SUPERINTENDENCIA DE INDUSTRIA Y COMERCIO

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División de Nuevas Creaciones

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SOLICITUD

PATENTE DE INVENCION

ENTRADA EN FASE NACIONAL

21 **EXPEDIENTE No** 06-120207

54 **TITULO** HETEROCICLOS BICICLICOS COMO INHIBIDORES DE LA INTEGRASA DEL VIRUS DE INMUNODEFICIENCIA HUMANA (VIH)

51 **CLASIFICACION INTERNACIONAL** A61K31/519 // A61P31/18

71 **SOLICITANTE** BRISTOL - MYERS SQUIBB COMPANY

DOMICILIO PRINCETON, NEW JERSEY, ESTADOS UNIDOS DE AMERICA

74 **APODERADO** JUAN PABLO CADENA SARMIENTO

22 **SANTAFE DE BOGOTA, D C** 28/11/2006

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Oficina de Comunicaciones

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Industria y Comercio
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Fec: 2006-11-28 17:02:49 Dep: 2020 NUEVAS SOLICITUDES
Tra: 11 PATENTES
Eve: 378 FASE NACIONAL
Act 411 PRESENTACION Folios: 6/5

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1 SOLICITUD DE:

☒ Patente de Invención. ☐ Patente de Modelo de Utilidad.

☒ Capítulo I. ☐ Capítulo II.

2 SOLICITANTE (71)	Nombre: **BRISTOL – MYERS SQUIBB COMPANY** Dirección: P.O. Box 4000, Route 206 and Province Line Road, Princeton, New Jersey 08543-4000, Estados Unidos de América Nacionalidad o Domicilio: Estados Unidos Lugar de Constitución: Estados Unidos Teléfono: Fax: E-mail:	**IDENTIFICACION** C.C. ☐ NIT ☐ C.E. ☐ Otro ☐ Cual_____ Número _____
3 REPRESENTANTE O APODERADO	Nombre: JUAN PABLO CADENA SARMIENTO Dirección: Carrera 7 # 71 – 21 Torre B – Piso 4 Teléfono: 744-2200 Fax: 744-2200 E-mail:	**IDENTIFICACION** C.C. ☒ NIT ☐ C.E. ☐ Otro ☐ Cual_____ Número 80.410.337 TP 57492
4 INVENTOR (ES) (72)	**Nombre:** Narasimhulu NAIDU B., Jacques BANVILLE, Francis BEAULIEU, Timothy P. CONNOLLY, Mark R. KRYSTAL, John D. MATISKELLA, Carl OUELLET, Serge PLAMONDON, Roger REMILLARD, Margaret E. SORENSON, Yasutsugu UEDA, Michael A. WALKER **Dirección:** 12 Skeetfield Point Road, Durham, CT 06422 (US); 1209 Girard, St-Hubert, Québec J4T 1H3 (CA); 370 Lecable Dubuc, Laprairie, Québec J5R 5M4 (CA); 6 Elizabeth Road, Portland, CT 06480 (US); 12 Salem Road, Westport, CT 06880 (US); 130 High Hill Road, Wallingford, CT 06492 (US); 555 Rue de la Verendrye, Boucherville, Québec J4B 2Y3 (CA); 705 du Cabestan, Ste-Catherine, Québec J5C 1W9 (CA); 13 des Cedres, Napierville, Québec J0L 1L0 (CA); 27 Harrison Street, Apt. 13, Meriden, CT 06450 (US); 46 Olde Orchard Road, Clinton, CT 06413 (US); 76R Ivy Way, Durham, CT 06422 (US) (Respectivamente) **Nacionalidad o Domicilio:** Estados Unidos de América y Canadá (Respectivamente)	

5 PCT (86)
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Título (54): HETEROCICLOS BICÍCLICOS COMO INHIBIDORES DE LA INTEGRASA DEL VIRUS DE INMUNODEFICIENCIA HUMANA (VIH)

7 Clasificación Internacional (51) A61K31/519 // A61P31/18

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	US	28-05-2004	60/575,513
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	US	11-05-2005	11/126,891

9 Comprobante de pago No. 06-76,642 **Fecha** 27-11-2006

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

2020-F06 (01-11-15)

10 **ANEXOS**

- [x] Comprobante de pago de la tasa de presentación de la solicitud. $463.000
- [x] Documento que acredita la existencia y representación legal cuando el solicitante sea persona jurídica.
- [x] Poderes, si fuere el caso. **Fotocopia autenticada**
- [x] Documento de cesión del inventor al solicitante o a su causante.
- [ ] Declaraciones
- [x] Copia de la solicitud internacional. (Resumen, descripción, reivindicaciones, dibujos)
- [x] Traducción de la solicitud internacional al castellano. (Resumen, descripción, reivindicaciones, dibujos)
- [ ] Copia del examen preliminar efectuado por la IPEA.
- [ ] Traducción del examen preliminar efectuado por la IPEA.
- [ ] De ser el caso, copia del contrato de acceso.
- [ ] De ser el caso, documento que acredite la licencia o autorización de uso de conocimientos tradicionales de las comunidades indígenas.
- [ ] De ser el caso, certificado de depósito del material biológico.
- [ ] Arte final 12x12.
- [ ] De ser el caso, información sobre otras solicitudes de patente o títulos obtenidos en el extranjero por el mismo titular o su causante, relacionadas parcial o totalmente con la invención de esta solicitud.
- [x] Otros: Tarjeta de Propietarios
  Documentos PCT
  Extracto para Publicación y Tarjeta de Archivo Temático

11 FIGURA CARACTERÍSTICA:

12 Solicito la concesión de la patente,

NOMBRE: JUAN PABLO CADENA SARMIENTO

FIRMA:

C.C. 80.410.337 de Usaquén T.P. 57492 del C.S.J.

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

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4 3

SUPERINTENDENCIA DE INDUSTRIA Y COMERCIO

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SOLICITANTE	TIPO PAGO	BANCO	CUENTA	No. PAGO	FECHA PGO	Vr. PAGO
BRIGARD & CASTRO LTDA	CONSIGNACION	BANCO POPULAR	050-00110-6	58188063	04/10/2006	32,860,000.00

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

CANT.	RENTISTICO	CONCEPTO	TOTAL CONCEPTO
1	50005-01-01 SOLICITUDES	1 TRAMITES DE SOL. DE PATENTE DE IN	463,000.00
		TOTAL : $	463,000.00

SON: CUATROCIENTOS SESENTA Y TRES MIL PESOS

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4

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

(72) Inventors; and

(75) Inventors/Applicants *(for US only)*: NAIDU, B., Narasimhulu [IN/US]; 12 Skeetfield Point Road, Durham, CT 06422 (US). BANVILLE, Jacques [CA/CA]; 1209 Girard, St-Hubert, Québec J4T 1H3 (CA). BEAULIEU, Francis [CA/CA]; 370 Leotable Dubuc, Lapraire, Québec J5R 5M4 (CA). CONNOLLY, Timothy, P. [CA/US]; 6 Elizabeth Road, Portland, CT 06480 (US). KRYSTAL, Mark, R. [US/US]; 12 Salem Road, Westport, CT 06880 (US). MATISKELLA, John, D. [US/US]; 130 High Hill Road, Wallingford, CT 06492 (US). OUELLET, Carl [CA/CA]; 555 Rue de la Verendrye, Boucherville, Québec J4B 2Y3 (CA). PLAMONDON, Serge [CA/CA]; 705 du Cabestan, Ste-Catherine, Québec J5C 1W9 (CA). REMILLARD, Roger [CA/CA]; 13 des Cedres, Napierville, Québec J0L 1L0 (CA). SORENSON, Margaret, E. [US/US]; 27 Harrison Street, Apt. 13, Meriden, CT 06450 (US). UEDA, Yasutsugu [JP/US]; 46 Olde Orchard Road, Clinton, CT 06413 (US). WALKER, Michael, A. [US/US]; 76R Ivy Way, Durham, CT 06422 (US).

(74) Agents: EPPERSON, James et al.; Bristol-Myers Squibb Company, P.O. Box 4000, Princeton, NJ 08543-4000 (US).

(81) Designated States *(unless otherwise indicated, for every kind of national protection available)*: AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BW, BY, BZ, CA, CH, CN, CO, CR, CU, CZ, DE, DK, DM, DZ, EC, EE, EG, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KM, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NA, NG, NI, NO, NZ, OM, PG, PH, PL, PT, RO, RU, SC, SD, SE, SG, SK, SL, SM, SY, TJ, TM, TN, TR, TT, TZ, UA, UG, US, UZ, VC, VN, YU, ZA, ZM, ZW.

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Declarations under Rule 4.17:

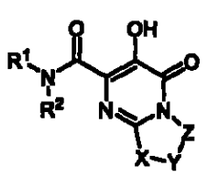
— *as to applicant's entitlement to apply for and be granted a patent (Rule 4.17(ii)) for the following designations AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BW, BY, BZ, CA, CH, CN, CO, CR, CU, CZ, DE, DK, DM, DZ, EC, EE, EG, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KM, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NA, NG, NI, NO, NZ, OM, PG, PH, PL, PT, RO, RU, SC, SD, SE, SG, SK, SL, SM, SY, TJ, TM, TN, TR, TT, TZ, UA, UG, UZ, VC, VN, YU, ZA, ZM, ZW, ARIPO patent (BW, GH, GM, KE, LS, MW, MZ, NA, SD, SL, SZ, TZ, UG, ZM, ZW), Eurasian patent (AM, AZ, BY, KG, KZ, MD, RU, TJ, TM), European patent (AT, BE, BG, CH, CY, CZ, DE, DK, EE, ES, FI, FR, GB, GR, HU, IE, IS, IT, LT, LU, MC, NL, PL, PT, RO, SE, SI, SK, TR), OAPI patent (BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, ML, MR, NE, SN, TD, TG)*

— *as to the applicant's entitlement to claim the priority of the earlier application (Rule 4.17(iii)) for all designations*

— *as to the applicant's entitlement to claim the priority of the earlier application (Rule 4.17(iii)) for all designations*

[Continued on next page]

(54) Title: BICYCLIC HETEROCYCLES AS HIV INTEGRASE INHIBITORS



I

(57) Abstract: The invention encompasses a series cyclic bicyclic pyrimidinone compounds of Formula I which inhibit HIV integrase and prevent viral integration into human DNA. This action makes the compounds useful for treating HIV infection and AIDS. The invention also encompasses pharmaceutical compositions and methods for treating those infected with HIV.

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

BICYCLIC HETEROCYCLES AS HIV INTEGRASE INHIBITORS

CROSS REFERENCE TO RELATED APPLICATIONS

This application claims the benefit of U.S. Provisional Application Serial Numbers 60/603,371 filed August 20, 2004 and 60/575,513 filed May 28, 2004.

BACKGROUND OF THE INVENTION

Human immunodeficiency virus (HIV) has been identified as the etiological agent responsible for acquired immune deficiency syndrome (AIDS), a fatal disease characterized by destruction of the immune system and the inability to fight off life threatening opportunistic infections. Recent statistics (UNAIDS: Report on the Global HIV/AIDS Epidemic, December 1998), indicate that as many as 33 million people worldwide are infected with the virus. In addition to the large number of individuals already infected, the virus continues to spread. Estimates from 1998 point to close to 6 million new infections in that year alone. In the same year there were approximately 2.5 million deaths associated with HIV and AIDS.

There are currently a number of antiviral drugs available to combat the infection. These drugs can be divided into three classes based on the viral protein they target and their mode of action. In particular, saquinavir, indinavir, ritonavir, nelfinavir and amprenavir are competitive inhibitors of the aspartyl protease expressed by HIV. Zidovudine, didanosine, stavudine, lamivudine, zalcitabine and abacavir are nucleoside reverse transcriptase inhibitors that behave as substrate mimics to halt viral cDNA synthesis. The non-nucleoside reverse transcriptase inhibitors, nevaripine, delavirdine and efavirenz inhibit the synthesis of viral cDNA via a non-competitive (or uncompetitive) mechanism. Used alone these drugs are effective in reducing viral replication. The effect is only temporary as the virus readily develops resistance to all known agents. However, combination therapy has proven very effective at both reducing virus and suppressing the emergence of resistance in a number of patients. In the US, where combination therapy is widely

available, the number of HIV-related deaths has declined (Palella, F. J.; Delany, K. M.; Moorman, A. C.; Loveless, M. O.; Furher, J.; Satten, G. A.; Aschman, D. J.; Holmberg, S. D. *N. Engl. J. Med.* 1998, *338*, 853-860).

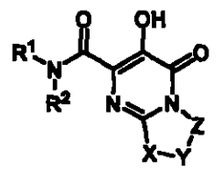
Unfortunately, not all patients are responsive and a large number fail this therapy. In fact, approximately 30-50% of patients ultimately fail combination therapy. Treatment failure in most cases is caused by the emergence of viral resistance. Viral resistance in turn is caused by the rapid turnover of HIV-1 during the course of infection combined with a high viral mutation rate. Under these circumstances incomplete viral suppression caused by insufficient drug potency, poor compliance to the complicated drug regiment as well as intrinsic pharmacological barriers to exposure provides fertile ground for resistance to emerge. More disturbing are recent findings which suggest that low-level replication continues even when viral plasma levels have dropped below detectable levels (< 50 copies/ml) (Carpenter, C. C.; Cooper, D. A.; Fischl, M. A.; Gatell, J. M.; Gazzard, B. G.; Hammer, S. M.; Hirsch, M. S.; Jacobsen, D. M.; Katzenstein, D. A.; Montaner, J. S.; Richman, D. D.; Saag, M. S.; Schechter, M.; Schooley, R. T.; Thompson, M. A.; Vella, S.; Yeni, P. G.; Volberding, P. A. *JAMA* 2000, *283*, 381-390). Clearly there is a need for new antiviral agents, preferably targeting other viral enzymes to reduce the rate of resistance and suppress viral replication even further.

HIV expresses three enzymes, reverse transcriptase, an aspartyl protease, and integrase. All three are targets for treating AIDS and HIV infection. HIV integrase catalyzes insertion of the viral cDNA into the host cell genome, which is a critical step in the viral life cycle. HIV integrase inhibitors belonging to a class of diketo acid compounds prevented viral integration and inhibited HIV-1 replication in cells (Hazuda et al. *Science* 2000, *287*, 646). And recently, HIV integrase inhibitors have been accepted into clinical trials for treating AIDS and HIV infection (Neamati *Expert. Opin. Ther. Patents* 2002, *12*, 709, Pais and Burke *Drugs Fut.* 2002, *27*, 1101).

DESCRIPTION OF THE INVENTION

The invention encompasses compounds of Formula I, including pharmaceutically acceptable salts and solvates, their pharmaceutical compositions, and their use in inhibiting HIV integrase and treating those infected with HIV or AIDS.

One aspect of the invention are compounds of Formula I



I

wherein:

R^1 is $C_{1-6}(Ar^1)$alkyl, $C_{1-6}(Ar^1)(CON(R^8)(R^9))$alkyl, $C_{1-6}(Ar^1)(CO_2R^{14})$alkyl, $C_{1-6}(Ar^1)$hydroxyalkyl, or $C_{1-6}(Ar^1)$oxyalkyl;

R^2 is hydrogen, C_{1-6}alkyl, or OR^{14};

R^3 is hydrogen, halo, hydroxy, cyano, C_{1-6}alkyl, C_{3-7}cycloalkyl, C_{5-7}cycloalkenyl, C_{1-6}haloalkyl, C_{1-6}alkoxy, C_{1-6}alkylthio, C_{1-6}haloalkoxy, $N(R^8)(R^9)$, $NHAr^2$, $N(R^6)SO_2R^7$, $N(R^6)COR^7$, $N(R^6)CO_2R^7$, $OCOR^7$, OCO_2R^7, $OCON(R^8)(R^9)$, $OCH_2CO_2R^7$, $OCH_2CON(R^8)(R^9)$, COR^6, CO_2R^6, $CON(R^8)(R^9)$, SOR^7, $S(=N)R^7$, SO_2R^7, $SO_2N(R^6)(R^6)$, $PO(OR^6)_2$, $C_{2-4}(R^{12})$alkynyl, R^{13}, Ar^2, or Ar^3;

R^4 is hydrogen, halo, hydroxy, cyano, C_{1-6}alkyl, C_{1-6}alkoxy, C_{1-6}haloalkyl, C_{1-6}haloalkoxy, or $N(R^6)(R^6)$;

R^5 is hydrogen, halo, hydroxy, cyano, C_{1-6}alkyl, C_{1-6}alkoxy, C_{1-6}haloalkyl, C_{1-6}haloalkoxy, or $N(R^6)(R^6)$;

R^6 is hydrogen, C_{1-6}alkyl, or C_{3-7}cycloalkyl;

R^7 is C_{1-6}alkyl or C_{3-7}cycloalkyl;

R^8 is hydrogen, C_{1-6}alkyl, C_{1-6}hydroxyalkyl, C_{1-6}(C_{1-6}alkoxy)alkyl or C_{1-6}(C_{1-6}dialkylamino)alkyl;

R^9 is hydrogen, C_{1-6}alkyl, C_{1-6}hydroxyalkyl, C_{1-6}(C_{1-6}alkoxy)alkyl or C_{1-6}(C_{1-6}dialkylamino)alkyl; or

$N(R^8)(R^9)$ taken together is azetidinyl, pyrrolidinyl, (R^{10})-piperidinyl, N-(R^{11})-piperazinyl, morpholinyl, thiomorpholinyl, or dioxothiazinyl;

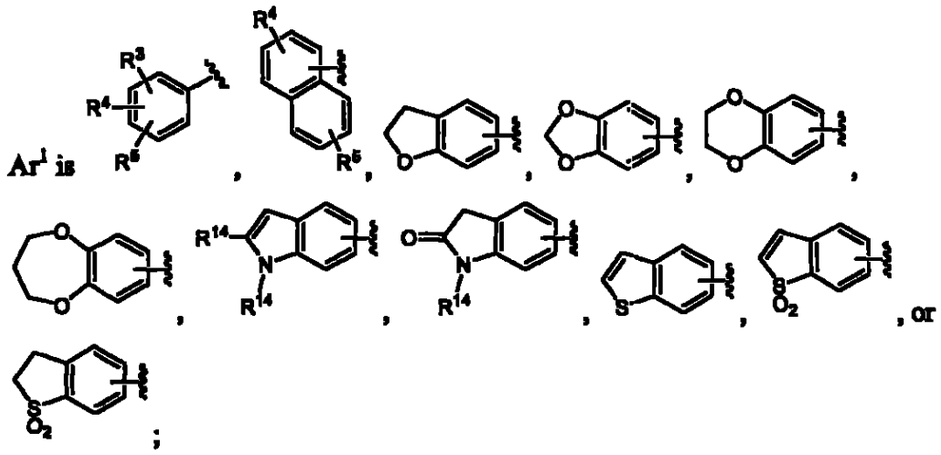
R^{10} is hydrogen, C_{1-6}alkyl, or C_{1-6}hydroxyalkyl;

R^{11} is hydrogen, C_{1-6}alkyl, C_{3-7}cyclolkyl, COR^6, or CO_2R^6;

R^{12} is hydrogen, hydroxy, $N(R^6)(R^6)$, SO_2R^7, OSO_2R^7, or dioxothiazinyl;

R^{13} is azetidinonyl, pyrrolidinonyl, valerolactamyl, caprolactamyl, maleimido, oxazolidonyl, or dioxothiazinyl, and is substituted with 0-1 substituents selected from the group consisting of hydroxymethyl, acetoxymethyl, and aminomethyl;

R^{14} is hydrogen or C_{1-6}alkyl;

Ar^1 is  ;

Ar^2 is tetrazolyl, triazolyl, oxadiazolyl, thiadiazolyl, pyrazolyl, imidazolyl, oxazolyl, thiazolyl, isoxazolyl, isothiazolyl, furanyl, thienyl, pyrrolyl, pyrimidinyl, pyrazinyl, pyridinyl, hydroxypyridinyl, quinolinyl, isoquinolinyl, or indolyl, and is substituted with 0-2 substituents selected from the group consisting of halo, cyano, benzyl, C_{1-6}alkyl, C_{1-6}alkoxy, $N(R^8)(R^9)$, $CON(R^8)(R^9)$, CO_2R^6, $CONHSO_2N(R^6)(R^6)$, $CONHSO_2N(R^6)$(phenyl), and $CONHSO_2N(R^6)$(halophenyl);

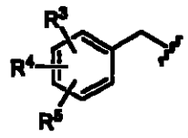
Ar^3 is phenyl substituted with 0-2 substituents selected from the group consisting of halo, cyano, hydroxy, C_{1-6}alkyl, C_{1-6}alkoxy, (C_{1-6}alkoxy)methyl, C_{1-6}haloalkyl, C_{1-6}haloalkoxy, $N(R^8)(R^9)$, $CON(R^6)(R^6)$, and $CH_2N(R^8)(R^9)$, or is dioxolanylphenyl; and

X-Y-Z is $C(R^{14})_2OC(R^{14})_2$, $C(R^{14})_2OC(R^{14})_2C(R^{14})_2$, or $C(R^{14})_2OC(R^{14})_2C(R^{14})_2C(R^{14})_2$;

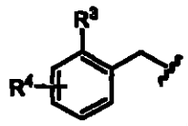
or a pharmaceutically acceptable salt or solvate thereof.

Another aspect of the invention is a compound of Formula I where R^1 is $C_{1-6}(Ar^1)$alkyl.

Another aspect of the invention is a compound of Formula I where R^1 is



Another aspect of the invention is a compound of Formula I where R^1 is



Another aspect of the invention is a compound of Formula I where R^2 is hydrogen.

Another aspect of the invention is a compound of Formula I where R^3 is hydrogen, halo, $N(R^8)(R^9)$, $N(R^6)COR^7$, $OCON(R^8)(R^9)$, $CON(R^8)(R^9)$, SOR^7, SO_2R^7, $SO_2N(R^6)(R^6)$, $PO(OR^6)_2$, R^{13}, or Ar^2.

Another aspect of the invention is a compound of Formula I where X-Y-Z is $C(R^{14})_2OCH_2$, $C(R^{14})_2OCH_2CH_2$, or $C(R^{14})_2OCH_2CH_2CH_2$.

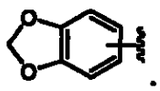
Another aspect of the invention is a compound of Formula I where X-Y-Z is CH_2OCH_2, $C(CH_3)HOCH_2$, $C(CH_3)_2OCH_2$, $CH_2OCH_2CH_2$, $C(CH_3)HOCH_2CH_2$, $C(CH_3)_2OCH_2CH_2$, $CH_2OCH_2CH_2CH_2$, $C(CH_3)HOCH_2CH_2CH_2$, or $C(CH_3)_2OCH_2CH_2CH_2$.

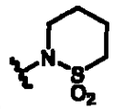
For a compound of Formula I, any scope of R^1, R^2, R^3, R^4, R^5, R^6, R^7, R^8, R^9, R^{10}, R^{11}, R^{12}, R^{13}, R^{14}, Ar^1, Ar^2, Ar^3, and X-Y-Z can be used independently with any scope of any other substituent.

"Alkyl," "alkoxy," "hydroxyalkyl," and related terms with an alkyl moiety include straight and branched configurations. A term such as "C_{1-6}(R)alkyl" means a straight or branched alkyl group of one to six carbons substituted with the substituent

R. "Haloalkyl" and "halophenyl" include all permutations of halogenated alkyl or phenyl groups, from monohalo to perhalo. "Aryl" means an aromatic ring system and includes carbocyclic and heterocyclic systems. Some substituents are divalent, such as X-Y-Z. Asymmetric divalent substituents may be attached in either of the two configurations.

"$C_{1-6}(Ar^1)$oxyalkyl" means Ar^1 is attached at the oxygen.

"Dioxolanyphenyl" means  .

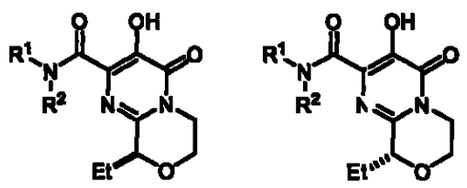
"Dioxothiazinyl" means  .

The invention includes all pharmaceutically acceptable salt forms of the compounds. Pharmaceutically acceptable salts are those in which the counter ions do not contribute significantly to the physiological activity or toxicity of the compounds and as such function as pharmacological equivalents. These salts can be made according to common organic techniques employing commercially available reagents. Some anionic salt forms include acetate, acistrate, besylate, bromide, chloride, citrate, fumarate, glucouronate, hydrobromide, hydrochloride, hydroiodide, iodide, lactate, maleate, mesylate, nitrate, pamoate, phosphate, succinate, sulfate, tartrate, tosylate, and xinofoate. Some cationic salt forms include ammonium, aluminum, benzathine, bismuth, calcium, choline, diethylamine, diethanolamine, lithium, magnesium, meglumine, 4-phenylcyclohexylamine, piperazine, potassium, sodium, tromethamine, and zinc.

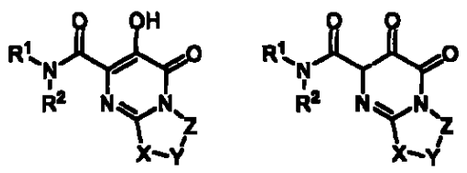
The invention also includes all solvated forms of the compounds, particularly hydrates. Solvates do not contribute significantly to the physiological activity or toxicity of the compounds and as such function as pharmacological equivalents. Solvates may form in stoichiometric amounts or may form from adventitious solvent

or a combination of both. One type of solvate is hydrate, and some hydrated forms include monohydrate, hemihydrate, and dihydrate.

Some of the compounds of the invention exist in stereoisomeric forms. The invention includes all stereoisomeric forms of the compounds including enantiomers and diastereromers. An example of enantiomers is shown below. Methods of making and separating stereoisomers are known in the art.



The invention includes all tautomeric forms of the compounds. An example of a tautomeric pair is shown below.



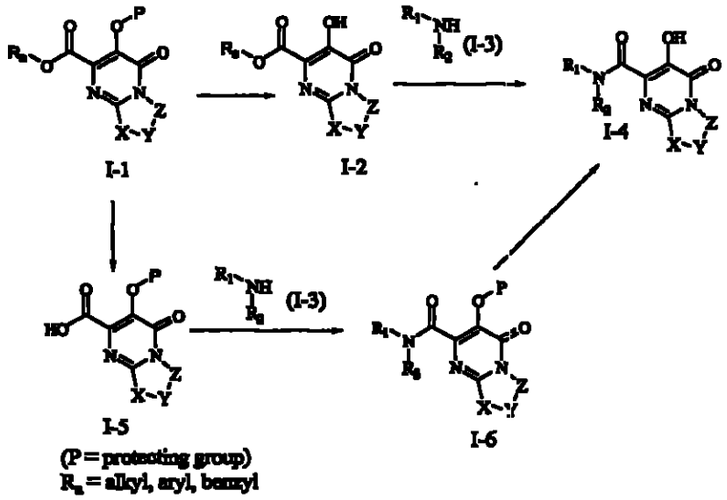
Synthetic Methods

The compounds of this invention can be made by various methods known in the art including those of the following schemes and in the specific embodiments section. The variables shown in the synthetic schemes are distinct from and should not be confused with the variables in the claims or the rest of the specification. The variables in the schemes are meant only to illustrate how to make some of the compounds of this invention.

Some compounds can be synthesized from an appropriately substituted heterocycle I-1 according to Scheme I, where R_a and P can serve as protecting groups

(see Greene, T. W. and Wutz, P. G. M. Protective Groups in Organic Synthesis, Second Edition, 1991, John Wiley and Sons, New York). When P is benzyl or substituted benzyl it can be removed by hydrogenolysis (H_2-Pd/C) or acid hydrolysis (trifluoroacetic acid) to yield intermediate I-2. I-2 can be transaminated to I-4 by reaction with amine I-3. In a number of cases this reaction can be carried out by heating I-3 and I-2 together in the presence of base. Alternatively, standard amide coupling reagents can be used to effect the formation of the amide bond. When R_a is a lower alkyl group, R_a can be removed under ester hydrolysis conditions, such as treatment with NaOH, LiOH, or KOH to deliver the corresponding carboxylic acid I-5. Alternatively, R_a can be removed by nucleophilic displacement using NaI. When R_a is benzyl and substituted benzyl, R_a can be removed by hydrogenolysis. Intermediate I-5 can be coupled using amide bond forming reagents such as BOP, DCC, EDCI, PyBrop, PyBop or other reagents (see March, J. Advanced Organic Chemistry, Fourth Edition 1992 John Wiley & Sons, New York). The resulting intermediate I-6 can be deprotected as described for intermediate I-1.

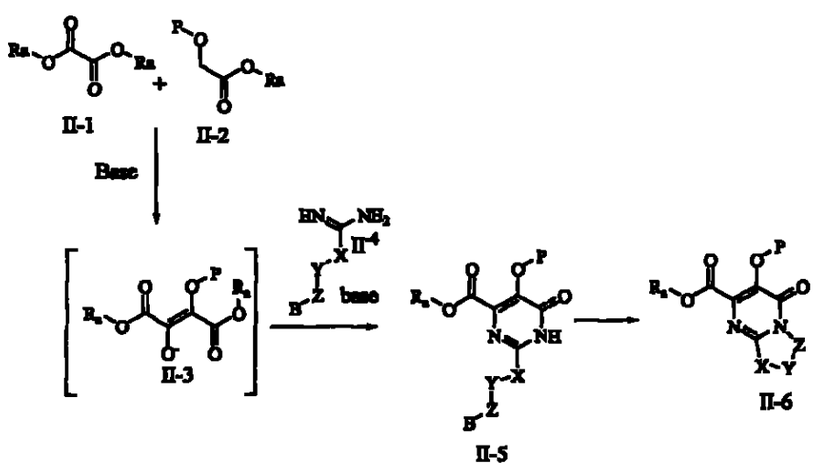
Scheme I.



In Scheme II, intermediate II-3 can be prepared using methods similar to those described in Sunderland, J. S.; Botta, M.; Aime, S.; Raymond, K. N. Inorg. Chem. (2001), 40, 6756-6756, where II-1 and II-2 are condensed, to provide intermediate II-3. This reaction is usually conducted in the presence of a base such as

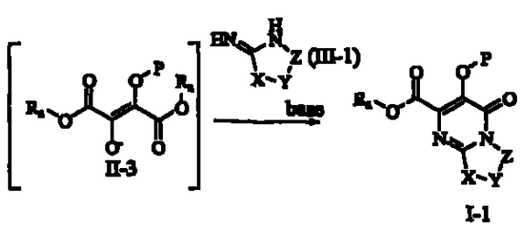
sodium hydride (NaH), sodium ethoxide (EtONa) or lithium hexamethyldisilazide (LiHMDS). Using the methods described in the reference, II-3 can be condensed with an appropriately substituted amidine II-4 to form II-5. Substituent B can be a leaving group, such as –halo (Cl, Br or I) or can be converted to a leaving group under appropriate conditions such as by forming the corresponding methylsulfonate ester. When substituent B is a methyl sulphide group it can be treated with iodomethane to form a dimethylsulfonium intermediate which is activated towards nucleophilic attack to effect ring closure.

Scheme II.



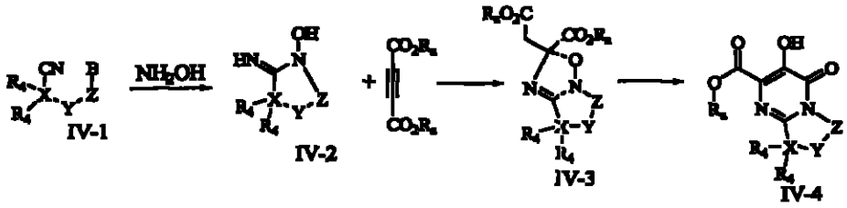
In Scheme III, intermediate II-3 can be condensed with a cyclic-amidine to yield intermediate I-1. Intermediate III-1 can be prepared using known methods (see Patai, S. and Rappoport, Z. The Chemistry of Amidines and Imidates, Volume 2, 1991, John Wiley & Sons, New York).

Scheme III.



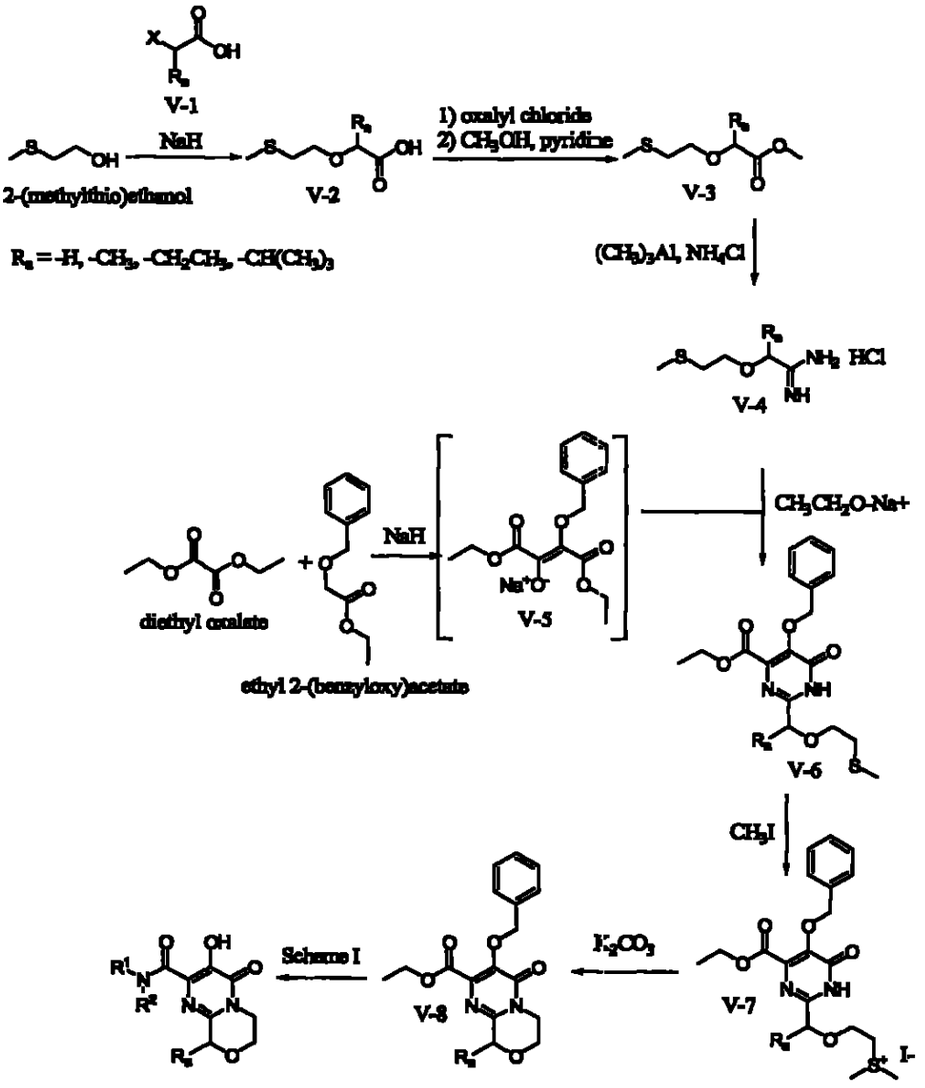
In Scheme IV, nitrile IV-1, possessing a potential leaving group B, can be reacted with hydroxylamine to form intermediate IV-2. This intermediate can be reacted with a suitably protected alkyne to form IV-3 which can rearrange to from intermediate IV-4 according to literature methods (Culbertson, T. P. *Journal of Heterocyclic Chemistry*, **1979**, *16*, 1423-1424).

Scheme IV.



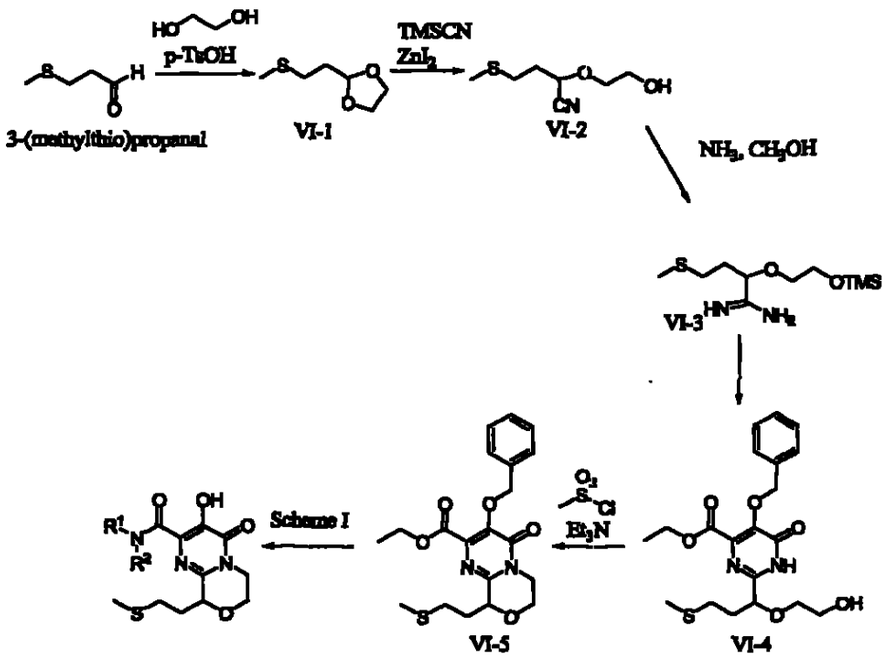
As shown in Scheme V, 2-(methylthio)ethanol can be alkylated with an appropriate α-haloacetic acid (V-1) wherein X is a leaving group such as Cl, Br, OTs, OMs or OTf, to deliver intermediate V-2. Following this, the carboxylic acid can be transformed to the corresponding amidine derivative using known synthetic methods (Geilen et al. *Tetrahedron Letters* **2002**, *43*, 419-421). As described in the above, the amidine can further be reacted with intermediate V-5, in the presence of a base (for example, sodium ethoxide) affording intermediate V-6. Methylation of the sulphide ether can be accomplished by treating V-6 with iodomethane and the resulting sulfonium derivative (V-7) treated with base to form the bicyclic template V-8. This intermediate can be used in the synthesis of final compounds using methods described in Scheme I.

Scheme V



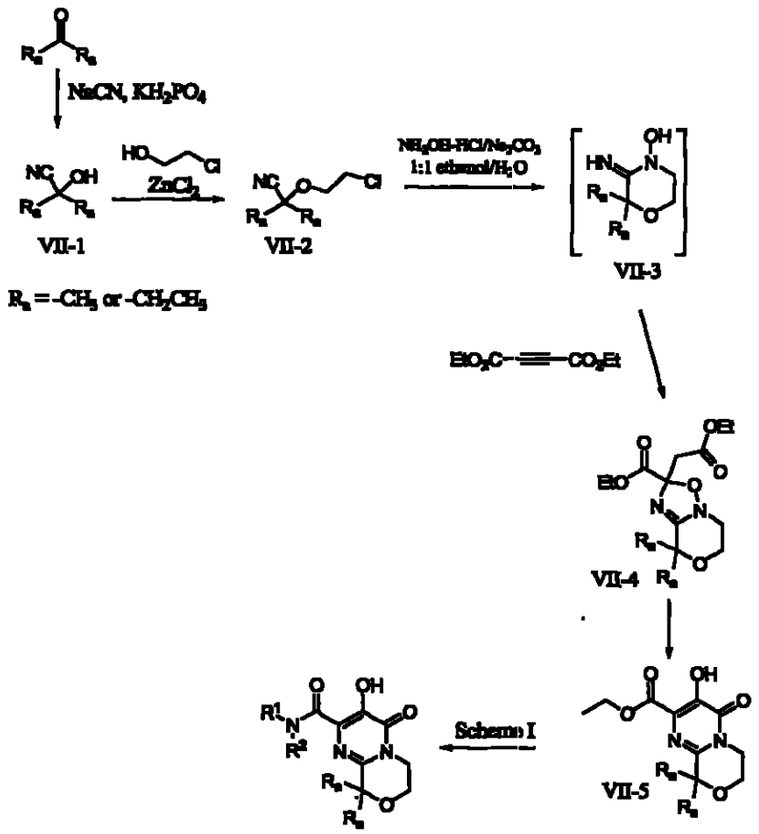
In Scheme VI, 3-methylthiopropanal is converted to dioxolane VI-1 using well known chemistry. Treatment with trimethylsilylcyanide (TMSCN), in the presence of zinc iodide (ZnI_2) produces intermediate VI-2. Reaction with ammonia provides amidine VI-3 which is used in the synthesis of pyrimidinone VI-4 according to the methods described in the previous schemes. Subsequent treatment with CH_3SO_2Cl and triethylamine (Et_3N) results in the corresponding bicyclic intermediate VI-5. Completion of the synthesis can be carried out as illustrated in Scheme I.

Scheme VI



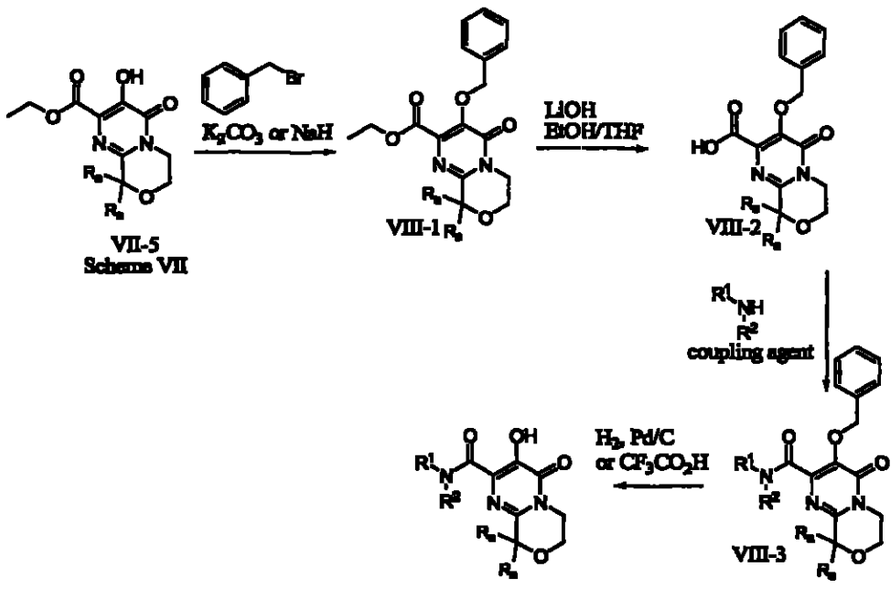
Another method is illustrated in Scheme VII. This synthetic path begins with an appropriately substituted ketone which can be transformed to the corresponding nitrile intermediate VII-1. This in turn can be reacted with 2-chloroethanol to produce compound VII-2, which can be reacted with hydroxylamine and an acetylene dicarboxylate ester to yield intermediate VII-4. Heating of the intermediate can yield intermediate VII-5. Synthesis of the corresponding amide derivatives can be accomplished according to Scheme I.

Scheme VII



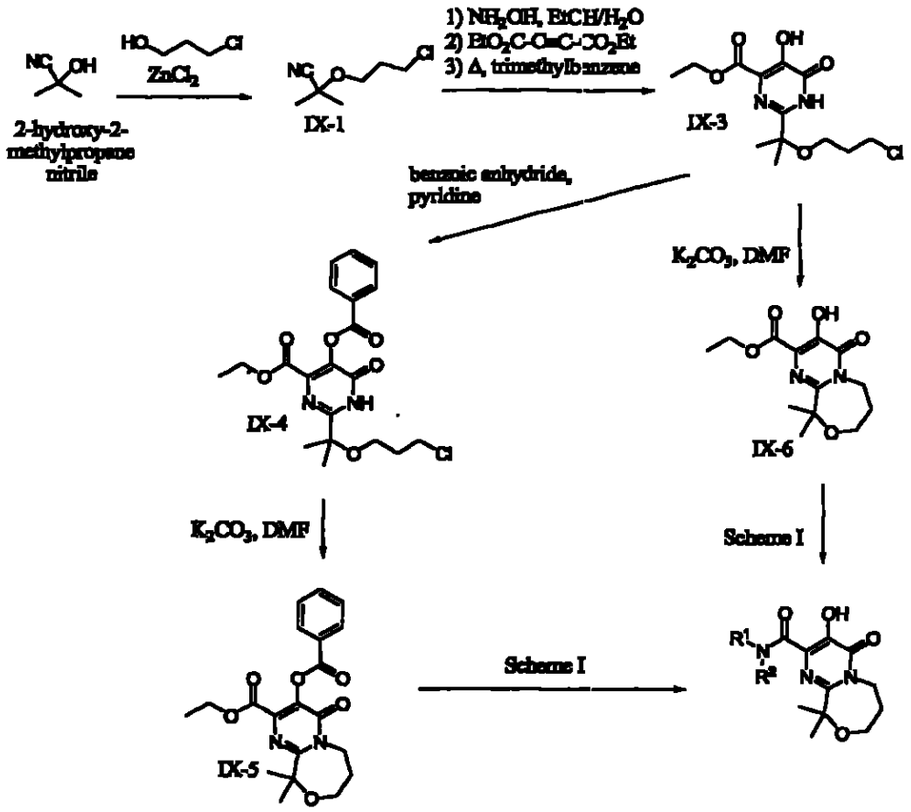
In Scheme VIII, benzylation of the hydroxyl group of VII-5, as a means of functional group protection, can be achieved using benzyl bromide under basic conditions (for example, K_2CO_3 or NaH). Saponification of the ester group of VIII-1 can provide VIII-2 which can be coupled with appropriately substituted amines (R^1R^2NH) using well known amide bond forming reagents, such as benzotriazole-1-yloxy-tris-pyrrolidino-phosphonium hexafluorophosphate (PyBOP) or O-(7-azabenzotriazol-1-yl)-N,N,N',N'-tetramethyluronium hexafluorophosphate (HATU). Alternatively, the corresponding acid chloride can be formed, by treatment with oxalyl chloride, and reacted with an appropriate amine to form the amide bond. Removal of the benzyl group can be accompliahed under a variety of conditions including treatment with CF_3CO_2H or H_2 (Pd-C).

Scheme VIII



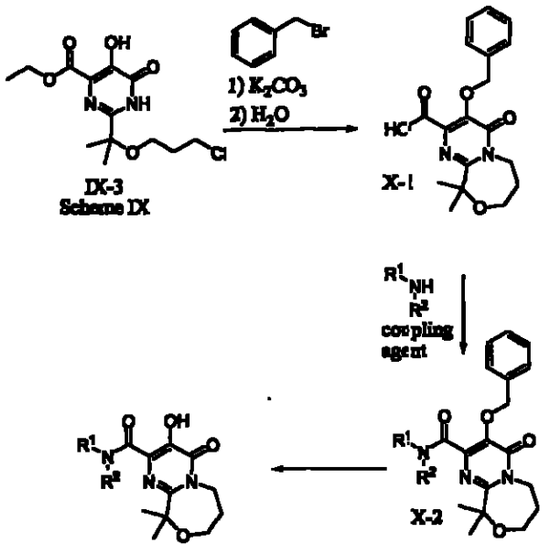
In yet another method, some compounds of this invention can be synthesized according to Scheme IX. In Scheme IX, pyrimidinone IX-3, can be produced using methods similar to those described in the previous schemes. This intermediate can be carried on to the final product according to a variety of paths. In one, the hydroxyl group can be benzoylated to provide intermediate IX-4 which can be further treated with K_2CO_3 to effect ring closure to form the bicyclic template IX-5. Alternatively, direct treatment of IX-3 with K_2CO_3 can provide intermediate IX-6. Intermediates IX-5, an IX-6 can be used in the synthesis the final products using the methods described in Scheme I.

Scheme IX



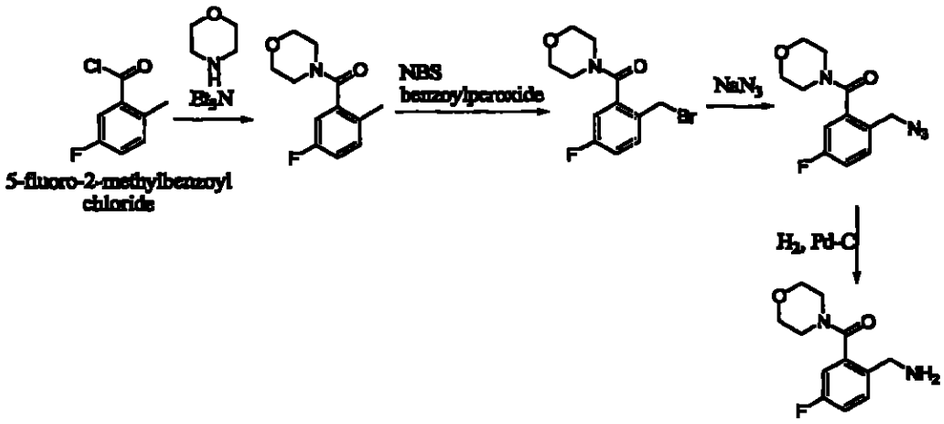
In Scheme X, IX-3 can be used to synthesize the benzylated intermediate X-1. This intermediate can be carried on to final product using methods analogous to those described in Scheme VIII.

Scheme X



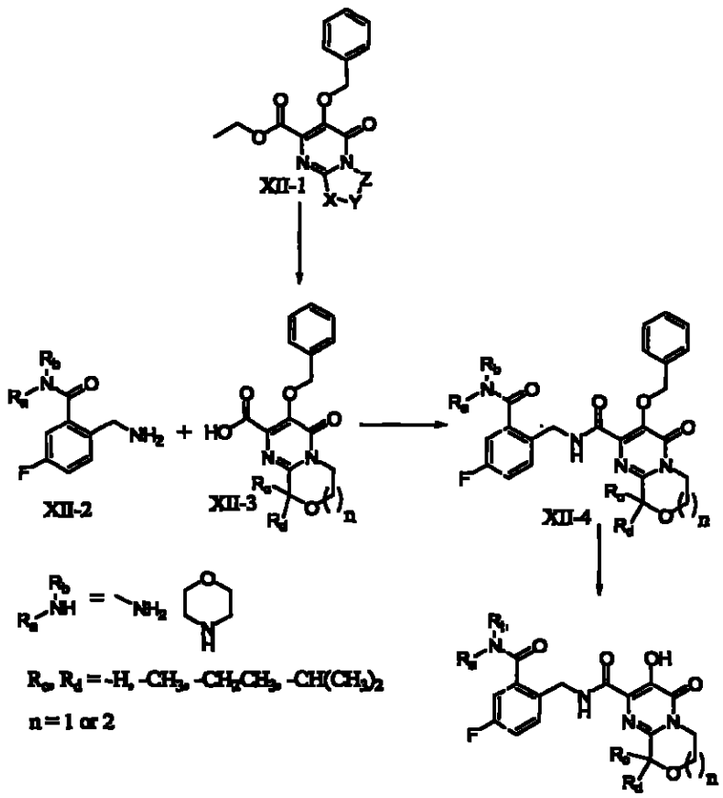
The synthesis of (2-(aminomethyl)-5-fluorophenyl)(morpholino)methanone hydrochloride is illustrated in Scheme XI.

Scheme XI



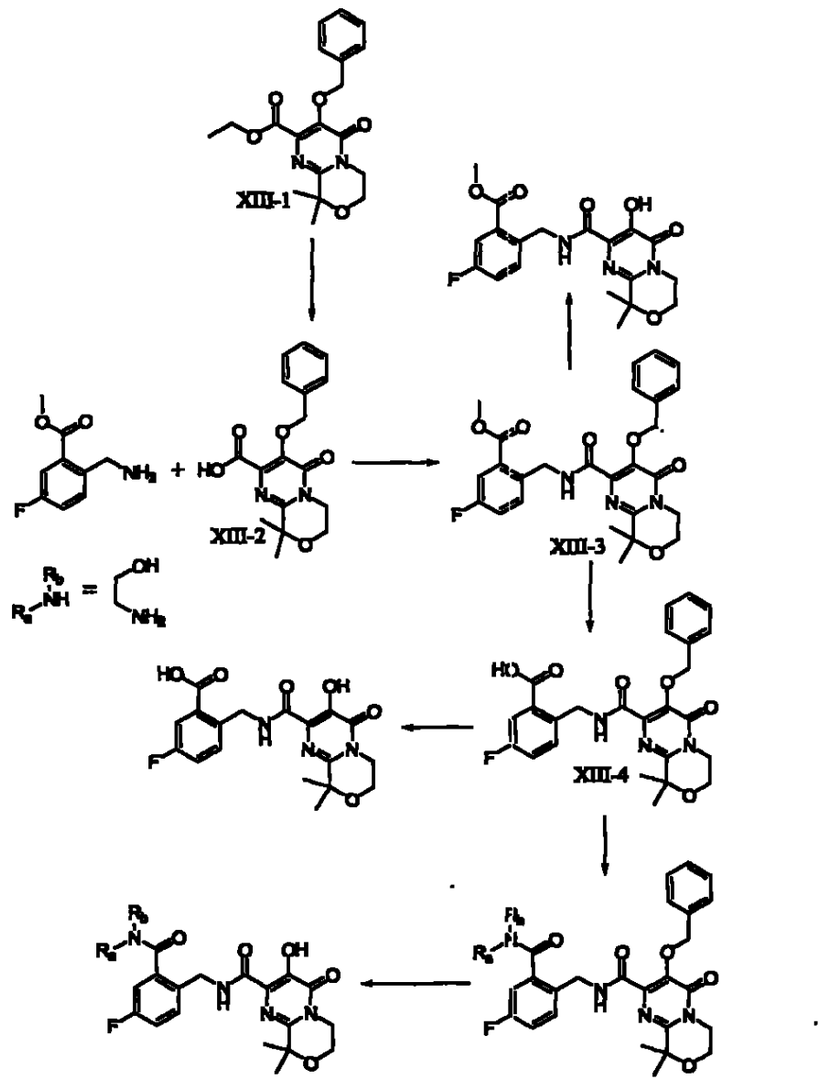
In Scheme XII, bicyclic intermediate XII-1, prepared according to the methods described above, can be saponified using well known methods. The resulting carboxylic acid, XII-3, can then be coupled to amine XII-2 using standard amide bond forming reagents and methods. Removal of the benzyl group, by hydrogenolysis or acid mediated hydrolysis provides the final products.

Scheme XII



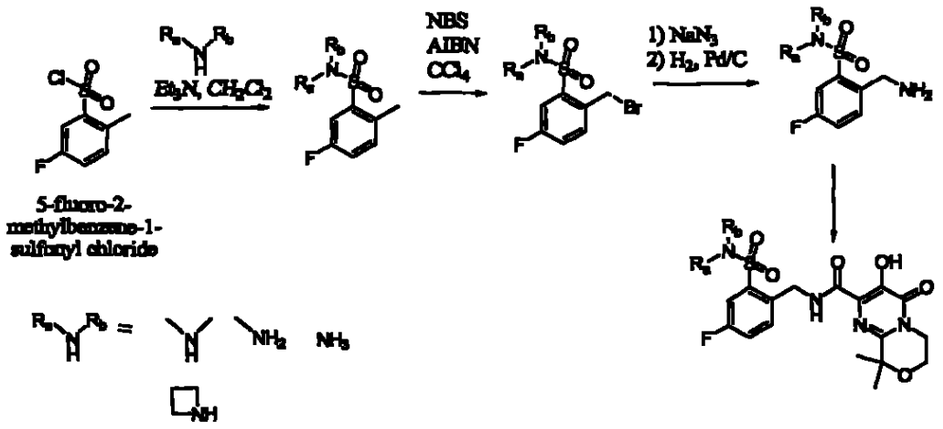
An alternative route to compounds similar to those presented in Scheme XII is given in Scheme XIII. In this scheme the ester group of XIII-1 can be hydrolyzed and the resulting carboxylic acid coupled to methyl 2-(aminomethyl)-5-fluorobenzoate. A second hydrolysis reaction can produce XIII-4 which can be coupled with a second amine. This is followed by removal of the benzyl group to provide the final products.

Scheme XIII



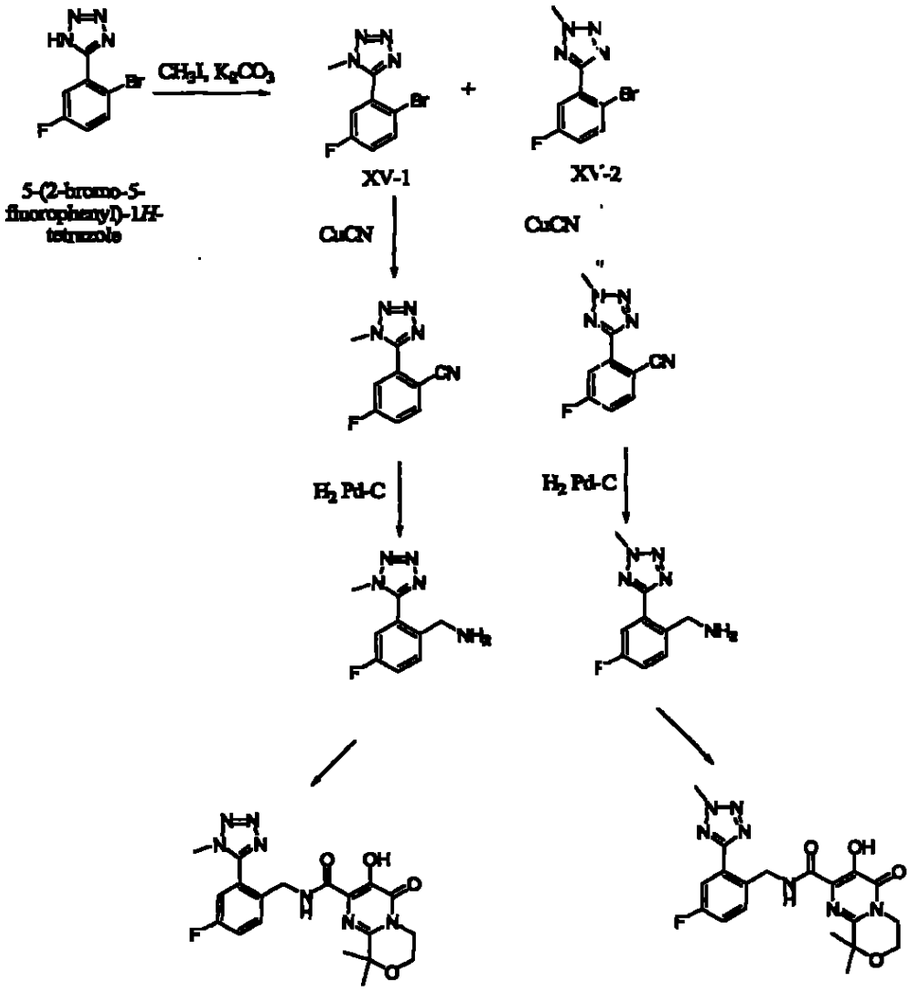
In yet another method, Scheme XIV illustrates the synthesis of sulfonamide containing examples, starting from 5-fluoro-2-methylbenzen-1-sulfonyl chloride.

Scheme XIV



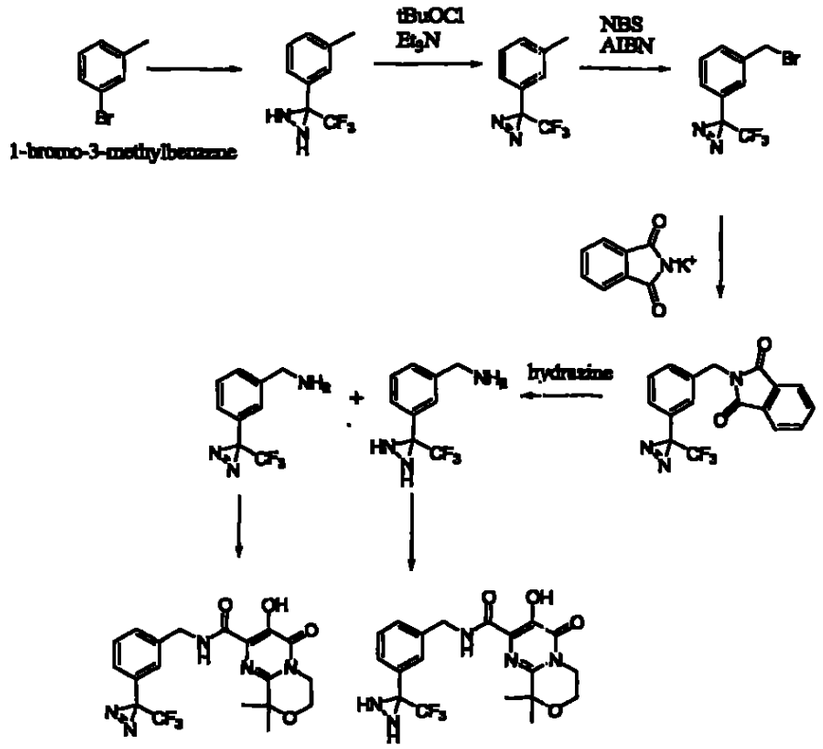
Further illustration of methods used for the synthesis of certain compounds of the invention is shown in Scheme XV. Methylation of 5-(2-bromo-5-fluorophenyl)-1H-tetrazole can yield a mixture of XV-1 and XV-2 that can be separated and each of the compounds carried on to the corresponding final products.

Scheme XV



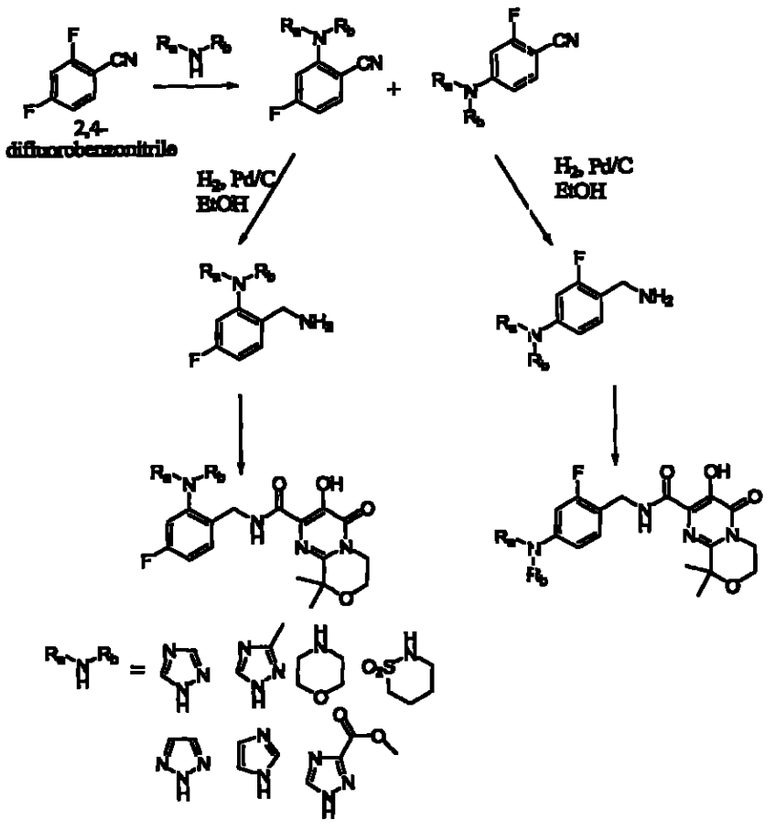
Some diazarine and diaziradine analogues can be synthesized according to Scheme XVI.

Scheme XVI

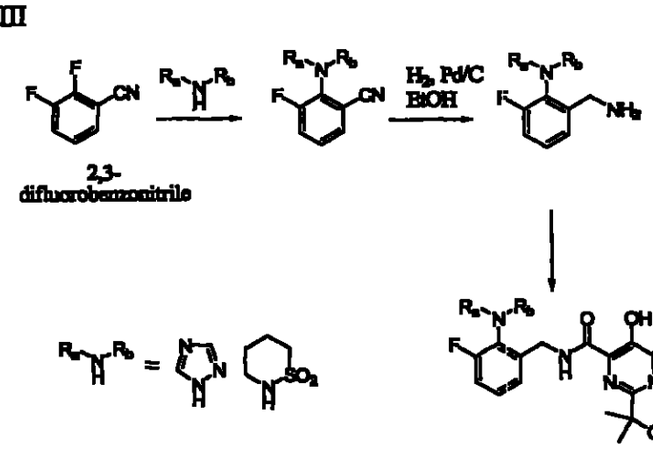


Some examples of the invention can be synthesized according to the methods illustrated in Schemes XVII-XX.

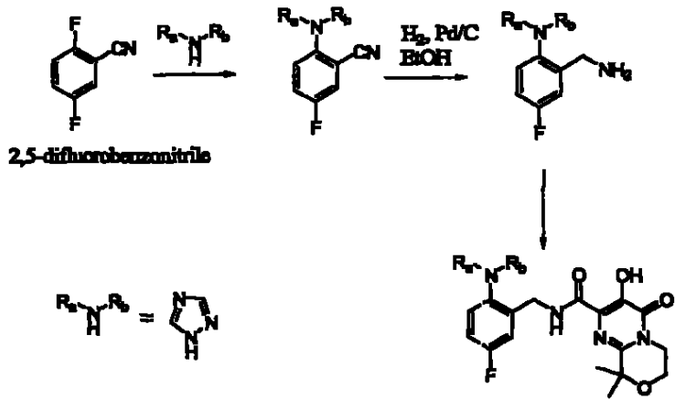
Scheme XVII



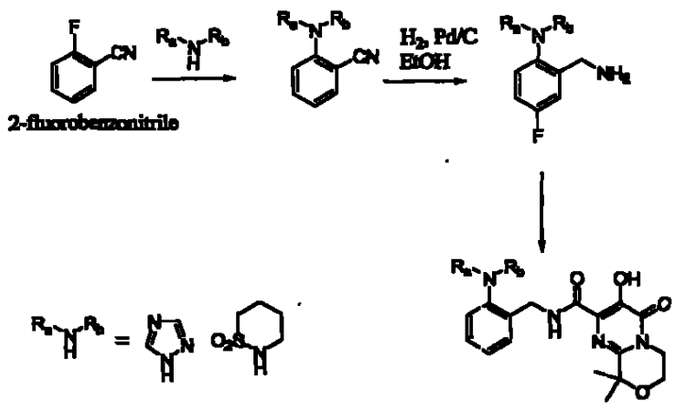
Scheme XVIII



Scheme XIX

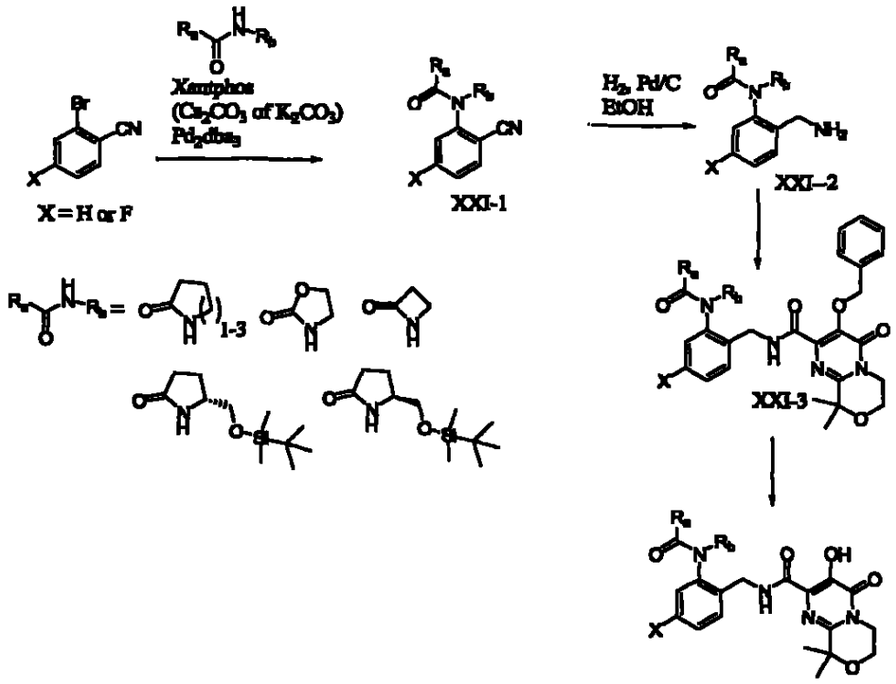


Scheme XX



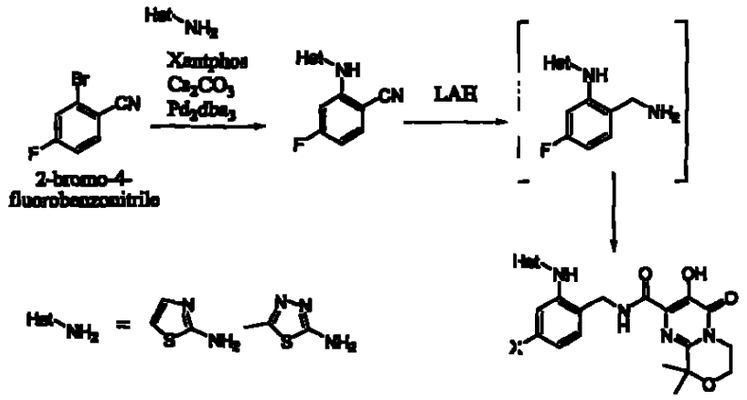
In Scheme XXI, 2-bromo-benzonitrile or 2-bromo-4-fluoro-benzonitrile can be coupled with an appropriate amide to provide XXI-1. Reduction of the nitrile group provides XXI-2 which can be used in the synthesis of the final product according to the methods described in the previous schemes. In most cases, compound XXI-1 need not be isolated but can be carried directly into the coupling reaction to form XXI-3.

Scheme XXI



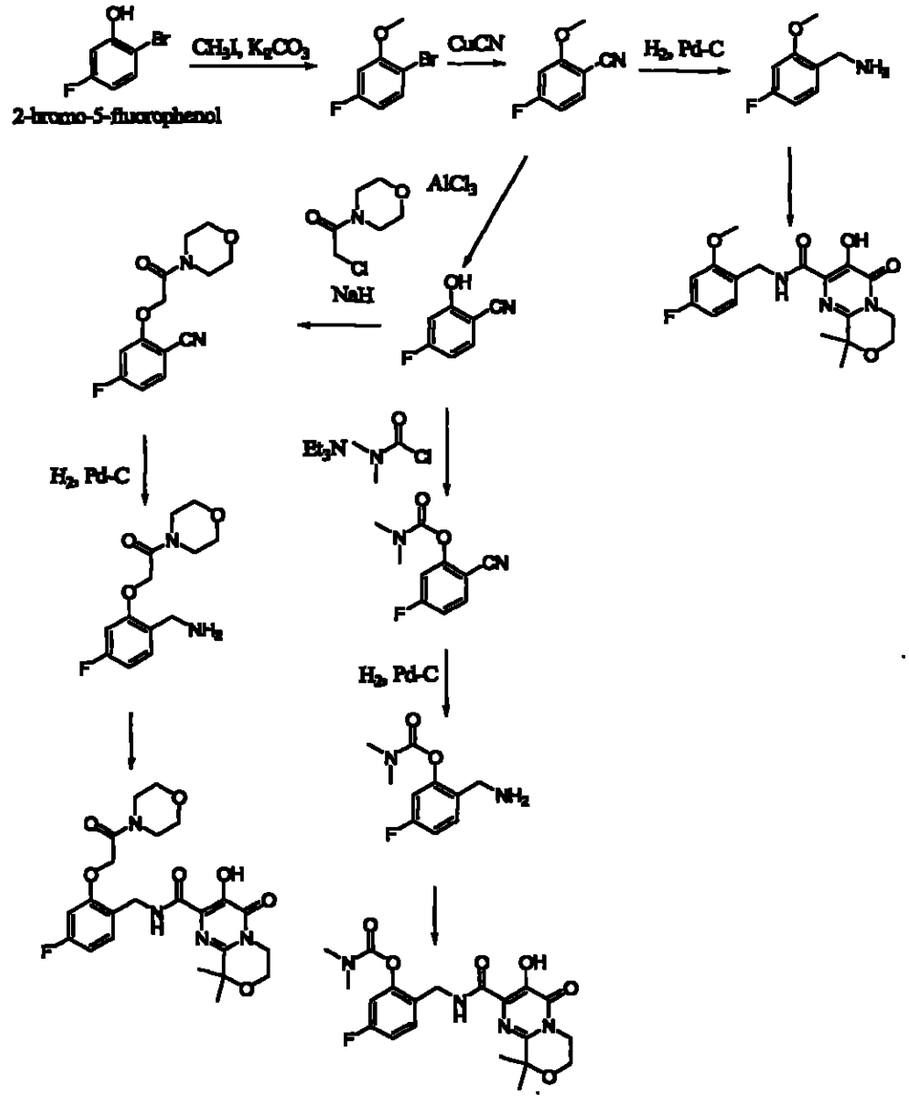
The examples and methods shown in Scheme XXII are similar to those depicted in Scheme XXI.

Scheme XXII

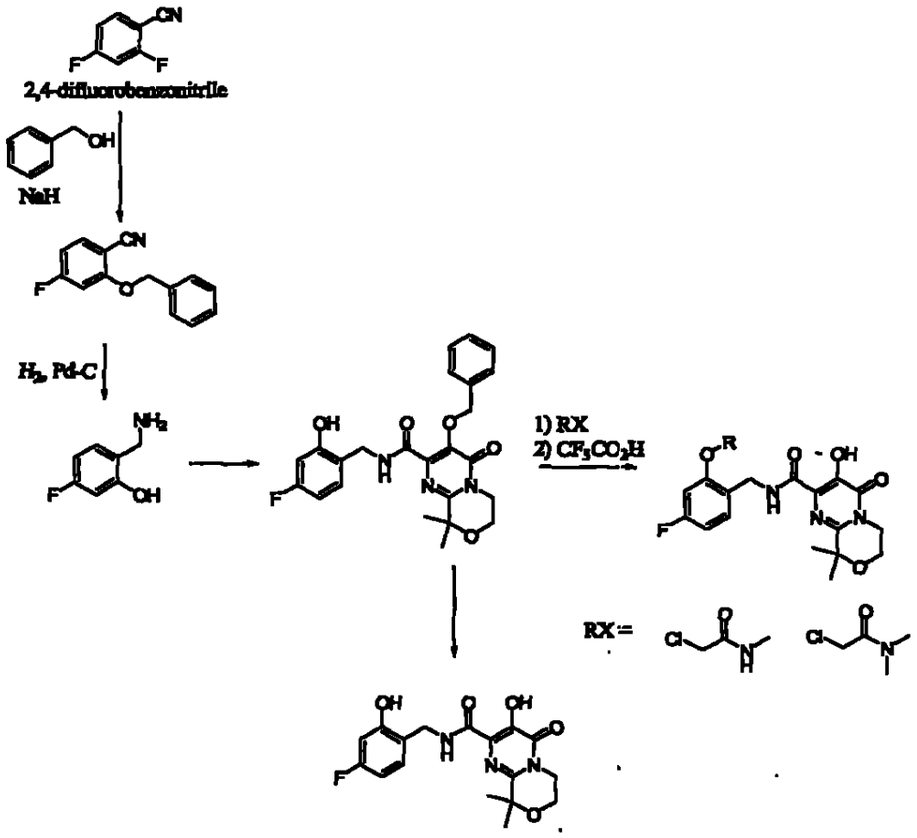


Schemes XXIV and XXV further illustrate methods useful for the synthesis of some compounds of the invention.

Scheme XXIV

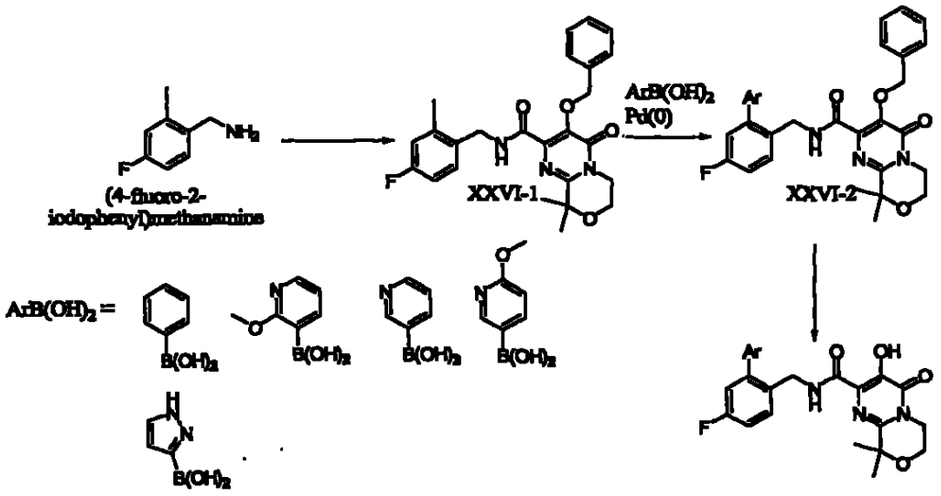

2-bromo-5-fluorophenol
CH3I, K2CO3
CuCN
H2, Pd-C
AlCl3
NaH
Et3N
H2, Pd-C
H2, Pd-C

Scheme XXV



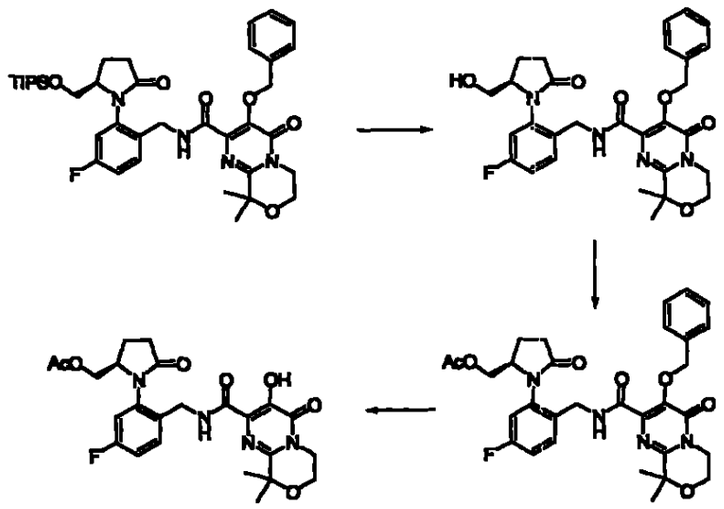
In Scheme XXVI, intermediate XXVI-1 can be used to synthesize intermediates XXVI-2 via palladium catalyzed coupling. These intermediates can be further modified to provide some of the compounds of this invention.

Scheme XXVI



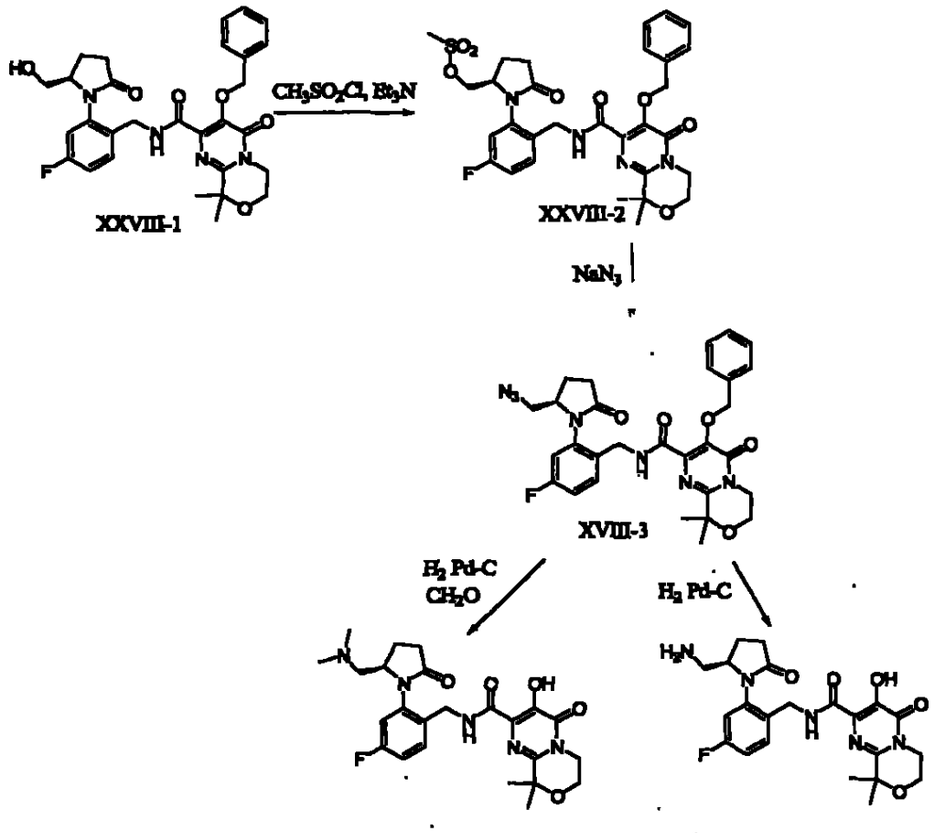
Another method is illustrated in Scheme XXVII.

Scheme XXVII



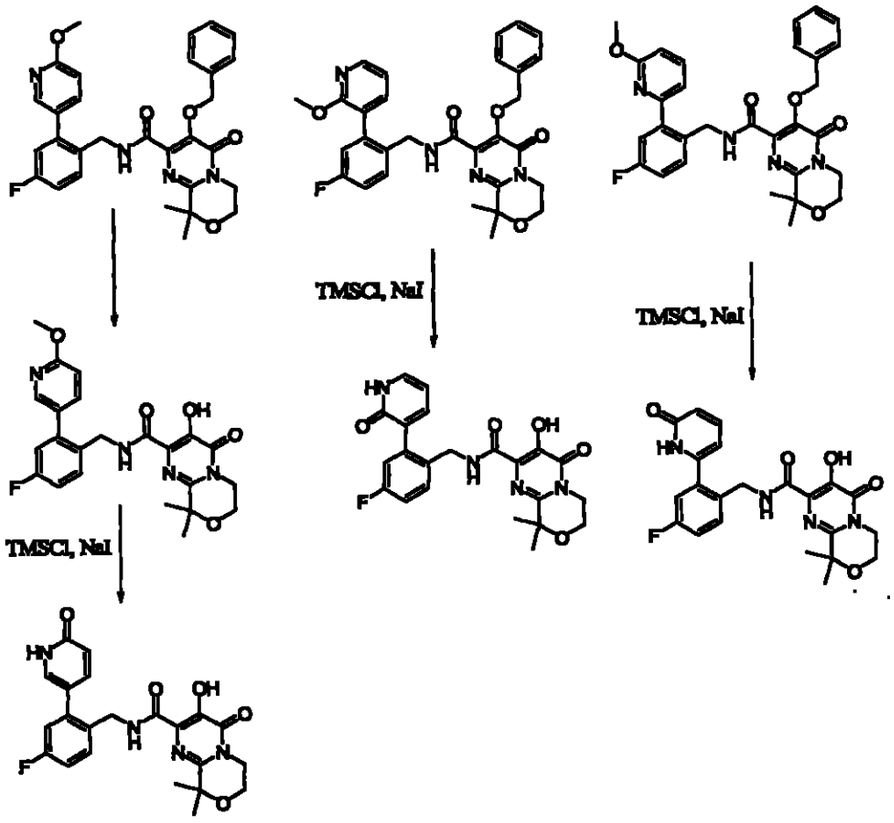
In Scheme XXVIII, compound XXVIII -1 can be converted to the corresponding methylsulfonate derivate, XXVIII -2, which can be subsequently treated with sodium azide to yield XXVIII -3. This compound in turn can serve as an intermediate for further transformation as illustrated in the scheme.

Scheme XXVIII

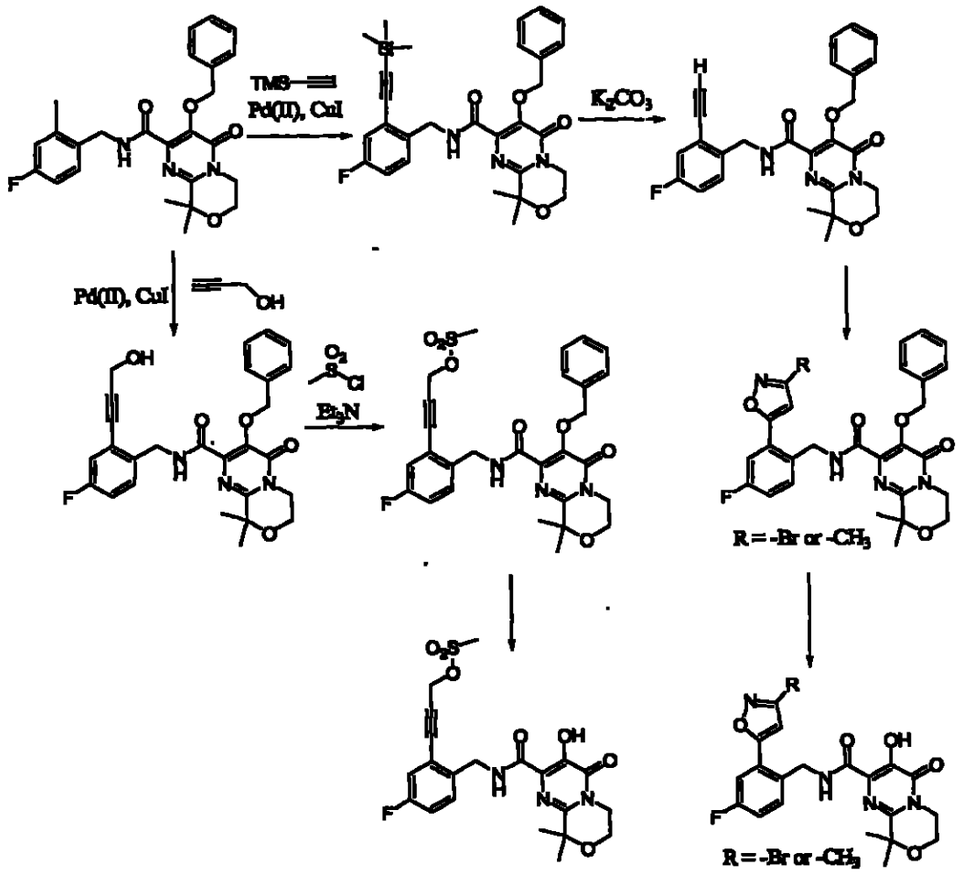


Certain examples of the current invention can be synthesized according to the methods illustrated in Schemes XXIX-XXXVIII.

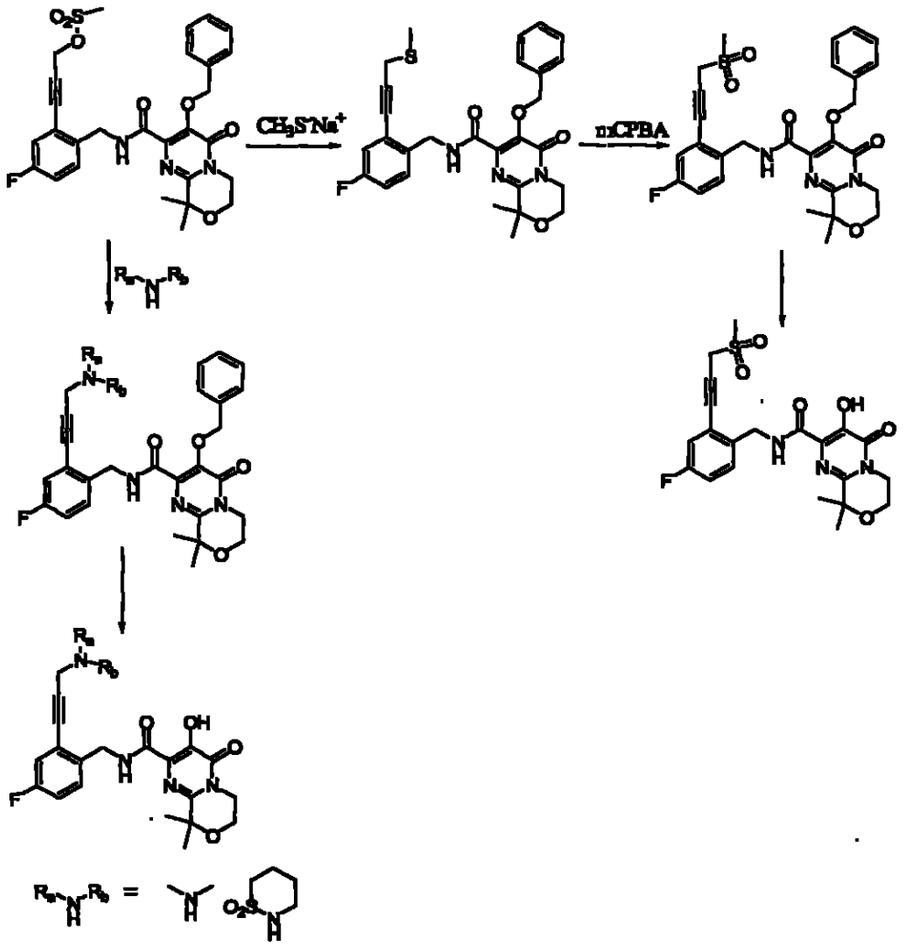
Scheme XXIX



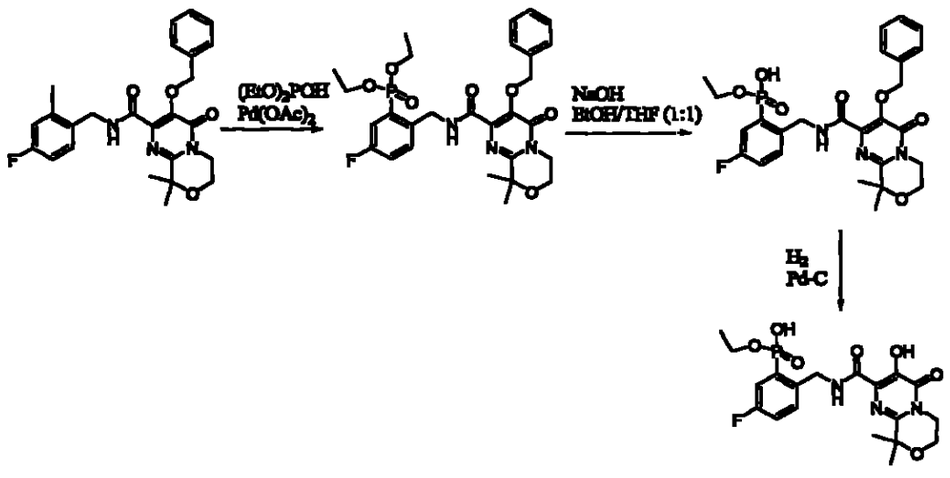
Scheme XXX



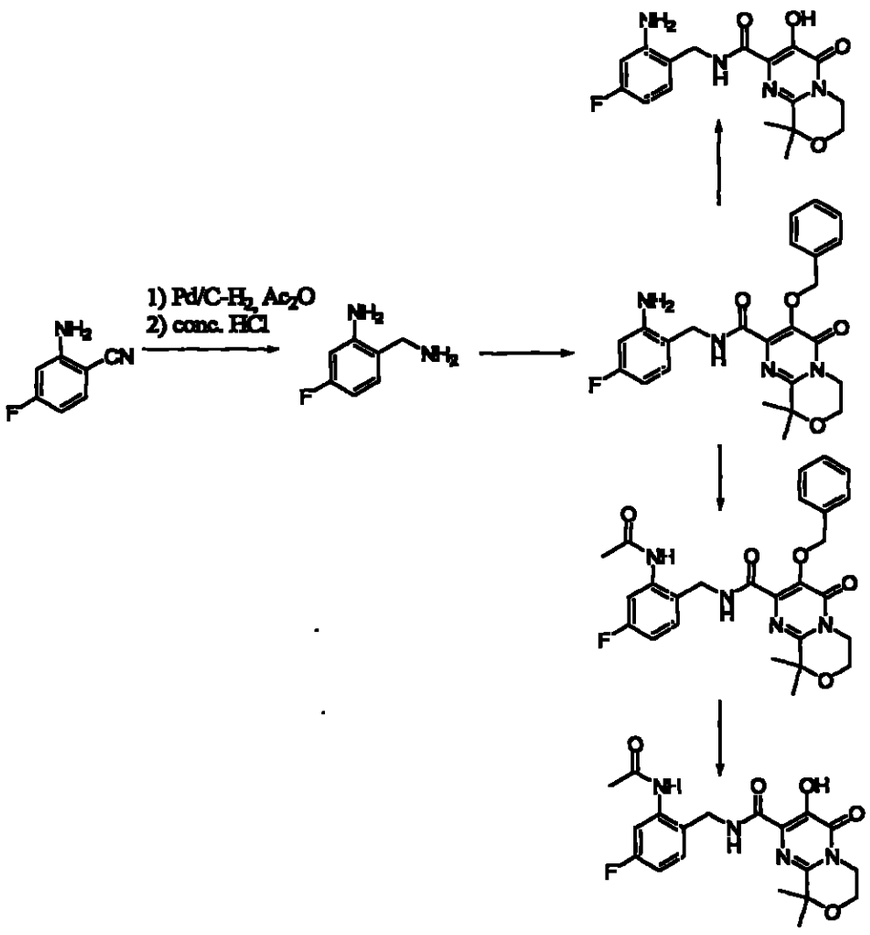
Scheme XXXI



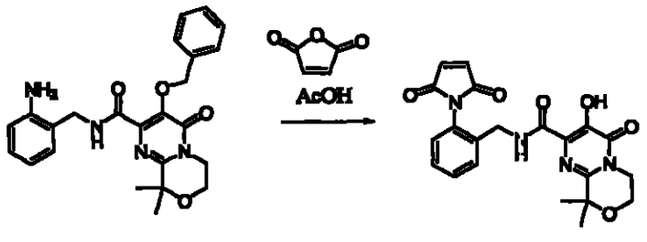
Scheme XXXII



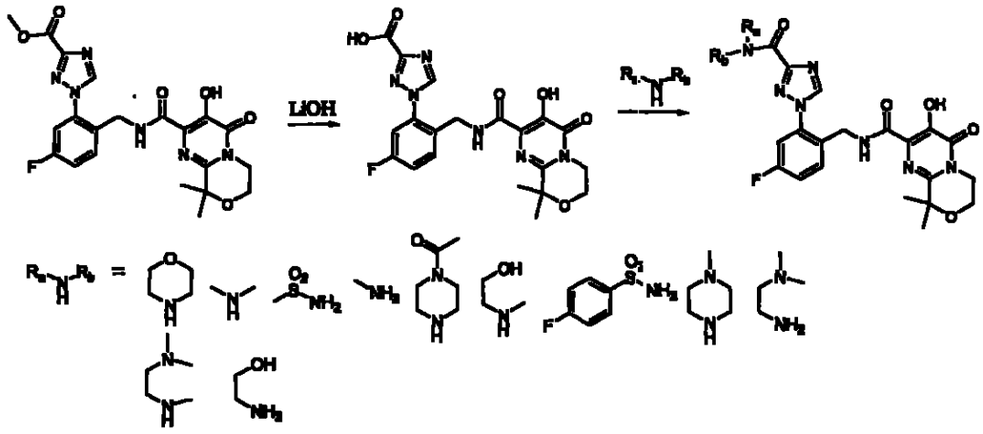
Scheme XXXIII



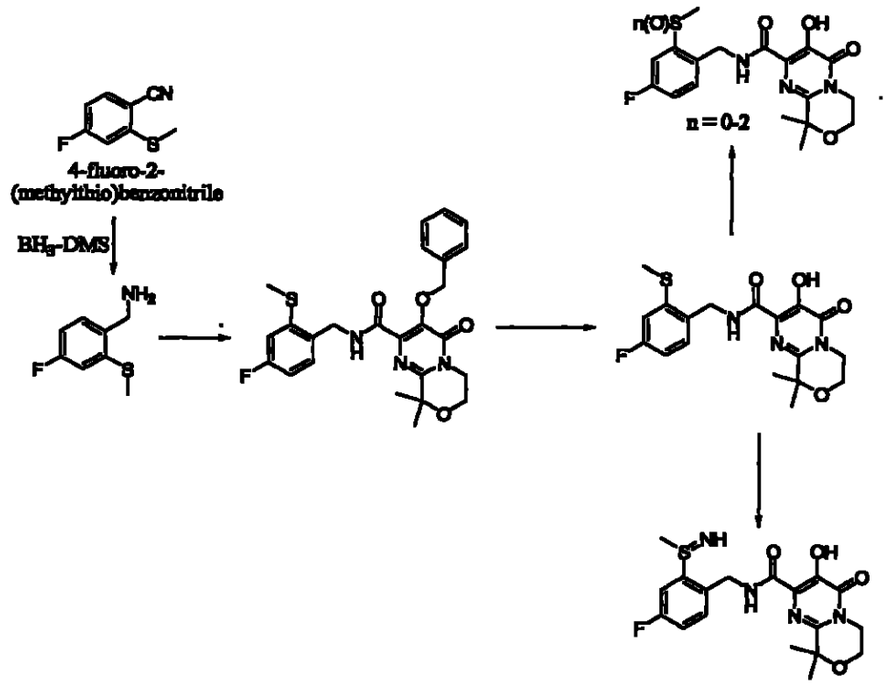
Scheme XXXIV



Scheme XXXV

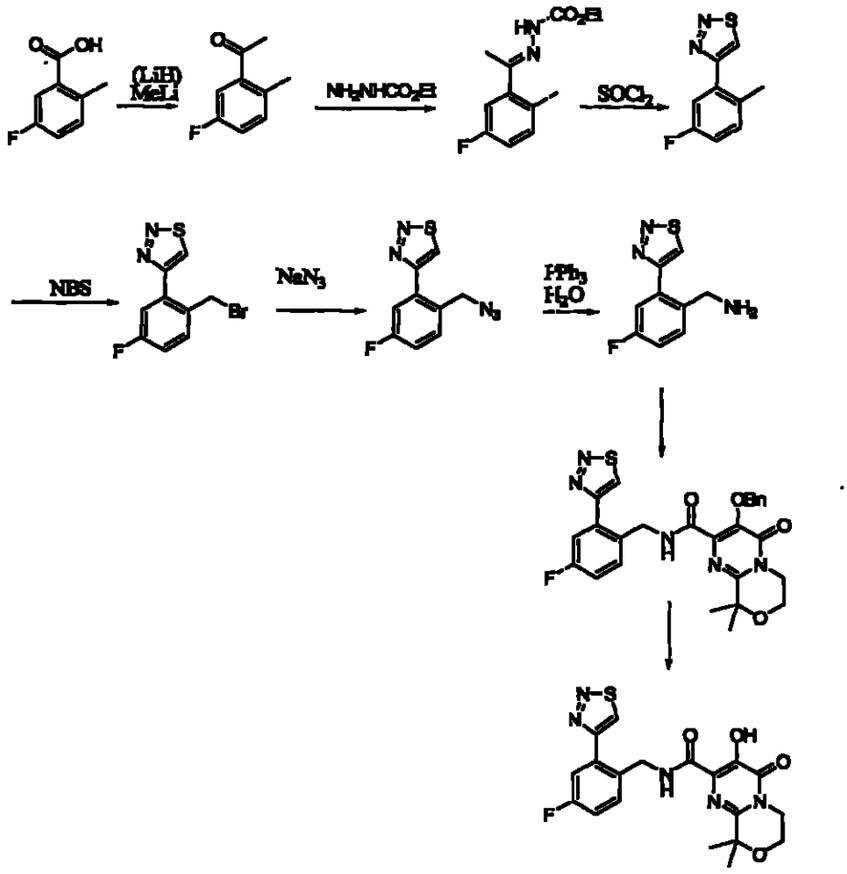


Schemes XXXVI

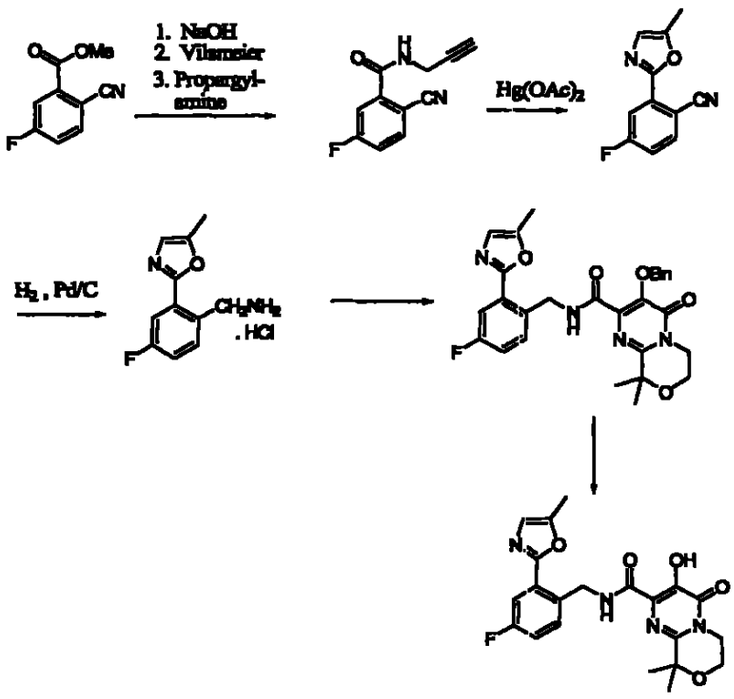


5

Scheme XXXVII



Scheme XXXVIII



Biological Methods

HIV-Integrase InhibitionActivity. To evaluate *in-vitro* activity against HIV-integrase, 5 pmole of biotin labeled substrate DNA was bound to 100 µg of Streptavidin coated PVT SPA beads (Amersham Pharmacia Biotech). Recombinant integrase (0.26 ng) was incubated with the beads for 90 min at 37 °C. Unbound enzyme was removed by washing the complex followed by addition of inhibitors and 0.1 fmol of P33 labeled target DNA. The reaction was stopped by adding EDTA to a final concentration of 10 mM. Samples were counted in TopCountNXT (Packard) and the CPM was used as a measure of integration. The reaction condition was as described in A. Engelman and R. Craigie , *J. Virol.* 69, 5908-5911 (1995). The sequences of substrate and target DNA were described in *Nucleic Acid Research* 22,1121-1122 (1994). Results are shown in the Table 1. Activity equal to A refers to a compound having IC_{50} = 0.002 to 0.10 µM while B and C denote compounds having IC_{50} = 0.1 to1.0 µM and $IC_{50} \geq 1.0$ µM respectively.

Table 1.

Example	Activity
1	A
2	A
3	A
4	A
5	A
6	A
7	A
8	A
9	A
10	A
11	A
12	A
13	A
14	A
15	A
16	A
17	A
18	A
19	A
20	A
21	A
22	B
23	A
24	B
25	B
26	A
27	A
28	A
29	A
30	A
31	A
32	A
33	A
34	A
35	A
36	A
37	A
38	A
39	A
40	A
41	A
42	A
43	A
44	A
45	A

Example	Activity
46	A
47	A
48	A
49	A
50	A
51	A
52	A
53	A
54	A
55	A
56	A
57	A
58	A
59	A
60	A
61	A
62	A
63	A
64	A
65	A
66	A
67	A
68	A
69	A
70	A
71	A
72	A
73	A
74	A
75	A
76	A
77	A
78	A
79	A
80	A
81	A
82	A
83	C
84	A
85	A
86	A
87	A
88	A
89	A
90	A
91	A

Example	Activity
92	A
93	A
94	A
95	A
96	A
97	A
98	A
99	A
100	A
101	A
102	A
103	A
104	B
105	A
106	A
107	A
108	A
109	A
110	A
111	A
112	A
113	A
114	A
115	A
116	A
117	A
118	A
119	A
120	A
121	A
122	A
123	A
124	A
125	A
126	A
127	A
128	A
129	A
130	A
131	B
132	A
133	B
134	A
135	A
136	A
137	A

Example	Activity
138	A
139	A
140	A
141	A
142	A
143	A
144	B
145	C
146	A
147	A
148	B
149	A
150	A
151	A
152	A
153	A
154	A
155	A
156	A
157	A
158	A
159	B
160	A
161	A
162	A
163	A
164	A
165	A
166	B
167	A
168	A
169	A
170	A
171	A
172	A
173	A
174	A
175	A
176	A
177	A
178	A
179	A
180	A
181	A
187	A
188	A

Example	Activity
189	A
190	A
191	A
192	A
193	A
194	A
195	A
196	A
197	A
198	A
199	A
200	A
201	A
202	A
203	A
204	A
205	A
206	A
207	A
208	A
209	A
210	A
211	A
212	A
213	A
214	C
215	A
216	A
217	A
218	A
219	A
220	A
221	A
222	A
223	A
224	A
225	A
226	A
227	A
228	A
229	A
230	A
231	A
232	A
233	A
234	A

Example	Activity
235	A
236	A
237	A
238	A
239	A
240	A
241	A
242	A
243	A
244	A
245	A
246	A
247	A
248	A
249	A
250	A
251	A
252	B
253	C
254	A
255	A
256	B
257	A
258	A
259	A
260	A
261	A
262	A
263	A
264	A
265	A
266	A
267	A
268	A
269	A
270	A
271	A
272	A
273	A
274	A
275	A
276	A
277	A
278	A
279	A
280	A

Example	Activity
281	A
282	A

Inhibition of HIV replication. A recombinant NL-Rluc virus was constructed in which a section of the nef gene from NL4-3 was replaced with the *Renilla* Luciferase gene. The NL-RLuc virus was prepared by co-transfection of two plasmids, pNLRLuc and pVSVenv. The pNLRLuc contains the NL-Rluc DNA cloned into pUC18 at the *Pvu*II site, while the pVSVenv contains the gene for VSV G protein linked to an LTR promoter. Transfections were performed at a 1:3 ratio of pNLRLuc to pVSVenv on 293T cells using the LipofectAMINE PLUS kit from Invitrogen (Carlsbad, CA) according to manufactures instruction, and the pseudotype virus generated was titered in MT-2 cells.

Susceptibility of viruses to compounds was determined by incubation in the presence of serial dilutions of the compound. The 50% effective concentration (EC_{50}) was calculated by using the exponential form of the median effect equation where $(Fa) = 1/[1+ (ED_{50}/\text{drug conc.})^{m}]$ (Johnson VA, Byington RT. Infectivity Assay. In *Techniques in HIV Research*. ed. Aldovini A, Walker BD. 71-76. New York: Stockton Press.1990). The anti-viral activity of compounds was evaluated under three serum conditions, 10% FBS, 15mg/ml human serum albumin/10% FBS or 40% human serum/5% FBS, and the results from at least 2 experiments were used to calculate the EC_{50} values. Results are shown in the Table 2. Activity equal to A refers to a compound having $EC_{50} = 0.003$ to 0.10 μM while B and C denote compounds with $EC_{50} = 0.1$ to1.0 μM and $EC_{50} \geq 1.0$ μM respectively.

Table 2.

Example	Activity
1	B
2	A
3	C
4	A
5	A
6	A
7	A

Example	Activity
8	A
9	A
10	A
11	A
12	A
13	A
14	A
15	A
16	A
17	A
18	A
19	A
20	A
21	A
22	B
23	A
24	C
25	C
26	A
27	A
28	B
29	A
30	A
31	A
32	A
33	A
34	A
35	A
36	A
37	B
38	A
39	A
40	A
41	A
42	A
43	A
44	A
45	A
46	A
47	A
48	B
49	A
50	A
51	A
52	A
53	B

Example	Activity
54	A
55	A
56	A
57	A
58	A
59	B
60	A
61	B
62	A
63	A
64	C
65	A
66	B
67	A
68	C
69	A
70	B
71	B
72	B
73	A
74	A
75	A
76	B
77	A
78	A
79	B
80	B
81	A
82	A
83	C
84	A
85	A
86	A
87	A
88	A
89	A
90	A
91	A
92	A
93	A
94	A
95	A
96	A
97	A
98	A
99	A

Example	Activity
100	A
101	A
102	A
103	B
104	B
105	A
106	A
107	A
108	A
109	A
110	A
111	A
113	A
114	A
115	A
116	A
117	A
118	A
119	A
120	A
121	A
122	A
123	A
124	A
125	A
126	A
127	A
128	A
129	A
130	A
132	A
133	B
134	A
135	A
136	A
137	B
138	A
139	A
140	A
141	C
142	B
144	C
146	A
147	B
148	B
149	B

Example	Activity
150	B
151	B
152	B
153	B
154	B
155	B
156	B
157	A
158	A
159	A
160	B
161	B
162	A
163	B
164	B
165	A
166	C
167	B
168	A
169	A
170	A
171	B
172	B
173	A
174	A
175	B
176	A
177	A
178	A
179	B
180	C
181	A
187	B
188	B
189	A
190	A
191	B
192	B
193	C
194	B
195	B
196	A
197	C
198	B
199	B
200	A

Example	Activity
201	B
202	A
203	A
204	A
205	A
206	A
207	A
208	A
209	B
210	A
211	A
212	A
213	A
214	B
215	A
216	A
217	A
218	A
219	A
220	A
221	A
222	A
223	A
224	B
225	A
226	A
227	B
228	B
229	A
230	A
231	A
232	A
233	A
234	A
235	A
236	B
237	A
238	A
239	A
240	A
241	A
242	A
243	A
244	A
245	A
246	A

Example	Activity
247	A
248	A
249	A
250	A
251	A
252	C
253	C
254	A
255	A
256	B
257	A
258	A
259	A
260	A
262	A
263	B
265	B
266	A
267	A
268	A
270	A
273	B
279	A
281	A
282	A

Combination studies

Example 19 demonstrated synergistic or additive-synergistic HIV antiviral activity when used in conjunction with a variety of other antiviral agents, as described below.

Virus and cell lines. The T-cell line, MT-2, was obtained through the AIDS Research and Reference Reagent Program. MT-2 cells were sub-cultured twice a week in RPMI 1640 medium supplemented with 10% fetal bovine serum, 2 mM L-glutamine, and 10 mM HEPES buffer pH 7.5. The HIV-1 303B virus is a molecular clone derived from the NL4-3 strain of HIV-1 that was obtained from the NIH AIDS Research and Reference Reagent Program. For combinations with enfuvirtide, the NL36G virus was used. This NL4-3 derivative has the naturally occurring enfuvirtide resistance mutation in gp41 (36D) changed to a sensitive phenotype

(D36G). Virus stocks were made by transfecting 293T cells with a proviral DNA clone using LipofectAMINE PLUS (Invitrogen), according to the manufacturer's instructions. Three days post-transfection, virus was harvested and passaged once in MT-2 cells before titration in MT-2 cells.

Chemicals. Example 19, atazanavir, didanosine, stavudine, efavirenz, and enfuvirtide (T-20) were synthesized by Bristol-Myers Squibb using published or known reactions. Amprenavir, indinavir, nelfinavir, nevirapine, lopinavir, lamivudine, ritonavir, tenofovir, saquinavir, delavirdine and abacavir were extracted from commercial formulations of the prescribed drugs and purified using published or common techniques. Tenofovir was tested as tenofovir disopoxil fumerate. Zidovudine and zalcitabine were purchased from Sigma, and emtricitabine from Moravek Biochemicals.

Drug Susceptibility and Cytotoxicity Assays. For drug susceptibility assays, MT-2 cells were infected with HIV-1 303B (or NL36G), at an MOI of 0.001, and seeded into 96-well microtiter plates (2.5×10^5 cells/ml) containing serial dilutions of test compounds. The drug combinations were set up using ratios of the two drugs of 1:1, 1:2.5 and 2.5:1 times the EC_{50} value determined for each drug in prior experiments. Each drug ratio consisted of an array of 3-fold serial dilutions, and was performed with eight or more replicas on separate multi-well plates. HIV infected cells were incubated at 37°C in 5% CO_2, and on day five post-infection, the extent of virus replication was measured by determining cell viability using the CellTiter 96 Aqueous Non-Radioactive Cell Proliferation Assay (Promega). Maximal cell protection was typically seen in samples treated with the highest drug concentration. In the cell viability assay, the tetrazolium compound MTS (3-(4,5-dimethylthiazol-2-yl)-5-(3-carboxymethoxyphenyl)-2-4-sulphophenyl-2H-tetrazolium) is added to cells, whereby enzymes in metabolically active cells convert it into a colored formazan product, which is quantitated by reading absorbance at 490nm. Cytotoxicity assays were performed in parallel with the combination experiments. Here, uninfected cells were exposed to the same drug combinations, and assayed after five days for cell viability using the MTS assay.

Analysis of Drug Combination Effects. For determination of combination index (CI) values, drugs were diluted in a fixed ratio and multiple ratios were analyzed. The drug serial dilutions spanned a range of concentrations near the EC_{50} value of each compound, so that equivalent antiviral activities could be compared. The normalized responses from each therapy are fit to the four-parameter logistic model with a common minimum and maximum across all therapies. Conceptually, this equation can be written as

$$Fa_i = A + \frac{D - A}{1 + \left(\frac{C_1^{I_1} C_2^{I_2} C_3^{I_3} C_4^{I_4} C_5^{I_5}}{\text{concentration}_i}\right)^{B_1^{I_1} B_2^{I_2} B_3^{I_3} B_4^{I_4} B_5^{I_5}}},$$

$$\text{where } I_j = \begin{cases} 1 & \text{if therapy} = j \\ 0 & \text{otherwise} \end{cases}$$

for j=1, 2, 3, 4, or 5.

In this equation, Fa stands for "fraction affected," and represents the fraction of the viral load that has been inactivated. For example, Fa of 0.75 indicates that viral replication had been inhibited by 75%, relative to the no-drug controls. The EC_{50}, represented by the C_i in the above equation, is the drug concentration that is expected to reduce the amount of virus by 50%, and the B_i are the parameters that reflects the slope of the concentration-response curve. For this assay, A is the bottom plateau common to all curves, D is the common top plateau, B_j is the "slope" parameter for the jth therapy, and C_j is the concentration that produces an effect equal to the average of A and D for the jth therapy. Therapies 1 and 2 correspond to mono therapies 1 and 2, respectively. Therapies 3, 4, and 5 correspond to the three combination therapies. EC_{50} values for each drug were determined from the single drug experiments, using the above equation. The equation was fit using a nonlinear regression routine (Proc Nlin) in PC SAS version 8.2 (SAS Institute Inc.).

To assess antiviral effects of different drug combination treatments, combination indices (CIs) were calculated according to Chou and Rideout. The combination index was computed as

$$CI = \frac{[D]_1}{[Dm]_1} + \frac{[D]_2}{[Dm]_2}$$

In this equation $[Dm]_1$ and $[Dm]_2$ are the concentrations of drugs that would individually produce a specific level of effect, while $[D]_1$ and $[D]_2$ are the concentrations of drugs in combination that would produce the same level of effect.

Theoretically, additivity is implied if the CI is equal to one, synergy if the CI is less than one, and antagonism if the CI is greater than one. However, extensive experience with combination studies indicates that there are inherent laboratory variables that must be taken into account in interpreting the CIs. At best, a range can be constructed that contains the likely values for the CI, given the noise in the data. In this report, these ranges are reported in parentheses next to each point estimate of the CI. For example, when a CI of "0.52 (0.36, 0.69)" is reported this means that the best estimate of the CI is 0.52, but due to noise in the data, values from 0.36 to 0.69 are also reasonable values for the CI. This range, 0.36 to 0.69 falls entirely below the value of 1.0, and hence all likely values for the CI are less than 1.0. Therefore, synergistic behavior can be inferred for this combination. If the range fell entirely above 1.0, we would infer antagonistic behavior. If the range were to include 1.0, we would infer additivity.

In carrying out the combination experiments, the EC_{50} for Example 19 and each comparator compound was determined during the course of each study, and used in the subsequent data analysis. The determined values are consistent with previously published data and are shown in Table 3.

Table 3. Anti-HIV Activity of Compounds in Two-Drug Combination Studies

Compound	EC_{50} (μM)	Highest Drug Concentration (μM)
Example19	0.022	2.5
Zidovudine	0.012	2.5
Didanosine	10.7	100

Compound	EC_{50} (μM)	Highest Drug Concentration (μM)
Stavudine	0.241	15
Lamivudine	0.203	15
Abacavir	1.04	30
Tenofovir	0.018	2.5
Emtricitabine	0.053	20
Zalcitabine	0.124	10
Efavirenz	0.0016	0.2
Nevirapine	0.095	5
Delavirdine	0.043	5
Ritonavir	0.048	2.5
Indinavir	0.026	2.5
Nelfinavir	0.022	2.5
Saquinavir	0.011	2.5
Amprenavir	0.062	2.5
Atazanavir	0.010	1
Lopinavir	0.017	2.5
Enfuvirtide	0.061	2.2

Two-Drug Combinations of Example 19 with Nucleoside Reverse Transcriptase Inhibitors. Eight nucleoside RT inhibitors (didanosine, stavudine, zidovudine, lamivudine, abacavir, zalcitabine, emtricitibine and the nucleoside phosphonate, tenofovir) were combined with Example 19 at a range of concentrations near the EC_{50} value of each compound, so that equivalent antiviral activities could be compared. All estimates were computed using SAS Proc NLIN, and a two-parameter logistic. Data is presented in Table 4 as the combination indices and the asymptotic confidence intervals for RT inhibitors at different molar ratios.

Four nucleoside RT inhibitors; didanosine, stavudine, abacavir and emtricitibine, show synergistic antiviral effects in combination with Example 19 at all effective levels and all molar ratios. The other four RT inhibitors: zidovudine,

lamivudine, tenofovir and zalcitabine all have combination indices suggestive of synergistic behavior with Example 19. However, the upper ranges of the confidence intervals for some of the effective levels are greater than 1, so the overall effects of these compounds with Example 19 are classified as synergistic to additive. No significant antagonism of anti-HIV activity is observed. No enhanced cytotoxicity was encountered at the highest concentrations tested with any of the drug combinations, as measured by the XTT reduction assay.

Table 4. Two-Drug Combinations using Example 19 and Nucleoside Reverse Transcriptase Inhibitors.

Molar Ratio (EC_{50} Ratio)[a]	Combination Indices at % HIV Inhibition[b] (Confidence Interval)		
	50%	75%	90%
Zidovudine			
1:1 (1:1)	0.59 (0.49, 0.69)	0.56 (0.41, 0.70)	0.54 (0.36, 0.70)
2:5 (1:2.5)	0.65 (0.56, 0.75)	0.73 (0.59, 0.86)	0.81 (0.57, 1.06)
5:2 (2.5:1)	0.72 (0.61, 0.83)	0.83 (0.64, 1.02)	0.96 (0.63, 1.30)
Didanosine			
1:1000 (1:1)	0.58 (0.53, 0.63)	0.47 (0.35, 0.60)	0.39 (0.22, 0.56)
1:2500 (1:2.5)	0.56 (0.51, 0.62)	0.46 (0.40, 0.52)	0.38 (0.32, 0.44)
1:400 (2.5:1)	0.50 (0.46, 0.54)	0.49 (0.44, 0.53)	0.48 (0.42, 0.54)
Stavudine			
1:6 (1:1)	0.52 (0.43, 0.61)	0.46 (0.36, 0.56)	0.42 (0.26, 0.57)
1:15 (1:2.5)	0.60 (0.48, 0.71)	0.60 (0.46, 0.74)	0.61 (0.40, 0.83)
5:12 (2.5:1)	0.70 (0.57, 0.84)	0.63 (0.48, 0.79)	0.58 (0.37, 0.81)
Lamivudine			
1:6 (1:1)	0.80 (0.63, 0.98)	0.80 (0.55, 1.05)	0.81 (0.42, 1.21)
1:15 (1:2.5)	1.09 (0.88, 1.31)	1.00 (0.72, 1.27)	0.92 (0.52, 1.33)
5:12 (2.5:1)	0.94 (0.80, 1.08)	0.84 (0.65, 1.03)	0.75 (0.49, 1.02)
Abacavir			
1:30 (1:1)	0.68 (0.59, 0.76)	0.67 (0.56, 0.79)	0.67 (0.49, 0.84)
1:75 (1:2.5)	0.87 (0.77, 0.97)	0.74 (0.63, 0.85)	0.63 (0.50, 0.77)
1:12 (2.5:1)	0.86 (0.76, 0.96)	0.82 (0.68, 0.96)	0.79 (0.58, 0.99)
Tenofovir			
1:1 (1:1)	0.66 (0.57, 0.75)	0.54 (0.45, 0.62)	0.43 (0.33, 0.53)
2:5 (1:2.5)	0.68 (0.59, 0.77)	0.60 (0.48, 0.72)	0.52 (0.36, 0.69)
5:2 (2.5:1)	0.90 (0.77, 1.04)	0.84 (0.67, 1.01)	0.79 (0.55, 1.03)

Molar Ratio (EC_{50} Ratio)[a]	Combination Indices at % HIV Inhibition[b] (Confidence Interval)		
	50%	75%	90%
Zalcitabine			
1:4 (1:1)	0.61 (0.48, 0.73)	0.56 (0.39, 0.73)	0.53 (0.28, 0.79)
1:10 (1:2.5)	0.55 (0.44, 0.66)	0.40 (0.31, 0.49)	0.30 (0.18, 0.42)
5:8 (2.5:1)	0.80 (0.62, 0.97)	0.82 (0.58, 1.07)	0.86 (0.46, 1.26)
Emtricitabine			
1:8 (1:1)	0.31 (0.27, 0.36)	0.23 (0.18, 0.28)	0.18 (0.12, 0.24)
1:20 (1:2.5)	0.31 (0.26, 0.37)	0.23 (0.19, 0.29)	0.17 (0.12, 0.28)
5:16 (2.5:1)	0.33 (0.28, 0.38)	0.25 (0.20, 0.30)	0.19 (0.13, 0.25)

a Ratio of Example 19 to comparator compound

b A lower bound of the asymptotic confidence interval greater than 1 indicates antagonisms, an upper bound of less than 1 indicates synergism and a value of 1 being contained in the interval indicates additivity. The 95% confidence intervals are shown in parentheses, and represent a measure of variability in the data.

Two-Drug Combinations of Example 19 with Non-Nucleoside Reverse Transcriptase Inhibitors. Three non-nucleoside RT inhibitors were combined with Example 19 at a range of concentrations near the EC_{50} value of each compound, as described above for nucleoside RT inhibitors. Data is presented in Table 5 as the combination indices and the asymptotic confidence intervals at different molar ratios. Of the three, nevaripine shows strong synergistic effects in combination with Example 19. Synergy is seen at all effective concentrations and at all molar ratios. Sustiva and nevirapine also exhibit combination indices indicative of synergism at most effective concentrations and molar ratios. However, in some cases, the upper range of the asymptotic confidence interval is greater than 1, so an additive effect can not be ruled out. No enhanced cytotoxicity was observed at the highest concentrations tested with any of the drug combinations, suggesting a potential for therapeutic efficacy of Example 19 combinations with non-nucleoside RT inhibitors.

Table 5. Two-Drug Combinations using Example 19 and Non-Nucleoside Reverse Transcriptase Inhibitors.

Molar Ratio (EC_{50} Ratio)[a]	Combination Indices at % HIV Inhibition[b] (Confidence Interval)		
	50%	75%	90%
Efavirenz			
5:2 (1:1)	0.83 (0.75, 0.92)	0.76 (0.64, 0.88)	0.70 (0.54, 0.85)
1:1 (1:2.5)	0.95 (0.86, 1.04)	0.93 (0.85, 1.02)	0.93 (0.79, 1.06)
25:4 (2.5:1)	1.01 (0.92, 1.10)	0.96 (0.83, 1.10)	0.94 (0.73, 1.14)
Nevirapine			
1:2 (1:1)	0.72 (0.62, 0.82)	0.69 (0.55, 0.83)	0.66 (0.46, 0.87)
1:5 (1:2.5)	0.76 (0.64, 0.87)	0.81 (0.64, 0.97)	0.87 (0.59, 1.15)
5:4 (2.5:1)	0.73 (0.62, 0.83)	0.68 (0.55, 0.81)	0.64 (0.45, 0.84)
Delavirdine			
1:2 (1:1)	0.76 (0.64, 0.89)	0.60 (0.47, 0.74)	0.48 (0.31, 0.64)
1:5 (1:2.5)	0.68 (0.58, 0.77)	0.44 (0.32, 0.54)	0.28 (0.17, 0.39)
5:4 (2.5:1)	0.80 (0.68, 0.92)	0.53 (0.42, 0.63)	0.35 (0.25, 0.45)

a Ratio of Example 19 to comparator compound.

b A lower bound of the asymptotic confidence interval greater than 1 indicates antagonism, an upper bound of less than 1 indicates synergism, and a value of 1 being contained in the interval indicates additivity. The 95% confidence intervals are shown in parenthesis, and represent a measure of variability in the data.

Two-Drug Combinations Involving Example 19 and HIV Protease Inhibitors. Evaluation of Example 19 for drug combination therapy with protease inhibitors was carried out using indinavir, amprenavir, nelfinavir, lopinavir, saquinavir, ritonavir and atazanavir. Results from this two-drug combination study are summarized in Table 6. Again, the combination indices observed with Example 19 and all protease inhibitors at almost all effective levels and molar ratios are suggestive of a synergistic relationship. This is especially true for saquinavir and atazanavir, where the confidence interval is below one at all concentrations and effective levels. Meanwhile, the upper range of the confidence interval is greater than one in only one condition for ritonavir, indinavir and lopinavir, so an additive relationship with Example 19 cannot be ruled out. In addition, the upper range of the confidence interval for nelfinavir and amprenavir are slightly greater than 1 under a few conditions, suggestive of a synergistic-additive effect for these compounds with Example 19. No cytotoxicity was observed at the highest concentrations used in any of these combination antiviral assays.

Table 6. Two-Drug Combination using Example 19 and Protease Inhibitors.

Molar Ratio (EC_{50} Ratio)[a]	Combination Indices at % HIV Inhibition[b] (Confidence Interval)		
	50%	75%	90%
Indinavir			
1:1 (1:1)	0.86 (0.80, 0.92)	0.71 (0.62, 0.81)	0.60 (0.46, 0.73)
2:5 (1:2.5)	0.92 (0.84, 0.99)	0.84 (0.76, 0.92)	0.77 (0.66, 0.89)
5:2 (2.5:1)	0.94 (0.87, 1.02)	0.79 (0.71, 0.87)	0.67 (0.57, 0.77)
Nelfinavir			
1:1 (1:1)	0.79 (0.73, 0.86)	0.75 (0.67, 0.82)	0.71 (0.56, 0.84)
2:5 (1:2.5)	0.97 (0.89, 1.06)	0.87 (0.79, 0.95)	0.78 (0.68, 0.88)
5:2 (2.5:1)	1.09 (1.00, 1.18)	0.98 (0.89, 1.08)	0.90 (0.76, 1.03)
Saquinavir			
1:1 (1:1)	0.77 (0.70, 0.84)	0.67 (0.58, 0.75)	0.58 (0.47, 0.69)
2:5 (1:2.5)	0.43 (0.38, 0.48)	0.51 (0.42, 0.59)	0.59 (0.44, 0.74)
5:2 (2.5:1)	0.81 (0.72, 0.89)	0.77 (0.66, 0.89)	0.74 (0.57, 0.91)
Amprenavir			
1:1 (1:1)	0.83 (0.67, 1.00)	0.84 (0.61, 1.08)	0.89 (0.50, 1.23)
2:5 (1:2.5)	0.84 (0.69, 0.99)	0.77 (0.58, 0.96)	0.75 (0.46, 1.04)
5:2 (2.5:1)	0.90 (0.77, 1.04)	0.62 (0.50, 0.74)	0.44 (0.30, 0.57)
Atazanavir			
5:2 (1:1)	0.87 (0.79, 0.96)	0.67 (0.55, 0.80)	0.52 (0.37, 0.67)
1:1 (1:2.5)	0.65 (0.51, 0.78)	0.45 (0.31, 0.58)	0.31 (0.19, 0.44)
25:4 (2.5:1)	0.78 (0.69, 0.86)	0.60 (0.54, 0.67)	0.47 (0.40, 0.54)
Lopinavir			
1:1 (1:1)	0.74 (0.67, 0.82)	0.77 (0.66, 0.88)	0.84 (0.65, 1.02)
2:5 (1:2.5)	0.77 (0.66, 0.88)	0.56 (0.36, 0.75)	0.41 (0.19, 0.64)
5:2 (2.5:1)	0.76 (0.69, 0.83)	0.62 (0.55, 0.70)	0.54 (0.47, 0.61)
Ritonavir			
1:1 (1:1)	0.80 (0.67, 0.93)	0.57 (0.41, 0.73)	0.44 (0.23, 0.65)
2:5 (1:2.5)	0.73 (0.59, 0.88)	0.64 (0.48, 0.80)	0.61 (0.38, 0.85)
5:2 (2.5:1)	0.92 (0.72, 1.11)	0.72 (0.50, 0.93)	0.59 (0.32, 0.87)

a Ratio of Example 19 to comparator compound.

b A lower bound of the asymptotic confidence interval greater than 1 indicates antagonism, an upper bound of less than 1 indicates synergism, and a value of 1 being contained in the interval indicates additivity. The 95% confidence intervals are shown in parenthesis, and represent a measure of variability in the data.

Two-Drug Combination of Example 19 with Enfuvirtide. Enfuvirtide (T-20) is an HIV gp41 fusion inhibitor and the first approved entry class inhibitor. The results presented in Table 7 indicate that the combination of Example 19 with T-20 is synergistic. No significant cytotoxicity was observed at the highest concentration of the combined drugs.

Table 7. Two-Drug Combination study of Example 19 with Enfuvirtide.

Molar Ratio (EC_{50} Ratio)[a]	Combination Indices at % HIV Inhibition[b] (Confidence Interval)		
	50%	75%	90%
Enfuvirtide			
5:44 (1:1)	0.68 (0.59, 0.77)	0.59 (0.48, 0.70)	0.52 (0.37, 0.67)
1:22 (1:2.5)	0.75 (0.65, 0.85)	0.60 (0.49, 0.70)	0.48 (0.34, 0.61)
25:88 (2.5:1)	0.76 (0.65, 0.86)	0.73 (0.59, 0.86)	0.71 (0.50, 0.92)

a Ratio of Example 19 to comparator compound.

b A lower bound of the asymptotic confidence interval greater than 1 indicates antagonism, an upper bound of less than 1 indicates synergism, and a value of 1 being contained in the interval indicates additivity. The 95% confidence intervals are shown in parenthesis, and represent a measure of variability in the data.

Pharmaceutical Composition and Methods of Use

The compounds of this invention inhibit HIV integrase. HIV integrase inhibitors belonging to a class of diketo acid compounds prevented viral integration and inhibited HIV-1 replication in cells (Hazuda et al. *Science* **2000**, *287*, 646). Recently, HIV integrase inhibitors have been accepted into clinical trials for treating AIDS and HIV infection (Neamati *Expert. Opin. Ther. Patents* **2002**, *12*, 709, Pais and Burke *Drugs Fut.* **2002**, *27*, 1101).

Accordingly, another aspect of the invention is a method for treating HIV infection in a human patient comprising administering a therapeutically effective amount of a compound of Formula I, or a pharmaceutically acceptable salt or solvate thereof, with a pharmaceutically acceptable carrier.

Another aspect of the invention is a method for treating HIV infection in a human patient comprising the administration of a therapeutically effective amount of a compound of Formula I, or a pharmaceutically acceptable salt or solvate thereof, with a therapeutically effective amount of at least one other agent used for treatment of AIDS or HIV infection selected from the group consisting of nucleoside HIV reverse transcriptase inhibitors, non-nucleoside HIV reverse transcriptase inhibitors, HIV protease inhibitors, HIV fusion inhibitors, HIV attachment inhibitors, CCR5 inhibitors, CXCR4 inhibitors, HIV budding or maturation inhibitors, and HIV integrase inhibitors.

Another aspect of the invention is a method wherein the agent is a nucleoside HIV reverse transcriptase inhibitor.

Another aspect of the invention is a method wherein the nucleoside HIV reverse transcriptase inhibitor is selected from the group consisting of abacavir, didanosine, emtricitabine, lamivudine, stavudine, tenofovir, zalcitabine, and zidovudine, or a pharmaceutically acceptable salt or solvate thereof.

Another aspect of the invention is a method wherein the agent is a non-nucleoside HIV reverse transcriptase inhibitor.

Another aspect of the invention is a method wherein the non-nucleoside HIV reverse transcriptase inhibitor is selected from the group consisting of delavirdine, efavirenz, and nevirapine, or a pharmaceutically acceptable salt or solvate thereof.

Another aspect of the invention is a method wherein the agent is an HIV protease inhibitor.

Another aspect of the invention is a method wherein the HIV protease inhibitor is selected from the group consisting of amprenavir, atazanavir, indinavir, lopinavir, nelfinavir, ritonavir, saquinavir and fosamprenavir, or a pharmaceutically acceptable salt or solvate thereof.

Another aspect of the invention is a method wherein the agent is an HIV fusion inhibitor.

Another aspect of the invention is a method wherein the HIV fusion inhibitor is enfuvirtide or T-1249, or a pharmaceutically acceptable salt or solvate thereof.

Another aspect of the invention is a method wherein the agent is an HIV attachment inhibitor.

Another aspect of the invention is a method wherein the agent is a CCR5 inhibitor.

Another aspect of the invention is a method wherein the CCR5 inhibitor is selected from the group consisting of Sch-C, Sch-D, TAK-220, PRO-140, and UK-427,857, or a pharmaceutically acceptable salt or solvate thereof.

Another aspect of the invention is a method wherein the agent is a CXCR4 inhibitor.

Another aspect of the invention is a method wherein the CXCR4 inhibitor is AMD-3100, or a pharmaceutically acceptable salt or solvate thereof.

Another aspect of the invention is a method wherein the agent is an HIV budding or maturation inhibitor.

Another aspect of the invention is a method wherein the budding or maturation inhibitor is PA-457, or a pharmaceutically acceptable salt, or solvate thereof.

Another aspect of the invention is a method wherein the agent is an HIV integrase inhibitor.

Another aspect of the invention is a pharmaceutical composition comprising a therapeutically effective amount of a compound of Formula I, or a pharmaceutically acceptable salt or solvate thereof, with at least one other agent used for treatment of AIDS or HIV infection selected from the group consisting of nucleoside HIV reverse transcriptase inhibitors, non-nucleoside HIV reverse transcriptase inhibitors, HIV protease inhibitors, HIV fusion inhibitors, HIV attachment inhibitors, CCR5 inhibitors, CXCR4 inhibitors, HIV budding or maturation inhibitors, and HIV integrase inhibitors, and a pharmaceutically acceptable carrier.

Another aspect of the invention is the composition wherein the agent is a nucleoside HIV reverse transcriptase inhibitor.

Another aspect of the invention is the composition wherein the nucleoside HIV transcriptase inhibitor is selected from the group consisting of abacavir, didanosine, emtricitabine, lamivudine, stavudine, tenofovir, zalcitabine, and zidovudine, or a pharmaceutically acceptable salt or solvate thereof.

Another aspect of the invention is the composition wherein the agent is a non-nucleoside HIV reverse transcriptase inhibitor.

Another aspect of the invention is the composition wherein the non-nucleoside HIV reverse transcriptase inhibitor is selected from the group consisting of delavirdine, efavirenz, and nevirapine, or a pharmaceutically acceptable salt or solvate thereof.

Another aspect of the invention is the composition wherein the agent is an HIV protease inhibitor.

Another aspect of the invention is the composition wherein the HIV protease inhibitor is selected from the group consisting of amprenavir, atazanavir, indinavir, lopinavir, nelfinavir, ritonavir, saquinavir and fosamprenavir, or a pharmaceutically acceptable salt or solvate thereof.

Another aspect of the invention is the composition wherein the agent is an HIV fusion inhibitor.

Another aspect of the invention is the composition method wherein the HIV fusion inhibitor is enfuvirtide or T-1249, or a pharmaceutically acceptable salt or solvate thereof.

Another aspect of the invention is the composition wherein the agent is an HIV attachment inhibitor.

Another aspect of the invention is the composition wherein the agent is a CCR5 inhibitor.

Another aspect of the invention is the composition wherein the CCR5 inhibitor is selected from the group consisting of Sch-C, Sch-D, TAK-220, PRO-140, and UK-427,857, or a pharmaceutically acceptable salt or solvate thereof.

Another aspect of the invention is a method wherein the agent is a CXCR4 inhibitor.

Another aspect of the invention is a method wherein the CXCR4 inhibitor is AMD-3100 or a pharmaceutically acceptable salt or solvate thereof.

Another aspect of the invention is the composition wherein the agent is an HIV budding or maturation inhibitor.

Another aspect of the invention is the composition wherein the budding or maturation inhibitor is PA-457, or a pharmaceutically acceptable salt or solvate thereof.

Another aspect of the invention is the composition wherein the agent is an HIV integrase inhibitor.

"Combination," "coadministration," "concurrent," and similar terms referring to the administration of a compound of Formula I with at least one anti-HIV agent mean that the components are part of a combination antiretroviral therapy or highly active antiretroviral therapy (HAART) as understood by practitioners in the field of AIDS and HIV infection.

"*Therapeutically effective*" *means the amount of agent required to provide a* meaningful patient benefit as understood by practitioners in the field of AIDS and HIV infection. In general, the goals of treatment are suppression of viral load,

restoration and preservation of immunologic function, improved quality of life, and reduction of HIV-related morbidity and mortality.

"Patient" means a person infected with the HIV virus and suitable for therapy as understood by practitioners in the field of AIDS and HIV infection.

"Treatment," "therapy," "regimen," "HIV infection," "ARC," "AIDS" and related terms are used as understood by practitioners in the field of AIDS and HIV infection.

The compounds of this invention are generally given as pharmaceutical compositions comprised of a therapeutically effective amount of a compound of Formula I or its pharmaceutically acceptable salt and a pharmaceutically acceptable carrier and may contain conventional excipients. A therapeutically effective amount is that which is needed to provide a meaningful patient benefit. Pharmaceutically acceptable carriers are those conventionally known carriers having acceptable safety profiles. Compositions encompass all common solid and liquid forms including capsules, tablets, losenges, and powders as well as liquid suspensions, syrups, elixers, and solutions. Compositions are made using common formulation techniques, and conventional excipients (such as binding and wetting agents) and vehicles (such as water and alcohols) are generally used for compositions.

Solid compositions are normally formulated in dosage units and compositions providing from about 1 to 1000 mg of the active ingredient per dose are preferred. Some examples of dosages are 1 mg, 10 mg, 100 mg, 250 mg, 500 mg, and 1000 mg. Generally, other antiretroviral agents will be present in a unit range similar to agents of that class used clinically. Typically, this is 0.25-1000 mg/unit.

Liquid compositions are usually in dosage unit ranges. Generally, the liquid composition will be in a unit dosage range of 1-100 mg/mL. Some examples of dosages are 1 mg/mL, 10 mg/mL, 25 mg/mL, 50 mg/mL, and 100 mg/mL. Generally, other antiretroviral agents will be present in a unit range similar to agents of that class used clinically. Typically, this is 1-100 mg/mL.

The invention encompasses all conventional modes of administration; oral and parenteral methods are preferred. Generally, the dosing regimen will be similar to other antiretroviral agents used clinically. Typically, the daily dose will be 1-100 mg/kg body weight daily. Generally, more compound is required orally and less parenterally. The specific dosing regime, however, will be determined by a physician using sound medical judgement.

The invention also encompasses methods where the compound is given in combination therapy. That is, the compound can be used in conjunction with, but separately from, other agents useful in treating AIDS and HIV infection. Some of these agents include HIV attachment inhibitors, CCR5 inhibitors, CXCR4 inhibitors, HIV cell fusion inhibitors, HIV integrase inhibitors, HIV nucleoside reverse transcriptase inhibitors, HIV non-nucleoside reverse transcriptase inhibitors, HIV protease inhibitors, budding and maturation inhibitors, immunomodulators, and anti-infectives. In these combination methods, the compound of Formula I will generally be given in a daily dose of 1-100 mg/kg body weight daily in conjunction with other agents. The other agents generally will be given in the amounts used therapeutically. The specific dosing regime, however, will be determined by a physician using sound medical judgement.

Table 8 lists some agents useful in treating AIDS and HIV infection which are suitable for this invention.

Table 8. ANTIVIRALS

DRUG NAME	MANUFACTURER	INDICATION
097 (non-nucleoside reverse transcriptase inhibitor)	Hoechst/Bayer	HIV infection, AIDS, ARC
Amprenavir 141 W94 GW 141 (protease inhibitor)	Glaxo Wellcome	HIV infection, AIDS, ARC
Abacavir (1592U89) GW 1592 (RT inhibitor)	Glaxo Wellcome	HIV infection, AIDS, ARC

DRUG NAME	MANUFACTURER	INDICATION
Acemannan	Carrington Labs (Irving, TX)	ARC
Acyclovir	Burroughs Wellcome	HIV infection, AIDS, ARC, in combination with AZT
AD-439	Tanox Biosystems	HIV infection, AIDS, ARC
AD-519	Tanox Biosystems	HIV infection, AIDS, ARC
Adefovir dipivoxil AL-721	Gilead Sciences Ethigen (Los Angeles, CA)	HIV infection, ARC, PGL HIV positive, AIDS
Alpha Interferon HIV in combination w/Retrovir	Glaxo Wellcome	Kaposi's sarcoma
Ansamycin LM 427	Adria Laboratories (Dublin, OH) Erbamont (Stamford, CT)	ARC
Antibody which Neutralizes pH Labile alpha aberrant Interferon	Advanced Biotherapy Concepts (Rockville, MD)	AIDS, ARC
AR177	Aronex Pharm	HIV infection, AIDS, ARC
Beta-fluoro-ddA	Nat'l Cancer Institute	AIDS-associated diseases
BMS-232623 (CGP-73547) (protease inhibitor)	Bristol-Myers Squibb/ Novartis	HIV infection, AIDS, ARC
BMS-234475 (CGP-61755) (protease inhibitor)	Bristol-Myers Squibb/ Novartis	HIV infection, AIDS, ARC
CI-1012	Warner-Lambert	HIV-1 infection
Cidofovir	Gilead Science	CMV retinitis, herpes, papillomavirus
Curdlan sulfate	AJI Pharma USA	HIV infection
Cytomegalovirus Immune globin	MedImmune	CMV retinitis
Cytovene	Syntex	Sight threatening
Ganciclovir		CMV peripheral, CMV retinitis
Delaviridine (RT inhibitor)	Pharmacia-Upjohn	HIV infection, AIDS, ARC

DRUG NAME	MANUFACTURER	INDICATION
Dextran Sulfate	Ueno Fine Chem. Ind. Ltd. (Osaka, Japan)	AIDS, ARC, HIV positive asymptomatic
ddC Dideoxycytidine	Hoffman-La Roche	HIV infection, AIDS, ARC
ddI Dideoxyinosine	Bristol-Myers Squibb	HIV infection, AIDS, ARC; combinationwith AZT/d4T
DMP-450 (protease inhibitor)	AVID (Camden, NJ)	HIV infection, AIDS, ARC
Efavirenz (DMP 266) (-)6-Chloro-4-(S)-cyclopropylethynyl-4(S)-trifluoro-methyl-1,4-dihydro-2H-3,1-benzoxazin-2-one, STOCRINE (non-nucleoside RT inhibitor)	DuPont Merck	HIV infection, AIDS, ARC
EL10	Elan Corp, PLC (Gainesville, GA)	HIV infection
Famciclovir	Smith Kline	herpes zoster, herpes simplex
FTC (reverse transcriptase inhibitor)	Emory University	HIV infection, AIDS, ARC
GS 840 (reverse transcriptase inhibitor)	Gilead	HIV infection, AIDS, ARC
HBY097 (non-nucleoside reverse transcriptaseinhibitor)	Hoechst Marion Roussel	HIV infection, AIDS, ARC
Hypericin	VIMRx Pharm.	HIV infection, AIDS, ARC
Recombinant Human Interferon Beta	Triton Biosciences (Almeda, CA)	AIDS, Kaposi's sarcoma, ARC
Interferon alfa-n3	Interferon Sciences	ARC, AIDS
Indinavir	Merck	HIV infection, AIDS, ARC, asymptomatic HIV positive, also in combination with AZT/ddI/ddC
ISIS 2922	ISIS Pharmaceuticals	CMV retinitis
KNI-272	Nat'l Cancer Institute	HIV-associated diseases

DRUG NAME	MANUFACTURER	INDICATION
Lamivudine, 3TC (reverse transcriptase inhibitor)	Glaxo Wellcome	HIV infection, AIDS, ARC, also with AZT
Lobucavir	Bristol-Myers Squibb	CMV infection
Nelfinavir (protease inhibitor)	Agouron Pharmaceuticals	HIV infection, AIDS, ARC
Nevirapine (RT inhibitor)	Boehringer Ingleheim	HIV infection, AIDS, ARC
Novapren	Novaferon Labs, Inc. (Akron, OH)	HIV inhibitor
Peptide T Octapeptide Sequence	Peninsula Labs (Belmont, CA)	AIDS
Trisodium Phosphonoformate	Astra Pharm. Products, Inc.	CMV retinitis, HIV infection, other CMV infections
PNU-140690 (protease inhibitor)	Pharmacia Upjohn	HIV infection, AIDS, ARC
Probucol	Vyrex	HIV infection, AIDS
RBC-CD4	Sheffield Med. Tech (Houston, TX)	HIV infection, AIDS, ARC
Ritonavir (protease inhibitor)	Abbott	HIV infection, AIDS, ARC
Saquinavir (protease inhibitor)	Hoffmann-LaRoche	HIV infection, AIDS, ARC
Stavudine; d4T Didehydrodeoxy-thymidine	Bristol-Myers Squibb	HIV infection, AIDS, ARC
Valaciclovir	Glaxo Wellcome	Genital HSV & CMVinfections
Virazole Ribavirin	Viratek/ICN (Costa Mesa, CA)	asymptomatic HIV-positive, LAS, ARC
VX-478	Vertex	HIV infection, AIDS, ARC
Zalcitabine	Hoffmann-LaRoche	HIV infection, AIDS, ARC, with AZT
Zidovudine; AZT	Glaxo Wellcome	HIV infection, AIDS, ARC, Kaposi's sarcoma, in combination with other therapies
Tenofovir disoproxil, fumarate salt (Viread®) (reverse transcriptase inhibitor)	Gilead	HIV infection, AIDS
Combivir® (reverse transcriptase inhibitor)	GSK	HIV infection, AIDS

DRUG NAME	MANUFACTURER	INDICATION
abacavir succinate (or Ziagen®) (reverse transcriptase inhibitor)	GSK	HIV infection, AIDS
Reyataz® (atazanavir)	Bristol-Myers Squibb	HIV infection, AIDS
Fuzeon (Enfuvirtide, T-20)	Roche/Trimeris	HIV infection, AIDS, viral fusion inhibitor
Trizivir®		HIV infection, AIDS
Kaletra®	Abbott	HIV infection, AIDS, ARC

IMMUNOMODULATORS

DRUG NAME	MANUFACTURER	INDICATION
AS-101	Wyeth-Ayerst	AIDS
Bropirimine	Pharmacia Upjohn	Advanced AIDS
Acemannan	Carrington Labs, Inc. (Irving, TX)	AIDS, ARC
CL246,738	American Cyanamid Lederle Labs	AIDS, Kaposi's sarcoma
EL10	Elan Corp, PLC (Gainesville, GA)	HIV infection
FP-21399	Fuki ImmunoPharm	Blocks HIV fusion with CD4+ cells
Gamma Interferon	Genentech	ARC, in combination w/TNF (tumor necrosis factor)
Granulocyte Macrophage Colony Stimulating Factor	Genetics Institute Sandoz	AIDS
Granulocyte Macrophage Colony Stimulating Factor	Hoechst-Roussel Immunex	AIDS
Granulocyte Macrophage Colony Stimulating Factor	Schering-Plough	AIDS, combination w/AZT
HIV Core Particle Immunostimulant	Rorer	Seropositive HIV
IL-2 Interleukin-2	Cetus	AIDS, in combination w/AZT
IL-2 Interleukin-2	Hoffman-LaRoche Immunex	AIDS, ARC, HIV, in combination w/AZT

DRUG NAME	MANUFACTURER	INDICATION
IL-2 Interleukin-2 (aldesalukin)	Chiron	AIDS, increase in CD4 cell counts
Immune Globulin Intravenous (human)	Cutter Biological (Berkeley, CA)	Pediatric AIDS, in combination w/AZT
IMREG-1	Imreg (New Orleans, LA)	AIDS, Kaposi's sarcoma, ARC, PGL
IMREG-2	Imreg (New Orleans, LA)	AIDS, Kaposi's sarcoma, ARC, PGL
Imuthiol Diethyl Dithio Carbamate	Merieux Institute	AIDS, ARC
Alpha-2 Interferon	Schering Plough	Kaposi's sarcoma w/AZT, AIDS
Methionine-Enkephalin	TNI Pharmaceutical (Chicago, IL)	AIDS, ARC
MTP-PE Muramyl-Tripeptide Granulocyte Colony Stimulating Factor	Ciba-Geigy Corp. Amgen	Kaposi's sarcoma AIDS, in combination w/AZT
Remune	Immune Response Corp.	Immunotherapeutic
rCD4 Recombinant Soluble Human CD4	Genentech	AIDS, ARC
rCD4-IgG hybrids		AIDS, ARC
Recombinant Soluble Human CD4	Biogen	AIDS, ARC
Interferon Alfa 2a	Hoffman-La Roche in combination w/AZT	Kaposi's sarcoma, AIDS, ARC
SK&F106528 Soluble T4	Smith Kline	HIV infection
Thymopentin	Immunobiology Research Institute (Annandale, NJ)	HIV infection
Tumor Necrosis Factor; TNF	Genentech	ARC, in combination w/gamma Interferon

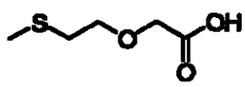
ANTI-INFECTIVES

DRUG NAME	MANUFACTURER	INDICATION
Clindamycin with Primaquine	Pharmacia Upjohn	PCP

DRUG NAME	MANUFACTURER	INDICATION
Fluconazole	Pfizer	Cryptococcal meningitis, candidiasis
Pastille Nystatin Pastille	Squibb Corp.	Prevention of oral candidiasis
Ornidyl Eflornithine	Merrell Dow	PCP
Pentamidine Isethionate (IM & IV)	LyphoMed (Rosemont, IL)	PCP treatment
Trimethoprim		Antibacterial
Trimethoprim/sulfa		Antibacterial
Piritrexim	Burroughs Wellcome	PCP treatment
Pentamidine Isethionate for Inhalation	Fisons Corporation	PCP prophylaxis
Spiramycin	Rhone-Poulenc diarrhea	Cryptosporidial
Intraconazole-R51211	Janssen-Pharm.	Histoplasmosis; cryptococcal meningitis
Trimetrexate	Warner-Lambert	PCP
Daunorubicin	NeXstar, Sequus	Kaposi's sarcoma
Recombinant Human Erythropoietin	Ortho Pharm. Corp.	Severe anemia assoc. with AZT therapy
Recombinant Human Growth Hormone	Serono	AIDS-related wasting, cachexia
Megestrol Acetate	Bristol-Myers Squibb	Treatment of anorexia assoc. W/AIDS
Testosterone	Alza, Smith Kline	AIDS-related wasting
Total Enteral Nutrition	Norwich Eaton Pharmaceuticals	Diarrhea and malabsorption related to AIDS

DESCRIPTION OF SPECIFIC EMBODIMENTS

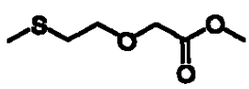
Intermediate 1



2-(2-(Methylthio)ethoxy)acetic acid. A solution of 2-methylthioethanol (10.0 g, 0.108 mol) in dry tetrahydrofuran (25 ml) was added dropwise, over 30 min, to a suspension of sodium hydride (9.54 g of a 60% dispersion in mineral oil, 0.238 mol, washed twice with hexane) in dry tetrahydrofuran (250 ml) at 22 °C. After 30 min, a

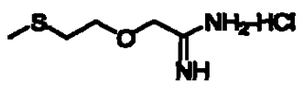
solution of chloroacetic acid (10.25 g, 0.108 mol) in dry tetrahydrofuran (20 ml) was added dropwise, over 30 min at 22 °C, and the resulting mixture was then heated under reflux for 5 h. The cooled mixture was treated with 250 ml of 1 N hydrochloric acid and sodium chloride added to the aqueous phase until saturation. The organic phase was separated and the aqueous phase washed with ethyl acetate. The combined organic extracts were washed with brine, dried over anhydrous magnesium sulfate and concentrated under reduced pressure. Distillation of the resulting residue *in vacuo* gave 11.27 g (69% yield) of the title acid as a clear oil; bp 85–95 °C / 0.3 torr (bulb to bulb distillation, air bath temperature). ^{1}HNMR 400 MHz ($CDCl_3$) δ ppm: 2.18 (3H, s, SCH_3), 2.76 (2H, t, J = 6.6 Hz, CH_2), 3.77 (2H, t, J = 6.6 Hz, CH_2), 4.20 (2H, s, OCH_2).

Intermediate 2



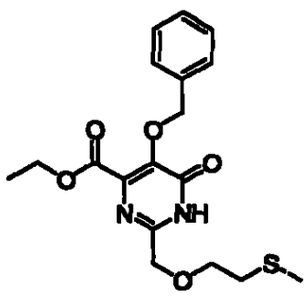
Methyl 2-(2-(methylthio)ethoxy)acetate. A solution of intermediate 1, 2-(2-(methylthio)ethoxy)acetic, (11.27 g, 0.075 mol) in dry dichloromethane (50 ml) was treated with oxalylchloride (13.0 ml, 0.15 mol) followed by a drop of N,N-dimethylformamide and the resulting mixture stirred at 22 °C for 5 h. The solvent and excess reagent were then evaporated under reduced pressure and the residual acid chloride was added dropwise to a cold mixture(0–5 °C) of methanol (30 ml) and pyridine (10 ml) in dichloromethane (50 ml). After 1 h at 22 °C, the solvent was evaporated under reduced pressure. The resulting residue was diluted with ethyl acetate, washed with 1 N hydrochloric acid, saturated sodium bicarbonate and brine, dried over anhydrous magnesium sulfate and then concentrated under reduced pressure. Distillation of the resulting residue *in vacuo* gave 11.42 g (93% yield) of the title ester as a clear oil; bp 65–75 °C / 0.1 torr (bulb to bulb distillation, air bath temperature). ^{1}HNMR 400 MHz ($CDCl_3$) δ ppm: 2.17 (3H, s, SCH_3), 2.75 (2H, t, J = 6.9 Hz, CH_2), 3.74 (2H, t, J = 6.9 Hz, CH_2), 3.77 (3H, s, OCH_3), 4.15 (2H, s, OCH_2).

Intermediate 3



2-(2-(Methylthio)ethoxy)acetamidine hydrochloride salt. Intermediate 2, methyl 2-(2-(methylthio)ethoxy)acetate, (4.69 g, 28.6 mmol) was added to a solution of methylchloroaluminum amide (H. Geilen, C. Alonso-Alija, M. Hendrix, U. Niewohner and D. Schauss, Tetrahedron Lett., 2002, 43, 419-421)(0.114 mol; prepared in toluene (50 ml) from ammonium chloride 6.30 g (0.117 mol) and 57.0 ml (0.114 mol) of a 2 M solution of trimethylaluminum in toluene) and the resulting mixture was heated at 80 °C for 18h. The reaction mixture was then cooled to 0 °C, treated dropwise with methanol (100 ml) and stirred for another hour at 25 °C. The solid which was formed was filtered and washed with methanol (300 ml). The combined filtrate was concentrated to give a white paste which was diluted with isopropanol (160 ml) and acetone (40 ml) and stirred at 25 °C for 1 h. The solid was then filtered off and the filtrate concentrated *in vacuo* to give 3.50 g (62% yield) of the title compound as an oil. ^{1}HNMR 400 MHz (DMSO-d_6) δ ppm: 2.10 (3H, s, SCH_3), 2.71 (2H, t, J = 6.8 Hz, CH_2), 3.66 (2H, t, J = 6.8 Hz, CH_2), 4.34 (2H, s, OCH_2). MS (ESI$^+$) m/z 149 [M+H$^+$].

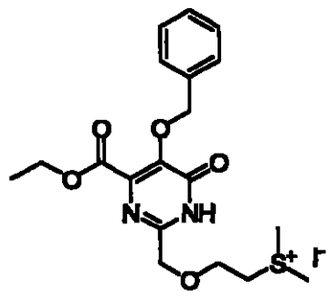
Intermediate 4



Ethyl 5-benzyloxy-2-{(2-(methylthio)ethoxy)methyl}-6-oxo-1,6-dihydropyrimidine-4-carboxylate. Diethyl oxalate (2.77 g, 19.0 mmol) and ethyl

benzyloxyacetate (3.69 g, 19.0 mmol) in dry tetrahydrofuran (30 ml) were treated at 22 °C with sodium hydride (0.83 g of a 60% dispersion in mineral oil, 20.9 mmol) followed by ethanol (10 µl) and the resulting mixture was stirred at 22 °C for 18h. The tetrahydrofuran was evaporated under reduced pressure to give an orange syrup. A mixture of intermediate 3, 2-(2-(methylthio)ethoxy)acetamidine hydrochloride salt, (3.50 g, 19.0 mmol) in a solution of sodium ethoxide (9.5 mmol, prepared from 0.22 g of sodium in ethanol 25 ml) was then added all at once to the above adduct and the resulting mixture heated at 60 °C for 3 h. Acetic acid (2 ml) was added and the ethanol was evaporated under reduced pressure. The residue was diluted with ethyl acetate washed successively with saturated sodium bicarbonate and brine, then dried over anhydrous magnesium sulfate and concentrated under reduced pressure. Chromatography on silica gel (elution with a gradient of ethyl acetate 20-30% in toluene) gave 0.728 g (10% yield) of the title ester as a clear oil. ^{1}HNMR 400 MHz ($CDCl_3$) δ (ppm): 1.33 (3H, t, J = 7.1 Hz, CH_3), 2.18 (3H, s, SCH_3), 2.78 (2H, t, J = 6.0 Hz, CH_2), 3.78 (2H, t, J = 6.0 Hz, CH_2), 4.36 (2H, q, J = 7.1 Hz, OCH_2), 4.54 (2H, s, OCH_2), 5.35 (2H, s, OCH_2), 7.37 (3H, m, aromatics), 7.48 (2H, m, aromatics). HRMS (ESI^+) calculated for $C_{18}H_{23}N_2O_5S$ [$M+H^+$]: 379.1328: found: 379.1314.

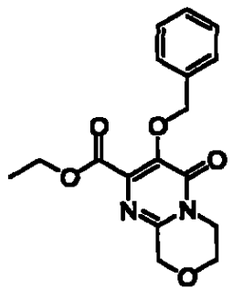
Intermediate 5



Ethyl 5-benzyloxy-2-{(2-(dimethylsulfonium)ethoxy)methyl}-6-oxo-1,6-dihydropyrimidine-4-carboxylate iodide. A solution of intermediate 4, ethyl 5-benzyloxy-2-{(2-(methylthio)ethoxy)methyl}-6-oxo-1,6-dihydropyrimidine-4-carboxylate, (0.555 g, 1.47 mmol) in dichloromethane (10 ml) was treated at 22 °C with iodomethane (2.0 ml, 21.5 mmol) for 10 days. Evaporation of the solvent and

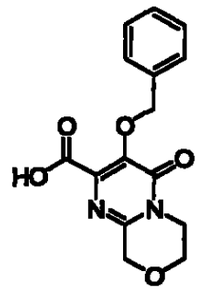
excess reagent gave the title compound (0.76 g) as an oil which was used without further purification. ^{1}HNMR 400 MHz ($CDCl_3$) δ (ppm): 1.32 (3H, t, J = 7.1 Hz, CH_3), 3.26 (6H, s, SCH_3), 4.02 (2H, m, CH_2), 4.23 (2H, m, CH_2), 4.34 (2H, q, J = 7.1 Hz, OCH_2), 4.69 (2H, s, OCH_2), 5.23 (2H, s, OCH_2), 7.35-7.5 (5H, m, aromatics). MS (ESI$^+$) m/z 393 [M^+].

Intermediate 6



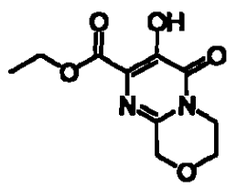
Ethyl 3-benzyloxy-4-oxo-4,6,7,9-tetrahydropyrimido[2,1-c][1,4]oxazine-2-carboxylate. A solution of intermediate 5, ethyl 5-benzyloxy-2-{(2-(dimethylsulfonium)ethoxy)methyl}-6-oxo-1,6-dihydropyrimidine-4-carboxylate iodide, (0.76 g, 1.47 mmol) in dry N,N-dimethylformamide (10 ml) was treated at 22 °C with powdered anhydrous potassium carbonate (2.5 g) and the resulting mixture stirred for 48h. The solid was then filtered and the filtrate evaporated *in vacuo*. The residue was diluted with ethyl acetate washed successively with 0.1 N hydrochloric acid, saturated sodium bicarbonate, brine and dried over anhydrous magnesium sulfate. Evaporation of the solvent followed by chromatography on silica gel (elution with a gradient of ethyl acetate 20-50% in toluene) gave 0.347 g (72% yield) of the title ester as white prisms; mp 103-104 °C (ethyl acetate-hexane). ^{1}HNMR 400 MHz ($CDCl_3$) δ ppm: 1.34 (3H, t, J = 7.1 Hz, CH_3), 4.03 (2H, t, J = 5.6 Hz, CH_2), 4.11 (2H, t, J = 5.6 Hz, CH_2), 4.37 (2H, q, J = 7.1 Hz, OCH_2), 4.74 (2H, s, OCH_2), 5.30 (2H, s, OCH_2), 7.38 (3H, m, aromatics), 7.50 (2H, m, aromatics). Anal. Calcd for $C_{17}H_{18}N_2O_5$: C 61.81, H 5.49, N 8.48. Found: C 61.55, H 5.53, N 8.39.

Intermediate 7



3-(Benzyloxy)-4-oxo-4,6,7,9-tetrahydropyrimido[2,1-c][1,4]oxazine-2-carboxylic acid. A solution of intermediate 6, ethyl 3-(benzyloxy)-4-oxo-4,6,7,9-tetrahydropyrimido[2,1-c][1,4]oxazine-2-carboxylate (0.300 g, 0.91 mmol) in ethanol (10 ml) was treated with 3 ml (3.0mmol) of 1 N sodium hydroxide and stirred at 25 °C for 30 min. The solution was then acidified with 1 N hydrochloric acid, extracted with ethyl acetate, washed with brine and dried over anhydrous magnesium sulfate. Evaporation of the solvent gave 0.264 g (96% yield) of the title acid as white crystals; mp 171 °C (ethyl acetate). ^{1}HNMR 400 MHz ($CDCl_3$) δ (ppm): 4.03 (2H, t, J = 5.3 Hz, CH_2), 4.12 (2H, t, J = 5.3 Hz, CH_2), 4.73 (2H, s, OCH_2), 5.53 (2H, s, OCH_2), 7.35- 7.42 (3H, m, aromatics), 7.53 (2H, m, aromatics). Anal. Calcd for $C_{15}H_{14}N_2O_5$: C 59.60, H 4.67, N 9.27. Found: C 59.35, H 4.69, N 9.10.

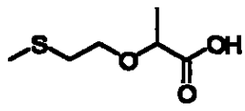
Intermediate 8



Ethyl 3-hydroxy-4-oxo-4,6,7,9-tetrahydropyrimido[2,1-c][1,4]oxazine-2-carboxylate. A solution of intermediate 6, ethyl 3-benzyloxy-4-oxo-4,6,7,9-tetrahydropyrimido[2,1-c][1,4]oxazine-2-carboxylate, (0.236 g, 0.714 mmol) in a mixture of ethyl acetate (60 ml) and ethanol (20 ml) was treated with 1 atm of

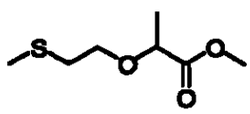
hydrogen at 25 °C over 10% palladium on activated carbon (0.10 g) for 2.5 h to give 0.160 g (94% yield) of the title compound as white needles; mp 172-174 °C (ethyl acetate). ^{1}HNMR 400 MHz ($CDCl_3$) δ ppm: 1.47 (3H, t, J = 7.3 Hz, CH_3), 4.08 (4H, m, 2 x CH_2), 4.54 (2H, q, J = 7.3 Hz, OCH_2), 4.72 (2H, s, OCH_2), 10.75 (1H, s, OH). Anal. Calcd for $C_{10}H_{12}N_2O_5$: C 50.00, H 5.03, N 11.66. Found: C 50.01, H 4.95, N 11.54.

Intermediate 9



2-(2-(Methylthio)ethoxy)propanoic acid. Addition of 2-methylthioethanol (10.0 g, 0.108 mol) to sodium hydride (9.54 g of a 60% dispersion in mineral oil, 0.238 mol, washed twice with hexane) followed by reaction with 2-bromopropionic acid (16.6 g, 0.108 mol) gave 13.81 g (78% yield) of the title compound as a clear oil; bp 80-90 °C/0.2 torr (bulb to bulb distillation, air bath temperature). ^{1}HNMR 400 MHz ($CDCl_3$) δ ppm: 1.49 (3H, d, J = 7.0 Hz, CH_3), 2.18 (3H, s, SCH_3), 2.76 (2H, t, J = 6.6 Hz, CH_2), 3.74 (2H, t, J = 6.6 Hz, CH_2), 4.07 (1H, d, J = 7.0 Hz, OCH).

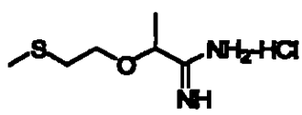
Intermediate 10



Methyl 2-(2-(methylthio)ethoxy)propanoate. Reaction of intermediate 9, 2-(2-(methylthio)ethoxy)propanoic acid, (13.70 g, 0.083 mol) with oxalyl chloride followed by reaction with methanol gave 14.27 g (96% yield) of the title ester as a clear oil; bp 55–60 °C / 0.3 torr (bulb to bulb distillation, air bath temperature). ^{1}HNMR 400 MHz ($CDCl_3$) δ ppm: 1.42 (3H, d, J = 7.0 Hz, CH_3), 2.15 (3H, s, SCH_3),

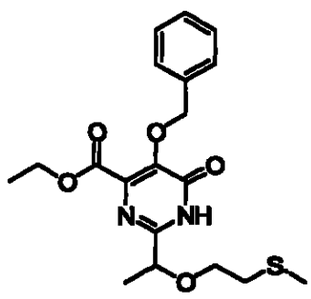
2.71 (2H, t, J = 6.8 Hz, CH_2), 3.56 (1H, m, CH), 3.75 (3H, s, OCH_3), 3.78 (1H, m, CH), 4.15 (1H, q, J = 7.0 Hz, OCH).

Intermediate 11



2-(2-(Methylthio)ethoxy)propanamidine hydrochloride salt. Intermediate 10, methyl 2-(2-(methylthio)ethoxy)propanoate, (10.00 g, 56.1 mmol) was added to a solution of methylchloroaluminum amide (0.224 mol; prepared in toluene (100 ml) from ammonium chloride 12.36 g (0.231 mol) and 112.0 ml (0.224 mol) of a 2 M solution of trimethylaluminum in toluene} as described in the preparation of intermediate 3 to give 7.70 g (69% yield) of the title compound as an oil. ^{1}HNMR 400 MHz (D_2O) δ ppm: 1.37 (3H, d, J = 6.6 Hz, CH_3), 2.01 (3H, s, SCH_3), 2.65 (2H, t, J = 5.6 Hz, CH_2), 3.64 (2H, m, CH_2), 4.30 (1H, q, J = 6.6 Hz, OCH). MS (ESI$^+$) m/z 163 [M+H$^+$].

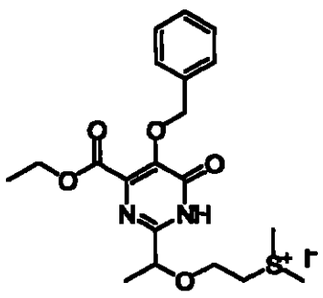
Intermediate 12



Ethyl 5-benzyloxy-2-{1-(2-(methylthio)ethoxy)ethyl}-6-oxo-1,6-dihydropyrimidine-4-carboxylate. Diethyl oxalate (5.66 g, 38.7 mmol) and ethyl benzyloxyacetate (7.52 g, 38.7 mmol) in dry tetrahydrofuran (60 ml) were treated at 22 °C with sodium hydride (1.70 g of a 60% dispersion in mineral oil, 42.5 mmol) and the condensation product was reacted with a mixture of intermediate 11, 2-(2-

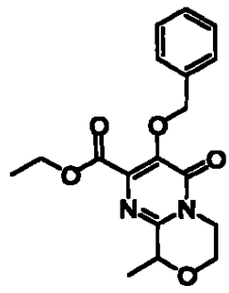
(methylthio)ethoxy)propanamidine hydrochloride salt, (7.70 g, 38.7 mmol) in a solution of sodium ethoxide (19.3 mmol, prepared from 0.445 g of sodium) in ethanol (50 ml) to give 2.29 g (15% yield) of the title ester as a clear oil after chromatography on silica gel. ^{1}HNMR 400 MHz ($CDCl_3$) δ ppm: 1.33 (3H, t, J = 7.1 Hz, CH_3), 1.54 (3H, d, J = 7.1 Hz, CH_3), 2.16 (3H, s, SCH_3), 2.7-2.8 (2H, m, CH_2), 3.54 (1H, m, CH), 3.86 (1H, m, CH), 4.37 (2H, q, J = 7.1 Hz, OCH_2), 4.47 (1H, q, J = 7.1 Hz, OCH), 5.34 (2H, ABq, J_{AB} = 11.0 Hz, OCH_2), 7.37 (3H, m, aromatics), 7.49 (2H, m, aromatics). MS (ESI^+) m/z 393 [$M+H^+$].

Intermediate 13



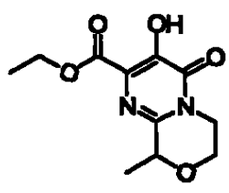
Ethyl 5-benzyloxy-2-{1-(2-(dimethylsulfonium)ethoxy)ethyl}-6-oxo-1,6-dihydropyrimidine-4-carboxylate iodide. A solution of intermediate 12, ethyl 5-benzyloxy-2-{1-(2-(methylthio)ethoxy)ethyl}-6-oxo-1,6-dihydropyrimidine-4-carboxylate, (1.63 g, 4.15 mmol) in dichloromethane (5 ml) was treated at 22 °C with iodomethane (5.0 ml, 53.9 mmol) for 5 days as described for the preparation of intermediate 5, to give the title compound (2.22 g) as an oil which was used without further purification. ^{1}HNMR 400 MHz ($CDCl_3$) δ ppm: 1.32 (3H, t, J = 7.1 Hz, CH_3), 1.66 (3H, d, J = 6.6 Hz, CH_3), 3.15 (3H, s, SCH_3), 3.32 (3H, s, SCH_3), 3.4 (1H, m, CH), 4.01 (2H, m, CH_2), 4.37 (2H, q, J = 7.1 Hz, OCH_2), 4.45 (1H, m, CH), 4.63 (1H, q, J = 6.6 Hz, OCH), 5.28 (2H, OCH_2), 7.38 (3H, m, aromatics), 7.50 (2H, m, aromatics). MS (ESI^+) m/z 407 [M^+].

Intermediate 14



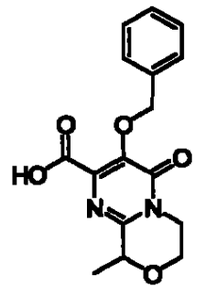
Ethyl 3-(benzyloxy)-9-methyl-4-oxo-4,6,7,9-tetrahydropyrimido[2,1-c][1,4]oxazine-2-carboxylate. A solution of intermediate 13, ethyl 5-benzyloxy-2-{1-(2-(dimethylsulfonium)ethoxy)ethyl}-6-oxo-1,6-dihydropyrimidine-4-carboxylate iodide (2.22 g, 4.15 mmol) in dry N,N-dimethylformamide (30 ml) was treated at 22 °C with powdered anhydrous potassium carbonate (6 g) and stirred for 40 h. The solid was then filtered and the filtrate was concentrated *in vacuo*. The residue was diluted with ethyl acetate, washed with 0.1 N hydrochloric acid, saturated sodium bicarbonate and brine then dried over anhydrous magnesium sulfate. Evaporation of the solvent and chromatography of the residue on silica gel (elution toluene-ethyl acetate 7:3) gave 1.0 g (70% yield) of the title ester as white crystals; mp 48-50 °C (ethyl acetate-hexane). ^{1}HNMR 400 MHz ($CDCl_3$) δ (ppm): 1.33 (3H, t, J = 7.1 Hz, CH_3), 1.68 (3H, d, J = 6.6 Hz, CH_3), 3.91 (2H, m, CH_2), 4.17-4.31 (2H, m, CH_2), 4.37 (2H, q, J = 7.1 Hz, OCH_2), 4.73 (1H, q, J = 6.6 Hz, OCH), 5.30 (2H, ABq, J_{AB} = 11.0 Hz, OCH_2), 7.38 (3H, m, aromatics), 7.50 (2H, m, aromatics). Anal. Calcd for $C_{18}H_{20}N_2O_5$: C 62.78, H 5.85, N 8.13. Found: C 62.69, H 6.01, N 8.16.

Intermediate 15



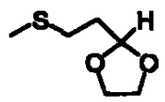
Ethyl 3-hydroxy-9-methyl-4-oxo-4,6,7,9-tetrahydropyrimido[2,1-c][1,4]oxazine-2-carboxylate. Hydrogenolysis of intermediate 14, ethyl 3-benzyloxy-9-methyl-4-oxo-4,6,7,9-tetrahydropyrimido[2,1-c][1,4]oxazine-2-carboxylate, (0.610 g, 1.77 mmol) in a mixture of ethyl acetate (75 ml) and ethanol (75 ml) at 25 °C over 10% palladium on activated carbon (0.20 g) under 1 atm of hydrogen for 2 h gave 0.430 g (95% yield) of the title ester as white crystals; mp 119-121 °C (ethyl acetate-hexane). ^{1}HNMR 400 MHz ($CDCl_3$) δ ppm: 1.46 (3H, t, J = 7.1 Hz, CH_3), 1.67 (3H, d, J = 6.6 Hz, CH_3), 3.90 (2H, m, CH_2), 4.13-4.32 (2H, m, CH_2), 4.51 (2H, m, OCH_2), 4.70 (1H, q, J = 6.6 Hz, CH), 10.7 (1H, broad, OH). Anal. Calcd for $C_{11}H_{14}N_2O_5$: C 51.96, H 5.55, N 11.01. Found: C 51.60, H 5.61, N 10.70.

Intermediate 16



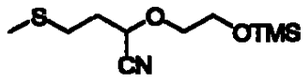
3-Benzyloxy-9-methyl-4-oxo-4,6,7,9-tetrahydropyrimido[2,1-c][1,4]oxazine-2-carboxylic acid. Saponification of intermediate 14, ethyl 3-benzyloxy-9-methyl-4-oxo-4,6,7,9-tetrahydropyrimido[2,1-c][1,4]oxazine-2-carboxylate, (0.225 g, 0.65 mmol) as described in the preparation of intermediate 7 gave 0.198 g (96% yield) of the title acid as white crystals; mp 167-168 °C (ethyl acetate-hexane). ^{1}HNMR 400 MHz ($CDCl_3$) δ ppm: 1.68 (3H, d, J = 6.6 Hz, CH_3), 3.93 (2H, m, CH_2), 4.12-4.21 (1H, m, CH), 4.27-4.35 (1H, m, CH), 4.70 (1H, q, J = 6.6 Hz, OCH), 5.53 (2H, ABq, J_{AB} = 11.1 Hz, OCH_2), 7.39 (3H, m, aromatics), 7.55 (2H, m, aromatics). MS (ESI^+) m/z 317 [$M+H^+$]. Anal. Calcd for $C_{16}H_{16}N_2O_5$: C 60.75, H 5.10, N 8.86. Found: C 60.65, H 5.05, N 8.72.

Intermediate 17



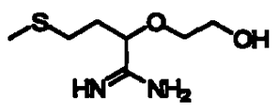
2-(2-(Methylthio)ethyl)-1,3-dioxolane. A solution of 3-(methylthio)propanal (5.2 g, 0.05 mol) and ethyleneglycol (3.4g. 0.055 mol) in 100mL of benzene was treated with 300 mg p-toluenesulfonic acid and heated at reflux for 4 hrs. The solution was cooled and decanted. Concentration and drying *in vacuo* provided the title compound as a light yellow oil. ^{1}H NMR (300 MHz, $CDCl_3$) δ ppm:4.93 (1 H, t, *J*=4.76 Hz) 3.74-4.03 (4 H, m) 2.46-2.68 (2 H, m) 2.08 (3 H, s) 1.83-2.00 (2 H, m).

Intermediate 18



4-(Methylthio)-2-(2-(trimethylsilyloxy)ethoxy)butanenitrile. Intermediate 17, 2-(2-(methylthio)ethyl)-1,3-dioxolane, (2.96g, 0.02mol), trimethylsilylcyanide (1.98g, 0.02 mol) and 20mg zinc iodide were combined under N_2 and stirred for 16 hrs at room temperature. The mixture was then concentrated *in vacuo* to provide 4.9g (approximately 100% yield) of the title compound as a yellow oil. ^{1}H NMR (300 MHz, $CDCl_3$) δ ppm:4.37-4.49 (1 H, m) 3.50-3.88 (4 H, m) 2.57-2.74 (2 H, m) 1.98-2.26 (5 H, m) 0.06-0.22 (9 H, m): LC/MS 198 (-TMS+Na).

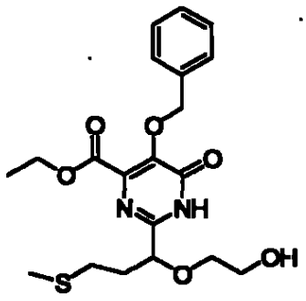
Intermediate 19



4-(Methylthio)-2-(2-(trimethylsilyloxy)ethoxy)butanamidine. A solution of intermediate 18, 4-(methylthio)-2 -(2-(trimethylsilyloxy)ethoxy)butanenitrile, (4.9g,

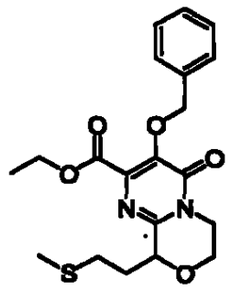
0.02mol) in 30 mL of methanol was saturated with ammonia. The flask was then sealed and heated in an oil bath at 80-90 °C for 16hrs. After cooling, the flask was opened and the mixture concentrated *in vacuo* to give the title compound in essentially quantitative yield as a very viscous oil. ^{1}H NMR (300 MHz, $CDCl_3$) δ ppm:3.94-4.02 (1 H, m) 3.76-3.94 (3 H, m) 3.68-3.77 (2 H, m) 3.52-3.62 (2 H, m) 2.53-2.67 (2 H, m) 2.07 (3 H, s) 1.89-2.01 (2 H, m); LC/MS 193 (M+ H).

Intermediate 20



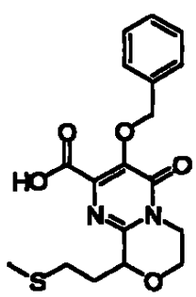
Ethyl 5-(benzyloxy)-2-(1-(2-hydroxyethoxy)-3-(methylthio)propyl)-6-oxo-1,6-dihydropyrimidine-4-carboxylate. Ethyl 2-(benzyloxy)acetate (7.76 g, 0.04 mole)and diethyloxalate (5.84 g, 0.04 mole) in 80 mL of tetrahydrofuran were treated with one equivalent of NaH and a few drops of ethanol. The resulting mixture was stirred for 1.5 hours after which the solvent was removed under vacuum and replaced with 30 mL of ethanol. Intermediate 19, 2-(2-hydroxyethoxy)-4 methylthio)butanamidine, in 30 mL ethanol was added to the mixture followed by NaH (60% in mineral oil, 800mg, 0.02 mol). This was stirred for 20 hrs at room temperature and 3hrs at 60 °C then concentrated under reduced pressure. The residue was dissolved in CH_2Cl_2 and washed with water. The CH_2Cl_2 layer was dried over $MgSO_4$, filtered and concentrated under vacuum. Chromatography on silica gel, eluting with 4:1 CH_2Cl_2; ether and ethyl acetate, gave 760 mg of the title compound (9% yield). ^{1}H NMR (300 MHz, $CDCl_3$) δ ppm: 7.24-7.54 (5 H, m) 5.17-5.36 (2 H, s) 4.50 (1 H, m) 4.30 (2 H, q, *J*=7.32 Hz) 3.38-4.00 (4 H, m) 2.59 (2 H, m) 1.95-2.11 (5 H, m) 1.20-1.36 (3 H, t, J=7.32 Hz); LC/MS m/z 423 (M+H).

Intermediate 21



Ethyl 3-(benzyloxy)-9-(2-(methylthio)ethyl)-4-oxo-4,6,7,9-tetrahydropyrimido[2,1-c][1,4]oxazine-2-carboxylate. To a solution of intermediate 20, ethyl 5-(benzyloxy)-2-(1-(2-hydroxyethoxy)-3-(methylthio)propyl)-6-oxo-1,6-dihydropyrimidine-4-carboxylate, (527 mg, 1.25 mmol) and Et_3N (505mg, 5 mmol) dissolved in 10mL of CH_2Cl_2 was added a solution of CH_3SO_2Cl (288mg, 2.5 mmol) dissolved in 2 mL of CH_2Cl_2. This was stirred for 20 hrs then concentrated. The crude product was purified by chromatography on silica gel, using 10:1 CH_2Cl_2:ether as eluent, to give the title compound 265mg (52% yield). (500 MHz, $CDCl_3$) δ ppm: 7.31-7.55 (5 H, m) 5.30 (2 H, s) 4.75 (1 H, dd, *J*=3.66 Hz) 4.32-4.40 (2 H, q, J=7.17 Hz) 4.13-4.30 (2 H, m) 3.75-3.97 (2 H, m) 2.20-2.84 (4 H, m) 2.06 (3 H, s) 1.32 (3 H, t, *J*=7.17 Hz); LC/MS m/z 405 (M+H).

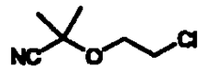
Intermediate 22



3-(Benzyloxy)-9-(2-(methylthio)ethyl)-4-oxo-4,6,7,9-tetrahydropyrimido[2,1-c][1,4]oxazine-2-carboxylic acid. To a stirred solution of intermediate 21, ethyl 3-

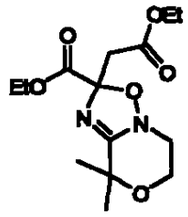
(benzyloxy)-9-(2-(methylthio)ethyl)-4-oxo-4,6,7,9-tetrahydropyrimido[2,1-c][1,4]oxazine-2-carboxylate (97mg, 0.2mmol) in 3mL tetrahydrofuran was added lithium hydroxide (15mg, .6mmol) in 3mL water. After 20 min the reaction mixture was acidified with 1N HCl and extracted with CH_2Cl_2. The extract was dried over $MgSO_4$, filtered and concentrated to give 82 mg of the title compound (88% yield). LC/MS m/e 377.

Intermediate 23



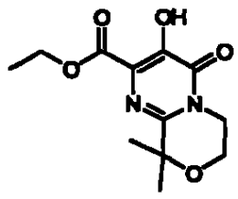
2-(2-Chloroethoxy)-2-methylpropanenitrile. (Navalokina, R. Et al J. Org. Chem. USSR (Engl. Trans.), 1980, 16, 1382-1386. 2) Ramalingam, K. US-4,864,051, 1989.). A 250 mL round bottom flask was charged with $ZnCl_2$ (68.14 g, 0.5 mole) which was then fused by heating under vacuum. After returning to room temperature the material was placed under an atmosphere of N_2. To this was added acetone cyanohydrin (45.66 mL, 0.5 mole) followed by 2-chloroethanol (50.24 mL, 0.75 mole) and the mixture placed in a preheated oil bath (60 °C). After stirring for 18-20 h at 60 °C, the reaction mixture was cooled, diluted with water (300 mL) and washed with CH_2Cl_2 (5 X 100 mL). The combined CH_2Cl_2 extracts were dried (Na_2SO_4), filtered and concentrated under vacuum to afford the crude product as a yellow liquid. Purification was accompliahed by vacuum distillation (10 mm Hg) using a vigreux column. The fraction boiling between 65-75 °C was collected to afford the desired product as a colorless oil (47.1 g, 63.8% yield). ^1H NMR (500 MHz, $CDCl_3$) δ ppm: 3.85 (2H, t, J = 5.8 Hz), 3.64 (2H, t, J = 5.8 Hz), 1.60 (6H, s).

Intermediate 24



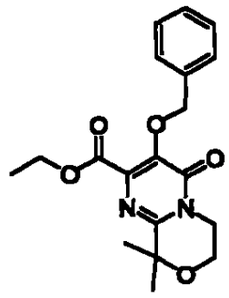
Ethyl 2-(2-ethoxy-2-oxoethyl)-8,8-dimethyl-2,5,6,8-tetrahydro-[1,2,4]oxadiazolo[3,2-c][1,4]oxazine-2-carboxylate. To a stirred solution of intermediate 23, 2-(2-chloroethoxy)-2-methylpropanenitrile (14.7 g, 0.10 mole) and NaI (1.5 g, 10 mmol) in ethanol (50 mL) was added an aqueous solution (50%) of hydroxylamine (18.4 g, 0.30 mole) resulting in an exothermic reaction. Following this the reaction mixture was heated at 80 °C for 2 h. Upon cooling to room temperature the solvent was removed. The resulting residue was dissolved in 1:1 ethanol/H_2O (100 mL) and cooled in an ice bath. To this was added diethyl acetylenedicarboxylate (17.6 mL, 0.110 mole) over 10 min. The reaction mixture was allowed to warm to room temperature and stirred for 1 h. Following this, it was diluted with ethyl acetate (250 mL), washed with H_2O (2 X 100 mL), brine (50 mL), dried over Na_2SO_4, filtered and concentrated to give the crude product as a yellow oil. Flash chromatography on a silica gel column, eluting with 20-40% ethyl acetate/Hexanes, provided the title compound as a viscous pale yellow oil (15.29 g, 48.6% yield). ^1H NMR (500 MHz, $CDCl_3$) δ ppm: 4.35-4.28 (2H, m), 4.18-4.12 (2H, m), 3.60-3.56 (1H, m), 3.51-3.47 (1H, m), 3.30 (1H, d, J = 16.2 Hz), 2.94 (1H, d, J = 16.2 Hz), 1.52 (3H, s), 1.51 (3H, s), 1.29 (3H, t, J = 7.0 Hz), 1.24 (3H, t, J = 7.0 Hz). LCMS (M+H) calcd for $C_{14}H_{23}N_2O_7$: 315.16; found: 315.33.

Intermediate 25



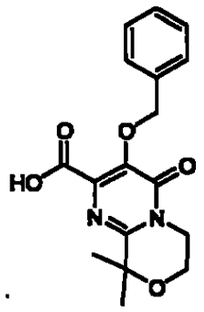
Ethyl 3-hydroxy-9,9-dimethyl-4-oxo-4,6,7,9-tetrahydropyrimido[2,1-c][1,4]oxazine-2-carboxylate. A solution of intermediate 24, ethyl 2-(2-ethoxy-2-oxoethyl)-8,8-dimethyl-2,5,6,8-tetrahydro-[1,2,4]oxadiazolo[3,2-c][1,4]oxazine-2-carboxylate (31.16 g) in 1,2,4-trimethylbenzene (200 mL) was heated at 180 °C for 5 h. The resulting dark reaction solution was cooled then concentrated to give a dark brown paste which was taken up into ethyl acetate (250 mL) and extracted with 0.5 M aq Na_2CO_3 (4 X 50 mL). The organic layer was discarded and the aqueous layer acidified by carefully adding conc. HCl (20 mL) before being extracted with CH_2Cl_2 (4 X 50 mL). The combined CH_2Cl_2 layers were dried (Na_2SO_4), filtered and concentrated to give a dark paste which was dissolved in ether (100 mL) and allowed to stand at room temperature in a open flask. The brown/light yellow solid that formed was filtered to afford the title compound. The mother liquor that contained product was re-processed to afford additional material (combined yield ~18-20% over two steps). ^1H NMR (500 MHz, $CDCl_3$) δ: 10.55 (1H, s), 4.45 (2H, q, J = 7.0 Hz), 4.02 (4H, s), 1.61 (6H, s), 1.43 (3H, t, J = 7.0 Hz). HRMS (M+H) calcd for $C_{12}H_{17}N_2O_5$: 269.1138; found: 269.1149. Anal calcd for $C_{12}H_{16}N_2O_5$: C, 53.72; H, 6.01; N, 10.44. Found: C, 53.71; H, 6.04; N, 10.30.

Intermediate 26



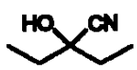
Ethyl 3-(benzyloxy)-9,9-dimethyl-4-oxo-4,6,7,9-tetrahydropyrimido[2,1-c][1,4]oxazine-2-carboxylate. To a stirred solution of intermediate 25, ethyl 3-hydroxy-9,9-dimethyl-4-oxo-4,6,7,9-tetrahydropyrimido[2,1-c][1,4]oxazine-2-carboxylate, (2.68 g, 10 mmol) and benzyl bromide (1.43 mL, 12 mmol) in DMF (40 mL) was added K_2CO_3 (2.07 g, 20 mmol). After stirring 48 h at ambient temperature, the reaction mixture was diluted with ether (100 mL), then washed with water (3 X 30 mL) and brine (20 mL). The organic layer was dried (Na_2SO_4/activated carbon), filtered and concentrated to give a yellow solid. Trituration with hexanes/ether (9:1) afforded the title compound as an off-white solid (2.79 g, 78% yield). ^{1}H NMR (500 MHz, $CDCl_3$) δ ppm: 7.48-7.45 (2H, m), 7.37-7.30 (3H, m), 5.25 (2H, s), 4.33 (2H, q, J = 7.3 Hz), 4.05-3.99 (4H, m), 1.62 (6H, s), 1.29 (3H, t, J = 7.3 Hz). HRMS (M+H) calcd for $C_{19}H_{23}N_2O_5$: 359.1607; found: 359.1611. Anal calcd for $C_{19}H_{22}N_2O_5$: C, 63.67; H, 6.18; N, 7.81; found: C, 63.63; H, 6.16; N, 7.78.

Intermediate 27



3-(Benzyloxy)-9,9-dimethyl-4-oxo-4,6,7,9-tetrahydropyrimido[2,1-c][1,4]oxazine-2-carboxylic acid. A mixture of intermediate 26, ethyl 3-(benzyloxy)-9,9-dimethyl-4-oxo-4,6,7,9-tetrahydropyrimido[2,1-c][1,4]oxazine-2-carboxylate, (2.93 g, 8.2 mmol) and $LiOH \cdot H_2O$ (0.84 g, 20 mmol) in 4:1 ethanol/tetrahydrofuran (50 mL) was stirred for 2 h at ambient temperature then concentrated under vacuum. The resulting yellow residue was treated with 1N HCl (25 mL) providing a precipitate that was filtered and dried under vacuum to yield the title compound as a white powder (2.68 g, 99% yield). ^1H NMR (500 MHz, $CDCl_3$) δ ppm: 7.54-7.48 (2H, m), 7.37-7.27 (3H, m), 5.44 (2H, s), 4.05-3.93 (4H, m), 1.60 (6H, s).). HRMS (M+H) calcd for $C_{17}H_{19}N_2O_5$: 331.1294; found: 331.1308. Anal calcd for $C_{17}H_{18}N_2O_5$: C, 61.81; H, 5.49; N, 8.48; found: C, 61.84; H, 5.36; N, 8.25.

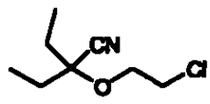
Intermediate 28



2-Ethyl-2-hydroxybutanenitrile. To a solution of potassium phosphate monobasic (140 g, 1.11 mole) in water (250 mL) was added 3-pentanone (75.8 g, 0.88 mole), followed by a solution of sodium cyanide (54 g, 1.10 mole) in water (250 mL), and the resulting mixture stirred for 3 hours. The mixture was extracted with diethyl ether (1 x 250 mL, then 2 x 100 mL) and the combined ether layers washed with 1.0 N HCl (200 mL). The ether solution was dried (Na_2SO_4), filtered, and

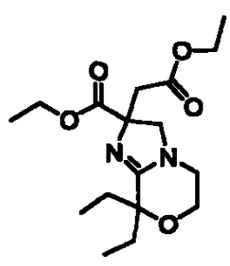
concentrated *in-vacuo*. The crude product was purified by vacuum distillation (bp 87 °C, 10 mmHg) to give the title compound (72.4 g, 3% yield) as a clear oil. ^{1}H NMR (500 MHz, $CDCl_3$) δ ppm: 2.71 (1H, s), 1.82 (2H, q, J = 7.5 Hz), 1.76 (2H, q, J = 7.5 Hz), 1.10 (6H, t, J = 7.5 Hz). ^{13}C NMR (500 MHz, $CDCl_3$) δ ppm: 121.21, 73.53, 32.81, 8.27.

Intermediate 29



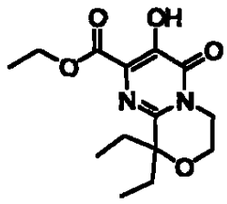
2-(2-Chloroethoxy)-2-ethylbutanenitrile. Zinc chloride (68.1 g, 0.5 mol) was fused under vacuum as described in the procedure for the synthesis of intermediate 23. The molten zinc was cooled and the evacuated flask was flushed with nitrogen. The flask was loaded with intermediate 28, 2-ethyl-2-hydroxybutanenitrile, (40.3 g, 0.5 mol) and 2-chloroethanol (50.5 mL, 0.75 mmol) then stirred at 60 °C for 20 hours. The reaction mixture was diluted with water (250 mL) and extracted with dichloromethane (1 x 250 mL, 4 x 100 mL). The combined organic layers were dried (sodium sulfate), filtered, and concentrated *in-vacuo*. The crude product was purified by vacuum distillation (bp 83 °C, 10 mmHg) to give the title compound (52g) containing unreacted intermediate 28. ^{1}H NMR (500 MHz, $CDCl_3$) δ ppm: 3.82 (2H, t, J = 5.8 Hz), 3.64 (2H, t, J = 5.8 Hz), 1.83 (4H, J = 7.3 Hz), 1.03 (6H, t, J = 7.6 Hz).

Intermediate 30



Diethyl 2-(2,2-diethyl-3-iminomorpholinooxy)but-2-enedioate. A solution of the product mixture obtained in the synthesis of intermediate 29, 2-(2-chloroethoxy)-2-ethylbutanenitrile, (0.171 mol) in absolute ethanol (150 mL) was added dropwise to a solution of hydroxylamine (50% aqueous solution, 33.8 mL, 0.51 mol), sodium carbonate (9.1 g, 0.086 mol) and sodium iodide (2.55 g, 0.017 mol) over 15 minutes. The mixture was heated at 80 °C for 3 hours. The reaction was then concentrated to a thick paste and azeotroped under vacuum with ethanol/water (1:1, 100 mL), water (100 mL) and finally ethanol (100 mL). The residue was taken up in ethanol/water (1:1, 160 mL), cooled (0 °C), and treated with diethyl acetylenedicarboxylate (30.1 mL, 0.188 mol). The reaction was stirred at room temperature for 2 hours, then diluted with water (200 mL) and ethyl acetate (200 mL). The organic layer was separated, washed with water (200 mL) and brine (100 mL),then dried (sodium sulfate), filtered and concentrated *in-vacuo*. The crude product was purified by column chromatography over silica gel, eluting with 10% to 40% ethyl acetate in hexanes to afford the title compound (25.7 g) as a yellow oil.

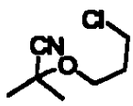
Intermediate 31



Ethyl 9,9-diethyl-3-hydroxy-4-oxo-4,6,7,9-tetrahydropyrimido[2,1-c][1,4]oxazine-2-carboxylate. A solution of intermediate 30, diethyl 2-(2,2-diethyl-3-iminomorpholinooxy)but-2-enedioate, (25.7 g) in 1,2,4-trimethylbenzene (100 mL) was heated at reflux (180 °C) for 16 hours. The solvent was then removed *in vacuo* and the resulting oil placed in a freezer until crystal formation began. The oil-crystal mixture was triturated with diethyl ether (50 mL) and the solid was collected by filtration, washing with a small volume of ether to provide the title compound (9.02 g). A second crop (1.62 g) was obtained from the filtrate. ^{1}H NMR (500 MHz, $CDCl_3$) δ ppm: 10.54 (1H, s), 4.44 (2H, q, J = 7.0 Hz), 4.00 (4H, m), 2.00 (2H, m),

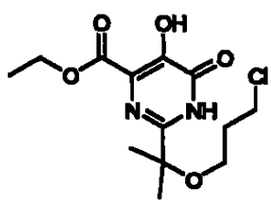
1.92 (2H, m), 1.42 (3H, t, J = 7.0 Hz), 0.85 (6H, t, J = 7.3 Hz). ^{13}C NMR (500 MHz, $CDCl_3$) δ ppm: 169.53, 157.82, 151.40, 147.58, 125.35, 87.27, 62.62, 58.35, 43.24, 31.06, 14.17, 7.79. HRMS $[M+H]^+$ calcd for $C_{14}H_{21}N_2O_5$: 297.14506; found: 297.1464.

Intermediate 32



2-(3-Chloropropoxy)-2-methylpropanenitrile. Zinc chloride (68.1 g, 0.5 mol) was fused using the procedure described for the synthesis of intermediate 23, 2-(2-chloroethoxy)-2-methylpropanenitrile. The molten zinc was cooled and the flask flushed with nitrogen. The flask was loaded with acetone cyanohydrin (46 mL, 0.5 mol) and 3-chloropropanol (64 mL, 0.75 mmol) and the reaction mixture stirred at 60 °C for 30 hours. The mixture was then diluted with water (200 mL) and extracted with dichloromethane (1 x 200 mL and 3 x 100 mL). The combined organic layers were dried (sodium sulfate), filtered, and concentrated *in-vacuo*. The crude product was purified by vacuum distillation (bp 78-84°C, 10 mmHg) to give the title compound (41g) as a 2:1 mixture with residual 3-chloropropanol. ^{1}H NMR (500 MHz, $CDCl_3$) δ ppm: 3.72 (2H, t, J = 5.8 Hz), 3.63 (2H, t, J = 6.4 Hz), 2.04 (2H, m), 1.57 (6H, br s).

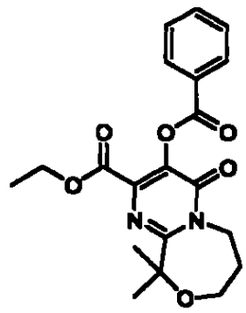
Intermediate 33



Ethyl 2-(2-(3-chloropropoxy)propan-2-yl)-5-hydroxy-6-oxo-1,6-dihydropyrimidine-4-carboxylate. A solution of intermediate 32, 2-(3-

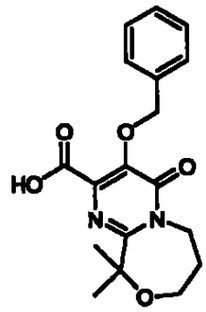
chloropropoxy)-2-methylpropanenitrile (0.186 mol) in absolute ethanol (40 mL) was added dropwise to a cold (0°C) solution of hydroxylamine (50% aqueous solution, 17 mL, 0.278 mol), 20 mL H_2O, sodium carbonate (9.91 g, 0.093 mol) and sodium iodide (2.80 g, 0.019 mol) over 15 minutes. (In an alternative procedure, sodium carbonate was omitted from the mixture). The mixture was stirred at room temperature for 30 min, then additional hydroxylamine (17 mL, 0.278 mol) was added. The reaction was then heated at 80°C for 16 hours. The mixture was concentrated to a thick paste which was azeotroped under vacuum with ethanol/water (1:1, 100 mL). The resulting residue was taken up in ethanol/water (1:1, 200 mL), cooled (0°C), and treated with diethyl acetylenedicarboxylate (30.1 mL, 0.188 mol) by dropwise addition over 10 min. The reaction was allowed to stir at room temperature for 2.5 hours, then diluted with water (300 mL) and ethyl acetate (300 mL). The separated organic layer was washed with water (100 mL) and brine (100 mL),then dried (sodium sulfate), filtered and concentrated *in-vacuo*. The crude product was purified by silica gel column chromatography, eluting with 10% to 40% ethyl acetate in hexanes, to give 21.2 g of a yellow oil. A solution of this oil (15.6 g) in 1,2,4-trimethylbenzene (300 mL) was heated at reflux (180 °C) for 2.5 hours after which the solvent was removed *in-vacuo*. The resulting oil was taken up in ethyl acetate (300 mL) and extracted with saturated aqueous sodium bicarbonate (1 x 200 mL, then 4 x 100 mL). The combined aqueous layers were acidified to pH 1-2 using 6 N HCl then extracted with ethyl acetate (3 x 150 mL). The organic extracts were dried (sodium sulfate), filtered, then concentrated *in vacuo*. The resulting oil was triturated with diethyl ether (50 mL) and the resulting solid collected by filtration and washed with a small volume of ether to afford the title compound (2.05 g). A second crop (0.70 g) was obtained from the filtrate. ^{1}H NMR (500 MHz, $CDCl_3$) δ ppm: 10.83 (1H, br), 10.02 (1H, br), 4.46 (2H, q, J = 7.0 Hz), 3.66 (2H, t, J = 6.1 Hz), 3.58 (2H, t, J = 5.8 Hz), 2.06 (2H, m), 1.55 (6H, s), 1.44 (3H, t, J = 7.0 Hz).

Intermediate 34



Ethyl 3-(benzoyloxy)-10,10-dimethyl-4-oxo-6,7,8,10-tetrahydro-4H-pyrimido[2,1-c][1,4]oxazepine-2-carboxylate. A solution of intermediate 33, ethyl 2-(2-(3-chloropropoxy)propan-2-yl)-5-hydroxy-6-oxo-1,6-dihydropyrimidine-4-carboxylate, (0.064 g, 0.2 mmol) in pyridine (1 mL) was treated with benzoic anhydride (0.047 g, 0.2 mmol) and stirred for 1 hr at 60°C. The solvent was removed and the residue taken up in N,N-dimethylformamide (1 mL) and treated with potassium carbonate (0.036 g, 0.2 mmol). The mixture was stirred for 1 hr at 80°C, and solvent was removed to give the title compound.

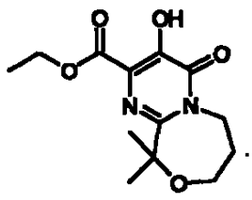
Intermediate 35



3-(Benzyloxy)-10,10-dimethyl-4-oxo-6,7,8,10-tetrahydro-4H-pyrimido[2,1-c][1,4]oxazepine-2-carboxylic acid. A suspension of intermediate 33, ethyl 2-(2-(3-chloropropoxy)propan-2-yl)-5-hydroxy-6-oxo-1,6-dihydropyrimidine-4-carboxylate, (0.205 g, 0.64 mmol) and anhydrous potassium carbonate (0.361 g, 2.6 mmol) in

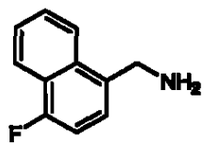
anhydrous dimethylformamide (4 mL) was stirred at 60°C for 5 hours. The reaction mixture was treated with benzyl bromide (0.122g, 0.71 mmol) and stirred for 16 hours. Following this, 2 mL of H_2O was added and the mixture stirred for an additional 24 hours. Solvent was removed by rotary evaporator and the resulting residue suspended in 0.5 N hydrochloric acid (16 mL). The crude product was extracted with ethyl acetate (2 x 15 mL), then dried (sodium sulfate), filtered, and concentrated to dryness by rotary evaporator to give 0.299 g (Yield >100%) of the title compound as a solid. LC/MS $[M+H]^+ = 345.21$.

Intermediate 36



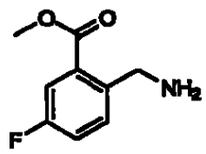
3-Hydroxy-10,10-dimethyl-4-oxo-6,7,8,10-tetrahydro-4H-pyrimido[2,1-c][1,4]oxazepine-2-carboxylate. A solution of intermediate 33, ethyl 2-(2-(3-chloropropoxy)propan-2-yl)-5-hydroxy-6-oxo-1,6-dihydropyrimidine-4-carboxylate, (7.01 g, 22 mmol) and anhydrous potassium carbonate (9.12 g, 66 mmol) in anhydrous dimethylformamide (50 mL) was stirred at 80 °C for 20 hours. Solvent was removed by rotary evaporator and the residue, dissolved in water (50 mL), was brought to pH 1 using 6.0 N HCl. The solution was extracted with ethyl acetate (4 x 25 mL). The combined organic layers were dried (sodium sulfate) and filtered. The solvent was removed by rotary evaporator to give the title compound (5.53 g, Yield 89%) as a brown solid: ^{1}H NMR (500 MHz, $CDCl_3$) δ ppm 10.49 (1H, s), 4.56 (2H, br), 4.43 (2H, q, *J*=7.2 Hz), 3.69 (2H, t, *J*=6.4 Hz), 1.93-1.99 (2H, m), 1.61 (6H, s), 1.42 (3H, t, *J*=7.2 Hz); ^{13}C NMR (126 MHz, $CDCl_3$) δ ppm 169.33, 158.30, 153.39, 148.73, 124.45, 82.85, 62.60, 60.71, 38.79, 27.67, 27.35, 14.15; HRMS (ESI) calcd for $C_{13}H_{19}N_2O_5$ (M+H) 283.1294, found 283.1305.

Intermediate 37



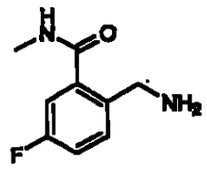
(4-Fluoronaphthalen-1-yl)methanamine hydrochloride. A solution of 1-cyano-4-fluoronapthalene (1.05 g, 6.12 mmol) and 1.5 mL of HCl (aq.) in absolute ethanol (50 mL) was stirred under a hydrogen atmosphere (balloon) with 10% palladium on carbon (0.20 g) for 16 hours. The catalyst was removed by filtration through Celite, and the filtrate concentrated under vacuum. The resulting solid was triturated with ether and collected by filtration to give the title compound (0.575 g, 44% yield) as an off white solid.

Intermediate 38



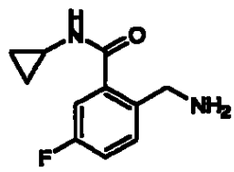
Methyl 2-(aminomethyl)-5-fluorobenzoate trifluoroacetic acid salt. Methyl 2-((*tert*-butoxycarbonyl)methyl)-5-fluorobenzoate, prepared according to literature methods, was treated with trifluoroacetic acid to provide the title compound. Yield 100%; ^{1}H NMR (300 MHz, DMSO-d6) δ ppm: 3.89 (3H, s) 4.32 (2H, q, *J*=5.61 Hz) 7.51-7.71 (2H, m) 7.78 (1H, dd, *J*=9.33, 2.38 Hz) 8.13 (2H, bra); LC/MS m/z 184 (M+H)

Intermediate 39



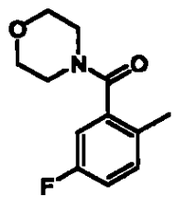
2-Aminomethyl-5-fluoro-N-methyl-benzamide trifluoroacetic acid salt. To a solution of *tert*-butyl 4-fluoro-2-(methylcarbamoyl)benzylcarbamate (7.70 g, 27.3 mmol; prepared from 2-bromo-5-fluorobenzoic acid using literature methods) in CH_2Cl_2 (100 mL) was added CF_3CO_2H (25 mL) and the mixture stirred at room temperature for 15 min. This was concentrated *in vacuo* and the residue triturated with diethyl ether to obtain 8.0 g (Yield 99%) of the title compound as a white powder. ^1H NMR (300 MHz, D_2O) δ ppm: 2.93 (3 H, s) 4.20 (2 H, s) 7.35 (1 H, dt, J=8.5, 3 Hz) 7.42 (1 H, dd, J=9.0, 2.7 Hz) 7.57 (1 H, dd, J=8.4, 5.5 Hz); LC/MS m/z 183 (M+H).

Intermediate 40



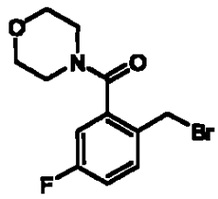
2-(Aminomethyl)-N-cyclopropyl-5-fluorobenzamide trifluoroacetic acid salt. A solution of *tert*-butyl 2-(cyclopropylcarbamoyl)-4-fluorobenzylcarbamate (130 mg, 0.42 mmol) prepared according to literature methods, in CH_2Cl_2 (5 mL) was stirred with trifluoroacetic acid (3 mL) at room temperature for 10 min, then concentrated *in vacuo* to give 140 mg (Yield 100%) of the title compound as a foam: ^1H NMR (DMSO-d6, 300 MHz) δ ppm: 0.62 (2H, m, CH_2), 0.73 (2H, m, CH_2), 2.86 (1H, m, CH), 4.02-4.07 (2H, ABq, NCH_2), 7.46 (2H, m, Ar-Hs), 7.58 (1H, m, Ar-H), 8.11 (3H, br, NH3), 8.81 (1H, d, J = 4.4 Hz, NH); LC/MS m/z 209 (M+H).

Intermediate 41



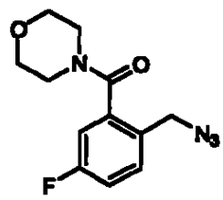
(5-Fluoro-2-methylphenyl)(morpholino)methanone. To a solution of morpholine (870 mg, 10 mmol) and triethylamine (1.1 g, 10.8 mmol) in CH_2Cl_2 (15 mL) was added a solution of 5-fluoro-2-methylbenzoyl chloride (1.72 g, 10 mmol) in CH_2Cl_2 (5 mL), dropwise, and the mixture stirred for 15 min. The mixture was then washed with water, and the organic phase dried ($MgSO_4$), filtered, and concentrated to obtain 2.19 g (Yield 98%) of the title compound as a solid: ^1H NMR (500 MHz, $CDCl_3$) δ ppm: 2.27 (3H, s) 3.24 (2H, d, J=4 Hz) 3.58 (2H, s) 3.79 (4 H, dd, J=18, 3.8 Hz) 6.88 (1H, dd, J=8.2, 2.8 Hz) 6.92-7.05 (1 H, m) 7.18 (1 H, dd, J=8.4, 5.3 Hz).

Intermediate 42



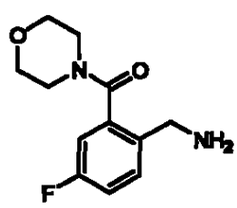
(2-(Bromomethyl)-5-fluorophenyl)(morpholino)methanone. A mixture of intermediate 41, (5-fluoro-2-methylphenyl)(morpholino)methanone, (2.1 g, 9.5mmol) and N-bromosuccinimide (2.0 g, 11 mmol) in CCl_4 (30 mL) was heated at reflux. To this mixture was added benzoylperoxide (242 mg, 1 mmol) and the mixture heated at reflux for 2hrs. After cooling, the insoluble materials were filtered and the filtrate purified by column chromatography (SiO_2, 0-10% ether in CH_2Cl_2) to give 1.1 g (Yield 38%) of the title compound as a clear oil: ^1H NMR (300 MHz, $CDCl_3$) δ ppm: 3.31 (2H, t, J=4.94 Hz) 3.55-4.02 (6H, m) 4.56 (2H, dd, J=128.81, 9.51 Hz) 6.89 (1H, dd, J=8.23, 2.74 Hz) 6.96-7.12 (1H, m) 7.33-7.49 (1H, m); LC/MS m/z 302 (M+H).

Intermediate 43



(2-(Azidomethyl)-5-fluorophenyl)(morpholino)methanone. To a solution of intermediate 42, (2-(bromomethyl)-5-fluorophenyl)(morpholino)methanone, (1.0 g, 3.32 mmol) in dimethylformamide (10 mL) was added sodium azide (230 mg, 3.5 mmol) and the mixture stirred under a nitrogen atmosphere for 1 h. The solvent was evaporated *in vacuo*, and the residue dissolved in CH_2Cl_2, then washed with water. The organic phase was dried (Na_2SO_4), filtered, concentrated, and the residue purified by column chromatography (SiO_2, CH_2Cl_2) to provide 770 mg (Yield 88%) of the title compound as an oil: ^{1}H NMR (300 MHz, $CDCl_3$) δ ppm: 3.27 (2H, s) 3.51-3.65 (2H, m) 3.66-3.97 (4H, m) 4.38 (2H, brs) 6.92 (1H, dd, J=8.2, 2.7 Hz) 7.07 (1H, dt, J=8.5, 3 Hz) 7.34 (1 H, dd, J=8.4, 5.5 Hz); LC/MS m/z 265 (M+H).

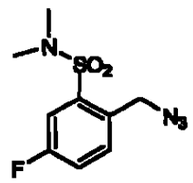
Intermediate 44



(2-(Aminomethyl)-5-fluorophenyl)(morpholino)methanone hydrochloride. To a solution of intermediate 43, (2-(azidomethyl)-5-fluorophenyl)(morpholino)methanone, (770 mg, 2.92 mmol,) in ethanol (20 mL) was added 4N HCl (1 mL) and 10% Pd-C (100 mg), and the mixture hydrogenated at 1 atm of H_2 for 3 hrs. The catalyst was removed by filtration and the filtrate concentrated. The residue was purified by C18 reverse phase silica gel column chromatography (YMC ODS, 0-5% CH_3CN/H_2O) to obtain 350 mg (Yield 44%) of

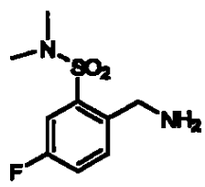
(AIBN, 100 mg) and stirring continued at 80-90 °C for 30 min. After cooling, the insoluble precipitates were filtered and the filtrate concentrated and purified by column chromatography (SiO_2, CH_2Cl_2) to provide 440 mg (Yield 74%) of the title compound; ^1H NMR (500 MHz, $CDCl_3$) δ ppm: 2.87 (6 H, s) 4.86 (2 H, s) 7.28 (1 H, dd, J=8.55, 2.75 Hz) 7.61-7.65 (2 H, m); LC/MC m/z 296/298 (M+H).

Intermediate 47



2-Azidomethyl-5-fluoro-N,N-dimethyl-benzenesulfonamide. A mixture of intermediate 46, 2-bromomethyl-5-fluoro-N,N-dimethyl-benzenesulfonamide, (880 mg, 2.97 mmol) and sodium azide (200 mg, 3 mmol) in dimethylformamide (4 mL) was stirred at 55-60 °C for 30 min after which the solvent was removed *in vacuo*. The residue was partitioned between CH_2Cl_2 and water, and the organic phase was washed with water, dried (Na_2SO_4), filtered and concentrated to provide 670 mg (Yield 87%) of the title compound as a yellow oil; ^1H NMR (500 MHz, $CDCl_3$) δ ppm: 2.84 (6 H, s) 4.78 (2 H, s) 7.29-7.34 (1 H, m) 7.59-7.64 (2 H, m).

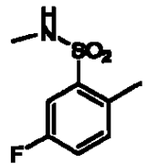
Intermediate 48



2-(Aminomethyl)-5-fluoro-N,N-dimethylbenzenesulfonamide. To a solution of intermediate 47, 2-azidomethyl-5-fluoro-N,N-dimethyl-benzenesulfonamide, (660 mg, 2.6 mmol) in tetrahydrofuran (10 mL) and water (2 mL) was added

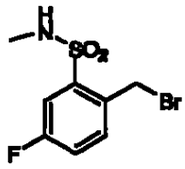
triphenylphosphine (740 mg, 2.8 mmol), and the mixture stirred under nitrogen for 1 hr. The tetrahydrofuran was evaporated in vacuo and a mixture of the residue and 6N HCl (3 mL) in MeOH (5 mL) was heated at 80 °C for 20 hrs. This was washed with CH_2Cl_2, and the aqueous phase basified with dilute NH_4OH and extracted with CH_2Cl_2. The organic extract was dried (Na_2SO_4), filtered and concentrated to provide 210 mg (0.91 mmol, Yield 35%) of the title compound; ^1H NMR (500 MHz, $CDCl_3$) δ ppm: 2.84 (6 H, s) 4.10 (2 H, s) 7.23-7.29 (1 H, m) 7.53-7.60 (2 H, m); LC/MS m/z 233 (M+H).

Intermediate 49



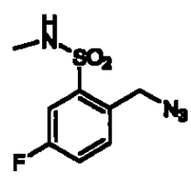
5-Fluoro-2,N-dimethyl-benzenesulfonamide. To a solution of 5-fluoro-2-methyl-benzenesulfonyl chloride (4.18 g, 20 mmol) in acetone (20 mL) was added a 40% aqueous solution of methylamine (4.5 mL, 60 mmol) under nitrogen and the mixture stirred for 5 min. Acetone was removed *in vacuo* and the aqueous residue extracted with CH_2Cl_2. The CH_2Cl_2 extract was dried (Na_2SO_4), filtered, concentrated and the residue purified by column chromatography (SiO_2, 10% ether in CH_2Cl_2) to provide 3.9 g (19.2 mmol, Yield 96%) of the title compound as a white solid; ^1H NMR (500 MHz, $CDCl_3$) δ ppm: 2.59 (3H, s), 2.67 (3H, d, J=5.5 Hz), 4.41 (1H, brs), 7.13-7.20 (1H, m), 7.29 (1H, dd, J=8.2, 5.5 Hz), 7.69 (1H, J=8.6, 2.1 Hz); LC/MS m/z 204 (M+H).

Intermediate 50



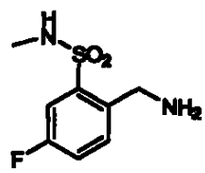
2-Bromomethyl-5-fluoro-N-methyl-benzenesulfonamide. The title compound can be prepared from intermediate 49, 5-fluoro-2,N-dimethyl-benzenesulfonamide, according to the method described for intermediate 46 and purified by column chromatography (SiO_2, 5% ether/CH_2Cl_2). ^1H NMR (500 MHz, $CDCl_3$) δ ppm: 2.64 (3 H, d, J=5.19 Hz) 4.91 (1 H, d, J=3.66 Hz) 4.98 (2 H, s) 7.26-7.30 (1 H, m) 7.54 (1 H, dd, J=8.6, 5.2 Hz) 7.73 (1 H, dd, J=8.4, 2.6 Hz); LC/MS m/z 282/284.

Intermediate 51



2-Azidomethyl-5-fluoro-N-methyl-benzenesulfonamide. The title compound can be prepared from intermediate 50, 2-bromomethyl-5-fluoro-N-methyl-benzenesulfonamide, according to the method described for intermediate 47 and purified by column chromatography (SiO_2, 5% ether- CH_2Cl_2). ^1H NMR (500 MHz, $CDCl_3$) δ ppm: 2.65 (3 H, d, J=5.19 Hz) 4.81 (2 H, s) 4.86 (1 H, d, J=4.6 Hz) 7.27-7.33 (1 H, m) 7.49 (1 H, dd, J=8.2, 5.2 Hz) 7.76 (1 H, dd, J=8.2, 2.8 Hz).

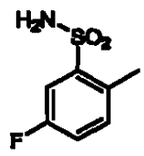
Intermediate 52



2-(Aminomethyl)-5-fluoro-N-methylbenzenesulfonamide hydrochloride. To a solution of intermediate 51, 2-azidomethyl-5-fluoro-N-methyl-benzenesulfonamide, (560 mg, 2.3 mmol) in ethanol (10 mL) was added 6N HCl (1 mL) and 10% Pd-C (100 mg) and the mixture hydrogenated with 1 atm of H_2 for 14 hrs. The catalyst was removed by filtration through Celite and the filtrate concentrated *in vacuo* to

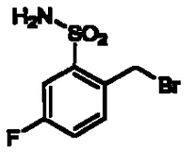
provide 630 mg (Yield >100%) of the title compound. ^{1}H NMR (500 MHz, DMSO-D6) δ ppm: 4.36 (2 H, d, J=5.2 Hz) 7.63-7.70 (2 H, m) 7.77-7.83 (1 H, m) 8.11 (1 H, d, J=4.9 Hz) 8.41 (3 H, s); LC/MS m/z 219 (M+H).

Intermediate 53



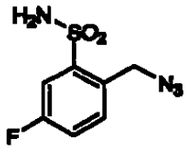
5-Fluoro-2-methyl-benzenesulfonamide. To a solution of 5-fluoro-2-methyl-benzenesulfonyl chloride (4.18 g, 20 mmol) in acetone (20 mL) was added, dropwise, concentrated NH_4OH (3 mL) and the resulting mixture stirred for 5 min. Acetone was removed *in vacuo* and the precipitates were filtered, washed thoroughly with water and dried *in vacuo* to provide 3.7 g (Yield 98%) of the title compound as a white solid; ^{1}H NMR (500 MHz, DMSO-D6) δ ppm: 2.55 (3 H, s) 7.33-7.40 (1 H, m) 7.40-7.46 (1 H, m) 7.54 (2 H, s) 7.59 (1 H, dd, J=9.2, 2.7 Hz); LC/MS m/z 190 (M+H).

Intermediate 54



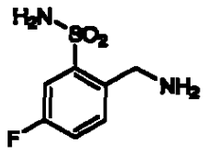
2-Bromomethyl-5-fluoro-benzenesulfonamide. The title compound can be prepared from intermediate 53, 5-fluoro-2-methyl-benzenesulfonamide, according to the method described for intermediate 46, and purified by column chromatography (SiO_2, 5% ether/CH_2Cl_2). ^{1}H NMR (500 MHz, $CDCl_3$) δ ppm: 5.01 (2 H, s) 5.16 (2 H, brs) 7.25-7.31 (1 H, m) 7.53 (1 H, dd, J=8.5, 5.2 Hz) 7.80 (1 H, dd, J=8.5, 2.7 Hz). LC/MS m/z 268/270 (M+H).

Intermediate 55



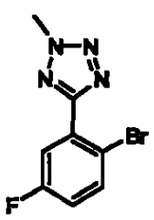
2-Azidomethyl-5-fluoro-N-methyl-benzenesulfonamide. The title compound can be prepared from intermediate 54, 2-bromomethyl-5-fluoro-benzenesulfonamide, according to the method described for the preparation of intermediate 47. ^{1}H NMR (300 MHz, $CDCl_3$) δ ppm: 4.82 (2 H, s) 5.18 (2 H, s) 7.27 (1 H, m) 7.45 (1 H, dd, J=8.4, 5.5 Hz) 7.79 (1 H, dd, J=8.4, 2.6 Hz). LC/MS m/z 253 (M+Na).

Intermediate 56



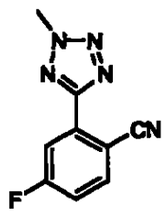
2-(Aminomethyl)-5-fluorobenzenesulfonamide hydrochloride. The title compound can be prepared from intermediate 55, 2-azidomethyl-5-fluoro-N-methyl-benzenesulfonamide, according to the method described for the preparation of intermediate 48. ^{1}H NMR (500 MHz, DMSO-D6) δ ppm: 4.05 (2 H, s) 5.05 (3 H, br) 7.44 (1 H, dt, J=8.5, 3 Hz) 7.58 (1 H, dd, J=9.2, 2.7 Hz) 7.66 (1 H, dd, J=8.5, 5.5 Hz). LC/MS m/z 205 (M+H).

Intermediate 57



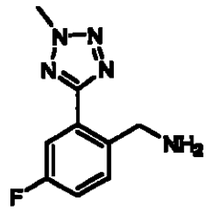
5-(2-Bromo-5-fluoro-phenyl)-2-methyl-2H-tetrazole. A mixture of 5-(2-bromo-5-fluoro-phenyl)-1H-tetrazole (1.0 g, 4.12 mmol), iodomethane (1.12 g, 10 mmol) and potassium carbonate (1.5 g) in dimethylformamide (5 mL) was stirred at room temperature for 16 hrs, then concentrated *in vacuo*. The residue was purified by column chromatography (SiO_2, CH_2Cl_2) to provide 650 mg (Yield 61%) of the title compound as a white powder. ^1H NMR (500 MHz, $CDCl_3$) δ ppm: 4.45 (3 H, s) 7.03-7.11 (1 H, m) 7.63 (1 H, dd, J=8.9, 3.1 Hz) 7.69 (1 H, dd, J=8.9, 5.5 Hz); ^{13}C NMR (126 MHz, $CDCl_3$) δ ppm: 39.86, 116.28, 118.66, 118.76, 130.13, 135.73, 161.74, 163.53; LC/MS m/z 257/259.

Intermediate 58



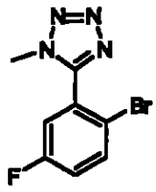
4-Fluoro-2-(2-methyl-2H-tetrazol-5-yl)-benzonitrile. A mixture of intermediate 57, 5-(2-bromo-5-fluoro-phenyl)-2-methyl-2H-tetrazole (650 mg, 2.53 mmol) and CuCN (224 mg, 2.5 mmol) in dimethylformamide (4 mL) was placed in a sealed tube and heated at 100-110 °C for 20 hrs. After cooling, the insoluble material was filtered, and the filtrate concentrated in vacuo. The residue was dissolved in CH_2Cl_2, washed with aq. 4N HCl and dil. NH_4OH, then dried ($MgSO_4$), filtered, and concentrated. The residual solid was purified by column chromatography (SiO_2, CH_2Cl_2) to obtain 375 mg (Yield 73%) of the title compound as an off-white solid; ^1H NMR (500 MHz, $CDCl_3$) δ ppm: 4.48 (3 H, s) 7.29 (1 H, dd, J=7.6, 2.8 Hz) 7.85 (1 H, dd, J=8.6, 5.2 Hz) 8.00 (1 H, dd, J=9.0, 2.6 Hz); LC/MS m/z 204.

Intermediate 59



(4-Fluoro-2-(2-methyl-2H-tetrazol-5-yl)phenyl)methanamine hydrochloride. A solution of intermediate 58, 4-fluoro-2-(2-methyl-2H-tetrazol-5-yl)-benzonitrile, (330 mg, 1.62 mmol) in ethanol (15 mL) was mixed with 6N HCl (1 mL) and 10% Pd-C (200 mg) under nitrogen. The mixture was then stirred under hydrogen (1 atm) for 3 hrs. After removing the catalyst, the filtrate was concentrated *in vacuo* to provide 360 mg (Yield 91%) of the title compound as an off-white solid; ^{1}H NMR (500 MHz, DMSO-D6) δ ppm: 4.42 (2 H, d, J=2.75 Hz) 4.49 (3 H, s) 7.48-7.56 (1 H, m) 7.78 (1 H, dd, J=8.7, 5.7 Hz) 7.86 (1 H, dd, J=9.8, 2.8 Hz) 8.45 (3 H, s); LC/MS m/z 208.

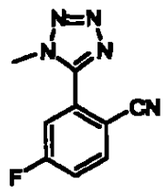
Intermediate 60



5-(2-Bromo-5-fluoro-phenyl)-1-methyl-2H-tetrazole. A mixture of 5-(2-bromo-5-fluoro-phenyl)-1H-tetrazole (1.0 g, 4.12 mmol), iodomethane (1.12 g, 10 mmol) and potassium carbonate (1.5 g) in dimethylformamide (5 mL) was stirred at room temperature for 16 hrs, then concentrated *in vacuo*. The residue was purified by column chromatography (SiO_2, CH_2Cl_2) to provide 350 mg (Yield 33%) of the title compound as white crystals. ^{1}H NMR (500 MHz, $CDCl_3$) δ ppm: 4.00 (3 H, s) 7.18-7.25 (2 H, m) 7.72 (1 H, dd, J=8.4, 5.0 Hz); ^{13}C NMR (126 MHz, $CDCl_3$) δ

ppm: 34.59, 117.73, 119.58, 120.43, 127.57, 135.11, 153.43, 161.69. LC/MS m/z 257/259.

Intermediate 61



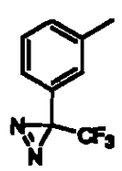
4-Fluoro-2-(1-methyl-2H-tetrazol-5-yl)-benzonitrile. ^{1}H NMR (300 MHz, $CDCl_3$) δ ppm: 4.13 (3 H, s) 7.38-7.49 (2 H, m) 7.86-7.97 (1 H, m); LC/MS m/z 204 (M+H).

Intermediate 62



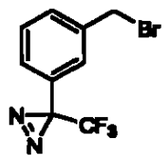
(4-Fluoro-2-(1-methyl-2H-tetrazol-5-yl)phenyl)methanamine hydrochloride. ^{1}H NMR (500 MHz, DMSO-D6) δ ppm: 4.05 (2 H, s) 4.09 (3 H, s) 7.58-7.67 (1 H, m) 7.77 (1 H, dd, J=9.3, 2.6 Hz) 7.87 (1 H, dd, J=8.7, 5.7 Hz) 8.38 (3 H, s); LC/MS m/z 208.

Intermediate 63



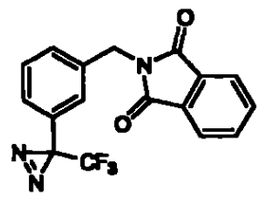
3-m-Tolyl-3-trifluoromethyl-3H-diazirine. To a cold stirring solution of 3-m-tolyl-3-trifluoromethyl-diaziridine (2.0 g, 10 mmol. prepared using the methods described in Doucet-Personeni C. et al., *J. Med. Chem.*, 2001, *44*, 3203 and Nassal, M. *Liebigs Ann. Chem.* 1983, 1510-1523 or in Stromgaard, K et al., *J. Med. Chem.*, 2002, *45*, 4038-46) in ethanol (20 mL) was added triethylamine (1.5 g, 15 mmol). To this mixture was added tert-butyl hypochlorite (3.25 g, 30 mmol), and the mixture stirred for 5 min. This mixture was poured into 10% aqueous sodium sulfite (100 mL), and extracted with ether. The ether extract was washed with brine, dried ($MgSO_4$), filtered and concentrated. The residue was purified by column chromatography (SiO_2, pentane) to provide 1.6 g (Yield 80%) of the title compound. ^1H NMR (300 MHz, $CDCl_3$) δ ppm: 2.33 (3 H, s) 6.90-7.03 (2 H, m) 7.15-7.31 (2 H, m).

Intermediate 64



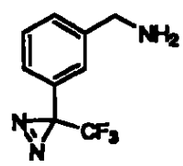
3-(3-Bromomethyl-phenyl)-3-trifluoromethyl-3H-diazirine. To a solution of intermediate 63, 3-m-tolyl-3-trifluoromethyl-3H-diazirine, (200 mg, 1 mmol) in CCl_4 (4 mL) was added N-bromosuccinimide (200 mg, 1.1 mmol, re-crystallized from water), and the stirred mixture heated at 85 °C. To this was added AIBN (50 mg) and the mixture heated at reflux for an additional 2.5 hrs. After cooling, the mixture was purified by column chromatography (SiO_2, pentane) to provide 150 mg (Yield 54%) of the title compound as a clear oil. ^1H NMR (300 MHz, $CDCl_3$) δ ppm: 4.42 (2 H, s) 7.10-7.17 (2 H, m) 7.31-7.45 (2 H, m).

Intermediate 65



2-[3-(3-Trifluoromethyl-diaziridin-3-yl)-benzyl]-isoindole-1,3-dione. A mixture of intermediate 64, 3-(3-bromomethyl-phenyl)-3-trifluoromethyl-3H-diazirine, (140 mg, 0.5 mmol) and potassium phthalimide (95 mg, 0.5 mmol) in dimethylformamide (1.5 mL) was stirred at room temperature for 3 hrs. Dimethylformamide was removed *in vacuo*. The residue was extracted with CH_2Cl_2, washed with water, then dried (Na_2SO_4), filtered, and concentrated. The resulting residue was purified by column chromatography (SiO_2, 1:1 CH_2Cl_2/pentane) to provide 140 mg (Yield 82%) of the title compound as a solid; ^{1}H NMR (300 MHz, $CDCl_3$) δ ppm: 4.80 (2 H, s) 7.09-7.21 (2 H, m) 7.32 (1 H, t, J=7.9 Hz) 7.41-7.49 (2 H, m) 7.66-7.71 (2 H, m) 7.81-7.85 (2 H, m); LC/MS m/z 346 (M+H).

Intermediate 66



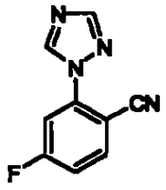
(3-(3-(Trifluoromethyl)diaziridin-3-yl)phenyl)methanamine. A stirred solution of intermediate 65, 2-[3-(3-trifluoromethyl-diaziridin-3-yl)-benzyl]-isoindole-1,3-dione, (150 mg, 0.43 mmol) in ethanol (2 mL) was treated with hydrazine hydrate (0.4 mL) at room temperature and the solution stirred for 3.5 hrs. After removing ethanol *in vacuo*, the residue was partitioned between CH_2Cl_2 and water. The aqueous phase was acidified with dilute HCl, and washed with CH_2Cl_2. The aqueous phase was basified with dilute NaOH, and extracted with CH_2Cl_2. The organic extract was dried ($MgSO_4$), filtered, and concentrated to obtain 50 mg (Yield

54%) of (3-(3-(trifluoromethyl)diaziridin-3-yl)phenyl)methanamine and (3-(3-(trifluoromethyl)-3H-diazirin-3-yl)phenyl)methanamine as a 1:1 mixture; ^{1}H NMR (300 MHz, $CDCl_3$) δ ppm: 3.85 (2 H, s) 3.88 (2 H, s) 7.08 (2 H, s) 7.31-7.40 (4 H, m) 7.43-7.50 (1 H, m, J=6.2 Hz) 7.54 (1 H, s); LC/MS m/z 216 (M+H for diazirine) and 218 (M+H for diaziridine).

Intermediates 67-68

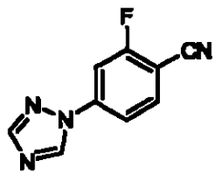
To a solution of 2,4-difluorobenzonitrile (10 g, 72 mmol) dissolved in tetrahydrofuran (20 mL), and dimethylformamide (40 mL) was added 1,2,4-triazole sodium salt (6.3 g, 70 mmol) and the mixture stirred at 90 °C for 3 h after which the mixture was filtered and the solvent removed. The resulting residue was adsorbed onto silica gel and intermediates 67 and 68 separated by flash chromatography, eluting with 0% to 30% ethyl acetate/hexanes.

Intermediate 67



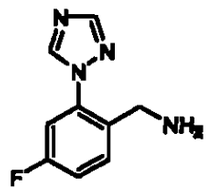
4-Fluoro-2-(1H-1,2,4-triazol-1-yl)benzonitrile. Colorless needles (2.46 g, 18% yield) ^{1}H NMR (500 MHz, $CDCl_3$) δ: 8.89 (1H, s), 8.19 (1H, s), 7.85 (1H, dd, *J* = 8.7, 5.6 Hz), 7.60 (1H, dd, *J* = 8.8, 2.4 Hz), 7.28-7.24 (1H, m). LCMS (M+H) calcd for $C_9H_6N_4F$: 189.05; found: 189.13.

Intermediate e 68



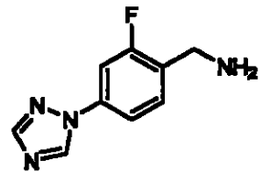
4-(1H-1,2,4-Triazol-1-yl)-2-fluorobenzonitrile. White solid (0.746 g, 6% yield) ^{1}H NMR (500 MHz, $CDCl_3$) δ: 8.66 (1H, s), 8.15 (1H, s), 7.79 (1H, dd, J= 8.5, 6.7 Hz), 7.69 (1H, dd, J= 9.5, 1.8 Hz), 7.65-7.63 (1H, m). LCMS (M+H) calcd for $C_9H_6N_4F$: 189.05; found: 189.13.

Intermediate 69



(4-Fluoro-2-(1H-1,2,4-triazol-1-yl)phenyl)methanamine hydrochloride). Intermediate 67, 4-fluoro-2-(1H-1,2,4-triazol-1-yl)benzonitrile, (2.46 g, 13.13 mmol) was dissolved in hot ethanol (150 mL). To this was added 1N HCl (15 mL) followed by 10% Pd-C (200 mg). The mixture was treated with H_2 at 55 psi for 4 h in a Parr shaker then filtered over Celite and the solvent removed under reduced pressure. The resulting residue was partitioned between ethyl acetate and water. The aqueous phase was separated and lyophilized to afford the title compound as a white powder (2.96 g, 99% yield). ^{1}H NMR (500 MHz, CD_3OD) δ ppm: 9.51 (1H, s), 8.63 (1H, s), 7.85 (1H, dd, J= 8.5, 5.8 Hz), 7.68 (1H, dd, J= 8.8, 2.4 Hz), 7.49 (1H, td, J= 8.3, 2.4 Hz), 4.20 (2H, s). LCMS (M+H) calcd for $C_9H_{10}N_4F$: 193.08; found: 193.16.

Intermediate 70

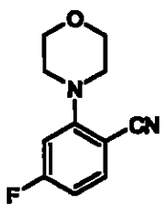


(2-Fluoro-4-(1H-1,2,4-triazol-1-yl)phenyl)methanamine hydrochloride. The title compound can be prepared from intermediate 68 according to the method described for the synthesis of intermediate 69. White powder (79% yield). ^{1}H NMR (500 MHz, CD_3OD) δ ppm: 9.25 (1H, s), 8.46 (1H, s), 7.80 (1H, dd, J = 8.6, 5.8 Hz), 7.64 (1H, dd, J = 8.8, 2.4 Hz), 7.44 (1H, td, J = 8.3, 2.6 Hz), 4.17 (2H, s). LCMS (M+H) calcd for $C_9H_{10}N_4F$: 193.08; found: 193.16.

Intermediates 71-74

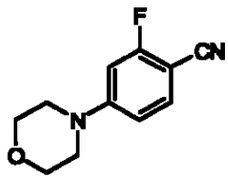
Intermediates 71-74 were prepared using the procedure described for the synthesis of intermediate 67-70.

Intermediate 71



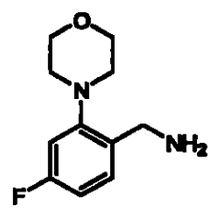
4-Fluoro-2-morpholinobenzonitrile ^{1}H NMR (500 MHz, $CDCl_3$) δ ppm: 7.55 (1H, dd, J = 8.5, 6.4 Hz), 6.71 (1H, td, J = 8.1, 2.3 Hz), 6.67 (1H, dd, J = 11.0, 2.4 Hz), 3.88 (4H, t, J = 4.6 Hz), 3.22 (4H, t, J = 4.6 Hz). LCMS (M+H) calcd for $C_{11}H_{12}N_2OF$: 207.09; found: 207.19.

Intermediate 72



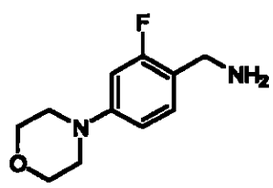
4-Morpholino-2-fluorobenzonitrile. ^{1}H NMR (500 MHz, $CDCl_3$) δ ppm: 7.42 (1H, dd, J = 8.8, 7.6 Hz), 6.63 (1H, dd, J = 8.8, 2.4 Hz), 6.56 (1H, dd, J = 12.8, 2.4 Hz), 3.84 (4H, t, J = 4.9 Hz), 3.28 (4H, t, J = 4.9 Hz). LCMS (M+H) calcd for $C_{11}H_{12}N_2OF$: 207.09; found: 207.19.

Intermediate 73



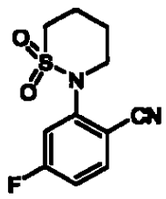
(4-Fluoro-2-morpholinophenyl)methanamine hydrochloride. ^{1}H NMR (500 MHz, $CDCl_3$) δ ppm: 7.54 (1H, t, J = 7.3 Hz), 7.20 (1H, dd, J = 10.5, 2.0 Hz), 7.05-7.02 (1H, m), 4.28 (2H, s), 3.93 (4H, bs), 3.03 (4H, bs). LCMS (M+H) calcd for $C_{11}H_{16}N_2OF$: 211.12; found: 211.23.

Intermediate 74



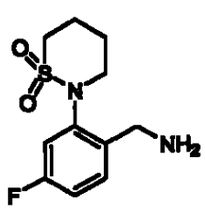
(2-Fluoro-4-morpholinophenyl)methanamine hydrochloride. ^{1}H NMR (500 MHz, CD_3OD) δ ppm: 7.73 (1H, t, J = 8.2 Hz), 7.62 (1H, d, J = 7.6 Hz), 7.58 (1H, d, J = 8.2 Hz), 4.26 (2H, s), 4.11 (4H, t, J = 4.4 Hz), 3.65 (4H, t, J = 4.4 Hz). LCMS (M+H) calcd for $C_{11}H_{16}N_2OF$: 211.12; found: 211.23.

Intermediate 75



4-Fluoro-2-(1,1-dioxo-1λ^6-[1,2]thiazinan-2-yl)benzonitrile. To a mixture of 2,4-difluorobenzonitrile (10.0 g, 72 mmol) and 1,1-dioxo-1λ6-[1,2]thiazin-2-ane (8.84 g, 65.4 mmol) in 1:1 tetrahydrofuran/dimethylformamide (40 mL) was added potassium carbonate (9.0 g, 65.4 mmol). The mixture was stirred at 90 °C for 18 h then filtered and concentrated. The residue was purified by flash chromatography (SiO_2) eluting with 10%-50% ethyl acetate/hexanes followed by recrystallization from hot ethyl acetate/hexane to give the title compound as white needles (0.537 g, 3% yield). ^{1}H NMR (500 MHz, CD_3OD) δ ppm: 7.70 (1H, dd, J = 8.8, 5.8 Hz), 7.30 (1H, dd, J = 8.8, 2.4 Hz), 7.15-7.12 (1H, m), 3.27 (2H, t, J = 5.3 Hz), 3.33 (2H, t, J = 6.1 Hz), 2.40-2.35 (2H, m), 2.05-2.01 (2H, m). LCMS (M+H) calcd for $C_{11}H_{16}N_2OF$: 255.06; found: 255.19.

Intermediate 76

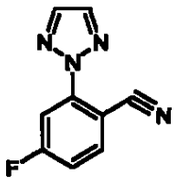


(4-Fluoro-2-(1,1-dioxo-1λ⁶-[1,2]thiazinan-2-yl)phenyl)methanamine hydrochloride. Intermediate 75, 4-fluoro-2-(1,1-dioxo-1λ⁶-[1,2]thiazinan-2-yl)benzonitrile (1. 37 g, 5.4 mmol) was dissolved in ethanol (120 mL). To this was added 1N HCl (20 mL) and a catalytic amount of 10% Pd-C. The mixture was shaken under hydrogen at 55 psi for 4 h then filtered through Celite and concentrated to give the title compound as white solid (1.58 g, 100% yield). ^{1}H-NMR (300 MHz, CD_3OD) δ ppm: 7.61 (1H, dd, J = 8.4, 6.2 Hz), 7.38 (1H, dd, J = 9.3, 2.7 Hz), 7.28 (1H, td, J = 8.2, 2,7 Hz), 7.26 (2H, dd, J = 21.4, 13.7 Hz), 3.93-3.84 (1H, m), 3.50-3.41 (3H, m), 2.40-2.31 (2H, m), 2.04-1.96 (2H, m). LCMS $[M+H]^+$ calcd for $C_{11}H_{16}N_2O_6FS$: 259.087; found: 259.24.

Intermediates 77-78

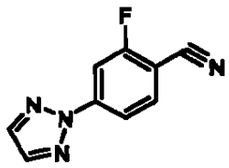
To a solution of 1H-1,2,3-triazole (3.5 g, 50.7 mmol) in tetrahydrofuran (10 mL) and dimethylformamide (20 mL) was added, portionwise, NaH (1.3 g, 51 mmol, 95%). The mixture was stirred at room temp for 30 min. 2,4-Difluorobenzonitrile (7.6 g, 55 mmol) was added and the mixture stirred at 85° C for 3 h. The white mixture was concentrated and purified by flash chromatography eluting with 0% to 10% ethyl acetate/hexanes to give intermediates 77 and 78.

Intermediate 77



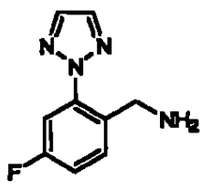
4-Fluoro-2-1,2,3-triazol-2-yl-benzonitrile. White needles (0.34 g, 3% yield). 1H-NMR (300 MHz, $CDCl_3$) δ ppm: 7.92 (2H, s), 7.88-7.79 (2H, m), 7.19-7.12 (1H, m). LCMS [M+H]+ calcd for $C_9H_6N_4F$: 189.05; found: 189.12.

Intermediate 78



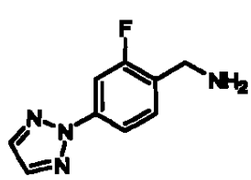
2-Fluoro-4-1,2,3-triazol-2-yl-benzonitrile. White solid (0.097 g, 1% yield). ^{1}H-NMR (300 MHz, $CDCl_3$) δ ppm: 8.03-7.95 (2H, m), 7.86 (2H, s), 7.74-7.69 (1H, m).

Intermediate 79



4-Fluoro-2-1,2,3-triazol-2-yl-benzylamine hydrochloride. Intermediate 77, 4-fluoro-2-1,2,3-triazol-2-yl-benzonitrile, (0.34 g, 1.8 mmol) was dissolved in ethanol (50 mL). 1N HCl (10 mL)was added along with a catalytic amount of 10%-Pd-C. The mixture was shaken under H_2 at 55 psi for 4 h after which it was filtered through Celite and concentrated to give the title compound as the corresponding HCl salt. Yellow solid (0.402 g, 98% yield). ^{1}H-NMR (500 MHz, CD_3OD) δ ppm: 8.13 (2H, s), 7.87 (1H, dd, J = 4.9, 2.6 Hz), 7.73 (1H, dd, J = 4.9, 2.6 Hz), 7.34 (1H, td, J = 8.2, 2.7 Hz), 4.35 (2H, s). LCMS $[M+H]^+$ calcd for $C_9H_{10}N_4F$: 193.08; found: 193.16.

Intermediate 80

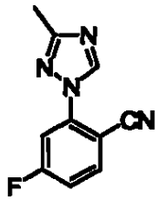


(2-Fluoro-4-(2H-1,2,3-triazol-2-yl)phenyl)methanamine: The title compound can be prepared from intermediate 78, 2-fluoro-4-1,2,3-triazol-2-yl-benzonitrile, according to the procedure provide for intermediate 79. ^{1}H-NMR (300 MHz, CD_3OD) δ ppm: 8.05-7.96 (2H,m), 8.00 (2H, s), 7.68 (1H, t, J = 8.2 Hz), 4.26 (2H, s). LCMS $[M+H]^+$ calcd for $C_9H_{10}N_4F$: 193.08; found: 193.14.

Intermediates 81-84

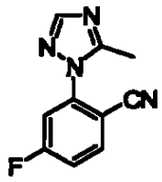
A solution of 2,4-difluorobenzonitrile (7.07 g, 50.8 mmol) and 3-methyl-1H-1,2,4-triazole (4.22 g, 50.8 mmol) in N,N-dimethylformamide (45 ml) was treated with powdered anhydrous potassium carbonate (10 g) and the resulting mixture stirred at 22 °C for 18h. The solid was then filtered and the filtrate concentrated *in vacuo*. The residue was diluted with ethyl acetate, washed with water and brine, then dried over anhydrous magnesium sulfate and concentrated. The resulting mixture was purified by a combination of chromatography on silica gel (elution gradient of ethyl acetate in hexane) and reversed phase silica gel to yield intermediates 81-84.

Intermediate 81



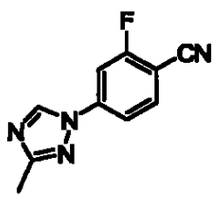
4Fluoro-2-(3-methyl-1H-1,2,4-triazol-1-yl)benzonitrile. White crystals (ethyl acetate-hexane); mp 117–118 °C. ^{1}HNMR 400 MHz ($CDCl_3$) δ ppm: 2.54 (3H, s, CH_3), 7.24 (1H, m, CH), 7.62 (1H, dd, J = 2.5 Hz and J = 9.1 Hz, CH), 7.84 (1H, dd, J = 5.6 Hz and J = 8.6 Hz, CH), 8.82 (1H, s, CH). Anal. Calcd for $C_{10}H_7FN_4$: C 59.40, H 3.49, N 27.71; Found: C 59.25, H 3.32, N 27.81.

Intermediate 82



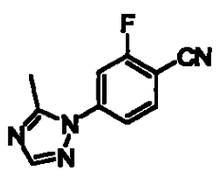
4-Fluoro-2-(5-methyl-1H-1,2,4-triazol-1-yl)benzonitrile. White crystals (ethyl acetate-hexane); mp 120-121 °C. ^{1}HNMR 400 MHz ($CDCl_3$) δ ppm: 2.56 (3H, s, CH_3); 7.30 (1H, dd, J = 2.5 Hz and J = 8.1 Hz, CH), 7.39 (1H, m, CH), 7.91 (1H, dd, J = 5.5 Hz and J = 8.6 Hz, CH), 8.06 (1H, s, CH). Anal. Calcd for $C_{10}H_7FN_4$: C 59.40, H 3.49, N 27.71; Found: C 59.35, H 3.70, N 27.77.

Intermediate 83



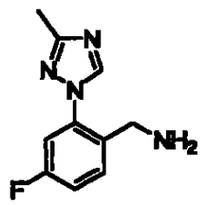
2-Fluoro-4-(3-methyl-1H-1,2,4-triazol-1-yl)benzonitrile. White crystals (ethyl acetate-hexane); mp 133-134 °C. ^{1}HNMR 400 MHz ($CDCl_3$) δ ppm: 2.52 (3H, s, CH_3), 7.61 (1H, dd, J = 2 Hz and J = 9.1 Hz, CH), 7.67 (1H, dd, J = 2 Hz and J = 9.6 Hz, CH), 7.79 (1H, dd, J = 6.5 Hz and J = 8.6 Hz, CH), 8.56 (1H, s, CH). Anal. Calcd for $C_{10}H_7FN_4$: C 59.40, H 3.49, N 27.71; Found: C 59.42, H 3.24, N 28.41.

Intermediate 84



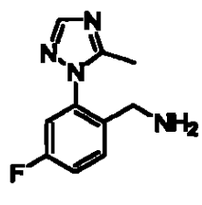
2-Fluoro-4-(5-methyl-1H-1,2,4-triazol-1-yl)benzonitrile. White crystals (ethyl acetate-hexane); mp 89-90 °C, ^{1}HNMR 400 MHz ($CDCl_3$) δ ppm: 2.69 (3H, s, CH_3), 7.49-7.55 (2H, m, 2 x CH), 7.83 (1H, dd, J = 6.8 Hz and J = 8.8 Hz, CH), 8.00 (1H, s, CH). Anal. Calcd for $C_{10}H_7FN_4$: C 59.40, H 3.49, N 27.71; Found: C 59.17, H 3.22, N 28.01.

Intermediate 85



(4-Fluoro-2-(3-methyl-1H-1,2,4-triazol-1-yl)phenyl)methanamine hydrochloride salt. Hydrogenation of intermediate 81, 4-fluoro-2-(3-methyl-1H-1,2,4-triazol-1-yl)benzonitrile, (0.680 g, 3.36 mmol) gave 0.720 g (88% yield) of the title hydrochloride salt as a white solid. ^{1}HNMR 400 MHz (DMSO-d_6) δ ppm: 2.40 (3H, s, CH_3), 4.02 (2H, m, NCH_2), 7.50 (1H, m, CH), 7.62 (1H, dd, J = 2.8 Hz and J = 9.3 Hz, CH), 7.84 (1H, dd, J = 6.1 Hz and J = 9.1 Hz, CH), 9.00 (1H, s, CH). HRMS (ESI$^+$) calculated for $C_{10}H_{12}FN_4$ [M+H$^+$]: 207.1046; found: 207.1047.

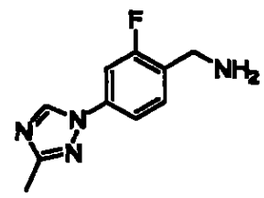
Intermediate 86



(4-Fluoro-2-(5-methyl-1H-1,2,4-triazol-1-yl)phenyl)methanamine hydrochloride salt. Hydrogenation of intermediate 82, 4-fluoro-2-(5-methyl-1H-1,2,4-triazol-1-yl)benzonitrile, (0.244 g, 1.20 mmol) gave 0.290 g (100% yield) of the title hydrochloride salt as a white solid. ^{1}HNMR 400 MHz (DMSO-d_6) δ ppm:

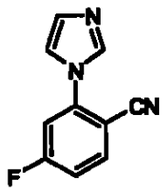
2.42 (3H, s, CH_3), 3.78 (2H, m, NCH_2), 7.58 (1H, m, CH), 7.67 (1H, dd, J = 2.8 Hz and J = 9.3 Hz, CH), 7.90 (1H, dd, J = 6.0 Hz and J = 8.5 Hz, CH), 8.22 (1H, s, CH). HRMS (ESI^+) calculated for $C_{10}H_{12}FN_4$ [$M+H^+$]: 207.1046; found: 207.1041.

Intermediate 87



(2-Fluoro-4-(3-methyl-1H-1,2,4-triazol-1-yl)phenyl)methanamine hydrochloride salt. Hydrogenation of intermediate 83, 2-fluoro-4-(3-methyl-1H-1,2,4-triazol-1-yl)benzonitrile, (0.220 g, 1.09 mmol) gave 0.260 g (98% yield) of the title hydrochloride salt as a white solid. ^{1}HNMR 400 MHz (DMSO-d_6) δ ppm: 2.38 (3H, s, CH_3), 4.09 (2H, m, NCH_2), 7.75-7.8 (2H, m, 2 xCH), 7.83 (1H, dd, J = 2 Hz and J = 9 Hz, CH), 9.29 (1H, s, CH). MS (ESI^+) m/e 207 [$M+H^+$].

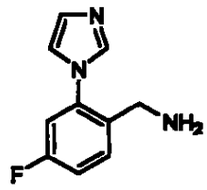
Intermediate 88



4-Fluoro-2-imidazol-1-yl-benzonitrile. To a solution of imidazole (4.45 g, 65.4 mmol) in tetrahydrofuran (30 mL) and dimethylformamide (10 mL) was added potassium carbonate (9.95 g, 72 mmol) and the mixture was stirred for 30 min at room temp. To this was added 2,4-difluorobenzonitrile (10.0 g, 72 mmol) and the mixture stirred at 90 °C for 3 h then at room temp for 2 days. The mixture was filtered and concentrated and the residue was purified by flash chromatography (SiO_2) eluting with 20% to 70% ethyl acetate/hexane to give the title compound as

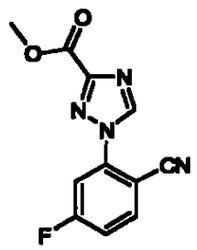
white needles (1.1 g, 9% yield). ^{1}H-NMR (500 MHz, $CDCl_3$) δ ppm: 7.94 (1H, s), 7.84 (1H, dd, J = 8.7, 5.6 Hz), 7.37 (1H, t, J = 8.7, 5.6 Hz), 7.37 (1H, t, J = 1.4 Hz), 7.29 (1H, t, J = 1.1 Hz), 7.27-7.21 (2H, m). LCMS $[M+H]^+$ calcd for $C_{10}H_7N_3F$: 188.058; found: 188.12.

Intermediate 89



(4-Fluoro-2-(1H-imidazo-1-yl)phenyl)methanamine) hydrochloride. The title compound can be prepared from intermediate 88, 4-fluoro-2-imidazol-1-yl-benzonitrile, according to the method provided for intermediate 79. Yellow solid, ^{1}H-NMR (500 MHz, CD_3OD) δ ppm: 9.39 (1H, s), 7.98 (1H, d, J = 1.5 Hz), 7.92-7.89 (2H, m), 7.63-7.59 (2H, m), 4.11 (2H, s). LCMS $[M+H]^+$ calcd for $C_{10}H_{11}N_3F$: 192.09; found: 192.15.

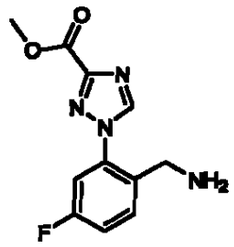
Intermediate 90



1-(2-Cyano-5-fluoro-phenyl)-1H-1,2,4-triazole-3-carboxylic acid methyl ester. To a solution of methyl 1*H*-1,2,4-triazole-3-carboxylate (27g, 215 mmol) in dimethylformamide (170 mL) was added sodium hydride (5.53 g, 95%, 217 mmol) and the mixture was stirred for 30 min. Added to this was 2,4-difluorobenzylnitrile (30 g, 217 mmol) and the resulting mixture stirred at room temp for 60 h. The

mixture was diluted with water and filtered to remove solids. The solution was extracted with ethyl acetate and the organic phase was washed with water (3X's) and brine, then dried (Na_2SO_4) and concentrated. The resulting residue was purified by flash chromatography (SiO_2) eluting with 30% tetrahydrofuran/20% CH_2Cl_2/50% hexane to give the title compound as white needles (5.34 g, 10% yield). ^{1}H-NMR (300 MHz, $CDCl_3$) δ ppm: 8.92 (1H, s), 7.85 (1H, dd, J = 8.8, 5.5 Hz), 7.67 (1H, dd, J = 8.8, 2,6 Hz), 7.34-7.27 (1H, m), 40.3 (3H, s). LCMS $[M+H]^+$ calcd for $C_{11}H_9N_4FO_2$: 247.06; found: 247.11.

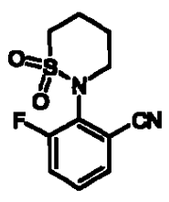
Intermediate 91



Methyl 1-(2-(aminomethyl)-5-fluorophenyl)-1H-1,2,4-triazole-3-carboxylate.

The title compound can be prepared from intermediate 90, 1-(2-cyano-5-fluoro-phenyl)-1H-1,2,4-triazole-3-carboxylic acid methyl ester ^{1}H-NMR (300 MHz, CD_3OD) δ ppm: 9.15 (1H, s), 7.80 (1H, dd, J = 8.8, 5.9 Hz), 7.71 (1H, dd, J = 8.8, 2.6 Hz), 7.46 (1 H, td J = 8.2, 2.6 Hz), 4.19 (2H, s), 4.03 (3H, s). LCMS $[M+H]^+$ calcd for $C_{11}H_{12}N_4O_2$: 251.09; found: 251.17.

Intermediate 92



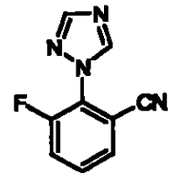
3-Fluoro-2-(1,1-dioxo-1λ6-[1,2]thiazinan-2-yl)benzonitrile. To a solution of 1,1-dioxo-1λ6-[1,2]thiazin-2-ane (1.90 g, 14.4 mmol) dissolved in tetrahydrofuran (8 mL) and dimethylformamide (2 mL) was added sodium hydride (0.36 g, 95%, 14.4 mmol) and the mixture stirred for 20 min. To this was added 2,3-difluorobenzonitrile (2.0 g, 14.4 mmol) and the mixture stirred at 90 °C for 2 h. The mixture was partitioned between ethyl acetate and water. The organic phase was washed with water and brine then concentrated. The solid residue was triturated with 1:1 ethyl acetate/hexane to give the title compound as a pale brown solid (0.47 g, 13% yield). ^{1}H-NMR (500 MHz, $CDCl_3$) δ ppm: 7.47-7.45 (1H, m), 7.32-7.36 (2H, m), 4.08-4.02 (1H, m), 3.57 (1H, td, J = 13.0, 3,7 Hz), 3.40-3.34 (1H, m), 3.32-3.27 (1H, m), 2.44-2.32 (2HF, m), 2.04-1.97 (2H, m), 1.90-1.84 (1H, m). LCMS $[M+H]^+$ calcd for $C_{11}H_{12}N_2FO_2S$: 255.28; found: 255.13.

Intermediate 93



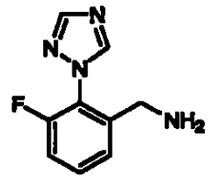
3-Fluoro-2-(1,1-dioxo-1λ6-[1,2]thiazinan-2-yl)benzylamine hydrochloride. The title compound can be prepared from intermediate 92, 3-fluoro-2-(1,1-dioxo-1λ6-[1,2]thiazinan-2-yl)benzonitrile according to the procedure provided for intermediate 79. White solid, ^{1}H-NMR (500 MHz, CD_3OD) δ ppm: 7.56-7.52 (1H, m), 7.40-7.34 (2H, m), 4.31 (2H, s), 3.98-3.93 (1H, m), 3.68-3.64 (1H, m), 3.42-3.39 (2H, m), 2.42-2.37 (2H, m), 2.03-1.92 (2H, m). LCMS $[M+H]^+$ calcd for $C_{11}H_{16}N_2O_2FS$: 259.09; found: 259.18.

Intermediate 94



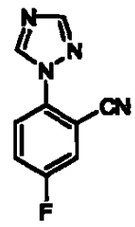
3-Fluoro-2-1,2,4-triazol-1-yl-benzonitrile. A mixture of 2,3-difluorobenzylnitrile (2.27 g, 16.3 mmol) and triazole sodium salt (1.33 g, 14.8 mmol) in tetrahydrofuran (5 mL) and dimethylformamide (10 mL) was stirred at 85 °C for 4 h. After concentration, the residue was purified by flash chromatography (SiO_2) eluting with 25%-50% ethyl acetate/hexane. The isolated product was recrystallized from hot ethyl acetate/hexane to give the title compound as white needles (1.51 g, 54% yield). ^{1}H-NMR (500 MHz, $CDCl_3$) δ ppm: 8.50 (1H, d, J = 2.4 Hz), 8.25 (1H, s), 7.69-7.67 (1H, m), 7.60-7.57 (2H, m). LCMS $[M+H]^+$ calcd for $C_9H_6N_4F$: 189.16; found: 189.14.

Intermediate 95



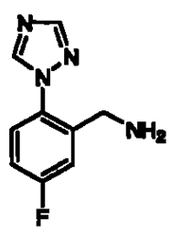
(3-Fluoro-2-(1H-1,2,4-triazol-1-yl)phenyl)methanamine. The title compound can be prepared from intermediate 94, 3-fluoro-2-1,2,4-triazol-1-yl-benzonitrile. ^{1}H-NMR (500 MHz, CD_3OD) δ ppm: 9.61 (1H, d, J = 2.9 Hz), 8.79 (1H, s), 7.82-7.74 (1H, m), 7.67-7.57 (2H, m), 4.14-4.13 (2H, m). LCMS $[M+H]^+$ calcd for $C_9H_{10}N_4F$: 193.08; found: 193.16.

Intermediate 96



5-Fluoro-2-(1H-1,2,4-triazol-1-yl)benzonitrile. A suspension of 2,5-difluorobenzonitrile (4.5 g, 32.35 mmol) and 1,2,4-triazole sodium salt (3.6 g, 40 mmol) in dimethylformamide (40 mL) was heated at 80 °C for 15 h. The reaction mixture was then cooled, diluted with CH_2Cl_2 (200 mL), washed with water (3 X 30 mL) and brine (30 mL), then dried (Na_2SO_4), filtered and concentrated to give a white solid which was purified by flash column chromatography (SiO_2) using 1:1 to 3:1 ethyl acetate/Hexanes to afford the title compound (2.98 g, 49% yield) as a white powder. ^{1}H NMR (500 MHz, $CDCl_3$) δ: 8.70 (1H, s), 8.18 (1H, s), 7.76 (1H, dd, J = 9.0, 4.8 Hz), 7.55 (1H, dd, J = 7.3, 2.8 Hz), 7.51-7.47 (1H, m). LCMS (M+H) calcd for $C_9H_6FN_4$: 189.17; found: 189.10.

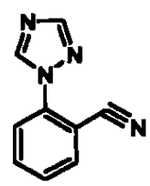
Intermediate 97



(5-Fluoro-2-(1H-1,2,4-triazol-1-yl)phenyl)methanamine hydrochloride. A solution of intermediate 96, 5-fluoro-2-(1H-1,2,4-triazol-1-yl)benzonitrile (2.94 g, 15.59 mmol) in ethanol (100 mL) and 1N HCl (50 mL) was degassed by bubbling N_2. Then, 10%Pd/C was added, the flask evacuated and vented to H_2 three times and left on a Parr shaker under a H_2 atmosphere (40 psi). After 6 h, the reaction mixture was filtered, concentrated and the aqueous solution lyophilized to afford the title

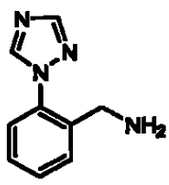
compound (4.07 g, 98%) as a white powder. LCMS (M+H) calcd for $C_9H_{10}FN_4$: 193.09; found: 193.15.

Intermediate 98



2-(1H-1,2,4-Triazol-1-yl)benzonitrile. A suspension of 2-fluorobenzylnitrile (3.0 g, 25 mmol) and 1,2,4-triazole sodium salt (2.4 g, 27 mmol) were stirred in tetrahydrofuran (7 mL) and dimethylformamide (14 mL) at 95 °C for 18 h. After cooling and concentrating, the product was crystallized from hot CH_2Cl_2/hexane (1:1) to give the title compound as a white solid (4.25 g, 100% yield). ^{1}H-NMR (300 MHz, $CDCl_3$) δ ppm: 8.74 (1H, s), 8.16 (1H, s), 7.82 (1H, dd, J = 4.9,1.3 Hz), 7.77-7.25 (2H, m), 7.57-7.51 (1H, m). LCMS $[M+H]^+$ calcd for $C_9H_7N_4$: 171.06; found: 171.12.

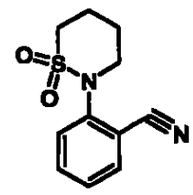
Intermediate 99



(2-(1H-1,2,4-Triazol-1-yl)phenyl)methanamine hydrochloride. Intermediate 98, 2-(1H-1,2,4-triazol-1-yl)benzonitrile (4.25 g, 25 mmol) was dissolved in ethanol (50 mL) and 1N HCl (25 mL). 10% Pd-C (1 g) was added and the mixture shaken under H_2 for 2 h at 50 psi. After filtration through Celite and concentration, the residue was triturated with diethyl ether and the title compound was collected as a white solid. (3.94 g, 75% yield). ^{1}H-NMR (300 MHz, CD_3OD) δ ppm: 9.01 (1H, s),

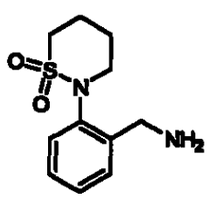
8.32 (1H, s), 7.78-7.64 (4H, m), 4.15 (2H, s). LCMS $[M+H]^+$ calcd for $C_9H_{11}N_4$: 175.09; found: 175.17.

Intermediate 100



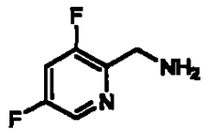
2-(1,1-Dioxo-1λ⁶-[1,2]thiazinan-2-yl)benzonitrile. Added to a solution of 1,1-dioxo[1,2]thiazinane (3.37 g, 25 mmol) in dimethylformamide (35 mL) was sodium hydride (0.675 g, 25 mmol, 95%) and the mixture stirred at room temperature for 15 min. 2-Fluorobenzonitrile (3.37 mL, 31.3 mmol) was added and the mixture stirred at 80 °C for 18 h. The mixture was cooled, diluted with water and extracted with ethyl acetate. The organic phase was washed with water and brine, then dried (Na_2SO_4) and concentrated. The residue was purified by flash chromatography (SiO_2) eluting with 10%-100% ethyl acetate/hexane. The isolated solid was recrystallized from hot ethyl acetate/hexane (2:1) to give the title compound as white crystals (4.15 g, 70% yield). ^{1}H-NMR (300 MHz, $CDCl_3$) δ ppm: 7.70 (1H, dd, J = 7.7,1.1 Hz), 7.64-7.53 (2H, m), 7.41 (1H, td, J = 7.3, 1.6 Hz), 3.72 (2H, t, J = 5.5 Hz), 3.32 (2H, t, J = 6.0 Hz), 2.40-2.32 (2H, m), 2.05-1.97 (2H, m). LCMS $[M+H]^+$ calcd for $C_{11}H_{12}N_2O_2S$: 237.06; found: 237.10.

Intermediate 101



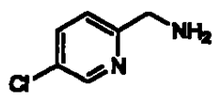
2-(1,1-Dioxo-1λ⁶-[1,2]thiazinan-2-yl)benzylamine hydrochloride. Intermediate 100, 2-(1,1-dioxo-1λ⁶-[1,2]thiazinan-2-yl)benzonitrile, (2.63 g, 11.14 mmol) was dissolved in ethanol (150 mL) and 1N HCl (13 mL). Added to this was10% Pd-C (0.5 g) and the mixture shaken under H_2 at 55 psi for 24 h. Filtration through Celite followed by concentration gave the title compound as a white solid (2.93 g, 95% yield). ^{1}H-NMR (300 MHz, CD_3OD) δ ppm: 7.61-7.47 (4H, m), 4.30 (2H, q, J = 13.7 Hz), 3.96-3.87 (1H, m), 3.49-3.36 (3H, m), 2.40-2.31 (2H, m), 2.05-1.96 (2H, m). LCMS $[M+H]^+$ calcd for $C_{11}H_{17}N_2SO_2$: 241.10; found: 241.10.

Intermediate 102



(3,5-Difluoropyridin-2-yl)methanamine hydrochloride. A mixture of 3,5-difluoropicolinonitrile (1.4 g, 10 mmol), conc. HCl (12 ml) and 10% Pd-C (200 mg) in 1:1 ethanol/tetrahydrofuran was shaken under a hydrogen atmosphere (50 psi) for 5h. The reaction mixture was filtered and the ethanol removed *in vacuo*. The remaining solution was lyophilized to afford an off-white solid (2.16 g, 100% yield). LCMS (M+H) calcd for $C_6H_7F_2N_2$: 145.06; found: 145.12.

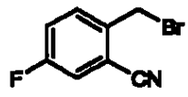
Intermediate 103



(5-Chloropyridin-2-yl)methanamine. A solution of 5-chloropicolinonitrile (3.8 g, 27.43 mmol), conc. HCl (3 mL) and 10% Pd-C (1.0 g) in ethanol (100 mL) was shaken under a hydrogen atmosphere (40 psi) for 2h. The reaction mixture was filtered, concentrated and the resulting residue taken up in satd $NaHCO_3$ (50 mL) and extracted with CH_2Cl_2 (4 X 25 mL). The combined CH_2Cl_2 layers were dried

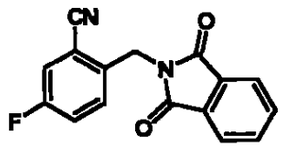
(Na_2SO_4), filtered and concentrated to give the title compound as a yellow oil (2.0 g, 51% yield). LCMS (M+H) calcd for $C_6H_5ClN_2$: 143.04; found: 143.07. ^{1}HNMR (500 MHz, $CDCl_3$) δ ppm: 8.56-8.51 (1H, br d), 7.66-7.60 (1H, m), 7.28-7.14 (1H, m), 3.97 (2H, s), 1.72 (2H, s).

Intermediate 104



2-(Bromomethyl)-5-fluorobenzonitrile. N_2 was passed through a mixture of 5-fluoro-2-methylbenzonitrile (28.51 g, 211 mmol), NBS (41.31 g, 232 mmol) and AIBN (2.5 g, 15 mmol) in CCl_4 (845 mL) for 10 min after which the reaction was heated at reflux for 8 h. After standing at room temperature overnight, the reaction mixture was filtered and the filter cake washed with CCl_4 (500 mL). The combined filtrate was evaporated to give a yellow oil. Flash chromatography (SiO_2) using 5-25% ethyl acetate/Hexanes as eluent afforded the title compound (29.74 g, 66% yield) as a pale yellow oil. ^{1}H NMR (500 MHz, $CDCl_3$) δ: 7.55 (1H, dd, J = 8.6, 5.2 Hz), 7.37 (1H, dd, J = 7.9, 2.8 Hz), 7.32-7.28 (1H, m), 4.61 (2H, s).

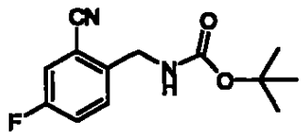
Intermediate 105



2-((1,3-Dioxoisoindolin-2-yl)methyl)-5-fluorobenzonitrile. To a stirred solution of intermediate 104, 2-(bromomethyl)-5-fluorobenzonitrile (29.72 g, 139 mmol) and phthalimide (32.69 g, 222 mmol) in dimethylformamide (300 mL) was added Cs_2CO_3 (67.87 g, 208 mmol). After stirring vigorously for 1 h, the reaction mixture was poured into water (1.2 L). The precipitated product was filtered, washed with water (600 mL) and methanol (150 mL) to give a white solid. The solid was

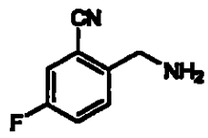
taken up into 1L of water/methanol (2:1) to which was added K_2CO_3 (12 g) and the mixture stirred at 40 °C. After 30 min., the mixture was cooled and filtered. The filter cake was washed with water (500 mL) ,and dried under vacuum to afford the title compound (38.91 g, 94% yield) as a white powder. ^{1}H NMR (500 MHz, $CDCl_3$) δ: 7.89 (2H, dd, J = 5.5, 3.1 HZ), 7.76 (5.5, 3.1 Hz), 7.41 (1H, dd, J = 8.6, 5.2 Hz), 7.38 (1H, dd, J = 7.9, 2.8 Hz), 7.24 (1H, td, J = 8.2, 2.8 Hz), 5.06 (2H, s). LCMS (M+H) calcd for $C_{16}H_{10}FN_2O_2$: 281.07; found: 281.15.

Intermediate 106



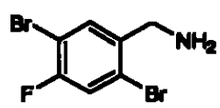
tert-Butyl 2-cyano-4-fluorobenzylcarbamate. A suspension of intermediate 105, 2-((1,3-dioxoisoindolin-2-yl)methyl)-5-fluorobenzonitrile, (5.6 g, 20 mmol) in dimethylformamide (20 mL) was warmed until it was dissolved. To this was added tetrahydrofuran (100 mL) and the mixture placed in a pre-heated (70 °C) oil bath. Hydrazine monohydrate was added to this and the reaction stirred for 8 h. The resulting white slurry was left at ambient temperature overnight. To this slurry was added di-tert-butyldicarbonate (6.55 g, 30 mmol) and the mixture stirred for 6 h at room temperature. The reaction mixture was diluted with ether (100 mL), filtered and the filtrate treated with activated carbon at 40 °C. After filtration and concentration the crude product was purified by flash chromatography, using 20-30% ethyl acetate/Hexanes as eluent, to provide the title compound (2.88 g, 58% yield) as a light yellow powder. ^{1}H NMR (500 MHz, $CDCl_3$) δ: 9.46 (1H, br s), 7.61 (1H, dd, J = 7.9, 2.1 Hz), 7.34 (1H, dd, J = 8.2, 4.6 Hz), 7.22 (1H, td, J = 8.6, 2.4 Hz), 4.71 (2H, s), 1.59 (9H, s). LCMS (M+H) calcd for $C_{13}H_{16}FN_2O_2$: 251.12; found: 251.22.

Intermediate 107



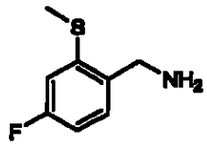
2-(Aminomethyl)-5-fluorobenzonitrile trifluoroacetic acid salt. A round-bottom flask was charged with intermediate 106, *tert*-butyl 2-cyano-4-fluorobenzylcarbamate, (1.9 g, 7.591 mmol) then treated with trifluoroacetic acid (20 ml) at room temperature. After 1 h, the reaction mixture was concentrated to give a yellow oil which was dissolved in $CHCl_3$ and re-concentrated to afford the title compound (2.01 g, 100% yield) as a pale yellow solid. LCMS (M+H) calcd for $C_8H_8FN_2$: 151.07; found: 151.08.

Intermediate 108



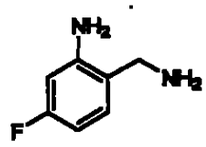
(2,5-Dibromo-4-fluorophenyl)methanamine. A solution of 2,5-dibromo-4-fluorobenzyl bromide (0.350 g, 1 mmol) in 7M NH_3/MeOH was heated in a sealed tube at 100 °C for 2 h. The reaction mixture was cooled and concentrated to give a white solid which was dissolved in CH_2Cl_2 and treated with Et_3N (1 mL) then concentrated. The resulting residue was triturated with ethyl acetate (25 mL), filtered and concentrated to give the title compound (0.291 g) as a pale yellow oil. HRMS (M+H) calcd for $C_7H_7Br_2FN$: 283.94; found: 283.93.

Intermediate 109



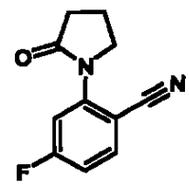
4-Fluoro-2-methylsulfanyl-benzylamine. Under N_2, 4-fluoro-2-(methylthio)benzonitrile (1.67 g, 0.1 mol) was dissolved in 20 mL tetrahydrofuran and treated with 10 mL 2M $BH_3.Me_2S$. This was heated at 60 °C for 2 hrs. Heating was discontinued and 5mL MeOH was cautiously added, followed by the cautious addition of 4 mL 6N HCl. Additional H_2O (20 mL) was added followed by ethyl acetate. The layers were separated. The aqueous layer was made basic with 1N NaOH and extracted with CH_2Cl_2. The extracts were dried ($MgSO_4$), filtered, concentrated and dried *in vacuo* to give 1.3g of the title compound as a solid (Yield = 76%). ^{1}H NMR (500 MHz, $CDCl_3$) δ ppm: 7.20-7.31 (1 H, m) 6.90 (1 H, dd, J=2.4 Hz) 6.75-6.86 (1 H, m) 3.86 (2 H, s) 2.47 (3 H, s); LC/MS m/z 172.

Intermediate 110



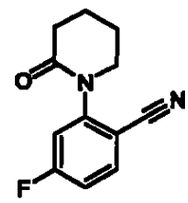
2-(Aminomethyl)-5-fluorobenzenamine hydrochloride. 2-Amino-4-fluorobenzonitrile (Fritz Hunziker *et al.* Eur. J. Med. Chem. 1981, 16, 391) (0.300 g, 1.68 mmol), was dissolved in acetic anhydride (5 mL) and the solution was stirred at 23 °C for 18 h. An additional portion of acetic anhydride (3 mL) was added to dissolve the *N*-(2-cyano-5-fluorophenyl)acetamide. Then palladium (10% on charcoal) (25 mg) was added and the mixture was agitated under H_2 (34 psi) for 72 h. The Pd-C was removed by filtration on Celite and the filtrate concentrated *in vacuo* to afford a bis-acetamide: LCMS $(M+H)^+$ m/z 225. This was heated at reflux with HCl (6N, 10 mL) for 30 min. The acid was removed under reduced pressure to give a solid which was crystallized from MeOH-ether to afford the title compound (0.120 g, 51% yield). ^{1}H NMR (400 MHz, MeOD) δ ppm: 7.51 (1H, m), 6.96(2H, m), 4.20 (2H, s).

Intermediate 111



4-Fluoro-2-(2-oxopyrrolidin-1-yl)benzonitrile. A 48 mL pressure vessel containing 2-bromo-4-fluorobenzonitrile (1.00 g, 5.00 mmol), 2-pyrrolidinone (0.46 mL, 6.00 mmol), Cs_2CO_3 (2.28 g, 7.0 mmol) and 9,9-dimethyl-4,5-bis(diphenylphosphino)xanthene (xantphos) (0.231 g, 0.40 mmol) in dioxane (6 mL) was degassed with argon for 15 min. Pd_2dba_3 was introduced and the reaction mixture heated at 105 °C for 48 h. The mixture was cooled, diluted with ethyl acetate or dioxane, and then filtered through Celite. The resulting mixture was concentrated *in vacuo* and subjected to column chromatography on silica gel with hexanes:ethyl acetate (3:7) gradient as the eluent to afford the title compound as a white solid (0.887 g, 87% yield): ^{1}H NMR (400 MHz, $CDCl_3$) δ ppm: 7.69 (1H, dd, J = 5.8, 8.6 Hz), 7.22 (1H, dd, J = 2.5, 9.6 Hz), 7.07 (1H, ddd, J = 2.5, 7.6, 8.6 Hz), 3.96 (2H, t,. J = 7.0 Hz), 2.62 (2H, t, J = 8.1 Hz), 2.30-2.22 (2H, m); LCMS ($^+$ESI, $M+H^+$) m/z 205.

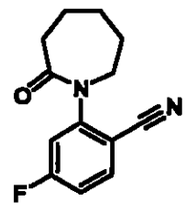
Intermediate 112



4-Fluoro-2-(2-oxopiperidin-1-yl)benzonitrile. The title compound can be prepared according to the procedure provided for intermediate 111 ^{1}H NMR (400 MHz, $CDCl_3$) δ ppm: 7.71 (1H, dd, J = 5.7, 8.7 Hz), 7.14-7.06 (1H, m), 7.08 (1H, dd,

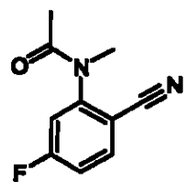
J = 2.4, 9.0 Hz), 3.65 (2H, t,. J = 5.7 Hz), 2.60 (2H, t, J = 6.3 Hz), 2.05-1.95 (4H, m); LCMS ($^+$ESI, M+H$^+$) m/z 219.

Intermediate 113



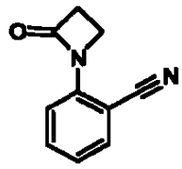
4-Fluoro-2-(2-oxoazepan-1-yl)benzonitrile. The title compound can be prepared according to the procedure provided for intermediate 111. ^{1}H NMR (400 MHz, $CDCl_3$) δ ppm: 7.68 (1H, dd, J = 5.8, 8.6 Hz), 7.08 (1H, ddd, J = 2.5, 7.6, 8.6 Hz), 7.01 (1H, dd, J = 2.5, 9.0 Hz), 3.77-3.76 (2H, m), 2.75-2.72 (2H, m), 1.91-1.86 (6H, m); LCMS ($^+$ESI, M+H$^+$) m/z 233.

Intermediate 114



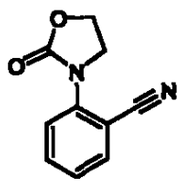
N-(2-Cyano-5-fluorophenyl)-N-methylacetamide. The title compound can be prepared according to the procedure provided for intermediate 111 ^{1}H NMR (400 MHz, $CDCl_3$) δ ppm: 7.79-7.75 (1H, m), 7.32-7.19 (1H, m), 7.10-7.07 (1H, m), 3.42 (0.6H, brs), 3.30 (2.4H, s), 2.32 (0.6H, brs), 1.91 (2.4H, s); LCMS ($^+$ESI, M+H$^+$) m/z 193; HPLC: 94% (220 nm).

Intermediate 115



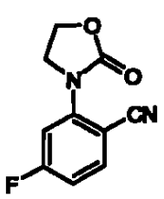
2-(2-Oxoazetidin-1-yl)benzonitrile. The title compound can be prepared according to the procedure provided for intermediate 111. ^{1}H NMR (400 MHz, DMSO-d_6) δ ppm: 8.02 (1H, d, J = 8.4 Hz), 7.76.(1H, dd, J = 1.5, 7.8 Hz), 7.69-7.65 (1H, m), 7.23 (1H, s), 4.04 (2H, t, J = 4.8 Hz), 3.16 (2H, t, J = 4.8 Hz). LCMS ($^+$ESI, M+H$^+$) m/z 173.

Intermediate 116



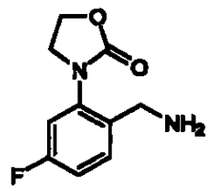
2-(2-Oxooxazolidin-3-yl)benzonitrile. The title compound can be prepared according to the procedure provided for intermediate 111. ^{1}H NMR (400 MHz, $CDCl_3$) δ ppm: 7.71 (1H, dd, J = 1.5, 7.6 Hz), 7.68-7.63 (1H, m), 7.58 (1H, d, J = 7.6 Hz), 7.38 (1H, dt, J = 1.3, 7.6 Hz), 4.57 (2H, t, J = 7.8 Hz), 4.21 (2H, t, J = 7.8 Hz); LCMS ($^+$ESI, M+H$^+$) m/z 189.

Intermediate 117



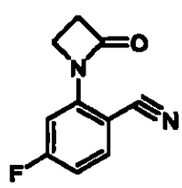
4-Fluoro-2-(2-oxooxazolidin-3-yl)benzonitrile. A 48 mL pressure vessel containing 2-bromo-4-fluorobenzonitrile (1.00 g, 5.00 mmol), 2-oxazolidone (0.390 g, 4.50 mmol), K_2CO_3 (0.970 g, 7.0 mmol) and xantphos (0.231 g, 0.40 mmol) in dioxane (10 mL) was degassed with argon for 15 min. Pd_2dba_3 (0.140 g, 0.15 mmol) was introduced and then the reaction mixture was heated at 70 °C for 18 h. The mixture was cooled, diluted with dioxane, and then filtered through Celite. The resulting mixture was concentrated *in vacuo* and subjected to column chromatography on silica gel with hexanes:ethyl acetate (1:1) to (3:7) gradient as the eluent to afford the title compound as a white solid (0.460 g, 50% yield): ^{1}H NMR (400 MHz, $CDCl_3$) δ ppm: 7.73 (1H, dd, J = 5.8, 8.6 Hz), 7.43 (1H, dd, J = 2.5, 9.6 Hz), 7.11 (1H, ddd, J = 2.5, 7.5, 8.7 Hz), 4.60 (2H, t, J = 7.1 Hz), 4.29 (2H, t, J = 7.1 HJz); LCMS ($^+$ESI, M+H$^+$) m/z 207.

Intermediate 118



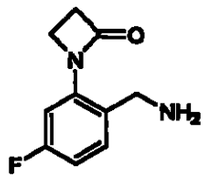
3-(2-(Aminomethyl)-5-fluorophenyl)oxazolidin-2-one hydrochloride. ^{1}H NMR (400 MHz, MeOD) δ ppm: 7.73 (1H, dd, J =6.0, 8.6 Hz), 7.43 (1H, dd, J = 2.5, 9.5 Hz), 7.11 (1H, ddd, J = 2.5, 7.5, 8.6 Hz), 4.64 (2H, t, J = 7.7 Hz), 4.17 (2H, t, J = 7.7 Hz), 4.14 (2H, s); LCMS ($^+$ESI, M+H$^+$) m/z 211.

Intermediate 119



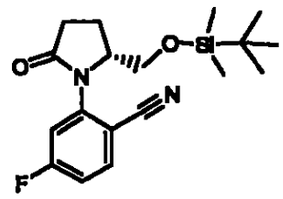
4-Fluoro-2-(2-oxoazetidin-1-yl)benzonitrile. The title compound can be prepared according to the procedure provided for intermediate 117 ^{1}H NMR (400 MHz, $CDCl_3$) δ ppm: 8.06 (1H, dd, J = 10.7, 2.6 Hz), 7.58 (1H, dd, J = 8.6, 6.3 Hz), 7.87 (1H, td, J = 8.6, 2.5 Hz), 4.25 (2H, t, J = 5.0 Hz), 3.26 (2H, t, J = 5.0 Hz); LCMS ($^+$ESI, M+H$^+$) m/z 191.

Intermediate 120



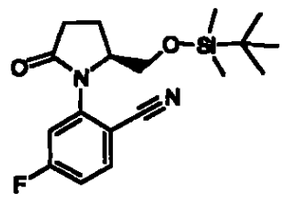
1-(2-(Aminomethyl)-5-fluorophenyl)azetidin-2-one hydrochloride. ^{1}H NMR (400 MHz, DMSO/D_2O) δ ppm: 7.54 (1H, dd, (t), J = 8.6 Hz), 7.25 (1H, dd, J = 10.8, 2.5 Hz), 7.17 (1H, td, J = 8.6, 2.5 Hz), 4.12 (2H, s), 3.79 (2H, t, J = 4.6 Hz), 3.09 (2H, t, J = 4.6 Hz); LCMS ($^+$ESI, M+H$^+$) m/z 195.

Intermediate 121



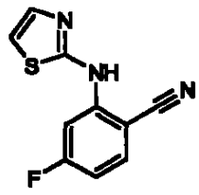
(R)-2-(2-((tert-Butyldimethylsilyloxy)methyl)-5-oxopyrrolidin-1-yl)-4-fluorobenzonitrile. The title compound can be prepared according to the procedure provided for intermediate 111. ^{1}H NMR (400 MHz, $CDCl_3$) δ ppm: 7.68 (1H, dd, J = 5.8, 8.8 Hz), 7.19 (1H, dd, J = 2.5, 9.1 Hz), 7.11-7.07 (1H, m), 4.46-4.42 (1H, m), 3.55(2H, d, J = 3.3 Hz), 2.72-2.52 (2H, m), 2.43-2.33 (1H, m), 2.09-2.01 (1H, m), 0.81 (9H, s), -0.04 (3H, s), -0.07 (3H, s); LCMS ($^+$ESI, M+H$^+$) m/z 349.

Intermediate 122



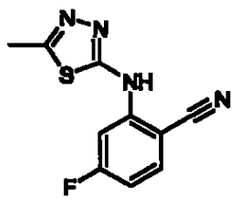
(S)-2-(2-((tert-Butyldimethylsilyloxy)methyl)-5-oxopyrrolidin-1-yl)-4-fluorobenzonitrile. The title compound can be prepared according to the procedure provided for intermediate 111. ^{1}H NMR (400 MHz, $CDCl_3$) δ ppm: 7.68 (1H, dd, J = 5.8, 8.6 Hz), 7.19 (1H, dd, J = 2.5, 9.4 Hz), 7.11-7.07 (1H, m), 4.46-4.43 (1H, m), 3.55(2H, d, J = 3.3 Hz), 2.72-2.52 (2H, m), 2.43-2.33 (1H, m), 2.09-2.01 (1H, m), 0.81 (9H, s), -0.04 (3H, s), -0.07 (3H, s); LCMS ($^+$ESI, M+H$^+$) m/z 349.

Intermediate 123



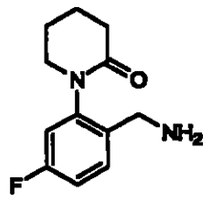
4-Fluoro-2-(thiazol-2-ylamino)benzonitrile. The title compound can be prepared according to the procedure provided for intermediate 111. ^{1}H NMR (400 MHz, DMSO-d_6) δ ppm: 9.21 (1H, s), 8.39-8.35 (1H, m), 7.97 (1H, d, J = 5.0 Hz), 7.23-7.13 (3H, m); LCMS ($^+$ESI, M+H$^+$) m/z 220.

Intermediate 124



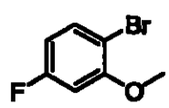
4-Fluoro-2-(5-methyl-1,3,4-thiadiazol-2-ylamino)benzonitrile. The title compound can be prepared according to the procedure provided for intermediate 111. ^{1}H NMR (400 MHz, DMSO-d_6) δ ppm: 8.30 (1H, dd, J = 6.5, 8.8 Hz), 7.96 (1H, s), 7.26-7.19 (2H, m), 2.64 (3H, s); LCMS ($^+$ESI, M+H$^+$) m/z 235.

Intermediate 125



1-(2-(Aminomethyl)-5-fluorophenyl)piperidin-2-one hydrochloride salt. To a stirred solution of intermediate 112, 4-fluoro-2-(2-oxopiperidin-1-yl)benzonitrile (150 mg, 0.69 mmol) in H_2O (10 mL) was added ethanol (10 mL) 10% palladium on charcoal (50 mg) and 1N HCl (2.1 mL, 20.6 mmol). The reaction was shaken in a Parr system under H_2 (40 psi) for 1h. Then the Pd/C catalyst was removed by filtration on Celite and the filtrate was concentrated *in vacuo* to yield a solid. Toluene (2 X 50 mL) was added to the solid and the solution was evaporated *in vacuo*. LCMS (M+H)$^+$ m/z 170.

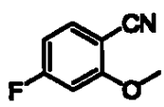
Intermediate 126



1-Bromo-4-fluoro-2-methoxybenzene. To a mixture of 2-bromo-5-fluorophenol (10 g, 50.8 mmol) and iodomethane (11.2 g, 78.7 mmol) in dimethylformamide (100 mL) was added potassium carbonate (10.9 g, 79 mmol) and the mixture stirred at room temperature for 3 hrs. The mixture was diluted with water (100 mL) and extracted with ether (50 mLx3). The combined extracts were washed

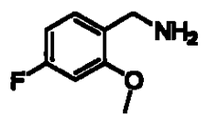
with brine, dried over anhydrous magnesium sulfate, and concentrated *in vacuo* to obtain 11.3 g of 1-bromo-4-fluoro-2-methoxybenzene as an amber colored oil.

Intermediate 127



4-Fluoro-2-methoxybenzonitrile. To a solution of intermediate 126, 1-bromo-4-fluoro-2-methoxybenzene (9.0 g) in N-methylpyrrolidone (100 mL, Sure Seal; Aldrich) was added CuCN (6.6 g, 73.7 mmol, 1.8 eq.; Aldrich), and the mixture stirred at 180 °C under anhydrous nitrogen for 5.5 hrs. After cooling, 14% aqueous NH_4OH (330 mL) was added and stirring continued for 45 min at room temperature. The mixture was extracted with ether (100 mL x 3), and the combined extracts washed sequentially with dilute aqueous NH_4OH, dilute HCl and brine, then dried ($MgSO_4$), and concentrated to provide the title compound (5.2 g, Yield 85% in 2 steps) as a white solid: ^1H NMR ($CDCl_3$, 500 MHz) δ ppm: 3.91 (3H, s, OMe), 6.69 (1H, dd, J = 2.3 Hz, J = 10.5 Hz, Ar-H), 6.72 (1H, dt, J= 2.5 Hz, J = J = 8.0 Hz, Ar-H), 7.55 (1H, dd, J = 6.5 Hz, J = 8.5 Hz, Ar-H); ^{13}C NMR ($CDCl_3$, 125.8 Hz) δ ppm: 56.49, 98.16, 100.06, 100.27, 108.31, 108.50, 115.83 135.37, 135.46, 163.25, 163.34 165.47, 167.50. An analytical sample was obtained by trituration with ether: Anal. calcd for C_8H_6FNO: C 63.57, H 4.00, N 9.26; found: C 63.36, H 3.91, N 9.16.

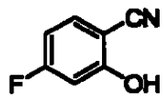
Intermediate 128



4-Fluoro-2-methoxybenzylamine hydrochloride. To a mixture of intermediate 127, 4-fluoro-2-methoxybenzonitrile, (800 mg, 5.3 mmol) and conc.HCl (0.53 mL, 6.36 mmol, 1.2 eq.) in ethanol (20 mL) was added 10% Pd-C (100 mg; Aldrich), and the mixture hydrogenated at 1 atm hydrogen for 15 hrs at room temperature. To this

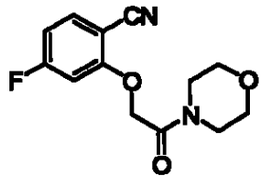
mixture was added an additional amount of conc.HCl (1 mL) and 10% Pd-C (200 mg) and the reaction allowed to continue for another 40 hrs. The mixture was filtered through Celite and the filtrate concentrated in vacuo to dryness. The residue was triturated with ether to provide the title compound (895 mg, Yield 88%) as a white powder: ^{1}H NMR ($CDCl_3$, 500 MHz) δ ppm: 3.84 (3H, s, OMe), 3.91 (2H, d, J = 5.5 Hz, N- CH_2), 6.81 (1H, dt, J = 2.5 Hz, J = J = 8.5 Hz, Ar-H), 6.99 (1H, dd, J = 2.5 Hz, J = 11.3 Hz, Ar-H), 7.47 (1H, dd, J = 7 Hz, J = 8.5 Hz, Ar-H); ^{13}C NMR ($CDCl_3$, 125.8 Hz) δ ppm: 36.76, 56.03, 99.30, 99.51 106.28, 106.45, 117.93, 117.95, 131.60, 131.69, 158.56, 158.64, 162.28, 164.22. HRMS (ESI) calcd for $C_8H_{11}FNO$ (M+H) 156.0825, found 156.0830.

Intermediate 129



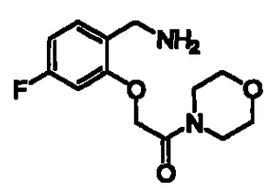
4-Fluoro-2-hydroxybenzonitrile. A mixture of intermediate 127, 4-fluoro-2-methoxybenzonitrile, (4.53 g, 30 mmol;) and $AlCl_3$ (5.0 g, 37.6 mmol; Aldrich) in anhydrous toluene (30 mL) was stirred at approximately 130 °C for 18 hrs. After cooling, ice water (~50 mL)was added and the resulting mixture extracted with ether (20 mL x 2). The combined extracts were washed sequentially with water and brine, then dried ($MgSO_4$), and concentrated in vacuo to provide the title compound (3.90 g, 28.5 mmol, Yield 95%) as a white solid: ^{1}H NMR (DMSO-d6, 300 MHz) δ ppm: 6.74-6.84 (2H, m, Ar-Hs), 7.71 (1H, dd, J = 7 Hz, J = 8.5 Hz, Ar-H), 11.64 (1H, s, OH); ^{13}C NMR (DMSO-d6, 75.5 Hz) δ ppm: 95.13 102.45, 102.78, 106.53, 106.83 115.53, 134.68, 134.84, 161.41, 161.58, 163.00, 166.35.HRMS (ESI-) calcd for C_7H_3NOF (M-H) 136.0199, found 136.0199.

Intermediate 130



4-Fluoro-2-(2-morpholino-2-oxoethoxy)benzonitrile. To a solution of intermediate 129, 4-fluoro-2-hydroxybenzonitrile, (685 mg, 5 mmol) in dimethylformamide (8 mL, Sure Seal; Aldrich) was added NaH (200 mg, 5 mmol; 60% oil dispersion; Aldrich), and the mixture stirred for 5 min under an anhydrous nitrogen atmosphere. To this was added 4-(2-chloroacetyl)morpholine (900 mg, 5.5 mmol, 1.1 eq.; Avocado Organics), and stirring continued at room temperature for 21 hrs. The reaction was quenched by careful addition of water (30 mL). The resulting mixture was extracted with CH_2Cl_2 (25 mLx2). The combined extracts were washed with brine, dried ($MgSO_4$) and concentrated. The residue was triturated to obtain 1.10 g (4.17 mmol, Yield 83%) of the title compound as a white solid: ^{1}H NMR ($CDCl_3$, 500 MHz) δ ppm: 3.63 (2H, t, J = 4 Hz, NCH_2), 3.67 (1H, m, OCH), 3.72 (1H, m, OCH), 4.86 (2H, s, OCH_2), 6.80-6.86 (2H, m, Ar-Hs), 7.61 (1H, dd, J = 8.5 Hz, 6.1 Hz, Ar-H); ^{13}C NMR ($CDCl_3$, 125.77 Hz) δ ppm: 42.63, 46.04, 66.80, 68.33, 98.45, 98.47, 101.57, 101.79, 109.56, 109.74, 115.42, 135.48, 135.57, 161.26, 161.35, 114.79, 165.23, 167.28. HRMS calcd for $C_{13}H_{14}N_2O_3F$ (M+H) 265.0988, found 265.0998.

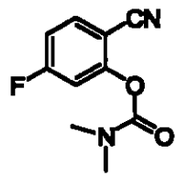
Intermediate 131



2-(2-(Aminomethyl)-5-fluorophenoxy)-1-morpholinoethanone hydrochloride. A solution of intermediate 130, 4-fluoro-2-(2-morpholino-2-oxoethoxy)benzonitrile,

(500 mg, 1.89 mmol) in warm ethanol (30 mL) and ethyl acetate (30 mL) was mixed with conc.HCl (0.32 mL, 3.78 mmol, 2 eq.). To this was added 10% Pd-C (100 mg; Aldrich), and the mixture was hydrogenated at 1 atm of hydrogen for 20 hrs at room temperature. To this mixture was added an additional amount of 10% Pd-C (50 mg) and stirring continued for another 7 hrs. The mixture was filtered through Celite and the filtrate concentrated *in vacuo* to dryness. The residue was triturated with ethyl acetate, then with ethanol to obtain the title compound (168 mg, Yield 29%) as an off-white powder: ^{1}H NMR (CD_3OD, 500 MHz) δ ppm: 3.55 (2H, t, J = 5 Hz, NCH_2), 3.62 (2H, t, J = 5 Hz, NCH_2), 3.70 (2H, t, J = 5 Hz, OCH_2), 3.75 (2H, t, J = 5 Hz, OCH_2), 4.17 (2H, s, NCH_2), 5.17 (2H, s, OCH_2), 6.82 (1H, dt, J = 2.5, 8.5 Hz, Ar-H), 7.05 (1H, dd, J = 2.5, 10.5 Hz, Ar-H), 7.43 (1H, dd, J = 6.5, 8.5 Hz, Ar-H); ^{13}C NMR (CD_3OD, 125.77 Hz) δ ppm: 39.40, 42.49, 44.97, 66.11, 66.46, 66.59, 101.38, 101.59, 108.40, 108.57, 118.40, 132.53, 132.62, 158.43, 158.52, 63.87, 165.83, 168.27. HRMS (ESI) calcd for $C_{13}H_{18}N_2O_3F$ (M+H) 269.1301, found 269.1301.

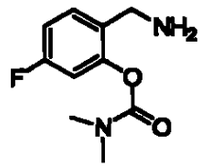
Intermediate 132



Dimethyl-carbamic acid 2-cyano-5-fluoro-phenyl ester. Under N_2, a stirred solution of intermediate 129, 4-fluoro-2-hydroxybenzonitrile (685 mg, 5.00 mmol), dimethylcarbamoyl chloride, and triethylamine (606 mg, 6 mmol) in dichloroethane (10 mL) was heated at reflux for 20 hrs. The cooled mixture was diluted with dichloroethane (10 mL) washed with water, and brine. The organic layer was separated, dried (Na_2SO_4), concentrated, and the residue purified by column chromatography (SiO_2, 5% ethyl acetate-CH_2Cl_2) to provide 700 mg (Yield 67%) of the title compound as a white crystalline solid: ^{1}H NMR ($CDCl_3$, 500 MHz) δ ppm: 3.03 (3H, s, NMe), 3.15 (3H, s, NMe), 6.99 (1H, dt, J = 2.5 Hz, 8.5 Hz, Ar-H), 7.23 (1H, dd, J = 2.5 Hz, 9.5 Hz, Ar-H), 7.61 (1H, dd, J = 9 Hz, 6 Hz, Ar-H); ^{13}C NMR

(CDCl$_3$, 125.77 Hz) δ ppm: 36.76, 37.06, 102.84, 102.86, 111.59, 111.79, 113.24, 113.42, 114.99, 134.36, 134.45, 152.54, 155.06, 155.16, 164.26, 166.31. HRMS (ESI) calcd for $C_{10}H_{10}N_2O_2F$ (M+H) 209.0726, found 209.0722.

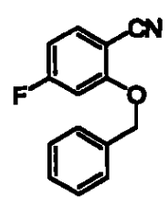
Intermediate 133



Dimethyl-carbamic acid 2-aminomethyl-5-fluoro-phenyl ester hydrochloride.

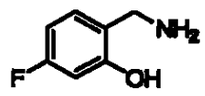
To a solution of intermediate 132, dimethyl-carbamic acid 2-cyano-5-fluoro-phenyl ester, (340 mg, 1.63 mmol) in ethyl acetate (20 mL) and ethanol (20 mL), was added conc.HCl (0.4 mL) and 10% Pd-C (100 mg) and the mixture hydrogenated in a Parr Shaker at 55psi of hydrogen for 20 hrs. The reaction mixture was filtered through Celite, and the filtrate concentrated in vacuo to give an oil which was partitioned between ethyl acetate (10 mL) and water (10 mL). After separation, the aqueous phase was washed with additional ethyl acetate (5 mL). The combined extracts were concentrated *in vacuo* to dryness. The residual oil was triturated with ether to provide 145 mg (Yield 38%) of the title compound, as a tan powder: ^{1}H NMR (CD_3OD, 500 MHz) δ ppm: 3.06 (3H, s, NMe), 3.21 (3H, s, NMe), 4.11 (2H, s, NCH_2), 7.13 (2H, m, Ar-Hs), 7.60 (1H, m, Ar-H); ^{13}C NMR (CD3OD, 125.77 Hz) δ ppm: 36.03, 36.25 37.58, 110.79, 110.99, 113.26, 113.43, 122.32, 132.18, 132.25, 151.55, 154.72, 162.69, 164.67. HRMS (ESI) calcd for $C_{10}H_{13}N_2O_2F$ (M+H) 213.1039, found 213.1039.

Intermediate 134



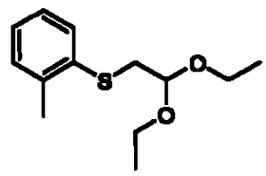
2-(Benzyloxy)-4-fluorobenzonitrile. Benzyl alcohol (13 mL, 125 mmol) was slowly added to a stirred suspension of NaH (95%, 2.86 g, 113 mmol) in toluene (200 mL) at room temperature. After 30 min, 2,4-difluorobenzonitrile (15.3 g, 110 mmol; Aldrich) was added all at once and stirring continued overnight (18 h). After this, the reaction mixture was washed with water (2 X 25 mL) and brine (25 ml). The organic layer was dried (Na_2SO_4), filtered and concentrated to give a white slurry which was triturated with hexanes and filtered to afford the title compound as a white solid (20.34 g, 81% yield). ^{1}H NMR (500 MHz, $CDCl_3$): 7.59-7.55 (1H, m), 7.45-7.34 (5H, m), 6.75-6.71 (2H, m), 5.19 (2H, s); ^{13}C NMR (125.76 MHz, DMSO-d6) δ ppm: 71.16, 98.75, 101.54, 101.75, 108.66, 108.84, 115.83, 127.16, 128.58, 128.94, 135.03, 135.44, 135.54, 162.22, 162.31, 165.26, 167.29. LCMS calcd for $C_{14}H_{11}FNO$: 228.2; found: 228.0.

Intermediate 135



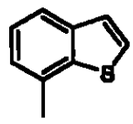
2-Hydroxy-4-fluoro-benzylamine hydrochloride. A solution of intermediate 134, 2-(benzyloxy)-4-fluorobenzonitrile, (9.03 g, 39.7 mmol) in ethanol (100 mL) and ethyl acetate (100 mL) was stirred with 10% palladium on carbon (1.67 g,) and concentrated hydrochloric acid (12 mL, 144 mmol) under a hydrogen atmosphere (60 psi) for four days. The catalyst was removed by filtration through Celite, and the filtrate was concentrated. The crude product was triturated with ether and the resulting solid collected by filtration to give the title compound (5.24 g, 74% yield) as a pale orange solid. ^{1}H NMR (500 MHz, DMSO-D6) δ ppm: 10.81 (1 H, s), 8.18 (3 H, s), 7.36 (1 H, t, J=7.3 Hz), 6.79 (1 H, dd, J=10.8, 2.6 Hz), 6.66 (1 H, dt, J=8.5, 2.3 Hz), 3.90 (2 H, d, J=5.2 Hz).

Intermediate 136



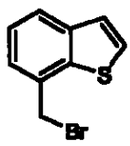
(2,2-Diethoxyethyl)(o-tolyl)sulfane. In ethanol (50 mL) was dissolved sodium metal (1.6 g, 66 mmol) at 23 °C. 2-Methylbenzenethiol (8.1 mL, 68 mmol) was slowly added to this solution, followed by bromoacetaldehyde diethylacetal (9.50 mL, 63 mmol). The reaction mixture was stirred at reflux for 18 h. The solvent was then evaporated *in vacuo* and the residue was washed with H_2O (100 mL) and extracted with ether (100 mL). The organic solution was dried ($MgSO_4$), concentrated *in vacuo* and purified by distillation to afford the title compound (13.48 g, 82% yield): ^{1}H NMR (400 MHz, $CDCl_3$) δ ppm: 7.33 (1H, d, J = 7.9 Hz), 7.16-7.08 (3H, m), 4.65 (1H, t, J = 5.6 Hz), 3.66 (2H, q, J = 7.0 Hz), 3.55 (2H, q, J = 7.0 Hz), 3.09 (2H, d, J = 5.6 Hz), 2.38 (3H, s), 1.20 (6H, t, J = 7.0 Hz). LCMS $(M+H)^+$ m/z 241 (t = 2.65min.).

Intermediate 137



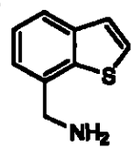
7-Methylbenzo[b]thiophene. To a solution of intermediate 136, (2,2-diethoxyethyl)(o-tolyl)sulfane (0.58 g, 2.41 mmol) in chlorobenzene (20 mL) was added polyphosphoric acid. The reaction mixture was stirred at reflux for 18 h. Water (100 mL) was then added and the organic material was extracted with CH_2Cl_2 (2 X 50 mL). The organic solution was dried ($MgSO_4$) and concentrated *in vacuo* to afford 335 mg (94% yield) of the title compound: ^{1}H NMR (400 MHz, $CDCl_3$) δ: 7.68 (1H, d, J = 7.8 Hz), 7.43 (1H, d, J = 5.4 Hz), 7.36 (1H, d, J = 5.4 Hz), 7.30 (1H, dd, J = 7.8, 7.1 Hz), 7.14 (1H, d, J = 7.1 Hz), 2.58 (3H, s); LCMS $(M+H)^+$ m/z 148.

Intermediate 138



7-(Bromomethyl)benzo[b]thiophene. To a solution of intermediate 137, 7-methylbenzo[b]thiophene (1.0 g, 6.5 mmol) in CCl_4 (20 mL) was added benzoyl peroxide (1.1g, 4.54 mmol) followed by portionwise addition of NBS (1.15g, 6.5 mmol). The reaction mixture stirred at reflux while irradiating with a 250 W lamp. The reaction mixture was stirred at reflux for 3 h. The solution was cooled, filtered and the solvent evaporated *in vacuo*. The residue was subjected to column chromatography on silica gel with hexanes as the eluent to afford the title compound (0.570 g, 33% yield): ^{1}H NMR (400 MHz, $CDCl_3$) δ: 7.30 (1H, dd, J = 7.8, 1.7 Hz), 7.49 (1H, d, J = 5.4 Hz), 7.40-7.33 (3H, m), 4.78 (2H, s). LCMS $(M+H)^+$ m/z 209.

Intermediate 139

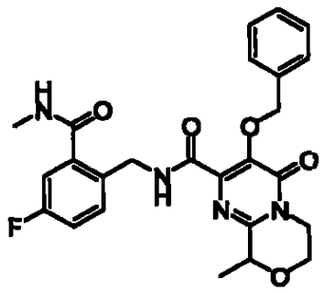


Benzo[b]thiophen-7-ylmethanamine hydrochloride. To intermediate 138, 7-(bromomethyl)benzo[b]thiophene (0.20g, 0.96 mmol) was added a methanolic solution saturated with ammonia (30 mL). The reaction mixture was heated in a steal bomb at 70 °C for 18 h. The solvent was evaporated *in vacuo* and the residue was dissolved in MeOH (10 mL). HCl (1M in ethanol, 1mL) was added to the solution and the solvents were removed *in vacuo* to afford the title compound (0.177 g, 99% yield); LCMS $(M+H)^+$ m/z 164.

Intermediates 140-148

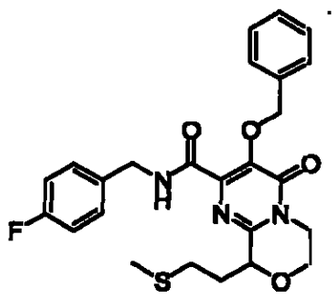
The synthesis of intermediates 140-148 provides representative procedures for the synthesis of other compounds in the invention.

Intermediate 140



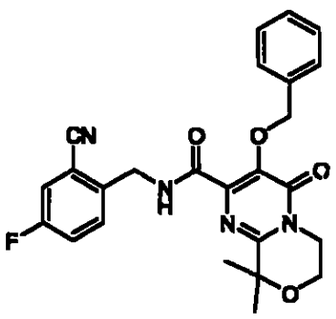
N-(4-Fluoro-2-(methylcarbamoyl)benzyl)-3-benzyloxy-9-methyl-4-oxo-4,6,7,9-tetrahydropyrimido[2,1-c][1,4]oxazine-2-carboxamide. A mixture of intermediate 27, 3-benzyloxy-9-methyl-4-oxo-4,6,7,9-tetrahydropyrimido[2,1-c][1,4]oxazine-2-carboxylic acid (0.172 g, 0.54 mmol) and intermediate 39, 2-(aminomethyl)-5-fluoro-N-methylbenzamide trifluoroacetate salt (0.177 g, 0.60 mmol) in dichloromethane (10 ml) was treated at 22 °C with triethylamine (0.17 ml, 1.22 mmol) followed by benzotriazole-1-yloxy-tris-pyrrolidino-phosphonium hexafluorophosphate (PyBOP) (0.340 g, 0.65 mmol). After 3 h, the reaction mixture was diluted with ethyl acetate, washed with saturated sodium bicarbonate and brine then dried over anhydrous magnesium sulfate. Evaporation of the solvent followed by chromatography of the residue on silica gel (elution gradient ethyl acetate 50–100% in toluene) gave 0.260 g (100% yield) of the title amide as a white solid. ^{1}HNMR 400 MHz ($CDCl_3$) δ (ppm): 1.70 (3H, d, J = 6.6 Hz, CH_3), 3.01 (3H, d, J = 4.7 Hz, NCH_3), 3.89 (2H, m, CH_2), 4.14 (1H, m, CH), 4.29 (1H, m, CH), 4.53 (2H, d, J = 6.7 Hz, NCH_2), 4.69 (1H, q, J = 6.6 Hz, OCH), 5.35 (2H, s, OCH_2), 6.69 (1H, broad q, NH); 7.09 (1H, m, aromatic), 7.16 (1H, m, aromatic), 7.32 (3H, m, aromatics), 7.42 (1H, m, aromatic), 7.47 (2H, m, aromatics), 8.61 (1H, broad t, NH). HRMS (ESI$^+$) calculated for $C_{25}H_{26}FN_4O_5$ [M+H$^+$]: 481.1887: found: 481.1884.

Intermediate 141



N-(4-fluorobenzyl)-3-(benzyloxy)-9-(2-(methylthio)ethyl)-4-oxo-4,6,7,9-tetrahydropyrimido[2,1-c][1,4]oxazine-2-carboxamide. A solution of intermediate 22 (82mg, 0.22mmol) and O-(7-azabenzotriazol-1-yl)-N,N,N',N'-tetramethyluronium hexafluorophosphate (HATU) (152mg, 0.4mmol) in 1mL dimethylformamide was stirred for 20 min under N_2. 4-Fluorobenzylamine (38mg, 0.3mmol) was then added and stirring continued for 16hrs. The dimethylformamide was evaporated under reduced pressure and the remaining residue dissolved in CH_2Cl_2. The resulting solution was washed with dil HCl. The solvent was removed under reduced pressure and the crude product purified by chromatography (SiO_2, ethyl acetate)to provide the title compound (70mg, Yield = 66%). LC/MS m/e 484 (M+H).

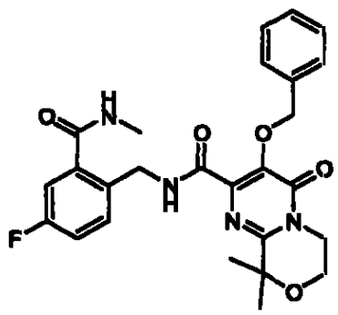
Intermediate 142



3-(Benzyloxy)-2-(6-fluoro-1-oxoisoindoline-2-carbonyl)-9,9-dimethyl-6,7-dihydropyrimido[2,1-c][1,4]oxazin-4(9H)-one. To a stirred suspension of

intermediate 27, 3-(benzyloxy)-9,9-dimethyl-4-oxo-4,6,7,9-tetrahydropyrimido-[2,1-c][1,4]oxazine-2-carboxylic acid, (1.65 g, 5 mmol) in CH_2Cl_2 (15 mL) was added a catalytic amount of dimethylformamide and 10 mL of a 2 M oxalylchloride in CH_2Cl_2. After 30 min., the resulting clear yellow solution was concentrated to afford a light brown solid. This solid was dissolved in CH_2Cl_2 (50 mL) and added to a stirred mixture of intermediate 107, 2-(aminomethyl)-5-fluorobenzonitrile trifluoroacetic acid salt, (1.77 g, 5.97 mmol) and diethylisopropylamine (2.6 mL, 15 mmol) in CH_2Cl_2 (100 mL). After 1 h, the clear brown reaction mixture was concentrated and the resulting residue dissolved in ethyl acetate (200 mL) then washed sequentially with water (25 mL), 1N HCl (25 mL), water (25 mL) and brine (25 mL). The combined aqueous layers were extracted with CH_2Cl_2 (3 X 50 mL). The combined organic phases were dried (Na_2SO_4), filtered, concentrated and purified by flash chromatography (SiO_2), using 30-50% ethyl acetate/Hexanes as eluent to afford the title compound (0.331 g, 14% yield) as a yellow powder. ^1H NMR (500 MHz, $CDCl_3$) δ: 7.48-7.45 (1H, m), 7.88 (2H, d, J = 7.9 Hz), 7.30 (2H, d, J = 7.0 Hz), 7.12 (2H, t, J = 7.6 Hz), 7.05-7.01 (1H, m), 5.22 (2H, s), 4.77 (2H, s), 4.06 (4H, s), 1.59 (6H, s). HRMS (M+H) calcd for $C_{25}H_{23}FN_3O_5$: 464.1622; found: 464.1628.

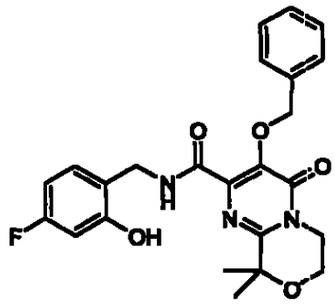
Intermediate 143



N-(4-Fluoro-2-(methylcarbamoyl)benzyl)-3-(benzyloxy)-9,9-dimethyl-4-oxo-4,6,7,9-tetrahydropyrimido[2,1-c][1,4]oxazine-2-carboxamide. A 25 mL round-bottom flask was charged with intermediate 27, 3-(benzyloxy)-9,9-dimethyl-4-oxo-4,6,7,9-tetrahydropyrimido-[2,1-c][1,4]oxazine-2-carboxylic acid, (0.991 g, 3.0

mmol), intermediate 39, 2-(aminomethyl)-5-fluoro-N-methylbenzamide trifluoroacetic acid salt (1.185 g, 4.0 mmol), 4-dimethylaminopyridine (DMAP, 1.1 g, 9.0 mmol) and O-(7-azabenzotriazol-1-yl)-N,N,N',N'-tetramethyluronium hexafluorophosphate (HATU, 1.722 g, 4.5 mmol). Dimethylformamide (20 mL) was added and the mixture stirred for 1 h at ambient temperature. After this, the reaction mixture was diluted with ethyl acetate (100 mL) then washed with water (3 X 25 mL) and brine (25 mL). The organic layer was dried (Na_2SO_4), filtered, concentrated and purified by flash chromatography (SiO_2), eluting with hexanes/ethyl acetate (1:1 to 1:3) followed by ethyl acetate, to afford the title compound as an off-white solid (1.48 g, 100% yield). ^1H NMR (500 MHz, $CDCl_3$) δ ppm: 8.49 (1H, t, J = 6.1 Hz), 7.48-7.46 (2H, m), 7.43 (1H, dd, J = 8.5, 5.5 Hz), 7.31-7.27 (3H, m), 7.12 (1H, dd, J = 8.9, 2.7 Hz), 7.05 (1H, td, J = 8.2, 2.7 Hz), 6.52 (1H, br s), 5.26 (2H, s), 4.53 (2H, d, J = 6.4 Hz), 4.01 (2H, t, J = 4.9 Hz), 3.96 (2H, t, J = 4.9 Hz), 2.97 (3H, d, J = 4.9 Hz), 1.62 (6H, s). HRMS (M+H) calcd for $C_{26}H_{28}FN_4O_5$: 495.2044; found: 495.2032.

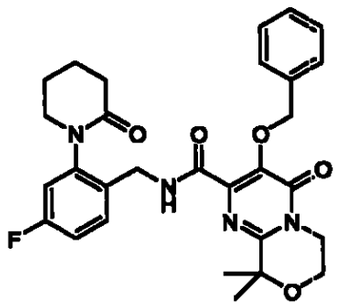
Intermediate 144



N-(4-Fluoro-2-hydroxybenzyl)-3-(benzyloxy)-9,9-dimethyl-4-oxo-4,6,7,9-tetrahydropyrimido[2,1-c][1,4]oxazine-2-carboxamide. A solution of intermediate 27, 3-(benzyloxy)-9,9-dimethyl-4-oxo-4,6,7,9-tetrahydropyrimido-[2,1-c][1,4]oxazine-2-carboxylic acid, (1.50 g, 4.54 mmol) and HATU (2.07 g, 5.45 mmol) in anhydrous dimethylformamide was stirred for 20 minutes under a nitrogen atmosphere at room temperature. To the solution was added intermediate 135, 2-hydroxy-4-fluoro-benzylamine hydrochloride, (1.05 g, 5.9 mmol) followed by DMAP (1.39 g, 11.4 mmol), and the reaction mixture stirred at 60 °C for 90 minutes.

The solvent was removed *in vacuo* and the crude residue purified by flash column chromatography (SiO_2), eluting with 40%-60% ethyl acetate in hexanes to give the title compound (1.31 g, 64% yield) as a solid. ^{1}H NMR (500 MHz, $CDCl_3$) δ ppm: 9.69 (1H, br s), 8.18 (1H, t, *J*=6.3 Hz), 7.44 (2H, dd, *J*=6.6, 2.6 Hz), 7.30-7.35 (3H, m), 7.00 (1H, dd, *J*=8.2, 6.7 Hz), 6.68 (1H, dd, *J*=10.4, 2.4 Hz), 6.54 (1H, dt, *J*=8.2, 2.4 Hz), 5.29 (2H, s), 4.36 (2H, d, *J*=6.7 Hz), 3.97-4.05 (4H, m), 1.61 (6H, s).

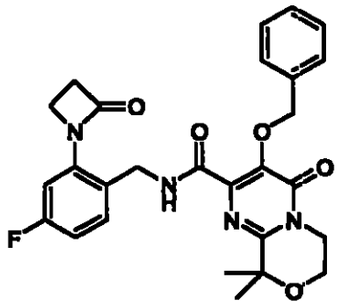
Intermediate 145



N-(4-Fluoro-2-(2-oxopiperidin-1-yl)benzyl)-3-(benzyloxy)-9,9-dimethyl—4-oxo-4,6,7,9-tetrahydropyrimido[2,1-c][1,4]oxazin-4(9H)-one. To intermediate 27, 3-(benzyloxy)-9,9-dimethyl-4-oxo-4,6,7,9-tetrahydropyrimido[2,1-c][1,4]oxazine-2-carboxylic acid, (80 mg, 0.242 mmol) in CH_3CN/dimethylformamide (5 mL:1 mL:) was added intermediate 125, 1-(2-(aminomethyl)-5-fluorophenyl)piperidin-2-one hydrochloride salt, (69 mg, 0.266 mmol), benzotriazole-1-yl-oxy-tris-pyrrolidino-phosphonium hexafluorophosphate (PyBOP) (139 mg, 0.266 mmol) and diisopropylethylamine (169 μL, 0.968 mmol). The reaction mixture was stirred at 23 °C for 3h. The solvents were then removed *in vacuo* and an aqueous solution of HCl (1N, 25 mL) was added. This was extracted with ethyl acetate (3 X 25 mL). The combined organic fractions were dried ($MgSO_4$), filtered and concentrated *in vacuo*. The crude material was purified on a Biotage system using a silica gel column with Hexanes/ethyl acetate (1:1) to (1:5) as eluent to afford 114 mg (88% yield) of the title compound. ^{1}HNMR 400 MHz (DMSO) δ ppm: 8.73 (1H, dd, (t), J = 6.0 Hz), 7.46 (2H, m), 7.35 (4H, m), 7.18 (1H, dd, J = 9.8, 3.0 Hz) 7.0 (1H, m), 5.10 (2H, s), 4.43 (1H, dd, J =15.0, 7.08 Hz), 4.06 (1H, dd, J = 15.0, 5.56), 4.02 (2H, t, J = 5.0 Hz),

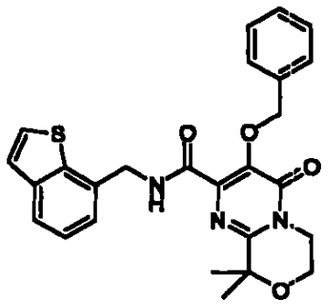
3.90 (2H, t, J = 5.0 Hz), 3.64 (1H, m), 3.44 (1H, m), 2.45 (1H, m), 2.35 (1H, m), 1.86 (4H, m), 1.56 (6H, s). LCMS $(M+H)^+$ m/z 535.

Intermediate 146



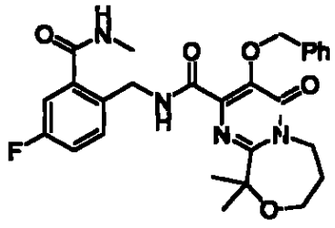
N-(4-Fluoro-2-(2-oxoazetidin-1-yl)benzyl)-3-(benzyloxy)-9,9-dimethyl-4-oxo-4,6,7,9-tetrahydropyrimido[2,1-c][1,4]oxazine-2-carboxamide. To a solution of intermediate 27, 3-(benzyloxy)-9,9-dimethyl-4-oxo-4,6,7,9-tetrahydropyrimido[2,1-c][1,4]oxazine-2-carboxylic acid, (0.142 g, 0.430 mmol) in CH_3CN: dimethylformamide (30 mL: 5 mL) was added intermediate 120, 1-(2-(aminomethyl)-5-fluorophenyl)azetidin-2-one hydrochloride, (0.100 g, 0.43 mmol), (benzotriazole-1-yloxy)tris(dimethylamino)phosphonium hexafluorophosphate (0.207 g, 0.470 mmol) and diisopropylethylamine (280 µL, 1.72 mmol). The reaction mixture was stirred at 23 °C for 18h. The solvents were removed *in vacuo* and 1N HCl (50 mL) added. This was extracted with ethyl acetate (2 X 50 mL). The combined organic extracts were dried ($MgSO_4$), filtered and concentrated *in vacuo*. The residue was purified on a Biotage system using a silica gel column with ethyl acetate as eluent to afford the title compound (0.157 g, 72% yield). ^1H NMR (400 MHz, MeOD) δ ppm: 7.88 (1H, d, J = 8.3 Hz), 7.76 (1H, d, J = 8.0Hz), 7.58-7.30 (4H, m), 7.10 (1H, dd, J = 10.2, 2.5 Hz), 6.90 (1H, m), 5.20 (2H, s), 4.55 (2H, s), 4.04 (2H, m), 3.96 (2H, m), 3.78 (2H, t, J = 4.2 Hz), 3.10 (2H, t, J = 4.2 Hz),1.58 (6H, s); LCMS $(M+H)^+$ m/z 506.

Intermediate 147



N-(Benzo[b]thiophen-7-ylmethyl)-3-(benzyloxy)-9,9-dimethyl-4-oxo-4,6,7,9-tetrahydropyrimido[2,1-c][1,4]oxazine-2-carboxamide. To a solution of intermediate 27, 3-(benzyloxy)-9,9-dimethyl-4-oxo-4,6,7,9-tetrahydropyrimido[2,1-c][1,4]oxazine-2-carboxylic acid (0.200 g, 0.60 mmol) in CH_3CN:dimethylformamide (30 mL: 5 mL) was added intermediate 139, benzo[b]thiophen-7-ylmethanamine hydrochloride (0.069 g, 0.266 mmol), benzotriazole-1-yl-oxy-tris-pyrrolidino-phosphonium hexafluorophosphate (PyBOP) (0.347 g, 0.670 mmol) and diisopropylethylamine (420 µL, 2.40 mmol). The reaction mixture was stirred at 23 °C for 60 h. The solvents were then removed *in vacuo* and 1N HCl (50 mL) added. This was extracted with ethyl acetate (2 X 50 mL). The combined organic extracts were dried ($MgSO_4$), filtered and concentrated *in vacuo*. The residue was purified on a Biotage system using a silica gel column with hexane:ethyl acetate (1:1) to (1:5) gradient as eluent to afford the title compound (0.279 g, 87% yield): ^1H NMR (400 MHz, DMSO-d_6) δ: 9.11 (1H, dd, J = 5.6 Hz), 7.81 (1H, m), 7.77 (1H, d, J = 5.6 Hz), 7.52 (1H, d, J = 5.6 Hz), 7.48-7.26 (6H, m), 5.09 (2H, s), 4.67 (2H, d, J = 5.2 Hz), 4.04 (2H, m), 3.90 (2H, m), 1.58 (6H, s). LCMS $(M+H)^+$ m/z 476.

Intermediate 148



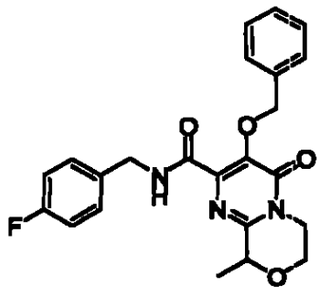
N-(4-Fluoro-2-(methylcarbamoyl)benzyl)-3-(benzyloxy)-10,10-dimethyl-4-oxo-6,7,8,10-tetrahydro-4H-pyrimido[2,1-c][1,4]oxazepine-2-carboxamide. A solution of intermediate 35, 3-(benzyloxy)-10,10-dimethyl-4-oxo-6,7,8,10-tetrahydro-4H-pyrimido[2,1-c][1,4]oxazepine-2-carboxylic acid in anhydrous dimethylformamide (4 mL) was treated with HATU (0.278 g, 0.70 mmol) and stirred for 10 minutes. The reaction mixture was treated with 2-(aminomethyl)-5-fluoro-N-methylbenzamide trifluoroacetic acid salt (0.24 g, 0.8 mmol), followed by dimethylaminopyridine (0.121 g, 0.97 mmol), then stirred for 4 hours at 60 °C. Following this, the solvent was removed *in vacuo* and the remaining residue dissolved in ethyl acetate (15 mL) and washed with 1.0 N HCl (15 mL). The organic layer was dried (sodium sulfate), filtered, and concentrated to dryness. The crude product was purified by flash column chromatography (SiO_2), eluting with ethyl acetate. Fractions containing the product were pooled, concentrated to dryness and triturated with ether to provide 0.366 g of the title compound as a white glassy solid. ^{1}H NMR (500 MHz, d_6-acetone) δ ppm: 8.71-8.82 (1H, m), 7.84-7.95 (1H, br), 7.47-7.62 (4H, m), 7.27-7.40 (5H, m), 7.20 (1H, dt, *J*=8.5, 2.7 Hz), 5.15-5.21 (2H, br s), 4.48-4.60 (4H, m), 2.96 (2H, s), 2.94 (2H, s), 1.62-1.64 (6H, s).

Intermediates 149-174

Intermediates 149-174 were prepared according to the coupling procedures described for intermediates 140-148.

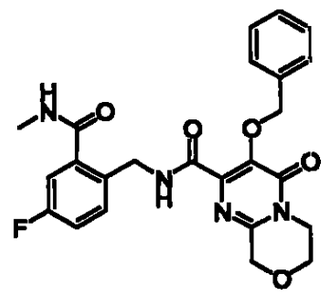
156

Intermediate 149



N-(4-Fluorobenzyl)-3-(benzyloxy)-9-methyl-4-oxo-4,6,7,9-tetrahydropyrimido[2,1-c][1,4]oxazine-2-carboxamide. The title compound can be prepared from intermediate 16, 3-benzyloxy-9-methyl-4-oxo-4,6,7,9-tetrahydropyrimido[2,1-c][1,4]oxazine-2-carboxylic acid and 4-fluorobenzylamine. ^{1}HNMR 400 MHz ($CDCl_3$) δ (ppm): 1.67 (3H, d, J = 6.6 Hz, CH_3), 3.91 (2H, m, CH_2), 4.12-4.35 (2H, m, CH_2), 4.52 (2H, d, J = 5.9 Hz, NCH_2), 4.70 (1H, q, J = 6.6 Hz, OCH), 5.33 (2H, s, OCH_2), 7.02 (2H, m, aromatics), 7.25 (2H, m, aromatics), 7.35 (3H, m, aromatics), 7.47 (2H, m, aromatics), 7.71 (1H, broad t, NH).

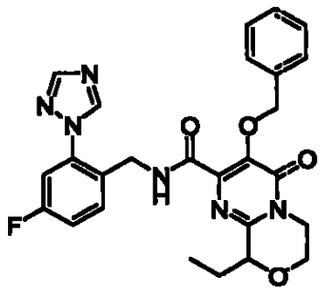
Intermediate 150



N-(4-Fluoro-2-(methylcarbamoyl)benzyl)-3-(benzyloxy)-4-oxo-4,6,7,9-tetrahydropyrimido[2,1-c][1,4]oxazine-2-carboxamide. The title compound can be prepared from intermediate 7, 3-(benzyloxy)-4-oxo-4,6,7,9-tetrahydropyrimido[2,1-c][1,4]oxazine-2-carboxylic acid and intermediate 39, 2-(aminomethyl)-5-fluoro-N-methylbenzamide. White crystals; mp 189-190 °C (ethyl acetate). ^{1}HNMR 400 MHz

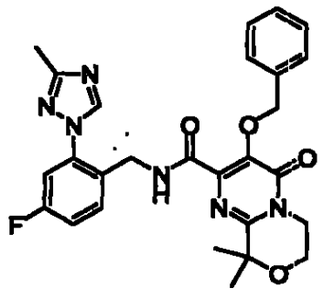
($CDCl_3$) δ (ppm): 3.01 (3H, d, J = 4.5 Hz, NCH_3), 4.00 (2H, m, CH_2), 4.08 (1H, m, CH), 4.50 (2H, d, J = 6.6 Hz, NCH_2), 4.71 (2H, s, OCH_2), 5.38 (2H, s, OCH_2), 6.88 (1H, broad q, NH), 7.07 (1H, m, aromatic), 7.16 (1H, dd, J =2.5 Hz and J = 8.6 Hz, aromatic), 7.30-7.44 (6H, m, aromatics), 8.55 (1H, broad t, NH). Anal. Calcd for $C_{24}H_{23}FN_4O_5$: C 61.80, H 4.97, N 12.01. Found: C 61.84, H 4.82, N 12.00.

Intermediate 151



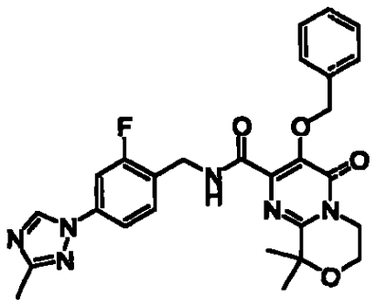
N-(4-Fluoro-2-(1H-1,2,4-triazol-1-yl)benzyl)-3-(benzyloxy)-9-ethyl-4-oxo-4,6,7,9-tetrahydropyrimido[2,1-c][1,4]oxazine-2-carboxamide. The title compound can be prepared from 3-(benzyloxy)-9-ethyl-4-oxo-4,6,7,9-tetrahydropyrimido[2,1-c][1,4]oxazine-2-carboxylic acid which was synthesized using the method described for the synthesis or intermediates 7 and 16, and intermediate 69, (4-fluoro-2-(1H-1,2,4-triazol-1-yl)phenyl)methanamine. White needles; mp 155-157 °C (ethyl acetate). ^{1}HNMR 400 MHz ($CDCl_3$) δ (ppm): 1.03 (3H, t, J = 7.5 Hz, CH_3), 1.97–2.02 (1H, m, CH), 2.29-2.32 (1H, m, CH),.3.83–3.88 (2H, m, CH_2), 4.15-4.31 (2H, m, CH_2), 4.44 (2H, m, CH_2), 4.53 (1H, m, CH), 5.34 (2H, s, OCH_2), 7.08 (1H, dd, J = 2.5 Hz and J = 8.6 Hz, aromatic), 7.20 (1H, m, aromatic), 7.29 -7.31 (3H, m, aromatics), 7.47 (2H, m, aromatics), 7.74 (1H, dd, J = 6.1 Hz and J = 8.6 Hz, aromatic), 8.02 (1H, s, CH), 8.41 (1H, s, CH), 8.55 (1H, broad t, NH). Anal. Calcd for $C_{26}H_{25}FN_6O_4$: C 61.89, H 4.99, N 16.65. Found: C 61.67, H 5.13, N 16.61.

Intermediate 152



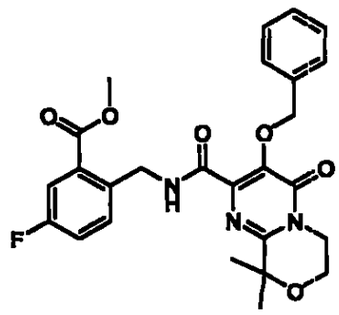
N-(4-Fluoro-2-(3-methyl-1H-1,2,4-triazol-1-yl)benzyl)-3-(benzyloxy)-9,9-dimethyl-4-oxo-4,6,7,9-tetrahydropyrimido[2,1-c][1,4]oxazine-2-carboxamide. The title compound can be prepared from intermediate 27, 3-(benzyloxy)-9,9-dimethyl-4-oxo-4,6,7,9-tetrahydropyrimido-[2,1-c][1,4]oxazine-2-carboxylic acid and intermediate 85, (4-fluoro-2-(3-methyl-1H-1,2,4-triazol-1-yl)phenyl)methanamine. White crystals; mp 203 °C (ethyl acetate). ^{1}HNMR 400 MHz ($CDCl_3$) δ (ppm): 1.65 (6H, s, 2 x CH_3), 2.50 (3H, s, CH_3), 4.03 (4H, m, 2 x CH_2), 4.46 (2H, d, J = 6.6 Hz, NCH_2), 5.31 (2H, s, OCH_2), 7.06 (1H, dd, J = 3 Hz and J = 8.6 Hz, aromatic), 7.16 (1H, m, aromatic), 7.30–7.34 (3H, m, aromatics), 7.50 (2H, m, aromatics), 7.74 (1H, dd, J = 6.0 Hz and J = 8.6 Hz, aromatic), 8.28 (1H, s, CH), 8.45 (1H, broad t, NH). Anal. Calcd for $C_{27}H_{27}FN_6O_4$: C 62.54, H 5.25, N 16.21. Found: C 62.48, H 5.31, N 16.29.

Intermediate 153



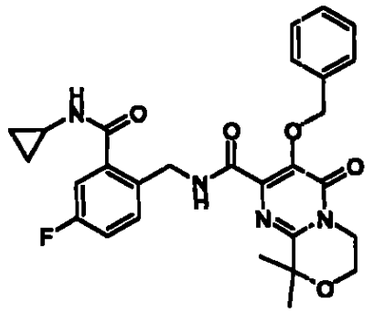
N-(2-Fluoro-4-(3-methyl-1H-1,2,4-triazol-1-yl)benzyl)-3-(benzyloxy)-9,9-dimethyl-4-oxo-4,6,7,9-tetrahydropyrimido[2,1-c][1,4]oxazine-2-carboxamide. The title compound can be prepared from intermediate 27, 3-(benzyloxy)-9,9-dimethyl-4-oxo-4,6,7,9-tetrahydropyrimido-[2,1-c][1,4]oxazine-2-carboxylic acid and intermediate 87, (2-fluoro-4-(3-methyl-1H-1,2,4-triazol-1-yl)phenyl)methanamine. White crystals; mp 183 -185 °C (ethyl acetate). ^{1}HNMR 400 MHz ($CDCl_3$) δ (ppm): 1.65 (6H, s, 2 x CH_3), 2.52 (3H, s, CH_3), 4.05 (4H, m, 2 x CH_2), 4.64 (2H, d, J = 6.1 Hz, NCH_2), 5.33 (2H, s, OCH_2), 7.29 -7.55 (8H, m, aromatics), 7.84 (1H, broad t, NH), 8.45 (1H, s, CH). Anal. Calcd for $C_{27}H_{27}FN_6O_4$: C 62.54, H 5.25, N 16.21. Found: C 62.41, H 5.40, N 16.23.

Intermediate 154



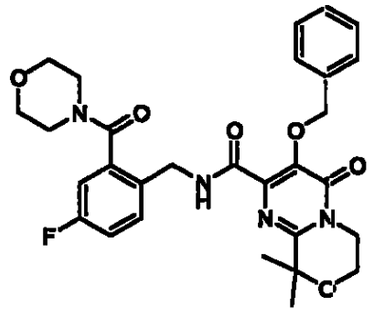
Methyl 2-((3-(benzyloxy)-9,9-dimethyl-4-oxo-4,6,7,9-tetrahydropyrimido[2,1-c][1,4]oxazine-2-carboxamido)methyl)-5-fluorobenzoate. The title compound can be prepared from intermediate 27, 3-(benzyloxy)-9,9-dimethyl-4-oxo-4,6,7,9-tetrahydropyrimido-[2,1-c][1,4]oxazine-2-carboxylic acid and intermediate 38, methyl 2-(aminomethyl)-5-fluorobenzoate. ^{1}H NMR ($CDCl_3$, 500 MHz) δ ppm: 1.61 (6H, s, gem-Me), 3.88 (3H, s, OMe), 3.97 (2H, t, J = 5.5 Hz, CH_2), 4.02 (2H, t, J = 5.5 Hz, CH_2), 4.73 (2H, d, J = 6.7 Hz, NCH_2), 5.25 (2H, s, OCH_2), 7.19 (1H, dt, J = 3, 8.5 Hz, Ar-H), 7.27-7.31 (3H, m, Ar-Hs), 7.48-7.50 (2H, m, Ar-Hs), 7.61 (1H, dd, J = 5.5, 8.5 Hz, Ar-H), 7.66 (1H, dd, J = 3, 9.5 Hz, Ar-H). LC/MS m/z 496 (M+H).

Intermediate 155



N-(2-(Cyclopropylcarbamoyl)-4-fluorobenzyl)-3-(benzyloxy)-9,9-dimethyl-4-oxo-4,6,7,9-tetrahydropyrimido[2,1-c][1,4]oxazine-2-carboxamide. The title compound can be prepared from intermediate 27, 3-(benzyloxy)-9,9-dimethyl-4-oxo-4,6,7,9-tetrahydropyrimido-[2,1-c][1,4]oxazine-2-carboxylic acid and intermediate 40, 2-(aminomethyl)-N-cyclopropyl-5-fluorobenzamide. LC/MS m/z 521 (M+H).

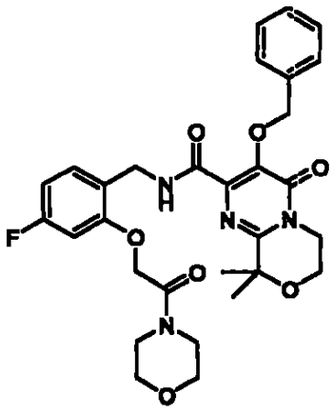
Intermediate 156



N-(4-Fluoro-2-(morpholine-4-carbonyl)benzyl)-3-(benzyloxy)-9,9-dimethyl-4-oxo-4,6,7,9-tetrahydropyrimido[2,1-c][1,4]oxazine-2-carboxamide. The title compound can be prepared from intermediate 27, 3-(benzyloxy)-9,9-dimethyl-4-oxo-4,6,7,9-tetrahydropyrimido-[2,1-c][1,4]oxazine-2-carboxylic acid and intermediate 44, (2-(aminomethyl)-5-fluorophenyl)(morpholino)methanone. ^{1}H NMR ($CDCl_3$, 500 MHz) δ ppm: 1.59 (6H, s), 3.29 (2H, brs), 3.57 (2H, m), 3.74 (4H, s), 3.98 (4H, m), 5.26 (2H, s), 6.88 (1H, dd, J=8.2, 2.7 Hz), 7.03 (1H, dt, J=8.5, 2.5 Hz), 7.24-7.33

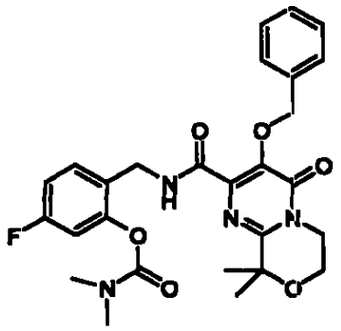
(3H, m), 7.42 (2 H, dd, J=8.6, 5.3 Hz), 7.47 (2H, dd, J=7.5, 2.0 Hz), 8.18 (1H, t, J=6.4 Hz); LC/MS m/z 551 (M+H).

Intermediate 157



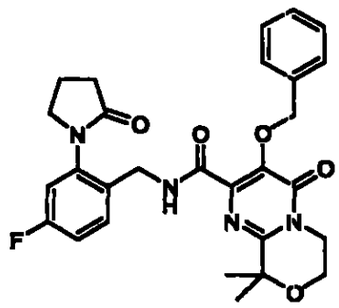
N-(4-Fluoro-2-(2-morpholino-2-oxoethoxy)benzyl)-3-(benzyloxy)-9,9-dimethyl-4-oxo-4,6,7,9-tetrahydropyrimido[2,1-c][1,4]oxazine-2-carboxamide. The title compound can be prepared from intermediate 27, 3-(benzyloxy)-9,9-dimethyl-4-oxo-4,6,7,9-tetrahydropyrimido-[2,1-c][1,4]oxazine-2-carboxylic acid and intermediate 131, 2-(2-(aminomethyl)-5-fluorophenoxy)-1-morpholinoethanone. ^{1}H NMR ($CDCl_3$, 500 MHz) δ ppm: 1.59 (6H, s, gem-Me), 3.38, 3.54 (4H, br, NCH_2), 3.62 (4H, m, OCH_2), 3.96 (2H, m, NCH_2), 4.01 (2H, m, OCH_2), 4.55 (2H, s, OCH_2), 4.55 (2H, d, J = 4.3 Hz, NCH_2), 5.17 (2H, s, OCH_2), 6.53 (1H, dd, J = 10, 2.1 Hz, Ar-H), 6.63 (1H, dt, J = 2.5, 8 Hz, Ar-H), 7.23-7.26 (1H, m, Ar-H), 7.28-7.30 (3H, m, Ar-Hs), 7.42-7.44 (2H, m, Ar-Hs), 8.00 (1H, t, J = 5.5 Hz, NH); ^{13}C NMR ($CDCl_3$, 125.77 Hz) δ ppm: 27.74, 38.76, 42.30, 42.98, 45.38, 58.06, 66.55, 66.78, 66.91, 74.72, 76.27, 100.40, 100.61, 108.07, 108.23, 122.56, 128.37, 128.49, 128.84, 130.88, 130.96, 139.69, 141.36, 141.98, 156.70, 157.02, 157.10, 159.58, 162.04, 163.99, 162.86, 165.79. HRMS (ESI) calcd for $C_{30}H_{34}N_4O_7F$ (M+H) 581.2412, found 581.2393.

Intermediate 158



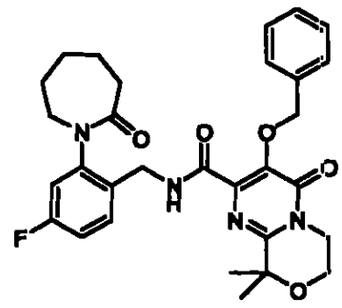
Dimethyl-carbamic acid 2-{[(3-benzyloxy-9,9-dimethyl-4-oxo-4,6,7,9-tetrahydro-pyrimido[2,1-c][1,4]oxazine-2-carbonyl)-amino]-methyl}-5-fluoro-phenyl ester. The title compound can be prepared from intermediate 27, 3-(benzyloxy)-9,9-dimethyl-4-oxo-4,6,7,9-tetrahydropyrimido-[2,1-c][1,4]oxazine-2-carboxylic acid and intermediate 133, 2-(aminomethyl)-5-fluorophenyl dimethylcarbamate. ^{1}H NMR ($CDCl_3$, 500 MHz) δ ppm: 1.58 (6H, s, gem-Me), 2.92, 3.05 (2s, NMe), 3.96 (2H, m, NCH_2), 4.00 (2H, m, OCH_2), 4.48 (2H, d, J = 5.5 Hz, NCH_2), 5.26 (2H, s, OCH_2), 6.84 (1H, dd, J = 2.5 Hz, 9 Hz, Ar-H), 6.87 (1H, dt, J = 2.5 Hz, 8 Hz, Ar-H), 7.25-7.33 (4H, m, Ar-Hs), 7.53 (2H, d, J = ~7 Hz, Ar-Hs), 7.78 (1H, brt, J = 5 Hz, NH); ^{13}C NMR ($CDCl_3$, 125.77 Hz) δ ppm: 27.68, 36.61, 36.89, 37.97, 42.97, 58.06, 74.73, 76.23, 110.58, 110.77, 113.06, 113.23, 126.55, 126.58, 128.31, 128.45, 128.91, 131.23, 131.31, 136.76, 140.70, 142.00, 150.60, 150.69, 154.50, 156.30, 159.79, 161.40, 163.37, 162.43. HRMS (ESI) calcd for $C_{27}H_{30}N_4O_6F$ (M+H) 525.2149, found 525.2163.

Intermediate 159



N-(4-Fluoro-2-(2-oxopyrrolidin-1-yl)benzyl)-3-(benzyloxy)-9,9-dimethyl-4-oxo-4,6,7,9-tetrahydropyrimido[2,1-c][1,4]oxazine-2-carboxamide. The title compound can be prepared from intermediate 27, 3-(benzyloxy)-9,9-dimethyl-4-oxo-4,6,7,9-tetrahydropyrimido-[2,1-c][1,4]oxazine-2-carboxylic acid and 1-(2-(aminomethyl)-5-fluorophenyl)pyrrolidin-2-one, derived from reduction of intermediate 111, 4-fluoro-2-(2-oxopyrrolidin-1-yl)benzonitrile. ^{1}HNMR 400 MHz (MeOD) δ ppm: 7.44 (3H, m), 7.33 (3H, m), 7.11 (1H, dd, J = 9.2, 3.0 Hz) 7.03 (1H, m), 5.21 (2H, s), 4.43 (2H, s), 4.08 (2H, t, J = 5.0 Hz), 3.98 (2H, t, J = 5.0 Hz), 3.85 (2H, t, J = 7.1 Hz), 2.58 (2H, t, J = 8.0 Hz), 2.23 (2H, m), 1.61 (6H, s). LCMS $(M+H)^+$ m/z 521.

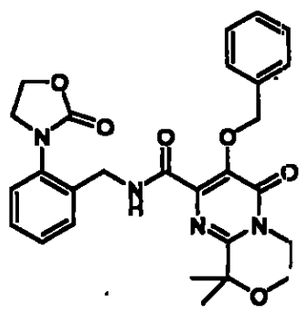
Intermediate 160



N-(4-Fluoro-2-(2-oxoazepan-1-yl)benzyl)-3-(benzyloxy)-9,9-dimethyl-4-oxo-4,6,7,9-tetrahydropyrimido[2,1-c][1,4]oxazine-2 carboxamide. The title compound

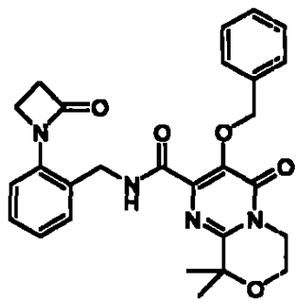
can be prepared from intermediate 27, 3-(benzyloxy)-9,9-dimethyl-4-oxo-4,6,7,9-tetrahydropyrimido-[2,1-c][1,4]oxazine-2-carboxylic acid and 1-(2-(aminomethyl)-5-fluorophenyl)azepan-2-one, derived from reduction of intermediate 113, 4-fluoro-2-(2-oxoazepan-1-yl)benzonitrile. ^{1}HNMR 400 MHz (DMSO) δ ppm: 8.80 (1H, dd, (t), J = 6.0 Hz), 7.46 (2H, m), 7.36 (4H, m), 7.08 (1H, dd, J = 9.8, 2.8 Hz), 7.0 (1H, m), 5.09 (2H, s), 4.43 (1H, dd, J =15.2, 7.1 Hz), 4.06 (1H, dd, J = 15.2, 5.0 Hz), 4.02 (2H, t, J = 5.0 Hz), 3.90 (2H, t, J = 5.0 Hz), 3.77 (1H, m), 3.51 (1H, m), 2.70 (1H, m), 2.51 (2H, m), 1.76 (6H, m), 1.56 (6H, s). LCMS $(M+H)^+$ m/z 549.

Intermediate 161



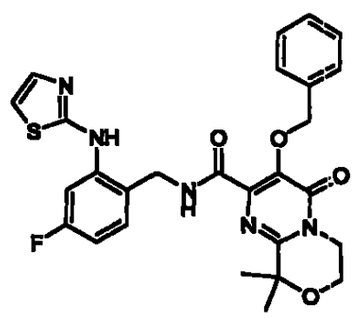
N-(2-(2-Oxooxazolidin-3-yl)benzyl)-3-(benzyloxy)-9,9-dimethyl-4-oxo-4,6,7,9-tetrahydropyrimido[2,1-c][1,4]oxazine-2-carboxamide. The title compound can be prepared from intermediate 27, 3-(benzyloxy)-9,9-dimethyl-4-oxo-4,6,7,9-tetrahydropyrimido-[2,1-c][1,4]oxazine-2-carboxylic acid and 3-(2-(aminomethyl)phenyl)oxazolidin-2-one, derived from reduction of intermediate 116, 2-(2-oxooxazolidin-3-yl)benzonitrile. ^{1}H NMR (400 MHz, DMSO-d_6) δ ppm: 8.90 (1H, t, J = 6.0 Hz), 7.58-7.32 (7H, m), 7.22 (2H, t, J = 7.5 Hz), 5.08 (2H, s), 4.48 (2H, t, J = 7.8 Hz), 4.44 (2H, d, J = 6.0 Hz), 4.06-3.97 (4H, m), 3.88 (2H, m), 1.56 (6H, s); LCMS $(M+H)^+$ m/z 505.

Intermediate 162



N-(2-(2-Oxoazetidin-1-yl)benzyl)-3-(benzyloxy)-9,9-dimethyl-4-oxo-4,6,7,9-tetrahydropyrimido[2,1-c][1,4]oxazine-2-carboxamide. The title compound can be prepared from intermediate 27, 3-(benzyloxy)-9,9-dimethyl-4-oxo-4,6,7,9-tetrahydropyrimido-[2,1-c][1,4]oxazine-2-carboxylic acid and 1-(2-(aminomethyl)phenyl)azetidin-2-one, derived from reduction of intermediate 115, 2-(2-oxoazetidin-1-yl)benzonitrile. ^{1}H NMR (400 MHz, $CDCl_3$) δ ppm: 8.67 (1H, brt, J = 6.3 Hz), 7.60 (1H, dd, J = 1.3, 7.6 Hz), 7.53-7.50 (1H, dd, m), 7.34-7.24 (5H, m), 7.18 (1H, ddd(dt), J = 1.2, 7.4 Hz), 7.10 (1H, dd, J = 1.2, 8.0 Hz), 5.27 (2H, s), 4.60 (2H, d, J = 6.3 Hz), 4.01-3.95 (4H, m), 3.71 (2H, t, J = 4.5 Hz), 3.10 (2H, t, J = 4.5 Hz), 1.60 (6H, s); LCMS ($^+$ ESI, $M+H^+$) m/z 489.

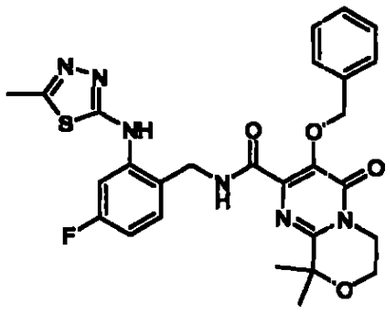
Intermediate 163



N-(4-Fluoro-2-(thiazol-2-ylamino)benzyl)-3-(benzyloxy)-9,9-dimethyl-4-oxo-4,6,7,9-tetrahydropyrimido[2,1-c][1,4]oxazine-2-carboxamide. The title compound

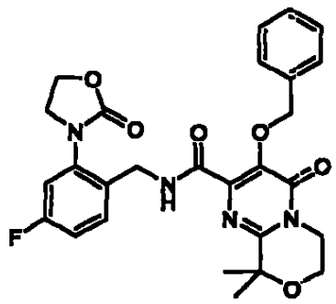
can be prepared from intermediate 27, 3-(benzyloxy)-9,9-dimethyl-4-oxo-4,6,7,9-tetrahydropyrimido-[2,1-c][1,4]oxazine-2-carboxylic acid and N-(2-(aminomethyl)-5-fluorophenyl)thiazol-2-amine, derived from reduction of intermediate 123, 4-fluoro-2-(thiazol-2-ylamino)benzonitrile. ^{1}H NMR (400 MHz, DMSO-d6) δ ppm: 9.92 (1H, s), 9.10 (1H, t, J = 6.3 Hz), 8.19 (1H, dd, J = 2.8, 12.3 Hz), 7.41-7.38 (2H, m), 7.32-7.28 (5H, m), 6.99 (1H, d, J = 3.8 Hz), 6.71 (1H, ddd(dt), J = 2.8, 8.3), 5.05 (2H, s), 4.45 (2H, d, J = 6.3 Hz), 4.01-3.98 (2H, m), 3.88-3.85 (2H, m), 1.54 (6H, s) LCMS (+ ESI, M+H$^+$) m/z 536.

Intermediate 164



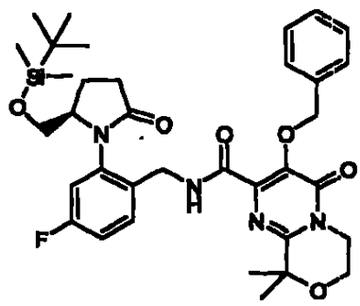
N-(4-Fluoro-2-(5-methyl-1,3,4-thiadiazol-2-ylamino)benzyl)-3-(benzyloxy)-9,9-dimethyl-4-oxo-4,6,7,9-tetrahydropyrimido[2,1-c][1,4]oxazine-2-carboxamide. The title compound can be prepared from intermediate 27, 3-(benzyloxy)-9,9-dimethyl-4-oxo-4,6,7,9-tetrahydropyrimido-[2,1-c][1,4]oxazine-2-carboxylic acid and N-(2-(aminomethyl)-5-fluorophenyl)-5-methyl-1,3,4-thiadiazol-2-amine, derived from reduction of intermediate 124, 4-fluoro-2-(5-methyl-1,3,4-thiadiazol-2-ylamino)benzonitrile. LCMS (+ ESI, M+H$^+$) m/z 551.

Intermediate 165



N-(4-Fluoro-2-(2-oxooxazolidin-3-yl)benzyl)-3-(benzyloxy)-9,9-dimethyl-4-oxo-4,6,7,9-tetrahydropyrimido[2,1-c][1,4]oxazine-2-carboxamide. The title compound can be prepared from intermediate 27, 3-(benzyloxy)-9,9-dimethyl-4-oxo-4,6,7,9-tetrahydropyrimido-[2,1-c][1,4]oxazine-2-carboxylic acid and 3-(2-(aminomethyl)-5-fluorophenyl)oxazolidin-2-one, derived from reduction of intermediate 117, 4-fluoro-2-(2-oxooxazolidin-3-yl)benzonitrile. ^{1}H NMR (400 MHz, MeOD) δ ppm: 9.48 (1H, dd, J = 8.6, 6.5 Hz), 7.41 (2H, m), 7.32 (3H, m), 7.22 (1H, dd, J = 9.6, 2.5 Hz), 7.08 (1H, td, J =8.6, 2.7 Hz), 5.21 (2H, s), 4.57 (2H, t, J = 7.7 Hz), 4.50 (2H, s), 4.07 (4H, m), 3.99 (2H, m), 1.61 (6H, s). LCMS $(M+H)^+$ m/z 523.

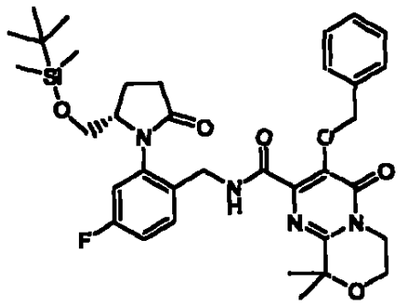
Intermediate 166



(R)-N-(2-(2-((tert-Butyldimethylsilyloxy)methyl)-5-oxopyrrolidin-1-yl)-4-fluorobenzyl)-3-(benzyloxy)-9,9-dimethyl-4-oxo-4,6,7,9-tetrahydropyrimido[2,1-c][1,4]oxazine-2-carboxamide. The title compound can be prepared from

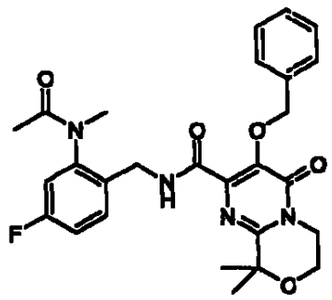
intermediate 27, 3-(benzyloxy)-9,9-dimethyl-4-oxo-4,6,7,9-tetrahydropyrimido-[2,1-c][1,4]oxazine-2-carboxylic acid and (S)-1-(2-(aminomethyl)-5-fluorophenyl)-5-((tert-butyldimethylsilyloxy)methyl)pyrrolidin-2-one, derived from reduction of intermediate 122, (R)-2-(2-((tert-butyldimethylsilyloxy)methyl)-5-oxopyrrolidin-1-yl)-4-fluorobenzonitrile ^{1}HNMR 400 MHz (DMSO) δ ppm: 8.82 (1H, broad s), 7.47 (2H, m), 7.35 (4H, m), 7.00 (1H, broad s), 5.09 (2H, s), 4.60-4.10 (3H, m), 4.02 (3H, m), 3.88 (2H, m), 3.53 (2H, broad s), 2.42-2.35 (2H, m), 1.94 (1H, m), 1.56 (3H, s), 1.55 (3H, s), 0.82 (9H, broad s), -0.01 (6H, s). LCMS $(M+H)^+$ m/z 665.

Intermediate 167



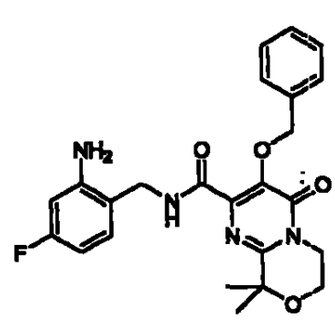
(S)-N-(2-(2-((tert-Butyldimethylsilyloxy)methyl)-5-oxopyrrolidin-1-yl)-4-fluorobenzyl)-3-(benzyloxy)-9,9-dimethyl-4-oxo-4,6,7,9-tetrahydropyrimido[2,1-c][1,4]oxazine-2-carboxamide. The title compound can be prepared from intermediate 27, 3-(benzyloxy)-9,9-dimethyl-4-oxo-4,6,7,9-tetrahydropyrimido-[2,1-c][1,4]oxazine-2-carboxylic acid and (S)-1-(2-(aminomethyl)-5-fluorophenyl)-5-((tert-butyldimethylsilyloxy)methyl)pyrrolidin-2-one, derived from reduction of intermediate 121, (R)-2-(2-((tert-butyldimethylsilyloxy)methyl)-5-oxopyrrolidin-1-yl)-4-fluorobenzonitrile. ^{1}HNMR 400 MHz (DMSO) δ ppm: 8.82 (1H, broad s), 7.52-7.33 (7H, m), 7.02 (1H, broad s), 5.60 (2H, s), 4.60-4.20 (2H, m), 4.02 (3H, t, J = 5.0 Hz), 3.89 (3H, t, 5.0 Hz), 3.53 (2H, broad s), 2.51 (2H, s), 2.44-2.26 (2H, m), 1.94 (1H, broad s), 1.57 (3H, s), 1.55 (3H, s), 0.82 (9H, broad s), -0.02 (6H, s). LCMS $(M+H)^+$ m/z 665.

Intermediate 168



N-(4-Fluoro-2-(N-methylacetamido)benzyl)-3-(benzyloxy)-9,9-dimethyl-4-oxo-4,6,7,9-tetrahydropyrimido[2,1-c][1,4]oxazine-2-carboxamide. The title compound can be prepared from intermediate 27, 3-(benzyloxy)-9,9-dimethyl-4-oxo-4,6,7,9-tetrahydropyrimido-[2,1-c][1,4]oxazine-2-carboxylic acid N-(2-(aminomethyl)-5-fluorophenyl)-N-methylacetamide, derived from reduction of intermediate 114, N-(2-cyano-5-fluorophenyl)-N-methylacetamide. ^{1}HNMR 400 MHz (MeOD) δ ppm: 7.49-7.33 (6H, m), 7.15 -7.06 (2H, m), 5.22 (2H, s), 4.41 (2H, d, J = 2.4 Hz), 4.09 (2H, t, J = 5.1 Hz), 4.01 (2H, t, J = 5.1 Hz), 3.25 (0.4H, s), 3.22 (2.6H, s), 1.85 (3H, s), 1.63 (6H, s). LCMS $(M+H)^+$ m/z 509.

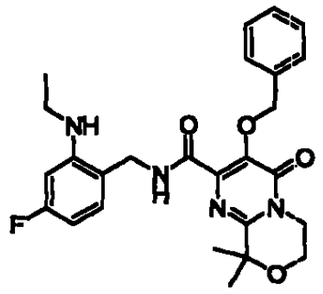
Intermediate 169



N-(2-Amino-4-fluorobenzyl)-3-(benzyloxy)-9,9-dimethyl-4-oxo-4,6,7,9-tetrahydropyrimido[2,1-c][1,4]oxazine-2-carboxamide. The title compound can be prepared from intermediate 27, 3-(benzyloxy)-9,9-dimethyl-4-oxo-4,6,7,9-

tetrahydropyrimido-[2,1-c][1,4]oxazine-2-carboxylic acid 2-(aminomethyl)-5-fluorobenzenamine. ^{1}HNMR 400 MHz (MeOD) δ ppm: ^{1}HNMR 400 MHz (MeOD) δ ppm: 7.36 (2H, m), 7.30 (3H, m), 7.10 (1H, dd, J = 8.3, 6.5 Hz), 6.47 (1H, dd, J = 11.1, 2.5 Hz), 6.32 (1H, ddd, (dt), J = 8.6, 2.5 Hz), 5.19 (2H, s), 4.40 (2H, s), 4.07 (2H, t, J = 5.0 Hz), 3.99 (2H, t, J= 5.0 Hz), 1.61 (6H, s). LCMS $(M+H)^+$ m/z 453.

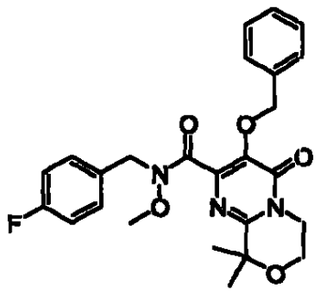
Intermediate 170



N-(2-(Ethylamino)-4-fluorobenzyl)-3-(benzyloxy)-9,9-dimethyl-4-oxo-4,6,7,9-tetrahydropyrimido[2,1-c][1,4]oxazine-2-carboxamide. The title compound can be prepared from intermediate 27, 3-(benzyloxy)-9,9-dimethyl-4-oxo-4,6,7,9-tetrahydropyrimido-[2,1-c][1,4]oxazine-2-carboxylic acid and 2-(aminomethyl)-N-ethyl-5-fluorobenzenamine. ^{1}HNMR 400 MHz ($CDCl_3$) δ (ppm): 1.27 (3H, t, J = 7.1 Hz, CH_3), 1.63 (6H, s, 2 x CH_3), 3.10 (2H, q, J = 7.1 Hz, CH_2), 4.04 (4H, m, 2 x CH_2), 4.45 (2H, d, J = 6.6 Hz, NCH_2), 5.27 (2H, s, OCH_2), 6.28 (1H, broad s, aromatic), 6.31 (1H, m, aromatic), 6.98 (1H, m, aromatic), 7.3- 7.38 (3H, m, aromatics), 7.49 (2H, m, aromatics), 7.54 (1H, broad t, NH). HRMS (ESI^+) calculated for $C_{26}H_{30}FN_4O_4$ $[M+H^+]$: 481.2251: found: 481.2254.

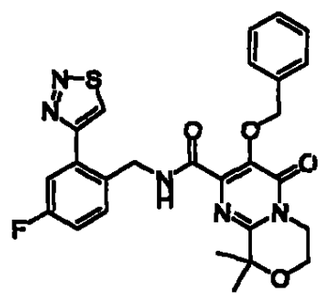
171

Intermediate 171



N-(4-Fluorobenzyl)-3-(benzyloxy)-N-methoxy-9,9-dimethyl-4-oxo-4,6,7,9-tetrahydropyrimido[2,1-c][1,4]oxazine-2-carboxamide. The title compound can be prepared from intermediate 27, 3-(benzyloxy)-9,9-dimethyl-4-oxo-4,6,7,9-tetrahydropyrimido-[2,1-c][1,4]oxazine-2-carboxylic acid and (4-fluorophenyl)-N-methoxymethanamine. White crystals; mp 141 °C (ethyl acetate-hexane). ^{1}HNMR 400 MHz ($CDCl_3$) δ (ppm): 1.66 (6H, s, 2 x CH_3), 3.59 (3H, s, OCH_3), 4.07 (4H, m, 2 x CH_2), 4.90 (2H, s, NCH_2), 5.20 (2H, s, OCH_2), 6.81 (2H, m, aromatics), 7.26-7.30 (3H, m, aromatics), 7.36 (2H, m, aromatics), 7.44 (2H, m, aromatics). HRMS (ESI^+) calculated for $C_{25}H_{27}FN_3O_5$ [$M+H^+$]: 468.1935: found: 468.1916.

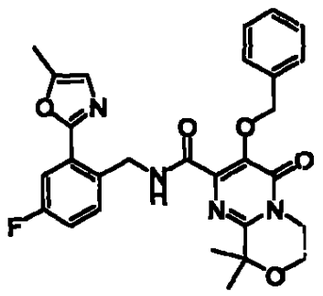
Intermediate 172



N-(4-Fluoro-2-(1,2,3-thiadiazol-4-yl)benzyl)-3-(benzyloxy)-9,9-dimethyl-4-oxo-4,6,7,9-tetrahydropyrimido[2,1-c][1,4]oxazine-2-carboxamide. The title compound can be prepared from intermediate 27, 3-(benzyloxy)-9,9-dimethyl-4-oxo-4,6,7,9-tetrahydropyrimido-[2,1-c][1,4]oxazine-2-carboxylic acid and (4-fluoro-2-

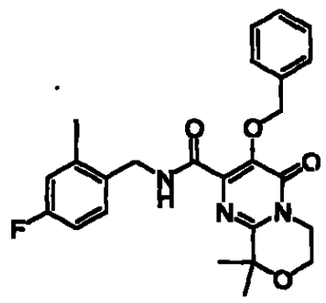
(1,2,3-thiadiazol-4-yl)phenyl)methanamine. ^{1}HNMR 400 MHz ($CDCl_3$) δ (ppm): 1.66 (6H, s, 2 x CH_3), 4.02 (4H, m, 2 x CH_2), 4.57 (2H, d, J = 6.6 Hz, NCH_2), 5.32 (2H, s, OCH_2), 7.18 (1H, m, aromatic), 7.27-7.34 (4H, m, aromatics), 7.54 (2H, m, aromatics), 7.74 (1H, dd, J = 6.2 Hz and J = 8.6 Hz, aromatic), 8.71 (1H, s, CH), 8.80 (1H, broad t, NH). HRMS (ESI^+) calculated for $C_{26}H_{25}FN_5O_4S$ [$M+H^+$]: 522.1611: found: 522.1601.

Intermediate 173



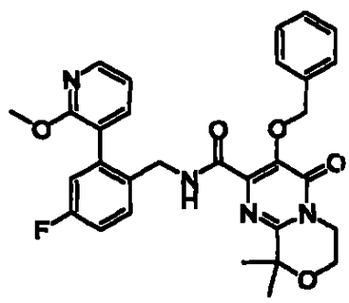
N-(4-Fluoro-2-(5-methyloxazol-2-yl)benzyl)-3-(benzyloxy)-9,9-dimethyl-4-oxo-4,6,7,9-tetrahydropyrimido[2,1-c][1,4]oxazine-2-carboxamide. The title compound can be prepared from intermediate 27, 3-(benzyloxy)-9,9-dimethyl-4-oxo-4,6,7,9-tetrahydropyrimido-[2,1-c][1,4]oxazine-2-carboxylic acid and (4-fluoro-2-(5-methyloxazol-2-yl)phenyl)methanamine. White crystals; mp 186 °C (ethyl acetate-hexane). ^{1}HNMR 400 MHz ($CDCl_3$) δ (ppm): 1.61 (6H, s, 2 x CH_3), 2.43 (3H, s, CH_3), 4.02 (4H, m, 2 x CH_2), 4.80 (2H, d, J = 6.3 Hz, NCH_2), 5.25 (2H, s, OCH_2), 6.82 (1H, s, CH), 7.11 (1H, m, aromatic), 7.29- 7.34 (3H, m, aromatics), 7.52 (2H, m, aromatics), 7.65 (1H, dd, J = 2.5 Hz and J = 9.6 Hz, aromatic), 7.69 (1H, dd, J = 6.1 Hz and J = 8.6 Hz, aromatic), 9.32 (1H, broad t, NH). HRMS (ESI^+) calculated for $C_{28}H_{28}FN_4O_5$ [$M+H^+$]: 519.2044: found: 519.2024.

Intermediate 174



N-(4-Fluoro-2-iodobenzyl)-3-(benzyloxy)-9,9-dimethyl-4-oxo-4,6,7,9-tetrahydropyrimido[2,1-c][1,4]oxazine-2-carboxamide. The title compound can be prepared from intermediate 27, 3-(benzyloxy)-9,9-dimethyl-4-oxo-4,6,7,9-tetrahydropyrimido-[2,1-c][1,4]oxazine-2-carboxylic acid and (4-fluoro-2-iodophenyl)methanamine. White solid. ^{1}HNMR 400 MHz ($CDCl_3$) δ ppm: 1.66 (6H, s, 2 x CH_3), 4.04 (4H, m, 2 x CH_2), 4.57 (2H, d, J = 6.6 Hz, NCH_2), 7.05 (1H, m, aromatic), 7.3–7.38 (3H, m, aromatics), 7.42 (1H, dd, J = 6.1 Hz and J = 8.6 Hz, aromatic), 7.53 (2H, m, aromatics), 7.56 (1H, dd, J = 2.6 Hz and J = 8.0 Hz, aromatic), 8.05 (1H, broad t, NH). HRMS (ESI^+) calculated for $C_{24}H_{24}FIN_3O_4$ [$M+H^+$]: 564.0796; found: 564.0809.

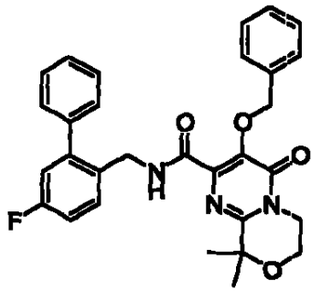
Intermediate 175



N-(4-Fluoro-2-(2-methoxypyridin-3-yl)benzyl)-3-(benzyloxy)-9,9-dimethyl-4-oxo-4,6,7,9-tetrahydropyrimido[2,1-c][1,4]oxazine-2-carboxamide. Intermediate 174, N-(4-fluoro-2-iodobenzyl)-3-(benzyloxy)-9,9-dimethyl-4-oxo-4,6,7,9-

tetrahydropyrimido[2,1-c][1,4]oxazine-2-carboxamide (0.350 g, 0.62 mmol) in a mixture of acetonitrile (12 ml) and water (12 ml) was treated with 2-methoxypyridin-3-ylboronic acid (0.190 g, 1.24 mmol), sodium carbonate (0.20 g, 1.88 mmol) and tetrakis(triphenylphosphine)palladium(0) (0.15 g). The reaction mixture was degassed, flushed with argon and heated at 90 °C for 30 min. The reaction mixture was then diluted with ethyl acetate, washed with water and brine, dried over anhydrous magnesium sulfate and concentrated. Chromatography of the residue on silica gel (elution gradient of ethyl acetate in hexane) gave 0.245 g (72% yield) of the title material as a white solid. ^{1}HNMR 400 MHz ($CDCl_3$) δ ppm: 1.63 (6H, s, 2 x CH_3), 3.89 (3H, s, OCH_3), 4.04 (4H, m, 2 x CH_2), 4.37 (2H, broad, NCH_2), 5.26 (2H, s, OCH_2), 6.93 (1H,dd, J = 2.5 Hz and J = 9 Hz, aromatic), 7.0 (1H,dd, J = 5 Hz and J = 7 Hz, aromatic), 7.06 (1H, m, aromatic), 7.3-7.5 (8H, m, aromatics and NH), 8.24 (1H, m, aromatic). HRMS (ESI^+) calculated for $C_{30}H_{30}FN_4O_5$ [$M+H^+$]: 545.2200; found: 545.2184.

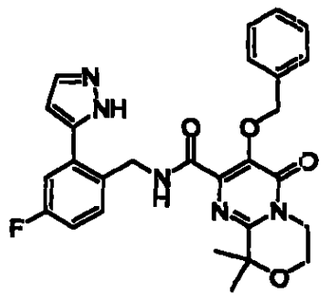
Intermediate 176



N-(4-Fluoro-2-phenyl-benzyl)-3-(benzyloxy)-9,9-dimethyl-4-oxo-4,6,7,9-tetrahydropyrimido[2,1-c][1,4]oxazine-2-carboxamide. Intermediate 174, N-(4-Fluoro-2-iodobenzyl)-3-(benzyloxy)-9,9-dimethyl-4-oxo-4,6,7,9-tetrahydropyrimido[2,1-c][1,4]oxazine-2-carboxamide (0.150 g, 0.266 mmol) in a mixture of acetonitrile (10 ml) and water (10 ml) was treated with phenylboronic acid (0.042 g, 0.35 mmol), sodium carbonate (0.062 g, 0.58 mmol) and tetrakis(triphenylphosphine)palladium(0) (0.070 g). The reaction mixture was degassed, flushed with argon and heated at 90 °C for 30 min. The reaction mixture

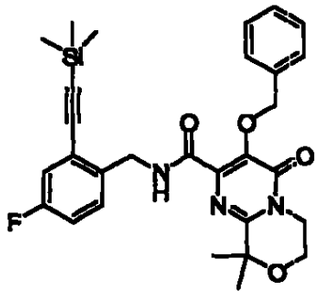
was then diluted with ethyl acetate, washed with water and brine, dried over anhydrous magnesium sulfate and concentrated. Chromatography of the residue on silica gel (elution gradient of ethyl acetate in hexane) gave 0.124 g (91% yield) of the title material as a light yellow solid. ^{1}HNMR 400 MHz ($CDCl_3$) δ ppm: 1.61 (6H, s, 2 x CH_3), 4.03 (4H, m, 2 x CH_2), 4.49 (2H, d, J = 6.1 Hz, NCH_2), 7.02 (2H, m, aromatics), 7.29-7.51 (12H, m, aromatics and NH). HRMS (ESI^+) calculated for $C_{30}H_{29}FN_3O_4$ [M+H^+]: 514.2142; found: 514.2137.

Intermediate 177



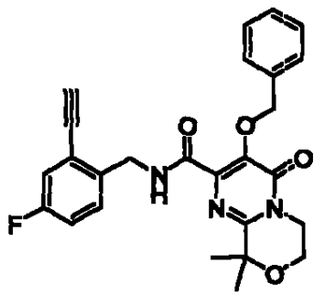
N-(4-Fluoro-2-(1H-pyrazol-5-yl)benzyl)-3-(benzyloxy)-9,9-dimethyl-4-oxo-4,6,7,9-tetrahydropyrimido[2,1-c][1,4]oxazine-2-carboxamide. Intermediate 174, N-(4-fluoro-2-iodobenzyl)-3-(benzyloxy)-9,9-dimethyl-4-oxo-4,6,7,9-tetrahydropyrimido[2,1-c][1,4]oxazine-2-carboxamide (0.150 g, 0.27 mmol) was reacted with 1H-pyrazol-5-ylboronic acid (0.060 g, 0.54 mmol), sodium carbonate (0.085 g, 0.81 mmol) and tetrakis(triphenylphosphine)palladium(0) (0.070 g) to give 0.085 g (62% yield) of the title material as a white solid after chromatography on silica gel. ^{1}HNMR 400 MHz ($CDCl_3$) δ (ppm): 1.63 (6H, s, 2 x CH_3), 4.03 (4H, m, 2 x CH_2), 4.65 (2H, d, J = 6.5 Hz, NCH_2), 5.25 (2H, s, OCH_2), 6.54 (1H, d, J = 2.5 Hz, CH), 7.03 (1H, m, aromatic), 7.25 (1H, dd, J = 2.5 Hz and J = 9.8 Hz, aromatic), 7.35 (3H, m, aromatics), 7.53 (2H, m, aromatics), 7.56 (1H, d, J = 2.5 Hz, CH), 7.60 (1H, dd, J = 6.1 Hz and J = 8.6 Hz, aromatic), 8.96 (1H, broad t, NH). HRMS (ESI^+) calculated for $C_{27}H_{27}FN_5O_4$ [M+H^+]: 504.2047: found: 504.2068.

Intermediate 178



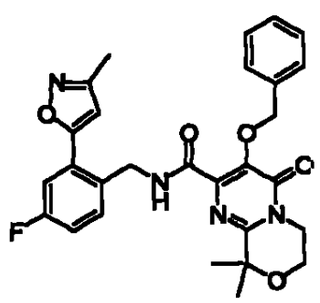
N-(4-Fluoro-2-(2-(trimethylsilyl)ethynyl)benzyl)-3-(benzyloxy)-9,9-dimethyl-4-oxo-4,6,7,9-tetrahydropyrimido[2,1-c][1,4]oxazine-2-carboxamide. A solution of intermediate 174, N-(4-fluoro-2-iodobenzyl)-3-(benzyloxy)-9,9-dimethyl-4-oxo-4,6,7,9-tetrahydropyrimido[2,1-c][1,4]oxazine-2-carboxamide (0.277 g, 0.49 mmol) in a mixture of N,N-dimethylformamide (3 ml) and piperidine (1.2 ml) was treated under argon with dichlorobis(triphenylphosphine)palladium(II) (0.020 g), triphenylphosphine (0.010 g), copper(I) iodide (0.010 g) followed by (trimethylsilyl)acetylene (0.21 ml, 1.47 mmol). The resulting mixture was sealed and heated at 50 °C for one hour. The reaction mixture was then diluted with ethyl acetate, washed with water and brine, dried over anhydrous magnesium sulfate and concentrated under reduced pressure. Chromatography of the residue on silica gel (elution gradient of ethyl acetate in hexane) gave 0.164 g (63% yield) of the title material as a light yellow solid. ^{1}HNMR 400 MHz ($CDCl_3$) δ ppm: 0.27 (9H, s, $SiCH_3$), 1.64 (6H, s, 2 x CH_3), 4.04 (4H, m, 2 x CH_2), 4.71 (2H, d, J = 6.1 Hz, NCH_2), 5.32 (2H, s, OCH_2), 6.99 (1H, m, aromatic), 7.19 (1H,dd, J = 2.6 Hz and J = 9.1 Hz, aromatic), 7.3-7.37 (4H, m, aromatics), 7.48-7.51 (2H, m, aromatics), 7.75 (1H, broad t, NH). HRMS (ESI^+) calculated for $C_{29}H_{33}FN_3O_4Si$ [$M+H^+$]: 534.2224; found: 534.2229.

Intermediate 179



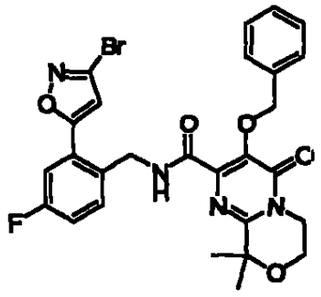
N-(2-Ethynyl-4-fluorobenzyl)-3-(benzyloxy)-9,9-dimethyl-4-oxo-4,6,7,9-tetrahydropyrimido[2,1-c][1,4]oxazine-2-carboxamide. A solution of intermediate 178, N-(4-fluoro-2-(2-(trimethylsilyl)ethynyl)benzyl)-3-(benzyloxy)-9,9-dimethyl-4-oxo-4,6,7,9-tetrahydropyrimido[2,1-c][1,4]oxazine-2-carboxamide (0.150 g, 0.28 mmol) in methanol (5 ml) was treated with potassium carbonate (0.120 g, 0.84 mmol) and the resulting mixture stirred at 22 °C for one hour. The reaction mixture was then diluted with ethyl acetate, washed with water and brine, dried over anhydrous magnesium sulfate and concentrated under reduced pressure to give 0.129 g (100% yield) of the title material as a light yellow solid. ^{1}HNMR 400 MHz ($CDCl_3$) δ ppm: 1.64 (6H, s, 2 x CH_3), 3.31 (1H, s, CH), 4.04 (4H, m, 2 x CH_2), 4.69 (2H, d, J = 6.6 Hz, NCH_2), 5.31 (2H, s, OCH_2), 7.04 (1H, m, aromatic), 7.21 (1H,dd, J = 2.6 Hz and J = 9.1 Hz, aromatic), 7.32-7.42 (3H, m, aromatics), 7.40 (1H,dd, J = 6.1 Hz and J = 8.6 Hz, aromatic), 7.52-7.54 (2H, m, aromatics), 8.00 (1H, broad t, NH). HRMS (ESI^+) calculated for $C_{26}H_{25}FN_3O_4$ [M+H]: 462.1829; found: 462.1822.

Intermediate 180



N-(4-Fluoro-2-(3-methylisoxazol-5-yl)benzyl)-3-(benzyloxy)-9,9-dimethyl-4-oxo-4,6,7,9-tetrahydropyrimido[2,1-c][1,4]oxazine-2-carboxamide. A solution of intermediate 179, N-(2-ethynyl-4-fluorobenzyl)-3-(benzyloxy)-9,9-dimethyl-4-oxo-4,6,7,9-tetrahydropyrimido[2,1-c][1,4]oxazine-2-carboxamide (0.150 g, 0.32 mmol) in dimethyl sulfoxide (5 ml) was treated with nitromethane (0.14 ml, 1.92 mmol), 4-(4,6-dimethoxy-1,3,5-triazin-2-yl)-4-methylmorpholinium chloride (DMTMM) (0.241 g, 1.0 mmol) (M. Kunishima et al., Tetrahedron, 55, 1999, 13159 -13170) and 4-(dimethylamino)pyridine (DMAP) (0.010 g) and the resulting mixture stirred at 22 °C for 16 h. Identical quantities of nitromethane, DMTMM and DMAP were then added and the mixture was stirred for another 24 h. The reaction mixture was diluted with ethyl acetate, washed with saturated sodium bicarbonate and brine, then dried over anhydrous magnesium sulfate and concentrated under reduced pressure. Chromatography of the residue on silica gel (elution gradient of ethyl acetate in dichloromethane) gave 0.122 g (73% yield) of the title material as a white solid. ^{1}HNMR 400 MHz ($CDCl_3$) δ ppm: 1.62 (6H, s, 2 x CH_3), 2.39 (3H, s, CH_3), 4.04 (4H, m, 2 x CH_2), 4.69 (2H, d, J = 6.1 Hz, NCH_2), 5.31 (2H, s, OCH_2), 6.36 (1H, m, CH), 7.13 (1H, m, aromatic), 7.30-7.35 (4H, m, aromatics), 7.50-7.53 (2H, m, aromatics), 7.58 (1H,dd, J = 5.5 Hz and J = 8.6 Hz, aromatic), 8.06 (1H, broad t, NH). HRMS (ESI^+) calculated for $C_{28}H_{28}FN_4O_5$ [$M+H^+$]: 519.2044; found: 519.2059.

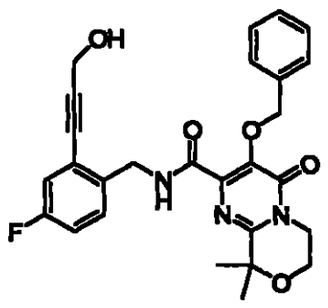
Intermediate 181



N-(2-(3-Bromoisoxazol-5-yl)-4-fluorobenzyl)-3-(benzyloxy)-9,9-dimethyl-4-oxo-4,6,7,9-tetrahydropyrimido[2,1-c][1,4]oxazine-2-carboxamide. A solution of

intermediate 179, N-(2-ethynyl-4-fluorobenzyl)-3-(benzyloxy)-9,9-dimethyl-4-oxo-4,6,7,9-tetrahydropyrimido[2,1-c][1,4]oxazine-2-carboxamide (0.350 g, 0.76 mmol) in a mixture of ethyl acetate (10 ml) and water (2 ml) was treated with potassium bicarbonate (0.230 g, 2.3 mmol) followed by dibromoformaldoxime (0.354 g, 1.75 mmol) (D.M. Vyas, Y. Chiang and T.W. Doyle, Tetrahedron Letters, 1984, 25, 487-490) and the resulting mixture stirred at 22 °C. After 1 h, identical quantities of potassium bicarbonate and dibromoformaldoxime were added and the mixture stirred for another 1.5 h. The reaction mixture was then diluted with ethyl acetate, washed with brine, dried over anhydrous magnesium sulfate and concentrated under reduced pressure. Crystallization of the residue from ether gave 0.300 g (68% yield) of the title material as a white solid. ^{1}HNMR 400 MHz ($CDCl_3$) δ ppm: 1.63 (6H, s, 2 x CH_3), 4.04 (4H, m, 2 x CH_2), 4.67 (2H, d, J = 6.6 Hz, NCH_2), 5.32 (2H, s, OCH_2), 6.60 (1H, s, CH), 7.17 (1H, m, aromatic), 7.30-7.36 (4H, m, aromatics), 7.51-7.53 (2H, m, aromatics), 7.60 (1H,dd, J = 5.5 Hz and J = 8.6 Hz, aromatic), 8.01 (1H, broad t, NH). HRMS (ESI^+) calculated for $C_{27}H_{25}BrFN_2O_5$ [$M+H^+$]: 583.0992; found: 583.0986.

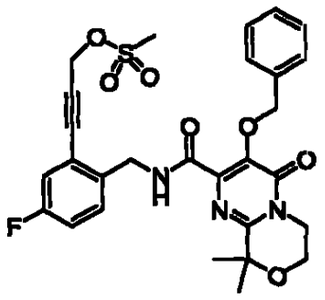
Intermediate 182



N-(4-Fluoro-2-(3-hydroxyprop-1-ynyl)benzyl)-3-(benzyloxy)-9,9-dimethyl-4-oxo-4,6,7,9-tetrahydropyrimido[2,1-c][1,4]oxazine-2-carboxamide. Reaction of intermediate 174, N-(4-fluoro-2-iodobenzyl)-3-(benzyloxy)-9,9-dimethyl-4-oxo-4,6,7,9-tetrahydropyrimido[2,1-c][1,4]oxazine-2-carboxamide (0.563 g, 1.00 mmol) with propargyl alcohol (0.18 ml, 3.2 mmol) using the conditions described for intermediate 178 gave 0.415 g (85% yield) of the title material as a white solid.

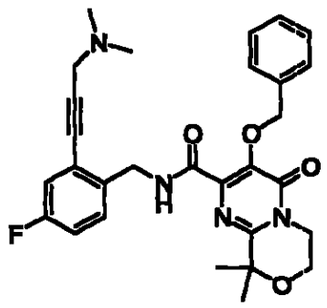
^{1}HNMR 400 MHz ($CDCl_3$) δ ppm: 1.64 (6H, s, 2 x CH_3), 4.04 (4H, m, 2 x CH_2), 4.39 (2H, d, J = 6.6 Hz, CH_2), 4.68 (2H, d, J = 6.0 Hz, CH_2), 5.29 (2H, s, OCH_2), 6.99 (1H, m, aromatic), 7.13 (1H,dd, J = 2.5 Hz and J = 9.1 Hz, aromatic), 7.22 (1H,dd, J = 5.6 Hz and J = 8.6 Hz, aromatic), 7.33-7.37 (3H, m, aromatics), 7.44-7.47 (2H, m, aromatics), 7.68 (1H, broad t, NH). HRMS (ESI^+) calculated for $C_{27}H_{27}FN_3O_5$ [$M+H^+$]: 492.1935; found: 492.1939.

Intermediate 183



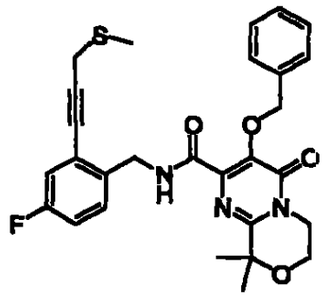
3-[2-((3-(Benzyloxy)-9,9-dimethyl-4-oxo-4,6,7,9-tetrahydropyrimido[2,1-c][1,4]oxazine-2-carboxamido)methyl)-5-fluorophenyl]prop-2-ynyl methanesulfonate. A solution of intermediate 182, N-(4-fluoro-2-(3-hydroxyprop-1-ynyl)benzyl)-3-(benzyloxy)-9,9-dimethyl-4-oxo-4,6,7,9-tetrahydropyrimido[2,1-c][1,4]oxazine-2-carboxamide (0.280 g, 0.57 mmol) and triethylamine (0.12 ml, 0.86 mmol) in dichloromethane (5 ml) was cooled to 0 °C, treated drop wise with methanesulfonyl chloride (0.050 ml, 0.64 mmol) and then stirred for 30 min. The reaction mixture was then diluted with ethyl acetate, washed with saturated sodium bicarbonate, brine, dried over anhydrous magnesium sulfate and concentrated under reduced pressure. Chromatography of the residue on silica gel (elution gradient of ethyl acetate in hexane) gave 0.245 g (75% yield) of the title material as a white solid. ^{1}HNMR 400 MHz ($CDCl_3$) δ ppm: 1.65 (6H, s, 2 x CH_3), 3.10 (3H, s, SCH_3), 4.05 (4H, m, 2 x CH_2), 4.67 (2H, d, J = 6.1 Hz, NCH_2), 5.03 (2H, s, CH_2), 5.29 (2H, s, OCH_2), 7.07 (1H, m, aromatic), 7.18 (1H,dd, J = 2.5 Hz and J = 9.1 Hz, aromatic), 7.32-7.36 (3H, m, aromatics), 7.38 (1H,dd, J = 5.5 Hz and J = 8.6 Hz, aromatic), 7.49-7.51 (2H, m, aromatics), 7.77 (1H, broad t, NH). MS (ESI^+) m/e 570 [$M+H^+$].

Intermediate 184



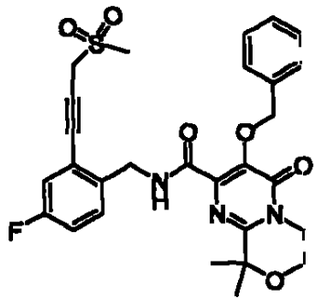
N-(2-(3-(Dimethylamino)prop-1-ynyl)-4-fluorobenzyl)-3-(benzyloxy)-9,9-dimethyl-4-oxo-4,6,7,9-tetrahydropyrimido[2,1-c][1,4]oxazine-2-carboxamide. A solution of intermediate 183, 3-[2-((3-(benzyloxy)-9,9-dimethyl-4-oxo-4,6,7,9-tetrahydropyrimido[2,1-c][1,4]oxazine-2-carboxamido)methyl)-5-fluorophenyl]prop-2-ynyl methanesulfonate (0.100 g, 0.18 mmol) in acetonitrile (5 ml) was treated at 22 °C with 0.3 ml (0.6 mmol) of a 2 M solution of dimethylamine in tetrahydrofuran and the resulting mixture was stirred for 30 min. The reaction mixture was then diluted with ethyl acetate, washed with saturated sodium bicarbonate, brine, then dried over anhydrous magnesium sulfate and concentrated under reduced pressure to give 0.080 g (88% yield) of the title material as a white solid. ^{1}HNMR 400 MHz ($CDCl_3$) δ ppm: 1.64 (6H, s, 2 x CH_3), 2.43 (6H, s, 2 x NCH_3), 3.58 (2H, broad s, CH_2), 4.05 (4H, m, 2 x CH_2), 4.70 (2H, d, J = 6.0 Hz, NCH_2), 5.30 (2H, s, OCH_2), 7.01 (1H, m, aromatic), 7.18 (1H,dd, J = 3 Hz and J = 9.1 Hz, aromatic), 7.32-7.38 (4H, m, aromatics), 7.50-7.53 (2H, m, aromatics), 7.79 (1H, broad t, NH). HRMS (ESI^+) calculated for $C_{29}H_{32}FN_4O_4$ [$M+H^+$]: 519.2408; found: 519.2407.

Intermediate 185



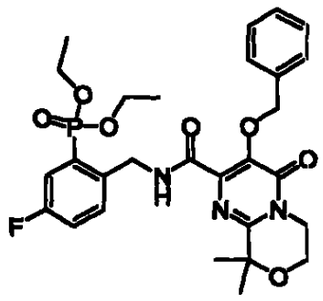
N-(4-Fluoro-2-(3-(methylthio)prop-1-ynyl)benzyl)-3-(benzyloxy)-9,9-dimethyl-4-oxo-4,6,7,9-tetrahydropyrimido[2,1-c][1,4]oxazine-2-carboxamide. A solution of intermediate 183, 3-[2-((3-(benzyloxy)-9,9-dimethyl-4-oxo-4,6,7,9-tetrahydropyrimido[2,1-c][1,4]oxazine-2-carboxamido)methyl)-5-fluorophenyl]prop-2-ynyl methanesulfonate (0.160 g, 0.28 mmol) in N,N-dimethylformamide (3 ml) was treated at 0 °C with sodium thiomethoxide (0.026 g, 0.37 mmol) and the resulting mixture stirred for 2 h. The reaction mixture was then diluted with ethyl acetate, washed with saturated sodium bicarbonate and brine, then dried over anhydrous magnesium sulfate and concentrated under reduced pressure. Chromatography of the residue on silica gel (elution gradient of ethyl acetate in hexane) gave 0.114 g (78% yield) of the title material as a white solid. ^{1}HNMR 400 MHz ($CDCl_3$) δ ppm: 1.64 (6H, s, 2 x CH_3), 2.28 (3H, s, SCH_3), 3.45 (2H, s, SCH_2), 4.05 (4H, m, 2 x CH_2), 4.69 (2H, d, J = 6.1 Hz, NCH_2), 5.31 (2H, s, OCH_2), 6.98 (1H, m, aromatic), 7.15 (1H,dd, J = 3 Hz and J = 9.1 Hz, aromatic), 7.32-7.38 (4H, m, aromatics), 7.50-7.53 (2H, m, aromatics), 7.80 (1H, broad t, NH). HRMS (ESI^+) calculated for $C_{28}H_{29}FN_3O_4S$ [$M+H^+$]: 522.1863; found: 522.1844.

Intermediate 186



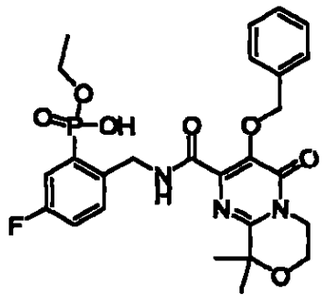
N-(4-Fluoro-2-(3-(methylsulfonyl)prop-1-ynyl)benzyl)-3-(benzyloxy)-9,9-dimethyl-4-oxo-4,6,7,9-tetrahydropyrimido[2,1-c][1,4]oxazine-2-carboxamide. A solution of intermediate 185, N-(4-fluoro-2-(3-(methylthio)prop-1-ynyl)benzyl)-3-(benzyloxy)-9,9-dimethyl-4-oxo-4,6,7,9-tetrahydropyrimido[2,1-c][1,4]oxazine-2-carboxamide (0.110 g, 0.21 mmol) in dichloromethane (3 ml) was treated at 0 °C with 3-chloroperoxybenzoic acid (0.120 g of 85%, 0.59 mmol) and the resulting mixture was stirred at 22 °C for 30 min. The reaction mixture was then diluted with ethyl acetate, washed with saturated sodium bicarbonate, brine, then dried over anhydrous magnesium sulfate and concentrated under reduced pressure. Chromatography of the residue on silica gel (elution gradient of ethyl acetate in dichloromethane) gave 0.074 g (64% yield) of the title material as a white solid. ^{1}HNMR 400 MHz ($CDCl_3$) δ ppm: 1.64 (6H, s, 2 x CH_3), 3.03 (3H, s, SCH_3), 4.03 (2H, s, SCH_2), 4.05 (4H, m, 2 x CH_2), 4.65 (2H, d, J = 6.0 Hz, NCH_2), 5.27 (2H, s, OCH_2), 7.06 (1H, m, aromatic), 7.17 (1H,dd, J = 3 Hz and J = 8.6 Hz, aromatic), 7.31-7.38 (6H, m, aromatics), 8.12 (1H, broad t, NH). HRMS (ESI^+) calculated for $C_{28}H_{29}FN_3O_6S$ [$M+H^+$]: 554.1761; found: 554.1784.

Intermediate 187



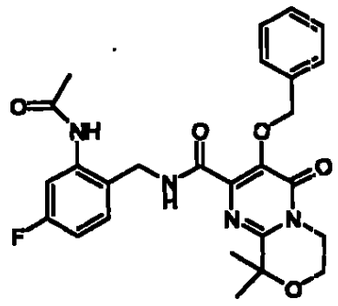
Diethyl 2-((3-(benzyloxy)-9,9-dimethyl-4-oxo-4,6,7,9-tetrahydropyrimido[2,1-c][1,4]oxazine-2-carboxamido)methyl)-5-fluorophenylphosphonate. A solution of intermediate 174, N-(4-fluoro-2-iodobenzyl)-3-(benzyloxy)-9,9-dimethyl-4-oxo-4,6,7,9-tetrahydropyrimido[2,1-c][1,4]oxazine-2-carboxamide (0.200 g, 0.35 mmol) and triphenylphosphine (0.020 mg) in ethanol (5 ml) was flushed with argon and then treated with N,N-diisopropylethylamine (0.25 ml, 1.4 mmol), palladium(II) acetate (0.020 g) and diethyl phosphite (0.15 ml, 1.16 mmol). The reaction mixture was then sealed and heated at 80 °C for 18 h. The reaction mixture was then diluted with ethyl acetate, washed with 0.1 N hydrochloric acid, saturated sodium bicarbonate, brine, then dried over anhydrous magnesium sulfate and concentrated. Chromatography of the residue on silica gel (elution gradient of acetonitrile in dichloromethane) gave 0.103 g (51% yield) of the title compound as a white solid. ^{1}HNMR 400 MHz ($CDCl_3$) δ ppm: 1.36 (6H, t, J = 6.6 Hz, 2 x CH_3), 1.64 (6H, s, 2 x CH_3), 4.04 (4H, m, 2 x CH_2), 4.08-4.22 (4H, m, 2 x OCH_2), 4.78 (2H, d, J = 6.6 Hz, NCH_2), 5.29 (2H, s, OCH_2), 7.21 (1H, m, aromatic), 7.29-7.34 (3H, m, aromatics), 7.45-7.52 (3H, m, aromatics), 7.65-7.72 (1H, m, aromatic), 8.67 (1H, broad t, NH). HRMS (ESI^+) calculated for $C_{28}H_{34}FN_3O_7P$ [$M+H^+$]: 574.2118; found: 574.2126.

Intermediate 188



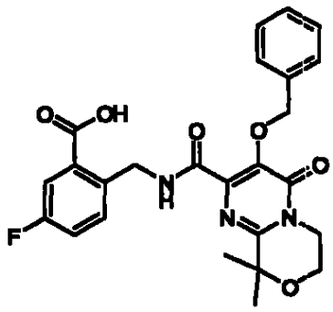
Ethyl hydrogen 2-((3-(benzyloxy)-9,9-dimethyl-4-oxo-4,6,7,9-tetrahydropyrimido[2,1-c][1,4]oxazine-2-carboxamido)methyl)-5-fluorophenylphosphonate. A solution of intermediate 187, diethyl 2-((3-(benzyloxy)-9,9-dimethyl-4-oxo-4,6,7,9-tetrahydropyrimido[2,1-c][1,4]oxazine-2-carboxamido)methyl)-5-fluorophenylphosphonate (0.115 g, 0.20 mmol) in tetrahydrofuran (3ml)/ethanol (3mL) was treated with 1 N aqueous sodium hydroxide (1.0 ml, 1.0 mmol) and the resulting mixture heated at 45 °C for 2 h. The reaction mixture was then diluted with ethyl acetate, washed with 0.1 N hydrochloric acid, brine, dried over anhydrous magnesium sulfate and concentrated. The residue was purified on a Shimadzu automated preparative HPLC system (column YMC Pack C-18, 5μ, 20 x 250 mm, elution gradient acetonitrile-water 0.1% trifluoroacetic acid) to give 0.070 g (64% yield) of the title material as a clear oil. ^{1}HNMR 400 MHz ($CDCl_3$) δ ppm: 1.37 (3H, t, J = 7.1 Hz, CH_3), 1.62 (6H, s, 2 x CH_3), 4.04 (4H, m, 2 x CH_2), 4.18 (2H, m, OCH_2), 4.75 (2H, broad d, J = 5 Hz, NCH_2), 5.32 (2H, s, OCH_2), 7.21 (1H, m, aromatic), 7.30-7.33 (3H, m, aromatics), 7.38-7.40 (2H, m, aromatics), 7.47-7.52 (1H, m, aromatic), 7.56-7.63 (1H, m, aromatic), 8.56 (1H, broad t, NH). HRMS (ESI$^+$) calculated for $C_{26}H_{30}FN_3O_7P$ [M+H$^+$]: 546.1805; found: 546.1786.

Intermediate 189



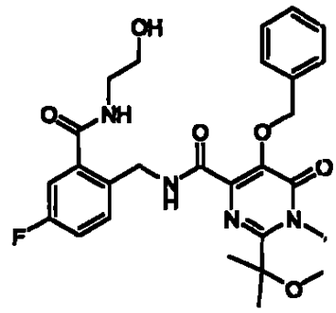
N-(2-Acetamido-4-fluorobenzyl)-3-(benzyloxy)-9,9-dimethyl-4-oxo-4,6,7,9-tetrahydropyrimido[2,1-c][1,4]oxazine-2-carboxamide. To a solution of intermediate 169, *N*-(2-amino-4-fluorobenzyl)-3-(benzyloxy)-9,9-dimethyl-4-oxo-4,6,7,9-tetrahydropyrimido[2,1-c][1,4]oxazine-2-carboxamide (0.033 g, 0.073 mmol) in dry tetrahydrofuran (10 mL) was added acetyl chloride (5.7 μL, 0.08 mmol) and diisopropylethylamine (38 μL, 0.22 mmol). The reaction mixture was stirred at 23 °C for 3 h. $NaHCO_3$ (0.25 M, 20 mL) was then added and the organic material extracted with ethyl acetate (3 X 25 mL). The organic extracts were combined, dried ($MgSO_4$) and concentrated *in vacuo*. The residue was purified on a Biotage system using a silica gel column with ethyl acetate:Hex (1:2 to 2:1) as eluent to afford the title compound (0.025 g, 69% yield). ^{1}HNMR 400 MHz (MeOD) δ (ppm): 7.66 (1H, dd, J = 10.5, 2.8 Hz), 7.43-7.25 (6H, m), 6.87 (1H, ddd, (dt), J = 8.8, 2.6 Hz), 5.19 (2H, s), 4.47 (2H, m), 4.08 (2H, t, J = 4.9 Hz), 3.99 (2H, t, J = 4.9 Hz), 2.19 (3H, s), 1.62 (6H, s). LCMS $(M+H)^+$ m/z 495.

Intermediate 190



2-((3-(Benzyloxy)-9,9-dimethyl-4-oxo-4,6,7,9-tetrahydropyrimido[2,1-c][1,4]oxazine-2-carboxamido)methyl)-5-fluorobenzoic acid. To a suspension of intermediate 154, methyl 2-((3-(benzyloxy)-9,9-dimethyl-4-oxo-4,6,7,9-tetrahydropyrimido[2,1-c][1,4]oxazine-2-carboxamido)methyl)-5-fluorobenzoate. (500 mg, 1.01 mmol) in MeOH (10 mL) and CH_3CN (5 mL) was added 1N NaOH (2 mL) and the mixture stirred at room temperature for 2 hrs. The mixture was concentrated *in vacuo* and the residue purified by reverse phase column chromatography (YMC, C-18 ODS, 10-25% CH_3CN/H_2O) to provide 90 mg (Yield 19%) of the title compound as an off-white powder: LC/MS m/z 482 (M+H).

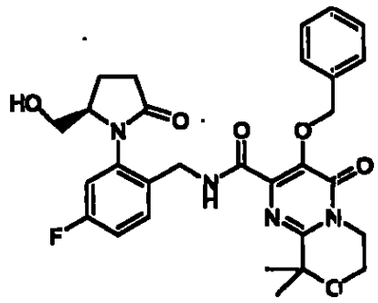
Intermediate 191



N-(2-((2-Aminoethyl)carbamoyl)-4-fluorobenzyl)-3-(benzyloxy)-9,9-dimethyl-4-oxo-4,6,7,9-tetrahydropyrimido[2,1-c][1,4]oxazine-2-carboxamide. A mixture of intermediate 190, 2-((3-(benzyloxy)-9,9-dimethyl-4-oxo-4,6,7,9-

tetrahydropyrimido[2,1-c][1,4]oxazine-2-carboxamido)methyl)-5-fluorobenzoic acid, (59 mg, 0.12 mmol) and O-(7-azabenzotriazol-1-yl)-N,N,N',N'-tetramethyluronium hexafluorophosphate, HATU (76 mg, 0.2 mmol; Aldrich) in DMF (1 mL) was stirred for 20 min. To this mixture was added ethanolamine (20 mg, 0.3 mmol) and the stirring continued overnight. The mixture was concentrated *in vacuo*, dissolved in CH_2Cl_2, washed with water then dried ($MgSO_4$), filtered, and concentrated to provide 55 mg (Yield 87%) of the title compound: LC/MS m/z 525 (M+H).

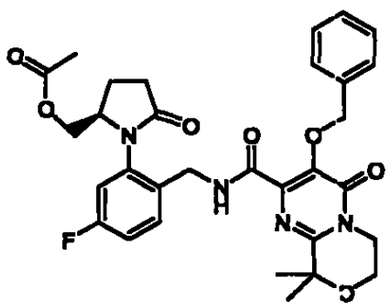
Intermediate 192



(R)-N-(4-Fluoro-2-(2-(hydroxymethyl)-5-oxopyrrolidin-1-yl)benzyl)-3-(benzyloxy)-9,9-dimethyl-4-oxo-4,6,7,9-tetrahydropyrimido[2,1-c][1,4]oxazine-2-carboxamide. To a stirred solution of intermediate 166, (R)-*N*-(2-(2-((tert-butyldimethylsilyloxy)methyl)-5-oxopyrrolidin-1-yl)-4-fluorobenzyl)-3-(benzyloxy)-9,9-dimethyl-4-oxo-4,6,7,9-tetrahydropyrimido[2,1-c][1,4]oxazine-2-carboxamide (0.10 g, 0.150 mmol) in tetrahydrofuran (5mL) at 23 °C was added a solution of tetrabutylammonium fluoride (1M in tetrahydrofuran) (180 µL, 0.18 mmol). The reaction mixture was stirred at 23 °C for 3 h. $NaHCO_3$ (1N in H_2O, 30 mL) was then added and the organic material was extracted with ethyl acetate (2 X 25 mL). The combined organic extracts were dried ($MgSO_4$), filtered and concentrated *in vacuo*. The residue was purified on a Biotage system using a silica gel column with ethyl acetate/Hexanes (1:1) to ethyl acetate 100% as eluent to afford the title compound (0.060 g, 73% yield): ^{1}HNMR 400 MHz (MeOD) δ (ppm): 7.55 (1H, dd, (t), 6.6 Hz), 7.43 (2H, m), 7.13 (1H, dd, J = 9.5, 2.4 Hz), 7.03 (1H, m), 5.26 (2H, s), 4.57 (1H, m),

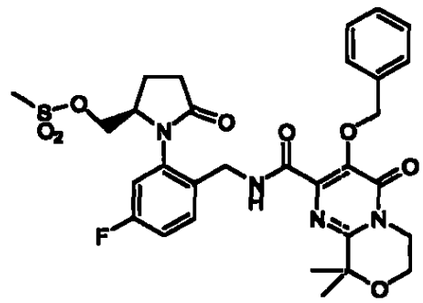
4.32 (2H, m), 4.08 (2H, t, J = 5.0 Hz), 7.03 (2H, t, J = 5.0 Hz), 3.53 (2H, m), 2.69-2.56 (2H, m), 2.38 (1H, m), 2.22 (1H, m), 1.62 (6H, s). LCMS $(M+H)^+$ m/z 551.

Intermediate 193



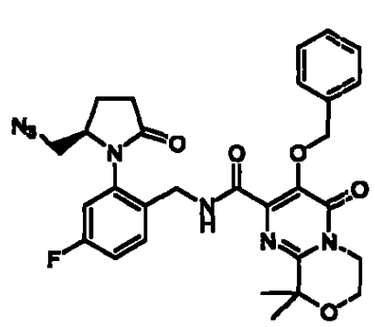
(R)-(1-(2-((3-(Benzyloxy)-9,9-dimethyl-4-oxo-4,6,7,9-tetrahydropyrimido[2,1-c][1,4]oxazine-2-carboxamido)methyl)-5-fluorophenyl)-5-oxopyrrolidin-2-yl)methyl acetate. To a solution of intermediate 192, (R)-*N*-(4-fluoro-2-(2-(hydroxymethyl)-5-oxopyrrolidin-1-yl)benzyl)-3-(benzyloxy)-9,9-dimethyl-4-oxo-4,6,7,9-tetrahydropyrimido[2,1-c][1,4]oxazine-2-carboxamide (0.045 g, 0.082 mmol) in tetrahydrofuran (5mL) was added acetyl chloride (12.8µL, 0.180 mmol) and diisopropylethylamine (31.4 µL, 0.180 mmol). The reaction mixture was stirred at 23 °C for 4 h. $NaHCO_3$ (1N in H_2O, 30 mL) was then added and the organic material was extracted with ethyl acetate (2 X 25 mL). The combined organic extracts were dried ($MgSO_4$), filtered and concentrated *in vacuo*. The residue was purified on a Biotage system using a silica gel column with ethyl acetate/Hexanes (1:1) to ethyl acetate 100% as eluent to afford the title compound (0.032 g, 67% yield): ^{1}HNMR 400 MHz (MeOD) δ ppm: 7.48 (3H, m), 7.33 (3H, m), 7.16 (1H, m), 7.03 (1H, m), 5.24 (2H, s), 4.60 (1H, m), 4.55 (1H, m), 4.22 (1H, dd, J = 12.0, 4.5 Hz), 4.08 (2H, t, J = 5.0 Hz), 3.99 (3H, m), 2.62 (2H, m), 2.44 (1H, m), 2.09-1.92 (5H, m), 1.62 (3H, s), 1.61 (3H, s). LCMS $(M+H)^+$ m/z 593.

Intermediate 194



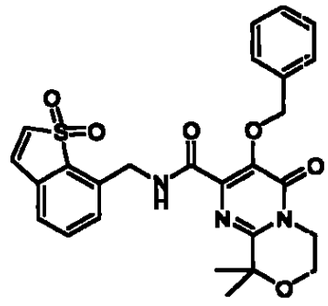
(R)-(1-(2-((3-(Benzyloxy)-9,9-dimethyl-4-oxo-4,6,7,9-tetrahydropyrimido[2,1-c][1,4]oxazine-2-carboxamido)methyl)-5-fluorophenyl)-5-oxopyrrolidin-2-yl)methyl methanesulfonate. To a stirred solution of intermediate 192, (R)-N-(4-fluoro-2-(2-(hydroxymethyl)-5-oxopyrrolidin-1-yl)benzyl)-3-(benzyloxy)-9,9-dimethyl-4-oxo-4,6,7,9-tetrahydropyrimido[2,1-c][1,4]oxazine-2-carboxamide (0.160 g, 0.291 mmol) in CH_2Cl_2 (10 mL) at 0 °C was added triethylamine (81 µL, 0.582 mmol) and methanesulfonyl chloride (27 µL, 0.349 mmol). The reaction mixture was stirred at 23 °C for 4 h. Water (50 mL) was then added and the organic material was extracted with CH_2Cl_2 (2 X 50 mL). The combined organic extracts were dried ($MgSO_4$), filtered and concentrated in vacuo to afford the title compound (0.178 g, 98% yield). The crude material was used without further purification for the next step: LCMS $(M+H)^+$ m/z 629.

Intermediate 195



(R)-N-(2-(2-(Azidomethyl)-5-oxopyrrolidin-1-yl)-4-fluorobenzyl)-3-(benzyloxy)-9,9-dimethyl-4-oxo-4,6,7,9-tetrahydropyrimido[2,1-c][1,4]oxazine-2-carboxamide. To a solution of intermediate 194, (R)-(1-(2-((3-(benzyloxy)-9,9-dimethyl-4-oxo-4,6,7,9-tetrahydropyrimido[2,1-c][1,4]oxazine-2-carboxamido)methyl)-5-fluorophenyl)-5-oxopyrrolidin-2-yl)methyl methanesulfonate (0.150 g, 0.239 mmol) in DMF (10 mL) was added sodium azide (0.019 g, 0.287 mmol). The resulting mixture was stirred at 50 °C for 6 h. Water (50 mL) was then added and the organic material was extracted with ethyl acetate (2 X 50 mL). The combined organic extracts were washed with H_2O (50 mL), dried ($MgSO_4$), filtered and concentrated in vacuo to afford the title compound (0.125 g, 91% yield). LCMS $(M+H)^+$ m/z 576.

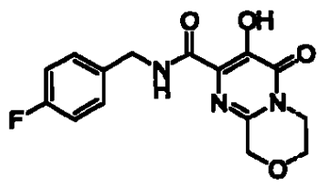
Intermediate 196



N-(Benzo[b]thiophen-1,1-dione-7-ylmethyl)-3-(benzyloxy)-9,9-dimethyl-4-oxo-4,6,7,9-tetrahydropyrimido[2,1-c][1,4]oxazine-2-carboxamide. To a solution of intermediate 147, N-(benzo[b]thiophen-7-ylmethyl)-3-(benzyloxy)-9,9-dimethyl-4-oxo-4,6,7,9-tetrahydropyrimido[2,1-c][1,4]oxazine-2-carboxamide (0.100 g, 0.21 mmol) in dichloroethane (10 mL) was added per-acetic acid (32% in H_2O) (1.0 mmol, 200 µL). The reaction mixture was stirred at 23 °C for 48 h. Water (50 mL) was added and the organic material was extracted with CH_2Cl_2 (2 X 50 mL). The combined organic extracts were dried ($MgSO_4$), filtered and concentrated *in vacuo* to afford the title compound (0.106 g, 99% yield): ^1H NMR (400 MHz, DMSO-d_6) δ ppm: 9.11(1H, t, J = 6.4 Hz), 7.65 (1H, d, J = 6.8 Hz) 7.59-7.29 (9H, m), 5.15 (2H, s),

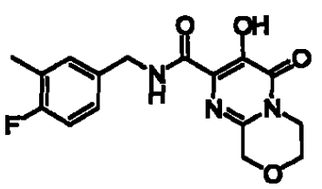
4.77 (2H, d, J = 6.5 Hz), 4.04 (2H, t , J = 5.0 Hz), 3.90 (2H, m), 1.59 (6H, s). LCMS $(M+H)^+$ m/z 508.

Example 1



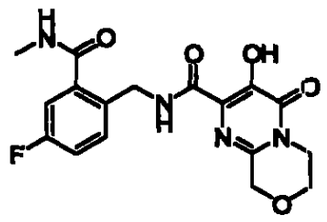
Pyrimido[2,1-c][1,4]oxazine-2-carboxamide, N-[(4-fluorophenyl)methyl]-4,6,7,9-tetrahydro-3-hydroxy-4-oxo-. A mixture of intermediate 7, ethyl 3-hydroxy-4-oxo-4,6,7,9-tetrahydropyrimido[2,1-c][1,4]oxazine-2-carboxylate, (0.036 g, 0.15 mmol) and 4-fluorobenzylamine (0.11 g, 0.87 mmol) in anhydrous ethyl alcohol (5 ml) and N,N-dimethylformamide (2 ml) was heated under reflux for 18 h. The solvent was then evaporated *in vacuo* and the residue was partitioned between ethyl acetate and 0.1 N hydrochloric acid. The organic phase was washed with water, brine and dried over anhydrous sodium sulfate. Evaporation of the solvent and recrystallization of the resulting solid from ethanol gave 0.023 g (47% yield) of the title amide as white crystals; mp 211 °C (ethyl acetate-hexane). ^{1}HNMR 400 MHz ($CDCl_3$) δ ppm: 4.06 (4H, m, 2 x CH_2), 4.59 (2H, d, J = 7.6 Hz, NCH_2), 4.61 (2H, s, OCH_2), 7.09 (2H, m, aromatics), 7.33 (2H, m, aromatics), 7.84 (1H, broad t, NH), 12.06 (1H, s, OH). MS (ESI^+) m/z 320 $[M+H^+]$.

Example 2



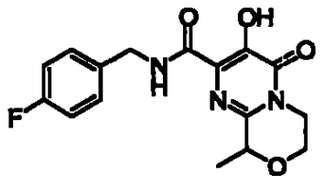
Pyrimido[2,1-c][1,4]oxazine-2-carboxamide, N-[(4-fluoro-3-methylphenyl)methyl]-4,6,7,9-tetrahydro-3-hydroxy-4-oxo-. Reaction of intermediate 7, ethyl 3-hydroxy-4-oxo-4,6,7,9-tetrahydropyrimido[2,1-c][1,4]oxazine-2-carboxylate, (0.100 g, 0.42 mmol) with 4-fluoro-3-methylbenzylamine (0.23 g, 1.66 mmol) as described in the preparation of example 1 gave 0.101 g (73% yield) of the title amide as white crystals; mp 206-208 °C (ethyl acetate). ^{1}HNMR 400 MHz ($CDCl_3$) δ ppm: 2.30 (3H, s, CH_3), 4.06 (4H, m, 2 x CH_2), 4.55 (2H, d, J = 6.1 Hz, NCH_2), 4.60 (2H, s, OCH_2), 7.01 (1H, m, aromatic), 7.14 (2H, m, aromatics), 7.81 (1H, broad t, NH), 12.09 (1H, s, OH). MS (ESI^+) m/z 334 [$M+H^+$].

Example 3



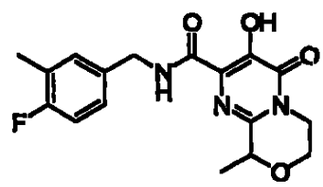
Pyrimido[2,1-c][1,4]oxazine-2-carboxamide, N-[[4-fluoro-2-[(methylamino)carbonyl]phenyl]methyl]-4,6,7,9-tetrahydro-3-hydroxy-4-oxo-. The title compound can be prepared from intermediate 150, N-(4-fluoro-2-(methylcarbamoyl)benzyl)-3-(benzyloxy)-4-oxo-4,6,7,9-tetrahydropyrimido[2,1-c][1,4]oxazine-2-carboxamide. ^{1}HNMR 400 MHz (DMSO-d_6) δ ppm: 2.79 (3H, d, J = 4.5 Hz, NCH_3), 3.83 (2H, m, CH_2), 4.02 (2H, m, CH_2), 4.54 (2H, d, J = 6.7 Hz, NCH_2), 4.58 (2H, s, OCH_2), 7.31 (2H, m, aromatics), 7.38 (1H, m, aromatic), 8.54 (1H, broad q, NH), 9.21 (1H, broad t, NH), 12.24 (1H, s, OH). HRMS (ESI^+) calculated for $C_{17}H_{18}FN_4O_5$ [$M+H^+$]: 377.1261; found: 377.1249.

Example 4



Pyrimido[2,1-c][1,4]oxazine-2-carboxamide, N-[(4-fluorophenyl)methyl]-4,6,7,9-tetrahydro-3-hydroxy-9-methyl-4-oxo-. Reaction of intermediate 15, ethyl 3-hydroxy-9-methyl-4-oxo-4,6,7,9-tetrahydropyrimido[2,1-c][1,4]oxazine-2-carboxylate (0.050 g, 0.20 mmol) with 4-fluorobenzylamine (0.11 g, 0.87 mmol) as described in the preparation of example 1 gave 0.056 g (84% yield) of the title amide as white crystals; mp 165-167 °C (ethyl acetate-hexane). ^{1}HNMR 400 MHz ($CDCl_3$) δ ppm: 1.62 (3H, d, J = 7.0 Hz, CH_3), 3.90 (2H, m, CH_2), 4.15-4.32 (2H, m, CH_2), 4.61 (3H, m, NCH_2 and OCH), 7.08 (2H, m, aromatics), 7.34 (2H, m, aromatics), 7.82 (1H, broad t, NH), 12.06 (1H, s, OH). Anal. Calcd for $C_{16}H_{16}FN_3O_4$: C 57.65, H 4.83, N 12.60. Found: C 57.44, H 4.69, N 12.37.

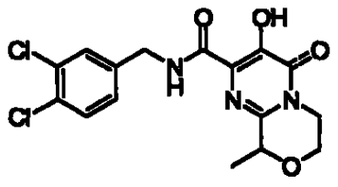
Example 5



Pyrimido[2,1-c][1,4]oxazine-2-carboxamide, N-[(4-fluoro-3-methylphenyl)methyl]-4,6,7,9-tetrahydro-3-hydroxy-9-methyl-4-oxo-. Reaction of intermediate 15, ethyl 3-hydroxy-9-methyl-4-oxo-4,6,7,9-tetrahydropyrimido[2,1-c][1,4]oxazine-2-carboxylate, (0.090 g, 0.35 mmol) with 4-fluoro-3-methylbenzylamine (0.180 g, 1.3 mmol) as described in the preparation of example 1 gave 0.068 g (55% yield) of the title amide as white crystals; mp 134 °C (ethyl acetate-hexane). ^{1}HNMR 400 MHz ($CDCl_3$) δ ppm: 1.62 (3H, d, J = 6.6 Hz, CH_3),

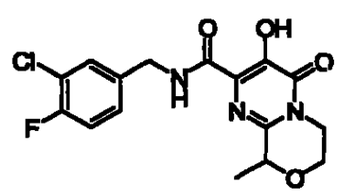
2.30 (3H, s, CH_3), 3.90 (2H, m, CH_2), 4.13-4.32 (2H, m, CH_2), 4.49-4.64 (3H, m, NCH_2 and OCH), 7.01 (1H, m, aromatic), 7.16 (2H, m, aromatics), 7.79 (1H, broad t, NH), 12.09 (1H, s, OH). Anal. Calcd for $C_{17}H_{18}FN_3O_4$: C 58.78, H 5.22, N 12.09. Found: C 58.57, H 5.55, N 11.90.

Example 6



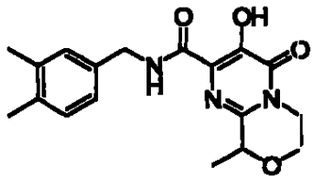
Pyrimido[2,1-c][1,4]oxazine-2-carboxamide, N-[(3,4-dichlorophenyl)methyl]-4,6,7,9-tetrahydro-3-hydroxy-9-methyl-4-oxo-. Reaction of intermediate 15, ethyl 3-hydroxy-9-methyl-4-oxo-4,6,7,9-tetrahydropyrimido[2,1-c][1,4]oxazine-2-carboxylate (0.075 g, 0.29 mmol) with 3,4-dichlorobenzylamine (0.140 g, 0.8 mmol) as described in the preparation of example 1 gave 0.085 g (75% yield) of the title amide as white crystals; mp 192 °C (ethyl acetate-hexane). ^{1}HNMR 400 MHz ($CDCl_3$) δ ppm: 1.64 (3H, d, J = 6.6 Hz, CH_3), 3.91 (2H, m, CH_2), 4.17-4.32 (2H, m, CH_2), 4.50-4.68 (3H, m, NCH_2 and OCH), 7.20 (1H, dd, J = 2.0 Hz and J = 8.0 Hz, aromatic), 7.44 (1H, d, J = 2.0 Hz, aromatic), 7.46 (1H, d, J = 8.0 Hz, aromatic), 7.86 (1H, broad t, NH), 11.92 (1H, s, OH). MS (ESI^+) m/z 384 [$M+H^+$]. Anal. Calcd for $C_{16}H_{15}Cl_2N_3O_4$: C 50.02, H 3.94, N 10.94. Found: C 49.40, H 4.06, N 10.41.

Example 7



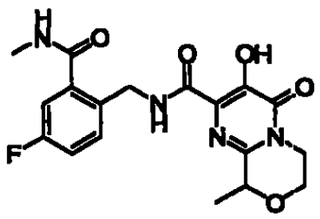
Pyrimido[2,1-c][1,4]oxazine-2-carboxamide, N-[(3-chloro-4-fluorophenyl)methyl]-4,6,7,9-tetrahydro-3-hydroxy-9-methyl-4-oxo-. Reaction of intermediate 15, ethyl 3-hydroxy-9-methyl-4-oxo-4,6,7,9-tetrahydropyrimido[2,1-c][1,4]oxazine-2-carboxylate, (0.075 g, 0.30 mmol) with 3-chloro-4-fluorobenzylamine (0.14 g, 0.88 mmol) as described in the preparation of example 1 gave 0.050 g (46% yield) of the title amide as white crystals; mp 172 °C (ethyl acetate-ether). ^{1}HNMR 400 MHz ($CDCl_3$) δ ppm: 1.63 (3H, d, J = 6.6 Hz, CH_3), 3.91 (2H, m, CH_2), 4.17-4.32 (2H, m, CH_2), 4.50-4.67 (3H, m, NCH_2 and OCH), 7.16 (1H, m, aromatic), 7.24 (1H, m, aromatic), 7.40 (1H, m, aromatic), 7.85 (1H, broad t, NH), 11.95 (1H, s, OH). Anal. Calcd for $C_{16}H_{15}ClFN_3O_4$: C 52.25, H 4.11, N 11.42. Found: C 51.99, H 4.01, N 11.09.

Example 8



Pyrimido[2,1-c][1,4]oxazine-2-carboxamide, N-[(3,4-dimethylphenyl)methyl]-4,6,7,9-tetrahydro-3-hydroxy-9-methyl-4-oxo-. Reaction of intermediate 15, ethyl 3-hydroxy-9-methyl-4-oxo-4,6,7,9-tetrahydropyrimido[2,1-c][1,4]oxazine-2-carboxylate, (0.075 g, 0.30 mmol) with 3,4-dimethylbenzylamine (0.15 g, 1.1 mmol) as described in the preparation of example 1 gave 0.033 g (33% yield) of the title amide as a white solid. ^{1}HNMR 400 MHz ($CDCl_3$) δ ppm: 1.61 (3H, d, J = 6.6 Hz, CH_3), 2.28 (3H, s, CH_3), 2.29 (3H, s, CH_3), 3.90 (2H, m, CH_2), 4.16-4.30 (2H, m, CH_2), 4.50-4.65 (3H, m, NCH_2 and OCH), 7.08-7.17 (3H, m, aromatics), 7.78 (1H, broad t, NH), 12.17 (1H, s, OH). MS (ESI^+) m/z 344 [$M+H^+$].

Example 9

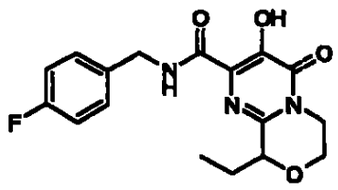


Pyrimido[2,1-c][1,4]oxazine-2-carboxamide, N-[[4-fluoro-2-[(methylamino)carbonyl]phenyl]methyl]-4,6,7,9-tetrahydro-3-hydroxy-9-methyl-4-oxo-. A solution of intermediate 140, N-(4-fluoro-2-(methylcarbamoyl)benzyl)-3-benzyloxy-9-methyl-4-oxo-4,6,7,9-tetrahydropyrimido[2,1-c][1,4]oxazine-2-carboxamide, (0.268 g, 0.56 mmol) in a mixture of ethyl acetate (25 ml) and ethanol (25 ml) was hydrogenated under 1 atm of hydrogen at 25 °C over 10% palladium on activated carbon (0.09 g) for 2.5 h to give 0.121 g (56% yield) of the title ester as a white solid. ^{1}HNMR 400 MHz (DMSO-d_6) δ ppm: 1.57 (3H, d, J = 6.7 Hz, CH_3), 2.79 (3H, d, J = 4.6 Hz, NCH_3), 3.70 (1H, m, CH), 3.87 (1H, m, CH), 3.98 (1H, m, CH), 4.15 (1H, m, CH), 4.55 (2H, m, NCH_2), 4.62 (1H, q, J = 6.6 Hz, OCH), 7.25-7.44 (3H, m, aromatics), 8.59 (1H, broad q, NH), 9.39 (1H, broad , NH), 12.18 (1H, s, OH). HRMS (ESI$^+$) calculated for $C_{18}H_{20}FN_4O_5$ [M+H$^+$]: 391.1418; found: 391.1431.

Examples 10-14

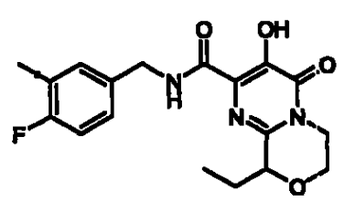
Examples 10-14 can be prepared from ethyl 9-ethyl-3-hydroxy-4-oxo-4,6,7,9-tetrahydropyrimido[2,1-c][1,4]oxazine-2-carboxylate and the indicated amines according to the method described for the synthesis of example 1. Ethyl 9-ethyl-3-hydroxy-4-oxo-4,6,7,9-tetrahydropyrimido[2,1-c][1,4]oxazine-2-carboxylate was prepared according to the method used to prepare intermediate 15.

Example 10



Pyrimido[2,1-c][1,4]oxazine-2-carboxamide, 9-ethyl-N-[(4-fluorophenyl)methyl]-4,6,7,9-tetrahydro-3-hydroxy-4-oxo-. The title compound can be prepared from 4-fluorobenzylamine. ^{1}HNMR 400 MHz ($CDCl_3$) δ ppm: 1.02 (3H, t, J = 7.3 Hz, CH_3), 1.93 (1H, m, CH), 2.15 (1H, m, CH), 3.88 (2H, m, CH_2), 4.2-4.29 (2H, m, CH_2), 4.46 (1H, m, CH), 4.53-4.69 (2H, m, CH_2), 7.06 (2H, m, aromatics), 7.34 (2H, m, aromatics), 7.82 (1H, broad t, NH), 12.05 (1H, s, OH). HRMS (ESI^+) calculated for $C_{17}H_{19}FN_3O_4$ [$M+H^+$]: 348.1360; found: 348.1355.

Example 11



Pyrimido[2,1-c][1,4]oxazine-2-carboxamide, 9-ethyl-N-[(4-fluoro-3-methylphenyl)methyl]-4,6,7,9-tetrahydro-3-hydroxy-4-oxo-. The title compound can be prepared from (4-fluoro-3-methylphenyl)methanamine. ^{1}HNMR 400 MHz ($CDCl_3$) δ ppm: 1.01 (3H, t, J = 7.4 Hz, CH_3), 1.91 (1H, m, CH), 2.16 (1H, m, CH), 2.30 (3H, s, CH_3), 3.87 (2H, m, CH_2), 4.2-4.30 (2H, m, CH_2), 4.46 (1H, m, CH), 4.48-4.65 (2H, m, CH_2), 7.01 (1H, m, aromatic), 7.14 (2H, m, aromatics), 7.81 (1H, broad t, NH), 12.07 (1H, s, OH). Anal. Calcd for $C_{18}H_{21}FN_3O_4$: C 59.82, H 5.57, N 11.62; Found: C 59.53, H 5.86, N 11.42.

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Industria y Comercio
SUPERINTENDENCIA

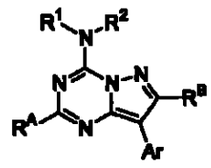
SUPERINTENDENCIA DE INDUSTRIA Y COMERCIO
DIVISION DE NUEVAS CREACIONES
EXTRACTO PARA PUBLICACIÓN
SOLICITUD DE PATENTE DE INVENCIÓN PCT

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(54) Título:	

Reivindicación(es)

1. Un proceso para preparar un compuesto de Formula I:



I

en la que:

Ar es fenilo o piridilo sustituido con de 0 a 5 R^3;

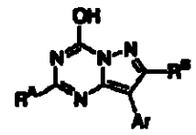
cada uno de R^1 y R^2 es, independientemente, H, alquilo (C_1-C_8), o alcoxialquio (C_1-C_8),

cada R^3 es, independientemente, H, halo, CN, nitro, alquilo (C_1-C_4),

alcoxi (C_1-C_4), haloalquilo (C_1-C_4), o haloalcoxi (C_1-C_4); y

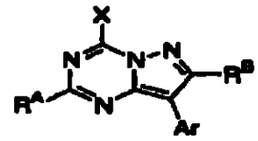
cada uno de R^A y R^B es, independientemente, alquilo (C_1-C_4). que comprende:

(a) poner en contacto un compuesto de Formula III:



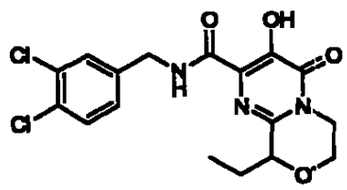
III

con PDX_3 en presencia de una amina seleccionada entre diisopropiletilamina, dietilfenilamina, diisopropilanilina, dietilanilina, diisopropilisobutilamina, tribencilamina, trifenilamina, triciclohexilamina, o dietilisopropilamina, donde X es halo, durante un tiempo y en unas condiciones de reacción suficientes para proporcionar un compuesto de Formula II:



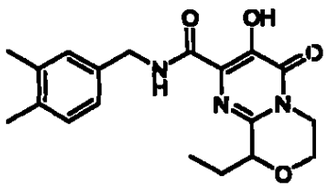
II

Example 12



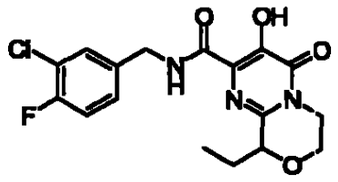
Pyrimido[2,1-c][1,4]oxazine-2-carboxamide, N-[(3,4-dichlorophenyl)methyl]-9-ethyl-4,6,7,9-tetrahydro-3-hydroxy-4-oxo-. The title compound can be prepared from (3,4-dichlorophenyl)methanamine. ^{1}HNMR 400 MHz ($CDCl_3$) δ ppm: 1.00 (3H, t, J = 7.3 Hz, CH_3), 1.91 (1H, m, CH), 2.15 (1H, m, CH), 3.85 (2H, m, CH_2), 4.19-4.28 (2H, m, CH_2), 4.45 (1H, m, CH), 4.48-4.66 (2H, m, CH_2), 7.19 (1H, m, aromatic), 7.43 (2H, m, aromatics), 7.84 (1H, broad t, NH), 11.88 (1H, s, OH). Anal. Calcd for $C_{17}H_{17}Cl_2N_3O_4$: C 51.27, H 4.30, N 10.55; Found: C 51.16, H 4.21, N 10.34.

Example 13



Pyrimido[2,1-c][1,4]oxazine-2-carboxamide, N-[(3,4-dimethylphenyl)methyl]-9-ethyl-4,6,7,9-tetrahydro-3-hydroxy-4-oxo-. The title compound can be prepared from (3,4-dimethylphenyl)methanamine. ^{1}HNMR 400 MHz ($CDCl_3$) δ ppm: 0.98 (3H, t, J = 7.3 Hz, CH_3), 1.87 (1H, m, CH), 2.12 (1H, m, CH), 2.26 (3H, s, CH_3), 2.27 (3H, s, CH_3), 3.83 (2H, m, CH_2), 4.17-4.26 (2H, m, CH_2), 4.41 (1H, m, CH), 4.45-4.64 (2H, m, CH_2), 7.05-7.24 (3H, m, aromatics), 7.75 (1H, broad t, NH), 12.13 (1H, s, OH). Anal. Calcd for $C_{19}H_{23}N_3O_4$: C 63.85, H 6.49, N 11.76; Found: C 63.55, H 6.48, N 11.74.

Example 14

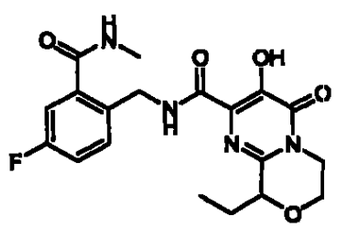


Pyrimido[2,1-c][1,4]oxazine-2-carboxamide, N-[(3-chloro-4-fluorophenyl)methyl]-9-ethyl-4,6,7,9-tetrahydro-3-hydroxy-4-oxo-. The title compound can be prepared from (3-chloro-4-fluorophenyl)methanamine. ^{1}HNMR 400 MHz ($CDCl_3$) δ ppm: 1.03 (3H, t, J = 7.3 Hz, CH_3), 1.92 (1H, m, CH), 2.17 (1H, m, CH), 3.88 (2H, m, CH_2), 4.18-4.32 (2H, m, CH_2), 4.46 (1H, m, CH), 4.5-4.68 (2H, m, CH_2), 7.16 (1H, m, aromatic), 7.24 (1H, m, aromatic), 7.40 (1H, m, aromatic), 7.84 (1H, broad t, NH), 11.93 (1H, s, OH). Anal. Calcd for $C_{17}H_{17}ClFN_3O_4$: C 53.48, H 4.48, N 11.00; Found: C 53.25, H 4.49, N 10.79.

Examples 15-16

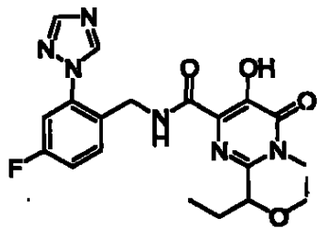
Examples 15-16 can be prepared from 3-(benzyloxy)-9-ethyl-4-oxo-4,6,7,9-tetrahydropyrimido[2,1-c][1,4]oxazine-2-carboxylic acid and the indicated amines according to the methods described for the synthesis of intermediate 140 and example 9. 3-(Benzyloxy)-9-ethyl-4-oxo-4,6,7,9-tetrahydropyrimido[2,1-c][1,4]oxazine-2-carboxylic acid was prepared according to the method used to prepare intermediate 16.

Example 15



Pyrimido[2,1-c][1,4]oxazine-2-carboxamide, 9-ethyl-N-[[4-fluoro-2-[(methylamino)carbonyl]phenyl]methyl]-4,6,7,9-tetrahydro-3-hydroxy-4-oxo-. The title compound can be prepared from intermediate 39. ^{1}HNMR 400 MHz ($CDCl_3$) δ ppm: 1.03 (3H, t, J = 7.3 Hz, CH_3), 1.98 (1H, m, CH), 2.28 (1H, m, CH), 3.06 (3H, d, J = 4.5 Hz, NCH_3), 3.86 (2H, m, CH_2), 4.14-4.29 (2H, m, CH_2), 4.48 (1H, m, CH), 4.60 (2H, m, CH_2), 6.2 (1H, broad, NH), 7.14-7.21 (2H, m, aromatics), 7.54 (1H, m, aromatic), 8.85 (1H, broad t, NH), 12.1 (1H, s, OH). HRMS (ESI^+) calculated for $C_{19}H_{22}FN_4O_5$ [$M+H^+$]: 405.1574; found: 405.1579.

Example 16

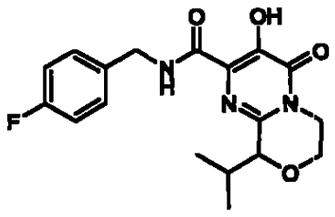


Pyrimido[2,1-c][1,4]oxazine-2-carboxamide, 9-ethyl-N-[[4-fluoro-2-(1H-1,2,4-triazol-1-yl)phenyl]methyl]-4,6,7,9-tetrahydro-3-hydroxy-4-oxo-. The title compound can be prepared from intermediate 151, N-(4-fluoro-2-(1H-1,2,4-triazol-1-yl)benzyl)-3-(benzyloxy)-9-ethyl-4-oxo-4,6,7,9-tetrahydropyrimido[2,1-c][1,4]oxazine-2-carboxamide, according to a procedure similar to that described in example 9. ^{1}HNMR 400 MHz (DMSO-d_6) δ ppm: 0.94 (3H, t, J = 7.5 Hz, CH_3), 1.88 (1H, m, CH), 2.27 (1H, m, CH), 3.68 (1H, m, CH), 3.87 (1H, m, CH), 4.0 (1H, m, CH), 4.19 (1H, m, CH), 4.36-4.49 (3H, m, CH_2 and CH), 7.43 (1H, m, aromatic), 7.56 (2H, m, aromatics), 8.32 (1H, m, CH), 9.05 (1H, m, CH), 9.3 (1H, broad t, NH), 12.04 (1H, s, OH). HRMS (ESI^+) calculated for $C_{19}H_{20}FN_6O_4$ [$M+H^+$]: 415.1530; found: 415.1515.

Examples 17-18

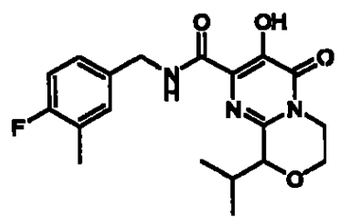
Examples 17-18 can be prepared from ethyl 3-hydroxy-9-isopropyl-4-oxo-4,6,7,9-tetrahydropyrimido[2,1-c][1,4]oxazine-2-carboxylate and the indicated amines according to the method described for the synthesis of example 1. Ethyl 3-hydroxy-9-isopropyl-4-oxo-4,6,7,9-tetrahydropyrimido[2,1-c][1,4]oxazine-2-carboxylate can be prepared according to the method used to prepare intermediate 15.

Example 17



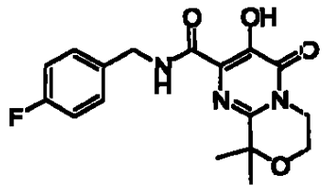
Pyrimido[2,1-c][1,4]oxazine-2-carboxamide, N-[(4-fluorophenyl)methyl]-4,6,7,9-tetrahydro-3-hydroxy-9-(1-methylethyl)-4-oxo-. The title compound can be prepared from 4-fluorobenzylamine. ^{1}HNMR 400 MHz ($CDCl_3$) δ ppm: 0.80 (3H, d, J = 6.7 Hz, CH_3), 1.13 (3H, d, J = 7.1 Hz, CH_3), 2.54 (1H, m, CH), 3.77 (2H, m, CH_2), 4.3 (2H, m, CH_2), 4.40 (1H, d, J = 2.5 Hz, CH), 4.50-4.72 (2H, m, CH_2), 7.09 (2H, m, aromatics), 7.34 (2H, m, aromatics), 7.82 (1H, broad t, NH), 12.04 (1H, s, OH). Anal. Calcd for $C_{18}H_{20}FN_3O_4$: C 59.82, H 5.57, N 11.62; Found: C 59.22, H 5.81, N 11.50.

Example 18



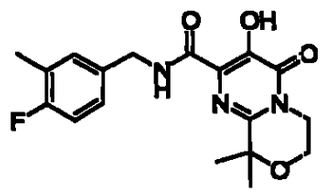
Pyrimido[2,1-c][1,4]oxazine-2-carboxamide, N-[(4-fluoro-3-methylphenyl)methyl]-4,6,7,9-tetrahydro-3-hydroxy-9-(1-methylethyl)-4-oxo-. The title compound can be prepared from (4-fluoro-3-methylphenyl)methanamine. ^{1}HNMR 400 MHz ($CDCl_3$) δ ppm: 0.80 (3H, d, J = 6.6 Hz, CH_3), 1.13 (3H, d, J = 7.1 Hz, CH_3), 2.30 (3H, s, CH_3), 2.54 (1H, m, CH), 3.77 (2H, m, CH_2), 4.3 (2H, m, CH_2), 4.40 (1H, broad s, CH), 4.46-4.68 (2H, m, CH_2), 7.02 (1H, m, aromatic), 7.17 (2H, m, aromatics), 7.80 (1H, broad t, NH), 12.07 (1H, s, OH). HRMS (ESI^+) calculated for $C_{19}H_{23}FN_3O_4$ [$M+H^+$]: 376.1673; found: 376.1671.

Example 19



Pyrimido[2,1-c][1,4]oxazine-2-carboxamide, N-[(4-fluorophenyl)methyl]-4,6,7,9-tetrahydro-3-hydroxy-9,9-dimethyl-4-oxo-. To a solution of intermediate 25, ethyl 3-hydroxy-9,9-dimethyl-4-oxo-4,6,7,9-tetrahydropyrimido[2,1-c][1,4]oxazine-2-carboxylate, (3.0 g, 11.19 mmol) in DMF (20 mL) and ethanol (10 mL) was added triethylamine (1.55 mL) followed by 4-fluorobenzylamine (3.82 mL, 33.57 mmol). The mixture was stirred at 90 °C for 2 h and then concentrated. The resultant oil was partitioned between ethyl acetate (50 mL) and 1N aqueous HCl (35 mL). The aqueous layer was back-extracted with ethyl acetate (20 mL) and the organic layers were combined and washed with H_2O (4 x 20 mL) and brine then dried (Na_2SO_4) and concentrated. The brown residue was triturated with ether and the solids filtered and washed with ether. The pale brown solids were recrystallized from 95:5 MeOH/H_2O to give the title compound as colorless needles (3.18 g, 82% yield). ^{1}H NMR (500 MHz, $CDCl_3$) δ ppm: 11.96 (1H, s), 7.77 (1H, brs), 7.30 (2H, dd, J = 8.4, 5.3 Hz), 7.04 (2H, t, J = 8.7 Hz), 4.57 (2H, d, J = 6.1 Hz), 4.01 (4H, s), 1.56 (6H, s). HRMS (M+H) calcd for $C_{17}H_{19}FN_3O_4$: 348.13597; found: 348.1365. Anal calcd for $C_{17}H_{18}FN_3O_4$: C, 58.78; H, 5.22; N, 12.09. Found: C, 58.38; H, 5.23; N, 11.80.

Example 20

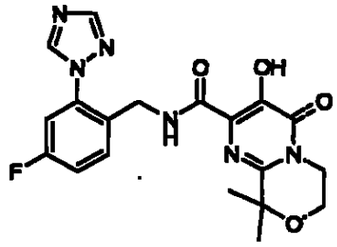


Pyrimido[2,1-c][1,4]oxazine-2-carboxamide, N-[(4-fluoro-3-methylphenyl)methyl]-4,6,7,9-tetrahydro-3-hydroxy-9,9-dimethyl-4-oxo-. A DMF solution of intermediate 25, ethyl 3-hydroxy-9,9-dimethyl-4-oxo-4,6,7,9-tetrahydropyrimido[2,1-c][1,4]oxazine-2-carboxylate, (4 mL, 1 mmol), Et_3N (0.14 mL, 1mmol) and 3-methy-4-fluorobenzylamine (0.418 g, 3 mmol) was heated at 90 °C for 5 h. The reaction mixture was cooled and the product isolated by reverse phase preparative HPLC using MeOH/H_2O-0.1% CF_3CO_2H as eluent. The fractions containing the desired material were combined and concentrated to afford the title compound as a yellow powder (0.19 g, 52% yield). ^1H NMR (500 MHz, $CDCl_3$) δ ppm: 11.99 (1H, s), 7.73 (1H, s), 7.14 (1H, d, J = 7.3 Hz), 7.12-7.09 (1H, m), 6.98 (1H, t, J = 9.0 Hz), 4.54 (2H, d, J = 6.4 Hz), 4.01 (4H, s), 2.27 (3H, s), 1.56 (6H, s). HRMS (M+H) calcd for $C_{18}H_{21}FN_3O_4$: 362.1516; found: 362.1509. Anal calcd for $C_{18}H_{20}FN_3O_4 + 0.07H_2O$: C, 59.26; H, 5.55; N, 11.48. Found: C, 58.88; H, 5.36; N, 11.34.

Examples 21-41

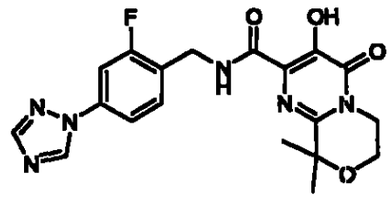
Examples 21-41 can be prepared from intermediate 25, ethyl 3-hydroxy-9,9-dimethyl-4-oxo-4,6,7,9-tetrahydropyrimido[2,1-c][1,4]oxazine-2-carboxylate, and the indicated amines according to the method described for the synthesis of examples 1, 19 and 20.

Example 21



Pyrimido[2,1-c][1,4]oxazine-2-carboxamide, N-[[4-fluoro-2-(1H-1,2,4-triazol-1-yl)phenyl]methyl]-4,6,7,9-tetrahydro-3-hydroxy-9,9-dimethyl-4-oxo-. The title compound can be prepared from intermediate 69. Solid, ^{1}H NMR (500 MHz, DMSO-d_6) δ ppm: 11.93 (1H, s), 9.29 (1H, t, J = 6.2 Hz), 9.05 (1H, s), 8.32 (1H, s), 7.57-7.53 (2H, m), 7.43 (1H, td, J = 7.9, 1.7 Hz), 4.44 (2H, d, J = 6.1 Hz), 3.98 (2H, t, J = 4.9 Hz), 3.83 (2H, t, J = 4.9 Hz), 1.56 (6H, s). HRMS (M+H) calcd for $C_{19}H_{20}N_6O_4F$: 415.15302; found: 415.1520. Anal Calcd for $C_{19}H_{19}N_6O_4F$: C, 55.07; H, 4.62; N, 20.28; F, 4.58; found: C, 54.95; H, 4.67; N, 20.27; F, 4.56.

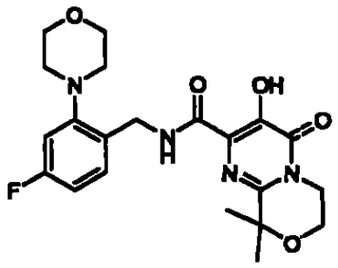
Example 22



Pyrimido[2,1-c][1,4]oxazine-2-carboxamide, N-[[2-fluoro-4-(1H-1,2,4-triazol-1-yl)phenyl]methyl]-4,6,7,9-tetrahydro-3-hydroxy-9,9-dimethyl-4-oxo-. The title compound can be prepared from intermediate 70. Solid, ^{1}H NMR (500 MHz, DMSO-d_6) δ ppm: 12.07 (1H, s), 9.46 (1H, bs), 9.33 (1H, s), 8.26 (1H, s), 7.81 (1H, dd, J = 11.1, 2.0 Hz), 7.73 (1H, dd, J = 8.2, 1.8 Hz), 7.52 (1H, t, J = 8.2 Hz), 4.59 (2H, d, J = 6.1 Hz), 3.98 (2H, t, J = 5.0 Hz), 3.84 (2H, t, J = 5.0 Hz), 1.58 (6H, s). HRMS (M+H) calcd for $C_{19}H_{20}N_6O_4F$: 415.15302; found: 415.1520. Anal calcd for

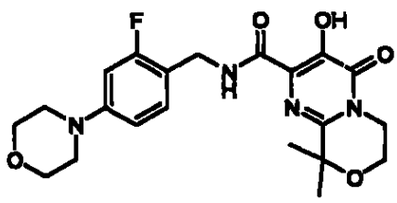
$C_{19}H_{19}N_6O_4F + 1.25\ H_20$: C, 52.23; H, 4.96; N, 19.23; F, 4.35; found: C, 52.29; H, 4.66; N, 19.23; F, 4.35.

Example 23



Pyrimido[2,1-c][1,4]oxazine-2-carboxamide, N-[[4-fluoro-2-(4-morpholinyl)phenyl]methyl]-4,6,7,9-tetrahydro-3-hydroxy-9,9-dimethyl-4-oxo-. The title compound can be prepared from intermediate 73. Solid, ^{1}H NMR (500 MHz, $CDCl_3$) δ ppm: 12.09 (1H, s), 7.91 (1H, brs), 7.31-7.28 (1H, m), 6.90 (1H, dd, J= 10.4, 2.4 Hz), 6.84 (1H, td, J= 8.1, 2.4 Hz), 4.66 (2H, d, J= 6.4 Hz), 4.02 (4H, s), 3.89-3.87 (4H, m), 2.94-2.92 (4H, m), 1.59 (6H, s). HRMS (M-H) calcd for $C_{21}H_{24}N_4O_5F$: 431.17307; found: 431.1719. Anal calcd for $C_{21}H_{25}N_4O_5F$: C, 58.32; H, 5.82; N, 12.95; F, 4.39; found: C, 58.13; H, 5.81; N, 12.79; F, 4.33.

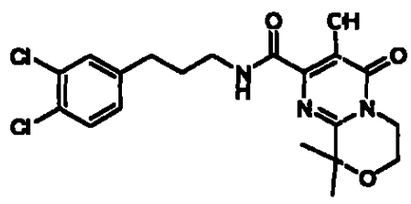
Example 24



Pyrimido[2,1-c][1,4]oxazine-2-carboxamide, N-[[2-fluoro-4-(4-morpholinyl)phenyl]methyl]-4,6,7,9-tetrahydro-3-hydroxy-9,9-dimethyl-4-oxo-. The title compound can be prepared from intermediate 74. ^{1}H NMR (500 MHz, $CDCl_3$) δ ppm: 12.01 (1H, s), 7.80 (1H, brs), 7.28-7.24 (1H, m), 6.66 (1H, d, J= 8.5 Hz), 6.61

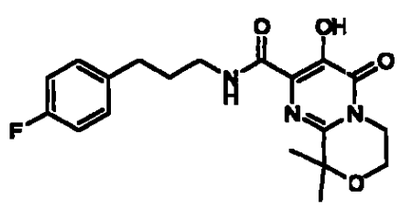
(1H, dd, J= 13.4, 1.8 Hz), 4.56 (2H, d, J= 6.1 Hz), 4.01 (4H, s), 3.85-3.84 (4H, m), 3.17-3.15 (4H, m), 1.60 (6H, s). HRMS (M-H) calcd for $C_{21}H_{24}N_4O_5F$: 431.17307; found: 431.1729. Anal calcd for $C_{21}H_{25}N_4O_5F$: C, 58.32; H, 5.82; N, 12.95; F, 4.39; found: C, 58.23; H, 5.73; N, 12.82; F, 4.21.

Example 25



Pyrimido[2,1-c][1,4]oxazine-2-carboxamide, N-[3-(3,4-dichlorophenyl)propyl]-4,6,7,9-tetrahydro-3-hydroxy-9,9-dimethyl-4-oxo-. The title compound can be prepared from 3-(3,4-dichlorophenyl)propan-1-amine. ^{1}H NMR (500 MHz, $CDCl_3$) δ ppm: 12.05 (1H, s), 7.46 (1H, brs), 7.35 (1H, d, J= 8.2 Hz), 7.28 (1H, d, J= 2.1 Hz), 7.04 (1H, dd, J= 8.2, 2.1 Hz), 4.02 (4H, s), 3.46 (2H, q, J= 6.9 Hz), 2.67 (2H, t, J= 7.6 Hz), 1.95 (2H, m), 1.59 (6H, s). HRMS (M+H) calcd for $C_{19}H_{22}N_3O_4Cl_2$: 426.09875; found: 426.0996. Anal calcd for $C_{19}H_{21}N_3O_4Cl_2$: C, 53.53; H, 4.96; N, 9.85; Cl, 16.63; found: C, 53.57; H, 4.96; N, 9.76; Cl, 16.63.

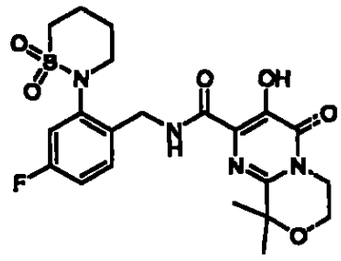
Example 26



Pyrimido[2,1-c][1,4]oxazine-2-carboxamide, N-[3-(4-fluorophenyl)propyl]-4,6,7,9-tetrahydro-3-hydroxy-9,9-dimethyl-4-oxo-. The title compound can be prepared from 3-(4-fluorophenyl)propan-1-amine. ^{1}H NMR (500 MHz, $CDCl_3$) δ ppm: 12.09 (1H, s), 7.15 (2H, dd, J= 8.2, 5.5 Hz), 6.97 (2H, t, J= 8.5 Hz), 4.02 (4H,

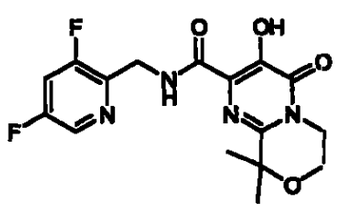
s), 3.44 (2H, q, J= 13.9, 6.9 Hz), 2.68 (2H, t, J= 7.6 Hz), 1.98-1.92 (2H, m), 1.62 (6H, s). HRMS (M+H) calcd for $C_{19}H_{23}N_3O_4F$: 376.16727; found: 376.1687. Anal calcd for $C_{19}H_{22}N_3O_4F$: C, 60.79; H, 5.90; N, 11.19; F, 5.06; found: C, 60.70; H, 5.87; N, 11.14; F, 4.92.

Example 27



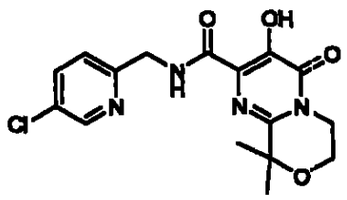
Pyrimido[2,1-c][1,4]oxazine-2-carboxamide, N-[[4-fluoro-2-(tetrahydro-1,1-dioxido-2H-1,2-thiazin-2-yl)phenyl]methyl]-4,6,7,9-tetrahydro-3-hydroxy-9,9-dimethyl-4-oxo-. The title compound can be prepared from intermediate 76. ^{1}H NMR (500 MHz, $CDCl_3$) δ ppm: 12.07 (1H, s), 8.31 (1H, d, J= 6.44 Hz), 7.46 (1H, dd, J= 8.5, 6.4 Hz), 7.19 (1H, dd, J= 9.0, 2.6 Hz), 7.08 (1H, td, J= 8.2, 2.7 Hz), 4.92 (1H, dd, J= 14.0, 8.8 Hz), 4.37 (1H, dd, J= 14.0, 3.4 Hz), 4.02-3.97 (2H, m), 3.99 (2H, s), 3.87-3.82 (1H, m), 3.45-3.41 (1H, m), 3.30-3.20 (2H, m), 2.46-2.32 (2H, m), 2.00-1.88 (2H, m), 1.57 (3H, s), 1.53 (3H, s). HRMS (M-H) calcd for $C_{21}H_{26}N_4O_6FS$: 481.15572; found: 481.1570. Anal calcd for $C_{21}H_{25}N_4O_6FS$: C, 52.49; H, 5.24; N, 11.66; F, 3.95; S, 6.67; found: C, 52.29; H, 5.37; N, 11.40; F, 3.91; S, 6.70.

Example 28



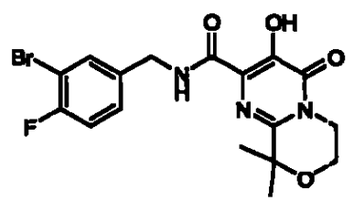
Pyrimido[2,1-c][1,4]oxazine-2-carboxamide, N-[(3,5-difluoro-2-pyridinyl)methyl]-4,6,7,9-tetrahydro-3-hydroxy-9,9-dimethyl-4-oxo-. The title compound can be prepared from intermediate 102. ^{1}H NMR (500 MHz, $CDCl_3$) δ ppm: 11.86 (1H, s), 8.58 (1H, brs), 8.33 (1H, d, J = 2.4 Hz), 7.27-7.24 (1H, m), 4.76 (2H, d, J = 5.2 Hz), 4.03 (4H, s), 1.63 (6H, s). HRMS (M+H) calcd for $C_{16}H_{17}F_2N_4O_4$: 367.1218; found: 367.1230.

Example 29



N-((5-Chloropyridin-2-yl)methyl)-3-hydroxy-9,9-dimethyl-4-oxo-4,6,7,9-tetrahydropyrimido[2,1-c][1,4]oxazine-2-carboxamide. The title compound can be prepared from intermediate 103. ^{1}H NMR (500 MHz, $CDCl_3$) δ ppm: 11.80 (1H, brs), 8.64 (1H, brs), 8.57 (1H, d, J = 2.4 Hz), 7.78 (1H, dd, J = 8.6, 2.4 Hz), 7.44 (1H, d, J = 8.6 Hz), 4.72 (2H, d, J = 6.1 Hz), 4.02 (4H, s), 1.61 (6H, s). HRMS (M+H) calcd for $C_{17}H_{18}ClN_4O_4$: 365.1017; found: 365.1028. Anal calcd for $C_{16}H_{17}ClN_4O_4 \cdot 0.25H_2O \cdot 0.5\ CF_3CO_2H$: C, 47.90; H, 4.26; N, 13.14, Cl, 8.32; found: C, 47.88; H, 3.98; N, 12.94, Cl, 8.57.

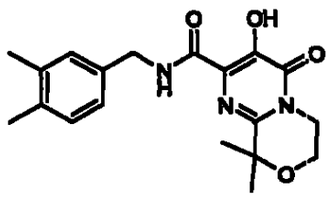
Example 30



Pyrimido[2,1-c][1,4]oxazine-2-carboxamide, N-[(3-bromo-4-fluorophenyl)methyl]-4,6,7,9-tetrahydro-3-hydroxy-9,9-dimethyl-4-oxo-. The title

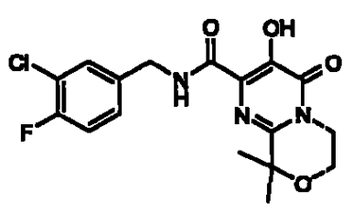
compound can be prepared from (3-bromo-4-fluorophenyl)methanamine Off white solid, ^{1}H-NMR (500 MHz, $CDCl_3$) δ ppm: 11.88 (1H, s), 7.76-7.84 (1H, br), 7.53 (1H, dd, J=6.3, 2.0 Hz), 7.26-7.29 (H, m), 7.07-7.14 (1H, m), 4.57 (2H, d, J=6.4 Hz), 4.02 (4H, s), 1.58 (6H, s). ^{13}C-NMR (126 MHz, $CDCl_3$) δ ppm: 168.41, 157.79, 151.99, 146.52, 134.91, 132.89, 128.44, 128.39, 125.30, 117.04, 116.86, 77.69, 75.84, 58.21, 43.22, 41.98, 28.11. HRMS $[M+H]^+$ calcd for $C_{17}H_{18}N_3O_4FBr$: 426.04648; found: 426.0468.

Example 31



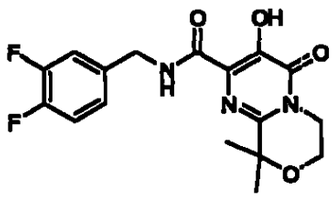
Pyrimido[2,1-c][1,4]oxazine-2-carboxamide, N-[(3,4-dimethylphenyl)methyl]-4,6,7,9-tetrahydro-3-hydroxy-9,9-dimethyl-4-oxo-. The title compound can be prepared from (3,4-dimethylphenyl)methanamine .Off white solid, ^{1}H-NMR (500 MHz, $CDCl_3$) δ ppm: 7.74 (1H), 7.04-7.15 (3H, m), 4.56 (2H, d, *J*=5.8 Hz), 4.00-4.07 (4H, m), 2.27 (3H, s), 2.26 (3H, s), 1.57 (6H, s). ^{13}C-NMR (126 MHz, $CDCl_3$) δ ppm: 167.92, 158.58, 151.61, 146.22, 137.37, 136.47, 134.53, 130.23, 129.11, 126.12, 125.12, 75.93, 58.10, 43.42, 43.00, 28.04, 19.85, 19.53. HRMS $[M+H]^+$ calcd for $C_{19}H_{24}N_3O_4$: 358.17669; found: 358.1783.

Example 32



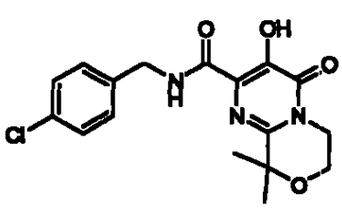
Pyrimido[2,1-c][1,4]oxazine-2-carboxamide, N-[(3-chloro-4-fluorophenyl)methyl]-4,6,7,9-tetrahydro-3-hydroxy-9,9-dimethyl-4-oxo-. The title compound can be prepared from (3-chloro-4-fluorophenyl)methanamine. Off white solid, ^{1}H-NMR (500 MHz, $CDCl_3$) δ ppm: 11.88 (1H, br s), 7.80 (1H, t, *J*=5.5 Hz), 7.38 (1H, dd, *J*=6.7, 2.1 Hz), 7.19-7.23 (1H, m), 7.13 (1H, t, *J*=8.5 Hz), 4.57 (2H, d, *J*=6.4 Hz), 4.02 (4H, s), 1.58 (6H, s). ^{13}C-NMR (126 MHz, $CDCl_3$) δ ppm: 168.41, 157.82, 151.99, 146.52, 134.54, 130.02, 127.58, 127.52, 125.32, 121.61, 117.18, 117.01, 75.84, 58.21, 43.23, 42.08, 28.11. HRMS $[M+H]^+$ calcd for $C_{17}H_{18}N_3O_4FCl$: 382.09644; found: 382.0980.

Example 33



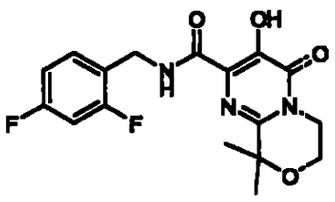
Pyrimido[2,1-c][1,4]oxazine-2-carboxamide, N-[(3,4-difluorophenyl)methyl]-4,6,7,9-tetrahydro-3-hydroxy-9,9-dimethyl-4-oxo-. The title compound can be prepared from (3,4-difluorophenyl)methanamine. Light brown solid, ^{1}H-NMR (500 MHz, $CDCl_3$) δ ppm: 7.77 (1H), 7.30-7.36 (2H, m), 7.27 (1H, s), 4.59 (2H, d, *J*=6.4 Hz), 4.01-4.06 (4H, m), 1.58 (6H, s). ^{13}C-NMR (126 MHz, $CDCl_3$) δ ppm: 168.22, 158.36, 151.98, 151.17, 146.35, 134.33, 125.74, 123.70, 123.67, 117.87, 117.73, 116.88, 116.73, 75.90, 58.13, 43.42, 42.28, 28.06. HRMS $[M+H]^+$ calcd for $C_{17}H_{18}N_3O_4F_2$: 366.12655; found: 365.1269.

Example 34



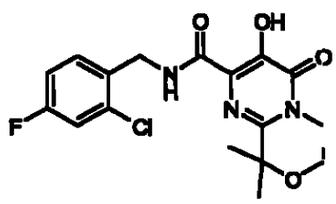
Pyrimido[2,1-c][1,4]oxazine-2-carboxamide, N-[(4-chlorophenyl)methyl]-4,6,7,9-tetrahydro-3-hydroxy-9,9-dimethyl-4-oxo-. The title compound can be prepared from (4-chlorophenyl)methanamine. Pale pink solid. ^{1}H-NMR (500 MHz, $CDCl_3$) δ ppm: 7.77 (1H, br), 7.33-7.35 (2H, m), 7.25-7.28 (2H, m), 4.59 (2H, d, *J*=6.4 Hz), 4.04 (4H, ddd, *J*=14.0, 7.9, 2.7 Hz), 1.58 (6H, s). ^{13}C-NMR (126 MHz, $CDCl_3$) δ ppm: 168.12, 158.48, 151.87, 146.28, 135.72, 133.98, 129.92, 129.18, 129.09, 125.90, 75.92, 58.12, 43.45, 42.61, 28.06. HRMS $[M+H]^+$ calcd for $C_{17}H_{19}N_3O_4Cl$: 364.10642; found: 364.1060.

Example 35



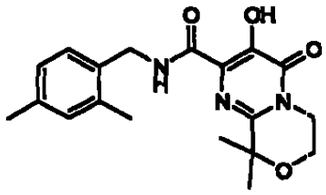
Pyrimido[2,1-c][1,4]oxazine-2-carboxamide, N-[(2,4-difluorophenyl)methyl]-4,6,7,9-tetrahydro-3-hydroxy-9,9-dimethyl-4-oxo-. The title compound can be prepared from (2,4-difluorophenyl)methanamine. Off white solid, ^{1}H-NMR (500 MHz, $CDCl_3$) δ ppm: 7.86 (1H, t, *J*=5.6 Hz), 7.34-7.40 (1H, m), 6.83-6.90 (2H, m), 4.62 (2H, d, *J*=6.4 Hz), 4.01-4.06 (4H, m), 1.59 (6H, s). ^{13}C-NMR (126 MHz, $CDCl_3$) δ ppm: 168.09, 158.43, 151.81, 146.22, 131.30, 131.25, 131.22, 131.18, 125.87, 120.37, 120.34, 111.85, 111.82, 111.68, 111.65, 104.47, 104.27, 104.07, 75.94, 58.12, 43.43, 37.00, 28.07. HRMS $[M+H]^+$ calcd for $C_{17}H_{18}N_3O_4F_2$: 366.12655; found: 366.1281.

Example 36



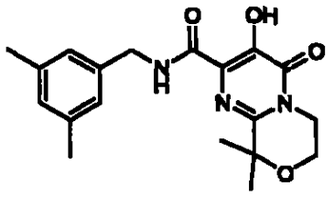
Pyrimido[2,1-c][1,4]oxazine-2-carboxamide, N-[(2-chloro-4-fluorophenyl)methyl]-4,6,7,9-tetrahydro-3-hydroxy-9,9-dimethyl-4-oxo-. The title compound can be prepared from (2-chloro-4-fluorophenyl)methanamine. Off white solid, ^{1}H-NMR (500 MHz, $CDCl_3$) δ ppm: 8.05 (1H, br), 7.41 (1H, dd, *J*=8.4, 6.0 Hz), 7.17 (1H, dd, *J*=8.2, 2.4 Hz), 6.99 (1H, td, *J*=8.2, 2.7 Hz), 4.66 (2H, d, *J*=6.4 Hz), 4.04 (4H, s), 1.60 (6H, s). ^{13}C-NMR (126 MHz, $CDCl_3$) δ ppm: 167.88, 163.30, 161.31, 158.70, 151.77, 146.08, 134.55, 134.47, 131.65, 131.58, 130.70, 130.67, 126.12, 117.48, 117.28, 114.68, 114.51, 109.67, 75.99, 58.10, 43.51, 40.82, 28.08. HRMS $[M+H]^+$ calcd for $C_{17}H_{18}N_3O_4FCl$: 382.09644; found: 382.0987.

Example 37



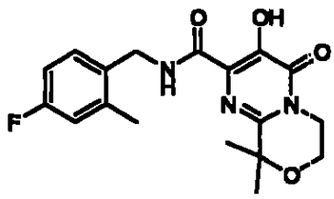
Pyrimido[2,1-c][1,4]oxazine-2-carboxamide, N-[(2,4-dimethylphenyl)methyl]-4,6,7,9-tetrahydro-3-hydroxy-9,9-dimethyl-4-oxo-. The title compound can be prepared from (2,4-dimethylphenyl)methanamine. Off white solid, ^{1}H-NMR (500 MHz, $CDCl_3$) δ ppm: 12.08 (1H, brs), 7.63 (1H, br), 7.15 (1H, d, *J*=7.6 Hz), 7.00-7.05 (2H, m), 4.57 (2H, d, *J*=5.8 Hz), 4.01 (4H, s), 2.32 (3H, s), 2.32 (3H, s), 1.55 (6H, s). ^{13}C-NMR (126 MHz, $CDCl_3$) δ ppm: 167.97, 157.98, 151.74, 146.35, 137.95, 136.22, 131.90, 131.67, 128.38, 127.10, 125.64, 75.84, 58.21, 43.21, 41.15, 28.07, 21.11, 19.13. HRMS $[M+H]^+$ calcd for $C_{19}H_{24}N_3O_4$: 358.17669; found: 358.1771.

Example 38



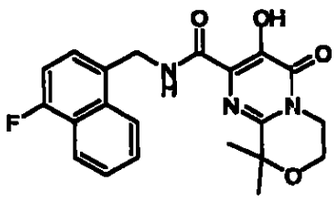
Pyrimido[2,1-c][1,4]oxazine-2-carboxamide, N-[(3,5-dimethylphenyl)methyl]-4,6,7,9-tetrahydro-3-hydroxy-9,9-dimethyl-4-oxo-. The title compound can be prepared from (3,5-dimethylphenyl)methanamine. Off white solid, ^{1}H-NMR (500 MHz, $CDCl_3$) δ ppm: 12.09 (1H, s), 7.72-7.80 (1H, br), 6.95 (1H, s), 6.94 (2H, s), 4.55 (2H, d, *J*=6.4 Hz), 4.00-4.04 (4H, s), 2.32 (6H, s), 1.57 (6H, s). ^{13}C-NMR (126 MHz, $CDCl_3$) δ ppm: 168.19, 157.89, 151.73, 146.44, 138.71, 137.25, 129.58, 125.61, 125.48, 75.86, 58.23, 43.18, 43.06, 28.08, 21.38. HRMS $[M+H]^+$ calcd for $C_{19}H_{24}N_3O_4$: 358.17669; found: 358.1758.

Example 39



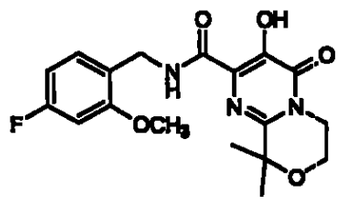
Pyrimido[2,1-c][1,4]oxazine-2-carboxamide, N-[(4-fluoro-2-methylphenyl)methyl]-4,6,7,9-tetrahydro-3-hydroxy-9,9-dimethyl-4-oxo-. The title compound can be prepared from (4-fluoro-2-methylphenyl)methanamine. Off white solid, ^{1}H-NMR (500 MHz, $CDCl_3$) δ ppm: 11.97 (1H, s), 7.64 (1H, br), 7.23 (1H, dd, *J*=8.2, 5.8 Hz), 6.87-6.94 (2H, m), 4.57 (2H, d, *J*=6.1 Hz), 4.02 (4H, s), 2.36 (3H, s), 1.56 (6H, s). ^{13}C-NMR (126 MHz, $CDCl_3$) δ ppm: 168.07, 163.40, 161.44, 157.82, 151.86, 146.43, 138.81, 138.75, 130.78, 130.75, 129.97, 129.90, 125.42, 117.69, 117.52, 113.20, 113.03, 75.81, 58.23, 43.21, 40.71, 28.09, 19.32. HRMS $[M+H]^+$ calcd for $C_{18}H_{21}N_3O_4F$: 362.15162; found: 362.1521.

Example 40



Pyrimido[2,1-c][1,4]oxazine-2-carboxamide, N-[(4-fluoro-1-naphthalenyl)methyl]-4,6,7,9-tetrahydro-3-hydroxy-9,9-dimethyl-4-oxo-. The title compound can be prepared from intermediate 37. White solid. ^{1}H-NMR (500 MHz, $CDCl_3$) δ ppm:12.00 (1H, s), 8.15-8.20 (1H, m), 8.05 (1H, d, *J*=8.2 Hz), 7.73 (1H, br), 7.58-7.65 (2H, m), 7.43 (1H, dd, *J*=7.8, 5.3 Hz), 7.12 (1H, dd, *J*=10.1, 7.9 Hz), 5.02 (2H, d, *J*=6.1 Hz), 3.99 (4H, ddd, *J*=13.8, 8.0, 2.9 Hz), 1.49 (6H, s). ^{13}C-NMR (126 MHz, $CDCl_3$) δ ppm: 168.01, 160.13, 158.12, 157.77, 151.87, 146.51, 132.72, 132.68, 128.59, 128.56, 127.86, 126.54, 126.46, 125.42, 124.45, 123.23, 121.65, 121.60, 109.00, 108.84, 75.76, 58.21, 43.14, 40.86, 27.99. HRMS $[M+H]^+$ calcd for $C_{21}H_{21}N_3O_4F$: 398.15162; found: 398.1536.

Example 41



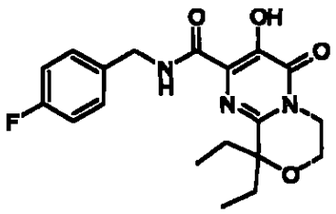
Pyrimido[2,1-c][1,4]oxazine-2-carboxamide, N-[(4-fluoro-2-methoxyphenyl)methyl]-4,6,7,9-tetrahydro-3-hydroxy-9,9-dimethyl-4-oxo-. The title compound can be prepared from (4-fluoro-2-methoxyphenyl)methanamine. HRMS $[M+H]^+$ calcd for $C_{18}H_2FN_3O_5$: 378.1465; found: 378.1480. Light yellow crystals; ^{1}H NMR ($CDCl_3$, 500 MHz) δ ppm: 1.58 (6H. s, gem-di-Me), 3.88 (3H, s, OMe), 4.00 (4H, s, CH_2), 4.53 (2H, d, J = 6.5 Hz, CH_2), 6.61-6.64 (2H, m, Ar-Hs), 7.24 (1H, m, Ar-Hs); ^{13}C NMR ($CDCl_3$, 125.8 Hz) δ ppm: 28.03 (CH_3), 38.79 (CH_2), 43.09 (CH_2),

55.72 (CH_3), 58.27 (CH_2), 75.78 (C), 99.15, 99.35 (d, J = 27 Hz, CH), 106.97, 107.14 (d, J = 21 Hz, CH), 121.17, 121.20 (d, J = 3.8 Hz, C), 125.75 (C), 130.44, 130.51 (d, J = 9.6 Hz, CH), 146.26 (C), 151.50 (C), 157.87 (C=O), 158.77, 158.83 (d, J = 9.6 Hz, C), 162.63, 164.48 (d, J = 234 Hz, CF), 167.81 (C=O); HRMS (ESI) calcd for $C_{18}H_{21}FN_3O_5$ (M+H) 378.1465, found 378.1480; UV (MeOH) λmax 219 nm (ε $1.66x10^4$), 245 (ε $9.69x10^3$), 305 (ε $7.70x10^3$); Anal. Calcd for $C_{18}H_{20}FN_3O_5 \cdot 0.2H_2O$: C 55.95, H 5.48, N 10.88; found C 55.99, H 5.11, N 10.63.

Examples 42-43

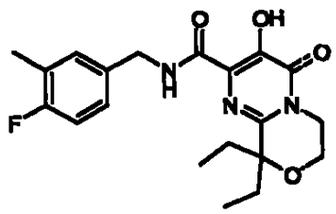
Examples 42-43 can be prepared from intermediate 31, ethyl 9,9-diethyl-3-hydroxy-4-oxo-4,6,7,9-tetrahydropyrimido[2,1-c][1,4]oxazine-2-carboxylate and the indicated amines according to the methods described for examples 1, 19 and 20.

Example 42



Pyrimido[2,1-c][1,4]oxazine-2-carboxamide, 9,9-diethyl-N-[(4-fluorophenyl)methyl]-4,6,7,9-tetrahydro-3-hydroxy-4-oxo-. The title compound can be prepared from 4-fluorobenzylamine. ^1H NMR (500 MHz, $CDCl_3$) δ ppm: 11.96 (1H, br), 7.76 (1H, br), 7.30 (2H, m), 7.06 (2H, m), 4.58 (2H, d, *J* = 6.4 Hz), 4.00, (4H, m), 1.93 (2H, m), 1.86 (2H, m), 0.86 (6H, t, *J* = 7.3 Hz). ^{13}C NMR (500 MHz, $CDCl_3$) δ ppm: 168.36, 163.46, 157.87, 151.61, 143.23, 133.14, 129.50, 125.58, 115.99, 115.82, 80.89, 58.46, 43.13, 42.50, 31.36, 7.79. HRMS $[M+H]^+$ calcd for $C_{19}H_{23}N_3O_4F$: 376.16727; found: 376.1675.

Example 43

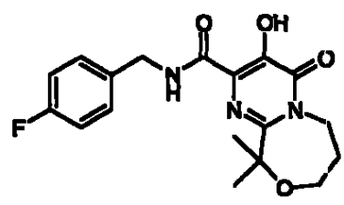


Pyrimido[2,1-c][1,4]oxazine-2-carboxamide, 9,9-diethyl-N-[(4-fluoro-3-methylphenyl)methyl]-4,6,7,9-tetrahydro-3-hydroxy-4-oxo-). The title compound can be prepared from 3-methyl, 4-fluorobenzylamine. ^{1}H NMR (500 MHz, $CDCl_3$) δ ppm: 11.99 (1H, br), 7.74 (1H, br), 7.15-7.09 (2H, m), 6.99 (1H, m), 4.54 (2H, d, J= 6.1 Hz), 4.00, (4H, m), 2.27 (1H, s), 1.93 (2H, m), 1.86 (2H, m), 0.84 (6H, t, J=7.3 Hz). ^{13}C NMR (126 MHz, $CDCl_3$) δ ppm: 168.32, 161.97, 160.02, 157.84, 151.56, 146.23, 132.83, 130.96, 126.64, 125.59, 115.38, 80.88, 58.48, 43.11, 42.52, 31.36, 14.66, 7.79. HRMS $[M+H]^+$ calcd for $C_{20}H_{25}N_3O_4F$: 390.18292; found: 390.1835.

Examples 44-45

Examples 44-45 can be prepared from intermediate 36, 3-hydroxy-10,10-dimethyl-4-oxo-6,7,8,10-tetrahydro-4H-pyrimido[2,1-c][1,4]oxazepine-2-carboxylate and the indicated amines according to the methods described for examples 1, 19 and 20.

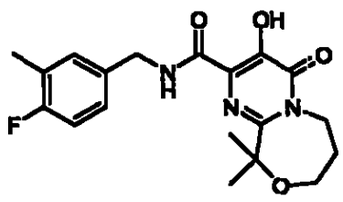
Example 44



6H-Pyrimido[2,1-c][1,4]oxazepine-2-carboxamide, N-[(4-fluorophenyl)methyl]-4,7,8,10-tetrahydro-3-hydroxy-10,10-dimethyl-4-oxo-. The

title compound can be prepared from 4-fluorobenzylamine ^{1}H NMR (500 MHz, $CDCl_3$) δ ppm: 11.97 (1H, s), 7.72 (1H, br), 7.31 (1H, d, J = 8.5 Hz), 7.30 (1H, d, J = 8.5 Hz), 7.05 (1H, t, J = 8.5 Hz), 4.58 (2H, d, J = 6.4 Hz), 4.57 (2H, br), 3.67 (2H, t, J = 6.4 Hz), 1.95 (2H, p, J = 6.1 Hz), 1.57 (6H, s). ^{13}C NMR (126 MHz, $CDCl_3$) δ ppm: 168.32, 163.45, 161.49, 158.20, 153.63, 147.44, 133.17, 129.50, 129.43, 124.70, 115.97, 115.81, 82.29, 60.87, 42.47, 38.68, 27.82, 27.30. HRMS $[M+H]^+$ calcd for $C_{18}H_{21}N_3O_4F$: 362.15162; found: 362.1530.

Example 45

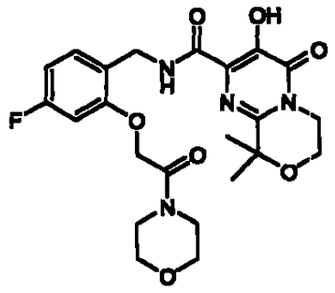


6H-Pyrimido[2,1-c][1,4]oxazepine-2-carboxamide, N-[(4-fluoro-3-methylphenyl)methyl]-4,7,8,10-tetrahydro-3-hydroxy-10,10-dimethyl-4-oxo-. The title compound can be prepared from 3-methyl, 4-fluorobenzylamine. ^{1}H NMR (500 MHz, $CDCl_3$) δ ppm: 12.00 (1H, s), 7.70 (1H, br), 7.14 (1H, m), 7.1 (1H, m), 6.98 (1H, t, J = 8.9 Hz), 4.56 (2H, br), 4.54 (2H, d, J = 6.4 Hz), 3.68 (2H, t, J = 6.4 Hz), 2.27 (3H, s), 1.95 (2H, p, J = 6.1 Hz), 1.57 (6H, s). ^{13}C NMR (126 MHz, $CDCl_3$) δ ppm: 168.26, 164.98, 160.02, 158.22, 153.59, 147.44, 132.82, 130.97, 126.58, 125.46, 124.75, 115.38, 82.30, 60.87, 42.51, 38.68, 27.83, 27.31, 14.66. HRMS $[M+H]^+$ calcd for $C_{19}H_{23}N_3O_4F$: 376.16727; found: 376.1686.

Examples 46-51

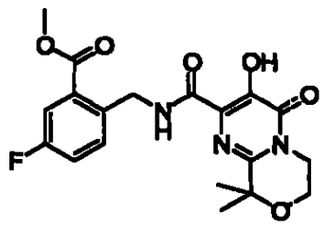
Examples 46-52 can be prepared from the indicated intermediates according to the method provide for example 46.

Example 46



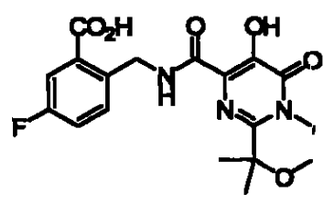
Pyrimido[2,1-c][1,4]oxazine-2-carboxamide, N-[[4-fluoro-2-[2-(4-morpholinyl)-2-oxoethoxy]phenyl]methyl]-4,6,7,9-tetrahydro-3-hydroxy-9,9-dimethyl-4-oxo-. A solution of intermediate 157, 3-benzyloxy-9,9-dimethyl-4-oxo-4,6,7,9-tetrahydro-pyrimido[2,1-c][1,4]oxazine-2-carboxylic acid 4-fluoro-2-(2-morpholin-4-yl-2-oxo-ethoxy)-benzylamide, (187 mg, 0.32 mmol) in trifluoroacetic acid (2 mL) was stirred at room temperature for 2.5 hrs, after which the mixture was concentrated *in vacuo* to dryness. The residual oil was crystallized from 95% ethanol to provide 120 mg (0.25 mmol, Yield 77%) of the title compound as a white crystalline powder: ^{1}H NMR ($CDCl_3$, 500 MHz) δ ppm: 1.57 (6H, s, Me), 3.51, 3.64 (4H, brs, NCH_2), 3.70 (4H, m, OCH_2), 3.99 (4H, s, NCH_2, OCH_2), 4.60 (2H, d, J = 6 Hz, NCH_2), 4.76 (2H, s, OCH_2), 6.59 (1H, dd, J = 10, 2.5 Hz, Ar-H), 6.63 (1H, dt, J = 2.5, 8 Hz, Ar-H), 7.29 (1H, dd, J = 6.5, 8.5 Hz, Ar-H), 8.25 (1H, t, J = 6 Hz, NH), 12.2 (br, OH). ^{13}C NMR ($CDCl_3$, 125.77 Hz) δ ppm: 27.93 (CH_3), 38.44 (NCH_2), 42.39 (NCH_2), 43.14 (NCH_2), 45.31 (NCH_2), 58.19 (OCH_2), 66.40 (OCH_2), 66.59, 66.86 (OCH_2), 75.94 (C), 100.26, 100.46 (d, J = 26 Hz, CH), 108.19, 108.36 (d, J = 21 Hz, CH), 122.03, 122.06 (d, J = 3 Hz, C), 125.84 (C), 131.06, 131.14 (d, J = 11 Hz, CH), 146.37 (C), 151.46 (C), 157.06, 157.14 (d, J = 11 Hz, C), 157.96 (C=O), 162.25, 164.21 (d, J = 248 Hz, CF), 165.47 (C=O), 168.23 (C=O); HRMS calcd for $C_{23}H_{28}N_4O_7F$ (M+H) 491.1942, found 491.1958; UV (MeOH) λmax 249 nm (ε $7.84x10^3$), 290 nm (ε $3.06x10^3$), 303 nm (ε $2.2x10^3$); Anal. Calcd for $C_{23}H_{27}N_4O_7F \cdot 1.7H_2O$: C 53.01, H 5.88, N 10.75; found C 52.53, H 5.37, N 10.48.

Example 47



Benzoic acid, 5-fluoro-2-[[[(4,6,7,9-tetrahydro-3-hydroxy-9,9-dimethyl-4-oxopyrimido[2,1-c][1,4]oxazin-2-yl)carbonyl]amino]methyl]-, methyl ester. The title compound can be prepared from intermediate 154, methyl 2-((3-(benzyloxy)-9,9-dimethyl-4-oxo-4,6,7,9-tetrahydropyrimido[2,1-c][1,4]oxazine-2-carboxamido)methyl)-5-fluorobenzoate. White solid; ^{1}H NMR (300 MHz, $CDCl_3$) δ ppm: 11.94 (1H, br s), 8.76 (1H, t, *J*=6.77 Hz), 7.69 (1H, dd, *J*=9.2, 2.9 Hz), 7.53 (1H, dd, *J*=8.4, 5.5 Hz), 7.15-7.22 (1H, m), 4.71 (2H, d, *J*=7.0 Hz), 3.97 (4H, s), 3.89-3.94 (3H, m), 1.56 (6H, s); HRMS (ESI) calcd for $C_{19}H_{20}FN_4O_6$ (M+H) 406.1414, found 406.1432.

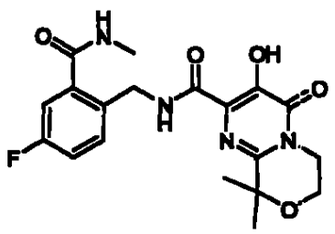
Example 48



Benzoic acid, 5-fluoro-2-[[[(4,6,7,9-tetrahydro-3-hydroxy-9,9-dimethyl-4-oxopyrimido[2,1-c][1,4]oxazin-2-yl)carbonyl]amino]methyl]-. The title compound can be prepared from intermediate 190, 2-((3-(benzyloxy)-9,9-dimethyl-4-oxo-4,6,7,9-tetrahydropyrimido[2,1-c][1,4]oxazine-2-carboxamido)methyl)-5-fluorobenzoic acid. White solid; ^{1}H NMR (500 MHz, $CDCl_3$) δ ppm: 11.92 (1H, br s), 8.68 (1H, t, *J*=6.4 Hz), 7.80 (1H, dd, *J*=8.7, 2.6 Hz), 7.60 (1H, dd, *J*=8.5, 5.5 Hz),

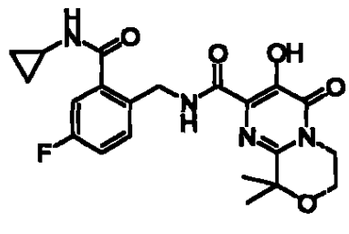
7.30 (1H, dt, *J*=8.1, 2.8 Hz), 4.78 (2H, d, *J*=6.7 Hz), 4.00 (4H, s), 1.58 (6H, s); HRMS (ESI) calcd for $C_{18}H_{18}FN_3O_6$ (M+H) 392.1258, found 392.1250.

Example 49



Pyrimido[2,1-c][1,4]oxazine-2-carboxamide, N-[[4-fluoro-2-[(methylamino)carbonyl]phenyl]methyl]-4,6,7,9-tetrahydro-3-hydroxy-9,9-dimethyl-4-oxo-. The title compound can be prepared from intermediate 143, N-(4-fluoro-2-(methylcarbamoyl)benzyl)-3-(benzyloxy)-9,9-dimethyl-4-oxo-4,6,7,9-tetrahydropyrimido[2,1-c][1,4]oxazine-2-carboxamide. ^{1}H NMR (500 MHz, DMSO-d_6) δ ppm: 11.97 (1H, br s), 9.46 (1H, br s), 8.55-8.51 (1H, m), 7.40-7.38 (1H, m), 7.32-7.27 (2H, m), 4.56 (2H, d, J = 6.1 Hz), 3.97 (2H, t, J = 4.9 Hz), 3.82 (2H, t, J = 4.9 Hz), 2.80 (3H, d, J = 4.6 Hz), 1.55 (6H, s). HRMS (M+H) calcd for $C_{19}H_{22}FN_4O_5$: 405.1574; found: 405.1588.

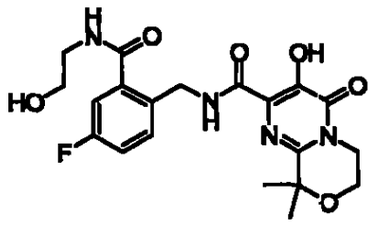
Example 50



Pyrimido[2,1-c][1,4]oxazine-2-carboxamide, N-[[2-[(cyclopropylamino)carbonyl]-4-fluorophenyl]methyl]-4,6,7,9-tetrahydro-3-hydroxy-9,9-dimethyl-4-oxo-. The title compound can be prepared from intermediate 155, N-(2-(cyclopropylcarbamoyl)-4-fluorobenzyl)-3-(benzyloxy)-9,9-dimethyl-4-oxo-

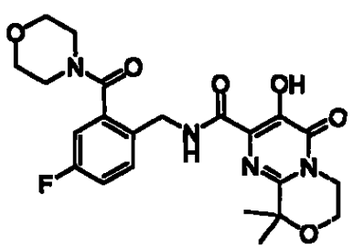
4,6,7,9-tetrahydropyrimido[2,1-c][1,4]oxazine-2-carboxamide. White solid; ^{1}H NMR (300 MHz, $CDCl_3$) δ ppm: 11.98 (1H, br s), 8.84 (1H, t, *J*=7.32 Hz), 7.48 (1H, dd, *J*=9.0, 5.3 Hz), 7.05-7.16 (2H, m), 6.20-6.31 (1H, br s), 4.56 (2 H, d, *J*=6.6 Hz), 3.92-4.02 (4H, m), 2.90 (1H, dt, *J*=7.1, 3.3 Hz), 1.59 (6H, s), 0.88 (2H, q, *J*=6.6 Hz), 0.57-0.66 (2H, m); HRMS (ESI) calcd for $C_{21}H_{23}FN_4O_5$ (M+H) 431.1731, found 431.1734.

Example 51



Pyrimido[2,1-c][1,4]oxazine-2-carboxamide, N-[[4-fluoro-2-[[(2-hydroxyethyl)amino]carbonyl]phenyl]methyl]-4,6,7,9-tetrahydro-3-hydroxy-9,9-dimethyl-4-oxo-. The title compound can be prepared from intermediate 191, N-(2-((2-aminoethyl)carbamoyl)-4-fluorobenzyl)-3-(benzyloxy)-9,9-dimethyl-4-oxo-4,6,7,9-tetrahydropyrimido[2,1-c][1,4]oxazine-2-carboxamide. ^{1}H NMR (500 MHz, $CDCl_3$) δ ppm: 11.98 (1H, br s), 8.88 (1H, t, *J*=6.0 Hz), 7.51 (1H, dd, *J*=8.2, 5.5 Hz), 7.21 (1H, dd, *J*=8.5, 2.8 Hz), 7.14 (1H, dt, *J*=8.3, 2.6 Hz), 6.57-6.63 (1H, m), 4.58 (2H, d, *J*=6.7 Hz), 4.00 (4H, s), 3.87 (2H, t, *J*=5.1 Hz), 3.63-3.68 (2H, m), 1.60 (6H, s); HRMS (ESI) calcd for $C_{20}H_{23}FN_4O_6$ (M+H) 435.1680, found 435.1700.

Example 52

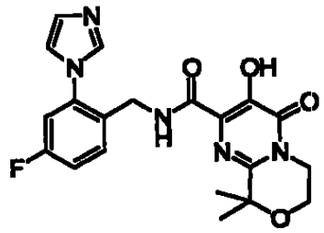


Pyrimido[2,1-c][1,4]oxazine-2-carboxamide, N-[[4-fluoro-2-(4-morpholinylcarbonyl)phenyl]methyl]-4,6,7,9-tetrahydro-3-hydroxy-9,9-dimethyl-4-oxo-. The title compound can be prepared from intermediate 156, N-(4-fluoro-2-(morpholine-4-carbonyl)benzyl)-3-(benzyloxy)-9,9-dimethyl-4-oxo-4,6,7,9-tetrahydropyrimido[2,1-c][1,4]oxazine-2-carboxamide. White solid; ^{1}H NMR (500 MHz, $CDCl_3$) δ ppm: 11.94 (1H, s), 8.46 (1H, t, *J*=5.5 Hz), 7.47 (1H, dd, *J*=8.5, 5.5 Hz), 7.10 (1H, dt, *J*=8.4, 2.4 Hz), 6.94 (1H, dd, *J*=8.2, 2.4 Hz), 4.00 (4H, s), 3.79-3.88 (2H, br), 3.78 (2H, br), 3.61 (2H, br), 3.31-3.40 (2H, br), 1.61 (6H, s); HRMS (ESI) calcd for $C_{22}H_{25}FN_4O_6$ (M+H) 461.1836, found 461.1852.

Example 53-60

Examples 53-60 can be prepared from intermediate 25, ethyl 3-hydroxy-9,9-dimethyl-4-oxo-4,6,7,9-tetrahydropyrimido[2,1-c][1,4]oxazine-2-carboxylate and the indicated amines according to the method described for the synthesis of examples 1, 19 and 20.

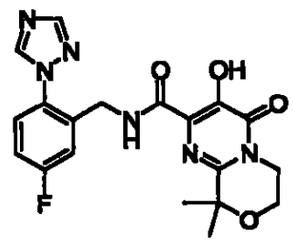
Example 53



Pyrimido[2,1-c][1,4]oxazine-2-carboxamide, N-[[4-fluoro-2-(1H-imidazol-1-yl)phenyl]methyl]-4,6,7,9-tetrahydro-3-hydroxy-9,9-dimethyl-4-oxo-. The title compound can be prepared from intermediate 89. ^{1}H-NMR (500 MHz, $CDCl_3$) δ ppm: 11.66 (1H, bs), 8.07 (1H, s), 7.74 (1H, t, J = 5.5 Hz), 7.57 (1H, dd, J= 8.7, 5.9 Hz), 7.35 (1H, s), 7.25-7.21 (2H, m), 7.08 (1H, dd, J = 8.2, 2.4 Hz), 4.42 (2H, d, J = 6.4 Hz), 4.01 (4H, s), 1.59 (6H, s). HRMS $[M+H]^+$ calcd for $C_{20}H_{21}N_5O_4F$:

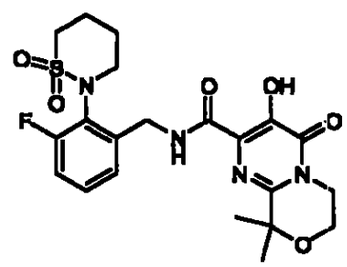
414.15777; found: 414.1563. Anal calcd for $C_{20}H_{20}N_5O_4F \cdot 0.25\ H_2O$: C, 57.48; H, 4.94; N, 16.76; F, 4.55; found: C, 57.77; H, 4.89; N, 16.29; F, 4.48.

Example 54



Pyrimido[2,1-c][1,4]oxazine-2-carboxamide, N-[[5-fluoro-2-(1H-1,2,4-triazol-1-yl)phenyl]methyl]-4,6,7,9-tetrahydro-3-hydroxy-9,9-dimethyl-4-oxo-e. The title compound can be prepared from intermediate 97. ^{1}H NMR (500 MHz, $CDCl_3$) δ ppm: 11.82 (1H, s), 8.70 (1H, t, J = 6.5 Hz), 8.39 (1H, s), 8.17 (1H, s), 7.40 (1H, dd, J = 8.6, 2.7 Hz), 7.34 (1H, dd, J = 8.9, 4.9 Hz), 7.17-7.13 (1H, m), 4.44 (2H, d, J = 6.7 Hz), 4.01 (4H, s), 1.62 (6H, s). HRMS (M+H) calcd for $C_{19}H_{20}FN_6O_4$: 415.1530; found: 415.1544. Anal calcd for $C_{19}H_{19}FN_6O_4$: C, 55.07; H, 4.62; N, 20.28, F, 4.58; found: C, 54.83; H, 4.51; N, 19.89, F, 4.56.

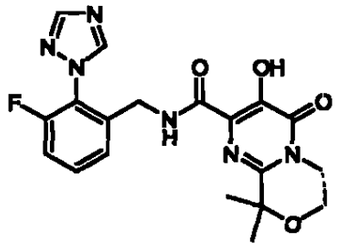
Example 55



Pyrimido[2,1-c][1,4]oxazine-2-carboxamide, N-[[3-fluoro-2-(tetrahydro-1,1-dioxido-2H-1,2-thiazin-2-yl)phenyl]methyl]-4,6,7,9-tetrahydro-3-hydroxy-9,9-dimethyl-4-oxo-. The title compound can be prepared from intermediate 93. White solid. 36% yield. ^{1}H-NMR (500 MHz, $CDCl_3$) δ ppm: 11.96 (1H, s), 8.42-8.39 (2H,

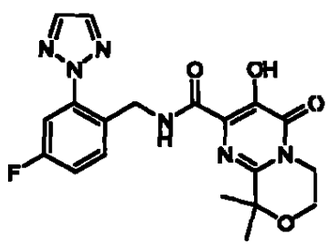
m), 7.14-7.11 (1H, m), 4.97 (1H, dd J = 14.3, 8.8 Hz), 4.37 (1H, dd, J = 14.3, 4.0 Hz), 4.00 (4H, s), 3.86-3.80 (1H, m), 3.75-3.70 (1H, m), 3.34-3.24 (2H, m), 2.44-2.39 (2H, m), 2.08-2.00 (1H, m), 1.83-1.77 (1H, m), 1.60 (3H, s), 1.57 (3H, s). HRMS $[M+H]^+$ calcd for $C_{21}H_{26}N_4O_6FS$: 481.15572; found: 481.1559. Anal calcd for $C_{21}H_{25}N_4O_6FS$: C, 52.49; H, 5.24; N, 11.66; S, 6.67; F, 3.95; found: C, 52.43; H, 5.21; N, 11.61; S, 6.56; F, 4.16.

Example 56



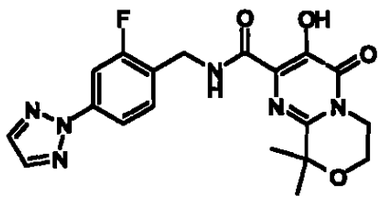
Pyrimido[2,1-c][1,4]oxazine-2-carboxamide, N-[[3-fluoro-2-(1H-1,2,4-triazol-1-yl)phenyl]methyl]-4,6,7,9-tetrahydro-3-hydroxy-9,9-dimethyl-4-oxo-. The title compound can be prepared from intermediate 95. White solid. ^{1}H-NMR (500 MHz, $CDCl_3$) δ ppm: 11.86 (1H, s), 8.76 (1H, brs), 8.46 (1H, d, J = 3.0 Hz), 8.22 (1H, s), 7.48-7.47 (2H, m), 7.29-7.26 (1H, m), 4.44 (2H, d, J = 6.7 Hz), 4.01 (4H, s), 1.63 (6H, s). HRMS $[M+H]^+$ calcd for $C_{19}H_{20}N_6O_4F$: 415.15302; found: 415.1541. Anal calcd for $C_{19}H_{19}N_6O_4F$: C, 55.07; H, 4.62; N, 20.28; F, 4.58; found: C, 55.18; H, 4.42; N, 20.17; F, 4.51.

Example 57



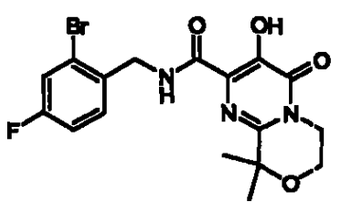
Pyrimido[2,1-c][1,4]oxazine-2-carboxamide, N-[[4-fluoro-2-(2H-1,2,3-triazol-2-yl)phenyl]methyl]-4,6,7,9-tetrahydro-3-hydroxy-9,9-dimethyl-4-oxo-. The title compound can be prepared from intermediate 77. Pale orange solid. ^{1}H-NMR (300 MHz, $CDCl_3$) δ ppm: 11.99 (1H, s), 8.99 (1H, t, J = 6.4 Hz), 7.91 (2H, s), 7.65-7.58 (2H, m), 7.10 (1H, td, J = 8.1, 2.6 Hz), 4.61 (2H, d, J = 7.0 Hz), 3.97 (4H, s), 1.55 (6H, s). HRMS $[M-H]^-$ calcd for $C_{19}H_{18}N_6O_4F$: 413.13736; found: 413.1354. Anal calcd for $C_{19}H_{17}N_6O_4F$: C, 55.07; H, 4.62; N, 20.28; F, 4.58; found: C, 54.94; H, 4.78; N, 20.32; F, 4.53.

Example 58



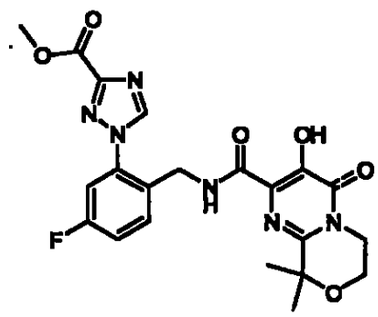
Pyrimido[2,1-c][1,4]oxazine-2-carboxamide, N-[[2-fluoro-4-(2H-1,2,3-triazol-2-yl)phenyl]methyl]-4,6,7,9-tetrahydro-3-hydroxy-9,9-dimethyl-4-oxo-. The title compound can be prepared from intermediate 77. Pale brown solid ^{1}H-NMR (300 MHz, $CDCl_3$) δ ppm: 11.85 (1H, s), 7.88-7.82 (3H, m), 7.79 (2H, s), 7.47 (1H, t, J = 8.3 Hz), 4.67 (2H, d, J = 6.2 Hz), 3.99 (4H, s), 1.56 (6H, s). HRMS $[M+H]^+$ calcd for $C_{19}H_{20}N_6O_4F$: 415.15302; found: 415.1513. Anal calcd for $C_{19}H_{19}N_6O_4F$: C, 55.07; H, 4.62; N, 20.28; F, 4.58; found: C, 54.94; H, 4.76; N, 19.94; F, 4.26.

Example 59



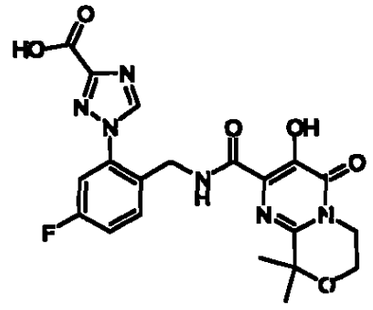
Pyrimido[2,1-c][1,4]oxazine-2-carboxamide, N-[(2-bromo-4-fluorophenyl)methyl]-4,6,7,9-tetrahydro-3-hydroxy-9,9-dimethyl-4-oxo-. The title compound can be prepared from (2-bromo-4-fluorophenyl)methanamine. White needles. ^{1}H-NMR (300 MHz, $CDCl_3$) δ ppm: 11.78 (1H, s), 8.08 (1H, t, J = 6.0 Hz), 7.39 (1H, dd, J = 8.8, 5.8 Hz), 7.31 (1H, dd, J = 8.0, 2,6 Hz), 7.01 (1H, dt, J = 8.2, 2.6 Hz), 4.61 (2H, d, J = 6.6 Hz), 3.99 (4H, s), 1.56 (6H, s). HRMS $[M+H]^+$ calcd for $C_{17}H_{18}N_3O_4FBr$: 426.04648; found: 426.0465.

Example 60



1H-1,2,4-Triazole-3-carboxylic acid, 1-[5-fluoro-2-[[[(4,6,7,9-tetrahydro-3-hydroxy-9,9-dimethyl-4-oxopyrimido[2,1-c][1,4]oxazin-2-yl)carbonyl]amino]methyl]phenyl]-, methyl este. The title compound can be prepared from intermediate 91. White solid. ^{1}H-NMR (300 MHz, $CDCl_3$) δ ppm: 11.90 (1H, s), 8.49 (1H, s), 8.36 (1H, t, J = 6.2 Hz), 7.72 (1H, dd, J = 8.8, 5.9 Hz), 7.26-7.20 (1H, m), 7.14 (1H, dd, J = 8.4, 2,6 Hz), 4.49 (2H, d, J = 6.6 Hz), 4.01 (3H, s), 3.98 (4H, s), 1.58 (6H, s). HRMS $[M+H]^+$ calcd for $C_{21}H_{22}N_6O_6F$: 473.1585; found: 473.1563. Anal calcd for $C_{21}H_{21}N_6O_6F \cdot 0.5\ H_2O$: C, 52.39; H, 4.61; N, 17.46; F, 3.95; found: C, 52.14; H, 4.70; N, 17.41; F, 4.12.

Example 61

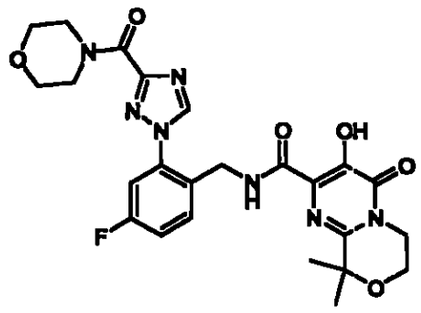


1H-1,2,4-Triazole-3-carboxylic acid, 1-[5-fluoro-2-[[[(4,6,7,9-tetrahydro-3-hydroxy-9,9-dimethyl-4-oxopyrimido[2,1-c][1,4]oxazin-2-yl)carbonyl]amino]methyl]phenyl]-. To a solution of example 60, 1H-1,2,4-triazole-3-carboxylic acid, 1-[5-fluoro-2-[[[(4,6,7,9-tetrahydro-3-hydroxy-9,9-dimethyl-4-oxopyrimido[2,1-c][1,4]oxazin-2-yl)carbonyl]amino]methyl]phenyl]-, methyl ester, (2.156g, 4.6 mmol) in tetrahydrofuran (200 mL) and water (50 mL) at 0° C was added lithium hydroxide monohydrate (0.58 g, 13.8 mmol). The mixture was stirred at 0° C 2 h and at room temp for 1 h. The resulting solution was partitioned between ethyl acetate and water. The aqueous phase was acidified with 1 N HCl and extracted with ethyl acetate and CH_2Cl_2. The organic extracts were combined, dried (Na_2SO_4) and concentrated to give the title compound as a white solid (2.05 g, 97% yield). ^{1}H-NMR (300 MHz, $CDCl_3$) δ ppm: 11.91 (1H, bs), 8.55 (1H, s), 8.43 (1H, t, J = 6.6 Hz), 7.77 (1H, dd, J = 8.8, 5.9 Hz), 7.28-7.23 (1H, m), 7.16 (1H, dd, J = 8.0, 2.6 Hz), 4.47 (2H, d, J = 6.9 Hz), 3.98 (4H, s), 1.59 (6H, s). HRMS $[M+H]^+$ calcd for $C_{20}H_{20}N_6O_6F$: 459.14285; found: 459.1442.

Examples 62-72

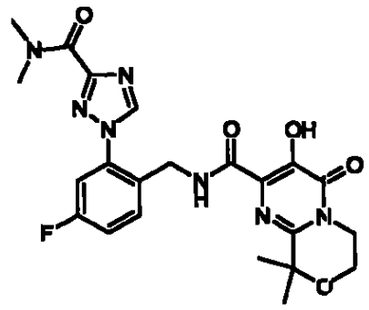
Examples 62-72 can be prepared from intermediate 61, 1H-1,2,4-triazole-3-carboxylic acid, 1-[5-fluoro-2-[[[(4,6,7,9-tetrahydro-3-hydroxy-9,9-dimethyl-4-oxopyrimido[2,1-c][1,4]oxazin-2-yl)carbonyl]amino]methyl]phenyl]-, according to the method described for the synthesis of example 62.

Example 62



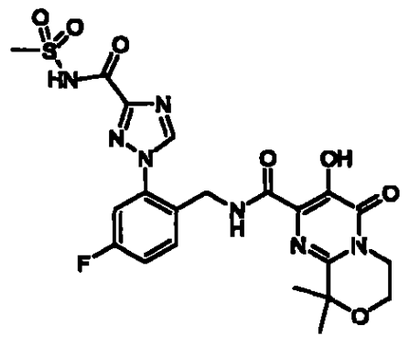
Pyrimido[2,1-c][1,4]oxazine-2-carboxamide, N-[[4-fluoro-2-[3-(4-morpholinylcarbonyl)-1H-1,2,4-triazol-1-yl]phenyl]methyl]-4,6,7,9-tetrahydro-3-hydroxy-9,9-dimethyl-4-oxo-. To a solution of example 61, 1H-1,2,4-triazole-3-carboxylic acid, 1-[5-fluoro-2-[[[(4,6,7,9-tetrahydro-3-hydroxy-9,9-dimethyl-4-oxopyrimido[2,1-c][1,4]oxazin-2-yl)carbonyl]amino]methyl]phenyl]-, (0.0259 g, 0.057 mmol) in DMF (2mL), at 0° C, was added O-(7-azabenzotriazol-1-yl)-N,N,N^1,N^1-tetramethyluronium hexafluorophosphate (0.044 g, 0.115 mmol). The solution was stirred at 0° C for 10 min before adding morpholine (0.025 mL, 0.285 mmol) after which it was stirred at room temp for 2 h. Purification by reverse phase preparative HPLC chromatography (YMC Combiprep ODS-A, 30mm x 50mm, MeOH/H_2O/0.1% CF_3CO_2H) gave the title compound as a white solid (0.015 g, 50% yield). ^{1}H-NMR (500 MHz, $CDCl_3$) δ ppm: 8.50 (1H, t, J = 6.9 Hz), 8.45 (1H, s), 7.69 (1H, dd, J = 8.7, 5.9 Hz), 7.22 (1H, td, J = 8.2, 2,3 Hz), 7.13 (1H, dd, J = 8.2, 2.4 Hz), 4.49 (2H, s), 3.98 (4H, s), 3.88-3.72 (8H, m), 1.57 (6H, s). HRMS $[M+H]^+$ calcd for $C_{24}H_{27}N_7O_6F$: 528.20069; found: 528.2025.

Example 63



Pyrimido[2,1-c][1,4]oxazine-2-carboxamide, N-[[2-[3-[(dimethylamino)carbonyl]-1H-1,2,4-triazol-1-yl]-4-fluorophenyl]methyl]-4,6,7,9-tetrahydro-3-hydroxy-9,9-dimethyl-4-oxo-. Pale purple solid. ^{1}H-NMR (300 MHz, $CDCl_3$) δ ppm: 8.51-8.45 (2H, m), 7.70 (1H, dd, J = 8.4, 5.9 Hz), 7.24-7.18 (1H, m), 7.12 (1H, dd, J = 8.2, 2.4 Hz), 4.47 (2H, d, J = 6.9 Hz), 3.97 (4H, s), 3.24 (3H, s), 3.15 (3H, s), 1.54 (6H, s). HRMS $[M+H]^+$ calcd for $C_{22}H_{25}N_7O_5F$: 486.19013; found: 486.1887.

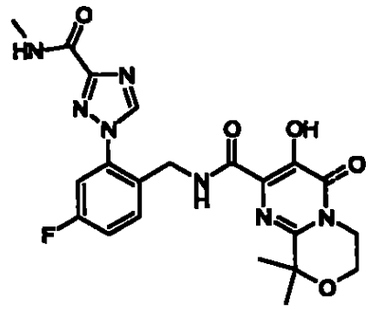
Example 64



Pyrimido[2,1-c][1,4]oxazine-2-carboxamide, N-[[4-fluoro-2-[3-[[(methylsulfonyl)amino]carbonyl]-1H-1,2,4-triazol-1-yl]phenyl]methyl]-4,6,7,9-tetrahydro-3-hydroxy-9,9-dimethyl-4-oxo-. White solid. ^{1}H-NMR (300 MHz, $CDCl_3$) δ ppm: 8.52 (1H, s), 8.36 (1H, t, J = 6.8 Hz), 7.70 (1H, dd, J = 8.6, 5.7 Hz), 7.26-7.19 (1H, m), 7.13 (1H, dd, J = 8.4, 2.6 Hz), 4.46 (2H, d, J = 7.0 Hz), 3.95 (4H, s), 3.39

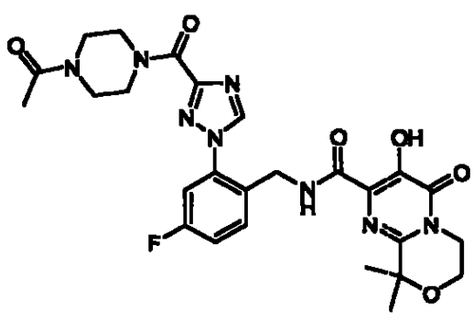
(4H, s), 1.57 (6H, s). HRMS $[M+H]^+$ calcd for $C_{21}H_{23}N_7O_7FS$: 536.1364; found: 536.1376. Anal calcd for $C_{21}H_{22}N_7O_7FS \cdot 0.07CF_3CO_2H$: C, 46.72; H, 4.09; N, 18.04; F, 4.23; found: C, 46.42; H, 3.91; N, 17.70; F, 4.17.

Example 65



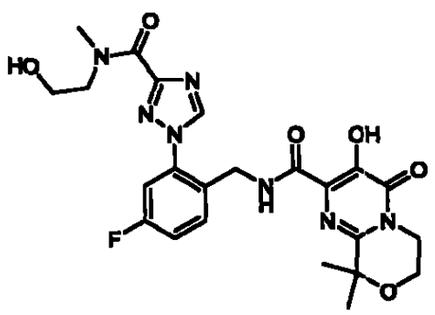
Pyrimido[2,1-c][1,4]oxazine-2-carboxamide, 4,6,7,9-tetrahydro-3-hydroxy-N-[(1R)-2-hydroxy-1-phenylethyl]-9,9-dimethyl-4-oxo-. White solid. ^{1}H-NMR (300 MHz, $CDCl_3$) δ ppm: 8.43 (1H, s), 8.20 (1H, t, J = 6.0 Hz), 7.64 (1H, dd, J = 8.8, 5.9 Hz), 7.42-7.40 (1H, m), 7.26-7.19 (1H, m), 7.11 (1H, dd, J = 8.0, 2.6 Hz), 4.53 (2H, d, J = 6.6 Hz), 3.99 (4H, s), 3.06 (3H, d, J = 4.7 Hz), 1.56 (6H, s). HRMS $[M+H]^+$ calcd for $C_{21}H_{23}N_7O_5F$: 472.1745; found: 472.1741. Anal calcd for $C_{21}H_{22}N_7O_5F$: C, 53.50; H, 4.70; N, 20.79; F, 4.03; found: C, 53.22; H, 4.51; N, 20.70; F, 4.01.

Example 66



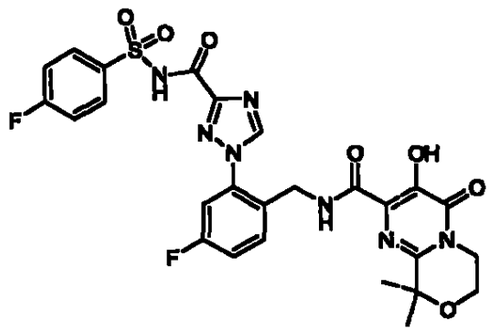
Pyrimido[2,1-c][1,4]oxazine-2-carboxamide, N-[[2-[3-[(4-acetyl-1-piperazinyl)carbonyl]-1H-1,2,4-triazol-1-yl]-4-fluorophenyl]methyl]-4,6,7,9-tetrahydro-3-hydroxy-9,9-dimethyl-4-oxo-. White solid. ^{1}H-NMR (300 MHz, $CDCl_3$) δ ppm: 8.46 (1H, s), 8.36 (1H, t, J = 5.7 Hz), 7.68 (1H, dd, J = 8.6, 5.7 Hz), 7.27-7.21 (1H, m), 7.14 (1H, dd, J = 8.2, 2.7 Hz), 4.48 (2H, d, J = 6.6 Hz), 3.98 (4H, s), 3.94-3.61 (8H, m), 2.13 (3H, s), 1.55 (6H, s). HRMS $[M+H]^+$ calcd for $C_{26}H_{30}N_8O_6F$: 569.2272; found: 569.2269. Anal calcd for $C_{26}H_{29}N_8O_6F \cdot 0.8\ H_2O$: C, 53.57; H, 5.29; N, 19.22; F, 3.26; found: C, 53.48; H, 4.95; N, 19.21; F, 3.21.

Example 67



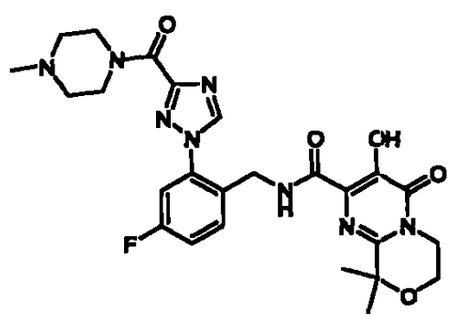
Pyrimido[2,1-c][1,4]oxazine-2-carboxamide, N-[[4-fluoro-2-[3-[[(2-hydroxyethyl)methylamino]carbonyl]-1H-1,2,4-triazol-1-yl]phenyl]methyl]-4,6,7,9-tetrahydro-3-hydroxy-9,9-dimethyl-4-oxo-. White solid. ^{1}H-NMR (300 MHz, $CDCl_3$) δ ppm: 8.54 (1H, t, J = 7.3 Hz), 8.44 (1H, s), 7.66 (1H, dd, J = 8.8, 5.8 Hz), 7.21-7.09 (2H, m), 4.44 (2H, d, J = 4.4 Hz), 3.93 (4H, s), 3.86-3.78 (2H, m), 3.70-3.65 (2H, m), 3.13 (3H, s), 1.94 (1H, bs), 1.55 (6H, s). HRMS $[M+H]^+$ calcd for $C_{23}H_{27}N_7O_6F$: 516.2007; found: 516.2011. Anal calcd for $C_{23}H_{26}N_7O_6F$: C, 53.59; H, 5.08; N, 19.02; F, 3.68; found: C, 53.31; H, 5.06; N, 18.80; F, 3.60.

Example 68



Pyrimido[2,1-c][1,4]oxazine-2-carboxamide, N-[[4-fluoro-2-[3-[[[(4-fluorophenyl)sulfonyl]amino]carbonyl]-1H-1,2,4-triazol-1-yl]phenyl]methyl]-4,6,7,9-tetrahydro-3-hydroxy-9,9-dimethyl-4-oxo-. White solid. ^{1}H-NMR (300 MHz, $CDCl_3$) δ ppm: 8.47 (1H, s), 8.18-8.13 (2H, m), 7.68 (1H, dd, J = 8.8, 5.9 Hz), 7.24-7.16 (3H, m), 7.08 (1H, dd, J = 8.0, 2.6 Hz), 4.39 (2H, s), 3.96 (4H, s), 1.55 (6H, s). HRMS $[M+H]^+$ calcd for $C_{26}H_{24}N_7O_7F_2S$: 616.1426; found: 616.1426. Anal calcd for $C_{26}H_{23}N_7O_7F_2S$: C, 50.73; H, 3.76; N, 15.92; F, 6.17; found: C, 50.49; H, 3.66; N, 15.98; F, 6.12.

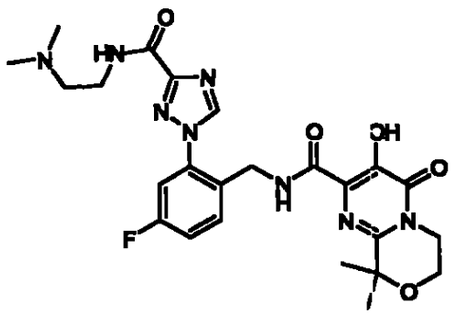
Example 69



Pyrimido[2,1-c][1,4]oxazine-2-carboxamide, N-[[4-fluoro-2-[3-[(4-methyl-1-piperazinyl)carbonyl]-1H-1,2,4-triazol-1-yl]phenyl]methyl]-4,6,7,9-tetrahydro-3-hydroxy-9,9-dimethyl-4-oxo-. Pale brown foam. ^{1}H-NMR (300 MHz, $CDCl_3$) δ ppm: 8.43 (1H, s), 8.29 (1H, t, J = 6.8 Hz), 7.63 (1H, dd, J = 8.4, 5.9 Hz), 7.25-7.19 (1H,

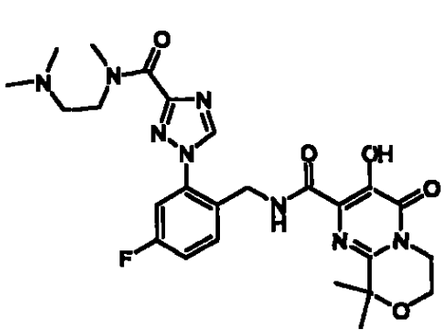
m), 7.11 (1H, dd, J = 8.0, 2.6 Hz), 4.46 (2H, d, J = 6.6 Hz), 3.95 (4H, s), 3.30 (4H, bs), 2.86 (3H, s), 1.91 (4H, bs), 1.53 (6H, s). HRMS $[M+H]^+$ calcd for $C_{25}H_{30}N_8O_5F$: 541.2323; found: 541.2341. Anal calcd for $C_{25}H_{29}N_8O_5F \cdot 0.5CF_3CO_2H \cdot 0.5\ H_2O$: C, 46.67; H, 4.41; N, 15.55; F, 14.50; found: C, 46.86; H, 4.44; N, 15.67; F, 14.48.

Example 70



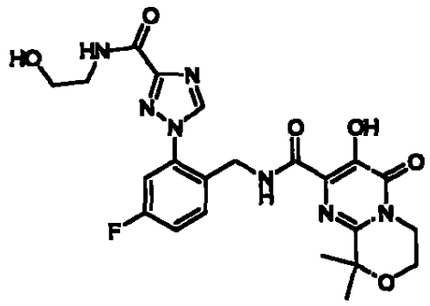
Pyrimido[2,1-c][1,4]oxazine-2-carboxamide, N-[[2-[3-[[[2-(dimethylamino)ethyl]amino]carbonyl]-1H-1,2,4-triazol-1-yl]-4-fluorophenyl]methyl]-4,6,7,9-tetrahydro-3-hydroxy-9,9-dimethyl-4-oxo-. Pale brown foam. ^{1}H-NMR (300 MHz, $CDCl_3$) δ ppm: 8.39 (1H, s), 7.58 (1H, dd, J = 8.6, 5.7 Hz), 7.23-7.14 (1H, m), 7.09 (1H, dd, J = 8.4, 2.6 Hz), 4.50 (2H, s), 3.95 (4H, s), 3.84 (2H, t, J = 5.5 Hz), 3.34 (2H, t, J = 6.0 Hz), 2.89 (6H, s), 1.55 (6H, s). HRMS $[M+H]^+$ calcd for $C_{24}H_{30}N_8O_5F$: 529.2323; found: 529.2315.

Example 71



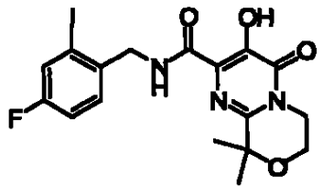
Pyrimido[2,1-c][1,4]oxazine-2-carboxamide, N-[[2-[3-[[[2-(dimethylamino)ethyl]methylamino]carbonyl]-1H-1,2,4-triazol-1-yl]-4-fluorophenyl]methyl]-4,6,7,9-tetrahydro-3-hydroxy-9,9-dimethyl-4-oxo-. Pale brown foam. ^{1}H-NMR (300 MHz, $CDCl_3$) δ ppm: 8.44 (1H, s), 8.21 (1H, t, J = 6.5 Hz), 7.67-7.58 (1H, m), 7.24-7.09 (2H, m), 4.48-4.45 (2H, m), 3.95 (4H, s), 3.94-3.89 (2H, m), 3.37-3.33 (2H, m), 2.91 (6H, s), 2.88 (3H, s), 1.56 (6H, s). HRMS $[M+H]^+$ calcd for $C_{25}H_{32}N_8O_5F$: 543.2480; found: 543.2491. Anal calcd for $C_{25}H_{31}N_8O_5F \cdot CF_3CO_2H$: C, 45.20; H, 4.32; N, 14.54; F, 17.26; found: C, 45.13; H, 4.14; N, 14.74; F, 17.01.

Example 72



Pyrimido[2,1-c][1,4]oxazine-2-carboxamide, N-[[4-fluoro-2-[3-[[(2-hydroxyethyl)amino]carbonyl]-1H-1,2,4-triazol-1-yl]phenyl]methyl]-4,6,7,9-tetrahydro-3-hydroxy-9,9-dimethyl-4-oxo-. White solid. ^{1}H-NMR (300 MHz, $CDCl_3$) δ ppm: 8.41 (1H, s), 8.32 (1H, t, J = 6.2 Hz), 7.63 (1H, dd, J = 8.4, 5.9 Hz), 7.20 (1H, dt, J = 8.4, 2.6 Hz), 7.11 (1H, dd, J = 8.4, 2.6 Hz), 4.52-4.50 (2H, m), 3.95 (4H, s), 3.78 (2H, t, J = 5.1 Hz), 3.59 (2H, t, J = 5.1 Hz), 1.56 (6H, s). HRMS $[M+H]^+$ calcd for $C_{22}H_{25}N_7O_6F$: 502.1850; found: 502.1850.

Example 73

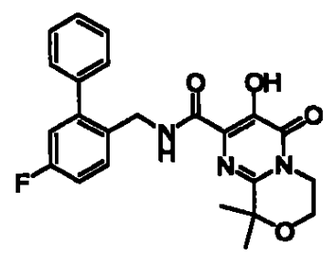


Pyrimido[2,1-c][1,4]oxazine-2-carboxamide, N-[(4-fluoro-2-iodophenyl)methyl]-4,6,7,9-tetrahydro-3-hydroxy-9,9-dimethyl-4-oxo-. The title compound can be prepared from intermediate 174, N-(4-fluoro-2-iodobenzyl)-3-(benzyloxy)-9,9-dimethyl-4-oxo-4,6,7,9-tetrahydropyrimido[2,1-c][1,4]oxazine-2-carboxamide. ^{1}HNMR 400 MHz ($CDCl_3$) δ ppm: 1.63 (6H, s, 2 x CH_3), 4.05 (4H, s, 2 x CH_2), 4.63 (2H, d, J = 7.1 Hz, NCH_2), 7.11 (1H, m, aromatic), 7.42 (1H, dd, J = 5.6 Hz and J = 8.6 Hz, aromatic), 7.62 (1H, dd, J = 2.5 Hz and J = 8.1 Hz, aromatic), 8.20 (1H, broad t, NH), 11.82 (1H, s, OH). HRMS (ESI^+) calculated for $C_{17}H_{18}FIN_3O_4$ [$M+H^+$]: 474.0326; found: 474.0328.

Examples 74-77

Examples 74-77 can be prepared from the indicated intermediates by hydrogenolysis or trifluoroacetic acid mediated hydrolysis.

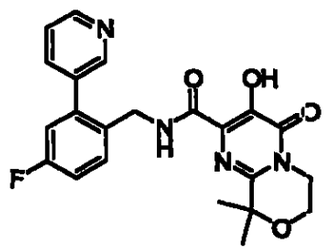
Example 74



Pyrimido[2,1-c][1,4]oxazine-2-carboxamide, N-[(5-fluoro[1,1'-biphenyl]-2-yl)methyl]-4,6,7,9-tetrahydro-3-hydroxy-9,9-dimethyl-4-oxo-. The title compound

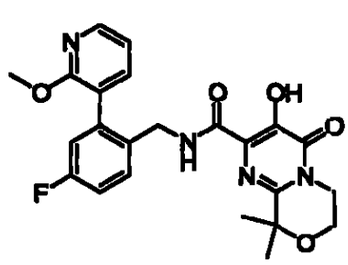
can be prepared from intermediate 176, N-(4-fluoro-2-phenyl-benzyl)-3-(benzyloxy)-9,9-dimethyl-4-oxo-4,6,7,9-tetrahydropyrimido[2,1-c][1,4]oxazine-2-carboxamide. ^{1}HNMR 400 MHz ($CDCl_3$) δ ppm: 1.56 (6H, s, 2 x CH_3), 4.03 (4H, s, 2 x CH_2), 4.56 (2H, d, J = 6.0 Hz, NCH_2), 7.03 (1H, dd, J = 2.5 Hz and J = 9.3 Hz, aromatic), 7.09 (1H, m, aromatic), 7.36 (2H, m, aromatics), 7.42-7.51 (5H, m, aromatics and NH), 11.96 (1H, s, OH). HRMS (ESI$^+$) calculated for $C_{23}H_{23}FN_3O_4$ [M+H$^+$]: 424.1673; found: 424.1675.

Example 75



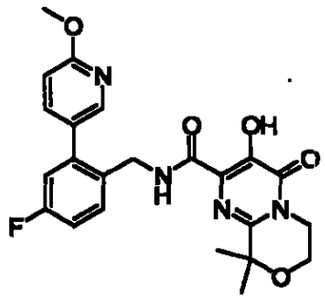
Pyrimido[2,1-c][1,4]oxazine-2-carboxamide, N-[[4-fluoro-2-(3-pyridinyl)phenyl]methyl]-4,6,7,9-tetrahydro-3-hydroxy-9,9-dimethyl-4-oxo-. ^{1}HNMR 400 MHz ($CDCl_3$) δ ppm: 1.57 (6H, s, 2 x CH_3), 4.04 (4H, s, 2 x CH_2), 4.55 (2H, d, J = 6.1 Hz, NCH_2), 7.04 (1H, dd, J = 2.5 Hz and J = 9.1 Hz, aromatic), 7.16 (1H, m, aromatic), 7.43 (1H, m, aromatic), 7.49 (1H, dd, J = 5.6 Hz and J = 8.6 Hz, aromatic), 7.52 (1H, broad t, NH), 7.71 (1H, m, aromatic), 8.63 (1H, m, aromatic), 8.70 (1H, m, aromatic),11.84 (1H, s, OH). HRMS (ESI$^+$) calculated for $C_{22}H_{22}FN_4O_4$ [M+H$^+$]: 425.1625; found: 425.1616.

Example 76



Pyrimido[2,1-c][1,4]oxazine-2-carboxamide, N-[[4-fluoro-2-(2-methoxy-3-pyridinyl)phenyl]methyl]-4,6,7,9-tetrahydro-3-hydroxy-9,9-dimethyl-4-oxo-. Hydrogenolysis of intermediate 175, N-(4-fluoro-2-(2-methoxypyridin-3-yl)benzyl)-3-(benzyloxy)-9,9-dimethyl-4-oxo-4,6,7,9-tetrahydropyrimido[2,1-c][1,4]oxazine-2-carboxamide gave the title material as a white solid; mp 227 °C. ^{1}HNMR 400 MHz ($CDCl_3$) δ ppm: 1.58 (6H, s, 2 x CH_3), 3.99 (3H, s, OCH_3), 4.04 (4H, s, 2 x CH_2), 4.43 (2H, broad, NCH_2), 6.97 (1H, dd, J = 2.5 Hz and J = 8.5 Hz, aromatic), 7.03 (1H, dd, J = 5.0 Hz and J = 8.5 Hz, aromatic), 7.12 (1H, m, aromatic), 7.45 (1H, dd, J = 4.5 Hz and J = 8.6 Hz, aromatic), 7.53 (1H, dd, J = 2.0 Hz and J = 7.1 Hz, aromatic), 7.57 (1H, broad t, NH), 8.28 (1H, dd, J = 2.5 Hz and J = 5.0 Hz, aromatic), 12.03 (1H, s, OH). HRMS (ESI^+) calculated for $C_{23}H_{24}FN_4O_5$ [M+H$^+$]: 455.1731; found: 455.1737.

Example 77

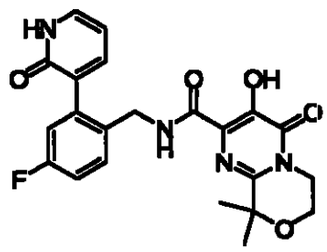


Pyrimido[2,1-c][1,4]oxazine-2-carboxamide, N-[[4-fluoro-2-(6-methoxy-3-pyridinyl)phenyl]methyl]-4,6,7,9-tetrahydro-3-hydroxy-9,9-dimethyl-4-oxo. ^{1}HNMR 400 MHz ($CDCl_3$) δ ppm: 1.58 (6H, s, 2 x CH_3), 4.02 (3H, s, OCH_3), 4.04 (4H, s, 2 x CH_2), 4.55 (2H, d, J = 6.1 Hz, NCH_2), 6.87 (1H, d, J = 9.0 Hz, aromatic), 7.01 (1H, dd, J = 2.0 Hz and J = 9.0 Hz, aromatic), 7.12 (1H, m, aromatic), 7.46 (1H, dd, J = 5.5 Hz and J = 8.6 Hz, aromatic), 7.55 (1H, broad t, NH), 7.60 (1H, dd, J = 2.0 Hz and J = 8.6 Hz, aromatic), 8.17 (1H, d, J = 2.0 Hz, aromatic), 11.89 (1H, s, OH). HRMS (ESI^+) calculated for $C_{23}H_{24}FN_4O_5$ [M+H$^+$]: 455.1731; found: 455.1717.

Examples 78-80

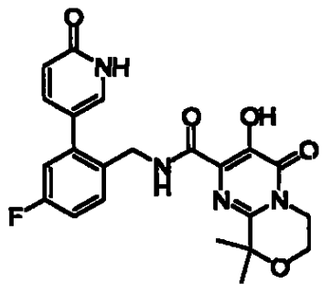
Examples 78-80 can be prepared from the indicated intermediates according to the method described for example 78.

Example 78



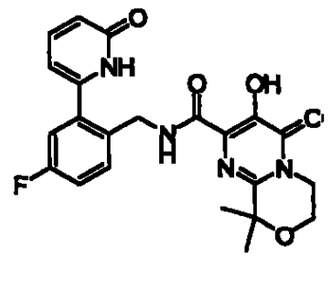
Pyrimido[2,1-c][1,4]oxazine-2-carboxamide, N-[[2-(1,2-dihydro-2-oxo-3-pyridinyl)-4-fluorophenyl]methyl]-4,6,7,9-tetrahydro-3-hydroxy-9,9-dimethyl-4-oxo-. A solution of intermediate 175, N-(4-fluoro-2-(2-methoxypyridin-3-yl)benzyl)-3-(benzyloxy)-9,9-dimethyl-4-oxo-4,6,7,9-tetrahydropyrimido[2,1-c][1,4]oxazine-2-carboxamide, (0.125 g, 0.23 mmol) in acetonitrile (5 ml) was treated with sodium iodide (0.090 g, 0.6 mmol) and chlorotrimethylsilane (0.45 ml, 3.5 mmol), sealed in a pressure resistant vessel and heated at 80 °C for 1.5 h. The mixture was diluted with ethyl acetate washed with water and brine then dried over anhydrous magnesium sulfate. Filtration and removal of solvent provided the title compound. ^{1}HNMR 400 MHz ($CDCl_3$) δ ppm: 1.60 (6H, s, 2 x CH_3), 4.03 (4H, s, 2 x CH_2), 4.5 (2H, broad, NCH_2), 6.47 (1H, m, aromatic), 6.95 (1H, dd, J = 2 Hz and J = 9 Hz, aromatic), 7.12 (1H, m, aromatic), 7.45 (1H, dd, J = 2 Hz and J = 7 Hz, aromatic), 7.50 (1H, dd, J = 6 Hz and J = 9 Hz, aromatic), 7.53 (1H, dd, J = 2 Hz and J = 7 Hz, aromatic), 8.64 (1H, broad t, NH). HRMS (ESI^+) calculated for $C_{22}H_{22}FN_4O_5$ [$M+H^+$]: 441.1574; found: 441.1585.

Example 79



Pyrimido[2,1-c][1,4]oxazine-2-carboxamide, N-[[2-(1,6-dihydro-6-oxo-3-pyridinyl)-4-fluorophenyl]methyl]-4,6,7,9-tetrahydro-3-hydroxy-9,9-dimethyl-4-oxo-. The title compound can be prepared from example 77. ^{1}HNMR 400 MHz ($CDCl_3$) δ ppm: 1.59 (6H, s, 2 x CH_3), 4.02 (3H, s, OCH_3), 4.05 (4H, s, 2 x CH_2), 4.55 (2H, d, J = 6.6 Hz, NCH_2), 6.95 (1H, d, J = 9.0 Hz, aromatic), 7.00 (1H, dd, J = 2.6 Hz and J = 9.0 Hz, aromatic), 7.17 (1H, m, aromatic), 7.46 (1H, dd, J = 5.5 Hz and J = 8.6 Hz, aromatic), 7.63 (1H, d, J = 2.6 Hz, aromatic), 7.71 (1H, broad t, NH), 7.79 (1H, dd, J = 2.6 Hz and J = 9.1 Hz, aromatic). HRMS (ESI^+) calculated for $C_{22}H_{22}FN_4O_5$ [$M+H^+$]: 441.1574; found: 441.1570.

Example 80



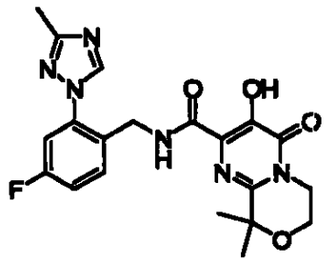
Pyrimido[2,1-c][1,4]oxazine-2-carboxamide, N-[[2-(1,6-dihydro-6-oxo-2-pyridinyl)-4-fluorophenyl]methyl]-4,6,7,9-tetrahydro-3-hydroxy-9,9-dimethyl-4-oxo-. The title compound can be prepared from N-(4-fluoro-2-(6-methoxypyridin-2-yl)benzyl)-3-(benzyloxy)-9,9-dimethyl-4-oxo-4,6,7,9-tetrahydropyrimido[2,1-c][1,4]oxazine-2-carboxamide, which can be prepared according to the methods

described for the synthesis of intermediate 175. ^{1}HNMR 400 MHz ($CDCl_3$) δ (ppm): 1.62 (6H, s, 2 x CH_3), 4.04 (4H, s, 2 x CH_2), 4.60 (2H, d, J = 7.0 Hz, NCH_2), 6.38 (1H, d, J = 7.0 Hz, aromatic), 6.68 (1H, d, J = 9.0 Hz, aromatic), 7.14 (1H, dd, J = 2.5 Hz and J = 9.1 Hz, aromatic), 7.23 (1H, m, aromatic), 7.50 (1H, dd, J = 5.6 Hz and J = 8.6 Hz, aromatic), 7.58 (1H, dd, J = 7.0 Hz and J = 9.0 Hz, aromatic), 8.15 (1H, broad t, NH).

Examples 81-93

Examples 81-93 can be prepared from the indicated intermediates by hydrogenolysis or trifluoroacetic acid mediated hydrolysis.

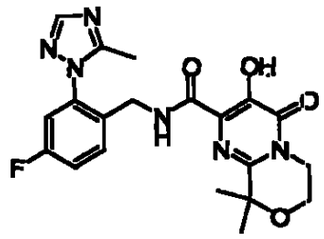
Example 81



Pyrimido[2,1-c][1,4]oxazine-2-carboxamide, N-[[4-fluoro-2-(3-methyl-1H-1,2,4-triazol-1-yl)phenyl]methyl]-4,6,7,9-tetrahydro-3-hydroxy-9,9-dimethyl-4-oxo-.

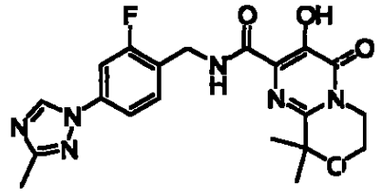
The title compound can be prepared from intermediate 152, N-(4-fluoro-2-(3-methyl-1H-1,2,4-triazol-1-yl)benzyl)-3-(benzyloxy)-9,9-dimethyl-4-oxo-4,6,7,9-tetrahydropyrimido[2,1-c][1,4]oxazine-2-carboxamide ^{1}HNMR 400 MHz ($CDCl_3$) δ ppm: 1.64 (6H, s, 2 x CH_3), 2.59 (3H, s, CH_3), 4.04 (4H, s, 2 x CH_2), 4.50 (2H, d, J = 7.1 Hz, NCH_2), 7.1 (1H, dd, J = 2.5 Hz and J = 8.6 Hz, aromatic), 7.20 (1H, m, aromatic), 7.72 (1H, dd, J = 6.0 Hz and J = 8.6 Hz, aromatic), 8.34 (1H, s, CH), 8.80 (1H, broad t, NH), 12.11 (1H, s, OH). HRMS (ESI^+) calculated for $C_{20}H_{22}FN_6O_4$ [$M+H^+$]: 429.1687; found: 429.1675.

Example 82



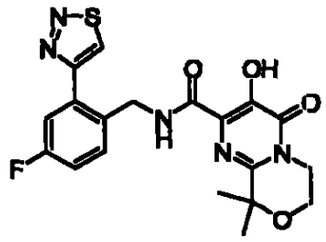
Pyrimido[2,1-c][1,4]oxazine-2-carboxamide, N-[[4-fluoro-2-(5-methyl-1H-1,2,4-triazol-1-yl)phenyl]methyl]-4,6,7,9-tetrahydro-3-hydroxy-9,9-dimethyl-4-oxo-. ^{1}HNMR 400 MHz ($CDCl_3$) δ ppm: 1.66 (6H, s, 2 x CH_3), 2.50 (3H, s, CH_3), 4.04 (4H, s, 2 x CH_2), 4.32 (2H, d, J = 7.0 Hz, NCH_2), 7.05 (1H, dd, J = 2.5 Hz and J = 8.1 Hz, aromatic), 7.27 (1H, m, aromatic), 7.70 (1H, dd, J = 6.1 Hz and J = 8.6 Hz, aromatic), 8.04 (1H, s, CH), 8.61 (1H, broad t, NH), 11.90 (1H, s, OH). HRMS (ESI^+) calculated for $C_{20}H_{22}FN_6O_4$ [$M+H^+$]: 429.1687; found: 429.1688.

Example 83



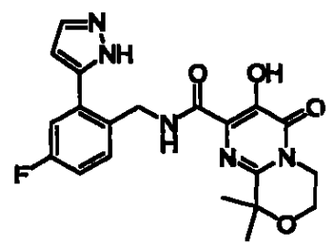
Pyrimido[2,1-c][1,4]oxazine-2-carboxamide, N-[[2-fluoro-4-(3-methyl-1H-1,2,4-triazol-1-yl)phenyl]methyl]-4,6,7,9-tetrahydro-3-hydroxy-9,9-dimethyl-4-oxo-. The title compound can be prepared from intermediate 153, N-(2-fluoro-4-(3-methyl-1H-1,2,4-triazol-1-yl)benzyl)-3-(benzyloxy)-9,9-dimethyl-4-oxo-4,6,7,9-tetrahydropyrimido[2,1-c][1,4]oxazine-2-carboxamide. ^{1}HNMR 400 MHz ($CDCl_3$) δ ppm: 1.61 (6H, s, 2 x CH_3), 2.51 (3H, s, CH_3), 4.05 (4H, s, 2 x CH_2), 4.72 (2H, d, J = 6.6 Hz, NCH_2), 7.44-7.55 (3H, m, aromatics), 7.94 (1H, broad t, NH), 8.46 (1H, s, CH), 11.86 (1H, s, OH). HRMS (ESI^+) calculated for $C_{20}H_{22}FN_6O_4$ [$M+H^+$]: 429.1687; found: 429.1695.

Example 84



Pyrimido[2,1-c][1,4]oxazine-2-carboxamide, N-[[4-fluoro-2-(1,2,3-thiadiazol-4-yl)phenyl]methyl]-4,6,7,9-tetrahydro-3-hydroxy-9,9-dimethyl-4-oxo-. The title compound can be prepared from intermediate 172, N-(4-fluoro-2-(1,2,3-thiadiazol-4-yl)benzyl)-3-(benzyloxy)-9,9-dimethyl-4-oxo-4,6,7,9-tetrahydropyrimido[2,1-c][1,4]oxazine-2-carboxamide. ^{1}HNMR 400 MHz (DMSO-d_6) δ ppm: 1.54 (6H, s, 2 x CH_3), 3.83 (2H, broad t, CH_2), 3.96 (2H, broad t, CH_2), 4.61 (2H, d, J = 6.7 Hz, NCH_2), 7.39 (1H, m, aromatic), 7.55 (1H, m, aromatic), 7.62 (1H, m, aromatic), 9.41 (1H, broad t, NH), 9.63 (1H, s, CH), 12.0 (1H, s, OH). HRMS (ESI$^+$) calculated for $C_{19}H_{19}FN_5O_4S$ [M+H$^+$]: 432.1142; found: 432.1124.

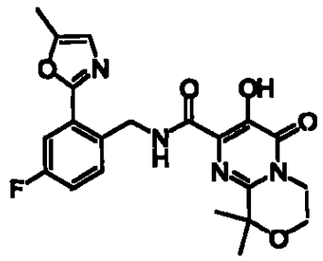
Example 85



Pyrimido[2,1-c][1,4]oxazine-2-carboxamide, N-[[4-fluoro-2-(1H-pyrazol-5-yl)phenyl]methyl]-4,6,7,9-tetrahydro-3-hydroxy-9,9-dimethyl-4-oxo-. The title compound can be prepared from intermediate 177, N-(4-fluoro-2-(1H-pyrazol-5-yl)benzyl)-3-(benzyloxy)-9,9-dimethyl-4-oxo-4,6,7,9-tetrahydropyrimido[2,1-c][1,4]oxazine-2-carboxamide. ^{1}HNMR 400 MHz ($CDCl_3$) δ ppm: 1.59 (6H, s, 2 x CH_3), 4.03 (4H, s, 2 x CH_2), 4.67 (2H, d, J = 6.6 Hz, NCH_2), 6.65 (1H, d, J = 2.5 Hz,

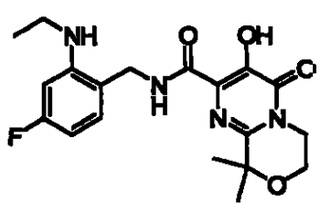
CH), 7.07 (1H, m, aromatic), 7.31 (1H, dd, J = 2.5 Hz and J = 9.8 Hz, aromatic), 7.56 (1H, dd, J = 5.8 Hz and J = 8.3 Hz, aromatic), 7.75 (1H, d, J = 2.5 Hz, CH), 9.22 (1H, broad t, NH), 10.33 (1H, broad, NH), 12.2 (1H, s, OH). HRMS (ESI$^+$) calculated for $C_{20}H_{21}FN_5O_4$ [M+H$^+$]: 414.1578; found: 414.1560.

Example 86



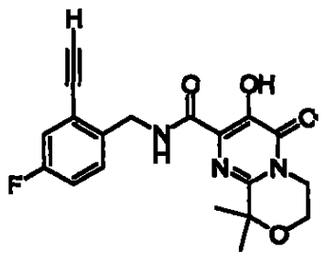
Pyrimido[2,1-c][1,4]oxazine-2-carboxamide, N-[[4-fluoro-2-(5-methyl-2-oxazolyl)phenyl]methyl]-4,6,7,9-tetrahydro-3-hydroxy-9,9-dimethyl-4-oxo-. The title compound can be prepared from intermediate 173, N-(4-fluoro-2-(5-methyloxazol-2-yl)benzyl)-3-(benzyloxy)-9,9-dimethyl-4-oxo-4,6,7,9-tetrahydropyrimido[2,1-c][1,4]oxazine-2-carboxamide. ^{1}HNMR 400 MHz ($CDCl_3$) δ ppm: 1.58 (6H, s, 2 x CH_3), 2.48 (3H, s, CH_3), 4.01 (4H, s, 2 x CH_2), 4.77 (2H, d, J = 7.0 Hz, NCH_2), 6.96 (1H, s, CH), 7.13 (1H, m, aromatic), 7.61 (1H, dd, J = 5.8 Hz and J = 8.3 Hz, aromatic), 7.70 (1H, dd, J = 3.2 Hz and J = 9.6 Hz, aromatic), 9.76 (1H, broad t, NH), 12.15 (1H, s, OH). HRMS (ESI$^+$) calculated for $C_{21}H_{22}FN_4O_5$ [M+H$^+$]: 429.1574; found: 429.1564.

Example 87



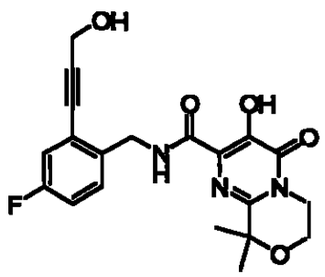
Pyrimido[2,1-c][1,4]oxazine-2-carboxamide, N-[[2-(ethylamino)-4-fluorophenyl]methyl]-4,6,7,9-tetrahydro-3-hydroxy-9,9-dimethyl-4-oxo-. The title compound can be prepared from intermediate 170, N-(2-(ethylamino)-4-fluorobenzyl)-3-(benzyloxy)-9,9-dimethyl-4-oxo-4,6,7,9-tetrahydropyrimido[2,1-c][1,4]oxazine-2-carboxamide. ^{1}HNMR 400 MHz ($CDCl_3$) δ ppm: 1.30 (3H, t, J = 7.3 Hz, CH_3), 1.59 (6H, s, 2 x CH_3), 3.12 (2H, m, CH_2), 4.04 (4H, s, 2 x CH_2), 4.52 (2H, d, J = 6.6 Hz, NCH_2), 5.09 (1H, broad, NH), 6.3-6.37 (2H, m, aromatics), 7.10 (1H, dd, J = 6.6 Hz and J = 8.1 Hz, aromatic), 7.67 (1H, broad t, NH), 11.93 (1H, s, OH). HRMS (ESI^+) calculated for $C_{19}H_{24}FN_4O_4$ [$M+H^+$]: 391.1782; found: 391.1774.

Example 88



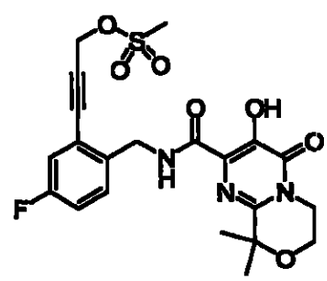
Pyrimido[2,1-c][1,4]oxazine-2-carboxamide, N-[(2-ethynyl-4-fluorophenyl)methyl]-4,6,7,9-tetrahydro-3-hydroxy-9,9-dimethyl-4-oxo-. The title compound can be prepared from intermediate 179, N-(2-ethynyl-4-fluorobenzyl)-3-(benzyloxy)-9,9-dimethyl-4-oxo-4,6,7,9-tetrahydropyrimido[2,1-c][1,4]oxazine-2-carboxamide. ^{1}HNMR 400 MHz ($CDCl_3$) δ ppm: 1.61 (6H, s, 2 x CH_3), 3.46 (1H, s, CH), 4.04 (4H, s, 2 x CH_2), 4.73 (2H, d, J = 6.5 Hz, NCH_2), 7.1 (1H, m, aromatic), 7.26 (1H, dd, J = 2.5 Hz and J = 8.5 Hz, aromatic), 7.40 (1H, dd, J = 5.6 Hz and J = 8.6 Hz, aromatic), 8.18 (1H, broad t, NH), 11.92 (1H, s, OH). HRMS (ESI^+) calculated for $C_{19}H_{19}FN_3O_4$ [$M+H^+$]: 372.1360; found: 372.1345.

Example 89



Pyrimido[2,1-c][1,4]oxazine-2-carboxamide, N-[[4-fluoro-2-(3-hydroxy-1-propynyl)phenyl]methyl]-4,6,7,9-tetrahydro-3-hydroxy-9,9-dimethyl-4-oxo-. The title compound can be prepared from intermediate 182, N-(4-fluoro-2-(3-hydroxyprop-1-ynyl)benzyl)-3-(benzyloxy)-9,9-dimethyl-4-oxo-4,6,7,9-tetrahydropyrimido[2,1-c][1,4]oxazine-2-carboxamide. ^{1}HNMR 400 MHz ($CDCl_3$) δ ppm: 1.60 (6H, s, 2 x CH_3), 4.04 (4H, s, 2 x CH_2), 4.55 (2H, broad d, CH_2), 4.73 (2H, d, J = 6.6 Hz, NCH_2), 7.07 (1H, m, aromatic), 7.20 (1H, dd, J = 2.5 Hz and J = 9.1 Hz, aromatic), 7.38 (1H, dd, J = 5.3 Hz and J = 8.3 Hz, aromatic), 7.95 (1H, broad t, NH), 11.90 (1H, s, OH). HRMS (ESI^+) calculated for $C_{20}H_{21}FN_3O_5$ [$M+H^+$]: 402.1465; found: 402.1463.

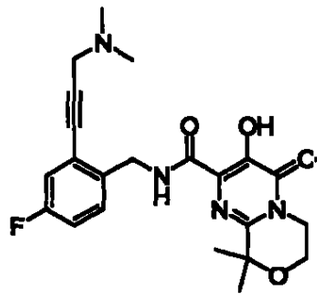
Example 90



Pyrimido[2,1-c][1,4]oxazine-2-carboxamide, N-[[4-fluoro-2-[3-[(methylsulfonyl)oxy]-1-propynyl]phenyl]methyl]-4,6,7,9-tetrahydro-3-hydroxy-9,9-dimethyl-4-oxo-. The title compound can be prepared from intermediate 183, 3-[2-((3-(benzyloxy)-9,9-dimethyl-4-oxo-4,6,7,9-tetrahydropyrimido[2,1-c][1,4]oxazine-

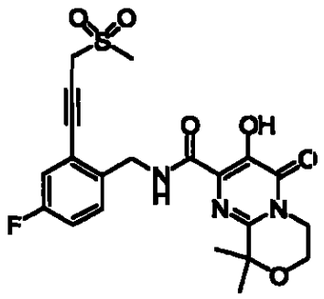
2-carboxamido)methyl)-5-fluorophenyl]prop-2-ynyl methanesulfonate. ^{1}HNMR 400 MHz ($CDCl_3$) δ ppm: 1.62 (6H, s, 2 x CH_3), 3.16 (3H, s, CH_3), 4.05 (4H, s, 2 x CH_2), 4.72 (2H, d, J = 6.0 Hz, NCH_2), 5.12 (2H, s, OCH_2), 7.12 (1H, m, aromatic), 7.21 (1H, dd, J = 2.6 Hz and J = 8.6 Hz, aromatic), 7.45 (1H, dd, J = 5.1 Hz and J = 8.6 Hz, aromatic), 8.03 (1H, broad t, NH).

Example 91



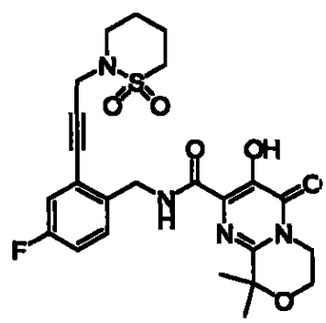
Pyrimido[2,1-c][1,4]oxazine-2-carboxamide, N-[[2-[3-(dimethylamino)-1-propynyl]-4-fluorophenyl]methyl]-4,6,7,9-tetrahydro-3-hydroxy-9,9-dimethyl-4-oxo-. The title compound can be prepared from intermediate 184, N-(2-(3-(dimethylamino)prop-1-ynyl)-4-fluorobenzyl)-3-(benzyloxy)-9,9-dimethyl-4-oxo-4,6,7,9-tetrahydropyrimido[2,1-c][1,4]oxazine-2-carboxamide. The title compound was isolated as a trifluoroacetic acid salt. ^{1}HNMR 400 MHz ($CDCl_3$) δ ppm: 1.62 (6H, s, 2 x CH_3), 3.03 (6H, s, 2 x CH_3), 4.06 (4H, s, 2 x CH_2), 4.23 (2H, s, NCH_2), 4.75 (2H, d, J = 6.0 Hz, NCH_2), 7.16 (1H, m, aromatic), 7.24 (1H, dd, J = 2.5 Hz and J = 8.6 Hz, aromatic), 7.42 (1H, dd, J = 5.6 Hz and J = 8.6 Hz, aromatic), 8.04 (1H, broad t, NH). HRMS (ESI^+) calculated for $C_{22}H_{26}FN_4O_4$ [$M+H^+$]: 429.1938; found: 429.1917.

Example 92



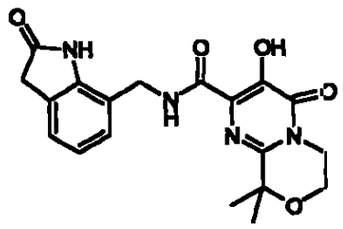
Pyrimido[2,1-c][1,4]oxazine-2-carboxamide, N-[[4-fluoro-2-[3-(methylsulfonyl)-1-propynyl]phenyl]methyl]-4,6,7,9-tetrahydro-3-hydroxy-9,9-dimethyl-4-oxo-. The title compound can be prepared from intermediate 186, N-(4-fluoro-2-(3-(methylsulfonyl)prop-1-ynyl)benzyl)-3-(benzyloxy)-9,9-dimethyl-4-oxo-4,6,7,9-tetrahydropyrimido[2,1-c][1,4]oxazine-2-carboxamide. ^{1}HNMR 400 MHz ($CDCl_3$) δ ppm: 1.63 (6H, s, 2 x CH_3), 3.16 (3H, s, SCH_3), 4.04 (4H, s, 2 x CH_2), 4.17 (2H, s, SCH_2), 4.70 (2H, d, J = 6.0 Hz, NCH_2), 7.12 (1H, m, aromatic), 7.21 (1H, dd, J = 2.5 Hz and J = 8.6 Hz, aromatic), 7.49 (1H, dd, J = 5.6 Hz and J = 8.6 Hz, aromatic), 8.16 (1H, broad t, NH)., 11.99 (1H, s, OH). HRMS (ESI$^+$) calculated for $C_{21}H_{23}FN_3O_6S$ [M+H$^+$]: 464.1292; found: 464.1271.

Example 93



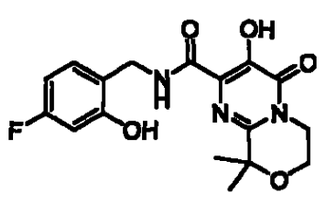
Pyrimido[2,1-c][1,4]oxazine-2-carboxamide, N-[[4-fluoro-2-[3-(tetrahydro-1,1-dioxido-2H-1,2-thiazin-2-yl)-1-propynyl]phenyl]methyl]-4,6,7,9-tetrahydro-3-hydroxy-9,9-dimethyl-4-oxo-. ^{1}HNMR 400 MHz ($CDCl_3$) δ ppm: 1.63 (6H, s, 2 x CH_3), 1.86 (2H, m, CH_2), 2.28 (2H, m, CH_2), 3.11 (2H, m, CH_2), 3.53 (2H, m, CH_2), 4.05 (4H, s, 2 x CH_2), 4.27 (2H, s, NCH_2), 4.73 (2H, d, J = 6.0 Hz, NCH_2), 7.07 (1H, m, aromatic), 7.17 (1H, dd, J = 2.5 Hz and J = 8.6 Hz, aromatic), 7.47 (1H, dd, J = 5.6 Hz and J = 8.6 Hz, aromatic), 8.12 (1H, broad t, NH).

Example 94



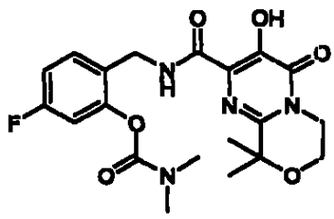
Pyrimido[2,1-c][1,4]oxazine-2-carboxamide, 4,6,7,9-tetrahydro-3-hydroxy-9,9-dimethyl-4-oxo-N-[2-(phenylsulfonyl)ethyl]-. The title compound can be prepared from intermediate 25, ethyl 3-hydroxy-9,9-dimethyl-4-oxo-4,6,7,9-tetrahydropyrimido[2,1-c][1,4]oxazine-2-carboxylate and 7-(aminomethyl)indolin-2-one according to the methods described for examples 1, 19 and 20. ^{1}H NMR (500 MHz, DMSO-d_6) δ ppm: 1.58 (s, 6), 3.50 (s, 2), 3.83 (m, 2), 3.97 (m, 2), 4.42 (d, 2), 6.9-7.13 (overlapping m, 3). Anal calcd $C_{19}H_{20}N_4O_5$: C, 59.36; H, 5.24; N, 14.57. Found: C, 59.61; H, 5.43; N, 14.46.

Example 95



Pyrimido[2,1-c][1,4]oxazine-2-carboxamide, N-[(4-fluoro-2-hydroxyphenyl)methyl]-4,6,7,9-tetrahydro-3-hydroxy-9,9-dimethyl-4-oxo-. A solution of intermediate 144, N-(4-fluoro-2-hydroxybenzyl)-3-(benzyloxy)-9,9-dimethyl-4-oxo-4,6,7,9-tetrahydropyrimido[2,1-c][1,4]oxazine-2-carboxamide, (0.070 g, 0.154 mmol) in dichloromethane (3 mL) and trifluoroacetic acid (3 mL) was stirred for 2 hours. The solvent was then removed *in vacuo* and the resulting residue dissolved in ethyl acetate. The ethyl acetate solution was washed with 1.0 N HCl (10 mL), dried over sodium sulfate, then filtered. Solvent was removed by rotary evaporator and the crude product purified by reverse phase preparative HPLC, (C18, 30%-40% CH_3CN/H_2O-0.1% CF_3CO_2H). Fractions containing product were concentrated by rotary evaporator and the resulting aqueous suspension extracted with ethyl acetate (3 x 50 mL). The combined organic layers were dried (sodium sulfate), filtered, and concentrated to dryness by rotary evaporator. The residue was triturated with ether and dried *in vacuo* to give the title compound as a white solid. ^1H NMR (500 MHz, d_6-Acetone) δ ppm: 11.96 (2H, s), 9.25 (2H, s), 8.98 (1H, br s), 7.23 (1H, t, *J*=7.6 Hz), 6.63 (1H, dd, *J*=8.2, 2.4 Hz), 6.57 (1H, dt, *J*=8.4, 2.4 Hz), 4.53 (2H, d, *J*=6.7 Hz), 4.05 (2H, d, *J*=5.2 Hz), 3.90 (2H, t, *J*=5.2 Hz), 1.55 (6H, s); HRMS $[M+H]^+$ calcd for $C_{17}H_{19}N_3O_5F$: 364.13088; found: 364.1302.

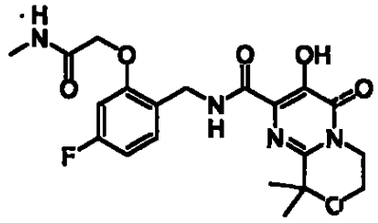
Example 96



Carbamic acid, dimethyl-, 5-fluoro-2-[[[(4,6,7,9-tetrahydro-3-hydroxy-9,9-dimethyl-4-oxopyrimido[2,1-c][1,4]oxazin-2-yl)carbonyl]amino]methyl]phenyl ester. The title compound can be prepared from intermediate 158, dimethyl-carbamic acid 2-{[(3-benzyloxy-9,9-dimethyl-4-oxo-4,6,7,9-tetrahydro-pyrimido[2,1-c][1,4]oxazine-2-carbonyl)-amino]-methyl}-5-fluoro-phenyl ester according to the method described for example 95. White crystalline powder; ^1H NMR ($CDCl_3$, 500

MHz) δ ppm: 1.56 (6H, s, Me), 2.96, 3.11 (2s, NMe), 3.99 (4H, s, CH_2), 4.51 (2H, d, J = 6 Hz, NCH_2), 6.85 (1H, dd, J = 2.5 Hz, 9 Hz, CH), 6.94 (1H, dt, J = 2.5 Hz, 8.3 Hz, Ar-H), 7.37 (1H, dd, J = 6.5 Hz, 8.5 Hz, Ar-H), 8.05 (1H, brt, J = 5 Hz, NH), 12.0 (1H, s, OH); ^{13}C NMR ($CDCl_3$, 125.77 Hz) δ ppm: 27.90 (CH_3), 36.68, 36.92 (2s, NCH_3), 37.80 (NCH_2), 43.14 (NCH_2), 58.20 (OCH_2), 75.99 (OC), 110.88, 110.07 (d, J = 24 Hz, CH), 113.41, 113.57 (d, J = 21 Hz, CH), 125.71 (C), 125.91, 125.94 (d, J = 3.6 Hz, C), 131.57, 131.64 (d, J = 9.6 Hz, CH), 146.22 (C), 150.83, 150.92 (d, J = 11 Hz, C), 151.66 (C), 154.68 (C=O), 157.92 (C=O), 161.70, 163.68 (d, J = 249 Hz, CF), 167.86 (C=O); HRMS calcd for $C_{23}H_{24}N_4O_6F$ (M+H) 435.1680, found 435.1695 (δ+3.5 ppm). UV (MeOH): λmax 245 nm (ε $1.05x10^4$), 306 nm (ε $8.00x10^3$); Anal. calcd for $C_{20}H_{23}N_4O_6F$; C 55.30, H 5.34, N 12.90: found C 55.32, H 5.38, N 12.77.

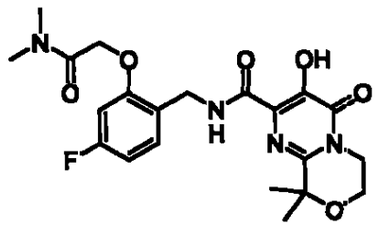
Example 97



Pyrimido[2,1-c][1,4]oxazine-2-carboxamide, N-[[4-fluoro-2-[2-(methylamino)-2-oxoethoxy]phenyl]methyl]-4,6,7,9-tetrahydro-3-hydroxy-9,9-dimethyl-4-oxo-. A solution of intermediate144, N-(4-fluoro-2-hydroxybenzyl)-3-(benzyloxy)-9,9-dimethyl-4-oxo-4,6,7,9-tetrahydropyrimido[2,1-c][1,4]oxazine-2-carboxamide (0.150 g, 0.331 mmol) and sodium hydride (0.015 g, 0.37 mmol, 60% oil dispersion) in anhydrous dimethylformamide (4 mL) was stirred for 5 minutes under a nitrogen atmosphere. The reaction mixture was treated with 2-chloro-*N*-methylacetamide (0.054 g, 0.50 mmol), and stirred for an additional 16 hours. Solvent was removed by rotary evaporator, and the resulting residue purified by short path flash silica gel chromatography (ethyl acetate). The fractions containing product were combined and concentrated to dryness. The residue was dissolved in

dichloromethane (5 mL) and trifluoroacetic acid (5 mL) and stirred for 1 hour. Solvent was removed by rotary evaporator and the crude product was triturated with a minimal volume of 95% ethanol. The resulting solid was collected by filtration, and dried under vacuum resulting in 93 mg (0.21 mmol, Yield 65%) of the title compound as a white powder: ^{1}H NMR (500 MHz, $CDCl_3$) δ ppm: 11.92 (1H, s), 7.67 (1H, t, *J*=6.3 Hz), 7.57 (1H, br), 7.30 (1H, dd, *J*=8.2, 6.4 Hz), 6.74 (1H, dt, *J*=8.2, 2.3 Hz), 6.60 (1H, dd, *J*=10.4, 2.4 Hz), 4.68 (2H, d, *J*=6.7 Hz), 4.45 (2H, s), 4.00 (4H, s), 2.93 (3H, d, *J*=4.9 Hz), 1.55 (6H, s). ^{13}C NMR (125.77 MHz, $CDCl_3$) δ ppm: 168.05, 167.44, 164.79, 162.82, 157.71, 156.57, 156.50, 152.14, 146.60, 131.94, 131.86, 125.23, 120.71, 120.68, 108.37, 108.20, 100.76, 100.55, 75.81, 67.46, 58.15, 43.24, 38.19, 28.08, 25.83. HRMS $[M+H]^+$ calcd for $C_{20}H_{24}N_4O_6F$: 435.1680; found: 435.1668.

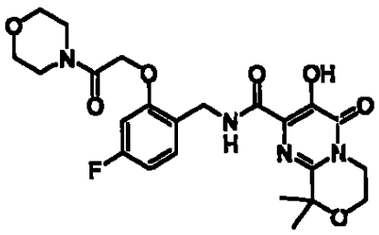
Example 98



Pyrimido[2,1-c][1,4]oxazine-2-carboxamide, N-[[2-[2-(dimethylamino)-2-oxoethoxy]-4-fluorophenyl]methyl]-4,6,7,9-tetrahydro-3-hydroxy-9,9-dimethyl-4-oxo-. The title compound can be prepared from intermediate 144, N-(4-fluoro-2-hydroxybenzyl)-3-(benzyloxy)-9,9-dimethyl-4-oxo-4,6,7,9-tetrahydropyrimido[2,1-c][1,4]oxazine-2-carboxamide according to the method described for example 97. White powder; ^{1}H NMR (500 MHz, $CDCl_3$) δ ppm: 12.25 (1H, br s), 8.36 (1H, t, *J*=5.65 Hz), 7.31 (1H, dd, *J*=8.39, 6.56 Hz), 6.67 (1H, dt, *J*=8.32, 2.29 Hz), 6.57 (1H, dd, *J*=10.38, 2.14 Hz), 4.76 (2H, s), 4.62 (2H, d, *J*=6.10 Hz), 4.00 (4H, s), 3.06 (3H, s), 3.01 (3H, s), 1.58 (6H, s). ^{13}C NMR (125.77 MHz, $CDCl_3$) δ ppm: 168.25, 166.62, 164.23, 162.27, 158.02, 157.39, 151.36, 146.39, 131.25, 131.18, 125.95, 122.23,

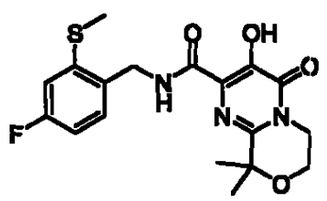
122.20, 108.25, 108.08, 100.47, 100.27, 76.03, 66.24, 58.22, 43.15, 38.59, 36.07, 35.77, 27.94. HRMS $[M+H]^+$ calcd for $C_{21}H_{26}N_4O_6F$: 449.18365; found: 449.1837.

Example 99



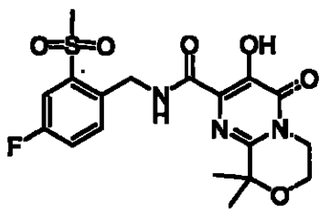
4-Morpholinecarboxylic acid, 5-fluoro-2-[[[(4,6,7,9-tetrahydro-3-hydroxy-9,9-dimethyl-4-oxopyrimido[2,1-c][1,4]oxazin-2-yl)carbonyl]amino]methyl]phenyl ester. The title compound can be prepared from intermediate 144, N-(4-fluoro-2-hydroxybenzyl)-3-(benzyloxy)-9,9-dimethyl-4-oxo-4,6,7,9-tetrahydropyrimido[2,1-c][1,4]oxazine-2-carboxamide according to the method described for example 97. White powder; ^1H NMR (500 MHz, $CDCl_3$) δ ppm: 12.01 (1H, br s), 7.96 (1H, t, *J*=5.34 Hz), 7.38 (1H, dd, *J*=8.39, 6.26 Hz), 6.97 (1H, dt, *J*=8.24, 2.44 Hz), 6.87 (1H, dd, *J*=8.85, 2.44 Hz), 4.51 (2H, d, *J*=6.10 Hz), 4.00 (4H, s), 3.70-3.76 (4H, m), 3.65-3.70 (2H, m), 3.49-3.54 (2H, m), 1.55 (6H, s). ^{13}C NMR (125.77 MHz, $CDCl_3$) δ ppm: 167.91, 163.68, 157.86, 153.48, 151.71, 150.51, 150.42, 146.31, 131.58, 131.50, 125.83, 125.59, 113.84, 113.67, 111.03, 110.84, 75.93, 66.59, 66.52, 58.22, 45.17, 44.41, 43.16, 37.70, 27.95. HRMS $[M+H]^+$ calcd for $C_{22}H_{26}N_4O_7F$: 477.17856; found: 477.1788.

Example 100



Pyrimido[2,1-c][1,4]oxazine-2-carboxamide, N-[[4-fluoro-2-(methylthio)phenyl]methyl]-4,6,7,9-tetrahydro-3-hydroxy-9,9-dimethyl-4-oxo-. The title compound can be prepared from intermediate 25, ethyl 3-hydroxy-9,9-dimethyl-4-oxo-4,6,7,9-tetrahydropyrimido[2,1-c][1,4]oxazine-2-carboxylate, and (4-fluoro-2-(methylthio)phenyl)methanamine according to the methods described for the synthesis of examples 1, 19 and 20. White solid. ^{1}H NMR (300 MHz, $CDCl_3$) δ ppm: 11.88 (1H, br), 8.03 (1H, t, *J*=6.04 Hz), 7.28 (1H, dd, *J*=8.42, 5.85 Hz), 6.93 (1H, dd, *J*=9.51, 2.20 Hz), 6.81 (1H, dt, *J*=8.23, 2.56 Hz), 4.58 (2H, d, *J*=6.22 Hz), 3.98 (4H, s), 2.49 (3H, s), 1.55 (6H, s); HRMS (ESI) calcd for $C_{18}H_{21}FN_3O_4S$ (M+H) 394.1237, found 394.1218.

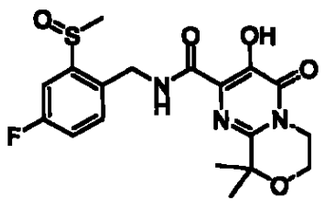
Example 101



Pyrimido[2,1-c][1,4]oxazine-2-carboxamide, N-[[4-fluoro-2-(methylsulfonyl)phenyl]methyl]-4,6,7,9-tetrahydro-3-hydroxy-9,9-dimethyl-4-oxo-. To a solution of example 100 pyrimido[2,1-c][1,4]oxazine-2-carboxamide, N-[[4-fluoro-2-(methylthio)phenyl]methyl]-4,6,7,9-tetrahydro-3-hydroxy-9,9-dimethyl-4-oxo- (158 mg, 0.4 mmol), in CH_2Cl_2 (4 mL) was added 3-chloroperoxybenzoic acid (132 mg, 0.6 mmol; 77%, Aldrich) and the mixture stirred at room temperature for 2 hrs. After removing the solvent *in vacuo*, the residue was triturated with diethyl ether. The crude powder was purified by reverse phase column chromatography (YMC, ODS, 8% CH_3CN/H_2O-0.1% CF_3CO_2H) to provide 32 mg (0.075 mmol, Yield 19%) of the title compound as a white powder after trituration with diethyl ether, and 35 mg (0.086 mmol, Yield 21%) of the corresponding sulfoxide. ^{1}H NMR (300 MHz, $CDCl_3$) δ ppm: 11.71 (1 H, s), 8.58 (1 H, t, *J*=6.04 Hz), 7.73 (1 H, dd, *J*=8.23, 2.74 Hz), 7.68 (1 H, dd, *J*=8.42, 5.12 Hz), 7.32 (1 H, dt, *J*=8.05, 2.93 Hz),

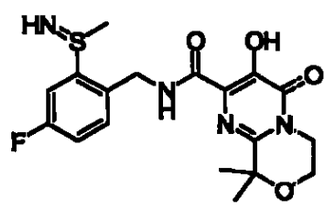
4.79 (2 H, d, *J*=6.95 Hz), 3.97 (4 H, s), 3.15 (3 H, s), 1.56 (6 H, s); HRMS (ESI) calcd for $C_{18}H_{19}FN_3O_6S$ (M-H) 424.0979, found 424.0973.

Example 102



Pyrimido[2,1-c][1,4]oxazine-2-carboxamide, N-[[4-fluoro-2-(methylsulfinyl)phenyl]methyl]-4,6,7,9-tetrahydro-3-hydroxy-9,9-dimethyl-4-oxo. Formed in the reaction described for example 101. ^{1}H NMR (300 MHz, $CDCl_3$) δ ppm: 11.73 (1H, s), 8.19 (1H, t, J=6.59 Hz), 7.54 (1H, dd, J=8.05, 2.93 Hz), 7.47 (1H, dd, J=8.42, 5.12 Hz), 7.16 (1H, dt, J=8.14, 2.74 Hz), 4.57-4.81 (2H, m), 3.99 (4H, s), 2.80 (3H, s), 1.56 (6H, s); HRMS (ESI) calcd for $C_{18}H_{21}FN_3O_5S$ (M-H) 410.1196, found 410.1194.

Example 103

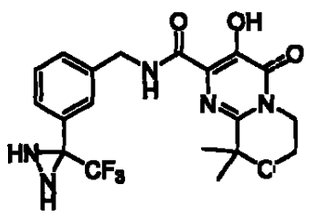


Pyrimido[2,1-c][1,4]oxazine-2-carboxamide, N-[[4-fluoro-2-(S-methylsulfinimidoyl)phenyl]methyl]-4,6,7,9-tetrahydro-3-hydroxy-9,9-dimethyl-4-oxo-. To a solution of example 100, pyrimido[2,1-c][1,4]oxazine-2-carboxamide, N-[[4-fluoro-2-(methylthio)phenyl]methyl]-4,6,7,9-tetrahydro-3-hydroxy-9,9-dimethyl-4-oxo-, (245 mg, 0.75 mmol) in CH_2Cl_2 (3 mL) was added tert-butyl azido formate (115 mg, 0.8 mmol; prepared following the procedure described in Organic Synthesis 1979, 50, 9-12) and ferrous chloride ($FeCl_2$, 50 mg) and the resulting mixture stirred

for 18 hrs. The mixture was diluted with dichloromethane, washed with water, dried ($MgSO_4$), filtered and concentrated to yield 450 mg of 3-hydroxy-9,9-dimethyl-4-oxo-4,6,7,9-tetrahydro-pyrimido[2,1-c][1,4]oxazine-2-carboxylic acid 4-fluoro-2-(N-tert-butoxycarbonyl-S-methyl) sulfiliminyl-benzylamide as a dark gum; LC/MS m/z 509 (M+H).

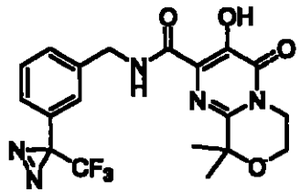
A solution of this material, (100 mg) in CF_3CO_2H (1 mL), was stirred for 20 min then concentrated. The residue was purified by C-18 reverse phase HPLC (YMC ODS, 5-10% CH_3CN/H_2O-0.1% CF_3CO_2H) to provide 15 mg (0.037 mmol, Yield 21%) of the title compound as the corresponding trifluoroacetic acid salt. ^1H NMR (300 MHz, DMSO-D6) δ ppm: 11.62 (1 H, s), 9.57 (1 H, t, J=6.0 Hz), 8.11 (1 H, dd, J=8.8, 1.8 Hz), 7.62-7.71 (2 H, m), 4.58-4.82 (2 H, m), 3.97 (2 H, t, J=4.8 Hz), 3.82 (2 H, t, J=4.8 Hz), 3.37 (3 H, s), 1.57 (6 H, s); HRMS (ESI) calcd for $C_{18}H_{22}FN_4O_4S$ (M+H) 409.1346, found 409.1333.

Example 104



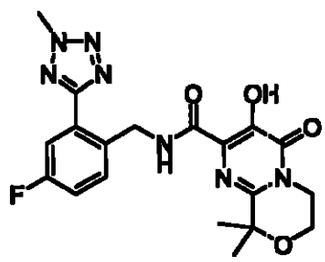
Pyrimido[2,1-c][1,4]oxazine-2-carboxamide, 4,6,7,9-tetrahydro-3-hydroxy-9,9-dimethyl-4-oxo-N-[[3-[3-(trifluoromethyl)-3-diaziridinyl]phenyl]methyl]-. The title compound can be prepared from intermediate 25, ethyl 3-hydroxy-9,9-dimethyl-4-oxo-4,6,7,9-tetrahydropyrimido[2,1-c][1,4]oxazine-2-carboxylate and (4-(diaziridin-3-yl)phenyl)methanamine (formed in the preparation of intermediate 66) according to the methods described for the synthesis of examples 1, 19 and 20. White solid; ^1H NMR (300 MHz, $CDCl_3$) δ ppm: 11.89 (1H, s), 7.81 (1H, t, *J*=6.0 Hz), 7.52-7.59 (2H, m), 7.38-7.44 (2H, m), 4.63 (2H, d, *J*=6.2 Hz), 4.00 (4H, s), 2.78 (1H, d, *J*=7.3 Hz), 2.21 (1H, d, *J*=8.1 Hz), 1.51-1.57 (6H, m); HRMS (ESI) calcd for $C_{19}H_{21}F_3N_5O_4$ (M+H) 440.1546, found 440.1537.

Example 105



Pyrimido[2,1-c][1,4]oxazine-2-carboxamide, 4,6,7,9-tetrahydro-3-hydroxy-9,9-dimethyl-4-oxo-N-[[3-[3-(trifluoromethyl)-3H-diazirin-3-yl]phenyl]methyl]-. The title compound can be prepared from intermediate 25, ethyl 3-hydroxy-9,9-dimethyl-4-oxo-4,6,7,9-tetrahydropyrimido[2,1-c][1,4]oxazine-2-carboxylate and intermediate 66, (3-(3-(trifluoromethyl)diaziridin-3-yl)phenyl)methanamine, according to the methods described for the synthesis of examples 1, 19 and 20. White solid; ^{1}H NMR (300 MHz, $CDCl_3$) δ ppm: 11.86 (1H, s), 7.73-7.84 (1H, m), 7.35-7.40 (2H, m), 7.11-7.17 (1H, m, *J*=2.9 Hz), 7.08-7.11 (1H, m), 4.60 (2H, d, *J*=6.2 Hz), 4.00 (4H, s), 1.55 (6H, s); HRMS (ESI) calcd for $C_{19}H_{19}F_3N_5O_4$ (M+H) 438.1389, found 438.1371.

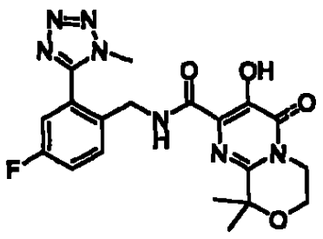
Example 106



Pyrimido[2,1-c][1,4]oxazine-2-carboxamide, N-[[4-fluoro-2-(2-methyl-2H-tetrazol-5-yl)phenyl]methyl]-4,6,7,9-tetrahydro-3-hydroxy-9,9-dimethyl-4-oxo-. The title compound can be prepared from intermediate 25, ethyl 3-hydroxy-9,9-dimethyl-4-oxo-4,6,7,9-tetrahydropyrimido[2,1-c][1,4]oxazine-2-carboxylate and intermediate 59, (4-fluoro-2-(2-methyl-2H-tetrazol-5-yl)phenyl)methanamine hydrochloride, according to the methods described for the synthesis of examples 1, 19 and 20. (white

solid); ^{1}H NMR (300 MHz, $CDCl_3$) δ ppm: 12.01 (1H, s), 9.24 (1H, t, *J*=6.8 Hz), 7.75 (1H, dd, *J*=9.5, 2.6 Hz), 7.63 (1H, dd, *J*=8.4, 5.5 Hz), 7.15 (1H, dt, *J*=8.2, 2.6 Hz), 4.70 (2H, d, *J*=7.0 Hz), 4.45 (3H, s), 3.96 (4 H, s), 1.53 (6H, s); HRMS (ESI) calcd for $C_{19}H_{21}FN_7O_4$ (M+H) 430.1639, found 430.1649.

Example 107

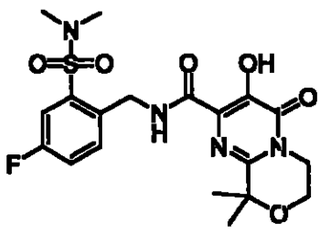


Pyrimido[2,1-c][1,4]oxazine-2-carboxamide, N-[[4-fluoro-2-(1-methyl-1H-tetrazol-5-yl)phenyl]methyl]-4,6,7,9-tetrahydro-3-hydroxy-9,9-dimethyl-4-oxo-. The title compound can be prepared from intermediate 25, ethyl 3-hydroxy-9,9-dimethyl-4-oxo-4,6,7,9-tetrahydropyrimido[2,1-c][1,4]oxazine-2-carboxylate and intermediate 62, (4-fluoro-2-(1-methyl-2H-tetrazol-5-yl)phenyl)methanamine hydrochloride, according to the methods described for the synthesis of examples 1, 19 and 20. Off-white solid; ^{1}H NMR (500 MHz, $CDCl_3$) δ ppm: 11.83 (1H, s), 9.17 (1H, t, *J*=5.8 Hz), 7.75 (1H, dd, *J*=8.4, 5.7 Hz), 7.30 (1H, t, *J*=8.2 Hz), 7.14 (1H, d, *J*=7.9 Hz), 4.43 (2H, d, *J*=6.7 Hz), 4.14-4.16 (3H, m), 4.00 (4 H, s), 1.67 (6H, s); HRMS (ESI) calcd for $C_{19}H_{21}FN_7O_4$ (M+H) 430.1639, found 430.1619.

Examples 108-112

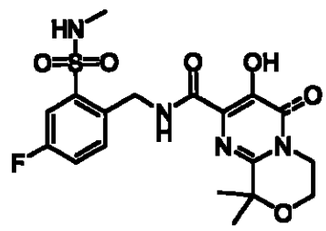
Examples 108-112 can be prepared from intermediate 25, ethyl 3-hydroxy-9,9-dimethyl-4-oxo-4,6,7,9-tetrahydropyrimido[2,1-c][1,4]oxazine-2-carboxylate and the indicated amines according to the methods described for the synthesis of examples 1, 19 and 20.

Example 108



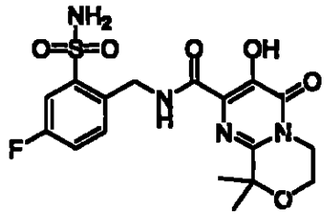
Pyrimido[2,1-c][1,4]oxazine-2-carboxamide, N-[[2-[(dimethylamino)sulfonyl]-4-fluorophenyl]methyl]-4,6,7,9-tetrahydro-3-hydroxy-9,9-dimethyl-4-oxo-. The title compound can be prepared from intermediate 48, 2-(aminomethyl)-5-fluoro-N,N-dimethylbenzenesulfonamide. White solid; ^{1}H NMR (500 MHz, $CDCl_3$) δ ppm: 11.83 (1H, s), 8.64 (1H, t, *J*=6.6 Hz), 7.68 (1H, dd, *J*=8.6, 5.5 Hz), 7.50 (1H, dd, *J*=8.2, 2.8 Hz), 7.26-7.30 (1H, m), 4.80 (2H, d, *J*=7.0 Hz), 3.99 (4H, s), 2.91 (6H, s), 1.58 (6H, s); HRMS (ESI) calcd for $C_{19}H_{24}FN_4O_6S$ (M+H) 455.1401, found 455.1402.

Example 109



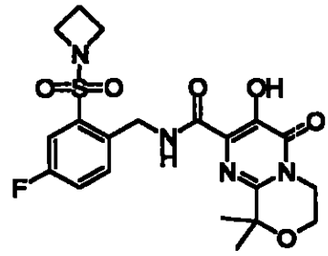
Pyrimido[2,1-c][1,4]oxazine-2-carboxamide, N-[[4-fluoro-2-[(methylamino)sulfonyl]phenyl]methyl]-4,6,7,9-tetrahydro-3-hydroxy-9,9-dimethyl-4-oxo-. The title compound can be prepared from intermediate 52, 2-(aminomethyl)-5-fluoro-N-methylbenzenesulfonamide hydrochloride. Off-white solid; ^{1}H NMR (300 MHz, $CDCl_3$) δ ppm: 11.69 (1H, s), 8.55 (1H, br), 7.58-7.67 (2H, m), 7.24-7.29 (1H, m), 4.87-4.97 (1H, br), 4.82 (2H, d, *J*=6.2 Hz), 3.97 (4H, s), 2.71 (3H, d, *J*=4.4 Hz), 1.56 (6H, s); HRMS (ESI) calcd for $C_{18}H_{22}FN_4O_6S$ (M+H) 441.1244, found 441.1237.

Example 110



Pyrimido[2,1-c][1,4]oxazine-2-carboxamide, N-[[2-(aminosulfonyl)-4-fluorophenyl]methyl]-4,6,7,9-tetrahydro-3-hydroxy-9,9-dimethyl-4-oxo-. The title compound can be prepared from intermediate 56, 2-(aminomethyl)-5-fluorobenzenesulfonamide hydrochloride. Off-white solid, ^{1}H NMR (300 MHz, DMSO-D6) δ ppm: 11.92 (1H, s), 9.33 (1H, t, *J*=6.4 Hz), 7.66 (1H, dd, *J*=8.8, 2.2 Hz), 7.41-7.52 (2H, m), 4.89 (2H, d, *J*=6.2 Hz), 3.98 (2H, t, *J*=4.9 Hz), 3.83 (2H, t, *J*=4.9 Hz), 3.37 (2H, br), 1.55 (6H, s); HRMS (ESI) calcd for $C_{17}H_{20}FN_4O_6S$ (M+H) 427.1088, found 427.1082.

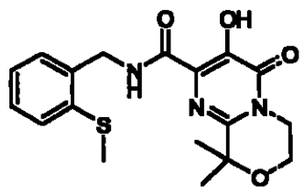
Example 111



Pyrimido[2,1-c][1,4]oxazine-2-carboxamide, N-[[2-(1-azetidinylsulfonyl)-4-fluorophenyl]methyl]-4,6,7,9-tetrahydro-3-hydroxy-9,9-dimethyl-4-oxo-. The title compound can be prepared from (2-(azetidin-1-ylsulfonyl)-4-fluorophenyl)methanamine, which was synthesized according to the methods used to prepare intermediate 48. White solid, ^{1}H NMR (500 MHz, $CDCl_3$) δ ppm 11.86 (1H, s), 8.57 (1H, t, *J*=6.3 Hz), 7.65-7.72 (2H, m), 7.26-7.31 (1H, m), 4.82 (2H, d, *J*=6.7

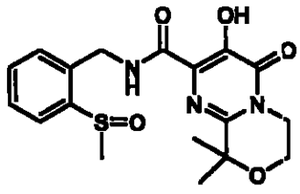
Hz), 3.99 (4H, s), 3.96 (4H, t, *J*=7.8 Hz), 2.23-2.32 (2H, m), 1.58 (6H, s); HRMS (ESI) calcd for $C_{20}H_{24}FN_4O_6S$ (M+H) 467.1401, found 467.1398.

Example 112



Pyrimido[2,1-c][1,4]oxazine-2-carboxamide, 4,6,7,9-tetrahydro-3-hydroxy-9,9-dimethyl-N-[[2-(methylthio)phenyl]methyl]-4-oxo-. Prepared according to the method described for the synthesis of example 100. White solid, ^{1}H NMR (300 MHz, $CDCl_3$) δ ppm: 1.55 (6H, s), 2.50 (3H, s), 3.98 (4H, s), 4.65 (2H, d, J=6.6 Hz), 7.1-7.4 (3H, m), 8.11 (1H, t, J=5.9 Hz), 11.94 (1H, s); LC/MS m/z 376 (M+H).

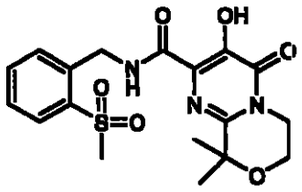
Example 113



Pyrimido[2,1-c][1,4]oxazine-2-carboxamide, 4,6,7,9-tetrahydro-3-hydroxy-9,9-dimethyl-N-[[2-(methylsulfinyl)phenyl]methyl]-4-oxo-. To a solution example 112, pyrimido[2,1-c][1,4]oxazine-2-carboxamide, 4,6,7,9-tetrahydro-3-hydroxy-9,9-dimethyl-N-[[2-(methylthio)phenyl]methyl]-4-oxo-, (112 mg, 0.3 mmol) in CH_2Cl_2 (5 mL) was added 3-chloroperoxybenzoic acid (69 mg, 0.3 mmol; 77%, Aldrich) and the mixture stirred for 5 min. After removing the solvent *in vacuo*, the residue was purified by preparative reverse phase HPLC (YMC, ODS, 8-15% CH_3CN/H_2O-0.1% CF_3CO_2H) to provide 58 mg (0.16 mmol, Yield 53%) of the title compound as a white powder after trituration with diethyl ether. ^{1}H NMR (300 MHz, $CDCl_3$) δ ppm:

1.56 (6H, s), 2.80 (3H,s), 3.98 (4H, s), 4.60-4.94 (2H, m), 7.38-7.61 (3H, m), 7.65-7.89 (1H, m), 8.34 (1H, t, J=6.4 Hz), 11.82 (1H, s). HRMS (ESI) calcd for $C_{18}H_{22}N_3O_5S$ (M+H) 392.1280, found 392.1281.

Example 114

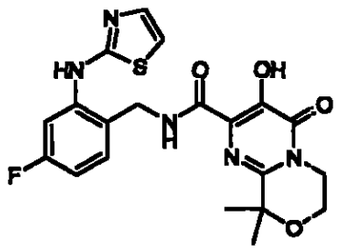


Pyrimido[2,1-c][1,4]oxazine-2-carboxamide, 4,6,7,9-tetrahydro-3-hydroxy-9,9-dimethyl-N-[[2-(methylsulfonyl)phenyl]methyl]-4-oxo-. To a solution of example 112, pyrimido[2,1-c][1,4]oxazine-2-carboxamide, 4,6,7,9-tetrahydro-3-hydroxy-9,9-dimethyl-N-[[2-(methylthio)phenyl]methyl]-4-oxo- (112 mg, 0.3 mmol) in CH_2Cl_2 (5 mL) was added 3-chloroperoxybenzoic acid (140 mg, 0.62 mmol; 77%, Aldrich) and the mixture stirred for 20 hrs. After removing the solvent *in vacuo*, the residue was purified by preparative reverse phase HPLC (YMC, ODS, 15% CH_3CN/H_2O-0.1% CF_3CO_2H) to provide 61 mg (0.15 mmol, Yield 50%) of the title compound as a white powder after trituration with diethyl ether. ^1H NMR (300 MHz, $CDCl_3$) δ ppm: 1.56 (6H, s), 3.14 (3H,s), 3.96 (4H, s), 4.83 (2H, d, J=7.0 Hz), 7.39-7.57 (1H, m), 7.60-7.68 (2H, m), 8.02 (1H, d, J=8.4 Hz), 8.65 (1H, t, J=7.0 Hz), 11.78 (1H, brs). HRMS (ESI) calcd for $C_{18}H_{22}N_3O_6S$ (M+H) 408.1229, found 408.1217.

Examples 115-116

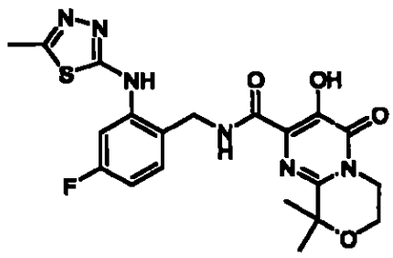
Examples 115-116 can be prepared from the indicated intermediates by hydrogenolysis or trifluoroacetic acid mediated hydrolysis.

Example 115



Pyrimido[2,1-c][1,4]oxazine-2-carboxamide, N-[[4-fluoro-2-(2-thiazolylamino)phenyl]methyl]-4,6,7,9-tetrahydro-3-hydroxy-9,9-dimethyl-4-oxo-. The title compound can be prepared from intermediate 163, N-(4-fluoro-2-(thiazol-2-ylamino)benzyl)-3-(benzyloxy)-9,9-dimethyl-4-oxo-4,6,7,9-tetrahydropyrimido[2,1-c][1,4]oxazine-2-carboxamide. ^{1}H NMR (400 MHz, DMSO-d6) δ ppm: 11.97 (1H, brs), 9.72 (1H, brs), 9.39 (1H, t, J = 6.3 Hz), 8.14 (1H, dd, J = 2.5, 12.0 Hz), 7.31-7.28 (2H, m), 6.99 (1H, d, J = 3.8 Hz), 6.84 (1H, ddd(dt), J = 2.5, 8.3 Hz), 4.52 (2H, d, J = 6.3 Hz), 3.96-3.94 (2H, m), 3.82-3.79 (2H, m), 1.54 (6H, s) LCMS ($^+$ESI, M+H$^+$) m/z 446. HRMS (ESI$^+$) calculated for $C_{20}H_{21}FN_5O_4S$ [M+H$^+$]: 446.1298; found: 446.1292.

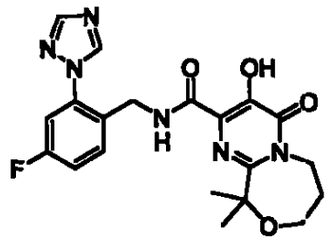
Example 116



Pyrimido[2,1-c][1,4]oxazine-2-carboxamide, N-[[4-fluoro-2-[(5-methyl-1,3,4-thiadiazol-2-yl)amino]phenyl]methyl]-4,6,7,9-tetrahydro-3-hydroxy-9,9-dimethyl-4-oxo-. The title compound can be prepared from intermediate 164, N-(4-fluoro-2-(5-methyl-1,3,4-thiadiazol-2-ylamino)benzyl)-3-(benzyloxy)-9,9-dimethyl-4-oxo-4,6,7,9-tetrahydropyrimido[2,1-c][1,4]oxazine-2-carboxamide. ^{1}H NMR (400

MHz, DMSO-d6) δ ppm: 11.97 (1H, brs), 9.66 (1H, brs), 9.37 (1H, brt, J = 6.1 Hz), 7.99 (1H, brd), 7.29 (1H, brt, J = 7.1 Hz), 6.88 (1H, ddd(dt), J = 2.5, 8.0 Hz), 4.52 (2H, d, J = 6.1 Hz), 3.97-3.94 (2H, m), 3.82-3.80 (2H, m), 2.55 (3H, s), 1.54 (6H, s); LCMS ($^+$ ESI, M+H$^+$) m/z 461. HRMS (ESI$^+$) calculated for $C_{20}H_{22}FN_6O_4S$ [M+H$^+$]: 461.1407; found: 461.1425.

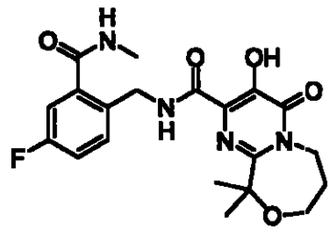
Example 117



6H-Pyrimido[2,1-c][1,4]oxazepine-2-carboxamide, N-[[4-fluoro-2-(1H-1,2,4-triazol-1-yl)phenyl]methyl]-4,7,8,10-tetrahydro-3-hydroxy-10,10-dimethyl-4-oxo- A solution of intermediate 33, ethyl 2-(2-(3-chloropropoxy)propan-2-yl)-5-hydroxy-6-oxo-1,6-dihydropyrimidine-4-carboxylate, (0.208 g, 0.65 mmol) in anhydrous dimethylformamide (2 mL) was stirred with anhydrous potassium carbonate (0.366 g, 2.6 mmol) at 60 °C for 16 hours. This was treated with intermediate 69, (4-fluoro-2-(1H-1,2,4-triazol-1-yl)phenyl)methanamine hydrochloride, (0.451 g, 2.08 mmol) and triethylamine (0.5 mL, 3.6 mmol) and stirring continued at 100 °C for 16 hours. The solvent was removed by rotary evaporator and the was purified by preparative reverse phase HPLC (C18, 10%-35% CH_3CN/H_2O-0.1% trifluoroacetic acid). Fractions containing product were pooled and concentrated by rotary evaporator. The resulting aqueous solution was extracted with ethyl acetate (2 x 50 mL), and the combined organic fractions dried (sodium sulfate), filtered, and concentrated to dryness. The resulting residue was triturated with a minimal volume of 95% ethanol, and the solid collected by filtration to give 103 mg (0.24 mmol, Yield 37%) of the title compound as a white solid: ^{1}H NMR (500 MHz, $CDCl_3$) δ ppm: 11.96 (1H, br s), 8.83 (1H, t, *J*=6.6 Hz), 8.46 (1H, s), 8.17 (1H, s), 7.71 (1H, dd, *J*=8.5, 6.1 Hz), 7.21 (1H, dt, *J*=8.2, 2.6 Hz), 7.11 (1H, dd,

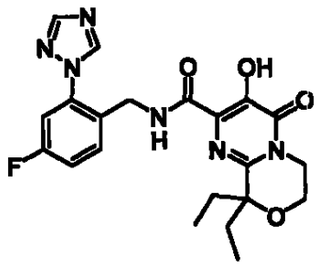
J=8.4, 2.6 Hz), 4.55 (2H, br), 4.44 (2H, d, *J*=6.7 Hz), 3.67 (2H, t, *J*=6.4 Hz), 1.91-1.97 (2H, p *J*=6.10 Hz), 1.63 (6H, s). ^{13}C NMR (125.76 MHz, $CDCl_3$) δ ppm: 167.97, 163.19, 161.20, 158.28, 153.35, 152.90, 147.34, 143.94, 136.89, 134.45, 134.37, 128.65, 128.62, 125.01, 117.09, 116.93, 112.42, 112.23, 82.46, 60.88, 39.13, 38.56, 27.73, 27.36. HRMS $[M+H]^+$ calcd for $C_{20}H_{22}N_6O_4F$: 429.16867; found: 429.1687. Anal calcd for $C_{20}H_{21}N_6O_4F \cdot 0.06\ H_2O$: C, 55.93; H, 4.96; N, 19.57, F, 4.42; found: C, 55.80; H, 5.14; N, 19.74, F, 4.46.

Example 118



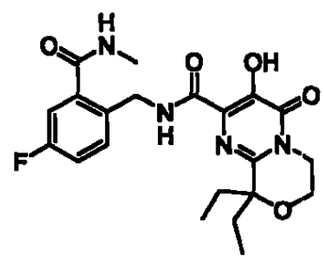
6H-Pyrimido[2,1-c][1,4]oxazepine-2-carboxamide, N-[[4-fluoro-2-[(methylamino)carbonyl]phenyl]methyl]-4,7,8,10-tetrahydro-3-hydroxy-10,10-dimethyl-4-oxo-. The title compound can be prepared from intermediate 148, N-(4-fluoro-2-(methylcarbamoyl)benzyl)-3-(benzyloxy)-10,10-dimethyl-4-oxo-6,7,8,10-tetrahydro-4H-pyrimido[2,1-c][1,4]oxazepine-2-carboxamide according to the method described for example 46. White powder; ^{1}H NMR (500 MHz, DMSO-D6) δ ppm: 12.17 (1H, s), 9.23 (1H, t, *J*=6.4 Hz), 8.56 (1H, q, *J*=4.3 Hz), 7.41 (1H, dd, *J*=8.6, 5.8 Hz), 7.34 (1H, dd, *J*=9.2, 2.8 Hz), 7.30 (1H, dt, *J*=8.6, 2.8 Hz), 4.55 (2H, d, *J*=6.4 Hz), 4.37 (2H, br), 3.64 (2H, t, *J*=6.4 Hz), 2.80 (3H, d, *J*=4.6 Hz), 1.80-1.86 (2H, m), 1.57 (6H, s); HRMS $[M+H]^+$ calcd for $C_{20}H_{23}N_4O_5F$: 419.17308; found: 419.1713.

Example 119



Pyrimido[2,1-c][1,4]oxazine-2-carboxamide, 9,9-diethyl-N-[[4-fluoro-2-(1H-1,2,4-triazol-1-yl)phenyl]methyl]-4,6,7,9-tetrahydro-3-hydroxy-4-oxo-. The title compound can be prepared from intermediate 31, ethyl 9,9-diethyl-3-hydroxy-4-oxo-4,6,7,9-tetrahydropyrimido[2,1-c][1,4]oxazine-2-carboxylate, and intermediate 69, (4-fluoro-2-(1H-1,2,4-triazol-1-yl)phenyl)methanamine hydrochloride, according to the methods described for examples 1, 19 and 20. White powder; ^{1}H NMR (500 MHz, $CDCl_3$) δ ppm: 11.89 (1H, br s), 8.81 (1H, t, *J*=6.6 Hz), 8.46 (1H, s), 8.15 (1H, s), 7.69 (1H, dd, *J*=8.6, 5.8 Hz), 7.22 (1H, dt, *J*=8.2, 2.6 Hz), 7.12 (1H, dd, *J*=8.4, 2.6 Hz), 4.45 (2H, d, *J*=6.7 Hz), 3.95-4.02 (4H, m), 1.95-2.03 (2H, m), 1.87-1.96 (2H, m), 0.86 (6H, t, *J*=7.5 Hz). ^{13}C NMR (125.76 MHz, $CDCl_3$) δ ppm: 167.98, 163.19, 161.20, 157.88, 152.81, 151.29, 146.05, 143.97, 137.00, 136.93, 134.28, 134.21, 128.62, 128.59, 125.85, 117.10, 116.94, 112.58, 112.36, 80.93, 58.63, 43.02, 39.20, 31.43, 7.86. HRMS $[M+H]^+$ calcd for $C_{21}H_{24}N_6O_4F$: 443.18432; found: 443.1845.

Example 120



Pyrimido[2,1-c][1,4]oxazine-2-carboxamide, 9,9-diethyl-N-[[4-fluoro-2-[(methylamino)carbonyl]phenyl]methyl]-4,6,7,9-tetrahydro-3-hydroxy-4-oxo-. A solution of intermediate 31, ethyl 9,9-diethyl-3-hydroxy-4-oxo-4,6,7,9-tetrahydropyrimido[2,1-c][1,4]oxazine-2-carboxylate, (0.228 g, 0.77 mmol)in anhydrous dimethylformamide (5 mL) was treated with anhydrous potassium carbonate (0.279 g, 2.0 mmol) followed by benzyl bromide (0.145 g, 0.85 mmol), and the mixture stirred for 16 hours. The mixture was treated with lithium hydroxide (0.042 g, 1.75 mmol) and water (2 mL) and stirred for 20 hours. The reaction mixture was diluted with water (30 mL) and brought to pH 1 with 6 N hydrochloric acid. The crude product was extracted with ethyl acetate (2 x 30 mL). The combined organic layers were dried (sodium sulfate), filtered, and concentrated to dryness.

A solution of this material, in anhydrous dimethylformamide (4 mL), was treated with HATU (0.32 g, 0.83 mmol) and stirred for 10 minutes. The reaction mixture was treated with intermediate 39, 2-aminomethyl-5-fluoro-N-methyl-benzamide trifluoroacetic acid salt, (0.281 g, 0.94 mmol), followed by dimethylaminopyridine, DMAP, (0.140 g, 1.125 mmol), and stirred at 60°C for 3 hours. Solvent was removed by rotary evaporator and the residue purified by flash column chromatography, eluting with 50% to 60% ethyl acetate in hexanes. Fractions containing the product were pooled and concentrated to dryness, which gave a white glassy solid. A sample (approximately 10 mg) was further dried under vacuum, and the remainder used in the following reaction: ^{1}H NMR (500 MHz, $CDCl_3$) δ ppm: 8.47 (1H, t, *J*=6.2 Hz), 7.36-7.45 (3H, m), 7.23-7.27 (2H, m), 7.10 (1H, dd, *J*=8.8, 2.9 Hz), 7.04 (1H, dt, *J*=8.3, 2.7 Hz), 6.60-6.69 (1H, br), 5.25 (2H, s), 4.50 (2H, d, *J*=6.2 Hz), 3.94 (4H, s), 2.95 (3H, d, *J*=5.1 Hz), 1.90-2.02 (5H, m), 0.75-0.82 (6H, m).

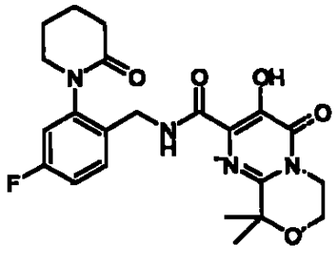
A solution of the above compound in dichloromethane (5 mL) and trifluoroacetic acid (5 mL) was stirred for 2 hours. The solvent was removed and the crude product was purified by preparative reverse phase HPLC (C-18 column, 10% to 40% CH_3CN/H_2O-0.1% CF_3CO_2H). Fractions containing product were pooled and concentrated *in vacuo*. The resulting aqueous suspension was extracted with dichloromethane (4 x 100 mL), and the combined organic extracts, dried (sodium

sulfate), filtered, and concentrated to dryness. The residue was recrystallized ethanol/H_2O to provide 0.012 g (0.028 mmol, Yield 4%) of the title compound as a white solid. ^{1}H NMR (500 MHz, DMSO-D6) δ ppm: 12.10 (1H, s), 9.30 (1H, t, *J*=6.4 Hz), 8.52 (1H, m), 7.39 (1H, dd, *J*=8.4, 5.7 Hz), 7.26-7.35 (2H, m), 4.57 (2H, d, *J*=6.4 Hz), 3.94 (2H, t, *J*=4.9 Hz), 3.84 (2H, t, *J*=4.9 Hz), 2.79 (3H, d, *J*=4.6 Hz), 1.99-2.09 (2H, m), 1.81-1.91 (2H, m), 0.77 (6H, t, *J*=7.3 Hz). ^{13}C NMR (125.76 MHz, DMSO-D6) δ ppm: 167.86, 167.57, 159.65, 156.86, 151.21, 145.10, 137.26, 137.21, 132.52, 130.75, 130.68, 125.39, 116.69, 116.52, 114.71, 114.53, 80.04, 57.60, 42.62, 40.05, 30.04, 26.03, 7.47. HRMS $[M+H]^+$ calcd for $C_{21}H_{26}N_4O_5F$: 433.18873; found: 433.1872.

Examples 121-130

Examples 121-130can be prepared from the indicated intermediates according to the methods described for examples 121 and 122. Alternatively, the examples can be formed by treating the indicated intermediates with trifluoroacetic acid.

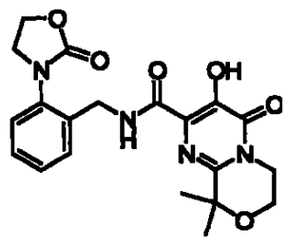
Example 121



Pyrimido[2,1-c][1,4]oxazine-2-carboxamide, N-[[4-fluoro-2-(2-oxo-1-piperidinyl)phenyl]methyl]-4,6,7,9-tetrahydro-3-hydroxy-9,9-dimethyl-4-oxo-. To intermediate 145, N-(4-fluoro-2-(2-oxopiperidin-1-yl)benzyl)-3-(benzyloxy)-9,9-dimethyl—4-oxo-4,6,7,9-tetrahydropyrimido[2,1-c][1,4]oxazin-4(*9H*)-one, (100 mg, 0.187 mmol) in ethyl acetate (10 mL) was added palladium (10% on charcoal) (30 mg). The reaction mixture was stirred at 23 °C under a hydrogen atmosphere (balloon) for 3h. The catalyst was removed by filtration on Celite. The filtrate was

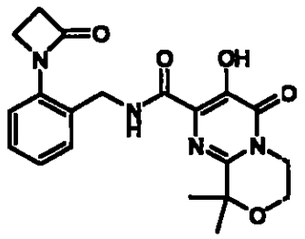
concentrated *in vacuo* and the resulting residue triturated with diethyl ether (10 ml) and dried *in vacuo* to afford 37 mg (45% yield) of the title compound. IR (KBr, cm^{-1}) 3397, 2943, 1636, 1539, 1173. ^{1}HNMR 400 MHz (MeOD) δ ppm: 7.51 (1H, dd, (t), J =7.0 Hz), 7.11 (2H, m), 4.70 (1H, d, J = 15.3 Hz), 4.24 (1H, d, J =15.3 Hz), 4.05 (2H, m), 3.96 (2H, m,), 3.73 (1H, m), 3.62 (1H, m), 2.63-2.48 (2H, m), 2.03 (4H, broad s), 1.62 (6H, s). LCMS $(M+H)^+$ m/z 445.

Example 122



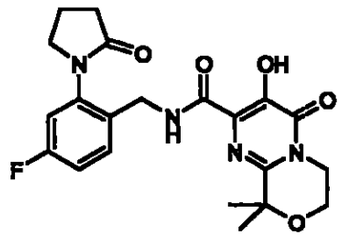
Pyrimido[2,1-c][1,4]oxazine-2-carboxamide, 4,6,7,9-tetrahydro-3-hydroxy-9,9-dimethyl-4-oxo-N-[[2-(2-oxo-3-oxazolidinyl)phenyl]methyl]-. To intermediate 161, N-(4-fluoro-2-(2-oxopiperidin-1-yl)benzyl)-3-(benzyloxy)-9,9-dimethyl—4-oxo-4,6,7,9-tetrahydropyrimido[2,1-c][1,4]oxazin-4(*9H*)-one (100 mg, 0.187 mmol) in ethyl acetate (10 mL) was added palladium (10% on charcoal) (30 mg) . The reaction mixture was stirred at 23 °C under a hydrogen atmosphere (balloon) for 3h. The catalyst was removed by filtration on Celite. The filtrate was concentrated *in vacuo* and the resulting residue triturated with diethyl ether (10 ml) and dried *in vacuo* to afford 37 mg (45%) of the title compound. IR (KBr, cm^{-1}) 3397, 2943, 1636, 1539, 1173. ^{1}HNMR 400 MHz (MeOD) δ ppm: 7.51 (1H, dd, (t), J =7.0 Hz), 7.11 (2H, m), 4.70 (1H, d, J = 15.3 Hz), 4.24 (1H, d, J =15.3 Hz), 4.05 (2H, m), 3.96 (2H, m,), 3.73 (1H, m), 3.62 (1H, m), 2.63-2.48 (2H, m), 2.03 (4H, broad s), 1.62 (6H, s). LCMS $(M+H)^+$ m/z 445.

Example 123



Pyrimido[2,1-c][1,4]oxazine-2-carboxamide, 4,6,7,9-tetrahydro-3-hydroxy-9,9-dimethyl-4-oxo-N-[[2-(2-oxo-1-azetidinyl)phenyl]methyl]-. The title compound can be prepared from intermediate 162, N-(2-(2-oxoazetidin-1-yl)benzyl)-3-(benzyloxy)-9,9-dimethyl-4-oxo-4,6,7,9-tetrahydropyrimido[2,1-c][1,4]oxazine-2-carboxamide. ^{1}H NMR (400 MHz, $CDCl_3$) δ ppm: 12.15 (1H, brs), 9.65 (1H, brs), 7.33-7.20 (4H, m), 4.54 (2H, d, J = 6.6 Hz), 3.96-3.94 (2H, m), 3.82-3.79 (2H, m), 3.76 (2H, t, J = 4.3 Hz), 3.10 (2H, t, J = 4.3 Hz), 1.53 (6H, s); LCMS ($^+$ESI, M+H$^+$) m/z 399.

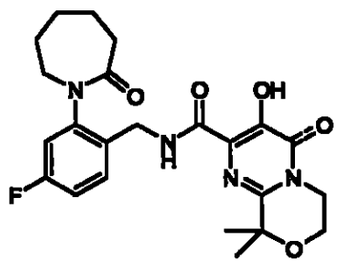
Example 124



Pyrimido[2,1-c][1,4]oxazine-2-carboxamide, N-[[4-fluoro-2-(2-oxo-1-pyrrolidinyl)phenyl]methyl]-4,6,7,9-tetrahydro-3-hydroxy-9,9-dimethyl-4-oxo. The title compound can be prepared from intermediate 159, N-(4-fluoro-2-(2-oxopyrrolidin-1-yl)benzyl)-3-(benzyloxy)-9,9-dimethyl-4-oxo-4,6,7,9-tetrahydropyrimido[2,1-c][1,4]oxazine-2-carboxamide. IR (KBr, cm^{-1}) 3432, 2980, 1689, 1543, 1183. ^{1}HNMR 400 MHz (MeOD) δ ppm: 7.53 (1H, dd, J = 9.2, 6.3 Hz), 7.11 (2H, m), 4.52 (2H, s), 4.05 (2H, t, J = 5.0 Hz), 3.96 (2H, m), 3.87 (2H, t, J = 7.1

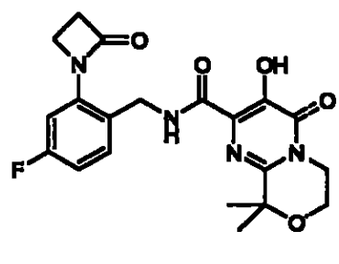
Hz), 2.61 (2H, t, J = 8.0 Hz), 2.26 (2H, m), 1.6 (6H, s).HRMS (ESI^+) calculated for $C_{21}H_{24}FN_4O_5$ [$M+H^+$]: 431.1731; found: 431.1714.

Example 125



Pyrimido[2,1-c][1,4]oxazine-2-carboxamide, N-[[4-fluoro-2-(hexahydro-2-oxo-1H-azepin-1-yl)phenyl]methyl]-4,6,7,9-tetrahydro-3-hydroxy-9,9-dimethyl-4-oxo-. The title compound can be prepared from intermediate 160, N-(4-fluoro-2-(2-oxoazepan-1-yl)benzyl)-3-(benzyloxy)-9,9-dimethyl-4-oxo-4,6,7,9-tetrahydropyrimido[2,1-c][1,4]oxazine-2 carboxamide. IR (KBr, cm^{-1}) 3392, 2934, 1646, 1522, 1292. ^{1}HNMR 400 MHz (MeOD) δ ppm: 7.50 (1H, broad s), 7.06 (1H, broad s), 7.01 (1H, d, J = 9.0 Hz), 4.64 (1H, d, J_{AB} = 15.0 Hz), 4.31 (1H, d, J_{AB} = 15 Hz), 4.04 (2H, m), 3.96 (3H, m), 3.66 (1H, m), 2.86 (1H, m), 2.65 (1H, m), 2.03-1.80 (6H, m), 1.62 (6H, s), (2H, m). LCMS $(M+H)^+$ m/z 459.

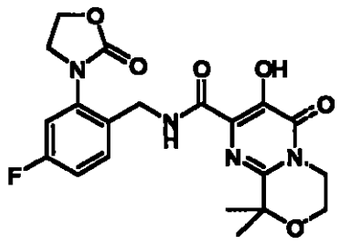
Example 126



N-(4-Fluoro-2-(2-oxoazetidin-1-yl)benzyl)-3-hydroxy-9,9-dimethyl-4-oxo-4,6,7,9-tetrahydropyrimido[2,1-c][1,4]oxazine-2-carboxamide. The title compound can be prepared from intermediate 146, N-(4-fluoro-2-(2-oxoazetidin-1-yl)benzyl)-3-

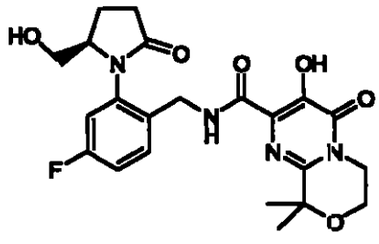
(benzyloxy)-9,9-dimethyl-4-oxo-4,6,7,9-tetrahydropyrimido[2,1-c][1,4]oxazine-2-carboxamide. ^{1}H NMR (400 MHz, DMSO-d_6) δ: 9.46 (d, J = 6.4 Hz), 7.34 (1H, dd, J = 8.5, 6.4 Hz), 7.25 (1H, dd, J = 10.2, 2.6 Hz), 7.08 (1H, td, J = 8.5, 2.6 Hz), 6.90 (1H, m), 4.52 (2H, d, J = 6.4 Hz), 3.96 (2H, t, J = 5.0 Hz), 3.83-3.77 (4H, m), 3.11 (2H, t, J = 5.0 Hz), 1.53 (6H, s); LCMS $(M+H)^+$ m/z 417.

Example 127



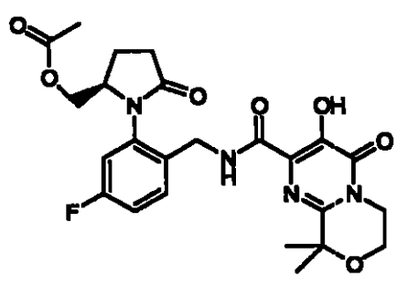
N-(4-Fluoro-2-(2-oxooxazolidin-3-yl)benzyl)-3-hydroxy-9,9-dimethyl-4-oxo-4,6,7,9-tetrahydropyrimido[2,1-c][1,4]oxazine-2-carboxamide. The title compound can be prepared from intermediate 165, N-(4-fluoro-2-(2-oxooxazolidin-3-yl)benzyl)-3-(benzyloxy)-9,9-dimethyl-4-oxo-4,6,7,9-tetrahydropyrimido[2,1-c][1,4]oxazine-2-carboxamide. ^{1}H NMR (400 MHz, DMSO-d_6) δ ppm: 12.12 (1H, s), 9.34 (1H, t, J = 6.2 Hz), 7.41 (1H, m), 7.23 (1H, td, J = 8.6, 2.5 Hz), 4.48 (4H, m), 4.06 (2H, t, J = 7.7 Hz), 3.97 (2H, t, J = 5.0 Hz), 3.83 (2H, t, J = 5.0 Hz), 1.55 (6H, s). LCMS $(M+H)^+$ m/z 433.

Example 128



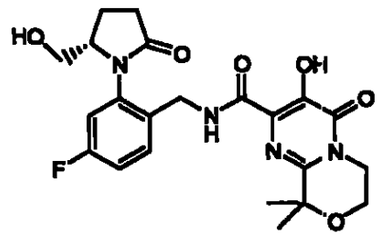
Pyrimido[2,1-c][1,4]oxazine-2-carboxamide, N-[[4-fluoro-2-[(2R)-2-(hydroxymethyl)-5-oxo-1-pyrrolidinyl]phenyl]methyl]-4,6,7,9-tetrahydro-3-hydroxy-9,9-dimethyl-4-oxo-. The title compound can be prepared from intermediate 192, (R)-N-(4-fluoro-2-(2-(hydroxymethyl)-5-oxopyrrolidin-1-yl)benzyl)-3-(benzyloxy)-9,9-dimethyl-4-oxo-4,6,7,9-tetrahydropyrimido[2,1-c][1,4]oxazine-2-carboxamide. IR (KBr, cm^{-1}) 3441, 2979, 1684, 1540, 1172. ^{1}HNMR 400 MHz (MeOD) δ ppm: 7.56 (1H, m), 7.15 (2H, m), 4.86-4.31 (3H, m), 4.06 (2H, t, 5.0 Hz), 3.98 (2H, t, 5.0 Hz), 3.57 (2H, broad s), 2.72-2.55 (2H, m), 2.41 (1H, m), 2.25 (1H, m), 1.62 (6H, s). LCMS $(M+H)^+$ m/z 461.

Example 129



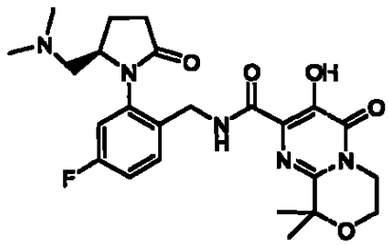
Pyrimido[2,1-c][1,4]oxazine-2-carboxamide, N-[[2-[(2R)-2-[(acetyloxy)methyl]-5-oxo-1-pyrrolidinyl]-4-fluorophenyl]methyl]-4,6,7,9-tetrahydro-3-hydroxy-9,9-dimethyl-4-oxo-. The title compound can be prepared from intermediate 193, (R)-(1-(2-((3-(benzyloxy)-9,9-dimethyl-4-oxo-4,6,7,9-tetrahydropyrimido[2,1-c][1,4]oxazine-2-carboxamido)methyl)-5-fluorophenyl)-5-oxopyrrolidin-2-yl)methyl acetate. ^{1}HNMR 400 MHz (MeOD) δ ppm: 7.58 (1H, m), 7.21-7.04 (2H, m), 5.24 (2H, s), 4.66-4.21 (3H, m), 4.02-3.92 (5H, m), 2.73-2.34 (3H, m), 2.23-1.61 (5H, m), 1.60 (6H, s). LCMS $(M+H)^+$ m/z 503.

Example 130



Pyrimido[2,1-c][1,4]oxazine-2-carboxamide, N-[[4-fluoro-2-[(2S)-2-(hydroxymethyl)-5-oxo-1-pyrrolidinyl]phenyl]methyl]-4,6,7,9-tetrahydro-3-hydroxy-9,9-dimethyl-4-oxo-. The title compound can be prepared from intermediate 167, (S)-N-(2-(2-((tert-butyldimethylsilyloxy)methyl)-5-oxopyrrolidin-1-yl)-4-fluorobenzyl)-3-(benzyloxy)-9,9-dimethyl-4-oxo-4,6,7,9-tetrahydropyrimido[2,1-c][1,4]oxazine-2-carboxamide. ^{1}HNMR 400 MHz (DMSO) δ ppm: 7.36 (1H, m), 7.18 (2H, m), 5.07 (1H, broad s), 4.66-4.11 (3H, m), 3.95 (2H, t, 5.1 Hz), 3.80 (2H, t, 5.1 Hz), 3.39 (2H, s), 2.43 (1H, m), 2.25 (1H, m), 2.08 (1H, m), 1.51 (6H, s). LCMS $(M+H)^+$ m/z 461.

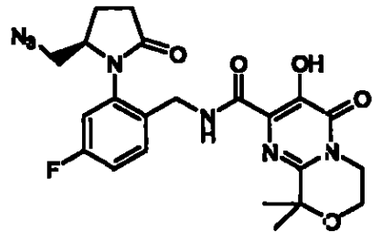
Example 131



(R)-N-(2-(2-((Dimethylamino)methyl)-5-oxopyrrolidin-1-yl)-4-fluorobenzyl)-3-hydroxy-9,9-dimethyl-4-oxo-4,6,7,9-tetrahydropyrimido[2,1-c][1,4]oxazine-2-carboxamide. To a solution of intermediate 195, (R)-N-(2-(2-(azidomethyl)-5-oxopyrrolidin-1-yl)-4-fluorobenzyl)-3-(benzyloxy)-9,9-dimethyl-4-oxo-4,6,7,9-tetrahydropyrimido[2,1-c][1,4]oxazine-2-carboxamide, (0.050 g, 0.087 mmol) in MeOH (5 mL) was added Palladium (10%) on charcoal (0.020 g) and formaldehyde (0.30 mL, 10 mmol). The reaction mixture was stirred at 23 °C under H_2 (balloon)

for 5 h. Palladium on charcoal was then removed by filtration and the solvent was evaporated *in vacuo*. The residue was purified by preparative HPLC (YMC-Pack C-18) to afford the title compound (0.013 g, 29% yield): ^{1}H NMR (400 MHz, MeOD) δ ppm: 7.56 (1H, dd, J = 7.0 Hz), 7.30-7.17 (2H, m), 4.70 (2H, m), 4.15 (1H, d, J = 15.3 Hz), 4.07 (2H, m), 3.99 (2H, m,), 3.54 (1H, m), 2.93 (6H, s), 2.84-2.64 (4H, m), 2.20 (1H, m), 1.65 (6H, s). HRMS calcd for $C_{24}H_{31}N_5O_5F$: 488.2309; found 488.2328.

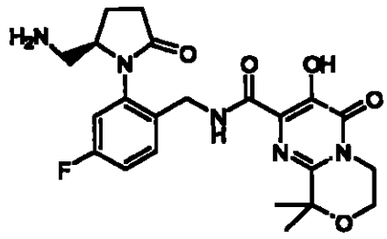
Example 132



(R)-N-(2-(2-(Azidomethyl)-5-oxopyrrolidin-1-yl)-4-fluorobenzyl)-3-hydroxy-9,9-dimethyl-4-oxo-4,6,7,9-tetrahydropyrimido[2,1-c][1,4]oxazine-2-carboxamide.

To a solution of intermediate 195, (R)-N-(2-(2-(azidomethyl)-5-oxopyrrolidin-1-yl)-4-fluorobenzyl)-3-(benzyloxy)-9,9-dimethyl-4-oxo-4,6,7,9-tetrahydropyrimido[2,1-c][1,4]oxazine-2-carboxamide, (0 030 g, 0.052 mmol) in CH_2Cl_2 (1 mL) was added CF_3CO_2H (1 mL) at 23 °C. The reaction mixture was stirred at 23 °C for 3h. Toluene (20 mL) was then added and the solvents evaporated *in vacuo*. The residue was purified by preparative HPLC (YMC-Pack C-18) to afford the title compound (0.008 g, 31%): ^{1}H NMR (400 MHz, MeOD) δ ppm: 7.55 (1H, dd, J = 6.6 Hz), 7.16 (2H, m), 4.47-4.24 (2H, m), 4.05 (2H, m), 3.98 (2H, m), 3.56 (2H, s), 2.70-2.45 (4H, m), 2.11 (1H, m), 1.64 (3H, s), 1.61 (3H, s). HRMS calcd for $C_{22}H_{25}N_7O_5F$: 486.1901; found 486.1923.

Example 133

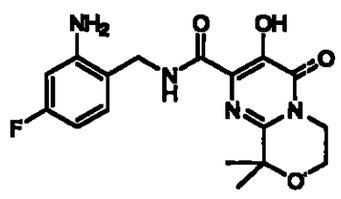


(R)-N-(2-(2-(Aminomethyl)-5-oxopyrrolidin-1-yl)-4-fluorobenzyl)-3-hydroxy-9,9-dimethyl-4-oxo-4,6,7,9-tetrahydropyrimido[2,1-c][1,4]oxazine-2-carboxamide. The title compound can be prepared by hydrogenolysis (H_2, 10%Pd-C) of intermediate195, (R)-N-(2-(2-(azidomethyl)-5-oxopyrrolidin-1-yl)-4-fluorobenzyl)-3-(benzyloxy)-9,9-dimethyl-4-oxo-4,6,7,9-tetrahydropyrimido[2,1-c][1,4]oxazine-2-carboxamide. ^{1}H NMR (400 MHz, MeOD) δ ppm: 7.54 (1H, dd, J = 7.0 Hz), 7.25-7.13 (2H, m), 4.62 (2H, m), 4.17 (1H, d, J =15.6 Hz), 4.07 (2H, m), 3.99 (2H, m,), 3.23 (2H, d, J = 3.1 Hz), 2.79-2.59 (3H, m), 2.14 (1H, m), 1.66 (6H, s). HRMS calcd for $C_{22}H_{27}N_5O_5F$: 460.1996; found 460.2014.

Examples 134-136

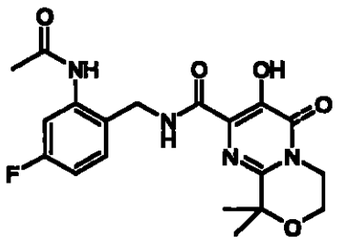
Examples 134-136 can be prepared from the indicated intermediates by hydrogenolysis or trifluoroacetic acid mediated hydrolysis.

Example 134



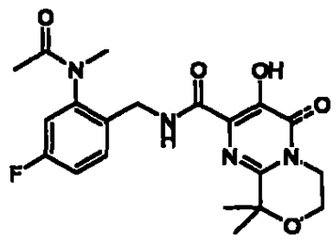
Pyrimido[2,1-c][1,4]oxazine-2-carboxamide, N-[(2-amino-4-fluorophenyl)methyl]-4,6,7,9-tetrahydro-3-hydroxy-9,9-dimethyl-4-oxo-. The title compound can be prepared from intermediate 169, N-(2-amino-4-fluorobenzyl)-3-(benzyloxy)-9,9-dimethyl-4-oxo-4,6,7,9-tetrahydropyrimido[2,1-c][1,4]oxazine-2-carboxamide. IR (KBr, cm^{-1}) 3383, 2979, 1636, 1540, 1288. ^{1}HNMR 400 MHz (MeOD) δ ppm: 7.14 (1H, dd, J = 7.3 Hz), 6.44-6-31 (2H, m), 4.69 (1H, broad s), 4.48 (2H, broad s), 4.03 (2H, t, J = 4.6 Hz), 3.95 (2H, t, J= 4.6 Hz), 1.62 (6H, s). HRMS (ESI$^+$) calculated for $C_{17}H_{20}FN_4O_4$ [M+H$^+$]:363.1469; found:363.1454.

Example 135



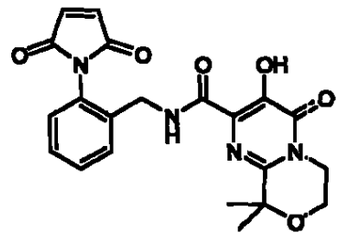
Pyrimido[2,1-c][1,4]oxazine-2-carboxamide, N-[[2-(acetylamino)-4-fluorophenyl]methyl]-4,6,7,9-tetrahydro-3-hydroxy-9,9-dimethyl-4-oxo-. The title compound can be prepared from intermediate 189, N-(2-acetamido-4-fluorobenzyl)-3-(benzyloxy)-9,9-dimethyl-4-oxo-4,6,7,9-tetrahydropyrimido[2,1-c][1,4]oxazine-2-carboxamide. ^{1}HNMR 400 MHz (MeOD) δ ppm: 7.66 (1H, broad d, J = 10.5 Hz), 7.40 (1H, broad t, 6.5 Hz), 6.87 (1H, broad t, J = 6.5 Hz), 4.55 (2H, m), 4.02 (2H, t, J = 5.0 Hz), 3.92 (2H, t, J = 5.0 Hz), 2.28 (3H, s), 1.62 (6H, s). HRMS (ESI$^+$) calculated for $C_{19}H_{22}FN_4O_5$ [M+H$^+$]:405.1574; found:405.1571.

Example 136



Pyrimido[2,1-c][1,4]oxazine-2-carboxamide, N-[[2-(acetylmethylamino)-4-fluorophenyl]methyl]-4,6,7,9-tetrahydro-3-hydroxy-9,9-dimethyl-4-oxo-. The title compound can be prepared from intermediate 168, N-(4-fluoro-2-(N-methylacetamido)benzyl)-3-(benzyloxy)-9,9-dimethyl-4-oxo-4,6,7,9-tetrahydropyrimido[2,1-c][1,4]oxazine-2-carboxamide. IR (KBr, cm^{-1}) 3407, 2979, 1653, 1539, 1116. ^{1}HNMR 400 MHz (MeOD) δ ppm: 7.53 (1H, m), 7.24 -7.06 (2H, m), 4.61-4.45 (2H, m), 4.08 (2H, t, J = 5.1 Hz), 4.00 (2H, t, J = 5.1 Hz), 3.40 (0.6H, s), 3.25 (2.4H, s), 1.85 (2.4H, s), 1.81 (0.6H, s), 1.65 (2.4H, s), 1.64 (2.4H, s), 1.62 (1.2H, s). LCMS $(M+H)^+$ m/z 419.

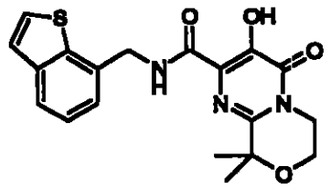
Example 137



N-(2-(2,5-Dioxo-2H-pyrrol-1(5H)-yl)benzyl)-3-hydroxy-9,9-dimethyl-4-oxo-4,6,7,9-tetrahydropyrimido[2,1-c][1,4]oxazine-2-carboxamide. To a solution of *N*-(2-aminobenzyl)-3-(benzyloxy)-9,9-dimethyl-4-oxo-4,6,7,9-tetrahydropyrimido [2,1-c][1,4]oxazine-2-carboxamide (0 050 g, 0.114 mmol) in acetic acid (1.5 mL) was added maleic anhydride (0.013 g, 0.131 mmol) and the reaction mixture stirred in a sealed tube at 115 C for 18 h. Acetic acid was evaporated *in vacuo* and the residue

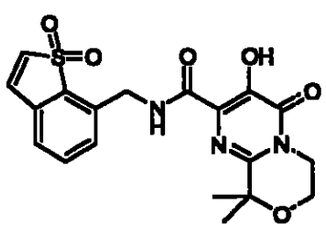
was purified by preparative HPLC (YMC-Pack C-18) to afford the title compound (0.013 g, 27% yield): ^{1}H NMR (400 MHz, $CDCl_3$) δ ppm: 8.03 (1H, broad t), 7.59 (1H, m), 7.48 (2H, m), 7.19 (1H, m), 6.92 (2H, s), 4.48 (2H, d, J = 6.1 Hz), 4.04 (4H, s), 1.62 (6H, s); HRMS calcd for $C_{21}H_{21}N_4O_6$: 425.1461; found 425.1451.

Example 138

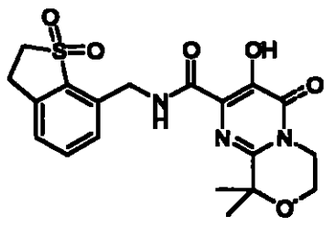


Pyrimido[2,1-c][1,4]oxazine-2-carboxamide, N-(benzo[b]thien-7-ylmethyl)-4,6,7,9-tetrahydro-3-hydroxy-9,9-dimethyl-4-oxo-. To intermediate 147, N-(benzo[b]thiophen-7-ylmethyl)-3-(benzyloxy)-9,9-dimethyl-4-oxo-4,6,7,9-tetrahydropyrimido[2,1-c][1,4]oxazine-2-carboxamide, (60 mg, 0.13 mmol) was added CF_3CO_2H (2 mL) at 23 °C. The reaction mixture was stirred at 23 °C for 1.5 h. Toluene (20 mL) was then added and the solvents were evaporated *in vacuo*. The residue was purified by preparative HPLC (YMC-Pack C-18) to afford the title compound (0.017 g, 34% yield): ^{1}H NMR (400 MHz, $CDCl_3$) δ: 8.00 (1H, broad t), 7.86 (1H, d, J = 8.0 Hz), 7.51 -7.28 (3H, m), 4.93 (2H, d, J = 3.9 Hz), 4.05 (4H, s), 1.58 (6H, s). HRMS calcd for $C_{19}H_{20}N_3O_4S$: 386.1175; found 386.1165.

Example 139



Pyrimido[2,1-c][1,4]oxazine-2-carboxamide, N-[(1,1-dioxidobenzo[b]thien-7-yl)methyl]-4,6,7,9-tetrahydro-3-hydroxy-9,9-dimethyl-4-oxo-. To intermediate 196, *N*-(benzo[b]thiophen-1,1-dione-7-ylmethyl)-3-(benzyloxy)-9,9-dimethyl-4-oxo-4,6,7,9-. tetrahydropyrimido[2,1-c][1,4]oxazine-2-carboxamide, (0.080 g, 0.16 mmol) was added CF_3CO_2H (2 mL) at 23 °C. The reaction mixture was stirred at 23 °C for 2.5 h. Toluene (20 mL) was then added and the solvents evaporated *in vacuo*. The residue was purified by crystallization with MeOH (10 mL) to afford the title compound (0.037 g, 55% yield). ^{1}H NMR (400 MHz, DMSO-d_6) δ: 11.87 (1H, s), 9.44 (1H, t, J = 6.5 Hz), 7.65 (2H, m), 7.51 (1H, d, J = 7.0 Hz), 7.42-7.37 (2H, m), 4.84 (2H, d, J = 6.2 Hz), 3.99 (2H, t, 5.4 Hz), 3.85 (2H, t, J = 5.4 Hz), 1.59 (6H, s). HRMS calcd for $C_{19}H_{20}N_3O_6S$: 418.1073; found 418.1078.



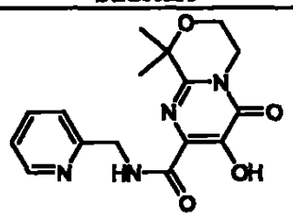
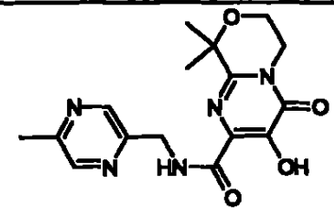
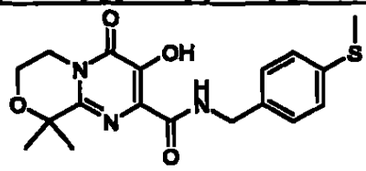
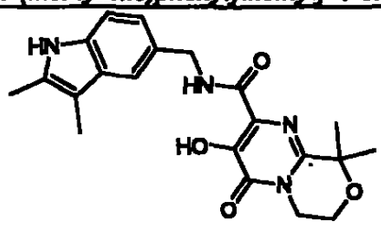
Pyrimido[2,1-c][1,4]oxazine-2-carboxamide, N-[(2,3-dihydro-1,1-dioxidobenzo[b]thien-7-yl)methyl]-4,6,7,9-tetrahydro-3-hydroxy-9,9-dimethyl-4-oxo-. The title compound was obtained from intermediate 196, *N*-(benzo[b]thiophen-1,1-dione-7-ylmethyl)-3-(benzyloxy)-9,9-dimethyl-4-oxo-4,6,7,9-tetrahydropyrimido[2,1-c][1,4]oxazine-2-carboxamide by reduction, Palladium (10%) on charcoal under H_2. ^{1}HNMR (400 MHz, CDCl3) δ: 8.65 (1H, s), 7.58-7.49 (2H, m), 7.32 (1H, d, J = 7.0 Hz), 4.86 (2H, d, J = 6.8 Hz), 3.99 (4H, s), 3.54 (2H, t, J = 6.8 Hz), 3.40 (2H, t, J = 6.8), 1.61 (6H, s). LCMS $(M+H)^+$ m/z 420.

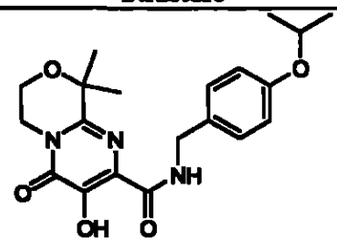
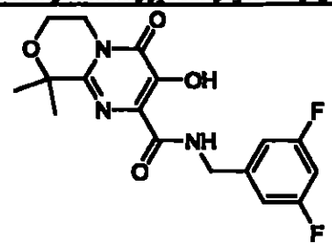
Examples 141-146

Examples 141-146 , listed in Table 9, can be prepared from intermediate 25, ethyl 3-hydroxy-9,9-dimethyl-4-oxo-4,6,7,9-tetrahydropyrimido[2,1-c][1,4]oxazine-2-carboxylate, according to the methods described for examples 1, 19, and 20. The compounds in the table were characterized by LCMS; (Xterra MS-C18, 4.6 X 50

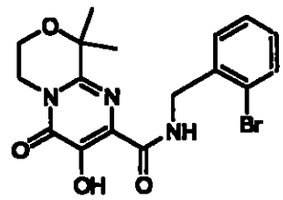
mm); eluted with 10% to 100% B, 4.5 min gradient, (A = H_2O-0.1% CF_3CO_2H, B = CH_3CN-0.1% CF_3CO_2H); flow rate at 2.5 mL/min. UV detection at 220 nm). Product retention time (RT, minutes) and molecular weight (MS [M+1]) results are listed in the table.

Table 9.

Example	Structure	RT	MS
141	 *Pyrimido[2,1-c][1,4]oxazine-2-carboxamide, 4,6,7,9-tetrahydro-3-hydroxy-9,9-dimethyl-4-oxo-N-(2-pyridinylmethyl)-*	1.1	331.17
142	 *Pyrimido[2,1-c][1,4]oxazine-2-carboxamide, 4,6,7,9-tetrahydro-3-hydroxy-9,9-dimethyl-N-[(5-methylpyrazinyl)methyl]-4-oxo-*	2.07	346.18
143	 *Pyrimido[2,1-c][1,4]oxazine-2-carboxamide, 4,6,7,9-tetrahydro-3-hydroxy-9,9-dimethyl-N-[[4-(methylthio)phenyl]methyl]-4-oxo-*	3.35	376.16
144	 *Pyrimido[2,1-c][1,4]oxazine-2-carboxamide, N-[(2,3-dimethyl-1H-indol-5-yl)methyl]-4,6,7,9-tetrahydro-3-hydroxy-9,9-dimethyl-4-oxo-*	2.37	397

Example	Structure	RT	MS
145	 *Pyrimido[2,1-c][1,4]oxazine-2-carboxamide, 4,6,7,9-tetrahydro-3-hydroxy-9,9-dimethyl-N-[[4-(1-methylethoxy)phenyl]methyl]-4-oxo-*	2.54	388.2
146	 *Pyrimido[2,1-c][1,4]oxazine-2-carboxamide, N-[(3,5-difluorophenyl)methyl]-4,6,7,9-tetrahydro-3-hydroxy-9,9-dimethyl-4-oxo-*	3.23	366.15

Example 147



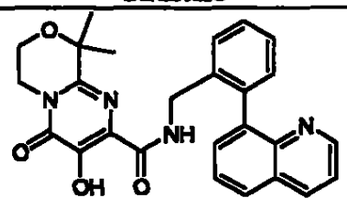
Pyrimido[2,1-c][1,4]oxazine-2-carboxamide, N-[(2-bromophenyl)methyl]-4,6,7,9-tetrahydro-3-hydroxy-9,9-dimethyl-4-oxo-. The title compound can be prepared from intermediate 25, ethyl 3-hydroxy-9,9-dimethyl-4-oxo-4,6,7,9-tetrahydropyrimido[2,1-c][1,4]oxazine-2-carboxylate, and 2-bromobenzylamine according to the methods described for examples 1, 19 and 20. ^{1}H NMR (300 MHz, DMSO-D6) δ ppm: 1.58 (s, 1), 3.84 (t, 2), 3.98 (t, 2), 4.54 (d, 2), 7.25 (m, 2), 7.38 (m, 2), 7.64 (d, 1), 9.43 (brm, 1), 12.01 (s, 1).

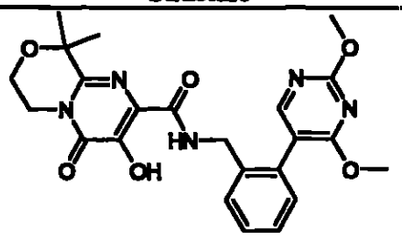
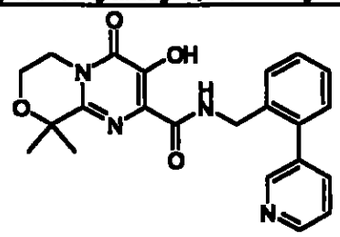
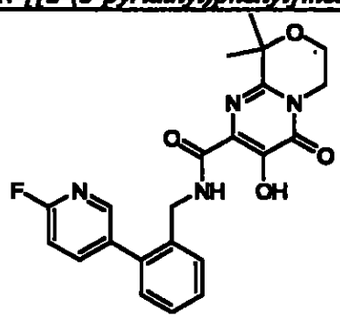
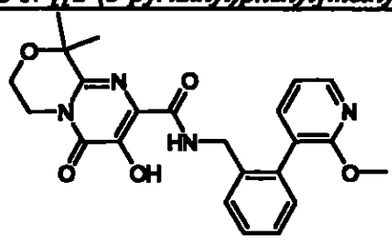
Examples 148-200

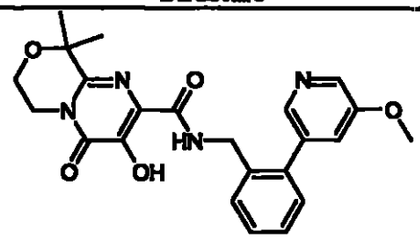
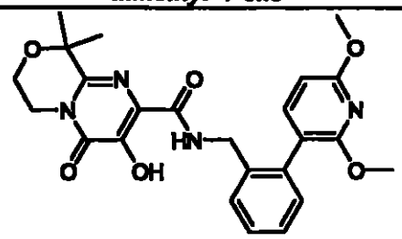
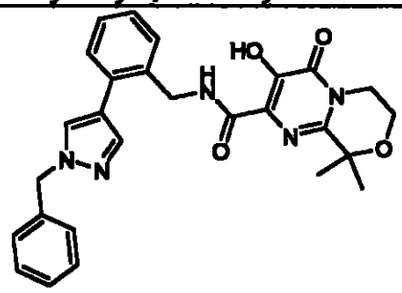
Examples 148-200, listed in table 10, were synthesized according to the following procedure. To a microwave reaction vessel containing a stir bar, was added $Pd(Ph_3P)_4$ (30 mg, 25 µmol), followed by anhydrous dioxane (0.5 mL). To this was added example 147, pyrimido[2,1-c][1,4]oxazine-2-carboxamide, N-[(2-bromophenyl)methyl]-4,6,7,9-tetrahydro-3-hydroxy-9,9-dimethyl-4-oxo-, (50 µmol), boronic acid or boronate ester reagent (200 µmol), anhydrous dioxane (0.5 mL) and 2M K_3PO_4 aqueous solution (0.25 mL). The reaction vessel was flushed with nitrogen, capped and heated at 120 °C for 10 minutes in a microwave reactor. The reaction mixture was filtered through a Whatman 0.45 µm syringe filter and the crude product purified using preparative HPLC (Xterra MS-C18, 30 X 50 mm); Eluted with 30% to 100% B, 8 min gradient, (A = 10 mM NH_4OAC (aq.), B = CH_3CN); flow rate at 30 mL/min. UV detection at 220 nm) to give the title compound.

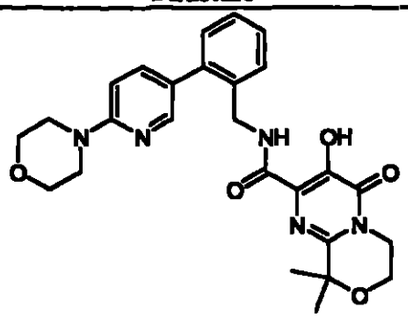
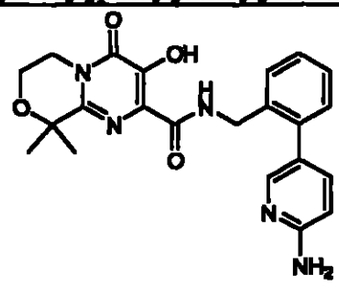
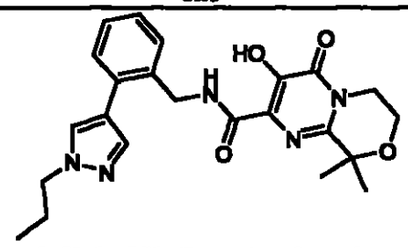
The compounds in the table were characterized by LCMS; (Xterra MS-C18, 4.6 X 50 mm); eluted with 10% to 100% B, 4.5 min gradient, (A = H_2O-0.1% CF_3CO_2H, B = CH_3CN-0.1% CF_3CO_2H); flow rate at 2.5 mL/min. UV detection at 220 nm). Product retention time (RT, minutes) and observed molecular weight (MS [M+1]) results are listed in the table.

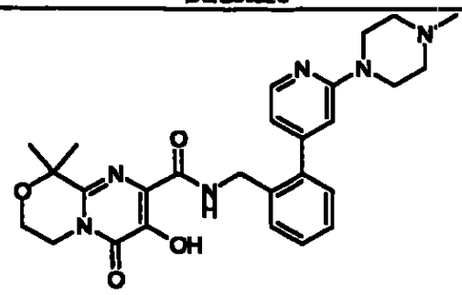
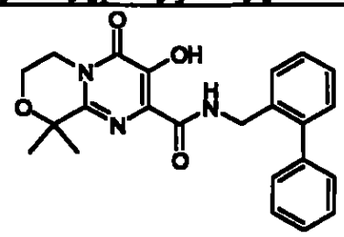
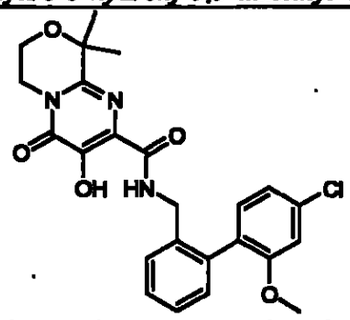
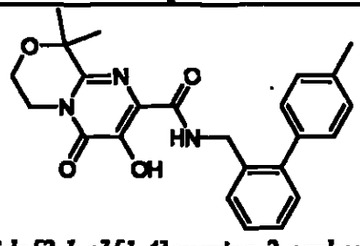
Table 10.

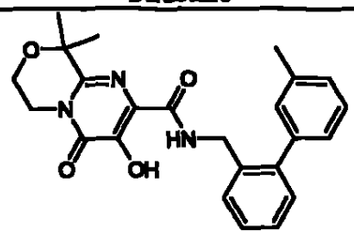
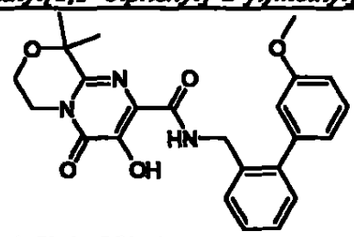
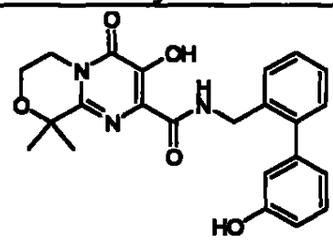
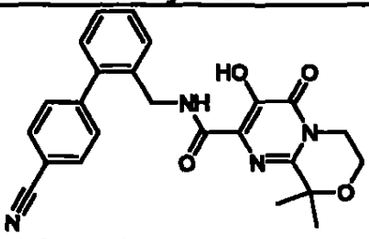
Example	Structure	RT	MS
148	 *Pyrimido[2,1-c][1,4]oxazine-2-carboxamide, 4,6,7,9-tetrahydro-3-hydroxy-9,9-dimethyl-4-oxo-N-[[2-(8-quinolinyl)phenyl]methyl]-*	2.08	457

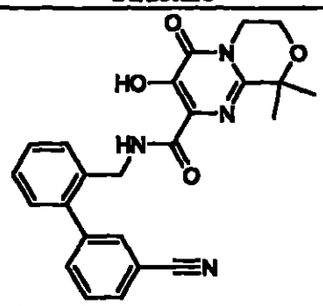
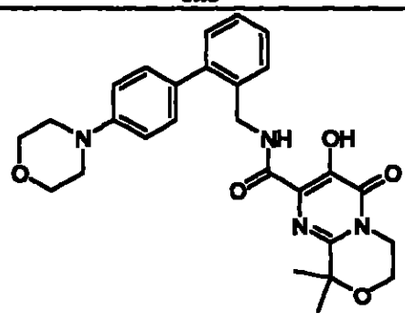
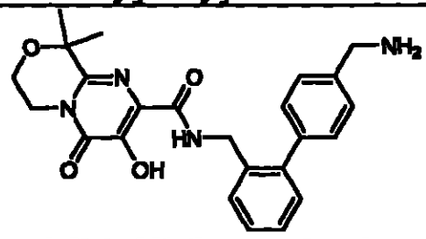
Example	Structure	RT	MS
149	 *Pyrimido[2,1-c][1,4]oxazine-2-carboxamide, N-[[2-(2,4-dimethoxy-5-pyrimidinyl)phenyl]methyl]-4,6,7,9-tetrahydro-3-hydroxy-9,9-dimethyl-4-oxo-*	1.91	467.95
150	 *Pyrimido[2,1-c][1,4]oxazine-2-carboxamide, 4,6,7,9-tetrahydro-3-hydroxy-9,9-dimethyl-4-oxo-N-[[2-(3-pyridinyl)phenyl]methyl]-*	1.71	407
151	 *Pyrimido[2,1-c][1,4]oxazine-2-carboxamide, 4,6,7,9-tetrahydro-3-hydroxy-9,9-dimethyl-4-oxo-N-[[2-(3-pyridinyl)phenyl]methyl]-*	1.98	425.01
152	 *Pyrimido[2,1-c][1,4]oxazine-2-carboxamide, 4,6,7,9-tetrahydro-3-hydroxy-N-[[2-(2-methoxy-3-pyridinyl)phenyl]methyl]-9,9-dimethyl-4-oxo-*	2.04	437.04

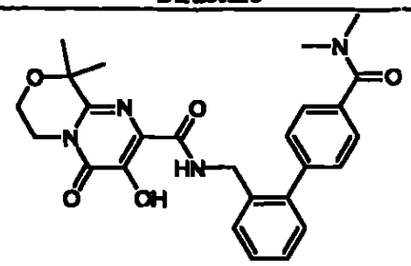
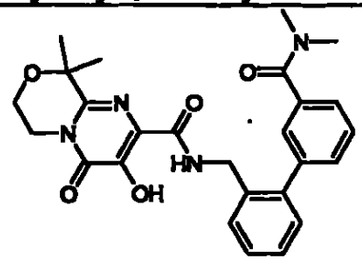
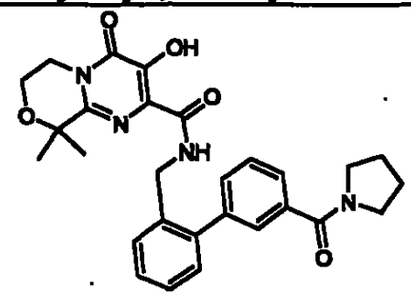
Example	Structure	RT	MS
153	 *Pyrimido[2,1-c][1,4]oxazine-2-carboxamide, 4,6,7,9-tetrahydro-3-hydroxy-N-[[2-(5-methoxy-3-pyridinyl)phenyl]methyl]-9,9-dimethyl-4-oxo-*	2.1	436.97
154	 *Pyrimido[2,1-c][1,4]oxazine-2-carboxamide, N-[[2-(2,6-dimethoxy-3-pyridinyl)phenyl]methyl]-4,6,7,9-tetrahydro-3-hydroxy-9,9-dimethyl-4-oxo-*	2.41	467.01
155	 *Pyrimido[2,1-c][1,4]oxazine-2-carboxamide, 4,6,7,9-tetrahydro-3-hydroxy-9,9-dimethyl-4-oxo-N-[[2-[1-(phenylmethyl)-1H-pyrazol-4-yl]phenyl]methyl]-*	2.19	486.03

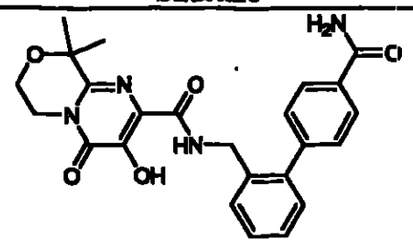
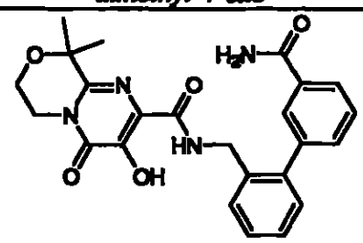
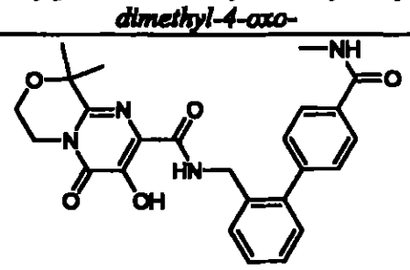
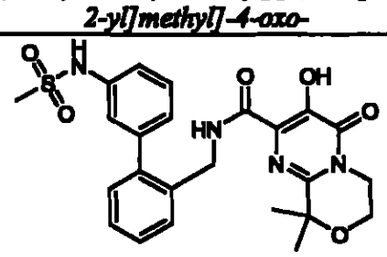
Example	Structure	RT	MS
156	 *Pyrimido[2,1-c][1,4]oxazine-2-carboxamide, 4,6,7,9-tetrahydro-3-hydroxy-9,9-dimethyl-N-[[2-[6-(4-morpholinyl)-3-pyridinyl]phenyl]methyl]-4-oxo-*	2	492.01
157	 *Pyrimido[2,1-c][1,4]oxazine-2-carboxamide, N-[[2-(6-amino-3-pyridinyl)phenyl]methyl]-4,6,7,9-tetrahydro-3-hydroxy-9,9-dimethyl-4-oxo-*	3.02	454.97
158	 *Pyrimido[2,1-c][1,4]oxazine-2-carboxamide, 4,6,7,9-tetrahydro-3-hydroxy-9,9-dimethyl-4-oxo-N-[[2-(1-propyl-1H-pyrazol-4-yl)phenyl]methyl]-*	1.99	438.04

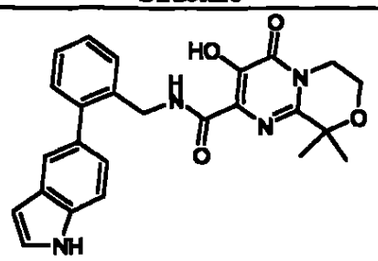
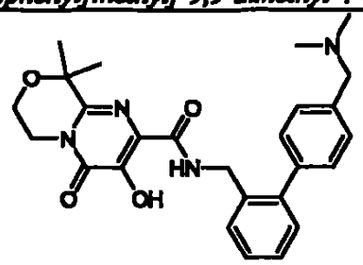
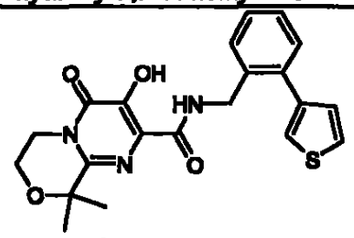
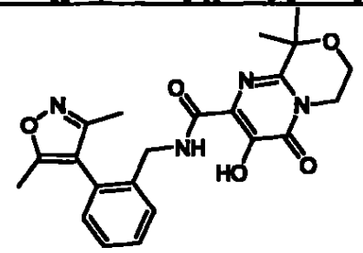
Example	Structure	RT	MS
159	 *Pyrimido[2,1-c][1,4]oxazine-2-carboxamide, 4,6,7,9-tetrahydro-3-hydroxy-9,9-dimethyl-N-[[2-[2-(4-methyl-1-piperazinyl)-4-pyridinyl]phenyl]methyl]-4-oxo-*	1.66	505.05
160	 *Pyrimido[2,1-c][1,4]oxazine-2-carboxamide, N-([1,1'-biphenyl]-2-ylmethyl)-4,6,7,9-tetrahydro-3-hydroxy-9,9-dimethyl-4-oxo-*	3.2	406
161	 *Pyrimido[2,1-c][1,4]oxazine-2-carboxamide, N-[(4'-chloro-2'-methoxy[1,1'-biphenyl]-2-yl)methyl]-4,6,7,9-tetrahydro-3-hydroxy-9,9-dimethyl-4-oxo-*	3.36	469.91
162	 *Pyrimido[2,1-c][1,4]oxazine-2-carboxamide, 4,6,7,9-tetrahydro-3-hydroxy-9,9-dimethyl-N-[(4'-methyl[1,1'-biphenyl]-2-yl)methyl]-4-oxo-*	3.39	419.97

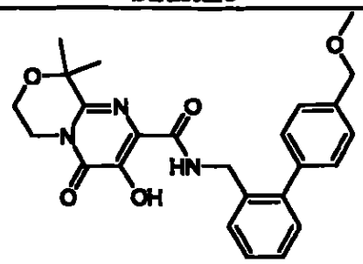
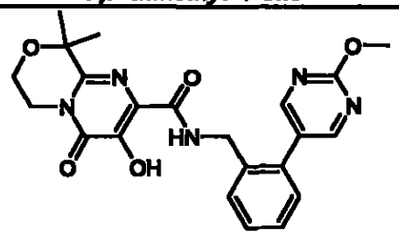
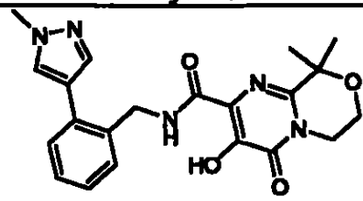
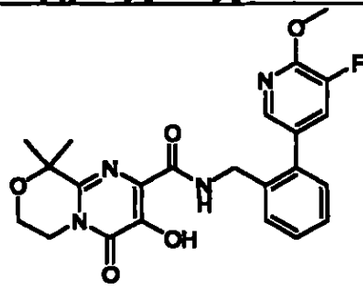
Example	Structure	RT	MS
163	 *Pyrimido[2,1-c][1,4]oxazine-2-carboxamide, 4,6,7,9-tetrahydro-3-hydroxy-9,9-dimethyl-N-[(3'-methyl[1,1'-biphenyl]-2-yl)methyl]-4-oxo-*	3.36	419.97
164	 *Pyrimido[2,1-c][1,4]oxazine-2-carboxamide, 4,6,7,9-tetrahydro-3-hydroxy-N-[(3'-methoxy[1,1'-biphenyl]-2-yl)methyl]-9,9-dimethyl-4-oxo-*	3.14	435.97
165	 *Pyrimido[2,1-c][1,4]oxazine-2-carboxamide, 4,6,7,9-tetrahydro-3-hydroxy-N-[(3'-hydroxy[1,1'-biphenyl]-2-yl)methyl]-9,9-dimethyl-4-oxo-*	2.65	421.99
166	 *Pyrimido[2,1-c][1,4]oxazine-2-carboxamide, N-[(4'-cyano[1,1'-biphenyl]-2-yl)methyl]-4,6,7,9-tetrahydro-3-hydroxy-9,9-dimethyl-4-oxo-*	2.91	430.99

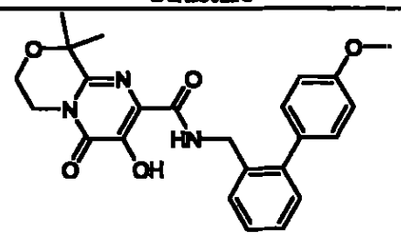
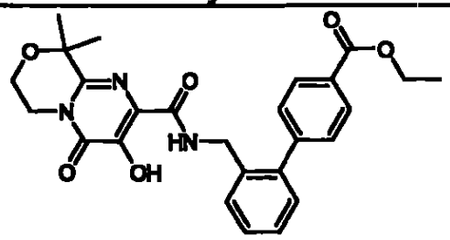
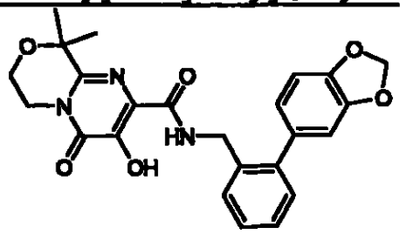
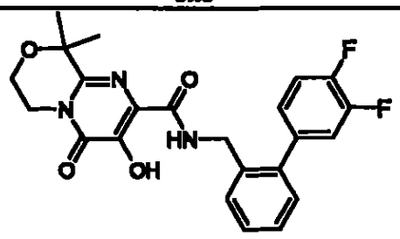
Example	Structure	RT	MS
167	 *Pyrimido[2,1-c][1,4]oxazine-2-carboxamide, N-[(3'-cyano[1,1'-biphenyl]-2-yl)methyl]-4,6,7,9-tetrahydro-3-hydroxy-9,9-dimethyl-4-oxo-*	2.93	430.99
168	 *Pyrimido[2,1-c][1,4]oxazine-2-carboxamide, 4,6,7,9-tetrahydro-3-hydroxy-9,9-dimethyl-N-[[4'-(4-morpholinyl)[1,1'-biphenyl]-2-yl]methyl]-4-oxo-*	3.02	491
169	 *Pyrimido[2,1-c][1,4]oxazine-2-carboxamide, 4,6,7,9-tetrahydro-3-hydroxy-9,9-dimethyl-N-[[4'-(4-morpholinyl)[1,1'-biphenyl]-2-yl]methyl]-4-oxo-*	2.11	435.02

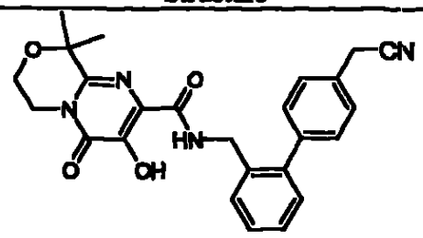
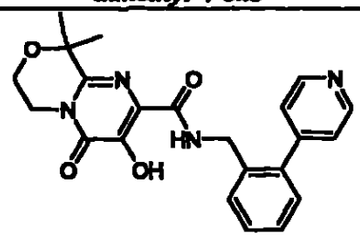
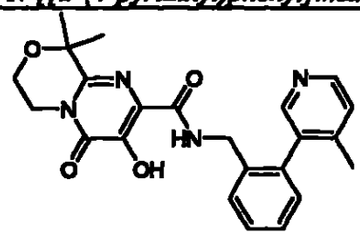
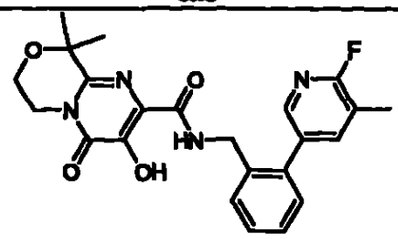
Example	Structure	RT	MS
170	 *Pyrimido[2,1-c][1,4]oxazine-2-carboxamide, N-[[4'-[(dimethylamino)carbonyl][1,1'-biphenyl]-2-yl]methyl]-4,6,7,9-tetrahydro-3-hydroxy-9,9-dimethyl-4-oxo-*	2.54	476.96
171	 *Pyrimido[2,1-c][1,4]oxazine-2-carboxamide, N-[3'-[(dimethylamino)carbonyl][1,1'-biphenyl]-2-yl]methyl]-4,6,7,9-tetrahydro-3-hydroxy-9,9-dimethyl-4-oxo-*	2.53	476.96
172	 *Pyrimido[2,1-c][1,4]oxazine-2-carboxamide, 4,6,7,9-tetrahydro-3-hydroxy-9,9-dimethyl-4-oxo-N-[[3'-(1-pyrrolidinylcarbonyl)[1,1'-biphenyl]-2-yl]methyl]-*	2.66	502.97

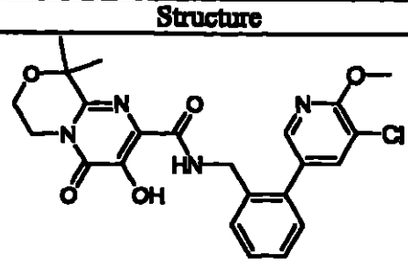
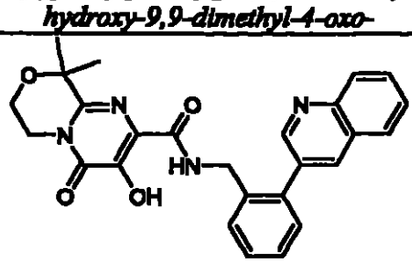
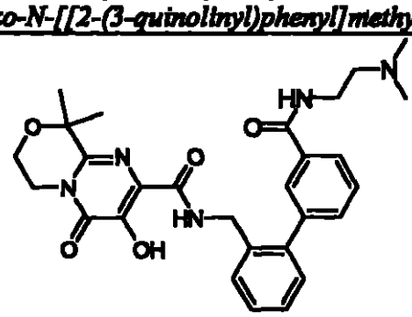
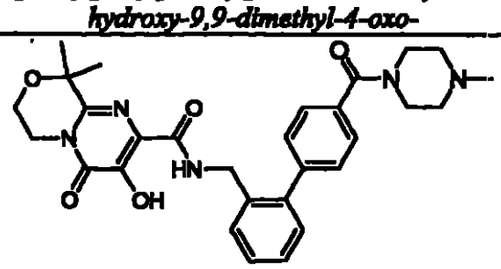
Example	Structure	RT	MS
173	 *Pyrimido[2,1-c][1,4]oxazine-2-carboxamide, N-[[4'-(aminocarbonyl)[1,1'-biphenyl]-2-yl]methyl]-4,6,7,9-tetrahydro-3-hydroxy-9,9-dimethyl-4-oxo-*	2.26	448.94
174	 *Pyrimido[2,1-c][1,4]oxazine-2-carboxamide, N-[[3'-(aminocarbonyl)[1,1'-biphenyl]-2-yl]methyl]-4,6,7,9-tetrahydro-3-hydroxy-9,9-dimethyl-4-oxo-*	2.27	448.94
175	 *Pyrimido[2,1-c][1,4]oxazine-2-carboxamide, 4,6,7,9-tetrahydro-3-hydroxy-9,9-dimethyl-N-[[4'-[(methylamino)carbonyl][1,1'-biphenyl]-2-yl]methyl]-4-oxo-*	2.36	462.98
176	 *Pyrimido[2,1-c][1,4]oxazine-2-carboxamide, 4,6,7,9-tetrahydro-3-hydroxy-9,9-dimethyl-N-[[3'-[(methylsulfonyl)amino][1,1'-biphenyl]-2-yl]methyl]-4-oxo-*	2.63	498.94

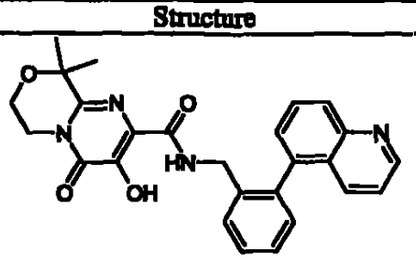
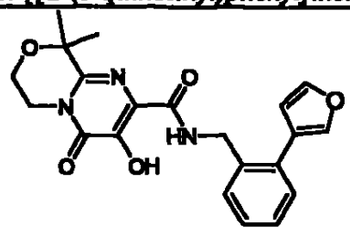
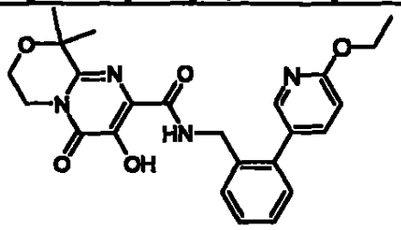
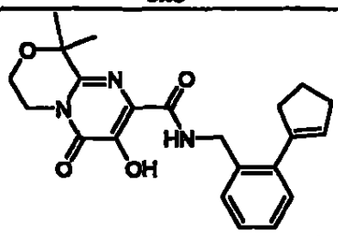
Example	Structure	RT	MS
177	 *Pyrimido[2,1-c][1,4]oxazine-2-carboxamide, 4,6,7,9-tetrahydro-3-hydroxy-N-[[2-(1H-indol-5-yl)phenyl]methyl]-9,9-dimethyl-4-oxo-*	3	444.97
178	 *Pyrimido[2,1-c][1,4]oxazine-2-carboxamide, N-[[4'-[(dimethylamino)methyl][1,1'-biphenyl]-2-yl]methyl]-4,6,7,9-tetrahydro-3-hydroxy-9,9-dimethyl-4-oxo-*	2.56	462.98
179	 *Pyrimido[2,1-c][1,4]oxazine-2-carboxamide, 4,6,7,9-tetrahydro-3-hydroxy-9,9-dimethyl-4-oxo-N-[[2-(3-thienyl)phenyl]methyl]-*	3.09	411.98
180	 *Pyrimido[2,1-c][1,4]oxazine-2-carboxamide, N-[[2-(3,5-dimethyl-4-isoxazolyl)phenyl]methyl]-4,6,7,9-tetrahydro-3-hydroxy-9,9-dimethyl-4-oxo-*	2.66	425.01

Example	Structure	RT	MS
181	 *Pyrimido[2,1-c][1,4]oxazine-2-carboxamide, 4,6,7,9-tetrahydro-3-hydroxy-N-[[4'-(methoxymethyl)[1,1'-biphenyl]-2-yl]methyl]-9,9-dimethyl-4-oxo-*	3.08	450.01
182	 *Pyrimido[2,1-c][1,4]oxazine-2-carboxamide, 4,6,7,9-tetrahydro-3-hydroxy-N-[[2-(2-methoxy-5-pyrimidinyl)phenyl]methyl]-9,9-dimethyl-4-oxo-*	2.43	438
183	 *Pyrimido[2,1-c][1,4]oxazine-2-carboxamide, 4,6,7,9-tetrahydro-3-hydroxy-9,9-dimethyl-N-[[2-(1-methyl-1H-pyrazol-4-yl)phenyl]methyl]-4-oxo-*	1.71	410
184	 *Pyrimido[2,1-c][1,4]oxazine-2-carboxamide, N-[[2-(5-fluoro-6-methoxy-3-pyridinyl)phenyl]methyl]-4,6,7,9-tetrahydro-3-hydroxy-9,9-dimethyl-4-oxo-*	3.02	455

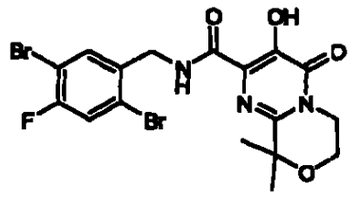
Example	Structure	RT	MS
185	 *Pyrimido[2,1-c][1,4]oxazine-2-carboxamide, 4,6,7,9-tetrahydro-3-hydroxy-N-[(4'-methoxy[1,1'-biphenyl]-2-yl)methyl]-9,9-dimethyl-4-oxo-*	3.14	436
186	 *[1,1'-Biphenyl]-4-carboxylic acid, 2'-[[[(4,6,7,9-tetrahydro-3-hydroxy-9,9-dimethyl-4-oxopyrimido[2,1-c][1,4]oxazin-2-yl)carbonyl]amino]methyl]-, ethyl ester*	3.30	478
187	 *Pyrimido[2,1-c][1,4]oxazine-2-carboxamide, N-[[2-(1,3-benzodioxol-5-yl)phenyl]methyl]-4,6,7,9-tetrahydro-3-hydroxy-9,9-dimethyl-4-oxo-*	2.76	450.2
188	 *Pyrimido[2,1-c][1,4]oxazine-2-carboxamide, N-[(3',4'-difluoro[1,1'-biphenyl]-2-yl)methyl]-4,6,7,9-tetrahydro-3-hydroxy-9,9-dimethyl-4-oxo-*	2.92	442.13

Example	Structure	RT	MS
189	 *Pyrimido[2,1-c][1,4]oxazine-2-carboxamide, N-[[4'-(cyanomethyl)[1,1'-biphenyl]-2-yl]methyl]-4,6,7,9-tetrahydro-3-hydroxy-9,9-dimethyl-4-oxo-*	2.57	445.15
190	 *Pyrimido[2,1-c][1,4]oxazine-2-carboxamide, 4,6,7,9-tetrahydro-3-hydroxy-9,9-dimethyl-4-oxo-N-[[2-(4-pyridinyl)phenyl]methyl]-*	1.34	407.34
191	 *Pyrimido[2,1-c][1,4]oxazine-2-carboxamide, 4,6,7,9-tetrahydro-3-hydroxy-9,9-dimethyl-N-[[2-(4-methyl-3-pyridinyl)phenyl]methyl]-4-oxo-*	1.40	421.2
192	 *Pyrimido[2,1-c][1,4]oxazine-2-carboxamide, N-[[2-(6-fluoro-5-methyl-3-pyridinyl)phenyl]methyl]-4,6,7,9-tetrahydro-3-hydroxy-9,9-dimethyl-4-oxo-*	2.57	439.36

Example	Structure	RT	MS
193	 *Pyrimido[2,1-c][1,4]oxazine-2-carboxamide, N-[[2-(5-chloro-6-methoxy-3-pyridinyl)phenyl]methyl]-4,6,7,9-tetrahydro-3-hydroxy-9,9-dimethyl-4-oxo-*	2.84	471.13
194	 *Pyrimido[2,1-c][1,4]oxazine-2-carboxamide, 4,6,7,9-tetrahydro-3-hydroxy-9,9-dimethyl-4-oxo-N-[[2-(3-quinolinyl)phenyl]methyl]-*	1.62	457.26
195	 *Pyrimido[2,1-c][1,4]oxazine-2-carboxamide, N-[[3'-[[[2-(dimethylamino)ethyl]amino]carbonyl][1,1'-biphenyl]-2-yl]methyl]-4,6,7,9-tetrahydro-3-hydroxy-9,9-dimethyl-4-oxo-*	1.57	520.31
196	 *Pyrimido[2,1-c][1,4]oxazine-2-carboxamide, 4,6,7,9-tetrahydro-3-hydroxy-9,9-dimethyl-N-[[4'-[(4-methyl-1-piperazinyl)carbonyl][1,1'-biphenyl]-2-yl]methyl]-4-oxo-*	1.57	532.41

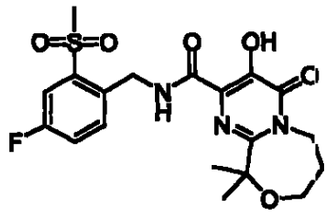
Example	Structure	RT	MS
197	 *Pyrimido[2,1-c][1,4]oxazine-2-carboxamide, 4,6,7,9-tetrahydro-3-hydroxy-9,9-dimethyl-4-oxo-N-[[2-(5-quinolinyl)phenyl]methyl[-*	1.55	457.26
198	 *Pyrimido[2,1-c][1,4]oxazine-2-carboxamide, N-[[2-(3-furanyl)phenyl]methyl]-4,6,7,9-tetrahydro-3-hydroxy-9,9-dimethyl-4-oxo-*	2.86	396.2
199	 *Pyrimido[2,1-c][1,4]oxazine-2-carboxamide, N-[[2-(6-ethoxy-3-pyridinyl)phenyl]methyl]-4,6,7,9-tetrahydro-3-hydroxy-9,9-dimethyl-4-oxo-*	3.08	451.2
200	 *Pyrimido[2,1-c][1,4]oxazine-2-carboxamide, N-[[2-(1-cyclopenten-1-yl)phenyl]methyl]-4,6,7,9-tetrahydro-3-hydroxy-9,9-dimethyl-4-oxo-*	3.33	396.34

Example 201



Pyrimido[2,1-c][1,4]oxazine-2-carboxamide, N-[(4-fluoro-2,5-dibromophenyl)methyl]-4,6,7,9-tetrahydro-3-hydroxy-9,9-dimethyl-4-oxo. A mixture of (2,5-dibromo-4-fluorophenyl)methanamine (1 mmol), intermediate 25 (0.268 g, 1 mmol) and triethylamine (0.5 mL, 3.5 mmol) in ethanol/dimethylformamide (1:1, 3 mL) was heated at 100 °C for 6 h. After cooling, the reaction mixture was purified by preparative HPLC to afford the title compound (0.31 g, 62% yield) as an off-white solid. ^{1}H NMR (500 MHz, $CDCl_3$) δ ppm: 11.72 (1H, s), 8.08 (1H, t, J = 6.1 Hz), 7.61 (1H, d, J = 7.0 Hz), 7.38 (1H, d, J = 7.6 Hz), 4.61 (2H, d, J = 6.4 Hz), 4.02 (4H, s), 1.59 (6H, s).

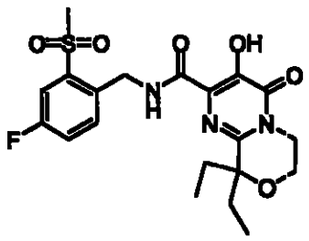
Example 202



6H-Pyrimido[2,1-c][1,4]oxazepine-2-carboxamide, N-[[4-fluoro-2-(methylsulfonyl)phenyl]methyl]-4,7,8,10-tetrahydro-3-hydroxy-10,10-dimethyl-4-oxo-. Off-white solid. ^{1}H NMR (500 MHz, $CDCl_3$) δ ppm: 11.77 (1H, br s), 8.55 (1H, t, *J*=6.3 Hz), 7.75 (1H, dd, *J*=8.1, 2.6 Hz), 7.72 (1H, dd, *J*=8.5, 5.2 Hz), 7.34 (1H, td, *J*=8.0, 2.6 Hz), 4.81 (2H, d, *J*=6.7 Hz), 4.54 (2H, br), 3.65 (2H, t, *J*=6.1 Hz), 3.18 (3H, s), 1.93 (2H, m), 1.59 (6H, s); ^{13}C NMR (126 MHz, $CDCl_3$) δ ppm: 168.14, 163.14, 161.13, 158.23, 153.73, 147.26, 140.77, 140.72, 135.31, 135.25, 132.83,

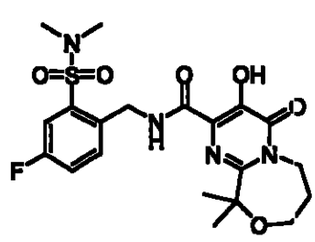
132.80, 124.83, 121.69 121.52, 117.63, 117.43, 82.56, 60.80, 45.14, 40.24, 38.62, 27.76, 27.35. HRMS (ESI) calcd for $C_{19}H_{23}N_3O_6FS$ (M+H): 440.1292; found: 440.1300. Anal. Calcd for $C_{19}H_{22}N_3O_6FS \cdot 0.06\ H_2O$: C 51.80, H 5.06, N 9.54, F 4.31; found C 51.83, H 4.97, N 9.29, F 4.12.

Example 203



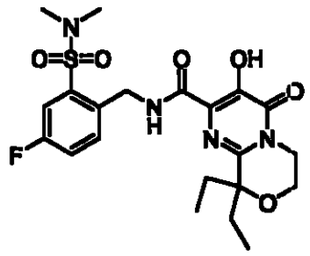
Pyrimido[2,1-c][1,4]oxazine-2-carboxamide, 9,9-diethyl-N-[[4-fluoro-2-(methylsulfonyl)phenyl]methyl]-4,6,7,9-tetrahydro-3-hydroxy-4-oxo-. ^{1}H NMR (500 MHz, $CDCl_3$) δ ppm: 11.74 (1H, s), 8.54 (1H, t, *J*=6.6 Hz), 7.75 (1H, dd, *J*=8.2, 2.7 Hz), 7.71 (1H, dd, *J*=8.5, 5.2 Hz), 7.34 (1H, td, *J*=8.0, 2.6 Hz), 4.82 (2H, d, *J*=7.0 Hz), 3.94-4.00 (4H, m), 3.17 (3H, s), 1.93-2.00 (2 H, m), 1.84-1.92 (2H, m), 0.83 (6H, t, *J*=7.3 Hz); ^{13}C NMR (126 MHz, $CDCl_3$) δ ppm: 168.26, 163.13, 161.11, 157.83, 151.66, 146.05, 140.69, 140.64, 135.13, 135.07, 132.80, 132.77, 125.63, 121.65, 121.48, 117.65, 117.45, 81.03, 58.51, 45.14, 43.08, 40.33, 31.38, 7.87. HRMS (ESI) calcd for $C_{20}H_{25}N_3O_6FS$ (M+H): 454.1448; found: 454.1448. Anal. calcd for $C_{20}H_{24}N_3O_6FS$: C 52.97, H 5.33, N 9.27, S 7.07; found: C 53.01, H 5.60, N 9.10, S 7.00.

Example 204



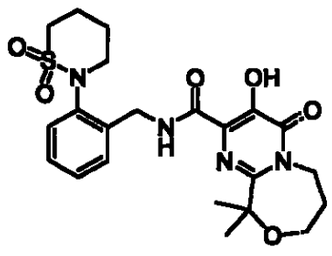
6H-Pyrimido[2,1-c][1,4]oxazepine-2-carboxamide, N-[[2-[(dimethylamino)sulfonyl]-4-fluorophenyl]methyl]-4,7,8,10-tetrahydro-3-hydroxy-10,10-dimethyl-4-oxo-. Pale orange solid. ^{1}H NMR (500 MHz, $CDCl_3$) δ ppm: 11.87 (1H, br s), 8.59 (1H, t, *J*=6.4 Hz), 7.69 (1H, dd, *J*=8.5, 5.2 Hz), 7.49 (1H, dd, *J*=8.2, 2.4 Hz), 7.26 (1H, td, *J*=7.7, 3.2 Hz), 4.79 (2H, d, *J*=6.7 Hz), 4.53 (2H, br), 3.65 (2H, t, *J*=6.1 Hz), 2.90 (6H, s), 1.89-1.96 (2H, m), 1.57-1.61 (6H, s); ^{13}C NMR (126 MHz, $CDCl_3$) δ ppm: 168.03, 162.71, 160.70, 158.29, 153.57, 147.23, 138.51, 138.46, 135.30, 135.25, 132.70, 132.67, 124.99, 120.40, 120.24, 116.93, 116.73, 82.59, 60.79, 58.57, 40.26, 38.58, 37.59, 27.74, 27.36, 18.55. HRMS (ESI) calcd for $C_{20}H_{26}N_4O_6FS$ (M+H) 469.1557; found 469.1557. Anal. calcd for $C_{20}H_{26}N_4O_6FS \cdot CH_3CH_2OH$: C 51.29, H 6.07, N 10.89, S 6.01, F 3.69; found C 51.29, H 6.33, N 10.85, S 6.01, F 3.54.

Example 205



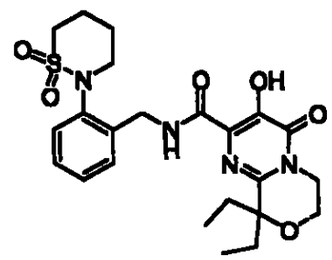
Pyrimido[2,1-c][1,4]oxazine-2-carboxamide, N-[[2-[(dimethylamino)sulfonyl]-4-fluorophenyl]methyl]-9,9-diethyl-4,6,7,9-tetrahydro-3-hydroxy-4-oxo-. White glassy solid. ^{1}H NMR (500 MHz, $CDCl_3$) δ ppm: 11.85 (1H, br), 8.59 (1H, t, *J*=6.4 Hz), 7.68 (1H, dd, *J*=8.5, 5.2 Hz), 7.49 (1H, dd, *J*=8.2, 2.4 Hz), 7.24-7.30 (1H, m), 4.80 (2H, d, *J*=7.0 Hz), 3.94-4.01 (4H, m), 2.90 (6H, s), 1.93-2.01 (2H, m), 1.85-1.93 (2H, m), 0.83 (6H, t, *J*=7.3 Hz); ^{13}C NMR (126 MHz, $CDCl_3$) δ ppm: 168.04, 162.70, 160.70, 158.06, 151.44, 145.95, 138.53, 138.49, 135.17, 135.12, 132.62, 132.59, 125.95, 120.37, 120.21, 116.87, 116.68, 81.08, 58.51, 43.11, 40.32, 37.58, 31.35, 7.87. HRMS (ESI) calcd for $C_{21}H_{28}N_4O_6FS$ (M+H) 483.1714; found 483.1702. Anal. calcd for $C_{21}H_{27}N_4O_6FS \cdot 0.15\ CF_3CO_2H$: C 51.20, H 5.48, N 11.21, F 5.51, S 6.42; found: C 51.10, H 5.23, N 11.21, F 5.49, S 6.32.

Example 206



6H-pyrimido[2,1-c][1,4]oxazepine-2-carboxamide, 4,7,8,10-tetrahydro-3-hydroxy-10,10-dimethyl-4-oxo-N-[[2-(tetrahydro-1,1-dioxido-2H-1,2-thiazin-2-yl)phenyl]methyl]-. Off-white solid. ^{1}H NMR (500 MHz, $CDCl_3$) δ ppm: 12.18 (1H, br s), 8.14-8.25 (1H, br), 7.41-7.50 (2H, m), 7.31-7.39 (2H, m), 4.96 (1H, dd, *J*=14.0, 8.9 Hz), 4.54 (2H, br s), 4.44 (1H, dd, *J*=14.2, 3.2 Hz), 3.83-3.92 (1H, m), 3.65 (2H, br), 3.38-3.46 (1H, m), 3.18-3.28 (2H, m), 2.32-2.42 (2H, m), 1.89-1.98 (4H, m), 1.55 (6H, d, *J*=15.9 Hz); ^{13}C NMR (126 MHz, $CDCl_3$) δ ppm: 168.22, 158.38, 153.54, 147.32, 138.80, 137.00, 130.88, 129.47, 129.29, 127.68, 125.17, 82.60, 60.74, 54.15, 51.05, 39.11, 38.63, 27.76, 27.73, 27.36, 25.04, 24.32. HRMS (ESI) calcd for $C_{22}H_{29}N_4O_6S$ (M+H): 477.1808; found: 477.1794. Anal. calcd for $C_{22}H_{28}N_4O_6S$•0.5CH_3CH_2OH: C 55.45, H 5.92, N 11.76, S 6.73; found: C 55.36, H 6.11, N 11.46, S 6.48.

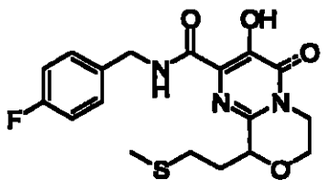
Example 207



Pyrimido[2,1-c][1,4]oxazine-2-carboxamide, 4,6,7,9-tetrahydro-3-hydroxy-9,9-diethyl-4-oxo-N-[[2-(tetrahydro-1,1-dioxido-2H-1,2-thiazin-2-yl)phenyl]methyl]. Off-white crystalline solid. ^{1}H NMR (500 MHz, $CDCl_3$) δ ppm: 12.11 (1H, br s),

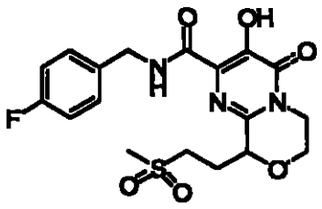
8.20 (1H, br), 7.42-7.48 (2H, m), 7.33-7.40 (2H, m), 4.93 (1H, dd, *J*=14.2, 8.4 Hz), 4.45 (1H, dd, *J*=14.2, 3.8 Hz), 3.94-4.02 (4H, m), 3.87 (1H, ddd, *J*=13.0, 9.9, 3.7 Hz), 3.39-3.46 (1H, m), 3.15-3.24 (2H, m), 2.29-2.46 (2H, m), 1.79-2.04 (6H, m), 0.81 (3H, t, *J*=6.7 Hz), 0.78 (3H, t, *J*=7.3 Hz); ^{13}C NMR (126 MHz, $CDCl_3$) δ ppm: 168.25, 157.91, 151.43, 146.14, 139.14, 136.81, 130.79, 129.46, 129.25, 127.90, 125.96, 81.15, 58.55, 54.22, 51.09, 43.03, 39.57, 31.21, 25.03, 24.34, 7.82, 7.68. HRMS (ESI) calcd for $C_{23}H_{31}N_4O_6S$ (M+H): 491.1964; found: 491.1953. Anal. calcd for $C_{23}H_{30}N_4O_6S$: C 56.12, H 6.48, N 10.91, S 6.24; found: C 56.14, H 6.44, N 11.07, S 6.05.

Example 208



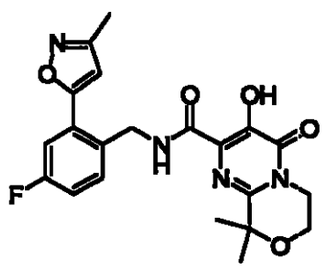
Pyrimido[2,1-c][1,4]oxazine-2-carboxamide, N-[(4-fluorophenyl)methyl]-4,6,7,9-tetrahydro-3-hydroxy-9-[2-(methylthio)ethyl]-4-oxo-. A solution of intermediate 141, N-(4-fluorobenzyl)-3-(benzyloxy)-9-(2-(methylthio)ethyl)-4-oxo-4,6,7,9-tetrahydropyrimido[2,1-c][1,4]oxazine-2-carboxamide in 4mL CF_3CO_2H was stirred at 60 °C for 1hr then concentrated. The residue was dissolved in CH_2Cl_2 and washed with water then concentrated. Trituration with hexanes gave the title compound as a solid. ^{1}H NMR (300 MHz, $CDCl_3$) δ ppm: 12.03 (1 H, s) 7.75 (1 H, m) 6.84-7.40 (4 H, m) 4.39-4.72 (3 H, m) 4.04-4.36 (2 H, m) 3.68-3.92 (2 H, m) 2.49-2.73 (2 H, m) 2.07-2.50 (2 H, m) 2.02 (3 H, s); HRMS (ESI) calcd for $C_{18}H_{20}FN_3O_4S$ (M+H): 394.1237, found: 394.1234.

Example 209



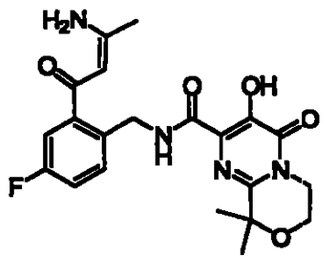
Pyrimido[2,1-c][1,4]oxazine-2-carboxamide, N-[(4-fluorophenyl)methyl]-4,6,7,9-tetrahydro-3-hydroxy-9-[2-(methylsulfonyl)ethyl]-4-oxo-. A solution of example 208, pyrimido[2,1-c][1,4]oxazine-2-carboxamide, N-[(4-fluorophenyl)methyl]-4,6,7,9-tetrahydro-3-hydroxy-9-[2-(methylthio)ethyl]-4-oxo-, (40mg, 0.11mmol) in 2mL CH_2Cl_2 was treated with excess m-chloroperbenzoic acid (100mg, 0.4mmol) and stirred at room temperature for 20 hrs. The reaction mixture was washed with water and concentrated. The crude material was purified by reverse phase HPLC (C18, 12% CH_3CN/H_2O). The fractions containing the product were concentrated and lyophilized to afford 5mg (12% yield) of the title compound. ^1H NMR (300 MHz, $CDCl_3$) δ ppm: 12.10-12.27 (1 H, s) 7.80-8.02 (1 H, m) 7.25-7.39 (2 H, m) 6.90-7.09 (2 H, m) 4.05-4.72 (5 H, m) 3.73-3.99 (2 H, m) 3.02-3.34 (2 H, m) 2.86-2.91 (3 H, s) 2.35-2.78 (2 H, m); HRMS (ESI) calcd for $C_{18}H_{20}FN_3O_6S$ (M+H): 426.1135, found: 426.1143.

Example 210



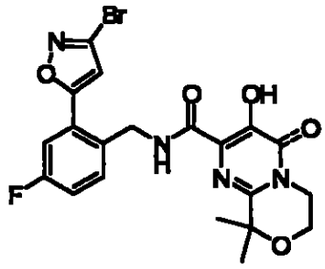
Pyrimido[2,1-c][1,4]oxazine-2-carboxamide, N-[[4-fluoro-2-(3-methyl-5-isoxazolyl)phenyl]methyl]-4,6,7,9-tetrahydro-3-hydroxy-9,9-dimethyl-4-oxo-. The title compound can be prepared from intermediate 180, N-(4-fluoro-2-(3-methylisoxazol-5-yl)benzyl)-3-(benzyloxy)-9,9-dimethyl-4-oxo-4,6,7,9-tetrahydropyrimido[2,1-c][1,4]oxazine-2-carboxamide. ^{1}HNMR 400 MHz ($CDCl_3$) δ ppm: 1.59 (6H, s, 2 x CH_3), 2.42 (3H, s, CH_3), 4.03 (4H, s, 2 x CH_2), 4.74 (2H, d, J = 6.6 Hz, NCH_2), 6.40 (1H, s, aromatic), 7.18 (1H, m, aromatic), 7.32 (1H, dd, J = 2.5 Hz and J = 9.1 Hz, aromatic), 7.59 (1H, dd, J = 5.6 Hz and J = 8.6 Hz, aromatic), 8.29 (1H, broad t, NH), 11.87 (1H, s, OH). HRMS (ESI^+) calculated for $C_{21}H_{22}FN_4O_5$ [$M+H^+$]: 429.1574; found: 429.1584.

Example 211



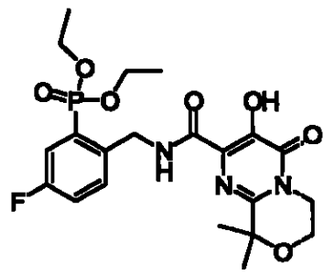
Pyrimido[2,1-c][1,4]oxazine-2-carboxamide, N-[[2-[(2Z)-3-amino-1-oxo-2-butenyl]-4-fluorophenyl]methyl]-4,6,7,9-tetrahydro-3-hydroxy-9,9-dimethyl-4-oxo-. ^{1}HNMR 400 MHz ($CDCl_3$) δ ppm: 1.63 (6H, s, 2 x CH_3), 2.11 (3H, s, CH_3), 4.03 (4H, s, 2 x CH_2), 4.58 (2H, d, J = 6.5 Hz, NCH_2), 5.38 (1H, broad, NH), 5.49 (1H, s, CH), 7.09 (1H, m, aromatic), 7.29 (1H, dd, J = 3.0 Hz and J = 9.1 Hz, aromatic), 7.48 (1H, dd, J = 5.6 Hz and J = 8.6 Hz, aromatic), 9.19 (1H, broad t, NH), 10.26 (1H, broad, NH), 12.21 (1H, s, OH).

Example 212



Pyrimido[2,1-c][1,4]oxazine-2-carboxamide, N-[[2-(3-bromo-5-isoxazolyl)-4-fluorophenyl]methyl]-4,6,7,9-tetrahydro-3-hydroxy-9,9-dimethyl-4-oxo-. The title compound can be prepared from intermediate 181, N-(2-(3-bromoisoxazol-5-yl)-4-fluorobenzyl)-3-(benzyloxy)-9,9-dimethyl-4-oxo-4,6,7,9-tetrahydropyrimido[2,1-c][1,4]oxazine-2-carboxamide. ^{1}HNMR 400 MHz ($CDCl_3$) δ ppm: 1.60 (6H, s, 2 x CH_3), 4.03 (4H, s, 2 x CH_2), 4.74 (2H, d, J = 7.1 Hz, NCH_2), 6.63 (1H, s, aromatic), 7.24 (1H, m, aromatic), 7.32 (1H, dd, J = 2.5 Hz and J = 9.1 Hz, aromatic), 7.63 (1H, dd, J = 5.5 Hz and J = 8.6 Hz, aromatic), 8.20 (1H, broad t, NH), 11.77 (1H, s, OH).

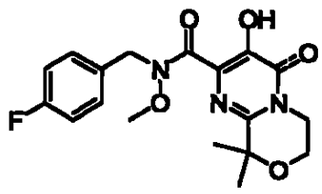
Example 213



Phosphonic acid, [5-fluoro-2-[[[(4,6,7,9-tetrahydro-3-hydroxy-9,9-dimethyl-4-oxopyrimido[2,1-c][1,4]oxazin-2-yl)carbonyl]amino]methyl]phenyl]-, diethyl ester. Hydrogenolysis of intermediate 187, diethyl 2-((3-(benzyloxy)-9,9-dimethyl-4-oxo-4,6,7,9-tetrahydropyrimido[2,1-c][1,4]oxazine-2-carboxamido)methyl)-5-fluorophenylphosphonate (0.089 g, 0.15 mmol) gave 0.065 g (90% yield) of the title compound as a white solid: mp 124 °C. ^{1}HNMR 400 MHz ($CDCl_3$) δ ppm: 1.39 (6H,

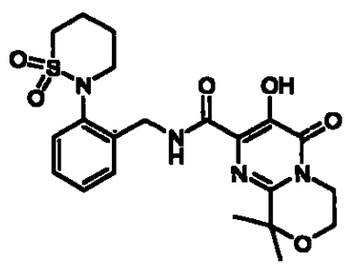
t, J = 7.1 Hz, 2 x CH_3), 1.63 (6H, s, 2 x CH_3), 4.02 (4H, s, 2 x CH_2), 4.20 (4H, m, 2 x OCH_2), 4.78 (2H, d, J = 6.6 Hz, NCH_2), 7.25 (1H, m, aromatic), 7.49 (1H, m, aromatic), 7.63 (1H, m, aromatic), 9.12 (1H, broad t, NH)., 12.1 (1H, broad, OH). HRMS (ESI^+) calculated for $C_{21}H_{28}FN_3O_7P$ [$M+H^+$]: 484.1649; found: 484.1646.

Example 214



Pyrimido[2,1-c][1,4]oxazine-2-carboxamide, N-[(4-fluorophenyl)methyl]-4,6,7,9-tetrahydro-3-hydroxy-N-methoxy-9,9-dimethyl-4-oxo-. The title compound can be prepared from intermediate 171, N-(4-fluorobenzyl)-3-(benzyloxy)-N-methoxy-9,9-dimethyl-4-oxo-4,6,7,9-tetrahydropyrimido[2,1-c][1,4]oxazine-2-carboxamide. ^{1}HNMR 400 MHz (DMSO-d_6) δ ppm: (mixture of rotamers) 1.52 (6H, s, 2 x CH_3), 3.59 (3H, s, OCH_3), 3.89 (2H, broad, CH_2), 4.01 (2H, broad, CH_2), 4.68 and 4.91 (2H, broad, NCH_2), 7.18 (2H, m, aromatics), 7.43 (2H, m, aromatics), 9.88 and 10.2 (1H, broad, OH).

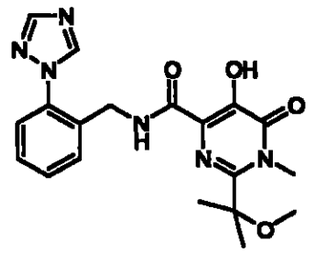
Example 215



Pyrimido[2,1-c][1,4]oxazine-2-carboxamide, 4,6,7,9-tetrahydro-3-hydroxy-9,9-dimethyl-4-oxo-N-[[2-(tetrahydro-1,1-dioxido-2H-1,2-thiazin-2-yl)phenyl]methyl]-. The title compound can be prepared from intermediate 101. Pale

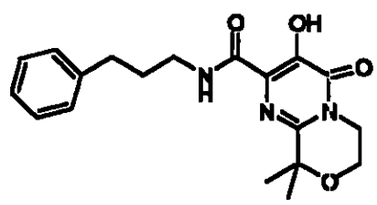
brown solid. ^{1}H-NMR (300 MHz, $CDCl_3$) δ ppm: 12.11 (1H, s), 8.32-8.29 (1H, m), 7.46-7.42 (2H, m), 7.36-7.32 (2H, m), 4.92 (1H, dd, *J*= 14.3, 8.8 Hz), 4.40 (1H, dd, *J* = 14.1, 3.5 Hz), 3.97 (4H, s), 3.90-3.81 (1H, m), 3.47-3.37 (1H, m), 3.24-3.18 (2H, m), 2.42-2.28 (2H, m), 1.97-1.86 (2H, m), 1.54 (3H, s), 1.50 (3H, s). HRMS $[M+H]^+$ calcd for $C_{21}H_{27}N_4SO_6$: 463.1651; found: 463.1669. Anal calcd for $C_{21}H_{26}N_4SO_6$: C, 54.53; H, 5.67; N, 12.11; S, 6.93; found: C, 54.53; H, 5.41; N, 12.40; S, 6.69.

Example 216



Pyrimido[2,1-c][1,4]oxazine-2-carboxamide, 4,6,7,9-tetrahydro-3-hydroxy-9,9-dimethyl-4-oxo-N-[[2-(1H-1,2,4-triazol-1-yl)phenyl]methyl]-. White solid. ^{1}H-NMR (300 MHz, $CDCl_3$) δ ppm: 11.94 (1H, s), 8.86 (1H, t, *J*= 6.2 Hz), 8.42 (1H, s), 8.16 (1H, s), 7.66 (1H, dd, *J*= 7.3, 1.8 Hz), 7.51-7.42 (2H, m), 7.35-7.32 (1H, m), 4.45 (2H, d, *J*= 6.6 Hz), 3.98 (4H, s), 1.59 (6H, s). HRMS $[M+H]^+$ calcd for $C_{19}H_{21}N_6O_4$: 397.1624; found: 397.1609. Anal calcd for $C_{19}H_{20}N_6O_4$: C, 57.57; H, 5.08; N, 21.20; found: C, 57.40; H, 4.96; N, 21.09.

Example 217

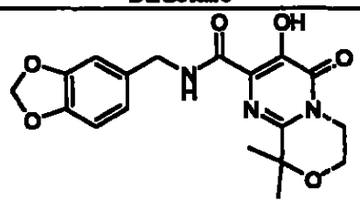
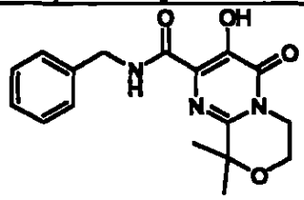


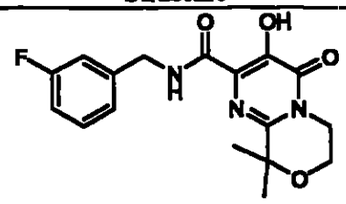
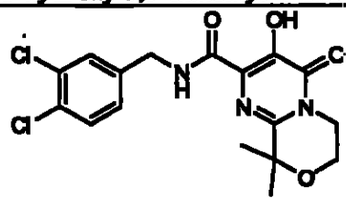
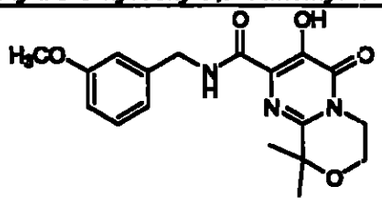
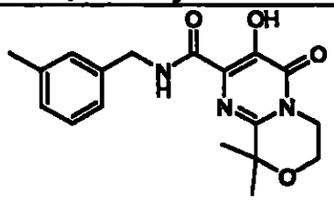
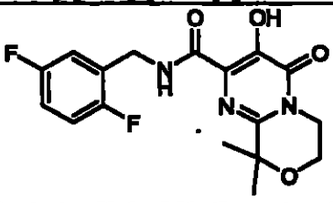
Pyrimido[2,1-c][1,4]oxazine-2-carboxamide, 4,6,7,9-tetrahydro-3-hydroxy-9,9-dimethyl-4-oxo-N-(3-phenylpropyl)- ^{1}H NMR (500 MHz, DMSO-D6) δ ppm: 1.56 (s, 6 H) 1.82-1.89 (m, 2 H) 2.62 (t, J=7.48 Hz, 2 H) 3.31 (m, 2 H) 3.82 (t, J=5.04 Hz, 2 H) 3.97 (t, J=5.04 Hz, 2 H) 7.16-7.24 (m, 3 H) 7.29 (m, 2 H) 8.91 (s, 1 H) 12.41 (s, 1 H). Anal calcd for $C_{19}H_{23}N_3O_4$: C, 63.85; H, 6.48; N, 11.75. Found: C, 63.56; H, 6.67; N, 12.01.

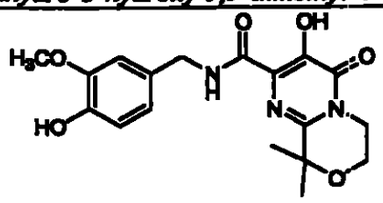
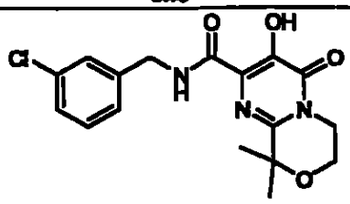
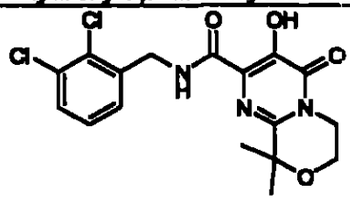
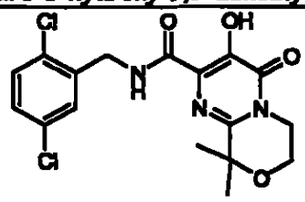
Examples 218-259

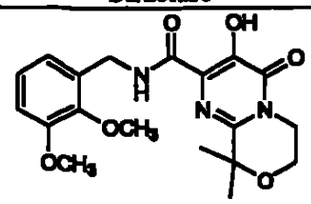
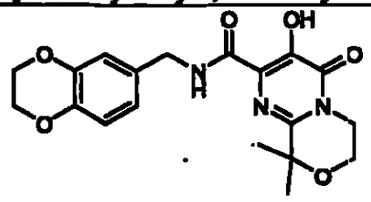
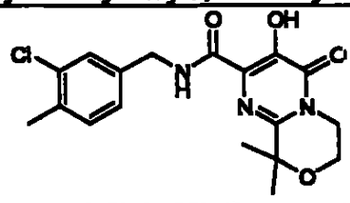
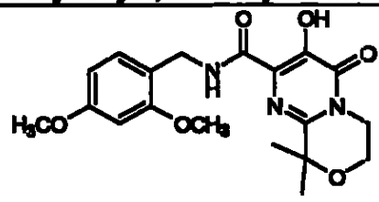
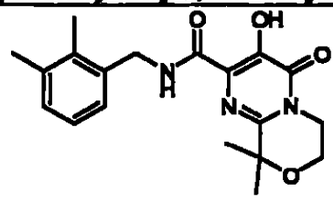
Examples 218-259, in table 11, were prepared using methods similar to those described for examples 1, 19, 20. The compounds were characterized by LCMS with the observed retention time (RT, minutes) and molecular weight (MS [M+1])listed in the table.

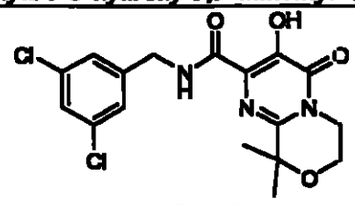
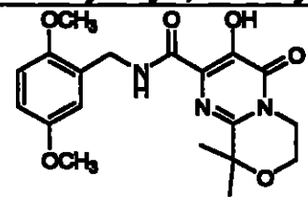
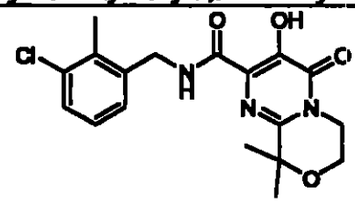
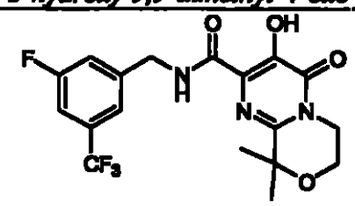
Table 11.

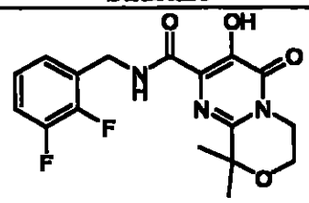
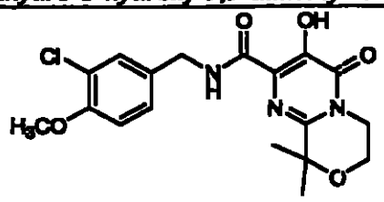
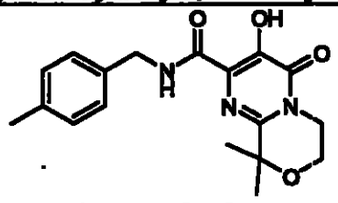
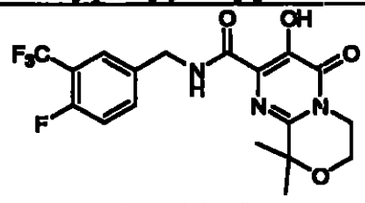
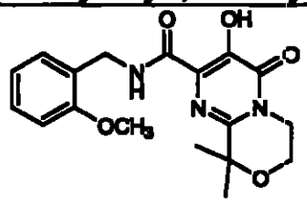
Example	Structure	RT	MS
218	 *Pyrimido[2,1-c][1,4]oxazine-2-carboxamide, N-(1,3-benzodioxol-5-ylmethyl)-4,6,7,9-tetrahydro-3-hydroxy-9,9-dimethyl-4-oxo-*	1.55	374.2
219	 *Pyrimido[2,1-c][1,4]oxazine-2-carboxamide, 4,6,7,9-tetrahydro-3-hydroxy-9,9-dimethyl-4-oxo-N-(phenylmethyl)-*	1.60	330.2

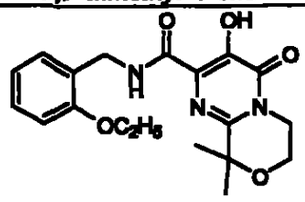
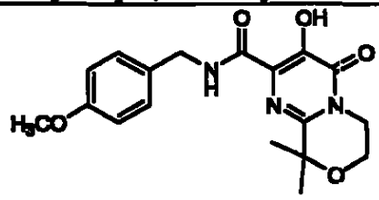
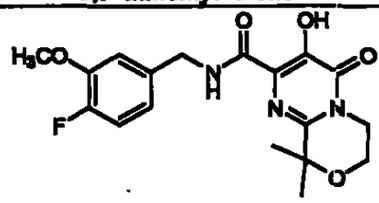
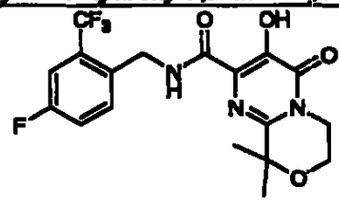
Example	Structure	RT	MS
220	 *Pyrimido[2,1-c][1,4]oxazine-2-carboxamide, N-[(3-fluorophenyl)methyl]-4,6,7,9-tetrahydro-3-hydroxy-9,9-dimethyl-4-oxo-*	1.63	348.2
221	 *Pyrimido[2,1-c][1,4]oxazine-2-carboxamide, N-[(3,4-dichlorophenyl)methyl]-4,6,7,9-tetrahydro-3-hydroxy-9,9-dimethyl-4-oxo-*	1.99	398.16
222	 *Pyrimido[2,1-c][1,4]oxazine-2-carboxamide, 4,6,7,9-tetrahydro-3-hydroxy-N-[(3-methoxyphenyl)methyl]-9,9-dimethyl-4-oxo-*	1.61	360.2
223	 *Pyrimido[2,1-c][1,4]oxazine-2-carboxamide, 4,6,7,9-tetrahydro-3-hydroxy-9,9-dimethyl-N-[(3-methylphenyl)methyl]-4-oxo-*	1.79	344.2
224	 *Pyrimido[2,1-c][1,4]oxazine-2-*	1.65	366.2

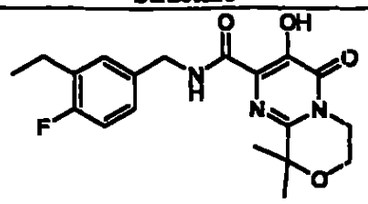
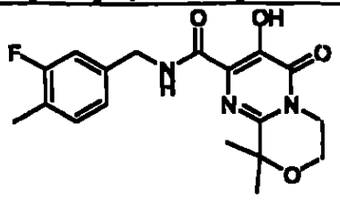
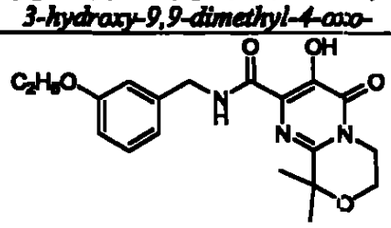
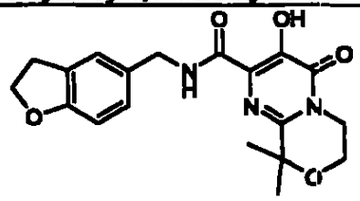
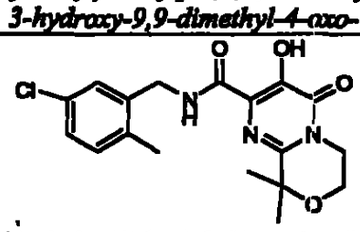
Example	Structure	RT	MS
	carboxamide, N-[(2,5-difluorophenyl)methyl]-4,6,7,9-tetrahydro-3-hydroxy-9,9-dimethyl-4-oxo-		
225	 *Pyrimido[2,1-c][1,4]oxazine-2-carboxamide, 4,6,7,9-tetrahydro-3-hydroxy-N-[(4-hydroxy-3-methoxyphenyl)methyl]-9,9-dimethyl-4-oxo-*	1.27	376.2
226	 *Pyrimido[2,1-c][1,4]oxazine-2-carboxamide, N-[(3-chlorophenyl)methyl]-4,6,7,9-tetrahydro-3-hydroxy-9,9-dimethyl-4-oxo-*	1.80	364.2
227	 *Pyrimido[2,1-c][1,4]oxazine-2-carboxamide, N-[(2,3-dichlorophenyl)methyl]-4,6,7,9-tetrahydro-3-hydroxy-9,9-dimethyl-4-oxo-*	2.00	398.2
228	 *Pyrimido[2,1-c][1,4]oxazine-2-carboxamide, N-[(2,5-dichlorophenyl)methyl]-4,6,7,9-tetrahydro-3-hydroxy-9,9-dimethyl-4-oxo-*	1.97	398.1

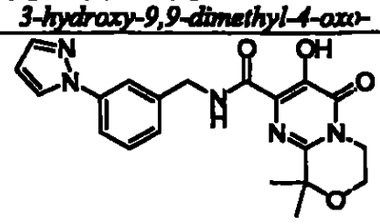
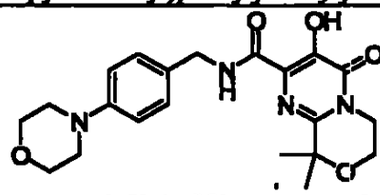
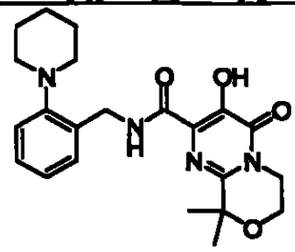
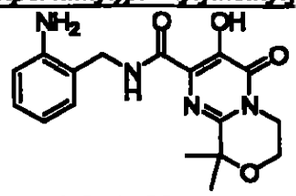
Example	Structure	RT	MS
229	 *Pyrimido[2,1-c][1,4]oxazine-2-carboxamide, N-[(2,3-dimethoxyphenyl)methyl]-4,6,7,9-tetrahydro-3-hydroxy-9,9-dimethyl-4-oxo-*	1.64	390.2
230	 *Pyrimido[2,1-c][1,4]oxazine-2-carboxamide, N-[(2,3-dihydro-1,4-benzodioxin-6-yl)methyl]-4,6,7,9-tetrahydro-3-hydroxy-9,9-dimethyl-4-oxo-*	1.64	390.24
231	 *Pyrimido[2,1-c][1,4]oxazine-2-carboxamide, N-[(3-chloro-4-methylphenyl)methyl]-4,6,7,9-tetrahydro-3-hydroxy-9,9-dimethyl-4-oxo-*	2.01	378.1
232	 *Pyrimido[2,1-c][1,4]oxazine-2-carboxamide, N-[(2,4-dimethoxyphenyl)methyl]-4,6,7,9-tetrahydro-3-hydroxy-9,9-dimethyl-4-oxo-*	1.75	390.2
233	 *Pyrimido[2,1-c][1,4]oxazine-2-*	1.92	358.2

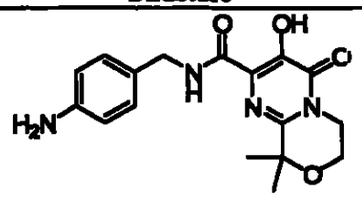
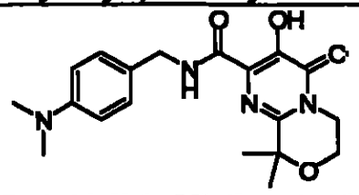
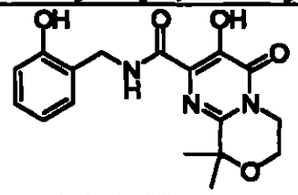
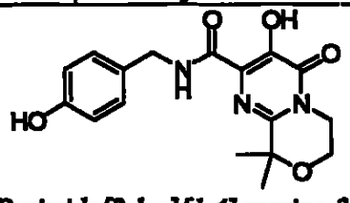
Example	Structure	RT	MS
	carboxamide, N-[(2,3-dimethylphenyl)methyl]-4,6,7,9-tetrahydro-3-hydroxy-9,9-dimethyl-4-oxo-		
234	 *Pyrimido[2,1-c][1,4]oxazine-2-carboxamide, N-[(3,5-dichlorophenyl)methyl]-4,6,7,9-tetrahydro-3-hydroxy-9,9-dimethyl-4-oxo-*	2.01	398.0
235	 *Pyrimido[2,1-c][1,4]oxazine-2-carboxamide, N-[(2,5-dimethoxyphenyl)methyl]-4,6,7,9-tetrahydro-3-hydroxy-9,9-dimethyl-4-oxo-*	1.71	390.1
236	 *Pyrimido[2,1-c][1,4]oxazine-2-carboxamide, N-[(3-chloro-2-methylphenyl)methyl]-4,6,7,9-tetrahydro-3-hydroxy-9,9-dimethyl-4-oxo-*	1.98	378.1
237	 *Pyrimido[2,1-c][1,4]oxazine-2-carboxamide, N-[[3-fluoro-5-(trifluoromethyl)phenyl]methyl]-4,6,7,9-tetrahydro-3-hydroxy-9,9-dimethyl-4-oxo-*	1.95	416.1

Example	Structure	RT	MS
238	 *Pyrimido[2,1-c][1,4]oxazine-2-carboxamide, N-[(2,3-difluorophenyl)methyl]-4,6,7,9-tetrahydro-3-hydroxy-9,9-dimethyl-4-oxo-*	1.70	366.0
239	 *Pyrimido[2,1-c][1,4]oxazine-2-carboxamide, N-[(3-chloro-4-methoxyphenyl)methyl]-4,6,7,9-tetrahydro-3-hydroxy-9,9-dimethyl-4-oxo-*	1.71	394.0
240	 *Pyrimido[2,1-c][1,4]oxazine-2-carboxamide, 4,6,7,9-tetrahydro-3-hydroxy-9,9-dimethyl-N-[(4-methylphenyl)methyl]-4-oxo-*	1.80	344.0
241	 *Pyrimido[2,1-c][1,4]oxazine-2-carboxamide, N-[[4-fluoro-3-(trifluoromethyl)phenyl]methyl]-4,6,7,9-tetrahydro-3-hydroxy-9,9-dimethyl-4-oxo-*	1.90	416.1
242	 *Pyrimido[2,1-c][1,4]oxazine-2-*	1.80	360.1

Example	Structure	RT	MS
	carboxamide, 4,6,7,9-tetrahydro-3-hydroxy-N-[(2-methoxyphenyl)methyl]-9,9-dimethyl-4-oxo-		
243	 *Pyrimido[2,1-c][1,4]oxazine-2-carboxamide, N-[(2-ethoxyphenyl)methyl]-4,6,7,9-tetrahydro-3-hydroxy-9,9-dimethyl-4-oxo-*	1.90	374.1
244	 *Pyrimido[2,1-c][1,4]oxazine-2-carboxamide, 4,6,7,9-tetrahydro-3-hydroxy-N-[(4-methoxyphenyl)methyl]-9,9-dimethyl-4-oxo-*	1.60	360.1
245	 *Pyrimido[2,1-c][1,4]oxazine-2-carboxamide, N-[(4-fluoro-3-methoxyphenyl)methyl]-4,6,7,9-tetrahydro-3-hydroxy-9,9-dimethyl-4-oxo-*	1.23	378.1
246	 *Pyrimido[2,1-c][1,4]oxazine-2-carboxamide, N-[[4-fluoro-2-(trifluoromethyl)phenyl]methyl]-4,6,7,9-tetrahydro-3-hydroxy-9,9-dimethyl-4-oxo-*	1.99	416.1

Example	Structure	RT	MS
247	 *Pyrimido[2,1-c][1,4]oxazine-2-carboxamide, N-[(3-ethyl-4-fluorophenyl)methyl]-4,6,7,9-tetrahydro-3-hydroxy-9,9-dimethyl-4-oxo-*	1.98	376.1
248	 *Pyrimido[2,1-c][1,4]oxazine-2-carboxamide, N-[(3-fluoro-4-methylphenyl)methyl]-4,6,7,9-tetrahydro-3-hydroxy-9,9-dimethyl-4-oxo-*	1.83	362.1
249	 *Pyrimido[2,1-c][1,4]oxazine-2-carboxamide, N-[(3-ethoxyphenyl)methyl]-4,6,7,9-tetrahydro-3-hydroxy-9,9-dimethyl-4-oxo-*	1.77	374.1
250	 *Pyrimido[2,1-c][1,4]oxazine-2-carboxamide, N-[(2,3-dihydro-5-benzofuranyl)methyl]-4,6,7,9-tetrahydro-3-hydroxy-9,9-dimethyl-4-oxo-*	1.59	372.0
251	 *Pyrimido[2,1-c][1,4]oxazine-2-*	1.96	378.1

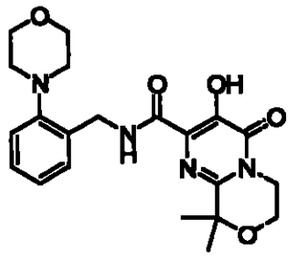
Example	Structure	RT	MS
	carboxamide, N-[(5-chloro-2-methylphenyl)methyl]-4,6,7,9-tetrahydro-3-hydroxy-9,9-dimethyl-4-oxo-		
252	 *Pyrimido[2,1-c][1,4]oxazine-2-carboxamide, 4,6,7,9-tetrahydro-3-hydroxy-9,9-dimethyl-4-oxo-N-[[3-(1H-pyrazol-1-yl)phenyl]methyl]-*	1.50	396.27
253	 *Pyrimido[2,1-c][1,4]oxazine-2-carboxamide, 4,6,7,9-tetrahydro-3-hydroxy-9,9-dimethyl-N-[[4-(4-morpholinyl)phenyl]methyl]-4-oxo-*	1.27	415.29
254	 *Pyrimido[2,1-c][1,4]oxazine-2-carboxamide, 4,6,7,9-tetrahydro-3-hydroxy-9,9-dimethyl-4-oxo-N-[[2-(1-piperidinyl)phenyl]methyl]-*	1.12	413.31
255	 *Pyrimido[2,1-c][1,4]oxazine-2-carboxamide, N-[(2-aminophenyl)methyl]-4,6,7,9-tetrahydro-3-hydroxy-9,9-dimethyl-4-oxo-*	1.05	345.26

Example	Structure	RT	MS
256	 *Pyrimido[2,1-c][1,4]oxazine-2-carboxamide, N-[(4-aminophenyl)methyl]-4,6,7,9-tetrahydro-3-hydroxy-9,9-dimethyl-4-oxo-*	0.98	345.25
257	 *Pyrimido[2,1-c][1,4]oxazine-2-carboxamide, N-[[4-(dimethylamino)phenyl]methyl]-4,6,7,9-tetrahydro-3-hydroxy-9,9-dimethyl-4-oxo-*	0.98	373.29
258	 *Pyrimido[2,1-c][1,4]oxazine-2-carboxamide, 4,6,7,9-tetrahydro-3-hydroxy-N-[(2-hydroxyphenyl)methyl]-9,9-dimethyl-4-oxo-*	1.44	346.24
259	 *Pyrimido[2,1-c][1,4]oxazine-2-carboxamide, 4,6,7,9-tetrahydro-3-hydroxy-N-[(4-hydroxyphenyl)methyl]-9,9-dimethyl-4-oxo-*	1.22	346.24

Examples 260-278

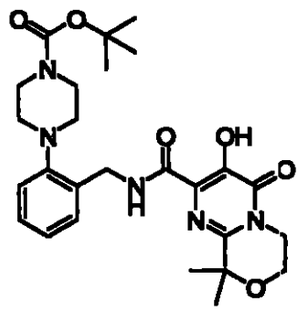
Examples 260-278 were prepared according to the methods used for the preparation of the compounds in table 3 and characterized by LCMS.

Example 260



Pyrimido[2,1-c][1,4]oxazine-2-carboxamide, 4,6,7,9-tetrahydro-3-hydroxy-9,9-dimethyl-N-[[2-(4-morpholinyl)phenyl]methyl]-4-oxo-. LCMS: HPLC retention time = 4.03 min, MS = [M+1] 415.23.

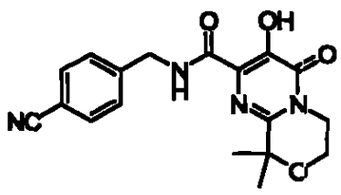
Example 261



1-Piperazinecarboxylic acid, 4-[2-[[[(4,6,7,9-tetrahydro-3-hydroxy-9,9-dimethyl-4-oxopyrimido[2,1-c][1,4]oxazin-2-yl)carbonyl]amino]methyl]phenyl]-, 1,1-dimethylethyl ester. LCMS: HPLC retention time = 4.93 min, MS = [M+1] 514.24.

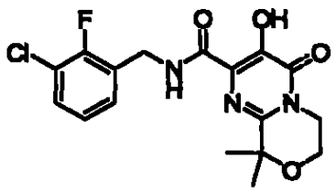
Benzoic acid, 3-[[[(4,6,7,9-tetrahydro-3-hydroxy-9,9-dimethyl-4-oxopyrimido[2,1-c][1,4]oxazin-2-yl)carbonyl]amino]methyl]-, methyl ester. LCMS: HPLC retention time = 3.97 min, MS = [M+1] 388.18.

Example 265



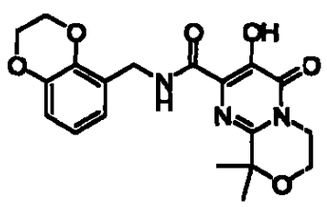
Pyrimido[2,1-c][1,4]oxazine-2-carboxamide, N-[(4-cyanophenyl)methyl]-4,6,7,9-tetrahydro-3-hydroxy-9,9-dimethyl-4-oxo-. LCMS: HPLC retention time = 3.59 min, MS = [M+1] 355.2.

Example 266



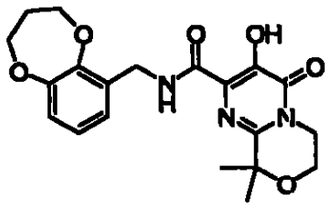
Pyrimido[2,1-c][1,4]oxazine-2-carboxamide, N-[(3-chloro-2-fluorophenyl)methyl]-4,6,7,9-tetrahydro-3-hydroxy-9,9-dimethyl-4-oxo-. LCMS: HPLC retention time = 4.47 min, MS = [M+1] 382.14.

Example 267



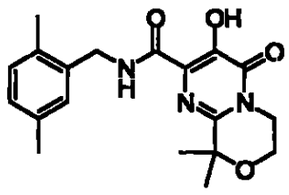
Pyrimido[2,1-c][1,4]oxazine-2-carboxamide, N-[(2,3-dihydro-1,4-benzodioxin-5-yl)methyl]-4,6,7,9-tetrahydro-3-hydroxy-9,9-dimethyl-4-oxo-. LCMS: HPLC retention time = 4.15 min, MS = [M+1] 388.2.

Example 268



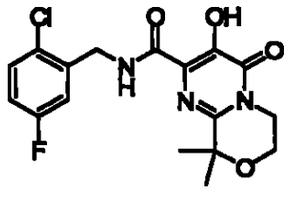
Pyrimido[2,1-c][1,4]oxazine-2-carboxamide, N-[(3,4-dihydro-2H-1,5-benzodioxepin-6-yl)methyl]-4,6,7,9-tetrahydro-3-hydroxy-9,9-dimethyl-4-oxo-. LCMS: HPLC retention time = 4.12 min, MS = [M+1] 402.21.

Example 269



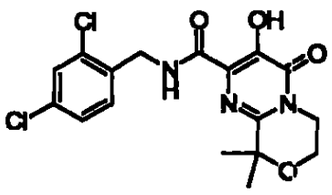
Pyrimido[2,1-c][1,4]oxazine-2-carboxamide, N-[(2,5-dimethylphenyl)methyl]-4,6,7,9-tetrahydro-3-hydroxy-9,9-dimethyl-4-oxo-. LCMS: HPLC retention time = 4.64 min, MS = [M+1] 358.22

Example 270



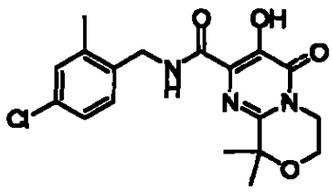
Pyrimido[2,1-c][1,4]oxazine-2-carboxamide, N-[(5-chloro-2-fluorophenyl)methyl]-4,6,7,9-tetrahydro-3-hydroxy-9,9-dimethyl-4-oxo-. LCMS: HPLC retention time = 4.44 min, MS = [M+1] 382.15

Example 271



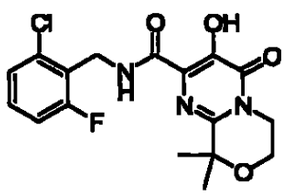
Pyrimido[2,1-c][1,4]oxazine-2-carboxamide, N-[(2,4-dichlorophenyl)methyl]-4,6,7,9-tetrahydro-3-hydroxy-9,9-dimethyl-4-oxo-. LCMS: HPLC retention time = 4.88 min, MS = [M+1] 398.11.

Example 272



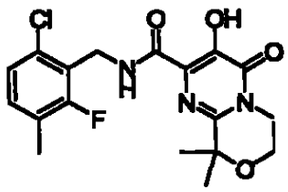
Pyrimido[2,1-c][1,4]oxazine-2-carboxamide, N-[(4-chloro-2-methylphenyl)methyl]-4,6,7,9-tetrahydro-3-hydroxy-9,9-dimethyl-4-oxo-. LCMS: HPLC retention time = 4.69 min, MS = [M+1] 378.17.

Example 273



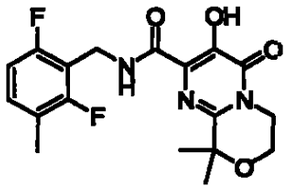
Pyrimido[2,1-c][1,4]oxazine-2-carboxamide, N-[(2-chloro-6-fluorophenyl)methyl]-4,6,7,9-tetrahydro-3-hydroxy-9,9-dimethyl-4-oxo-. LCMS: HPLC retention time = 4.39 min, MS = [M+1] 382.13.

Example 274



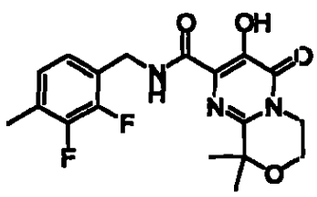
Pyrimido[2,1-c][1,4]oxazine-2-carboxamide, N-[(6-chloro-2-fluoro-3-methylphenyl)methyl]-4,6,7,9-tetrahydro-3-hydroxy-9,9-dimethyl-4-oxo-. LCMS: HPLC retention time = 4.74 min, MS = [M+1] 396.14.

Example 275



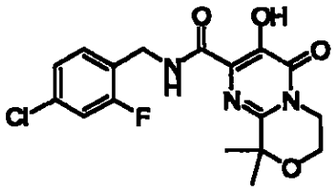
Pyrimido[2,1-c][1,4]oxazine-2-carboxamide, N-[(2,6-difluoro-3-methylphenyl)methyl]-4,6,7,9-tetrahydro-3-hydroxy-9,9-dimethyl-4-oxo-. LCMS: HPLC retention time = 4.49 min, MS = [M+1] 380.18.

Example 276



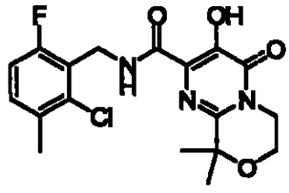
Pyrimido[2,1-c][1,4]oxazine-2-carboxamide, N-[(2,3-difluoro-4-methylphenyl)methyl]-4,6,7,9-tetrahydro-3-hydroxy-9,9-dimethyl-4-oxo-. LCMS: HPLC retention time = 4.53 min, MS = [M+1] 380.18.

Example 277



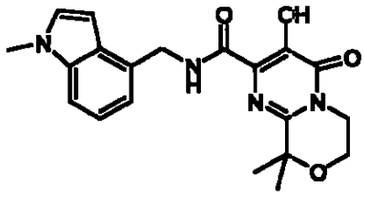
Pyrimido[2,1-c][1,4]oxazine-2-carboxamide, N-[(4-chloro-2-fluorophenyl)methyl]-4,6,7,9-tetrahydro-3-hydroxy-9,9-dimethyl-4-oxo-. LCMS: HPLC retention time = 4.57min, MS = [M+1] 382.13.

Example 278



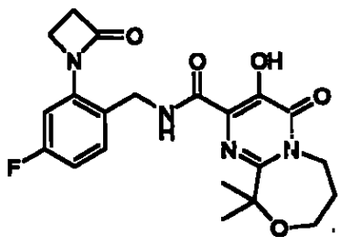
Pyrimido[2,1-c][1,4]oxazine-2-carboxamide, N-[(2-chloro-6-fluoro-3-methylphenyl)methyl]-4,6,7,9-tetrahydro-3-hydroxy-9,9-dimethyl-4-oxo-. LCMS: HPLC retention time = 4.68 min, MS = [M+1] 396.16.

Example 279



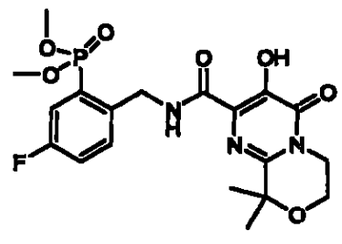
Pyrimido[2,1-c][1,4]oxazine-2-carboxamide, 4,6,7,9-tetrahydro-3-hydroxy-9,9-dimethyl-N-[(1-methyl-1H-indol-4-yl)methyl]-4-oxo-. ^{1}H NMR (500 MHz, DMSO-d_6) δ ppm: 1.56 (s, 6), 3.79 (s, 3), 3.82 (m, 2), 3.97 (m, 2), 4.76 (d, 2), 6.62 (d, 1), 6.96 (d, 1), 7.12 (m, 1), 7.27-7.38 (overlapping m, 2). HRMS [M+1] calcd for $C_{20}H_{23}N_4O_4$, 383.1641; found, 383.1717. Anal calcd for $C_{20}H_{22}N_4O_4$: C, 62.81; H, 5.79; N, 14.65. Found: C, 62.88; H, 6.08; N, 13.56.

Example 280



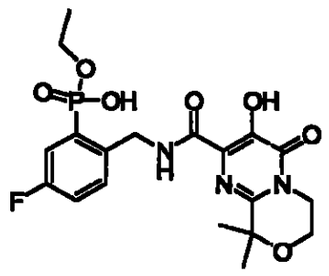
6H-Pyrimido[2,1-c][1,4]oxazepine-2-carboxamide, N-[[4-fluoro-2-(2-oxo-1-azetidinyl)phenyl]methyl]-4,7,8,10-tetrahydro-3-hydroxy-10,10-dimethyl-4-oxo-. ^{1}H NMR (400 MHz, DMSO-d_6) δ: 12.17 (1H, s), 9.28 (1H, broad s), 7.37 (1H, dd, J = 8.2, 6.7 Hz), 7.23 (1H, dd, J =10.2, 2.4 Hz), 7.04 (1H, m), 4.51 (2H, broad s), 4.35 (2H, broad s), 3.79 (2H, t, J = 4.4 Hz), 3.62 (2H, m), 3.11 (2H, t, J = 4.4 Hz), 1.81 (2H, m), 1.55 (6H, s). LCMS $(M+H)^+$ m/z 431.

Example 281



Phosphonic acid, [5-fluoro-2-[[[(4,6,7,9-tetrahydro-3-hydroxy-9,9-dimethyl-4-oxopyrimido[2,1-c][1,4]oxazin-2-yl)carbonyl]amino]methyl][phenyl]-, dimethyl ester. Hydrogenation of dimethyl 2-((3-(benzyloxy)-9,9-dimethyl-4-oxo-4,6,7,9-tetrahydropyrimido[2,1-c][1,4]oxazine-2-carboxamido)methyl)-5-fluorophenylphosphonate (0.030 g, 0.055 mmol) gave 0.018 g (72 %) of the title compound as a white solid ^{1}HNMR 400 MHz ($CDCl_3$) δ (ppm) : 1.63 (6H, s, 2 x CH_3), 3.84 (3H, s, OCH_3), 3.87 (3H, s, OCH_3), 4.03 (4H, s, 2 x CH_2), 4.77 (2H, d, J = 6.5 Hz, NCH_2), 7.28 (1H, m, aromatic), 7.47 (1H, m, aromatic), 7.65 (1H, m, aromatic), 9.0 (1H, broad t , NH) 12.0 (1H, broad, OH). MS (ESI^+) m/z 456 [$M+H^+$].

Example 282

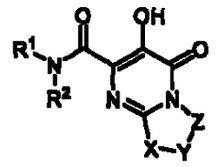


Phosphonic acid, [5-fluoro-2-[[[(4,6,7,9-tetrahydro-3-hydroxy-9,9-dimethyl-4-oxopyrimido[2,1-c][1,4]oxazin-2-yl)carbonyl]amino]methyl][phenyl]-, monoethyl ester. The title compound can be prepared from intermediate 188, ethyl hydrogen 2-((3-(benzyloxy)-9,9-dimethyl-4-oxo-4,6,7,9-tetrahydropyrimido[2,1-c][1,4]oxazine-2-carboxamido)methyl)-5-fluorophenylphosphonate. ^{1}HNMR 400 MHz ($CDCl_3$) δ (ppm) : 1.32 (3H, t, J = 7.1 Hz, CH_3), 1.60 (6H, s, 2 x CH_3), 4.02 (4H, s, 2 x CH_2), 4.12 (2H, m, OCH_2), 4.83 (2H, broad, NCH_2), 7.18 (1H, m, aromatic), 7.54 (2H, m, aromatics), 8.49 (1H, broad , NH). HRMS (ESI^+) calculated for $C_{19}H_{24}FN_3O_7P$ [$M+H^+$] : 456.1336 ; found : 456.1353.

CLAIMS

We claim:

1. A compound of Formula I



I

wherein:

R^1 is $C_{1-6}(Ar^1)$alkyl, $C_{1-6}(Ar^1)(CON(R^8)(R^9))$alkyl, $C_{1-6}(Ar^1)(CO_2R^{14})$alkyl, $C_{1-6}(Ar^1)$hydroxyalkyl, or $C_{1-6}(Ar^1)$oxyalkyl;

R^2 is hydrogen, C_{1-6}alkyl, or OR^{14};

R^3 is hydrogen, halo, hydroxy, cyano, C_{1-6}alkyl, C_{3-7}cycloalkyl, C_{3-7}cycloalkenyl, C_{1-6}haloalkyl, C_{1-6}alkoxy, C_{1-6}alkylthio, C_{1-6}haloalkoxy, $N(R^5)(R^5)$, $NHAr^2$, $N(R^6)SO_2R^7$, $N(R^6)COR^7$, $N(R^6)CO_2R^7$, $OCOR^7$, OCO_2R^7, $OCON(R^8)(R^9)$, $OCH_2CO_2R^7$, $OCH_2CON(R^8)(R^9)$, COR^6, CO_2R^6, $CON(R^5)(R^5)$, SOR^7, $S(=N)R^7$, SO_2R^7, $SO_2N(R^6)(R^6)$, $PO(OR^6)_2$, $C_{2-4}(R^{12})$alkynyl, R^{13}, Ar^2, or Ar^3;

R^4 is hydrogen, halo, hydroxy, cyano, C_{1-6}alkyl, C_{1-6}alkoxy, C_{1-6}haloalkyl, C_{1-6}haloalkoxy, or $N(R^6)(R^6)$;

R^5 is hydrogen, halo, hydroxy, cyano, C_{1-6}alkyl, C_{1-6}alkoxy, C_{1-6}haloalkyl, C_{1-6}haloalkoxy, or $N(R^6)(R^6)$;

R^6 is hydrogen, C_{1-6}alkyl, or C_{3-7}cycloalkyl;

R^7 is C_{1-6}alkyl or C_{3-7}cycloalkyl;

R^8 is hydrogen, C_{1-6}alkyl, C_{1-6}hydroxyalkyl, C_{1-6}(C_{1-6}alkoxy)alkyl or C_{1-6}(C_{1-6}dialkylamino)alkyl;

R^9 is hydrogen, C_{1-6}alkyl, C_{1-6}hydroxyalkyl, C_{1-6}(C_{1-6}alkoxy)alkyl or C_{1-6}(C_{1-6}dialkylamino)alkyl; or

$N(R^8)(R^9)$ taken together is azetidinyl, pyrrolidinyl, (R^{10})-piperidinyl, N-(R^{11})-piperazinyl, morpholinyl, thiomorpholinyl, or dioxothiazinyl;

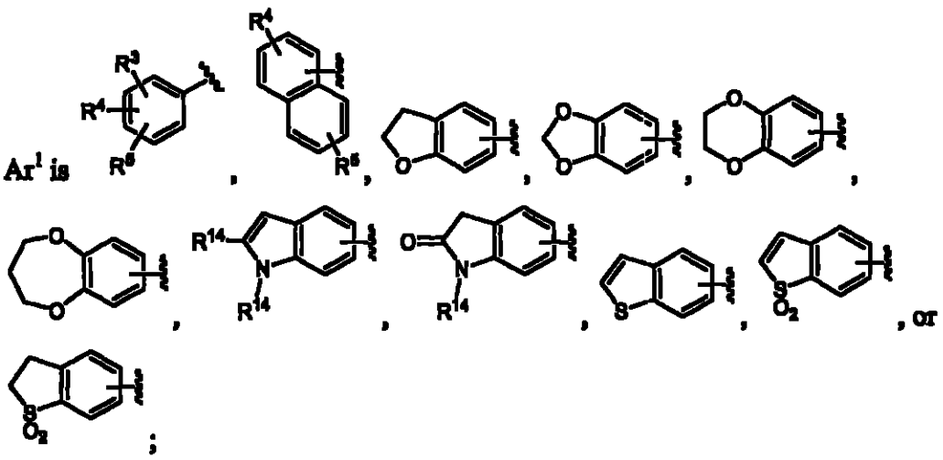
R^{10} is hydrogen, C_{1-6}alkyl, or C_{1-6}hydroxyalkyl;

R^{11} is hydrogen, C_{1-6}alkyl, C_{3-7}cyclolkyl, COR^6, or CO_2R^6;

R^{12} is hydrogen, hydroxy, $N(R^6)(R^6)$, SO_2R^7, OSO_2R^7, or dioxothiazinyl;

R^{13} is azetidinonyl, pyrrolidinonyl, valerolactamyl, caprolactamyl, maleimido, oxazolidonyl, or dioxothiazinyl, and is substituted with 0-1 substituents selected from the group consisting of hydroxymethyl, acetoxymethyl, and aminomethyl;

R^{14} is hydrogen or C_{1-6}alkyl;

Ar^1 is  ;

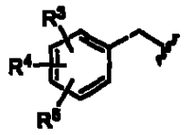
Ar^2 is tetrazolyl, triazolyl, oxadiazolyl, thiadiazolyl, pyrazolyl, imidazolyl, oxazolyl, thiazolyl, isoxazolyl, isothiazolyl, furanyl, thienyl, pyrrolyl, pyrimidinyl, pyrazinyl, pyridinyl, hydroxypyridinyl, quinolinyl, isoquinolinyl, or indolyl, and is substituted with 0-2 substituents selected from the group consisting of halo, cyano, benzyl, C_{1-6}alkyl, C_{1-6}alkoxy, $N(R^5)(R^5)$, $CON(R^5)(R^5)$, CO_2R^6, $CONHSO_2N(R^5)(R^6)$, $CONHSO_2N(R^6)$(phenyl), and $CONHSO_2N(R^6)$(halophenyl);

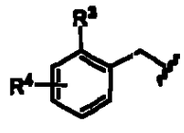
Ar^3 is phenyl substituted with 0-2 substituents selected from the group consisting of halo, cyano, hydroxy, C_{1-6}alkyl, C_{1-6}alkoxy, (C_{1-6}alkoxy)methyl, C_{1-6}haloalkyl, C_{1-6}haloalkoxy, $N(R^5)(R^5)$, $CON(R^6)(R^6)$, and $CH_2N(R^5)(R^5)$, or is dioxolanylphenyl; and

X-Y-Z is $C(R^{14})_2OC(R^{14})_2$, $C(R^{14})_2OC(R^{14})_2C(R^{14})_2$, or $C(R^{14})_2OC(R^{14})_2C(R^{14})_2C(R^{14})_2$;

or a pharmaceutically acceptable salt or solvate thereof.

2. A compound of claim 1 where R^1 is $C_{1-6}(Ar^1)$alkyl.

3. A compound of claim 1 where R^1 is  .

4. A compound of claim 1 where R^1 is  .

5. A compound of claim 1 where R^2 is hydrogen.

6. A compound of claim 1 where R^3 is hydrogen, halo, $N(R^5)(R^5)$, $N(R^6)COR^7$, $OCON(R^5)(R^5)$, $CON(R^5)(R^5)$, SOR^7, SO_2R^7, $SO_2N(R^6)(R^6)$, $PO(OR^6)_2$, R^{13}, or Ar^2.

7. A compound of claim 1 where X-Y-Z is $C(R^{14})_2OCH_2$, $C(R^{14})_2OCH_2CH_2$, or $C(R^{14})_2OCH_2CH_2CH_2$.

8. A compound of claim 1 where X-Y-Z is CH_2OCH_2, $C(CH_3)HOCH_2$, $C(CH_3)_2OCH_2$, $CH_2OCH_2CH_2$, $C(CH_3)HOCH_2CH_2$, $C(CH_3)_2OCH_2CH_2$, $CH_2OCH_2CH_2CH_2$, $C(CH_3)HOCH_2CH_2CH_2$, or $C(CH_3)_2OCH_2CH_2CH_2$.

9. A compound of claim 1 selected from the group consisting of

N-[[4-fluoro-2-[(methylamino)carbonyl]phenyl]methyl]-4,6,7,9-tetrahydro-3-hydroxy-9,9-dimethyl-4-oxo-pyrimido[2,1-c][1,4]oxazine-2-carboxamide;

9,9-diethyl-N-[[4-fluoro-2-(1H-1,2,4-triazol-1-yl)phenyl]methyl]-4,6,7,9-tetrahydro-3-hydroxy-4-oxo-pyrimido[2,1-c][1,4]oxazine-2-carboxamide;

9,9-diethyl-N-[[4-fluoro-2-(methylsulfonyl)phenyl]methyl]-4,6,7,9-tetrahydro-3-hydroxy-4-oxo-pyrimido[2,1-c][1,4]oxazine-2-carboxamide;

N-[[2-[(dimethylamino)sulfonyl]-4-fluorophenyl]methyl]-9,9-diethyl-4,6,7,9-tetrahydro-3-hydroxy-4-oxo-pyrimido[2,1-c][1,4]oxazine-2-carboxamide;

N-[[4-fluoro-2-(2-oxo-1-azetidinyl)phenyl]methyl]-4,6,7,9-tetrahydro-3-hydroxy-9,9-dimethyl-4-oxo-pyrimido[2,1-c][1,4]oxazine-2-carboxamide;

9,9-diethyl-N-[[4-fluoro-2-[(methylamino)carbonyl]phenyl]methyl]-4,6,7,9-tetrahydro-3-hydroxy-4-oxo-pyrimido[2,1-c][1,4]oxazine-2-carboxamide;

N-[[4-fluoro-2-(2-oxo-3-oxazolidinyl)phenyl]methyl]-4,6,7,9-tetrahydro-3-hydroxy-9,9-dimethyl-4-oxo-pyrimido[2,1-c][1,4]oxazine-2-carboxamide;

N-[[4-fluoro-2-(methylsulfonyl)phenyl]methyl]-4,6,7,9-tetrahydro-3-hydroxy-9,9-dimethyl-4-oxo-pyrimido[2,1-c][1,4]oxazine-2-carboxamide;

N-[[4-fluoro-2-(1H-1,2,4-triazol-1-yl)phenyl]methyl]-4,7,8,10-tetrahydro-3-hydroxy-10,10-dimethyl-4-oxo-6H-pyrimido[2,1-c][1,4]oxazepine-2-carboxamide;

N-[[4-fluoro-2-(3-methyl-1H-1,2,4-triazol-1-yl)phenyl]methyl]-4,6,7,9-tetrahydro-3-hydroxy-9,9-dimethyl-4-oxo-pyrimido[2,1-c][1,4]oxazine-2-carboxamide;

N-[[4-fluoro-2-(2-oxo-1-pyrrolidinyl)phenyl]methyl]-4,6,7,9-tetrahydro-3-hydroxy-9,9-dimethyl-4-oxo-pyrimido[2,1-c][1,4]oxazine-2-carboxamide;

N-[[4-fluoro-2-(tetrahydro-1,1-dioxido-2H-1,2-thiazin-2-yl)phenyl]methyl]-4,6,7,9-tetrahydro-3-hydroxy-9,9-dimethyl-4-oxo-pyrimido[2,1-c][1,4]oxazine-2-carboxamide;

N-[[4-fluoro-2-(1H-1,2,4-triazol-1-yl)phenyl]methyl]-4,6,7,9-tetrahydro-3-hydroxy-9,9-dimethyl-4-oxo-pyrimido[2,1-c][1,4]oxazine-2-carboxamide;

N-[[4-fluoro-2-[(methylamino)carbonyl]phenyl]methyl]-4,7,8,10-tetrahydro-3-hydroxy-10,10-dimethyl-4-oxo-6H-pyrimido[2,1-c][1,4]oxazepine-2-carboxamide;

9,9-diethyl-4,6,7,9-tetrahydro-3-hydroxy-4-oxo-N-[[2-(tetrahydro-1,1-dioxido-2H-1,2-thiazin-2-yl)phenyl]methyl]-pyrimido[2,1-c][1,4]oxazine-2-carboxamide;

N-[[4-fluoro-2-(1,2,3-thiadiazol-4-yl)phenyl]methyl]-4,6,7,9-tetrahydro-3-hydroxy-9,9-dimethyl-4-oxo-pyrimido[2,1-c][1,4]oxazine-2-carboxamide;

N-[[4-fluoro-2-(methylsulfonyl)phenyl]methyl]-4,7,8,10-tetrahydro-3-hydroxy-10,10-dimethyl-4-oxo-6H-pyrimido[2,1-c][1,4]oxazepine-2-carboxamide;

N-[[4-fluoro-2-(1-methyl-1H-tetrazol-5-yl)phenyl]methyl]-4,6,7,9-tetrahydro-3-hydroxy-9,9-dimethyl-4-oxo-pyrimido[2,1-c][1,4]oxazine-2-carboxamide;

N-[[4-fluoro-2-(5-methyl-1H-1,2,4-triazol-1-yl)phenyl]methyl]-4,6,7,9-tetrahydro-3-hydroxy-9,9-dimethyl-4-oxo-pyrimido[2,1-c][1,4]oxazine-2-carboxamide;

N-[[4-fluoro-2-(2-oxo-1-piperidinyl)phenyl]methyl]-4,6,7,9-tetrahydro-3-hydroxy-9,9-dimethyl-4-oxo-pyrimido[2,1-c][1,4]oxazine-2-carboxamide;

N-[[2-[(dimethylamino)sulfonyl]-4-fluorophenyl]methyl]-4,6,7,9-tetrahydro-3-hydroxy-9,9-dimethyl-4-oxo-pyrimido[2,1-c][1,4]oxazine-2-carboxamide;

N-[(4-fluorophenyl)methyl]-4,6,7,9-tetrahydro-3-hydroxy-9,9-dimethyl-4-oxo-pyrimido[2,1-c][1,4]oxazine-2-carboxamide;

4,6,7,9-tetrahydro-3-hydroxy-9,9-dimethyl-4-oxo-N-[[2-(2-oxo-3-oxazolidinyl)phenyl]methyl]-pyrimido[2,1-c][1,4]oxazine-2-carboxamide;

N-[[4-fluoro-2-[(methylamino)sulfonyl]phenyl]methyl]-4,6,7,9-tetrahydro-3-hydroxy-9,9-dimethyl-4-oxo-pyrimido[2,1-c][1,4]oxazine-2-carboxamide;

N-[[2-(acetylamino)-4-fluorophenyl]methyl]-4,6,7,9-tetrahydro-3-hydroxy-9,9-dimethyl-4-oxo-pyrimido[2,1-c][1,4]oxazine-2-carboxamide;

N-[[4-fluoro-2-[3-[(4-methyl-1-piperazinyl)carbonyl]-1H-1,2,4-triazol-1-yl]phenyl]methyl]-4,6,7,9-tetrahydro-3-hydroxy-9,9-dimethyl-4-oxo-pyrimido[2,1-c][1,4]oxazine-2-carboxamide;

N-[[4-fluoro-2-(4-morpholinylcarbonyl)phenyl]methyl]-4,6,7,9-tetrahydro-3-hydroxy-9,9-dimethyl-4-oxo-pyrimido[2,1-c][1,4]oxazine-2-carboxamide;

N-[[4-fluoro-2-[[(2-hydroxyethyl)amino]carbonyl]phenyl]methyl]-4,6,7,9-tetrahydro-3-hydroxy-9,9-dimethyl-4-oxo-pyrimido[2,1-c][1,4]oxazine-2-carboxamide;

N-[[4-fluoro-2-[3-(4-morpholinylcarbonyl)-1H-1,2,4-triazol-1-yl]phenyl]methyl]-4,6,7,9-tetrahydro-3-hydroxy-9,9-dimethyl-4-oxo-pyrimido[2,1-c][1,4]oxazine-2-carboxamide;

4,6,7,9-tetrahydro-3-hydroxy-9,9-dimethyl-4-oxo-N-[[2-(2-oxo-1-azetidinyl)phenyl]methyl]-pyrimido[2,1-c][1,4]oxazine-2-carboxamide;

N-[[4-fluoro-2-(1H-pyrazol-5-yl)phenyl]methyl]-4,6,7,9-tetrahydro-3-hydroxy-9,9-dimethyl-4-oxo-pyrimido[2,1-c][1,4]oxazine-2-carboxamide;

N-[[2-[3-[(dimethylamino)carbonyl]-1H-1,2,4-triazol-1-yl]-4-fluorophenyl]methyl]-4,6,7,9-tetrahydro-3-hydroxy-9,9-dimethyl-4-oxo-pyrimido[2,1-c][1,4]oxazine-2-carboxamide;

N-[(4-fluorophenyl)methyl]-4,6,7,9-tetrahydro-3-hydroxy-9,9-dimethyl-4-oxo-pyrimido[2,1-c][1,4]oxazine-2-carboxamide;

N-[[3-fluoro-2-(tetrahydro-1,1-dioxido-2H-1,2-thiazin-2-yl)phenyl]methyl]-4,6,7,9-tetrahydro-3-hydroxy-9,9-dimethyl-4-oxo-pyrimido[2,1-c][1,4]oxazine-2-carboxamide;

4,6,7,9-tetrahydro-3-hydroxy-9,9-dimethyl-N-[[2-(methylsulfonyl)phenyl]methyl]-4-oxo-pyrimido[2,1-c][1,4]oxazine-2-carboxamide;

N-[[4-fluoro-2-(4-morpholinyl)phenyl]methyl]-4,6,7,9-tetrahydro-3-hydroxy-9,9-dimethyl-4-oxo-pyrimido[2,1-c][1,4]oxazine-2-carboxamide;

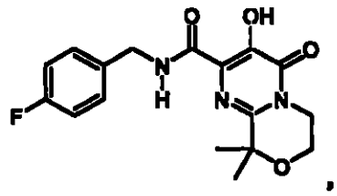
N,N-dimethyl-carbamic acid, 5-fluoro-2-[[[(4,6,7,9-tetrahydro-3-hydroxy-9,9-dimethyl-4-oxopyrimido[2,1-c][1,4]oxazin-2-yl)carbonyl]amino]methyl]phenyl ester;

N-[[2-(aminosulfonyl)-4-fluorophenyl]methyl]-4,6,7,9-tetrahydro-3-hydroxy-9,9-dimethyl-4-oxo-pyrimido[2,1-c][1,4]oxazine-2-carboxamide; and

[5-fluoro-2-[[[(4,6,7,9-tetrahydro-3-hydroxy-9,9-dimethyl-4-oxopyrimido[2,1-c][1,4]oxazin-2-yl)carbonyl]amino]methyl]phenyl]-phosphonic acid, dimethyl ester;

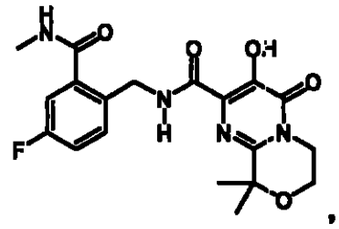
or a pharmaceutically acceptable salt or solvate thereof.

10. The compound of claim 1



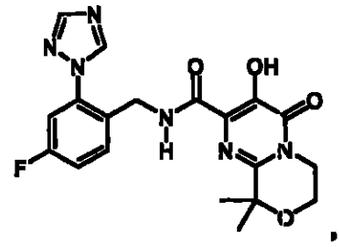
or a pharmaceutically acceptable salt or solvate thereof.

11. The compound of claim 1



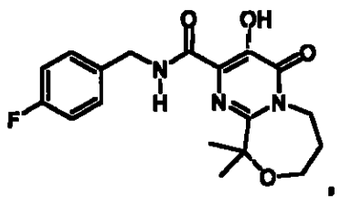
or a pharmaceutically acceptable salt or solvate thereof.

12. The compound of claim 1



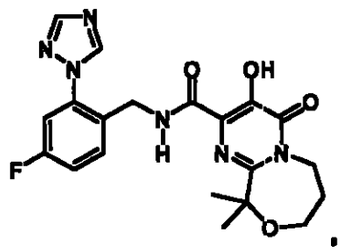
or a pharmaceutically acceptable salt or solvate thereof.

13. The compound of claim 1



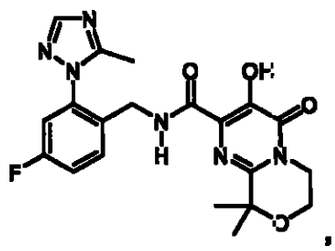
or a pharmaceutically acceptable salt or solvate thereof.

14. The compound of claim 1



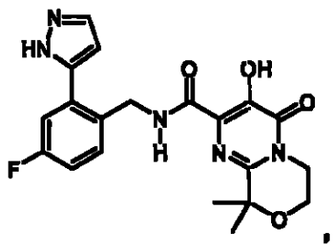
or a pharmaceutically acceptable salt or solvate thereof.

15. The compound of claim 1



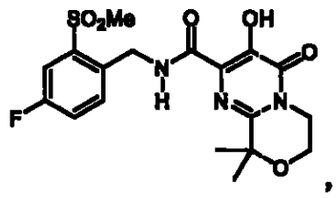
or a pharmaceutically acceptable salt or solvate thereof.

16. The compound of claim 1



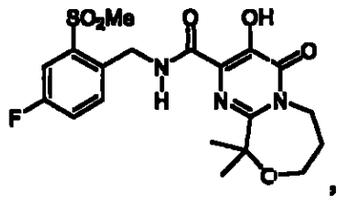
or a pharmaceutically acceptable salt or solvate thereof.

17. The compound of claim 1



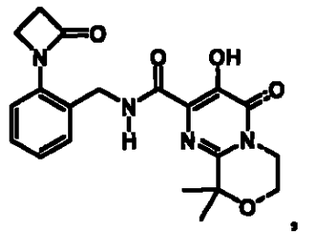
or a pharmaceutically acceptable salt or solvate thereof.

18. The compound of claim 1



or a pharmaceutically acceptable salt or solvate thereof.

19. The compound of claim 1



or a pharmaceutically acceptable salt or solvate thereof.

20. A composition useful for treating HIV infections comprising a therapeutic amount of a compound of claim 1 and a pharmaceutically acceptable carrier.

21. The composition of claim 20 further comprising a therapeutically effective amount at least one other agent used for treatment of AIDS or HIV infection selected from the group consisting of nucleoside HIV reverse transcriptase inhibitors, non-nucleoside HIV reverse transcriptase inhibitors, HIV protease inhibitors, HIV fusion inhibitors, HIV attachment inhibitors, CCR5 inhibitors, CXCR4 inhibitors, HIV budding or maturation inhibitors, and HIV integrase inhibitors, and a pharmaceutically acceptable carrier.

22. The composition of claim 20 wherein the compound of claim 1 is N-[(4-fluorophenyl)methyl]-4,6,7,9-tetrahydro-3-hydroxy-9,9-dimethyl-4-oxo-pyrimido[2,1-c][1,4]oxazine-2-carboxamide.

23. The composition of claim 22 further comprising a therapeutically effective amount at least one other agent used for treatment of AIDS or HIV infection selected from the group consisting of nucleoside HIV reverse transcriptase inhibitors, non-nucleoside HIV reverse transcriptase inhibitors, HIV protease inhibitors, HIV fusion inhibitors, HIV attachment inhibitors, CCR5 inhibitors, CXCR4 inhibitors, HIV budding or maturation inhibitors, and HIV integrase inhibitors, and a pharmaceutically acceptable carrier.

24. A method for treating HIV infection comprising administering a therapeutically effective amount of a compound of Claim 1, or a pharmaceutically acceptable salt or solvate thereof, to a patient in need thereof.

25. The method of claim 24 further comprising administering a therapeutically effective amount of at least one other agent used for treatment of AIDS or HIV infection selected from the group consisting of nucleoside HIV reverse transcriptase inhibitors, non-nucleoside HIV reverse transcriptase inhibitors, HIV protease inhibitors, HIV fusion inhibitors, HIV attachment inhibitors, CCR5 inhibitors,

CXCR4 inhibitors, HIV budding or maturation inhibitors, and HIV integrase inhibitors.

26. The method of claim 24 wherein the compound of claim 1 is N-[(4-fluorophenyl)methyl]-4,6,7,9-tetrahydro-3-hydroxy-9,9-dimethyl-4-oxo-pyrimido[2,1-c][1,4]oxazine-2-carboxamide.

27. The method of claim 26 further comprising a therapeutically effective amount at least one other agent used for treatment of AIDS or HIV infection selected from the group consisting of nucleoside HIV reverse transcriptase inhibitors, non-nucleoside HIV reverse transcriptase inhibitors, HIV protease inhibitors, HIV fusion inhibitors, HIV attachment inhibitors, CCR5 inhibitors, CXCR4 inhibitors, HIV budding or maturation inhibitors, and HIV integrase inhibitors, and a pharmaceutically acceptable carrier.

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INTERNATIONAL SEARCH REPORT

International Application No
PCT/US2005/016473

A. CLASSIFICATION OF SUBJECT MATTER
IPC 7 C07D498/04 A61K31/519 A61P31/18
//(C07D498/04,263:00,239:00),(C07D498/04,265:00,239:00),(C07D498/04 267:00,239:00)

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

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)
IPC 7 C07D

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

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)
EPO-Internal, WPI Data, PAJ, BEILSTEIN Data, CHEM ABS Data

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
A	WO 03/035077 A (ISTITUTO DI RICERCHE DI BIOLOGIA MOLECOLARE P. ANGELETTI SPA; CRESCENZ) 1 May 2003 (2003-05-01) claims 1,30; tables 1,2	1-27
P,A	WO 2004/058756 A (ISTITUTO DI RICERCHE DI BIOLOGIA MOLECOLARE P. ANGELETTI SPA; CRESCENZ) 15 July 2004 (2004-07-15) claims 1,14; table 1	1-27
P,A	WO 2004/058757 A (ISTITUTO DI RICERCHE DI BIOLOGIA MOLECOLARE P. ANGELETTI SPA; CRESCENZ) 15 July 2004 (2004-07-15) claims 1,8; table 1	1-27

☐ Further documents are listed in the continuation of box C.

☒ Patent family members are listed in annex.

* Special categories of cited documents :

"A" document defining the general state of the art which is not considered to be of particular relevance

"E" earlier document but published on or after the international filing date

"L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)

"O" document referring to an oral disclosure, use, exhibition or other means

"P" document published prior to the international filing date but later than the priority date claimed

"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention

"X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone

"Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art.

"&" document member of the same patent family

Date of the actual completion of the international search	Date of mailing of the international search report
11 August 2005	19/08/2005

Name and mailing address of the ISA	Authorized officer
European Patent Office, P.B. 5818 Patentlaan 2 NL - 2280 HV Rijswijk Tel. (+31-70) 340-2040, Tx. 31 651 epo nl, Fax: (+31-70) 340-3016	Seymour, L

Form PCT/ISA/210 (second sheet) (January 2004)

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INTERNATIONAL SEARCH REPORT

International application No.
PCT/US2005/016473

Box II Observations where certain claims were found unsearchable (Continuation of item 2 of first sheet)

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

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

Although claims 24-27 are directed to a method of treatment of the human/animal body, the search has been carried out and based on the alleged effects of the compound/composition.

2. [ ] Claims Nos.:
because they relate to parts of the International Application that do not comply with the prescribed requirements to such an extent that no meaningful International Search can be carried out, specifically:

3. [ ] Claims Nos.:
because they are dependent claims and are not drafted in accordance with the second and third sentences of Rule 6.4(a).

Box III Observations where unity of invention is lacking (Continuation of item 3 of first sheet)

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

1. [ ] As all required additional search fees were timely paid by the applicant, this International Search Report covers all searchable claims.

2. [ ] As all searchable claims could be searched without effort justifying an additional fee, this Authority did not invite payment of any additional fee.

3. [ ] As only some of the required additional search fees were timely paid by the applicant, this International Search Report covers only those claims for which fees were paid, specifically claims Nos.:

4. [ ] No required additional search fees were timely paid by the applicant. Consequently, this International Search Report is restricted to the invention first mentioned in the claims; it is covered by claims Nos.:

Remark on Protest

[ ] The additional search fees were accompanied by the applicant's protest.

[ ] No protest accompanied the payment of additional search fees.

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INTERNATIONAL SEARCH REPORT

International Application No
PCT/US2005/016473

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			AU	2003292437 A1	22-07-2004
			WO	2004058756 A1	15-07-2004
			WO	2004058757 A1	15-07-2004

(12) SOLICITUD INTERNACIONAL PUBLICADA BAJO EL TRATADO DE COOPERACION EN MATERIA DE PATENTES (PCT)

(19)Organizacion Mundial de la Propiedad Intelectual
Oficina Internacional

(43) Fecha de publicación internacional
15 Diciembre 2005 (15.12..05)

PCT

(10) Número de publicación internacional:
WO 2005/118593 A3

(51) Clasificación de patente internacional⁷: C07D 498/04, A61K 31/519, A61P 31/18 // (C07D 498/04, 263:00), 239:00) (C07D 498/04, 265:00), 239:00) (CO7D 498/04, 267:00), 239:00)

(21) Número de solicitud internacional: PCT/US2005/016473

(22) Fecha de presentación internacional:
12 Mayo 2005 (12.05.2005)

(25) Lenguaje de presentación: Inglés

(26) Lenguaje de publicación: Inglés

(30) Datos de prioridad:

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60/603,371	20 Agosto 2004 (20.08.2004)	US
11/126,891	11 Mayo 2005 (11.05.2005)	US

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(74) Agente: **EPPERSON, James** et al.; Bristol-Myers Squibb Company, P.O. Box 4000, Princeton, NJ 08543-4000 (US)

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

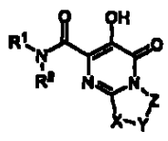
(84) Estados designados (Regional): Patente ARIPO (GH,GM,KE,LS,MW,MZ,SD,SL,SZ,TZ,UG,ZM,ZW) Patente Euroasiatica (AM,AZ,BY,KG,KZ,MD,RU,TJ,TM) Patente Europea (AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR ,IE, IT, LU, MC, NL, PT ,SE, TR) Patente OAPI (BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, ML, MR, NE, SN, TD, TG).

Declaraciones bajo la regla 4.17:
as to applicant's entitlement to apply for and be granted a patent (Rule 4.17(ii)) for the following designations AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BW, BY, BZ, CA, CH, CN, CO, CR, CU, CZ, DE, DK, DM, DZ, EC, EE, EG, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP,KE, KG, KM, KP, KR, KZ, LC,LK,LR, LS, LTLU,LV, MA, MD, MG, MK, MN, MW, MX, M4 NA, NG, NI, NO, NZ, OM, PG, PH, PL, PT, RO, RU, SC, SD, SE, SG, SK, SL, SM, SY, Ti, TM, TN, TR, TT TZ, UA, UG, UZ, VC, VN, YU, ZA, ZM, ZW, ARIPO patent (BW, GH, GM, KE, LS, MW, MZ, NA, SD, SL, SZ, T7,, UG, ZM, ZW), Eurasian patent (AM, AZ, BY, KG, KZ, MD, RU, TI, "I'M), European patent (AT, BE, BG, CH, CY, CZ, DE, DK, EE, ES, FI, FR, GB, GR, HU, IE, IS, IT, LT, LU, MC, NL, PL, PT, RO, SE, SI, SK, TR), OAPI patent (BF BJ, CF, CG, CI, CM, GA, GN, GQ, GIP, ML, MR, NE, SN, TD, TG)

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Para códigos de dos letras y otras abreviaciones. Referirse a "Guia de Notas para códigos y abreviaciones" que aparece al inicio de cada tema regular en la Gaceta PCT.

(54) Título: HETEROCICLOS BICÍCLICOS COMO INHIBIDORES DE LA INTEGRASA DEL VIRUS DE INMUNODEFICIENCIA HUMANA(VIH).



I

(57) Extracto: La invención abarca una serie de compuestos de pirimidinona cíclicos bicíclicos de Fórmula I que inhiben la integrasa del VIH y previenen la integración viral al ADN humano. Esta acción hace a los compuestos útiles para tratar infección por VIH y SIDA. La invención también abarca composiciones farmacéuticas y métodos para tratar aquellos infectados con VIH.

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HETEROCICLOS BICÍCLICOS COMO INHIBIDORES DE LA INTEGRASA DEL VIH.

ANTECEDENTES DE LA INVENCIÓN

El virus de la inmunodeficiencia humana (VIH) se ha identificado como el agente etiológico responsable del síndrome de inmunodeficiencia adquirida (SIDA), una enfermedad fatal caracterizada por la destrucción del sistema inmune, y por la incapacidad de combatir infecciones oportunistas que amenazan la vida. Las estadísticas recientes (UNAIDS: Report on the Global HIV/AIDS Epidemic, Diciembre 1998), indican que a nivel mundial están infectadas tanto como 33 millones de personas con el virus. Además del gran número de individuos que ya están infectados, el virus continua distribuyéndose. Los estimados de 1998, señalan cerca de 6 millones de nuevas infecciones solamente en ese año. En el mismo año, hubieron aproximadamente 2.5 millones de muertes asociadas con el VIH y el SIDA.

Existen actualmente varios fármacos antivirales disponibles para combatir la infección. Estos fármacos se pueden dividir en tres clases con base en la proteína viral que atacan y su modo de acción. En particular, saquinavir, indinavir, ritonavir, nelfinavir y amprenavir son inhibidores competitivos de la aspartil proteasa expresada por el VIH. La zidovudina, didanosina, estavudina, lamivudina, zalcitavina y abacavir, son inhibidores nucleósidos de la transcriptasa

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inversa, que se comportan como miméticos del substrato para detener la síntesis viral del ADNc. Los inhibidores de la transcriptasa inversa no nucleósidos, nevaripina, delavirdina, y efavirenz inhiben la síntesis del ADNc viral por medio de un mecanismo no competitivo (o incompetitivo). Al usarse solos, estos fármacos son efectivos en la reducción de la replicación viral. El efecto es solamente temporal, ya que el virus se desarrolla fácilmente con resistencia para todos los agentes conocidos. Sin embargo, la terapia de combinación ha demostrado ser muy efectiva en la reducción del virus y en suprimir la aparición de la resistencia en diversos pacientes. En los Estados Unidos, en donde está ampliamente disponible la terapia de combinación, ha declinado el número de muertes relacionadas por VIH (Palella, F. J.; Delany, K. M.; Moorman, A. C.; Loveless, M.O.; Furher, J.; Satten, G. A.; Aschman, D. J.; Holmberg, S. D. N. Engl. J. Med. 1998, 338, 860).

Desafortunadamente, no todos los pacientes tienen respuesta y un gran número falla con esta terapia. De hecho, aproximadamente 30-50% de los pacientes, fallan finalmente a la terapia de combinación. La falla en el tratamiento de la mayoría de los casos, se provoca por la aparición de la resistencia viral. La resistencia viral a su vez, se provoca por un rápido retorno del VIH-1 durante el curso de la infección, combinado con una alta tasa de mutación viral.

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Bajo estas circunstancias, la supresión viral incompleta provocada por una potencia insuficiente del fármaco, un pobre apego a un régimen complicado de fármacos, así como barreras farmacológicas intrínsecas a la exposición, proporcionan un terreno fértil para que aparezca la resistencia. Son más perturbadores los recientes hallazgos que sugieren que continúa una replicación de bajo nivel aún cuando los niveles de plasma virales han caído debajo de los niveles detectables (< 50 copias/ml) (Carpenter, C. C. J.; Cooper, D. A.; Fischl, M. A.; Gatell, J. M.; Gazzard, B. G.; Hammer, S. M.; Hirsch, M. S.; Jacobsen, D. M.; Katzenstein, D. A.; Montaner, J. S. G.; Richman, D. D.; Saag, M. S.; Schechter, M.; Schooley, R. T.; Thompson, M. A.; Vella, S.; Yeni, P. G.; Volberding, P. A. JAMA 2000, 283, 381-390). Existe claramente una necesidad de nuevos agentes antivirales, preferiblemente que ataquen a otras enzimas virales para reducir la tasa de resistencia y suprimir la replicación viral aún adicionalmente.

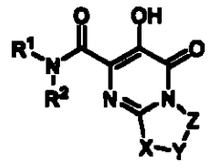
El VIH expresa tres enzimas, la transcriptasa inversa, la aspartil proteasa y la integrasa. Las tres son objetivos para el tratamiento del SIDA e infección por VIH. La integrasa del VIH cataliza la inserción del ADNc viral al genoma de la célula hospedadora, lo que es una etapa crítica en el ciclo de vida viral. Los inhibidores de integrasa del VIH pertenecen a la clase de compuestos de ácido diceto que previenen la integración viral e inhiben la replicación del

VIH-1 en células (Hazuda et al. Science 2000, 287, 646). Y recientemente, los inhibidores de la integrasa del VIH se han aceptado en ensayos clínicos para el tratamiento del SIDA e infección por VIH (Neamati, Expert. Opin. Ther. Patents 2002, 12, 709, Pais and Burke Drugs Fut. 2002, 27, 1101).

BREVE DESCRIPCIÓN DE LA INVENCIÓN

Esta invención comprende compuestos de la fórmula I, incluye sales y solvatos farmacéuticamente aceptable, sus composiciones farmacéuticas, y su uso en inhibición de integrasa de VIH y tratar aquellos infectados con VIH o SIDA.

Un aspecto de la invención son compuestos de la Fórmula I.



I

en donde:

R^1 es $C_{1-6}(Ar^1)$alquilo, $C_{1-6}(Ar^1)(CON(R^8)(R^9))$alquilo, $C_{1-6}Ar^1)(CO_2R^{14})$alquilo, $C_{1-6}(Ar^1)$hidroxialquilo, o $C_{1-6}(Ar^1)$oxialquilo;

R^2 es hidrógeno, C_{1-6}alquilo, o OR^{14};

R^3 es hidrógeno, halo, hidroxi, ciano, C_{1-6}alquilo, C_{3-7}cicloalquilo, C_{5-7}cicloalquenilo, C_{1-6}haloalquilo, C_{1-6}alcoxi, C_{1-6}alquiltio, C_{1-6}haloalcoxi, $N(R^8)(R^9)$, $NHAr^2$, $N(R^6)SO_2R^7$, $N(R^6)COR^7$, $N(R^6)CO_2R^7$, $OCOR^7$, OCO_2R^7, $OCON(R^8)(R^9)$, $OCH_2CO_2R^7$, $OCH_2CON(R^8)(R^9)$, COR^6, CO_2R^6, $CON(R^8)(R^9)$, SOR^7, $S(=N)R^7$, SO_2R^7,

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$SO_2N(R^6)(R^6)$, $PO(OR^6)$, $C_{2-4}(R^{12})$alquinilo, R^{13}, Ar^2, o Ar^3;

R^4 es hidrógeno, halo, hidroxi, ciano, C_{1-6}alquilo, C_{1-6}alcoxi, C_{1-6}haloalquilo, C_{1-6}haloalcoxi, o $N(R^6)(R^6)$;

R^5 es hidrógeno, halo, hidroxi, ciano, C_{1-6}alquilo, C_{1-6}alcoxi, C_{1-6}haloalquilo, C_{1-6}haloalcoxi, o $N(R^6)(R^6)$;

R^6 es hidrógeno, C_{1-6}alquilo, o C_{3-7}cicloalquilo;

R^7 es C_{1-6}alquilo o C_{3-7}cicloalquilo;

R^8 es hidrógeno, C_{1-6}alquilo, C_{1-6}hidroxialquilo, $C_{1-6}(C_{1-6}$alcoxi)alquilo o $C_{1-6}(C_{1-6}$dialquilamino)alquilo;

R^9 es hidrógeno, C_{1-6}alquilo, C_{1-6}hidroxialquilo, $C_{1-6}(C_{1-6}$alcoxi)alquilo o $C_{1-6}(C_{1-6}$dialquilamino)alquilo; o $N(R^8)(R^9)$ tomados juntos son azetidinilo, pirrolidinilo, (R^{10})-piperidinilo, N-(R^{11})-piperazinilo, morfolinilo, tiomorfolinilo, o dioxotiazinilo;

R^{10} es hidrógeno, C_{1-6}alquilo, o C_{1-5}hidroxialquilo;

R^{11} es hidrógeno, C_{1-6}alquilo, C_{3-7}cicloalquilo, COR^6, o CO_2R^6;

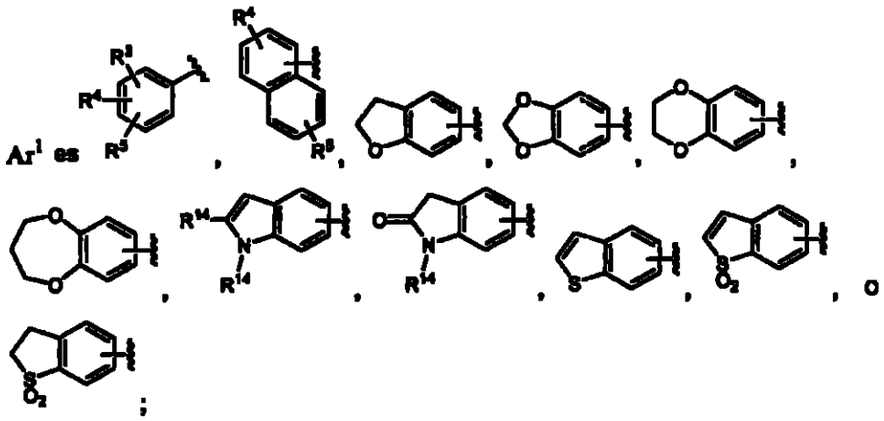
R^{12} es hidrógeno, hidroxi, $N(R^6)(R^6)$, SO_2R^7, OSO_2R^7, o dioxotiazinilo;

R^{13} es azetidinonilo, pirrolidinonilo, valerolactamilo, caprolactamilo, maleimido, oxazolidonilo, o dioxotiazinilo, y es substituido con 0-1 substituyentes seleccionado del grupo que consiste de hidroximetilo, acetoximetilo, y

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aminometilo;

R^{14} es hidrógeno o C_{1-6}alquilo;

Ar^1 es  ;

A^{r2} es tetrazolilo, triazolilo, oxadiazolilo, tiadiazolilo, pirazolilo, imidazolilo, oxazolilo, tiazolilo, isoxazolilo, isotiazolilo, furanilo, tienilo, pirrolilo, pirimidinilo, pirazinilo, piridinilo, hidroxipiridinilo, quinolinilo, isoquinolinilo, o indolilo, y es substituido con 0-2 substituyentes seleccionados del grupo que consiste de halo, ciano, bencilo, C_{1-6}alquilo, C_{1-6}alcoxi, $N(R^8)(R^9)$, $CON(R^8)(R^9)$, CO_2R^6, $CONHSO_2N(R^6)(R^6)$, $CONHSO_2N(R^6)$(fenilo), y $CONHSO_2N(R^6)$(halofenilo);

Ar^3 es fenilo substituido con 0-2 substituyentes seleccionados del grupo que consiste de halo, ciano, hidroxi, C_{1-6}alquilo, C_{1-6}alcoxi, (C_{1-6}alcoxi)metilo, C_{1-6}haloalquilo, C_{1-6}haloalcoxi, $N(R^8)(R^9)$, $CON(R^6)(R^6)$, y $CH_2N(R^8)(R^9)$, o es dioxolanilfenilo; y

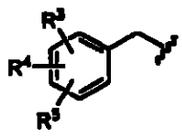
X-Y-Z es $C(R^{14})_2OC(R^{14})_2$, $C(R^{14})OC(R^{14})_2C(R^{14})_2$, o

$C(R^{14})_2OC(R^{14})_2C(R^{14})_2C(R^{14})_2$;

o un sal o solvato farmacéuticamente aceptable del mismo.

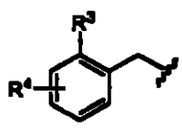
Otro aspecto de la invención es un compuesto de la fórmula I donde R^1 es $C_{1-6}(Ar^1)$alquilo.

Otro aspecto de la invención es un compuesto de la Fórmula I donde R^1 es



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Otro aspecto de la invención es un compuesto de la Fórmula I donde R^1 es



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Otro aspecto de la presente invención es un compuesto de la Fórmula I donde R^2 es hidrógeno.

Otro aspecto de la invención es un compuesto de la Fórmula I donde R^3 es hidrógeno, halo, $N(R^8)(R^9)$, $N(R^6)COR^7$, $OCON(R^8)(R^9)$, $CON(R^8)(R^9)$, SOR^7, SO_2R^7, $SO_2N(R^6)(R^6)$, $PO(OR^6)_2$, R^{13}, o Ar^2.

Otro aspecto de la invención es un compuesto de la Fórmula I donde X-Y-Z es $C(R^{14})_2OCH_2$, $C(R^{14})_2OCH_2CH_2$, o $C(R^{14})_2OCH_2CH_2CH_2$.

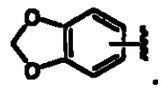
Otro aspecto de la invención es un compuesto de la Fórmula I donde X-Y-Z es CH_2OCH_2, $C(CH_3)HOCH_2$, $C(CH_3)_2OCH_2$,

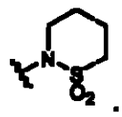
$CH_2OCH_2CH_2$, $C(CH_3)HOCH_2CH_2$, $C(CH_3)_2OCH_2CH_2$, $CH_2OCH_2CH_2CH_2$, $C(CH_3)HOCH_2CH_2CH_2$, o $C(CH_3)_2OCH_2CH_2CH_2$.

Para un compuesto de la Fórmula I, cualquier campo de acción de R^1, R^2, R^3, R^4, R^5, R^6, R^7, R^8, R^9, R^{10}, R^{11}, R^{12}, R^{13}, R^{14}, Ar^1, Ar^2, Ar^3, y X-Y-Z puede usarse independientemente con cualquier campo de acción de cualquier otro substituyente.

"Alquilo," "alcoxi," "hidroxialquilo," y términos relacionados con una porción alquilo incluyen configuraciones rectas o ramificadas. Un término tal como "C_{1-6}(R)alquilo" significa un grupo alquilo recto o ramificado de uno hasta seis carbonos substituidos con el substituyente R. "Haloalquilo" y "halofenilo" incluye todas las permutaciones de grupos alquilo o fenilo halogenados, de monohalo o perhalo. "Arilo" significa un sistema de anillo aromático e incluye sistemas carbocíclico y heterocíclico. Los substituyentes son divalentes, tal como X-Y-Z. Los substituyentes asimétricos divalentes pueden unirse en cualesquiera de las dos configuraciones.

"C_{1-6}(Ar^1)oxialquilo" significa Ar^1 es unido al oxígeno.

"Dioxolanifenilo" significa  .

"Dioxotiazinilo" significa  .

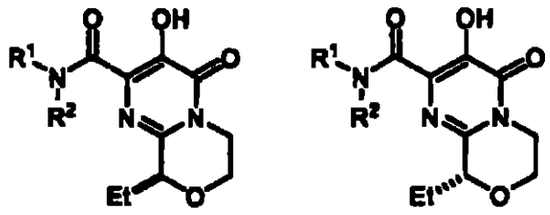
La invención incluye todas las formas de sal

farmacéuticamente aceptables de los compuestos. Las sales farmacéuticamente aceptables son aquellas en las cuales los contraiones no contribuyen significativamente a la actividad o toxicidad fisiológica de los compuestos, y como tales funcionan como equivalentes farmacológicos. Estas sales pueden hacerse de conformidad con técnicas orgánicas comunes que emplean reactivos comercialmente disponibles. Algunas formas de sal aniónicas incluyen acetato, acistrato, besilato, bromuro, cloruro, citrato, fumarato, glucouronato, bromohidrato, clorohidrato, yodohidrato, yoduro, lactato, maleato, mesilato, nitrato, pamoato, fosfato, succinato, sulfato, tartrato, tosilato, y xinofoato. Algunas formas de sal catiónica incluyen amonio, aluminio, benzatina, bismuto, calcio, colina, dietilamina, dietanolamina, litio, magnesio, meglumina, 4-fenilciclohexilamina, piperazina, potasio, sodio, trometamina y zinc.

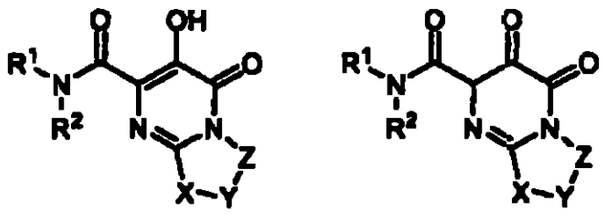
La invención también incluye todas las formas solvatadas de los compuestos, particularmente hidratos. Los solvatos no contribuyen significativamente a la actividad o toxicidad fisiológica de los compuestos, y como tales funcionan como equivalentes farmacológicos. Los solvatos pueden formarse en cantidades estequiométricas o pueden formarse de un solvente accidental o una combinación de ambos. Un tipo de solvato es el hidrato, y algunas formas hidratadas incluyen monohidrato, hemihidrato, y dihidrato.

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Algunos de los compuestos de la invención existen en formas estereoisoméricas. La invención incluye todas las formas estereoisoméricas de los compuestos incluyendo enantiómeros y diastereómeros. Un ejemplo de enantiómeros se muestra abajo. Los métodos para hacer y separar estereoisómeros se conocen en el arte.



La invención incluye todas las formas tautoméricas de los compuestos. Un ejemplo de un par tautómerico se muestra abajo.



Métodos Sintéticos

Los compuestos de esta invención pueden hacerse por varios métodos conocidos en el arte incluyendo aquellos de los siguientes esquemas de reacción en la sección de modalidades especificas. Las variables mostradas en los esquemas sintéticos son distintas de estas y no deberán confundirse con las variables en las reivindicaciones o el

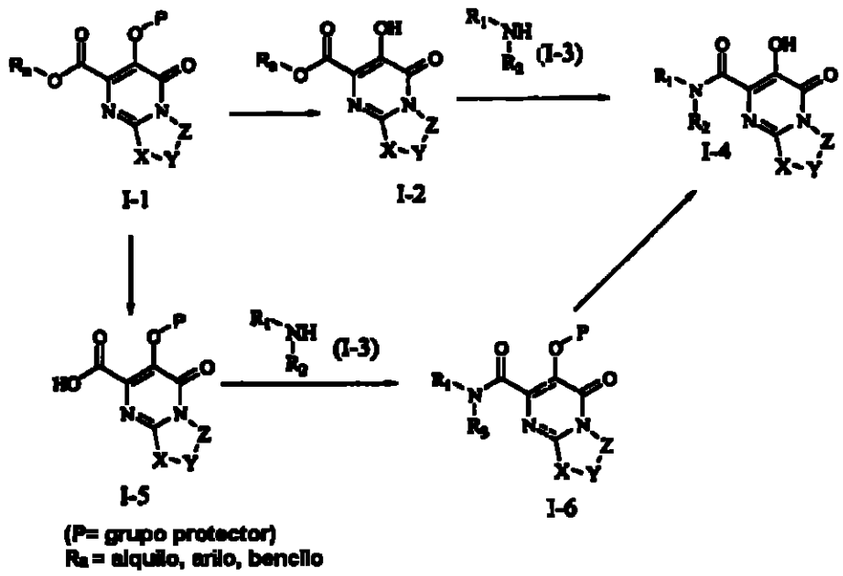
resto de la especificación. Las variables en los esquemas son un medio únicamente para ilustrar como hacer algunos de los compuestos de esta invención.

Algunos compuestos pueden sintetizarse de un heterociclo I-1 apropiadamente substituido de conformidad con el esquema de reacción 1, donde R_a y P pueden servir como grupos protectores (ver Greene, T. W. y Wutz, P. G. M. Protective Groups in Organic Synthesis, Segunda Edición, 1991, John Wiley and Sons, New York). Cuando P es bencilo o bencilo substituido, puede removerse por hidrogenólisis (H_2-Pd/C) o hidrólisis ácida (ácido trifluoroacético) para proporcionar el intermediario I-2. El I-2 puede transaminarse a I-4 por la reacción con la amina I-3. En un número de casos, esta reacción puede llevarse a cabo al calentar I-3 y I-2 en conjunto en presencia de una base. Alternativamente, los reactivos de acoplamiento amida estándar pueden usarse para efectuar la formación de un enlace amida. Cuando R_a es un grupo alquilo inferior, R_a puede removerse bajo condiciones de hidrólisis éster, tales como tratamiento con NaOH, LiOH, o KOH para entregar el correspondiente ácido carboxílico I-5. Alternativamente, R_a puede removerse por el desplazamiento nucleofílico usando NaI. Cuando R_a es bencilo y bencilo substituido, R_a puede removerse por hidrogenólisis. El intermediario I-5 puede acoplarse usando reactivos formadores de enlace de amida tales como BOP, DCC, EDCI, PyBrop, PyBop u

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otros reactivos (ver March, J. Advanced Organic Chemistry, Fourth Edition 1992 John Wiley & Sons, New York). El intermediario resultante I-6 puede desprotegerse como se describe por el intermediario I-1.

Esquema de reacción I

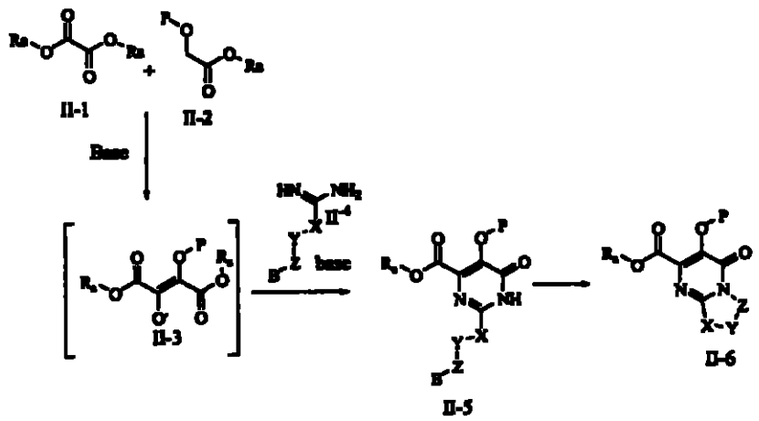


En el esquema de reacción II, el intermediario II-3 puede prepararse usando métodos similares a aquellos descritos en Sunderland, J. S.: Botta, M.; Aime, S.; Raymond, K. N. Inorg. Chem (2001), 40, 6756-6756, donde II-1 y II-2 se condensan, para proporcionar el intermediario II-3. Esta reacción se conduce usualmente un presencia de una base tal como hidruro de sodio (NaH), etóxido de sodio (EtONa) o hexametildisilazida de litio (LiHMDS). Usando los métodos descritos en la referencia, II-3 puede condensarse con una amidina apropiadamente substituida II-4 para formar II-5. El

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substituyente B puede ser un grupo de partida, tal como -halo (Cl, Br o I) o puede convertirse a un grupo de partida bajo condiciones apropiadas tales como al formar el correspondiente éster de metilsulfonato. Cuando el substituyente B es un grupo de metil sulfuro, puede tratarse con yodometano para formar el intermediario de dimetilsulfonio que se activa hacia el ataque nucleofílico para efectuar el cerrado del anillo.

Esquema de reacción II

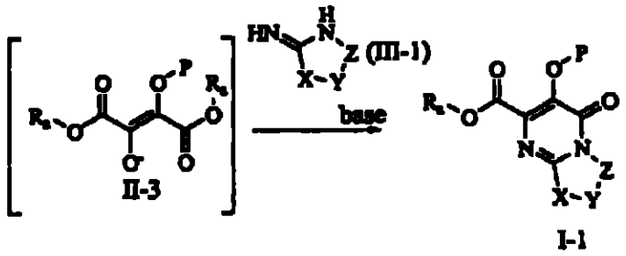


En el esquema de reacción III, el intermediario II-3 puede condensarse con una amidina cíclica para proporcionar el intermediario I-1.

El intermediario III-1 puede prepararse usando métodos conocidos (ver Patai, S. and Rappoport, Z. The Chemistry of Amidines and Imidates, Volumen 2, 1991, John Wiley & Sons, New York).

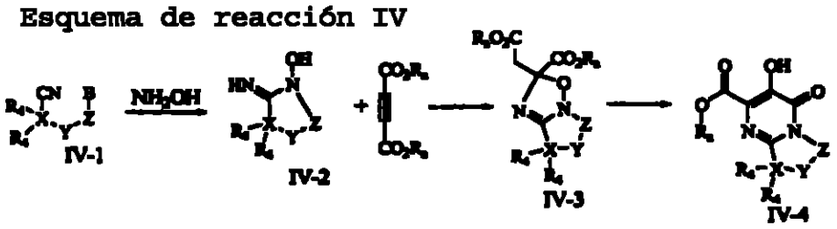
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Esquema de reacción III



En el esquema de reacción IV, el nitrilo IV-1 que posee un grupo de partida potencial B, puede hacerse reaccionar con hidroxilamina para formar el intermediario IV-2. Este intermediario puede hacerse reaccionar con un alquino apropiadamente protegido para formar IV-3 que puede reconfigurarse para formar el intermediario IV-4 de conformidad con métodos de la literatura (Culbertson, T. P. Journal of Heterocyclic chemistry, 1979, 16, 1423-1424).

Esquema de reacción IV

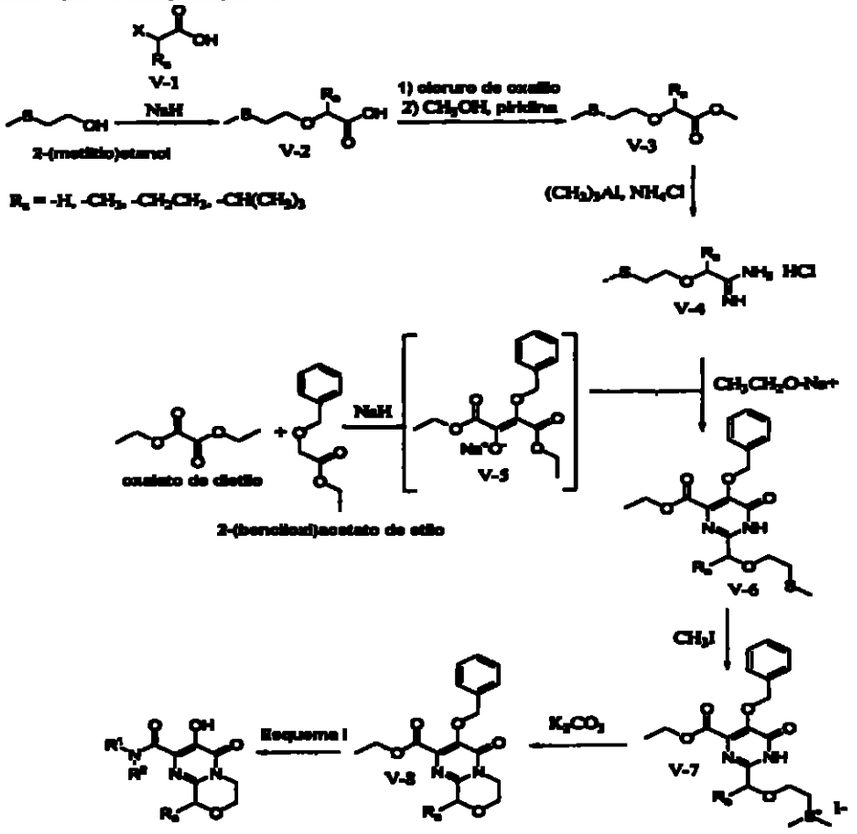


Como se muestra en el esquema de reacción V, el 2-(metiltio)etanol puede alquilarse con un ácido α-haloacético apropiado (V-1) en donde X es un grupo de partida tal como Cl, Br, OTs, OMs o OTf, para entregar el intermediario V-2. Después de esto, el ácido carboxílico puede transformarse al correspondiente derivado de amidina usando métodos sintéticos

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conocidos (Geilen et al. Tetrahedron Letters 2002, 43, 419-421). Como se describe arriba, la amidina puede hacerse reaccionar además con el intermediario V-5 en presencia de una base (por ejemplo, etóxido de sodio) proporcionando el intermediario V-6. La metilación del éter de sulfuro puede lograrse al tratar V-6 con yodometano y el derivado de sulfonio resultante (V-7) tratado con base para formar la plantilla bicíclica V-8. Este intermediario puede usarse en la síntesis de los compuestos finales usando los métodos descritos en el esquema de reacción I.

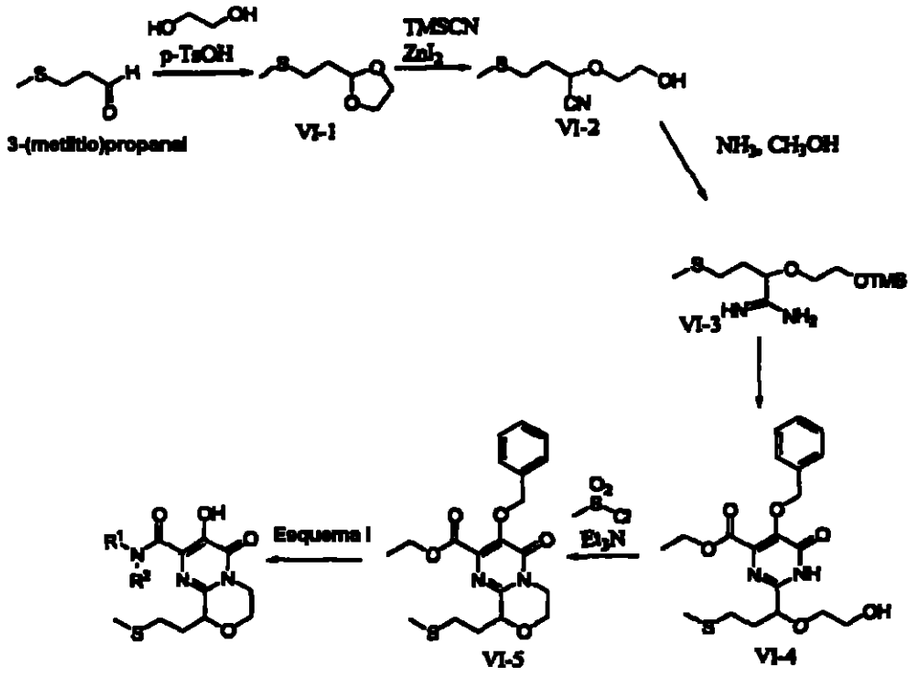
Esquema de reacción V



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En el esquema de reacción VI, 3-metiltiopropanal se convierte al dioxolano VI-1 usando la química bien conocida. El tratamiento con trimetilsililcianuro (TMSCN), en presencia de yoduro de zinc (ZnI_2) produce el intermediario VI-2. La reacción con amoniaco proporciona la amidina VI-3 que se usa en la síntesis de pirimidinona VI-4 de conformidad con los métodos descritos en los esquemas de reacción previos. El tratamiento posterior con CH_3SO_2Cl y trietilamina (Et_3N) resulta en el correspondiente intermediario bicíclico VI-5. Para completar la síntesis puede llevarse a cabo como se ilustra en el esquema de reacción I.

Esquema de reacción VI

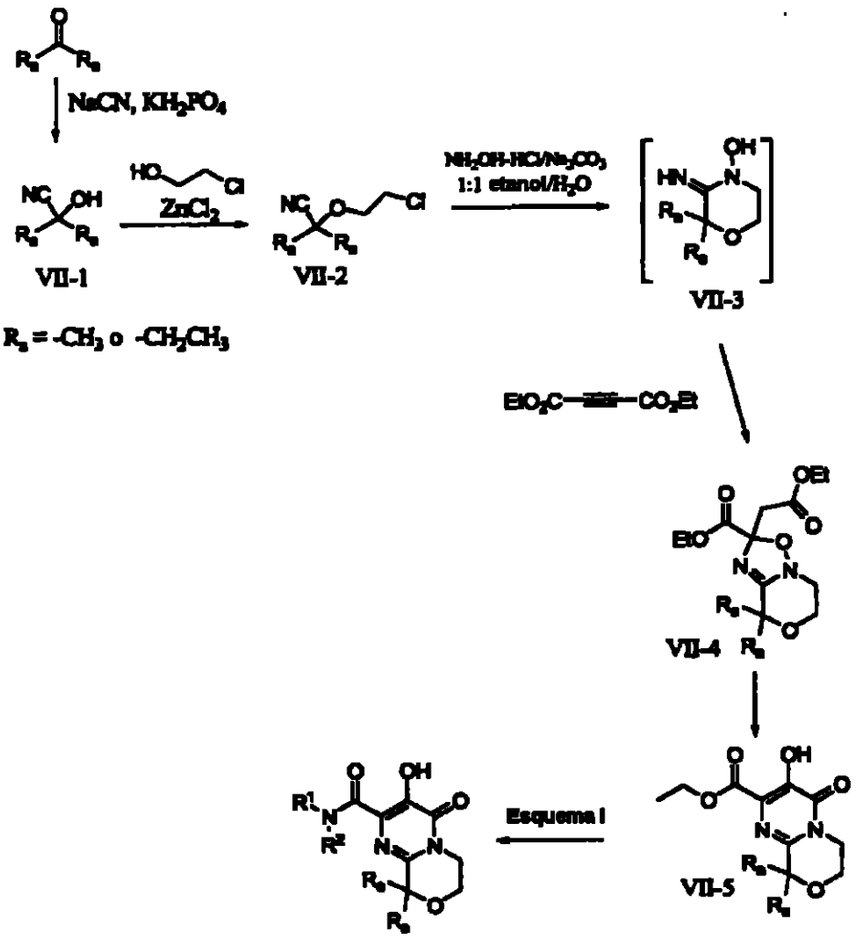


Otro método se ilustra en el esquema de reacción VII. Esta vía

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sintética inicia con una cetona apropiadamente substituida que puede transformarse al correspondiente nitrilo intermediario VII-1. De nuevo puede hacerse reaccionar con 2-cloroetano para producir el compuesto VII-2, que puede hacerse reaccionar con hidroxilamina y un éster de acetilen dicarboxilato para proporcionar el intermediario VII-4. Al calentar el intermediario puede proporcionarse el intermediario VII-5. La síntesis de los correspondientes derivados amida puede realizarse de conformidad con el esquema de reacción I.

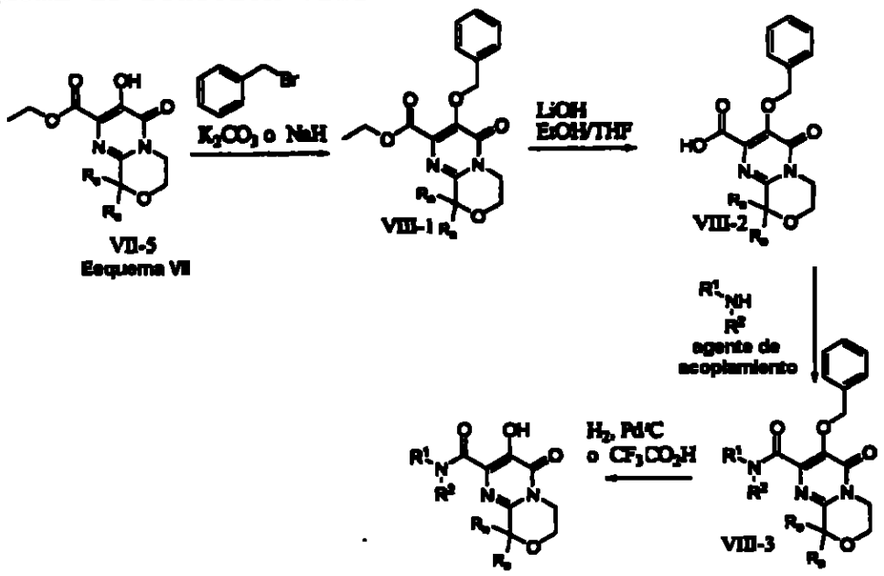
Esquema de reacción VII



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En el esquema de reacción VIII, la bencilación del grupo hidroxilo de VII-5, como un medio de protección del grupo funcional, puede realizarse usando bromuro de bencilo bajo condiciones básicas (por ejemplo, K_2CO_3 o NaH). La saponificación del grupo éster de VIII-1 puede proporcionar VIII-2 que puede acoplarse con aminas apropiadamente substituidas (R^1R^2NH) usando reactivos de formación de enlace amida bien conocidos, tales como hexafluorofosfato de benzotriazol-1-iloxi-tris-pirrolidino-fosfonio (PyBOP) o hexafluorofosfato de O-(7-azabenzotriazol-1-il)-N,N,N',N'-tetrametiluronio (HATU). Alternativamente, el cloruro ácido correspondiente puede formarse, por el tratamiento con cloruro de oxalilo, y hacer reaccionar con una amina apropiada para formar el enlace amida. La remoción del grupo bencilo puede realizarse bajo una variedad de condiciones que incluyen el tratamiento con CF_3CO_2H o H_2 (Pd-C).

Esquema de reacción VIII



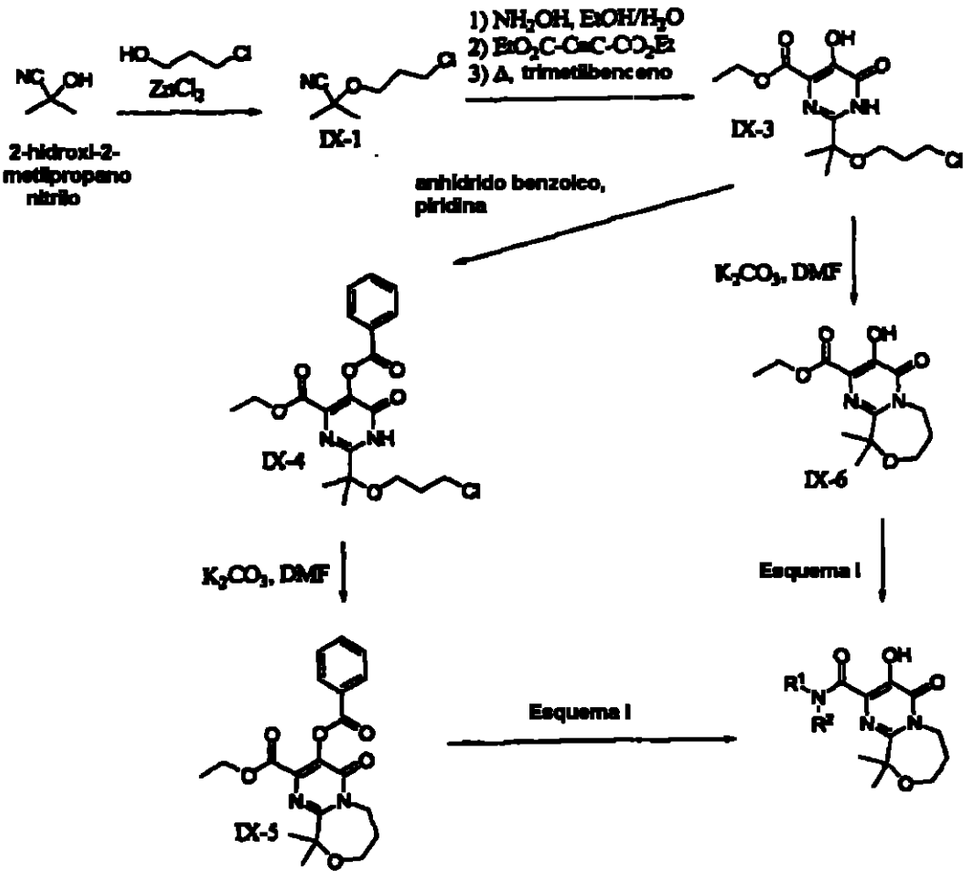
Aún en otro método, algunos de los compuestos de esta

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invención pueden sintetizarse de conformidad con el esquema IX. En el esquema de reacción IX, la pirimidinona IX-3, puede producirse usando métodos similares a aquellos descritos en los esquemas de reacción previos. Este intermediario puede portarse al producto final de conformidad con una variedad de trayectorias. En una, el grupo hidroxilo puede benzoilarse para proporcionar el intermediario IX-4 que puede tratarse además con K_2CO_3 para efectuar el cerrado del anillo para formar la plantilla bicíclica IX-5. Alternativamente, el tratamiento directo de IX-3 con K_2CO_3 puede proporcionar el intermediario IX-6. Los intermediarios IX-5, un IX-6 puede usarse en la síntesis de los productos finales usando los métodos descritos en el esquema de reacción I.

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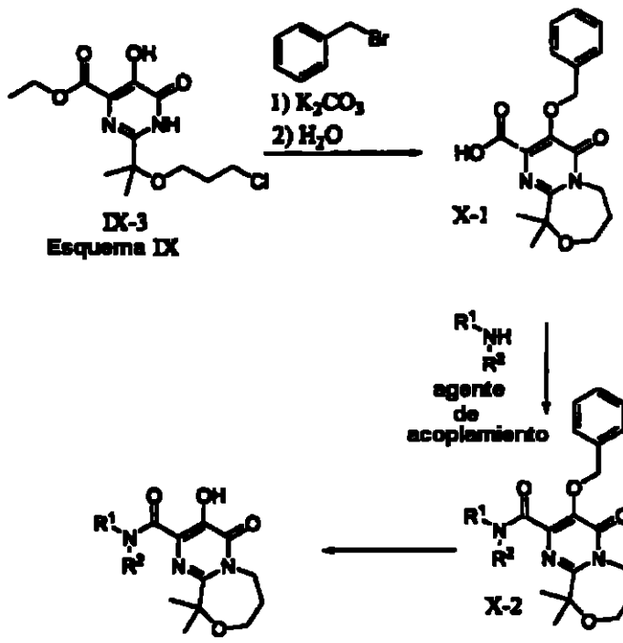
Esquema de reacción IX



En el esquema de reacción X, IX-3 puede usarse para sintetizar el intermediario X-1 bencilado. Este intermediario puede llevarse al producto final usando métodos análogos a aquellos descritos en el esquema de reacción VIII.

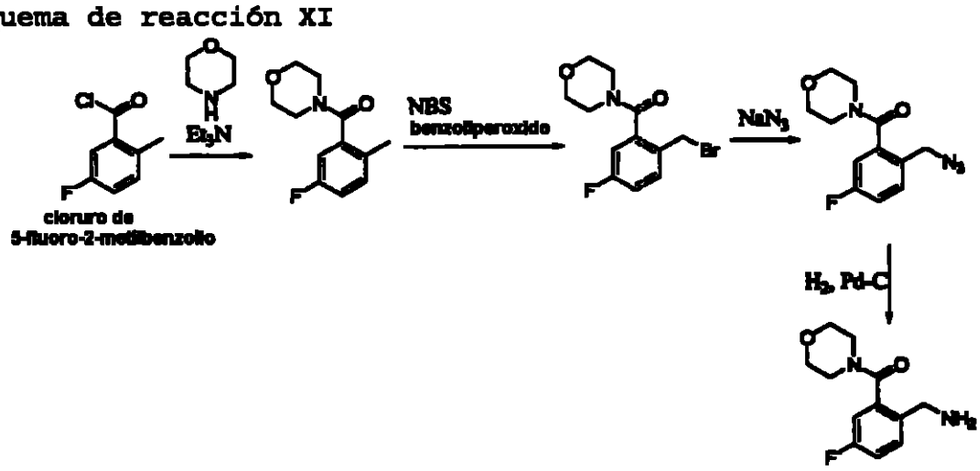
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Esquema de reacción X



La síntesis de clorohidrato de (2-(aminometil)-5-fluorofenil)(morfolino)metanona se ilustra en el esquema de reacción XI.

Esquema de reacción XI

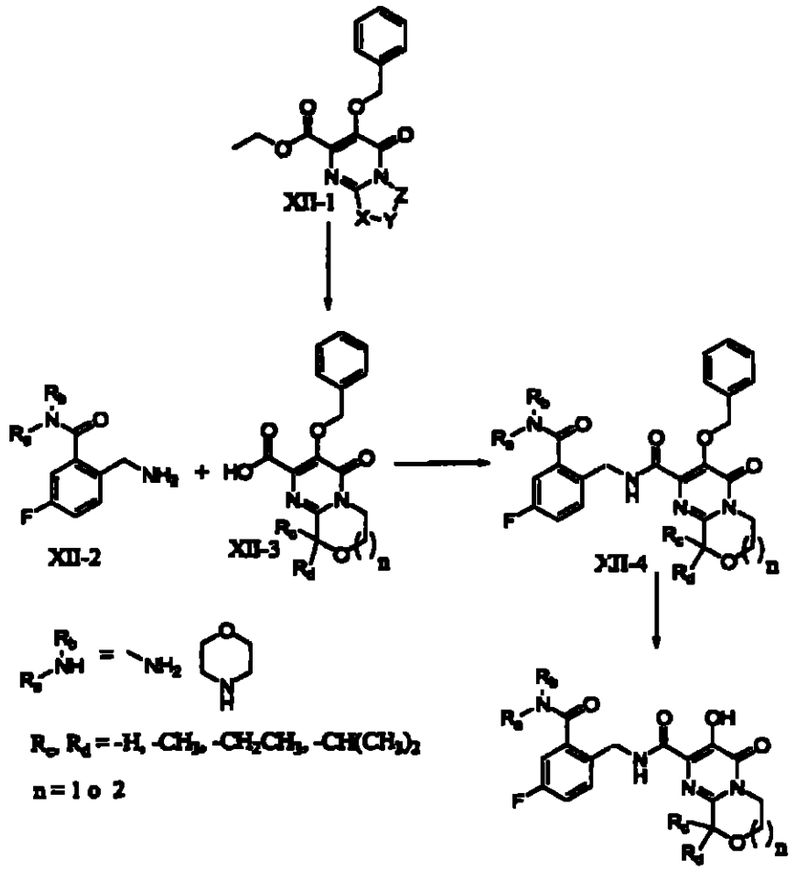


En el esquema de reacción XII, el intermediario bicíclico XII-1, preparado de conformidad con los métodos descritos arriba,

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puede saponificarse usando métodos bien conocidos. El ácido carboxílico resultante, XII-3 puede entonces acoplarse a la amina XII-2 usando reactivos y métodos formadores de enlace amida estándar. La remoción del grupo bencilo, por hidrogenólisis o hidrólisis mediada por ácido proporciona los productos finales.

Esquema de reacción XII

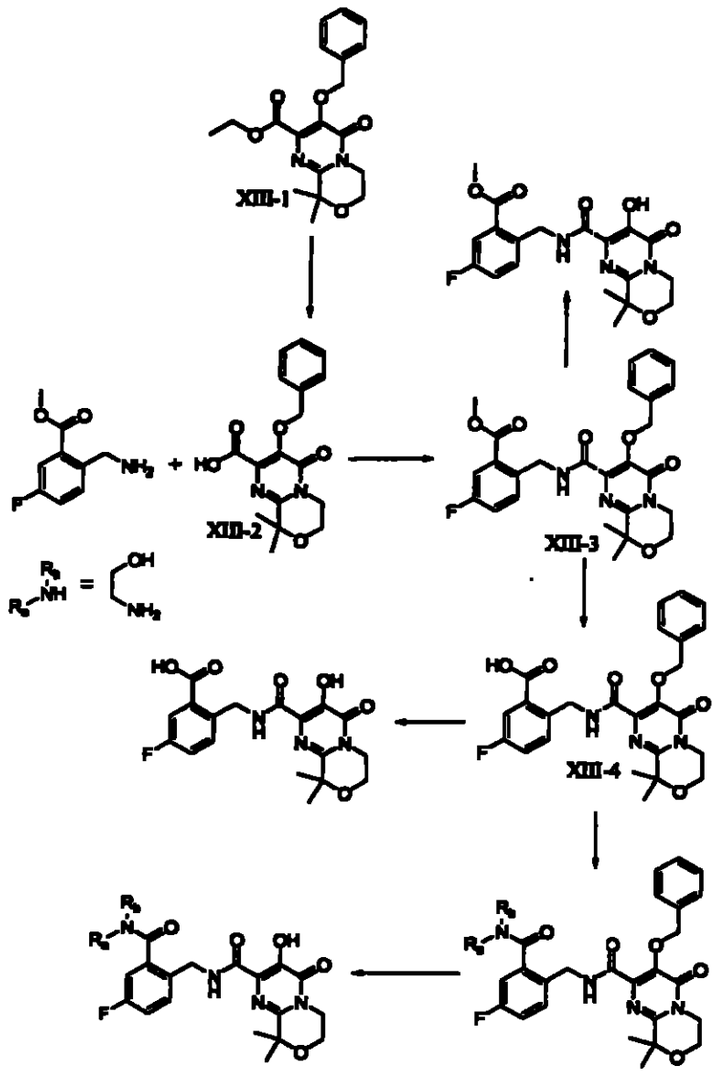


Una ruta alternativa a los compuestos similares presentados a aquellos presentados en el esquema de reacción XII, se da en el esquema XIII. En este esquema de reacción, el grupo éster de XIII-1 puede hidrolizarse y el ácido carboxílico resultante

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acoplarse a 2-(aminometil)-5-fluorobenzoato de metilo. Una segunda reacción de hidrólisis puede producir XIII-4 que puede acoplarse con una segunda amina. Esto se sigue por la remoción del grupo bencilo para proporcionar los productos finales.

Esquema de reacción XIII

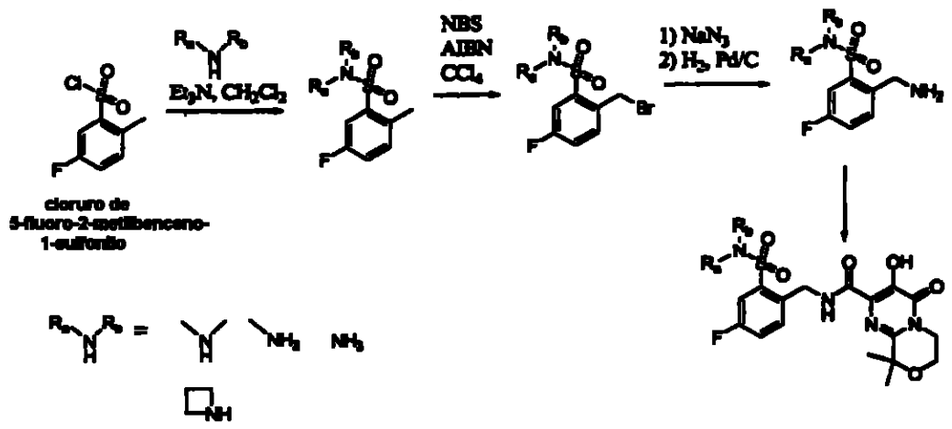


Aún en otro método, el esquema de reacción XIV ilustra la síntesis de los ejemplos que contienen sulfonamida,

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partiendo del cloruro de 5-fluoro-2-metilbenzen-1-sulfonilo.

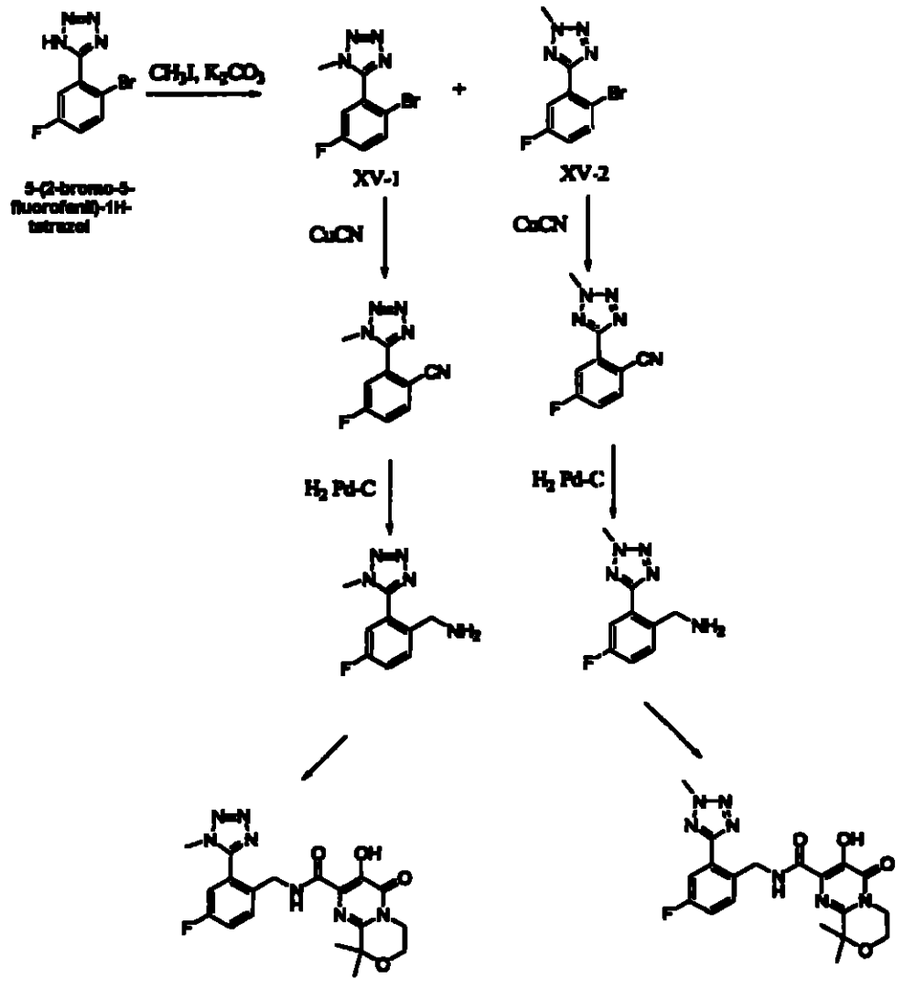
Esquema de reacción XIV



La ilustración adicional de los métodos usados para la síntesis de ciertos compuestos de la invención se muestra en el esquema de reacción XV. La metilación de 5-(2-bromo-5-fluorofenil)-1H-tetrazol puede proporcionar una mezcla de XV-1 y XV-2 que puede separarse y cada uno de los compuestos llevarse a los productos finales correspondientes.

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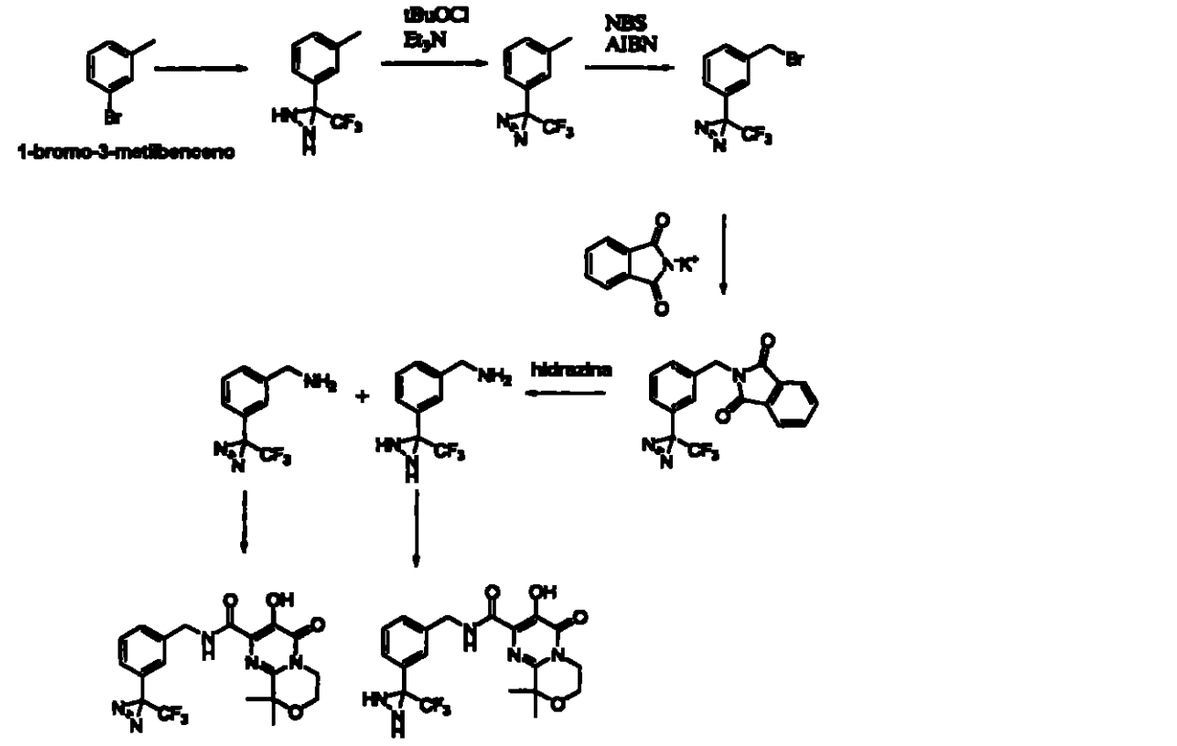
Esquema de reacción XV



Algunos análogos de diazarina y diaziradina puede sintetizarse de conformidad con el esquema de reacción XVI.

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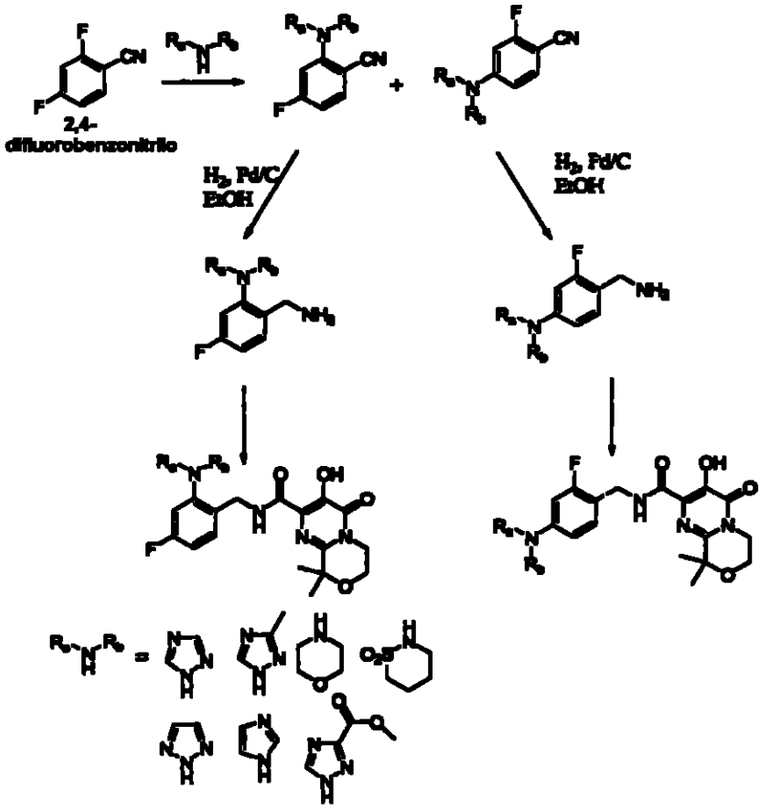
Esquema de reacción XVI



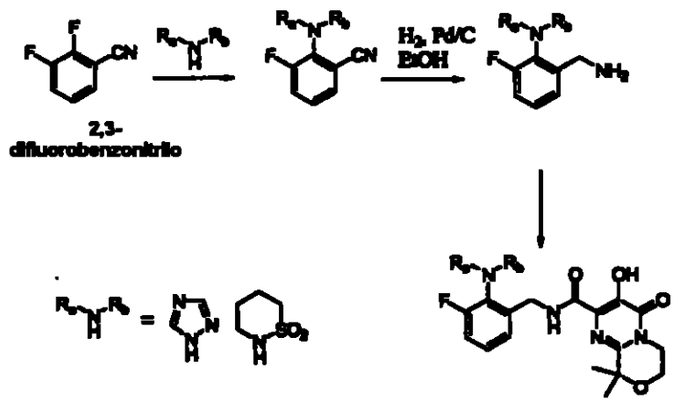
Algunos ejemplos de la invención pueden sintetizarse de conformidad con los métodos ilustrados en los esquemas de reacción XVII-XX.

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Esquema de reacción XVII

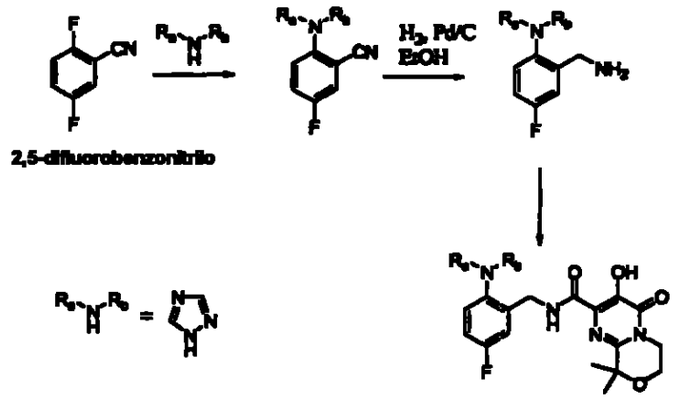


Esquema de reacción XVIII

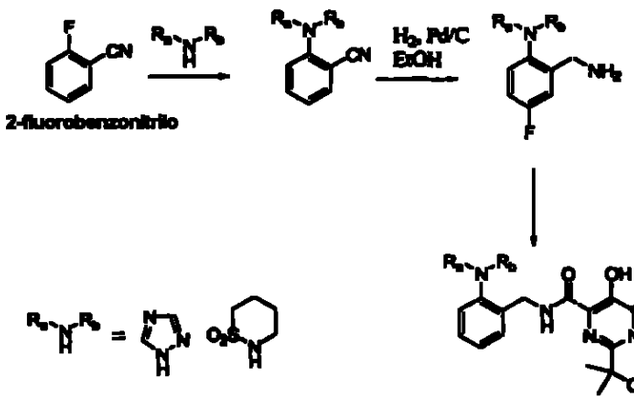


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Esquema de reacción XIX



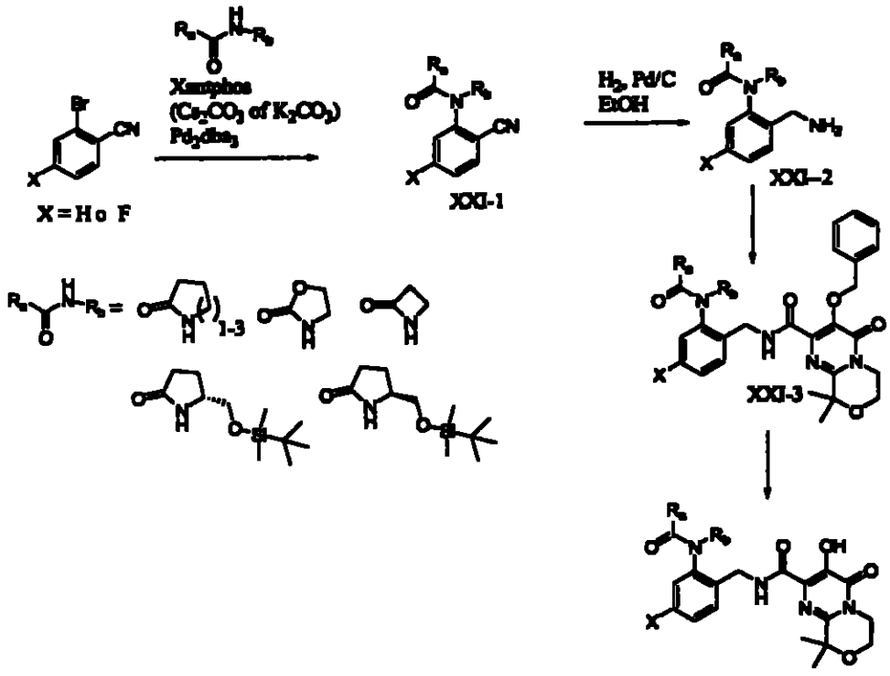
Esquema de reacción XX



En el esquema de reacción XXI, el 2-bromo-benzonitrilo o 2-bromo-4-fluoro-benzonitrilo puede acoplarse con una amida apropiada para proporcionar XXI-1. La reducción del grupo nitrilo proporciona XXI-2 que puede usarse en la síntesis del producto final de conformidad con los métodos descritos en los esquemas de reacción previos. En la mayoría de los casos, el compuesto XXI-1 no necesita aislarse pero puede llevarse directamente en la reacción de acoplamiento para formar XXI-3.

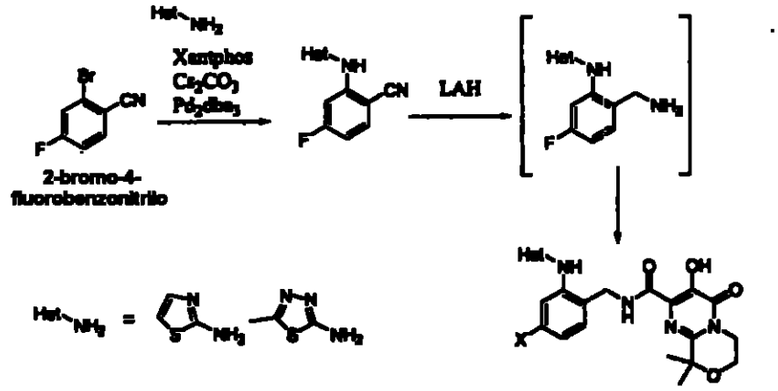
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Esquema de reacción XXI



Los ejemplos y métodos mostrados en el esquema de reacción XXII son similares a aquellos descritos en el esquema de reacción XXI.

Esquema de reacción XXII

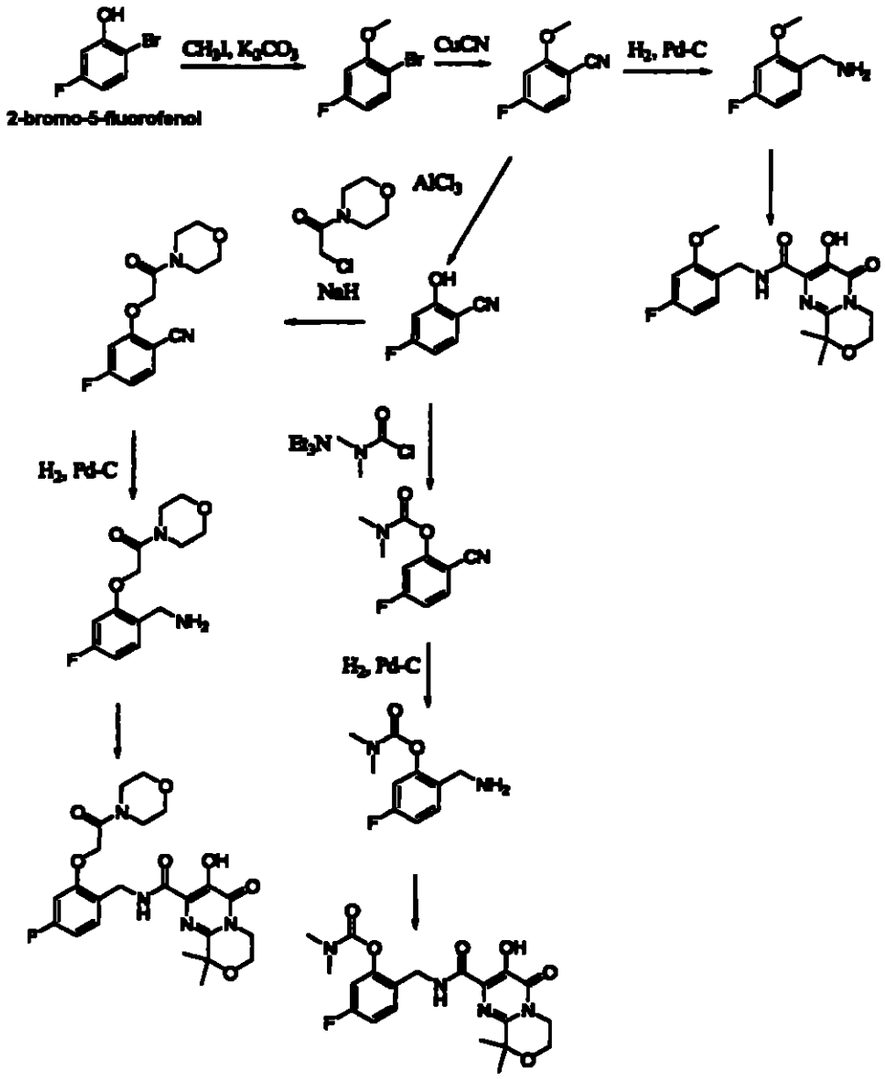


Los esquemas de reacción XXIV y XXV ilustran además

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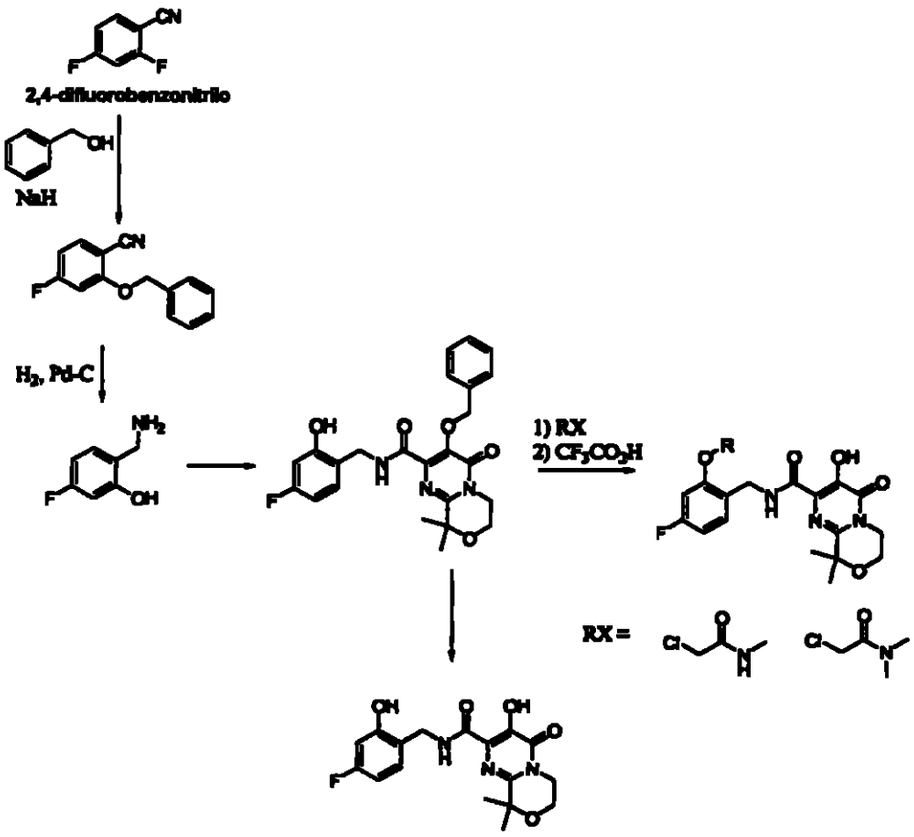
métodos útiles para la síntesis de algunos compuestos de la invención.

Esquema de reacción XXIV



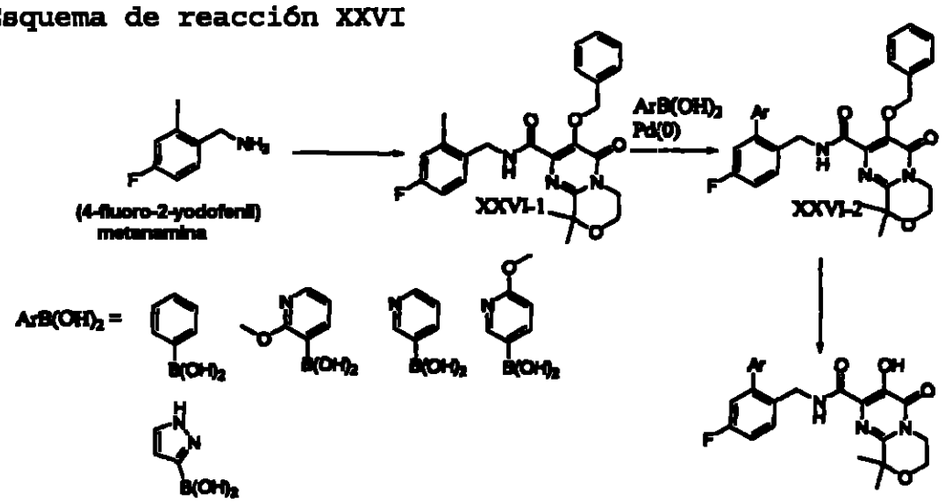
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Esquema de reacción XXV



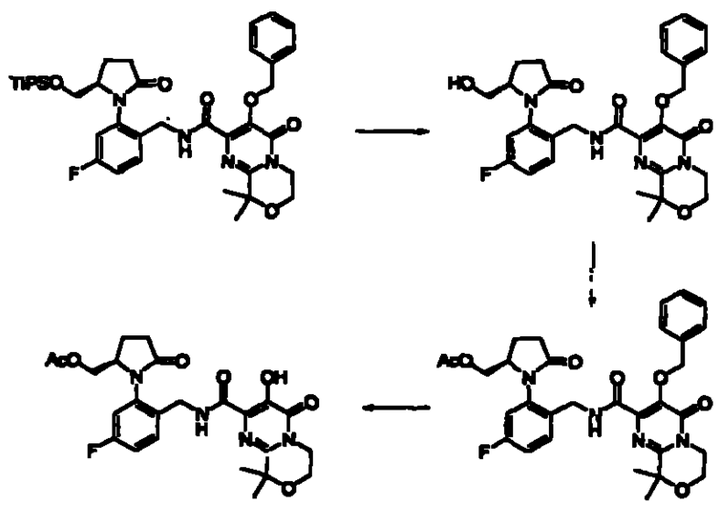
En el esquema de reacción XXVI el intermediario XXVI-1 puede usarse para sintetizar los intermediarios XXVI-2 por medio de acoplamiento catalizado por paladio. Estos intermediarios puede modificarse además para proporcionar algunos de los compuestos de esta invención.

Esquema de reacción XXVI



Otro método se ilustra en el esquema de reacción XXVII.

Esquema de reacción XXVII

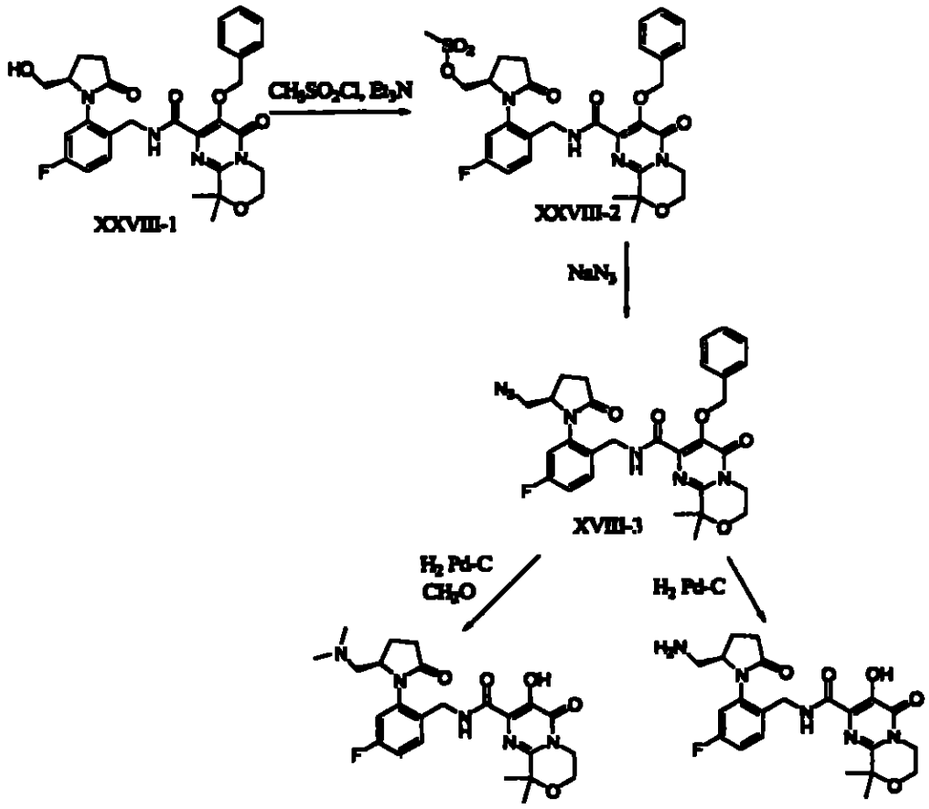


En el esquema de reacción XXVIII, el compuesto XXVIII-1 puede convertirse al correspondiente derivado de metilsulfonato, XXVIII-2, que puede posteriormente tratarse con azida de sodio para proporcionar XXVIII-3. Este compuesto de nuevo puede servir como un intermediario para la

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transformación adicional tal como se ilustra en el esquema.

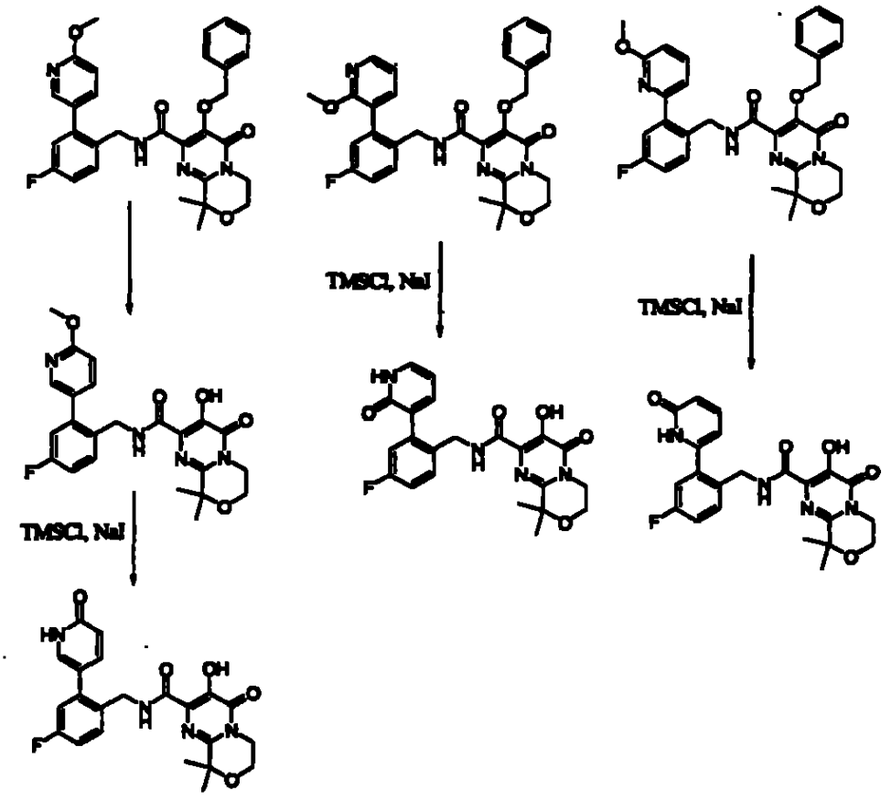
Esquema de reacción XXVIII



Ciertos ejemplos de la actual invención pueden sintetizarse de conformidad con los métodos ilustrados en los esquemas de reacción XXIX-XXXVIII.

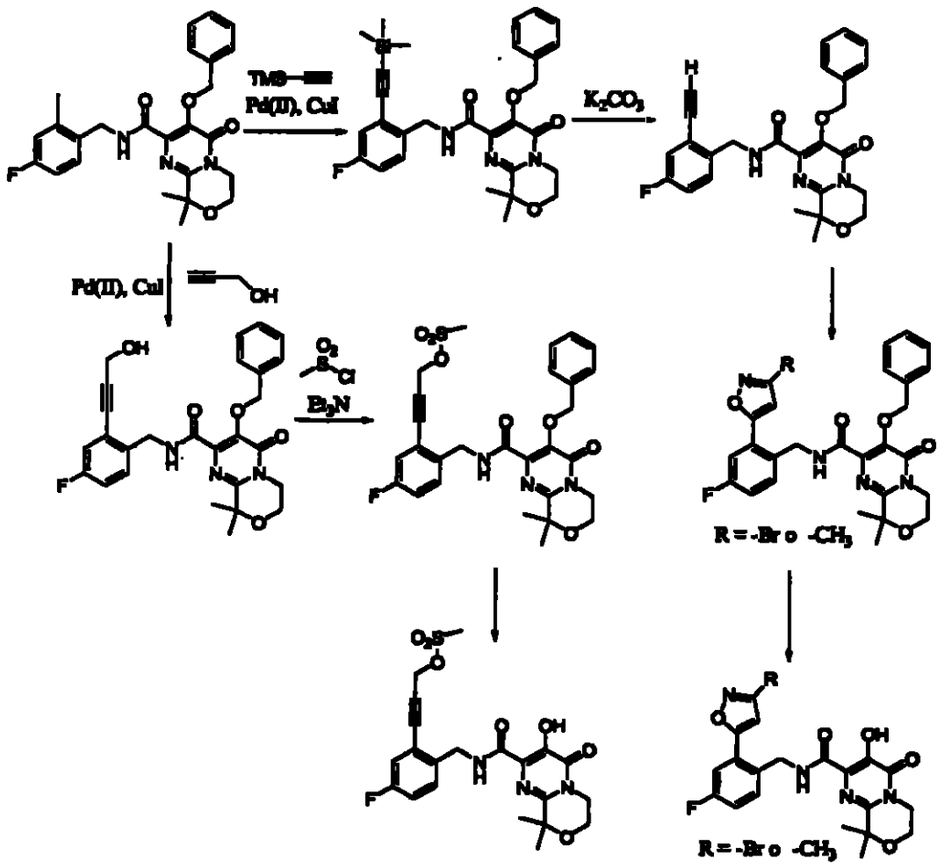
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Esquema de reacción XXIX

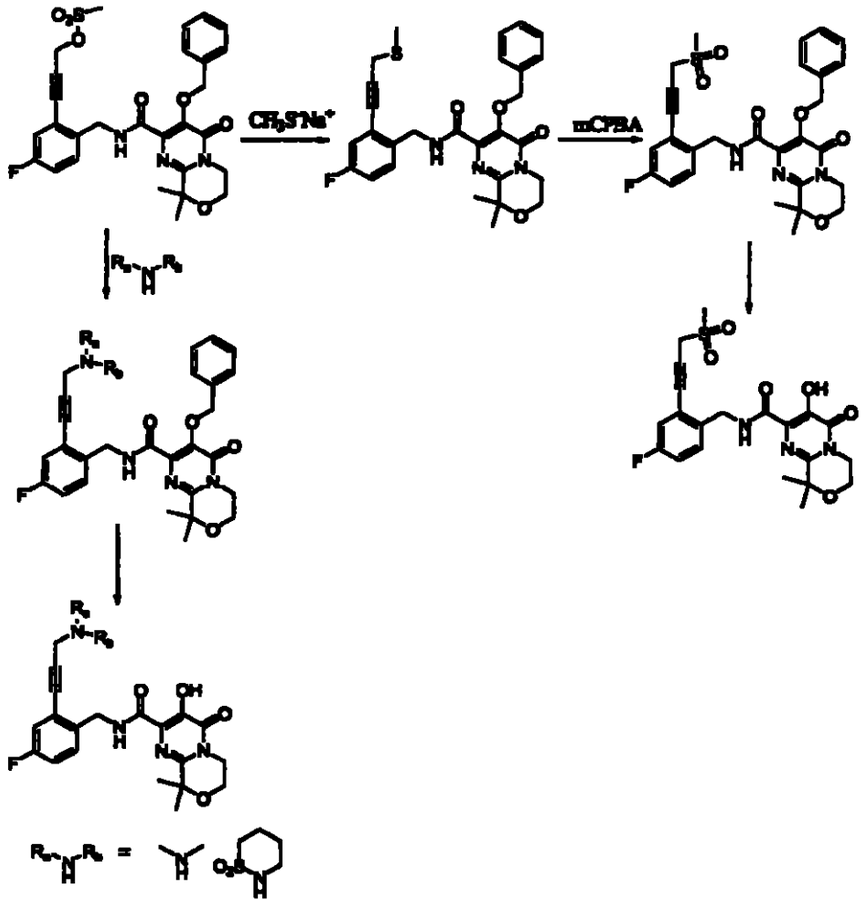


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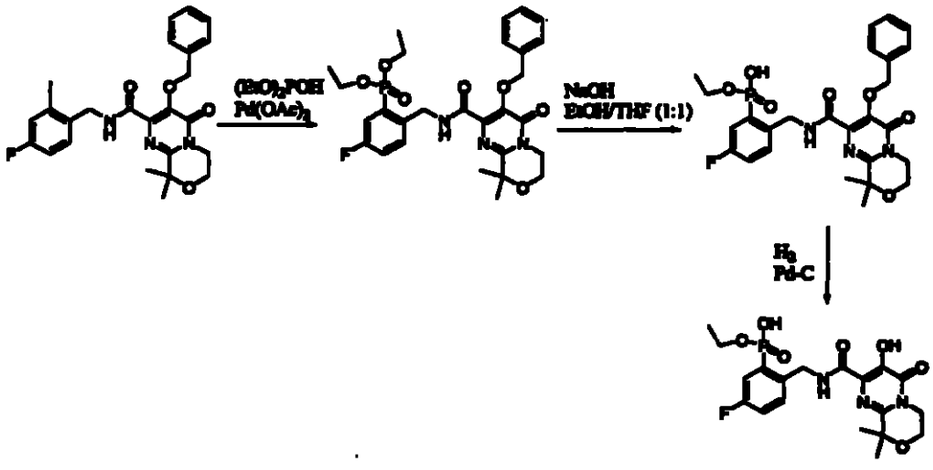
Esquema de reacción XXX



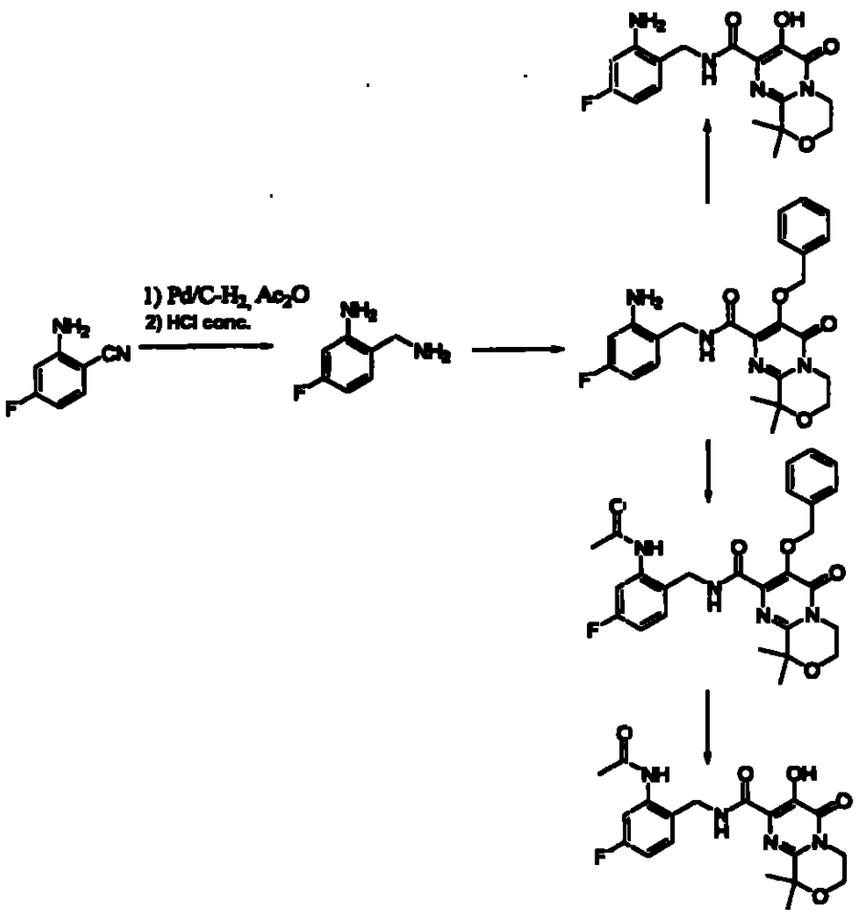
Esquema de reacción XXXI



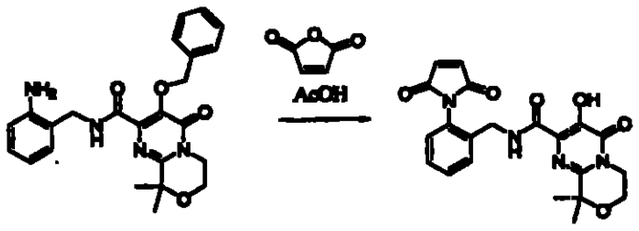
Esquema de reacción XXXII



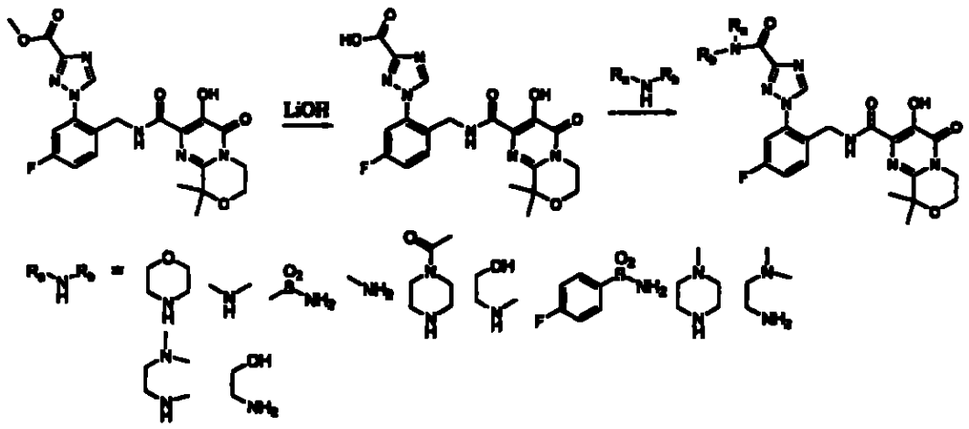
Esquema de reacción XXXIII



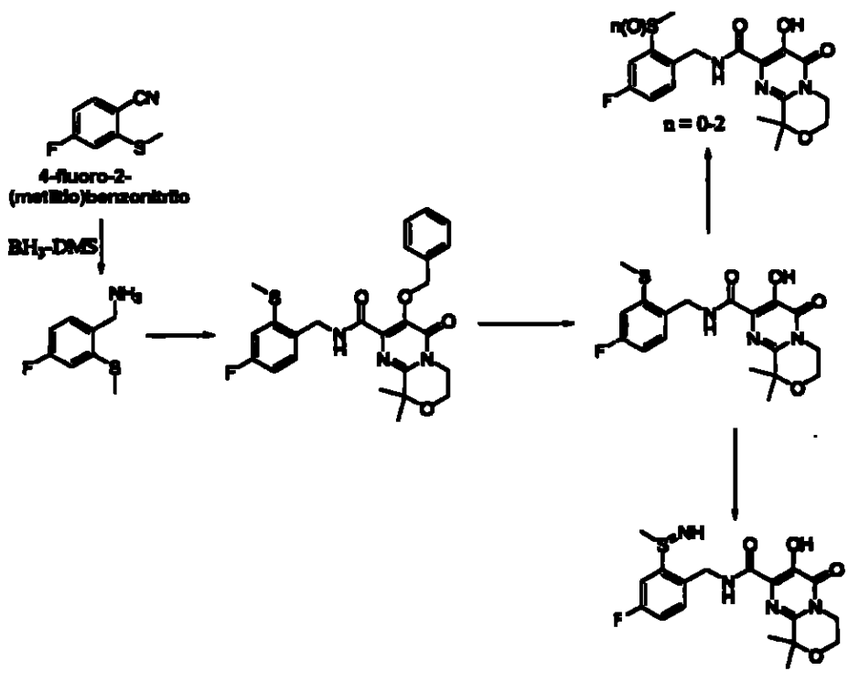
Esquema de reacción XXXIV



Esquema de reacción XXXV

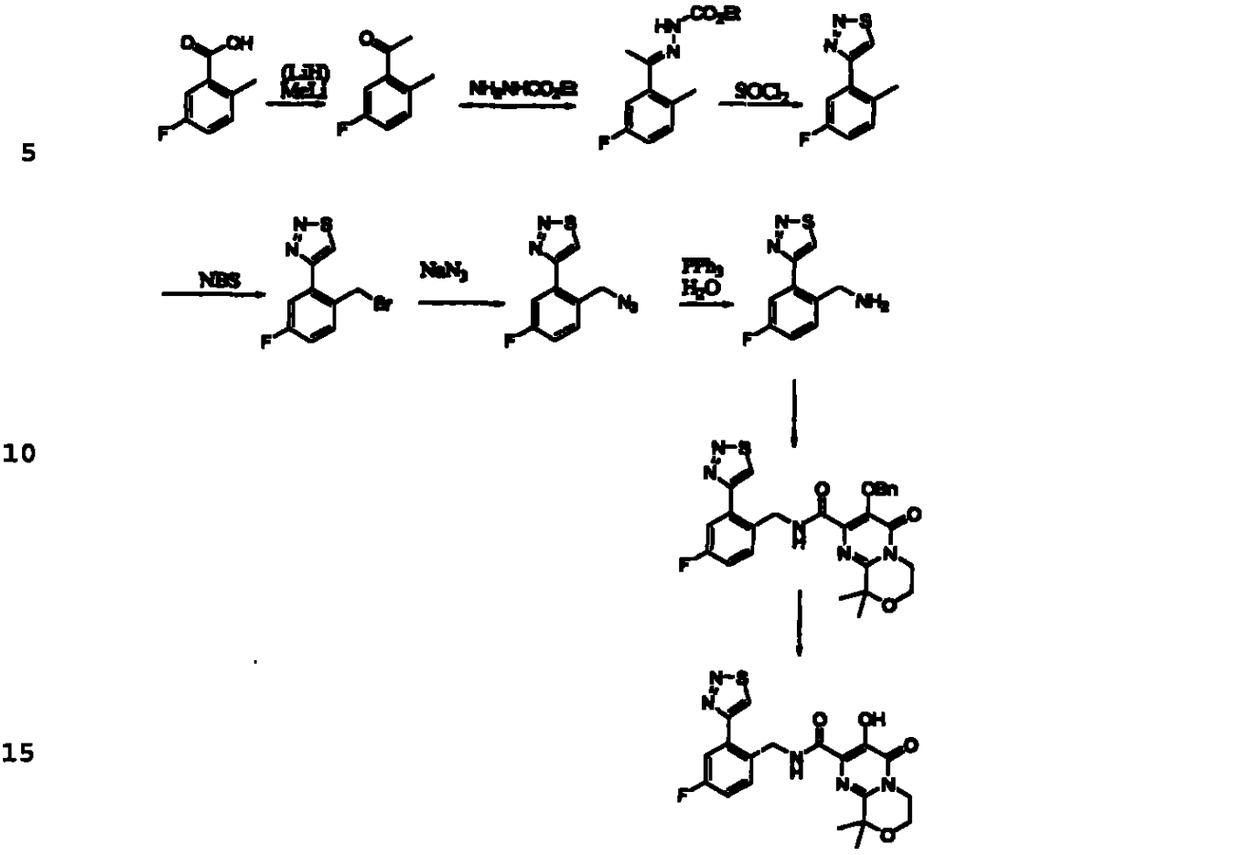


Esquema de reacción XXXVI



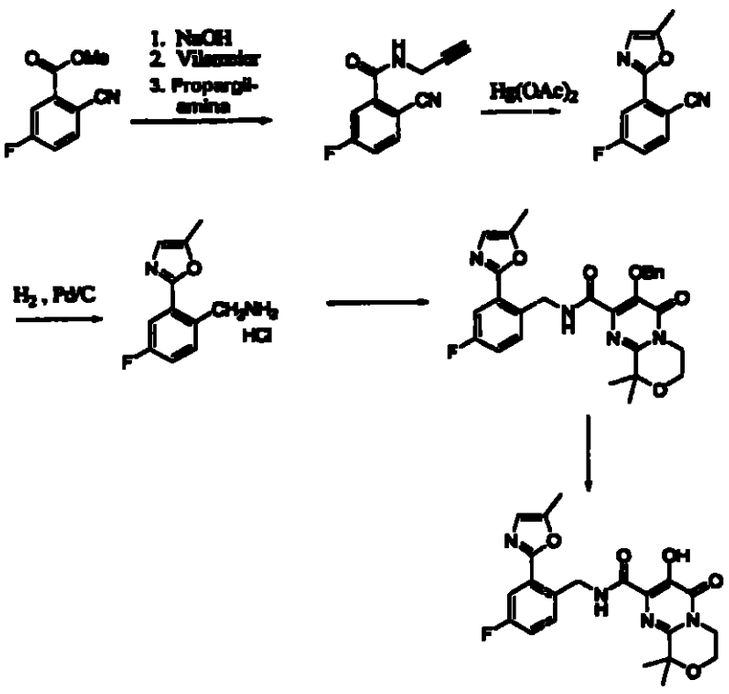
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Esquema de reacción XXXVII



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Esquema de reacción XXXVIII



Métodos Biológicos

Actividad de inhibición de la integrasa de VIH. Para evaluar la actividad in vitro contra integrasa de VIH, se enlazaron 5 pmol de ADN de substrato etiquetado con biotina a 100µg de perlas de PVT SPA recubiertas con estreptavidina (Amersham Pharmacia Biotech). La integrasa recombinante (0.26 ng) se incuba con las perlas durante 90 minutos a 37°C. La enzima sin enlazar se retira al lavar el complejo seguido por la adición de inhibidores y 0.1 fmol de ADN objetivo etiquetado en P33. La reacción se detiene al agregar EDTA hasta una concentración final de 10mM. Se cuentan las muestras en un TopCountNXT (Packard) y el CPM se usa como una

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medida de integración. La condición de reacción fue como se describe en A. Engelman and R. Craigie, J. Virol 69, 5908-5911 (1995). Las secuencias del substrato y ADN objetivo se describen en Nucleic Acid Research 22, 1121-1122 (1994). Los resultados se muestran en la Tabla 1. Una actividad igual a A se refiere a un compuesto que tiene IC_{50} =0.002 hasta 0.10 μM mientras que B y C significan compuestos que tienen IC_{50}= 0.1 hasta 1.0 μM y $IC_{50} \geq$ 1.0 μM respectivamente.

340
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Tabla 1

Ejemplo	Actividad
1	A
2	A
3	A
4	A
5	A
6	A
7	A
8	A
9	A
10	A
11	A
12	A
13	A
14	A
15	A
16	A
17	A
18	A
19	A
20	A
21	A
22	B
23	A
24	B
25	B
26	A
27	A
28	A
29	A
30	A
31	A
32	A
33	A
34	A
35	A
36	A
37	A
38	A
39	A
40	A
41	A
42	A
43	A
44	A
45	A

384

389

Ejemplo	Actividad
46	A
47	A
48	A
49	A
50	A
51	A
52	A
53	A
54	A
55	A
56	A
57	A
58	A
59	A
60	A
61	A
62	A
63	A
64	A
65	A
66	A
67	A
68	A
69	A
70	A
71	A
72	A
73	A
74	A
75	A
76	A
77	A
78	A
79	A
80	A
81	A
82	A
83	C
84	A
85	A
86	A
87	A
88	A
89	A
90	A
91	A

390

Ejemplo	Actividad
92	A
93	A
94	A
95	A
96	A
97	A
98	A
99	A
100	A
101	A
102	A
103	A
104	B
105	A
106	A
107	A
108	A
109	A
110	A
111	A
112	A
113	A
114	A
115	A
116	A
117	A
118	A
119	A
120	A
121	A
122	A
123	A
124	A
125	A
126	A
127	A
128.	A
129	A
130	A
131	B
132	A
133	B
134	A
135	A
136	A
137	A

391

Ejemplo	Actividad
138	A
139	A
140	A
141	A
142	A
143	A
144	B
145	C
146	A
147	A
148	B
149	A
150	A
151	A
152	A
153	A
154	A
155	A
156	A
157	A
158	A
159	B
160	A
161	A
162	A
163	A
164	A
165	A
166	B
167	A
168	A
169	A
170	A
171	A
172	A
173	A
174	A
175	A
176	A
177	A
178	A
179	A
180	A
181	A
187	A
188	A

Ejemplo	Actividad
189	A
190	A
191	A
192	A
193	A
194	A
195	A
196	A
197	A
198	A
199	A
200	A
201	A
202	A
203	A
204	A
205	A
206	A
207	A
208	A
209	A
210	A
211	A
212	A
213	A
214	C
215	A
216	A
217	A
218	A
219	A
220	A
221	A
222	A
223	A
224	A
225	A
226	A
227	A
228	A
229	A
230	A
231	A
232	A
233	A
234	A

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Ejemplo	Actividad
235	A
236	A
237	A
238	A
239	A
240	A
241	A
242	A
243	A
244	A
245	A
246	A
247	A
248	A
249	A
250	A
251	A
252	B
253	C
254	A
255	A
256	B
257	A
258	A
259	A
260	A
261	A
262	A
263	A
264	A
265	A
266	A
267	A
268	A
269	A
270	A
271	A
272	A
273	A
274	A
275	A
276	A
277	A
278	A
279	A
280	A

394

Ejemplo	Actividad
281	A
282	A

Inhibición de la replicación del VIH. Un virus NL-Rluc recombinante se construye en el cual una sección del gen nef de NL4-3 se reemplaza con el gen de Renilla Luciferaza. El virus NL-Rluc se prepara por co-transfección de 2 plásmidos, pNLRLuc y pVSVenv. El pNLRLuc contiene el ADN NL-Rluc clonado en pUC18 en el sitio PvuII, mientras que el pVSVenv contiene el gen para la proteína VSV G enlazada a un promotor LTR. Las transfecciones se realizan a una relación 1:3 de pNLRLuc para pVSVenv en células 293T usando el kit LipofectAMINE PLUS de Invitrogen (Carlsbad, CA) de conformidad con las instrucciones de los fabricantes, y el virus de pseudotipo generado se titula en células MT-2.

La susceptibilidad de los virus de los compuestos se determina por la incubación en presencia de diluciones en serie del compuesto. El 50% de concentración efectiva (EC_{50}) se calcula al usar la forma exponencial de la ecuación de efecto medio donde (Fa)= 1/[1+ (ED_{50}/concentración de fármaco)^m](Johnson VA, Byington RT. Infectivity Assay. In Techniques in HIV Research. ed Aldovini A, Walker BD. 71-76. New York: Stockton Press,

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1990). La actividad antiviral de los compuestos se evalúa bajo 3 condiciones de suero, FBS al 10%, 15 mg/ml de albúmina de suero humano/FBS al 10% o suero humano al 40%/ FBS al 5%, y los resultados de al menos 2 experimentos se usan para calcular los valores EC_{50}. Los resultados se muestran en la tabla 2. La actividad igual a A se refiere a un compuesto que tiene EC_{50} = 0.003 hasta 0.10 µM mientras que B y C significa compuestos con EC_{50} = 0.1 hasta 1.0 µM y $EC_{50} \geq 1.0$ µM respectivamente.

Tabla 2.

Ejemplo	Actividad
1	B
2	A
3	C
4	A
5	A
6	A
7	A

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Ejemplo	Actividad
8	A
9	A
10	A
11	A
12	A
13	A
14	A
15	A
16	A
17	A
18	A
19	A
20	A
21	A
22	B
23	A
24	C
25	C
26	A
27	A
28	B
29	A
30	A
31	A
32	A
33	A
34	A
35	A
36	A
37	B
38	A
39	A
40	A
41	A
42	A
43	A
44	A
45	A
46	A
47	A
48	B
49	A
50	A
51	A
52	A
53	B

397

397

Ejemplo	Actividad
54	A
55	A
56	A
57	A
58	A
59	B
60	A
61	B
62	A
63	A
64	C
65	A
66	B
67	A
68	C
69	A
70	B
71	B
72	B
73	A
74	A
75	A
76	B
77	A
78	A
79	B
80	B
81	A
82	A
83	C
84	A
85	A
86	A
87	A
88	A
89	A
90	A
91	A
92	A
93	A
94	A
95	A
96	A
97	A
98	A
99	A

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398

Ejemplo	Actividad
100	A
101	A
102	A
103	B
104	B
105	A
106	A
107	A
108	A
109	A
110	A
111	A
113	A
114	A
115	A
116	A
117	A
118	A
119	A
120	A
121	A
122	A
123	A
124	A
125	A
126	A
127	A
128	A
129	A
130	A
132	A
133	B
134	A
135	A
136	A
137	B
138	A
139	A
140	A
141	C
142	B
144	C
146	A
147	B
148	B
149	B

Not 399

Ejemplo	Actividad
150	B
151	B
152	B
153	B
154	B
155	B
156	B
157	A
158	A
159	A
160	B
161	B
162	A
163	B
164	B
165	A
166	C
167	B
168	A
169	A
170	A
171	B
172	B
173	A
174	A
175	B
176	A
177	A
178	A
179	B
180	C
181	A
187	B
188	B
189	A
190	A
191	B
192	B
193	C
194	B
195	B
196	A
197	C
198	B
199	B
200	A

Hoa
400

Ejemplo	Actividad
201	B
202	A
203	A
204	A
205	A
206	A
207	A
208	A
209	B
210	A
211	A
212	A
213	A
214	B
215	A
216	A
217	A
218	A
219	A
220	A
221	A
222	A
223	A
224	B
225	A
226	A
227	B
228	B
229	A
230	A
231	A
232	A
233	A
234	A
235	A
236	B
237	A
238	A
239	A
240	A
241	A
242	A
243	A
244	A
245	A
246	A

401

Ejemplo	Actividad
247	A
248	A
249	A
250	A
251	A
252	C
253	C
254	A
255	A
256	B
257	A
258	A
250	A
260	A
262	A
263	B
265	B
266	A
267	A
268	A
270	A
273	B
279	A
281	A
282	A

Estudios de Combinación

El ejemplo 19 demuestra la actividad antiviral del VIH aditiva/sinérgica o sinérgica cuando se usa en conjunto con una variedad de otros agentes antivirales, como se describe abajo.

Virus y líneas celulares. La línea de célula T, MT-2, se obtiene a través de un AIDS Research and Reference Reagent Program. Se sub-cultivan células MT-2 2 veces a la semana en un medio RPMI 1640 complementado con suero de bovino fetal al 10%, L-glutamina 2 mM, y solución amortiguadora HEPES 10 mM

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pH 7.5. El virus HIV-1 303 B es un clon molecular derivado de la cepa NL4-3 del VIH-1 que se obtiene de NIH AIDS Research and Reference Reagent Program. Para combinaciones con enfuvirtida, el virus NL36G se usó. Este derivado NL4-3 tiene la mutación de resistencia a enfuvirtida que se presenta naturalmente en gp41(36D) cambiada a un fenotipo sensible(D36G). Las reservas de virus se hacen al transfectar células 293T con el clon de ADN proviral usando LipofectAMINE PLUS (Invitrogen), de conformidad con las instrucciones del fabricante. Tres días después de la transfección, se cosechan los virus y se pasan 1 vez en células MT-2 antes de la titulación en células MT-2.

Químicos. El ejemplo 19, atazanavir, didanosina, estavudina, efavirenz y enfuvirtida (t-20), se sintetizaron por Bristol-Myers Squibb usando las reacciones publicadas o conocidas. Amprenavir, indinavir, nelfinavir, nevirapina, lopinavir, lamivudina, ritonavir, tenofovir, saquinavir, delavirdina y abacavir se extraen de formulaciones comerciales de los fármacos preescritos y se purifican usando las técnicas publicadas o comunes. Tenofovir se probó como fumerato de tenofovir disopoxilo. Zidovudina y zalcitabina se adquieren de Sigma y emtricitabina de Moravek Biochemicals.

Ensayos de susceptibilidad y citotoxicidad al fármaco. Para ensayos de susceptibilidad al fármaco, se infectan células MT-2 con VIH-1 303 B (o NL36G), a un MOI de 0.001 y

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se siembran en placas de microtitulación de 96 pozos (2.5 x 10^5 células/ml) que contienen disoluciones en serie de los compuestos de prueba. Las combinaciones de fármaco se establecen usando relaciones de los 2 fármacos de 1:1, 1:2.5 y 2.5:1 veces el valor EC_{50} determinado para cada fármaco en experimentos previos. Cada relación de fármaco consiste de una configuración de diluciones en serie de 3 veces, y se realiza con 8 o más replicas en placas de pozos múltiples separadas. Las células infectadas con VIH se incuban a 37°C en CO_2 al 5%, y el quinto día después de la infección, la extensión de la replicación de virus se mide al determinar la viabilidad celular usando el ensayo de proliferación de células no radioactivo acuoso CellTiter 96 (Promega). La protección celular máxima se aprecia típicamente en muestras tratadas con la concentración de fármaco más alta. En el ensayo de viabilidad celular, el compuesto de tetrazolio MTS (3-(4,5-dimetiltiazol-2-il)-5-(3-carboximetoxifenil)-2-4-sulfofenil-2H-tetrazolio) se agrega a las células, en donde las enzimas en células metabólicamente activas se convierten en un producto de formazan coloreado, que se cuantifica al leer la absorbancia a 490nm. Los ensayos de citotoxicidad se realizan en paralelo con los experimentos de combinación. Aquí, las células no infectadas se exponen a las mismas combinaciones de fármaco, y se evalúan después de 5 días para la viabilidad celular usando el ensayo MTS.

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Análisis de efecto de combinación de fármaco. Para la determinación de los valores de índice de combinación (CI), se diluyen fármacos en una relación fija y las relaciones múltiples se analizan. Las diluciones en serie del fármaco giran en un intervalo de concentraciones cercano al valor EC_{50} de cada compuesto, de manera que las actividades antivirales equivalentes podrán compararse. Las respuestas normalizadas para cada terapia se colocan al modelo logístico de 4 parámetros con un mínimo y máximo común a través de todas las terapias. Conceptualmente, esta ecuación puede escribirse como

$$Fa_i = A + \frac{D-A}{1+\left(\frac{C_1^{b_1}C_2^{b_2}C_3^{b_3}C_4^{b_4}C_5^{b_5}}{\text{concentración}_i}\right)^{b_1^{I_1}b_2^{I_2}b_3^{I_3}b_4^{I_4}b_5^{I_5}}},$$

$$\text{donde } I_j = \begin{cases} 1 & \text{si la terapia} = j \\ 0 & \text{de otra manera} \end{cases}$$

para j=1,2,3,4,o 5.

En esta ecuación Fa se establece para "fracción afectada", y representa la fracción de la carga viral que se ha inactivado. Por ejemplo, Fa de 0.75 indica que la replicación viral se ha inhibido por un 75%, con relación a los controles sin fármaco. El EC_{50}, representado por C_i en la ecuación anterior, es la concentración de fármaco que se espera que reduzca la cantidad de virus por el 50%, y B_i son los parámetros que reflejan la inclinación de la curva

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concentración-respuesta. Para este ensayo, A es el plano del fondo común para todas las curvas, D es el plano superior común, B_j es el parámetro "inclinado" para la terapia j-ésima, y C_j es la concentración que produce un efecto igual al promedio de A y D para la terapia j-ésima. Las terapias 1 y 2 corresponden a las monoterapias 1 y 2, respectivamente. Las terapias 3, 4 y 5 corresponden a las tres terapias de combinación. Los valores EC_{50} para cada fármaco se determinan del experimento de fármaco sencillo, usando la ecuación anterior. La ecuación se establece usando una rutina de regresión no lineal (Proc Nlin) en PC SAS versión 8.2 (SAS Institute Inc.)

Para evaluar los efectos antivirales de diferentes tratamientos de fármaco de combinación, los índices de combinación (CIs) se calculan de conformidad con Chou and Rideout. El índice de combinación se computa como

$$CI = \frac{[D]_1}{[Dm]_1} + \frac{[D]_2}{[Dm]_2}$$

En esta ecuación, $[Dm]_1$ y $[Dm]_2$ son las concentraciones de fármaco que podrían producir individualmente un nivel específico de efecto, mientras que $[D]_1$ y $[D]_2$ son las concentraciones de fármaco en la combinación que producirían el mismo nivel de efecto.

Teóricamente, la capacidad aditiva está implicada si el CI

es igual a 1, sinergia si el CI es igual a 1, y antagonista si el CI es igual a 1. Sin embargo, la experiencia extensiva con los estudios de combinación indica que hay variables de laboratorio inherentes que deberán tomarse en cuenta al interpretar los Cis. Como lo mejor, un intervalo puede construirse que contenga los valores similares para el CI, dado el ruido en los datos. En este reporte, estos intervalos se reportan en los paréntesis que siguen a cada punto estimado del CI.

Por ejemplo, cuando un CI de "0.52 (0.36, 0.69)" se reporta, significa que el mejor estimado de CI es 0.52, pero debido al ruido en los datos, los valores desde 0.36 hasta 0.69 también son valores razonables para el CI.

Este intervalo, 0.36 hasta 0.69 cae completamente debajo del valor de 1.0, y por lo tanto todos los valores similares para el CI son menores a 1.0.

Por lo tanto, el comportamiento sinérgico puede inferirse por esta combinación. Si el intervalo cayera completamente abajo de 1.0, se inferiría un comportamiento antagonista. Si el intervalo fuera para incluir 1.0, se inferiría una capacidad aditiva.

Para llevar a cabo los experimentos de combinación, el EC_{50} para el ejemplo 19 y cada compuesto comparador se determina durante el curso de cada estudio, y se usa en el análisis de datos posterior. Los valores determinados son consistentes con los datos previamente publicados y se muestran en la Tabla 3.

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Tabla 3. Actividad anti-VIH de compuestos en estudios de combinación de 2 fármacos.

Compuesto	EC_{50} (μM)	Concentración de fármaco más alta (μM)
Ejemplo 19	0.022	2.5
Zidovudine	0.012	2.5
Didanosine	10.7	100
Estavudina	0.241	15
Lamivudina	0.203	15
Abacavir	1.04	30
Tenofovir	0.018	2.5
Emtricitabina	0.053	20
Zalcitabina	0.124	10
Efavirenz	0.0016	0.2
Nevirapina	0.095	5
Delavirdina	0.043	5
Ritonavir	0.048	2.5
Indinavir	0.026	2.5
Nelfinavir	0.022	2.5
Saquinavir	0.011	2.5
Amprenavir	0.062	2.5
Atazanavir	0.010	1
Lopinavir	0.017	2.5
Enfuvirtida	0.061	2.2

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Combinaciones de 2 fármacos del Ejemplo 19 con inhibidores nucleósidos de la transcriptasa inversa.

Ocho inhibidores RT de nucleósido (didanosina, estavudina, zidovudina, lamivudina, abacavir, zalcitabina, emtricitibina y el fosfonato de nucleósido, tenofovir) se combinaron con el ejemplo 19 a un intervalo de concentraciones cercano al valor EC_{50} de cada compuesto, de manera que las actividades antivirales equivalentes podrán compararse. Todos los estimados se compararon usando SAS Proc NLIN, y una logística de 2 parámetros. Los datos se presentan en la Tabla 4 como índices de combinación e intervalos de confianza asintótica para inhibidores RT a diferentes relaciones molares.

Cuatro inhibidores RT de nucleósido; didanosina, estavudina, abacavir y emtricitibina, muestran efectos antivirales sinérgicos en combinación con el ejemplo 19 a todos los niveles efectivos y todas las relaciones molares. Los otros inhibidores RT: zidovudina, lamivudina, tenofovir y zalcitabina todos tienen índices de combinación que sugieren el comportamiento sinérgico con el ejemplo 19. Sin embargo, los intervalos superiores de los intervalos de confianza para alguno de los niveles efectivos son mayores a 1, de manera que los efectos generales de estos ejemplos con el ejemplo 19 se clasifican como sinérgicos a aditivos. No hay un antagonismo importante de la actividad anti-VIH observada. No

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se encuentra citotoxicidad aumentada a las concentraciones más altas probadas con cualesquiera de las combinaciones de fármaco, como se mide por el ensayo de reducción en XTT.

Tabla 4. Combinaciones de dos fármacos usando el ejemplo 19 e inhibidores de la transcriptasa inversa de nucleósido.

Relación molar (Relación EC_{50})[a]	Índices de combinación al % de inhibición de VIH[b] (Intervalo confianza)		
	50%	75%	90%
Zidovudina			
1:1 (1:1)	0.59 (0.49, 0.69)	0.56 (0.41, 0.70)	0.54 (0.36, 0.70)
2:5 (1:2.5)	0.65 (0.56, 0.75)	0.73 (0.59, 0.86)	0.81 (0.57, 1.06)
5:2 (2.5:1)	0.72 (0.61, 0.83)	0.83 (0.64, 1.02)	0.96 (0.63, 1.30)
Didanosina			
1:1000 (1:1)	0.58 (0.53, 0.63)	0.47 (0.35, 0.60)	0.39 (0.22, 0.56)
1:2500 (1:2.5)	0.56 (0.51, 0.62)	0.46 (0.40, 0.52)	0.38 (0.32, 0.44)
1:400 (2.5:1)	0.50 (0.46, 0.54)	0.49 (0.44, 0.53)	0.48 (0.42, 0.54)
Stavudina			
1:6 (1:1)	0.52 (0.43, 0.61)	0.46 (0.36, 0.56)	0.42 (0.26, 0.57)
1:15 (1:2.5)	0.60 (0.48, 0.71)	0.60 (0.46, 0.74)	0.61 (0.40, 0.83)
5:12 (2.5:1)	0.70 (0.57, 0.84)	0.63 (0.48, 0.79)	0.58 (0.37, 0.81)
Lamivudina			
1:6 (1:1)	0.80 (0.63, 0.98)	0.80 (0.55, 1.05)	0.81 (0.42, 1.21)
1:15 (1:2.5)	1.09 (0.88, 1.31)	1.00 (0.72, 1.27)	0.92 (0.52, 1.33)
5:12 (2.5:1)	0.94 (0.80, 1.08)	0.84 (0.65, 1.03)	0.75 (0.49, 1.02)
Abacavir			
1:30 (1:1)	0.68 (0.59, 0.76)	0.67 (0.56, 0.79)	0.67 (0.49, 0.84)
1:75 (1:2.5)	0.87 (0.77, 0.97)	0.74 (0.63, 0.85)	0.63 (0.50, 0.77)
1:12 (2.5:1)	0.86 (0.76, 0.96)	0.82 (0.68, 0.96)	0.79 (0.58, 0.99)
Tenofovir			
1:1 (1:1)	0.66 (0.57, 0.75)	0.54 (0.45, 0.62)	0.43 (0.33, 0.53)
2:5 (1:2.5)	0.68 (0.59, 0.77)	0.60 (0.48, 0.72)	0.52 (0.36, 0.69)
5:2 (2.5:1)	0.90 (0.77, 1.04)	0.84 (0.67, 1.01)	0.79 (0.55, 1.03)

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Relación molar (Relación EC_{50})[a]	Índices de combinación al % de inhibición de VIH[b] (Intervalo confianza)		
	50%	75%	90%
Zalcitabina			
1:4 (1:1)	0.61 (0.48, 0.73)	0.56 (0.39, 0.73)	0.53 (0.28, 0.79)
1:10 (1:2.5)	0.55 (0.44, 0.66)	0.40 (0.31, 0.49)	0.30 (0.18, 0.42)
5:8 (2.5:1)	0.80 (0.62, 0.97)	0.82 (0.58, 1.07)	0.86 (0.46, 1.26)
Emtricitabina			
1:8 (1:1)	0.31 (0.27, 0.36)	0.23 (0.18, 0.28)	0.18 (0.12, 0.24)
1:20 (1:2.5)	0.31 (0.26, 0.37)	0.23 (0.19, 0.29)	0.17 (0.12, 0.28)
5:16 (2.5:1)	0.33 (0.28, 0.38)	0.25 (0.20, 0.30)	0.19 (0.13, 0.25)

a Relación del Ejemplo 19 al compuesto comparador

b Un enlace más bajo del intervalo de confianza asintótica mayor a 1 indica antagonismos, un enlace superior de menos de 1 indica sinergia y un valor de 1 contenido en el intervalo indica capacidad aditiva. El 95% de los intervalos de confianza se muestran entre paréntesis, y representan una medida de variabilidad en los datos.

Combinaciones de dos fármacos del ejemplo 19 con inhibidores de transcriptasa inversa no nucleósidos. Se combinan tres inhibidores RT no nucleósidos con el ejemplo 19 con un intervalo de concentraciones cercano al valor EC_{50} de cada compuesto, como se describe arriba por los inhibidores RT de nucleósidos. Los datos se presentan en la Tabla 5 como los índices de combinación y los intervalos de confianza asintótica de diferentes relaciones molares. De los tres, nevaripina muestra efectos sinérgicos fuertes en combinación con el ejemplo 19. La sinergia es apreciada en todas las concentraciones efectivas y todas las relaciones molares.

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Sustiva y nevirapina también exhiben índices de combinación que indican sinergia a concentraciones más efectivas y relaciones molares. Sin embargo, en algunos casos, el intervalo superior del intervalo de confianza asintótico es mayor a 1, de manera que no puede descartarse un efecto aditivo. No se observa citotoxicidad aumentada a las concentraciones más altas probadas con cualesquiera de las combinaciones de fármaco, lo que sugiere un potencial para una eficacia terapéutica de las combinaciones del ejemplo 19 con inhibidores RT no nucleósidos.

Tabla 5. Combinaciones de dos fármacos usando el ejemplo 19 e inhibidores de transcriptasa inversa no nucleósidos.

Relación molar (Relación EC_{50})[a]	Índices de combinación al % de inhibición de VIH[b] (intervalo confianza)		
	50%	75%	90%
Efavirenz			
5:2 (1:1)	0.83 (0.75, 0.92)	0.76 (0.64, 0.88)	0.70 (0.54, 0.85)
1:1 (1:2.5)	0.95 (0.86, 1.04)	0.93 (0.85, 1.02)	0.93 (0.79, 1.06)
25:4 (2.5:1)	1.01 (0.92, 1.10)	0.96 (0.83, 1.10)	0.94 (0.73, 1.14)
Nevirapina			
1:2 (1:1)	0.72 (0.62, 0.82)	0.69 (0.55, 0.83)	0.66 (0.46, 0.87)
1:5 (1:2.5)	0.76 (0.64, 0.87)	0.81 (0.64, 0.97)	0.87 (0.59, 1.15)
5:4 (2.5:1)	0.73 (0.62, 0.83)	0.68 (0.55, 0.81)	0.64 (0.45, 0.84)
Delavirdina			
1:2 (1:1)	0.76 (0.64, 0.89)	0.60 (0.47, 0.74)	0.48 (0.31, 0.64)
1:5 (1:2.5)	0.68 (0.58, 0.77)	0.44 (0.32, 0.54)	0.28 (0.17, 0.39)
5:4 (2.5:1)	0.80 (0.68, 0.92)	0.53 (0.42, 0.63)	0.35 (0.25, 0.45)

a Relación del Ejemplo 19 al compuesto comparador

b Un enlace más bajo del intervalo de confianza asintótica mayor a 1 indica antagonismos, un enlace superior de menos de 1 indica sinergia y un valor de 1 contenido en el intervalo indica capacidad aditiva. El 95% de los intervalos de confianza se muestran entre paréntesis, y

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representan una medida de variabilidad en los datos.

Combinaciones de dos fármacos que involucran el ejemplo 19 e inhibidores de la proteasa del VIH. La evaluación del ejemplo 19 para una terapia de combinación de fármaco con inhibidores de proteasa se lleva a cabo usando indinavir, amprenavir, nelfinavir, lopinavir, saquinavir, ritonavir, y atazanavir. Los resultados de este estudio de combinación de dos fármacos se resumen en la Tabla 6. Nuevamente, los índices de combinación observados con el ejemplo 19 y todos los inhibidores de proteasa a casi todos los niveles efectivos y relaciones molares sugieren una relación sinérgica.

Esto es especialmente cierto para saquinavir y atazanavir, donde el intervalo de confianza está debajo de uno en todas las concentraciones y niveles efectivos. Mientras tanto, el intervalo superior del intervalo de confianza es mayor a 1 solo en una condición para ritonavir, indinavir y lopinavir, de manera que una relación aditiva con el ejemplo 19 no puede descartarse.

Además, el intervalo superior del intervalo de confianza para nelfinavir y amprenavir es ligeramente mayor a 1 bajo algunas condiciones, lo que sugiere un efecto sinérgico-aditivo para estos compuestos con el Ejemplo 19. No se observa citotoxicidad a las concentraciones más altas usadas en ninguno de estos ensayos de combinación antivirales.

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Tabla 6. Combinación de dos fármacos usando el ejemplo 19 e inhibidores de proteasa.

Relación molar (Relación EC_{50})[a]	Índices de combinación al % de inhibición de VIH[b] (intervalo confianza)		
	50%	75%	90%
Indinavir			
1:1 (1:1)	0.86 (0.80, 0.92)	0.71 (0.62, 0.81)	0.60 (0.46, 0.73)
2:5 (1:2.5)	0.92 (0.84, 0.99)	0.84 (0.76, 0.92)	0.77 (0.66, 0.89)
5:2 (2.5:1)	0.94 (0.87, 1.02)	0.79 (0.71, 0.87)	0.67 (0.57, 0.77)
Nelfinavir			
1:1 (1:1)	0.79 (0.73, 0.86)	0.75 (0.67, 0.82)	0.71 (0.56, 0.84)
2:5 (1:2.5)	0.97 (0.89, 1.06)	0.87 (0.79, 0.95)	0.78 (0.68, 0.88)
5:2 (2.5:1)	1.09 (1.00, 1.18)	0.98 (0.89, 1.08)	0.90 (0.76, 1.03)
Saquinavir			
1:1 (1:1)	0.77 (0.70, 0.84)	0.67 (0.58, 0.75)	0.58 (0.47, 0.69)
2:5 (1:2.5)	0.43 (0.38, 0.48)	0.51 (0.42, 0.59)	0.59 (0.44, 0.74)
5:2 (2.5:1)	0.81 (0.72, 0.89)	0.77 (0.66, 0.89)	0.74 (0.57, 0.91)
Amprenavir			
1:1 (1:1)	0.83 (0.67, 1.00)	0.84 (0.61, 1.08)	0.89 (0.50, 1.23)
2:5 (1:2.5)	0.84 (0.69, 0.99)	0.77 (0.58, 0.96)	0.75 (0.46, 1.04)
5:2 (2.5:1)	0.90 (0.77, 1.04)	0.62 (0.50, 0.74)	0.44 (0.30, 0.57)
Atazanavir			
5:2 (1:1)	0.87 (0.79, 0.96)	0.67 (0.55, 0.80)	0.52 (0.37, 0.67)
1:1 (1:2.5)	0.65 (0.51, 0.78)	0.45 (0.31, 0.58)	0.31 (0.19, 0.44)
25:4 (2.5:1)	0.78 (0.69, 0.86)	0.60 (0.54, 0.67)	0.47 (0.40, 0.54)
Lopinavir			
1:1 (1:1)	0.74 (0.67, 0.82)	0.77 (0.66, 0.88)	0.84 (0.65, 1.02)
2:5 (1:2.5)	0.77 (0.66, 0.88)	0.56 (0.36, 0.75)	0.41 (0.19, 0.64)
5:2 (2.5:1)	0.76 (0.69, 0.83)	0.62 (0.55, 0.70)	0.54 (0.47, 0.61)
Ritonavir			
1:1 (1:1)	0.80 (0.67, 0.93)	0.57 (0.41, 0.73)	0.44 (0.23, 0.65)
2:5 (1:2.5)	0.73 (0.59, 0.88)	0.64 (0.48, 0.80)	0.61 (0.38, 0.85)
5:2 (2.5:1)	0.92 (0.72, 1.11)	0.72 (0.50, 0.93)	0.59 (0.32, 0.87)

a Relación del Ejemplo 19 al compuesto comparador

b Un enlace más bajo del intervalo de confianza asintótica mayor a 1 indica antagonismo, un enlace superior de menos de 1 indica sinergia y un valor de 1 contenido en el intervalo indica capacidad aditiva. El 95% de los intervalos de confianza se muestran entre paréntesis, y representan una medida de variabilidad en los datos.

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Combinación de dos fármacos del ejemplo 19 con Enfuvirtida. Enfuvirtida (T-20) es un inhibidor de la fusión del VIH gp41 y el primer inhibidor de clase de entrada aprobado. El resultado presentado en la Tabla 7 indica que la combinación del ejemplo 19 con T-20 es sinérgica. No se observa citotoxicidad importante a las concentraciones más altas de los fármacos combinados.

Tabla 7 Estudio de combinación de dos fármacos del ejemplo 19 con Enfuvirtida.

Relación molar (Relación EC_{50})[a]	Índices de combinación al % de inhibición de VIH[b] (intervalo confianza)		
	50%	75%	90%
Enfuvirtida			
5:44 (1:1)	0.68 (0.59, 0.77)	0.59 (0.48, 0.70)	0.52 (0.37, 0.67)
1:22 (1:2.5)	0.75 (0.65, 0.85)	0.60 (0.49, 0.70)	0.48 (0.34, 0.61)
25:88 (2.5:1)	0.76 (0.65, 0.86)	0.73 (0.59, 0.86)	0.71 (0.50, 0.92)

a Relación del Ejemplo 19 al compuesto comparador

b Un enlace más bajo del intervalo de confianza asintótica mayor a 1 indica antagonismos, un enlace superior de menos de 1 indica sinergia y un valor de 1 contenido en el intervalo indica capacidad aditiva. El 95% de los intervalos de confianza se muestran entre paréntesis, y representan una medida de variabilidad en los datos.

Composición Farmacéutica y Métodos de Uso

Los compuestos de esta invención inhiben la integrasa del VIH. Los inhibidores de la integrasa de VIH pertenecen a la clase de compuestos de ácido diceto que evitan la integración viral e inhiben la replicación del VIH-1 en células (Hazuda et al. Science 2000, 287, 646).

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Recientemente, se han aceptado inhibidores de la integrasa del VIH en ensayos clínicos para tratar el SIDA e infección por VIH (Neamati Expert. Opin. Ther. Patents 2002, 12, 709, Pais y Burke Drugs Fut. 2002, 27, 1101).

En consecuencia, otro aspecto de la invención es un método para tratar una infección por VIH en un paciente humano que comprende administrar una cantidad terapéuticamente efectiva de un compuesto de la Fórmula I, o una sal o solvato farmacéuticamente aceptable del mismo, con un portador farmacéuticamente aceptable.

Otro aspecto de la invención es un método para tratar la infección por VIH en un paciente humano, que comprende la administración de una cantidad terapéuticamente efectiva de un compuesto de la Fórmula I, o una sal o un solvato farmacéuticamente aceptable del mismo, con una cantidad terapéuticamente efectiva de al menos otro agente usado para el tratamiento del SIDA o infección por VIH seleccionado del grupo que consiste de inhibidores de la transcriptasa inversa del VIH nucleósidos, inhibidores de la transcriptasa inversa del VIH no nucleósidos, inhibidores de la proteasa del VIH, inhibidores de la fusión del VIH, inhibidores del enlace del VIH, inhibidores CCR5, inhibidores CXCR4, inhibidores del florecimiento o maduración del VIH, e inhibidores de la integrasa del VIH.

Otro aspecto de la invención es un método en donde el

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agente es un inhibidor de la transcriptasa inversa del VIH nucleósido.

Otro aspecto de la invención es un método en donde el inhibidor de la transcriptasa inversa del VIH nucleósido se selecciona del grupo que consiste de abacavir, didanosina, emtricitabina, lamivudina, estavudina, tenofovir, zalcitabina, y zidovudina o una sal o solvato farmacéuticamente aceptable de los mismos.

Otro aspecto de la invención es un método en donde el agente es un inhibidor de la transcriptasa inversa del VIH no nucleósido.

Otro aspecto de la invención es un método en donde el inhibidor de la transcriptasa inversa del VIH no nucleósido se selecciona del grupo que consiste de delavirdina, efavirenz y nevirapina o una sal o solvato farmacéuticamente aceptable de los mismos.

Otro aspecto de la invención es un método en donde el agente es un inhibidor de la proteasa del VIH.

Otro aspecto de la invención es un método en donde el inhibidor de la proteasa del VIH se selecciona del grupo que consiste de amprenavir, atazanavir, indinavir, lopinavir, nelfinavir, ritonavir, saquinavir y fosamprenavir o una sal o solvato farmacéuticamente aceptable de los mismos.

Otro aspecto de la invención es un método en donde el agente es un inhibidor de la fusión del VIH.

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Otro aspecto de la invención es un método en donde el inhibidor de la fusión del VIH es enfuvirtida o T-1249 o una sal o solvato farmacéuticamente aceptable de los mismos.

Otro aspecto de la invención es un método en donde el agente es un inhibidor del enlace de VIH.

Otro aspecto de la invención es un método en donde el agente es un inhibidor CCR5.

Otro aspecto de la invención es un método en donde el inhibidor CCR5 se selecciona del grupo que consiste de Sch-C, Sch-D, TAK-220, PRO-140, y UK-427,857, o una sal o solvato farmacéuticamente aceptable de los mismos.

Otro aspecto de la invención es un método en donde el agente es un agente inhibidor CXCR4.

Otro aspecto de la invención es un método en donde el inhibidor CXCR4 es AMD-3100, o una sal o solvato farmacéuticamente aceptable del mismo.

Otro aspecto de la invención es un método en donde el agente es un inhibidor del florecimiento o maduración del VIH.

Otro aspecto de la invención es un método en donde el inhibidor del florecimiento o maduración es PA-457, o una sal o solvato farmacéuticamente aceptable del mismo.

Otro aspecto de la invención es un método en donde el agente es un inhibidor de la integrasa del VIH.

Otro aspecto de la invención es una composición

farmacéutica que comprende una cantidad terapéuticamente efectiva del compuesto de la Fórmula I, o una sal o solvato farmacéuticamente aceptable del mismo, con al menos otro agente usado para el tratamiento del SIDA o infección por VIH, seleccionado del grupo que consiste de inhibidores de la transcriptasa inversa del VIH nucleósidos, inhibidores de la transcriptasa inversa del VIH no nucleósidos, inhibidores de proteasa del VIH, inhibidores de la fusión del VIH, inhibidores del enlace de VIH, inhibidores CCR5, inhibidores CXCR4, inhibidores del florecimiento o maduración del VIH, inhibidores de la integrasa del VIH, y un portador farmacéuticamente aceptable.

Otro aspecto de la invención es la composición en donde el agente es un inhibidor de la transcriptasa inversa del VIH nucleósido.

Otro aspecto de la invención es la composición en donde el inhibidor de la transcriptasa inversa del VIH nucleósido se selecciona del grupo consiste de abacavir, didanosina, emtricitabina, lamivudina, estavudina, tenofovir, zalcitabina, y zidovudina o una sal o solvato farmacéuticamente aceptable de los mismos.

Otro aspecto de la invención es la composición en donde el agente es un inhibidor de la transcriptasa inversa del VIH no nucleósido.

Otro aspecto de la invención es la composición en donde

el inhibidor de la transcriptasa inversa del VIH no nucleósido se selecciona del grupo que consiste de delavirdina, efavirenz y nevirapina, o una sal o solvato farmacéuticamente aceptable de los mismos.

Otro aspecto de la invención es la composición en donde el agente es un inhibidor de la proteasa del VIH.

Otro aspecto de la invención es la composición en donde el inhibidor de la proteasa del VIH se selecciona del grupo consiste de amprenavir, atazanavir, indinavir, lopinavir, nelfinavir, ritonavir, saquinavir y fosamprenavir o una sal o solvato farmacéuticamente aceptable de los mismos.

Otro aspecto de la invención es la composición en donde el agente es un inhibidor de la fusión del VIH.

Otro aspecto de la invención es el método de la composición en donde el inhibidor de la fusión del VIH es enfuvirtida o T-1249 o una sal o solvato farmacéuticamente aceptable del mismo.

Otro aspecto de la invención es la composición en donde el agente es un inhibidor del enlace de VIH.

Otro aspecto de la invención es la composición en donde el agente es un inhibidor CCR5.

Otro aspecto de la invención es la composición en donde el inhibidor CCR5 se selecciona del grupo que consiste de Sch-C, Sch-D, TAK-220, PRO-140, y UK-427,857

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o sus análogos o una sal o solvato farmacéuticamente aceptable de los mismos.

Otro aspecto de la invención es un método en donde el agente es un inhibidor CXCR4.

Otro aspecto de la invención es un método en donde el inhibidor CXCR4 es AMD-3100 o sus análogos, o una sal o solvato farmacéuticamente aceptable de los mismos.

Otro aspecto de la invención es la composición en donde el agente es un inhibidor del florecimiento o maduración del VIH.

Otro aspecto de la invención es la composición en donde el inhibidor del florecimiento o maduración es PA-457, o sus análogos, o una sal o solvato farmacéuticamente aceptable de los mismos.

Otro aspecto de la invención es la composición en donde el agente es un inhibidor de la integrasa del VIH.

"Combinación", "coadministración", "concurrente", y términos similares que se refieren a la administración del Compuesto 1 con al menos un agente anti-VIH, significa que los componentes son parte de una terapia antiretroviral de combinación o terapia antiretroviral altamente activa (HAART, por sus siglas en inglés) como se entiende por los practicantes en el campo del SIDA e infección por VIH.

"Terapéuticamente efectivo" significa la cantidad de

agente requerido para proporcionar un beneficio importante al paciente como se entiende por los practicantes en el campo del SIDA y la infección por VIH. En general, los puntos de tratamiento son supresión de la carga viral, restauración y conservación de la función inmunológica, calidad de vida mejorada, y reducción de la morbilidad y mortalidad relacionada con el VIH.

"Paciente" significa una persona infectada con el virus del VIH y apropiada para la terapia como se entiende por los practicantes en el campo del SIDA y la infección por VIH.

"Tratamiento", "terapia", "régimen", "infección por VIH", "ARC", "SIDA" y términos relacionados se usan como se entienden por los practicantes en el campo del SIDA y la infección por VIH.

Los compuestos de esta invención generalmente se dan como composiciones farmacéuticas que comprenden una cantidad terapéuticamente efectiva de un compuesto de la Fórmula I o su sal farmacéuticamente aceptable y un portador farmacéuticamente aceptable, y puede contener excipientes convencionales. Una cantidad terapéuticamente efectiva es la que se necesita para proporcionar un beneficio importante al paciente. Los portadores farmacéuticamente aceptables son aquellos portadores convencionalmente conocidos que tienen perfiles de

seguridad aceptables. Las composiciones abarcan todas las formas sólidas y líquidas comunes que incluyen cápsulas, tabletas, pastillas y polvos así como suspensiones líquidas, jarabes, elíxires, y soluciones. Composiciones hechas usando técnicas de formulación común, y excipientes convencionales (tales como agentes de enlace y humectantes) y vehículos (tales como agua y alcoholes) se usan generalmente para composiciones.

Las composiciones sólidas se formulan normalmente en unidades de dosis y se prefieren composiciones que proporcionan desde alrededor de 1 hasta 1000 mg del ingrediente activo por dosis. Algunos ejemplos de dosis son 1 mg, 10 mg, 100 mg, 250 mg, 500 mg y 1000 mg. Generalmente, otros agentes antiretrovirales estarán presentes en un intervalo de unidad similar para los agentes de tal clase usados clínicamente. Típicamente, esto es 0.25-1000 mg/unidad.

Las composiciones líquidas están usualmente en intervalos unitarios de dosis. Generalmente, la composición líquida estará en un intervalo de dosis unitaria de 1-100 mg/mL. Algunos ejemplos de dosis son 1 mg/mL, 10 mg/mL, 25 mg/mL, 50 mg/mL y 100 mg/mL. Generalmente otros agentes retrovirales estarán presentes en un intervalo de unidad similar a los agentes de tal clase utilizados clínicamente. Típicamente, esto es 1-

100mg/mL.

La invención abarca todos los modos convencionales de administración; los métodos oral y parenteral se prefieren. Generalmente, el régimen de dosis será similar a otros agentes antiretrovirales usados clínicamente. Típicamente, la dosis diaria será 1-100 mg/kg peso corporal diariamente. Generalmente, se requiere más compuesto oralmente y menos parenteralmente. El régimen de dosis específico, sin embargo, se determina por un médico usando el juicio médico sólido.

La invención también abarca métodos en donde el compuesto se da en una terapia de combinación. Esto es, el compuesto puede usarse en conjunto con, pero separadamente de, otros agentes útiles en el tratamiento del SIDA e infección por VIH. Algunos de estos agentes incluyen inhibidores del enlace del VIH, inhibidores CCR5, inhibidores CXCR4, inhibidores de la fusión celular del VIH, inhibidores de la integrasa del VIH, inhibidores de la transcriptasa inversa del VIH nucleósidos, inhibidores de la transcriptasa inversa del VIH no nucleósidos, inhibidores de la proteasa del VIH, inhibidores del florecimiento y maduración, inmunomoduladores, y anti-infecciosos. En estos métodos de combinación, el compuesto de la Fórmula I generalmente se da en una dosis diaria de 1-100 mg/kg peso corporal diariamente en conjunto con otros

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agentes. Los otros agentes generalmente se dan en cantidades usadas terapéuticamente. El régimen de dosis específico, sin embargo, se determina por un médico usando el juicio médico sólido.

La Tabla 8 enlista algunos agentes útiles en el tratamiento del SIDA e infección por VIH, que son apropiados para esta invención.

Tabla 8

ANTIVIRALES

Nombre del Fármaco	Fabricante	Indicación
097 (inhibidor de la transcriptasa inversa no nucleósido)	Hoechst/Bayer	infección por VIH, SIDA, ARC
Amprenavir 141 W94 GW 141 (inhibidor de la proteasa)	Glaxo Wellcome	Infección por VIH SIDA, ARC
Abacavir (1592U89) GW 1592 (inhibidor de RT)	Glaxo Wellcome	Infección por VIH, SIDA, ARC
Acemannan	Carrington Labs (Irving, TX)	ARC
Aciclovir	Burroughs Wellcome	Infección por VIH, SIDA, ARC, en combinación con AZT
AD-439	Tanox Biosystems	Infección por VIH, SIDA, ARC
AD-519	Tanox Biosystems	Infección por VIH, SIDA, ARC
Adefovir dipivoxil AL-721	Gilead Sciences Ethigen (Los Angeles, CA)	Infección por VIH, ARC, PGL, VIH positivo, SIDA
Alfa interferón VIH en combinación c/Retrovir	Glaxo Wellcome	Sarcoma de Kaposi
Ansamicina LM 427	Adria Laboratories (Dublín, OH) Erbamont (Stamford,	ARC

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Nombre del Fármaco	Fabricante	Indicación
Anticuerpo que neutraliza el pH Alfa interferón inestable aberrante	Advance Biotherapy Concepts (Rockville, MD)	SIDA, ARC
AR177	Aronex Pharm.	Infección por VIH, SIDA, ARC
Beta-fluoro-ddA	Nat'l Cancer Institute	Enfermedades asociadas con el SIDA
BMS-232623 (CGP-73547) (inhibidor de la proteasa)	Bristol-Myers Squibb/Novartis	Infección por VIH, SIDA, ARC
BMS-234475 (CGP-61755) (inhibidor de la proteasa)	Bristol-Myers Squibb/Novartis	Infección por VIH, SIDA, ARC
CI-1012	Warner-Lambert	Infección por VIH-1
Cidofovir	Gilead Science	CMV retinitis, herpes, papilomavirus
Sulfato de curdlan	AJI Pharma USA	Infección por VIH
Citomegalovirus inmuno globina	MedImmune	Retinitis CMV
Cytovene	Syntex	Amenaza a la visión
Ganciclovir		CMV Retinitis, CMV periférica
Delaviridina (inhibidor RT)	Pharmacia-Upjohn	Infección por VIH, SIDA, ARC
Sulfato de dextrano	Ueno Fine Chem. Ind. Ltd (Osaka, Japón)	SIDA, ARC, VIH asintomático positivo
ddC Didesoxicitidina	Hoffman-La Roche	Infección por VIH, SIDA, ARC
ddI Didesoxiinosina	Bristol-Myers Squibb	Infección por VIH, SIDA, ARC; combinación con AZT/d4T

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Nombre del Fármaco	Fabricante	Indicación
DMP-450 (inhibidor de la proteasa)	AVID (Camden, NJ)	Infección por VIH, SIDA, ARC
Efavirenz (DMP 266) (-)6-cloro-4-(S)-ciclopropiletinil-4(S)-trifluoro-metil-1,4,-dihidro-2H-3,1-benzoxazin-2-ona, STOCRINE (inhibidor RT no nucleósido)	DuPont Merck	Infección por VIH, SIDA, ARC
EL10	Elan Corp, PLC (Gainesville, GA)	Infección por VIH
Famciclovir	Smith Kline	Herpes zoster, Herpes simplex
FTC (inhibidor de la transcriptasa inversa)	Emory University	Infección por VIH, SIDA, ARC
GS 840 (inhibidor de la transcriptasa inversa)	Gilead	Infección por VIH, SIDA, ARC
HBY097 (inhibidor de la transcriptasa inversa no nucleósido)	Hoechst Marion Roussel	Infección por VIH, SIDA, ARC
Hypericin	VIMRx Pharm.	Infección por VIH, SIDA, ARC
Beta Interferón Humano Recombinante	Triton Biosciences (Almeda, CA)	SIDA, sarcoma de Kaposi, ARC
Interferón alfa-n3	Interferon Sciences	ARC, SIDA
Indinavir	Merck	Infección por VIH, SIDA, ARC, VIH positivo asintomático, también en combinación con AZT/ddI/ddC
ISIS 2922	ISIS Pharmaceuticals	Retinitis CMV

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Nombre del Fármaco	Fabricante	Indicación
Nelfinavir (inhibidor de la proteasa)	Agouron Pharmaceuticals	Infección por VIH, SIDA, ARC
Nevirapina (inhibidor RT)	Boeheringer Ingleheim	Infección VIH, SIDA, ARC
Novapren	Novaferon Labs, Inc. (Akron, OH)	Inhibidor del VIH
Secuencia del octapéptido del péptido T	Peninsula Labs (Belmont, CA)	SIDA
Fosfonoformiato de trisodio	Astra Pharm. Products, Inc.	Retinitis CMV, infección por VIH, otras infecciones de CMV
PNU-140690 (inhibidor de la proteasa)	Pharmacia-Upjohn	Infección por VIH, SIDA, ARC
Probucol	Vyrex	Infección por VIH, SIDA
RBC-CD4	Sheffield Med Tech (Houston, TX)	Infección por VIH, SIDA, ARC
Ritonavir (inhibidor de la proteasa)	Abbott	Infección por VIH, SIDA, ARC
Saquinavir (inhibidor de la proteasa)	Hoffman-La Roche	Infección por VIH, SIDA, ARC
Estavudina, d4T dideshidrodesoxi timidina	Bristol-Myers Squibb	Infección por VIH, SIDA, ARC
Valaciclovir	Glaxo Wellcome	Infecciones HSV y CMV genitales
Virazol Ribavirin	Viratek/ICN (Costa Mesa, CA)	VIH positivo asintomático, LAS, ARC
VX-478	Vertex	Infección por VIH, SIDA, ARC
Zalcitabina	Hoffman-La Roche	Infección por VIH, SIDA, ARC, con AZT
Zidovudina; AZT	Glaxo Wellcome	Infección por VIH, SIDA, ARC, sarcoma de Kaposi, en combinación con otras terapias

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Nombre del Fármaco	Fabricante	Indicación
Sal de fumarato Tenofovir disoproxil (Viread®) (inhibidor transcriptasa inversa)	Gilead	Infección por VIH, SIDA,
Combivir® (inhibidor transcriptasa inversa)	GSK	Infección por VIH, SIDA,
Succinato de abacavir (o Ziagen®) (inhibidor transcriptasa inversa)	GSK	Infección por VIH, SIDA,
Reyataz® (o atazanavir)	Bristol-Myers Squibb	Infección por VIH, SIDA,
Fuzeon (Enfuvirtida, T-20)	Roche/Trimeris	Infección por VIH, SIDA, inhibidor de fusión viral
Trizivir®		Infección por VIH, SIDA
Kaletra®	Abbott	Infección por VIH, SIDA, ARC

INMUNOMODULADORES

Nombre del Fármaco	Fabricante	Indicación
AS-101	Wyeth-Ayerst	SIDA
Bropirimina	Pharmacia-Upjohn	SIDA avanzado,
Acemannan	Carrington Labs, Inc. (Irving, TX)	SIDA, ARC
CL246,738	American Cyanamid Lederle Labs	SIDA, sarcoma de Kaposi
EL10	Elan Corp, PLC (Gainesville, GA)	Infección por VIH
FP-21399	Fuki ImmunoPharm	Bloqueo de fusión del VIH con células CD4+
Gamma Interferón	Genentech	ARC, en combinación con TNF (factor de necrosis de tumor)
Factor estimulante de la colonia de macrófagos granulocitos	Genetics Institute Sandoz	SIDA

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Nombre del Fármaco	Fabricante	Indicación
Factor estimulante de la colonia de macrófagos granulocitos	Hoechst-Roussel Immunex	SIDA
Factor estimulante de la colonia de macrófagos granulocitos	Schering-Plough	SIDA, combinación con AZT
Inmunoestimulante de la partícula de núcleo de VIH	Rorer	VIH seropositivo
IL-2 Interleucina-2	Cetus	SIDA, en combinación con AZT
IL-2 Interleucina-2	Hoffman-La Roche Immunex	SIDA, ARC, VIH, en combinación con AZT
IL-2 Interleucina-2 (aldeslucina)	Chiron	SIDA, incremento en cuentas de células CD4
Inmunoglobulina intravenosa (humana)	Cutter Biological (Berkeley, CA)	SIDA pediátrico, en combinación con AZT
IMREG-1	Imreg (New Orleans, LA)	SIDA, sarcoma de Kaposi, ARC, PGL
IMREG-2	Imreg (New Orleans, LA)	SIDA, sarcoma de Kaposi, ARC, PGL
Inmutiol dietil ditio carbamato	Merieux Institute	SIDA, ARC
Alfa-2 Interferon	Schering Plough	Sarcoma de Kaposi con AZT, SIDA
Metionina-encefalina	TNI Pharmaceutical (Chicago, IL)	SIDA, ARC
MTP-PE Muramil-tripéptido Factor estimulante de la colonia de granulocitos	Ciba-Geigy Corp. Amgen	Sarcoma de Kaposi SIDA, en combinación con AZT
Remune	Immune Response Corp.	Inmuno terapéutico
rCD4 CD4 humano soluble recombinante	Genentech	SIDA, ARC
Híbridos rCD4-IgG		SIDA, ARC
CD4 humano soluble recombinante	Biogen	SIDA, ARC
Interferón alfa 2a	Hoffman-La Roche en combinación con AZT	Sarcoma de Kaposi, SIDA, ARC

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Nombre del Fármaco	Fabricante	Indicación
SK&F106528 T4 soluble	Smith Kline	Infección por VIH
Timopentina	Immunobiology Research Institute (Annandale, NJ)	Infección por VIH
Factor de Necrosis de Tumor; TNF	Genentech	ARC, en combinación con gamma interferón

ANTI-INFECCIOSOS

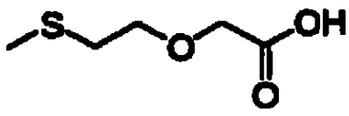
Nombre del Fármaco	Fabricante	Indicación
Clindamicina con Primaquina	Pharmacia-Upjohn	PCP
Fluconazol	Pfizer	Meningitis criptococal, candidiasis
Pastille Nystatin Pastille	Squibb Corp.	Prevención de candidiasis oral
Ornidil Eflornitina	Merrell Dow	PCP
Pentamidina Isetionato (IM y IV)	LyphoMed (Rosemont, IL)	Tratamiento del PCP
Trimetoprim		Antibacterial
Trimetoprim/sulfa		Antibacterial
Piritrexim	Burroughs Wellcome	Tratamiento del PCP
Pentamidina Isetionato para Inhalación	Fisons Corporation	Profilaxis de PCP
Espiramicina	Rhone-Poulenc diarrea	Criptosporidial
Intraconazol-R51211	Janssen-Pharm.	Histoplasmosis; meningitis criptococal
Trimetrexato	Warner-Lambert	PCP
Daunorrubicina	NeXstar, Sequus	Sarcoma de Kaposi
Eritropoyetina humana recombinante	Ortho Pharm. Corp.	Anemia severa asociada con terapia de AZT
Hormona de crecimiento humana recombinante	Serono	Desgaste relacionado con el SIDA, caquexia

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Nombre del Fármaco	Fabricante	Indicación
Acetato de Megestrol	Bristol-Myers Squibb	Tratamiento de anorexia asociada con SIDA
Testosterona	Alza, Smith Kline	Desgaste relacionado con el SIDA
Nutrición Enteral Total	Norwich Eaton Pharmaceuticals	Diarrea y mala absorción relacionada con SIDA

DESCRIPCIÓN DETALLADA DE MODALIDADES ESPECÍFICAS

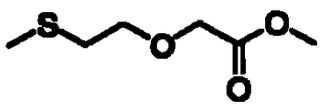
Intermediario 1



Ácido 2-(2-(Metiltio)etoxi)acético. Una solución de 2-metiltioetanol (10.0 g, 0.108 mol) en tetrahidrofurano seco (25 ml) se agregó gota a gota, durante 30 minutos, a una suspensión de hidruro de sodio (9.54 g de un 60% de dispersión en aceite mineral, 0.238 mol, se lavó dos veces con hexano) en tetrahidrofurano seco (250 ml) a 22°C. Después de 30 minutos, se agregó gota a gota una solución de ácidc cloroacético (10.25 g, 0.108 mol) en tetrahidrofurano seco (20 ml), durante 30 minutos a 22°C, y la mezcla resultante luego se calentó bajo reflujo durante 5 h. La mezcla enfriada se trató con 250 ml de ácido clorhídrico 1N y se agregó cloruro de sodio a la fase acuosa hasta saturarse. La fase orgánica se separó y la fase acuosa se lavó con acetato de etilo. Los extractos orgánicos combinados se lavaron con salmuera, se secaron sobre sulfato de magnesio

anhidro y se concentraron bajo presión reducida. La destilación del residuo resultante in vacuo dio 11.27 g (69% rendimiento) del ácido del título como un aceite claro; p.e 85-95°C/0.3 torr (destilación bulbo a bulbo, temperatura del baño al aire). ^{1}HRMN 400 MHz ($CDCl_3$) δ ppm: 2.18 (3H, s, SCH_3), 2.76 (2H, t, J=6.6 Hz, CH_2), 3.77 (2H, t, J=6.6 Hz, CH_2), 4.20 (2H, s, OCH_2).

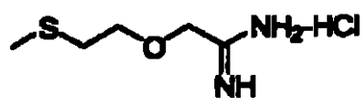
Intermediario 2



2-(2-(metiltio)etoxi)acetato de metilo. Una solución del intermediario 1, el 2-(2-(metiltio)etoxi)acético, (11.27 g, 0.075 mol) en diclorometano seco (50 ml) se trató con cloruro de oxalilo (13.0 ml, 0.15 mol) seguido por una gota de N,N-dimetilformamida y la mezcla resultante se agitó a 22°C durante 5 h. El solvente y reactivo en exceso luego se evaporaron bajo presión reducida y el residuo de cloruro del ácido se agregó gota a gota a una mezcla fría (0-5°C) de metanol (30 ml) y piridina (10 ml) en diclorometano (50 ml). Después de 1 h a 22°C, el solvente se evaporó bajo presión reducida. El residuo resultante se diluyó con acetato de etilo, se lavó con ácido clorhídrico 1N, bicarbonato de sodio saturado y salmuera, se secó sobre sulfato de magnesio anhidro y luego se concentró bajo presión reducida. La destilación del residuo resultante in

vacuo dio 11.42 g (93% rendimiento) del éster del título como un aceite claro; p.e. 65-75°C/0.1 torr (destilación bulbo a bulbo, temperatura del baño al aire). ^{1}HRMN 400 MHz ($CDCl_3$) δ ppm: 2.17 (3H, s, SCH_3), 2.75 (2H, t, J=6.9 Hz, CH_2), 3.74 (2H, t, J=6.9 Hz, CH_2), 3.77 (3H, s, OCH_3), 4.15 (2H, s, OCH_2).

Intermediario 3

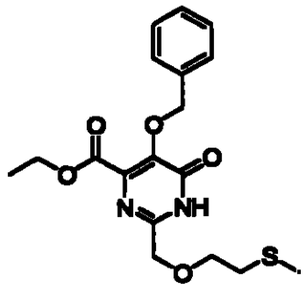


Sal de clorohidrato de 2-(2-(Metiltio)etoxi)acetamidina. Intermediario 2, se agregó 2-(2-(metiltio)etoxi)acetato de metilo, (4.69 g, 28.6 mmol) a una solución de una amida de metilcloroaluminio (H. Geilen, C. Alonso-Alija, M. Hendrix, U. Niewohner and D. Schauss, Tetrahedron Lett., 2002, 43, 419-421) (0.114 mol; preparado en tolueno (50 ml) de cloruro de amonio 6.30 g (0.117 mol) y 57.0 ml (0.114 mol) de una solución 2M de trimetilaluminio en tolueno) y la mezcla resultante se calentó a 80°C durante 18h. La mezcla de reacción luego se enfrió a 0°C, se trató gota a gota con metanol (100 ml) y se agitó durante otra hora a 25°C. El sólido el cual se formó se filtró y se lavó con metanol (300 ml). El filtrado combinado se concentró para dar una pasta blanca la cual se diluyó con isopropanol (160 ml) y acetona (40 ml) y se

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agitó a 25°C durante 1 h. El sólido luego se filtró completamente y el filtrado se concentró in vacuo para dar 3.50 g (62% rendimiento) del compuesto del título como un aceite. ^{1}HRMN 400 MHz (DMSO-d_6) δ ppm: 2.10 (3H, s, SCH_3), 2.71 (2H, t, J=6.8 Hz, CH_2), 3.66 (2H, t, J=6.8 Hz, CH_2), 4.34 (2H, s, OCH_2). EM (ESI$^+$) m/z 149 [M+H$^+$].

Intermediario 4

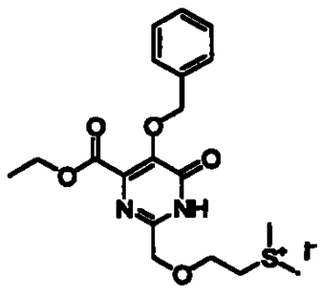


5-Benciloxi-2-{(2-(metiltio)etoxi)metil}-6-oxo-1,6-dihidropirimidina-4-carboxilato de etilo. El oxalato de dietilo (2.77 g, 19.0 mmol) y benciloxiacetato de etilo (3.69 g, 19.0 mmol) en tetrahidrofurano seco (30 ml) se trataron a 22°C con hidruro de sodio (0.83 g de un 60% de dispersión en aceite mineral, 20.9 mmol) seguido por etanol (10 µl) y la mezcla resultante se agitó a 22°C durante 18h. El tetrahidrofurano se evaporó bajo presión reducida para dar un jarabe anaranjado. Una mezcla del intermediario 3, la sal de clorohidrato de 2-(2-(metiltio)etoxi)acetamidina (3.50 g, 19.0 mmol) en una solución de etóxido de sodio (9.5 mmol, se preparó de 0.22 g de sodio en etanol 25 ml) luego se agregó todo a la vez al aducto anterior y la mezcla resultante se

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calentó a 60°C durante 3 h. Se agregó ácido acético (2 ml) y el etanol se evaporó bajo presión reducida. El residuo se diluyó con acetato de etilo, se lavó sucesivamente con bicarbonato de sodio saturado y salmuera, luego se secó sobre sulfato de magnesio anhidro y se concentró bajo presión reducida. La cromatografía en gel de sílice (se eluyó con un gradiente de acetato de etilo al 20-30% en tolueno) dio 0.728 g (10% rendimiento) del éster del título como un aceite claro. ^{1}HRMN 400 MHz ($CDCl_3$) δ (ppm): 1.33 (3H, t, J=7.1 Hz, CH_3), 2.18 (3H, s, SCH_3), 2.78 (2H, t, J=6.0 Hz, CH_2), 3.78 (2H, t, J=6.0 Hz, CH_2), 4.36 (2H, q, J=7.1 Hz, OCH_2), 4.54 (2H, s, OCH_2), 5.35 (2H, s, OCH_2), 7.37 (3H, m, aromáticos), 7.48 (2H, m, aromáticos). EMAR (ESI^+) calculado para $C_{18}H_{23}N_2O_5S$ [$M+H^+$]: 379.1328: encontrado: 379.1314.

Intermediario 5

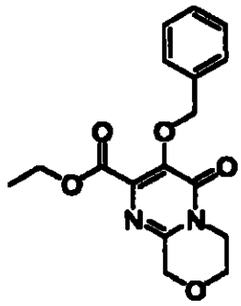


Yoduro de 5-benciloxi-2-{(2-(dimetilsulfonio)etoxi)metil}-6-oxo-1,6-dihidropirimidina-4-carboxilato de etilo. Una solución del intermediario 4, el 5-benciloxi-2-{(2-(metiltio)etoxi)metil}-6-oxo-1,6-dihidropirimidina-4-carboxilato de etilo, (0.555 g, 1.47

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mmol) en diclorometano (10 ml) se trató a 22°C con yodometano (2.0 ml, 21.5 mmol) durante 10 días. La evaporación del solvente y el reactivo en exceso dio el compuesto del título (0.76 g) como un aceite el cual se usó sin purificación adicional. ^{1}HRMN 400 MHz ($CDCl_3$) δ (ppm): 1.32 (3H, t, J=7.1 Hz, CH_3), 3.26 (6H, s, SCH_3), 4.02 (2H, m, CH_2), 4.23 (2H, m, CH_2), 4.34 (2H, q, J=7.1 Hz, OCH_2), 4.69 (2H, s, OCH_2), 5.23 (2H, s, OCH_2), 7.35-7.5 (5H, m, aromáticos). EM (ES^+) m/z 393 [M^+].

Intermediario 6

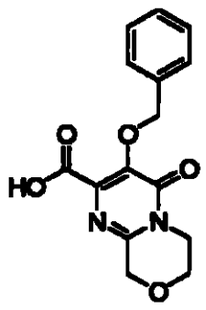


3-Benciloxi-4-oxo-4,6,7,9-tetrahidropirimido[2,1-c][1,4]oxazina-2-carboxilato de etilo. Una solución del intermediario 5, el yoduro de 5-benciloxi-2-{(2-(dimetilsulfonio)etoxi)metil}-6-oxo-1,6-dihidropirimidina-4-carboxilato de etilo, (0.76 g, 1.47 mmol) en N,N-dimetilformamida seco (10 ml) se trató a 22°C con carbonato de potasio anhidro en polvo (2.5 g) y la mezcla resultante se agitó durante 48h. El sólido luego se filtró y el filtrado se evaporó in vacuo. El residuo se diluyó con acetato de etilo, se lavó sucesivamente con ácido clorhídrico 0.1N, bicarbonato de

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sodio saturado, salmuera y se secó sobre sulfato de magnesio anhidro. La evaporación del solvente seguida por la cromatografía en gel de sílice (se eluyó con un gradiente de acetato de etilo al 20-50% en tolueno) dio 0.347 g (72% rendimiento) del éster del título como prismas blancos; p.f. 103-104°C (acetato de etilo-hexano). ^{1}HRMN 400 MHz ($CDCl_3$) δ ppm: 1.34 (3H, t, J=7.1 Hz, CH_3), 4.03 (2H, t, J=5.6 Hz, CH_2), 4.11 (2H, t, J=5.6 Hz, CH_2), 4.37 (2H, q, J=7.1 Hz, OCH_2), 4.74 (2H, s, OCH_2), 5.30 (2H, s, OCH_2), 7.38 (3H, m, aromáticos), 7.50 (2H, m, aromáticos). Análisis calculado para $C_{17}H_{18}N_2O_5$: C 61.81, H 5.49, N 8.48. Encontrado: C 61.55, H 5.53, N 8.39.

Intermediario 7

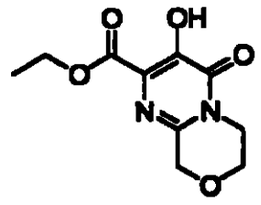


Ácido 3-(Benciloxi)-4-oxo-4,6,7,9-tetrahidropirimido[2,1-c][1,4]oxazina-2-carboxílico. Una solución del intermediario 6, el 3-(benciloxi)-4-oxo-4,6,7,9-tetrahidropirimido[2,1-c][1,4]oxazina-2-carboxilato de etilo (0.300 g, 0.91 mmol) en etanol (10 ml) se trató con 3 ml (3.0 mmol) de hidróxido de sodio 1N y se agitó a 25°C durante 30 minutos. La solución luego se acidificó con ácido clorhídrico

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1N, se extrajo con acetato de etilo, se lavó con salmuera y se secó sobre sulfato de magnesio anhidro. La evaporación del solvente dio 0.264 g (96% rendimiento) del ácido del título como cristales blancos; p.f. 171°C (acetato de etilo). ^{1}HRMN 400 MHz ($CDCl_3$) δ (ppm): 4.03 (2H, t, J=5.3 Hz, CH_2), 4.12 (2H, t, J=5.3 Hz, CH_2), 4.73 (2H, s, OCH_2), 5.53 (2H, s, OCH_2), 7.35-7.42 (3H, m, aromáticos), 7.53 (2H, m, aromáticos). Análisis calculado para $C_{15}H_{14}N_2O_5$: C 59.60, H 4.67, N 9.27. Encontrado: C 59.35, H 4.69, N 9.10.

Intermediario 8

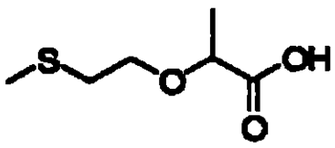


3-Hidroxi-4-oxo-4,6,7,9-tetrahidropirimido[2,1-c][1,4]oxazina-2-carboxilato de etilo. Una solución del intermediario 6, el 3-benciloxi-4-oxo-4,6,7,9-tetrahidropirimido[2,1-c][1,4]oxazina-2-carboxilato de etilo, (0.236 g, 0.714 mmol) en una mezcla de acetato de etilo (60 ml) y etanol (20 ml) se trató con 1 atm de hidrógeno a 25°C sobre 10% de paladio en carbono activado (0.10 g) durante 2.5 h para dar 0.160 g (94% rendimiento) del compuesto del título como agujas blancas; p.f. 172-174°C (acetato de etilo). ^{1}HRMN 400 MHz ($CDCl_3$) δ ppm: 1.47 (3H, t, J=7.3 Hz, CH_3), 4.08 (4H, m, 2 x CH_2), 4.54 (2H, q, J=7.3 Hz, OCH_2), 4.72 (2H, s, OCH_2),

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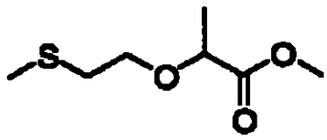
10.75 (1H, s, OH). Análisis calculado para $C_{10}H_{12}N_2O_5$: C 50.00, H 5.03, N 11.66. Encontrado: C 50.01, H 4.95, N 11.54.

Intermediario 9



Ácido 2-(2-(Metiltio)etoxi)propanoico. Además del 2-metiltioetanol (10.0 g, 0.108 mol) al hidruro de sodio (9.54 g de un 60% de dispersión en aceite mineral, 0.238 mol, se lavó dos veces con hexano) seguido por la reacción con ácido 2-bromopropionico (16.6 g, 0.108 mol) dio 13.81 g (78% rendimiento) del compuesto del título como un aceite claro; p.e. 80-90°C/0.2 torr (destilación bulbo a bulbo, temperatura del baño al aire). ^{1}HRMN 400 MHz ($CDCl_3$) δ ppm: 1.49 (3H, d, J=7.0 Hz, CH_3), 2.18 (3H, s, SCH_3), 2.76 (2H, t, J=6.6 Hz, CH_2), 3.74 (2H, t, J=6.6 Hz, CH_2), 4.07 (1H, d, J=7.0 Hz, OCH).

Intermediario 10

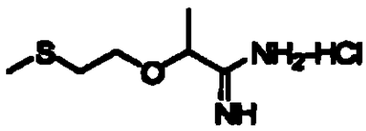


2-(2-(Metiltio)etoxi)propanoato de metilo. La reacción del intermediario 9, el ácido 2-(2-(metiltio)etoxi)propanoico, (13.70 g, 0.083 mol) con cloruro de oxalilo seguido por la reacción con metanol

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dio 14.27 g (96% rendimiento) del éster del título como un aceite claro; p.e. 55-60°C/0.3 torr (destilación bulbo a bulbo, temperatura del baño al aire). ^{1}HRMN 400 MHz ($CDCl_3$) δ ppm: 1.42 (3H, d, J=7.0 Hz, CH_3), 2.15 (3H, s, SCH_3), 2.71 (2H, t, J=6.8 Hz, CH_2), 3.56 (1H, m, CH), 3.75 (3H, s, OCH_3), 3.78 (1H, m, CH), 4.15 (1H, q, J=7.0 Hz, OCH).

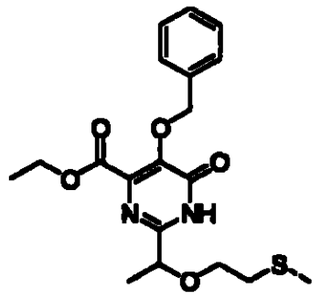
Intermediario 11



Sal de clorohidrato de 2-(2-(metiltio)etoxi)propanamidina. Intermediario 10, se agregó 2-(2-(metiltio)etoxi)propanoato de metilo, (10.00 g, 56.1 mmol) a una solución de amida de metilcloroaluminio (0.224 mol; preparado en tolueno (100 ml) de cloruro de amonio 12.36 g (0.231 mol) y 112.0 ml (0.224 mml) de una solución 2M de trimetilaluminio en tolueno} como se describe en la preparación del intermediario 3 para dar 7.70 g (69% rendimiento) del compuesto del título como un aceite. ^{1}HRMN 400 MHz (D_2O) δ ppm: 1.37 (3H, d, J=6.6 Hz, CH_3), 2.01 (3H, s, SCH_3), 2.65 (2H, t, J=5.6 Hz, CH_2), 3.64 (2H, m, CH_2), 4.30 (1H, q, J=6.6 Hz, OCH). EM (ESI^+) m/z 163 [$M+H^+$].

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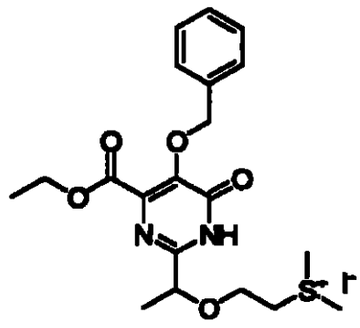
Intermediario 12



5-Benciloxi-2-(1-(2-(metiltio)etoxi)etil)-6-oxo-1,6-dihidropirimidina-4-carboxilato de etilo. El oxalato de dietilo (5.66 g, 38.7 mmol) y benciloxiacetato de etilo (7.52 g, 38.7 mmol) en tetrahidrofurano seco (60 ml) se trataron a 22°C con hidruro de sodio (1.70 g de un 60% de dispersión en aceite mineral, 42.5 mmol) y el producto condensado se hace reaccionar con una mezcla del intermediario 11, la sal de clorohidrato de 2-(2-(metiltio)etoxi)propanamidina, (7.70 g, 38.7 mmol) en una solución de etóxido de sodio (19.3 mmol, se preparó de 0.445 g de sodio) en etanol (50 ml) para dar 2.29 g (15% rendimiento) del éster del título como un aceite claro después de la cromatografía en gel de sílice. ^{1}HRMN 400 MHz ($CDCl_3$) δ ppm: 1.33 (3H, t, J=7.1 Hz, CH_3), 1.54 (3H, d, J=7.1 Hz, CH_3), 2.16 (3H, s, SCH_3), 2.7-2.8 (2H, m, CH_2), 3.54 (1H, m, CH), 3.86 (1H, m, CH), 4.37 (2H, q, J=7.1 Hz, OCH_2), 4.47 (1H, q, J=7.1 Hz, OCH), 5.34 (2H, ABq, J_{AB} = 11.0 Hz, OCH_2), 7.37 (3H, m, aromáticos), 7.49 (2H, m, aromáticos). EM (ESI^+) m/z 393 [$M+H^+$].

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Intermediario 13

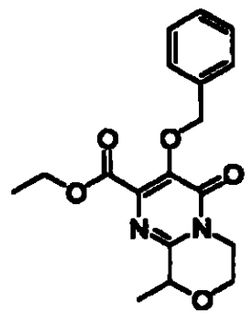


Yoduro de 5-benciloxi-2-{1-(2-(dimetilsulfonio)etoxi)etil}-6-oxo-1,6-dihidropirimidina-4-carboxilato de etilo. Una solución del intermediario 12, el 5-benciloxi-2-{1-(2-(metiltio)etoxi)etil}-6-oxo-1,6-dihidropirimidina-4-carboxilato de etilo, (1.63 g, 4.15 mmol) en diclorometano (5 ml) se trató a 22°C con yodometano (5.0 mI, 53.9 mmol) durante 5 días como se describe para la preparación del intermediario 5, para dar el compuesto del título (2.22 g) como un aceite el cual se usó sin purificación adicional.

^{1}HRMN 400 MHz ($CDCl_3$) δ ppm: 1.32 (3H, t, J=7.1 Hz, CH_3), 1.66 (3H, d, J=6.6 Hz, CH_3), 3.15 (3H, s, SCH_3), 3.32 (3H, s, SCH_3), 3.4 (1H, m, CH), 4.01 (2H, m, CH_2), 4.37 (2H, q, J=7.1 Hz, OCH_2), 4.45 (1H, m, CH), 4.63 (1H, q, J=6.6 Hz, OCH), 5.28 (2H, OCH_2), 7.38 (3H, m, aromáticos), 7.50 (2H, m, aromáticos). EM (ESI) m/z 407 [M^+].

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CHH 443

Intermediario 14



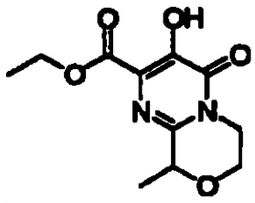
3-(Benciloxi)-9-metil-4-oxo-4,6,7,9-tetrahidropirimido[2,1-c][1,4]oxazina-2-carboxilato de etilo.

Una solución del intermediario 13, yoduro de 5-benciloxi-2-{1-(2-(dimetilsulfonio)etoxi)etil}-6-oxo-1,6-dihidropirimidina-4-carboxilato de etilo (2.22 g, 4.15 mmol) en N,N-dimetilformamida seco (30 ml) se trató a 22°C con carbonato de potasio anhidro en polvo (6 g) y se agitó durante 40 h. El sólido luego se filtró y el filtrado se concentró in vacuo. El residuo se diluyó con acetato de etilo, se lavó con ácido clorhídrico 0.1N, bicarbonato de sodio saturado y salmuera luego se secó sobre sulfato de magnesio anhidro. La evaporación del solvente y la cromatografía del residuo en gel de sílice (elución de tolueno-acetato de etilo 7:3) dio 1.0 g (70% rendimiento) del éster del título como cristales blancos; p.f. 48-50°C (acetato de etilo-hexano). ^{1}HRMN 400 MHz ($CDCl_3$) δ (ppm): 1.33 (3H, t, J=7.1 Hz, CH_3), 1.68 (3H, d, J=6.6 Hz, CH_3), 3.91 (2H, m, CH_2), 4.17-4.31 (2H, m, CH_2), 4.37 (2H, q, J=7.1 Hz, OCH_2),

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4.73 (1H, q, J=6.6 Hz, OCH), 5.30 (2H, ABq, J_{AB} = 11.0 Hz, OCH_2), 7.38 (3H, m, aromáticos), 7.50 (2H, m, aromáticos). Análisis calculado para $C_{18}H_{20}N_2O_5$: C 62.78, H 5.85, N 8.13. Encontrado: C 62.69, H 6.01, N 8.16.

Intermediario 15

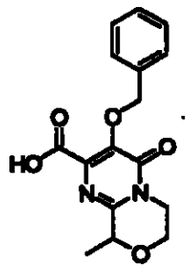


3-Hidroxi-9-metil-4-oxo-4,6,7,9-tetrahidropirimido[2,1-c][1,4]oxazina-2-carboxilato de etilo. La hidrogenólisis del intermediario 14, el 3-benciloxi-9-metil-4-oxo-4,6,7,9-tetrahidropirimido[2,1-c][1,4]oxazina-2-carboxilato de etilo, (0.610 g, 1.77 mmol) en una mezcla de acetato de etilo (75 mI) y etanol (75 ml) a 25°C durante 10% de paladio en carbono activado (0.20 g) bajo 1 atm de hidrógeno durante 2 h dio 0.430 g (95% rendimiento) del éster del título como cristales blancos; p.f. 119-121°C (acetato de etilo-hexano).

^{1}HRMN 400 MHz ($CDCl_3$) δ ppm: 1.46 (3H, t, J=7.1 Hz, CH_3), 1.67 (3H, d, J=6.6 Hz, CH_3), 3.90 (2H, m, CH_2), 4.13-4.32 (2H, m, CH_2), 4.51 (2H, m, OCH_2), 4.70 (1H, q, J=6.6 Hz, CH), 10.7 (1H, amplio, OH). Análisis calculado para $C_{11}H_{14}N_2O_5$: C 51.96, H 5.55, N 11.01. Encontrado: C 51.60, H 5.61, N 10.70.

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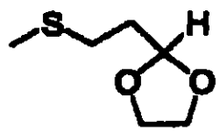
Intermediario 16



Ácido 3-Benciloxi-9-metil-4-oxo-4,6,7,9-tetrahidropirimido[2,1-c][1,4]oxazina-2-carboxílico. La saponificación del intermediario 14, el 3-benciloxi-9-metil-4-oxo-4,6,7,9-tetrahidropirimido[2,1-c][1,4]oxazina-2-carboxilato de etilo, (0.225 g, 0.65 mmol) como se describe en la preparación del intermediario 7 dio 0.198 g (96% rendimiento) del ácido del título como cristales blancos; p.f. 167-168°C (acetato de etilo-hexano). ^{1}HRMN 400 MHz ($CDCl_3$) δ ppm: 1.68 (3H, d, J=6.6 Hz, CH_3), 3.93 (2H, m, CH_2), 4.12-4.21 (1H, m, CH), 4.27-4.35 (1H, m, CH), 4.70 (1H, q, J=6.6 Hz, OCH), 5.53 (2H, ABq, J_{AB} = 11.1 Hz, OCH_2), 7.39 (3H, m, aromáticos), 7.55 (2H, m, aromáticos). EM (ESI) m/z 317 [$M+H^+$]. Análisis calculado para $C_{16}H_{16}N_2O_5$: C 60.75, H 5.10, N 8.86. Encontrado: C 60.65, H 5.05, N 8.72.

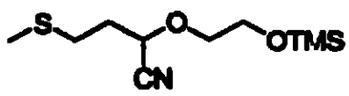
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Intermediario 17



2-(2-(Metiltio)etil)-1,3-dioxolano. Una solución de 3-(metiltio)propanal (5.2 g, 0.05 mol) y etilenglicol (3.4g. 0.055 mol) en 100 ml de benceno se trató con 300 mg de ácido p-toluensulfónico y se calentó a reflujo durante 4 horas. La solución se enfrió y se decantó. La concentración y el secado in vacuo proporcionaron el compuesto del título como un aceite amarillo ligero. ^{1}H RMN (300 MHz, $CDCl_3$) δ ppm:4.93 (1 H, t, J=4.76 Hz) 3.74-4.03 (4 H, m) 2.46-2.68 (2 H, m) 2.08 (3 H, s) 1.83-2.00 (2 H, m).

Intermediario 18

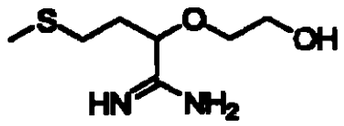


4-(Metiltio)-2-(2-(trimetilsililoxi)etoxi)butanonitrilo. Intermediario 17, el 2-(2-(metiltio)etil)-1,3-dioxolano, (2.96g, 0.02mol), trimetilsililcianuro (1.98g, 0.02 mol) y 20mg de yoduro de zinc se combinaron bajo N_2 y se agitó durante 16 horas a temperatura ambiente. La mezcla luego se concentró in vacuo para proporcionar 4.9g (aproximadamente 100% rendimiento) del compuesto del título como un aceite amarillo. ^{1}H RMN (300 MHz, $CDCl_3$) δ ppm:4.37-4.49 (1 H, m) 3.50-3.88 (4 H, m) 2.57-2.74 (2 H, m) 1.98-2.26 (5 H, m)

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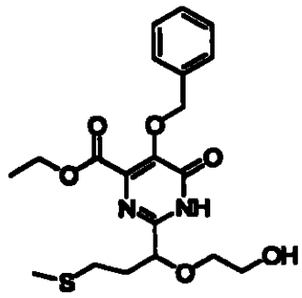
0.06-0.22 (9 H, m): CL/EM 198 (-TMS+ Na).

Intermediario 19



4-(Metiltio)-2-(2-(trimetilsililoxi)etoxi)butanamidina. Una solución del intermediario 18, el 4-(metiltio)-2-(2-(trimetilsililoxi)etoxi)butanonitrilo, (4.9g, 0.02 mol) en 30 mL de metanol se saturo con amonio. El matraz luego se selló y se calentó en un baño de aceite a 80-90°C durante 16 horas. Después de enfriarse, el matraz se abrió y la mezcla se concentró in vacuo para dar el compuesto del título en rendimiento cuantitativo esencialmente como un aceite muy viscoso. ^{1}H RMN (300 MHz, $CDCl_3$) δ ppm: 3.94-4.02 (1 H, m) 3.76-3.94 (3 H, m) 3.68-3.77 (2 H, m) 3.52-3.62 (2 H, m) 2.53-2.67 (2 H, m) 2.07 (3 H, s) 1.89-2.01 (2 H, m); CL/EM 193 (M + H).

Intermediario 20

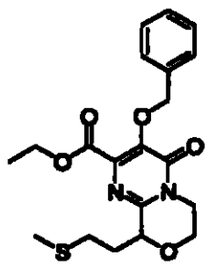


5-(Benciloxi)-2-(1-(2-hidroxietoxi)-3-(metiltio)propil}-6-oxo-1,6-dihidropirimidina-4-carboxilato de etilo. El 2-(benciloxi)acetato de etilo (7.76 g, 0.04 mol) y dietiloxalato (5.84 g, 0.04 mol)

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en 80 mL de tetrahidrofurano se trataron con un equivalente de NaH y algunas gotas de etanol. La mezcla resultante se agitó durante 1.5 horas, después el solvente se removió bajo vacío y se reemplazó con 30 mL de etanol. El intermediario 19, la 2-(2-hidroxietoxi)-4 metiltio)butanamidina en 30 mL de etanol se agregó a la mezcla seguido por NaH (60% en aceite mineral, 800mg, 0.02 mol). Esto se agitó durante 20 horas a temperatura ambiente y 3 horas a 60°C, luego se concentró bajo presión reducida. El residuo se disolvió en CH_2Cl_2 y se lavó con agua. La capa CH_2Cl_2 se secó sobre $MgSO_4$, se filtró y se concentró bajo vacío. La cromatografía en gel de sílice, se eluyó con 4:1 CH_2Cl_2; éter y acetato de etilo, dio 760 mg del compuesto del título (9% rendimiento). ^1H RMN (300 MHz, $CDCl_3$) δ ppm: 7.24-7.54 (5 H, m) 5.17-5.36 (2 H, s) 4.50 (1 H, m) 4.30 (2 H, q, J=7.32 Hz) 3.38-4.00 (4 H, m) 2.59 (2 H, m) 1.95-2.11 (5 H, m) 1.20-1.36 (3 H, t, J=7.32 Hz); CL/EM m/z 423 (M+H)

Intermediario 21

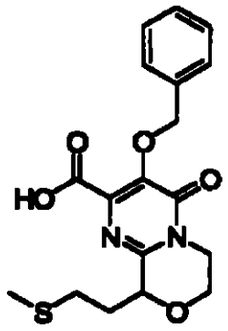


3-(Benciloxi)-9-(2-(metiltio)etil)-4-oxo-4,6,7,9-tetrahidropirimido[2,1-c][1,4]oxazina-2-carboxilato.

A una solución del intermediario 20, el 5-

(benciloxi)-2-(1-(2-hidroxietoxi)-3-(metiltio)propil)-6-oxo-1,6-dihidropirimidina-4-carboxilato de etilo, (527 mg, 1.25 mmol) y Et_3N (505mg, 5 mmol) se disolvió en 10mL de CH_2Cl_2 se agregó una solución de CH_3SO_2Cl (288mg, 2.5 mmol) se disolvió en 2 mL de CH_2Cl_2. Esto se agitó durante 20 horas, luego se concentró. El producto crudo se purificó por cromatografía en gel de sílice, usando 10:1 CH_2Cl_2: éter como eluyente, para dar el compuesto del título 265mg (52% rendimiento). (500 MHz, $CDCl_3$) δ ppm: 7.31-7.55 (5 H, m) 5.30 (2 H, s) 4.75 (1 H, dd, J=3.66 Hz) 4.32-4.40 (2 H, q, J=7.17 Hz) 4.13-4.30 (2 H, m) 3.75-3.97 (2 H, m) 2.20-2.84 (4 H, m) 2.06 (3 H, s) 1.32 (3 H, t, J=7.17 Hz); CL/EM m/z 405 (M+H).

Intermediario 22

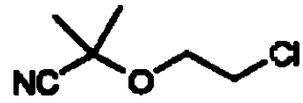


Ácido 3-(Benciloxi)-9-(2-(metiltio)etil)-4-oxo-4,6,7,9-tetrahidropirimido[2,1-c][1.4]oxazina-2-carboxílico. A una solución agitada del intermediario 21, el 3-(benciloxi)-9-(2-(metiltio)etil)-4-oxo-4,6,7,9-tetrahidropirimido[2,1-

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e][1,4]oxazina-2-carboxilato de etilo (97mg, 0.2mmol) en 3mL de tetrahidrofurano se agregó hidróxido de litio (15mg, .6mmol) en 3mL de agua. Después de 20 minutos, la mezcla de reacción se acidificó con HCl 1N y se extrajo con CH_2Cl_2. El extracto se secó sobre $MgSO_4$, se filtró y se concentró para dar 82 mg del compuesto del título (88% rendimiento). CL/EM m/e 377.

Intermediario 23

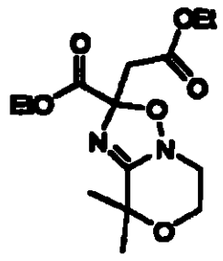


2-(2-Cloroetoxi)-2-metilpropanonitrilo. (Navalokina, R. Et al J. Org. Chem. USSR (Engl. Trans.), 1980, 16, 1382-1386.2) Ramalingam, K. US-4,864,051, 1989.). Un matraz de fondo redondo de 250 mL se cargó con $ZnCl_2$ (68.14 g, 0.5 mol) el cual luego se fundió por calentamiento bajo vacío. Después de volver a temperatura ambiente el material se colocó bajo una atmósfera de N_2. A esto se agregó acetona cianohidrina (45.66 mL, 0.5 mol) seguido por 2-cloroetanol (50.24 mL, 0.75 mol) y la mezcla se colocó en un baño de aceite precalentado (60°C). Después de agitarse durante 18-20 h a 60°C, la mezcla de reacción se enfrió, se diluyó con agua (300 mL) y se lavó con CH_2Cl_2 (5 X 100 mL). Los extractos combinados CH_2Cl_2 se secaron (Na_2SO_4), se filtraron y se concentraron bajo vacío para prcporcionar el producto crudo como líquido amarillo. La purificación se completó por

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destilación al vació (10 mm Hg) usando una columna vigreux. La fracción que ebulle entre 65-75°C se colectó para proporcionar el producto deseado como un aceite incoloro (47.1 g, 63.8% rendimiento). ^{1}H RMN (500 MHz, $CDCl_3$) δ ppm: 3.85 (2H, t, J=5.8 Hz), 3.64 (2H, t, J=5.8 Hz), 1.60 (6H, s).

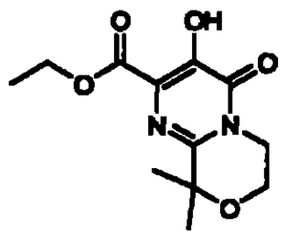
Intermediario 24



2-(2-etoxi-2-oxoetil)-8,8-dimetil-2,5,6,8-tetrahidro-[1,2,4]oxadiazolo[3,2-c][1,4]oxazina-2-carboxilato de etilo. A una solución agitada del intermediario 23, el 2-(2-cloroetoxi)-2-metilpropanonitrilo (14.7 g, 0.10 mol) y NaI (1.5 g, 10 mmol) en etanol (50 mL) se agregó a una solución acuosa (50%) de hidroxilamina (18.4 g, 0.30 mol) resultando en una reacción exotérmica. Siguiendo esto la mezcla de reacción se calentó a 80°C durante 2 h. Durante el enfriamiento a temperatura ambiente el solvente se removió. El residuo resultante se disolvió en 1:1 etanol/H_2O (100 mL) y se enfrió en una baño de hielo. A esto se agregó dietil acetilenodicarboxilato (17.6 mL, 0.110 mol) durante 10 minutos. La mezcla de reacción se permitió calentar a temperatura ambiente y se agitó durante 1

h. Siguiendo esto, se diluyó con acetato de etilo (250 mL), se lavó con H_2O (2 X 100 mL), salmuera (50 mL), se secó sobre Na_2SO_4, se filtró y se concentró para dar el producto crudo como un aceite amarillo. La cromatografía instantánea en una columna de gel de sílice, se eluyó con 20-40% de acetato de etilo/Hexanos, proporcionando el compuesto del título como un aceite amarillo pálido viscoso (15.29 g, 48.6% rendimiento). ^1H RMN (500 MHz, $CDCl_3$) δ ppm: 4.35-4.28 (2H, m), 4.18-4.12 (2H, m), 3.60-3.56 (1H, m), 3.51-3.47 (1H, m), 3.30 (1H, d, J=16.2 Hz), 2.94 (1H, d, J=16.2 Hz), 1.52 (3H, s), 1.51 (3H, s), 1.29 (3H, t, J=7.0 Hz), 1.24 (3H, t, J=7.0 Hz). CLEM (M+H) calculado para $C_{14}H_{23}N_2O_7$: 315.16; encontrado: 315.33.

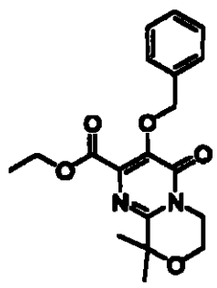
Intermediario 25



3-Hidroxi-9,9-dimetil-4-oxo-4,6,7,9-tetrahidropirimido[2,1-c][1,4]oxazina-2-carboxilato de etilo. Una solución del intermediario 24, el 2-(2-etoxi-2-oxoetil)-8,8-dimetil-2,5,6,8-tetrahidro-[1,2,4]oxadiazolo[3,2-c][1,4]oxazina-2-carboxilato de etilo (31.16 g) en 1,2,4-trimetilbenceno (200 mL) se calentó a 180°C durante 5 h. La solución de reacción oscura resultante se enfrió, luego se

concentró para dar una pasta café oscura la cual se tomó en acetato de etilo (250 mL) y se extrajo con 0.5 M de Na_2CO_3 acuoso (4 X 50 mL). La capa orgánica se descartó y la capa acuosa se acidificó por agregar cuidadosamente HCl concentrado (20 mL) antes de extraerse con CH_2Cl_2 (4 X 50 mL). Las capas combinadas CH_2Cl_2 se secaron (Na_2SO_4), se filtraron y se concentraron para dar una pasta oscura la cual se disolvió en éter (100 mL) y se permitió mantener a temperatura ambiente en un matraz abierto. El sólido café/amarillo ligero que se formó, se filtró para proporcionar el compuesto del título. El licor madre que contenía el producto se re-procesó para proporcionar material adicional (rendimiento combinado ~18-20% durante 2 etapas). ^1H RMN (500 MHz, $CDCl_3$) δ: 10.55 (1H, s), 4.45 (2H, q, J=7.0 Hz), 4.02 (4H, s), 1.61 (6H, s), 1.43 (3H, t, J=7.0 Hz). EMAR (M+H) calculado para $C_{12}H_{17}N_2O_5$: 269.1138; encontrado: 269.1149. Análisis calculado para $C_{12}H_{16}N_2O_5$: C, 53.72; H, 6.01; N, 10.44. Encontrado: C, 53.71; H, 6.04; N, 10.30.

Intermediario 26

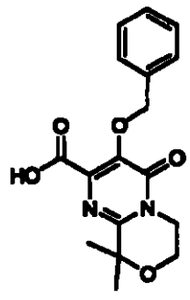


3-(Benciloxi)-9,9-dimetil-4-oxo-4,6,7,9-

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tetrahidropirimido[2,1-c][1,4]oxazina-2-carboxilato de etilo. A una solución agitada del intermediario 25, el 3-hidroxi-9,9-dimetil-4-oxo-4,6,7,9-tetrahidropirimido[2,1-c][1,4]oxazina-2-carboxilato de etilo, (2.68 g, 10 mmol) y bromuro de bencilo (1.43 mL, 12 mmol) en DMF (40 ml) se agregó K_2CO_3 (2.07 g, 20 mmol). Después de agitarse 48 h a temperatura ambiente, la mezcla de reacción se diluyó con éter (100 mL), luego se lavó con agua (3 X 30 ml) y salmuera (20 ml). La capa orgánica se secó (Na_2SO_4/carbono activado), se filtró y se concentró para dar un sólido amarillo. La trituración con hexanos/éter (9:1) proporcionó el compuesto del título como un sólido blanco opaco (2.79 g, 78% rendimiento). ^1H RMN (500 MHz, $CDCl_3$) δ ppm: 7.48-7.45 (2H, m), 7.37-7.30 (3H, m), 5.25 (2H, s), 4.33 (2H, q, J=7.3 Hz), 4.05-3.99 (4H, m), 1.62 (6H, s), 1.29 (3H, t, J=7.3 Hz). EMAR (M+H) Calculado para $C_{19}H_{23}N_2O_5$: 359.1607; Encontrado: 359.1611. Análisis calculado para $C_{19}H_{22}N_2O_5$: C, 63.67; H, 6.18; N, 7.81; encontrado: C, 63.63; H, 6.16; N, 7.78.

Intermediario 27



Ácido 3-(Benciloxi)-9,9-dimetil-4-oxo-4,6,7,9-

tetrahidropirimido[2,1-c][1,4]oxazina-2-carboxílico. Una mezcla del intermediario 26, el 3-(benciloxi)-9,9-dimetil-4-oxo-4,6,7,9-tetrahidropirimido[2,1-c][1,4]oxazina-2-carboxilato de etilo, (2.93 g, 8.2 mmol) y $LiOH \cdot H_2O$ (0.84 g, 20 mmol) en 4:1 etanol/tetrahidrofurano (50 mL) se agitó durante 2 h a temperatura ambiente luego se concentró bajo vacío. El residuo amarillo resultante se trató con HCl 1N (25 mL) proporcionando un precipitado que se filtró y se secó bajo vacío para proporcionar el compuesto del título como un polvo blanco (2.68 g, 99% rendimiento). ^1H RMN (500 MHz, $CDCl_3$) δ ppm: 7.54-7.48 (2H, m), 7.37-7.27 (3H, m), 5.44 (2H, s), 4.05-3.93 (4H, m), 1.60 (6H, s).). EMAR (M+H) calculado para $C_{17}H_{19}N_2O_5$: 331.1294; encontrado: 331.1308. Análisis calculado para $C_{17}H_{18}N_2O_5$: C, 61.81; H, 5.49; N, 8.48; encontrado: C, 61.84; H, 5.36; N, 8.25.

Intermediario 28

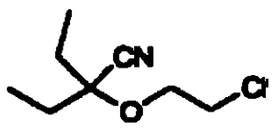


2-Etil-2-hidroxibutanonitrilo. A una solución de fofato de potasio monobásico (140 g, 1.11 mol) en agua (250 mL) se agregó 3-pentanona (75.8 g, 0.88 mol), seguido por una solución de cianuro de sodio (54 g, 1.10 mol) en agua (250 mL), y la mezcla resultante se agitó durante 3 horas.

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La mezcla se extrajo con dietil éter (1 x 250 mL, luego 2 x 100 mL) y las capas combinadas de éter se lavaron con HCl 1.0N (200 mL). La solución de éter se secó (Na_2SO_4), se filtró y se concentró in vacuo. El producto crudo se purificó por destilación al vacío (p.e. 87°C, 10 mmHg) para dar el compuesto del título (72.4 g, 3% rendimiento) como un aceite claro. ^1H RMN (500 MHz, $CDCl_3$) δ ppm: 2.71 (1H, s), 1.82 (2H, q, J=7.5 Hz), 1.76 (2H, q, J=7.5 Hz), 1.10 (6H, t, J=7.5 Hz). ^{13}C RMN (500 MHz, $CDCl_3$) δ ppm: 121.21, 73.53, 32.81, 8.27.

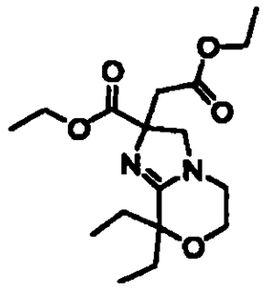
Intermediario 29



2-(2-Cloroetoxi)-2-etilbutanonitrilo. El Cloruro de zinc (68.1 g, 0.5 mol) se fundió bajo vacío como se describe en el procedimiento para la síntesis del intermediario 23. El zinc fundido se enfrió y el matraz evacuado se limpió con nitrógeno. El matraz se cargó con el intermediario 28, el 2-etil-2-hidroxibutanonitrilo, (40.3 g, 0.5 mol) y 2-cloroetanol (50.5 mL, 0.75 mmol) luego se agitaron a 60°C durante 20 horas. La mezcla de reacción se diluyó con agua (250 mL) y se extrajo con diclorometano (1 x 250 mL, 4 x 100 mL). Las capas orgánicas combinadas se secaron (sulfato de sodio), se filtraron, y se concentraron

in-vacuo. El producto crudo se purificó por destilación al vacío (p.e. 83°C, 10 mmHg) para dar el compuesto del título (52g) que contiene el intermediario 28 sin reaccionar. ^{1}H RMN (500 MHz, $CDCl_3$) δ ppm: 3.82 (2H, t, J=5.8 Hz), 3.64 (2H, t, J=5.8 Hz), 1.83 (4H, J=7.3 Hz), 1.03 (6H, t, J=7.6 Hz).

Intermediario 30

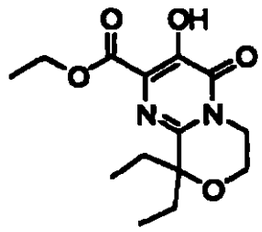


2-(2,2-Dietil-3-iminomorfolinooxi)but-2-enodioato de dietilo. Una solución de la mezcla del producto se obtuvo en la síntesis del intermediario 29, el 2-(2-cloroetoxi)-2-etilbutanonitrilo, (0.171 mol) en etanol absoluto (150 mL) se agregó gota a gota a una solución de hidroxilamina (50% de solución acuosa, 33.8 mL, 0.51 mol), carbonato de sodio (9.1 g, 0.086 mol) y yoduro de sodio (2.55 g, 0.017 mol) durante 15 minutos. La mezcla se calentó a 80°C durante 3 horas. La reacción luego se concentró hasta dar una pasta espesa y formó azeótropo bajo vacío con etanol/agua (1:1, 100 mL), agua (100 mL) y finalmente etanol (100 mL). El residuo se tomó en etanol/agua (1:1,160 mL), se enfrió (0°C), y se trató con dietil acetilendicarboxilato (30.1 mL, 0.188 mol). La

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reacción se agitó a temperatura ambiente durante 2 horas, luego se diluyó con agua (200 mL) y acetato de etilo (200 mL). La capa orgánica se separó, se lavó con agua (200 mL) y salmuera (100 mL), luego se secó (sulfato de sodio), se filtró y se concentró in-vacuo. El producto crudo se purificó por cromatografía de columna sobre gel de sílice, se eluyó con 10% hasta 40% de acetato de etilo en hexanos para proporcionar el compuesto del título (25.7 g) como un aceite amarillo.

Intermediario 31

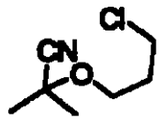


9,9-Dietil-3-hidroxi-4-oxo-4,6,7,9-tetrahidropirimido[2,1-c][1,4]oxazina-2-carboxilato de etilo. Una solución del intermediario 30, el 2-(2,2-dietil-3-iminomorfolinooxi)but-2-enodioato de etilo, (25.7 g) en 1,2,4-trimetilbenceno (100 mL) se calentó a reflujo (180°C) durante 16 horas. El solvente luego se removió in vacuo y el aceite resultante se colocó en un congelador hasta que inició la formación del cristal. La mezcla aceite y cristales se trituró con dietil éter (50 mL) y el sólido se colectó por filtración, se lavó con un volumen pequeño de éter para proporcionar el compuesto del título (9.02 g). Una segunda

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recolección (1.62 g) se obtuvo del filtrado. ^{1}H RMN (500 MHz, $CDCl_3$) δ ppm: 10.54 (1H, s), 4.44 (2H, q, J=7.0 Hz), 4.00 (4H, m), 2.00 (2H, m), 1.92 (2H, m), 1.42 (3H, t, J=7.0 Hz), 0.85 (6H, t, J=7.3 Hz). ^{13}C RMN (500 MHz, $CDCl_3$) δ ppm: 169.53, 157.82, 151.40, 147.58, 125.35, 87.27, 62.62, 58.35, 43.24, 31.06, 14.17, 7.79. EMAR $[M+H]^+$ calculado para $C_{14}H_{21}N_2O_5$: 297.14506; encontrado: 297.1464.

Intermediario 32

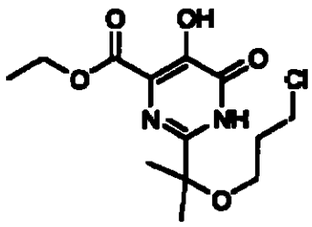


2-(3-Cloropropoxi)-2-metilpropanonitrilo. El cloruro de zinc (68.1 g, 0.5 mol) se fundió usando el procedimiento descrito para la síntesis del intermediario 23, 2-(2-cloroetoxi)-2-metilpropanonitrilo. El zinc fundido se enfrió y el matraz se limpió con nitrógeno. El matraz se cargó con cianohidrina de acetona (46 mL, 0.5 mol) y 3-cloropropanol (64 mL, 0.75 mmol) y la mezcla de reacción se agitó a 60°C durante 30 horas. La mezcla luego se diluyó con agua (200 mL) y se extrajo con diclorometano (1 x 200 mL y 3 x 100 mL). Las capas orgánicas combinadas se secaron (sulfato de sodio), se filtraron, y se concentraron in-vacuo. El producto crudo se purificó por destilación al vacío (p.e. 78-84°C, 10 mmHg) para dar el compuesto del título (41 g) como una mezcla 2:1 con residuo de 3-

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cloropropanol. ^{1}H RMN (500 MHz, $CDCl_3$) δ ppm: 3.72 (2H, t, J=5.8 Hz), 3.63 (2H, t, J=6.4 Hz), 2.04 (2H, m), 1.57 (6H, br s).

Intermediario 33



2-(2-(3-Cloropropoxi)propan-2-il)-5-hidroxi-6-oxo-1,6-dihidropirimidina-4-carboxilato de etilo. Una solución del intermediario 32, el 2-(3-cloropropoxi)-2-metilpropanonitrilo (0.186 mol) en etanol absoluto (40 mL) se agregó gota a gota hasta enfriar una solución (0°C) de hidroxilamina (50% de una solución acuosa, 17 mL, 0.278 mol), 20 mL de H_2O, carbonato de sodio (9.91 g, 0.093 mol) y yoduro de sodio (2.80 g, 0.019 mol) durante 15 minutos. (En un procedimiento alternativo, el carbonato de sodio se omitió de la mezcla). La mezcla se agitó a temperatura ambiente durante 30 min, luego se agregó hidroxilamina adicional (17 mL, 0.278 mol). La reacción luego se calentó a 80°C durante 16 horas. La mezcla se concentró hasta dar una pasta espesa la cual formó azeótropo bajo vacío con etanol/agua (1:1, 100 mL). El residuo resultante se tomó en etanol/agua (1:1, 200 mL), se enfrió (0°C), y se trató con dietil

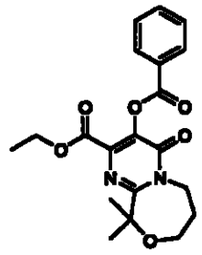
467 461

acetilendicarboxilato (30.1 mL, 0.188 mol) por adición gota a gota durante 10 minutos. La reacción se permitió agitar a temperatura ambiente durante 2.5 horas, luego se diluyó con agua (300 mL) y acetato de etilo (300 mL). La capa orgánica separada se lavó con agua (100 mL) y salmuera (100 mL), luego se secó (sulfato de sodio), se filtró y se concentró in-vacuo. El producto crudo se purificó por cromatografía de columna de gel de sílice, se eluyó con 10% hasta 40% de acetato de etilo en hexanos, para dar 21.2 g de un aceite amarillo. Una solución de este aceite (15.6 g) en 1,2,4-trimetilbenceno (300 mL) se calentó a reflujo (180°C) durante 2.5 horas después el solvente se removió in-vacuo. El aceite resultante se tomó en acetato de etilo (300 mL) y se extrajo con bicarbonato de sodio acuoso saturado (1 x 200 mL, luego 4 x 100 mL). Las capas acuosas combinadas se acidificaron hasta un pH 1-2 usando HCl 6N luego se extrajo con acetato de etilo (3 x 150 mL). Los extractos orgánicos se secaron (sulfato de sodio), se filtraron, luego se concentraron in vacuo. El aceite resultante se trituró con dietil éter (50 mL) y el sólido resultante se colectó por filtración y se lavó con una volumen pequeño de éter para proporcionar el compuesto del título (2.05 g). Una segunda gota (0.70 g) se obtuvo del filtrado. ^{1}H RMN (500 MHz, $CDCl_3$) δ ppm: 10.83 (1H, br), 10.02 (1H,

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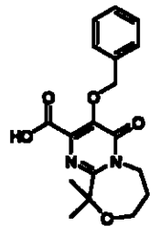
br), 4.46 (2H, q, J=7.0 Hz), 3.66 (2H, t, J=6.1 Hz), 3.58 (2H, t, J=5.8 Hz), 2.06 (2H, m), 1.55 (6H, s), 1.44 (3H, t, J=7.0 Hz).

Intermediario 34



3-(Benzoiloxi)-10,10-dimetil-4-oxo-6,7,8,10-tetrahidro-4H-pirimido[2,1-c][1,4]oxazepina-2-carboxilato de etilo. Una solución del intermediario 33, el 2-(2-(3-cloropropoxi)propan-2-il)-5-hidroxi-6-oxo-1,6-dihidropirimidina-4-carboxilato de etilo, (0.064 g, 0.2 mmol) en piridina (1 mL) se trató con anhidrido benzoico (0.047 g, 0.2 mmol) y se agitó durante 1 hr a 60°C. El solvente se removió y el residuo se tomó en N,N-dimetilformamida (1 mL) y se trató con carbonato de potasio (0.036 g, 0.2 mmol). La mezcla se agitó durante 1 hr a 80°C, y el solvente se removió para dar el compuesto del título.

Intermediario 35

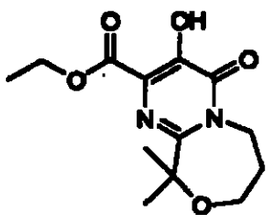


Ácido 3-(benciloxi)-10,10-dimetil-4-oxo-6,7,8,10-tetrahidro-4H-pirimido[2,1-c][1,4]oxazepina-2-carboxílico. Una suspensión del intermediario 33, el 2-(2-(3-

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cloropropoxi)propan-2-il)-5-hidroxi-6-oxo-1,6-dihidropirimidina-4-carboxilato de etilo, (0.205 g, 0.64 mmol) y carbonato de potasio anhidro (0.361 g, 2.6 mmol) en dimetilformamida anhidra (4 mL) se agitó a 60°C durante 5 horas. La mezcla de reacción se trató con bromuro de bencilo (0.122g, 0.71 mmol) y se agitó durante 16 horas. Siguiendo esto, se agregaron 2 mL de H_2O y la mezcla se agitó durante 24 horas adicionales. El solvente se removió por evaporador rotatorio y el residuo resultante se suspendió en ácido clorhídrico 0.5 N (16 mL). El producto crudo se extrajo con acetato de etilo (2 x 15 mL), luego se secó (sulfato de sodio), se filtró, y se concentró hasta secarse por un evaporador rotatorio para dar 0.299 g (Rendimiento > 100%) del compuesto del título como un sólido. CL/EM $[M+H]^+$ = 345.21.

Intermediario 36

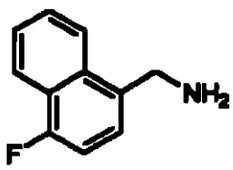


3-Hidroxi-10,10-dimetil-4-oxo-6,7,8,10-tetrahidro-4H-pirimido[2,1-c][1,4]oxazepina-2-carboxilato. Una solución del intermediario 33, el 2-(2-(3-cloropropoxi)propan-2-il)-5-hidroxi-6-oxo-1,6-dihidropirimidina-4-carboxilato de etilo,

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(7.01 g, 22 mmol) y el carbonato de potasio anhidro (9.12 g, 66 mmol) en dimetilformamida anhidro (50 mL) se agitó a 80°C durante 20 horas. El solvente se removió por evaporador rotatorio y el residuo se disolvió en agua (50 mL), hasta ajustar el pH 1 usando HCl 6.0 N. La solución se extrajo con acetato de etilo (4 x 25 mL). Las capas orgánicas combinadas se secaron (sulfato de sodio) y se filtraron. El solvente se removió por un evaporador rotatorio para dar el compuesto del título (5.53 g, Rendimiento 89%) como un sólido café: ^{1}H RMN (500 MHz, $CDCl_3$) δ ppm 10.49 (1H, s), 4.56 (2H, br), 4.43 (2H, q, J=7.2 Hz), 3.69 (2H, t, J=6.4 Hz), 1.93-1.99 (2H, m), 1.61 (6H, s), 1.42 (3H, t, J=7.2 Hz); ^{13}C RMN (126 MHz, $CDCl_3$) δ ppm 169.33, 158.30, 153.39, 148.73, 124.45, 82.85, 62.60, 60.71, 38.79, 27.67, 27.35, 14.15; EMAR (ESI) calculado para $C_{13}H_{19}N_2O_5$ (M+H) 283.1294, encontrado 283.1305.

Intermediario 37

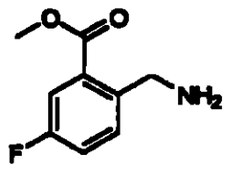


Clorohidrato de (4-fluoronaftalen-1-il)metanamina. Una solución de 1-ciano-4-fluoronaftaleno (1.05 g, 6.12 mmol) y 1.5 mL de HCl (acuoso) en etanol absoluto (50 mL) se agitó bajo una atmósfera de hidrógeno (globo) con 10% de paladio en carbono (0.20 g) durante 16 horas. El catalizador se

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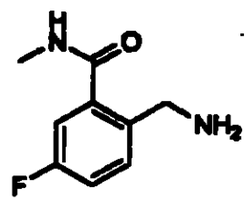
removió por filtración a través de celite, y el filtrado se concentró bajo vacío. El sólido resultante se trituró con éter y se colectó por filtración para dar el compuesto del título (0.575 g, 44% rendimiento) como un sólido blanco opaco.

Intermediario 38



Sal del ácido metil 2-(aminometil)-5-fluorobenzoato trifluoroacético. El 2-((tert-butoxicarbonil)metil)-5-fluorobenzoato de etilo, se preparó de conformidad a los métodos de la literatura, se trató con ácido trifluoroacético para proporcionar el compuesto del título. Rendimiento 100%; ^{1}H RMN (300 MHz, DMSO-d_6) δ ppm: 3.89 (3H, s) 4.32 (2H, q, J=5.61 Hz) 7.51-7.71 (2H, m) 7.78 (1H, dd, J=9.33, 2.38 Hz) 8.13 (2H, brs); CL/EM m/z 184 (M+H).

Intermediario 39

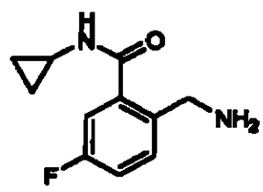


Sal del ácido 2-Aminometil-5-fluoro-N-metil-benzamida trifluoroacético. A una solución de tert-butil 4-fluoro-2-

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(metilcarbamoil)bencilcarbamato (7.70 g, 27.3 mmol; se preparó del ácido 2-bromo-5-fluorobenzoico usando los métodos de la literatura) en CH_2Cl_2 (100 mL) se agregó CF_3CO_{2H} (25 mL) y la mezcla se agitó a temperatura ambiente durante 15 minutos. Esto se concentró in vacuo y el residuo se trituró con dietil éter para obtener 8.0 g (Rendimiento 99%) del compuesto del título como un polvo blanco. ^1H RMN (300 MHz, D_2O) δ ppm: 2.93 (3 H, s) 4.20 (2 H, s) 7.35 (1 H, dt, J=8.5, 3 Hz) 7.42 (1 H, dd, J=9.0, 2.7 Hz) 7.57 (1 H, dd, J=8.4, 5.5 Hz); CL/EM m/z 183 (M+H).

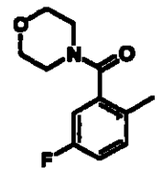
Intermediario 40



Sal del ácido 2-(Aminometil)-N-ciclopropil-5-fluorobenzamida trifluoroacético. Una solución del tert-butil 2-(ciclopropilcarbamoil)-4-fluorobencilcarbamato (130 mg, 0.42 mmol) se preparó de conformidad a los métodos de la literatura, en CH_2Cl_2 (5 mL) se agitó con ácido trifluoroacético (3 mL) a temperatura ambiente durante 10 minutos, luego se concentró in vacuo para dar 140 mg (rendimiento 100%) del compuesto del título como una espuma: ^1H RMN (DMSO-d_6, 300 MHz) δ ppm: 0.62 (2H, m, CH_2), 0.73 (2H, m, CH_2), 2.86 (1H, m, CH), 4.02-4.07 (2H, ABq, NCH_2), 7.46

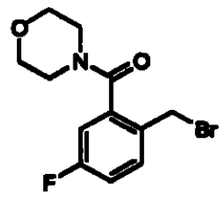
(2H, m, Ar-Hs), 7.58 (1H, m, Ar-H), 8.11 (3H, br, NH3), 8.81 (1H, d, J=4.4 Hz, NH); CL/EM m/z 209 (M+H).

Intermediario 41



(5-Fluoro-2-metilfenil)(morfolino)metanona. A una solución de morfolina (870 mg, 10 mmcl) y trietilamina (1.1 g, 10.8 mmol) en CH_2Cl_2 (15 mL) se agregó una solución de cloruro de 5-fluoro-2-metilbenzoilo (1.72 g, 10 mmol) en CH_2Cl_2 (5 mL), gota a gota y la mezcla se agitó durante 15 minutos. La mezcla luego se lavó con agua, y la fase orgánica se secó ($MgSO_4$), se filtró y se concentró para obtener 2.19 g (Rendimiento 98%) del compuesto del título como un sólido: ^1H RMN (500 MHz, $CDCl_3$) δ ppm: 2.27 (3H, s) 3.24 (2H, d, J=4 Hz), 3.58 (2H, s) 3.79 (4H, dd, J=18, 3.8 Hz), 6.88 (1H, dd, J=8.2, 2.8 Hz), 6.92-7.05 (1H, m), 7.18 (1H, dd, J=8.4, 5.3 Hz).

Intermediario 42

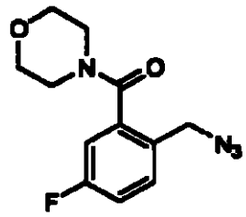


(2-(Bromometil)-5-fluorofenil)(morfolino)metanona. Una mezcla del intermediario 41, la (5-fluoro-2-metilfenil)(morfolino)metanona, (2.1 g, 9.5 mmol) y N-

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bromosuccinimida (2.0 g, 11 mmol) en CCl_4 (30 mL) se calentó a reflujo. A esta mezcla se agregó benzoilperóxido (242 mg, 1 mmol) y la mezcla se calentó a reflujo durante 2horas. Después de enfriarse, los materiales insolubles se filtraron y el filtrado se purificó por cromatografía de columna (SiO_2, 0-10% de éter en CH_2Cl_2) para dar 1.1 g (Rendimiento 38%) del compuesto del título como un aceite claro: ^1H RMN (300 MHz, $CDCl_3$) δ ppm: 3.31 (2H, t, J=4.94 Hz), 3.55-4.02 (6H, m), 4.56 (2H, dd, J=128.81, 9.51 Hz), 6.89 (1H, dd, J=8.23, 2.74 Hz), 6.96-7.12 (1H, m), 7.33-7.49 (1H, m); CL/EM m/z 302 (M+H).

Intermediario 43

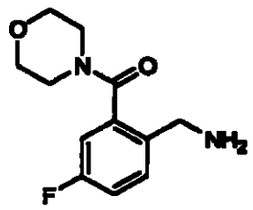


(2-(Azidometil)-5-fluorofenil)(morfolino)metanona. A una solución del intermediario 42, la (2-(bromometil)-5-fluorofenil)(morfolino)metanona, (1.0 g, 3.32 mmol) en dimetilformamida (10 mL) se agregó azida de sodio (230 mg, 3.5 mmol) y la mezcla se agitó bajo una atmósfera de nitrógeno durante 1 h. El solvente se evaporó in vacuo, y el residuo se disolvió en CH_2Cl_2, luego se lavó con agua. La fase orgánica se secó (Na_2SO_4), se filtró, se concentró y el

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residuo se purificó por cromatografía de columna (SiO_2, CH_2Cl_2) para proporcionar 770 mg (Rendimiento 88%) del compuesto del título como un aceite: ^1H RMN (300 MHz, $CDCl_3$) δ ppm: 3.27 (2H, s), 3.51-3.65 (2H, m), 3.66-3.97 (4H, m), 4.38 (2R, brs), 6.92 (1R, dd, J=8.2, 2.7 Hz), 7.07 (1R, dt, J=8.5, 3 Hz), 7.34 (1H, dd, J=8.4, 5.5 Hz); CL/EM m/z 265 (M+H).

Intermediario 44

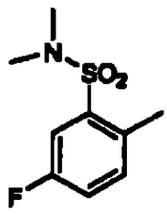


Clorohidrato de (2-(Aminometil)-5-fluorofenil)(morfolino)metanona. A una solución del intermediario 43, la (2-(azidometil)-5-fluorofenil)(morfolino)metanona, (770 mg, 2.92 mmol) en etanol (20 m) se agregó HCl 4N (1 mL) y 10% de Pd-C (100 mg), y la mezcla se hidrogenó a 1 átomo de H_2 durante 3 horas. El catalizador se removió por filtración y el filtrado se concentró. El residuo se purificó por cromatografía de columna de gel de sílice de fase inversa C18 (YMC ODS, 0-5% de CH_3CN/H_2O) para obtener 350 mg (Rendimiento 44%) del compuesto del título, clorohidrato de (2-(aminometil)-5-fluorofenil)(morfolino)-metanona como un polvo blanco: ^1H RMN (300 MHz, DMSO-d_6) δ ppm: 3.0-4.0 (8H, m), 3.78 (2H, t, J=5 Hz), 7.32 (1H, dd, J=8.8, 2.6 Hz), 7.35-7.44 (1H, t, J=8.5, 3

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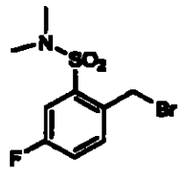
Hz), 7.75 (1H, dd, J=8.8, 5.5 Hz); CL/EM m/z 239 (M+H).

Intermediario 45



5-Fluoro-2,N,N-trimetil-bencenosulfonamida. A una solución del cloruro de 5-fluoro-2-metil-bencenosulfonilo (4.18 g, 20 mmol) en tetrahidrofurano (25 ml) se agregó gota a gota, una solución de dimetilamina en tetrahidrofurano (2M, 25 mL, 50 mmol) durante 15 minutos y la mezcla se agitó durante 5 minutos. Los materiales insolubles se filtraron y el filtrado se concentró. El residuo se purificó por cromatografía de columna (SiO_2, 5% de éter en CH_2Cl_2) para proporcionar 4.3 g (Rendimiento 90%) del compuesto del título como un aceite claro: ^1H RMN (500 MHz, $CDCl_3$) δ ppm: 2.57 (3H, s), 2.82 (3H, s), 2.82 (3H, s), 7.12-7.18 (1H, m), 7.28 (1H, dd, J=8.2, 5.5 Hz), 7.59 (1H, dd, J=8.2, 2.1 Hz); LC/MC m/z 218 (M+H).

Intermediario 46

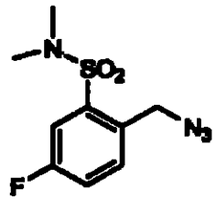


2-Bromometil-5-fluoro-N,N-dimetil-bencenosulfonamida. Bajo nitrógeno, una mezcla del intermediario 45, la 5-fluoro-

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2,N,N-trimetil-bencenosulfonamida (435 mg, 2.0 mmol) y N-bromosuccinimida (391 mg, 2.2 mmol) en CCl_4 (20 mL) se agitó a 80-90°C durante 5 minutos. A esta mezcla se agregó 2,2'-azobisisobutironitrilo (AIBN, 100 mg) y se agitó continuamente a 80-90°C durante 30 minutos. Después de enfriarse, los precipitados insolubles se filtraron y el filtrado se concentró y se purificó por cromatografía de columna (SiO_2, CH_2Cl_2) para proporcionar 440 mg (Rendimiento 74%) del compuesto del título; ^1H RMN (500 MHz, $CDCl_3$) δ ppm: 2.87 (6H, s), 4.86 (2H, s), 7.28 (1H, dd, J=8.55, 2.75 Hz), 7.61-7.65 (2H, m); LC/MC m/z 296/298 (M+H).

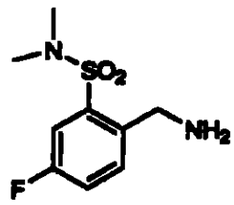
Intermediario 47



2-Azidometil-5-fluoro-N,N-dimetil-bencenosulfonamida. Una mezcla del intermediario 46, la 2-bromometil-5-fluoro-N,N-dimetil-bencenosulfonamida, (880 mg, 2.97 mmol) y azida de sodio (200 mg, 3 mmol) en dimetilformamida (4 mL) se agitó a 55-60°C durante 30 minutos después de lo cual el solvente se removió in vacuo. El residuo se dividió entre CH_2Cl_2 y agua, y la fase orgánica se lavó con agua, se secó (Na_2SO_4), se filtró y se concentró para proporcionar 670 mg (Rendimiento 87%) del compuesto del título como un aceite amarillo; ^1H RMN (500 MHz, $CDCl_3$) δ ppm: 2.84 (6H,

s), 4.78 (2H, s), 7.29-7.34 (1H, m), 7.59-7.64 (2H, m).

Intermediario 48

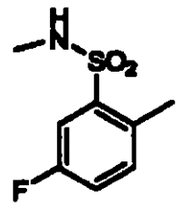


2-(Aminometil)-5-fluoro-N,N-dimetilbencenosulfonamida. A una solución del intermediario 47, la 2-azidometil-5-fluoro-N,N-dimetil-bencenosulfonamida, (660 mg, 2.6 mmol) en tetrahidrofurano (10 mL) y agua (2 mL) se agregó trifenilfosfina (740 mg, 2.8 mmol), y la mezcla se agitó bajo nitrógeno durante 1 hr. El tetrahidrofurano se evaporó in vacuo y una mezcla del residuo y HCl 6N (3 mL) en MeOH (5 mL) se calentaron a 80°C durante 20 horas. Esto se lavó con CH_2Cl_2, y la fase acuosa se basificó con NH_4OH diluido y se extrajo con CH_2Cl_2. El extracto orgánico se secó (Na_2SO_4), se filtró y se concentró para proporcionar 210 mg (0.91 mmol, rendimiento 35%) del compuesto del título; ^1H RMN (500 MHz, $CDCl_3$) δ ppm: 2.84 (6H, s), 4.10 (2H, s), 7.23-7.29 (1H, m), 7.53-7.60 (2H, m); CL/EM m/z 233 (M+H).

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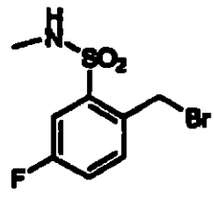
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Intermediario 49



5-Fluoro-2,N-dimetil-bencenosulfonamida. A una solución del cloruro de 5-fluoro-2-metil-bencenosulfonilo (4.18 g, 20 mmol) en acetona (20 mL) se agregó a una solución acuosa al 40% de metilamina (4.5 mL, 60 mmol) bajo nitrógeno y la mezcla se agitó durante 5 minutos. La acetona se removió in vacuo y el residuo acuoso se extrajo con CH_2Cl_2. El extracto CH_2Cl_2 se secó (Na_2SO_4), se filtró, se concentró y el residuo se purificó por cromatografía de columna (SiO_2, 10% de éter en CH_2Cl_2) para proporcionar 3.9 g (19.2 mmol, rendimiento 96%) del compuesto del título como un sólido blanco; ^1H RMN (500 MHz, $CDCl_3$) δ ppm: 2.59 (3H, s), 2.67 (3H, d, J=5.5 Hz), 4.41 (1H, brs), 7.13-7.20 (1H, m), 7.29 (1H, dd, J=8.2, 5.5 Hz), 7.69 (1H, J=8.6, 2.1 Hz); CL/EM m/z 204 (M+H).

Intermediario 50

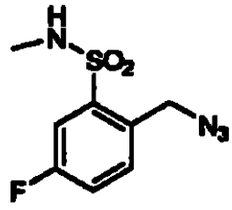


2-Bromometil-5-fluoro-N-metil-bencenosulfonamida. El

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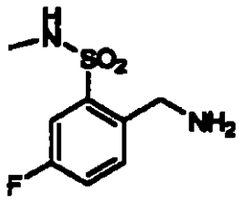
compuesto del título se preparó del intermediario 49, la 5-fluoro-2,N-dimetil-bencenosulfonamida, de conformidad al método descrito por el intermediario 46 y se purificó por cromatografía de columna (SiO_2, 5% de éter/CH_2Cl_2). ^1H RMN (500 MHz, $CDCl_3$) δ ppm: 2.64 (3H, d, J=5.19 Hz), 4.91 (1H, d, J=3.66 Hz), 4.98 (2H, s), 7.26-7.30 (1H, m), 7.54 (1H, dd, J=8.6, 5.2 Hz), 7.73 (1H, dd, J=8.4, 2.6 Hz); CL/EM m/z 282/284.

Intermediario 51



2-Azidometil-5-fluoro-N-metil-bencenosulfonamida. El compuesto del título se preparó del intermediario 50, la 2-bromometil-5-fluoro-N-metil-bencenosulfonamida, de conformidad al método descrito por el intermediario 47 y se purificó por cromatografía de columna (SiO_2, 5% de éter-CH_2Cl_2). ^1H RMN (500 MHz, $CDCl_3$) δ ppm: 2.65 (3H, d, J=5.19 Hz), 4.81 (2H, s), 4.86 (1H, d, J=4.6 Hz), 7.27-7.33 (1H, m), 7.49 (1H, dd, J=8.2, 5.2 Hz), 7.76 (1H, dd, J=8.2, 2.8 Hz).

Intermediario 52

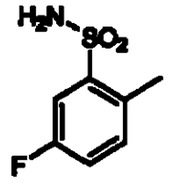


Clorohidrato de 2-(Aminometil)-5-fluoro-N-

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metilbencenosulfonamida. A una solución del intermediario 51, la 2-azidometil-5-fluoro-N-metil-bencenosulfonamida, (560 mg, 2.3 mmol) en etanol (10 ml) se agregó HCl 6N (1 mL) y 10% de Pd-C (100 mg) y la mezcla se hidrogenó con 1 atm de H_2 durante 14 horas. El catalizador se removió por filtración a través de celite y el filtrado se concentró in vacuo para proporcionar 630 mg (Rendimiento >100%) del compuesto del título. ^{1}H RMN (500 MHz, DMSO-D_6) δ ppm: 4.36 (2H, d, J=5.2 Hz), 7.63-7.70 (2H, m), 7.77-7.83 (1H, m), 8.11 (1H, d, J=4.9 Hz), 8.41 (3H, s); CL/EM m/z 219 (M+H).

Intermediario 53

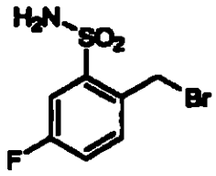


5-Fluoro-2-metil-bencenosulfonamida. A una solución de cloruro de 5-fluoro-2-metil-bencenosulfonilo (4.18 g, 20 mmol) en acetona (20 mL) se agregó gota a gota, se concentró NH_4OH (3 mL) y la mezcla resultante se agitó durante 5 minutos. La acetona se removió in vacuo y los precipitados se filtraron, se lavaron completamente con agua y se secó in vacuo para proporcionar 3.7 g (Rendimiento 98%) del compuesto del título como un sólido blanco;

^{1}H RMN (500 MHz, DMSO-D_6) δ ppm: 2.55 (3H, s), 7.33-7.40 (1H, m), 7.40-7.46 (1H, m), 7.54 (2H, s), 7.59 (1H, dd, J=9.2, 2.7 Hz); CL/EM m/z 190 (M+H).

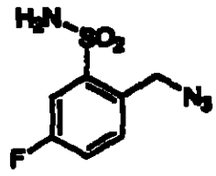
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Intermediario 54



2-Bromometil-5-fluoro-bencenosulfonamida. El compuesto del título puede prepararse a partir del intermediario 53, la 5-fluoro-2-metil-bencenosulfonamida, de conformidad al método descrito por el intermediario 46, y se purificó por cromatografía de columna (SiO_2, 5% de éter/CH_2Cl_2). ^1H RMN (500 MHz, $CDCl_3$) δ ppm: 5.01 (2H, s), 5.16 (2H, brs), 7.25-7.31 (1H, m), 7.53 (1H, dd, J=8.5, 5.2 Hz), 7.80 (1H, dd, J=8.5, 2.7 Hz). CL/EM m/z 268/270 (M+H).

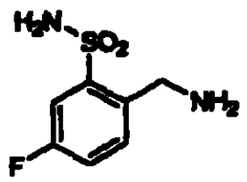
Intermediario 55



2-Azidometil-5-fluoro-N-metil-bencenosulfonamida. El compuesto del título puede ser preparado a partir del intermediario 54, la 2-bromometil-5-fluoro-bencenosulfonamida, de conformidad al método descrito por la preparación del intermediario 47. ^1H RMN (300 MHz, $CDCl_3$) δ ppm: 4.82 (2H, s), 5.18 (2H, s), 7.27 (1H, m), 7.45 (1H, dd, J=8.4, 5.5 Hz), 7.79 (1H, dd, J=8.4, 2.6 Hz). CL/EM m/z 253

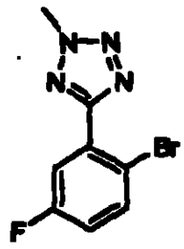
(M+Na).

Intermediario 56



Clorohidrato de 2-(Aminometil)-5-fluorobencenosulfonamida. El compuesto del título puede ser preparado a partir del intermediario 55, 2-azidometil-5-fluoro-N-metil-bencenosulfonamida, de conformidad al método descrito por la preparación del intermediario 48. ^{1}H RMN (500 MHz, DMSO-D_6) δ ppm: 4.05 (2H, s), 5.05 (3H, br), 7.44 (1H, dt, J=8.5, 3Hz), 7.58 (1H, dd, J=9.2, 2.7 Hz), 7.66 (1H, dd, J=8.5, 5.5 Hz). CL/EM m/z 205 (M+H).

Intermediario 57

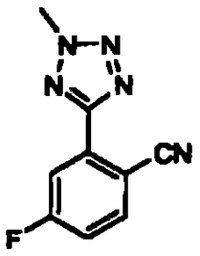


5-(2-Bromo-5-fluoro-fenil)-2-metil-2H-tetrazol. Una mezcla del 5-(2-bromo-5-fluoro-fenil)-1H-tetrazol (1.0 g, 4.12 mmol), yodometano (1.12 g, 10 mmol) y carbonato de potasio (1.5 g) en dimetilformamida (5 ml) se agitó a temperatura ambiente durante 16 horas, luego se concentró in vacuo. El residuo se purificó por cromatografía de columna (SiO_2, CH_2Cl_2) para proporcionar 650

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mg (Rendimiento 61%) del compuesto del título como un polvo blanco. ^{1}H RMN (500 MHz, $CDCl_3$) δ ppm: 4.45 (3H, s), 7.03-7.11 (1H, m), 7.63 (1H, dd, J=8.9, 3.1 Hz), 7.69 (1H, dd, J=8.9, 5.5 Hz); ^{13}C RMN (126 MHz, $CDCl_3$) δ ppm: 39.86, 116.28, 118.66, 118.76, 130.13, 135.73, 161.74, 163.53; CL/EM m/z 257/259.

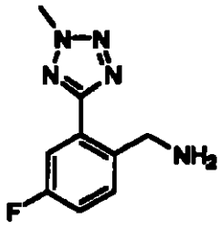
Intermediario 58



4-Fluoro-2-(2-metil-2H-tetrazol-5-il)-benzonitrilo. Una mezcla del intermediario 57, el 5-(2-bromo-5-fluoro-fenil)-2-metil-2H-tetrazol (650 mg, 2.53 mmol) y CuCN (224 mg, 2.5 mmol) en dimetilformamida (4 mL) se colocó en un tubo sellado y se calentó a 100-110°C durante 20 horas. Después de enfriarse, el material insoluble se filtró, y el filtrado se concentró in vacuo. El residuo se disolvió en CH_2Cl_2, se lavó con HCl 4N acuoso y NH_4OH diluido, luego se secó ($MgSO_4$), se filtró y se concentró.

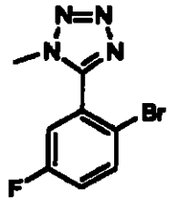
El residuo sólido se purificó por cromatografía de columna (SiO_2, CH_2Cl_2) para obtener 375 mg (Rendimiento 73%) del compuesto del título como un sólido blanco opaco; ^{1}H RMN (500 MHz, $CDCl_3$) δ ppm: 4.48 (3H, s), 7.29 (1H, dd, J=7.6, 2.8 Hz), 7.85 (1H, dd, J=8.6, 5.2 Hz), 8.00 (1H, dd, J=9.0, 2.6 Hz); CL/EM m/z 204.

Intermediario 59



Clorohidrato de (4-Fluoro-2-(2-metil-2H-tetrazol-5-il)fenil)metanamina. Una solución del intermediario 58, el 4-fluoro-2-(2-metil-2H-tetrazol-5-il)-benzonitrilo, (330 mg, 1.62 mmol) en etanol (15 mL) se mezcló con HCl 6N (1 mL) y 10% de Pd-C (200 mg) bajo nitrógeno. La mezcla luego se agitó bajo hidrógeno (1 átomo) durante 3 horas. Después de remover el catalizador, el filtrado se concentró in vacuo para proporcionar 360 mg (Rendimiento 91 %) del compuesto del título como un sólido blanco opaco; ^{1}H RMN (500 MHz, DMSO-D^6) δ ppm: 4.42 (2H, d, J=2.75 Hz), 4.49 (3H, s), 7.48-7.56 (1H, m), 7.78 (1H, dd, J=8.7, 5.7 Hz), 7.86 (1H, dd, J=9.8, 2.8 Hz), 8.45 (3H, s); CL/EM m/z 208.

Intermediario 60

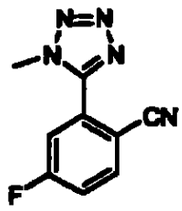


5-(2-Bromo-5-fluoro-fenil)-1-metil-2H-tetrazol. Una mezcla del 5-(2-bromo-5-fluoro-fenil)-1H-tetrazol (1.0 g, 4.12 mmol), yodometano (1.12 g, 10 mmol) y carbonato de

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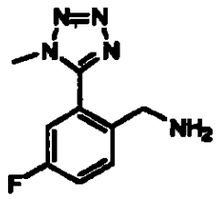
potasi (1.5 g) en dimetilformamida (5 mL) se agitó a temperatura ambiente durante 16 horas, luego se concentró in vacuo. El residuo se purificó por cromatografía de columna (SiO_2, CH_2Cl_2) para proporcionar 350 mg (Rendimiento 33%) del compuesto del título cristales blancos. ^1H RMN (500 MHz, $CDCl_3$) δ ppm: 4.00 (3H, s), 7.18-7.25 (2H, m), 7.72 (1H, dd, J=8.4, 5.0 Hz); ^{13}C RMN (126 MHz, $CDCl_3$) δ ppm: 34.59, 117.73, 119.58, 120.43, 127.57, 135.11, 153.43, 161.69. CL/EM m/z 257/259.

Intermediario 61



4-Fluoro-2-(1-metil-2H-tetrazol-5-il)-benzonitrilo. ^1H RMN (300 MHz, $CDCl_3$) δ ppm: 4.13 (3H, s), 7.38-7.49 (2H, m), 7.86-7.97 (1H, m); CL/EM m/z 204 (M+H).

Intermediario 62

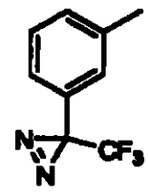


Clorohidrato de (4-Fluoro-2-(1-metil-2H-tetrazol-5-il)fenil)metanamina. ^1H RMN (500 MHz, DMSO-D_6) δ ppm: 4.05 (2H, s), 4.09 (3H, s), 7.58-7.67 (1H, m), 7.77 (1H, dd,

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J=9.3, 2.6 Hz), 7.87 (1H, dd, J=8.7, 5.7 Hz), 8.38 (3H, s); CL/EM m/z 208.

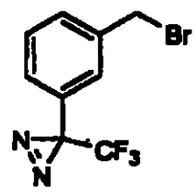
Intermediario 63



3-m-Tolil-3-trifluorometil-3H-diazirina. A una solución agitada fría de 3-m-tolil-3-trifluorometil-diaziridina (2.0 g, 10 mmol. Se preparó usando los métodos descritos en Doucet-Personeni C. et al., J. Med. Chem., 2001, 44, 3203 y Nassal, M. Liebigs Ann. Chem. 1983, 1510-1523 ó en Stromgaard, K et al., J. Med. Chem., 2002, 45, 4038-46) en etanol (20 mL) se agregó trietilamina (1.5 g, 15 mmol). A esta mezcla se agregó tert-butil hipocloruro (3.25 g, 30 mmol), y la mezcla se agitó durante 5 minutos. Esta mezcla se vació en 10% de sulfito de sodio acuoso (100 mL), y se extrajo con éter. El extracto de éter se lavó con salmuera, se secó ($MgSO_4$), se filtró y se concentró. El residuo se purificó por cromatografía de columna (SiO_2, pentano) para proporcionar 1.6 g (Rendimiento 80%) del compuesto del título. ^1H RMN (300 MHz, $CDCl_3$) δ ppm: 2.33 (3H, s), 6.90-7.03 (2H, m), 7.15-7.31 (2 H, m).

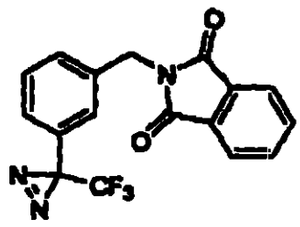
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Intermediario 64



3-(3-Bromometil-fenil)-3-trifluorometil-3H-diazirina. A una solución del intermediario 63, la 3-m-tolil-3-trifluorometil-3H-diazirina, (200 mg, 1 mmol) en CCl_4 (4 mL) se agregó N-bromosuccinimida (200 mg, 1.1 mmol, se recristalizó de agua), y la mezcla agitada se calentó a 85°C. A esto se agregó AIBN (50 mg) y la mezcla se calentó a reflujo durante 2.5 horas adicionales. Después de enfriarse, la mezcla se purificó por cromatografía de columna (SiO1, pentano) para proporcionar 150 mg (Rendimiento 54%) del compuesto del título como un aceite claro. ^1H RMN (300 MHz, $CDCl_3$) δ ppm: 4.42 (2H, s), 7.10-7.17 (2H, m), 7.31-7.45 (2 H, m).

Intermediario 65

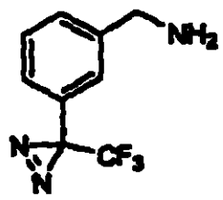


2-[3-(3-Trifluorometil-diaziridin-3-il)-bencil]-isoindol-1,3-diona. Una mezcla del intermediario 64, la 3-(3-bromometil-fenil)-3-trifluorometil-3H-diazirina, (140 mg, 0.5 mmol) y

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ftalamida de potasio (95 mg, 0.5 mmol) en dimetilformamida (1.5 mL) se agitó a temperatura ambiente durante 3 horas. La dimetilformamida se removió in vacuo. El residuo se extrajo con CH_2Cl_2, se lavó con agua, luego se secó (Na_2SO_4), se filtró y se concentró. El residuo resultante se purificó por cromatografía de columna (SiO_2, 1:1 CH_2Cl_2/pentano) para proporcionar 140 mg (Rendimiento 82%) del compuesto del título como un sólido; ^1H RMN (300 MHz, $CDCl_3$) δ ppm: 4.80 (2H, s), 7.09-7.21 (2H, m), 7.32 (1H, t, J=7.9 Hz), 7.41-7.49 (2H, m), 7.66-7.71 (2H, m), 7.81-7.85 (2H, m); CL/EM m/z 346 (M+H).

Intermediario 66



(3-(3-(Trifluorometil)diaziridin-3-il)fenil)metanamina.

Una solución agitada del intermediario 65, la 2-[3-(3-trifluorometil-diaziridin-3-il)-bencil]-isoindol-1,3-diona, (150 mg, 0.43 mmol) en etanol (2 mL) se trató con hidrato de hidrazina (0.4 mL) a temperatura ambiente y la solución se agitó durante 3.5 horas. Después de remover el etanol in vacuo, el residuo se dividió entre CH_2Cl_2 y agua. La fase acuosa se acidificó con HCl diluido y se lavó con CH_2Cl_2. La fase acuosa se basificó con NaOH diluido, y se extrajo con CH_2Cl_2. El extracto orgánico se secó ($MgSO_4$), se filtró, y se concentró

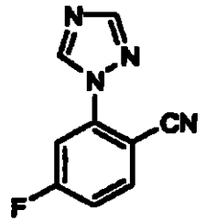
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para obtener 50 mg (Rendimiento 54%) de (3-(3-(trifluorometil)diaziridin-3-il)fenil)metanamina y (3-(3-(trifluorometil)-3H-diazirin-3-il)fenil)metanamina como una mezcla 1:1; ^{1}H RMN (300 MHz, $CDCl_3$) δ ppm: 3.85 (2H, s), 3.88 (2H, s), 7.08 (2H, s), 7.31-7.40 (4H, m), 7.43-7.50 (1H, m, J=6.2 Hz), 7.54 (1H, s); CL/EM m/z 216 (M+H para la diazirina) y 218 (M+H para la diaziridina).

Intermediarios 67-68

A una solución de 2,4-difluorobenzonitrilo (10 g, 72 mmol) se disolvió en tetrahidrofurano (20 ml), y se agregó dimetilformamida (40 ml), sal de sodio 1,2,4-triazol (6.3 g, 70 mmol) y la mezcla se agitó a 90°C durante 3 h después de lo cual la mezcla se filtró y el solvente se removió. El residuo resultante se adsorbió en gel de sílice y los intermediarios 67 y 68 se separaron por cromatografía instantánea, se eluyó con 0% hasta 30% de acetato de etilo/hexanos.

Intermediario 67

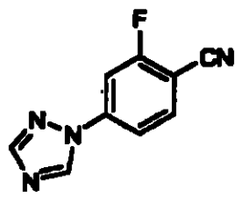


4-Fluoro-2-(1H-1,2,4-triazol-1-il)benzonitrilo. Agujas incoloras (2.46 g, 18% rendimiento). ^{1}H RMN (500 MHz, $CDCl_3$) δ: 8.89 (1H, s), 8.19 (1H, s), 7.85 (1H, dd, J=8.7, 5.6 Hz), 7.60 (1H, dd, J=8.8, 2.4 Hz), 7.28-7.24 (1H, m). CLEM (M+H)

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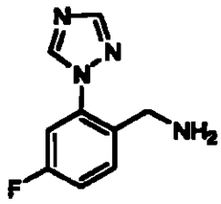
calculado para $C_9H_6N_4F$: 189.05; encontrado: 189.13.

Intermediario 68



4-(1H-1,2,4-Triazol-1-il)-2-fluorobenzonitrilo. Sólido blanco (0.746 g, 6% rendimiento) ^1H RMN (500 MHz, $CDCl_3$) δ: 8.66 (1H, s), 8.15 (1H, s), 7.79 (1H, dd, J=8.5, 8.7 Hz), 7.69 (1H, dd, J=9.5, 1.8 Hz), 7.65-7.63 (1H, m). CLEM (M+H) calculado para $C_9H_6N_4F$: 189.05; encontrado: 189.13.

Intermediario 69

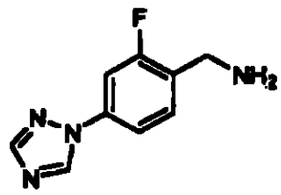


Clorohidrato de (4-Fluoro-2-(1H-1,2,4-triazol-1-il)fenil)metanamina). Intermediario 67, el 4-fluoro-2-(1H-1,2,4-triazol-1-il)benzonitrilo, (2.46 g, 13.13 mmol) se disolvió en etanol caliente (150 mL). A esto se agregó HCl 1N (15 mL) seguido por 10% de Pd-C (200 mg). La mezcla se trató con H_2 a 55 psi (3.8665 kg/cm^2) durante 4 h en un agitador Parr, luego se filtró durante Celite y el solvente se removió bajo presión reducida. El residuo resultante se dividió entre acetato de etilo

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y agua. La fase acuosa se separó y se liofilizó para proporcionar el compuesto del título como un polvo blanco (2.96 g, 99% rendimiento). ^{1}H RMN (500 MHz, CD_3OD) δ ppm: 9.51 (1H, s), 8.63 (1H, s), 7.85 (1H, dd, J=8.5, 5.8 Hz), 7.68 (1H, dd, J=8.8, 2.4 Hz), 7.49 (1H, td, J=8.3, 2.4 Hz), 4.20 (2H, s). CLEM (M+H) calculado para $C_9H_{10}N_4F$: 193.08; encontrado: 193.16.

Intermediario 70

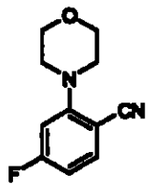


Clorohidrato de (2-Fluoro-4-(1H-1,2,4-triazol-1-il)fenil)metanamina. El compuesto del título puede ser preparado a partir del intermediario 68 de conformidad al método descrito por la síntesis del intermediario 69. Polvo blanco (79% rendimiento). ^{1}H RMN (500 MHz, CD_3OD) δ ppm: 9.25 (1H, s), 8.46 (1H, s), 7.80 (1H, dd, J=8.6, 5.8 Hz), 7.64 (1H, dd, J=8.8, 2.4 Hz), 7.44 (1H, dd, J=8.3, 2.6 Hz), 4.17 (2H, s). CLEM (M+H) calculado para $C_9H_{10}N_4F$: 193.08; encontrado: 193.16.

Intermediarios 71-74

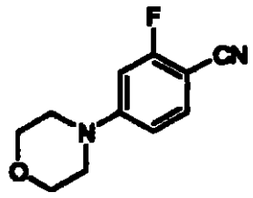
Los intermediarios 71-74 se prepararon usando el procedimiento descrito para la síntesis del intermediario 67-70.

Intermediario 71



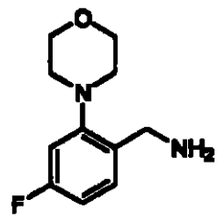
4-Fluoro-2-morfolinobenzonitrilo. ^{1}H RMN (500 MHz, $CDCl_3$) δ ppm: 7.55 (1H, dd, J=8.5, 6.4 Hz), 6.71 (1H, dd, J=8.1, 2.3 Hz), 6.67 (1H, dd, J=11.0, 2.4 Hz), 3.88 (4H, t, J=4.6 Hz), 3.22 (4H, t, J=4.6 Hz). CLEM (M+H) calculado para $C_{11}H_{12}N_2OF$: 207.09; encontrado: 207.19.

Intermediario 72



4-Morfolino-2-fluorobenzonitrilo. ^{1}H RMN (500 MHz, $CDCl_3$) δ ppm: 7.42 (1H, dd, J=8.8, 7.6 Hz), 6.63 (1H, dd, J=8.8, 2.4 Hz), 6.56 (1H, dd, J=12.8, 2.4 Hz), 3.84 (4H, t, J=4.9 Hz), 3.28 (4H, t, J=4.9 Hz). CLEM (M+H) calculado para $C_{11}H_{12}N_2OF$: 207.09; encontrado: 207.19.

Intermediario 73

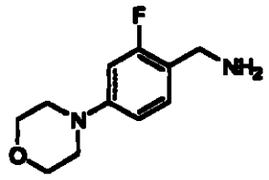


Clorohidrato de (4-Fluoro-2-morfolinofenil)metanamina. ^{1}H RMN (500 MHz, $CDCl_3$) δ ppm: 7.54 (1H, t, J=7.3 Hz), 7.20

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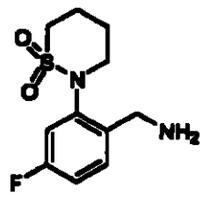
(1H, dd, J=10.5, 2.0 Hz), 7.05-7.02 (1H, m), 4.28 (2H, s), 3.93 (4H, bs), 3.03 (4H, bs). CLEM (M+H) calculado para $C_{11}H_{16}N_2OF$: 211.12; encontrado: 211.23.

Intermediario 74



Clorohidrato de (2-Fluoro-4-morfolinofenil)metanamina. ^{1}H RMN (500 MHz, CD_3OD) δ ppm: 7.73 (1H, t, J=8.2 Hz), 7.62 (1H, d, J=7.6 Hz), 7.58 (1H, d, J=8.2 Hz), 4.26 (2H, s), 4.11 (4H, t, J=4.4 Hz), 3.65 (4H, t, J=4.4 Hz). CLEM (M+H) calculado para $C_{11}H_{16}N_2OF$: 211.12; encontrado: 211.23.

Intermediario 75

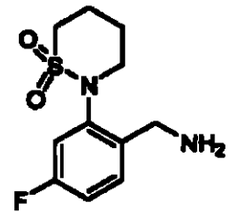


4-Fluoro-2-(1,1-dioxo-1λ^6-[1,2]tiazinan-2-il)benzonitrilo. A una mezcla de 2,4-difluorobenzonitrilo (10.0 g, 72 mmol) y 1,1-dioxo-1λ^6-[1,2]tiazin-2-ano (8.84 g, 65.4 mmol) en 1:1 tetrahidrofurano/dimetilformamida (40 ml) se agregó carbonato de potasio (9.0 g, 65.4 mmol). La mezcla se agitó a 90°C durante 18 h luego se filtró y se concentró. El residuo se purificó por cromatografía

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instantánea (SiO_2), se eluyó con 10%-50% de acetato de etilo/hexanos seguido por la recristalización de acetato de etilo/hexano caliente para dar el compuesto del título como agujas blancas (0.537 g, 3% rendimiento). ^1H RMN (500 MHz, CD_3OD) δ ppm: 7.70 (1H, dd, J=8.8, 5.8 Hz), 7.30 (1H, dd, J=8.8, 2.4 Hz), 7.15-7.12 (1H, m), 3.27 (2H, t, J=5.3 Hz), 3.33 (2H, t, J=6.1 Hz), 2.40-2.35 (2H, m), 2.05-2.01 (2H, m). CLEM (M+H) calculado para $C_{11}H_{16}N_2OF$: 255.06; encontrado: 255.19.

Intermediario 75



Clorohidrato de (4-Fluoro-2-(1,1-dioxo-1λ⁶-[1,2]tiazinan-2-il)fenil)metanamina. Intermediario 75, el 4-fluoro-2-(1,1-dioxo-1λ⁶-[1,2]tiazinan-2-il)benzonitrilo (1.37 g, 5.4 mmol) se disolvió en etanol (120 mL). A esto se agregó HCl 1N (20 mL) y una cantidad catalítica de 10% de Pd-c. La mezcla se agitó bajo hidrógeno a 55 psi (3.8665 kg/cm^2) durante 4 h luego se filtró a través de celite y se concentró para dar el compuesto del título como un sólido blanco (1.58 g, 100% rendimiento). ^1H-RMN (300 MHz, CD_3OD) δ ppm: 7.61 (1H, dd, J=8.4, 6.2 Hz), 7.38 (1H, dd, J=9.3, 2.7 Hz), 7.28 (1H, td, J=8.2, 2,7 Hz), 7.26 (2H, dd, J=21.4, 13.7 Hz), 3.93-3.84

(1H, m), 3.50-3.41 (3H, m), 2.40-2.31 (2H, m), 2.04-1.96 (2H, m). CLEM $[M+H]^+$ calculado para $C_{11}H_{16}N_2O_6FS$: 259.087; encontrado: 259.24.

Intermediarios 77-78

A una solución de 1H-1,2,3-triazol (3.5 g, 50.7 mmol) en tetrahidrofurano (10 mL) y dimetilformamida (20 mL) se agregó en porciones NaH (1.3 g, 51 mmol, 95%). La mezcla se agitó a temperatura ambiente durante 30 minutos, se agregó 2,4-difluorobenzonitrilo (7.6 g, 55 mmol) y la mezcla se agitó a 85°C durante 3 h. La mezcla blanca se concentró y se purificó por cromatografía instantánea y se eluyó con 0% hasta 10% de acetato de etilo/hexanos para dar los intermediarios 77 y 78.

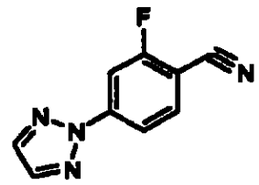
Intermediario 77



4-Fluoro-2-1,2,3-triazol-2-il-benzonitrilo. Agujas blancas (0.34 g, 3% rendimiento). ^{1}H-RMN (300 MHz, $CDCl_3$) δ ppm: 7.92 (2H, s), 7.88-7.79 (2H, m), 7.19-7.12 (1H, m). CLEM $[M+H]^+$ calculado para $C_9H_6N_4F$: 189.05; encontrado: 189.12.

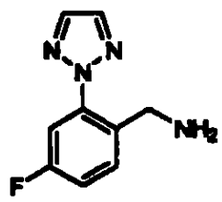
491

Intermediario 78



2-Fluoro-4-1,2,3-triazol-2-il-benzonitrilo. Sólido blanco (0.097 g, 1% rendimiento). ^{1}H-RMN (300 MHz, $CDCl_3$) δ ppm: 8.03-7.95 (2H, m), 7.86 (2H, s), 7.74-7.69 (1H, m).

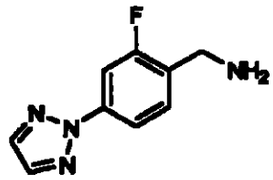
Intermediario 79



Clorohidrato de 4-Fluoro-2-1,2,3-triazol-2-il-bencilamina. Intermediario 77, el 4-fluoro-2-1,2,3-triazol-2-il-benzonitrilo, (0.34 g, 1.8 mmol) se disolvió en etanol (50 ml). Se agregó HCl 1N (10 ml) a lo largo con una cantidad catalítica de 10% de Pd-C. La mezcla se agitó bajo H_2 a 55 psi (3.8665 kg/cm^2) durante 4 h después de lo cual esto se filtró a través de Celite y se concentró para dar el compuesto del título como la sal de HCl correspondiente. Sólido amarillo (0.402 g, 98% rendimiento). ^{1}H-RMN (500 MHz, CD_3OD) δ ppm: 8.13 (2H, s), 7.87 (1H, dd, J=4.9, 2.6 Hz), 7.73 (1H, dd, J=4.9, 2.6 Hz), 7.34 (1H, td, J=8.2, 2.7 Hz), 4.35 (2H, s). CLEM $[M+H]^+$ calculado para $C_9H_{10}N_4F$: 193.08;

encontrado: 193.16.

Intermediario 80



(2-Fluoro-4-(2H-1,2,3-triazol-2-il)fenil)metanamina: El compuesto del título puede ser preparado a partir del intermediario 78, el 2-fluoro-4-1,2,3-triazol-2-il-benzonitrilo, de conformidad al procedimiento proporcionado por el intermediario 79. ^{1}H-RMN (300 MHz, CD_3OD) δ ppm: 8.05-7.96 (2H, m), 8.00 (2H, s), 7.68 (1H, t, J=8.2 Hz), 4.26 (2H, s). CLEM $[M+H]^+$ calculado para $C_9H_{10}N_4F$: 193.08; encontrado: 193.14.

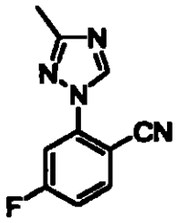
Intermediarios 81-84

Una solución de 2,4-difluorobenzonitrilo (7.07 g, 50.8 mmol) y 3-metil-1H-1,2,4-triazol (4.22 g, 50.8 mmol) en N,N-dimetilformamida (45 ml) se trató con carbonato de potasio anhidro en polvo (10 g) y la mezcla resultante se agitó a 22°C durante 18h. El sólido luego se filtró y el filtrado se concentró in vacuo. El residuo se diluyó con acetato de etilo, se lavó con agua y salmuera, luego se secó sobre sulfato de magnesio anhidro y se concentró. La mezcla resultante se purificó por una combinación de la cromatografía en gel de sílice (gradiente de elución de acetato de etilo en hexano) y fase de gel de sílice inversa

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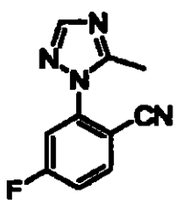
para proporcionar los intermediarios 81-84.

Intermediario 81



4Fluoro-2-(3-metil-1H-1,2,4-triazol-1-il)benzonitrilo. Cristales blancos (acetato de etilo-hexano); p.f. 117-118°C. ^{1}HRMN 400 MHz ($CDCl_3$) δ ppm: 2.54 (3H, s, CH_3), 7.24 (1H, m, CH), 7.62 (1H, dd, J=2.5 Hz y J=9.1 Hz, CH), 7.84 (1H, dd, J=5.6 Hz y J=8.6 Hz, CH), 8.82 (1H, s, CH). Análisis calculado para $C_{10}H_7FN_4$: C 59.40, H 3.49, N 27.71; Encontrado: C 59.25, H 3.32, N 27.81.

Intermediario 82

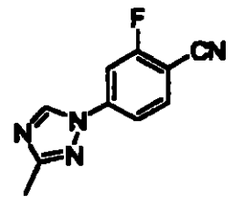


4-Fluoro-2-(5-metil-1H-1,2,4-triazol-1-il)benzonitrilo. Cristales blancos (acetato de etilo-hexano); p.f. 120-121 ee. ^{1}HRMN 400 MHz ($CDCl_3$) δ ppm: 2.56 (3H, S, CH_3), 7.30 (1H, dd, J=2.5 Hz y J=8.1 Hz, CH), 7.39 (1H, m, CH), 7.91 (1H, dd, J=5.5 Hz y J=8.6 Hz, CH), 8.06 (1H, s, CH).

Análisis calculado para $C_{10}H_7FN_4$: C 59.40, H 3.49, N 27.71; Encontrado: C 59.35, H 3.70, N 27.77.

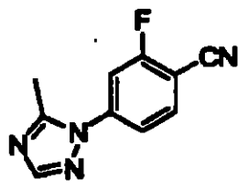
494

Intermediario 83



2-Fluoro-4-(3-metil-1H-1,2,4-triazol-1-il)benzonitrilo. Cristales blancos (acetato de etilo-hexano); p.f. 133-134 ee. ^{1}HRMN 400 MHz ($CDCl_3$) δ ppm: 2.52 (3H, s, CH_3), 7.61 (1H, dd, J=2 Hz y J=9.1 Hz, CH), 7.67 (1H, dd, J=2Hz y J=9.6 Hz, CH), 7.79 (1H, dd, J=6.5 Hz y J=8.6 Hz, CH), 8.56 (1H, s, CH). Análisis calculado para $C_{10}H_7FN_4$: C 59.40, H 3.49, N 27.71; Encontrado: C 59.42, H 3.24, N 28.41.

Intermediario 84

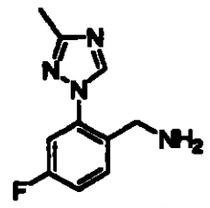


2-Fluoro-4-(5-metil-1H-1,2,4-triazol-1-il)benzonitrilo. Cristales blancos (acetato de etilo-hexano); p.f. 89-90°C,

^{1}HRMN 400 MHz ($CDCl_3$) δ ppm: 2.69 (3H, s, CH_3), 7.49-7.55 (2H, m, 2 x CH), 7.83 (1H, dd, J=6.8 Hz y J=8.8 Hz, CH), 8.00 (1H, s, CH). Análisis calculado para $C_{10}H_7FN_4$: C 59.40, H 3.49, N 27.71; Encontrado: C 59.17, H 3.22, N 28.01.

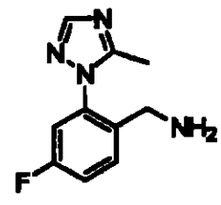
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Intermediario 85



Sal de Clorohidrato de (4-Fluoro-2-(3-metil-1H-1,2,4-triazol-1-il)fenil)metanamina. La hidrogenación del intermediario 81, el 4-fluoro-2-(3-metil-1H-1,2,4-triazol-1-il)benzonitrilo, (0.680 g, 3.36 mmol) dio 0.720 g (88% rendimiento) de la sal de clorohidrato como un sólido blanco ^{1}HRMN 400 MHz (DMSO-d_6) δ ppm: 2.40 (3H, S, CH_3), 4.02 (2H, m, NCH_2), 7.50 (1H, m, CH), 7.62 (1H, dd, J=2.8 Hz y J=9.3 Hz, CH), 7.84 (1H, dd, J=6.1 Hz y J=9.1 Hz, CH), 9.00 (1H, s, CH). EMAR (ESI) calculado para $C_{10}H_{12}FN_4$ [M+H$^+$]: 207.1046; encontrado: 207.1047.

Intermediario 86

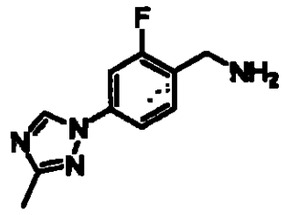


Sal de clorohidrato de (4-Fluoro-2-(5-metil-1H-1,2,4-triazol-1-il)fenil)metanamina. La hidrogenación del intermediario 82, el 4-fluoro-2-(5-metil-1H-1,2,4-triazol-1-il)benzonitrilo, (0.244 g, 1.20 mmol) dio 0.290 g (100% rendimiento) de la sal de clorohidrato como un sólido blanco.

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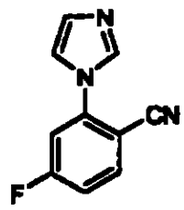
^{1}HRMN 400 MHz (DMSO-d_6) δ ppm: 2.42 (3H, s, CH_3), 3.78 (2H, m, NCH_2), 7.58 (1H, m, CH), 7.67 (1H, dd, J=2.8 Hz y J=9.3 Hz, CH), 7.90 (1H, dd, J=6.0 Hz y J=8.6 Hz, CH), 8.22 (1H, s, CH). EMAR (ESI^+) calculado para $C_{10}H_{12}FN_4$ $[M+H^+]$: 207.1046; encontrado: 207.1041.

Intermediario 87



Sal de *Clorohidrato de (2-Fluoro-4-(3-metil-1H-1,2,4-triazol-1-il)fenil)metanamina*. La hidrogenación del intermediario 83, el 2-fluoro-4-(3-metil-1H-1,2,4-triazol-1-il)benzonitrilo, (0.220 g, 1.09 mmol) dio 0.260 g (98% rendimiento) de la sal de clorohidrato como un sólido blanco. ^{1}HRMN 400 MHz (DMSO-d_6) δ ppm: 2.38 (3H, s, CH_3), 4.09 (2H, m, NCH_2), 7.75-7.8 (2H, m, 2 xCH), 7.83 (1H, dd, J=2 Hz y J=9 Hz, CH), 9.29 (1H, s, CH). EM (ESI^+) m/e 207 $[M+H^+]$.

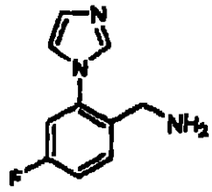
Intermediario 88



4-Fluoro-2-imidazol-1-il-benzonitrilo. A una solución de imidazol (4.45 g, 65.4 mmol) en tetrahidrofurano (30 mL) y

dimetilformamida (10 mL) se agregó carbonato de potasio (9.95 g, 72 mmol) y la mezcla se agitó durante 30 minutos a temperatura ambiente. A esto se agregó 2,4-difluorobenzonitrilo (10.0 g, 72 mmol) y la mezcla se agitó a 90°C durante 3 h luego a temperatura ambiente durante 2 días. La mezcla se filtró y se concentró y el residuo se purificó por cromatografía instantánea (SiO_2) se eluyó con 20% hasta 70% de acetato de etilo/hexano para dar el compuesto del título como agujas blancas (1.1 g, 9% rendimiento). ^1H RMN (500 MHz, $CDCl_3$) δ ppm: 7.94 (1H, s), 7.84 (1H, dd, J=8.7, 5.6 Hz), 7.37 (1H, t, J=8.7, 5.6 Hz), 7.37 (1H, t, J=1.4 Hz), 7.29 (1H, t, J=1.1 Hz), 7.27-7.21 (2H, m). CLEM $[M+H]^+$ calculado para $C_{10}H_7N_3F$: 188.058; encontrado 188.12.

Intermediario 89

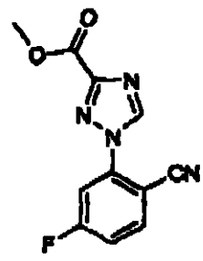


Clorohidrato de (4-fluoro-2-(1H-imidaz-1-il)fenil)metanamina). El compuesto del título puede prepararse a partir del intermediario 88, 4-fluoro-2-imidazol-1-il-benzonitrilo, de conformidad con el método proporcionado por el intermediario 79. Sólido amarillo, 1H-RMN (500 MHz, CD3OD) δ ppm: 9.39 (1H, s), 7.98 (1H, d, J = 1.5 Hz), 7.92-7.89 (2H, m), 7.63-7.59 (2H, m), 4.11 (2H, s).

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CLAR [M+H]+ calculado para $C_{10}H_{11}N_3F$: 192.09; encontrado: 192.15.

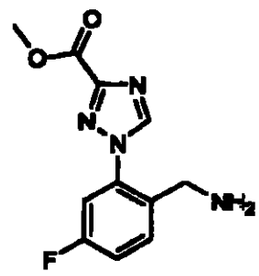
Intermediario 90



Éster de metilo del ácido 1-(2-ciano-5-fluoro-fenil)-1H-1,2,4-triazol-3-carboxílico. A una solución de 1H-1,2,4-triazol-3-carboxilato de metilo (27g, 215 mmol) en dimetilformamida (170 mL) se le agregó hidruro de sodio (5.53 g, 95%, 217 mmol) y la mezcla se agitó durante 30 minutos. A esto se le agregó 2,4-difluorobencilnitrilo (30 g, 217 mmol) y la mezcla resultante se agitó a temperatura ambiente durante 60 horas. La mezcla se diluyó con agua y se filtró para remover los sólidos. La solución se extrajo con acetato de etilo y la fase orgánica se lavó con agua (3X's) y salmuera, luego se secó (Na_2SO_4) y se concentró. El residuo resultante se purificó por cromatografía instantánea (SiO_2) se eluyó con 30% tetrahidrofurano/20% CH_2Cl_2/50% hexano para dar el compuesto del título como agujas blancas (5.34 g, 10% rendimiento). ^{1}H-RMN (300 MHz, $CDCl_3$) δ ppm: 8.92 (1H, s), 7.85 (1H, dd, J= 8.8, 5.5 Hz), 7.67 (1H, dd, J= 8.8, 2,6 Hz), 7.34-7.27 (1H, m), 40.3 (3H, s). CLEM $[M+H]^+$ calculado para

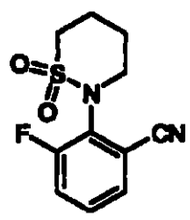
$C_{11}H_8N_4FO_2$: 247.06; encontrado: 247.11.

Intermediario 91



Metil 1-(2-(aminometil)-5-fluorofenil)-1H-1,2,4-triazol-3-carboxilato. El compuesto del título puede ser preparado a partir del intermediario 90, éster metilo del ácido 1-(2-ciano-5-fluoro-fenil)-1H-1,2,4-triazol-3-carboxílico. ^{1}H-RMN (300 MHz, CD_3OD) δ ppm: 9.15 (1H, s), 7.80 (1H, dd, J=8.8, 5.9 Hz), 7.71 (1H, dd, J=8.8, 2.6 Hz), 7.46 (1H, td J=8.2, 2.6 Hz), 4.19 (2H, s), 4.03 (3H, s). CLEM $[M+H]^+$ calculado para $C_{11}H_{12}N_4O_2$: 251.09; encontrado: 251.17.

Intermediario 92

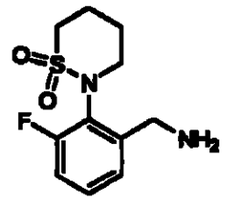


3-Fluoro-2-(1,1-dioxo-1λ^6-[1,2]tiazinan-2-il)benzonitrilo. A una solución de 1,1-dioxo-1λ^6-[1,2]tiazin-2-ano (1.90 g, 14.4 mmol) se disolvió en tetrahidrofurano (8 mL) y dimetilformamida (2 mL) se agregó hidruro de sodio (0.36 g, 95%, 14.4 mmol) y la mezcla se agitó durante 20

500

minutos. A esto se agregó 2,3-difluorobenzonitrilo (2.0 g, 14.4 mmol) y la mezcla se agitó a 90°C durante 2 h. La mezcla se dividió entre acetato de etilo y agua. La fase orgánica se lavó con agua y salmuera luego se concentró. El residuo sólido se trituró con 1:1 acetato de etilo/hexano para dar el compuesto del título como un sólido café pálido (0.47 g, 13% rendimiento). ^{1}H-RMN (500 MHz, $CDCl_3$) δ ppm: 7.47-7.45 (1H, m), 7.32-7.36 (2H, m), 4.08-4.02 (1H, m), 3.57 (1H, td, J=13.0, 3,7 Hz), 3.40-3.34 (1H, m), 3.32-3.27 (1H, m), 2.44-2.32 (2HF, m), 2.04-1.97 (2H, m), 1.90-1.84 (1H, m). CLEM $[M+H]^+$ calculado para $C_{11}H_{12}N_2FO_2S$: 255.28; encontrado: 255.13.

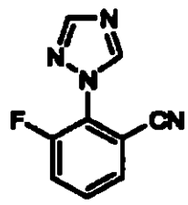
Intermediario 93



Clorohidrato de 3-Fluoro-2-(1,1-dioxo-1λ6-[1,2]tiazinan-2-il)bencilamina. El compuesto del título puede ser preparado a partir del intermediario 92, 3-fluoro-2-(1,1-dioxo-1λ6-[1,2]tiazinan-2-il)benzonitrilo de conformidad al procedimiento proporcionado por el intermediario 79. sólido blanco, ^{1}H-RMN (500 MHz, CD_3OD) δ ppm: 7.56-7.52 (1H, m), 7.40-7.34 (2H, m), 4.31 (2H, s), 3.98-3.93 (1H, m), 3.68-3.64 (1H, m), 3.42-3.39 (2H, m), 2.42-2.37 (2H, m), 2.03-1.92 (2H, m). CLEM $[M+H]^+$ calculado para $C_{11}H_{16}N_2O_2FS$: 259.09;

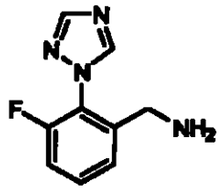
encontrado: 259.18.

Intermediario 94



3-Fluoro-2-1,2,4-triazol-1-il-benzonitrilo. Una mezcla de 2,3-difluorobencilnitrilo (2.27 g, 16.3 mmol) y sal de triazol de sodio (1.33 g, 14.8 mmol) en tetrahidrofurano (5 ml) y dimetilformamida (10 ml) se agitó a 85°C durante 4 h. Después de la concentration, el residuo se purificó por cromatografía instantánea (SiO_2) eluyendo con 25%-50% de acetato de etilo/hexano. El producto aislado se recristalizó de acetato de etilo/hexano caliente para dar el compuesto del título como agujas blancas (1.51 g, 54% rendimiento). ^{1}H-RMN (500 MHz, $CDCl_3$) δ ppm: 8.50 (1H, d, J=2.4 Hz), 8.25 (1H, s), 7.69-7.67 (1H, m), 7.60-7.57 (2H, m). CLEM $[M+H]^+$ calculado para $C_9H_6N_4F$: 189.16; encontrado: 189.14.

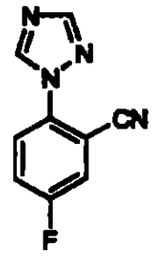
Intermediario 95



(3-Fluoro-2-(1H-1,2,4-triazol-1-il)fenil)metanamina. El compuesto del título puede ser preparado a partir del intermediario 94, el 3-fluoro-2-1,2,4-triazol-1-il-

benzonitrilo. ^{1}H-RMN (500 MRz, CD_3OD) δ ppm: 9.61 (1H, d, J=2.9 Hz), 8.79 (1H, s), 7.82-7.74 (1H, m), 7.67-7.57 (2R, m), 4.14-4.13 (2H, m). CLEM $[M+H]^+$ calculado para $C_9H_{10}N_4F$: 193.08; encontrado: 193.16.

Intermediario 96

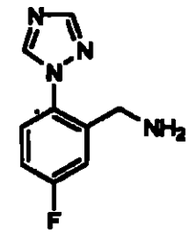


5-Fluoro-2-(1H-1,2,4-triazol-1-il)benzonitrilo. Una suspensión de 2,5-diflurobenzonitrilo (4.5 g, 32.35 mmol) y sal de 1,2,4-triazol de sodio (3.6 g, 40 mmol) en dimetilformamida (40 mL) se calentó a 80°C durante 15 h.

La mezcla de reacción luego se enfrió, se diluyó con CH_2Cl_2 (200 mL), se lavó con agua (3 X 30 mL) y salmuera (30 mL), luego se secó (Na_2SO_4), se filtró y se concentró para dar un sólido blanco el cual se purificó por cromatografía de columna instantánea (SiO_2) usando 1:1 hasta 3:1 acetato de etilo/Hexanos para proporcionar el compuesto del título (2.98 g, 49% rendimiento) como un polvo blanco.

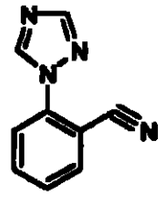
^{1}H RMN (500 MHz, $CDCl_3$) δ: 8.70 (1H, s), 8.18 (1H, s), 7.76 (1H, dd, J=9.0,4.8 Hz), 7.55 (1H, dd, J=7.3, 2.8 Hz), 7.51-7.47 (1H, m). CLEM (M+H) calculado para $C_9H_6FN_4$: 189.17; encontrado: 189.10.

Intermediario 97



Clorohidrato de (5-Fluoro-2-(1H-1,2,4-triazol-1-il)fenil)metanamina. Una solución del intermediario 96, el 5-fluoro-2-(1H-1,2,4-triazol-1-il)benzonitrilo (2.94 g, 15.59 mmol) en etanol (100 mL) y HCl 1N (50 mL) se desgasificó por burbujeo de N_2. Luego, se agregó 10% de Pd/C, el matraz se evacuó y se abrió el H_2 hasta tres veces y se dejó en un agitador Parr bajo una atmósfera de H_2 40 psi (2.812 kg/cm^2). Después de 6 h, la mezcla de reacción se filtró, se concentró y la solución acuosa se liofilizó para proporcionar el compuesto del título (4.07 g, 98%) como un polvo blanco. CLEM (M+H) calculado para $C_9H_{10}FN_4$: 193.09; encontrado: 193.15.

Intermediario 98



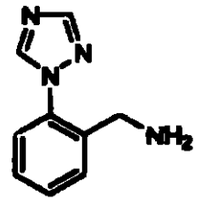
2-(1H-1,2,4-Triazol-1-il)benzonitrilo. Una suspensión de 2-fluorobencilnitrilo (3.0 g, 25 mmol) y sal de 1,2,4-triazol de sodio (2.4 g, 27 mmol) se agitó en tetrahidrofurano (7 ml) y dimetilformamida (14 mL) a 95°C durante 18 h. Después de

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enfriarse y concentrarse, el producto se cristalizó de CH_2Cl_2 caliente/hexano (1:1) para dar el compuesto del título como un sólido blanco (4.25 g, 100% rendimiento).

^{1}H-RMN (300 MHz, $CDCl_3$) δ ppm: 8.74 (1H, s), 8.16 (1H, s), 7.82 (1H, dd, J=4.9,1.3 Hz), 7.77-7.25 (2H, m), 7.57-7.51 (1H, m). CLEM $[M+H]^+$ calculado para $C_9H_7N_4$: 171.06; encontrado: 171.12.

Intermediario 99

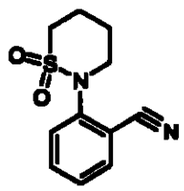


Clorohidrato de (2-(1H-1,2,4-Triazol-1-il)fenil)metanamina. Intermediario 98, el 2-(1H-1,2,4-triazol-1-il)benzonitrilo (4.25 g, 25 mmol) se disolvió en etanol (50 mL) y HCl 1N (25 ml). Se agregó 10% de Pd-C (1 g) y la mezcla se agitó bajo H2 durante 2 h a 50 psi (3.515 kg/cm2).

Después de filtrarse a través de Celite y concentrarse, el residuo se trituró con dietil éter y el compuesto del título se colectó como un sólido blanco (3.94 g, 75% rendimiento).

^{1}H-RMN (300 MHz, CD_3OD) δ ppm: 9.01 (1H, s), 8.32 (1H, s), 7.78-7.64 (4H, m), 4.15 (2H, s). CLEM $[M+H]^+$ calculado para $C_9H_{11}N_4$: 175.09; encontrado: 175.17.

Intermediario 100



2-(1,1-Dioxo-1λ⁶-[1,2]tiazinan-2-il)benzonitrilo. Se agregó a una solución de 1,1-dioxo[1,2]tiazinana (3.37 g, 25 mmol) en dimetilformamida (35 mL) hidruro de sodio (0.675 g, 25 mmol, 95%) y la mezcla se agitó a temperatura ambiente durante 15 minutos. Se agregó 2-fluorobenzonitrilo (3.37 mL, 31.3 mmol) y la mezcla se agitó a 80°C durante 18 h.

La mezcla se enfrió, se diluyó con agua y se extrajo con acetato de etilo. La fase orgánica se lavó con agua y salmuera, luego se secó (Na_2SO_4) y se concentró.

El residuo se purificó por cromatografía instantánea (SiO_2) se eluyó con 10%-100% de acetato de etilo/hexano.

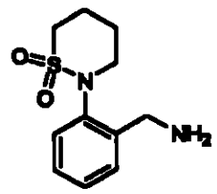
El sólido aislado se recristalizó de acetato de etilo/hexano caliente (2:1) para dar el compuesto del título como cristales blancos (4.15 g, 70% rendimiento).

^{1}H-RMN (300 MHz, $CDCl_3$) δ ppm: 7.70 (1H, dd, J=7.7, 1.1 Hz), 7.64-7.53 (2H, m), 7.41 (1H, td, J=7.3, 1.6 Hz), 3.72 (2H, t, J=5.5 Hz), 3.32 (2H, t, J=6.0 Hz), 2.40-2.32 (2H, m), 2.05-1.97 (2H, m). CLEM $[M+H]^+$ calculado para $C_{11}H_{12}N_2O_2S$: 237.06; encontrado:

506

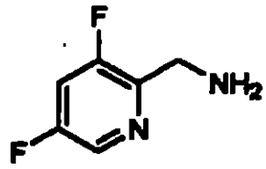
237.10.

Intermediario 101



Clorohidrato de 2-(1,1-Dioxo-1λ⁶-[1,2]tiazinan-2-il)bencilamina. Intermediario 100, el 2-(1,1-dioxo-1λ⁶-[1,2]tiazinan-2-il)benzonitrilo, (2.63 g, 11.14 mmol) se disolvió en etanol (150 mL) y HCl 1N (13 mL). Se agregó a esto 10% de Pd-C (0.5 g) y la mezcla se agitó bajo H_2 a 55 psi (3.8665 kg/cm^2) durante 24 h. La filtración a través de Celite seguido por la concentración dio el compuesto del título como un sólido blanco (2.93 g, 95% rendimiento). ^{1}H-RMN (300 MHz, CD_3OD) δ ppm: 7.61-7.47 (4H, m), 4.30 (2H, q, J=13.7 Hz), 3.96-3.87 (1H, m), 3.49-3.36 (3H, m), 2.40-2.31 (2H, m), 2.05-1.96 (2H, m). CLEM $[M+H]^+$ calculado para $C_{11}H_{17}N_2SO_2$: 241.10; encontrado: 241.10.

Intermediario 102

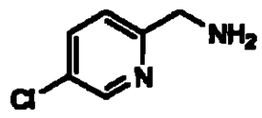


Clorohidrato de (3,5-Difluoropiridin-2-il)metanamina. Una mezcla de 3,5-difluoropicolinonitrilo (1.4 g, 10 mmol), HCl concentrado (12 ml) y 10% de Pd-C (200 mg) en 1:1 de

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etanol/tetrahidrofurano se agitó bajo una atmósfera de hidrógeno a 50 psi (3.515 kg/cm^2) durante 5h. La mezcla de reacción se filtró y el etanol se removió in vacuo. La solución resultante se liofilizó para proporcionar un sólido blanco opaco (2.16 g, 100% rendimiento). CLEM (M+H) calculado para $C_6H_7F_2N_2$: 145.06; encontrado: 145.12.

Intermediario 103



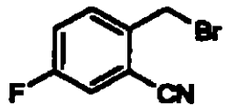
(5-Cloropiridin-2-il)metanamina. Una solución de 5-cloropicolinonitrilo (3.8 g, 27.43 mmol), HCl concentrado (3 mL) y 10% de Pd-C (1.0 g) en etanol (100 mL) se agitó bajo una atmósfera de hidrógeno 40 psi (2.812 kg/cm^2) durante 2h.

La mezcla de reacción se filtró, se concentró y el residuo resultante se tomó en $NaHCO_3$ saturado (50 mL) y se extrajo con CH_2Cl_2 (4 X 25 mL).

Las capas combinadas CH_2Cl_2 se secaron (Na_2SO_4), se filtraron y se concentraron para dar el compuesto del título como un aceite amarillo (2.0 g, 51% rendimiento).

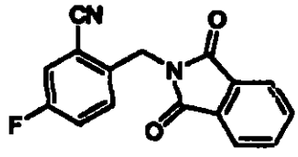
CLEM (M+H) calculado para $C_6H_8ClN_2$: 143.04; encontrado: 143.07. ^{1}HRMN (500 MHz, $CDCl_3$) δ ppm: 8.56-8.51 (1H, br d), 7.66-7.60 (1H, m), 7.28-7.14 (1H, m), 3.97 (2H, s), 1.72 (2H, s).

Intermediario 104



2-(Bromometil)-5-fluorobenzonitrilo. La N_2 se pasó a través de una mezcla de 5-fluoro-2-metilbenzonitrilo (28.51 g, 211 mmol), NBS (41.31 g, 232 mmol) y AIBN (2.5 g, 15 mmol) en CCl_4 (845 ml) durante 10 minutos, después de lo cual la reacción se calentó a reflujo durante 8 h. Después de estar a temperatura ambiente durante la noche, la mezcla de reacción se filtró y la torta filtro se lavó con CCl_4 (500 ml). El filtrado combinado se evaporó para dar un aceite amarillo. La cromatografía instantánea (SiO_2) usando 5-25% de acetato de etilo/Hexanos como eluyente proporcionó el compuesto del título (29.74 g, 66% rendimiento) como un aceite amarillo pálido. ^1H RMN (500 MHz, $CDCl_3$) δ: 7.55 (1H, dd, J=8.6, 5.2 Hz), 7.37 (1H, dd, J=7.9, 2.8 Hz), 7.32-7.28 (1H, m), 4.61 (2H, s).

Intermediario 105

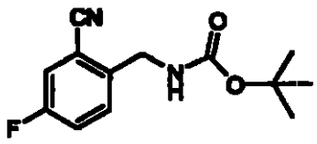


2-((1,3-Dioxoisoindolin-2-il)metil)-5-fluorobenzonitrilo. A una solución agitada del intermediario 104, el 2-(bromometil)-5-fluorobenzonitrilo (29.72 g, 139 mmol) y ftalamida (32.69 g, 222 mmol) en dimetilformamida (300 ml) se agregó Cs_2CO_3 (67.87 g, 208 mmol). Después de

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agitarse vigorosamente durante 1h, la mezcla de reacción se vació en agua (1.2 L). El producto purificado se filtró, se lavó con agua (600 ml) y metanol (150 ml) para dar un sólido blanco. El sólido se tomó en 1L de agua/metanol (2:1) al cual se agregó K_2CO_3 (12 g) y la mezcla se agitó a 40°C. Después de 30 minutos, la mezcla se enfrió y se filtró. La torta filtro se lavó con agua (500 mL) y se secó bajo vacío para proporcionar el compuesto del título (38.91 g, 94% rendimiento) como un polvo blanco. ^{1}H RMN (500 MHz, $CDCl_3$) δ 7.89 (2H, dd, J=5.5, 3.1 Hz), 7.76 (5.5, 3.1 Hz), 7.41 (1H, dd, J=8.6, 5.2 Hz), 7.38 (1H, dd, J=7.9, 2.8 Hz), 7.24 (1H, dd, J=8.2, 2.8 Hz), 5.06 (2H, s). CLEM (M+H) calculado para $C_{16}H_{10}FN_2O_2$: 281.07; encontrado: 281.15.

Intermediario 106

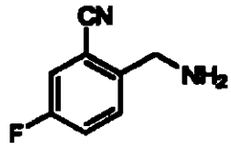


tert-Butil 2-ciano-4-fluorobencilcarbamato. Una suspensión del intermediario 105, el 2-((1,3-dioxoisoindolin-2-il)metil)-5-fluorobenzonitrilo, (5.6 g, 20 mmol) en dimetilformamida (20 ml) se calentó hasta que se disolvió. A esto se agregó tetrahidrofurano (100 ml) y la mezcla se colocó en un baño de aceite precalentado (70°C). Se agregó monohidrato de hidracina a esto y la reacción se agitó durante 8 h. La mezcla espesa blanca resultante se dejó a

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temperatura ambiente durante la noche. A esta mezcla espesa se agregó di-tert-butildicarbonato (6.55 g, 30 mmol) y la mezcla se agitó durante 6 h a temperatura ambiente. La mezcla de reacción se diluyó con éter (100 mL), se filtró y el filtrado se trató con carbono activado a 40°C. Después de filtrarse y concentrarse, el producto crudo se purificó por cromatografía instantánea usando 20-30% de acetato de etilo/Hexanos como eluyente, para proporcionar el compuesto del título (2.88 g, 58% rendimiento) como un polvo amarillo ligero. ^{1}H RMN (500 MHz, $CDCl_3$) δ 9.46 (1H, br s), 7.61 (1H, dd, J=7.9, 2.1 Hz), 7.34 (1H, dd, J=8.2, 4.6 Hz), 7.22 (1H, dd, J=8.6, 2.4 Hz), 4.71 (2H, s), 1.59 (9H, s). CLEM (M+H) calculado para $C_{13}H_{16}FN_2O_2$: 251.12; encontrado: 251.22.

Intermediario 107

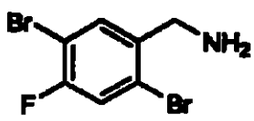


Sal del ácido 2-(Aminometil)-5-fluorobenzonitrilo trifluoroacético. Un matraz de fondo redondo se cargó con el intermediario 106, el tert-butil 2-ciano-4-fluorobencilcarbamato, (1.9 g, 7.591 mmol) luego se trató con ácido trifluoroacético (20 ml) a temperatura ambiente. Después de 1 h, la mezcla de reacción se concentró para dar un aceite amarillo el cual se disolvió en $CHCl_3$ y se re-concentró para proporcionar el compuesto del título

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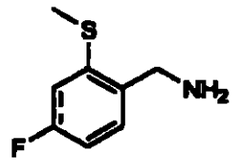
(2.01 g, 100% rendimiento) como un sólido amarillo pálido. CLEM (M+H) calculado para $C_8H_8FN_2$: 151.07; encontrado: 151.08.

Intermediario 108



(2,5-Dibromo-4-fluorofenil)metanamina. Una solución de 2,5-dibromo-4-fluorobromuro de bencilo (0.350 g, 1 mmol) en NH_3/MeOH 7M se calentó en un tubo sellado a 100°C durante 2 h. La mezcla de reacción se enfrió y se concentró para dar un sólido blanco el cual se disolvió en CH_2Cl_2 y se trató con Et_3N (1 ml) luego se concentró. El residuo resultante se trituró con acetato de etilo (25 ml), se filtró y se concentró para dar el compuesto del título (0.291 g) como un aceite amarillo pálido. EMAR (M+H) calculado para $C_7H_7Br_2FN$: 283.94; encontrado: 283.93.

Intermediario 109

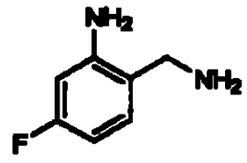


4-Fluoro-2-metilsulfanil-bencilamina. Bajo N_2, se disolvió el 4-fluoro-2-(metiltio)benzonitrilo (1.67 g, 0.1 mol) en 20 mL de tetrahidrofurano y se trató con 10 mL de 2M

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$BH_3.Me_2S$. Esto se calentó a 60°C durante 2 horas. Se calentó continuamente y se agregó cuidadosamente 5mL de MeOH, seguido por la adición cuidadosa de 4 mL de HCl 6N. Se agregó H_2O adicional (20 mL) seguido por acetato de etilo. Las capas se separaron. La capa acuosa se hizo básica con NaOH 1N y se extrajo con CH_2Cl_2, Los extractos se secaron ($MgSO_4$), se filtraron, se concentraron y se secaron in vacuo para dar 1.3g del compuesto del título como un sólido (Rendimiento = 76%). ^1H RMN (500 MHz, $CDCl_3$) δ ppm: 7.20-7.31 (1H, m), 6.90 (1H, dd, J=2.4 Hz), 6.75-6.86 (1H, m), 3.86 (2H, s), 2.47 (3 H, s); CL/EM m/z 172.

Intermediario 110

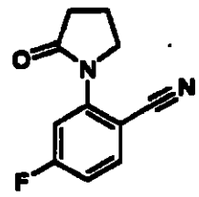


Clorohidrato de 2-(Aminometil)-5-fluorobencenamina. El 2-amino-4-fluorobenzonitrilo (Fritz Hunziker et al. Eur. J. Med. Chem. 1981, 16, 391) (0.300 g, 1.68 mmol), se disolvió en anhidrido acético (5 mL) y la solución se agitó a 23°C durante 18 h. Una porción adicional de anhidrido acético (3 ml) se agregó hasta disolver la N-(2-ciano-5-fluorofenil)acetamida. Luego se agregó paladio (10% en carbón mineral) (25 mg) y la mezcla se agitó bajo H_2 34 psi (2.3902 kg/cm^2) durante 72 h. El Pd-C se removió por filtración en

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Celite y el filtrado se concentró in vacuo para proporcionar una bis-acetamida: CLEM $(M+H)^+$ m/z 225. Esto se calentó a reflujo con HCl (6N, 10 ml) durante 30 minutos. El ácido se removió bajo presión reducida para dar un sólido el cual se cristalizó de MeOH-éter para proporcionar el compuesto del título (0.120 g, 51% rendimiento). ^{1}H RMN (400 MHz, MeOD) δ ppm: 7.51 (1H, m), 6.96 (2H, m), 4.20 (2H, s).

Intermediario 111

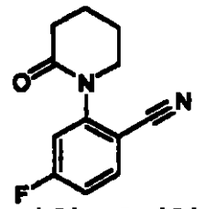


4-Fluoro-2-(2-oxopirrolidin-1-il)benzonitrilo. A un recipiente de presión de 48 ml que contenía 2-bromo-4-fluorobenzonitrilo (1.00 g, 5.00 mmol), 2-pirrolidinona (0.46 mL, 6.00 mmol), Cs_2CO_3 (2.28 g, 7.0 mmol) y 9,9-dimetil-4,5-bis(difenilfosfino)xanteno (xantfos) (0.231 g, 0.40 mmol) en dioxano (6 mL) se desgasificó con argón durante 15 minutos. El Pd_2dba_3 se introdujo y la mezcla de reacción se calentó a 105°C durante 48 h. La mezcla se enfrió, se diluyó con acetato de etilo o dioxano, y luego se filtró a través de Celite. La mezcla resultante se concentró in vacuo y se sujetó a cromatografía de columna en gel de sílice con gradient de hexanos:acetato de etilo (3:7) como el eluyente para proporcionar el compuesto del título como un sólido

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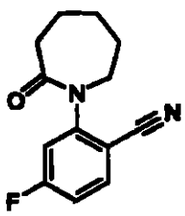
blanco (0.887 g, 87% rendimiento): ^{1}H RMN (400 MHz, $CDCl_3$) δ ppm: 7.69 (1H, dd, J=5.8, 8.6 Hz), 7.22 (1H, dd, J=2.5, 9.6 Hz), 7.07 (1H, ddd, J=2.5, 7.6, 8.6 Hz), 3.96 (2H, t,. J=7.0 Hz), 2.62 (2H, t, J=8.1 Hz), 2.30-2.22 (2H, m); CLEM ($^+$ESI, M+H$^+$) m/z 205.

Intermediario 112



4-Fluoro-2-(2-oxopiperidin-1-il)benzonitrilo. El compuesto del título puede prepararse de conformidad al procedimiento proporcionado por el intermediario 111. ^{1}H RMN (400 MHz, $CDCl_3$) δ ppm: 7.71 (1H, dd, J=5.7, 8.7 Hz), 7.14-7.06 (1H, m), 7.08 (1H, dd, J=2.4, 9.0 Hz), 3.65 (2H, t,. J=5.7 Hz), 2.60 (2H, t, J=6.3 Hz), 2.05-1.95 (4H, m); CLEM ($^+$ESI, M+H$^+$) m/z 219.

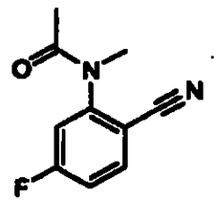
Intermediario 113



4-Fluoro-2-(2-oxoazepan-1-il)benzonitrilo. El compuesto del título puede prepararse de conformidad al procedimiento proporcionado por el intermediario 111. ^{1}H RMN (400 MHz, $CDCl_3$) δ ppm: 7.68 (1H, dd, J=5.8, 8.6 Hz), 7.08 (1H, ddd,

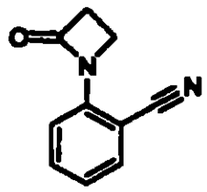
J=2.5, 7.6, 8.6 Hz), 7.01 (1H, dd, J=2.5, 9.0 Hz), 3.77-3.76 (2H, m), 2.75-2.72 (2H, m), 1.91-1.86 (6H, m); CLEM ($^+$ESI, $M+H^+$) m/z 233.

Intermediario 114



N-(2-Ciano-5-fluorofenil)-N-metilacetamida. El compuesto del título puede prepararse de conformidad al procedimiento proporcionado por el intermediario 111. ^{1}H RMN (400 MHz, $CDCl_3$) δ ppm: 7.79-7.75 (1H, m), 7.32-7.19 (1H, m), 7.10-7.07 (1H, m), 3.42 (0.6H, brs), 3.30 (2.4H, s), 2.32 (0.6H, brs), 1.91 (2.4H, s); CLEM ($^+$ESI, $M+H^+$) m/z 193; CLAR: 94% (220 nm).

Intermediario 115

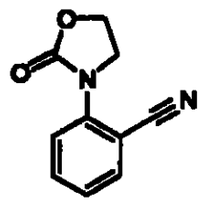


2-(2-Oxoazetidin-1-il)benzonitrilo. El compuesto del título puede prepararse de conformidad al procedimiento proporcionado por el intermediario 111. ^{1}H RMN (400 MHz, DMSO-d_6) δ ppm: 8.02 (1H, d, J=8.4 Hz), 7.76 (1H, dd, J=1.5, 7.8 Hz), 7.69-7.65 (1H, m), 7.23 (1H, s), 4.04 (2H, t, J=4.8 Hz), 3.16 (2H, t, J = 4.8 Hz). CLEM (ESI, $M+H^+$) m/z 173.

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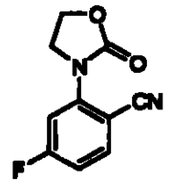
516

Intermediario 116



2-(2-Oxooxazolidin-3-il)benzonitrilo. El compuesto del título puede prepararse de conformidad al procedimiento proporcionado por el intermediario 111. ^{1}H RMN (400 MHz, $CDCl_3$) δ ppm: 7.71 (1H, dd, J=1.5, 7.6 Hz), 7.68-7.63 (1H, m), 7.58 (1H, d, J=7.6 Hz), 7.38 (1H, dt, J=1.3, 7.6 Hz), 4.57 (2H, t, J=7.8 Hz), 4.21 (2H, t, J=7.8 Hz); CLEM ($^+$ESI, $M+H^+$) m/z 189.

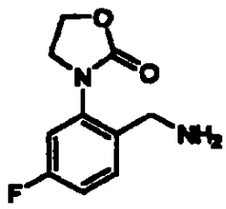
Intermediario 117



4-Fluoro-2-(2-oxooxazolidin-3-il)benzonitrilo. Un recipiente a presión de 48 mL que contenía 2-bromo-4-fluorobenzonitrilo (1.00 g, 5.00 mmol), 2-oxazolidona (0.390 g, 4.50 mmol), K_2CO_3 (0.970 g, 7.0 mmol) y xantfos (0.231 g, 0.40 mmol) en dioxano (10 ml) se desgasificó con argón durante 15 minutos. El Pd_2dba_3 (0.140 g, 0.15 mmol) se introdujo y luego la mezcla de reacción se calentó a 70°C durante 18 h. La mezcla se enfrió, se diluyó con dioxano, y luego se filtró a través de Celite. La mezcla resultante se concentró in vacuo y se sometió

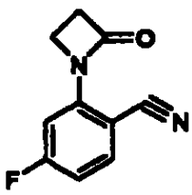
a cromatografía de columna en gel de sílice con gradiente de hexanos:acetato de etilo (1:1) hasta (3:7) como eluyente para proporcionar el compuesto del título como un sólido blanco (0.460 g, 50% rendimiento): ^{1}H RMN (400 MHz, $CDCl_3$) δ ppm: 7.73 (1H, dd, J=5.8, 8.6 Hz), 7.43 (1H, dd, J=2.5, 9.6 Hz), 7.11 (1H, ddd, J=2.5, 7.5, 8.7 Hz), 4.60 (2H, t, J=7.1 Hz), 4.29 (2H, t, J=7.1 HJz); CLEM ($^+$ESI, M+H$^+$) m/z 207.

Intermediario 118



Clorohidrato de 3-(2-(Aminometil)-5-fluorofenil)oxazolidin-2-ona. ^{1}H RMN (400 MHz, MeOD) δ ppm: 7.73 (1H, dd, J=6.0, 8.6 Hz), 7.43 (1H, dd, J=2.5, 9.5 Hz), 7.11 (1H, ddd, J=2.5, 7.5, 8.6 Hz), 4.64 (2H, t, J=7.7 Hz), 4.17 (2H, t, J=7.7 Hz), 4.14 (2H, s); CLEM ($^+$ESI, M+H$^+$) m/z 211.

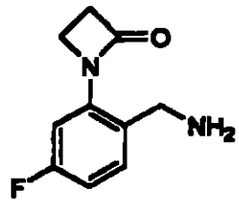
Intermediario 119



4-Fluoro-2-(2-oxoazetidin-1-il)benzonitrilo. El compuesto del título puede prepararse de conformidad al

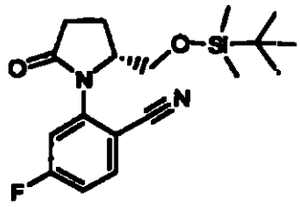
procedimiento proporcionado por el intermediario 117. ^{1}H RMN (400 MHz, $CDCl_3$) δ ppm: 8.06 (1H, dd, J=10.7, 2.6 Hz), 7.58 (1H, dd, J=8.6, 6.3 Hz), 7.87 (1H, dd, J=8.6, 2.5 Hz), 4.25 (2H, t, J=5.0 Hz), 3.26 (2H, t, J=5.0 Hz); CLEM ($^+$ESI, M+H$^+$) m/z 191.

Intermediario 120



Clorohidrato de 1-(2-(Aminometil)-5-fluorofenil)azetidin-2-ona. ^{1}H RMN (400 MHz, DMSO/D_2O) δ ppm: 7.54 (1H, dd, (t), J=8.6 Hz), 7.25 (1H, dd, J=10.8, 2.5 Hz), 7.17 (1H, td, J=8.6, 2.5 Hz), 4.12 (2H, s), 3.79 (2H, t, J=4.6 Hz), 3.09 (2H, t, J=4.6 Hz); CLEM ($^+$ESI, M+H$^+$) m/z 195.

Intermediario 121

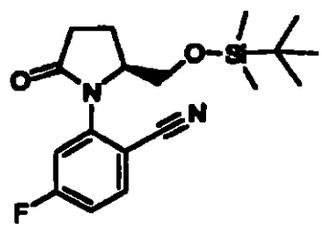


(R)-2-(2-((tert-Butildimetilsililoxi)metil)-5-oxopirrolidin-1-il)-4-fluorobenzonitrilo. El compuesto del título puede prepararse de conformidad al procedimiento proporcionado por el intermediario 111. ^{1}H RMN (400 MHz, $CDCl_3$) δ ppm: 7.68 (1H, dd, J=5.8, 8.8 Hz), 7.19 (1H, dd,

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519

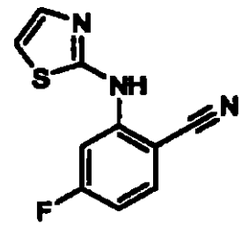
J=2.5, 9.1 Hz), 7.11-7.07 (1H, m), 4.46-4.42 (1H, m), 3.55 (2H, d, J=3.3 Hz), 2.72-2.52 (2H, m), 2.43-2.33 (1H, m), 2.09-2.01 (1H, m), 0.81 (9H, s), -0.04 (3H, s), -0.07 (3H, s); CLEM ($^+$ESI, M+H$^+$) m/z 349.

Intermediario 122



(S)-2-(2-((tert-Butildimetilsililoxi)metil)-5-oxopirrolidin-1-il)-4-fluorobenzonitrilo. El compuesto del título puede prepararse de conformidad al procedimiento proporcionado por el intermediario 111. ^{1}H RMN (400 MHz, $CDCl_3$) δ ppm: 7.68 (1H, dd, J=5.8, 8.6 Hz), 7.19 (1H, dd, J=2.5, 9.4 Hz), 7.11-7.07 (1H, m), 4.46-4.43 (1H, m), 3.55 (2H, d, J=3.3 Hz), 2.72-2.52 (2H, m), 2.43-2.33 (1H, m), 2.09-2.01 (1H, m), 0.81 (9H, s), -0.04 (3H, s), -0.07 (3H, s); CLEM ($^+$ESI, M+H$^+$) m/z 349.

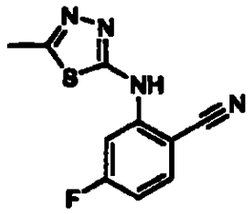
Intermediario 123



4-Fluoro-2-(tiazol-2-ilamino)benzonitrilo. El compuesto del título puede prepararse de conformidad al procedimiento

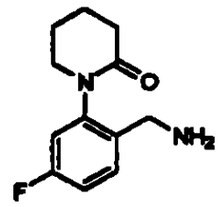
proporcionado por el intermediario 111. ^{1}H RMN (400 MHz, DMSO-d_6) δ ppm: 9.21 (1H, s), 8.39-8.35 (1H, m), 7.97 (1H, d, J=5.0 Hz), 7.23-7.13 (3H, m); CLEM ($^+$ESI, M+H$^+$) m/z 220.

Intermediario 124



4-Fluoro-2-(5-metil-1,3,4-tiadiazol-2-ilamino)benzonitrilo. El compuesto del título puede prepararse de conformidad al procedimiento proporcionado por el intermediario 111. ^{1}H RMN (400 MHz, DMSO-d_6) δ ppm: 8.30 (1H, dd, J=6.5, 8.8 Hz), 7.96 (1H, s), 7.26-7.19 (2H, m), 2.64 (3H, s); CLEM ($^+$ESI, M+H$^+$) m/z 235.

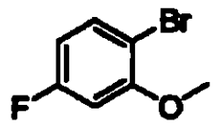
Intermediario 125



Sal de clorohidrato del ácido 1-(2-(Aminometil)-5-fluorofenil)piperidin-2-ona. A una solución agitada del intermediario 112, el 4-fluoro-2-(2-oxopiperidin-1-il)benzonitrilo (150 mg, 0.69 mmol) en H_2O (10 ml) se agregó etanol (10 ml) 10% de paladio en carbón mineral (50 mg) y HCl 1N (2.1 mL, 20.6 mmol). La reacción se agitó en un sistema

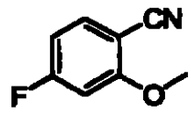
Parr bajo H_2 40 psi (2.812 kg/cm^2) durante 1h. Luego se removió el catalizador Pd/C por filtración en Celite y el filtrado se concentró in vacuo para proporcionar un sólido. Se agregó tolueno (2 X 50 ml) al sólido y la solución se evaporó in vacuo. CLEM ($M+H^+$) m/z 170.

Intermediario 126



1-Bromo-4-fluoro-2-metoxibenceno. A una mezcla de 2-bromo-5-fluorofenol (10 g, 50.8 mmol) y yodometano (11.2 g, 78.7 mmol) en dimetilformamida (100 ml) se agregó carbonato de potasio (10.9 g, 79 mmol) y la mezcla se agitó a temperatura ambiente durante 3 horas. La mezcla se diluyó con agua (100 ml) y se extrajo con éter (50 mL x 3). Los extractos combinados se lavaron con salmuera, se secaron sobre sulfato de magnesio anhidro, y se concentraron in vacuo para obtener 11.3 g de 1-bromo-4-fluoro-2-metoxibenceno como un aceite color ámbar.

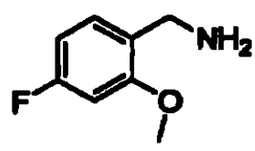
Intermediario 127



4-Fluoro-2-metoxibenzonitrilo. A una solución del intermediario 126, el 1-bromo-4-fluoro-2-metoxibenceno (9.0

g) en N-metilpirrolidona (100 mL, Sure Seal; Aldrich) se agregó CuCN (6.6 g, 73.7 mmol, 1.8 eq.; Aldrich), y la mezcla se agitó a 180°C bajo nitrógeno anhidro durante 5.5 horas. Después de enfriarse, se agregó 14% de NH_4OH acuoso (330 ml) y se agitó continuamente durante 45 minutos a temperatura ambiente. La mezcla se extrajo con éter (100 mL x 3), y los extractos combinados se lavaron secuencialmente con NH_4OH acuoso diluido, HCl diluido y salmuera, luego se secaron ($MgSO_4$), y se concentraron para proporcionar el compuesto del título (5.2 g, 85% Rendimiento en 2 etapas) como un sólido blanco: ^1H RMN ($CDCl_3$, 500 MHz) δ ppm: 3.91 (3H, s, OMe), 6.69 (1H, dd, J=2.3 Hz, J=10.5 Hz, Ar-H), 6.72 (1H, dt, J=2.5 Hz, J=J= 8.0 Hz, Ar-H), 7.55 (1H, dd, J=6.5 Hz, J=8.5 Hz, Ar-H); ^{13}C RMN ($CDCl_3$, 125.8 Hz) δ ppm: 56.49, 98.16, 100.06, 100.27, 108.31, 108.50, 115.83, 135.37, 135.46, 163.25, 163.34 165.47, 167.50. Una muestra analítica se obtuvo por trituración con éter: Análisis calculado para C_8H_6FNO: C 63.57, H 4.00, N 9.26; encontrado: C 63.36, H 3.91, N 9.16.

Intermediario 128

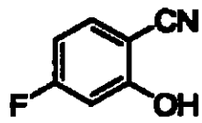


Clorohidrato de 4-Fluoro-2-metoxibencilamina. A una mezcla del intermediario 127, el 4-fluoro-2-metoxibenzonitrilo, (800 mg, 5.3 mmol) y HCl concentrado

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(0.53 mL, 6.36 mmol, 1.2 eq.) en etanol (20 ml) se agregó 10% de Pd-C (100 mg; Aldrich), y la mezcla se hidrogenó con 1 atm de hidrógeno durante 15 horas a temperatura ambiente. A esta mezcla se agregó una cantidad adicional de HCl concentrado (1 ml) y 10% de Pd-C (200 mg) y la reacción se permitió continuar durante otras 40 horas. La mezcla se filtró a través Celite y el filtrado se concentró in vacuo hasta secarse. El residuo se trituró con éter para proporcionar el compuesto del título (895 mg, Rendimiento 88%) como un polvo blanco: ^{1}H RMN ($CDCl_3$, 500 MHz) δ ppm: 3.84 (3H, s, OMe), 3.91 (2H, d, J=5.5 Hz, N-CH_2), 6.81 (1H, dt, J=2.5 Hz, J=J=8.5 Hz, Ar-H), 6.99 (1H, dd, J=2.5 Hz, J=11.3 Hz, Ar-H), 7.47 (1H, dd, J=7 Hz, J=8.5 Hz, Ar-H); ^{13}C RMN ($CDCl_3$, 125.8 Hz) δ ppm: 36.76, 56.03, 99.30, 99.51, 106.28, 106.45, 117.93, 117.95, 131.60, 131.69, 158.56, 158.64, 162.28, 164.22. EMAR (ESI) calculado para $C_8H_{11}FNO$ (M+H) 156.0825, encontrado 156.0830.

Intermediario 129

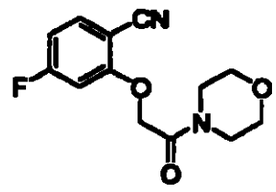


4-Fluoro-2-hidroxibenzonitrilo. Una mezcla del intermediario 127, el 4-fluoro-2-metoxibenzonitrilo, (4.53 g, 30 mmol) y $AlCl_3$ (5.0 g, 37.6 mmol; Aldrich) en tolueno anhidro (30 ml) se agitó a aproximadamente 130°C durante 18 horas. Después de enfriarse, se agregó agua con hielo (~50 mL) y la mezcla resultante se extrajo con éter (20 mL x 2).

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Los extractos combinados se lavaron secuencialmente con agua y salmuera, luego se secaron ($MgSO_4$) y se concentraron in vacuo para proporcionar el compuesto del título (3.90 g, 28.5 mmol, Rendimiento 95%) como un sólido blanco: ^1H RMN (DMSO-d6, 300 MHz) δ ppm: 6.74-6.84 (2H, m, Ar-Hs), 7.71 (1H, dd, J=7 Hz, J=8.5 Hz, Ar-H), 11.64 (1H, s, OH); ^{13}C RMN (DMSO-d6, 75.5 Hz) δ ppm: 95.13, 102.45, 102.78, 106.53, 106.83, 115.53, 134.68, 134.84, 161.41, 161.58, 163.00, 166.35. EMAR (ESI-) calculado para C_7H_3NOF (M-H) 136.0199, encontrado 136.0199.

Intermediario 130

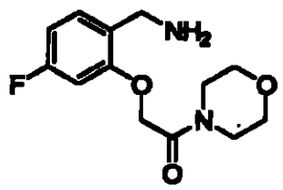


4-Fluoro-2-(2-morfolino-2-oxoetoxi)benzonitrilo. A una solución del intermediario 129, el 4-fluoro-2-hidroxibenzonitrilo, (685 mg, 5 mmol) en dimetilformamida (8 mL, Sure Seal; Aldrich) se agregó NaH (200 mg, 5 mmol; 60% de dispersión de aceite; Aldrich), y la mezcla se agitó durante 5 minutos bajo una atmósfera de nitrógeno anhidro. A esto se agregó 4-(2-cloroacetil)morfolina (900 mg, 5.5 mmol, 1.1 eq.; Avocado Organics), y se agitó continuamente a temperatura ambiente durante 21 horas. La reacción se apagó por adición cuidadosa de agua (30 mL). La mezcla resultante se extrajo con

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CH_2Cl_2 (25 mL x 2). Los extractos combinados se lavaron con salmuera, se secaron ($MgSO_4$) y se concentraron. El residuo se trituró para obtener 1.10 g (4.17 mmol, Rendimiento 83%) del compuesto del título como un sólido blanco: ^1H RMN ($CDCl_3$, 500 MHz) δ ppm: 3.63 (2H, t, J=4 Hz, NCH_2), 3.67 (1H, m, OCH), 3.72 (1H, m, OCH), 4.86 (2H, s, OCH_2), 6.80-6.86 (2H, m, Ar-Hs), 7.61 (1H, dd, J=8.5 Hz, 6.1 Hz, Ar-H); ^{13}C RMN ($CDCl_3$, 125.77 Hz) δ ppm: 42.63, 46.04, 66.80, 68.33, 98.45, 98.47, 101.57, 101.79, 109.56, 109.74, 115.42, 135.48, 135.57, 161.26, 161.35, 114.79, 165.23, 167.28. EMAR calculado para $C_{13}H_{14}N_2O_3F$ (M+H) 265.0988, encontrado 265.0998.

Intermediario 131

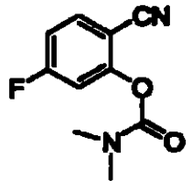


Clorohidrato de 2-(2-(Aminometil)-5-fluorofenoxi)-1-morfolinoetanona. Una solución del intermediario 130, el 4-fluoro-2-(2-morfolino-2-oxoetoxi)benzonitrilo, (500 mg, 1.89 mmol) en etanol caliente (30 ml) y acetato de etilo (30 ml) se mezcló con HCl concentrado (0.32 mL, 3.78 mmol, 2 eq.). A esto se agregó 10% de Pd-C (100 mg; Aldrich), y la mezcla se hidrogenó a 1 atm de hidrógeno durante 20 horas a temperatura ambiente. A esta mezcla se agregó una cantidad adicional de 10% de Pd-C (50 mg) y se agitó continuamente durante otras 7

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horas. La mezcla se filtró a través Celite y el filtrado se concentró in vacuo hasta secarse. El residuo se trituró con acetato de etilo, luego con etanol para obtener el compuesto del título (168 mg, Rendimiento 29%) como un polvo blanco opaco: ^{1}H RMN (CD_3OD, 500 MHz) δ ppm: 3.55 (2H, t, J=5 Hz, NCH_2), 3.62 (2H, t, J=5 Hz, NCH_2), 3.70 (2H, t, J=5 Hz, OCH_2), 3.75 (2H, t, J=5 Hz, OCH_2), 4.17 (2H, s, NCH_2), 5.17 (2H, s, OCH_2), 6.82 (1H, dt, J=2.5, 8.5 Hz, Ar-H), 7.05 (1H, dd, J=2.5, 10.5 Hz, Ar-H), 7.43 (1H, dd, J=6.5, 8.5 Hz, Ar-H); ^{13}C RMN (CD_3OD, 125.77 Hz) δ ppm: 39.40, 42.49, 44.97, 66.11, 66.46, 66.59, 101.38, 101.59, 108.40, 108.57, 118.40, 132.53, 132.62, 158.43, 158.52, 63.87, 165.83, 168.27. EMAR (ESI) calculado para $C_{13}H_{18}N_2O_3F$ (M+H) 269.1301, encontrado 269.1301.

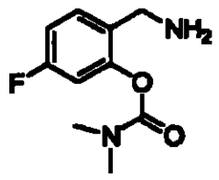
Intermediario 132



éster de 2-ciano-5-fluoro-fenilo del ácido dimetil-carbámico. Bajo N_2, una solución agitada del intermediario 129, el 4-fluoro-2-hidroxibenzonitrilo (685 mg, 5.00 mmol), cloruro de dimetilcarbamoilo, y trietilamina (606 mg, 6 mmol) en dicloroetano (10 ml) se calentó a reflujo durante 20 horas. La mezcla fría se diluyó con dicloroetano (10 ml) se lavó con agua, y salmuera. La capa

orgánica se separó, se secó (Na_2SO_4), se concentró, y el residuo se purificó por cromatografía de columna (SiO_2, 5% de acetato de etilo-CH_2Cl_2) para proporcionar 700 mg (67% Rendimiento) del compuesto del título como un sólido cristalino: ^1H RMN ($CDCl_3$, 500 MHz) δ ppm: 3.03 (3H, s, NMe), 3.15 (3H, s, NMe), 6.99 (1H, dt, J=2.5 Hz, 8.5 Hz, Ar-H), 7.23 (1H, dd, J=2.5 Hz, 9.5 Hz, Ar-H), 7.61 (1H, dd, J=9 Hz, 6 Hz, Ar-H); ^{13}C RMN ($CDCl_3$, 125.77 Hz) δ ppm: 36.76, 37.06, 102.84, 102.86, 111.59, 111.79, 113.24, 113.42, 114.99, 134.36, 134.45, 152.54, 155.06, 155.16, 164.26, 166.31. EMAR (ESI) calculado para $C_{10}H_{10}N_2O_2F$ (M+H) 209.0726, encontrado 209.0722.

Intermediario 133

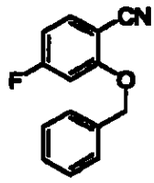


Clorohidrato de éster de 2-aminometil-5-fluoro-fenilo del ácido dimetil-carbámico. A una solución del intermediario 132, el éster de 2-ciano-5-fluoro-fenilo del ácido dimetil-carbamico (340 mg, 1.63 mmol) en acetato de etilo (20 ml) y etanol (20 ml), se agregó HCl concentrado (0.4 ml) y 10% de Pd-C (100 mg) y la mezcla hidrógeno en un agitador Parr con 55 psi (3.8665 kg/cm^2) de hidrógeno durante 20 horas. La mezcla de reacción se filtró a través de celite, y el filtrado se concentró in vacuo

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para dar un aceite, el cual se dividió entre acetato de etilo (10 ml) y agua (10 ml). Después de la separación, la fase acuosa se lavó con acetato de etilo adicional (5 ml). Los extractos combinados se concentraron in vacuo hasta secarse. El residuo del aceite se trituró con éter para proporcionar 145 mg (Rendimiento 38%) del compuesto del título, como un polvo color marrón: ^{1}H RMN (CD_3OD, 500 MHz) δ ppm: 3.06 (3H, s, NMe), 3.21 (3H, s, NMe), 4.11 (2H, s, NCH_2), 7.13 (2H, m, Ar-Hs), 7.60 (1H, m, Ar-H); ^{13}C RMN (CD_3OD, 125.77 Hz) δ ppm: 36.03, 36.25, 37.58, 110.79, 110.99, 113.26, 113.43, 122.32, 132.18, 132.25, 151.55, 154.72, 162.69, 164.67. EMAR (ESI) calculado para $C_{10}H_{13}N_2O_2F$ (M+H) 213.1039, encontrado 213.1039.

Intermediario 134

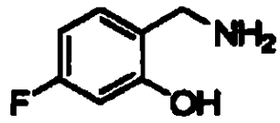


2-(Benciloxi)-4-fluorobenzonitrilo. Se agregó alcohol de bencilo (13 mL, 125 mmol) lentamente a una suspensión agitada de NaH (95%, 2.86 g, 113 mmol) en tolueno (200 mL) a temperatura ambiente. Después de 30 minutos, se agregó 2,4-difluorobenzonitrilo (15.3 g, 110 mmol; Aldrich) todo de una vez y se agitó continuamente durante la noche (18 h). Después de esto, la mezcla de reacción se lavó con agua (2 X 25 mL) y salmuera (25 mI). La capa orgánica se secó (Na_2SO_4), se filtró y se concentró para dar una mezcla espesa la cual se trituró

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con hexanos y se filtró para proporcionar el compuesto del título como un sólido blanco (20.34 g, 81 % rendimiento). ^{1}H RMN (500 MHz, $CDCl_3$): 7.59-7.55 (1H, m), 7.45-7.34 (5H, m), 6.75-6.71 (2H, m), 5.19 (2H, s); ^{13}C RMN (125.76 MHz, DMSO-d6) δ ppm: 71.16, 98.75, 101.54, 101.75, 108.66, 108.84, 115.83, 127.16, 128.58, 128.94, 135.03, 135.44, 135.54, 162.22, 162.31, 165.26, 167.29. CLEM calculado para $C_{14}H_{11}FNO$: 228.2; encontrado: 228.0.

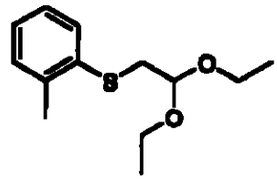
Intermediario 135



Clorohidrato de 2-Hidroxi-4-fluoro-bencilamina. Una solución del intermediario 134, el 2-(benciloxi)-4-fluorobenzonitrilo, (9.03 g, 39.7 mmol) en etanol (100 mL) y acetato de etilo (100 mL) se agitó con 10% de paladio en carbono (1.67 g,) y se concentró el ácido clorhídrico (12 mL, 144 mmol) bajo una atmósfera de hidrógeno a 60 psi (4.218 kg/cm^2) durante 4 días. El catalizador se removió por filtración a través de celite, y el filtrado se concentró. El producto crudo se trituró con éter y el sólido resultante se colectó por filtración para dar el compuesto del título (5.24 g, 74% rendimiento) como un sólido anaranjado pálido. ^{1}H RMN (500 MHz, DMSO-D6) δ ppm: 10.81 (1H, s), 8.18 (3H, s), 7.36 (1H, t, J=7.3 Hz), 6.79 (1H, dd, J=10.8, 2.6 Hz), 6.66 (1H,

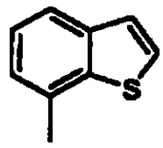
dt, J=8.5, 2.3 Hz), 3.90 (2H, d, J=5.2 Hz).

Intermediario 136



(2,2-Dietoxietil)(o-tolil)sulfano. En etanol (50 ml) se disolvió metal de sodio (1.6 g, 66 mmol) a 23°C. Se agregó 2-Metilbencenotiol (8.1 mL, 68 mmol) lentamente a esta solución, seguido por bromoacetaldehido dietilacetal (9.50 mL, 63 mmol). La mezcla de reacción se agitó a reflujo durante 18 h. El solvente luego se evaporó in vacuo y el residuo se lavó con H_2O (100 ml) y se extrajo con éter (100 ml). La solución orgánica se secó ($MgSO_4$), se concentró in vacuo y se purificó por destilación para proporcionar el compuesto del título (13.48 g, 82% rendimiento): ^1H RMN (400 MHz, $CDCl_3$) δ ppm: 7.33 (1H, d, J=7.9 Hz), 7.16-7.08 (3H, m), 4.65 (1H, t, J=5.6 Hz), 3.66 (2H, q, J=7.0 Hz), 3.55 (2H, q, J=7.0 Hz), 3.09 (2H, d, J=5.6 Hz), 2.38 (3H, s), 1.20 (6H, t, J=7.0 Hz). CLEM $(M+H)^+$ m/z 241 (t = 2.65 min.).

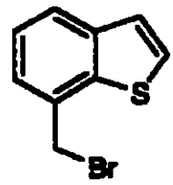
Intermediario 137



7-Metilbenzo[b]tiofeno. A una solución del

intermediario 136, el (2,2-dietoxietil)(o-tolil)sulfano (0.58 g, 2.41 mmol) en clorobenceno (20 mL) se agregó ácido polifosfórico. La mezcla de reacción se agitó a reflujo durante 18 h. Luego se agregó agua (100 ml) y el material orgánico se extrajo con CH_2Cl_2 (2 X 50 mL). La solución orgánica se secó ($MgSO_4$) y se concentró in vacuo para proporcionar 335 mg (94% rendimiento) del compuesto del título: ^1H RMN (400 MHz, $CDCl_3$) δ: 7.68 (1H, d, J=7.8 Hz), 7.43 (1H, d, J=5.4 Hz), 7.36 (1H, d, J=5.4 Hz), 7.30 (1H, dd, J=7.8, 7.1 Hz), 7.14 (1H, d, J=7.1 Hz), 2.58 (3H, s); CLEM $(M+H)^+$ m/z 148.

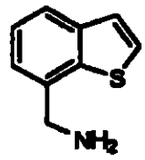
Intermediario 138



7-(Bromometil)benzo[b]tiofeno. A una solución del intermediario 137, el 7-metilbenzo[b]tiofeno (1.0 g, 6.5 mmol) en CCl_4 (20 ml) se agregó peróxido de benzoilo (1.1 g, 4.54 mmol) seguido por una adición en porciones de NBS (1.15g, 6.5 mmol). La mezcla de reacción se agitó a reflujo mientras se irradió con una lámpara de 250 W. La mezcla de reacción se agitó a reflujo durante 3 h. La solución se enfrió, se filtró y el solvente se evaporó in vacuo. El residuo se sujetó a cromatografía de columna en gel de sílice con hexanos como el eluyente para proporcionar el compuesto

del título (0.570 g, 33% rendimiento): ^{1}H RMN (400 MHz, $CDCl_3$) δ 7.80 (1H, dd, J=7.8, 1.7 Hz), 7.49 (1H, d, J=5.4 Hz), 7.40-7.33 (3H, m), 4.78 (2H, s). CLEM $(M+H)^+$ m/z 209.

Intermediario 139

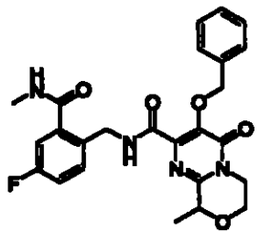


Clorohidrato de Benzo[b]tiofen-7-ilmetanamina. Al intermediario 138, el 7-(bromometil)benzo[b]tiofeno (0.20g, 0.96 mmol) se agregó una solución metanólica saturada con amonio (30 ml). La mezcla de reacción se calentó en una bomba de regalo a 70°C durante 18 h. El solvente se evaporó in vacuo y el residuo se disolvió en MeOH (10 ml). Se agregó HCl (1M en etanol, 1 mL) a la solución y los solventes se removieron in vacuo para proporcionar el compuesto del título (0.177 g, 99% rendimiento); CLEM $(M+H)^+$ m/z 164.

Intermediarios 140-148

La síntesis de los intermediarios 140-148 proporcionó los procedimientos representativos para la síntesis de los otros compuestos de la invención.

Intermediario 140



N-{4-Fluoro-2-(metilcarbamoil)bencil}-3-benciloxi-9-metil-

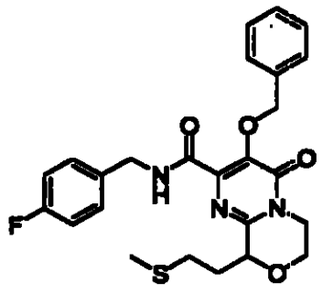
4-oxo-4,6,7,9-tetrahidropirimido[2,1-c][1,4]oxazina-2-carboxamida. Una mezcla del intermediario 27, el ácido 3-benciloxi-9-metil-4-oxo-4,6,7,9-tetrahidropirimido[2,1-c][1,4]oxazina-2-carboxílico (0.172 g, 0.54 mmol) y el intermediario 39, la sal de trifluoroacetato de 2-(aminometil)-5-fluoro-N-metilbenzamida (0.177 g, 0.60 mmol) en diclorometano (10 ml) se trató a 22°C con trietilamina (0.17 ml, 1.22 mmol) seguido por benzotriazol-1-iloxi-tris-pirrolidino-fosfonio hexafluorofosfato (PyBOP) (0.340 g, 0.65 mmol). Después de 3 h, la mezcla de reacción se diluyó con acetato de etilo, se lavó con bicarbonato de sodio saturado y salmuera luego se secó sobre sulfato de magnesio anhidro.

La evaporación del solvente seguida por cromatografía del residuo en gel de sílice (gradiente de elución acetato de etilo 50-100% en tolueno) dio 0.260 g (100% rendimiento) de la amida del título como un sólido blanco.

^{1}HRMN 400 MHz ($CDCl_3$) δ (ppm): 1.70 (3H, d, J=6.6 Hz, CH_3), 3.01 (3H, d, J=4.7 Hz, NCH_3), 3.89 (2H, m, CH_2), 4.14 (1H, m, CH), 4.29 (1H, m, CH), 4.53 (2H, d, J=6.7 Hz, NCH_2), 4.69 (1H, q, J=6.6 Hz, OCH), 5.35 (2H, s, OCH_2), 6.69 (1H, amplio q, NH), 7.09 (1H, m, aromático), 7.16 (1H, m, aromático), 7.32 (3H, m, aromáticos), 7.42 (1H, m, aromático), 7.47 (2H, m, aromáticos), 8.61 (1H, amplio t, NH). EMAR (ESI^+)

calculado para $C_{25}H_{26}FN_4O_5$ $[M+H^+]$: 481.1887: encontrado: 481.1884.

Intermediario 141



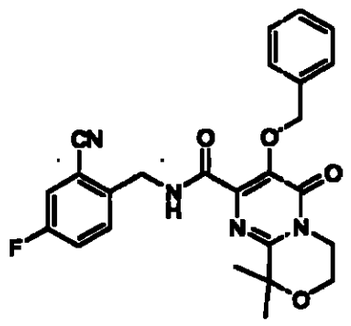
N-(4-fluorobencil)-3-(benciloxi)-9-(2-(metiltio)etil)-4-oxo-4,6,7,9-tetrahidropirimido[2,1-c][1,4]oxazina-2-carboxamida. Una solución del intermediario 22 (82mg, 0.22 mmol) y O-(7-azabenzotriazol-1-il)-N,N,N',N'-tetrametiluronio hexafluorofosfato (HATU) (152mg, 0.4 mmol) en 1 mL de dimetilformamida se agitó durante 20 minutos bajo N_2.

Luego se agregó 4-Fluorobencilamina (38mg, 0.3mmol) y se agitó continuamente durante 16 horas. La dimetilformamida se evaporó bajo presión reducida y el residuo restante se disolvió en CH_2Cl_2.

La solución resultante se lavó con HCl diluido. El solvente se removió bajo presión reducida y el producto crudo se purificó por cromatografía (SiO_2, acetato de etilo) para proporcionar el compuesto del título (70mg, Rendimiento = 66%). CL/EM m/e 484 (M+H).

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Intermediario 142



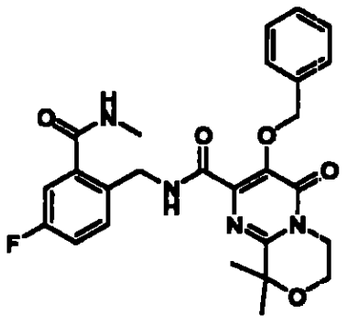
3-(Benciloxi)-2-(6-fluoro-1-oxoisoindolina-2-carbonil)-9,9-dimetil-6,7-dihidropirimido[2,1-c][1,4]oxazin-4(9H)-ona.

A una suspensión agitada del intermediario 27, el ácido 3-(benciloxi)-9,9-dimetil-4-oxo-4,6,7,9-tetrahidropirimido-[2,1-c][1,4]oxazina-2-carboxílico, (1.65 g, 5 mmol) en CH_2Cl_2 (15 ml) se agregó una cantidad catalítica de dimetilformamida y 10 mL de cloruro de oxalilo 2 M en CH_2Cl_2. Después de 30 minutos, la solución amarilla clara resultante se concentró para proporcionar un solido café ligero. Este sólido se disolvió en CH_2Cl_2 (50 ml) y se agregó a una mezcla agitada del intermediario 107, la sal del ácido 2-(aminometil)-5-fluorobenzonitrilo trifluoroacético, (1.77 g, 5.97 mmol) y dietilisopropilamina (2.6 mL, 15 mmol) en CH_2Cl_2 (100 ml). Después de 1h, la mezcla de reacción café clara se concentró y el residuo resultante se disolvió en acetato de etilo (200 ml) luego se lavó secuencialmente con agua (25 mL), HCl 1N (25 ml), agua (25 ml) y salmuera (25 ml). Las capas acuosas combinadas se extrajeron con CH_2Cl_2 (3 X 50

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ml). Las fases orgánicas combinadas se secaron (Na_2SO_4), se filtraron, se concentraron y se purificaron por cromatografía instantánea (SiO_2), usando 30-50% de acetato de etilo/Hexanos como eluyente para proporcionar el compuesto del título (0.331 g, 14% rendimiento) como un polvo amarillo. ^1H RMN (500 MHz, $CDCl_3$) δ 7.48-7.45 (1H, m), 7.88 (2H, d, J=7.9 Hz), 7.30 (2H, d, J=7.0 Hz), 7.12 (2H, t, J=7.6 Hz), 7.05-7.01 (1H, m), 5.22 (2H, s), 4.77 (2H, s), 4.06 (4H, s), 1.59 (6H, s). EMAR (M+H) calculado para $C_{25}H_{23}FN_3O_5$: 464.1622; encontrado: 464.1628.

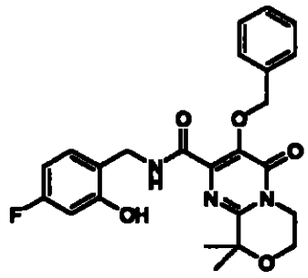
Intermediario 143



N-(4-Fluoro-2-(metilcarbamoil)bencil)-3-(benciloxi)-9,9-dimetil-4-oxo-4,6,7,9-tetrahidropirimido[2,1-c][1,4]oxazina-2-carboxamida. Un matraz de fondo redondo de 25 mL se cargó con el intermediario 27, el ácido 3-(benciloxi)-9,9-dimetil-4-oxo-4,6,7,9-tetrahidropirimido-[2,1-c][1,4]oxazina-2-carboxílico (0.991 g, 3.0 mmol), el intermediario 39, la sal del ácido 2-(aminometil)-5-fluoro-N-metilbenzamida trifluoroacético (1.185 g, 4.0 mmol), 4-dimetilaminopiridina

(DMAP, 1.1 g, 9.0 mmol) y O-(7-azabenzotriazol-1-il)-N,N,N',N'-tetrametiluronio hexafluorofosfato (HATU, 1.722 g, 4.5 mmol). Se agregó dimetilformamida (20 mL) y la mezcla se agitó durante 1 h a temperatura ambiente. Después de esto, la mezcla de reacción se diluyó con acetato de etilo (100 mL) luego se lavó con agua (3 X 25 mL) y salmuera (25 mL). La capa orgánica se secó (Na_2SO_4), se filtró, se concentró y se purificó por cromatografía instantánea (SiO_2), se eluyó con hexanos/acetato de etilo (1:1 hasta 1:3) seguido por acetato de etilo, para proporcionar el compuesto del título como un sólido blanco opaco (1.48 g, 100% rendimiento). ^1H RMN (500 MHz, $CDCl_3$) δ ppm: 8.49 (1H, t, J=6.1 Hz), 7.48-7.46 (2H, m), 7.43 (1H, dd, J=8.5, 5.5 Hz), 7.31-7.27 (3H, m), 7.12 (1H, dd, J=8.9, 2.7 Hz), 7.05 (1H, td, J=8.2, 2.7 Hz), 6.52 (1H, br s), 5.26 (2H, s), 4.53 (2H, d, J=6.4 Hz), 4.01 (2H, t, J=4.9 Hz), 3.96 (2H, t, J=4.9 Hz), 2.97 (3H, d, J=4.9 Hz), 1.62 (6H, s). EMAR (M+H) calculado para $C_{26}H_{28}FN_4O_5$: 495.2044; encontrado: 495.2032.

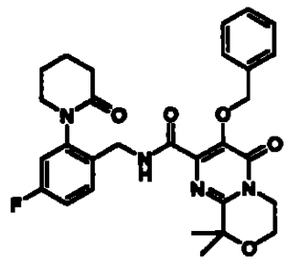
Intermediario 144



N-(4-Fluoro-2-hidroxibencil)-3-(benciloxi)-9,9-

dimetil-4-oxo-4,6,7,9-tetrahidropirimido[2,1-c][1,4]oxazina-2-carboxamida. Una solución del intermediario 27, el ácido 3-(benciloxi)-9,9-dimetil-4-oxo-4,6,7,9-tetrahidropirimido-[2,1-c][1,4]oxazina-2-carboxílico, (1.50 g, 4.54 mmol) y HATU (2.07 g, 5.45 mmol) en dimetilformamida anhidro se agitó durante 20 minutos bajo una atmósfera de nitrógeno a temperatura ambiente. A la solución se agregó el intermediario 135, el clorohidrato de 2-hidroxi-4-fluoro-bencilamina, (1.05 g, 5.9 mmol) seguido por DMAP (1.39 g, 11.4 mmol), y la mezcla de reacción se agitó a 60°C durante 90 minutos. El solvente se removió in vacuo y el residuo se purificó por cromatografía de columna instantánea (SiO2), se eluyó con 40%-60% de acetato de etilo en hexanos para dar el compuesto del título (1.31 g, 64% rendimiento) como un sólido. ^{1}H RMN (500 MHz, $CDCl_3$) δ ppm: 59.69 (1H, br s), 8.18 (1H, t, J=6.3 Hz), 7.44 (2H, dd, J=6.6, 2.6 Hz), 7.30-7.35 (3H, m), 7.00 (1H, dd, J=8.2, 6.7 Hz), 6.68 (1H, dd, J=10.4, 2.4 Hz), 6.54 (1H, dd, J=8.2, 2.4 Hz), 5.29 (2H, s), 4.36 (2H, d, J=6.7 Hz), 3.97-4.05 (4H, m), 1.61 (6H, s).

Intermediario 145



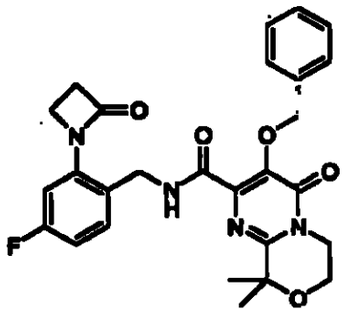
N-(4-Fluoro-2-(2-oxopiperidin-1-il)bencil)-3-(benciloxi)-9,9-dimetil-4-oxo-4,6,7,9-

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tetrahidropirimido[2,1-c][1,4]oxazin-4(9H)-ona. Al intermediario 27, el ácido 3-(benciloxi)-9,9-dimetil-4-oxo-4,6,7,9-tetrahidropirimido[2,1-c][1,4]oxazina-2-carboxílico, (80 mg, 0.242 mmol) en CH_3CN/dimetilformamida (5 mL:1 mL:) se agregó el intermediario 125, la sal del clorohidrato de 1-(2-(aminometil)-5-fluorofenil)piperidin-2-ona (69 mg, 0.266 mmol), benzotriazol-1-il-oxi-tris-pirrolidino-fosfonio hexafluorofosfato (PyBOP) (139 mg, 0.266 mmol) y diisopropiletilamina (169 µL, 0.968 mmol). La mezcla de reacción se agitó a 23°C durante 3h. Los solventes luego se removieron in vacuo y se agregó una solución de HCl acuoso (1N, 25 ml). Esto se extrajo con acetato de etilo (3 X 25 mL). Las fracciones orgánicas combinadas se secaron ($MgSO_4$), se filtraron y se concentraron in vacuo. El material crudo se purificó en un sistema Biotage usando una columna de gel de sílice con Hexanos/acetat de etilo (1:1) hasta (1:5) como eluyente para proporcionar 114 mg (88% rendimiento) del compuesto del título. ^{1}HRMN 400 MHz (DMSO) δ ppm: 8.73 (1H, dd, (t), J=6.0 Hz), 7.46 (2H, m), 7.35 (4H, m), 7.18 (1H, dd, J=9.8, 3.0 Hz) 7.0 (1H, m), 5.10 (2H, s), 4.43 (1H, dd, J=15.0, 7.08 Hz), 4.06 (1H, dd, J=15.0, 5.56), 4.02 (2H, t, J=5.0 Hz), 3.90 (2H, t, J=5.0 Hz), 3.64 (1H, m), 3.44 (1H, m), 2.45 (1H, m), 2.35 (1H, m), 1.86 (4H, m), 1.56

(6H, s). CLEM $(M+H)^+$ m/z 535.

Intermediario 146

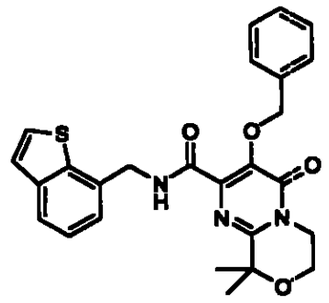


N-(4-Fluoro-2-(2-oxoazetidin-1-il)bencil)-3-(benciloxi)-9,9-dimetil-4-oxo-4,6,,7,9-tetrahidropirimido[2,1-c][1,4]oxazina-2-carboxamida. A una solución del intermediario 27, el ácido 3-(benciloxi)-9,9-dimetil-4-oxo-4,6,7,9-tetrahidropirimido[2,1-c][1,4]oxazina-2-carboxílico, (0.142 g, 0.430 mmol) en CH_3CN:dimetilformamida (30 mL: 5 ml) se agregó el intermediario 120, el clorohidrato de 1-(2-(aminometil)-5-fluorofenil)azetidin-2-ona (0.100 g, 0.43 mmol), (benzotriazol-1-iloxi)tris(dimetilamino)fosfonio hexafluorofosfato (0.207 g, 0.4 70 mmol) y diisopropiletilamina (280 µL, 1.72 mmol). La mezcla de reacción se agitó a 23°C durante 18h. Los solventes se removieron in vacuo y se agregó HCl 1N (50 ml). Esto se extrajo con acetato de etilo (2 X 50 ml). Los extractos orgánicos combinados se secaron ($MgSO_4$), se filtraron y se concentraron in vacuo. El residuo se purificó en un sistema Biotage usando una columna de gel de sílice con acetato de

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etilo como eluyente para proporcionar el compuesto del título (0.157 g, 72% rendimiento). ^{1}H RMN (400 MHz, MeOD) δ ppm: 7.88 (1H, d, J=8.3 Hz), 7.76 (1H, d, J=8.0Hz), 7.58-7.30 (4H, m), 7.10 (1H, dd, J=10.2, 2.5 Hz), 6.90 (1H, m), 5.20 (2H, s), 4.55 (2H, s), 4.04 (2H, m), 3.96 (2H, m), 3.78 (2H, t, J=4.2 Hz), 3.10 (2H, t, J=4.2 Hz), 1.58 (6H, s); CLEM $(M+H)^+$ m/z 506.

Intermediario 147

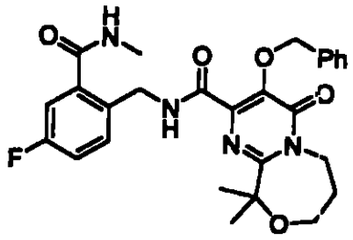


N-(Benzo[b]tiofen-7-ilmetil)-3-(benciloxi)-9,9-dimetil-4-oxo-4,6,7,9-tetrahidropirimido[2,1-c][1,4]oxazina-2-carboxamida. A una solución del intermediario 27, el ácido 3-(benciloxi)-9,9-dimetil-4-oxo-4,6,7,9-tetrahidropirimido[2,1-c][1,4]oxazina-2-carboxílico (0.200 g, 0.60 mmol) en CH_3CN: dimetilformamida (30 mL: 5 mL) se agregó al intermediario 139, el clorohidrato de benzo[b]tiofen-7-ilmetanamina (0.069 g, 0.266 mmol), benzotriazol-1-il-oxi-tris-pirrolidino-fosfonio hexafluorofosfato (PyBOP) (0.347 g, 0.670 mmol) y diisopropiletilamina (420 µL, 2.40 mmol). La mezcla de reacción se agitó a 23°C durante 60 h. Los solventes luego se removieron in vacuo y se agregó HCl 1N (50 mL). Esto se

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extrajo con acetato de etilo (2 X 50 mL). Los extractos orgánicos combinados se secaron ($MgSO_4$), se filtraron y se concentraron in vacuo. El residuo se purificó en un sistema Biotage usando una columna de gel de sílice con un gradiente hexano:acetato de etilo (1:1) hasta (1:5) como eluyente para proporcionar el compuesto del título (0.279 g, 87% rendimiento): ^1H RMN (400 MHz, DEMO-d_6) δ: 9.11 (1H, dd, J=5.6 Hz), 7.81 (1H, m), 7.77 (1H, d, J=5.6 Hz), 7.52 (1H, d, J=5.6 Hz), 7.48-7.26 (6H, m), 5.09 (2H, s), 4.67 (2H, d, J=5.2 Hz), 4.04 (2H, m), 3.90 (2H, m), 1.58 (6H, s). CLEM $(M+H)^+$ m/z 476.

Intermediario 148



N-(4-Fluoro-2-(metilcarbamoil)bencil)-3-(benciloxi)-10,10-dimetil-4-oxo-6,7,8,10-tetrahidro-4H-pirimido[2,1-c][1,4]oxazepina-2-carboxamida. Una solución del intermediario 35, el ácido 3-(benciloxi)-10,10-dimetil-4-oxo-6,7,8,10-tetrahidro-4H-pirimido[2,1-c][1,4]oxazepina-2-carboxílico en dimetilformamida anhidra (4 mL) se trató con HATU (0.278 g, 0.70 mmol) y se agitó durante 10 minutos. La mezcla de reacción se

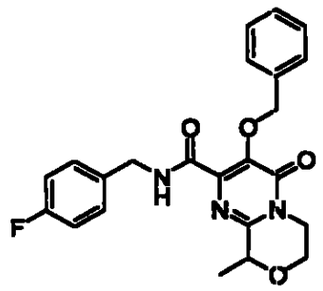
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trató con la sal del ácido 2-(aminometil)-5-fluoro-N-metilbenzamida trifluoroacético (0.24 g, 0.8 mmol), seguido por dimetilaminopiridina (0.121 g, 0.97 mmol), luego se agitó durante 4 horas a 60°C. Siguiendo esto, el solvente se removió in vacuo y el residuo restante se disolvió en acetato de etilo (15 mL) y se lavó con HCl 1.0N (15 mL). La capa orgánica se secó (sulfato de sodio), se filtró, y se concentró hasta secarse. El producto crudo se purificó por cromatografía de columna instantánea (SiO_2), se eluyó con acetato de etilo. Las fracciones que contenía el producto se vaciaron, se concentraron hasta secarse y se trituraron con éter para proporcionar 0.366 g del compuesto del título como un sólido cristalino blanco. ^1H RMN (500 MHz, d_6-acetona) δ ppm: 8.71-8.82 (1H, m), 7.84-7.95 (1H, br), 7.47-7.62 (4H, m), 7.27-7.40 (5H, m), 7.20 (1H, dt, J=8.5, 2.7 Hz), 5.15-5.21 (2H, br s), 4.48-4.60 (4H, m), 2.96 (2H, s), 2.94 (2H, s), 1.62-1.64 (6H, s).

Intermediarios 149-174

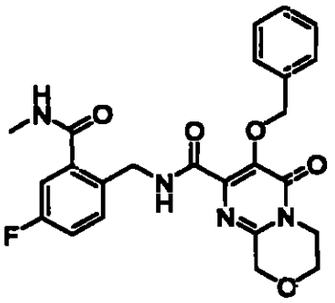
Los intermediarios 149-174 se prepararon de conformidad a los procedimientos de acoplamiento descritos en los intermediarios 140-148.

Intermediario 149



N-(4-Fluorobencil)-3-(benciloxi)-9-metil-4-oxo-4,6,7,9-tetrahidropirimido[2,1-c][1,4]oxazina-2-carboxamida. El compuesto del título puede ser preparado a partir del intermediario 16, el ácido 3-benciloxi-9-metil-4-oxo-4,6,7,9-tetrahidropirimido[2,1-c][1,4]oxazina-2-carboxílico y 4-fluorobencilamina. ^{1}H RMN 400 MHz ($CDCl_3$) δ (ppm): 1.67 (3H, d, J=6.6 Hz, CH_3), 3.91 (2H, m, CH_2), 4.12-4.35 (2H, m, CH_2), 4.52 (2H, d, J=5.9 Hz, NCH_2), 4.70 (1H, q, J = 6.6 Hz, OCH), 5.33 (2H, s, OCH_2), 7.02 (2H, m, aromáticos), 7.25 (2H, m, aromáticos), 7.35 (3H, m, aromáticos), 7.47 (2H, m, aromáticos), 7.71 (1H, amplio t, NH).

Intermediario 150

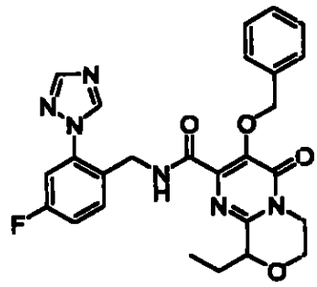


N-(4-Fluoro-2-(metilcarbamoil)bencil)-3-(benciloxi)-4-

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oxo-4,6,7,9-tetrahidropirimido[2,1-c][1,4]oxazina-2-carboxamida. El compuesto del título puede ser preparado del intermediario 7, el ácido 3-(benciloxi)-4-oxo-4,6,7,9-tetrahidropirimido[2,1-c][1,4]oxazina-2-carboxílico y intermediario 39, 2-(aminometil)-5-fluoro-N-metilbenzamida. Cristales blancos; p.f. 189-190°C (acetato de etilo). ^{1}H RMN 400 MHz ($CDCl_3$) δ (ppm): 3.01 (3H, d, J=4.5 Hz, NCH_3), 4.00 (2H, m, CH_2), 4.08 (1H, m, CH), 4.50 (2H, d, J=6.6 Hz, NCH_2), 4.71 (2H, s, OCH_2), 5.38 (2H, s, OCH_2), 6.88 (1H, amplio q, NH), 7.07 (1H, m, aromático), 7.16 (1H, dd, J=2.5 Hz y J=8.6 Hz, aromático), 7.30-7.44 (6H, m, aromáticos), 8.55 (1H, amplio t, NH). Análisis calculado para $C_{24}H_{23}FN_4O_5$: C 61.80, H 4.97, N 12.01. Encontrado: C 61.84, H 4.82, N 12.00.

Intermediario 151

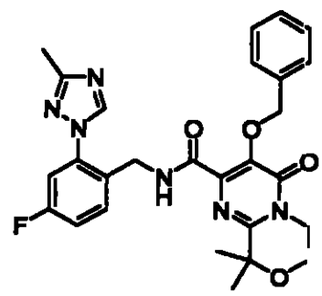


N-(4-Fluoro-2-(1H-1,2,4-triazol-1-il)bencil)-3-(benciloxi)-9-etil-4-oxo-4,6,7,9-tetrahidropirimido[2,1-c][1,4]oxazina-2-carboxamida. El compuesto del título puede ser preparado del ácido 3-(benciloxi)-9-etil-4-oxo-4,6,7,9-tetrahidropirimido[2,1-c][1,4]oxazina-2-carboxílico el cual se sintetizó usando el método descrito para la síntesis o

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intermediarios 7 y 16, y el intermediario 69, (4-fluoro-2-(1H-1,2,4-triazol-1-il)fenil)metanamina. Agujas blancas; p.f. 155-157°C (acetato de etilo). ^{1}HRMN 400 MHz ($CDCl_3$) δ (ppm): 1.03 (3H, t, J=7.5 Hz, CH_3), 1.97-2.02 (1H, m, CH), 2.29-2.32 (1H, m, CH),. 3.83-3.88 (2H, m, CH_2), 4.15-4.31 (2H, m, CH_2), 4.44 (2H, m, CH_2), 4.53 (1H, m, CH), 5.34 (2H, s, OCH_2), 7.08 (1H, dd, J = 2.5 Hz y J=8.6 Hz, aromático), 7.20 (1H, m, aromático), 7.29-7.31 (3H, m, aromáticos), 7.47 (2H, m, aromáticos), 7.74 (1H, dd, J=6.1 Hz y J=8.6 Hz, aromático), 8.02 (1H, s, CH), 8.41 (1H, s, CH), 8.55 (1H, amplio t, NH). Análisis calculado para $C_{26}H_{25}FN_6O_4$: C 61.89, H 4.99, N 16.65. Encontrado: C 61.67, H 5.13, N 16.61.

Intermediario 152

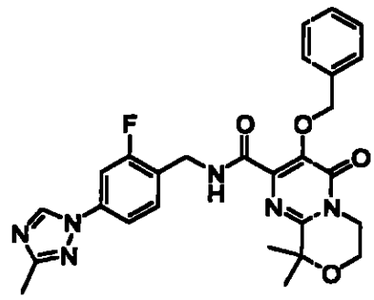


N-(4-Fluoro-2-(3-metil-1H-1,2,4-triazol-1-il)bencil)-3-(benciloxi)-9,9-dimetil-4-oxo-4,6,7,9-tetrahidropirimido[2,1-c][1,4]oxazina-2-carboxamida. El compuesto del título puede ser preparado a partir del intermediario 27, el ácido 3-(benciloxi)-9,9-dimetil-4-oxo-4,6,7,9-tetrahidropirimido-[2,1-c][1,4]oxazina-2-carboxílico y el intermediario 85, (4-fluoro-2-(3-metil-1H-1,2,4-triazol-1-il)fenil)metanamina.

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Cristales blancos; p.f. 203°C (acetato de etilo). ^{1}HRMN 400 MHz ($CDCl_3$) δ (ppm): 1.65 (6H, s, 2 x CH_3), 2.50 (3H, s, CH_3), 4.03 (4H, m, 2 x CH_2), 4.46 (2H, d, J=6.6 Hz, NCH_2), 5.31 (2H, s, OCH_2), 7.06 (1H, dd, J=3 Hz y J=8.6 Hz, aromático), 7.16 (1H, m, aromático), 7.30-7.34 (3H, m, aromáticos), 7.50 (2H, m, aromáticos), 7.74 (1H, dd, J=6.0 Hz y J=8.6 Hz, aromático), 8.28 (1H, s, CH), 8.45 (1H, amplio t; NH). Análisis calculado para $C_{27}H_{27}FN_6O_4$: C 62.54, H 5.25, N 16.21. Encontrado: C 62.48, H 5.31, N 16.29.

Intermediario 153

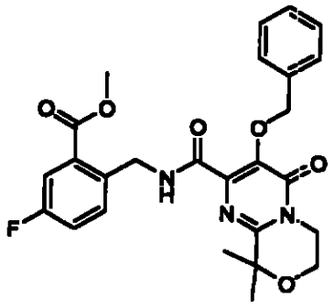


N-(2-Fluoro-4-(3-metil-1H-1,2,4-triazol-1-il)bencil)-3-(benciloxi)-9,9-dimetil-4-oxo-4,6,7,9-tetrahidropirimido[2,1-c][1,4]oxazina-2-carboxamida. El compuesto del título puede ser preparado a partir del intermediario 27, el ácido 3-(benciloxi)-9,9-dimetil-4-oxo-4,6,7,9-tetrahidropirimido-[2,1-c][1,4]oxazina-2-carboxílico y el intermediario 87, (2-fluoro-4-(3-metil-1H-1,2,4-triazol-1-il)fenil)metanamina. Cristales blancos; p.f. 183-185°C (acetato de etilo). ^{1}HRMN 400 MHz ($CDCl_3$) δ (ppm): 1.65 (6H, s, 2 x CH_3), 2.52 (3H, s, CH_3), 4.05 (4H, m, 2 x CH_2), 4.64 (2H, d, J=6.1 Hz, NCH_2),

548

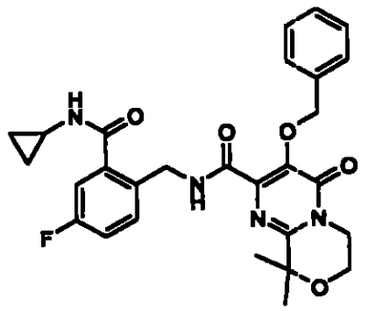
5.33 (2H, s, OCH_2), 7.29-7.55 (8H, m, aromáticos), 7.84 (1H, amplio t, NH), 8.45 (1H, s, CH). Análisis calculado para $C_{27}H_{27}FN_6O_4$: C 62.54, H 5.25, N16.21. Encontrado: C 62.41, H 5.40, N 16.23.

Intermediario 154



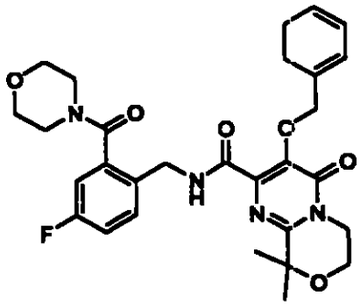
2-((3-(Benciloxi)-9,9-dimetil-4-oxo-4,6,7,9-tetrahidropirimido[2,1-c][1,4]oxazina-2-carboxamido)metil)-5-fluorobenzoato de metilo. El compuesto del título puede ser preparado a partir del intermediario 27, el ácido 3-(benciloxi)-9,9-dimetil-4-oxo-4,6,7,9-tetrahidropirimido-[2,1-c][1,4]oxazina-2-carboxílico y el intermediario 38, 2-(aminometil)-5-fluorobenzoato de metilo. ^1H RMN ($CDCl_3$, 500 MHz) δ ppm: 1.61 (6H, s, gem-Me), 3.88 (3H, s, OMe), 3.97 (2H, t, J=5.5 Hz, CH_2), 4.02 (2H, t, J=5.5 Hz, CH_2), 4.73 (2H, d, J=6.7 Hz, NCH_2), 5.25 (2H, s, OCH_2), 7.19 (1H, dt, J=3, 8.5 Hz, Ar-H), 7.27-7.31 (3H, m, Ar-Hs), 7.48-7.50 (2H, m, Ar-Hs), 7.61 (1H, dd, J=5.5, 8.5 Hz, Ar-H), 7.66 (1H, dd, J=3, 9.5 Hz, Ar-H). CL/EM m/z 496 (M+H).

Intermediario 155



N-(2-(Ciclopropilcarbamoil)-4-fluorobencil)-3-(benciloxi)-9,9-dimetil-4-oxo-4,6,7,9-tetrahidropirimido[2,1-c][1,4]oxazina-2-carboxamida. El compuesto del título puede ser preparado a partir del intermediario 27, ácido 3-(benciloxi)-9,9-dimetil-4-oxo-4,6,7,9-tetrahidropirimido-[2,1-c][1,4]oxazina-2-carboxílico y el intermediario 40, 2-(aminometil)-N-ciclopropil-5-fluorobenzamide. CL/EM m/z 521 (M+H).

Intermediario 156

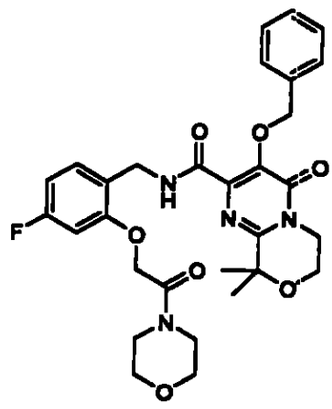


N-(4-Fluoro-2-(morfolina-4-carbonil)bencil)-3-(benciloxi)-9,9-dimetil-4-oxo-4,6,7,9-tetrahidropirimido[2,1-c][1,4]oxazina-2-carboxamida. El compuesto del título puede ser preparado a partir del intermediario 27, ácido 3-(benciloxi)-9,9-dimetil-4-oxo-4,6,7,9-tetrahidropirimido-

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[2,1-c][1,4]oxazina-2-carboxílico y el intermediario 44, (2-(aminometil)-5-fluorofenil)(morfolino)metanona. ^{1}H RMN ($CDCl_3$, 500 MHz) δ ppm: 1.59 (6H, s), 3.29 (2H, brs), 3.57 (2H, m), 3.74 (4H, s), 3.98 (4H, m), 5.26 (2H, s), 6.88 (1H, dd, J=8.2, 2.7 Hz), 7.03 (1H, dt, J=8.5, 2.5 Hz), 7.24-7.33 (3H, m), 7.42 (2 H, dd, J=8.6, 5.3 Hz), 7.47 (2H, dd, J=7.5, 2.0 Hz), 8.18 (1H, t, J=6.4 Hz); CL/EM m/z 551 (M+H).

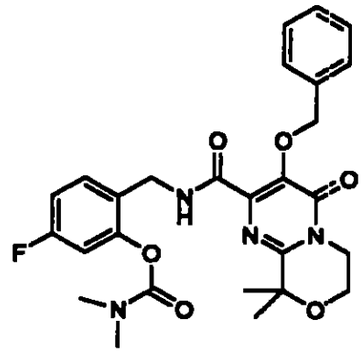
Intermediario 157



N-(4-Fluoro-2-(2-morfolino-2-oxoetoxi)bencil)-3-(benciloxi)-9,9-dimetil-4-oxo-4,6,7,9-tetrahidropirimido[2,1-c][1,4]oxazina-2-carboxamida. El compuesto del título puede ser preparado a partir del intermediario 27, ácido 3-(benciloxi)-9,9-dimetil-4-oxo-4,6,7,9-tetrahidropirimido-[2,1-c][1,4]oxazina-2-carboxílico y el intermediario 131, 2-(2-(aminometil)-5-fluorophenoxi)-1-morfolinoetanona. ^{1}H RMN ($CDCl_3$, 500 MHz) δ ppm: 1.59 (6H, s, gem-Me), 3.38, 3.54 (4H, br, NCH_2), 3.62 (4H, m, OCH_2), 3.96 (2H, m, NCH_2), 4.01 (2H, m, OCH_2), 4.55 (2H, s, OCH_2), 4.55 (2H, d, J=4.3 Hz, NCH_2),

5.17 (2H, s, OCH_2), 6.53 (1 H, dd, J=10, 2.1 Hz, Ar-H), 6.63 (1H, dt, J=2.5, 8 Hz, Ar-H), 7.23-7.26 (1H, m, Ar-H), 7.28-7.30 (3H, m, Ar-Hs), 7.42-7.44 (2H, m, Ar-Hs), 8.00 (1H, t, J=5.5 Hz, NH); ^{13}C RMN ($CDCl_3$, 125.77 Hz) δ ppm: 27.74, 38.76, 42.30, 42.98, 45.38, 58.06, 66.55, 56.78, 66.91, 74.72, 76.27, 100.40, 100.61, 108.07, 108.23, 122.56, 128.37, 128.49, 128.84, 130.88, 130.96, 139.69, 141.36, 141.98, 156.70, 157.02, 157.10, 159.58, 162.04, 163.99, 162.86, 165.79. HREM (ESI) calculado para $C_{30}H_{34}N_4O_7F$ (M+H) 581.2412, encontrado 581.2393.

Intermediario 158

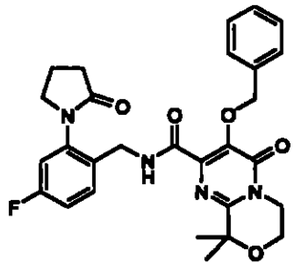


Éster 2-{[(3-benciloxi-9,9-dimetil-4-oxo-4,6,7,9-tetrahidro-pirimido[2,1-c][1,4]oxazina-2-carbonil)-amino]-metil}-5-fluoro-fenilo del ácido dimetil-carbámico. El compuesto del título puede ser preparado a partir del intermediario 27, ácido 3-(benciloxi)-9,9-dimetil-4-oxo-4,6,7,9-tetrahidropirimido-[2,1-c][1,4]oxazina-2-carboxílico y el intermediario 133, 2-(aminometil)-5-fluorofenil

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552

dimetilcarbamato. ^{1}H RMN ($CDCl_3$, 500 MHz) δ ppm: 1.58 (6H, s, gem-Me), 2.92, 3.05 (2s, NMe), 3.96 (2H, m, NCH_2), 4.00 (2H, m, OCH_2), 4.48 (2H, d, J=5.5 Hz, NCH_2), 5.26 (2H, s, OCH_2), 6.84 (1H, dd, J=2.5 Hz, 9 Hz, Ar-H), 6.87 (1H, dt, J=2.5 Hz, 8Hz, Ar-H), 7.25-7.33 (4H, m, Ar-Hs), 7.53 (2H, d, J=~7 Hz, Ar-Hs), 7.78 (1H, brt, J=5 Hz, NH); ^{13}C RMN ($CDCl_3$, 125.77 Hz) δ ppm: 27.68, 36.61, 36.89, 37.97, 42.97, 58.06, 74.73, 76.23, 110.58, 110.77, 113.06, 113.23, 126.55, 126.58, 128.31, 128.45, 128.91, 131.23, 131.31, 136.76, 140.70, 142.00, 150.60, 150.69, 154.50, 156.30, 159.79, 161.40, 163.37, 162.43. HREM (ESI) calculado para $C_{27}H_{30}N_4O_6F$ (M+H) 525.2149.encontrado 525.2163.

Intermediario 159

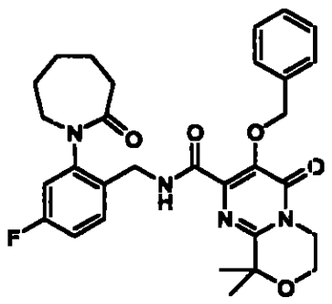


N-(4-Fluoro-2-(2-oxopirrolidin-1-il)bencil)-3-(benciloxi)-9,9-dimetil-4-oxo-4,6,7,9-tetrahidropirimido[2,1-c][1,4]oxazina-2-carboxamida. El compuesto del título puede ser preparado a partir del intermediario 27, ácido 3-(benciloxi)-9,9-dimetil-4-oxo-4,6,7,9-tetrahidropirimido-[2,1-c][1,4]oxazina-2-carboxílico y 1-(2-(aminometil)-5-fluorofenil)pirrolidin-2-ona, derivado de la reducción del intermediario 111, 4-fluoro-2-(2-oxopirrolidin-1-

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il)benzonitrilo. ^{1}HRMN 400 MHz (MeOD) δ ppm: 7.44 (3H, m), 7.33 (3H, m), 7.11 (1H, dd, J=9.2, 3.0 Hz) 7.03 (1H, m), 5.21 (2H, s), 4.43 (2H, s), 4.08 (2H, t, J=5.0 Hz), 3.98 (2H, t, J=5.0 Hz), 3.85 (2H, t, J=7.1 Hz), 2.58 (2H, t, J=8.0 Hz), 2.23 (2H, m), 1.61 (6H, s). CLEM $(M+H)^+$ m/z 521.

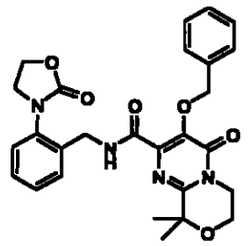
Intermediario 160



N-(4-Fluoro-2-(2-oxoazepan-1-il)bencil)-3-(benciloxi)-9,9-dimetil-4-oxo-4,6,7,9-tetrahidropirimido[2,1-c][1,4]oxazina-2 carboxamida. El compuesto del título puede ser preparado a partir del intermediario 27, ácido 3-(benciloxi)-9,9-dimetil-4-oxo-4,6,7,9-tetrahidropirimido-[2,1-c][1,4]oxazina-2-carboxílico y 1-(2-(aminometil)-5-fluorofenil)azepan-2-ona, derivado de la reducción del intermediario 113, 4-fluoro-2-(2-oxoazepan-1-il)benzonitrilo. ^{1}HRMN 400 MHz (DMSO) δ ppm: 8.80 (1H, dd, (t), J=6.0 Hz), 7.46 (2H, m), 7.36 (4H, m), 7.08 (1H, dd, J=9.8, 2.8 Hz), 7.0 (1H, m), 5.09 (2H, s), 4.43 (1H, dd, J=15.2, 7.1 Hz), 4.06 (1H, dd, J=15.2, 5.0 Hz), 4.02 (2H, t, J=5.0 Hz), 3.90 (2H, t, J=5.0 Hz), 3.77 (1H, m), 3.51 (1H, m), 2.70 (1H, m), 2.51 (2H, m), 1.76 (6H, m), 1.56 (6H, s). CLEM $(M+H)^+$ m/z 549.

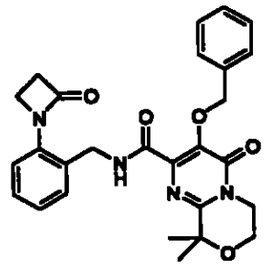
554

Intermediario 161



N-(2-(2-Oxooxazolidin-3-il)bencil)-3-(benciloxi)-9,9-dimetil-4-oxo-4,6,7,9-tetrahidropirimido[2,1-c][1,4]oxazina-2-carboxamida. El compuesto del título puede ser preparado a partir del intermediario 27, ácido 3-(benciloxi)-9,9-dimetil-4-oxo-4,6,7,9-tetrahidropirimido-[2,1-c]·[1,4]oxazina-2-carboxílico y 3-(2-(aminometil)fenil)oxazolidin-2-ona, derivado de la reducción del intermediario 116, 2-(2-oxooxazolidin-3-il)benzonitrilo. ^{1}H RMN (400 MHz, DMSO-d_6) δ ppm: 8.90 (1H, t, J=6.0 Hz), 7.58-7.32 (7H, m), 7.22 (2H, t, J=7.5 Hz), 5.08 (2H, s), 4.48 (2H, t, J=7.8 Hz), 4.44 (2H, d, J=6.0 Hz), 4.06-3.97 (4H, m), 3.88 (2H, m), 1.56 (6H, s); CLEM $(M+H)^+$ m/z 505.

Intermediario 162

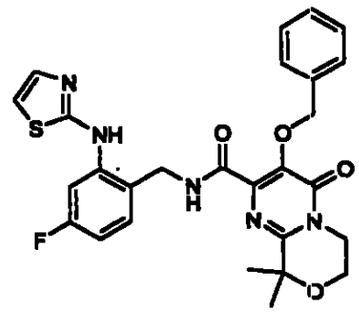


N-(2-(2-Oxoazetidin-1-il)bencil)-3-(benciloxi)-9,9-dimetil-4-oxo-4,6,7,9-tetrahidropirimido[2,1-

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c][1,4]oxazina-2-carboxamida. El compuesto del título puede ser preparado a partir del intermediario 27, ácido 3-(benciloxi)-9,9-dimetil-4-oxo-4,6,7,9-tetrahidropirimido-[2,1-c][1,4]oxazina-2-carboxílico y 1-(2-(aminometil)fenil)azetidin-2-ona, derivado de la reducción del intermediario 115, 2-(2-oxoazetidin-1-il)benzonitrilo. ^{1}H RMN (400 MHz, $CDCl_3$) δ ppm: 8.67 (1H, brt, J=6.3 Hz), 7.60 (1H, dd, J=1.3, 7.6 Hz), 7.53-7.50 (1H, dd, m), 7.34-7.24 (5H, m), 7.18 (1H, ddd(dt), J=1.2, 7.4 Hz), 7.10 (1H, dd, J=1.2, 8.0 Hz), 5.27 (2H, s), 4.60 (2H, d, J=6.3 Hz), 4.01-3.95 (4H, m), 3.71 (2H, t, J=4.5 Hz), 3.10 (2H, t, J=4.5 Hz), 1.60 (6H, s); CLEM ($^+$ESI, M+H$^+$) m/z 489.

Intermediario 163

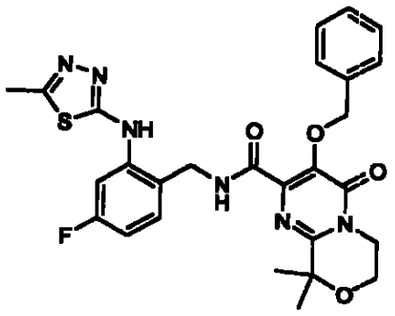


N-(4-Fluoro-2-(tiazol-2-ilamino)bencil)-3-(benciloxi)-9,9-dimetil-4-oxo-4,6,7,9-tetrahidropirimido[2,1-c][1,4]oxazina-2-carboxamida. El compuesto del título puede ser preparado a partir del intermediario 27, ácido 3-(benciloxi)-9,9-dimetil-4-oxo-4,6,7,9-tetrahidropirimido-[2,1-

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c][1,4]oxazina-2-carboxílico y N-(2-(aminometil)-5-fluorofenil)tiazol-2-amina, derivado de la reducción del intermediario 123, 4-fluoro-2-(tiazol-2-ilamino)benzonitrilo. ^{1}H RMN (400 MHz, DMSO-d_6) δ ppm: 9.92 (1H, s), 9.10 (1H, t, J=6.3 Hz), 8.19 (1H, dd, J=2.8, 12.3 Hz), 7.41-7.38 (2H, m), 7.32-7.28 (5H, m), 6.99 (1H, d, J=3.8 Hz), 6.71 (1H, ddd(dt), J=2.8, 8.3), 5.05 (2H, s), 4.45 (2H, d, J=6.3 Hz), 4.01-3.98 (2H, m), 3.88-3.85 (2H, m), 1.54 (6H, s) CLEM ($^+$ESI, M+H$^+$) m/z 536.

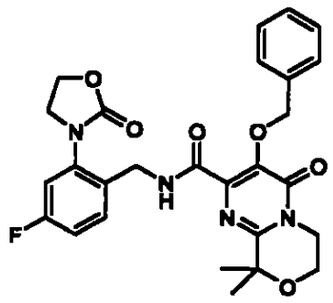
Intermediario 164



N-(4-Fluoro-2-(5-metil-1,3,4-tiadiazol-2-ilamino)bencil)-3-(benciloxi)-9,9-dimetil-4-oxo-4,6,7,9-tetrahidropirimido[2,1-c][1,4]oxazina-2-carboxamida. El compuesto del título puede ser preparado a partir del intermediario 27, ácido 3-(benciloxi)-9,9-dimetil-4-oxo-4,6,7,9-tetrahidropirimido-[2,1-c][1,4]oxazina-2-carboxílico y N-(2-(aminometil)-5-fluorofenil)-5-metil-1,3,4-tiadiazol-2-amina, derivado de la reducción del intermediario 124, 4-

fluoro-2-(5-metil-1,3,4-tiadiazol-2-ilamino)benzonitrilo. CLEM ($^+$ESI, M+H$^+$) m/z 551.

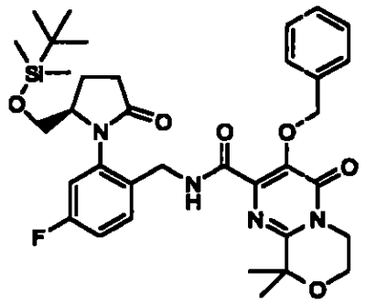
Intermediario 165



N-(4-Fluoro-2-(2-oxooxazolidin-3-il)bencil)-3-(benciloxi)-9,9-dimetil-4-oxo-4,6,7,9-tetrahidropirimido[2,1-c][1,4]oxazina-2-carboxamida. El compuesto del título puede ser preparado a partir del intermediario 27, ácido 3-(benciloxi)-9,9-dimetil-4-oxo-4,6,7,9-tetrahidropirimido-[2,1-c][1,4]oxazina-2-carboxílico y 3-(2-(aminometil)-5-fluorofenil)oxazolidin-2-ona, derivado de la reducción del intermediario 117, 4-fluoro-2-(2-oxooxazolidin-3-il)benzonitrilo. ^{1}H RMN (400 MHz, MeOD) δ ppm: 9.48 (1H, dd, J=8.6, 6.5 Hz), 7.41 (2H, m), 7.32 (3H, m), 7.22 (1H, dd, J=9.6, 2.5 Hz), 7.08 (1H, td, J=8.6, 2.7 Hz), 5.21 (2H, s), 4.57 (2H, t, J=7.7 Hz), 4.50 (2H, s), 4.07 (4H, m), 3.99 (2H, m), 1.61 (6H, s). CLEM (M+H)$^+$ m/z 523.

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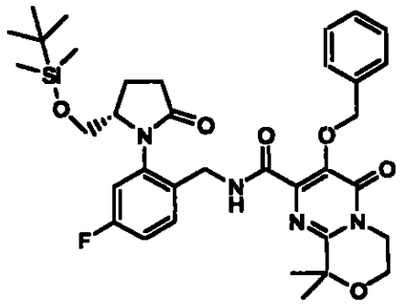
Intermediario 166



(R)-N-(2-(2-((tert-Butildimetilsililoxi)metil)-5-oxopirrolidin-1-il)-4-fluorobencil)-3-(benciloxi)-9,9-dimetil-4-oxo-4,6,7,9-tetrahidropirimido[2,1-c][1,4]oxazina-2-carboxamida. El compuesto del título puede ser preparado a partir del intermediario 27, ácido 3-(benciloxi)-9,9-dimetil-4-oxo-4,6,7,9-tetrahidropirimido-[2,1-c][1,4]oxazina-2-carboxílico y (S)-1-(2-(aminometil)-5-fluorofenil)-5-((tert-butildimetilsililoxi)metil)pirrolidin-2-ona, derivado de la reducción del intermediario 122, (R)-2-(2-((tert-butildimetilsililoxi)metil)-5-oxopirrolidin-1-il)-4-fluorobenzonitrilo. ^{1}HRMN 400 MHz (DMSO) δ ppm: 8.82 (1H, amplio s), 7.47 (2H, m), 7.35 (4H, m), 7.00 (1H, amplio s), 5.09 (2H, s), 4.60-4.10 (3H, m), 4.02 (3H, m), 3.88 (2H, m), 3.53 (2H, amplio s), 2.42-2.35 (2H, m), 1.94 (1H, m), 1.56 (3H, s), 1.55 (3H, s), 0.82 (9H, amplio s), -0.01 (6H, s). CLEM $(M+H)^+$ m/z 665.

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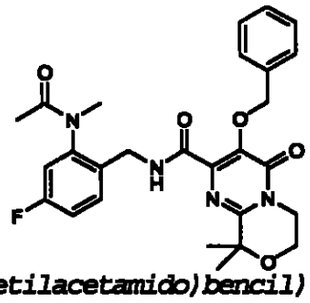
Intermediario 167



(S)-N-(2-(2-((tert-Butildimetilsililoxi)metil)-5-oxopirrolidin-1-il)-4-fluorobencil)-3-(benciloxi)-9,9-dimetil-4-oxo-4,6,7,9-tetrahidropirimido[2,1-c][1,4]oxazina-2-carboxamida. El compuesto del título puede ser preparado a partir del intermediario 27, ácido 3-(benciloxi)-9,9-dimetil-4-oxo-4,6,7,9-tetrahidropirimido-[2,1-c][1,4]oxazina-2-carboxílico y (S)-1-(2-(aminometil)-5-fluorofenil)-5-((tert-butildimetilsililoxi)metil)pirrolidin-2-ona, derivado de la reducción del intermediario 121, (R)-2-(2-((tert-butildimetilsililoxi)metil)-5-oxopirrolidin-1-il)-4-fluorobenzonitrilo. ^{1}HRMN 400 MHz (DMSO) δ ppm: 8.82 (1H, amplio s), 7.52-7.33 (7H, m), 7.02 (1H, amplio s), 5.60 (2H, s), 4.60-4.20 (2H, m), 4.02 (3H, t, J=5.0 Hz), 3.89 (3H, t, 5.0 Hz), 3.53 (2H, amplio s), 2.51 (2H, s), 2.44-2.26 (2H, m), 1.94 (1H, amplio s), 1.57 (3H, s), 1.55 (3H, s), 0.82 (9H, amplio s), -0.02 (6H, s). CLEM $(M+H)^+$ m/z 665.

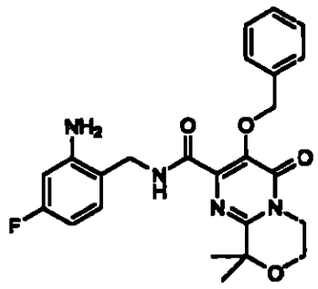
560

Intermediario 168



N-(4-Fluoro-2-(N-metilacetamido)bencil)-3-(benciloxi)-9,9-dimetil-4-oxo-4,6,7,9-tetrahidropirimido[2,1-c][1,4]oxazina-2-carboxamida. El compuesto del título puede ser preparado a partir del intermediario 27, N-(2-(aminometil)-5-fluorofenil)-N-metilacetamida del ácido 3-(benciloxi)-9,9-dimetil-4-oxo-4,6,7,9-tetrahidropirimido-[2,1-c][1,4]oxazina-2-carboxílico, derivado de la reducción del intermediario 114, N-(2-ciano-5-fluorofenil)-N-metilacetamida. ^{1}HRMN 400 MHz (MeOD) δ ppm: 7.49-7.33 (6H, m), 7.15-7.06 (2H, m), 5.22 (2H, s), 4.41 (2H, d, J=2.4 Hz), 4.09 (2H, t, J=5.1 Hz), 4.01 (2H, t, J=5.1 Hz), 3.25 (0.4H, s), 3.22 (2.6H, s), 1.85 (3H, s), 1.63 (6H, s). CLEM $(M+H)^+$ m/z 509.

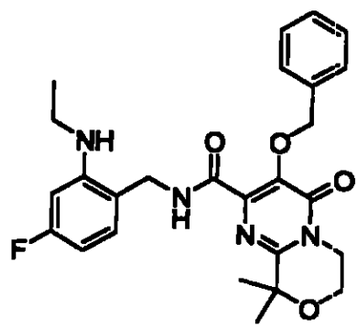
Intermediario 169



N-(2-Amino-4-fluorobencil)-3-(benciloxi)-9,9-dimetil-4-oxo-4,6,7,9-tetrahidropirimido[2,1-c][1,4]oxazina-2-

carboxamida. El compuesto del título puede ser preparado a partir del intermediario 27, 2-(aminometil)-5-fluorobencenamina del ácido 3-(benciloxi)-9,9-dimetil-4-oxo-4,6,7,9-tetrahidropirimido-[2,1-c][1,4]oxazina-2-carboxílico. ^{1}HRMN 400 MHz (MeOD) δ ppm: ^{1}HRMN 400 MHz (MeOD) δ ppm: 7.36 (2H, m), 7.30 (3H, m), 7.10 (1H, dd, J=8.3, 6.5 Hz), 6.47 (1H, dd, J=11.1, 2.5 Hz), 6.32 (1H, ddd, (dt), J=8.6, 2.5 Hz), 5.19 (2H, s), 4.40 (2H, s), 4.07 (2H, t, J=5.0 Hz), 3.99 (2H, t, J=5.0 Hz), 1.61 (6H, s). CLEM $(M+H)^+$ m/z 453.

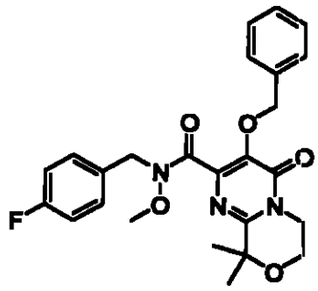
Intermediario 170



N-(2-(Etilamino)-4-fluorobencil)-3-(benciloxi)-9,9-dimetil-4-oxo-4,6,7,9-tetrahidropirimido[2,1-c][1,4]oxazina-2-carboxamida. El compuesto del título puede ser preparado a partir del intermediario 27, ácido 3-(benciloxi)-9,9-dimetil-4-oxo-4,6,7,9-tetrahidropirimido-[2,1-c][1,4]oxazina-2-carboxílico y 2-(aminometil)-N-etil-5-fluorobencenamina. ^{1}HRMN 400 MHz

(CDCl$_3$) δ (ppm): 1.27 (3H, t, J=7.1 Hz, CH$_3$), 1.63 (6H, s, 2 x CH$_3$), 3.10 (2H, q, J=7.1 Hz, CH$_2$), 4.04 (4H, m, 2 x CH$_2$), 4.45 (2H, d, J=6.6 Hz, NCH$_2$), 5.27 (2H, s, OCH$_2$), 6.28 (1H, amplio s, aromático), 6.31 (1H, m, aromático), 6.98 (1H, m, aromático), 7.3-7.38 (3H, m, aromáticos), 7.49 (2H, m, aromáticos), 7.54 (1H, amplio t, NH). HREM (ESI$^+$) calculado para $C_{26}H_{30}FN_4O_4$ [M+H$^+$]: 481.2251: encontrado: 481.2254.

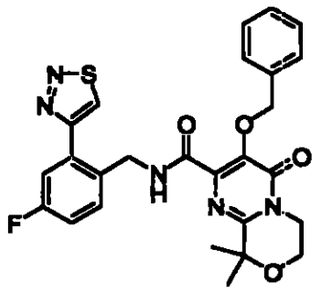
Intermediario 171



N-(4-Fluorobencil)-3-(benciloxi)-N-metoxi-9,9-dimetil-4-oxo-4,6,7,9-tetrahidropirimido[2,1-c][1,4]oxazina-2-carboxamida. El compuesto del título puede ser preparado a partir del intermediario 27, ácido 3-(benciloxi)-9,9-dimetil-4-oxo-4,6,7,9-tetrahidropirimido-[2,1-c][1,4]oxazina-2-carboxílico y (4-fluorofenil)-N-metoximetanamina. Cristales blancos; p.f. 141°C (acetato de etilo-hexano). ^{1}HRMN 400 MHz (CDCl$_3$) δ (ppm): 1.66 (6H, s, 2 x CH$_3$), 3.59 (3H, s, OCH$_3$), 4.07 (4H, m, 2 x CH$_2$), 4.90 (2H, s, NCH$_2$), 5.20 (2H, s, OCH$_2$), 6.81 (2H, m, aromáticos), 7.26-7.30 (3H, m, aromáticos), 7.36 (2H, m, aromáticos), 7.44 (2H, m, aromáticos). HREM (ESI$^+$) calculado

para $C_{25}H_{27}FN_3O_5$ [M+H$^+$]: 468.1935: encontrado: 468.1916.

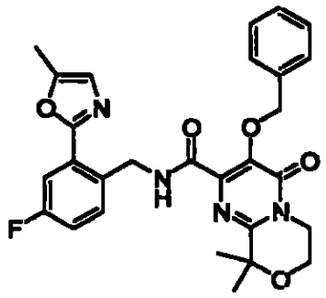
Intermediario 172



N-(4-Fluoro-2-(1,2,3-tiadiazol-4-il)bencil)-3-(benciloxi)-9,9-dimetil-4-oxo-4,6,7,9-tetrahidropirimido[2,1-c][1,4]oxazina-2-carboxamida. El compuesto del título puede ser preparado a partir del intermediario 27, ácido 3-(benciloxi)-9,9-dimetil-4-oxo-4,6,7,9-tetrahidropirimido-[2,1-c][1,4]oxazina-2-carboxílico y (4-fluoro-2-(1,2,3-tiadiazol-4-il)fenil)metanamina. ^{1}HRMN 400 MHz ($CDCl_3$) δ (ppm): 1.66 (6H, s, 2 x CH_3), 4.02 (4H, m, 2 x CH_2), 4.57 (2H, d, J=6.6 Hz, NCH_2), 5.32 (2H, s, OCH_2), 7.18 (1H, m, aromático), 7.27-7.34 (4H, m, aromáticos), 7.54 (2H, m, aromáticos), 7.74 (1H, dd, J=6.2 Hz y J=8.6 Hz, aromático), 8.71 (1H, s, CH), 8.80 (1H, amplio t, NH). HREM (ESI$^+$) calculado para $C_{26}H_{25}FN_5O_4S$ [M+H$^+$]: 522.1611: encontrado: 522.1601.

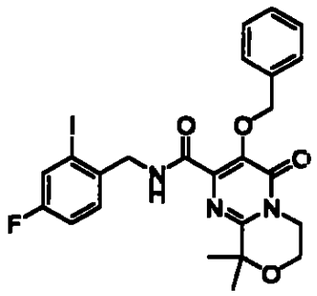
564

Intermediario 173



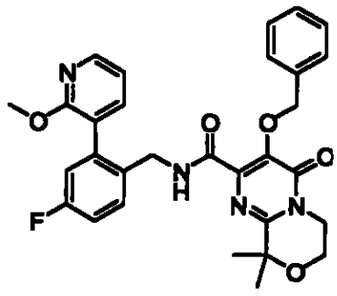
N-(4-Fluoro-2-(5-metiloxazol-2-il)bencil)-3-(benciloxi)-9,9-dimetil-4-oxo-4,6,7,9-tetrahidropirimido[2,1-c][1,4]oxazina-2-carboxamida. El compuesto del título puede ser preparado a partir del intermediario 27, ácido 3-(benciloxi)-9,9-dimetil-4-oxo-4,6,7,9-tetrahidropirimido-[2,1-c][1,4]oxazina-2-carboxílico y (4-fluoro-2-(5-metiloxazol-2-il)fenil)metanamina. Cristales blancos; p.f. 186°C (acetato de etilo-hexano). ^{1}HRMN 400 MHz ($CDCl_3$ δ (ppm): 1.61 (6H, s, 2 x CH_3), 2.43 (3H, s, CH_3), 4.02 (4H, m, 2 x CH_2), 4.80 (2H, d, J=6.3 Hz, NCH_2), 5.25 (2H, s, OCH_2), 6.82 (1H, s, CH), 7.11 (1H, m, aromáticc), 7.29-7.34 (3H, m, aromáticos), 7.52 (2H, m, aromáticos), 7.65 (1H, dd, J=2.5 Hz y J=9.6 Hz, aromático), 7.69 (1H, dd, J=6.1 Hz y J=8.6 Hz, aromático), 9.32 (1H, amplio t, NH). HREM (ESI^+) calculado para $C_{28}H_{28}FN_4O_5$ [$M+H^+$]: 519.2044: encontrado: 519.2024.

Intermediario 174



N-(4-Fluoro-2-yodobencil)-3-(benciloxi)-9,9-dimetil-4-oxo-4,6,7,9-tetrahidropirimido[2,1-c][1,4]oxazina-2-carboxamida. El compuesto del título puede ser preparado a partir del intermediario 27, ácido 3-(benciloxi)-9,9-dimetil-4-oxo-4,6,7,9-tetrahidropirimido-[2,1-c][1,4]oxazina-2-carboxílico y (4-fluoro-2-yodofenil)metanamina. Sólido blanco. ^{1}HRMN 400 MHz ($CDCl_3$) δ ppm: 1.66 (6H, s, 2 x CH_3), 4.04 (4H, m, 2 x CH_2,), 4.57 (2H, d, J=6.6 Hz, NCH_2), 7.05 (1H, m, aromático), 7.3-7.38 (3H, m, aromáticos), 7.42 (1H, dd, J=6.1 Hz y J=8.6 Hz, aromático), 7.53 (2H, m, aromáticos), 7.56 (1H, dd, J=2.6 Hz y J=8.0 Hz, aromático), 8.05 (1H, amplio t, NH). HREM (ESI^+) calculado para $C_{24}H_{24}FIN_3O_4$ [$M+H^+$]: 564.0796; encontrado: 564.0809.

Intermediario 175

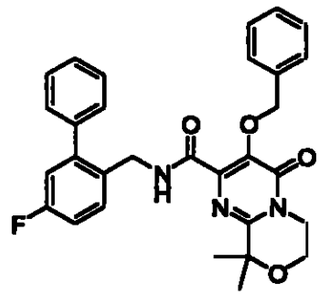


N-(4-Fluoro-2-(2-metoxipiridin-3-il)bencil)-3-(benciloxi)-9,9-dimetil-4-oxo-4,6,7,9-tetrahidropirimido[2,1-

569
566.

c][1,4]oxazina-2-carboxamida. Intermediario 174, la N-(4-fluoro-2-yodobencil)-3-(benciloxi)-9,9-dimetil-4-oxo-4,6,7,9-tetrahidropirimido[2,1-c][1,4]oxazina-2-carboxamida (0.350 g, 0.62 mmol) en una mezcla de acetonitrilo (12 ml) y agua (12 ml) se trató con ácido 2-metoxipiridin-3-ilborónico (0.190 g, 1.24 mmol), carbonato de sodio (0.20 g, 1.88 mmol) y tetrakis(trifenilfosfina)paladio(0) (0.15 g). La mezcla de reacción se desgasificó, se limpió con argón y se calentó a 90°C durante 30 min. La mezcla de reacción luego se diluyó con acetato de etilo, se lavó con agua y salmuera, se secó sobre sulfato de magnesio anhidro y se concentró. La cromatografía del residuo en gel de sílice (gradiente de elución de acetato de etilo en hexano) dio 0.245 g (72% rendimiento) del material del título como un sólido blanco. ^{1}HRMN 400 MHz ($CDCl_3$) δ ppm: 1.63 (6H, s, 2 x CH_3), 3.89 (3H, s, OCH_3), 4.04 (4H, m, 2 x CH_2), 4.37 (2H, amplio, NCH_2), 5.26 (2H, s, OCH_2), 6.93 (1H, dd, J=2.5 Hz y J=9 Hz, aromático), 7.0 (1H, dd, J=5 Hz y J=7 Hz, aromático), 7.06 (1H, m, aromático), 7.3-7.5 (8H, m, aromáticos and NH), 8.24 (1H, m, aromático). HREM (ESI^+) calculado para $C_{30}H_{30}FN_4O_5$ [$M+H^+$]: 545.2200; encontrado: 545.2184.

Intermediario 176

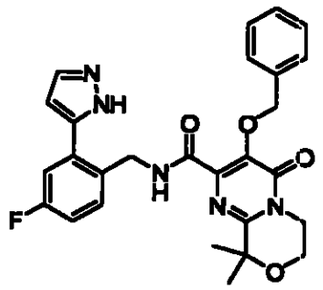


N-(4-Fluoro-2-fenil-bencil)-3-(benciloxi)-9,9-dimetil-4-oxo-4,6,7,9-tetrahidropirimido[2,1-c][1,4]oxazina-2-carboxamida. Intermediario 174, la N-(4-Fluoro-2-yodobencil)-3-(benciloxi)-9,9-dimetil-4-oxo-4,6,7,9-tetrahidropirimido[2,1-c][1,4]oxazina-2-carboxamida (0.150 g, 0.266 mmol) en una mezcla de acetonitrilo (10 ml) y agua (10 mi) se trató con ácido fenilborónico (0.042 g, 0.35 mmol), carbonato de sodio (0.062 g, 0.58 mmol) y tetrakis(trifenilfosfina)paladio(0) (0.070 g). La mezcla de reacción se desgasificó, se limpió con argón y se calentó a 90°C durante 30 minutos. La mezcla de reacción luego se diluyó con acetato de etilo, se lavó con agua y salmuera, se secó sobre sulfato de magnesio anhidro y se concentró. La cromatografía del residuo en gel de sílice (gradiente de elución de acetato de etilo en hexano) dio 0.124 g (91% rendimiento) del material del título como un sólido amarillo ligero. ^{1}HRMN 400 MHz ($CDCl_3$) δ ppm: 1.61 (6H, s, 2 x CH_3), 4.03 (4H, m, 2 x CH_2), 4.49 (2H, d, J = 6.1 Hz, NCH_2), 7.02 (2H, m, aromáticos), 7.29-7.51 (12H, m, aromáticos and NH).

568

HREM (ESI^+) calculado para $C_{30}H_{29}FN_3O_4$ $[M+H^+]$: 514.2142; encontrado: 514.2137.

Intermediario 177

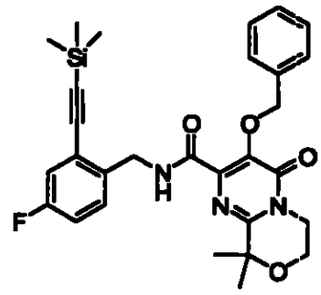


N-(4-Fluoro-2-(1H-pirazol-5-il)bencil)-3-(benciloxi)-9,9-dimetil-4-oxo-4,6,7,9-tetrahidropirimido[2,1-c][1,4]oxazina-2-carboxamida. Intermediario 174, la N-(4-fluoro-2-yodobencil)-3-(benciloxi)-9,9-dimetil-4-oxo-4,6,7,9-tetrahidropirimido[2,1-c][1,4]oxazina-2-carboxamida (0.150 g, 0.27 mmol) se hace reaccionar con ácido 1H-pirazol-5-ilborónico (0.060 g, 0.54 mmol), carbonato de sodio (0.085 g, 0.81 mmol) y tetrakis(trifenilfosfina)paladio(0) (0.070 g) para dar 0.085 g (62% rendimiento) del material del título como un sólido blanco después de la cromatografía en gel de sílice. ^{1}HRMN 400 MHz ($CDCl_3$) δ (ppm): 1.63 (6H, s, 2 x CH_3), 4.03 (4H, m, 2 x CH_2), 4.65 (2H, d, J=6.5 Hz, NCH_2), 5.25 (2H, s, OCH_2), 6.54 (1H, d, J=2.5 Hz, CH), 7.03 (1H, m, aromático), 7.25 (1H, dd, J=2.5 Hz y J=9.8 Hz, arcmático), 7.35 (3H, m, aromáticos), 7.53 (2H, m, aromáticos), 7.56 (1H, d, J=2.5 Hz, CH), 7.60 (1H, dd, J=6.1 Hz y J=8.6 Hz, aromático),

569

8.96 (1H, amplio t, NH). HREM (ESI^+) calculado para $C_{27}H_{27}FN_5O_4$ $[M+H^+]$: 504.2047: encontrado: 504.2068.

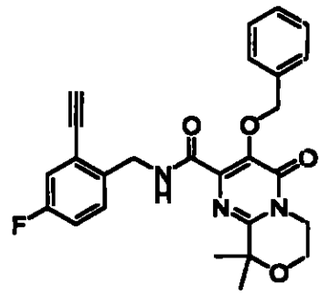
Intermediario 178



N-(4-Fluoro-2-(2-(trimetilsilil)etinil)bencil)-3-(benciloxi)-9,9-dimetil-4-oxo-4,6,7,9-tetrahidropirimido[2,1-c][1,4]oxazina-2-carboxamida. Una solución del intermediario 174, la N-(4-fluoro-2-yodobencil)-3-(benciloxi)-9,9-dimetil-4-oxo-4,6,7,9-tetrahidropirimido[2,1-c][1,4]oxazina-2-carboxamida (0.277 g, 0.49 mmol) en una mezcla de N,N-dimetilformamida (3 ml) y piperidina (1.2 ml) se trató bajo argón con diclorobis(trifenilfosfina)paladio(II) (0.020 g), trifenilfosfina (0.010 g), yoduro de cobre(I) (0.010 g) seguido por (trimetilsilil)acetileno (0.21 ml, 1.47 mmol). La mezcla resultante se selló y se calentó a 50°C durante 1 hora. La mezcla de reacción luego se diluyó con acetato de etilo, se lavó con agua y salmuera, se secó sobre sulfato de magnesio anhidro y se ccncentró bajo presión reducida. La cromatografía del residuo on gel de sílice (gradiente de elución de acetato de etilo en hexano) dio

0.164 g (63% rendimiento) del material del título como un sólido amarillo ligero. ^{1}HRMN 400 MHz ($CDCl_3$) δ ppm: 0.27 (9H, s, $SiCH_3$), 1.64 (6H, s, 2 x CH_3), 4.04 (4H, m, 2 x CH_2), 4.71 (2H, d, J=6.1 Hz, NCH_2), 5.32 (2H, s, OCH_2), 6.99 (1H, m, aromático), 7.19 (1H, dd, J=2.6 Hz y J=9.1 Hz, aromático), 7.3-7.37 (4H, m, aromáticos), 7.48-7.51 (2H, m, aromáticos), 7.75 (1H, amplio t, NH). HREM (ESI^+) calculado para $C_{29}H_{33}FN_3O_4Si$ [$M+H^+$]: 534.2224; encontrado: 534.2229.

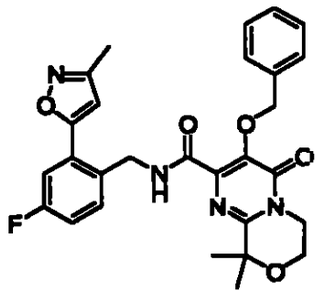
Intermediario 179



N-(2-Etinil-4-fluorobencil)-3-(benciloxi)-9,9-dimetil-4-oxo-4,6,7,9-tetrahidropirimido[2,1-c][1,4]oxazina-2-carboxamida. Una solución del intermediario 178, la N-(4-fluoro-2-(2-(trimetilsilil)etinil)bencil)-3-(benciloxi)-9,9-dimetil-4-oxo-4,6,7,9-tetrahidropirimido[2,1-c][1,4]oxazina-2-carboxamida (0.150 g, 0.28 mmol) en metanol (5 ml) se trató con carbonato de potasio (0.120 g, 0.84 mmol) y la mezcla resultante se agitó a 22°C durante 1 hora. La mezcla de reacción luego se diluyó con acetato de etilo, se lavó con agua y salmuera, se secó sobre sulfato de magnesio anhidro y se concentró bajo presión reducida

para dar 0.129 g (100% rendimiento) del material del título como un sólido amarillo ligero. ^{1}HRMN 400 MHz ($CDCl_3$) δ ppm: 1.64 (6H, s, 2 x CH_3), 3.31 (1H, s, CH), 4.04 (4H, m, 2 x CH_2), 4.69 (2H, d, J=6.6 Hz, NCH_2), 5.31 (2H, s, OCH_2), 7.04 (1H, m, aromático), 7.21 (1H, dd, J=2.6 Hz y J=9.1 Hz, aromático), 7.32-7.42 (3H, m, aromáticos), 7.40 (1H, dd, J=6.1 Hz y J=8.6 Hz, aromático), 7.52-7.54 (2H, m, aromáticos), 8.00 (1H, amplio t, NH). HREM (ESI^+) calculado para $C_{26}H_{25}FN_3O_4$ [M+H]: 462.1829; encontrado: 462.1822.

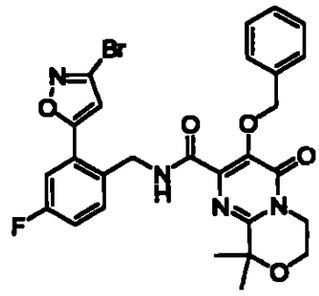
Intermediario 180



N-(4-Fluoro-2-(3-metilisoxazol-5-il)bencil)-3-(benciloxi)-9,9-dimetil-4-oxo-4,6,7,9-tetrahidropirimido[2,1-c][1,4]oxazina-2-carboxamida. Una solución del intermediario 179, la N-(2-etinil-4-fluorobencil)-3-(benciloxi)-9,9-dimetil-4-oxo-4,6,7,9-tetrahidropirimido[2,1-c][1,4]oxazina-2-carboxamida (0.150 g, 0.32 mmol) en dimetil sulfóxido (5 ml) se trató con nitrometano (0.14 ml, 1.92 mmol), cloruro de 4-(4,6-dimetoxi-1,3,5-triazin-2-il)-4-metilmorfolino (DMTMM) (0.241 g, 1.0 mmol) (M. Kunishima et al., Tetrahedron, 55, 1999, 13159-13170) y 4-(dimetilamino)piridina (DMAP) (0.010

g) y la mezcla resultante se agitó a 22°C durnante 16 h. Las cantidades idénticas de nitrometano, DMTMM y DMAP luego se agregaron y la mezcla se agitó durante otras 24 h. La mezcla de reacción se diluyó con acetato de etilo, se lavó con bicarbonato de sodio saturado y salmuera, luego se secó sobre sulfato de magnesio anhidro y se concentró bajo presión reducida. La cromatografía del residuo en gel de sílice (gradiente de elución de acetato de etilo en diclorometano) dio 0.122 g (73% rendimiento) del material del título como un sólido blanco. ^{1}H RMN 400 MHz ($CDCl_3$) δ ppm: 1.62 (6H, s, 2 x CH_3), 2.39 (3H, s, CH_3), 4.04 (4H, m, 2 x CH_2), 4.69 (2H, d, J=6.1 Hz, NCH_2), 5.31 (2H, s, OCH_2), 6.36 (1H, m, CH), 7.13 (1H, m, aromático), 7.30-7.35 (4H, m, aromáticos), 7.50-7.53 (2H, m, aromáticos), 7.58 (1H, dd, J=5.5 Hz y J=8.6 Hz, aromático), 8.06 (1H, amplio t, NH). HREM (ESI^+) calculado para $C_{28}H_{28}FN_4O_5$ [$M+H^+$]: 519.2044; encontrado: 519.2059.

Intermediario 181



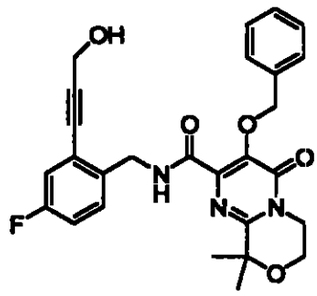
N-(2-(3-Bromoisoxazol-5-il)-4-fluorobencil)-3-(benciloxi)-9,9-dimetil-4-oxo-4,6,7,9-tetrahidropirimido[2,1-c][1,4]oxazina-2-carboxamida. Una solución del intermediario

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179, la N-(2-etinil-4-fluorobencil)-3-(benciloxi)-9,9-dimetil-4-oxo-4,6,7,9-tetrahidropirimido[2,1-c][1,4]oxazina-2-carboxamida (0.350 g, 0.76 mmol) en una mezcla de acetato de etilo (10 ml) y agua (2 ml) se trató con bicarbonato de potasio (0.230 g, 2.3 mmol) seguido por dibromoformaldoxima (0.354 g, 1.75 mmol) (D.M. Vyas, Y. Chiang and T.W. Doyle, Tetrahedron Letters, 1984, 25, 487-490) y la mezcla resultante se agitó a 22°C. Después de 1 h, las cantidades idénticas de bicarbonato de potasio y dibromoformaldoxima se agregaron y la mezcla se agitó durante otra 1.5 h. La mezcla de reacción luego se diluyó con acetato de etilo, se lavó con salmuera, se secó sobre sulfato de magnesio anhidro y se concentró bajo presión reducida. La cristalización del residuo de éter dio 0.300 g (68% rendimiento) del material del título como un sólido blanco. ^{1}HRMN 400 MHz ($CDCl_3$) δ ppm: 1.63 (6H, s, 2 x CH_3), 4.04 (4H, m, 2 x CH_2), 4.67 (2H, d, J=6.6 Hz, NCH_2), 5.32 (2H, s, OCH_2), 6.60 (1H, s, CH), 7.17 (1H, m, aromático), 7.30-7.36 (4H, m, aromáticos), 7.51-7.53 (2H, m, aromáticos), 7.60 (1H, dd, J=5.5 Hz y J=8.6 Hz, aromático), 8.01 (1H, amplio t, NH). HREM (ESI^+) calculado para $C_{27}H_{25}BrFN_4O_5$ [$M+H^+$]: 583.0992; encontrado: 583.0986.

574

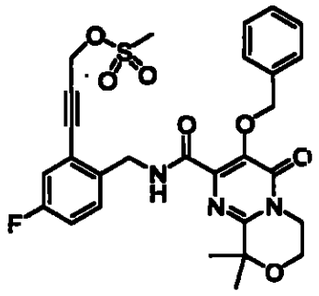
Intermediario 182



N-(4-Fluoro-2-(3-hidroxiprop-1-inil)bencil)-3-(benciloxi)-9,9-dimetil-4-oxo-4,6,7,9-tetrahidropirimido[2,1-c][1,4]oxazina-2-carboxamida. La reducción del intermediario 174, la N-(4-fluoro-2-yodobencil)-3-(benciloxi)-9,9-dimetil-4-oxo-4,6,7,9-tetrahidropirimido[2,1-c][1,4]oxazina-2-carboxamida (0.563 g, 1.00 mmol) con alcohol de propargilo (0.18 ml, 3.2 mmol) usando las condiciones descritas por el intermediario 178 dio 0.415 g (85% rendimiento) del material del título como un sólido blanco. ^{1}HRMN 400 MHz ($CDCl_3$) δ ppm: 1.64 (6H, s, 2 x CH_3), 4.04 (4H, m, 2 x CH_2), 4.39 (2H, d, J=6.6 Hz, CH_2), 4.68 (2H, d, J=6.0 Hz, CH_2), 5.29 (2H, s, OCH_2), 6.99 (1H, m, aromático), 7.13 (1H, dd, J=2.5 Hz y J=9.1 Hz, aromático), 7.22 (1H, dd, J=5.6 Hz y J=8.6 Hz, aromático), 7.33-7.37 (3H, m, aromáticos), 7.44-7.47 (2H, m, aromáticos), 7.68 (1H, amplio t, NH). HREM (ESI^+) calculado para $C_{27}H_{27}FN_3O_5$ [$M+H^+$]: 492.1935; encontrado: 492.1939.

575

Intermediario 183

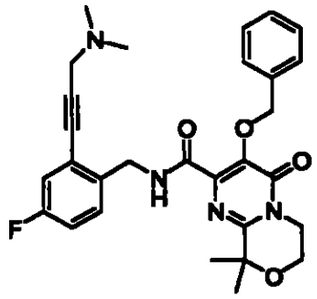


3-[2-((3-(Benciloxi)-9,9-dimetil-4-oxo-4,6,7,9-tetrahidropirimido[2,1-c][1,4]oxazina-2-carboxamido)metil)-5-fluorofenil]prop-2-inil metanosulfonato. Una solución del intermediario 182, la N-(4-fluoro-2-(3-hidroxiprop-1-inil)bencil)-3-(benciloxi)-9,9-dimetil-4-oxo-4,6,7,9-tetrahidropirimido[2,1-c][1,4]oxazina-2-carboxamida (0.280 g, 0.57 mmol) y trietilamina (0.12 ml, 0.86 mmol) en diclorometano (5 ml) se enfrió a 0°C, se trató gota a gota con cloruro de metanosulfonilo (0.050 ml, 0.64 mmol) y luego se agitó durante 30 min. La mezcla de reacción luego se diluyó con acetato de etilo, se lavó con bicarbonato de sodio saturado, salmuera, se secó sobre sulfato de magnesio anhidro y se concentró bajo presión reducida. La cromatografía del residuo en gel de sílice (gradiente de elución de acetato de etilo en hexano) dio 0.245 g (75% rendimiento) del material del título como un sólido blanco. ^{1}HRMN 400 MHz ($CDCl_3$) δ ppm: 1.65 (6H, s, 2 x CH_3), 3.10 (3H, s, SCH_3), 4.05 (4H, m, 2 x CH_2), 4.67 (2H, d, J=6.1 Hz, NCH_2), 5.03 (2H, s, CH_2), 5.29 (2H, s, OCH_2), 7.07 (1H, m, aromatíc), 7.18 (1H, dd, J=2.5 Hz y J=9.1 Hz, aromático), 7.32-

576

7.36 (3H, m, aromáticos), 7.38 (1H, dd, J=5.5 Hz y J=8.6 Hz, aromático), 7.49-7.51 (2H, m, aromáticos), 7.77 (1H, amplio t, NH). EM (ESI^+) m/e 570 $[M+H^+]$.

Intermediario 184



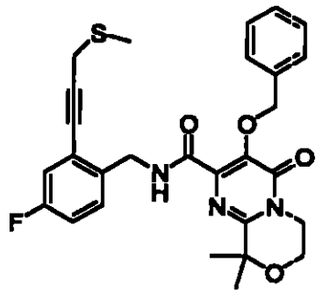
N-(2-(3-(Dimetilamino)prop-1-inil)-4-fluorobencil)-3-(benciloxi)-9,9-dimetil-4-oxo-4,6,7,9-tetrahidropirimido[2,1-c][1,4]oxazina-2-carboxamida. Una solución del intermediario 183, el 3-[2-((3-(benciloxi)-9,9-dimetil-4-oxo-4,6,7,9-tetrahidropirimido[2,1-c][1,4]oxazina-2-carboxamido)metil)-5-fluorofenil]prop-2-inil metanosulfonato (0.100 g, 0.18 mmol) en acetonitrilo (5 ml) se trató a 22°C con 0.3 ml (0.6 mmol) de una solución 2M de dimetilamina en tetrahidrofurano y la mezcla resultante se agitó durante 30 minutos. La mezcla de reacción luego se diluyó con acetato de etilo, se lavó con bicarbonato de sodio saturado, salmuera, luego se secó sobre sulfato de magnesio anhidro y se concentró bajo presión reducida para dar 0.080 g (88% rendimiento) del material del título como un sólido blanco. ^{1}HRMN 400 MHz ($CDCl_3$) δ ppm: 1.64 (6H, s, 2 x CH_3), 2.43 (6H, s, 2 x NCH_3), 3.58 (2H, amplio s, CH_2), 4.05 (4H, m, 2 x CH_2), 4.70 (2H, d, J=6.0 Hz,

580

577

NCH_2), 5.30 (2H, s, OCH_2), 7.01 (1H, m, aromático), 7.18 (1H, dd, J=3 Hz y J=9.1 Hz, aromático), 7.32-7.38 (4H, m, aromáticos), 7.50-7.53 (2H, m, aromáticos), 7.79 (1H, amplio t, NH). HREM (ESI^+) calculado para $C_{29}H_{32}FN_4O_4$ $[M+H^+]$: 519.2408; encontrado: 519.2407.

Intermediario 185

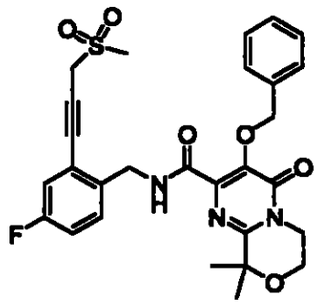


N-(4-Fluoro-2-(3-(metiltio)prop-1-inil)bencil)-3-(benciloxi)-9,9-dimetil-4-oxo-4,6,7,9-tetrahidropirimido[2,1-c][1,4]oxazina-2-carboxamida. Una solución del intermediario 183, el 3-[2-((3-(benciloxi)-9,9-dimetil-4-oxo-4,6,7,9-tetrahidropirimido[2,1-c][1,4]oxazina-2-carboxamido)metil)-5-fluorofenil]prop-2-inil metanosulfonato (0.160 g, 0.28 mmol) en N,N-dimetilformamida (3 ml) se trató a 0°C con tiometóxido de sodio (0.026 g, 0.37 mmol) y la mezcla resultante se agitó durante 2 h. La mezcla de reacción luego se diluyó con acetato de etilo, se lavó con bicarbonato de sodio saturado y salmuera, luego se secó sobre sulfato de magnesio anhidro y se concentró bajo presión reducida. La cromatografía del residuo en gel de sílice (gradiente de

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elución de acetato de etilo en hexano) dio 0.114 g (78% rendimiento) del material del título como un sólido blanco. ^{1}HRMN 400 MHz ($CDCl_3$) δ ppm: 1.64 (6H, s, 2 x CH_3), 2.28 (3H, s, SCH_3), 3.45 (2H, s, SCH_2), 4.05 (4H, m, 2 x CH_2), 4.69 (2H, d, J=6.1 Hz, NCH_2), 5.31 (2H, s, OCH_2), 6.98 (1H, m, aromático), 7.15 (1H, dd, J=3 Hz y J=9.1 Hz, aromático), 7.32-7.38 (4H, m, aromáticos), 7.50-7.53 (2H, m, aromáticos), 7.80 (1H, amplio t, NH). HREM (ESI^+) calculado para $C_{28}H_{29}FN_3O_4S$ [$M+H^+$]: 522.1863; encontrado: 522.1844.

Intermediario 186

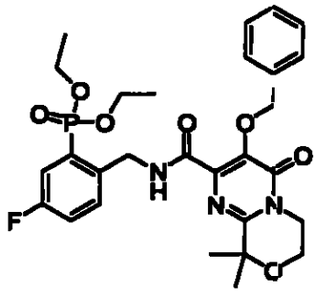


N-(4-Fluoro-2-(2-(metilsulfonilo)prop-1-inil)bencil)-3-(benciloxi)-9,9-dimetil-4-oxo-4,6,7,9-tetrahidropirimido[2,1-c][1,4]oxazina-2-carboxamida. Una solución del intermediario 185, la N-(4-fluoro-2-(3-(metiltio)prop-1-inil)bencil)-3-(benciloxi)-9,9-dimetil-4-oxo-4,6,7,9-tetrahidropirimido[2,1-c][1,4]oxazina-2-carboxamida (0.110 g, 0.21 mmol) en diclorometano (3 ml) se trató a 0°C con ácido 3-cloroperoxibenzoico (0.120 g de 85%, 0.59 mmol) y la mezcla resultante se agitó a 22°C durante 30 min. La mezcla de

578
579

reacción luego se diluyó con acetato de etilo, se lavó con bicarbonato de sodio saturado, salmuera, luego se secó sobre sulfato de magnesio anhidro y se concentró bajo presión reducida. La cromatografía del residuo en gel de sílice (gradiente de elución de acetato de etilo en diclorometano) dio 0.074 g (64% rendimiento) del material del título como un sólido blanco. ^{1}HRMN 400 MHz ($CDCl_3$) δ ppm: 1.64 (6H, s, 2 x CH_3), 3.03 (3H, s, SCH_3), 4.03 (2H, s, SCH_2), 4.05 (4H, m, 2 x CH_2), 4.65 (2H, d, J=6.0 Hz, NCH_2), 5.27 (2H, s, OCH_2), 7.06 (1H, m, aromático), 7.17 (1H, dd, J=3 Hz y J=8.6 Hz, aromático), 7.31-7.38 (6H, m, aromáticos), 8.12 (1H, amplio t, NH). HREM (ESI^+) calculado para $C_{28}H_{29}FN_3O_6S$ [$M+H^+$]: 554.1761; encontrado: 554.1784.

Intermediario 187

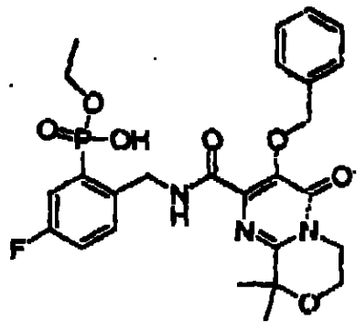


Dietil 2-((3-(benciloxi)-9,9-dimetil-4-oxo-4,6,7,9-tetrahidropirimido[2,1-c][1,4]oxazina-2-carboxamido)metil)-5-fluorofenilfosfonato. Una solución del intermediario 174, la N-(4-fluoro-2-yodobencil)-3-(benciloxi)-9,9-dimetil-4-oxo-4,6,7,9-tetrahidropirimido[2,1-c][1,4]oxazina-2-carboxamida (0.200 g, 0.35 mmol) y trifenilfosfina (0.020 mg) en etanol (5

580

ml) se limpió con argón y luego se trató con N,N-diisopropiletilamina (0.25 ml, 1.4 mmol), acetato de paladio (II) (0.020 g) y dietil fosfito (0.15 ml, 1.16 mmol). La mezcla de reacción luego se selló y se calentó a 80°C durante 18 h. La mezcla de reacción luego se diluyó con acetato de etilo, se lavó con ácido clorhídrico 0.1 N, bicarbonato de sodio saturado, salmuera, luego se secó sobre sulfato de magnesio anhidro y se concentró. La cromatografía del residuo en gel de sílice (gradiente de elución de acetonitrilo en diclorometano) dio 0.103 g (51% rendimiento) del compuesto del título como un sólido blanco. ^{1}HRMN 400 MHz ($CDCl_3$) δ ppm: 1.36 (6H, t, J=6.6 Hz, 2 x CH_3), 1.64 (6H, s, 2 x CH_3), 4.04 (4H, m, 2 x CH_2), 4.08-4.22 (4H, m, 2 x OCH_2), 4.78 (2H, d, J=6.6 Hz, NCH_2), 5.29 (2H, s, OCH_2), 7.21 (1H, m, aromático), 7.29-7.34 (3H, m, aromáticos), 7.45-7.52 (3H, m, aromáticos), 7.65-7.72 (1H, m, aromático), 8.67 (1H, amplio t, NH). HREM (ESI^+) calculado para $C_{28}H_{34}FN_3O_7P$ [$M+H^+$]: 574.2118; encontrado: 574.2126.

Intermediario 188



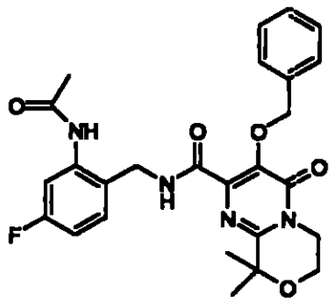
2-((3-(benciloxi)-9,9-dimetil-4-oxo-4,6,7,9-

581.

tetrahidropirimido[2,1-c][1,4]oxazina-2-carboxamido)metil)-5-fluorofenilfosfonato de etil hidrógeno. Una solución del intermediario 187, 2-((3-(benciloxi)-9,9-dimetil-4-oxo-4,6,7,9-tetrahidropirimido[2,1-c][1,4]oxazina-2-carboxamido)metil-5-fluorofenilfosfonato de dietilo (0.115 g, 0.20 mmol) en tetrahidrofurao (3 ml)/etanol (3 ml) se trató con hidroxido de sodio acuoso 1N (1.0 ml, 1.0 mmol) y la mezcla resultante se calentó a 45°C durante 2h. La mezcla de reacción se diluyó con acetato de etilo, se lavó con ácido clorhídrico 0.1 N, salmuera, se secó sobre sulfato de magnesio anhidro y se concentró. El residuo se purificó en un sistema CLAR preparativo automatizado Shimadzu (columna YMC Pack C-18, 5 µ, 20 x 250 mm, gradiente de elución acetonitrilo-agua 0.1% de ácido trifluoroacético) para dar 0.070 g (64% rendimiento) del material del título como un aceite claro. ^{1}HRMN 400 MHz ($CDCl_3$) δ ppm: 1.37 (3H, t, J=7.1 Hz, CH_3), 1.62 (6H, s, 2 x CH_3), 4.04 (4H, m, 2 x CH_2), 4.18 (2H, m, OCH_2), 4.75 (2H, amplio d, J=5 Hz, NCH_2), 5.32 (2H, s, OCH_2), 7.21 (1H, m, aromático), 7.30-7.33 (3H, m, aromáticos), 7.38-7.40 (2H, m, aromáticos), 7.47-7.52 (1H, m, aromáticos), 7.56-7.63 (1H, m, aromático), 8.56 (1H, amplio t, NH). EMAR (ESI$^+$) calculado para $C_{26}H_{30}FN_3O_7P$ [M+H$^+$]; 546.1805; encontrado; 546.1786.

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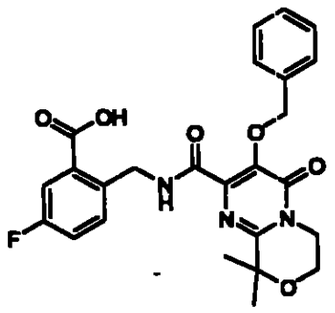
Intermediario 189



N-(2-Acetamido-4-fluorobencil)-3-(benciloxi)-9,9-dimetil-4-oxo-4,6,7,9-tetrahidropirimido[2,1-c][1,4]oxazina-2-carboxamida. A una solución del intermediario 169, la N-(2-amino-4-fluorobencil)-3-(benciloxi)-9,9-dimetil-4-oxo-4,6,7,9-tetrahidropirimido[2,1-c][1,4]oxazina-2-carboxamida (0.033 g, 0.073 mmol) en tetrahidrofurano seco (10 mL) se agregó cloruro de acetilo (5.7 µL, 0.08 mmol) y diisopropiletilamina (38 µL, 0.22 mmol). La mezcla de reacción se agitó a 23°C durante 3 h. Luego se agregó $NaHCO_3$ (0.25 M, 20 mL) y el material orgánico se extrajo con acetato de etilo (3 X 25 mL). Los extractos orgánicos combinados, se secaron ($MgSO_4$) y se concentraron in vacuo. El residuo se purificó en un sistema Biotage en una columna de gel de sílice con acetato de etilo:Hex (1:2 to 2:1) como eluyente para proporcionar el compuesto del título (0.025 g, 69% rendimiento). ^{1}HRMN 400 MHz (MeOD) δ (ppm): 7.66 (1H, dd, J=10.5, 2.8 Hz), 7.43-7.25 (6H, m), 6.87 (1H, ddd, (dt), J=8.8, 2.6 Hz), 5.19 (2H, s), 4.47 (2H, m), 4.08 (2H, t, J=4.9 Hz), 3.99 (2H, t, J=4.9 Hz), 2.19 (3H, s), 1.62 (6H,

s). CLEM $(M+H)^+$ m/z 495.

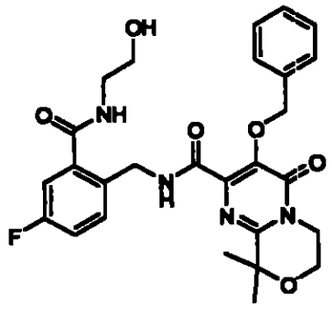
Intermediario 190



Ácido 2-((3-(Benciloxi)-9,9-dimetil-4-oxo-4,6,7,9-tetrahidropirimido[2,1-c][1,4]oxazina-2-carboxamido)metil)-5-fluorobenzoico. A una suspensión del intermediario 154, el 2-((3-(benciloxi)-9,9-dimetil-4-oxo-4,6,7,9-tetrahidropirimido[2,1-c][1,4]oxazina-2-carboxamido)metil)-5-fluorobenzoato de metilo (500 mg, 1.01 mmol) en MeOH (10 mL) y CH_3CN (5 mL) se agregó NaOH 1N (2 mL) y la mezcla se agitó a temperatura ambiente durante 2 horas. La mezcla se concentró in vacuo y el residuo se purificó por cromatografía de columna de fase inversa (YMC, C-18 ODS, 10-25% CH_3CN/H_2O) para proporcionar 90 mg (Rendimiento 19%) del compuesto del título como un polvo blanco opaco: CL/EM m/z 482 (M+H).

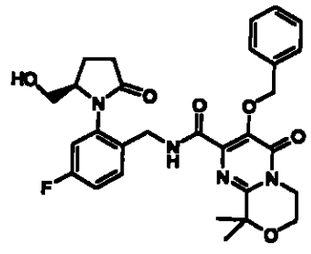
584

Intermediario 191



N-(2-((2-Aminoetil)carbamoil)-4-fluorobencil)-3-(benciloxi)-9,9-dimetil-4-oxo-4,6,7,9-tetrahidropirimido[2,1-c][1,4]oxazina-2-carboxamida. Una mezcla del intermediario 190, el ácido 2-((3-(benciloxi)-9,9-dimetil-4-oxo-4,6,7,9-tetrahidropirimido[2,1-c][1,4]oxazina-2-carboxamido)metil)-5-fluorobenzoico (59 mg, 0.12 mmol) y O-(7-azabenzotriazol-1-il)-N,N,N',N'-tetrametiluronio hexafluorofosfato, HATU (76 mg, 0.2 mmol; Aldrich) en DMF (1 mL) se agitó durante 20 minutos. A esta mezcla se agregó etanolamina (20 mg, 0.3 mmol) y se agitó continuamente durante la noche. La mezcla se concentró in vacuo, se disolvió en CH_2Cl_2, se lavó con agua luego se secó ($MgSO_4$), se filtró, y se concentró para proporcionar 55 mg (Rendimiento 87%) del compuesto del título: CL/EM m/z 525 (M+H).

Intermediario 192

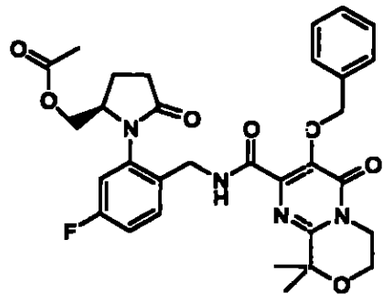


(R)-N-(4-Fluoro-2-(2-(hidroximetil)-5-oxopirrolidin-1-

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il)bencil)-3-(benciloxi)-9,9-dimetil-4-oxo-4,6,7,9-tetrahidropirimido[2,1-c][1,4]oxazina-2-carboxamida. A una solución agitada del intermediario 166, la (R)-N-(2-(2-((tert-butildimetilsililoxi)metil)-5-oxopirrolidin-1-il)-4-fluorobencil)-3-(benciloxi)-9,9-dimetil-4-oxo-4,6,7,9-tetrahidropirimido[2,1-c][1,4]oxazina-2-carboxamida (0.10 g, 0.150 mmol) en tetrahidrofurano (5mL) a 23°C se agregó una solución de fluoruro de tetrabutilamonio (1M en tetrahidrofurano) (180 µL, 0.18 mmol). La mezcla de reacción se agitó a 23°C durante 3 h. Luego se agregó $NaHCO_3$ (1N en H_2O, 30 mL) y el material orgánico se extrajo con acetato de etilo (2 X 25 mL). Los extractos orgánicos combinados se secaron ($MgSO_4$), se filtraron y se concentraron in vacuo. El residuo se purificó en un sistema Biotage en una columna de gel de sílice con acetato de etilo/Hexanos (1:1) a 100% de acetato de etilo como eluyente para proporcionar el compuesto del título (0.060 g, 73% rendimiento): ^{1}HRMN 400 MHz (MeOD) δ (ppm): 7.55 (1H, dd, (t), 6.6 Hz), 7.43 (2H, m), 7.13 (1H, dd, J=9.5, 2.4 Hz), 7.03 (1H, m), 5.26 (2H, s), 4.57 (1H, m), 4.32 (2H, m), 4.08 (2H, t, J = 5.0 Hz), 7.03 (2H, t, J = 5.0 Hz), 3.53 (2H, m), 2.69-2.56 (2H, m), 2.38 (1H, m), 2.22 (1H, m), 1.62 (6H, s). CLEM $(M+H)^+$ m/z 551.

Intermediario 193

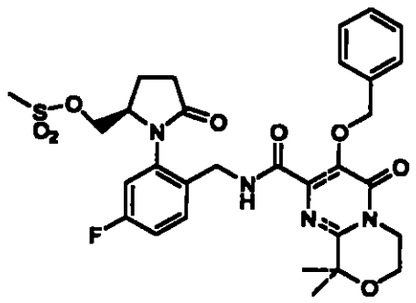


Acetato de (R)-(1-(2-((3-(Benciloxi)-9,9-dimetil-4-oxo-4,6,7,9-tetrahidropirimido[2,1-c][1,4]oxazina-2-carboxamido)metil)-5-fluorofenil)-5-oxopirrolidin-2-il)metilo. A una solución del intermediario 192, la (R)-N-(4-fluoro-2-(2-(hidroximetil)-5-oxopirrolidin-1-il)bencil)-3-(benciloxi)-9,9-dimetil-4-oxo-4,6,7,9-tetrahidropirimido[2,1-c][1,4]oxazina-2-carboxamida (0.045 g, 0.082 mmol) en tetrahidrofurano (5mL) se agregó cloruro de acetilo (12.8 µL, 0.180 mmol) y diisopropiletilamina (31.4 µL, 0.180 mmol). La mezcla de reacción se agitó a 23°C durante 4 h. Luego se agregó $NaHCO_3$ (1N en H_2O, 30 mL) y el material orgánico se extrajo con acetato de etilo (2 X 25 mL). Los extractos orgánicos combinados se secaron ($MgSO_4$), se filtraron y se concentraron in vacuo. El residuo se purificó en un sistema Biotage en una columna de gel de sílice column con acetato de etilo/Hexanos (1:1) a 100% de acetato de etilo como eluyente para proporcionar el compuesto del título (0.032 g, 67% rendimiento): ^{1}HRMN

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400 MHz (MeOD) δ ppm: 7.48 (3H, m), 7.33 (3H, m), 7.16 (1H, m), 7.03 (1H, m), 5.24 (2H, s), 4.60 (1H, m), 4.55 (1H, m), 4.22 (1H, dd, J=12.0, 4.5 Hz), 4.08 (2H, t, J=5.0 Hz), 3.99 (3H, m), 2.62 (2H, m), 2.44 (1H, m), 2.09-1.92 (5H, m), 1.62 (3H, s), 1.61 (3H, s). CLEM $(M+H)^+$ m/z 593.

Intermediario 194

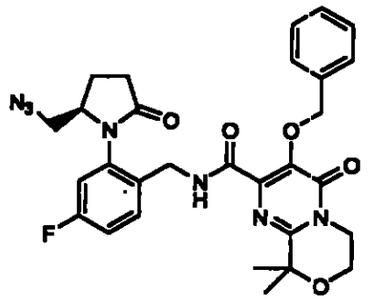


(R)-(1-(2-((3-(Benciloxi)-9,9-dimetil-4-oxo-4,6,7,9-tetrahidropirimido[2,1-c][1,4]oxazina-2-carboxamido)metil)-5-fluorofenil)-5-oxopirrolidin-2-il)metil metanosulfonato. A una solución agitada del intermediario 192, la (R)-N-(4-fluoro-2-(2-(hidroximetil)-5-oxopirrolidin-1-il)bencil)-3-(benciloxi)-9,9-dimetil-4-oxo-4,6,7,9-tetrahidropirimido[2,1-c][1,4]oxazina-2-carboxamida (0.160 g, 0.291 mmol) en CH_2Cl_2 (10 mL) a 0°C se agregó trietilamina (81 µL, 0.582 mmol) y cloruro de metansulfonilo (27 µL, 0.349 mmol). La mezcla de reacción se agitó a 23°C durante 4 h. Luego se agregó

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agua (50 mL) y el material orgánico se extrajo con CH_2Cl_2 (2 X 50 mL). Los extractos orgánicos combinados se secaron ($MgSO_4$), se filtraron y se concentraron in vacuo para proporcionar el compuesto del título (0.178 g, 98% rendimiento). El material crudo se usó sin purificación adicional para la siguiente etapa: CLEM $(M+H)^+$ m/z 629.

Intermediario 195

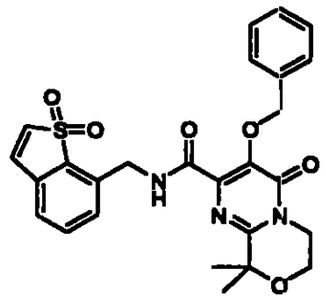


(R)-N-(2-(2-(Azidometil)-5-oxopirrolidin-1-il)-4-fluorobencil)-3-(benciloxi)-9,9-dimetil-4-oxo-4,6,7,9-tetrahidropirimido[2,1-c][1,4]oxazina-2-carboxamida. A una solución del intermediario 194, el (R)-(1-(2-((3-(benciloxi)-9,9-dimetil-4-oxo-4,6,7,9-tetrahidropirimido[2,1-c][1,4]oxazina-2-carboxamido)metil)-5-fluorofenil)-5-oxopirrolidin-2-il)metil metanosulfonato (0.150 g, 0.239 mmol) en DMF (10 mL) se agregó azida de sodio (0.019 g, 0.287 mmol). La mezcla resultante se agitó a 50°C durante 6 h. Luego se agregó agua (50 mL) y el material orgánico se extrajo con acetato de etilo (2 X 50 mL). Los extractos orgánicos combinados se lavaron con H_2O (50 mL), se secaron

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($MgSO_4$), se filtraron y se concentraron in vacuo para proporcionar el compuesto del título (0.125 g, 91% rendimiento). CLEM $(M+H)^+$ m/z 576.

Intermediario 196

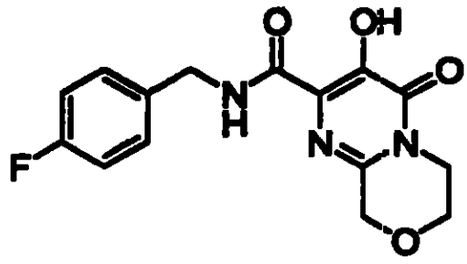


N-(Benzo[b]tiofen-1,1-diona-7-ilmetil)-3-(benciloxi)-9,9-dimetil-4-oxo-4,6,7,9-tetrahidropirimido[2,1-c][1,4]oxazina-2-carboxamida. A una solución del intermediario 147, la N-(benzo[b]tiofen-7-ilmetil)-3-(benciloxi)-9,9-dimetil-4-oxo-4,6,7,9-tetrahidropirimido[2,1-c][1,4]oxazina-2-carboxamida (0.100 g, 0.21 mmol) en dicloroetano (10 mL) se agregó ácido per-acético (32% en H_2O) (1.0 mmol, 200 µL). La mezcla de reacción se agitó a 23°C durante 48 h. Se agregó agua (50 mL) y el material orgánico se extrajo con CH_2Cl_2 (2 X 50 mL). Los extractos orgánicos combinados se secaron ($MgSO_4$), se filtraron y se concentraron in vacuo para proporcionar el compuesto del título (0.106 g, 99% rendimiento): ^1H RMN (400 MHz, DMSO-d_6) δ ppm: 9.11 (1H, t, J=6.4 Hz), 7.65 (1H, d, J=6.8 Hz) 7.59-7.29 (9H, m), 5.15 (2H, s), 4.77 (2H, d, J=6.5 Hz), 4.04 (2H, t, J=5.0

590

Hz), 3.90 (2H, m), 1.59 (6H, s). CLEM $(M+H)^+$ m/z 508.

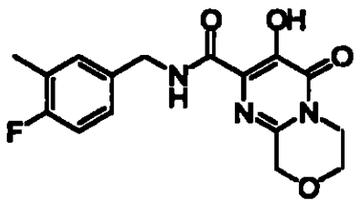
Ejemplo 1



Pirimido[2,1-c][1,4]oxazin-2-carboxamida, N-[(4-fluorofenil)metil]-4,6,7,9-tetrahidro-3-hidroxi-4-oxo-. Una mezcla del intermediario 7, 3-hidroxi-4-oxo-4,6,7,9-tetrahidropirimido[2,1-c][1,4]oxazin-2-carboxilato de etilo, (0.036 g, 0.15 mmol) y 4-fluorobencilamina (0.11 g, 0.87 mmol) en alcohol etílico anhidro (5 ml) y N,N-dimetilformamida (2 ml) se calentó bajo reflujo durante 18 horas. El solvente se evaporó entonces in vacuo y el residuo se dividió entre acetato de etilo y ácido clorhídrico 0.1 N. La fase orgánica se lavó con agua, salmuera y se secó sobre sulfato de sodio anhidro. La evaporación del solvente y la recristalización del sólido resultante del etanol dio 0.023 g (47% de rendimiento) de la amida del título como cristales blancos; pf 211°C (acetato de etilo-hexano). ^{1}HRMN 400 MHz ($CDCl_3$) δ ppm: 4.06 (4H, m, 2 x CH_2), 4.59 (2H, d, J = 7.6 Hz, NCH_2), 4.61 (2H, s, OCH_2), 7.09 (2H, m, aromáticos), 7.33 (2H, m, aromáticos), 7.84 (1H, amplio t, NH), 12.06 (1H, s, OH). EM (ES^+) m/z 320 $[M+H^+]$.

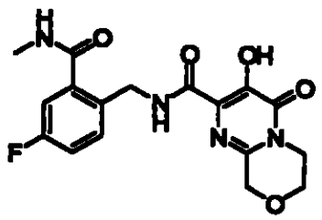
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Ejemplo 2



Pirimido[2,1-c][1,4]oxazin-2-carboxamida, N-[(4-fluoro-3-metilfenil)metil]-4,6,7,9-tetrahidro-3-hidroxi-4-oxo-. La reacción del intermediario 7, 3-hidroxi-4-oxo-4,6,7,9-tetrahidropirimido[2,1-c][1,4]oxazin-2-carboxilato de etilo, (0.100 g, 0.42 mmol) con 4-fluoro-3-metilbencilamina (0.23 g, 1.66 mmol) como se describe en la preparación del ejemplo 1 dio 0.101 g (73% de rendimiento) de la amida del título como cristales blancos; pf 206-208°C (acetato de etilo). ^{1}HRMN 400 MHz ($CDCl_3$) δ ppm: 2.30 (3H, s, CH_3), 4.06 (4H, m, 2 x CH_2), 4.55 (2H, d, J = 6.1 Hz, NCH_2), 4.60 (2H, s, OCH_2), 7.01 (1H, m, aromático), 7.14 (2H, m, aromáticos), 7.81 (1H, amplio t, NH), 12.09 (1H, s, OH). EM (ESI$^+$) m/z 334 [M+H$^+$].

Ejemplo 3

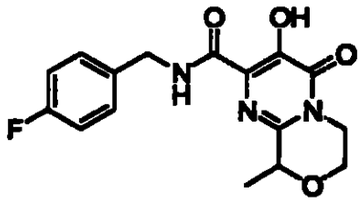


Pirimido[2,1-c][1,4]oxazin-2-carboxamida, N-[[4-fluoro-2-[(metilamino)carbonil]fenil]metil]-4,6,7,9-tetrahidro-3-hidroxi-4-oxo-. El compuesto del título puede prepararse del

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intermediario 150, N-(4-fluoro-2-(metilcarbamoil)bencil)-3-(benciloxi)-4-oxo-4,6,7,9-tetrahidropirimido[2,1-c][1,4]oxazin-2-carboxamida. ^{1}HRMN 400 MHz (DMSO-d_6) δ ppm: 2.79 (3H, d, J = 4.5 Hz, NCH_3), 3.83 (2H, m, CH_2), 4.02 (2H, m, CH_2), 4.54 (2H, d, J = 6.7 Hz, NCH_2), 4.58 (2H, s, OCH_2), 7.31 (2H, m, aromáticos), 7.38 (1H, m, aromático), 8.54 (1H, amplio q, NH), 9.21 (1H, amplio t, NH), 12.24 (1H, s, OH). EMAR (ESI^+) calculado para $C_{17}H_{18}FN_3O_5$ [$M+H^+$]: 377.1261; encontrado: 377.1249.

Ejemplo 4

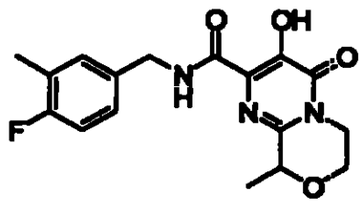


Pirimido[2,1-c][1,4]oxazin-2-carboxamida, N-[(4-fluorofenil)metil]-4,6,7,9-tetrahidro-3-hidroxi-9-metil-4-oxo-. La reacción del intermediario 15, 3-hidroxi-9-metil-4-oxo-4,6,7,9-tetrahidropirimido[2,1-c][1,4]oxazin-2-carboxilato de etilo (0.050 g, 0.20 mmol) con 4-fluorobencilamina (0.11 g, 0.87 mmol) como se describe en la preparación del ejemplo 1 dio 0.056 g (84% de rendimiento) de la amida del título como cristales blancos; pf 165-167°C (acetato de etilo-hexano). ^{1}HRMN 400 MHz ($CDCl_3$) δ ppm: 1.62 (3H, d, J = 7.0 Hz, CH_3), 3.90 (2H, m, CH_2), 4.15-4.32 (2H, m, CH_2), 4.61 (3H, m, NCH_2 y OCH), 7.08 (2H, m, aromáticos), 7.34

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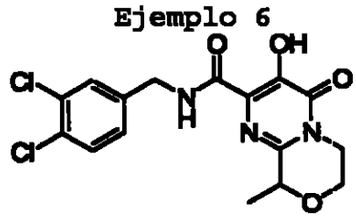
(2H, m, aromáticos), 7.82 (1H, amplio t, NH), 12.06 (1H, s, OH). Análisis calculado para $C_{16}H_{16}FN_3O_4$: C 57.65, H 4.83, N 12.60. Encontrado: C 57.44, H 4.69, N 12.37.

Ejemplo 5



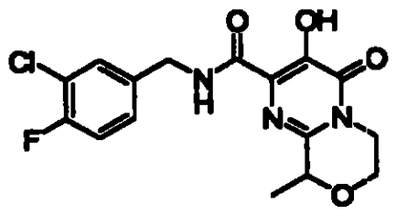
Pirimido[2,1-c][1,4]oxazin-2-carboxamida, N-[(4-fluoro-3-metilfenil)metil]-4,6,7,9-tetrahidro-3-hidroxi-9-metil-4-oxo-. La reacción del intermediario 15, 3-hidroxi-9-metil-4-oxo-4,6,7,9-tetrahidropirimido(2,1-c][1,4]oxazin-2-carboxilato de etilo, (0.090 g, 0.35 mmol) con 4-fluoro-3-metilbencilamina (0.180 g, 1.3 mmol) como se describe en la preparación del ejemplo 1 dio 0.068 g (55% de rendimiento) de la amida del título como cristales blancos; pf 134°C (acetato de etilo-hexano). ^{1}HRMN 400 MHz ($CDCl_3$) δ ppm: 1.62 (3H, d, J = 6.6 Hz, CH_3), 2.30 (3H, s, CH_3), 3.90 (2H, m, CH_2), 4.13-4.32 (2H, m, CH_2), 4.49-4.64 (3H, m, NCH_2 y OCH), 7.01 (1H, m, aromático), 7.16 (2H, m, aromáticos), 7.79 (1H, amplio t, NH), 12.09 (1H, s, OH). Análisis calculado para $C_{17}H_{18}FN_3O_4$: C 58.78, H 5.22, N 12.09. Encontrado: C 58.57, H 5.55, N 11.90.

Ejemplo 6



Pirimido[2,1-c][1,4]oxazin-2-carboxamida, N-[(3,4-diclorofenil)metil]-4,6,7,9-tetrahidro-3-hidroxi-9-metil-4-oxo-. La reacción del intermediario 15, 3-hidroxi-9-metil-4-oxo-4,6,7,9-tetrahidropirimido[2,1-c][1,4]oxazin-2-carboxilato de etilo (0.075 g, 0.29 mmol) con 3,4-diclorobencilamina (0.140 g, 0.8 mmol) como se describe en la preparación del ejemplo 1 dio 0.085 g (75% de rendimiento) de la amida del título como cristales blancos; pf 192°C (acetato de etilo-hexano). ^{1}HRMN 400 MHz ($CDCl_3$) δ ppm: 1.64 (3H, d, J = 6.6 Hz, CH_3), 3.91 (2H, m, CH_2), 4.17-4.32 (2H, m, CH_2), 4.50-4.68 (3H, m, NCH_2 y OCH), 7.20 (1H, dd, J = 2.0 Hz y J = 8.0 Hz, aromático), 7.44 (1H, d, J = 2.0 Hz, aromático), 7.46 (1H, d, J = 8.0 Hz, aromático), 7.86 (1H, amplio t, NH), 11.92 (1H, s, OH). EM (ESI$^+$) m/z 384 [M+H$^+$]. Análisis calculado para $C_{16}H_{15}Cl_2N_3O_4$: C 50.02, H 3.94, N 10.94. Encontrado: C 49.40, H 4.06, N 10.41.

Ejemplo 7

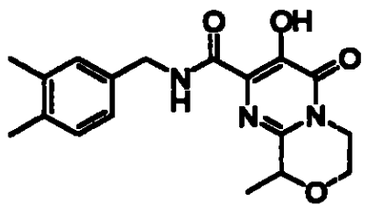


Pirimido[2,1-c][1,4]oxazin-2-carboxamida, N-[(3-cloro-4-

595

fluorofenil)metil]-4,6,7,9-tetrahidro-3-hidroxi-9-metil-4-oxo-. La reacción del intermediario 15, 3-hidroxi-9-metil-4-oxo-4,6,7,9-tetrahidropirimido[2,1-c][1,4]oxazin-2-carboxilato de etilo, (0.075 g, 0.30 mmol) con 3-cloro-4-fluorobencilamina (0.14 g, 0.88 mmol) como se describe en la preparación del ejemplo 1 dio 0.050 g (46% de rendimiento) de la amida del título como cristales blancos; pf 172°C (acetato de etilo-éter). ^{1}HRMN 400 MHz ($CDCl_3$) δ ppm: 1.63 (3H, d, J = 6.6 Hz, CH_3), 3.91 (2H, m, CH_2), 4.17-4.32 (2H, m, CH_2), 4.50-4.67 (3H, m, NCH_2 y OCH), 7.16 (1H, m, aromático), 7.24 (1H, m, aromático), 7.40 (1H, m, aromático), 7.85 (1H, amplio t, NH), 11.95 (1H, s, OH). Análisis calculado para $C_{16}H_{15}ClFN_3O_4$: C 52.25, H 4.11, N 11.42. Encontrado: C 51.99, H 4.01, N 11.09.

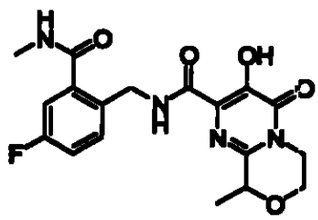
Ejemplo 8



Pirimido[2,1-c][1,4]oxazin-2-carboxamida, N-[(3,4-dimetilfenil)metil]-4,6,7,9-tetrahidro-3-hidroxi-9-metil-4-oxo-. La reacción del intermediario 15, 3-hidroxi-9-metil-4-oxo-4,6,7,9-tetrahidropirimido[2,1-c][1,4]oxazin-2-carboxilato de etilo, (0.075 g, 0.30 mmol) con 3,4-dimetilbencilamina (0.15 g, 1.1 mmol) como se describe en la preparación del ejemplo 1 dio 0.033 g (33% de rendimiento) de

la amida del título como un sólido blanco. ^{1}HRMN 400 MHz ($CDCl_3$) δ ppm: 1.61 (3H, d, J = 6.6 Hz, CH_3), 2.28 (3H, s, CH_3), 2.29 (3H, s, CH_3), 3.90 (2H, m, CH_2), 4.16-4.30 (2H, m, CH_2), 4.50-4.65 (3H, m, NCH_2 y OCH), 7.08-7.17 (3H, m, aromáticos), 7.78 (1H, amplio 1, NH), 12.17 (1H, s, OH). EM (ESI^+) m/z 344 [$M+H^+$].

Ejemplo 9



Pirimido[2,1-c][1,4]oxazin-2-carboxamida, N-[[4-fluoro-2-[(metilamino)carbonil]fenil]metil]-4,6,7,9-tetrahidro-3-hidroxi-9-metil-4-oxo-. Una solución del intermediario 140, N-(4-fluoro-2-(metilcarbamoil)bencil)-3-benciloxi-9-metil-4-oxo-4,6,7,9-tetrahidropirimido[2,1-c][1,4]oxazin-2-carboxamida, (0.268 g, 0.56 mmol) en una mezcla de acetato de etilo (25 ml) y etanol (25 ml) se hidrogenó bajo 1 atmósfera de hidrógeno a 25°C sobre 10% paladio en carbono activado (0.09 g) durante 2.5 h para dar 0.121 g (56% de rendimiento) del éster del título como un sólido blanco. ^{1}HRMN 400 MHz (DMSO-d_6) δ ppm: 1.57 (3H, d, J = 6.7 Hz, CH_3), 2.79 (3H, d, J = 4.6 Hz, NCH_3), 3.70 (1H, m, CH), 3.87 (1H, m, CH), 3.98 (1H, m, CH), 4.15 (1H, m, CH), 4.55 (2H, m, NCH_2), 4.62 (1H, q, J = 6.6 Hz, OCH), 7.25-7.44 (3H, m, aromáticos), 8.59 (1H,

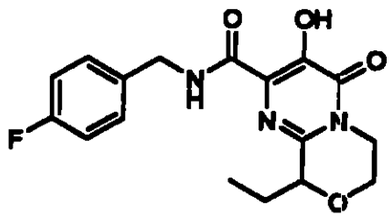
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amplio q, NH), 9.39 (1H, amplio, NH), 12.18 (1H, s, OH). EMAR (ESI^+) calculado para $C_{18}H_{20}FN_4O_5$ [$M+H^+$]: 391.1418; encontrado: 391.1431.

Ejemplos 10-14

Ejemplos 10-14 pueden prepararse a partir del 9-etil-3-hidroxi-4-oxo-4,6,7,9-tetrahidropirimido[2,1-c][1,4]oxazin-2-carboxilato de etilo y las aminas indicadas de conformidad con el método descrito por la síntesis del ejemplo 1. 9-Etil-3-hidroxi-4-oxo-4,6,7,9-tetrahidropirimido[2,1-c][1,4]oxazin-2-carboxilato de etilo se preparó de conformidad con el método usado para preparar el intermediario 15.

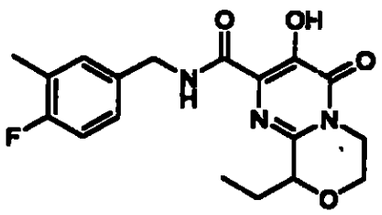
Ejemplo 10



Pirimido[2,1-c][1,4]oxazin-2-carboxamida, 9-etil-N-[(4-fluorofenil)metil]-4,6,7,9-tetrahidro-3-hidroxi-4-oxo-. El compuesto del título puede prepararse a partir del 4-fluorobencilamina. ^{1}HRMN 400 MHz ($CDCl_3$) δ ppm: 1.02 (3H, t, J = 7.3 Hz, CH_3), 1.93 (1H, m, CH), 2.15 (1H, m, CH), 3.88 (2H, m, CH_2), 4.2-4.29 (2H, m, CH_2), 4.46 (1H, m, CH), 4.53-4.69 (2H, m, CH_2), 7.06 (2H, m, aromáticos), 7.34 (2H, m, aromáticos), 7.82 (1H, amplio t, NH), 12.05 (1H, s, OH). EMAR (ESI^+) calculado para $C_{17}H_{19}FN_3O_4$ [$M+H^+$]: 348.1360; encontrado: 348.1355.

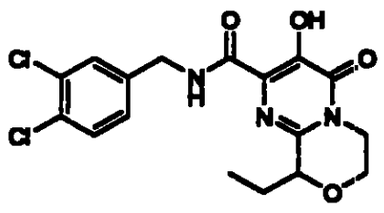
598

Ejemplo 11



Pirimido[2,1-c][1,4]oxazin-2-carboxamida, 9-etil-N-[(4-fluoro-3-metilfenil)metil]-4,6,7,9-tetrahidro-3-hidroxi-4-oxo-. El compuesto del título puede prepararse a partir de (4-fluoro-3-metilfenil)metanamina. ^{1}HRMN 400 MHz ($CDCl_3$) δ ppm: 1.01 (3H, t, J = 7.4 Hz, CH_3), 1.91 (1H, m, CH), 2.16 (1H, m, CH), 2.30 (3H, s, CH_3), 3.87 (2H, m, CH_2), 4.2-4.30 (2H, m, CH_2), 4.46 (1H, m, CH), 4.48-4.65 (2H, m, CH_2), 7.01 (1H, m, aromático), 7.14 (2H, m, aromáticos), 7.81 (1H, amplio t, NH), 12.07 (1H, s, OH). Análisis calculado para $C_{18}H_{20}FN_3O_4$: C 59.82, H 5.57, N 11.62; Encontrado: C 59.53, H 5.86, N 11.42.

Ejemplo 12

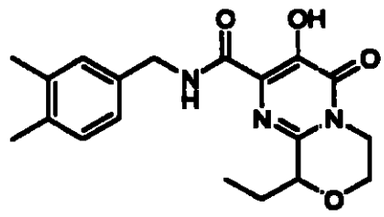


Pirimido[2,1-c][1,4]oxazin-2-carboxamida, N-[(3,4-diclorofenil)metil]-9-etil-4,6,7,9-tetrahidro-3-hidroxi-4-oxo-. El compuesto del título puede prepararse a partir de (3,4-diclorofenil)metanamina. ^{1}HRMN 400 MHz ($CDCl_3$) δ ppm:

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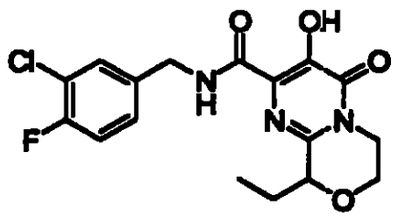
1.00 (3H, t, J = 7.3 Hz, CH_3), 1.91 (1H, m, CH), 2.15 (1H, m, CH), 3.85 (2H, m, CH_2), 4.19-4.28 (2H, m, CH_2), 4.45 (1H, m, CH), 4.48-4.66 (2H, m, CH_2), 7.19 (1H, m, aromático), 7.43 (2H, m, aromáticos), 7.84 (1H, amplio t, NH), 11.88 (1H, s, OH). Análisis calculado para $C_{17}H_{17}Cl_2N_3O_4$: C 51.27, H 4.30, N 10.55; Encontrado: C 51.16, H 4.21, N 10.34.

Ejemplo 13



Pirimido[2,1-c][1,4]oxazin-2-carboxamida, N-[(3,4-dimetilfenil)metil]-9-etil-4,6,7,9-tetrahidro-3-hidroxi-4-oxo-. El compuesto del título puede prepararse a partir de (3,4-dimetilfenil)metanamina. ^{1}HRMN 400 MHz ($CDCl_3$) δ ppm: 0.98 (3H, t, J = 7.3 Hz, CH_3), 1.87 (1H, m, CH), 2.12 (1H, m, CH), 2.26 (3H, s, CH_3), 2.27 (3H, s, CH_3), 3.83 (2H, m, CH_2), 4.17-4.26 (2H, m, CH_2), 4.41 (1H, m, CH), 4.45-4.64 (2H, m, CH_2), 7.05-7.24 (3H, m, aromáticos), 7.75 (1H, amplio t, NH), 12.13 (1H, s, OH). Análisis calculado para $C_{19}H_{23}N_3O_4$: C 63.85, H 6.49, N 11.76; Encontrado: C 63.55, H 6.48, N 11.74.

Ejemplo 14



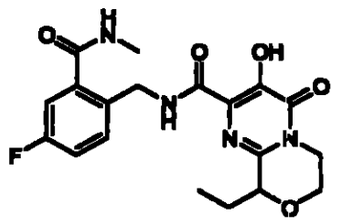
Pirimido[2,1-c][1,4]oxazin-2-carboxamida, N-[(3-cloro-4-fluorofenil)metil]-9-etil-4,6,7,9-tetrahidro-3-hidroxi-4-oxo-. El compuesto del título puede prepararse a partir de (3-cloro-4-fluorofenil)metanamina. ^{1}HRMN 400 MHz ($CDCl_3$) δ ppm: 1.03 (3H, t, J = 7.3 Hz, CH_3), 1.92 (1H, m, CH), 2.17 (1H, m, CH), 3.88 (2H, m, CH_2), 4.18-4.32 (2H, m, CH_2), 4.46 (1H, m, CH), 4.5-4.68 (2H, m, CH_2), 7.16 (1H, m, aromático), 7.24 (1H, m, aromático), 7.40 (1H, m, aromático), 7.84 (1H, amplio t, NH), 11.93 (1H, s, OH). Análisis calculado para $C_{17}H_{17}ClFN_3O_4$: C 53.48, H 4.48, N 11.00; Encontrado: C 53.25, H 4.49, N 10.79.

Ejemplos 15-16

Los Ejemplos 15-16 pueden prepararse a partir del ácido 3-(benciloxi)-9-etil-4-oxo-4,6,7,9-tetrahidropirimido[2,1-c][1,4]oxazin-2-carboxílico y las aminas indicadas de conformidad con los métodos descritos para la síntesis del intermediario 140 y ejemplo 9. El ácido 3-(benciloxi)-9-etil-4-oxo-4,6,7,9-tetrahidropirimido[2,1-c][1,4]oxazin-2-carboxílico se preparó de conformidad con el método usado para preparar el intermediario 16.

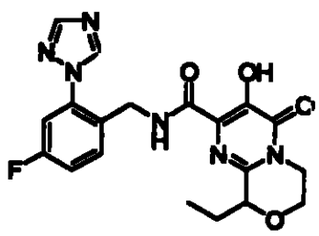
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Ejemplo 15



Pirimido[2,1-c][1,4]oxazin-2-carboxamida, 9-etil-N-[[4-fluoro-2-[(metilamino)carbonil]fenil]metil]-4,6,7,9-tetrahidro-3-hidroxi-4-oxo-. El compuesto del título puede prepararse a partir del intermediario 39. ^{1}HRMN 400 MHz ($CDCl_3$) δ ppm: 1.03 (3H, t, J = 7.3 Hz, CH_3), 1.98 (1H, m, CH), 2.28 (1H, m, CH), 3.06 (3H, d, J = 4.5 Hz, NCH_3), 3.86 (2H, m, CH_2), 4.14-4.29 (2H, m, CH_2), 4.48 (1H, m, CH), 4.60 (2H, m, CH_2), 6.2 (1H, amplio, NH), 7.14-7.21 (2H, m, aromáticos), 7.54 (1H, m, aromático), 8.85 (1H, amplio t, NH), 12.1 (1H, s, OH). EMAR (ESI^+) calculado para $C_{19}H_{22}FN_4O_5$ [$M+H^+$]: 405.1574; encontrado: 405.1579.

Ejemplo 16



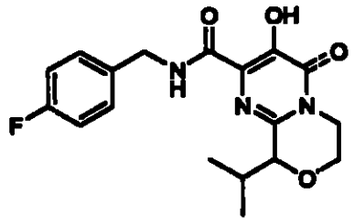
Pirimido[2,1-c][1,4]oxazin-2-carboxamida, 9-etil-N-[[4-fluoro-2-(1H-1,2,4-triazol-1-il)fenil}metil]-4,6,7,9-tetrahidro-3-hidroxi-4-oxo-. El compuesto del título puede prepararse a partir del intermediario 151, N-(4-fluoro-2-(1H-

1,2,4-triazol-1-il)bencil)-3-(benciloxi)-9-etil-4-oxo-4,6,7,9-tetrahidropirimido[2,1-c][1,4]oxazin-2-carboxamida, de conformidad con un procedimiento similar al que se describió en ejemplo 9. ^{1}HRMN 400 MHz (DMSO-d_6) δ ppm: 0.94 (3H, t, J = 7.5 Hz, CH_3), 1.88 (1H, m, CH), 2.27 (1H, m, CH), 3.68 (1H, m, CH), 3.87 (1H, m, CH), 4.0 (1H, m, CH), 4.19 (1H, m, CH), 4.36-4.49 (3H, m, CH_2 y CH), 7.43 (1H, m, aromático), 7.56 (2H, m, aromáticos), 8.32 (1H, m, CH), 9.05 (1H, m, CH), 9.3 (1H, amplio 1, NH), 12.04 (1H, s, OH). EMAR (ESI$^+$) calculado para $C_{19}H_{20}FN_6O_4$ [M+H$^+$]: 415.1530; encontrado: 415.1515.

Ejemplos 17-18

Los Ejemplos 17-18 pueden prepararse a partir de 3-hidroxi-9-isopropil-4-oxo-4,6,7,9-tetrahidropirimido[2,1-c][1,4]oxazin-2-carboxilato de etilo y las aminas indicadas de conformidad con el método descrito por la síntesis del ejemplo 1. 3-Hidroxi-9-isopropil-4-oxo-4,6,7,9-tetrahidropirimido[2,1-c][1,4]oxazin-2-carboxilato de etilo puede prepararse de conformidad con el método usado para preparar el intermediario 15.

Ejemplo 17

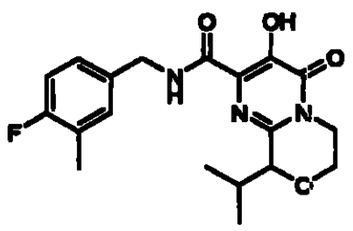


Pirimido[2,1-c][1,4]oxazin-2-carboxamida, N-[(4-fluorofenil)metil]-4,6,7,9-tetrahidro-3-hidroxi-9-(1-

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metiletil)-4-oxo-. El compuesto del título puede prepararse a partir de 4-fluorobencilamina. ^{1}HRMN 400 MHz ($CDCl_3$) δ ppm: 0.80 (3H, d, J = 6.7 Hz, CH_3), 1.13 (3H, d, J = 7.1 Hz, CH_3), 2.54 (1H, m, CH), 3.77 (2H, m, CH_2), 4.3 (2H, m, CH_2), 4.40 (1H, d, J = 2.5 Hz, CH), 4.50-4.72 (2H, m, CH_2), 7.09 (2H, m, aromáticos), 7.34 (2H, m, aromáticos), 7.82 (1H, amplio t, NH), 12.04 (1H, s, OH). Análisis calculado para $C_{18}H_{20}FN_3O_4$: C 59.82, H 5.57, N 11.62; Encontrado: C 59.22, H 5.81, N 11.50.

Ejemplo 18

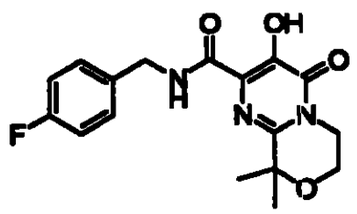


Pirimido[2,1-c][1,4]oxazin-2-carboxamida, N-[(4-fluoro-3-metilfenil)metil]-4,6,7,9-tetrahidro-3-hidroxi-9-(1-metiletil)-4-oxo-. El compuesto del título puede prepararse a partir de (4-fluoro-3-metilfenil)metanamina.

^{1}HRMN 400 MHz ($CDCl_3$) δ ppm: 0.80 (3H, d, J = 6.6 Hz, CH_3), 1.13 (3H, d, J = 7.1 Hz, CH_3), 2.30 (3H, s, CH_3), 2.54 (1H, m, CH), 3.77 (2H, m, CH_2), 4.3 (2H, m, CH_2), 4.40 (1H, amplio s, CH), 4.45-4.68 (2H, m, CH_2), 7.02 (1H, m, aromático), 7.17 (2H, m, aromáticos), 7.80 (1H, amplio t, NH), 12.07 (1H, s, OH). EMAR (ESI$^+$) calculado para $C_{19}H_{23}FN_3O_4$ [M+H$^+$]: 376.1673;

encontrado: 376.1671.

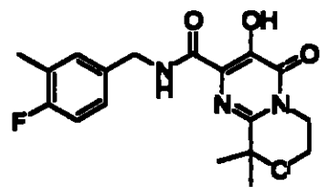
Ejemplo 19



Pirimido[2,1-c][1,4]oxazin-2-carboxamida, N-[(4-fluorofenil)metil]-4,6,7,9-tetrahidro-3-hidroxi-9,9-dimetil-4-oxo-. A una solución del intermediario 25, 3-hidroxi-9,9-dimetil-4-oxo-4,6,7,9-tetrahidropirimido[2,1-c][1,4]oxazin-2-carboxilato de etilo, (3.0 g, 11.19 mmol) en DMF (20 mL) y etanol (10 mL) se agregó trietilamina (1.55 mL) seguido por 4-fluorobencilamina (3.82 mL, 33.57 mmol). La mezcla se agitó a 90°C durante 2 horas y luego se concentró. El aceite resultante se dividió entre acetato de etilo (50 mL) y HCl acuoso 1N (35 mL). La capa acuosa nuevamente se extrajo con acetato de etilo (20 mL) y las capas orgánicas se combinaron y se lavaron con H_2O (4 x 20 mL) y salmuera entonces se secaron (Na_2SO_4) y se concentraron. El residuo café se trituró con éter y los sólidos se filtraron y se lavaron con éter. Los sólidos café pálido se recristalizaron a partir del 95:5 MeOH/H_2O para dar el compuesto del título como agujas incoloras (3.18 g, 82% de rendimiento). ^1H RMN (500 MHz, $CDCl_3$) δ ppm: 11.96 (1H, s), 7.77 (1H, brs), 7.30 (2H, dd, J= 8.4, 5.3 Hz), 7.04 (2H, t, J= 8.7 Hz), 4.57 (2H, d, J= 6.1 Hz), 4.01 (4H, s), 1.56 (6H, s). EMAR (M+H) calculado

para $C_{17}H_{19}FN_3O_4$: 348.13597; encontrado: 348.1365. Análisis calculado para $C_{17}H_{18}FN_3O_4$: C, 58.78; H, 5.22; N, 12.09. Encontrado: C, 58.38; H, 5.23; N, 11.80.

Ejemplo 20



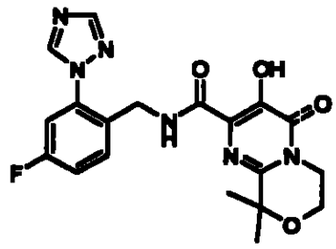
Pirimido[2,1-c][1,4]oxazin-2-carboxamida,N-[(4-fluoro-3-metilfenil)metil]-4,6,7,9-tetrahidro-3-hidroxi-9,9-dimetil-4-oxo-. Una solución DMF del intermediario 25, 3-hidroxi-9,9-dimetil-4-oxo-4,6,7,9-tetrahidropirimido[2,1-c][1,4]oxazin-2-carboxilato de etilo, (4 mL, 1 mmol), Et_3N (0.14 mL, 1 mmol) y 3-meti-4-fluorobencilamina (0.418 g. 3 mmol) se calentó a 90°C durante 5 horas. La mezcla de reacción se enfrió y el producto se aisló por CLAR preparativa de fase inversa usand MeOH/H_2O-0.1% CF_3CO_2H como eluyente. Las fracciones que contienen el material deseado se combinaron y se concentraron para proporcionar el compuesto del título como un polvo amarillo (0.19 g, 52% de rendimiento). ^1H RMN (500 MHz, $CDCl_3$) δ ppm: 11.99 (1H, s), 7.73 (1H, s), 7.14 (1H, d, J = 7.3 Hz), 7.12-7.09 (1H, m), 6.98 (1H, t, J = 9.0 Hz), 4.54 (2H, d, J = 6.4 Hz), 4.01 (4H, s), 2.27 (3H, s), 1.56 (6H, s). EMAR (M+H) calculado para $C_{18}H_{21}FN_3O_4$: 362.1516; encontrado: 362.1509. Análisis calculado para $C_{18}H_{20}FN_3O_4$ + 0.07H_2O: C, 59.26; H,

5.55; N, 11.48. Encontrado: C, 58.88; H, 5.36; N, 11.34.

Ejemplos 21-41

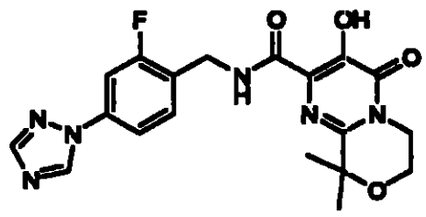
Los Ejemplos 21-41 pueden prepararse a partir del intermediario 25, 3-hidroxi-9,9-dimetil-4-oxo-4,6,7,9-tetrahidropirimido[2,1-c][1,4]oxazin-2-carboxilato de etilo, y las aminas indicadas de conformidad con el método descrito por la síntesis de los ejemplos 1, 19 y 20.

Ejemplo 21



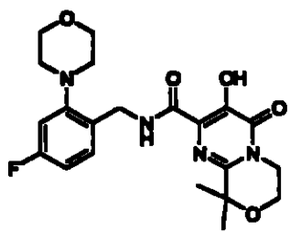
Pirimido[2,1-c][1,4]oxazin-2-carboxamida, N-[[4-fluoro-2-(1H-1,2,4-triazol-1-il)fenil]metil]-4,6,7,9-tetrahidro-3-hidroxi-9,9-dimetil-4-oxo-. El compuesto del título puede prepararse a partir del intermediario 69. Sólido, ^{1}H RMN (500 MHz, DMSO-d_6) δ ppm: 11.93 (1H, s), 9.29 (1H, t, J = 6.2 Hz), 9.05 (1H, s), 8.32 (1H, s), 7.57-7.53 (2H, m), 7.43 (1H, td, J= 7.9, 1.7 Hz), 4.44 (2H, d, J= 6.1 Hz), 3.98 (2H, t, J= 4.9 Hz), 3.83 (2H, t, J= 4.9 Hz), 1.56 (6H, s). EMAR (M+H) calculado para $C_{19}H_{20}N_6O_4F$: 415.15302; encontrado: 415.1520. Análisis calculado para $C_{19}H_{19}N_6O_4F$: C, 55.07; H, 4.62; N, 20.28; F, 4.58; encontrado: C, 54.95; H, 4.67; N, 20.27; F, 4.56.

Ejemplo 22



Pirimido[2,1-c][1,4]oxazin-2-carboxamida, N-[[2-fluoro-4-(1H-1,2,4-triazol-1-il)fenil]metil]-4,6,7,9-tetrahidro-3-hidroxi-9,9-dimetil-4-oxo-. El compuesto del título puede prepararse a partir del intermediario 70. Sólido, ^{1}H RMN (500 MHz, DMSO-d_6) δ ppm: 12.07 (1H, s), 9.46 (1H, bs), 9.33 (1H, s), 8.26 (1H, s), 7.81 (1H, dd, J= 11.1, 2.0 Hz), 7.73 (1H, dd, J= 8.2, 1.8 Hz), 7.52 (1H, t, J= 8.2 Hz), 4.59 (2H, d, J= 6.1 Hz), 3.98 (2H, t, J= 5.0 Hz), 3.84 (2H, t, J= 5.0 Hz), 1.58 (6H, s). EMAR (M+H) calculado para $C_{19}H_{20}N_6O_4F$: 415.15302; encontrado: 415.1520. Análisis calculado para $C_{19}H_{19}N_6O_4F$ + 1.25 H_2O: C, 52.23; H, 4.96; N, 19.23; F, 4.35; encontrado: C, 52.29; H, 4.66; N, 19.23; F, 4.35.

Ejemplo 23

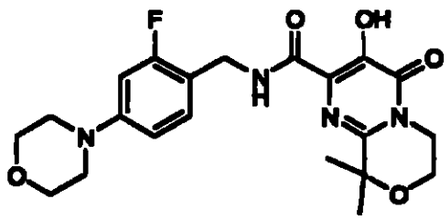


Pirimido[2,1-c][1,4]oxazin-2-carboxamida, N-[[4-fluoro-2-(4-morfolinil)fenil]metil]-4,6,7,9-tetrahidro-3-hidroxi-9,9-dimetil-4-oxo-. El compuesto del título puede prepararse

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a partir del intermediario 73. Sólido, ^{1}H RMN (500 MHz, $CDCl_3$) δ ppm: 12.09 (1H, s), 7.91 (1H, brs), 7.31-7.28 (1H, m), 6.90 (1H, dd, J= 10.4, 2.4 Hz), 6.84 (1H, td, J= 8.1, 2.4 Hz), 4.66 (2H, d, J= 6.4 Hz), 4.02 (4H, g), 3.89-3.87 (4H, m), 2.94-2.92 (4H, m), 1.59 (6H, s). EMAR (M-H) calculado para $C_{21}H_{24}N_4O_5F$: 431.17307; encontrado: 431.1719. Análisis calculado para $C_{21}H_{25}N_4O_5F$: C, 58.32; H, 5.82; N, 12.95; F, 4.39; encontrado: C, 58.13; H, 5.81; N, 12.79; F, 4.33.

Ejemplo 24

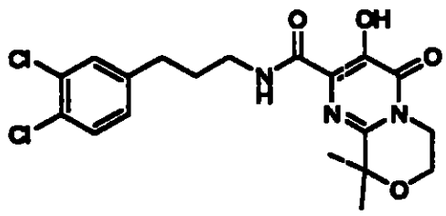


Pirimido[2,1-c][1,4]oxazin-2-carboxamida, N-[[2-fluoro-4-(4-morfolinil)fenil]metil]-4,6,7,9-tetrahidro-3-hidroxi-9,9-dimetil-4-oxo-. El compuesto del título puede prepararse a partir del intermediario 74. ^{1}H RMN (500 MHz, $CDCl_3$) δ ppm: 12.01 (1H, g), 7.80 (1H, brs), 7.28-7.24 (1H, m), 6.66 (1H, d, J= 8.5 Hz), 6.61 (1H, dd, J= 13.4, 1.8 Hz), 4.56 (2H, d, J= 6.1 Hz), 4.01 (4H, s), 3.85-3.84 (4H, m), 3.17-3.15 (4H, m), 1.60 (6H, s).

EMAR (M-H) calculado para $C_{21}H_{24}N_4O_5F$: 431.17307; encontrado: 431.1729. Análisis calculado para $C_{21}H_{25}N_4O_5F$: C, 58.32; H, 5.82; N, 12.95; F, 4.39; encontrado: C, 58.23; H, 5.73; N, 12.82; F, 4.21.

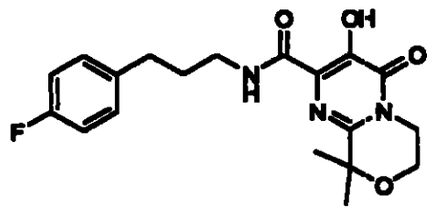
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Ejemplo 25



Pirimido[2,1-c][1,4]oxazin-2-carboxamida, N-[3-(3,4-diclorofenil)propil]-4,6,7,9-tetrahidro-3-hidroxi-9,9-dimetil-4-oxo-. El compuesto del título puede prepararse a partir de 3-(3,4-diclorofenil)propan-1-amina. ^{1}H RMN (500 MHz, $CDCl_3$) δ ppm: 12.05 (1H, g), 7.46 (1H, brs), 7.35 (1H, d, J= 8.2 Hz), 7.28 (1H, d, J= 2.1 Hz), 7.04 (1H, dd, J= 8.2, 2.1 Hz), 4.02 (4H, s), 3.46 (2H, q, J= 6.9 Hz), 2.67 (2H, t, J= 7.6 Hz), 1.95 (2H, m), 1.59 (6H, s). EMAR (M+H) calculado para $C_{19}H_{22}N_3O_4Cl_2$: 426.09875; encontrado: 426.0996. Análisis calculado para $C_{19}H_{21}N_3O_4Cl_2$: C, 53.53; H, 4.96; N, 9.85; Cl, 16.63; encontrado: C, 53.57; H, 4.96; N, 9.76; Cl, 16.63.

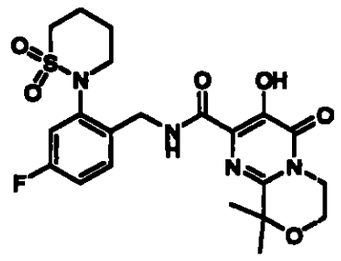
Ejemplo 26



Pirimido[2,1-c][1,4]oxazin-2-carboxamida, N-[3-(4-fluorofenil)propil]-4,6,7,9-tetrahidro-3-hidroxi-9,9-dimetil-4-oxo-. El compuesto del título puede prepararse a partir de 3-(4-fluorofenil)propan-1-amina. ^{1}H RMN (500 MHz, $CDCl_3$) δ

ppm: 12.09 (1H, s), 7.15 (2H, dd, J= 8.2, 5.5 Hz), 6.97 (2H, t, J= 8.5 Hz), 4.02 (4H, s), 3.44 (2H, q, J= 13.9, 6.9 Hz), 2.68 (2H, t, J= 7.6 Hz), 1.98-1.92 (2H, m), 1.62 (6H, s). EMAR (M+H) calculado para $C_{19}H_{23}N_3O_4F$: 376.16727; encontrado: 376.1687. Análisis calculado para $C_{19}H_{22}N_3O_4F$: C, 60.79; H, 5.90; N, 11.19; F, 5.06; encontrado: C, 60.70; H, 5.87; N, 11.14; F, 4.92.

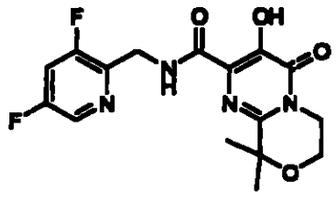
Ejemplo 27



Pirimido[2,1-c][1,4]oxazin-2-carbcxamida, N-[[4-fluoro-2-(tetrahidro-1,1-dioxido-2H-1,2-tiazin-2-il)fenil]metil]-4,6,7,9-tetrahidro-3-hidroxi-9,9-dimetil-4-oxo-. El compuesto del título puede prepararse a partir del intermediario 76. ^{1}H RMN (500 MHz, $CDCl_3$) δ ppm: 12.07 (1H, s), 8.31 (1H, d, J= 6.44 Hz), 7.46 (1H, dd, J= 8.5, 6.4 Hz), 7.19 (1H, dd, J= 9.0, 2.6 Hz), 7.08 (1H, td, J= 8.2, 2.7 Hz), 4.92 (1H, dd, J= 14.0, 8.8 Hz), 4.37 (1H, dd, J= 14.0, 3.4 Hz), 4.02-3.97 (2H, m), 3.99 (2H, s), 3.87-3.82 (1H, m), 3.45-3.41 (1H, m), 3.30-3.20 (2H, m), 2.46-2.32 (2H, m), 2.00-1.88 (2H, m), 1.57 (3H, s), 1.53 (3H, s). EMAR (M-H) calculado para $C_{21}H_{26}N_4O_6FS$: 481.15572; encontrado: 481.1570. Análisis calculado para

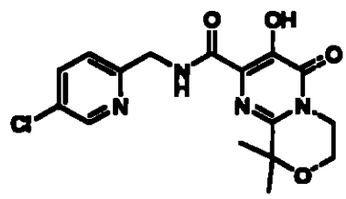
$C_{21}H_{25}N_4O_6FS$: C, 52.49; H, 5.24; N, 11.66; F, 3.95; S, 6.67; encontrado: C, 52.29; H, 5.37; N, 11.40; F, 3.91; S, 6.70.

Ejemplo 28



Pirimido[2,1-c][1,4]oxazin-2-carboxamida, N-[(3,5-difluoro-2-piridinil)metil]-4,6,7,9-tetrahidro-3-hidroxi-9,9-dimetil-4-oxo-. El compuesto del título puede prepararse a partir del intermediario 102. ^{1}H RMN (500 MHz, $CDCl_3$) δ ppm: 11.86 (1H, s), 8.58 (1H, brs), 8.33 (1H, d, J = 2.4 Hz), 7.27-7.24 (1H, m), 4.76 (2H, d, J = 5.2 Hz), 4.03 (4H, s), 1.63 (6H, s). EMAR (M+H) calculado para $C_{16}H_{17}F_2N_4O_4$: 367.1218; encontrado: 367.1230.

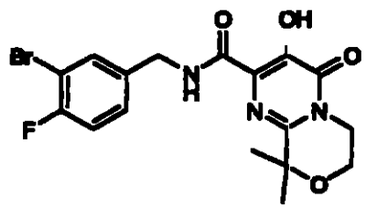
Ejemplo 29



N-((5-Cloropiridin-2-il)metil)-3-hidroxi-9,9-dimetil-4-oxo-4,6,7,9-tetrahidropirimido[2,1-c][1,4]oxazin-2-carboxamida. El compuesto del título puede prepararse a partir del intermediario 103. ^{1}H RMN (500 MHz, $CDCl_3$) δ ppm: 11.80 (1H, brs), 8.64 (1H, brs), 8.57 (1H, d, J = 2.4 Hz),

7.78 (1H, dd, J = 8.6, 2.4 Hz), 7.44 (1H, d, J = 8.6 Hz), 4.72 (2H, d, J = 6.1 Hz), 4.02 (4H, s), 1.61 (6H, s). EMAR (M+H) calculado para $C_{17}H_{18}ClN_4O_4$: 365.1017; encontrado: 365.1028. Análisis calculado para $C_{16}H_{17}ClN_4O_4 \bullet 0.25H_2O \bullet 0.5$ CF_3CO_2H: C, 47.90; H, 4.26; N, 13.14, Cl, 8.32; encontrado: C, 47.88; H, 3.98; N, 12.94, Cl, 8.57.

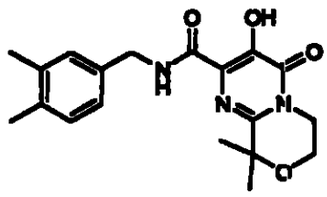
Ejemplo 30



Pirimido[2,1-c][1,4]oxazin-2-carboxamida, N-[(3-bromo-4-fluorofenil)metil]-4,6,7,9-tetrahidro-3-hidroxi-9,9-dimetil-4-oxo-. El compuesto del título puede prepararse a partir de (3-bromo-4-fluorofenil)metanamina. Sólido blanco opaco, ^{1}H-RMN (500 MHz, $CDCl_3$) δ ppm: 11.88 (1H, s), 7.76-7.84 (1H, br), 7.53 (1H, dd, J=6.3, 2.0 Hz), 7.26-7.29 (H, m), 7.07-7.14 (1H, m), 4.57 (2H, d, J=6.4 Hz), 4.02 (4H, s), 1.58 (6H, s). ^{13}C-RMN (126 MHz, $CDCl_3$) δ ppm: 168.41, 157.79, 151.99, 146.52, 134.91, 132.89, 128.44, 128.39, 125.30, 117.04, 116.86, 77.69, 75.84, 58.21, 43.22, 41.98, 28.11. EMAR $[M+H]^+$ calculado para $C_{17}H_{18}N_3O_4FBr$: 426.04648; encontrado: 426.0468.

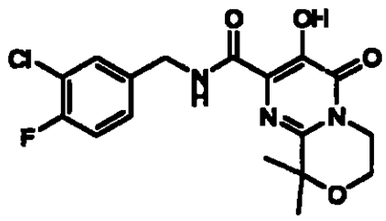
613

Ejemplo 31



Pirimido[2,1-c][1,4]oxazin-2-carboxamida, N-[(3,4-dimetilfenil)metil]-4,6,7,9-tetrahidro-3-hidroxi-9,9-dimetil-4-oxo-. El compuesto del título puede prepararse a partir de (3,4-dimetilfenil)metanamina. Sólido blanco opaco, ^{1}H-RMN (500 MHz, $CDCl_3$) δ ppm: 7.74 (1H), 7.04-7.15 (3H, m), 4.56 (2H, d, J=5.8 Hz), 4.00-4.07 (4H, m), 2.27 (3H, s), 2.26 (3H, s), 1.57 (6H, s). ^{13}C-RMN (126 MHz, $CDCl_3$) δ ppm: 167.92, 158.58, 151.61, 146.22, 137.37, 136.47, 134.53, 130.23, 129.11, 126.12, 125.12, 75.93, 58.10, 43.42, 43.00, 28.04, 19.85, 19.53. EMAR $[M+H]^+$ calculado para $C_{19}H_{24}N_3O_4$: 358.17669; encontrado: 358.1783.

Ejemplo 32

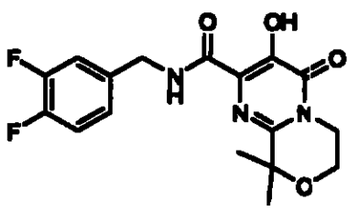


Pirimido[2,1-c][1,4]oxazin-2-carboxamida, N-[(3-cloro-4-fluorofenil)metil]-4,6,7,9-tetrahidro-3-hidroxi-9,9-dimetil-4-oxo-. El compuesto del título puede prepararse a partir de (3-cloro-4-fluorofenil)metanamina. Sólido blanco opaco, ^{1}H-

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RMN (500 MHz, $CDCl_3$) δ ppm: 11.88 (1H, br s), 7.80 (1H, t, J=5.5 Hz), 7.38 (1H, dd, J=6.7, 2.1 Hz), 7.19-7.23 (1H, m), 7.13 (1H, t, J=8.5 Hz), 4.57 (2H, d, J=6.4 Hz), 4.02 (4H, s), 1.58 (6H, s). ^{13}C-RMN (126 MHz, $CDCl_3$) δ ppm: 168.41, 157.82, 151.99, 146.52, 134.54, 130.02, 127.58, 127.52, 125.32, 121.61, 117.18, 117.01, 75.84, 58.21, 43.23, 42.08, 28.11. EMAR $[M+H]^+$ calculado para $C_{17}H_{18}N_3O_4FCl$: 382.09644; encontrado: 382.0980.

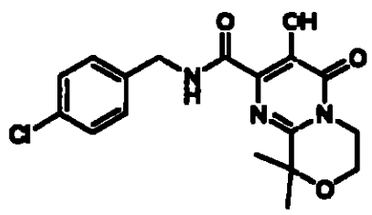
Ejemplo 33



Pirimido[2,1-c][1,4]oxazin-2-carboxamida, N-[(3,4-difluorofenil)metil]-4,6,7,9-tetrahidro-3-hidroxi-9,9-dimetil-4-oxo-. El compuesto del título puede prepararse a partir de (3,4-difluorofenil)metanamina. Sólido café ligero, ^{1}H-RMN (500 MHz, $CDCl_3$) δ ppm: 7.77 (1 H), 7.30-7.36 (2H, m), 7.27 (1H, s), 4.59 (2H, d, J=6.4 Hz), 4.01-4.06 (4H, m), 1.58 (6H, s).

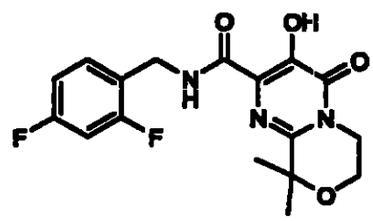
^{13}C-RMN (126 MHz, $CDCl_3$) δ ppm: 168.22, 158.36, 151.98, 151.17, 146.35, 134.33, 125.74, 123.70, 123.67, 117.87, 117.73, 116.88, 116.73, 75.90, 58.13, 43.42, 42.28, 28.06. EMAR $[M+H]^+$ calculado para $C_{17}H_{18}N_3O_4F_2$: 366.12655; encontrado: 366.1269.

Ejemplo 34



Pirimido[2,1-c][1,4]oxazin-2-carboxamida, N-[(4-clorofenil)metil]-4,6,7,9-tetrahidro-3-hidroxi-9,9-dimetil-4-oxo-. El compuesto del título puede prepararse a partir de (4-clorofenil)metanamina. Sólido color rosa pálido. ^{1}H-RMN (500 MHz, $CDCl_3$) δ ppm: 7.77 (1H, br), 7.33-7.35 (2H, m), 7.25-7.28 (2H, m), 4.59 (2H, d, J=6.4 Hz), 4.04 (4H, ddd, J=14.0, 7.9, 2.7 Hz), 1.58 (6H, s). ^{13}C-RMN (126 MHz, $CDCl_3$) δ ppm: 168.12, 158.48, 151.87, 146.28, 135.72, 133.98, 129.92, 129.18, 129.09, 125.90, 75.92, 58.12, 43.45, 42.61, 28.06. EMAR $[M+H]^+$ calculado para $C_{17}H_{19}N_3O_4Cl$: 364.10642; encontrado: 364.1060.

Ejemplo 35

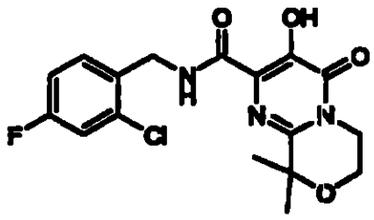


Pirimido[2,1-c][1,4]oxazin-2-carboxamida, N-[(2,4-difluorofenil)metil]-4,6,7,9-tetrahidro-3-hidroxi-9,9-dimetil-4-oxo-. El compuesto del título puede prepararse a partir de (2,4-difluorofenil)metanamina. Sólido blanco opaco,

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^{1}H-RMN (500 MHz, $CDCl_3$) δ ppm: 7.86 (1H, t, J=5.6 Hz), 7.34-7.40 (1H, m), 6.83-6.90 (2H, m), 4.62 (2H, d, J=6.4 Hz), 4.01-4.06 (4H, m), 1.59 (6H, s). ^{13}C-RMN (126 MHz, $CDCl_3$) δ ppm: 168.09, 158.43, 151.81, 146.22, 131.30, 131.25, 131.22, 131.18, 125.87, 120.37, 120.34, 111.85, 111.82, 111.68, 111.65, 104.47, 104.27, 104.07, 75.94, 58.12, 43.43, 37.00, 28.07. EMAR $[M+H]^+$ calculado para $C_{17}H_{18}N_3O_4F_2$: 366.12655; encontrado: 366.1281.

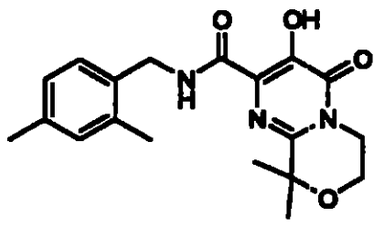
Ejemplo 36



Pirimido[2,1-c][1,4]oxazin-2-carboxamida, N-[(2-cloro-4-fluorofenil)metil]-4,6,7,9-tetrahidro-3-hidroxi-9,9-dimetil-4-oxo-. El compuesto del título puede prepararse a partir de (2-cloro-4-fluorofenil)metanamina. Sólido blanco opaco, ^{1}H-RMN (500 MHz, $CDCl_3$) δ ppm: 8.05 (1H, br), 7.41 (1H, dd, J=8.4, 6.0 Hz), 7.17 (1H, dd, J=8.2, 2.4Hz), 6.99 (1H, td, J=8.2, 2.7 Hz), 4.66 (2H, d, J=6.4 Hz), 4.04 (4H, s), 1.60 (6H, s). ^{13}C-RMN (126 MHz, $CDCl_3$) δ ppm: 167.88, 163.30, 161.31, 158.70, 151.77, 146.08, 134.55, 134.47, 131.65, 131.58, 130.70, 130.67, 126.12, 117.48, 117.28, 114.68, 114.51, 109.67, 75.99, 58.10, 43.51, 40.82, 28.08. EMAR $[M+H]^+$ calculado para $C_{17}H_{18}N_3O_4FCl$: 382.09644; encontrado:

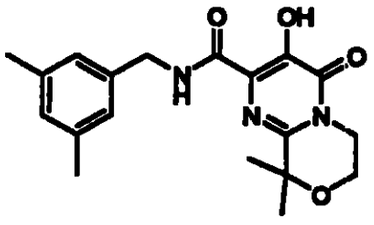
382.0987.

Ejemplo 37



Pirimido[2,1-c][1,4]oxazin-2-carboxamida,N-[(2,4-dimetilfenil)metil]-4,6,7,9-tetrahidro-3-hidroxi-9,9-dimetil-4-oxo-. El compuesto del título puede prepararse a partir de (2,4-dimetilfenil)metanamina. Sólido blanco opaco, ^{1}H-RMN (500 MHz, $CDCl_3$) δ ppm: 12.08 (1H, brs), 7.63 (1H, br), 7.15 (1H, d, J=7.6 Hz), 7.00-7.05 (2H, m), 4.57 (2H, d, J=5.8 Hz), 4.01 (4H, s), 2.32 (3H, s), 2.32 (3H, s), 1.55 (6H, s). ^{13}C-RMN (126 MHz, $CDCl_3$) δ ppm: 167.97, 157.98, 151.74, 146.35, 137.95, 136.22, 131.90, 131.67, 123.38, 127.10, 125.64, 75.84, 58.21, 43.21, 41.15, 28.07, 21.11, 19.13. EMAR $[M+H]^+$ calculado para $C_{19}H_{24}N_3O_4$: 358.17669; encontrado: 358.1771.

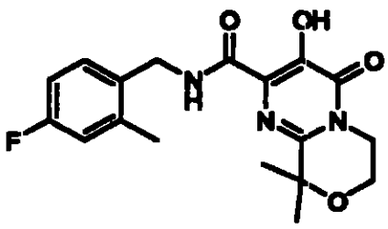
Ejemplo 38



Pirimido[2,1-c][1,4]oxazin-2-carboxamida, N-[(3,5-dimetilfenil)metil]-4,6,7,9-tetrahidro-3-hidroxi-9,9-dimetil-4-oxo-. El compuesto del título puede prepararse a partir de

(3,5-dimetilfenil)metanamina. Sólido blanco opaco, ^{1}H-RMN (500 MHz, $CDCl_3$) δ ppm: 12.09 (1H, s), 7.72-7.80 (1H, br), 6.95 (1H, s), 6.94 (2H, s), 4.55 (2H, d, J=6.4 Hz), 4.00-4.04 (4H, s), 2.32 (6H, s), 1.57 (6H, s). ^{13}C-RMN (126 MHz, $CDCl_3$) δ ppm: 168.19, 157.89, 151.73, 146.44, 138.71, 137.25, 129.58, 125.61, 125.48, 75.86, 58.23, 43.18, 43.06, 28.08, 21.38. EMAR $[M+H]^+$ calculado para $C_{19}H_{24}N_3O_4$: 358.17669; encontrado: 358.1758.

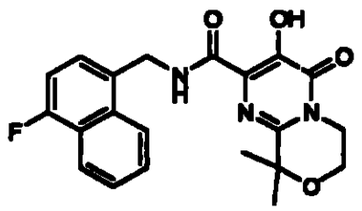
Ejemplo 39



Pirimido[2,1-c][1,4]oxazin-2-carboxamida, N-[(4-fluoro-2-metilfenil)metil]-4,6,7,9-tetrahidro-3-hidroxi-9,9-dimetil-4-oxo-. El compuesto del título puede prepararse a partir de (4-fluoro-2-metilfenil)metanamina. Sólido blanco opaco, ^{1}H-RMN (500 MHz, $CDCl_3$) δ ppm: 11.97 (1H, s), 7.64 (1H, br), 7.23 (1H, dd, J=8.2, 5.8 Hz), 6.87-6.94 (2H, m), 4.57 (2H, d, J=6.1 Hz), 4.02 (4H, s), 2.36 (3H, g), 1.56 (6H, s). ^{13}C-RMN (126 MHz, $CDCl_3$) δ ppm: 168.07, 163.40, 161.44, 157.82, 151.86, 146.43, 138.81, 138.75, 130.78, 130.75, 129.97, 129.90, 125.42,117.69, 117.52, 113.20, 113.03, 75.81, 58.23, 43.21, 40.71, 28.09, 19.32. EMAR $[M+H]^+$ calculado para $C_{18}H_{21}N_3O_4F$: 362.15162; encontrado: 362.1521.

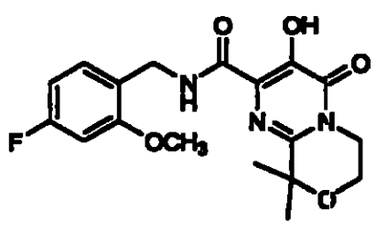
619

Ejemplo 40



Pirimido[2,1-c][1,4]oxazin-2-carboxamida, N-[(4-fluoro-1-naftalenil)metil]-4,6,7,9-tetrahidro-3-hidroxi-9,9-dimetil-4-oxo-. El compuesto del título puede prepararse a partir del intermediario 37. Sólido blanco. ^{1}H-RMN (500 MHz, $CDCl_3$) δ ppm: 12.00 (1H, s), 8.15-8.20 (1H, m), 8.05 (1H, d, J=8.2 Hz), 7.73 (1H, br), 7.58-7.65 (2H, m), 7.43 (1H, dd, J=7.8, 5.3 Hz), 7.12 (1H, dd, J=10.1, 7.9 Hz), 5.02 (2H, d, J=6.1 Hz), 3.99 (4H, ddd, J=13.8, 8.0, 2.9 Hz), 1.49 (6H, s). ^{13}C-RMN (126 MHz, $CDCl_3$) δ ppm: 168.01, 160.13, 158.12, 157.77, 151.87, 146.51, 132.72, 132.68, 128.59, 128.56, 127.86, 126.54, 126.46, 125.42,124.45, 123.23, 121.65, 121.60, 109.00, 108.84, 75.76, 58.21, 43.14, 40.86, 27.99. EMAR $[M+H]^+$ calculado para $C_{21}H_{21}N_3O_4F$: 398.15162; encontrado: 398.1536.

Ejemplo 41



Pirimido[2,1-c][1,4]oxazin-2-carboxamida, N-[(4-fluoro-

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2-metoxifenil)metil]-4,6,7,9-tetrahidro-3-hidroxi-9,9-dimetil-4-oxo-. El compuesto del título puede prepararse a partir de (4-fluoro-2-metoxifenil)metanamina. EMAR $[M+H]^+$ calculado para $C_{18}H_2FN_3O_5$: 378.1465; encontrado: 378.1480. Cristales color amarillo ligero; ^1H RMN ($CDCl_3$, 500 MHz) δ ppm: 1.58 (6H. s, gem-di-Me), 3.88 (3H, s, OMe), 4.00 (4H, s, CH_2), 4.53 (2H, d, J = 6.5 Hz, CH_2), 6.61-6.64 (2H, m, Ar-Hs), 7.24 (1H, m, Ar-Hs); ^{13}C RMN ($CDCl_3$, 125.8 Hz) δ ppm: 28.03 (CH_3), 38.79 (CH_2), 43.09 (CH_2), 55.72 (CH_3), 58.27 (CH_2), 75.78 (C), 99.15, 99.35 (d, J = 27 Hz, CH), 106.97, 107.14 (d, J = 21 Hz, CH), 121.17, 121.20 (d, J = 3.8 Hz, C), 125.75 (C), 130.44, 130.51 (d, J = 9.6 Hz, CH), 146.26 (C), 151.50 (C), 157.87 (C=O), 158.77, 158.83 (d, J = 9.6 Hz, C), 162.63, 164.48 (d, J = 234 Hz, CF), 167.81 (C=O); EMAR (ESI) calculado para C18H21FN3O5 (M+H) 378.1465, encontrado 378.1480; UV (MeOH) λmax 219 nm (ε 1.66x104), 245 (ε 9.69x103), 305 (ε 7.70x103); Análisis calculado para C18H20FN3O5•0.2H2O: C 55.95, H 5.48, N 10.88; encontrado C 55.99, H 5.11, N 10.63.

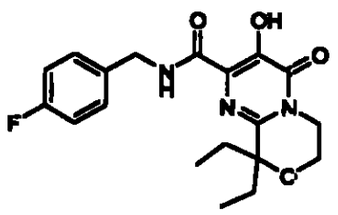
Ejemplos 42-43

Ejemplos 42-43 pueden prepararse a partir del intermediario 31, 9,9-dietil-3-hidroxi-4-oxo-4,6,7,9-tetrahidropirimido[2,1-c][1,4]oxazin-2-carboxilato de etilo y las aminas indicadas de conformidad con los

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métodos descritos por los ejemplos 1, 19 y 20.

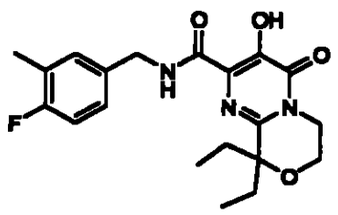
Ejemplo 42



Pirimido[2,1-c][1,4]oxazin-2-carboxamida,9,9-dietil-N-[(4-fluorofenil)metil]-4,6,7,9-tetrahidro-3-hidroxi-4-oxo-.

El compuesto del título puede prepararse a partir de 4-fluorobencilamina. ^{1}H RMN (500 MHz, $CDCl_3$) δ ppm: 11.96 (1H, br), 7.76 (1H, br), 7.30 (2H, m), 7.06 (2H, m), 4.58 (2H, d, J= 6.4 Hz), 4.00, (4H, m), 1.93 (2H, m), 1.86 (2H, m), 0.86 (6H, t, J= 7.3 Hz). ^{13}C RMN (500 MHz, $CDCl_3$) δ ppm: 168.36, 163.46, 157.87, 151.61, 143.23, 133.14, 129.50, 125.58, 115.99, 115.82, 80.89, 58.46, 43.13, 42.50, 31.36, 7.79. EMAR $[M+H]^+$ calculado para $C_{19}H_{23}N_3O_4F$: 376.16727; encontrado: 376.1675.

Ejemplo 43



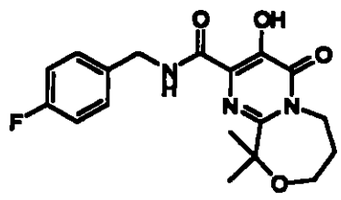
Pirimido[2,1-c][1,4]oxazin-2-carboxamida, 9,9-dietil-N-[(4-fluoro-3-metilfenil)metil]-4,6,7,9-tetrahidro-3-

hidroxi-4-oxo-). El compuesto del título puede prepararse a partir de 3-metil, 4-fluorobencilamina. ^{1}H RMN (500 MHz, $CDCl_3$) δ ppm: 11.99 (1H, br), 7.74 (1H, br), 7.15-7.09 (2H, m), 6.99 (1H, m), 4.54 (2H, d, J= 6.1 Hz), 4.00, (4H, m), 2.27 (1H, s), 1.93 (2H, m), 1.86 (2H, m), 0.84 (6H, t, J= 7.3 Hz). ^{13}C RMN (126 MHz, $CDCl_3$) δ ppm: 168.32, 161.97, 160.02, 157.84, 151.56, 146.23, 132.83, 130.96, 126.64, 125.59, 115.38, 80.88, 58.48, 43.11, 42.52, 31.36, 14.66, 7.79. EMAR $[M+H]^+$ calculado para $C_{20}H_{25}N_3O_4F$: 390.18292; encontrado: 390.1835.

Ejemplos 44-45

Los Ejemplos 44-45 pueden prepararse a partir del intermediario 36, 3-hidroxi-10,10-dimetil-4-oxo-6,7,8,10-tetrahidro-4H-pirimido[2,1-c][1,4]oxazepin-2-carboxilato y las aminas indicadas de conformidad con los métodos descritos para los ejemplos 1, 19 y 20.

Ejemplo 44

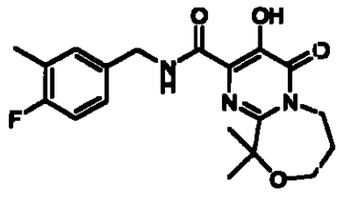


6H-Pirimido[2,1-c][1,4]oxazepin-2-carboxamida, N-[(4-fluorofenil)metil]-4,7,8,10-tetrahidro-3-hidroxi-10,10-dimetil-4-oxo-. El compuesto del título puede prepararse a partir de 4-fluorobencilamina ^{1}H RMN (500

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MHz, $CDCl_3$) δ ppm: 11.97 (1H, s), 7.72 (1H, br), 7.31 (1H, d, J= 8.5 Hz), 7.30 (1H, d, J= 8.5 Hz), 7.05 (1H, t, J= 8.5 Hz), 4.58 (2H, d, J= 6.4 Hz), 4.57 (2H, br), 3.67 (2H, t, J= 6.4 Hz), 1.95 (2H, p, J= 6.1 Hz), 1.57 (6H, s). ^{13}C RMN (126 MHz, $CDCl_3$) δ ppm: 168.32, 163.45, 161.49, 158.20, 153.63, 147.44, 133.17, 129.50, 129.43, 124.70, 115.97, 115.81, 82.29, 60.87, 42.47, 38.68, 27.82, 27.30. EMAR $[M+H]^+$ calculado para $C_{18}H_{21}N_3O_4F$: 362.15162; encontrado: 362.1530.

Ejemplo 45



6H-Pirimido[2,1-c][1,4]oxazepin-2-carboxamida, N-[(4-fluoro-3-metilfenil)metil]-4,7,8,10-tetrahidro-3-hidroxi-10,10-dimetil-4-oxo-. El compuesto del título puede prepararse a partir de 3-metil, 4-fluorobencilamina. ^1H RMN (500 MHz, $CDCl_3$) δ ppm: 12.00 (1H, s), 7.70 (1H, br), 7.14 (1H, m), 7.1 (1H, m), 6.98 (1H, t, J= 8.9 Hz), 4.56 (2H, br), 4.54 (2H, d, J= 6.4 Hz), 3.68 (2H, t, J= 6.4 Hz), 2.27 (3H, s), 1.95 (2H, p, J= 6.1 Hz), 1.57 (6H, s). ^{13}C RMN (126 MHz, $CDCl_3$) δ ppm: 168.26, 164.98, 160.02, 158.22, 153.59, 147.44, 132.82, 130.97, 126.58, 125.46, 124.75, 115.38, 82.30, 60.87, 42.51, 38.68, 27.83, 27.31, 14.66. EMAR $[M+H]^+$ calculado para

624

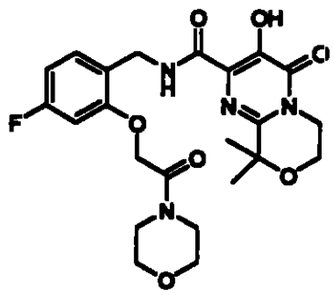
624

$C_{19}H_{23}N_3O_4F$: 376.16727; encontrado: 376.1686.

Ejemplos 46-51

Los Ejemplos 46-52 pueden prepararse a partir de los intermediarios indicados de conformidad con el método proporcionado para el ejemplo 46.

Ejemplo 46

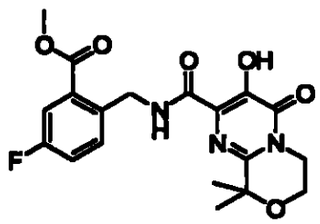


Pirimido[2,1-c][1,4]oxazin-2-carboxamida, N-[[4-fluoro-2-[2-(4-morfolinil)-2-oxoetoxi]fenil]metil]-4,6,7,9-tetrahidro-3-hidroxi-9,9-dimetil-4-oxo-. Una solución del intermediario 157, 4-fluoro-2-(2-morfolin-4-il-2-oxo-etoxi)-bencilamida del ácido 3-benciloxi-9,9-dimetil-4-oxo-4,6,7,9-tetrahidro-pirimido[2,1-c][1,4]oxazin-2-carboxílico, (187 mg, 0.32 mmol) en ácido trifluoroacético (2 mL) se agitó a temperatura ambiente durante 2.5 horas, después de lo cual la mezcla se concentró in vacuo hasta secarse. El aceite residual se cristalizó a partir de etanol al 95% para proporcionar 120 mg (0.25 mmol, Rendimiento 77%) del compuesto del título como un polvo cristalino blanco: ^{1}H RMN ($CDCl_3$, 500 MHz) δ ppm: 1.57 (6H, s, Me), 3.51, 3.64 (4H, brs, NCH_2), 3.70 (4H, m, OCH_2), 3.99 (4H, s, NCH_2, OCH_2), 4.60

624
625

(2H, d, J = 6 Hz, NCH_2), 4.76 (2H, s, OCH_2), 6.59 (1H, dd, J = 10, 2.5 Hz, Ar-H), 6.63 (1H, dt, J = 2.5, 8 Hz, Ar-H), 7.29 (1H, dd, J = 6.5, 8.5 Hz, Ar-H), 8.25 (1H, t, J = 6 Hz, NH), 12.2 (br, OH). ^{13}C RMN ($CDCl_3$, 125.77 Hz) δ ppm: 27.93 (CH_3), 38.44 (NCH_2), 42.39 (NCH_2), 43.14 (NCH_2), 45.31 (NCH_2), 58.19 (OCH_2), 66.40 (OCH_2), 66.59, 66.86 (OCH_2), 75.94 (C), 100.26, 100.46 (d, J = 26 Hz, CH), 108.19, 108.36 (d, J = 21 Hz, CH), 122.03, 122.06 (d, J = 3 Hz, C), 125.84 (C), 131.06, 131.14 (d, J = 11 Hz, CH), 146.37 (C), 151.46 (C), 157.06, 157.14 (d, J = 11 Hz, C), 157.96 (C=O), 162.25, 164.21 (d, J = 248 Hz, CF), 165.47 (C=O), 168.23 (C=O); EMAR calculado para $C_{23}H_{28}N_4O_7F$ (M+H) 491.1942, encontrado 491.1958; UV (MeOH) λmax 249 nm (ε $7.84x10^3$) 290 nm (ε $3.06x10^3$) 303 nm (ε $2.2x10^3$) Análisis calculado para $C_{23}H_{27}N_4O_7F \cdot 1.7H_2O$: C 53.01, H 5.88, N 10.75; encontrado C 52.53, H 5.37, N 10.48.

Ejemplo 47

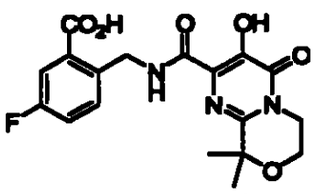


Éster de 5-fluoro-2-[[[(4,6,7,9-tetrahidro-3-hidroxi-9,9-dimetil-4-oxopirimido[2,1-c][1,4]oxazin-2-il)carbonil]amino]metil]-metilo del ácido benzoico. El compuesto del título puede prepararse a partir del intermediario 154, 2-((3-(benciloxi)-9,9-dimetil-4-oxo-

~~670~~ 626

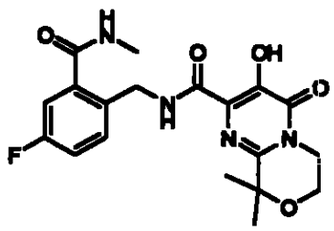
4,6,7,9-tetrahidropirimido[2,1-c][1,4]oxazin-2-carboxamido)metil)-5-fluorobenzoato de metilo. Sólido blanco; 1H RMN (300 MHz, CDCl3) δ ppm: 11.94 (1H, br s), 8.76 (1H, t, J=6.77 Hz), 7.69 (1H, dd, J=9.2, 2.9 Hz), 7.53 (1H, dd, J=8.4, 5.5 Hz), 7.15-7.22 (1H, m), 4.71 (2H, d, J=7.0 Hz), 3.97 (4H, s), 3.89-3.94 (3H, m), 1.56 (6H, s); EMAR (ESI) calculado para C19H20FN4O6 (M+H) 406.1414, encontrado 406.1432.

Ejemplo 48



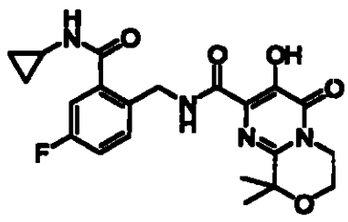
5-fluoro-2-[[[(4,6,7,9-tetrahidro-3-hidroxi-9,9-dimetil-4-oxopirimido[2,1-c][1,4]oxazin-2-il)carbonil]amino]metil]- del ácido benzoico. El compuesto del título puede prepararse a partir del intermediario 190, ácido 2-((3-(benciloxi)-9,9-dimetil-4-oxo-4,6,7,9-tetrahidropirimido[2,1-c][1,4]oxazin-2-carboxamido)metil)-5-fluorobenzoico. Sólido blanco; ^{1}H RMN (500 MHz, $CDCl_3$) δ ppm: 11.92 (1H, br s), 8.68 (1H, t, J=6.4 Hz), 7.80 (1H, dd, J=8.7, 2.6 Hz), 7.60 (1H, dd, J=8.5, 5.5 Hz), 7.30 (1H, dt, J=8.1, 2.8 Hz), 4.78 (2H, d, J=6.7 Hz), 4.00 (4H, s), 1.58 (6H, s); EMAR (ESI) calculado para $C_{18}H_{18}FN_3O_6$ (M+H) 392.1258, encontrado 392.1250.

Ejemplo 49



Pirimido[2,1-c][1,4]oxazin-2-carboxamida, N-[[4-fluoro-2-[(metilamino)carbonil]fenil]metil]-4,6,7,9-tetrahidro-3-hidroxi-9,9-dimetil-4-oxo-. El compuesto del título puede prepararse a partir del intermediario 143, N-(4-fluoro-2-(metilcarbamoil)bencil)-3-(benciloxi)-9,9-dimetil-4-oxo-4,6,7,9-tetrahidropirimido[2,1-c][1,4]oxazin-2-carboxamida. ^{1}H RMN (500 MHz, DMSO-d_6) δ ppm: 11.97 (1H, br s), 9.46 (1H, br s), 8.55-8.51 (1H, m), 7.40-7.38 (1H, m), 7.32- 7.27 (2H, m), 4.56 (2H, d, J = 6.1 Hz), 3.97 (2H, t, J = 4.9 Hz), 3.82 (2H, t, J = 4.9 Hz), 2.80 (3H, d, J = 4.6 Hz), 1.55 (6H, s). EMAR (M+H) calculado para $C_{19}H_{22}FN_4O_5$: 405.1574; encontrado: 405.1588.

Ejemplo 50



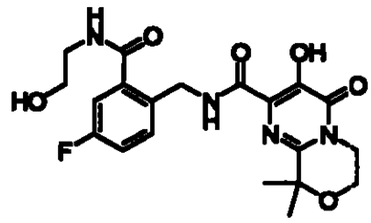
Pirimido[2,1-c][1,4]oxazin-2-carboxamida, N-[[2-[(ciclopropilamino)carbonil]-4-fluorofenil]metil]-4,6,7,9-tetrahidro-3-hidroxi-9,9-dimetil-4-oxo-. El compuesto del

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título puede prepararse a partir del intermediario 155, N-(2-(ciclopropilcarbamoil)-4-fluorobencil)-3-(benciloxi)-9,9-dimetil-4-oxo-4,6,7,9-tetrahidropirimido[2,1-c][1,4]oxazin-2-carboxamida. Sólido blanco; ^{1}H RMN (300 MHz, $CDCl_3$) δ ppm: 11.98 (1H, br s), 8.84 (1H, t, J=7.32 Hz), 7.48 (1H, dd, J=9.0, 5.3 Hz), 7.05-7.16 (2H, m), 6.20-6.31 (1H, br s), 4.56 (2 H, d, J=6.6 Hz), 3.92-4.02 (4H, m), 2.90 (1H, dt, 1=7.1, 3.3 Hz), 1.59 (6H, s), 0.88 (2H, g, J=6.6 Hz), 0.57-0.66 (2H, m); EMAR (ESI+) calculado para $C_{21}H_{23}FN_4O_5$ (M+H) 431.1731, encontrado 431.1734.

Ejemplo 51

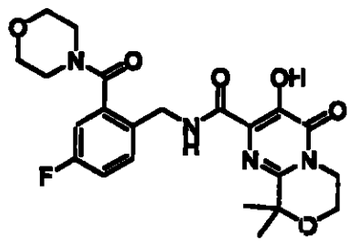


Pirimido[2,1-c][1,4]oxazin-2-carboxamida, N-[[4-fluoro-2-[[(2-hidroxietil]amino]carbonil]fenil]metil]-4,6,7,9-tetrahidro-3-hidroxi-9,9-dimetil-4-oxo-. El compuesto del título puede prepararse a partir del intermediario 191, N-(2-((2-aminoetil)carbamoil)-4-fluorobencil)-3-(benciloxi)-9,9-dimetil-4-oxo-4,6,7,9-tetrahidropirimido[2,1-c][1,4]oxazin-2-carboxamida. ^{1}H RMN (500 MHz, $CDCl_3$) δ ppm: 11.98 (1H, br s), 8.88 (1H, t, J=6.0 Hz), 7.51 (1H, dd, J=8.2, 5.5 Hz), 7.21 (1H, dd, J=8.5, 2.8 Hz), 7.14 (1H, dt, J=8.3, 2.6 Hz), 6.57-6.63 (1H, m), 4.58 (2H, d, J=6.7 Hz), 4.00 (4H, s), 3.87 (2H,

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t, J=5.1 Hz), 3.63-3.68 (2H, m), 1.60 (6H, s); EMAR (ESI) calculado para $C_{20}H_{23}FN_4O_6$ (M+H) 435.1680, encontrado 435.1700.

Ejemplo 52

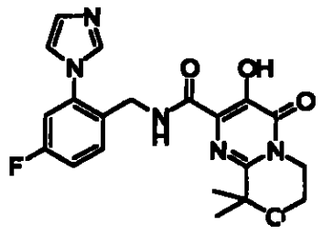


Pirimido[2,1-c][1,4]oxazin-2-carboxamida, N-[[4-fluoro-2-(4-morfolinilcarbonil)fenil]metil]-4,6,7,9-tetrahidro-3-hidroxi-9,9-dimetil-4-oxo-. El compuesto del título puede prepararse a partir del intermediario 156, N-(4-fluoro-2-(morfolin-4-carbonil)bencil)-3-(benciloxi)-9,9-dimetil-4-oxo-4,6,7,9-tetrahidropirimido[2,1-c][1,4]oxazin-2-carboxamida. Sólido blanco; ^{1}H RMN (500 MHz, $CDCl_3$) δ ppm: 11.94 (1H, s), 8.46 (1H, t, J=5.5 Hz), 7.47 (1H, dd, J=8.5, 5.5 Hz), 7.10 (1H, dt, J=8.4, 2.4 Hz), 6.94 (1H, dd, J=8.2, 2.4 Hz), 4.00 (4H, s), 3.79-3.88 (2H, br), 3.78 (2H, br), 3.61 (2H, br), 3.31-3.40 (2H, br), 1.61 (6H, s); EMAR (ESI) calculado para $C_{22}H_{25}FN_4O_6$ (M+H) 461.1836, encontrado 461.1852.

Ejemplo 53-60

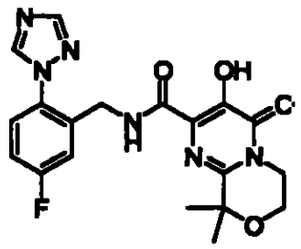
Los Ejemplos 53-60 pueden prepararse a partir del intermediario 25, 3-hidroxi-9,9-dimetil-4-oxo-4,6,7,9-tetrahidropirimido[2,1-c][1,4]oxazin-2-carboxilato de etilo y las aminas indicadas de conformidad con el método descrito por la síntesis de los ejemplos 1, 19 y 20.

Ejemplo 53



Pirimido[2,1-c][1,4]oxazin-2-carboxamida, N-[[4-fluoro-2-(1H-imidazol-1-il)fenil]metil]-4,6,7,9-tetrahidro-3-hidroxi-9,9-dimetil-4-oxo-. El compuesto del título puede prepararse a partir del intermediario 89. ^{1}H-RMN (500 MHz, $CDCl_3$) δ ppm: 11.66 (1H, bs), 8.07 (1H, s), 7.74 (1H, t, J = 5.5 Hz), 7.57 (1H, dd, J= 8.7, 5.9 Hz), 7.35 (1H, s), 7.25-7.21 (2H, m), 7.08 (1H, dd, J = 8.2, 2.4 Hz), 4.42 (2H, d, J = 6.4 Hz), 4.01 (4H, s), 1.59 (6H, s). EMAR $[M+H]^+$ calculado para $C_{20}H_{21}N_5O_4F$: 414.15777; encontrado: 414.1563. Análisis calculado para $C_{20}H_{20}N_5O_4F \cdot 0.25\ H_2O$: C, 57.48; H, 4.94; N, 16.76; F, 4.55; encontrado: C, 57.77; H, 4.89; N, 16.29; F, 4.48.

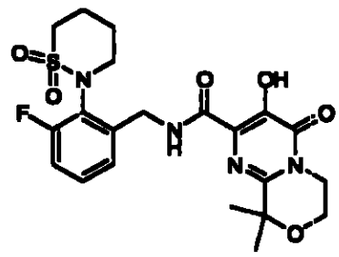
Ejemplo 54



Pirimido[2,1-c][1,4]oxazin-2-carboxamida, N-[[5-fluoro-2-(1H-1,2,4-triazol-1-il)fenil]metil]-4,6,7,9-tetrahidro-3-hidroxi-9,9-dimetil-4-oxo-e. El compuesto del título puede

prepararse a partir del intermediario 97. ^{1}H RMN (500 MHz, $CDCl_3$) δ ppm: 11.82 (1H, s), 8.70 (1H, t, J = 6.5 Hz), 8.39 (1H, s), 8.17 (1H, s), 7.40 (1H, dd, J = 8.6, 2.7 Hz), 7.34 (1H, dd, J = 8.9, 4.9 Hz), 7.17-7.13 (1H, m), 4.44 (2H, d, J = 6.7 Hz), 4.01 (4H, s), 1.62 (6H, s). EMAR (M+H) calculado para $C_{19}H_{20}FN_6O_4$: 415.1530; encontrado: 415.1544. Análisis calculado para $C_{19}H_{19}FN_6O_4$: C, 55.07; H, 4.62; N, 20.28, F, 4.58; encontrado: C, 54.83; H, 4.51; N, 19.89, F, 4.56.

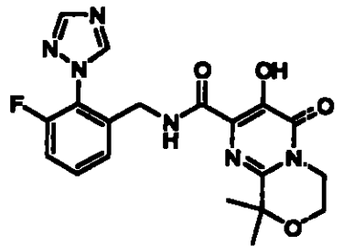
Ejemplo 55



Pirimido[2,1-c][1,4]oxazin-2-carboxamida, N-[[3-fluoro-2-(tetrahidro-1,1-dióxido-2H-1,2-tiazin-2-il)fenil]metil]-4,6,7,9-tetrahidro-3-hidroxi-9,9-dimetil-4-oxo-. El compuesto del título puede prepararse a partir del intermediario 93. Sólido blanco. 36% de rendimiento. ^{1}H-RMN (500 MHz, $CDCl_3$) δ ppm: 11.96 (1H, s), 8.42-8.39 (2H, m), 7.14-7.11 (1H, m), 4.97 (1H, dd J = 14.3, 8.8 Hz), 4.37 (1H, dd, J = 14.3, 4.0 Hz), 4.00 (4H, s), 3.86-3.80 (1H, m), 3.75-3.70 (1H, m), 3.34-3.24 (2H, m), 2.44-2.39 (2H, m), 2.08-2.00 (1H, m), 1.83-1.77 (1H, m), 1.60 (3H, s), 1.57 (3H, s). EMAR $[M+H]^+$ calculado para $C_{21}H_{25}N_4O_6FS$:

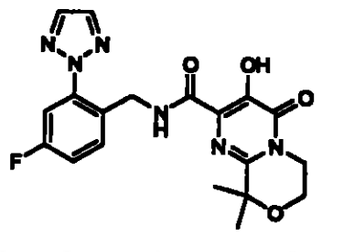
481.15572; encontrado: 481.1559. Análisis calculado para $C_{21}H_{25}N_4O_6FS$: C, 52.49; H, 5.24; N, 11.66; S, 6.67; F, 3.95; encontrado: C, 52.43; H, 5.21; N, 11.61; S, 6.56; F, 4.16.

Ejemplo 56



Pirimido[2,1-c][1,4]oxazin-2-carboxamida, N-[[3-fluoro-2-(1H-1,2,4-triazol-1-il)fenil]metil]-4,6,7,9-tetrahidro-3-hidroxi-9,9-dimetil-4-oxo-. El compuesto del título puede prepararse a partir del intermediario 95. Sólido blanco. ^{1}H-RMN (500 MHz, $CDCl_3$) δ ppm: 11.86 (1H, s), 8.76 (1H, brs), 8.46 (1H, d, J= 3.0 Hz), 8.22 (1H, s), 7.48-7.47 (2H, m), 7.29-7.26 (1H, m), 4.44 (2H, d, J= 6.7 Hz), 4.01 (4H, s), 1.63 (6H, s). EMAR $[M+H]^+$ calculado para $C_{19}H_{20}N_6O_4F$: 415.15302; encontrado: 415.1541. Análisis calculado para $C_{19}H_{19}N_6O_4F$: C, 55.07; H, 4.62; N, 20.28; F, 4.58; encontrado: C, 55.18; H, 4.42; N, 20.17; F, 4.51.

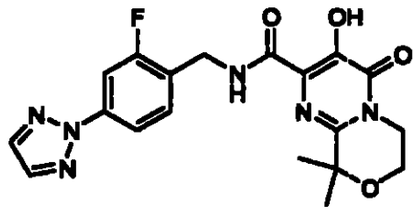
Ejemplo 57



Pirimido[2,1-c][1,4]oxazin-2-carboxamida, N-[[4-fluoro-

2-(2H-1,2,3-triazol-2-il)fenil]metil]-4,6,7,9-tetrahidro-3-hidroxi-9,9-dimetil-4-oxo-. El compuesto del título puede prepararse a partir del intermediario 77. Sólido naranja pálido. ^{1}H-RMN (300 MHz, $CDCl_3$) δ ppm: 11.99 (1H, s), 8.99 (1H, t, J= 6.4 Hz), 7.91 (2H, s), 7.65-7.58 (2H, m), 7.10 (1H, td, J= 8.1, 2.6 Hz), 4.61 (2H, d, J= 7.0 Hz), 3.97 (4H, s), 1.55 (6H, s). EMAR $[M-H]^-$ calculado para $C_{19}H_{18}N_6O_4F$: 413.13736; encontrado: 413.1354. Análisis calculado para $C_{19}H_{17}N_6O_4F$: C, 55.07; H, 4.62; N, 20.28; F, 4.58; encontrado: C, 54.94; H, 4.78; N, 20.32; F, 4.53.

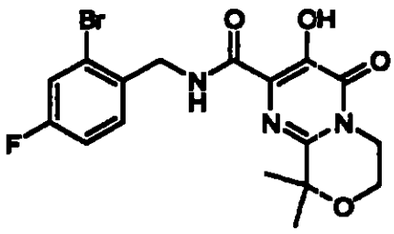
Ejemplo 58



Pirimido[2,1-c][1,4]oxazin-2-carboxamida, N-[[2-fluoro-4-(2H-1,2,3-triazol-2-il)fenil]metil]-4,6,7,9-tetrahidro-3-hidroxi-9,9-dimetil-4-oxo-. El compuesto del título puede prepararse a partir del intermediario 77. Sólido café pálido ^{1}H-RMN (300 MHz, $CDCl_3$) δ ppm: 11.85 (1H, s), 7.88-7.82 (3H, m), 7.79 (2H, s), 7.47 (1H, t, J= 8.3 Hz), 4.67 (2H, d, J= 6.2 Hz), 3.99 (4H, s), 1.56 (6H, s). EMAR $[M+H]^+$ calculado para $C_{19}H_{20}N_6O_4F$: 415.15302; encontrado: 415.1513. Análisis calculado para $C_{19}H_{19}N_6O_4F$: C, 55.07; H, 4.62; N, 20.28; F, 4.58; encontrado: C, 54.94; H, 4.76; N, 19.94; F, 4.26.

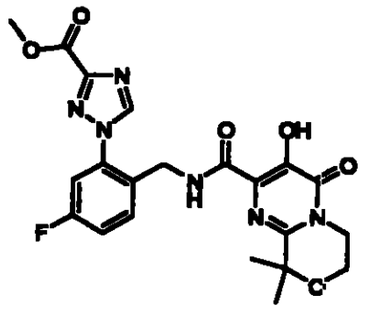
634

Ejemplo 59



Pirimido[2,1-c][1,4]oxazin-2-carboxamida, N-[(2-bromo-4-fluorofenil)metil]-4,6,7,9-tetrahidro-3-hidroxi-9,9-dimetil-4-oxo-. El compuesto del título puede prepararse a partir de (2-bromo-4-fluorofenil)metanamina. Agujas blancas. ^{1}H-RMN (300 MHz, $CDCl_3$) δ ppm: 11.78 (1H, s), 8.08 (1H, t, J= 6.0 Hz), 7.39 (1H, dd, J= 8.8, 5.8 Hz), 7.31 (1H, dd, J= 8.0, 2,6 Hz), 7.01 (1H, dt, J= 8.2, 2.6 Hz), 4.61 (2H, d, J= 6.6 Hz), 3.99 (4H, s), 1.56 (6H, s). EMAR $[M+H]^+$ calculado para $C_{17}H_{18}N_3O_4FBr$: 426.04648; encontrado: 426.0465.

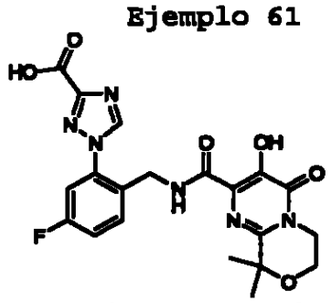
Ejemplo 60



Ácido 1H-1,2,4-Triazol-3-carboxílico, 1-[5-fluoro-2-[[[(4,6,7,9-tetrahidro-3-hidroxi-9,9-dimetil-4-oxopirimido[2,1-c][1,4)oxazin-2-il)carbonil]amino)metil)fenil]-, éster de metilo. El compuesto del título puede prepararse a partir del

intermediario 91. Sólido blanco. ^{1}H-RMN (300 MHz, $CDCl_3$) δ ppm: 11.90 (1H, s), 8.49 (1H, s), 8.36 (1H, t, J= 6.2 Hz), 7.72 (1H, dd, J= 8.8, 5.9 Hz), 7.26-7.20 (1H, m), 7.14 (1H, dd, J= 8.4, 2,6 Hz), 4.49 (2H, d, J= 6.6 Hz), 4.01 (3H, s), 3.98 (4H, s), 1.58 (6H, s). EMAR $[M+H]^+$ caculado para $C_{21}H_{22}N_6O_6F$: 473.1585; encontrado: 473.1563. Análisis calculado para $C_{21}H_{21}N_6O_6F \cdot 0.5\ H_2O$: C, 52.39; H, 4.61; N, 17.46; F, 3.95; encontrado: C, 52.14; H, 4.70; N, 17.41; F, 4.12.

Ejemplo 61



Ácido 1H-1,2,4-triazol-3-carboxílico, 1-[5-fluoro-2-[[[(4,6,7,9-tetrahidro-3-hidroxi-9,9-dimetil-4-oxopirimido[2,1-c][1,4]oxazin-2-il)carbonil]amino]metil]fenil]-. A una solución del ejemplo 60, ácido 1H-1,2,4-triazol-3-carboxílico, 1-[5-fluoro-2-[[[(4,6,7,9-tetrahidro-3-hidroxi-9,9-dimetil-4-oxopirimido[2,1-c][1,4]oxazin-2-il)carbonil]amino]metil]fenil]-, éster de metilo, (2.156 g, 4.6 mmol) en tetrahidrofurano (200 mL) y agua (50 mL) a 0°C se agregó monohidrato de hidróxido de litio (0.58 g, 13.8 mmol). La mezcla se agitó a 0°C 2 horas y a temperatura ambiente durante 1 hora. La solución resultante se dividió

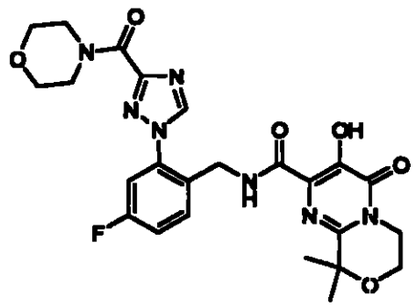
636

entre acetato de etilo y agua. La fase acuosa se acidificó con HCl 1 N y se extrajo con acetato de etilo y CH_2Cl_2. Los extractos orgánicos se combinaron, se secaron (Na_2SO_4) y se concentraron para dar el compuesto del título como un sólido blanco (2.05 g, 97% de rendimiento). ^{1}H-RMN (300 MHz, $CDCl_3$) δ ppm: 11.91 (1H, bs), 8.55 (1H, s), 8.43 (1H, t, J= 6.6 Hz), 7.77 (1H, dd, J= 8.8, 5.9 Hz), 7.28-7.23 (1H, m), 7.16 (1H, dd, J= 8.0, 2.6 Hz), 4.47 (2H, d, J= 6.9 Hz), 3.98 (4H, s), 1.59 (6H, s). EMAR $[M+H]^+$ calculado para $C_{20}H_{20}N_6O_6F$: 459.14285; encontrado: 459.1442.

Ejemplos 62-72

Los Ejemplos 62-72 pueden prepararse a partir del intermediario 61, ácido 1H-1,2,4-triazol-3-carboxílico, 1-[5-fluoro-2-[[[(4,6,7,9-tetrahidro-3-hidroxi-9,9-dimetil-4-oxopirimido[2,1-c][1,4]oxazin-2-il)carbonil]amino]metil]fenil]-, de conformidad con el método descrito por la síntesis del ejemplo 62.

Ejemplo 62

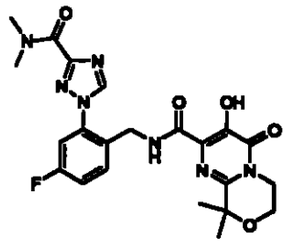


Pirimido[2,1-c][1,4]oxazin-2-carboxamida, N-[[4-fluoro-2-[3-(4-morfolinilcarbonil)-1H-1,2,4-triazol-1-

637

il]fenil]metil]-4,6,7,9-tetrahidro-3-hidroxi-9,9-dimetil-4-oxo-. A una solución del ejemplo 61, ácido 1H-1,2,4-triazol-3-carboxílico, 1-[5-fluoro-2-[[[(4,6,7,9-tetrahidro-3-hidroxi-9,9-dimetil-4-oxopirimido[2,1-c][1,4]oxazin-2-il)carbonil]amino]metil]fenil]-, (0.0259 g, 0.057 mmol) en DMF (2 mL), a 0°C, se agregó hexafluorofosfato de O-(7-azabenzotriazol-1-il)-N,N,N^1,N^1-tetrametiluronio (0.044 g, 0.115 mmol). La solución se agitó a 0°C durante 10 minutos antes de agregar morfolina (0.025 mL, 0.285 mmol) después de lo cual esto se agitó a temperatura ambiente durante 2 horas. La purificación por cromatografía CLAR preparativa de fase inversa (YMC Combiprep ODS-A, 30mm x 50mm, MeOH/H_2O/0.1% CF_3CO_2H) dio el compuesto del título como un sólido blanco (0.015 g, 50% de rendimiento). ^{1}H-RMN (500 MHz, $CDCl_3$) δ ppm: 8.50 (1H, t, J= 6.9 Hz), 8.45 (1H, s), 7.69 (1H, dd, J= 8.7, 5.9 Hz), 7.22 (1H, td, J= 8.2, 2,3 Hz), 7.13 (1H, dd, J= 8.2, 2.4 Hz), 4.49 (2H, s), 3.98 (4H, s), 3.88-3.72 (8H, m), 1.57 (6H, s). EMAR $[M+H]^+$ calculado para $C_{24}H_{27}N_7O_6F$: 528.20069; encontrado: 528.2025.

Ejemplo 63

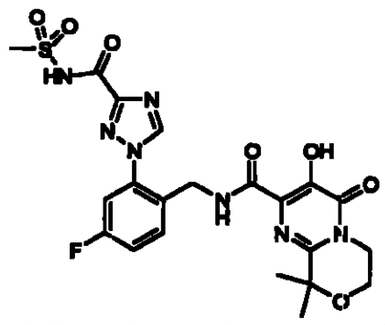


Pirimido[2,1-c][1,4]oxazin-2-carboxamida, N-[[2-[3-

638

[(dimetilamino)carbonil]-1H-1,2,4-triazol-1-il]-4-fluorofenil]metil]-4,6,7,9-tetrahidro-3-hidroxi-9,9-dimetil-4-oxo-. Sólido color púrpura pálido. ^{1}H-RMN (300 MHz, $CDCl_3$) δ ppm: 8.51-8.45 (2H, m), 7.70 (1H, dd, J= 8.4, 5.9 Hz), 7.24-7.18 (1H, m), 7.12 (1H, dd, J= 8.2, 2.4 Hz), 4.47 (2H, d, J= 6.9 Hz), 3.97 (4H, s), 3.24 (3H, s), 3.15 (3H, s), 1.54 (6H, s). EMAR $[M+H]^+$ calculado para $C_{22}H_{25}N_7O_5F$: 486.19013; encontrado: 486.1887.

Ejemplo 64

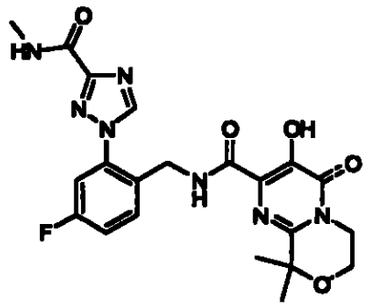


Pirimido[2,1-c][1,4]oxazin-2-carboxamida, N-[[4-fluoro-2-[3-[[(metilsulfonil)amino]carbonil]-1H-1,2,4-triazol-1-il]fenil]metil]-4,6,7,9-tetrahidro-3-hidroxi-9,9-dimetil-4-oxo-. Sólido blanco. ^{1}H-RMN (300 MHz, $CDCl_3$) δ ppm: 8.52 (1H, s), 8.36 (1H, t, J= 6.8 Hz), 7.70 (1H, dd, J= 8.6, 5.7 Hz), 7.26-7.19 (1H, m), 7.13 (1H, dd, J= 8.4, 2.6 Hz), 4.46 (2H, d, J= 7.0 Hz), 3.95 (4H, s), 3.39 (4H, s), 1.57 (6H, s). EMAR $[M+H]^+$ calculado para $C_{21}H_{23}N_7O_7FS$: 536.1364; encontrado: 536.1376. Análisis calculado para $C_{21}H_{22}N_7O_7FS \cdot 0.07CF_3CO_2H$: C, 46.72; H, 4.09; N, 18.04; F,

639

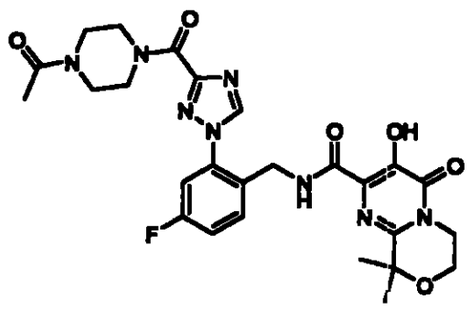
4.23; encontrado: C, 46.42; H, 3.91; N, 17.70; F, 4.17.

Ejemplo 65



Pirimido[2,1-c][1,4]oxazin-2-carboxamida, 4,6,7,9-tetrahidro-3-hidroxi-N-[(1R)-2-hidroxi-1-feniletil]-9,9-dimetil-4-oxo-. Sólido blanco. ^{1}H-RMN (300 MHz, $CDCl_3$) δ ppm: 8.43 (1H, s), 8.20 (1H, t, J= 6.0 Hz), 7.64 (1H, dd, J= 8.8, 5.9 Hz), 7.42-7.40 (1H, m), 7.26-7.19 (1H, m), 7.11 (1H, dd, J= 8.0, 2.6 Hz), 4.53 (2H, d, J= 6.6 Hz), 3.99 (4H, s), 3.06 (3H, d, J= 4.7 Hz), 1.56 (6H, s). EMAR $[M+H]^+$ calculado para $C_{21}H_{23}N_7O_5F$: 472.1745; encontrado: 472.1741. Análisis calculado para $C_{21}H_{22}N_7O_5F$: C, 53.50; H, 4.70; N, 20.79; F, 4.03; encontrado: C, 53.22; H, 4.51; N, 20.70; F, 4.01.

Ejemplo 66

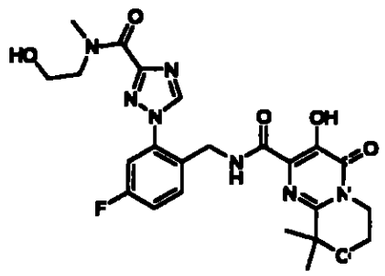


Pirimido[2,1-c][1,4]oxazin-2-carboxamida, N-[[2-[3-[(4-

644
640

acetil-1-piperazinil)carbonil]-1H-1,2,4-triazol-1-il]-4-fluorofenil]metil]-4,6,7,9-tetrahidro-3-hidroxi-9,9-dimetil-4-oxo-. Sólido blanco. ^{1}H-RMN (300 MHz, $CDCl_3$) δ ppm: 8.46 (1H, s), 8.36 (1H, t, J= 5.7 Hz), 7.68 (1H, dd, J= 8.6, 5.7 Hz), 7.27-7.21 (1H, m), 7.14 (1H, dd, J= 8.2, 2.7 Hz), 4.48 (2H, d, J= 6.6 Hz), 3.98 (4H, s), 3.94-3.61 (8H, m), 2.13 (3H, s), 1.55 (6H, s). EMAR $[M+H]^+$ calculado para $C_{26}H_{30}N_8O_6F$: 569.2272; encontrado: 569.2269. Análisis calculado para $C_{26}H_{29}N_8O_6F \cdot 0.8\ H_2O$: C, 53.57; H, 5.29; N, 19.22; F, 3.26; encontrado: C, 53.48; H, 4.95; N, 19.21; F, 3.21.

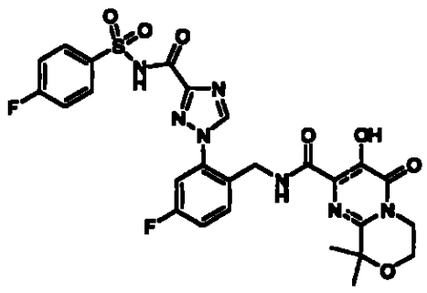
Ejemplo 67



Pirimido[2,1-c][1,4]oxazin-2-carboxamida, N-[[4-fluoro-2-[3-[[(2-hidroxietil)metilamino]carbonil]-1H-1,2,4-triazol-1-il]fenil]metil]-4,6,7,9-tetrahidro-3-hidroxi-9,9-dimetil-4-oxo-. Sólido blanco. ^{1}H-RMN (300 MHz, $CDCl_3$) δ ppm: 8.54 (1H, t, J= 7.3 Hz), 8.44 (1H, s), 7.66 (1H, dd, J= 8.8, 5.8 Hz), 7.21-7.09 (2H, m), 4.44 (2H, d, J= 4.4 Hz), 3.93 (4H, s), 3.86-3.78 (2H, m), 3.70-3.65 (2H, m), 3.13 (3H, s), 1.94 (1H, bs), 1.55 (6H, s). EMAR $[M+H]^+$ calculado para $C_{23}H_{27}N_7O_6F$: 516.2007; encontrado: 516.2011. Análisis calculado para

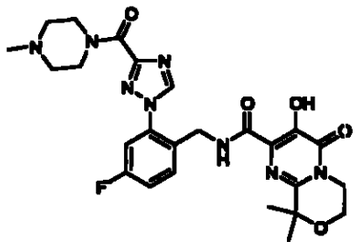
$C_{23}H_{26}N_7O_6F$: C, 53.59; H, 5.08; N, 19.02; F, 3.68; encontrado: C, 53.31; H, 5.06; N, 18.80; F, 3.60.

Ejemplo 68



Pirimido[2,1-c][1,4]oxazin-2-carboxamida, N-[[4-fluoro-2-[3-[[[(4-fluorofenil)sulfonil]amino]carbonil]-1H-1,2,4-triazol-1-il]fenil]metil]-4,6,7,9-tetrahidro-3-hidroxi-9,9-dimetil-4-oxo-. Sólido blanco. ^{1}H-RMN (300 MHz, $CDCl_3$) δ ppm: 8.47 (1H, s), 8.18-8.13 (2H, m), 7.68 (1H, dd, J= 8.8, 5.9 Hz), 7.24-7.16 (3H, m), 7.08 (1H, dd, J= 8.0, 2.6 Hz), 4.39 (2H, s), 3.96 (4H, s), 1.55 (6H, s). EMAR $[M+H]^+$ calculado para $C_{26}H_{24}N_7O_7F_2S$: 616.1426; encontrado: 616.1426. Análisis calculado para $C_{26}H_{23}N_7O_7F_2S$: C, 50.73; H, 3.76; N, 15.92; F, 6.17; encontrado: C, 50.49; H, 3.66; N, 15.98; F, 6.12.

Ejemplo 69

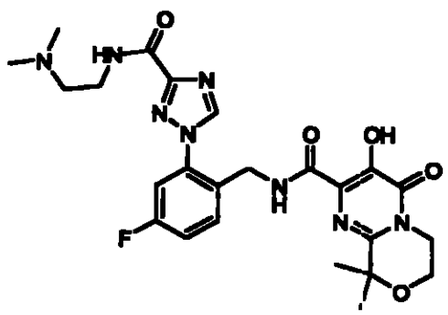


Pirimido[2,1-c][1,4]oxazin-2-carboxamida, N-[[4-fluoro-2-[3-[(4-metil-1-piperazinil)carbonil]-1H-1,2,4-triazol-1-

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il]fenil]metil]-4,6,7,9-tetrahidro-3-hidroxi-9,9-dimetil-4-oxo-. Espuma café pálido. ^{1}H-RMN (300 MHz, $CDCl_3$) δ ppm: 8.43 (1H, s), 8.29 (1H, t, J= 6.8 Hz), 7.63 (1H, dd, J= 8.4, 5.9 Hz), 7.25-7.19 (1H, m), 7.11 (1H, dd, J= 8.0, 2.6 Hz), 4.46 (2H, d, J= 6.6 Hz), 3.95 (4H, s), 3.30 (4H, bs), 2.86 (3H, s), 1.91 (4H, bs), 1.53 (6H, s). EMAR $[M+H]^+$ calculado para $C_{25}H_{30}N_8O_5F$: 541.2323; encontrado: 541.2341. Análisis calculado para $C_{25}H_{29}N_8O_5F \bullet 0.5CF_3CO_2H \bullet 0.5\ H_2O$: C, 46.67; H, 4.41; N, 15.55; F, 14.50; encontrado: C, 46.86; H, 4.44; N, 15.67; F, 14.48.

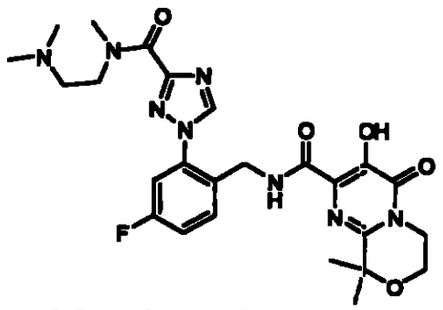
Ejemplo 70



Pirimido[2,1-c][1,4]oxazin-2-carboxamida, N-[[2-[3-[[[2-(dimetilamino)etil)amino)carbonil]-1H-1,2,4-triazol-1-il]-4-fluorofenil]metil]-4,6,7,9-tetrahidro-3-hidroxi-9,9-dimetil-4-oxo-. Espuma café pálido. ^{1}H-RMN (300 MHz, $CDCl_3$) δ ppm: 8.39 (1H, s), 7.58 (1H, dd, J= 8.6, 5.7 Hz), 7.23-7.14 (1H, m), 7.09 (1H, dd, J= 8.4, 2.6 Hz), 4.50 (2H, s), 3.95 (4H, s), 3.84 (2H, t, J= 5.5 Hz), 3.34 (2H, t, J= 6.0 Hz), 2.89 (6H, s), 1.55 (6H, s). EMAR $[M+H]^+$ calculado para $C_{24}H_{30}N_8O_5F$: 529.2323; encontrado: 529.2315.

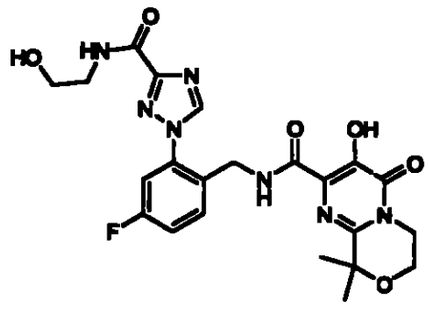
643

Ejemplo 71



Pirimido[2,1-c][1,4]oxazin-2-carboxamida, N-[[2-[3-[[[2-(dimetilamino)etil]metilamino)carbonil]-1H-1,2,4-triazol-1-il]-4-fluorofenil]metil]-4,6,7,9-tetrahidro-3-hidroxi-9,9-dimetil-4-oxo-. Espuma café pálido. ^{1}H-RMN (300 MHz, $CDCl_3$) δ ppm: 8.44 (1H, s), 8.21 (1H, t, J= 6.5 Hz), 7.67-7.58 (1H, m), 7.24-7.09 (2H, m), 4.48-4.45 (2H, m), 3.95 (4H, s), 3.94-3.89 (2H, m), 3.37-3.33 (2H, m), 2.91 (6H, s), 2.88 (3H, s), 1.56 (6H, s). EMAR $[M+H]^+$ calculado para $C_{25}H_{32}N_8O_5F$: 543.2480; encontrado: 543.2491. Análisis calculado para $C_{25}H_{31}N_8O_5F \bullet CF_3CO_2H$: C, 45.20; H, 4.32; N, 14.54; F, 17.26; encontrado: C, 45.13; H, 4.14; N, 14.74; F, 17.01.

Ejemplo 72

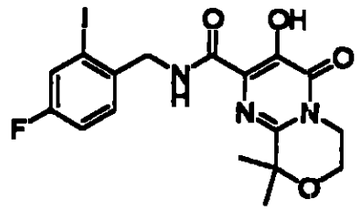


Pirimido[2,1-c][1,4]oxazin-2-carboxamida, N-[[4-fluoro-

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2-[3-[[(2-hidroxietil)amino]carbonil]-1H-1,2,4-triazol-1-il]fenil]metil]-4,6,7,9-tetrahidro-3-hidroxi-9,9-dimetil-4-oxo-. Sólido blanco. ^{1}H-RMN (300 MHz, $CDCl_3$) δ ppm: 8.41 (1H, s), 8.32 (1H, t, J= 6.2 Hz), 7.63 (1H, dd, J= 8.4, 5.9 Hz), 7.20 (1H, dt, J= 8.4, 2.6 Hz), 7.11 (1H, dd, J= 8.4, 2.6 Hz), 4.52-4.50 (2H, m), 3.95 (4H, s), 3.78 (2H, t, J= 5.1 Hz), 3.59 (2H, t, J= 5.1 Hz), 1.56 (6H, s). EMAR $[M+H]^+$ calculado para $C_{22}H_{25}N_7O_6F$: 502.1850; encontrado: 502.1850.

Ejemplo 73



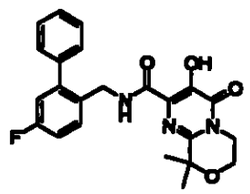
Pirimido[2,1-c][1,4]oxazin-2-carboxamida, N-[(4-fluoro-2-yodofenil)metil]-4,6,7,9-tetrahidro-3-hidroxi-9,9-dimetil-4-oxo-. El compuesto del título puede prepararse a partir del intermediario 174, N-(4-fluoro-2-yodobencil)-3-(benciloxi)-9,9-dimetil-4-oxo-4,6,7,9-tetrahidropirimido[2,1-c][1,4]oxazin-2-carboxamida. ^{1}HRMN 400 MHz ($CDCl_3$) δ ppm: 1.63 (6H, s, 2 x CH_3), 4.05 (4H, s, 2 x CH_2), 4.63 (2H, d, J = 7.1 Hz, NCH_2), 7.11 (1H, m, aromático), 7.42 (1H, dd, J = 5.6 Hz y J = 8.6 Hz, aromático), 7.62 (1H, dd, J = 2.5 Hz y J = 8.1 Hz, aromático), 8.20 (1H, amplio t, NH), 11.82 (1H, s, OH). EMAR (ESI) calculado para $C_{17}H_{18}FIN_3O_4$ $[M+H^+]$: 474.0326; encontrado: 474.0328.

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Ejemplos 74-77

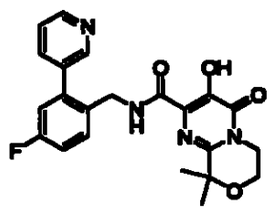
Los Ejemplos 74-77 pueden prepararse a partir de los intermediarios indicados por hidrogenólisis o hidrólisis mediada por ácido trifluoroacético.

Ejemplo 74



Pirimido[2,1-c][1,4]oxazin-2-carboxamida, N-[(5-fluoro[1,1'-bifenil]-2-il)metil]-4,6,7,9-tetrahidro-3-hidroxi-9,9-dimetil-4-oxo-. El compuesto del título puede prepararse a partir del intermediario 176, N-(4-fluoro-2-fenil-bencil)-3-(benciloxi)-9,9-dimetil-4-oxo-4,6,7,9-tetrahidropirimido[2,1-c][1,4]oxazin-2-carboxamida. ^{1}HRMN 400 MHz ($CDCl_3$) δ ppm: 1.56 (6H, s, 2 x CH_3), 4.03 (4H, s, 2 x CH_2), 4.56 (2H, d, J = 6.0 Hz, NCH_2), 7.03 (1H, dd, J = 2.5 Hz y J = 9.3 Hz, aromático), 7.09 (1H, m, aromático), 7.36 (2H, m, aromáticos), 7.42-7.51 (5H, m, aromáticos y NH), 11.96 (1H, s, OH). EMAR (ESI$^+$) calculado para $C_{23}H_{23}FN_3O_4$ [M+H$^+$]: 424.1673; encontrado: 424.1675.

Ejemplo 75

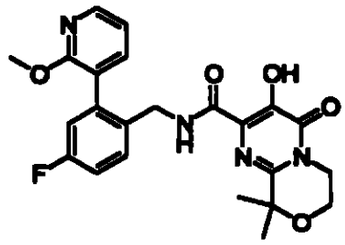


Pirimido[2,1-c][1,4]oxazin-2-carboxamida, N-[[4-fluoro-

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2-(3-piridinil)fenil]metil]-4,6,7,9-tetrahidro-3-hidroxi-9,9-dimetil-4-oxo-. ^{1}HRMN 400 MHz ($CDCl_3$) δ ppm: 1.57 (6H, s, 2 x CH_3), 4.04 (4H, s, 2 x CH_2), 4.55 (2H, d, J = 6.1 Hz, NCH_2), 7.04 (1H, dd, J = 2.5 Hz y J = 9.1 Hz, aromático), 7.16 (1H, m, aromático), 7.43 (1H, m, aromático), 7.49 (1H, dd, J = 5.6 Hz y J = 8.6 Hz, aromático), 7.52 (1H, amplio t, NH), 7.71 (1H, m, aromático), 8.63 (1H, m, aromático), 8.70 (1H, m, aromático), 11.84 (1H, s, OH). EMAR (ESI$^+$) calculado para $C_{22}H_{22}FN_4O_4$ [M+H$^+$]: 425.1625; encontrado: 425.1616.

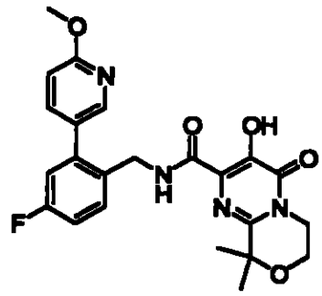
Ejemplo 76



Pirimido[2,1-c][1,4]oxazin-2-carboxamida, N-[[4-fluoro-2-(2-metoxi-3-piridinil)fenil]metil]-4,6,7,9-tetrahidro-3-hidroxi-9,9-dimetil-4-oxo-. La hidrogenólisis del intermediario 175, N-(4-fluoro-2-(2-metoxipiridin-3-il)bencil)-3-(benciloxi)-9,9-dimetil-4-oxo-4,6,7,9-tetrahidropirimido[2,1-c][1,4]oxazin-2-carboxamida dio el material del título como un sólido blanco; pf 227°C. ^{1}HRMN 400 MHz ($CDCl_3$) δ ppm: 1.58 (6H, s, 2 x CH_3), 3.99 (3H, s, OCH_3), 4.04 (4H, s, 2 x CH_2), 4.43 (2H, amplio, NCH_2), 6.97 (1H, dd, J = 2.5 Hz y J = 8.5 Hz, aromático), 7.03 (1H, dd, J = 5.0 Hz y J = 8.5 Hz, aromático), 7.12 (1H, m, aromático),

7.45 (1H, dd, J = 4.5 Hz y J = 8.6 Hz, aromático), 7.53 (1H, dd, J = 2.0 Hz y J = 7.1 Hz, aromático), 7.57 (1H, amplio t, NH), 8.28 (1H, dd, J = 2.5 Hz y J = 5.0 Hz, aromático), 12.03 (1H, s, OH). EMAR (ESI$^+$) calculado para $C_{23}H_{24}FN_4O_5$ [M+H$^+$]: 455.1731; encontrado: 455.1737.

Ejemplo 77



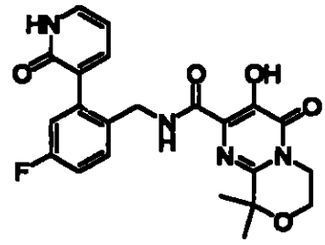
Pirimido[2,1-c][1,4]oxazin-2-carboxamida, N-[[4-fluoro-2-(6-metoxi-3-piridinil)fenil]metil]-4,6,7,9-tetrahidro-3-hidroxi-9,9-dimetil-4-oxo. ^{1}HRMN 400 MHz ($CDCl_3$) δ ppm: 1.58 (6H, s, 2 x CH_3), 4.02 (3H, s, OCH_3), 4.04 (4H, s, 2 x CH_2), 4.55 (2H, d, J = 6.1 Hz, NCH_2), 6.87 (1H, d, J = 9.0 Hz, aromático), 7.01 (1H, dd, J = 2.0 Hz y J = 9.0 Hz, aromático), 7.12 (1H, m, aromático), 7.46 (1H, dd, J = 5.5 Hz y J = 8.6 Hz, aromático), 7.55 (1H, amplio t, NH), 7.60 (1H, dd, J = 2.0 Hz y J = 8.6 Hz, aromático), 8.17 (1H, d, J = 2.0 Hz, aromático), 11.89 (1H, s, OH). EMAR (ESI$^+$) calculado para $C_{23}H_{24}FN_4O_5$ [M+H$^+$]: 455.1731; encontrado: 455.1717.

Ejemplos 78-80

Los Ejemplos 78-80 pueden prepararse a partir de los intermediarios indicados de conformidad con el método

descrito por el ejemplo 78.

Ejemplo 78

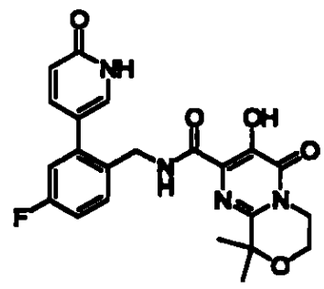


Pirimido[2,1-c][1,4]oxazin-2-carboxamida, N-[[2-(1,2-dihidro-2-oxo-3-piridinil]-4-fluorofenil]metil]-4,6,7,9-tetrahidro-3-hidroxi-9,9-dimetil-4-oxo-. Una solución del intermediario 175, N-(4-fluoro-2-(2-metoxipiridin-3-il)bencil)-3-(benciloxi)-9,9-dimetil-4-oxo-4,6,7,9-tetrahidropirimido[2,1-c][1,4]oxazin-2-carboxamida, (0.125 g, 0.23 mmol) en acetonitrilo (5 ml) se trató con yoduro de sodio (0.090 g, 0.6 mmol) y clorotrimetilsilano (0.45 ml, 3.5 mmol), se selló en un recipiente resistente a la presión y se calentó a 80°C durante 1.5 horas. La mezcla se diluyó con acetato de etilo se lavó con agua y salmuera luego se secó sobre sulfato de magnesio anhidro. La filtración y remoción del solvente proporcionó el compuesto del título. ^{1}HRMN 400 MHz ($CDCl_3$) δ ppm: 1.60 (6H, s, 2 x CH_3), 4.03 (4H, s, 2 x CH_2), 4.5 (2H, amplio, NCH_2), 6.47 (1H, m, aromático), 6.95 (1H, dd, J = 2 Hz y J = 9 Hz, aromático), 7.12 (1H, m, aromático), 7.45 (1H, dd, J = 2 Hz y J = 7 Hz, aromático), 7.50 (1H, dd, J = 6 Hz y J = 9 Hz, aromático), 7.53 (1H, dd, J = 2 Hz y J = 7 Hz, aromático), 8.64 (1H, amplio t, NH).

649

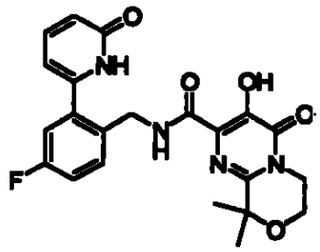
EMAR (ESI$^+$) calculado para $C_{22}H_{22}FN_4O_5$ $[M+H]^+$: 441.1574; encontrado: 441.1585.

Ejemplo 79



Pirimido[2,1-c][1,4]oxazin-2-carboxamida, N-[[2-(1,6-dihidro-6-oxo-3-piridinil]-4-fluorofenil]metil]-4,6,7,9-tetrahidro-3-hidroxi-9,9-dimetil-4-oxo-. El compuesto del título puede prepararse a partir del ejemplo 77. ^{1}HRMN 400 MHz ($CDCl_3$) δ ppm: 1.59 (6H, s, 2 x CH_3), 4.02 (3H, s, OCH_3), 4.05 (4H, s, 2 x CH_2), 4.55 (2H, d, J = 6.6 Hz, NCH_2), 6.95 (1H, d, J = 9.0 Hz, aromático), 7.00 (1H, dd, J = 2.6 Hz y J = 9.0 Hz, aromático), 7.17 (1H, m, aromático), 7.46 (1H, dd, J = 5.5 Hz y J = 8.6 Hz, aromático), 7.63 (1H, d, J = 2.6 Hz, aromático), 7.71 (1H, amplio t, NH), 7.79 (1H, dd, J = 2.6 Hz y J = 9.1 Hz, aromático). EMAR (ESI$^+$) calculado para $C_{22}H_{22}FN_4O_5$ $[M+H^+]$: 441.1574; encontrado: 441.1570.

Ejemplo 80



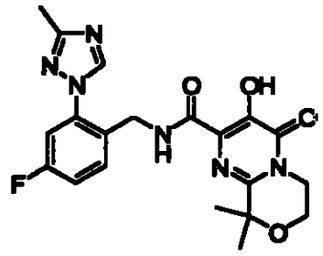
Pirimido[2,1-c][1,4]oxazin-2-carboxamida, N-[[2-(1,6-dihidro-6-oxo-2-piridinil)-4-fluorofenil]metil]-4,6,7,9-tetrahidro-3-hidroxi-9,9-dimetil-4-oxo-. El compuesto del título puede prepararse a partir de N-(4-fluoro-2-(6-metoxipiridin-2-il)bencil)-3-(benciloxi)-9,9-dimetil-4-oxo-4,6,7,9-tetrahidropirimido[2,1-c][1,4]oxazin-2-carboxamida, la cual puede prepararse de conformidad con los métodos descritos para la síntesis del intermediario 175. ^{1}HRMN 400 MHz ($CDCl_3$) δ (ppm): 1.62 (6H, s, 2 x CH_3), 4.04 (4H, s, 2 x CH_2), 4.60 (2H, d, J = 7.0 Hz, NCH_2), 6.38 (1H, d, J = 7.0 Hz, aromático), 6.68 (1H, d, J = 9.0 Hz, aromático), 7.14 (1H, dd, J = 2.5 Hz y J = 9.1 Hz, aromático), 7.23 (1H, m, aromático), 7.50 (1H, dd, J = 5.6 Hz y J = 8.6 Hz, aromático), 7.58 (1H, dd, J = 7.0 Hz y J = 9.0 Hz, aromático), 8.15 (1H, amplio t, NH).

Ejemplos 81-93

Los Ejemplos 81-93 pueden prepararse a partir de los intermediarios indicados por hidrogenólisis o hidrólisis mediada por ácido trifluoroacético.

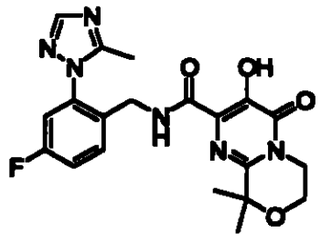
651

Ejemplo 81



Pirimido[2,1-c][1,4]oxazin-2-carbcxamida, N-[[4-fluoro-2-(3-metil-1H-1,2,4-triazol-1-il)fenil]metil]-4,6,7,9-tetrahidro-3-hidroxi-9,9-dimetil-4-oxo-. El compuesto del título puede prepararse a partir del intermediario 152, N-(4-fluoro-2-(3-metil-1H-1,2,4-triazol-1-il)bencil)-3-(benciloxi)-9,9-dimetil-4-oxo-4,6,7,9-tetrahidropirimido[2,1-c][1,4]oxazin-2-carboxamida ^{1}HRMN 400 MHz ($CDCl_3$) δ ppm: 1.64 (6H, s, 2 x CH_3), 2.59 (3H, s, CH_3), 4.04 (4H, s, 2 x CH_2), 4.50 (2H, d, J = 7.1 Hz, NCH_2), 7.1 (1H, dd, J = 2.5 Hz y J= 8.6 Hz, aromático), 7.20 (1H, m, aromático), 7.72 (1H, dd, J = 6.0 Hz y J = 8.6 Hz, aromático), 8.34 (1H, s, CH), 8.80 (1H, amplio t, NH), 12.11 (1H, s, OH). EMAR (ESI$^+$) calculado para $C_{20}H_{22}FN_6O_4$ [M+H$^+$]: 429.1687; encontrado: 429.1675.

Ejemplo 82

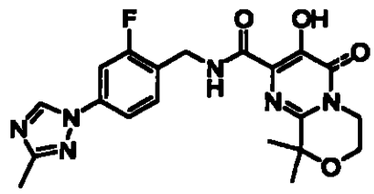


Pirimido[2,1-c][1,4]oxazin-2-carboxamida, N-[[4-fluoro-

652

2-(5-metil-1H-1,2,4-triazol-1-il)fenil]metil]-4,6,7,9-tetrahidro-3-hidroxi-9,9-dimetil-4-oxo-. ^{1}HRMN 400 MHz ($CDCl_3$) δ ppm: 1.66 (6H, s, 2 x CH_3), 2.50 (3H, s, CH_3), 4.04 (4H, s, 2 x CH_2), 4.32 (2H, d, J = 7.0 Hz, NCH_2), 7.05 (1H, dd, J = 2.5 Hz y J = 8.1 Hz, aromático), 7.27 (1H, m, aromático), 7.70 (1H, dd, J = 6.1 Hz y J = 8.6 Hz, aromático), 8.04 (1H, s, CH), 8.61 (1H, amplio t, NH), 11.90 (1H, s, OH). EMAR (ESI^+) calculado para $C_{20}H_{22}FN_6O_4$ [$M+H^+$]: 429.1687; encontrado: 429.1688.

Ejemplo 83

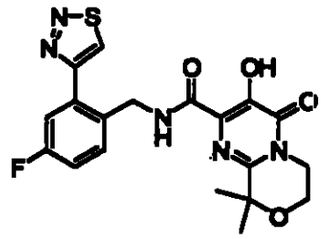


Pirimido[2,1-c][1,4]oxazin-2-carboxamida, N-[[2-fluoro-4-(3-metil-1H-1,2,4-triazol-1-il)fenil]metil]-4,6,7,9-tetrahidro-3-hidroxi-9,9-dimetil-4-oxo-. El compuesto del título puede prepararse a partir del intermediario 153, N-(2-fluoro-4-(3-metil-1H-1,2,4-triazol-1-il)bencil)-3-(benciloxi)-9,9-dimetil-4-oxo-4,6,7,9-tetrahidropirimido[2,1-c][1,4]oxazin-2-carboxamida. ^{1}HRMN 400 MHz ($CDCl_3$) δ ppm: 1.61 (6H, s, 2 x CH_3), 2.51 (3H, s, CH_3), 4.05 (4H, s, 2 x CH_2), 4.72 (2H, d, J = 6.6 Hz, NCH_2), 7.44-7.55 (3H, m, aromáticos), 7.94 (1H, amplio t, NH), 8.46 (1H, s, CH), 11.86 (1H, s, OH). EMAR (ESI^+) calculado para $C_{20}H_{22}FN_6O_4$ [$M+H^+$]:

653

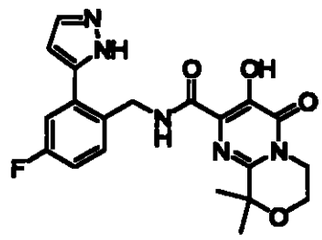
429.1687; encontrado: 429.1695.

Ejemplo 84



Pirimido[2,1-c][1,4]oxazin-2-carboxamida, N-[[4-fluoro-2-(1,2,3-tiadiazol-4-il)fenil]metil]-4,6,7,9-tetrahidro-3-hidroxi-9,9-dimetil-4-oxo-. El compuesto del título puede prepararse a partir del intermediario 172, N-(4-fluoro-2-(1,2,3-tiadiazol-4-yl)bencil)-3-(benciloxi)-9,9-dimetil-4-oxo-4,6,7,9-tetrahidropirimido[2,1-c][1,4]oxazin-2-carboxamida. ^{1}HRMN 400 MHz (DMSO-d_6) δ ppm: 1.54 (6H, s, 2 x CH_3), 3.83 (2H, amplio t, CH_2), 3.96 (2H, amplio t, CH_2), 4.61 (2H, d, J = 6.7 Hz, NCH_2), 7.39 (1H, m, aromático), 7.55 (1H, m, aromático), 7.62 (1H, m, aromático), 9.41 (1H, amplio t, NH), 9.63 (1H, s, CH), 12.0 (1H, s, OH). EMAR (ESI$^+$) calculado para $C_{19}H_{19}FN_5O_4S$ [M+H$^+$]: 432.1142; encontrado: 432.1124.

Ejemplo 85

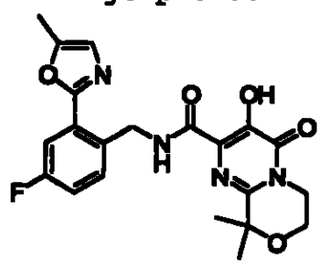


Pirimido[2,1-c][1,4]oxazin-2-carboxamida, N-[[4-fluoro-

654

2-(1H-pirazol-5-il)fenil]metil]-4,6,7,9-tetrahidro-3-hidroxi-9,9-dimetil-4-oxo-. El compuesto del título puede prepararse a partir del intermediario 177, N-(4-fluoro-2-(1H-pirazol-5-il)bencil)-3-(benciloxi)-9,9-dimetil-4-oxo-4,6,7,9-tetrahidropirimido[2,1-c][1,4]oxazin-2-carboxamida. ^{1}HRMN 400 MHz ($CDCl_3$) δ ppm: 1.59 (6H, s, 2 x CH_3), 4.03 (4H, s, 2 x CH_2), 4.67 (2H, d, J = 6.6 Hz, NCH_2), 6.65 (1H, d, J = 2.5 Hz, CH), 7.07 (1H, m, aromático), 7.31 (1H, dd, J = 2.5 Hz y J = 9.8 Hz, aromático), 7.56 (1H, dd, J = 5.8 Hz y J = 8.3 Hz, aromático), 7.75 (1H, d, J = 2.5 Hz, CH), 9.22 (1H, amplio t, NH), 10.33 (1H, amplio, NH), 12.2 (1H, s, OH). EMAR (ESI^+) calculado para $C_{20}H_{21}FN_5O_4$ [$M+H^+$]: 414.1578; encontrado: 414.1560.

Ejemplo 86

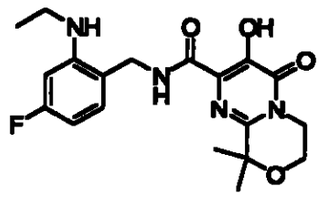


Pirimido[2,1-c][1,4]oxazin-2-carboxamida, N-[[4-fluoro-2-(5-metil-2-oxazolil)fenil]metil]-4,6,7,9-tetrahidro-3-hidroxi-9,9-dimetil-4-oxo-. El compuesto del título puede prepararse a partir del intermediario 173, N-(4-fluoro-2-(5-metiloxazol-2-il)bencil)-3-(benciloxi)-9,9-dimetil-4-oxo-4,6,7,9-tetrahidropirimido[2,1-c][1,4]oxazin-2-carboxamida. ^{1}HRMN 400 MHz ($CDCl_3$) δ ppm: 1.58 (6H, s, 2 x CH_3), 2.48 (3H,

655

s, CH_3), 4.01 (4H, s, 2 x CH_2), 4.77 (2H, d, J = 7.0 Hz, NCH_2), 6.96 (1H, s, CH), 7.13 (1H, m, aromático), 7.61 (1H, dd, J = 5.8 Hz y J = 8.3 Hz, aromático), 7.70 (1H, dd, J = 3.2 Hz y J = 9.6 Hz, aromático), 9.76 (1H, amplio t, NH), 12.15 (1H, s, OH). EMAR (ESI^+) calculado para $C_{21}H_{22}FN_4O_5$ [$M+H^+$]: 429.1574; encontrado: 429.1564.

Ejemplo 87



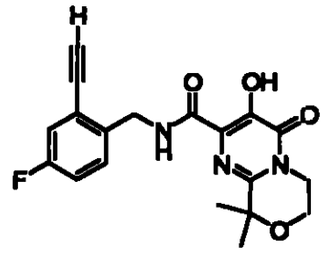
Pirimido[2,1-c][1,4]oxazin-2-carboxamida, N-[[2-(etilamino)-4-fluorofenil]metil]-4,6,7,9-tetrahidro-3-hidroxi-9,9-dimetil-4-oxo-. El compuesto del título puede prepararse a partir del intermediario 170, N-(2-(etilamino)-4-fluorobencil)-3-(benciloxi)-9,9-dimetil-4-oxo-4,6,7,9-tetrahidropirimido[2,1-c][1,4]oxazin-2-carboxamida.

^{1}HRMN 400 MHz ($CDCl_3$) δ ppm: 1.30 (3H, t, J = 7.3 Hz, CH_3), 1.59 (6H, s, 2 x CH_3), 3.12 (2H, m, CH_2), 4.04 (4H, s, 2 x CH_2), 4.52 (2H, d, J = 6.6 Hz, NCH_2), 5.09 (1H, amplio, NH), 6.3-6.37 (2H, m, aromáticos), 7.10 (1H, dd, J = 6.6 Hz y J = 8.1 Hz, aromático), 7.67 (1H, amplio t, NH), 11.93 (1H, s, OH). EMAR (ESI^+) calculado para $C_{19}H_{24}FN_4O_4$ [$M+H^+$]: 391.1782;

656

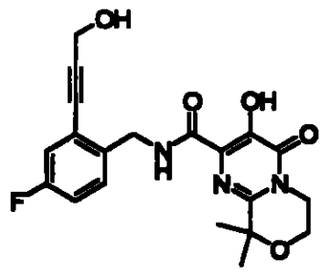
encontrado: 391.1774.

Ejemplo 88



Pirimido[2,1-c][1,4]oxazin-2-carboxamida, N-[(2-etinil-4-fluorofenil)metil]-4,6,7,9-tetrahidro-3-hidroxi-9,9-dimetil-4-oxo-. El compuesto del título puede prepararse a partir del intermediario 179, N-(2-etinil-4-fluorobencil)-3-(benciloxi)-9,9-dimetil-4-oxo-4,6,7,9-tetrahidropirimido[2,1-c][1,4]oxazin-2-carboxamida. ^{1}HRMN 400 MHz ($CDCl_3$) δ ppm: 1.61 (6H, s, 2 x CH_3), 3.46 (1H, s, CH), 4.04 (4H, s, 2 x CH_2), 4.73 (2H, d, J = 6.5 Hz, NCH_2), 7.1 (1H, m, aromático), 7.26 (1H, dd, J = 2.5 Hz y J = 8.5 Hz, aromático), 7.40 (1 H, dd, J = 5.6 Hz y J = 8.6 Hz, aromático), 8.18 (1H, amplio 1, NH), 11.92 (1H, s, OH). EMAR (ESI$^+$) calculado para $C_{19}H_{19}FN_3O_4$ [M+H$^+$]: 372.1360; encontrado: 372.1345.

Ejemplo 89

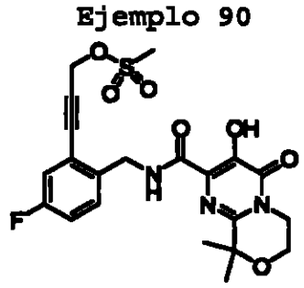


Pirimido[2,1-c][1,4]oxazin-2-carboxamida, N-[[4-fluoro-

657

2-(3-hidroxi-1-propinil)fenil)metil)-4,6,7,9-tetrahidro-3-hidroxi-9,9-dimetil-4-oxo-. El compuesto del título puede prepararse a partir del intermediario 182, N-(4-fluoro-2-(3-hidroxiprop-1-inil)bencil)-3-(benciloxi)-9,9-dimetil-4-oxo-4,6,7,9-tetrahidropirimido[2,1-c][1,4]oxazin-2-carboxamida. ^{1}HRMN 400 MHz ($CDCl_3$) δ ppm: 1.60 (6H, s, 2 x CH_3), 4.04 (4H, s, 2 x CH_2), 4.55 (2H, amplio d, CH_2), 4.73 (2H, d, J = 6.6 Hz, NCH_2), 7.07 (1H, m, aromático), 7.20 (1H, dd, J = 2.5 Hz y J = 9.1 Hz, aromático), 7.38 (1H, dd, J = 5.3 Hz y J = 8.3 Hz, aromático), 7.95 (1H, amplio t, NH), 11.90 (1H, s, OH). EMAR (ESI$^+$) calculado para $C_{20}H_{21}FN_3O_5$ [M+H$^+$]: 402.1465; encontrado: 402.1463.

Ejemplo 90

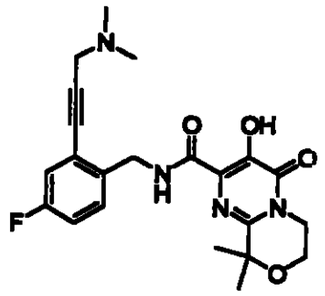


Pirimido[2,1-c][1,4]oxazin-2-carboxamida, N-[[4-fluoro-2-[3-[(metilsulfonil)oxi)-1-propinil)fenil)metil)-4,6,7,9-tetrahidro-3-hidroxi-9,9-dimetil-4-oxo-. El compuesto del título puede prepararse a partir del intermediario 183, metansulfonato de 3-[2-((3-(benciloxi)-9,9-dimetil-4-oxo-4,6,7,9-tetrahidropirimido(2,1-c][1,4]oxazin-2-carboxamido)metil)-5-fluorofenil]prop-2-inilo. ^{1}HRMN 400 MHz ($CDCl_3$) δ ppm: 1.62 (6H, s, 2 x CH_3), 3.16 (3H, s, CH_3), 4.05

658

(4H, s, 2 x CH_2), 4.72 (2H, d, J = 600 Hz, NCH_2), 5.12 (2H, s, OCH_2), 7.12 (1H, m, aromático), 7.21 (1H, dd, J = 2.6 Hz y J = 8.6 Hz, aromático), 7.45 (1H, dd, J = 5.1 Hz y J = 8.6 Hz, aromático), 8.03 (1H, amplio t, NH).

Ejemplo 91

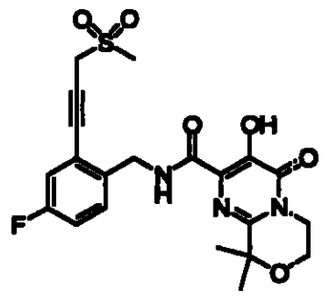


Pirimido[2,1-c][1,4]oxazin-2-carboxamida, N-[[2-[3-(dimetilamino)-1-propinil]-4-fluorofenil]metil]-4,6,7,9-tetrahidro-3-hidroxi-9,9-dimetil-4-oxo-. El compuesto del título puede prepararse a partir del intermediario 184, N-(2-(3-(dimetilamino)prop-1-inil)-4-fluorobencil)-3-(benciloxi)-9,9-dimetil-4-oxo-4,6,7,9-tetrahidropirimido[2,1-c][1,4]oxazin-2-carboxamida. El compuesto del título se aisló como una sal de ácido trifluoroacético.

^{1}HRMN 400 MHz ($CDCl_3$) δ ppm: 1.62 (6H, s, 2 x CH_3), 3.03 (6H, s, 2 x CH_3), 4.06 (4H, s, 2 x CH_2), 4.23 (2H, s, NCH_2), 4.75 (2H, d, J = 6.0 Hz, NCH_2), 7.16 (1H, m, aromático), 7.24 (1H, dd, J = 2.5 Hz y J = 8.6 Hz, aromático), 7.42 (1H, dd, J = 5.6 Hz y J = 8.6 Hz, aromático), 8.04 (1H, amplio t, NH). EMAR (ESI$^+$) calculado para $C_{22}H_{26}FN_4O_4$ [M+H$^+$]: 429.1938; encontrado: 429.1917.

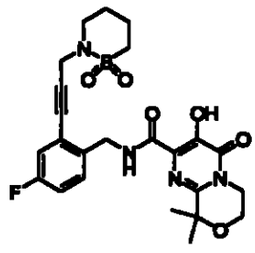
667
659

Ejemplo 92



Pirimido[2,1-c][1,4]oxazin-2-carboxamida, N-[[4-fluoro-2-[3-(metilsulfonil)-1-propinil]fenil]metil]-4,6,7,9-tetrahidro-3-hidroxi-9,9-dimetil-4-oxo-. El compuesto del título puede prepararse a partir del intermediario 186, N-(4-fluoro-2-(3-(metilsulfonil)prop-1-inil)bencil)-3-(benciloxi)-9,9-dimetil-4-oxo-4,6,7,9-tetrahidropirimido[2,1-c][1,4]oxazin-2-carboxamida. ^{1}HRMN 400 MHz ($CDCl_3$) δ ppm: 1.63 (6H, s, 2 x CH_3), 3.16 (3H, s, SCH_3), 4.04 (4H, s, 2 x CH_2), 4.17 (2H, s, SCH_2), 4.70 (2H, d, J = 6.0 Hz, NCH_2), 7.12 (1H, m, aromático), 7.21 (1H, dd, J = 2.5 Hz y J = 8.6 Hz, aromático), 7.49 (1H, dd, J = 5.6 Hz y J = 8.6 Hz, aromático), 8.16 (1H, amplio t, NH)., 11.99 (1H, s, OH). EMAR (ESI$^+$) calculado para $C_{21}H_{23}FN_3O_6S$ [M+H$^+$]: 464.1292; encontrado: 464.1271.

Ejemplo 93

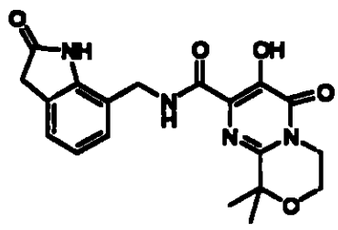


Pirimido[2,1-c][1,4]oxazin-2-carboxamida, N-[[4-

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fluoro-2-[3-(tetrahidro-1,1-dioxido-2H-1,2-tiazin-2-il)-1-propinil]fenil]metil]-4,6,7,9-tetrahidro-3-hidroxi-9,9-dimetil-4-oxo-. ^{1}HRMN 400 MHz ($CDCl_3$) δ ppm: 1.63 (6H, s, 2 x CH_3), 1.86 (2H, m, CH_2), 2.28 (2H, m, CH_2), 3.11 (2H, m, CH_2), 3.53 (2H, m, CH_2), 4.05 (4H, s, 2 x CH_2), 4.27 (2H, s, NCH_2), 4.73 (2H, d, J = 6.0 Hz, NCH_2), 7.07 (1H, m, aromático), 7.17 (1H, dd, J = 2.5 Hz y J = 8.6 Hz, aromático), 7.47 (1H, dd, J = 5.6 Hz y J = 8.6 Hz, aromático), 8.12 (1H, amplio t, NH).

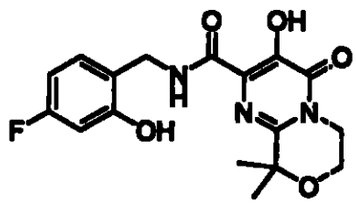
Ejemplo 94



Pirimido[2,1-c][1,4]oxazin-2-carboxamida,4,6,7,9-tetrahidro-3-hidroxi-9,9-dimetil-4-oxo-N-[2-(fenilsulfonil)etil]-. El compuesto del título puede prepararse a partir del intermediario 25, 3-hidroxi-9,9-dimetil-4-oxo-4,6,7,9-tetrahidropirimido[2,1-c][1,4]oxazin-2-carboxilato de etilo y 7-(aminometil)indolin-2-ona de conformidad con los métodos descritos para los ejemplos 1, 19 y 20. ^{1}H RMN (500 MHz, DMSO-d_6) δ ppm: 1.58 (s, 6), 3.50 (s, 2), 3.83 (m, 2), 3.97 (m, 2), 4.42 (d, 2), 6.9-7.13 (traslapado m, 3). Análisis calculado $C_{19}H_{20}N_4O_5$: C, 59.36; H, 5.24; N, 14.57. Encontrado: C, 59.61; H, 5.43; N, 14.46.

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Ejemplo 95

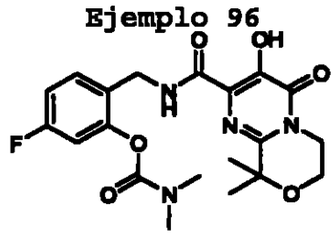


Pirimido[2,1-c][1,4]oxazin-2-carboxamida, N-[(4-fluoro-2-hidroxifenil)metil]-4,6,7,9-tetrahidro-3-hidroxi-9,9-dimetil-4-oxo-. Una solución del intermediario 144, N-(4-fluoro-2-hidroxibencil)-3-(benciloxi)-9,9-dimetil-4-oxo-4,6,7,9-tetrahidropirimido[2,1-c][1,4]oxazin-2-carboxamida, (0.070 g, 0.154 mmol) en diclorometano (3 mL) y ácido trifluoroacético (3 mL) se agitó durante 2 horas. El solvente se removió luego in vacuo y el residuo resultante se disolvió en acetato de etilo. La solución de acetato de etilo se lavó con HCl 1.0 N (10 mL), se secó sobre sulfato de sodio, luego se filtró. El solvente se removió por evaporador rotatorio y el producto crudo se purificó por CLAR preparativa de fase inversa, (C18, 30%-40% CH_3CN/H_2O-0.1% CF_3CO_2H). Las fracciones que contienen el producto se concentraron por evaporador rotatorio y la suspensión acuosa resultante se extrajo con acetato de etilo (3 x 50 mL). Las capas orgánicas combinadas se secaron (sulfato de sodio), filtraron, y se concentraron hasta secarse por evaporador rotatorio. El residuo se trituró con éter y se secó in vacuo para dar el compuesto

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del título como un sólido blanco. ^{1}H RMN (500 MHz, d_6-Acetona) δ ppm: 11.96 (2H, s), 9.25 (2H, s), 8.98 (1H, br s), 7.23 (1H, t, J=7.6 Hz), 6.63 (1H, dd, J=8.2, 2.4 Hz), 6.57 (1H, dt, J=8.4, 2.4 Hz), 4.53 (2H, d, J=6.7 Hz), 4.05 (2H, d, J=5.2 Hz), 3.90 (2H, t, J=5.2 Hz), 1.55 (6H, s); EMAR $[M+H]^+$ calculado para $C_{17}H_{19}N_3O_5F$: 364.13088; encontrado: 364.1302.

Ejemplo 96

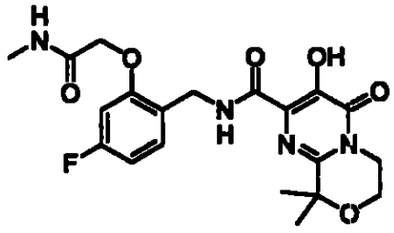


Ácido carbámico, dimetil-, éster de 5-fluoro-2-[[[(4,6,7,9-tetrahidro-3-hidroxi-9,9-dimetil-4-oxopirimido[2,1-c][1,4]oxazin-2-il)carbonil]amino]metil]fenilo. El compuesto del título puede prepararse a partir del intermediario 158, éster de 2-{[(3-benciloxi-9,9-dimetil-4-oxo-4,6,7,9-tetrahidro-pirimido[2,1-c][1,4]oxazin-2-carbonil)-amino]-metil}-5-fluoro-fenilo del ácido dimetil-carbámico de conformidad con el método descrito por el ejemplo 95. Polvo cristalino blanco; ^{1}H RMN ($CDCl_3$, 500 MHz) δ ppm: 1.56 (6H, s, Me), 2.96, 3.11 (2s, NMe), 3.99 (4H, s, CH_2), 4.51 (2H, d, J = 6 Hz, NCH_2), 5.85 (1H, dd, J = 2.5 Hz, 9 Hz, CH), 6.94 (1H, dt, J = 2.5 Hz, 8.3 Hz, Ar-H), 7.37 (1H, dd, J = 6.5 Hz, 8.5 Hz, Ar-H), 8.05 (1H, brt, J = 5 Hz, NH), 12.0 (1H, s, OH); ^{13}C RMN ($CDCl_3$, 125.77 Hz) δ ppm: 27.90

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(CH_3), 36.68, 36.92 (2s, NCH_3), 37.80 (NCH_2), 43.14 (NCH_2), 58.20 (OCH_2), 75.99 (OC), 110.88, 110.07 (d, J = 24, Hz, CH), 113.41, 113.57 (d, J = 21 Hz, CH), 125.71 (C), 125.91, 125.94 (d, J = 3.6 Hz, C), 131.57, 131.64 (d, J = 9.6 Hz, CH), 146.22 (C), 150.83, 150.92 (d, J = 11 Hz, C), 151.66 (C), 154.68 (C=O), 157.92 (C=O), 161.70, 163.68 (d, J = 249 Hz, CF), 167.86 (C=O); EMAR calculado para $C_{20}H_{24}N_4O_6F$ (M+H) 435.1680, encontrado 435.1695 (δ+3.5 ppm). UV (MeOH): λmax 245 nm (ε $1.05x10^4$), 306 nm (ε $8.00x10_3$) Análisis calculado para $C_{20}H_{23}N_4O_6F$; C 55.30, H 5.34, N 12.90: encontrado C 55.32, H 5.38, N 12.77.

Ejemplo 97



Pirimido[2,1-c][1,4]oxazin-2-carboxamida, N-[[4-fluoro-2-[2-(metilamino)-2-oxoetoxi]fenil]metil]-4,6,7,9-tetrahidro-3-hidroxi-9,9-dimetil-4-oxo-. Una solución del intermediario 144, N-(4-fluoro-2-hidroxibencil)-3-(benciloxi)-9,9-dimetil-4-oxo-4,6,7,9-tetrahidropirimido[2,1-c][1,4]oxazin-2-carboxamida (0.150 g, 0.331 mmol) e hidruro de sodio (0.015 g, 0.37 mmol, 60% aceite de dispersión) en dimetilformamida anhidra (4 mL) se agitó durante 5 minutos bajo una atmósfera de nitrógeno. La mezcla de reacción se trató con 2-cloro-N-

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metilacetamida (0.054 g, 0.50 mmol), y se agitó durante 16 horas adicionales. El solvente se removió por evaporador rotatorio, y el residuo resultante se purificó por cromatografía de gel de sílice instantánea de trayectoria corta (acetato de etilo).

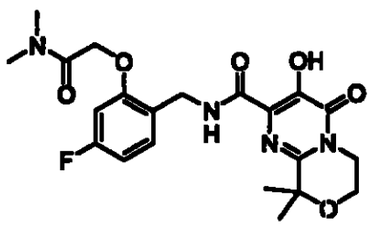
Las fracciones que contienen el producto se combinaron y se concentraron hasta secarse. El residuo se disolvió en diclorometano (5 mL) y ácido trifluoroacético (5 mL) y se agitó durante 1 hora.

El solvente se removió por evaporador rotatorio y el producto crudo se trituró con un volumen mínimo de 95% etanol. El sólido resultante se colectó por filtración, y se secó bajo vacío resultando en 93 mg (0.21 mmol, Rendimiento 65%) del compuesto del título como un polvo blanco: ^{1}H RMN (500 MHz, $CDCl_3$) δ ppm: 11.92 (1H, s), 7.67 (1H, t, J=6.3 Hz), 7.57 (1H, br), 7.30 (1H, dd, J=8.2, 6.4 Hz), 6.74 (1H, dt, J=8.2, 2.3 Hz), 6.60 (1H, dd, J=10.4, 2.4 Hz), 4.68 (2H, d, J=6.7 Hz), 4.45 (2H, s), 4.00 (4H, s), 2.93 (3H, d, J=4.9 Hz), 1.55 (6H, s).

^{13}C RMN (125.77 MHz, $CDCl_3$) δ ppm: 168.05, 167.44, 164.79, 162.82, 157.71, 156.57, 156.50, 152.14, 146.60, 131.94, 131.86, 125.23, 120.71, 120.68, 108.37, 108.20, 100.76, 100.55, 75.81, 67.46, 58.15, 43.24, 38.19, 28.08, 25.83. EMAR $[M+H]^+$ calculado para $C_{20}H_{24}N_4O_6F$: 435.1680; encontrado: 435.1668.

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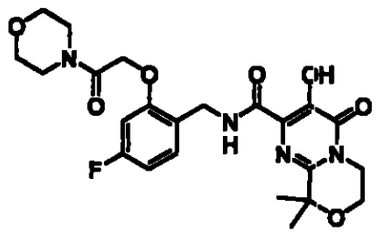
Ejemplo 98



Pirimido[2,1-c][1,4]oxazin-2-carboxamida, N-[[2-[2-(dimetilamino)-2-oxoetoxi]-4-fluorofenil]metil]-4,6,7,9- tetrahidro-3-hidroxi-9,9-dimetil-4-oxo-. El compuesto del título puede prepararse a partir del intermediario 144, N-(4-fluoro-2-hidroxibencil)-3-(benciloxi)-9,9-dimetil-4-oxo-4,6,7,9-tetrahidropirimido[2,1-c][1,4]oxazin-2-carboxamida de conformidad con el método descrito por el ejemplo 97. Polvo blanco; 1H RMN (500 MHz, CDCl3) δ ppm: 12.25 (1H, br s), 8.36 (1H, t, J=5.65 Hz), 7.31 (1H, dd, J=8.39, 6.56 Hz), 6.67 (1H, dt, J=8.32, 2.29 Hz), 6.57 (1H, dd, J=10.38, 2.14 Hz), 4.76 (2H, s), 4.62 (2H, d, J=6.10 Hz), 4.00 (4H, s), 3.06 (3H, s), 3.01 (3H, s), 1.58 (6H, s). ^{13}C RMN (125.77 MHz, $CDCl_3$) δ ppm: 168.25, 166.62, 164.23, 162.27, 158.02, 157.39, 151.36, 146.39, 131.25, 131.18, 125.95, 122.23, 122.20, 108.25, 108.08, 100.47, 100.27, 76.03, 66.24, 58.22, 43.15, 38.59, 36.07, 35.77, 27.94. EMAR $[M+H]^+$ calculado para $C_{21}H_{26}N_4O_6F$: 449.18365; encontrado:

449.1837.

Ejemplo 99

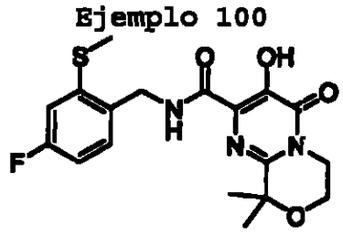


Ácido 4-morfolincarboxílico, éster de 5-fluoro-2-[[[(4,6,7,9-tetrahidro-3-hidroxi-9,9-dimetil-4-oxopirimido[2,1-c][1,4]oxazin-2-il)carbonil]amino]metil]fenilo. El compuesto del título puede prepararse a partir del intermediario 144, N-(4-fluoro-2-hidroxibencil)-3-(benciloxi)-9,9-dimetil-4-oxo-4,6,7,9-tetrahidropirimido[2,1-c][1,4]oxazin-2-carboxamida de conformidad con el método descrito por el ejemplo 97. Polvo blanco; ^{1}H RMN (500 MHz, $CDCl_3$) δ ppm: 12.01 (1H, br s), 7.96 (1H, t, J=5.34 Hz), 7.38 (1H, dd, J=8.39, 6.26 Hz), 6.97 (1H, dt, J=8.24, 2.44 Hz), 6.87 (1H, dd, J=8.85, 2.44 Hz), 4.51 (2H, d, J=6.10 Hz), 4.00 (4H, s), 3.70-3.76 (4H, m), 3.65-3.70 (2H, m), 3.49-3.54 (2H, m), 1.55 (6H, s).

^{13}C RMN (125.77 MHz, $CDCl_3$) δ ppm: 167.91, 163.68, 157.86, 153.48, 151.71, 150.51, 150.42, 146.31, 131.58, 131.50, 125.83, 125.59, 113.84, 113.67, 111.03, 110.84, 75.93, 66.59, 66.52, 58.22, 45.17, 44.41, 43.16, 37.70, 27.95. EMAR $[M+H]^+$ calculado para $C_{22}H_{26}N_4O_7F$: 477.17856; encontrado: 477.1788.

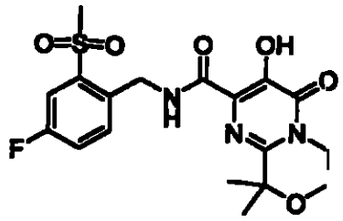
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Ejemplo 100



Pirimido[2,1-c][1,4]oxazin-2-carboxamida, N-[[4-fluoro-2-(metiltio)fenil]metil]-4,6,7,9-tetrahidro-3-hidroxi-9,9-dimetil-4-oxo-. El compuesto del título puede prepararse a partir del intermediario 25, 3-hidroxi-9,9-dimetil-4-oxo-4,6,7,9-tetrahidropirimido[2,1-c][1,4]oxazin-2-carboxilato de etilo, y (4-fluoro-2-(metiltio)fenil)metanamina de conformidad con los métodos descritos para la síntesis de los ejemplos 1, 19 y 20. Sólido blanco. ^{1}H RMN (300 MHz, $CDCl_3$) δ ppm: 11.88 (1H, br), 8.03 (1H, 1, J=6.04 Hz), 7.28 (1H, dd, J=8.42, 5.85 Hz), 6.93 (1H, dd, J=9.51, 2.20 Hz), 6.81 (1H, dt, J=8.23, 2.56 Hz), 4.58 (2H, d, J=6.22 Hz), 3.98 (4H, s), 2.49 (3H, s), 1.55 (6H, s); EMAR (ESI) calculado para $C_{18}H_{21}FN_3O_4S$ (M+H) 394.1237, encontrado 394.1218.

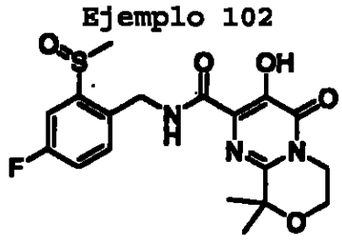
Ejemplo 101



Pirimido[2,1-c][1,4]oxazin-2-carboxamida, N-[[4-fluoro-2-(metilsulfonil)fenil]metil]-4,6,7,9-tetrahidro-3-hidroxi-9,9-dimetil-4-oxo-. A una solución del ejemplo 100

pirimido[2,1-c][1,4]oxazin-2-carboxamida, N-[[4-fluoro-2-(metiltio)fenil]metil]-4,6,7,9-tetrahidro-3-hidroxi-9,9-dimetil-4-oxo- (158 mg, 0.4 mmol), en CH_2Cl_2 (4 mL) se agregó ácido 3-cloroperoxibenzoico (132 mg, 0.6 mmol; 77%, Aldrich) y la mezcla se agitó a temperatura ambiente durante 2 horas. Después de remover el solvente in vacuo, el residuo se trituró con éter de dietilo. El polvo crudo se purificó por cromatografía de columna de fase inversa (YMC, ODS, 8% CH_3CN/H_2O-0.1% CF_3CO_2H) para proporcionar 32 mg (0.075 mmol, Rendimiento 19%) del compuesto del título como un polvo blanco después de la trituración con éter de dietilo, y 35 mg (0.086 mmol, Rendimiento 21%) del sulfóxido correspondiente. ^1H RMN (300 MHz, $CDCl_3$) δ ppm: 11.71 (1 H, s), 8.58 (1 H, t, J=6.04 Hz), 7.73 (1 H, dd, J=8.23, 2.74 Hz), 7.68 (1H, dd, J=8.42, 5.12 Hz), 7.32 (1 H, dt, J=8.05, 2.93 Hz), 4.79 (2 H, d, J=6.95 Hz), 3.97 (4 H, s), 3.15 (3 H, s), 1.56 (6 H, s); EMAR (ESI) calculado para $C_{18}H_{19}FN_3O_6S$ (M-H) 424.0979, encontrado 424.0973.

Ejemplo 102

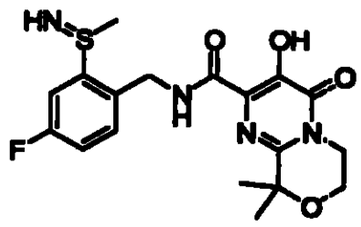


Pirimido[2,1-c][1,4]oxazin-2-carboxamida,N-[[4-fluoro-2-(metilsulfinil)fenil]metil]-4,6,7,9-tetrahidro-3-hidroxi-9,9-

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dimetil-4-oxo. Se formó en la reacción descrita por el ejemplo 101. ^{1}H RMN (300 MHz, $CDCl_3$) δ ppm: 11.73 (1H, s), 8.19 (1H, t, J=6.59 Hz), 7.54 (1H, dd, J=8.05, 2.93 Hz), 7.47 (1H, dd, J=8.42, 5.12 Hz), 7.16 (1H, dt, J=8.14, 2.74 Hz), 4.57-4.81 (2H, m), 3.99 (4H, s), 2.80 (3H, s), 1.56 (6H, s); EMAR (ESI) calculado para $C_{18}H_{21}FN_2O_5S$ (M-H) 410.1196, encontrado 410.1194.

Ejemplo 103



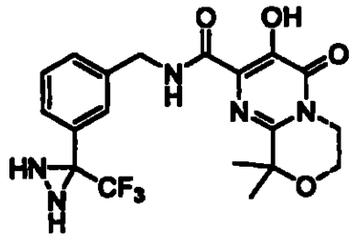
Pirimido[2,1-c][1,4]oxazin-2-carboxamida, N-[[4-fluoro-2-(S-metilsulfinimidoil)fenil]metil]-4,6,7,9-tetrahidro-3-hidroxi-9,9-dimetil-4-oxo-. A una solución del ejemplo 100, pirimido[2,1-c][1,4]oxazin-2-carboxamida, N-[[4-fluoro-2-(metiltio)fenil]metil]-4,6,7,9-tetrahidro-3-hidroxi-9,9-dimetil-4-oxo-, (245 mg, 0.75 mmol) en CH_2Cl_2 (3 mL) se agregó formiato de tert-butilo azida (115 mg, 0.8 mmol; se preparó siguiendo el procedimiento descrito en Organic Synthesis 1979, 50, 9-12) y cloruro ferroso ($FeCl_2$, 50 mg) y la mezcla resultante se agitó durante 18 horas. La mezcla se diluyó con diclorometano, se lavó con agua, se secó ($MgSO_4$), se filtró y se concentró para proporcionar 450 mg de la 4-fluoro-2-(N-tert-butoxicarbonil-S-metil)sulfiliminil-bencilamida del

674 670

ácido 3-hidroxi-9,9-dimetil-4-oxo-4,6,7,9-tetrahidropirimido[2,1-c][1,4]oxazin-2-carboxílico como una goma oscura; CL/EM m/z 509 (M+H).

Una solución de este material, (100 mg) en CF_3CO_2H (1 mL), se agitó durante 20 minutos, luego se concentró. El residuo se purificó por CLAR de fase inversa C-18 (YMC ODS, 5-10% de CH_3CN/H_2O-0.1% de CF_3CO_2H) para proporcionar 15 mg (0.037 mmol, 21% Rendimiento) del compuesto del título como la sal del ácido trifluoroacético correspondiente. ^1H RMN (300 MHz, DMSO-D6) δ ppm: 11.62 (1H, s), 9.57 (1H, t, J=6.0 Hz), 8.11 (1H, dd, J=8.8, 1.8 Hz), 7.62-7.71 (2H, m), 4.58-4.82 (2H, m), 3.97 (2H, t, J=4.8 Hz), 3.82 (2H, t, J=4.8 Hz), 3.37 (3H, s), 1.57 (6H, s); EMAR (ESI) calculado para $C_{18}H_{22}FN_4O_4S$ (M+H) 409.1346, encontrado 409.1333.

Ejemplo 104

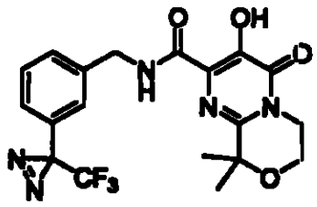


Pirimido[2,1-c][1,4]oxazin-2-carboxamida,4,6,7,9-tetrahidro-3-hidroxi-9,9-dimetil-4-oxo-N-[[3-[3-(trifluorometil)-3-diaziridinil]fenil]metil]. El compuesto del título puede prepararse a partir del intermediario 25, el 3-hidroxi-9,9-dimetil-4-oxo-4,6,7,9-tetrahidropirimido[2,1-c][1,4]oxazin-2-carboxilato de etilo

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y (4-(diaziridin-3-il)fenil)metanamina (formados en la preparación del intermediario 66) de conformidad con los métodos descritos para la síntesis de los ejemplos 1, 19 y 20. Sólido blanco; ^{1}H RMN (300 MHz, $CDCl_3$) δ ppm: 11.89 (1H, s), 7.81 (1H, t, J=6.0 Hz), 7.52-7.59 (2H, m), 7.38-7.44 (2H, m), 4.63 (2H, d, J=6.2 Hz), 4.00 (4H, s), 2.78 (1H, d, J=7.3 Hz), 2.21 (1H, d, J=8.1 Hz), 1.51-1.57 (6H, m); EMAR (ESI) calculado para $C_{19}H_{21}F_3N_5O_4$ (M+H) 440.1546, encontrado 440.1537.

Ejemplo 105

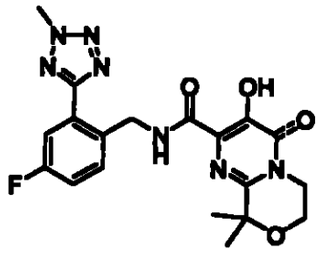


Pirimido[2,1-c][1,4]oxazin-2-carboxamida,4,6,7,9-tetrahidro-3-hidroxi-9,9-dimetil-4-oxo-N-[[3-[3-(trifluorometil)-3H-diazirin-3-il]fenil]metil]-. El compuesto del título puede prepararse a partir del intermediario 25, el 3-hidroxi-9,9-dimetil-4-oxo-4,6,7,9-tetrahidropirimido[2,1-c][1,4]oxazin-2-carboxilato de etilo y el intermediario 66, (3-(3-(trifluorometil)diaziridin-3-il)fenil)metanamina, de conformidad con los métodos descritos para la síntesis de los ejemplos 1, 19 y 20. Sólido blanco; ^{1}H RMN (300 MHz, $CDCl_3$) δ ppm: 11.86 (1H, s), 7.73-7.84 (1H, m), 7.35-7.40

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(2H, m), 7.11-7.17 (1H, m, J=2.9 Hz), 7.08-7.11 (1H, m), 4.60 (2H, d, J=6.2 Hz), 4.00 (4H, s), 1.55 (6H, s); EMAR (ESI) calculado para $C_{19}H_{19}F_3N_5O_4$ (M+H) 438.1389, encontrado 438.1371.

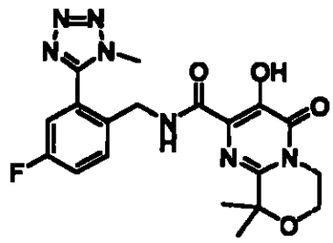
Ejemplo 106



Pirimido[2,1-c][1,4]oxazin-2-carboxamida, N-[[4-fluoro-2-(2-metil-2H-tetrazol-5-il)fenil]metil]-4,6,7,9-tetrahidro-3-hidroxi-9,9-dimetil-4-oxo-. El compuesto del título puede prepararse a partir del intermediario 25, el 3-hidroxi-9,9-dimetil-4-oxo-4,6,7,9-tetrahidropirimido[2,1-c][1,4]oxazin-2-carboxilato de etilo y el intermediario 59, clorohidrato de (4-fluoro-2-(2-metil-2H-tetrazol-5-il)fenil)metanamina, de conformidad con los métodos descritos para la síntesis de los ejemplos 1, 19 y 20. (sólido blanco); ^{1}H RMN (300 MHz, $CDCl_3$) δ ppm: 12.01 (1H, s), 9.24 (1H, t, J=6.8 Hz), 7.75 (1H, dd, J=9.5, 2.6 Hz), 7.63 (1H, dd, J=8.4, 5.5 Hz), 7.15 (1H, dt, J=8.2, 2.6 Hz), 4.70 (2H, d, J=7.0 Hz), 4.45 (3H, s), 3.96 (4 H, s), 1.53 (6H, s); EMAR (ESI) calculado para $C_{19}H_{21}FN_7O_4$ (M+H) 430.1639, encontrado 430.1649.

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Ejemplo 107



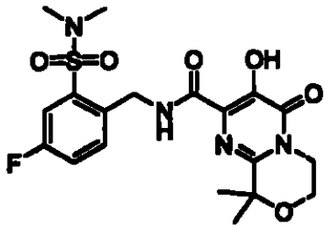
Pirimido[2,1-c][1,4]oxazin-2-carboxamida, N-[[4-fluoro-2-(1-metil-1H-tetrazol-5-il)fenil]metil]-4,6,7,9-tetrahidro-3-hidroxi-9,9-dimetil-4-oxo-. El compuesto del título puede prepararse a partir del intermediario 25, el 3-hidroxi-9,9-dimetil-4-oxo-4,6,7,9-tetrahidropirimido[2,1-c][1,4]oxazin-2-carboxilato y el intermediario 62, clorohidrato de (4-fluoro-2-(1-metil-2H-tetrazol-5-il)fenil)metanamina, de conformidad con los métodos descritos para la síntesis de los ejemplos 1, 19 y 20. Sólido blanco opaco; ^{1}H RMN (500 MHz, $CDCl_3$) δ ppm: 11.83 (1H, s), 9.17 (1H, t, J=5.8 Hz), 7.75 (1H, dd, J=8.4, 5.7 Hz), 7.30 (1H, t, J=8.2 Hz), 7.14 (1H, d, J=7.9 Hz), 4.43 (2H, d, J=6.7 Hz), 4.14-4.16 (3H, m), 4.00 (4H, s), 1.67 (6H, s); EMAR (ESI) calculado para $C_{19}H_{21}FN_7O_4$ (M+H) 430.1639, encontrado 430.1619.

Ejemplos 108-112

Los ejemplos 108-112 pueden prepararse a partir del intermediario 25, el 3-hidroxi-9,9-dimetil-4-oxo-4,6,7,9-tetrahidropirimido[2,1-c][1,4]oxazin-2-carboxilato de etilo y las aminas indicadas de conformidad con los métodos descritos para la síntesis de los ejemplos 1, 19 y 20.

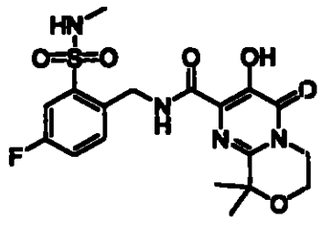
674

Ejemplo 108



Pirimido[2,1-c][1,4]oxazin-2-carboxamida, N-[[2-[(dimetilamino)sulfonil)-4-fluorofenil]metil]-4,6,7,9-tetrahidro-3-hidroxi-9,9-dimetil-4-oxo-. El compuesto del título puede prepararse a partir del intermediario 48, 2-(aminometil)-5-fluoro-N,N-dimetilbencensulfonamida. Sólido blanco; ^{1}H RMN (500 MHz, $CDCl_3$) δ ppm: 11.83 (1H, s), 8.64 (1H, t, J=6.6 Hz), 7.68 (1H, dd, J=8.6, 5.5 Hz), 7.50 (1H, dd, J=8.2, 2.8 Hz), 7.26-7.30 (1H, m), 4.80 (2H, d, J=7.0 Hz), 3.99 (4H, s), 2.91 (6H, s), 1.58 (6H, s); EMAR (ESI) calculado para $C_{19}H_{24}FN_4O_6S$ (M+H) 455.1401, encontrado 455.1402.

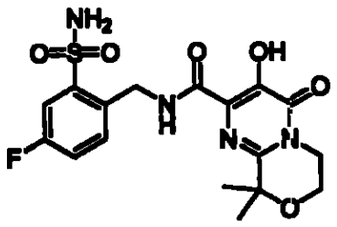
Ejemplo 109



Pirimido[2,1-c][1,4]oxazin-2-carboxamida, N-[[4-fluoro-2-[(metilamino}sulfonil]fenil]metil]-4,6,7,9-tetrahidro-3-hidroxi-9,9-dimetil-4-oxo-. El compuesto del título puede prepararse a partir del intermediario 52, clorohidrato de 2-

(aminometil)-5-fluoro-N-metilbencensulfonamida. Sólido blanco opaco; ^{1}H RMN (300 MHz, $CDCl_3$) δ ppm: 11.69 (1H, s), 8.55 (1H, br), 7.58-7.67 (2H, m), 7.24-7.29 (1H, m), 4.87-4.97 (1H, br), 4.82 (2H, d, J=6.2 Hz), 3.97 (4H, s), 2.71 (3H, d, J=4.4 Hz), 1.56 (6H, s); EMAR (ESI) calculado para $C_{18}H_{22}FN_4O_6S$ (M+H) 441.1244, encontrado 441.1237.

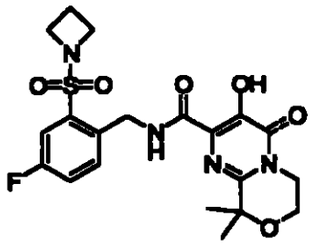
Ejemplo 110



Pirimido[2,1-c][1,4]oxazin-2-carboxamida, N-[[2-(aminosulfonil)-4-fluorofenil]metil]-4,6,7,9-tetrahidro-3-hidroxi-9,9-dimetil-4-oxo-. El compuesto del título puede prepararse a partir del intermediario 56, clorohidrato de 2-(aminometil)-5-fluorobencensulfonamida. Sólido blanco opaco, ^{1}H RMN (300 MHz, DMSO-D6) δ ppm: 11.92 (1H, s), 9.33 (1H, t, J=6.4 Hz), 7.66 (1H, dd, J=8.8, 2.2 Hz), 7.41-7.52 (2H, m), 4.89 (2H, d, J=6.2 Hz), 3.98 (2H, t, J=4.9 Hz), 3.83 (2H, t, J=4.9 Hz), 3.37 (2H, br), 1.55 (6H, s); EMAR (ESI) calculado para $C_{17}H_{20}FN_4O_6S$ (M+H) 427.1088, encontrado 427.1082.

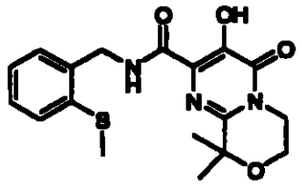
676

Ejemplo 111



Pirimido[2,1-c][1,4]oxazin-2-carboxamida, N-[[2-(1-azetidinilsulfonil)-4-fluorofenil]metil]-4,6,7,9-tetrahidro-3-hidroxi-9,9-dimetil-4-oxo-. El compuesto del título puede prepararse a partir de (2-(azetidin-1-ilsulfonil)-4-fluorofenil)metanamina, la cual se sintetizó de conformidad a los métodos usados para preparar el intermediario 48. Sólido blanco, ^{1}H RMN (500 MHz, $CDCl_3$) δ ppm 11.86 (1H, s), 8.57 (1H, 1, J=6.3 Hz), 7.65-7.72 (2H, m), 7.26-7.31 (1H, m), 4.82 (2H, d, J=6.7 Hz), 3.99 (4H, s), 3.96 (4H, 1, J=7.8 Hz), 2.23-2.32 (2H, m), 1.58 (6H, s); EMAR (ESI) calculado para $C_{20}H_{24}FN_4O_6S$ (M+H) 467.1401, encontrado 467.1398.

Ejemplo 112

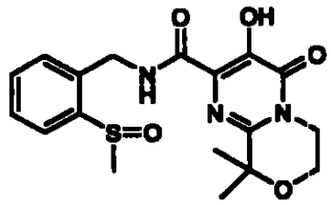


Pirimido[2,1-c][1,4]oxazin-2-carboxamida,4,6,7,9-tetrahidro-3-hidroxi-9,9-dimetil-N-[[2-(metiltio)fenil)metil]-4-oxo-. Se preparó de conformidad con

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el método descrito por la síntesis del ejemplo 100. Sólido blanco, ^{1}H RMN (300 MHz, $CDCl_3$) δ ppm: 1.55 (6H, s), 2.50 (3H, s), 3.98 (4H, s), 4.65 (2H, d, J=6.6 Hz), 7.1-7.4 (3H, m), 8.11 (1H, t, J=5.9 Hz), 11.94 (1H, s); CL/EM m/z 376 (M+H).

Ejemplo 113

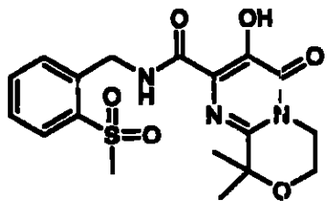


Pirimido[2,1-c][1,4]oxazin-2-carboxamida, 4,6,7,9-tetrahidro-3-hidroxi-9,9-dimetil-N-[[2-(metilsulfinil)fenil]metil]-4-oxo-. A una solución del ejemplo 112, el pirimido[2,1-c][1,4]oxazin-2-carboxamida, 4,6,7,9-tetrahidro-3-hidroxi-9,9-dimetil-N-[[2-(metiltio)fenil]metil]-4-oxo-, (112 mg, 0.3 mmol) en CH_2Cl_2 (5 mL) se agregó ácido 3-cloroperoxibenzoico (69 mg, 0.3 mmol; 77%, Aldrich) y la mezcla se agitó durante 5 minutos. Después de remover el solvente in vacuo, el residuo se purificó por CLAR preparativa de fase inversa (YMC, ODS, 8-15% de CH_3CN/H_2O-0.1% de CF_3CO_2H) para proporcionar 58 mg (0.16 mmol, Rendimiento 53%) del compuesto del título como un polvo blanco después de la trituración con éter de dietilo. ^{1}H RMN (300 MHz, $CDCl_3$) δ ppm: 1.56 (6H, s), 2.80 (3H, s), 3.98 (4H, s), 4.60-4.94 (2H, m), 7.38-7.61 (3H, m), 7.65-7.89 (1H, m), 8.34 (1H, t, J=6.4 Hz), 11.82 (1H, s). EMAR (ESI) calculado

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para $C_{18}H_{22}N_3O_5S$ (M+H) 392.1280, encontrado 392.1281.

Ejemplo 114



Pirimido[2,1-c][1,4]oxazin-2-carboxamida, 4,6,7,9-tetrahidro-3-hidroxi-9,9-dimetil-N-[[2-(metilsulfonil)fenil]metil]-4-oxo-. A una solución del ejemplo 112, pirimido[2,1-c][1,4]oxazin-2-carboxamida,4,6,7,9-tetrahidro-3-hidroxi-9,9-dimetil-N-[[2-(metiltio)fenil]metil]-4-oxo- (112 mg, 0.3 mmol) en CH_2Cl_2 (5 mL) se agregó ácido 3-cloroperoxibenzoico (140 mg, 0.62 mmol; 77%, Aldrich) y la mezcla se agitó durante 20 horas.

Después de remover el solvente in vacuo, el residuo se purificó por CLAR preparativa de fase inversa (YMC, ODS, 15% CH_3CN/H_2O-0.1% CF_3CO_2H) para proporcionar 61 mg (0.15 mmol, Rendimiento 50%) del compuesto del título como un polvo blanco después de la trituración con éter de dietilo.

^1H RMN (300 MHz, $CDCl_3$) δ ppm: 1.56 (6H, s), 3.14 (3H, s), 3.96 (4H, s), 4.83 (2H, d, J=7.0 Hz), 7.39-7.57 (1H, m), 7.60-7.68 (2H, m), 8.02 (1H, d, J=8.4 Hz), 8.65 (1H, t, J=7.0 Hz), 11.78 (1H, brs). EMAR (ESI) calculado para $C_{18}H_{22}N_3O_6S$ (M+H) 408.1229,

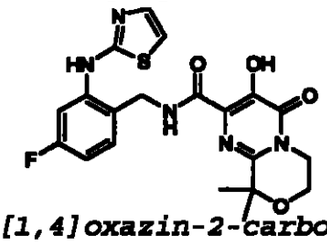
679

encontrado 408.1217.

Ejemplos 115-116

Los Ejemplos 115-116 pueden prepararse a partir de los intermediarios indicados por hidrogenólisis o hidrólisis mediada por ácido trifluoroacético.

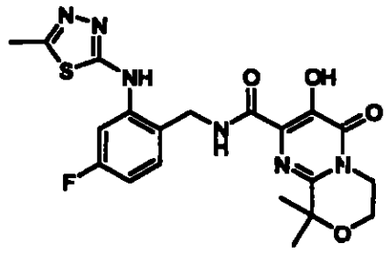
Ejemplo 115



Pirimido[2,1-c][1,4]oxazin-2-carboxamida, N-[[4-fluoro-2-(2-tiazolilamino)fenil]metil]-4,6,7,9-tetrahidro-3-hidroxi-9,9-dimetil-4-oxo-. El compuesto del título puede prepararse a partir del intermediario 163, N-(4-fluoro-2-(tiazol-2-ilamino)bencil)-3-(benciloxi)-9,9-dimetil-4-oxo-4,6,7,9-tetrahidropirimido(2,1-c)[1,4]oxazin-2-carboxamida. ^{1}H RMN (400 MHz, DMSO-d_6) δ ppm: 11.97 (1H, brs), 9.72 (1H, brs), 9.39 (1H, t, J = 6.3 Hz), 8.14 (1H, dd, J = 2.5, 12.0 Hz), 7.31-7.28 (2H, m), 6.99 (1H, d, J = 3.8 Hz), 6.84 (1H, ddd(dt), J = 2.5, 8.3 Hz), 4.52 (2H, d, J = 6.3 Hz), 3.96-3.94 (2H, m), 3.82-3.79 (2H, m), 1.54 (6H, s) CLEM ($^+$ESI, M+H$^+$) m/z 446. EMAR (ESI$^+$) calculado para $C_{20}H_{21}FN_5O_4S$ [M+H$^+$]: 446.1298; encontrado: 446.1292.

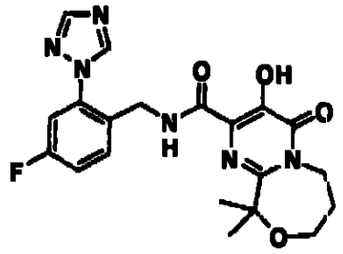
680

Ejemplo 116



Pirimido[2,1-c][1,4]oxazin-2-carboxamida, N-[[4-fluoro-2-[(5-metil-1,3,4-tiadiazol-2-il)amino]fenil]metil]-4,6,7,9-tetrahidro-3-hidroxi-9,9-dimetil-4-oxo-. El compuesto del título puede prepararse a partir del intermediario 164, N-(4-fluoro-2-(5-metil-1,3,4-tiadiazol-2-ilamino)bencil)-3-(benciloxi)-9,9-dimetil-4-oxo-4,6,7,9-tetrahidropirimido[2,1-c](1,4)oxazin-2-carboxamida. ^{1}H RMN (400 DMSO-d6) δ ppm: 11.97 (1H, brs), 9.66 (1H, brs), 9.37 (1H, brt, J=6.1 Hz), 7.99 (1H, brd), 7.29 (1H, brt, J=7.1 Hz), 6.88 (1H, ddd(dt), J=2.5, 8.0 Hz), 4.52 (2H, d, J=6.1 Hz), 3.97-3.94 (2H, m), 3.82-3.80 (2H, m), 2.55 (3H, s), 1.54 (6H, s); CLEM ($^+$ESI, M+H$^+$) m/z 461. EMAR (ESI$^+$) calculado para $C_{20}H_{22}FN_6O_4S$ [M+H$^+$]: 461.1407; encontrado 461.1425.

Ejemplo 117



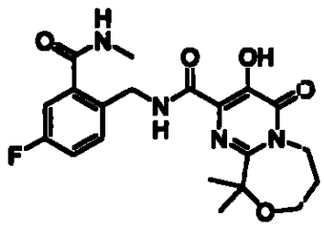
6H-Pirimido[2,1-c][1,4]oxazepin-2-carboxamida, N-[[4-

fluoro-2-(1H-1,2,4-triazol-1-il)fenil]metil]-4,7,8,10-tetrahidro-3-hidroxi-10,10-dimetil-4-oxo-. Una solución del intermediario 33, 2-(2-(3-cloropropoxi)propan-2-il)-5-hidroxi)-6-oxo-1,6-dihidropirimidin-4-carboxilato, (0.208 g, 0.65 mmol) en dimetilformamida anhidra (2 mL) se agitó con carbonato de potasio anhidro (0.366 g, 2.6 mmol) a 60°C durante 16 horas. Esto se trató con el intermediario 69, clorohidrato de (4-fluoro-2-(1H-1,2,4-triazol-1-il)fenil)metanamina, (0.451 g, 2.08 mmol) y trietilamina (0.5 mL, 3.6 mmol) y se continuó agitando a 100°C durante 16 horas. El solvente se removió por evaporador rotatorio y se purificó por CLAR de fase inversa preparativa (C18, 10%-35% CH_3CN/H_2O-0.1% ácido trifluoroacético). Las fracciones que contienen el producto se agruparon y concentraron por evaporador rotatorio. La solución acuosa resultante se extrajo con acetato de etilo (2 x 50 mL), y las fracciones orgánicas combinadas se secaron (sulfato de sodio), filtraron, y concentraron hasta secarse. El residuo resultante se trituró con un volumen mínimo de 95% de etanol, y el sólido se colectó por filtración para dar 103 mg (0.24 mmol, Rendimiento 37%) del compuesto del título como un sólido blanco: ^1H RMN (500 MHz, $CDCl_3$) δ ppm: 11.96 (1H, t, J=6.6 Hz), 8.46 (1H, s), 8.17 (1H, s), 7.71 (1H, dd, J=8.5, 6.1 Hz), 7.21 (1H, dt, J=8.2, 2.6 Hz), 7.11 (1H, dd, J=8.4, 2.6 Hz), 4.55 (2H, br), 4.44 (2H, d, J=6.7 Hz), 3.67 (2H, t,

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J=6.4 Hz), 1.91-1.97 (2H, p J=6.10 Hz), 1.63 (6H, s). ^{13}C RMN (125.76 MHz, $CDCl_3$) δ ppm: 167.97, 163.19, 161.20, 158.28, 153.35, 152.90, 147.34, 143.94, 136.89, 134.45, 134.37, 128.65, 128.62, 125.01, 117.09, 116.93, 112.42, 112.23, 82.46, 60.88, 39.13, 38.56, 27.73, 27.36. EMAR $[M+H]^+$ calculado para $C_{20}H_{22}N_6O_4F$: 429.16867; encontrado: 429.1687. Análisis calculado para $C_{20}H_{21}N_6O_4F \cdot 0.06\ H_2O$: C, 55.93; H, 4.96; N, 19.57, F, 4.42; encontrado: C, 55.80; H, 5.14; N, 19.74, F, 4.46.

Ejemplo 118

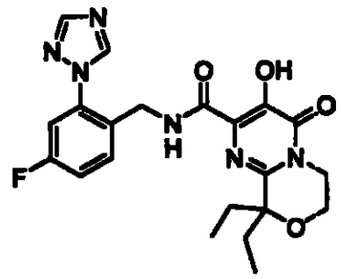


6H-Pirimido[2,1-c][1,4]oxazepin-2-carboxamida, N-[[4-fluoro-2-[(metilamino)carbonil]fenil]metil]-4,7,8,10-tetrahidro-3-hidroxi-10,10-dimetil-4-oxo-. El compuesto del título puede prepararse a partir del intermediario 148, N-(4-fluoro-2-(metilcarbamoil)bencil)-3-(benciloxi)-10,10-dimetil-4-oxo-6,7,8,10-tetrahidro-4H-pirimido[2,1-c][1,4]oxazepin-2-carboxamida de conformidad con el método descrito por el ejemplo 46. Polvo blanco; ^1H RMN (500 MHz, DMSO-D6) δ ppm: 12.17 (1H, s), 9.23 (1H, t, J=6.4 Hz), 8.56 (1H, q, J=4.3 Hz), 7.41 (1H, dd, J=8.6, 5.8 Hz), 7.34 (1H, dd, J=9.2, 2.8 Hz), 7.30 (1H, dt, J=8.6, 2.8 Hz), 4.55 (2H, d, J=6.4 Hz),

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4.37 (2H, br), 3.64 (2H, t, J=6.4 Hz), 2.80 (3H, d, J=4.6 Hz), 1.80-1.86 (2H, m), 1.57 (6H, s); EMAR $[M+H]^+$ calculado para $C_{20}H_{23}N_4O_5F$: 419.17308; encontrado: 419.1713.

Ejemplo 119

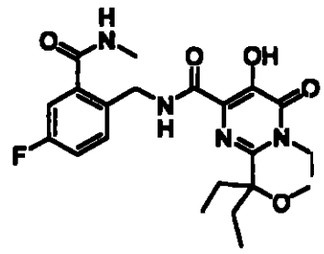


Pirimido[2,1-c][1,4]oxazin-2-carboxamida, 9,9-dietil-N-[[4-fluoro-2-(1H-1,2,4-triazol-1-il)fenil]metil]-4,6,7,9-tetrahidro-3-hidroxi-4-oxo-. El compuesto del título puede prepararse a partir del intermediario 31, 9,9-dietil-3-hidroxi-4-oxo-4,6,7,9-tetrahidropirimido[2,1-c][1,4]oxazin-2-carboxilato de etilo, y el intermediario 69, clorohidrato (4-fluoro-2-(1H-1,2,4-triazol-1-il)fenil)metanamina, de conformidad con los métodos descritos para los ejemplos 1, 19 y 20. Polvo blanco; ^{1}H RMN (500 MHz, $CDCl_3$) δ ppm: 11.89 (1H, br s), 8.81 (1H, t, J=6.6 Hz), 8.46 (1H, s), 8.15 (1H, s), 7.69 (1H, dd, J=8.6, 5.8 Hz), 7.22 (1H, dt, J=8.2, 2.6 Hz), 7.12 (1H, dd, J=8.4, 2.6 Hz), 4.45 (2H, d, J=6.7 Hz), 3.95-4.02 (4H, m), 1.95-2.03 (2H, m), 1.87-1.96 (2H, m), 0.86 (6H, t, J=7.5 Hz). ^{13}C RMN (125.76 MHz, $CDCl_3$) δ ppm: 167.98, 163.19, 161.20, 157.88, 152.81, 151.29, 146.05, 143.97, 137.00, 136.93, 134.28, 134.21, 128.62, 128.59, 125.85,

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117.10, 116.94, 112.58, 112.38, 80.93, 58.63, 43.02, 39.20, 31.43, 7.86. EMAR $[M+H]^+$ calculado para $C_{21}H_{24}N_6O_4F$: 443.18432; encontrado: 443.1845.

Ejemplo 120



Pirimido[2,1-c][1,4]oxazin-2-carboxamida, 9,9-dietil-N-[[4-fluoro-2-[(metilamino)carbonil]fenil]metil]-4,6,7,9-tetrahidro-3-hidroxi-4-oxo-. Una solución del intermediario 31, 9,9-dietil-3-hidroxi-4-oxo-4,6,7,9-tetrahidropirimido[2,1-c][1,4]oxazin-2-carboxilato de etilo, (0.228 g, 0.77 mmol) en dimetilformamida anhidra (5 mL) se trató con carbonato de potasio anhidro (0.279 g, 2.0 mmol) seguido por bromuro de bencilo (0.145 g, 0.85 mmol), y la mezcla se agitó durante 16 horas. La mezcla se trató con hidróxido de litio (0.042 g, 1.75 mmol) y agua (2 mL) y se agitó durante 20 horas. La mezcla de reacción se diluyó con agua (30 mL) y se llevó hasta un pH 1 con ácido clorhídrico 6 N. El producto crudo se extrajo con acetato de etilo (2 x 30 mL). Las capas orgánicas combinadas se secaron (sulfato de sodio), se filtraron, y se concentraron hasta secarse.

Una solución de este material, en dimetilformamida anhidra (4 mL), se trató con HATU (0.32 g, 0.83 mmol) y se

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agitó durante 10 minutos. La mezcla de reacción se trató con intermediario 39, sal del ácido trifluoroacético 2-aminometil-5-fluoro-N-metil-benzamida, (0.281 g, 0.94 mmol), seguido por dimetilaminopiridina, DMAP, (0.140 g, 1.125 mmol), y se agitó a 60°C durante 3 horas. El solvente se removió por evaporador rotatorio y el residuo se purificó por cromatografía de columna instantánea, eluyendo con 50% hasta 60% acetato de etilo en hexanos. Las fracciones que contienen el producto se agruparon y se concentraron hasta secarse, lo cual dio un sólido vidrioso blanco. Una muestra (aproximadamente 10 mg) se secó además bajo vacío, y el resto se usó en la siguiente reacción: ^{1}H RMN (500 MHz, $CDCl_3$) δ ppm: 8.47 (1H, t, J=6.2 Hz), 7.36-7.45 (3H, m), 7.23-7.27 (2H, m), 7.10 (1H, dd, J=8.8, 2.9 Hz), 7.04 (1H, dt, J=8.3, 2.7 Hz), 6.60-6.69 (1H, br), 5.25 (2H, s), 4.50 (2H, d, J=6.2 Hz), 3.94 (4H, s), 2.95 (3H, d, J=5.1 Hz), 1.90-2.02 (5H, m), 0.75-0.82 (6H, m).

Una solución del compuesto anterior en diclorometano (5 mL) y ácido trifluoroacético (5 mL) se agitó durante 2 horas. El solvente se removió y el producto crudo se purificó por CLAR preparativa de fase inversa (columna C-18, 10% hasta 40% CH_3CN/H_2O-0.1% CF_3CO_2H). Las fracciones que contienen el producto se agruparon y se concentraron in vacuo. La suspensión acuosa resultante se extrajo con diclorometano (4 x 100 mL), y los extractos orgánicos combinados, se secaron

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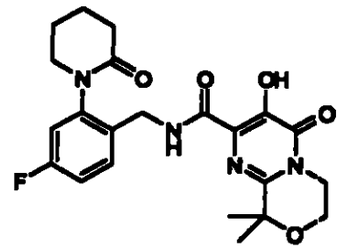
(sulfato de sodio), se filtraron, y se concentraron hasta secarse. El residuo se recristalizó etanol/H_2O para proporcionar 0.012 g (0.028 mmol, Rendimiento 4%) del compuesto del título como un sólido blanco. ^1H RMN (500 MHz, DMSO-D6) δ ppm: 12.10 (1H, s), 9.30 (1H, t, J=6.4 Hz), 8.52 (1H, m), 7.39 (1H, dd, J=8.4, 5.7 Hz), 7.26-7.35 (2H, m), 4.57 (2H, d, J=6.4 Hz), 3.94 (2H, t, J=4.9 Hz), 3.84 (2H, t, J=4.9 Hz), 2.79 (3H, d, J=4.6 Hz), 1.99-2.09 (2H, m), 1.81-1.91 (2H, m), 0.77 (6H, t, J=7.3 Hz). ^{13}C RMN (125.76 MHz, DMSO-D6) δ ppm: 167.86, 167.57, 159.65, 156.86, 151.21, 145.10, 137.26, 137.21, 132.52, 130.75, 130.68, 125.39, 116.69, 116.52, 114.71, 114.53, 80.04, 57.60, 42.62, 40.05, 30.04, 26.03, 7.47. EMAR $[M+H]^+$ calculado para $C_{21}H_{26}N_4O_5F$: 433.18873; encontrado: 433.1872.

Ejemplos 121-130

Los Ejemplos 121-130 pueden prepararse a partir de los intermediarios indicados de conformidad con los métodos descritos para los ejemplos 121 y 122. Alternativamente, los ejemplos pueden formarse por tratamiento de los intermediarios indicados con ácido trifluoroacético.

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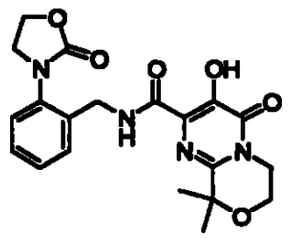
Ejemplo 121



Pirimido[2,1-c][1,4]oxazin-2-carbcxamida, N-[[4-fluoro-2-(2-oxo-1-piperidinil)fenil]metil]-4,6,7,9-tetrahidro-3-hidroxi-9,9-dimetil-4-oxo-. Al intermediario 145, N-(4-fluoro-2-(2-oxopiperidin-1-il)bencil)-3-(benciloxi)-9,9-dimetil-4-oxo-4,6,7,9-tetrahidropirimido[2,1-c][1,4]oxazin-4(9H)-ona, (100 mg, 0.187 mmol) en acetato de etilo (10 mL) se agregó paladio (10% en carbón vegetal) (30 mg). La mezcla de reacción se agitó a 23°C bajo una atmósfera de hidrógeno (globo) durante 3 horas. El catalizador se removió por filtración en Celite. El filtrado se concentró in vacuo y el residuo resultante se trituró con éter de dietilo (10 ml) y se secó in vacuo para proporcionar 37 mg (45% de rendimiento) del compuesto del título. IR (KBr, cm^{-1}) 3397, 2943, 1636, 1539, 1173. ^{1}HRMN 400 MHz (MeOD) δ ppm: 7.51 (1H, dd, (t), J =7.0 Hz), 7.11 (2H, m), 4.70 (1H, d, J = 15.3 Hz), 4.24 (1H, d, J =15.3 Hz), 4.05 (2H, m), 3.96 (2H, m,), 3.73 (1H, m), 3.62 (1H, m), 2.63-2.48 (2H, m), 2.03 (4H, amplio s), 1.62 (6H, s). CLEM $(M+H)^+$ m/z 445.

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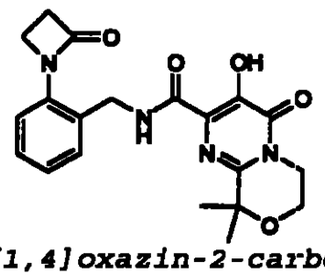
Ejemplo 122



Pirimido[2,1-c][1,4]oxazin-2-carbcxamida,4,6,7,9-tetrahidro-3-hidroxi-9,9-dimetil-4-oxo-N-[[2-(2-oxo-3-oxazolidinil)fenil]metil]-. Al intermediario 161, N-(4-fluoro-2-(2-oxopiperidin-1-il)bencil)-3-(benciloxi)-9,9-dimetil-4-oxo-4,6,7,9-tetrahidropirimido[2,1-c][1,4]oxazin-4(9H)-ona (100 mg, 0.187 mmol) en acetato de etilo (10 mL) se agregó paladio (10% en carbón vegetal) (30 mg) . La mezcla de reacción se agitó a 23°C bajo una atmósfera de hidrógeno (globo) durante 3 horas. El catalizador se removió por filtración en Celite. El filtrado se concentró in vacuo y el residuo resultante se trituró con éter de dietilo (10 ml) y se secó in vacuo para proporcionar 37 mg (45%) del compuesto del título. IR (KBr, cm-1) 3397, 2943, 1636, 1539, 1173. ^{1}HRMN 400 MHz (MeOD) δ ppm: 7.51 (1H, dd, (t), J =7.0 Hz), 7.11 (2H, m), 4.70 (1H, d, J = 15.3 Hz), 4.24 (1H, d, J =15.3 Hz), 4.05 (2H, m), 3.96 (2H, m,), 3.73 (1H, m), 3.62 (1H, m), 2.63-2.48 (2H, m), 2.03 (4H, amplio s), 1.62 (6H, s). CLEM $(M+H)^+$ m/z 445.

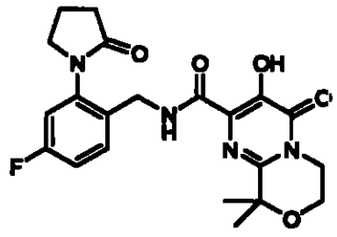
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Ejemplo 123



Pirimido[2,1-c][1,4]oxazin-2-carboxamida,4,6,7,9-tetrahidro-3-hidroxi-9,9-dimetil-4-oxo-N-[[2-(2-oxo-1-azetidinil)fenil]metil]-. El compuesto del título puede prepararse a partir del intermediario 162, N-(2-(2-oxoazetidin-1-il)bencil)-3-(benciloxi)-9,9-dimetil-4-oxo-4,6,7,9-tetrahidropirimido[2,1-c][1,4]oxazin-2-carboxamida. ^{1}H RMN (400 MHz, $CDCl_3$) δ ppm: 12.15 (1H, brs), 9.65 (1H, brs), 7.33-7.20 (4H, m), 4.54 (2H, d, J = 6.6 Hz), 3.96-3.94 (2H, m), 3.82-3.79 (2H, m), 3.76 (2H, t, J = 4.3 Hz), 3.10 (2H, t, J = 4.3 Hz), 1.53 (6H, s); CLEM ($^+$ESI, M+H$^+$) m/z 399.

Ejemplo 124

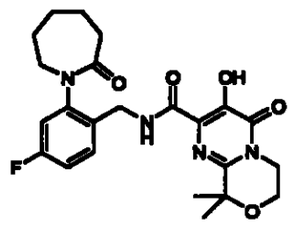


Pirimido[2,1-c][1,4]oxazin-2-carboxamida, N-[[4-fluoro-2-(2-oxo-1-pirrolidinil)fenil]metil]-4,6,7,9-tetrahidro-3-hidroxi-9,9-dimetil-4-oxo. El compuesto del título puede prepararse a partir del

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intermediario 159, N-(4-fluoro-2-(2-oxopirrolidin-1-il)bencil)-3-(benciloxi)-9,9-dimetil-4-oxo-4,6,7,9-tetrahidropirimido[2,1-c][1,4]oxazin-2-carboxamida. IR (KBr, cm^{-1}) 3432, 2980, 1689, 1543, 1183. ^{1}HRMN 400 MHz (MeoD) δ ppm: 7.53 (1H, dd, J = 9.2, 6.3 Hz), 7.11 (2H, m), 4.52 (2H, s), 4.05 (2H, t, J = 5.0 Hz), 3.96 (2H, m), 3.87 (2H, t, J = 7.1 Hz), 2.61 (2H, t, J = 8.0 Hz), 2.26 (2H, m), 1.6 (6H, s). EMAR (ESI$^+$) calculado para $C_{21}H_{24}FN_4O_5$ [M+H$^+$]: 431.1731; encontrado: 431.1714.

Ejemplo 125

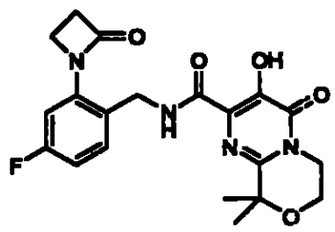


Pirimido[2,1-c][1,4]oxazin-2-carboxamida, N-[[4-fluoro-2-(hexahidro-2-oxo-1H-azepin-1-il)fenil]metil]-4,6,7,9-tetrahidro-3-hidroxi-9,9-dimetil-4-oxo-. El compuesto del título puede prepararse a partir del intermediario 160, N-(4-fluoro-2-(2-oxoazepan-1-il)bencil)-3-(benciloxi)-9,9-dimetil-4-oxo-4,6,7,9-tetrahidropirimido[2,1-c][1,4]oxazin-2-carboxamida. IR (KBr, cm^{-1}) 3392, 2934, 1646, 1522, 1292. ^{1}HRMN 400 MHz (MeOD) δ ppm: 7.50 (1H, amplio s), 7.06 (1H, amplio s), 7.01 (1H,

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d, J = 9.0 Hz), 4.64 (1H, d, J_{AB} = 15.0 Hz), 4.31 (1H, d, J_{AB} = 15 Hz), 4.04 (2H, m), 3.96 (3H, m), 3.66 (1H, m), 2.86 (1H, m), 2.65 (1H, m), 2.03-1.80 (6H, m), 1.62 (6H, s), (2H, m). CLEM $(M+H)^+$ m/z 459.

Ejemplo 126

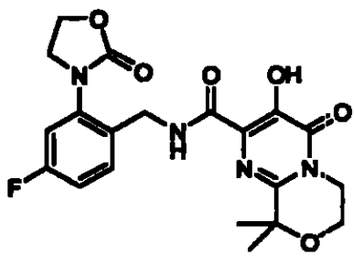


N-(4-Fluoro-2-(2-oxoazetidin-1-il)bencil)-3-hidroxi-9,9-dimetil-4-oxo-4,6,7,9-tetrahidropirimido[2,1-c][1,4]oxazin-2-carboxamida.

El compuesto del título puede prepararse a partir del intermediario 146, N-(4-flucro-2-(2-oxoazetidin-1-il)bencil)-3-(benciloxi)-9,9-dimetil-4-oxo-4,6,7,9-tetrahidropirimido[2,1-c][1,4]oxazin-2-carboxamida. ^{1}H RMN (400 MHz, DMSO-d_6) δ: 9.46 (d, J = 6.4 Hz), 7.34 (1H, dd, J = 8.5, 6.4 Hz), 7.25 (1H, dd, J = 10.2, 2.6 Hz), 7.08 (1H, td, J = 8.5, 2.6 Hz), 6.90 (1H, m), 4.52 (2H, d, J = 6.4 Hz), 3.96 (2H, t, J = 5.0 Hz), 3.83-3.77 (4H, m), 3.11 (2H, t, J = 5.0 Hz), 1.53 (6H, s); CLEM $(M+H)^+$ m/z 417.

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Ejemplo 127

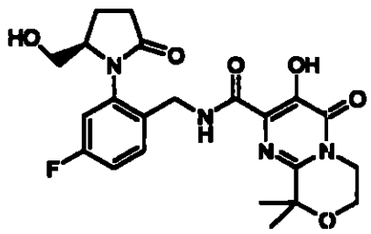


N-(4-Fluoro-2-(2-oxooxazolidin-3-il)bencil)-3-hidroxi-9,9-dimetil-4-oxo-4,6,7,9-tetrahidropirimido[2,1-c][1,4]oxazin-2-carboxamida.

El compuesto del título puede prepararse a partir del intermediario 165, N-(4-fluoro-2-(2-oxooxazolidin-3-il)bencil)-3-(benciloxi)-9,9-dimetil-4-oxo-4,6,7,9-tetrahidropirimido[2,1-c][1,4]oxazin-2-carboxamida.

1H RMN (400 MHz, DMSO-d_6) δ ppm: 12.12 (1H, s), 9.34 (1H, t, J = 6.2 Hz), 7.41 (1H, m), 7.23 (1H, td, J = 8.6, 2.5 Hz), 4.48 (4H, m), 4.06 (2H, t, J = 7.7 Hz), 3.97 (2H, t, J = 5.0 Hz), 3.83 (2H, t, J = 5.0 Hz), 1.55 (6H, s). CLEM $(M+H)^+$ m/z 433.

Ejemplo 128

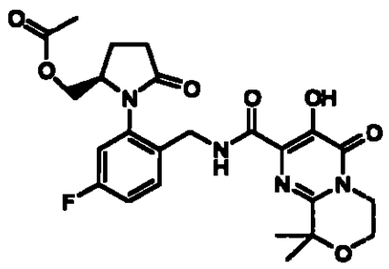


Pirimido[2,1-c][1,4]oxazin-2-carboxamida, N-[[4-fluoro-2-[(2R)-2-(hidroximetil)-5-oxo-1-pirrolidinil]fenil]metil]-4,6,7,9-tetrahidro-3-

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hidroxi-9,9-dimetil-4-oxo-. El compuesto del título puede prepararse a partir del intermediario 192, (R)-N-(4-fluoro-2-(2-(hidroximetil)-5-oxopirrolidin-1-il)bencil)-3-(benciloxi)-9,9-dimetil-4-oxo-4,6,7,9-tetrahidropirimido[2,1-c][1,4]oxazin-2-carboxamida. IR (KBr, cm^{-1}) 3441, 2979, 1684, 1540, 1172. ^{1}HRMN 400 MHz (MeOD) δ ppm: 7.56 (1H, m), 7.15 (2H, m), 4.86-4.31 (3H, m), 4.06 (2H, t, 5.0 Hz), 3.98 (2H, t, 5.0 Hz), 3.57 (2H, amplio s), 2.72-2.55 (2H, m), 2.41 (1H, m), 2.25 (1H, m), 1.62 (6H, s). CLEM $(M+H)^+$ m/z 461.

Ejemplo 129

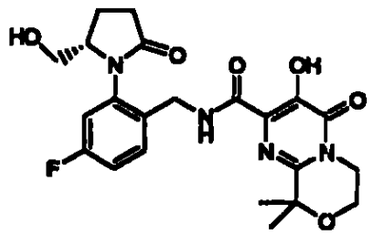


Pirimido[2,1-c][1,4]oxazin-2-carboxamida, N-[[2-[(2R)-2-[(acetiloxi)metil]-5-oxo-1-pirrolidinil]-4-fluorofenil]metil]-4,6,7,9-tetrahidro-3-hidroxi-9,9-dimetil-4-oxo-. El compuesto del título puede prepararse a partir del intermediario 193, acetato de (R)-(1-(2-((3-(benciloxi)-9,9-dimetil-4-oxo-4,6,7,9-tetrahidropirimido[2,1-c][1,4]oxazin-2-carboxamido)metil)-5-fluorofenil)-5-oxopirrolidin-2-

694

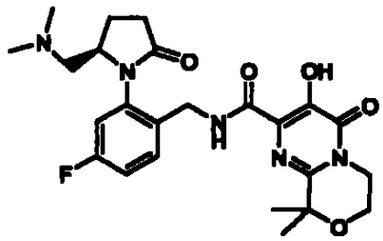
il)metilo. ^{1}HRMN 400 MHz (MeOD) δ ppm: 7.58 (1H, m), 7.21-7.04 (2H, m), 5.24 (2H, s), 4.66-4.21 (3H, m), 4.02-3.92 (5H, m), 2.73-2.34 (3H, m), 2.23-1.61 (5H, m), 1.60 (6H, s). CLEM $(M+H)^+$ m/z 503.

Ejemplo 130



Pirimido[2,1-c][1,4]oxazin-2-carboxamida, N-[[4-fluoro-2-[(2S)-2-(hidroximetil)-5-oxo-1-pirrolidinil]fenil]metil]-4,6,7,9-tetrahidro-3-hidroxi-9,9-dimetil-4-oxo-. El compuesto del título puede prepararse a partir del intermediario 167, (S)-N-(2-(2-((tert-butildimetilsililoxi)metil)-5-oxopirrolidin-1-il)-4-fluorobencil)-3-(benciloxi)-9,9-dimetil-4-oxo-4,6,7,9-tetrahidropirimido[2,1-c][1,4]oxazin-2-carboxamida. ^{1}HRMN 400 MHz (DMSO) δ ppm: 7.36 (1H, m), 7.18 (2H, m), 5.07 (1H, amplio s), 4.66-4.11 (3H, m), 3.95 (2H, t, 5.1 Hz), 3.80 (2H, t, 5.1 Hz), 3.39 (2H, s), 2.43 (1H, m), 2.25 (1H, m), 2.08 (1H, m), 1.51 (6H, s). CLEM $(M+H)^+$ m/z 451.

Ejemplo 131

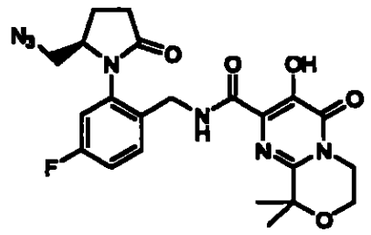


(R)-N-(2-(2-((Dimetilamino)metil)-5-oxopirrolidin-1-il)-

695

4-fluorobencil)-3-hidroxi-9,9-dimetil-4-oxo-4,6,7,9-tetrahidropirimido[2,1-c][1,4]oxazin-2-carboxamida. A una solución del intermediario 195, (R)-N-(2-(2-(azidometil)-5-oxopirrolidin-1-il)-4-fluorobencil)-3-(benciloxi)-9,9-dimetil-4-oxo-4,6,7,9-tetrahidropirimido[2,1-c][1,4]oxazin-2-carboxamida, (0.050 g, 0.087 mmol) en MeOH (5 mL) se agregó Paladio en carbón vegetal (10%) (0.020 g) y formaldehído (0.30 mL, 10 mmol). La mezcla de reacción se agitó a 23°C bajo H2 (globo) durante 5 horas. El paladio en carbón vegetal se removió entonces por filtración y el solvente se evaporó in vacuo. El residuo se purificó por CLAR preparativa (Empaque YMC C-18) para proporcionar el compuesto del título (0.013 g, 29% de rendimiento): ^{1}H RMN (400 MHz, MeOD) δ ppm: 7.56 (1H, dd, J = 7.0 Hz), 7.30-7.17 (2H, m), 4.70 (2H, m), 4.15 (1H, d, J = 15.3 Hz), 4.07 (2H, m.), 3.99 (2H, m,), 3.54 (1H, m), 2.93 (6H, s), 2.84-2.64 (4H, m), 2.20 (1H, m), 1.65 (6H, s). EMAR calculado para $C_{24}H_{31}N_5O_5F$: 488.2309; encontrado 488.2328.

Ejemplo 132

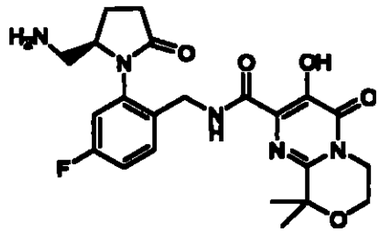


(R)-N-(2-(2-(Azidometil)-5-oxopirrolidin-1-il)-4-fluorobencil)-3-hidroxi-9,9-dimetil-4-oxo-4,6,7,9-

696

tetrahidropirimido[2,1-c][1,4]oxazin-2-carboxamida. A una solución del intermediario 195, (R)-N-(2-(2-(azidometil)-5-oxopirrolidin-1-il)-4-fluorobencil)-3-(benciloxi)-9,9-dimetil-4-oxo-4,6,7,9-tetrahidropirimido[2,1-c][1,4]oxazin-2-carboxamida, (0.030 g, 0.052 mmol) en CH_2Cl_2 (1 mL) se agregó CF_3CO_2H (1 mL) a 23°C. La mezcla de reacción se agitó a 23°C durante 3 horas. El tolueno (20 mL) se agregó entonces y los solventes se evaporaron in vacuo. El residuo se purificó por CLAR preparativa (Empaque YMC C-18) para proporcionar el compuesto del título (0.008 g, 31 %): ^{1}H RMN (400 MHz, MeOD) δ ppm: 7.55 (1H, dd, J = 6.6 Hz), 7.16 (2H, m), 4.47-4.24 (2H, m), 4.05 (2H, m), 3.98 (2H, m), 3.56 (2H, s), 2.70-2.45 (4H, m), 2.11 (1H, m), 1.64 (3H, s), 1.61 (3H, s). EMAR calculado para $C_{22}H_{25}N_7O_5F$: 486.1901; encontrado 486.1923.

Ejemplo 133



(R)-N-(2-(2-(Aminometil)-5-oxopirrolidin-1-il)-4-fluorobencil)-3-hidroxi-9,9-dimetil-4-oxo-4,6,7,9-tetrahidropirimido[2,1-c][1,4]oxazin-2-carboxamida. El compuesto del título puede prepararse por hidrogenólisis (H_2,10%Pd-C) del intermediario 195, (R)-N-(2-(2-(azidometil)-5-oxopirrolidin-1-il)-4-fluorobencil)-3-(benciloxi)-9,9-

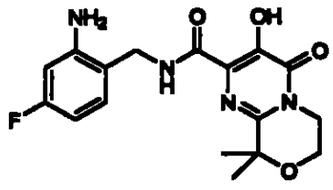
'697

dimetil-4-oxo-4,6,7,9-tetrahidropirimido[2,1-c][1,4]oxazin-2-carboxamida. ^{1}H RMN (400 MHz, MeOD) δ ppm: 7.54 (1H, dd, J = 7.0 Hz), 7.25-7.13 (2H, m), 4.62 (2H, m), 4.17 (1H, d, J =15.6 Hz), 4.07 (2H, m), 3.99 (2H, m,), 3.23 (2H, d, J = 3.1 Hz), 2.79-2.59 (3H, m), 2.14 (1H, m), 1.66 (6H, s). EMAR calculado para $C_{22}H_{27}N_5O_5F$: 460.1996; encontrado 460.2014.

Ejemplos 134-136

Los Ejemplos 134-136 pueden prepararse a partir de los intermediarios indicados por hidrogenólisis o hidrólisis mediada por ácido trifluoroacético.

Ejemplo 134

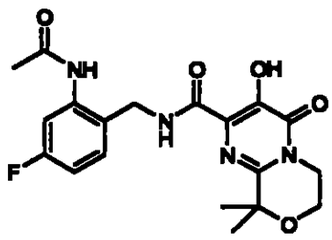


Pirimido[2,1-c][1,4]oxazin-2-carboxamida, N-[(2-amino-4-fluorofenil)metil]-4,6,7,9-tetrahidro-3-hidroxi-9,9-dimetil-4-oxo-. El compuesto del título puede prepararse a partir del intermediario 169, N-(2-amino-4-fluorobencil)-3-(benciloxi)-9,9-dimetil-4-oxo-4,6,7,9-tetrahidropirimido[2,1-c][1,4]oxazin-2-carboxamida. IR (KBr, cm^{-1}) 3383, 2979, 1636, 1540, 1288. ^{1}HRMN 400 MHz (MeOD) δ ppm: 7.14 (1H, dd, J = 7.3 Hz), 6.44-6-31 (2H, m), 4.69 (1H, amplio s), 4.48 (2H, amplio s), 4.03 (2H, t, J = 4.6 Hz), 3.95 (2H, t, J= 4.6 Hz), 1.62 (6H, s). EMAR (ESI$^+$) calculado para $C_{17}H_{20}FN_4O_4$ [M+H$^+$]:363.1469;

698

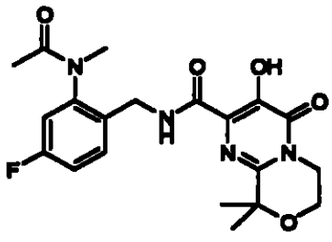
encontrado:363.1454.

Ejemplo 135



Pirimido[2,1-c][1,4]oxazin-2-carboxamida. *N-[[2-(acetilamino)-4-fluorofenil]metil]-4,6,7,9-tetrahidro-3-hidroxi-9,9-dimetil-4-oxo-*. El compuesto del título puede prepararse a partir del intermediario 189, N-(2-acetamido-4-fluorobencil)-3-(benciloxi)-9,9-dimetil-4-oxo-4,6,7,9-tetrahidropirimido[2,1-c][1,4]oxazin-2-carboxamida. ^{1}HRMN 400 MHz (MeOD) δ ppm: 7.66 (1H, amplio d, J = 10.5 Hz), 7.40 (1H, amplio t, 6.5 Hz), 6.87 (1H, amplio t, J = 6.5 Hz), 4.55 (2H, m), 4.02 (2H, t, J = 5.0 Hz), 3.92 (2H, t, J = 5.0 Hz), 2.28 (3H, s), 1.62 (6H, s). EMAR (ESI$^+$) calculado para $C_{19}H_{22}FN_4O_5$ [M+H$^+$]:405.1574; encontrado:405.1571.

Ejemplo 136

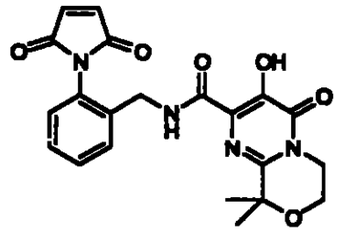


Pirimido[2,1-c][1,4]oxazin-2-carbcxamida, *N-[[2-(acetilmetilamino)-4-fluorofenil]metil]-4,6,7,9-tetrahidro-3-hidroxi-9,9-dimetil-4-oxo-*. El compuesto del título puede

699

prepararse a partir del intermediario 168, N-(4-fluoro-2-(N-metilacetamido)bencil)-3-(benciloxi)-9,9-dimetil-4-oxo-4,6,7,9-tetrahidropirimido[2,1-c][1,4]oxazin-2-carboxamida. IR (KBr, cm^{-1}) 3407, 2979, 1653, 1539, 1116. ^{1}HRMN 400 MHz (MeOD) δ ppm: 7.53 (1H, m), 7.24-7.06 (2H, m), 4.61-4.45 (2H, m), 4.08 (2H, t, J = 5.1 Hz), 4.00 (2H, t, J = 5.1 Hz), 3.40 (0.6H, s), 3.25 (2.4H, s), 1.85 (2.4H, s), 1.81 (0.6H, s), 1.65 (2.4H, s), 1.64 (2.4H, s), 1.62 (1.2H, s). CLEM $(M+H)^+$ m/z 419.

Ejemplo 137

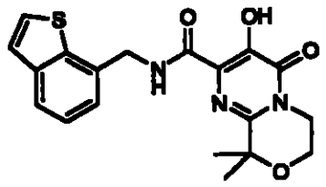


N-(2-(2,5-Dioxo-2H-pirrol-1(5H)-il)bencil)-3-hidroxi-9,9-dimetil-4-oxo-4,6,7,9-tetrahidropirimido[2,1-c][1,4]oxazin-2-carboxamida. A una solución del N-(2-aminobencil)-3-(benciloxi)-9,9-dimetil-4-oxo-4,6,7,9-tetrahidropirimido[2,1-c][1,4]oxazin-2-carboxamida (0 050 g, 0.114 mmol) en ácido acético (1.5 mL) se agregó anhídrido maleico (0.013 g, 0.131 mmol) y la mezcla de reacción se agitó en un tubo sellado a 115C durante 18 horas. El ácido acético se evaporó in vacuo y el residuo se purificó por CLAR preparativa (Empaque YMC C-18) para proporcionar el compuesto del título (0.013 g, 27% de rendimiento): ^{1}H RMN (400 MHz,

700

$CDCl_3$) δ ppm: 8.03 (1H, amplio t), 7.59 (1H, m), 7.48 (2H, m), 7.19 (1H, m), 6.92 (2H, s), 4.48 (2H, d, J = 6.1 Hz), 4.04 (4H, s), 1.62 (6H, s); EMAR calculado para $C_{21}H_{21}N_4O_6$: 425.1461; encontrado 425.1451.

Ejemplo 138

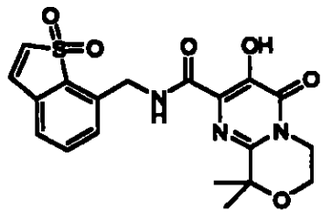


Pirimido[2,1-c][1,4]oxazin-2-carbcxamida, N-(benzo[b]tien-7-ilmetil)-4,6,7,9-tetrahidro-3-hidroxi-9,9-dimetil-4-oxo-. Al intermediario 147, N-(benzo[b]tiofen-7-ilmetil)-3-(benciloxi)-9,9-dimetil-4-oxo-4,6,7,9-tetrahidropirimido[2,1-c][1,4]oxazin-2-carboxamida, (60 mg, 0.13 mmol) se agregó CF_3CO_2H (2 mL) a 23°C.

La mezcla de reacción se agitó a 23°C durante 1.5 hora. El tolueno (20 mL) se agregó entonces y los solventes se evaporaron in vacuo. El residuo se purificó por CLAR preparativa (Empaque YMC C-18) para proporcionar el compuesto del título (0.017 g, 34% de rendimiento):

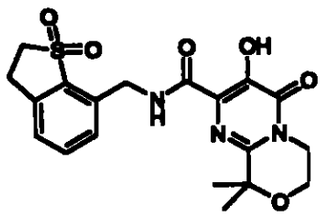
^1H RMN (400 MHz, $CDCl_3$) δ: 8.00 (1H, amplio t), 7.86 (1H, d, J = 8.0 Hz), 7.51-7.28 (3H, m), 4.93 (2H, d, J = 3.9 Hz), 4.05 (4H, s), 1.58 (6H, s). EMAR calculado para $C_{19}H_{20}N_3O_4S$: 386.1175; encontrado 386.1165.

Ejemplo 139



Pirimido[2,1-c][1,4]oxazin-2-carbcxamida, N-[(1,1-dioxidobenzo[b]tien-7-il)metil]-4,6,7,9-tetrahidro-3-hidroxi-9,9-dimetil-4-oxo-. Al intermediario 196, N-(benzo[b]tiofen-1,1-diona-7-ilmetil)-3-(benciloxi)-9,9-dimetil-4-oxo-4,6,7,9-tetrahidropirimido[2,1-c][1,4]cxazin-2-carboxamida, (0.080 g, 0.16 mmol), se le agregó CF_3CO_2H (2 mL) a 23°C. La mezcla de reacción se agitó a 23°C durante 2.5 horas. El tolueno (20 mL) se agregó entonces y los solventes se evaporaron in vacuo. El residuo se purificó por cristalización con MeOH (10 mL) para proporcionar el compuesto del título (0.037 g, 55% de rendimiento). ^1H RMN (400 MHz, DMSO-d_6) δ: 11.87 (1H, s), 9.44 (1H, t, J = 6.5 Hz), 7.65 (2H, m), 7.51 (1H, d, J = 7.0 Hz), 7.42-7.37 (2H, m), 4.84 (2H, d, J = 6.2 Hz), 3.99 (2H, t, 5.4 Hz), 3.85 (2H, t, J = 5.4 Hz), 1.59 (6H, s). EMAR calculado para $C_{19}H_{20}N_3O_6S$: 418.1073; encontrado 418.1078.

Ejemplo 140



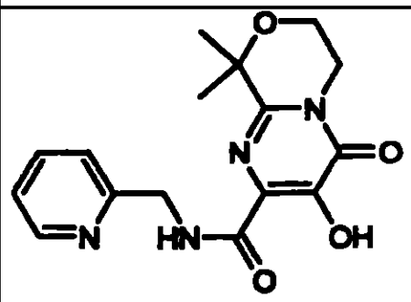
Pirimido[2,1-c][1,4]oxazin-2-carboxamida, N-[(2,3-dihidro-1,1-dioxidobenzo[b]tien-7-il)metil]-4,6,7,9-tetrahidro-3-hidroxi-9,9-dimetil-4-oxo-. El compuesto del título se obtiene del intermediario 196, N-(benzo[b]tiofen-1,1-diona-7-ilmetil)-3-(benciloxi)-9,9-dimetil-4-oxo-4,6,7,9-tetrahidropirimido[2,1-c][1,4]oxazin-2-carboxamida por reducción, paladio en carbón vegetal (10%) bajo H2. 1HRMN (400 MHz, CDCl3) δ: 8.65 (1H, s), 7.58-7.49 (2H, m), 7.32 (1H, d, J = 7.0 Hz), 4.86 (2H, d, J = 6.8 Hz), 3.99 (4H, s), 3.54 (2H, 1, J = 6.8 Hz), 3.40 (2H, 1, J = 6.8), 1.61 (6H, s). CLEM (M+H)+ m/z 420.

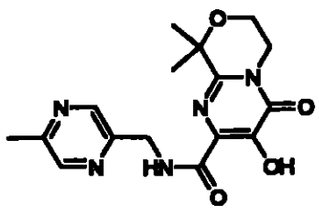
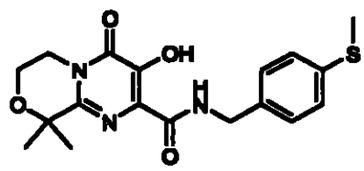
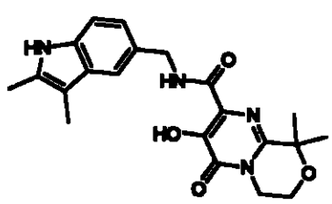
Ejemplos 141-145

Los Ejemplos 141-146, enlistados en la Tabla 9, pueden prepararse a partir del intermediario 25, 3-hidroxi-9,9-dimetil-4-oxo-4,6,7,9-tetrahidropirimido[2,1-c][1,4]oxazin-2-carboxilato de etilo, de conformidad con los métodos descritos para los ejemplos 1, 19, y 20. Los compuestos en la tabla se caracterizan por CLEM; (Xterra EM-C18, 4.6 X 50

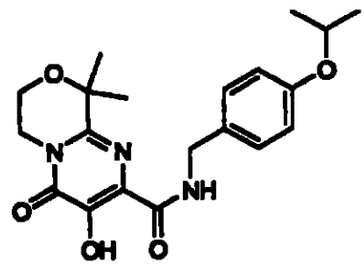
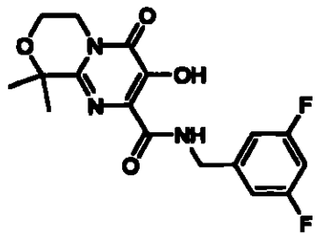
mm); eluyendo con 10% hasta 100% B, 4.5 min gradiente, (A = H_2O-0.1% CF_3CO_2H, B = CH_3CN-0.1% CF_3CO_2H); relación de flujo a 2.5 mL/min. Detección UV a 220 nm). Tiempo de retención del prcducto (TR, minutos) y peso molecular (EM [M+1]) resultantes se enlistan en la tabla.

Tabla 9

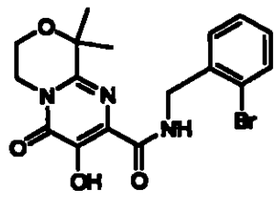
Ejemplo	Estructura	TR	EM
141	 *Pirimido[2,1-c][1,4]oxazin-2-carboxamida, 4,6,7,9-tetrahidro-3-hidroxi-9,9-dimetil-4-oxo-N-(2-piridinilmetil)-*	1.1	331.17

142	 *Pirimido[2,1-c][1,4]oxazin-2-carboxamida, 4,6,7,9-tetrahidro-3-hidroxi-9,9-dimetil-N-[(5-metilpirazinil)metil]-4-oxo-*	2.07	346.18
143	 *Pirimido[2,1-c][1,4]oxazin-2-carboxamida, 4,6,7,9-tetrahidro-3-hidroxi-9,9-dimetil-N-[[4-(metiltio)fenil]metil)-4-oxo-*	3.35	376.16
144	 *Pirimido[2,1-c][1,4]oxazin-2-carboxamida, 4,6,7,9-tetrahidro-3-hidroxi-9,9-dimetil-4-oxo-*	2.37	397

705

145	 *Pirimido[2,1-c][1,4]oxazin-2-carboxamida, 4,6,7,9-tetrahidro-3-hidroxi-9,9-dimetil-N-[[4-(1-metiletoxi)fenil]metil]-4-oxo-*	2.54	388.2
146	 *Pirimido[2,1-c][1,4]oxazin-2-carboxamida, N-[(3,5-difluorofenil)metil]-4,6,7,9-tetrahidro-3-hidroxi-9,9-dimetil-4-oxo-*	3.23	366.15

Ejemplo 147



Pirimido[2,1-c][1,4]oxazin-2-carboxamida, N-[(2-bromofenil)metil]-4,6,7,9-tetrahidro-3-hidroxi-9,9-dimetil-4-oxo-. El compuesto del título puede prepararse a partir del

706

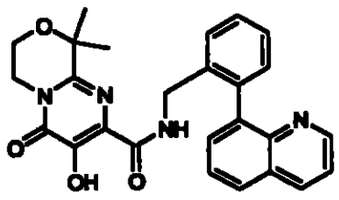
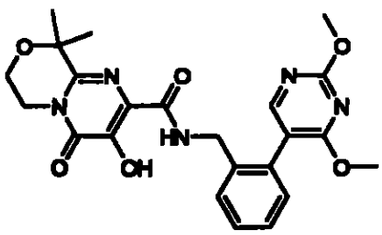
intermediario 25, 3-hidroxi-9,9-dimetil-4-oxo-4,6,7,9-tetrahidropirimido[2,1-c][1,4]oxazin-2-carboxilato de etilo, y 2-bromobencilamina de conformidad con los métodos descritos para los ejemplos 1, 19 y 20. ^{1}H RMN (300 MHz, DMSO-D6) δ ppm: 1.58 (s, 1),3.84 (1, 2), 3.98 (t, 2), 4.54 (d, 2), 7.25 (m, 2), 7.38 (m, 2), 7.64 (d, 1),9.43 (brm, 1), 12.01 (s, 1).

Ejemplos 148-200

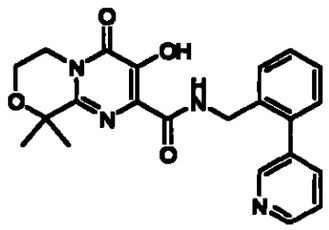
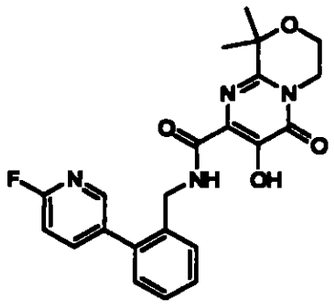
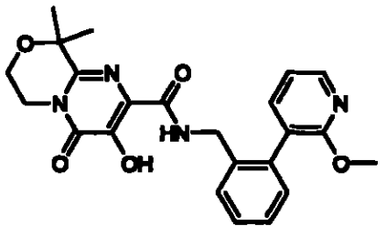
Los Ejemplos 148-200, enlistados en la Tabla 10, se sintetizaron de conformidad con el siguiente procedimiento. A un recipiente de reacción de microondas que contiene una barra de agitación, se le agregó $Pd(Ph_3P)_4$ (30 mg, 25 µmol), seguido por dioxano anhidro (0.5 mL). A esto se le agregó el ejemplo 147, pirimido[2,1-c][1,4]oxazin-2-carboxamida, N-[(2-bromofenil)metil]-4,6,7,9-tetrahidro-3-hidroxi-9,9-dimetil-4-oxo-, (50 µmol), ácido borónico o reactivo de éster de boronato (200 µmol), dioxano anhidro (0.5 mL) y solución de K_3PO_4 2M acuoso (0.25 mL). El recipiente de reacción se limpió con nitrógeno, se tapó y calentó a 120°C durante 10 minutos en un reactor de microondas. La mezcla de reacción se filtró a través de un filtro de jeringa Whatman 0.45 µm y el producto crudo se purificó usando CLAR preparativa (Xterra EM-C18, 30 X 50 mm); Eluyendo con 30% hasta 100% B, 8 min gradiente, (A = 10 mM NH_4OAC (ac.), B = CH_3CN); relación de flujo a 30 mL/min. Detección UV a 220 nm) para dar el compuesto del título.

Los compuestos en la tabla se caracterizan por CLEM; (Xterra EM-C18, 4.6 X 50 mm); eluyendo con 10% hasta 100% B, 4.5 min gradiente, (A = H_2O-0.1% CF_3CO_2H, B = CH_3CN-0.1% CF_3CO_2H); relación de flujo a 2.5 mL/min. Detección UV a 220 nm). Tiempo de retención del productc (TR, minutos) y peso molecular observados (EM [M+1]) resultantes se enlistan en la tabla.

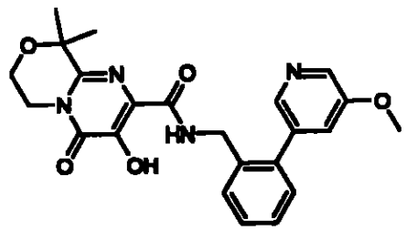
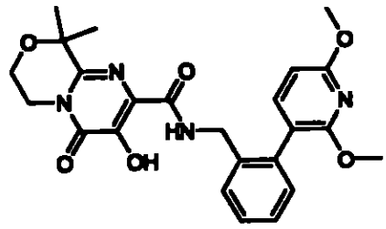
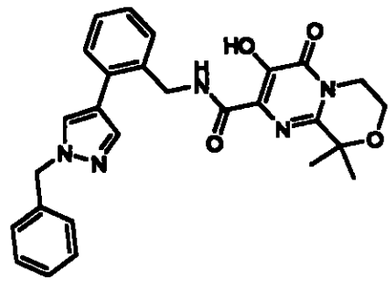
Tabla 10.

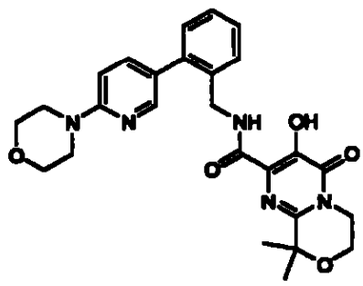
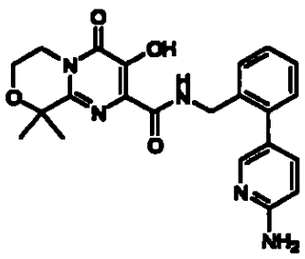
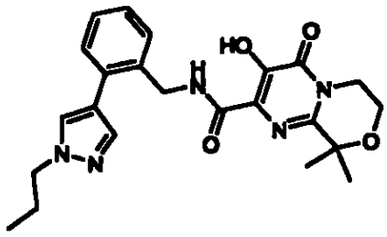
Ejemplo	Estructura	TR	EM
148	 *Pirimido[2,1-c][1,4]oxazin-2-carboxamida, 4,6,7,9-tetrahidro-3-hidroxi-9,9-dimetil-4-oxo-N-[[2-(8-quinolinil)fenil]metil]-*	2.08	457
149	 *Pirimido[2,1-c][1,4]oxazin-2-carboxamida, N-[[2-(2,4-dimetoxi-5-pirimidinil)fenil]metil]-4,6,7,9-tetrahidro-3-hidroxi-9,9-dimetil-4-oxo-*	1.91	467.95

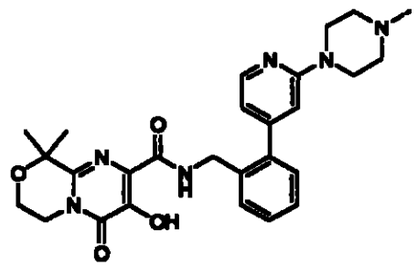
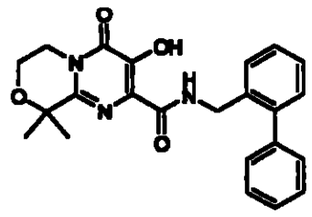
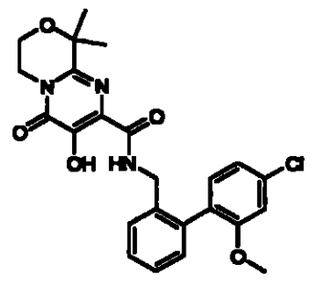
24 708

Ejemplo	Estructura	TR	EM
150	 *Pirimido[2,1-c][1,4]oxazin-2-carboxamida, 4,6,7,9-tetrahidro-3-hidroxi-9,9-dimetil-4-oxo-N-[[2-(3-piridinil)fenil]metil]-*	1.71	407
151	 *Pirimido[2,1-c][1,4]oxazin-2-carboxamida, 4,6,7,9-tetrahidro-3-hidroxi-9,9-dimetil-4-oxo-N-[[2-(3-piridinil)fenil]metil]-*	1.98	425.01
152	 *Pirimido[2,1-c][1,4]oxazin-2-carboxamida, 4,6,7,9-tetrahidro-3-hidroxi-N-[[2-(2-metoxi-3-piridinil)fenil]metil]-9,9-dimetil-4-oxo-*	2.04	437.04

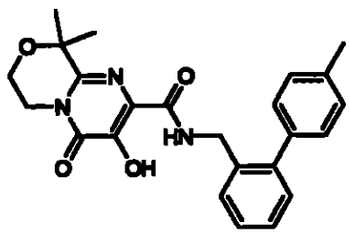
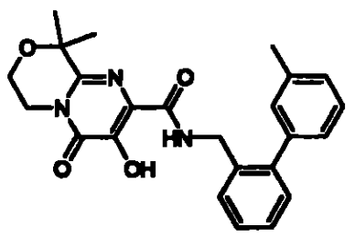
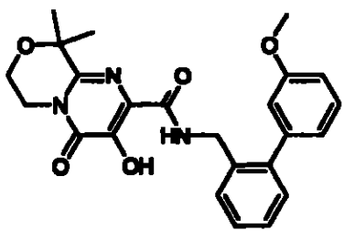
709

Ejemplo	Estructura	TR	EM
153	 Pirimido[2,1-c][1,4]oxazin-2-carboxamida, 4,6,7,9-tetrahidro-3-hidroxi-N-[[2-(5-metoxi-3-piridinil)fenil]metil]-9,9-dimetil-4-oxo-	2.1	436.97
154	 Pirimido[2,1-c][1,4]oxazin-2-carboxamida,N-[[2-(2,6-dimetoxi-3-pirdinil)fenil]metil]-4,6,7,9-tetrahidro-3-hidroxi-9,9-dimetil-4-oxo-	2.41	467.01
155	 Pirimido[2,1-c][1,4]oxazin-2-carboxamida, 4,6,7,9-tetrahidro-3-hidroxi-9,9-dimetil-4-oxo-N-[[2-[1-(fenilmetil)-1H-pirazol-4-il]fenil]metil]-	2.19	486.03

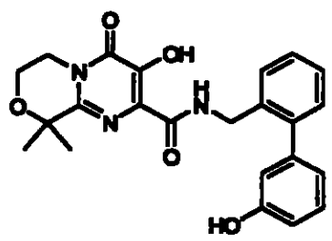
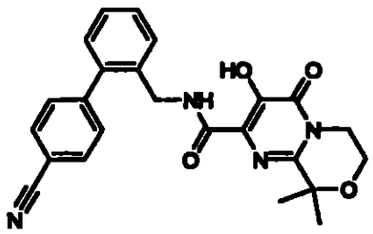
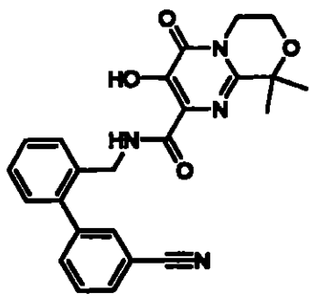
Ejemplo	Estructura	TR	EM
156	 *Pirimido[2,1-c][1,4]oxazin-2-carboxamida, 4,6,7,9-tetrahidro-3-hidroxi-9,9-dimetil-N-[[2-[6-(4-morfolinil)-3-piridinil]fenil]metil]-4-oxo-*	2	492.01
157	 *Pirimido[2,1-c][1,4]oxazin-2-carboxamida, N-[[2-(6-amino-3-piridinil)fenil]metil]-4,6,7,9-tetrahidro-3-hidroxi-9,9-dimetil-4-oxo-*	3.02	454.97
158	 *Pirimido[2,1-c][1,4]oxazin-2-carboxamida, 4,6,7,9-tetrahidro-3-hidroxi-9,9-dimetil-4-oxo-N-[[2-(1-propil-1H-pirazol-4-il)fenil]metil]-*	1.99	438.04

Ejemplo	Estructura	TR	EM
159	 *Pirimido[2,1-c][1,4]oxazin-2-carboxamida, 4,6,7,9-tetrahidro-3-hidroxi-9,9-dimetil-N-[[2-[2-(4-metil-1-piperazinil)-4-piridinil]fenil]metil]-4-oxo-*	1.66	505.05
160	 *Pirimido[2,1-c][1,4]oxazin-2-carboxamida, N-([1,1'-bifenil]-2-ilmetil)-4,6,7,9-tetrahidro-3-hidroxi-9,9-dimetil-4-oxo-*	3.2	406
161	 *Pirimido[2,1-c][1,4]oxazin-2-carboxamida, N-[(4'-cloro-2'-metoxi[1,1'-bifenil]-2-il)metil]-4,6,7,9-tetrahidro-3-hidroxi-9,9-dimetil-4-oxo-*	3.36	469.91

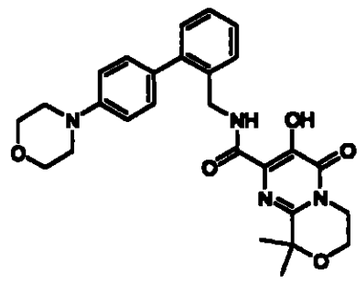
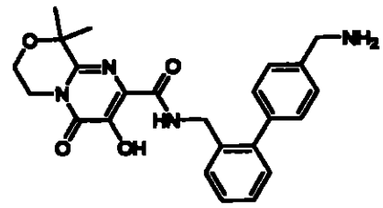
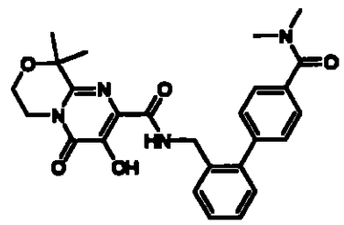
712

Ejemplo	Estructura	TR	EM
162	 *Pirimido[2,1-c][1,4]oxazin-2-carboxamida,4,6,7,9-tetrahidro-3-hidroxi-9,9-dimetil-N-[(4'-metil[1,1'-bifenil]-2-il)metil]-4-oxo-*	3.39	419.97
163	 *Pirimido[2,1-c][1,4]oxazin-2-carboxamida, 4,6,7,9-tetrahidro-3-hidroxi-9,9-dimetil-N-[(3'-metil[1,1'-bifenil]-2-il)metil]-4-oxo-*	3.36	419.97
164	 *Pirimido[2,1-c][1,4]oxazin-2-carboxamida, 4,6,7,9-tetrahidro-3-hidroxi-N-[(3'-metoxi[1,1'-bifenil]-2-il)metil]-9,9-dimetil-4-oxo-*	3.14	435.97

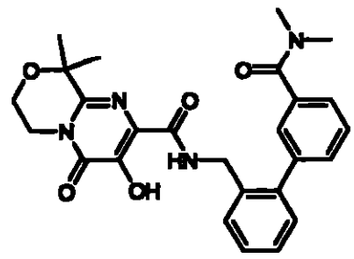
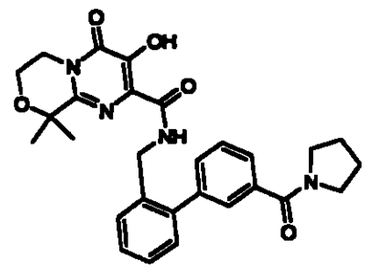
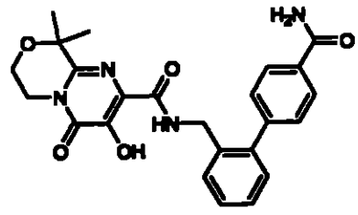
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Ejemplo	Estructura	TR	EM
165	 *Pirimido[2,1-c][1,4]oxazin-2-carboxamida, 4,6,7,9-tetrahidro-3-hidroxi-N-[(3'-hidroxi[1,1'-bifenil]-2-il)metil]-9,9-dimetil-4-oxo-*	2.65	421.99
166	 *Pirimido[2,1-c][1,4]oxazin-2-carboxamida, N-[(4'-ciano[1,1'-bifenil]-2-il)metil]-4,6,7,9-tetrahidro-3-hidroxi-9,9-dimetil-4-oxo-*	2.91	430.99
167	 *Pirimido[2,1-c][1,4]oxazin-2-carboxamida, N-[(3'-ciano[1,1'-bifenil]2-il)metil]-4,6,7,9-tetrahidro-3-hidroxi-9,9-dimetil-4-oxo-*	2.93	430.99

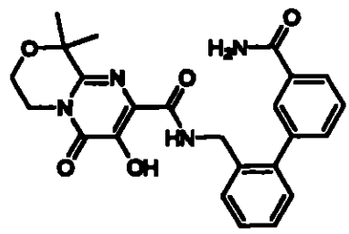
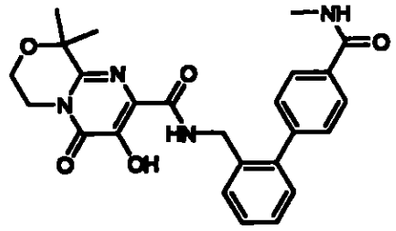
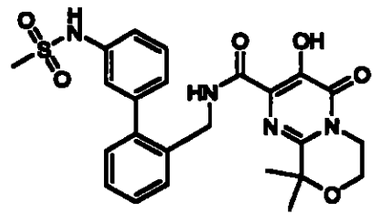
714

Ejemplo	Estructura	TR	EM
168	 *Pirimido[2,1-c][1,4]oxazin-2-carboxamida, 4,6,7,9-tetrahidro-3-hidroxi-9,9-dimetil-N-[[4'-(4-morfolinil)[1,1'-bifenil]-2-il]metil]-4-oxo-*	3.02	491
169	 *Pirimido[2,1-c][1,4]oxazin-2-carboxamida, 4,6,7,9-tetrahidro-3-hidroxi-9,9-dimetil-N-[[4'-(4-morfolinil)[1,1'-bifenil]-2-il]metil]-4-oxo-*	2.11	435.02
170	 *Pirimido[2,1-c][1,4]oxazin-2-carboxamida, N-[[4'-[(dimetilamino)carbonil][1,1'-bifenil]-2-il]metil]-4,6,7,9-tetrahidro-3-hidroxi-9,9-dimetil-4-oxo-*	2.54	476.96

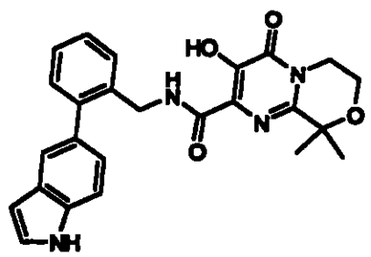
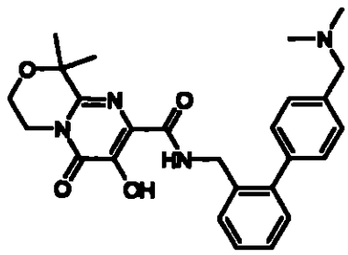
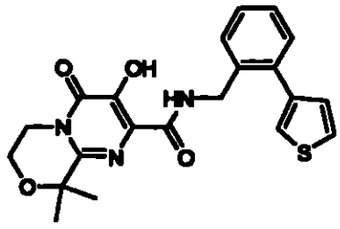
715

Ejemplo	Estructura	TR	EM
171	 *Pirimido[2,1-c][1,4]oxazin-2-carboxamida, N-[3'-[(dimetilamino)carbonil][1,1'-bifenil]-2-il]metil]-4,6,7,9-tetrahidro-3-hidroxi-9,9-dimetil-4-oxo-*	2.53	476.96
172	 *Pirimido[2,1-c][1,4]oxazin-2-carboxamida, 4,6,7,9-tetrahidro-3-hidroxi-9,9-dimetil-4-oxo-N-[[3'-(1-pirrolidinilcarbonil)[1,1'-bifenil]-2-il]metil]-*	2.66	502.97
173	 *Pirimido[2,1-c][1,4]oxazin-2-carboxamida, N-[[4'-(aminocarbonil)[1,1'-bifenil]-2-il]metil]-4,6,7,9-tetrahidro-3-hidroxi-9,9-dimetil-4-oxo-*	2.26	448.94

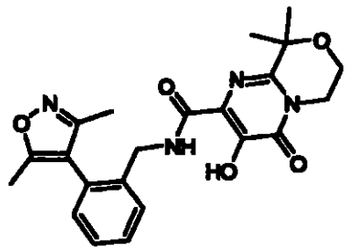
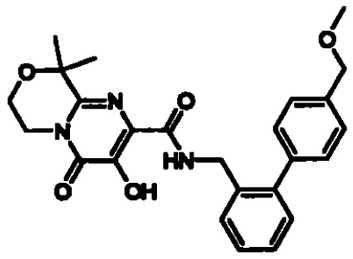
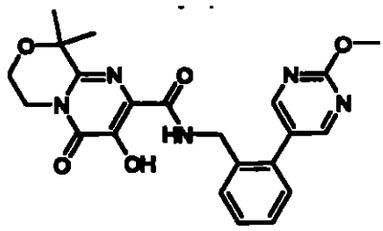
716

Ejemplo	*Estructura*	TR	EM
174	 *Pirimido[2,1-c][1,4]oxazin-2-carboxamida, N-[[3'-(aminocarbonil)[1,1'-bifenil]-2-il]metil]-4,6,7,9-tetrahidro-3-hidroxi-9,9-dimetil-4-oxo-*	2.27	448.94
175	 *Pirimido[2,1-c][1,4]oxazin-2-carboxamida, 4,6,7,9-tetrahidro-3-hidroxi-9,9-dimetil-N-[[4'-(metilamino)carbonil][1,1'-bifenil]-2-il]metil]-4-oxo-*	2.36	462.98
176	 *Pirimido[2,1-c][1,4]oxazin-2-carboxamida, 4,6,7,9-tetrahidro-3-hidroxi-9,9-dimetil-N-[[3'-[(metilsulfonil)amino][1,1'-bifenil]-2-il]metil]-4-oxo-*	2.63	498.94

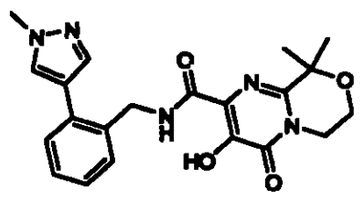
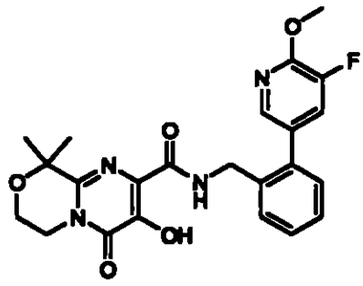
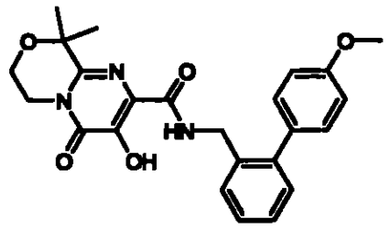
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Ejemplo	Estructura	TR	EM
177	 Pirimido[2,1-c][1,4]oxazin-2-carboxamida, 4,6,7,9-tetrahidro-3-hidroxi-N-[[2-(1H-indol-5-il)fenil]metil]-9,9-dimetil-4-oxo-	3	444.97
178	 Pirimido[2,1-c][1,4]oxazin-2-carboxamida, N-[[4'-[(dimetilamino)metil][1,1'-bifenil]-2-il]metil]-4,6,7,9-tetrahidro-3-hidroxi-9,9-dimetil-4-oxo-	2.56	462.98
179	 Pirimido[2,1-c][1,4]oxazin-2-carboxamida, 4,6,7,9-tetrahidro-3-hidroxi-9,9-dimetil-4-oxo-N-[[2-(3-tienil)fenil]metil]-	3.09	411.98

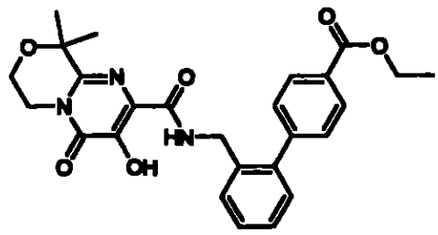
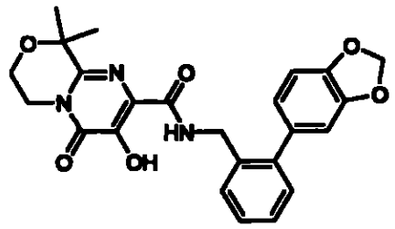
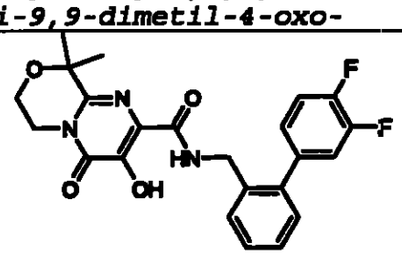
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Ejemplo	Estructura	TR	EM
180	 *Pirimido[2,1-c][1,4]oxazin-2-carboxamida, N-[[2-(3,5-dimetil-4-isoxazolil)fenil]metil]-4,6,7,9-tetrahidro-3-hidroxi-9,9-dimetil-4-oxo-*	2.66	425.01
181	 *Pirimido[2,1-c][1,4]oxazin-2-carboxamida, 4,6,7,9-tetrahidro-3-hidroxi-N-[[4'-(metoximetil)[1,1'-bifenil]-2-il]metil]-9,9-dimetil-4-oxo-*	3.08	450.01
182	 *Pirimido[2,1-c][1,4]oxazin-2-carboxamida, 4,6,7,9-tetrahidro-3-hidroxi-N-[[2-(2-metoxi-5-pirimidinil)fenil]metil]-9,9-dimetil-4-oxo-*	2.43	438

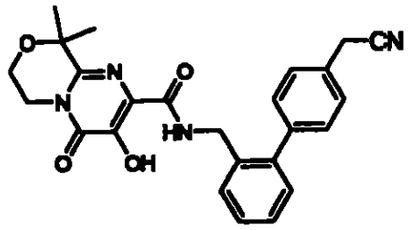
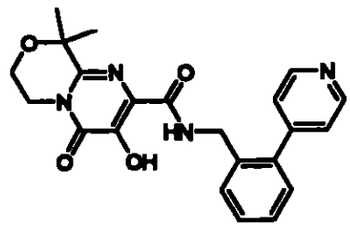
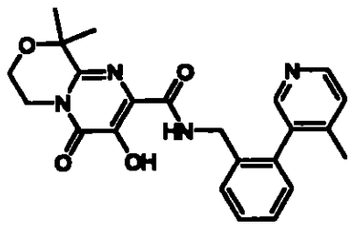
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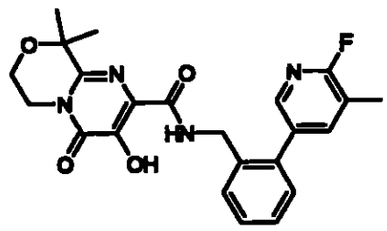
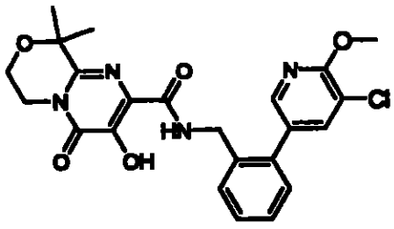
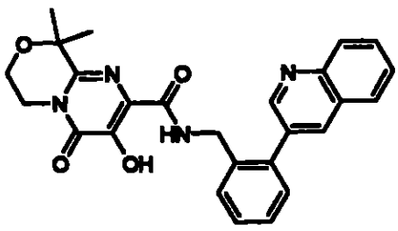
Ejemplo	Estructura	TR	EM
183	 *Pirimido[2,1-c][1,4]oxazin-2-carboxamida, 4,6,7,9-tetrahidro-3-hidroxi-9,9-dimetil-N-[[2-(1-(metil-1H-pirazol-4-il)fenil]metil]-4-oxo-*	1.71	410
184	 *Pirimido[2,1-c][1,4]oxazin-2-carboxamida, N-[[2-(5-fluoro-6-metoxi-3-piridinil)fenil]metil]-4,6,7,9-tetrahidro-3-hidroxi-9,9-dimetil-4-oxo-*	3.02	455
185	 *Pirimido[2,1-c][1,4]oxazin-2-carboxamida, 4,6,7,9-tetrahidro-3-hidroxi-N-[(4'-metoxi[1,1'-bifenil]-2-il)metil]-9,9-dimetil-4-oxo-*	3.14	436

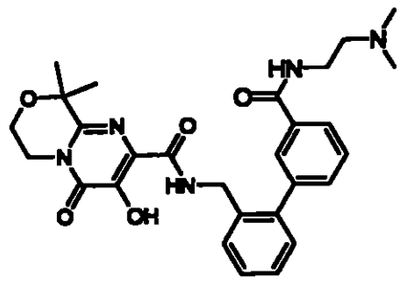
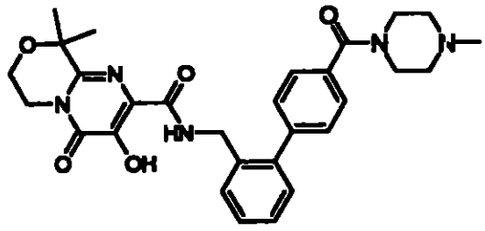
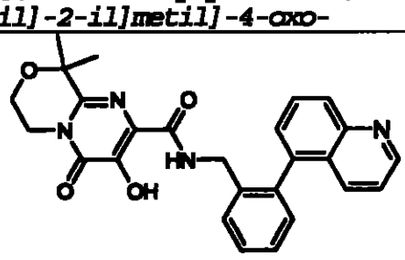
720

Ejemplo	*Estructura*	TR	EM
186	 *Éster de 2'-[[[(4,6,7,9-tetrahidro-3-hidroxi-9,9-dimetil-4-oxopirimido[2,1-c][1,4]oxazin-2-il)carbonil]amino]metil]-etilo del ácido [1,1'-Bifenil]-4-carboxílico*	3.30	478
187	 *Pirimido[2,1-c][1,4]oxazin-2-carboxamida, N-[[2-(1,3-benzodioxol-5-il)fenil]metil]-4,6,7,9-tetrahidro-3-hidroxi-9,9-dimetil-4-oxo-*	2.76	450.2
188	 *Pirimido[2,1-c][1,4]oxazin-2-carboxamida, N-[(3',4'-difluoro[1,1'-bifenil]-2-il)metil]-4,6,7,9-tetrahidro-3-hidroxi-9,9-dimetil-4-oxo-*	2.92	442.13

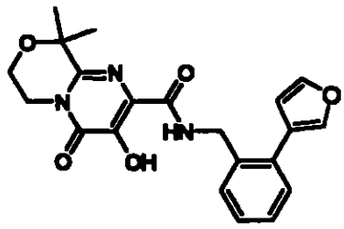
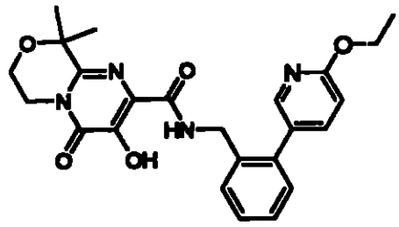
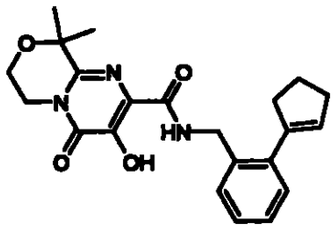
721

Ejemplo	Estructura	TR	EM
189	 *Pirimido[2,1-c][1,4]oxazin-2-carboxamida, N-[[4'-(cianometil)[1,1'-bifenil]-2-il)metil]-4,6,7,9-tetrahidro-3-hidroxi-9,9-dimetil-4-oxo-*	2.57	445.15
190	 *Pirimido[2,1-c][1,4]oxazin-2-carboxamida, 4,6,7,9-tetrahidro-3-hidroxi-9,9-dimetil-4-oxo-N-[[2-(4-piridinil)fenil]metil]-*	1.34	407.34
191	 *Pirimido[2,1-c][1,4]oxazin-2-carboxamida, 4,6,7,9-tetrahidro-3-hidroxi-9,9-dimetil-N-[[2-(4-metil-3-piridinil)fenil]metil]-4-oxo-*	1.40	421.2

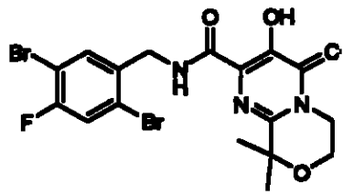
Ejemplo	Estructura	TR	EM
192	 *Pirimido[2,1-c][1,4]oxazin-2-carboxamida, N-[[2-(6-fluoro-5-metil-3-piridinil)fenil]metil]-4,6,7,9-tetrahidro-3-hidroxi-9,9-dimetil-4-oxo-*	2.57	439.36
193	 *Pirimido[2,1-c][1,4]oxazin-2-carboxamida, N-[[2-(5-cloro-6-metoxi-3-piridinil)fenil]metil]-4,6,7,9-tetrahidro-3-hidroxi-9,9-dimetil-4-oxo-*	2.84	471.13
194	 *Pirimido[2,1-c][1,4]oxazin-2-carboxamida, 4,6,7,9-tetrahidro-3-hidroxi-9,9-dimetil-4-oxo-N-[[2-(3-quinolinil)fenil]metil]-*	1.62	457.26

Ejemplo	Estructura	TR	EM
195	 *Pirimido[2,1-c][1,4]oxazin-2-carboxamida, N-[[3'-[[[2-(dimetilamino)etil]amino]carbonil][1,1'-bifenil]-2-il]metil]-4,6,7,9-tetrahidro-3-hidroxi-9,9-dimetil-4-oxo-*	1.57	520.31
196	 *Pirimido[2,1-c][1,4]oxazin-2-carboxamida, 4,6,7,9-tetrahidro-3-hidroxi-9,9-dimetil-N-[[4'-[(4-metil-1-piperazinil)carbonil][1,1'-bifenil]-2-il]metil]-4-oxo-*	1.57	532.41
197	 *Pirimido[2,1-c][1,4]oxazin-2-carboxamida, 4,6,7,9-tetrahidro-3-hidroxi-9,9-dimetil-4-oxo-N-[[2-(5-quinolinil)fenil]metil]-*	1.55	457.26

724

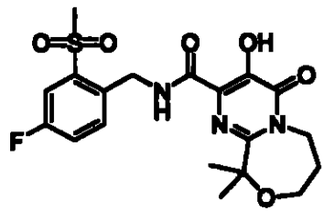
Ejemplo	Estructura	TR	EM
198	 *Pirimido[2,1-c][1,4]oxazin-2-carboxamida, N-[[2-(3-furanilo)fenil]metilo]-4,6,7,9-tetrahidro-3-hidroxi-9,9-dimetil-N-oxo-*	2.86	396.2
199	 *Pirimido[2,1-c][1,4]oxazin-2-carboxamida, N-[[2-(6-etoxi-3-piridinil)fenil]metil]-4,6,7,9-tetrahidro-3-hidroxi-9,9-dimetil-4-oxo-*	3.08	451.2
200	 *Pirimido[2,1-c][1,4]oxazin-2-carboxamida, N-[[2-(1-ciclopenten-1-il)fenil]metil]-4,6,7,9-tetrahidro-3-hidroxi-9,9-dimetil-4-oxo-*	3.33	396.34

Ejemplo 201



Pirimido[2,1-c][1,4]oxazin-2-carbcxamida, N-[(4-fluoro-2,5-dibromofenil)metil]-4,6,7,9-tetrahidro-3-hidroxi-9,9-dimetil-4-oxo. Una mezcla de (2,5-dibromo-4-fluorofenil)metanamina (1 mmol), intermediario 25 (0.268 g, 1 mmol) y trietilamina (0.5 mL, 3.5 mmol) en etanol/dimetilformamida (1:1, 3 mL) se calentó a 100°C durante 6 horas. Después del enfriamiento, la mezcla de reacción se purificó por CLAR preparativa para proporcionar el compuesto del título (0.31 g, 62% de rendimiento) como un sólido blanco opaco. ^{1}H RMN (500 MHz, $CDCl_3$) δ ppm: 11.72 (1H, s), 8.08 (1H, t, J = 6.1 Hz), 7.61 (1H, d, J = 7.0 Hz), 7.38 (1H, d, J = 7.6 Hz), 4.61 (2H, d, J = 6.4 Hz), 4.02 (4H, s), 1.59 (6H, s).

Ejemplo 202

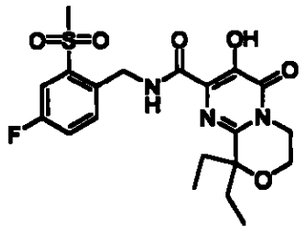


6H-Pirimido[2,1-c][1,4]oxazepin-2-carboxamida, N-[[4-fluoro-2-(metilsulfonil)fenil]metil]-4,7,8,10-tetrahidro-3-

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hidroxi-10,10-dimetil-4-oxo-. Sólido blanco opaco. ^{1}H RMN (500 MHz, $CDCl_3$) δ ppm: 11.77 (1H, br s), 8.55 (1H, t, .1=6.3 Hz), 7.75 (1H, dd, J=8.1, 2.6 Hz), 7.72 (1H, dd, J=8.5, 5.2 Hz), 7.34 (1H, td, J=8.0, 2.6 Hz), 4.81 (2H, d, J=6.7 Hz), 4.54 (2H, br), 3.65 (2H, t, J=6.1 Hz), 3.18 (3H, s), 1.93 (2H, m), 1.59 (6H, s); ^{13}C RMN (126 MHz, $CDCl_3$) δ ppm: 168.14, 163.14, 161.13, 158.23, 153.73, 147.26, 140.77, 140.72, 135.31, 135.25, 132.83, 132.80, 124.83, 121.69, 121.52, 117.63, 117.43, 82.56, 60.80, 45.14, 40.24, 38.62, 27.76, 27.35. EMAR (ESI) calculado para $C_{19}H_{23}N_3O_6FS$ (M+H): 440.1292; encontrado: 440.1300. Análisis calculado para $C_{19}H_{22}N_3O_6FS \cdot 0.06$ H_2O: C 51.80, H 5.06, N 9.54, F 4.31; encontrado C 51.83, H 4.97, N 9.29, F 4.12.

Ejemplo 203

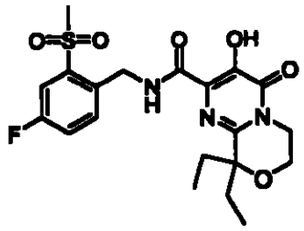


Pirimido[2,1-c][1,4]oxazin-2-carboxamida, 9,9-dietil-N-[[4-fluoro-2-(metilsulfonil)fenil]metil]-4,6,7,9-tetrahidro-3-hidroxi-4-oxo-. ^{1}H RMN (500 MHz, $CDCl_3$) δ ppm: 11.74 (1H, s), 8.54 (1H, t, J=6.6 Hz), 7.75 (1H, dd, J=8.2, 2.7 Hz), 7.71 (1H, dd, J=8.5, 5.2 Hz), 7.34 (1H, td, J=8.0, 2.6 Hz), 4.82 (2H, d, J=7.0 Hz), 3.94-4.00 (4H, m), 3.17 (3H, s), 1.93-2.00 (2 H, m), 1.84-1.92 (2H, m), 0.83 (6H, t, J=7.3

727

hidroxi-10,10-dimetil-4-oxo-. Sólido blanco opaco. ^{1}H RMN (500 MHz, $CDCl_3$) δ ppm: 11.77 (1H, br s), 8.55 (1H, t, .1=6.3 Hz), 7.75 (1H, dd, J=8.1, 2.6 Hz), 7.72 (1H, dd, J=8.5, 5.2 Hz), 7.34 (1H, td, J=8.0, 2.6 Hz), 4.81 (2H, d, J=6.7 Hz), 4.54 (2H, br), 3.65 (2H, t, J=6.1 Hz), 3.18 (3H, s), 1.93 (2H, m), 1.59 (6H, s); ^{13}C RMN (126 MHz, $CDCl_3$) δ ppm: 168.14, 163.14, 161.13, 158.23, 153.73, 147.26, 140.77, 140.72, 135.31, 135.25, 132.83, 132.80, 124.83, 121.69, 121.52, 117.63, 117.43, 82.56, 60.80, 45.14, 40.24, 38.62, 27.76, 27.35. EMAR (ESI) calculado para $C_{19}H_{23}N_3O_6FS$ (M+H): 440.1292; encontrado: 440.1300. Análisis calculado para $C_{19}H_{22}N_3O_6FS \cdot 0.06$ H_2O: C 51.80, H 5.06, N 9.54, F 4.31; encontrado C 51.83, H 4.97, N 9.29, F 4.12.

Ejemplo 203



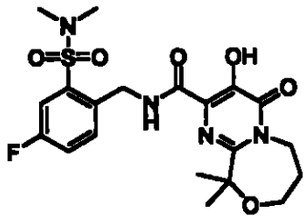
Pirimido[2,1-c][1,4]oxazin-2-carboxamida, 9,9-dietil-N-[[4-fluoro-2-(metilsulfonil)fenil]metil]-4,6,7,9-tetrahidro-3-hidroxi-4-oxo-. ^{1}H RMN (500 MHz, $CDCl_3$) δ ppm: 11.74 (1H, s), 8.54 (1H, t, J=6.6 Hz), 7.75 (1H, dd, J=8.2, 2.7 Hz), 7.71 (1H, dd, J=8.5, 5.2 Hz), 7.34 (1H, td, J=8.0, 2.6 Hz), 4.82 (2H, d, J=7.0 Hz), 3.94-4.00 (4H, m), 3.17 (3H, s), 1.93-2.00 (2 H, m), 1.84-1.92 (2H, m), 0.83 (6H, t, J=7.3

927

928

Hz); ^{13}C RMN (126 MHz, $CDCl_3$) δ ppm: 168.26, 163.13, 161.11, 157.83, 151.66, 146.05, 140.69, 140.64, 135.13, 135.07, 132.80, 132.77, 125.63, 121.65, 121.48, 117.65, 117.45, 81.03, 58.51, 45.14, 43.08, 40.33, 31.38, 7.87. EMAR (ESI) calculado para $C_{20}H_{25}N_3O_6FS$ (M+H): 454.1448; encontrado: 454.1448. Análisis calculado para $C_{20}H_{24}N_3O_6FS$: C 52.97, H 5.33, N 9.27, S 7.07; encontrado: C 53.01, H 5.60, N 9.10, S 7.00.

Ejemplo 204

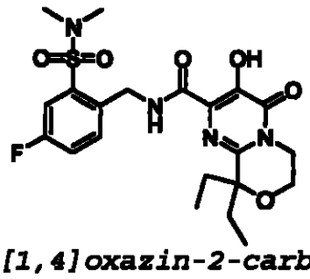


6H-Pirimido[2,1-c][1,4]oxazepin-2-carboxamida, N-[[2-[(dimetilamino)sulfonil]-4-fluorofenil]metil]-4,7,8,10-tetrahidro-3-hidroxi-10,10-dimetil-4-oxo-. Sólido anaranjado pálido. ^1H RMN (500 MHz, $CDCl_3$) δ ppm: 11.87 (1H, br s), 8.59 (1H, t, J=6.4 Hz), 7.69 (1H, dd, J=8.5,5.2 Hz), 7.49 (1H, dd, J=8.2, 2.4 Hz), 7.26 (1H, td, J=7.7,3.2 Hz), 4.79 (2H, d, J=6.7 Hz), 4.53 (2H, br), 3.65 (2H, t, J=6.1 Hz), 2.90 (6H, s), 1.89-1.96 (2H, m), 1.57-1.61 (6H, s); ^{13}C RMN (126 MHz, $CDCl_3$) δ ppm: 168.03, 162.71, 160.70, 158.29, 153.57, 147.23, 138.51, 138.46, 135.30, 135.25, 132.70, 132.67, 124.99, 120.40, 120.24, 116.93, 116.73, 82.59, 60.79, 58.57, 40.26, 38.58, 37.59, 27.74, 27.36, 18.55. EMAR (ESI) calculado para

729

$C_{20}H_{26}N_4O_6FS$ (M+H) 469.1557; encontrado 469.1557. Análisis calculado para $C_{20}H_{26}N_4O_6FS \cdot CH_3CH_2OH$: C 51.29, H 6.07, N 10.89, S 6.01, F 3.69; encontrado C 51.29, H 6.33, N 10.85, S 6.01, F 3.54.

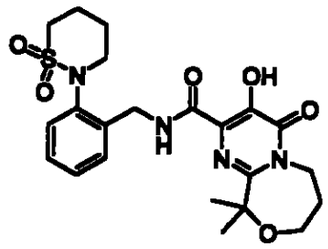
Ejemplo 205



Pirimido[2,1-c][1,4]oxazin-2-carboxamida, N-[[2-[(dimetilamino)sulfonil]-4-fluorofenil]metil]-9,9-dietil-4,6,7,9-tetrahidro-3-hidroxi-4-oxo-. Sólido vidrioso blanco. ^{1}H RMN (500 MHz, $CDCl_3$) δ ppm: 11.85 (1H, br), 8.59 (1H, t, J=6.4 Hz), 7.68 (1H, dd, J=8.5, 5.2 Hz), 7.49 (1H, dd, J=8.2, 2.4 Hz), 7.24-7.30 (1H, m), 4.80 (2H, d, J=7.0 Hz), 3.94-4.01 (4H, m), 2.90 (6H, s), 1.93-2.01 (2H, m), 1.85-1.93 (2H, m), 0.83 (6H, t, J=7.3 Hz); ^{13}C RMN (126 MHz, $CDCl_3$) δ ppm: 168.04, 162.70, 160.70, 158.06, 151.44, 145.95, 138.53, 138.49, 135.17, 135.12, 132.62, 132.59, 125.95, 120.37, 120.21, 116.87, 116.68, 81.08, 58.51, 43.11, 40.32, 37.58, 31.35, 7.87.

EMAR (ESI) calculado para $C_{21}H_{28}N_4O_6FS$ (M+H) 483.1714; encontrado 483.1702. Análisis calculado para $C_{21}H_{27}N_4O_6FS \cdot 0.15$ CF_3CO_2H: C 51.20, H 5.48, N 11.21, F 5.51, S 6.42; encontrado: C 51.10, H 5.23, N 11.21, F 5.49, S 6.32.

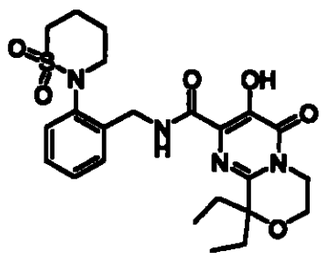
Ejemplo 206



6H-pirimido[2,1-c][1,4]oxazepin-2-carboxamida, 4,7,8,10-tetrahidro-3-hidroxi-10,10-dimetil-4-oxo-N-[[2-(tetrahidro-1,1-dióxido-2H-1,2-tiazin-2-il)fenil]metil]-.

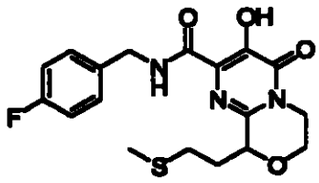
Sólido blanco opaco. ^{1}H RMN (500 MHz, $CDCl_3$) δ ppm: 12.18 (1H, br s), 8.14-8.25 (1H, br), 7.41-7.50 (2H, m), 7.31-7.39 (2H, m), 4.96 (1H, dd, J=14.0, 3.9 Hz), 4.54 (2H, br s), 4.44 (1H, dd, J=14.2, 3.2 Hz), 3.83-3.92 (1H, m), 3.65 (2H, br), 3.38-3.46 (1H, m), 3.18-3.28 (2H, m), 2.32-2.42 (2H, m), 1.89-1.98 (4H, m), 1.55 (6H, d, J=15.9 Hz); ^{13}C RMN (126 MHz, $CDCl_3$) δ ppm: 168.22, 158.38, 153.54, 147.32, 138.80, 137.00, 130.88, 129.47, 129.29, 127.68, 125.17, 82.60, 60.74, 54.15, 51.05, 39.11, 38.63, 27.76, 27.73, 27.36, 25.04, 24.32. EMAR (ESI) calculado para $C_{22}H_{29}N_4O_6S$ (M+H): 477.1808; encontrado: 477.1794. Análisis calculado para $C_{22}H_{28}N_4O_6S \cdot 0.5CH_3CH_2OH$: C 55.45, H 5.92, N 11.76, S 6.73; encontrado: C 55.36, H 6.11, N 11.46, S 6.48.

Ejemplo 207



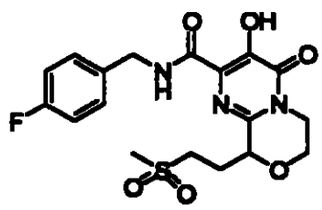
Pirimido[2,1-c][1,4]oxazin-2-carboxamida,4,6,7,9-tetrahidro-3-hidroxi-9,9-dietil-4-oxo-N-[[2-(tetrahidro-1,1-dióxido-2H-1,2-tiazin-2-il)fenil]metil]. Sólido cristalino blanco opáco. ^{1}H RMN (500 MHz, $CDCl_3$) δ ppm: 12.11 (1H, br s), 8.20 (1H, br), 7.42-7.48 (2H, m), 7.33-7.40 (2H, m), 4.93 (1H, dd, J=14.2, 8.4 Hz), 4.45 (1H, dd, J=14.2, 3.8 Hz), 3.94-4.02 (4H, m), 3.87 (1H, ddd, J=13.0, 9.9, 3.7 Hz), 3.39-3.46 (1H, m), 3.15-3.24 (2H, m), 2.29-2.46 (2H, m), 1.79-2.04 (6H, m), 0.81 (3H, t, J=6.7 Hz), 0.78 (3H, t, J=7.3 Hz); ^{13}C RMN (126 MHz, $CDCl_3$) δ ppm: 168.25, 157.91, 151.43, 146.14, 139.14, 136.81, 130.79, 129.46, 129.25, 127.90, 125.96, 81.15, 58.55, 54.22, 51.09, 43.03, 39.57, 31.21, 25.03, 24.34, 7.82, 7.68. EMAR (ESI) calculado para $C_{23}H_{31}N_4O_6S$ (M+H): 491.1964; encontrado: 491.1953. Análisis calculado para $C_{23}H_{30}N_4O_6S$: C 56.12, H 6.48, N 10.91, S 6.24; encontrado: C 56.14, H 6.44, N 11.07, S 6.05.

Ejemplo 208



Pirimido[2,1-c][1,4]oxazin-2-carboxamida, N-[(4-fluorofenil)metil]-4,6,7,9-tetrahidro-3-hidroxi-9-[2-(metiltio)etil]-4-oxo-. Una solución del intermediario 141, N-(4-fluorobencil)-3-(benciloxi)-9-(2-(metiltio)etil)-4-oxo-4,6,7,9-tetrahidropirimido[2,1-c][1,4]oxazin-2-carboxamida en 4mL de CF_3CO_2H se agitó a 60°C durante 1 hora, luego se concentró. El residuo se disolvió en CH_2Cl_2 y se lavó con agua, luego se concentró. La trituración con hexanos dio el compuesto del título como un sólido. ^1H RMN (300 MHz, $CDCl_3$) δ ppm: 12.03 (1 H, s) 7.75 (1 H, m) 6.84-7.40 (4 H, m) 4.39-4.72 (3 H, m) 4.04-4.36 (2 H, m) 3.68-3.92 (2 H, m) 2.49-2.73 (2 H, m) 2.07-2.50 (2 H, m) 2.02 (3 H, s); EMAR (ESI) calculado para $C_{18}H_{20}FN_3O_4S$ (M+H): 394.1237, encontrado: 394.1234.

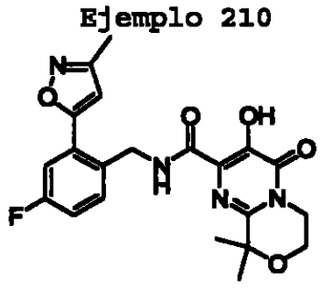
Ejemplo 209



Pirimido[2,1-c][1,4]oxazin-2-carboxamida, N-[(4-fluorofenil)metil]-4,6,7,9-tetrahidro-3-hidroxi-9-[2-

(metilsulfonil)etil]-4-oxo-. Una solución del ejemplo 208, pirimido[2,1-c][1,4]oxazin-2-carboxamida, N-[(4-fluorofenil)metil]-4,6,7,9-tetrahidro-3-hidroxi-9-[2-(metiltio)etil]-4-oxo-, (40mg, 0.11mmol) en 2mL de CH_2Cl_2 se trató con ácido m-cloroperbenzoico en exceso (100mg, 0.4mmol) y se agitó a temperatura ambiente durante 20 horas. La mezcla de reacción se lavó con agua y se concentró. El material crudo se purificó por CLAR de fase inversa (C18, 12% CH_3CN/H_2O). Las fracciones que contienen el producto se concentraron y liofilizaron para proporcionar 5mg (12% de rendimiento) del compuesto del título. ^1H RMN (300 MHz, $CDCl_3$) δ ppm: 12.10-12.27 (1 H, s) 7.80-8.02 (1 H, m) 7.25-7.39 (2 H, m) 6.90-7.09 (2 H, m) 4.05-4.72 (5 H, m) 3.73-3.99 (2 H, m) 3.02-3.34 (2 H, m) 2.86-2.91 (3 H, s) 2.35-2.78 (2 H, m); EMAR (ESI) calculado para $C_{18}H_{20}FN_3O_6S$ (M+H): 426.1135, encontrado: 426.1143.

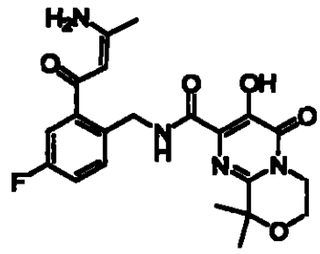
Ejemplo 210



Pirimido[2,1-c][1,4]oxazin-2-carbcxamida, N-[[4-fluoro-2-(3-metil-5-isoxazolil)fenil]metil]-4,6,7,9-tetrahidro-3-hidroxi-9,9-dimetil-4-oxo-. El compuesto del título puede prepararse a partir del intermediario 180, N-(4-fluoro-2-(3-

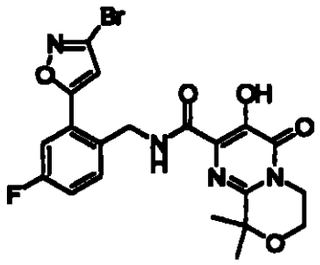
metilisoxazol-5-il)bencil)-3-(benciloxi)-9,9-dimetil-4-oxo-4,6,7,9-tetrahidropirimido[2,1-c][1,4]oxazin-2-carboxamida. ^{1}HRMN 400 MHz ($CDCl_3$) δ ppm: 1.59 (6H, s, 2 x CH_3), 2.42 (3H, s, CH_3), 4.03 (4H, s, 2 x CH_2), 4.74 (2H, d, J = 6.6 Hz, NCH_2), 6.40 (1H, s, aromático), 7.18 (1H, m, aromático), 7.32 (1H, dd, J = 2.5 Hz y J = 9.1 Hz, aromático), 7.59 (1H, dd, J = 5.6 Hz y J = 8.6 Hz, aromático), 8.29 (1H, amplio t, NH), 11.87 (1H, s, OH). EMAR (ESI^+) calculado para $C_{21}H_{22}FN_4O_5$ [$M+H^+$]: 429.1574; encontrado: 429.1584.

Ejemplo 211



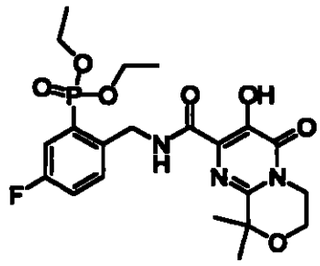
Pirimido[2,1-c][1,4]oxazin-2-carboxamida, N-[[2-[(2Z)-3-amino-1-oxo-2-butenil]-4-fluorofenil]metil]-4,6,7,9-tetrahidro-3-hidroxi-9,9-dimetil-4-oxo-. ^{1}HRMN 400 MHz ($CDCl_3$) δ ppm: 1.63 (6H, s, 2 x CH_3), 2.11 (3H, s, CH_3), 4.03 (4H, s, 2 x CH_2), 4.58 (2H, d, J = 6.5 Hz, NCH_2), 5.38 (1H, amplio, NH), 5.49 (1H, s, CH), 7.09 (1H, m, aromático), 7.29 (1H, dd, J = 3.0 Hz y J = 9.1 Hz, aromático), 7.48 (1H, dd, J = 5.6 Hz y J = 8.6 Hz, aromático), 9.19 (1H, amplio t, NH), 10.26 (1H, amplio, NH), 12.21 (1H, s, OH).

Ejemplo 212



Pirimido[2,1-c][1,4]oxazin-2-carbcxamida, N-[[2-(3-bromo-5-isoxazolil)-4-fluorofenil]metil]-4,6,7,9-tetrahidro-3-hidroxi-9,9-dimetil-4-oxo-. El compuesto del título puede prepararse a partir del intermediario 181, N-(2-(3-bromoisoxazol-5-il)-4-fluorobencil)-3-(benciloxi)-9,9-dimetil-4-oxo-4,6,7,9-tetrahidropirimido[2,1-c][1,4]oxazin-2-carboxamida. ^{1}HRMN 400 MHz ($CDCl_3$) δ ppm: 1.60 (6H, s, 2 x CH_3), 4.03 (4H, s, 2 x CH_2), 4.74 (2H, d, J = 7.1 Hz, NCH_2), 6.63 (1H, s, aromático), 7.24 (1H, m, aromático), 7.32 (1H, dd, J = 2.5 Hz y J = 9.1 Hz, aromático), 7.63 (1H, dd, J = 5.5 Hz y J = 8.6 Hz, aromático), 8.20 (1H, amplio t, NH), 11.77 (1H, s, OH).

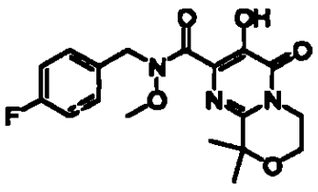
Ejemplo 213



Éster de [5-fluoro-2-[[[(4,6,7,9-tetrahidro-3-

hidroxi-9,9-dimetil-4-oxopirimido[2,1-c][1,4]oxazin-2-il)carbonil]amino]metil]fenil]-dietilo del ácido fosfónico. La hidrogenólisis del intermediario 187, 2-((3-(benciloxi)-9,9-dimetil-4-oxo-4,6,7,9-tetrahidropirimido[2,1-c][1,4]oxazin-2-carboxamido)metil)-5-fluorofenilfosfonato de dietilo (0.089 g, 0.15 mmol) dio 0.065 g (90% de rendimiento) del compuesto del título como un sólido blanco: pf 124°C. ^{1}HRMN 400 MHz ($CDCl_3$) δ ppm: 1.39 (6H, t, J = 7.1 Hz, 2 x CH_3), 1.63 (6H, s, 2 x CH_3), 4.02 (4H, s, 2 x CH_2), 4.20 (4H, m, 2 x OCH_2), 4.78 (2H, d, J = 6.6 Hz, NCH_2), 7.25 (1H, m, aromático), 7.49 (1H, m, aromático), 7.63 (1H, m, aromático), 9.12 (1H, amplio t, NH)., 12.1 (1H, amplio, OH). EMAR (ESI^+) calculado para $C_{21}H_{28}FN_3O_7P$ [$M+H^+$]: 484.1649; encontrado: 484.1646.

Ejemplo 214

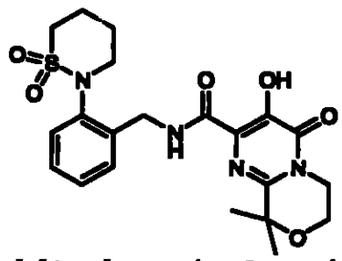


Pirimido[2,1-c][1,4]oxazin-2-carboxamida, N-[(4-fluorofenil)metil]-4,6,7,9-tetrahidro-3-hidroxi-N-metoxi-9,9-dimetil-4-oxo-. El compuesto del título. puede prepararse a partir del intermediario 171, N-(4-fluorobencil)-3-(benciloxi)-N-metoxi-9,9-dimetil-4-oxo-4,6,7,9-

737

tetrahidropirimido[2,1-c][1,4]oxazin-2-carboxamida. ^{1}HRMN 400 MHz (DMSO-d_6) δ ppm: (mezcla de rotámeros) 1.52 (6H, s, 2 x CH_3), 3.59 (3H, s, OCH_3), 3.89 (2H, amplio, CH_2), 4.01 (2H, amplio, CH_2), 4.68 y 4.91 (2H, amplio, NCH_2), 7.18 (2H, m, aromáticos), 7.43 (2H, m, aromáticos), 9.88 y 10.2 (1H, amplio, OH).

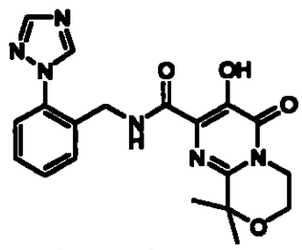
Ejemplo 215



Pirimido[2,1-c][1,4]oxazin-2-carboxamida, 4,6,7,9-tetrahidro-3-hidroxi-9,9-dimetil-4-oxo-N-[[2-(tetrahidro-1,1-dióxido-2H-1,2-tiazin-2-il)fenil]metil]-. El compuesto del título puede prepararse a partir del intermediario 101. Sólido café pálido. ^{1}H-RMN (300 MHz, $CDCl_3$) δ ppm: 12.11 (1H, s), 8.32-8.29 (1H, m), 7.46-7.42 (2H, m), 7.36-7.32 (2H, m), 4.92 (1H, dd, J= 14.3, 8.8 Hz), 4.40 (1H, dd, J = 14.1, 3.5 Hz), 3.97 (4H, s), 3.90-3.81 (1H, m), 3.47-3.37 (1H, m), 3.24-3.18 (2H, m), 2.42-2.28 (2H, m), 1.97-1.86 (2H, m), 1.54 (3H, s), 1.50 (3H, s). EMAR $[M+H]^+$ calculado para $C_{21}H_{27}N_4SO_6$: 463.1651; encontrado: 463.1669.

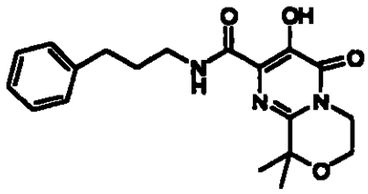
Análisis calculado para $C_{21}H_{26}N_4SO_6$: C, 54.53; H, 5.67; N, 12.11; S, 6.93; encontrado: C, 54.53; H, 5.41; N, 12.40; S, 6.69.

Ejemplo 216



Pirimido[2,1-c][1,4]oxazin-2-carboxamida,4,6,7,9-tetrahidro-3-hidroxi-9,9-dimetil-4-oxo-N-[[2-(1H-1,2,4-triazol-1-il)fenil]metil]-. Sólido blanco. ^{1}HRMN (300 MHz, $CDCl_3$) δ ppm: 11.94 (1H, s), 8.86 (1H, t, J= 6.2 Hz), 8.42 (1H, s), 8.16 (1H, s), 7.66 (1H, dd, J= 7.3, 1.8 Hz), 7.51-7.42 (2H, m), 7.35-7.32 (1H, m), 4.45 (2H, d, J= 6.6 Hz), 3.98 (4H, s), 1.59 (6H, s). EMAR $[M+H]^+$ calculado para $C_{19}H_{21}N_6O_4$: 397.1624; encontrado: 397.1609. Análisis calculado para $C_{19}H_{20}N_6O_4$: C, 57.57; H, 5.08; N, 21.20; encontrado: C, 57.40; H, 4.96; N, 21.09.

Ejemplo 217



Pirimido[2,1-c][1,4]oxazin-2-carbcxamida,4,6,7,9-tetrahidro-3-hidroxi-9,9-dimetil-4-oxo-N-(3-fenilpropil)-

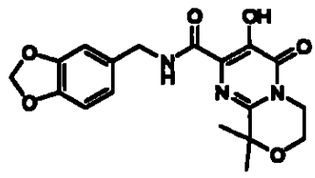
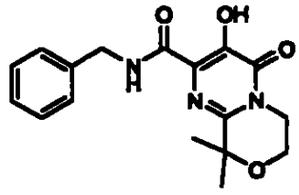
^{1}HRMN (500 MHz, DMSO-D6) δ ppm: 1.56 (s, 6 H) 1.82-1.89 (m, 2 H) 2.62 (t, J=7.48 Hz, 2 H) 3.31 (m, 2 H) 3.82 (t, J=5.04 Hz, 2 H) 3.97 (t, J=5.04 Hz, 2 H) 7.16-7.24 (m, 3 H) 7.29 (m, 2 H) 8.91 (s, 1 H) 12.41 (s, 1 H). Análisis

calculado para $C_{19}H_{23}N_3O_4$: C, 63.85; H, 6.48; N, 11.75. Encontrado: C, 63.56; H, 6.67; N, 12.01.

Ejemplos 218-259

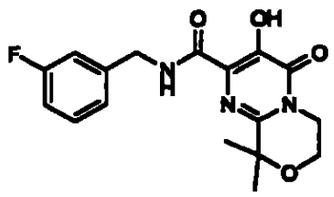
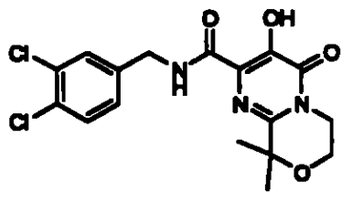
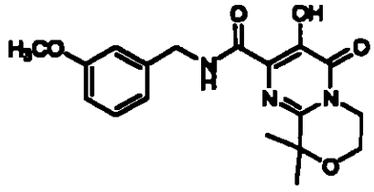
Los Ejemplos 218-259, en la tabla 11, se prepararon usando métodos similares a aquellos descritos para los ejemplos 1, 19,20. Los compuestos se caracterizan por CLEM con el tiempo de retención observado (TR, minutos) y peso molecular (EM [M+1]) enlistados en la tabla.

Tabla 11.

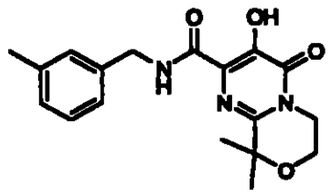
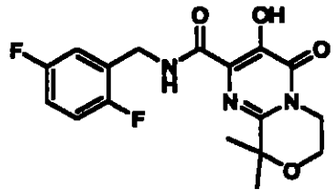
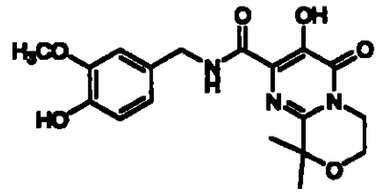
Ejemplo	*Estructura*	TR	EM
218	 *Pirimido[2,1-c][1,4]oxazin-2-carboxamida, N-(1,3-benzodioxol-5-ilmetil)-4,6,7,9-tetrahidro-3-hidroxi-9,9-dimetil-4-oxo-*	1.55	374.2
219	 *Pirimido[2,1-c][1,4]oxazin-2-carboxamida,4,6,7,9-tetrahidro-3-hidroxi-9,9-dimetil-4-oxo-N-(fenilmetil)-*	1.60	330.2

947

740

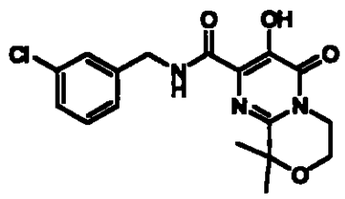
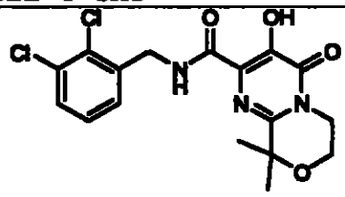
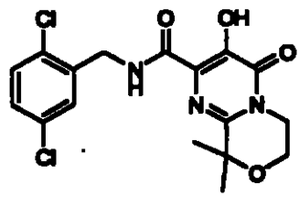
Ejemplo	Estructura	TR	EM
220	 *Pirimido[2,1-c][1,4]oxazin-2-carboxamida, N-[(3-fluorofenil)metil]-4,6,7,9-tetrahidro-3-hidroxi-9,9-dimetil-4-oxo-*	1.63	348.2
221	 *Pirimido[2,1-c][1,4]oxazin-2-carboxamida, N-[(3,4-diclorofenil)metil]-4,6,7,9-tetrahidro-3-hidroxi-9,9-dimetil-4-oxo-*	1.99	398.16
222	 *Pirimido[2,1-c][1,4]oxazin-2-carboxamida, 4,6,7,9-tetrahidro-3-hidroxi-N-[(3-metoxifenil)metil]-9,9-dimetil-4-oxo-*	1.61	360.2

741

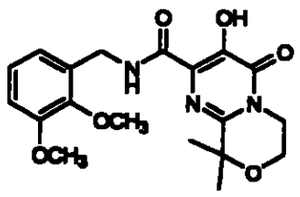
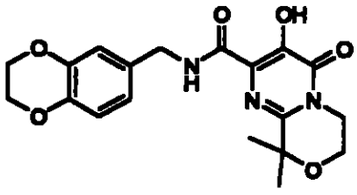
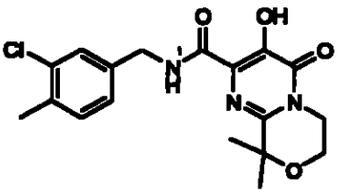
Ejemplo	Estructura	TR	EM
223	 *Pirimido[2,1-c][1,4]oxazin-2-carboxamida, 4,6,7,9-tetrahidro-3-hidroxi-9,9-dimetil-N-[(3-metilfenil)metil]-4-oxo-*	1.79	344.2
224	 *Pirimido[2,1-c][1,4]oxazin-2-carboxamida, N-[(2,5-difluorofenil)metil]-4,6,7,9-tetrahidro-3-hidroxi-9,9-dimetil-4-oxo-*	1.65	366.2
225	 *Pirimido[2,1-c][1,4]oxazin-2-carboxamida, 4,6,7,9-tetrahidro-3-hidroxi-N-[(4-hidroxi-3-metoxifenil)metil]-9,9-dimetil-4-oxo-*	1.27	376.2

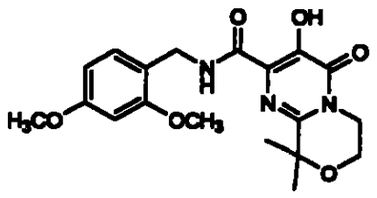
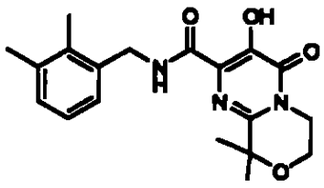
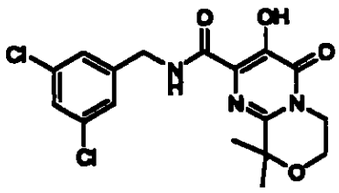
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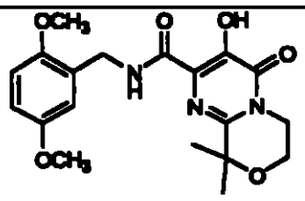
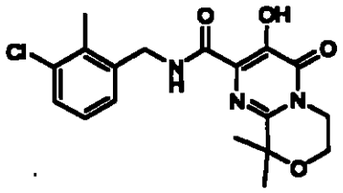
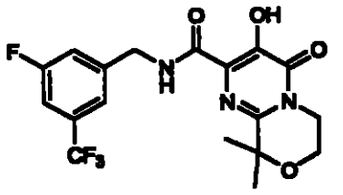
Ejemplo	Estructura	TR	EM
226	 *Pirimido[2,1-c][1,4]oxazin-2-carboxamida, N-[(3-clorofenil)metil]-4,6,7,9-tetrahidro-3-hidroxi-9,9-dimetil-4-oxo-*	1.80	364.2
227	 *Pirimido[2,1-c][1,4]oxazin-2-carboxamida, N-[(2,3-diclorofenil)metil]-4,6,7,9-tetrahidro-3-hidroxi-9,9-dimetil-4-oxo-*	2.00	398.2
228	 *Pirimido[2,1-c][1,4]oxazin-2-carboxamida, N-[(2,5-diclorofenil)metil]-4,6,7,9-tetrahidro-3-hidroxi-9,9-dimetil-4-oxo-*	1.97	398.1

743

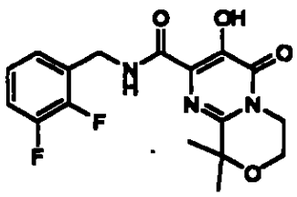
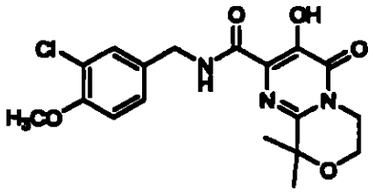
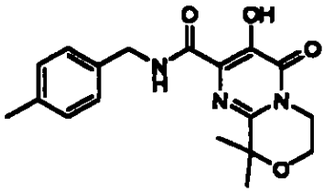
Ejemplo	Estructura	TR	EM
229	 *Pirimido[2,1-c][1,4]oxazin-2-carboxamida, N-[(2,3-dimetoxifenil)metil]-4,6,7,9-tetrahidro-3-hidroxi-9,9-dimetil-4-oxo-*	1.64	390.2
230	 *Pirimido[2,1-c][1,4]oxazin-2-carboxamida, N-[(2,3-dihidro-1,4-benzodioxin-6-il)metil]-4,6,7,9-tetrahidro-3-hidroxi-9,9-dimetil-4-oxo-*	1.64	390.24
231	 *Pirimido[2,1-c][1,4]oxazin-2-carboxamida, N-[(3-cloro-4-metilfenil)metil]-4,6,7,9-tetrahidro-3-hidroxi-9,9-dimetil-4-oxo-*	2.01	378.1

Ejemplo	Estructura	TR	EM
232	 *Pirimido[2,1-c][1,4]oxazin-2-carboxamida, N-[(2,4-dimetoxifenil)metil]-4,6,7,9-tetrahidro-3-hidroxi-9,9-dimetil-4-oxo-*	1.75	390.2
233	 *Pirimido[2,1-c][1,4]oxazin-2-carboxamida, N-[(2,3-dimetilfenil)metil]-4,6,7,9-tetrahidro-3-hidroxi-9,9-dimetil-4-oxo-*	1.92	358.2
234	 *Pirimido[2,1-c][1,4]oxazin-2-carboxamida, N-[(3,5-diclorofenil)metil]-4,6,7,9-tetrahidro-3-hidroxi-9,9-dimetil-4-oxo-*	2.01	398.0

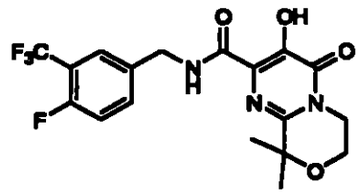
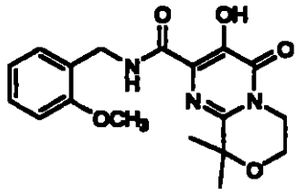
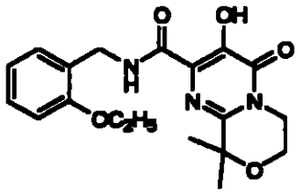
745

Ejemplo	Estructura	TR	EM
235	 *Pirimido[2,1-c][1,4]oxazin-2-carboxamida, N-[(2,5-dimetoxifenil)metil]-4,6,7,9-tetrahidro-3-hidroxi-9,9-dimetil-4-oxo-*	1.71	390.1
236	 *Pirimido[2,1-c][1,4]oxazin-2-carboxamida, N-[(3-cloro-2-metilfenil)metil]-4,6,7,9-tetrahidro-3-hidroxi-9,9-dimetil-4-oxo-*	1.98	378.1
237	 *Pirimido[2,1-c][1,4]oxazin-2-carboxamida, N-[(3-fluoro-5-(trifluorometil)fenil]metil]-4,6,7,9-tetrahidro-3-hidroxi-9,9-dimetil-4-oxo-*	1.95	416.1

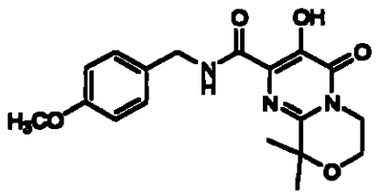
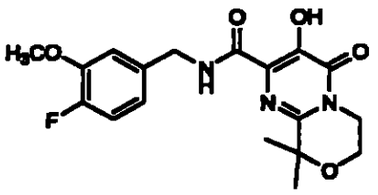
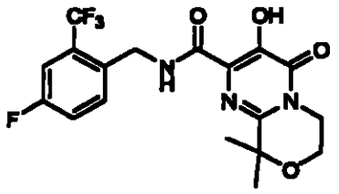
746

Ejemplo	Estructura	TR	EM
238	 Pirimido[2,1-c][1,4]oxazin-2-carboxamida, N-[(2,3-difluorofenil)metil]-4,6,7,9-tetrahidro-3-hidroxi-9,9-dimetil-4-oxo-	1.70	366.0
239	 Pirimido[2,1-c][1,4]oxazin-2-carboxamida, N-[(3-cloro-4-metoxifenil)metil]-4,6,7,9-tetrahidro-3-hidroxi-9,9-dimetil-4-oxo-	1.71	394.0
240	 Pirimido[2,1-c][1,4]oxazin-2-carboxamida, 4,6,7,9-tetrahidro-3-hidroxi-9,9-dimetil-N-[(4-metilfenil)metil]-4-oxo-	1.80	344.0

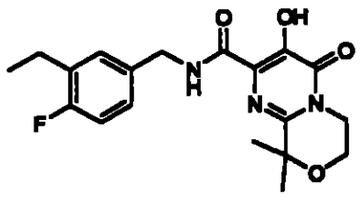
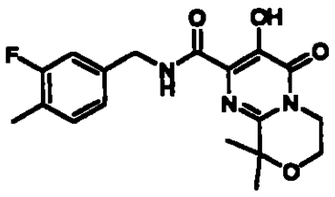
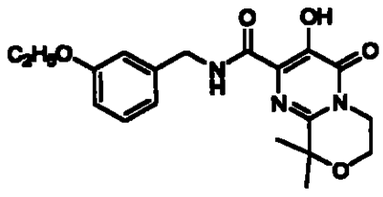
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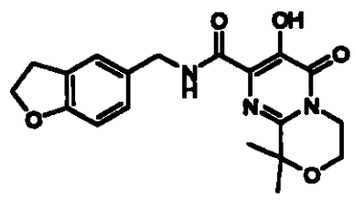
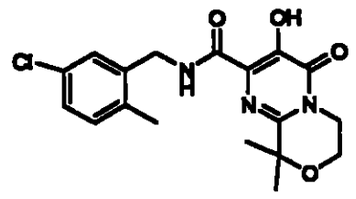
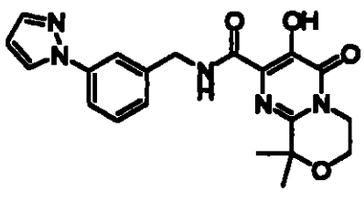
Ejemplo	Estructura	TR	EM
241	 *Pirimido[2,1-c][1,4]oxazin-2-carboxamida, N-[[4-fluoro-3-(trifluorometil)fenil]metil]-4,6,7,9-tetrahidro-3-hidroxi-9,9-dimetil-4-oxo-*	1.90	416.1
242	 *Pirimido[2,1-c][1,4]oxazin-2-carboxamida, 4,6,7,9-tetrahidro-3-hidroxi-N-[(2-metoxifenil)metil]-9,9-dimetil-4-oxo-*	1.80	360.1
243	 *Pirimido[2,1-c][1,4]oxazin-2-carboxamida, N-[(2-etoxifenil)metil]-4,6,7,9-tetrahidro-3-hidroxi-9,9-dimetil-4-oxo-*	1.90	374.1

748

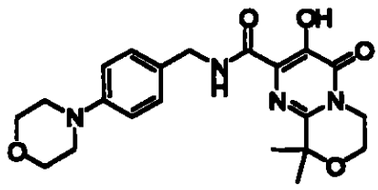
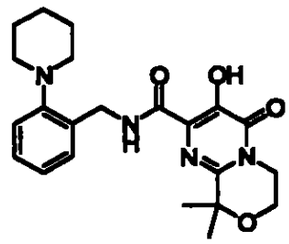
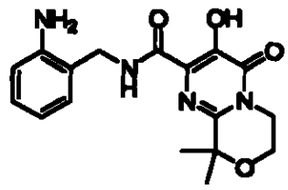
Ejemplo	Estructura	TR	EM
244	 Pirimido[2,1-c][1,4]oxazin-2-carboxamida, 4,6,7,9-tetrahidro-3-hidroxi-N-[[4-metoxifenil)metil]-9,9-dimetil-4-oxo-	1.60	360.1
245	 Pirimido[2,1-c][1,4]oxazin-2-carboxamida, N-[(4-fluoro-3-metoxifenil)metil]-4,6,7,9-tetrahidro-3-hidroxi-9,9-dimetil-4-oxo-	1.23	378.1
246	 Pirimido[2,1-c][1,4]oxazin-2-carboxamida, N-[[4-fluoro-2-(trifluorometil)fenil]metil]-4,6,7,9-tetrahidro-3-hidroxi-9,9-dimetil-4-oxo-	1.99	416.1

749

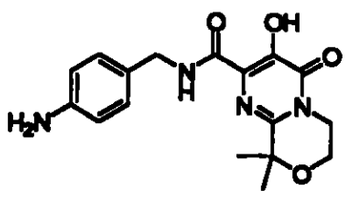
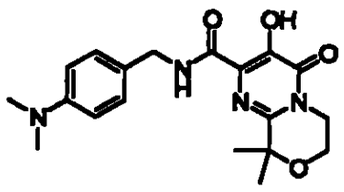
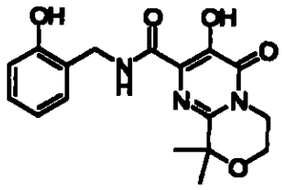
Ejemplo	Estructura	TR	EM
247	 *Pirimido[2,1-c][1,4]oxazin-2-carboxamida, N-[(3-etil-4-fluorofenil)metil]-4,6,7,9-tetrahidro-3-hidroxi-9,9-dimetil-4-oxo-*	1.98	376.1
248	 *Pirimido[2,1-c][1,4]oxazin-2-carboxamida, N-[(3-fluoro-4-metilfenil)metil]-4,6,7,9-tetrahidro-3-hidroxi-9,9-dimetil-4-oxo-*	1.83	362.1
249	 *Pirimido[2,1-c][1,4]oxazin-2-carboxamida, N-[(3-etoxifenil)metil]-4,6,7,9-tetrahidro-3-hidroxi-9,9-dimetil-4-oxo-*	1.77	374.1

Ejemplo	Estructura	TR	EM
250	 *Pirimido[2,1-c][1,4]oxazin-2-carboxamida, N-[(2,3-dihidro-5-benzofuranil)metil]-4,6,7,9-tetrahidro-3-hidroxi-9,9-dimetil-4-oxo-*	1.59	372.0
251	 *Pirimido[2,1-c][1,4]oxazin-2-carboxamida, N-[(5-cloro-2-metilfenil)metil]-4,6,7,9-tetrahidro-3-hidroxi-9,9-dimetil-4-oxo-*	1.96	378.1
252	 *Pirimido[2,1-c][1,4]oxazin-2-carboxamida, 4,6,7,9-tetrahidro-3-hidroxi-9,9-dimetil-4-oxo-N-[[3-(1H-pirazol-1-il)fenil]metil]-*	1.50	396.27

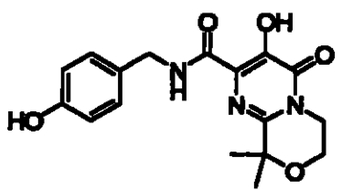
751

Ejemplo	*Estructura*	TR	EM
253	 *Pirimido[2,1-c][1,4]oxazin-2-carboxamida, 4,6,7,9-tetrahidro-3-hidroxi-9,9-dimetil-N-[[4-(4-morfolinil)fenil]metil]-4-oxo-*	1.27	415.29
254	 *Pirimido[2,1-c][1,4]oxazin-2-carboxamida, 4,6,7,9-tetrahidro-3-hidroxi-9,9-dimetil-4-oxo-N[[2-(1-piperidinil)fenil]metil]-*	1.12	413.31
255	 *Pirimido[2,1-c][1,4]oxazin-2-carboxamida, N-[(2-aminofenil)metil]-4,6,7,9-tetrahidro-3-hidroxi-9,9-dimetil-4-oxo-*	1.05	345.26

752

Ejemplo	Estructura	TR	EM
256	 *Pirimido[2,1-c][1,4]oxazin-2-carboxamida, N-[(4-aminofenil)metil]-4,6,7,9-tetrahidro-3-hidroxi-9,9-dimetil-4-oxo-*	0.98	345.25
257	 *Pirimido[2,1-c][1,4]oxazin-2-carboxamida, N-[[4-(dimetilamino)fenil]metil]-4,6,7,9-tetrahidro-3-hidroxi-9,9-dimetil-4-oxo-*	0.98	373.29
258	 *Pirimido[2,1-c][1,4]oxazin-2-carboxamida, 4,6,7,9-tetrahidro-3-hidroxi-N-[(2-hidroxifenil)metil]-9,9-dimetil-4-oxo-*	1.44	346.24

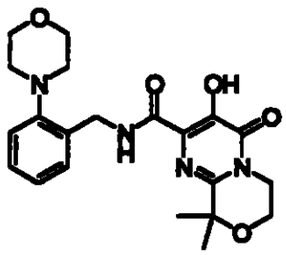
753

Ejemplo	*Estructura*	TR	EM
259	 *Pirimido[2,1-c][1,4]oxazin-2-carboxamida, 4,6,7,9-tetrahidro-3-hidroxi-N-[(4-hidroxifenil)metil]-9,9-dimetil-4-oxo-*	1.22	346.24

Ejemplos 260-278

Los ejemplos 260-278 se prepararon de conformidad con los métodos usados para la preparación de los compuestos en la tabla 3 y caracterizados por CLAR.

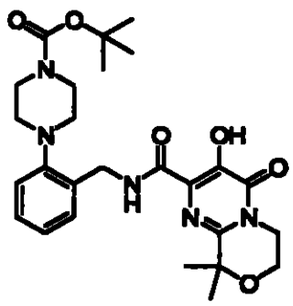
Ejemplo 260



Pirimido[2,1-c][1,4]oxazin-2-carboxamida, 4,6,7,9-tetrahidro-3-hidroxi-9,9-dimetil-N-[[2-(4-morfolinil)fenil]metil]-4-oxo-. CLEM: tiempo de retención CLAR = 4.03 min, EM = [M+ 1] 415.23.

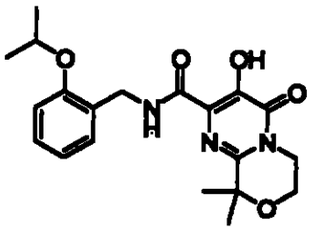
754

Ejemplo 261



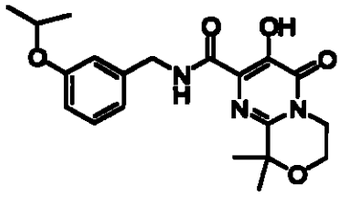
Ácido 1-piperazincarboxílico, 4-[2-[[[(4,6,7,9-tetrahidro-3-hidroxi-9,9-dimetil-4-oxopirimido[2,1-c][1,4]oxazin-2-il)carbonil]amino]metil]fenil]-, éster de 1,1-dimetiletilo. CLEM: tiempo de retención CLAR = 4.93 min, EM = [M+1] 514.24.

Ejemplo 262



Pirimido[2,1-c][1,4]oxazin-2-carboxamida, 4,6,7,9-tetrahidro-3-hidroxi-9,9-dimetil-N-[[2-(1-metiletoxi)fenil]metil]-4-oxo-. CLEM: tiempo de retención CLAR = 4.66 min, EM = [M+1] 388.21.

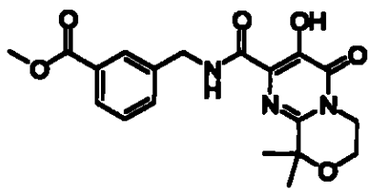
Ejemplo 263



Pirimido[2,1-c][1,4]oxazin-2-carboxamida, 4,6,7,9-

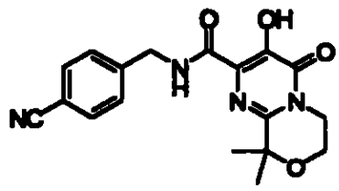
tetrahidro-3-hidroxi-9,9-dimetil-N-[[3-(1-metiletoxi)fenil]metil]-4-oxo-. CLEM: tiempo de retención CLAR = 3.97 min., EM = [M+ 1] 4388.21.

Ejemplo 264



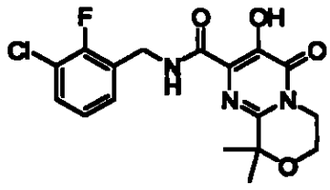
Ácido benzoico, 3-[[[(4,6,7,9-tetrahidro-3-hidroxi-9,9-dimetil-4-oxopirimido[2,1-c][1,4]oxazin-2-il)carbonil]amino]metil]-, éster de metilo. CLEM: tiempo de retención CLAR = 3.97 min, EM = [M+1] 388.18.

Ejemplo 265



Pirimido[2,1-c][1,4]oxazin-2-carboxamida, N-[(4-cianofenil)metil]-4,6,7,9-tetrahidro-3-hidroxi-9,9-dimetil-4-oxo-. CLEM: tiempo de retención CLAR = 3.59 min, EM = [M+ 1] 355.2.

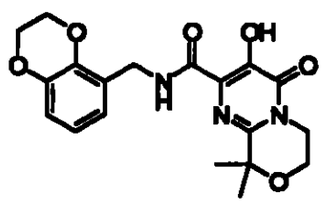
Ejemplo 266



Pirimido[2,1-c][1,4]oxazin-2-carboxamida, N-[(3-cloro-2-

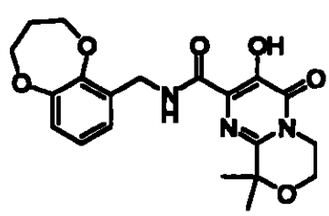
fluorofenil)metil]-4,6,7,9-tetrahidro-3-hidroxi-9,9-dimetil-4-oxo-. CLEM: tiempo de retención CLAR = 4.47 min, EM = [M+1] 382.14.

Ejemplo 267



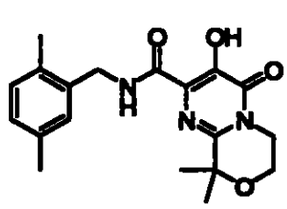
Pirimido[2,1-c][1,4]oxazin-2-carboxamida, N-[(2,3-dihidro-1,4-benzodioxin-5-il)metil]-4,6,7,9-tetrahidro-3-hidroxi-9,9-dimetil-4-oxo-. *CLEM: tiempo de retención CLAR = 4.15 min, EM = [M+1] 388.2.*

Ejemplo 268



Pirimido[2,1-c][1,4]oxazin-2-carboxamida, N-[(3,4-dihidro-2H-1,5-benzodioxepin-6-il)metil]-4,6,7,9-tetrahidro-3-hidroxi-9,9-dimetil-4-oxo-. CLEM: tiempo de retención CLAR = 4.12 min, EM = [M+1] 402.21.

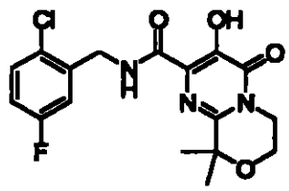
Ejemplo 269



Pirimido[2,1-c][1,4]oxazin-2-carboxamida, N-[(2,5-

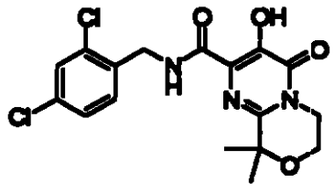
dimetilfenil)metil]-4,6,7,9-tetrahidro-3-hidroxi-9,9-dimetil-4-oxo-. CLEM: tiempo de retención CLAR = 4.64 min, EM = [M+1] 358.22

Ejemplo 270



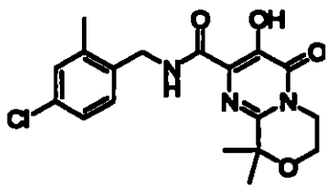
Pirimido[2,1-c][1,4]oxazin-2-carboxamida, N-[(5-cloro-2-fluorofenil)metil]-4,6,7,9-tetrahidro-3-hidroxi-9,9-dimetil-4-oxo-. CLEM: tiempo de retención CLAR = 4.44 min, EM = [M+1] 382.15

Ejemplo 271



Pirimido[2,1-c][1,4]oxazin-2-carboxamida, N-[(2,4-diclorofenil)metil]-4,6,7,9-tetrahidro-3-hidroxi-9,9-dimetil-4-oxo-. CLEM: tiempo de retención CLAR = 4.88 min, EM = [M+1] 398.11.

Ejemplo 272

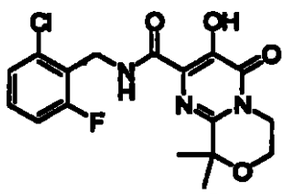


Pirimido[2,1-c][1,4]oxazin-2-carboxamida, N-[(4-cloro-2-

758

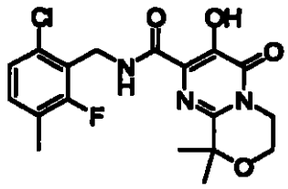
metilfenil)metil]-4,6,7,9-tetrahidro-3-hidroxi-9,9-dimetil-4-oxo-. CLEM: tiempo de retención CLAR = 4.69 min, EM = [M+1] 378.17.

Ejemplo 273



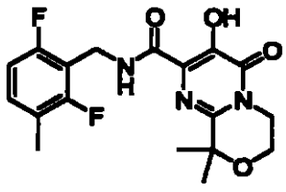
Pirimido[2,1-c][1,4]oxazin-2-carboxamida, N-[(2-cloro-6-fluorofenil)metil]-4,6,7,9-tetrahidro-3-hidroxi-9,9-dimetil-4-oxo-. CLEM: tiempo de retención CLAR = 4.39 min, EM = [M+1] 382.13.

Ejemplo 274



Pirimido[2,1-c][1,4]oxazin-2-carboxamida, N-[(6-cloro-2-fluoro-3-metilfenil)metil]-4,6,7,9-tetrahidro-3-hidroxi-9,9-dimetil-4-oxo-. CLEM: tiempo de retención CLAR = 4.74 min, EM = [M+1] 396.14.

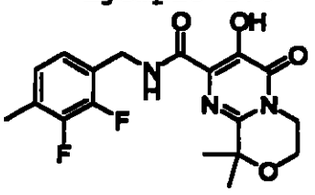
Ejemplo 275



759

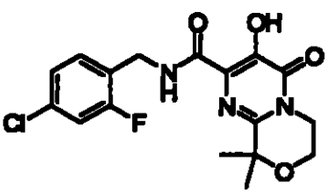
Pirimido[2,1-c][1,4]oxazin-2-carboxamida, N-[(2,6-difluoro-3-metilfenil)metil]-4,6,7,9-tetrahidro-3-hidroxi-9,9-dimetil-4-oxo-. CLEM: tiempo de retención CLAR = 4.49 min, EM = [M+1] 380.18.

Ejemplo 276



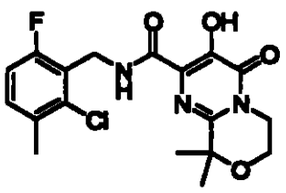
Pirimido[2,1-c][1,4]oxazin-2-carboxamida, N-[(2,3-difluoro-4-metilfenil)metil]-4,6,7,9-tetrahidro-3-hidroxi-9,9-dimetil-4-oxo-. CLEM: tiempo de retención CLAR = 4.53 min, EM = [M+1] 380.18.

Ejemplo 277



Pirimido[2,1-c][1,4]oxazin-2-carboxamida, N-[(4-cloro-2-fluorofenil)metil]-4,6,7,9-tetrahidro-3-hidroxi-9,9-dimetil-4-oxo-. CLEM: tiempo de retención CLAR = 4.57min, EM = [M+1] 382.13.

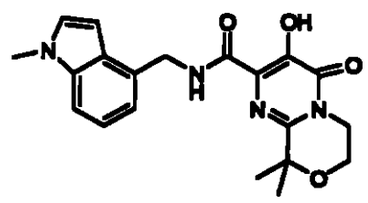
Ejemplo 278



Pirimido[2,1-c][1,4]oxazin-2-carbcxamida, N-[(2-cloro-6-

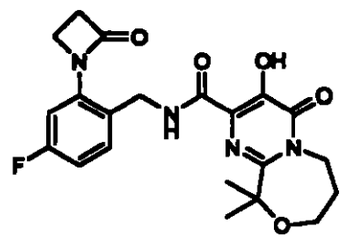
fluoro-3-metilfenil)metil]-4,6,7,9-tetrahidro-3-hidroxi-9,9-dimetil-4-oxo-. CLEM: tiempo de retención CLAR = 4.68 min, EM = [M+1] 396.16.

Ejemplo 279



Pirimido[2,1-c][1,4]oxazin-2-carboxamida, 4,6,7,9-tetrahidro-3-hidroxi-9,9-dimetil-N-[(1-metil-1H-indol-4-il)metil}-4-oxo-. ^{1}H RMN (500 MHz, DMSO-d_6) δ ppm: 1.56 (s, 6), 3.79 (s, 3), 3.82 (m, 2), 3.97 (m, 2), 4.76 (d, 2), 6.62 (d, 1), 6.96 (d, 1), 7.12 (m, 1), 7.27-7.38 (traslapado m, 2). EMAR [M+1] calculado para $C_{20}H_{23}N_4O_4$, 383.1641; encontrado, 383.1717. Análisis calculado para $C_{20}H_{22}N_4O_4$: C, 62.81; H, 5.79; N, 14.65. Encontrado: C, 62.88; H, 6.08; N, 13.56.

Ejemplo 280

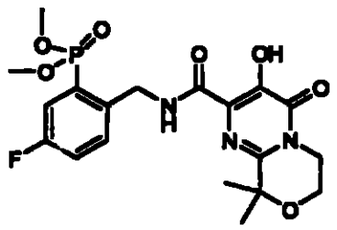


6H-Pirimido[2,1-c][1,4]oxazepin-2-carboxamida, N-[[4-fluoro-2-(2-oxo-1-azetidinil)fenil]metil]-4,7,8,10-tetrahidro-3-hidroxi-10,10-dimetil-4-oxo-. ^{1}H RMN (400 MHz,

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DMSO-d_6) δ: 12.17 (1H, s), 9.28 (1H, amplio s), 7.37 (1H, dd, J = 8.2, 6.7 Hz), 7.23 (1H, dd, J =10.2, 2.4 Hz), 7.04 (1H, m), 4.51 (2H, amplio s), 4.35 (2H, amplio s), 3.79 (2H, t, J = 4.4 Hz), 3.62 (2H, m), 3.11 (2H, t, J = 4.4 Hz), 1.81 (2H, m), 1.55 (6H, s). CLEM $(M+H)^+$ m/z 431.

Ejemplo 281

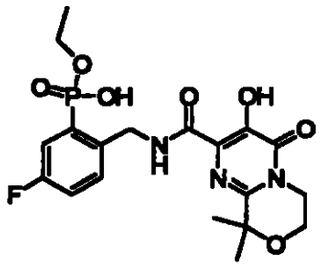


Ácido fosfónico, [5-fluoro-2-[[[(4,6,7,9-tetrahidro-3-hidroxi-9,9-dimetil-4-oxopirimido[2,1-c][1,4]oxazin-2-il)carbonil]amino]metil]fenil]-, éster de dimetilo.

La hidrogenación del 2-((3-(benciloxi)-9,9-dimetil-4-oxo-4,6,7,9-tetrahidropirimido[2,1-c][1,4]oxazin-2-carboxamido)metil)-5-fluorofenilfosfonato de dimetilo (0.030 g, 0.055 mmol) dio 0.018 g (72 %) del compuesto del título como un sólido blanco.

^{1}HRMN 400 MHz ($CDCl_3$) δ (ppm): 1.63 (6H, s, 2 x CH_3), 3.84 (3H, s, OCH_3), 3.87 (3H, s, OCH_3), 4.03 (4H, s, 2 x CH_2), 4.77 (2H, d, J = 6.5 Hz, NCH_2), 7.28 (1H, m, aromático), 7.47 (1H, m, aromático), 7.65 (1H, m, aromático), 9.0 (1H, amplio t, NH) 12.0 (1H, amplio, OH). EM (ES+) m/z 456 $[M+H^+]$.

Ejemplo 282

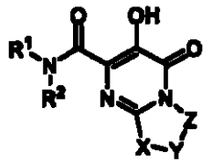


Ácido fosfónico, [5-fluoro-2-[[[(4,6,7,9-tetrahidro-3-hidroxi-9,9-dimetil-4-oxopirimido[2,1-c][1,4]oxazin-2-il)carbonil]amino]metil]fenil]-, éster de monoetilo. El compuesto del título puede prepararse a partir del intermediario 188, 2-((3-(benciloxi)-9,9-dimetil-4-oxo-4,6,7,9-tetrahidropirimido[2,1-c][1,4]oxazin-2-carboxamido)metil)-5-fluorofenilfosfonato ácido de etilo. ^{1}HRMN 400 MHz ($CDCl_3$) δ (ppm): 1.32 (3H, t, J = 7.1 Hz, CH_3), 1.60 (6H, s, 2 x CH_3), 4.02 (4H, s, 2 x CH_2), 4.12 (2H, m, OCH_2), 4.83 (2H, amplio, NCH_2), 7.18 (1 H, m, aromático), 7.54 (2H, m, aromáticos), 8.49 (1H, amplio, NH). EMAR (ESI$^+$) calculado para $C_{19}H_{24}FN_3O_7P$ [M+H$^+$]: 456.1336; encontrado: 456.1353.

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REIVINDICACIONES

1. Un compuesto de la fórmula I



I

caracterizado porque

R^1 es $C_{1-6}(Ar^1)$alquilo, $C_{1-6}(Ar^1)(CON(R^8)(R^9))$alquilo, $C_{1-6}Ar^1)(CO_2R^{14})$alquilo, $C_{1-6}(Ar^1)$hidroxialquilo, o $C_{1-6}(Ar^1)$oxialquilo;

R^2 es hidrógeno, C_{1-6}alquilo, o OR^{14};

R^3 es hidrógeno, halo, hidroxi, ciano, C_{1-6}alquilo, C_{3-7}cicloalquilo, C_{5-7}cicloalquenilo, C_{1-6}haloalquilo, C_{1-6}alcoxi, C_{1-6}alquiltio, C_{1-6}haloalcoxi, $N(R^8)(R^9)$, $NHAr^2$, $N(R^6)SO_2R^7$, $N(R^6)COR^7$, $N(R^6)CO_2R^7$, $OCOR^7$, OCO_2R^7, $OCON(R^8)(R^9)$, $OCH_2CO_2R^7$, $OCH_2CON(R^8)(R^9)$, COR^6, CO_2R^6, $CON(R^8)(R^9)$, SOR^7, $S(=N)R^7$, SO_2R^7, $SO_2N(R^6)(R^6)$, $PO(OR^6)_2$, $C_{2-4}(R^{12})$alquinilo, R^{13}, Ar^2, o Ar^3;

R^4 es hidrógeno, halo, hidroxi, ciano, C_{1-6}alquilo, C_{1-6}alcoxi, C_{1-6}haloalquilo, C_{1-6}haloalcoxi, o $N(R^6)(R^6)$;

R^5 es hidrógeno, halo, hidroxi, ciano, C_{1-6}alquilo, C_{1-6}alcoxi, C_{1-6}haloalquilo, C_{1-6}haloalcoxi, o $N(R^6)(R^6)$;

R^6 es hidrógeno, C_{1-6}alquilo, o C_{3-7}cicloalquilo;

R^7 es C_{1-6}alquilo o C_{3-7}cicloalquilo;

R^8 es hidrógeno, C_{1-6}alquilo, C_{1-6}hidroxialquilo, $C_{1-6}(C_{1-6}$alcoxi)alquilo o $C_{1-6}(C_{1-6}$dialquilamino)alquilo;

R^9 es hidrógeno, C_{1-6}alquilo, C_{1-6}hidroxialquilo, $C_{1-6}(C_{1-}$

$_{6}$alcoxi)alquilo o C_{1-6}(C_{1-6}dialquilamino)alquilo; o $N(R^8)(R^9)$ tomados juntos son azetidinilo, pirrolidinilo, (R^{10})-piperidinilo, N-(R^{11})-piperazinilo, morfolinilo, tiomorfolinilo, o dioxotiazinilo;

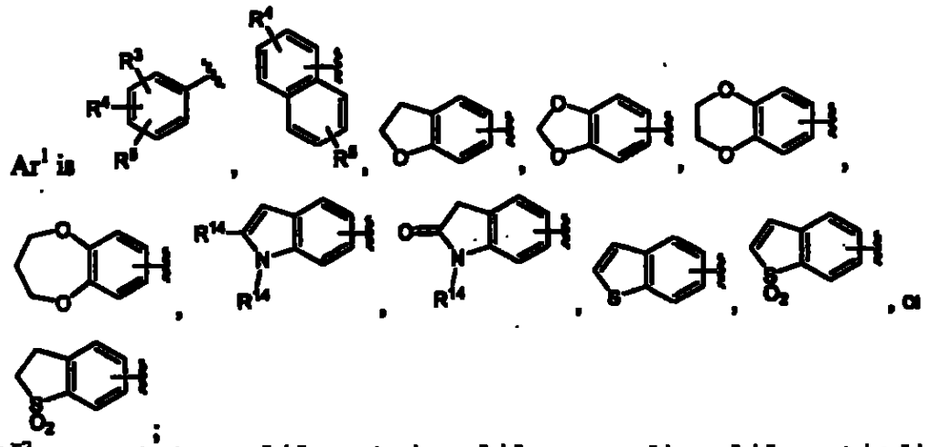
R^{10} es hidrógeno, C_{1-6}alquilo, o C_{1-6}hidroxialquilo;

R^{11} es hidrógeno, C_{1-6}alquilo, C_{3-7}cicloalquilo, COR^6, o CO_2R^6;

R^{12} es hidrógeno, hidroxi, $N(R^6)(R^6)$, SO_2R^7, OSO_2R^7, o dioxotiazinilo;

R^{13} es azetidinonilo, pirrolidinonilo, valerolactamilo, caprolactamilo, maleimido, oxazolidonilo, o dioxotiazinilo, y está substituido con 0-1 substituyentes seleccionados del grupo que consiste de hidroximetilo, acetoximetilo, y aminometilo;

R^{14} es hidrógeno o C_{1-6}alquilo;

Ar^1 is 

;

A^{r2} es tetrazolilo, triazolilo, oxadiazolilo, tiadiazolilo, pirazolilo, imidazolilo, oxazolilo, tiazolilo, isoxazolilo, isotiazolilo, furanilo, tienilo, pirrolilo, pirimidinilo, pirazinilo, piridinilo, hidroxipiridinilo, quinolinilo,

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isoquinolinilo, o indolilo, y está substituido con 0-2 substituyentes seleccionados del grupo que consiste de halo, ciano, bencilo, C_{1-6}alquilo, C_{1-6}alcoxi, $N(R^8)(R^9)$, $CON(R^8)(R^9)$, CO_2R^6, $CONHSO_2N(R^6)(R^6)$, $CONHSO_2N(R^6)$(fenilo), y $CONHSO_2N(R^6)$(halofenilo);

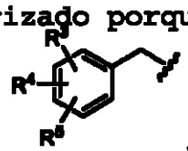
Ar^3 es fenilo substituido con 0-2 substituyentes seleccionados del grupo que consiste de halo, ciano, hidroxi, C_{1-6}alquilo, C_{1-6}alcoxi, (C_{1-6}alcoxi)metilo, C_{1-6}haloalquilo, C_{1-6}haloalcoxi, $N(R^8)(R^9)$, $CON(R^6)(R^6)$, y $CH_2N(R^8)(R^9)$, o es dioxolanilfenilo; y

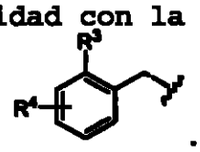
X-Y-Z es $C(R^{14})_2OC(R^{14})_2$, $C(R^{14})_2OC(R^{14})_2C(R^{14})_2$, o $C(R^{14})_2OC(R^{14})_2C(R^{14})_2C(R^{14})_2$;

o un sal o solvato farmacéuticamente aceptable de los mismos.

2. Compuesto de conformidad con la reivindicación 1, caracterizado porque R^1 es $C_{1-6}(Ar^1)$alquilo.

3. Compuesto de conformidad con la reivindicación 1, caracterizado porque

R^1 es  .

4. Compuesto de conformidad con la reivindicación 1 caracterizado porque R^1 es  .

5. Compuesto de conformidad con la reivindicación 1, caracterizado porque R^2 es hidrógeno.

6. Compuesto de conformidad con la reivindicación 1,

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caracterizado porque R^3 es hidrógeno, halo, $N(R^8)(R^9)$, $N(R^6)COR^7$, $OCON(R^8)(R^9)$, $CON(R^8)(R^9)$, SOR^7, SO_2R^7, $SO_2N(R^6)(R^6)$, $PO(OR^6)_2$, R^{13}, o Ar^2.

7. Compuesto de conformidad con la reivindicación 1, caracterizado porque X-Y-Z es $C(R^{14})_2OCH_2$, $C(R^{14})_2OCH_2CH_2$, o $C(R^{14})_2OCH_2CH_2CH_2$.

8. Compuesto de conformidad con la reivindicación 1, caracterizado porque X-Y-Z es CH_2OCH_2, $C(CH_3)HOCH_2$, $C(CH_3)_2OCH_2$, $CH_2OCH_2CH_2$, $C(CH_3)HOCH_2CH_2$, $C(CH_3)OCH_2CH_2$, $CH_2OCH_2CH_2CH_2$, $C(CH_3)HOCH_2CH_2CH_2$, o $C(CH_3)_2OCH_2CH_2CH_2$.

9. Compuesto de conformidad con la reivindicación 1,caracterizado porque es seleccionado del grupo que consiste de

N-[[4-fluoro-2-[(metilamino)carbonil]fenil]metil]-4,6,7,9-tetrahidro-3-hidroxi-9,9-dimetil-4-oxo-pirimido[2,1-c][1,4]oxazin-2-carboxamida;

9,9-dietil-N-[[4-fluoro-2-(1H-1,2,4-triazol-1-il)fenil]metil]-4,6,7,9-tetrahidro-3-hidroxi-4-oxo-pirimido[2,1c][1,4]oxazin-2-carboxamida;

9,9-dietil-N-[[4-fluoro-2-(metilsulfonil)fenil]metil]-4,6,7,9-tetrahidro-3-hidroxi-4-oxo-pirimido[2,1-c][1,4]oxazin-2-carboxamida;

N-[[2-[(dimetilamino)sulfonil]-4-fluorofenil]metil]-9,9-dietil-4,6,7,9-tetrahidro-3-hidroxi-4-oxo-pirimido[2,1-c][1,4]oxazin-2-carboxamida;

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N-[[4-fluoro-2-(2-oxo-1-azetidinil)fenil]metil]-4,6,7,9-tetrahidro-3-hidroxi-9,9-dimetil-4-oxo-pirimido[2,1-c][1,4]oxazin-2-carboxamida;

9,9-dietil-N-[[4-fluoro-2-[(metilamino)carbonil]fenil]metil]-4,6,7,9-tetrahidro-3-hidroxi-4-oxo-pirimido[2,1-c][1,4]oxazin-2-carboxamida;

N-[[4-fluoro-2-(2-oxo-3-oxazolidinil)fenil]metil]-4,6,7,9-tetrahidro-3-hidroxi-9,9-dimetil-4-oxo-pirimido[2,1-c][1,4]oxazin-2-carboxamida;

N-[[4-fluoro-2-(metilsulfonil)fenil]metil]-4,6,7,9-tetrahidro-3-hidroxi-9,9-dimetil-4-oxo-pirimido[2,1-c][1,4]oxazin-2-carboxamida;

N-[[4-fluoro-2-(1H-1,2,4-triazol-1-il)fenil]metil]-4,7,8,10-tetrahidro-3-hidroxi-10,10-dimetil-4-oxo-6H-pirimido[2,1-c][1,4]oxazepin-2-carboxamida;

N-[[4-fluoro-2-(3-metil-1H-1,2,4-triazol-1-il)fenil]metil]-4,6,7,9-tetrahidro-3-hidroxi-9,9-dimetil-4-oxo-pirimido[2,1-c][1,4]oxazin-2-carboxamida;

N-[[4-fluoro-2-(2-oxo-1-pirrolidinil)fenil]metil]-4,6,7,9-tetrahidro-3-hidroxi-9,9-dimetil-4-oxo-pirimido[2,1-c][1,4]oxazin-2-carboxamida;

N-[[4-fluoro-2-(tetrahidro-1,1-dióxido-2H-1,2-tiazin-2-il)fenil]metil]-4,6,7,9-tetrahidro-3-hidroxi-9,9-dimetil-4-oxo-pirimido[2,1-c][1,4]oxazin-2-carboxamida;

N-[[4-fluoro-2-(1H-1,2,4-triazol-1-il)fenil]metil]-

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4,6,7,9-tetrahidro-3-hidroxi-9,9-dimetil-4-oxo-pirimido[2,1-c][1,4]oxazin-2-carboxamida;

N-[[4-fluoro-2-[(metilamino)carbonil]fenil]metil]-4,7,8,10-tetrahidro-3-hidroxi-10,10-dimetil-4-oxo-6H-pirimido[2,1-c][1,4]oxazepin-2-carboxamida;

9,9-dietil-4,6,7,9-tetrahidro-3-hidroxi-4-oxo-N-[[2-(tetrahidro-1,1-dióxido-2H-1,2-tiazin-2-il)fenil]metil]-pirimido[2,1-c][1,4]oxazin-2-carboxamida;

N-[[4-fluoro-2-(1,2,3-tiadiazol-4-il)fenil]metil]-4,6,7,9-tetrahidro-3-hidroxi-9,9-dimetil-4-oxo-pirimido[2,1-c][1,4]oxazin-2-carboxamida;

N-[[4-fluoro-2-(metilsulfonil)fenil]metil]-4,7,8,10-tetrahidro-3-hidroxi-10,10-dimetil-4-oxo-6H-pirimido[2,1-c][1,4]oxazepin-2-carboxamida;

N-[[4-fluoro-2-(1-metil-1H-tetrazol-5-il)fenil]metil]-4,6,7,9-tetrahidro-3-hidroxi-9,9-dimetil-4-oxo-pirimido[2,1-c][1,4]oxazin-2-carboxamida;

N-[[4-fluoro-2-(5-metil-1H-1,2,4-triazol-1-il)fenil]metil]-4,6,7,9-tetrahidro-3-hidroxi-9,9-dimetil-4-oxo-pirimido[2,1-c][1,4]oxazin-2-carboxamida;

N-[[4-fluoro-2-(2-oxo-1-piperidinil)fenil]metil]-4,6,7,9-tetrahidro-3-hidroxi-9,9-dimetil-4-oxo-pirimido[2,1-c][1,4]oxazin-2-carboxamida;

N-[[2-[(dimetilamino)sulfonil]-4-fluorofenil]metil]-4,6,7,9-tetrahidro-3-hidroxi-9,9-dimetil-4-oxo-pirimido[2,1-

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c][1,4]oxazin-2-carboxamida;

N-[(4-fluorofenil)metil]-4,6,7,9-tetrahidro-3-hidroxi-9,9-dimetil-4-oxo-pirimido[2,1-c][1,4]oxazin-2-carboxamida;

4,6,7,9-tetrahidro-3-hidroxi-9,9-dimetil-4-oxo-N-[[2-(2-oxo-3-oxazolidinil)fenil]metil]-pirimido[2,1-c][1,4]oxazin-2-carboxamida;

N-[[4-fluoro-2-[(metilamino)sulfonil]fenil]metil]-4,6,7,9-tetrahidro-3-hidroxi-9,9-dimetil-4-oxo-pirimido[2,1-c][1,4]oxazin-2-carboxamida;

N-[[2-(acetilamino)-4-fluorofenil]metil]-4,6,7,9-tetrahidro-3-hidroxi-9,9-dimetil-4-oxo-pirimido[2,1-c][1,4]oxazin-2-carboxamida;

N-[[4-fluoro-2-[3-[(4-metil-1-piperazinil)carbonil]-1H-1,2,4-triazol-il]fenil]metil]-4,6,7,9-tetrahidro-3-hidroxi-9,9-dimetil-4-oxo-pirimido[2,1-c][1,4]oxazin-2-carboxamida;

N-[[4-fluoro-2-(4-morfolinilcarbonil)fenil]metil]-4,6,7,9-tetrahidro-3-hidroxi-9,9-dimetil-4-oxo-pirimido[2,1-c][1,4]oxazin-2-carboxamida;

N-[[4-fluoro-2-[[(2-hidroxietil)amino]carbonil]fenil]metil]-4,6,7,9-tetrahidro-3-hidroxi-9,9-dimetil-4-oxo-pirimido[2,1-c][1,4]oxazin-2-carboxamida;

N-[[4-fluoro-2-[3-(4-morfolinilcarbonil)-1H-1,2,4-triazol-1-il]fenil]metil]-4,6,7,9-tetrahidro-3-hidroxi-9,9-dimetil-4-oxo-pirimido[2,1-c][1,4]oxazin-2-carboxamida;

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4,6,7,9-tetrahidro-3-hidroxi-9,9-dimetil-4-oxo-N-[[2-(2-oxo-1-azetidinil)fenil]metil]-pirimido[2,1-c][1,4]oxazin-2-carboxamida;

N-[[4-fluoro-2-(1H-pirazol-5-il)fenil]metil]-4,6,7,9-tetrahidro-3-hidroxi-9,9-dimetil-4-oxo-pirimido[2,1-c][1,4]oxazin-2-carboxamida;

N-[[2-[3-[(dimetilamino)carbonil]-1H-1,2,4-triazol-1-il]-4-fluorofenil]metil]-4,6,7,9-tetrahidro-3-hidroxi-9,9-dimetil-4-oxo-pirimido[2,1-c][1,4]oxazin-2-carboxamida;

N-[(4-fluorofenil)metil]-4,6,7,9-tetrahidro-3-hidroxi-9,9-dimetil-4-oxo-pirimido[2,1-c][1,4]oxazin-2-carboxamida;

N-[[3-fluoro-2-(tetrahidro-1,1-dióxido-2H-1,2-tiazin-2-il)fenil]metil]-4,6,7,9-tetrahidro-3-hidroxi-9,9-dimetil-4-oxo-pirimido[2,1-c][1,4]oxazin-2-carboxamida;

4,6,7,9-tetrahidro-3-hidroxi-9,9-dimetil-N-[[2-(metilsulfonil)fenil]metil]-4-oxo-pirimido[2,1-c][1,4]oxazin-2-carboxamida;

N-[[4-fluoro-2-(4-morfolinil)fenil]metil]-4,6,7,9-tetrahidro-3-hidroxi-9,9-dimetil-4-oxo-pirimido[2,1-c][1,4]oxazin-2-carboxamida;

Éster de 5-fluoro-2-[[[(4,6,7,9-tetrahidro-3-hidroxi-9,9-dimetil-4-oxo-pirimido[2,1-c][1,4]oxazin-2-il)carbonil]amino]metil]fenilo del ácido N,N-dimetil-carbámico;

N-[[2-(aminosulfonil)-4-fluorofenil]metil]-4,6,7,9-

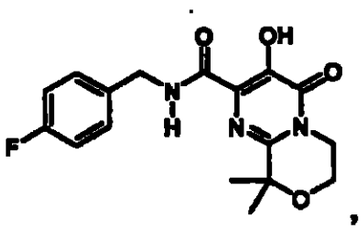
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tetrahidro-3-hidroxi-9,9-dimetil-4-oxo-pirimido[2,1-c][1,4]oxazin-2-carboxamida; y

Éster de dimetilo del ácido [5-fluoro-2-[[[(4,6,7,9-tetrahidro-3-hidroxi-9,9-dimetil-4-oxopirimido[2,1-c][1,4]oxazin-2-il)carbonil]amino]metil]fenil]-fosfónico;

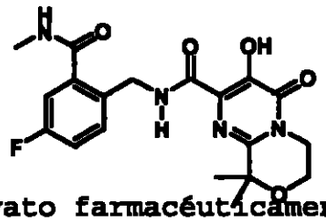
o una sal o solvato farmacéuticamente aceptable de los mismos.

10. Compuesto de conformidad con la reivindicación 1,



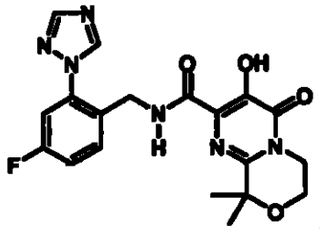
o un sal o solvato farmacéuticamente aceptable del mismo.

11. Compuesto de conformidad con la reivindicación 1,



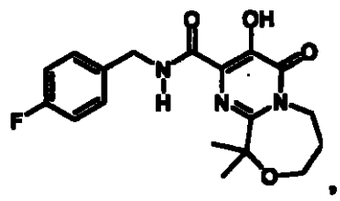
o un sal o solvato farmacéuticamente aceptable del mismo.

12. Compuesto de conformidad con la reivindicación 1,



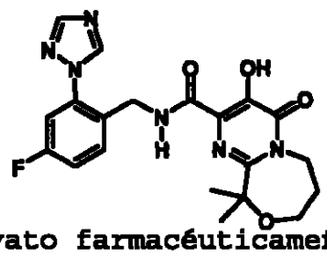
o una sal o solvato farmacéuticamente aceptable del mismo.

13. Compuesto de conformidad con la reivindicación 1,



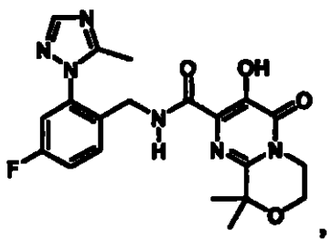
o una sal o solvato farmacéuticamente aceptable del mismo.

14. Compuesto de conformidad con la reivindicación 1,



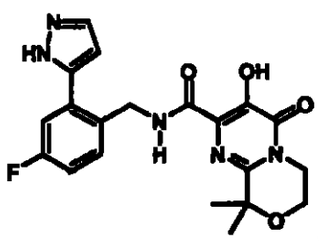
o una sal o solvato farmacéuticamente aceptable del mismo.

15. Compuesto de conformidad con la reivindicación 1,



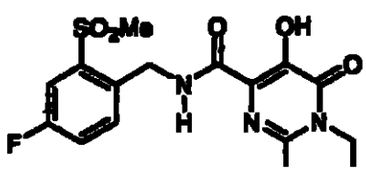
o una sal o solvato farmacéuticamente aceptable del mismo.

16. Compuesto de conformidad con la reivindicación 1,



o una sal o solvato farmacéuticamente aceptable del mismo.

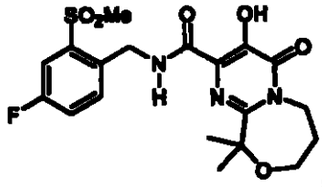
17. Compuesto de conformidad con la reivindicación 1,



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o una sal o solvato farmacéuticamente aceptable del mismo.

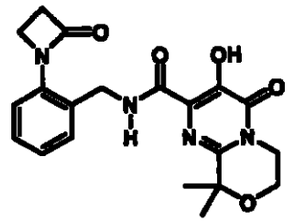
18. Compuesto de conformidad con la reivindicación 1,



,

o una sal o solvato farmacéuticamente aceptable del mismo.

19. Compuesto de conformidad con la reivindicación 1,



,

o una sal o solvato farmacéuticamente aceptable del mismo.

20. Composición útil para el tratamiento de infecciones por VIH, caracterizada porque comprende una cantidad terapéutica de un compuesto de conformidad con la reivindicación 1 y un portador farmacéuticamente aceptable.

21. Composición de conformidad con la reivindicación 20, caracterizada porque además comprende una cantidad terapéuticamente efectiva de al menos otro agente usado para el tratamiento del SIDA o infección por VIH seleccionado del grupo que consiste de inhibidores de la transcriptasa inversa

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del VIH nucleósidos, inhibidores de la transcriptasa inversa del VIH no nucleósidos, inhibidores de la proteasa del VIH, inhibidores de la fusión del VIH, inhibidores del enlace del VIH, inhibidores CCR5, inhibidores CXCR4, inhibidores del florecimiento o maduración del VIH, e inhibidores de la integrasa del VIH, y un portador farmacéuticamente aceptable.

22. Composición de conformidad con la reivindicación caracterizada porque el compuesto de conformidad con la reivindicación 1 es N-[(4-fluorofenil)metil]-4,6,7,9-tetrahidro-3-hidroxi-9,9-dimetil-4-oxo-pirimido[2,1-c][1,4]oxazina-2-carboxamida.

23. Composición de conformidad con la reivindicación 22, caracterizada porque comprende además una cantidad terapéuticamente efectiva de al menos otro agente usado para el tratamiento del SIDA o infección por VIH seleccionado del grupo que consiste de inhibidores de la transcriptasa inversa del VIH nucleósidos, inhibidores de la transcriptasa inversa del VIH no nucleósidos, inhibidores de la proteasa del VIH, inhibidores de la fusión del VIH, inhibidores del enlace del VIH, inhibidores CCR5, inhibidores CXCR4, inhibidores del florecimiento o maduración del VIH, e inhibidores de la integrasa del VIH, y un portador farmacéuticamente aceptable.

24. Método para el tratamiento de la infección por VIH, caracterizado porque comprende administrar una cantidad terapéuticamente efectiva de un compuesto de conformidad con

la reivindicación 1, o una sal o solvato farmacéuticamente aceptable del mismo, a una paciente que necesita del mismo.

25. Método de conformidad con la reivindicación 24, caracterizado porque comprende además administrar una cantidad terapéuticamente efectiva de al menos otro agente usando para el tratamiento del SIDA o infección por VIH seleccionado del grupo que consiste de inhibidores de la transcriptasa inversa del VIH nucleósidos, inhibidores de la transcriptasa inversa del VIH no nucleósidos, inhibidores de la proteasa del VIH, inhibidores de la fusión del VIH, inhibidores del enlace del VIH, inhibidores CCR5, inhibidores CXCR4, inhibidores del florecimiento o maduración del VIH, e inhibidores de la integrasa del VIH.

26. Método de conformidad con la reivindicación 24, caracterizado porque el compuesto de conformidad con la reivindicación 1 es N-[(4-fluorofenil)metil]-4,6,7,9-tetrahidro-3-hidroxi-9,9-dimetil-4-oxo-pirimido[2,1-c][1,4]oxazina-2-carboxamida.

27. Método de conformidad con la reivindicación 26, caracterizado porque comprende además una cantidad terapéuticamente efectiva de al menos otro agente usado para el tratamiento del SIDA o infección por VIH seleccionado del grupo que consiste de inhibidores de la transcriptasa inversa del VIH nucleósidos, inhibidores de la transcriptasa inversa del VIH no nucleósidos, inhibidores de la proteasa del VIH,

inhibidores de la fusión del VIH, inhibidores del enlace del VIH, inhibidores CCR5, inhibidores CXCR4, inhibidores del florecimiento o maduración del VIH, e inhibidores de la integrasa del VIH, y un portador farmacéuticamente aceptable.

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RESUMEN DE LA INVENCIÓN

La invención abarca una serie de compuestos de pirimidinona cíclicos bicíclicos de Fórmula I que inhiben la integrasa del VIH y previenen la integración viral al ADN humano. Esta acción hace a los compuestos útiles para tratar infección por VIH y SIDA. La invención también abarca composiciones farmacéuticas y métodos para tratar aquellos infectados con VIH.

10253-100 PCT
102-485

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PATENT COOPERATION TREATY

From the INTERNATIONAL SEARCHING AUTHORITY

To: RECEIVED
BRISTOL-MYERS SQUIBB COMPANY
P[illegible]
BMS PATENT LAW
Attn. Epperson, James
Lawrenceville-Princeton Road
Princeton, [illegible] 08543-4000
UNITED STATES OF AMERICA
AUG 24 2005
Docketed Item Claims Amended 1/19/05
Due Date Int'l Exam 3/28/06
Attorney CDQuinn

PCT

NOTIFICATION OF TRANSMITTAL OF THE INTERNATIONAL SEARCH REPORT AND THE WRITTEN OPINION OF THE INTERNATIONAL SEARCHING AUTHORITY, OR THE DECLARATION

~~U.S.S.N. 10/053,104 filed 1/19/05~~

(PCT Rule 44.1)

Applicant's or agent's file reference 10253PCT	Date of mailing (day/month/year) 19/08/2005
International application No. PCT/US2005/016473	FOR FURTHER ACTION See paragraphs 1 and 4 below
Applicant BRISTOL-MYERS SQUIBB COMPANY	International filing date (day/month/year) 12/05/2005

1. [x] The applicant is hereby notified that the international search report and the written opinion of the International Searching Authority have been established and are transmitted herewith.

   Filing of amendments and statement under Article 19:
   The applicant is entitled, if he so wishes, to amend the claims of the International Application (see Rule 46):

   When? The time limit for filing such amendments is normally 2 months from the date of transmittal of the International Search Report; however, for more details, see the notes on the accompanying sheet.

   Where? Directly to the International Bureau of WIPO, 34 chemin des Colombettes 1211 Geneva 20, Switzerland, Facsimile No.: (41-22) 740.14.35

   For more detailed instructions, see the notes on the accompanying sheet.

2. [ ] The applicant is hereby notified that no international search report will be established and that the declaration under Article 17(2)(a) to that effect and the written opinion of the International Searching Authority are transmitted herewith.

3. [ ] With regard to the protest against payment of (an) additional fee(s) under Rule 40.2, the applicant is notified that:

   [ ] the protest together with the decision thereon has been transmitted to the International Bureau together with the applicant's request to forward the texts of both the protest and the decision thereon to the designated Offices.

   [ ] no decision has been made yet on the protest; the applicant will be notified as soon as a decision is made.

4. **Reminders**

   Shortly after the expiration of 18 months from the priority date, the international application will be published by the International Bureau. If the applicant wishes to avoid or postpone publication, a notice of withdrawal of the international application, or of the priority claim, must reach the International Bureau as provided in Rules 90*bis*.1 and 90*bis*.3, respectively, before the completion of the technical preparations for international publication.

   The applicant may submit comments on an informal basis on the written opinion of the International Searching Authority to the International Bureau. The International Bureau will send a copy of such comments to all designated Offices unless an international preliminary examination report has been or is to be established. These comments would also be made available to the public but not before the expiration of 30 months from the priority date.

   Within 19 months from the priority date, but only in respect of some designated Offices, a demand for international preliminary examination must be filed if the applicant wishes to postpone the entry into the national phase until 30 months from the priority date (in some Offices even later); otherwise, the applicant must, within 20 months from the priority date, perform the prescribed acts for entry into the national phase before those designated Offices.

   In respect of other designated Offices, the time limit of 30 months (or later) will apply even if no demand is filed within 19 months.

   See the Annex to Form PCT/IB/301 and, for details about the applicable time limits, Office by Office, see the *PCT Applicant's Guide*, Volume II, National Chapters and the WIPO Internet site.

Name and mailing address of the International Searching Authority European Patent Office, P.B. 5818 Patentlaan 2 NL-2280 HV Rijswijk Tel. (+31-70) 340-2040, Tx. 31 651 epo nl, Fax (+31-70) 340-3016	Authorized officer Dominique Hundt

Form PCT/ISA/220 (January 2004) *(See notes on accompanying sheet)*

PATENT COOPERATION TREATY

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INTERNATI_NAL SEARCH REPORT

(PCT Article 18 and Rules 43 and 44)

Applicant's or agent's file reference	FOR FURTHER ACTION	see Form PCT/ISA/220 as well as, where applicable, item 5 below.
10253PCT		
International application No.	International filing date *(day/month/year)*	(Earliest) Priority Date *(day/month/year)*
PCT/US2005/016473	12/05/2005	28/05/2004
Applicant		
BRISTOL-MYERS SQUIBB COMPANY		

This International Search Report has been prepared by this International Searching Authority and is transmitted to the applicant according to Article 18. A copy is being transmitted to the international Bureau.

This International Search Report consists of a total of 4 sheets.

[X] It is also accompanied by a copy of each prior art document cited in this report.

1. **Basis of the report**
   a. With regard to the language, the international search was carried out on the basis of the international application in the language in which it was filed, unless otherwise indicated under this item.
      [ ] The international search was carried out on the basis of a translation of the international application furnished to this Authority (Rule 23.1(b)).
   b. [ ] With regard to any nucleotide and/or amino acid sequence disclosed in the international application, see Box No. I.

2. [X] Certain claims were found unsearchable (See Box II).

3. [ ] Unity of invention is lacking (see Box III).

4. With regard to the title,
   [X] the text is approved as submitted by the applicant.
   [ ] the text has been established by this Authority to read as follows:

5. With regard to the abstract,
   [X] the text is approved as submitted by the applicant.
   [ ] the text has been established, according to Rule 38.2(b), by this Authority as it appears in Box No. IV. The applicant may, within one month from the date of mailing of this international search report, submit comments to this Authority.

6. With regard to the drawings,
   a. the figure of the drawings to be published with the abstract is Figure No. _____
      [ ] as suggested by the applicant.
      [ ] as selected by this Authority, because the applicant failed to suggest a figure.
      [ ] as selected by this Authority, because this figure better characterizes the invention.
   b. [ ] none of the figures is to be published with the abstract.

INTERNATIONAL SEARCH REPORT

International Application No
PCT/US2005/016473

A. CLASSIFICATION OF SUBJECT MATTER
IPC 7 C07D498/04 A61K31/519 A61P31/18
//(C07D498/04,263:00,239:00),(C07D498/04,265:00,239:00),(C07D498/04 267:00,239:00)

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

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B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)
IPC 7 C07D

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

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)
EPO-Internal, WPI Data, PAJ, BEILSTEIN Data, CHEM ABS Data

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
A	✓ WO 03/035077 A (ISTITUTO DI RICERCHE DI BIOLOGIA MOLECOLARE P. ANGELETTI SPA; CRESCENZ) 1 May 2003 (2003-05-01) claims 1,30; tables 1,2	1-27
P,A	✓ WO 2004/058756 A (ISTITUTO DI RICERCHE DI BIOLOGIA MOLECOLARE P. ANGELETTI SPA; CRESCENZ) 15 July 2004 (2004-07-15) claims 1,14; table 1	1-27
P,A	✓ WO 2004/058757 A (ISTITUTO DI RICERCHE DI BIOLOGIA MOLECOLARE P. ANGELETTI SPA; CRESCENZ) 15 July 2004 (2004-07-15) claims 1,8; table 1	1-27

☐ Further documents are listed in the continuation of box C.

☒ Patent family members are listed in annex.

* Special categories of cited documents :

"A" document defining the general state of the art which is not considered to be of particular relevance

"E" earlier document but published on or after the international filing date

"L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)

"O" document referring to an oral disclosure, use, exhibition or other means

"P" document published prior to the international filing date but later than the priority date claimed

"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention

"X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone

"Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art.

"&" document member of the same patent family

Date of the actual completion of the international search	Date of mailing of the international search report
11 August 2005	19/08/2005

Name and mailing address of the ISA	Authorized officer
European Patent Office, P.B. 5818 Patentlaan 2 NL - 2280 HV Rijswijk Tel. (+31-70) 340-2040, Tx. 31 651 epo nl, Fax: (+31-70) 340-3016	Seymour, L

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Form PCT/ISA/210 (second sheet) (January 2004)

INTERNATIONAL SEARCH REPORT

International application No.
PCT/US2005/016473

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Box II Observations where certain claims were found unsearchable (Continuation of item 2 of first sheet)

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

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

Although claims 24-27 are directed to a method of treatment of the human/animal body, the search has been carried out and based on the alleged effects of the compound/composition.

2. [ ] Claims Nos.:
because they relate to parts of the International Application that do not comply with the prescribed requirements to such an extent that no meaningful International Search can be carried out, specifically:

3. [ ] Claims Nos.:
because they are dependent claims and are not drafted in accordance with the second and third sentences of Rule 6.4(a).

Box III Observations where unity of invention is lacking (Continuation of item 3 of first sheet)

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

1. [ ] As all required additional search fees were timely paid by the applicant, this International Search Report covers all searchable claims.

2. [ ] As all searchable claims could be searched without effort justifying an additional fee, this Authority did not invite payment of any additional fee.

3. [ ] As only some of the required additional search fees were timely paid by the applicant, this International Search Report covers only those claims for which fees were paid, specifically claims Nos.:

4. [ ] No required additional search fees were timely paid by the applicant. Consequently, this International Search Report is restricted to the invention first mentioned in the claims; it is covered by claims Nos.:

Remark on Protest

[ ] The additional search fees were accompanied by the applicant's protest.

[ ] No protest accompanied the payment of additional search fees.

INTERNATI NAL SEARCH REP RT

Information on patent family members

International Application No
PCT/US2005/016473

Patent document cited in search report	Publication date	Patent family member(s)	Publication date
WO 03035077 A	01-05-2003	BR 0213522 A	08-09-2004
		CA 2463976 A1	01-05-2003
		EP 1441735 A1	04-08-2004
		WO 03035077 A1	01-05-2003
		HU 0401740 A2	28-12-2004
		JP 2005511543 T	28-04-2005
		MX PA04003932 A	18-06-2004
		US 2005025774 A1	03-02-2005
		ZA 200402796 A	20-01-2005
WO 2004058756 A	15-07-2004	AU 2003292436 A1	22-07-2004
		AU 2003292437 A1	22-07-2004
		WO 2004058756 A1	15-07-2004
		WO 2004058757 A1	15-07-2004
WO 2004058757 A	15-07-2004	AU 2003292436 A1	22-07-2004
		AU 2003292437 A1	22-07-2004
		WO 2004058756 A1	15-07-2004
		WO 2004058757 A1	15-07-2004

PATENT COOPERATION TREATY

From the
INTERNATIONAL SEARCHING AUTHORITY

To:

see form PCT/ISA/220

PCT

WRITTEN OPINION OF THE INTERNATIONAL SEARCHING AUTHORITY

(PCT Rule 43*bis*.1)

Date of mailing (day/month/year) see form PCT/ISA/210 (second sheet)	
Applicant's or agent's file reference see form PCT/ISA/220	**FOR FURTHER ACTION** See paragraph 2 below

International application No.	International filing date (day/month/year)	Priority date (day/month/year)
PCT/US2005/016473	12.05.2005	28.05.2004

International Patent Classification (IPC) or both national classification and IPC
C07D498/04, A61K31/519, A61P31/18

Applicant
BRISTOL-MYERS SQUIBB COMPANY

1. This opinion contains indications relating to the following items:

- ☒ Box No. I Basis of the opinion
- ☒ Box No. II Priority
- ☒ Box No. III Non-establishment of opinion with regard to novelty, inventive step and industrial applicability
- ☐ Box No. IV Lack of unity of invention
- ☒ Box No. V Reasoned statement under Rule 43*bis*.1(a)(i) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement
- ☒ Box No. VI Certain documents cited
- ☐ Box No. VII Certain defects in the international application
- ☐ Box No. VIII Certain observations on the international application

2. **FURTHER ACTION**

If a demand for international preliminary examination is made, this opinion will usually be considered to be a written opinion of the International Preliminary Examining Authority ("IPEA"). However, this does not apply where the applicant chooses an Authority other than this one to be the IPEA and the chosen IPEA has notified the International Bureau under Rule 66.1*bis*(b) that written opinions of this International Searching Authority will not be so considered.

If this opinion is, as provided above, considered to be a written opinion of the IPEA, the applicant is invited to submit to the IPEA a written reply together, where appropriate, with amendments, before the expiration of three months from the date of mailing of Form PCT/ISA/220 or before the expiration of 22 months from the priority date, whichever expires later.

For further options, see Form PCT/ISA/220.

3. For further details, see notes to Form PCT/ISA/220.

Name and mailing address of the ISA:	Authorized Officer
European Patent Office D-80298 Munich Tel. +49 89 2399 - 0 Tx: 523656 epmu d Fax: +49 89 2399 - 4465	Seymour, L Telephone No. +49 89 2399-8694

Form (PCT/ISA/237) (Cover Sheet) (January 2004)

WRITTEN OPINION OF THE INTERNATIONAL SEARCHING AUTHORITY

International application No. PCT/US2005/016473

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Box No. I Basis of the opinion

1. With regard to the **language**, this opinion has been established on the basis of the international application in the language in which it was filed, unless otherwise indicated under this item.

   ☐ This opinion has been established on the basis of a translation from the original language into the following language , which is the language of a translation furnished for the purposes of international search (under Rules 12.3 and 23.1(b)).

2. With regard to any **nucleotide and/or amino acid sequence** disclosed in the international application and necessary to the claimed invention, this opinion has been established on the basis of:

   a. type of material:

   ☐ a sequence listing

   ☐ table(s) related to the sequence listing

   b. format of material:

   ☐ in written format

   ☐ in computer readable form

   c. time of filing/furnishing:

   ☐ contained in the international application as filed.

   ☐ filed together with the international application in computer readable form.

   ☐ furnished subsequently to this Authority for the purposes of search.

3. ☐ In addition, in the case that more than one version or copy of a sequence listing and/or table relating thereto has been filed or furnished, the required statements that the information in the subsequent or additional copies is identical to that in the application as filed or does not go beyond the application as filed, as appropriate, were furnished.

4. Additional comments:

Box No. II Priority

1. ☒ The validity of the priority claim has not been considered because the International Searching Authority does not have in its possession a copy of the earlier application whose priority has been claimed or, where required, a translation of that earlier application. This opinion has nevertheless been established on the assumption that the relevant date (Rules 43*bis*.1 and 64.1) is the claimed priority date.

2. ☐ This opinion has been established as if no priority had been claimed due to the fact that the priority claim has been found invalid (Rules 43*bis*.1 and 64.1). Thus for the purposes of this opinion, the international filing date indicated above is considered to be the relevant date.

3. Additional observations, if necessary:

Box No. III Non-establishment of opinion with regard to novelty, inventive step and industrial applicability

The questions whether the claimed invention appears to be novel, to involve an inventive step (to be non obvious), or to be industrially applicable have not been examined in respect of:

☐ the entire international application,

☒ claims Nos. 24-27 with respect to industrial applicability

because:

☒ the said international application, or the said claims Nos. 24-27 with respect to industrial applicability relate to the following subject matter which does not require an international preliminary examination *(specify)*:

see separate sheet

☐ the description, claims or drawings *(indicate particular elements below)* or said claims Nos. are so unclear that no meaningful opinion could be formed *(specify)*:

☐ the claims, or said claims Nos. are so inadequately supported by the description that no meaningful opinion could be formed.

☐ no international search report has been established for the whole application or for said claims Nos.

☐ the nucleotide and/or amino acid sequence listing does not comply with the standard provided for in Annex C of the Administrative Instructions in that:

the written form	☐	has not been furnished
	☐	does not comply with the standard
the computer readable form	☐	has not been furnished
	☐	does not comply with the standard

☐ the tables related to the nucleotide and/or amino acid sequence listing, if in computer readable form only, do not comply with the technical requirements provided for in Annex C-*bis* of the Administrative Instructions.

☐ See separate sheet for further details

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Box No. V Reasoned statement under Rule 43*bis*.1(a)(i) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement

1. Statement

Novelty (N)	Yes:	Claims	1-27
	No:	Claims	
Inventive step (IS)	Yes:	Claims	1-27
	No:	Claims	
Industrial applicability (IA)	Yes:	Claims	1-23
	No:	Claims	

2. Citations and explanations

see separate sheet

Box No. VI Certain documents cited

1. Certain published documents (Rules 43*bis*.1 and 70.10)

and / or

2. Non-written disclosures (Rules 43*bis*.1 and 70.9)

see form 210

Re Item III

Claims 24-27 relate to subject-matter considered by this Authority to be covered by the provisions of Rule 67.1(iv) PCT. Consequently, no opinion will be formulated with respect to the industrial applicability of the subject-matter of these claims (Article 34(4)(a)(I) PCT).

Re Item V

1. Reference is made to the following document:

   D1 : WO 03/035077 A

2. The subject-matter of claim 1 is novel (Article 33(2) PCT): The present compounds differ from those of D1 in that the pyrimidinone ring is fused to a second ring.

3. The problem to be solved by the present application lies in the provision of further HIV integrase inhibitors (see present description, p. 3, lines 3-6 and Table 1).

   There is no incentive in the prior art for the skilled person to modify the HIV integrase inhibitors of D1 by fusion to a moiety -X-Y-Z- as defined in present claim 1. The solution proposed in claim 1 of the present application is therefore considered to involve an inventive step (Article 33(3) PCT).

4. Industrial applicability (Article 33(4) PCT)

   For the assessment of the present claims 24-27 on the question whether they are industrially applicable, no unified criteria exist in the PCT Contracting States. The patentability can also be dependent upon the formulation of the claims. The EPO, for example, does not recognize as industrially applicable the subject-matter of claims to the use of a compound in medical treatment, but may allow, however, claims to a known compound for first use in medical treatment and the use of such a compound for the manufacture of a medicament for a new medical treatment.

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Re Item VI

Certain published documents

	Application No Patent No	Publication date (day/month/year)	Filing date (day/month/year)	Priority date (valid claim) (day/month/year)
D2:	WO 2004/058756 A	15.07.2004	18.12.2003	
D3:	WO 2004/058757 A	15.07.2004	18.12.2003	

Documents D2 and D3 disclose HIV integrase inhibitors wherein the chain -X-Y-Z- contains only carbon atoms whereas in the present compounds -X-Y-Z- additionally contains an oxygen atom.

REPORTE DE BUSQUEDA INTERNACIONAL

No. de solicitud internacional
PCT/US2005/016473

A. CLASIFICACION DEL TEMA

IPC 7 C07D498/04, A61K 31/519, A61P 31/18
//(C07D498/04, 263:00), 239:00), (C07D498/04, 265:00, 239:00), (C07D498/04, 267:00), 239:00)

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De acuerdo a la Clasificación de Patentes Internacional (IPC) o a la clasificación nacional y a la IPC.

B. CAMPOS BUSCADOS

Documentación mínima buscada (sistema de clasificación seguido por los símbolos de clasificación):
IPC 7 C07D

Documentación buscada diferente a la documentación mínima, a la extensión que tales documentos están incluidos en los campos buscados :

Base de datos electrónicos consultados durante la búsqueda internacional (nombre de la base de datos y, en donde sea práctico, términos de búsqueda utilizados) :
EPO-Internal, WPI Data, PAJ, BEILSTEIN Data, CHEMS ABS Data,

C. DOCUMENTOS QUE SE CONSIDERA QUE SON RELEVANTES

Categoría	Cita del documento, con indicación, en donde sea apropiado, de los pasajes relevantes	Relevante para la Reiv. No.
A	WO 03/035077 A (ISTITUTO DI RICERCHE DI BIOLOGIA MOLECOLARE P. ANGELETTI SPA; CRESCENZ) 1 Mayo 2003 (2003-05-01) reivindicaciones 1,30; tablas 1,2	1-27
P,A	WO 2004/058756 A (ISTITUTO DI RICERCHE DI BIOLOGIA MOLECOLARE P. ANGELETTI SPA; CRESCENZ) 15 Julio 2004 (2004-07-15) reivindicaciones 1,14; tabla 1	1-27
P,A	WO 2004/058757 A (ISTITUTO DI RICERCHE DI BIOLOGIA MOLECOLARE P. ANGELETTI SPA; CRESCENZ) 15 Julio 2004 (2004-07-15) reivindicaciones 1,8; tabla 1	1-27

☐ Documentos adicionales se enlistan en la continuación del bloque C ☒ Véase familia de patentes anexa.

* Categorías especiales de los documentos citados
"A" documento que define el estado general de la técnica el cual no se considera ser de particular relevancia.
"E" documento anterior publicado en o después de la fecha de presentación internacional.
"L" documento el cual puede arrojar dudas sobre la(s) reivindicacion(es) de prioridad o el cual se cita para establecer la fecha de publicación de otra cita u otra razón especial (como se especifica)
"O" documento que se refiere a una descripción oral, uso, exhibición u otro medio
"P" documento publicado antes de la fecha de presentación internacional pero después de la fecha de prioridad reivindicada.
"T" documento posterior publicado después de la fecha de presentación internacional o fecha de prioridad y no en conflicto con la solicitud, pero citado para entender el principio o teoría fundamental de la invención.
"X" documento de relevancia particular; la invención reivindicada no puede ser considerada nueva o no se puede considerar que involucre una etapa inventiva cuando el documento es considerado de manera aislada.
"Y" documento de particular relevancia; no se puede considerar que la invención involucre una etapa inventiva cuando el documento es combinado con uno o más de tales documentos, tal combinación sería obvia para una persona experimentada en la técnica.
"&" documento miembro de la misma familia de patentes.

Fecha de la terminación real de la búsqueda internacional	Fecha de envío del reporte de búsqueda internacional
11 Agosto 2005	19/08/2006
Nombre y dirección de correspondencia de la ISA European Patent Office ,PB. 5818 Patentlaan 2 NL-2280 HV Rijswijk Tel (+31-70)340-2040, Tx. 31 551 epo nl Fax: (+31-70)340-3016	Funcionario Autorizado Seymour, L

REPORTE DE BUSQUEDA INTERNACIONAL

No. de solicitud internacional
PCT/US2005/016473

Bloque I Observaciones en donde ciertas reivindicaciones se encontraron inescrutables (Continuación del ítem 1 de la primera hoja)

Este reporte internacional no ha sido establecido con respecto a ciertas reivindicaciones bajo el Artículo 17(2) del PCT por las siguientes razones:

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1. [X] Reivindicaciones Nos.:
debido a que se relacionan con temas que no requieren ser buscados por esta Autoridad, a saber:

Aunque las reivindicaciones 24-27 estan dirigidas a un método de tratamiento del cuerpo humano/animal (Articulo 52(4) EPC), la búsqueda ha sido llevada a cabo y basada en los efectos alegados del compuesto/composición.

2. [ ] Reivindicaciones Nos.:
debido a que se relacionan con partes de la solicitud internacional que no cumplen con los requerimientos prescritos a tal extensión que ninguna búsqueda internacional significativa se puede llevar a cabo, específicamente:

[ ] Reivindicaciones Nos.:
debido a que son reivindicaciones dependientes y no están redactadas de acuerdo con las segundas y terceras oraciones de la Regla 6.4(a).

Bloque II Observaciones en donde se carece de unidad de la invención (Continuación del ítem 2 de la primera hoja)

La Autoridad de Búsqueda Internacional encontró múltiples invenciones en esta solicitud internacional, como sigue:

1. [ ] Ya que todas las cuotas de búsqueda adicionales fueron pagadas a tiempo por la solicitante, este reporte de búsqueda cubre todas las reivindicaciones escrutables.
2. [ ] Ya que todas las reivindicaciones escrutables pudieron ser buscadas sin esfuerzo que justifique una cuota adicional, esta Autoridad no invita al pago de ninguna cuota adicional.
3. [ ] Ya que solamente algunas de las cuotas de búsqueda adicionales requeridas fueron pagadas oportunamente por la Solicitante, este reporte de búsqueda internacional cubre solamente aquellas reivindicaciones para las cuales se pagaron Cuotas, específicamente las reivindicaciones Nos.:

4. [ ] Ninguna cuota de búsqueda adicional requerida fue pagada oportunamente por la solicitante. Consecuentemente, este Reporte de búsqueda internacional está restringido a la invención primero mencionada en las reivindicaciones; está Cubierta por las reivindicaciones Nos.:

Observación en protesta

[ ] Las cuotas de búsqueda adicionales estuvieron acompañadas por la protesta de la solicitante.

[ ] Ninguna protesta acompañó el pago de las cuotas de búsqueda adicional.

REPORTE DE BUSQUEDA INTERNACIONAL

No. De solicitud internacional
PCT/US2005/016473

Documento de patente citado en el Reporte de Búsquoda	Fecha de publicación	Miembro(s) de la familia de patente(s)		Fecha de publicación
WO 03035077 A	01-05-2003	BR	0213522 A	08-09-2004
		CA	2463976 A1	01-05-2003
		EP	1441735 A1	04-08-2004
		WO	03035077 A1	01-05-2003
		HU	0401740 A2	28-12-2004
		JP	2005511543 T	28-04-2005
		MX	PA04003932 A	18-06-2004
		US	2005025774 A1	03-02-2005
		ZA	200402796 A	20-01-2005
WO 2004058756 A	15-07-2004	AU	2003292436 A1	22-07-2004
		AU	2003292437 A1	22-07-2004
		WO	2004058756 A1	15-07-2004
		WO	2004058757 A1	15-07-2004
WO 2004058757 A	15-07-2004	AU	2003292436 A1	22-07-2004
		AU	2003292437 A1	22-07-2004
		WO	2004058756 A1	15-07-2004
		WO	2004058757 A1	15-07-2004

TRATADO DE COOPERACION EN MATERIA DE PATENTES

De la
AUTORIDAD EXAMINADORA PRELIMINAR INTERNACIONAL

Para: ver forma PCT/ISA/220	**PCT** **OPINIÓN ESCRITA DE LA AUTORIDAD DE BÚSQUEDA INTERNACIONAL** (Regla 43*bis*.1 PCT)
	Fecha de envio (día/mes/año) ver forma PCT/ISA/210 (segunda hoja)
Referencia de archivo del solicitante o agente ver forma PCT/ISA/220	**PARA ACCIÓN ADICIONAL** Ver párrafo 2 siguiente

No. de solicitud internacional	Fecha de presentación internacional (día/mes/año)	Fecha de prioridad (día/mes/año)
PCT/US2005/016473	12.05.2005	28.05.2004

Clasificación de Patente Internacional (IPC) o ambos clasificación nacional e IPC
C07D498/04, A61K 31/519, A61P 31/18

Solicitante
BRISTOL-MYERS SQUIBB COMPANY

1. Esta opinión contiene las indicaciones relacionadas a los siguientes incisos:
   - ☒ Cuadro No. I Bases de la Opinión
   - ☒ Cuadro No. II Prioridad
   - ☒ Cuadro No. III Sin establecimiento de la opinión con respecto a la novedad, etapa inventiva y aplicabilidad industrial
   - ☐ Cuadro No. IV Carente de unidad de la invención
   - ☒ Cuadro No. V Declaración razonada bajo la Regla 43bis.1(a)(i) con respecto a la novedad, etapa inventiva y aplicabilidad industrial; citas y explicaciones que soportan esta declaración.
   - ☒ Cuadro No. VI Ciertos documentos citados
   - ☐ Cuadro No. VII Ciertos defectos en la solicitud internacional
   - ☐ Cuadro No. VIII Ciertas observaciones en la solicitud internacional

2. **ACCIÓN ADICIONAL**
   Si se hace una demanda para el examen preliminar internacional, esta opinión será considerada ser una opinión escrita de la Autoridad de Examen Preliminar Internacional ("IPEA") a menos que ese esto no aplique donde el aspirante elige una Autoridad de otra manera que uno sea la IPEA y la IPEA elegida haya notificado a la Oficina Internacional bajo la Regla 66.1bis(b) donde las opiniones escritas de esta Autoridad de Búsqueda Internacional no serán así consideraba.

   Si esta opinión es, como la provista anteriormente, considerada para ser una opinión escrita de la IPEA, se invita al solicitante a someter a la IPEA una reapuesta escrita a la vez, cuando sea apropiado, con enmiendas, antes de la expiración de 3 meses a partir de la fecha del correo de la forma PCT/ISA/220 o antes de la expiración de 22 meses a partir de la fecha de prioridad, cualquiera expira más adelante.

   Para otras opciones, ver Forma PCT/ISA/220.

3. Para otros detalles, ver notas para la Formar PCT/ISA/220.

Nombre y dirección de correspondencia de la Autoridad de examen preliminar internacional	Oficial autorizado
European Patent Office (LOGOTIPO) D-80298 Munich Tel. +49 2399 – 0 Tx: 523656 epmu d Fax: +49 89 2399 - 4465	Seymour, L (SELLO) Teléfono No. +49 89 2399 8694

Forma PCT/ISA/237 (carátula) (enero de 2004)

Cuadro No. I Bases de la opinión

1. Con respecto al idioma, esta opinión se estableció basada en la solicitud internacional en el idioma en el que fue presentado, a menos que por otra parte se indique bajo este artículo.

   ☐ Esta opinión se estableció basado en la traducción del idioma original en el siguiente idioma, que es el idioma de una traducción proporcionada para los propósitos de la búsqueda internacional (bajo las Reglas 12.3 y 23.1 (b)).

2. Con respecto a cualquier **secuencia nucleótido y amino ácido** publicada en la solicitud internacional y necesaria para la invención reivindicada esta opinión se estableció basada en:

a. tipo de material:

   ☐ un listado de secuencia

   ☐ tabla(s) relacionada con el listado de secuencia

b. formato de material:

   ☐ en formato escrito

   ☐ en forma leíble en computadora

c. tiempo de limite/proporcionar:

   ☐ contenido en la solicitud internacional como se archivo.

   ☐ archivado junto con la solicitud internacional en forma leíble en computadora.

   ☐ proporcionado subsecuencialmente para esta autoridad para el propósito de búsqueda.

3. ☐ Además, en el caso que más de una versión o copia del listado de secuencia y/o en relación a la misma tabla se archivo o proporciono, las declaraciones requeridas de la información en las copias subsecuentes o adicionales son idénticas a esa solicitud archivada o no va más allá de la solicitud archivada, como apropiadamente, fue proporcionada.

4. Comentarios adicionales:

Cuadro No. III. Sin establecimiento de la opinión con respecto a la novedad, etapa inventiva y aplicabilidad industrial.

1. Las cuestiones de si la invención reivindicada parece que es nueva, que comprende una etapa inventiva (que sea obvio), o que es aplicable industrialmente no serán examinadas con respecto de:

☐ la solicitud internacional completa

☒ reivindicaciones Nos. 24-27 con respecto a la aplicabilidad industrial
debido a que:

☒ la solicitud internacional, o las reivindicaciones Nos. 24-27 se relacionan al siguiente tema que no requiere un examen preliminar internacional (*especifica*):
ver hoja separada

☐ la descripción, reivindicaciones o dibujos (indicar los elementos particulares a continuación) o las reivindicaciones Nos. _____ no son claras de modo que no se puede formar una opinión (especifica):

☐ las reivindicaciones, o las reivindicaciones Nos. ____ se soportan inadecuadamente por la descripción de modo que no se puede formar una opinión significante.

☐ no se ha establecido ningún reporte de búsqueda internacional para las reivindicaciones Nos.

☐ el listado de secuencias del nucleótido y/o aminoácidos no cumple con el estándar proporcionado para un Anexo C de las Instrucciones Administrativas en que:

la forma escrita	☐ no se ha suministrado
	☐ no cumple con el estándar
la forma legible por computadora	☐ no se ha suministrado
	☐ no cumple con el estándar

☐ las tablas relacionadas el listado de secuencias del nucleótido y/o aminoácidos, si solo en la forma legible por computadora, no cumplen con los requisitos técnicos proporcionados para el Anexo C – bis de las Instrucciones Administrativas

☐ ver hoja separada para detalles adicionales

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Cuadro No. V Declaración razonada bajo el Artículo 43bis.1(a)(i) con respecto a la novedad, etapa inventiva o aplicabilidad industrial; citas y explicaciones que soportan esta declaración.

1. DECLARACIÓN

Novedad (N)	Sí: Reivindicaciones	1-27
	No: Reivindicaciones	
Etapa Inventiva (EI)	Sí: Reivindicaciones	1-27
	No: Reivindicaciones	
Aplicabilidad Industrial (AI)	Sí: Reivindicaciones	1-23
	No: Reivindicaciones	

2. Citas y Explicaciones (Regla 70.7):
   ver hoja separada

Cuadro No. VI Ciertos documentos citados

1. Ciertos documentos publicados: (Regla 43bis.1 y 70.10)
   y/o

2. Ninguna declaración escrita (Regla 43bis.1 y 70.9)
   ver forma 210

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Recuadro III

Las reivindicaciones 24-27 se relacionan a la materia objeto considerada por esta Autoridad a protegerse por las provisiones de la Regla 67.1(iv) PCT. Por consiguiente, ninguna opinión será formulada con respecto a la aplicabilidad industrial de la materia objeto de estas reivindicaciones (Artículo 34(4)(a)(i)PCT).

Recuadro V

1. Se hace referencia al siguiente documento:
D1: WO 03/035077 A
2. La materia objeto de la reivindicación 1 es nueva (Artículo 33(2)PCT): El presente compuesto difiere de los de D1 en que el anillo pirimidinona se fusiona a un segundo anillo.

3. El problema a resolverse por la presente solicitud se encuentra en la provisión de otros inhibidores de la integrasa del VIH (ver presente descripción, p. 3, líneas 3-6 y tabla 1).

No hay incentivo en la técnica anterior para que el experto modifique los inhibidores de la integrasa del VIH de D1 por la fusión a un radical -X-Y-Z según lo definido en la presente reivindicación 1. La solución propuesta en la reivindicación 1 de la presente solicitud es por lo tanto considerada que involucra una etapa inventiva (Artículo 33(3) PCT).

4. Aplicabilidad Industrial (Artículo 33(4) PCT)

Para la valoración de las presentes reivindicaciones 24-27 en la cuestión si son industrialmente aplicables, ningún criterio unificado existe en los Estados Contratantes del PCT. La patentabilidad puede también depender de la formulación de las reivindicaciones. La EPO, por ejemplo, no reconoce como industrialmente aplicable la materia objeto de las reivindicaciones para el uso de un compuesto para el tratamiento médico, pero puede permitir, sin embargo, las reivindicaciones para un compuesto conocido para un primer uso en el tratamiento médico y el uso de tal compuesto para la fabricación de un medicamento para un nuevo tratamiento médico.

Recuadro VI
Cierto documento publicados

Solicitud No Patente No. (día/mes/año)	Fecha de Public. (día/mes/año)	Fecha de present. (día/mes/año)	Fecha de prioridad (reivindicación valida (día/mes/año)
D2:WO2004/058756	15.07.2004	18.12.2003	
A	15.07.2004	18.12.2003	
D3:WO2004/058757			
A			

Los documentos D2 y D3 describen los inhibidores de la integrasa del VIH en donde la cadena -X-Y-Z- contiene solamente átomos de carbono mientras que en los presentes compuestos -X-Y-Z- adicionalmente contienen un átomo de oxígeno.

102.485
10253-US-PCT

ATENT COOPERATION TREAT - PCT/US2005/016473

Expired

From the INTERNATIONAL BUREAU

798

PCT

NOTIFICATION CONCERNING
SUBMISSION OR TRANSMITTAL
OF PRIORITY DOCUMENT

(PCT Administrative Instructions, Section 411)

To:

RECEIVED
BMS PATENT LAW

EPPERSON, James
Bristol-Myers Squibb Company
P.O. Box 4000
Princeton, NJ 08543-4000
ETATS-UNIS D'AMERIQUE

SEP 06 2005

Docketed Item
Due Date
Attorney JE

9/13/05

Date of mailing *(day/month/year)* 26 August 2005 (26.08.2005)	
Applicant's or agent's file reference 10253PCT	IMPORTANT NOTIFICATION
International application No. PCT/US2005/016473	International filing date *(day/month/year)* 12 May 2005 (12.05.2005)
International publication date *(day/month/year)*	Priority date *(day/month/year)* 28 May 2004 (28.05.2004)
Applicant BRISTOL-MYERS SQUIBB COMPANY et al	

SEP 12 2005

1. By means of this Form, which replaces any previously issued notification concerning submission or transmittal of priority documents, the applicant is hereby notified of the date of receipt by the International Bureau of the priority document(s) relating to all earlier application(s) whose priority is claimed. Unless otherwise indicated by the letters "NR", in the right-hand column or by an asterisk appearing next to a date of receipt, the priority document concerned was submitted or transmitted to the International Bureau in compliance with Rule 17.1(a) or (b).

2. *(If applicable)* The letters "NR" appearing in the right-hand column denote a priority document which, on the date of mailing of this Form, had not yet been received by the International Bureau under Rule 17.1(a) or (b). Where, under Rule 17.1(a), the priority document must be submitted by the applicant to the receiving Office or the International Bureau, but the applicant fails to submit the priority document within the applicable time limit under that Rule, the attention of the applicant is directed to Rule 17.1(c) which provides that no designated Office may disregard the priority claim concerned before giving the applicant an opportunity, upon entry into the national phase, to furnish the priority document within a time limit which is reasonable under the circumstances.

3. *(If applicable)* An asterisk (*) appearing next to a date of receipt, in the right-hand column, denotes a priority document submitted or transmitted to the International Bureau but not in compliance with Rule 17.1(a) or (b) (the priority document was received after the time limit prescribed in Rule 17.1(a) or the request to prepare and transmit the priority document was submitted to the receiving Office after the applicable time limit under Rule 17.1(b)). Even though the priority document was not furnished in compliance with Rule 17.1(a) or (b), the International Bureau will nevertheless transmit a copy of the document to the designated Offices, for their consideration. In case such a copy is not accepted by the designated Office as the priority document, Rule 17.1(c) provides that no designated Office may disregard the priority claim concerned before giving the applicant an opportunity, upon entry into the national phase, to furnish the priority document within a time limit which is reasonable under the circumstances.

Priority date	Priority application No.	Country or regional Office or PCT receiving Office	Date of receipt of priority document
28 May 2004 (28.05.2004)	60/575,513	US	27 June 2005 (27.06.2005)
20 August 2004 (20.08.2004)	60/603,371	US	27 June 2005 (27.06.2005)
11 May 2005 (11.05.2005)	11/126,891	US	08 August 2005 (08.08.2005)

The International Bureau of WIPO 34, chemin des Colombettes 1211 Geneva 20, Switzerland	Authorized officer A. ZOLTANSKI (Fax : 338 89 75)
Facsimile No. +41 22 338 82 70	Facsimile No. (41-22) 338.89.75 Telephone No. +41 22 338 8608

Form PCT/IB/304 (January 2004) CJ8EPQ66

102.485

10253PCT

1/11

PCT REQUEST

Original (for SUBMISSION)

0	For receiving Office use only	
0-1	International Application No.	
0-2	International Filing Date	
0-3	Name of receiving Office and "PCT International Application"	
0-4	Form PCT/RO/101 PCT Request	
0-4-1	Prepared Using	PCT-SAFE [EASY mode] Version 3.50 (Build 0002.170)
0-5	Petition The undersigned requests that the present international application be processed according to the Patent Cooperation Treaty	
0-6	Receiving Office (specified by the applicant)	United States Patent and Trademark Office (USPTO) (RO/US)
0-7	Applicant's or agent's file reference	10253PCT
I	Title of Invention	BICYCLIC HETEROCYCLES AS HIV INTEGRASE INHIBITORS
II	Applicant	
II-1	This person is	applicant only
II-2	Applicant for	all designated States except US
II-4	Name	BRISTOL-MYERS SQUIBB COMPANY
II-5	Address	Route 206 and Province Line Road Princeton, New Jersey 08543-4000 United States of America
II-6	State of nationality	US
II-7	State of residence	US
II-8	Telephone No.	609-252-4000
II-9	Facsimile No.	609-252-4526
III-1	Applicant and/or Inventor	
III-1-1	This person is	applicant and inventor
III-1-2	Applicant for	US only
III-1-4	Name (LAST, First)	NAIDU, B. Narasimhulu
III-1-5	Address	12 Skeetfield Point Road Durham, Connecticut 06422 United States of America
III-1-6	State of nationality	IN
III-1-7	State of residence	US

800

III-2	Applicant and/or inventor	
III-2-1	This person is	applicant and inventor
III-2-2	Applicant for	US only
III-2-4	Name (LAST, First)	BANVILLE, Jacques
III-2-5	Address	1209 Girard St-Hubert, Québec J4T 1E3 Canada
III-2-6	State of nationality	CA
III-2-7	State of residence	CA
III-3	Applicant and/or inventor	
III-3-1	This person is	applicant and inventor
III-3-2	Applicant for	US only
III-3-4	Name (LAST, First)	BEAULIEU, Francis
III-3-5	Address	370 Leotable Dubuc Laprairie, Québec J5R 5M4 Canada
III-3-6	State of nationality	CA
III-3-7	State of residence	CA
III-4	Applicant and/or inventor	
III-4-1	This person is	applicant and inventor
III-4-2	Applicant for	US only
III-4-4	Name (LAST, First)	CONNOLLY, Timothy, P.
III-4-5	Address	6 Elizabeth Road Portland, Connecticut 06480 United States of America
III-4-6	State of nationality	CA
III-4-7	State of residence	US
III-5	Applicant and/or inventor	
III-5-1	This person is	applicant and inventor
III-5-2	Applicant for	US only
III-5-4	Name (LAST, First)	KRYSTAL, Mark, R.
III-5-5	Address	12 Salem Road Westport, Connecticut 06880 United States of America
III-5-6	State of nationality	US
III-5-7	State of residence	US

III-6	Applicant and/or inventor	
III-6-1	This person is	applicant and inventor
III-6-2	Applicant for	US only
III-6-4	Name (LAST, First)	MATISKELLA, John, D.
III-6-5	Address	130 High Hill Road Wallingford, Connecticut 06492 United States of America
III-6-6	State of nationality	US
III-6-7	State of residence	US
III-7	Applicant and/or inventor	
III-7-1	This person is	applicant and inventor
III-7-2	Applicant for	US only
III-7-4	Name (LAST, First)	OUELLET, Carl
III-7-5	Address	555 Rue de la Verendrye Boucherville, Québec J4B 2Y3 Canada
III-7-6	State of nationality	CA
III-7-7	State of residence	CA
III-8	Applicant and/or inventor	
III-8-1	This person is	applicant and inventor
III-8-2	Applicant for	US only
III-8-4	Name (LAST, First)	PLAMONDON, Serge
III-8-5	Address	705 du Cabestan Ste-Catherine, Québec J5C 1W9 Canada
III-8-6	State of nationality	CA
III-8-7	State of residence	CA
III-9	Applicant and/or inventor	
III-9-1	This person is	applicant and inventor
III-9-2	Applicant for	US only
III-9-4	Name (LAST, First)	REMILLARD, Roger
III-9-5	Address	13 des Cedres Napierville, Québec J0L 1L0 Canada
III-9-6	State of nationality	CA
III-9-7	State of residence	CA

III-10	Applicant and/or inventor	
III-10-1	This person is	applicant and inventor
III-10-2	Applicant for	US only
III-10-4	Name (LAST, First)	SORENSON, Margaret, E.
III-10-5	Address	27 Harrison Street Apt. 13 Meriden, Connecticut 06450 United States of America
III-10-6	State of nationality	US
III-10-7	State of residence	US
III-11	Applicant and/or inventor	
III-11-1	This person is	applicant and inventor
III-11-2	Applicant for	US only
III-11-4	Name (LAST, First)	UEDA, Yasutsugu
III-11-5	Address	46 Olde Orchard Road Clinton, Connecticut 06413 United States of America
III-11-6	State of nationality	JP
III-11-7	State of residence	US
III-12	Applicant and/or inventor	
III-12-1	This person is	applicant and inventor
III-12-2	Applicant for	US only
III-12-4	Name (LAST, First)	WALKER, Michael, A.
III-12-5	Address	76R Ivy Way Durham, Connecticut 06422 United States of America
III-12-6	State of nationality	US
III-12-7	State of residence	US
IV-1	Agent or common representative; or address for correspondence	
	The person identified below is hereby/ has been appointed to act on behalf of the applicant(s) before the competent International Authorities as:	agent
IV-1-1	Name (LAST, First)	EPPERSON, James
IV-1-2	Address	Bristol-Myers Squibb Company P.O. Box 4000 Princeton, New Jersey 08543-4000 United States of America
IV-1-3	Telephone No.	203-677-6974
IV-1-4	Facsimile No.	203-677-6900
IV-1-6	Agent's registration No.	52,867

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IV-2	Additional agent(s)	additional agent(s) with same address as first named agent
IV-2-1	Name(s)	DUBOFF,Samuel(25,969); GOLIAN,Paul, D.(42,591); BABAJKO,Suzanne, E.(32,880); BAXAM,Deanna, L.(45,266); SUN,Jing, G.(45,914); BOGIE,Terence, J.(44,544); BERGEN,Briana, C.(39,123); D'AMICO,Stephen, C.(46,652); DAVIS,Stephen, B.(26,693); DUNCAN,Laurelee, A.(44,096); DUNCAN,Sammy, G. Jr.(46,675); GIBBONS,Maureen, S.(44,121); KILCOYNE,John, M.(33,100); KORSEN,Elliott(32,705); LANKERDIN,John, A.(44,858); LANGE,Keith, R.(44,201); O'BRIEN,Maureen, P.(42,043); PROVOOST,Jonathan, M.(44,292); RODNEY,Burton(22,076); SHER,Audrey, F.(39,024); VANATTEN,Mary, K.(39.408); WINSLOW,Anastasia, P.(40,875); ALGIERI,Aldo, A.(31,697); MAKUJINA,Shah, R.(41,174); RYAN,Richard, P.(30,491); VOLLES,Warren, K.(33,810); MINGO,Pamela, A.(48,256); GREENBLATT,Gary, D.(47,609); GU,Henry, H.(55,227); PATEL,Rena(41,412); CHIN,Jennifer, T.(47,487); WANG,Joseph, C.(44,391); WILLE,Louis, J.(32,954); PARLET,Nickki, L.(44,996); COHEN,Jacqueline, M.(51,574); KRIEGER,Stuart, R.(28,731); SCHMIDT,Richard, D.(31,301)
V	DESIGNATIONS	
V-1	The filing of this request constitutes under Rule 4.9(a), the designation of all Contracting States bound by the PCT on the International filing date, for the grant of every kind of protection available and, where applicable, for the grant of both regional and national patents.	
VI-1	Priority claim of earlier national application	
VI-1-1	Filing date	28 May 2004 (28.05.2004)
VI-1-2	Number	60/575,513
VI-1-3	Country	US

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VI-2	Priority claim of earlier national application		
VI-2-1	Filing date	20 August 2004 (20.08.2004)	
VI-2-2	Number	60/603,371	
VI-2-3	Country	US	
VI-3	Priority claim of earlier national application		
VI-3-1	Filing date	11 May 2005 (11.05.2005)	
VI-3-2	Number		
VI-3-3	Country	US	
VI-4	Priority document request		
	The receiving Office is requested to prepare and transmit to the International Bureau a certified copy of the earlier application(s) identified above as item(s):	VI-1, VI-2, VI-3	
VII-1	International Searching Authority Chosen	European Patent Office (EPO) (ISA/EP)	
VIII	Declarations	Number of declarations	
VIII-1	Declaration as to the identity of the inventor	-	
VIII-2	Declaration as to the applicant's entitlement, as at the international filing date, to apply for and be granted a patent	1	
VIII-3	Declaration as to the applicant's entitlement, as at the international filing date, to claim the priority of the earlier application	2	
VIII-4	Declaration of inventorship (only for the purposes of the designation of the United States of America)	-	
VIII-5	Declaration as to non-prejudicial disclosures or exceptions to lack of novelty	-	

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VIII-2-1	Declaration: Entitlement to apply for and be granted a patent Declaration as to the applicant's entitlement, as at the international filing date, to apply for and be granted a patent (Rules 4.17(ii) and 51bis.1(a)(ii)), in a case where the declaration under Rule 4.17(iv) is not appropriate: Name (LAST, First)	in relation to this international application BRISTOL-MYERS SQUIBB COMPANY is entitled to apply for and be granted a patent by virtue of the following:
VIII-2-1(iv)		an assignment from MAIDU, B. Narasimhulu to BRISTOL-MYERS SQUIBB COMPANY, dated 27 September 2004 (27.09.2004)
VIII-2-1(iv)		an assignment from BANVILLE, Jacques to BRISTOL-MYERS SQUIBB COMPANY, dated 04 October 2004 (04.10.2004)
VIII-2-1(iv)		an assignment from REMILLARD, Roger to BRISTOL-MYERS SQUIBB COMPANY, dated 04 October 2004 (04.10.2004),
VIII-2-1(iv)		an assignment from PLAMONDON, Serge to BRISTOL-MYERS SQUIBB COMPANY, dated 04 October 2004 (04.10.2004)
VIII-2-1(iv)		an assignment from WALKER, Michael, A. to BRISTOL-MYERS SQUIBB COMPANY, dated 28 September 2004 (28.09.2004)
VIII-2-1(iv)		an assignment from MAIDU, B. Narasimhulu to BRISTOL-MYERS SQUIBB COMPANY, dated 02 July 2004 (02.07.2004)
VIII-2-1(iv)		an assignment from BANVILLE, Jacques to BRISTOL-MYERS SQUIBB COMPANY, dated 31 August 2004 (31.08.2004)
VIII-2-1(iv)		an assignment from REMILLARD, Roger to BRISTOL-MYERS SQUIBB COMPANY, dated 31 August 2004 (31.08.2004)
VIII-2-1(iv)		an assignment from PLAMONDON, Serge to BRISTOL-MYERS SQUIBB COMPANY, dated 31 August 2004 (31.08.2004)
VIII-2-1(iv)		an assignment from WALKER, Michael, A. to BRISTOL-MYERS SQUIBB COMPANY, dated 23 August 2004 (23.08.2004)
VIII-2-1(ix)	This declaration is made for the purposes of:	all designations except the designation of the United States of America

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VIII-3-1	Declaration: Entitlement to claim priority Declaration as to the applicant's entitlement, as at the international filing date, to claim the priority of the earlier application specified below, where the applicant is not the applicant who filed the earlier application or where the applicant's name has changed since the filing of the earlier application (Rules 4.17(iii) and 51bis.1(a)(iii)) Name	in relation to this international application BRISTOL-MYERS SQUIBB COMPANY is entitled to claim priority of earlier application No. 60/575,513 by virtue of the following:
VIII-3-1(iv)		an assignment from NAIDU, B. Narasimhulu to BRISTOL-MYERS SQUIBB COMPANY, dated 02 July 2004 (02.07.2004)
VIII-3-1(iv)		an assignment from BANVILLE, Jacques to BRISTOL-MYERS SQUIBB COMPANY, dated 31 August 2004 (31.08.2004)
VIII-3-1(iv)		an assignment from REMILLARD, Roger to BRISTOL-MYERS SQUIBB COMPANY, dated 31 August 2004 (31.08.2004)
VIII-3-1(iv)		an assignment from PLAMONDON, Serge to BRISTOL-MYERS SQUIBB COMPANY, dated 31 August 2004 (31.08.2004)
VIII-3-1(iv)		an assignment from WALKER, Michael, A. to BRISTOL-MYERS SQUIBB COMPANY, dated 23 August 2004 (23.08.2004)
VIII-3-1(ix)	This declaration is made for the purposes of:	all designations

VIII-3-2	Declaration: Entitlement to claim priority Declaration as to the applicant's entitlement, as at the international filing date, to claim the priority of the earlier application specified below, where the applicant is not the applicant who filed the earlier application or where the applicant's name has changed since the filing of the earlier application (Rules 4.17(iii) and 51bis.1(a)(iii)) Name	in relation to this international application BRISTOL-MYERS SQUIBB COMPANY is entitled to claim priority of earlier application No. 60/603,371 by virtue of the following:
VIII-3-2(iv)		an assignment from MAIDU, B. Narasimhulu to BRISTOL-MYERS SQUIBB COMPANY, dated 27 September 2004 (27.09.2004)
VIII-3-2(iv)		an assignment from RANVILLE, Jacques to BRISTOL-MYERS SQUIBB COMPANY, dated 04 October 2004 (04.10.2004)
VIII-3-2(iv)		an assignment from REMILLARD, Roger to BRISTOL-MYERS SQUIBB COMPANY, dated 04 October 2004 (04.10.2004)
VIII-3-2(iv)		an assignment from PLAMONDON, Serge to BRISTOL-MYERS SQUIBB COMPANY, dated 04 October 2004 (04.10.2004)
VIII-3-2(iv)		an assignment from WALKER, Michael, A. to BRISTOL-MYERS SQUIBB COMPANY, dated 28 September 2004 (28.09.2004)
VIII-3-2(ix)	This declaration is made for the purposes of:	all designations

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PCT REQUEST

Original (for SUBMISSION)

IX	Check list	number of sheets	electronic file(s) attached
IX-1	Request (including declaration sheets)	11	✓
IX-2	Description	326	-
IX-3	Claims	12	-
IX-4	Abstract	1	✓
IX-5	Drawings	0	-
IX-7	TOTAL	350	
	Accompanying items	paper document(s) attached	electronic file(s) attached
IX-8	Fee calculation sheet	✓	-
IX-9	Original separate power of attorney	✓	-
IX-17	PCT-SAFE physical media	-	✓
IX-18	other		
IX-18	other	Postcard receipt; Certificate of Express Mailing; Certification	
IX-19	Figure of the drawings which should accompany the abstract		
IX-20	Language of filing of the international application	English	
X-1	Signature of applicant, agent or common representative	James Epperson	
X-1-1	Name (LAST, First)	EPPERSON, James	
X-1-2	Name of signatory		
X-1-3	Capacity		

FOR RECEIVING OFFICE USE ONLY

10-1	Date of actual receipt of the purported international application	
10-2	Drawings:	
10-2-1	Received	
10-2-2	Not received	
10-3	Corrected date of actual receipt due to later but timely received papers or drawings completing the purported international application	
10-4	Date of timely receipt of the required corrections under PCT Article 11(2)	
10-5	International Searching Authority	ISA/EP
10-6	Transmittal of search copy delayed until search fee is paid	

PCT REQUEST

Original (for SUBMISSION)

FOR INTERNATIONAL BUREAU USE ONLY

11-1	Date of receipt of the record copy by the International Bureau	

PCT (ANNEX - FEE CALCULATION SHEET)

Original (for SUBMISSION)

(This sheet is not part of and does not count as a sheet of the international application)

8	For receiving Office use only			
0-1	International Application No.			
0-2	Date stamp of the receiving Office			
0-4	Form PCT/RO/101 (Annex) PCT Fee Calculation Sheet			
0-4-1	Prepared Using	PCT-SAFE [EASY mode] Version 3.50 (Build 0002.170)		
0-5	Applicant's or agent's file reference	10253PCT		
2	Applicant	BRISTOL-MYERS SQUIBB COMPANY		
12	Calculation of prescribed fees	fee amount/multiplier	Total amounts (USD)	
12-1	Transmittal fee T	⇨	300	
12-2-1	Search fee S	⇨	2075	
12-2-2	International search to be carried out by	EP		
12-3	International filing fee (first 30 sheets) I1	1211		
12-4	Remaining sheets	320		
12-5	Additional amount (X)	13		
12-6	Total additional amount I2	4160		
12-7	I1 + I2 = I	5371		
12-12	EASY Filing reduction R	-87		
12-13	Total international filing fee (I-R) I	⇨	5284	
12-14	Fee for priority document Number of priority documents requested	3		
12-15	Fee per document (X)	20		
12-16	Total priority document fee: P	⇨	60	
12-17	TOTAL FEES PAYABLE (T+S+I+P)	⇨	7719	
12-19	Mode of payment	authorization to charge deposit account		
12-20	Deposit account instructions The receiving Office	United States Patent and Trademark Office (USPTO) (RO/US)		
12-20-1	Authorization to charge the total fees indicated above	✓		
12-20-2	Authorization to charge any deficiency or credit any overpayment in the total fees indicated above	✓		
12-20-3	Authorization to charge the fee for priority document	✓		
12-21	Deposit account No.	19-3880		
12-22	Date	11 May 2005 (11.05.2005)		
12-23	Name and signature	EPPERSON, James James Epperson		

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0	Para uso de la Oficina receptora únicamente	
0-1	Solicitud internacional N°	
0-2	Fecha de presentación internacional	
0-3	Nombre de la oficina receptora y Solicitud internacional PCT	
0-4	Forma - PCT/RO/101 petitoria	
0-4-1	Preparado usando	PCT-SAFE [EASY model] versión 3.50 (construida 0002.170)
0-5	Petición El abajo firmante pide que la presente solicitud sea tramitada de conformidad con el Tratado de Cooperación en materia de Patentes.	
0-6	Oficina Receptora (especificada por el solicitante)	Oficina de Patentes y Marcas de los Estados Unidos (USPTO) (RO/DE)
0-7	Referencia de archivo de solicitantes o agentes	10253 PCT
I	TITULO DE LA INVENCION	HETEROCICLOS BICÍCLICOS COMO INHIBIDORES DE LA INTEGRASA DEL VIRUS DE INMUNODEFICIENCIA HUMANA(VIH).
II	Solicitante	
II-1	Esta persona es:	Solicitante únicamente
II-2	Solicitante para	Todos los estados designados excepto US
II-4	Nombre	BRISTOL-MYERS SQUIBB COMPANY
II-5	Dirección:	Route 206 and Province Line Road Princeton, New Jersey 08543-4000 Estados Unidos de América
II-6	Estado de Nacionalidad	US
II-7	Estado de Residencia	US
II-8	Teléfono No.	609-252-4000
II-9	Fax No.	609-252-4526
III-1	Solicitante y/o inventor	
III-1-1	Esta persona es:	Inventor y solicitante
III-1-2	Solicitante para:	Solo US
III-1-4	Nombre (primero y ultimo)	NAIDU, B. Narasimhulu
III-1-5	Dirección	12 Skeetfield Point Road Durham, Connecticut 06422 Estados Unidos de América
III-1-6	Estado de Nacionalidad	IN
III-1-7	Estado de Residencia	US

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III-2	Solicitante y/o inventor	
III-2-1	Esta persona es:	Inventor y solicitante
III-2-2	Solicitante para:	Solo US
III-2-4	Nombre (primero, ultimo)	BANVILLE, Jacques
III-2-5	Dirección:	1209 Girard St-Hubert, Québec J4T 1H3 Canada
III-2-6	Estado de Nacionalidad	CA
III-2-7	Estado de Residencia	CA
III-3	Solicitante y/o inventor	
III-3-1	Esta persona es:	Inventor y solicitante
III-3-2	Solicitante para:	Solo US
III-3-4	Nombre (primero, ultimo)	BEAULIEU, Francis
III-3-5	Dirección:	370 Leotable Dubuc Laprairie, Québec J5R 5M4 Canada
III-3-6	Estado de Nacionalidad	CA
III-3-7	Estado de residencia	CA
III-4	Solicitante y/o inventor	
III-4-1	Esta persona es:	Inventor y solicitante
III-4-2	Solicitante para:	Solo US
III-4-4	Nombre (primero, ultimo)	CONNOLLY, Timothy, P.
III-4-5	Dirección:	6 Elizabeth Road Portland, Connecticut 06480 Estados Unidos de América
III-4-6	Estado de Nacionalidad	CA
III-4-7	Estado de Residencia	EU
III-5	Solicitante y/o inventor	
III-5-1	Esta persona es:	Inventor y solicitante
III-5-2	Solicitante para:	Solo US
III-5-4	Nombre (primero, ultimo)	KRYSTAL, Mark, R.
III-5-5	Dirección:	12 Salem Road Westport, Connecticut 06880 Estados Unidos de América
III-5-6	Estado de Nacionalidad	EU
III-5-7	Estado de Residencia	EU

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III-6	Solicitante y/o inventor	
III-6-1	Esta persona es:	Inventor y solicitante
III-6-2	Solicitante para:	Solo US
III-6-4	Nombre (primero, ultimo)	MATISKELLA, John, D.
III-6-5	Dirección:	130 High Hill Road Wallingford, Connecticut 06492 Estados Unidos de América
III-6-6	Estado de Nacionalidad	EU
III-6-7	Estado de Residencia	EU
III-7	Solicitante y/o inventor	
III-7-1	Esta persona es:	Inventor y solicitante
III-7-2	Solicitante para:	Solo US
III-7-4	Nombre (primero, ultimo)	OUELLET, Carl
III-7-5	Dirección:	555 Rue de la Verandrye Boucherville, Québec J4B 2Y3 Canada
III-7-6	Estado de Nacionalidad	CA
III-7-7	Estado de residencia	CA
III-8	Solicitante y/o inventor	
III-8-1	Esta persona es:	Inventor y solicitante
III-8-2	Solicitante para:	Solo US
III-8-4	Nombre (primero, ultimo)	PLAMONDON, Serge
III-8-5	Dirección:	705 du Cabestan, Ste-Catherine, Québec J5C 1W9 Canada
III-8-6	Estado de Nacionalidad	CA
III-8-7	Estado de Residencia	CA
III-9	Solicitante y/o inventor	
III-9-1	Esta persona es:	Inventor y solicitante
III-9-2	Solicitante para:	Solo US
III-9-4	Nombre (primero, ultimo)	REMILLARD, Roger
III-9-5	Dirección:	13 des Cedres Napierville, Québec JOL 1L0 Canada
III-9-6	Estado de Nacionalidad	EU
III-9-7	Estado de Residencia	EU

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III-10	Solicitante y/o inventor	
III-10-1	Esta persona es:	Inventor y solicitante
III-10-2	Solicitante para:	Solo US
III-10-4	Nombre (primero, ultimo)	SORENSON, Margaret, E.
III-10-5	Dirección:	27 Harrison Street Apt. 13 Meriden, Connecticut 06450 Estados Unidos de América
III-10-6	Estado de Nacionalidad	EU
III-10-7	Estado de Residencia	EU
III-11	Solicitante y/o inventor	
III-11-1	Esta persona es:	Inventor y solicitante
III-11-2	Solicitante para:	Solo US
III-11-4	Nombre (primero, ultimo)	UEDA, Yasutsugu
III-11-5	Dirección:	45 Olde Orchard Road Clinton, Connecticut 06413 Estados Unidos de America
III-11-6	Estado de Nacionalidad	JP
III-11-7	Estado de residencia	EU
III-12	Solicitante y/o inventor	
III-12-1	Esta persona es:	Inventor y solicitante
III-12-2	Solicitante para:	Solo US
III-12-4	Nombre (primero, ultimo)	WALKER, Michael, A.
III-12-5	Dirección:	76R Ivy Way Durham, Connecticut 06422 Estados Unidos de America
III-12-6	Estado de Nacionalidad	EU
III-12-7	Estado de residencia	EU
IV-1	La persona abajo identificada se designa/ha sido designada para actuar en nombre del/ de los solicitante(s) ante las administraciones internacionales competentes como:	Agente
IV-1-1	Nombre	EPPERSON, James
IV-1-2	Dirección:	Bristol-Myers Squibb Company P.O. Box 4000 Princeton, New Jersey 08543-4000 Estados Unidos de América
IV-1-3	Teléfono No.	203-677-6974
IV-1-4	Faxsimile No.	203-677-6900
IV-1-5	Registro del Agente No.	52,867

Petitorio PCT

IV-2	Agente adicional	Agente(s) adicional con misma dirección como primer nombre agente
IV-2-1	Nombre(s):	DUBOFF,Samuel(25,969); GOLIAN,Paul, D.(42,591); BABAJKO,Suzanne, E.(32,880); BAXAM,Deanna, L.(45,266); SUN,Jing, G.(45,914); BOGIE,Terence, C.(44,544); BERGEN,Briana, C.(39,123); D'AMICO,Stephen, C.(46,652); DAVIS,Stephen, B.(26,693); DUNCAN,Laurelee, A.(44,096); DUNCAN,Sammy, G. Jr.(46,675); GIBBONS,Maureen, S.(44,121); KILCOYNE,John, M.(33,100); KORSEN,Elliott(32,705); LAMERDIN,John, A.(44,858); LANGE,Keith, R.(44,201); O'BRIEN,Maureen, P.(42,043); PROVOOST,Jonathan, M.(44,292); RODNEY,Burton(22,076); SHER,Audrey, F.(39,024); VANATTEN,Mary, K.(39.408); WINSLOW,Anastasia, P.(40,875); ALGIERI,Aldo, A.(31,697); MAKUJINA,Shah, R.(41,174); RYAN,Richard, P.(30,491); VOLLES,Warren, K.(33,810); MINGO,Pamela, A.(48,256); GREENBLATT,Gary, D.(47,609); GU,Henry, H.(55,227); PATEL,Rena(41,412); CHIN,Jennifer, T.(47,487); WANG,Joseph, C.(44,391); WILLE,Louis, J.(32,954); PARLET,Nickki, L.(44,996); COHEN,Jacqueline,M.(51,574); KRIEGER,Stuart, E.(28,731); SCHMIDT,Richard, D.(31,301)
V	Designaciones	
V-1	El llenado de este petitorio hechas bajo la Regla 4.9(b)	
VI-1	Solicitud de reivindicación de prioridad previa nacional	
VI-1-1	Fecha de presentación	28 de Mayo 2004 (28.05.2004)
VI-1-2	Solicitud Nº	60/575,513
VI-1-3	País	EU

Petitorio PCT

VI-2	Solicitud de reivindicación de prioridad previa nacional		
VI-2-1	Fecha de presentación	20 de Agosto 2004 (20.08.2004)	
VI-2-2	Solicitud Nº	60/603,371	
VI-2-3	País	EU	
VI-3	Solicitud de reivindicación de prioridad previa nacional		
VI-3-1	Fecha de presentación	11 de Mayo 2004 (11.05.2004)	
VI-3-2	Solicitud Nº		
VI-3-3	País	EU	
VI-4	Prioridad documento petitorio Se ruega a la Oficina receptora que prepare y transmita a la Oficina Internacional una copia certificada de la solicitud anterior/de las solicitudes anteriores identificada(s) supra como punto o punto(s)	VI-1, VI-2, VI-3	
VII-1	Autoridad de Búsqueda Internacional Elegida	Oficina Europea de Patente (EPO) (ISA/EP)	
VIII	Declaraciones	Número de declaraciones	
VIII-1	Declaración como para la identidad del inventor	-	
VIII-2	Declaración como para la autorización del solicitante, como en la fecha de presentación internacional, para solicitar y garantizar una patente	1	
VIII-3	Declaración como para la autorización del solicitante, como en la fecha de presentación internacional, para reivindicar la prioridad de la solicitud previa	2	
VIII-4	Declaración de los inventores (sólo para los propósitos de designación de los Estados Unidos de América)	-	
VIII-5	Declaración como descripciones o excepciones no perjudiciales para carecer de novedad	-	

VIII-2-1	Declaración: autorización para solicitar y otorgar una patente Declaración como autoriza el solicitante, como en la fecha de presentación internacional, para solicitar y otorgar una patente (Reglas 4.17(iii) y 51 bis. 1(a)(ii)), en caso donde la declaración bajo la Regla 4.17(iv) no sea apropiada: Nombre:	En relación a esta solicitud internacional BRISTOL-MYERS SQUIBB COMPANY Se autoriza a reivindicar la prioridad de la solicitud previa en virtud de lo siguiente:
VIII-2-1 (iv)		Una cesión de NAIDU, B. Narasimhulu a BRISTOL-MYERS SQUIBB COMPANY, con fecha 27 Septiembre 2004 (27.09.2004)
VIII-2-1 (iv)		Una cesión de BANVILLE, Jacques a BRISTOL-MYERS SQUIBB COMPANY, con fecha 04 Octubre 2004 (04.10.2004)
VIII-2-1 (iv)		Una cesión de REMILLARD, Roger a BRISTOL-MYERS SQUIBB COMPANY, con fecha 04 Octubre 2004 (04.10.2004)
VIII-2-1 (iv)		Una cesión de PLAMONDON, Serge a BRISTOL-MYERS SQUIBB COMPANY, con fecha 04 Octubre 2004 (04.10.2004)
VIII-2-1 (iv)		Una cesión de WALKER, Michael, A. a BRISTOL-MYERS SQUIBB COMPANY, con fecha 28 Septiembre 2004 (28.09.2004)
VIII-2-1 (iv)		Una cesión de NAIDU, B. Narasimhulu a BRISTOL-MYERS SQUIBB COMPANY, con fecha 02 Julio 2004 (02.07.2004)
VIII-2-1 (iv)		Una cesión de BANVILLE, Jacques a BRISTOL-MYERS SQUIBB COMPANY, con fecha 31 Agosto 2004 (31.08.2004)
VIII-2-1 (iv)		Una cesión de REMILLARD, Roger a BRISTOL-MYERS SQUIBB COMPANY, con fecha 31 Agosto 2004 (31.08.2004)
VIII-2-1 (iv)		Una cesión de PLAMONDON, Serge a BRISTOL-MYERS SQUIBB COMPANY, con fecha 31 Agosto 2004 (31.08.2004)
VIII-2-1 (iv)		Una cesión de WALKER, Michael, A. a BRISTOL-MYERS SQUIBB COMPANY, con fecha 23 Agosto 2004 (23.08.2004)
VIII-2-1 (ix)	Esta declaración esta hecha para el propósito de:	Todas las designaciones excepto la designación de los Estados Unidos de América

VIII-2-1	Declaración: autorización para solicitar y otorgar una patente Declaración como autoriza el solicitante, como en la fecha de presentación internacional, para solicitar y otorgar una patente (Reglas 4.17(iii) y 51 bis. 1(a)(ii)), en caso donde la declaración bajo la Regla 4.17(iv) no sea apropiada: Nombre:	En relación a esta solicitud internacional BRISTOL-MYERS SQUIBB COMPANY Se autoriza a reivindicar la prioridad de la solicitud No. 60/575,513 en virtud de lo siguiente:
VIII-2-1 (iv)		Una cesión de NAIDU, B. Narasimhulu a BRISTOL-MYERS SQUIBB COMPANY, con fecha 02 Julio 2004 (02.07.2004)
VIII-2-1 (iv)		Una cesión de BANVILLE, Jacques a BRISTOL-MYERS SQUIBB COMPANY, con fecha 31 Agosto 2004 (31.08.2004)
VIII-2-1 (iv)		Una cesión de REMILLARD, Roger a BRISTOL-MYERS SQUIBB COMPANY, con fecha 31 Agosto 2004 (31.08.2004)
VIII-2-1 (iv)		Una cesión de PLAMONDON, Serge a BRISTOL-MYERS SQUIBB COMPANY, con fecha 31 Agosto 2004 (31.08.2004)
VIII-2-1 (iv)		Una cesión de WALKER, Michael, A. a BRISTOL-MYERS SQUIBB COMPANY, con fecha 23 Agosto 2004 (23.08.2004)
VIII-2-1 (ix)	Esta declaración esta hecha para el propósito de:	Todas las designacinoes

Petitori PCT

819

VIII-2-1	Declaración: autorización para solicitar y otorgar una patente Declaración como autoriza el solicitante, como en la fecha de presentación internacional, para solicitar y otorgar una patente (Reglas 4.17(iii) y 51 bis. 1(a)(ii)), en caso donde la declaración bajo la Regla 4.17(iv) no sea apropiada: Nombre:	En relación a esta solicitud internacional BRISTOL-MYERS SQUIBB COMPANY Se autoriza a reivindicar la prioridad de la solicitud No. 60/603,371 en virtud de lo siguiente:
VIII-2-1 (iv)		Una cesión de MAIDU, B. Narasimhulu a BRISTOL-MYERS SQUIBB COMPANY, con fecha 27 Septiembre 2004 (27.09.2004)
VIII-2-1 (iv)		Una cesión de BANVILLE, Jacques a BRISTOL-MYERS SQUIBB COMPANY, con fecha 04 Octubre 2004 (04.10.2004)
VIII-2-1 (iv)		Una cesión de REMILLARD, Roger a BRISTOL-MYERS SQUIBB COMPANY, con fecha 04 Octubre 2004 (04.10.2004)
VIII-2-1 (iv)		Una cesión de PLAMONDON, Serge a BRISTOL-MYERS SQUIBB COMPANY, con fecha 04 Octubre 2004 (04.10.2004)
VIII-2-1 (iv)		Una cesión de WALKER, Michael, A. a BRISTOL-MYERS SQUIBB COMPANY, con fecha 28 Septiembre 2004 (28.09.2004)
VIII-2-1 (ix)	Esta declaración esta hecha para el propósito de:	Todas las designaciones

Petit ri PCT

IX	Lista de verificación	Numero de hojas	Archivos electronicos anexos
IX-1	Petitorio	11	✔
IX-2	Descripción	326	-
IX-3	Reivindicaciones	12	-
IX-4	Resumen	1	✔
IX-5	Dibujos	0	-
IX-7	Total	350	
	Puntos acompañantes	Papel de documento(s) anexos	Archivo(s) electronico anexos
IX-8	Hoja de calculo de tasa	✔	-
IX-10	Original del poder general Protesta del Abogado	✔	-
IX-17	Diskette PCT-SAFE	-	✔
IX-18	Otro		
IX-18	Otro	Postcard receipt; Certificado de Correo Express Certificación	
IX-19	Figura de los dibujos para acompañar el resumen en el momento de su publicación.		
IX-20	Idioma de presentación de la solicitud internacional de patente	INGLES	
X-1	Firma del solicitante o del mandatario	Rúbrica	
X-1-1	Nombre	EPPERSON, James	
X-1-2	Nombre de signatura		
X-1-3	Capacidad		
	PARA LA OFICINA RECEPTORA ÚNICAMENTE		
10-1	Fecha efectiva de recepción de la pretendida solicitud internacional		
10-2 10-2-1 10-2-2	Dibujos Recibidos No recibidos		
10-3	Fecha efectiva de recepción, rectificada de la recepción ulterior pero dentro del plazo, de documentos o de dibujos que completa la pretendida solicitud internacional		
10-4	Fecha de recepción, dentro del plazo de las correcciones solicitadas según el Articulo 11(2) del PCT		
10-5	Autoridad de búsqueda internacional	ISA/EU	
10-6	Transmisión de la copia para la búsqueda diferida hasta que se pague la tasa de búsqueda		

	PARA USO UNICAMENTE DE LA OFICINA INTERNACIONAL	
11-1	Fecha de recepción del ejemplar Original por la Oficina Internacional	

A.S. 102485

821

APOSTILLE

(CONVENTION DE LA HAYE DU 5 OCTOBRE 1961)

1. COUNTRY: UNITED STATES OF AMERICA

2. THIS PUBLIC DOCUMENT HAS BEEN SIGNED BY:
EVELYN VAZQUEZ

3. ACTING IN THE CAPACITY OF:
NOTARY PUBLIC OF NEW JERSEY

4. BEARS THE SEAL/STAMP OF:
EVELYN VAZQUEZ, NOTARY

CERTIFIED

5. AT TRENTON, NEW JERSEY

6. THE 14TH DAY OF NOVEMBER 2006

7. BY: Bradley Abelow, NEW JERSEY TREASURER

8. NO. A275783

9. SEAL/STAMP:

10. SIGNATURE

Bradley Abelow

CO

10253-PCT

822

AFFIDAVIT

I, Suzanne E. Babajko, Senior Patent Counsel, Patent Department – Bristol-Myers Squibb Company do hereby certify that attached documents are notarized true and accurate copies of the original assignments signed by the inventors.

Suzanne E. Babajko
Senior Patent Counsel

STATE OF NEW JERSEY)
) ss.
COUNTY OF MERCER)

Subscribed before me on this 6th day of November, 2006

Notary Public
Evelyn Vazquez
Notary Public of New Jersey
No. 2106805
My Commission Expires December 9, 2007
Registered in Middlesex County

(SEAL)

Worldwide
Case 10253 PSP

823

ASSIGNMENT

We,

Jacques Banville	residing at	1209 Girard St-Hubert, Quebec J4T 1H3 Canada
B. Narasimhulu Naidu	residing at	12 Skeetfield Point Rd. Durham, Connecticut 06422 United States of America
Roger Remillard	residing at	13 des Cedres Napierville, Quebec J0L 1L0 Canada
Gilles Bouthillier	residing at	147 des Cerisiers Granby, Quebec J2J 1Z5 Canada
Serge Plamondon	residing at	705 du Cabestan Ste-Catherine, Quebec J0L 1E0 Canada
Michael A. Walker	residing at	76R Ivy Way Durham, Connecticut 06422 United States of America,

pursuant to contractual obligations heretofore assumed by us and/or for good and valuable consideration, the receipt and adequacy of which is hereby acknowledged, do hereby sell and assign to **Bristol-Myers Squibb Company**, a Delaware corporation, having a place of business at Lawrenceville-Princeton Road, Princeton, NJ 08543-4000, its successors, assigns and legal representatives, all our right, title and interest, which includes the right to and full benefit of such priorities as may now or hereafter be granted to us by local laws or by treaty, including any international convention for the protection of industrial property, in and for all countries of the world, including the United States and its territories and possessions, in and to the invention entitled:

Bicyclic Heterocycles as HIV Integrase Inhibitors

invented by us and described in the provisional United States patent application

Application No. 60/575,513, filed May 28, 2004,

including said provisional United States patent application and any application claiming priority from said provisional application, filed in any country, and any patents which may be issued and/or granted thereon, and all divisions, continuations, reissues, reexamination certificates and extensions thereof in all countries, the said interest being the entire ownership of said invention and all of said applications, patents (including reissue patents), extensions and reexamination certificates to be held and enjoyed by the said Bristol-Myers Squibb Company and its successors and assigns to the full end of the terms to which said patents (including reissue patents), extensions and reexamination certificates may be granted and/or issued, as fully and entirely as the same would have been held and enjoyed by us if this sale, assignment and transfer had not been made;

And we hereby agree to communicate to said assignee or its representatives any facts known to us respecting said invention, to testify in any legal proceedings, to sign and/or execute any further documents and/or instruments which may be necessary, lawful and proper in and/or for the filing and/or prosecution of all applications, including divisional, continuation and reissue applications, extensions and reexamination certificates and/or the granting and/or issuance thereof and/or to otherwise secure title to said invention and all of said applications, patents (including reissue patents, extensions and reexamination certificates in said assignee, and in general to do everything possible to aid said assignee, its successors and assigns to obtain and enforce proper protection for said invention in all countries.

Signed this 31st day of August, 2004 by _____
Jacques Banville

Signed this 2 day of July, 2004 by _____
B. Narasimhulu Naidu

Signed this 31st day of August 2004 by _____
Roger Remillard

Signed this 31st day of August, 2004 by _____
Gilles Bouthillier

Signed this 31st day of August 2004 by _____
Serge Plamondon

Signed this 23 day of August, 2004 by _____
Michael A. Walker

COUNTRY OF Canada)
) ss.
PROVINCE OF Quebec)

On the 9th day of August, 2004, before me came Jacques Banville, to me known to be the person of that name mentioned in, and who executed the foregoing Assignment and acknowledged that he executed it.

Notary Public (Signature)

JEAN BOUCHER
Notary Public (Printed Name)

Date Commission Expires

STATE OF Connecticut)
) ss. Wallingford
COUNTY OF New Haven)

On the 2ND day of July, 2004, before me came B. Narasimhulu Naidu, to me known to be the person of that name mentioned in, and who executed the foregoing Assignment and acknowledged that he executed it.

[SEAL]

Annemarie Bodisch
Notary Public

ANNAMARIE BODISCH
Notary Public
My Commission Expires March 31, 2005

827

COUNTRY OF Canada)
) ss.
PROVINCE OF Quebec)

On the 31st day of August 2004, before me came **Roger Remillard**, to me known to be the person of that name mentioned in, and who executed the foregoing Assignment and acknowledged that he executed it.

Notary Public (Signature)

JEAN BOUCHER
Notary Public (Printed Name)

1 CM 2007
Date Commission Expires

COUNTRY OF Canada)
) ss.
PROVINCE OF Quebec)

On the 31st day of August 2004, before me came **Gilles Bouthillier**, to me known to be the person of that name mentioned in, and who executed the foregoing Assignment and acknowledged that he executed it.

Notary Public (Signature)

JEAN BOUCHER
Notary Public (Printed Name)

1 CM 2007
Date Commission Expires

COUNTRY OF Canada)
) ss.
PROVINCE OF Quebec)

On the 31st day of August 2004, before me came **Serge Plamondon**, to me known to be the person of that name mentioned in, and who executed the foregoing Assignment and acknowledged that he executed it.

Notary Public (Signature)

JEAN BOUCHER
Notary Public (Printed Name)

Date Commission Expires

STATE OF Connecticut)
) ss. Wallingford
COUNTY OF New Haven)

On the 23rd day of August, 2004, before me came **Michael A. Walker**, to me known to be the person of that name mentioned in, and who executed the foregoing Assignment and acknowledged that he executed it.

Annamarie Bodisch
Notary Public

ANNAMARIE BODISCH
Notary Public
My Commission Expires March 31, 2005

Worldwide
Case 10253 PSP2

829

ASSIGNMENT

We,

Jacques Banville	residing at	1209 Girard St-Hubert, Quebec J4T 1H3 Canada
B. Narasimhulu Naidu	residing at	12 Skeetfield Point Rd. Durham, Connecticut 06422 United States of America
Roger Remillard	residing at	13 des Cedres Napierville, Quebec J0L 1L0 Canada
Gilles Bouthillier	residing at	147 des Cerisiers Granby, Quebec J2J 1Z5 Canada
Serge Piamondon	residing at	705 du Cabestan Ste-Catherine, Quebec J0L 1E0 Canada
Michael A. Walker	residing at	76R Ivy Way Durham, Connecticut 06422 United States of America,

pursuant to contractual obligations heretofore assumed by us and/or for good and valuable consideration, the receipt and adequacy of which is hereby acknowledged, do hereby sell and assign to **Bristol-Myers Squibb Company**, a Delaware corporation, having a place of business at Lawrenceville-Princeton Road, Princeton, NJ 08543-4000, its successors, assigns and legal representatives, all our right, title and interest, which includes the right to and full benefit of such priorities as may now or hereafter be granted to us by local laws or by treaty, including any international convention for the protection of industrial property, in and for all countries of the world, including the United States and its territories and possessions, in and to the invention entitled:

Bicyclic Heterocycles as HIV Integrase Inhibitors

invented by us and described in the provisional United States patent application

Application No. 60/603,371, filed August 20, 2004.

including said provisional United States patent application and any application claiming priority from said provisional application, filed in any country, and any patents which may be issued and/or granted thereon, and all divisions, continuations, reissues, reexamination certificates and extensions thereof in all countries, the said interest being the entire ownership of said invention and all of said applications, patents (including reissue patents), extensions and reexamination certificates to be held and enjoyed by the said Bristol-Myers Squibb Company and its successors and assigns to the full end of the terms to which said patents (including reissue patents), extensions and reexamination certificates may be granted and/or issued, as fully and entirely as the same would have been held and enjoyed by us if this sale, assignment and transfer had not been made;

And we hereby agree to communicate to said assignee or its representatives any facts known to us respecting said invention, to testify in any legal proceedings, to sign and/or execute any further documents and/or instruments which may be necessary, lawful and proper in and/or for the filing and/or prosecution of all applications, including divisional, continuation and reissue applications, extensions and reexamination certificates and/or the granting and/or issuance thereof and/or to otherwise secure title to said invention and all of said applications, patents (including reissue patents, extensions and reexamination certificates in said assignee, and in general to do everything possible to aid said assignee, its successors and assigns to obtain and enforce proper protection for said invention in all countries.

831

Signed this 4 day of OCTOBER, 2004 by _____
Jacques Banville

Signed this 27 day of September, 2004 by _____
B. Narasimhulu Naidu

Signed this 4 day of OCTOBER, 2004 by _____
Roger Remillard

Signed this 4 day of OCTOBER, 2004 by _____
Gilles Bouthillier

Signed this 4 day of OCTOBER, 2004 by _____
Serge Plamondon

Signed this 28th day of September, 2004 by _____
Michael A. Walker

COUNTRY OF Canada)
) ss.
PROVINCE OF Quebec)

On the 4th day of October, 2004, before me came Jacques Banville, to me known to be the person of that name mentioned in, and who executed the foregoing Assignment and acknowledged that he executed it.

Notary Public (Signature)

JEAN BOUCHER
Notary Public (Printed Name)

Date Commission Expires

STATE OF Connecticut)
) ss. Wallingford
COUNTY OF New Haven)

On the 27th day of September 2004, before me came B. Narasimhulu Naidu, to me known to be the person of that name mentioned in, and who executed the foregoing Assignment and acknowledged that he executed it.

[SEAL]

Annamarie Bodisch
Notary Public

ANNAMARIE BODISCH
Notary Public
My Commission Expires March 31, 2005

633

COUNTRY OF Canada)
) ss.
PROVINCE OF Quebec)

On the 4th day of October, 2004, before me came **Roger Remillard**, to me known to be the person of that name mentioned in, and who executed the foregoing Assignment and acknowledged that he executed it.

Notary Public (Signature)

Jean Bourassa
Notary Public (Printed Name)

Date Commission Expires

COUNTRY OF Canada)
) ss.
PROVINCE OF Quebec)

On the 4th day of October, 2004, before me came **Gilles Bouthillier**, to me known to be the person of that name mentioned in, and who executed the foregoing Assignment and acknowledged that he executed it.

Notary Public (Signature)

Jean Bourassa
Notary Public (Printed Name)

Date Commission Expires

834

COUNTRY OF Canada)
) ss.
PROVINCE OF Quebec)

On the 4th day of October, 2004, before me came **Serge Plamondon**, to me known to be the person of that name mentioned in, and who executed the foregoing Assignment and acknowledged that he executed it.

Notary Public (Signature)

Notary Public (Printed Name)

Date Commission Expires

STATE OF Connecticut)
) ss. Wallingford
COUNTY OF New Haven)

On the 28th day of September 2004, before me came **Michael A. Walker**, to me known to be the person of that name mentioned in, and who executed the foregoing Assignment and acknowledged that he executed it.

Notary Public

ANNAMARIE BODISCH
Notary Public
My Commission Expires March 31, 2005

834

835

ASSIGNMENT

We,

B. Narasimhulu Naidu	residing at	12 Skeetfield Point Rd. Durham, Connecticut 06422 United States of America
Jacques Banville	residing at	1209 Girard St-Hubert, Quebec J4T 1H3 Canada
Francis Beaulieu	residing at	370 Leotable Dubuc Laprairie, Quebec J5R 5M4 Canada
Timothy P. Connolly	residing at	6 Elizabeth Road Portland, Connecticut 06480 United States of America
Mark R. Krystal	residing at	12 Salem Road Westport, Connecticut 06880 United States of America
John D. Matiskella	residing at	130 High Hill Road Wallingford, Connecticut 06492 United States of America
Carl Ouellet	residing at	555 Rue de la Verendrye Boucherville, Quebec J4B 2Y3 Canada
Serge Plamondon	residing at	705 du Cabestan Ste-Catherine, Quebec J5C 1W9 Canada
Roger Remillard	residing at	13 des Cedres Napierville, Quebec J0L 1L0 Canada
Margaret E. Sorenson	residing at	27 Harrisor Street Apt. 13 Meriden, Connecticut 06450 United States of America
Yasutsugu Ueda	residing at	46 Olde Orchard Road Clinton, Connecticut 06413 United States of America

Michael A. Walker residing at 76R Ivy Way
Durham, Connecticut 06422
United States of America,

pursuant to contractual obligations heretofore assumed by us and/or for good and valuable consideration, the receipt and adequacy of which is hereby acknowledged, do hereby sell and assign to **Bristol-Myers Squibb Company**, a Delaware corporation, having a place of business at Lawrenceville-Princeton Road, Princeton, NJ 08543-4000, its successors, assigns and legal representatives, all our right, title and interest, which includes the right to and full benefit of such priorities as may now or hereafter be granted to us by local laws or by treaty, including any international convention for the protection of industrial property, in and for all countries of the world, including the United States and its territories and possessions, in and to the invention entitled:

Bicyclic Heterocycles as HIV Integrase Inhibitors

Invented by us and described in the non-provisional United States patent application

Application No. 11/126,691, filed May 11, 2005,

including said non-provisional United States patent application and any application claiming priority from said non-provisional application, filed in any country, and any patents which may be issued and/or granted thereon, and all divisions, continuations, reissues, reexamination certificates and extensions thereof in all countries, the said interest being the entire ownership of said invention and all of said applications, patents (including reissue patents), extensions and reexamination certificates to be held and enjoyed by the said Bristol-Myers Squibb Company and its successors and assigns to the full end of the terms to which said patents (including reissue patents), extensions and reexamination certificates may be granted and/or issued, as fully and entirely as the same would have been held and enjoyed by us if this sale, assignment and transfer had not been made;

837

And we hereby agree to communicate to said assignee or its representatives any facts known to us respecting said invention, to testify in any legal proceedings, to sign and/or execute any further documents and/or instruments which may be necessary, lawful and proper in and/or for the filing and/or prosecution of all applications, including divisional, continuation and reissue applications, extensions and reexamination certificates and/or the granting and/or issuance thereof and/or to otherwise secure title to said invention and all of said applications, patents (including reissue patents, extensions and reexamination certificates in said assignee, and in general to do everything possible to aid said assignee, its successors and assigns to obtain and enforce proper protection for said invention in all countries.

Signed this 15 day of June, 2005 by _____
B. Narasimhulu Naidu

Signed this 22 day of June, 2005 by _____
Jacques Banville

Signed this 22 day of June, 2005 by _____
Francis Beaulieu

Signed this 15 day of June, 2005 by _____
Timothy P. Connolly

Signed this 16th day of June, 2005 by _____
Mark R. Krystal

Signed this 15th day of June, 2005 by _____
John D. Matiskella

Signed this 22 day of June, 2005 by _____
Carl Ouellet

Signed this 22 day of June, 2005 by _____
Serge Plamondon

838

Signed this 22 day of JUNE, 2005 by _____
Roger Remillard

Signed this 22nd day of June, 2005 by _____
Margaret E. Sorenson

Signed this 17th day of June, 2005 by _____
Yasutsugu Ueda

Signed this 16th day of June, 2005 by _____
Michael A. Walker

839

STATE OF Connecticut)
) ss. Wallingford
COUNTY OF New Haven)

On the 15 day of June, 2005, before me came B. Narasimhulu Naidu, to me known to be the person of that name mentioned in, and who executed the foregoing Assignment and acknowledged that he executed it.

[SEAL]

Annamarie Bodnick
Notary Public

ANNAMARIE BODNICK
NOTARY PUBLIC
MY COMMISSION EXPIRES MARCH 31, 2010

COUNTRY OF Canada)
) ss.
PROVINCE OF Quebec)

On the 22 day of June, 2005, before me came Jacques Banville, to me known to be the person of that name mentioned in, and who executed the foregoing Assignment and acknowledged that he executed it.

[SEAL]

Notary Public (Signature)

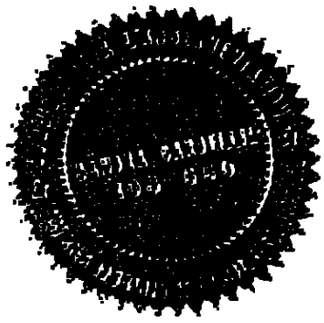
SANDRA CARDILLINI
Notary Public (Printed Name)

June 06, 2008
Date Commission Expires

840

COUNTRY OF Canada)
) ss.
PROVINCE OF Quebec)

On the 22 day of June, 2005, before me came Francis Beaulieu, to me known to be the person of that name mentioned in, and who executed the foregoing Assignment and acknowledged that he executed it.



Notary Public (Signature)

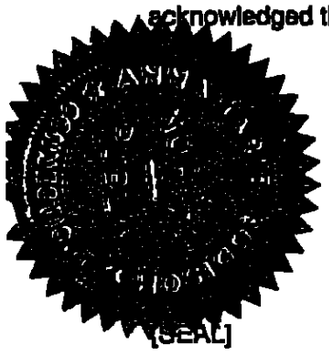
SANDRA CARDILLI
Notary Public (Printed Name)

June 6, 2008
Date Commission Expires

[SEAL]

STATE OF Connecticut)
) ss. Wallingford
COUNTY OF New Haven)

On the 15 day of June, 2005, before me came Timothy P. Connolly, to me known to be the person of that name mentioned in, and who executed the foregoing Assignment and acknowledged that he executed it.



Notary Public

ANNAMARIE BOOSICH
NOTARY PUBLIC
MY COMMISSION EXPIRES MARCH 31, 2010

[SEAL]

641

STATE OF Connecticut)
) ss. Wallingford
COUNTY OF New Haven)

On the 16 day of June, 2005, before me came Mark R. Krystal, to me known to be the person of that name mentioned in, and who executed the foregoing Assignment and acknowledged that he executed it.

[SEAL]

Annamarie Bodisch
Notary Public

ANNAMARIE BODISCH
NOTARY PUBLIC
MY COMMISSION EXPIRES MARCH 31, 2010

STATE OF Connecticut)
) ss. Wallingford
C UNTY OF New Haven)

On the 15 day of June, 2005, before me came John D. Matiskella, to me known to be the person of that name mentioned in, and who executed the foregoing Assignment and acknowledged that he executed it.

[SEAL]

Annamarie Bodisch
Notary Public

ANNAMARIE BODISCH
NOTARY PUBLIC
MY COMMISSION EXPIRES MARCH 31, 2010

942

COUNTRY OF Canada)
) ss.
PROVINCE OF Quebec)

On the 22 day of June, 2005, before me came Carl Ouellet, to me known to be the person of that name mentioned in, and who executed the foregoing Assignment and acknowledged that he executed it.

Notary Public (Signature)

SANDRA CARDELLINI
Notary Public (Printed Name)

June 6, 2008
Date Commission Expires

[SEAL]

COUNTRY OF Canada)
) ss.
PROVINCE OF Quebec)

On the 22 day of June, 2005, before me came Serge Plamondon, to me known to be the person of that name mentioned in, and who executed the foregoing Assignment and acknowledged that he executed it.

Notary Public (Signature)

SANDRA CARDELLINI
Notary Public (Printed Name)

June 6, 2008
Date Commission Expires

[SEAL]

843

COUNTRY OF Canada)
) ss.
PROVINCE OF Quebec)

On the 22 day of June, 2005, before me came Roger Remillard, to me known to be the person of that name mentioned in, and who executed the foregoing Assignment and acknowledged that he executed it.

Notary Public (Signature)

SANDRA CARDELLINI
Notary Public (Printed Name)

June 6, 2008
Date Commission Expires

[SEAL]

STATE OF Connecticut)
) ss. Wallingford
COUNTY OF New Haven)

On the 20 day of June, 2005, before me came Margaret E. Sorenson, to me known to be the person of that name mentioned in, and who executed the foregoing Assignment and acknowledged that she executed it.

Annamarie Bodisch
Notary Public

ANNAMARIE BODISCH
NOTARY PUBLIC
MY COMMISSION EXPIRES MARCH 31, 2010

[SEAL]

STATE OF Connecticut)
) ss. Wallingford
COUNTY OF New Haven)

On the 15 day of June, 2005, before me came Yasuteugu Ueda, to me known to be the person of that name mentioned in, and who executed the foregoing Assignment and acknowledged that he executed it.



[SEAL]

Annamarie Bodisch
Notary Public

ANNAMARIE BODISCH
NOTARY PUBLIC
MY COMMISSION EXPIRES MARCH 31, 2010

STATE OF Connecticut)
) ss. Wallingford
COUNTY OF New Haven)

On the 16 day of June, 2005, before me came Michael A. Walker, to me known to be the person of that name mentioned in, and who executed the foregoing Assignment and acknowledged that he executed it.



[SEAL]

Annamarie Bodisch
Notary Public

ANNAMARIE BODISCH
NOTARY PUBLIC
MY COMMISSION EXPIRES MARCH 31, 2010

TRADUCCIÓN OFICIAL No. 1005/06 de un documento escrito en Inglés, el cual para su identificación se sella con el sello del Traductor. Esta es una Traducción Oficial efectuada el día 23 de noviembre de 2.006 por Patricia Silva Aldana, Traductora Oficial acreditada por el Gobierno Colombiano según Resolución No. 0486 de 2 de abril de 2004 del Ministerio del Interior y de Justicia.

Apostilla de la Convención de la Haya de 5 de octubre de 1.961; Declaración Jurada; Cesión 10253 PSP; Certificaciones Notariales; Cesión 10253PSP2; Certificaciones Notariales; Cesión 10253NP de Bristol Myers Squibb Company.

APOSTILLE

(Convention de La Haye du 5 de Octobre de 1961)

1. PAÍS: ESTADOS UNIDOS DE AMÉRICA
2. ESTE INSTRUMENTO PÚBLICO HA SIDO FIRMADO POR.
   EVELYN VAZQUEZ
3. EN SU CONDICIÓN DE
   NOTARIO PÚBLICO DE NEW JERSEY
4. POSEE EL SELLO/ESTAMPILLA DE
   EVELYN VAZQUEZ, NOTARIO

CERTIFICADO

5. EN TRENTON, NEW JERSEY
6. EL 14 DE NOVIEMBRE DE 2006
7. POR: Bradley Abelow, TESORERO DE NEW JERSEY
8. No. A 275783
9. SELLO/ESTAMPILLA:

   Oblea Dorada Estado de New Jersey

10. Firma:

(Fdo. Bradley Abelow)

PATRICIA SILVA ALDANA
RES No. 0486
ABRIL 2 2004
MINISTERIO DE JUSTICIA
TRADUCTORA OFICIAL

10253-PCT 846

DECLARACIÓN JURADA

La suscrita, Suzanne E. Babajko, Asesor Principal de Patentes, Departamento de Patentes –

Bristol-Myers Squibb Company por el presente certifico que los documentos anexos son copias notarizadas genuinas y correctas de las cesiones originales firmadas por los inventores.

(Fdo.)

Suzanne E. Babajko
Asesor Principal de Patentes

CONDADO DE NEW JERSEY)
ESTADO DE MERCER) ss.

Suscrito y juramentado ante mí el 6 de noviembre de 2006.

(Fdo. Ilegible)

Notario Público
Evelyn Vazquez
Notario Público de New Jersey
No. 2106805
Mi comisión Vence el 9 de diciembre de 2007
Registrada en el Condado de Middlesex

(SELLO)

PATRICIA SILVA ALDANA
RES No. 0486
ABRIL 2 2004
MINISTERIO DE JUSTICIA
TRADUCTORA OFICIAL

Mundialmente
Caso 10253 PSP

847

CESIÓN

Nosotros,

Jacques Banville	residente en	1209 Girard St-Hubert, Québec J4T 1H3 Canada
B. Narasihulu Naidu	residente en	12 Skeetfield Point Rd. Durham, Connecticut 06422 Estados Unidos de América
Roger Remillard	residente en	13 des Cedres Napierville, Québec J0L 1L0 Canadá
Gilles Bouthillier	residente en	147 des Cerisiers Granby, Québec J2J 1Z5 Canadá
Serge Plamondon	residente en	705 du Cabestan Ste-Catherine, Québec J0L 1E0 Canadá
Michael A. Walter	residente en	76R Ivy Way Dirham, Connecticut 06422 Estados Unidos de América,

de acuerdo con las obligaciones contractuales asumidas hasta ahora y/o, mediante la debida contraprestación, cuyo recibo y suficiencia se reconoce por el presente, en efecto por el presente vendemos y cedemos a **Bristol-Myers Squibb Company**, una sociedad de Delaware, con oficinas comerciales en Lawrenceville-Princeton Road, Princeton, NJ 08543-4000, sus sucesores, cesionarios y representantes legales, la totalidad de nuestros derechos, titularidad e interés que incluye el derecho y total beneficio de dichas prioridades según nos otorguen las leyes locales o mediante tratado incluyendo toda convención internacional para la protección de propiedad industrial, en y para todos los países del mundo, incluyendo los Estados Unidos y sus territorios y posesiones, en y para la invención titulada:

Bicíclicos Heterocíclicos como Inhibidores del Integrase del VIH

inventado por nosotros y descrito en la solicitud de patente provisional de los Estados Unidos

Solicitud No. **60/575,513**, radicada el **28 de mayo de 2004**,

PATRICIA SILVA ALDANA
RES No. 0486
ABRIL 2 2004
MINISTERIO DE JUSTICIA
TRADUCTORA OFICIAL

incluyendo la mencionada solicitud de patente de los Estados Unidos y cualquier solicitud que reclame prioridad de dicha solicitud provisional, radicada en cualquier país, y cualesquiera patentes que puedan ser expedidas y/o otorgadas sobre ella, y todas las divisiones, continuaciones, re-expediciones, certificados de re-examinación y extensiones de los mismos en todos los países, siendo dicho interés la total titularidad de dicha invención y la totalidad de dichas solicitudes, patentes (incluyendo reexpedición de patentes), extensiones y certificados de re-examinación a poseerse y disfrutarse por la mencionada Bristol-Myers Squibb Company y sus sucesores y cesionarios para el propósito total de los términos para los cuales dichas patentes (incluyendo patentes de re-expedición); extensiones y certificados de re-examinación puedan ser concedidos y/o emitidos, tanto y completamente como los mismos sean mantenidos y disfrutados por nosotros si esta venta, cesión y transferencia no hubiere sido efectuada;

Y nosotros por el presente acordamos comunicar a dicho cesionario o a sus representantes cualesquiera hechos conocidos de nosotros con respecto de dicha invención, para testificar en todo proceso legal, para firma y/o firmar cualesquiera documentos adicionales y/o instrumentos que sean necesarios, legales y adecuados en y/o para la radicación y/o procesamiento de todas las solicitudes, incluyendo solicitudes divisionales, de continuación y de re-expedición, prórrogas y certificados de re-examinación y/o el otorgamiento y/o emisión de los mismos y/o con el fin de en contrario garantizar la titularidad de dicha invención y todas las mencionadas solicitudes, patentes, (incluyendo patentes de re-expedición, extensiones y certificados de re-examinación en dicho cesionario, y en general para llevar a cabo todo lo que sea posible para asistir a dicho cesionario, sus sucesores y cesionarios para obtener y ejercer la debida protección para dicha invención en todos los países.

Firmado el 31 de agosto de 2004 por (Fdo. Ilegible)

_____

Jacques Banville

Firmado el 2 de julio de 2004 por (Fdo. Ilegible)

_____

B. Narasihulu Naidu

Firmado el 31 de agosto de 2004 por (Fdo. Ilegible)

_____

Roger Remillard

PATRICIA SILVA ALDANA
RES No. 0486
ABRIL 2 2004
MINISTERIO DE JUSTICIA
TRADUCTORA OFICIAL

Mundialmente
Caso 10253 PSP 849

Firmado el 31 de agosto de 2004 por **(Fdo. Ilegible)**

Gilles Bouthillier

Firmado el 31 de agosto de 2004 por **(Fdo. Ilegible)**

Serge Plamodon

Firmado el 23 de agosto de 2004 por **(Fdo. Ilegible)**

Michael A. Walker

PATRICIA SILVA ALDANA
RES No. 0498
ABRIL 2 2004
MINISTERIO DE JUSTICIA
TRADUCTORA OFICIAL

País de Canadá)
)ss.
Provincia de Québec)

El 31 de agosto de 2004, compareció ante mí **Jacques Banville**, de quien me consta es la persona del nombre mencionado y quien firmó la anterior Cesión y reconoció que él la firmó.

(Fdo. Ilegible)
_____
Notario Público (Firma)

Jean Boucher
_____
Notario Público (Nombre Impreso)

(Ilegible)
_____
Fecha en que vence la Comisión

ESTADO de Connecticut)
)ss. Wallingford
CONDADO DE New Haven)

El 2 de julio de 2004, compareció ante mí **B. Narasimhulu Naidu**, de quien me consta es la persona del nombre mencionado y quien firmó la anterior Cesión y reconoció que él la firmó.

(Fdo. Ilegible)
Notario Público

Annamarie Bodisch
Notario Público
Mi Comisión Vence el 31 de Marzo de 2005

(SELLO)

PATRICIA SILVA ALDANA
RES No. 0486
ABRIL 2 2004
MINISTERIO DE JUSTICIA
TRADUCTORA OFICIAL

651

País de Canadá)
)ss.
Provincia de Québec)

El 31 de agosto de 2004, compareció ante mí, **Roger Remillard**, de quien me consta es la persona del nombre mencionado y quien firmó la anterior Cesión y reconoció que él la firmó.

(Fdo. Ilegible)
_____
Notario Público (Firma)

Jean Boucher
_____
Notario Público (Nombre Impreso)

(Ilegible)
_____
Fecha en que Vence la Comisión

PAÍS DE Canadá)
)ss.
PROVINCIA DE Québec)

El 31 de agosto de 2004, compareció ante mí **Gilles Bouthillier**, de quien me consta es la persona del nombre mencionado y quien firmó la anterior Cesión y reconoció que él la firmó.

(Fdo. Ilegible)
_____
Notario Público (Firma)

Jean Boucher
_____
Notario Público (Nombre Impreso)

(Fdo.)
_____
Fecha en que Vence la Comisión

PATRICIA SILVA ALDANA
RES No. 0486
ABRIL 2 2004
MINISTERIO DE JUSTICIA
TRADUCTORA OFICIAL

PAÍS DE Canadá)
)ss.
PROVINCIA DE Québec)

El 31 de agosto de 2004, compareció ante mí, **Serge Plamondon**, de quien me consta es la persona del nombre mencionado y quien firmó la anterior Cesión y reconoció que él la firmó.

(Fdo. Ilegible)
Notario Público (Firma)

Jean Boucher
Notario Público (Nombre Impreso)

(Ilegible)
Fecha en que Vence la Comisión

ESTADO DE Connecticut)
) ss. Wallingford
CONDADO DE New Haven)

El 23 de agosto de 2004, compareció ante mí **Michel A. Walker**, de quien me consta es la persona del nombre mencionado y quien firmó la anterior Cesión y reconoció que él la firmó.

(Fdo. Ilegible)
Notario Público (Firma)

Annamarie Bodisch
Notario Público
Mi comisión Vence el 31 de marzo de 2005

PATRICIA SILVA ALDANA
RES No. 0486
ABRIL 2 2004
MINISTERIO DE JUSTICIA
TRADUCTORA OFICIAL

Mundialmente
Caso 10253
PSP2

853

CESIÓN

Nosotros,

Jacques Banville	residente en	1209 Girard St-Hubert, Québec J4T 1H3 Canada
B. Narasimhulu Naidu	residente en	12 Skeetfield Point Rd. Durham, Connecticut 06422 Estados Unidos de América
Roger Remillard	residente en	13 des Cedres Napierville, Québec J0L 1L0 Canadá
Gilles Bouthillier	residente en	147 des Cerisiers Granby, Québec J2J 1Z5 Canadá
Serge Plamondon	residente en	705 du Cabestan Ste-Catherine, Québec J0L 1E0 Canadá
Michael A. Walter	residente en	76R Ivy Way Dirham, Connecticut 06422 Estados Unidos de América,

de acuerdo con las obligaciones contractuales asumidas hasta ahora y/o, mediante la debida contraprestación, cuyo recibo y suficiencia se reconoce por el presente, en efecto por el presente vendemos y cedemos a **Bristol-Myers Squibb Company**, una sociedad de Delaware, con oficinas comerciales en Lawrenceville-Princeton Road, Princeton, NJ 08543-4000, sus sucesores, cesionarios y representantes legales, la totalidad de nuestros derechos, titularidad e interés que incluye el derecho y total beneficio de dichas prioridades según nos otorguen las leyes locales o mediante tratado incluyendo toda convención internacional para la protección de propiedad industrial, en y para todos los países del mundo, incluyendo los Estados Unidos y sus territorios y posesiones, en y para la invención titulada:

Bicíclicos Heterocíclicos como Inhibidores del Integrase del VIH

inventado por nosotros y descrito en la solicitud de patente provisional de los Estados Unidos

Solicitud No. 60/603,371, radicada el 20 de agosto de 2004.

PATRICIA SILVA ALDANA
RES No. 0486
ABRIL 2 2004
MINISTERIO DE JUSTICIA
TRADUCTORA OFICIAL

incluyendo la mencionada solicitud de patente de los Estados Unidos y cualquier solicitud que reclame prioridad de dicha solicitud provisional, radicada en cualquier país, y cualesquiera patentes que puedan ser expedidas y/o otorgadas sobre ella, y todas las divisiones, continuaciones, re-expediciones, certificados de re-examinación y extensiones de los mismos en todos los países, siendo dicho interés la total titularidad de dicha invención y la totalidad de dichas solicitudes, patentes (incluyendo reexpedición de patentes), extensiones y certificados de re-examinación a poseerse y disfrutarse por la mencionada Bristol-Myers Squibb Company y sus sucesores y cesionarios para el propósito total de los términos para los cuales dichas patentes (incluyendo patentes de re-expedición); extensiones y certificados de re-examinación puedan ser concedidos y/o emitidos, tanto y completamente como los mismos sean mantenidos y disfrutados por nosotros si esta venta, cesión y transferencia no hubiere sido efectuada;

Y nosotros por el presente acordamos comunicar a dicho cesionario o a sus representantes cualesquiera hechos conocidos de nosotros con respecto de dicha invención, para testificar en todo proceso legal, para firma y/o firmar cualesquiera documentos adicionales y/o instrumentos que sean necesarios, legales y adecuados en y/o para la radicación y/o procesamiento de todas las solicitudes, incluyendo solicitudes divisionales, de continuación y de re-expedición, prórrogas y certificados de re-examinación y/o el otorgamiento y/o emisión de los mismos y/o con el fin de en contrario garantizar la titularidad de dicha invención y todas las mencionadas solicitudes, patentes, (incluyendo patentes de re-expedición, extensiones y certificados de re-examinación en dicho cesionario, y en general para llevar a cabo todo lo que sea posible para asistir a dicho cesionario, sus sucesores y cesionarios para obtener y ejercer la debida protección para dicha invención en todos los países.

Firmado el 4 de octubre de 2004 por (Fdo. Ilegible)

_____

Jacques Banville

Firmado el 27 de septiembre de 2004 por (Fdo. Ilegible)

_____

B. Narasimhulu Naidu

Firmado el 4 de octubre de 2004 por (Fdo. Ilegible)

_____

Roger Remillard

PATRICIA SILVA ALDANA
RES No. 0486
ABRIL 2 2004
MINISTERIO DE JUSTICIA
TRADUCTORA OFICIAL

855

Mundialmente
Caso 10253PSP2

Firmado el 4 de octubre de 2004 por **(Fdo. Ilegible)**

Gilles Bouthillier

Firmado el 4 de octubre de 2004 por **(Fdo. Ilegible)**

Serge Plamondon

Firmado el 28 de septiembre de 2004 por **(Fdo. Ilegible)**

Michael A. Walker

PATRICIA SILVA ALDANA
RES No. 0488
ABRIL 2 2004
MINISTERIO DE JUSTICIA
TRADUCTORA OFICIAL

Mundialmente
Caso 10253PSP2

País de Canadá)
)ss.
Provincia de Québec)

El 4 de octubre de 2004, compareció ante mí **Jacques Banville**, de quien me consta es la persona del nombre mencionado y quien firmó la anterior Cesión y reconoció que él la firmó.

(Fdo. Ilegible)
Notario Público (Firma)

Jean Boucher
Notario Público (Nombre Impreso)

(Ilegible)
Fecha en que vence la Comisión

ESTADO de Connecticut)
)ss. Wallingford
CONDADO DE New Haven)

El 27 de septiembre de 2004, compareció ante mí **B. Narasimhulu Naidu**, de quien me consta es la persona del nombre mencionado y quien firmó la anterior Cesión y reconoció que él la firmó.

(Fdo. Ilegible)
Notario Público

Annamarie Bodisch
Notario Público
Mi Comisión Vence el 31 de Marzo de 2005

PATRICIA SILVA ALDANA
RES No. 0488
ABRIL 2 2004
MINISTERIO DE JUSTICIA
TRADUCTORA OFICIAL

PAÍS DE Canadá)
)ss.
Provincia de Québec)

El 4 de octubre de 2004, compareció ante mí, **Roger Remillard**, de quien me consta es la persona del nombre mencionado y quien firmó la anterior Cesión y reconoció que él la firmó.

(Fdo. Ilegible)

Notario Público (Firma)

Jean Boucher

Notario Público (Nombre Impreso)

(Ilegible)

Fecha en que Vence la Comisión

PAÍS DE Canadá)
)ss.
PROVINCIA DE Québec)

El 4de octubre 2004, compareció ante mí **Gilles Bouthillier**, de quien me consta es la persona del nombre mencionado y quien firmó la anterior Cesión y reconoció que él la firmó.

(Fdo. Ilegible)

Notario Público (Firma)

Jean Boucher

Notario Público (Nombre Impreso)

(Ilegible)

Fecha en que Vence la Comisión

PATRICIA SILVA ALDANA
RES No. 0486
ABRIL 2 2004
MINISTERIO DE JUSTICIA
TRADUCTORA OFICIAL

Mundialmente
Caso 10253 PSP2

858

PAÍS DE Canadá)
)ss.
PROVINCIA DE Québec)

El 4 de octubre de 2004, compareció ante mí, **Serge Plamondon**, de quien me consta es la persona del nombre mencionado y quien firmó la anterior Cesión y reconoció que él la firmó.

(Fdo. Ilegible)
_____
Notario Público (Firma)

Jean Boucher
_____
Notario Público (Nombre Impreso)

(Ilegible)
_____
Fecha en que Vence la Comisión

ESTADO DE Connecticut)
) ss. Wallingford
CONDADO DE New Haven)

El 28 de septiembre de 2004, compareció ante mí **Michel A. Walker**, de quien me consta es la persona del nombre mencionado y quien firmó la anterior Cesión y reconoció que él la firmó.

(Fdo. Ilegible)
_____
Notario Público (Firma)

Annamarie Bodisch
Notario Público
Mi comisión Vence el 31 de marzo de 2005

PATRICIA SILVA ALDANA
RES No. 0486
ABRIL 2 2004
MINISTERIO DE JUSTICIA
TRADUCTORA OFICIAL

Mundialmente
Caso 10253 NP

854
859

CESIÓN

Nosotros,

B. Narasimhulu Naidu	residente en	12 Sketfield Point Rd. Dirham, Connecticut 06422 Estados Unidos de América
Jacques Banville	residente en	1209 Girard St-Hubert, Québec J4T 1H3 Canadá
Francis Beaulieu	residente en	370 Leotabe Dubuc Laprairie, Quebec J5R 5M4 Canadá
Timothy P. Connolly	residente en	6 Elizabeth Road Portland, Connecticut 06480 Estados Unidos de América
Mark Krystal	residente en	12 Salem Road Westport, Connecticut 06880 Estados Unidos de América
John D. Matiskella	residente en	130 High Hill Road Wallingford, Connecticut 06492 Estados Unidos de América
Carl Ouellet	residente en	555 Rue de la Verendrye Boucherville, Québec J4B 2Y3 Canadá
Serge Plamondon	residente en	705 du Cabestan Ste-Catherine, Québec J5C 1W9 Canadá
Roger Remillard	residente en	13 des Cedres Napierville, Quebec J9L 1L0 Canadá
Margaret E. Sorenson	residente en	27 Harrison Street Apt. 13 Meriden, Connecticut 06450 Estados Unidos de América
Yasutsugu Ueda	residente en	46 Olde Orchard Road Clinton, Connecticut 06413 Estados Unidos de América
Michael A. Walter	residente en	76R Ivy Way Dirham, Connecticut 06422 Estados Unidos de América

PATRICIA SILVA ALDANA
RES No. 0486
ABRIL 2 2004
MINISTERIO DE JUSTICIA
TRADUCTORA OFICIAL

de acuerdo con las obligaciones contractuales asumidas hasta ahora y/o, mediante la debida contraprestación, cuyo recibo y suficiencia se reconoce por el presente, en efecto por el presente vendemos y cedemos a **Bristol-Myers Squibb Company**, una sociedad de Delaware, con oficinas comerciales en Lawrenceville-Princeton Road, Princeton, NJ 08543- 4000, sus sucesores, cesionarios y representantes legales, la totalidad de nuestros derechos, titularidad e interés que incluye el derecho y total beneficio de dichas prioridades según nos otorguen las leyes locales o mediante tratado incluyendo toda convención internacional para la protección de propiedad industrial, en y para todos los países del mundo, incluyendo los Estados Unidos y sus territorios y posesiones, en y para la invención titulada:

Bicíclicos Heterocíclicos como Inhibidores del Integrase del VIH

inventado por nosotros y descrito en la solicitud de patente provisional de los Estados Unidos

Solicitud No. 11/126,891, radicada el 11 de mayo de 2005,

incluyendo la mencionada solicitud de patente de los Estados Unidos y cualquier solicitud que reclame prioridad de dicha solicitud provisional, radicada en cualquier país, y cualesquiera patentes que puedan ser expedidas y/o otorgadas sobre ella, y todas las divisiones, continuaciones, re-expediciones, certificados de re-examinación y extensiones de los mismos en todos los países, siendo dicho interés la total titularidad de dicha invención y la totalidad de dichas solicitudes, patentes (incluyendo reexpedición de patentes), extensiones y certificados de re-examinación a poseerse y disfrutarse por la mencionada Bristol-Myers Squibb Company y sus sucesores y cesionarios para el propósito total de los términos para los cuales dichas patentes (incluyendo patentes de re-expedición); extensiones y certificados de re-examinación puedan ser concedidos y/o emitidos, tanto y completamente como los mismos sean mantenidos y disfrutados por nosotros si esta venta, cesión y transferencia no hubiere sido efectuada;

Y nosotros por el presente acordamos comunicar a dicho cesionario o a sus representantes cualesquiera hechos conocidos de nosotros con respecto de dicha invención, para testificar en todo proceso legal, para firma y/o firmar cualesquiera documentos adicionales y/o instrumentos que sean necesarios, legales y adecuados en y/o para la radicación y/o procesamiento de todas las solicitudes, incluyendo solicitudes divisionales, de continuación y de re-expedición, prórrogas y certificados de re-examinación y/o el otorgamiento y/o

PATRICIA SILVA ALDANA
RES No. 0486
ABRIL 2 2004
MINISTERIO DE JUSTICIA
TRADUCTORA OFICIAL

861

emisión de los mismos y/o con el fin de en contrario garantizar la titularidad de dicha invención y todas las mencionadas solicitudes, patentes, (incluyendo patentes de re-expedición, extensiones y certificados de re-examinación en dicho cesionario, y en general para llevar a cabo todo lo que sea posible para asistir a dicho cesionario, sus sucesores y cesionarios para obtener y ejercer la debida protección para dicha invención en todos los países.

Firmado el 15 de junio de 2005 por (Fdo. Ilegible)
B. Narasimhulu Naidu

Firmado el 22 de junio de 2005 por (Fdo. Ilegible)
Jacques Banville

Firmado el 22 de junio de 2005 por (Fdo. Ilegible)
Francis Beaulieu

Firmado el 15 de junio de 2005 por (Fdo. Ilegible)
Timothy P. Connolly

Firmado el 16 de junio de 2005 por (Fdo. Ilegible)
Mark R. Krystal

Firmado el 15 de junio de 2005 por (Fdo. Ilegible)
John D. Matiskella

Firmado el 22 de junio de 2005 por (Fdo. Ilegible)
Carl Ouellet

Firmado el 22 de junio de 2005 por (Fdo. Ilegible)
Serge Plamondon

Firmado el 22 de junio de 2005 por (Fdo. Ilegible)
Roger Remillard

Firmado el __ de junio de 2005 por (Fdo. Ilegible)
Margaret E. Sorenson

Firmado el 15 de junio de 2005 por (Fdo. Ilegible)
Yasutsugu Ueda

Firmado el 16 de junio de 2005 por (Fdo. Ilegible)
Michael A. Walker

PATRICIA SILVA ALDANA
RES No. 0486
ABRIL 2 2004
MINISTERIO DE JUSTICIA
TRADUCTORA OFICIAL

ESTADO de Connecticut)
)ss. Wallingford
CONDADO DE New Haven)

El 15 de junio de 2005, compareció ante mí **B. Narasimhulu Naidu**, de quien me consta es la persona del nombre mencionado y quien firmó la anterior Cesión y reconoció que él la firmó.

(Fdo. Ilegible)
Notario Público

Annamarie Bodisch
Notario Público
Mi Comisión Vence el 31 de Marzo de 2010

(SELLO)

PAÍS DE Canadá)
)ss.
PROVINCIA DE Québec)

El 22 de junio de 2005, compareció ante mí, **Jacques Banville**, de quien me consta es la persona del nombre mencionado y quien firmó la anterior Cesión y reconoció que él la firmó.

(Fdo. Ilegible)
Notario Público (Firma)

Sandra Cardellini
Notario Público (Nombre Impreso)

6 de junio de 2008
Fecha en que Vence la Comisión

(SELLO)

PAÍS DE Canadá)
)ss.
PROVINCIA DE Québec)

El 22 de junio de 2005, compareció ante mí, **Francis Beaulieu**, de quien me consta es la persona del nombre mencionado y quien firmó la anterior Cesión y reconoció que él la firmó.

(Fdo. Ilegible)
Notario Público (Firma)

Sandra Cardellini
Notario Público (Nombre Impreso)

6 de junio de 2,008
Fecha en que Vence la Comisión

PATRICIA SILVA ALDANA
RES No. 0486
ABRIL 2 2004
MINISTERIO DE JUSTICIA
TRADUCTORA OFICIAL

863

ESTADO DE Connecticut)
) ss. Wallingford
CONDADO DE New Haven)

El 15 de junio de 2005, compareció ante mí **Timothy P. Connolly**, de quien me consta es la persona del nombre mencionado y quien firmó la anterior Cesión y reconoció que él la firmó.

(Fdo. Ilegible)
_____
Notario Público

Annamarie Bodisch
Notario Público
Mi comisión Vence el 31 de marzo de 2010

(SELLO)

ESTADO DE Connecticut)
) ss. Wallingford
CONDADO DE New Haven)

El 16 de junio de 2005, compareció ante mí **Mark R. Krystal**, de quien me consta es la persona del nombre mencionado y quien firmó la anterior Cesión y reconoció que él la firmó.

(Fdo. Ilegible)
_____
Notario Público

Annamarie Bodisch
Notario Público
Mi comisión Vence el 31 de marzo de 2010

(SELLO)

ESTADO DE Connecticut)
) ss. Wallingford
CONDADO DE New Haven)

El 15 de junio de 2005, compareció ante mí **John D. Matiskella**, de quien me consta es la persona del nombre mencionado y quien firmó la anterior Cesión y reconoció que él la firmó.

(Fdo. Ilegible)
_____
Notario Público

Annamarie Bodisch
Notario Público
Mi comisión Vence el 31 de marzo de 2010

PATRICIA SILVA ALDANA
RES No. 0486
ABRIL 2 2004
MINISTERIO DE JUSTICIA
TRADUCTORA OFICIAL

Mundialmente
Caso 10253 NP

PAÍS DE Canadá)
)ss.
PROVINCIA DE Québec)

El 22 de junio de 2005, compareció ante mí, **Carl Ouellet**, de quien me consta es la persona del nombre mencionado y quien firmó la anterior Cesión y reconoció que él la firmó.

(Fdo. Ilegible)
Notario Público (Firma)

Sandra Cardellini
Notario Público (Nombre Impreso)

6 de junio de 2008
Fecha en que Vence la Comisión

(SELLO)

PAÍS DE Canadá)
)ss.
PROVINCIA DE Québec)

El 22 de junio de 2005, compareció ante mí, **Serge Plamondon**, de quien me consta es la persona del nombre mencionado y quien firmó la anterior Cesión y reconoció que él la firmó.

(Fdo. Ilegible)
Notario Público (Firma)

Sandra Cardellini
Notario Público (Nombre Impreso)

6 de junio de 2008
Fecha en que Vence la Comisión

(SELLO)

PATRICIA SILVA ALDANA
RES No. 0486
ABRIL 2 2004
MINISTERIO DE JUSTICIA
TRADUCTORA OFICIAL

Mundialmente
Caso 10253 NP

865

PAÍS DE Canadá)
)ss.
PROVINCIA DE Québec)

El 22 de junio de 2005, compareció ante mí, **Roger Remillard**, de quien me consta es la persona del nombre mencionado y quien firmó la anterior Cesión y reconoció que él la firmó.

(Fdo. Ilegible)

Notario Público (Firma)

Sandra Cardellini

Notario Público (Nombre Impreso)

6 de junio de 2008

Fecha en que Vence la Comisión

(SELLO)

ESTADO DE Connecticut)
) ss. Wallingford
CONDADO DE New Haven)

El 20 de junio de 2005, compareció ante mí **Margaret E. Sorenson**, de quien me consta es la persona del nombre mencionado y quien firmó la anterior Cesión y reconoció que él la firmó.

(Fdo. Ilegible)

Notario Público

Annamarie Bodisch
Notario Público
Mi comisión Vence el 31 de marzo de 2010

(SELLO)

ESTADO DE Connecticut)
) ss. Wallingford
CONDADO DE New Haven)

El 15 de junio de 2005, compareció ante mí **Yasutsugu Ueda**, de quien me consta es la persona del nombre mencionado y quien firmó la anterior Cesión y reconoció que él la firmó.

(Fdo. Ilegible)

Notario Público

Annamarie Bodisch
Notario Público
Mi comisión Vence el 31 de marzo de 2010

PATRICIA SILVA ALDANA
RES No. 0486
ABRIL 2 2004
MINISTERIO DE JUSTICIA
TRADUCTORA OFICIAL

866

ESTADO DE Connecticut)
) ss. Wallingford
CONDADO DE New Haven)

El 16 de junio de 2005, compareció ante mí **Michael A. Walker**, de quien me consta es la persona del nombre mencionado y quien firmó la anterior Cesión y reconoció que él la firmó.

(Fdo. Ilegible)

Notario Público

Annamarie Bodisch
Notario Público
Mi comisión Vence el 31 de marzo de 2010

La anterior es traducción fiel y completa del documento en referencia, del cual se deja copia en este archivo para su confrontación.

Patricia Silva A.
Traductora Oficial
Resolución No. 0486
Ministerio del Interior y de Justicia

PATRICIA SILVA ALDANA
RES No. 0486
ABRIL 2 2004
MINISTERIO DE JUSTICIA
TRADUCTORA OFICIAL

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APOSTILLE

(CONVENTION DE LA HAYE DU 5 OCTOBRE 1961)

1. COUNTRY: UNITED STATES OF AMERICA

2. THIS PUBLIC DOCUMENT HAS BEEN SIGNED BY:
MAURA O KNOBL

3. ACTING IN THE CAPACITY OF:
NOTARY PUBLIC OF NEW JERSEY

4. BEARS THE SEAL/STAMP OF:
MAURA O KNOBL, NOTARY

CERTIFIED

5. AT TRENTON, NEW JERSEY

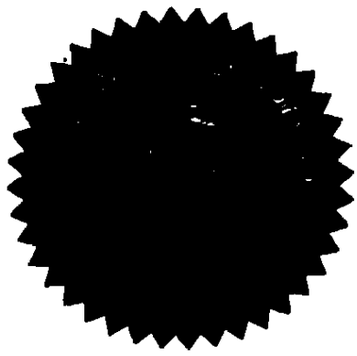
6. THE 13TH DAY OF JANUARY 2006

7. BY: John E McCormac, CPA, NEW JERSEY TREASURER

8. NO. A248886

9. SEAL/STAMP:

10. SIGNATURE





Brigard & Castro
BOGOTA - COLOMBIA

868

PODER

Yo (nosotros)

domiciliado(s) en

Nombro(amos) a: **JUAN PABLO CADENA SARMIENTO** y/o **CARLOS H. PALACIO EASTMAN** y/o **MARTIN E. TORRES CARDOZO**, de Bogotá, Colombia, apoderados verdaderos y legales con poder especial, amplio y suficiente, para recabar de las oficinas y autoridades colombianas administrativas, judiciales y de policía, en cualquier instancia o recurso, la obtención de patentes de invención, registros de marcas, diseños industriales, modelos de utilidad, depósitos de nombres comerciales, lemas comerciales y enseñas, registros de derechos de autor y contratos sobre los mismos, obtención de certificados de obtentor de variedades vegetales, así como sus prórrogas, renovaciones, anotaciones de traspaso, cambios de nombre y/o domicilio; elaborar, tramitar y registrar contratos de licencia y licencias de cualesquiera clases; intervenir como demandante o como demandado en cualquier instancia y recurso ante cualquier juez, corporación, funcionario público o autoridad en acciones judiciales, administrativas y de policía tales como: oposiciones al registro de marcas; acciones de caducidad, cancelación y nulidad; acciones reivindicatorias, acciones derivadas de la obtención o explotación de licencias; acciones de competencia desleal; demandas penales; acciones de indemnización de perjuicios, reclamos y observaciones a solicitudes de patentes, diseños industriales, modelos de utilidad, en el ejercicio de medidas cautelares y en otras acciones o medidas similares.

A este efecto, lo(s) faculto(amos) para elevar solicitudes, formular descripciones, enmiendas, protestas, declaraciones, oposiciones, cancelaciones, nulidades, apelaciones y reclamos; pagar impuestos, cuotas y gravámenes prescritos por la ley; renunciar o desistir a derechos concedidos o en curso de concesión; recibir toda clase de documentos y valores, dando el descargo respectivo, y, en general, para dar ante dichas autoridades todos los pasos necesarios al efecto indicado y tomar todas las medidas que creyeren conducentes al resguardo de mis (nuestros intereses), con todas las demás facultades legales necesarias.

Este poder comprende la facultad de ratificar o confirmar en mi (nuestro) nombre lo actuado así como la facultad de desistir, transigir, comprometer, y la de sustituirlo en todo o en parte y revocar sustituciones. Asimismo nombro(amos) a: **JUAN PABLO CADENA SARMIENTO** y/o **CARLOS H. PALACIO EASTMAN** y/o **MARTIN E. TORRES CARDOZO**, domiciliado(s) en la Carrera 7 No. 16-56 Piso 9, mis (nuestros) apoderados en Colombia, con facultades para recibir notificaciones y designar apoderados judiciales o extrajudiciales.

Otorgado y firmado en

hoy de de 200_

Firma

Nombre
Cargo

POWER OF ATTORNEY

I (We) BRISTOL-MYERS SQUIBB COMPANY

domiciled in Princeton, New Jersey, USA

Hereby appoints **JUAN PABLO CADENA SARMIENTO** and/or **CARLOS H. PALACIO EASTMAN** and/or **MARTIN E. TORRES CARDOZO**, of Bogotá, Colombia, my (our) true and lawful attorneys with special, ample and sufficient power to obtain from the Colombian administrative, judicial and police offices and authorities, in any instance, privileges of patents of invention, registration of trademarks, industrial designs and utility models; registration of commercial names, slogans and emblems, registration of copyright and contracts related thereto, certificates of obtainers of vegetables varieties, as well as extensions, renewals and recordal of assignments and changes of name and domicile related to the above; to prepare, prosecute and register licenses of any kind; to act as plaintiff or defendant in any instance or recourse, and before any judge, corporation, public official or authority in judicial, administrative and police actions, such as: oppositions to the registration of trademarks; caducity, cancellation and nullity actions; claim actions derived from the obtaining or exploitation of licenses, action of unfair competition; criminal proceedings, actions for payment of damages; claims or observations on patent applications, models, industrial designs and utility models; in the exercise of preventive measures and in other actions or similar proceedings.

To that effect they hereby empowered to file applications, formulate descriptions, amendments, protests, declarations, oppositions, cancellations, nullities, appeals and claims; to pay taxes, quotas and assessments prescribed by law, renounce or waive the rights granted or in the process of granting; to receive all kinds of documents and valuables, giving the respective release of receipt, and, in general, to take before said authorities the necessary steps to such effect, and any measures that they may deem pertinent to the safeguard of my (our) interest(s) with all the other necessary legal powers.

This power includes the faculty to ratify or confirm desist, settle and compromise on my (our) behalf, and to substitute this power in whole or in part and to revoke substitutions. At the same time I (We) hereby appoints **JUAN PABLO CADENA SARMIENTO** and/or **CARLOS H. PALACIO EASTMAN** and/or **MARTIN E. TORRES CARDOZO**, domiciled in Carrera 7 No. 16-56, Piso 9, my (our) attorney(s) [illegible] to receive notifications and to [illegible] extrajudicial attorneys.

Dated and signed 30 DIC 2006

CESAR ALARCON NUÑEZ

Signature
Name Suzanne E. Babajko
Title Senior Patent Counsel

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CERTIFICADO NOTARIAL (SOCIEDAD)

Hoy de de
personalmente compareció ante mí

a quien conozco, y de quien me consta que firmó el anterior documento, debidamente juramentado declaró y dijo que él (ella) es

de

Sociedad legalmente constituida para un período de duración que aún no ha terminado; que el declarante está autorizado por dicha compañía para conferir este poder; que el sello estampado por él al pie de tal poder, en nombre y representación de la expresada compañía, es el sello oficial de ella; y que el objeto para el cual se confiere este instrumento está comprendido dentro del objeto social de la sociedad.

El suscrito Notario hace constar que tuvo a la vista las pruebas de la existencia de la sociedad.

Estado de
con fecha

y que quien confiere el presente poder es su representante.

Notario Público (sello)

NOTARIAL CERTIFICATE (CORP RATION)

On this 11 day of January of 2006 personally appeared before me SUZANNE E. BABAJKO

to me known, and known to me to be the person who signed the foregoing instrument who being by me duly sworn did depose and say that he (she) is the
SENIOR PATENT COUNSEL

of BRISTOL-MYERS SQUIBB COMPANY

Which is legally constituted for a term not yet expired, that deponent is authorized by said Company to confer this Power of Attorney; that the seal affixed hereunto by the deponent in the name and on behalf of said Corporation is the corporate seal thereof; and that the purpose for which this instrument is granted is included within the corporate purpose of company.

The undersigned Notary Public attests that he has seen the documents that prove the existence of the company.

State of
under date of

and that he (she) who grants the present power of attorney is its Representative.

Public Notary (Seal)

CERTIFICADO NOTARIAL PERSONA NATURAL

Hoy de de , compareció(eron) ante mí

a quien (es) conozco y me consta que es(son) la(s) persona(s) firmante(s) del documento que precede y quien(es) declara(n) que otorgan el mismo para los fines y propósitos que en él se expresan.

Notario Público (sello)

NOTARIAL CERTIFICATE NATURAL PERSON

On this 11th day of January of 2006
personally appeared before me
Suzanne E. Babajko
who is(are) known to me and who I attest executed the foregoing document and he (they) declared he (they) grant(s) the document for the uses and purposes therein expressed.

Maura O. Knobl
Notary Public
MAURA O. KNOBL
NOTARY PUBLIC OF NEW JERSEY
My Commission Expires July 27, 2008
Notary Public (Seal)

CONSUL NOTARIAL DE ESPAÑA
EL PRESENTE ES EL SELLO QUE SE ESTAMPA EN TODO LO QUE ESTA COPIA FOTOSTATICA ES FIEL Y EXACTA REPRODUCCION DE SU ORIGINAL QUE HE TENIDO A LA VISTA
BOGOTA D.C. REPUBLICA DE COLOMBIA
30 OCT 2006
CONSUL ALARCON MUÑOZ
NOTARIO CUARENTA Y SEIS

LEGALIZACION POR APOSTILLA ES REQUERIDA.

LEGALIZATION BY APOSTILLE IS REQUIRED.

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TRADUCCION AL ESPAÑOL del Documento de Poder otorgado por **BRISTOL-MYERS SQUIBB COMPANY** domiciliada en **Princeton, New Jersey, Estados Unidos de América.**

APOSTILLA

(CONVENCION DE LA HAYA DEL 5 DE OCTUBRE DE 1961)

1. PAÍS: ESTADOS UNIDOS DE AMÉRICA

2. ESTE DOCUMENTO PUBLICO HA SIDO FIRMADO POR:
MAURA O KNOBL

3. ACTUANDO EN CAPACIDAD DE:
NOTARIO PUBLICO DE NEW JERSEY

4. LLEVA EL SELLO/TIMBRE DE:
MAURA O KNOBL, NOTARIO

CERTIFICADO

5. EN TRENTON, NEW JERSEY

6. EL 13 DE ENERO DE 2006

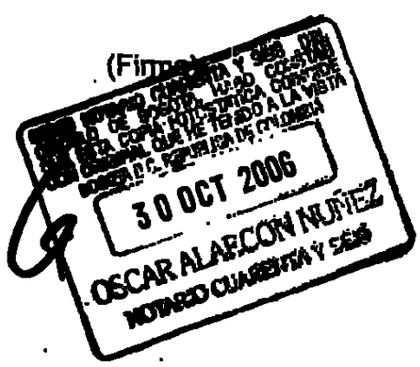
7. POR: John E. McCormac, CPA, TESORERO DE NEW JERSEY

8. NO. A248886

9. SELLO/TIMBRE:

10. FIRMA

(Firma)



SUPERINTENDENCIA DE INDUSTRIA Y COMERCIO
Rad: 08-120207- -00000-0000
Fec: 2008-11-28 17:32:49 Dep: 2020 NUEVOS RADICADOS
Tip. 11 PATENTES
Eve: 376 PRESENTACION
Act 411 PRESENTACION Folios: 5

871

REQUISITOS MINIMOS PARA ADMISION A TRAMITE PCT

PATENTE DE INVENCION [X] MODELO DE UTILIDAD [ ]

- Indicación de que se solicita la concesión de una patente [X]
- Datos de identificación del solicitante o de la persona que presenta la solicitud [X]
- Descripción de la invención [X]
- Dibujos de ser estos pertinentes [ ]
- Comprobante de pago de las tasas establecidas [X]

COMPLETA [X] INCOMPLETA [ ]

DISEÑO INDUSTRIAL [ ]

- Indicación de que se solicita el registro de Diseño Industrial [ ]
- Datos de identificación del solicitante o de la persona que presenta la solicitud [ ]
- Representación gráfica y fotográfica del Diseño Industrial o muestra del material que incorpora el diseño [ ]
- Comprobante de pago de las tasas establecidas [ ]

COMPLETA [ ] INCOMPLETA [ ]

ESQUEMA DE TRAZADO [ ]

- Indicación de que se solicita el registro de un Esquema de Trazado [ ]
- Datos de identificación del solicitante o de la persona que presenta la solicitud [ ]
- Representación gráfica del esquema trazado [ ]
- Comprobante de pago de las tasas establecidas [ ]

COMPLETA [ ] INCOMPLETA [ ]

Firma Responsable

Fecha_____

Carrera 13 No. 27-00 Piso 5, 7 y 10
Conmutador: 3 82 08 40
Fax: 350 52 20
E-mail: Info@sic.gov.co
www.sic.gov.co
Bogotá, D.C., Colombia

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REPUBLICA DE COLOMBIA

SUPERINTENDENCIA DE INDUSTRIA Y COMERCIO

Folio ~~877~~

872

2020
Bogotá D.C.,

Doctor(a)
CADENA SARMIENTO JUAN PABLO
Apoderado(a) y/o Representante de
BRISTOL MYERS SQUIBB COMPANY

REFERENCIA	Radicación No.	06 120207
	Solicitud internacional	PCT/US2005/016473
	Fecha inicio fase nacional	28/12/2006
	Trámite	11
	Evento	378
	Actuación	416
	Oficio No.	2518
	Folios	1

Teniendo en cuenta que la solicitud de privilegio de patente que se tramita bajo el expediente indicado en la referencia, reúne los requisitos de forma establecidos en la Decisión 486 de la Comisión de la Comunidad Andina, el Tratado de Cooperación en Materia de Patentes (PCT), el Reglamento y la Circular Única de la Superintendencia de Industria y Comercio, se envía el extracto de la solicitud a la Oficina de Comunicaciones para efecto de su publicación en la Gaceta de Propiedad Industrial.

Cúmplase
Dado en Bogotá DC, 02 FEB. 2007

ALIX CARMENZA CESPEDES DE VERGEL
Jefe de la división de Nuevas Creaciones

lerazo