

04-10956.

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E. S. D.

Trámite : 011 Evento : 379 Actuación : 444

Referencia : Expediente No. 04010956
Asunto : REGISTRO - PATENTE PCT COMPUESTOS DE
ALQUILAMIDA N- (3-AMINO-2-HYDROXY-PROPIYL)
SUSTITUIDOS
Solicitante : ELAN PHARMACEUTICALS, INC. AND PHARMACIA
& UPJOHN COMPANY
Clase : A61K 031/164, A61P 025/028, C07C 233/035

1. Yo, Emilio FERRERO, obrando como apoderado del solicitante en el asunto antes identificado, me refiero al Oficio No. 14734 notificado por fijación en lista del 16 de Noviembre de 2007. Mediante memorial radicado el 8 de febrero de 2008 solicité un plazo de treinta (30) días para dar respuesta a este oficio.

2. Mediante el Oficio No. 14734 se puso en conocimiento del solicitante el informe del examen de fondo que contiene las observaciones hechas por su Despacho sobre la presente solicitud de patente. Atiendo a las observaciones de la siguiente manera:

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3. De la solicitud de patente:

Con el fin de atender las anteriores observaciones y de acuerdo al artículo 34 de la Decisión 486, se presenta un nuevo capítulo reivindicatorio como sustituto del anteriormente presentado.

En este nuevo capítulo reivindicatorio se cancelan las reivindicaciones 1 a 14, y las reivindicaciones 17 a 20. De tal manera que el nuevo capítulo reivindicatorio esta constituido por cuatro (4) reivindicaciones (donde se incluyen las reivindicaciones 15 y 16 del anterior capítulo reivindicatorio), las cuales son ahora independientes.

De esta manera las siguientes objeciones quedan superadas:

3.1 Descripción (artículo 28 D.486)

Su Despacho enuncia lo siguiente:

"Esta oficina se permite señalar que los estudios de actividad de inhibición realizados a los compuestos de la invención no reportan resultados que permitan evidenciar la ventaja comparativa de los mismos frente a otros conocidos en el estado de la técnica"

Con respecto a lo señalado por su Despacho mi representada desea señalar lo siguiente:

En la presente solicitud de patente en la ultima oración del ejemplo A se dice que: " En este ensayo, los compuestos de la invención exhibieron un IC_{50} menor a 50 micro molar". Por lo

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tanto, la solicitud si proporciona datos experimentales que ilustran la ventaja de los compuestos reivindicados en comparación a los compuestos definidos en el estado del arte.

Adicional se presentara anexo a esta respuesta, datos experimentales específicos de IC₅₀, datos MS y estructura que sustentan las ventajas de los compuestos en la tabla de las páginas 94-116.

3.2 Reivindicaciones (artículo 30 D 486)

Las reivindicaciones objetadas fueron eliminadas del nuevo pliego reivindicatorio.

4. Unidad de invención (artículo 25 D486)

Eliminada la reivindicación 1, la gran cantidad de compuestos generados al realizar las sustituciones de los radicales (en especial B,R4, R'4 y Rc) no se presentan diversas estructuras químicas, por lo cual la invención acá reivindicada guarda unidad de invención.

5. Excepción a la patentabilidad (artículo 20 D486 a)-d))

Debido a que las reivindicaciones 17 y 18 fueron canceladas, la objeción formulada a este respecto se debe tener por superada.

6. Reivindicaciones relativas a un uso o a un uso distinto (artículos 14 y 21 D486)

La reivindicación 19 fue cancelada y por tanto la objeción se debe tener por superada.

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7. Evaluación de los requisitos de patentabilidad:

Su Despacho concluye que el nivel inventivo de las reivindicaciones 1 a 16 de la presente solicitud de patente se ven afectadas por los documentos GB2184730 (D1) y WO9833795 (D2).

Su despacho enuncia:

"...resultaría obvio el diseño de fármacos inhibidores de la betasecretasa de las reivindicaciones 1 a 16"

Con respecto a que los documentos D1 y D2 afectan el nivel inventivo de la presente solicitud, mi representada desea señalar lo siguiente:

La referencia DI (GB 2184730) define compuestos de formula:

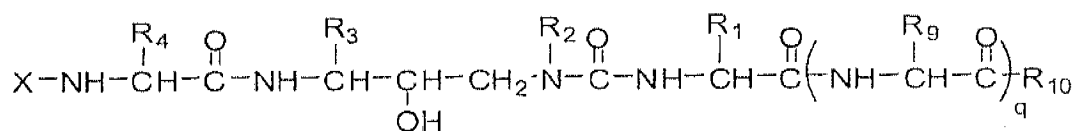


Ilustración 1

Donde, según lo que se entiende R₃ en la ilustración 1 corresponde a R1 en la presente solicitud de patente. Siendo esto así, entonces la fracción mostrada en la ilustración 2 corresponde a la fracción mostrada en la ilustración 3 de las reivindicaciones estudiadas.

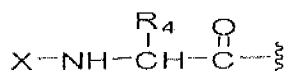


Ilustración 2

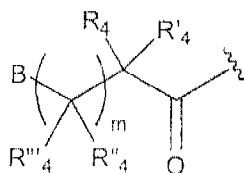


Ilustración 3

El grupo X de la referencia D1 esta definido como uno de los siete (7) grupos diferentes, de los cuales ninguno esta incluido en el grupo B de las reivindicaciones estudiadas.

Adicionalmente, la fracción derecha de la molécula descrita en D1 es:

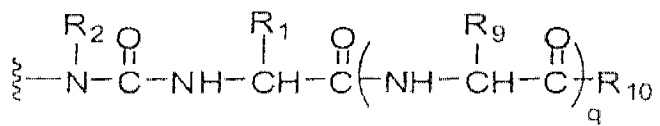


Ilustración 4

Y contiene un grupo urea sustituido opcionalmente (-N(R2)-C(O)-NH-), los cuales no están incluidos en los grupos -NHRc de las reivindicaciones estudiadas.

Por lo tanto, la materia revelada en las reivindicaciones estudiadas difieren de las enseñanzas del documento D1 y adicionalmente, es inventiva.

De otro lado, la referencia D2 (W09833795), enseña los compuestos de formula:

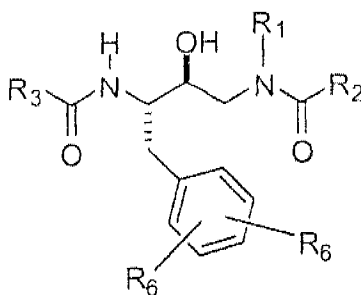


Ilustración 5

Donde R_1 es "seleccionado del grupo que consiste de alquilo, alquilo sustituido, arilo sustituido, ariloalquilo, ariloalquilo sustituido, ariloxialquilo, ariloxialquilo sustituido, heteroaril, heteroaril sustituido, heteroarilalquilo, heteroarilalquilo sustituido, heterociclo, heterociclo sustituido, heterocicloalquilo y heterocicloalquilo sustituido."

(Ver página 4, líneas 15 a 19. Ver también página 5, líneas 1-5, y figures 4A, 5A y 6A, donde los grupos R_1 preferidos son divulgados).

Al examinar las definiciones anteriormente mencionadas y la aplicación como un todo, está claro que el hidrógeno no esta comprendido en R_1 .

En contraste, las reivindicaciones pendientes incluyen componentes de formula:

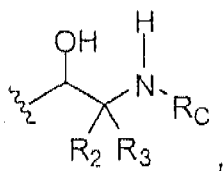


Ilustración 6

Donde el grupo $-NH-R_C$ de las reivindicaciones estudiadas corresponde al grupo $-N(R_1)-C(O)-R_2$ de la referencia D2. Es decir,

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las reivindicaciones estudiadas requieren de la presencia de un grupo NH; en cambio la estructura correspondiente en la referencia D2 no permite un grupo NH. Además, D2 no enseña o sugiere que habría alguna ventaja en el caso que el radical R1 fuera un hidrógeno. Como resultado, las estructuras son diferentes y las reivindicaciones estudiadas son inventivas con respecto a D2.

Así entonces, no se considera que para una persona versada en la materia correspondiente, esta invención pudiera resultar obvia o se derive de manera evidente de la combinación de los documentos referenciados en el estado de la técnica debido a que es difícil imaginar obtener los compuestos reivindicados en la presente solicitud a partir de los documentos referenciados.

Incluso si la persona versada en el tema fuera capaz de derivar las reivindicaciones actualmente solicitadas a patentar (propuesta que no compartimos), no hay razón alguna para que esta persona combine de una manera particular las enseñanzas de los documentos D1 y D2 obteniendo la combinación particular de los grupos reivindicados en la presente solicitud.

Por ejemplo, como se discutió anteriormente, D2 no permite la presencia de hidrógeno en el nitrógeno. Por tanto, no se vislumbra en los documentos referenciados enseñanzas que orienten a una persona versada a reemplazar el radical R1 (anteriormente mencionado) con hidrógeno, simultáneamente previendo expectativas razonables de éxito.

De modo que, se debe tener en cuenta que la combinación de los documentos D1 y D2, y los documentos por si solos no afectan el nivel inventivo de la presente invención por cuanto sus

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enseñanzas no llevarían a una persona versada en la materia a cambiar el producto de D1 o D2 hacia los compuestos reivindicados en la presente solicitud.

Teniendo en cuenta las modificaciones hechas al capítulo reivindicatorio y los argumentos a favor del nivel inventivo se puede concluir que la presente invención es inventiva frente a los documentos D1 y D2 citados por su Despacho, porque: 1) las referencias citadas no enseñan los compuestos reivindicados en la presente solicitud, 2) las referencias citadas no enseñan la combinación de los grupos reivindicados en la presente solicitud y 3) el estado del arte no dirige a una persona versada en el tema a cambiar las referencias de tal forma que se obtengan los compuestos reivindicados. Por consiguiente, no resulta obvia la invención y no se deriva de manera evidente del estado de la técnica ya que un técnico medio que realiza el examen debe partir del conocimiento general que se tiene sobre el estado de la técnica y determinar si con tales conocimientos técnicos ya existentes se puede producir tal invención y este no es el caso.

Con las anteriores modificaciones se debe tener por superada la objeción formulada por nivel inventivo a las reivindicaciones 15 y 16, nuevas reivindicaciones 1 y 2.

Puesto que se han atendido a cabalidad las observaciones hechas por su Despacho sobre la presente solicitud de patente, respetuosamente solicito se continúe con su tramitación.

De acuerdo con el artículo 36 de la Decisión 486, mi representado se reserva el derecho a presentar una solicitud divisional de patente con las reivindicaciones eliminadas,

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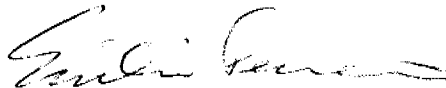
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beneficiándose de la fecha de prioridad inicialmente reivindicada.

6. Anexos:

- Nuevo pliego reivindicatorio conformado por 4 reivindicaciones.
- Formulario para modificaciones.
- Recibo por concepto de modificaciones en solicitud pendiente.
- Anexos de los datos IC50, estructura y hoja de seguridad para los compuestos en la tabla en las páginas 94-116.

Señora Jefe,



EMILIO FERRERO

T.P.A. No. 31.929

COLO-13562-841-003-1

127 MGM\MGM\ID-121819\WPC13562

No. M-2008-121819\MGM

FORMULARIO UNICO DE CORRECCIONES Y MODIFICACIONES

1	SOLICITUD DE: ☐ Corrección de Error Material ☒ Modificación a una solicitud	
2 SOLICITANTE	Nombre: ELAN PHARMACEUTICALS, INC. y PHARMACIA & UPJOHN COMPANY Sociedades constituidas y existentes bajo las leyes de los Estados de California y Delaware, Estados Unidos de América. Dirección: 800 Gateway Boulevard, South San Francisco, California 94080, Estados Unidos de América Y 301 Henrieta Street, Kalamazoo, Michigan 49007, Estados Unidos de América Domicilio: South San Francisco, California, Estados Unidos de América Y Kalamazoo, Michigan, Estados Unidos de América Respectivamente Teléfono: 546 09 70 Fax: 249 40 70 E-mail: clientes@cavelier.com	IDENTIFICACION C.C. ☐ NIT ☐ C.E. ☐ Otro ☐ Número: _____
3 REPRESENTANTE O APODERADO	Nombre: Emilio FERRERO Dirección: Carrera 4ª No. 72-35 Teléfono: 347 36 11 Fax: 217 92 11 E-mail: cavelier@cavelier.com	IDENTIFICACION C.C. ☒ NIT ☐ C.E. ☐ Otro ☐ Número: <u>438.019 TP 31.929</u>
4	Número de expediente: <u>04.010.956</u>	
5	Descripción de la corrección o modificación solicitada: Presento nuevo capítulo reivindicatorio compuesto por 4 reivindicaciones con el fin de superar las objeciones hechas por Su Despacho a la presente solicitud de patente y pido que el examen de patentabilidad sea realizado sobre este nuevo capítulo reivindicatorio.	
6	Comprobante de pago No. <u>08-23.310</u> Fecha: <u>17 de marzo de 2008</u>	

7	Anexos	
☒	Comprobante de pago de la tasa por \$103.000.00 por concepto de modificaciones.	
☐	Poderes, si fuere el caso	
☐	Documento que acredita la existencia y representación legal de las partes, cuando sean personas jurídicas.	
8	NOMBRE: EMILIO FERRERO	FIRMA: 
C.C. 438.019 de Usaquén T.P.A. 31.929		
MGM		

REIVINDICACIONES

1. Un compuesto seleccionado de

5

N-{(1S,2R)-1-bencil-2-hidroxi-3-[(3-metoxibencil)aminopropil]}-3-(1,1-dióxido-3-oxo-1,2-bencisotiazol-2(3H)-il)propanamida;

10

N-{(1S,2R)-1-bencil-2-hidroxi-3-[(3-metoxibencil)aminopropil]}-3-(1,3-dioxo-1,3-dihidro-2H-isoindol-2-il) propanamida;

15

N-{(1S,2R)-1-bencil-2-hidroxi-3-[(3-metoxibencil)aminopropil]}-4-(4-fluorofenil)-4-oxobutanamida;

N-{(1S,2R)-1-bencil-3-[(2,3-dimetilciclohexil)amino]-2-hidroxi-3-fenilbutanamida;

20

N-((1S,2R)-1-bencil-3-{[3-(dimetilamino)-2,2-dimetilpropil]amino}-2-hidroxi-3-fenilbutanamida;

25

N-((1S,2R)-1-bencil-3-{[3-(dimetilamino)-2,2-dimetilpropil]amino}-2-hidroxi-3-fenilbutanamida;

N-{(1S,2R)-1-bencil-2-hidroxi-3-[(1-feniletil)aminopropil]}-3-fenilbutanamida;

30

N-{(1S,2R)-1-bencil-2-hidroxi-3-[(1,2,2-trimetilpropil)aminopropil]}-2-fenilbutanamida;

N-{(1S,2R)-1-bencil-2-hidroxi-3-[(1,2,2-trimetilpropil)aminopropil]}-3-fenilbutanamida;

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N-{(1S,2R)-1-bencil-3-[(1,3-dimetilbutil)amino]-2-hidroxi-3-fenilbutanamida;

N-{(1S,2R)-1-bencil-3-[(1,3-dimetilbutil)amino]-2-hidroxi-
hidroxipropil}-3-fenilbutanamida;

- 5 N-{(1S,2R)-1-bencil-3-[(1-etilpropil)amino]-2-hidroxi-
2-hidroxi-3-fenilbutanamida;

N-{(1S,2R)-1-bencil-3-[(1-etilpropil)amino]-2-hidroxi-
3-fenilbutanamida;

10

N-{(1S,2R)-1-(3,5-difluorobencil)-2-hidroxi-3-[(3-
yodobencil)amino]propil}-2-(5-metoksi-1,2,3,4-
tetrahidronaftalen-1-il) acetamida;

- 15 2-[4-(2-amino-2-oxoetoksi)fenil]-N-{(1S,2R)-1-(3,5-
difluorobencil)-2-hidroxi-3-[(3-yodobencil)amino]
propil}acetamida;

- 20 N-{(1S,2R)-1-(3,5-difluorobencil)-2-hidroxi-3-[(3-
yodobencil)amino]propil}-2-[4-(2-oxo-2-pirrolidin-1-iletoksi)
fenil] acetamida;

- N-{(1S,2R)-1-(3,5-difluorobencil)-2-hidroxi-3-[(3-
yodobencil)amino]propil}-2-(4-[(metilsulfonil)amino]
25 fenil}acetamida;

N-{(1S,2R)-1-(3,5-difluorobencil)-2-hidroxi-3-[(3-
yodobencil)amino] propil}-4-oxo-4-piridin-2-ilbutanamida;

- 30 N-{(1S,2R)-1-(3,5-difluorobencil)-2-hidroxi-3-[(3-
yodobencil)amino]propil}-2-(4-[2-(4-metilpiperazin-1-
il)etoksi] fenil}acetamida;

- 2-[3-(2-amino-2-oxoetoksi)fenil]-N-{(1S,2R)-1-(3,5-
difluorobencil)-2-hidroxi-3-[(3-yodobencil)amino]propil}
35 acetamida;

N-{(1S,2R)-1-(3,5-difluorobencil)-2-hidroxi-3-[(3-

yodobencil) amino] propil}-4-(2,3-dihidro-1H-inden-1-il)
butanamida;

5 N-{(1S,2R)-1-(3,5-difluorobencil)-2-hidroxi-3-[(3-
yodobencil) amino] propil}-2-metil-2-(2-metil-2,3-dihidro-1-
benzofuran-5-il) propanamida;

10 N-{(1S,2R)-1-(3,5-difluorobencil)-2-hidroxi-3-[(3-
yodobencil) amino] propil}-3-hidroxi-4-fenoxi-3-
fenilbutanamida;

2-(1,1'-bifenil-4-il)-N-{(1S,2R)-1-(3,5-difluorobencil)-2-
hidroxi-3-[(3-yodobencil) amino] propil}butanamida;

15 N-{(1S,2R)-1-(3,5-difluorobencil)-2-hidroxi-3-[(3-
yodobencil) amino] propil}-4-(4-fenoxifenil)butanamida;

20 N-{(1S,2R)-1-(3,5-difluorobencil)-2-hidroxi-3-[(3-
yodobencil) amino] propil}-2-(4-fenoxifenil) acetamida;

2-[3-cloro-4-(1-oxo-1,3-dihidro-2H-isoindol-2-il) fenil]-N-
{(1S,2R)-1-(3,5-difluorobencil)-2-hidroxi-3-[(3-
yodobencil) amino] propil}propanamida;

25 N-{(1S,2R)-1-(3,5-difluorobencil)-2-hidroxi-3-[(3-
yodobencil) amino] propil}-4-(2,4-dimetifenil)-4-oxobutanamida;

30 N-{(1S,2R)-1-(3,5-difluorobencil)-2-hidroxi-3-[(3-
yodobencil) amino] propil}-4-(7-metoxi-2-metil-1-benzofuran-4-
il)-4-oxobutanamida;

4'-[4-({(1S,2R)-1-(3,5-difluorobencil)-2-hidroxi-3-[(3-
yodobencil) amino] propil} amino)-4-oxobutanoil]-1,1'-bifenil-2-
carboxamida;

35 N-{(1S,2R)-1-(3,5-difluorobencil)-2-hidroxi-3-[(3-
yodobencil) amino] propil}-4-{2-[(metilsulfonil) amino] fenil}-4-

oxobutanamida;

(2Z)-N-{(1S,2R)-1-(3,5-difluorobencil)-2-hidroxi-3-[(3-yodobencil)amino]propil}-2-fenil-3-piridin-4-ilprop-2-enamida;

N-{(1S,2R)-1-(3,5-difluorobencil)-2-hidroxi-3-[(3-yodobencil)amino]propil}-2-[4-(1,3-dihidro-2H-isoindol-2-il)fenil]propanamida;

N-{(1S,2R)-1-(3,5-difluorobencil)-2-hidroxi-3-[(3-yodobencil)amino]propil}-2-(2,3-dihidro-1H-inden-5-il)butanamida;

N-((1S,2R)-1-(3,5-difluorobencil)-2-hidroxi-3-[(3-yodobencil)amino]propil)-2-(6-oxopiridazin-1(6R)-il)acetamida;

N-{(1S,2R)-1-(3,5-difluorobencil)-2-hidroxi-3-[(3-yodobencil)amino]propil}-2-[(metilsulfonil)amino]-4-fenilbutanamida;

N-{(1S,2R)-1-(3,5-difluorobencil)-2-hidroxi-3-[(3-yodobencil)amino]propil}-2-(4-hidroxi-5-isopropil-2-metilfenil)acetamida;

N-{(1S,2R)-1-(3,5-difluorobencil)-2-hidroxi-3-[(3-yodobencil)amino]propil}-2-[4-(2-metilprop-1-enil)fenil]propanamida;

N-{(1S,2R)-1-(3,5-difluorobencil)-2-hidroxi-3-[(3-yodobencil)amino]propil}-2-[4-(tien-2-ilcarbonil)fenil]propanamida;

(2R)-N-{(1S,2R)-1-(3,5-difluorobencil)-2-hidroxi-3-[(3-yodobencil)amino]propil}-2-(6-metoxi-2-naftil)propanamida;

N-{(1S,2R)-1-(3,5-difluorobencil)-2-hidroxi-3-[(3-yodobencil)amino]propil}-2-[4-(2-oxopirrolidin-1-

il)fenil]acetamida;

N-{(1S,2R)-1-(3,5-difluorobencil)-2-hidroxi-3-[(3-yodobencil)amino]propil}-2-(3,4-dihidronaftalen-1-

5 il)butanamida;

N-{(1S,2R)-1-bencil-2-hidroxi-3-[(3-metoxibencil)amino]propil}-2-(4-isopropilfenil)acetamida;

10 N-{(1S,2R)-1-bencil-2-hidroxi-3-[(3-metoxibencil)amino]propil}-2-[4-(metiltio)fenil]acetamida;

N-{(1S,2R)-1-(3,5-difluorobencil)-2-hidroxi-3-[(piridin-2-ilmetil)amino]propil}-3-fenilpropanamida

15

N-((1S,2R)-1-(3,5-difluorobencil)-2-hidroxi-3-[(2-metoxi-1-metiletil)amino]propil)-3-fenilpropanamida;

N-{(1S,2R)-1-(3,5-difluorobencil)-2-hidroxi-3-[(2-hidroxi-1-

20 metiletil)amino]propil}-3-fenilpropanamida;

N-[(1S,2R)-3-(bencilamino)-1-(3,5-difluorobencil)-2-hidroxipropil]-3-fenilpropanamida;

25 N-{(1S,2R)-1-(3,5-difluorobencil)-2-hidroxi-3-[(3-metoxibencil)amino]propil}-3-fenilpropanamida;

N-((1S,2R)-1-(3,5-difluorobencil)-3-[(2-furilmetil)amino]-2-hidroxipropil)-3-fenilpropanamida;

30

N-((1S,2R)-1-(3,5-difluorobencil)-2-hidroxi-3-[(2-metoxi-1-metiletil)amino]propil)-3-(1H-indol-1-il)propanamida;

N-{(1S,2R)-1-(3,5-difluorobencil)-2-hidroxi-3-[(2-hidroxi-1-

35 metiletil)amino]propil}-3-(1H-indol-1-il)propanamida;

N-[(1S,2R)-3-(bencilamino)-1-(3,5-difluorobencil)-2-

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hidroxipropil]-3-(1H-indol-1-il)propanamida;

N-{(1S,2R)-1-(3,5-difluorobencil)-3-[(2-furilmetil)amino]-2-hidroxipropil}-3-(1H-indol-1-il)propanamida;

5

N-[(1S,2R)-3-[(ciclopropilmetil)amino]-1-(3,5-difluorobencil)-2-hidroxipropil]-3-(1H-indol-1-il)propanamida;

10 N-((1S,2R)-1-(3,5-difluorobencil)-2-hidroxi-3-[(3-yodobencil)amino]propil)-3-(1H-indol-1-il)propanamida;

N-{(1S,2R)-1-(3,5-difluorobencil)-2-hidroxi-3-[(4-metilbencil)amino]propil}-2-(4-isopropilfenil)acetamida;

15

N-{(1S,2R)-1-(3,5-difluorobencil)-2-hidroxi-3-[(2-metoxi-1-metiletil)amino]propil}-2-(4-isopropilfenil)acetamida;

20 N-{(1S,2R)-1-(3,5-difluorobencil)-2-hidroxi-3-[(2-metoxi-1-metiletil)amino]propil}-2-(4-isopropilfenil)acetamida;

N-{(1S,2R)-1-(3,5-difluorobencil)-2-hidroxi-3-[(2-hidroxi-1-metiletil)amino]propil}-2-(4-isopropilfenil)acetamida;

25 N-[(1S,2R)-3-(bencilamino)-1-(3,5-difluorobencil)-2-hidroxipropil]-2-(4-isopropilfenil)acetamida;

N-{(1S,2R)-1-(3,5-difluorobencil)-2-hidroxi-3-[(4-metilbencil)amino]propil}-2-[4-(metiltio)fenil]acetamida;

30

N-((1S,2R)-1-(3,5-difluorobencil)-2-hidroxi-3-[(2-metoxi-1-metiletil)amino]propil)-2-[4-(metiltio)fenil]acetamida;

35 N-{(1S,2R)-1-(3,5-difluorobencil)-2-hidroxi-3-[(2-hidroxi-1-metiletil)amino]propil}-2-[4-(metiltio)fenil]acetamida;

N-[(1S,2R)-3-(bencilamino)-1-(3,5-difluorobencil)-2-hidroxi-3-[(3,5-difluorobencil)-2-hidroxi-3-[(3-yodobencil)amino]propil]-2-(4-isopropilfenil)acetamida;

5 N-[(1S,2R)-1-(3,5-difluorobencil)-2-hidroxi-3-[(3,5-difluorobencil)amino]propil]-2-(4-isopropilfenil)acetamida;

N-[(1S,2R)-3-(butilamino)-1-(3,5-difluorobencil)-2-hidroxi-3-[(3,5-difluorobencil)-2-hidroxi-3-[(3-yodobencil)amino]propil]-2-(4-isopropilfenil)acetamida;

10 N-[(1S,2R)-1-(3,5-difluorobencil)-3-{[2-(1,3-dioxolan-2-il)etil]amino}-2-hidroxi-3-[(3,5-difluorobencil)-2-hidroxi-3-[(3-yodobencil)amino]propil]-2-(4-isopropilfenil)acetamida;

15 N-[(1S,2R)-1-(3,5-difluorobencil)-2-hidroxi-3-[(3,5-difluorobencil)amino]propil]-2-(4-isopropilfenil)acetamida;

N-[(1S,2R)-1-(3,5-difluorobencil)-2-hidroxi-3-[(3,5-difluorobencil)amino]propil]-2-[4-(metiltio)fenil]acetamida;

20 N-[(1S,2R)-1-(3,5-difluorobencil)-3-[(2-furilmetil)amino]-2-hidroxi-3-[(3,5-difluorobencil)-2-hidroxi-3-[(3-yodobencil)amino]propil]-2-[4-(metiltio)fenil]acetamida;

N-[(1S,2R)-3-(butilamino)-1-(3,5-difluorobencil)-2-hidroxi-3-[(3,5-difluorobencil)-2-hidroxi-3-[(3-yodobencil)amino]propil]-2-[4-(metiltio)fenil]acetamida;

25 N-[(1S,2R)-1-(3,5-difluorobencil)-3-{[2-(1,3-dioxolan-2-il)etil]amino}-2-hidroxi-3-[(3,5-difluorobencil)-2-hidroxi-3-[(3-yodobencil)amino]propil]-2-[4-(metiltio)fenil]acetamida;

30 N-[(1S,2R)-1-(3,5-difluorobencil)-2-hidroxi-3-[(3,5-difluorobencil)amino]propil]-2-(4-isopropilfenil)acetamida;

35 3-[2-(benciloxi)-4,6-dimetilfenil]-N-[(1S,2R)-1-(3,5-difluorobencil)-2-hidroxi-3-[(3-yodobencil)amino]propil]-3-metilbutanamida;

2-[4-(benciloxi)fenil]-N-[(1S,2R)-1-(3,5-difluorobencil)-2-

N-{(1S,2R)-1-(3,5-difluorobenz~)-2-hidroxi-3-[(3-yodobencil)amino]propil}-3-(2-fluorofenil)propanamida;

N-{ (1S,2R)-1-(3,5-difluorobencil)-2-hidroxi-3-[(3-yodobencil) amino]propil}-4-(7-metoxi-2,3-dihidro-1-benzofuran-4-il)-4-oxobutanamida;

N-{(1S,2R)-1-(3,5-difluorobencil)-3-[(3-etilbencil) amino]-2-hidroxiopropil}-2-(4-hidroxi-3-metoxifenil) acetamida;

N-{(1S,2R)-1-(3,5-difluorobencil)-3-[(3-etilbencil) amino]-2-hidroxiopropil}-2-(3-hidroxifenil)acetamida;

N-{(1S,2R)-1-(3,5-difluorobencil)-3-(3-etilbencil)amino}-2-hidroxiopropil}-2-(3-tien-2-il-1H-pirazol-1-il)acetamida;

3-(1H-benzimidazol-2-il)-N-{(1S,2R)-1-(3,5-difluorobencil)-3-
[(3-etilbencil)amino]-2-hidroxiopropil}-3-hidroxiopropanamida;

N-{ (1S,2R) -1-(3,5-difluorobencil)-3-[(3-etilbencil) amino]-2-hidroxiopropil }-2-(4-morfolin-4-ilfenil) acetamida;

N-{ (1S,2R) -1-(3,5-difluorobencil) -3- [(3-etilbencil) amino] -2-

hidroxipropil}-3-(3-piridin-2-il-1,2,4-oxadiazol-5-il)propanamida;

5 N-((1S,2R)-1-(3,5-difluorobencil)-3-[(3-etilbencil)amino]-2-hidroxipropil)-2-(2-etil-1H-bencimidazol-1-il)acetamida;

N-((1S,2R)-1-(3,5-difluorobencil)-3-[(3-etilbencil)amino]-2-hidroxipropil)-2-(5-hidroxi-7-metil[1,2,4]triazolo[4,3-a]pirimidin-3-il)acetamida;

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N-((1S,2R)-1-(3,5-difluorobencil)-3-[(3-etilbencil)amino]-2-hidroxipropil)-2-[(4-metil-4H-1,2,4-triazol-3-il)tio]-2-fenilacetamida;

15 N-((1S,2R)-1-(3,5-difluorobencil)-3-[(3-etilbencil)amino]-2-hidroxipropil)-2-[5-(2-metilfenil)-2H-tetraazol-2-il]acetamida;

20 3-(1,3-benzotiazol-2-il)-N-((1S,2R)-1-(3,5-difluorobencil)-3-[(3-etilbencil)ainino]-2-hidroxipropil)-3-metoxipropanamida;

1-acetil-N-((1S,2R)-1-(3,5-difluorobencil)-3-[(3-etilbencil)amino]-2-hidroxipropil)-2-fenilprolinamida;

25 N-((1S,2R)-1-(3,5-difluorobencil)-3-[(3-etilbencil)amino]-2-hidroxipropil)-2-(2-metil-2,3-dihidro-1-benzofuran-5-il)propanamida;

30 N-((1S,2R)-1-(3,5-difluorobencil)-3-[(3-etilbencil)amino]-2-hidroxipropil)-2-(3-metil-2-oxo-2,3-dihidro-1H-bencimidazol-1-il)acetamida;

N-((1S,2R)-1-(3,5-difluorobencil)-3-((3-etilbencil)amino)-2-hidroxipropil)-3-(6-etoxi-1H-bencimidazol-2-il)propanamida;

35

N-((1S,2R)-1-(3,5-difluorobencil)-3-[(3-etilbencil)amino]2-hidroxipropil)-4-(2,3-dihidro-1H-indol-1-il)-4-oxobutanamida;

N-{(1S,2R)-1-(3,5-difluorobencil)-3-[(3-etilbencil)amino]-2-hidroxi-
propil}-4-(2-oxo-1,3-benzoxazol-3(2H)-il)butanamida;

5 N-{(1S,2R)-1-(3,5-difluorobencil)-3-[(3-etilbencil)amino]-2-hidroxi-
propil}-2-(5-fenil-1H-tetrazol-1-il)acetamida;

2-[5-(1,3-benzodioxol-5-il)-2H-tetrazol-2-il]-N-{(1S,2R)-1-(3,5-difluorobencil)-3-[(3-etilbencil)amino]-2-
10 hidroxi-propil}acetamida;

2-(1H-1,2,3-benzotriazol-1-il)-N-{(1S,2R)-1-(3,5-difluorobencil)-3-[(3-etilbencil)amino]-2-
hidroxi-propil}hexanamida;

15 3-(1,3-benzodioxol-5-il)-N-{(1S,2R)-1-(3,5-difluorobencil)-3-[(3-etilbencil)amino]-2-hidroxi-
propil}propanamida;

N-{(1S,2R)-1-(3,5-difluorobencil)-3-[(3-etilbencil)amino]-2-hidroxi-
20 propil}-2-(1,3-dioxo-1,3-dihidro-2H-isoindol-2-il)acetamida;

N-{(1S,2R)-1-(3,5-difluorobencil)-3-[(3-etilbencil)amino]-2-hidroxi-
25 propil}-3-(1,3-dioxo-1,3-dihidro-2H-isoindol-2-il)propanamida;

N-{(1S,2R)-1-(3,5-difluorobencil)-3-[(3-etilbencil)amino]-2-hidroxi-
propil}-4-oxo-4-fenilbutanamida;

30 2-(5-acetiltien-2-il)-N-{(1S,2R)-1-(3,5-difluorobencil)-3-[(3-etilbencil)amino]-2-hidroxi-
propil}acetamida;

N-{(1S,2R)-1-(3,5-difluorobencil)-3-[(3-etilbencil)amino]-2-hidroxi-
propil}-2-tien-2-ilacetamida;

35 N-{(1S,2R)-1-(3,5-difluorobencil)-3-[(3-etilbencil)amino]-2-hidroxi-
propil}-2-(1,3-dimetil-2,6-dioxo-1,2,3,6-tetrahidro-

7H-purin-7-il)acetamida;

N-{(1S,2R)-1-(3,5-difluorobencil)-3-[(3-etilbencil)amino]-2-hidroxi-
propil}-4-(3-hidroxi-fenil)-4-oxobutanamida;

5

N-{(1S,2R)-1-(3,5-difluorobencil)-3-[(3-etilbencil)amino]-2-hidroxi-
propil}-4-(3-metoksi-fenil)-4-oxobutanamida;

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N-{(1S,2R)-1-(3,5-difluorobencil)-3-[(3-etilbencil)amino]-2-hidroxi-
propil}-4-(1H-indol-3-il)-4-oxobutanamida;

2-(1-benzotien-4-il)-N-{(1S,2R)-1-(3,5-difluorobencil)-3-[3-
etilbencil)amino]-2-hidroxi-propil}acetamida;

15

N-{(1S,2R)-1-(3,5-difluorobencil)-3-[(3-etilbencil)amino]-2-hidroxi-
propil}-2-(1,3-dimetil-2-dioxi-1,2,3,6-tetrahidro-9H-purin-9-il)acetamida;

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N-{(1S,2R)-1-(3,5-difluorobencil)-3-[(3-etilbencil)amino]-2-hidroxi-
propil}-2-hidroxi-2-fenil-2-tien-2-ilacetamida;

N-{(1S,2R)-1-(3,5-difluorobencil)-3-[(3-etilbencil)amino]-2-hidroxi-
propil}-2-(1-oxidopiridin-3-il)acetamida;

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2-(4-cloro-2-oxo-1,3-benzotiazol-3(2H)-il)-N-{(1S,2R)-1-(3,5-difluorobencil)-3-[(3-
etilbencil)amino]-2-hidroxi-propil}acetamida;

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N-{(1S,2R)-1-(3,5-difluorobencil)-3-[(3-etilbencil)amino]-2-hidroxi-
propil}-2-(2,4-dihidroxi-1,3-tiazol-5-il)acetamida;

N-{(1S,2R)-1-(3,5-difluorobencil)-3-[(3-etilbencil)amino]-2-hidroxi-
propil}-2-[2-(4-fluorofenil)-1,3-benzoxazol-5-il]acetamida;

35

N-{(1S,2R)-1-(3,5-difluorobencil)-3-[(3-etilbencil)amino]-2-hidroxi-
propil}-2-(2-piridin-4-il-1,3-benzoxazol-5-

700
101

il) acetamida;

N-{(1S,2R)-1-(3,5-difluorobencil)-3-[(3-etilbencil)amino]-2-hidroxi-
propil}-2-(2-etil-1,3-benzoxazol-5-il) acetamida;

5

2-(2H-1,2,3-benzotriazol-2-il)-N-{(1S,2R)-1-(3,5-difluorobencil)-3-[(3-etilbencil)amino]-2-hidroxi-
propil}butanamida;

10 N-{(1S,2R)-1-(3,5-difluorobencil)-3-[(3-etilbencil)amino]-2-hidroxi-
propil}-4-(1,3-dioxo-1,3-dihidro-2H-isoindol-2-il)-2-hidroxi-
butanamida;

15 2-[2-(acetilamino)-1,3-tiazol-4-il]-N-{(1S,2R)-1-(3,5-difluorobencil)-3-[(3-etilbencil)amino]-2-hidroxi-
propil}acetamida;

N-(1S,2R)-1-(3,5-difluorobencil)-3-[(3-etilbencil)amino]-2-hidroxi-
propil}-2-(2-piridin-2-il-1,3-tiazol-4-il) acetamida;

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N-{(1S,2R)-1-(3,5-difluorobencil)-3-[(3-etilbencil)amino]-2-hidroxi-
propil}-4-{4-[(metilsulfonil)amino]fenil}-4-oxobutanamida;

25 N-{(1S,2R)-1-(3,5-difluorobencil)-3-[(3-etilbencil)amino]-2-hidroxi-
propil}-3-{4-[(metilsulfonil)amino]fenil}propanamida;

N-{(1S,2R)-1-(3,5-difluorobencil)-3-[(3-etilbencil)amino]-2-hidroxi-
propil}-5-(1H-pirazol-1-il)pentanamida;

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N-{(1S,2R)-1-(3,5-difluorobencil)-3-[(3-etilbencil)amino]-2-hidroxi-
propil}-5-(1H-1,2,4-triazol-1-il)pentanamida;

35 N-{(1S,2R)-1-(3,5-difluorobencil)-3-[(3-etilbencil)amino]-2-hidroxi-
propil}-2-(1,3-dioxo-1,3-dihidro-2H-isoindol-2-il)propanamida;

701
702

N-{(1S,2R)-1-(3,5-difluorobencil)-3-[(3-etilbencil)amino]-2-hidroxi-
propil}-4-(1H-imidazol-1-il)butanamida;

5 N-{(1S,2R)-1-(3,5-difluorobencil)-3-[(3-etilbencil)amino]-2-
hidroxi-
propil}-2-(2,6-dihidroxi-
pirimidin-4-il)acetamida;

N-{(1S,2R)-1-(3,5-difluorobencil)-3-[(3-etilbencil)amino]-2-
hidroxi-
propil}-4-(3-fluoro-4-metoxifenil)-4-oxobutanamida;

10 3-(2-clorofenil)-2-ciano-N-{(1S,2R)-1-(3,5-difluorobencil)-3-
[(3-etilbencil)amino]-2-hidroxi-
propil}propanamida;

N-acetil-N-{(1S,2R)-1-(3,5-difluorobencil)-3-[(3-
etilbencil)amino]-2-hidroxi-
propil}-D-fenilalaninamida;

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N-{(1S,2R)-1-(3,5-difluorobencil)-3-[(3-etilbencil)amino]-2-
hidroxi-
propil}-4-(4-metilfenil)-4-oxobutanamida;

20 N-{(1S,2R)-1-(3,5-difluorobencil)-3-[(3-etilbencil)amino]-2-
hidroxi-
propil}-4-(2-hidroxi-5-metilfenil)-4-oxobutanamida;

N-{(1S,2R)-1-(3,5-difluorobencil)-3-[(3-etilbencil)amino]-2-
hidroxi-
propil}-4-oxo-4-tien-2-ilbutanamida;

25 N-{(1S,2R)-1-(3,5-difluorobencil)-3-[(3-etilbencil)amino]-2-
hidroxi-
propil}-4-(2-naftil)-4-oxobutanamida;

4-(1,3-benzodioxol-5-il)-N-{(1S,2R)-1-(3,5-difluorobencil)-3-
[(3-etilbencil)amino]-2-hidroxi-
propil}butanamida;

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N-{(1S,2R)-1-(3,5-difluorobencil)-3-[(3-etilbencil)amino]-2-
hidroxi-
propil}-4-(3-piridin-2-il-1,2,4-oxadiazol-5-
il)butanamida;

35 N-{(1S,2R)-1-(3,5-difluorobencil)-3-[(3-etilbencil)amino]-2-
hidroxi-
propil}-3-[3-(4-metoxifenil)-1,2,4-oxadiazol-5-
il]propanamida;

N-{(1S,2R)-1-(3,5-difluorobencil)-3-[(3-etilbencil)amino]-2-hidroxi-
propil}-4-(2-furil)-4-oxobutanamida;

- 5 4-(1,3-benzotiazol-2-il)-N-{(1S,2R)-1-(3,5-difluorobencil)-3-
[(3-etilbencil)amino]-2-hidroxi-
propil}butanamida;

N-acetil-4-cloro-N-{(1S,2R)-1-(3,5-difluorobencil)-3-[(3-
etilbencil)amino]-2-hidroxi-
propil}fenilalaninamida;

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2-(acetilamino)-2-(1H-1,2,3-benzotriazol-1-il)-N-{(1S,2R)-
1-(3,5-difluorobencil)-3-[(3-etilbencil)amino]-2-
hidroxi-
propil}acetamida;

- 15 N-{(1S,2R)-1-(3,5-difluorobencil)-3-[(3-etilbencil)amino]-2-
hidroxi-
propil}-2-(2-etil-4H-[1,2,4]triazolo[1,5-
a]bencimidazol-4-il)acetamida;

- 20 N-{(1S,2R)-1-(3,5-difluorobencil)-3-[(3-etilbencil)amino]-2-
hidroxi-
propil}-2-metil-2-(1H-1,2,4-triazol-1-il)propanamida;

N-{(1S,2R)-1-(3,5-difluorobencil)-3-[(3-etilbencil)amino]-2-
hidroxi-
propil}-2-(5-pirrolidin-1-il-2H-tetraazol-2-
il)acetamida;

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N-{(1S,2R)-1-(3,5-difluorobencil)-3-[(3-etilbencil)amino]-2-
hidroxi-
propil}-3-{[(metilamino)carbonil]amino}-3-tien-3-
ilpropanamida;

- 30 N-{(1S,2R)-1-(3,5-difluorobencil)-3-[(3-etilbencil)amino]-2-
hidroxi-
propil}-2-[1-metil-3-(metiltio)-1H-indol-2-
il]acetamida;

- 35 N-{(1S,2R)-1-(3,5-difluorobencil)-3-[(3-etilbencil)amino]-2-
hidroxi-
propil}-4-(3,4-dihidro-2H-1,5-benzodioxepin-7-il)-4-
oxobutanamida;

703
704

N-{(1S,2R)-1-(3,5-difluorobencil)-3-[(3-etilbencil)amino]-2-hidroxi-
propil}-3-[(metoxiacetil)amino]-3-fenilpropanamida;

5 N-{(1S,2R)-1-(3,5-difluorobencil)-3-[(3-etilbencil)amino]-2-
hidroxi-
propil}-3-[2-oxo-5-(trifluorometil)piridin-1(2H)-
il]propanamida;

10 2-ciano-N-{(1S,2R)-1-(3,5-difluorobencil)-3-[(3-
etilbencil)amino]-2-hidroxi-
propil}-3-(3,4-dimetoxifenil)-2-
metilpropanamida;

4-(3,4-diclorofenil)-N-{(1S,2R)-1-(3,5-difluorobencil)-3-[(3-
etilbencil)amino]-2-hidroxi-
propil}-4-oxobutanamida;

15 N-{(1S,2R)-1-(3,5-difluorobencil)-3-[(3-etilbencil)amino]-
2-hidroxi-
propil}-4-(3,4-difluorofenil)-4-oxobutanamida;

20 N-{(1S,2R)-1-(3,5-difluorobencil)-3-[(3-etilbencil)amino]-2-
hidroxi-
propil}-4-(3,4-difluorofenil)-2-metil-4-oxobutanamida;

N-{(1S,2R)-1-(3,5-difluorobencil)-3-[(3-etilbencil)amino]-2-
hidroxi-
propil}-2-hidroxi-4-oxo-4-tien-2-ilbutanamida;

25 N-{(1S,2R)-1-(3,5-difluorobencil)-3-[(3-etilbencil)amino]-2-
hidroxi-
propil}-4-(7-metoksi-1-benzofuran-2-il)-4-
oxobutanamida;

30 4-dibenzo[b,d]furan-2-il-N-{(1S,2R)-1-(3,5-difluorobencil)-3-
[(3-etilbencil)amino]-2-hidroxi-
propil}-4-oxobutanamida;

N-{(1S,2R)-1-(3,5-difluorobencil)-3-[(3-etilbencil)amino]-2-
hidroxi-
propil}-2-(6-oxo-3-fenilpiridazin-1(6H)-il)acetamida;

35 2-(1H,1'H-2,2'-biimidazol-1-il)-N-{(1S,2R)-1-(3,5-
difluorobencil)-3-[(3-etilbencil)amino]-2-
hidroxi-
propil}acetamida;

~~704~~
705

N-{(1S,2R)-1-(3,5-difluorobencil)-3-[(3-etilbencil)amino]-2-hidroxi-
propil}-4-(3,4-dihidro-2H-cromen-6-il)-4-
oxobutanamida;

5 N-{(1S,2R)-1-(3,5-difluorobencil)-3-[(3-etilbencil)amino]-2-
hidroxi-
propil}-2-(3-oxo-1,2-bencisotiazol-2(3H)-il)acetamida;

4-[2-(acetilamino)-4,5-dimetilfenil]-N-{(1S,2R)-1-(3,5-
difluorobencil)-3-[(3-etilbencil)amino]-2-hidroxi-
propil}-4-
10 oxobutanamida;

N-{(1S,2R)-1-(3,5-difluorobencil)-3-[(3-etilbencil)amino]-2-
hidroxi-
propil}-2-(3-oxo-2,3-dihidro-1H-isoindol-1-
il)acetamida;

15 N-{(1S,2R)-1-(3,5-difluorobencil)-3-[(3-etilbencil)amino]-2-
hidroxi-
propil}-4-(4-hidroxi-
fenil)-4-oxobutanamida;

N-{(1S,2R)-1-(3,5-difluorobencil)-3-[(3-etilbencil)amino]-2-
20 hidroxi-
propil}-2-hidroxi-4-oxo-4-tien-3-ilbutanamida;

N-{(1S,2R)-1-(3,5-difluorobencil)-3-[(3-etilbencil)amino]-2-
hidroxi-
propil}-2-fenil-2-(1H-pirrol-1-il)acetamida;

25 4-(4-cloro-2-hidroxi-
fenil)-N-{(1S,2R)-1-(3,5-difluorobencil)-
3-[(3-etilbencil)amino]-2-hidroxi-
propil}-4-oxobutanamida;

N-{(1S,2R)-1-(3,5-difluorobencil)-3-[(3-etilbencil)amino]-2-
hidroxi-
propil}-2-(5-metil-1,3-dioxo-1,3-dihidro-2H-isoindol-
30 2-il)acetamida;

N-{(1S,2R)-1-(3,5-difluorobencil)-3-[(3-etilbencil)amino]-2-
hidroxi-
propil}-2-(1-oxo-1,3-dihidro-2H-isoindol-2-
il)butanamida;

35 N-{(1S,2R)-1-(3,5-difluorobencil)-3-f(3-etilbencil)aminol-2-
hidroxi-
propil}-2-metil-2-(1-oxo-1,3-dihidro-2H-isoindol-2-

205
206

il)propanamida;

N-{ (1S,2R) -1- (3,5-difluorobencil) -3- [(3-etilbencil) amino] -2-
hidroxipropil} -2- (1-metil-1H-indol-3-il) -2-oxoacetamida;

5

N-{ (1S,2R) -1- (3,5-difluorobencil) -3- [(3-etilbencil) amino] -2-
hidroxipropil} -2- (2-tioxo-2,3-dihidro-1,3-tiazol-4-
il) acetamida;

10 N-{ (1S,2R) -1- (3,5-difluorobencil) -3- [(3-etilbencil) amino] -2-
hidroxipropil} -2- [4- (1H-pirrol-1-il) fenil]propanamida;

2- (1-benzofuran-2-il) -N-{ (1S,2R) -1- (3,5-difluorobencil) -3-
[(3-etilbencil) amino] -2- hidroxipropil} -2- metilpropanamida;

15

4- (1-benzofuran-2-yi) -N-{ (1S,2R) -1- (3,5-difluorobencil) -3-
[(3-etilbencil) amino] -2- hidroxipropil} -4- oxobutanamida;

20 N-{ (1S,2R) -1- (3,5-difluorobencil) -3- (3-etilbencil) amino) -2-
hidroxipropil} -4- (6-metoxi-1,1'-bifenil-3-il) -4-
oxobutanamida;

3- (3-cloroisoxazol-5-il) -N-{ (1S,2R) -1- (3,5-difluorobencil) -3-
[(3-etilbencil) amino] -2- hidroxipropil}propanamida;

25

N-{ (1S,2R) -1- (3,5-difluorobencil) -3- [(3-etilbencil) amino] -2-
hidroxipropil} -4- (4-metoxifenil) -4- oxobutanamida;

30 N-{ (1S,2R) -1- (3,5-difluorobencil) -3- [(3-etilbencil) amino] -2-
hidroxipropil} -4- (2,3-dihidro-1,4-benzodioxin-6-il) -4-
oxobutanamida;

35 N-{ (1S,2R) -1- (3,5-difluorobencil) -3- [(3-etilbencil) amino] -2-
hidroxipropil} -3- (2-oxo-2H-1,3-benzoxazin-3 (4H) -
il)propanamida;

N-{ (1S,2R) -1- (3,5-difluorobencil) -3- [(3-etilbencil) amino] -2-

hidroxipropil}-2-(2-oxo-2,3-dihidro-1,3-benzoxazol-5-il)acetamida;

5 N-{(1S,2R)-1-(3,5-difluorobencil)-3-[(3-etilbencil)amino]-2-hidroxipropil}-2-(2-oxo-2,3-dihidro-1H-bencimidazol-5-il)acetamida;

10 N-{(1S,2R)-1-(3,5-difluorobencil)-3-[(3-etilbencil)amino]-2-hidroxipropil}-4-(5-inetil-1H-pirrol-2-il)-4-oxobutanamida;

N-{(1S,2R)-1-(3,5-difluorobencil)-3-[(3-etilbencil)amino]-2-hidroxipropil}-2-(5-piridin-2-il-2H-tetraazol-2-il)acetamida;

15 N-{(1S,2R)-1-(3,5-difluorobencil)-3-[(3-etilbencil)amino]-2-hidroxipropil}-2-(5,7-dimetil[1,2,4]triazolo[1,5-a]pirimidin-2-il)acetamida;

20 N-{(1S,2R)-1-(3,5-difluorobencil)-3-[(3-etilbencil)amino]-2-hidroxipropil}-4-[5-(metilsuifinil)-2,3-dihidro-1H-indol-1-il]-4-oxobutanamida;

N-{(1S,2R)-1-(3,5-difluorobencil)-3-[(3-etilbencil)amino]-2-hidroxipropil}-2-fenil-2-(4H-1,2,4-triazol-3-iltio)acetamida;

25 N-{(1S,2R)-1-(3,5-difluorobencil)-3-[(3-etilbencil)amino]-2-hidroxipropil}-2-(5,6-dimetil-2,4-dioxo-1,2,3,4-tetrahidropiridin-3-il)acetamida;

30 N-{(1S,2R)-1-(3,5-difluorobencil)-3-[(3-etilbencil)amino]-2-hidroxipropil}-3-(3-oxo-2,1-bencisotiazol-1(3H)-il)propanamida;

N-{(1S,2R)-1-(3,5-difluorobencil)-3-[(3-etilbencil)amino]-2-hidroxipropil}-3-fenil-2-(1H-tetraazol-1-il)propanamida;

35

N-{(1S,2R)-1-(3,5-difluorobencil)-3-[(3-etilbencil)amino]-2-hidroxipropil}-2-[5-(4-metilfenil)-2H-tetraazol-2-

708 704

il]acetamida;

N-{(1S,2R)-1-(3,5-difluorobencil)-3-[(3-etilbencil)amino]-2-hidroxi-3-(3-
hidroxipropil)-2-(3-hidroxi-4-metilfenil)acetamida;

5

N'-(1S,2R)-1-(3,5-difluorobencil)-3-[(3-etilbencil)amino]-2-hidroxi-3-(3-
hidroxipropil)-2-fenil-N,N-dipropilpentanediamida;

10 N-{(1S,2R)-1-(3,5-difluorobencil)-3-[(3-etilbencil)amino]-2-hidroxi-3-(3-
hidroxipropil)-2-fenilacetamida;

N-{(1S,2R)-1-(3,5-difluorobencil)-3-[(3-etilbencil)amino]-2-hidroxi-3-(3-
hidroxipropil)-2-(3-fluoro-4-propoxifenil)acetamida;

15 N-{(1S,2R)-1-(3,5-difluorobencil)-3-[(3-etilbencil)amino]-2-hidroxi-3-(3-
hidroxipropil)-2-(3-metoxi-4-propoxifenil)acetamida;

N-{(1S,2R)-1-(3,5-difluorobencil)-3-[(3-etilbencil)amino]-2-hidroxi-3-(3-
hidroxipropil)-2-(4-etoxifenil)acetamida;

20

N-{(1S,2R)-1-(3,5-difluorobencil)-3-[(3-etilbencil)amino]-2-hidroxi-3-(3-
hidroxipropil)-2-(3-hidroxi-4-metoxifenil)acetamida;

25 N-(1S,2R)-1-(3,5-difluorobencil)-2-hidroxi-3-(3-metoxibencil)amino]propil}-3-fenilpropanamida;

N-{(1S,2R)-1-(3,5-difluorobencil)-3-[(3-etilbencil)amino]-2-hidroxi-3-(3-
hidroxipropil)-3-fenilpropanamida;

30 N-{(1S,2R)-1-(3,5-difluorobencil)-3-[(3-etilbencil)amino]-2-hidroxi-3-(3-
hidroxipropil)-2-[1-metil-5-(4-metilbenzoil)-1H-pirrol-2-il]acetamida; y

35 3-(1-butil-1H-pirazol-4-il)-N-{(1S,2R)-1-(3,5-difluorobencil)-3-[(3-etilbencil)amino]-2-
hidroxipropil}propanamida.

709 706

2. Un compuesto que se selecciona de

clorhidrato de N-{(1S,2R)-1-(3,5-difluorobencil)-3-[(3-etilbencil)amino]-2-hidroxi-3-[(3-etilbencil)amino]propil}-2-(4-etil-2,3-

5 dioxopiperazin-1-il)acetamida;

clorhidrato 2-(4-butil-2,3-dioxopiperazin-1-il)-N-{(1S,2R)-1-(3,5-difluorobencil)-3-[(3-etilbencil)amino]-2-hidroxi-3-[(3-etilbencil)amino]propil}acetamida;

10

N-{(1S,2R)-1-(3,5-difluorobencil)-3-[(3-etilbencil)amino]-2-hidroxi-3-[(3-etilbencil)amino]propil}-2-(3-oxopiperazin-1-il)acetamida;

N-{(1S,2R)-1-bencil-3-[(3-etilbencil)amino]-2-hidroxi-3-[(3-etilbencil)amino]propil}-2-(3-oxopiperazin-1-il)acetamida;

15

N-{(1S,2R)-1-(3,5-difluorobencil)-2-hidroxi-3-[(3-yodobencil)amino]propil}-2-(3-oxopiperazin-1-il)acetamida;

20

N-{(1S,2R)-1-(3,5-difluorobencil)-2-hidroxi-3-[(3-yodobencil)amino]propil}-2-(4-metil-3-oxopiperazin-1-il)acetamida;

N-{(1S,2R)-1-(3,5-difluorobencil)-3-[(3-etilbencil)amino]-2-hidroxi-3-[(3-etilbencil)amino]propil}-2-(4-metil-3-oxopiperazin-1-il)acetamida;

25

N-{(1S,2R)-1-(3,5-difluorobencil)-2-hidroxi-3-[(3-yodobencil)amino]propil}-2-(4-etil-3-oxopiperazin-1-il)acetamida;

30

N-{(1S,2R)-1-(3,5-difluorobencil)-3-[(3-etilbencil)amino]-2-hidroxi-3-[(3-etilbencil)amino]propil}-2-(4-etil-3-oxopiperazin-1-il)acetamida;

N-{(1S,2R)-1-(3,5-difluorobencil)-2-hidroxi-3-[(3-yodobencil)amino]propil}-2-(3-oxo-4-propilpiperazin-1-il)acetamida;

35

2-(4-butyl-3-oxopiperazin-1-il)-N-{(1S,2R)-1-(3,5-difluorobencil)-2-hidroxi-3-[(3-yodobencil)amino]propil}acetamida;

5 N-{(1S,2R)-1-(3,5-difluorobencil)-2-hidroxi-3-[(3-yodobencil)amino]propil}-2-(4-isopropil-3-oxopiperazin-1-il)acetamida;

10 N-{(1S,2R)-1-(3,5-difluorobencil)-2-hidroxi-3-[(3-yodobencil)amino]propil}-2-(4-yodobutil-3-oxopiperazin-1-il)acetamida;

15 N-{(1S,2R)-1-(3,5-difluorobencil)-2-hidroxi-3-[(3-yodobencil)amino]propil}-2-[(3R)-3,4-dimetil-5-oxopiperazin-1-il]acetamida;

20 N-{(1S,2R)-1-(3,5-difluorobencil)-2-hidroxi-3-[(3-yodobencil)amino]propil}-2-[(3S)-3,4-dimetil-5-oxopiperazin-1-il]acetamida;

N-{(1S,2R)-1-(3,5-difluorobencil)-2-hidroxi-3-[(3-yodobencil)amino]propil}-2-[(3R)-4-etil-3-metil-5-oxopiperazin-1-il]acetamida;

25 N-{(1S,2R)-1-(3,5-difluorobencil)-2-hidroxi-3-[(3-yodobencil)amino]propil}-2-[(3S)-4-etil-3-metil-5-oxopiperazin-1-il]acetamida;

30 N-{(1S,2R)-1-(3,5-difluorobencil)-2-hidroxi-3-[(3-yodobencil)amino]propil}-2-[(3R)-3-metil-5-oxo-4-propilpiperazin-1-il]acetamida;

35 N-{(1S,2R)-1-(3,5-difluorobencil)-2-hidroxi-3-[(3-yodobencil)amino]propil}-2-[(3S)-3-metil-5-oxo-4-propilpiperazin-1-il]acetamida;

2-[(3R)-4-butyl-3-metil-S-oxopiperazin-1-il]-N-{(1S,2R)-1-

711 710

(3,5-difluorobencil)-2-hidroxi-3-[(3-yodobencil) amino]propil}acetamida;

2-[(3S)-4-butil-3-metil-5-oxopiperazin-1-il]-N-{(1S,2R)-1-(3,5-difluorobencil)-2-hidroxi-3-[(3-yodobencil) amino]propil}acetamida;

N-{(1S,2R)-1-(3,5-difluorobencil)-2-hidroxi-3-[(3-yodobencil) amino]propil}-2-[(3R)-3-etil-4-metil-5-oxopiperazin-1-il]acetamida;

N-{(1S,2R)-1-(3,5-difluorobencil)-2-hidroxi-3-[(3-yodobencil) amino]propil}-2-[(3S)-3-etil-4-metil-5-oxopiperazin-1-il]acetamida;

2-[(3R)-3,4-dietil-5-oxopiperazin-1-il]-N-{(1S,2R)-1-(3,5-difluorobencil)-2-hidroxi-3-[(3-yodobencil) amino]propil}acetamida;

2-[(3S)-3,4-dietil-5-oxopiperazin-1-il]-N-{(1S,2R)-1-(3,5-difluorobencil)-2-hidroxi-3-[(3-yodobencil) amino]propil}acetamida;

N-{(1S,2R)-1-(3,5-difluorobencil)-2-hidroxi-3-[(3-yodobencil) amino]propil}-2-[(3R)-3-etil-5-oxo-4-propilpiperazin-1-il]acetamida;

N-{(1S,2R)-1-(3,5-difluorobencil)-2-hidroxi-3-[(3-yodobencil) amino]propil}-2-[(3S)-3-etil-5-oxo-4-propilpiperazin-1-il]acetamida;

2-[(3R)-4-butil-3-etil-5-oxopiperazin-1-il]-N-{(1S,2R)-1-(3,5-difluorobencil)-2-hidroxi-3-[(3-yodobencil) amino]propil}acetamida;

2-[(3S)-4-butil-3-etil-5-oxopiperazin-1-il]-N-{(1S,2R)-1-(3,5-difluorobencil)-2-hidroxi-3-[(3-

712 ~~714~~

yodobencil) amino]propil}acetamida;

5 N-{ (1S,2R) -1- (3,5-difluorobencil) -2-hidroxi-3- [(3-
yodobencil) amino]propil} -2- [(3R) -3-isopropil-5-oxo-4-
propilpiperazin-1-il]acetamida;

10 N-{ (1S,2R) -1- (3,5-difluorobencil) -2-hidroxi-3- [(3-
yodobencil) amino]propil} -2- [(3S) -3-isopropil-5-oxo-4-
propilpiperazin-1-il]acetamida;

2- [(3R) -4-butil-3-isopropil-5-oxopiperazin-1-il] -N- { (1S,2R) -
1- (3,5-difluorobencil) -2-hidroxi-3- [(3-
yodobencil) amino]propil}acetamida;

15 2- [(3S-4-butil-3-isopropil-5-oxopiperazin-1-il] -N- { (1S,2R) -1-
(3,5-difluorobencil) -2-hidroxi-3- [(3-
yodobencil) amino]propil}acetamida;

20 N- { (1S,2R) -1- (3,5-difluorobencil) -3- [(3-etilbencil) amino] -2-
hidroxipropil} -2- (4-metil-2,5-dioxopiperazin-1-il)acetamida;

N- { (1S,2R) -1- (3,5-difluorobencil) -3- [(3-etilbencil) amino] -2-
hidroxipropil} -2- (4-etil-2,5-dioxopiperazin-1-il)acetamida;

25 N- { (1S,2R) -1- (3,5-difluorobencil) -3- [(3-etilbencil) amino] -2-
hidroxipropil} -2- (2,5-dioxo-4-propilpiperazin-1-il)acetamida;

30 2- (4-butil-2,5-dioxopiperazin-1-il) -N- { (1S,2R) -1- (3,5-
difluorobencil) -3- [(3-etilbencil) amino] -2-
hidroxipropil}acetamida;

N- { (1S,2R) -1- (3,5-difluorobencil) -3- [(3-etilbencil) amino] -2-
hidroxipropil} -2- (2,5-dioxo-4-pentilpiperazin-1-il)acetamida;

35 N- { (1S,2R) -1- (3,5-difluorobencil) -3- [(3-etilbencil) amino] -2-
hidroxipropil} -2- [(3R) -3,4-dimetil-2,5-dioxopiperazin-1-
il]acetamida;

N-{(1S,2R)-1-(3,5-difluorobencil)-3-[(3-etilbencil)amino]-2-hidroxi-
propil}-2-[(3S)-3,4-dimetil-2,5-dioxopiperazin-1-il]acetamida;

5

N-{(1S,2R)-1-(3,5-difluorobencil)-3-[(3-etilbencil)amino]-2-hidroxi-
propil}-2-[(3R)-4-etil-3-metil-2,5-dioxopiperazin-1-il]acetamida;

10 N-{(1S,2R)-1-(3,5-difluorobencil)-3-[(3-etilbencil)amino]-2-hidroxi-
propil}-2-[(3S)-4-etil-3-metil-2,5-dioxopiperazin-1-il]acetamida;

15 N-{(1S,2R)-1-(3,5-difluorobencil)-3-[(3-etilbencil)amino]-2-hidroxi-
propil}-2-[(3R)-3-metil-2,5-dioxo-4-propilpiperazin-1-il]acetamida;

20 N-{(1S,2R)-1-(3,5-difluorobencil)-3-[(3-etilbencil)amino]-2-hidroxi-
propil}-2-[(3S)-3-metil-2,5-dioxo-4-propilpiperazin-1-il]acetamida;

2-[(3R)-4-butil-3-metil-2,5-dioxopiperazin-1-il]-N-{(1S,2R)-1-(3,5-difluorobencil)-3-[(3-etilbencil)amino]-2-hidroxi-
propil}acetamida;

25

2-[(3S)-4-butil-3-metil-2,5-dioxopiperazin-1-il]-N-{(1S,2R)-1-(3,5-difluorobencil)-3-[(3-etilbencil)amino]-2-hidroxi-
propil}acetamida;

30 N-{(1S,2R)-1-(3,5-difluorobencil)-3-[(3-etilbencil)amino]-2-hidroxi-
propil}-2-[(3R)-3-etil-4-metil-2,5-dioxopiperazin-1-il]acetamida;

35 N-{(1S,2R)-1-(3,5-difluorobencil)-3-[(3-etilbencil)amino]-2-hidroxi-
propil}-2-[(3S)-3-etil-4-metil-2,5-dioxopiperazin-1-il]acetamida;

7/4 7/3

2-[(3R)-3,4-dietil-2,5-dioxopiperazin-1-il]-N-{(1S,2R)-1-(3,5-difluorobencil)-3-[(3-etilbencil)amino]-2-hidroxiopropil}acetamida;

5 2-[(3S)-3,4-dietil-2,5-dioxopiperazin-1-il]-N-{(1S,2R)-1-(3,5-difluorobencil)-3-[(3-etilbencil)amino]-2-hidroxiopropil}acetamida;

10 N-{(1S,2R)-1-(3,5-difluorobencil)-3-[(3-etilbencil)amino]-2-hidroxiopropil}-2-[(3R)-3-etil-2,5-dioxo-4-propilpiperazin-1-il]acetamida;

15 N-{(1S,2R)-1-(3,5-difluorobencil)-3-[(3-etilbencil)amino]-2-hidroxiopropil}-2-[(3S)-3-etil-2,5-dioxo-4-propilpiperazin-1-il]acetamida;

20 2-[(3R)-4-butil-3-etil-2,5-dioxopiperazin-1-il]-N-({(1S,2R)-1-(3,5-difluorobencil)-3-[(3-etilbencil)amino]-2-hidroxiopropil}acetamida;

2-[(3S)-4-butil-3-etil-2,5-dioxopiperazin-1-il]-N-{(1S,2R)-1-(3,5-difluorobencil)-3-[(3-etilbencil)amino]-2-hidroxiopropil}acetamida;

25 N-{(1S,2R)-1-(3,5-difluorobencil)-3-[(3-etilbencil)amino]-2-hidroxiopropil}-2-[(3R)-3-isopropil-4-metil-2,5-dioxopiperazin-1-il]acetamida;

30 N-{(1S,2R)-1-(3,5-difluorobencil)-3-[(3-etilbencil)amino]-2-hidroxiopropil}-2-[(3S)-3-isopropil-4-metil-2,5-dioxopiperazin-1-il]acetamida;

35 N-{(1S,2R)-1-(3,5-difluorobencil)-3-[(3-etilbencil)amino]-2-hidroxiopropil}-2-[(3R)-4-etil-3-isopropil-2,5-dioxopiperazin-1-il]acetamida;

N-{(1S,2R)-1-(3,5-difluorobencil)-3-[(3-etilbencil)amino]-2-

7/15 7/14

hidroxipropil}-2-(3S)-4-etil-3-isopropil-2,5-dioxopiperazin-1-il]acetamida;

5 N-{(1S,2R)-1-(3,5-difluorobencil)-3-[(3-etilbencil)amino]-2-hidroxipropil}-2-[(3R)-3-isopropil-2,5-dioxo-4-propilpiperazin-1-il]acetamida;

10 N-{(1S,2R)-1-(3,5-difluorobencil)-3-[(3-etilbencil)amino]-2-hidroxipropil}-2-[(3S)-3-isopropil-2,5-dioxo-4-propilpiperazin-1-il]acetamida;

15 2-[(3R)-4-butil-3-isopropil-2,5-dioxopiperazin-1-il]-N-{(1S,2R)-1-(3,5-difluorobencil)-3-[(3-etilbencil)amino]-2-hidroxipropil}acetamida;

2-[(3S)-4-butil-3-isopropil-2,5-dioxopiperazin-1-il]-N-{(1S,2R)-1-(3,5-difluorobencil)-3-[(3-etilbencil)amino]-2-hidroxipropil}acetamida;

20 N-{(1S,2R)-1-(3,5-difluorobencil)-3-[(3-etilbencil)amino]-2-hidroxipropil}-2-(4-metil-2,3-dioxopiperazin-1-il)acetamida;

N-{(1S,2R)-1-(3,5-difluorobencil)-3-[(3-etilbencil)amino]-2-hidroxipropil}-2-(4-etil-2,3-dioxopiperazin-1-il)acetamida;

25 N-{(1S,2R)-1-(3,5-difluorobencil)-3-[(3-etilbencil)amino]-2-hidroxipropil}-2-(2,3-dioxo-4-propilpiperazin-1-il)acetamida;

30 2-(4-butil-2,3-dioxopiperazin-1-il)-N-{(1S,2R)-1-(3,5-difluorobencil)-3-[(3-etilbencil)amino]-2-hidroxipropil}acetamida;

N-{(1S,2R)-1-(3,5-difluorobencil)-3-[(3-etilbencil)amino]-2-hidroxipropil}-2-(2,3-dioxo-4-pentilpiperazin-1-il)acetamida;

35 N-{(1S,2R)-1-(3,5-difluorobencil)-3-[(3-etilbencil)amino]-2-hidroxipropil}-2-[(5R)-4,5-dimetil-2,3-dioxopiperazin-1-

il]acetamida;

N-{(1S,2R)-1-(3,5-difluorobencil)-3-[(3-etilbencil)amino]-2-hidroxi
propil}-2-[(5S)-4,5-dimetil-2,3-dioxopiperazin-1-

5 il]acetamida;

N-{(1S,2R)-1-(3,5-difluorobencil)-3-[(3-etilbencil)amino]-2-hidroxi
propil}-2-[(SR)-4-etil-5-metil-2,3-dioxopiperazin-1-il]acetamida;

10

N-{(1S,2R)-1-(3,5-difluorobencil)-3-[(3-etilbencil)amino]-2-hidroxi
propil}-2-[(5S)-4-etil-5-metil-2,3-dioxopiperazin-1-il]acetamida;

15 N-{(1S,2R)-1-(3,5-difluorobencil)-3-[(3-etilbencil)amino]-2-hidroxi
propil}-2-[(5R)-5-metil-2,3-dioxo-4-propilpiperazin-1-il]acetamida;

N-{(1S,2R)-1-(3,5-difluorobencil)-3-[(3-etilbencil)amino]-2-hidroxi
20 propil}-2-[(5S)-5-metil-2,3-dioxo-4-propilpiperazin-1-il]acetamida;

2-[(5R)-4-butil-5-metil-2,3-dioxopiperazin-1-il]-N-{(1S,2R)-1-(3,5-difluorobencil)-3-[(3-etilbencil)amino]-2-
25 hidroxi propil}acetamida;

2-[(5S)-4-butil-5-metil-2,3-dioxopiperazin-1-il]-N-{(1S,2R)-1-(3,5-difluorobencil)-3-[(3-etilbencil)amino]-2-hidroxi
propil}acetamida;

30

N-{(1S,2R)-1-(3,5-difluorobencil)-3-[(3-etilbencil)amino]-2-hidroxi
propil}-2-[(5R)-5-etil-4-metil-2,3-dioxopiperazin-1-il]acetamida;

35 N-{(1S,2R)-1-(3,5-difluorobencil)-3-[(3-etilbencil)amino]-2-hidroxi
propil}-2-[(5S)-5-etil-4-metil-2,3-dioxopiperazin-1-il]acetamida;

717 216

2-[(5R)-4,5-dietil-2,3-dioxopiperazin-1-il]-N-{(1S,2R)-1-(3,5-difluorobencil)-3-[(3-etilbencil)amino]-2-hidroxiopropil}acetamida;

5

2-[(5S)-4,5-dietil-2,3-dioxopiperazin-1-il]-N-{(1S,2R)-1-(3,5-difluorobencil)-3-[(3-etilbencil)amino]-2-hidroxiopropil}acetamida;

10 N-{(1S,2R)-1-(3,5-difluorobencil)-3-[(3-etilbencil)amino]-2-hidroxiopropil}-2-[(5R)-5-etil-2,3-dioxo-4-propilpiperazin-1-il]acetamida;

15 N-{(1S,2R)-1-(3,5-difluorobencil)-3-[(3-etilbencil)amino]-2-hidroxiopropil}-2-[(5S)-5-etil-2,3-dioxo-4-propilpiperazin-1-il]acetamida;

20 2-[(5R)-4-butil-5-etil-2,3-dioxopiperazin-1-il]-N-{(1S,2R)-1-(3,5-difluorobencil)-3-[(3-etilbencil)amino]-2-hidroxiopropil}acetamida;

25 2-[(5S)-4-butil-5-etil-2,3-dioxopiperazin-1-il]-N-{(1S,2R)-1-(3,5-difluorobencil)-3-[(3-etilbencil)amino]-2-hidroxiopropil}acetamida;

N-{(1S,2R)-1-(3,5-difluorobencil)-3-[(3-etilbencil)amino]-2-hidroxiopropil}-2-[(5R)-5-isopropil-4-metil-2,3-dioxopiperazin-1-il]acetamida;

30 N-{(1S,2R)-1-(3,5-difluorobencil)-3-[(3-etilbencil)amino]-2-hidroxiopropil}-2-[(5S)-5-isopropil-4-metil-2,3-dioxopiperazin-1-il]acetamida;

35 N-(1S,2R)-1-(3,5-difluorobencil)-3-[(3-etilbencil)amino]-2-hidroxiopropil}-2-[(5R)-4-etil-5-isopropil-2,3-dioxopiperazin-1-il]acetamida;

7/18 7/19

N-{(1S,2R)-1-(3,5-difluorobencil)-3-[(3-etilbencil)amino]-2-hidroxi-
propil}-2-[(5S)-4-etil-5-isopropil-2,3-dioxopiperazin-1-il]acetamida;

5 N-{(1S,2R)-1-(3,5-difluorobencil)-3-[(3-etilbencil)amino]-2-hidroxi-
propil}-2-[(5R)-5-isopropil-2,3-dioxo-4-propilpiperazin-1-il]acetamida;

10 N-{(1S,2R)-1-(3,5-difluorobencil)-3-[(3-etilbencil)amino]-2-hidroxi-
propil}-2-[(5S)-5-isopropil-2,3-dioxo-4-propilpiperazin-1-il]acetamida;

15 2-[(5R)-4-butil-5-isopropil-2,3-dioxopiperazin-1-il]-N-{(1S,2R)-1-(3,5-difluorobencil)-3-[(3-etilbencil)amino]-2-hidroxi-
propil}acetamida;

2-[(5S)-4-butil-5-isopropil-2,3-dioxopiperazin-1-il]-N-{(1S,2R)-1-(3,5-difluorobencil)-3-[(3-etilbencil)amino]-2-hidroxi-
propil}acetamida;

20

N-{(1S,2R)-1-(3,5-difluorobencil)-3-[(3-etilbencil)amino]-2-hidroxi-
propil}-2-(4-metil-3,5-dioxopiperazin-1-il)acetamida;

25 N-{(1S,2R)-1-(3,5-difluorobencil)-3-[(3-etilbencil)amino]-2-hidroxi-
propil}-2-(4-etil-3,5-dioxopiperazin-1-il)acetamida;

N-{(1S,2R)-1-(3,5-difluorobencil)-3-[(3-etilbencil)amino]-2-hidroxi-
propil}-2-(3,5-dioxo-4-propilpiperazin-1-il)acetamida;

30 2-(4-butil-3,5-dioxopiperazin-1-il)-N-{(1S,2R)-1-(3,5-difluorobencil)-3-[(3-etilbencil)amino]-2-hidroxi-
propil}acetamida;

35 N-{(1S,2R)-1-(3,5-difluorobencil)-3-[(3-etilbencil)amino]-2-hidroxi-
propil}-2-(3,5-dioxo-4-pentilpiperazin-1-il)acetamida;

N-{(1S,2R)-1-(3,5-difluorobencil)-3-[(3-etilbencil)amino]-2-

7/19 7/8

hidroxipropil}-2-(4-isobutil-3,5-dioxopiperazin-1-il)acetamida;

5 N-((1S,2R)-1-[(3,5-difluorofenil)metil]-3-{[(3-etilfenil)metil]amino}-2-hidroxipropil)-2-(1,1-dioxotiolan-2-il)acetamida;

10 N-((1S,2R)-1-[(3,5-difluorofenil)metil]-3-{[(3-etilfenil)metil]amino}-2-hidroxipropil}-4-oxo-4-[4-bencil(1,4-diazaperhidroepinil)]butanamida;

15 N-((1S,2R)-1-[(3,5-difluorofenil)metil]-3-{[(3-etilfenil)metil]amino}-2-hidroxipropil}-4-(1-oxo(1,4-tiazaperhidroin-4-il))butanamida;

N-((1S,2R)-1-[(3,5-difluorofenil)metil]-3-{[(3-etilfenil)metil]amino}-2-hidroxipropil)-2-(1,1-dioxotiolan-3-il)acetamida;

20 N-((1S,2R)-1-[(3,5-difluorofenil)metil]-3-{[(3-etilfenil)metil]amino}-2-hidroxipropil}-4-morfolin-4-il-4-oxobutanamida;

25 N-((1S,2R)-1-[(3,5-difluorofenil)metil]-3-{[(3-etilfenil)metil]amino}-2-hidroxipropil)-2-(1,3-dioxo(4,5,6,7,3a,7a-hexahidroisoindol-2-il))butanamida;

30 N-((1S,2R)-1-[(3,5-difluorofenil)metil]-2-hidroxi-3-{[(3-yodofenil)metil]amino}propil)-2-(3-azabicciclo[3.2.2]non-3-il)acetamida;

35 N-((1S,2R)-1-[(3,5-difluorofenil)metil]-3-{[(3-etilfenil)metil]amino}-2-hidroxipropil)-3-(4,4-dimetil-2,5-dioxo(1,3-diazolidinil))-2-{[(propilbutil)sulfonil]metil}propanamida;

N-((2S,1R)-1-[(3,5-difluorofenil)metil]-3-([[(3-

etilfenil)metil]amino}-2-hidroxiopropil}-3-(4,4-dimetil-2,5-dioxo(1,3-diazolidinil))-2-
{[(propilbutil)sulfonil]metil}propanamida;

5 2-(4-butil-2,3-dioxopiperazin-1-il)-N-{(1S,2R)-1-(3,5-difluorobencil)-3-[(3-etilbencil)amino]-2-hidroxiopropil}acetamida clorhidrato;

10 2-(4-etil-2,3-dioxopiperazin-1-il)-N-{(1S,2R)-1-(3,5-difluorobencil)-3-[(3-etilbencil)amino]-2-hidroxiopropil}acetamida clorhidrato;

15 2-(4-butil-3-oxopiperazin-1-il)-N-{(1S,2R)-1-(3,5-difluorobencil)-3-[(3-etilbencil)amino]-2-hidroxiopropil}acetamida dihidrocloruro;

20 (2R)-2-(4-butil-3-oxopiperazin-1-il)-N-{(1S,2R)-1-(3,5-difluorobencil)-3-[(3-etilbencil)amino]-2-hidroxiopropil}propanamida;

2-(1-butil-2-oxo-1,2-dihidropiridin-4-il)-N-{(1S,2R)-1-(3,5-difluorobencil)-3-[(3-etilbencil)amino]-2-hidroxiopropil}acetamida;

25 2-(1-butil-2-oxopiperidin-4-il)-N-{(1S,2R)-1-(3,5-difluorobencil)-3-[(3-etilbencil)amino]-2-hidroxiopropil}acetamida;

30 2-(4-butil-2,5-dioxopiperazin-1-il)-N-{(1S,2R)-1-(3,5-difluorobencil)-3-[(3-etilbencil)amino]-2-hidroxiopropil}acetamida;

35 N-{(1S,2R)-1-(3,5-difluorobencil)-3-[(3-etilbencil)amino]-2-hidroxiopropil}-2-(3-oxo-4-propilciclohexil)acetamida;

N-{(1S,2R)-1-(3,5-difluorobencil)-3-[(3-etilbencil)amino]-2-hidroxiopropil}-2-(3-oxociclohexil)acetamida;

721 220

N-{(1S,2R)-1-(3,5-difluorobencil)-3-[(3-etilbencil)amino]-2-hidroxi
propil}-2-[4-(etoximetil)piperidin-1-il]hexanamida;

5 (2S)-N-{(1S,2R)-1-(3,5-difluorobencil)-3-[(3-etilbencil)amino]-2-hidroxi
propil}-2-[4-(etoximetil)piperidin-1-il]hexanamida;

10 N-{(1S,2R)-1-(3,5-difluorobencil)-3-[(3-etilbencil)amino]-2-hidroxi
propil}-2-[4-(etoximetil)piperidin-1-il]pentanamida;

(2S)-N-{(1S,2R)-1-(3,5-difluorobencil)-3-[(3-etilbencil)amino]-2-hidroxi
propil}-2-[4-(etoximetil)piperidin-1-il]pentanamida;

15

N-{(1S,2R)-1-(3,5-difluorobencil)-3-[(3-etilbencil)amino]-2-hidroxi
propil}-2-[4-(etoximetil)piperidin-1-il]-4-(metiltio)butanamida;

20 (2S)-N-{(1S,2R)-1-(3,5-difluorobencil)-3-[(3-etilbencil)amino]-2-hidroxi
propil}-2-[4-(etoximetil)piperidin-1-il]-4-(metiltio)butanamida;

25 2-(4-butil-2-oxopiperazin-1-il)-N-{(1S,2R)-1-(3,5-difluorobencil)-3-[(3-etilbencil)amino]-2-hidroxi
propil}acetamida;

30 2-(4-butil-2,3-dioxopiperazin-1-il)-N-{(1S,2R)-1-(3,5-difluorobencil)-3-[(3-etilbencil)amino]-2-hidroxi
propil}hexanamida;

(2S)-N-{(1S,2R)-1-(3,5-difluorobencil)-3-[(3-etilbencil)amino]-2-hidroxi
propil}-2-[4-(2-metoxietil)piperidin-1-il]-4-(metiltio)butanamida;

35

(2S)-N-{(1S,2R)-1-(3,5-difluorobencil)-3-[(3-etilbencil)amino]-2-hidroxi
propil}-2-[4-(2-

222 721

metoxietil)piperidin-1-il]hexanamida;

(2S)-N-{(1S,2R)-1-(3,5-difluorobencil)-3-[(3-etilbencil)amino]-2-hidroxiopropil}-2-[4-(2-

5 metoxietil)piperidin-1-il]pentanamida;

(2S)-N-{(1S,2R)-1-(3,5-difluorobencil)-3-[(3-etilbencil)amino]-2-hidroxiopropil}-4-(metiltio)-2-(4-propoxipiperidin-1-il)butanamida;

10

(2S)-N-{(1S,2R)-1-(3,5-difluorobencil)-3-[(3-etilbencil)amino]-2-hidroxiopropil}-2-(4-propoxipiperidin-1-il)hexanamida;

15 (2S)-N-{(1S,2R)-1-(3,5-difluorobencil)-3-[(3-etilbencil)amino]-2-hidroxiopropil}-2-(4-propoxipiperidin-1-il)pentanamida;

20 2-(4-butil-2,3-dioxopiperazin-1-il)-N-((1S,2R)-1-(3,5-difluorobencil)-3-{[1-(3-etilfenil)ciclopropil]amino}-2-hidroxiopropil)hexanamida;

(2S)-N-((1S,2R)-1-(3,5-difluorobencil)-3-{[1-(3-etilfenil)ciclopropil]amino}-2-hidroxiopropil)-2-[4-(etoximetil)piperidin-1-il]-4-(metiltio)butanamida;

25

(2S)-N-((1S,2R)-1-(3,5-difluorobencil)-3-{[1-(3-etilfenil)ciclopropil]amino}-2-hidroxiopropil)-2-[4-(etoximetil)piperidin-1-il]hexanamida;

30

(2S)-N-((1S,2R)-1-(3,5-difluorobencil)-3-{[1-(3-etilfenil)ciclopropil]amino}-2-hidroxiopropil)-2-[4-(etoximetil)piperidin-1-il]pentanamida; y

35 N-{(1S,2R)-1-(3,5-difluorobencil)-3-[(3-etilbencil)amino]-2-hidroxiopropil}-2-(2,3-dioxo-4-pentilpiperazin-1-il)acetamida.

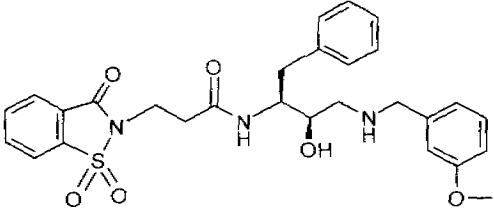
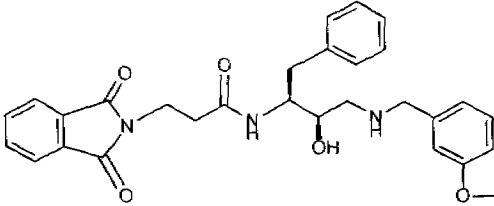
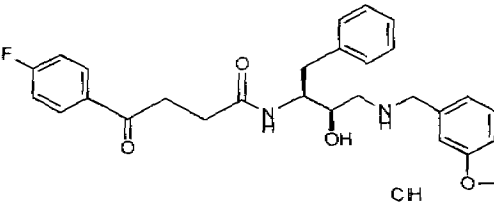
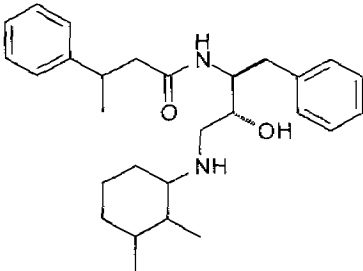
723 722

3. Una composición farmacéutica caracterizada comprende el compuesto según la reivindicación 1.

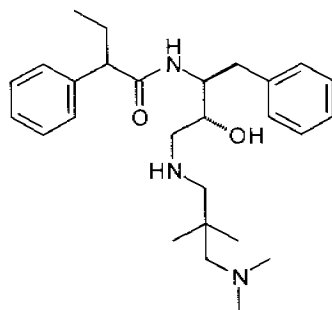
4. Una composición farmacéutica caracterizada comprende el
5 compuesto según la reivindicación 2.

10 MGM\MGM\ID-121718\WPC13562

Analogs-
BA15-FP
Assay---A.
Laborde

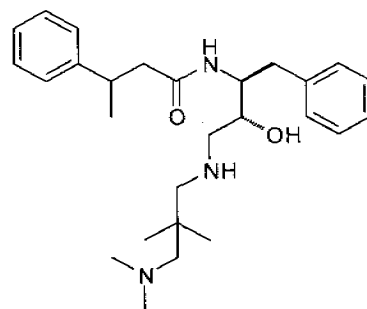
Structure	Compound Name(s)	IC50 (nM)	Mol. Wt.	MS
 HCl	N-((1S,2R)-1-benzyl-2-hydroxy-3-[(3-methoxybenzyl)amino]propyl)-3-(1,1-dioxo-3-oxo-1,2-benzisothiazol-2(3H)-yl)propanamide hydrochloride (Generated by ACD/Name software)	>20000	574,1	538.1994 HRMS calcd 538.2012
 HCl	N-((1S,2R)-1-benzyl-2-hydroxy-3-[(3-methoxybenzyl)amino]propyl)-3-(1,3-dioxo-1,3-dihydro-2H-isoindol-2-yl)propanamide hydrochloride (Generated by ACD/Name software)	>20000	538,05	488.2177 HRMS calcd 488.2185
 CH	N-((1S,2R)-1-benzyl-2-hydroxy-3-[(3-methoxybenzyl)amino]propyl)-4-(4-fluorophenyl)-4-oxobutanamide hydrochloride (Generated by ACD/Name software)	>20000	515,03	479.2325 HRMS calcd 479.2346
	N-((1S,2R)-1-benzyl-3-[(2,3-dimethylcyclohexyl)amino]-2-hydroxypropyl)-3-phenylbutanamide (Generated by ACD/Name software)	>20000	436,64	437,3

729-223



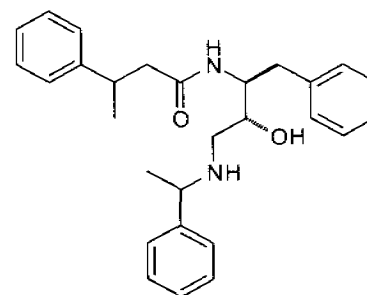
N-((1S,2R)-1-benzyl-3-([3-(dimethylamino)-2,2-dimethylpropyl]amino)-2-hydroxypropyl)-2-phenylbutanamide (Generated by ACD/Name software)

>20000 439,65 440,3



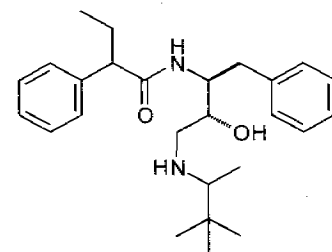
N-((1S,2R)-1-benzyl-3-([3-(dimethylamino)-2,2-dimethylpropyl]amino)-2-hydroxypropyl)-3-phenylbutanamide (Generated by ACD/Name software)

>20000 439,65 440,3



N-((1S,2R)-1-benzyl-2-hydroxy-3-[(1-phenylethyl)amino]propyl)-3-phenylbutanamide (Generated by ACD/Name software)

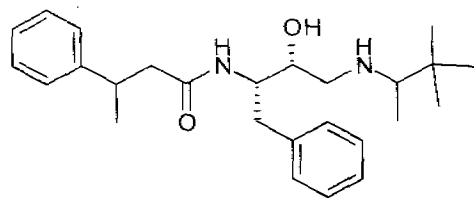
>20000 430,6 431,3



N-((1S,2R)-1-benzyl-2-hydroxy-3-[(1,2,2-trimethylpropyl)amino]propyl)-2-phenylbutanamide (Generated by ACD/Name software)

>20000 410,61 411,3

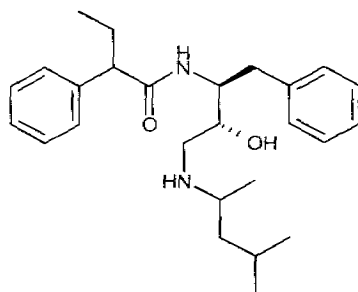
205 205



N-((1S,2R)-1-benzyl-2-hydroxy-3-((1,2,2-dimethylpropyl)amino)propyl)-3-phenylbutanamide compound with methyl hydroperoxide (1:1) (Generated by ACD/Name software)

>20000 458,65 411,3

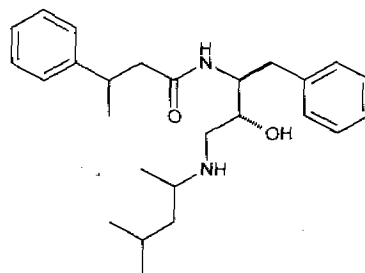
HCOOH



N-((1S,2R)-1-benzyl-3-((1,3-dimethylbutyl)amino)-2-hydroxypropyl)-2-phenylbutanamide compound with methyl hydroperoxide (1:1) (Generated by ACD/Name software)

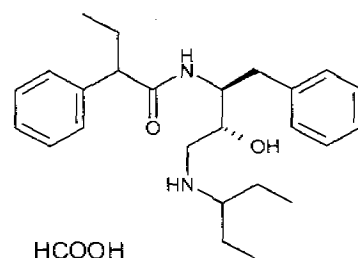
>20000 458,65 411,3

HCOOH



N-((1S,2R)-1-benzyl-3-((1,3-dimethylbutyl)amino)-2-hydroxypropyl)-3-phenylbutanamide (Generated by ACD/Name software)

>20000
>20000 410,61 411,3



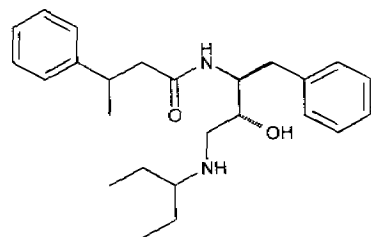
N-((1S,2R)-1-benzyl-3-((1-ethylpropyl)amino)-2-hydroxypropyl)-2-phenylbutanamide compound with methyl hydroperoxide (1:1) (Generated by ACD/Name software)

>20000 444,62 397,3

HCOOH

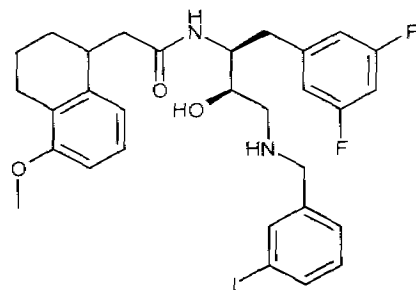
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326 328



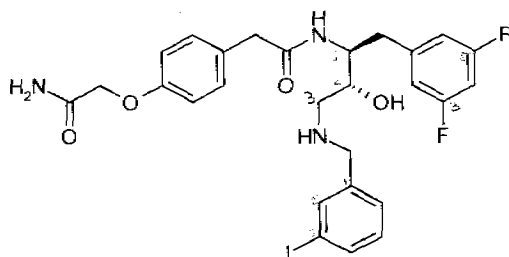
N-((1S,2R)-1-benzyl-3-((1-ethylpropyl)amino)-2-hydroxypropyl)-3-phenylbutanamide (Generated by ACD/Name software)

>20000 396,58 397,3



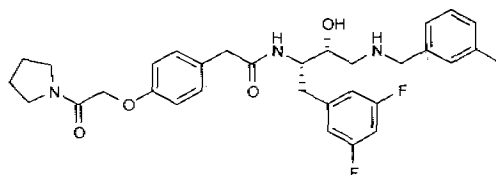
N-((1S,2R)-1-(3,5-difluorobenzyl)-2-hydroxy-3-((3-iodobenzyl)amino)propyl)-2-(5-methoxy-1,2,3,4-tetrahydronaphthalen-1-yl)acetamide (Generated by ACD/Name software)

>20000 634,51 635,82



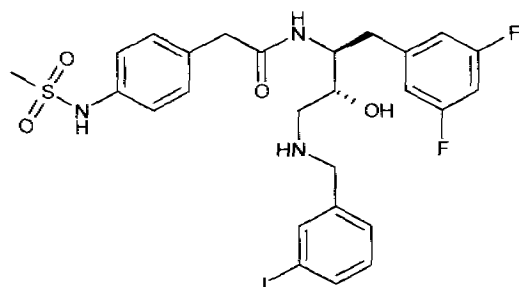
2-[4-(2-amino-2-oxoethoxy)phenyl]-N-((1S,2R)-1-(3,5-difluorobenzyl)-2-hydroxy-3-((3-iodobenzyl)amino)propyl)acetamide (Generated by ACD/Name software)

2003 623,44 624,33



N-((1S,2R)-1-(3,5-difluorobenzyl)-2-hydroxy-3-((3-iodobenzyl)amino)propyl)-2-[4-(2-oxo-2-pyrrolidin-1-ylethoxy)phenyl]acetamide (Generated by ACD/Name software)

2722
9109 677,54 678,58

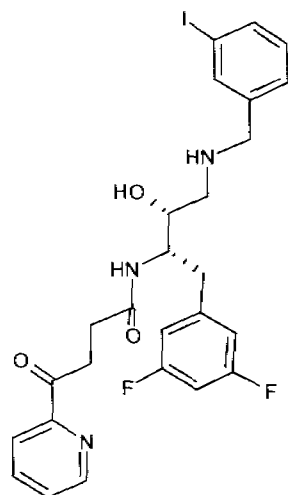


N-((1S,2R)-1-(3,5-difluorobenzyl)-2-hydroxy-3-((3-iodobenzyl)amino)propyl)-2-[4-[(methylsulfonyl)amino]phenyl]acetamide (Generated by ACD/Name software)

3833
4330 643,5 643,86

5704

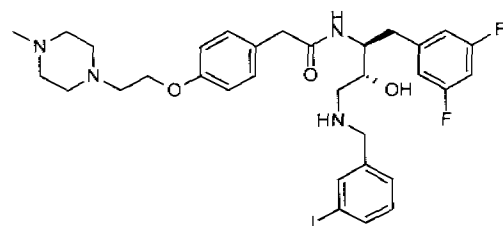
722
722



N-((1S,2R)-1-(3,5-difluorobenzyl)-2-hydroxy-3-((3-iodobenzyl)amino)propyl)-4-oxo-4-pyridin-2-ylbutanamide (Generated by ACD/Name software)

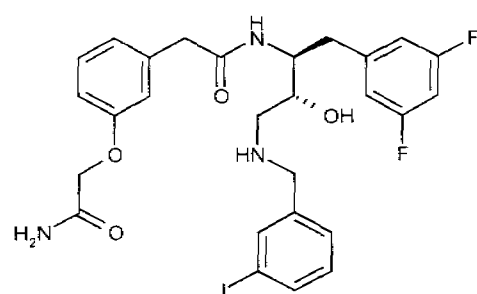
8277 593,42 594,34

(9)



N-((1S,2R)-1-(3,5-difluorobenzyl)-2-hydroxy-3-((3-iodobenzyl)amino)propyl)-2-(4-(2-(4-methylpiperazin-1-yl)ethoxy)phenyl)acetamide (Generated by ACD/Name software)

>20000
>20000 692,59 693,43



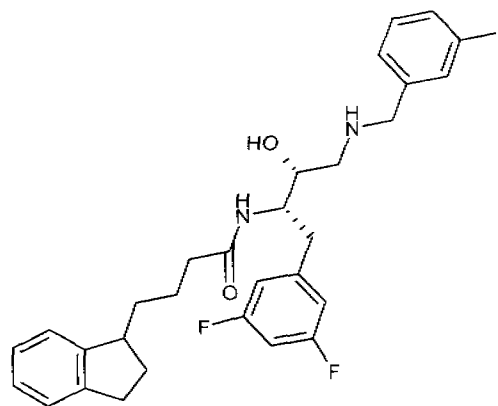
2-(3-(2-amino-2-oxoethoxy)phenyl)-N-((1S,2R)-1-(3,5-difluorobenzyl)-2-hydroxy-3-((3-iodobenzyl)amino)propyl)acetamide (Generated by ACD/Name software) or ELAN-151113

203 623,44 624,82

367
4601,98
3139

726

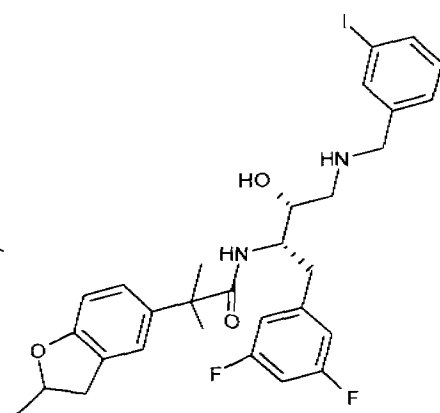
21



N-((1S,2R)-1-(3,5-difluorobenzyl)-2-hydroxy-3-((3-iodobenzyl)amino)propyl)-4-(2,3-dihydro-1H-inden-1-yl)butanamide
(Generated by ACD/Name software)

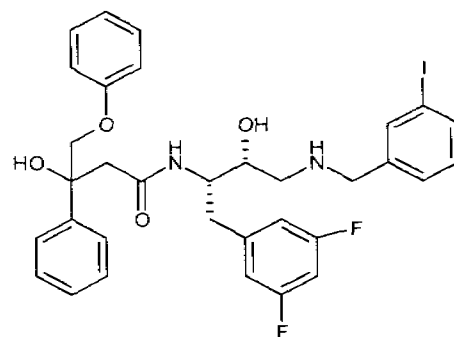
>20000 618,51 619,51

22



N-((1S,2R)-1-(3,5-difluorobenzyl)-2-hydroxy-3-((3-iodobenzyl)amino)propyl)-2-methyl-2-(2-methyl-2,3-dihydro-1-benzofuran-5-yl)propanamide (Generated by ACD/Name software)

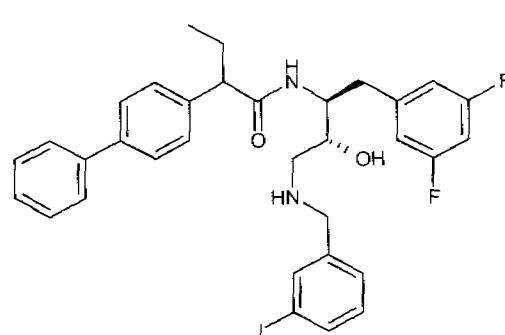
>20000 634,51 635,44



N-((1S,2R)-1-(3,5-difluorobenzyl)-2-hydroxy-3-((3-iodobenzyl)amino)propyl)-3-hydroxy-4-phenoxy-3-phenylbutanamide (Generated by ACD/Name software)

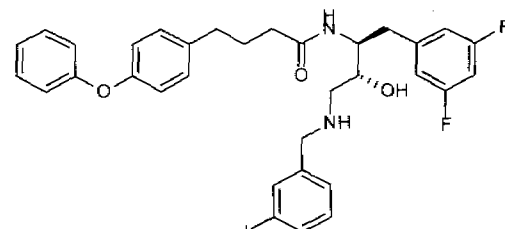
>20000 686,54 687,89

724 725



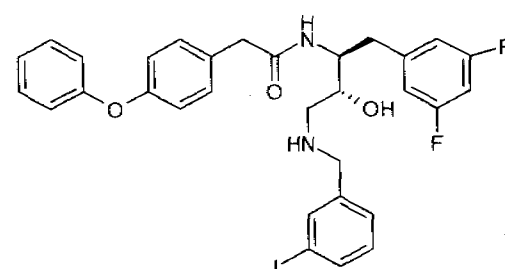
2-((1,1'-biphenyl-4-yl)-N-((1S,2R)-1-(3,5-difluorobenzyl)-2-hydroxy-3-((3-iodobenzyl)amino)propyl)butanamide (Generated by ACD/Name software)

>20000 654,54 655,88



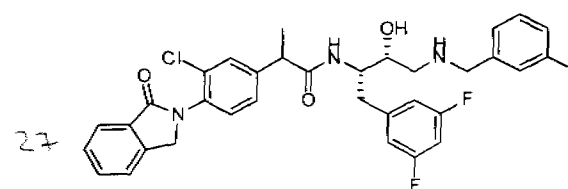
N-((1S,2R)-1-(3,5-difluorobenzyl)-2-hydroxy-3-((3-iodobenzyl)amino)propyl)-4-(4-phenoxyphenyl)butanamide (Generated by ACD/Name software)

>20000 670,54 671,91



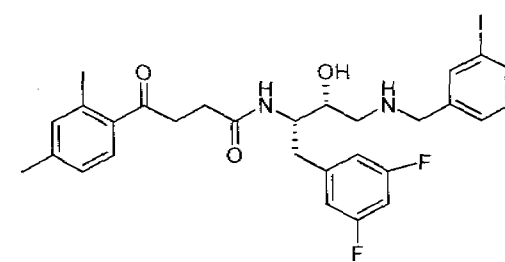
N-((1S,2R)-1-(3,5-difluorobenzyl)-2-hydroxy-3-((3-iodobenzyl)amino)propyl)-2-(4-phenoxyphenyl)acetamide (Generated by ACD/Name software)

>20000 642,49 643,85



2-[3-chloro-4-(1-oxo-1,3-dihydro-2H-isoindol-2-yl)phenyl]-N-((1S,2R)-1-(3,5-difluorobenzyl)-2-hydroxy-3-((3-iodobenzyl)amino)propyl)propanamide (Generated by ACD/Name software)

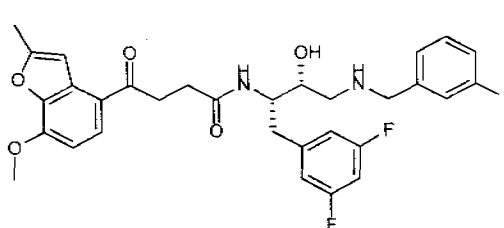
>20000 730 730,7



N-((1S,2R)-1-(3,5-difluorobenzyl)-2-hydroxy-3-((3-iodobenzyl)amino)propyl)-4-(2,4-dimethylphenyl)-4-oxobutanamide (Generated by ACD/Name software)

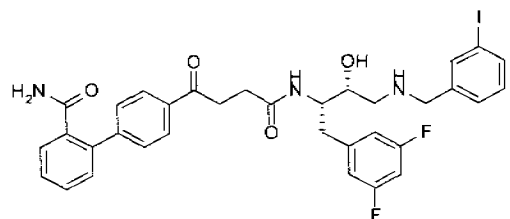
>20000 620,48 621,78

730



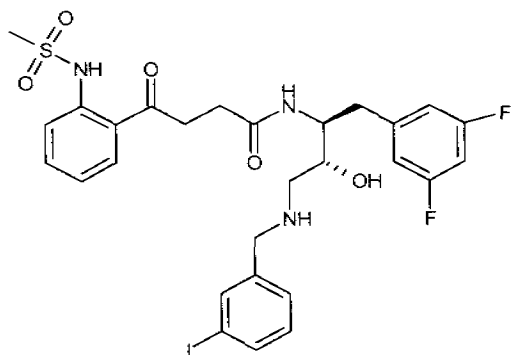
N-((1S,2R)-1-(3,5-difluorobenzyl)-2-hydroxy-3-iodobenzyl)amino]propyl)-4-(7-methoxy-2-methyl-1-benzofuran-4-yl)-4-oxobutanamide (Generated by ACD/Name software)

>20000 676,5 677,83



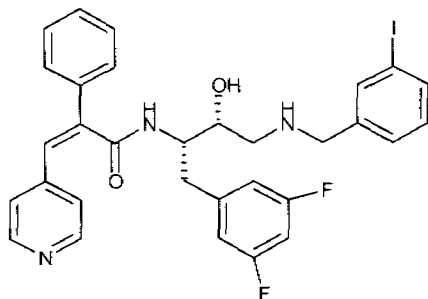
4'-[4-(((1S,2R)-1-(3,5-difluorobenzyl)-2-hydroxy-3-iodobenzyl)amino]propyl)amino]-4-oxobutanoyl]-1,1'-biphenyl-2-carboxamide (Generated by ACD/Name software) or ELAN-151132

305 711,55 712,97



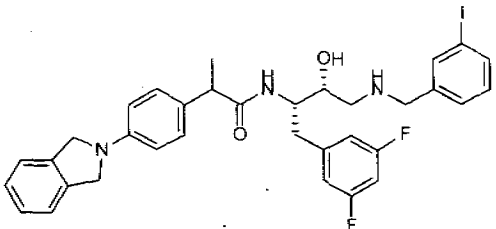
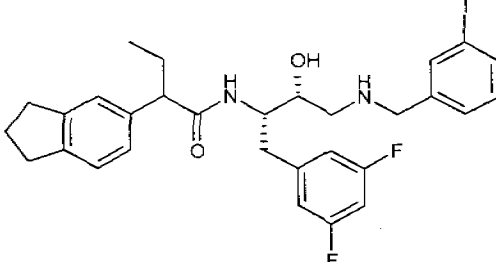
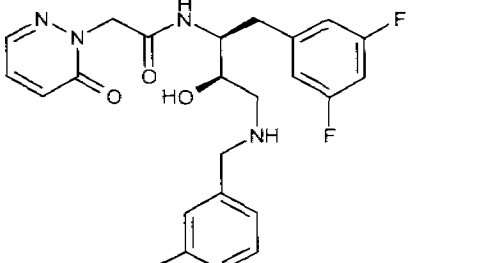
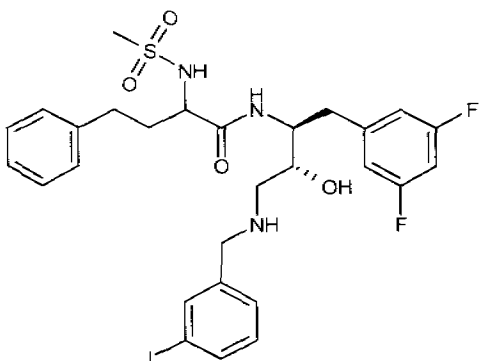
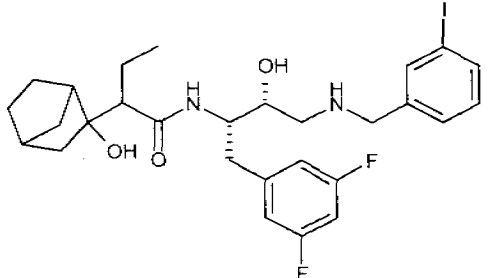
N-((1S,2R)-1-(3,5-difluorobenzyl)-2-hydroxy-3-iodobenzyl)amino]propyl)-4-{2-[(methylsulfonyl)amino]phenyl}-4-oxobutanamide (Generated by ACD/Name software)

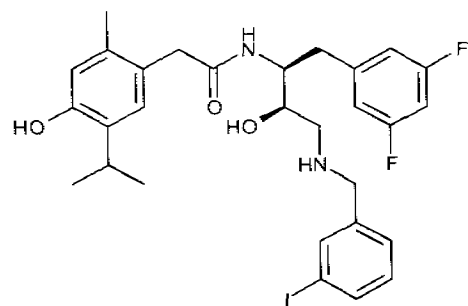
451
2261,92
1844
2779 685,53 686,89



(2Z)-N-((1S,2R)-1-(3,5-difluorobenzyl)-2-hydroxy-3-iodobenzyl)amino]propyl)-2-phenyl-3-pyridin-4-ylprop-2-enamide (Generated by ACD/Name software)

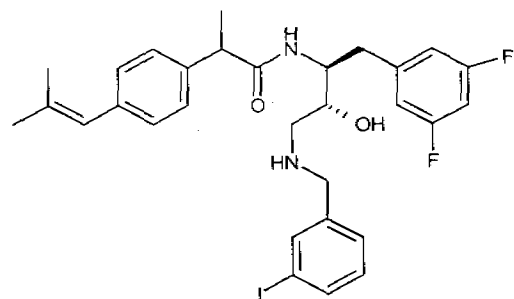
3067
>20000 639,49 640,89

	N-((1S,2R)-1-(3,5-difluorobenzyl)-2-hydroxy-3-((3-iodobenzyl)amino)propyl)-2-[4-(1,3-dihydro-2H-isoindol-2-yl)phenyl]propanamide (Generated by ACD/Name software)	>20000	681,57	682,87
	N-((1S,2R)-1-(3,5-difluorobenzyl)-2-hydroxy-3-((3-iodobenzyl)amino)propyl)-2-(2,3-dihydro-1H-inden-5-yl)butanamide (Generated by ACD/Name software)	>20000	618,51	619,91
	N-((1S,2R)-1-(3,5-difluorobenzyl)-2-hydroxy-3-((3-iodobenzyl)amino)propyl)-2-(6-oxopyridazin-1(6H)-yl)acetamide (Generated by ACD/Name software)	>20000	568,37	569,67
	N-((1S,2R)-1-(3,5-difluorobenzyl)-2-hydroxy-3-((3-iodobenzyl)amino)propyl)-2-((methylsulfonyl)amino)-4-phenylbutanamide (Generated by ACD/Name software)	>20000	671,55	672,93
	N-((1S,2R)-1-(3,5-difluorobenzyl)-2-hydroxy-3-((3-iodobenzyl)amino)propyl)-2-(2-hydroxybicyclo[2.2.1]hept-2-yl)butanamide (Generated by ACD/Name software)	>20000	612,5	613,9



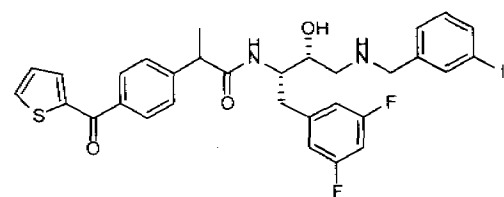
N-((1S,2R)-1-(3,5-difluorobenzyl)-2-hydroxy-3-((3-iodobenzyl)amino)propyl)-2-(4-hydroxy-5-isopropyl-2-methylphenyl)acetamide
(Generated by ACD/Name software)

>20000 622,5 623,24



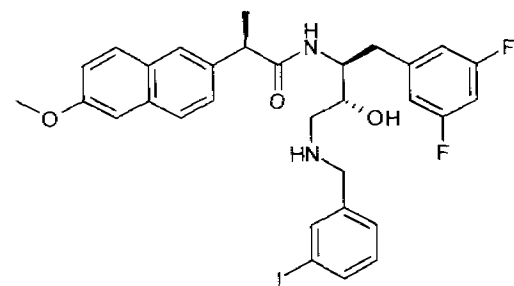
N-((1S,2R)-1-(3,5-difluorobenzyl)-2-hydroxy-3-((3-iodobenzyl)amino)propyl)-2-[4-(2-methylprop-1-enyl)phenyl]propanamide
(Generated by ACD/Name software)

>20000 618,51 619,38



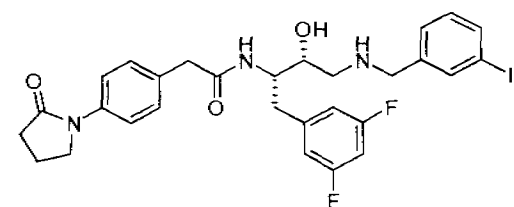
N-((1S,2R)-1-(3,5-difluorobenzyl)-2-hydroxy-3-((3-iodobenzyl)amino)propyl)-2-[4-(thien-2-ylcarbonyl)phenyl]propanamide
(Generated by ACD/Name software)

>20000 674,55 675,74



(2R)-N-((1S,2R)-1-(3,5-difluorobenzyl)-2-hydroxy-3-((3-iodobenzyl)amino)propyl)-2-(6-methoxy-2-naphthyl)propanamide
(Generated by ACD/Name software)

>20000 644,51 645,63



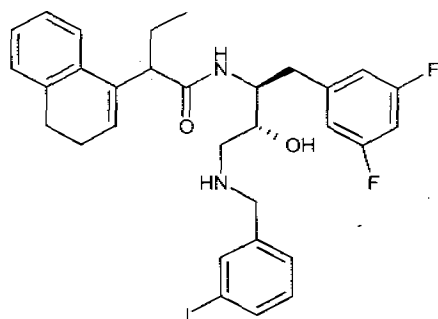
N-((1S,2R)-1-(3,5-difluorobenzyl)-2-hydroxy-3-((3-iodobenzyl)amino)propyl)-2-[4-(2-oxopyrrolidin-1-yl)phenyl]acetamide
(Generated by ACD/Name software) or ELAN-151166

432,72 633,48 634,68

566
3313,48
2990

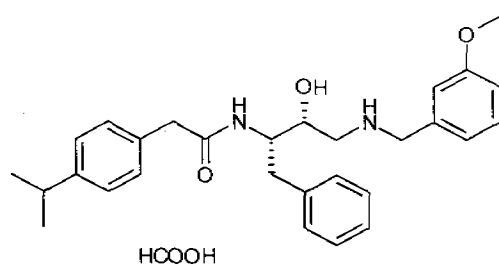
733

732



N-((1S,2R)-1-(3,5-difluorobenzyl)-2-hydroxy-3-((3-iodobenzyl)amino)propyl)-2-(3,4-dihydronaphthalen-1-yl)butanamide
(Generated by ACD/Name software)

>20000 630,52 631,75

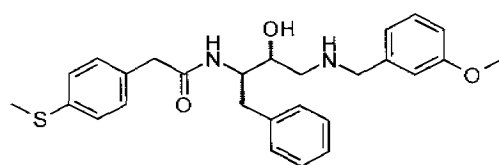


HCOOH

C₂₉H₃₆N₂O₃ · CH₂O₂
Mol. wt. 506.65

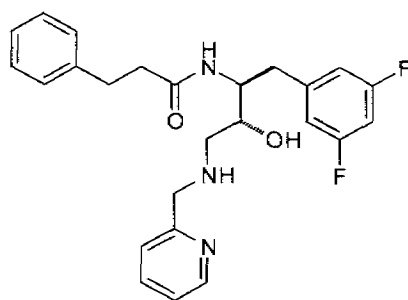
N-((1S,2R)-1-benzyl-2-hydroxy-3-((3-methoxybenzyl)amino)propyl)-2-(4-isopropylphenyl)acetamide compound with methyl hydroperoxide (1:1) (Generated by ACD/Name software)

>20000 508,66 461,2



N-((1S,2R)-1-benzyl-2-hydroxy-3-((3-methoxybenzyl)amino)propyl)-2-(4-(methylthio)phenyl)acetamide (Generated by ACD/Name software)

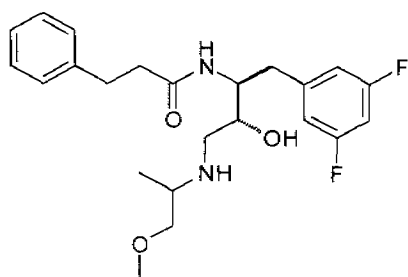
>20000 464,63 465,2



N-((1S,2R)-1-(3,5-difluorobenzyl)-2-hydroxy-3-((pyridin-2-ylmethyl)amino)propyl)-3-phenylpropanamide (Generated by ACD/Name software)

>20000 439,51 440,2

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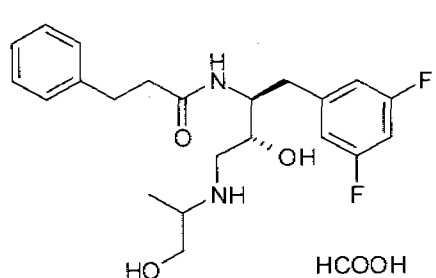
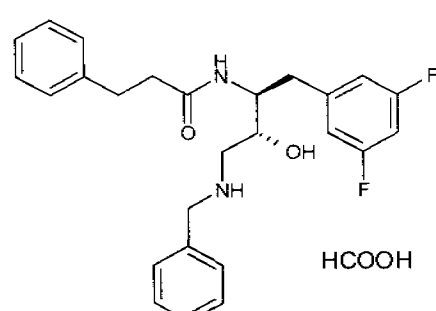
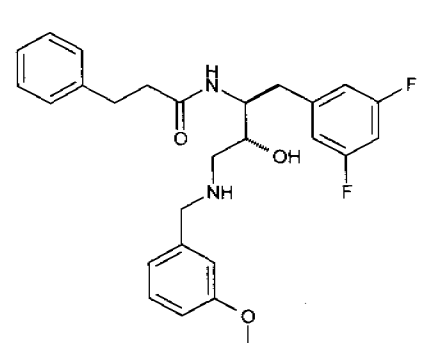
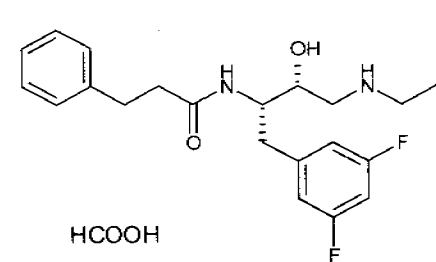


N-((1S,2R)-1-(3,5-difluorobenzyl)-2-hydroxy-3-((2-methoxy-1-methylethyl)amino)propyl)-3-phenylpropanamide (Generated by ACD/Name software)

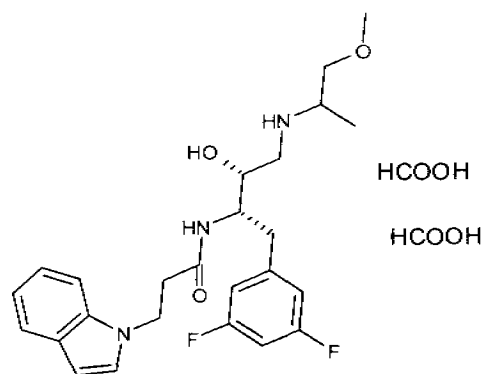
>20000 420,5 421,2

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734
733

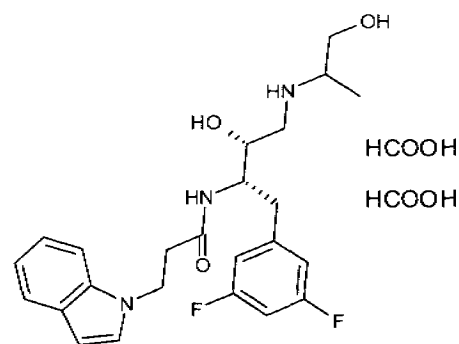
	N-((1S,2R)-1-(3,5-difluorobenzyl)-2-hydroxy-3-((2-hydroxy-1-methylethyl)amino)propyl)-3-phenylpropanamide compound with methyl hydroperoxide (1:1) (Generated by ACD/Name software)	>20000	454,52	407,3
	N-[(1S,2R)-3-(benzylamino)-1-(3,5-difluorobenzyl)-2-hydroxypropyl]-3-phenylpropanamide (Generated by ACD/Name software)	>20000	486,56	439,3
	N-((1S,2R)-1-(3,5-difluorobenzyl)-2-hydroxy-3-[(3-methoxybenzyl)amino]propyl)-3-phenylpropanamide	128,89	468,55	469,3
	N-((1S,2R)-1-(3,5-difluorobenzyl)-3-[(2-furylmethyl)amino]-2-hydroxypropyl)-3-phenylpropanamide (Generated by ACD/Name software)	>20000	476,53	429,3

735
734



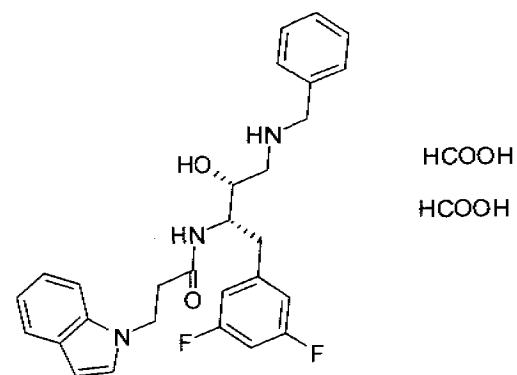
N-((1S,2R)-1-(3,5-difluorobenzyl)-2-hydroxy-3-((2-methoxy-1-methylethyl)amino)propyl)-3-(1H-indol-1-yl)propanamide compound with methyl hydroperoxide (1:2) (Generated by ACD/Name software)

>20000 555,63 460,2



N-((1S,2R)-1-(3,5-difluorobenzyl)-2-hydroxy-3-((2-hydroxy-1-methylethyl)amino)propyl)-3-(1H-indol-1-yl)propanamide compound with methyl hydroperoxide (1:2) (Generated by ACD/Name software)

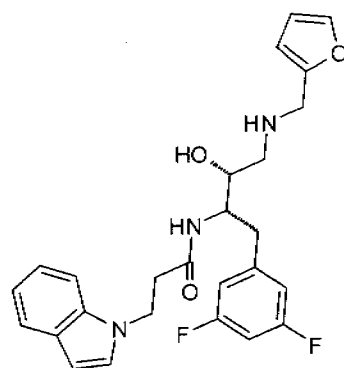
>20000 541,6 446,3



N-[(1S,2R)-3-(benzylamino)-1-(3,5-difluorobenzyl)-2-hydroxypropyl]-3-(1H-indol-1-yl)propanamide compound with methyl hydroperoxide (1:2) (Generated by ACD/Name software)

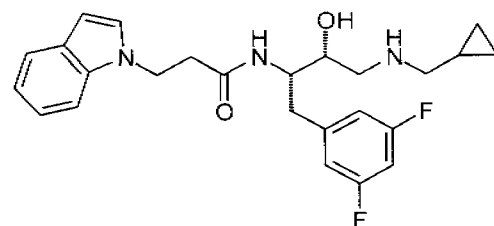
>20000 573,64 478,2

2/20
9/1



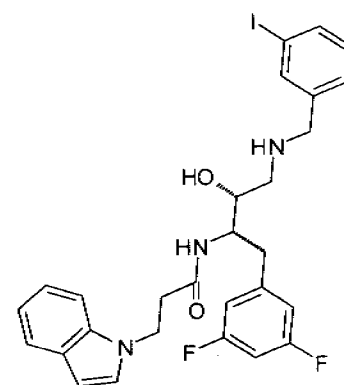
N-((1S,2R)-1-(3,5-difluorobenzyl)-3-[(2-furylmethyl)amino]-2-hydroxypropyl)-3-(1H-indol-1-yl)propanamide (Generated by ACD/Name software)

>20000 467,52 468,2



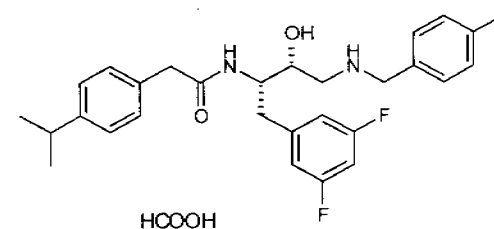
N-((1S,2R)-3-[(cyclopropylmethyl)amino]-1-(3,5-difluorobenzyl)-2-hydroxypropyl)-3-(1H-indol-1-yl)propanamide (Generated by ACD/Name software)

>20000 441,53 443,3



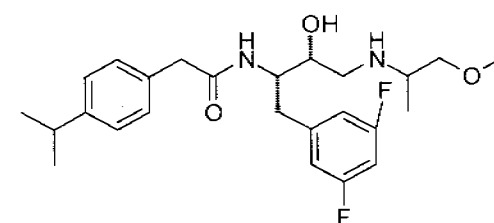
N-((1S,2R)-1-(3,5-difluorobenzyl)-2-hydroxy-3-[(3-iodobenzyl)amino]propyl)-3-(1H-indol-1-yl)propanamide (Generated by ACD/Name software)

>20000 603,46 604



N-((1S,2R)-1-(3,5-difluorobenzyl)-2-hydroxy-3-[(4-methylbenzyl)amino]propyl)-2-(4-isopropylphenyl)acetamide compound with methyl hydroperoxide (1:1) (Generated by ACD/Name software)

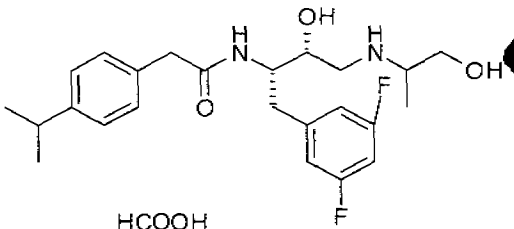
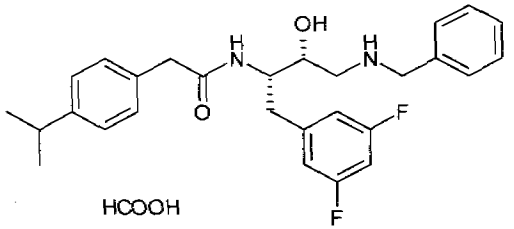
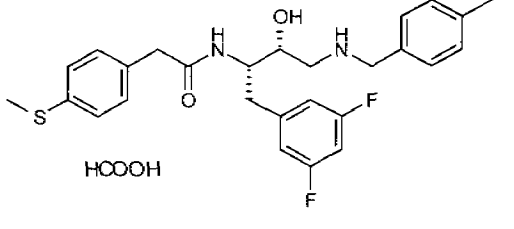
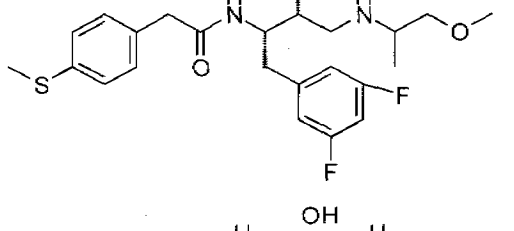
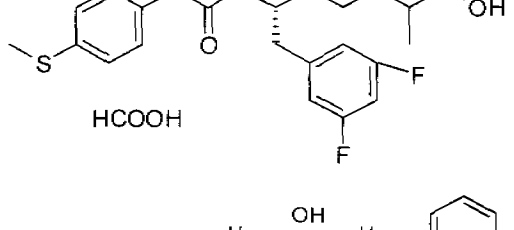
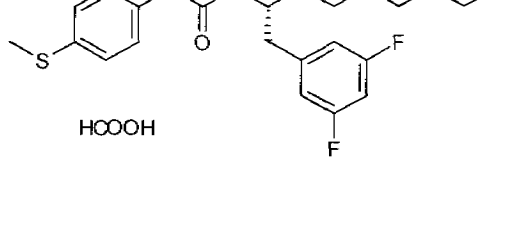
>20000 528,64 481,3



N-((1S,2R)-1-(3,5-difluorobenzyl)-2-hydroxy-3-[(2-methoxy-1-methylethyl)amino]propyl)-2-(4-isopropylphenyl)acetamide (Generated by ACD/Name software)

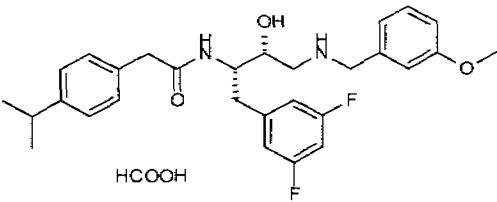
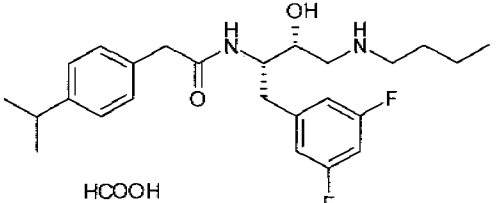
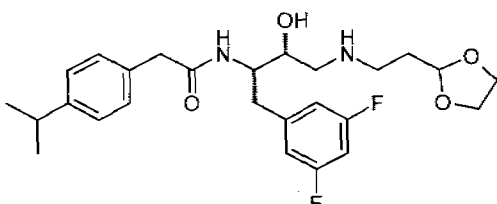
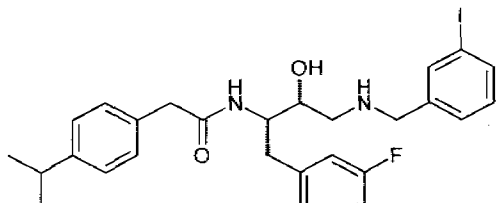
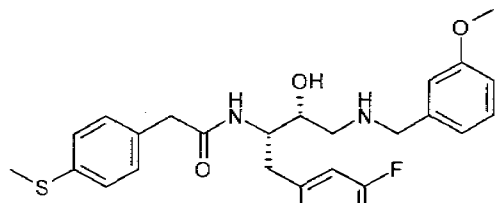
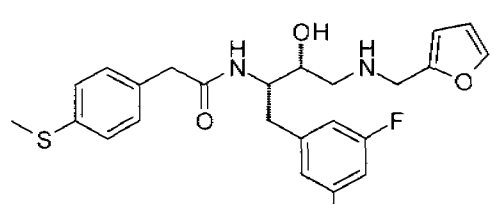
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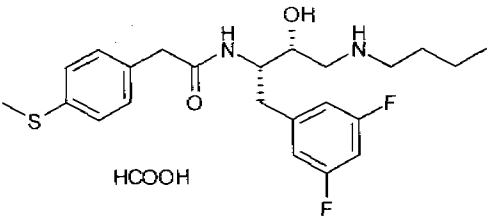
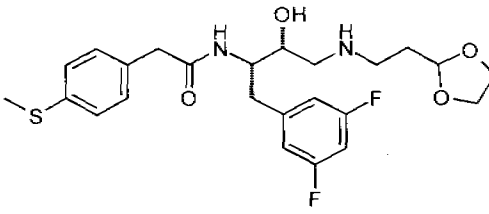
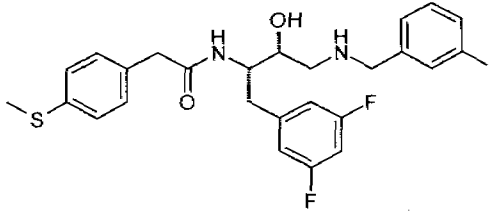
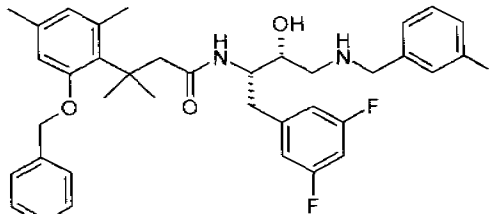
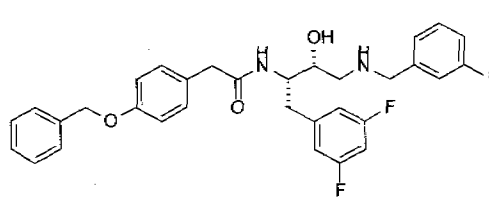
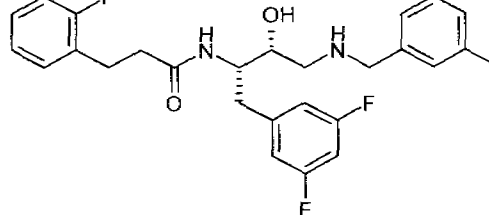
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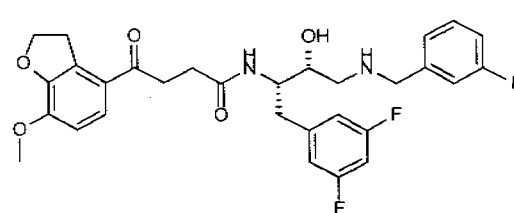
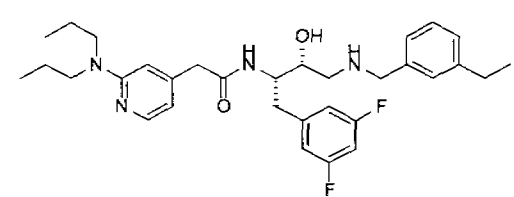
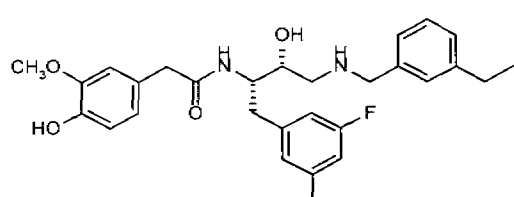
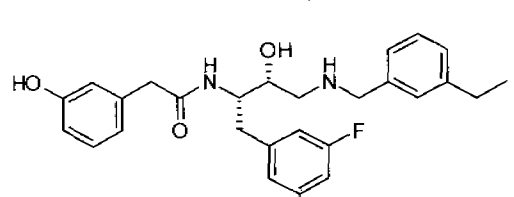
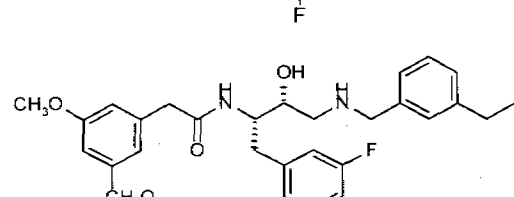
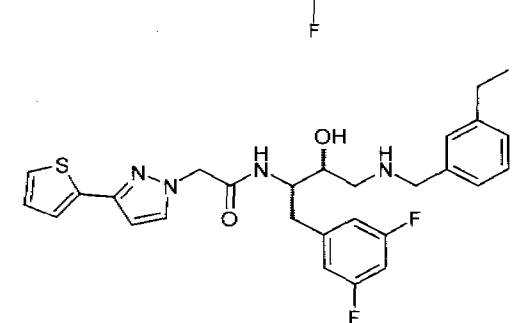
	N-((1S,2R)-1-(3,5-difluorobenzyl)-2-hydroxy-3-[(2-hydroxy-1-methylethyl)amino]propyl)-2-(4-isopropylphenyl)acetamide compound with methyl hydroperoxide (1:1) (Generated by ACD/Name software)	>20000	482,57	435,3
	N-[(1S,2R)-3-(benzylamino)-1-(3,5-difluorobenzyl)-2-hydroxypropyl]-2-(4-isopropylphenyl)acetamide compound with methyl hydroperoxide (1:1) (Generated by ACD/Name software)	>20000	514,62	467,3
	N-((1S,2R)-1-(3,5-difluorobenzyl)-2-hydroxy-3-[(4-methylbenzyl)amino]propyl)-2-[4-(methylthio)phenyl]acetamide compound with methyl hydroperoxide (1:1) (Generated by ACD/Name software)	>20000	532,65	485,2
	N-((1S,2R)-1-(3,5-difluorobenzyl)-2-hydroxy-3-[(2-methoxy-1-methylethyl)amino]propyl)-2-[4-(methylthio)phenyl]acetamide (Generated by ACD/Name software)	>20000	452,57	453,2
	N-((1S,2R)-1-(3,5-difluorobenzyl)-2-hydroxy-3-[(2-hydroxy-1-methylethyl)amino]propyl)-2-[4-(methylthio)phenyl]acetamide compound with methyl hydroperoxide (1:1) (Generated by ACD/Name software)	>20000	486,58	439,2
	N-[(1S,2R)-3-(benzylamino)-1-(3,5-difluorobenzyl)-2-hydroxypropyl]-2-[4-(methylthio)phenyl]acetamide compound with methyl hydroperoxide (1:1) (Generated by ACD/Name software)	>20000	518,63	471,2

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	N-((1S,2R)-1-(3,5-difluorobenzyl)-2-hydroxy-3-((3-methoxybenzyl)amino)propyl)-2-(4-isopropylphenyl)acetamide compound with methyl hydroperoxide (1:1) (Generated by ACD/Name software)	>20000	544,64	497,3
	N-((1S,2R)-3-(butylamino)-1-(3,5-difluorobenzyl)-2-hydroxypropyl)-2-(4-isopropylphenyl)acetamide compound with methyl hydroperoxide (1:1) (Generated by ACD/Name software)	>20000	480,6	433
	N-((1S,2R)-1-(3,5-difluorobenzyl)-3-([2-(1,3-dioxolan-2-yl)ethyl]amino)-2-hydroxypropyl)-2-(4-isopropylphenyl)acetamide (Generated by ACD/Name software)	>20000	476,57	477,3
	N-((1S,2R)-1-(3,5-difluorobenzyl)-2-hydroxy-3-((3-iodobenzyl)amino)propyl)-2-(4-isopropylphenyl)acetamide (Generated by ACD/Name software)	2439,27	592,47	593
	N-((1S,2R)-1-(3,5-difluorobenzyl)-2-hydroxy-3-((3-methoxybenzyl)amino)propyl)-2-(4-(methylthio)phenyl)acetamide compound with methyl hydroperoxide (1:1) (Generated by ACD/Name software)	>20000	548,65	400,8
	N-((1S,2R)-1-(3,5-difluorobenzyl)-3-((2-furylmethyl)amino)-2-hydroxypropyl)-2-(4-(methylthio)phenyl)acetamide (Generated by ACD/Name software)	>20000	460,55	461,2

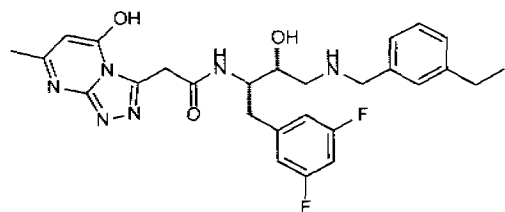
 HCOOH	N-[(1S,2R)-3-(butylamino)-1-(3,5-difluorobenzyl)-2-hydroxypropyl]-2-[4-(methylthio)phenyl]acetamide compound with methyl hydroperoxide (1:1) (Generated by ACD/Name software)	>20000	484,61	436,9
	N-[(1S,2R)-1-(3,5-difluorobenzyl)-3-[[2-(1,3-dioxolan-2-yl)ethyl]amino]-2-hydroxypropyl]-2-[4-(methylthio)phenyl]acetamide (Generated by ACD/Name software)	>20000	480,58	481,2
	N-[(1S,2R)-1-(3,5-difluorobenzyl)-2-hydroxy-3-[(3-iodobenzyl)amino]propyl]-2-[4-(methylthio)phenyl]acetamide (Generated by ACD/Name software)	4598,1	596,48	597
	3-[2-(benzyloxy)-4,6-dimethylphenyl]-N-[(1S,2R)-1-(3,5-difluorobenzyl)-2-hydroxy-3-[(3-iodobenzyl)amino]propyl]-3-methylbutanamide	>20000	726,65	727,97
	2-[4-(benzyloxy)phenyl]-N-[(1S,2R)-1-(3,5-difluorobenzyl)-2-hydroxy-3-[(3-iodobenzyl)amino]propyl]acetamide (Generated by ACD/Name software)	6009,02	656,52	657,33
	N-[(1S,2R)-1-(3,5-difluorobenzyl)-2-hydroxy-3-[(3-iodobenzyl)amino]propyl]-3-(2-fluorophenyl)propanamide (Generated by ACD/Name software)	5984,6	582,41	583,79

	N-((1S,2R)-1-(3,5-difluorobenzyl)-2-hydroxy-3-[(3-iodobenzyl)amino]propyl)-4-(7-methoxy-2,3-dihydro-1-benzofuran-4-yl)-4-oxobutanamide (Generated by ACD/Name software)	>20000	664,49	665,89
	N-((1S,2R)-1-(3,5-difluorobenzyl)-3-[(3-ethylbenzyl)amino]-2-hydroxypropyl)-2-[2-(dipropylamino)pyridin-4-yl]acetamide	3165,66	552,71	553,4
	N-((1S,2R)-1-(3,5-difluorobenzyl)-3-[(3-ethylbenzyl)amino]-2-hydroxypropyl)-2-(4-hydroxy-3-methoxyphenyl)acetamide (Generated by ACD/Name software)	9682,73	498,58	499
	N-((1S,2R)-1-(3,5-difluorobenzyl)-3-[(3-ethylbenzyl)amino]-2-hydroxypropyl)-2-(3-hydroxyphenyl)acetamide (Generated by ACD/Name software)	3754,04	468,55	469,3
	N-((1S,2R)-1-(3,5-difluorobenzyl)-3-[(3-ethylbenzyl)amino]-2-hydroxypropyl)-2-(3,5-dimethoxyphenyl)acetamide (Generated by ACD/Name software)	9860,7	512,6	513,3
	1794 or N-((1S,2R)-1-(3,5-difluorobenzyl)-3-[(3-ethylbenzyl)amino]-2-hydroxypropyl)-2-(3-thien-2-yl-1H-pyrazol-1-yl)acetamide (Generated by ACD/Name software)	7072,15	524,64	525,4

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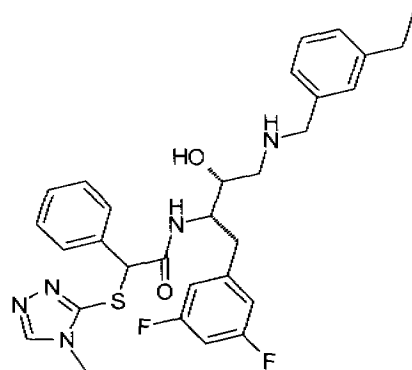
	1803 or N-((1S,2R)-1-(3,5-difluorobenzyl)-3-((3-ethylbenzyl)amino)-2-hydroxypropyl)-3-(2-oxo-1,3-benzoxazol-3(2H)-yl)propanamide (Generated by ACD/Name software)	17961,55	523,59	524,5
	1804 or 3-(1H-benzimidazol-2-yl)-N-((1S,2R)-1-(3,5-difluorobenzyl)-3-((3-ethylbenzyl)amino)-2-hydroxypropyl)-3-hydroxypropanamide (Generated by ACD/Name software)		522,6	523,3
	1807 or N-((1S,2R)-1-(3,5-difluorobenzyl)-3-((3-ethylbenzyl)amino)-2-hydroxypropyl)-2-(4-morpholin-4-ylphenyl)acetamide (Generated by ACD/Name software)	3677,37	537,66	538,5
	1808 or N-((1S,2R)-1-(3,5-difluorobenzyl)-3-((3-ethylbenzyl)amino)-2-hydroxypropyl)-2-(2-thioxo-1,3-benzothiazol-3(2H)-yl)acetamide (Generated by ACD/Name software)	7171,04	541,69	542,4
	1812 or N-((1S,2R)-1-(3,5-difluorobenzyl)-3-((3-ethylbenzyl)amino)-2-hydroxypropyl)-3-(3-pyridin-2-yl-1,2,4-oxadiazol-5-yl)propanamide (Generated by ACD/Name software)	6391,77	535,6	536,4
	1825 or N-((1S,2R)-1-(3,5-difluorobenzyl)-3-((3-ethylbenzyl)amino)-2-hydroxypropyl)-2-(2-ethyl-1H-benzimidazol-1-yl)acetamide (Generated by ACD/Name software)	16933,99	520,63	521,4

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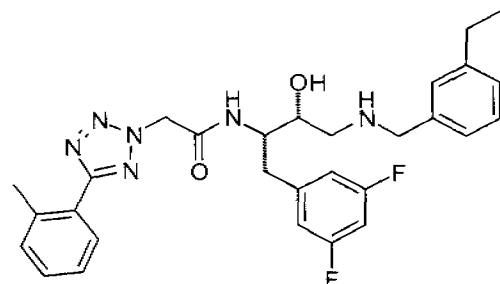
N-((1S,2R)-1-(3,5-difluorobenzyl)-3-[(3-ethylbenzyl)amino]-2-hydroxypropyl)-2-(5-hydroxy-7-methyl[1,2,4]triazolo[4,3-a]pyrimidin-3-yl)acetamide

6780,16 524,58 525,3



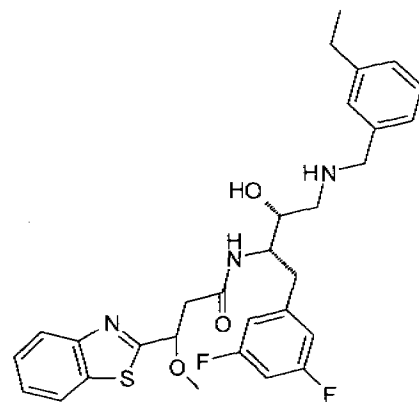
N-((1S,2R)-1-(3,5-difluorobenzyl)-3-[(3-ethylbenzyl)amino]-2-hydroxypropyl)-2-[(4-methyl-4H-1,2,4-triazol-3-yl)thio]-2-phenylacetamide

6495,67 565,69 566,3



N-((1S,2R)-1-(3,5-difluorobenzyl)-3-[(3-ethylbenzyl)amino]-2-hydroxypropyl)-2-[5-(2-methylphenyl)-2H-tetrazol-2-yl]acetamide

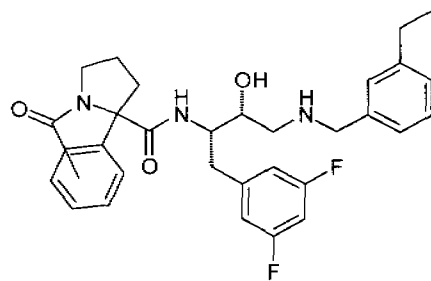
>20000 534,61 535,5



3-(1,3-benzothiazol-2-yl)-N-((1S,2R)-1-(3,5-difluorobenzyl)-3-[(3-ethylbenzyl)amino]-2-hydroxypropyl)-3-methoxypropanamide

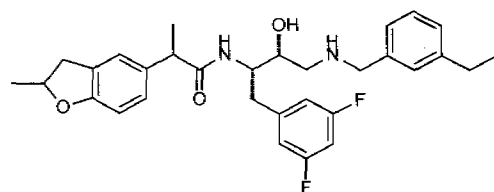
8969,76 553,68 554,4

742



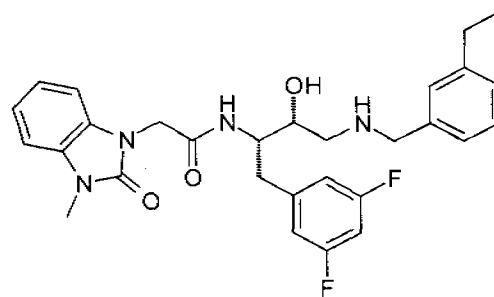
1-acetyl-N-((1S,2R)-1-(3,5-difluorobenzyl)-3-((3-ethylbenzyl)amino)-2-hydroxypropyl)-2-phenylprolinamide

>20000 549,67 550,5



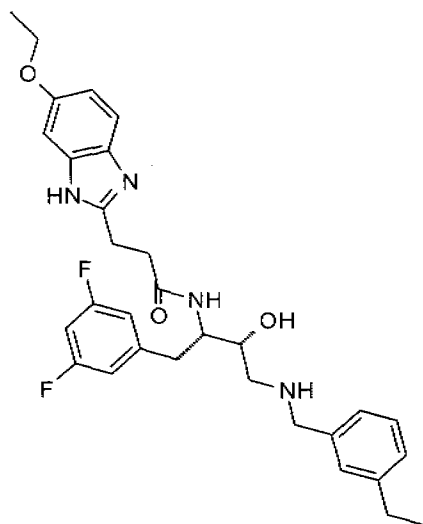
N-((1S,2R)-1-(3,5-difluorobenzyl)-3-((3-ethylbenzyl)amino)-2-hydroxypropyl)-2-(2-methyl-2,3-dihydro-1-benzofuran-5-yl)propanamide

>20000 522,64 523,4



N-((1S,2R)-1-(3,5-difluorobenzyl)-3-((3-ethylbenzyl)amino)-2-hydroxypropyl)-2-(3-methyl-2-oxo-2,3-dihydro-1H-benzimidazol-1-yl)acetamide

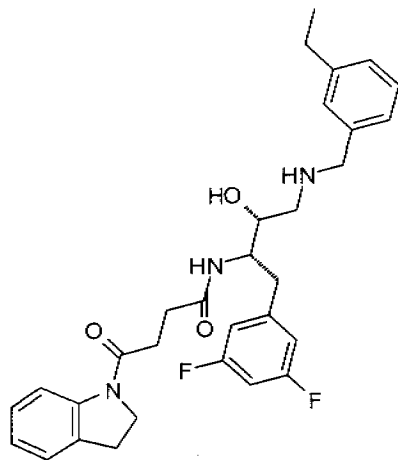
>20000 522,6 523,5



N-((1S,2R)-1-(3,5-difluorobenzyl)-3-((3-ethylbenzyl)amino)-2-hydroxypropyl)-3-(6-ethoxy-1H-benzimidazol-2-yl)propanamide

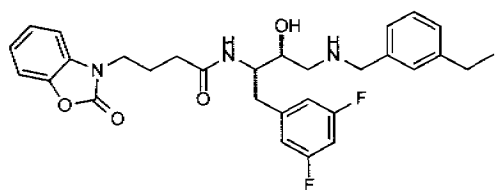
>20000 550,65 551,4

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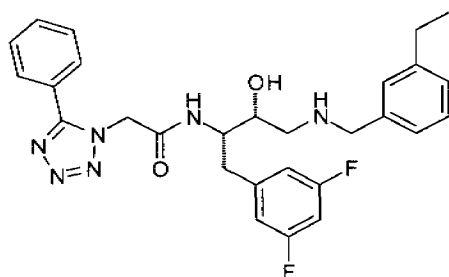
1874 or N-((1S,2R)-1-(3,5-difluorobenzyl)-3-
[(3-ethylbenzyl)amino]-2-hydroxypropyl)-4-
(2,3-dihydro-1H-indol-1-yl)-4-oxobutanamide
(Generated by ACD/Name software)

>20000 535,64 536,5



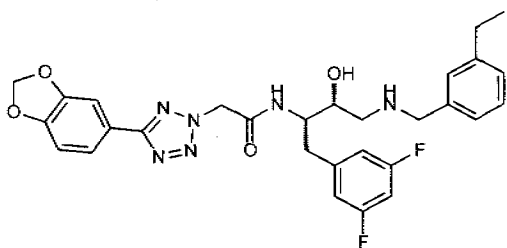
1878 or N-((1S,2R)-1-(3,5-difluorobenzyl)-3-
[(3-ethylbenzyl)amino]-2-hydroxypropyl)-4-(2-
oxo-1,3-benzoxazol-3(2H)-yl)butanamide
(Generated by ACD/Name software)

>20000 537,61 538,4



1880 or N-((1S,2R)-1-(3,5-difluorobenzyl)-3-
[(3-ethylbenzyl)amino]-2-hydroxypropyl)-2-(5-
phenyl-1H-tetrazol-1-yl)acetamide
(Generated by ACD/Name software)

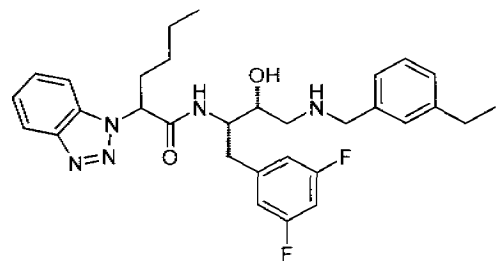
>20000 520,59 521,3



2-[5-(1,3-benzodioxol-5-yl)-2H-tetrazol-2-yl]-
N-((1S,2R)-1-(3,5-difluorobenzyl)-3-[(3-
ethylbenzyl)amino]-2-
hydroxypropyl)acetamide

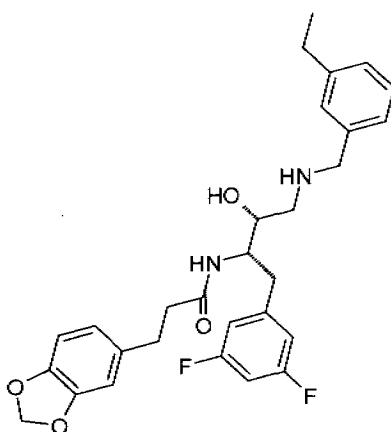
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745
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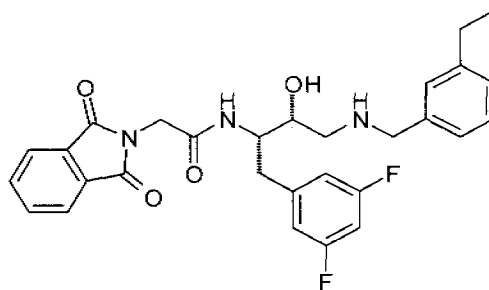
2-(1H-1,2,3-benzotriazol-1-yl)-N-((1S,2R)-1-(3,5-difluorobenzyl)-3-((3-ethylbenzyl)amino)-2-hydroxypropyl)hexanamide

2122,31 549,67 550,5



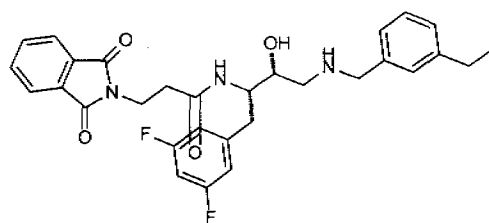
3-(1,3-benzodioxol-5-yl)-N-((1S,2R)-1-(3,5-difluorobenzyl)-3-((3-ethylbenzyl)amino)-2-hydroxypropyl)propanamide

>20000 510,59 511,5



N-((1S,2R)-1-(3,5-difluorobenzyl)-3-((3-ethylbenzyl)amino)-2-hydroxypropyl)-2-(1,3-dioxo-1,3-dihydro-2H-isoindol-2-yl)acetamide

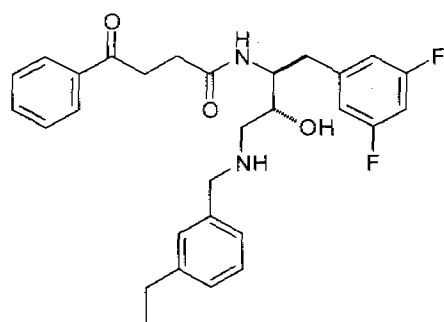
521,57 522,2



N-((1S,2R)-1-(3,5-difluorobenzyl)-3-((3-ethylbenzyl)amino)-2-hydroxypropyl)-3-(1,3-dioxo-1,3-dihydro-2H-isoindol-2-yl)propanamide

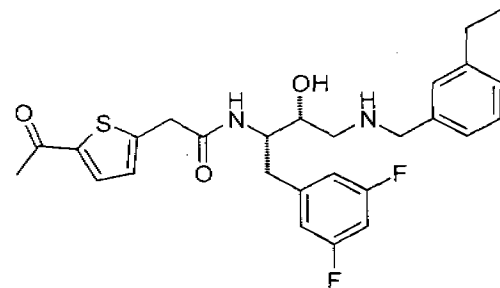
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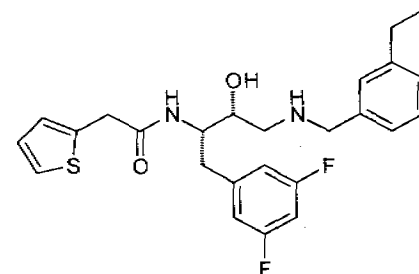
N-((1S,2R)-1-(3,5-difluorobenzyl)-3-((3-ethylbenzyl)amino)-2-hydroxypropyl)-4-oxo-4-phenylbutanamide

>20000 494,59 495,5



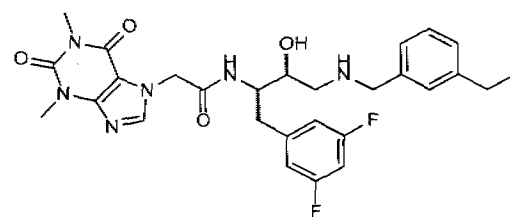
2-(5-acetylthien-2-yl)-N-((1S,2R)-1-(3,5-difluorobenzyl)-3-((3-ethylbenzyl)amino)-2-hydroxypropyl)acetamide

379,19 500,61 501,4



N-((1S,2R)-1-(3,5-difluorobenzyl)-3-((3-ethylbenzyl)amino)-2-hydroxypropyl)-2-thien-2-ylacetamide

>20000
>20000 458,58 459,3



N-((1S,2R)-1-(3,5-difluorobenzyl)-3-((3-ethylbenzyl)amino)-2-hydroxypropyl)-2-(1,3-dimethyl-2,6-dioxo-1,2,3,6-tetrahydro-7H-purin-7-yl)acetamide

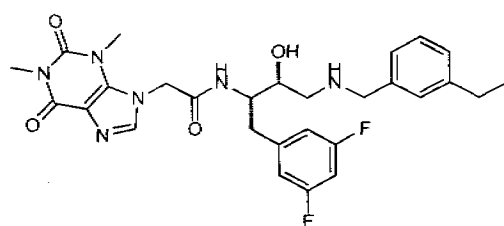
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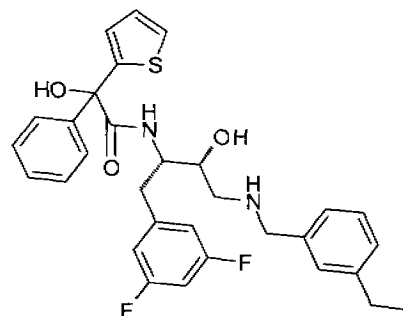
	N-((1S,2R)-1-(3,5-difluorobenzyl)-3-[(3-ethylbenzyl)amino]-2-hydroxypropyl)-4-(3-hydroxyphenyl)-4-oxobutanamide	11034,58	510,59	511,4
	N-((1S,2R)-1-(3,5-difluorobenzyl)-3-[(3-ethylbenzyl)amino]-2-hydroxypropyl)-4-(3-methoxyphenyl)-4-oxobutanamide	>20000	524,61	525,4
	1916 or N-((1S,2R)-1-(3,5-difluorobenzyl)-3-[(3-ethylbenzyl)amino]-2-hydroxypropyl)-4-(1H-indol-3-yl)-4-oxobutanamide (Generated by ACD/Name software)	3497,67	533,62	534,3
	1923 or 2-(1-benzothien-4-yl)-N-((1S,2R)-1-(3,5-difluorobenzyl)-3-[(3-ethylbenzyl)amino]-2-hydroxypropyl)acetamide (Generated by ACD/Name software)	>20000	508,64	509,3

798-799



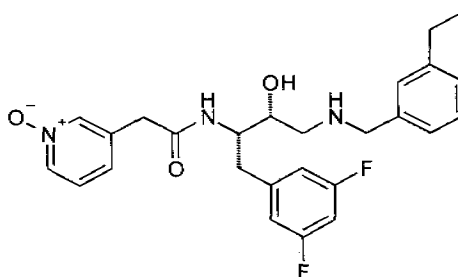
1930 or N-((1S,2R)-1-(3,5-difluorobenzyl)-3-((3-ethylbenzyl)amino)-2-hydroxypropyl)-2-(1,3-dimethyl-2,6-dioxo-1,2,3,6-tetrahydro-9H-purin-9-yl)acetamide (Generated by ACD/Name software)

>20000 554,6 555,4



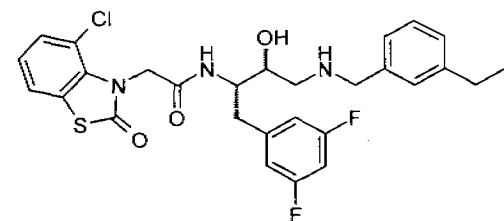
N-((1S,2R)-1-(3,5-difluorobenzyl)-3-((3-ethylbenzyl)amino)-2-hydroxypropyl)-2-hydroxy-2-phenyl-2-thien-2-ylacetamide

>20000 550,67 551,4



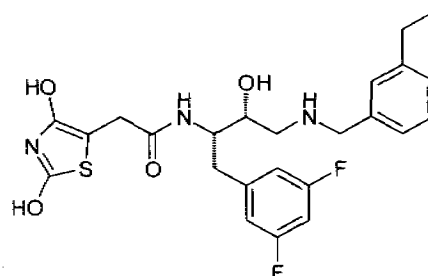
N-((1S,2R)-1-(3,5-difluorobenzyl)-3-((3-ethylbenzyl)amino)-2-hydroxypropyl)-2-(1-oxidopyridin-3-yl)acetamide

>20000 469,54 470,3



2-(4-chloro-2-oxo-1,3-benzothiazol-3(2H)-yl)-N-((1S,2R)-1-(3,5-difluorobenzyl)-3-((3-ethylbenzyl)amino)-2-hydroxypropyl)acetamide

>20000 560,07 560,3



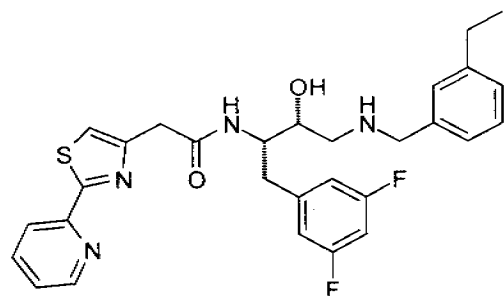
N-((1S,2R)-1-(3,5-difluorobenzyl)-3-((3-ethylbenzyl)amino)-2-hydroxypropyl)-2-(2,4-dihydroxy-1,3-thiazol-5-yl)acetamide

>20000 491,56 492,3

7019 7018

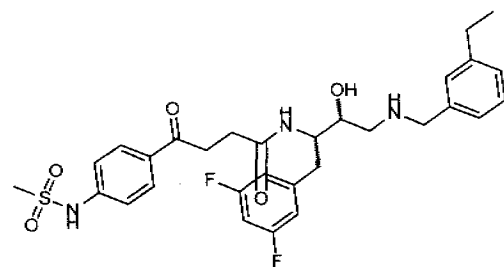
	1964 or N-((1S,2R)-1-(3,5-difluorobenzyl)-3-((3-ethylbenzyl)amino)-2-hydroxypropyl)-2-[2-(4-fluorophenyl)-1,3-benzoxazol-5-yl]acetamide (Generated by ACD/Name software)	5811,93	587,65	588,4
	1965 or N-((1S,2R)-1-(3,5-difluorobenzyl)-3-((3-ethylbenzyl)amino)-2-hydroxypropyl)-2-(2-pyridin-4-yl-1,3-benzoxazol-5-yl)acetamide (Generated by ACD/Name software)	>20000	570,64	571,4
	1967 or N-((1S,2R)-1-(3,5-difluorobenzyl)-3-((3-ethylbenzyl)amino)-2-hydroxypropyl)-2-(2-methyl-1,3-benzoxazol-5-yl)acetamide (Generated by ACD/Name software)	>20000	507,59	508,5
	1987 or 2-(2H-1,2,3-benzotriazol-2-yl)-N-((1S,2R)-1-(3,5-difluorobenzyl)-3-((3-ethylbenzyl)amino)-2-hydroxypropyl)butanamide (Generated by ACD/Name software)	>20000	521,62	522,5
	1988 or N-((1S,2R)-1-(3,5-difluorobenzyl)-3-((3-ethylbenzyl)amino)-2-hydroxypropyl)-4-(1,3-dioxo-1,3-dihydro-2H-isoindol-2-yl)-2-hydroxybutanamide (Generated by ACD/Name software)	>20000	565,62	566,4
	2011 or 2-[2-(acetamino)-1,3-thiazol-4-yl]-N-((1S,2R)-1-(3,5-difluorobenzyl)-3-((3-ethylbenzyl)amino)-2-hydroxypropyl)acetamide (Generated by ACD/Name software)	6410,6	516,62	517,3

450 214



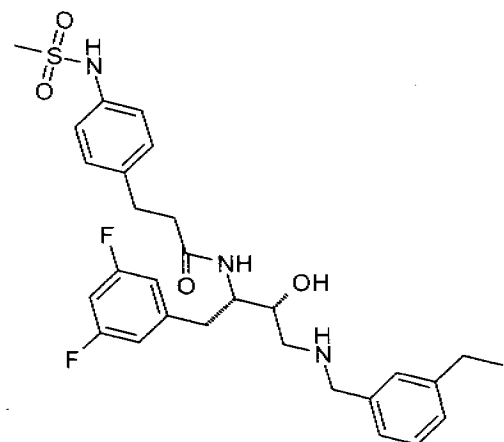
2015 or N-((1S,2R)-1-(3,5-difluorobenzyl)-3-
[(3-ethylbenzyl)amino]-2-hydroxypropyl)-2-(2-
pyridin-2-yl-1,3-thiazol-4-yl)acetamide
(Generated by ACD/Name software)

>20000 536,65 537,4



2023 or N-((1S,2R)-1-(3,5-difluorobenzyl)-3-
[(3-ethylbenzyl)amino]-2-hydroxypropyl)-4-
[(methylsulfonyl)amino]phenyl)-4-
oxobutanamide (Generated by ACD/Name
software)

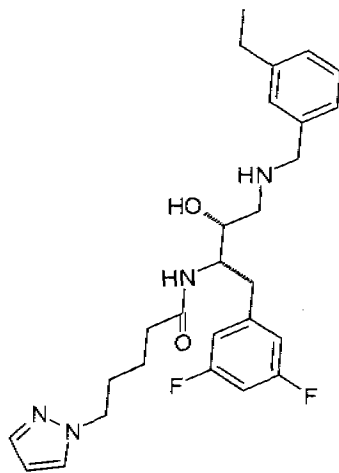
>20000 587,69 588,4



2025 or N-((1S,2R)-1-(3,5-difluorobenzyl)-3-
[(3-ethylbenzyl)amino]-2-hydroxypropyl)-3-{4-
[(methylsulfonyl)amino]phenyl}propanamide
(Generated by ACD/Name software)

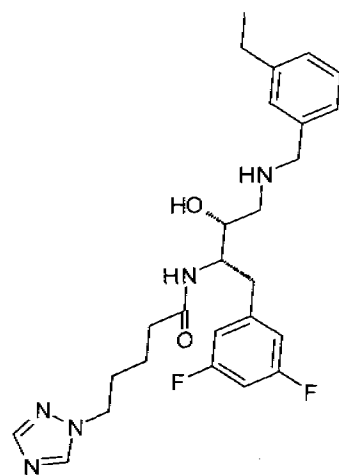
4910,18 559,68 560,4

151



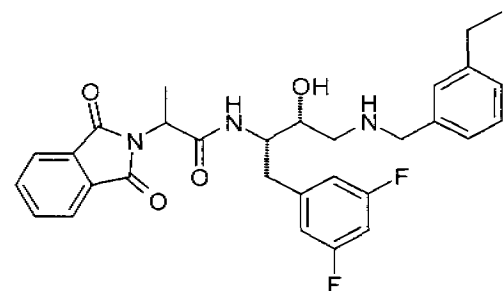
2028 or N-((1S,2R)-1-(3,5-difluorobenzyl)-3-((3-ethylbenzyl)amino)-2-hydroxypropyl)-5-(1H-pyrazol-1-yl)pentanamide (Generated by ACD/Name software)

940,43 484,59 485,4



2029 or N-((1S,2R)-1-(3,5-difluorobenzyl)-3-((3-ethylbenzyl)amino)-2-hydroxypropyl)-5-(1H-1,2,4-triazol-1-yl)pentanamide (Generated by ACD/Name software)

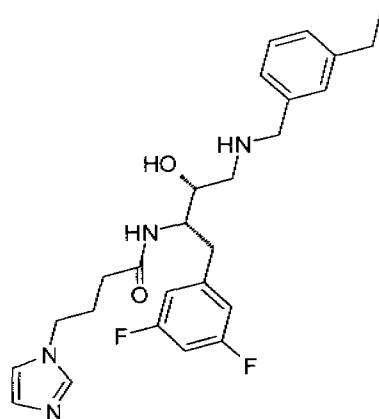
3654,94
>20000 485,58 486,5



2033 or N-((1S,2R)-1-(3,5-difluorobenzyl)-3-((3-ethylbenzyl)amino)-2-hydroxypropyl)-2-(1,3-dioxo-1,3-dihydro-2H-isoindol-2-yl)propanamide (Generated by ACD/Name software)

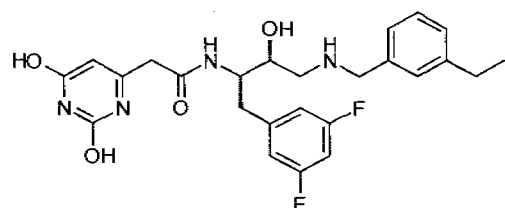
10088,18 535,6 536,1

752 24



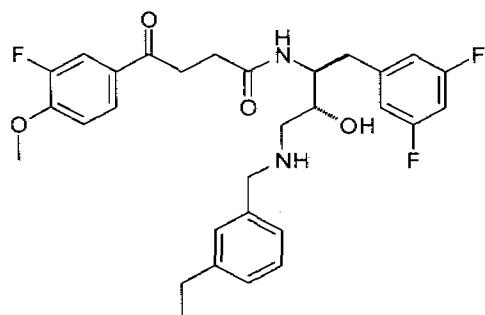
2036 or N-((1S,2R)-1-(3,5-difluorobenzyl)-3-((3-ethylbenzyl)amino)-2-hydroxypropyl)-4-(1H-imidazol-1-yl)butanamide (Generated by ACD/Name software)

1713,51 470,57 471,3



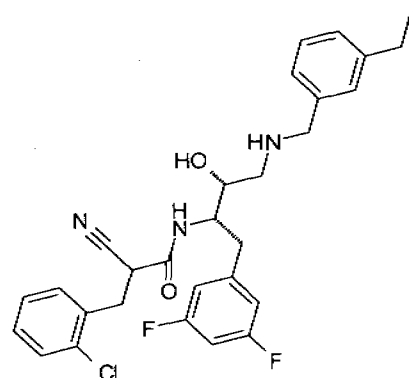
2042 or N-((1S,2R)-1-(3,5-difluorobenzyl)-3-((3-ethylbenzyl)amino)-2-hydroxypropyl)-2-(2,6-dihydroxypyrimidin-4-yl)acetamide (Generated by ACD/Name software)

5671,55 486,52 487,3



2043 or N-((1S,2R)-1-(3,5-difluorobenzyl)-3-((3-ethylbenzyl)amino)-2-hydroxypropyl)-4-(3-fluoro-4-methoxyphenyl)-4-oxobutanamide (Generated by ACD/Name software)

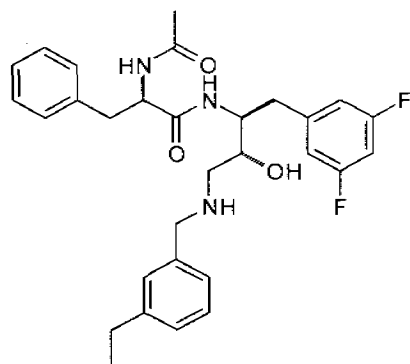
3512,62 542,6 543,4



2054 or 3-(2-chlorophenyl)-2-cyano-N-((1S,2R)-1-(3,5-difluorobenzyl)-3-((3-ethylbenzyl)amino)-2-hydroxypropyl)propanamide (Generated by ACD/Name software)

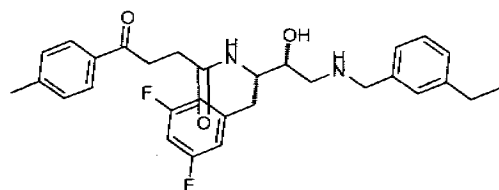
>20000 526,03 526,3

453-252



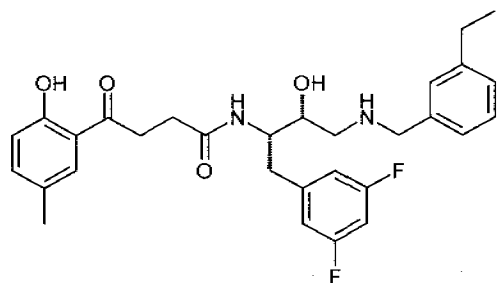
2059 or N-acetyl-N-((1S,2R)-1-(3,5-difluorobenzyl)-3-[(3-ethylbenzyl)amino]-2-hydroxypropyl)-D-phenylalaninamide (Generated by ACD/Name software)

>20000 523,63 524,4



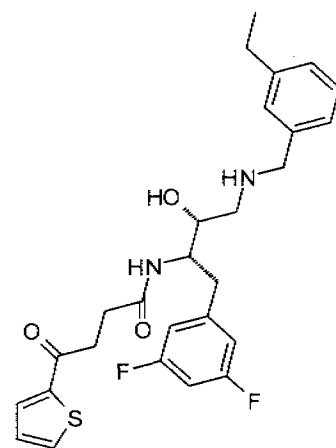
2063 or N-((1S,2R)-1-(3,5-difluorobenzyl)-3-[(3-ethylbenzyl)amino]-2-hydroxypropyl)-4-(4-methylphenyl)-4-oxobutanamide (Generated by ACD/Name software)

5055,29 508,61 509,4



2065 or N-((1S,2R)-1-(3,5-difluorobenzyl)-3-[(3-ethylbenzyl)amino]-2-hydroxypropyl)-4-(2-hydroxy-5-methylphenyl)-4-oxobutanamide (Generated by ACD/Name software)

2579,68 524,61 525,5

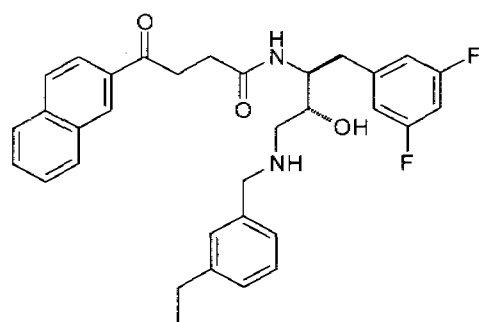


2070 or N-((1S,2R)-1-(3,5-difluorobenzyl)-3-[(3-ethylbenzyl)amino]-2-hydroxypropyl)-4-oxo-4-thien-2-ylbutanamide (Generated by ACD/Name software) or 2379

>20000 500,61 501,3

4327,54

754 2379

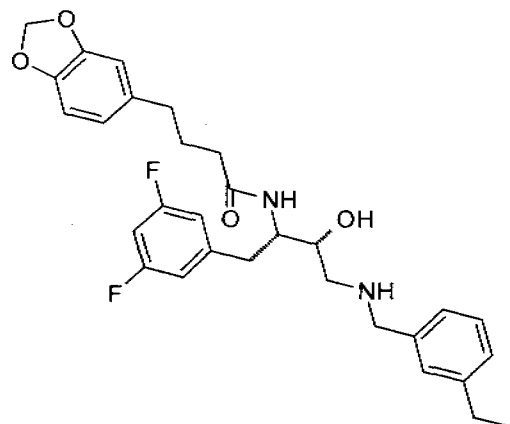


2375 or N-((1S,2R)-1-(3,5-difluorobenzyl)-3-((3-ethylbenzyl)amino)-2-hydroxypropyl)-4-(2-naphthyl)-4-oxobutanamide (Generated by ACD/Name software)

5461,46

544,65

545,4

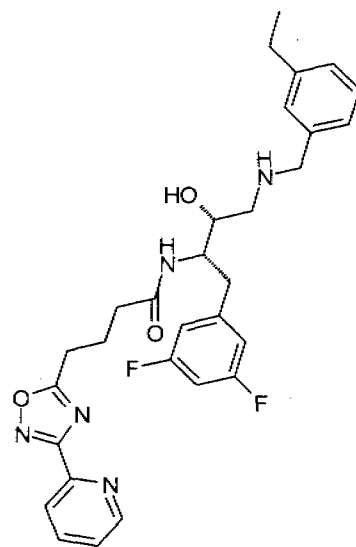


2377 or 4-(1,3-benzodioxol-5-yl)-N-((1S,2R)-1-(3,5-difluorobenzyl)-3-((3-ethylbenzyl)amino)-2-hydroxypropyl)butanamide (Generated by ACD/Name software)

>20000

524,61

525,5



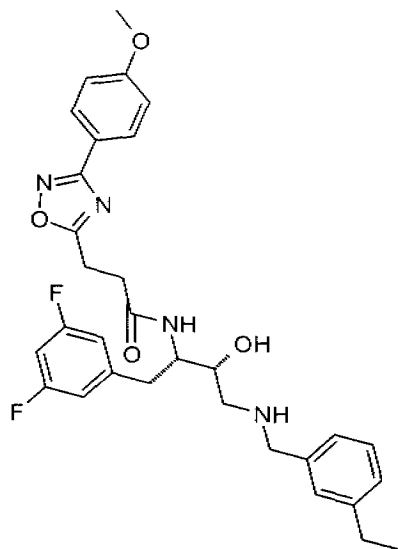
2381 or N-((1S,2R)-1-(3,5-difluorobenzyl)-3-((3-ethylbenzyl)amino)-2-hydroxypropyl)-4-(3-pyridin-2-yl-1,2,4-oxadiazol-5-yl)butanamide (Generated by ACD/Name software)

>20000

549,63

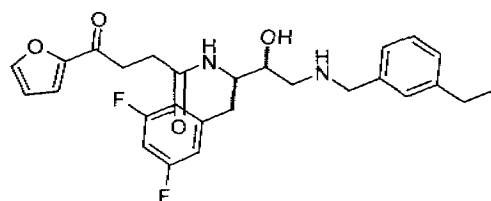
550,5

763



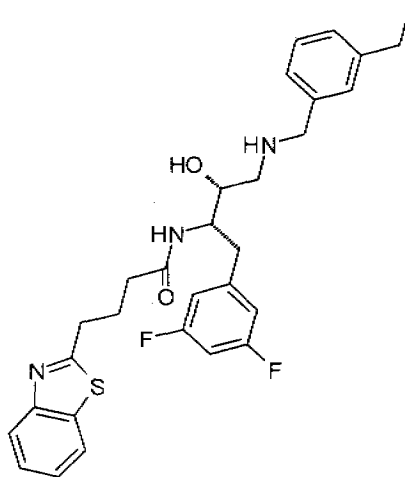
2385 or N-((1S,2R)-1-(3,5-difluorobenzyl)-3-((3-ethylbenzyl)amino)-2-hydroxypropyl)-3-[3-(4-methoxyphenyl)-1,2,4-oxadiazol-5-yl]propanamide (Generated by ACD/Name software)

>20000 564,64 565,5



2388 or N-((1S,2R)-1-(3,5-difluorobenzyl)-3-((3-ethylbenzyl)amino)-2-hydroxypropyl)-4-(2-furyl)-4-oxobutanamide (Generated by ACD/Name software)

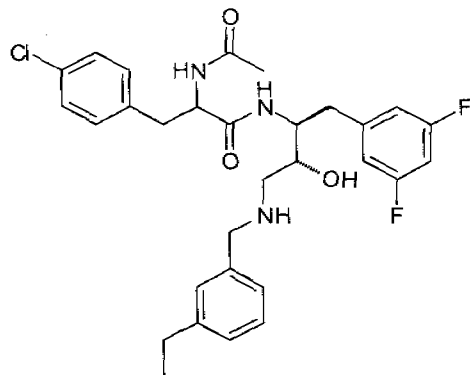
6321,46 484,55 485,4



2390 or 4-(1,3-benzothiazol-2-yl)-N-((1S,2R)-1-(3,5-difluorobenzyl)-3-((3-ethylbenzyl)amino)-2-hydroxypropyl)butanamide (Generated by ACD/Name software)

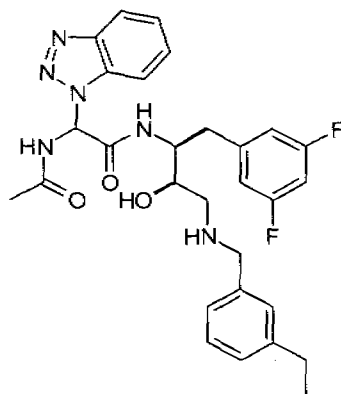
6507,39 537,68 538,4

7/30



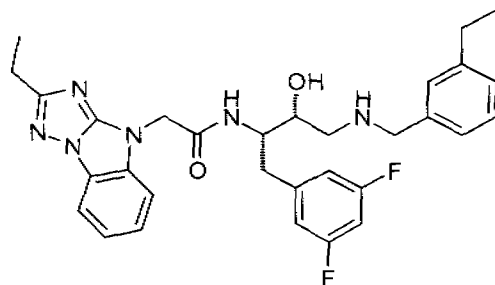
2402 or N-acetyl-4-chloro-N-((1S,2R)-1-(3,5-difluorobenzyl)-3-((3-ethylbenzyl)amino)-2-hydroxypropyl)phenylalaninamide
(Generated by ACD/Name software)

>20000 558,07 558,3



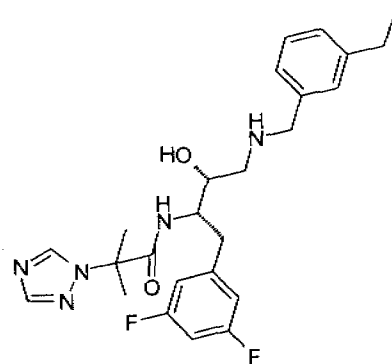
2425 or 2-(acetylamino)-2-(1H-1,2,3-benzotriazol-1-yl)-N-((1S,2R)-1-(3,5-difluorobenzyl)-3-((3-ethylbenzyl)amino)-2-hydroxypropyl)acetamide (Generated by ACD/Name software)

12434,15 550,61 551,4



2430 or N-((1S,2R)-1-(3,5-difluorobenzyl)-3-((3-ethylbenzyl)amino)-2-hydroxypropyl)-2-(2-ethyl-4H-[1,2,4]triazolo[1,5-a]benzimidazol-4-yl)acetamide (Generated by ACD/Name software)

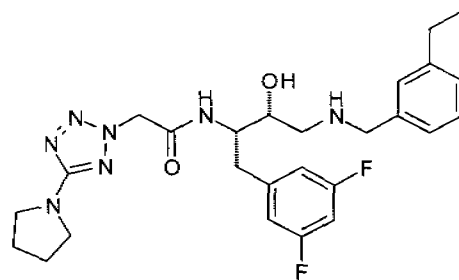
9908,09 560,65 561,4



2431 or N-((1S,2R)-1-(3,5-difluorobenzyl)-3-((3-ethylbenzyl)amino)-2-hydroxypropyl)-2-methyl-2-(1H-1,2,4-triazol-1-yl)propanamide
(Generated by ACD/Name software)

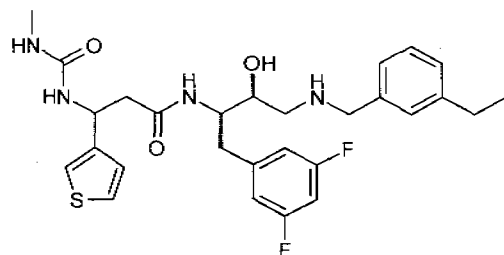
>20000 471,56 472,4

752
756



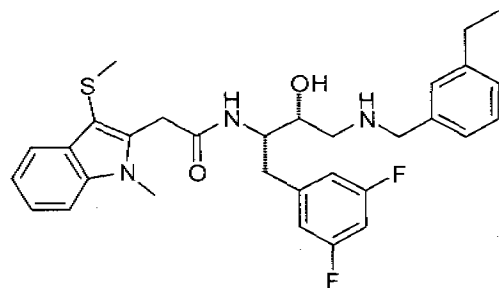
2438 or N-((1S,2R)-1-(3,5-difluorobenzyl)-3-((3-ethylbenzyl)amino)-2-hydroxypropyl)-2-(5-pyrrolidin-1-yl-2H-tetrazol-2-yl)acetamide (Generated by ACD/Name software)

>20000 513,6 514,4



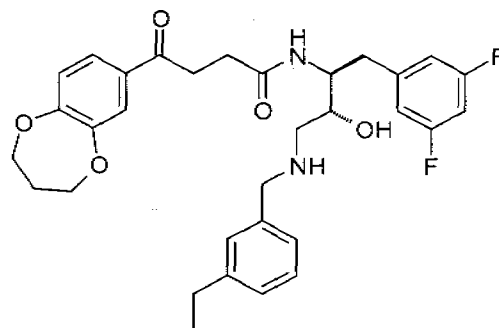
2440 or N-((1S,2R)-1-(3,5-difluorobenzyl)-3-((3-ethylbenzyl)amino)-2-hydroxypropyl)-3-[[[(methylamino)carbonyl]amino]-3-thien-3-ylpropanamide (Generated by ACD/Name software)

8988,52 544,67 545,4



2444 or N-((1S,2R)-1-(3,5-difluorobenzyl)-3-((3-ethylbenzyl)amino)-2-hydroxypropyl)-2-[1-methyl-3-(methylthio)-1H-indol-2-yl]acetamide (Generated by ACD/Name software)

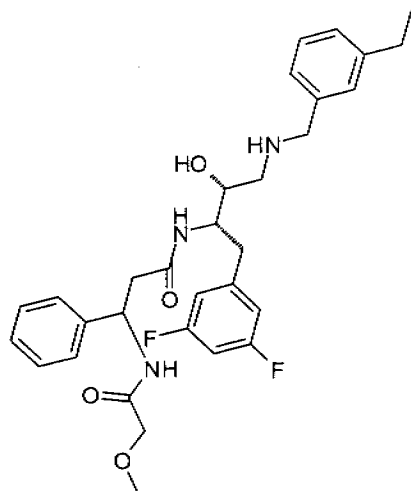
6301,05 551,7 552,4



2451 or N-((1S,2R)-1-(3,5-difluorobenzyl)-3-((3-ethylbenzyl)amino)-2-hydroxypropyl)-4-(3,4-dihydro-2H-1,5-benzodioxepin-7-yl)-4-oxobutanamide (Generated by ACD/Name software)

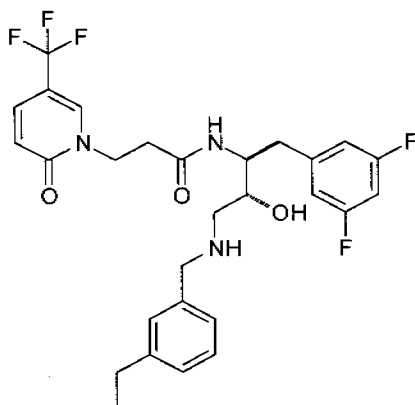
7262,89 566,65 567,5

758
758



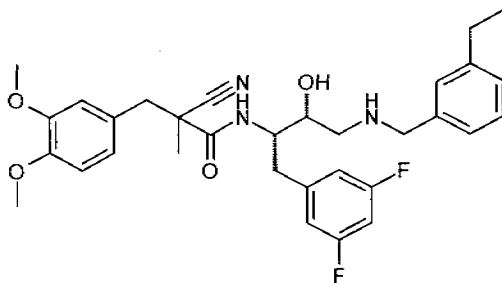
2456 or N-((1S,2R)-1-(3,5-difluorobenzyl)-3-((3-ethylbenzyl)amino)-2-hydroxypropyl)-3-((methoxyacetyl)amino)-3-phenylpropanamide (Generated by ACD/Name software)

>20000 553,65 554,4



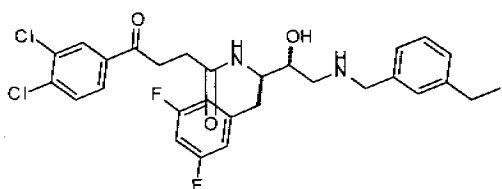
2466 or N-((1S,2R)-1-(3,5-difluorobenzyl)-3-((3-ethylbenzyl)amino)-2-hydroxypropyl)-3-[2-oxo-5-(trifluoromethyl)pyridin-1(2H)-yl]propanamide (Generated by ACD/Name software)

>20000 551,56 552,5



2469 or 2-cyano-N-((1S,2R)-1-(3,5-difluorobenzyl)-3-((3-ethylbenzyl)amino)-2-hydroxypropyl)-3-(3,4-dimethoxyphenyl)-2-methylpropanamide (Generated by ACD/Name software)

>20000 565,67 566,4



2473 or 4-(3,4-dichlorophenyl)-N-((1S,2R)-1-(3,5-difluorobenzyl)-3-((3-ethylbenzyl)amino)-2-hydroxypropyl)-4-oxobutanamide (Generated by ACD/Name software)

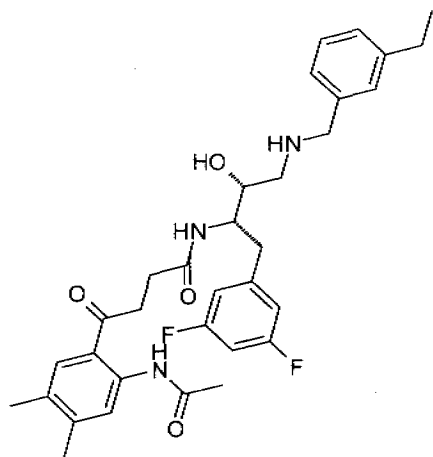
4475,74 563,48 563,3

159

	2476 or N-((1S,2R)-1-(3,5-difluorobenzyl)-3-((3-ethylbenzyl)amino)-2-hydroxypropyl)-4-(3,4-difluorophenyl)-4-oxobutanamide (Generated by ACD/Name software)	5375,73	530,57	531,5
	2477 or N-((1S,2R)-1-(3,5-difluorobenzyl)-3-((3-ethylbenzyl)amino)-2-hydroxypropyl)-4-(3,4-difluorophenyl)-2-methyl-4-oxobutanamide (Generated by ACD/Name software)	5721,67	544,6	545,4
	2481 or N-((1S,2R)-1-(3,5-difluorobenzyl)-3-((3-ethylbenzyl)amino)-2-hydroxypropyl)-2-hydroxy-4-oxo-4-thien-2-ylbutanamide (Generated by ACD/Name software)	2488,61	516,61	517,6
	2486 or N-((1S,2R)-1-(3,5-difluorobenzyl)-3-((3-ethylbenzyl)amino)-2-hydroxypropyl)-4-(7-methoxy-1-benzofuran-2-yl)-4-oxobutanamide (Generated by ACD/Name software)	>20000	564,63	565,4
	4-dibenzo[b,d]furan-2-yl-N-((1S,2R)-1-(3,5-difluorobenzyl)-3-((3-ethylbenzyl)amino)-2-hydroxypropyl)-4-oxobutanamide	>20000	585,68	586,5

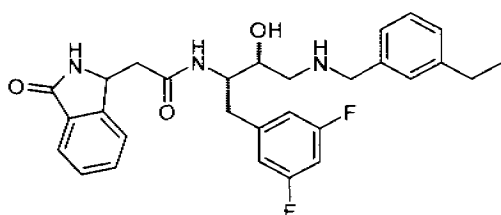
	2494 or N-((1S,2R)-1-(3,5-difluorobenzyl)-3-((3-ethylbenzyl)amino)-2-hydroxypropyl)-2-(6-oxo-3-phenylpyridazin-1(6H)-yl)acetamide (Generated by ACD/Name software)	4884,11	546,62	547,4
	2496 or 2-(1H,1'H-2,2'-biimidazol-1-yl)-N-((1S,2R)-1-(3,5-difluorobenzyl)-3-((3-ethylbenzyl)amino)-2-hydroxypropyl)acetamide (Generated by ACD/Name software)	>20000	508,58	509,4
	2498 or N-((1S,2R)-1-(3,5-difluorobenzyl)-3-((3-ethylbenzyl)amino)-2-hydroxypropyl)-4-(3,4-dihydro-2H-chromen-6-yl)-4-oxobutanamide (Generated by ACD/Name software)	8423,29	550,65	551,5
	2499 or N-((1S,2R)-1-(3,5-difluorobenzyl)-3-((3-ethylbenzyl)amino)-2-hydroxypropyl)-2-(3-oxo-1,2-benzisothiazol-2(3H)-yl)acetamide (Generated by ACD/Name software)	5283,18	525,62	526,4

761
780



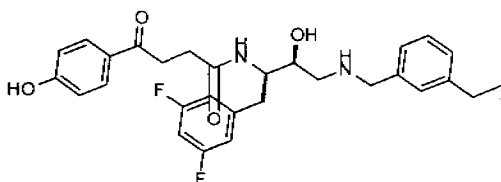
2504 or 4-[2-(acetylamino)-4,5-dimethylphenyl]-N-((1S,2R)-1-(3,5-difluorobenzyl)-3-[(3-ethylbenzyl)amino]-2-hydroxypropyl)-4-oxobutanamide
(Generated by ACD/Name software)

>20000 579,69 580,4



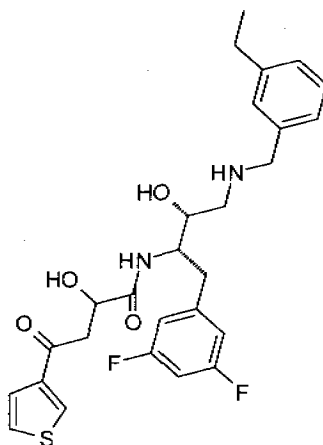
2506 or N-((1S,2R)-1-(3,5-difluorobenzyl)-3-[(3-ethylbenzyl)amino]-2-hydroxypropyl)-2-(3-oxo-2,3-dihydro-1H-isoindol-1-yl)acetamide
(Generated by ACD/Name software)

>20000 507,59 508,5



2507 or N-((1S,2R)-1-(3,5-difluorobenzyl)-3-[(3-ethylbenzyl)amino]-2-hydroxypropyl)-4-(4-hydroxyphenyl)-4-oxobutanamide
(Generated by ACD/Name software)

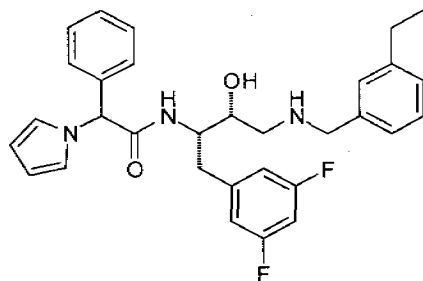
4725,94 510,59 511,4



2510 or N-((1S,2R)-1-(3,5-difluorobenzyl)-3-[(3-ethylbenzyl)amino]-2-hydroxypropyl)-2-hydroxy-4-oxo-4-thien-3-ylbutanamide
(Generated by ACD/Name software)

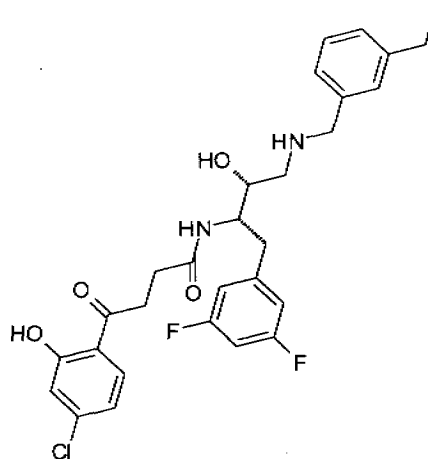
2104,15 516,61 517,4

462



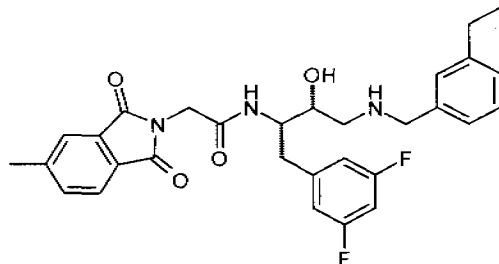
2513 or N-((1S,2R)-1-(3,5-difluorobenzyl)-3-
[(3-ethylbenzyl)amino]-2-hydroxypropyl)-2-
phenyl-2-(1H-pyrrol-1-yl)acetamide
(Generated by ACD/Name software)

>20000 517,62 518,5



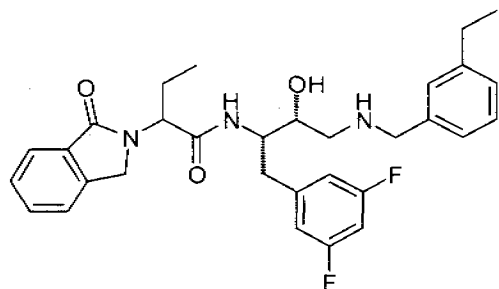
2517 or 4-(4-chloro-2-hydroxyphenyl)-N-
((1S,2R)-1-(3,5-difluorobenzyl)-3-[(3-
ethylbenzyl)amino]-2-hydroxypropyl)-4-
oxobutanamide (Generated by ACD/Name
software)

545,03 545,4



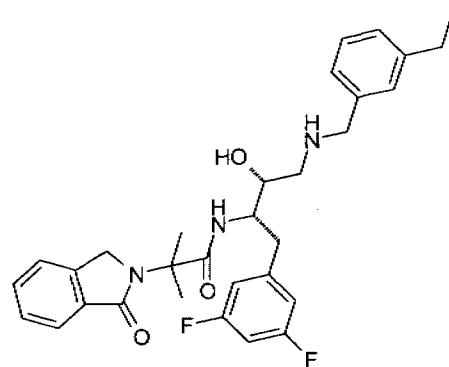
2523 or N-((1S,2R)-1-(3,5-difluorobenzyl)-3-
[(3-ethylbenzyl)amino]-2-hydroxypropyl)-2-(5-
methyl-1,3-dioxo-1,3-dihydro-2H-isoindol-2-
yl)acetamide (Generated by ACD/Name
software)

2188,42 535,6 536,5



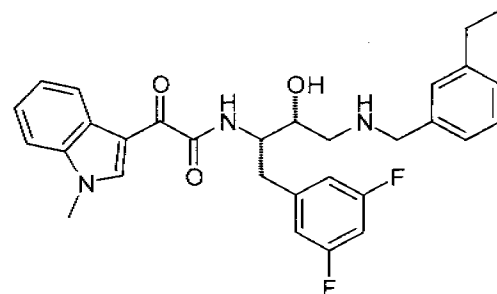
2524 or N-((1S,2R)-1-(3,5-difluorobenzyl)-3-
[(3-ethylbenzyl)amino]-2-hydroxypropyl)-2-(1-
oxo-1,3-dihydro-2H-isoindol-2-yl)butanamide
(Generated by ACD/Name software)

1932,33 535,64 536,5



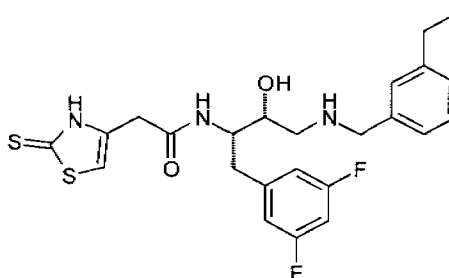
2525 or N-((1S,2R)-1-(3,5-difluorobenzyl)-3-[(3-ethylbenzyl)amino]-2-hydroxypropyl)-2-methyl-2-(1-oxo-1,3-dihydro-2H-indol-2-yl)propanamide (Generated by ACD/Name software)

>20000 535,64 536,4



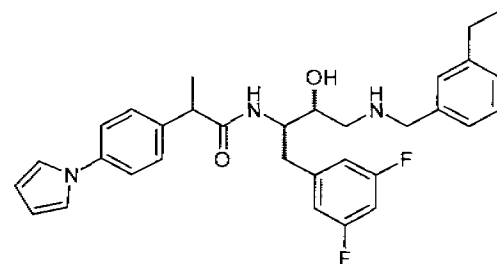
N-((1S,2R)-1-(3,5-difluorobenzyl)-3-[(3-ethylbenzyl)amino]-2-hydroxypropyl)-2-(1-methyl-1H-indol-3-yl)-2-oxoacetamide

3222,16 519,6 520,4



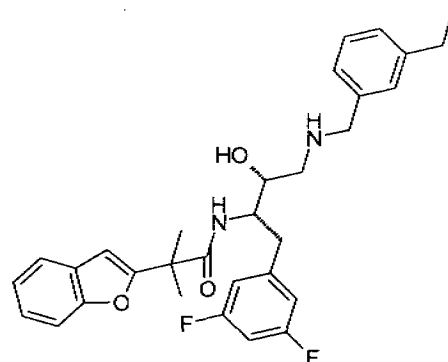
N-((1S,2R)-1-(3,5-difluorobenzyl)-3-[(3-ethylbenzyl)amino]-2-hydroxypropyl)-2-(2-thioxo-2,3-dihydro-1,3-thiazol-4-yl)acetamide

491,63 492,4



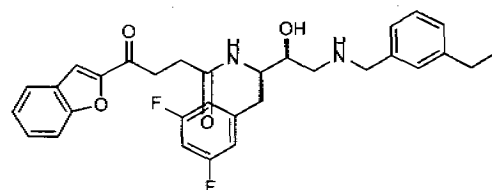
2561 or N-((1S,2R)-1-(3,5-difluorobenzyl)-3-[(3-ethylbenzyl)amino]-2-hydroxypropyl)-2-[4-(1H-pyrrol-1-yl)phenyl]propanamide (Generated by ACD/Name software)

>20000 531,65 532,4



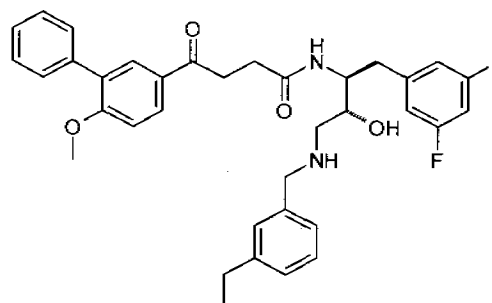
2563 or 2-((1-benzofuran-2-yl)-N-((1S,2R)-1-(3,5-difluorobenzyl)-3-((3-ethylbenzyl)amino)-2-hydroxypropyl)-2-methylpropanamide (Generated by ACD/Name software)

>20000 520,63 521,4



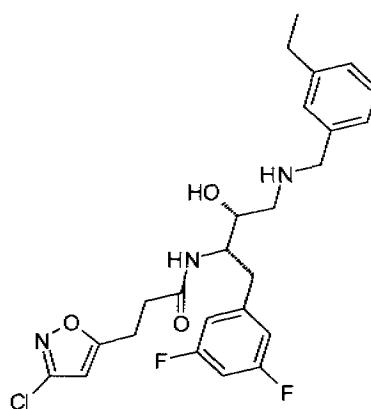
2565 or 4-((1-benzofuran-2-yl)-N-((1S,2R)-1-(3,5-difluorobenzyl)-3-((3-ethylbenzyl)amino)-2-hydroxypropyl)-4-oxobutanamide (Generated by ACD/Name software)

>20000 534,61 535,4



2566 or N-((1S,2R)-1-(3,5-difluorobenzyl)-3-((3-ethylbenzyl)amino)-2-hydroxypropyl)-4-(6-methoxy-1,1'-biphenyl-3-yl)-4-oxobutanamide (Generated by ACD/Name software)

>20000 600,71 601,4



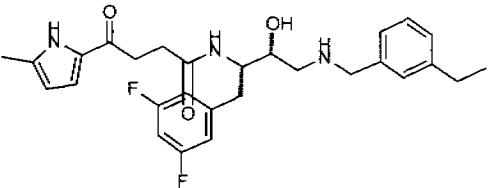
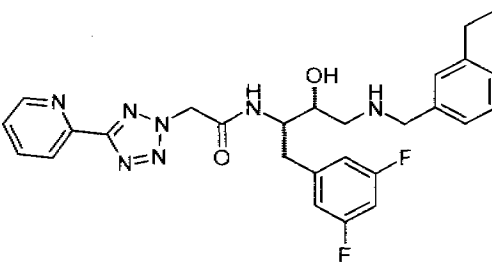
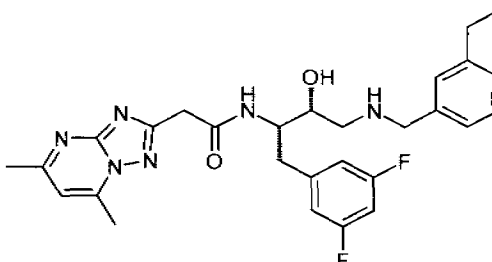
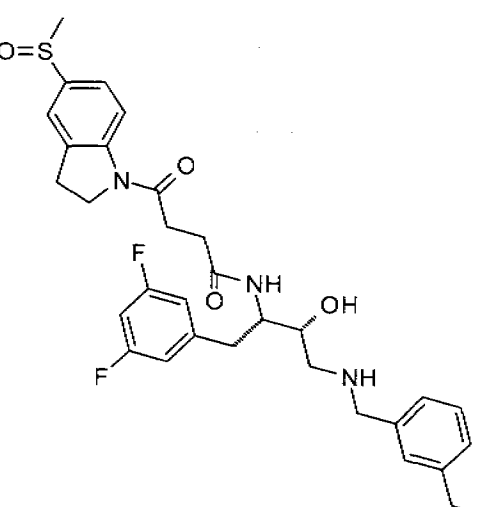
2568 or 3-(3-chloroisoxazol-5-yl)-N-((1S,2R)-1-(3,5-difluorobenzyl)-3-((3-ethylbenzyl)amino)-2-hydroxypropyl)propanamide (Generated by ACD/Name software)

>20000 491,97 492,4

165

	2570 or N-((1S,2R)-1-(3,5-difluorobenzyl)-3-[(3-ethylbenzyl)amino]-2-hydroxypropyl)-4-(4-methoxyphenyl)-4-oxobutanamide (Generated by ACD/Name software)	4217,33	524,61	525,4
	2571 or N-((1S,2R)-1-(3,5-difluorobenzyl)-3-[(3-ethylbenzyl)amino]-2-hydroxypropyl)-4-(2,3-dihydro-1,4-benzodioxin-6-yl)-4-oxobutanamide (Generated by ACD/Name software)	10549,88	552,62	553,3
	2572 or N-((1S,2R)-1-(3,5-difluorobenzyl)-3-[(3-ethylbenzyl)amino]-2-hydroxypropyl)-3-(2-oxo-2H-1,3-benzoxazin-3(4H)-yl)propanamide (Generated by ACD/Name software)	10177,11	537,61	538,6
	2574 or N-((1S,2R)-1-(3,5-difluorobenzyl)-3-[(3-ethylbenzyl)amino]-2-hydroxypropyl)-2-(2-oxo-2,3-dihydro-1,3-benzoxazol-5-yl)acetamide (Generated by ACD/Name software)	>20000	509,56	510,4
	2575 or N-((1S,2R)-1-(3,5-difluorobenzyl)-3-[(3-ethylbenzyl)amino]-2-hydroxypropyl)-2-(2-oxo-2,3-dihydro-1H-benzimidazol-5-yl)acetamide (Generated by ACD/Name software)	>20000	508,57	509,4

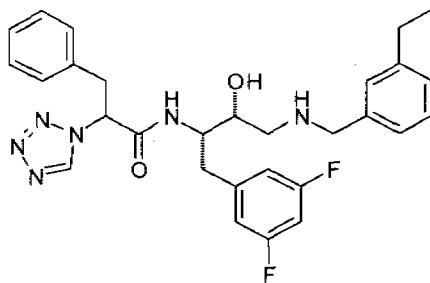
26-10-2023

	2588 or N-((1S,2R)-1-(3,5-difluorobenzyl)-3-((3-ethylbenzyl)amino)-2-hydroxypropyl)-4-(5-methyl-1H-pyrrol-2-yl)-4-oxobutanamide (Generated by ACD/Name software)	5522,41	497,59	498,6
	N-((1S,2R)-1-(3,5-difluorobenzyl)-3-((3-ethylbenzyl)amino)-2-hydroxypropyl)-2-(5-pyridin-2-yl-2H-tetrazol-2-yl)acetamide	5143,58	521,58	522,4
	N-((1S,2R)-1-(3,5-difluorobenzyl)-3-((3-ethylbenzyl)amino)-2-hydroxypropyl)-2-(5,7-dimethyl[1,2,4]triazolo[1,5-a]pyrimidin-2-yl)acetamide	>20000	522,6	523,5
	N-((1S,2R)-1-(3,5-difluorobenzyl)-3-((3-ethylbenzyl)amino)-2-hydroxypropyl)-4-[5-(methylsulfinyl)-2,3-dihydro-1H-indol-1-yl]-4-oxobutanamide	>20000	597,73	598,4

24
*66

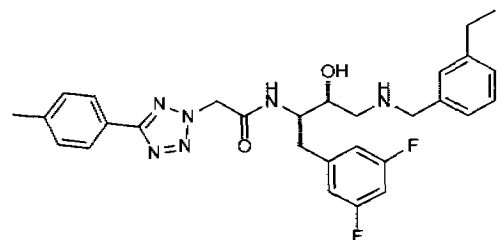
	N-((1S,2R)-1-(3,5-difluorobenzyl)-3-[(3-ethylbenzyl)amino]-2-hydroxypropyl)-3-(2-pyridin-3-ylpiperidin-1-yl)propanamide		550,7	551,5
	N-((1S,2R)-1-(3,5-difluorobenzyl)-3-[(3-ethylbenzyl)amino]-2-hydroxypropyl)-2-phenyl-2-(4H-1,2,4-triazol-3-ylthio)acetamide	>20000	551,66	552,4
	N-((1S,2R)-1-(3,5-difluorobenzyl)-3-[(3-ethylbenzyl)amino]-2-hydroxypropyl)-2-(5,6-dimethyl-2,4-dioxo-1,2,3,4-tetrahydropyridin-3-yl)acetamide	9300,8	513,59	514,3
	N-((1S,2R)-1-(3,5-difluorobenzyl)-3-[(3-ethylbenzyl)amino]-2-hydroxypropyl)-3-(3-oxo-2,1-benzisothiazol-1(3H)-yl)propanamide	5662,78	539,65	540,4

162 163



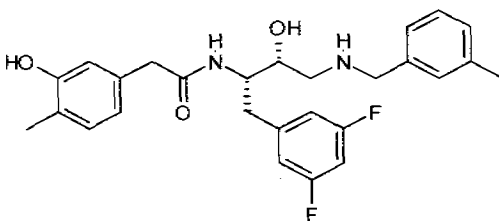
N-((1S,2R)-1-(3,5-difluorobenzyl)-3-[(3-ethylbenzyl)amino]-2-hydroxypropyl)-3-phenyl-2-(1H-tetrazol-1-yl)propanamide

>20000 534,61 535,5



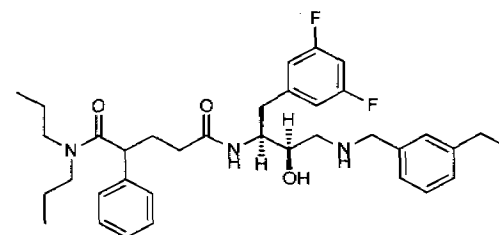
N-((1S,2R)-1-(3,5-difluorobenzyl)-3-[(3-ethylbenzyl)amino]-2-hydroxypropyl)-2-[5-(4-methylphenyl)-2H-tetrazol-2-yl]acetamide

3261,3 534,61 535,4



N-((1S,2R)-1-(3,5-difluorobenzyl)-3-[(3-ethylbenzyl)amino]-2-hydroxypropyl)-2-(3-hydroxy-4-methylphenyl)acetamide
(Generated by ACD/Name software)

7231,98 482,58 483,2



ELAN-153623 or N(u)5(d)-((1S,2R)-1-(3,5-difluorobenzyl)-3-[(3-ethylbenzyl)amino]-2-hydroxypropyl)-2-phenyl-N(u)1(d),N(u)1(d)-dipropylpentanediamide (Generated by ACD/Name software) or ELAN-153623

607,79

159-768

110 789

SUPERINTENDENCIA DE INDUSTRIA Y COMERCIO

NIT : 800170077-2

SUPERINTENDENCIA DE INDUSTRIA Y COMERCIO



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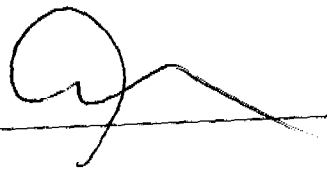
***** C O N D I C I O N A C I O N *****

DEPOSITANTE	TITO CASH	VALOR	CUENTA	NO. VOUCHER	FECHA VOUCHER	VAL. VOUCHER
CANILLER ASSOCIADOS	RECIBO DE CAJA			25381	17/07/2008	10,918,000.00

***** D E M O N S T R A C I O N *****

CONT. ACTIVIDADES	CONCEPTO	TOTAL CONCEPTO
50005-01-02 CAMBIO DE LOCALIDAD Y MODIFICAR	12 CARTAS Y LEYAS COMERCIALES	103,000.00
	TOTAL :	103,000.00

SON: DIENTO TRES MIL PESOS

RESPONSABLE : 

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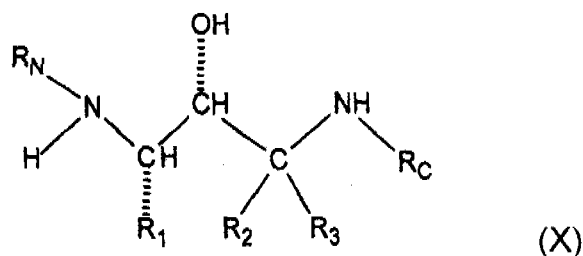
60/215,323	30 June 2000 (30.06.2000)	US
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60/255,956	15 December 2000 (15.12.2000)	US
60/268,497	13 February 2001 (13.02.2001)	US
60/279,779	29 March 2001 (29.03.2001)	US
60/295,589	4 June 2001 (04.06.2001)	US

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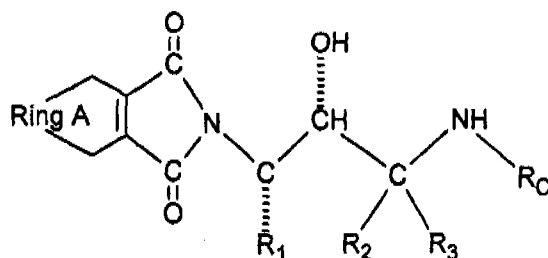
(74) Agent: **DAIGNAULT, Ronald, A.**; Merchant & Gould P.C., P.O. Box 2903, Minneapolis, MN 55402-0903 (US).(81) Designated States (*national*): AE, AG, AL, AM, AT, AT (utility model), AU, AZ, BA, BB, BG, BR, BY, BZ, CA, CH, CN, CO, CR, CU, CZ, CZ (utility model), DE, DE (utility model), DK, DK (utility model), DM, DZ, EC, EE, EE (utility model), ES, FI, FI (utility model), GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NO, NZ, PL, PT, RO, RU, SD, SE, SG, SI, SK, SK (utility model), SL, TJ, TM, TR, TT, TZ, UA, UG, UZ, VN, YU, ZA, ZW.

[Continued on next page]

(54) Title: **COMPOUNDS TO TREAT ALZHEIMER'S DISEASE**

(X)

(57) Abstract: The present invention is substituted amines of formula (X) and of formula (X') useful in treating Alzheimer's disease and other similar diseases.



(X')

COMPOUNDS TO TREAT ALZHEIMER'S DISEASE

This application is being filed as a PCT International Patent Application in the name of Elan Pharmaceuticals, Inc., a U.S. national corporation and resident, (Applicant for all countries) and Pharmacia & Upjohn Company, a U.S. national corporation (Applicant for all countries), on 29 June 2001, designating all countries except US.

CROSS-REFERENCE TO RELATED APPLICATIONS

This application claims priority to the following provisional applications: United States provisional application Serial No. 60/215, 323, filed June 30, 2000; United States provisional application Serial No. 60/252,736, filed November 22, 2000; United States provisional application Serial No. 60/255,956, filed December 15, 2000; United States provisional application Serial No. 60/268,497, filed February 13, 2001; United States provisional application Serial No. 60/279,779, filed March 29, 2001; and United States provisional application Serial No. 60/295,589, filed June 4, 2001.

BACKGROUND OF THE INVENTION

1. Field of the Invention

The present invention is directed to compounds useful in treatment of Alzheimer's disease and similar diseases.

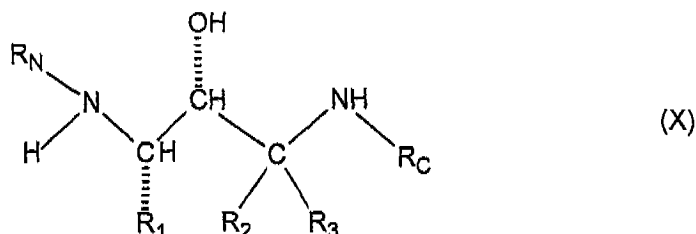
2. Description of the Related Art

Alzheimer's disease (AD) is a progressive degenerative disease of the brain primarily associated with aging. Clinical presentation of AD is characterized by loss of memory, cognition, reasoning, judgement, and orientation. As the disease progresses, motor, sensory, and linguistic abilities are also affected until there is global impairment of multiple cognitive functions. These cognitive losses occur gradually, but typically lead to severe impairment and eventual death in the range of four to twelve years.

Alzheimer's disease is characterized by two major pathologic observations in the brain: neurofibrillary tangles and beta amyloid (or neuritic) plaques, comprised predominantly of an aggregate of a peptide fragment known as A beta. Individuals with AD exhibit characteristic beta-amyloid deposits in the brain (beta amyloid

SUMMARY OF INVENTION

Disclosed is a substituted amine of formula (X)



5

where R_1 is:

- (I) $\text{C}_1\text{-C}_6$ alkyl, optionally substituted with one, two or three substituents selected from the group consisting of $\text{C}_1\text{-C}_3$ alkyl, $\text{C}_1\text{-C}_7$ alkyl (optionally substituted with $\text{C}_1\text{-C}_3$ alkyl and $\text{C}_1\text{-C}_3$ alkoxy), -F, -Cl, -Br, -I, -OH, -SH, $-\text{C}\equiv\text{N}$, $-\text{CF}_3$, $\text{C}_1\text{-C}_3$ alkoxy, $-\text{NR}_{1-a}\text{R}_{1-b}$ where R_{1-a} and R_{1-b} are -H or $\text{C}_1\text{-C}_6$ alkyl, $-\text{OC}=\text{O}$ $\text{NR}_{1-a}\text{R}_{1-b}$ where R_{1-a} and R_{1-b} are as defined above,
- (II) $-\text{CH}_2\text{-S(O)}_{0-2}\text{-(C}_1\text{-C}_6\text{ alkyl)}$,
- (III) $-\text{CH}_2\text{-CH}_2\text{-S(O)}_{0-2}\text{-(C}_1\text{-C}_6\text{ alkyl)}$,
- (IV) $\text{C}_2\text{-C}_6$ alkenyl with one or two double bonds, optionally substituted with one, two or three substituents selected from the group consisting of -F, -Cl, -OH, -SH, $-\text{C}\equiv\text{N}$, $-\text{CF}_3$, $\text{C}_1\text{-C}_3$ alkoxy, $-\text{NR}_{1-a}\text{R}_{1-b}$ where R_{1-a} and R_{1-b} are -H or $\text{C}_1\text{-C}_6$ alkyl,
- (V) $\text{C}_2\text{-C}_6$ alkynyl with one or two triple bonds, optionally substituted with one, two or three substituents selected from the group consisting of -F, -Cl, -OH, -SH, $-\text{C}\equiv\text{N}$, $-\text{CF}_3$, $\text{C}_1\text{-C}_3$ alkoxy, $-\text{NR}_{1-a}\text{R}_{1-b}$ where R_{1-a} and R_{1-b} are -H or $\text{C}_1\text{-C}_6$ alkyl,
- (VI) $-(\text{CH}_2)_{n_1}\text{-(R}_{1\text{-aryl}})$ where n_1 is zero or one and where $\text{R}_{1\text{-aryl}}$ is phenyl, 1-naphthyl, 2-naphthyl and indanyl, indenyl, dihydronaphthyl, tetralinyl optionally substituted with one, two, three or four of the following substituents on the aryl ring:

(A) $\text{C}_1\text{-C}_6$ alkyl optionally substituted with one, two or three substituents selected from the group consisting of $\text{C}_1\text{-C}_3$ alkyl, -F, -Cl, -Br, -I, -OH, -SH, $-\text{NR}_{1-a}\text{R}_{1-b}$ where R_{1-a} and R_{1-b} are as defined above, $-\text{C}\equiv\text{N}$, $-\text{CF}_3$, $\text{C}_1\text{-C}_3$ alkoxy,

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(B) C₂-C₆ alkenyl with one or two double bonds, optionally substituted with one, two or three substituents selected from the group consisting of -F, -Cl, -OH, -SH, -C≡N, -CF₃, C₁-C₃ alkoxy, -NR_{1-a}R_{1-b} where R_{1-a} and R_{1-b} are -H or C₁-C₆ alkyl,

5 (C) C₂-C₆ alkynyl with one or two triple bonds, optionally substituted with one, two or three substituents selected from the group consisting of -F, -Cl, -OH, -SH, -C≡N, -CF₃, C₁-C₃ alkoxy, -NR_{1-a}R_{1-b} where R_{1-a} and R_{1-b} are -H or C₁-C₆ alkyl,

(D) -F, Cl, -Br and -I,

10 (F) -C₁-C₆ alkoxy optionally substituted with one, two or three -F,

(G) -NR_{N-2}R_{N-3} where R_{N-2} and R_{N-3} are as defined below,

(H) -OH,

(I) -C≡N,

15 (J) C₃-C₇ cycloalkyl, optionally substituted with one, two or three substituents selected from the group consisting of -F, -Cl, -OH, -SH, -C≡N, -CF₃, C₁-C₃ alkoxy, -NR_{1-a}R_{1-b} where R_{1-a} and R_{1-b} are -H or C₁-C₆ alkyl,

(K) -CO-(C₁-C₄ alkyl),

(L) -SO₂-NR_{1-a}R_{1-b} where R_{1-a} and R_{1-b} are as defined above,

20 (M) -CO-NR_{1-a}R_{1-b} where R_{1-a} and R_{1-b} are as defined above,

(N) -SO₂-(C₁-C₄ alkyl),

(VII) -(CH₂)_{n1}-(R_{1-heteroaryl}) where n₁ is as defined above and where R_{1-heteroaryl} is selected from the group consisting of:

pyridinyl,

25 pyrimidinyl,

quinolinyl,

benzothienyl,

indolyl,

indolinyl,

30 pyridazinyl,

pyrazinyl,

isoindolyl,

isoquinolyl,

(V) C₂-C₆ alkynyl with one or two triple bonds, optionally substituted with one, two or three substituents selected from the group consisting of -F, -Cl, -OH, -SH, -C≡N, -CF₃, C₁-C₃ alkoxy, -NR_{1-a}R_{1-b} where R_{1-a} and R_{1-b} are -H or C₁-C₆ alkyl,

5 (VI) -(CH₂)₀₋₄- C₃-C₇ cycloalkyl, optionally substituted with one, two or three substituents selected from the group consisting of -F, -Cl, -OH, -SH, -C≡N, -CF₃, C₁-C₃ alkoxy, -NR_{1-a}R_{1-b} where R_{1-a} and R_{1-b} are -H or C₁-C₆ alkyl,

where R₃ is selected from the group consisting of:

(I)-H,

10 (II) C₁-C₆ alkyl, optionally substituted with one, two or three substituents selected from the group consisting of C₁-C₃ alkyl, -F, -Cl, -Br, -I, -OH, -SH, -C≡N, -CF₃, C₁-C₃ alkoxy, -NR_{1-a}R_{1-b} where R_{1-a} and R_{1-b} are as defined above,

(III) -(CH₂)₀₋₄-R₂₋₁ where R₂₋₁ is R_{1-aryl} or R_{1-heteroaryl} where R_{1-aryl} and R_{1-heteroaryl} are as defined above;

15 (IV) C₂-C₆ alkenyl with one or two double bonds,

(V) C₂-C₆ alkynyl with one or two triple bonds,

(VI) -(CH₂)₀₋₄- C₃-C₇ cycloalkyl, optionally substituted with one, two or three substituents selected from the group consisting of -F, -Cl, -OH, -SH, -C≡N, -CF₃, C₁-C₃ alkoxy, -NR_{1-a}R_{1-b} where R_{1-a} and R_{1-b} are -H or C₁-C₆ alkyl,

20 and where R₂ and R₃ are taken together with the carbon to which they are attached to form a carbocycle of three, four, five, six, and seven carbon atoms, optionally where one carbon atom is replaced by a heteroatom selected from the group consisting of -O-, -S-, -SO₂-, -NR_{N-2}-, where R_{N-2} is as defined below;

where R_N is:

25 (I) R_{N-1}-X_N- where X_N is selected from the group consisting of:

(A) -CO-,

(B) -SO₂-,

(C) -(CR'R'')₁₋₆ where R' and R'' are the same or different and are -H and C₁-C₄ alkyl,

30 (D) -CO-(CR'R'')₁₋₆-X_{N-1} where X_{N-1} is selected from the group consisting of -O-, -S- and -NR'- and where R' and R'' are as defined above,

(E) a single bond;

where R_{N-1} is selected from the group consisting of:

746 24

(A) ~~R_{N-aryl}~~ where R_{N-aryl} is phenyl, 1-naphthyl, 2-naphthyl, tetralinyl, indanyl, dihydronaphthyl or 6,7,8,9-tetrahydro-5H-benzo[a]cycloheptenyl, optionally substituted with one, two or three of the following substituents which can be the same or different and are:

5 (1) C₁-C₆ alkyl, optionally substituted with one, two or three substituents selected from the group consisting of C₁-C₃ alkyl, -F, -Cl, -Br, -I, -OH, -SH, -C≡N, -CF₃, C₁-C₃ alkoxy, -NR_{1-a}R_{1-b} where R_{1-a} and R_{1-b} are as defined above,

(2) -OH,

10 (3) -NO₂,

(4) -F, -Cl, -Br, -I,

(5) -CO-OH,

(6) -C≡N,

(7) -(CH₂)₀₋₄-CO-NR_{N-2}R_{N-3} where R_{N-2} and R_{N-3} are

15 the same or different and are selected from the group consisting of:

(a) -H,

(b) -C₁-C₆ alkyl optionally substituted with one substituent selected from the group consisting of:

(i) -OH,

20 (ii) -NH₂,

(c) -C₁-C₆ alkyl optionally substituted with one

to three -F, -Cl, -Br, -I,

(d) -C₃-C₇ cycloalkyl,

(e) -(C₁-C₂ alkyl)-(C₃-C₇ cycloalkyl),

25 (f) -(C₁-C₆ alkyl)-O-(C₁-C₃ alkyl),

(g) -C₂-C₆ alkenyl with one or two double

bonds,

(h) -C₂-C₆ alkynyl with one or two triple

bonds,

30 (i) -C₁-C₆ alkyl chain with one double bond

and one triple bond,

(j) -R_{1-aryl} where R_{1-aryl} is as defined above,

277-16

(37) C₂-C₆ alkynyl with one or two triple bonds

optionally substituted with C₁-C₃ alkyl, -F, -Cl, -Br, -I, -OH, -SH, -C≡N, -CF₃, C₁-C₃ alkoxy, -NR_{1-a}R_{1-b} where R_{1-a} and R_{1-b} are as defined above,

(38) -(CH₂)₀₋₄-N(-H or R_{N-5})-SO₂-R_{N-2} where R_{N-5} and

5 R_{N-2} can be the same or different and are as described above,

(39) -(CH₂)₀₋₄-C₃-C₇ cycloalkyl,(B) -R_{N-heteroaryl} where R_{N-heteroaryl} is selected from the group

consisting of:

10 pyridinyl,
pyrimidinyl,
quinolinyl,
benzothienyl,
indolyl,
indolinyl,
15 pyridazinyl,
pyrazinyl,
isoindolyl,
isoquinolyl,
quinazolinyl,
20 quinoxalinyl,
phthalazinyl,
imidazolyl,
isoxazolyl,
pyrazolyl,
25 oxazolyl,
thiazolyl,
indolizinyl,
indazolyl,
benzothiazolyl,
30 benzimidazolyl,
benzofuranyl,
furanyl,
thienyl,

778 777

pyrrolyl,
oxadiazolyl,
thiadiazolyl,
triazolyl,
5 tetrazolyl,
oxazolopyridinyl,
imidazopyridinyl,
isothiazolyl,
naphthyridinyl,
10 cinnolinyl,
carbazolyl,
beta-carbolinyl,
isochromanyl,
chromanyl,
15 tetrahydroisoquinolinyl,
isoindolinyl,
isobenzotetrahydrofuranyl,
isobenzotetrahydrothienyl,
isobenzothienyl,
20 benzoxazolyl,
pyridopyridinyl,
benzotetrahydrofuranyl,
benzotetrahydrothienyl,
purinyl,
25 benzodioxolyl,
triazinyl,
henoxazinyl,
phenothiazinyl,
pteridinyl,
30 benzothiazolyl,
imidazopyridinyl,
imidazothiazolyl,
dihydrobenzisoxazinyl,
benzisoxazinyl,

779 + 78

	benzoxazinyl,
	dihydrobenzisothiazinyl,
	benzopyranyl,
	benzothiopyranyl,
5	coumarinyl,
	isocoumarinyl,
	chromonyl,
	chromanonyl,
	pyridinyl-N-oxide,
10	tetrahydroquinolinyl
	dihydroquinolinyl
	dihydroquinolinonyl
	dihydroisoquinolinonyl
	dihydrocoumarinyl
15	dihydroisocoumarinyl
	isoindolinonyl
	benzodioxanyl
	benzoxazolinonyl
	pyrrolyl N-oxide,
20	pyrimidinyl N-oxide,
	pyridazinyl N-oxide,
	pyrazinyl N-oxide,
	quinolinyl N-oxide,
	indolyl N-oxide,
25	indolinyl N-oxide,
	isoquinolyl N-oxide,
	quinazolinyl N-oxide,
	quinoxalinyl N-oxide,
	phthalazinyl N-oxide,
30	imidazolyl N-oxide,
	isoxazolyl N-oxide,
	oxazolyl N-oxide,
	thiazolyl N-oxide,
	indolizinyl N-oxide,

780 779

- indazolyl N-oxide,
benzothiazolyl N-oxide,
benzimidazolyl N-oxide,
pyrrolyl N-oxide,
5 oxadiazolyl N-oxide,
thiadiazolyl N-oxide,
triazolyl N-oxide,
tetrazolyl N-oxide,
benzothiopyranyl S-oxide,
10 benzothiopyranyl S,S-dioxide,

where the $R_{N\text{-heteroaryl}}$ group is bonded by any atom of the parent $R_{N\text{-heteroaryl}}$ group substituted by hydrogen such that the new bond to the $R_{N\text{-heteroaryl}}$ group replaces the hydrogen atom and its bond, where heteroaryl is optionally substituted with one, two, three, or four of:

- 15 (1) $C_1\text{-}C_6$ alkyl, optionally substituted with one, two or three substituents selected from the group consisting of $C_1\text{-}C_3$ alkyl, -F, -Cl, -Br, -I, -OH, -SH, -C $\equiv$ N, -CF₃, $C_1\text{-}C_3$ alkoxy, -NR_{1-a}R_{1-b} where R_{1-a} and R_{1-b} are as defined above,

- (2) -OH,
20 (3) -NO₂,
(4) -F, -Cl, -Br, -I,
(5) -CO-OH,
(6) -C $\equiv$ N,
(7) -(CH₂)₀₋₄-CO-NR_{N-2}R_{N-3} where R_{N-2} and R_{N-3} are

- 25 the same or different and are selected from the group consisting of:

- (a) -H,
(b) -C₁-C₆ alkyl optionally substituted with one substituent selected from the group consisting of:
(i) -OH,
30 (ii) -NH₂,
(c) -C₁-C₆ alkyl optionally substituted with one to three -F, -Cl, -Br, -I,
(d) -C₃-C₇ cycloalkyl,

(I) $-(CH_2)_{0-4}-NH-CO-(C_1-C_6 \text{ alkyl})$,

(J) $-NH-CO-O-R_{N-8}$ where R_{N-8} is as defined above,

(K) $-(CH_2)_{0-4}-NR_{N-2}R_{N-3}$ where R_{N-2} and R_{N-3} are the same or different and are as defined above,

5 (L) $-(CH_2)_{0-4}-R_{N-4}$ where R_{N-4} is as defined above,

(M) $-O-CO-(C_1-C_6 \text{ alkyl})$,

(N) $-O-CO-NR_{N-8}R_{N-8}$ where the R_{N-8} s are the same or different and are as defined above,

(O) $-O-(C_1-C_5 \text{ alkyl})-COOH$,

10 (P) $-O-(C_1-C_6 \text{ alkyl})$ optionally substituted with one, two, or three of $-F$, $-Cl$, $-Br$, $-I$,

(Q) $-NH-SO_2-(C_1-C_6 \text{ alkyl})$,

(R) $-F$, $-Cl$,

where R_C is:

15 (I) $-C_1-C_{10} \text{ alkyl}$ optionally substituted with one, two or three substituents selected from the group consisting of $C_1-C_3 \text{ alkyl}$, $-F$, $-Cl$, $-Br$, $-I$, $-OH$, $-SH$, $-C\equiv N$, $-CF_3$, $C_1-C_6 \text{ alkoxy}$, $-O\text{-phenyl}$, $-NR_{1-a}R_{1-b}$ where R_{1-a} and R_{1-b} are as defined above, $-OC(=O)NR_{1-a}R_{1-b}$ where R_{1-a} and R_{1-b} are as defined above, $-S(=O)_{0-2}R_{1-a}$ where R_{1-a} is as defined above, $-NR_{1-a}C(=O)NR_{1-a}R_{1-b}$ where R_{1-a} and R_{1-b} are as defined above, $-C(=O)NR_{1-a}R_{1-b}$ where R_{1-a} and R_{1-b} are as defined above, and $-S(=O)_2NR_{1-a}R_{1-b}$ where R_{1-a} and R_{1-b} are as defined above,

(II) $-(CH_2)_{0-3}-(C_3-C_8) \text{ cycloalkyl}$ where cycloalkyl can be optionally substituted with one, two or three substituents selected from the group consisting of $C_1-C_3 \text{ alkyl}$, $-F$, $-Cl$, $-Br$, $-I$, $-OH$, $-SH$, $-C\equiv N$, $-CF_3$, $C_1-C_6 \text{ alkoxy}$, $-O\text{-phenyl}$, $-CO-$
 25 OH , $-CO-O-(C_1-C_4 \text{ alkyl})$, $-NR_{1-a}R_{1-b}$ where R_{1-a} and R_{1-b} are as defined above,

(III) $-(CR_{C-x}R_{C-y})_{0-4}-R_{C-aryl}$ where R_{C-x} and R_{C-y} are

$-H$,

$C_1-C_4 \text{ alkyl}$ optionally substituted with one or two $-OH$,

$C_1-C_4 \text{ alkoxy}$ optionally substituted with one, two, or three of

30 $-F$,

$-(CH_2)_{0-4}-C_3-C_7 \text{ cycloalkyl}$,

$C_2-C_6 \text{ alkenyl}$ containing one or two double bonds,

$C_2-C_6 \text{ alkynyl}$ containing one or two triple bonds,

phenyl,

and where R_{C-x} and R_{C-y} are taken together with the carbon to which they are attached to form a carbocycle of three, four, five, six and seven carbon atoms, optionally where one carbon atom is replaced by a heteroatom selected from the group consisting of -O-, -S-, -SO₂-, -NR_{N-2}- and R_{C-aryl} is defined as R_{N-aryl} is defined above;

(IV) $-(CR_{C-x}R_{C-y})_{0-4}-R_{C-heteroaryl}$ where $R_{C-heteroaryl}$ is defined as $R_{N-heteroaryl}$ is defined above and R_{C-x} and R_{C-y} are as defined above,

(V) $-(CR_{C-x}R_{C-y})_{0-4}-R_{C-aryl}-R_{C-aryl}$ where R_{C-aryl} , R_{C-x} and R_{C-y} are as defined above,

(VI) $-(CR_{C-x}R_{C-y})_{0-4}-R_{C-aryl}-R_{C-heteroaryl}$ where R_{C-aryl} , $R_{C-heteroaryl}$, R_{C-x} and R_{C-y} are as defined above,

(VII) $-(CR_{C-x}R_{C-y})_{0-4}-R_{C-heteroaryl}-R_{C-aryl}$ where $R_{C-heteroaryl}$, R_{C-aryl} , R_{C-x} and R_{C-y} are as defined above,

(VIII) $-(CR_{C-x}R_{C-y})_{0-4}-R_{C-heteroaryl}-R_{C-heteroaryl}$ where $R_{C-heteroaryl}$, R_{C-x} and R_{C-y} are as defined above,

(IX) $-(CR_{C-x}R_{C-y})_{0-4}-R_{C-aryl}-R_{C-heterocycle}$ where R_{C-aryl} , R_{C-x} and R_{C-y} are as defined above, and $R_{C-heterocycle}$ is defined as $R_{N-heterocycle}$ is defined above,

(X) $-(CR_{C-x}R_{C-y})_{0-4}-R_{C-heteroaryl}-R_{C-heterocycle}$ where $R_{C-heteroaryl}$, $R_{C-heterocycle}$, R_{C-x} and R_{C-y} are as defined above,

(XI) $-(CR_{C-x}R_{C-y})_{0-4}-R_{C-heterocycle}-R_{C-aryl}$ where $R_{C-heterocycle}$, R_{C-aryl} , R_{C-x} and R_{C-y} are as defined above,

(XII) $-(CR_{C-x}R_{C-y})_{0-4}-R_{C-heterocycle}-R_{C-heteroaryl}$ where $R_{C-heterocycle}$, $R_{C-heteroaryl}$, R_{C-x} and R_{C-y} are as defined above,

(XIII) $-(CR_{C-x}R_{C-y})_{0-4}-R_{C-heterocycle}-R_{C-heterocycle}$ where $R_{C-heterocycle}$, R_{C-x} and R_{C-y} are as defined above,

(XIV) $-(CR_{C-x}R_{C-y})_{0-4}-R_{C-heterocycle}$ where $R_{C-heterocycle}$, R_{C-x} and R_{C-y} are as defined above,

(XV) $-[C(R_{C-1})(R_{C-2})]_{1-3}-CO-N-(R_{C-3})_2$ where R_{C-1} and R_{C-2} are the same or different and are selected from the group consisting of:

(A) -H,

(B) -C₁-C₆ alkyl, optionally substituted with one, two or three substituents selected from the group consisting of C₁-C₃ alkyl, -F, -Cl, -Br, -I, -OH,

783-782

Amyloidosis of the Dutch-Type, for treating cerebral amyloid angiopathy and preventing its potential consequences, i.e. single and recurrent lobar hemorrhages, for treating other degenerative dementias, including dementias of mixed vascular and degenerative origin, dementia associated with Parkinson's disease, dementia
5 associated with progressive supranuclear palsy, dementia associated with cortical basal degeneration, diffuse Lewy body type of Alzheimer's disease and who is in need of such treatment.

The ~~present~~ invention provides compounds, compositions, kits, and methods for inhibiting beta-secretase-mediated cleavage of amyloid precursor protein (APP).
10 More particularly, the compounds, compositions, and methods of the invention are effective to inhibit the production of A beta peptide and to treat or prevent any human or veterinary disease or condition associated with a pathological form of A beta peptide.

The compounds, compositions, and methods of the invention are useful for
15 treating humans who have Alzheimer's Disease (AD), for helping prevent or delay the onset of AD, for treating patients with mild cognitive impairment (MCI), and preventing or delaying the onset of AD in those patients who would otherwise be expected to progress from MCI to AD, for treating Down's syndrome, for treating Hereditary Cerebral Hemorrhage with Amyloidosis of the Dutch Type, for treating
20 cerebral beta-amyloid angiopathy and preventing its potential consequences such as single and recurrent lobar hemorrhages, for treating other degenerative dementias, including dementias of mixed vascular and degenerative origin, for treating dementia associated with Parkinson's disease, dementia associated with progressive supranuclear palsy, dementia associated with cortical basal degeneration, and diffuse
25 Lewy body type AD.

The compounds of the invention possess beta-secretase inhibitory activity. The inhibitory activities of the compounds of the invention are readily demonstrated, for example, using one or more of the assays described herein or known in the art.

SUPERINTENDENCIA DE INDUSTRIA Y COMERCIO

CONSULTA DE NUEVAS CREACIONES

Viernes 23 de Enero de 2009

Ver Afectaciones	Ver Actuaciones	Datos Publicación	Consulta Actos Administrativos	Cerrar Ventana
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Datos de PCT-PATENTE DE INVENCION CAPITULOS I Y II

Expediente 2 117312 Fecha de 2002-12-30 00:00:00
solicitud

Sector QUIMICA FARMACEUTICA Clasificación Ipc C7C 237/0 ;
Certificado 0 Tipo concesión TOTAL

Datos Pct
-Inicio Fase nacional 30/01/2003
-Fecha presentación 29/06/2001
Internacional
-Solicitud Internacional N° US2001/021012
-Publicación Internacional N° WO2002/002512
-Fecha publicación 10/01/2002
Internacional

lupac
-Nombre lupac N1-((1S,2R)-1-(3,5-DIFLUOROBENZIL)-2-HIDROXI-3-[(3-METOXIBENZIL)AMINO]PROPIL]-5-METIL-N3,N3-DIPROPILISOFTALAMIDA
-Nombre Comun AMINA SUSTITUIDA
-Indicación ALZHEIMER

Título COMPUESTOS PARA TRATAR ENFERMEDAD DE ALZHEIMER

Solicitante(s) ELAN PHARMACEUTICAL, INC.
PHARMACIA & UPJOHN COMPANY

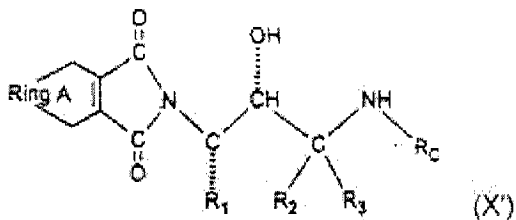
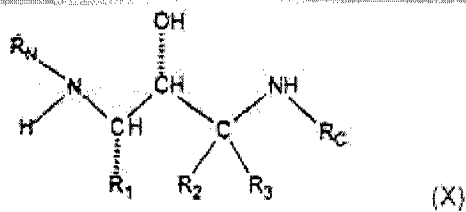
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Prioridad
US 60/215.323 30/06/2000 AC
US 60/252.736 22/11/2000 AC
US 60/255.956 15/12/2000 AC
US 60/268.497 13/02/2001 AC
US 60/279.779 29/03/2001 AC
US 60/295.589 04/06/2001 AC

Gaceta
Numero Fecha NP
539 30/04/2004 1303

Estado REQUERIMIENTO 46 2008-06-19 14:05:29

Resumen
1.- La presente invención es de aminas sustituidas de la fórmula (X) y (X') útiles en el tratamiento de la enfermedad de Alzheimer y otras enfermedades similares.



REGISTRO INICIAL

Expediente 2 117312 Secu even.0 Fecha de 2002-12-30 00:00:00

solicitud

Solicitante(s) ELAN PHARMACEUTICAL, INC.
PHARMACIA & UPJOHN COMPANY

Apoderado EMILIO FERRERO

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Actos OFICIO 6404 de 06/08/2003

Administrativos OFICIO 8168 de 19/06/2008

OFICIO 8169 de 19/06/2008

Estado REQUERIMIENTO 46 2008-06-19 14:05:29

Ver Anualidades

Ver Afectaciones

Ver Actuaciones

Consulta Actos Administrativos

Cerrar Ventana

786

SUPERINTENDENCIA DE INDUSTRIA Y COMERCIO
DIVISION DE NUEVAS CREACIONES

2020
Bogotá, D.C.,

Abogado
EMILIO FERRERO

ASUNTO

Radicación	04-10956
Trámite	011
Evento	379
Actuación	411
Oficio	
Folios	020

3184

Patente de Invención	☒	Patente de Modelo de Utilidad	☐
Vía Nacional	☐		
Vía PCT (fase nacional)	☒	Cap. I	☐
		Cap. II	☒

No. Sol. Internacional: PCT/IB01/01940
Fecha de Presentación Internal.: 15/10/2001

Como resultado del examen de fondo, realizado con fundamento en el artículo 45 de la Decisión 486 de la Comisión de la Comunidad Andina, se le comunica:

1. Documentos estudiados

- 1.1. Descripción: Folios: 248 a 929 como se radicó inicialmente.
- 1.2. Reivindicaciones: Reivindicaciones 1 - 20 como se radicaron inicialmente. Folios 510 a 615.
- 1.3. Prioridad: Folios 20 - 218. US 60/304.525 del 11/07/2001, US 60/308.756 del 30/07/2001, US 60/341.341 del 17/12/2001, US 60/341.416 del 17/12/2001, US 60/344.872 del 21/12/2001, US 60/380.574 del 21/12/2001.
- 1.4. Respuesta al solicitante: Folios 679 a 769.

2. Objeto de la invención

Título de la solicitud: Compuestos de alquilamida N-(3-amino-2-hidroxi-propil) sustituidos.

El objeto de la presente solicitud de patente de invención es proporcionar compuestos de alquilamida útiles como inhibidores de la betasecretasa para el tratamiento del Alzheimer y condiciones relacionadas; y procesos para su preparación.

Reivindicación 1: Un compuesto seleccionado entre otros de: N-[(1S,2R)-1-bencil-2-hidroxi-3-[(3-metoxibencil)amino]propil]-3-(1,1-dioxido-3-oxo-1,2-bencisotiazol-2(3H)-il)propanamida; N-[(1S,2R)-1-bencil-2-hidroxi-3-[(3-metoxibencil)amino]propil]-3-(1,3-dioxo-1,3-dihidro-2H-isoindol-2-il)propanamida; N-[(1S,2R)-1-bencil-2-hidroxi-3-[(3-metoxibencil)amino]propil]-4-(4-fluorofenil)-4-oxobutamida; etc.

Reivindicación 2: Un compuesto seleccionado entre otros de: clorhidrato de N-[(1S,2R)-1-(3,5-difluorobencil)-3-[(3-etilbencil)amino]-2-hidroxipropil]-2-(4-etilbencil)amino]-2-hidroxipropil}acetamida; clorhidrato de 2-(4-butil-2,3-dioxopiperazin-1-il)-N-[(1S,2R)-1-(3,5-difluorobencil)-3-[(3-etilbencil)amino]-2-hidroxipropil}acetamida; N-[(1S,2R)-1-(3,5-difluorobencil)-3-[(3-etilbencil)amino]-2-hidroxipropil]-2-(3-oxopiperazin-1-il)acetamida; etc...

Reivindicación 3: Composición farmacéutica caracterizada porque comprende el compuesto de la reivindicación 1.

Reivindicación 4: Composición farmacéutica caracterizada porque comprende el compuesto de la reivindicación 2.

El problema planteado en esta solicitud es la necesidad de compuestos inhibidores de la betasecretasa efectivos para reducir los depósitos o placas betaamiloide en el cerebro, características en el Alzheimer.

Para resolver este problema técnico, la solicitud en estudio proporciona compuestos de alquilamida como N-[(1S,2R)-1-(3,5-difluorobencil)-3-[(3-etilbencil)amino]-2-hidroxipropil]-2-(4-etilbencil)amino]-2-hidroxipropil} acetamida y N-[(1S,2R)-1-(3,5-difluorobencil)-3-[(3-etilbencil)amino]-2-hidroxipropil]-2-(3-oxopiperazin-1-il)acetamida, entre otros; y composiciones que los contienen.

Clasificación Internacional de Patentes (IPC): A61K31/164; A61K31/165; A61K31/401; A61K31/4196; A61P25/00; A61P25/28; C07C233/22; C07C233/35; C07C233/40; C07C235/20; C07C235/34; C07D257/04; C07D261/10; C07D265/00.

3. De la solicitud de Patente

3.1. Reivindicaciones (artículo 30 D 486)

Los compuestos de la reivindicación 2 no se encuentran sustentados de la mejor forma en el capítulo descriptivo, esto es, mediante ejemplos.

4. Unidad de invención (artículo 25 D 486)

La presente solicitud no contiene un único concepto inventivo, ya que a través de todo el capítulo reivindicatorio se pueden observar los siguientes grupos de invenciones, las cuales pueden no relacionarse entre sí:

- I. Compuestos que contienen en la posición terminal de la cadena, un anillo aromático de seis miembros donde los miembros de dicho anillo son N, N⁺, O⁻ o CH₂, y compuestos que contienen en la posición terminal de la

cadena, un grupo aromático **Ar** seleccionado de los presentes en el folio 296, de la reivindicación 1; y composición farmacéutica que los contiene de la reivindicación 3.

- II. Compuestos que contienen en la posición terminal de la cadena, un grupo seleccionado de los presentes en el folio 298 (**B1**), y compuestos que contienen en la posición terminal de la cadena, un grupo ciclohexilo (**B2**), de la reivindicación 2; y composición farmacéutica que los contiene de la reivindicación 4.

Teniendo en cuenta lo anterior, el capítulo reivindicatorio tal y como está presentado no cumple con el requisito de unidad de invención, pues no se observa con claridad UN UNICO CONCEPTO INVENTIVO.

Por lo tanto, se requiere al solicitante definir un único concepto inventivo de carácter común a todas las modalidades de la invención o realizar las divisionales del caso dada la amplitud de la materia que se pretende proteger.

5. Determinación del Estado de la Técnica

La fecha que se ha tenido en cuenta para determinar el Estado de la Técnica es la fecha de presentación de la solicitud prioritaria: 11/07/2001.

Teniendo en cuenta la fecha indicada se realizó la búsqueda en el estado de la técnica de documentos relacionados con la solicitud encontrándose el siguiente documento más relevante:

Nº	Documento	Título	Fecha de Publicación*
D3	CO02 117312 WO0202512	Compuestos para tratar el Alzheimer	Presentación I/nal: 26/06/2001 Prioridad: 30/062000 – 04/06/2001

Documento D3 folios 770 a 782.

4. Análisis de patentabilidad (artículo 14 D486)

4.1 Novedad (artículo 16 D486)

1. Respecto a la solicitud en estudio:

I Grupo inventivo:

La reivindicación 1 se refiere a un compuesto seleccionado entre otros de: N-
{(1S,2R)-1-bencil-2-hidroxi-3-[(3-metoxibencil)amino]propil}-3-(1,1-dioxido-3-oxo-
1,2-bencisotiazol-2(3H)-il)propanamida; N-
{(1S,2R)-1-bencil-2-hidroxi-3-[(3-metoxibencil)amino]propil}-3-(1,3-dioxo-1,3-dihidro-2H-isoindol-2-il)propanamida;
N-
{(1S,2R)-1-bencil-2-hidroxi-3-[(3-metoxibencil)amino]propil}-4-(4fluorofenil)-4-oxobutamida; etc...

2. Respecto al estado de la Técnica:

D1 enseña aminos sustituidas de fórmula X para el tratamiento del Alzheimer y condiciones relacionadas (Folios 770 a 782).

novedosos, pues ya se conocían en el estado de la técnica. Por consiguiente, el contenido de la reivindicación 1, tal y como está reivindicado carece de novedad. En esta medida, se sugiere al solicitante realizar una revisión cuidadosa de los compuestos reivindicados para limitar el alcance de su invención a aquellos compuestos que no están revelados en D1.

1. Respecto a la solicitud en estudio:

La reivindicación 3 se refiere a una composición farmacéutica que comprende un compuesto según las reivindicación 1.

Dicha composición que comprende los compuestos de la reivindicación 1, ve afectada su novedad por D1, ya que los compuestos que la caracterizan no parecen ser novedosos y porque en D1 se enseñan composiciones que comprenden compuestos de fórmula X (Folio 782).

6. Conclusión:

Los requisitos de patentabilidad de la presente solicitud se encuentran afectados así:

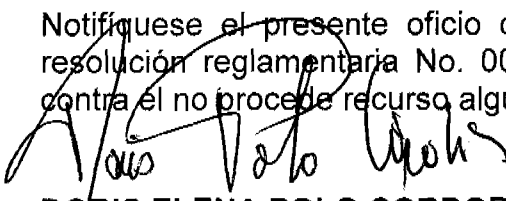
N°	Documento N°	Reivindicaciones Afectadas	Requisito que Afecta
D3	CO02 117312	1, 3	Novedad

7. Respuesta a los argumentos del solicitante:

Los argumentos presentados por el solicitante objetando la ausencia de nivel inventivo con que se concluyó el concepto técnico N° 2140, fueron aceptados por este Despacho, y por lo tanto, se procedió a efectuar un nuevo análisis de patentabilidad donde se cita una anterioridad diferente, para uno de los grupos inventivos contenidos en la presente solicitud.

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

Notifíquese el presente oficio conforme a lo dispuesto en el artículo 8 de la resolución reglamentaria No. 00210 del 15 de enero de 2001, advirtiéndole que contra el no procede recurso alguno en la vía gubernativa.


DORIS ELENA POLO CORDOBA
Jefe (E) de División de Nuevas Creaciones

El anterior requerimiento fue notificado por fijación en lista, de fecha

CONCEPTO TECNICO No. 3883	EXAMINADOR TECNICO Código No.202071
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