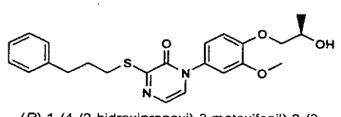
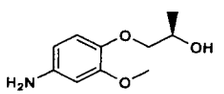
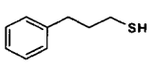
Ej. Nº.	Estructura	Componente de Anilina/Bromuro	Componente de Tiol	Proc.	Rend. (%)	HPLC (Min) Proc. 1	CL-EM (M+H)	Datos de H RMN ($CDCl_3$)
1	 3-(4-clorobenciltio)-1-(3,4-dimethoxifenil)pirazin-2(1*H*)-ona			1	50	4,09	389/391	7,36 (d, J = 8,4 Hz, 2H), 7,26 (d, J = 8,4 Hz, 2H), 7,41 (d, J = 2,4 Hz, 1H), 7,25 (d, J = 4,6 Hz, 1H), 6,98 (d, J = 4,6 Hz, 1H), 6,94 (d, J = 2,2 Hz, 1H), 6,91 (d, J = 8,5 Hz, 1H), 6,88 (dd, J = 2,2 y 8,5 Hz, 1H), 4,28 (s, 2H), 3,91 (s, 3H), 3,87 (s, 3H).
2	 1-(4-(benciloxi)fenil)-3-(4-clorobenciltio)pirazin-2(1*H*)-ona			1		4,60	435/437	7,44-7,24 (m, 12H), 7,05 (d, J = 8,9 Hz, 2H), 6,96 (d, J = 4,5 Hz, 1H), 5,09 (s, 2H), 4,27 (s, 2H).
3	 3-(4-clorofenetiltio)-1-(3,4-dimetoxifenil)pirazin-2(1*H*)-ona			1	9	4,23	403/405	7,27 (m, 6H), 6,93 (m, 3H), 3,92 (s, 3H), 3,89 (s, 3H), 3,30 (t, J = 7,3 Hz, 2H), 2,98 (t, J = 7,3 Hz, 2H)

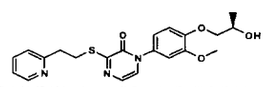
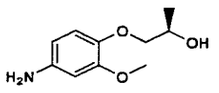
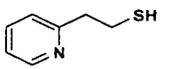
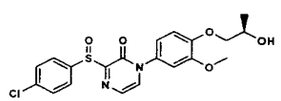
Ej. Nº.	Estructura	Componente de Anilina/Bromuro	Componente de Tiol	Proc.	Rend. (%)	HPLC (Min) Proc. 1	CL-EM (M+H)	Datos de H RMN ($CDCl_3$)
4	 1-(3,4-dimetoxifenil)-3-(fenetiltio)pirazin-2(1*H*)-ona			1	68	4,01	369	7,28 (m, 6H), 6,92 (m, 4H), 3,91 (s, 3H), 3,88 (s, 3H), 3,32 (dd, J = 2,2 y 7,5 Hz, 2H), 3,02 (dd, J = 2,2 y 7,5 Hz, 2H)
5	 1-(3,4-dimetoxifenil)-3-(2-(piridin-2-il)etiltio)pirazin-2(1*H*)-ona			2	11	2,36	370	(CD_3OD) 8,35 (dd, J = 1,0 y 4,5 Hz, 1H), 7,65 (m, 1H), 7,27 (d, J = 7,8 Hz, 1H), 7,23 (d, J = 4,3 Hz, 1H), 7,16 (m, 1H), 7,11 (d, J = 4,3 Hz, 1H), 6,93 (d, J = 2,3 Hz, 1H), 6,92 (d, J = 8,5 Hz, 1H), 6,82 (dd, J = 2,3 y 8,5 Hz, 1H), 3,74 (s, 3H), 3,69 (s, 3H), 3,33 (t, J = 7,1 Hz, 2H), 3,06 (t, J = 7,1 Hz, 2H).
6	 1-(3,4-dimetoxifenil)-3-(2-(pirazin-2-il)etiltio)pirazin-2(1*H*)-ona			2	37	3,01	371	8,45 (s, 1H), 8,44 (d, J = 3,0 Hz, 1H), 8,33 (d, J = 3,0 Hz, 1H), 7,22 (d, J = 4,5 Hz, 1H), 7,12 (d, J = 4,5 Hz, 1H), 6,94 (d, J = 2,4 Hz, 1H), 6,93 (d, J = 8,5 Hz, 1H), 6,83 (dd, J = 2,4 y 8,5 Hz, 1H), 3,74 (s, 3H), 3,71 (s, 3H), 3,39 (t, J = 7,2 Hz, 2H), 3,13 (t, J = 7,2 Hz, 2H)

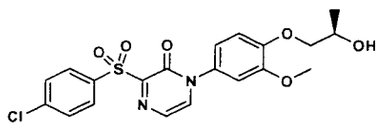
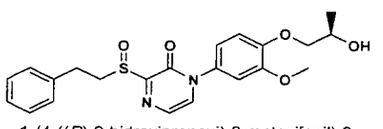
Ej. Nº.	Estructura	Componente de Anilina/Bromuro	Componente de Tiol	Proc.	Rend. (%)	HPLC (Min) Proc. 1	CL-EM (M+H)	Datos de H RMN ($CDCl_3$)
7	 3-(4-clorofeniltio)-1-(3,4-dimetoxifenil)pirazin-2(1*H*)-ona			2	9	3,87	375/377	7,52 (d, J = 8,5 Hz, 2H), 7,42 (d, J = 8,5 Hz, 2H), 7,13 (d, J = 4,5 Hz, 1H), 6,97 (d, J = 4,5 Hz, 1H), 6,95 (m, 1H), 6,92 (m, 2H), 3,93 (s, 3H), 3,89 (s, 3H).
8	 3-(2-clorofeniltio)-1-(3,4-dimetoxifenil)pirazin-2(1*H*)-ona			2	23	3,59	375/377	7,67 (dd, J = 1,7 y 7,6 Hz, 1H), 7,57 (dd, J = 1,3 y 8,0 Hz, 1H), 7,43 (dd, J = 1,7 y 7,6 Hz, 1H), 7,35 Hz (dd, J = 1,3 y 7,5 Hz, 1H), 7,12 (d, J = 4,4 Hz, 1H), 7,00 (d, J = 1,6 Hz, 1H), 6,98 (d, J = 4,4 Hz, 1H), 6,95 (m, 2H), 3,93 (s, 3H), 3,91 (s, 3H).
9	 1-(3,4-dimetoxifenil)-3-(4-isopropilfeniltio)-pirazin-2(1*H*)-ona			2	70	4,13	383	7,51 (d, J = 8,2 Hz, 2H), 7,32 (d, J = 8,2 Hz, 2H), 7,13 (d, J = 4,5 Hz, 1H), 6,99 (m, 1H), 6,96 (d, J = 4,5 Hz, 1H), 6,91 (m, 2H), 3,92 (s, 3H), 3,90 (s, 3H), 2,96 (sept., J = 7,7 Hz, 1H), 1,28 (d, J = 7,7 Hz, 6H).
10	 1-(3,4-dimetoxifenil)-3-(4-trifluoro-metoxifeniltio)-pirazin-2(1*H*)-ona			2	60	4,02	425	7,61 (d, J = 8,5 Hz, 2H), 7,29 (d, J = 8,5 Hz, 2H), 7,13 (d, J = 4,4 Hz, 1H), 7,00 (d, J = 4,4 Hz, 1H), 6,96 (m, 1H), 6,92 (m, 2H), 3,93 (s, 3H), 3,90 (s, 3H)

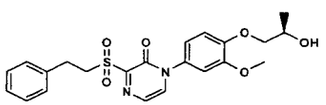
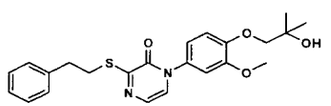
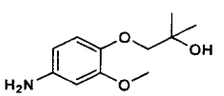
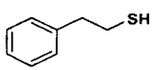
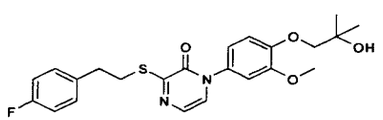
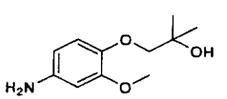
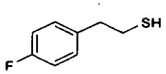
Ej. Nº.	Estructura	Componente de Anilina/Bromuro	Componente de Tiol	Proc.	Rend. (%)	HPLC (Min) Proc. 1	CL-EM (M+H)	Datos de H RMN ($CDCl_3$)
11	 2-(4-(3-(4-clorofeniltio)-2-oxopirazin-1(2*H*)-il)-2-metoxifenoxi)acetato de metilo			1	2,5	3,94	433/435	7,36 (m, 2H), 7,28 (m, 3H), 6,96 (m, 3H), 6,87 (m, 1H), 4,72 (s, 3H), 4,28 (s, 2H), 3,87 (s, 3H).
12	 ácido 2-(2-metox-4-(2-oxo-3-(fenetiltio)pirazin-1(2*H*)-il)fenoxi)acético			1	8		413	9,45 (s ancho, 1H), 7,39 (m, 1H), 7,28 (m, 5H), 6,98 (m, 2H), 6,87 (m, 2H), 4,73 (s, 2H), 3,85 (s, 3H), 3,34 (t, J = 8,2 Hz, 2H), 3,01 (t, J = 8,2 Hz, 2H)
13	 1-(3-metoxi-4-(2-oxo-2-(pirrolidin-1-il)etoxi)-fenil)-3-(fenetiltio)pirazin-2(1*H*)-ona			WSC, acopl. mediado por HOBT del Ej. 15	27	3,95	466	7,30 (m, 6H), 7,05 (d, J = 7,5 Hz, 1H), 7,01 (d, J = 1,6 Hz, 1H), 6,96 (d, J = 6,6 Hz, 1H) 6,84 (dd, J = 1,6 y 7,5 Hz, 1H), 4,72 (s, 2H), 3,87 (s, 3H), 3,55 (m, 4H), 3,32 (t, J = 7,4 Hz, 2H), 3,02 (t, J = 7,4 Hz, 2H), 1,97 (m, 2H), 1,86 (m, 2H).
14	 3-(4-clorobenciltio)-1-(4-(2-hidroxietoxi)-3-metoxifenil)pirazin-2(1*H*)-ona			4	3,9	3,96	419/421	7,36 (m, 2H), 7,26 (m, 3H), 6,97 (m, 3H), 6,87 (m, 1H), 4,28 (s, 2H), 4,15 (t, J = 4,2 Hz, 2H), 3,98 (t, J = 4,2 Hz, 2H), 3,85 (s, 3H).

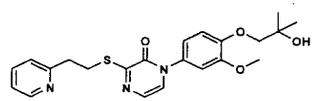
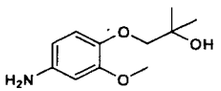
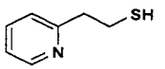
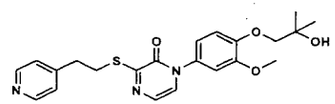
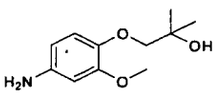
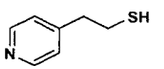
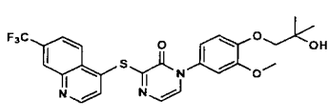
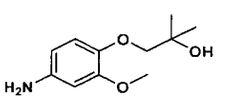
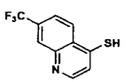
Ej. Nº.	Estructura	Componente de Anilina/Bromuro	Componente de Tiol	Proc.	Rend. (%)	HPLC (Min) Proc. 1	CL-EM (M+H)	Datos de H RMN ($CDCl_3$)
15	 1-(3-(2-hidroxietoxi)-4-metoxifenil)-3-(fenetiltio)pirazin-2(1*H*)-ona			2 Proc. 4 para hidrólisis del éster	2	3,86	399	(CD_3OD) 7,41 (d, J = 4,3 Hz, 1H), 7,31 (m, 4H), 7,26 (d, J = 4;3 Hz, 1H), 7,20 (m, 1H), 7,10 (d, J = 8,6 Hz, 1H), 7,12 (d, J = 2,4 Hz, 1H), 7,00 (dd, J = 2,4 y 8,6 Hz, 1H), 4,09 (t, J = 4,7 Hz, 2H), 3,92 (s, 3H), 3,90 (t, J = 4,7 Hz, 2H), 3,33 (dd, J = 6,0 y 8,0 Hz, 2H), 3,00 (dd, J = 6,0 y 8,0 Hz, 2H).
16	 (*R*)-3-(4-clorofeniltio)-1-(4-(2-hidroxipropoxi)-3-metoxifenil)pirazin-2(1*H*)-ona			4	12	3,93	419/421	7,51 (d, J = 8,5 Hz, 2H), 7,42 (d, J = 8,5 Hz, 2H), 7,13 (d, J = 4,5 Hz, 1H), 6,99 (m, 3H), 6,90 (dd, J = 1,8 y 5,9 Hz, 1H), 4,22 (m, 1H), 4,04 (dd, J = 3,0 y 9,5 Hz, 1H), 3,87 (s, 3H), 3,84 (dd, J = 1,2 y 9,5 Hz, 1H), 2,77 (s ancho, 1H), 1,28 (d, J = 6,4 Hz, 3H).
17	 (*R*)-1-(4-(2-hidroxipropoxi)-3-metoxifenil)-3-(fenetiltio)pirazin-2(1*H*)-ona			4		4,06	413	7,27 (m, 6H), 6,97 (m, 3H), 6,89 (dd, J = 2,2 y 8,4 Hz, 1H), 4,23 (m, 1H), 4,03 (dd, J = 3,0 y 9,6 Hz, 1H), 3,86 (s, 3H), 3,84 (dd, J = 1,0 y 9,6 Hz, 1H), 3,32 (t, J = 5,4 Hz, 2H), 3,02 (t, J = 5,4 Hz, 2H), 2,83 (s ancho, 1H), 1,27 (d, J = 6,4 Hz, 3H).

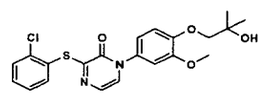
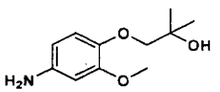
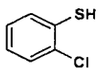
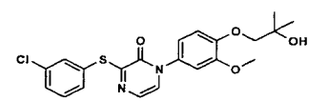
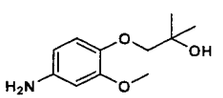
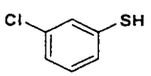
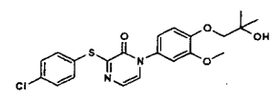
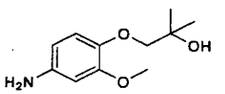
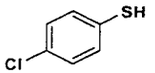
Ej. Nº.	Estructura	Componente de Anilina/Bromuro	Componente de Tiol	Proc.	Rend. (%)	HPLC (Min) Proc. 1	CL-EM (M+H)	Datos de H RMN ($CDCl_3$)
18	 (*R*)-3-(4-clorofenetiltio)-1-(4-(2-hidroxipropoxi)-3-metoxifenil)pirazin-2(1*H*)-ona			4		4,20	447/449	7,27 (m, 5H), 6,98 (m, 3H), 6,89 (dd, J = 2,4 y 8,5 Hz, 1H), 4,23 (m, 1H), 4,02 (dd, J = 3,0 y 9,6 Hz, 1H), 3,86 (s, 3H), 3,83 (dd, J = 1,0 y 9,6 Hz, 1H), 3,30 (t, J = 7,3 Hz, 2H), 2,98 (t, J = 7,3 Hz, 2H), 2,81 (s ancho, 1H), 1,27 (d, J = 6,3 Hz, 3H).
19	 (*R*)-1-(4-(2-hidroxipropoxi)-3-metoxifenil)-3-(3-fenilpropiltio)pirazin-2(1*H*)-ona			4		4,13	427	7,23 (m, 6H), 6,98 (m, 2H), 6,97 (d, J = 4,6 Hz, 1H), 6,95 (dd, J = 2,2 y 8,4 Hz, 1H), 4,23 (m, 1H), 4,07 (dd, J = 3,0 y 9,6 Hz, 1H), 3,87 (s, 3H), 3,84 (dd, J = 1,0 y 9,6 Hz, 1H), 3,12 (m, 2H), 2,81 (m, 2H), 2,67 (s ancho, 1H), 2,07 (m, 2H), 1,27 (d, J = 6,5 Hz, 3H).

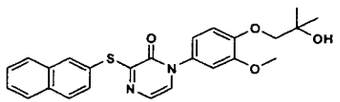
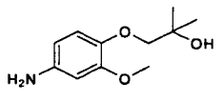
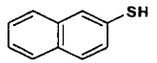
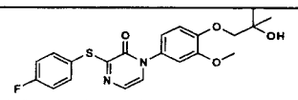
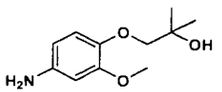
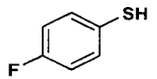
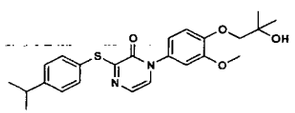
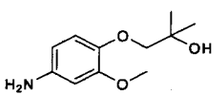
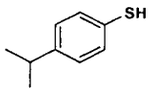
Ej. Nº.	Estructura	Componente de Anilina/Bromuro	Componente de Tiol	Proc.	Rend. (%)	HPLC (Min) Proc. 1	CL-EM (M+H)	Datos de H RMN ($CDCl_3$)
20	 (*R*)-1-(4-(2-hidroxipropoxi)-3-metoxifenil)-3-(2-(piridin-2-il)etiltio)pirazin-2(1*H*)-ona			4		2,45	414	8,57 (d, J = 4,4 Hz, 1H), 7,62 (dd, J = 1,6 y 6,5 Hz, 1H), 7,27 (m, 2H), 7,15 (dd, J = 1,2 y 5,5 Hz, 1H), 6,96 (m, 3H), 6,88 (dd, J = 2,4 y 8,5 Hz, 1H), 4,22 (m, 1H), 4,02 (dd, J = 3,0 y 9,5 Hz, 1H), 3,85 (s, 3H), 3,86 (dd, J = 1,0 y 9,6 Hz, 1H), 3,50 (t, J = 6,8 Hz, 2H), 3,22 (t, J = 6,8 Hz, 2H), 2,98 (s ancho, 1H), 1,27 (d, J = 8,6 Hz, 3H).
21	 3-(4-clorofenilsulfinil)-1-(4-((*R*)-2-hidroxipropoxi)-3-metoxifenil)pirazin-2(1*H*)-ona			MCPBA oxidación del Ej. 19	57	3,18	435/437	7,90 (d, J = 8,6 Hz, 2H), 7,65 (d, J = 4,2 Hz, 1H), 7,44 (d, J = 8,6 Hz, 2H), 7,35 (d, J = 4,2 Hz, 1H), 6,97 (d, J = 8,5 Hz, 1H), 6,87 (d, J = 2,1 Hz, 1H), 6,84 (dd, J = 2,1 y 8,5 Hz, 1H), 4,23 (m, 1H), 4,01 (dd, J = 2,9 y 9,4 Hz, 1H), 3,85 (s, 3H), 3,83 (dd, J = 1,1 y 9,4 Hz, 1H) 1,27 (d, J = 6,4 Hz, 3H).

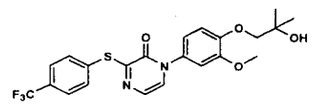
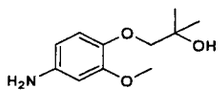
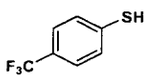
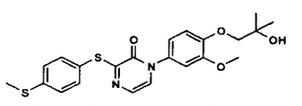
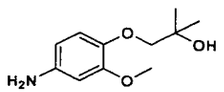
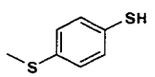
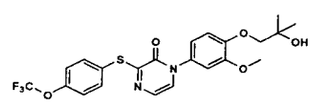
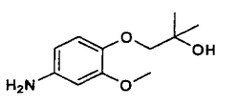
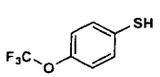
Ej. Nº.	Estructura	Componente de Anilina/Bromuro	Componente de Tiol	Proc.	Rend. (%)	HPLC (Min) Proc. 1	CL-EM (M+H)	Datos de H RMN ($CDCl_3$)
22	 (*R*)-3-(4-clorofenilsulfonil)-1-(4-(2-hidroxi-propoxi)-3-metoxifenil)pirazin-2(1*H*)-ona			MCPBA oxidación del Ej. 19	10	3,18	451/453	8,12 (d, J = 8,6 Hz, 2H), 7,60 (d, J = 6,1 Hz, 1H), 7,51 (d, J = 6,1 Hz, 1H), 7,50 (d, J = 8,6 Hz, 2H), 6,96 (d, J = 8,6 Hz, 1H), 6,90 (d, J = 2,4 Hz, 1H), 6,84 (dd, J = 2,4 y 8,6 Hz, 1H), 4,23 (m, 1H), 4,01 (dd, J = 3,0 y 9,5 Hz, 1H), 3,86 (s, 3H), 3,84 (dd, J = 1,2 y 9,5 Hz, 1H) 1,28 (d, J = 6,0 Hz, 3H).
23	 1-(4-((*R*)-2-hidroxipropoxi)-3-metoxifenil)-3-(fenetilsulfinil)pirazin-2(1*H*)-ona			MCPBA oxidación del Ej. 20	17	2,96	445	7,52 (d, J = 4,1 Hz, 1H), 7,40 (d, J = 4,1 Hz, 1H), 7,20 (m, 5H), 7,00 (d, J = 8,6 Hz, 1H), 6,90 (d, J = 2,5 Hz, 1H), 6,81 (dd, J = 2,5 y 8,6 Hz, 1H) 4,25 (m, 1H), 4,05 (dd, J = 3,1 y 9,5 Hz, 1H), 3,88 (s, 3H), 3,86 (m, 3H), 3,20 (t, H = 7,8 Hz, 2H), 1,29 (d, J = 6,2 Hz, 3H).

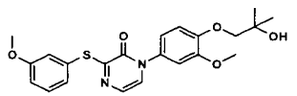
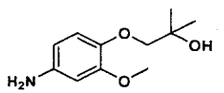
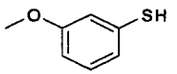
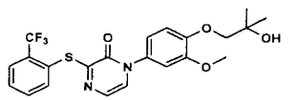
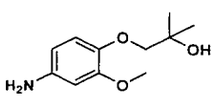
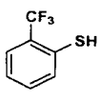
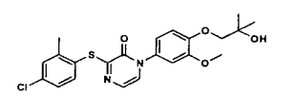
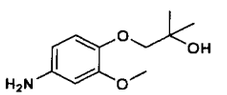
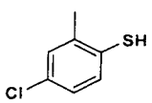
Ej. Nº.	Estructura	Componente de Anilina/Bromuro	Componente de Tiol	Proc.	Rend. (%)	HPLC (Min) Proc. 1	CL-EM (M+H)	Datos de H RMN ($CDCl_3$)
24	 (*R*)-1-(4-(2-hidroxipropoxi)-3-metoxifenil)-3-(fenetilsulfonil)pirazin-2(1*H*)-ona			MCPBA oxidación del Ej. 20	61	3,02	429	7,65 (d, J = 6,2 Hz, 1H), 7,30 (d, J = 6,2 Hz, 1H), 7,20 (m, 5H), 6,99 (d, J = 8,4 Hz, 1H), 6,85 (d, J = 1,0 Hz, 1H), 6,84 (dd, J = 1,0 y 8,4 Hz, 1H) 4,25 (m, 1H), 4,02 (dd, J = 2,9 y 9,6 Hz, 1H), 3,87 (s, 3H), 3,85 (dd, J = 1,2 y 9,6 Hz, 1H), 3,61 (m, 2H), 3,53 (m, 1H), 3,17 (m, 2H), 1,28 (d, J = 6,8 Hz, 3H).
25	 1-(4-(2-hidroxi-2-metilpropoxi)-3-metoxifenil)-3-(fenetiltio)pirazin-2(1*H*)-ona			2a	33	4,11	427	7,28 (m, 7H), 6,97 (d, J = 2,3 Hz, 1H), 6,97 (d, J = 8,5 Hz, 1H), 6,88 (dd, J = 2,3, 8,5 Hz, 1H), 3,86 (s, 5H), 3,33 (dd, J = 7,6 y 8,8 Hz, 2H), 3,02 (dd, J = 5,9 y 8,8 Hz, 2H), 1,36 (s, 6H).
26	 3-(4-fluorofenetiltio)-1-(4-(2-hidroxi-2-metilpropoxi)-3-metoxifenil)pirazin-2(1*H*)-ona			2a	10	3,8	445	7,25 (d, J = 4,4 Hz, 1H), 7,17 (m, 2H), 6,94 (m, 5 H), 6,84 (dd, J = 2,2 y 8,5 Hz, 1H), 3,82 (s, 3H), 3,77 (s, 2H), 3,23 (t, J = 7,4 Hz, 2H), 2,91 (t, J = 7,4 Hz, 2H), 1,27 (s, 6H)

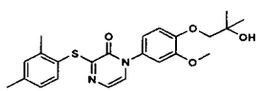
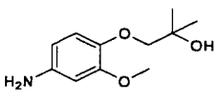
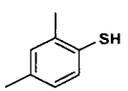
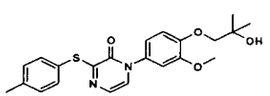
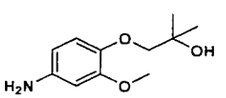
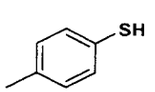
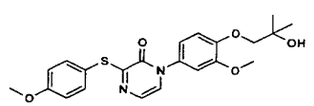
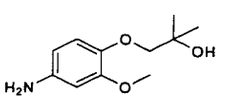
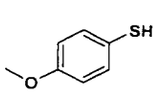
Ej. Nº.	Estructura	Componente de Anilina/Bromuro	Componente de Tiol	Proc.	Rend. (%)	HPLC (Min) Proc. 1	CL-EM (M+H)	Datos de H RMN ($CDCl_3$)
27	 1-(4-(2-hidroxi-2-metilpropoxi)-3-metoxifenil)-3-(2-(piridin-2-il)etiltio)pirazin-2(1*H*)-ona			2a	29	2,67	428	8,57 (d, J = 4,2 Hz, 1H), 7,62 (dd, J = 5,9 y 7,6 Hz, 1H), 7,27 (m, 2H), 7,15 (m, 1H), 6,97 (m, 3H), 6,88 (dd, J = 2,3, 8,4 Hz, 1H), 3,85 (s, 5H), 3,50 (t, J = 7,2 Hz, 2H), 3,22 (t, J = 7,2 Hz, 2H), 1,36 (s, 6H).
28	 1-(4-(2-hidroxi-2-metilpropoxi)-3-metoxifenil)-3-(2-(piridin-4-il)etiltio)pirazin-2(1*H*)-ona			2a	31	2,74	428	8,68 (d, J = 6,1 Hz, 2H), 7,97 (d, J = 6,1 Hz, 2H), 7,29 (d, J = 5,4 Hz, 1H), 7,21 (d, J = 5,4 Hz, 1H), 7,00 (d, J = 2,0 Hz, 1H), 6,98 (d, J = 8,8 Hz, 1H), 6,86 (dd, J = 2,0 y 8,8 Hz, 1H), 3,77 (s, 3H), 3,75 (s, 2H), 3,42 (t, J = 7,2 Hz, 2H), 3,30 (t, J = 7,2 Hz, 2H), 1,24 (s, 6H).
29	 1-(4-(2-hidroxi-2-metilpropoxi)-3-metoxifenil)-3-(7-(trifluorometil)quinolin-4-iltio)pirazin-2(1*H*)-ona			2a	12	4,02	518	8,94 (d, J = 4,5 Hz, 1H), 8,36 (d, J = 8,8 Hz, 1H), 8,32 (s, 1H), 7,92 (d, J = 4,5 Hz, 1H), 7,74 (dd, J = 1,5 y 8,9 Hz, 1H), 7,21 (d, J = 4,4 Hz, 1H), 7,06 (d, J = 2,3 Hz, 1H), 7,00 (d, J = 8,6 Hz, 1H), 6,92 (dd, J = 2,3 y 8,6 Hz, 1H), 6,90 (d, J = 4,4 Hz, 1H), 3,79 (s, 3H), 3,75 (s, 2H), 1,24 (s, 6H).

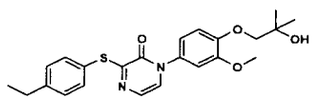
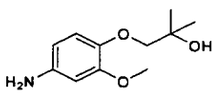
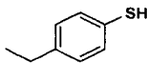
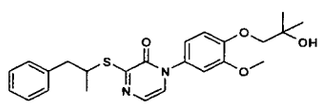
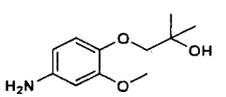
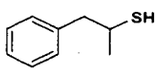
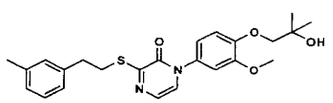
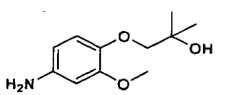
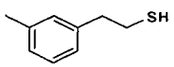
Ej. Nº.	Estructura	Componente de Anilina/Bromuro	Componente de Tiol	Proc.	Rend. (%)	HPLC (Min) Proc. 1	CL-EM (M+H)	Datos de H RMN ($CDCl_3$)
30	 3-(2-clorofeniltio)-1-(4-(2-hidroxi-2-metilpropoxi)-3-metoxifenil)pirazin-2(1*H*)-ona			2a	50	3,76	433/435	7,67 (dd, J = 1,4 y 7,5 Hz, 1H), 7,56 (dd, J = 1,2 y 8,0 Hz, 1H), 7,42 (dt, J = 1,4 y 7,5 Hz, 1H), 7,36 (dt, J = 1,2 y 7,5 Hz, 1H), 7,11 (d, J = 4,5 Hz, 1H), 7,01 (d, J = 2,3 Hz, 1H), 6,96 (d, J = 8,4 Hz, 1H), 6,93 (d, J = 4,5 Hz, 1H), 6,90 (dd, J = 2,3 y 8,4 Hz, 1H), 3,87 (s, 3H), 3,86 (s, 2H), 2,72 (s ancho, 1H), 1,36 (s, 6H).
31	 3-(3-clorofeniltio)-1-(4-(2-hidroxi-2-metilpropoxi)-3-metoxifenil)pirazin-2(1*H*)-ona			2a	62	3,98	433/435	7,59 (d, J = 1,7 Hz, 1H), 7,48 (m, 1H), 7,41 (m, 2H), 7,14 (d, J = 4,5 Hz, 1H), 7,00 (m, 3H), 6,90 (dd, J = 2,4 y 8,5 Hz, 1H), 3,87 (s, 3H), 3,86 (s, 2H), 2,71 (s ancho, 1H), 1,36 (s, 6H).
32	 3-(4-clorofeniltio)-1-(4-(2-hidroxi-2-metilpropoxi)-3-metoxifenil)pirazin-2(1*H*)-ona			2a	58	4,00	433/435	7,52 (dd, J = 1,9 y 6,7 Hz, 2H), 7,43 (dd, J = 1,9 y 6,7 Hz, 2H), 7,13 (d, J = 4,4 Hz, 1H), 6,99 (d, J = 2,3 Hz, 1H), 6,98 (d, J = 4,4 Hz, 1H), 6,96 (d, J = 8,4 Hz, 1H), 6,90 (dd, J = 2,3 y 8,4 Hz, 1H), 3,87 (s, 3H), 3,86 (s, 2H), 2,70 (s ancho, 1H), 1,36 (s, 6H).

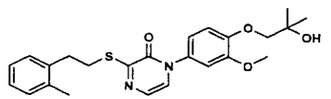
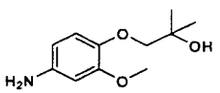
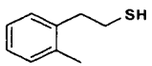
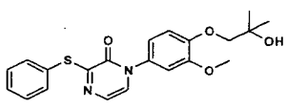
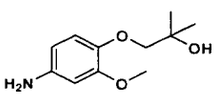
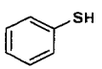
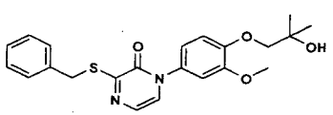
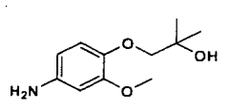
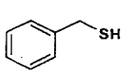
Ej. Nº.	Estructura	Componente de Anilina/Bromuro	Componente de Tiol	Proc.	Rend. (%)	HPLC (Min) Proc. 1	CL-EM (M+H)	Datos de H RMN ($CDCl_3$)
33	 1-(4-(2-hidroxi-2-metilpropoxi)-3-metoxifenil)-3-(naftalen-2-iltio)pirazin-2(1*H*)-ona			2a	70	4,11	449	8,12 (s, 1H), 7,88 (m, 3H), 7,61 (dd, J = 1,4 y 8,6 Hz, 1H), 7,53 (m, 2H), 7,09 (d, J = 4,5 Hz, 1H), 7,02 (d, J = 2,3 Hz, 1H), 6,98 (d, J = 8,5 Hz, 1H), 6,96 (d, J = 4,5 Hz, 1H), 6,91 (dd, J = 2,3 y 8,5 Hz, 1H), 3,88 (s, 3H), 3,87 (s, 2H), 2,75 (s ancho, 1H), 1,37 (s, 6H).
34	 3-(4-fluorofeniltio)-1-(4-(2-hidroxi-2-metilpropoxi)-3-metoxifenil)pirazin-2(1*H*)-ona			2a	34	3,72	417	7,56 (m, 2H), 7,12 (m, 3H), 6,98 (m, 3H), 6,89 (m, 1H), 386 (s, 5H), 1,36 (s, 6H).
35	 1-(4-(2-hidroxi-2-metilpropoxi)-3-metoxifenil)-3-(4-isopropilfeniltio)pirazin-2(1*H*)-ona			2a	39	4,24	441	7,50 (d, J = 8,2 Hz, 2H), 7,32 (d, J = 8,2 Hz, 2H), 7,15 (d, J = 4,5 Hz, 1H), 7,02 (d, J = 2,3 Hz, 1H), 6,97 (d, J = 4,5 Hz, 1H), 6,96 (d, J = 8,5 Hz, 1H), 6,92 (dd, J = 2,3 y 8,5 Hz, 1H), 3,90 (s, 3H), 3,85 (s, 2H), 2,98 (m, 1H), 2,85 (s ancho, 1H), 1,35 (s, 6H), 1,24 (d, J = 6,8 Hz, 6H).

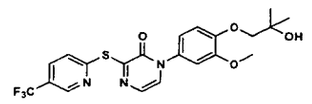
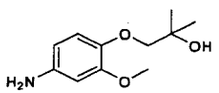
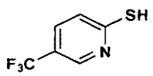
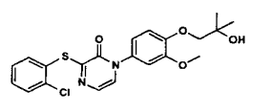
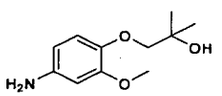
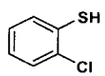
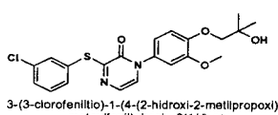
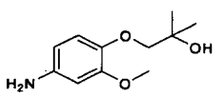
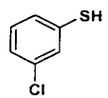
Ej. Nº.	Estructura	Componente de Anilina/Bromuro	Componente de Tiol	Proc.	Rend. (%)	HPLC (Min) Proc. 1	CL-EM (M+H)	Datos de H RMN ($CDCl_3$)
36	 1-(4-(2-hidroxi-2-metilpropoxi)-3-metoxifenil)-3-(4-(trifluorometil)feniltio)pirazin-2(1*H*)-ona			2a	16	4,10	467	7,64 (d, J = 9,0 Hz, 2H), 7,62 (d, J = 9,0 Hz, 2H), 7,18 (d, J = 4,5 Hz, 1H), 7,04 (d, J = 4,5 Hz, 1H), 7,00 (d, J = 2,2 Hz, 1H), 6,98 (d, J = 8,5 Hz, 1H), 6,86 (dd, J = 2,2 y 8,5 Hz, 1H), 3,75 (s, 3H), 3,73 (s, 2H), 1,22 (s, 6H).
37	 1-(4-(2-hidroxi-2-metilpropoxi)-3-metoxifenil)-3-(4-(metiltio)feniltio)pirazin-2(1*H*)-ona			2a	50	3,96	445	7,48 (d, J = 8,4 Hz, 2H), 7,30 (d, J = 8,4 Hz, 2H), 7,28 (d, J = 4,5 Hz, 1H), 7,12 (d, J = 4,5 Hz, 1H), 6,99 (d, J = 8,5 Hz, 1H), 6,96 (d, J = 2,4 Hz, 1H), 6,89 (dd, J = 2,4 y 8,5 Hz, 1H), 3,86 (s, 5H), 2,51 (s, 3H), 1,35 (s, 6H).
38	 1-(4-(2-hidroxi-2-metilpropoxi)-3-metoxifenil)-3-(4-(trifluorometoxi)feniltio)pirazin-2(1*H*)-ona			2a	52	4,15	483	7,62 (d, J = 8,6 Hz, 2H), 7,30 (d, J = 8,6 Hz, 2H), 7,16 (d, J = 4,4 Hz, 1H), 7,06 (d, J = 4,4 Hz, 1H), 7,00 (d, J = 8,5 Hz, 1H), 6,98 (d, J = 2,3 Hz, 1H), 6,93 (dd, J = 2,3 y 8,5 Hz, 1H), 3,91 (s, 3H), 3,86 (s, 2H), 1,36 (s, 6H).

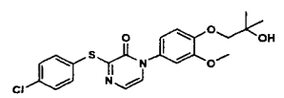
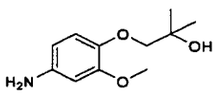
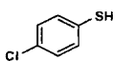
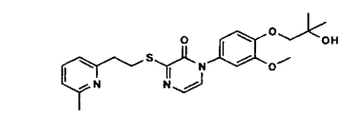
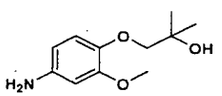
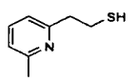
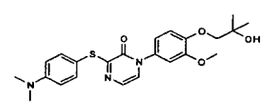
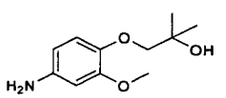
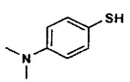
Ej. Nº.	Estructura	Componente de Anilina/Bromuro	Componente de Tiol	Proc.	Rend. (%)	HPLC (Min) Proc. 1	CL-EM (M+H)	Datos de H RMN ($CDCl_3$)
39	 1-(4-(2-hidroxi-2-metilpropoxi)-3-metoxifenil)-3-(3-metoxifeniltio)pirazin-2(1*H*)-ona			2a	60	3,72	429	7,37 (t, J = 8,0 Hz, 1H), 7,18 (d, J = 8,0 Hz, 1H), 7,14 (m, 2H), 6,98 (m, 4H), 6,90 (m, 1H), 3,86 (s, 5H), 3,77 (s, 3H), 1,36 (s, 6H).
40	 1-(4-(2-hidroxi-2-metilpropoxi)-3-metoxifenil)-3-(2-(trifluorometil)feniltio)pirazin-2(1*H*)-ona			2a	49	3,88	467	7,84 (d, J = 7,5 Hz, 1H), 7,71 (d, J = 7,5 Hz, 1H), 7,62 (t, J = 7,5 Hz, 1H), 7,60 (t, J = 7,5 Hz, 1H), 7,05 (d, J = 4,4 Hz, 1H), 7,01 (d, J = 2,4 Hz, 1H), 6,98 (d, J = 8,5 Hz, 1H), 6,97 (d, J = 4,4 Hz, 1H), 6,90 (dd, J = 2,4 y 8,5 Hz, 1H), 3,88 (s, 3H), 3,86 (s, 2H), 1,36 (s, 6H).
41	 3-(4-cloro-2-metilfeniltio)-1-(4-(2-hidroxi-2-metilpropoxi)-3-metoxifenil)pirazin-2(1*H*)-ona			2a	50	4,20	447/449	7,48 (d, J = 8,4 Hz, 1H), 7,36 (d, J = 2,0 Hz, 1H), 7,24 (dd, J = 2,0 y 8,4 Hz, 1H), 7,10 (d, J = 4,5 Hz, 1H), 7,00 (d, J = 2,4 Hz, 1H), 6,98 (d, J = 8,5 Hz, 1H), 6,96 (d, J = 4,5 Hz, 1H), 6,90 (dd, J = 2,4 y 8,5 Hz, 1H), 3,88 (s, 3H), 3,87 (s, 2H), 2,40 (s, 3H), 1,38 (s, 6H).

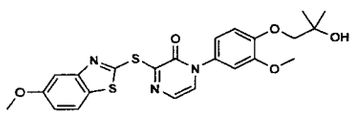
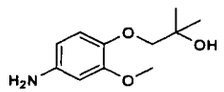
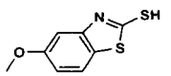
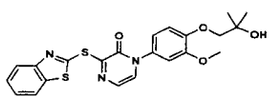
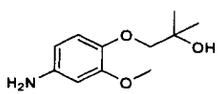
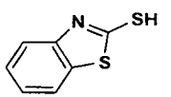
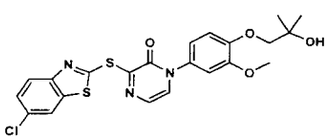
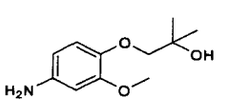
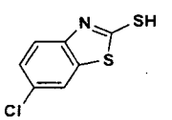
Ej. Nº.	Estructura	Componente de Anilina/Bromuro	Componente de Tiol	Proc.	Rend. (%)	HPLC (Min) Proc. 1	CL-EM (M+H)	Datos de H RMN ($CDCl_3$)
42	 3-(2,4-dimetilfeniltio)-1-(4-(2-hidroxi-2-metilpropoxi)-3-metoxifenil)pirazin-2(1*H*)-ona			2a	60	4,04	427	7,44 (d, J = 7,9 Hz, 1H), 7,19 (s, 1H), 7,11 (d, J = 4,5 Hz, 1H), 7,08 (d, J = 7,9 Hz, 1H), 7,01 (d, J = 2,3 Hz, 1H), 6,97 (d, J = 8,6 Hz, 1H), 6,93 (d, J = 4,5 Hz, 1H), 6,90 (dd, J = 2,3 y 8,6 Hz, 1H), 3,87 (s, 3H), 3,86 (s, 2H), 2,39 (s, 3H), 2,37 (s, 3H), 1,36 (s, 6H).
43	 1-(4-(2-hidroxi-2-metilpropoxi)-3-metoxifenil)-3-(*p*-toliltio)pirazin-2(1*H*)-ona			2a	60	3,87	413	7,46 (d, J = 8,0 Hz, 2H), 7,27 (d, J = 8,0 Hz, 2H), 7,15 (d, J = 4,4 Hz, 1H), 7,01 (d, J = 2,3 Hz, 1H), 6,97 (d, J = 8,5 Hz, 1H), 6,96 (d, J = 4,4 Hz, 1H), 6,92 (dd, J = 2,3 y 8,5 Hz, 1H), 3,91 (s, 3H), 3,85 (s, 2H), 2,40 (s, 3H), 1,35 (s, 6H).
44	 1-(4-(2-hidroxi-2-metilpropoxi)-3-metoxifenil)-3-(4-metoxifeniltio)pirazin-2(1*H*)-ona			2a	39	3,71	429	7,48 (d, J = 8,7 Hz, 2H), 7,14 (d, J = 4,5 Hz, 1H), 7,00 (d, J = 2,3 Hz, 1H), 6,99 (d, J = 8,0 Hz, 2H), 6,97 (d, J = 4,5 Hz, 1H), 6,97 (d, J = 8,5 Hz, 1H), 6,92 (dd, J = 2,3 y 8,5 Hz, 1), 3,89 (s, 3H), 3,85 (s, 5H), 1,35 (s, 6H).

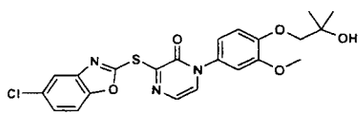
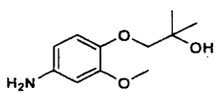
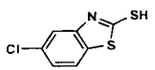
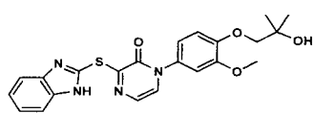
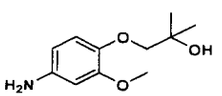
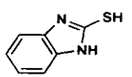
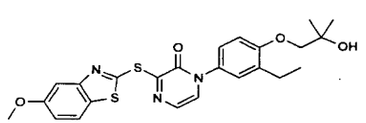
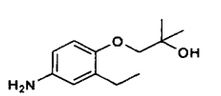
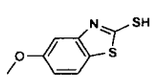
Ej. Nº.	Estructura	Componente de Anilina/Bromuro	Componente de Tiol	Proc.	Rend. (%)	HPLC (Min) Proc. 1	CL-EM (M+H)	Datos de H RMN ($CDCl_3$)
45	 3-(4-etilfeniltio)-1-(4-(2-hidroxi-2-metilpropoxi)-3-metoxifenil)pirazin-2(1*H*)-ona			2a	64	4,05	427	7,45 (d, J = 8,3 Hz, 2H), 7,25 (d, J = 8,3 Hz, 2H), 7,11 (d, J = 3,9 Hz, 1H), 6,97 (d, J = 2,2 Hz, 1H), 6,93 (d, J = 8,2 Hz, 1H), 6,92 (d, J = 3,9 Hz, 1H), 6,87 (dd, J = 2,2 y 8,2 Hz, 1H), 3,86 (s, 3H), 3,81 (s, 2H), 2,66 (c, J =5,5 Hz, 2H), 1,31 (s, 6H), 1,22 (t, J = 5,5 Hz, 3H).
46	 1-(4-(2-hidroxi-2-metilpropoxi)-3-metoxifenil)-3-(1-fenilpropan-2-iltio)pirazin-2(1*H*)-ona			2a	29	4,25	441	7,27 (m, 5H), 7,20 (m, 1H), 6,92 (m, 3H), 6,85 (dd, J = 2,2, 8,0 Hz, 1H), 3,97 (m, 1H), 3,84 (s, 3H), 3,81 (s, 2H), 3,16 (dd, J = 2,0 y 8,0 Hz, 1H), 2,74 (dd, J = 5,0 y 8,0 Hz, 1H), 1,33 (s, 6H), 1,32 (d, J = 9,3 Hz, 3H).
47	 1-(4-(2-hidroxi-2-metilpropoxi)-3-metoxifenil)-3-(3-metilfenetiltio)pirazin-2(1*H*)-ona			2a	59	4,31	441	7,30 (m, 1H), 7,21 (m, 1H), 7,11 (m, 1H), 7,05 (m, 1H), 6,97 (m, 4H), 6,89 (m, 1H), 3,87 (s, 3H), 3,84 (s, 2H), 3,31 (dd, J = 6,0 y 8,3 Hz, 2H), 2,98 (t, J = 8,3 Hz, 2H), 2,35 (s, 3H), 1,35 (s, 6H)

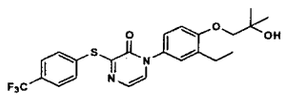
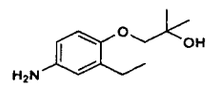
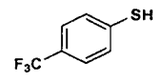
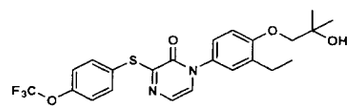
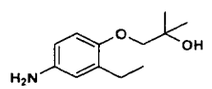
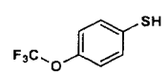
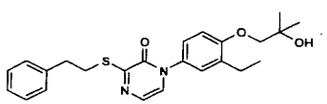
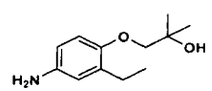
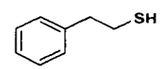
Ej. Nº.	Estructura	Componente de Anilina/Bromuro	Componente de Tiol	Proc.	Rend. (%)	HPLC (Min) Proc. 1	CL-EM (M+H)	Datos de H RMN ($CDCl_3$)
48	 1-(4-(2-hidroxi-2-metilpropoxi)-3-metoxifenil)-3-(2-metilfenetiltio)pirazin-2(1*H*)-ona			2a	88	4,30	441	7,26 (d, J = 4,4 Hz, 1H), 7,19 (d, J = 7,2 Hz, 1H), 7,10 (m, 3H), 6,95 (m, 3H), 6,84 (dd, J = 2,2 y 8,2 Hz, 1H), 3,83 (s, 3H), 3,79 (s, 2H), 3,22 (dd, J = 5,7 y 8,5 Hz, 2H), 2,96 (dd, J = 5,5 y 8,5 Hz, 2H), 2,34 (s, 3H), 1,29 (s, 6H).
49	 1-(4-(2-hidroxi-2-metilpropoxi)-3-metoxifenil)-3-(feniltio)pirazin-2(1*H*)-ona			2a	51	3,62	399	7,52 (m, 2H), 7,39 (m, 3H), 7,05 (d, J = 4,4 Hz, 1H), 6,92 (d, J = 2,4 Hz, 1H), 6,90 (d, J = 8,4 Hz, 1H), 6,89 (d, J = 4,4 Hz, 1H), 6,83 (dd, J = 2,4 y 8,4 Hz, 1H), 3,80 (s, 3H), 3,79 (s, 2H), 1,29 (s, 6H).
50	 3-(benciltio)-1-(4-(2-hidroxi-2-metilpropoxi)-3-metoxifenil)pirazin-2(1*H*)-ona			2a	51	3,95	413	7,43 (d, J = 7,1 Hz, 2H), 7,30 (m, 4H), 6,96 (m, 3H), 6,88 (dd, J = 2,4 y 8,5 Hz, 1H), 4,33 (s, 2H), 3,87 (s, 3H), 3,84 (s, 2H), 1,35 (s, 6H).

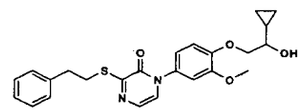
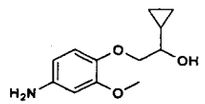
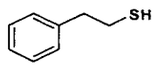
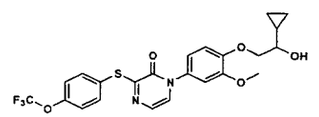
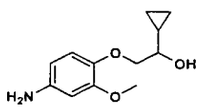
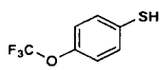
Ej. Nº.	Estructura	Componente de Anilina/Bromuro	Componente de Tiol	Proc.	Rend. (%)	HPLC (Min) Proc. 1	CL-EM (M+H)	Datos de H RMN ($CDCl_3$)
51	 1-(4-(2-hidroxi-2-metilpropoxi)-3-metoxifenil)-3-(5-(trifluorometil)piridin-2-iltio)pirazin-2(1*H*)-ona			2a	6	3,63	468	8,89 (s, 1H), 8,17 (d, J = 7,2 Hz, 1H), 8,10 (d, J = 7,2 Hz, 1H), 7,45 (d, J = 4,4 Hz, 1H), 7,30 (d, J = 4,4 Hz, 1H), 7,15 (d, J = 2,4 Hz, 1H), 7,12 (d, J = 8,6 Hz, 1H), 7,01 (dd, J = 2,4 y 8,6 Hz, 1H), 3,91 (s, 3H), 3,87 (s, 2H), 1,35 (s, 6H).
52	 3-(2-clorofeniltio)-1-(4-(2-hidroxi-2-metilpropoxi)-3-metoxifenil)pirazin-2(1*H*)-ona			2a	50	4,02	433/435	7,67 (dd, J = 1,4 y 7,5 Hz, 1H), 7,56 (dd, J = 1,2 y 8,0 Hz, 1H), 7,42 (dt, J = 1,4 y 7,5 Hz, 1H), 7,36 (dt, J = 1,2 y 7,5 Hz, 1H), 7,11 (d, J = 4,5 Hz, 1H), 7,01 (d, J = 2,3 Hz, 1H), 6,96 (d, J = 8,4 Hz, 1H), 6,93 (d, J = 4,5 Hz, 1H), 6,90 (dd, J = 2,3 y 8,4 Hz, 1H), 3,87 (s, 3H), 3,86 (s, 2H), 2,72 (s ancho, 1H), 1,36 (s, 6H).
53	 3-(3-clorofeniltio)-1-(4-(2-hidroxi-2-metilpropoxi)-3-metoxifenil)pirazin-2(1*H*)-ona			2a	62	3,76	433/435	7,59 (d, J = 1,7 Hz, 1H), 7,48 (m, 1H), 7,41 (m, 2H), 7,14 (d, J = 4,5 Hz, 1H), 7,00 (m, 3H), 6,90 (dd, J = 2,4 y 8,5 Hz, 1H), 3,87 (s, 3H), 3,86 (s, 2H), 2,71 (s ancho, 1H), 1,36 (s, 6H).

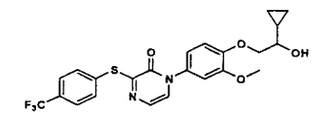
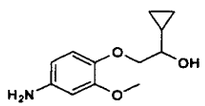
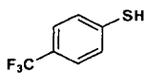
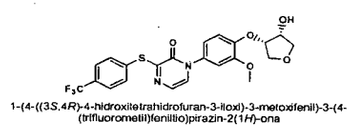
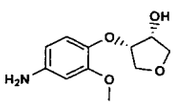
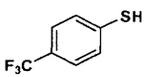
Ej. Nº.	Estructura	Componente de Anilina/Bromuro	Componente de Tiol	Proc.	Rend. (%)	HPLC (Min) Proc. 1	CL-EM (M+H)	Datos de H RMN ($CDCl_3$)
54	 3-(4-clorofenilitio)-1-(4-(2-hidroxi-2-metilpropoxi)-3-metoxifenil)pirazin-2(1*H*)-ona			2a	58	3,98	433/435	7,52 (dd, J = 1,9 y 6,7 Hz, 2H), 7,43 (dd, J = 1,9 y 6,7 Hz, 2H), 7,13 (d, J = 4,4 Hz, 1H), 6,99 (d, J = 2,3 Hz, 1H), 6,98 (d, J = 4,4 Hz, 1H), 6,96 (d, J = 8,4 Hz, 1H), 6,90 (dd, J = 2,3 y 8,4 Hz, 1H), 3,87 (s, 3H), 3,86 (s, 2H), 2,70 (s ancho, 1H), 1,36 (s, 6H).
55	 1-(4-(2-hidroxi-2-metilpropoxi)-3-metoxifenil)-3-(2-(6-metilpiridin-2-il)etilitio)pirazin-2(1*H*)-ona			2a	50%	2,74	442	7,67 (t, J = 7,7 Hz, 1H), 7,38 (d, J = 4,4 Hz, 1H), 7,25 (d, J = 4,4 Hz, 1H), 7,16 (m, 2H), 7,10 (d, J = 2,4 Hz, 1H), 7,08 (d, J = 8,6 Hz, 1H), 6,95 (dd, J = 2,4 y 8,6 Hz, 1H), 3,89 (s, 3H), 3,86 (s, 2H), 3,45 (t, J = 7,1 Hz, 2H), 3,15 (t, J = 7,1 Hz, 2H), 2,53 (s, 3H), 1,34 (s, 6H).
56	 3-(4-(dimetilamino)fenilitio)-1-(4-(2-hidroxi-2-metilpropoxi)-3-metoxifenil)pirazin-2(1*H*)-ona			2a	44%	3,03	442	7,40 (d, J = 8,9 Hz, 2H), 7,13 (d, J = 4,8 Hz, 1H), 7,00 (d, J = 2,3 Hz, 1H), 6,97 (d, J = 8,5 Hz, 1H), 6,92 (d, J = 4,8 Hz, 1H), 6,90 (dd, J = 2,3 y 8,5 Hz, 1H), 6,76 (d, J = 8,9 Hz, 2H), 3,87 (s, 3H), 3,86 (s, 2H), 3,01 (s, 6H), 1,36 (s, 6H).

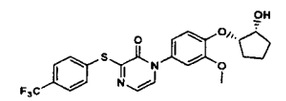
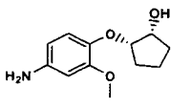
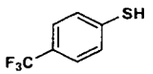
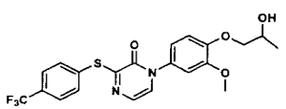
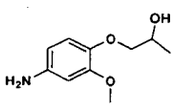
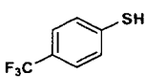
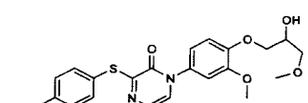
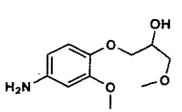
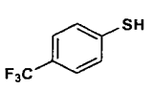
Ej. Nº.	Estructura	Componente de Anilina/Bromuro	Componente de Tiol	Proc.	Rend. (%)	HPLC (Min) Proc. 1	CL-EM (M+H)	Datos de H RMN ($CDCl_3$)
57	 1-(4-(2-hidroxi-2-metilpropoxi)-3-metoxifenil)-3-(5-metoxibenzo[*d*]tiazol-2-iltio)pirazin-2(1*H*)-ona			5	3	3,68	486	7,77 (d, J = 8,8 Hz, 1H), 7,57 (d, J = 2,5 Hz, 1H), 7,37 (d, J = 4,4 Hz, 1H), 7,14 (d, J = 4,4 Hz, 1H), 7,08 (dd, J = 2,5, 8,8 Hz, 1H, 7,02 (m, 2H), 6,93 (dd, J = 2,5, 8,5 Hz, 1H), 3,92 (s, 3H), 3,90 (s, 2H), 1,39 (s, 6H).
58	 3-(benzo[*d*]tiazol-2-iltio)-1-(4-(2-hidroxi-2-metilpropoxi)-3-metoxifenil)pirazin-2(1*H*)-ona			5		3,64	456	7,93 (d, J = 8,3 Hz, 1H), 7,87 (d, J = 8,1 Hz, 1H), 7,43 (t, J = 8,2 Hz, 1H), 7,35 (m, 3H), 7,07 (d, J = 2,3 Hz, 1H), 7,01 (d, J = 8,6 Hz, 1H), 6,93 (dd, J = 2,3 y 8,5 Hz, 1H), 3,79 (s, 3H), 3,76 (s, 2H), 1,24 (s, 6H).
59	 3-(6-clorobenzo[*d*]thiazol-2-iltio)-1-(4-(2-hidroxi-2-metilpropoxi)-3-metoxifenil)pirazin-2(1*H*)-ona			5		3,99	490/492	7,87 (d, J = 8,6 Hz, 1H), 7,79 (d, J = 2,0 Hz, 1H), 7,38 (dd, J = 2,0 y 8,6 Hz, 1H), 7,30 (d, J = 4,4 Hz, 1H), 7,08 (d, J = 4,4 Hz, 1H), 6,92 (d, J = 2,5 Hz, 1H), 6,91 (d, J = 8,6 Hz, 1H), 6,85 (dd, J = 2,5 y 8,6 Hz, 1H), 3,80 (s, 5H), 1,30 (s, 6H).

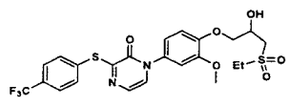
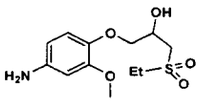
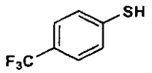
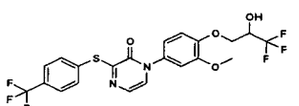
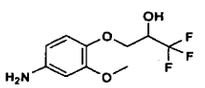
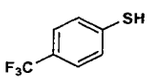
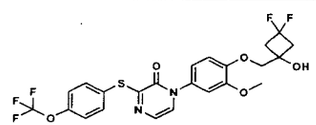
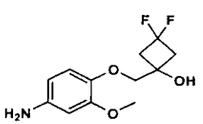
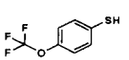
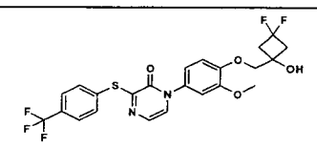
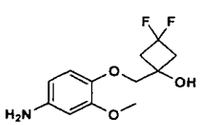
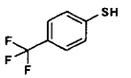
Ej. Nº.	Estructura	Componente de Anilina/Bromuro	Componente de Tiol	Proc.	Rend. (%)	HPLC (Min) Proc. 1	CL-EM (M+H)	Datos de H RMN ($CDCl_3$)
60	 3-(5-clorobenzo[*d*]oxazol-2-iltio)-1-(4-(2-hidroxi-2-metilpropoxi)-3-metoxifenil)pirazin-2(1*H*)-ona			5		3,67	474/476	7,71 (d, J = 2,0, 1H), 7,45 (d, J = 8,7 Hz, 1H), 7,32 (dd, J = 2,0 y 8,7 Hz, 1H), 7,11 (d, J = 4,4 Hz, 1H), 7,04 (d, J = 4,4 Hz, 1H), 6,91 (d, J = 8,6 Hz, 1H), 6,90 (d, J = 2,4 Hz, 1H), 6,84 (dd, J = 2,4 y 8,6 Hz, 1H), 3,81 (s, 3H), 3,79 (s, 2H), 1,29 (s, 6H).
61	 3-(1*H*-benzo[*d*]imidazol-2-iltio)-1-(4-(2-hidroxi-2-metilpropoxi)-3-metoxifenil)pirazin-2(1*H*)-ona			5		2,68	439	7,71 (dd, J = 3,1 y 6,2 Hz, 2H), 7,49 (dd, J = 3,1 y 6,2 Hz, 2H), 7,43 (d, J = 4,4 Hz, 1H), 7,22 (d, J = 4,4 Hz, 1H), 7,04 (d, J = 2,5 Hz, 1H), 7,01 (d, J = 8,5 Hz, 1H), 6,91 (dd, J = 2,4 y 8,5 Hz, 1H), 3,79 (s, 3H), 3,75 (s, 2H), 1,24 (s, 6H).
62	 1-(3-etil-4-(2-hidroxi-2-metilpropoxi)fenil)-3-(5-metoxibenzo[*d*]tiazol-2-iltio)pirazin-2(1*H*)-ona			5		4,11	484	7,68 (d, J = 8,8 Hz, 1H), 7,46 (d, J = 2,4 Hz, 1H), 7,27 (d, J = 4,4 Hz, 1H), 7,16 (m, 2H), 7,04 (d, J = 4,4 Hz, 1H), 7,00 (dd, J = 2,5 y 8,7 Hz, 1H), 6,85 (d, J = 9,4 Hz, 1H), 3,82 (s, 3H), 3,78 (s, 2H), 2,65 (c, J = 7,5 Hz, 2H), 1,32 (s, 6H), 1,15 (t, J = 7,5 Hz, 3H).

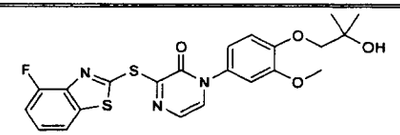
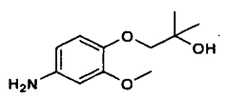
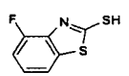
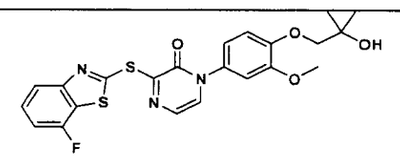
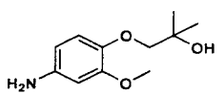
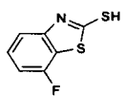
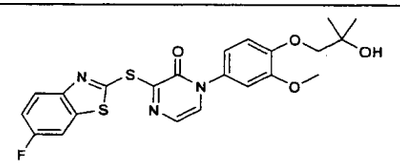
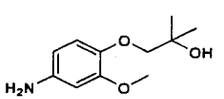
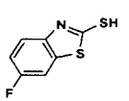
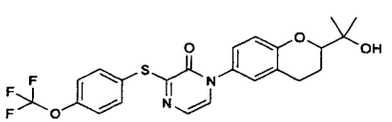
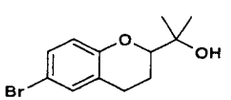
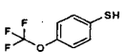
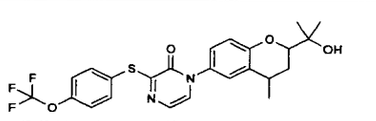
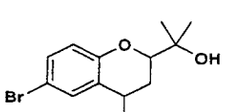
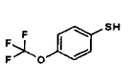
Ej. Nº.	Estructura	Componente de Anilina/Bromuro	Componente de Tiol	Proc.	Rend. (%)	HPLC (Min) Proc. 1	CL-EM (M+H)	Datos de H RMN ($CDCl_3$)
63	 1-(3-etil-4-(2-hidroxi-2-metilpropoxi)fenil)-3-(4-(trifluorometil)feniltio)pirazin-2(1*H*)-ona			2a		4,05	465	7,64 (d, J = 8,5 Hz, 2H), 7,62 (d, J = 8,5 Hz, 2H), 7,15 (m, 2H) 7,04 (d, J = 4,4 Hz, 1H), 6,93 (d, J = 4,4 Hz, 1H), 6,84 (d, J = 9,2 Hz, 1H), 3,77 (s, 2H), 2,63 (c, J = 7,5 Hz, 2H), 1,30 (s, 6H), 1,17 (t, J = 7,5 Hz, 3H)
64	 1-(3-etil-4-(2-hidroxi-2-metilpropoxi)fenil)-3-(4-(trifluorometoxi)feniltio)pirazin-2(1*H*)-ona			2a		4,15	481	7,43 (d, J = 8,8 Hz, 2H), 7,31 (d, J = 8,8 Hz, 2H), 7,24 (d, J = 2,4 Hz, 1H), 7,22 (d, J = 8,5 Hz, 1H), 7,14 (d, J = 4,4 Hz, 1H), 7,00 (d, J = 4,4 Hz, 1H), 6,94 (dd, J = 2,4, 8,5 Hz, 1H), 3,86 (s, 2H), 2,74 (c, J = 7,5 Hz, 2H), 1,41 (s, 6H), 1,26 (t, J = 7,5 Hz, 3H).
65	 1-(3-etil-4-(2-hidroxi-2-metilpropoxi)fenil)-3-(fenetiltio)pirazin-2(1*H*)-ona			2a		4,08 Proc. 2	425	7,10 (m, 8H), 6,84 (d, J = 4,4 Hz, 1H), 6,76 (d, J = 8,5 Hz, 1H), 3,70 (s, 2H), 3,21 (m, 2H), 2,90 (m, 2H), 2,59 (c, J = 7,4 Hz, 2H), 1,26 (s, 6H), 1,12 (t, J = 7,4 Hz, 3H)

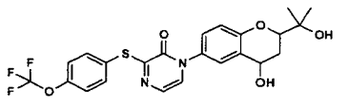
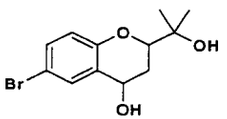
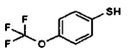
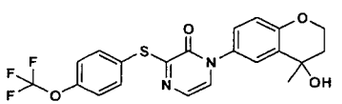
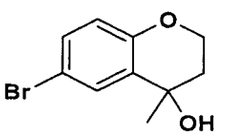
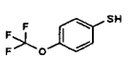
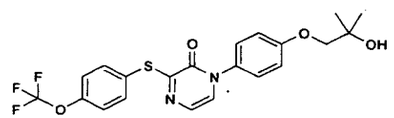
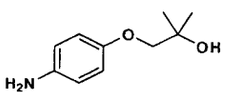
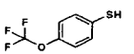
Ej. Nº.	Estructura	Componente de Anilina/Bromuro	Componente de Tiol	Proc.	Rend. (%)	HPLC (Min) Proc. 1	CL-EM (M+H)	Datos de H RMN ($CDCl_3$)
66	 1-(4-(2-ciclopropil-2-hidroxietoxi)-3-metoxifenil)-3-(fenetiltio)pirazin-2(1*H*)-ona			2a		3,81	439	7,23 (m, 5H), 7,14 (m, 1H), 6,92 (m, 3H), 6,83 (dd, J = 2,4, 8,6 Hz), 4,08 (dd, J = 2,6, 9,7 Hz, 1H), 3,93 (t, J = 8,2 Hz, 1H), 3,80 (s, 3H), 3,25 (m, 3H), 2,94 (m, 2H), 0,88 (m, 1H), 0,57 (m, 1H), 0,51 (m, 1H), 0,36 (m, 1H), 0,22 (m, 1H)
67	 1-(4-(2-ciclopropil-2-hidroxietoxi)-3-metoxifenil)-3-(4-(trifluorometoxi)feniltio)pirazin-2(1*H*)-ona			2a		3,87	495	7,54 (d, J = 8,8 Hz, 2H), 7,21 (d, J = 8,8 Hz, 2H), 7,05 (d, J = 4,4 Hz, 1H), 6,93 (d, J = 8,5 Hz, 1H), 6,92 (d, J = 2,4 Hz, 1H), 6,91 (d, J = 4,4 Hz, 1H), 6,84 (dd, J = 2,4, 8,5 Hz, 1H) 4,13 (dd, J = 2,8, 9,7 Hz, 1H), 3,96 (dd, J = 1,3, 8,2 Hz, 1H), 3,79 (s, 3H), 3,29 (dt, J = 2,5, 9,8 Hz, 1H), 0,93 (m, 1H), 0,57 (m, 1H), 0,51 (m, 1H), 0,41 (m, 1H), 0,25 (m, 1H)

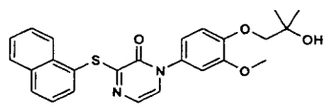
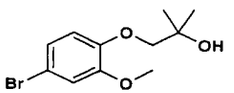
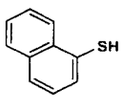
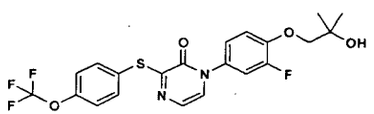
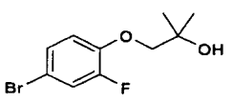
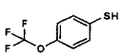
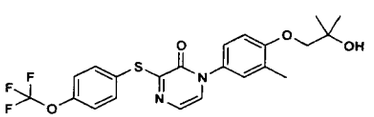
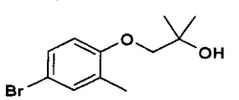
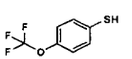
Ej. Nº.	Estructura	Componente de Anilina/Bromuro	Componente de Tiol	Proc.	Rend. (%)	HPLC (Min) Proc. 1	CL-EM (M+H)	Datos de H RMN ($CDCl_3$)
68	 1-(4-(2-ciclopropil-2-hidroxietoxi)-3-metoxifenil)-3-(4-(trifluorometil)feniltio)pirazin-2(1*H*)-ona			2a		3,74 Proc. 2	479	7,66 (d, J = 8,5 Hz, 2H), 7,64 (d, J = 8,5 Hz, 2H), 7,51 (d, J = 4,4 Hz, 1H), 7,09 (d, J = 4,4 Hz, 1H), 7,00 (d, J = 8,2 Hz, 1H), 6,98 (d, J = 2,2 Hz, 1H), 6,89 (dd, J = 2,2, 8,2 Hz, 1H), 4,22 (dd, J = 2,2, 9,3 Hz, 1H), 3,96 (dd, J = 1,1, 9,4 Hz, 1H), 3,84 (s, 3H), 3,27 (dt, J = 2,5, 9,8 Hz, 1H), 0,93 (m, 1H), 0,57 (m, 1H), 0,51 (m, 1H), 0,41 (m, 1H), 0,25 (m, 1H)
69	 1-(4-((3*S*,4*R*)-4-hidroxitetrahidrofuran-3-iloxi)-3-metoxifenil)-3-(4-(trifluorometil)feniltio)pirazin-2(1*H*)-ona			2a		3,59 Proc. 2	481	7,64 (m, 4H), 7,06 (d, J = 4,4 Hz, 1H), 6,98 (d, J = 2,8 Hz, 1H), 6,95 (d, J = 9,7 Hz, 1H), 6,93 (d, J = 4,4 Hz, 1H), 6,86 (dd, J = 2,8 y 9,7 Hz, 1H), 4,63 (m, 1H), 4,34 (m, 1H), 4,09 (m, 1H), 3,97 (m, 2H), 3,83 (s, 3H), 3,78 (m, 1H), 3,07 (d, J = 6,4 Hz, 1H).

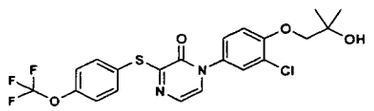
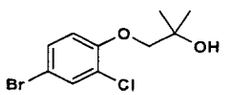
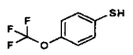
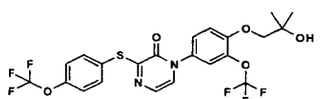
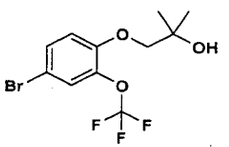
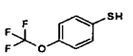
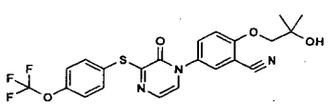
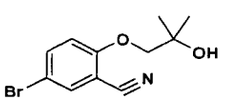
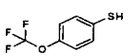
Ej. Nº.	Estructura	Componente de Anilina/Bromuro	Componente de Tiol	Proc.	Rend. (%)	HPLC (Min) Proc. 1	CL-EM (M+H)	Datos de H RMN ($CDCl_3$)
70	 1-(4-((1*S*,2*R*)-2-hidroxiciclopentiloxi)-3-metoxifenil)-3-(4-(trifluorometil)feniltio)pirazin-2(1*H*)-ona			2a		3,87 Proc. 2	479	7,62 (m, 4 H), 7,05 (d, J = 4,5 Hz, 1H), 6,95 (d, J = 8,5 Hz, 1H), 6,93 (d, J = 4,5 Hz, 1H), 6,92 (d, J = 2,4 Hz, 1H), 6,83 (dd, J = 2,4 y 8,5 Hz, 1H), 4,42 (m, 1H), 4,13 (m, 1H), 3,75 (s, 3H), 3,04 (m, 1H), 1,99 (m, 1H), de 1,70 a 1,90 (m, 4H), 1,52 (m, 1H).
71	 1-(4-(2-hidroxipropoxi)-3-metoxifenil)-3-(4-(trifluorometil)feniltio)pirazin-2(1*H*)-ona			2a		3,74 Proc. 2	453	7,85 (d, J = 8,4 Hz, 2H), 7,80 (d, J = 8,4 Hz, 2H), 7,48 (d, J = 4,4 Hz, 1H), 7,16 (d, J = 4,4 Hz, 1H), 7,15 (d, J = 2,4 Hz, 1H), 7,10 (d, J = 8,6 Hz, 1H), 7,01 (dd, J = 2,4, 8,6 Hz, 1H), 3,97 (m, 1H), 3,90 (m, 1H), 3,81 (m, 1H), 3,78 (s, 3H), 1,16 (d, 3H)
72	 1-(4-(2-hidroxi-3-metoxipropoxi)-3-metoxifenil)-3-(4-(trifluorometil)feniltio)pirazin-2(1*H*)-ona			2a		3,72 Proc. 2	483	7,64 (m, 4H), 7,06 (d, J = 4,5 Hz, 1H), 6,96 (d, J = 8,5 Hz, 1H), 6,94 (d, J = 4,5 Hz, 1H), 6,92 (d, J = 2,5 Hz, 1H), 6,84 (dd, J = 2,5, 8,5 Hz, 1H), 4,04 (m, 2H), 3,81 (s, 3H), 3,50 (m, 2H), 3,36 (s, 3H)

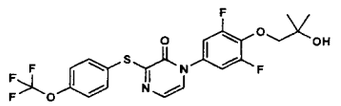
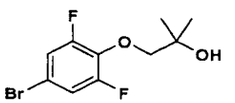
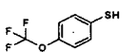
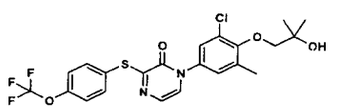
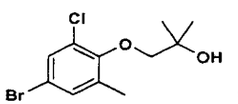
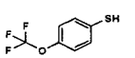
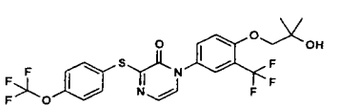
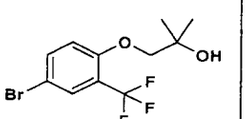
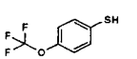
Ej. N°.	Estructura	Componente de Anilina/Bromuro	Componente de Tiol	Proc.	Rend. (%)	HPLC (Min) Proc. 1	CL-EM (M+H)	Datos de H RMN ($CDCl_3$)
73	 1-(4-(3-(etilsulfonil)-2-hidroxipropoxi)-3-metoxifenil)-3-(4-(trifluorometil)feniltio)pirazin-2(1*H*)-ona			2a		3,62 Proc. 2	545	7,63 (m, 4H), 7,06 (d, J = 4,4 Hz, 2H), 6,94 (d, J = 4,4 Hz, 1H), 6,92 (d, J = 2,0 Hz, 1H), 6,90 (d, J = 8,5 Hz, 1H), 6,83 (dd, J = 2,0 y 8,5 Hz, 1H), 4,54 (m, 1H), 4,02 (d, J = 5,4 Hz, 2H), 3,78 (s, 3H), 3,62 (m, 1 H), de 3,0 a 3,40 (m, 3H), 1,86 (m, 1 H), 1,38 (t, J = 7,4 Hz, 3H).
74	 1-(3-metoxi-4-(3,3,3-trifluoro-2-hidroxipropoxi)fenil)-3-(4-(trifluorometil)feniltio)pirazin-2(1*H*)-ona			2a			507	3,90 (s, 3 H), 4,14 - 4,22 (m, 1 H), 4,32 (dd, J = 10,45, 3,65 Hz, 1 H), 4,36 - 4,47 (m, 1 H), 7,03 (dd, J = 8,56, 2,27 Hz, 1 H), 7,14 - 7,22 (m, 3 H), 7,34 (d, J = 4,28 Hz, 1 H), 7,74 - 7,83 (m, 4 H)
75	 1-(4-((3,3-difluoro-1-hidroxiciclobutil)metoxi)-3-metoxifenil)-3-(4-(trifluorometoxi)feniltio)pirazin-2(1*H*)-ona			2a			531	RMN ^{1}H (400 MHz, MeOD) δ ppm 7,69 (d, 2H), 7,38 (d, 2H), 7,33 (d, 1H), 7,18 (m, 3H), 7,03 (d, 1H), 4,09 (s, 2H), 3,91 (s, 3H), 2,93 (m, 2H), 2,66 (m, 2H).
76	 1-(4-((3,3-difluoro-1-hidroxiciclobutil)metoxi)-3-metoxifenil)-3-(4-(trifluorometil)feniltio)pirazin-2(1*H*)-ona			2a			515	RMN ^{1}H (400 MHz, MeOD) δ ppm 7,78 (s, 4H), 7,34 (s, 1H), 7,19 (m, 3H), 7,03 (d, 1H), 4,09 (s, 2H), 3,90 (s, 3H), 2,93 (m, 2H), 2,66 (m, 2H).

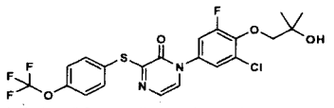
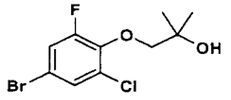
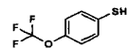
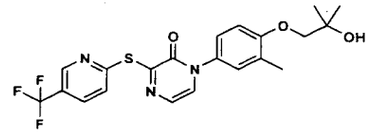
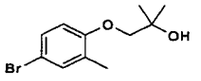
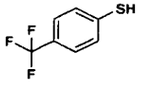
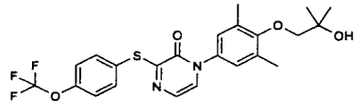
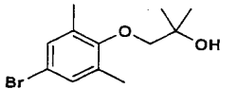
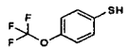
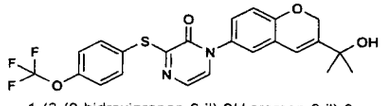
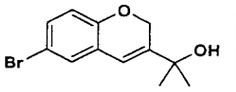
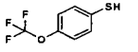
Ej. Nº.	Estructura	Componente de Anilina/Bromuro	Componente de Tiol	Proc.	Rend. (%)	HPLC (Min) Proc. 1	CL-EM (M+H)	Datos de H RMN ($CDCl_3$)
77	 3-(4-fluorobenzo[*d*]tiazol-2-iltio)-1-(4-(2-hidroxi-2-metilpropoxi)-3-metoxifenil)pirazin-2(1*H*)-ona			2a			474	RMN ^{1}H (400 MHz, MeOD) δ ppm 7,78 (d, 1H), 7,53 (m, 3H), 7,30 (m, 1H), 7,20 (s, 1H), 7,12 (m, 1H), 7,06 (d, 1H), 3,91 (s, 3H), 3,88 (s, 2H), 1,36 (s, 6H).
78	 3-(7-fluorobenzo[*d*]tiazol-2-iltio)-1-(4-(2-hidroxi-2-metilpropoxi)-3-metoxifenil)pirazin-2(1*H*)-ona			2a			474	RMN ^{1}H (400 MHz, MeOD) δ ppm 7,85 (d, 1H), 7,53 (m, 3H), 7,21 (m, 4H), 3,91 (s, 3H), 3,88 (s, 2H), 1,36 (s, 6H).
79	 3-(6-fluorobenzo[*d*]tiazol-2-iltio)-1-(4-(2-hidroxi-2-metilpropoxi)-3-metoxifenil)pirazin-2(1*H*)-ona			2a			474	RMN ^{1}H (400 MHz, MeOD) δ ppm 7,97 (d, 1H), 7,85 (d, 1H), 7,53 (d, 2H), 7,35 (t, 1H), 7,21 (s, 1H), 7,16 (m, 1H), 7,07 (m, 1H), 3,91 (s, 3H), 3,88 (s, 2H), 1,36 (s, 6H).
80	 1-(2-(2-hidroxipropan-2-il)croman-6-il)-3-(4-(trifluorometoxi)feniltio)pirazin-2(1*H*)-ona			6			479	RMN ^{1}H (400 MHz, MeOD) δ ppm 7,68 (d, 2H), 7,40 (d, 2H), 7,28 (s, 1H), 7,17 (m, 3H), 6,97 (d, 1H), 3,82 (s, 1H), 2,96 (m, 2H), 2,24 (m, 1H), 2,81 (m, 1H), 1,33 (s, 6H).
81	 1-(2-(2-hidroxipropan-2-il)-4-metilcroman-6-il)-3-(4-(trifluorometoxi)feniltio)pirazin-2(1*H*)-ona			6			491	RMN ^{1}H (400 MHz, MeOD) δ ppm 7,69 (d, 2H), 7,40 (d, 2H), 7,28 (m, 2H), 7,20 (m, 2H), 6,91 (d, 1H), 5,79 (s, 1H), 4,70 (s, 1H), 2,08 (s, 2H), 1,31 (d, 6H).

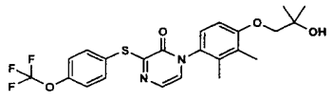
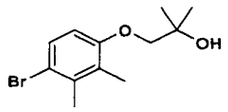
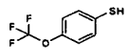
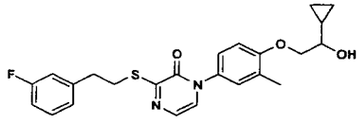
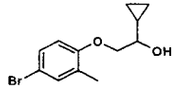
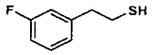
Ej. Nº.	Estructura	Componente de Anilina/Bromuro	Componente de Tiol	Proc.	Rend. (%)	HPLC (Min) Proc. 1	CL-EM (M+H)	Datos de H RMN ($CDCl_3$)
82	 1-(4-hidroxi-2-(2-hidroxipropan-2-il)croman-6-il)-3-(4-(trifluorometoxi)feniltio)pirazin-2(1*H*)-ona			6			495	RMN ^1H (400 MHz, $CDCl_3$) δ ppm 7,61 (d, 2H), 7,59 (s, 1H), 7,28 (m, 2H), 7,14 (m, 2H), 6,99 (s, 1H), 6,92 (d, 1H), 4,87 (t, 1H), 4,00 (d, 1H), 2,36 (m, 1H), 1,84 (c, 1H), 1,38 (d, 6H).
83	 1-(4-hidroxi-4-metilcroman-6-il)-3-(4-(trifluorometoxi)feniltio)pirazin-2(1*H*)-ona			6			433 (M+H-H_2O)	RMN ^1H (400 MHz, MeOD) δ ppm 7,70 (d, 2H), 7,61 (s, 1H), 7,43 (d, 2H), 7,28 (m, 2H), 7,20 (s, 1H), 6,95 (d, 1H), 4,35 (m,2H), 2,12 (s a, 2H), 1,62 (s, 3H).
84	 1-(4-(2-hidroxi-2-metilpropoxi)fenil)-3-(4-(trifluorometoxi)feniltio)pirazin-2(1*H*)-ona			6			453	RMN ^1H (500 MHz, cloroformo-d) δ ppm 7,62 (2 H, d, J = 8,80 Hz), 7,36 (2 H, d, J = 8,80 Hz), 7,29 (2 H, d, J = 7,97 Hz), 7,13 (1 H, d, J = 4,67 Hz), 7,04 (2 H, d, J = 8,80 Hz), 6,98 (1 H, d, J = 4,40 Hz), 3,84 (2 H, s), 1,37 (6 H, s).

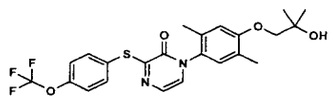
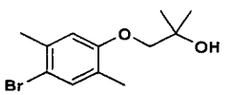
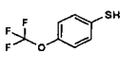
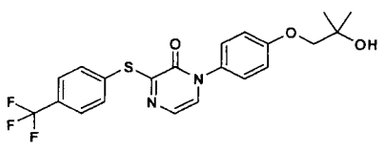
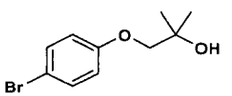
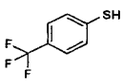
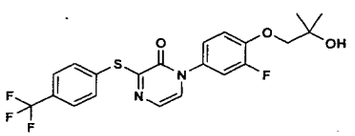
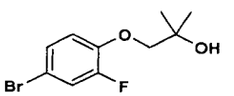
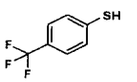
Ej. Nº.	Estructura	Componente de Anilina/Bromuro	Componente de Tiol	Proc.	Rend. (%)	HPLC (Min) Proc. 1	CL-EM (M+H)	Datos de H RMN ($CDCl_3$)
85	 1-(4-(2-hidroxi-2-metilpropoxi)-3-metoxifenil) -3-(naftalen-1-iltio)pirazin-2(1*H*)-ona			6			449	RMN ^{1}H (500 MHz, cloroformo-d) δ ppm 8,31 (1 H, dd, J = 6,19, 3,44 Hz), 8,00 (1 H, d, J = 8,25 Hz), 7,85 - 7,95 (2 H, m), 7,51 - 7,56 (3 H, m), 7,04 (1 H, d, J = 2,20 Hz), 6,97 - 7,02 (1 H, m), 6,89 - 6,96 (3 H, m), 3,90 (3 H, s), 3,88 (2 H, s), 1,37 (6 H, s).
86	 1-(3-fluoro-4-(2-hidroxi-2-metilpropoxi)fenil) -3-(4-(trifluorometoxi)feniltio)pirazin-2(1*H*)-ona			6			471	RMN ^{1}H (500 MHz, metanol-d_3) δ ppm 7,62 - 7,68 (2 H, m), 7,34 - 7,39 (3 H, m), 7,21 - 7,29 (3 H, m), 7,15 (1 H, d, J = 4,40 Hz), 3,91 (2 H, s), 1,34 (6 H, s).
87	 1-(4-(2-hidroxi-2-metilpropoxi)-3-metilfenil) -3-(4-(trifluorometoxi)feniltio)pirazin-2(1*H*)-ona			6			467	RMN ^{1}H (500 MHz, metanol-d_3) δ ppm 7,62 - 7,69 (2 H, m), 7,36 (2 H, d, J = 7,97 Hz), 7,21 - 7,28 (3 H, m), 7,15 (1 H, d, J = 4,40 Hz), 7,02 (1 H, d, J = 8,52 Hz), 3,84 (2 H, s), 2,31 (3 H, s), 1,36 (6 H, s).

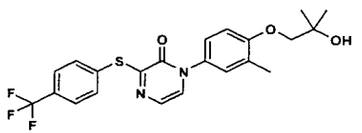
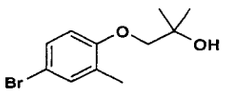
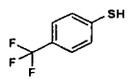
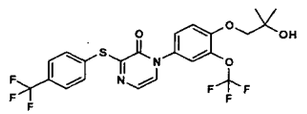
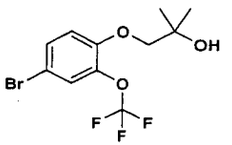
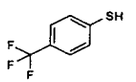
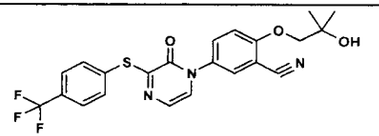
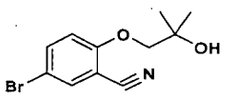
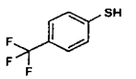
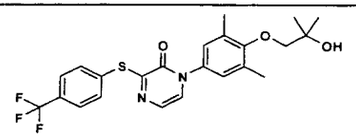
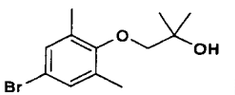
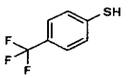
Ej. Nº.	Estructura	Componente de Anilina/Bromuro	Componente de Tiol	Proc.	Rend. (%)	HPLC (Min) Proc. 1	CL-EM (M+H)	Datos de H RMN ($CDCl_3$)
88	 1-(3-cloro-4-(2-hidroxi-2-metilpropoxi)fenil) -3-(4-(trifluorometoxi)feniltio)pirazin-2(1*H*)-ona			6			487	RMN ^{1}H (500 MHz, metanol-d_3) δ ppm 7,65 (2 H, d, J = 8,80 Hz), 7,59 (1 H, d, J = 2,75 Hz), 7,33 - 7,41 (3 H, m), 7,27 (1 H, d, J = 4,40 Hz), 7,22 (1 H, d, J = 8,80 Hz), 7,15 (1 H, d, J = 4,40 Hz), 3,91 (2 H, s), 1,37 (6 H, s)
89	 1-(4-(2-hidroxi-2-metilpropoxi)-3-(trifluorometoxi)fenil) -3-(4-(trifluorometoxi)feniltio)pirazin-2(1*H*)-ona			6			537	RMN ^{1}H (500 MHz, metanol-d_3) δ ppm 7,66 (2 H, d), 7,52 - 7,56 (1 H, m), 7,46 (1 H, dd, J = 8,94, 2,61 Hz), 7,37 (2 H, d, J = 7,97 Hz), 7,33 (1 H, d, J = 8,80 Hz), 7,29 (1 H, d, J = 4,40 Hz), 7,16 (1 H, d, J = 4,67 Hz), 3,91 (2 H, s), 1,34 (6 H, s).
90	 2-(2-hidroxi-2-metilpropoxi)-5-(2-oxo-3- (4-(trifluorometoxi)feniltio)pirazin-1(2*H*)-il)benzonitrilo			6			478	RMN ^{1}H (500 MHz, metanol-d_3) δ ppm 7,85 (1 H, d, J = 2,75 Hz), 7,74 (1 H, dd, J = 8,94, 2,61 Hz), 7,65 (2 H, d), 7,33 - 7,39 (3 H, m), 7,29 (1 H, d, J = 4,67 Hz), 7,16 (1 H, d, J = 4,40 Hz), 4,01 (2 H, s), 1,38 (6 H, s).

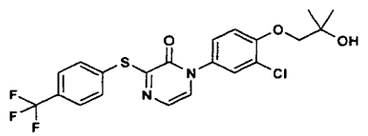
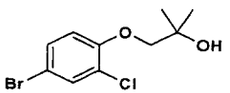
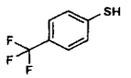
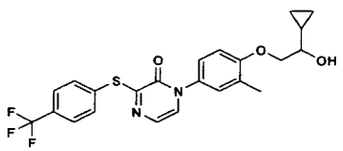
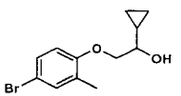
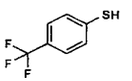
Ej. Nº.	Estructura	Componente de Anilina/Bromuro	Componente de Tiol	Proc.	Rend. (%)	HPLC (Min) Proc. 1	CL-EM (M+H)	Datos de H RMN ($CDCl_3$)
91	 1-(3,5-difluoro-4-(2-hidroxi-2-metilpropoxi)fenil)-3-(4-(trifluorometoxi)feniltio)pirazin-2(1*H*)-ona			6			489	RMN ^{1}H (500 MHz, metanol-d_3) δ ppm 7,65 (2 H, d, J = 8,80 Hz), 7,37 (2 H, d, J = 7,97 Hz), 7,24 - 7,32 (3 H, m), 7,15 (1 H, d, J = 4,40 Hz), 4,00 (2 H, s), 1,33 (6 H, s).
92	 1-(3-cloro-4-(2-hidroxi-2-metilpropoxi)-5-metilfenil) -3-(4-(trifluorometoxi)feniltio)pirazin-2(1*H*)-ona			6			501	RMN ^{1}H (500 MHz, metanol-d_3) δ ppm 7,65 (2 H, d, J = 8,80 Hz), 7,45 (1 H, d, J = 2,75 Hz), 7,37 (2 H, d, J = 7,97 Hz), 7,30 (1 H, d, J = 1,92 Hz), 7,27 (1 H, d, J = 4,40 Hz), 7,15 (1 H, d, J = 4,67 Hz), 3,78 (2 H, s), 2,40 (3 H, s), 1,39 (6 H, s).
93	 1-(4-(2-hidroxi-2-metilpropoxi)-3-(trifluorometil)fenil) -3-(4-(trifluorometoxi)feniltio)pirazin-2(1*H*)-ona			6			521	RMN ^{1}H (500 MHz, metanol-d_3) δ ppm 7,77 (1 H, d, J = 2,47 Hz), 7,62 - 7,71 (3 H, m), 7,35 (3 H, dd, J = 14,57, 8,52 Hz), 7,30 (1 H, d, J = 4,40 Hz), 7,17 (1 H, d, J = 4,40 Hz), 3,94 (2 H, s), 1,35 (6 H, s).

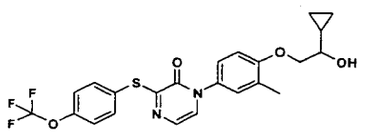
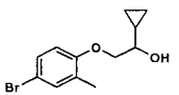
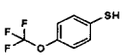
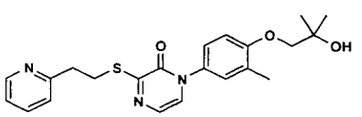
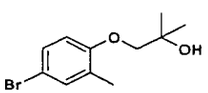
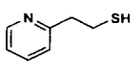
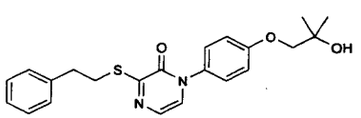
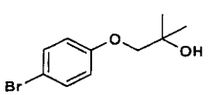
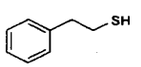
Ej. Nº.	Estructura	Componente de Anilina/Bromuro	Componente de Tiol	Proc.	Rend. (%)	HPLC (Min) Proc. 1	CL-EM (M+H)	Datos de H RMN ($CDCl_3$)
94	 1-(3-cloro-5-fluoro-4-(2-hidroxi-2-metilpropoxi)fenil) -3-(4-(trifluorometoxi)feniltio)pirazin-2(1*H*)-ona			6			505	RMN ^{1}H (500 MHz, metanol-d_3) δ ppm 7,65 (2 H, d), 7,46 - 7,51 (1 H, m), 7,42 (1 H, dd, J = 11,27, 2,47 Hz), 7,37 (2 H, d, J = 7,97 Hz), 7,28 (1 H, d, J = 4,40 Hz), 7,15 (1 H, d, J = 4,40 Hz), 3,98 (2 H, s), 1,37 (6 H, s).
95	 1-(4-(2-hidroxi-2-metilpropoxi)-3-metilfenil) -3-(5-(trifluorometoxi)piridin-2-iltio)pirazin-2(1*H*)-ona			6			452	RMN ^{1}H (500 MHz, cloroformo-d) δ ppm 8,88 (1 H, s), 7,89 - 7,99 (2 H, m), 7,16 - 7,24 (3 H, m), 7,07 (1 H, d, J = 4,40 Hz), 6,90 (1 H, d, J = 8,52 Hz), 3,84 (2 H, s), 2,30 (3 H, s), 1,39 (6 H, s)
96	 1-(4-(2-hydroxy-2-methylpropoxy)-3,5-dimethylphenyl) -3-(4-(trifluoromethoxy)phenylthio)pyrazin-2(1*H*)-one			6			481	RMN ^{1}H (400 MHz, cloroformo-d) δ ppm 7,62 (2 H, d, J = 8,78 Hz), 7,29 (2 H, d, J = 8,03 Hz), 7,11 (1 H, d, J = 4,52 Hz), 7,08 (2 H, s), 6,96 (1 H, d, J = 4,52 Hz), 3,64 (2 H, s), 2,33 (6 H, s), 1,39 (6 H, s).
97	 1-(3-(2-hidroxipropan-2-il)-2*H*-cromen-6-il)-3- (4-(trifluorometoxi)feniltio)pirazin-2(1*H*)-ona			6			477	RMN ^{1}H (400 MHz, MeOD) δ ppm 7,68 (d, 2H), 7,39 (d, 2H), 7,28 (d, 1H), 7,18 (m, 3H), 6,93 (d, 1H), 6,49 (s, 1H), 1,42 (s, 6H).

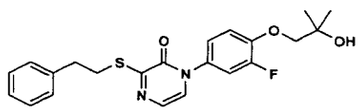
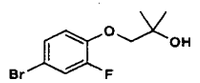
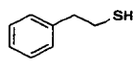
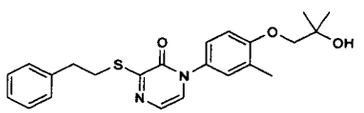
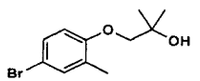
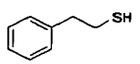
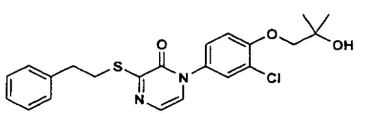
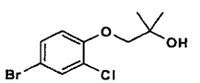
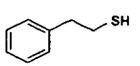
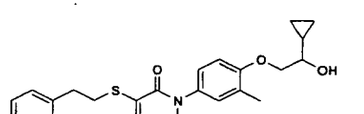
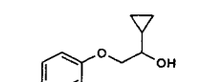
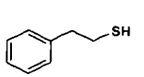
Ej. Nº.	Estructura	Componente de Anilina/Bromuro	Componente de Tiol	Proc.	Rend. (%)	HPLC (Min) Proc. 1	CL-EM (M+H)	Datos de H RMN ($CDCl_3$)
98	 1-(4-(2-hidroxi-2-metilpropoxi)-2,3-dimetilfenil)-3-(4-(trifluorometoxi)feniltio)pirazin-2(1*H*)-ona			6			481	RMN ^{1}H (400 MHz, MeOD) δ ppm 7,69 (2 H, d), 7,39 (2 H, d, J = 8,03 Hz), 7,18 (2 H, dd), 7,08 (1 H, d, J = 8,53 Hz), 6,93 (1 H, d, J = 8,78 Hz), 3,84 (2 H, s), 2,30 (3 H, s), 2,02 (3 H, s), 1,38 (6 H, s).
99	 1-(4-(2-ciclopropil-2-hidroxietoxi)-3-metilfenil) -3-(3-fluorofenetiltio)pirazin-2(1*H*)-ona			6			441	RMN ^{1}H (500 MHz, cloroformo-d) δ ppm 7,23 - 7,31 (2 H, m), 7,16 - 7,23 (2 H, m), 7,07 (1 H, d, J = 7,42 Hz), 6,98 - 7,04 (1 H, m), 6,88 - 6,98 (3 H, m), 4,14 (1 H, dd, J = 9,35, 3,30 Hz), 4,04 (1 H, dd, J = 9,35, 7,15 Hz), 3,26 - 3,40 (3 H, m), 2,97 - 3,06 (2 H, m), 2,27 (3 H, s), 0,99 - 1,10 (1 H, m), 0,55 - 0,68 (2 H, m), 0,43 - 0,51 (1 H, m), 0,30 - 0,38 (1 H, m)

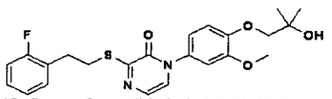
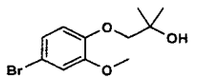
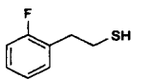
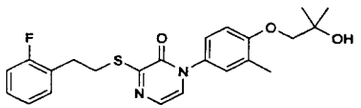
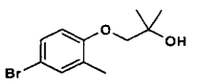
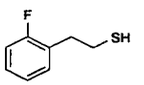
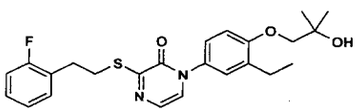
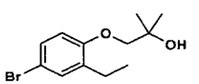
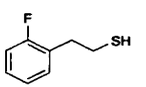
Ej. Nº.	Estructura	Componente de Anilina/Bromuro	Componente de Tiol	Proc.	Rend. (%)	HPLC (Min) Proc. 1	CL-EM (M+H)	Datos de H RMN ($CDCl_3$)
100	 1-(4-(2-hidroxi-2-metilpropoxi)-2,5-dimetilfenil)-3-(4-(trifluorometoxi)feniltio)pirazin-2(1*H*)-ona			6			481	RMN ^{1}H (400 MHz, cloroformo-d) δ ppm 7,63 (2 H, dd, J = 8,78, 2,26 Hz), 7,30 (2 H, d, J = 7,78 Hz), 7,11 (1 H, dd, J = 4,27, 2,26 Hz), 6,98 (1 H, s), 6,84 (1 H, dd, J = 4,52, 2,26 Hz), 6,76 (1 H, s), 3,84 (2 H, s a), 2,24 (3 H, s), 2,14 (3 H, s), 1,39 (6 H, d, J = 2,26 Hz).
101	 1-(4-(2-hidroxi-2-metilpropoxi)fenil)-3-(4-(trifluorometil)feniltio)pirazin-2(1*H*)-ona			6			437	RMN ^{1}H (500 MHz, cloroformo-d) δ ppm 7,71 (4 H, m), 7,36 (2 H, d, J = 8,80 Hz), 7,13 (1 H, d, J = 4,40 Hz), 7,04 (2 H, d, J = 9,35 Hz), 7,00 (1 H, d, J = 4,40 Hz), 3,84 (2 H, s), 1,37 (6 H, s).
102	 1-(3-fluoro-4-(2-hidroxi-2-metilpropoxi)fenil)-3-(4-(trifluorometil)feniltio)pirazin-2(1*H*)-ona			6			455	RMN ^{1}H (500 MHz, cloroformo-d) δ ppm 7,71 (4 H, m), 7,26 (1 H, dd, J = 11,00, 2,75 Hz), 7,11 – 7,19 (2 H, m), 7,05 – 7,11 (1 H, m), 6,98 (1 H, d, J = 4,95 Hz), 3,91 (2 H, s), 1,38 (6 H, s)

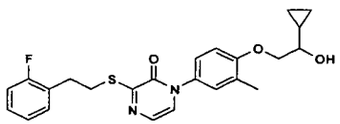
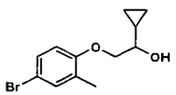
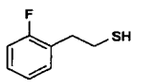
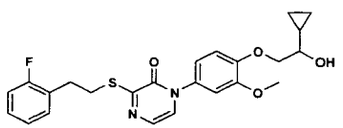
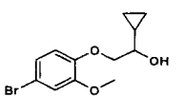
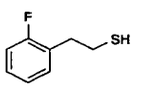
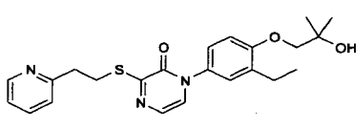
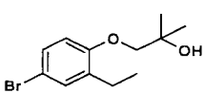
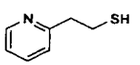
Ej. Nº.	Estructura	Componente de Anilina/Bromuro	Componente de Tiol	Proc.	Rend. (%)	HPLC (Min) Proc. 1	CL-EM (M+H)	Datos de H RMN ($CDCl_3$)
103	 1-(4-(2-hidroxi-2-metilpropoxi)-3-metilfenil)-3-(4-(trifluorometil)feniltio)pirazin-2(1*H*)-ona			6			451	RMN ^{1}H (500 MHz, cloroformo-d) δ ppm 7,67 – 7,75 (4 H, m), 7,18 – 7,25 (2 H, m), 7,12 (1 H, d, J = 4,40 Hz), 6,99 (1 H, d, J = 4,40 Hz), 6,91 (1 H, d, J = 8,25 Hz), 3,85 (2 H, s), 2,31 (3 H, s), 1,39 (6 H, s)
104	 1-(4-(2-hidroxi-2-metilpropoxi)-3-(trifluorometoxi)fenil)-3-(4-(trifluorometil)feniltio)pirazin-2(1*H*)-ona			6			521	RMN ^{1}H (500 MHz, cloroformo-d) δ ppm 7,66 - 7,78 (4 H, m), 7,35 - 7,42 (2 H, m), 7,08 - 7,17 (2 H, m), 6,99 (1 H, d, J = 4,40 Hz), 3,90 (2 H, s), 1,38 (6 H, s)
105	 2-(2-hidroxi-2-metilpropoxi)-5-(2-oxo-3-(4-(trifluorometil)feniltio)pirazin-1(2*H*)-il)benzonitrilo			6			462	RMN ^{1}H (500 MHz, cloroformo-d) δ ppm 7,60 - 7,78 (6 H, m), 7,09 - 7,17 (2 H, m), 6,95 (1 H, d, J = 4,40 Hz), 3,97 (2 H, s), 1,43 (6 H, s)
106	 1-(4-(2-hidroxi-2-metilpropoxi)-3,5-dimetilfenil)-3-(4-(trifluorometil)feniltio)pirazin-2(1*H*)-ona			6			465	RMN ^{1}H (500 MHz, cloroformo-d) δ ppm 7,71 (4 H, d, J = 6,05 Hz), 7,07 - 7,14 (3 H, m), 6,98 (1 H, d, J = 4,40 Hz), 3,64 (2 H, s), 2,33 (6 H, s), 1,40 (6 H, s)

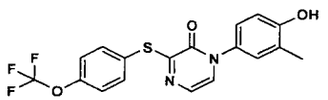
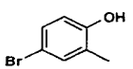
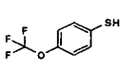
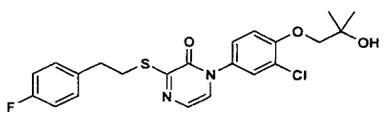
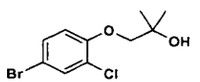
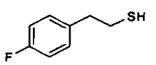
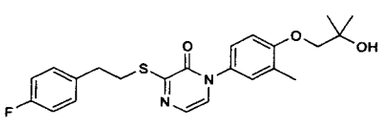
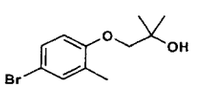
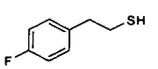
Ej. Nº.	Estructura	Componente de Anilina/Bromuro	Componente de Tiol	Proc.	Rend. (%)	HPLC (Min) Proc. 1	CL-EM (M+H)	Datos de H RMN ($CDCl_3$)
107	 1-(3-cloro-4-(2-hidroxi-2-metilpropoxi)fenil) -3-(4-(trifluorometil)feniltio)pirazin-2(1*H*)-ona			6			471	RMN ^{1}H (500 MHz, cloroformo-d) δ ppm 7,67 - 7,74 (4 H, m), 7,50 (1 H, d, J = 2,47 Hz), 7,32 (1 H, dd, J = 8,80, 2,47 Hz), 7,13 (1 H, d, J = 4,67 Hz), 7,03 (1 H, d, J = 8,80 Hz), 6,97 (1 H, d, J = 4,40 Hz), 3,91 (2 H, s), 1,40 (6 H, s)
108	 1-(4-(2-ciclopropil-2-hidroxietoxi)-3-metilfenil) -3-(4-(trifluorometil)feniltio)pirazin-2(1*H*)-ona			6			463	RMN ^{1}H (500 MHz, cloroformo-d) δ ppm 7,64 - 7,77 (4 H, m), 7,19 - 7,24 (2 H, m), 7,12 (1 H, d, J = 4,40 Hz), 7,00 (1 H, d, J = 4,40 Hz), 6,94 (1 H, d, J = 8,80 Hz), 4,16 (1 H, dd, J = 9,35, 3,30 Hz), 4,06 (1 H, dd, J = 9,35, 7,15 Hz), 3,31 - 3,42 (1 H, m), 2,29 (3 H, s), 0,99 - 1,11 (1 H, m), 0,55 - 0,71 (2 H, m), 0,43 - 0,52 (1 H, m), 0,29 - 0,41 (1 H, m)

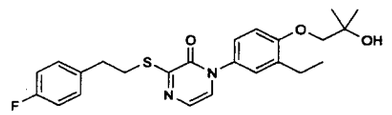
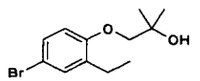
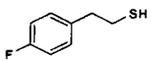
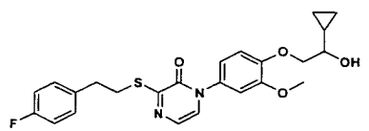
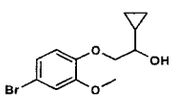
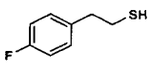
Ej. Nº.	Estructura	Componente de Anilina/Bromuro	Componente de Tiol	Proc.	Rend. (%)	HPLC (Min) Proc. 1	CL-EM (M+H)	Datos de H RMN ($CDCl_3$)
109	 1-(4-(2-ciclopropil-2-hidroxietoxi)-3-metilfenil) -3-(4-(trifluorometoxi)feniltio)pirazin-2(1*H*)-ona			6			479	RMN ^{1}H (500 MHz, cloroformo-d) δ ppm 7,61 (2 H, d), 7,29 (2 H, d, J = 7,97 Hz), 7,19 - 7,24 (2 H, m), 7,11 (1 H, d, J = 4,67 Hz), 6,98 (1 H, d, J = 4,40 Hz), 6,94 (1 H, d, J = 8,52 Hz), 4,15 (1 H, dd, J = 9,35, 3,30 Hz), 4,05 (1 H, dd, J = 9,35, 7,15 Hz), 3,30 - 3,42 (1 H, m), 2,28 (3 H, s), 0,99 - 1,11 (1 H, m), 0,55 - 0,70 (2 H, m), 0,42 - 0,52 (1 H, m), 0,30 - 0,39 (1 H, m)
110	 1-(4-(2-hidroxi-2-metilpropoxi)-3-metilfenil) -3-(2-(piridin-2-il)etiltio)pirazin-2(1*H*)-ona			6			412	RMN ^{1}H (400 MHz, MeOD) δ ppm 8,67 (1 H, d), 8,48 (1 H, td, J = 7,91, 1,51 Hz), 8,02 (1 H, d, J = 8,28 Hz), 7,81 - 7,95 (1 H, m), 7,07 - 7,29 (4 H, m), 6,93 (1 H, d, J = 8,78 Hz), 3,76 (2 H, s), 3,35 - 3,57 (4 H, m), 2,22 (3 H, s), 1,27 (6 H, s)
111	 1-(4-(2-hidroxi-2-metilpropoxi)fenil) -3-(fenetiltio)pirazin-2(1*H*)-ona			6			397	RMN ^{1}H (500 MHz, metanol-d_3) δ ppm 7,32 - 7,40 (3 H, m), 7,25 - 7,29 (4 H, m), 7,16 - 7,23 (2 H, m), 7,08 (2 H, d, J = 8,80 Hz), 3,83 (2 H, s), 3,31 (2 H, s), 2,89 - 3,03 (2 H, m), 1,32 (6 H, s)

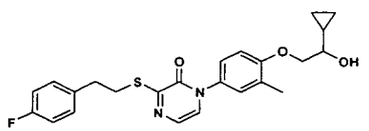
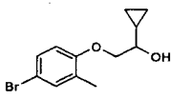
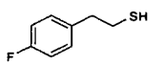
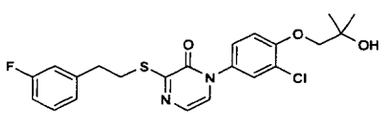
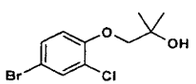
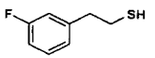
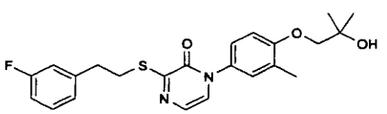
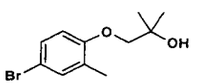
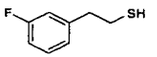
Ej. Nº.	Estructura	Componente de Anilina/Bromuro	Componente de Tiol	Proc.	Rend. (%)	HPLC (Min) Proc. 1	CL-EM (M+H)	Datos de H RMN ($CDCl_3$)
112	 1-(3-fluoro-4-(2-hidroxi-2-metilpropoxi) fenil)-3-(fenetiltio)pirazin-2(1*H*)-ona			6			415	RMN ^{1}H (500 MHz, metanol-d_3) δ ppm 7,12 - 7,46 (10 H, m), 3,90 (1 H, s), 3,21 - 3,42 (2 H, m), 2,90 - 3,03 (2 H, m), 1,33 (6 H, s)
113	 1-(4-(2-hidroxi-2-metilpropoxi)-3-metilfenil) -3-(fenetiltio)pirazin-2(1*H*)-ona			6			411	RMN ^{1}H (500 MHz, metanol-d_3) δ ppm 7,38 (1 H, d, J = 4,40 Hz), 7,25 - 7,32 (4 H, m), 7,16 - 7,24 (4 H, m), 7,00 (1 H, d, J = 8,25 Hz), 3,83 (1 H, s), 3,24 - 3,39 (2 H, m), 2,90 - 3,05 (2 H, m), 2,29 (3 H, s), 1,35 (6 H, s)
114	 1-(3-cloro-4-(2-hidroxi-2-metilpropoxi) fenil)-3-(fenetiltio)pirazin-2(1*H*)-ona			6			431	RMN ^{1}H (500 MHz, metanol-d_3) δ ppm 7,56 (1 H, d, J = 2,20 Hz), 7,33 - 7,42 (2 H, m), 7,17 - 7,31 (7 H, m), 3,90 (2 H, s), 3,23 - 3,42 (2 H, m), 2,89 - 3,08 (2 H, m), 1,36 (6 H, s)
115	 1-(4-(2-ciclopropil-2-hidroxietoxi)-3-metilfenil) -3-(fenetiltio)pirazin-2(1*H*)-ona			6			423	RMN ^{1}H (500 MHz, metanol-d_3) δ ppm 7,37 (1 H, d, J = 4,40 Hz), 7,25 - 7,32 (4 H, m), 7,16 - 7,23 (4 H, m), 7,03 (1 H, d, J = 9,35 Hz), 3,99 - 4,17 (2 H, m), 3,25 - 3,39 (3 H, m), 2,91 - 3,04 (2 H, m), 2,28 (3 H, s), 0,98 - 1,11 (1 H, m), 0,51 - 0,61 (2 H, m), 0,29 - 0,47 (2 H, m)

Ej. N°.	Estructura	Componente de Anilina/Bromuro	Componente de Tiol	Proc.	Rend. (%)	HPLC (Min) Proc. 1	CL-EM (M+H)	Datos de H RMN ($CDCl_3$)
116	 3-(2-fluorofenetiltio)-1-(4-(2-hidroxi-2-metilpropoxi)-3-metoxifenil)pirazin-2(1H)-ona			6			445	RMN ^{1}H (500 MHz, metanol-d_3) δ ppm 7,30 - 7,39 (2 H, m), 7,20 - 7,27 (2 H, m), 7,01 - 7,13 (4 H, m), 6,95 (1 H, dd, J = 8,52, 2,47 Hz), 3,86 (2 H, s), 3,24 - 3,39 (2 H, m), 2,97 - 3,11 (2 H, m), 1,32 (6 H, s)
117	 3-(2-fluorofenetiltio)-1-(4-(2-hidroxi-2-metil propoxi)-3-metilfenil)pirazin-2(1*H*)-ona			6			429	RMN ^{1}H (500 MHz, metanol-d_3) δ ppm 7,29 - 7,38 (2 H, m), 7,17 - 7,26 (4 H, m), 6,97 - 7,13 (3 H, m), 3,83 (2 H, s), 3,28 - 3,36 (2 H, m), 3,04 (2 H, t, J = 7,42 Hz), 2,29 (3 H, s), 1,35 (6 H, s)
118	 1-(3-etil-4-(2-hidroxi-2-metilpropoxi)fenil) -3-(2-fluorofenetiltio)pirazin-2(1*H*)-ona			6			443	RMN ^{1}H (400 MHz, cloroformo-d) δ ppm 7,16 - 7,35 (5 H, m), 6,86 - 7,13 (4 H, m), 3,84 (2 H, s), 3,26 - 3,41 (2 H, m), 3,07 (2 H, t, J = 7,65 Hz), 2,71 (2 H, c, J = 7,53 Hz), 1,32 - 1,47 (6 H, m), 1,23 (3 H, t, J = 7,65 Hz)

Ej. Nº.	Estructura	Componente de Anilina/Bromuro	Componente de Tiol	Proc.	Rend. (%)	HPLC (Min) Proc. 1	CL-EM (M+H)	Datos de H RMN ($CDCl_3$)
119	 1-(4-(2-ciclopropil-2-hidroxietoxi)-3-metilfenil) -3-(2-fluorofenetiltio)pirazin-2(1*H*)-ona			6			441	RMN ^{1}H (500 MHz, metanol-d_3) δ ppm 7,28 - 7,37 (2 H, m), 7,16 - 7,26 (4 H, m), 6,99 - 7,12 (3 H, m), 3,95 - 4,18 (2 H, m), 3,22 - 3,42 (3 H, m), 3,04 (2 H, t, J = 7,42 Hz), 2,27 (3 H, s), 0,97 - 1,13 (1 H, m), 0,46 - 0,63 (2 H, m), 0,29 - 0,46 (2 H, m)
120	 1-(4-(2-ciclopropil-2-hidroxietoxi)-3-metoxifenil) -3-(2-fluorofenetiltio)pirazin-2(1*H*)-ona			6			457	RMN ^{1}H (500 MHz, metanol-d_3) δ ppm 7,20 - 7,30 (2 H, m), 7,11 - 7,18 (2 H, m), 6,92 - 7,04 (4 H, m), 6,86 (1 H, dd, J = 8,52, 2,47 Hz), 3,85 - 4,12 (2 H, m), 3,76 (3 H, s), 3,16 - 3,31 (3 H, m), 2,87 - 3,03 (2 H, m), 0,82 - 1,00 (1 H, m), 0,38 - 0,54 (2 H, m), 0,18 - 0,37 (2 H, m)
121	 1-(3-etil-4-(2-hidroxi-2-metilpropoxi)fenil) -3-(2-(piridin-2-il)etiltio)pirazin-2(1*H*)-ona			6			426	RMN ^{1}H (400 MHz, MeOD) δ ppm 8,29 (1 H, d, J = 4,02 Hz), 7,60 (1 H, td, J = 7,65, 1,76 Hz), 7,16 - 7,26 (2 H, m), 6,98 - 7,14 (4 H, m), 6,85 (1 H, d, J = 9,03 Hz), 3,66 (2 H, s), 3,29 (2 H, t, J = 7,28 Hz), 3,02 (2 H, t, J = 7,40 Hz), 2,56 (2 H, c, J = 7,53 Hz), 1,18 (6 H, s), 1,05 (3 H, t, J = 7,53 Hz)

Ej. Nº.	Estructura	Componente de Anilina/Bromuro	Componente de Tiol	Proc.	Rend. (%)	HPLC (Min) Proc. 1	CL-EM (M+H)	Datos de H RMN ($CDCl_3$)
122	 1-(4-hidroxi-3-metilfenil)-3-(4-(trifluorometoxi)feniltio)pirazin-2(1*H*)-ona			6			395	RMN ^{1}H (400 MHz, cloroformo-d) δ ppm 7,62 (2 H, d, J = 8,78 Hz), 7,30 (2 H, d, J = 8,03 Hz), 7,16 (1 H, d, J = 4,52 Hz), 7,10 (1 H, d, J = 2,01 Hz), 6,91 - 7,05 (2 H, m), 6,70 (1 H, d, J = 8,53 Hz), 6,22 (1 H, s), 2,21 (3 H, s)
123	 1-(3-cloro-4-(2-hidroxi-2-metilpropoxi)fenil) -3-(4-fluorofenetiltio)pirazin-2(1*H*)-ona			6			449	RMN ^{1}H (500 MHz, cloroformo-d) δ ppm 7,47 (1 H, d, J = 2,47 Hz), 7,21 - 7,32 (4 H, m), 6,97 - 7,04 (3 H, m), 6,93 (1 H, d, J = 4,67 Hz), 3,89 (2 H, s), 3,30 (2 H, t, J = 7,70 Hz), 2,98 (2 H, t, J = 7,84 Hz), 1,40 (6 H, s)
124	 3-(4-fluorofenetiltio)-1-(4-(2-hidroxi-2-metil propoxi)-3-metilfenil)pirazin-2(1*H*)-ona			6			429	RMN ^{1}H (500 MHz, cloroformo-d) δ ppm 7,22 - 7,29 (3 H, m), 7,16 - 7,22 (2 H, m), 6,99 (2 H, t, J = 8,66 Hz), 6,95 (1 H, d, J = 4,40 Hz), 6,88 (1 H, d, J = 8,52 Hz), 3,84 (2 H, s), 3,21 - 3,36 (2 H, m), 2,90 - 3,08 (2 H, m), 2,29 (3 H, s), 1,38 (6 H, s)

Ej. Nº.	Estructura	Componente de Anilina/Bromuro	Componente de Tiol	Proc.	Rend. (%)	HPLC (Min) Proc. 1	CL-EM (M+H)	Datos de H RMN ($CDCl_3$)
125	 1-(3-etil-4-(2-hidroxi-2-metilpropoxi) fenil)-3-(4-fluorofenetiltio)pirazin-2(1*H*)-ona			6			443	RMN ^{1}H (500 MHz, cloroformo-d) δ ppm 7,22 - 7,29 (3 H, m), 7,17 - 7,22 (2 H, m), 6,94 - 7,03 (3 H, m), 6,90 (1 H, d, J = 8,25 Hz), 3,84 (2 H, s), 3,25 - 3,35 (2 H, m), 2,92 - 3,05 (2 H, m), 2,71 (2 H, c), 1,39 (6 H, s), 1,23 (3 H, t, J = 7,56 Hz)
126	 1-(4-(2-ciclopropil-2-hidroxietoxi)-3-metoxifenil) -3-(4-fluorofenetiltio)pirazin-2(1*H*)-ona			6			457	RMN ^{1}H (500 MHz, cloroformo-d) δ ppm 7,23 - 7,28 (2 H, m), 6,95 - 7,03 (6 H, m), 6,90 (1 H, dd, J = 8,52, 2,20 Hz), 4,20 (1 H, dd, J = 9,62, 2,75 Hz), 4,03 (1 H, dd, J = 9,62, 8,25 Hz), 3,86 (3 H, s), 3,26 - 3,40 (3 H, m), 2,93 - 3,06 (2 H, m), 0,89 - 1,04 (1 H, m), 0,52 - 0,66 (2 H, m), 0,41 - 0,49 (1 H, m), 0,27 - 0,36 (1 H, m)

Ej. Nº.	Estructura	Componente de Anilina/Bromuro	Componente de Tiol	Proc.	Rend. (%)	HPLC (Min) Proc. 1	CL-EM (M+H)	Datos de H RMN ($CDCl_3$)
127	 1-(4-(2-ciclopropil-2-hidroxietoxi)-3-metilfenil) -3-(4-fluorofenetiltio)pirazin-2(1*H*)-ona			6			441	RMN ^{1}H (500 MHz, cloroformo-d) δ ppm 7,22 - 7,28 (3 H, m), 7,16 - 7,22 (2 H, m), 6,90 - 7,03 (4 H, m), 4,14 (1 H, dd, J = 9,35, 3,30 Hz), 4,04 (1 H, dd, J = 9,35, 7,15 Hz), 3,24 - 3,41 (3 H, m), 2,93 - 3,05 (2 H, m), 2,27 (3 H, s), 0,99 - 1,09 (1 H, m), 0,55 - 0,70 (2 H, m), 0,43 - 0,51 (1 H, m), 0,29 - 0,39 (1 H, m)
128	 1-(3-cloro-4-(2-hidroxi-2-metilpropoxi) fenil)-3-(3-fluorofenetiltio)pirazin-2(1*H*)-ona			6			449	RMN ^{1}H (500 MHz, cloroformo-d) δ ppm 7,47 (1 H, d, J = 2,75 Hz), 7,21 - 7,34 (3 H, m), 6,88 - 7,10 (5 H, m), 3,89 (2 H, s), 3,27 - 3,37 (2 H, m), 2,97 - 3,06 (2 H, m), 1,40 (6 H, s)
129	 3-(3-fluorofenetiltio)-1-(4-(2-hidroxi-2-metil propoxi)-3-metilfenil)pirazin-2(1*H*)-ona			6			429	RMN ^{1}H (500 MHz, cloroformo-d) δ ppm 7,23 - 7,31 (3 H, m), 7,16 - 7,22 (2 H, m), 6,86 - 7,09 (4 H, m), 3,84 (2 H, s), 3,27 - 3,35 (2 H, m), 2,96 - 3,05 (2 H, m), 2,29 (3 H, s), 1,38 (6 H, s)

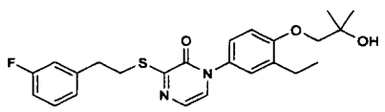
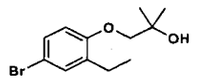
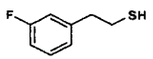
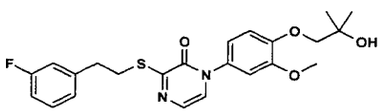
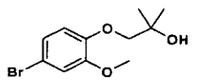
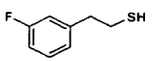
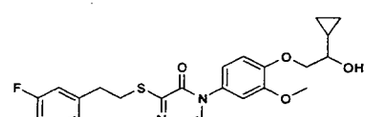
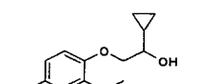
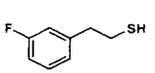
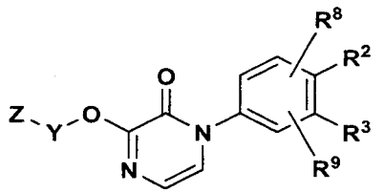
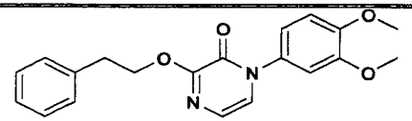
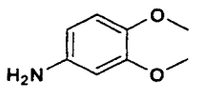
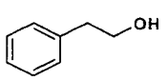
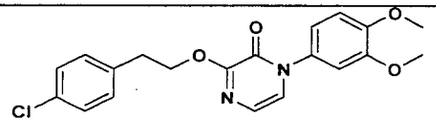
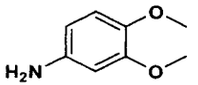
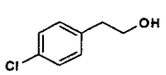
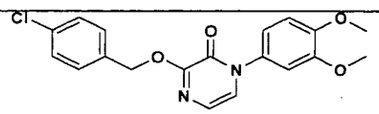
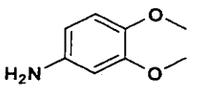
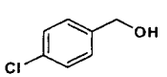
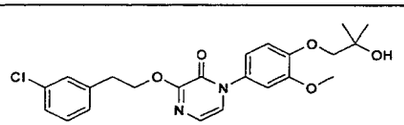
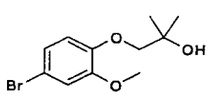
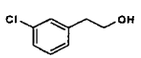
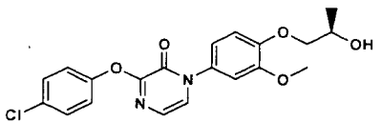
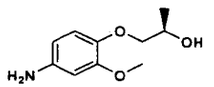
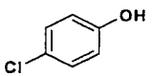
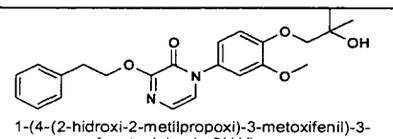
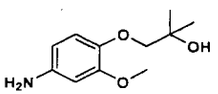
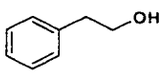
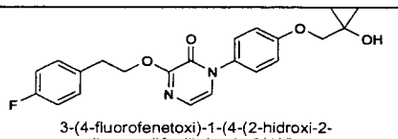
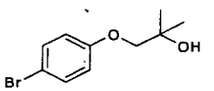
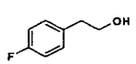
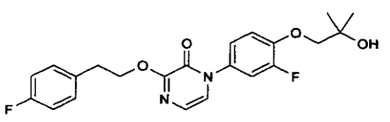
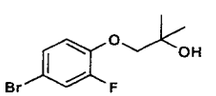
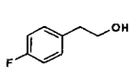
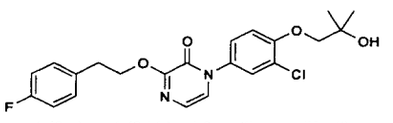
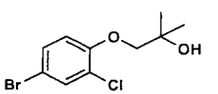
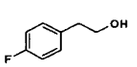
Ej. Nº.	Estructura	Componente de Anilina/Bromuro	Componente de Tiol	Proc.	Rend. (%)	HPLC (Min) Proc. 1	CL-EM (M+H)	Datos de H RMN ($CDCl_3$)
130	 1-(3-etil-4-(2-hidroxi-2-metilpropoxi) fenil)-3-(3-fluorofenetiltio)pirazin-2(1*H*)-ona			6			443	RMN ^{1}H (500 MHz, cloroformo-d) δ ppm 7,24 - 7,30 (2 H, m), 7,17 - 7,22 (2 H, m), 6,86 - 7,11 (5 H, m), 3,84 (2 H, s), 3,24 - 3,38 (2 H, m), 2,96 - 3,08 (2 H, m), 2,71 (2 H, c, J = 7,70 Hz), 1,38 (6 H, s), 1,23 (3 H, t, J = 7,56 Hz)
131	 3-(3-fluorofenetiltio)-1-(4-(2-hidroxi-2-metil propoxi)-3-metoxifenil)pirazin-2(1*H*)-ona			6			445	RMN ^{1}H (500 MHz, cloroformo-d) δ ppm 7,20 - 7,38 (2 H, m), 6,83 - 7,14 (7 H, m), 3,86 (5 H, s), 3,23 - 3,40 (2 H, m), 2,93 - 3,10 (2 H, m), 1,36 (6 H, s)
132	 1-(4-(2-ciclopropil-2-hidroxietoxi)-3-metoxifenil) -3-(3-fluorofenetiltio)pirazin-2(1*H*)-ona			6			457	RMN ^{1}H (500 MHz, cloroformo-d) δ ppm 7,24 - 7,31 (2 H, m), 7,07 (1 H, d, J = 7,42 Hz), 6,96 - 7,04 (4 H, m), 6,87 - 6,96 (2 H, m), 4,20 (1 H, dd, J = 9,62, 2,75 Hz), 4,03 (1 H, dd, J = 9,90, 8,25 Hz), 3,86 (5 H, s), 3,26 - 3,43 (3 H, m), 2,96 - 3,06 (2 H, m), 0,91 - 1,03 (1 H, m), 0,52 - 0,68 (2 H, m), 0,41 - 0,50 (1 H, m), 0,26 - 0,35 (1 H, m)

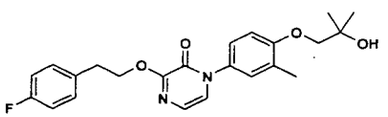
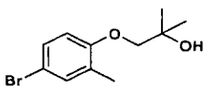
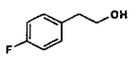
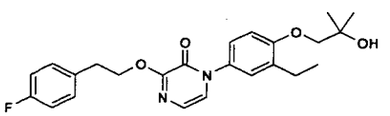
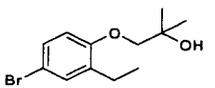
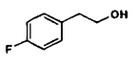
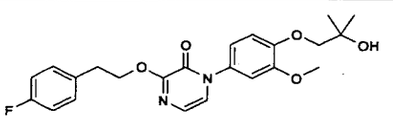
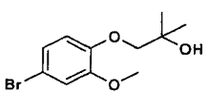
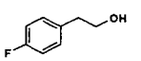
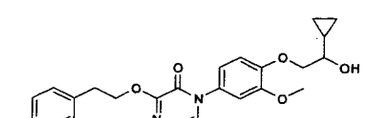
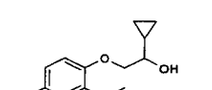
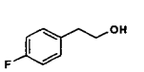
TABLA 2

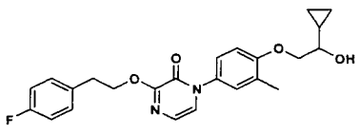
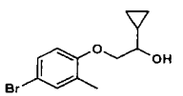
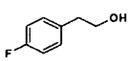
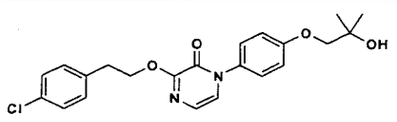
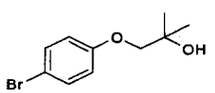
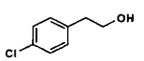
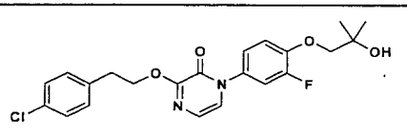
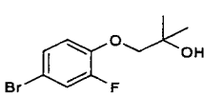
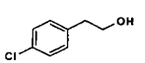
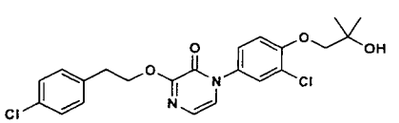
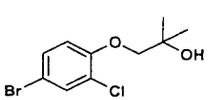
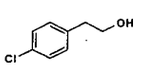
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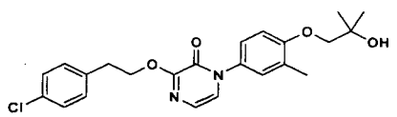
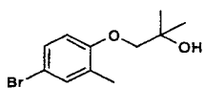
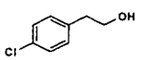
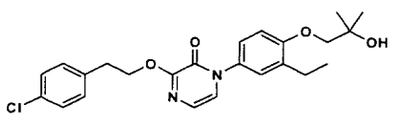
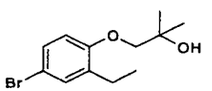
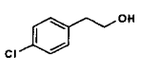
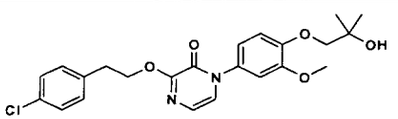
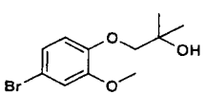
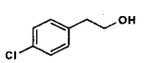
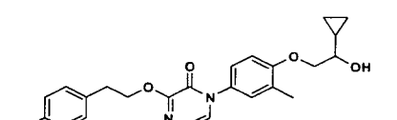
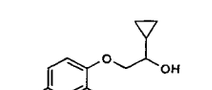
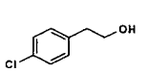


Ej. Nº	Estructura	Componente de Anilina/Bromuro	Componente de Alcohol	Proc.	Rend. (%)	HPLC	CL-EM	Datos de H RMN ($CDCl_3$)
133	 1-(3,4-dimetoxifenil)-3-fenetoxipirazin-2(1*H*)-ona			1	18	3,71	353	7,27 (m, 5H), 6,93 (m, 5H), 4,55 (t, J = 7,5 Hz, 2H), 3,92 (s, 3H), 3,89 (s, 3H), 3,17 (t, J = 7,5 Hz, 2H).
134	 3-(4-clorofenetoxi)-1-(3,4-dimetoxifenil)pirazin-2(1*H*)-ona			1	26	3,96	387/389	7,25 (m, 4H), 6,92 (m, 5H), 4,52 (t, J = 7,2 Hz, 2H), 3,92 (s, 3H), 3,89 (s, 3H), 3,12 (t, J = 7,2 Hz, 2H).
135	 3-(4-clorobenciloxi)-1-(3,4-dimetoxifenil)pirazin-2(1*H*)-ona			1	68	3,83	373/375	7,37 (d, J = 8,4 Hz, 2H), 7,25 (d, J = 8,4 Hz, 2H), 6,60 (m, 5H), 5,32 (s, 2H), 3,84 (s, 3H), 3,80 (s, 3H)
136	 3-(3-clorofenetoxi)-1-(4-(2-hidroxi-2-metil propoxi)-3-metoxifenil)pirazin-2(1*H*)-ona			7			445	RMN ^{1}H (500 MHz, cloroformo-d) δ ppm 7,30 (1 H, s), 7,22 (3 H, d, J = 4,95 Hz), 6,94 - 7,00 (2 H, m), 6,83 - 6,91 (3 H, m), 4,54 (2 H, t, J = 7,42 Hz), 3,86 (5 H, s), 3,15 (2 H, t, J = 7,42 Hz), 1,36 (6 H, s)

Ej. Nº	Estructura	Componente de Anilina/Bromuro	Componente de Alcohol	Proc.	Rend. (%)	HPLC	CL-EM	Datos de H RMN ($CDCl_3$)
137	 (*R*)-3-(4-clorofenoxi)-1-(4-(2-hidroxipropoxi)-3-metoxifenil)pirazin-2(1*H*)-ona			4		3,59	403/405	7,42 (d, J = 8,9 Hz, 2H), 7,18 (d, J = 8,9 Hz, 2H), 7,02 (m, 2H), 6,80 (d, J = 4,6 Hz, 1H), 6,93 (dd, J = 2,2 y 8,4 Hz, 1H), 6,81 (d, J = 4,6 Hz, 1H) 4,25 (m, 1H), 4,05 (dd, J = 3,0 y 9,6 Hz, 1H), 3,88 (s, 3H), 3,86 (dd, J = 1,0 y 9,6 Hz, 1H), 2,73 (s ancho, 1H), 1,27 (d, J = 4,3 Hz, 3H).
138	 1-(4-(2-hidroxi-2-metilpropoxi)-3-metoxifenil)-3-fenetoxipirazin-2(1*H*)-ona			1	5	3,86	411	7,32 (m, 5H), 7,23 (m, 1H), 6,96 (m, 2H), 6,87 (m, 2H), 4,55 (t, J = 2,0 Hz, 2H), 3,86 (s, 5H), 3,18 (t, J = 2,0 Hz, 2H), 1,35 (s, 6H).
139	 3-(4-fluorofenetoxi)-1-(4-(2-hidroxi-2-metilpropoxi)fenil)pirazin-2(1*H*)-ona			7			399	RMN ^{1}H (500 MHz, cloroformo-d) δ ppm 7,23 - 7,38 (4 H, m), 6,95 - 7,05 (4 H, m), 6,84 (2 H, s), 4,51 (2 H, t, J = 7,29 Hz), 3,83 (2 H, s), 3,14 (2 H, s), 1,36 (6 H, s)
140	 1-(3-fluoro-4-(2-hidroxi-2-metilpropoxi)fenil) -3-(4-fluorofenetoxi)pirazin-2(1*H*)-ona			7			417	RMN ^{1}H (500 MHz, cloroformo-d) δ ppm 7,25 - 7,30 (2 H, m), 7,21 (1 H, dd, J = 11,00, 2,47 Hz), 6,96 - 7,15 (4 H, m), 6,75 - 6,90 (2 H, m), 4,51 (2 H, t, J = 7,29 Hz), 3,89 (2 H, s), 3,13 (2 H, t, J = 7,15 Hz), 1,38 (6 H, s)
141	 1-(3-cloro-4-(2-hidroxi-2-metilpropoxi)fenil) -3-(4-fluorofenetoxi)pirazin-2(1*H*)-ona			7			433	RMN ^{1}H (500 MHz, cloroformo-d) δ ppm 7,45 (1 H, d, J = 2,75 Hz), 7,22 - 7,35 (3 H, m), 6,94 - 7,07 (3 H, m), 6,75 - 6,88 (2 H, m), 4,51 (2 H, t, J = 7,15 Hz), 3,89 (2 H, s), 3,13 (2 H, t, J = 7,15 Hz), 1,40 (6 H, s)

Ej. Nº	Estructura	Componente de Anilina/Bromuro	Componente de Alcohol	Proc.	Rend. (%)	HPLC	CL-EM	Datos de H RMN ($CDCl_3$)
142	 3-(4-fluorofenetoxi)-1-(4-(2-hidroxi-2-metil propoxi)-3-metilfenil)pirazin-2(1*H*)-ona			7			413	RMN ^{1}H (500 MHz, cloroformo-d) δ ppm 7,24 - 7,31 (2 H, m), 7,15 - 7,21 (2 H, m), 6,99 (2 H, t, J = 8,66 Hz), 6,89 (1 H, d, J = 7,97 Hz), 6,83 (2 H, s), 4,50 (2 H, t, J = 7,29 Hz), 3,84 (2 H, s), 3,13 (2 H, t, J = 7,29 Hz), 2,29 (3 H, s), 1,38 (6 H, s)
143	 1-(3-etil-4-(2-hidroxi-2-metilpropoxi) fenil)-3-(4-fluorofenetoxi)pirazin-2(1*H*)-ona			7			427	RMN ^{1}H (500 MHz, cloroformo-d) δ ppm 7,24 - 7,31 (2 H, m), 7,16 - 7,21 (2 H, m), 6,99 (2 H, t, J = 8,66 Hz), 6,90 (1 H, d, J = 9,35 Hz), 6,82 - 6,86 (2 H, m), 4,51 (2 H, t, J = 7,29 Hz), 3,84 (2 H, s), 3,14 (2 H, t, J = 7,29 Hz), 2,71 (2 H, c), 1,39 (6 H, s), 1,24 (3 H, t, J = 7,56 Hz)
144	 3-(4-fluorofenetoxi)-1-(4-(2-hidroxi-2-metil propoxi)-3-metoxifenil)pirazin-2(1*H*)-ona			7			429	RMN ^{1}H (500 MHz, cloroformo-d) δ ppm 7,23 - 7,32 (2 H, m), 6,94 - 7,03 (4 H, m), 6,82 - 6,90 (3 H, m), 4,51 (2 H, t, J = 7,29 Hz), 3,85 (5 H, s), 3,14 (2 H, t, J = 7,29 Hz), 1,36 (6 H, s)
145	 1-(4-(2-ciclopropil-2-hidroxietoxi)-3-metoxifenil) -3-(4-fluorofenetoxi)pirazin-2(1*H*)-ona			7			441	RMN ^{1}H (500 MHz, cloroformo-d) δ ppm 7,24 - 7,32 (2 H, m), 6,95 - 7,04 (4 H, m), 6,83 - 6,91 (3 H, m), 4,51 (2 H, t, J = 7,29 Hz), 4,20 (1 H, dd, J = 9,76, 2,89 Hz), 4,03 (1 H, dd, J = 9,90, 8,25 Hz), 3,31 - 3,43 (1 H, m), 3,14 (2 H, t, J = 7,29 Hz), 0,90 - 1,05 (1 H, m), 0,52 - 0,68 (2 H, m), 0,41 - 0,49 (1 H, m), 0,26 - 0,35 (1 H, m)

Ej. Nº	Estructura	Componente de Anilina/Bromuro	Componente de Alcohol	Proc.	Rend. (%)	HPLC	CL-EM	Datos de H RMN ($CDCl_3$)
146	 1-(4-(2-ciclopropil-2-hidroxietoxi)-3-metilfenil) -3-(4-fluorofenetoxi)pirazin-2(1*H*)-ona			7			425	RMN ^{1}H (500 MHz, cloroformo-d) δ ppm 7,25 - 7,31 (2 H, m), 7,16 - 7,20 (2 H, m), 6,95 - 7,02 (2 H, m), 6,90 - 6,94 (1 H, m), 6,81 - 6,86 (2 H, m), 4,50 (2 H, t, J = 7,29 Hz), 4,14 (1 H, dd, J = 9,35, 3,30 Hz), 4,04 (1 H, dd, J = 9,35, 7,15 Hz), 3,36 (1 H, dt, J = 8,45, 3,61 Hz), 3,13 (2 H, t, J = 7,15 Hz), 2,27 (3 H, s), 0,99 - 1,09 (1 H, m), 0,55 - 0,70 (2 H, m), 0,43 - 0,51 (1 H, m), 0,30 - 0,39 (1 H, m)
147	 3-(4-clorofenetoxi)-1-(4-(2-hidroxi-2-metilpropoxi)fenil)pirazin-2(1*H*)-ona			7			415	RMN ^{1}H (500 MHz, cloroformo-d) δ ppm 7,32 (2 H, d), 7,23 - 7,29 (4 H, m), 7,02 (2 H, d), 6,84 (2 H, s), 4,51 (2 H, t, J = 7,29 Hz), 3,83 (2 H, s), 3,13 (2 H, t, J = 7,15 Hz), 1,36 (6 H, s)
148	 3-(4-clorofenetoxi)-1-(3-fluoro-4-(2-hidroxi-2-metilpropoxi)fenil)pirazin-2(1*H*)-ona			7			433	RMN ^{1}H (500 MHz, cloroformo-d) δ ppm 7,18 - 7,31 (5 H, m), 7,03 - 7,15 (2 H, m), 6,75 - 6,89 (2 H, m), 4,51 (2 H, t, J = 7,15 Hz), 3,89 (2 H, s), 3,13 (2 H, t, J = 7,15 Hz), 1,38 (6 H, s)
149	 1-(3-cloro-4-(2-hidroxi-2-metilpropoxi)fenil) -3-(4-clorofenetoxi)pirazin-2(1*H*)-ona			7			449	RMN ^{1}H (500 MHz, cloroformo-d) δ ppm 7,45 (1 H, d, J = 2,75 Hz), 7,22 - 7,32 (5 H, m), 7,00 (1 H, d, J = 8,80 Hz), 6,77 - 6,90 (2 H, m), 4,51 (2 H, t, J = 7,29 Hz), 3,89 (2 H, s), 3,13 (2 H, t, J = 7,15 Hz), 1,40 (6 H, s)

Ej. Nº	Estructura	Componente de Anilina/Bromuro	Componente de Alcohol	Proc.	Rend. (%)	HPLC	CL-EM	Datos de H RMN ($CDCl_3$)
150	 3-(4-clorofenetoxi)-1-(4-(2-hidroxi-2-metil propoxi)-3-metilfenil)pirazin-2(1*H*)-ona			7			429	RMN ^{1}H (500 MHz, cloroformo-d) δ ppm 7,23 - 7,30 (4 H, m), 7,14 - 7,20 (2 H, m), 6,88 (1 H, d, J = 8,25 Hz), 6,83 (2 H, s), 4,51 (2 H, t, J = 7,15 Hz), 3,84 (2 H, s), 3,13 (2 H, t, J = 7,15 Hz), 2,29 (3 H, s), 1,38 (6 H, s)
151	 3-(4-clorofenetoxi)-1-(3-etil-4-(2-hidroxi -2-metilpropoxi)fenil)pirazin-2(1*H*)-ona			7			443	RMN ^{1}H (500 MHz, cloroformo-d) δ ppm 7,23 - 7,29 (4 H, m), 7,16 - 7,21 (2 H, m), 6,90 (1 H, d, J = 9,35 Hz), 6,84 (2 H, c, J = 4,49 Hz), 4,51 (2 H, t, J = 7,29 Hz), 3,84 (2 H, s), 3,13 (2 H, t, J = 7,29 Hz), 2,71 (2 H, c, J = 7,51 Hz), 1,39 (6 H, s), 1,23 (3 H, t, J = 7,56 Hz)
152	 3-(4-clorofenetoxi)-1-(4-(2-hidroxi-2-metil propoxi)-3-metoxifenil)pirazin-2(1*H*)-ona			7			445	RMN ^{1}H (500 MHz, cloroformo-d) δ ppm 7,18 - 7,33 (4 H, m), 6,93 - 7,04 (2 H, m), 6,79 - 6,91 (3 H, m), 4,51 (2 H, t, J = 7,15 Hz), 3,85 (5 H, s), 3,14 (2 H, t, J = 7,29 Hz), 1,36 (6 H, s)
153	 3-(4-clorofenetoxi)-1-(4-(2-ciclopropil-2-hidroxietoxi) -3-metilfenil)pirazin-2(1*H*)-ona			7			441	RMN ^{1}H (500 MHz, cloroformo-d) δ ppm 7,23 - 7,29 (4 H, m), 7,16 - 7,20 (2 H, m), 6,92 (1 H, d), 6,80 - 6,85 (2 H, m), 4,51 (2 H, t, J = 7,29 Hz), 4,14 (1 H, dd, J = 9,35, 3,57 Hz), 4,04 (1 H, dd, J = 9,35, 7,15 Hz), 3,31 - 3,42 (1 H, m), 3,13 (2 H, t, J = 7,29 Hz), 2,27 (3 H, s), 0,97 - 1,11 (1 H, m), 0,55 - 0,70 (2 H, m), 0,42 - 0,51 (1 H, m), 0,30 - 0,40 (1 H, m)

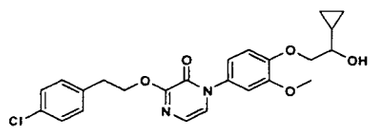
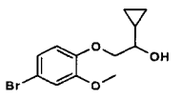
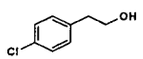
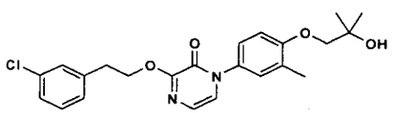
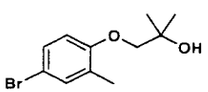
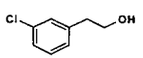
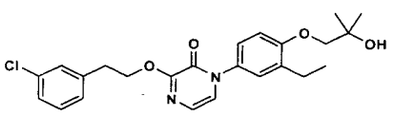
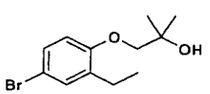
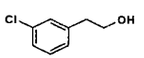
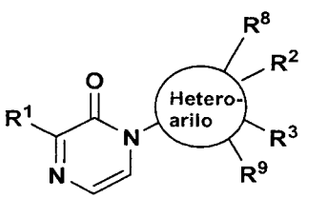
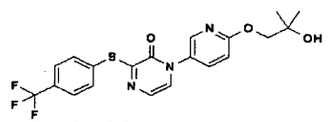
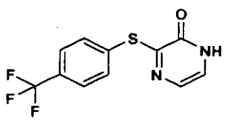
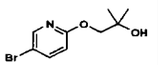
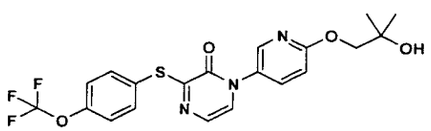
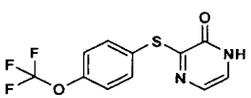
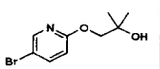
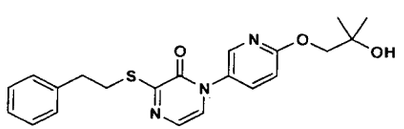
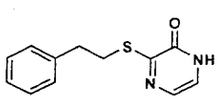
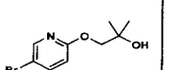
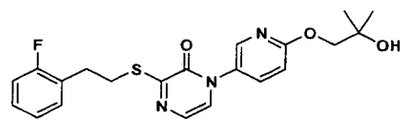
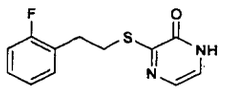
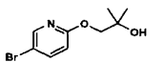
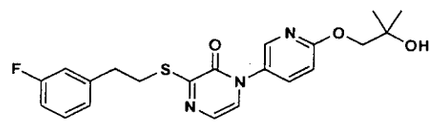
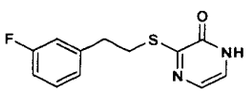
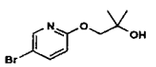
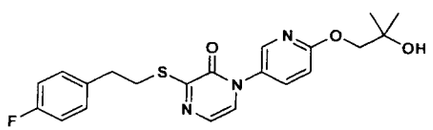
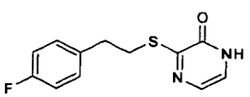
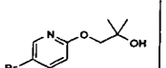
Ej. Nº	Estructura	Componente de Anilina/Bromuro	Componente de Alcohol	Proc.	Rend. (%)	HPLC	CL-EM	Datos de H RMN ($CDCl_3$)
154	 3-(4-clorofenetoxi)-1-(4-(2-ciclopropil-2-hidroxietoxi)-3-metoxifenil)pirazin-2(1*H*)-ona			7			457	RMN ^{1}H (500 MHz, cloroformo-d) δ ppm 7,23 - 7,29 (4 H, m), 7,01 (1 H, d, J = 8,80 Hz), 6,97 (1 H, d, J = 2,47 Hz), 6,82 - 6,91 (3 H, m), 4,51 (2 H, t, J = 7,15 Hz), 4,20 (1 H, dd, J = 9,76, 2,89 Hz), 4,03 (1 H, dd, J = 9,62, 8,25 Hz), 3,86 (3 H, s), 3,30 - 3,41 (1 H, m), 3,14 (2 H, t, J = 7,15 Hz), 0,89 - 1,04 (1 H, m), 0,52 - 0,68 (2 H, m), 0,42 - 0,50 (1 H, m), 0,25 - 0,37 (1 H, m)
155	 3-(3-clorofenetoxi)-1-(4-(2-hidroxi-2-metil propoxi)-3-metilfenil)pirazin-2(1*H*)-ona			7			429	RMN ^{1}H (500 MHz, cloroformo-d) δ ppm 7,30 (1 H, s), 7,16 - 7,25 (5 H, m), 6,89 (1 H, d, J = 8,52 Hz), 6,83 (2 H, s), 4,53 (2 H, t, J = 7,42 Hz), 3,84 (2 H, s), 3,14 (2 H, t, J = 7,29 Hz), 2,29 (3 H, s), 1,38 (6 H, s)
156	 3-(3-clorofenetoxi)-1-(3-etil-4-(2-hidroxi-2-metilpropoxi)fenil)pirazin-2(1*H*)-ona			7			443	RMN ^{1}H (500 MHz, cloroformo-d) δ ppm 7,30 (1 H, s), 7,16 - 7,25 (5 H, m), 6,90 (1 H, d, J = 9,35 Hz), 6,82 - 6,87 (2 H, m), 4,53 (2 H, t, J = 7,42 Hz), 3,84 (2 H, s), 3,15 (2 H, t, J = 7,29 Hz), 2,65 - 2,76 (2 H, m), 1,38 (6 H, s), 1,24 (3 H, t, J = 7,56 Hz)

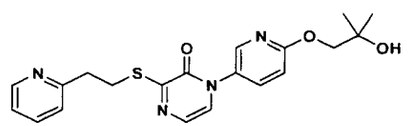
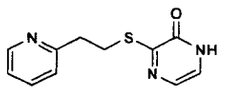
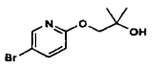
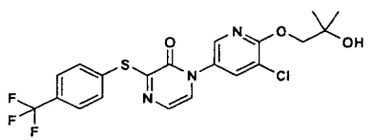
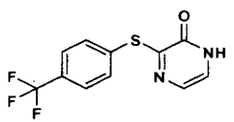
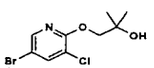
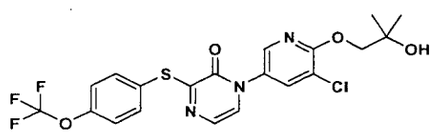
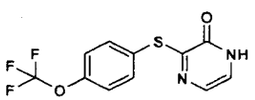
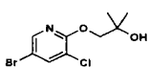
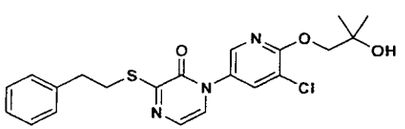
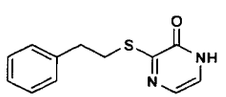
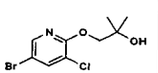
TABLA 3

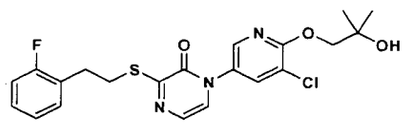
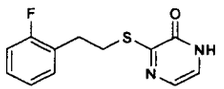
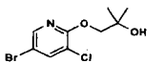
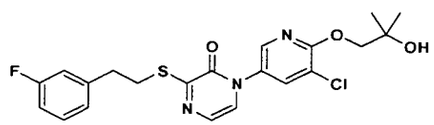
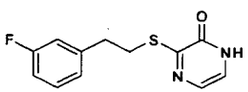
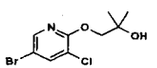
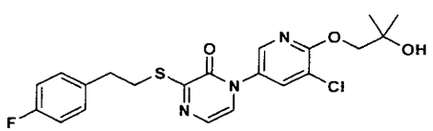
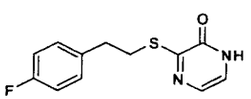
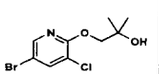
1-Heteroarilpirazin-2(1*H*)-onas 3-sustituidas

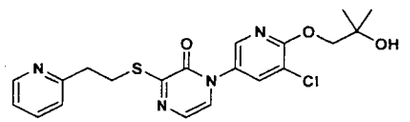
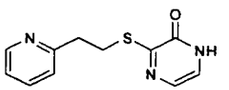
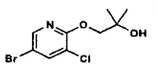
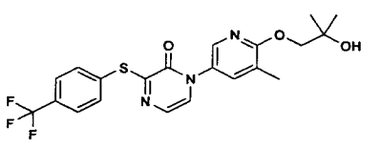
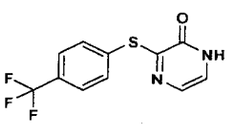
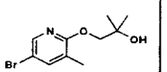
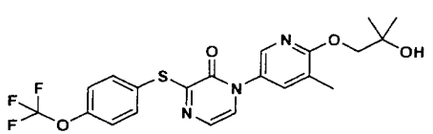
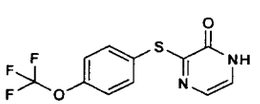
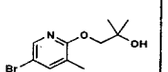


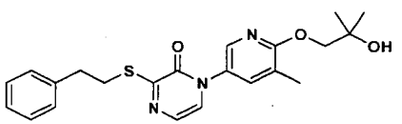
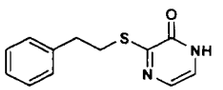
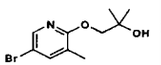
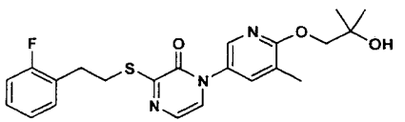
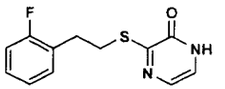
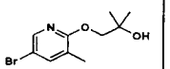
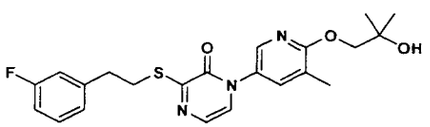
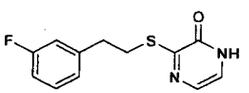
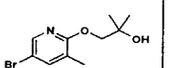
Ej. Nº	Estructura	Componente de Anilina/Bromuro	Comp. de Alcohol	Proc.	Rend. (%)	HPLC	CL-EM	Datos de H RMN ($CDCl_3$)
157	 1-(6-2-hidroxi-2-metilpropoxi)piridin-3-il) -3-(4-(trifluorometil)feniltio)pirazin-2(1H)-ona			8			438	RMN ^{1}H (500 MHz, metanol-d_3) δ ppm 8,41 (1 H, d, J = 2,47 Hz), 8,09 (1 H, dd, J = 9,07, 2,75 Hz), 7,72 - 7,79 (4 H, m), 7,35 (1 H, d, J = 4,40 Hz), 7,24 (1 H, d, J = 9,07 Hz), 7,19 (1 H, d, J = 4,67 Hz), 4,25 (2 H, s), 1,33 (6 H, s).
158	 1-(6-(2-hidroxi-2-metilpropoxi)piridin-3-il)-3 -(4-(trifluorometoxi)feniltio)pirazin-2(1*H*)-ona			8			454	RMN ^{1}H (500 MHz, metanol-d_3) δ ppm 8,25 (1 H, d, J = 2,47 Hz), 7,84 (1 H, dd, J = 8,80, 2,75 Hz), 7,63 - 7,69 (2 H, m), 7,37 (2 H, d, J = 7,97 Hz), 7,31 (1 H, d, J = 4,40 Hz), 7,17 (1 H, d, J = 4,67 Hz), 7,00 (1 H, d, J = 8,80 Hz), 4,19 (2 H, s), 1,31 (6 H, s)
159	 1-(6-(2-hidroxi-2-metilpropoxi)piridin-3-il) -3-(fenetiltio)pirazin-2(1*H*)-ona			8			398	RMN ^{1}H (400 MHz, metanol-d_3) δ ppm 8,23 (1 H, d, J = 2,64 Hz), 7,80 (1 H, dd, J = 8,90, 2,75 Hz), 7,39 (1 H, d, J = 4,39 Hz), 7,15 - 7,33 (6 H, m), 6,98 (1 H, d, J = 8,79 Hz), 4,18 (2 H, s), 3,30 - 3,38 (2 H, m), 2,91 - 3,08 (2 H, m), 1,31 (6 H, s)

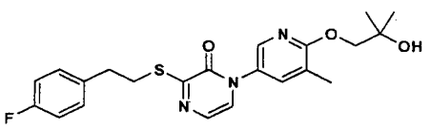
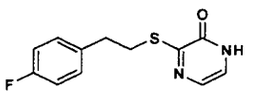
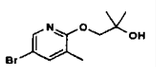
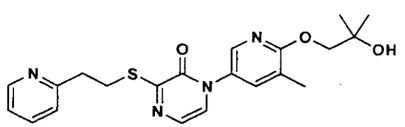
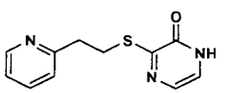
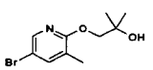
Ej. Nº	Estructura	Componente de Anilina/Bromuro	Comp. de Alcohol	Proc.	Rend. (%)	HPLC	CL-EM	Datos de H RMN ($CDCl_3$)
160	 3-(2-fluorofenetiltio)-1-(6-(2-hidroxi-2-metilpropoxi)piridin-3-il)pirazin-2(1*H*)-ona			8			416	RMN ^{1}H (400 MHz, metanol-d_3) δ ppm 8,22 (1 H, d, J = 2,64 Hz), 7,80 (1 H, dd, J = 8,90, 2,75 Hz), 7,37 (1 H, d, J = 4,61 Hz), 7,28 - 7,35 (1 H, m), 7,17 - 7,28 (2 H, m), 6,88 - 7,16 (3 H, m), 4,18 (1 H, s), 3,25 - 3,43 (2 H, m), 3,04 (2 H, t, J = 7,47 Hz), 1,30 (6 H, s)
161	 3-(3-fluorofenetiltio)-1-(6-(2-hidroxi-2-metilpropoxi)piridin-3-il)pirazin-2(1*H*)-ona			8			416	RMN ^{1}H (400 MHz, metanol-d_3) δ ppm 8,23 (1 H, d, J = 2,64 Hz), 7,80 (1 H, dd, J = 8,90, 2,75 Hz), 7,40 (1 H, d, J = 4,61 Hz), 7,23 - 7,34 (2 H, m), 6,89 - 7,14 (4 H, m), 4,18 (1 H, s), 3,29 - 3,40 (2 H, m), 2,95 - 3,06 (2 H, m), 1,30 (6 H, s)
162	 3-(4-fluorofenetiltio)-1-(6-(2-hidroxi-2-metilpropoxi)piridin-3-il)pirazin-2(1*H*)-ona			8			416	RMN ^{1}H (400 MHz, metanol-d_3) δ ppm 8,15 (1 H, d, J = 2,42 Hz), 7,73 (1 H, dd, J = 8,90, 2,75 Hz), 7,31 (1 H, d, J = 4,39 Hz), 7,15 - 7,26 (3 H, m), 6,85 - 7,00 (3 H, m), 4,10 (2 H, s), 3,22 - 3,29 (2 H, m), 2,89 (2 H, t, J = 7,58 Hz), 1,23 (6 H, s)

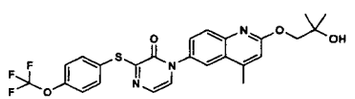
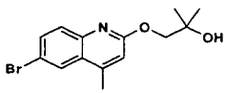
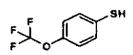
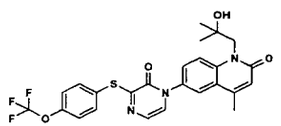
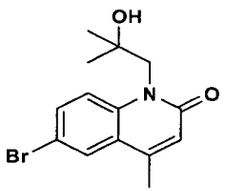
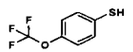
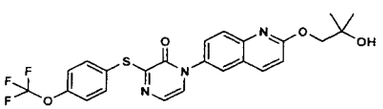
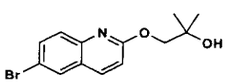
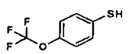
Ej. Nº	Estructura	Componente de Anilina/Bromuro	Comp. de Alcohol	Proc.	Rend. (%)	HPLC	CL-EM	Datos de H RMN ($CDCl_3$)
163	 1-(6-(2-hidroxi-2-metilpropoxi)piridin-3-il) -3-(2-(piridin-2-il)etiltio)pirazin-2(1*H*)-ona			8			399	RMN ^{1}H (400 MHz, metanol-d_3) δ ppm 8,40 - 8,54 (1 H, m), 8,22 (1 H, d, J = 2,20 Hz), 7,72 - 7,86 (2 H, m), 7,35 - 7,44 (2 H, m), 7,23 - 7,32 (2 H, m), 6,98 (1 H, d, J = 9,01 Hz), 4,18 (2 H, s), 3,47 (2 H, t, J = 7,36 Hz), 3,19 (2 H, t, J = 7,36 Hz), 1,30 (6 H, s)
164	 1-(5-cloro-6-(2-hidroxi-2-metilpropoxi)piridin -3-il)-3-(4-(trifluorometil)feniltio)pirazin-2(1*H*)-ona			8			472	RMN ^{1}H (500 MHz, cloroformo-d) δ ppm 8,11 (1 H, d, J = 2,47 Hz), 7,89 (1 H, d, J = 2,47 Hz), 7,71 (4 H, s), 7,16 (1 H, d, J = 4,40 Hz), 6,95 (1 H, d, J = 4,40 Hz), 4,30 (2 H, s), 1,38 (6 H, s)
165	 1-(5-cloro-6-(2-hidroxi-2-metilpropoxi)piridin-3-il) -3-(4-(trifluorometoxi)feniltio)pirazin-2(1*H*)-ona			8			488	RMN ^{1}H (500 MHz, cloroformo-d) δ ppm 8,10 (1 H, d, J = 2,47 Hz), 7,88 (1 H, d, J = 2,47 Hz), 7,61 (2 H, d, J = 8,80 Hz), 7,30 (2 H, d, J = 7,97 Hz), 7,16 (1 H, d, J = 4,67 Hz), 6,94 (1 H, d, J = 4,40 Hz), 4,30 (2 H, s), 1,38 (6 H, s)
166	 1-(5-cloro-6-(2-hidroxi-2-metilpropoxi) piridin-3-il)-3-(fenetiltio)pirazin-2(1*H*)-ona			8			432	RMN ^{1}H (400 MHz, cloroformo-d) δ ppm 8,09 (1 H, d, J = 2,42 Hz), 7,86 (1 H, d, J = 2,64 Hz), 7,21 - 7,37 (6 H, m), 6,91 (1 H, d, J = 4,39 Hz), 4,29 (2 H, s), 3,28 - 3,43 (2 H, m), 2,94 - 3,09 (2 H, m), 1,37 (6 H, s)

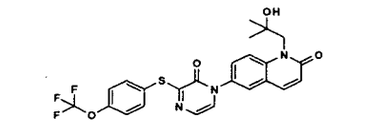
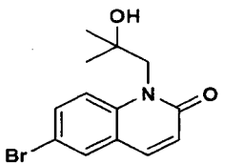
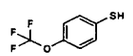
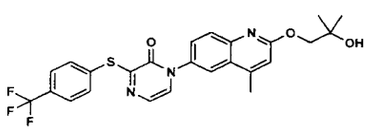
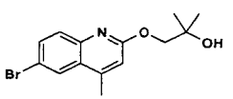
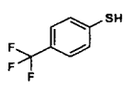
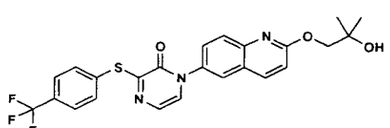
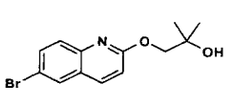
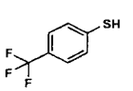
Ej. Nº	Estructura	Componente de Anilina/Bromuro	Comp. de Alcohol	Proc.	Rend. (%)	HPLC	CL-EM	Datos de H RMN ($CDCl_3$)
167	 1-(5-cloro-6-(2-hidroxi-2-metilpropoxi)piridin-3-il)-3-(2-fluorofenetiltio)pirazin-2(1*H*)-ona			8			450	RMN ^{1}H (400 MHz, cloroformo-d) δ ppm 8,08 (1 H, d, J = 2,42 Hz), 7,86 (1 H, d, J = 2,42 Hz), 7,16 - 7,33 (3 H, m), 6,98 - 7,13 (2 H, m), 6,90 (1 H, d, J = 4,61 Hz), 4,29 (2 H, s), 3,29 - 3,41 (2 H, m), 3,07 (2 H, t, J = 7,69 Hz), 1,37 (6 H, s)
168	 1-(5-cloro-6-(2-hidroxi-2-metilpropoxi) piridin-3-il)-3-(3-fluorofenetiltio)pirazin-2(1*H*)-ona			8			450	RMN ^{1}H (500 MHz, cloroformo-d) δ ppm 8,09 (1 H, d, J = 2,20 Hz), 7,86 (1 H, d, J = 2,47 Hz), 7,26 - 7,34 (2 H, m), 7,06 (1 H, d, J = 7,70 Hz), 6,98 - 7,03 (1 H, m), 6,89 - 6,97 (2 H, m), 4,29 (2 H, s), 3,27 - 3,40 (2 H, m), 2,94 - 3,10 (2 H, m), 1,37 (6 H, s)
168	 1-(5-cloro-6-(2-hidroxi-2-metilpropoxi)piridin-3-il) -3-(4-fluorofenetiltio)pirazin-2(1*H*)-ona			8			450	RMN ^{1}H (500 MHz, cloroformo-d) δ ppm 8,08 (1 H, d, J = 2,47 Hz), 7,86 (1 H, d, J = 2,47 Hz), 7,30 (1 H, d, J = 4,40 Hz), 7,21 - 7,25 (2 H, m), 7,00 (2 H, t, J = 8,66 Hz), 6,91 (1 H, d, J = 4,67 Hz), 4,29 (2 H, s), 3,23 - 3,39 (2 H, m), 2,91 - 3,05 (2 H, m), 1,37 (6 H, s)

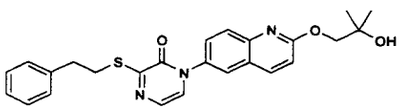
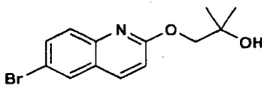
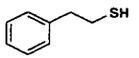
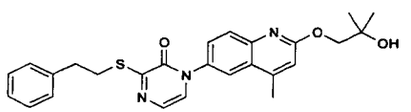
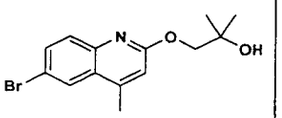
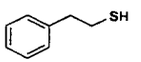
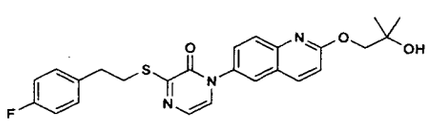
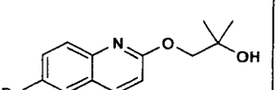
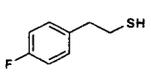
Ej. Nº	Estructura	Componente de Anilina/Bromuro	Comp. de Alcohol	Proc.	Rend. (%)	HPLC	CL-EM	Datos de H RMN ($CDCl_3$)
169	 1-(5-cloro-6-(2-hidroxi-2-metilpropoxi)piridin -3-il)-3-(2-(piridin-2-il)etiltio)pirazin-2(1*H*)-ona			8			433	RMN ^{1}H (500 MHz, cloroformo-d) δ ppm 8,57 (1 H, d, J = 3,85 Hz), 8,08 (1 H, d, J = 2,47 Hz), 7,85 (1 H, d, J = 2,47 Hz), 7,63 (1 H, td, J = 7,63, 1,79 Hz), 7,31 (1 H, d, J = 4,67 Hz), 7,24 (1 H, d, J = 7,70 Hz), 7,11 - 7,18 (1 H, m), 6,90 (1 H, d, J = 4,40 Hz), 4,29 (2 H, s), 3,45 - 3,59 (2 H, m), 3,22 (2 H, t, J = 7,42 Hz), 1,37 (6 H, s)
170	 1-(6-(2-hidroxi-2-metilpropoxi)-5-metilpiridin-3-il)-3-(4-(trifluorometil)feniltio)pirazin-2(1*H*)-ona			8			452	RMN ^{1}H (500 MHz, cloroformo-d) δ ppm 8,00 (1 H, d, J = 2,75 Hz), 7,67 - 7,76 (4 H, m), 7,60 (1 H, d, J = 1,92 Hz), 7,14 (1 H, d, J = 4,40 Hz), 6,96 (1 H, d, J = 4,40 Hz), 4,28 (2 H, s), 2,30 (3 H, s), 1,36 (6 H, s)
171	 1-(6-(2-hidroxi-2-metilpropoxi)-5-metilpiridin-3-il) -3-(4-(trifluorometoxi)feniltio)pirazin-2(1*H*)-ona			8			468	RMN ^{1}H (500 MHz, cloroformo-d) δ ppm 8,00 (1 H, d, J = 2,75 Hz), 7,57 - 7,65 (3 H, m), 7,29 (2 H, d, J = 7,97 Hz), 7,14 (1 H, d, J = 4,40 Hz), 6,94 (1 H, d, J = 4,40 Hz), 4,28 (2 H, s), 2,29 (3 H, s), 1,35 (6 H, s)

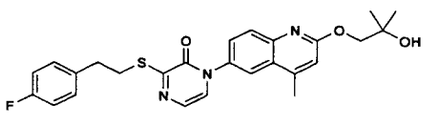
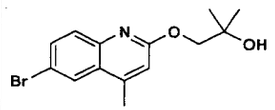
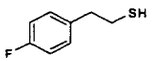
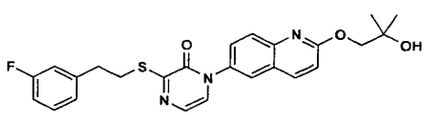
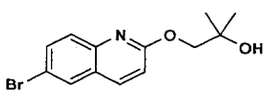
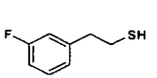
Ej. Nº	Estructura	Componente de Anilina/Bromuro	Comp. de Alcohol	Proc.	Rend. (%)	HPLC	CL-EM	Datos de H RMN ($CDCl_3$)
172	 1-(6-(2-hidroxi-2-metilpropoxi)-5-metilpiridin -3-il)-3-(fenetiltio)pirazin-2(1*H*)-ona			8			412	RMN ^{1}H (500 MHz, cloroformo-d) δ ppm 7,98 (1 H, d, J = 2,20 Hz), 7,58 (1 H, d, J = 1,65 Hz), 7,27 - 7,36 (5 H, m), 7,21 - 7,25 (1 H, m), 6,91 (1 H, d, J = 4,40 Hz), 4,27 (2 H, s), 3,27 - 3,40 (2 H, m), 2,95 - 3,11 (2 H, m), 2,28 (3 H, s), 1,35 (6 H, s)
173	 3-(2-fluorofenetiltio)-1-(6-(2-hidroxi-2-metil propoxi)-5-metilpiridin-3-il)pirazin-2(1*H*)-ona			8			430	RMN ^{1}H (500 MHz, cloroformo-d) δ ppm 7,98 (1 H, d, J = 2,75 Hz), 7,58 (1 H, d, J = 1,92 Hz), 7,27 - 7,33 (2 H, m), 7,18 - 7,24 (1 H, m), 7,00 - 7,12 (2 H, m), 6,91 (1 H, d, J = 4,40 Hz), 4,27 (2 H, s), 3,29 - 3,41 (2 H, m), 3,07 (2 H, t, J = 7,70 Hz), 2,28 (3 H, s), 1,35 (6 H, s)
174	 3-(3-fluorofenetiltio)-1-(6-(2-hidroxi-2-metil propoxi)-5-metilpiridin-3-il)pirazin-2(1*H*)-ona			8			430	RMN ^{1}H (500 MHz, cloroformo-d) δ ppm 7,98 (1 H, d, J = 2,47 Hz), 7,58 (1 H, d, J = 1,92 Hz), 7,27 - 7,32 (1 H, m), 7,26 (1 H, d, J = 7,70 Hz), 7,06 (1 H, d, J = 7,70 Hz), 6,98 - 7,04 (1 H, m), 6,89 - 6,95 (2 H, m), 4,27 (2 H, s), 3,25 - 3,38 (2 H, m), 2,94 - 3,08 (2 H, m), 2,28 (3 H, s), 1,35 (6 H, s)

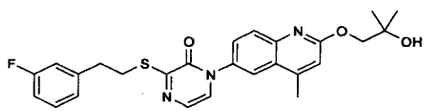
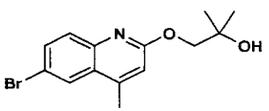
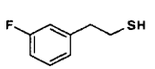
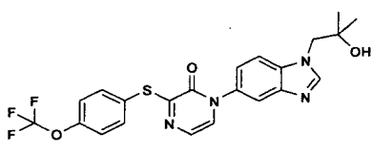
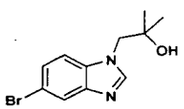
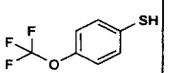
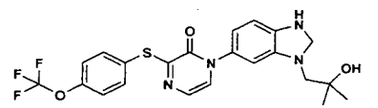
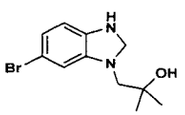
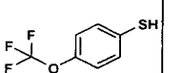
Ej. Nº	Estructura	Componente de Anilina/Bromuro	Comp. de Alcohol	Proc.	Rend. (%)	HPLC	CL-EM	Datos de H RMN ($CDCl_3$)
175	 3-(4-fluorofenetiltio)-1-(6-(2-hidroxi-2-metil propoxi)-5-metilpiridin-3-il)pirazin-2(1*H*)-ona			8			430	RMN ^{1}H (500 MHz, cloroformo-d) δ ppm 7,98 (1 H, d, J = 2,75 Hz), 7,58 (1 H, d, J = 1,92 Hz), 7,28 (1 H, d, J = 4,67 Hz), 7,21 - 7,25 (2 H, m), 7,00 (2 H, t, J = 8,66 Hz), 6,91 (1 H, d, J = 4,40 Hz), 4,27 (2 H, s), 3,22 - 3,38 (2 H, m), 2,92 - 3,07 (2 H, m), 2,28 (3 H, s), 1,35 (6 H, s)
176	 1-(6-(2-hidroxi-2-metilpropoxi)-5-metilpiridin -3-il)-3-(2-(piridin-2-il)etiltio)pirazin-2(1*H*)-ona			8			413	RMN ^{1}H (500 MHz, cloroformo-d) δ ppm 8,57 (1 H, d, J = 3,85 Hz), 7,97 (1 H, d, J = 2,20 Hz), 7,62 (1 H, td, J = 7,63, 1,79 Hz), 7,57 (1 H, d, J = 1,92 Hz), 7,29 (1 H, d, J = 4,40 Hz), 7,24 (1 H, d, J = 7,97 Hz), 7,15 (1 H, dd, J = 6,60, 4,95 Hz), 6,90 (1 H, d, J = 4,67 Hz), 4,27 (2 H, s), 3,51 (2 H, t, J = 7,42 Hz), 3,22 (2 H, t, J = 7,42 Hz), 2,27 (3 H, s), 1,35 (6 H, s)

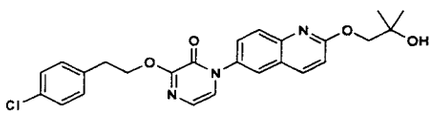
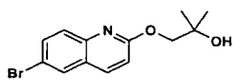
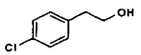
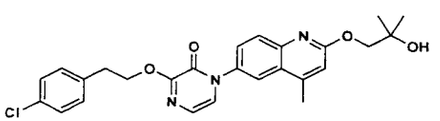
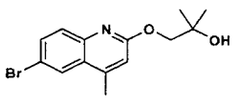
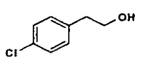
Ej. Nº	Estructura	Componente de Anilina/Bromuro	Comp. de Alcohol	Proc.	Rend. (%)	HPLC	CL-EM	Datos de H RMN ($CDCl_3$)
177	 1-(2-(2-hidroxi-2-metilpropoxi)-4-metilquinolin-6-il)-3-(4-(trifluorometoxi)feniltio)pirazin-2(1*H*)-ona			6			518	RMN ^{1}H (500 MHz, metanol-d_3) d ppm 8,08 (1 H, d, J = 2,47 Hz), 7,93 (1 H, d, J = 8,80 Hz), 7,65 - 7,74 (3 H, m), 7,43 (1 H, d, J = 4,67 Hz), 7,38 (2 H, d, J = 7,97 Hz), 7,22 (1 H, d, J = 4,40 Hz), 6,98 (1 H, d, J = 1,10 Hz), 4,31 (2 H, s), 2,66 (3 H, d, J = 1,10 Hz), 1,34 (6 H, s)
178	 1-(2-hidroxi-2-metilpropil)-4-metil-6-(2-oxo-3-(4-(trifluorometoxi)feniltio)pirazin-1(2*H*)-il)quinolin-2(1*H*)-ona			6			518	RMN ^{1}H (500 MHz, metanol-d_3) δ ppm 8,09 (1 H, d, J = 9,35 Hz), 7,96 (1 H, d, J = 2,47 Hz), 7,64 - 7,75 (3 H, m), 7,29 - 7,49 (3 H, m), 7,21 (1 H, d, J = 4,40 Hz), 6,69 (1 H, s), 4,38 - 4,58 (2 H, m), 2,54 (3 H, s), 1,28 (6 H, s)
179	 1-(2-(2-hidroxi-2-metilpropoxi)quinolin-6-il)-3-(4-(trifluorometoxi)feniltio)pirazin-2(1*H*)-ona			6			504	RMN ^{1}H (500 MHz, metanol-d_3) δ ppm 8,21 (1 H, d, J = 8,80 Hz), 7,90 - 7,98 (2 H, m), 7,73 (1 H, dd, J = 8,80, 2,47 Hz), 7,67 (2 H, d), 7,35 - 7,42 (3 H, m), 7,21 (1 H, d, J = 4,40 Hz), 7,11 (1 H, d, J = 9,07 Hz), 4,34 (2 H, s), 1,35 (6 H, s).

Ej. Nº	Estructura	Componente de Anilina/Bromuro	Comp. de Alcohol	Proc.	Rend. (%)	HPLC	CL-EM	Datos de H RMN ($CDCl_3$)
180	 1-(2-hidroxi-2-metilpropil)-6-(2-oxo-3-(4-(trifluorometoxi)feniltio) pirazin-1(2*H*)-il)quinolin-2(1*H*)-ona			6			504	RMN ^{1}H (500 MHz, metanol-d_3) δ ppm 8,08 (1 H, d, J = 9,35 Hz), 7,97 (1 H, d, J = 9,35 Hz), 7,84 (1 H, d, J = 2,47 Hz), 7,63 - 7,73 (3 H, m), 7,31 - 7,42 (3 H, m), 7,20 (1 H, d, J = 4,40 Hz), 6,78 (1 H, d, J = 9,35 Hz), 4,50 (2 H, s a), 1,29 (6 H, s).
181	 1-(2-(2-hidroxi-2-metilpropoxi)-4-metilquinolin-6-il) -3-(4-(trifluorometil)feniltio)pirazin-2(1*H*)-ona			6			502	RMN ^{1}H (400 MHz, cloroformo-d) δ ppm 7,89 - 8,00 (2 H, m), 7,68 - 7,79 (4 H, m), 7,64 (1 H, dd, J = 8,79, 2,42 Hz), 7,19 (1 H, d, J = 4,39 Hz), 7,11 (1 H, d, J = 4,39 Hz), 6,92 (1 H, d, J = 0,88 Hz), 4,41 (2 H, s), 2,64 (3 H, s), 1,36 (6 H, s)
182	 1-(2-(2-hidroxi-2-metilpropoxi)quinolin-6-il) -3-(4-(trifluorometil)feniltio)pirazin-2(1*H*)-ona			6			488	RMN ^{1}H (400 MHz, cloroformo-d) δ ppm 8,06 (1 H, d, J = 8,79 Hz), 7,94 (1 H, d, J = 9,01 Hz), 7,85 (1 H, d, J = 2,42 Hz), 7,64 - 7,78 (5 H, m), 7,18 (1 H, d, J = 4,61 Hz), 7,11 (1 H, d, J = 4,39 Hz), 7,06 (1 H, d, J = 9,01 Hz), 4,43 (2 H, s), 1,38 (6 H, s)

Ej. Nº	Estructura	Componente de Anilina/Bromuro	Comp. de Alcohol	Proc.	Rend. (%)	HPLC	CL-EM	Datos de H RMN ($CDCl_3$)
183	 1-(2-(2-hidroxi-2-metilpropoxi)quinolin-6-il) -3-(fenetiltio)pirazin-2(1*H*)-ona			6			448	RMN ^{1}H (400 MHz, cloroformo-d) δ ppm 8,04 (1 H, d, J = 8,78 Hz), 7,92 (1 H, d, J = 9,04 Hz), 7,83 (1 H, d, J = 2,51 Hz), 7,65 (1 H, dd, J = 8,91, 2,38 Hz), 7,28 - 7,36 (5 H, m), 7,20 - 7,28 (1 H, m), 7,02 - 7,09 (2 H, m), 4,42 (2 H, s), 3,28 - 3,44 (2 H, m), 2,93 - 3,12 (2 H, m), 1,37 (6 H, s)
184	 1-(2-(2-hidroxi-2-metilpropoxi)-4-metilquinolin -6-il)-3-(fenetiltio)pirazin-2(1*H*)-ona			6			462	RMN ^{1}H (400 MHz, cloroformo-d) δ ppm 7,88 - 7,98 (2 H, m), 7,62 (1 H, dd, J = 8,91, 2,38 Hz), 7,20 - 7,37 (6 H, m), 7,07 (1 H, d, J = 4,27 Hz), 6,90 (1 H, s), 4,40 (2 H, s), 3,30 - 3,39 (2 H, m), 2,98 - 3,12 (2 H, m), 2,63 (3 H, s), 1,35 (6 H, s)
185	 3-(4-fluorofenetiltio)-1-(2-(2-hidroxi-2- metilpropoxi)quinolin-6-il)pirazin-2(1*H*)-ona			6			466	RMN ^{1}H (500 MHz, cloroformo-d) δ ppm 8,04 (1 H, d, J = 8,80 Hz), 7,92 (1 H, d, J = 9,07 Hz), 7,83 (1 H, d, J = 2,20 Hz), 7,65 (1 H, dd, J = 8,94, 2,34 Hz), 7,32 (1 H, d, J = 4,40 Hz), 7,23 - 7,30 (2 H, m), 6,92 - 7,12 (4 H, m), 4,42 (2 H, s), 3,43 - 3,57 (2 H, m), 3,25 - 3,33 (2 H, m), 2,91 - 3,08 (2 H, m), 1,37 (6 H, s)

Ej. Nº	Estructura	Componente de Anilina/Bromuro	Comp. de Alcohol	Proc.	Rend. (%)	HPLC	CL-EM	Datos de H RMN ($CDCl_3$)
186	 3-(4-fluorofenetiltio)-1-(2-(2-hidroxi-2-metil propoxi)-4-metilquinolin-6-il)pirazin-2(1*H*)-ona			6			480	RMN ^{1}H (500 MHz, cloroformo-d) δ ppm 7,88 - 7,97 (2 H, m), 7,62 (1 H, dd, J = 8,80, 2,47 Hz), 7,33 (1 H, d, J = 4,40 Hz), 7,23 - 7,29 (2 H, m), 7,07 (1 H, d, J = 4,40 Hz), 7,01 (2 H, t, J = 8,66 Hz), 6,90 (1 H, s), 4,40 (2 H, s), 3,27 - 3,38 (2 H, m), 2,95 - 3,08 (2 H, m), 2,63 (3 H, s), 1,35 (6 H, s)
187	 3-(3-fluorofenetiltio)-1-(2-(2-hidroxi-2-metilpropoxi)quinolin-6-il)pirazin-2(1*H*)-ona			6			466	RMN ^{1}H (500 MHz, cloroformo-d) δ ppm 8,04 (1 H, d, J = 8,80 Hz), 7,92 (1 H, d, J = 9,07 Hz), 7,83 (1 H, d, J = 2,47 Hz), 7,65 (1 H, dd, J = 8,80, 2,47 Hz), 7,34 (1 H, d, J = 4,40 Hz), 7,27 - 7,31 (1 H, m), 6,99 - 7,10 (4 H, m), 6,89 - 6,97 (1 H, m), 4,42 (2 H, s), 3,30 - 3,38 (2 H, m), 2,98 - 3,08 (2 H, m), 1,37 (6 H, s)

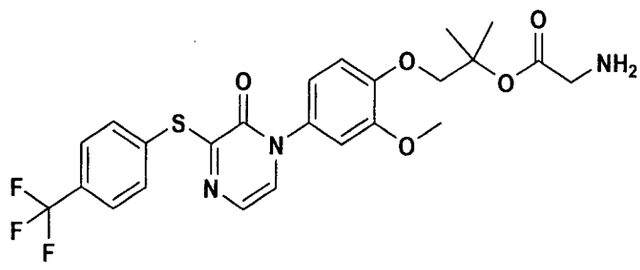
Ej. Nº	Estructura	Componente de Anilina/Bromuro	Comp. de Alcohol	Proc.	Rend. (%)	HPLC	CL-EM	Datos de H RMN ($CDCl_3$)
188	 3-(3-fluorofenetiltio)-1-(2-(2-hidroxi-2-metil propoxi)-4-metilquinolin-6-il)pirazin-2(1*H*)-ona			6			480	RMN ^{1}H (500 MHz, cloroformo-d) δ ppm 7,95 (1 H, d, J = 2,20 Hz), 7,91 (1 H, d, J = 8,80 Hz), 7,62 (1 H, dd, J = 8,94, 2,34 Hz), 7,34 (1 H, d, J = 4,67 Hz), 7,28 (1 H, dd, J = 7,97, 1,92 Hz), 7,00 - 7,10 (3 H, m), 6,89 - 6,97 (2 H, m), 4,40 (2 H, s), 3,28 - 3,41 (2 H, m), 2,97 - 3,10 (2 H, m), 2,63 (3 H, s), 1,35 (6 H, s)
189	 1-(1-(2-hidroxi-2-metilpropil)-1*H*-benzo[*d*]imidazol -5-il)-3-(4-(trifluorometoxi)feniltio)pirazin-2(1*H*)-ona			6			477	RMN ^{1}H (500 MHz, metanol-d_3) δ ppm 8,28 (1 H, s), 7,70 - 7,80 (2 H, m), 7,55 - 7,61 (2 H, m), 7,25 - 7,32 (4 H, m), 7,11 (1 H, d, J = 4,40 Hz), 4,19 (2 H, s), 1,14 (6 H, s)
190	 1-(3-(2-hidroxi-2-metilpropil)-2,3-dihidro-1*H*-benzo[*d*]imidazol -5-il)-3-(4-(trifluorometoxi)feniltio)pirazin-2(1*H*)-ona			6			477	RMN ^{1}H (500 MHz, metanol-d_3) δ ppm 8,30 (1 H, s), 7,76 - 7,85 (2 H, m), 7,65 - 7,71 (2 H, m), 7,34 - 7,42 (3 H, m), 7,20 (1 H, d, J = 4,40 Hz), 4,29 (2 H, s), 1,24 (6 H, s)

Ej. Nº	Estructura	Componente de Anilina/Bromuro	Comp. de Alcohol	Proc.	Rend. (%)	HPLC	CL-EM	Datos de H RMN ($CDCl_3$)
191	 3-(4-clorofenetoxi)-1-(2-(2-hidroxi-2-metil propoxi)quinolin-6-il)pirazin-2(1*H*)-ona			7			466	RMN ^{1}H (500 MHz, cloroformo-d) δ ppm 8,04 (1 H, d, J = 8,80 Hz), 7,92 (1 H, d, J = 8,80 Hz), 7,80 (1 H, d, J = 2,47 Hz), 7,64 (1 H, dd, J = 8,94, 2,34 Hz), 7,23 - 7,30 (4 H, m), 7,04 (1 H, d, J = 8,80 Hz), 6,95 (1 H, d, J = 4,67 Hz), 6,90 (1 H, d, J = 4,67 Hz), 4,54 (2 H, t, J = 7,15 Hz), 4,42 (2 H, s), 3,15 (2 H, t, J = 7,29 Hz), 1,37 (6 H, s)
192	 3-(4-clorofenetoxi)-1-(2-(2-hidroxi-2-metil propoxi)-4-metilquinolin-6-il)pirazin-2(1*H*)-ona			7			480	RMN ^{1}H (500 MHz, cloroformo-d) δ ppm 7,88 - 7,95 (2 H, m), 7,61 (1 H, dd, J = 8,80, 2,47 Hz), 7,27 - 7,30 (4 H, m), 6,96 (1 H, d, J = 4,67 Hz), 6,90 (2 H, d, J = 4,67 Hz), 4,54 (2 H, t, J = 7,15 Hz), 4,40 (2 H, s), 3,15 (2 H, t, J = 7,15 Hz), 2,62 (3 H, s), 1,35 (6 H, s)

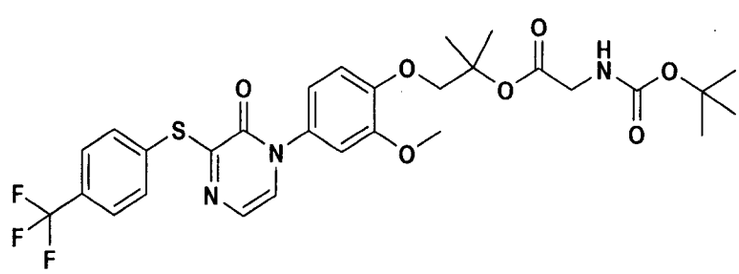
Se prepararon profármacos de los alcoholes secundarios y terciarios seleccionados para mejorar la solubilidad y la exposición. Las condiciones convencionales, empleadas para generar ésteres de aminoácidos de todos menos el éster de glicina de los alcoholes terciarios, se ejemplifican en el Ejemplo 193. La preparación del éster de glicina de los alcoholes terciarios se ejemplifica en el Ejemplo 202. La preparación de un éster de fosfato se ejemplifica por el Ejemplo 204.

EJEMPLO 193

2-Aminoacetato de 1-(2-metoxi-4-(2-oxo-3-(4-(trifluorometil)feniltio)pirazin-1(2*H*)-il)fenoxi)-2-metilpropan-2-ilo



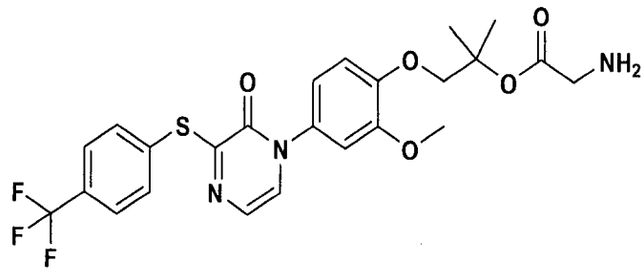
Parte A. 2-(*terc*-Butoxicarbonilamino)acetato de 1-(2-metoxi-4-(2-oxo-3-(4-(trifluorometil)feniltio)pirazin-1(2H)-il)fenoxi)-2-metilpropan-2-ilo



A una suspensión agitada del alcohol preparado en el Ejemplo 36 (3,0 g, 6,4 mmol), 4-pirrolidinopiridina (0,95 g, 6,4 mmol) y BOC-glicina (3,4 g, 19 mmol) en CH_2Cl_2 (60 ml) a 42°C se le añadió *N,N'*-diisopropilcarbodiimida 3,0 ml, 19 mmol) durante 3,5 h. Después de agitar a la temperatura de reflujo durante 2,5 h, el análisis por HPLC mostró que aún quedaba un 25% del alcohol. Se añadió más cantidad de BOC-glicina (3,4 g, 19 mmol) seguido de más cantidad de *N,N'*-diisopropilcarbodiimida (3,0 ml, 19 mmol) que se añadió lentamente durante 3,5 h; después de ello, el análisis por HPLC mostró que aún quedaba <5% del alcohol. La reacción se dejó enfriar a TA antes de la adición de hidrazina monohidrato (18 ml, 370 mmol). Después de agitar durante 5 minutos, la mezcla de reacción se enfrió a 0°C y se filtró. Los filtrados se lavaron secuencialmente con HCl 1 M frío (3 x 20 ml) y $NaHCO_3$ frío al 2% (3 x 20 ml) antes del secado sobre $MgSO_4$ y la concentración al vacío, proporcionando 5,6 g del producto en bruto. La cromatografía (gel de sílice, malla 230-400, gradiente de elución: EtOAc del 0 al 60%/hexano durante 47 min) del residuo proporcionó el éster deseado (3,9 g, rendimiento del 88%).

HPLC 4,42 min. CL EM (M+1 = 624), RMN H ($CDCl_3$) 7,72 (m, 4H), 7,12 (d, *J* = 4,4 Hz, 1H), 7,02 (d, *J* = 4,4 Hz, 1H), 7,00 (d, *J* = 8,3 Hz, 1H), 6,99 (d, *J* = 2,5 Hz, 1H), 6,90 (dd, *J* = 2,5 y 8,3 Hz, 1H), 4,21 (s, 2H), 3,87 (s, 3H), 3,78 (m, 2H), 1,61 (s, 6H), 1,45 (s, 9H).

Parte B. 2-Aminoacetato de 1-(2-metoxi-4-(2-oxo-3-(4-(trifluorometil)feniltio) pirazin-1(2H)-il)fenoxi)-2-metilpropan-2-ilo



El éster de glicinato de BOC descrito en la Parte A (3,9 g, 6,2 mmol) se trató con 1:2 de TFA/CH_2Cl_2 (145 ml) a TA durante 25 min. Después de la retirada de los volátiles al vacío, el TFA residual se retiró por coevaporación con CH_2Cl_2 (3 x 8 ml) y secado al vacío durante 20 min. Después de la disolución en CH_2Cl_2 (70 ml), la solución se lavó con $NaHCO_3$ frío al 5% (3 x 30 ml), se secó sobre $MgSO_4$ y se concentró, produciendo 3,3 g del producto en bruto. La purificación por cromatografía ultrarrápida (120 g gel de sílice, MeOH del 0 al 5%/CH_2Cl_2 durante 24 min) proporcionó la amina libre deseada (2,5 g, rendimiento del 77%).

HPLC 3,72 min. CL EM 2,18 min (M+1 = 524), RMN H ($CDCl_3$) 7,75 (d, *J* = 8,7 Hz, 2H), 7,72 (d, *J* = 8,7 Hz, 2H), 7,14 (d, *J* = 4,4 Hz, 1H), 7,02 (d, *J* = 4,4 Hz, 1H), 7,00 (d, *J* = 8,5 Hz, 1H), 6,99 (d, *J* = 2,4 Hz, 1H), 6,92 (dd, *J* = 2,4 y 8,5 Hz, 1H), 4,24 (s, 2H), 3,89 (s, 3H), 3,36 (m, 2H), 1,63 (s, 6H), 1,54 (s ancho, 2H).

EJEMPLOS 194 A 201

Los Ejemplos 104 - 201 se prepararon de una manera similar al Ejemplo 193 usando el alcohol apropiado y BOC glicina seguido de retirada del TFA del grupo BOC

TABLA 4

Ésteres de Profármaco de Glicina

Nº de Ejemplo	Éster de glicina del Ejemplo Nº	HPLC (Proc. 1)	CL EM	RMN ^{1}H ($CDCl_3$)
194	38	3,86	540	7,55 (d, J = 9,3 Hz, 2H), 7,27 (d, J = 9,3 Hz, 2H), 7,18 (d, J = 4,4 Hz, 1H), 7,06 (d, J = 4,4 Hz, 1H), 7,01 (d, J = 2,2 Hz, 1H), 6,99 (d, J = 8,2 Hz, 1H), 6,86 (dd, J = 2,2 y 8,2 Hz, 1H), 4,15 (s, 2H), 3,76 (s, 3H), 3,17 (s, 2H), 1,50 (s, 6H).
195	32	3,59	470	7,47 (d, J = 8,7 Hz, 2H), 7,27 (d, J = 8,7 Hz, 2H), 7,11 (d, J = 4,4 Hz, 1H), 6,98 (d, J = 2,3 Hz, 1H), 6,97 (d, J = 8,5 Hz, 1H), 6,95 (d, J = 4,4 Hz, 1H), 6,88 (dd, J = 2,3 y 8,5 Hz, 1H), 4,20 (s, 2H), 3,86 (s, 3H), 3,33 (s, 2H), 2,40 (s, 3H), 1,50 (s, 6H).
196	50	3,78	484	7,34 (d, J = 8,3 Hz, 2H), 7,22 (d, J = 8,3 Hz, 2H), 7,05 (d, J = 4,4 Hz, 1H), 6,92 (d, J = 2,2 Hz, 1H), 6,90 (d, J = 8,2 Hz, 1H), 6,87 (d, J = 4,4 Hz, 1H), 6,83 (dd, J = 2,2 y 8,2 Hz, 1H), 4,14 (s, 2H), 3,79 (s, 3H), 3,27 (s, 2H), 2,63 (c, H = 7,7 Hz, 2H), 1,54 (s, 6H), 1,19 (t, J = 7,7 Hz, 3H).

Nº de Ejemplo	Éster de glicina del Ejemplo Nº	HPLC (Proc. 1)	CL EM	RMN ^{1}H ($CDCl_3$)
197	65		482	7,25-7,09 (m, 8H), 6,87 (d, J = 4,4 Hz, 1H), 6,80 (d, J = 9,4 Hz, 1H), 4,09 (s, 2H), 3,30 (2, 2H), 3,23 (dd, J = 7,2, 9,8 Hz, 2H), 2,94 (dd, J = 7,2 y 8,2 Hz, 2H), 2,58 (c, J = 7,6 Hz, 2H), 1,55 (s, 6H), 1,13 (t, J = 7,6 Hz, 3H).
198	87		524	RMN ^{1}H (400 MHz, cloroformo-d) δ ppm 8,40 (2 H, s a), 7,59 (2 H, d, J = 8,78 Hz), 7,28 (2 H, d, J = 8,03 Hz), 7,09 - 7,23 (3 H, m), 6,97 (2 H, d, J = 4,27 Hz), 4,22 (2 H, s a), 3,79 (2 H, s a), 2,27 (3 H, s), 1,62 (6 H, s)
199	88		544	RMN ^{1}H (500 MHz, metanol-d_3) δ ppm 7,65 (2 H, d, J = 9,07 Hz), 7,61 (1 H, d, J = 2,47 Hz), 7,34 - 7,43 (3 H, m), 7,23 - 7,29 (2 H, m), 7,16 (1 H, d, J = 4,40 Hz), 4,38 (2 H, s), 3,75 (2 H, s), 1,68 (6 H, s)
200	123		486	RMN ^{1}H (500 MHz, metanol-d_3) δ ppm 7,38 (1 H, d, J = 4,40 Hz), 7,29 (2 H, dd, J = 8,52, 5,50 Hz), 7,19 - 7,25 (3 H, m), 6,98 - 7,05 (3 H, m), 4,29 (2 H, s), 3,74 (2 H, s), 3,31 - 3,35 (2 H, m), 2,98 (2 H, t, J = 7,56 Hz), 2,28 (3 H, s), 1,67 (6 H, s)

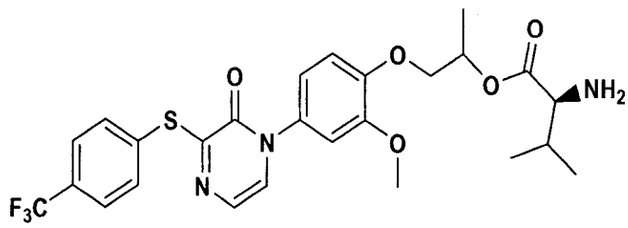
Nº de Ejemplo	Éster de glicina del Ejemplo Nº	HPLC (Proc. 1)	CL EM	RMN ^1H ($CDCl_3$)
201	113		468	RMN ^1H (500 MHz, metanol-d_3) δ ppm 7,39 (1 H, d, J = 4,40 Hz), 7,25 - 7,31 (4 H, m), 7,17 - 7,25 (4 H, m), 7,03 (1 H, d, J = 8,25 Hz), 4,28 (2 H, s), 3,74 (2 H, s), 3,24 - 3,39 (2 H, m), 2,91 - 3,04 (2 H, m), 2,28 (3 H, s), 1,67 (6 H, s)

Si se desea, los ésteres profármaco de aminoácidos pueden convertirse en la sal HCl correspondiente. Por ejemplo, la sal HCl del Ejemplo 197 se preparó disolviendo el compuesto (0,655 mg, 1,36 mmol) en CH_2Cl_2 (10 ml) y MeOH (1 ml) y enfriando a -30ºC. Se añadió HCl 1 N en éter (2,3 ml, 1,7 equiv.) con agitación. La evaporación al vacío proporcionó la sal deseada (0,71 g).

La CL EM era idéntica a la de la base libre. RMN H (CD_3OD) 7,30 (d, *J* = 4,4 Hz, 1H), 7,20 (m, 4H), 7,13 (m, 4H), 6,93 (d, *J* = 8,5 Hz, 1H), 4,19 (s, 2H), 3,64 (s, 2H), 3,23 (dd, *J* = 7,4, 15,4 Hz, 2H), 2,90 (dd, *J* = 8,0 y 15,4 Hz, 2H), 2,62 (c, *J* = 7,5 Hz, 2H), 1,59 (s, 6H), 1,14 (t, *J* = 7,5 Hz, 3H).

EJEMPLO 202

2-Amino-3-metilbutanoato de 1-(2-metoxi-4-(2-oxo-3-(4-(trifluorometil)feniltio)pirazin-1(2H)-il)fenoxi)propan-2-ilo



A una mezcla agitada del alcohol descrito en el Ejemplo 71 (0,882 g, 1,949 mmol), 4-dimetilaminopiridina (0,714 g, 5,85 mmol) y *N*-(t-butoxicarbonil)-*L*-valina (1,271 g, 5,85 mmol) en 18 ml de CH_2Cl_2 a ta se le añadió WSC (1,121 g, 5,85 mmol). Después de agitar a temperatura ambiente durante 30 min, la mezcla de reacción se transfirió a un embudo de decantación, se lavó con H_2SO_4 frío al 5% (3 veces), Na_2CO_3 al 5% (2 veces) y agua y s secó sobre $MgSO_4$. La evaporación del disolvente proporcionó 1,03 g de producto en bruto en forma de la BOC amina. El producto en bruto se disolvió en una mezcla 1:2 de TFA/CH_2Cl_2 (18 ml). Después de agitar durante 15 min, el disolvente se evaporó al vacío. El residuo se transfirió a un embudo de decantación con CH_2Cl_2, se lavó con Na_2CO_3 frío al 5% (2 veces) y se secó sobre $MgSO_4$, proporcionando 790 mg del producto en bruto después de la evaporación del disolvente. El producto se purificó por cromatografía ultrarrápida (80 g gel de sílice, gradiente de elución: MeOH del 1 al 8%/CH_2Cl_2 durante 24 min), proporcionando el éster de valina desdado en forma de una base libre (0,69 g, rendimiento del 64%).

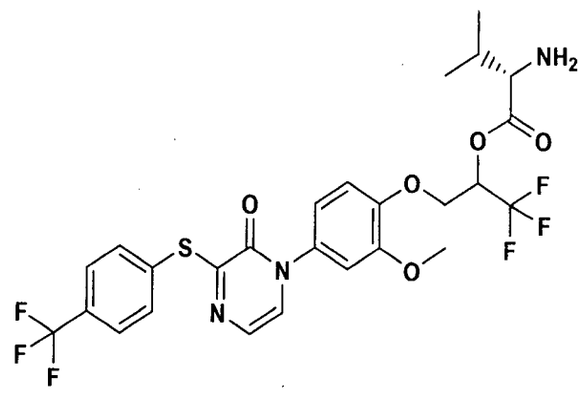
HPLC (Proc. 1) 3,84 min. CL EM 2,26 min (M+1 = 552), RMN H ($CDCl_3$) 7,74 (d, *J* = 8,7 Hz, 2H), 7,72 (d, *J* = 8,7 Hz, 2H), 7,13 (d, *J* = 4,4 Hz, 1H), 7,02 (d, *J* = 4,4 Hz, 1H), 7,00 (d, *J* = 8,5 Hz, 1H), 6,99 (d, *J* = 2,4 Hz, 1H), 6,91 (dd, *J* = 2,4 y 8,5 Hz, 1H), 5,34 (m, 1H), 4,12 (m, 2H), 3,86 (d, 3H), 3,30 (t, *J* = 5,2 Hz, 1H), 2,05 (m, 1H), 1,40 (d, *J* = 6,4 Hz), 0,98 (m, 3H), 0,92 (m, 3H).

La sal HCl del Ejemplo 176 se preparó disolviendo el compuesto en CH_2Cl_2 (9 ml). Después de enfriar la solución a -30°C, se añadió HCl 1 N en éter (2,85 ml, 1,7 equiv.) con agitación. El precipitado de color amarillo se recogió y se secó, proporcionando la sal HCl (0,74 g).

La CL EM era idéntica a la de la base libre. RMN H ($CDCl_3$) 7,74 (d, *J* = 8,7 Hz, 2H), 7,79 (m, 4H), 7,33 (d, *J* = 4,4 Hz, 1H), 7,18 (d, *J* = 8,5 Hz, 1H), 7,15 (d, *J* = 2,4 Hz, 1H), 7,02 (dd, *J* = 2,4 y 8,5 Hz, 1H), 5,51 (m, 1H), 4,24 (m, 2H), 3,86 (d, 3H), 3,33 (s, 1H), 2,30 (m, 1H), 1,41 (d, *J* = 6,4 Hz), 1,12 (m, 6H).

EJEMPLO 203

2-Amino-3-metilbutanoato de (2*S*)-1,1,1-trifluoro-3-(2-metoxi-4-(2-oxo-3-(4-(trifluorometil)feniltio)pirazin-1(2*H*)-il)fenoxi)propan-2-ilo



De una manera análoga a la descrita en el Ejemplo 96, se preparó el éster de valina del alcohol descrito en el Ejemplo 79.

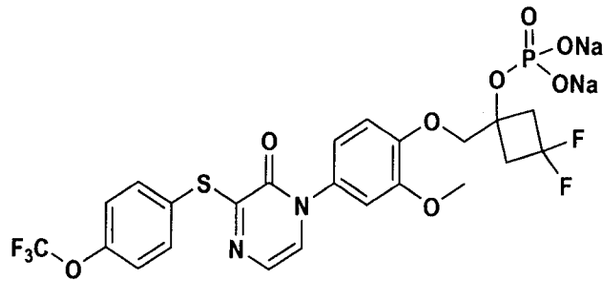
CL EM a t = 2,35 min. (m+1 = 606) columna Phenomenex S5 C18 4,6 x 30 mm / gradiente de 90:10:0,1 a 10:90:0,1 de agua-MeOH-TFA durante 2 min a 5 ml/min con 1 min mantenido al final del gradiente.

RMN ^1H (500 MHz, CDCl3) δ ppm 0,97 (dd, *J* = 35,13, 6,92 Hz, 6 H), 1,97 -

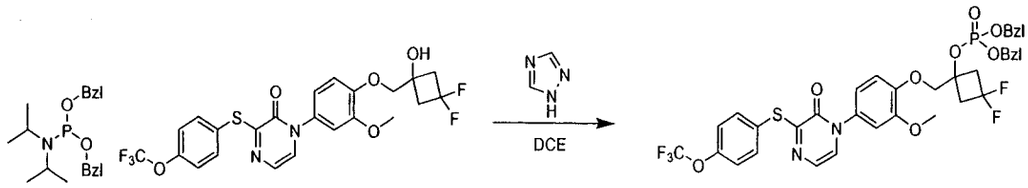
2,20 (m, 1 H), 3,42 (d, *J* = 4,78 Hz, 1 H), 3,86 (s, 4 H), 4,26 - 4,36 (m, 1 H), 4,44 (dd, *J* = 11,08, 3,53 Hz, 1 H), 5,73 - 5,87 (m, 1 H), 6,91 (dd, *J* = 8,56, 2,27 Hz, 1 H), 6,97 - 7,06 (m, 2 H), 7,13 (d, *J* = 4,53 Hz, 1 H), 7,58 (s, 1 H), 7,66 - 7,77 (m, 4 H)

EJEMPLO 204

3,3-Difluoro-1-((2-metoxi-4-(2-oxo-3-(4-(trifluorometoxi)-feniltio)pirazin-1(2*H*)-il)fenoxi)metil)ciclobutilfosfato sódico



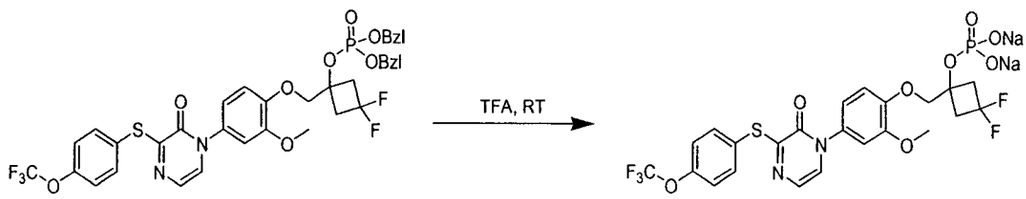
Parte A. 3,3-Difluoro-1-((2-metoxi-4-(2-oxo-3-(4-(trifluorometoxi)feniltio)pirazin-1(2*H*)-il)fenoxi)metil)ciclobutilfosfato de dibencilo



A una mezcla de diisopropilfosforamidita de dibencilo (135 mg, 0,390 mmol), 1-(4-((3,3-difluoro-1-hidroxiciclobutil)metoxi)-3-metoxifenil)-3-(4-(trifluorometoxi)feniltio)pirazin-2(1*H*)-ona (Ejemplo 75) (69 mg, 0,130 mmol) y 1*H*-1,2,4-triazol (27,0 mg, 0,390 mmol) en DCE (20 ml) se agitó a la temperatura de reflujo durante 6 horas. La mezcla se enfrió a TA. se añadió

lentamente peróxido de hidrógeno al 30% en agua (10 ml) y la mezcla se agitó a TA durante 30 min. La mezcla se diluyó con una solución de tiosulfato sódico acuoso al 10% (40 ml) y se extrajo con DCM (50 ml). La fase de DCM se secó sobre sulfato sódico y se concentró. El producto en bruto se purificó con una Columna de gel de sílice ISCO (40 g) y el producto se eluyó con hexano a acetato de etilo al 100% en 10 min. Se produjo 3,3-difluoro-1-((2-metoxi-4-(2-oxo-3-(4-(trifluorometoxi)feniltio)pirazin-1(2*H*)-il)fenoxi)metil)ciclobutilfosfato de dibencilo (79 mg, 0,100 mmol, rendimiento del 77%) en forma de un sólido de color blanquecino. RMN ^{1}H (400 MHz, cloroformo-d) δ ppm 7,57 - 7,66 (2 H, m), 7,27 - 7,39 (12 H, m), 7,13 (1 H, d, J = 4,53 Hz), 6,81 - 7,00 (4 H, m), 4,97 - 5,14 (4 H, m), 4,29 (2 H, s), 3,75 (3 H, s), 2,93 - 3,20 (4 H, m).

Parte B. 3,3-Difluoro-1-((2-metoxi-4-(2-oxo-3-(4-(trifluorometoxi)feniltio)pirazin-1(2*H*)-il)fenoxi)metil)ciclobutilfosfato sódico

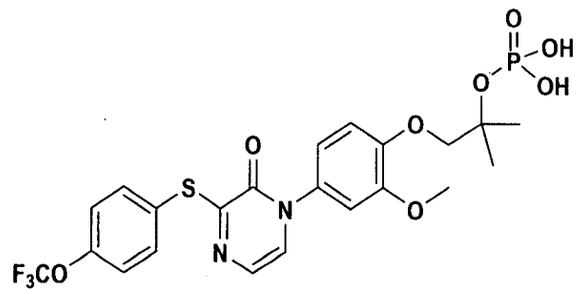


Una solución de 3,3-difluoro-1-((2-metoxi-4-(2-oxo-3-(4-(trifluorometoxi)feniltio)pirazin-1(2*H*)-il)fenoxi)metil)ciclobutilfosfato de dibencilo (79 mg, 0,100 mmol) en TFA (2 ml) se agitó a TA durante 3,5 horas. La mezcla se concentró. El producto en bruto se purificó por HPLC prep. (Phenomenex, Luna 5 micrómetros, 25 x 250 mm, caudal = 30 ml/min, gradiente = de 20% de A a 100% de B en 10 min, A = 90% de H2O/10% de MeOH/0,1% de TFA, B = 10% de H2O/90% de MeOH/0,1% de TFA). Rendimiento de 46 mg, 0,075

mmol, en forma de una goma de color amarillo. A la goma de color amarillo en ACN (2 ml) se le añadió bicarbonato sódico acuoso 0,5 N (302 µl, 0,151 mmol) y la mezcla se diluyó con agua (5 ml). Después, la solución se liofilizó. Se produjo 3,3-difluoro-1-((2-metoxi-4-(2-oxo-3-(4-(trifluorometoxi)feniltio)pirazin-1(2*H*)-il)fenoxi)metil)ciclobutilfosfato sódico (51,08 mg, 0,078 mmol, rendimiento del 78%) en forma de un polvo de color blanquecino. EM (M+H = 611). RMN ^{1}H (400 MHz, MeOD) δ ppm 7,54 - 7,63 (2 H, m), 7,19 - 7,33 (3 H, m), 7,02 - 7,17 (3 H, m), 6,91 (1 H, dd, J = 8,44, 2,39 Hz), 4,28 (2 H, s), 3,80 (3 H, s), 3,13 - 3,32 (2 H, m), 2,75 - 2,90 (2 H, m).

EJEMPLO 205

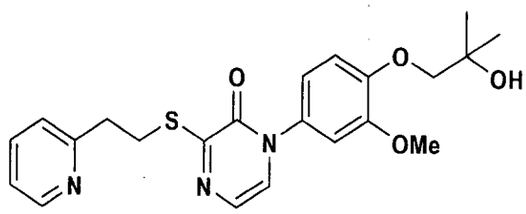
1-(2-Metoxi-4-(2-oxo-3-(4-(trifluorometoxi)feniltio)pirazin-1(2*H*)-il)fenoxi)-2-metilpropan-2-ilfosfato sódico



De una manera análoga a la descrita en el Ejemplo 204, se preparó el profármaco de fosfato del alcohol descrito en el Ejemplo 38. EM (M-H = 561). RMN ^{1}H (400 MHz, MeOD) δ ppm 7,57 (2 H, d, J = 8,56 Hz), 7,28 (2 H, d, J = 8,31 Hz), 7,20 (1 H, d, J = 4,28 Hz), 6,97 - 7,12 (3 H, m), 6,88 (1 H, dd, J = 8,56, 2,27 Hz), 4,00 (2 H, s), 3,78 (3 H, s), 1,48 (6 H, s).

Las siguientes descripciones experimentales ejemplifican la preparación de compuestos específicos como se muestra en los Ejemplos 27, 95, 110, 113 y 124.

EJEMPLO 27

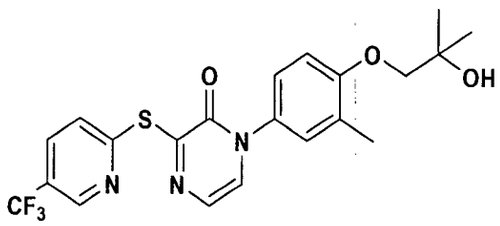


1-(4-(2-Hidroxi-2-metilpropoxi)-3-metoxifenil)-3-(2-(piridin-2-il)-etiltio)pirazin-2(1*H*)-ona

Siguiendo los procedimientos descritos en las partes A-D del ejemplo 134, se convirtió 2-metoxi-4-nitrofenol en 1-(4-(2-hidroxi-2-metilpropoxi)-3-metoxifenil)pirazina-2,3(1H,4H)-diona. Una solución de 1-(4-(2-hidroxi-2-metilpropoxi)-3-metoxifenil)pirazina-2,3(1*H*,4*H*)-diona preparada en la Parte ? (2,28 g, 7,44 mmol), $EtN(iPr)_2$ (3,9 ml, 22,3 mmol) y PyBOP (6,78 g, 13,0 mmol) en DMF (35 ml) se agitó a temperatura ambiente durante 1,5 h. Después de la adición de 2-piridiletil mercaptano (1,24 g, 8,93 mmol), la reacción se agitó a temperatura ambiente. Después de agitar durante una noche, la mezcla de reacción se concentró parcialmente a presión reducida, inactivando mediante la adición de $NaHCO_3$ ac. y se extrajo con EtOAc. Los extractos de EtOAc se lavaron con salmuera, se secaron sobre $MgSO_4$ y se concentraron. La cromatografía sobre sílice empleando un gradiente de elución con metanol al 2,5-10%/cloruro de metileno, seguido de cromatografía sobre sílice eluyendo con EtOAc y trituración con EtOAc/Hexanos produjo el producto deseado 1-(4-

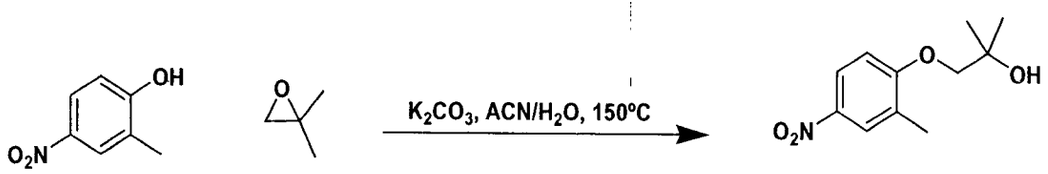
(2-hidroxi-2-metilpropoxi)-3-metoxifenil)-3-(2-(piridin-2-il)etiltio)pirazin-2(1*H*)-ona (2,15 g, rendimiento del 68%).

EJEMPLO 95



1-(4-(2-Hidroxi-2-metilpropoxi)-3-metilfenil)-3-(5-(trifluorometil)piridin-2-iltio)pirazin-2(1*H*)-ona

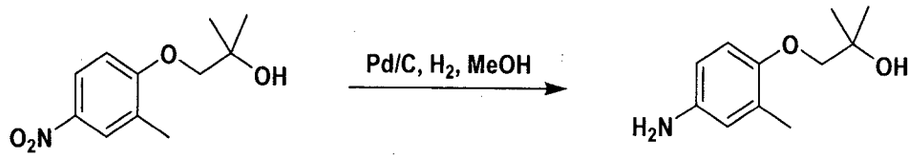
Parte A. 2-Metil-1-(2-metil-4-nitrofenoxi)propan-2-ol



Una mezcla de 2-metil-4-nitrofenol (5,50 g, 35,9 mmol), 2,2-dimetiloxirano (7,77 g, 108 mmol), K_2CO_3 (4,96 g, 35,9 mmol) y NaH_2PO_4 (4,31 g, 35,9 mmol) en MeCN (50 ml) y H_2O (8,82 ml) se agitó a 140°C en una bomba de acero durante 6 horas. Después de enfriar a TA, la reacción se diluyó con $NaHCO_3$ ac. saturado (80 ml) antes de la extracción con EtOAc (100 ml). La fase de EtOAc se secó sobre Na_2SO_4 y se concentró. El producto en bruto se purificó por cromatografía sobre gel de sílice empleando un gradiente disolvente (de hexano a acetato de etilo al 60%) para eluir 2-metil-1-(2-metil-4-nitrofenoxi)propan-2-ol (7,3 g, 32,4 mmol, rendimiento del 90%) en forma de un aceite amarillo. EM (M+1 = 226). RMN ^1H (500 MHz, cloroformo-d) δ ppm 8,00 -

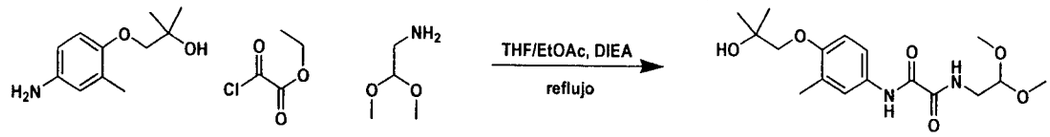
8,15 (2 H, m), 6,86 (1 H, d, J = 8,80 Hz), 3,90 (2 H, s), 2,33 (3 H, s), 1,40 (6 H, s).

Parte B. 1-(4-Amino-2-metilfenoxi)-2-metilpropan-2-ol



Una mezcla de 2-metil-1-(2-metil-4-nitrofenoxi)propan-2-ol (7,30 g, 32,4 mmol) y Pd al 10%/C (0,345 g, 3,24 mmol) en MeOH (150 ml) se hidrogenó a 1 atm de H_2 durante 18 horas. Después de la retirada del Pd/C por filtración, la solución se concentró para producir 1-(4-amino-2-metilfenoxi)-2-metilpropan-2-ol (6,10 g, 29,7 mmol, rendimiento del 92%) en forma de una goma transparente que se usó a continuación sin purificación adicional.

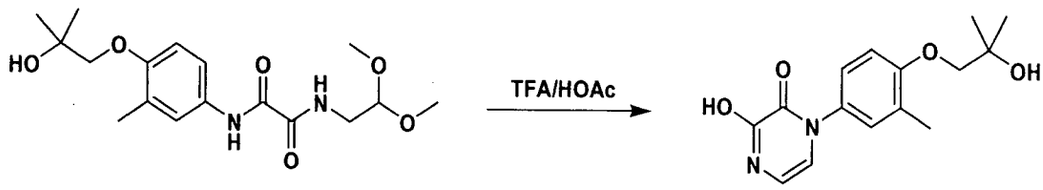
Parte C. *N*1-(2,2-Dimetoxietil)-*N*2-(4-(2-hidroxi-2-metilpropoxi)-3-metilfenil)oxalamida



La lenta adición de una solución de 2-cloro-2-oxoacetato de etilo (4,69 g, 34,4 mmol) en THF (30 ml) a una solución de 1-(4-amino-2-metilfenoxi)-2-metilpropan-2-ol (6,10 g, 31,2 mmol) en THF (100 ml) dio como resultado la formación de un precipitado según se agitaba la reacción a TA durante 30 min. En ese momento, se añadió una solución de Et_3N (13,06 ml, 94 mmol) y 2,2-dimetoxietanamina (3,94 g, 37,5 mmol) en EtOAc (100 ml) antes de calentar la mezcla a la temperatura de reflujo durante 25 horas. Después de la

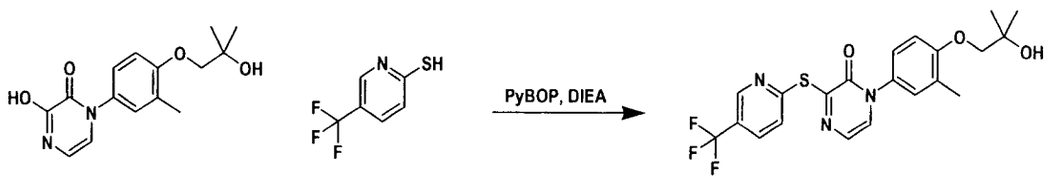
refrigeración y la concentración al vacío, el residuo, tras la dilución con CH_2Cl_2, se extrajo con HCl acuoso 0,5 N (2 x 150 ml). La fase de CH_2Cl_2 se secó sobre sulfato sódico y se concentró para producir *N*1-(2,2-dimetoxietil)-*N*2-(4-(2-hidroxi-2-metilpropoxi)-3-metilfenil)-oxalamida (11,40 g, 30,6 mmol, rendimiento del 98%) en forma de un sólido de color blanco que se usó a continuación sin purificación adicional.

Parte D. 3-Hidroxi-1-(4-(2-hidroxi-2-metilpropoxi)-3-metilfenil)pirazin-2(1*H*)-ona



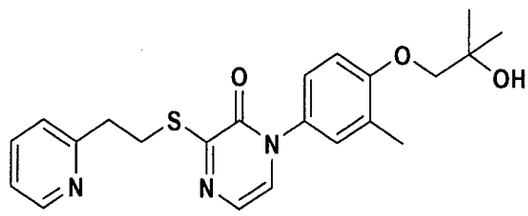
Una solución de *N*1-(2,2-dimetoxietil)-*N*2-(4-(2-hidroxi-2-metilpropoxi)-3-metilfenil)oxalamida (11,4 g, 32,2 mmol) y TFA (2,97 ml, 38,6 mmol) en AcOH (120 ml) se agitó a 135ºC en un tubo cerrado herméticamente durante 60 min. Después de la refrigeración y la concentración al vacío, la adición de CH_2Cl_2 (300 ml) produjo un precipitado que se recogió por filtración y se lavó con CH_2Cl_2 (150 ml) para producir 3-hidroxi-1-(4-(2-hidroxi-2-metilpropoxi)-3-metilfenil)pirazin-2(1*H*)-ona (7,19 g, 23,53 mmol, rendimiento del 73,1%) en forma de un sólido de color pardo. EM (M+1 = 226). RMN ^1H (500 MHz, metanol-d_3) δ ppm 7,13 - 7,26 (2 H, m), 6,98 (1 H, d, J = 8,52 Hz), 6,50 (1 H, d, J = 5,77 Hz), 6,41 (1 H, d, J = 6,05 Hz), 3,82 (2 H, s), 2,29 (3 H, s), 1,35 (6 H, s).

Parte E. 1-(4-(2-Hidroxi-2-metilpropoxi)-3-metilfenil)-3-(5-(trifluorometil)-piridin-2-iltio)pirazin-2(1*H*)-ona

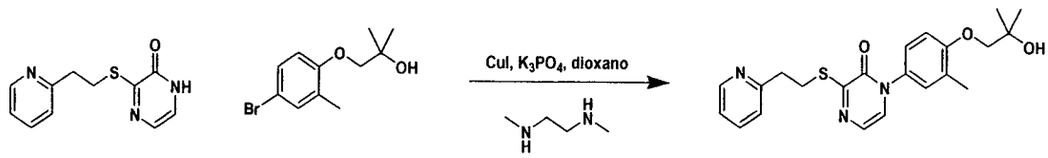


Una mezcla de 3-hidroxi-1-(4-(2-hidroxi-2-metilpropoxi)-3-metilfenil)pirazin-2(1*H*)-ona (100 mg, 0,344 mmol), PyBOP (314 mg, 0,603 mmol) y $EtN(iPr)_2$ (0,180 ml, 1,033 mmol) en DMF (6 ml) se agitó a TA durante 3 horas antes de la adición de 5-(trifluorometil)piridina-2-tiol (74,1 mg, 0,413 mmol). Después de agitar durante 3 días, la reacción se diluyó con $NaHCO_3$ ac. saturado (15 ml) antes de la extracción con EtOAc (20 ml). La fase de EtOAc se secó sobre Na_2SO_4 y se concentró. El producto en bruto se purificó por HPLC prep. (Phenomenex, Luna 5 micrómetros, 30 x 250 mm, caudal = 30 ml/min, gradiente = de 20% de A a 100% de B en 30 min, A =90% de H_2O/10% de MeOH/0,1% de TFA, B = 10% de H_2O/90% de MeOH/0,1% de TFA). Después de la concentración, el residuo en EtOAc (30 ml) se convirtió en la base libre lavándolo con $NaHCO_3$ ac. saturado (30 ml). La fase de EtOAc se secó sobre Na_2SO_4 y se concentró. Se produjo 1-(4-(2-hidroxi-2-metilpropoxi)-3-metilfenil)-3-(5-(trifluorometil)piridin-2-iltio)pirazin-2(1*H*)-ona (22,76 mg, 14%) en forma de un sólido de color blanquecino. EM (M+1 = 452). RMN ^1H (500 MHz, cloroformo-d) δ ppm 8,88 (1 H, s), 7,89 - 7,99 (2 H, m), 7,16 - 7,24 (3 H, m), 7,07 (1 H, d, J = 4,40 Hz), 6,90 (1 H, d, J = 8,52 Hz), 3,84 (2 H, s), 2,30 (3 H, s), 1,39 (6 H, s).

EJEMPLO 110

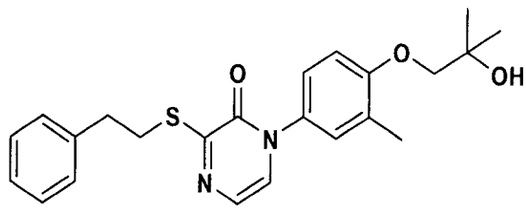


1-(4-(2-Hidroxi-2-metilpropoxi)-3-metilfenil)-3-(2-(piridin-2-il)etiltio)pirazin-2(1*H*)-ona

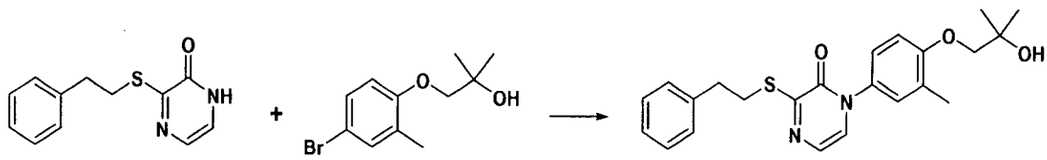


Una mezcla de 3-(2-(piridin-2-il)etiltio)pirazin-2(1*H*)-ona (100 mg, 0,429 mmol), que se preparó por el procedimiento descrito en el Procedimiento 7 con la excepción de que se sustituyó 2-(4-clorofenetanol) por 2-(2-piridiletiltiol), 1-(4-bromo-2-metilfenoxi)-2-metilpropan-2-ol (133 mg, 0,514 mmol), *N1*,*N2*-dimetiletano-1,2-diamina (113 mg, 1,286 mmol), K_3PO_4 (0,106 ml, 1,286 mmol) y yoduro de cobre (1) (82 mg, 0,429 mmol) en dioxano (1,0 ml), se agitó a 115ºC durante 90 min. Después de la refrigeración a TA, la mezcla de reacción se filtró y el filtrado se concentró. El producto en bruto se purificó por cromatografía sobre gel de sílice empleando un gradiente disolvente (de hexano a acetato de etilo al 100%) para producir 1-(4-(2-hidroxi-2-metilpropoxi)-3-metilfenil)-3-(2-(piridin-2-il)etiltio)pirazin-2(1*H*)-ona (140 mg, 0,340 mmol, rendimiento del 79%) en forma de un sólido de color blanco. EM (M+H 412). RMN ^{1}H (400 MHz, MeOD) δ ppm 8,67 (1 H, d), 8,48 (1 H, td, J = 7,91, 1,51 Hz), 8,02 (1 H, d, J = 8,28 Hz), 7,81 - 7,95 (1 H, m), 7,07 - 7,29 (4 H, m), 6,93 (1 H, d, J = 8,78 Hz), 3,76 (2 H, s), 3,35 - 3,57 (4 H, m), 2,22 (3 H, s), 1,27 (6 H, s).

EJEMPLO 113



1-(4-(2-Hidroxi-2-metilpropoxi)-3-metilfenil)-3-(fenetiltio)pirazin-2(1*H*)-ona



Una mezcla de 3-(fenetiltio)pirazin-2(1*H*)-ona (25 mg, 0,108 mmol), que se preparó por el procedimiento descrito en el Procedimiento 7 con la excepción de que se sustituyó 2-(4-clorofenetanol) por 2-fenetiltiol, 1-(4-bromo-2-metilfenoxi)-2-metilpropan-2-ol (33,5 mg, 0,129 mmol), yoduro de cobre (20,50 mg, 0,108 mmol), K_3PO_4 (70 mg, 0,323 mmol) y *N,N'*-dimetiletilendiamina (28,5 mg, 0,323 mmol) en dioxano (1,0 ml) se agitó a 115ºC durante 2 horas. Después de la refrigeración a TA, la mezcla de reacción se filtró y el filtrado se concentró. El producto en bruto se purificó por cromatografía sobre gel de sílice empleando un gradiente disolvente (de hexano a acetato de etilo al 100%) para eluir y producir 1-(4-(2-hidroxi-2-metilpropoxi)-3-metilfenil)-3-(fenetiltio)-pirazin-2(1*H*)-ona (26,74 mg, 0,062 mmol, rendimiento del 57,5%) en forma de un sólido de color blanquecino. EM (M+1 = 411). RMN ^{1}H (500 MHz, metanol-d_3) δ ppm 7,38 (1 H, d, J = 4,40 Hz), 7,25 - 7,32 (4 H, m), 7,16 - 7,24 (4 H, m), 7,00 (1 H, d, J = 8,25 Hz), 3,83 (1 H, s), 3,24 - 3,39 (2 H, m), 2,90 - 3,05 (2 H, m), 2,29 (3 H, s), 1,35 (6 H, s).

ENSAYO DE UNIÓN A RADIOLIGANDO PARA LA EVALUACIÓN DE LA ACTIVIDAD DE MCHR1

Ensayo y Evaluación Biológica

Los compuestos de Fórmula I se caracterizaron inicialmente en un ensayo de unión *in vitro* para determinar su Ki o su capacidad para antagonizar la unión de un agonista peptídico con el receptor de la hormona concentradora de melanina humana (MCHR1).

Se prepararon membranas de células HEK-293 transfectadas de forma estable que expresaban un receptor hMCHR1 mutado (E4Q, A5T) por homogeneización en Dounce y centrifugación diferencial. Se llevaron a cabo experimentos de unión con 0,5 -1,0 µg de proteína de membrana incubados en un total de 0,2 ml de HEPES 25 mM (pH 7,4) con $MgCl_2$ 10 mM, EGTA 2 mM y BSA al 0,1% (Tampón de unión) durante 90 min. Para los ensayos de unión competitiva, se llevaron a cabo reacciones en presencia de [Phe^{13}, [^{125}I]Tyr^{19}]-MCH 0,06-0,1 nM y concentraciones crecientes de moléculas de ensayo no marcadas. Las reacciones se terminaron por filtración rápida al vacío sobre placas de 96 pocillos GFC Unifilter revestidas previamente con 0,075 ml de tampón de unión que contenía BSA al 1% y se lavaron 3 veces con 0,4 ml de solución salina tamponada con fosfato (pH 7,4) que contenía TX-100 al 0,01%. Los filtros se secaron; se añadieron 0,05 ml de Microscint 20 a cada pocillo y se cuantificó posteriormente la radiactividad mediante recuento de centelleo en un contador de centelleo de microplaca TopCount™ (Packard). Se determinaron las constantes inhibitorias por análisis de mínimos cuadrados no lineal usando una ecuación logística de cuatro parámetros.

Datos biológicos

Los siguientes datos biológicos *in vitro* representativos se midieron en un ensayo de unión para los compuestos de los Ejemplos descritos anteriormente en este documento:

Ejemplo	Ki (nM)
113	8
124	9
65	10
110	17
125	17
131	18
38	20
181	21
67	28
36	33
95	41
155	45
69	49
71	62
27	63
151	64
141	78
172	85
59	125
170	132

Ejemplo	Ki (nM)
10	141
46	232
178	290
3	576
169	1294
39	1580
157	1730
49	3043
19	3127
28	3153
40	3218
50	4664

EVALUACIÓN DE PROFÁRMACOS

La capacidad relativa del profármaco para potenciar la exposición (biodisponibilidad) se evaluó en un estudio PK de ocho horas usando ratas Sprague Dawley canuladas (CD, Charles River Breeding Laboratory). Los compuestos (parentales y ésteres de profármacos) se administraron p.o. a 2,0 ml/kg en forma de una suspensión en metilcelulosa al 0,5%, Tween 80 al 0,1% en agua a 10 mg/kg p.o. Se tomaron muestras de sangre a 1, 2, 4 y 8 h. Después de determinar la concentración de partida, se calculó un AUC para el estudio de ocho horas.

Evaluación de la Actividad de MCHR1 *In Vivo*

Se colocaron ratas Sprague Dawley macho (CD, Charles River Breeding Laboratory) que pesaban aproximadamente 240 gramos en jaulas de plástico individuales con cama de AlphaDri. La habitación se mantuvo a 22,22ºC (72 grados F) y humedad al 50% y un ciclo de 12/12 h de luz/oscuridad, apagando las luces a las 16:00 horas. Las ratas se condicionaron durante 5 días antes del comienzo del estudio a tener una selección de alimentos. Un pienso normal (Harlan Teklad, 2018) que contenía proteína al 18%, grasa al 5% e hidratos de carbono al 73% y una dieta rica en grasa y en azúcares (Research Diets (D2327)) que contenía proteína al 20%, grasa al 40% e hidratos de carbono al 40%, en la que los hidratos de carbono eran en su totalidad sacarosa y la grasa era aceite de soja y de coco. Los estudios habían revelado que las ratas presentaban una gran preferencia por la dieta rica en grasa y en sacarosa (preferencia del 80%). Se midió diariamente el peso corporal y el consumo de ambas clases de alimento, así como la ingesta de agua. El agua estaba disponible *ad libitum* durante todo el estudio. El consumo de alimento se presenta como consumo calórico diario, que es la suma de los gramos de pienso multiplicada por las Kcal por gramo (3,5) más los gramos de pienso rico en grasa y en azúcares multiplicados por Kcal por gramo (4,59).

Se midió el peso corporal de valor basal antes del tratamiento farmacológico el día 0 del estudio. El consumo de alimento de valor basal era la media de los 3 días anteriores al primer tratamiento farmacológico. El fármaco se administró diariamente p.o. a 2,0 ml/kg a las 15:00 horas, comenzando el día 0 y continuando diariamente hasta el día 4 como una suspensión en metilcelulosa al 0,5%, Tween 80 al 0,1% en agua a 3,0, 10 y 30 mg/kg p.o. Todos los datos se evaluaron usando los análisis estadísiticos ANOVA y

Fishers PLSD.

Datos biológicos

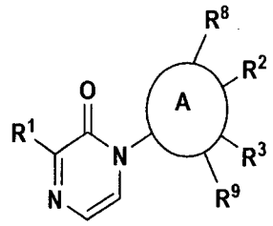
Ejemplo	Dosis (mg/kg)	Reducción de Peso frente a Vehículo
193	3	0,7%
	10	2,1%
	30	3,4%
194	3	0,9%
	10	2,7%
	30	7,4%
202	30	2,2%
27	45	4,1%
113	45	4,2%

Aunque la invención se ha descrito de acuerdo con varias realizaciones, diversas modificaciones de la misma, además de las descritas en este documento, serán evidentes para los especialistas en la técnica a partir de la descripción anterior. También se pretende que dichas modificaciones estén dentro del alcance de las reivindicaciones adjuntas.

Habiendo descrito la invención como antecede, se declara como propiedad lo contenido en las siguientes

REIVINDICACIONES

1. Un compuesto de Fórmula I o una sal farmacéuticamente aceptable del mismo

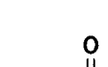


I

donde

(A) es un anillo fenileno o un anillo heteroarilo que contiene uno o dos átomos de nitrógeno o un átomo de oxígeno;

R^1 es Z-Y-X-, donde

X es O, S, , o  ;

Y es un enlace, un cicloalquilo de 3 a 6 miembros o una cadena alquilo; y

Z es arilo o heteroarilo;

R^2 es -E-G-$(J)_m$, donde m es un número entero de 1 a 3;

E es O, S o un enlace;

G es alquilo inferior, fenilalquilo, cicloalquilo, cicloalquilalquilo, alquilcicloalquilo, cicloalcoxi, alquilcicloalcoxi o cicloalcoxialquilo, y

cada J es independientemente hidrógeno, hidroxilo, CN, $-SO_2R^7$, $-SR^7$, $-SOR^7$, alquilo inferior, alcoxi inferior, CF_3, CF_3O-, $-COOR^5$ o $-CO-NR^{5a}R^6$, donde cada uno de R^{5a} y R^6 se selecciona independientemente entre el grupo constituido por H, alquilo C_{1-3} y cicloalquilo, o R^{5a} y R^6 tomados juntos pueden ser propanodiilo, butanodiilo o pentanodiilo con el átomo de N al que están unidos para formar una amina cíclica de 4, 5 ó 6 miembros que puede estar opcionalmente sustituida;

R^5 es H, alquilo C_{1-6} o cicloalquilo;

R^7 es alquilo inferior; y

R^3 es alquilo C_{1-6}, cicloalquilo, alcoxi C_{1-6}, halógeno, hidrógeno, -S-alquilo C_{1-6}, CN, CF_3O o CF_3;

y donde R^2 y R^3 pueden tomarse juntos para formar un anillo de 5 a 7 miembros que está saturado o parcialmente insaturado y puede incluir opcionalmente un heteroátomo E que es O o 0, 1 ó 2 átomos de N, donde el anillo está sustituido con uno o dos grupos $-O-G-(J)_m$, donde al menos un J es OH, y que puede estar opcionalmente sustituido con otros sustituyentes como los indicados para "alquilo" o "heteroarilo";

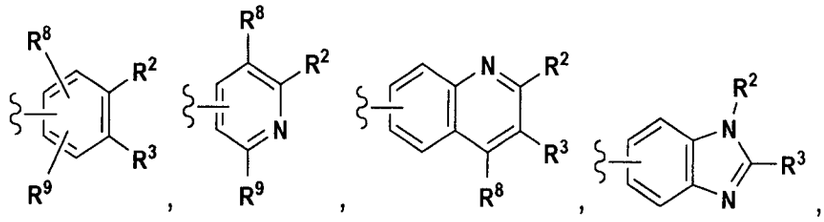
con la condición de que cuando (A) es un grupo fenileno, E-G y R^3 no sean grupos alcoxi inferior no sustituidos iguales, y cuando G es alquilo inferior y J es H, R^3 no sea hidrógeno; y

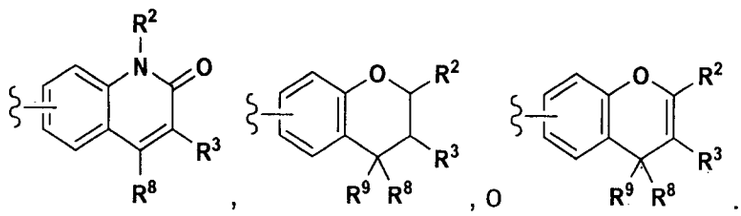
cada uno de R^8 y R^9 es independientemente hidrógeno, halógeno o alquilo inferior;

incluyendo ésteres de los mismos, profármacos de los mismos, solvatos de los mismos y todos los estereoisómeros de los mismos.

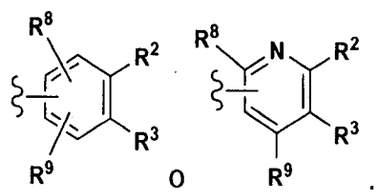
2. El compuesto que se ha definido en la reivindicación 1, en el que (A) es un fenileno o en el que (A) es un anillo heteroarilo monocíclico o bicíclico.

3. El compuesto que se ha definido en la reivindicación 1, en el que (A) es

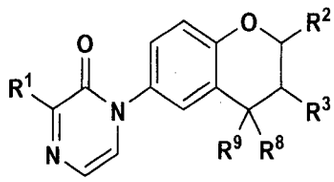




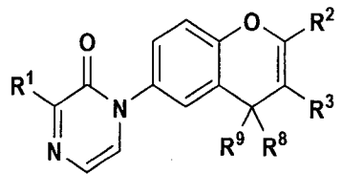
4. El compuesto que se ha definido en la reivindicación 1, en el que (A) es



5. El compuesto que se ha definido en la reivindicación 1, que tiene la estructura



IF , o



IG ,

o una sal farmacéuticamente aceptable del mismo o un profármaco de cualquiera de los anteriores.

6. El compuesto que se ha definido en la reivindicación 4, en el que

X es O o S; y/o

R^1 es Z-Y-X,

donde Y es un enlace o una cadena alquileno de 1 a 3 átomos; y/o

donde Z es fenilo o arilo;

donde Z es heteroarilo; y/o

donde R^2 es -E-G-J; y/o

donde E es O o S; y/o

donde G es una cadena alquileno o alquilcicloalquilo; y/o

donde J es H, OH, SO_2R^7, alquilo inferior, alcoxi inferior o CF_3; y/o

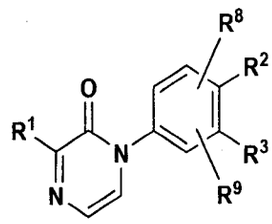
R^3 es alquilo C_{1-6}, alcoxi C_{1-6}, H o halo; y/o

R^8 es H o alquilo; y/o

R^9 es H; y/o

R^2 y R^3 pueden tomarse opcionalmente juntos para formar un anillo de 5 a 7 miembros que está saturado, insaturado o parcialmente insaturado, y puede incluir un átomo de O o 1 ó 2 átomos de N, donde el anillo está sustituido con uno o dos grupos -O-G-$(J)_m$, donde al menos un J es OH, y que puede estar opcionalmente sustituido con otros sustituyentes como los indicados para "alquilo" o "heteroarilo".

7. El compuesto que se ha definido en la reivindicación 1 o una sal farmacéuticamente aceptable del mismo



IA

8. El compuesto que se ha definido en la reivindicación 7, en el que

R^1 es Z-Y-X;

X es S; y/o

Y es un enlace o una cadena alquileno; y/o

Z es fenilo o piridilo; y/o

E es O; y/o

G es una cadena alquileno o alquilcicloalquilo; y/o

J es H o OH; y/o

R^3 es H, alcoxi, alquilo o halo; y/o

R^8 es H o CH_3; y/o

R^9 es H;

donde R^2 y R^3 pueden tomarse juntos para formar un anillo de 5 a 7 miembros que está saturado, insaturado o parcialmente insaturado, y puede incluir un átomo de O o 1 ó 2 átomos de N, donde el anillo está sustituido con 1 ó 2 grupos -O-G-$(J)_m$, donde al menos un J es OH, y que puede estar opcionalmente sustituido adicionalmente con alquilo y/o OH.

9. El compuesto que se ha definido en la reivindicación 1, en el que

Z es arilo o heteroarilo, con cualquiera de los restos Z anteriores sin sustituir o sustituido con 1, 2 ó 3 de amino, halo, alquilo C_{1-6}, alquilamino C_{1-3}, di-alquilamino C_{1-3}, alcoxi C_{1-3}, tioalquilo C_{1-3}, trifluoroalcoxi C_{1-3}, trifluorometilo, cicloalquilo, cicloalcoxi o heteroarilo; y/o

J es hidrógeno, hidroxilo, CN, $-SO_2R^7$, $-SR^7$, $-SOR^7$, alquilo inferior, alcoxi inferior, CF_3, CF_3O-, $-COOR^5$ o $-CO-NR^{5a}R^6$, donde cada uno de R^{5a} y R^6 se selecciona independientemente entre el grupo constituido por H, alquilo C_{1-3} y cicloalquilo, o R^{5a} y R^6 tomados juntos pueden ser propanodiilo, butanodiilo o pentanodiilo con el átomo de N al que están unidos para formar una amina cíclica de 4, 5 ó 6 miembros opcionalmente sustituida con alquilo inferior, alcoxi inferior, hidroxilo, CF_3 o CF_3O.

10. El compuesto de la reivindicación 1, en el que:

Z es

(1) arilo, que está opcionalmente sustituido con:

a) halógeno,

b) alquilo,

c) alcoxi,

d) polihaloalquilo,

e) polihaloalcoxi,

f) amino, alquilamino o dialquilamino,

g) alquiltio,

h) OH,

i) un éster, o

j) arilo,

(2) heteroarilo, que es:

a) piridinilo,

b) pirazinilo, o

c) pirimidinilo,

estando cada uno de a), b) o c) opcionalmente sustituido con alquilo, polihaloalquilo, alcoxi o halógeno,

(3) benzotiazol opcionalmente sustituido con halo o alcoxi,

(4) benzoxazol opcionalmente sustituido con halo,

(5) bencimidazol,

(6) tiazol opcionalmente sustituido con arilo o alquilo,

(7) indanilo,

(8) quinolinilo opcionalmente sustituido con CF_3, o

(9) imidazolidinilo; y/o

Y es un enlace o alquileno; y/o

X es S, O, SO o SO_2; y/o

J es

(1) H,

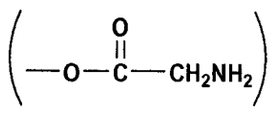
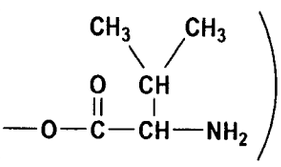
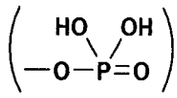
(2) -CO-$NR^{5a}R^6$, donde R^{5a} y R^6 junto con el N al que están unidos forman un anillo pirrolidinilo,

(3) OH,

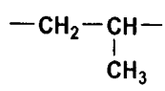
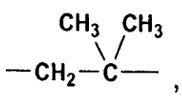
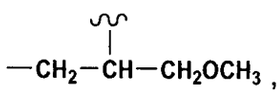
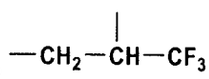
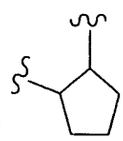
(4) COOH,

(5) COO-alquilo,

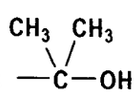
(6) SO_2R^7, o

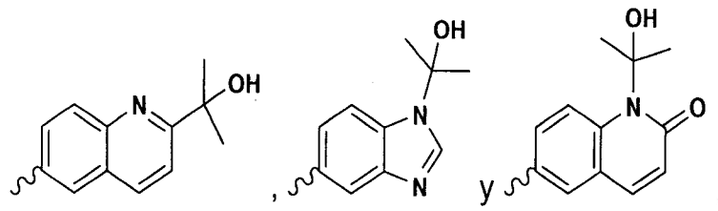
(7) ésteres de profármacos que se seleccionan entre glicina  , valina  y fosfato  ; y/o

m es 1 ó 2; y/o

G es un enlace o CH_2, $(CH_2)_2$, $(CH_2)_3$,  ,  ,  ,  , cicloalquilo que es  , o cicloalcoxi que es  ;

E es O; y/o

donde R^2 y R^3 pueden tomarse opcionalmente juntos para formar un anillo insaturado o aromático, de 5 ó 6 miembros, que contiene uno o dos átomos de N, donde el anillo está opcionalmente sustituido con hidroxialquilo que es  , y es



y donde R^2 y R^3 pueden tomarse opcionalmente juntos para formar un anillo que contiene O, saturado o parcialmente insaturado, de 6 miembros, donde el anillo está opcionalmente sustituido con hidroxialquilo, alquilo y/o OH; y/o

R^3 es H, alcoxi, hidroxialquilo, alquilo, halo o hidroxialcoxi; y/o

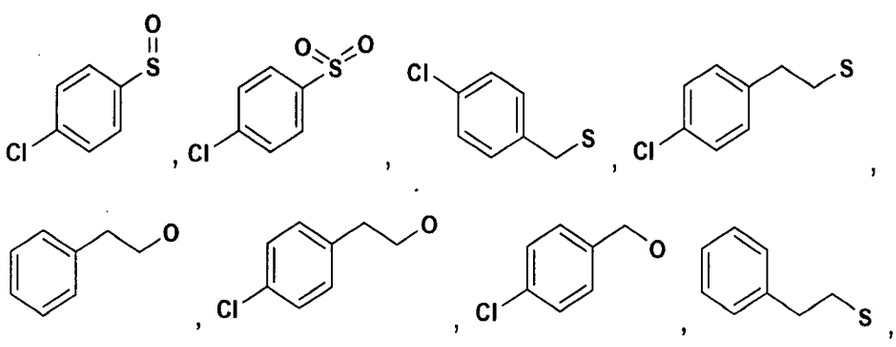
R^8 es H, halo o alquilo; y/o

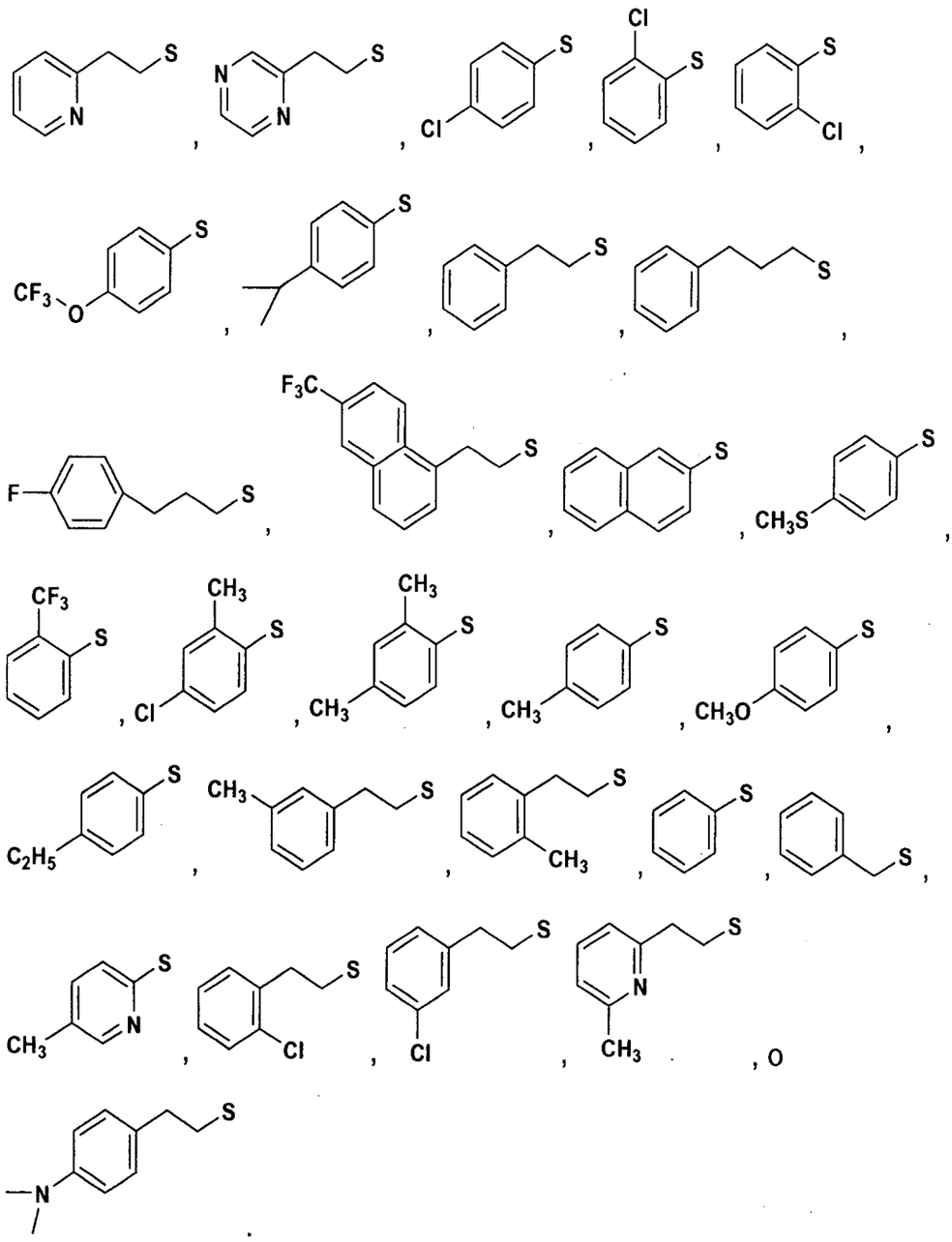
R^9 es H.

11. El compuesto de la reivindicación 7, en el que Z se selecciona entre el grupo constituido por fenilo, naftilo, piridinilo, pirimidinilo, pirazinilo, bencimidazolilo y benzoxazolilo.

12. El compuesto de la reivindicación 7, en el que R^3 es alcoxi C_1-C_6 o alquilo C_{1-6}.

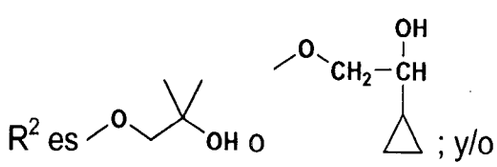
13. El compuesto de la reivindicación 7, en el que R^1 se selecciona entre el grupo constituido por:





14. El compuesto de la reivindicación 7, en el que

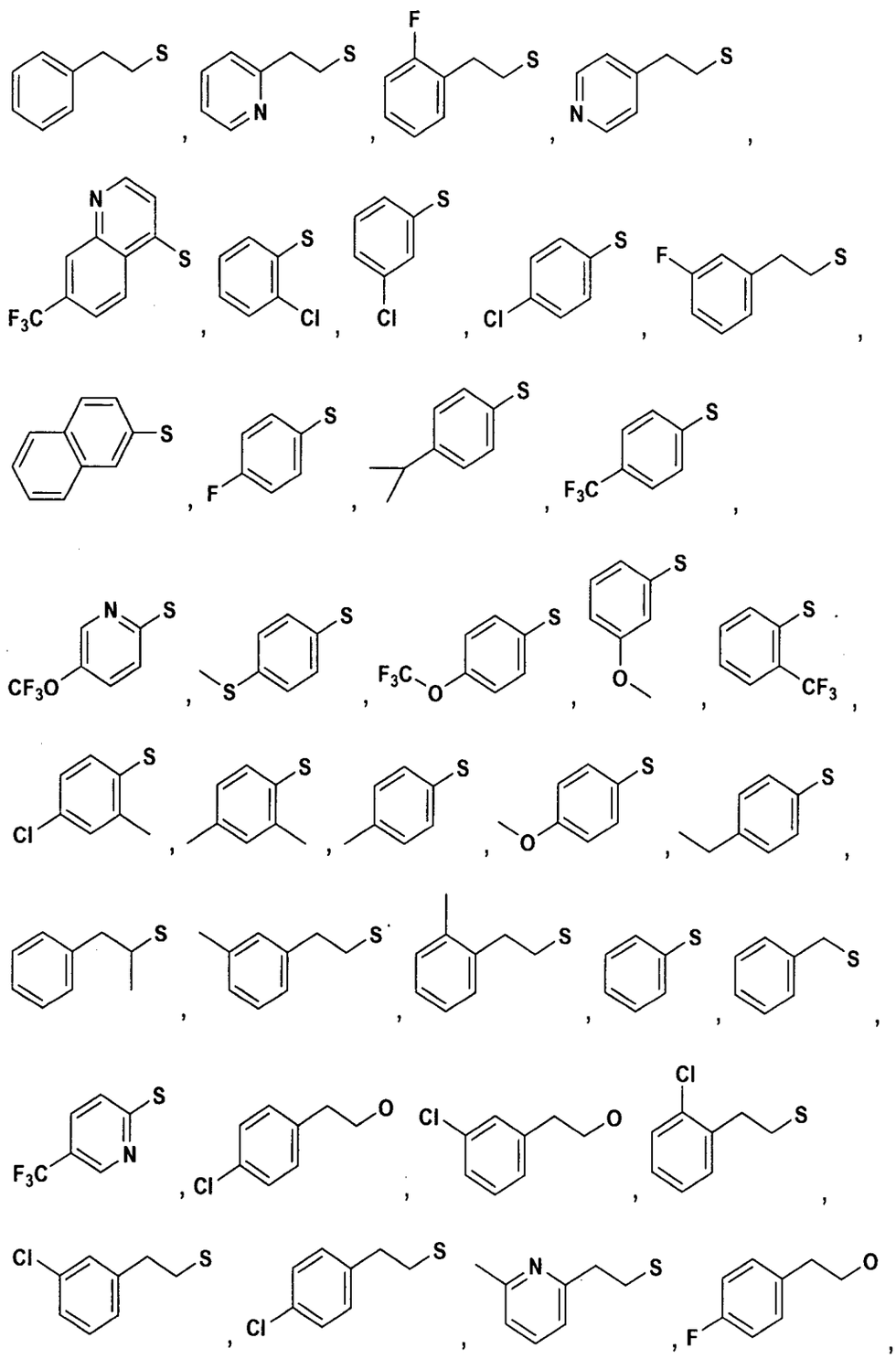
(A) es a fenileno; y/o

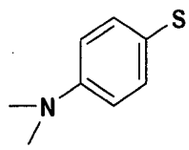
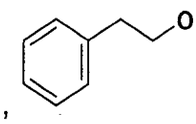
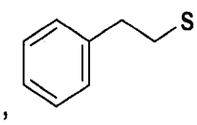
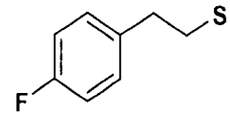
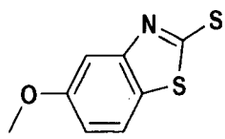
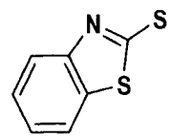
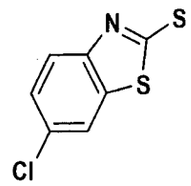
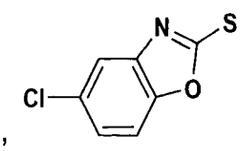


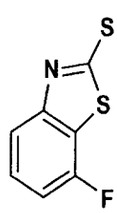
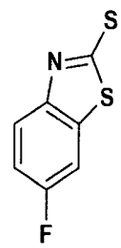
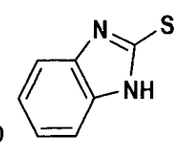
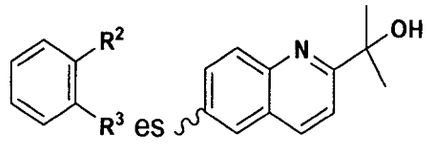
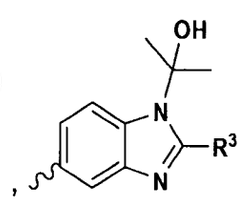
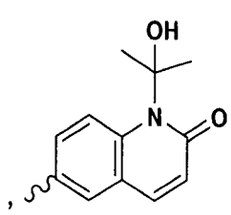
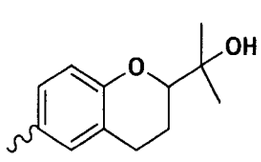
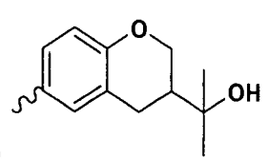
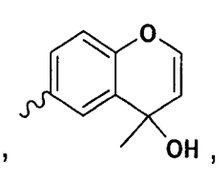
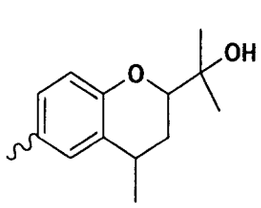
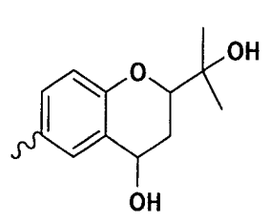
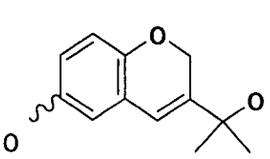
R^2 es o ; y/o

R^3 es metoxi o metilo;

R^1 se selecciona entre el grupo constituido por:



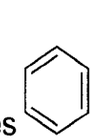
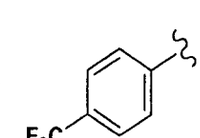
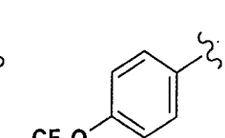
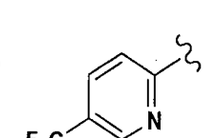









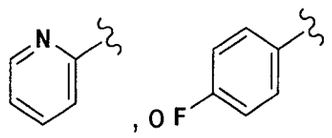













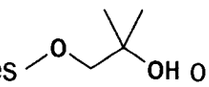
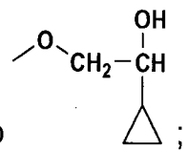
15. El compuesto que se ha definido en la reivindicación 7, en el que

X es S;

Y es un enlace o $(CH_2)_2$;

Z es 






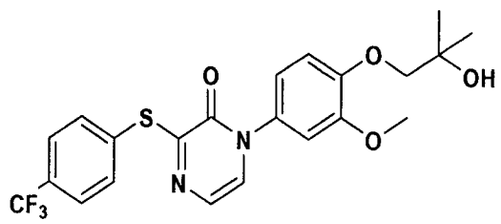
E-G-J es  o  ;

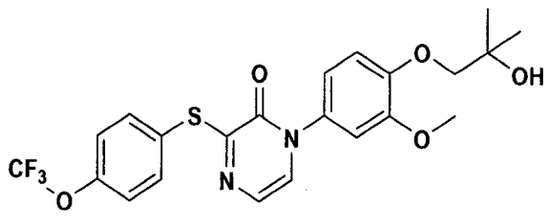
R^3 es CH_3O o CH_3;

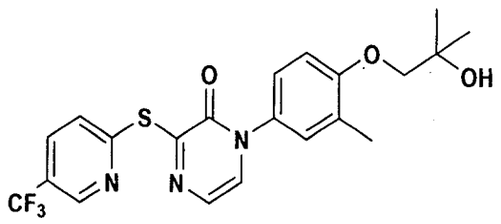
R^8 es H; y

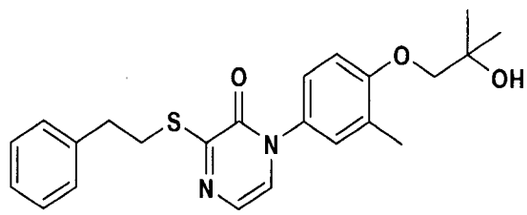
R^9 es H.

16. El compuesto que se ha definido en la reivindicación 1, que tiene la siguiente fórmula:

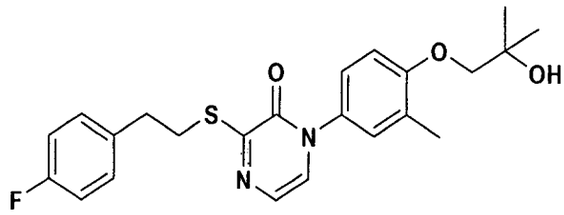
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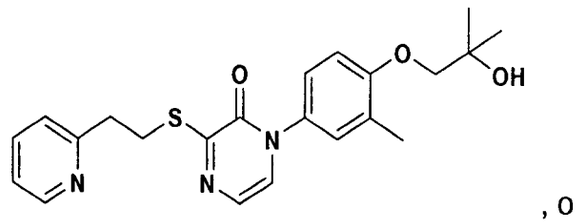
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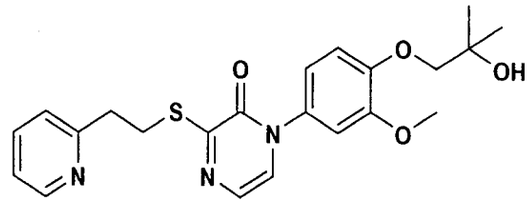
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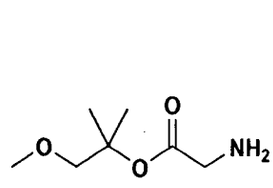


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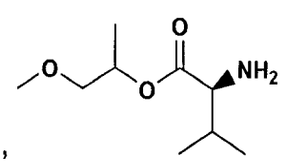


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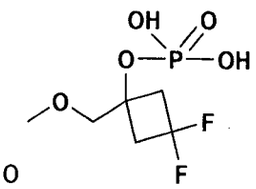
17. El compuesto de la reivindicación 1 en una forma de éster de profármaco, donde R^2 es



,

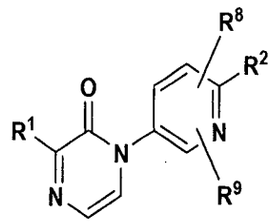


, o



.

18. Un compuesto de Fórmula IB o una sal farmacéuticamente aceptable del mismo, que tiene la estructura



IB

19. El compuesto que se ha definido en la reivindicación 18, en el que

R^1 es Z-Y-X- donde

X es S,

Y es una cadena alquilo de 1 a 3 carbonos o un enlace,

Z es heteroarilo o fenilo,

cada uno de Z está opcionalmente sustituido con CF_3, CF_3O o halo;

R^2 es -E-G-J, donde

E es O,

G es alquilo inferior o alquilcicloalquilo, y

J es OH;

R^3 es alcoxi, alquilo o halo;

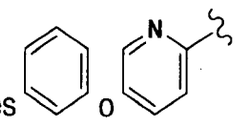
R^8 es H o alquilo; y

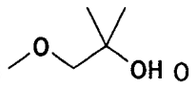
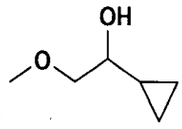
R^9 es H.

20. El compuesto que se ha definido en la reivindicación 18, en el que

X es S;

Y es un enlace o $(CH_2)_2$;

Z es  ;

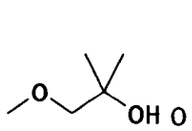
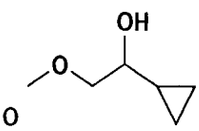
R^2 es E-G-J que es  o  ;

R^3 es H, Cl, CH_3, o CH_3O; y

cada uno de R^8 y R^9 es H.

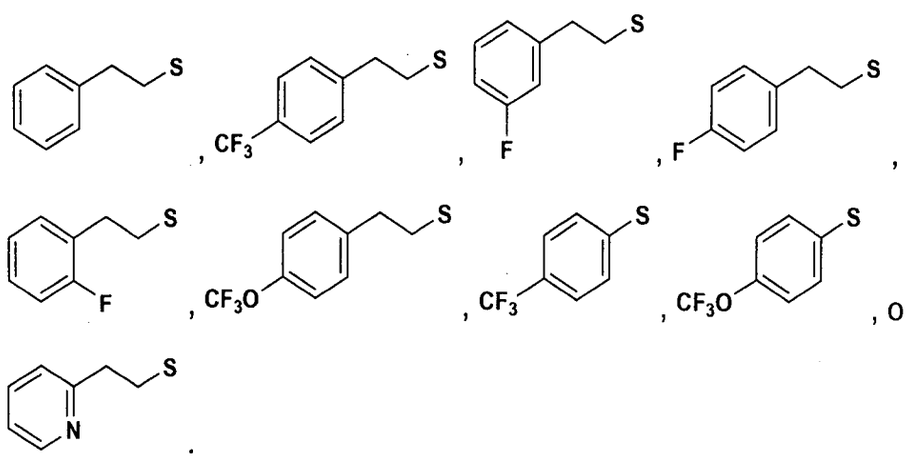
21. El compuesto de la reivindicación 1, en el que

(A) es un anillo heteroarilo;

R^2 es  o  ;

R^3 es metoxi, Cl, H o metilo; y

R^1 se selecciona entre el grupo constituido por:



22. Una composición farmacéutica que comprende una cantidad terapéuticamente eficaz de un compuesto que se ha definido en la reivindicación 1, solo o en combinación con al menos un agente terapéutico adicional, junto con un vehículo o diluyente farmacéuticamente aceptable.

23. Una combinación farmacéutica que comprende:
al menos un compuesto de acuerdo con la reivindicación 1 y
al menos un agente terapéutico adicional.

24. La combinación que se ha definido en la reivindicación 23, donde el agente terapéutico adicional es un inhibidor de acetil-colinasterasa, un agonista del receptor muscarínico 1, un agonista nicotínico, un modulador del receptor de ácido glutámico (AMPA y NMDA), un agente nootrópico, un agente para la enfermedad de Alzheimer, un agente para el tratamiento de la enfermedad de Parkinson, un agente hipolipidémico, un agente anti-obesidad; agente antidiabético, un supresor del apetito; agente hipocolesterolémico/hipolipidémico, agente de aumento de HDL, agente potenciador de la cognición, un agente usado para tratar neurodegeneración, un agente usado para tratar afecciones respiratorias, un agente usado para tratar trastornos intestinales, un agente antiinflamatorio; un agente ansiolítico; un antidepresivo; un agente antihipertensivo; un agente anti-trastorno del sueño; un glicósido cardiaco; o un agente antitumoral.

25. La combinación que se ha definido en la reivindicación 24, donde el agente antiobesidad es un agonista del receptor de melanocortina (MC4R), un modulador del receptor de cannabinoides, un antagonista del receptor de secretagogos de la hormona del crecimiento (GHSR), un modulador del receptor de galanina, un antagonista de orexina, un agonista de CCK, un agonista de GLP-1, un péptido obtenidos a partir de Pre-proglucagón; un antagonista de NPY1 o NPY5, un modulador de NPY2 o NPY4, un agonista del

factor de liberación de corticotropina, un modulador del receptor 3 de histamina (H3), un inhibidor de aP2, un modulador de PPAR gamma, un modulador de PPAR delta, un inhibidor de acetil-CoA carboxilasa (ACC), un inhibidor de 11-β-HSD-1, un modulador del receptor de adinopectina; un agonista beta 3 adrenérgico, un modulador del receptor beta tiroideo, un inhibidor de lipasa, un agonista del receptor de serotonina, un agente inhibidor de la recaptación o liberador de monoamina, un agente anoréctico, un CNTF (factor neurotrófico ciliar), un BDNF (factor neurotrófico derivado del cerebro), un modulador de leptina y del receptor de leptina, o un antagonista del receptor de cannabinoide 1, y el agente antidiabético es un secretagogo de insulina o un sensibilizador a insulina, que es una biguanida, una sulfonil urea, un inhibidor de glucosidasa, un inhibidor de aldosa reductasa, un agonista de PPAR γ, un agonista de PPAR α, un antagonista o agonista de PPAR δ, un agonista dual de PPAR α/γ, un inhibidor de 11-β-HSD-1, un inhibidor de dipeptidil peptidasa IV (DP4), un inhibidor de SGLT2, un inhibidor de glicógeno fosforilasa, una meglitinida, un péptido similar a glucagón de tipo 1 (GLP-1), un agonista de GLP-1 y/o un inhibidor de PTP-1B (inhibidor de la proteína tirosina fosfatasa-1B), y donde el agente terapéutico adicional es un agente hipolipidémico, o un agente usado para tratar arteriosclerosis, que es un inhibidor de HMG CoA reductasa, un inhibidor de escualeno sintetasa, un derivado de ácido fíbrico, aspirina, un secuestrante de ácidos biliares, un inhibidor de ACAT, un regulador positivo de la actividad del receptor de LDL, un inhibidor de la absorción de colesterol, un inhibidor de la proteína de transferencia de colesterilo (CETP), un inhibidor del cotransportador ileal de Na+/ácidos biliares, un fitoestrógeno, un inhibidor de la absorción de colesterol de beta-lactama, un regulador positivo de HDL, un

agonista de PPAR α y/o un agonista de FXR; un promotor del catabolismo de LDL, tal como un inhibidor del intercambio de sodio-protones, un inductor del receptor de LDL o un glicósido esteroideo, un anti-oxidante, o un agente antihomocisteína, isoniazid, un inhibidor de HMG-CoA sintasa, o un inhibidor de lanosterol desmetilasa, un agonista de PPAR δ, o una proteína de unión al elemento regulador de esterol I (SREBP-1), y el agente anti-hipertensivo, que es un bloqueante beta adrenérgico, un bloqueante del canal de calcio (tipo L y/o tipo T), un diurético, un inhibidor de renina, un inhibidor de ACE, un antagonista del receptor de AT-1, un antagonista del receptor de ET, un antagonista dual de ET/AII, un inhibidor de endopeptidasa neutra (NEP), un inhibidor de vasopeptidasa (inhibidor dual de NEP-ACE) o un nitrato; el agente para el trastorno del sueño es un análogo de melatonina, un antagonista del receptor de melatonina, un agonista de ML 1 B, un modulador del receptor de GABA, un modulador del receptor de NMDA, un modulador del receptor de histamina 3 (H3), un agonista de dopamina o un modulador del receptor de orexina; un agente para tratar el abuso de sustancias o trastornos adictivos que es un modulador del receptor de cannabinoides, un inhibidor selectivo de la recaptación de serotonina (SSRI), metadona, buprenorfina, nicotina o bupropión; los agentes ansiolíticos o antidepresivos, que es una benzodiazepina, un agonista del receptor 5HT1A, o un antagonista del factor de liberación de corticotropina (CRF); o un inhibidor de la recaptación de norepinefrina (aminas tricíclicas terciarias y secundarias), un inhibidor selectivo de la recaptación de serotonina (SSRI), un inhibidor de monoamina oxidasa (IMAO), un inhibidor reversible de monoamina oxidasa (RIMA), un inhibidor de la recaptación de serotonina y norepinefrina (SNRI), un antagonista del

receptor del factor de liberación de corticotropina (CRF), un antagonista del receptor alfa-adrenérgico, o un antidepresivo atípico.

26. Un procedimiento para tratar obesidad, diabetes, arteriosclerosis, hipertensión, enfermedad de ovario poliquístico, enfermedad cardiovascular, osteoartritis, trastornos dermatológicos, hemostasis de glucosa alterada, resistencia a insulina, hipercolesterolemia, hipertrigliceridemia, colelitiasis, dislipidemia, bulimia nerviosa y trastornos compulsivos de la alimentación; trastornos del sueño; y trastornos psiquiátricos, depresión, ansiedad, esquizofrenia, abuso de sustancias, mejora de la cognición o enfermedad de Parkinson, que comprende administrar a un paciente que necesita tratamiento un compuesto que se ha definido en la reivindicación 1.

27. El procedimiento que se ha definido en la reivindicación 26 para tratar la obesidad o la diabetes tipo II.

28. Un procedimiento para tratar la diabetes tipo II, que comprende administrar a un paciente que necesita tratamiento un compuesto que se ha definido en la reivindicación 1.

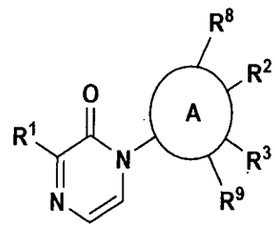
29. Uso de un compuesto que se ha definido en la reivindicación 1 en la preparación de un medicamento para el tratamiento de la diabetes.

30. Uso de un compuesto que se ha definido en la reivindicación 1 en la preparación de un medicamento para el tratamiento de la diabetes, donde

ANTAGONISTAS NO BÁSICOS DEL RECEPTOR DE LA HORMONA CONCENTRADORA DE MELANINA 1 Y PROCEDIMIENTOS

RESUMEN DE LA DESCRIPCIÓN

La presente solicitud proporciona compuestos, incluyendo todos los estereoisómeros, solvatos, profármacos y formas farmacéuticamente aceptables de los mismos de acuerdo con la Fórmula I



I

en la que (A) , R^1, R^2, R^3, R^8, y R^9 se definen en la presente memoria.

Además, la presente solicitud proporciona composiciones farmacéuticas que contienen al menos un compuesto de acuerdo con la Fórmula I y opcionalmente al menos un agente terapéutico adicional. Finalmente, la presente solicitud proporciona procedimientos para tratar a un paciente que padece de una enfermedad o trastorno modulado por MCHR-1 tal como, por ejemplo, obesidad, diabetes, depresión o ansiedad, mediante la administración de una dosis terapéuticamente eficaz de un compuesto de acuerdo con la Fórmula I.

10899-WO-PCT

PATENT COOPERATION TREATY

From the
INTERNATIONAL PRELIMINARY EXAMINING AUTHORITY

To:

Bristol-Myers Squibb Pharma Company
Patent Department
P.O. Box 4000
Princeton NJ 08543-4000
ETATS-UNIS D'AMERIQUE

NOV 13 2009

Docketed Date IPRP

PCT

NOTIFICATION OF TRANSMITTAL OF THE INTERNATIONAL PRELIMINARY REPORT ON PATENTABILITY

(PCT Rule 71.1)

Date of mailing *(day/month/year)*	05.11.2009
Applicant's or agent's file reference: 10899 PCT Attorney M. Gibbons	**IMPORTANT NOTIFICATION**

International application No.	International filing date *(day/month/year)*	Priority date *(day/month/year)*
PCT/US2008/069361	07.07.2008	06.07.2007

Applicant
Bristol-Myers Squibb Company

1. The applicant is hereby notified that this International Preliminary Examining Authority transmits herewith the international preliminary report on patentability and its annexes, if any, established on the international application.

2. A copy of the report and its annexes, if any, is being transmitted to the International Bureau for communication to all the elected Offices.

3. Where required by any of the elected Offices, the International Bureau will prepare an English translation of the report (but not of any annexes) and will transmit such translation to those Offices.

4. **REMINDER**

The applicant must enter the national phase before each elected Office by performing certain acts (filing translations and paying national fees) within 30 months from the priority date (or later in some Offices) (Article 39(1)) (see also the reminder sent by the International Bureau with Form PCT/IB/301).

Where a translation of the international application must be furnished to an elected Office, that translation must contain a translation of any annexes to the international preliminary report on patentability. It is the applicant's responsibility to prepare and furnish such translation directly to each elected Office concerned.

For further details on the applicable time limits and requirements of the elected Offices, see Volume II of the PCT Applicant's Guide.

The applicant's attention is drawn to Article 33(5), which provides that the criteria of novelty, inventive step and industrial applicability described in Article 33(2) to (4) merely serve the purposes of international preliminary examination and that "any Contracting State may apply additional or different criteria for the purposes of deciding whether, in that State, the claimed inventions is patentable or not" (see also Article 27(5)). Such additional criteria may relate, for example, to exemptions from patentability, requirements for enabling disclosure, clarity and support for the claims.

Name and mailing address of the international preliminary examining authority:	Authorized Officer
European Patent Office Gitschiner Str. 103 D-10958 Berlin Tel. +49 30 25901 - 0 Fax: +49 30 25901 - 840	Geier, Adolf Tel. +49 30 25901-706

Form PCT/IPEA/416 (January 2004)

PATENT COOPERATION TREATY

PCT

INTERNATIONAL PRELIMINARY REPORT ON PATENTABILITY

(Chapter II of the Patent Cooperation Treaty)

(PCT Article 36 and Rule 70)

Applicant's or agent's file reference 10899 PCT	**FOR FURTHER ACTION**	See Form PCT/IPEA/416
International application No. PCT/US2008/069361	International filing date *(day/month/year)* 07.07.2008	Priority date *(day/month/year)* 06.07.2007
International Patent Classification (IPC) or national classification and IPC INV. C07D241/18		
Applicant Bristol-Myers Squibb Company		

1. This report is the international preliminary examination report, established by this International Preliminary Examining Authority under Article 35 and transmitted to the applicant according to Article 36.
2. This REPORT consists of a total of 8 sheets, including this cover sheet.
3. This report is also accompanied by ANNEXES, comprising:
   a. ☒ *sent to the applicant and to the International Bureau)* a total of 37 sheets, as follows:
      ☒ sheets of the description, claims and/or drawings which have been amended and are the basis of this report and/or sheets containing rectifications authorized by this Authority (see Rule 70.16 and Section 607 of the Administrative Instructions).
      ☒ sheets which supersede earlier sheets, but which this Authority considers contain an amendment that goes beyond the disclosure in the international application as filed, as indicated in item 4 of Box No. I and the Supplemental Box.
   b. ☐ *(sent to the International Bureau only)* a total of (indicate type and number of electronic carrier(s)) , containing a sequence listing and/or tables related thereto, in electronic form only, as indicated in the Supplemental Box Relating to Sequence Listing (see Section 802 of the Administrative Instructions).

4. This report contains indications relating to the following items:

☒	Box No. I	Basis of the report
☐	Box No. II	Priority
☐	Box No. III	Non-establishment of opinion with regard to novelty, inventive step and industrial applicability
☒	Box No. IV	Lack of unity of invention
☒	Box No. V	Reasoned statement under Article 35(2) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement
☒	Box No. VI	Certain documents cited
☐	Box No. VII	Certain defects in the international application
☒	Box No. VIII	Certain observations on the international application

Date of submission of the demand	Date of completion of this report
2009-05-13	05.11.2009
Name and mailing address of the international preliminary examining authority: European Patent Office Gitschiner Str. 103 D-10958 Berlin Tel. +49 30 25901 - 0 Fax: +49 30 25901 - 840	Authorized officer Hoepfner, Wolfgang Telephone No. +49 30 25901-337

INTERNATIONAL PRELIMINARY REPORT ON PATENTABILITY

International application No.
PCT/US2008/069361

Box No. I Basis of the report

1. With regard to the **language**, this report is based on

☒ the international application in the language in which it was filed

☐ a translation of the international application into , which is the language of a translation furnished for the purposes of:
- ☐ international search (under Rules 12.3(a) and 23.1(b))
- ☐ publication of the international application (under Rule 12.4(a))
- ☐ international preliminary examination (under Rules 55.2(a) and/or 55.3(a))

2. With regard to the **elements*** of the international application, this report is based on *(replacement sheets which have been furnished to the receiving Office in response to an invitation under Article 14 are referred to in this report as "originally filed" and are not annexed to this report)*:

Description, Pages

1-113 as originally filed

Claims, Numbers

1, 6, 8-10, 12, 18-23, 29-30, 32 filed with telefax on 13-05-2009

☐ a sequence listing and/or any related table(s) - see Supplemental Box Relating to Sequence Listing

3. ☒ The amendments have resulted in the cancellation of:
- ☐ the description, pages
- ☒ the claims, Nos. 2-5, 7,11,13-17,24-28,31
- ☐ the drawings, sheets/figs
- ☐ the sequence listing *(specify)*:
- ☐ any table(s) related to sequence listing *(specify)*:

4. ☒ This report has been established as if (some of) the amendments annexed to this report and listed below had not been made, since they have been considered to go beyond the disclosure as filed, as indicated in the Supplemental Box (Rule 70.2(c)).
- ☐ the description, pages
- ☒ the claims, Nos. 1
- ☐ the drawings, sheets/figs
- ☐ the sequence listing *(specify)*:
- ☐ any table(s) related to sequence listing *(specify)*:

5. ☐ This opinion has been established taking into account the **rectification of an obvious mistake** authorized by or notified to this Authority under Rule 91 (Rule 70.2 (e)).

6. ☐ Supplementary international search report(s) from Authority(ies) have been received and taken into account in drawing up this report (Rule 45bis.8(b) and (c)).

Box No. IV Lack of unity of invention

1. ☐ In response to the invitation to restrict or pay additional fees, the applicant has, within the applicable time limit:

   ☐ restricted the claims.

   ☐ paid additional fees.

   ☐ paid additional fees under protest and, where applicable, the protest fee.

   ☐ paid additional fees under protest but the applicable protest fee was not paid.

   ☐ neither restricted the claims nor paid additional fees.

2. ☒ This Authority found that the requirement of unity of invention is not complied with and chose, according to Rule 68.1, not to invite the applicant to restrict or pay additional fees.

3. This Authority considers that the requirement of unity of invention in accordance with Rules 13.1, 13.2 and 13.3 is:

   ☐ complied with.

   ☒ not complied with for the following reasons:

   see separate sheet

4. Consequently, this report has been established in respect of the following parts of the international application:

   ☒ all parts.

   ☐ the parts relating to claims Nos. .

Box No. V Reasoned statement under Article 35(2) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement

1. Statement

Novelty (N)	Yes:	Claims	6, 8, 18-23, 29-30, 32
	No:	Claims	1, 9-10, 12
Inventive step (IS)	Yes:	Claims	6, 8, 18-23, 29-30, 32
	No:	Claims	1, 9-10, 12
Industrial applicability (IA)	Yes:	Claims	1, 6, 8-10, 12, 18-23, 29-30, 32
	No:	Claims	

2. Citations and explanations (Rule 70.7):

   see separate sheet

INTERNATIONAL PRELIMINARY REPORT ON PATENTABILITY

International application No.
PCT/US2008/069361

Box No. VI Certain documents cited

1. Certain published documents (Rule 70.10)

   and / or

2. Non-written disclosures (Rule 70.9)

   see separate sheet

Box No. VIII Certain observations on the international application

The following observations on the clarity of the claims, description, and drawings or on the question whether the claims are fully supported by the description, are made:

see separate sheet

Re Item IV

Lack of unity of invention

The international patent application WO-A-2007071646, hereinafter referred to as D10, discloses pyrazinone derivatives and and their medical use (see paragraph "novelty" below). These compounds have in common the same structural feature as the compounds of Formula (I) of claim 1, namely a central pyrazinone moiety which is attached to two further optionally substituted (hetero)aromatic systems by means of suitable spacers.

Hence, the distinguishing feature between the said compounds of Formula (I) and the said compounds of D10 has to be seen as the particular kind of variable "J", which is an equivalent of variable "X" of the compounds of Formula (I) of D10, namely

- hydrogen or lower alkyl;
- optionally substituted oxygen;
- a carboxylic group or a derivative thereof; or
- a sulfur-containing group.

However, with the presence of four different distinguishing features and with the umbrella of any common structural feature being lost, the subject - matter of claim 1 can no longer be regarded as being unitary within the meaning of Rule 13 PCT and is therefore split into four different inventions (non-unity *a posteriori*), the said inventions being as follows:

Provision of a compound of Formula (I) and its medical use, wherein variable "J" is selected from

- hydrogen or lower alkyl (invention #1);
- optionally substituted oxygen (invention #2);
- a carboxylic group or a derivative thereof (invention #3); or
- a sulfur-containing group (invention #4).

Re Item V

Reasoned statement with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement

Reference is made to the following document/s/:

D1 DATABASE REGISTRY CHEMICAL ABSTRACTS SERVICE, COLUMBUS, OHIO, US; 17 July 2006 (2006-07-17) , XP002511730

D2 DATABASE REGISTRY CHEMICAL ABSTRACTS SERVICE, COLUMBUS, OHIO, US; 23 July 2006 (2006-07-23) , XP002511731

D3 DATABASE REGISTRY CHEMICAL ABSTRACTS SERVICE, COLUMBUS, OHIO, US; 8 August 2006 (2006-08-08) , XP002511732

D4 DATABASE REGISTRY CHEMICAL ABSTRACTS SERVICE, COLUMBUS, OHIO, US; 9 August 2006 (2006-08-09) , XP002511733

D5 DATABASE REGISTRY CHEMICAL ABSTRACTS SERVICE, COLUMBUS, OHIO, US; 28 February 2007 (2007-02-28) , XP002511734

D6 DATABASE REGISTRY CHEMICAL ABSTRACTS SERVICE, COLUMBUS, OHIO, US; 24 April 2007 (2007-04-24) , XP002511735

D7 DATABASE REGISTRY CHEMICAL ABSTRACTS SERVICE, COLUMBUS, OHIO, US; 24 April 2007 (2007-04-24) , XP002511736

D8 DATABASE REGISTRY CHEMICAL ABSTRACTS SERVICE, COLUMBUS, OHIO, US; 26 April 2007 (2007-04-26) , XP002511737

D9 WO 2007/071646 A1 (JANSSEN PHARMACEUTICA NV [BE]; ANDRES-GIL JOSE IGNACIO [ES]; ALCAZAR-V) 28 June 2007 (2007-06-28)

Novelty

The document D4 (see abstract) discloses several chemical compounds which appear to take away novelty form the subject-matter of independent claim 1 and dependent claims 9, 10 and 12.

Inventive step

For any remaining novel subject-matter the document D9 may be deemed the closest prior art (see page 1, lines 5-8; page 3, Formula (I); page 24, lines 30, 32; page 25, lines 18, 19; Examples), since it addresses a very similar problem, namely the provision of compounds suitable for the treatment of metabolic disorders such as diabetes.

The distinguishing feature between such novel subject-matter and D9 could be the nature of variable "J", namely

- hydrogen or lower alkyl (invention #1);
- optionally substituted oxygen (invention #2);
- a carboxylic group or a derivative thereof (invention #3); or
- a sulfur-containing group (invention #4).

From the experimental data on file it appears to be credible that the said remaining novel subject-matter could be a solution to the above identified (*subjective*) problem (see description, page 2). However, since these data do not allow to decide, if the novel subject-matter gives rise to *unexpected* improvements when compared to the

compounds of D9, the *objective* problem underlying any remaining novel subject-matter could merely be seen as the provision of *further* compounds suitable for the treatment of metabolic disorders such as diabetes.

However, since the modification of the compounds of D9 by replacing the basic group "X" with

- hydrogen or lower alkyl (invention #1);
- optionally substituted oxygen (invention #2);
- a carboxylic group or a derivative thereof (invention #3); or
- a sulfur-containing group (invention #4)

as solution to such a very general problem was not derivable from any of the prior art on file, either read alone or in combination, and since it may be deemed surprising that of all things these modified compounds would likewise be useful medicaments, the presence of inventive step could have been acknowledged to any independent claim directed to one of these four inventions, even in the absence of comprehensible technical progress.

Re Item VI

Certain documents cited

Certain published documents

Application No Patent No	Publication date *(day/month/year)*	Filing date *(day/month/year)*	Priority date *(valid claim)* *(day/month/year)*
Database "Registry"	07/09/2007		

Re Item VIII

Certain observations on the international application

The subject-matter of claim 1 does not meet the requirements of Arts. 19(2) and 34(2)(b) PCT, since the phrase "optionally substituted" goes beyond the content of the description insofar as "phenyl" or "naphthyl" are concerned, since line 24 on page 8 of the description reads: ... "may be optionally substituted ... with 1, 2 or 3 groups selected from ...".

Likewise, "optionally substituted" implies possible substitution with ***any kind*** of substituent. However, the group of possible substituents referred to in the description is rather limited (see page 8, line 25 - page 9, line 8).

"Optionally substituted", however, implies that phenyl or naphthyl may be substituted with ***more than 3*** groups.

The following terms do not comply with the requirement of clarity (Art. 6 PCT): "lower" alkyl (see e.g. claim 1); "esters, "prodrugs" (see e.g. claim 1).

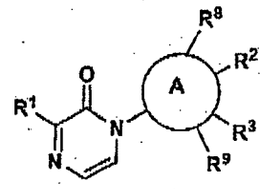
In claims 22 and 23, the therapeutic application is functionally defined by a mechanism of action which does not allow any practical application in the form of a defined, real treatment of a pathological condition (disease) (acetyl-cholinesterase inhibitor, muscarinic receptor-1 agonist and so on).

This objection could have been overcome by either introducing in the claims a list of pathological conditions (diseases) cited in the application, or by showing that means are available which would allow the skilled person to recognise which additional condition(s) would fall within the functional definition.

SUBSTITUTE SHEET

WHAT IS CLAIMED IS:

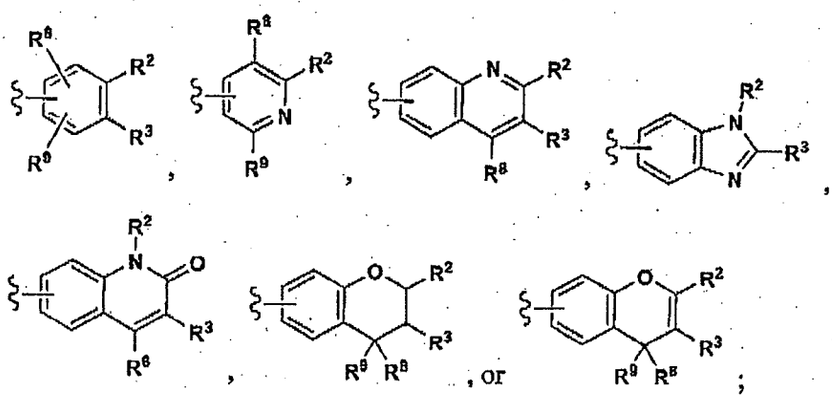
1. A compound of Formula I or a pharmaceutically acceptable salt thereof



I

wherein

(A) is



R^1 is Z-Y-X-, wherein

X is O, S,  , or  ;

Y is a bond, a 3- to 6-membered cycloalkyl, an alkylene chain; and

Z is optionally substituted phenyl or naphthyl, pyridinyl, pyrazinyl, pyrimidinyl, pyridinonyl, benzothiazolyl, benzoxalyl, benzimidazolyl, quinolinyl, thiazolyl, indanyl, imidazolinyl;

R^2 is -E-G-$(J)_m$, with m being an integer from 1 to 3;

E is O, S or a bond;

G is lower alkyl, phenylalkyl, cycloalkyl, cycloalkylalkyl, alkylcycloalkyl, cycloalkoxy, alkylcycloalkoxy, or cycloalkoxyalkyl, and

each J is independently hydrogen, hydroxyl, CN, $-SO_2R^7$, $-SR^7$, $-SOR^7$, lower alkyl, lower alkoxy, CF_3, CF_3O-, $-COOR^5$, or $-CO-NR^{5a}R^6$, wherein R^{5a} and R^6 are

AMENDED SHEET

Received at the EPO on May 13, 2009 17:13:41. Page 8 of 81

each independently selected from the group consisting of H, C_{1-3} alkyl, and cycloalkyl, or R^{5a} and R^6 taken together can be propanediyl, butanediyl or pentanediyl with the N atom to which they are attached to form a 4-, 5- or 6-membered cyclic amine which may be optionally substituted;

R^5 is H, C_{1-6} alkyl, or cycloalkyl;

R^7 is lower alkyl; and

R^3 is C_{1-6} alkyl, cycloalkyl ,C_{1-6} alkoxy, halogen, hydrogen, -S-C_{1-6} alkyl, CN, CF_3O, or CF_3;

with the proviso that where (A) is a phenylene group, E is O or S, and further providing that E-G and R^3 are not identical unsubstituted lower alkoxy groups, and when G is lower alkyl and J is H, R^3 is not hydrogen; and

R^8 and R^9 are each independently hydrogen, halogen, or lower alkyl;

including esters thereof, prodrugs thereof, solvates thereof, and all stereoisomers thereof.

2. Cancel.

3. Cancel.

4. Cancel.

5. Cancel.

6. The compound as defined in Claim 1 wherein

X is O or S;

R^1 is Z-Y-X-;

wherein Y is a bond or an alkylene chain of 1 to 3 atoms;

Z is phenyl, or pyridinyl, pyrazinyl, pyrimidinyl, pyridinonyl, benzothiazolyl, benzoxazolyl, benzimidazolyl, quinolinyl, thiazolyl, indanyl, or imidazolinyl;

R^2 is -E-G-J;

E is O or S;

G is an alkylene chain or alkylcycloalkyl;

J is H, OH, SO_2R^7, lower alkyl, lower alkoxy, or CF_3;

R^3 is C_{1-6} alkyl, C_{1-6} alkoxy, H, or halo;

R^8 is H or alkyl; and

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R^9 is H.

7. Cancel.

8. The compound as defined in Claim 1 wherein
R^1 is Z-Y-X-;
X is S;
Y is a bond or alkylene chain;
Z is phenyl or pyridyl;
E is O;
G is an alkylene chain or alkylcycloalkyl;
J is H or OH;
R^3 is H, alkoxy, alkyl, or halo;
R^8 is H or CH_3; and
R^9 is H.

9. The compound as defined in Claim 1 wherein
Z is phenyl, pyridinyl, pyrazinyl, pyrimidinyl, pyridinonyl, benzothiazolyl, benzoxazolyl, benzimidazolyl, quinolinyl, thiazolyl, indanyl, or imidazolinyl; any of which may either be unsubstituted or substituted with 1, 2 or 3 of amino, halo, C_{1-6} alkyl, C_{1-3} alkylamino, di-C_{1-3} alkylamino, C_{1-3} alkoxy, C_{1-3} thioalkyl, C_{1-3} trifluoroalkoxy, trifluoromethyl, cycloalkyl, cycloalkoxy, or heteroaryl; and
J is hydrogen, hydroxyl, CN, $-SO_2R^7$, $-SR^7$, $-SOR^7$, lower alkyl, lower alkoxy, CF_3, CF_3O-, $-COOR^5$, or $-CO-NR^{5a}R^6$, wherein R^{5a} and R^6 are each independently selected from the group consisting of H, C_{1-3} alkyl, and cycloalkyl, or R^{5a} and R^6 taken together can be propanediyl, butanediyl or pentanediyl with the N atom to which they are attached to form a 4-, 5- or 6-membered cyclic amine optionally substituted with lower alkyl, lower alkoxy, hydroxyl, CF_3, or CF_3O.

10. The compound of Claim 1 wherein:
Z is
(1) phenyl which is optionally substituted with:

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a) halogen,
b) alkyl,
c) alkoxy,
d) polyhaloalkyl,
e) polyhaloalkoxy,
f) amino, alkylamino or dialkylamino,
g) alkylthio,
h) OH,
i) an ester, or
j) aryl,

(2) heteroaryl which is:

a) pyridinyl,
b) pyrazinyl, or
c) pyrimidinyl,

each of a), b) or c) being optionally substituted with alkyl, polyhaloalkyl, alkoxy, or halogen,

(3) benzothiazolyl optionally substituted with halo or alkoxy,
(4) benzoxazolyl optionally substituted with halo,
(5) benzimidazolyl,
(6) thiazolyl optionally substituted with aryl or alkyl,
(7) indanyl,
(8) quinolinyl optionally substituted with CF_3, or
(9) imidazolidinyl;

Y is a bond or alkylene;

X is S, O, SO, or SO_2;

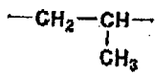
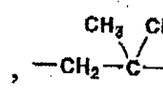
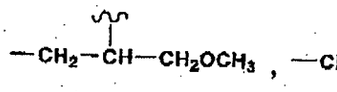
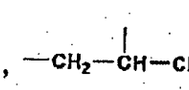
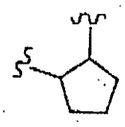
J is

(1) H,
(2) -CO-$NR^{5a}R^6$ wherein R^{5a} and R^6 together with the N to which they are attached form a pyrrolidinyl ring,
(3) OH,
(4) COOH,
(5) COOalkyl, or

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(6) SO_2R^7,

m is 1 or 2;

G is a bond or CH_2, $(CH_2)_2$, $(CH_2)_3$,  ,  ,  ,  , cycloalkyl which is  , or cycloalkoxy which is  ;

E is O;

R^3 is H, alkoxy, hydroxyalkyl, alkyl, halo, or hydroxyalkoxy;

R^8 is H, halo or alkyl; and

R^9 is H

or a prodrug ester of said compound selected from the group consisting of glycine prodrug esters, valine prodrug esters, and phosphate prodrug esters.

11. Cancel.

12. The compound of Claim 7, wherein R^3 is C_1-C_6 alkoxy or C_{1-6} alkyl.

13. Cancel.

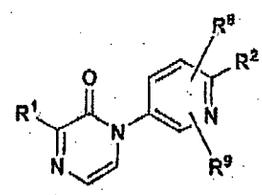
14. Cancel.

15. Cancel.

16. Cancel.

17. Cancel.

18. A compound of Formula IB or a pharmaceutically acceptable salt thereof having the structure



IB

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19. The compound as defined in Claim 18 wherein

R^1 is Z-Y-X- wherein

X is S,

Y is an alkyl chain of 1 to 3 carbons or a bond,

Z is pyridinyl, pyrazinyl, pyrimidinyl, pyridinonyl, benzothiazolyl, benzoxalyl, benzimidazolyl, quinolinyl, thiazolyl, indanyl, imidazolinyl or phenyl,

each of which Z is optionally substituted with CF_3, CF_3O, or halo;

R^2 is -E-G-J wherein

E is O,

G is lower alkyl or alkylcycloalkyl, and

J is OH;

R^3 is alkoxy, alkyl or halo;

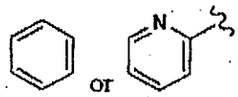
R^8 is H or alkyl; and

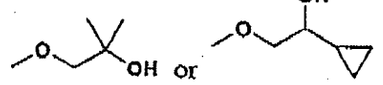
R^9 is H.

20. The compound as defined in Claim 18 wherein

X is S;

Y is a bond or $(CH_2)_2$;

Z is  ;

R^2 is E-G-J which is  ;

R^3 is H, Cl, CH_3, or CH_3O; and

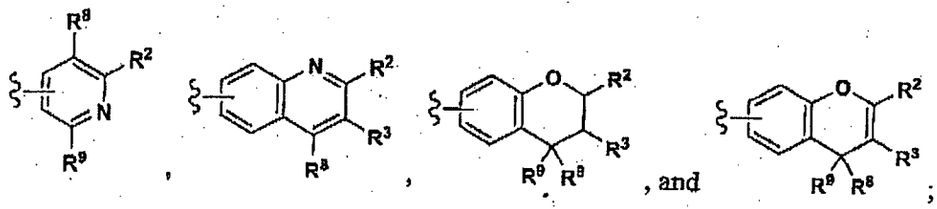
R^8 and R^9 are each H.

21. The compound of Claim 1 wherein

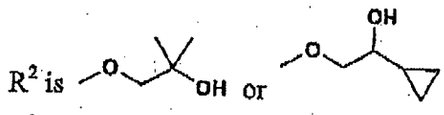
(A) is selected from the group consisting of;

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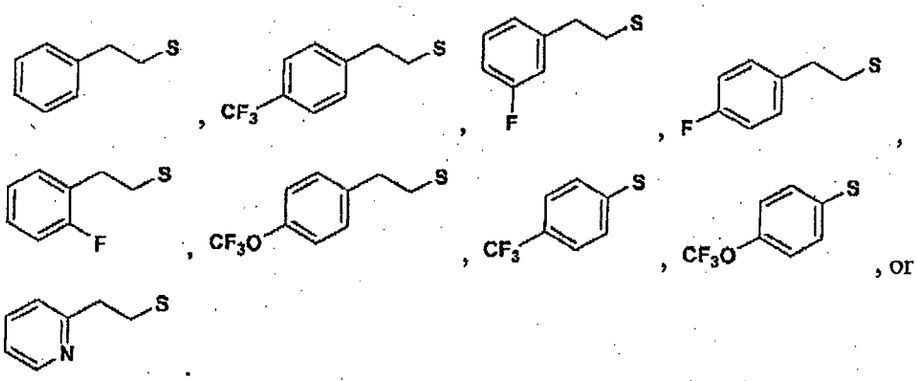
, and ;



;

R^3 is methoxy, Cl, H, or methyl; and

R^1 is selected from the group consisting of:



, or

.

22. A pharmaceutical composition comprising a therapeutically effective amount of a compound as defined in Claim 1, alone or in combination with at least one additional therapeutic agent, in association with a pharmaceutically acceptable carrier or diluent wherein said additional therapeutic agent is selected from the group consisting of an acetyl-cholinesterase inhibitor, a muscarinic receptor-1 agonist, a nicotinic agonist, a glutamic acid receptor (AMPA and NMDA) modulator, a nootropic agent, an agent for Alzheimer's disease, an agent for treatment of Parkinson's disease, anti-hyperlipidemia agent, an anti-obesity agent; anti-diabetic agent, appetite suppressant; cholesterol/lipid-lowering agent, HDL-raising agent, cognition enhancing agent, an agent used to treat neurodegeneration, an agent used to treat respiratory conditions, an agent used to treat bowel disorders, an anti-inflammatory agent; anti-anxiety agent; an anti-depressant; an anti-hypertensive agent; an anti-sleep disorder agent; a cardiac glycoside; and an anti-tumor agent.

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23. A pharmaceutical combination comprising: at least one compound according to claim 1, and at least one additional therapeutic agent selected from the group consisting of an acetyl-cholinesterase inhibitor, a muscarinic receptor-1 agonist, a nicotinic agonist, a glutamic acid receptor (AMPA and NMDA) modulator, a nootropic agent, an agent for Alzheimer's disease, an agent for treatment of Parkinson's disease, anti-hyperlipidemia agent, an anti-obesity agent; anti-diabetic agent, appetite suppressant; cholesterol/lipid-lowering agent, HDL-raising agent, cognition enhancing agent, an agent used to treat neurodegeneration, an agent used to treat respiratory conditions, an agent used to treat bowel disorders, an anti-inflammatory agent; anti-anxiety agent; an anti-depressant; an anti-hypertensive agent; an anti-sleep disorder agent; a cardiac glycoside; and an anti-tumor agent.

24. Cancel.

25. Cancel.

26. Cancel.

27. Cancel.

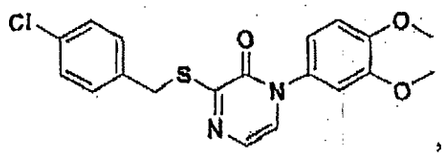
28. Cancel.

29. Use of a compound as defined in Claim 1 in the manufacture of a medicament for the treatment of obesity.

30. Use of a compound as defined in Claim 1 in the manufacture of a medicament for treatment of diabetes.

31. Cancel.

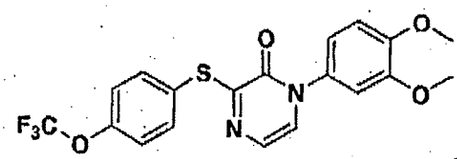
32. New. The compound according to claim 1 selected from the group consisting of:

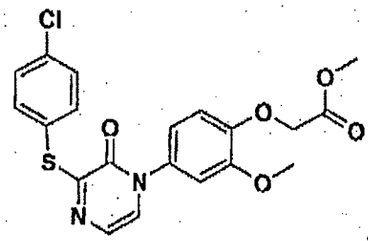


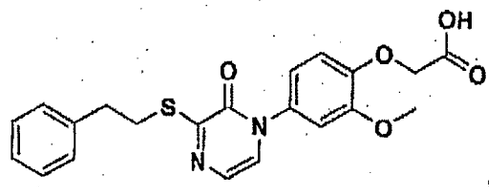
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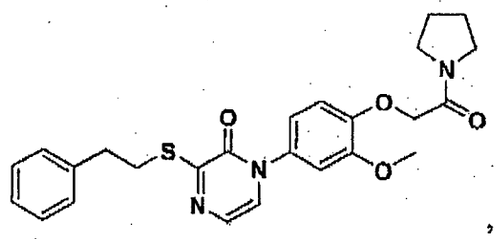
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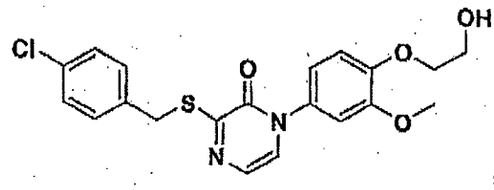
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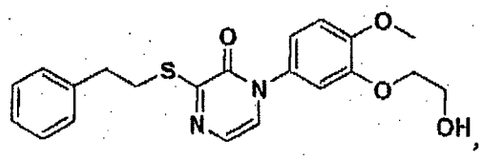


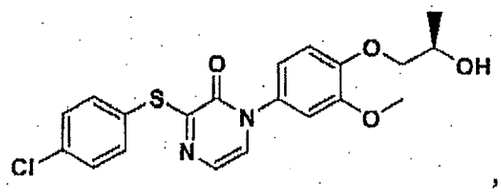






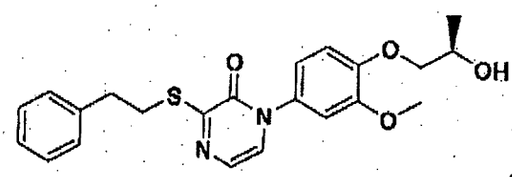


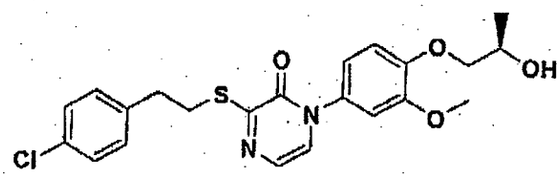


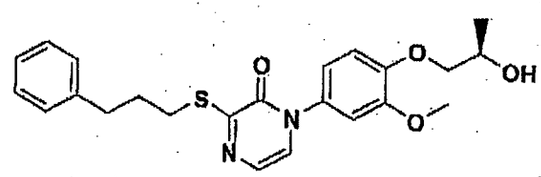


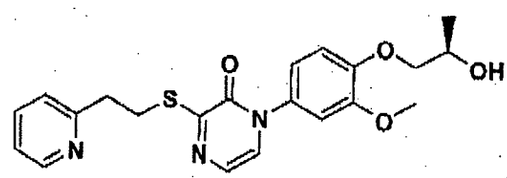
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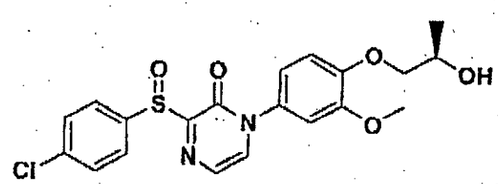
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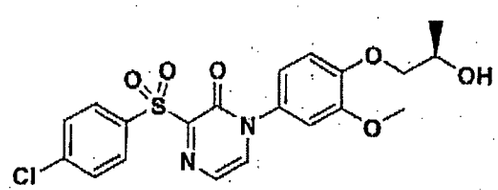

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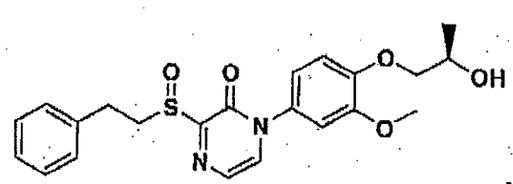

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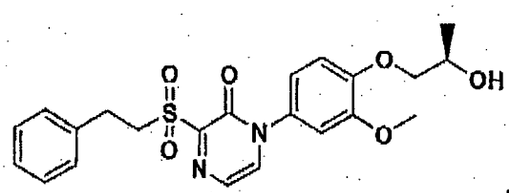

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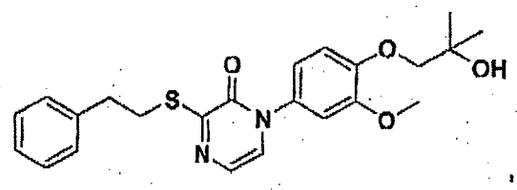

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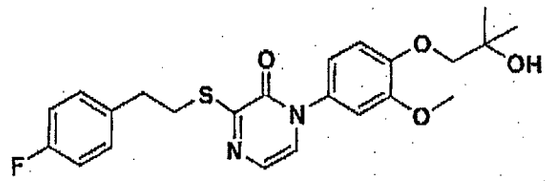

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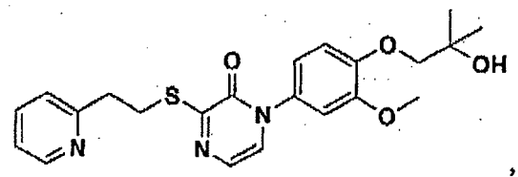

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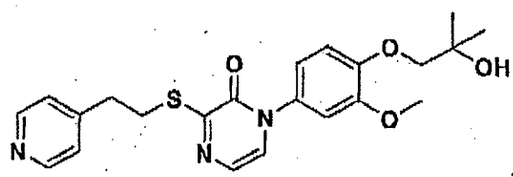

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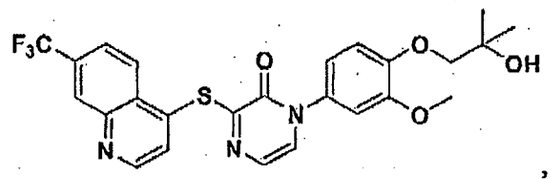
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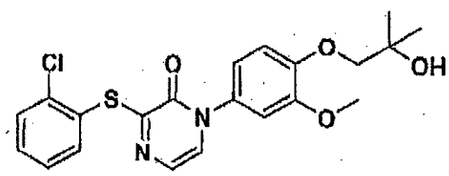


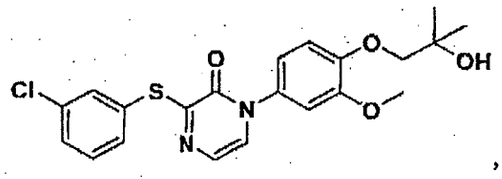


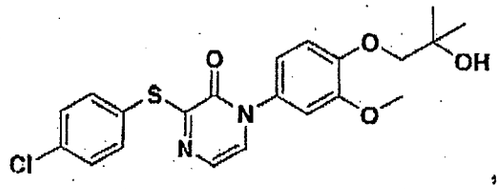






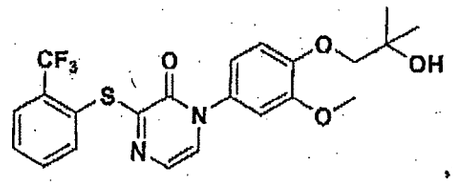


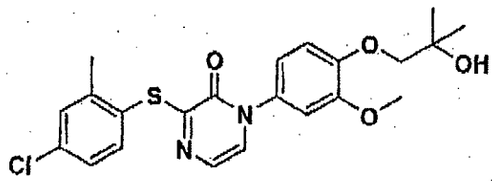


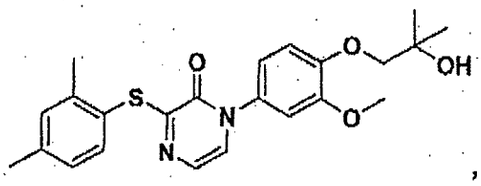


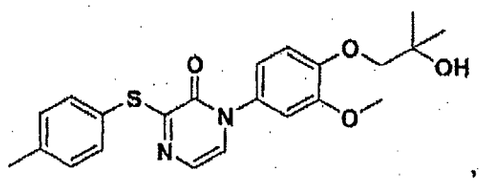
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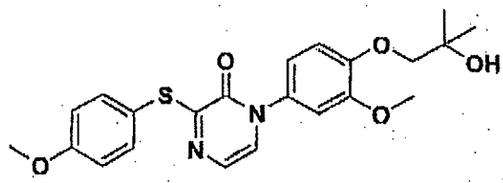
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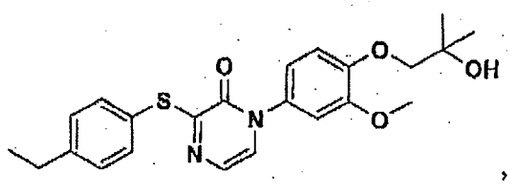


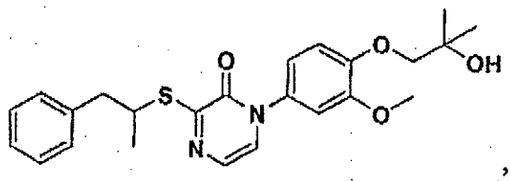


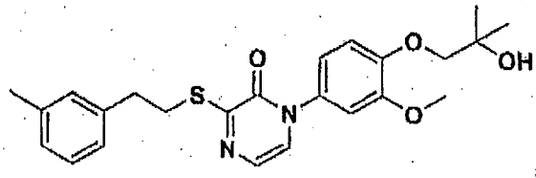








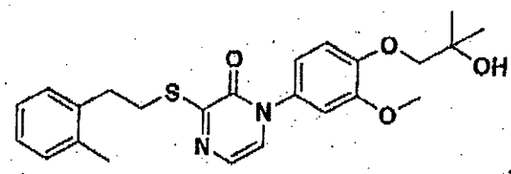


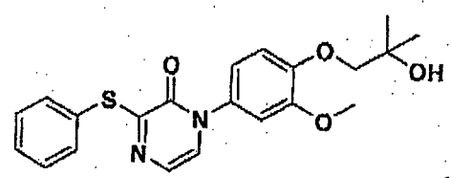


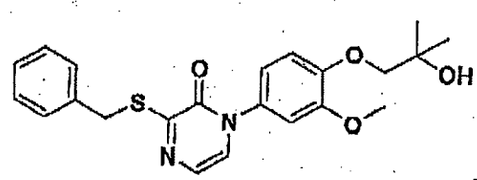
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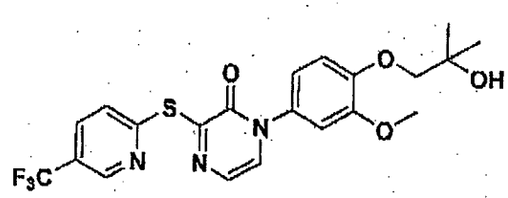
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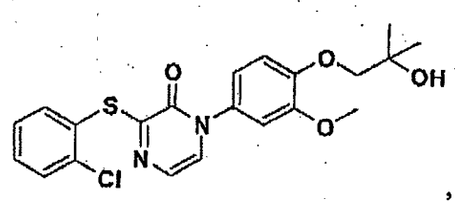
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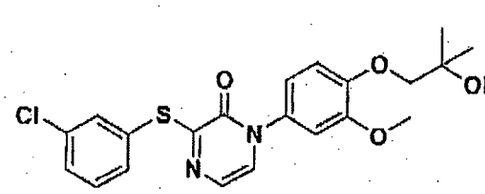


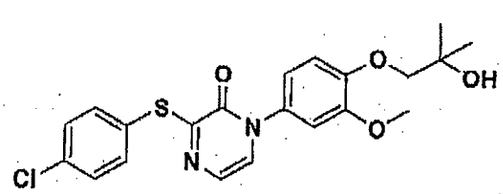






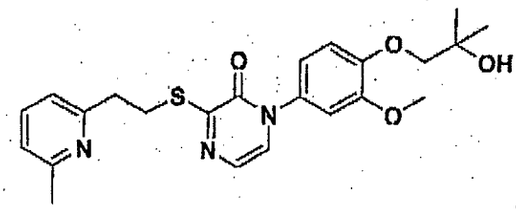




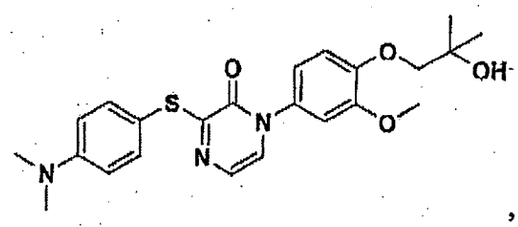


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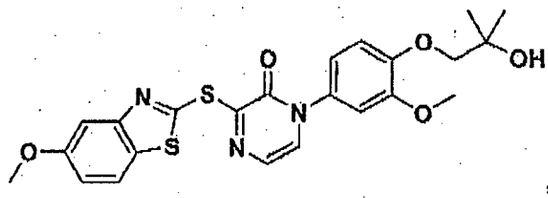
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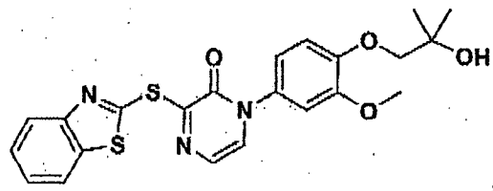
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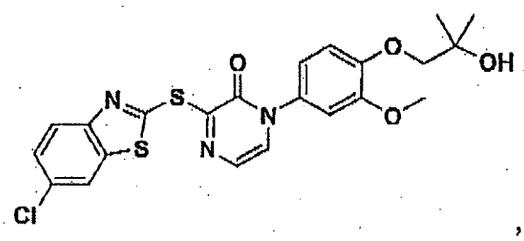
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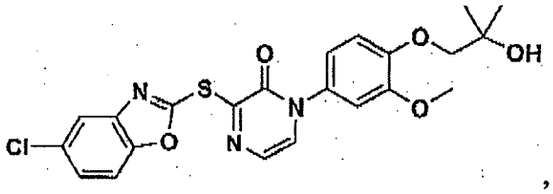
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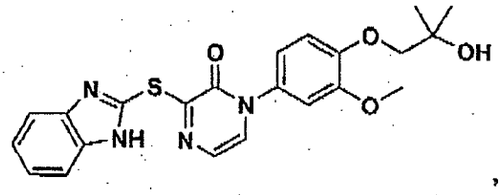
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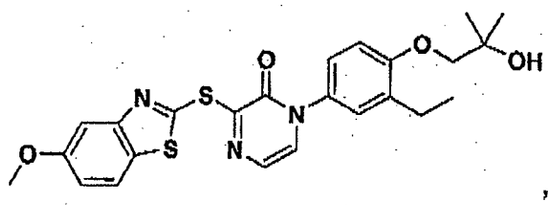


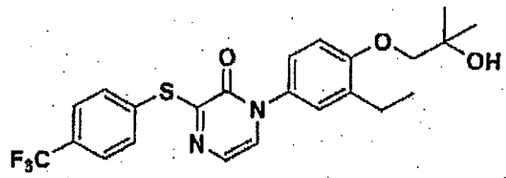
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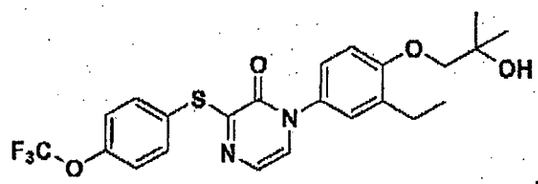
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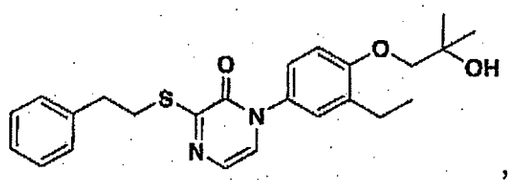
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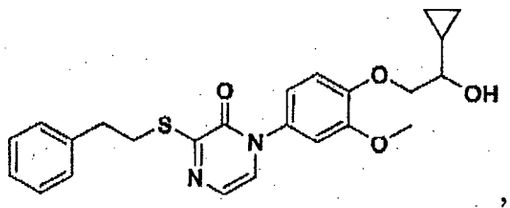
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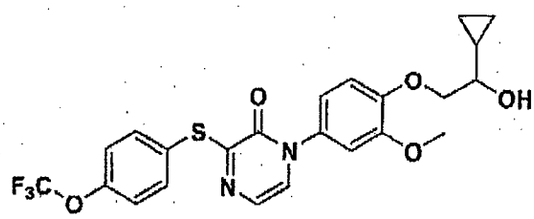

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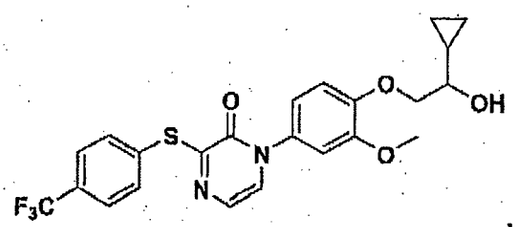

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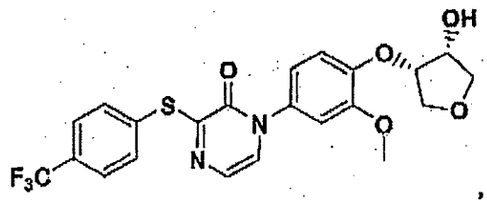

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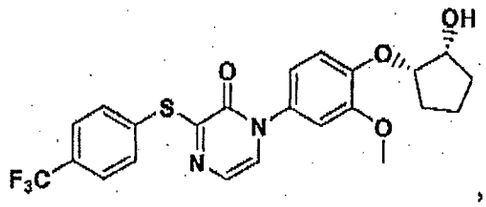

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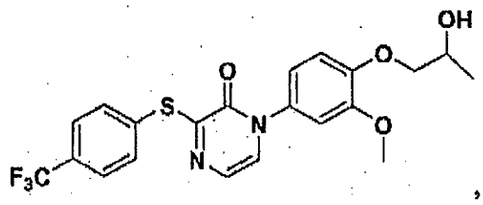
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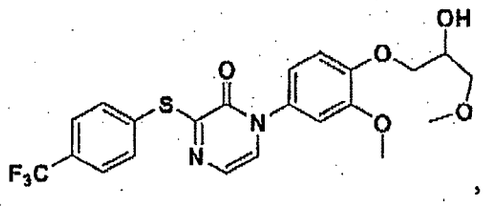
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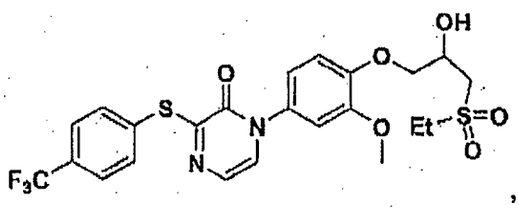
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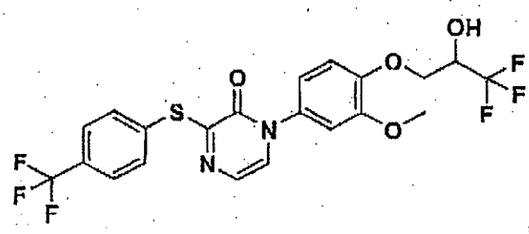
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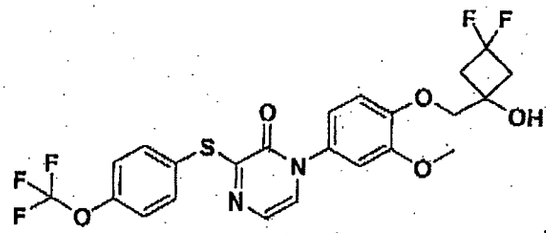
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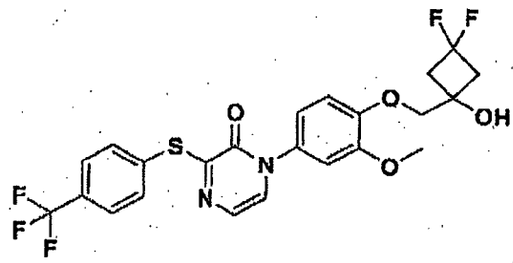
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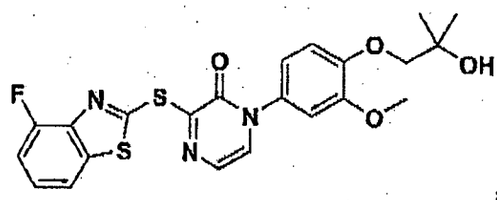
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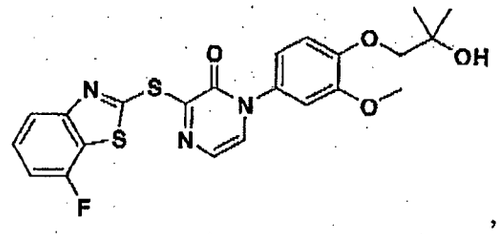
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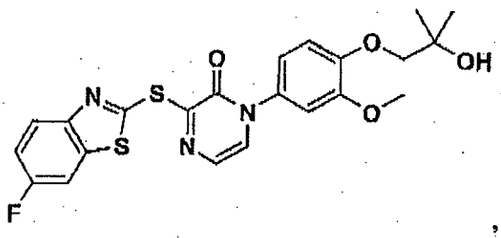
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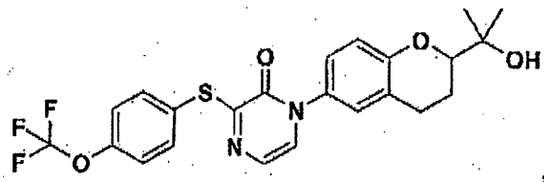
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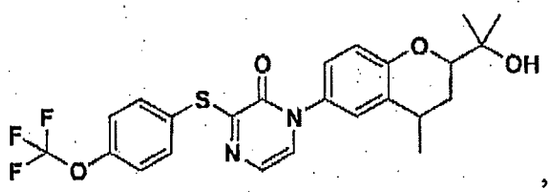


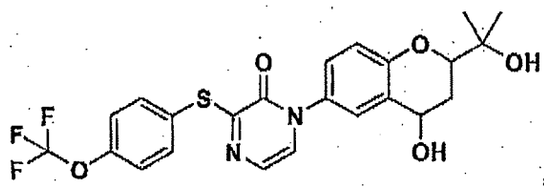
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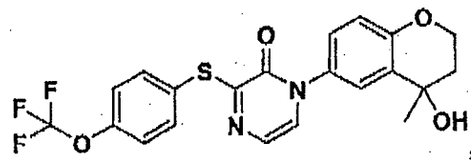


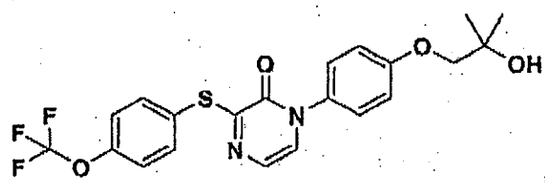
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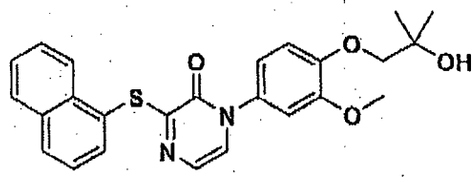
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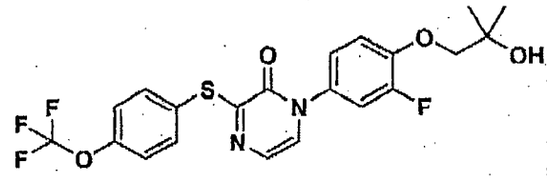

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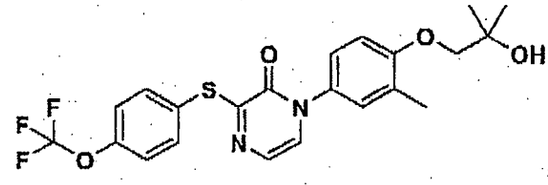

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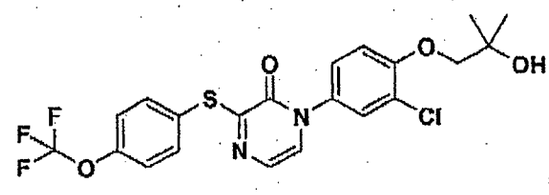

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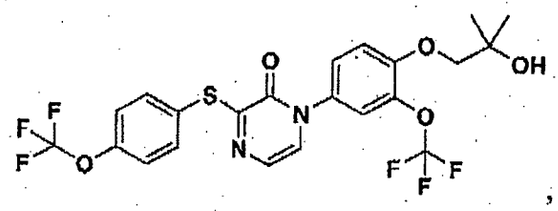

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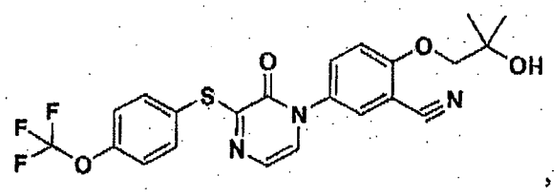

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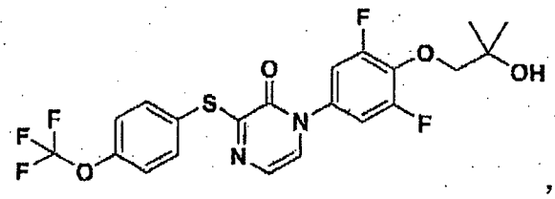

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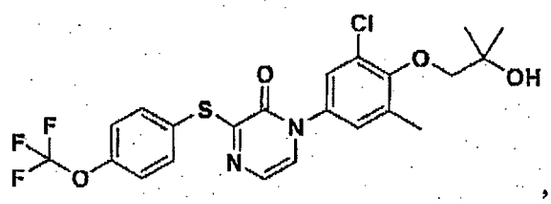
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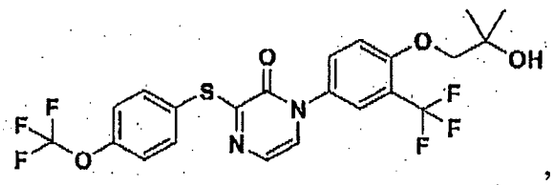
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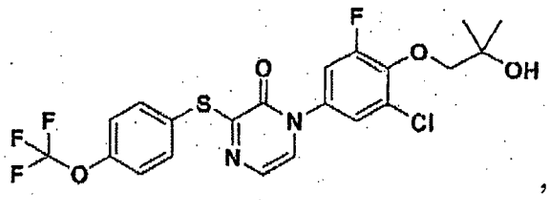

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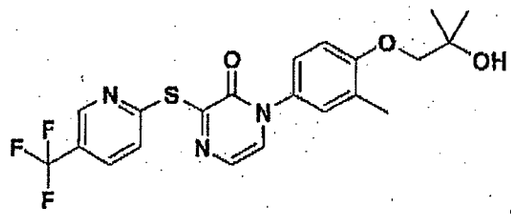

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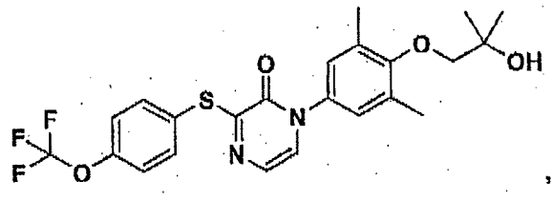

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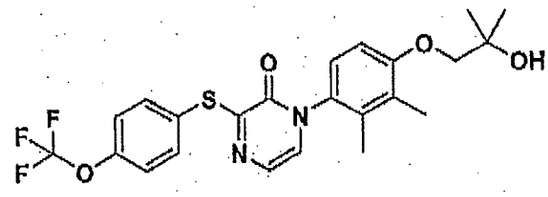

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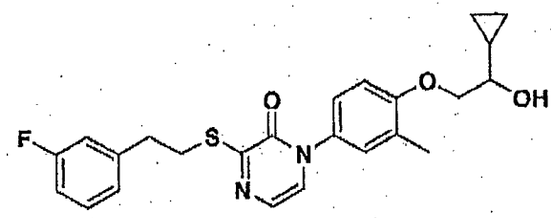

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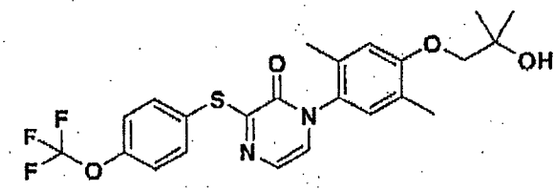
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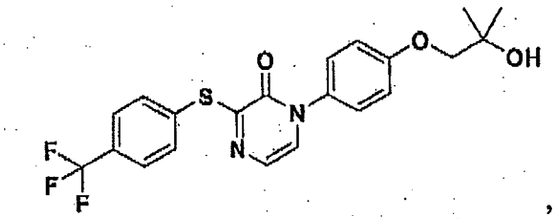
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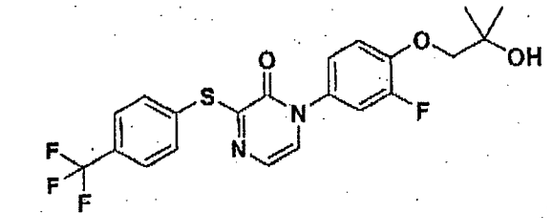

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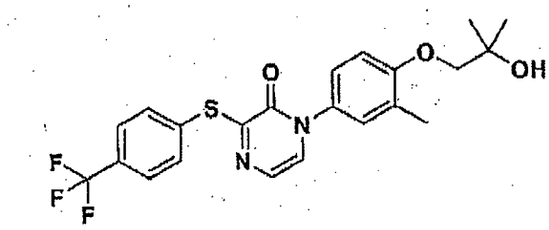

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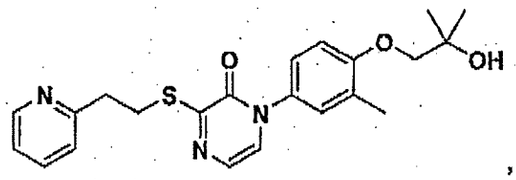

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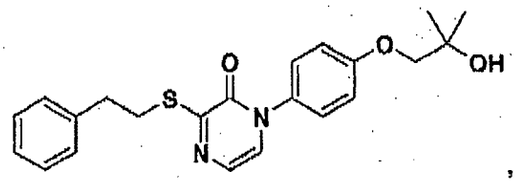

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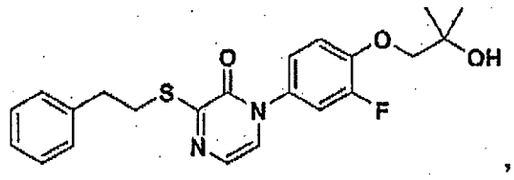

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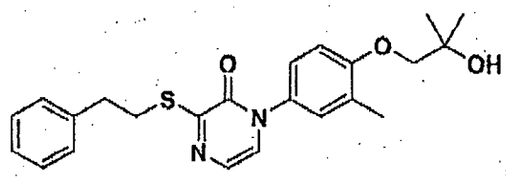
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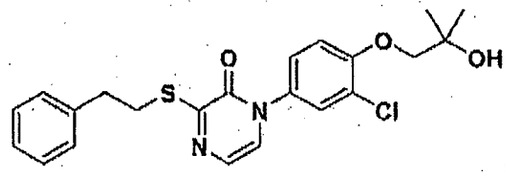
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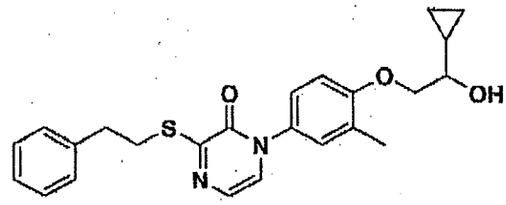

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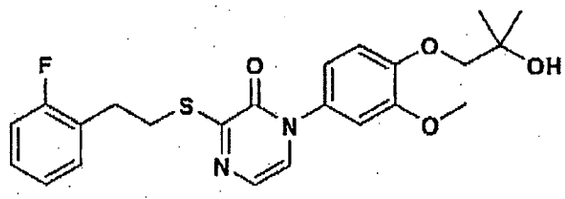

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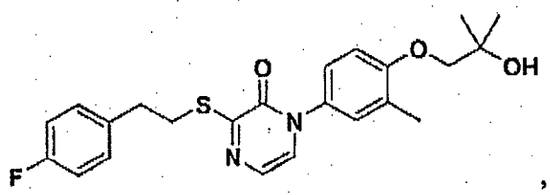

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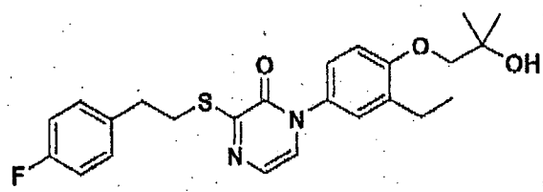

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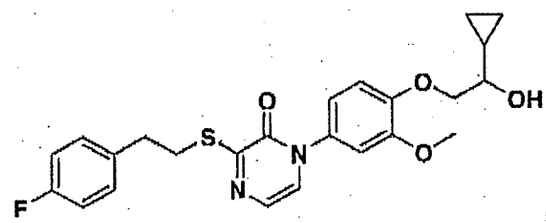

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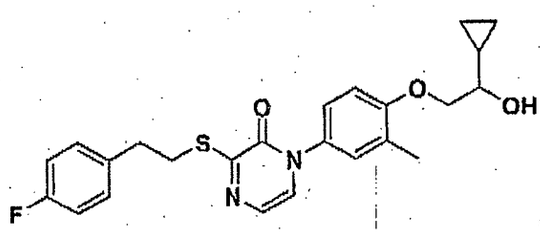
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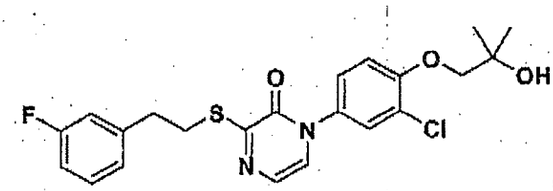
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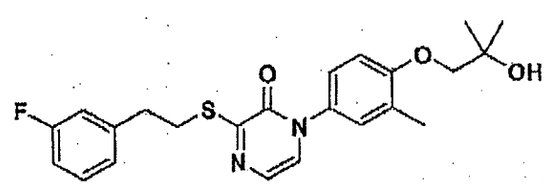

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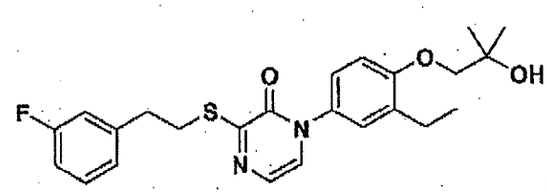

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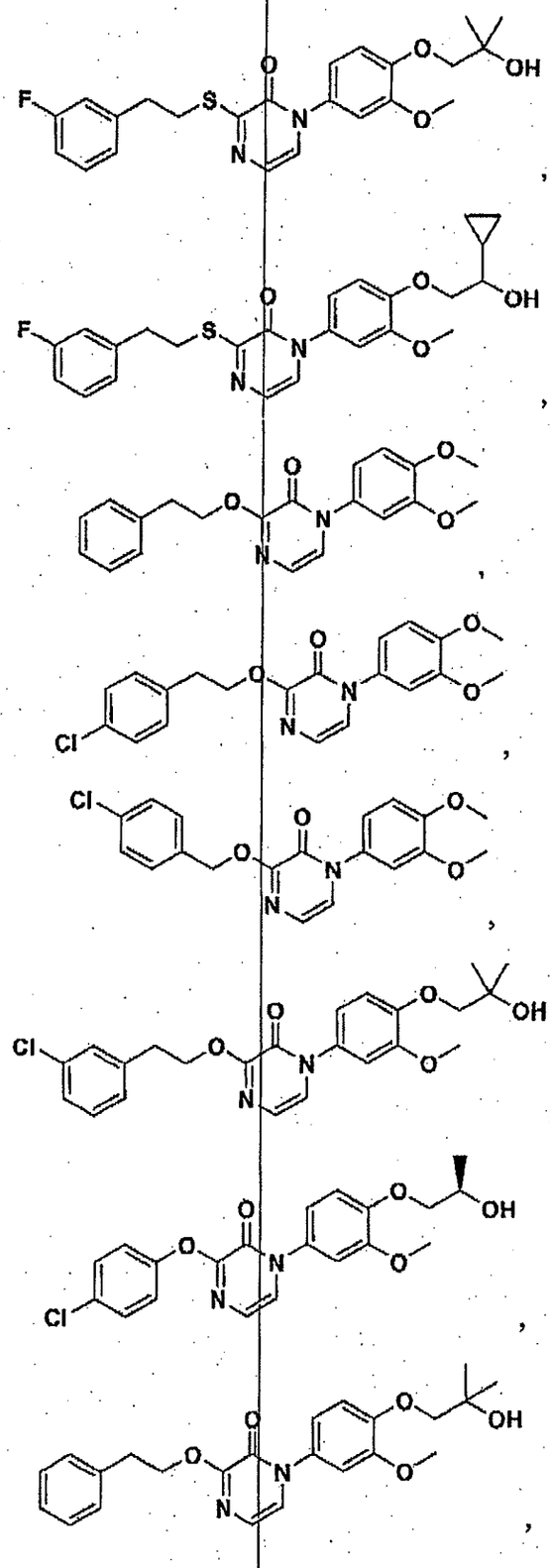

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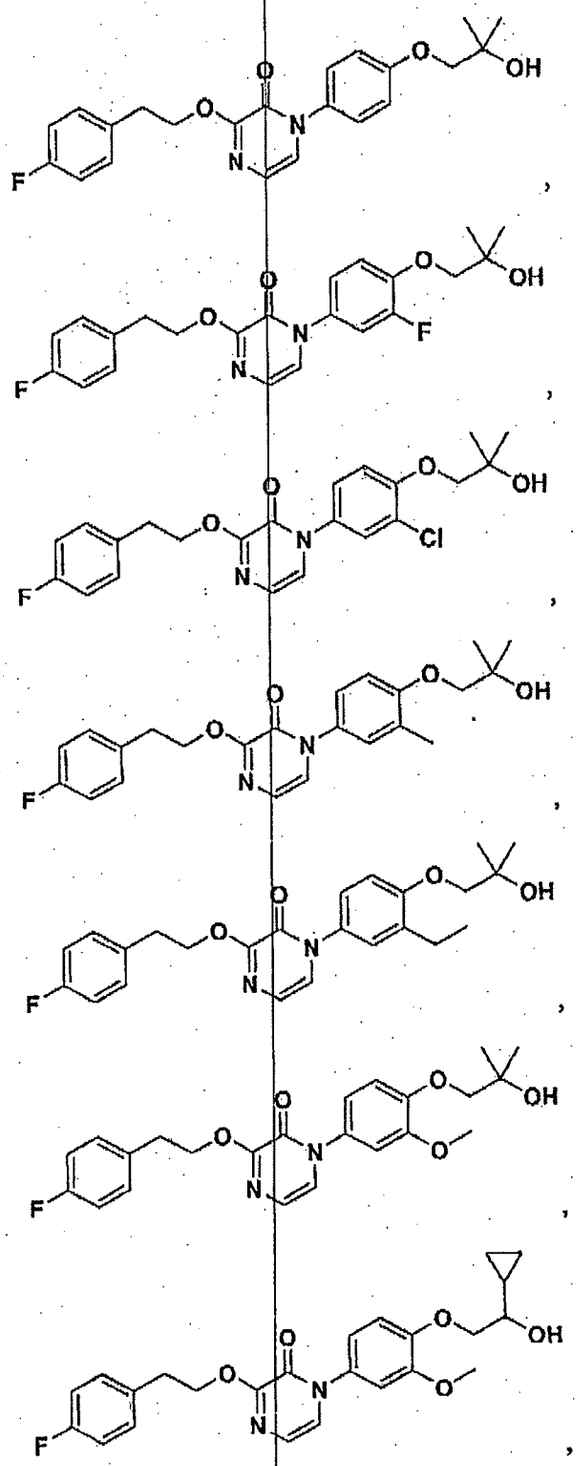
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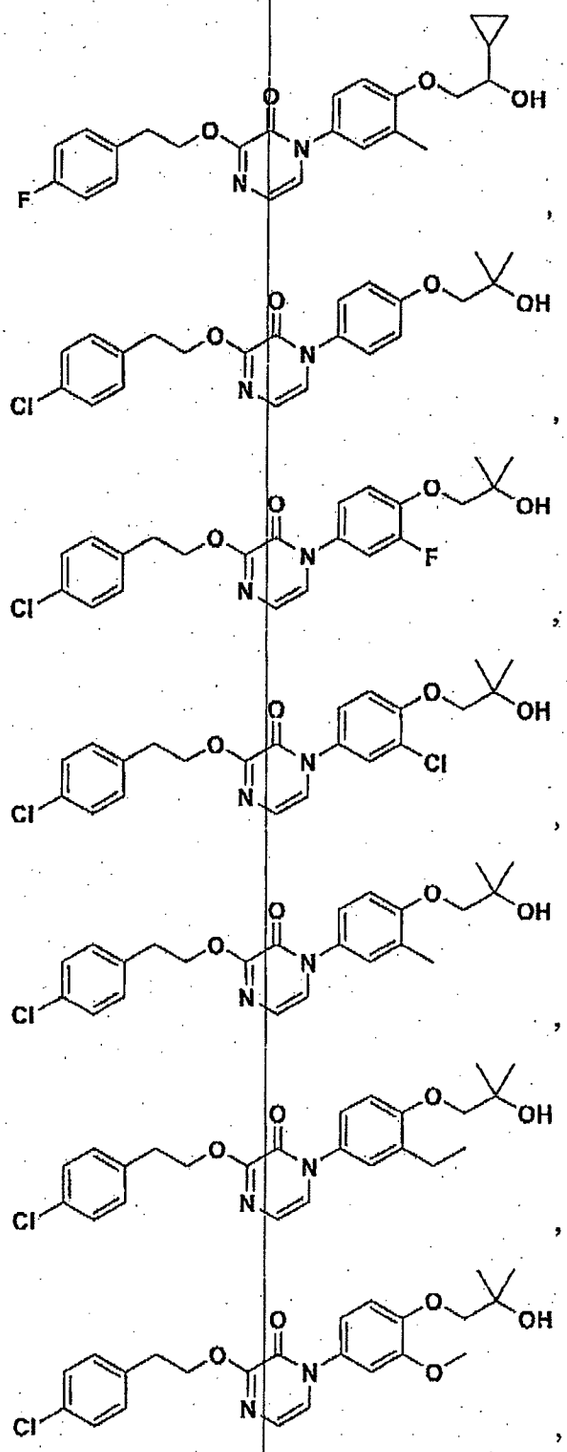
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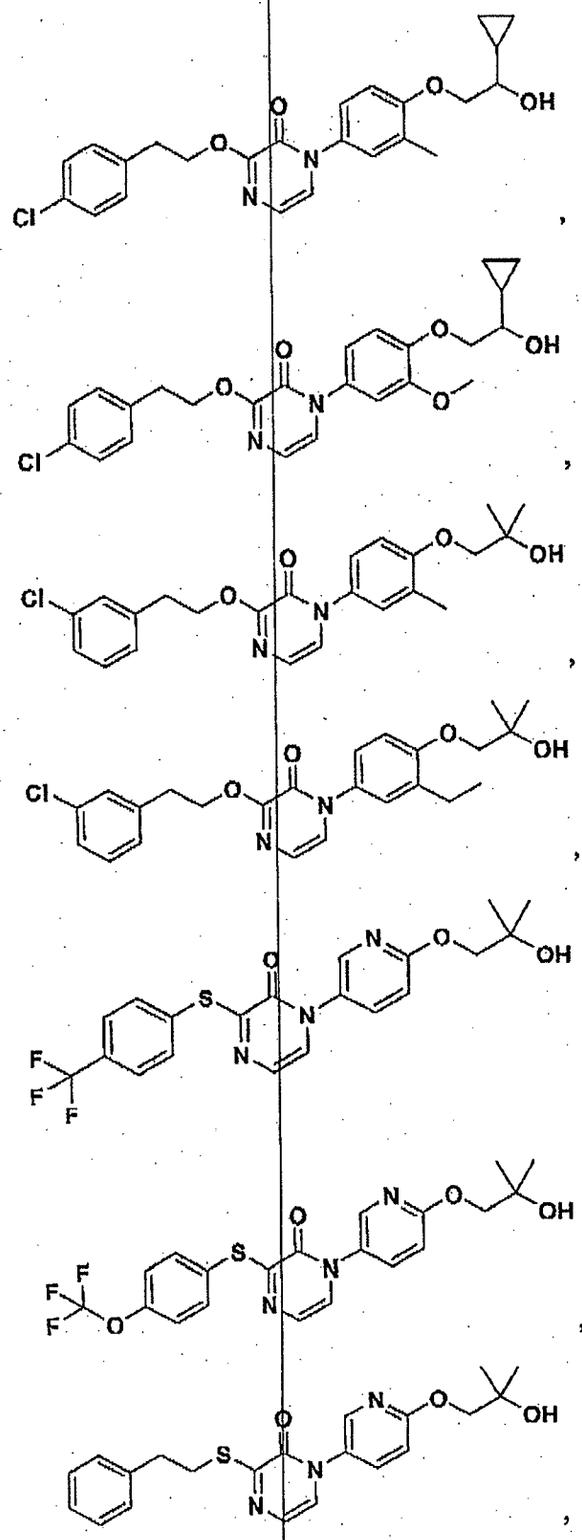
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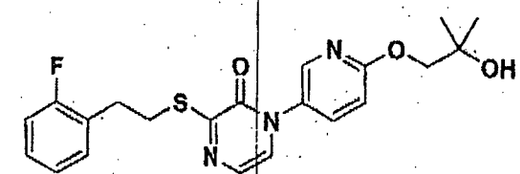
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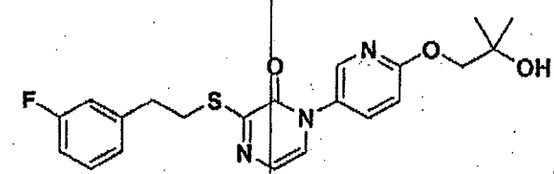


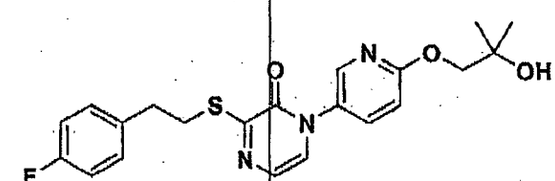
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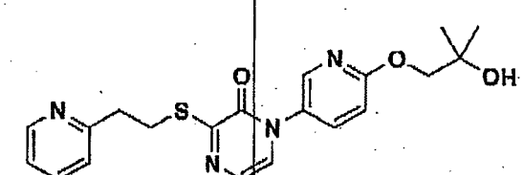
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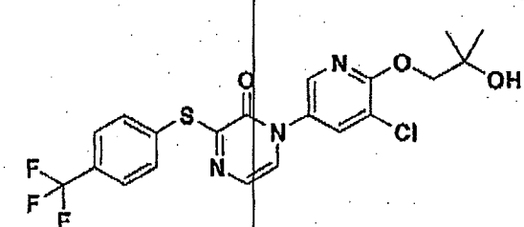
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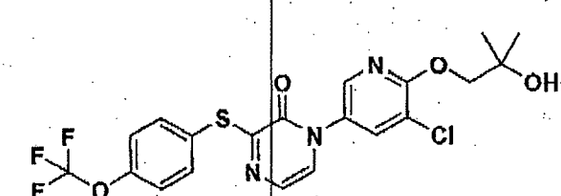

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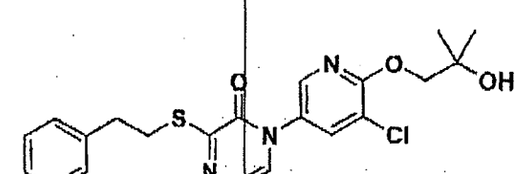

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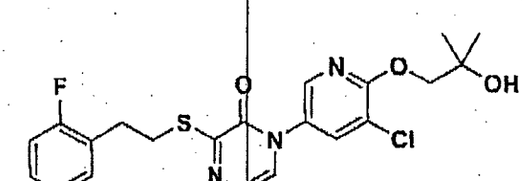

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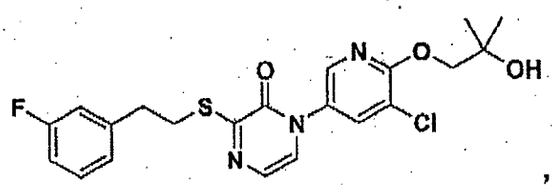

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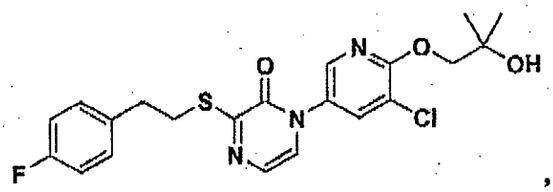

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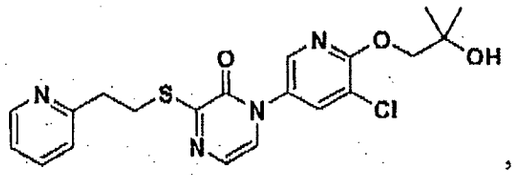

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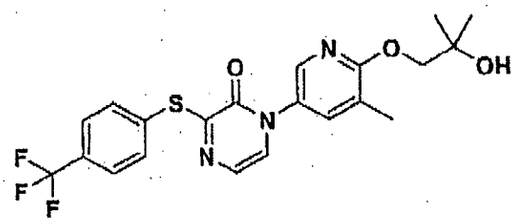
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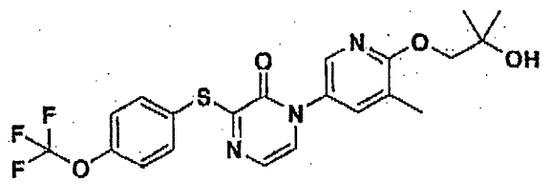
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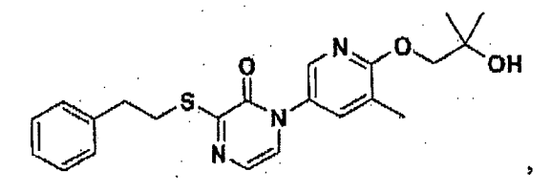


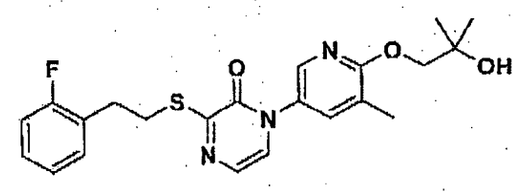


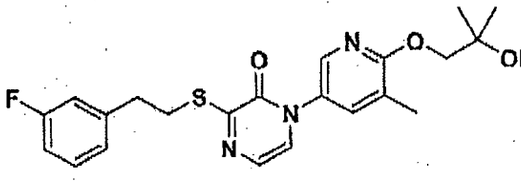


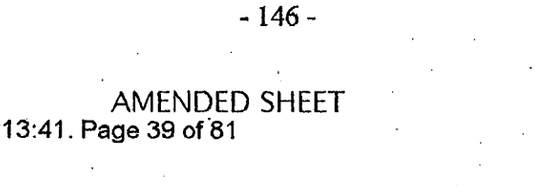






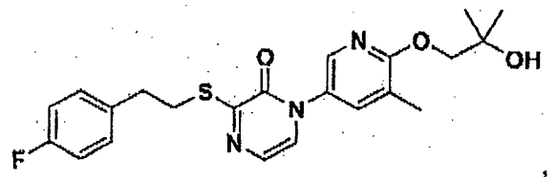


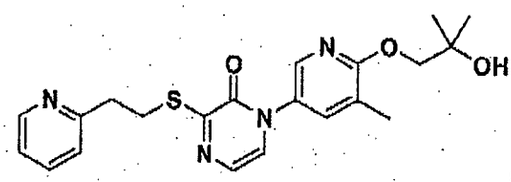


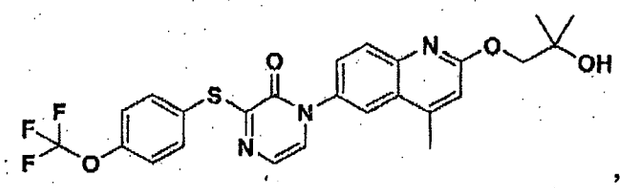


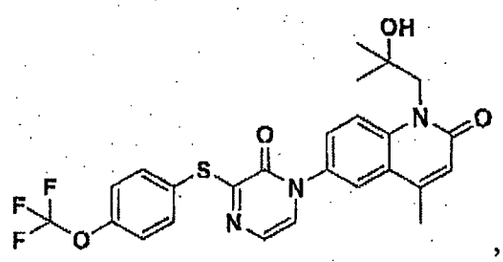
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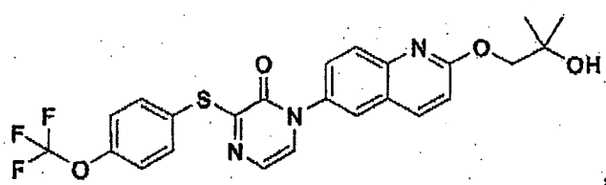
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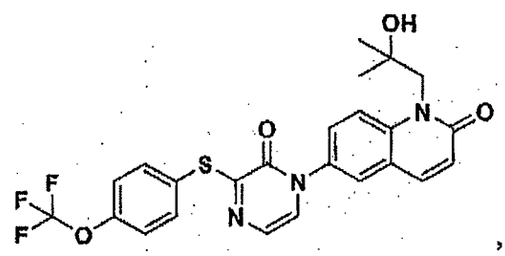


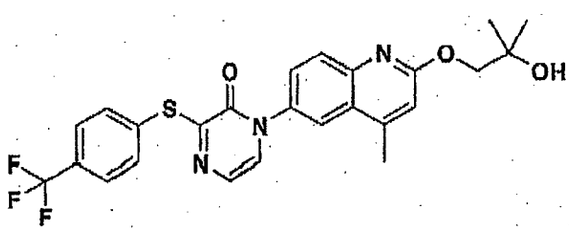






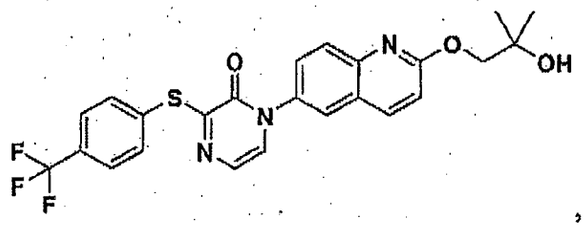


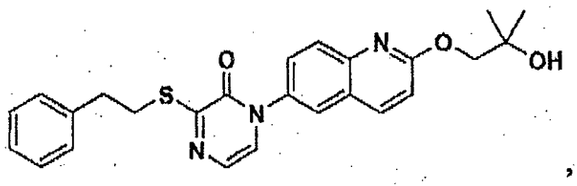


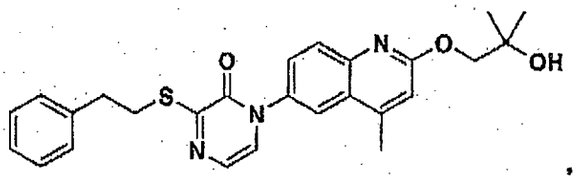


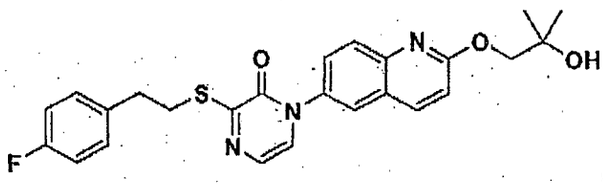
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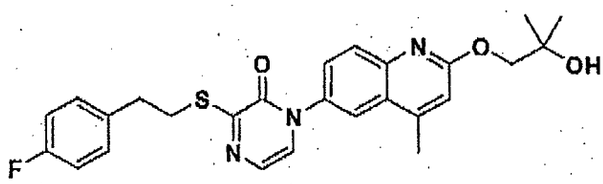
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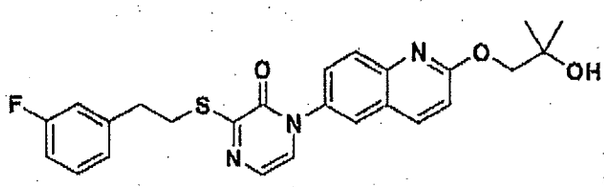


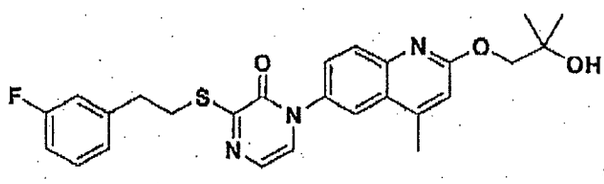






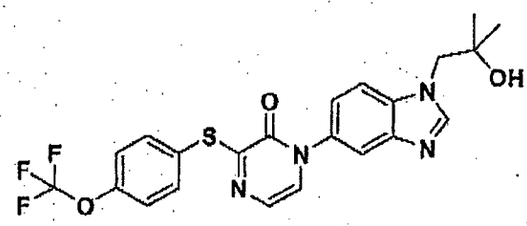




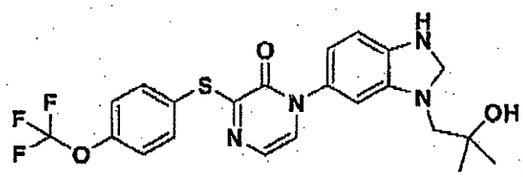


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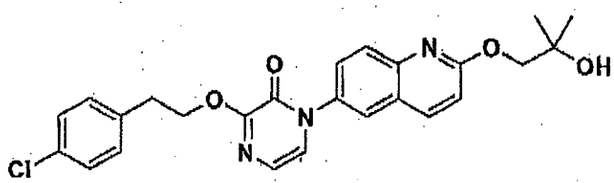
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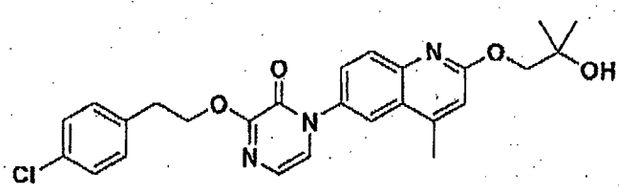
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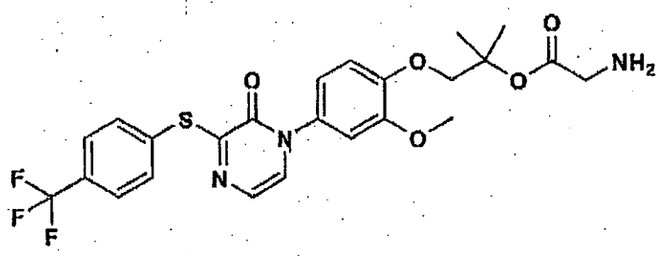
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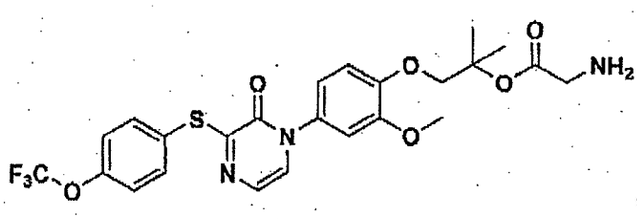
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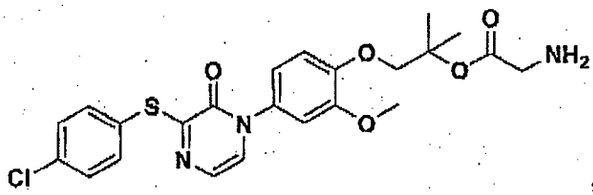
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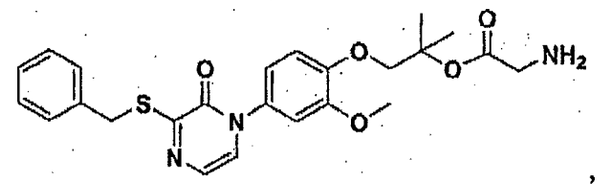
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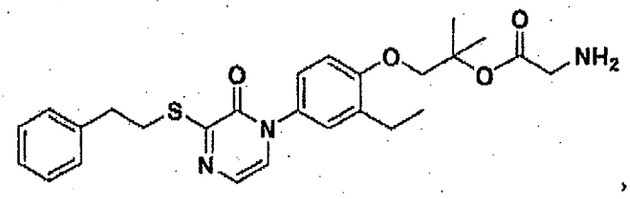


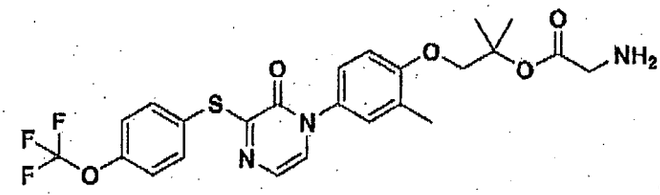
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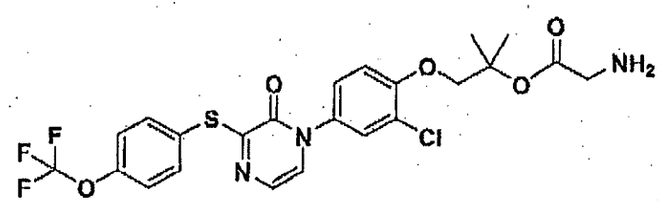
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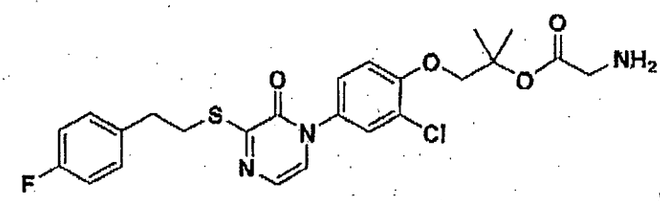
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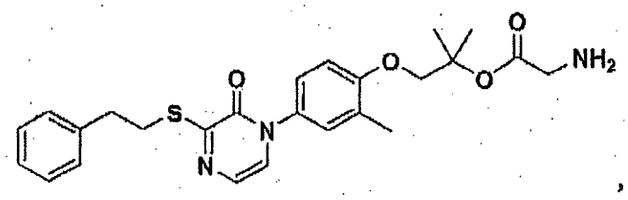


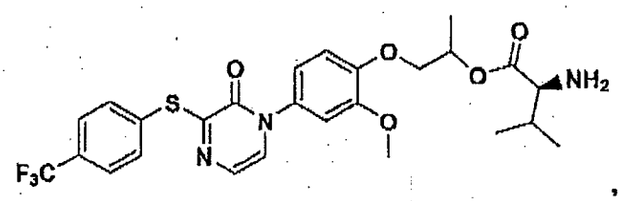












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Docket No.: **10899 PCT**

PATENT COOPERATION TREATY

International Filing No: **PCT/US2008/069361**

International Filing Date: **07 July 2008**

Priority Date: **06 July 2007**

Applicant: **BRISTOL-MYERS SQUIBB COMPANY**

For: NON-BASIC MELANIN CONCENTRATING HORMONE RECEPTOR-1 ANTAGONISTS AND METHODS

International Bureau of WIPO
34, chemin des Colombettes
1211 Geneva 20, Switzerland
Facsimile No. 41 22 338 82 70

AMENDMENT UNDER ARTICLE 19

Applicants wish to make amendments to the claims. Please enter the amendments made to claims 1, 6, 8, 9, 10, 19, 21, 22, 23, 29, and 30 by replacing originally filed pages 115 to 131 with substituted pages 115 to 151. Support for these amendments can be found in the specification and claims as originally filed. No new matter has been added. Claims 2 to 5, 7, 11, 13 to 17, 24 to 28 and 31 are canceled. Claims 12, 18, and 20 remain unchanged. Claim 32 is new. Substitute Pages 115 to 151 are enclosed herewith. A marked up version of the Claims showing the changes to the originally filed claims is also included.

Remarks

The claims have been amended in response to the Written Opinion of the International Searching Authority to distinguish the claims over the references cited therein, D1 to D9. New claim 32 is directed to the compounds exemplified in the specification as originally filed.

Acceptance of the enclosed Substitute Pages is respectfully requested.

Respectfully submitted,

Maureen S. Gibbons
Agent for Applicant
Reg. No. 44,121
Phone: 609-252-3453
Fax: 609-252-4526

Bristol-Myers Squibb Company
Patent Department
P.O. Box 4000
Princeton, NJ 08543-4000
April 16, 2009

CERTIFICATE OF FACSIMILE
I hereby certify that this paper (along with any paper referred to as being attached or enclosed) is being facsimile transmitted to the International Bureau of WIPO, Fax No. 41 22 338 82 70 on the date shown below.

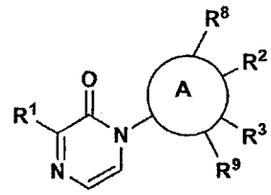
Date of Deposit: April 16, 2009

Debra A. Wojcik

SUBSTITUTE SHEET

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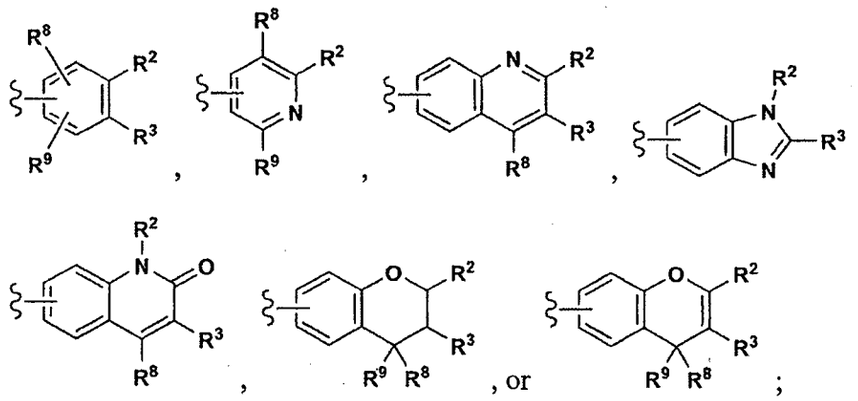
1. A compound of Formula I or a pharmaceutically acceptable salt thereof



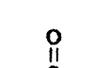
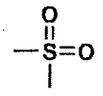
I

wherein

(A) is



R^1 is Z-Y-X-, wherein

X is O, S,  , or  ;

Y is a bond, a 3- to 6-membered cycloalkyl, an alkylene chain; and

Z is optionally substituted phenyl or naphthyl, pyridinyl, pyrazinyl, pyrimidinyl, pyridinonyl, benzothiazolyl, benzoxalyl, benzimidazolyl, quinolinyl, thiazolyl, indanyl, imidazolinyl;

R^2 is -E-G-$(J)_m$, with m being an integer from 1 to 3;

E is O, S or a bond;

G is lower alkyl, phenylalkyl, cycloalkyl, cycloalkylalkyl, alkylcycloalkyl, cycloalkoxy, alkylcycloalkoxy, or cycloalkoxyalkyl, and

each J is independently hydrogen, hydroxyl, CN, $-SO_2R^7$, $-SR^7$, $-SOR^7$, lower alkyl, lower alkoxy, CF_3, CF_3O-, $-COOR^5$, or $-CO-NR^{5a}R^6$, wherein R^{5a} and R^6 are

R^9 is H.

7. Cancel.

8. The compound as defined in Claim 1 wherein

R^1 is Z-Y-X-;

X is S;

Y is a bond or alkylene chain;

Z is phenyl or pyridyl;

E is O;

G is an alkylene chain or alkylcycloalkyl;

J is H or OH;

R^3 is H, alkoxy, alkyl, or halo;

R^8 is H or CH_3; and

R^9 is H.

4 9. The compound as defined in Claim 1 wherein

Z is phenyl, pyridinyl, pyrazinyl, pyrimidinyl, pyridinonyl, benzothiazolyl, benzoxazolyl, benzimidazolyl, quinolinyl, thiazolyl, indanyl, or imidazolinyl; any of which may either be unsubstituted or substituted with 1, 2 or 3 of amino, halo, C_{1-6} alkyl, C_{1-3} alkylamino, di-C_{1-3} alkylamino, C_{1-3} alkoxy, C_{1-3} thioalkyl, C_{1-3} trifluoroalkoxy, trifluoromethyl, cycloalkyl, cycloalkoxy, or heteroaryl; and

J is hydrogen, hydroxyl, CN, $-SO_2R^7$, $-SR^7$, $-SOR^7$, lower alkyl, lower alkoxy, CF_3, CF_3O-, $-COOR^5$, or $-CO-NR^{5a}R^6$, wherein R^{5a} and R^6 are each independently selected from the group consisting of H, C_{1-3} alkyl, and cycloalkyl, or R^{5a} and R^6 taken together can be propanediyl, butanediyl or pentanediyl with the N atom to which they are attached to form a 4-, 5- or 6-membered cyclic amine optionally substituted with lower alkyl, lower alkoxy, hydroxyl, CF_3, or CF_3O.

10. The compound of Claim 1 wherein:

Z is

(1) phenyl which is optionally substituted with:

each independently selected from the group consisting of H, C_{1-3} alkyl, and cycloalkyl, or R^{5a} and R^6 taken together can be propanediyl, butanediyl or pentanediyl with the N atom to which they are attached to form a 4-, 5- or 6-membered cyclic amine which may be optionally substituted;

R^5 is H, C_{1-6} alkyl, or cycloalkyl;

R^7 is lower alkyl; and

R^3 is C_{1-6} alkyl, cycloalkyl ,C_{1-6} alkoxy, halogen, hydrogen, -S-C_{1-6} alkyl, CN, CF_3O, or CF_3;

with the proviso that where (A) is a phenylene group, E is O or S, and further providing that E-G and R^3 are not identical unsubstituted lower alkoxy groups, and when G is lower alkyl and J is H, R^3 is not hydrogen; and

R^8 and R^9 are each independently hydrogen, halogen, or lower alkyl;

including esters thereof, prodrugs thereof, solvates thereof, and all stereoisomers thereof.

2. Cancel.

3. Cancel.

4. Cancel.

5. Cancel.

6. The compound as defined in Claim 1 wherein

X is O or S;

R^1 is Z-Y-X-;

wherein Y is a bond or an alkylene chain of 1 to 3 atoms;

Z is phenyl, or pyridinyl, pyrazinyl, pyrimidinyl, pyridinonyl, benzothiazolyl, benzoxazolyl, benzimidazolyl, quinolinyl, thiazolyl, indanyl, or imidazolinyl;

R^2 is -E-G-J;

E is O or S;

G is an alkylene chain or alkylcycloalkyl;

J is H, OH, SO_2R^7, lower alkyl, lower alkoxy, or CF_3;

R^3 is C_{1-6} alkyl, C_{1-6} alkoxy, H, or halo;

R^8 is H or alkyl; and

a) halogen,

b) alkyl,

c) alkoxy,

d) polyhaloalkyl,

e) polyhaloalkoxy,

f) amino, alkylamino or dialkylamino,

g) alkylthio,

h) OH,

i) an ester, or

j) aryl,

(2) heteroaryl which is:

a) pyridinyl,

b) pyrazinyl, or

c) pyrimidinyl,

each of a), b) or c) being optionally substituted with alkyl, polyhaloalkyl, alkoxy, or halogen,

(3) benzothiazolyl optionally substituted with halo or alkoxy,

(4) benzoxazolyl optionally substituted with halo,

(5) benzimidazolyl,

(6) thiazolyl optionally substituted with aryl or alkyl,

(7) indanyl,

(8) quinolinyl optionally substituted with CF_3, or

(9) imidazolidinyl;

Y is a bond or alkylene;

X is S, O, SO, or SO_2;

J is

(1) H,

(2) -CO-$NR^{5a}R^6$ wherein R^{5a} and R^6 together with the N to which they are attached form a pyrrolidinyl ring,

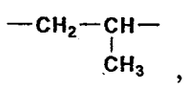
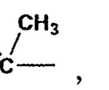
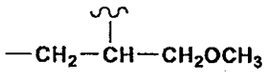
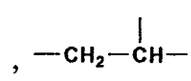
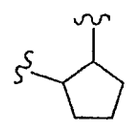
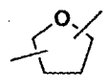
(3) OH,

(4) COOH,

(5) COOalkyl, or

(6) SO_2R^7,

m is 1 or 2;

G is a bond or CH_2, $(CH_2)_2$, $(CH_2)_3$,  ,  ,  ,  , cycloalkyl which is  , or cycloalkoxy which is  ;

E is O;

R^3 is H, alkoxy, hydroxyalkyl, alkyl, halo, or hydroxyalkoxy;

R^8 is H, halo or alkyl; and

R^9 is H

or a prodrug ester of said compound selected from the group consisting of glycine prodrug esters, valine prodrug esters, and phosphate prodrug esters.

11. Cancel.

12. The compound of Claim 7, wherein R^3 is C_1-C_6 alkoxy or C_{1-6} alkyl.

13. Cancel.

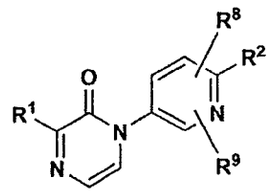
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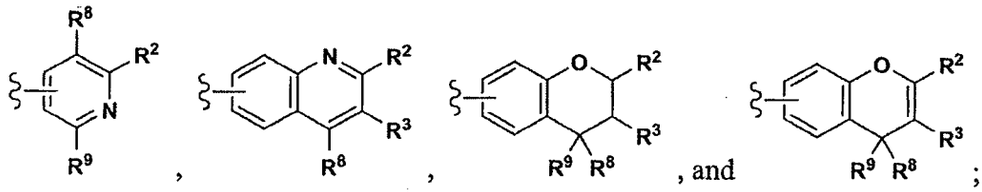
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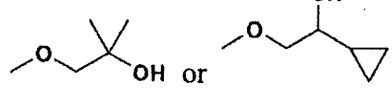
17. Cancel.

18. A compound of Formula IB or a pharmaceutically acceptable salt thereof having the structure



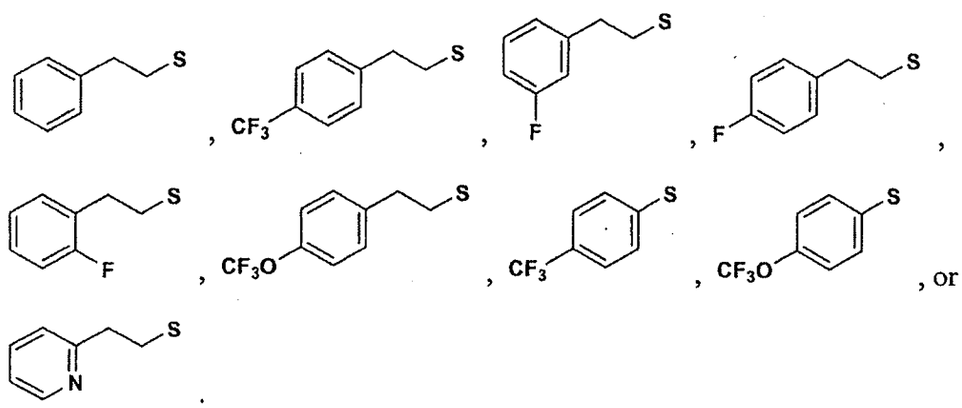
IB



R^2 is  ;

R^3 is methoxy, Cl, H, or methyl; and

R^1 is selected from the group consisting of:



22. A pharmaceutical composition comprising a therapeutically effective amount of a compound as defined in Claim 1, alone or in combination with at least one additional therapeutic agent, in association with a pharmaceutically acceptable carrier or diluent wherein said additional therapeutic agent is selected from the group consisting of an acetyl-cholinesterase inhibitor, a muscarinic receptor-1 agonist, a nicotinic agonist, a glutamic acid receptor (AMPA and NMDA) modulator, a nootropic agent, an agent for Alzheimer's disease, an agent for treatment of Parkinson's disease, anti-hyperlipidemia agent, an anti-obesity agent; anti-diabetic agent, appetite suppressant; cholesterol/lipid-lowering agent, HDL-raising agent, cognition enhancing agent, an agent used to treat neurodegeneration, an agent used to treat respiratory conditions, an agent used to treat bowel disorders, an anti-inflammatory agent; anti-anxiety agent; an anti-depressant; an anti-hypertensive agent; an anti-sleep disorder agent; a cardiac glycoside; and an anti-tumor agent.

19. The compound as defined in Claim 18 wherein

R^1 is Z-Y-X- wherein

X is S,

Y is an alkyl chain of 1 to 3 carbons or a bond,

Z is pyridinyl, pyrazinyl, pyrimidinyl, pyridinonyl, benzothiazolyl, benzoxalyl, benzimidazolyl, quinolinyl, thiazolyl, indanyl, imidazolinyl or phenyl,

each of which Z is optionally substituted with CF_3, CF_3O, or halo;

R^2 is -E-G-J wherein

E is O,

G is lower alkyl or alkylcycloalkyl, and

J is OH;

R^3 is alkoxy, alkyl or halo;

R^8 is H or alkyl; and

R^9 is H.

20. The compound as defined in Claim 18 wherein

X is S;

Y is a bond or $(CH_2)_2$;

Z is or

;

R^2 is E-G-J which is

or

;

R^3 is H, Cl, CH_3, or CH_3O; and

R^8 and R^9 are each H.

21. The compound of Claim 1 wherein

is selected from the group consisting of;

23. A pharmaceutical combination comprising: at least one compound according to claim 1, and at least one additional therapeutic agent selected from the group consisting of an acetyl-cholinesterase inhibitor, a muscarinic receptor-1 agonist, a nicotinic agonist, a glutamic acid receptor (AMPA and NMDA) modulator, a nootropic agent, an agent for Alzheimer's disease, an agent for treatment of Parkinson's disease, anti-hyperlipidemia agent, an anti-obesity agent; anti-diabetic agent, appetite suppressant; cholesterol/lipid-lowering agent, HDL-raising agent, cognition enhancing agent, an agent used to treat neurodegeneration, an agent used to treat respiratory conditions, an agent used to treat bowel disorders, an anti-inflammatory agent; anti-anxiety agent; an anti-depressant; an anti-hypertensive agent; an anti-sleep disorder agent; a cardiac glycoside; and an anti-tumor agent.

24. Cancel.

25. Cancel.

26. Cancel.

27. Cancel.

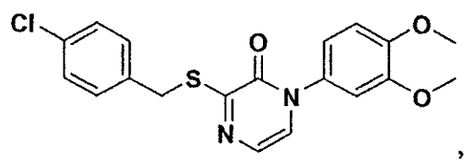
28. Cancel.

29. Use of a compound as defined in Claim 1 in the manufacture of a medicament for the treatment of obesity.

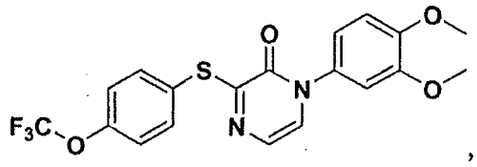
30. Use of a compound as defined in Claim 1 in the manufacture of a medicament for treatment of diabetes.

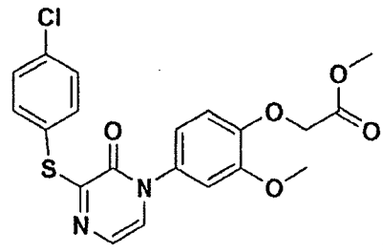
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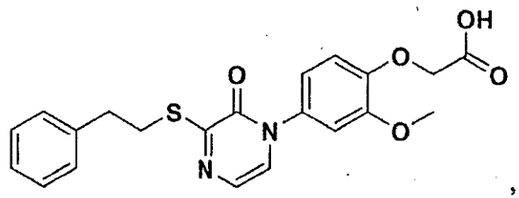
32. New. The compound according to claim 1 selected from the group consisting of:

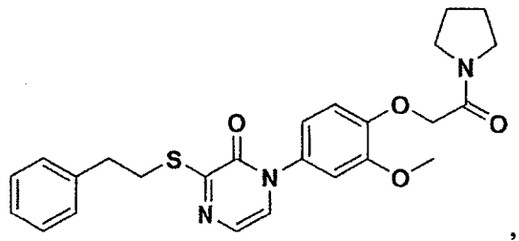


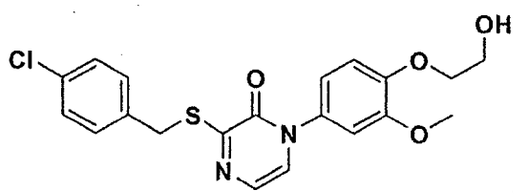
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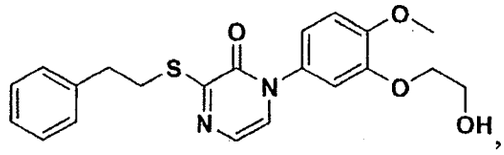


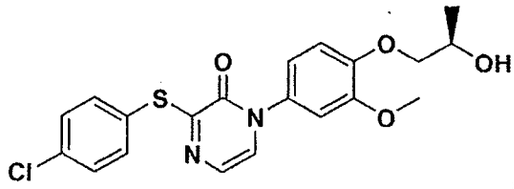


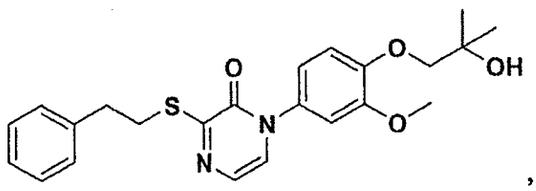


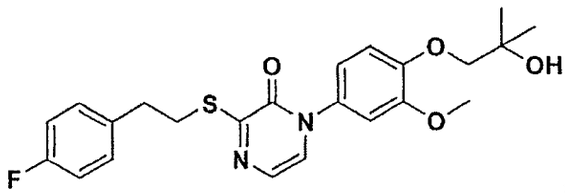


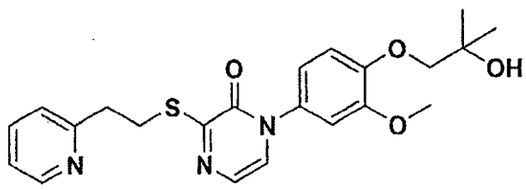


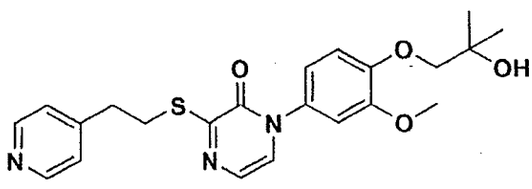


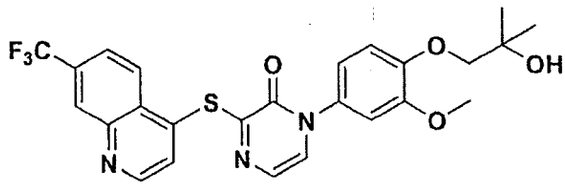


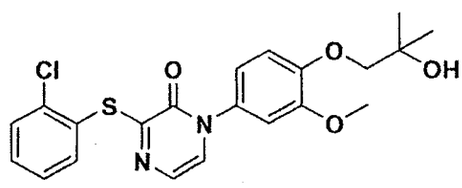


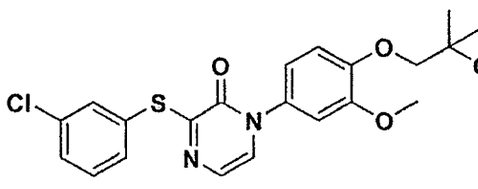


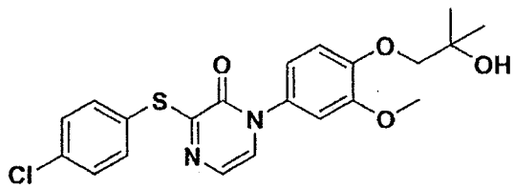


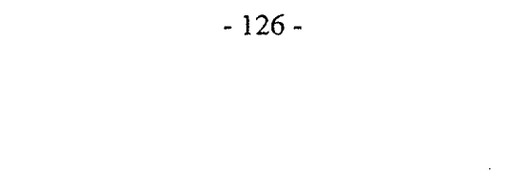


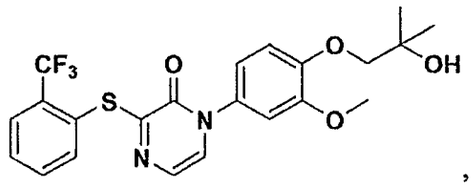




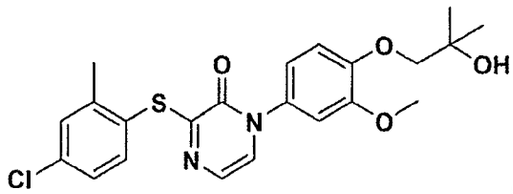




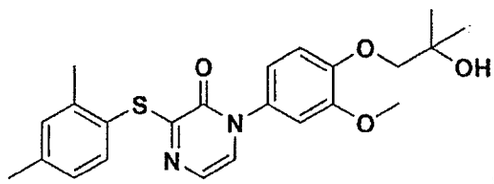



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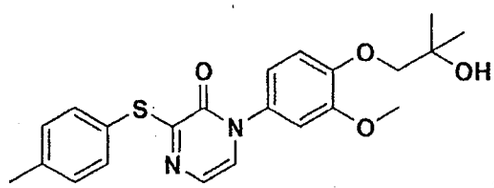
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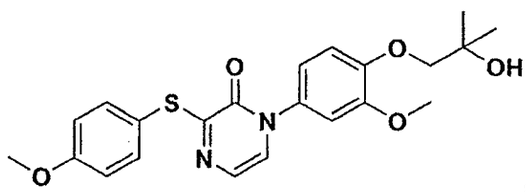
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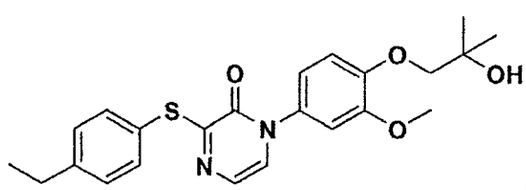
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O
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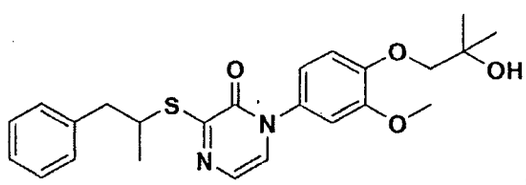
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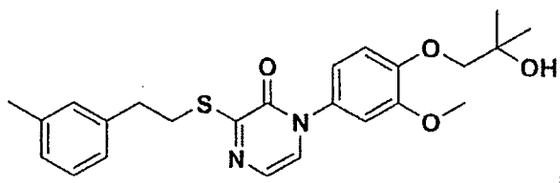
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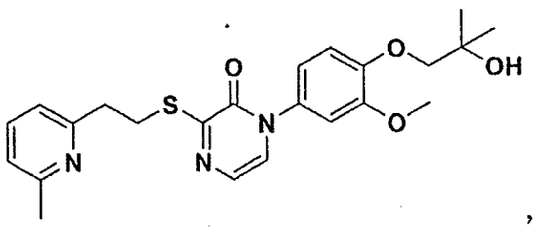
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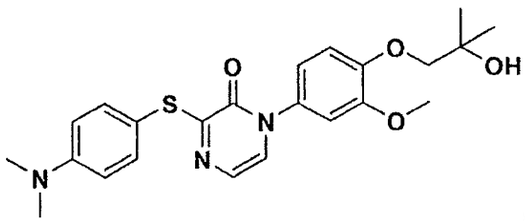
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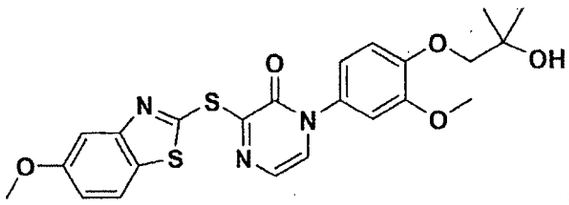
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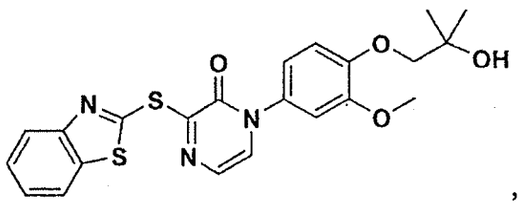
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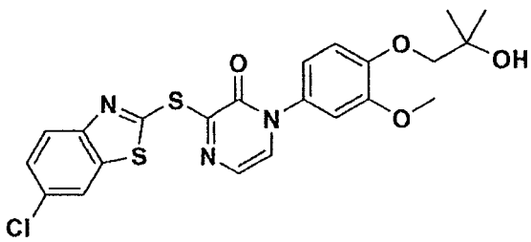
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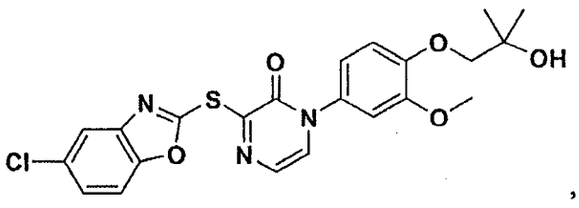
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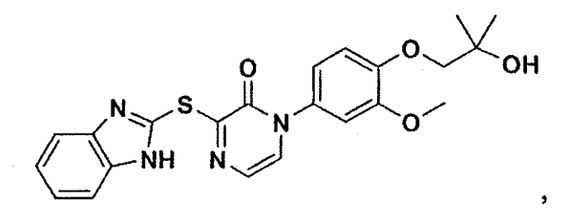
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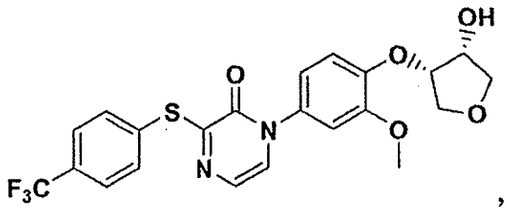
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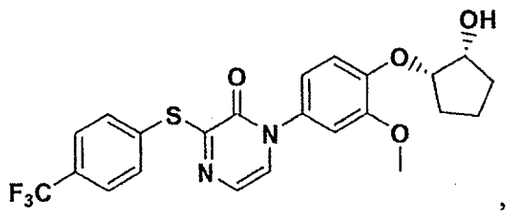
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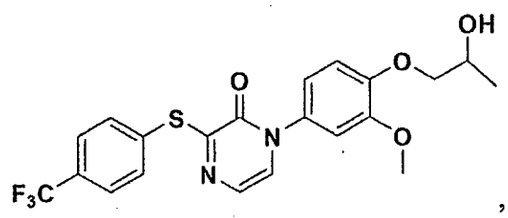
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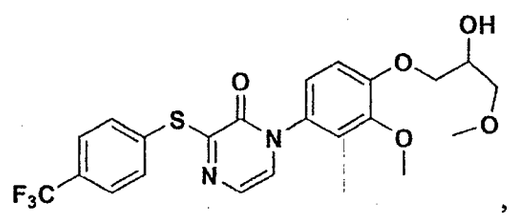
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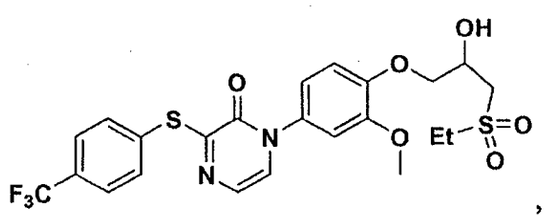
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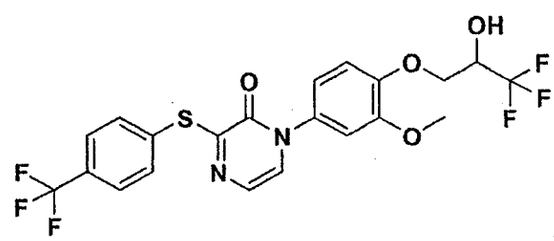
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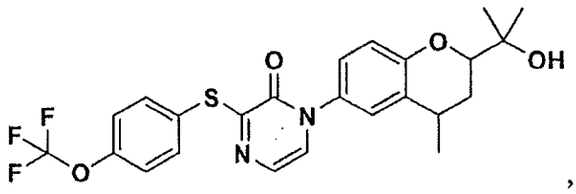
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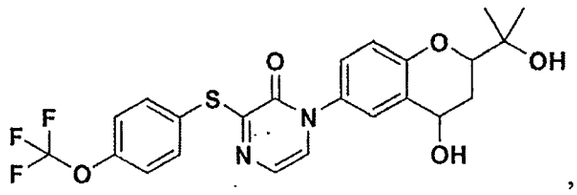

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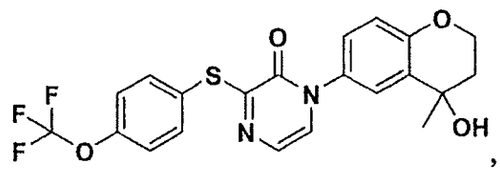
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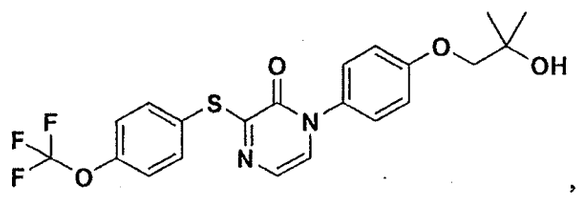

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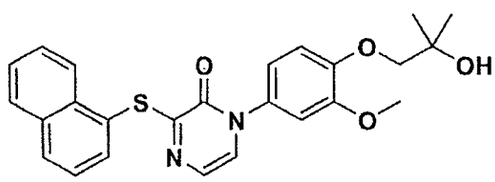
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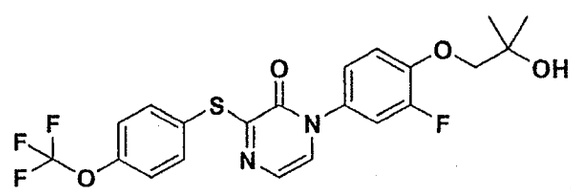

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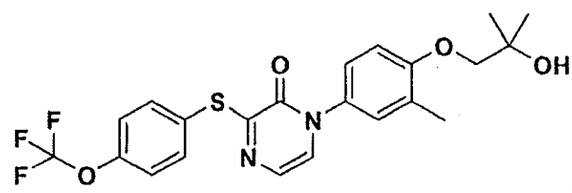

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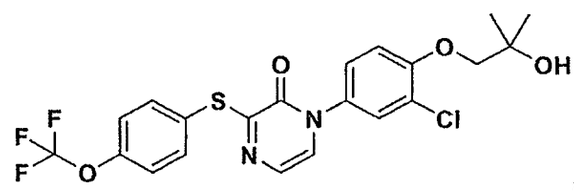

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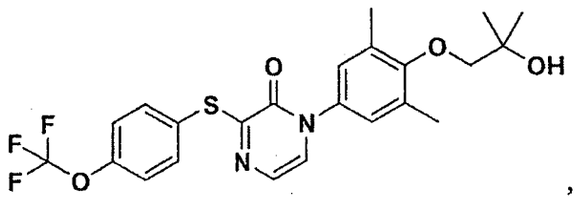

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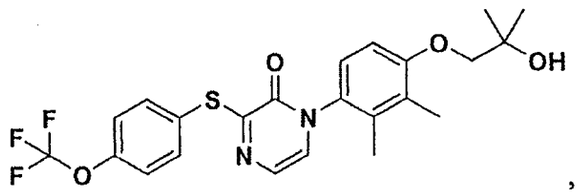

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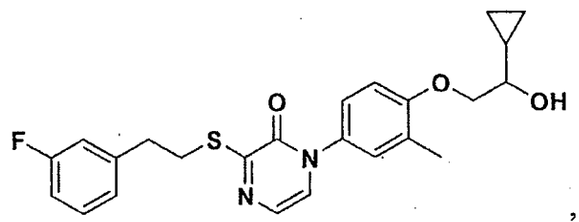

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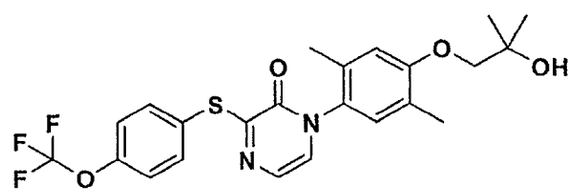
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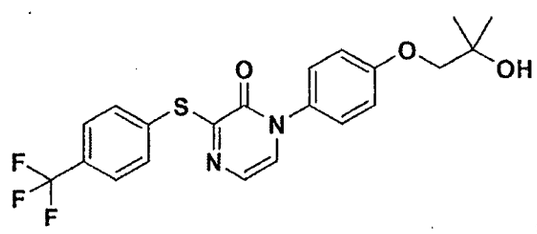
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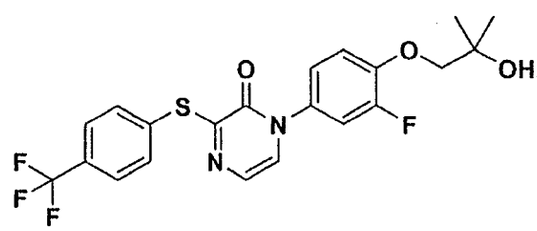
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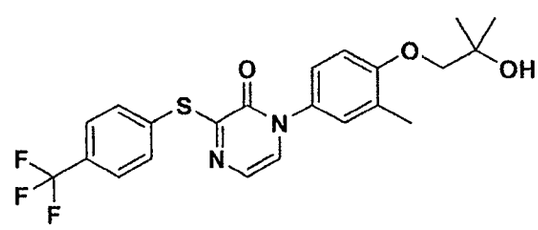
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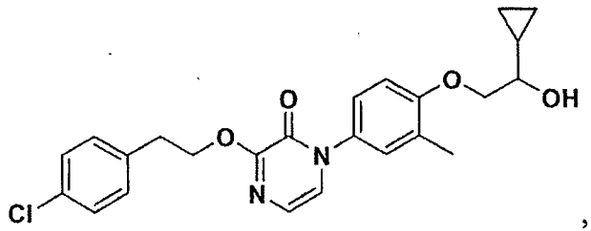
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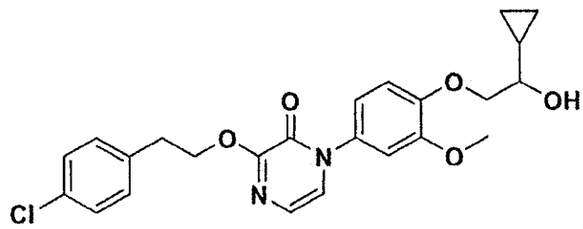
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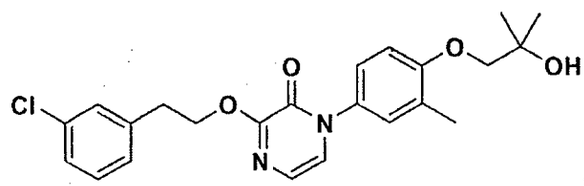
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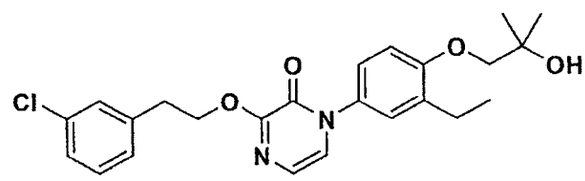
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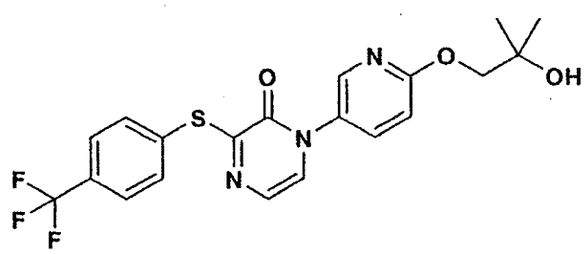
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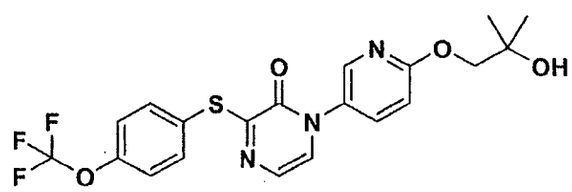
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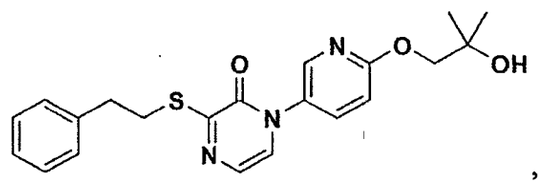
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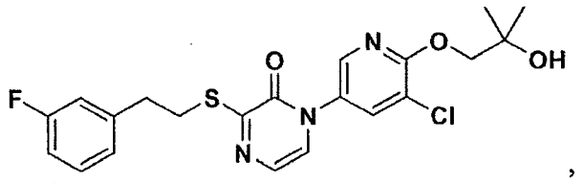
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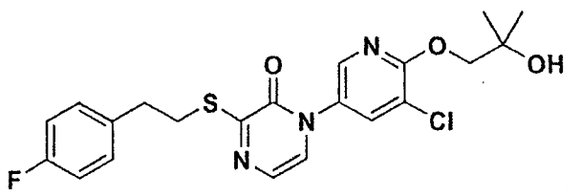
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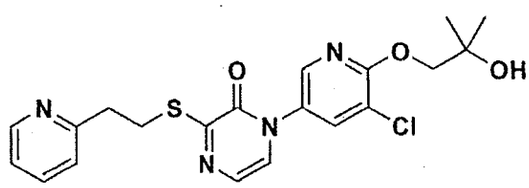
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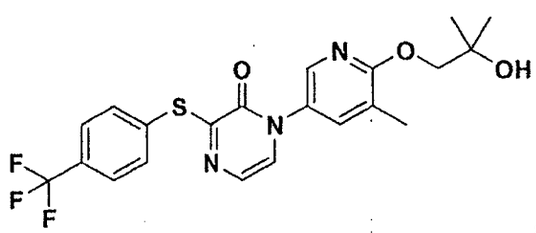
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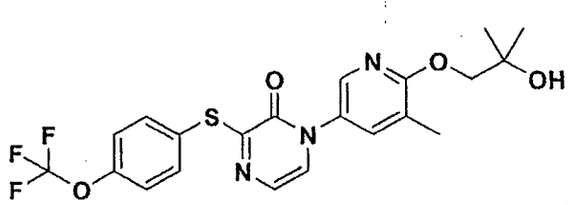
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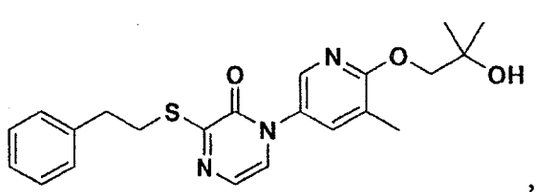
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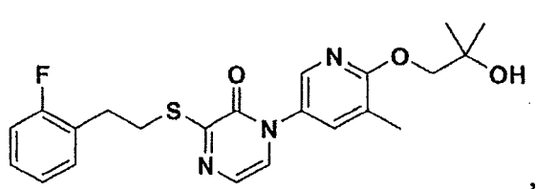
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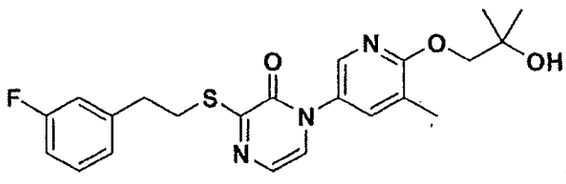
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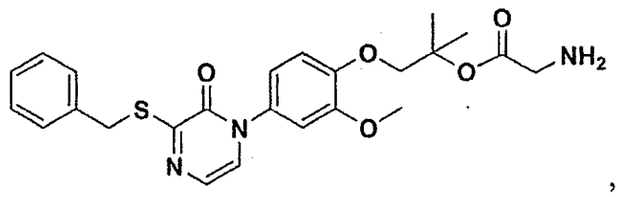


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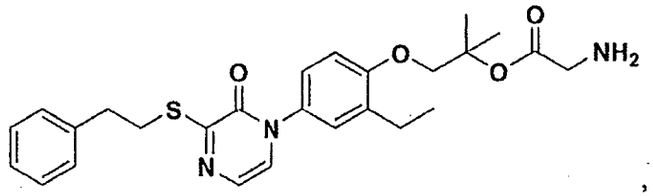


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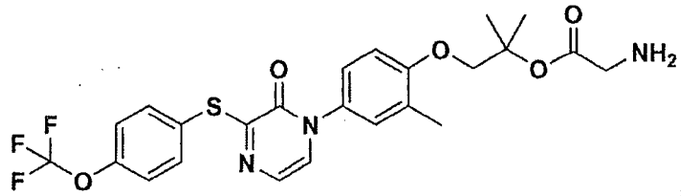
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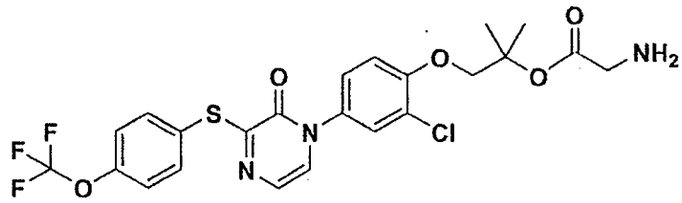
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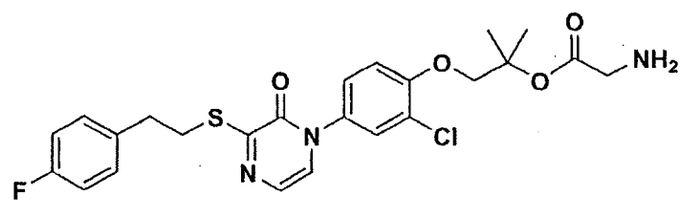
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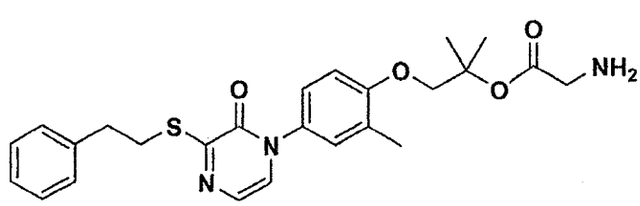
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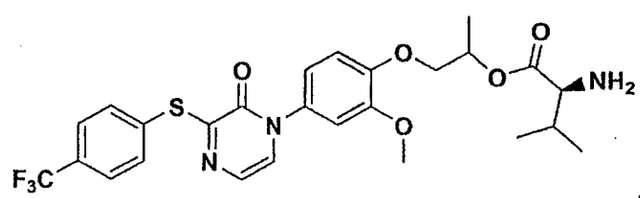
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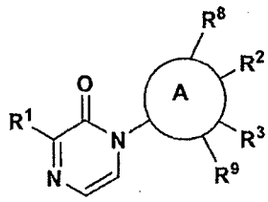
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MARKED-UP CLAIMS

WHAT IS CLAIMED IS:

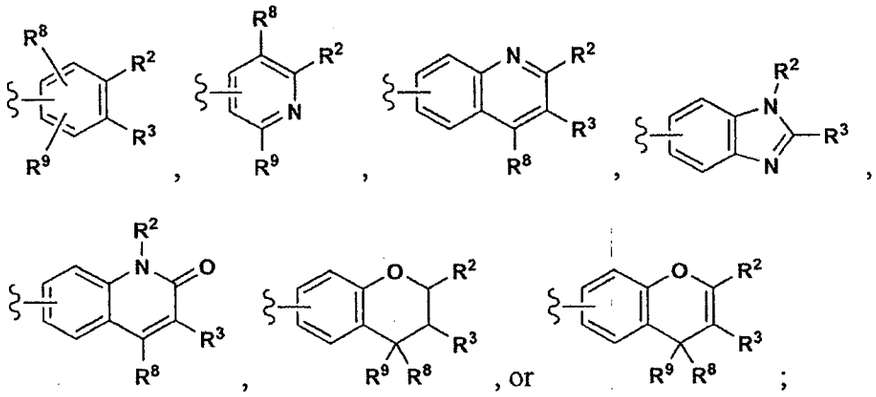
1. A compound of Formula I or a pharmaceutically acceptable salt thereof



I

wherein

 is



R^1 is Z-Y-X-, wherein

X is O, S,  , or  ;

Y is a bond, a 3- to 6-membered cycloalkyl, an ~~alkyl~~ alkylene chain; and

Z is ~~aryl~~ optionally substituted phenyl or ~~heteroaryl~~ naphthyl, pyridinyl, pyrazinyl, pyrimidinyl, pyridinonyl, benzothiazolyl, benzoxalyl, benzimidazolyl, quinolinyl, thiazolyl, indanyl, imidazolinyl;

R^2 is -E-G-$(J)_m$, with m being an integer from 1 to 3;

E is O, S or a bond;

G is lower alkyl, phenylalkyl, cycloalkyl, cycloalkylalkyl, alkylcycloalkyl, cycloalkoxy, alkylcycloalkoxy, or cycloalkoxyalkyl, and

MARKED-UP CLAIMS

each J is independently hydrogen, hydroxyl, CN, $-SO_2R^7$, $-SR^7$, $-SOR^7$, lower alkyl, lower alkoxy, CF_3, CF_3O-, $-COOR^5$, or $-CO-NR^{5a}R^6$, wherein R^{5a} and R^6 are each independently selected from the group consisting of H, C_{1-3} alkyl, and cycloalkyl, or R^{5a} and R^6 taken together can be propanediyl, butanediyl or pentanediyl with the N atom to which they are attached to form a 4-, 5- or 6-membered cyclic amine which may be optionally substituted;

R^5 is H, C_{1-6} alkyl, or cycloalkyl;

R^7 is lower alkyl; and

R^3 is C_{1-6} alkyl, cycloalkyl ,C_{1-6} alkoxy, halogen, hydrogen, -S-C_{1-6} alkyl, CN, CF_3O, or CF_3;

with the proviso that where (A) is a phenylene group, <u>E is O or S, and further providing that</u> E-G and R^3 are not identical unsubstituted lower alkoxy groups, and when G is lower alkyl and J is H, R^3 is not hydrogen; and

R^8 and R^9 are each independently hydrogen, halogen, or lower alkyl;

including esters thereof, prodrugs thereof, solvates thereof, and all stereoisomers thereof.

2. Cancel.

3. Cancel.

4. Cancel.

5. Cancel.

6. The compound as defined in Claim 1 wherein

X is O or S;

R^1 is Z-Y-X-;

wherein Y is a bond or an alkylene chain of 1 to 3 atoms;

Z is phenyl, or pyridinyl, pyrazinyl, pyrimidinyl, pyridinonyl, benzothiazolyl, benzoxazolyl, benzimidazolyl, quinolinyl, thiazolyl, indanyl, or imidazolinyl;

R^2 is -E-G-J;

E is O or S;

G is an alkylene chain or alkylcycloalkyl;

J is H, OH, SO_2R^7, lower alkyl, lower alkoxy, or CF_3;

MARKED-UP CLAIMS

R^3 is C_{1-6} alkyl, C_{1-6} alkoxy, H, or halo;

R^8 is H or alkyl; and

R^9 is H.

7. Cancel.

8. The compound as defined in Claim ~~7~~ 1 wherein

R^1 is Z-Y-X-;

X is S;

Y is a bond or alkylene chain;

Z is phenyl or pyridyl;

E is O;

G is an alkylene chain or alkylcycloalkyl;

J is H or OH;

R^3 is H, alkoxy, alkyl, or halo;

R^8 is H or CH_3; and

R^9 is H.

9. The compound as defined in Claim 1 wherein

Z is phenyl, pyridinyl, pyrazinyl, pyrimidinyl, pyridinonyl, benzothiazolyl, benzoxazolyl, benzimidazolyl, quinolinyl, thiazolyl, indanyl, or imidazolinyl; any of which may either be unsubstituted or substituted with 1, 2 or 3 of amino, halo, C_{1-6} alkyl, C_{1-3} alkylamino, di-C_{1-3} alkylamino, C_{1-3} alkoxy, C_{1-3} thioalkyl, C_{1-3} trifluoroalkoxy, trifluoromethyl, cycloalkyl, cycloalkoxy, or heteroaryl; and

J is hydrogen, hydroxyl, CN, $-SO_2R^7$, $-SR^7$, $-SOR^7$, lower alkyl, lower alkoxy, CF_3, CF_3O-, $-COOR^5$, or $-CO-NR^{5a}R^6$, wherein R^{5a} and R^6 are each independently selected from the group consisting of H, C_{1-3} alkyl, and cycloalkyl, or R^{5a} and R^6 taken together can be propanediyl, butanediyl or pentanediyl with the N atom to which they are attached to form a 4-, 5- or 6-membered cyclic amine optionally substituted with lower alkyl, lower alkoxy, hydroxyl, CF_3, or CF_3O.

10. The compound of Claim 1 wherein:

MARKED-UP CLAIMS

Z is

(1) phenyl which is optionally substituted with:

a) halogen,

b) alkyl,

c) alkoxy,

d) polyhaloalkyl,

e) polyhaloalkoxy,

f) amino, alkylamino or dialkylamino,

g) alkylthio,

h) OH,

i) an ester, or

j) aryl,

(2) heteroaryl which is:

a) pyridinyl,

b) pyrazinyl, or

c) pyrimidinyl,

each of a), b) or c) being optionally substituted with alkyl, polyhaloalkyl, alkoxy, or halogen,

(3) benzothiazolyl optionally substituted with halo or alkoxy,

(4) benzoxazolyl optionally substituted with halo,

(5) benzimidazolyl,

(6) thiazolyl optionally substituted with aryl or alkyl,

(7) indanyl,

(8) quinolinyl optionally substituted with CF_3, or

(9) imidazolidinyl;

Y is a bond or alkylene;

X is S, O, SO, or SO_2;

J is

(1) H,

(2) -CO-$NR^{5a}R^6$ wherein R^{5a} and R^6 together with the N to which they are attached form a pyrrolidinyl ring,

(3) OH,

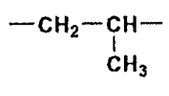
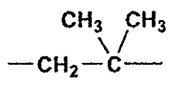
MARKED-UP CLAIMS

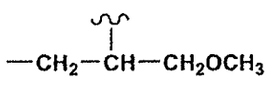
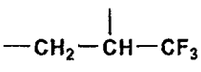
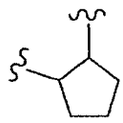
(4) COOH,

(5) COOalkyl, or

(6) SO_2R^7,

m is 1 or 2;

G is a bond or CH_2, $(CH_2)_2$, $(CH_2)_3$,  ,  ,

 ,  , cycloalkyl which is  , or

cycloalkoxy which is  ;

E is O;

R^3 is H, alkoxy, hydroxyalkyl, alkyl, halo, or hydroxyalkoxy;

R^8 is H, halo or alkyl; and

R^9 is H

or a prodrug ester of said compound selected from the group consisting of glycine prodrug esters, valine prodrug esters, and phosphate prodrug esters..

11. Cancel.

12. The compound of Claim 7, wherein R^3 is C_1-C_6 alkoxy or C_{1-6} alkyl.

13. Cancel.

14. Cancel.

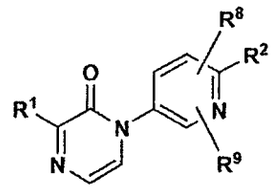
15. Cancel.

16. Cancel.

17. Cancel.

18. A compound of Formula IB or a pharmaceutically acceptable salt thereof having the structure

MARKED-UP CLAIMS



IB

19. The compound as defined in Claim 18 wherein

R^1 is Z-Y-X- wherein

X is S,

Y is an alkyl chain of 1 to 3 carbons or a bond,

Z is ~~heteroaryl~~ ~~heteroaryl~~ pyridinyl, pyrazinyl, pyrimidinyl, pyridinonyl, benzothiazolyl, benzoxalyl, benzimidazolyl, quinolinyl, thiazolyl, indanyl, imidazolinyl or phenyl,

each of which Z is optionally substituted with CF_3, CF_3O, or halo;

R^2 is -E-G-J wherein

E is O,

G is lower alkyl or alkylcycloalkyl, and

J is OH;

R^3 is alkoxy, alkyl or halo;

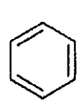
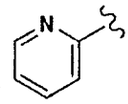
R^8 is H or alkyl; and

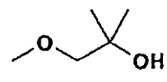
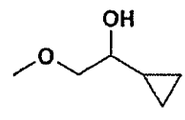
R^9 is H.

20. The compound as defined in Claim 18 wherein

X is S;

Y is a bond or $(CH_2)_2$;

Z is  or  ;

R^2 is E-G-J which is  or  ;

R^3 is H, Cl, CH_3, or CH_3O; and

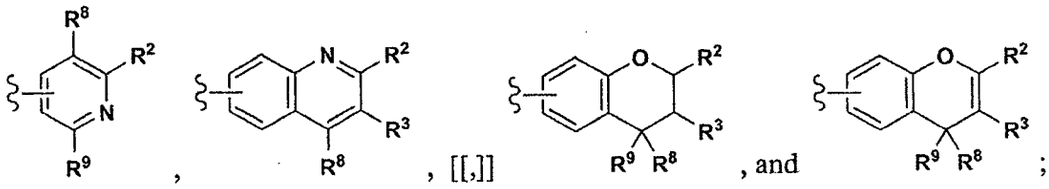
R^8 and R^9 are each H.

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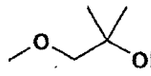
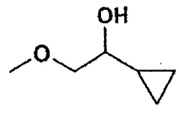
MARKED-UP CLAIMS

21. The compound of Claim 1 wherein

(A) is selected from the group consisting of;

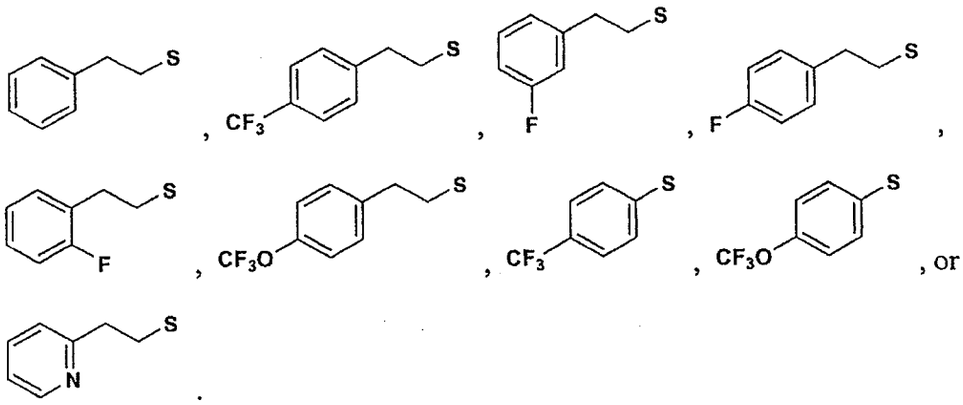


, , [[,]] , and ;

R^2 is  or  ;

R^3 is methoxy, Cl, H, or methyl; and

R^1 is selected from the group consisting of:



.

22. A pharmaceutical composition comprising a therapeutically effective amount of a compound as defined in Claim 1, alone or in combination with at least one additional therapeutic agent, in association with a pharmaceutically acceptable carrier or diluent wherein said additional therapeutic agent is selected from the group consisting of an acetyl-cholinesterase inhibitor, a muscarinic receptor-1 agonist, a nicotinic agonist, a glutamic acid receptor (AMPA and NMDA) modulator, a nootropic agent, an agent for Alzheimer's disease, an agent for treatment of Parkinson's disease, anti-hyperlipidemia agent, an anti-obesity agent; anti-diabetic agent, appetite suppressant; cholesterol/lipid-lowering agent, HDL-raising agent, cognition enhancing agent, an agent used to treat neurodegeneration, an agent used to

MARKED-UP CLAIMS

treat respiratory conditions, an agent used to treat bowel disorders, an anti-inflammatory agent; anti-anxiety agent; an anti-depressant; an anti-hypertensive agent; an anti-sleep disorder agent; a cardiac glycoside; and an anti-tumor agent.

23. A pharmaceutical combination comprising: at least one compound according to claim 1, and at least one additional therapeutic agent selected from the group consisting of an acetyl-cholinesterase inhibitor, a muscarinic receptor-1 agonist, a nicotinic agonist, a glutamic acid receptor (AMPA and NMDA) modulator, a nootropic agent, an agent for Alzheimer's disease, an agent for treatment of Parkinson's disease, anti-hyperlipidemia agent, an anti-obesity agent; anti-diabetic agent, appetite suppressant; cholesterol/lipid-lowering agent, HDL-raising agent, cognition enhancing agent, an agent used to treat neurodegeneration, an agent used to treat respiratory conditions, an agent used to treat bowel disorders, an anti-inflammatory agent; anti-anxiety agent; an anti-depressant; an anti-hypertensive agent; an anti-sleep disorder agent; a cardiac glycoside; ~~or~~ and an anti-tumor agent.

24. Cancel.

25. Cancel.

26. Cancel.

27. Cancel.

28. Cancel.

29. Use of a compound as defined in Claim 1 in the manufacture of a medicament for the treatment of ~~diabetes~~ obesity.

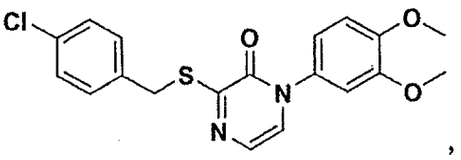
30. Use of a compound as defined in Claim 1 in the manufacture of a medicament for treatment of diabetes.~~, in which such treatment comprises a combination with another therapeutic agent, for concurrent or sequential use, in any order.~~

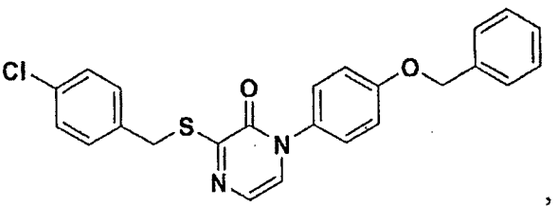
31. Cancel.

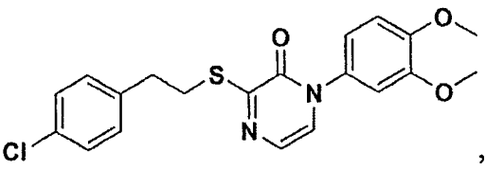
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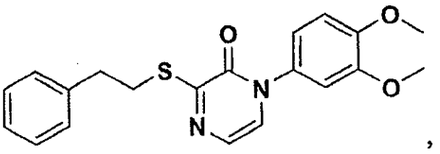
MARKED-UP CLAIMS

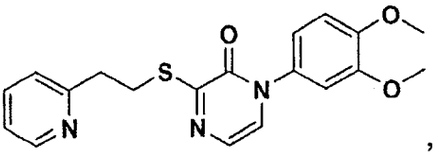
32. New. The compound according to claim 1 selected from the group consisting of:

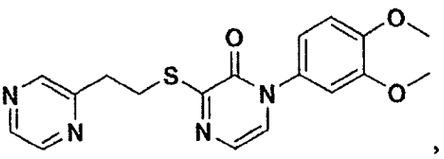

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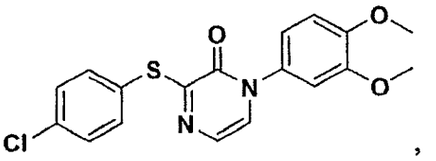

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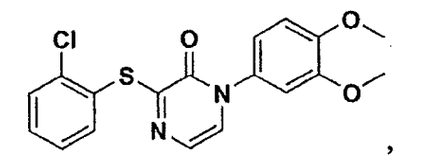

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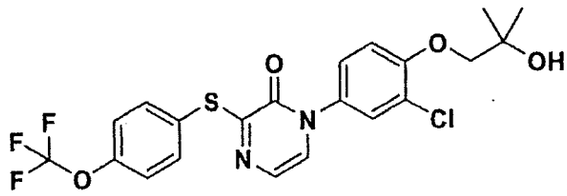

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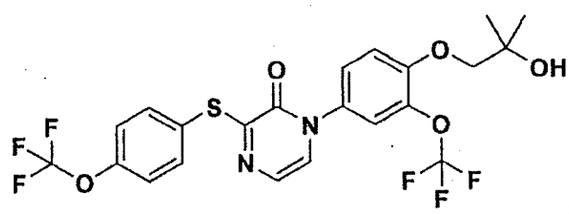

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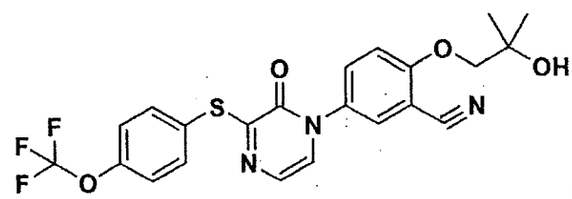

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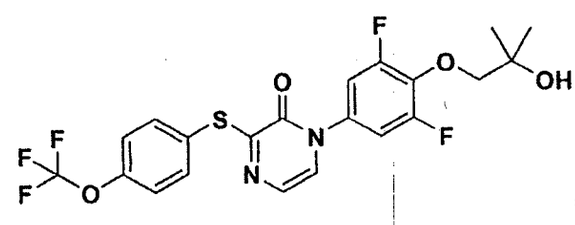
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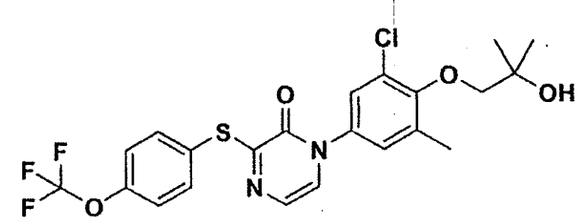
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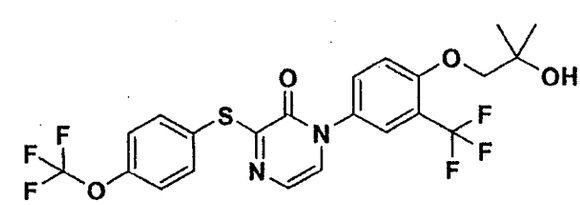

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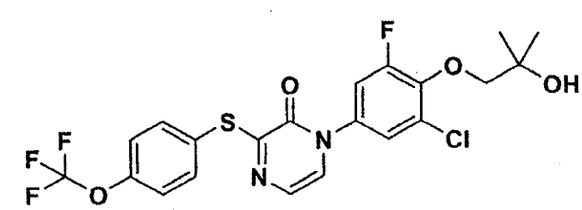

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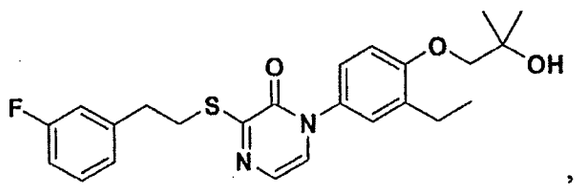

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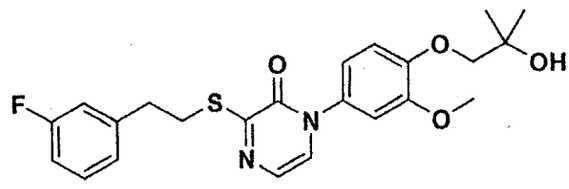

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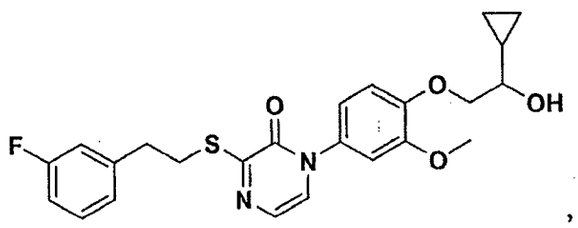

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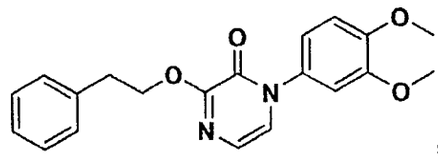
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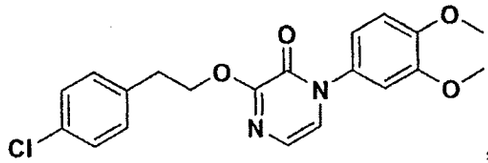
MARKED-UP CLAIMS

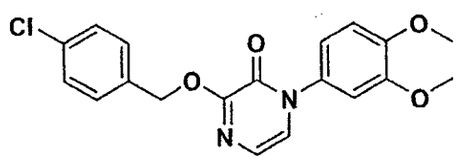

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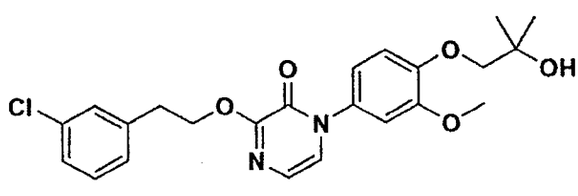

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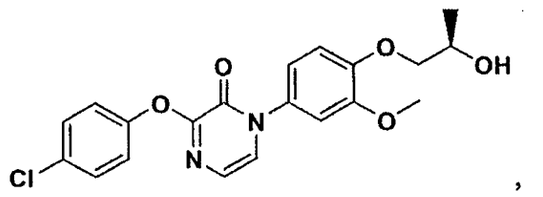

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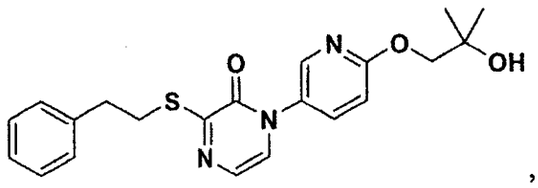

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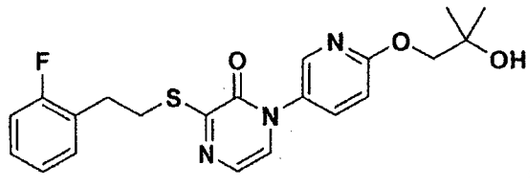

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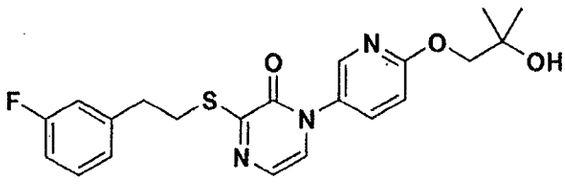

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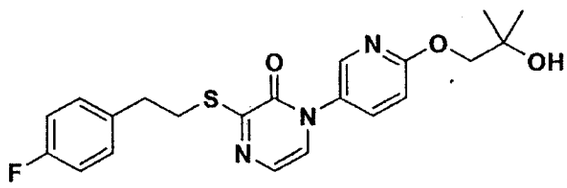
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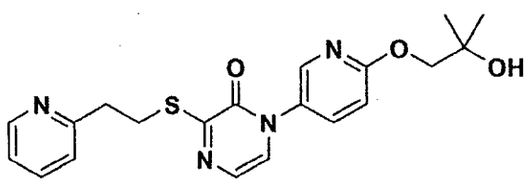
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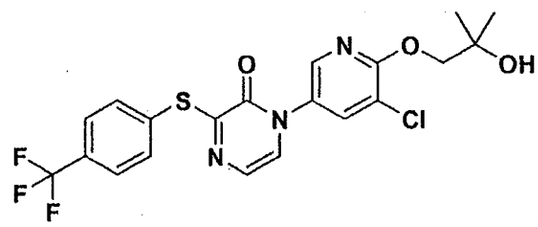

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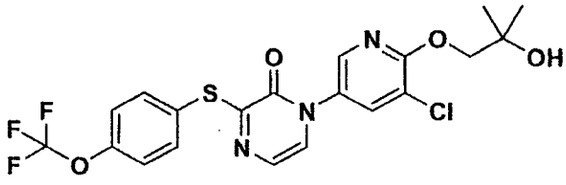

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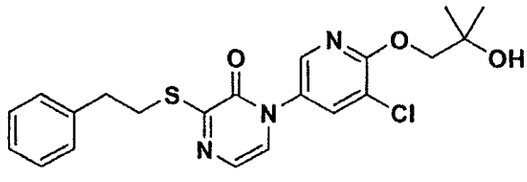

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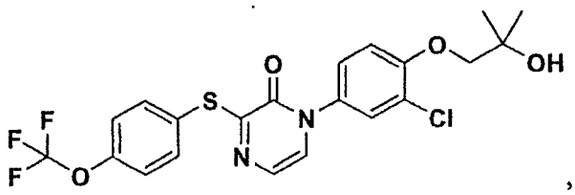

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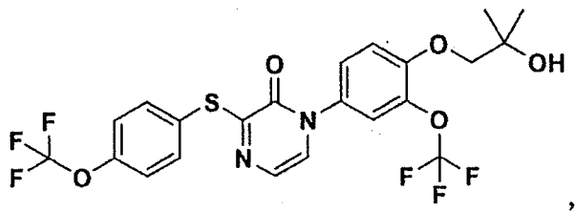

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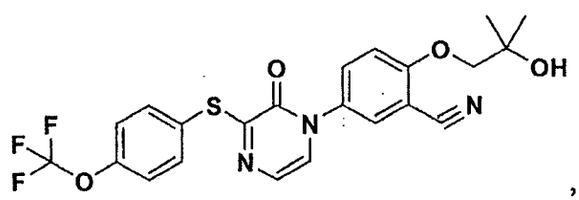

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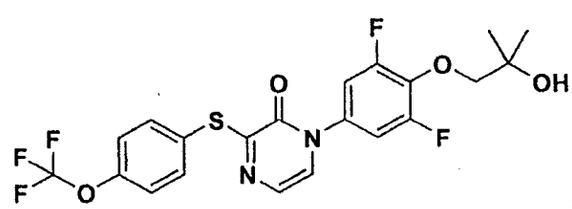
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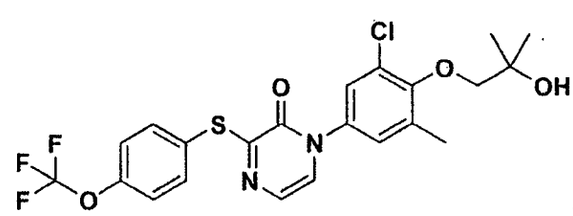
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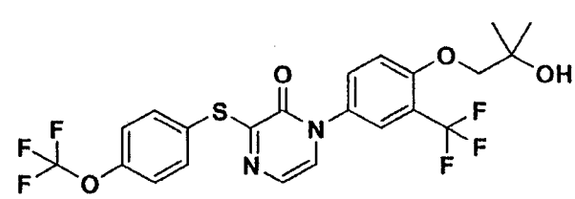

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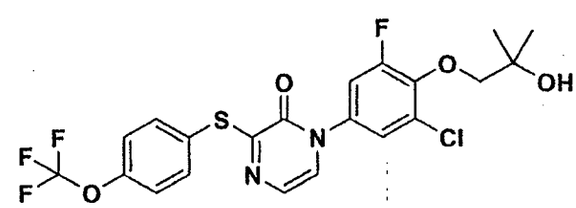

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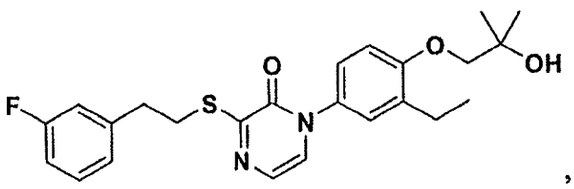

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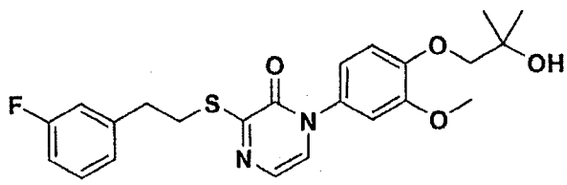

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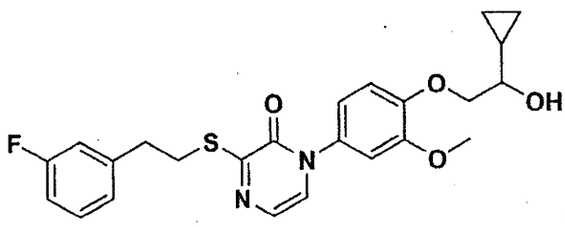
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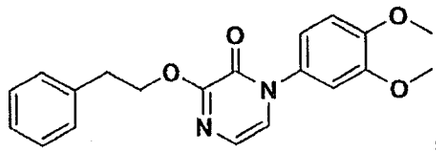
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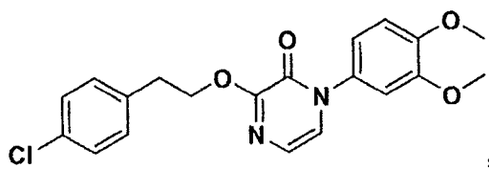
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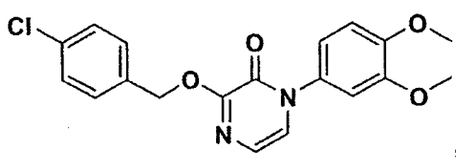
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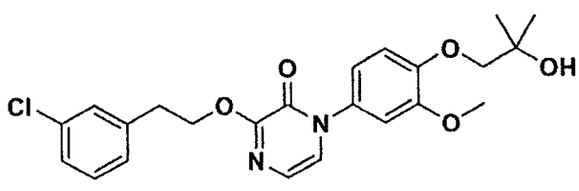
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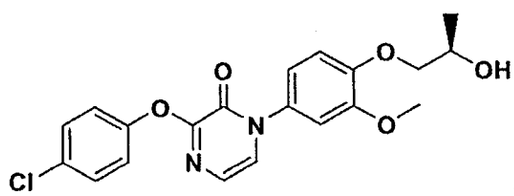
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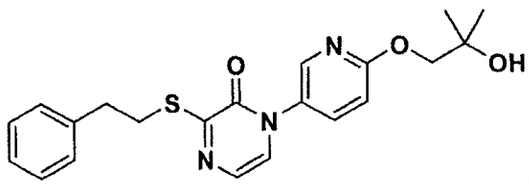
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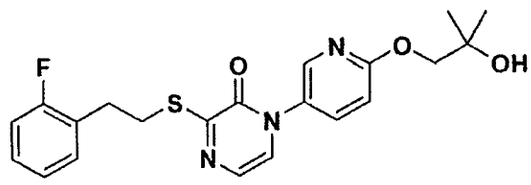
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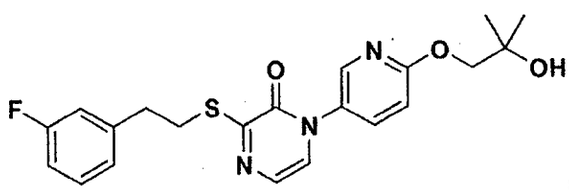
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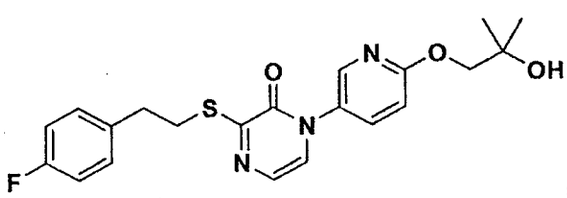
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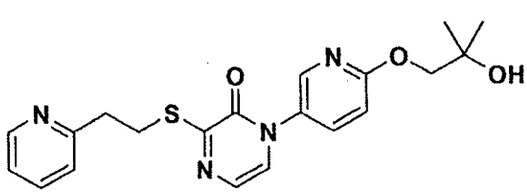
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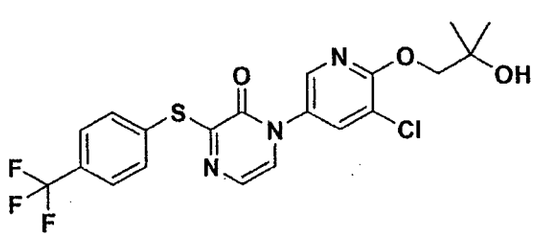
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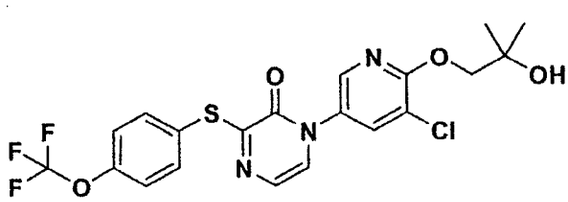
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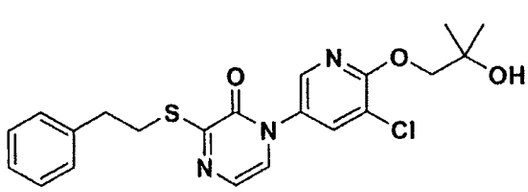
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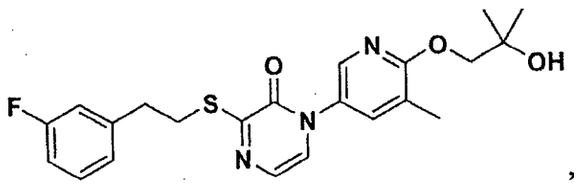
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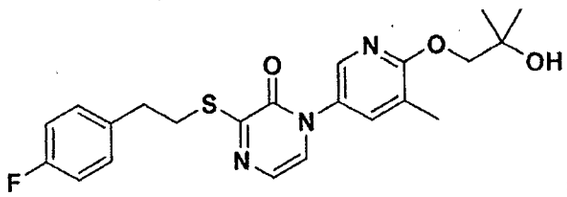


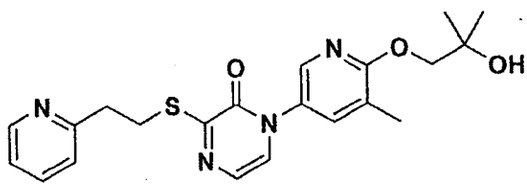
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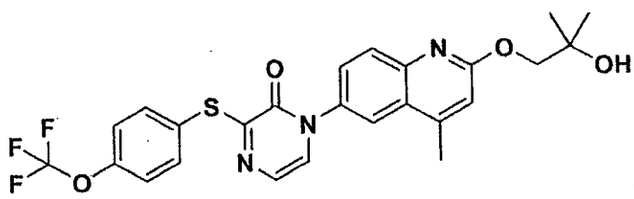
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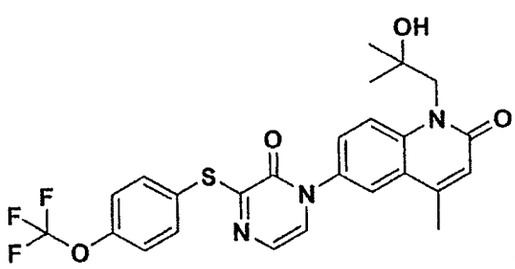
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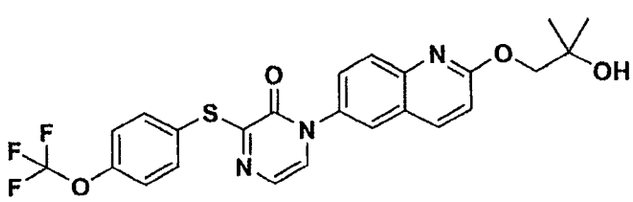

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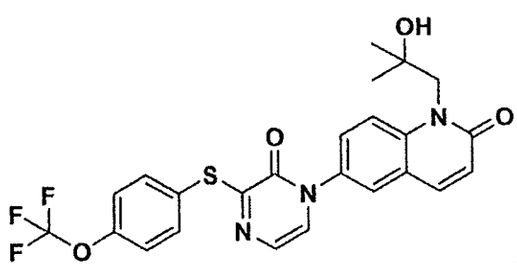

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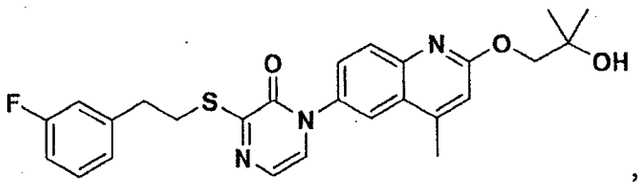

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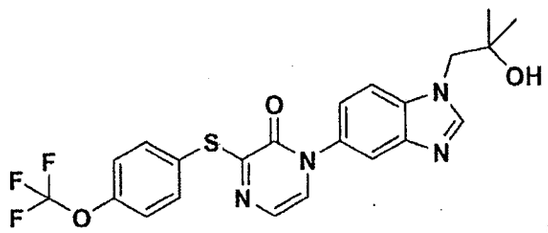

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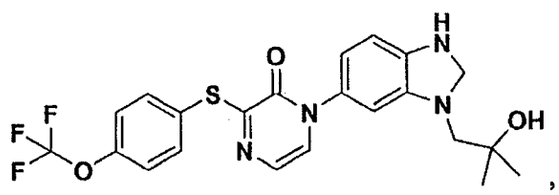

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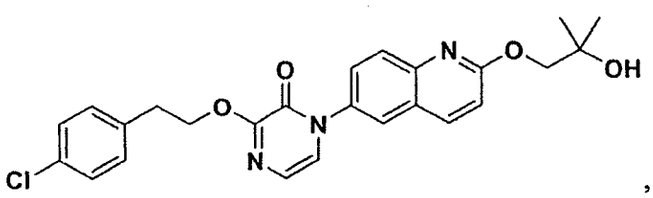
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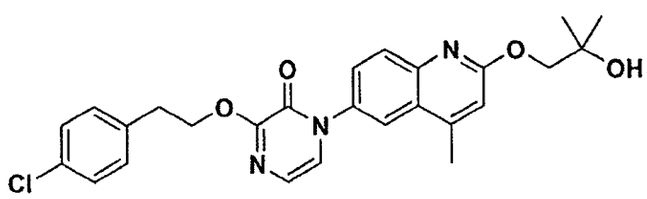
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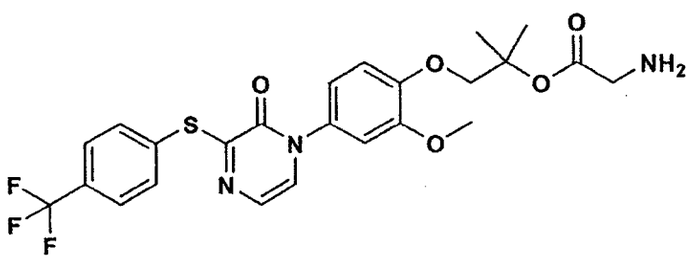

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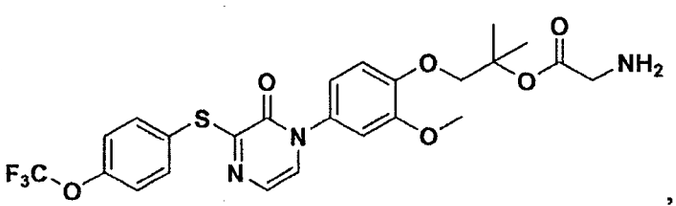

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