Industria y Comercio

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INVENTARIO

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21. **EXPEDIENTE No.** 09-97263

54. **TÍTULO** Compuestos para el tratamiento de Hepatitis C.

51. **CLASIFICACIÓN INTERNACIONAL**

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

DOMICILIO Estados Unidos de America

74. **APODERADO** Alvaro Correa Ordoñez
C.C. 79.143.366 de Usaquen

22. **BOGOTÁ, D.C.,**

(FORMA P-10) FV. 14-10-2001

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SOLICITUD DE :

(1)

[X] Patente de Invención [ ] Patente de Modelo de Utilidad

[X] Capítulo I. [ ] Capítulo II.

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(71)

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Nacionalidad o Domicilio: Estados Unidos de América
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C.C. [ ] NIT [ ]

C.E. [ ] Otro [ ]

Cual

Número

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C.C. [X] NIT [ ]

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Nacionalidad o Domicilio: Estados Unidos de América

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(6) **Título (54)** COMPUESTOS PARA EL TRATAMIENTO DE HEPATITIS C

(7) **Clasificación Internacional (51)** C07D 487; A61K 31/55 ; A61P 31/12

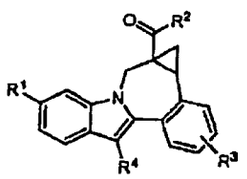
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(10) **ANEXOS**

- [X] Comprobante de pago de la tasa de presentación de la solicitud
- [X] Documento que acredita la existencia y representación legal cuando el solicitante sea persona jurídica
- [X] Poderes, si fuere el caso (ver radicado No. 08.129.339 poder General Bristol-Myers Squibb Company)
- [ ] 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 internacional efectuado por la Autoridad Internacional de Examen preliminar (IPEA)
- [ ] Traducción del examen preliminar internacional efectuado por la IPEA
- [ ] De ser el caso, copia del contrato de acceso
- [ ] De ser el caso, documento que acredite la licencia o autorización de uso de conocimientos tradicionales de las comunidades indígenas
- [ ] De ser el caso, certificado de depósito del material biológico
- [X] Arte final 12 x 12
- [ ] De ser el caso, información sobre otras solicitudes de patente o títulos obtenidos en el extranjero por el mismo titular o su causante, relacionadas parcial o totalmente con la invención de esta solicitud
- [ ] De ser el caso, modificaciones efectuadas a la solicitud internacional.
- [X] Otros: Extractos

(11) **FIGURA CARATERISTICA**



(I)

(12) Solicito la concesión de la patente,

NOMBRE: ALVARO CORREA ORDOÑEZ

FIRMA:

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

(72) Inventors; and

(75) Inventors/Applicants *(for US only)*: **GENTLES, Robert G.** [GB/US]; Bristol-Myers Squibb Company, 5 Research Parkway, Wallingford, Connecticut 06492 (US). **ZHENG, Xiaofan** [CN/US]; Bristol Myers Squibb Company, 5 Research Parkway, Wallingford, Connecticut 06492 (US). **DING, Min** [US/US]; Bristol Myers Squibb Company, 5 Research Parkway, Wallingford, Connecticut 06492 (US). **TU, Yong** [CN/US]; Bristol Myers Squibb Company, 5 Research Parkway, Wallingford, Connecticut 06492 (US). **HAN, Ying** [US/US]; Bristol Myers Squibb Company, 5 Research Parkway, Wallingford, Connecticut 06492 (US). **HEWAWASAM, Piyasena** [US/US]; Bristol Myers Squibb Company, 5 Research Parkway, Wallingford, Connecticut 06492 (US). **KADOW, John F.** [US/US]; Bristol Myers Squibb Company, 5 Research Parkway, Wallingford, Connecticut 06492 (US). **BENDER, John A.** [US/US]; Bristol Myers Squibb Company, 5 Research Parkway, Wallingford, Connecticut 06492 (US). **YEUNG, Kap-sun** [US/US]; Bristol Myers Squibb Company, 5 Research Parkway, Wallingford, Connecticut 06492 (US). **GRANT-YOUNG, Katharine A.** [US/US]; Bristol Myers Squibb Company, 5 Research Parkway, Wallingford, Connecticut 06492 (US). **HUDYMA, Thomas W.** [US/US]; 105R Black Walnut Drive, P.O. Box 245, Durham, Connecticut 06422 (US).

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

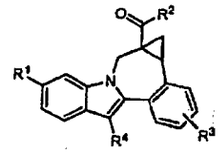
(81) Designated States *(unless otherwise indicated, for every kind of national protection available)*: AE, AG, AL, AM, AO, AT, AU, AZ, BA, BB, BG, BH, BR, BW, BY, BZ, CA, CH, CN, CO, CR, CU, CZ, DE, DK, DM, DO, DZ, EC, EE, EG, ES, FI, GB, GD, GE, GH, GM, GT, HN, HR, HU, ID, IL, IN, IS, JP, KE, KG, KM, KN, KP, KR, KZ, LA, LC, LK, LR, LS, LT, LU, LY, MA, MD, ME, MG, MK, MN, MW, MX, MY, MZ, NA, NG, NI, NO, NZ, OM, PG, PH, PL, PT, RO, RS, RU, SC, SD, SE, SG, SK, SL, SM, SV, SY, TJ, TM, TN, TR, TT, TZ, UA, UG, US, UZ, VC, VN, 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))*
— *as to the applicant's entitlement to claim the priority of the earlier application (Rule 4.17(iii))*

Published:
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(54) Title: COMPOUNDS FOR THE TREATMENT OF HEPATITIS C



(I)

(57) Abstract: The invention encompasses compounds of formula I, including pharmaceutically acceptable salts, as well as compositions and methods of using. these compounds. The compounds have activity against hepatitis C virus (HCV) and are useful in treating those infected with HCV.

WO 2008/112473 A1

COMPOUNDS FOR THE TREATMENT OF HEPATITIS C

CROSS REFERENCE TO RELATED APPLICATIONS

This application claims the benefit of U.S. provisional application serial numbers USSN 60/894887 filed March 14, 2007 and 60/989474 filed November 21, 2007.

BACKGROUND OF THE INVENTION

Hepatitis C virus (HCV) is a major human pathogen, infecting an estimated 170 million persons worldwide - roughly five times the number infected by human immunodeficiency virus type 1. A substantial fraction of these HCV infected individuals develop serious progressive liver disease, including cirrhosis and hepatocellular carcinoma (Lauer, G. M.; Walker, B. D. *N. Engl. J. Med.* **2001**, *345*, 41-52).

HCV is a positive-stranded RNA virus. Based on a comparison of the deduced amino acid sequence and the extensive similarity in the 5'-untranslated region, HCV has been classified as a separate genus in the Flaviviridae family. All members of the Flaviviridae family have enveloped virions that contain a positive stranded RNA genome encoding all known virus-specific proteins via translation of a single, uninterrupted, open reading frame.

Considerable heterogeneity is found within the nucleotide and encoded amino acid sequence throughout the HCV genome. At least six major genotypes have been characterized, and more than 50 subtypes have been described. The major genotypes of HCV differ in their distribution worldwide, and the clinical significance of the genetic heterogeneity of HCV remains elusive despite numerous studies of the possible effect of genotypes on pathogenesis and therapy.

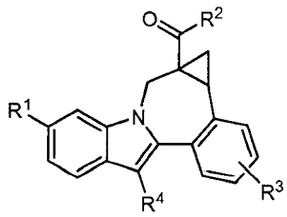
The single strand HCV RNA genome is approximately 9500 nucleotides in length and has a single open reading frame (ORF) encoding a single large polyprotein of about 3000 amino acids. In infected cells, this polyprotein is cleaved at multiple sites by cellular and viral proteases to produce the structural and non-structural (NS)

proteins. In the case of HCV, the generation of mature non-structural proteins (NS2, NS3, NS4A, NS4B, NS5A, and NS5B) is effected by two viral proteases. The first one is believed to be a metalloprotease and cleaves at the NS2-NS3 junction; the second one is a serine protease contained within the N-terminal region of NS3 (also referred to as NS3 protease) and mediates all the subsequent cleavages downstream of NS3, both in cis, at the NS3-NS4A cleavage site, and in trans, for the remaining NS4A-NS4B, NS4B-NS5A, NS5A-NS5B sites. The NS4A protein appears to serve multiple functions, acting as a cofactor for the NS3 protease and possibly assisting in the membrane localization of NS3 and other viral replicase components. The complex formation of the NS3 protein with NS4A seems necessary to the processing events, enhancing the proteolytic efficiency at all of the sites. The NS3 protein also exhibits nucleoside triphosphatase and RNA helicase activities. NS5B (also referred to as HCV polymerase) is a RNA-dependent RNA polymerase that is involved in the replication of HCV. The HCV NS5B protein is described in "Structural Analysis of the Hepatitis C Virus RNA Polymerase in Complex with Ribonucleotides (Bressanelli; S. et al., *Journal of Virology* **2002**, 3482-3492; and Defrancesco and Rice, *Clinics in Liver Disease* **2003**, *7*, 211-242.

Currently, the most effective HCV therapy employs a combination of alpha-interferon and ribavirin, leading to sustained efficacy in 40% of patients (Poynard, T. et al. *Lancet* **1998**, *352*, 1426-1432). Recent clinical results demonstrate that pegylated alpha-interferon is superior to unmodified alpha-interferon as monotherapy (Zeuzem, S. et al. *N. Engl. J. Med.* **2000**, *343*, 1666-1672). However, even with experimental therapeutic regimens involving combinations of pegylated alpha-interferon and ribavirin, a substantial fraction of patients do not have a sustained reduction in viral load. Thus, there is a clear and important need to develop effective therapeutics for treatment of HCV infection.

DESCRIPTION OF THE INVENTION

One aspect of the invention is a compound of formula I

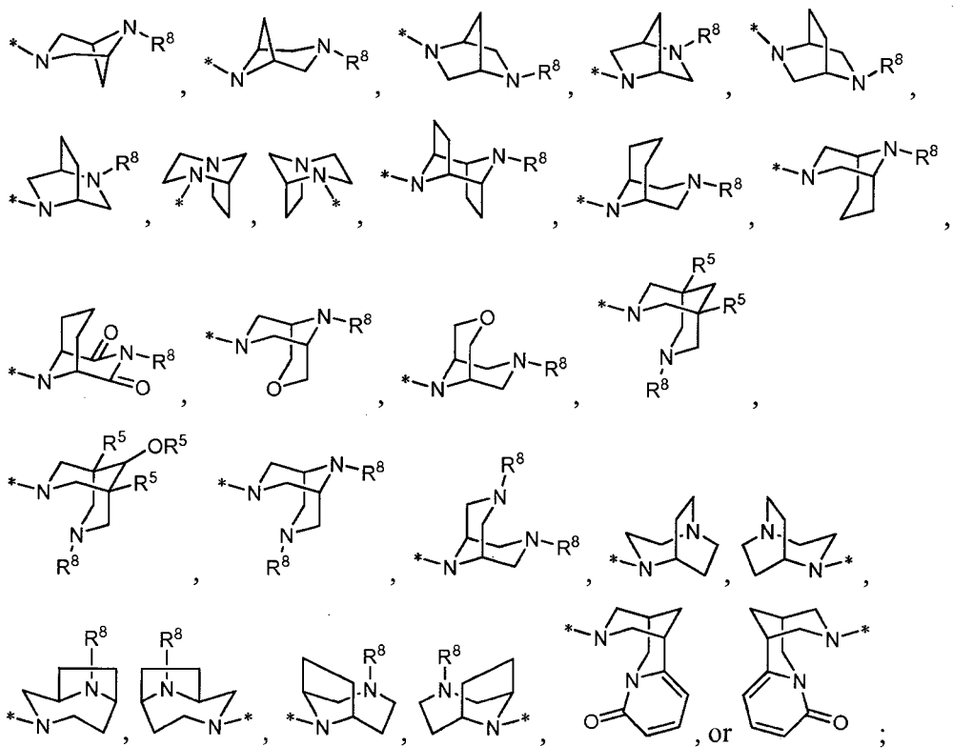


I

where:

R^1 is CO_2R^5 or $CONR^6R^7$;

R^2 is



R^3 is hydrogen, halo, alkyl, alkenyl, hydroxy, benzyloxy, or alkoxy;

R^4 is cycloalkyl;

R^5 is hydrogen or alkyl;

R^6 is hydrogen, alkyl, alkylSO_2, alkenylSO_2, , cycloalkylSO_2, (cycloalkyl)alkylSO_2, haloalkylSO_2, (R^9)(R^{10})NSO_2, or (R^{11})SO_2;

R^7 is hydrogen or alkyl;

R^8 is hydrogen, alkyl, cycloalkyl, (cycloalkyl)alkyl, hydroxyalkyl, alkoxyalkyl, alkylcarbonyl, cycloalkylcarbonyl, haloalkylcarbonyl, alkoxycarbonyl, alkylSO_2, cycloalkylSO_2, haloalkylSO_2, aminocarbonyl, (alkylamino)carbonyl, (dialkylamino)carbonyl, benzyl, benzyloxycarbonyl, or pyridinyl;

R^9 is hydrogen or alkyl;

R^{10} is hydrogen or alkyl;

R^{11} is azetidinyl, pyrrolidinyl, piperidinyl, N-(R^{12})piperazinyl, morpholinyl, thiomorpholinyl, homopiperidinyl, homomorpholinyl, tetrahydrofuranyl, tetrahydropyranyl, (tetrahydrofuranyl)alkyl, or (tetrahydropyranyl)alkyl; and

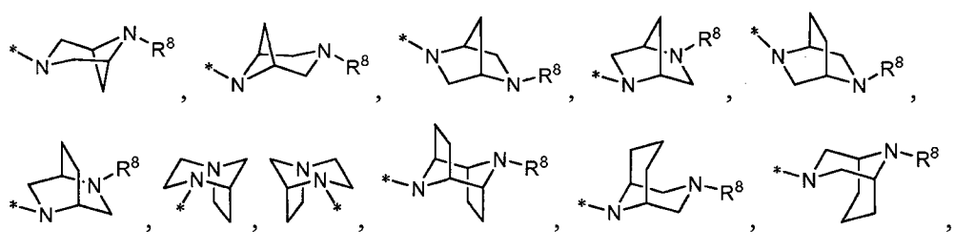
R^{12} is hydrogen or alkyl;

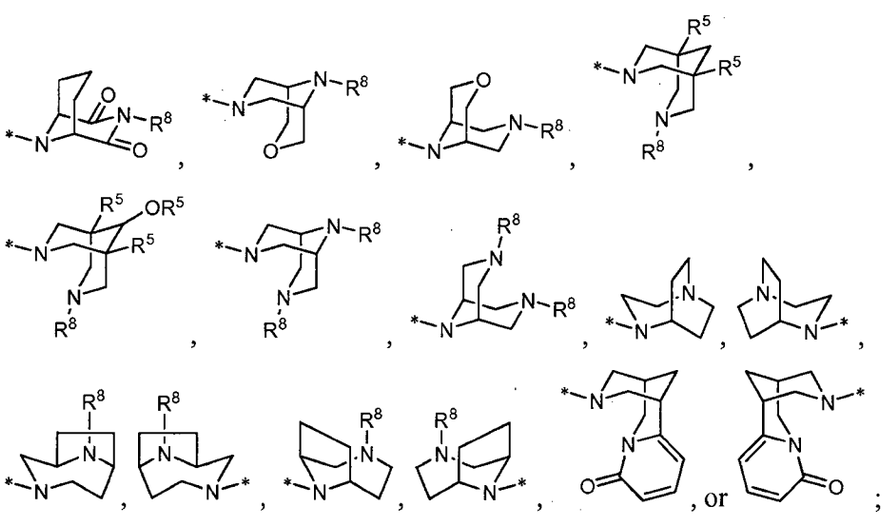
or a pharmaceutically acceptable salt thereof.

Another aspect of the invention is a compound of formula I where

R^1 is CO_2R^5 or $CONR^6R^7$;

R^2 is





R^3 is hydrogen, halo, alkyl, alkenyl, hydroxy, benzyloxy, or alkoxy;

R^4 is cycloalkyl;

R^5 is hydrogen or alkyl;

R^6 is hydrogen, alkyl, alkylSO_2, alkenylSO_2, , cycloalkylSO_2, (cycloalkyl)alkylSO_2, haloalkylSO_2, (R^9)(R^{10})NSO_2, or (R^{11})SO_2;

R^7 is hydrogen or alkyl;

R^8 is hydrogen, alkyl, cycloalkyl, (cycloalkyl)alkyl, alkylcarbonyl, cycloalkylcarbonyl, haloalkylcarbonyl, alkoxycarbonyl, alkylSO_2, cycloalkylSO_2, haloalkylSO_2, aminocarbonyl, (alkylamino)carbonyl, (dialkylamino)carbonyl, benzyl, benzyloxycarbonyl, or pyridinyl;

R^9 is hydrogen or alkyl;

R^{10} is hydrogen or alkyl;

R^{11} is azetidinyl, pyrrolidinyl, piperidinyl, N-(R^{12})piperazinyl, morpholinyl, thiomorpholinyl, homopiperidinyl, homomorpholinyl, tetrahydrofuranyl, tetrahydropyranyl, (tetrahydrofuranyl)alkyl, or (tetrahydropyranyl)alkyl; and

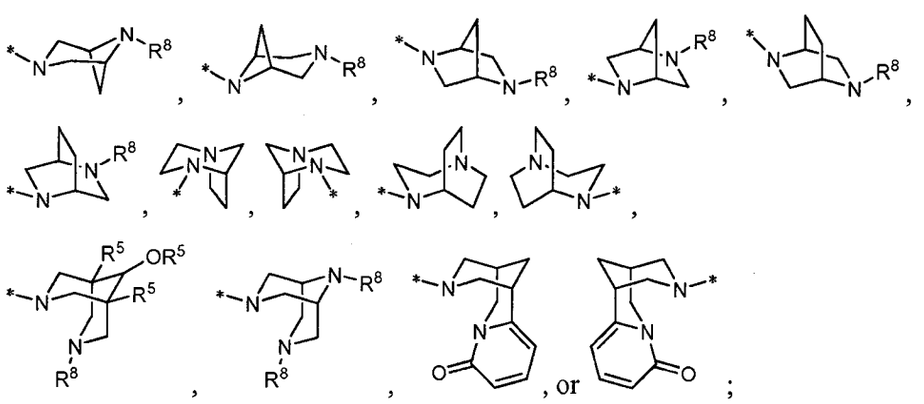
R^{12} is hydrogen or alkyl;

or a pharmaceutically acceptable salt thereof.

Another aspect of the invention is a compound of formula I where

R^1 is CO_2R^5 or $CONR^6R^7$;

R^2 is



R^3 is hydrogen, halo, alkyl, alkenyl, hydroxy, benzyloxy, or alkoxy;

R^4 is cycloalkyl;

R^5 is hydrogen or alkyl;

R^6 is hydrogen, alkyl, alkylSO_2, cycloalkylSO_2, haloalkylSO_2, (R^9)(R^{10})NSO_2, or (R^{11})SO_2;

R^7 is hydrogen or alkyl;

R^8 is hydrogen, alkyl, cycloalkyl, (cycloalkyl)alkyl, alkylcarbonyl, cycloalkylcarbonyl, haloalkylcarbonyl, alkoxycarbonyl, alkylSO_2, cycloalkylSO_2, haloalkylSO_2, aminocarbonyl, (alkylamino)carbonyl, (dialkylamino)carbonyl, benzyl, benzyloxycarbonyl, or pyridinyl;

R^9 is hydrogen or alkyl;

R^{10} is hydrogen or alkyl;

R^{11} is azetidinyl, pyrrolidinyl, piperidinyl, N-(R^{12})piperazinyl, morpholinyl, thiomorpholinyl, homopiperidinyl, or homomorpholinyl; and

R^{12} is hydrogen or alkyl.

Another aspect of the invention is a compound of formula I where R^1 is $CONR^6R^7$; R^6 is alkylSO_2, cycloalkylSO_2, haloalkylSO_2, $(R^9)_2NSO_2$, or $(R^{10})SO_2$; and R^7 is hydrogen.

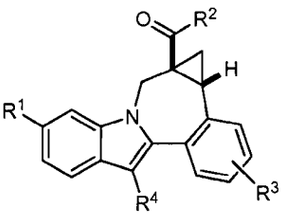
Another aspect of the invention is a compound of formula I where R^3 is hydrogen.

Another aspect of the invention is a compound of formula I where R^3 is methoxy.

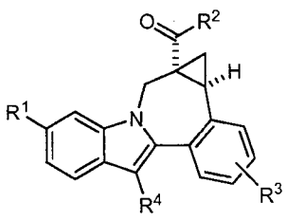
Another aspect of the invention is a compound of formula I where R^4 is cyclohexyl.

Another aspect of the invention is a compound of formula I where R^6 is $(R^9)(R^{10})NSO_2$ or $(R^{11})SO_2$.

Another aspect of the invention is a compound of formula I according to the following stereochemistry.



Another aspect of the invention is a compound of formula I according to the following stereochemistry.

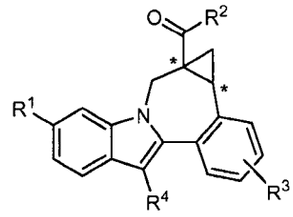


Any scope of any variable, including R^1, R^2, R^3, R^4, R^5, R^6, R^7, R^8, R^9, R^{10}, R^{11}, or R^{12}, can be used independently with the scope of any other instance of a variable.

Unless specified otherwise, these terms have the following meanings. "Alkyl" means a straight or branched alkyl group composed of 1 to 6 carbons. "Alkenyl" means a straight or branched alkyl group composed of 2 to 6 carbons with at least one double bond. "Cycloalkyl" means a monocyclic ring system composed of 3 to 7 carbons. "Hydroxyalkyl," "alkoxy" and other terms with a substituted alkyl moiety include straight and branched isomers composed of 1 to 6 carbon atoms for the alkyl moiety. "Haloalkyl" and "haloalkoxy" include all halogenated isomers from monohalo substituted alkyl to perhalo substituted alkyl. "Aryl" includes carbocyclic and heterocyclic aromatic substituents. Parenthetic and multiparenthetic terms are intended to clarify bonding relationships to those skilled in the art. For example, a term such as ((R)alkyl) means an alkyl substituent further substituted with the substituent R.

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.

Some of the compounds of the invention possess asymmetric carbon atoms (see, for example, the compound below). The invention includes all stereoisomeric forms, including enantiomers and diastereomers as well as mixtures of stereoisomers such as racemates. Some stereoisomers can be made using methods known in the art. Stereoisomeric mixtures of the compounds and related intermediates can be separated into individual isomers according to methods commonly known in the art.



Synthetic Methods

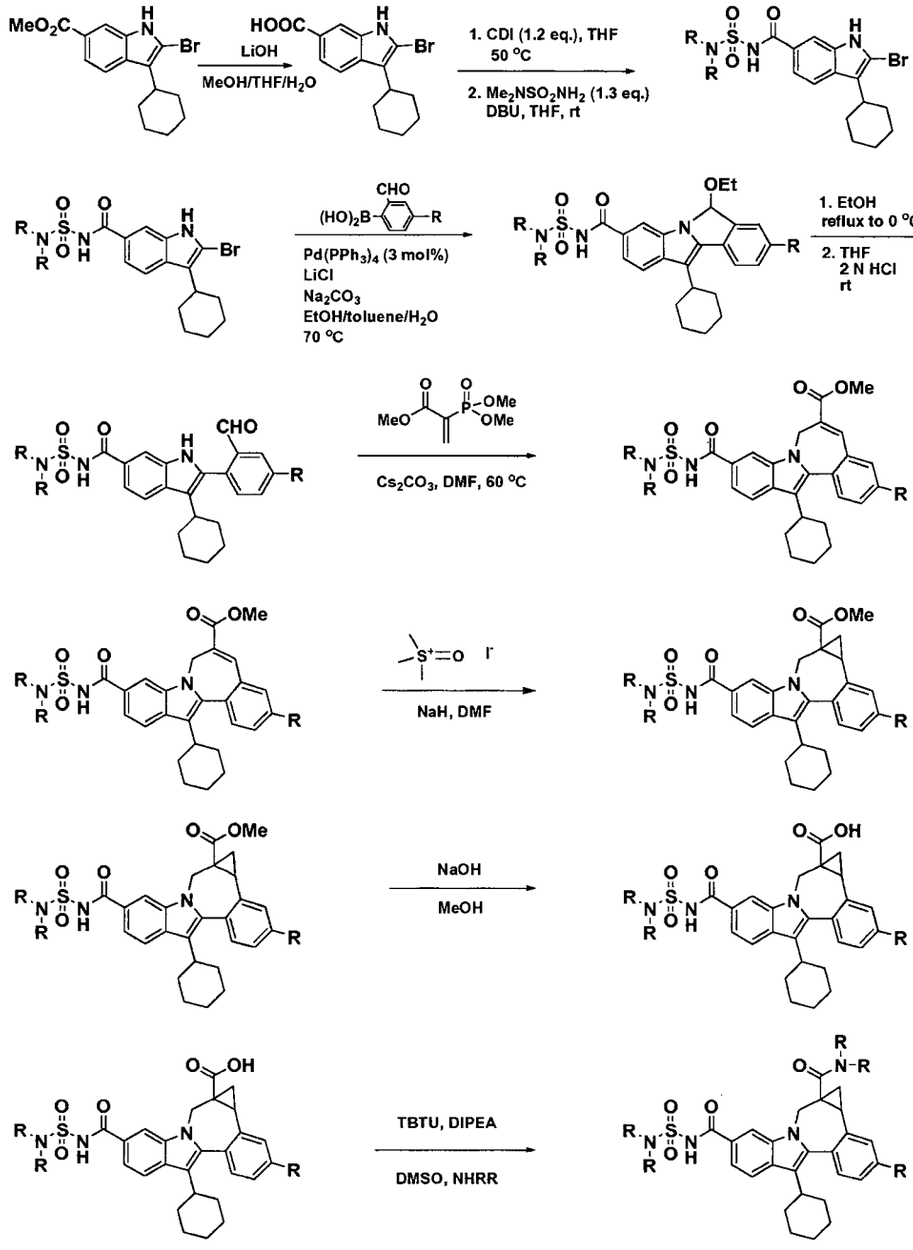
The compounds may be made by methods known in the art including those described below. Some reagents and intermediates are known in the art. Other reagents and intermediates can be made by methods known in the art using readily available materials. The variables (e.g. numbered "R" substituents) used to describe the synthesis of the compounds are intended only to illustrate how to make and are

not to be confused with variables used in the claims or in other sections of the specification. Abbreviations used within the schemes generally follow conventions used in the art.

Methyl 2-bromo-3-cyclohexyl-1H-indole-6-carboxylate can be hydrolyzed to 2-bromo-3-cyclohexyl-1H-indole-6-carboxylic acid (See Scheme 1). This compound can be condensed with a variety of sulfonyl ureas, using for example, 1,1'-carbonyldiimidazole in combination with 1,8-diazabicyclo[5.4.0]undec-7-ene in anhydrous THF. The resultant acyl sulfamides can be subjected to known coupling reactions with a diversity of 2-formyl boronic acids or esters, using for example, Suzuki coupling conditions, to provide cyclic hemiaminal intermediates of the type depicted. These compounds can be converted to indolobenzazepines derivatives by treatment with methyl 2-(dimethoxyphosphoryl)acrylate under the influence of cesium carbonate in DMF via consecutive Michael and Horner Emmons reactions.

Related fused cyclopropyl ester derivatives can be generated by methods known in the art, including treatment of the indolobenzazepine esters with trimethyl sulfoxonium iodide under strongly basic conditions in DMSO. The residual aliphatic ester moiety in the resultant fused cyclopropanes can be hydrolyzed and the product acids can be condensed with a variety of alkyl-bridged diamines. For example, O-(1H-benzotriazol-1-yl)-N,N, N',N'-tetramethyluronium tetrafluoroborate and diisopropyl ethyl amine in DMSO can give alkyl bridged diamine carboxamides.

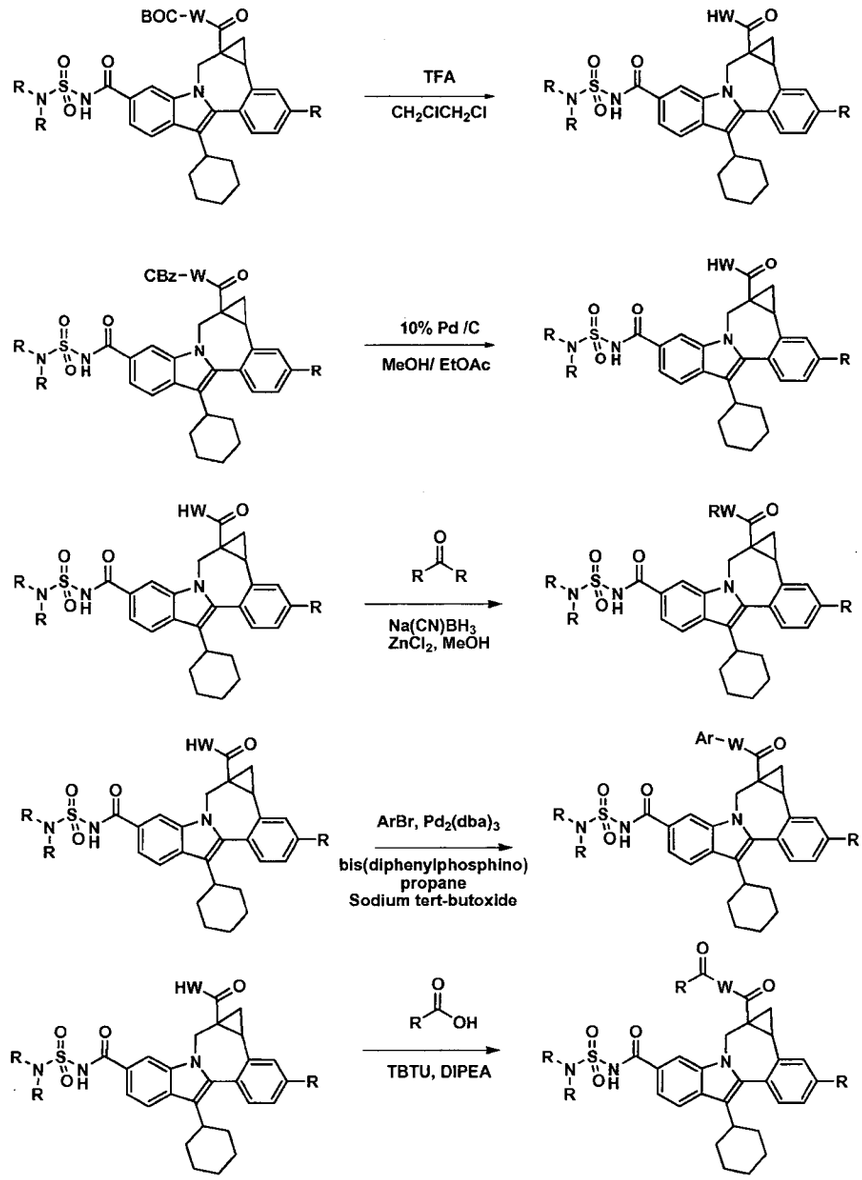
Scheme 1.



N-protected diamines, for example where W is a protected Diamine, can also be coupled to the intermediate indolobenzazepine acids and the resultant diamine carboxamides can be deprotected using methods known in the art and derivatized

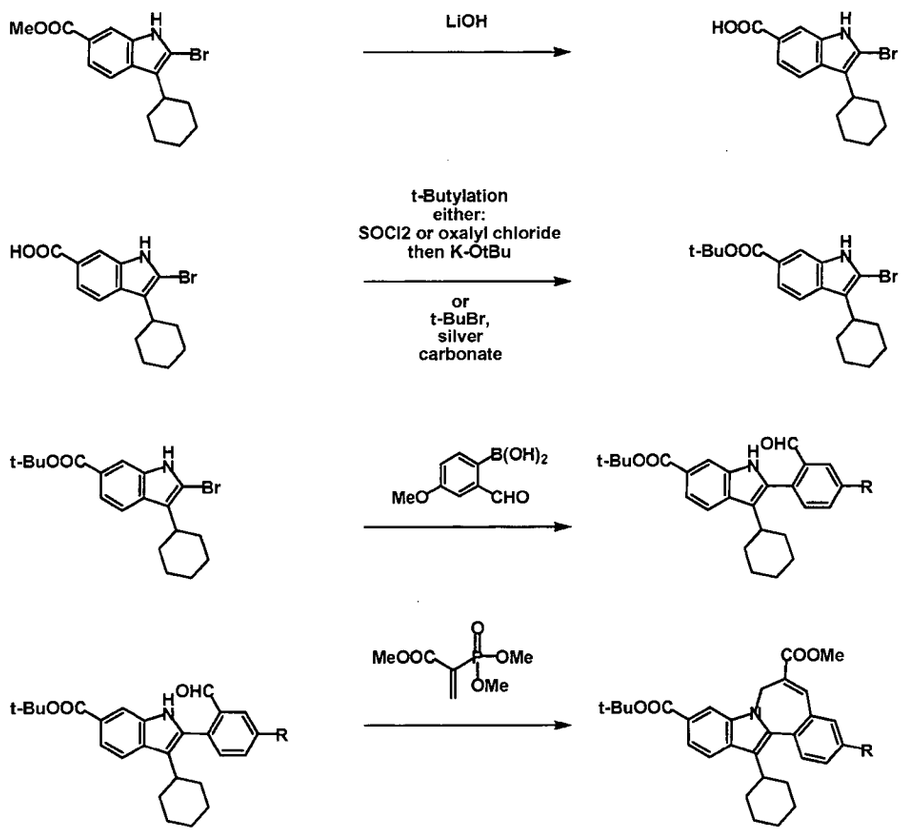
using a variety of synthetic protocols, some illustrative examples of which are shown below (See Scheme 2).

Scheme 2.



An intermediate useful for the synthesis of some compounds of the invention involves the preparation of the tert-butyl ester indolobenzazepine shown in Scheme 3.

Scheme 3.

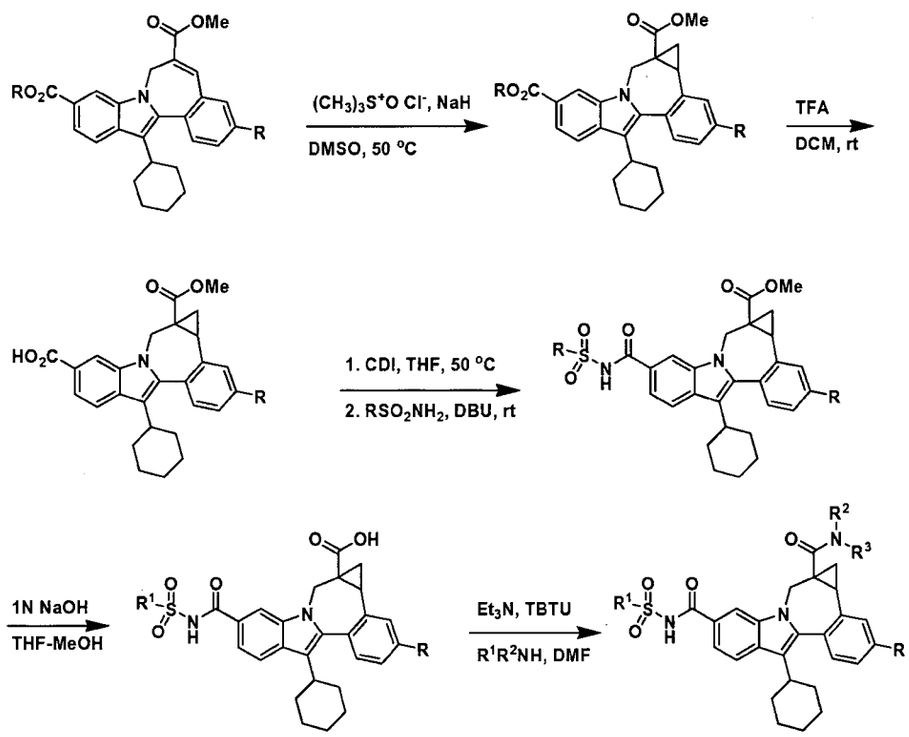


This methodology involves base catalyzed hydrolysis of the indole methyl ester shown, followed by its reaction with either thionyl chloride and potassium tertiary butoxide, or alkylation with silver carbonate and tertiary butyl bromides. The resultant compound can be transformed using chemistry analogous to that outlined previously to provide the mixed ester indolobenzazepines shown above.

These intermediates are useful in an alternative procedure that can be employed for the preparation of acylsulfamide and acylsulfonamide alkyl-bridged diamines, as shown in Scheme 4. Cyclopropanation of an intermediate t-butyl ester indolobenzazepine and subsequent cleavage of the t-butyl ester group can generate the acid which can be coupled to a diversity of sulfonamides and sulfonylureas. Subsequent hydrolysis affords the related aliphatic acid, which can be coupled with a diversity of alkyl-bridged diamines. For example, O-(1H-benzotriazol-1-yl)-N,N,

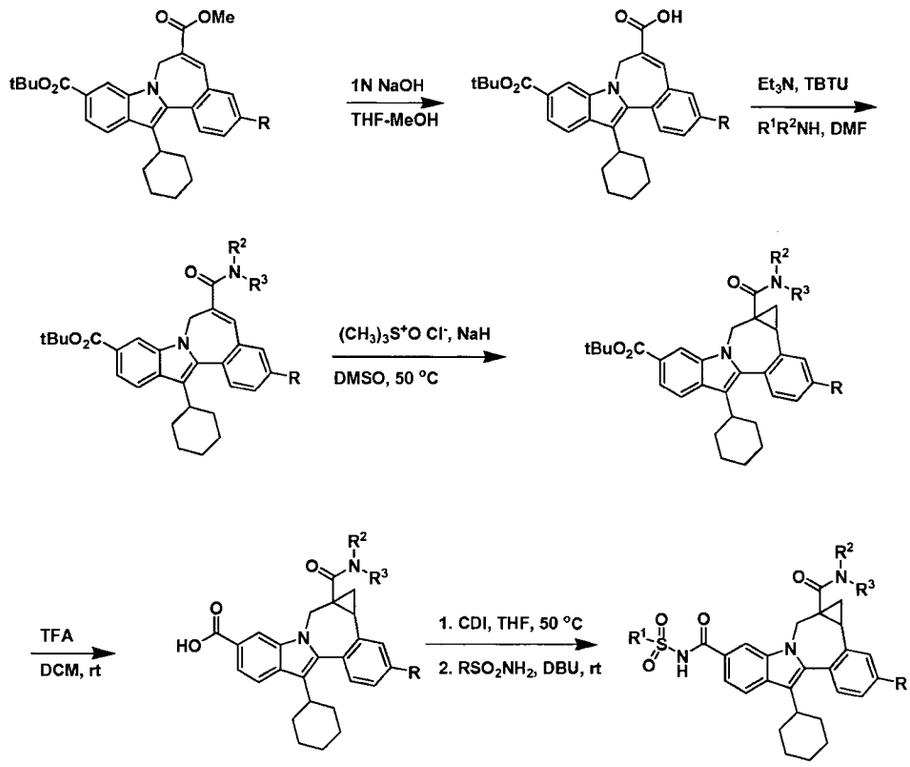
N',N'-tetramethyluronium tetrafluoroborate and diisopropyl ethyl amine in DMSO can give the alkyl bridged diamine carboxamides.

Scheme 4.

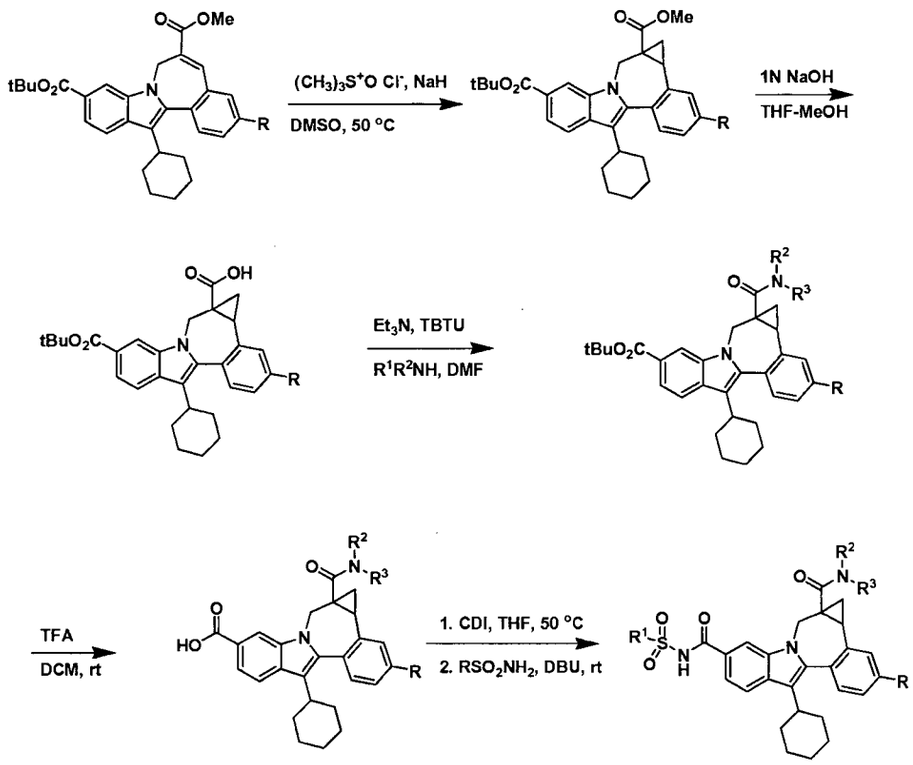


The reactions depicted in Scheme 4 can be carried out in alternative order to provide the same products. Schemes 4a and 4b show two alternatives. Additionally, a diamine with two secondary amines could be employed at any of the depicted points in the schemes where coupling to the acid on the seven membered ring is depicted and the free NH functionalized prior to completing the remaining steps in the scheme.

Scheme 4a.

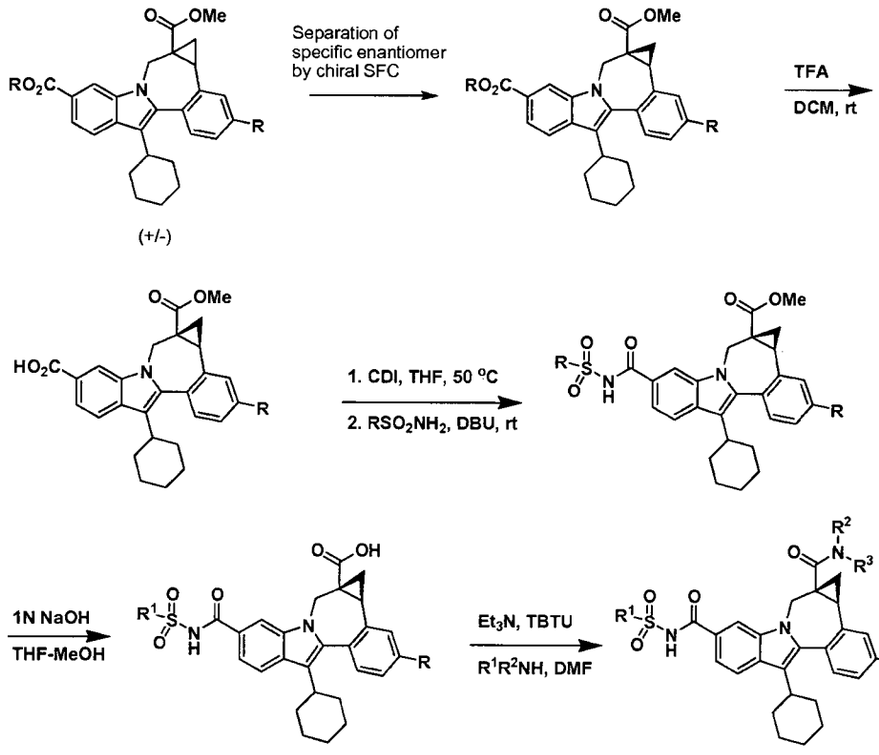

tBuO2C
OMe
1N NaOH
THF-MeOH
OH
Et3N, TBTU
R1R2NH, DMF
(CH3)3S+O Cl-, NaH
DMSO, 50 °C
TFA
DCM, rt
HO
1. CDI, THF, 50 °C
2. RSO2NH2, DBU, rt
R1
R2
R3
R

Scheme 4b.



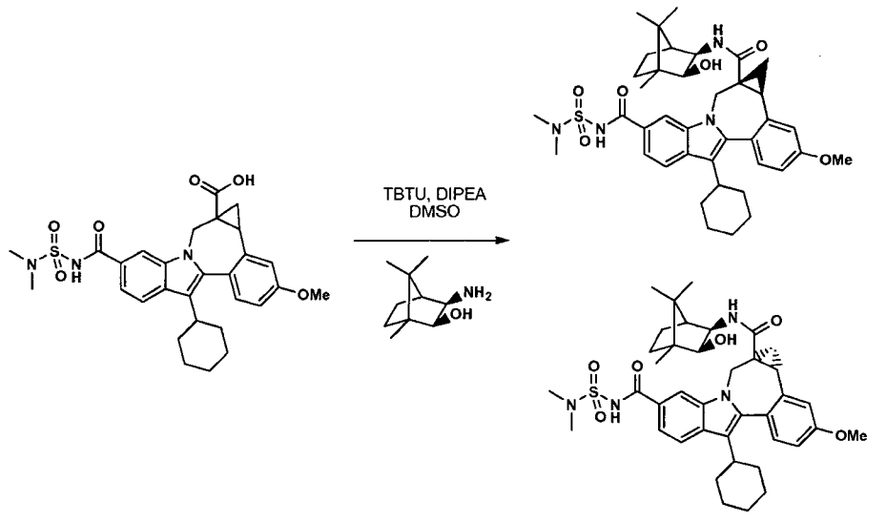
Some examples exist as stereoisomeric mixtures. The invention encompasses all stereoisomers of the compounds. Methods of fractionating stereoisomeric mixtures are well known in the art, and include but are not limited to; preparative chiral supercritical fluid chromatography (SFC) and chiral high performance liquid chromatography (HPLC). An example using this approach is shown in scheme 5.

Scheme 5.



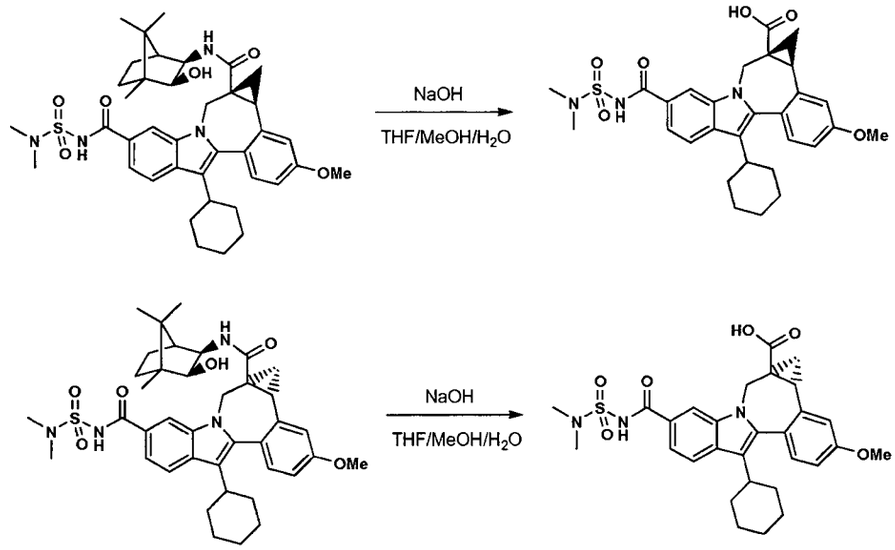
An additional method to achieve such separations involves the preparation of mixtures of diastereomers which can be separated using a variety of methods known in the art. One example of this approach is shown below (Scheme 6).

Scheme 6.



Some diastereomeric amides can be separated using reverse phase HPLC. After hydroysis, the resultant optically active acids can be coupled with bridged diamines derivatives (Scheme 7). For example, O-(1H-benzotriazol-1-yl)-N,N, N',N'-tetramethyluronium tetrafluoroborate and diisopropyl ethyl amine in DMSO can be used to give the alkyl bridged carboxamides. Other standard acid amine coupling methods can also be used to give optically active carboxamides.

Scheme 7.



Biological Methods

The compounds demonstrated activity against HCV NS5B as determined in the following HCV RdRp assays.

HCV NS5B RdRp cloning, expression, and purification. The cDNA encoding the NS5B protein of HCV, genotype 1b, was cloned into the pET21a expression vector. The protein was expressed with an 18 amino acid C-terminal truncation to enhance the solubility. The E. coli competent cell line BL21(DE3) was used for expression of the protein. Cultures were grown at 37 °C for ~ 4 hours until the cultures reached an optical density of 2.0 at 600 nm. The cultures were cooled to 20 °C and induced with 1 mM IPTG. Fresh ampicillin was added to a final concentration of 50 μg/ml and the cells were grown overnight at 20 °C.

Cell pellets (3L) were lysed for purification to yield 15-24 mgs of purified NS5B. The lysis buffer consisted of 20 mM Tris-HCl, pH 7.4, 500 mM NaCl, 0.5% triton X-100, 1 mM DTT, 1mM EDTA, 20% glycerol, 0.5 mg/ml lysozyme, 10 mM MgCl2, 15 ug/ml deoxyribonuclease I, and Complete TM protease inhibitor tablets (Roche). After addition of the lysis buffer, frozen cell pellets were resuspended using a tissue homogenizer. To reduce the viscosity of the sample, aliquots of the lysate

were sonicated on ice using a microtip attached to a Branson sonicator. The sonicated lysate was centrifuged at 100,000 x g for 1hr at 4 °C and filtered through a 0.2 μm filter unit (Corning).

The protein was purified using two sequential chromatography steps: Heparin sepharose CL-6B and polyU sepharose 4B (Pharmacia). The chromatography buffers were identical to the lysis buffer but contained no lysozyme, deoxyribonuclease I, MgCl2 or protease inhibitor and the NaCl concentration of the buffer was adjusted according to the requirements for charging the protein onto the column. Each column was eluted with a NaCl gradient which varied in length from 5-50 column volumes depending on the column type. After the final chromatography step, the resulting purity of the enzyme is >90% based on SDS-PAGE analysis. The enzyme was aliquoted and stored at –80 °C.

Standard HCV NS5B RdRp enzyme assay. HCV RdRp genotype 1b assays were run in a final volume of 60 μl in 96 well plates (Corning 3600). The assay buffer is composed of 20 mM Hepes, pH 7.5, 2.5 mM KCl, 2.5 mM MgCl2, 1 mM DTT, 1.6 U RNAse inhibitor (Promega N2515), 0.01 mg/ml BSA (Sigma B6917), and 2 % glycerol. All compounds were serially diluted (3-fold) in DMSO and diluted further in water such that the final concentration of DMSO in the assay was 2%. HCV RdRp genotype 1b enzyme was used at a final concentration of 28 nM. A polyA template was used at 6 nM, and a biotinylated oligo-dT12 primer was used at 180 nM final concentration. Template was obtained commercially (Amersham 27-4110). Biotinylated primer was prepared by Sigma Genosys. 3H-UTP was used at 0.6 μCi (0.29 μM total UTP). Reactions were initiated by the addition of enzyme, incubated at 30 °C for 60 min, and stopped by adding 25 μl of 50 mM EDTA containing SPA beads (4 μg/μl, Amersham RPNQ 0007). Plates were read on a Packard Top Count NXT after >1hr incubation at room temperature.

Modified HCV NS5B RdRp enzyme assay. A modified enzyme assay was performed essentially as described for the standard enzyme assay except for the following: The biotinylated oligo dT12 primer was precaptured on streptavidin-coated SPA beads by mixing primer and beads in assay buffer and incubating at room

temperature for one hour. Unbound primer was removed after centrifugation. The primer-bound beads were resuspended in 20 mM Hepes buffer, pH 7.5 and used in the assay at final concentrations of 20 nM primer and 0.67 μg/μl beads. Order of addition in the assay: enzyme (1.75 nM) was added to diluted compound followed by the addition of a mixture of template (0.36 nM), 3H-UTP (0.6 μCi, 0.29 μM), and primer-bound beads, to initiate the reaction; concentrations given are final. Reactions were allowed to proceed for 4 hours at 30° C.

IC_{50} values for compounds were determined using seven different [I]. IC_{50} values were calculated from the inhibition using the formula y = A+((B-A)/(1+((C/x)^D))).

FRET Assay Preparation. The HCV FRET screening assay was performed in 96-well cell culture plates. The FRET peptide (Anaspec, Inc.) (Taliani et al., *Anal. Biochem.* **1996**, *240*, 60-67) contains a fluorescence donor, EDANS, near one end of the peptide and an acceptor, DABCYL, near the other end. The fluorescence of the peptide is quenched by intermolecular resonance energy transfer (RET) between the donor and the acceptor, but as the NS3 protease cleaves the peptide the products are released from RET quenching and the fluorescence of the donor becomes apparent. The assay reagent was made as follows: 5X cell Luciferase cell culture lysis reagent from Promega (#E153A) diluted to 1X with dH_2O, NaCl added to 150 mM final, the FRET peptide diluted to 20 μM final from a 2 mM stock.

To prepare plates, HCV replicon cells, with or without a Renilla luciferase reporter gene, were trypsinized and plated in a 96-well plate with titrated test compounds added in columns 3 through 12; columns 1 and 2 contained a control compound (HCV control inhibitor), and the bottom row contained cells with DMSO only. The plates were then placed in a CO_2 incubator at 37 °C.

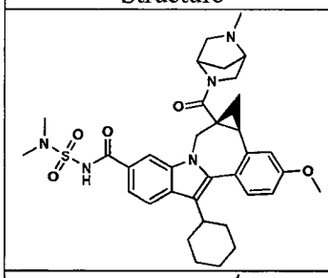
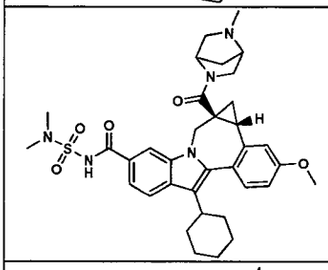
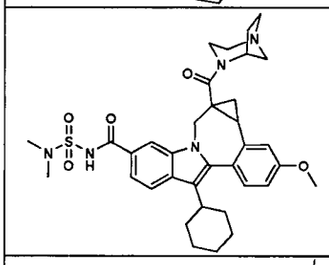
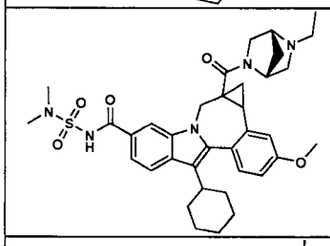
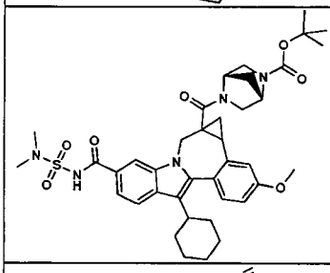
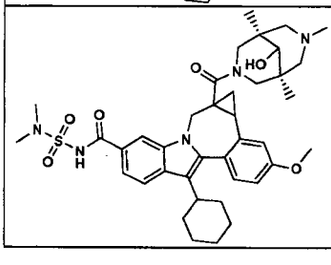
Assays. Subsequent to addition of the test compounds described above (FRET Assay Preparation), at various times the plate was removed and Alamar blue solution (Trek Diagnostics, #00-100) was added to measure cellular toxicity. After reading in a Cytoflour 4000 instrument (PE Biosystems), plates were rinsed with PBS

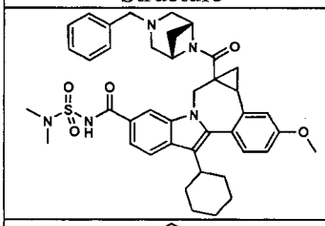
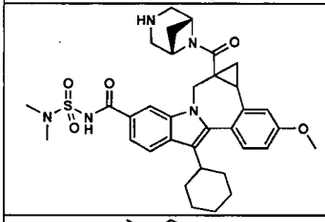
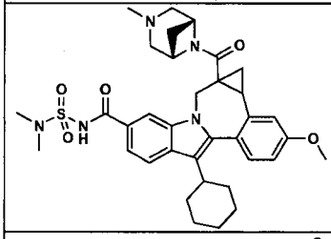
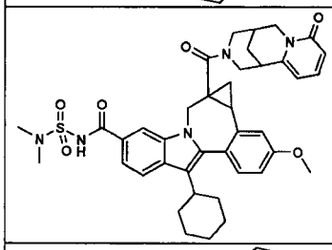
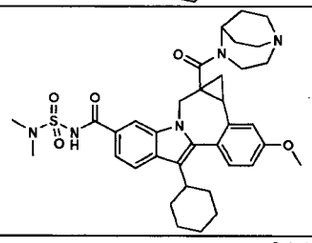
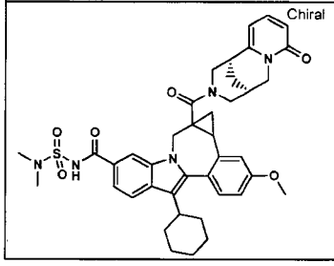
and then used for FRET assay by the addition of 30 ul of the FRET peptide assay reagent described above (FRET Assay Preparation) per well. The plate was then placed into the Cytoflour 4000 instrument which had been set to 340 excite/490 emission, automatic mode for up to 20 cycles and the plate read in a kinetic mode. Typically, the signal to noise using an endpoint analysis after the reads was at least three-fold. Alternatively, after Alamar blue reading, plates were rinsed with PBS, then used for luciferase assay using the Promega Dual-Glo Luciferase Assay System or the Promega EnduRen Live Cell Substrate assay.

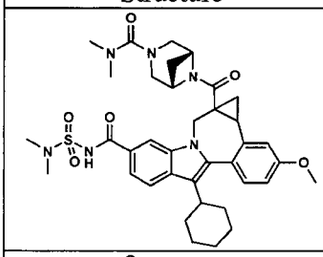
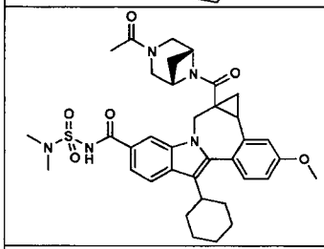
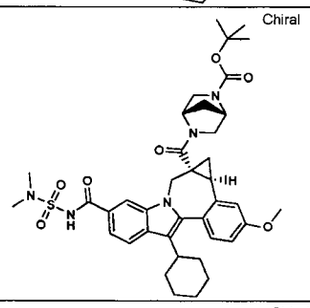
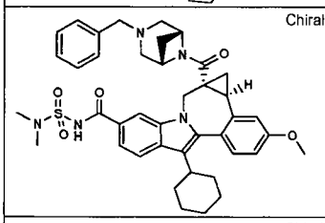
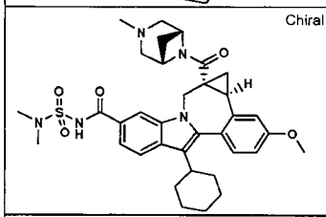
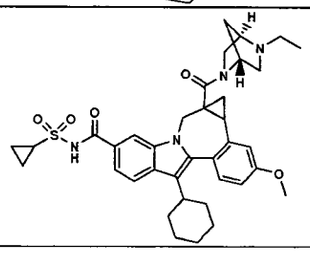
Compound analysis was performed by quantification of the relative HCV replicon inhibition and the relative cytotoxicity values. To calculate cytoxicity values, the average Alamar Blue fluorescence signals from the control wells were set as 100% non-toxic. The individual signals in each of the compound test wells were then divided by the average control signal and multiplied by 100% to determine percent cytotoxicity. To calculate the HCV replicon inhibition values, an average background value was obtained from the two wells containing the highest amount of HCV control inhibitor at the end of the assay period. These numbers were similar to those obtained from naïve Huh-7 cells. The background numbers were then subtracted from the average signal obtained from the control wells and this number was used as 100% activity. The individual signals in each of the compound test wells were then divided by the averaged control values after background subtraction and multiplied by 100% to determine percent activity. EC_{50} values were calculated as the concentration which caused a 50% reduction in FRET or luciferase activity. The two numbers generated for the compound plate, percent cytoxicity and percent activity, were used to determine compounds of interest for further analysis.

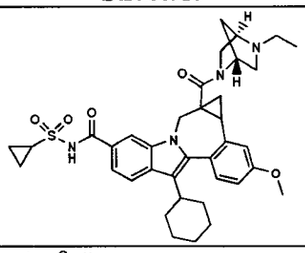
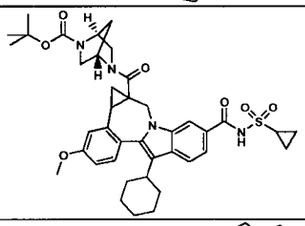
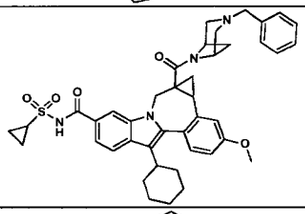
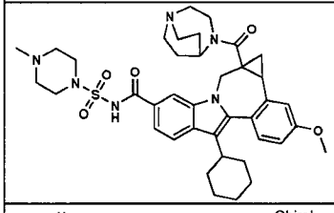
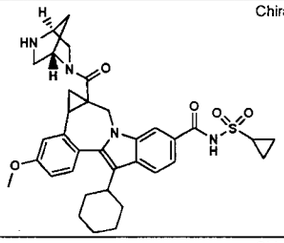
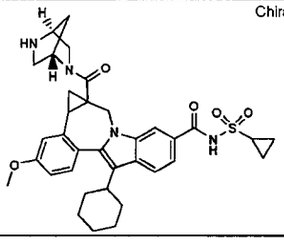
Representative data for compounds are reported in Table 1.

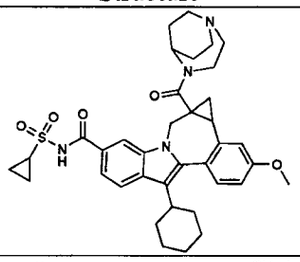
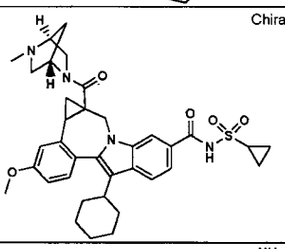
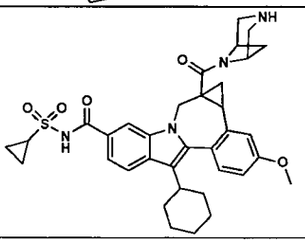
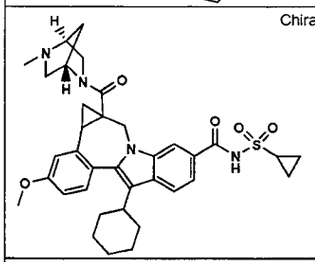
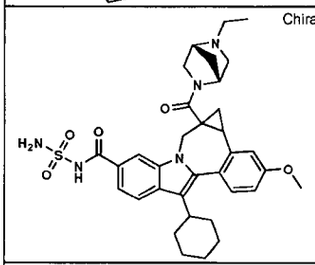
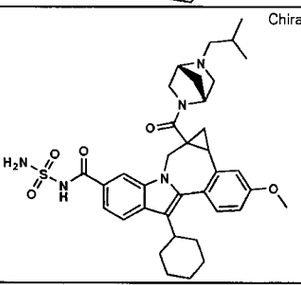
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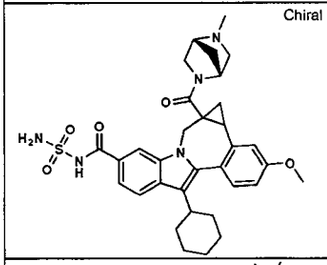
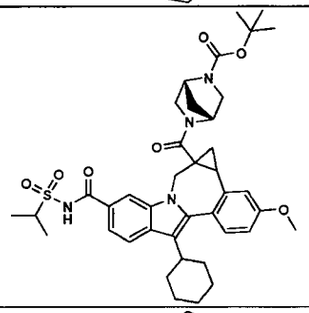
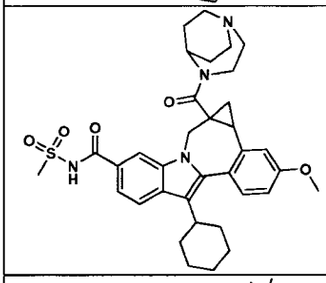
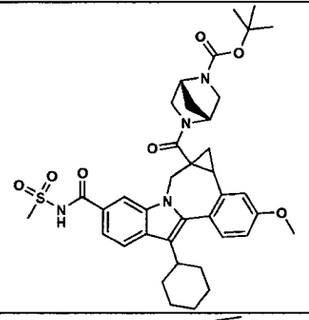
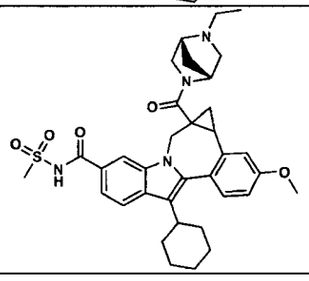
Structure	IC_{50}	EC_{50}
	C	B
	B	B
	B	B
	B	B
	B	B
	B	B

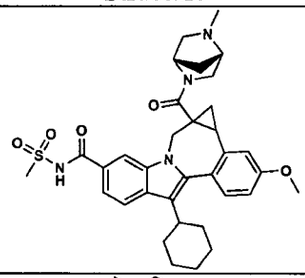
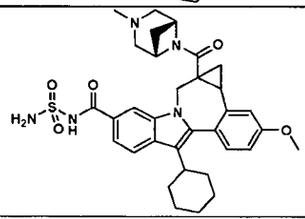
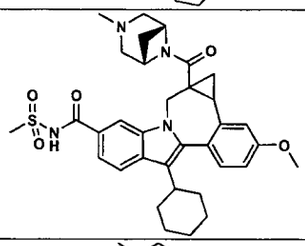
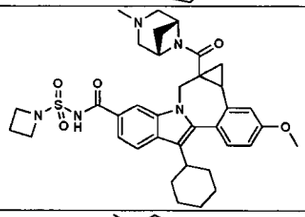
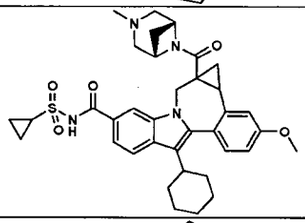
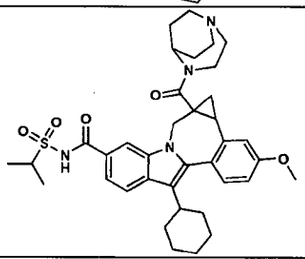
Structure	IC_{50}	EC_{50}
	B	B
	B	B
	B	B
	B	B
	B	B
 Chiral	E	B

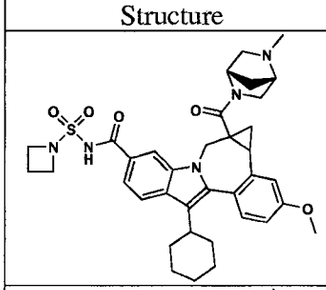
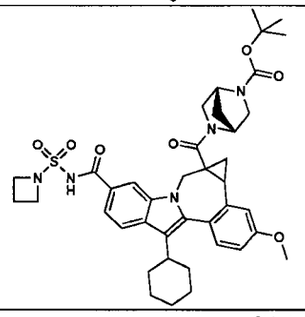
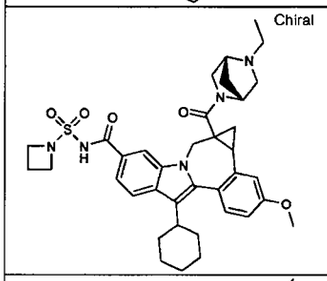
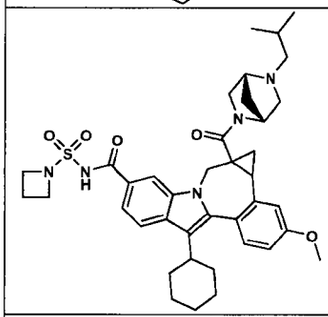
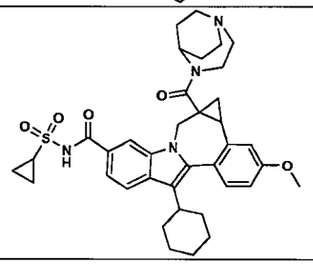
Structure	IC_{50}	EC_{50}
	B	B
	B	B
 Chiral	B	B
 Chiral	B	B
 Chiral	B	B
	C	B

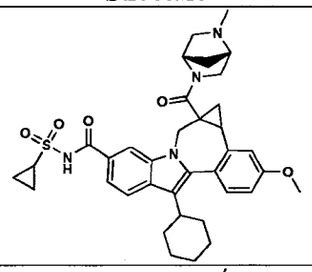
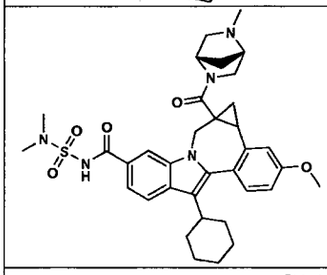
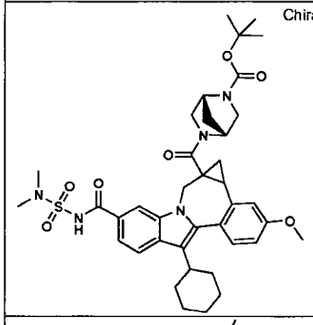
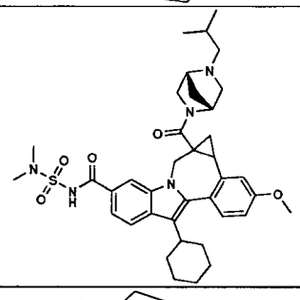
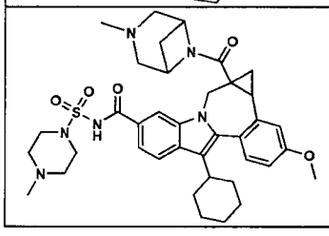
Structure	IC_{50}	EC_{50}
	B	B
	B	B
	B	B
	B	B
Chiral 		
Chiral 	B	

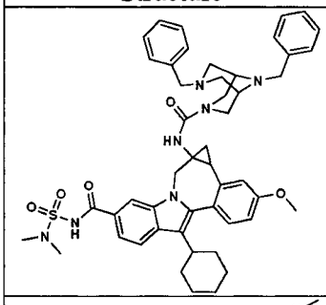
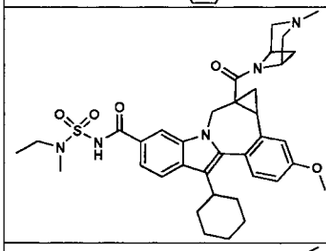
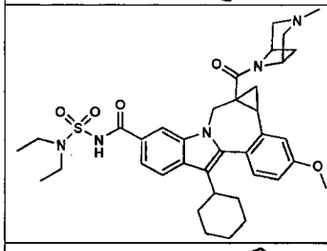
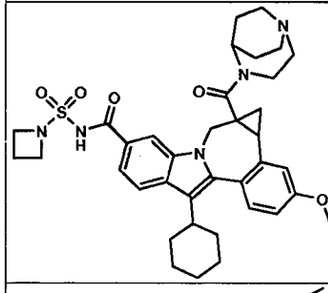
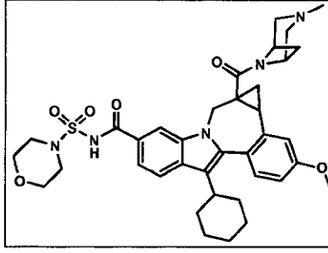
Structure	IC_{50}	EC_{50}
	B	B
Chiral 	B	A
	B	B
Chiral 	B	B
Chiral 	B	B
Chiral 	B	B

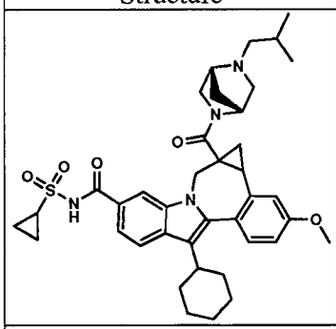
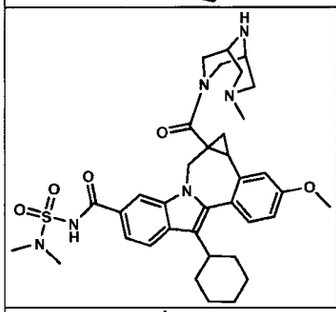
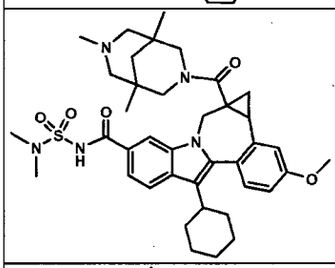
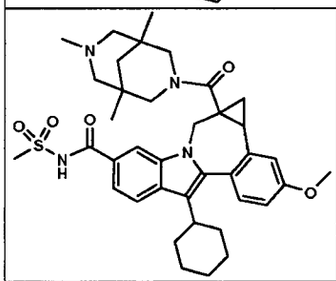
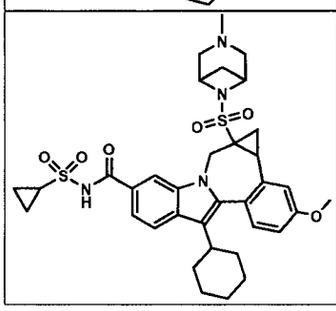
Structure	IC_{50}	EC_{50}
 Chiral	B	B
	B	B
	B	B
	B	B
	B	B

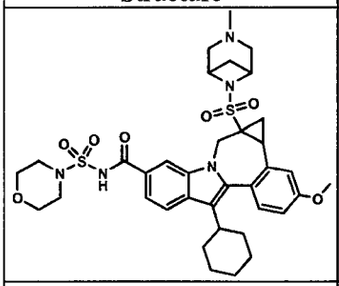
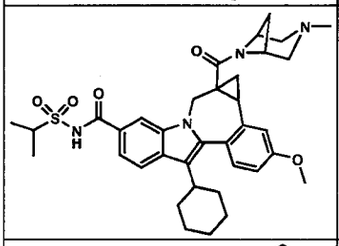
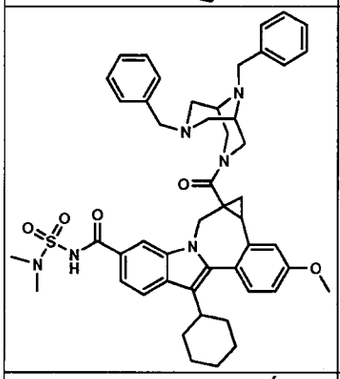
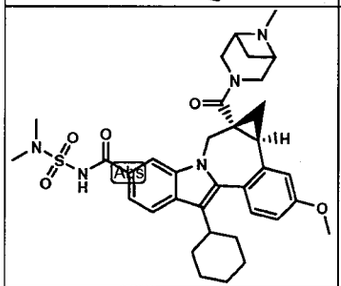
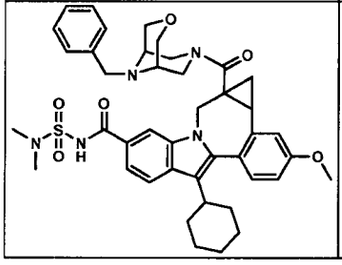
Structure	IC_{50}	EC_{50}
	B	B
	B	B
	B	B
	B	B
	B	B
	B	B

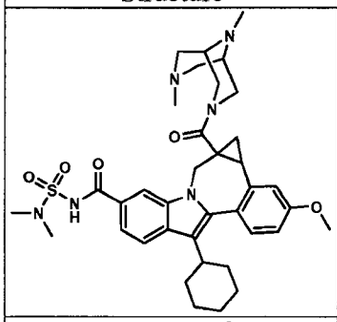
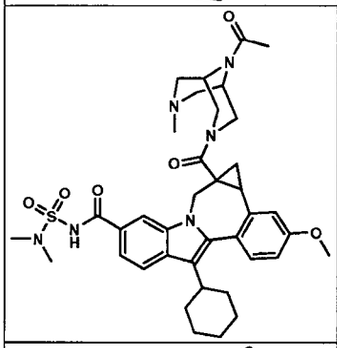
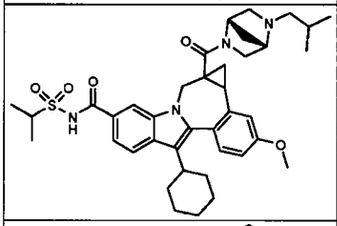
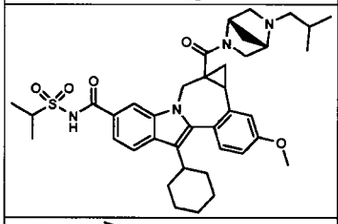
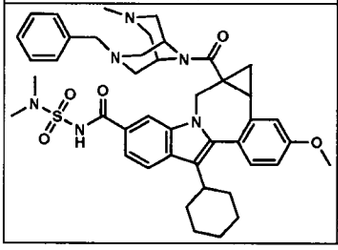
Structure	IC_{50}	EC_{50}
	B	B
	B	B
 Chiral	B	B
	B	B
	B	B

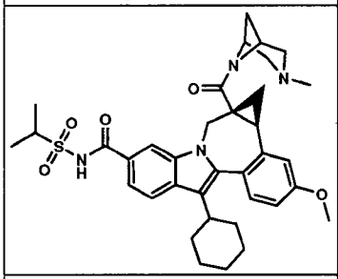
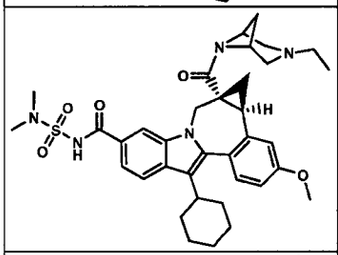
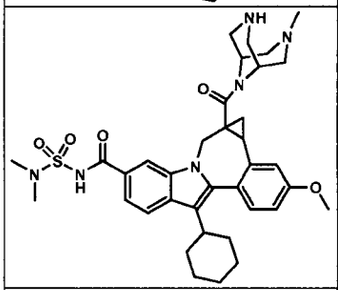
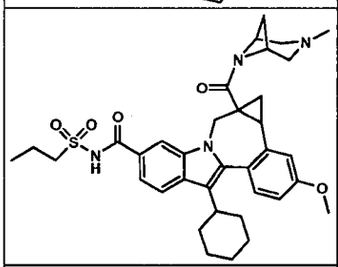
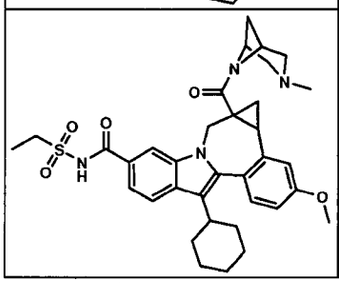
Structure	IC_{50}	EC_{50}
	C	B
	C	B
Chiral 	B	
	B	B
	B	B

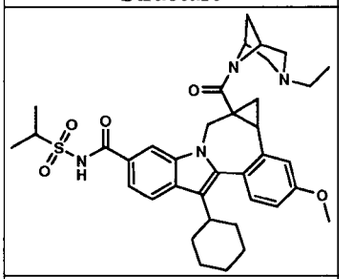
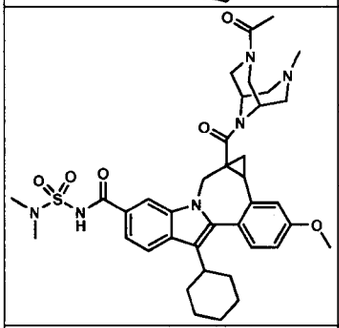
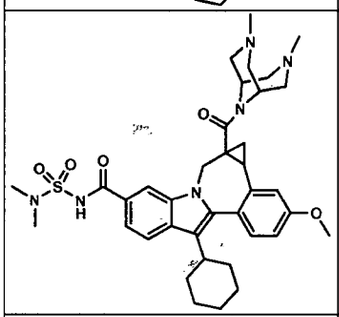
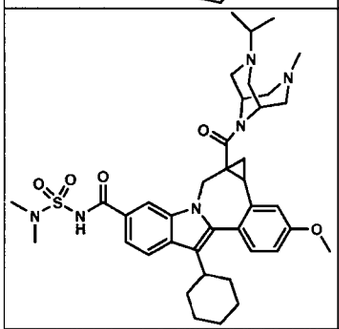
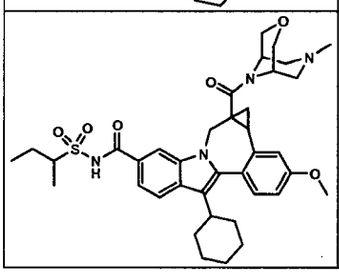
Structure	IC_{50}	EC_{50}
	G	
	B	B
	B	B
	B	B
	B	B

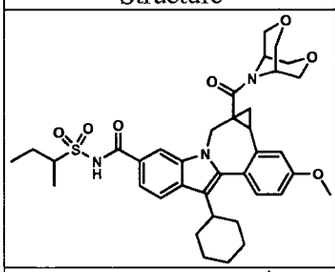
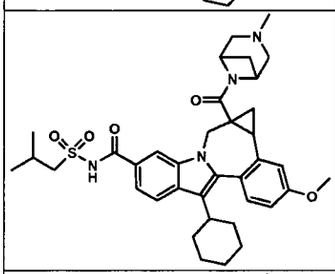
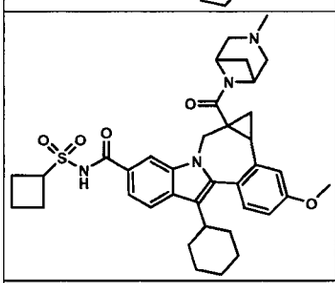
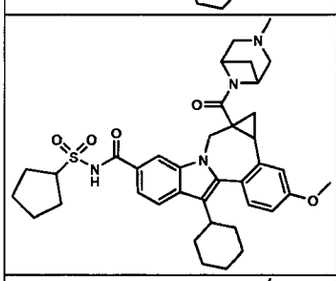
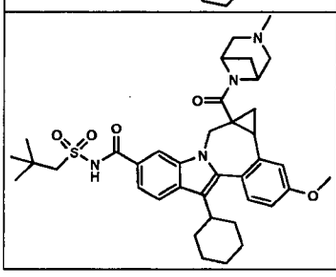
Structure	IC_{50}	EC_{50}
	B	B
	B	B
	B	B
	B	B
	B	B

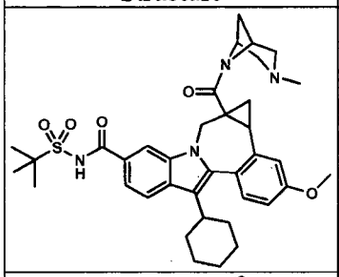
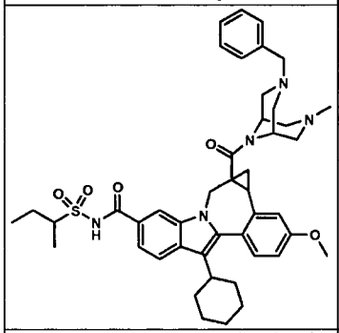
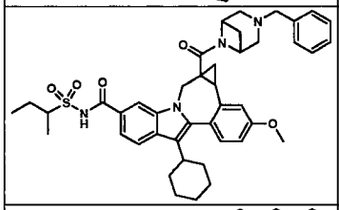
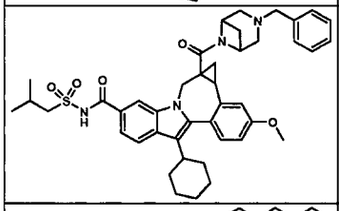
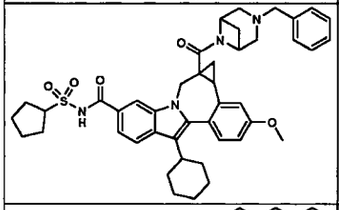
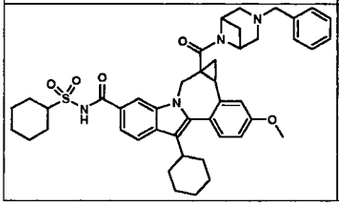
Structure	IC_{50}	EC_{50}
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	B	B
	B	G
	B	B
	B	B

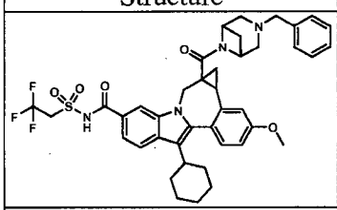
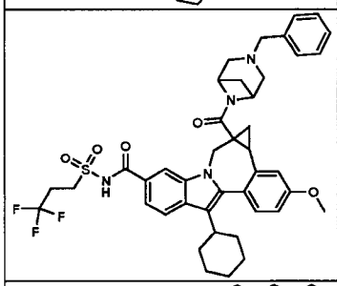
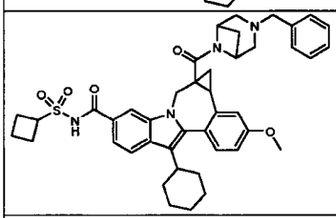
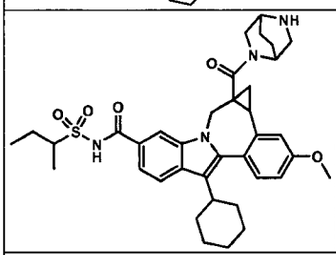
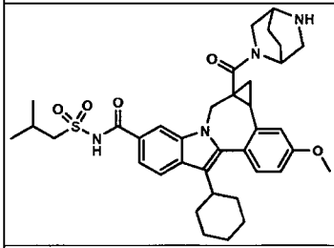
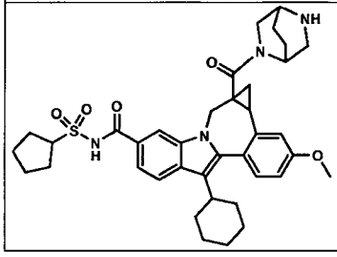
Structure	IC_{50}	EC_{50}
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	B	B
	B	B
	B	B

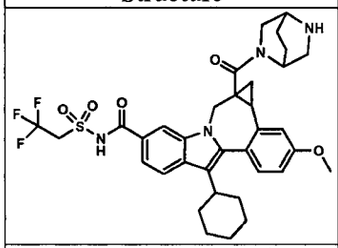
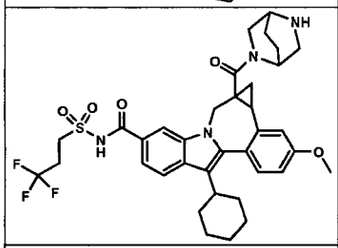
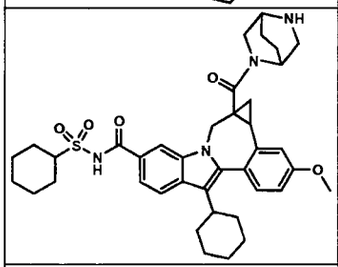
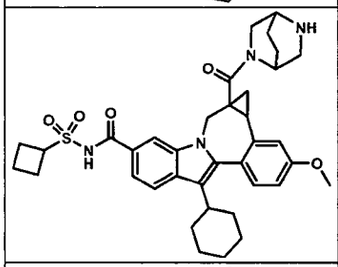
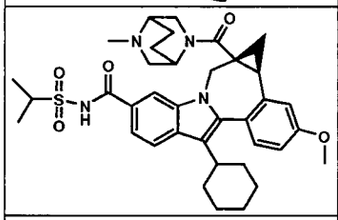
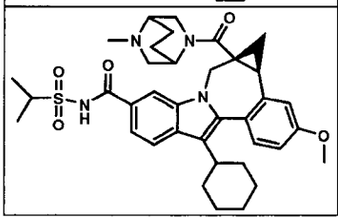
Structure	IC_{50}	EC_{50}
	B	B
	B	B
	B	
	B	B
		

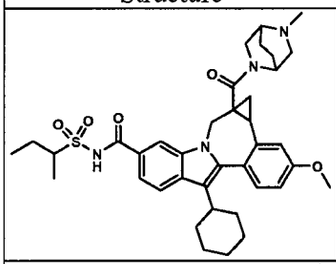
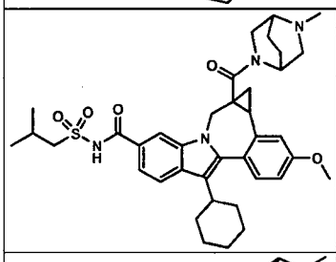
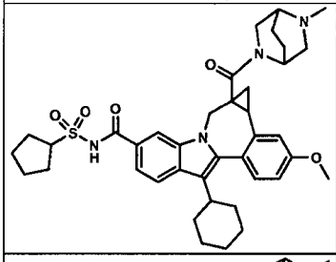
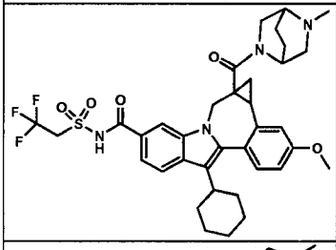
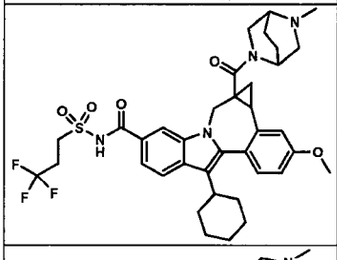
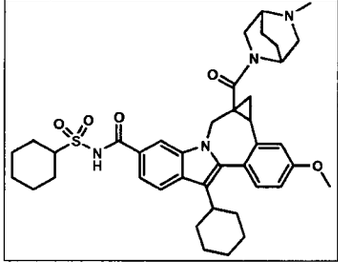
Structure	IC_{50}	EC_{50}
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	B	B
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	B	B
	B	

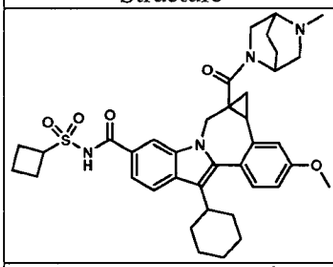
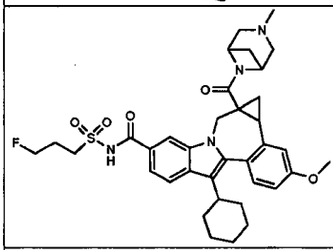
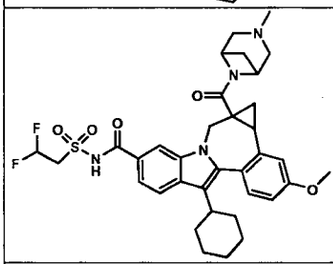
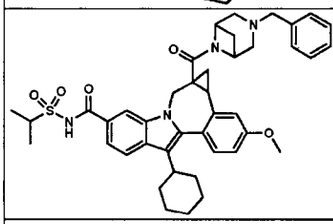
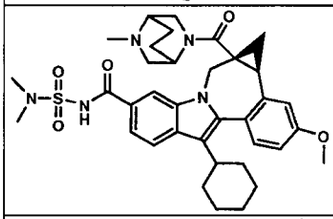
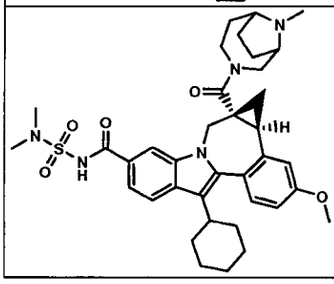
Structure	IC_{50}	EC_{50}
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	B	B
	B	B
	B	B
	B	B

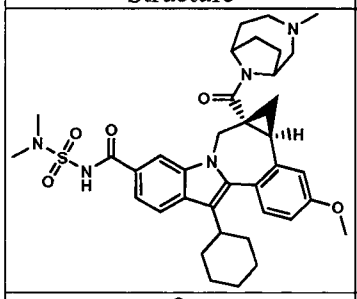
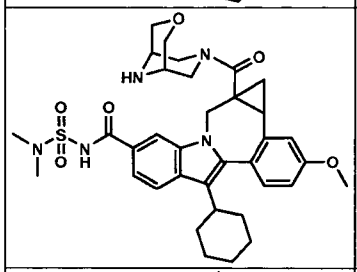
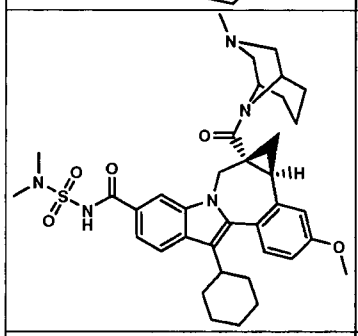
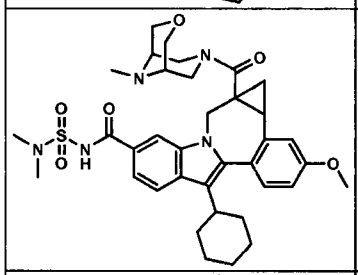
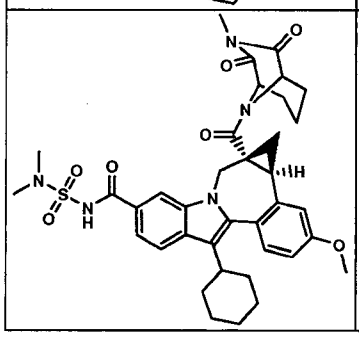
Structure	IC_{50}	EC_{50}
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	B	B
	B	B
	B	B
	B	B
	B	G

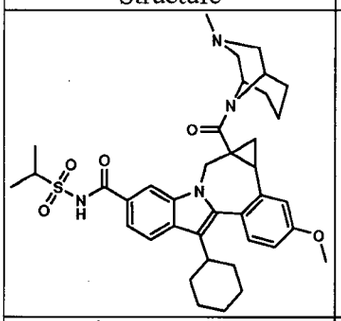
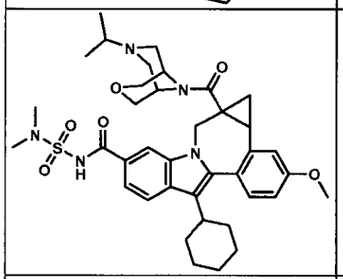
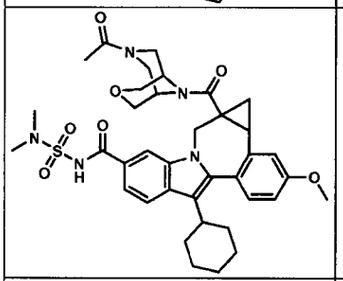
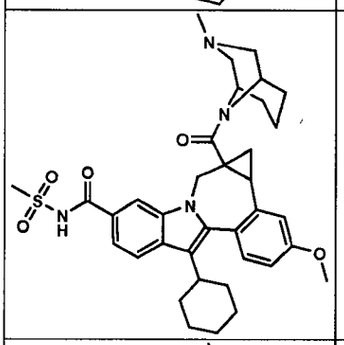
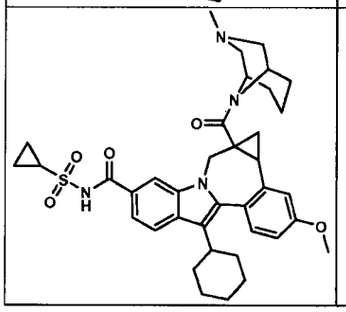
Structure	IC_{50}	EC_{50}
	B	G
	B	G
	B	G
	B	G
	B	H
	B	H

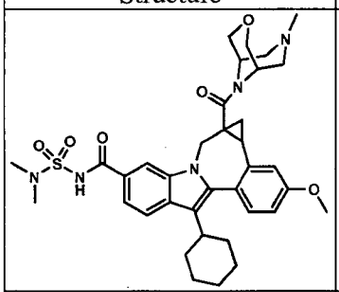
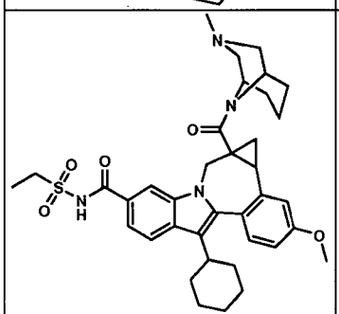
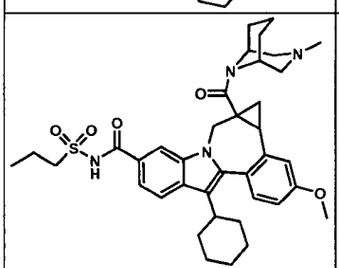
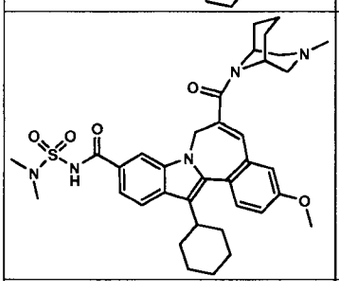
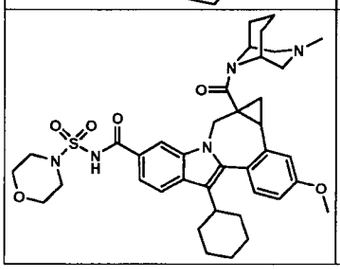
Structure	IC_{50}	EC_{50}
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	B	H
	B	H
	B	B
		B
		B

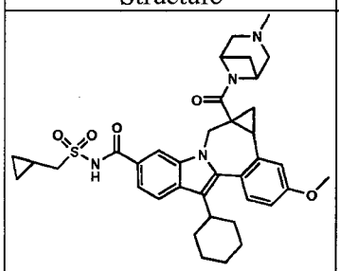
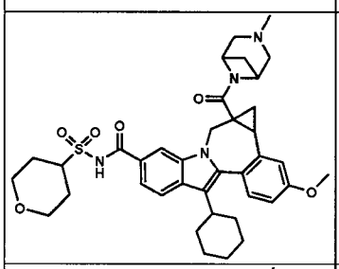
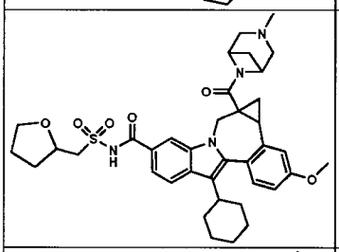
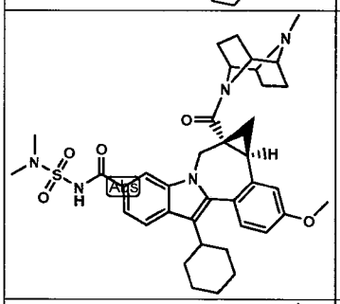
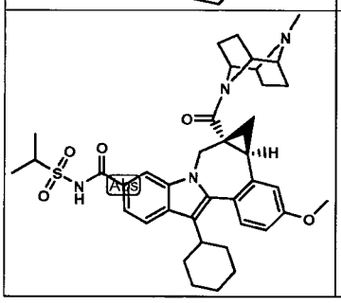
Structure	IC_{50}	EC_{50}
		
		
		
		
		
		

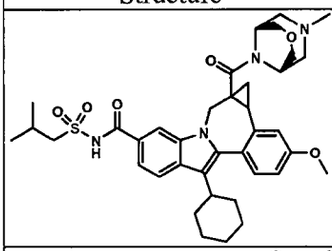
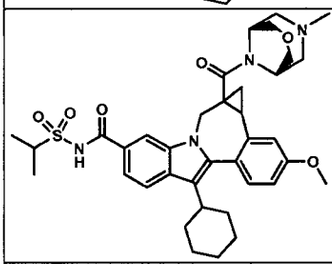
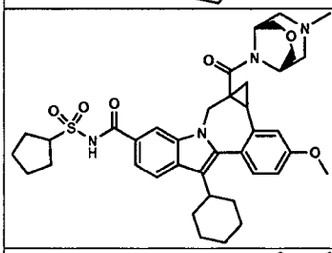
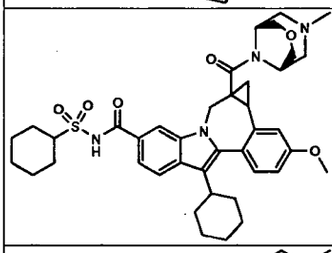
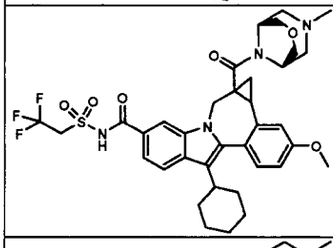
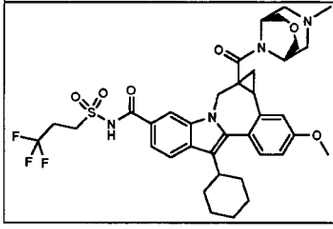
Structure	IC_{50}	EC_{50}
		
	B	B
	B	B
	B	B
	B	B
	B	B

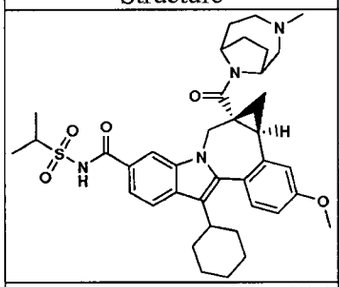
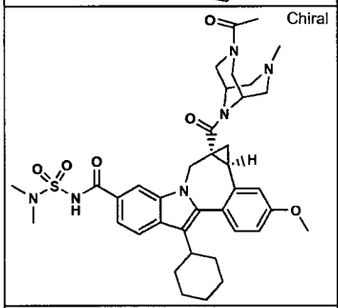
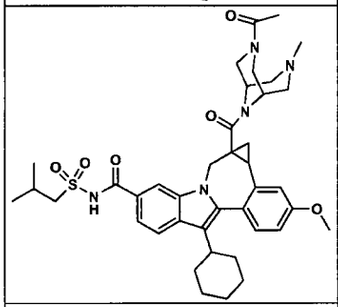
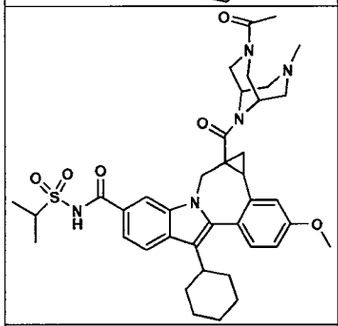
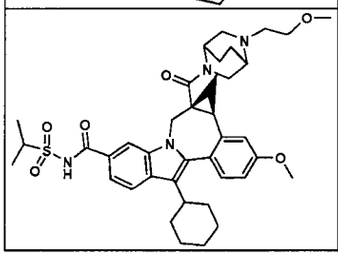
Structure	IC_{50}	EC_{50}
		
	B	B
	B	B
	B	B
	B	B

Structure	IC_{50}	EC_{50}
	B	B
	B	B
	B	B
	B	B
	B	B

Structure	IC_{50}	EC_{50}
	B	B
	B	B
	B	B
	B	B
	B	B

Structure	IC_{50}	EC_{50}
	B	B
	B	B
	B	B
	B	B
	B	B

Structure	IC_{50}	EC_{50}
	B	B
	B	B
	B	B
	B	B
	B	B
	B	B

Structure	IC_{50}	EC_{50}
	B	B
 Chiral	B	B
		
		
	B	B

A>0.5 μM; B 0.0024 μM – 0.5 μM; C <0.02 μM but an exact value was not determined; D>0.04 μM but an exact value was not determined; E<0.07 μM but an exact value was not determined; G >0.5 μM to 5.0μM; H>1.0 μM but an exact value was not determined.

Pharmaceutical Compositions and Methods of Treatment

The compounds demonstrate activity against HCV NS5B and can be useful in treating HCV and HCV infection. Therefore, another aspect of the invention is a composition comprising a compound, or a pharmaceutically acceptable salt thereof, and a pharmaceutically acceptable carrier.

Another aspect of the invention is a composition further comprising a compound having anti-HCV activity.

Another aspect of the invention is a composition where the compound having anti-HCV activity is an interferon. Another aspect of the invention is where the interferon is selected from interferon alpha 2B, pegylated interferon alpha, consensus interferon, interferon alpha 2A, and lymphoblastoid interferon tau.

Another aspect of the invention is a composition where the compound having anti-HCV activity is a cyclosporin. Another aspect of the invention is where the cyclosporin is cyclosporin A.

Another aspect of the invention is a composition where the compound having anti-HCV activity is selected from the group consisting of interleukin 2, interleukin 6, interleukin 12, a compound that enhances the development of a type 1 helper T cell response, interfering RNA, anti-sense RNA, Imiqimod, ribavirin, an inosine 5'-monophospate dehydrogenase inhibitor, amantadine, and rimantadine.

Another aspect of the invention is a composition where the compound having anti-HCV activity is effective to inhibit the function of a target selected from HCV metalloprotease, HCV serine protease, HCV polymerase, HCV helicase, HCV NS4B protein, HCV entry, HCV assembly, HCV egress, HCV NS5A protein, IMPDH, and a nucleoside analog for the treatment of an HCV infection.

Another aspect of the invention is a composition comprising a compound, or a pharmaceutically acceptable salt thereof, a pharmaceutically acceptable carrier, an interferon and ribavirin.

Another aspect of the invention is a method of inhibiting the function of the HCV replicon comprising contacting the HCV replicon with a compound or a pharmaceutically acceptable salt thereof.

Another aspect of the invention is a method of inhibiting the function of the HCV NS5B protein comprising contacting the HCV NS5B protein with a compound or a pharmaceutically acceptable salt thereof.

Another aspect of the invention is a method of treating an HCV infection in a patient comprising administering to the patient a therapeutically effective amount of a compound or a pharmaceutically acceptable salt thereof. In another embodiment the compound is effective to inhibit the function of the HCV replicon. In another embodiment the compound is effective to inhibit the function of the HCV NS5B protein.

Another aspect of the invention is a method of treating an HCV infection in a patient comprising administering to the patient a therapeutically effective amount of a compound, or a pharmaceutically acceptable salt thereof, in conjunction with (prior to, after, or concurrently) another compound having anti-HCV activity.

Another aspect of the invention is the method where the other compound having anti-HCV activity is an interferon.

Another aspect of the invention is the method where the interferon is selected from interferon alpha 2B, pegylated interferon alpha, consensus interferon, interferon alpha 2A, and lymphoblastoid interferon tau.

Another aspect of the invention is the method where the other compound having anti-HCV activity is a cyclosporin.

Another aspect of the invention is the method where the cyclosporin is cyclosporin A.

Another aspect of the invention is the method where the other compound having anti-HCV activity is selected from interleukin 2, interleukin 6, interleukin 12,

a compound that enhances the development of a type 1 helper T cell response, interfering RNA, anti-sense RNA, Imiqimod, ribavirin, an inosine 5'-monophospate dehydrogenase inhibitor, amantadine, and rimantadine.

Another aspect of the invention is the method where the other compound having anti-HCV activity is effective to inhibit the function of a target selected from the group consisting of HCV metalloprotease, HCV serine protease, HCV polymerase, HCV helicase, HCV NS4B protein, HCV entry, HCV assembly, HCV egress, HCV NS5A protein, IMPDH, and a nucleoside analog for the treatment of an HCV infection.

Another aspect of the invention is the method where the other compound having anti-HCV activity is effective to inhibit the function of target in the HCV life cycle other than the HCV NS5B protein.

"Therapeutically effective" means the amount of agent required to provide a meaningful patient benefit as understood by practitioners in the field of hepatitis and HCV infection.

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

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

The compounds of this invention are generally given as pharmaceutical compositions comprised of a therapeutically effective amount of a compound 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 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 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 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 hepatitis and HCV infection. In these combination methods, the compound 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.

Some examples of compounds suitable for compositions and methods are listed in Table 2.

Table 2.

Brand Name	Type of Inhibitor or Target	Source Company
Omega IFN	IFN-ω	Intarcia Therapeutics
BILN-2061	serine protease inhibitor	Boehringer Ingelheim Pharma KG, Ingelheim, Germany
Summetrel	antiviral	Endo Pharmaceuticals Holdings Inc., Chadds Ford, PA
Roferon A	IFN-α2a	F. Hoffmann-La Roche LTD, Basel, Switzerland
Pegasys	PEGylated IFN-α2a	F. Hoffmann-La Roche LTD, Basel, Switzerland
Pegasys and Ribavirin	PEGylated IFN-α2a/ribavirin	F. Hoffmann-La Roche LTD, Basel, Switzerland
CellCept	HCV IgG immunosuppressant	F. Hoffmann-La Roche LTD, Basel, Switzerland
Wellferon	lymphoblastoid IFN-αn1	GlaxoSmithKline plc, Uxbridge, UK
Albuferon - α	albumin IFN-α2b	Human Genome Sciences Inc., Rockville, MD
Levovirin	ribavirin	ICN Pharmaceuticals, Costa Mesa, CA
IDN-6556	caspase inhibitor	Idun Pharmaceuticals Inc., San Diego, CA
IP-501	antifibrotic	Indevus Pharmaceuticals Inc., Lexington, MA
Actimmune	INF-γ	InterMune Inc., Brisbane, CA
Infergen A	IFN alfacon-1	InterMune Pharmaceuticals Inc., Brisbane, CA
ISIS 14803	antisense	ISIS Pharmaceuticals Inc, Carlsbad, CA/Elan Phamaceuticals Inc., New York, NY
JTK-003	RdRp inhibitor	Japan Tobacco Inc., Tokyo, Japan
Pegasys and Ceplene	PEGylated IFN-α2a/ immune modulator	Maxim Pharmaceuticals Inc., San Diego, CA
Ceplene	immune modulator	Maxim Pharmaceuticals Inc., San Diego, CA
Civacir	HCV IgG immunosuppressant	Nabi Biopharmaceuticals Inc., Boca Raton, FL

Brand Name	Type of Inhibitor or Target	Source Company
Intron A and Zadaxin	IFN-α2b/α1-thymosin	RegeneRx Biopharmiceuticals Inc., Bethesda, MD/ SciClone Pharmaceuticals Inc, San Mateo, CA
Levovirin	IMPDH inhibitor	Ribapharm Inc., Costa Mesa, CA
Viramidine	Ribavirin Prodrug	Ribapharm Inc., Costa Mesa, CA
Heptazyme	ribozyme	Ribozyme Pharmaceuticals Inc., Boulder, CO
Intron A	IFN-α2b	Schering-Plough Corporation, Kenilworth, NJ
PEG-Intron	PEGylated IFN-α2b	Schering-Plough Corporation, Kenilworth, NJ
Rebetron	IFN-α2b/ribavirin	Schering-Plough Corporation, Kenilworth, NJ
Ribavirin	ribavirin	Schering-Plough Corporation, Kenilworth, NJ
PEG-Intron / Ribavirin	PEGylated IFN-α2b/ribavirin	Schering-Plough Corporation, Kenilworth, NJ
Zadazim	Immune modulator	SciClone Pharmaceuticals Inc., San Mateo, CA
Rebif	IFN-β1a	Serono, Geneva, Switzerland
IFN-β and EMZ701	IFN-β and EMZ701	Transition Therapeutics Inc., Ontario, Canada
Batabulin (T67)	β-tubulin inhibitor	Tularik Inc., South San Francisco, CA
Merimepodib (VX-497)	IMPDH inhibitor	Vertex Pharmaceuticals Inc., Cambridge, MA
Telaprevir (VX-950, LY-570310)	NS3 serine protease inhibitor	Vertex Pharmaceuticals Inc., Cambridge, MA/ Eli Lilly and Co. Inc., Indianapolis, IN
Omniferon	natural IFN-α	Viragen Inc., Plantation, FL

Brand Name	Type of Inhibitor or Target	Source Company
XTL-6865 (XTL-002)	monoclonal antibody	XTL Biopharmaceuticals Ltd., Rehovot, Isreal
HCV-796	NS5B Replicase Inhibitor	Wyeth / Viropharma
NM-283	NS5B Replicase Inhibitor	Idenix / Novartis
GL-59728	NS5B Replicase Inhibitor	Gene Labs / Novartis
GL-60667	NS5B Replicase Inhibitor	Gene Labs / Novartis
2'C MeA	NS5B Replicase Inhibitor	Gilead
PSI 6130	NS5B Replicase Inhibitor	Roche
R1626	NS5B Replicase Inhibitor	Roche
SCH 503034	serine protease inhibitor	Schering Plough
NIM811	Cyclophilin Inhibitor	Novartis
Suvus	Methylene blue	Bioenvision
Multiferon	Long lasting IFN	Viragen/Valentis
Actilon (CPG10101)	TLR9 agonist	Coley
Interferon-β	Interferon-β-1a	Serono
Zadaxin	Immunomodulator	Sciclone
Pyrazolopyrimidine compounds and salts From WO-2005047288 26 May 2005	HCV Inhibitors	Arrow Therapeutics Ltd.
2'C Methyl adenosine	NS5B Replicase Inhibitor	Merck
GS-9132 (ACH-806)	HCV Inhibitor	Achillion / Gilead

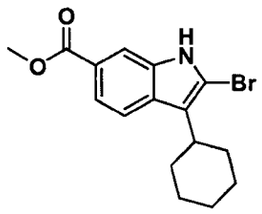
DESCRIPTION OF SPECIFIC EMBODIMENTS

Unless otherwise specified, analytical LCMS data on the following intermediates and examples were acquired using the following columns and conditions. Stop time: Gradient time + 1 minute; Starting conc: 0% B unless otherwise noted; Eluent A: 5% CH_3CN / 95% H_2O with 10 mM NH_4OAc (for columns A, D and E); 10 % MeOH / 90 % H_2O with 0.1% TFA (for columns B and C); Eluent B: 95% CH_3CN / 5% H_2O with 10 mM NH_4OAc (for columns A, D and

E); 90 % MeOH / 10 % H_2O with 0.1% TFA (for columns B and C); Column A: Phenomenex 10μ 4.6 x 50 mm C18; Column B: Phenomenex C18 10μ 3.0 x 50 mm; Column C: Phenomenex 4.6 x 50 mm C18 10μ; Column D: Phenomenex Lina C18 5μ 3.0 x 50 mm; Column E: Phenomenex 5μ 4.6 x 50 mm C18.

As as artifact of the software used, some chemical structures have some hydrogen atoms omitted.

Intermediate 1

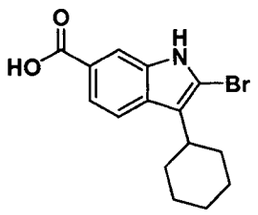


1H-Indole-6-carboxylic acid, 2-bromo-3-cyclohexyl-, methyl ester.

Freshly recrystallized pyridinium tribromide (recrystallization from hot AcOH (5 mL per 1 g), rinsed with cold AcOH and dried under high vacuum over KOH) was added in portions (over 10 min.) to a stirring solution of methyl 3-cyclohexyl-1H-indole-6-carboxylate (60 g, 233 mmol) (prepared using procedures describe in WO2004/065367) in $CHCl_3$/THF (1:1, 1.25 L) at 2o C. The reaction solution was stirred at 0-5 °C for 2.5h, and washed with sat. aq. $NaHSO_3$ (1 L), 1 N HCl (1 L) and brine (1 L). The organic layer was dried ($MgSO_4$) and concentrated. The resulting red oil was diluted with Et_2O and concentrated. The resulting pink solid was dissolved into Et_2O (200 mL) treated with hexanes (300 mL) and partially concentrated. The solids were collected by filtration and rinsed with hexanes. The mother liquor was concentrated to dryness and the procedure repeated. The solids were combined to yield 1H-indole-6-carboxylic acid, 2-bromo-3-cyclohexyl-, methyl ester (64 g, 190 mmol, 82%) as a fluffy pink solid, which was used without further purification. 1HNMR (300 MHz, $CDCl_3$) δ 8.47 (br s, 1H), 8.03 (d, J = 1.4 Hz, 1H), 7.74 (dd, J = 1.4, 8.8 Hz, 1H), 7.69 (d, J = 8.8 Hz, 1H), 3.92 (s, 3H), 2.82 (tt, J = 3.7, 11.7 Hz, 1H), 1.98 - 1.72 (m, 7H), 1.50 - 1.27 (m, 3H). 13CNMR (75 MHz, CDCl3)

δ 168.2, 135.6, 130.2, 123.1, 120.8, 120.3, 118.7, 112.8, 110.7, 52.1, 37.0, 32.2(2), 27.0(2), 26.1. LCMS: m/e 334 $(M-H)^-$, ret time 3.34 min, column A, 4 minute gradient.

Intermediate 2



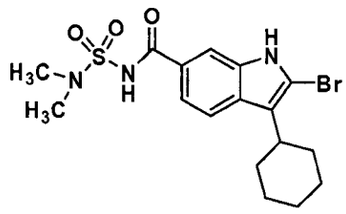
1H-Indole-6-carboxylic acid, 2-bromo-3-cyclohexyl-. A solution of methyl 2-bromo-3-cyclohexyl-1*H*-indole-6-carboxylate (20 g, 60 mmol) and LiOH (3.8 g, 160 mmol) in MeOH/THF/H_2O (1:1:1, 300 mL) was heated at 90 °C for 2h. The reaction mixture was cooled in an ice/H_2O bath, neutralized with 1M HCl (~160 mL) diluted with H_2O (250 mL) and stirred for 1h at rt. The precipitates were collected by filtration rinse with H_2O and dried to yield 1H-indole-6-carboxylic acid, 2-bromo-3-cyclohexyl- (quant.) which was used without further purification.

An alternative procedure that can by used to provide 1H-indole-6-carboxylic acid, 2-bromo-3-cyclohexyl- is described below:

A solution of methyl 2-bromo-3-cyclohexyl-1H-indole-6-carboxylate (117 g, 349 mmol) and LiOH.H_2O (26.4 g, 629 mmol) in MeOH/THF/H2O (1:1:1, 1.8 L) was heated at reflux for 3h. The reaction mixture was cooled in an ice/H2O bath to ~2 °C, neutralized with 1M HCl (~650 mL) (added at such a rate that temperature did not exceed 5 °C), diluted with H2O (1 L) and stirred while warming to ambient temperature. The precipitates were collected by filtration rinsed with H_2O and dried to yield the mono THF solvate of 1H-indole-6-carboxylic acid, 2-bromo-3-cyclohexyl- (135.5 g, 345 mmol, 99%) as a yellow solid, which was used without further purification. 1HNMR (300 MHz, $CDCl_3$) δ 11.01 (br s, 1H), 8.77 (s, 1H), 8.07 (d, J = 1.5 Hz, 1H), 7.82 (dd, J = 1.5, 8.8 Hz, 1H), 7.72 (d, J = 8.8 Hz, 1H), 3.84

- 3.74 (m, 4H), 2.89 (m, 1H), 1.98 - 1.72 (m, 11H), 1.50 - 1.24 (m, 3H). 13CNMR (75 MHz, CDCl3) δ 172.7, 135.5, 130.7, 122.3, 120.9(2), 118.8, 113.3, 111.1, 67.9(2), 37.0, 32.2(2), 27.0(2), 26.1, 25.5(2). LCMS: m/e 320 $(M-H)^-$, ret time 2.21 min, column A, 4 minute gradient.

Intermediate 3



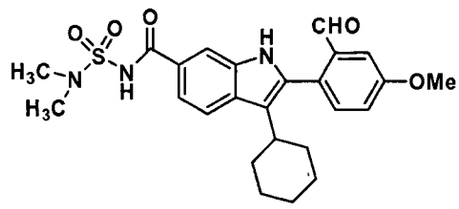
1H-Indole-6-carboxamide, 2-bromo-3-cyclohexyl-N-[(dimethylamino)sulfonyl]-. 1,1'-Carbonyldiimidazole (1.17 g, 7.2 mmol) was added to a stirred solution of 2-bromo-3-cyclohexyl-1H-indole-6-carboxylic acid (2.03 g, 6.3 mmol) in THF (6 mL) at 22 °C. The evolution of CO_2 was instantaneous and when it slowed the solution was heated at 50°C for 1 hr and then cooled to 22°C. N,N-Dimethylsulfamide (0.94 g, 7.56 mmol) was added followed by the dropwise addition of a solution of DBU (1.34 g ,8.8 mmol) in THF (4 mL). Stirring was continued for 24 hr. The mixture was partitioned between ethyl acetate and dilute HCl. The ethyl acetate layer was washed with water followed by brine and dried over Na_2SO_4. The extract was concentrated to dryness to leave the title product as a pale yellow friable foam, (2.0 g, 74 %, >90 % purity , estimated from NMR). ^1H NMR (300 MHz, DMSO-D6) δ ppm 1.28 - 1.49 (m, 3 H) 1.59 - 2.04 (m, 7 H) 2.74 - 2.82 (m, 1 H) 2.88 (s, 6 H) 7.57 (dd, *J*=8.42, 1.46 Hz, 1 H) 7.74 (d, *J*=8.78 Hz, 1 H) 7.91 (s, 1 H) 11.71 (s, 1 H) 12.08 (s, 1 H).

An alternative method for the preparation of 1H-indole-6-carboxamide, 2-bromo-3-cyclohexyl-N-[(dimethylamino)sulfonyl]- is described below.

To a 1 L four necked round bottom flask equipped with a mechanical stirrer, a temperature controller, a N2 inlet , and a condenser, under N2, was added 2-bromo-3-

cyclohexyl-1*H*-indole-6-carboxylic acid (102.0 g, 0.259 mol) and dry THF (300 mL). After stirring for 10 min, CDI (50.3 g, 0.31 mol) was added portion wise. The reaction mixture was then heated to 50 oC for 2 h. After cooling to 30 oC, *N,N*-dimethylaminosulfonamide (41.7 g, 0.336 mol) was added in one portion followed by addition of DBU (54.1 mL, 0.362 mol) drop wise over a period of 1 h. The reaction mixture was then stirred at rt for 20 h. The solvent was removed in vacuo and the residue was partitioned between EtOAc and 1 N HCl (1 : 1, 2 L). The organic layer was separated and the aqueous layer was extracted with EtOAc (500 mL). The combined organic layers were washed with brine (1.5 L) and dried over MgSO4. The solution was filtered and concentrated in vacuo to give the crude product (111.0 g). The crude product was suspended in EtOAc (400 mL) at 60 oC. To the suspension was added heptane (2 L) slowly. The resulting suspension was stirred and cooled to 0 oC. It was then filtered. The filter cake was rinsed with small amount of heptane and house vacuum air dried for 2 days. The product was collected as a white solid (92.0 g, 83%). ^{1}H NMR (MeOD, 300 MHz) δ 7.89 (s, H), 7.77 (d, J = 8.4 Hz, 1H), 7.55 (dd, J = 8.4 and 1.8 Hz, 1H), 3.01 (s, 6H), 2.73-2.95 (m, 1H), 1.81-2.05 (m, 8H), 1.39-1.50 (m, 2H); m/z 429 (M +H)+.

Intermediate 4



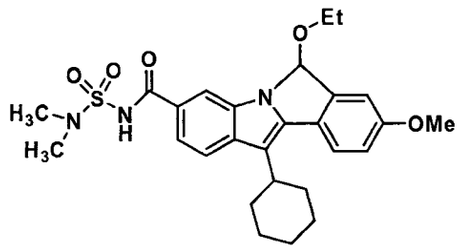
1H-Indole-6-carboxamide, 3-cyclohexyl-N-[(dimethylamino)sulfonyl]-2-(2-formyl-4-methoxyphenyl)-. A mixture of the 2-Bromo-3-cyclohexyl- N-[(dimethylamino)sulfonyl]-1H-indole-6-carboxamide (4.28g, 0.01 mol), 4-methoxy-2-formylphenyl boronic acid (2.7g, 0.015 mol), 2-dicyclohexylphosphino-2',6'-dimethoxy-biphenyl (41 mg, 0.0001 mol), palladium acetate (11.2 mg), and finely ground potassium carbonate (4.24g, 0.02 mol) in toluene (30 mL) was stirred under reflux and under nitrogen for 30 min, at which time LC/MS analysis showed the

reaction to be complete. The reaction mixture was then diluted with ethyl acetate and water, and then acidified with an excess of dilute HCl. The ethyl acetate layer was then collected and washed with dilute HCl, water and brine. The organic solution was then dried (magnesium sulfate), filtered and concentrated to give a gum. The gum was diluted with hexanes (250 ml) and ethyl acetate (25 mL), and the mixture was stirred for 20 hr at 22° C during which time the product was transformed into a bright yellow granular solid (4.8 g) which was used directly without further purification.

An alternative procedure for the preparation of 1H-indole-6-carboxamide, 3-cyclohexyl-N-[(dimethylamino)sulfonyl]-2-(2-formyl-4-methoxyphenyl)- is provided below:

To a slurried solution of 2-bromo-3-cyclohexyl-N-[(dimethylamino)sulfonyl]-indole-6-carboxamide (54.0 g, 126 mmol), 4-methoxy-2-formylphenylboronic acid (29.5 g, 164 mmol) and LiCl (13.3 g, 315 mmol) in EtOH/toluene (1:1, 1 L) was added a solution of Na_2CO_3 (40.1 g, 379 mmol) in water (380 mL). The reaction mixture was stirred 10 min. and then Pd(PPh3)4 (11.3 g, 10.0 mmol) was added. The reaction solution was flushed with nitrogen and heated at 70 °C (internal monitoring) overnight and then cooled to rt. The reaction was diluted with EtOAc (1 L) and EtOH (100 mL), washed carefully with 1N aqueous HCl (1 L) and brine (500 mL), dried (MgSO4), filtered and concentrated. The residual solids were stirred with Et2O (600 mL) for 1h and collected by filtration to yield 1H-indole-6-carboxamide, 3-cyclohexyl-N-[(dimethylamino)sulfonyl]-2-(2-formyl-4-methoxyphenyl)- (52.8g, 109 mmol, 87%) as a yellow powder which was used without further purification. 1HNMR (300 MHz, d6-DMSO) δ 11.66 (s, 1H), 8.17 (s, 1H), 7.75 (d, J = 8.4 Hz, 1H), 7.74 (d, J = 8.4 Hz, 1H), 7.59 (dd, J = 1.4, 8.4 Hz, 1H), 7.23 - 7.16 (m, 2H), 7.08 (dd, J = 2.6, 8.4 Hz, 1H), 6.54 (d, J = 8.8 Hz, 1H), 3.86 (s, 3H), 3.22 - 3.08 (m, 1H), 2.91 (s, 6H), 2.00 - 1.74 (m, 7H), 1.60 - 1.38 (m, 3H). 13CNMR (75 MHz, CDCl3) δ 165.7, 158.8, 147.2, 139.1, 134.3, 132.0, 123.4, 122.0, 119.2, 118.2, 114.8, 112.3, 110.4, 109.8, 79.6, 45.9, 37.2(2), 34.7, 32.0(2), 25.9(2), 24.9. LCMS: m/e 482 $(M-H)^-$, ret time 2.56 min, column A, 4 minute gradient.

Intermediate 5

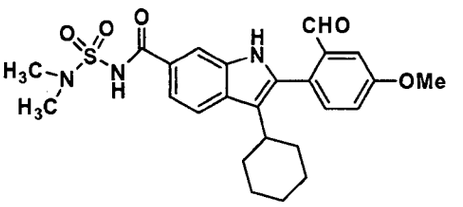


6H-Isoindolo[2,1-a]indole-3-carboxamide, 11-cyclohexyl-N-[(dimethylamino)sulfonyl]-6-ethoxy-8-methoxy-. To a 5 L four necked round bottom flask equipped with a temperature controller, a condenser, a N2 inlet and a mechanical stirrer, was charged toluene (900 mL), EtOH (900 mL), 2-bromo-3-cyclohexyl-*N*-(*N*,*N*-dimethylsulfamoyl)-1*H*-indole-6-carboxamide (90 g, 0.21 mol), 2-formyl-4-methoxyphenylboronic acid (49.2 g, 0.273 mol) and LiCl (22.1 g, 0.525 mol). The resulting solution was bubbled with N_2 for 15 mins. A solution of Na_2CO_3 (66.8 g, 0.63 mol) in H_2O (675 mL) was added and the reaction mixture was bubbled with N_2 for another (10 mins). $Pd(PPh_3)_4$ (7.0 g, 6.3 mmol) was added and the reaction mixture was heated to 70 °C for 20 h. After cooling to 35 °C, a solution of 1 N HCl (1.5 L) was added slowly. The resulting mixture was transferred to a 6 L separatory funnel and extracted with EtOAc (2 X 1.5 L). The combined organic extracts were washed with brine (2 L), dried over MgSO4, filtered and concentrated in vacuo to give a yellow solid, which was triturated with 20% EtOAc in hexane (450 mL, 50 °C to 0 °C) to give 3-cyclohexyl-N-(N,N-dimethylsulfamoyl)-2-(2-formyl-4-methoxyphenyl)-1H-indole-6-carboxamide(65.9 g) as a yellow solid. HPLC purity, 98%.

The mother liquid from the trituration was concentrated in vacuo. The residue was refluxed with EtOH (50 mL) for 3 h. The solution was then cooled to 0 °C. The precipitates were filtered and washed with cooled TBME (5 °C) (20 mL). The filter cake was house vacuum air dried to give a further quantity of the title compound as a white solid (16.0 g). HPLC purity, 99%. ^{1}H NMR (CDCl3, 300 MHz) δ 8.75 (s, 1H), 7.96 (s, 1H), 7.73 (d, J = 8.4 Hz, 1H), 7.67 (d, J = 8.4 Hz, 1H), 7.45

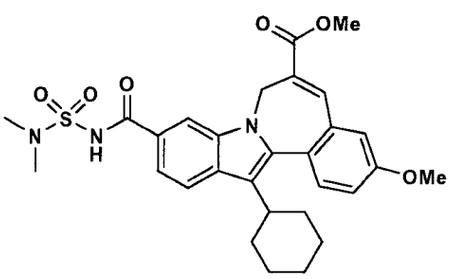
(dd, J = 8.4 and 1.4 Hz, 1H), 7.09 (d, J = 2.2 Hz, 1H), 6.98 (dd, J = 8.4 and 2.2 Hz, 1H), 6.50 (s, 1H), 3.86 (s, 3H), 3.05 (s, 6H), 2.92-3.13 (m, 3H), 1.85-1.93 (m, 7 H), 1.40-1.42 (m, 3H), 1.05 (t, J = 7.1 Hz, 3H). m/z 512 (M + H)+.

Intermediate 6



1H-indole-6-carboxamide, 3-cyclohexyl-N-[(dimethylamino)sulfonyl]-2-(2-formyl-4-methoxyphenyl)-. 11-cyclohexyl-N-(N,N-dimethylsulfamoyl)-6-ethoxy-8-methoxy-6H-isoindolo[2,1-a]indole-3-carboxamide was dissolved in THF (75 mL). To the solution was added a solution of 2 N HCl (300 mL). The mixture was vigorously stirred under N2 at rt for 16 h. The resulting suspension was filtered and washed with cooled TBME (2 X 30 mL). the filer cake was vacuum air dried overnight to give the title compound as a yellow solid. HPLC purity, 99% ^{1}H NMR (DMSO-d6, 300 MHz) δ 11.65 (s, 1H), 8.16 (s, 1H), 7.76 (d, J = 5.9 Hz, 1H), 7.73 (d, J = 5.9 Hz, 1H), 7.58 (dd, J = 8.5 and 1.5 Hz, 1H), 7.17-7.20 (m, 2H), 7.08 (dd, J = 8.5 and 1.4 Hz, 1H), 6.55 (d, J = 8.6 Hz, 1H), 3.86 (s, 3H), 3.14-3.18 (m, 1H), 2.91 (s, 6H), 1.75-1.99 (m, 7H), 1.48-1.60 (m, 3H); m/z 484 (M + H)+.

Intermediate 7



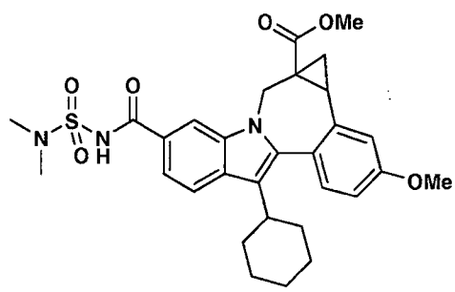
7H-Indolo[2,1-a][2]benzazepine-6-carboxylic acid, 13-cyclohexyl-10-[[[(dimethylamino)sulfonyl]amino]carbonyl]-3-methoxy-, methyl ester. A mixture of the 3-cyclohexyl-N-(N,N-dimethylsulfamoyl)-2-(2-formyl-4-methoxyphenyl)-1H-indole-6-carboxamide (4.8g, 0.01 mol), methyl 2-(dimethoxyphosphoryl)acrylate (9.7 g, 0.02 mol) and cesium carbonate (7.1g, 0.02 mol) in DMF (28mL) was stirred for 20 hr at an oil bath temperature of 55 ^{0}C. The mixture was poured into ice–water and acidified with dilute HCl to precipitate the crude product. The solid was collected, dried and flash chromatographed on SiO_2 (110g) using an ethyl acetate and methylene chloride (1:10) solution containing 2% acetic acid. Homogeneous fractions were combined and evaporated to afford the title compound as a pale yellow solid (3.9g, 71 % yield). MS: 552 (M=H+).

An alternate procedure for the preparation of 7H-indolo[2,1-a][2]benzazepine-6-carboxylic acid, 13-cyclohexyl-10-[[[(dimethylamino)sulfonyl]amino]carbonyl]-3-methoxy-, methyl ester is provided below.

A solution of 11-cyclohexyl-N-[(dimethylamino)sulfonyl]-6-hydroxy-8-methoxy-6H-isoindolo[2,1-a]indole-3-carboxamide (cyclic hemiaminal) (63.0 g, 130 mmol), methyl 2-(dimethoxyphosphoryl)acrylate (60 g, 261 mmol), cesium carbonate (106 g, 326 mmol) in DMF (400 mL) was heated at 60 °C (bath temp) for 4.5h. Additional methyl 2-(dimethoxyphosphoryl)acrylate (15 g, 65 mmol) and cesium carbonate (21.2 g, 65 mmol) were added and the reaction was heated at 60 °C overnight then and cooled to rt. The stirring reaction mixture was diluted with H_2O (1 L), slowly neutralized with 1N aqueous HCl (800 mL), stirred 3h, and then the precipitates were collected by filtration. The solids were triturated with Et2O (800 mL) and dried to yield methyl 7H-indolo[2,1-a][2]benzazepine-6-carboxylic acid, 13-cyclohexyl-10-[[[(dimethylamino)sulfonyl]amino]carbonyl]-3-methoxy-, methyl ester (70.2 g, 127 mmol, 98%) as a yellow solid which was used without further purification. 1HNMR (300 MHz, CDCl3) δ 8.67 (s, 1H), 8.09 (s, 1H), 7.86 (d, J = 8.4 Hz, 1H), 7.80 (s, 1H), 7.50 (d, J = 8.4 Hz, 1H), 7.42 (d, J = 8.8 Hz, 1H), 7.08 (dd, J = 2.6, 8.8 Hz, 1H), 6.98 (d, J = 2.6 Hz, 1H), 5.75 - 5.51 (m, 1H), 4.29 - 4.01 (m,

1H), 3.89 (s, 3H), 3.82 (s, 3H), 3.05 (s, 6H), 2.87 - 2.73 (m, 1H), 2.11 - 1.12 (m, 10H). LCMS: m/e 550 (M-H)-, ret time 3.21 min, column A, 4 minute gradient.

Intermediate 8

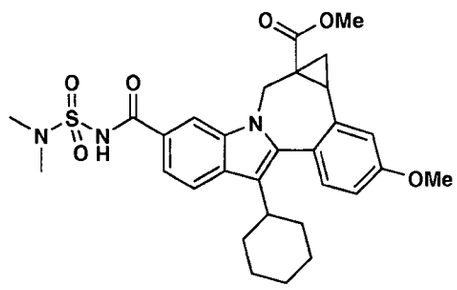


Cycloprop[d]indolo[2,1-a][2]benzazepine-1a(2H)-carboxylic acid, 8-cyclohexyl-5-[[[(dimethylamino)sulfonyl]amino]carbonyl]-1,12b-dihydro-11-methoxy-, methyl ester, (+/-)-. DMSO (5 mL) was added to a mixture of trimethylsulfoxonium iodide (199 mg, 0.906 mmol) and NaH (38 mg in 60% oil dispersion, 0.953 mmol) in a round-bottomed flask. The reaction mixture was stirred at rt for 0.5 hr. 7H-Indolo[2,1-a][2]benzazepine-6-carboxylic acid, 13-cyclohexyl-10-[[[(dimethylamino)sulfonyl]amino]carbonyl]-3-(methoxy)-, methyl ester (125 mg, 0.227 mmol) was then added and the reaction mixture was stirred at rt. for 3 hr., and then at 50^{0}C for a further 3 hr. The reaction was then quenched with water and acidified with 1N HCl solution. The crude product then precipitated as a light yellow solid which was collected by filtration and air dried, (106 mg, 83% yield). 6 mg of this material was then purified by Prep. HPLC to afford the title compound as a light yellow solid (1.8 mg). MS m/z 566(MH^+), Retention time: 3.850 min.1H NMR (500 MHz, MeOD) δ ppm 0.28 (m, 0.36 H) 1.19 - 2.20 (m, 11.64 H) 2.70 - 3.02 (m, 2 H) 3.03 (s, 2.16 H) 3.05 (s, 3.84 H) 3.49 (d, J=15.26 Hz, 0.64 H) 3.54 (s, 1.92 H) 3.83 (s, 1.08 H) 3.91 (s, 3 H) 4.08 (d, J=15.26 Hz, 0.36 H) 5.29 (d, J=15.26 Hz, 0.36 H) 5.50 (d, J=14.95 Hz, 0.64 H) 6.98 - 7.06 (m, 1 H) 7.16 (d, J=2.44 Hz, 0.36 H) 7.23 (d, J=2.44 Hz, 0.64 H) 7.30 (d, J=8.55 Hz, 0.64 H) 7.34 (d, J=8.55 Hz, 0.36 H) 7.56 (dd, J=8.55, 1.53 Hz, 0.64 H) 7.63 (dd, J=8.55, 1.53 Hz, 0.36 H) 7.88 (d, J=8.55 Hz, 0.64 H) 7.91 (d, J=8.55 Hz, 0.36 H) 8.12 (s, 0.36 H) 8.33 (d, J=1.53 Hz, 0.64 H).

An alternative procedure for the preparation of the title compounds is provided below.

To a flame dried, four necked, 1 L round bottom flask equipped with a mechanical stirrer, N2 inlet and a thermometer, under N2, was charged sodium hydride (95%) (3.09 g, 129.2 mmol) and dry DMF (200 mL). With vigorous stirring, trimethylsulfoxonium iodide (32.5 g, 147.3 mmol) portion wise during which time the temperature rose to 30 °C. After stirring for 30 mins, a solution of 7H-Indolo[2,1-a][2]benzazepine-6-carboxylic acid, 13-cyclohexyl-10-[[[(dimethylamino)sulfonyl]amino]carbonyl]-3-(methoxy)-, methyl ester (33.8 g, 61.3 mmol) in dry DMF (70 mL) was added quickly. The reaction mixture was stirred below 30 °C for 30 mins and then poured into an ice cold solution of 1 N HCl (130 mL) in H2O (2 L) portion wise. After the resulting suspension was mechanically stirred for 1 h, the precipitates were filtered and the filter cake was washed with H2O (100 mL). The filter cake was partitioned between EtOAc and 0.5 N HCl (1:1, 4 L). The organic phase was separated, washed with H2O (1 L) and brine (1 L), dried over $MgSO_4$, filtered and concentrated in vacuo. The residue was dissolved in EtOAc (150 mL), and the solution was filtered through a silica gel pad (300 g in hexane) and rinsed with 50% EtOAc in hexane (5 L). The filtrate was concentrated in vacuo to give a slightly yellow solid which was triturated with 10% EtOAc in TBME (220 mL) from 50 °C to 0 °C to to give cycloprop[d]indolo[2,1-a][2]benzazepine-1a(2H)-carboxylic acid, 8-cyclohexyl-5-[[[(dimethylamino)sulfonyl]amino]carbonyl]-1,12b-dihydro-11-methoxy-, methyl ester, (+/-)- as a white solid (26.1 g, 75% yield). HPLC purity, 100%. ^{1}H NMR (DMSO-d_6, 300 MHz) δ 11.61 (s, 1H), 8.47 (s, 0.5H), 8.25 (s, 0.5H), 7.81-7.88 (m, 1H), 7.57-7.63 (m, 1H), 7.23-7.29 (m, 2H), 7.01-7.07 (m, 1H), 5.43 (d, J = 15.0 Hz, 0.5H), 5.22 (d, J = 15 Hz, 0.5H), 4.04 (dd, J = 15.4 and 6.6 Hz, 0.5H), 3.83 (s, 3H), 3.75 (s, 1H), 3.08-3.47 (m, 0.5H), 3.29 (s, 3H), 2.73-2.92 (m, 8H), 1.11-1.99 (m, 10.5H), 0.20 (m, 0.5H); m/z 566 $(M + H)^+$.

Intermediate 9



Cycloprop[d]indolo[2,1-a][2]benzazepine-1a(2H)-carboxylic acid, 8-cyclohexyl-5-[[[(dimethylamino)sulfonyl]amino]carbonyl]-1,12b-dihydro-11-methoxy-, methyl ester, (-)-. A sample of (+/-) cycloprop[d]indolo[2,1-a][2]benzazepine-1a(2H)-carboxylic acid, 8-cyclohexyl-5-[[[(dimethylamino)sulfonyl]amino]carbonyl]-1,12b-dihydro-11-methoxy- methyl ester was dissolved in EtOH/CH_3CN 1/1 + 0.5% DEA at a concentration of 50 mg/ml. [The addition of DEA ensures the compound remains in solution during the injection process]. This solution was then injected onto a Thar SFC-350 preparative SFC under the conditions shown below.

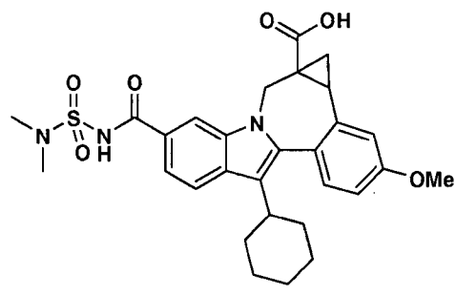
Preparative conditions on Thar SFC-350: Column: Chiralcel OJ-H 5x25 cm; mobile phase: 25% MeOH/ CH3CN (1/1) in CO2; pressure (bar): 100; flow rate (ml/ min): 240; solution concentration (mg/ml): 50; injection amount (ml): 4.5-5; Cycle time (min/inj): 6.5-7; Temperature (°C): 45; throughput (g/ hr): ~2; Detector wavelength (nm): 254.

From 371.4 g of racemic starting material, a total of 177.3g of the desired second eluting (-) isomer was obtained, containing ~1 Meq of diethylamine. This material was purified using the following procedure. The mixture (24.7 g) dissolved in dichloromethane (800 mL)) was washed sequentially with; 0.5 N HCl (1 x 400 mL, 1 x 240 mL), H_2O (2 x 240 mL), and brine (2 x 240 mL). The organic layer was then dried (Anhy. Na_2SO_4), filtered and evaporated to give 22.33 g of (cycloprop[d]indolo[2,1-a][2]benzazepine-1a(2H)-carboxylic acid, 8-cyclohexyl-5-[[[(dimethylamino)sulfonyl]amino]carbonyl]-1,12b-dihydro-11-methoxy-, methyl

ester, (-)- as a yellow solid (92% recovery). HPLC[1] > 99% (Rt 2.38 min); LC/MS (ES^+) 566.51 (M+H, 100); $[\alpha]_D^{25\,C}$ - 194.64 ° (c 1.03, MeOH). Anal. Calcd for $C_{30}H_{35}N_3O_6S \bullet 0.33H_2O$: C, 63.04; H, 6.29; N, 7.35; S, 5.61; H_2O, 1.04. Found: C, 63.07; H, 6.01; N, 7.24; S, 5.58; H_2O, 1.03. The NMR shows the absence of Et_2NH. The EE of this material was determined to be > 99% using the following analytical HPLC procedure.

Analytical conditions of ee determination on Thar analytical SFC. Analytical Column: Chiralcel OJ (.46x25cm, 10µl); BPR pressure: 100 bars; Temperature: 35 °C; Flow rate: 3.0 ml/min; Mobile Phase: 15% MeOH/ CH_3CN (1/1) in CO_2; Detector Wavelength: 254 nm; Retention time (min): 4, 6.5.

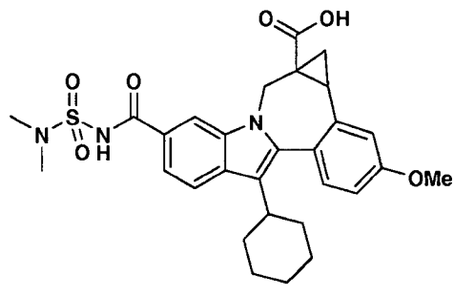
Intermediate 10



Cycloprop[d]indolo[2,1-a][2]benzazepine-1a(2H)-carboxylic acid, 8-cyclohexyl-5-[[[(dimethylamino)sulfonyl]amino]carbonyl]-1,12b-dihydro-11-methoxy-, (-)-. To a solution of (-) cycloprop[d]indolo[2,1-a][2]benzazepine-1a(2H)-carboxylic acid, 8-cyclohexyl-5-[[[(dimethylamino)sulfonyl]amino]carbonyl]-1,12b-dihydro-11-methoxy-, methyl ester (22.33 g, 39.5 mmol) in MeOH (300 mL) was added 1 N NaOH (120 mL) slowly over 20 min., while maintaining the reaction temperature < 30 °C. The mixture was stirred at rt under N_2 for 18 h. The HPLC indicated the reaction was complete. To the reaction solution was added 1 N HCl (130 mL). After addition was complete, the pH of the reaction mixture was about 2. The methanol in the reaction mixture was evaporated. Water (300 mL) was added to the mixture which was then extracted with CH_2Cl_2 (1 x 600 mL, 1 x 200 mL). The combined extracts were

washed with H_2O (2 x 300 mL), brine (2 x 300 mL), dried (Na_2SO_4) and evaporated to give 20.82 g (96% yield) of the title compound as a yellow solid. HPLC conditions column: Phenomenoex Synergi Polar-RP 4 um 4.6 x 50 mm; UV: 220 nm; gradient time: 4 min; flow rate: 4 mL/min, 75 - 100% B; solvent A: 10% MeOH/90% H_2O with 0.2% H_3PO_4, solvent B: 90% MeOH/10% H_2O with 0.2% H_3PO_4. HPLC > 99% (Rt 1.80 min.) LC/MS (ES^+) 552.25 (M+H, 100); $[\alpha]_D^{25\,C}$ - 166.99 ° (c 1.00, MeOH). GC analysis: CH_2Cl_2 4.94%; Anal. Calcd for $C_{29}H_{33}N_3O_6S \bullet 0.16\ H_2O \bullet 0.35\ CH_2Cl_2$: C, 60.37; H, 5.87; N, 7.20; S, 5.49; H_2O, 0.49; CH_2Cl_2, 5.02. Found: C, 59.95; H, 5.89; N, 7.03; S, 5.38; H_2O, 0.47; CH_2Cl_2, 4.94.

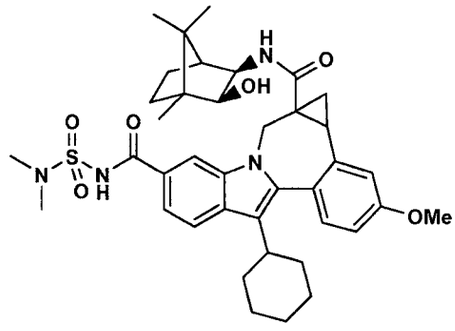
Intermediate 11



Cycloprop[d]indolo[2,1-a][2]benzazepine-1a(2H)-carboxylic acid, 8-cyclohexyl-5-[[[(dimethylamino)sulfonyl]amino]carbonyl]-1,12b-dihydro-11-methoxy-, (+/-)-. To a solution of (+/-) cycloprop[d]indolo[2,1-a][2]benzazepine-1a(2H)-carboxylic acid, 8-cyclohexyl-5-[[[(dimethylamino)sulfonyl]amino]carbonyl]-1,12b-dihydro-11-methoxy-, methyl ester (100 mg, 0.177 mmol) in THF/Methanol mixture (2.0 mL/2.0 mL), 2N NaOH solution (1.0 mL) was added. The reaction mixture was heated at 90°C under microwave conditions for 5 min. It was then concentrated, acidified with 1N HCl solution and extracted with ethyl acetate (2X20 mL). The organic layers were combined, dried ($MgSO_4$), filtered and concentrated. The residue was purified by preparative HPLC to afford the desired product as a light yellow solid, (59 mg, 60% yield). MS m/z 552(MH^+), Retention time: 3.850 min.1H NMR (300 MHz, MeOD) δ ppm 0.25 (m, 0.38 H) 1.14 - 2.22 (m, 11.62 H) 2.69 - 2.98 (m, 2 H) 3.02 (s, 2.28 H)

3.02 (s, 3.72 H) 3.41 (d, J=15.00 Hz, 0.62 H) 3.88 (s, 3 H) 4.01 (d, J=15.00 Hz, 0.38 H) 5.26 (d, J=15.00 Hz, 0.38 H) 5.45 (d, J=14.64 Hz, 0.62 H) 6.94 - 7.02 (m, 1 H) 7.13 (d, J=2.56 Hz, 0.38 H) 7.21 (d, J=2.20 Hz, 0.62 H) 7.26 (d, J=8.42 Hz, 0.62 H) 7.30 (d, J=8.78 Hz, 0.38 H) 7.53 (dd, J=8.42, 1.46 Hz, 0.62 H) 7.61 (dd, J=8.60, 1.65 Hz, 0.38 H) 7.85 (d, J=8.42 Hz, 0.62 H) 7.89 (d, J=8.42 Hz, 0.38 H) 8.10 (s, 0.38 H) 8.28 (d, J=1.46 Hz, 0.62 H).

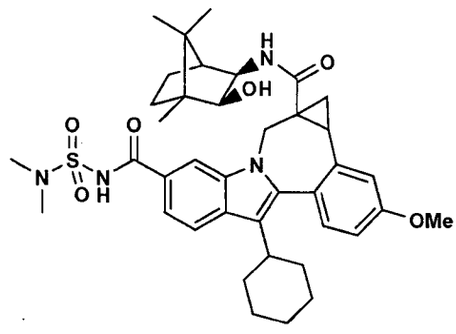
Intermediate 12



Cycloprop[d]indolo[2,1-a][2]benzazepine-1a,5(2H)-dicarboxamide, 8-cyclohexyl-N^5-[(dimethylamino)sulfonyl]-1,12b-dihydro-N^{1a}-[(2R,3S)-3-hydroxy-4,7,7-trimethylbicyclo[2.2.1]hept-2-yl]-11-methoxy-, (1aR)-[partial]-. TBTU (437 mg, 1.36 mmol) and DIPEA (0.95 mL, 5.436 mmol) were added to a solution of (+/-) cycloprop[d]indolo[2,1-a][2]benzazepine-1a(2H)-carboxylic acid, 8-cyclohexyl-5-[[[(dimethylamino)sulfonyl]amino]carbonyl]-1,12b-dihydro-11-methoxy- (500 mg, 0.906 mmol) in DMSO (20.0 mL). The reaction mixture was stirred at rt for 15 min. (2S,3R)-3-Amino-1,7,7-trimethylbicyclo[2.2.1]heptan-2-ol (280 mg, 1.36mmol) was then added and the reaction mixture was stirred at rt overnight. The reaction mixture was quenched with water and acidified with 1N HCl solution. A brown solid separated which was collected by filtration. This material was then fractionated by Preparative HPLC under the following conditions. Column: Waters Sunfire 19mm x 100mm; Solvent A: 10% CH3CN-90% H2O-0.1% TFA; Solvent B: 90% CH3CN-10% H2O-0.1% TFA; Program: Start with 65% solvent B, initial hold time for 5 min, then gradually increase to 90% solvent B in 30 min with flow rate 25 mL/min. Load: 50-60 mg/run.

Cycloprop[d]indolo[2,1-a][2]benzazepine-1a,5(2H)-dicarboxamide, 8-cyclohexyl-N^5-[(dimethylamino)sulfonyl]-1,12b-dihydro-N^{1a}-[(2R,3S)-3-hydroxy-4,7,7-trimethylbicyclo[2.2.1]hept-2-yl]-11-methoxy-, (1aR)- [partial]- elutes before Cycloprop[d]indolo[2,1-a][2]benzazepine-1a,5(2H)-dicarboxamide, 8-cyclohexyl-N^5-[(dimethylamino)sulfonyl]-1,12b-dihydro-N^{1a}-[(2R,3S)-3-hydroxy-4,7,7-trimethylbicyclo[2.2.1]hept-2-yl]-11-methoxy-, (1aS)- *[partial]*- under the HPLC conditions described above. Product obtained as a light yellow solid, 230 mg, 36% yield). MS m/ 703(MH^+), Retention time: 3.936 min. 1H NMR (500 MHz, MeOD) δ ppm 0.14 - 0.24 (m, 2.64 H) 0.51 (s, 2.46 H) 0.72 - 2.21 (m, 20.9 H) 2.49 (m, 0.18 H) 2.62 (m, 0.82 H) 2.85 (m, 0.18 H) 2.96 (m, 0.82 H) 3.03 (s, 6 H) 3.39 (m, 0.82 H) 3.49 - 3.58 (m, 1.64 H) 3.71 - 3.80 (m, 0.36 H) 3.90 (s, 3 H) 4.17 (d, *J*=14.65 Hz, 0.18 H) 5.06 (d, *J*=14.65 Hz, 0.18 H) 5.37 (d, *J*=14.95 Hz, 0.82 H) 6.73 (d, *J*=5.49 Hz, 0.82 H) 6.98 - 7.05 (m, 1 H) 7.08 (d, *J*=4.58 Hz, 0.18 H) 7.10 (d, *J*=2.44 Hz, 0.18 H) 7.21 (d, *J*=2.44 Hz, 0.82 H) 7.31 (d, *J*=8.55 Hz, 0.82 H) 7.34 (d, *J*=8.55 Hz, 0.18 H) 7.59 - 7.64 (m, 1 H) 7.87 - 7.93 (m, 1 H) 7.99 (s, 0.18 H) 8.09 (d, *J*=1.22 Hz, 0.82 H).

Intermediate 13

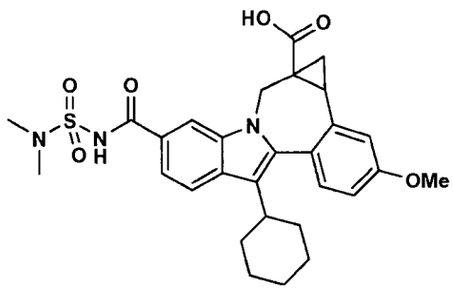


Cycloprop[d]indolo[2,1-a][2]benzazepine-1a,5(2H)-dicarboxamide, 8-cyclohexyl-N^5-[(dimethylamino)sulfonyl]-1,12b-dihydro-N^{1a}-[(2R,3S)-3-hydroxy-4,7,7-trimethylbicyclo[2.2.1]hept-2-yl]-11-methoxy-, (1aS)- [partial]-. TBTU (437 mg, 1.36 mmol) and DIPEA (0.95 mL, 5.436 mmol) were added to a solution of (+/-) cycloprop[d]indolo[2,1-a][2]benzazepine-1a(2H)-carboxylic acid, 8-cyclohexyl-5-[[[(dimethylamino)sulfonyl]amino]carbonyl]-1,12b-dihydro-11-methoxy- (500 mg,

0.906 mmol) in DMSO (20.0 mL). The reaction mixture was stirred at rt for 15 min. Then (2S,3R)-3-amino-1,7,7-trimethylbicyclo[2.2.1]heptan-2-ol (280 mg, 1.36mmol) was added, and the reaction mixture was stirred at rt overnight. The reaction mixture was quenched with water and then acidified with 1N HCl solution. A brown colored solid separated that was collected by filtration. This material was then fractionated by preparative HPLC under the following conditions. Column: Waters Sunfire 19mm x 100mm; Solvent A: 10% CH3CN-90% H2O-0.1% TFA; Solvent B: 90% CH3CN-10% H2O-0.1% TFA; Program: Start with 65% solvent B, initial hold time for 5 min, then gradually increase to 90% solvent B in 30 min with flow rate 25 mL/min. Load: 50-60 mg/run.

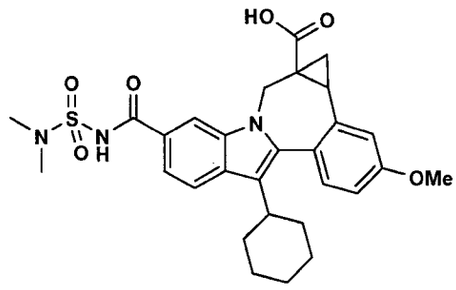
Cycloprop[d]indolo[2,1-a][2]benzazepine-1a,5(2H)-dicarboxamide, 8-cyclohexyl-N^5-[(dimethylamino)sulfonyl]-1,12b-dihydro-N^{1a}-[(2R,3S)-3-hydroxy-4,7,7-trimethylbicyclo[2.2.1]hept-2-yl]-11-methoxy-, (1aS)- [partial]- elutes after cycloprop[d]indolo[2,1-a][2]benzazepine-1a,5(2H)-dicarboxamide, 8-cyclohexyl-N^5-[(dimethylamino)sulfonyl]-1,12b-dihydro-N^{1a}-[(2R,3S)-3-hydroxy-4,7,7-trimethylbicyclo[2.2.1]hept-2-yl]-11-methoxy-, (1aR)- [partial]- under the HPLC conditions described above. Product obtained as a light yellow solid, 215 mg, 34% yield). MS m/ 703(MH^+), Retention time: 4.038 min. 1H NMR (500 MHz, MeOD) δ ppm 0.20 (m, 0.38 H) 0.75 (s, 1.86 H) 0.76 (s, 1.86 H) 0.84 (s, 1.86 H) 0.85 (s, 1.14 H) 0.89 - 2.18 (m, 18.9 H) 2.52 (m, 0.38 H) 2.70 (m, 0.62 H) 2.85 (m, 0.38 H) 2.97 (m, 0.62 H) 3.03 (s, 2.28 H) 3.04 (s, 3.72 H) 3.33 - 3.39 (m, 0.62 H) 3.43 - 3.51 (m, 1.24 H) 3.73 - 3.77 (m, 0.38 H) 3.78 - 3.84 (m, 0.38 H) 3.90 (s, 1.86 H) 3.90 (s, 1.14 H) 4.14 (d, J=14.65 Hz, 0.38 H) 5.11 (d, J=14.65 Hz, 0.38 H) 5.44 (d, J=15.26 Hz, 0.62 H) 6.68 (d, J=4.88 Hz, 0.62 H) 6.96 - 7.03 (m, 1 H) 7.07 (d, J=5.19 Hz, 0.38 H) 7.12 (d, J=2.44 Hz, 0.38 H) 7.23 (d, J=2.14 Hz, 0.62 H) 7.27 (d, J=8.54 Hz, 0.62 H) 7.33 (d, J=8.54 Hz, 0.38 H) 7.55 (dd, J=8.39, 1.68 Hz, 0.62 H) 7.62 (dd, J=8.55, 1.53 Hz, 0.38 H) 7.87 (d, J=8.54 Hz, 0.62 H) 7.91 (d, J=8.55 Hz, 0.38 H) 8.08 (d, J=1.22 Hz, 0.38 H) 8.10 (d, J=1.22 Hz, 0.62 H).

Intermediate 14



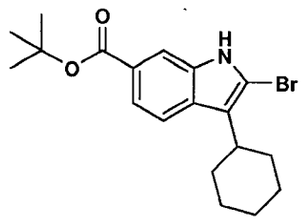
Cycloprop[d]indolo[2,1-a][2]benzazepine-1a(2H)-carboxylic acid, 8-cyclohexyl-5-[[[(dimethylamino)sulfonyl]amino]carbonyl]-1,12b-dihydro-11-methoxy-, (-)-. 10 N NaOH (2.0 mL, 20 mmol) solution and 4 mL of water were added to a solution of cycloprop[d]indolo[2,1-a][2]benzazepine-1a,5(2H)-dicarboxamide, 8-cyclohexyl-N^5-[(dimethylamino)sulfonyl]-1,12b-dihydro-N^{1a}-[(2R,3S)-3-hydroxy-4,7,7-trimethylbicyclo[2.2.1]hept-2-yl]-11-methoxy-, (1aR)-[partial]- (160 mg, 0.228 mmol) in THF/MeOH (7 mL/7 mL). The reaction mixture was heated at 120°C under microwave conditions for 1 hr. It was then concentrated, acidified with conc. HCl solution and extracted with ethyl acetate twice (2X 30 mL). The organic layers were combined, dried ($MgSO_4$), filtered and concentrated in vacuo to an orange oil. The crude product was then purified by Prep. HPLC column to afford the product a light yellow solid, (80 mg, 64% yield). Average specific rotation -130.85°; Solvent MeOH; Wavelength 589 nm; 50 cm cell. MS m/ 552(MH^+), Retention time: 3.760 min. 1H NMR (500 MHz, MeOD) δ ppm 0.27 (m, 0.38 H) 1.14 - 2.22 (m, 11.62 H) 2.76 (m, 0.38 H) 2.80 - 2.92 (m, 1 H) 2.92 - 3.09 (m, 6.62 H) 3.45 (d, J=14.95 Hz, 0.62 H) 3.90 (s, 1.86 H) 3.91 (s, 1.14 H) 4.04 (d, J=15.26 Hz, 0.38 H) 5.28 (d, J=15.26 Hz, 0.38 H) 5.47 (d, J=15.26 Hz, 0.62 H) 6.95 - 7.05 (m, 1 H) 7.15 (d, J=2.75 Hz, 0.38 H) 7.23 (d, J=1.83 Hz, 0.62 H) 7.28 (d, J=8.55 Hz, 0.62 H) 7.33 (d, J=8.54 Hz, 0.38 H) 7.54 (dd, J=8.39, 1.68 Hz, 0.62 H) 7.63 (dd, J=8.55, 1.53 Hz, 0.38 H) 7.86 (d, J=8.55 Hz, 0.62 H) 7.91 (d, J=8.55 Hz, 0.38 H) 8.11 (d, J=1.22 Hz, 0.62 H) 8.29 (d, J=1.22 Hz, 0.38 H).

Intermediate 15



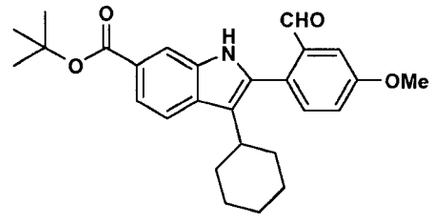
Cycloprop[d]indolo[2,1-a][2]benzazepine-1a(2H)-carboxylic acid, 8-cyclohexyl-5-[[[(dimethylamino)sulfonyl]amino]carbonyl]-1,12b-dihydro-11-methoxy-, (+)-. 10 N NaOH (1.8 mL, 18 mmol) solution and 4 mL of water were added to a solution of cycloprop[d]indolo[2,1-a][2]benzazepine-1a,5(2H)-dicarboxamide, 8-cyclohexyl-N^5-[(dimethylamino)sulfonyl]-1,12b-dihydro-N^{1a}-[(2R,3S)-3-hydroxy-4,7,7-trimethylbicyclo[2.2.1]hept-2-yl]-11-methoxy-, (1aS)-[partial]- (130 mg, 0.185 mmol) in bTHF/MeOH (7 mL/7 mL). The reaction mixture was heated at 120^0C under microwave conditions for 1 hr. It was concentrated, acidified with conc. HCl solution and extracted with ethyl acetate twice (2X 30 mL). The organic layers were combined, dried ($MgSO_4$), filtered and concentrated in vacuo to give an orange oil. The crude product was then purified by Prep. HPLC column to afford the product as a light yellow solid, (68 mg, 67% yield). Average specific rotation + 174.73°; Solvent MeOH; Wavelength 589 nm; 50 cm cell MS m/ 552(MH^+), Retention time: 3.773 min. 1H NMR (500 MHz, MeOD) δ ppm 0.27 (m, 0.38 H) 1.14 - 2.22 (m, 11.62 H) 2.76 (m, 0.38 H) 2.80 - 2.92 (m, 1 H) 2.92 - 3.09 (m, 6.62 H) 3.45 (d, J=14.95 Hz, 0.62 H) 3.90 (s, 1.86 H) 3.91 (s, 1.14 H) 4.04 (d, J=15.26 Hz, 0.38 H) 5.28 (d, J=15.26 Hz, 0.38 H) 5.47 (d, J=15.26 Hz, 0.62 H) 6.95 - 7.05 (m, 1 H) 7.15 (d, J=2.75 Hz, 0.38 H) 7.23 (d, J=1.83 Hz, 0.62 H) 7.28 (d, J=8.55 Hz, 0.62 H) 7.33 (d, J=8.54 Hz, 0.38 H) 7.54 (dd, J=8.39, 1.68 Hz, 0.62 H) 7.63 (dd, J=8.55, 1.53 Hz, 0.38 H) 7.86 (d, J=8.55 Hz, 0.62 H) 7.91 (d, J=8.55 Hz, 0.38 H) 8.11 (d, J=1.22 Hz, 0.62 H) 8.29 (d, J=1.22 Hz, 0.38 H).

Intermediate 16



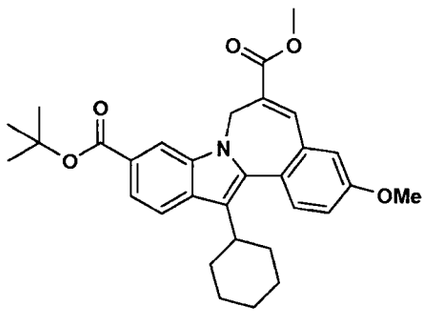
1H-Indole-6-carboxylic acid, 2-bromo-3-cyclohexyl-, 1,1-dimethylethyl ester. To a mechanically stirred solution of 2-bromo-3-cyclohexyl-1H-indole-6-carboxylic acid (80 g, 0.24 m) in dry methylene dichloride(1.2 L) and THF (100 mL) were added activated molecular sieves (4A, 80 g) and silver carbonate (275 g, 0.99 m). The reaction mixture was cooled to 0°C and t-Butyl bromide (142 g, 1.04 m) was added drop wise. The mixture was stirred overnight at rt and monitored by TLC (Hexane-Ethyl acetate 80:20, R_f (Product) = 0.7). If any bromo acid was left unconverted a further 10% of silver carbonate was added and stirring was continued for an addition 2 – 4 h. On completion, the reaction mixture was filtered through a thin bed of celite. The filtrand was washed with methylene dichloride (500 mL). The combined filtrates were concentrated in-vacuo, and the crude product thus obtained was purified by silica gel chromatography: (230 - 400 mesh, eluted with a gradient of ethyl acetate in pet ether 0 – 2%). Homogeneous fractions were combined and evaporated under reduced pressure to give 80 g (85%) of the title compound. HPLC : 90.1% (RT = 6.56 min), Column : C18 BDS, (50X4.6mm), Mobile Phase : Gradient of 0.1% TFA in water : ACN (30 → 100 → 30), Flow rate 0.8 mL / min. LCMS : 99.8% (RT = 4.44 min), Column : Geneis, C18 50X4.6 mm Mobile Phase : Gradient of 0.1% Formic acid in water : ACN (70 → 95 → 70), Flow rate : 0.8 mL / min; M – 1 = 376.5; ^{1}H NMR $CDCl_3$) (400 MHz) δ 1.37 – 1.40 (m, 3H, cyc.Hexyl), 1.62 (s, 9H, t-Bu), 1.80 – 1.94 (two sets of m, 3H, & 4H respectively, cyc.Hexyl part), 2.81 (m, 1H, CH of cyc.Hexyl - benzylic), 7.70 – 7.75 (m, 2H, Indole-$H_{4\&5}$), 8.04 (s, 1H, Indole-H_7), 8.52 (s, 1H, Indole-NH).

Intermediate 17



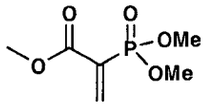
1H-Indole-6-carboxylic acid, 3-cyclohexyl-2-(2-formyl-4-methoxyphenyl)-, 1,1-dimethylethyl ester. tert-Butyl 2-bromo-3-cyclohexyl-1H-indole-6-carboxylate (72 g, 0.19 m) was dissolved in a 1:1 mixture of toluene and ethanol (720 mL) and degasified. LiCl (23.9 g, 0.51 m) was then added, followed by sodium carbonate (720 mL, 1.0 M solution degasified separately,) and Pd-tetrakis (13.1 g, 0.011 m). After stirring for 0.25 h, 2-formyl-4-methoxyphenylboronic acid (41.1 g, 0.22 m) was added and the reaction mixture was heated to 85°C for 4 h. The reaction was then monitored by TLC, (Hexane-Ethyl acetate 80:20, R_f (Product) = 0.55). On completion, the reaction mixture was cooled to rt and water (1.0 L) was added followed by ethyl acetate (1.0 L). The organic layer was washed with brine, and dried and concentrated under vacuum to afford the title compound as a yellow solid. Yield 75 g (74%). HPLC : 99.7% (RT = 6.30 min), Column : C18 BDS (4.6 X 50 mm), SC-307, Mobile Phase : Gradient of 0.1% TFA in water : ACN (30 → 100 → 30), Flow rate 0.8 mL / min. LCMS : 98.0% (RT = 5.28 min), Column : Geneis, C18 (50X4.6 mm), Mobile Phase : Gradient of 0.1% Formic acid in water : ACN (70 → 95 → 70), Flow rate : 0.8 mL / min; M - 1 = 432.2; ^{1}H NMR (DMSO –d_6) (400 MHz) δ 1.40 – 1.48 (m, 3H, cyc.Hexyl), 1.57 (s, 9H, t-Bu), 1.84 – 1.90 (m, 7H, cyc.Hexyl part), 3.09 (m, 1H, CH of cyc.Hexyl - benzylic), 3.84 (s, 3H, OCH_3), 6.55 (d, J = 4 Hz, 1H, aryl $H_{2'}$), 7.06 (d, 1H, aryl $H_{3'}$), 7.08 (s, 1H, aryl $H_{6'}$), 7.23 (d, 1H, Indole-H_5), 7.53 (d, J = 8 Hz, 1H, Indole-H_4), 7.70 – 7.75 (m, 2H, NH + Indole-H_7), 8.06 (s, 1H, CHO).

Intermediate 18



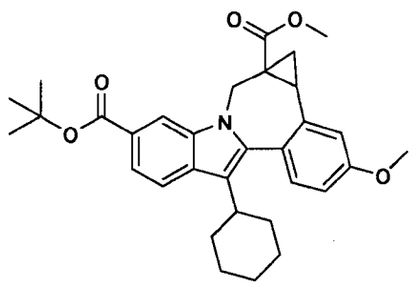
7H-Indolo[2,1-a][2]benzazepine-6,10-dicarboxylic acid, 13-cyclohexyl-, 10-(1,1-dimethylethyl) 6-methyl ester. tert-Butyl 3-cyclohexyl-2-(2-formyl-4-methoxyphenyl)-1H-indole-6-carboxylate (62.5 g, 0.144 m) was dissolved in dry DMF (1.2 L) and stirred mechanically. Cesium carbonate (84 g, 0.17 m) and methyl 2-(dimethoxyphosphoryl)acrylate (65 – 70% GC pure, 56.2 g, 0.18 m) were then added and the reaction mixture was heated to 65°C for 4h, and the reaction was monitored by TLC (Hexane-Ethyl acetate 80:20, R_f (Product) = 0.7). On completion, the mixture was cooled to rt, then quenched with water (1.0 L). A yellow solid precipitated, which was collected by filtration and air dried. This material was then slurried in methanol, filtered, and dried under vacuum to give the product as a yellow powder, (70 g, 90%). HPLC : 99.1% (RT = 6.45 min), Column : C18 BDS (4.6 X 50 mm), Mobile Phase : Gradient of 0.1% TFA in water : ACN (30 → 100 → 30), Flow rate 0.8 mL / min. LCMS : 100% (RT = 7.00 min), Column : Geneis, C18 (50X4.6 mm), Mobile Phase : Gradient of 0.1% Formic acid in water : ACN (70 → 95 → 70), Flow rate : 0.8 mL / min; M + 1 = 502.2; ^{1}H NMR ($CDCl_3$) (400 MHz) δ 1.10 – 1.30 (m, 3H, cyc.Hexyl), 1.64 (s, 9H, t-Bu), 1.77 – 2.07 (m, 7H, cyc.Hexyl part), 2.80 (m, 1H, CH of cyc.Hexyl - benzylic), 3.84 (s, 3H, OCH_3), 3.93 (s, 3H, $COOCH_3$), 4.15 & 5.65 (two br. peak., 1H each, allylic CH_2), 6.95 (s, 1H, aryl $H_{6'}$), 7.01 (d, 1H, aryl $H_{2'}$), 7.53 (d, J = 8 Hz, 1H, aryl $H_{3'}$), 7.70 (d, J = 4 Hz, 1H, Indole-H_5), 7.84 (s + d, 2H, olefinic H + Indole-H_4), 8.24 (s, 1H, indole – H_7); ^{13}C NMR ($CDCl_3$) (100.0 MHz) δ 166.92, 165.71, 158.96, 142.28, 136.47, 13.50, 134.61, 132.43, 132.01, 129.73, 124.78, 124.68, 120.33, 119.39, 119.04, 115.62, 115.05, 111.27, 80.27, 55.49, 52.50, 39.09, 36.81, 33.40, 28.38, 27.15, 26.28.

Intermediate 19



2-Propenoic acid, 2-(dimethoxyphosphinyl)-, methyl ester. To a 5 L four necked round bottom flask equipped with a mechanical stirrer, a condenser, a temperature controller and a N2 inlet , was charged paraformaldehyde (40.5 g, 1.35 mol), MeOH (2 L) and piperidine (2 mL). The reaction mixture was heated to reflux under N2 for 3 h. After cooling to 50 oC, 2-(dimethoxyphosphoryl)acetate (150 g, 0.824 mol) was added in one portion. The reaction mixture was continued to reflux for 18 h. After cooling to rt, the reaction solution was concentrated in vacuo to give a clear colorless oil. The above oil was dissolved in dry toluene (1 L) in a 3 L four necked round bottom flask equipped a temperature controller, a N_2 inlet, a magnetic stirrer and a Dean-Stark apparatus. To the solution was added $TsOH.H_2O$ (5.2 g). The reaction mixture was then refluxed azeotropically to remove methanol for 18 h. After cooling to rt, the solution was concentrated in vacuo to give a yellow oil which was vacuum distilled at 150 – 155 oC /0.2 mmHg to afford the product as a colorless oil (135.0 g). Purity, 90% based on 1H NMR. ^{1}H NMR (CDCl3, 300 MHz) δ 7.0 (dd, J = 42.4 and 1.5 Hz, 1H), 6.73 (dd, J = 20.5 and 1.8 Hz, 1H), 3.80 (s, 6H), 3.76 (s, 3H).

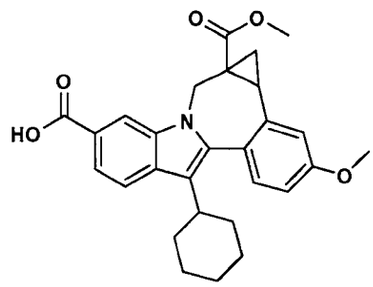
Intermediate 20



Cycloprop[d]indolo[2,1-a][2]benzazepine-1a,5(2H)-dicarboxylic acid, 8-cyclohexyl-1,12b-dihydro-11-methoxy-, 5-(1,1-dimethylethyl) 1a-methyl ester, (+/-). Sodium hydride (96 mg, 4 mmol) was added to a stirred suspension of trimethylsulfoxonium chloride (567 mg, 4.4 mmol) in anhydrous DMSO (10 mL) under nitrogen. The resultant mixture was stirred at rt for 30-45 min and then neat 7H-indolo[2,1-a][2]benzazepine-6,10-dicarboxylic acid, 13-cyclohexyl-3-methoxy-, 10-(1,1-dimethylethyl) 6-methyl ester (1.0, 2 mmol) was added in small portions. The suspension was diluted with DMSO (5 mL) and heated at 50 ^{0}C for 3-4 h. The reaction mixture was allowed to cool to rt and water was added. A solid separated, which was collected by filtration and washed with water and then air dried overnight to afford 1.15 g of crude product. This material was purified by flash column chromatography (silica gel, 3% MeOH in DCM) to provide pure title compound (0.96 g): LC/MS: Retention time 3.816 min; m/e 516 (MH^+). ^{1}H NMR (400 MHz, $CDCl_3$): The product was observed to exist as inter-converting rotamers, as evidenced from the compound's NMR spectrum.

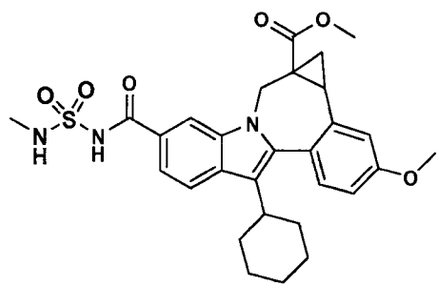
The following procedure is an example of a method to effect the resolution of racemic cycloprop[d]indolo[2,1-a][2]benzazepine-1a,5(2H)-dicarboxylic acid, 8-cyclohexyl-1,12b-dihydro-11-methoxy-, 5-(1,1-dimethylethyl) 1a-methyl ester, (+/-). A sample of cycloprop[d]indolo[2,1-a][2]benzazepine-1a,5(2H)-dicarboxylic acid, 8-cyclohexyl-1,12b-dihydro-11-methoxy-, 5-(1,1-dimethylethyl) 1a-methyl ester, (+/-)- was dissolved in a mixture of isopropanol and acetonitrile (8:2) to give a final concentration of 20mg/mL. This mixture was injected on a preparative chiral SFC chromatography system using the following conditions: Chiralcel OJ-H column, 4.6 x 250mm, 5μm; Mobile Phase: 8% MeOH in CO_2; Temp: 35 °C; Flow rate: 2 mL/min for 16 min; UV monitored @ 260nm; Injection: 5μL of ~20.0mg/mL in IPA:ACN (8:2).

Intermediate 21



Cycloprop[d]indolo[2,1-a][2]benzazepine-1a,5(2H)-dicarboxylic acid, 8-cyclohexyl-1,12b-dihydro-11-methoxy-, 1a-methyl ester, (+/-)-. TFA (5 mL) was added to a solution of (+/-) 8-Cyclohexyl-1,1a,2,12b-tetrahydro-11-methoxy-1a-(methoxycarbonyl)-cycloprop[d]indolo[2,1-a][2]benzazepine-5-carboxylic acid, tert-butyl ester (515 mg, 1 mmol) in anhydrous DCM (10 mL). The resultant solution was stirred at rt for approximately 8 to 12 hr. The reaction was then evaporated to dryness to afford the title compound (0.47g, 100%). LC/MS: Retention time 2.245 min; m/e 460 (MH^+). ^1H NMR (400 MHz, $CDCl_3$): From the compounds NMR spectrum, the product was observed to exist as a mixture of interconverting rotamers.

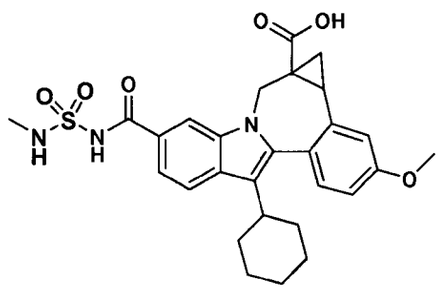
Intermediate 22



Cycloprop[d]indolo[2,1-a][2]benzazepine-1a(2H)-carboxylic acid, 8-cyclohexyl-1,12b-dihydro-11-methoxy-5-[[[(methylamino)sulfonyl]amino]carbonyl]-, methyl ester. A solution of 8-Cyclohexyl-1,1a,2,12b-tetrahydro-11-methoxy-1a-(methoxycarbonyl)-

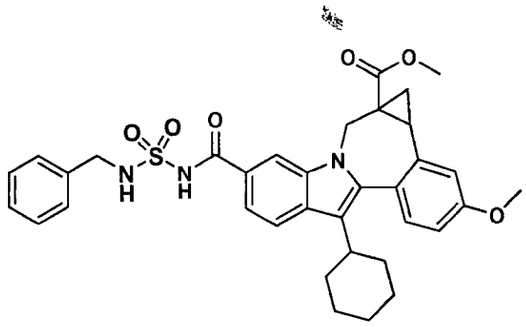
cycloprop[d]indolo[2,1-a][2]benzazepine-5-carboxylic acid (140 mg, 0.31 mmol) and CDI (64 mg, 0.40 mmol) in THF (3 mL) was stirred for 1 hr at 60 °C. N-methylsulfamide (68 mg, 0.62 mmol) and DBU (71.6 mg, 0.47 mmol) were added and the mixture was stirred at 60 °C overnight. The reaction was then poured into cold water, acidified with dilute hydrochloric acid and extracted into ethyl acetate. The extracts were washed sequentially with dilute hydrochloric acid (0.1 N), and brine, and then dried (anhy. sodium sulfate), filtered and evaporated to provide the title compound as a brown solid. ESI-MS m/e 552 (MH^+). This material was used without further purification.

Intermediate 23



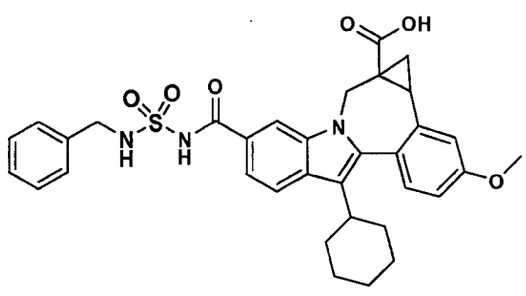
Cycloprop[d]indolo[2,1-a][2]benzazepine-1a(2H)-carboxylic acid, 8-cyclohexyl-1,12b-dihydro-11-methoxy-5-[[[(methylamino)sulfonyl]amino]carbonyl]-. Cycloprop[d]indolo[2,1-a][2]benzazepine-1a(2H)-carboxylic acid, 8-cyclohexyl-5-[[[(methylamino)sulfonyl]amino]carbonyl]-1,12b-dihydro-11-methoxy-, methyl ester was dissolved in THF, MeOH mixture (2 mL,2 mL). 2.5 M NaOH (aq.) (1.2 mL, 3 mmol) was then added and the reaction was shaken at 22 °C for 2 hr. The solution was then neutralized with 1M HCl (aq.) (3 mL) and concentrated to remove the organic solvents. The residue was slurried with H_2O and the solids were collected by filtration, washed with H_2O and dried to yield compound the title compound (160 mg, 0.30 mmol). ESI-MS m/e 538 (MH^+). This material was used without further purification.

Intermediate 24



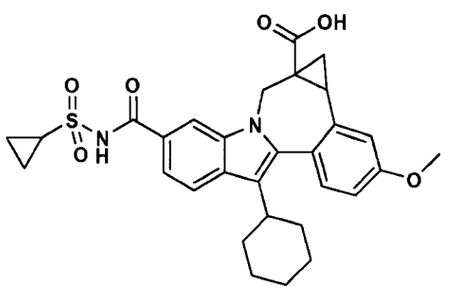
Cycloprop[d]indolo[2,1-a][2]benzazepine-1a(2H)-carboxylic acid, 8-cyclohexyl-5-[[[(benzylamino)sulfonyl]amino]carbonyl]-1,12b-dihydro-11-(methoxy)-12-(methoxy)-, methyl ester, (+/-)-. A solution of (+/-) 8-cyclohexyl-1,1a,2,12b-tetrahydro-11-methoxy-1a-(methoxycarbonyl)-cycloprop[d]indolo[2,1-a][2]benzazepine-5-carboxylic acid (200 mg, 0.44 mmol) and CDI (92 mg, 0.57 mmol) in THF (5 mL) was stirred for 1 hr at 60 °C. N-benzylsulfamide (164 mg, 0.88 mmol) and DBU (100 mg, 0.66 mmol) were then added and the resultant mixture was stirred at 60 °C overnight. The reaction was then poured into cold water, acidified with dilute hydrochloric acid and extracted into ethyl acetate. The organic phase was washed hydrochloric acid (0.1 N), brine and dried (sodium sulfate) and evaporated in vacuo to provide the title compound as a brown solid. ESI-MS m/e 628 (MH^+).

Intermediate 25



Cycloprop[d]indolo[2,1-a][2]benzazepine-1a(2H)-carboxylic acid, 8-cyclohexyl-1,12b-dihydro-11-methoxy-5-[[[[(phenylmethyl)amino]sulfonyl]amino]carbonyl]-, (+/-)-. The title compound was prepared using a similar procedure to that described for cycloprop[d]indolo[2,1-a][2]benzazepine-1a(2H)-carboxylic acid, 8-cyclohexyl-5-[[[(methylamino)sulfonyl]amino]carbonyl]-1,12b-dihydro-11-methoxy-cycloprop[d]indolo[2,1-a][2]benzazepine-1a(2H)-carboxylic acid starting from (+/-) 8-cyclohexyl-1,1a,2,12b-tetrahydro-11-methoxy-1a-(methoxycarbonyl)-cycloprop[d]indolo[2,1-a][2]benzazepine-5-carboxylic acid. ESI-MS m/e 613 (MH+), 1H NMR (500 MHz, MeOD) δ ppm 1.22 - 2.20 (m, 13 H) 3.27 - 3.31 (m, 1 H) 3.47 (d, J=14.95 Hz, 0.6 H) 3.92 (d, J=2.44 Hz, 3 H) 4.04 (d, 0.4 H) 4.31 (d, J=2.75 Hz, 2 H) 5.24 (d, 0.4 H) 5.48 (d, 0.6 H) 7.02 (d, 1 H) 7.17 (d, J=2.75 Hz, 1 H) 7.19 - 7.35 (m, 5 H) 7.39 (t, J=7.48 Hz, 2 H) 7.45 - 7.52 (m, 1 H) 7.80 (d, J=1.53 Hz, 0.4 H) 7.85 (dd, J=8.39, 6.87 Hz, 1 H) 8.22 (d, J=1.53 Hz, 0.6 H).

Intermediate 26

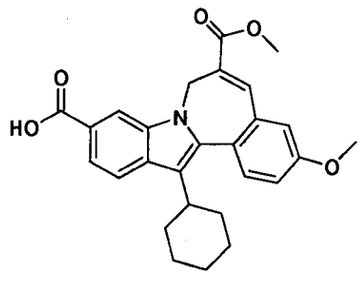


Cycloprop[d]indolo[2,1-a][2]benzazepine-1a(2H)-carboxylic acid, 8-cyclohexyl-5-[[(cyclopropylsulfonyl)amino]carbonyl]-1,12b-dihydro-11-methoxy-, (+/-)-. A mixture of (+/-) 8-cyclohexyl-1,1a,2,12b-tetrahydro-11-methoxy-1a-(methoxycarbonyl)-cycloprop[d]indolo[2,1-a][2]benzazepine-5-carboxylic acid (1 equiv), and carbonyldiimidazole (1.5 equiv) in anhydrous THF was heated at 50 ^{0}C for 30 min and allowed to cool to rt. Then 1 equiv of cyclopropanesulfonamide and 1,8-diazabicyclo[5.4.0]undec-7-ene (2 equiv) were added consecutively. The resultant mixture was stirred at rt overnight. After acidic aqueous workup, the isolated crude product was purified by prep. HPLC. The

intermediate ester was then hydrolyzed using 1N NaOH in THF-MeOH to afford the title compound. LC/MS: Retention time: 2.030 min; m/e 549 (MH^+). ^1H NMR (400 MHz, $CDCl_3$): The product was observed to exist as inter-converting rotamers, as evidenced from the compound's NMR spectrum.

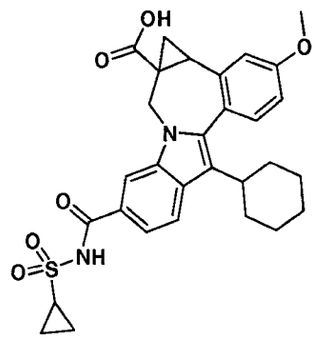
Intermediates 26 -37 use the experimental procedures that follow until otherwise noted. LCMS data: Stop time: Gradient time + 1 minute; Starting conc: 0% B unless otherwise noted; Ending conc: 100% B unless otherwise noted; Eluent A: 5% CH_3CN / 95% H_2O with 10mM NH_4OAc (for columns A, D and E); 10 % MeOH / 90 % H_2O with 0.1% TFA (for columns B and C); Eluent B: 95% CH_3CN / 5% H_2O with 10mM NH_4OAc (for columns A, D and E); 90 % MeOH / 10 % H_2O with 0.1% TFA (for columns B and C); Column A: Phenomenex 10µ 4.6 x 50 mm C18; Column B: Phenomenex C18 10µ 3.0 x 50 mm; Column C: Phenomenex 4.6 x 50 mm C18 10µ; Column D: Phenomenex Lina C18 5µ 3.0 x 50 mm; Column E: Phenomenex 5µ 4.6 x 50 mm C18; Preparative HPLC data: Conditions for H_2O/CH_3CN with 10mM NH_4OAc buffer; Gradient: Linear over 20 min. unless otherwise noted; Starting conc: 15% B unless otherwise noted; Ending conc: 100% B; Eluent A: 5% CH_3CN / 95% H_2O with 10mM NH_4OAc; Eluent B:95% CH_3CN / 5% H_2O with 10mM NH_4OAc; Column: Sunfire Prep C_{18} OBD 5µ 30 x 100 mm; Conditions for H_2O/MeOH with 0.1% TFA buffer; Gradient: Linear over 20 min. unless otherwise noted; Starting conc: 30% B unless otherwise noted; Ending conc: 100% B; Eluent A: 10 % MeOH / 90 % H_2O with 0.1% TFA; Eluent B: 90 % MeOH / 10 % H_2O with 0.1% TFA; Column: phenomenex 21 x 100 mmC18 H_2O.

Intermediate 26



13-Cyclohexyl-3-methoxy-6-(methoxycarbonyl)-7H-indolo[2,1-a][2]benzazepine-10-carboxylic acid. Trifluoroacetic acid (30 mL) was added dropwise to a stirring slurry of 10-tert-butyl 6-methyl 13-cyclohexyl-3-methoxy-7*H*-indolo[2,1-*a*][2]benzazepine-6,10-dicarboxylate (10 g, 20 mmol) in dichloroethane (30 mL) under N_2. The clear dark green solution was stirred at rt for 2.5h, concentrated to dryness and stirred with EtOAc (100 mL) overnight. The solids were collected by filtration, washed with EtOAc and Et_2O to yield 13-cyclohexyl-3-methoxy-6-(methoxycarbonyl)-7*H*-indolo[2,1-*a*][2]benzazepine-10-carboxylic acid (8.35 g, 18.8 mmol, 94%) was as a yellow solid which was used without further purification. ^{1}HNMR (300 MHz, $CDCl_3$) δ 1.13 - 2.16 (m, 10H), 2.74 - 2.88 (m, 1H), 3.84 (s, 3H), 3.89 (s, 3H), 4.06 - 4.29 (m, 1H), 5.54 - 5.76 (m, 1H), 6.98 (d, J = 2.6 Hz, 1H), 7.08 (dd, J = 8.4, 2.6 Hz, 1H), 7.52 (d, J = 8.4 Hz, 1H), 7.78 (dd, J = 8.8, 1.1 Hz, 1H), 7.80 (s, 1H), 7.86 (d, J = 8.8 Hz, 1H), 8.34 (d, J = 1.1Hz, 1H). LCMS: m/e 446 $(M+H)^+$, ret time 3.21 min, column B, 4 minute gradient.

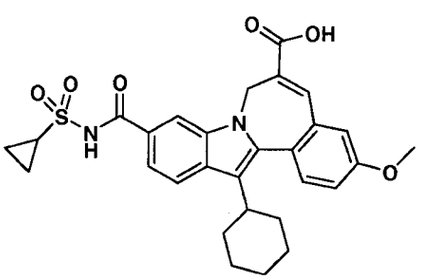
Intermediate 27



Methyl 13-cyclohexyl-10-((cyclopropylsulfonyl)carbamoyl)-3-methoxy-7H-indolo[2,1-a][2]benzazepine-6-carboxylate. 1,1'-Carbonyldiimidazole (1.82 g, 11.2 mmol) was added to a slurry of 13-cyclohexyl-3-methoxy-6-(methoxycarbonyl)-7*H*-indolo[2,1-*a*][2]benzazepine-10-carboxylic acid (3.85 g, 8.65 mmol) in THF (15 mL). The reaction mixture was heated at 60 °C for 1.5h, cooled to rt, treated with cyclopropanesulfonamide (1.36 g, 11.2 mmol), stirred 10 min and then treated with the dropwise addition of a solution of DBU (2.0 mL, 13 mmol) in THF (3 mL). The

reaction mixture was stirred at rt overnight, diluted with EtOAc (100 mL) and washed with H_2O (~30 mL), 1N HCl (aq.) (2 x 50 mL) and brine (~30 mL). The combined aqueous layers were extracted with EtOAc (100 mL) and the organic layer was washed with 1N HCl (aq.) (~50 mL). The combined organic layers were washed with brine (~30 mL), dried ($MgSO_4$), filtered and concentrated. The residue was stirred with Et_2O (~100 mL) for 2h and the solids were collected by filtration, rinsed with Et_2O and dried to yield methyl 13-cyclohexyl-10-((cyclopropylsulfonyl)carbamoyl)-3-methoxy-7*H*-indolo[2,1-*a*][2]benzazepine-6-carboxylate (4.24 g, 7.73 mmol, 89%) as a pale yellow solid which was used without further purification. ^{1}HNMR (300 MHz, $CDCl_3$) δ 1.08 - 2.13 (m, 14H), 2.73 - 2.87 (m, 1H), 3.13 - 3.24 (m, 1H), 3.82 (s, 3H), 3.89 (s, 3H), 4.04 - 4.27 (m, 1H), 5.50 - 5.71 (m, 1H), 6.98 (d, J = 2.6 Hz, 1H), 7.08 (dd, J = 8.8, 2.6 Hz, 1H), 7.44 (dd, J = 8.4, 1.1 Hz, 1H), 7.50 (d, J = 8.8 Hz, 1H), 7.80 (s, 1H), 7.86 (d, J = 8.4 Hz, 1H), 8.11 (br s, 1H), 8.78 (br s, 1H). LCMS: m/e 549 $(M+H)^+$, ret time 3.79 min, column B, 4 minute gradient.

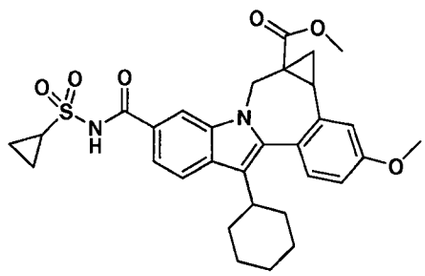
Intermediate 28



13-Cyclohexyl-10-((cyclopropylsulfonyl)carbamoyl)-3-methoxy-7H-indolo[2,1-a][2]benzazepine-6-carboxylic acid. Methyl 13-cyclohexyl-10-((cyclopropylsulfonyl)carbamoyl)-3-methoxy-7*H*-indolo[2,1-*a*][2]benzazepine-6-carboxylate (1.0 g, 1.8 mmol) was dissolved into MeOH//THF (1:1, 24 mL) and treated with 1M aqueous NaOH (5 mL). The reaction mixture was stirred and heated at 60 °C for 1.5h and cooled to rt. The clear solution was neutralized with 1M aqueous HCl (5 mL) and concentrated to remove organic solvents. The resultant solids were collected by filtration, washed with H_2O and dried under vacuum to yield

13-cyclohexyl-10-((cyclopropylsulfonyl)carbamoyl)-3-methoxy-7*H*-indolo[2,1-*a*][2]benzazepine-6-carboxylic acid (1.0 g, 1.7 mmol, 94%) as a bright yellow solid (with 0.75 equiv. of THF) which was used without further purification. ^{1}HNMR (300 MHz, CD_3OD) δ 1.11 - 2.24 (m, 17H, 3H from THF), 2.81 - 2.96 (m, 1H), 3.17 - 3.28 (m, 1H), 3.69 - 3.79 (m, 3H, from THF), 3.94 (s, 3H), 4.07 - 4.33 (m, 1H), 5.55 - 5.81 (m, 1H), 7.14 - 7.24 (m, 2H), 7.55 - 7.64 (m, 2H), 7.88 - 7.94 (m, 2H), 8.20 (br s, 1H). LCMS: m/e 535 $(M+H)^+$, ret time 3.73 min, column B, 4 minute gradient.

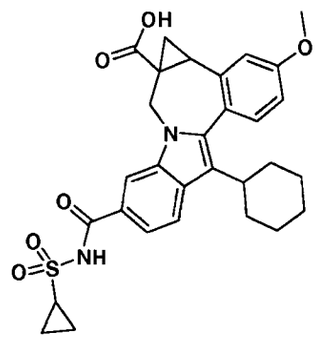
Intermediate 29



Methyl 8-cyclohexyl-5-((cyclopropylsulfonyl)carbamoyl)-11-methoxy-1,12b-dihydrocyclopropa[d]indolo[2,1-a][2]benzazepine-1a(2H)-carboxylate. To slurry of sodium hydride (60% dispersion in mineral oil, 370 mg, 9.2 mmol) in DMSO (8 mL) stirring under N_2 was added trimethylsulfoxonium iodide (2.03 g, 9.2 mmol). The reaction mixture was stirred for 45 min and then methyl 13-cyclohexyl-10-((cyclopropylsulfonyl)carbamoyl)-3-methoxy-7*H*-indolo[2,1-*a*][2]benzazepine-6-carboxylate (2.2 g, 4.0 mmol) in DMSO (5 mL) was added (flask rinsed with DMSO (2 x 3 mL)). The reaction mixture was stirred 1h, poured into 0.25N HCl (100 mL), and extracted with EtOAc (150 mL). The organic layer was washed with brine (20 mL) and the combined aqueous layers were extracted with EtOAc (100 mL). The combine organic layers were washed with brine (~20 mL), dried ($MgSO_4$), filtered and concentrated to dryness. The residue was stirred with EtOAc/Et_2O (1:3, 50 mL) and the solids were removed by filtration. The motherliquor was concentrated and dried under high vacuum to yield methyl 8-cyclohexyl-5-((cyclopropylsulfonyl)carbamoyl)-11-methoxy-1,12b-dihydrocyclopropa[*d*]indolo[2,1-*a*][2]benzazepine-1a(2*H*)-carboxylate (1.92 g, 3.4

mmol, 85%) as a yellow solid which was used without further purification. Presents as a ~2:1 mixture of rotamers or atrope isomers. ^{1}HNMR (300 MHz, CD_3OD) δ 0.19 - 0.26 (m, 0.4H), 0.78 - 2.19 (m, 15.6H), 2.64 - 3.02 (m, 2H), 3.16 - 3.28 (m, 1H), 3.41 (d, J = 15.0 Hz, 0.6H), 3.51 (s, 1.8H), 3.80 (s, 1.2H), 3.88 (s, 3H), 4.00 (d, J = 15.0 Hz, 0.4H), 5.22 (d, J = 15.0 Hz, 0.4H), 5.42 (d, J = 15.0 Hz, 0.6H), 6.93 - 7.01 (m, 1H), 7.12 (d, J = 2.6 Hz, 0.4H), 7.19 (d, J = 2.6 Hz, 0.6H), 7.25 (d, J = 8.8 Hz, 0.6H), 7.29 (d, J = 8.8 Hz, 0.4H), 7.55 (dd, J = 8.8, 1.5 Hz, 0.6H), 7.63 (dd, J = 8.8, 1.5 Hz, 0.4H), 7.85 (d, J = 8.8 Hz, 0.6H), 7.88 (d, J = 8.8 Hz, 0.4H), 8.08 (d, J = 1.5 Hz, 0.4H), 8.31 (d, J = 1.5 Hz, 0.6H). LCMS: m/e 563 $(M+H)^+$, ret time 3.75 min, column B, 4 minute gradient.

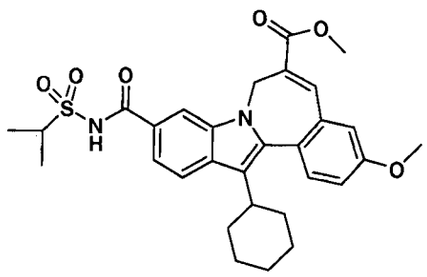
Intermediate 30



8-Cyclohexyl-5-((cyclopropylsulfonyl)carbamoyl)-11-methoxy-1,12b-dihydrocyclopropa[d]indolo[2,1-a][2]benzazepine-1a(2H)-carboxylic acid. Methyl 8-cyclohexyl-5-((cyclopropylsulfonyl)carbamoyl)-11-methoxy-1,12b-dihydrocyclopropa[*d*]indolo[2,1-*a*][2]benzazepine-1a(2*H*)-carboxylate (1.92 g, 3.41 mmol) was dissolved into MeOH//THF (1:1, 40 mL) and treated with 1M aqueous NaOH (8 mL). The reaction mixture was stirred and heated at 60 °C for 2h and cooled to rt. The clear solution was neutralized with 1M aqueous HCl (8 mL) and concentrated to remove organic solvents. The resultant solids were collected by filtration, washed with H_2O and dried under vacuum to yield 8-cyclohexyl-5-((cyclopropylsulfonyl)carbamoyl)-11-methoxy-1,12b-dihydrocyclopropa[*d*]indolo[2,1-*a*][2]benzazepine-1a(2*H*)-carboxylic acid (1.66 g,

3.03 mmol, 89%) as a yellow powder which was used without further purification. Presents as a 1:1 mixture of rotamers or atrope isomers. ^{1}HNMR (300 MHz, $CDCl_3$) δ 0.32 (t, J = 6.2 Hz, 0.5H), 0.71 - 2.12 (m, 15.5H), 2.61 - 2.94 (m, 2H), 3.16 - 3.27 (m, 1H), 3.41 (d, J = 15.0 Hz, 0.5H), 3.82 (s, 1.5H), 3.86 (s, 1.5H), 3.99 (d, J = 15.0 Hz, 0.5H), 5.28 (d, J = 15.0 Hz, 0.5H), 5.49 (d, J = 15.0 Hz, 0.5H), 6.85 (dd, J = 8.4, 2.6 Hz, 0.5H), 6.91 (dd, J = 8.4, 2.6 Hz, 0.5H), 6.96 (d, J = 2.6 Hz, 0.5H), 7.08 (d, J = 2.6 Hz, 0.5H), 7.19 (d, J = 8.4 Hz, 0.5H), 7.24 (d, J = 8.4 Hz, 0.5H), 7.61 (d, J = 8.4 Hz, 0.5H), 7.67 (d, J = 8.4 Hz, 0.5H), 7.83 (d, J = 8.4 Hz, 0.5H), 7.85 (d, J = 8.4 Hz, 0.5H), 8.06 (s, 0.5H), 8.35 (s, 0.5H), 9.31 - 10.35 (m, 1H). LCMS: m/e 547 $(M-H)^-$, ret time 2.06 min, column A, 4 minute gradient.

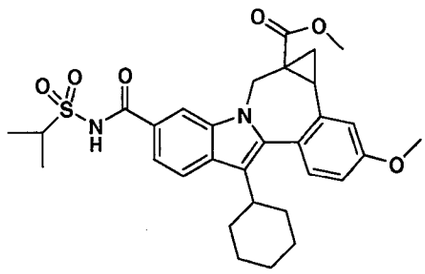
Intermediate 31



Methyl 13-cyclohexyl-10-((isopropylsulfonyl)carbamoyl)-3-methoxy-7H-indolo[2,1-a][2]benzazepine-6-carboxylate. 1,1'-Carbonyldiimidazole (262 mg, 1.62 mmol) was added to a slurry of 13-cyclohexyl-3-methoxy-6-(methoxycarbonyl)-7*H*-indolo[2,1-*a*][2]benzazepine-10-carboxylic acid (603 mg, 1.36 mmol) in THF (3 mL). The reaction mixture was heated at 60 °C for 1.5h, cooled to rt, treated with propane-2-sulfonamide (200 mg, 1.62 mmol), stirred 10 min and then treated with the dropwise addition of a solution of DBU (0.27 mL, 1.8 mmol) in THF (0.75 mL). The reaction mixture was stirred at rt overnight, diluted with EtOAc (15 mL) and washed with H_2O (~5 mL), 1N HCl (aq.) (2 x 10 mL) and brine (~5 mL). The combined aqueous layers were extracted with EtOAc (15 mL) and the organic layer was washed with 1N HCl (aq.) (~10 mL). The combined organic layers were washed with brine (~5 mL), dried ($MgSO_4$), filtered and concentrated. The residue was stirred with Et_2O (~15 mL) for 2h and the solids were collected by filtration, rinsed

with Et_2O and dried to yield methyl 13-cyclohexyl-10-((isopropylsulfonyl)carbamoyl)-3-methoxy-7*H*-indolo[2,1-*a*][2]benzazepine-6-carboxylate (640 mg, 1.2 mmol, 85%) as a bright yellow solid which was used without further purification. ^{1}HNMR (300 MHz, $CDCl_3$) δ 1.12 - 2.13 (m, 10H), 1.47 (d, J = 7.0 Hz, 6H), 2.73 - 2.86 (m, 1H), 3.82 (s, 3H), 3.89 (s, 3H), 4.06 - 4.26 (m, 1H), 4.09 (septet, J = 7.0 Hz, 1H), 5.51 - 5.71 (m, 1H), 6.98 (d, J = 2.6 Hz, 1H), 7.08 (dd, J = 8.4, 2.6 Hz, 1H), 7.44 (dd, J = 8.4, 1.5 Hz, 1H), 7.50 (d, J = 8.4 Hz, 1H), 7.80 (s, 1H), 7.87 (d, J = 8.4 Hz, 1H), 8.10 (d, J = 1.5 Hz, 1H), 8.57 (s, 1H). LCMS: m/e 551 $(M+H)^+$, ret time 3.87 min, column B, 4 minute gradient.

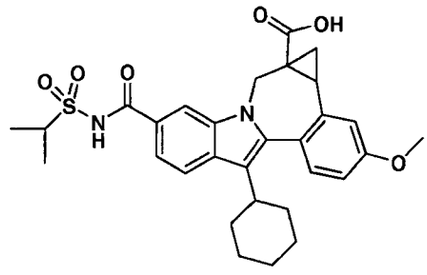
Intermediate 32



Methyl 8-cyclohexyl-5-((isopropylsulfonyl)carbamoyl)-11-methoxy-1,12b-dihydrocyclopropa[d]indolo[2,1-a][2]benzazepine-1a(2H)-carboxylate. To slurry of sodium hydride (60% dispersion in mineral oil, 97 mg, 2.4 mmol) in DMSO (2 mL) stirring under N_2 was added trimethylsulfoxonium iodide (530 g, 2.4 mmol). The reaction mixture was stirred for 45 min and then methyl 13-cyclohexyl-10-((isopropylsulfonyl)carbamoyl)-3-methoxy-7*H*-indolo[2,1-*a*][2]benzazepine-6-carboxylate (578 g, 1.05 mmol) in DMSO (1.5 mL) was added (flask rinsed with DMSO (2 x 0.75 mL)). The reaction mixture was stirred 1h, poured into 0.25N HCl (25 mL), and extracted with EtOAc (40 mL). The organic layer was washed with brine (10 ml) and the combined aqueous layers were extracted with EtOAc (25 mL). The combine organic layers were washed with brine (~10 mL), dried ($MgSO_4$), filtered and concentrated to dryness. The residue was stirred with EtOAc/Et_2O (1:4, 10 mL) and the solids were removed by filtration. The motherliquor was concentrated and dried under high vacuum to yield methyl 8-cyclohexyl-5-

((isopropylsulfonyl)carbamoyl)-11-methoxy-1,12b-dihydrocyclopropa[*d*]indolo[2,1-*a*][2]benzazepine-1a(2*H*)-carboxylate (620 mg, 1.0 mmol, quant.) as a yellow solid which was used without further purification. Presents as a ~2:1 mixture of rotamers or atrope isomers. ^{1}HNMR (300 MHz, $CDCl_3$) δ 0.32 - 0.39 (m, 0.4H), 0.77 - 2.09 (m, 17.6H), 2.60 - 2.96 (m, 2H), 3.41 (d, *J* = 15.0 Hz, 0.6H), 3.53 (s, 1.8H), 3.79 (s, 1.2H), 3.87 (s, 3H), 4.02 - 4.14 (m, 1.4H), 5.14 (d, *J* = 15.0 Hz, 0.4H), 5.39 (d, *J* = 15.0 Hz, 0.6H), 6.89 (dd, *J* = 8.4, 2.6 Hz, 0.4H), 6.91 (dd, *J* = 8.4, 2.6 Hz, 0.6H), 7.00 (d, *J* = 2.6 Hz, 0.4H), 7.11 (d, *J* = 2.6 Hz, 0.6H), 7.23 (d, *J* = 8.4 Hz, 0.6H), 7.25 (d, *J* = 8.4 Hz, 0.4H), 7.38 (dd, *J* = 8.4, 1.5 Hz, 0.6H), 7.43 (dd, *J* = 8.4, 1.5 Hz, 0.4H), 7.83 (d, *J* = 8.4 Hz, 0.6H), 7.86 (d, *J* = 8.4 Hz, 0.4H), 7.96 (d, *J* = 1.5 Hz, 0.4H), 8.20 (d, *J* = 1.5 Hz, 0.6H), 8.39 (s, 0.4H), 8.43 (s, 0.6H). LCMS: m/e 563 $(M-H)^-$, ret time 3.00 min, column A, 4 minute gradient.

Intermediate 33

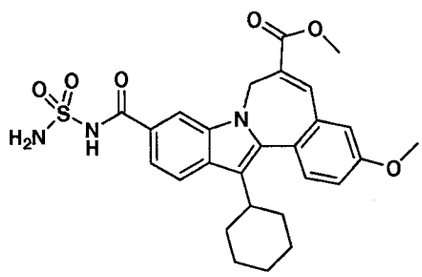


8-Cyclohexyl-5-((isopropylsulfonyl)carbamoyl)-11-methoxy-1,12b-dihydrocyclopropa[d]indolo[2,1-a][2]benzazepine-1a(2H)-carboxylic acid.

Methyl 8-cyclohexyl-5-((isopropylsulfonyl)carbamoyl)-11-methoxy-1,12b-dihydrocyclopropa[d]indolo[2,1-*a*][2]benzazepine-1a(2H)-carboxylate (606 mg, 1.07 mmol) was dissolved into MeOH//THF (1:1, 14 mL) and treated with 1M aqueous NaOH (2.5 mL). The reaction mixture was stirred and heated at 60 °C for 2h and cooled to rt. The clear solution was neutralized with 1M aqueous HCl (2.5 mL) and concentrated to remove organic solvents. The residue was stirred with H_2O (10 mL) overnight and the resultant solids were collected by filtration, washed with H_2O and dried under vacuum to yield 8-cyclohexyl-5-((isopropylsulfonyl)carbamoyl)-11-methoxy-1,12b-dihydrocyclopropa[*d*]indolo[2,1-*a*][2]benzazepine-1a(2*H*)-carboxylic

acid (530 mg, 0.96 mmol, 90%) as a bright yellow solid which was used without further purification. Presents as a ~2:1 mixture of rotamers or atrope isomers. ^{1}HNMR (300 MHz, CD_3OD) δ 0.23 - 0.30 (m, 0.4H), 0.80 - 2.24 (m, 17.6H), 2.70 - 3.11 (m, 2H), 3.46 (d, J = 15.0 Hz, 0.6H), 3.95 (s, 3H), 3.93 - 4.10 (m, 1.4H), 5.29 (d, J = 15.0 Hz, 0.4H), 5.48 (d, J = 15.0 Hz, 0.6H), 6.98 - 7.05 (m, 1H), 7.16 (d, J = 2.6 Hz, 0.4H), 7.23 (d, J = 2.6 Hz, 0.6H), 7.29 (d, J = 8.8 Hz, 0.6H), 7.33 (d, J = 8.8 Hz, 0.4H), 7.56 (dd, J = 8.8, 1.5 Hz, 0.6H), 7.64 (dd, J = 8.4, 1.5 Hz, 0.4H), 7.87 (d, J = 8.8 Hz, 0.6H), 7.92 (d, J = 8.4 Hz, 0.4H), 8.13 (d, J = 1.5 Hz, 0.4H), 8.31 (d, J = 1.5 Hz, 0.6H). LCMS: m/e 551 $(M+H)^+$, ret time 3.74 min, column B, 4 minute gradient.

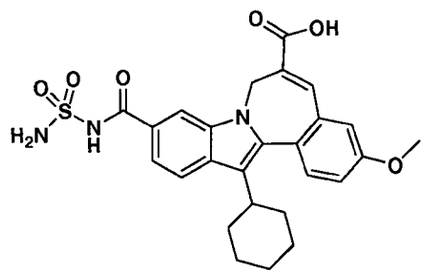
Intermediate 34



Methyl 10-((aminosulfonyl)carbamoyl)-13-cyclohexyl-3-methoxy-7H-indolo[2,1-a][2]benzazepine-6-carboxylate. 1,1'-Carbonyldiimidazole (1.23 g, 7.60 mmol) was added to a slurry of 13-cyclohexyl-3-methoxy-6-(methoxycarbonyl)-7*H*-indolo[2,1-*a*][2]benzazepine-10-carboxylic acid (2.6 g, 5.8 mmol) in THF (11 mL). The reaction mixture was heated at 60 °C for 1.5h, cooled to rt, treated with sulfamide (1.12 g, 11.7 mmol), stirred 10 min and then treated with the dropwise addition of a solution of DBU (1.8 mL, 11.7 mmol) in THF (3 mL). The reaction mixture was stirred at rt for 3h, diluted with EtOAc (80 mL) and CH_2Cl_2 (100 mL) and concentrated to dryness. The residue was diluted with CH_2Cl_2 (100 mL) and washed with 1N HCl (aq.) (2 x 100 mL). The combined aqueous layers were extracted with CH_2Cl_2 (100 mL) and the combined organic layers were washed with ½ saturated brine (~50 mL), dried ($MgSO_4$), filtered and concentrated. The residue was stirred with Et_2O (~75 mL) for 1h and the solids were collected by filtration,

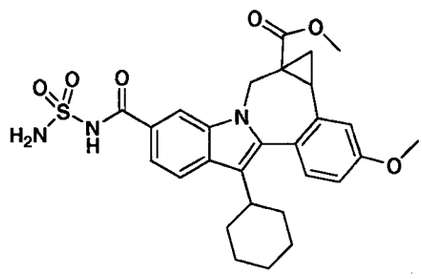
rinsed with Et_2O and dried to yield methyl 10-((aminosulfonyl)carbamoyl)-13-cyclohexyl-3-methoxy-7*H*-indolo[2,1-*a*][2]benzazepine-6-carboxylate (2.8 g, 5.3 mmol, 91%) as a bright yellow solid which was used without further purification. ^{1}HNMR (300 MHz, $CDCl_3$) δ 1.08 - 2.10 (m, 10H), 2.71 - 2.84 (m, 1H), 3.79 (s, 3H), 3.89 (s, 3H), 4.00 - 4.18 (m, 1H), 5.50 - 5.64 (m, 1H), 5.68 (s, 2H), 6.97 (d, *J* = 2.6 Hz, 1H), 7.07 (dd, *J* = 8.8, 2.6 Hz, 1H), 7.46 (dd, *J* = 8.4, 1.5 Hz, 1H), 7.49 (d, *J* = 8.8 Hz, 1H), 7.78 (s, 1H), 7.82 (d, *J* = 8.4 Hz, 1H), 8.10 (br s, 1H), 9.49 (s, 1H). LCMS: m/e 524 $(M+H)^+$, ret time 3.60 min, column B, 4 minute gradient.

Intermediate 35



10-((Aminosulfonyl)carbamoyl)-13-cyclohexyl-3-methoxy-7H-indolo[2,1-a][2]benzazepine-6-carboxylic acid. Methyl 10-((aminosulfonyl)carbamoyl)-13-cyclohexyl-3-methoxy-7*H*-indolo[2,1-*a*][2]benzazepine-6-carboxylate (725 mg, 1.39 mmol) was dissolved into MeOH//THF (1:1, 16 mL) and treated with 1M aqueous NaOH (3 mL). The reaction mixture was stirred and heated at 60 °C for 0.5h and cooled to rt. The reaction solution was diluted with MeOH/H_2O (2:1, 15 mL), neutralized with 1M aqueous HCl (3 mL) and concentrated to remove organic solvents. The resultant solids were collected by filtration, washed with H_2O and dried under vacuum to yield 10-((aminosulfonyl)carbamoyl)-13-cyclohexyl-3-methoxy-7*H*-indolo[2,1-*a*][2]benzazepine-6-carboxylic acid (650 g, 1.3 mmol, 92%) as a bright yellow solid which was used without further purification. ^{1}HNMR (300 MHz, $CDCl_3$) δ 1.16 - 2.22 (m, 10H), 2.82 - 2.96 (m, 1H), 3.94 (s, 3H), 4.07 - 4.29 (m, 1H), 5.57 - 5.80 (m, 1H), 7.14 - 7.23 (m, 2H), 7.55 - 7.63 (m, 2H), 7.88 - 7.94 (m 2H), 8.18 (s, 1H). LCMS: m/e 510 $(M+H)^+$, ret time 2.85 min, column B, 4 minute gradient.

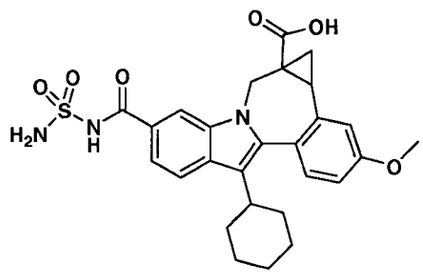
Intermediate 36



Methyl 5-((aminosulfonyl)carbamoyl)-8-cyclohexyl-11-methoxy-1,12b-dihydrocyclopropa[d]indolo[2,1-a][2]benzazepine-1a(2H)-carboxylate. To slurry of sodium hydride (60% dispersion in mineral oil, 350 mg, 8.8 mmol) in DMSO (8 mL) stirring under N_2 was added trimethylsulfoxonium iodide (1.93 g, 8.8 mmol) in three portions. The reaction mixture was stirred for 0.5h and then methyl 10-((aminosulfonyl)carbamoyl)-13-cyclohexyl-3-methoxy-7*H*-indolo[2,1-*a*][2]benzazepine-6-carboxylate (2.0 g, 3.8 mmol) in DMSO (8 mL) was added (flask rinsed with DMSO (2 x 2 mL)). The reaction mixture was stirred 1h, poured into 0.25N HCl (100 mL), and diluted with CH_2Cl_2 (100 mL). The solution was filtered to collect solids, and the organic layer of the motherliquor was separated and concentrated to dryness. The residue was dissolved into EtOAc (~150 mL) was washed with H_2O (~50 mL) and brine (~50 mL) dried ($MgSO_4$), filtered and concentrated to dryness. The residue was stirred with EtOAc/Et_2O (4:1, 50 mL) and the solids were collected by filtration and washed with EtOAc. These solids were combined with the initially collected solids to yield methyl 5-((aminosulfonyl)carbamoyl)-8-cyclohexyl-11-methoxy-1,12b-dihydrocyclopropa[*d*]indolo[2,1-*a*][2]benzazepine-1a(2*H*)-carboxylate (1.39 g, 2.6 mmol, 68%) as a tan solid which was used without further purification. Presents as a 1:1 mixture of rotamers or atrope isomers. ^{1}HNMR (300 MHz, DMSO-d_6) δ 0.13 - 0.21 (m, 0.5H), 1.06 - 2.12 (m, 11.5H), 2.64 - 2.94 (m, 2H), 3.46 (s, 1.5H), 3.49 (d, *J* = 15.0 Hz, 0.5H), 3.75 (s, 1.5H), 3.85 (s, 3H), 4.02 (d, *J* = 15.0 Hz, 0.5H), 5.21 (d, *J* = 15.0 Hz, 0.5H), 5.42 (d, *J* = 15.0 Hz, 0.5H), 6.99 - 7.09 (m, 1H), 7.17 - 7.31 (m, 1H), 7.41 (s, 0.5H), 7.43 (s, 0.5H), 7.66 - 7.56 (m, 1H), 7.82 (d, *J* = 8.4 Hz, 0.5H),

7.87 (d, J = 8.8 Hz, 0.5H), 8.25 (s, 0.5H), 8.47 (s, 0.5H), 11.62 (s, 0.5H), 11.69 (s, 0.5H). LCMS: m/e 538 $(M+H)^+$, ret time 3.56 min, column B, 4 minute gradient.

Intermediate 37

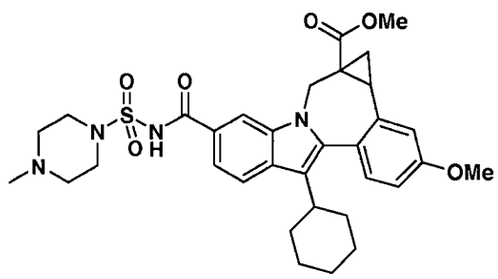


5-((Aminosulfonyl)carbamoyl)-8-cyclohexyl-11-methoxy-1,12b-dihydrocyclopropa[d]indolo[2,1-a][2]benzazepine-1a(2H)-carboxylic acid.

Methyl 5-((aminosulfonyl)carbamoyl)-8-cyclohexyl-11-methoxy-1,12b-dihydrocyclopropa[*d*]indolo[2,1-*a*][2]benzazepine-1a(2*H*)-carboxylate (1.1 mg, 2.0 mmol) was dissolved into MeOH//THF (1:1, 24 mL) and treated with 1M aqueous NaOH (5 mL). The reaction mixture was stirred and heated at 60 °C for 2h and cooled to rt. The clear solution was neutralized with 1M aqueous HCl (5 mL) and concentrated to remove organic solvents. The residue was stirred with H_2O (10 mL) for 1h and the resultant solids were collected by filtration, washed with H_2O and dried under vacuum to yield 5-((aminosulfonyl)carbamoyl)-8-cyclohexyl-11-methoxy-1,12b-dihydrocyclopropa[*d*]indolo[2,1-*a*][2]benzazepine-1a(2*H*)-carboxylic acid (1.05 mg, 2.0 mmol, 98%) as a light yellow solid which was used without further purification. Presents as a 1:1 mixture of rotamers or atrope isomers. ^{1}HNMR (300 MHz, DMSO-d_6) δ 0.08 - 0.17 (m, 0.5H), 0.79 - 2.13 (m, 11.5H), 2.65 - 2.94 (m, 2H), 3.44 (d, J = 14.6 Hz, 0.5H), 3.85 (s, 3H), 3.96 (d, J = 14.6 Hz, 0.5H), 5.20 (d, J = 14.6 Hz, 0.5H), 5.40 (d, J = 14.6 Hz, 0.5H), 6.98 - 7.08 (m, 1H), 7.17 - 7.46 (m, 4H), 7.58 (d, J = 8.1 Hz, 0.5H), 7.62 (d, J = 8.1 Hz, 0.5H), 7.81 (d, J = 8.8 Hz, 0.5H), 7.87 (d, J = 8.8 Hz, 0.5H), 8.25 (s, 0.5H), 8.44 (s, 0.5H), 11.48 - 13.19 (m, 2H). LCMS: m/e 524 $(M+H)^+$, ret time 3.51 min, column B, 4 minute gradient.

Intermediate 38 was analyzed by the following LC/MS method: Column: PHENOMENNEX-LUNA 3.0 x 50mm S10; Mobile Phase:(A) 10:90 methanol-water; (B) 90:10 methanol-water; Buffer: 0.1% TFA; Gradient Range: 0-100% B; Gradient Time: 2 min; Flow Rate: 4 mL/min; Analysis Time: 3 min; Detection: Detector 1: UV at 220 nm; Detector 2: MS (ESI+) .

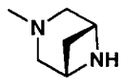
Intermediate 38



(+/-)-8-Cyclohexyl-N-4-(4-methylpiperazin-1-ylsulfonyl)-1,1a,2,12b-tetrahydro-11-methoxy-1a-(methoxycarbonyl)cycloprop[d]indolo[2,1-a][2]benzazepine-5-carboxamide. To a stirred solution of the acid (1.15 g, 2.5 mmol) in an. THF (5 mL), neat CDI (0.61 g, 3.75 mmol) was added and the mixture was heated at 50 oC for 30 min. Then reagent the amine and DBU were added and the resultant mixture was stirred at rt overnight. Reaction was quenched with satd. NH4Cl and then extracted with EtOAc (2X 50 mL). Organic layer was washed with water and then dried (Na2SO4). Crude product was purified by flash column chromatography (silica gel, 8-10% MeOH in DCM) to afford the product (1.03 g, 66%) as a beige solid. LC/MS: Retention time: 2.913 min; m/e 621 (MH^+). The product was observed to exist as inter-converting rotamers by 1H NMR (400 MHz, CHLOROFORM-D): δ ppm 0.31 - 0.41 (m, 1 H), 1.16 - 1.28 (m, 2 H), 1.29 - 1.48 (m, 2 H), 1.50 - 1.61 (m, 1 H), 1.63 - 1.84 (m, 3 H), 1.85 - 2.10 (m, 6 H), 2.28 - 2.39 (m, 3 H), 2.38 - 2.50 (m, 1 H), 2.51 - 2.61 (m, 4 H), 2.61 - 2.82 (m, 1 H), 2.82 - 2.96 (m, 1 H), 3.36 - 3.48 (m, 1 H), 3.50 - 3.62 (m, 3 H), 3.77 - 3.92 (m, 3 H), 5.10 - 5.44 (m, 1 H), 6.69 (s, 1 H), 6.86 - 7.04 (m, 1 H), 7.08 - 7.15 (m, 1 H), 7.21 - 7.28 (m, 1 H), 7.33 - 7.55 (m, 1 H), 7.77 - 7.88 (m, 1 H), 7.94 - 8.25 (m, 1 H).

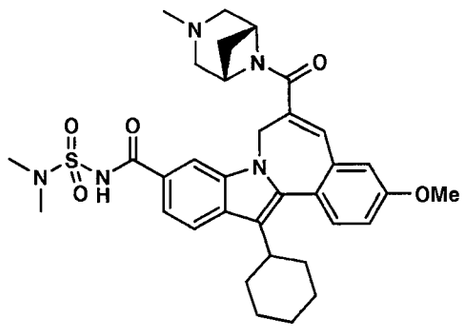
Intermediate 39 and Examples 1-11 the experimental procedures that follow until otherwise noted. HPLC method: Method A: Start% B= 0; Final% B= 100; Gradient time= 3 min; Flow Rate= 4 ml/min; Wavelength= 220; Solvent A= 10% MeOH- 90% H2O-0.1% TFA; Solvent B= 90% MeOH- 10% H2O-0.1% TFA; Column: Peneomenex-Luna 3.0 x 50 mm S10; Method B: Start% B= 0; Final% B= 100; Gradient time= 3 min; Flow Rate= 4 ml/min; Wavelength= 220 ; Solvent A= 5% Acetonitril-95% H2O-10 Mm Ammonium Acetate; Solvent B= 95% Acetonitril-5% H2O-10 Mm Ammonium Acetate; Column= Phenomenex-Luna 3.0 x 50 mm S10. Compounds for which LC/MS data was obtained with method B are noted. Unless noted LC/MS was obtained using Method A.

Intermediate 39



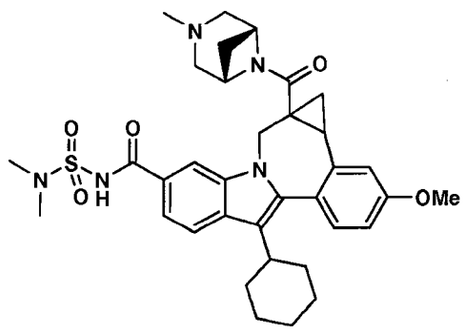
(1R,5S)-3-methyl-3,6-diazabicyclo[3.1.1]heptane. To a solution of (1R,5S)-tert-butyl 3,6-diazabicyclo[3.1.1]heptane-6-carboxylate (1.0 g, 5.04 mmol) in MeOH (25 mL), paraformaldehyde (0.227 g, 7.57 mmol) and zinc chloride (1.03 g, 7.57 mmol) were added. Then sodium cyanoborohydride (0.475 g, 7.57 mmol) was added in portions. The reaction mixture was stirred at rt. for overnight. Then insoluble solid was filtered out and the filtrated was concentrated. The residue was participated between 10% $NaHCO_3$ solution and ethyl acetate (2X 50 mL). The organic layers were combined, dried ($MgSO_4$) and concentrated to give a colorless oil. It was then dissolved in CH_2Cl_2 (10 mL) and TFA (2.5 mL) was added. The reaction mixture was stirred at rt. for overnight. TFA and solvent were evaporated to give a white solid as final product as diTFA salt. (1.14 g, 66% yield). MS m/ 113(MH^+). ^1H NMR (500 MHz, MeOD) δ ppm 2.25 (d, *J*=11.90 Hz, 1 H) 3.01 - 3.06 (m, 3 H) 3.08 - 3.18 (m, 1 H) 3.80 (d, *J*=13.73 Hz, 2 H) 4.13 (d, *J*=14.34 Hz, 2 H) 4.47 (d, *J*=6.10 Hz, 2 H).

Example 1



7H-Indolo[2,1-a][2]benzazepine-10-carboxamide, 13-cyclohexyl-N-[(dimethylamino)sulfonyl]-3-methoxy-6-[[(1R,5S)-3-methyl-3,6-diazabicyclo[3.1.1]hept-6-yl]carbonyl]-. MS m/z 632(MH^+), Retention time: 2.510 min. ^{1}H NMR (500 MHz, MeOD) δ ppm 1.12 - 1.61 (m, 4 H) 1.65 - 2.22 (m, 7 H) 2.28 - 3.09 (m, 12 H) 3.51 - 3.88 (m, 3 H) 3.95 (s, 3 H) 4.20 (d, *J*=13.42 Hz, 1 H) 4.63 (s, br, 2 H) 5.51 (d, *J*=13.43 Hz, 1 H) 7.17 - 7.25 (m, 2 H) 7.43 (s, 1 H) 7.54 - 7.62 (m, 2 H) 7.93 (d, *J*=8.24 Hz, 1 H) 8.18 (s, 1 H)

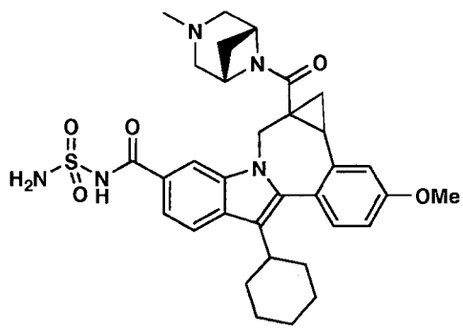
Example 2



Cycloprop[d]indolo[2,1-a][2]benzazepine-5-carboxamide, 8-cyclohexyl-N-[(dimethylamino)sulfonyl]-1,1a,2,12b-tetrahydro-11-methoxy-1a-[[(1R,5S)-3-methyl-3,6-diazabicyclo[3.1.1]hept-6-yl]carbonyl]-. MS m/z 644(MH^+), Retention time: 2.057 min (Method B). ^{1}H NMR (500 MHz, MeOD) δ ppm 0.14 (m, 0.2 H) 1.12 - 2.19 (m, 14.8 H) 2.39 - 3.08 (m, 12 H) 3.44 - 3.95 (m, 7.4 H) 4.15 (d, *J*=14.65

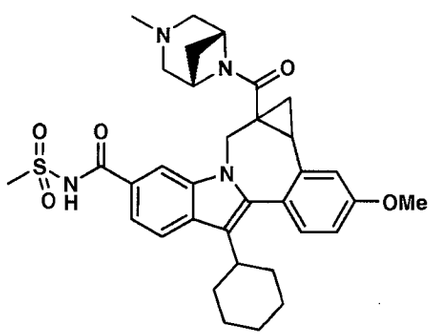
Hz, 0.2 H) 4.57 (s, br, 0.4 H) 5.01 (d, *J*=14.65 Hz, 0.2 H) 5.31 (s, br, 0.8 H) 6.98 - 7.04 (m, 1 H) 7.19 (s, 1 H) 7.30 (d, *J*=8.55 Hz, 0.8 H) 7.33 (d, *J*=8.55 Hz, 0.2 H) 7.59 (d, *J*=8.24 Hz, 1 H) 7.88 (d, *J*=8.55 Hz, 0.2 H) 7.93 (d, *J*=8.54 Hz, 0.8 H) 8.08 (s, 0.2 H) 8.10 (s, 0.8 H).

Example 3



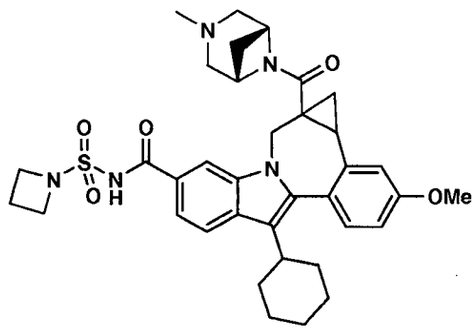
Cycloprop[d]indolo[2,1-a][2]benzazepine-5-carboxamide, N-(aminosulfonyl)-8-cyclohexyl-1,1a,2,12b-tetrahydro-11-methoxy-1a-[[(1R,5S)-3-methyl-3,6-diazabicyclo[3.1.1]hept-6-yl]carbonyl]-. MS m/z 618(MH^+), Retention time: 2.292 min. ^{1}H NMR (500 MHz, MeOD) δ ppm 0.18 (m, 0.17 H) 1.20 - 2.23 (m, 14.83 H) 2.55 - 3. 3.99 (m, 13.49 H) 4.19 (d, *J*=14.95 Hz, 0.17 H) 4.62 (s, br, 0.34 H) 5.05 (d, *J*=14.65 Hz, 0.17 H) 5.35 (s, br, 0.83 H) 7.01 - 7.09 (m, 1 H) 7.21 - 7.27 (m, 1 H) 7.30 - 7.38 (m, 1 H) 7.60 - 7.69 (m, 1 H) 7.91 (d, *J*=8.55 Hz, 0.17 H) 7.97 (d, *J*=8.55 Hz, 0.83 H) 8.12 (s, 0.17 H) 8.15 (s, 0.83 H).

Example 4



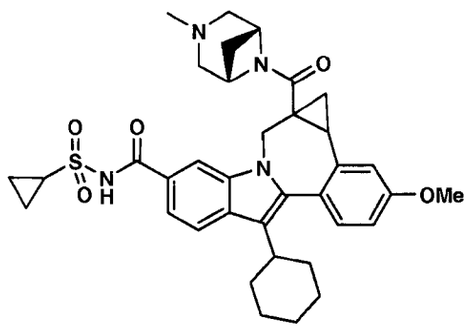
Cycloprop[d]indolo[2,1-a][2]benzazepine-5-carboxamide, 8-cyclohexyl-1,1a,2,12b-tetrahydro-11-methoxy-1a-[[(1R,5S)-3-methyl-3,6-diazabicyclo[3.1.1]hept-6-yl]carbonyl]-N-(methylsulfonyl)-. MS m/z 617(MH^+), Retention time: 2.383 min. ^{1}H NMR (500 MHz, MeOD) δ ppm 0.18 (m, 0.19 H) 1.17 - 2.25 (m, 14.81 H) 2.54 - 4.04 (m, 16.43 H) 4.19 (d, *J*=14.65 Hz, 0.19 H) 4.62 (s, br, 0.38 H) 5.06 (d, *J*=14.34 Hz, 0.19 H) 5.35 (s, br, 0.81 H) 7.01 - 7.10 (m, 1 H) 7.22 - 7.25 (m, 1 H) 7.32 - 7.39 (m, 1 H) 7.60 - 7.68 (m, 1 H) 7.93 (d, *J*=8.55 Hz, 0.19 H) 7.98 (d, *J*=8.55 Hz, 0.81 H) 8.14 (s, 0.19 H) 8.17 (s, 0.81 H).

Example 5



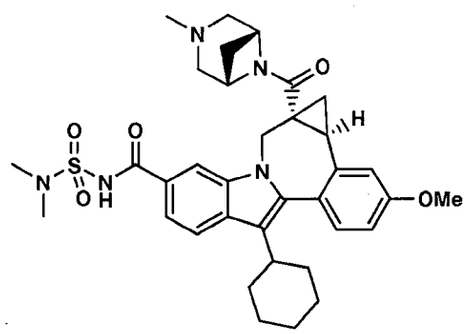
Cycloprop[d]indolo[2,1-a][2]benzazepine-5-carboxamide, N-(1-azetidinylsulfonyl)-8-cyclohexyl-1,1a,2,12b-tetrahydro-11-methoxy-1a-[[(1R,5S)-3-methyl-3,6-diazabicyclo[3.1.1]hept-6-yl]carbonyl]-. MS m/z 658(MH^+), Retention time: 2.467 min. ^{1}H NMR (500 MHz, MeOD) δ ppm 0.20 (m, 0.18 H) 1.18 - 2.23 (m, 14.82 H) 2.24 - 2.37 (m, 2 H) 2.53 - 3.99 (m, 13.46 H) 4.16 - 4.30 (m, 4.18 H) 4.62 (s, br, 0.36 H) 5.07 (d, *J*=14.65 Hz, 0.18 H) 5.36 (s, br, 0.82 H) 7.02 - 7.10 (m, 1 H) 7.22-7.25 (m, 1 H) 7.31 - 7.39 (m, 1 H) 7.66 (d, *J*=8.24 Hz, 1 H) 7.94 (d, *J*=8.55 Hz, 0.18 H) 7.99 (d, *J*=8.55 Hz, 0.82 H) 8.15 (s, 0.18 H) 8.19 (s, 0.82 H).

Example 6



Cycloprop[d]indolo[2,1-a][2]benzazepine-5-carboxamide, 8-cyclohexyl-N-(cyclopropylsulfonyl)-1,1a,2,12b-tetrahydro-11-methoxy-1a-[[(1R,5S)-3-methyl-3,6-diazabicyclo[3.1.1]hept-6-yl]carbonyl]-. MS m/z 643(MH^+), Retention time: 2.438 min. ^{1}H NMR (500 MHz, MeOD) δ ppm 0.14 - 0.23 (m, 0.16 H) 1.11 - 2.25 (m, 18.84 H) 2.51 - 4.01 (m, 14.52 H) 4.19 (d, *J*=14.95 Hz, 0.16 H) 4.62 (s, br, 0.32 H) 5.06 (d, *J*=14.95 Hz, 0.16H) 5.37 (s, br, 0.84 H) 7.00 - 7.11 (m, 1 H) 7.19 - 7.27 (m, 1 H) 7.32 - 7.41 (m, 1 H) 7.60 - 7.69 (m, 1 H) 7.94 (d, *J*=8.55 Hz, 0.16 H) 7.99 (d, *J*=8.55 Hz, 0.84 H) 8.13 (s, 0.16 H) 8.17 (s, 0.84 H).

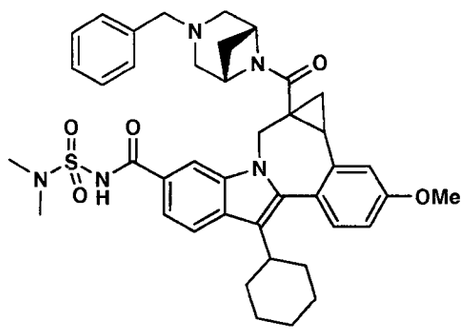
Example 7



Cycloprop[d]indolo[2,1-a][2]benzazepine-5-carboxamide, 8-cyclohexyl-N-[(dimethylamino)sulfonyl]-1,1a,2,12b-tetrahydro-11-methoxy-1a-[[(1R,5S)-3-methyl-3,6-diazabicyclo[3.1.1]hept-6-yl]carbonyl]-, (1aR,12bS)-. MS m/z 644(MH^+), Retention time: 2.175 min(Method B). ^{1}H NMR (500 MHz, MeOD) δ

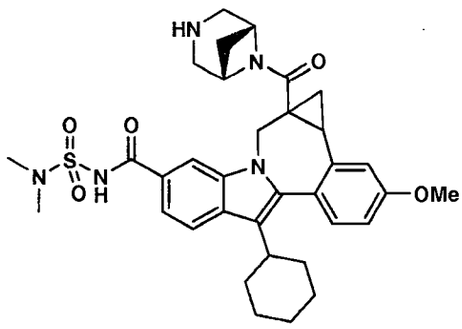
ppm 0.14 (m, 0.2 H) 1.12 - 2.19 (m, 14.8 H) 2.39 - 3.08 (m, 12 H) 3.44 - 3.95 (m, 7.4 H) 4.15 (d, *J*=14.65 Hz, 0.2 H) 4.57 (s, br, 0.4 H) 5.01 (d, *J*=14.65 Hz, 0.2 H) 5.31 (s, br, 0.8 H) 6.98 - 7.04 (m, 1 H) 7.19 (s, 1 H) 7.30 (d, *J*=8.55 Hz, 0.8 H) 7.33 (d, *J*=8.55 Hz, 0.2 H) 7.59 (d, *J*=8.24 Hz, 1 H) 7.88 (d, *J*=8.55 Hz, 0.2 H) 7.93 (d, *J*=8.54 Hz, 0.8 H) 8.08 (s, 0.2 H) 8.10 (s, 0.8 H).

Example 8



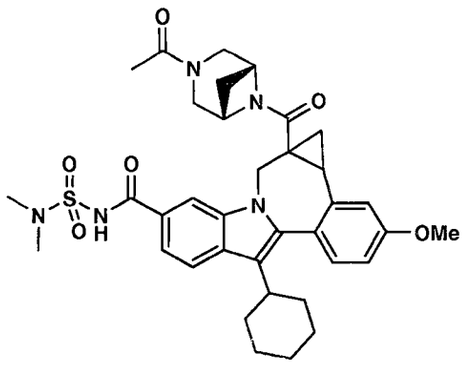
Cycloprop[d]indolo[2,1-a][2]benzazepine-5-carboxamide, 8-cyclohexyl-N-[(dimethylamino)sulfonyl]-1,1a,2,12b-tetrahydro-11-methoxy-1a-[[(1R,5S)-3-(phenylmethyl)-3,6-diazabicyclo[3.1.1]hept-6-yl]carbonyl]-. To a solution of cycloprop[*d*]indolo[2,1-*a*][2]benzazepine-1a(2*H*)-carboxylic acid, 8-cyclohexyl-5-[[[(dimethylamino)sulfonyl]amino]carbonyl]-1,12b-dihydro-11-methoxy- (300 mg, 0.544 mmol) in DMSO (10 mL), TBTU (262 mg, 0.816 mmol) and DIPEA (0.47 mL, 2.72 mmol) were added. The reaction mixture was stirred at rt for 15 min. Then (1R,5S)-3-benzyl-3,6-diazabicyclo[3.1.1]heptane (154 mg, 0. 816 mmol) was added and the reaction mixture was stirred at rt. for overnight. It was then concentrated and the residue was purified by Prep. HPLC column to give a light yellow solid as final product. (373 mg, 82% yield). MS m/z 722(MH^+), Retention time: 3.500 min (Method B). ^{1}H NMR (500 MHz, MeOD) δ ppm 0.13 (m, 0.24 H) 1.14 - 2.25 (m, 14.76 H) 2.49 - 4.03 (m, 18.28 H) 4.13 (d, *J*=14.65 Hz, 0.24 H) 4.45 - 4.66 (m, 0.48 H) 4.98 (d, *J*=14.95 Hz, 0.24 H) 5.36 (s, br, 0.76 H) 7.03 (dd, *J*=8.39, 2.59 Hz, 1 H) 7.16 - 7.64 (m, 8 H) 7.90 (d, *J*=8.54 Hz, 0.24 H) 7.92 (d, *J*=8.55 Hz, 0.76 H) 8.08 (s, 0.24 H) 8.19 (s, br, 0.76 H).

Example 9



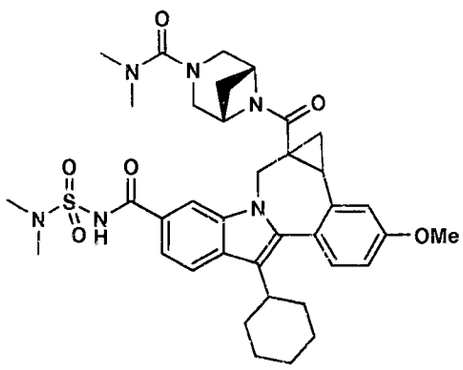
Cycloprop[d]indolo[2,1-a][2]benzazepine-5-carboxamide, 8-cyclohexyl-1a-[(1R,5S)-3,6-diazabicyclo[3.1.1]hept-6-ylcarbonyl]-N-[(dimethylamino)sulfonyl]-1,1a,2,12b-tetrahydro-11-methoxy-. To a solution of cycloprop[d]indolo[2,1-a][2]benzazepine-5-carboxamide, 8-cyclohexyl-N-[(dimethylamino)sulfonyl]-1,1a,2,12b-tetrahydro-11-methoxy-1a-[[(1R,5S)-3-(phenylmethyl)-3,6-diazabicyclo[3.1.1]hept-6-yl]carbonyl]- (60 mg, 0.072 mmol) in ethanol (5 mL), $Pd(OH)_2$ (60 mg) and 1N HCl solution (0.072 mL, 0.072 mmol) were added. The reaction mixture was shaken under a hydrogenator at 30-40 psi for 6 hr. Catalyst was filtered off celite and the filtrate was concentrated to give a yellowish solid as crude product. It was then purified by Prep. HPLC column to give a light yellow solid as final product as TFA salt. (42 mg, 78% yield). MS m/z 632(MH^+), Retention time: 1.795 min (Method B). ^1H NMR (500 MHz, MeOD) δ ppm 0.17 (m, 0.26 H) 1.15 - 2.25 (m, 14.74 H) 2.45 - 4.01 (m, 16.22 H) 4.20 (d, *J*=14.34 Hz, 0.26 H) 4.57 (s, br, 0.52 H) 5.00 - 5.04 (m, 0.26 H) 5.23 (d, *J*=14.95 Hz, 0.74 H) 7.01 - 7.09 (m, 1 H) 7.22 (s, 1 H) 7.33 (d, *J*=8.55 Hz, 0.74 H) 7.36 (d, *J*=8.54 Hz, 0.26 H) 7.63 (dd, *J*=8.55, 1.53 Hz, 1 H) 7.89 - 7.98 (m, 1 H) 8.14 (s, 1 H).

Example 10



Cycloprop[d]indolo[2,1-a][2]benzazepine-5-carboxamide, 1a-[[(1R,5S)-3-acetyl-3,6-diazabicyclo[3.1.1]hept-6-yl]carbonyl]-8-cyclohexyl-N-[(dimethylamino)sulfonyl]-1,1a,2,12b-tetrahydro-11-methoxy-. To a solution of acetic acid (0.002 mL, 0.040 mmol) in DMSO (1.0 mL), TBTU (16.1 mg, 0.050 mmol) and DIPEA (0.029 mL, 0.128 mmol) were added. The reaction mixture was stirred at rt. for 10 min. Then cycloprop[*d*]indolo[2,1-*a*][2]benzazepine-5-carboxamide, 8-cyclohexyl-1a-[(1*R*,5*S*)-3,6-diazabicyclo[3.1.1]hept-6-ylcarbonyl]-*N*-[(dimethylamino)sulfonyl]-1,1a,2,12b-tetrahydro-11-methoxy- (25 mg, 0.0335 mmol) was added. Ther reaction mixture was then stirred at rt. for overnight. It was then purified by Prep. HPLC column. Fractions were collected and concentrated to give a light yellow solid as final product. (16.5 mg, 73% yield). MS m/z 674(MH^+), Retention time: 2.718 min. ^{1}H NMR (500 MHz, MeOD) δ ppm 0.09 (m, 0.3 H) 0.49 - 2.28 (m, 17.7 H) 2.31 - 4.52 (m, 16.4 H) 4.66 - 5.43 (m, 1.6 H) 6.92 - 7.05 (m, 1 H) 7.06 - 7.21 (m, 1 H) 7.25 - 7.35 (m, 1 H) 7.45 - 7.69 (m, 1 H) 7.76 - 8.00 (m, 1 H) 8.02 - 8.16 (m, 1 H).

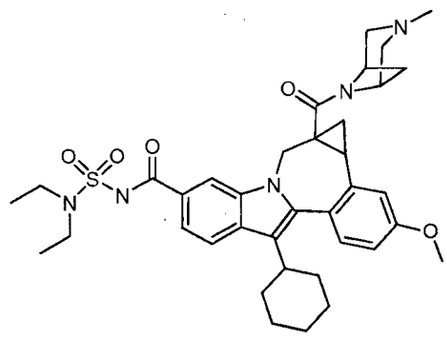
Example 11



Cycloprop[d]indolo[2,1-a][2]benzazepine-5-carboxamide, 8-cyclohexyl-1a-[[(1R,5S)-3-[(dimethylamino)carbonyl]-3,6-diazabicyclo[3.1.1]hept-6-yl]carbonyl]-N-[(dimethylamino)sulfonyl]-1,1a,2,12b-tetrahydro-11-methoxy-. To a solution of cycloprop[*d*]indolo[2,1-*a*][2]benzazepine-5-carboxamide, 8-cyclohexyl-1a-[(1*R*,5*S*)-3,6-diazabicyclo[3.1.1]hept-6-ylcarbonyl]-*N*-[(dimethylamino)sulfonyl]-1,1a,2,12b-tetrahydro-11-methoxy- (50 mg, 0.067 mmol) in CH2Cl2 (3 mL), DIPEA (0.052 mL, 0.3 mmol) and dimethylcarbamy chloride (0.009 mL, 0.1 mmol) were added. The reaction mixture was stirred at rt. for overnight. It was then concentrated and the residue was purified by Prep. HPLC column. The fractions were collected and concentrated to give a yellow solid as final product. (18.5 mg, 39% yield). MS m/z 703(MH^+), Retention time: 2.771 min. ^1H NMR (500 MHz, MeOD) δ ppm 0.08 (m, 0.4 H) 0.53 - 2.22 (m, 14.6 H) 2.29 - 4.43 (m, 22.2 H) 4.55-5.46 (m, 1.8 H) 6.93 - 7.04 (m, 1 H) 7.16 (d, *J*=2.44 Hz, 0.4 H) 7.19 (d, *J*=2.45 Hz, 0.6 H) 7.25 - 7.34 (m, 1 H) 7.44 - 7.70 (m, 1 H) 7.76 - 7.99 (m, 1 H) 8.00 - 8.16 (m, 0.6 H) 8.42 (s, br, 0.4 H).

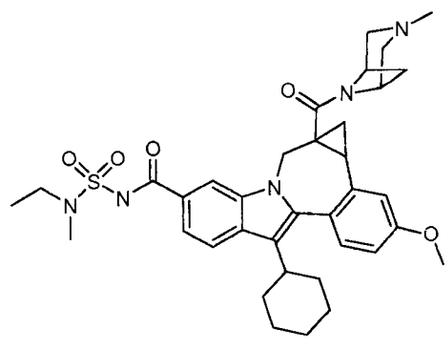
Examples 12 - 16 use the experimental procedures that follow until otherwise noted. All the compounds described below were analyzed by following LC/MS method: Start % B: 0; Final % B: 100; Gradient time: 3 min; Stop time: 4 min; Flow rate: 4 ml/min; Wavelenth:220; Solvent A: 10% MeOH / 90% H_2O / 0.1% Trifluoroacetic Acid; Solvent B: 10% H_2O / 90% MeOH / 0.1% Trifluoroacetic Acid; Column: XBridge 4.6 x 50 mm S5.

Example 12



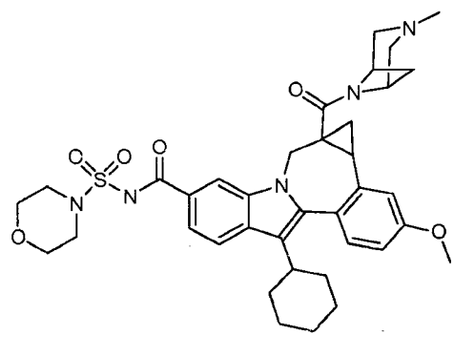
(+/-)-8-Cyclohexyl-N-(N,N-diethylaminosulfonyl)-1,1a,2,12b-tetrahydro-11-methoxy-1a-(1-(3-methyl-3,6-diazabicyclo[3.1.1]heptan-6-yl))-8-carbonyl)-cycloprop[d]indolo[2,1-a][2]benzazepine-5-carboxamide. To a mixture of the compound acid(0.050g, 0.86 mmol) and 3-methyl-3,6-diazabicyclo[3.1.1]heptane bis(2,2,2-trifluoroacetate) (44.0 mg, 0.129 mmol) in CH2Cl2 (1.5 ml) was added TEA (0.120 ml, 0.863 mmol) and HBTU (49.0 mg, 0.129 mmol) and stirred at r.t. for 80 min, diluted with MeOH, removed the solvent. The residue was dissolved in methanol, and purified by prep-HPLC to afford a TFA salt of compound 1 (0.0296g , 45%). LC-MS retention time: 3.150; MS m/z 674 (M+H)]. 1H NMR (400 MHz, CHLOROFORM-D): δ ppm 1.12 - 1.57 (m, 7 H) 1.23 (t, *J*=7.18 Hz, 6 H) 1.81 (s, 2 H) 1.87 - 2.17 (m, 5 H) 2.64 - 2.79 (m, 1 H) 2.83 - 3.02 (m, 2 H) 3.10 - 3.23 (m, *J*=7.30, 4.78 Hz, 1 H) 3.32 - 5.34 (m, 7 H) 3.54 (q, *J*=7.05 Hz, 4 H) 3.90 (s, 3 H) 4.36 (s, 1 H) 5.39 - 5.64 (m, 1 H) 6.97 (dd, *J*=8.56, 2.77 Hz, 1 H) 7.12 (d, *J*=2.52 Hz, 1 H) 7.22 - 7.32 (m, 1 H) 7.47 (d, *J*=8.31 Hz, 1 H) 7.86 - 7.90 (m, 1 H) 8.11 (s, 1H).

Example 13



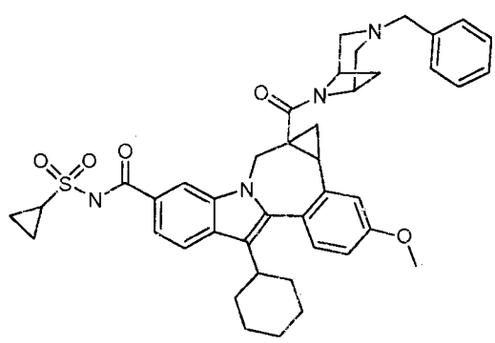
(+/-)-8-Cyclohexyl-N-(N-methyl-N-ethylaminosulfonyl)-1,1a,2,12b-tetrahydro-11-methoxy-1a-(1-(3-methyl-3,6-diazabicyclo[3.1.1]heptan-6-yl))-8-carbonyl)-cycloprop[d]indolo[2,1-a][2]benzazepine-5-carboxamide. A TFA salt of the product was prepared from the acid (0.0294 g, 55%). LC-MS retention time: 3.066; MS m/z 660(M+H). 1H NMR (400 MHz, CHLOROFORM-*d*): δ ppm 1.20 - 1.26 (m, 3 H) 1.25 - 1.56 (m, 6 H) 1.81 (s, 3 H) 1.88 - 2.12 (m, 5 H) 2.63 - 2.78 (m, 1 H) 3.06 (s, 3 H) 3.10 - 3.22 (m, *J*=7.18, 5.16 Hz, 1 H) 3.42 - 3.50 (m, 5 H) 3.55 - 3.76 (m, 1 H) 3.90 (s, 3 H) 3.93 - 4.40 (m, 5 H) 4.33 - 4.39 (m, 1 H) 5.38 - 5.53 (m, 1 H) 6.97 (dd, *J*=8.69, 2.64 Hz, 1 H) 7.12 (d, *J*=2.52 Hz, 1 H) 7.24 - 7.32 (m, 1 H) 7.49 (d, *J*=8.31 Hz, 1 H) 7.85 - 7.90 (m, 1 H) 8.12 (s, 1 H).

Example 14



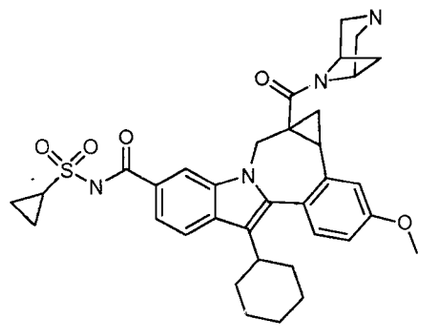
(+/-)-8-Cyclohexyl-N-(morpholinosulfonyl)-1,1a,2,12b-tetrahydro-11-methoxy-1a-(1-(3-methyl-3,6-diazabicyclo[3.1.1]heptan-6-yl))-8-carbonyl)-cycloprop[d]indolo[2,1-a][2]benzazepine-5-carboxamide. A TFA salt of the product was prepared (0.0323 g, 48%). LC-MS retention time: 2.955; MS m/z (M+H) 688. 1H NMR (400 MHz, CHLOROFORM-*d*): δ ppm 1.18 - 1.56 (m, 6 H) 1.81 (t, *J*=12.84 Hz, 3 H) 1.87 - 2.13 (m, 5 H) 2.62 - 2.78 (m, 1 H) 2.80 - 2.89 (m, *J*=18.51, 4.66 Hz, 1 H) 2.90 - 3.01 (m, 1 H) 3.08 - 3.20 (m, 1 H) 3.40 - 3.55 (m, 6 H) 3.56 - 3.69 (m, 1 H) 3.71 - 4.31 (m, 4 H) 3.73 - 3.79 (m, 4 H) 3.89 (s, 3 H) 4.31 - 4.41 (m, 1 H) 5.35 - 5.56 (m, 1 H) 6.97 (dd, *J*=8.69, 2.64 Hz, 1 H) 7.11 (d, *J*=2.27 Hz, 1 H) 7.20 - 7.33 (m, 1 H) 7.46 - 7.56 (m, 1 H) 7.87 (d, *J*=8.56 Hz, 1 H) 8.12 (s, 1 H).

Example 15



(+/-)-8-Cyclohexyl-N-(cyclopropylsulfonyl)-1,1a,2,12b-tetrahydro-11-methoxy-1a-(1-(3-benzyl-3,6-diazabicyclo[3.1.1]heptan-6-yl))-8-carbonyl)-cycloprop[d]indolo[2,1-a][2]benzazepine-5-carboxamide. A TFA salt of the product was prepared (0.056 g, 71%). LC-MS retention time: 3.11; MS m/z 719 (M+H). ^{1}H NMR (400 MHz, CHLOROFORM-*d*): δ ppm 1.02 - 1.60 (m, 9 1.69 - 2.17 (m, 9 2.48 - 3.03 (m, 3 3.06 - 3.34 (m, 3 3.46 (d, *J*=13.35 Hz, 1 3.62 - 4.06 (m, 4 3.90 (s, 3 4.28 - 4.68 (m, 2 6.88 - 7.02 (m, 2 7.13 (d, *J*=2.27 Hz, 2 7.23 - 7.30 (m, 1 7.35 (d, *J*=5.04 Hz, 2 7.38 - 7.54 (m, 2 7.87 (d, *J*=8.31 Hz, 1 8.32 (s, 1 H).

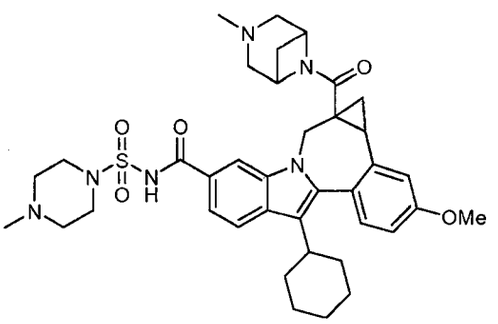
Example 16



(+/-) 8-Cyclohexyl-N-(cyclopropylsulfonyl)-1,1a,2,12b-tetrahydro-11-methoxy-1a-(1-(3,6-diazabicyclo[3.1.1]heptan-6-yl))-8-carbonyl)-cycloprop[d]indolo[2,1-a][2]benzazepine-5-carboxamide. A mixture of the benzyl compound (0.052g, 0.072 mmol) and Pd/C (w/w 10%, 0.05g), in MeOH (8 mL) was degassed and stirred under H_2 balloon for overnight. Filtered off the solid and removed the solvent to afford the product as a yellow solid (0.042g, 93%) in TFA salt form. LC-MS retention time: 2.976; MS m/z 629 (M+H). ^{1}H NMR (400 MHz, CHLOROFORM-*d*): δ ppm 0.99 - 2.13 (m, 18 2.38 - 2.51 (m, 1 2.71 - 3.76 (m, 7 3.88 (s, 3 4.09 - 4.26 (m, *J*=11.08 Hz, 1 4.50 (d, *J*=31.73 Hz, 1 4.90 (d, *J*=14.86 Hz, 1 6.89 - 6.98 (m, 1 7.05 (d, *J*=2.01 Hz, 1 7.21 - 7.31 (m, 1 7.69 (d, *J*=7.81 Hz, 1 7.82 - 7.92 (m, *J*=8.31 Hz, 1 8.24 - 8.33 (m, 1 H).

Example 17 was analyzed by the following LC/MS method: Column: PHENOMENNEX-LUNA 3.0 x 50mm S10; Mobile Phase:(A) 10:90 methanol-water; (B) 90:10 methanol-water; Buffer: 0.1% TFA; Gradient Range: 0-100% B; Gradient Time: 2 min; Flow Rate: 4 mL/min; Analysis Time: 3 min; Detection: Detector 1: UV at 220 nm; Detector 2: MS (ESI+).

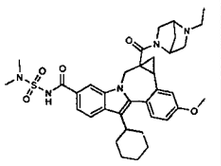
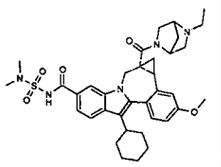
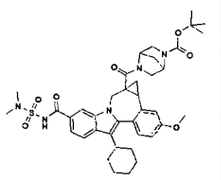
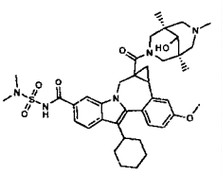
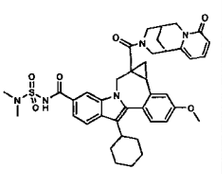
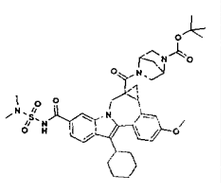
Example 17

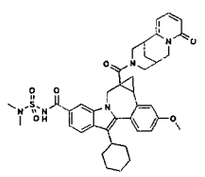
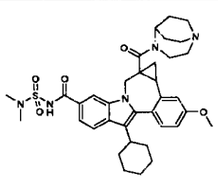
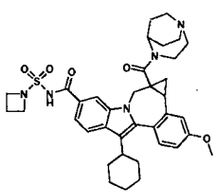
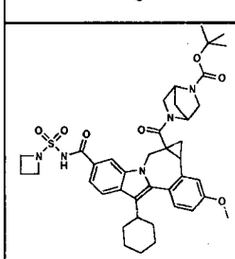
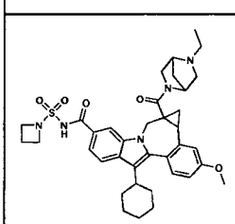
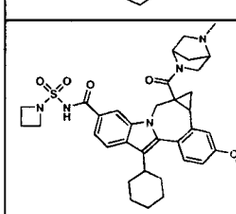


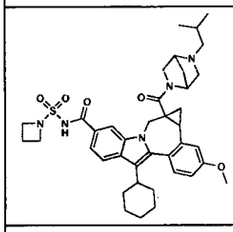
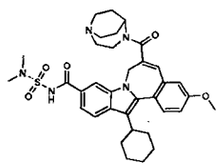
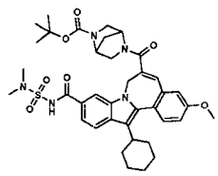
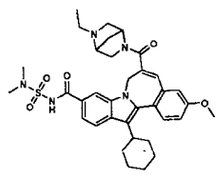
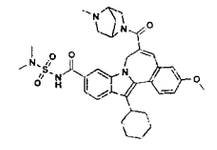
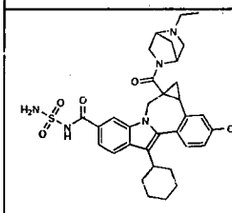
(+/-)-8-Cyclohexyl-N-4-(4-methylpiperazin-1-ylsulfonyl)-1,1a,2,12b-tetrahydro-11-methoxy-1a-(3-methyl-3,6-diazabicyclo[3.1.1]heptane-6-carbonyl) cycloprop[d]indolo[2,1-a][2]benzazepine-5-carboxamide. The starting material was hydrolyzed with 1N NaOH in THF-MeOH to afford the corresponding acid in quantitative yield. The acid was coupled with amine using TBTU and TEA to afford the amide which purified by reverse phase prep HPLC and isolated in bis-TFA salt form as a beige solid. LC/MS: Retention time: 1.562 min; m/e 701 (MH^+). The product was observed to exist as inter-converting rotamers by 1H NMR (500 MHz, CHLOROFORM-D): δ ppm 1.14 - 1.52 (m, 7 H), 1.70 - 2.11 (m, 9 H), 2.75 - 3.11 (m, 10 H), 3.11 - 3.23 (m, *J*=7.17, 4.73 Hz, 1 H), 3.38 - 3.74 (m, 7 H), 3.89 (s, 3 H), 4.09 (s, 3 H), 4.28 - 4.75 (m, 1 H), 6.88 - 7.05 (m, 1 H), 7.07 - 7.16 (m, 1 H), 7.20 - 7.32 (m, 1 H), 7.50 - 7.66 (m, 1 H), 7.75 - 7.93 (m, 1 H), 8.05 - 8.26 (m, 1 H).

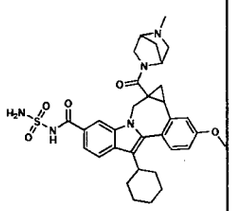
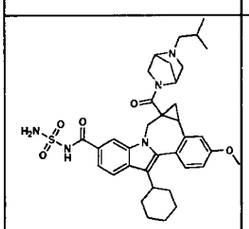
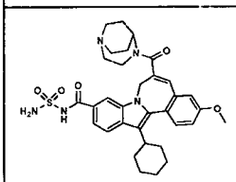
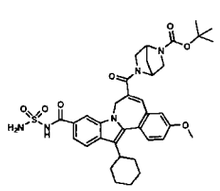
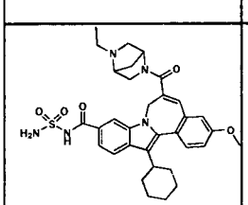
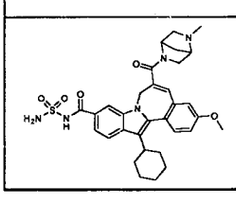
The general procedures below pertain to the experimental procedures that follow until noted. The acid (0.055 mmol, 1 eq.) was dissolved in dried DMF and followed by adding HATU (0.083 mmol, 1.5 eq.) and DIPEA(0.083. 1.5 eq.). The solution was stirred for 2 minutes and added into pre-weighted amine (0.083 mmol, 1.5 eq.) at room temperature. The mixture was stirred 14 h and purified by prep-HPLC. HPLC gradient methods: Method A: Column: Agilent SB CN4.6x100mm 3.5 um; mobile phase: water, 10 mM NH_4OH, ACN; Method B: Column: Phenomenex Gemini 4.6x100mm 5 um C18; mobile phase: water, 10 mM NH_4OH, ACN; Method C: Column: Waters x-Bidge C18 150x4.6mm 5 micron; mobile phase: water, 10 mM

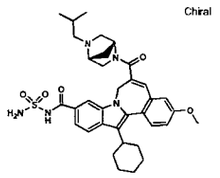
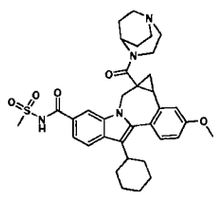
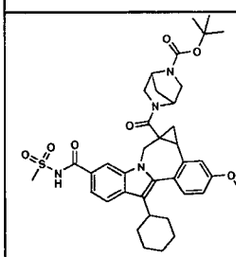
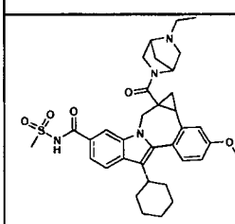
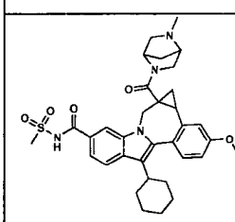
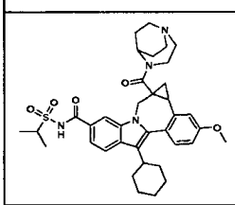
NH_4OH, ACN; Method D: Column: Waters Xbridge 2.1x50mm 5 um C18; mobile phase: water, 10 mM NH_4OH, ACN.

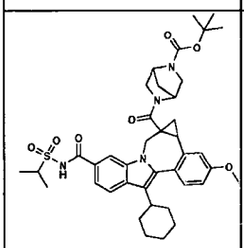
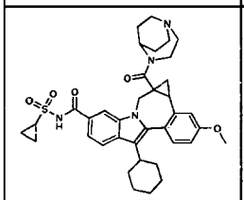
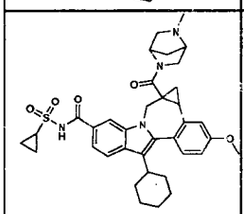
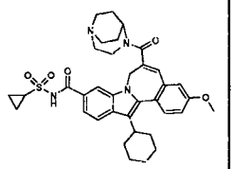
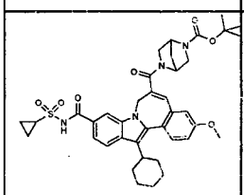
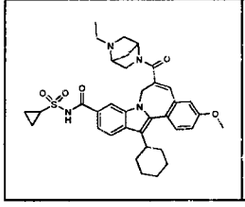
Structure	HPLC Ret. Time [min]	HPLC Purity [%]	MS Reported Mass	HPLC Method
	4.92	90.5	660.4	Method A
	2.11	100	660.39	Method D
	5.06	92.5	732.4	Method A
	5.32	100	718.43	Method A
	5.86	98.3	724.33	Method B
	7.79	99.4	732.33	Method B

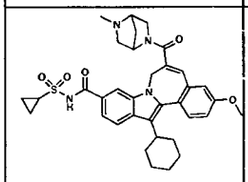
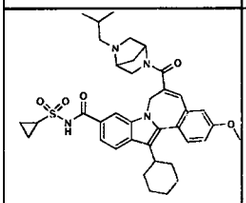
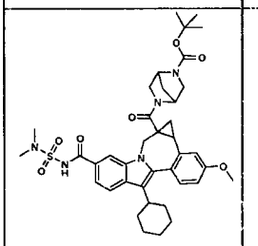
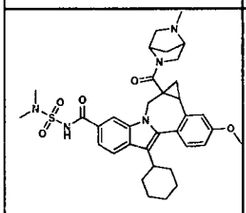
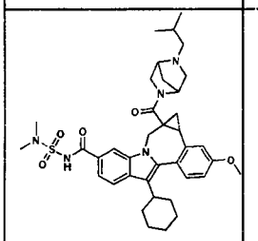
Structure	HPLC Ret. Time [min]	HPLC Purity [%]	MS Reported Mass	HPLC Method
	6.11	100	724.33	Method B
	5.01	100	660.34	Method B
	7.5	98.4	672.22	Method C
	9.6	99.3	744.22	Method C
	7.6	90.3	672.28	Method C
	7.41	93.6	658.23	Method C

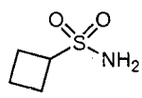
Structure	HPLC Ret. Time [min]	HPLC Purity [%]	MS Reported Mass	HPLC Method
	8.91	97	700.22	Method C
	2.46	100	646.74	Method D
	3.31	97	718.6	Method D
	2.38	100	646.73	Method D
	2.39	100	632.74	Method D
	1.94	96.4	631.8	Method D

Structure	HPLC Ret. Time [min]	HPLC Purity [%]	MS Reported Mass	HPLC Method
	2.06	100	617.84	Method D
	2.47	91.7	660.75	Method D
	6.99	93	618.12	Method D
	9.35	93.9	690.11	Method D
	7.16	100	618.12	Method D
	7.01	100	604.13	Method D

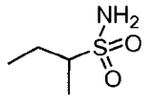
Structure	HPLC Ret. Time [min]	HPLC Purity [%]	MS Reported Mass	HPLC Method
	8.34	100	646.16	Method D
	2.05	96.3	631.39	Method D
	2.53	100	703.42	Method D
	1.96	90.6	631.38	Method D
	1.93	97.3	617.36	Method D
	7.28	100	659.2	Method D

Structure	HPLC Ret. Time [min]	HPLC Purity [%]	MS Reported Mass	HPLC Method
	7.02	100	731.07	Method D
	2.06	93.3	657.37	Method D
	2.17	93.2	643.35	Method D
	2.08	100	642.78	Method D
	2.95	100	714.66	Method D
	2.17	100	642.77	Method D

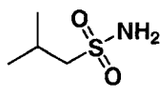
Structure	HPLC Ret. Time [min]	HPLC Purity [%]	MS Reported Mass	HPLC Method
	2.48	100	628.79	Method D
	2.39	100	670.71	Method D
	3.12	100.0	732.44	Method D
	2.10	100.0	646.39	Method D
	2.71	98.5	688.44	Method D



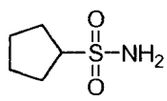
To a 250mL RBF equipped with a stir bar was added bromocyclobutane (3.49 mL, 37.0 mmol) and 70mL of diethyl ether. The flask was cooled to -78°C (acetone/dry ice bath). To this solution was then added, via syringe, 2.0eq. of a 1.7M solution of tert-butyllithium (43.6 mL, 74.1 mmol). The mixture was stirred for 60minutes, then cannulated into a 500mL flask containing sulfuryl chloride (6.00 mL, 74.1 mmol) in 30mL of diethylether at -78°C. The suspension was warmed to room temperature overnight. The white mixture was diluted with 40mL of diethylether, filtered and set aside. A 3 necked 500mL RBF equipped with a stir bar and dry THF (10 mL) was cooled to -65°C with the aid of a dry ice/isopropanol bath and gaseous ammonia was slowly sparged into the flask. Previously synthesized cyclobutanesulfonyl chloride (5.2g, 33.6 mmol) was then dripped in via syringe (crude mixture in ~200mL of ether/THF). Sparging of ammonia gas was continued for an additional 5 minutes. The mixture was kept at -65°C for 4 hours then allowed to slowly warm to room temperature. The reaction mixture was filtered and washed with 100mL of THF. The solvent was evaporated to give 2.1g of the desired sulfonamide (46% yield) as a pale yellow oily solid. ^{1}H NMR (500 MHz, DMSO-D6): δ ppm 1.81 - 1.89 (m, 2 H), 2.16 - 2.22 (m, 2 H), 2.23 - 2.31 (m, 2 H), 3.66 - 3.74 (m, 1 H), 6.68 (s, 2 H).



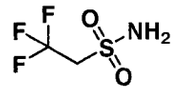
^{1}H NMR (500 MHz, DMSO-D6): δ ppm 0.94 (m, 3 H), 1.20 (m, 3 H), 1.30 – 1.45 (m, 1 H), 1.90 (m, 1 H), 2.76 (m, 1H), 6.59 (s, 2 H).



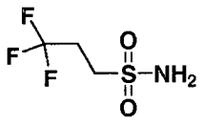
^{1}H NMR (500 MHz, DMSO-D6): δ ppm 1.02 (d, J = 6.95 Hz, 6 H), 2.11 (m, 1 H), 2.86 (d, J = 6.22 Hz, 2 H), 6.71 (s, 2 H).



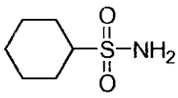
^{1}H NMR (500 MHz, DMSO-D6): δ ppm 1.51 – 1.66 (m, 4 H), 1.86 (m, 4 H), 3.37 (m, 1 H), 6.65 (s, 2 H).



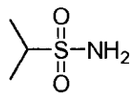
^{1}H NMR (500 MHz, DMSO-D6): δ ppm 4.24 (m, 2 H), 7.46 (s, 2 H).



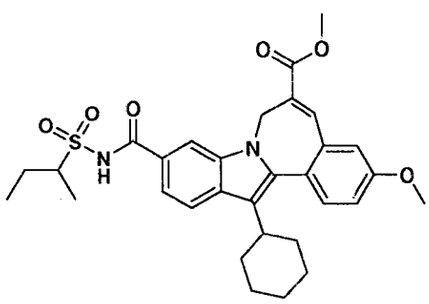
^{1}H NMR (500 MHz, DMSO-D6): δ ppm 2.70 (m, 2H), 3.20 (m, 2 H), 7.01 (s, 2 H).



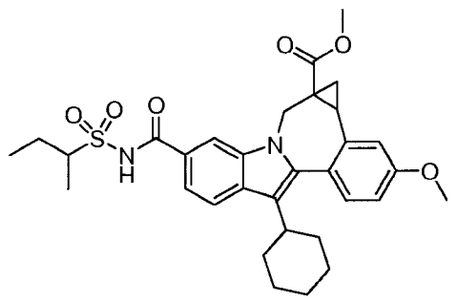
^{1}H NMR (500 MHz, DMSO-D6): δ ppm 1.07 – 1.17 (m, 1H), 1.22 – 1.38 (m, 4H), 1.62 (m, 1H), 1.78 (m, 2H), 2.05 (m, 2H), 2.68 – 2.77 (m, 1 H), 6.57 (s, 2 H).



^{1}H NMR (300 MHz, DMSO-D6): δ ppm 1.22 (d, *J*=6.59 Hz, 6 H), 3.00 (m, 1 H), 6.59 (s, 2 H).

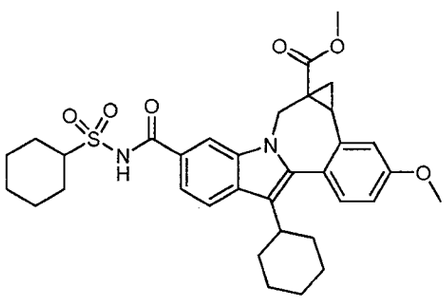


Methyl 10-((sec-butylsulfonyl)carbamoyl)-13-cyclohexyl-3-methoxy-7H-indolo[2,1-a][2]benzazepine-6-carboxylate . In a 100 mL round-bottomed flask (RBF) was added carboxylic acid 1 (575 mg, 1.291 mmol) and 1,1'-carbonyldiimidazole (460 mg, 2.84 mmol) in THF (15 mL) to give a yellow solution. The mixture was stirred at room temperature under nitrogen for 1 hour then heated to 70°C, in an oil bath, for 90 minutes. The mixture was cooled and sec-butyl sulfonamide (921 mg, 6.71 mmol) in 4 mL of THF was added along with neat DBU (0.389 mL, 2.58 mmol). The RBF was returned to the oil bath and heated overnight at 70°C. The reaction mixture was transferred to a separatory funnel, diluted with 100mL of DCM, washed x3 with 100 mL of 0.5 M HCl, then with 100 mL of H_2O, and finally saturated NaCl. The organic mixture was dried over MgSO4, filtered and concentrated to give 713mgs of the desired acylsulfonamide 2 as a yellow solid (96% yield) which was placed under vacuum overnight. LC data was recorded on a Shimadzu LC-10AS liquid chromatograph equipped with a Phenomenex-Luna 10μ, C18, 4.6x30mm column, using a SPD-10AV UV-Vis detector at a detector wave length of 220nM. The elution conditions employed a flow rate of 5 ml/min., a gradient of 100% solvent A / 0% solvent B to 0% solvent A / 100% solvent B, a gradient time of 2 min., a hold time of 1 min., and an analysis time of 3 min. where solvent A was 10% MeOH / 90% H2O / 0.1% trifluoroacetic acid and solvent B was 10% H2O / 90% MeOH / 0.1% trifluoroacetic acid. MS data was determined using a Micromass Platform for LC in electrospray mode.1H NMR (500 MHz, CD3OD): δ ppm 0.84 - 0.92 (m, 3 H), 1.03 (t, J =7.32 Hz, 3 H), 1.23 (m, 1 H), 1.28 - 1.44 (m, 7 H), 1.58 (m, 1 H), 1.72 (m, 2 H), 1.85 (m, 1 H), 1.95 - 2.07 (m, 3 H), 2.17 (m, 1 H), 2.78 (m, 1 H), 3.69 (m, 2 H), 3.83 - 3.91 (m, 3 H), 7.02 (s, 1 H), 7.11 (m, 1 H), 7.47 (d, J = 7.63 Hz, 1 H), 7.74 (m, 3 H), 8.25 (s, 1 H). LC/MS: m/z 565.22, Rf 2.192 min., 97.5 % purity.

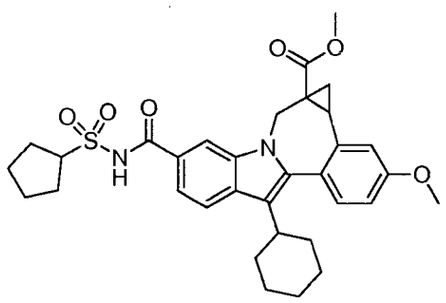


Methyl 5-((sec-butylsulfonyl)carbamoyl)-8-cyclohexyl-11-methoxy-1,12b-dihydro cyclopropa[d]indolo[2,1-a][2]benzazepine-1a(2H)-carboxylate. To 63.1 mgs of 95% NaH in 5 mL of dry DMF in a 100 mL RBF was added 629 mgs of trimethylsulfoxonium iodide at room temperature. The mixture was stirred at room temperature under nitrogen for 30minutes. A solution of Intermediate 9 (in 7 mL of DMF) was added via syringe and the reaction was stirred for 15 - 20 minutes. The reaction mixture was quickly cooled to 0°C with an ice bath, 1 mL of 1 M HCl was added followed by 60 mL of ice water. The heterogeneous mixture was stirred for 30 minutes. The mixture was filtered and the yellow solid was washed with ice water. The solid was taken up in 2% methanol/DCM and was purified using a Biotage Horizon MPLC employing a 40+M column with a solvent gradient of 2% methanol/DCM to 10% methanol/DCM. 450mgs (62%yield) of the compound was obtained as a yellow solid after solvent evaporation. LC data was recorded on a Shimadzu LC-10AS liquid chromatograph equipped with a Phenomenex-Luna 10μ, C18, 4.6x30mm column, using a SPD-10AV UV-Vis detector at a detector wave length of 220nM. The elution conditions employed a flow rate of 5 ml/min., a gradient of 100% solvent A / 0% solvent B to 0% solvent A / 100% solvent B, a gradient time of 2 min., a hold time of 1 min., and an analysis time of 3 min. where solvent A was 10% MeOH / 90% H2O / 0.1% trifluoroacetic acid and solvent B was 10% H2O / 90% MeOH / 0.1% trifluoroacetic acid. MS data was determined using a Micromass Platform for LC in electrospray mode. 1H NMR (300 MHz, CD3OD): δ ppm 0.19 (m, 0.35 H), 1.03 - 1.14 (m, 3 H), 1.19 - 1.34 (m, 2.65 H), 1.43 (m, 5 H), 1.55 - 1.66 (m, 2 H), 1.74 (m, 2 H), 1.89 - 1.94 (m, 2 H), 1.99 - 2.14 (m, 3 H), 2.64 - 2.95 (m, 2 H), 3.35 (d, J=15.00 Hz, 0.65 H), 3.48 (m, 2 H), 3.67 - 3.81 (m, 2 H), 3.85 (s, 3 H), 3.90 – 3.98 (m, 0.35 H), 5.17 (m, 0.35 H), 5.36 (m, 0.65 H), 6.91 - 6.98 (m, 1 H), 7.09 (m, 0.35 H), 7.16 (m, 0.65 H), 7.19 - 7.27 (m, 1 H), 7.52 - 7.65 (m, 1 H),

7.83 (m, 1 H), 8.09 (s, 0.35 H), 8.29 (s, 0.65 H). LC/MS: m/z 579.31, Rf 2.167 min., 95.2 % purity.

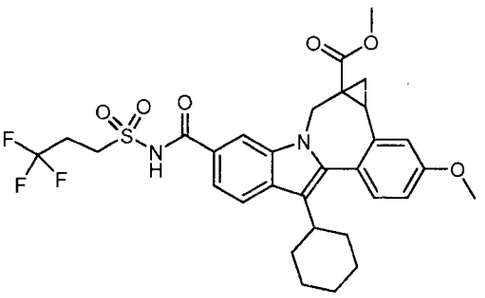


Methyl 8-cyclohexyl-5-((cyclohexylsulfonyl)carbamoyl)-11-methoxy-1,12b-dihydrocyclo propa[d]indolo[2,1-a][2]benzazepine-1a(2H)-carboxylate. 1H NMR (300 MHz, CD3OD): δ ppm 0.23 (m, 0.35 H), 1.14 - 1.53 (m, 10 H), 1.60 - 1.79 (m, 3 H), 1.91 (m, 3 H), 2.09 (m, 1.65 H), 2.18 (m, 3 H), 2.81 – 2.98 (m, 3 H), 3.41 – 3.46 (m, 0.65 H), 3.50 (m, 2 H), 3.71 - 3.79 (m, 2 H), 3.88 (s, 3 H), 3.99 – 4.04 (m, 0.35 H), 5.25 (m, 0.35 H), 5.45 (m, 0.65 H), 6.97 – 7.02 (m, 1 H), 7.13 (m, 0.35 H), 7.21 (m, 0.65 H), 7.26 - 7.32 (m, 1 H), 7.55 - 7.65 (m, 1 H), 7.85 – 7.92 (m, 1 H), 8.11 (s, 0.35 H), 8.32 (s, 0.65 H). LC/MS: m/z 605.42, Rf 2.223 min., 99.2 % purity.

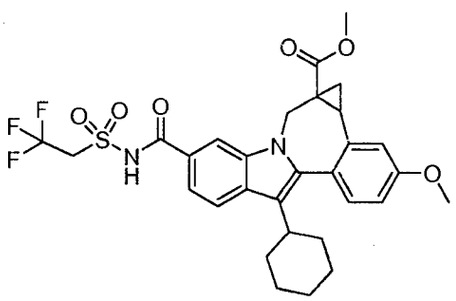


Methyl 8-cyclohexyl-5-((cyclopentylsulfonyl)carbamoyl)-11-methoxy-1,12b-dihydrocyclo propa[d]indolo[2,1-a][2]benzazepine-1a(2H)-carboxylate. 1H NMR (300 MHz, CD3OD): δ ppm 0.23 (m, 0.35 H), 1.27 (m, 2.65 H), 1.39 (m, 2 H), 1.60 - 1.79 (m, 7 H), 1.91 – 2.19 (m, 8 H), 2.67 – 2.97 (m, 2 H), 3.47 (m, 0.65 H), 3.50 (m, 3 H), 3.78 - 3.87 (m, 3 H), 4.10 (m, 0.35 H), 4.29 (m, 1 H), 5.22 (m, 0.35 H), 5.43 (m, 0.65 H), 6.98 – 7.02 (m, 1 H), 7.14 (m, 0.35 H), 7.21 (m, 0.65 H), 7.26 -

7.32 (m, 1 H), 7.55 - 7.65 (m, 1 H), 7.85 – 7.91 (m, 1 H), 8.10 (s, 0.35 H), 8.32 (s, 0.65 H). LC/MS: m/z 591.33, Rf 2.200 min., 100 % purity.

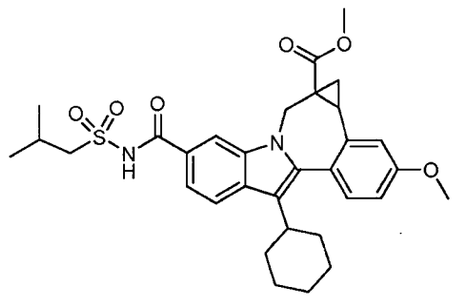


Methyl 8-cyclohexyl-11-methoxy-5-(((3,3,3-trifluoropropyl)sulfonyl)carbamoyl)-1,12b-dihydrocyclopropa[d]indolo[2,1-a][2]benzazepine-1a(2H)-carboxylate. 1H NMR (300 MHz, CD3OD): δ ppm 0.19 (m, 0.35 H), 1.25 (m, 1.65 H), 1.41 (m, 2 H), 1.65 (m, 1 H), 1.76 (m, 2 H), 1.94 (m, 2 H), 2.04 (m, 1 H), 2.61 – 2.84 (m, 6 H), 2.88 – 2.96 (m, 1 H), 3.35 – 3.40 (m, 0.65 H), 3.48 (m, 2 H), 3.80 (m, 2 H), 3.86 (m, 3 H), 3.89 – 3.98 (m, 0.35 H), 5.18 (m, 0.35 H), 5.38 (m, 0.65 H), 6.96 – 7.01 (m, 1 H), 7.13 (m, 0.35 H), 7.20 (m, 0.65 H), 7.24 - 7.30 (m, 1 H), 7.58 - 7.69 (m, 1 H), 7.84 – 7.90 (m, 1 H), 8.13 (s, 0.35 H), 8.34 (s, 0.65 H). LC/MS: m/z 619.32, Rf 2.188 min., 99.5 % purity.



Methyl 8-cyclohexyl-11-methoxy-5-(((2,2,2-trifluoroethyl)sulfonyl)carbamoyl)-1,12b-dihydro cyclopropa[d]indolo[2,1-a][2]benzazepine-1a(2H)-carboxylate. 1H NMR (300 MHz, CD3OD): δ ppm 0.13 (m, 0.35 H), 1.18 (m, 1.65 H), 1.38 (m, 2 H), 1.57 - 1.62 (m, 2 H), 1.73 (m, 2 H), 1.87 (m, 2 H), 1.96 - 2.05 (m, 1 H), 2.60 – 2.90 (m, 1.35 H), 3.17 – 3.22 (m, 0.65 H), 3.45 (m, 2 H), 3.74 (m, 1 H), 3.84 (m, 2 H), 4.04 – 4.10 (m, 3 H), 4.38 – 4.53 (m, 2

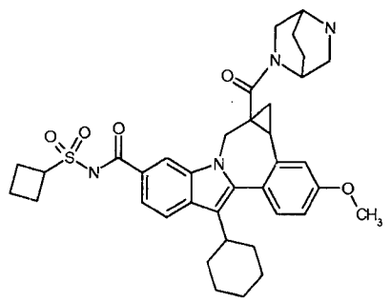
H), 5.06 (m, 0.35 H), 5.18 (m, 0.65 H), 6.90 – 6.96 (m, 1 H), 7.06 (m, 0.35 H), 7.13 (m, 0.65 H), 7.16 - 7.22 (m, 1 H), 7.63 (m, 0.65 H), 7.70 - 7.80 (m, 1.35 H), 8.14 (s, 0.35 H), 8.33 (s, 0.65 H). LC/MS: m/z 605.29, Rf 2.178 min., 96.5 % purity.



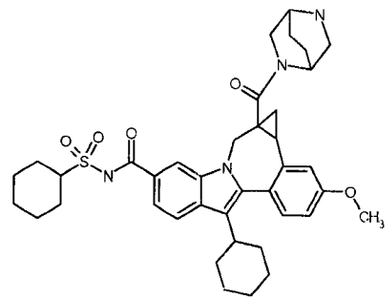
Methyl 8-cyclohexyl-5-((isobutylsulfonyl)carbamoyl)-11-methoxy-1,12b-dihydrocyclopropa [d]indolo[2,1-a][2]benzazepine-1a(2H)-carboxylate. 1H NMR (300 MHz, CD3OD): δ ppm 0.17 (m, 0.35 H), 1.09 (m, 6 H), 1.22 (m, 1.65 H), 1.38 (m, 2 H), 1.49 – 1.60 (m, 1 H), 1.73 (m, 2 H), 1.87 (m, 2 H), 1.96 - 2.05 (m, 2 H), 2.15 – 2.39 (m, 1 H), 2.61 – 2.87 (m, 2 H), 2.96 (d, J = 6.22 Hz, 2 H), 3.19 (m, 2 H), 3.43 (m, 2 H), 3.70 (m, 2 H), 3.84 (m, 2 H), 5.06 – 5.11 (m, 1 H), 6.90 – 6.95 (m, 1 H), 7.05 - 7.11 (m, 1 H), 7.16 - 7.23 (m, 1 H), 7.67 - 782 (m, 2 H), 8.20 (s, 0.35 H), 8.39 (s, 0.65 H). LC/MS: m/z 579.30, Rf 2.190 min., 96.2% purity.

General procedure for the transformation of esters of formula I to corresponding amides. In a 100 mL round-bottomed flask was added 1 N sodium hydroxide (3 eq., 1.583 ml, 1.583 mmol) and bridged ester 1 (1 eq., 0.528 mmol) in methanol (4.00 ml) and THF (4.00 ml) to give a yellow solution. The mixture was stirred for 3 hours at room temperature. 3 equivalents of 1 N HCl was then added, the product diluted with ethyl acetate then extracted, washed with brine and dried over $MgSO_4$. Filtration and subsequent evaporation of volatiles gave the carboxylic acids 2 in near quantitative yield. To a 0.10 mmol solution of carboxylic acid 2 in 1 mL of anhydrous N,N-Dimethylformamide (DMF) in a 2 dram vial equipped with a Teflon™ lined screw cap was added 0.3 mmol (3 eq.) of 2-(1H-Benzotriazole-1-yl)-1,1,3,3,-Tetramethyluronium Tetrafluoroborate (TBTU) in 1.0 mL of anhydrous DMF followed by the addition of 0.2 mmol (2 eq.) of amine 3 in 1.0 mL of

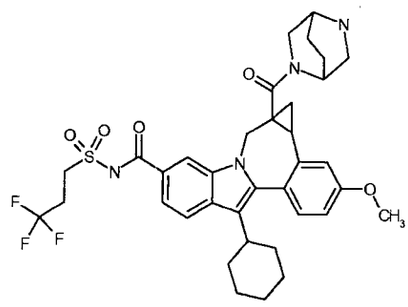
anhydrous DMF and 0.4 mmol of neat *N,N*-diisopropylethylamine . The reaction was shaken on a VWR Vortex-Genie 2 Mixer overnight at room temperature. The reaction volumes were then reduced in a Savant Speedvac and the crude products were taken up in 1.2 mL of methanol and purified using a Shimadzu preparative HPLC employing methanol/water and 0.1% trifluoroacetic acid buffer with a Phenomenex Luna, C18, 30 mm x 100 mm, 10 µm column at a gradient of 40-100% B and a flow rate of 40 mL/min. over 10 minutes with a 5-10 minute hold, to give carboxamides 4 as yellow amorphous solids (65% - 70% yield). Post-purification LC/MS data was obtained on a Shimadzu analytical LC /Micromass Platform LC (ESI+) at 220nm using the following set of conditions: Column I (Phenomenex 10µm C18, 4.6 x 30mm), Solvent system I (gradient of 0-100%B where B = 90% HPLC grade methanol/ 0.1% trifluoroacetic acid/ 10% HPLC grade water), in 2 minutes with a 1 minute hold at a flow rate of 5 mL/minute.



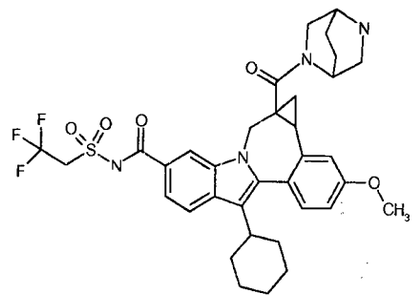
***N*-(cyclobutylsulfonyl)-8-cyclohexyl-1a-(2,5-diazabicyclo[2.2.2]oct-2-ylcarbonyl)-11-methoxy-1,1a,2,12b-tetrahydrocyclopropa[*d*]indolo[2,1-*a*][2]benzazepine-5-carboxamide**. LC/MS: m/z 657.51, Rf 1.783 min., 96.5 % purity.



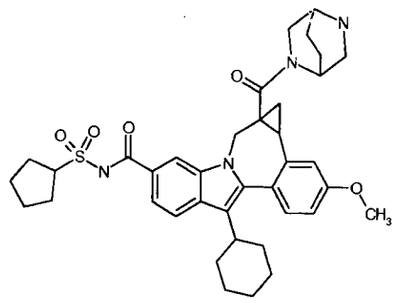
8-Cyclohexyl-N-(cyclohexylsulfonyl)-1a-(2,5-diazabicyclo[2.2.2]oct-2-ylcarbonyl)-11-methoxy-1,1a,2,12b-tetrahydrocyclopropa[d]indolo[2,1-a][2]benzazepine-5-carboxamide. LC/MS: m/z 685.52, Rf 1.872 min., 99.3 % purity.



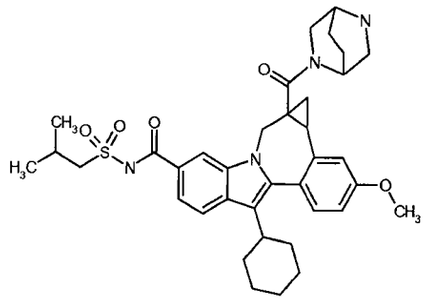
8-Cyclohexyl-1a-(2,5-diazabicyclo[2.2.2]oct-2-ylcarbonyl)-11-methoxy-*N*-((3,3,3-trifluoropropyl)sulfonyl)-1,1a,2,12b-tetrahydrocyclopropa[*d*]indolo[2,1-*a*] [2]benzazepine-5-carboxamide. LC/MS: m/z 699.49, Rf 1.793 min., 98.0 % purity.



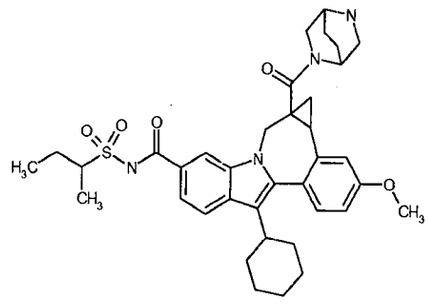
8-Cyclohexyl-1a-(2,5-diazabicyclo[2.2.2]oct-2-ylcarbonyl)-11-methoxy-N-((2,2,2-trifluoroethyl)sulfonyl)-1,1a,2,12b-tetrahydrocyclopropa[d]indolo[2,1-a][2]benzazepine-5-carboxamide. LC/MS: m/z 685.45, Rf 1.778 min., 96.5 % purity.



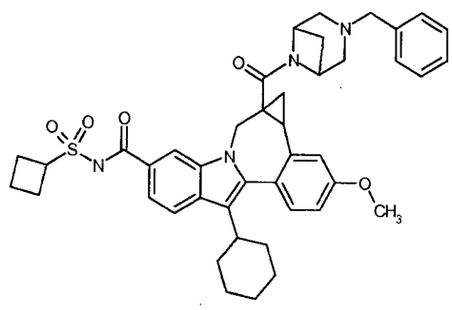
8-Cyclohexyl-N-(cyclopentylsulfonyl)-1a-(2,5-diazabicyclo[2.2.2]oct-2-ylcarbonyl)-11-methoxy-1,1a,2,12b-tetrahydrocyclopropa[d]indolo[2,1-a][2]benzazepine-5-carboxamide. LC/MS: m/z 671.51, Rf 1.833 min., 99.3 % purity.



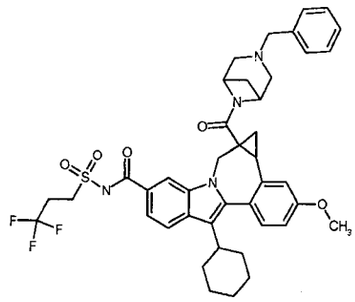
8-Cyclohexyl-1a-(2,5-diazabicyclo[2.2.2]oct-2-ylcarbonyl)-*N*-(isobutylsulfonyl)-11-methoxy-1,1a,2,12b-tetrahydrocyclopropa[*d*]indolo[2,1-*a*][2]benzazepine-5-carboxamide. LC/MS: m/z 659.52, Rf 1.808 min., 98.1 % purity.



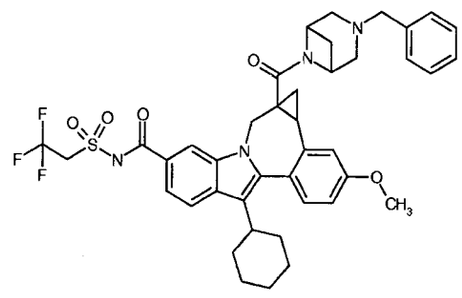
N-(sec-butylsulfonyl)-8-cyclohexyl-1a-(2,5-diazabicyclo[2.2.2]oct-2-ylcarbonyl)-11-methoxy-1,1a,2,12b-tetrahydrocyclopropa[d]indolo[2,1-a][2]benzazepine-5-carboxamide. LC/MS: m/z 659.52, Rf 1.805 min., 98.2 % purity.



1a-((3-Benzyl-3,6-diazabicyclo[3.1.1]hept-6-yl)carbonyl)-N-(cyclobutylsulfonyl)-8-cyclohexyl-11-methoxy-1,1a,2,12b-tetrahydrocyclopropa[d]indolo[2,1-a] [2]benzazepine-5-carboxamide. 1H NMR (300 MHz, CD3OD): δ ppm 0.16 (m, 0.35 H), 1.27 - 1.37 (m, 2 H), 1.41 (m, 1 H), 1.45 (m, 1.65 H), 1.62 (m, 1 H), 2.05 (m, 2 H), 2.06 - 2.15 (m, 7 H) 2.39 (m, 2 H), 2.59 - 2.68 (m, 2 H), 2.81 - 2.90 (m, 1 H), 3.02 (m, 1 H), 3.19 (m, 1 H), 3.36 - 3.45 (m, 1 H), 3.47 (m, 1 H), 3.53 (m, 1 H), 3.62 (m, 1 H), 3.90 - 3.97 (m, 3 H), 4.15 – 4.33 (m, 1 H), 4.50 (m, 1 H), 4.59 (m, 1 H), 4.77 (m, 2 H), 5.39 (m, 2 H), 7.06 (dd, J=8.55, 2.44 Hz, 1 H), 7.24 (d, J=2.44 Hz, 1 H), 7.32 - 7.41 (m, 2 H), 7.45 - 7.52 (m, 3 H), 7.55 - 7.64 (m, 2 H), 7.92 - 8.00 (m, 1 H), 8.21 (m, 1 H). LC/MS: m/z 733.48, Rf 1.833 min., 98.5 % purity.

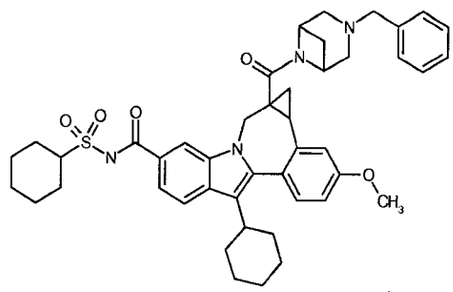


1a-((3-Benzyl-3,6-diazabicyclo[3.1.1]hept-6-yl)carbonyl)-8-cyclohexyl-11-methoxy-N-((3,3,3-trifluoropropyl)sulfonyl)-1,1a,2,12b-tetrahydrocyclopropa[d]indolo[2,1-a] [2]benzazepine-5-carboxamide. 1H NMR (500 MHz, CD3OD): δ ppm 0.16 (m, 0.35 H), 1.28 - 1.37 (m, 3 H), 1.41 (m, 1.65 H), 1.47 (m, 2 H), 1.70 (m, 1 H), 1.83 (m, 2 H), 1.98 - 2.14 (m, 5 H), 2.59 (m, 1 H), 2.78 - 2.86 (m, 4 H), 3.03 (m, 1 H), 3.16 - 3.24 (m, 1 H), 3.44 - 3.58 (m, 2 H), 3.85 - 3.96 (m, 6 H), 4.18 (m, 1 H), 4.47 (m, 1 H), 5.47 (m` 7.07 (m, 1 H), 7.20 - 7.26 (m, 1 H), 7.32 - 7.39 (m, 2 H), 7.46 (m, 3 H), 7.59 – 7.67 (m, 2 H), 7.94 – 7.98 (m, 1 H), 8.15 - 8.29 (m, 1 H). LC/MS: m/z 775.45, Rf 1.888 min., 95.7 % purity.

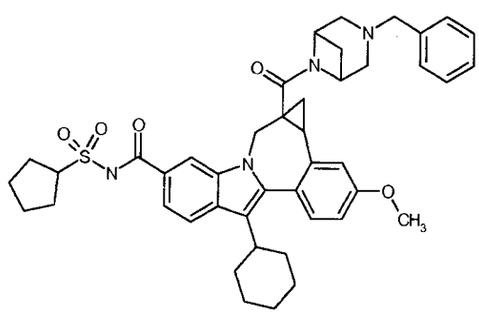


1a-((3-Benzyl-3,6-diazabicyclo[3.1.1]hept-6-yl)carbonyl)-8-cyclohexyl-11-methoxy-N-((2,2,2-trifluoroethyl)sulfonyl)-1,1a,2,12b-tetrahydrocyclopropa[d]indolo[2,1-a] [2]benzazepine-5-carboxamide. 1H NMR (300 MHz, CD3OD): δ ppm 0.10 (m, 0.35 H), 1.28 (m, 2 H), 1.35 (m, 3 H), 1.51 (m, 0.65 H), 1.68 - 1.84 (m, 3 H), 1.87 - 2.10 (m, 5 H), 2.53 (m, 1 H), 2.71 - 2.86 (m, 1 H), 2.89 - 3.04 (m, 1 H), 3.43 - 3.58 (m, 3 H), 3.67 - 3.80 (m, 1 H), 3.87 (s, 3 H), 4.13 (m, 1 H), 4.32 (m, 1 H), 4.49 - 4.74 (m, 3 H), 4.90 - 5.04 (m, 1 H), 5.30 (m, 1 H), 7.00 (m, 1 H), 7.15 - 7.23 (m, 1 H), 7.25 - 7.33 (m, 2 H), 7.36 - 7.46 (m, 3 H), 7.48 -

7.61 (m, 2 H), 7.89 (m, 1 H), 8.09 - 8.18 (m, 1 H). LC/MS: m/z 761.47, Rf 1.850 min., 97.0 % purity.

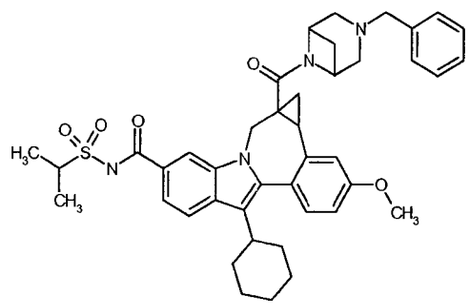


1a-((3-Benzyl-3,6-diazabicyclo[3.1.1]hept-6-yl)carbonyl)-8-cyclohexyl-N-(cyclohexylsulfonyl)-11-methoxy-1,1a,2,12b-tetrahydrocyclopropa[d]indolo [2,1-a][2]benzazepine-5-carboxamide. 1H NMR (500 MHz, CD3OD): δ ppm 0.14 (m, 0.35 H), 1.21 – 1.48 (m, 9.65 H), 1.63 (m, 3 H), 1.68 (m, 1 H), 1.80 (m, 3 H), 1.93 (m, 4 H), 1.98 - 2.08 - 2.17 (m, 5 H), 2.60 - 2.87 (m, 1 H), 2.99 (m, 1 H), 3.18 (m, 1 H), 3.44 (m, 1 H), 3.55 (m, 2 H), 3.68 - 3.77 (m, 2 H), 3.86 - 3.94 (m, 3 H), 4.16 (m, 1 H), 4.58 (m, 1 H), 5.36 (m, 1 H), 7.04 (dd, J=8.55, 2.75 Hz, 1 H), 7.18 - 7.27 (m, 1 H), 7.30 - 7.38 (m, 2 H), 7.42 - 7.50 (m, 3 H), 7.53 - 7.60 (m, 2 H), 7.92 (m, 1 H), 8.12 - 8.22 (m, 1 H). LC/MS: m/z 761.54, Rf 1.922 min., 98.6 % purity.

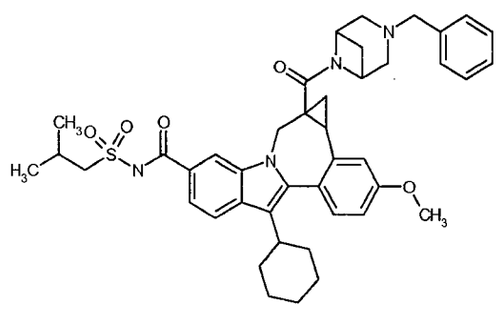


1a-((3-Benzyl-3,6-diazabicyclo[3.1.1]hept-6-yl)carbonyl)-8-cyclohexyl-N-(cyclopentylsulfonyl)-11-methoxy-1,1a,2,12b-tetrahydrocyclopropa[d]indolo[2,1-a] [2]benzazepine-5-carboxamide. 1H NMR (500 MHz, CD3OD): δ ppm 0.012 (m, 0.35), 1.33 (m, 2 H), 1.39 (m, 1.65 H), 1.45 (m, 3 H), 1.65 (m, 1 H), 1.79 (m, 3 H), 1.83 (m, 4 H), 1.91 (m, 2 H), 1.94 - 2.14 (m, 6 H), 2.58 - 2.89 (m, 2 H), 2.99 (m, 2

H), 3.16 (m, 1 H), 3.36 (m, 2 H), 3.40 - 3.56 (m, 2 H), 3.89 (m, 3 H), 4.30 (m, 1 H), 4.50 (m, 1 H), 5.38 (m, 1 H), 7.04 (dd, J=8.39, 2.59 Hz, 1 H), 7.18 - 7.22 (m, 1 H), 7.32 - 7.37 (m, 2 H), 7.44 (m, 3 H), 7.57 (m, 2 H), 7.91 - 7.95 (m, 1 H), 8.10 – 8.21 (m, 1 H). LC/MS: m/z 747.50, Rf 1.868 min., 96.3 % purity.

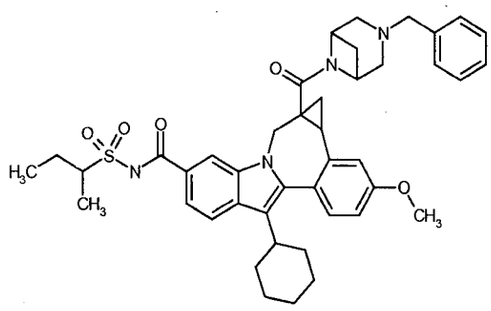


1a-((3-Benzyl-3,6-diazabicyclo[3.1.1]hept-6-yl)carbonyl)-8-cyclohexyl-N-(isopropyl sulfonyl)-11-methoxy-1,1a,2,12b-tetrahydrocyclopropa[d]indolo[2,1-a][2] benzazepine-5-carboxamide. 1H NMR (300 MHz, CD3OD): δ ppm 0.12 (m, 0.35 H), 1.34 (m, 6.65 H), 1.43 (m, 6 H), 1.59 (m, 1 H), 1.79 (m, 3 H), 1.97 (m, 5 H), 2.56 - 2.85 (m, 1 H), 2.92 - 3.07 (m, 1 H), 3.45 - 3.60 (m, 3 H), 3.85 (m, 1 H), 3.88 - 4.00 (m, 6 H), 4.52 (m, 1 H), 5.32 (m, 1 H), 7.03 (dd, J=8.78, 2.56 Hz, 1 H), 7.17 - 7.23 (m, 1 H), 7.29 - 7.36 (m, 2 H), 7.41 - 7.49 (m, 3 H), 7.51 - 7.65 (m, 2 H), 7.88 - 7.96 (m, 1 H), 8.08 - 8.19 (m, 1 H). LC/MS: m/z 721.50, Rf 1.828 min., 97.0 % purity.

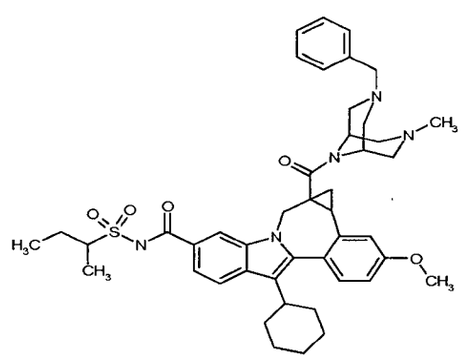


1a-((3-Benzyl-3,6-diazabicyclo[3.1.1]hept-6-yl)carbonyl)-8-cyclohexyl-N-(isobutylsulfonyl)-11-methoxy-1,1a,2,12b-tetrahydrocyclopropa[d]indolo[2,1-a][2]benzazepine-5-carboxamide. 1H NMR (500 MHz, CD3OD): δ ppm 0.14 (m,

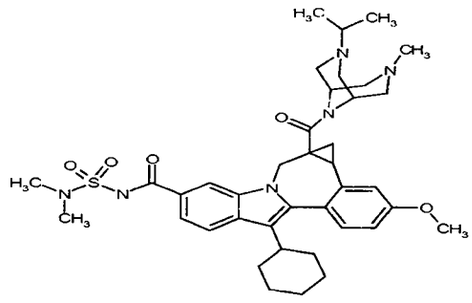
0.35 H), 1.13 (m, 6.65 H), 1.23 (m, 1 H), 1.26 - 1.35 (m, 2 H), 1.39 (m, 2 H), 1.42 (m, 2 H), 1.59 (m, 1 H), 1.81 (m, 2 H), 1.95 (m, 2 H), 2.02 (m, 1 H), 2.12 (m, 2 H), 2.27 - 2.36 (m, 2 H), 2.87 (m, 1 H), 3.01 (m, 1 H), 3.13 - 3.22 (m, 1 H), 3.39 – 3.44 (m, 2 H), 3.47 - 3.53 (m, 3 H), 3.88 - 3.95 (m, 4 H), 4.58 (m, 1 H), 5.36 (m, 1 H), 7.04 (dd, J=8.55, 2.44 Hz, 1 H), 7.17 - 7.24 (m, 1 H), 7.30 - 7.38 (m, 2 H), 7.45 (m, 3 H), 7.55 - 7.64 (m, 2 H), 7.92 - 8.00 (m, 1 H), 8.10 - 8.21 (m, 1 H). LC/MS: m/z 735.51, Rf 1.895 min., 95.0 % purity.



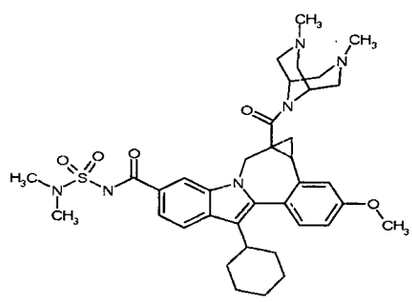
1a-((3-Benzyl-3,6-diazabicyclo[3.1.1]hept-6-yl)carbonyl)-N-(sec-butylsulfonyl)-8-cyclohexyl-11-methoxy-1,1a,2,12b-tetrahydrocyclopropa[d]indolo[2,1-a] [2]benzazepine-5-carboxamide. 1H NMR (300 MHz, CD3OD): δ ppm 0.13 (m, 0.35 H), 1.01 - 1.13 (m, 3.65 H), 1.21 (m, 3 H), 1.30 - 1.45 (m, 6 H), 1.50 - 1.80 (m, 6 H), 1.80 – 2.12 (m, 4 H), 2.57 - 2.86 (m, 2 H), 3.00 (m, 1 H), 3.55 (m, 3 H), 3.76 (m, 2 H), 3.84 - 3.94 (m, 3 H), 4.11 (m, 2 H), 4.56 (m, 1 H), 5.36 (m, 1 H), 7.03 – 7.09 (m, 1 H), 7.23 (m, 1 H), 7.27 - 7.40 (m, 3 H), 7.45 -7.86 (m, 4 H), 7.92 – 8.00 (m, 1 H), 8.13 - 8.23 (m, 1 H). LC/MS: m/z 735.60, Rf 1.865 min., 95.2 % purity.



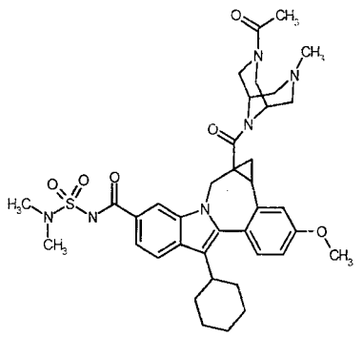
1a-((3-Benzyl-7-methyl-3,7,9-triazabicyclo[3.3.1]non-9-yl)carbonyl)-N-(sec-butyl sulfonyl)-8-cyclohexyl-11-methoxy-1,1a,2,12b-tetrahydrocyclopropa[d]indolo[2,1-a] [2]benzazepine-5-carboxamide. 1H NMR (300 MHz, CD3OD): δ ppm 0.20 (m, 0.20 H), 1.06 - 1.14 (m, 3 H), 1.20 - 1.36 (m, 2.80 H), 1.42 (m, 6 H), 1.72 (m, 4 H), 1.98 – 2.13 (m, 6 H), 2.62 (m, 2 H), 2.85 (m, 4 H), 3.15 (m, 1 H), 3.52 (m, 2 H), 3.63 (m, 2 H), 3.76 (m, 2 H), 3.87 (m, 4 H), 4.11 (m, 1 H), 4.38 (m, 1 H), 4.55 (m, 1 H), 5.06 (m, 1 H), 6.97 - 7.05 (m, 1 H), 7.11 - 7.17 (m, 1 H), 7.27 - 7.42 (m, 5 H), 7.59 (m, 2 H), 7.90 (m, 1 H), 8.01 – 8.09 (m, 1 H). LC/MS: m/z 779.48, Rf 1.897 min., 95.3 % purity.



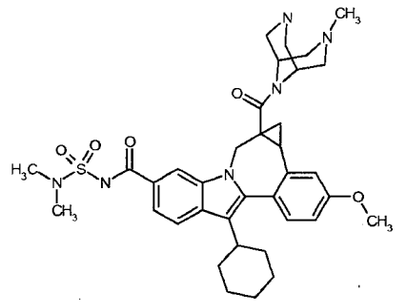
8-Cyclohexyl-N-(dimethylsulfamoyl)-1a-((3-isopropyl-7-methyl-3,7,9-triazabicyclo [3.3.1]non-9-yl)carbonyl)-11-methoxy-1,1a,2,12b-tetrahydrocyclopropa[d]indolo [2,1-a][2]benzazepine-5-carboxamide. 1H NMR (300 MHz, CD3OD): δ ppm 0.19 (m, 0.35 H), 1.12 (m, 3.65 H), 1.20 - 1.35 (m, 4 H), 1.39 (m, 2 H), 1.45 - 1.58 (m, 2 H), 1.64 (m, 2 H), 1.78 (m, 3 H), 2.00 (m, 6 H), 2.61 (m, 3 H), 2.74 - 2.90 (m, 2 H), 2.90 - 3.05 (m, 6 H), 3.48 (m, 1 H), 3.61 (m, 2 H), 3.84 - 3.91 (m, 4 H), 4.15 (m, 1 H), 4.45 (m, 1 H), 5.07 (m, 1 H), 7.01 (m, 1 H), 7.11 - 7.20 (m, 1 H), 7.26 - 7.35 (m, 1 H), 7.50 - 7.63 (m, 1 H), 7.88 (m, 1 H), 8.00 - 8.09 (m, 1 H). LC/MS: m/z 717.52, Rf 1.762 min., 97.8% purity.



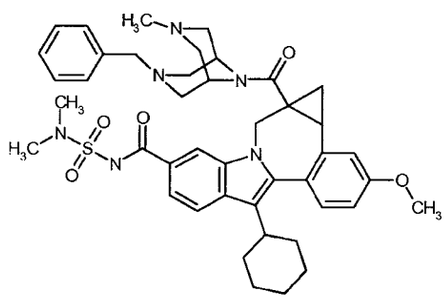
8-Cyclohexyl-N-(dimethylsulfamoyl)-1a-((3,7-dimethyl-3,7,9-triazabicyclo[3.3.1] non-9-yl)carbonyl)-11-methoxy-1,1a,2,12b-tetrahydrocyclopropa[d]indolo[2,1-a] [2]benzazepine-5-carboxamide. 1H NMR (300 MHz, CD3OD): δ ppm 0.24 (m, 0.20 H), 1.24 - 1.38 (m, 2.80 H), 1.45 (m, 4 H), 1.56 (m, 1 H), 1.83 (m, 2 H), 2.04 (m, 4 H), 2.65 (m, 1 H), 2.82 - 2.91 (m, 1 H), 2.93 - 3.05 (m, 9 H), 3.17 (m, 3 H), 3.49 (m, 1 H), 3.64 (m, 2 H), 3.78 (m, 1 H), 3.86 - 3.95 (m, 4 H), 4.03 (m, 1 H), 4.18 (m, 1 H), 4.37 (m, 1 H), 4.51 (m, 1 H), 5.08 (d, J=15.37 Hz, 1 H), 6.99 - 7.07 (m, 1 H), 7.13 - 7.22 (m, 1 H), 7.29 - 7.37 (m, 1 H), 7.51 - 7.63 (m, 1 H), 7.89 (m, 1 H), 7.99 - 8.10 (m, 1 H). LC/MS: m/z 689.50, Rf 1.813 min., 98.3 % purity.



1a-((3-Acetyl-7-methyl-3,7,9-triazabicyclo[3.3.1]non-9-yl)carbonyl)-8-cyclohexyl-N-(dimethylsulfamoyl)-11-methoxy-1,1a,2,12b-tetrahydrocyclopropa[d]indolo[2,1-a] [2]benzazepine-5-carboxamide. 1H NMR (300 MHz, CD3OD): δ ppm 0.51 (m, 0.20 H), 1.68 (m, 4.80 H), 1.98 (m, 2 H), 2.12 (m, 2 H), 2.41 (m, 7 H), 2.98 (m, 1 H), 3.19 (m, 2 H), 3.56 - 3.65 (m, 13 H), 3.94 - 4.10 (m, 2 H), 4.14 - 4.29 (m, 4 H), 4.95 (m, 2 H), 5.40 (m, 1 H), 7.35 (m, 1 H), 7.47 - 7.53 (m, 1 H), 7.60 - 7.67 (m, 1 H), 7.85 (m, 1 H), 8.16 - 8.25 (m, 1 H), 8.36 (s, 1 H). LC/MS: m/z 717.47, Rf 1.710 min., 97.1 % purity.

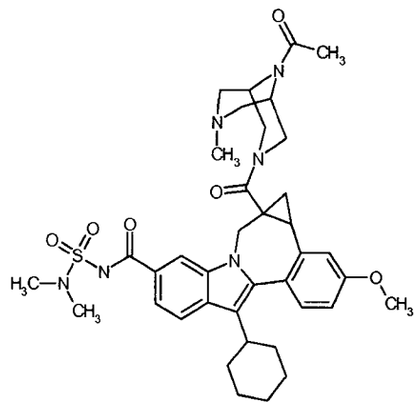


8-Cyclohexyl-N-(dimethylsulfamoyl)-11-methoxy-1a-((3-methyl-3,7,9-triazabicyclo [3.3.1]non-9-yl)carbonyl)-1,1a,2,12b-tetrahydrocyclopropa[d]indolo[2,1-a][2] benzazepine-5-carboxamide. 1H NMR (300 MHz, CD3OD): δ ppm 0.20 (m, 0.20 H), 1.24 - 1.36 (m, 1.80 H), 1.45 (m, 2 H), 1.55 (m, 3 H), 1.64 (m, 1 H), 1.80 (m, 1 H) 1.86 (m, 2 H) 2.08 (m, 6 H), 2.36 (m, 1 H), 2.48 (m, 1 H), 2.62 (m, 2 H), 2.86 (m, 1 H), 3.00 (m, 3 H), 3.16 (m, 1 H), 3.45 (m, 2 H) 3.66 (m, 4 H), 3.85 - 3.96 (m, 3 H), 4.18 (m, 1 H), 4.34 (m, 1 H), 4.46 (m, 1 H), 5.05 (m, 1 H), 7.01 (m, 1 H), 7.13 - 7.20 (m, 1 H), 7.32 (m, 1 H), 7.52 - 7.61 (m, 1 H), 7.89 (m, 1 H), 8.00 - 8.07 (m, 1 H). LC/MS: m/z 675.37, Rf 1.772 min., 95.3 % purity.

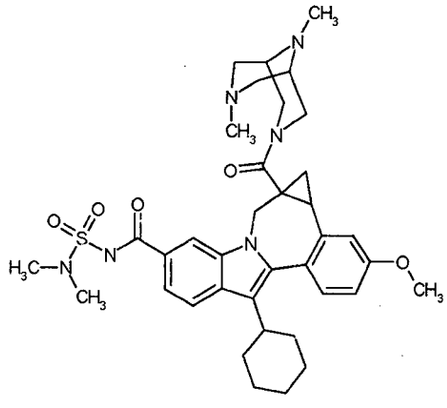


1a-((3-Benzyl-7-methyl-3,7,9-triazabicyclo[3.3.1]non-9-yl)carbonyl)-8-cyclohexyl-N-(dimethylsulfamoyl)-11-methoxy-1,1a,2,12b-tetrahydrocyclopropa[d]indolo[2,1-a] [2]benzazepine-5-carboxamide. 1H NMR (300 MHz, CD3OD): δ ppm 0.20 (m, 0.20 H), 1.32 (m, 2.80 H), 1.43 (m, 4 H), 1.77 (m, 2 H), 2.01 (m, 5 H), 2.59 - 2.72 (m, 2 H), 2.78 (m, 1 H), 2.87 (m, 1 H), 2.90 - 3.05 (m, 8 H), 3.25 (m, 2 H), 3.59 (m, 4 H), 3.75 (m, 1 H), 3.84 - 3.93 (m, 3 H), 4.15 (m, 1 H), 4.38 (m, 1 H), 4.56 (m, 1 H), 5.08 (d, J=15.00 Hz, 1 H), 6.97 - 7.04 (m, 1

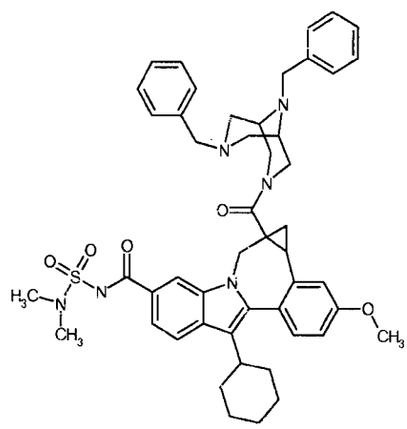
H), 7.07 - 7.17 (m, 1 H), 7.28 - 7.42 (m, 6 H), 7.53 – 7.61 (m, 1 H), 7.85 - 7.92 (m, 1 H), 7.99 - 8.13 (m, 1 H). LC/MS: m/z 765.45, Rf 1.840 min., 99.7 % purity.



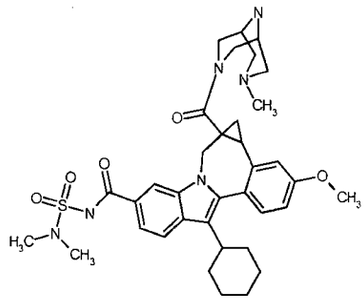
1a-((9-Acetyl-7-methyl-3,7,9-triazabicyclo[3.3.1]non-3-yl)carbonyl)-8-cyclohexyl-N-(dimethylsulfamoyl)-11-methoxy-1,1a,2,12b-tetrahydrocyclopropa[d]indolo[2,1-a] [2]benzazepine-5-carboxamide. 1H NMR (300 MHz, CD3OD): δ ppm 0.20 (m, 0.35 H), 1.01 – 1.30 (m, 0.65 H), 1.38 (m, 5 H), 1.79 (m, 3 H), 1.93 - 2.21 (m, 13 H), 2.62 (m, 1 H), 2.82 (m, 2 H), 2.99 (s, 6 H), 3.56 (m, 1 H), 3.90 (m, 3 H), 4.04 – 4.18 (m, 3 H), 4.53 (m, 1 H), 4.63 (m, 1 H), 4.99 (m, 1 H), 6.95 - 7.01 (m, 1 H), 7.19 (m, 1 H), 7.31 (m, 1 H), 7.50 - 7.60 (m, 1 H), 7.80 (m, 1 H), 7.88 - 8.07 (m, 1 H). LC/MS: m/z 717.92, Rf 1.760 min., 97.6 % purity.



8-Cyclohexyl-N-(dimethylsulfamoyl)-1a-((7,9-dimethyl-3,7,9-triazabicyclo[3.3.1] non-3-yl)carbonyl)-11-methoxy-1,1a,2,12b-tetrahydrocyclopropa[d]indolo[2,1-a][2] benzazepine-5-carboxamide. 1H NMR (300 MHz, CD3OD): δ ppm 0.24 (m, 0.35 H), 1.24 (m, 0.65 H), 1.29 - 1.49 (m, 5 H), 1.62 (m, 1 H), 1.79 (m, 2 H), 1.98 (m, 4 H), 2.42 (m, 1 H), 2.53 (m, 1 H), 2.62 (m, 1 H), 2.75 (m, 1 H), 2.87 (m, 2 H), 2.93 - 3.07 (m, 8 H), 3.12 - 3.22 (m, 2 H), 3.42 (m, 2 H), 3.51 - 3.66 (m, 1 H), 3.88 (m, 3 H), 4.13 (m, 3 H), 4.27 (m, 1 H), 4.60 (m, 1 H), 5.00 (m, 1 H), 6.97 - 7.04 (m, 1 H), 7.14 - 7.20 (m, 1 H), 7.31 (m, 1 H), 7.49 - 7.61 (m, 1 H), 7.81 - 7.92 (m, 1.65 H), 8.06 (m, 0.35 H). LC/MS: m/z 689.86, Rf 1.785 min., 96.2 % purity.

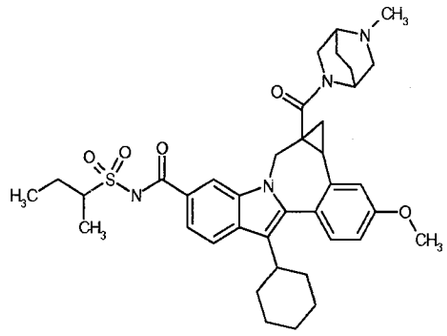


8-Cyclohexyl-1a-((7,9-dibenzyl-3,7,9-triazabicyclo[3.3.1]non-3-yl)carbonyl)-N-(dimethylsulfamoyl)-11-methoxy-1,1a,2,12b-tetrahydrocyclopropa[d]indolo[2,1-a][2] benzazepine-5-carboxamide. 1H NMR (500 MHz, CD3OD): δ ppm 0.22 (m, 0.25 H), 0.90 (m, 1 H), 1.19 - 1.28 (m, 1.75 H), 1.38 - 1.46 (m, 3 H), 1.76 (m, 3 H), 1.95 (m, 2 H), 2.00 (m, 2 H), 2.07 (m, 2 H), 2.54 (m, 1 H), 2.86 (m, 1 H), 2.99 (m, 9 H), 3.16 (m, 1 H), 3.43 (m, 1 H), 3.47 (m, 3 H), 3.84 - 3.91 (m, 4 H), 4.01 - 4.09 (m, 2 H), 4.75 (m, 1 H), 4.99 (d, J=15.26 Hz, 1 H), 6.94 - 7.02 (m, 1 H), 7.08 - 7.17 (m, 1 H), 7.27 - 7.56 (m, 11 H), 7.70 (m, 1 H), 7.86 - 8.07(m, 2 H). LC/MS: m/z 842.66, Rf 2.010 min., 98.0 % purity.

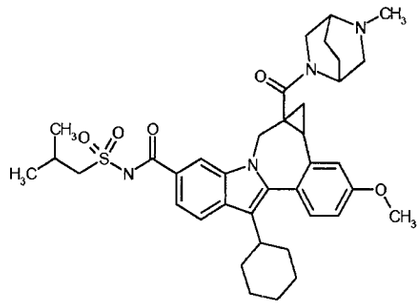


8-Cyclohexyl-N-(dimethylsulfamoyl)-11-methoxy-1a-((7-methyl-3,7,9-triazabicyclo [3.3.1]non-3-yl)carbonyl)-1,1a,2,12b-tetrahydrocyclopropa[d]indolo[2,1-a][2] benzazepine-5-carboxamide. 1H NMR (500 MHz, CD3OD): δ ppm 0.23 (m, 0.30 H), 1.07 -1.29 (m, 0.70 H), 1.36 - 1.45 (m, 5 H), 1.60 (m, 1 H), 1.73 - 1.82 (m, 2 H), 1.90 - 2.07 (m, 4 H), 2.17 (m, 1 H), 2.35 (m, 1 H), 2.54 – 2.70 (m, 3 H), 2.86 (m, 1 H), 3.00 (m, 8 H), 3.20 (m, 2 H), 3.59 (m, 1 H), 3.71 - 3.80 (m, 1 H), 3.84 - 3.91 (m, 3 H), 4.14 m, 1 H), 4.43 (m, 1 H), 4.65 (m, 1 H), 4.98 (m, 1 H), 6.98 - 7.01 (m, 1 H), 7.15 - 7.20 (m, 1 H), 7.28 - 7.32 (m, 1 H), 7.50 - 7.60 (m, 1 H), 7.85 – 8.05 (m, 2 H). LC/MS: m/z 675.61, Rf 1.783 min., 98.7 % purity.

General procedure for reductive alkylation. To a 2 dram vial was added 0.05mmol of piperidine carboxamide in 600μL of methanol and 60μL of water, along with 1.0 eq. of 1H-benzo[d][1,2,3]triazole, 2.0 eq. of aqueous formaldehyde and 2.0 equivalents of neat triethylamine. The vials were capped and shaken over night at room temperature on an orbital shaker. The reaction mixtures were then diluted with 2mL of methanol and dry sodium borohydride was slowly added (2 eq). When effervescence ceased, the vials were recapped and heated at 65°C with shaking in a dry block for ~90min.. After returning to room temperature the crude products were purified using a Shimadzu preparative HPLC employing methanol/water/0.1% TFA buffer where solvent A was 10% MeOH / 90% H2O / 0.1% trifluoroacetic acid and solvent B was 10% H2O / 90% MeOH / 0.1% trifluoroacetic acid with a Phenomenex-Luna 10u C18 30x100mm column at a gradient of 30-100% B and a flow rate of 40 mL/min. over 10 minutes with a 8 minute hold. The products were evaporated to dryness overnight in a Savant Speedvac yielding methylpiperidines as yellow amorphous solids (63% average yield).

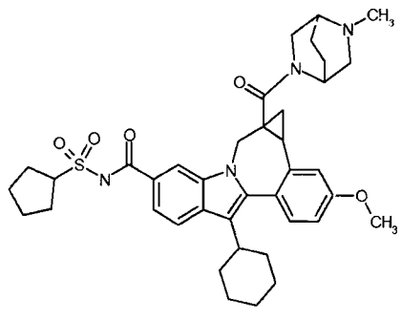


Cycloprop[d]indolo[2,1-a][2]benzazepine-5-carboxamide, 8-cyclohexyl-1,1a,2,12b-tetrahydro-11-methoxy-1a-[(5-methyl-2,5-diazabicyclo[2.2.2]oct-2-yl)carbonyl]-N-[(1-methylpropyl)sulfonyl]-. 1H NMR (500 MHz, CD3OD): δ ppm 0.13 (m, 0.20 H), 0.98 - 1.14 (m, 3 H), 1.17 - 1.35 (m, 1.80 H), 1.35 - 1.59 (m, 7 H), 1.60 - 1.73 (m, 2 H), 1.72 - 1.85 (m, 2 H), 1.87 - 2.16 (m, 6 H), 2.20 - 2.45 (m, 1 H), 2.56 (m, 1 H), 2.73 - 2.92 (m, 3 H), 2.97 – 3.17 (m, 3 H), 3.27 - 3.35 (m, 1H), 3.45 - 3.69 (m, 2 H), 3.69 - 3.81 (m, 2 H), 3.83 - 3.94 (m, 3 H), 3.93 - 4.20 (m, 1 H), 4.16 - 4.52 (m, 1 H), 4.92 - 5.26 (m, 1 H), 6.97 - 7.04 (m, 1 H), 7.18 (m, 1 H), 7.26 - 7.31 (m, 1 H), 7.47 - 7.61 (m, 1 H), 7.85 - 7.91 (m, 1 H), 7.93 - 8.17 (m, 1 H). LC/MS: m/z 673.35, Rf 1.823 min., 98.4 % purity.

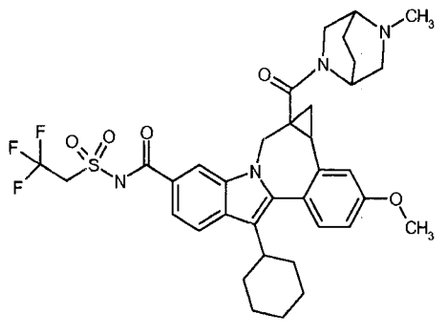


Cycloprop[d]indolo[2,1-a][2]benzazepine-5-carboxamide, 8-cyclohexyl-1,1a,2,12b-tetrahydro-11-methoxy-1a-[(5-methyl-2,5-diazabicyclo[2.2.2]oct-2-yl)carbonyl]-N-[(2-methylpropyl)sulfonyl]-. 1H NMR (500 MHz, CD3OD): δ ppm 0.13 (m, 0.20 H), 1.14 (d, J=6.71 Hz, 6 H), 1.24 - 1.32 (m, 1.80 H), 1.39 - 1.49 (m, 4 H), 1.50 (m, 1 H), 1.80 (m, 3 H), 1.93 – 2.08 (m, 5 H), 2.31 (m, 2 H), 2.52 (m, 1 H), 2.88 (m, 2 H), 2.97 (m, 2 H), 3.10 (m, 1 H), 3.33 (m, 1 H), 3.49 (m, 2 H), 3.67 (m, 3 H), 3.82 - 3.90 (m, 3 H), 4.03 (m, 1 H), 4.32 (m, 1 H), 5.05 (m, 1 H), 7.01 (m,1 H),

7.21 (m,1 H), 7.26 - 7.34 (m, 1 H), 7.55 - 7.64 (m, 1 H), 7.90 (m, 1 H), 7.93 - 8.02 (m, 1 H). LC/MS: m/z 673.45, Rf 1.827 min., 98.5 % purity.

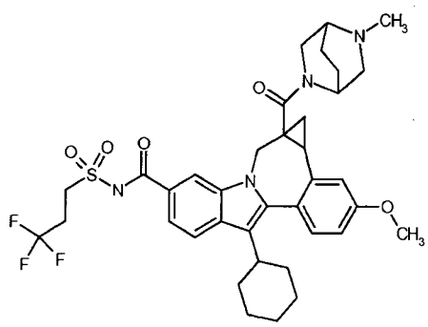


Cycloprop[d]indolo[2,1-a][2]benzazepine-5-carboxamide, 8-cyclohexyl-N-(cyclopentylsulfonyl)-1,1a,2,12b-tetrahydro-11-methoxy-1a-[(5-methyl-2,5-diazabicyclo[2.2.2]oct-2-yl)carbonyl]-. 1H NMR (500 MHz, CD3OD): δ ppm 0.13 (m, 0.20 H), 1.17 - 1.32 (m, 2 H), 1.39 - 1.48 (m, 3.80 H), 1.65 - 1.75 (m, 3 H), 1.76 - 1.85 (m, 4 H), 1.90 – 2.17 (m, 9 H), 2.40 (m, 1 H), 2.57 (m, 2 H), 2.83 - 2.92 (m, 2 H), 2.92 - 3.01 (m, 3 H), 3.34 (m, 1 H), 3.62 (m, 3 H), 3.82 - 3.90 (m, 3 H), 4.02 (m, 1 H), 4.22 - 4.31 (m, 2 H), 5.02 (m, 1 H), 7.00 (m, 1 H), 7.17 (m, 1 H), 7.27 - 7.32 (m, 1 H), 7.52 - 7.61 (m, 1 H), 7.84 – 8.20 (m, 2 H). LC/MS: m/z 685.47, Rf 1.827 min., 99.2 % purity.

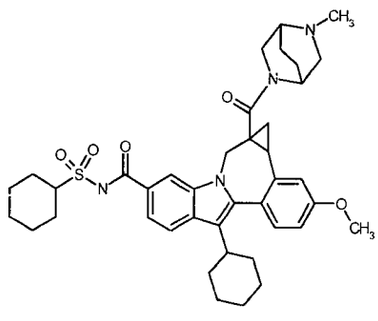


Cycloprop[d]indolo[2,1-a][2]benzazepine-5-carboxamide, 8-cyclohexyl-1,1a,2,12b-tetrahydro-11-methoxy-1a-[(5-methyl-2,5-diazabicyclo[2.2.2]oct-2-yl)carbonyl]-N-[(2,2,2-trifluoroethyl)sulfonyl]-. 1H NMR (500 MHz, CD3OD): δ ppm 0.15 (m, 0.20 H), 1.23 - 1.32 (m, 3 H), 1.39 - 1.49 (m, 3.80 H), 1.80 (m, 3 H), 1.94 - 2.30 (m, 4 H), 2.69 (m, 1 H), 2.84 - 2.93 (m, 2 H), 2.94 - 3.03 (m, 2 H), 3.14 - 3.21 (m, 2 H), 3.34 (m, 1 H), 3.58 (m, 2 H), 3.70 (m, 2 H), 3.75 (m 1 H), 3.85 - 3.91

(m, 3 H), 4.10 (m, 1 H), 4.36 (m, 1 H), 4.61 - 4.70 (m, 1 H), 5.08 (m, 1 H), 6.98 - 7.07 (m, 1 H), 7.15 - 7.24 (m, 1 H), 7.32 (m, 1 H), 7.47 – 7.64 (m, 1 H), 7.85 - 7.96 (m, 1 H), 8.02 (m, 1 H). LC/MS: m/z 699.25, Rf 1.813 min., 98.3 % purity.

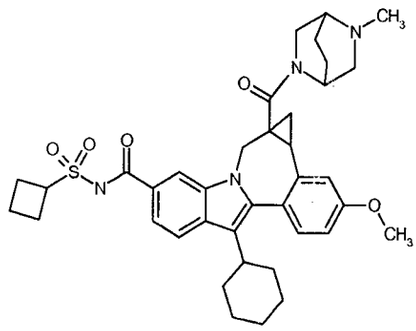


Cycloprop[d]indolo[2,1-a][2]benzazepine-5-carboxamide, 8-cyclohexyl-1,1a,2,12b-tetrahydro-11-methoxy-1a-[(5-methyl-2,5-diazabicyclo[2.2.2]oct-2-yl)carbonyl]-N-[(3,3,3-trifluoropropyl)sulfonyl]-. 1H NMR (500 MHz, CD3OD): δ ppm 0.12 (m, 0.20 H), 1.06 - 1.33 (m, 2 H), 1.36 - 1.70 (m, 4.80 H), 1.78 (m, 2 H), 1.93 – 2.09 (m, 5 H), 2.30 (m, 1 H), 2.56 (m, 2 H), 2.7 – 3.19 (m, 7 H), 3.34 (m, 1 H), 3.59 (m, 3 H), 3.88 (m, 5 H), 4.02 (m, 1 H), 4.28 (m, 1 H), 5.04 (m, 1 H), 7.00 - 7.07 (m, 1 H), 7.17 - 7.22 (m, 1 H), 7.23 - 7.34 (m, 1 H), 7.54 - 7.64 (m, 1 H), 7.84 – 8.02 (m, 2 H). LC/MS: m/z 713.30, Rf 1.818 min., 98.6 % purity.

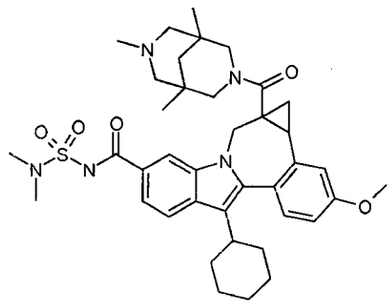


Cycloprop[d]indolo[2,1-a][2]benzazepine-5-carboxamide, 8-cyclohexyl-N-(cyclohexylsulfonyl)-1,1a,2,12b-tetrahydro-11-methoxy-1a-[(5-methyl-2,5-diazabicyclo[2.2.2]oct-2-yl)carbonyl]-. 1H NMR (500 MHz, CD3OD): δ ppm 0.19 (m, 0.20 H), 1.14 - 1.50 (m, 8.80 H), 1.66 (m, 3 H), 1.80 (m, 3 H), 1.96 (m, 3 H), 2.01 – 2.20 (m, 6 H), 2.40 (m, 1 H), 2.61 (m, 2 H), 2.89 (m, 2 H), 3.00 (m, 3 H), 3.37

(m, 1 H), 3.73 (m, 4 H), 3.91 (m, 3 H), 4.06 (m, 1 H), 4.32 (m, 1 H), 5.09 (m, 1 H), 7.02 - 7.08 (m, 1 H), 7.21 - 7.24 (m, 1 H), 7.33 (m, 1 H), 7.56 - 7.66 (m, 1 H), 7.88 – 8.02 (m, 2 H). LC/MS: m/z 699.46, Rf 1.895 min., 100% purity.

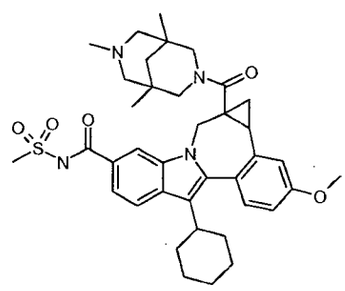


Cycloprop[d]indolo[2,1-a][2]benzazepine-5-carboxamide, N-(cyclobutylsulfonyl)-8-cyclohexyl-1,1a,2,12b-tetrahydro-11-methoxy-1a-[(5-methyl-2,5-diazabicyclo [2.2.2]oct-2-yl)carbonyl]-. 1H NMR (500 MHz, CD3OD): δ ppm 0.12 (m, 0.20 H), 1.21 - 1.31 (m, 3 H), 1.38 - 1.61 (m, 4.80 H), 1.99 (m, 3 H), 1.73 - 1.82 (m, 3 H), 1.90 - 2.09 (m, 4 H), 2.31 - 2.40 (m, 3 H), 2.54 - 2.63 (m, 3 H), 2.90 (m, 1 H), 2.93 – 3.17 (m, 4 H), 3.55 (m, 3 H), 3.89 (m, 3 H), 4.00 (m, 1 H), 4.29 (m, 1 H), 4.50 - 4.59 (m, 1 H), 5.05 (m, 1 H), 7.04 (m, 1 H), 7.20 (m, 1 H), 7.29 - 7.33 (m, 1 H), 7.54 - 7.61 (m, 1 H), 7.88 – 8.09 (m, 2 H). LC/MS: m/z 671.34, Rf 1.886 min., 100% purity.

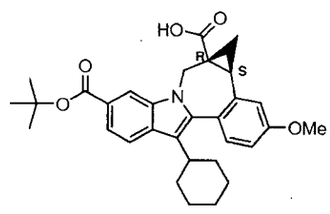


8-Cyclohexyl-*N*-(dimethylsulfamoyl)-11-methoxy-1a-((1,5,7-trimethyl-3,7-diazabicyclo[3.3.1]non-3-yl)carbonyl)-1,1a,2,12b-tetrahydrocyclopropa[*d*]indolo[2,1-*a*][2]benzazepine-5-carboxamide. HATU (36 mg, 0.094 mmol) was added to a stirring solution of the starting acid (40 mg, 0.073

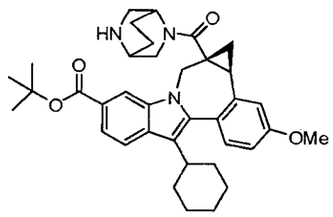
mmol) and 1,3,5-trimethyl-3,7-diazabicyclo[3.3.1]nonane (25 mg, 0.15 mmol) in DMF (0.5 mL) and TEA (0.06 mL, 0.4 mmol) and the reaction was stirred at rt for 1h. The reaction mixture was diluted with MeOH (~1 mL), filtered and purified by preparative HPLC (Xterra Prep MS C18 5u 30 x 100 mm, Eluent A: 5% acetonitrile/water with 10 mM ammonium acetate, Eluent B: 95% acetonitrile/water with 10 mM ammonium acetate, Flow Rate: 42 mL/min, linear gradient from 15% Eluent B to 100% Eluent B over 15 min) to yield 8-cyclohexyl-*N*-(dimethylsulfamoyl)-11-methoxy-1a-((1,5,7-trimethyl-3,7-diazabicyclo[3.3.1]non-3-yl)carbonyl)-1,1a,2,12b-tetrahydrocyclopropa[*d*]indolo[2,1-*a*][2]benzazepine-5-carboxamide (37.5 mg, 0.053 mmol, 74% yield) as a off-white solid. The compound was isolated as a mixture of enantiomers. Presents as a 1:1 mixture of rotamers or atrope isomers. ^{1}HNMR (300 MHz, $CDCl_3$) δ 0.17 - 3.20 (m, 31H), 3.02 (s, 6H), 3.77 - 5.05 (m, 4H), 3.87 (s, 3H), 6.84 - 6.95 (m, 1H), 6.99 - 7.11 (m, 1H), 7.26 (d, *J* = 8.8 Hz, 1H), 7.42 - 8.01 (m, 1.5H), 7.85 (d, *J* = 8.4 Hz, 1H), 8.04 (br s, 0.5H). LC-MS retention time: 3.45 min; m/z 700 (MH-). LC data was recorded on a Shimadzu LC-10AS liquid chromatograph equipped with a Phenomenex-Luna 10u C18 4.6x50mm column using a SPD-10AV UV-Vis detector at a detector wave length of 220nM. The elution conditions employed a flow rate of 5 mL/min, a gradient of 100% solvent A / 0% solvent B to 0% solvent A / 100% solvent B, a gradient time of 4 min, a hold time of 1 min, and an analysis time of 5 min where solvent A was 5% acetonitrile / 95% H_2O / 10 mM ammonium acetate and solvent B was 5% H_2O / 95% acetonitrile / 10 mM ammonium acetate. MS data was determined using a Micromass Platform for LC in electrospray mode.



8-Cyclohexyl-11-methoxy-N-(methylsulfonyl)-1a-((1,5,7-trimethyl-3,7-diazabicyclo[3.3.1]non-3-yl)carbonyl)-1,1a,2,12b-tetrahydrocyclopropa[d]indolo[2,1-a][2]benzazepine-5-carboxamide. HATU (38 mg, 0.10 mmol) was added to a stirring solution of the starting acid (40 mg, 0.077 mmol) and 1,3,5-trimethyl-3,7-diazabicyclo[3.3.1]nonane (26 mg, 0.15 mmol) in DMF (0.5 mL) and TEA (0.06 mL, 0.4 mmol) and the reaction was stirred at rt for 3h. The reaction mixture was diluted with MeOH (~1 mL), filtered and purified by preparative HPLC (Xterra Prep MS C18 5u 30 x 100 mm, Eluent A: 5% acetonitrile/water with 10 mM ammonium acetate, Eluent B: 95% acetonitrile/water with 10 mM ammonium acetate, Flow Rate: 42 mL/min, linear gradient from 15% Eluent B to 100% Eluent B over 15 min) to yield 8-cyclohexyl-11-methoxy-N-(methylsulfonyl)-1a-((1,5,7-trimethyl-3,7-diazabicyclo[3.3.1]non-3-yl)carbonyl)-1,1a,2,12b-tetrahydrocyclopropa[d]indolo[2,1-a][2]benzazepine-5-carboxamide (40.2 mg, 0.060 mmol, 78% yield) as a white solid. The compound was isolated as a mixture of enantiomers. 1HNMR (300 MHz, CDCl3) δ ppm 0.07 - 3.15 (m, 24H), 3.40 (s, 3H), 3.46 - 4.12 (m, 3H), 3.87 (s, 3H), 4.34 - 5.05 (m, 3H), 6.85 - 6.96 (m, 1H), 6.99 - 7.12 (m, 1H), 7.24 - 7.33 (m, 1H), 7.49 - 7.65 (m, 1H), 7.80 - 7.90 (m, 1H), 7.92 - 8.08 (m, 1H). LC-MS retention time: 2.43 min; m/z 671 (MH-). LC data was recorded on a Shimadzu LC-10AS liquid chromatograph equipped with a Phenomenex-Luna 10u C18 4.6x50mm column using a SPD-10AV UV-Vis detector at a detector wave length of 220nM. The elution conditions employed a flow rate of 5 mL/min, a gradient of 100% solvent A / 0% solvent B to 0% solvent A / 100% solvent B, a gradient time of 4 min, a hold time of 1 min, and an analysis time of 5 min where solvent A was 5% acetonitrile / 95% H2O / 10 mM ammonium acetate and solvent B was 5% H2O / 95% acetonitrile / 10 mM ammonium acetate. MS data was determined using a Micromass Platform for LC in electrospray mode.

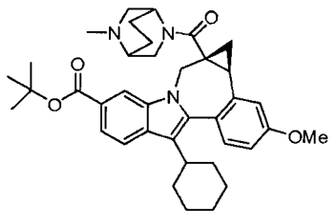


(1aR,12bS)-5-(tert-butoxycarbonyl)-8-cyclohexyl-11-methoxy-1,12b-dihydrocyclopropa[d]indolo[2,1-a][2]benzazepine-1a(2H)-carboxylic acid. Sodium hydroxide (aq. 1M, 31 mL) was added to a cooled solution (0°C, ice bath) containing 5-tert-butyl 1a-ethyl (1aR,12bS)-8-cyclohexyl-11-methoxy-1,12b-dihydrocyclopropa[d]indolo[2,1-a][2]benzazepine-1a,5(2H)-dicarboxylate (4.0 g, 7.76 mmol), THF (35 mL), and methanol (35 mL). After 20 min, the solution was removed from the cooling bath and maintained at ambient temperature for 3h. The solution was cooled again (0°C, ice bath) and the pH reduced to just below 4 by slow addition of 1N HCL (aq., 33mL). The mixture was immediately extracted with ethyl acetate (2 x 30 mL). The combined organic portions were washed with brine, (20 mL), dried (magnesium sulfate), filtered and concentrated to afford a white solid which was used without further purification in the next step. LCMS: retention time: 3.162 min. LC data was recorded on a Shimadzu LC-10AS liquid chromatograph equipped with a Phenomenex-Luna 10u C18 4.6x50mm column using a SPD-10AV UV-Vis detector at a detector wave length of 220nM. The elution conditions employed a flow rate of 4 mL/min, a gradient of 100% solvent A / 0% solvent B to 0% solvent A / 100% solvent B, a gradient time of 4 min, a hold time of 1 min, and an analysis time of 5 min where solvent A was 5% CH_3CN / 95% H_2O / 10 mM ammonium acetate and solvent B was 5% H_2O / 95% CH_3CN / 10 mM ammonium acetate. MS data was determined using a Micromass Platform for LC in electrospray mode. m/z 502(MH^+).



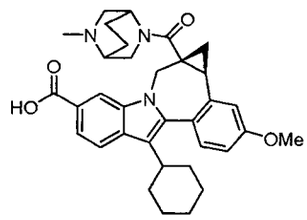
Tert-butyl (1aR,12bS)-8-cyclohexyl-1a-(2,5-diazabicyclo[2.2.2]oct-2-ylcarbonyl)-11-methoxy-1,1a,2,12b-tetrahydrocyclopropa[d]indolo[2,1-a][2]benzazepine-5-carboxylate. TBTU (691 mg, 2.15 mmol) was added in one portion to a cooled solution (0°C, ice bath) containing (1aR,12bS)-5-(tert-butoxycarbonyl)-8-cyclohexyl-11-methoxy-1,12b-dihydrocyclopropa[d]indolo[2,1-a][2]benzazepine-1a(2H)-carboxylic acid(900 mg, 1.79 mmol), DIEA (1.88 mL,

10.77 mmol), 2,5-diazabicyclo[2.2.2]octane (1:1) dihydrochloride ((498 mg, 2.69 mmol), (H. Newman, *J. Het. Chem.* 449 (1974); P.E. Thompson, J. B. Zeigler, J.W. McCall, *J. Med. Chem.*, 17, 481 (1974)), and dichloromethane (36 mL). The solution was maintained for 1.5 h and diluted with additional dichloromethane (20 mL). The solution was washed with water (3 x 20 mL), washed with brine (15 mL), dried (magnesium sulfate), filtered and concentrated to afford a white, tacky residue which was triturated with n-pentane (2 x 20 mL) to afford a white solid which was used without further purification in the next step. LCMS: retention time 3.841 min LC data was recorded on a Shimadzu LC-10AS liquid chromatograph equipped with a Phenomenex-Luna 10u C18 4.6x50mm column using a SPD-10AV UV-Vis detector at a detector wave length of 220nM. The elution conditions employed a flow rate of 4 mL/min, a gradient of 100% solvent A / 0% solvent B to 0% solvent A / 100% solvent B, a gradient time of 4 min, a hold time of 1 min, and an analysis time of 5 min where solvent A was 5% CH_3CN / 95% H_2O / 10 mM ammonium acetate and solvent B was 5% H_2O / 95% CH_3CN / 10 mM ammonium acetate. MS data was determined using a Micromass Platform for LC in electrospray mode., m/z 596(MH^+).



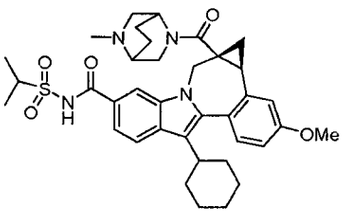
Tert-butyl (1aR,12bS)-8-cyclohexyl-11-methoxy-1a-((5-methyl-2,5-diazabicyclo[2.2.2]oct-2-yl)carbonyl)-1,1a,2,12b-tetrahydrocyclopropa[d]indolo[2,1-a][2]benzazepine-5-carboxylate. A suspension containing tert-butyl (1aR,12bS)-8-cyclohexyl-1a-(2,5-diazabicyclo[2.2.2]oct-2-ylcarbonyl)-11-methoxy-1,1a,2,12b-tetrahydrocyclopropa[d]indolo[2,1-a][2]benzazepine-5-carboxylate (904 mg, 1.51 mmol), formaldehyde (37% in water, 40 mL, 531 mmol), 10% palladium on carbon (323 mg, 0.303 mmol Pd), and ethanol (76 mL) was stirred under a hydrogen gas balloon for 26 hrs. The mixture was filtered through celite and the filtrate concentrated to dryness. The resultant solid was triturated with n-pentane (2 x 25 mL)

and used without further purification. LCMS: retention time 4.123 min LC data was recorded on a Shimadzu LC-10AS liquid chromatograph equipped with a Phenomenex-Luna 10u C18 4.6x50mm column using a SPD-10AV UV-Vis detector at a detector wave length of 220nM. The elution conditions employed a flow rate of 4 mL/min, a gradient of 100% solvent A / 0% solvent B to 0% solvent A / 100% solvent B, a gradient time of 4 min, a hold time of 1 min, and an analysis time of 5 min where solvent A was 5% CH_3CN / 95% H_2O / 10 mM ammonium acetate and solvent B was 5% H_2O / 95% CH_3CN / 10 mM ammonium acetate. MS data was determined using a Micromass Platform for LC in electrospray mode. m/z 610 (MH^+).



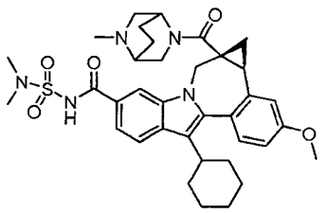
(1aR,12bS)-8-cyclohexyl-11-methoxy-1a-((5-methyl-2,5-diazabicyclo[2.2.2]oct-2-yl)carbonyl)-1,1a,2,12b-tetrahydrocyclopropa[d]indolo[2,1-a][2]benzazepine-5-carboxylic acid. TFA (11.6 mL, 1.164 mmol) was added to a solution containing tert-butyl (1aR,12bS)-8-cyclohexyl-11-methoxy-1a-((5-methyl-2,5-diazabicyclo[2.2.2]oct-2-yl)carbonyl)-1,1a,2,12b-tetrahydrocyclopropa[d]indolo[2,1-a][2]benzazepine-5-carboxylate (710 mg, 1.164 mmol) and DCM (11.6 mL). The solution was maintained at rt for 3 h and then concentrated to dryness. The resultant residue was charged with 1:1 methanol/water (20 mL) and the pH increased to above 8 by slow addition of aqueous, saturated, sodium bicarbonate (10 mL). The solution was concentrated to remove methanol and extracted with dichloromethane (6 x 10mL). The combined organic portions were washed with brine (20 mL), dried (magnesium sulfate), filtered and concentrated to afford a yellow solid which was used without further purification. LC/MS shows separate diastereomers under basic conditions at retention times 2.047 min and 2.178 min LC data was recorded on a Shimadzu LC-10AS liquid chromatograph equipped with a Phenomenex-Luna 10u C18 4.6x50mm column using a SPD-10AV UV-Vis detector at a detector wave length of 220nM.

The elution conditions employed a flow rate of 4 mL/min, a gradient of 100% solvent A / 0% solvent B to 0% solvent A / 100% solvent B, a gradient time of 4 min, a hold time of 1 min, and an analysis time of 5 min where solvent A was 5% CH_3CN / 95% H_2O / 10 mM ammonium acetate and solvent B was 5% H_2O / 95% CH_3CN / 10 mM ammonium acetate. MS data was determined using a Micromass Platform for LC in electrospray mode.; m/z 554 (MH^+).



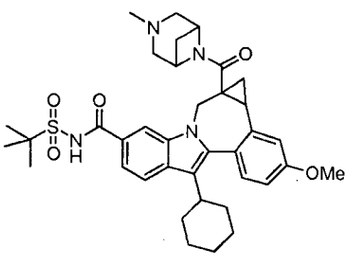
(1aR,12bS)-8-cyclohexyl-N-(isopropylsulfonyl)-11-methoxy-1a-((5-methyl-2,5-diazabicyclo[2.2.2]oct-2-yl)carbonyl)-1,1a,2,12b-tetrahydrocyclopropa[d]indolo[2,1-a][2]benzazepine-5-carboxamide. EDCI (208 mg, 1.084 mmol) was added at rt, in one portion, to a solution containing (1aR,12bS)-8-cyclohexyl-11-methoxy-1a-((5-methyl-2,5-diazabicyclo[2.2.2]oct-2-yl)carbonyl)-1,1a,2,12b-tetrahydrocyclopropa[d]indolo[2,1-a][2]benzazepine-5-carboxylic acid (300 mg, 0.542 mmol), DMAP (50 mg, 0.406 mmol), 2-isopropyl sulfonamide (100 mg, 0.813 mmol), and dichloromethane (6 mL). The solution was maintained at rt for 24 h, diluted with additional dichloromethane (20 mL), washed with aqueous, saturated sodium bicarbonate (2 x 20 mL), washed with water (20 mL), dried (magnesium sulfate), filtered and concentrated. The resultant yellow residue was purified by preparative, reverse phase HPLC under basic conditions using a Phenomenex, luna, 10 micron, 30 x 100 mm column. This separates two diastereomers, each as a white solid. LC/MS shows separate diastereomers under basic conditions at retention times 2.160 min and 2.292 min LC data was recorded on a Shimadzu LC-10AS liquid chromatograph equipped with a Phenomenex-Luna 10u C18 4.6x50mm column using a SPD-10AV UV-Vis detector at a detector wave length of 220nM. The elution conditions employed a flow rate of 4 mL/min, a gradient of 100% solvent A / 0% solvent B to 0% solvent A / 100% solvent B, a gradient time of 4 min, a hold time of 1 min, and an analysis time of 5 min where

solvent A was 5% CH_3CN / 95% H_2O / 10 mM ammonium acetate and solvent B was 5% H_2O / 95% CH_3CN / 10 mM ammonium acetate. MS data was determined using a Micromass Platform for LC in electrospray mode m/z 659 (MH^+).

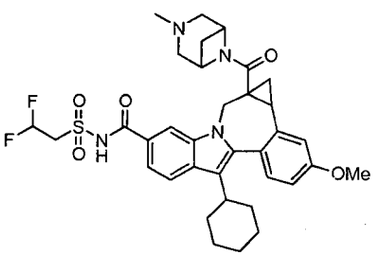


(1aR,12bS)-8-cyclohexyl-N-(dimethylsulfamoyl)-11-methoxy-1a-((5-methyl-2,5-diazabicyclo[2.2.2]oct-2-yl)carbonyl)-1,1a,2,12b-tetrahydrocyclopropa[d]indolo[2,1-a][2]benzazepine-5-carboxamide. The title compound was prepared from (1aR,12bS)-8-cyclohexyl-11-methoxy-1a-((5-methyl-2,5-diazabicyclo[2.2.2]oct-2-yl)carbonyl)-1,1a,2,12b-tetrahydrocyclopropa[d]indolo[2,1-a][2]benzazepine-5-carboxylic acid under similar conditions to those described for (1aR,12bS)-8-cyclohexyl-N-(isopropylsulfonyl)-11-methoxy-1a-((5-methyl-2,5-diazabicyclo[2.2.2]oct-2-yl)carbonyl)-1,1a,2,12b-tetrahydrocyclopropa[d]indolo[2,1-a][2]benzazepine-5-carboxamide. The resultant yellow residue was purified by preparative, reverse phase HPLC under basic conditions using a Phenomenex, luna, 10 micron, 30 x 100 mm column. This separates two diastereomers, each as a white solid. LC/MS shows separate diastereomers under basic conditions at retention time 2.285 min and 2.437 min LC data was recorded on a Shimadzu LC-10AS liquid chromatograph equipped with a Phenomenex-Luna 10u C18 4.6x50mm column using a SPD-10AV UV-Vis detector at a detector wave length of 220nM. The elution conditions employed a flow rate of 4 mL/min, a gradient of 100% solvent A / 0% solvent B to 0% solvent A / 100% solvent B, a gradient time of 4 min, a hold time of 1 min, and an analysis time of 5 min where solvent A was 5% CH_3CN / 95% H_2O / 10 mM ammonium acetate and solvent B was 5% H_2O / 95% CH_3CN / 10 mM ammonium acetate. MS data was determined using a Micromass Platform for LC in electrospray mode.; m/z 660 (MH^+).

Compounds described in the following procedures were analyzed by using the following LC / MS method: Analysis Conditions: Column: PHENOMENNEX-LUNA 3.0 x 50mm S10; Mobile Phase: (A) 10:90 methanol-water; (B) 90:10 methanol-water; Buffer: 0.1% TFA; Gradient Range: 0-100% B; Gradient Time: 2 min; Flow Rate: 4 mL/min; Analysis Time: 3 min; Detection: Detector 1: UV at 220 nm; Detector 2: MS (ESI+).

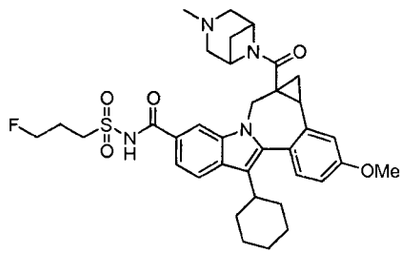


(+/-)-8-cyclohexyl-N-(tert-butylsulfonyl)-1,1a,2,12b-tetrahydro-11-methoxy-1a-(3-methyl-3,6-diazabicyclo[3.1.1]heptane-6-carbonyl) cycloprop[d]indolo[2,1-a][2]benzazepine-5-carboxamide. The product was purified by prep HPLC and isolated as a beige solid in mono TFA salt form. LC/MS: Retention time: 1.867 min; m/e 659 (MH^+). The product was observed to exist as inter-converting rotamers by 1H NMR (400 MHz, CHLOROFORM-D) δ ppm 1.09 - 1.69 (m, 16 H), 1.81 (s, 3 H), 2.01 (s, 5 H), 2.70 (s, 1 H), 2.95 (d, J=3.53 Hz, 2 H), 3.17 (s, 1 H), 3.24 - 3.77 (m, 6 H), 3.87 - 3.98 (m, 3 H), 4.07 (s, 1 H), 4.38 (s, 1 H), 5.44 (s, 1 H), 6.98 (dd, J=8.56, 2.52 Hz, 1 H), 7.12 (d, J=2.52 Hz, 1 H), 7.19 - 7.37 (m, 1 H), 7.57 (d, J=8.31 Hz, 1 H), 7.89 (d, J=8.31 Hz, 1 H), 8.11 (s, 1 H).

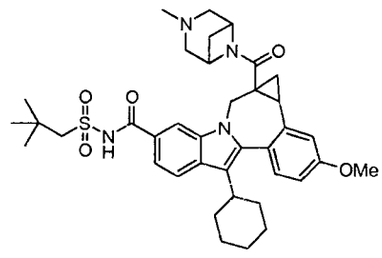


(+/-)-8-cyclohexyl-N-(2,2-difluoroethylsulfonyl)-1,1a,2,12b-tetrahydro-11-methoxy-1a-(3-methyl-3,6-diazabicyclo[3.1.1]heptane-6-carbonyl) cycloprop[d]indolo[2,1-a][2]benzazepine-5-carboxamide. The product was purified by prep HPLC and isolated as a beige solid in mono TFA salt form. LC/MS:

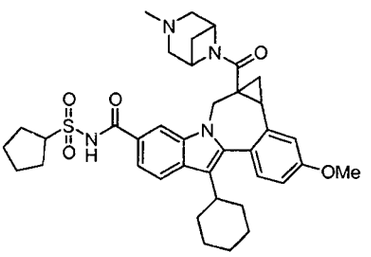
Retention time: 1.837 min; m/e 667 (MH^+). The product was observed to exist as inter-converting rotamers by 1H NMR (400 MHz, CHLOROFORM-D) δ ppm 0.73 - 1.59 (m, 6 H), 1.59 - 2.11 (m, 14 H), 2.59 - 2.87 (m, 1 H), 2.87 - 3.22 (m, 2 H), 3.26 - 3.65 (m, 3 H), 3.78 - 3.94 (m, 3 H), 3.98 - 4.46 (m, 3 H), 5.29 - 5.55 (m, 1 H), 6.08 - 6.48 (m, 1 H), 6.89 - 7.06 (m, 1 H), 7.04 - 7.19 (m, J=2.77 Hz, 1 H), 7.18 - 7.34 (m, 1 H), 7.60 - 7.77 (m, J=9.82 Hz, 1 H), 7.84 - 7.98 (m, J=8.56 Hz, 1 H), 8.01 - 8.12 (m, 1 H).



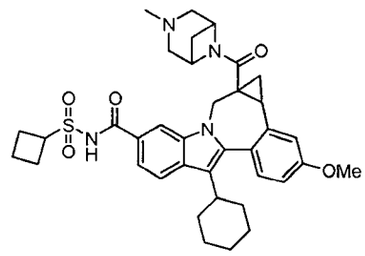
(+/-)-8-cyclohexyl-N-(3-fluoropropylsulfonyl)-1,1a,2,12b-tetrahydro-11-methoxy-1a-(3-methyl-3,6-diazabicyclo[3.1.1]heptane-6-carbonyl) cycloprop[d]indolo[2,1-a][2]benzazepine-5-carboxamide. The product was purified by prep HPLC and isolated as a beige solid in mono TFA salt form. LC/MS: Retention time: 1.811 min; m/e 663 (MH^+). The product was observed to exist as inter-converting rotamers by 1H NMR (400 MHz, CHLOROFORM-D) δ ppm 0.71 - 0.97 (m, 1 H), 1.09 - 1.59 (m, 5 H), 1.68 - 2.11 (m, J=74.28 Hz, 6 H), 2.16 - 2.49 (m, 2 H), 2.60 - 3.31 (m, 8 H), 3.35 - 3.56 (m, 4 H), 3.68 - 3.82 (m, 4 H), 3.84 - 3.95 (m, 3 H), 4.30 - 4.43 (m, 1 H), 4.46 - 4.56 (m, 1 H), 4.57 - 4.73 (m, 1 H), 5.31 - 5.57 (m, 1 H), 6.87 - 7.04 (m, J=8.56, 2.52 Hz, 1 H), 7.04 - 7.19 (m, J=2.27 Hz, 1 H), 7.18 - 7.34 (m, 1 H), 7.57 - 7.74 (m, J=8.81 Hz, 1 H), 7.80 - 7.95 (m, J=8.69, 8.69 Hz, 1 H), 8.04 - 8.19 (m, 1 H).



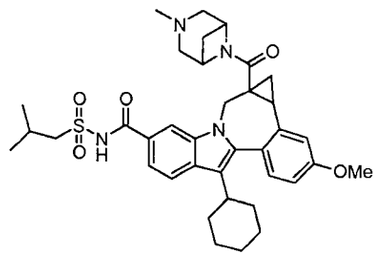
(+/-)-8-cyclohexyl-N-(neopentylsulfonyl)-1,1a,2,12b-tetrahydro-11-methoxy-1a-(3-methyl-3,6-diazabicyclo[3.1.1]heptane-6-carbonyl) cycloprop[d]indolo[2,1-a][2]benzazepine-5-carboxamide. The product was purified by prep HPLC and isolated as a beige solid in mono TFA salt form. LC/MS: Retention time: 1.935 min; m/e 673 (MH^+). The product was observed to exist as inter-converting rotamers by 1H NMR (500 MHz, CHLOROFORM-D) δ ppm 0.26 - 1.01 (m, 2 H), 0.97 - 1.65 (m, 14 H), 1.65 - 2.31 (m, 7 H), 2.50 - 3.35 (m, 9 H), 3.31 - 3.71 (m, 4 H), 3.80 - 3.95 (m, 3 H), 3.93 - 4.45 (m, 1 H), 4.44 - 5.01 (m, 1 H), 5.31 - 5.58 (m, 1 H), 6.87 - 7.06 (m, 1 H), 7.01 - 7.20 (m, J=2.14 Hz, 1 H), 7.16 - 7.34 (m, 1 H), 7.43 - 7.72 (m, J=8.24 Hz, 1 H), 7.80 - 8.00 (m, J=8.39, 8.39 Hz, 1 H), 8.01 - 8.20 (m, 1 H).



(+/-)-8-cyclohexyl-N-(cyclopentylsulfonyl)-1,1a,2,12b-tetrahydro-11-methoxy-1a-(3-methyl-3,6-diazabicyclo[3.1.1]heptane-6-carbonyl) cycloprop[d]indolo[2,1-a][2]benzazepine-5-carboxamide. The product was purified by prep HPLC and isolated as a beige solid in mono TFA salt form. LC/MS: Retention time: 1.895 min; m/e 671 (MH^+). The product was observed to exist as inter-converting rotamers by 1H NMR (500 MHz, CHLOROFORM-D) δ ppm 0.32 - 0.96 (m, 1 H), 1.17 - 1.60 (m, 5 H), 1.62 - 2.33 (m, 8 H), 2.38 - 2.82 (m, 10 H), 2.77 - 3.27 (m, 5 H), 3.32 - 3.75 (m, 3 H), 3.82 - 3.98 (m, 3 H), 3.93 - 4.22 (m, 1 H), 4.25 - 4.45 (m, 2 H), 4.50 - 4.90 (m, 1 H), 5.28 - 5.58 (m, 1 H), 6.90 - 7.05 (m, 1 H), 7.04 - 7.18 (m, 1 H), 7.17 - 7.37 (m, 1 H), 7.39 - 7.69 (m, 1 H), 7.72 - 7.96 (m, 1 H), 8.05 - 8.32 (m, 1 H).ppm.

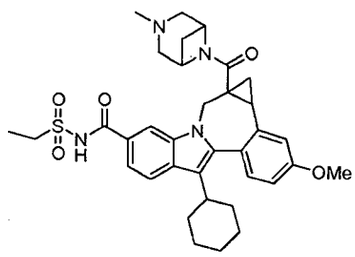


(+/-)-8-cyclohexyl-N-(cyclobutylsulfonyl)-1,1a,2,12b-tetrahydro-11-methoxy-1a-(3-methyl-3,6-diazabicyclo[3.1.1]heptane-6-carbonyl) cycloprop[d]indolo[2,1-a][2]benzazepine-5-carboxamide. The product was purified by prep HPLC and isolated as a beige solid in mono TFA salt form. LC/MS: Retention time: 1.850 min; m/e 657 (MH^+). The product was observed to exist as inter-converting rotamers by 1H NMR (500 MHz, CHLOROFORM-D) δ ppm 1.07 - 1.67 (m, 6 H), 1.71 - 2.17 (m, 7 H), 2.27 - 2.53 (m, 3 H), 2.51 - 3.31 (m, 11 H), 3.31 - 3.78 (m, 4 H), 3.80 - 3.95 (m, 3 H), 3.95 - 4.25 (m, J=53.41 Hz, 1 H), 4.26 - 4.48 (m, 1 H), 4.49 - 4.72 (m, 1 H), 5.33 - 5.63 (m, 1 H), 6.87 - 7.05 (m, 1 H), 7.05 - 7.19 (m, J=2.44 Hz, 1 H), 7.18 - 7.36 (m, 1 H), 7.52 - 7.80 (m, 1 H), 7.81 - 7.96 (m, 1 H), 8.04 - 8.36 (m, 1 H).

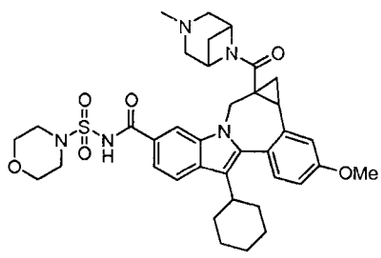


(+/-)-8-cyclohexyl-N-(isobutylsulfonyl)-1,1a,2,12b-tetrahydro-11-methoxy-1a-(3-methyl-3,6-diazabicyclo[3.1.1]heptane-6-carbonyl) cycloprop[d]indolo[2,1-a][2]benzazepine-5-carboxamide. The product was purified by prep HPLC and isolated as a beige solid in mono TFA salt form. LC/MS: Retention time: 1.935 min; m/e 659 (MH^+). The product was observed to exist as inter-converting rotamers by 1H NMR (500 MHz, CHLOROFORM-D) δ ppm 0.29 - 0.93 (m, J=272.84 Hz, 1 H), 1.07 - 1.19 (m, J=6.71, 6.71 Hz, 4 H), 1.17 - 1.66 (m, 7 H), 1.70 - 2.21 (m, 7 H), 2.25 - 2.55 (m, 2 H), 2.58 - 3.25 (m, 4 H), 3.29 - 3.75 (m, 8 H), 3.81 - 3.96 (m, 3 H), 3.94 - 4.27 (m, 1 H), 4.28 - 4.47 (m, 1 H), 4.52 - 4.97 (m, 1

H), 5.31 - 5.59 (m, 1 H), 6.87 - 7.05 (m, 1 H), 7.04 - 7.18 (m, J=1.83 Hz, 1 H), 7.18 - 7.34 (m, 1 H), 7.52 - 7.78 (m, 1 H), 7.81 - 7.97 (m, 1 H), 8.10 - 8.36 (m, 1 H).

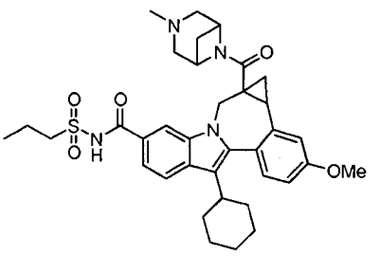


(+/-)-8-cyclohexyl-N-(ethylsulfonyl)-1,1a,2,12b-tetrahydro-11-methoxy-1a-(3-methyl-3,6-diazabicyclo[3.1.1]heptane-6-carbonyl) cycloprop[d]indolo[2,1-a][2]benzazepine-5-carboxamide. The product was purified by prep HPLC and isolated as a beige solid in mono TFA salt form. LC/MS: Retention time: 1.778 min; m/e 631 (MH^+). The product was observed to exist as inter-converting rotamers by 1H NMR (400 MHz, CHLOROFORM-D) δ ppm 0.30 - 0.97 (m, J=222.34 Hz, 1 H), 1.09 - 1.64 (m, 8 H), 1.66 - 2.24 (m, 6 H), 2.54 - 3.21 (m, 4 H), 3.21 - 3.76 (m, 10 H), 3.81 - 3.95 (m, 3 H), 3.92 - 4.26 (m, 1 H), 4.28 - 4.50 (m, 1 H), 4.51 - 5.01 (m, J=126.15 Hz, 1 H), 5.23 - 5.57 (m, 1 H), 6.90 - 7.02 (m, 1 H), 7.05 - 7.18 (m, J=2.52 Hz, 1 H), 7.19 - 7.35 (m, 1 H), 7.57 - 7.71 (m, J=8.31 Hz, 1 H), 7.80 - 7.99 (m, J=7.81, 7.81 Hz, 1 H), 8.02 - 8.22 (m, 1 H).

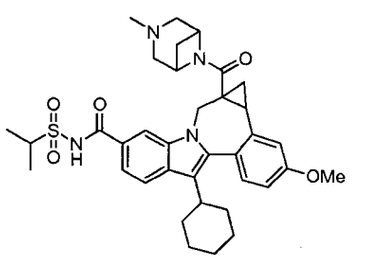


(+/-)-8-cyclohexyl-N-(morpholinosulfonyl)-1,1a,2,12b-tetrahydro-11-methoxy-1a-(3-methyl-3,6-diazabicyclo[3.1.1]heptane-6-carbonyl) cycloprop[d]indolo[2,1-a][2]benzazepine-5-carboxamide. The product was purified by prep HPLC and isolated as a beige solid in mono TFA salt form. LC/MS: Retention time: 1.847 min; m/e 688 (MH^+). The product was observed to exist as inter-converting rotamers by 1H NMR (400 MHz, CHLOROFORM-D) δ ppm 0.32 - 1.06 (m, 1 H), 1.13 - 1.67 (m, 6 H), 1.67 - 2.13 (m, 6 H), 2.14 - 2.78 (m, 9 H), 2.80 -

3.27 (m, 3 H), 3.36 - 3.70 (m, 5 H), 3.69 - 3.84 (m, J=4.28 Hz, 3 H), 3.84 - 3.93 (m, 3 H), 3.93 - 4.17 (m, 1 H), 4.25 - 4.49 (m, 1 H), 4.50 - 4.93 (m, J=112.56 Hz, 1 H), 5.26 - 5.54 (m, 1 H), 6.90 - 7.05 (m, J=8.44, 2.64 Hz, 1 H), 7.05 - 7.19 (m, J=2.52 Hz, 1 H), 7.17 - 7.34 (m, 1 H), 7.50 - 7.65 (m, 1 H), 7.79 - 7.95 (m, 1 H), 8.02 - 8.15 (m, 1 H).

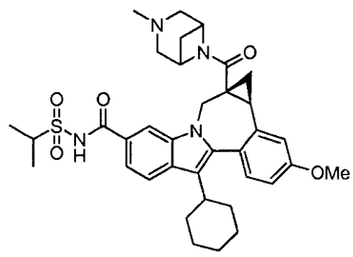


(+/-)-8-cyclohexyl-N-(propylsulfonyl)-1,1a,2,12b-tetrahydro-11-methoxy-1a-(3-methyl-3,6-diazabicyclo[3.1.1]heptane-6-carbonyl) cycloprop[d]indolo[2,1-a][2]benzazepine-5-carboxamide. The product was purified by prep HPLC and isolated as a beige solid in mono TFA salt form. LC/MS: Retention time: 1.888 min; m/e 645 (MH^+). The product was observed to exist as inter-converting rotamers by 1H NMR (400 MHz, CHLOROFORM-D) δ ppm 0.27 - 0.88 (m, 1 H), 0.97 - 1.15 (m, J=7.64, 7.64, 7.64 Hz, 3 H), 1.14 - 1.62 (m, 4 H), 1.69 - 2.23 (m, 8 H), 2.53 - 3.22 (m, 5 H), 3.22 - 3.79 (m, 10 H), 3.81 - 3.94 (m, 3 H), 3.94 - 4.25 (m, 1 H), 4.26 - 4.51 (m, 1 H), 4.53 - 4.97 (m, 1 H), 5.25 - 5.54 (m, 1 H), 6.89 - 7.05 (m, 1 H), 7.06 - 7.18 (m, J=2.27 Hz, 1 H), 7.19 - 7.33 (m, 1 H), 7.51 - 7.71 (m, J=8.31 Hz, 1 H), 7.79 - 7.95 (m, 1 H), 8.05 - 8.22 (m, 1 H).

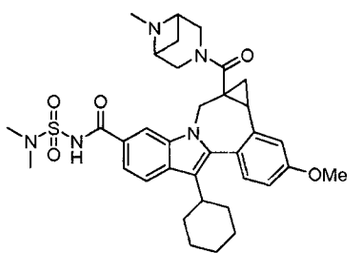


(+/-)-8-cyclohexyl-N-(isopropylsulfonyl)-1,1a,2,12b-tetrahydro-11-methoxy-1a-(3-methyl-3,6-diazabicyclo[3.1.1]heptane-6-carbonyl) cycloprop[d]indolo[2,1-a][2]benzazepine-5-carboxamide. The product was purified by prep HPLC and isolated as a beige solid in mono TFA salt form. LC/MS:

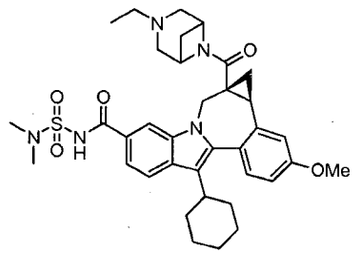
Retention time: 1.871 min; m/e 645 (MH^+). The product was observed to exist as inter-converting rotamers by 1H NMR (400 MHz, CHLOROFORM-D) δ ppm 1.05 - 1.57 (m, 9 H), 1.69 - 2.08 (m, J=79.57 Hz, 4 H), 2.08 - 2.42 (m, 9 H), 2.58 - 3.25 (m, 5 H), 3.35 - 3.75 (m, 4 H), 3.82 - 3.95 (m, 3 H), 3.95 - 4.18 (m, 2 H), 4.26 - 4.45 (m, 1 H), 5.26 - 5.52 (m, 1 H), 6.89 - 7.03 (m, J=8.18, 2.90 Hz, 1 H), 7.04 - 7.17 (m, J=2.27 Hz, 1 H), 7.21 - 7.34 (m, 1 H), 7.49 - 7.68 (m, J=34.75 Hz, 1 H), 7.81 - 7.96 (m, J=8.56 Hz, 1 H), 8.05 - 8.19 (m, 1 H).



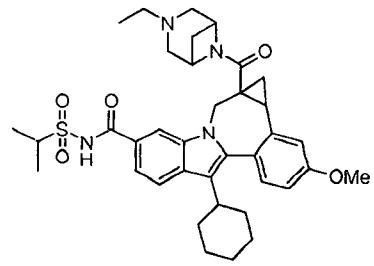
8-cyclohexyl-N-(isopropylsulfonyl)-1,1a,2,12b-tetrahydro-11-methoxy-1a-(3-methyl-3,6-diazabicyclo[3.1.1]heptane-6-carbonyl) cycloprop[d]indolo[2,1-a][2]benzazepine-5-carboxamide. The product was purified by prep HPLC and isolated as a beige solid in mono TFA salt form. LC/MS: Retention time: 1.855 min; m/e 645 (MH^+). The product was observed to exist as inter-converting rotamers by 1H NMR (400 MHz, CHLOROFORM-D) δ ppm 1.11 - 1.62 (m, 11 H), 1.68 - 2.16 (m, J=74.53 Hz, 6 H), 2.42 - 2.82 (m, 7 H), 2.78 - 3.23 (m, 4 H), 3.38 - 3.68 (m, 4 H), 3.81 - 3.94 (m, 3 H), 3.95 - 4.16 (m, 1 H), 4.55 - 4.92 (m, J=94.43 Hz, 1 H), 5.34 - 5.54 (m, 1 H), 6.87 - 7.04 (m, J=8.81, 2.27 Hz, 1 H), 7.04 - 7.19 (m, J=2.27 Hz, 1 H), 7.20 - 7.33 (m, 1 H), 7.50 - 7.67 (m, 1 H), 7.82 - 7.97 (m, J=8.31 Hz, 1 H), 8.05 - 8.23 (m, 1 H).



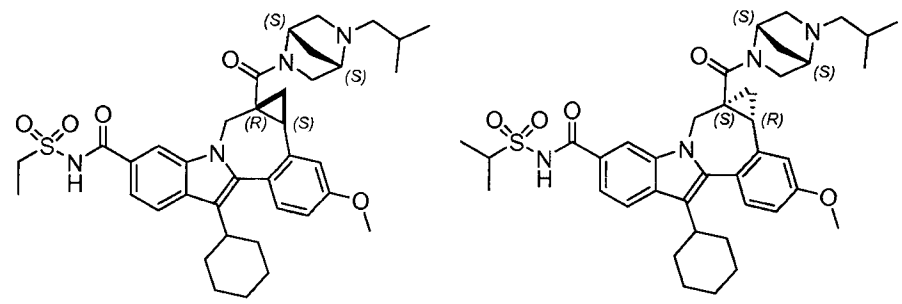
(+/-)-8-cyclohexyl-N-(N,N-dimethylsulfamoyl)-1,1a,2,12b-tetrahydro-11-methoxy-1a-(6-methyl-3,6-diazabicyclo[3.1.1]heptane-3-carbonyl)cycloprop[d]indolo[2,1-a][2]benzazepine-5-carboxamide. The product was purified by prep HPLC and isolated as a beige solid in mono TFA salt form. LC/MS: Retention time: 1.545 min; m/e 646 (MH^+). The product was observed to exist as inter-converting rotamers by 1H NMR (400 MHz, CHLOROFORM-D) δ ppm 0.38 - 1.08 (m, 1 H), 1.09 - 1.64 (m, 5 H), 1.66 - 2.21 (m, 6 H), 2.40 - 2.68 (m, J=50.86 Hz, 1 H), 2.75 - 3.04 (m, 11 H), 3.07 - 3.32 (m, 3 H), 3.47 - 3.84 (m, 2 H), 3.82 - 3.97 (m, 3 H), 3.98 - 4.37 (m, 2 H), 4.74 - 5.17 (m, 1 H), 5.22 - 5.70 (m, 2 H), 6.85 - 7.06 (m, 1 H), 7.04 - 7.19 (m, 1 H), 7.21 - 7.38 (m, 1 H), 7.47 - 7.85 (m, 1 H), 7.85 - 7.99 (m, 1 H), 8.26 - 8.71 (m, 1 H).



8-cyclohexyl-N-(N,N-dimethylsulfamoyl)-1,1a,2,12b-tetrahydro-11-methoxy-1a-(3-ethyl-3,6-diazabicyclo[3.1.1]heptane-6-carbonyl) cycloprop[d]indolo[2,1-a][2]benzazepine-5-carboxamide. The product was purified by prep HPLC and isolated as a beige solid in mono TFA salt form. LC/MS: Retention time: 1.823 min; m/e 660 (MH^+). The product was observed to exist as inter-converting rotamers by 1H NMR (400 MHz, CHLOROFORM-D) δ ppm 0.74 - 1.04 (m, J=19.89 Hz, 2 H), 1.09 - 1.60 (m, 6 H), 1.65 - 2.19 (m, 6 H), 2.61 - 3.22 (m, 14 H), 3.25 - 3.75 (m, 4 H), 3.82 - 3.95 (m, 3 H), 3.94 - 4.28 (m, 1 H), 4.27 - 4.46 (m, 1 H), 4.43 - 4.95 (m, 1 H), 5.33 - 5.60 (m, 1 H), 6.83 - 7.04 (m, 1 H), 7.05 - 7.18 (m, J=2.52 Hz, 1 H), 7.18 - 7.35 (m, 1 H), 7.47 - 7.65 (m, 1 H), 7.81 - 7.96 (m, 1 H), 8.03 - 8.21 (m, 1 H).

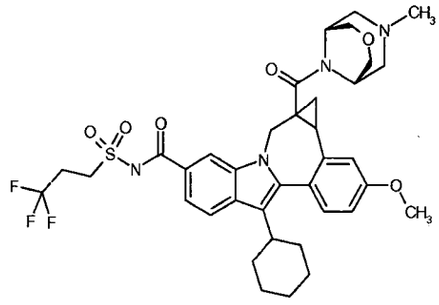


(+/-)-8-cyclohexyl-N-(isopropylsulfonyl)-1,1a,2,12b-tetrahydro-11-methoxy-1a-(3-ethyl-3,6-diazabicyclo[3.1.1]heptane-6-carbonyl) cycloprop[d]indolo[2,1-a][2]benzazepine-5-carboxamide. The product was purified by prep HPLC and isolated as a beige solid in mono TFA salt form. LC/MS: Retention time: 1.863 min; m/e 659 (MH^+). The product was observed to exist as inter-converting rotamers by 1H NMR (400 MHz, CHLOROFORM-D) δ ppm 0.70 - 1.09 (m, 3 H), 1.10 - 1.63 (m, 11 H), 1.69 - 2.12 (m, 5 H), 2.57 - 3.05 (m, J=4.28 Hz, 9 H), 3.04 - 3.24 (m, 1 H), 3.26 - 3.76 (m, 4 H), 3.80 - 3.95 (m, 3 H), 3.96 - 4.24 (m, 2 H), 4.27 - 4.48 (m, 1 H), 5.34 - 5.56 (m, 1 H), 6.87 - 7.04 (m, J=8.56, 2.52 Hz, 1 H), 7.04 - 7.19 (m, J=2.52 Hz, 1 H), 7.18 - 7.35 (m, 1 H), 7.54 - 7.71 (m, J=8.56 Hz, 1 H), 7.81 - 7.94 (m, J=9.06, 9.06 Hz, 1 H), 8.03 - 8.18 (m, 1 H).

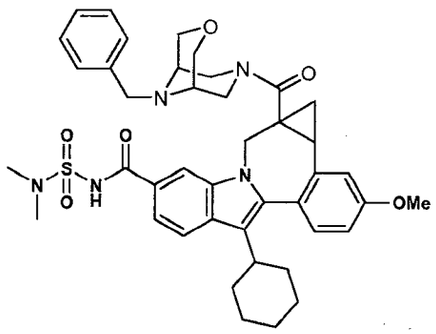


8-cyclohexyl-N-(isopropylsulfonyl)-1,1a,2,12b-tetrahydro-11-methoxy-1a-[(1S,4S)-5-isobutyl-2,5-diazabicyclo[2.2.1]heptane-2-carbonyl]cycloprop[d]indolo[2,1-a][2]benzazepine-5-carboxamide. Step 1: To a mixture of compound acid (50 mg, 0.091 mmol) and (1S,4S)-2-isobutyl-2,5-diazabicyclo[2.2.1]heptane, 2TFA (52 mg, 0.136 mmol) in dichloromethane (1.5 ml) was added TEA (0.127 ml, 0.908 mmol) and HBTU (48 mg, 0.127 mmol). The mixture was stirred at room temperature for 2 h. Diluted with MeOH (1 ml), removed the solvents, the residue was dissolved in MeOH, filtered and purified by prep-HPLC and isolated as TFA salts to afford the products (0.0094 g, 26%) and (0.0099 g,

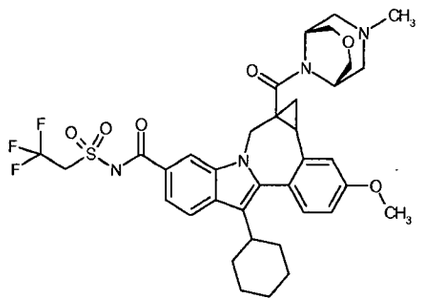
27%). First peak: LC-MS retention time: 3.138; MS m/z (M+H) 687; observed to exist as inter-converting rotamers 1H NMR (400 MHz, *CHLOROFORM-d*) δ ppm 0.93 (6 H, m), 1.35 (10 H, m), 1.74 (11 H, m), 2.45 (1 H, br. s.), 2.80 (4 H, m), 3.14 (2 H, br. s.), 3.64 (3 H, m), 3.90 (3 H, s), 3.98 (1 H, m), 4.15 (1 H, br. s.), 5.20 (1 H, d, *J*=15.11 Hz), 6.98 (1 H, dd, *J*=8.44, 2.64 Hz), 7.11 (1 H, d, *J*=2.01 Hz), 7.28 (1 H, m), 7.82 (1 H, br. s.), 7.96 (1 H, d, *J*=8.31 Hz), 8.53 (1 H, br. s.). Second peak: LC-MS retention time: 3.170; MS m/z (M+H) 687; observed to exist as inter-converting rotamers by 1H NMR.



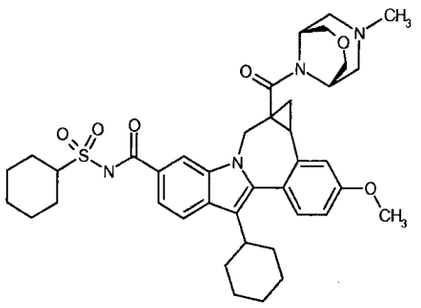
8-Cyclohexyl-11-methoxy-1a-(((1R,5S)-7-methyl-3-oxa-7,9-diazabicyclo[3.3.1]non-9-yl)carbonyl)-N-((3,3,3-trifluoropropyl)sulfonyl)-1,1a,2,12b-tetrahydrocyclopropa[d]indolo[2,1-a][2]benzazepine-5-carboxamide. 1H NMR (300 MHz, CD3OD): δ ppm 0.20 (m, 0.35 H), 1.21 (m, 1 H), 1.35 (m, 1.65 H), 1.45 (m, 2H), 1.58 (m, 2 H), 1.79 (m, 2 H), 1.91 - 2.07 (m, 4 H), 2.62 (m, 1 H), 2.74 - 2.90 (m, 4 H), 2.90 - 3.06 (m, 3 H), 3.34 (m, 1 H), 3.62 (d, J=15.37 Hz, 2 H), 3.72 (m, 1 H), 3.80 - 3.93 (m, 6 H), 4.00 (m, 2 H), 4.15 (d, J=15.00 Hz, 1 H), 4.38 (m, 2 H), 4.90 - 5.09 (m, 1 H), 7.02 (m, 1 H), 7.12 - 7.20 (m, 1 H), 7.27 - 7.33 (m, 1 H), 7.53 - 7.63 (m, 1 H), 7.89 (m, 1 H), 8.04 - 8.11 (m, 1 H). LC/MS: m/z 729.42, Rf 1.793 min., 95.7 % purity.



Cycloprop[*d*]indolo[2,1-*a*][2]benzazepine-5-carboxamide, 8-cyclohexyl-*N*-[(dimethylamino)sulfonyl]-1,1a,2,12b-tetrahydro-11-methoxy-1a-[[9-(phenylmethyl)-3-oxa-7,9-diazabicyclo[3.3.1]non-7-yl]carbonyl]-. was prepared from the coupling between the racemic acid and 9-benzyl-3-oxa-7,9-diazabicyclo[3.3.1]nonane hydrochloride in a similar manner as described above. Purification by Shimadzu-VP preparative reverse phase HPLC using the separation method: Solvent A = 10% MeOH–90% H_2O–0.1% TFA, Solvent B = 90% MeOH–10%H_2O–0.1% TFA, Start %B = 30, Final %B = 100, Gradient time = 10min, Flow Rate = 30mL/min, Column: Xterra Prep MS C18 5u 30x50mm, Fraction Collection: 8.31 – 8.91 min. (UV detection at 220 nm); LC/MS were performed by using Shimadzu-VP instrument with UV detection at 220 nm and Waters Micromass. HPLC method: Solvent A = 10% MeOH–90% H_2O–0.1% TFA, Solvent B = 90% MeOH–10%H_2O–0.1% TFA, Start %B = 0, Final %B = 100, Gradient time = 2 min, Flow Rate = 5 ml/min, Column: Xterra MS C18 S7 3.0 x 50mm; (ES+) m/z $(M+H)^+$ = 752.91, HPLC R_t = 1.752 min. HPLC method: Solvent A = 5% MeCN–95% H_2O–10 mM NH_4OAc, Solvent B = 95% MeCN–5%H_2O–10 mM NH_4OAc, Start %B = 0, Final %B = 100, Gradient time = 2 min, Flow Rate = 5 ml/min, Column: Phenomenex Lina C18 5um 3.0 x 50mm; (ES+) m/z $(M+H)^+$ = 752.48, HPLC R_t = 1.633 min.

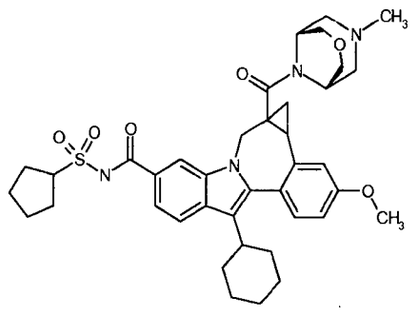


8-Cyclohexyl-11-methoxy-1a-(((1R,5S)-7-methyl-3-oxa-7,9-diazabicyclo[3.3.1]non-9-yl)carbonyl)-N-((2,2,2-trifluoroethyl)sulfonyl)-1,1a,2,12b-tetrahydrocyclopropa [d]indolo[2,1-a][2]benzazepine-5-carboxamide. 1H NMR (300 MHz, CD3OD): δ ppm 0.22 (m, 0.35 H), 1.19 (m, 1 H), 1.25 - 1.41 (m, 2 H), 1.44 (m, 2 H), 1.58 (m, 1.65 H), 1.79 (m, 2 H), 1.92 - 2.04 (m, 4 H), 2.63 (m, 2 H), 2.86 (m, 2 H), 2.90 - 3.04 (m, 2 H), 3.60 (m, 2 H), 3.66 (m, 1 H), 3.85 - 3.98 (m, 6 H), 4.16 (m, 1 H), 4.27 - 4.42 (m, 2 H), 4.67 (m, 2 H), 5.08 (d, J=15.00 Hz, 1 H), 6.98 - 7.06 (m, 1 H), 7.13 - 7.21 (m, 1 H), 7.27 - 7.35 (m, 1 H), 7.53 - 7.64 (m, 1 H), 7.90 (m, 1 H), 8.04 - 8.13 (m, 1 H). LC/MS: m/z 715.41, Rf 1.783 min., 98.0 % purity.

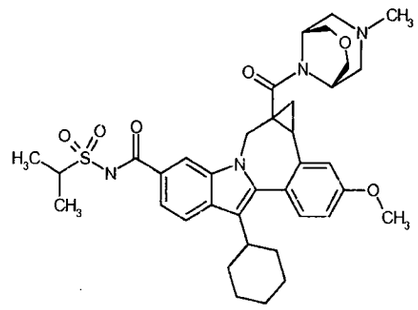


8-Cyclohexyl-N-(cyclohexylsulfonyl)-11-methoxy-1a-(((1R,5S)-7-methyl-3-oxa-7,9-diazabicyclo[3.3.1]non-9-yl)carbonyl)-1,1a,2,12b-tetrahydrocyclopropa[d]indolo [2,1-a][2]benzazepine-5-carboxamide. 1H NMR (300 MHz, CD3OD): δ ppm 0.24 (m, 0.35 H), 1.31 - 1.52 (m, 7.65 H), 1.59 - 1.74 (m, 4 H), 1.80 (m, 3 H), 1.95 (m, 4 H), 2.11 (m, 2 H), 2.21 (m, 2 H), 2.68 (m, 2 H), 2.89 (m, 2 H), 2.97 (m, 2 H), 3.64 - 3.79 (m, 4 H), 3.83 - 3.98 (m, 4 H), 4.10 (m, 3 H), 4.41 (m, 2 H), 5.12 (d, J=15.37 Hz, 1 H), 7.05 (m,1 H), 7.16 - 7.25 (m, 1 H), 7.34

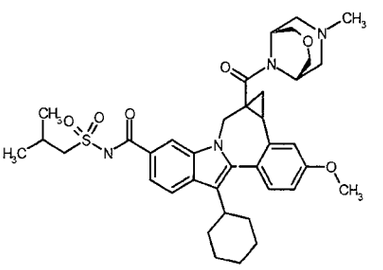
(m, 1 H), 7.56 - 7.69 (m, 1 H), 7.93 (m, 1 H), 8.04 - 8.19 (m, 1 H). LC/MS: m/z 715.51, Rf 1.840 min., 97.1 % purity.



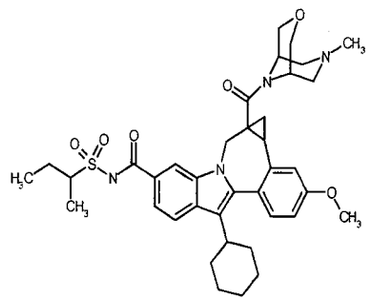
8-Cyclohexyl-N-(cyclopentylsulfonyl)-11-methoxy-1a-(((1R,5S)-7-methyl-3-oxa-7,9-diazabicyclo[3.3.1]non-9-yl)carbonyl)-1,1a,2,12b-tetrahydrocyclopropa[d]indolo [2,1-a][2]benzazepine-5-carboxamide. 1H NMR (300 MHz, CD3OD): δ ppm 0.21 (m, 0.35 H), 1.15 - 1.26 (m, 1.65 H) 1.32 - 1.37 (m, 1 H), 1.41 (m, 2 H), 1.58 (m, 1 H), 1.69 - 1.74 (m, 3 H), 1.76 - 1.86 (m, 4 H), 2.00 - 2.16 (m, 8 H), 2.63 (m, 1 H), 2.86 - 3.06 (m, 5 H), 3.63 (m, 3 H), 3.81 - 3.95 (m, 5 H), 4.01 (m, 1 H), 4.16 (m, 1 H), 4.23 - 4.38 (m, 3 H), 4.84 - 5.10 (m, 1 H), 6.95 - 7.06 (m, 1 H), 7.12 - 7.22(m, 1 H), 7.26 - 7.34 (m, 1 H), 7.52 - 7.62 (m, 1 H), 7.83 - 7.93 (m, 1 H), 8.01 - 8.09 (m, 1 H). LC/MS: m/z 701.49, Rf 1.778 min., 97.0 % purity.



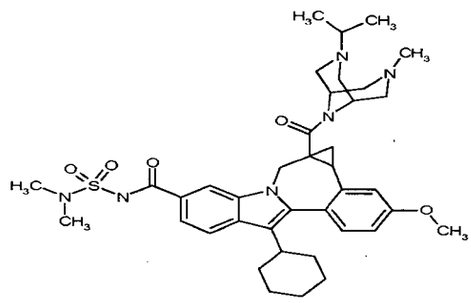
8-cyclohexyl-N-(isopropylsulfonyl)-11-methoxy-1a-(((1R,5S)-7-methyl-3-oxa-7,9-diazabicyclo[3.3.1]non-9-yl)carbonyl)-1,1a,2,12b-tetrahydrocyclopropa[d]indolo [2,1-a][2]benzazepine-5-carboxamide. 1H NMR (300 MHz, CD3OD): δ ppm 0.19 (m, 0.35 H), 1.28 (m, 1.65 H), 1.31 - 1.38 (m, 1 H), 1.38 - 1.48 (m, 6 H), 1.57 (m, 2 H), 1.78 (m, 2 H), 1.91 - 2.09 (m, 4 H), 2.64 (m, 1 H), 2.81 (m, 1 H), 2.89 - 3.02 (m, 4 H), 3.64 (m, 4 H), 3.85 - 3.99 (m, 7 H), 4.01 (m, 2 H), 4.37 (m, 2 H), 4.85 - 5.08 (m, 1 H), 7.02 - 7.07 (m, 1 H), 7.17 - 7.22 (m, 1 H), 7.32 - 7.36 (m, 1 H), 7.57 - 7.64 (m, 1 H), 7.90 - 7.94 (m, 1 H), 8.05 - 8.10 (m, 1 H). LC/MS: m/z 675.44, Rf 1.743 min., 97.2 % purity.



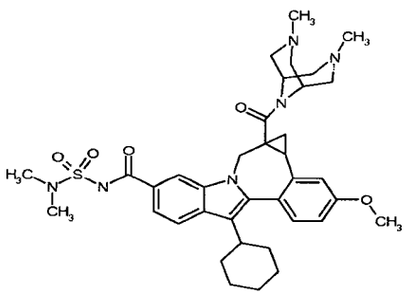
8-C yclohexyl-N-(isobutylsulfonyl)-11-methoxy-1a-(((1R,5S)-7-methyl-3-oxa-7,9-diazabicyclo[3.3.1]non-9-yl)carbonyl)-1,1a,2,12b-tetrahydrocyclopropa[d]indolo [2,1-a][2]benzazepine-5-carboxamide. 1H NMR (300 MHz, CD3OD): 0.19 (m, 0.35), 1.07 (td, J=7.50, 2.56 Hz, 3 H), 1.23 - 1.37 (m, 2.65 H), 1.37 - 1.49 (m, 5 H), 1.57 - 1.68 (m, 2 H), 1.70 - 1.82 (m, 3 H), 1.94 - 2.13 (m, 6 H), 2.61 (m, 2 H), 2.85 (m, 1 H), 2.89 - 3.03 (m, 3 H), 3.10 - 3.24 (m, 1 H), 3.61 (d, J=15.37 Hz, 1 H), 3.67 - 3.82 (m, 3 H), 3.83 - 3.91 (m, 3 H), 3.96 (m, 1 H), 4.15 (m, 1 H), 4.37 (m, 2 H), 4.90 - 5.08 (m, 1 H), 6.97 - 7.04 (m, 1 H), 7.13 (d, J=2.56 Hz, 0.35 H), 7.17 (d, J=2.56 Hz, 0.65 H), 7.26 - 7.33 (m, 1 H), 7.53 - 7.60 (m, 1 H), 7.84 - 7.92 (m, 1 H), 8.02 - 8.07 (s, 1 H). LC/MS: m/z 689.49, Rf 1.788 min., 97.0 % purity.



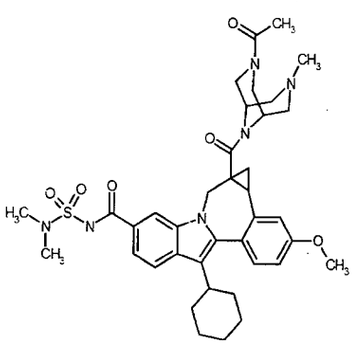
N-(sec-butylsulfonyl)-8-cyclohexyl-11-methoxy-1a-((7-methyl-3-oxa-7,9-diazabicyclo [3.3.1]non-9-yl)carbonyl)-1,1a,2,12b-tetrahydrocyclopropa[d]indolo[2,1-a][2] benzazepine-5-carboxamide. 1H NMR (300 MHz, CD3OD): δ ppm 0.21 (m, 0.20 H), 1.09 (m, 3 H), 1.30 (m, 1.80 H), 1.44 (m, 7 H), 1.56 - 1.79 (m, 5 H), 1.72 – 2.12 (m, 5 H), 2.65 (m, 1 H), 2.97 (m, 5 H), 3.63 (d, J=15.37 Hz, 1 H), 3.69 - 3.83 (m, 3 H), 3.84 - 3.97 (m, 4 H), 4.14 (m, 2 H), 4.39 (m, 2 H), 5.07 (m, 1 H), 6.98 - 7.06 (m, 1 H), 7.14 - 7.21 (m, 1 H), 7.28 - 7.34 (m, 1 H), 7.53 - 7.63 (m, 1 H), 7.85 - 7.93 (m, 1 H), 8.02 - 8.11 (m, 1 H). LC/MS: m/z 689.46, Rf 1.797 min., 96.0 % purity.



8-Cyclohexyl-N-(dimethylsulfamoyl)-1a-((3-isopropyl-7-methyl-3,7,9-triazabicyclo [3.3.1]non-9-yl)carbonyl)-11-methoxy-1,1a,2,12b-tetrahydrocyclopropa[d]indolo [2,1-a][2]benzazepine-5-carboxamide. 1H NMR (300 MHz, CD3OD): δ ppm 0.19 (m, 0.35 H), 1.12 (m, 3.65 H), 1.20 - 1.35 (m, 4 H), 1.39 (m, 2 H), 1.45 - 1.58 (m, 2 H), 1.64 (m, 2 H), 1.78 (m, 3 H), 2.00 (m, 6 H), 2.61 (m, 3 H), 2.74 - 2.90 (m, 2 H), 2.90 - 3.05 (m, 6 H), 3.48 (m, 1 H), 3.61 (m, 2 H), 3.84 - 3.91 (m, 4 H), 4.15 (m, 1 H), 4.45 (m, 1 H), 5.07 (m, 1 H), 7.01 (m, 1 H), 7.11 - 7.20 (m, 1 H), 7.26 - 7.35 (m, 1 H), 7.50 - 7.63 (m, 1 H), 7.88 (m, 1 H), 8.00 - 8.09 (m, 1 H). LC/MS: m/z 717.52, Rf 1.762 min., 97.8% purity.

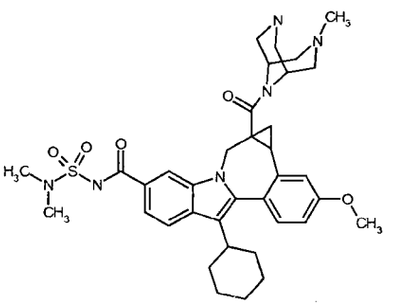


8-Cyclohexyl-N-(dimethylsulfamoyl)-1a-((3,7-dimethyl-3,7,9-triazabicyclo[3.3.1] non-9-yl)carbonyl)-11-methoxy-1,1a,2,12b-tetrahydrocyclopropa[d]indolo[2,1-a] [2]benzazepine-5-carboxamide. 1H NMR (300 MHz, CD3OD): δ ppm 0.24 (m, 0.20 H), 1.24 - 1.38 (m, 2.80 H), 1.45 (m, 4 H), 1.56 (m, 1 H), 1.83 (m, 2 H), 2.04 (m, 4 H), 2.65 (m, 1 H), 2.82 - 2.91 (m, 1 H), 2.93 - 3.05 (m, 9 H), 3.17 (m, 3 H), 3.49 (m, 1 H), 3.64 (m, 2 H), 3.78 (m, 1 H), 3.86 - 3.95 (m, 4 H), 4.03 (m, 1 H), 4.18 (m, 1 H), 4.37 (m, 1 H), 4.51 (m, 1 H), 5.08 (d, J=15.37 Hz, 1 H), 6.99 - 7.07 (m, 1 H), 7.13 - 7.22 (m, 1 H), 7.29 - 7.37 (m, 1 H), 7.51 - 7.63 (m, 1 H), 7.89 (m, 1 H), 7.99 - 8.10 (m, 1 H). LC/MS: m/z 689.50, Rf 1.813 min., 98.3 % purity.

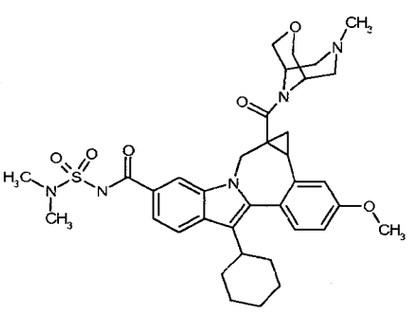


1a-((3-Acetyl-7-methyl-3,7,9-triazabicyclo[3.3.1]non-9-yl)carbonyl)-8-cyclohexyl-N-(dimethylsulfamoyl)-11-methoxy-1,1a,2,12b-tetrahydrocyclopropa[d]indolo[2,1-a] [2]benzazepine-5-carboxamide. 1H NMR (300 MHz, CD3OD): δ ppm 0.51 (m, 0.20 H), 1.68 (m, 4.80 H), 1.98 (m, 2 H), 2.12 (m, 2 H), 2.41 (m, 7 H), 2.98 (m, 1 H), 3.19 (m, 2 H), 3.56 - 3.65 (m, 13 H), 3.94 - 4.10 (m, 2 H), 4.14 - 4.29 (m, 4 H), 4.95 (m, 2 H), 5.40 (m, 1 H), 7.35 (m, 1 H), 7.47

- 7.53 (m, 1 H), 7.60 - 7.67 (m, 1 H), 7.85 (m, 1 H), 8.16 - 8.25 (m, 1 H), 8.36 (s, 1 H). LC/MS: m/z 717.47, Rf 1.710 min., 97.1 % purity.

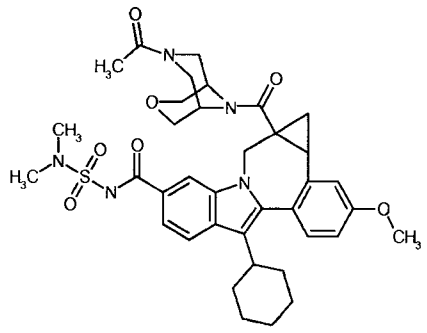


8-Cyclohexyl-N-(dimethylsulfamoyl)-11-methoxy-1a-((3-methyl-3,7,9-triazabicyclo [3.3.1]non-9-yl)carbonyl)-1,1a,2,12b-tetrahydrocyclopropa[d]indolo[2,1-a][2] benzazepine-5-carboxamide. 1H NMR (300 MHz, CD3OD): δ ppm 0.20 (m, 0.20 H), 1.24 - 1.36 (m, 1.80 H), 1.45 (m, 2 H), 1.55 (m, 3 H), 1.64 (m, 1 H), 1.80 (m, 1 H) 1.86 (m, 2 H) 2.08 (m, 6 H), 2.36 (m, 1 H), 2.48 (m, 1 H), 2.62 (m, 2 H), 2.86 (m, 1 H), 3.00 (m, 3 H), 3.16 (m, 1 H), 3.45 (m, 2 H) 3.66 (m, 4 H), 3.85 - 3.96 (m, 3 H), 4.18 (m, 1 H), 4.34 (m, 1 H), 4.46 (m, 1 H), 5.05 (m, 1 H), 7.01 (m, 1 H), 7.13 - 7.20 (m, 1 H), 7.32 (m, 1 H), 7.52 - 7.61 (m, 1 H), 7.89 (m, 1 H), 8.00 - 8.07 (m, 1 H). LC/MS: m/z 675.37, Rf 1.772 min., 95.3 % purity.

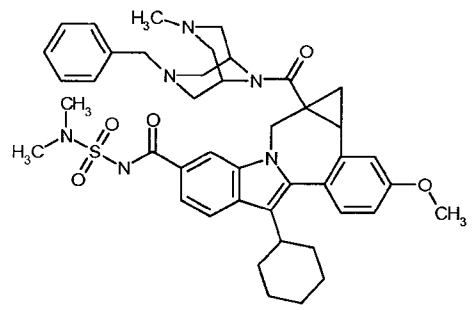


8-Cyclohexyl-N-(dimethylsulfamoyl)-11-methoxy-1a-((7-methyl-3-oxa-7,9-diaza bicyclo[3.3.1]non-9-yl)carbonyl)-1,1a,2,12b-tetrahydrocyclopropa[d]indolo [2,1-a][2]benzazepine-5-carboxamide. 1H NMR (300 MHz, CD3OD): δ ppm 0.22 (m, 0.20 H), 1.30 - 1.38 (m, 1.80 H), 1.44 (m, 2 H),

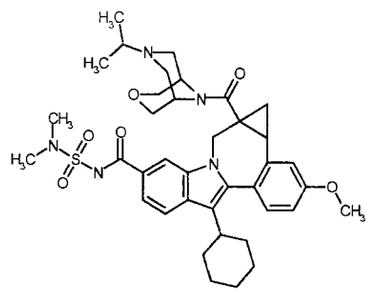
1.56 (m, 2 H), 1.70 (m, 1 H), 1.80 (m, 2 H), 2.02 (m, 4 H), 2.66 (m, 1 H), 2.86 (m, 2 H), 2.92 - 3.07 (m, 9 H), 3.66 (m, 3 H), 3.81 - 3.94 (m, 4 H), 4.02 (m, 2 H), 4.17 (m, 1 H), 4.36 (m, 2 H), 5.10 (m, 1 H), 7.03 (m, 1 H), 7.13 - 7.22 (m, 1 H), 7.32 (m, 1 H), 7.56 (m, 1 H), 7.86 - 7.95 (m, 1 H), 8.01 - 8.11 (m, 1 H). LC/MS: m/z 676.40, Rf 1.703 min., 98.2 % purity.



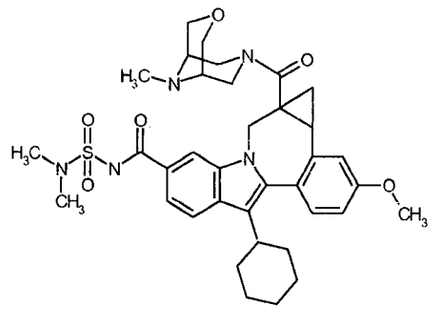
1a-((7-Acetyl-3-oxa-7,9-diazabicyclo[3.3.1]non-9-yl)carbonyl)-8-cyclohexyl-N-(dimethylsulfamoyl)-11-methoxy-1,1a,2,12b-tetrahydrocyclopropa[d]indolo[2,1-a] [2]benzazepine-5-carboxamide. 1H NMR (500 MHz, CD3OD): δ ppm 0.17 (m, 0.25 H), 1.12 (m, 0.75 H), 1.33 (m, 2 H), 1.51 (m, 3 H), 1.70 (m, 1 H), 1.80 (m, 2 H), 2.00 – 2.15 (m, 7 H), 2.55 - 2.65 (m, 1 H), 2.85 (m, 1 H), 2.94 - 3.02 (m, 6 H), 3.16 (m, 1 H), 3.34 (m, 1 H), 3.63 (m, 1 H), 3.75 (m, 1 H), 3.88 (m, 3 H), 4.12 (m, 3 H), 4.26 (m, 1 H), 4.78 (m, 1 H), 4.90 (m, 1 H), 5.06 (m, 1 H), 6.96 - 7.03 (m, 1 H), 7.11 - 7.20 (m, 1 H), 7.26 - 7.34 (m, 1 H), 7.51 - 7.57 (m, 1 H), 7.84 - 7.91 (m, 1 H), 8.04 – 8.12 (s, 1 H). LC/MS: m/z 704.34, Rf 1.938 min., 98.1 % purity.



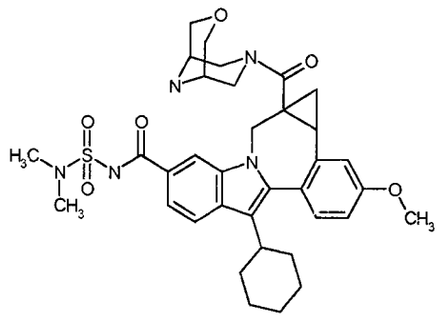
1a-((3-Benzyl-7-methyl-3,7,9-triazabicyclo[3.3.1]non-9-yl)carbonyl)-8-cyclohexyl-N-(dimethylsulfamoyl)-11-methoxy-1,1a,2,12b-tetrahydrocyclopropa[d]indolo[2,1-a] [2]benzazepine-5-carboxamide. 1H NMR (300 MHz, CD3OD): δ ppm 0.20 (m, 0.20 H), 1.32 (m, 2.80 H), 1.43 (m, 4 H), 1.77(m, 2 H), 2.01 (m, 5 H), 2.59 - 2.72 (m, 2 H), 2.78 (m, 1 H), 2.87 (m, 1 H), 2.90 - 3.05 (m, 8 H), 3.25 (m, 2 H), 3.59 (m, 4 H), 3.75 (m, 1 H), 3.84 - 3.93 (m, 3 H), 4.15 (m, 1 H), 4.38 (m, 1 H), 4.56 (m, 1 H), 5.08 (d, J=15.00 Hz, 1 H), 6.97 - 7.04 (m, 1 H), 7.07 - 7.17 (m, 1 H), 7.28 - 7.42 (m, 6 H), 7.53 – 7.61 (m, 1 H), 7.85 - 7.92 (m, 1 H), 7.99 - 8.13 (m, 1 H). LC/MS: m/z 765.45, Rf 1.840 min., 99.7 % purity.



8-Cyclohexyl-N-(dimethylsulfamoyl)-1a-((7-isopropyl-3-oxa-7,9-diazabicyclo[3.3.1] non-9-yl)carbonyl)-11-methoxy-1,1a,2,12b-tetrahydrocyclopropa[d]indolo[2,1-a][2] benzazepine-5-carboxamide. 1H NMR (500 MHz, CD3OD): δ ppm 0.24 (m, 0.25 H), 1.23 (m, 0.75 H), 1.36 (m, 2 H), 1.38(m, 1 H), 1.49 (m, 6 H), 1.61 (m, 1 H), 1.70 (m, 1 H), 1.84 (m, 2 H), 1.96 – 2.14 (m, 4 H), 2.64 - 2.71 (m, 1 H), 2.89 (m, 1 H), 2.98 - 3.07 (m, 6 H), 3.20 (m, 1 H), 3.29 (m, 2 H), 3.37 (m, 1 H), 3.41 (m, 1 H), 3.50 (m, 1 H), 3.69 (m, 1 H), 3.92 (m, 4 H), 4.00 (m, 2 H), 4.18 (m, 1 H), 4.43 (m, 1 H), 5.14 (m, 1 H), 7.05 (m, 1 H), 7.16 - 7.24 (m, 1 H), 7.35 (m, 1 H), 7.55 - 7.64 (m, 1 H), 7.93(m, 1 H), 8.05 - 8.12 (m, 1 H). LC/MS: m/z 704.40, Rf 1.755 min., 99.2 % purity.

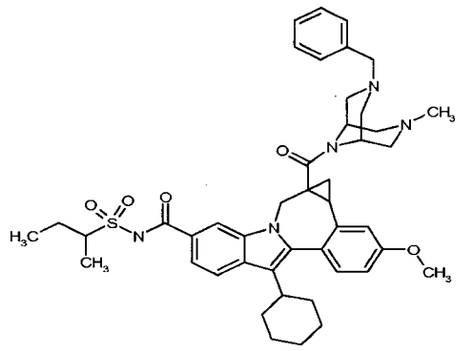


8-cyclohexyl-N-(dimethylsulfamoyl)-11-methoxy-1a-((9-methyl-3-oxa-7,9-diaza bicyclo[3.3.1]non-7-yl)carbonyl)-1,1a,2,12b-tetrahydrocyclopropa[d]indolo[2,1-a] [2]benzazepine-5-carboxamide. 1H NMR (300 MHz, CD3OD): δ ppm 0.24 (m, 0.25 H), 1.32 (m, 1.75 H), 1.43 (m, 4 H), 1.78 (m, 3 H), 1.98 (m, 4 H), 2.55 (m, 1 H), 2.77 - 2.90 (m, 1 H), 3.00 (s, 6 H), 3.11 - 3.26 (m, 4 H), 3.55 (m, 3 H), 3.88 (m, 3 H), 4.13 (m, 4 H), 4.54 (m, 2 H), 5.00 (d, J=15.00 Hz, 1 H), 7.00 (dd, J=8.42, 2.56 Hz, 1 H), 7.16 (m, 1 H), 7.21 - 7.33 (m, 1 H), 7.49 - 7.60 (m, 1 H), 7.81 - 7.88 (m, 1 H), 7.91 – 8.06 (m, 1 H). LC/MS: m/z 676.35, Rf 1.747 min., 98.2 % purity.

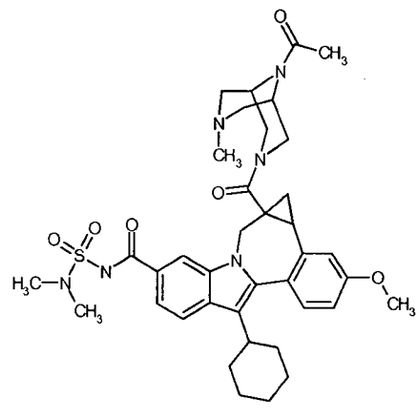


8-Cyclohexyl-N-(dimethylsulfamoyl)-11-methoxy-1a-(3-oxa-7,9-diazabicyclo[3.3.1] non-7-ylcarbonyl)-1,1a,2,12b-tetrahydrocyclopropa[d]indolo[2,1-a][2]benzazepine-5-carboxamide. 1H NMR (300 MHz, CD3OD): δ ppm 0.25 (m, 0.20 H), 1.08 -1.32 (m, 1.80 H), 1.44 (m, 4 H), 1.78 (m, 3 H), 1.99 (m, 4 H), 2.57 (m, 1 H), 2.77 (m, 1 H), 2.90 - 3.02 (m, 7 H), 3.62 (m, 3 H), 3.85 - 3.94 (m, 3 H), 4.00 - 4.15 (m, 4 H), 4.57 (m, 2 H), 5.00 (d, J=15.37 Hz, 1 H), 7.00 (dd, J=8.60, 2.38 Hz, 1 H), 7.17 (d, J=2.38 Hz, 1 H), 7.24 - 7.34 (m, 1

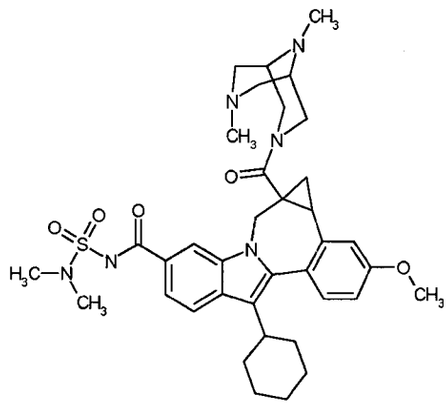
H), 7.50 - 7.61 (m, 1 H), 7.82 – 8.06 (m, 2 H). LC/MS: m/z 662.46, Rf 1.760 min., 98.2 % purity.



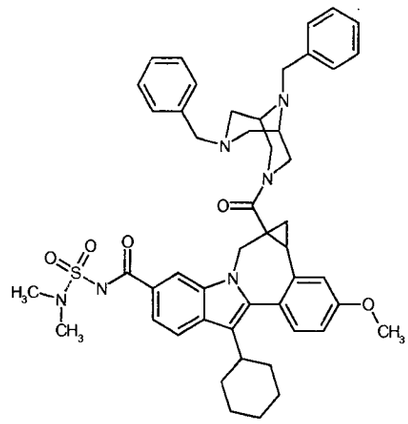
1a-((3-Benzyl-7-methyl-3,7,9-triazabicyclo[3.3.1]non-9-yl)carbonyl)-N-(sec-butyl sulfonyl)-8-cyclohexyl-11-methoxy-1,1a,2,12b-tetrahydrocyclopropa[d]indolo[2,1-a] [2]benzazepine-5-carboxamide. 1H NMR (300 MHz, CD3OD): δ ppm 0.20 (m, 0.20 H), 1.06 - 1.14 (m, 3 H), 1.20 - 1.36 (m, 2.80 H), 1.42 (m, 6 H), 1.72 (m, 4 H), 1.98 – 2.13 (m, 6 H), 2.62 (m, 2 H), 2.85 (m, 4 H), 3.15 (m, 1 H), 3.52 (m, 2 H), 3.63 (m, 2 H), 3.76 (m, 2 H), 3.87 (m, 4 H), 4.11 (m, 1 H), 4.38 (m, 1 H), 4.55 (m, 1 H), 5.06 (m, 1 H), 6.97 - 7.05 (m, 1 H), 7.11 - 7.17 (m, 1 H), 7.27 - 7.42 (m, 5 H), 7.59 (m, 2 H), 7.90 (m, 1 H), 8.01 – 8.09 (m, 1 H). LC/MS: m/z 779.48, Rf 1.897 min., 95.3 % purity.



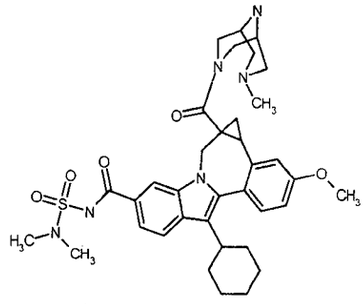
1a-((9-Acetyl-7-methyl-3,7,9-triazabicyclo[3.3.1]non-3-yl)carbonyl)-8-cyclohexyl-N-(dimethylsulfamoyl)-11-methoxy-1,1a,2,12b-tetrahydrocyclopropa[d]indolo[2,1-a] [2]benzazepine-5-carboxamide. 1H NMR (300 MHz, CD3OD): δ ppm 0.20 (m, 0.35 H), 1.01 – 1.30 (m, 0.65 H), 1.38 (m, 5 H), 1.79 (m, 3 H), 1.93 - 2.21 (m, 13 H), 2.62 (m, 1 H), 2.82 (m, 2 H), 2.99 (s, 6 H), 3.56 (m, 1 H), 3.90 (m, 3 H), 4.04 – 4.18 (m, 3 H), 4.53 (m, 1 H), 4.63 (m, 1 H), 4.99 (m, 1 H), 6.95 - 7.01 (m, 1 H), 7.19 (m, 1 H), 7.31 (m, 1 H), 7.50 - 7.60 (m, 1 H), 7.80 (m, 1 H), 7.88 - 8.07 (m, 1 H). LC/MS: m/z 717.92, Rf 1.760 min., 97.6 % purity.



8-Cyclohexyl-N-(dimethylsulfamoyl)-1a-((7,9-dimethyl-3,7,9-triazabicyclo[3.3.1] non-3-yl)carbonyl)-11-methoxy-1,1a,2,12b-tetrahydrocyclopropa[d]indolo[2,1-a][2] benzazepine-5-carboxamide. 1H NMR (300 MHz, CD3OD): δ ppm 0.24 (m, 0.35 H), 1.24 (m, 0.65 H), 1.29 - 1.49 (m, 5 H), 1.62 (m, 1 H), 1.79 (m, 2 H), 1.98 (m, 4 H), 2.42 (m, 1 H), 2.53 (m, 1 H), 2.62 (m, 1 H), 2.75 (m, 1 H), 2.87 (m, 2 H), 2.93 - 3.07 (m, 8 H), 3.12 - 3.22 (m, 2 H), 3.42 (m, 2 H), 3.51 - 3.66 (m, 1 H), 3.88 (m, 3 H), 4.13 (m, 3 H), 4.27 (m, 1 H), 4.60 (m, 1 H), 5.00 (m, 1 H), 6.97 - 7.04 (m, 1 H), 7.14 - 7.20 (m, 1 H), 7.31 (m, 1 H), 7.49 - 7.61 (m, 1 H), 7.81 - 7.92 (m, 1.65 H), 8.06 (m, 0.35 H). LC/MS: m/z 689.86, Rf 1.785 min., 96.2 % purity.



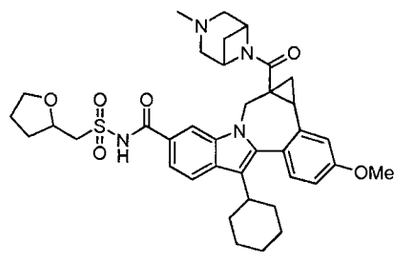
8-Cyclohexyl-1a-((7,9-dibenzyl-3,7,9-triazabicyclo[3.3.1]non-3-yl)carbonyl)-N-(dimethylsulfamoyl)-11-methoxy-1,1a,2,12b-tetrahydrocyclopropa[d]indolo[2,1-a][2] benzazepine-5-carboxamide. 1H NMR (500 MHz, CD3OD): δ ppm 0.22 (m, 0.25 H), 0.90 (m, 1 H), 1.19 - 1.28 (m, 1.75 H), 1.38 - 1.46 (m, 3 H), 1.76 (m, 3 H), 1.95 (m, 2 H), 2.00 (m, 2 H), 2.07 (m, 2 H), 2.54 (m, 1 H), 2.86 (m, 1 H), 2.99 (m, 9 H), 3.16 (m, 1 H), 3.43 (m, 1 H), 3.47 (m, 3 H), 3.84 - 3.91 (m, 4 H), 4.01 - 4.09 (m, 2 H), 4.75 (m, 1 H), 4.99 (d, J=15.26 Hz, 1 H), 6.94 - 7.02 (m, 1 H), 7.08 - 7.17 (m, 1 H), 7.27 - 7.56 (m, 11 H), 7.70 (m, 1 H), 7.86 - 8.07(m, 2 H). LC/MS: m/z 842.66, Rf 2.010 min., 98.0 % purity.



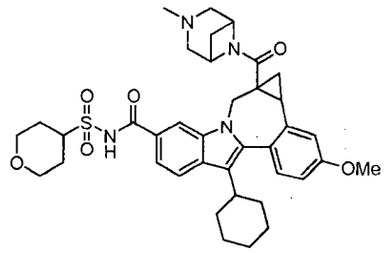
8-Cyclohexyl-N-(dimethylsulfamoyl)-11-methoxy-1a-((7-methyl-3,7,9-triazabicyclo [3.3.1]non-3-yl)carbonyl)-1,1a,2,12b-tetrahydrocyclopropa[d]indolo[2,1-a][2] benzazepine-5-carboxamide. 1H NMR (500 MHz, CD3OD): δ ppm 0.23 (m, 0.30 H), 1.07 -1.29 (m, 0.70 H), 1.36 - 1.45 (m, 5 H), 1.60 (m, 1 H), 1.73 - 1.82 (m, 2 H), 1.90 - 2.07 (m, 4 H), 2.17 (m, 1 H), 2.35 (m, 1 H), 2.54 – 2.70 (m, 3 H), 2.86 (m, 1 H), 3.00 (m, 8 H), 3.20 (m, 2 H), 3.59 (m,

1 H), 3.71 - 3.80 (m, 1 H), 3.84 - 3.91 (m, 3 H), 4.14 m, 1 H), 4.43 (m, 1 H), 4.65 (m, 1 H), 4.98 (m, 1 H), 6.98 - 7.01 (m, 1 H), 7.15 - 7.20 (m, 1 H), 7.28 - 7.32 (m, 1 H), 7.50 - 7.60 (m, 1 H), 7.85 – 8.05 (m, 2 H). LC/MS: m/z 675.61, Rf 1.783 min., 98.7 % purity.

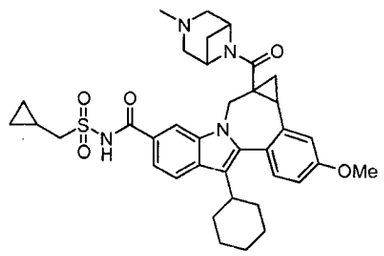
All compounds described in the procedures and examples that follow were analyzed by using the following LC / MS method until noted: Analysis Conditions: Column: PHENOMENNEX-LUNA 3.0 x 50mm S10; Mobile Phase: (A) 10:90 methanol-water; (B) 90:10 methanol-water; Buffer: 0.1% TFA; Gradient Range: 0-100% B; Gradient Time: 2 min; Flow Rate: 4 mL/min; Analysis Time: 3 min; Detection: Detector 1: UV at 220 nm; Detector 2: MS (ESI+).



8-cyclohexyl-N-((tetrahydrofuran-2-yl)methylsulfonyl)-1,1a,2,12b-tetrahydro-11-methoxy-1a-(3-methyl-3,6-diazabicyclo[3.1.1]heptane-6-carbonyl) cycloprop[d]indolo[2,1-a][2]benzazepine-5-carboxamide. The product was purified by prep HPLC and isolated as a mixture of diastereomers in mono TFA salt form. LC/MS: Retention time: 1.832 min; m/e 687 (MH^+). The product was observed to exist as inter-converting rotamers by 1H NMR (400 MHz, CHLOROFORM-D) δ ppm 1.07 - 1.58 (m, 6 H), 1.61 - 2.10 (m, 6 H), 2.11 - 2.51 (m, 8 H), 2.58 - 2.88 (m, 2 H), 2.89 - 3.04 (m, 2 H), 3.06 - 3.25 (m, 1 H), 3.38 - 3.82 (m, 7 H), 3.83 - 3.97 (m, 5 H), 4.31 - 4.52 (m, *J*=25.94 Hz, 2 H), 5.34 - 5.57 (m, 1 H), 6.91 - 7.02 (m, *J*=8.69, 2.64 Hz, 1 H), 7.05 - 7.18 (m, *J*=2.52 Hz, 1 H), 7.21 - 7.35 (m, 1 H), 7.54 - 7.69 (m, 1 H), 7.79 - 7.98 (m, 1 H), 8.04 - 8.23 (m, 1 H).



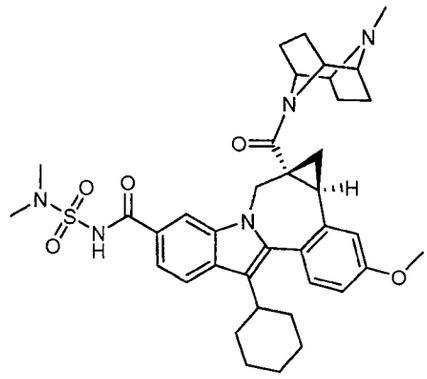
(+/-)-8-cyclohexyl-N-(tetrahydro-2H-pyran-4-ylsulfonyl)-1,1a,2,12b-tetrahydro-11-methoxy-1a-(3-methyl-3,6-diazabicyclo[3.1.1]heptane-6-carbonyl) cycloprop[d]indolo[2,1-a][2]benzazepine-5-carboxamide. The product was purified by prep HPLC and isolated as a beige solid in mono TFA salt form. LC/MS: Retention time: 1.810 min; m/e 687 (MH^+). The product was observed to exist as inter-converting rotamers by 1H NMR (400 MHz, CHLOROFORM-D) δ ppm 1.08 - 1.63 (m, 7 H), 1.72 - 1.86 (m, 2 H), 1.88 - 2.15 (m, 7 H), 2.15 - 2.60 (m, 7 H), 2.60 - 3.19 (m, 4 H), 3.34 - 3.52 (m, 3 H), 3.52 - 3.68 (m, 1 H), 3.83 - 3.94 (m, 3 H), 3.97 - 4.20 (m, 4 H), 4.28 - 4.49 (m, 1 H), 5.33 - 5.56 (m, 1 H), 6.87 - 7.04 (m, *J*=8.56, 2.77 Hz, 1 H), 7.05 - 7.17 (m, *J*=2.52 Hz, 1 H), 7.24 - 7.35 (m, 1 H), 7.55 - 7.73 (m, *J*=8.31 Hz, 1 H), 7.81 - 7.96 (m, *J*=8.56 Hz, 1 H), 8.02 - 8.21 (m, 1 H).



(+/-)-8-cyclohexyl-N-(cyclopropylmethylsulfonyl)-1,1a,2,12b-tetrahydro-11-methoxy-1a-(3-methyl-3,6-diazabicyclo[3.1.1]heptane-6-carbonyl) cycloprop[d]indolo[2,1-a][2]benzazepine-5-carboxamide. The product was purified by prep HPLC and isolated as a beige solid in mono TFA salt form. LC/MS: Retention time: 1.848 min; m/e 657 (MH^+). The product was observed to exist as inter-converting rotamers by 1H NMR (400 MHz, CHLOROFORM-D) δ ppm 0.29 - 0.48 (m, 2 H), 0.59 - 0.78 (m, 2 H), 1.10 - 1.61 (m, 6 H), 1.68 - 2.19 (m, *J*=81.58 Hz, 6 H), 2.21 - 2.78 (m, 10 H), 2.79 - 3.28 (m, 2 H), 3.31 - 3.72 (m, 4 H), 3.78 - 3.97 (m, 3 H), 3.97 - 4.70 (m, 2 H), 5.33 - 5.59 (m, 1 H), 6.86 - 7.04 (m, *J*=8.56, 2.52 Hz, 1

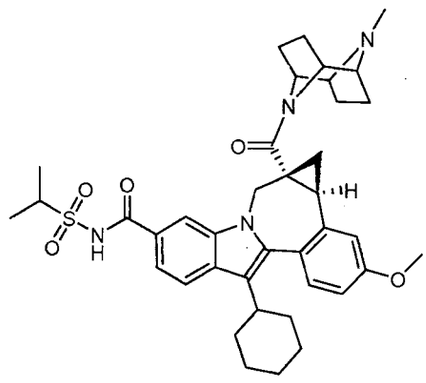
H), 7.05 - 7.18 (m, *J*=2.27 Hz, 1 H), 7.18 - 7.37 (m, 1 H), 7.47 - 7.70 (m, 1 H), 7.79 - 8.01 (m, 1 H), 8.03 - 8.35 (m, 1 H).

9-methyl-9,10-diazatricyclo[4.2.1.1^{2,5}]decane. To a cold (0 °C) solution of 9-benzyl-9,10-diazatricyclo[4.2.1.1^{2,5}]decane (*J. Med. Chem.* **2000**, *43*, 2115-2123) and TEA in an. DMF (1-2 ml) was added MeI. The mixture was allowed to warm to rt and stirred for 2-3 h. The rxn mixture was evaporated to dryness and partitioned between ether and satd. NaHCO3 and ether layer separated, washed with brine and dried (Na2SO4). Evaporation of ether afforded 9-benzyl-10-methyl-9,10-diazatricyclo[4.2.1.1^{2,5}]decane as a light-brown oil. A stirred suspension of 9-benzyl-10-methyl-9,10-diazatricyclo [4.2.1.1^{2,5}]decane in EtOH containing conc. HCl (0.5 ml) and 10% Pd-C was hydrogenated under balloon pressure of hydrogen overnight. The suspension was filtered and filtrate was added dry toluene (10-15 ml) and evaporated to dryness to afford the 9-methyl-9,10-diazatricyclo[4.2.1.1^{2,5}]decane and isolated as bis-HCl salt.



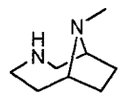
8-cyclohexyl-N-(N,N-dimethylsulfamoyl)-1,1a,2,12b-tetrahydro-11-methoxy-1a-(9-methyl-9,10-diazatricyclo[4.2.1.1^{2,5}]decane-10-carbonyl)cycloprop[d]indolo[2,1-a][2]benzazepine-5-carboxamide. Neat 2-(1H-enzotriazol-1-yl)-1,1,3,3-tetramethyluronium tetrafluoroborate (12.52 mg, 0.039 mmol) was added to a stirred solution of the acid (17 mg, 0.03 mmol), 9-methyl-9,10-diazatricyclo[4.2.1.1^{2,5}]decane (9 mg, 0.036 mmol) and TEA (0.025 ml, 0.180 mmol) in an. DCM (1 ml). The mixture stirred at rt overnight and then evaporated to dryness. The crude product was purified by reverse-phase prep. HPLC to afford the product and isolated as mono TFA salt: LC/MS: Retention time: 2.810 min; m/e 686

(MH^+). The product was observed to exist as inter-converting rotamers by 1H NMR (400 MHz, CHLOROFORM-D) δ ppm 0.18 - 0.35 (m, J=6.17, 6.17 Hz, 1 H), 1.10 - 1.28 (m, 2 H), 1.30 - 1.43 (m, 3 H), 1.43 - 1.61 (m, J=24.93 Hz, 1 H), 1.69 - 1.85 (m, 2 H), 1.83 - 2.08 (m, 4 H), 2.10 - 2.34 (m, 2 H), 2.37 - 2.55 (m, 2 H), 2.58 - 2.72 (m, 2 H), 2.73 - 2.94 (m, 3 H), 2.95 - 3.08 (m, 6 H), 3.37 - 3.61 (m, 3 H), 3.65 - 3.81 (m, J=18.63 Hz, 2 H), 3.82 - 3.94 (m, J=3.02 Hz, 3 H), 3.94 - 4.06 (m, J=14.60 Hz, 1 H), 4.09 - 4.25 (m, J=14.10 Hz, 1 H), 4.34 - 4.63 (m, 1 H), 4.73 - 4.88 (m, 1 H), 5.15 - 5.27 (m, 1 H), 6.91 - 6.99 (m, 1 H), 6.97 - 7.14 (m, 1 H), 7.26 - 7.35 (m, 1 H), 7.46 - 7.55 (m, J=9.32, 9.32 Hz, 1 H), 7.83 - 7.90 (m, J=8.18, 8.18 Hz, 1 H), 7.90 - 8.00 (m, 1 H).



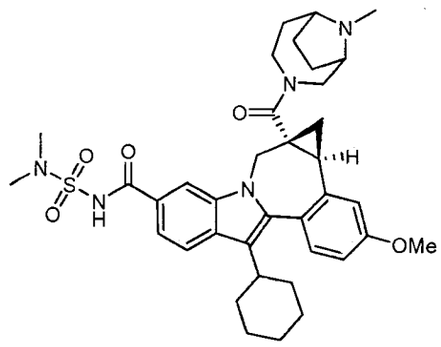
8-cyclohexyl-N-(isopropylsulfonyl)-1,1a,2,12b-tetrahydro-11-methoxy-1a-(9-methyl-9,10-diazatricyclo[4.2.1.1^{2,5}]decane-10-carbonyl)cycloprop[d]indolo[2,1-a][2]benzazepine-5-carboxamide. Neat 2-(1H-benzotriazol-1-yl)-1,1,3,3-tetramethyluronium tetrafluoroborate (12.52 mg, 0.039 mmol) was added to a stirred solution of the acid (17 mg, 0.03 mmol), 9-methyl-9,10-diazatricyclo[4.2.1.1^{2,5}]decane (9 mg, 0.036 mmol) and TEA (0.025 ml, 0.180 mmol) in an. DCM (1ml). The mixture stirred at rt overnight and then evaporated to dryness. The crude product was purified by reverse-phase prep. HPLC to afford the product and isolated as mono TFA salt: LC/MS: Retention time: 2.855 min; m/e 685 (MH^+). The product was observed to exist as inter-converting rotamers by 1H NMR (400 MHz, CHLOROFORM-D) δ ppm 0.16 - 0.36 (m, 1 H), 1.03 - 1.28 (m, 2 H), 1.29 - 1.57 (m, 8 H), 1.65 - 1.85 (m, 2 H), 1.84 - 2.06 (m, 4 H), 2.09 - 2.33 (m, 2 H), 2.36 - 2.54 (m, 1 H), 2.59 - 2.79 (m, 2 H), 2.80 - 2.89 (m, 2 H), 2.89 - 3.20 (m, 2 H), 3.41 - 3.63 (m, 3 H), 3.62 - 3.82 (m, 4 H), 3.83 - 3.93 (m, J=3.78 Hz, 3 H), 3.96 -

4.09 (m, 2 H), 4.10 - 4.25 (m, J=14.60 Hz, 1 H), 4.43 - 4.56 (m, 1 H), 4.71 - 4.85 (m, 1 H), 5.12 - 5.26 (m, 1 H), 6.91 - 6.98 (m, 1 H), 6.97 - 7.12 (m, 1 H), 7.27 - 7.34 (m, 1 H), 7.49 - 7.58 (m, J=8.31 Hz, 1 H), 7.84 - 7.90 (m, J=8.44, 6.17 Hz, 1 H), 7.90 - 7.99 (m, 1 H).

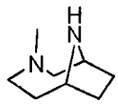


9-methyl-3,9-diazabicyclo[4.2.1]nonane. 9-Methyl-3,9-diazabicyclo[4.2.1]nonane (*J. Org. Chem.*, **1960**, 637).. Conc. H_2SO_4 (6.25 ml, 0.117 mol) was added dropwise to a stirred cold (-5 °C) solution of 8-methyl-8-azabicyclo[3.2.1]octan-3-one (2.78 g, 0.02 mol) in $CHCl_3$ (25 ml) while keeping the temperature below 15 °C. After cooling to 0-5 °C, neat sodium azide (2.60 g, 0.040 mol) was added in small portions while maintaing pot temperature below 35 °C. The mixture stirred at rt for 2h and then heated at 50 °C for 2 h. Rxn mixture was poured into ice and neutralized with Na_2CO_3 and then basify with 50% NaOH. Organic layer separated and the aq. layer re-extracted with $CHCl_3$ (2x25 ml). Combined organic layers were washed with water (10 ml), brine and dried ($MgSO_4$). Evaporation of $CHCl_3$ gave 9-methyl-3,9-diazabicyclo[4.2.1]nonan-4-one as a off-white solid (1.15 g, 37%). 1H NMR (400 MHz, CHLOROFORM-D) d ppm 1.67 - 1.75 (m, 1 H) 1.77 - 1.85 (m, 1 H) 2.05 - 2.16 (m, 2 H) 2.42 (s, 3 H) 2.46 (ddd, *J*=16.05, 6.23, 2.14 Hz, 1 H) 2.80 - 2.90 (m, 2 H) 3.17 (t, *J*=6.42 Hz, 1 H) 3.24 (t, *J*=6.30 Hz, 1 H) 3.60 (d, *J*=14.60 Hz, 1 H) 5.90 (s, 1 H).

Neat LAH (0.5 g, 13.17 mmol) was added in small portions to a stirred solution of 9-methyl-3,9-diazabicyclo[4.2.1]nonan-4-one (1.0 g, 6.48 mmol) in THF (40 ml) and the mixture was heated at reflux under nitrogen for 3-4 h. Reaction mixture was cooled in ace bath and quenched by consecutive addition of water (0.5 ml), 15% NaOH (1.5 ml) and water (0.5 ml) and then stirred for 30 min. Precipitated sodium aluminate was filtered off and the filtrate was dried over MgSO4, filtered and evaporated to dryness to afford 9-methyl-3,9-diazabicyclo[4.2.1]nonane as a light yellow oil.1H NMR (400 MHz, CHLOROFORM-D) δ ppm 1.08 - 1.67 (m, 4 H) 1.74 - 1.92 (m, 1 H) 2.01 - 2.31 (m, 2 H) 2.41 - 2.46 (m, 3 H) 2.66 (dd, *J*=13.09, 2.01 Hz, 1 H) 2.77 - 3.00 (m, 2 H) 3.07 - 3.36 (m, 2 H) 3.50 - 4.06 (m, 1 H).



8-cyclohexyl-N-(N,N-dimethylsulfamoyl)-1,1a,2,12b-tetrahydro-11-methoxy-1a-(9-methyl-3,9-diazabicyclo[4.2.1]nonane-3-carbonyl)cycloprop[d]indolo[2,1-a][2]benzazepine-5-carboxamide. Neat 2-(1H-benzotriazol-1-yl)-1,1,3,3-tetramethyluronium tetrafluoroborate (22 mg, 0.069 mmol) was added to a stirred solution of the acid (28 mg, 0.051 mmol), 9-methyl-3,9-diazabicyclo[4.2.1]nonane (15 mg, 0.102 mmol) and TEA (0.021 ml, 0.152 mmol) in an. DCM (1ml). The mixture stirred at rt for 30-45 min and then evaporated to dryness. The crude product was purified by reverse-phase prep. HPLC to afford the product as a mixture of diastereomers and isolated in mono TFA salt: LC/MS: Retention time: 1.788 min; m/e 674 (MH^+). The product was observed to exist as inter-converting rotamers by 1H NMR (400 MHz, CHLOROFORM-D) δ ppm 0.22 - 0.50 (m, 1 H), 1.13 - 1.46 (m, J=54.89 Hz, 4 H), 1.46 - 1.61 (m, 1 H), 1.63 - 1.84 (m, 3 H), 1.85 - 2.22 (m, 5 H), 2.28 - 2.69 (m, 7 H), 2.69 - 2.98 (m, 4 H), 2.98 - 3.12 (m, 6 H), 3.43 - 3.56 (m, 1 H), 3.55 - 3.82 (m, 2 H), 3.84 - 3.91 (m, J=4.28 Hz, 3 H), 3.92 - 4.08 (m, 2 H), 4.10 - 4.24 (m, 1 H), 4.64 - 5.10 (m, J=132.95 Hz, 1 H), 6.87 - 7.00 (m, 1 H), 7.01 - 7.12 (m, 1 H), 7.27 - 7.35 (m, 1 H), 7.40 - 7.63 (m, 1 H), 7.82 - 7.93 (m, 2 H).



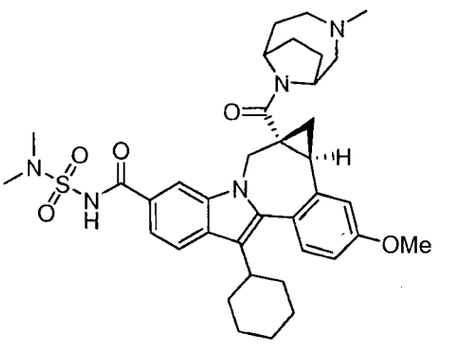
3-methyl-3,9-diazabicyclo[4.2.1]nonane. 3-Methyl-3,9-diazabicyclo[4.2.1]nonane was prepared by following the procedure described in reference: *J. Org. Chem.*, **1960**, 637. Conc. H2SO4 (3.25 ml, 0.061 mol) was added dropwise to a stirred cold (-5 °C) solution of 8-benzyl-8-azabicyclo[3.2.1]octan-3-one

(2.153 g, 0.01 mol) in CHCl3 (15 ml) while keeping the temperature below 15 °C. After cooling to 0-5 °C, neat sodium azide (1.30 g, 0.020 mol) was added in small portions while maintaining pot temperature below 35 °C. The mixture was stirred at rt overnight and then heated at 50 °C for 2 h. Rxn mixture was poured into ice and neutralized with Na2CO3 and then basify with 50% NaOH. Organic layer separated and the aq. layer re-extracted with CHCl3 (2x25 ml). Combined organic lyers were washed with water (10 ml), brine and dried (MgSO4). Evaporation of CHCl3 gave 9-benzyl-3,9-diazabicyclo[4.2.1]nonan-4-one as a beige semi-solid. LC/MS: m/e 231 (MH+).

Neat LAH (0.4 g, 10.54 mmol) was added in small portions to a stirred solution of 9-benzyl-3,9-diazabicyclo[4.2.1]nonan-4-one (1.2 g, 5.21 mmol) in THF (40 ml) and the mixture was stirred under nitrogen overnight. Reaction mixture was cooled in ace bath and quenched by consecutive addition of water (0.4 ml), 15% NaOH (1.2 ml) and water (0.4 ml) and then stirred for 30 min. Precipitated sodium aluminate was filtered off and the filtrate was dried over MgSO4, filtered and evaporated to dryness to afford 9-benzyl-3,9-diazabicyclo[4.2.1]nonane as a light yellow oil. LC/MS: m/e 217 (MH+).

Neat Iodomethane (0.173 ml, 2.77 mmol) was added dropwise to a stirred solution of 9-benzyl-3,9-diazabicyclo[4.2.1]nonane (0.4 g, 1.849 mmol) and TEA (2.58 ml, 18.49 mmol) in THF (5 ml). The resultant suspension was stirred at rt for 3 hrs and diluted with ether and then filtered. The filtrate was evaporated to dryness to afford 9-benzyl-3-methyl-3,9-diazabicyclo[4.2.1]nonane as a light yellow oil. LC/MS: m/e 231 (MH+).

Neat ammonium formate (2 g, 31.7 mmol) was added to stirred suspension of 9-benzyl-3-methyl-3,9-diazabicyclo[4.2.1]nonane (250 mg, 1.085 mmol) and 10% Pd-C (150 mg, 0.141 mmol) in abs. ethanol (50 ml). The mixture was heated to reflux for 2-3 h. The suspension was filtered and to the filtrate TFA (0.5 ml) was added and evaporated to dryness to afford 3-methyl-3,9-diazabicyclo[4.2.1]nonane and isolated as the bis-TFA salt. LC/MS: m/e 141 (MH+).



8-cyclohexyl-N-(N,N-dimethylsulfamoyl)-1,1a,2,12b-tetrahydro-11-methoxy-1a-(3-methyl-3,9-diazabicyclo[4.2.1]nonane-9-carbonyl)cycloprop[d]indolo[2,1-a][2]benzazepine-5-carboxamide. Neat 2-(1H-benzotriazol-1-yl)-1,1,3,3-tetramethyluronium tetrafluoroborate (22 mg, 0.069 mmol) was added to a stirred solution of the acid (28 mg, 0.051 mmol), 3-methyl-3,9-diazabicyclo[4.2.1]nonane, 2TFA (37.4 mg, 0.102 mmol) and TEA (0.035 ml, 0.254 mmol) in an. DCM (1ml). The mixture stirred at rt for 30-45 min and then evaporated to dryness. The crude product was purified by reverse-phase prep. HPLC to afford the product as a mixture of diastereomers and isolated in mono TFA salt: LC/MS: Retention time: 1.830 min; m/e 674 (MH^+). The product was observed to exist as inter-converting rotamers by 1H NMR (500 MHz, CHLOROFORM-D) δ ppm 0.09 - 0.66 (m, 1 H), 0.72 - 1.14 (m, 1 H), 1.13 - 1.47 (m, 5 H), 1.48 - 1.65 (m, 1 H), 1.65 - 1.83 (m, 3 H), 1.83 - 2.14 (m, 4 H), 2.14 - 2.40 (m, 2 H), 2.38 - 2.69 (m, 2 H), 2.70 - 2.87 (m, 3 H), 2.86 - 3.08 (m, 6 H), 3.09 - 3.42 (m, 2 H), 3.43 - 3.55 (m, 1 H), 3.56 - 3.73 (m, J=16.48 Hz, 1 H), 3.74 - 3.98 (m, 4 H), 3.95 - 4.26 (m, 1 H), 4.22 - 4.61 (m, 2 H), 4.61 - 4.87 (m, J=35.10 Hz, 1 H), 4.95 - 5.21 (m, J=64.39 Hz, 1 H), 6.86 - 7.01 (m, 1 H), 7.02 - 7.14 (m, 1 H), 7.25 - 7.34 (m, 1 H), 7.34 - 7.58 (m, 1 H), 7.78 - 8.00 (m, 2 H).

The following compounds were analyzed by the following method until noted: Analysis Conditions: Column: PHENOMENNEX-LUNA 3.0 x 50mm S10; Mobile Phase: (A) 10:90 methanol-water; (B) 90:10 methanol-water; Buffer: 0.1% TFA; Gradient Range: 0-100% B; Gradient Time: 2 min; Flow Rate: 4 mL/min; Analysis Time: 3 min; Detection: Detector 1: UV at 220 nm; Detector 2: MS (ESI+).

General procedure for the preparation of 3-alkyl-3,9-diazabicyclo[3.3.1]nonane. A suspension of pyridine-2,6-dicarboxylic acid (6.68 g, 40.0 mmol) and Platinum(IV) oxide (0.23 g, 1.013 mmol) in Acetic Acid (200 ml) was hydrogenated in a Parr shaker under 50 psi of hydrogen pressure for 4-5 h. The suspension was filtered and the filtrate was acidified with conc. HCl (50 ml) to the piperidine-2,6-dicarboxylic acid hydrochloride as a white solid (5.9 g, 70%). LCMS: m/e 174 (MH+).

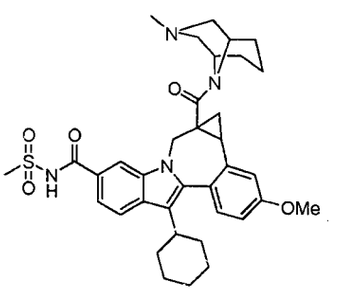
To a cold (0-5 °C) solution of piperidine-2,6-dicarboxylic acid hydrochloride (1.05 g, 5.01 mmol) in 1N NaOH (10.02 mL, 10.02 mmol) Benzyl chloroformate (1.430 mL, 10.02 mmol) was added at a rate that kept reaction temp. below 5 °C. Reaction mixture was allowed to warm to rt and stirred overnight. Excess benzyl chloroformate was removed by washing the rxn mixture with ether (2X10 ml). Aqueous layer was cooled in a ice bath and acidified with 6N HCl (4 ml) and white precipitate was extracted with EtOAc (2X25 ml), dried (MgSO4), evaporated to afford 1-(benzyloxycarbonyl)-piperidine-2,6-dicarboxylic acid as a white solid (1.35 g, 88%). LCMS: m/e 264 (M-CO2H)+.

Neat acetic anhydride (0.453 ml, 4.80 mmol) was added to a stirred suspension of 1-(benzyloxycarbonyl)piperidine-2,6-dicarboxylic acid (1.23 g, 4.00 mmol) in toluene (20 ml) and the mixture was heated to reflux for 1 h. Resultant clear solution was evaporated to dryness to afford the corresponding anhydride as a colorless viscous oil(1.2 g, 100%). A THF solution of methylamine (5.00 ml, 10.01 mmol) and TEA (0.558 ml, 4.00 mmol) were added to a cold (-20 °C) solution of the crude anhydride in an. THF (4 ml) and the mixture was allowed to warm to rt and stirred for 1-2 h. Rxn was diluted with ether (25 ml) and 2N HCl (10 ml) was added and organic layer separated, washed with water, brine and dried (MgSO4). Evaporation of solvents gave a viscous oil (1.13 g) which was dissolved in an. toluene (10 ml) and treated with acetic anhydride (0.453 ml, 4.80 mmol). The mixture was heated to reflux to for 2 h and then evaporated to dryness to afford an oil (1.32 g) which was purified by flash column chromatography (silica gel, 3% MeOH in DCM) to afford benzyl 3-methyl-2,4-dioxo-3,9-diazabicyclo[3.3.1]nonane-9-carboxylate as a colorless oil (0.805 g, 66.5%). LC/MS: m/e 303 (MH+).

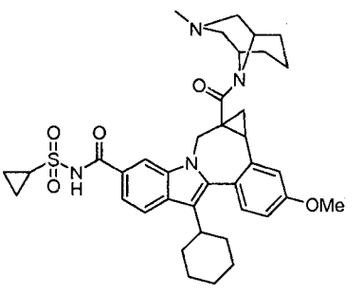
A stirred suspension of benzyl 3-methyl-2,4-dioxo-3,9-diazabicyclo[3.3.1] nonane-9-carboxylate (742 mg, 2.454 mmol) and 10% Pd-C (100 mg) in ethyl acetate (40 ml) was hydrogenated under balloon pressure of hydrogen overnight. The suspension was filtered to remove the catalyst and the filtrate was evaporated to dryness to afford 3-methyl-3,9-diazabicyclo[3.3.1]nonane-2,4-dione as a white solid (377 mg). MS: m/e 169 (MH^+).

To a stirred cold (0-5 °C) suspension of LAH (205 mg, 5.40 mmol) in an. THF (15 ml) a solution of 3-methyl-3,9-diazabicyclo[3.3.1]nonane-2,4-dione (375 mg) in THF (5 ml) was added and the mixture was heated to reflux for 1-2 h. Rxn was cooled in a ice bath and quenched by addition of water (0.2 ml), 15% NaOH (0.6 ml) and water (0.2 ml) and the the suspension was vigorously stirred and filtered and dried over Na2SO4. Evaporation of solvents gave light-brown oil which was dissolved in ether and treated with 1N HCl in ether to afford 3-methyl-3,9-diazabicyclo[3.3.1]nonane and isolated as bis-HCl salt. MS: m/e 141 (MH+). 1H NMR (500 MHz, CD3OD): δ ppm 1.34-1.59 (5H, m), 2.02-2.32 (6H, m), 2.57-2.97 (4H, m).

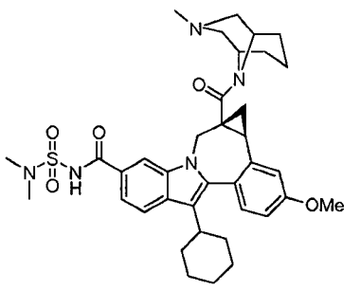
General procedure for the preparation of amides from corresponding acids via amide coupling using 3-methyl-3,9-diazabicyclo[3.3.1]nonane. A mixture of acid (1 eq), amine (1.2-1.5 eq), TBTU (1.3 eq) and TEA (4 eq) in an. DCM was stirred for 1-2 h at rt. to afford the amide which were purified by reverse phase prep HPLC and isolated as TFA salt.



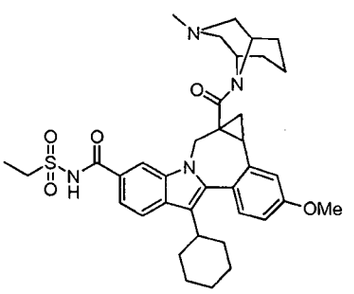
(+/-)-8-cyclohexyl-N-(methylsulfonyl)-1,1a,2,12b-tetrahydro-11-methoxy-1a-(3-methyl-3,9-diazabicyclo[3.3.1]nonane-9-carbonyl) cycloprop[d]indolo[2,1-a][2]benzazepine-5-carboxamide. The product was purified by prep HPLC and isolated as a beige solid. LC/MS: Retention time: 2.776 min; m/e 645 (MH^+). The product was observed to exist as inter-converting rotamers by 1H NMR (400 MHz, CHLOROFORM-D) δ ppm 0.17 - 0.49 (m, 1 H), 1.06 - 1.48 (m, 5 H), 1.48 - 2.16 (m, J=80.83 Hz, 10 H), 2.19 - 2.45 (m, 1 H), 2.48 - 3.17 (m, 10 H), 3.32 - 3.53 (m, 3 H), 3.54 - 3.76 (m, J=15.36 Hz, 2 H), 3.77 - 4.04 (m, 4 H), 4.54 - 4.77 (m, 1 H), 4.81 - 5.27 (m, J=119.61 Hz, 1 H), 6.86 - 7.05 (m, 1 H), 7.03 - 7.16 (m, J=2.52 Hz, 1 H), 7.19 - 7.34 (m, 1 H), 7.48 - 7.75 (m, 1 H), 7.80 - 8.16 (m, 2 H).



(+/-)-8-cyclohexyl-N-(cyclopropylsulfonyl)-1,1a,2,12b-tetrahydro-11-methoxy-1a-(3-methyl-3,9-diazabicyclo[3.3.1]nonane-9-carbonyl) cycloprop[d]indolo[2,1-a][2]benzazepine-5-carboxamide. The product was purified by prep HPLC and isolated as a beige solid. LC/MS: Retention time: 2.846 min; m/e 671 (MH^+). The product was observed to exist as inter-converting rotamers by 1H NMR (400 MHz, CHLOROFORM-D) δ ppm 1.04 - 1.57 (m, 6 H), 1.60 - 1.86 (m, J=44.57 Hz, 4 H), 1.85 - 2.29 (m, 18 H), 2.49 - 3.26 (m, 4 H), 3.52 - 3.74 (m, J=14.60 Hz, 2 H), 3.80 - 3.99 (m, 4 H), 4.54 - 4.77 (m, 1 H), 4.97 - 5.31 (m, 1 H), 6.88 - 7.04 (m, 1 H), 7.06 - 7.18 (m, J=2.77 Hz, 1 H), 7.18 - 7.35 (m, 2 H), 7.81 - 8.01 (m, 2 H).

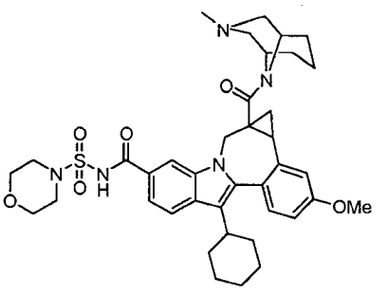


8-cyclohexyl-N-(N,N-dimethylsulfamoyl)-1,1a,2,12b-tetrahydro-11-methoxy-1a-(3-methyl-3,9-diazabicyclo[3.3.1]nonane-9-carbonyl) cycloprop[d]indolo[2,1-a][2]benzazepine-5-carboxamide. The product was purified by prep HPLC and isolated as a beige solid. LC/MS: Retention time: 2.890 min; m/e 674 (MH^+). The product was observed to exist as inter-converting rotamers by 1H NMR (400 MHz, CHLOROFORM-D) δ ppm 1.01 - 1.59 (m, 7 H), 1.58 - 2.36 (m, 9 H), 2.37 - 3.30 (m, 15 H), 3.42 - 3.74 (m, 2 H), 3.77 - 3.93 (m, J=3.02 Hz, 4 H), 3.93 - 4.22 (m, 1 H), 4.55 - 4.73 (m, 1 H), 4.71 - 5.20 (m, 1 H), 6.85 - 7.04 (m, 1 H), 7.02 - 7.17 (m, J=2.27 Hz, 1 H), 7.16 - 7.34 (m, 1 H), 7.41 - 7.66 (m, 1 H), 7.76 - 8.15 (m, 2 H).

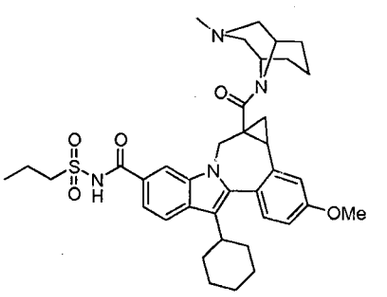


(+/-)-8-cyclohexyl-N-(ethylsulfonyl)-1,1a,2,12b-tetrahydro-11-methoxy-1a-(3-methyl-3,9-diazabicyclo[3.3.1]nonane-9-carbonyl) cycloprop[d]indolo[2,1-a][2]benzazepine-5-carboxamide. The product was purified by prep HPLC and isolated as a beige solid. LC/MS: Retention time: 2.846 min; m/e 659 (MH^+). The product was observed to exist as inter-converting rotamers by 1H NMR (400 MHz, CHLOROFORM-D) δ ppm 0.14 - 0.52 (m, 1 H), 1.10 - 1.49 (m, 7 H), 1.48 - 2.19 (m, 11 H), 2.18 - 2.39 (m, 1 H), 2.50 - 3.21 (m, 5 H), 3.28 - 3.75 (m, 7 H), 3.83 - 3.92 (m, 4 H), 3.92 - 4.34 (m, 2 H), 4.53 - 4.79 (m, 1 H), 4.86 - 5.24 (m, J=82.59 Hz, 1 H),

6.91 - 7.02 (m, 1 H), 7.08 - 7.15 (m, J=2.52 Hz, 1 H), 7.26 - 7.33 (m, 1 H), 7.48 - 7.73 (m, J=76.80 Hz, 1 H), 7.87 - 7.96 (m, J=8.56 Hz, 1 H), 7.96 - 8.17 (m, 1 H).

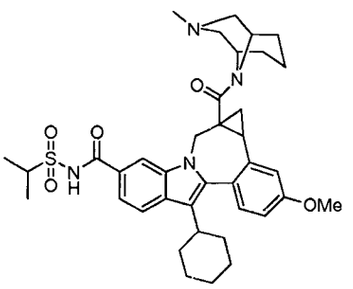


(+/-)-8-cyclohexyl-N-(morpholinosulfonyl)-1,1a,2,12b-tetrahydro-11-methoxy-1a-(3-methyl-3,9-diazabicyclo[3.3.1]nonane-9-carbonyl) cycloprop[d]indolo[2,1-a][2]benzazepine-5-carboxamide. The product was purified by prep HPLC and isolated as a beige solid. LC/MS: Retention time: 2.828 min; m/e 716 (MH^+). The product was observed to exist as inter-converting rotamers by 1H NMR (400 MHz, CHLOROFORM-D) δ ppm 0.14 - 0.57 (m, 1 H), 1.01 - 1.47 (m, 6 H), 1.47 - 1.88 (m, 6 H), 1.87 - 2.21 (m, 7 H), 2.24 - 3.13 (m, 11 H), 3.38 - 3.56 (m, 4 H), 3.57 - 3.69 (m, J=15.11 Hz, 2 H), 3.84 - 3.94 (m, 4 H), 4.56 - 4.74 (m, 1 H), 4.76 - 5.25 (m, 1 H), 6.93 - 7.03 (m, 1 H), 7.07 - 7.15 (m, J=2.52 Hz, 1 H), 7.29 (d, J=8.56 Hz, 1 H), 7.49 - 7.71 (m, 1 H), 7.84 - 8.00 (m, 2 H).

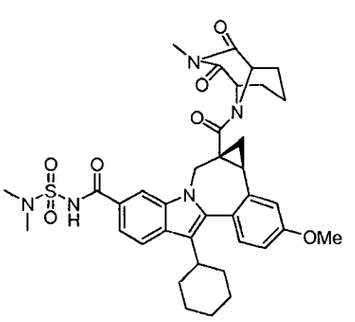


(+/-)-8-cyclohexyl-N-(propylsulfonyl)-1,1a,2,12b-tetrahydro-11-methoxy-1a-(3-methyl-3,9-diazabicyclo[3.3.1]nonane-9-carbonyl) cycloprop[d]indolo[2,1-a][2]benzazepine-5-carboxamide. The product was purified by prep HPLC and isolated as a beige solid. LC/MS: Retention time: 2.918 min; m/e 673 (MH^+). The product was observed to exist as inter-converting rotamers by 1H NMR (400 MHz, CHLOROFORM-D) δ ppm 0.12 - 0.53 (m, 1 H), 0.76 - 1.14 (m, 4 H), 1.14 - 1.52 (m,

5 H), 1.49 - 2.16 (m, 12 H), 2.20 - 2.46 (m, 1 H), 2.48 - 3.05 (m, 4 H), 3.05 - 3.71 (m, 9 H), 3.82 - 4.01 (m, 4 H), 4.55 - 4.79 (m, 1 H), 4.82 - 5.22 (m, J=86.12 Hz, 1 H), 6.91 - 7.02 (m, 1 H), 7.07 - 7.15 (m, J=2.52 Hz, 1 H), 7.26 - 7.33 (m, 1 H), 7.56 - 7.76 (m, 1 H), 7.85 - 7.96 (m, J=8.56 Hz, 1 H), 7.95 - 8.19 (m, 1 H).

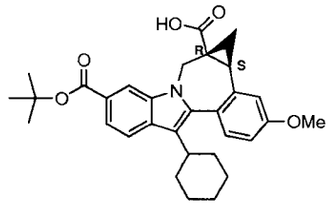


(+/-)-8-cyclohexyl-N-(isopropylsulfonyl)-1,1a,2,12b-tetrahydro-11-methoxy-1a-(3-methyl-3,9-diazabicyclo[3.3.1]nonane-9-carbonyl) cycloprop[d]indolo[2,1-a][2]benzazepine-5-carboxamide. The product was purified by prep HPLC and isolated as a beige solid. LC/MS: Retention time: 3.120 min; m/e 673 (MH^+). The product was observed to exist as inter-converting rotamers by 1H NMR (400 MHz, CHLOROFORM-D) δ ppm 0.14 - 0.53 (m, 1 H), 1.12 - 1.51 (m, 9 H), 1.50 - 2.19 (m, 12 H), 2.20 - 2.46 (m, 1 H), 2.48 - 3.27 (m, 8 H), 3.40 - 3.70 (m, 3 H), 3.81 - 3.95 (m, 4 H), 3.93 - 4.12 (m, J=22.66 Hz, 1 H), 4.52 - 4.76 (m, 1 H), 4.79 - 5.24 (m, J=105.76 Hz, 1 H), 6.91 - 7.03 (m, 1 H), 7.07 - 7.14 (m, J=2.52 Hz, 1 H), 7.26 - 7.32 (m, J=8.56 Hz, 1 H), 7.51 - 7.70 (m, 1 H), 7.85 - 8.00 (m, J=8.56 Hz, 2 H).



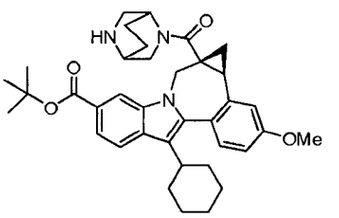
(+/-)-8-cyclohexyl-N-(N,N-dimethylsulfamoyl)-1,1a,2,12b-tetrahydro-11-methoxy-1a-(3-methyl-2,4-dioxo-3,9-diazabicyclo[3.3.1]nonane-9-carbonyl) cycloprop[d]indolo[2,1-a][2]benzazepine-5-carboxamide. The product was

purified by prep HPLC and isolated as a beige solid. LC/MS: Retention time: 3.306 min; m/e 702 (MH^+). The product was observed to exist as inter-converting rotamers by 1H NMR (500 MHz, CHLOROFORM-D) δ ppm 0.29 - 0.77 (m, 1 H), 0.98 - 1.64 (m, 4 H), 1.64 - 2.23 (m, 9 H), 2.44 - 2.97 (m, 2 H), 2.98 - 3.16 (m, 9 H), 3.31 - 3.67 (m, 6 H), 3.79 - 3.96 (m, 4 H), 3.96 - 4.54 (m, 1 H), 5.03 - 5.52 (m, 1 H), 6.83 - 6.96 (m, 1 H), 6.97 - 7.14 (m, 1 H), 7.17 - 7.33 (m, 1 H), 7.44 - 7.71 (m, 1 H), 7.73 - 7.90 (m, 1 H), 7.90 - 8.30 (m, 1 H).

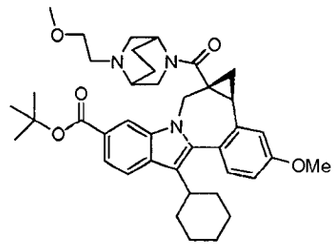


(1aR,12bS)-5-(tert-butoxycarbonyl)-8-cyclohexyl-11-methoxy-1,12b-dihydrocyclopropa[d]indolo[2,1-a][2]benzazepine-1a(2H)-carboxylic acid. Sodium hydroxide (aq. 1M, 31 mL) was added to a cooled solution (0°C, ice bath) containing 5-tert-butyl 1a-ethyl (1aR,12bS)-8-cyclohexyl-11-methoxy-1,12b-dihydrocyclopropa[d]indolo[2,1-a][2]benzazepine-1a,5(2H)-dicarboxylate (4.0 g, 7.76 mmol), THF (35 mL), and methanol (35 mL). After 20 min, the solution was removed from the cooling bath and maintained at ambient temperature for 3h. The solution was cooled again (0°C, ice bath) and the pH reduced to just below 4 by slow addition of 1N HCl (aq., 33mL). The mixture was immediately extracted with ethyl acetate (2 x 30 mL). The combined organic portions were washed with brine, (20 mL), dried (magnesium sulfate), filtered and concentrated to afford a white solid which was used without further purification in the next step. LCMS: retention time: 3.162 min. LC data was recorded on a Shimadzu LC-10AS liquid chromatograph equipped with a Phenomenex-Luna 10u C18 4.6x50mm column using a SPD-10AV UV-Vis detector at a detector wave length of 220nM. The elution conditions employed a flow rate of 4 mL/min, a gradient of 100% solvent A / 0% solvent B to 0% solvent A / 100% solvent B, a gradient time of 4 min, a hold time of 1 min, and an analysis time of 5 min where solvent A was 5% CH_3CN / 95% H_2O / 10 mM ammonium acetate and solvent B was 5% H_2O / 95% CH_3CN / 10 mM ammonium

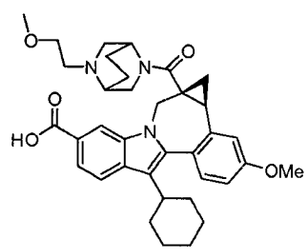
acetate. MS data was determined using a Micromass Platform for LC in electrospray mode. m/z 502(MH^+).



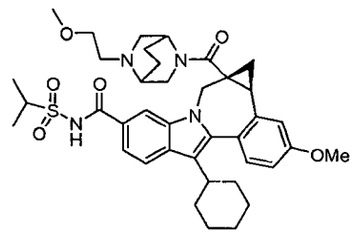
Tert-butyl (1aR,12bS)-8-cyclohexyl-1a-(2,5-diazabicyclo[2.2.2]oct-2-ylcarbonyl)-11-methoxy-1,1a,2,12b-tetrahydrocyclopropa[d]indolo[2,1-a][2]benzazepine-5-carboxylate. TBTU (691 mg, 2.15 mmol) was added in one portion to a cooled solution (0°C, ice bath) containing (1aR,12bS)-5-(tert-butoxycarbonyl)-8-cyclohexyl-11-methoxy-1,12b-dihydrocyclopropa[d]indolo[2,1-a][2]benzazepine-1a(2H)-carboxylic acid(900 mg, 1.79 mmol), DIEA (1.88 mL, 10.77 mmol), 2,5-diazabicyclo[2.2.2]octane (1:1) dihydrochloride ((498 mg, 2.69 mmol), (H. Newman, *J. Het. Chem.* 449 (1974); P.E. Thompson, J. B. Zeigler, J.W. McCall, *J. Med. Chem.*, 17, 481 (1974)), and dichloromethane (36 mL). The solution was maintained for 1.5 h and diluted with additional dichloromethane (20 mL). The solution was washed with water (3 x 20 mL), washed with brine (15 mL), dried (magnesium sulfate), filtered and concentrated to afford a white, tacky residue which was triturated with n-pentane (2 x 20 mL) to afford a white solid which was used without further purification in the next step. LCMS: retention time 3.841 min LC data was recorded on a Shimadzu LC-10AS liquid chromatograph equipped with a Phenomenex-Luna 10u C18 4.6x50mm column using a SPD-10AV UV-Vis detector at a detector wave length of 220nM. The elution conditions employed a flow rate of 4 mL/min, a gradient of 100% solvent A / 0% solvent B to 0% solvent A / 100% solvent B, a gradient time of 4 min, a hold time of 1 min, and an analysis time of 5 min where solvent A was 5% CH_3CN / 95% H_2O / 10 mM ammonium acetate and solvent B was 5% H_2O / 95% CH_3CN / 10 mM ammonium acetate. MS data was determined using a Micromass Platform for LC in electrospray mode. m/z 596(MH^+).



Tert-butyl (1aR,12bS)-8-cyclohexyl-11-methoxy-1a-((5-(2-methoxyethyl)-2,5-diazabicyclo[2.2.2]oct-2-yl)carbonyl)-1,1a,2,12b-tetrahydrocyclopropa[d]indolo[2,1-a][2]benzazepine-5-carboxylate. A suspension containing tert-butyl (1aR,12bS)-8-cyclohexyl-1a-(2,5-diazabicyclo[2.2.2]oct-2-ylcarbonyl)-11-methoxy-1,1a,2,12b-tetrahydrocyclopropa[d]indolo[2,1-a][2]benzazepine-5-carboxylate (400 mg, 0.671 mmol), 1-bromo-2-methoxyethane (373 mg, 2.69 mmol), potassium carbonate (978 mg, 6.71 mmol), and THF (7.0 mL) was stirred with rigor at 70°C for 20 hrs. The mixture was filtered and the filtrate concentrated to dryness. The resultant solid was triturated with n-pentane (2 x 5 mL) and used without further purification. LCMS: retention time 4.073 min. LC data was recorded on a Shimadzu LC-10AS liquid chromatograph equipped with a Phenomenex-Luna 10u C18 4.6x50mm column using a SPD-10AV UV-Vis detector at a detector wave length of 220nM. The elution conditions employed a flow rate of 4 mL/min, a gradient of 100% solvent A / 0% solvent B to 0% solvent A / 100% solvent B, a gradient time of 4 min, a hold time of 1 min, and an analysis time of 5 min where solvent A was 5% CH_3CN / 95% H_2O / 10 mM ammonium acetate and solvent B was 5% H_2O / 95% CH_3CN / 10 mM ammonium acetate. MS data was determined using a Micromass Platform for LC in electrospray mode. m/z 654 (MH^+).

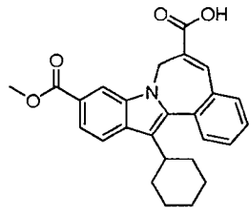


(1aR,12bS)-8-cyclohexyl-11-methoxy-1a-((5-methyl-2,5-diazabicyclo[2.2.2]oct-2-yl)carbonyl)-1,1a,2,12b-tetrahydrocyclopropa[d]indolo[2,1-a][2]benzazepine-5-carboxylic acid. TFA (8.4 mL) was added to a solution containing tert-butyl (1aR,12bS)-8-cyclohexyl-11-methoxy-1a-((5-methyl-2,5-diazabicyclo[2.2.2]oct-2-yl)carbonyl)-1,1a,2,12b-tetrahydrocyclopropa[d]indolo[2,1-a][2]benzazepine-5-carboxylate (550 mg, 0.841 mmol) and DCM (8.4 mL). The solution was maintained at rt for 3 h and then concentrated to dryness. The resultant residue was charged with 1:1 methanol/water (20 mL) and the pH increased to above 8 by slow addition of aqueous, saturated, sodium bicarbonate (10 mL). The solution was concentrated to remove methanol and extracted with dichloromethane (6 x 10mL). The combined organic portions were washed with brine (20 mL), dried (magnesium sulfate), filtered and concentrated to afford a light yellow solid which was used without further purification. LC/MS shows overlapping peaks at retention time 2.385 min. LC data was recorded on a Shimadzu LC-10AS liquid chromatograph equipped with a Phenomenex-Luna 10u C18 4.6x50mm column using a SPD-10AV UV-Vis detector at a detector wave length of 220nM. The elution conditions employed a flow rate of 4 mL/min, a gradient of 100% solvent A / 0% solvent B to 0% solvent A / 100% solvent B, a gradient time of 4 min, a hold time of 1 min, and an analysis time of 5 min where solvent A was 5% CH_3CN / 95% H_2O / 10 mM ammonium acetate and solvent B was 5% H_2O / 95% CH_3CN / 10 mM ammonium acetate. MS data was determined using a Micromass Platform for LC in electrospray mode.; m/z 598 (MH^+).



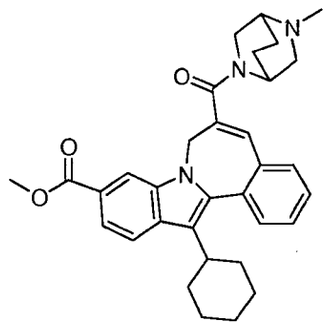
(1aR,12bS)-8-cyclohexyl-N-(isopropylsulfonyl)-11-methoxy-1a-((5-(2-methoxyethyl)-2,5-diazabicyclo[2.2.2]oct-2-yl)carbonyl)-1,1a,2,12b-tetrahydrocyclopropa[d]indolo[2,1-a][2]benzazepine-5-carboxamide. EDCI (178

mg, 928 mmol) was added at rt, in one portion, to a solution containing (1aR,12bS)-8-cyclohexyl-11-methoxy-1a-((5-(2-methoxyethyl)-2,5-diazabicyclo[2.2.2]oct-2-yl)carbonyl)-1,1a,2,12b-tetrahydrocyclopropa[d]indolo[2,1-a][2]benzazepine-5-carboxylic acid (378 mg, 0.619 mmol), DMAP (38 mg, 0.309 mmol), 2-isopropyl sulfonamide (191 mg, 1.547 mmol), and dichloromethane (7 mL). The solution was maintained at rt for 24 h, diluted with additional dichloromethane (20 mL), washed with aqueous, saturated sodium bicarbonate (2 x 20 mL), washed with water (20 mL), dried (magnesium sulfate), filtered and concentrated. The resultant light yellow residue was purified by preparative, reverse phase HPLC under basic conditions using a Phenomenex, luna, 10 micron, 30 x 100 mm column. Diastereomers were not seperable under these conditions. Product was a white solid. LC/MS shows separate diastereomers as overlapping peaks at retention times 2.288 min and 2.372 min. LC data was recorded on a Shimadzu LC-10AS liquid chromatograph equipped with a Phenomenex-Luna 10u C18 4.6x50mm column using a SPD-10AV UV-Vis detector at a detector wave length of 220nM. The elution conditions employed a flow rate of 4 mL/min, a gradient of 100% solvent A / 0% solvent B to 0% solvent A / 100% solvent B, a gradient time of 4 min, a hold time of 1 min, and an analysis time of 5 min where solvent A was 5% CH_3CN / 95% H_2O / 10 mM ammonium acetate and solvent B was 5% H_2O / 95% CH_3CN / 10 mM ammonium acetate. MS data was determined using a Micromass Platform for LC in electrospray mode m/z 703 (MH^+).



13-cyclohexyl-10-(methoxycarbonyl)-7H-indolo[2,1-a][2]benzazepine-6-carboxylic acid. Tetrabutylammoniumhydroxide (9.1 mL, 40% solution in water) was added dropwise to a cooled solution (0° C, ice bath) containing dimethyl 13-cyclohexyl-7H-indolo[2,1-a][2]benzazepine-6,10-dicarboxylate (Prepared as described in US Patent App. Publication US20070184024 A1, Intermediate 9) and THF (463 mL). The solution was maintained with continued cooling for 50 min. and then concentrated to a volume of about 50 mL. The resultant solution was diluted

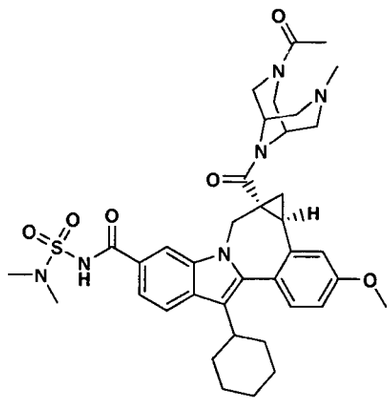
with ethyl acetate (250 mL), washed with aq. HCl (0.5 N, 3 x 150 mL), washed with brine (150 mL), dried (magnesium sulfate), filtered, and concentrated to afford a yellow solid. LCMS: retention time: 1.698 min. LC data was recorded on a Shimadzu LC-10AS liquid chromatograph equipped with a Phenomenex-Luna 10u C18 4.6x50mm column using a SPD-10AV UV-Vis detector at a detector wave length of 220nM. The elution conditions employed a flow rate of 4 mL/min, a gradient of 100% solvent A / 0% solvent B to 0% solvent A / 100% solvent B, a gradient time of 4 min, a hold time of 1 min, and an analysis time of 5 min where solvent A was 5% CH_3CN / 95% H_2O / 10 mM ammonium acetate and solvent B was 5% H_2O / 95% CH_3CN / 10 mM ammonium acetate. MS data was determined using a Micromass Platform for LC in electrospray mode: m/z 416(MH^+). ^1H NMR (300 MHz, DMSO-D6) δ ppm: 12.97 (s, 1 H), 8.17 (m, 1 H), 7.91(m, 2 H), 7.63 (m, 5 H), 5.56 (s, 1 H), 4.51(m, 1 H), 3.89 (m, 3 H), 2.80 (m, 1 H), 1.99 (m, 6 H), 1.30 (m, 4 H).



Prepared from the acid above via standard coupling between acid and diamine and then reductive methylation of diamine. Coupling of the N-monomethyldiamine could have been utilized. Standard cyclopropanation, esterhydrolysis, and coupling of the acid to an appropriate sulfamide or sulfonamide as detailed in the procedures and schemes would provide final compounds of the invention. The remaining steps could be carried out in the order described or the ester hydrolysis and coupling to the sulfonamide or sulfamide could be carried out prior to the cyclopropanation.
1H NMR (500 MHz, CD_3OD): δ ppm 0.92-2.69 (series of multiplets, 19 H), 2.90-3.19, (series of multiplets, 3 H), 3.41-3.85 (series of multiplets, 3 H), 3.96-3.98 (m, 2 H), (m, 1 H), 4.37 - 4.45 (m, 1 H), 5.19-5.28 (m, 1H), 6.98 (m, 0.7 H), 7.17 (m, 0.3 H), 6.98 - 7.07 (m, 1 H), 7.56 - 7.58 (m, 3 H), 7.64-7.65 (m, 1 H), 7.73 – 7.75 (m, 1

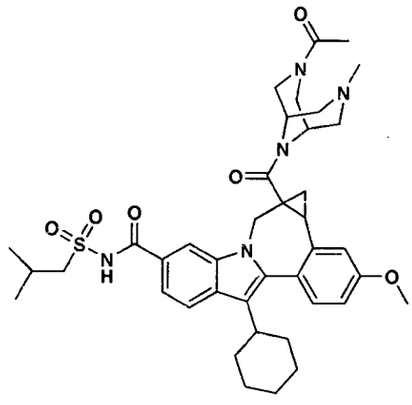
H), 7.92 - 7.94 (m, 1 H), 8.23 (m, 1 H). LCMS: retention time 4.008 min LC data was recorded on a Shimadzu LC-10AS liquid chromatograph equipped with a Phenomenex-Luna 10u C18 4.6x50mm column using a SPD-10AV UV-Vis detector at a detector wave length of 220nM. The elution conditions employed a flow rate of 4 mL/min, a gradient of 100% solvent A / 0% solvent B to 0% solvent A / 100% solvent B, a gradient time of 4 min, a hold time of 1 min, and an analysis time of 5 min where solvent A was 5% CH_3CN / 95% H_2O / 10 mM ammonium acetate and solvent B was 5% H_2O / 95% CH_3CN / 10 mM ammonium acetate. MS data was determined using a Micromass Platform for LC in electrospray mode. m/z 524(MH^+).

The following compounds were prepared using procedures analogous to those described above.



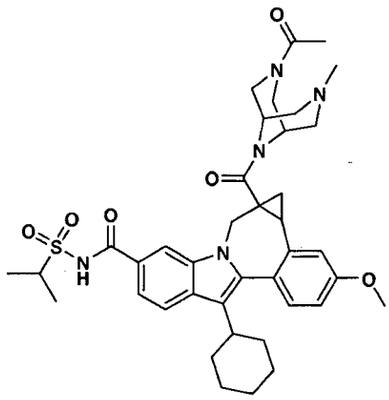
1a-((3-Acetyl-7-methyl-3,7,9-triazabicyclo[3.3.1]non-9-yl)carbonyl)-8-cyclohexyl-*N*-(dimethylsulfamoyl)-11-methoxy-1,1a,2,12b-tetrahydrocyclopropa[*d*]indolo[2,1-*a*] [2]benzazepine-5-carboxamide, (1aR, 12bS)-. ^1H NMR (500 MHz, CD3OD): δ ppm 0.21 (m, 0.25 H), 1.19 – 1.33 (m, 1 H), 1.43 (m, 3 H), 1.70 (m, 1.75 H), 1.80 (m, 2 H), 1.95 (m, 2 H), 2.25 (m, 5 H), 2.64 (m, 1 H), 2.83 (m, 2 H), 3.01 (m, 9 H), 3.16 (m, 1 H), 3.39 (m, 1 H), 3.44 (m, 1 H), 3.74 (m, 3 H), 3.91 (m, 4 H), 4.19 (m, 0.25 H), 5.54 (m, 2 H), 5.00 (m, 1.75 H), 7.03 (m, 1 H), 7.18 (m, 1 H), 7.28 (d, J = 8.55, 0.75 H), 7.34 (d, J = 8.55, 0.25 H), 7.53 (m, 0.75 H), 7.60 (m, 0.25 H), 7.86 (d, J = 8.24, 0.75 H), 7.91 (d, J = 8.24, 0.25 H), 8.05 (m, 1 H). LC/MS: m/z 717.43, Rf 1.705 min., 97.7 % purity. LC data was recorded on a Shimadzu LC-10AS liquid chromatograph equipped with a Phenomenex-Luna

10μ, C18, 4.6 x 30mm column, using a SPD-10AV UV-Vis detector at a detector wave length of 220nM. The elution conditions employed a flow rate of 5 ml/min., a gradient of 100% solvent A / 0% solvent B to 0% solvent A / 100% solvent B, a gradient time of 2 min., a hold time of 1 min., and an analysis time of 3 min. where solvent A was 10% MeOH / 90% H2O / 0.1% trifluoroacetic acid and solvent B was 10% H2O / 90% MeOH / 0.1% trifluoroacetic acid. MS data was determined using a Micromass Platform for LC in electrospray mode.



1a-((3-Acetyl-7-methyl-3,7,9-triazabicyclo[3.3.1]non-9-yl)carbonyl)-8-cyclohexyl -N-(isobutylsulfonyl)-11-methoxy-1,1a,2,12b-tetrahydrocyclopropa[d]indolo[2,1-a][2] benzazepine-5-carboxamide. 1H NMR (300 MHz, CD3OD): δ ppm 0.20 (m, 0.25 H), 1.14 (m, 6 H), 1.36 (m, 4 H), 1.64 (m, 1 H), 1.78 (m, 2.75 H), 1.99 (m, 4 H), 2.29 (m, 4 H), 2.63 (m, 2 H), 2.84 (m, 4 H), 2.97 (m, 3 H), 3.18 (m, 1 H), 3.47 (m, 2 H), 3.66 (m, 2 H), 3.88 (m, 4 H), 4.19 (m, 1 H), 4.50 (m, 2 H), 5.05 (m, 1 H), 7.01 (m, 1 H), 7.17 (m, 1 H), 7.29 (m, 1 H), 7.51 – 7.61 (m, 1 H), 7.88 (m, 1 H), 7.96 - 8.06 (m, 1 H). LC/MS: m/z 730.30, Rf 1.787 min., 96.0 % purity. LC data was recorded on a Shimadzu LC-10AS liquid chromatograph equipped with a Phenomenex-Luna 10μ, C18, 4.6 x 30mm column, using a SPD-10AV UV-Vis detector at a detector wave length of 220nM. The elution conditions employed a flow rate of 5 ml/min., a gradient of 100% solvent A / 0% solvent B to 0% solvent A / 100% solvent B, a gradient time of 2 min., a hold time of 1 min., and an analysis time of 3 min. where solvent A was 10% MeOH / 90% H2O / 0.1% trifluoroacetic acid and solvent B was 10% H2O / 90% MeOH /

0.1% trifluoroacetic acid. MS data was determined using a Micromass Platform for LC in electrospray mode.

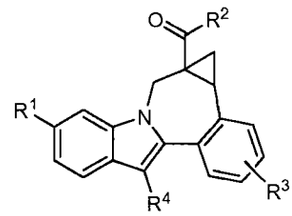


1a-((3-Acetyl-7-methyl-3,7,9-triazabicyclo[3.3.1]non-9-yl)carbonyl)-8-cyclohexyl -N-(isopropylsulfonyl)-11-methoxy-1,1a,2,12b-tetrahydrocyclopropa[d]indolo[2,1-a][2] benzazepine-5-carboxamide. 1H NMR (300 MHz, CD3OD): δ ppm 0.20 (m, 0.25 H), 0.98 (m, 2 H), 1.13 (m, 1 H), 1.24 - 1.49 (m, 9 H), 1.65 (m, 0.75 H), 1.83 (m, 2 H), 2.04 (m, 4 H), 2.50 (m, 4 H), 2.67 (m, 1 H), 2.83 (m, 1 H), 2.88 (m, 3 H), 3.01 (m, 3 H), 3.10 (m, 1 H), 3.17 (m, 2 H), 3.72 (m, 2 H), 3.92 (m, 3 H), 3.98 (m, 1 H), 4.50 (m, 1 H), 5.03 (m, 1 H), 7.06 (m, 1 H), 7.21 (m, 1 H), 7.35 (m, 1 H), 7.57 – 7.70 (m, 1 H), 7.92 (m, 1 H), 8.00 - 8.09 (m, 1 H). LC/MS: m/z 716.23, Rf 1.740 min., 98.0 % purity. LC data was recorded on a Shimadzu LC-10AS liquid chromatograph equipped with a Phenomenex-Luna 10μ, C18, 4.6 x 30mm column, using a SPD-10AV UV-Vis detector at a detector wave length of 220nM. The elution conditions employed a flow rate of 5 ml/min., a gradient of 100% solvent A / 0% solvent B to 0% solvent A / 100% solvent B, a gradient time of 2 min., a hold time of 1 min., and an analysis time of 3 min. where solvent A was 10% MeOH / 90% H2O / 0.1% trifluoroacetic acid and solvent B was 10% H2O / 90% MeOH / 0.1% trifluoroacetic acid. MS data was determined using a Micromass Platform for LC in electrospray mode.

CLAIMS

We claim:

1. A compound of formula I

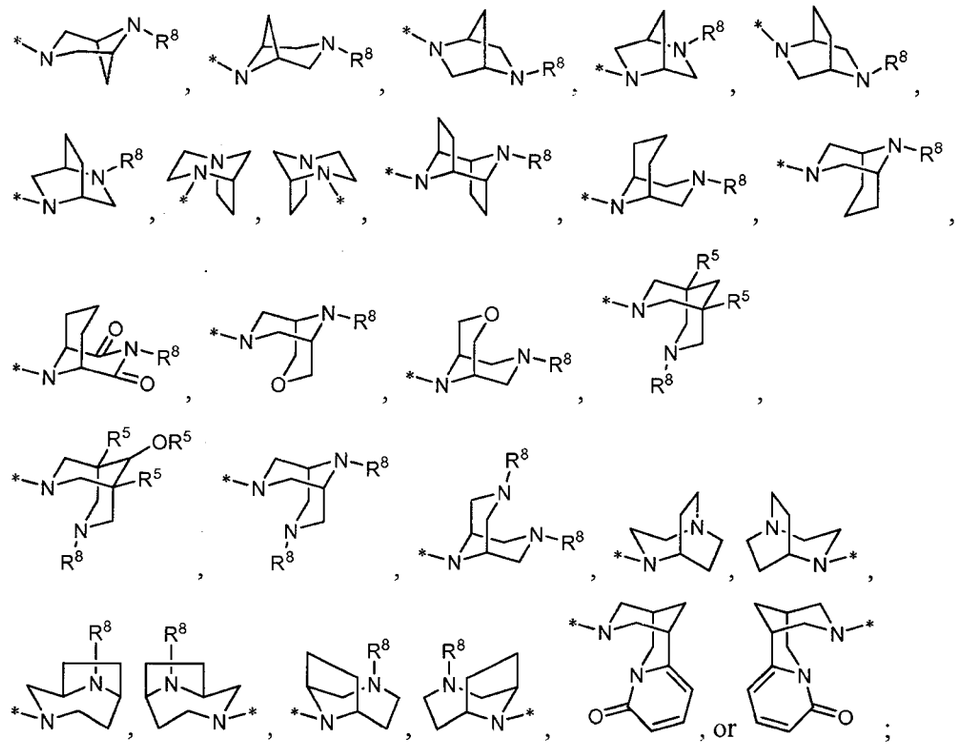


I

where:

R^1 is CO_2R^5 or $CONR^6R^7$;

R^2 is



R^3 is hydrogen, halo, alkyl, alkenyl, hydroxy, benzyloxy, or alkoxy;

R^4 is cycloalkyl;

R^5 is hydrogen or alkyl;

R^6 is hydrogen, alkyl, alkylSO_2, alkenylSO_2, , cycloalkylSO_2, (cycloalkyl)alkylSO_2, haloalkylSO_2, (R^9)(R^{10})NSO_2, or (R^{11})SO_2;

R^7 is hydrogen or alkyl;

R^8 is hydrogen, alkyl, cycloalkyl, (cycloalkyl)alkyl, hydroxyalkyl, alkoxyalkyl, alkylcarbonyl, cycloalkylcarbonyl, haloalkylcarbonyl, alkoxycarbonyl, alkylSO_2, cycloalkylSO_2, haloalkylSO_2, aminocarbonyl, (alkylamino)carbonyl, (dialkylamino)carbonyl, benzyl, benzyloxycarbonyl, or pyridinyl;

R^9 is hydrogen or alkyl;

R^{10} is hydrogen or alkyl;

R^{11} is azetidinyl, pyrrolidinyl, piperidinyl, N-(R^{12})piperazinyl, morpholinyl, thiomorpholinyl, homopiperidinyl, homomorpholinyl, tetrahydrofuranyl, tetrahydropyranyl, (tetrahydrofuranyl)alkyl, or (tetrahydropyranyl)alkyl; and

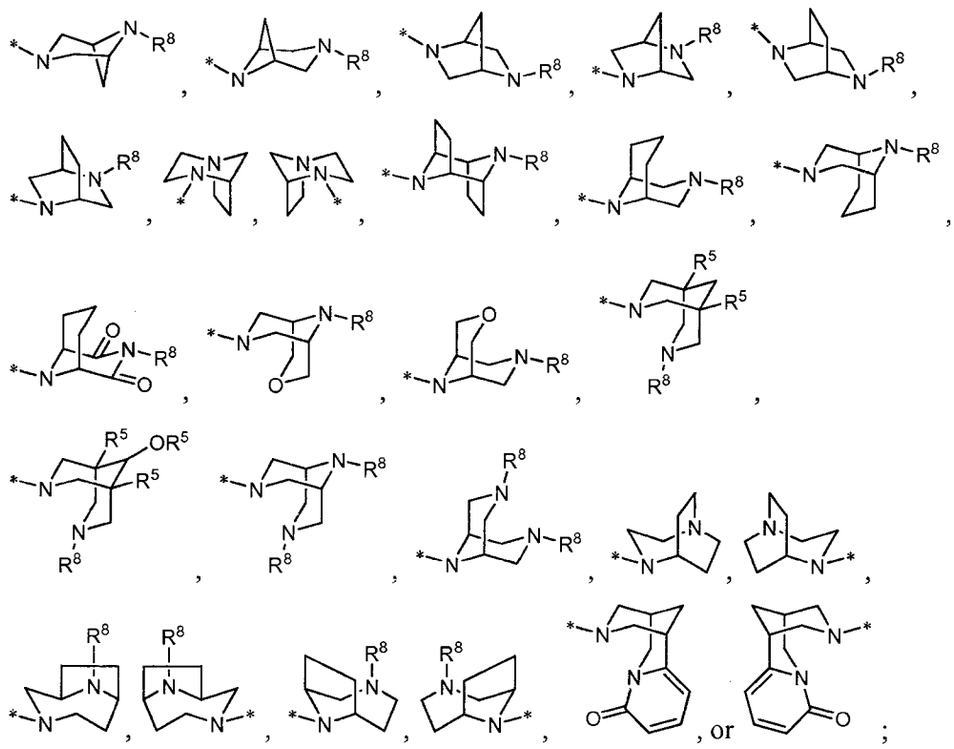
R^{12} is hydrogen or alkyl;

or a pharmaceutically acceptable salt thereof.

2. A compound of claim 1 where

R^1 is CO_2R^5 or $CONR^6R^7$;

R^2 is



; or

R^3 is hydrogen, halo, alkyl, alkenyl, hydroxy, benzyloxy, or alkoxy;

R^4 is cycloalkyl;

R^5 is hydrogen or alkyl;

R^6 is hydrogen, alkyl, alkylSO_2, alkenylSO_2, , cycloalkylSO_2, (cycloalkyl)alkylSO_2, haloalkylSO_2, (R^9)(R^{10})NSO_2, or (R^{11})SO_2;

R^7 is hydrogen or alkyl;

R^8 is hydrogen, alkyl, cycloalkyl, (cycloalkyl)alkyl, alkylcarbonyl, cycloalkylcarbonyl, haloalkylcarbonyl, alkoxycarbonyl, alkylSO_2, cycloalkylSO_2, haloalkylSO_2, aminocarbonyl, (alkylamino)carbonyl, (dialkylamino)carbonyl, benzyl, benzyloxycarbonyl, or pyridinyl;

R^9 is hydrogen or alkyl;

R^{10} is hydrogen or alkyl;

R^{11} is azetidinyl, pyrrolidinyl, piperidinyl, N-(R^{12})piperazinyl, morpholinyl, thiomorpholinyl, homopiperidinyl, homomorpholinyl, tetrahydrofuranyl, tetrahydropyranyl, (tetrahydrofuranyl)alkyl, or (tetrahydropyranyl)alkyl; and

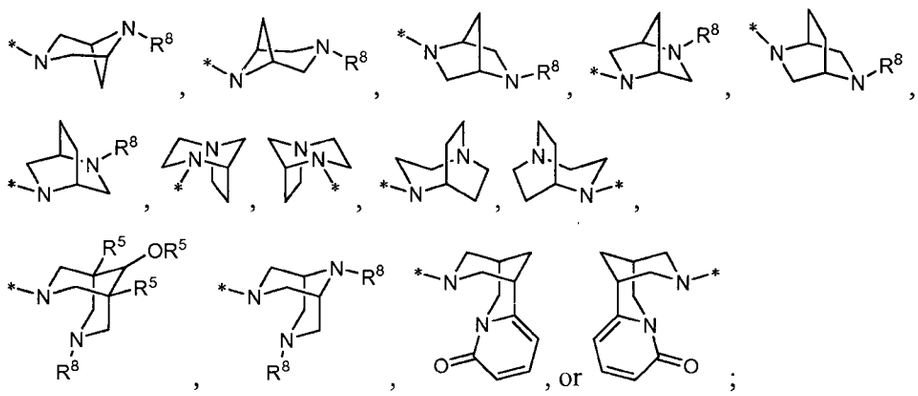
R^{12} is hydrogen or alkyl;

or a pharmaceutically acceptable salt thereof.

3. A compound of claim 1 where

R^1 is CO_2R^5 or $CONR^6R^7$;

R^2 is



;

R^3 is hydrogen, halo, alkyl, alkenyl, hydroxy, benzyloxy, or alkoxy;

R^4 is cycloalkyl;

R^5 is hydrogen or alkyl;

R^6 is hydrogen, alkyl, alkylSO_2, cycloalkylSO_2, haloalkylSO_2, (R^9)(R^{10})NSO_2, or (R^{11})SO_2;

R^7 is hydrogen or alkyl;

R^8 is hydrogen, alkyl, cycloalkyl, (cycloalkyl)alkyl, alkylcarbonyl, cycloalkylcarbonyl, haloalkylcarbonyl, alkoxycarbonyl, alkylSO_2, cycloalkylSO_2, haloalkylSO_2, aminocarbonyl, (alkylamino)carbonyl, (dialkylamino)carbonyl, benzyl, benzyloxycarbonyl, or pyridinyl;

R^9 is hydrogen or alkyl;

R^{10} is hydrogen or alkyl;

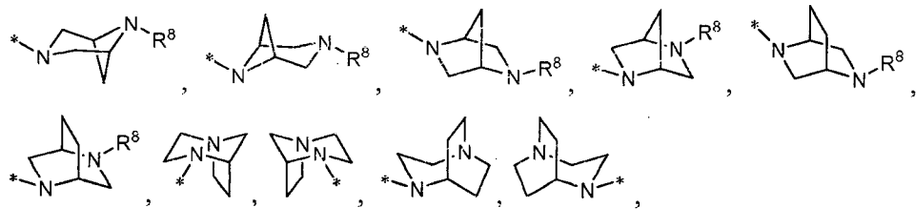
R^{11} is azetidinyl, pyrrolidinyl, piperidinyl, N-(R^{12})piperazinyl, morpholinyl, thiomorpholinyl, homopiperidinyl, or homomorpholinyl; and

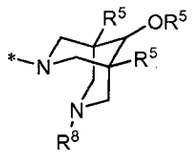
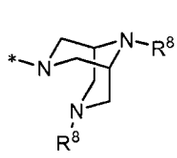
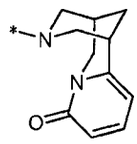
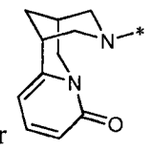
R^{12} is hydrogen or alkyl;

or a pharmaceutically acceptable salt thereof.

4. A compound of claim 1 where R^1 is $CONR^6R^7$; R^6 is alkylSO_2, cycloalkylSO_2, haloalkylSO_2, (R^9)$_2NSO_2$, or (R^{10})SO_2; and R^7 is hydrogen.

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




, 
, 
, or 
; and

R^{11} is azetidinyl, pyrrolidinyl, piperidinyl, N-(R^{12})piperazinyl, morpholinyl, thiomorpholinyl, homopiperidinyl, or homomorpholinyl.

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

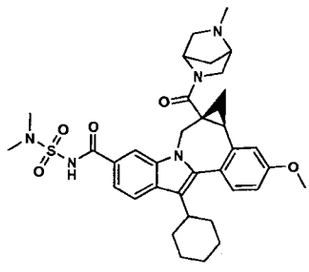
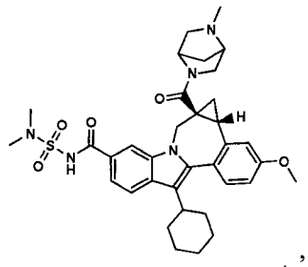
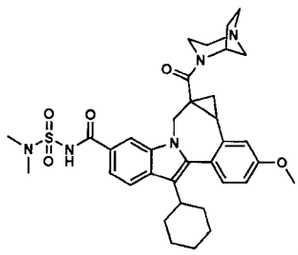
7. A compound of claim 1 where R^3 is methoxy.

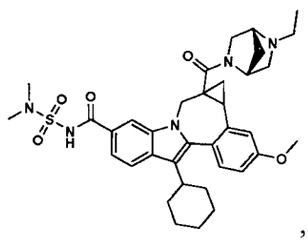
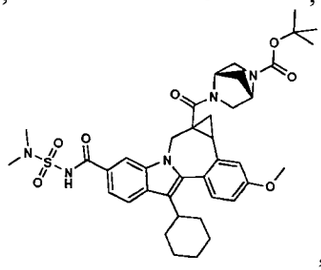
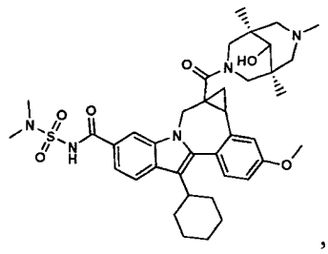
8. A compound of claim 1 where R^4 is cyclohexyl.

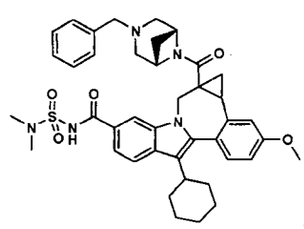
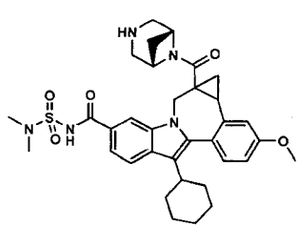
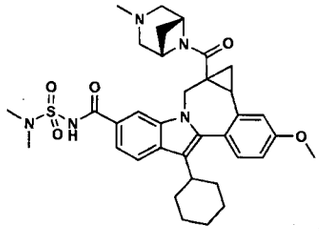
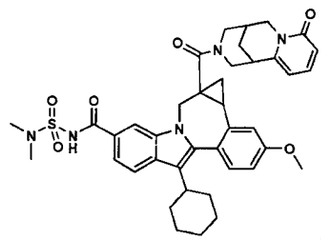
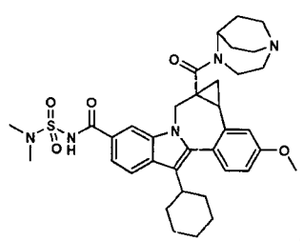
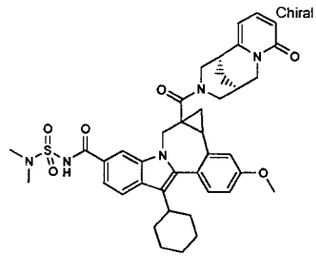
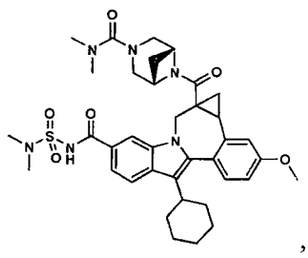
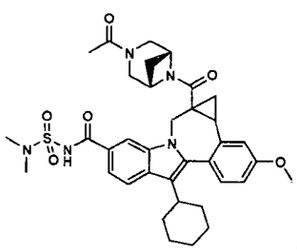
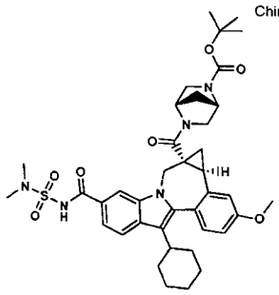
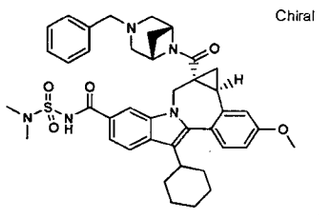
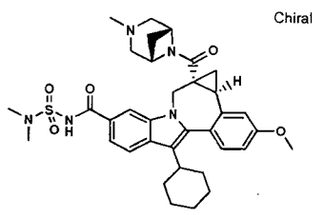
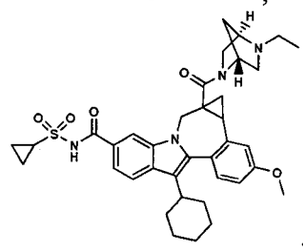
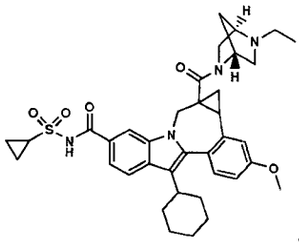
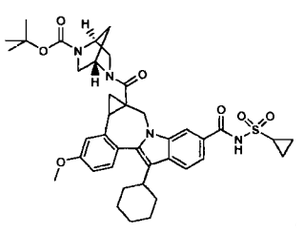
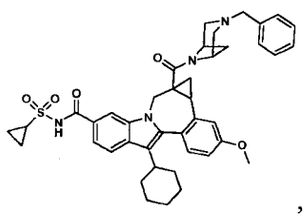
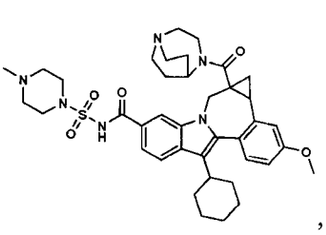
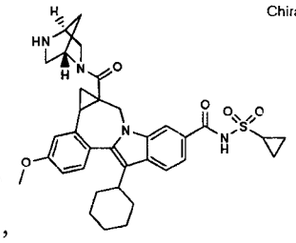
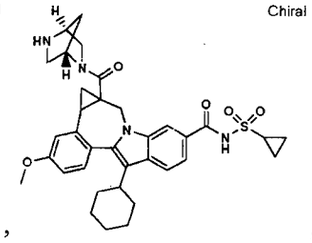
9. A compound of claim 1 where R^6 is (R^9)(R^{10})NSO_2 or (R^{11})SO_2.

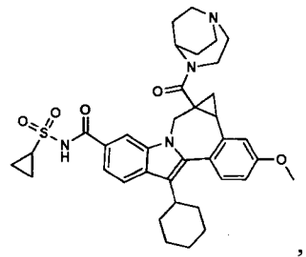
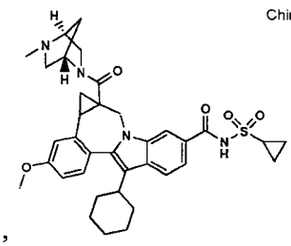
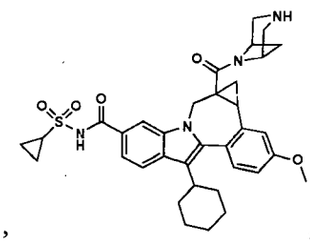
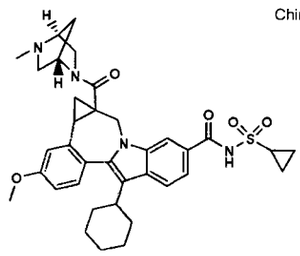
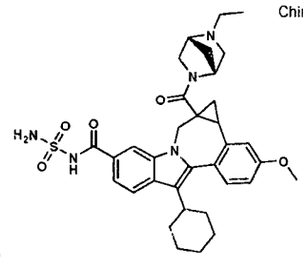
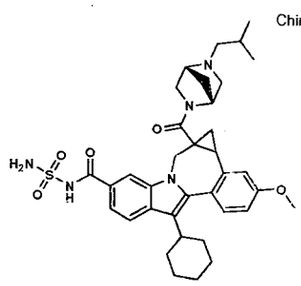
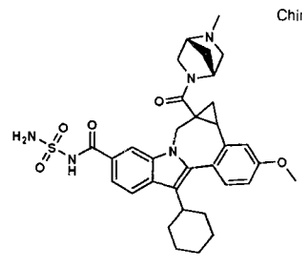
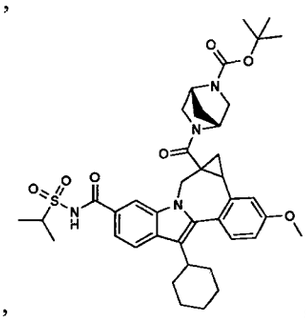
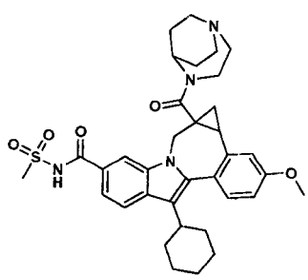
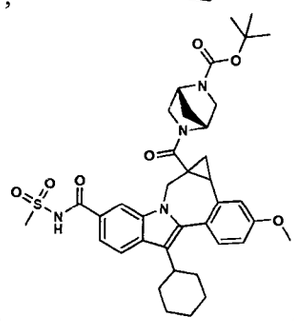
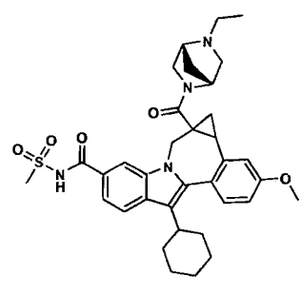
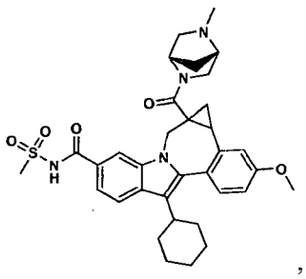
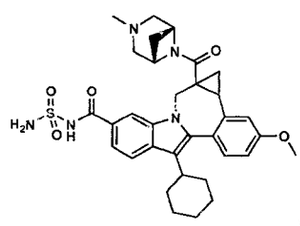
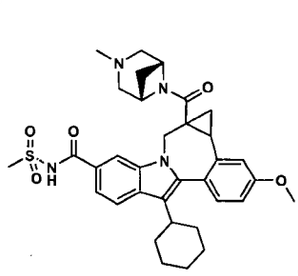
10. A compound of claim 1 where R^8 is alkyl or alkoxyalkyl.

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


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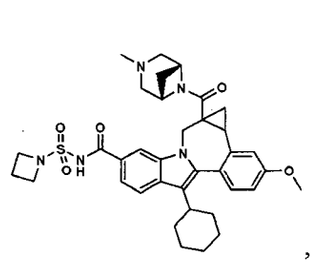
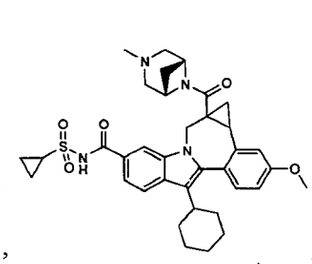
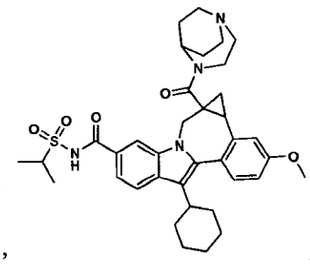
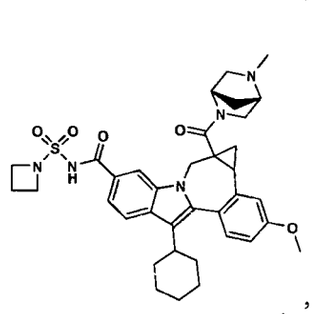
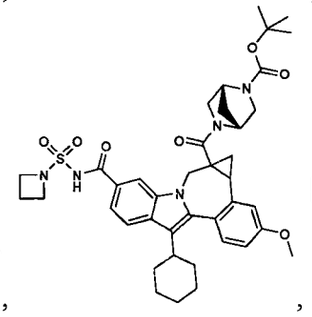
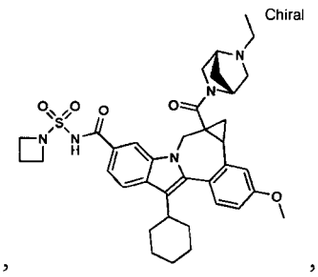
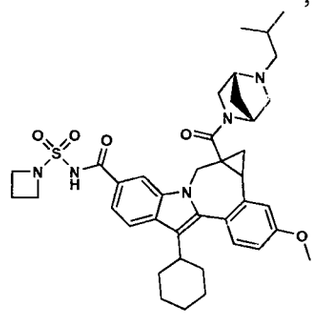
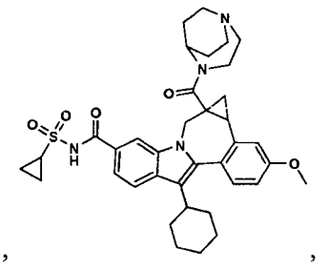
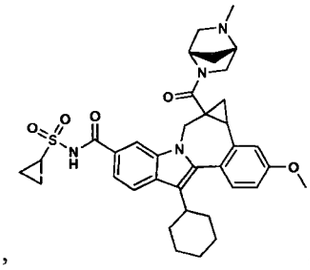
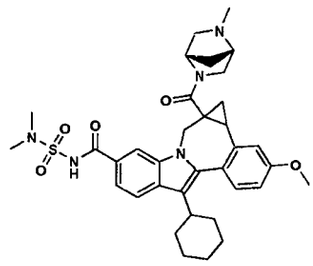
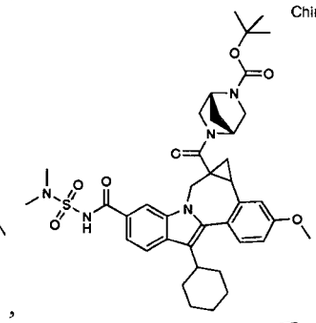
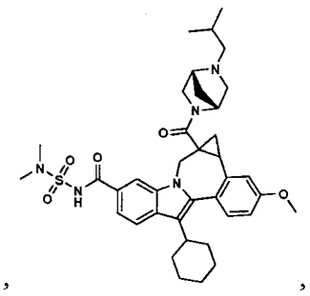
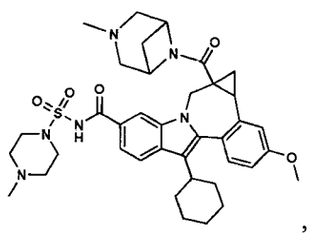
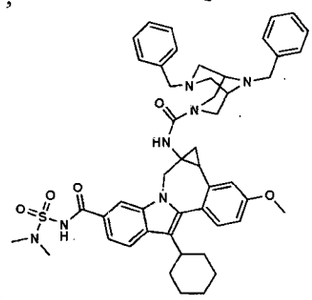
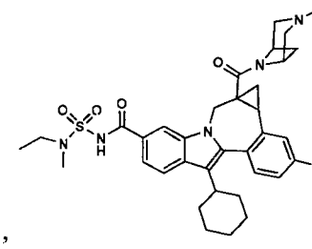

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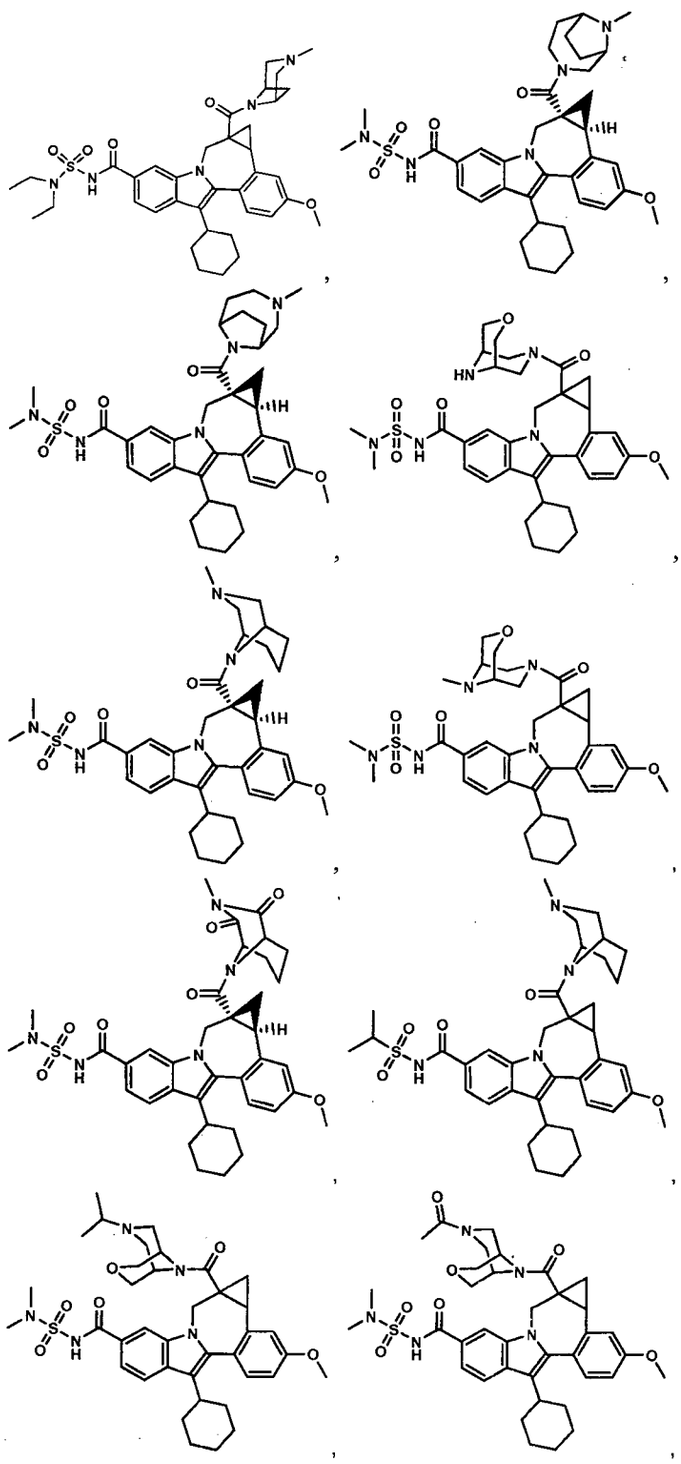

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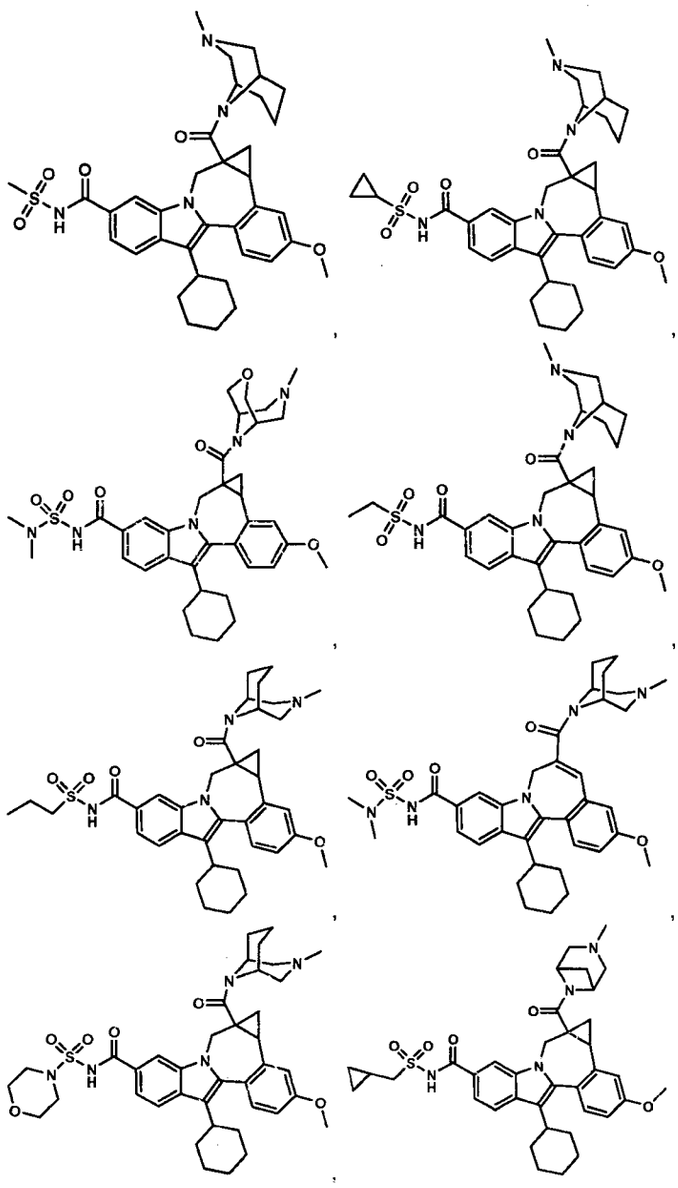
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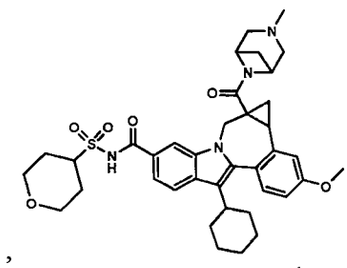
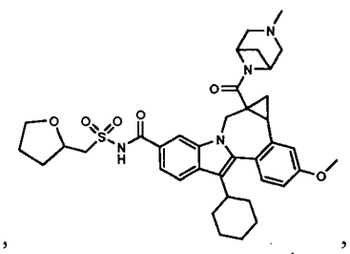
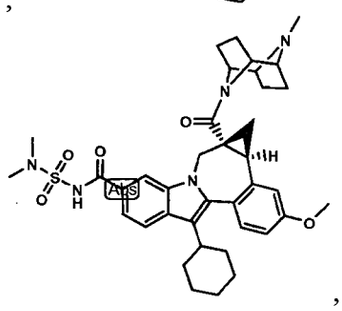
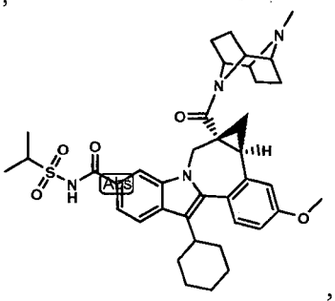
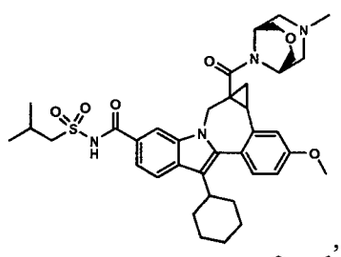
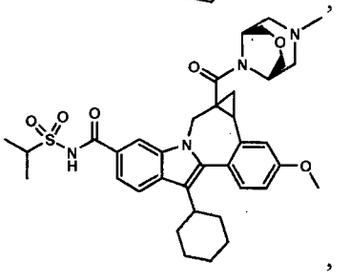
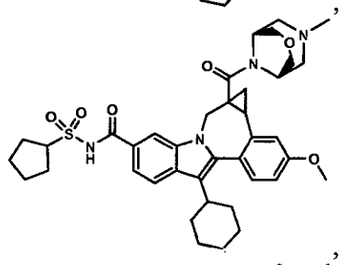
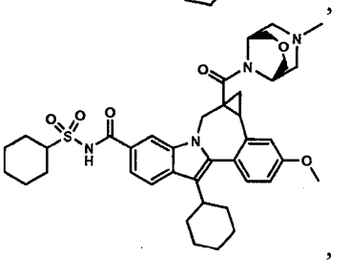
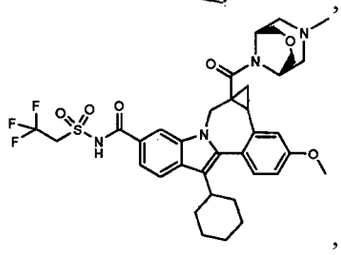
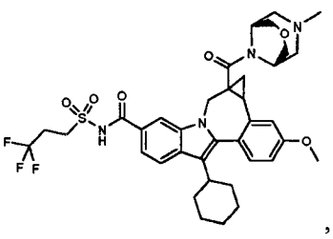
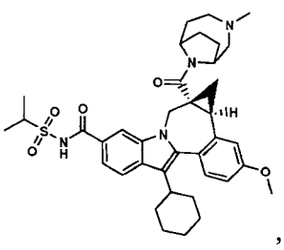
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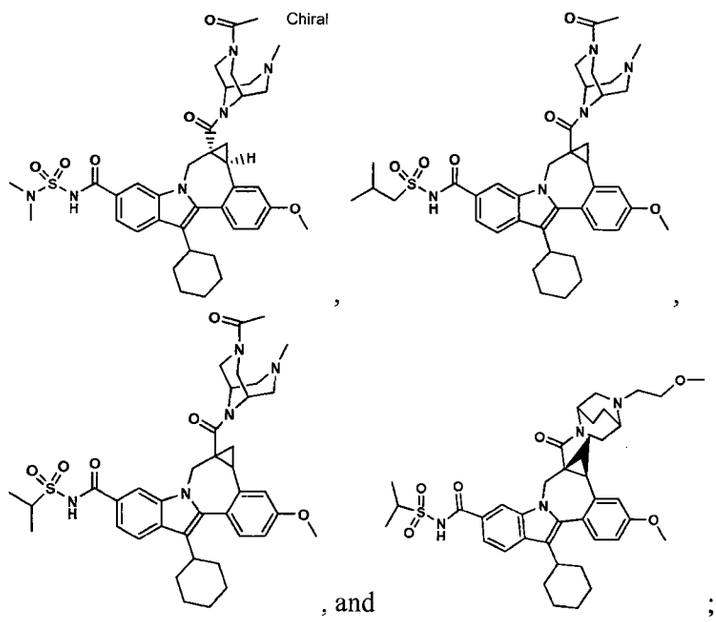
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or a pharmaceutically acceptable salt thereof.

12. A composition comprising a compound of claim 1, or a pharmaceutically acceptable salt thereof, and a pharmaceutically acceptable carrier.

13. The composition of claim 12 further comprising at least one additional compound having therapeutic benefits for HCV wherein the compound is selected from the group consisting of interferons, cyclosporins, interleukins, HCV metalloprotease inhibitors, HCV serine protease inhibitors, HCV polymerase inhibitors, HCV helicase inhibitors, HCV NS4B protein inhibitors, HCV entry inhibitors, HCV assembly inhibitors, HCV egress inhibitors, HCV NS5A protein inhibitors, HCV NS5B protein inhibitors, and HCV replicon inhibitors.

14. A method of treating hepatitis C infection comprising administering a therapeutically effective amount of a compound of claim 1 to a patient.

15. The method of claim 14 further comprising administering at least one additional compound having therapeutic benefits for HCV wherein the compound is selected from the group consisting of interferons, cyclosporins, interleukins, HCV

metalloprotease inhibitors, HCV serine protease inhibitors, HCV polymerase inhibitors, HCV helicase inhibitors, HCV NS4B protein inhibitors, HCV entry inhibitors, HCV assembly inhibitors, HCV egress inhibitors, HCV NS5A protein inhibitors, HCV NS5B protein inhibitors, and HCV replicon inhibitors.

000213

Título

COMPUESTOS PARA EL TRATAMIENTO DE HEPATITIS C

Traducción del inglés al español de la descripción y documentos PCT/US2008/055893

000214

COMPUESTOS PARA EL TRATAMIENTO DE HEPATITIS C

Campo de la Invención

El virus de la hepatitis C (VHC) es un patógeno humano principal, que infecta un estimado de 170 millones de personas en el mundo - aproximadamente cinco veces el número de infectados por el virus de inmunodeficiencia humana tipo 1. Una fracción substancial de estos individuos infectados con VHC desarrolla enfermedad hepática progresiva seria, incluyendo cirrosis y carcinoma hepatocelular (Lauer, G. M.; Walker, B. D. N. Engl. J. Med. 2001, 345, 41-52).

Antecedentes de la Invención

El VHC es un virus del ARN de hebra positiva. Con base en una comparación de la secuencia de aminoácidos deducida y la similitud extensiva en la región no traducida 5', el VHC se ha clasificado como un género separado en la familia de Flaviviridae. Todos los miembros de la familia Flaviviridae han encapsulado virus que contienen un genoma del ARN de hebra positiva que codifica todas las proteínas específicas del virus conocidas por medio de la traducción de una estructura de lectura abierta, no interrumpida, sencilla.

Se encuentra una heterogeneidad considerable dentro de las secuencias de nucleótidos y aminoácidos codificadas a lo largo del genoma del VHC. Al menos seis genotipos principales se han caracterizado, y más de 50 subtipos se han descrito.

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Los genotipos principales del VHC difieren en su distribución a nivel mundial, y la importancia clínica de la heterogeneidad genética del VHC permanece elusiva a pesar de los numerosos estudios del efecto posible de genotipos en patogénesis y terapia.

El genoma de ARN del VHC de hebra sencilla es de aproximadamente 9500 nucleótidos de longitud y tiene una estructura de lectura abierta sencilla (ORF, por sus siglas en inglés) que codifica una poliproteína grande sencilla de alrededor de 3000 aminoácidos. En células infectadas, esta poliproteína se desdobla en sitios múltiples por proteasas celulares y víricas para producir las proteínas estructurales y no estructurales (NS, por sus siglas en inglés). En el caso del VHC, la generación de proteínas no estructurales maduras (NS2, NS3, NS4A, NS4B, NS5A, y NS5B) se efectúa por dos proteasas víricas. La primera se considera que es una metaloproteasa y se desdobla en la unión NS2-NS3; la segunda es una serina proteasa que está contenida dentro de la región terminal N de NS3 (también referida como proteasa NS3) y que media todos los desdoblamientos posteriores cadena abajo de NS3, tanto en cis, en el sitio del desdoblamiento NS3-NS4A, como en trans, para los sitios restantes NS4A-NS4B, NS4B-NS5A, NS5A-NS5B. La proteína NS4A aparece para servir funciones múltiples, actuando como un cofactor para la proteasa NS3 y posiblemente ayudar en la localización de la membrana de NS3 y

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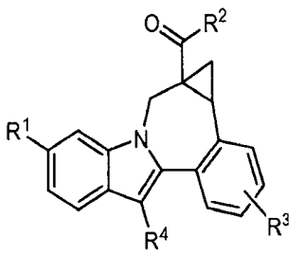
otros componentes de replicasa víricos. La formación del complejo de la proteína NS3 con NS4A necesariamente se aprecia para los eventos de procesamiento, aumentando la eficiencia proteolítica en todos los sitios. La proteína NS3 también muestra trifosfatasa de nucleósido y actividades de helicasa del ARN. El NS5B (también referido como polimerasa del VHC) es una polimerasa del ARN dependiente del ARN que está involucrada en la replicación del VHC. La proteína NS5B del VHC se describe en "Structural Analysis of the Hepatitis C Virus RNA Polymerase in Complex with Ribonucleotides (Bressanelli; S. et al., *Journal of Virology* 2002, 3482-3492; y Defrancesco and Rice, *Clinics in Liver Disease* 2003, 7, 211-242.

Actualmente, la terapia del VHC más efectiva emplea una combinación de interferón alfa y ribavirina, llevando a la eficacia sostenida en 40% de los pacientes (Poynard, T. et al. *Lancet* 1998, 352, 1426-1432). Los resultados clínicos recientes demuestran que el interferón alfa pegilado es superior al interferón alfa no modificado como monoterapia (Zeuzem, S. et al. N. Engl. J. Med. 2000, 343, 1666-1672). Sin embargo, aún con regímenes terapéuticos experimentales que involucran combinaciones de interferón alfa pegilado y ribavirina, una fracción substancial de pacientes no tiene una reducción sostenida en la carga vírica. De esta manera, existe una necesidad clara e importante para desarrollar terapéuticos

efectivos para el tratamiento de la infección por VHC.

Breve Descripcion de la Invencion

Un aspecto de la invención es un compuesto de la fórmula I

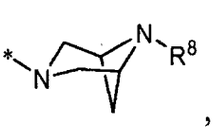
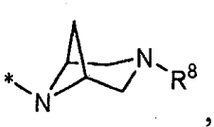
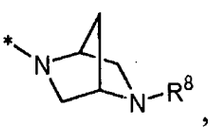
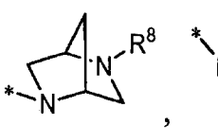
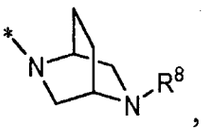
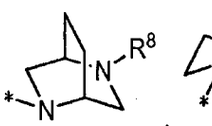
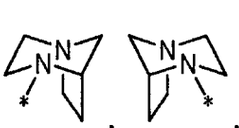
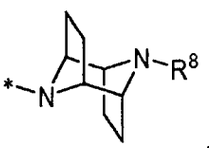
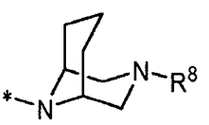
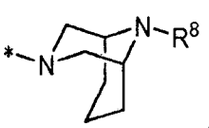
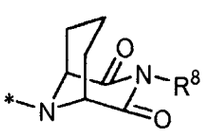
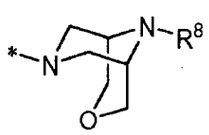
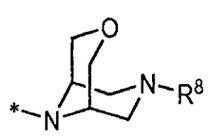
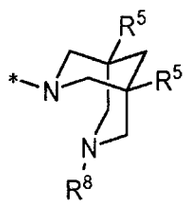
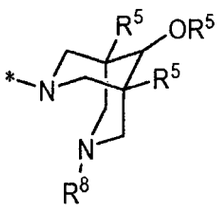
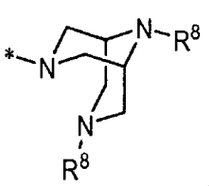
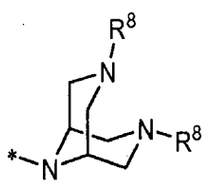
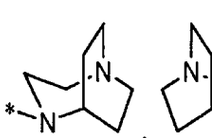
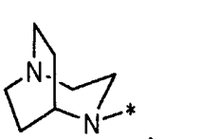
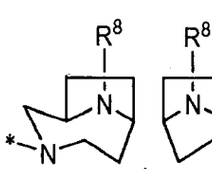
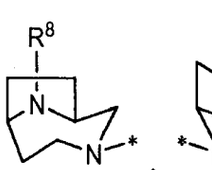
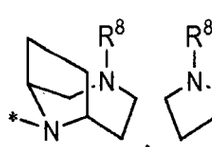
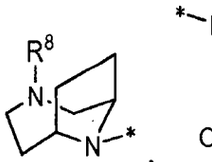
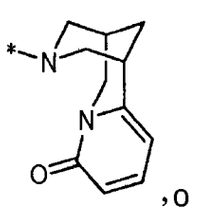
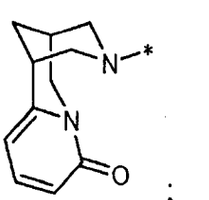


I

donde:

R^1 es CO_2R^5 o $CONR^6R^7$;

R^2 es

;

000218

R^3 es hidrógeno, halo, alquilo, alquenilo, hidroxi, benciloxi, o alcoxi;

R^4 es cicloalquilo;

R^5 es hidrógeno o alquilo;

R^6 es hidrógeno, alquilo, alquiloSO_2, alqueniloSO_2, cicloalquiloSO_2, (cicloalquilo)alquiloSO_2, haloalquiloSO_2, $(R^9)(R^{10})NSO_2$, o $(R^{11})SO_2$;

R^7 es hidrógeno o alquilo;

R^8 es hidrógeno, alquilo, cicloalquilo, (cicloalquilo)alquilo, hidroxialquilo, alcoxialquilo, alquilcarbonilo, cicloalquilcarbonilo, haloalquilcarbonilo, alcoxicarbonilo, alquiloSO_2, cicloalquiloSO_2, haloalquiloSO_2, aminocarbonilo, (alquilamino)carbonilo, (dialquilamino)carbonilo, bencilo, benciloxicarbonilo, o piridinilo;

R^9 es hidrógeno o alquilo;

R^{10} es hidrógeno o alquilo;

R^{11} es azetidinilo, pirrolidinilo, piperidinilo, N-(R^{12})piperazinilo, morfolinilo, tiomorfolinilo, homopiperidinilo, homomorfolinilo, tetrahidrofuranilo, tetrahidropiranilo, (tetrahidrofuranil)alquilo, o (tetrahidropiranil)alquilo; y

R^{12} es hidrógeno o alquilo;

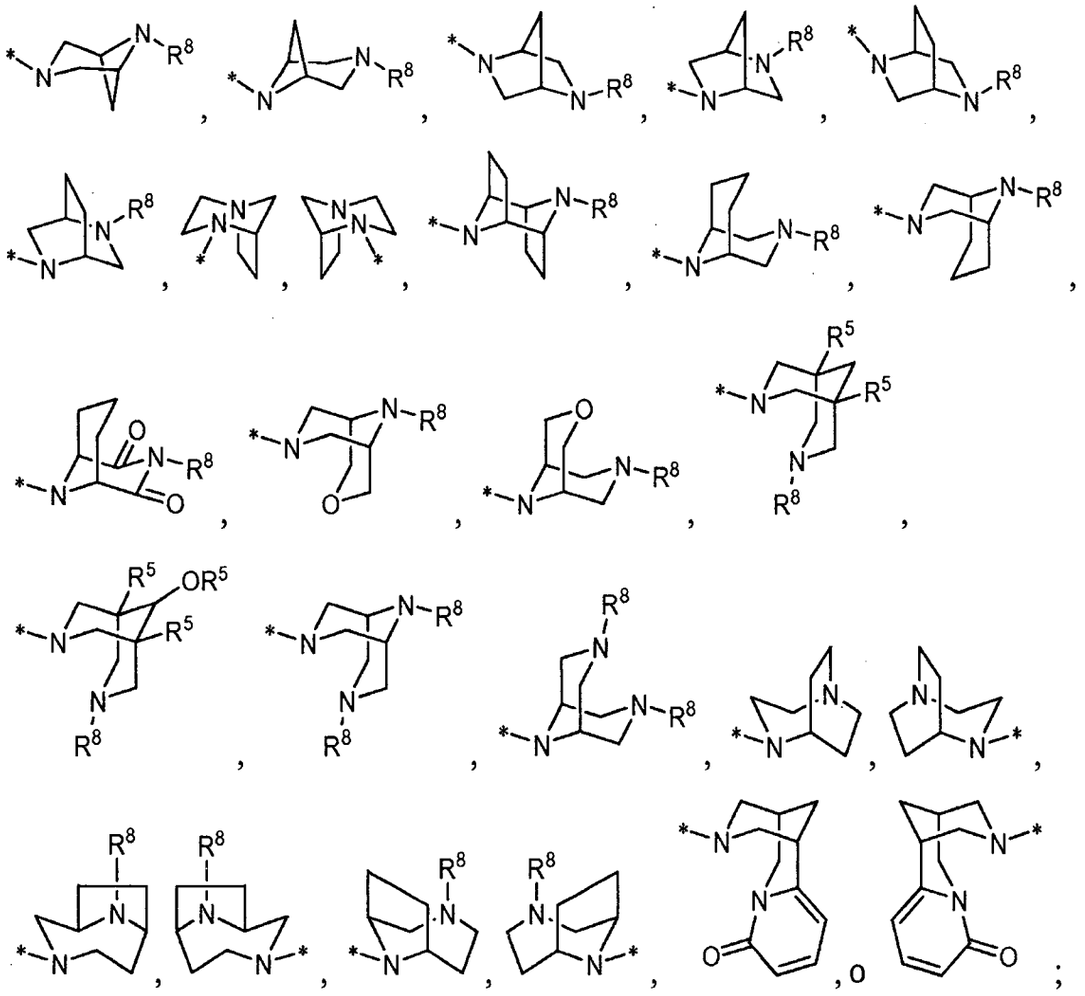
o una sal farmacéuticamente aceptable del mismo.

Otro aspecto de la invención es un compuesto de la

fórmula I donde

R^1 es CO_2R^5 o $CONR^6R^7$;

R^2 es



R^3 es hidrógeno, halo, alquilo, alquenilo, hidroxi, benciloxi, o alcoxi;

R^4 es cicloalquilo;

R^5 es hidrógeno o alquilo;

R^6 es hidrógeno, alquilo, alquiloSO_2, alqueniloSO_2, cicloalquiloSO_2, (cicloalquilo)alquiloSO_2, haloalquiloSO_2, $(R^9)(R^{10})NSO_2$, o $(R^{11})SO_2$;

R^7 es hidrógeno o alquilo;

R^8 es hidrógeno, alquilo, cicloalquilo, (cicloalquilo)alquilo, alquilcarbonilo, cicloalquilcarbonilo, haloalquilcarbonilo, alcoxicarbonilo, alquiloSO_2, cicloalquiloSO_2, haloalquiloSO_2, aminocarbonilo, (alquilamino)carbonilo, (dialquilamino)carbonilo, bencilo, benciloxicarbonilo, o piridinilo;

R^9 es hidrógeno o alquilo;

R^{10} es hidrógeno o alquilo;

R^{11} es azetidinilo, pirrolidinilo, piperidinilo, N-(R^{12})piperazinilo, morfolinilo, tiomorfolinilo, homopiperidinilo, homomorfolinilo, tetrahidrofuranilo, tetrahidropiranilo, (tetrahidrofuranil)alquilo, o (tetrahidropiranil)alquilo; y

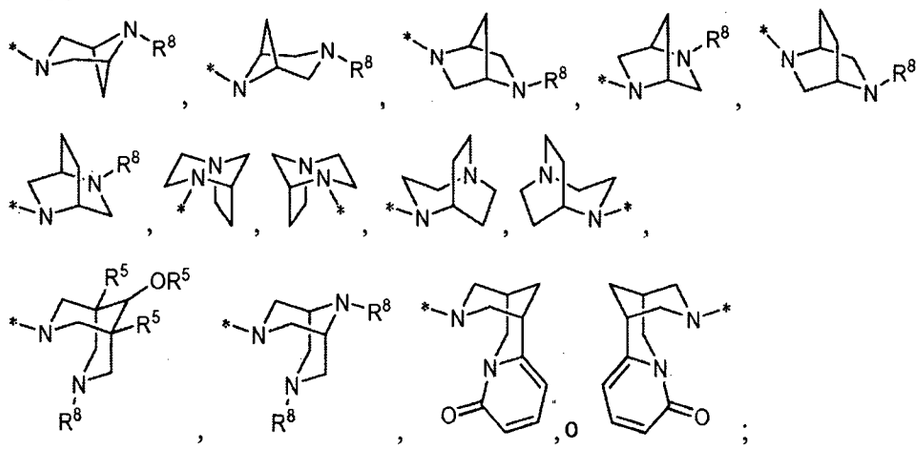
R^{12} es hidrógeno o alquilo;

o una sal farmacéuticamente aceptable del mismo.

Otro aspecto de la invención es un compuesto de la fórmula I donde

R^1 es CO_2R^5 o $CONR^6R^7$;

R^2 es



;

R^3 es hidrógeno, halo, alquilo, alquenilo, hidroxi,

benciloxi, o alcoxi;

R^4 es cicloalquilo;

R^5 es hidrógeno o alquilo;

R^6 es hidrógeno, alquilo, alquiloSO_2, cicloalquiloSO_2, haloalquiloSO_2, $(R^9)(R^{10})NSO_2$, o $(R^{11})SO_2$;

R^7 es hidrógeno o alquilo;

R^8 es hidrógeno, alquilo, cicloalquilo, (cicloalquilo)alquilo, alquilcarbonilo, cicloalquilcarbonilo, haloalquilcarbonilo, alcoxicarbonilo, alquiloSO_2, cicloalquiloSO_2, haloalquiloSO_2, aminocarbonilo, (alquilamino)carbonilo, (dialquilamino)carbonilo, bencilo, benciloxicarbonilo, o piridinilo;

R^9 es hidrógeno o alquilo;

R^{10} es hidrógeno o alquilo;

R^{11} es azetidinilo, pirrolidinilo, piperidinilo, N-(R^{12})piperazinilo, morfolinilo, tiomorfolinilo, homopiperidinilo, o homomorfolinilo; y

R^{12} es hidrógeno o alquilo.

Otro aspecto de la invención es un compuesto de la fórmula I donde R^1 es $CONR^6R^7$; R^6 es alquiloSO_2, cicloalquiloSO_2, haloalquiloSO_2, $(R^9)_2NSO_2$, o $(R^{10})SO_2$; y R^7 es hidrógeno.

Otro aspecto de la invención es un compuesto de la fórmula I donde R^3 es hidrógeno.

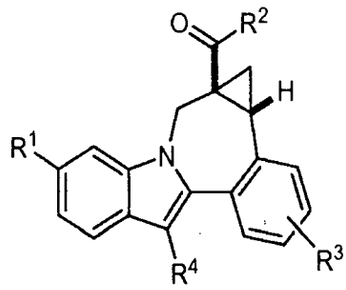
Otro aspecto de la invención es un compuesto de la

fórmula I donde R^3 es metoxi.

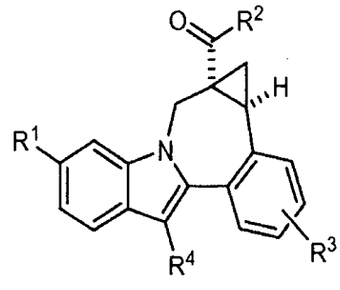
Otro aspecto de la invención es un compuesto de la fórmula I donde R^4 es ciclohexilo.

Otro aspecto de la invención es un compuesto de la fórmula I donde R^6 es $(R^9)(R^{10})NSO_2$ o $(R^{11})SO_2$.

Otro aspecto de la invención es un compuesto de la fórmula I, de acuerdo a la siguiente estereoquímica.



Otro aspecto de la invención es un compuesto de la fórmula I de acuerdo a la siguiente estereoquímica.



Cualquier ambito de cualquier variable, que incluye R^1, R^2, R^3, R^4, R^5, R^6, R^7, R^8, R^9, R^{10}, R^{11}, ó R^{12}, puede usarse independientemente con el ambito de cualquier otra instancia de una variable.

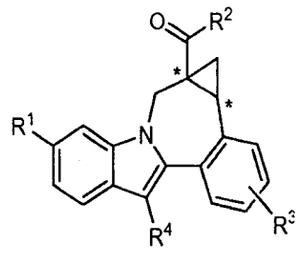
A menos de que se especifique de otra manera, estos términos tienen los siguientes significados. "Alquilo" significa un grupo alquilo recto o ramificado compuesto de 1 hasta 6 carbonos. "Alquenilo"

significa un grupo alquilo recto o ramificado compuesto de 2 hasta 6 carbonos con al menos un enlace doble. "Cicloalquilo" significa un sistema de anillo monocíclico compuesto de 3 hasta 7 carbonos. "Hidroxialquilo," "alcoxi" y otros términos con una porción de alquilo substituido incluyen isómeros rectos y ramificados compuestos de 1 hasta 6 átomos de carbono para la porción alquilo. "Haloalquilo" y "haloalcoxi" incluyen todos los isómeros halogenados de alquilo monohalo substituido a alquilo perhalo substituido. "Arilo" incluye substituyentes aromáticos carbocíclicos y heterocíclicos. Los términos parentéticos y multiparénteticos se pretenden que clarifiquen las relaciones de enlace para aquellos de habilidad en la técnica. Por ejemplo, un término tal como ((R)alquilo) significa un substituyente alquilo substituido además con el substituyente R.

La invención incluye todas las formas de sales farmacéuticamente aceptables de los compuestos. Las sales farmacéuticamente aceptables son aquellas en las cuales los contraiones no contribuyen significativamente a la actividad fisiológica o toxicidad de los compuestos y como tales funcionan como equivalentes farmacológicos. Estas sales pueden hacerse de acuerdo a las técnicas orgánicas comunes que emplean reactivos comercialmente disponibles. Algunas formas de sales 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.

Algunos de los compuestos de la invención poseen átomos de carbono asimétricos (ver, por ejemplo, el compuesto a continuación). La invención incluye todas las formas estereoisoméricas, incluyendo enantiómeros y diaestereómeros así como mezclas de estereoisómeros tales como racematos. Algunos estereoisómeros pueden hacerse usando métodos conocidos en la técnica. Las mezclas estereoisoméricas de los compuestos y compuestos intermedios relacionados pueden separarse en isómeros individuales de acuerdo a los métodos comúnmente conocidos en la técnica.



Métodos Sintéticos

Los compuestos pueden hacerse por métodos conocidos en la técnica incluyendo aquellos descritos a continuación. Algunos reactivos e Compuesto intermedios se conocen en la técnica. Otros reactivos e Compuesto intermedios pueden hacerse por los métodos conocidos en la técnica usando materiales fácilmente disponibles. Las variables (por ejemplo, substituyentes "R" numerados) usadas para describir la síntesis de los compuestos se pretenden sólo para ilustrar la forma de hacer y no deben confundirse con las variables usadas en las reivindicaciones o en otras secciones de la especificación. Las abreviaturas usadas dentro de

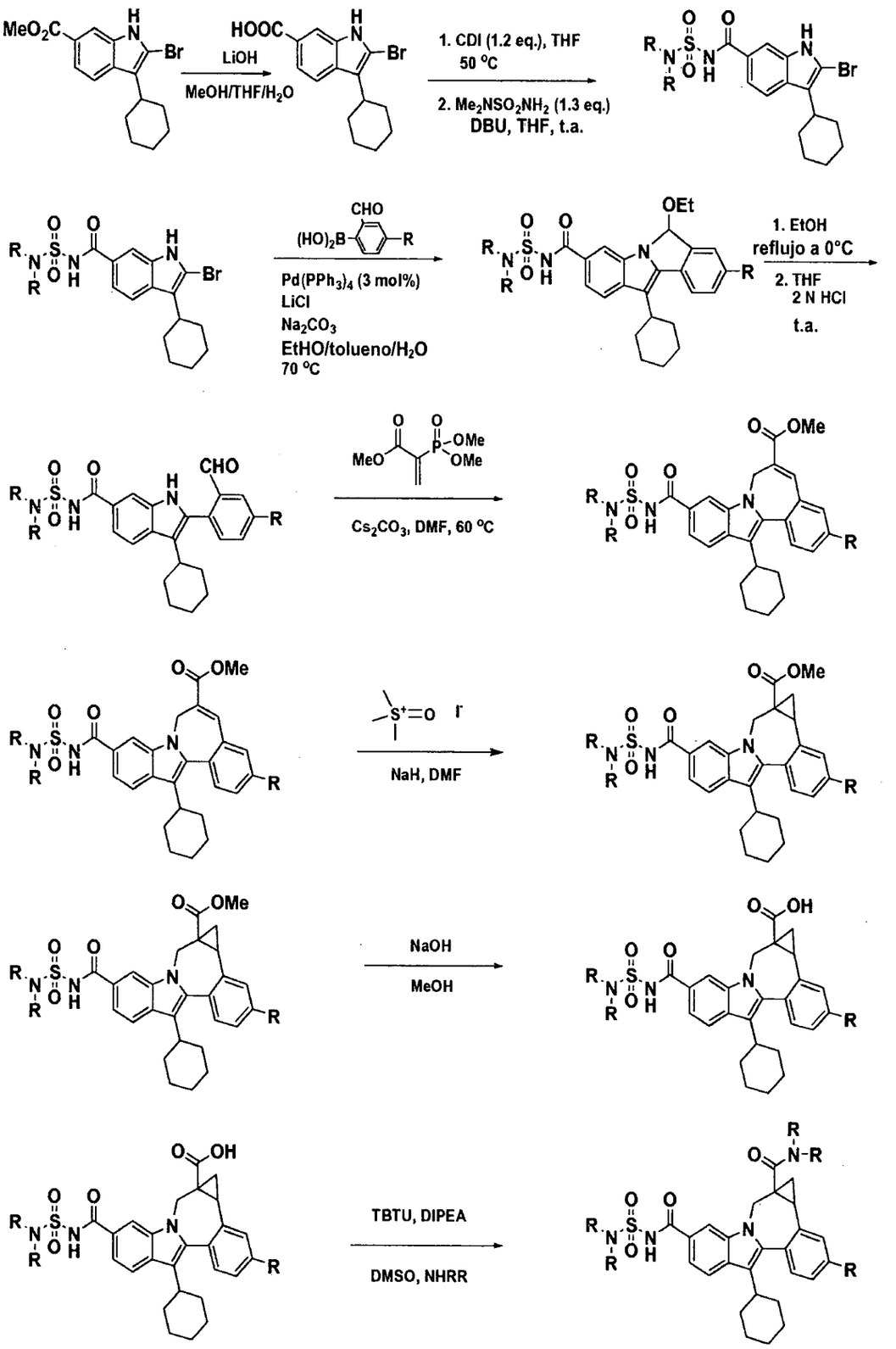
los esquemas de reacción generalmente siguen usos convencionales en la técnica.

El 2-bromo-3-ciclohexil-1H-indol-6-carboxilato de metilo puede hidrolizar al ácido 2-bromo-3-ciclohexil-1H-indol-6-carboxílico (ver Esquema de reacción 1). Este compuesto puede condensarse con una variedad de sulfonil ureas, usando por ejemplo, 1,1'-carbonildiimidazol en combinación con 1,8-diazabiciclo[5.4.0]undec-7-eno en THF anhidro. Las acil sulfamidas resultantes pueden someterse a reacciones de acoplamiento conocidas con una diversidad de ácidos o ésteres de 2-formil borónico, usando por ejemplo, condiciones de acoplamiento Suzuki, para proporcionar los compuestos intermedios hemiaminales cíclicos del tipo detallado. Estos compuestos pueden convertirse a derivados de indolbenzazepinas por el tratamiento con 2-(dimetoxifosforil)acrilato de metilo bajo la influencia de carbonato de cesio en DMF por medio de las reacciones Michael y Horner Emmons consecutivas.

Los derivados de éster de ciclopropilo fusionados relacionados pueden generarse por los métodos conocidos en la técnica, incluyendo el tratamiento de los ésteres de indolbenzazepina con yoduro de trimetil sulfoxonio bajo condiciones fuertemente básicas en DMSO. La porción de éster alifático residual en los ciclopropanos fusionados resultantes puede hidrolizarse y los ácidos de producto pueden condensarse con una variedad de diaminas ponteadas al alquilo. Por ejemplo, el tetrafluoroborato de O-(1H-benzotriazol-1-il)-N,N,N',N'-tetrametiluronio y diisopropil etil amina en DMSO pueden dar carboxamidas de diamina ponteadas al alquilo.

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Esquema de reacción 1.

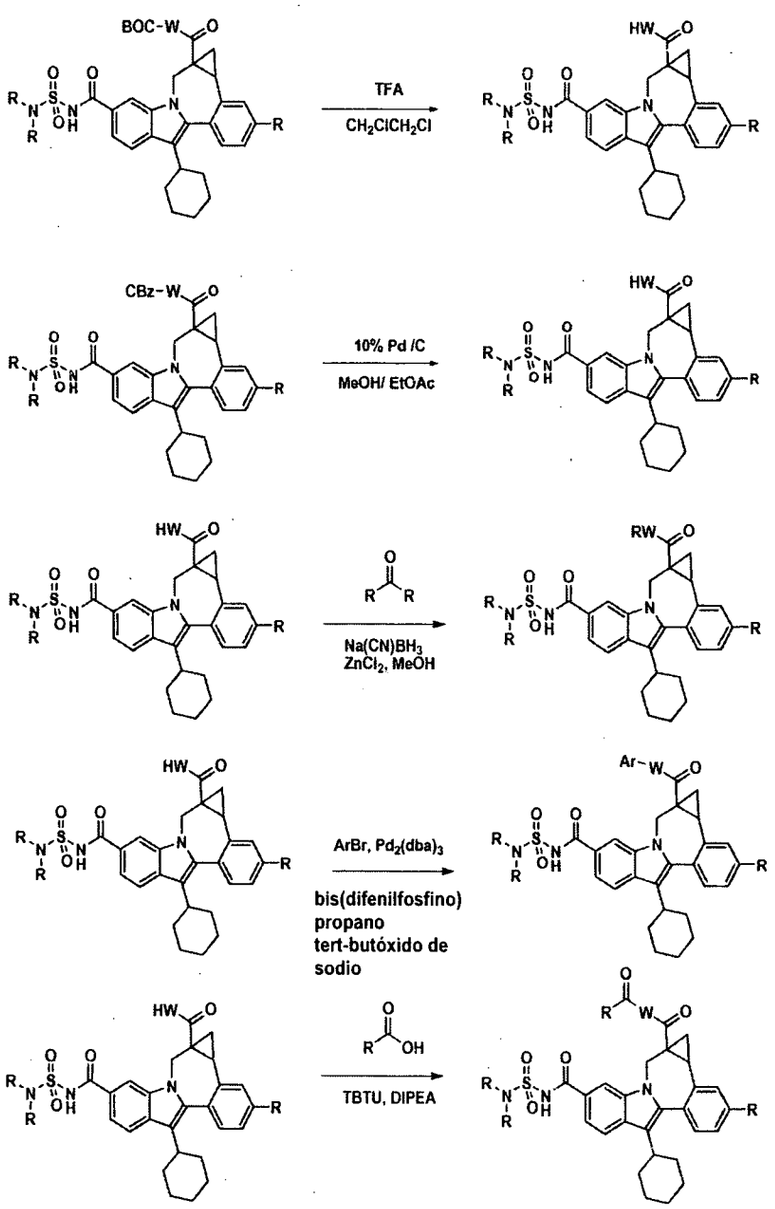


Las diaminas protegidas con N, por ejemplo donde W es una diamina protegida, pueden también acoplarse a los ácidos de

000227

indolbenzazepina intermedia y las carboxamidas de diamina resultantes pueden desprotegerse usando los métodos conocidos en la técnica y derivados usando una variedad de protocolos sintéticos, algunos ejemplos ilustrativos de los cuales se muestran a continuación (ver Esquema de reacción 2).

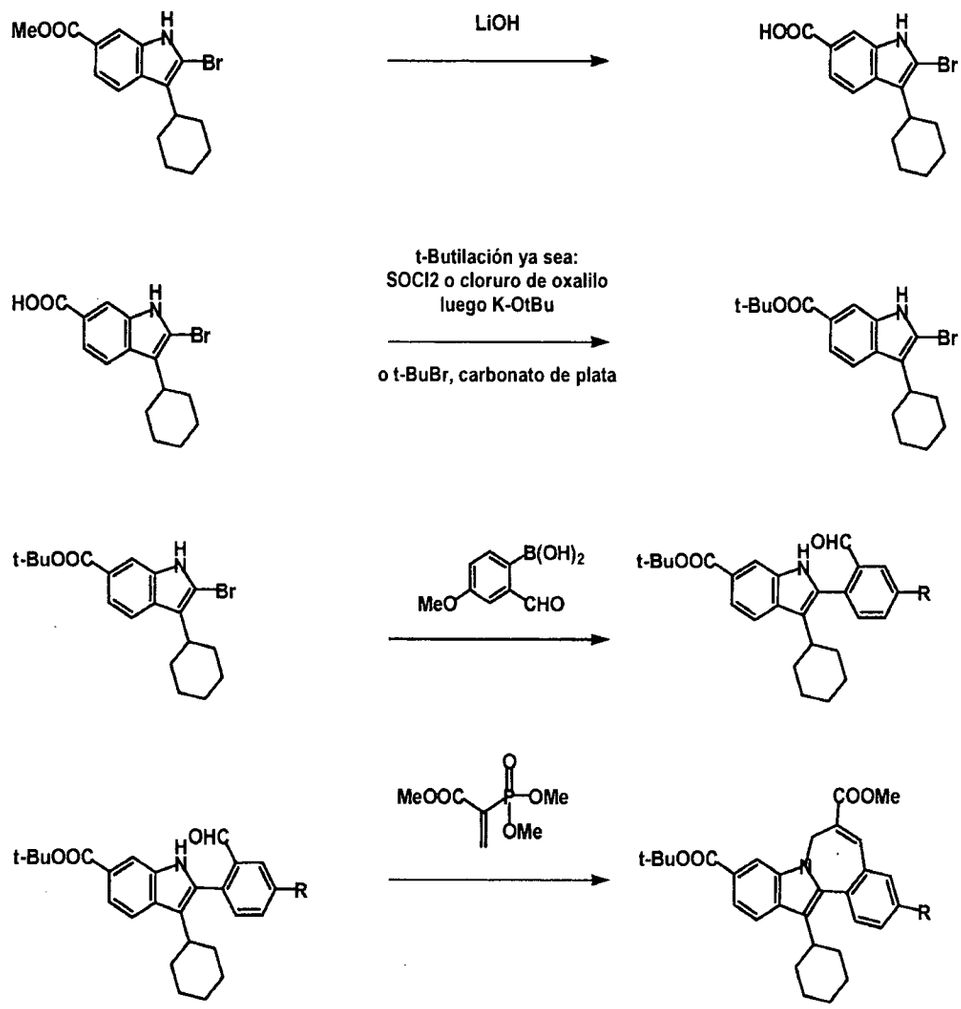
Esquema de reacción 2.



Un compuesto intermedio útil para la síntesis de algunos compuestos de la invención involucra la preparación del éster de tert-

butilo de indolbenzazepina mostrado en el Esquema de reacción 3.

Esquema de reacción 3.

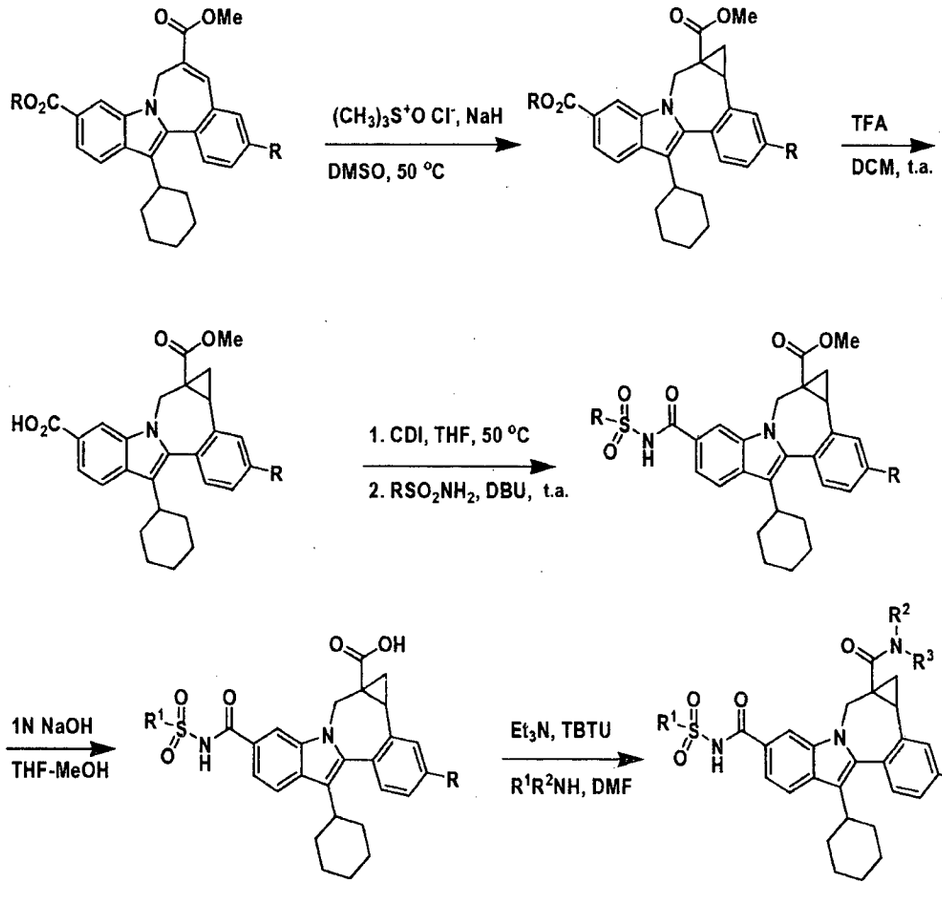


Esta metodología involucra hidrólisis de catalizador base del éster de metilo indol mostrado, seguido por su reacción con ya sea cloruro de tionilo y butóxido terciario de potasio, o alquilación con carbonato de plata y bromuro de butilo terciario. El compuesto resultante puede transformarse usando química análoga a aquella resumida previamente para proporcionar las indolbenzazepinas de éster mezcladas mostradas arriba.

Estos compuestos intermedios son útiles en un procedimiento alternativo que puede emplearse para la preparación de diaminas

ponteadas al alquil acilsulfamida y acilsulfonamida, como se muestra en el Esquema de reacción 4. La ciclopropanación de un Compuesto intermedio de indolbenzazepina de éster de t-butilo y el desdoblamiento posterior del grupo de éster de t-butilo puede generar el ácido el cual puede acoplarse a una diversidad de sulfonamidas y sulfonilureas. La hidrólisis posterior proporciona el ácido alifático relacionado, el cual puede acoplarse con una diversidad de diaminas ponteadas al alquilo. Por ejemplo, el tetrafluoroborato de O-(1H-benzotriazol-1-il)-N,N,N',N'-tetrametiluronio y diisopropil etil amina en DMSO puede dar las diamina carboxamidas ponteadas al alquilo.

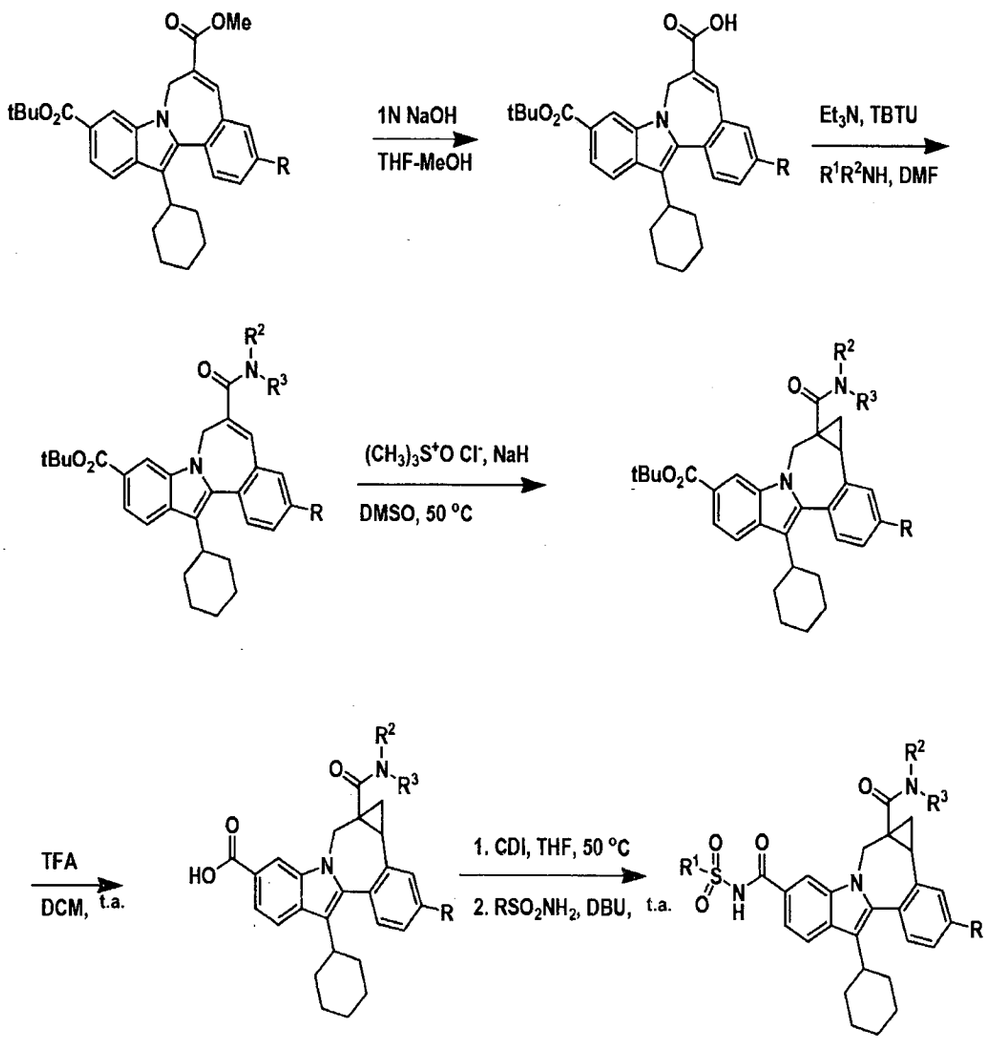
Esquema de reacción 4.



Las reacciones detalladas en el Esquema de reacción 4

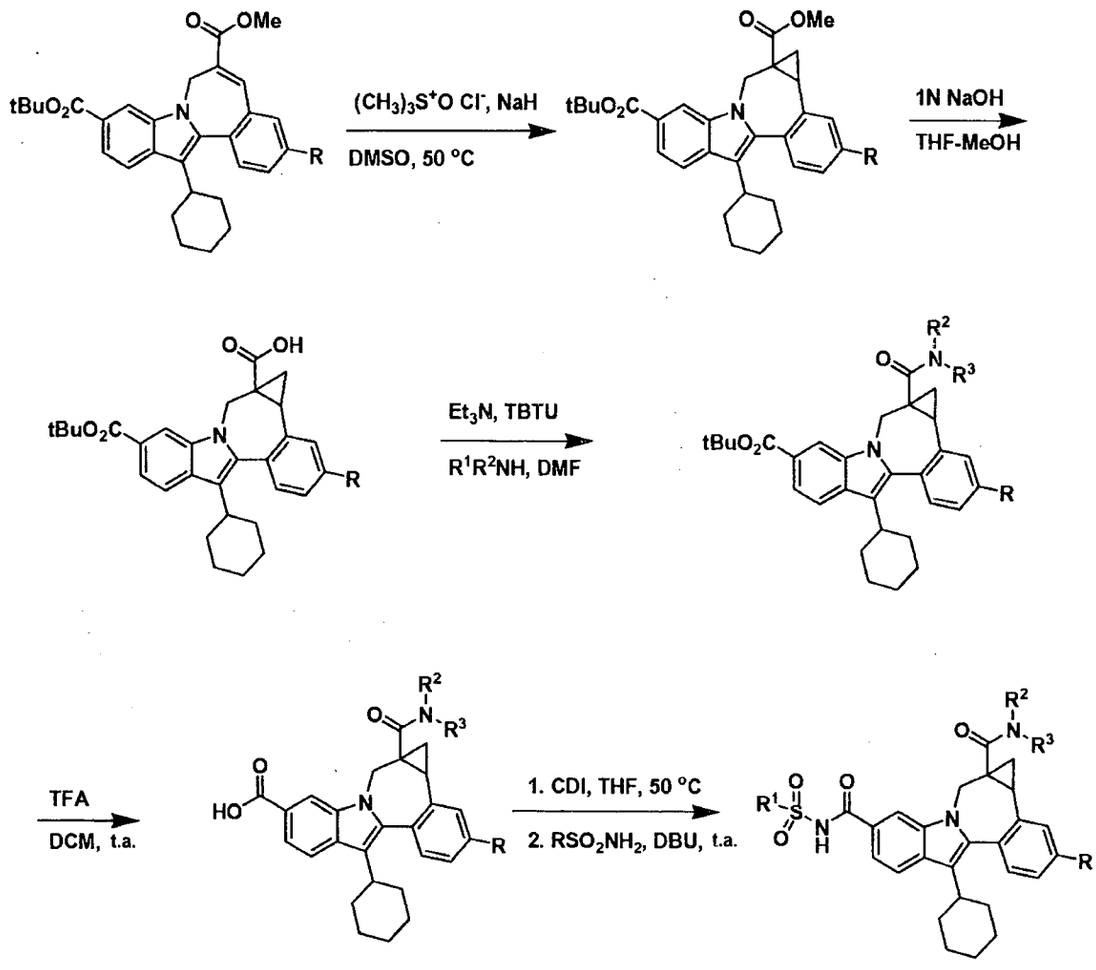
pueden realizarse en un orden alternativo para proporcionar los mismos productos. Los Esquemas de reacción 4a y 4b muestran dos alternativas. Adicionalmente, una diamina con dos aminas secundarias que podrían emplearse en cualquiera de los puntos detallados en los Esquemas de reacción donde el acoplamiento al ácido en el anillo de siete miembros se detalla y el NH libre se funcionaliza previo a complementar las etapas restantes en el Esquema de reacción.

Esquema de reacción 4a.



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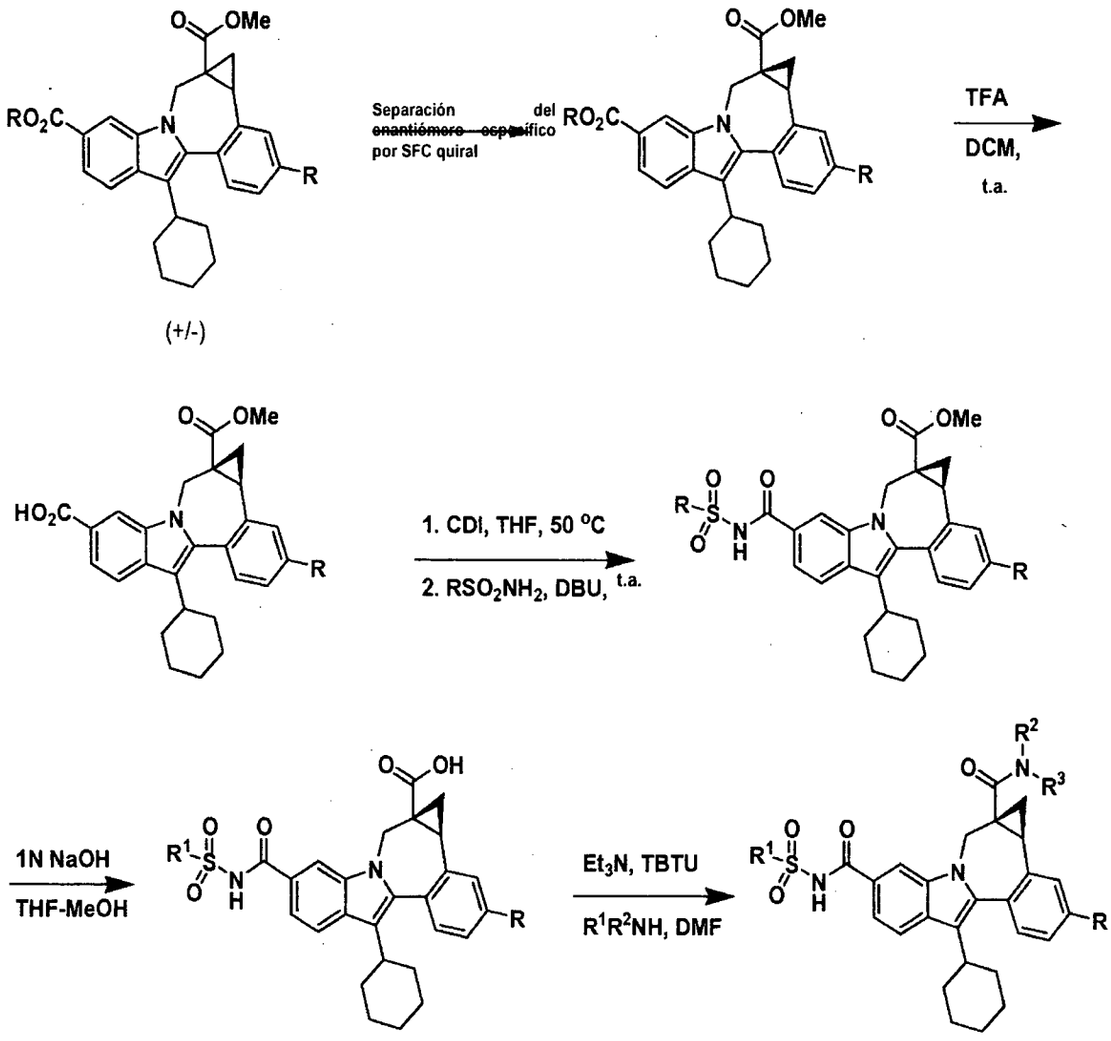
Esquema de reacción 4b.



Algunos ejemplos existen como mezclas estereoisoméricas. La invención también abarca todos estereoisómeros de los compuestos. Los métodos para fraccionar mezclas estereoisoméricas son bien conocidos en la técnica, e incluyen pero no se limitan a; cromatografía de fluido supercrítico quiral preparativa (SFC, por sus siglas en inglés) y cromatografía líquida de alto desempeño quiral (HPLC, por sus siglas en inglés). Un ejemplo usado en este enfoque se muestra en el Esquema de reacción 5.

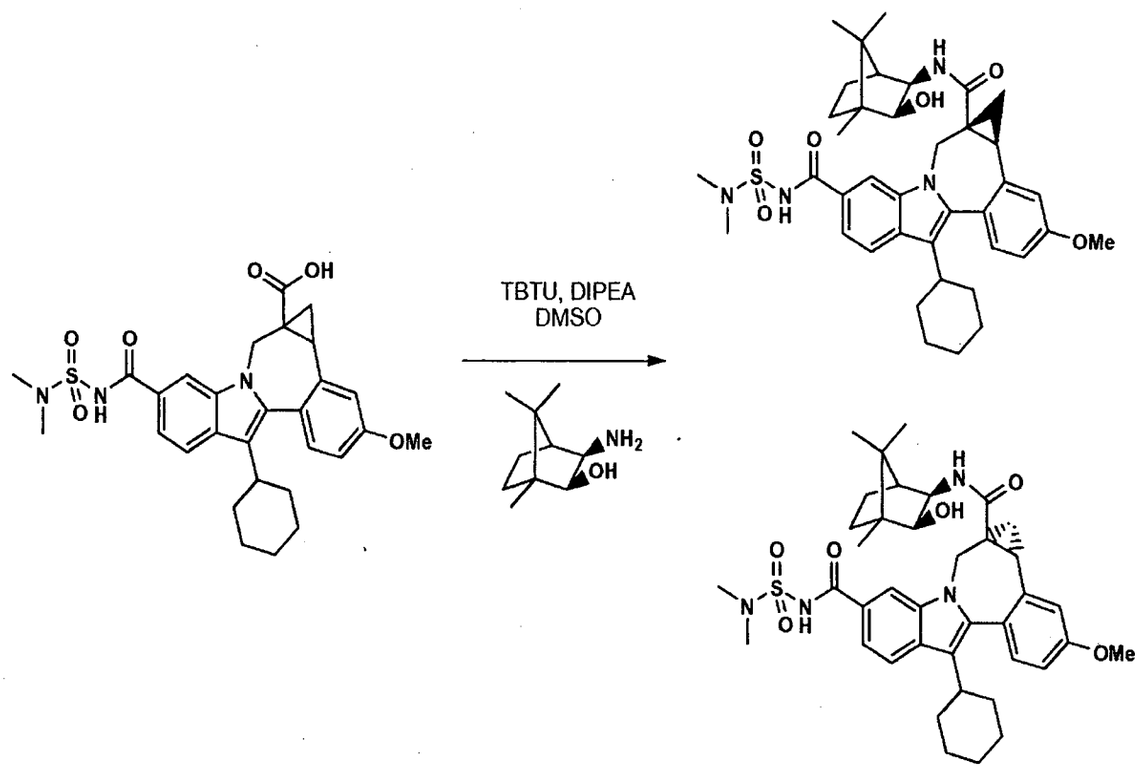
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Esquema de reacción 5.



Un método adicional para alcanzar tales preparaciones involucra la preparación de las mezclas de diaestereómeros los cuales pueden separarse usando una variedad de métodos conocidos en la técnica. Un ejemplo de este enfoque se muestra a continuación (Esquema de reacción 6).

Esquema de reacción 6.

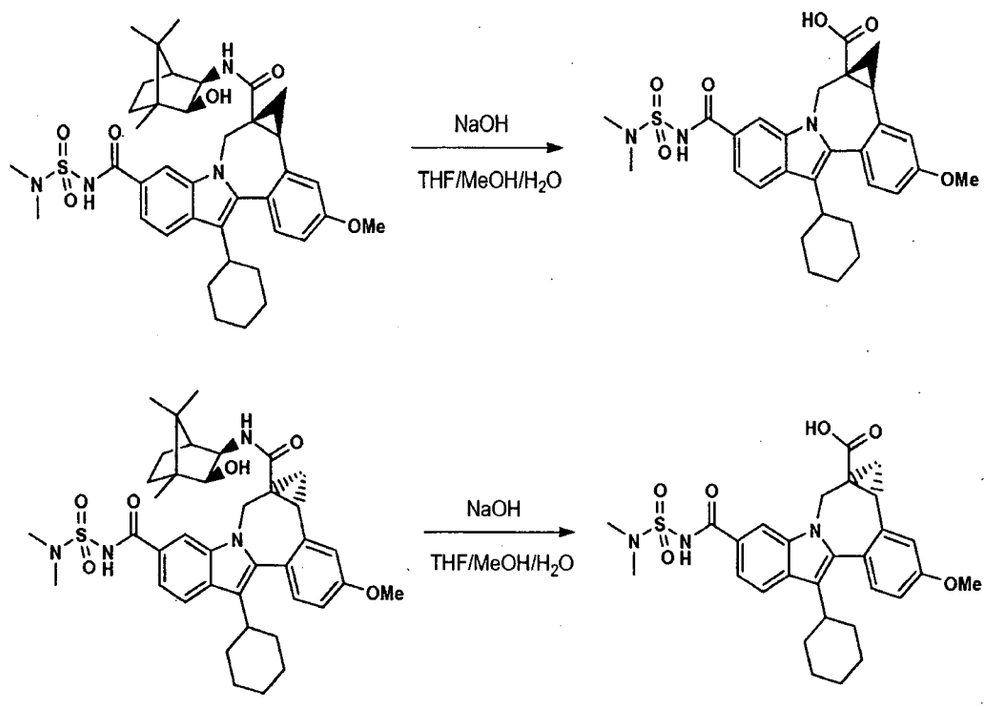


Diaestereómeros separados por HPLC de fase inversa

Algunas amidas diaestereoméricas pueden separarse usando HPLC de fase inversa. Después de la hidrólisis, los ácidos ópticamente activos resultantes pueden acoplarse con derivados de diaminas ponteadas (Esquema de reacción 7). Por ejemplo, el tetrafluoroborato de O-(1H-benzotriazol-1-il)-N,N,N',N'-tetrametiluronio y diisopropil etil amina en DMSO pueden usarse para dar las carboxamidas ponteadas al alquilo. Otros métodos de acoplamiento de amina del ácido estándar pueden usarse para dar las carboxamidas ópticamente activas.

000234

Esquema de reacción 7.



Métodos Biológicos

Los compuestos demuestran actividad contra el NS5B del VHC como se determina en los siguientes ensayos RdRp del VHC.

Clonación, expresión y purificación del NS5B RdRp del VHC. El cADN que codifica la proteína NS5B del VHC, genotipo 1b, se clonó en el vector de expresión pET21a. La proteína se expresó con una truncación de la terminal C de 18 aminoácidos para aumentar la solubilidad. La línea celular BL21(DE3) competente de E. coli se usó para la expresión de la proteína. Los cultivos se hicieron crecer a 37°C durante ~4 horas hasta que los cultivos alcanzan una densidad óptica de 2.0 a 600 nm. Los cultivos se enfriaron a 20°C e indujeron con IPTG 1 mM. Se agregó ampicilina fresca a una concentración final de 50 µg/ml

y las células se hicieron crecer durante la noche a 20°C.

Los peletizados celulares (3L) se lisaron por purificación para proporcionar 15-24 mgs de NS5B purificado. La solución amortiguadora de lisis consiste de Tris-HCl 20 mM, pH 7.4, NaCl 500 mM, tritón X-100 al 0.5%, DTT 1 mM, EDTA 1 mM, glicerol al 20%, 0.5 mg/ml de lisozima, MgCl2 10 mM, 15 ug/ml de desoxiribonucleasa I, y comprimidos del inhibidor de proteasa TM completos (Roche). Después de la adición de la solución amortiguadora de lisis, los peletizados celulares congelados se volvieron a suspender usando un homogenizador de tejido. Para reducir la viscosidad de la muestra, las alícuotas del lisado se sonicaron en hielo usando un micropunta enlazado a un sonicador Branson. El lisado sonicado se centrifugó a 100,000 x g durante 1 hr a 4°C y filtró a través de una unidad de filtro de 0.2 µm (Corning).

La proteína se purificó usando dos etapas de cromatografía secuenciales: sefarosa de heparina CL-6B y sefarosa de polyU 4B (Pharmacia). Las solucioes amortiguadoras de cromatografía fueron idénticas a la solución amortiguadora de lisis pero no contienen lisozima, desoxiribonucleasa I, MgCl2 o inhibidor de proteasa y la concentración NaCl de la solución amortiguadora se ajustó de acuerdo con los requerimientos para cargar la proteína en la columna. Cada columna se eluyó con un gradiente NaCl el cual varía en longitud desde 5-50 volúmenes de la columna dependiendo del

000236

tipo de columna. Después de la etapa de cromatografía final, la pureza resultante de la enzima es >90% con base en el análisis SDS-PAGE. La enzima se hizo alícuota y almacenó a -80°C.

Ensayo de enzima NS5B RdRp del VHC estándar. Los ensayos del genotipo 1b RdRp del VHC se corrieron en un volumen final de 60 µl en placas de 96 pozos (Corning 3600). La solución amortiguadora de ensayo está compuesta de Hepes 20 mM, pH 7.5, KCl 2.5 mM, MgCl2 2.5 mM, DTT 1 mM, inhibidor de ARNsa 1.6 U (Promega N2515), 0.01 mg/ml de BSA (Sigma B6917), y glicerol al 2%. Todos los compuestos se diluyeron en serie (3 veces) en DMSO y diluyeron además en agua de manera que la concentración final de DMSO en el ensayo fue 2%. La enzima del genotipo 1b RdRp del VHC se usó en una concentración final de 28 nM. Una plantilla polyA se usó en 6 nM, y un cebador oligo-dT12 biotinilado se usó en una concentración final de 180 nM. La plantilla se obtuvo comercialmente (Amersham 27-4110). El cebador biotinilado se preparó por Sigma Genosys. El 3H-UTP se usó en 0.6 µCi (UTP total 0.29 µM). Las reacciones se iniciaron por la adición de la enzima, incubaron a 30°C durante 60 min, y detuvieron al agregar 25 µl de EDTA 50 mM que contiene microesferas de SPA (4 µg/µl, Amersham RPNQ 0007). Las placas se leyeron en un Packard Top Count NXT después de >1hr de incubación a temperatura ambiente.

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Ensayo de la enzima NS5B RdRp del VHC modificada. Un ensayo de la enzima modificada se realizó esencialmente como se describe para el ensayo de la enzima estándar excepto por lo siguiente: el cebador oligo dT12 biotinilado se precapturó en microesferas SPA recubiertas con estreptavidina al mezclar el cebador y las microesferas en solución amortiguadora de ensayo e incubar a temperatura ambiente durante una hora. El cebador no enlazado se removió después de la centrifugación. Las microesferas enlazadas al cebador se volvieron a suspender en solución amortiguadora de Hepes 20 mM, pH 7.5 y se usaron en el ensayo en concentraciones finales del cebador 20 nM y 0.67 µg/µl de las microesferas. Orden de la adición en el ensayo: la enzima (1.75 nM) se agregó al compuesto diluido seguido por la adición de una mezcla de la plantilla (0.36 nM), 3H-UTP (0.6 µCi, 0.29 µM), y las microesferas enlazadas al cebador, para iniciar la reacción; las concentraciones dadas son finales. Las reacciones se permitieron continuar durante 4 horas a 30°C.

Los valores IC_{50} para los compuestos se determinaron usando siete diferentes [I]. Los valores IC_{50} se calcularon de la inhibición usando la fórmula y = A+((B-A)/(1+((C/x)^D))).

Preparación del ensayo FRET. El ensayo de separación por exclusión FRET del VHC se realizó en

000238

placas de cultivo celular de 96 pozos. El peéptido FRET (Anaspec, Inc.) (Taliani et al., *Anal. Biochem.* 1996, 240, 60-67) contiene un donador de fluorescencia, EDANS, cerca de un extremo del péptido y un aceptor, DABCYL, cerca del otro extremo. La fluorescencia del péptido se apaga por transferencia de energía de resonancia intermolecular (RET, por sus siglas en inglés) entre el donador y el aceptor, pero como la proteasa NS3 desdobla el péptido los productos se liberan de la RET apagada y la fluorescencia del donador se vuelve aparente. El reactivo del ensayo se hizo como sigue: reactivo de lisis del cultivo celular de Luciferasa de célula 5X de Promega (#E153A) diluido hasta 1X con dH_2O, NaCl agregado hasta 150 mM final, el péptido FRET diluido hasta 20 µM final de una reserva 2 mM.

Para preparar las placas, las células de replicón del VHC, con o sin un gen reportero de luciferasa Renilla, se tripsinaron y colocaron en placas en una placa de 96 pozos con compuestos de prueba titrados agregados en las columnas 3 hasta 12; columnas 1 y 2 que contienen un compuesto de control (inhibidor de control del VHC), y la hilera del fondo contiene células con DMSO solamente. Las placas luego se colocaron en un incubador CO_2 a 37°C.

000239

Ensayos. Posterior a la adición de los compuestos de prueba descritos arriba (Preparación del Ensayo FRET), varias veces la placa se removió y la solución Alamar blue (Trek Diagnostics, #00-100) se agregó para medir la toxicidad celular. Después de leer en un instrumento Cytoflour 4000 (PE Biosystems), las placas se enjuagaron con PBS y luego se usaron para el ensayo FRET por la adición de 30 ul del reactivo de ensayo de péptido FRET descrito arriba (Preparación del Ensayo FRET) por pozo. La placa luego se colocó en el instrumento Cytoflour 4000 que se ha establecido hasta 340 excitaciones/490 emisiones, en modo automático durante hasta 20 ciclos y la lecutra de placa en un modo cinético. Típicamente, la señal propagada usando un análisis de punto final después de las lecturas fue al menos tres veces. Alternativamente, después de la lecutra de Alamar blue, las placas se enjuagaron con PBS, luego se usaron para el ensayo de luciferase usando el sistema de ensayo de Luciferasa Promega Dual-Glo o el ensayo de substrato de célula vida Promega EnduRen.

El análisis del compuesto se realizó por cuantificación de la inhibición de replicón del VHC relativo y los valores de citotoxicidad relativos. Para calcular los valores de citovoxicidad, las señales de fluorescencia de Alamar Blue promedio de

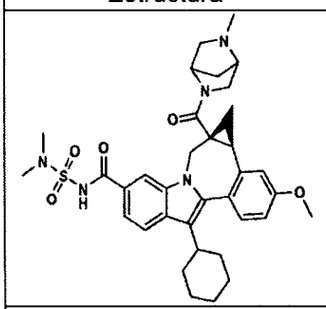
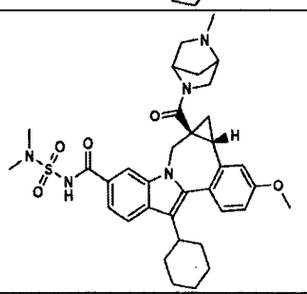
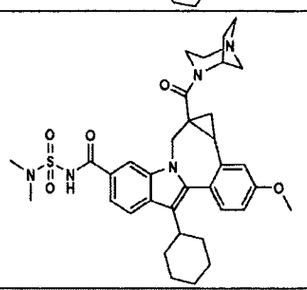
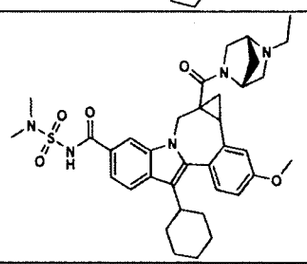
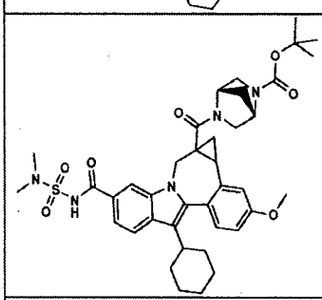
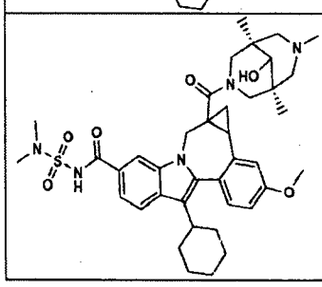
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los pozos de control se establecieron como 100% no tóxicos. Las señales individuales en cada uno de los pozos de prueba del compuesto luego se dividieron por la señal de control promedio y se multiplicaron al 100% para determinar el porcentaje de citotoxicidad. Para calcular los valores de inhibición de replicón del VHC, un valor de respaldo promedio se obtuvo de los dos pozos que contienen la cantidad más alta del inhibidor de control del VHC en el extremo del periodo del ensayo. Estos números fueron similares a aquellos obtenidos de las células Huh-7 originales. Los números de respaldo luego se substrajeron de la señal promedio obtenida de los pozos de control y este número se usó como la actividad al 100%. Las señales individuales en cada uno de los pozos de prueba del compuesto luego se dividieron por los valores de control promedio después de la substracción de respaldo y se multiplicaron al 100% para determinar el porcentaje de la actividad. Los valores EC_{50} se calcularon como la concentración que provoca una reducción al 50% en FRET o la actividad de luciferasa. Los dos números generados para la placa del compuesto, el porcentaje de citotoxicidad y el porcentaje de la actividad, se usaron para determinar los compuestos de interés para el análisis adicional.

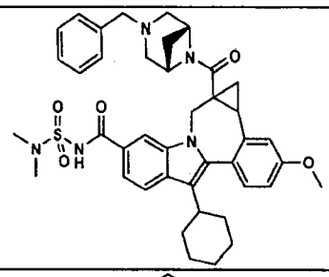
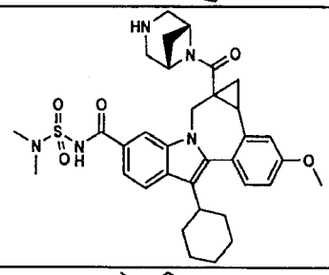
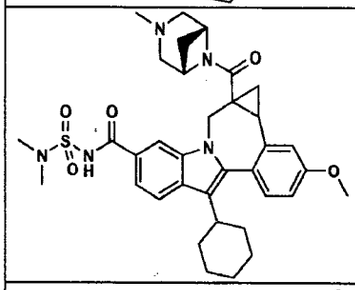
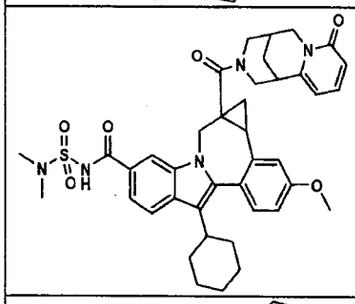
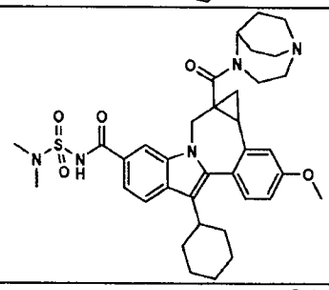
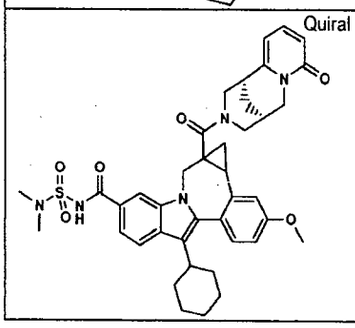
Los datos representativos para los compuestos se reportan en la Tabla 1.

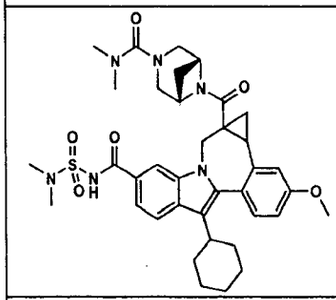
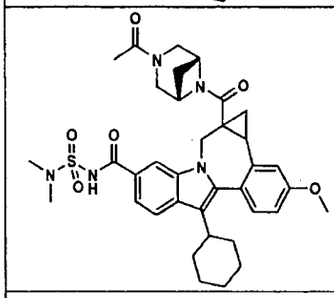
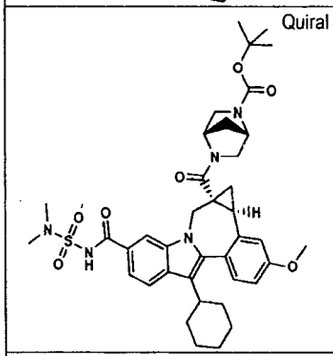
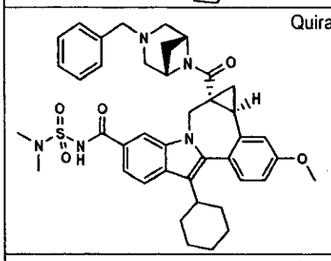
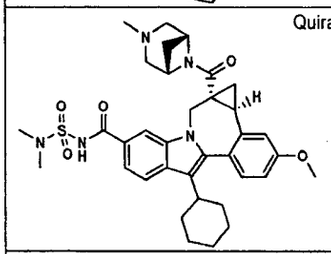
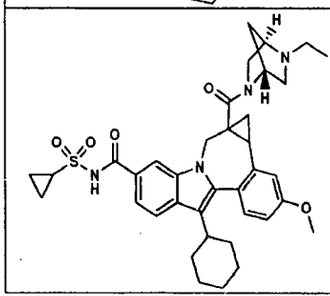
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Tabla 1.

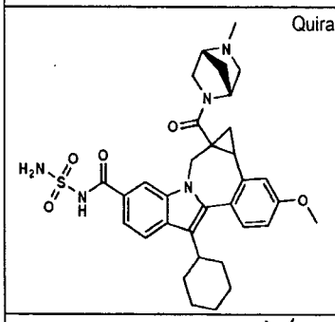
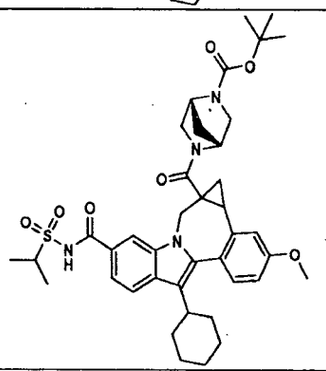
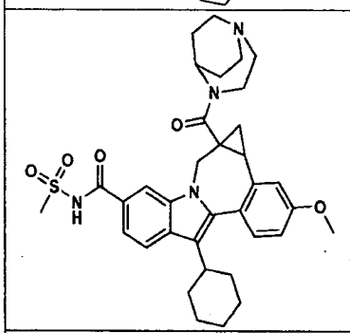
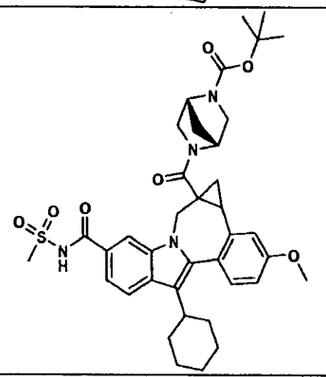
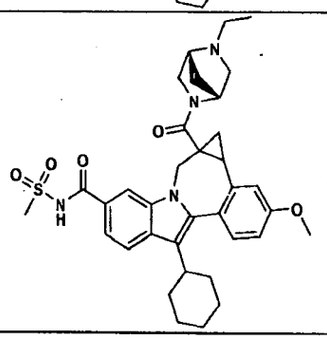
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	B	B
	B	B
	B	B
	B	B
	B	B

000242

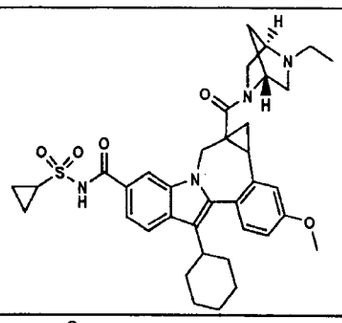
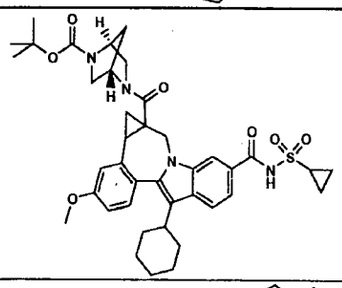
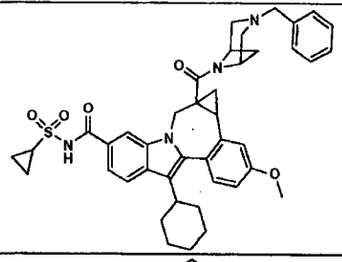
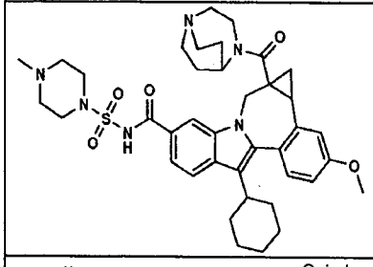
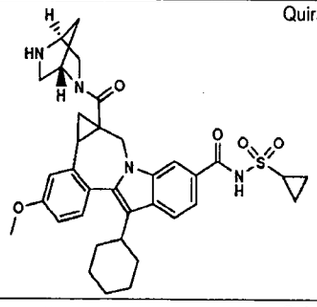
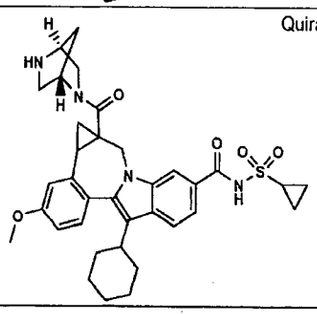
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	B	B
	B	B
Quiral 	E	B

Estructura	IC_{50}	EC_{50}
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	B	B
 Quiral	B	B
 Quiral	B	B
 Quiral	B	B
	C	B

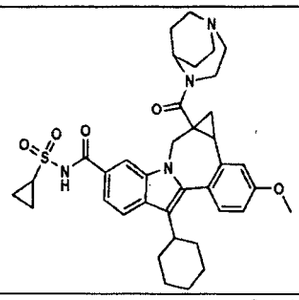
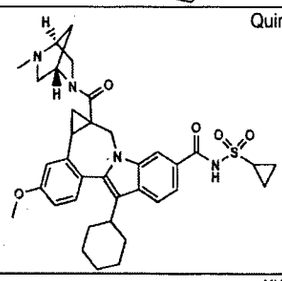
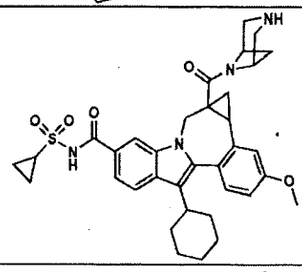
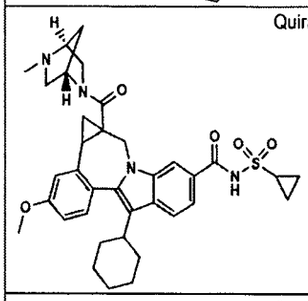
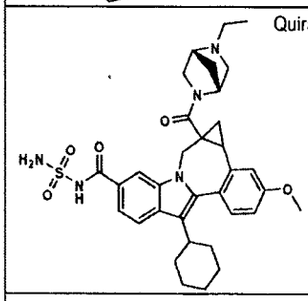
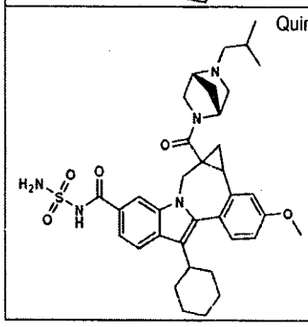
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	B	B
	B	B

000244

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	B	B
	B	B
	B	B
Quiral 		
Quiral 	B	

000245

Estructura	IC_{50}	EC_{50}
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	B	B
Quiral 	B	B
Quiral 	B	B
Quiral 	B	B

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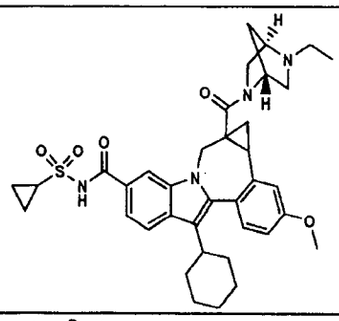
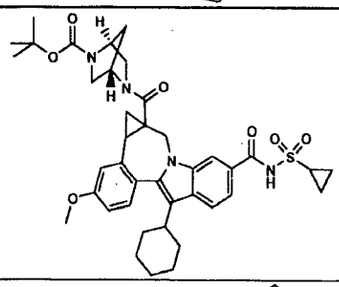
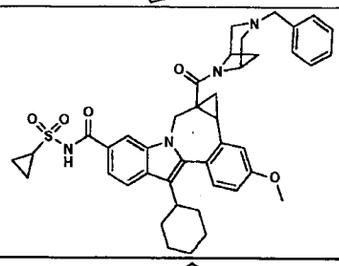
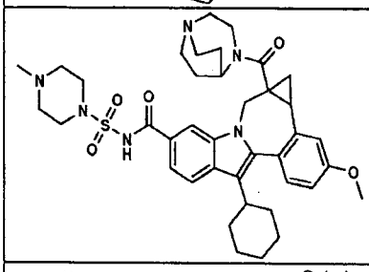
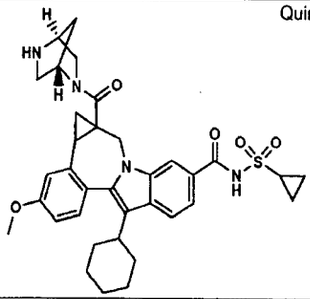
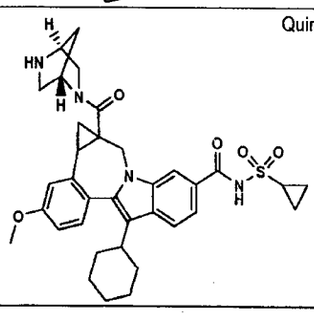
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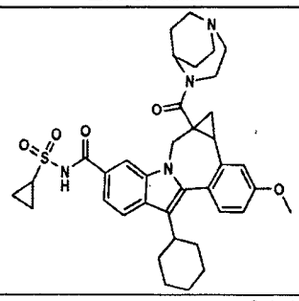
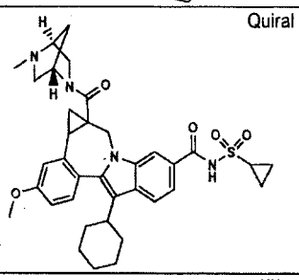
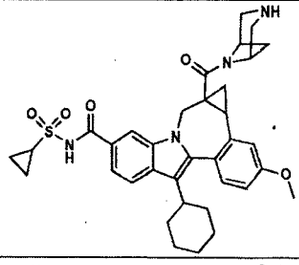
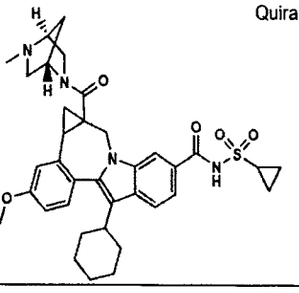
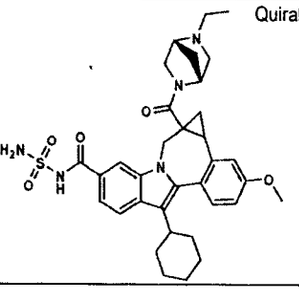
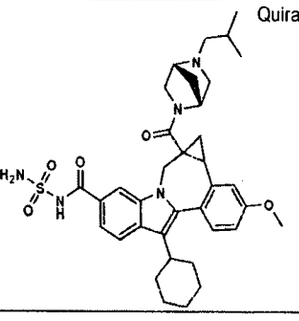
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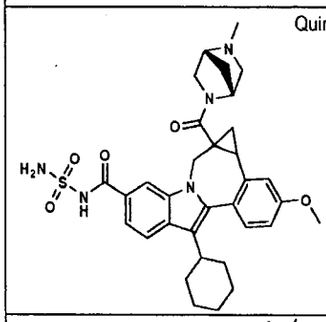
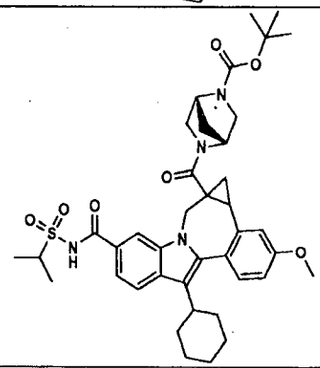
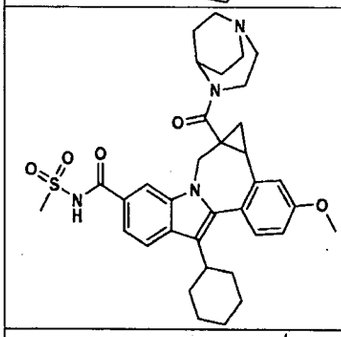
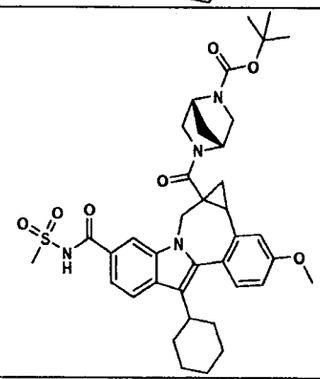
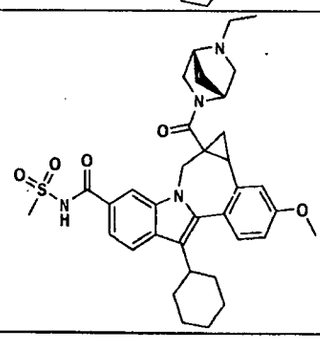
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	B	B
	B	B
Quiral 		
Quiral 	B	

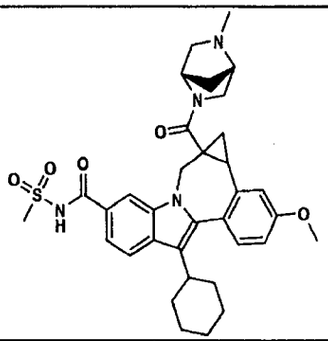
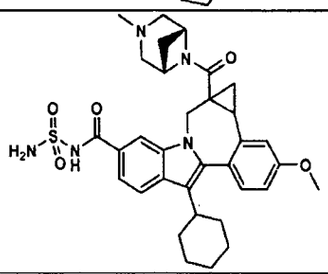
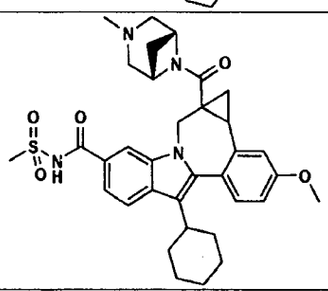
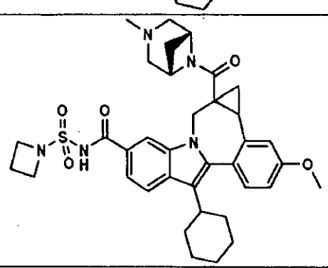
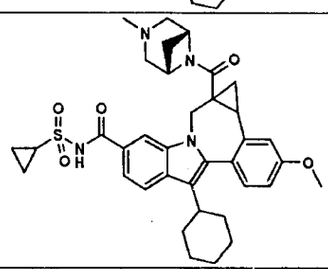
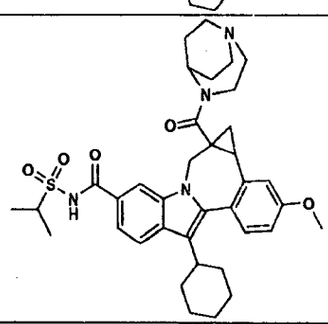
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Estructura	IC_{50}	EC_{50}
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Quiral 	B	A
	B	B
Quiral 	B	B
Quiral 	B	B
Quiral 	B	B

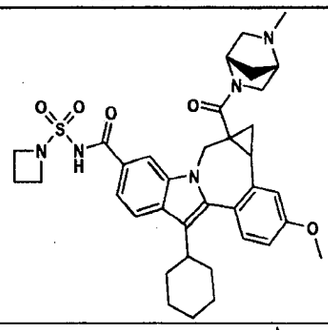
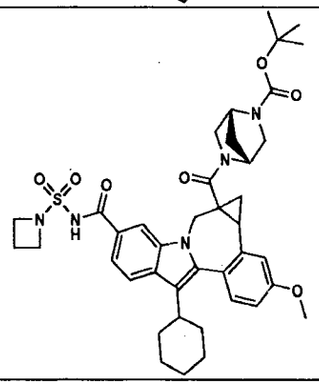
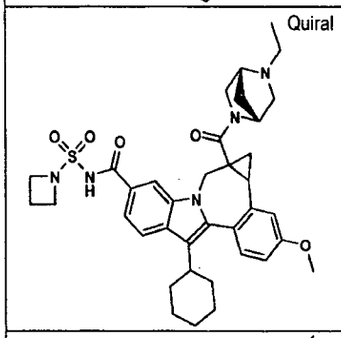
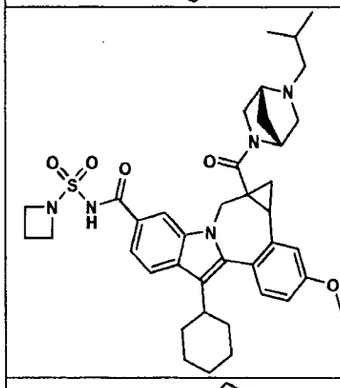
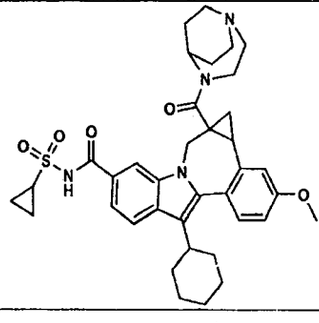
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Estructura	IC_{50}	EC_{50}
Quiral 	B	B
	B	B
	B	B
	B	B
	B	B

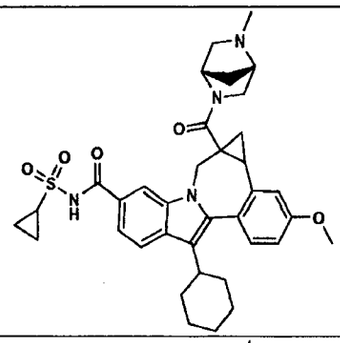
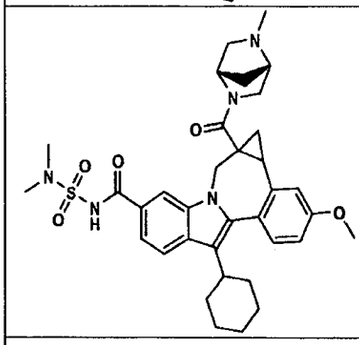
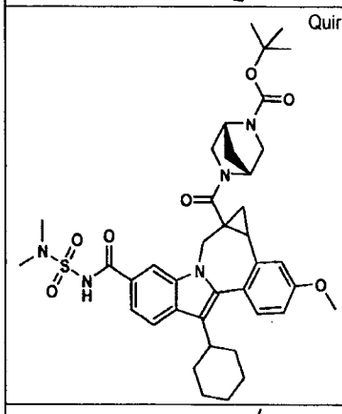
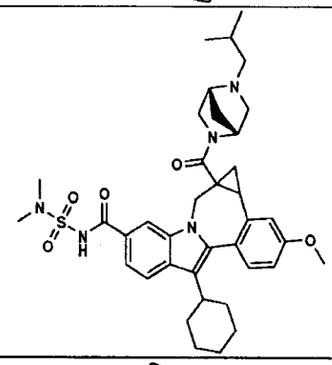
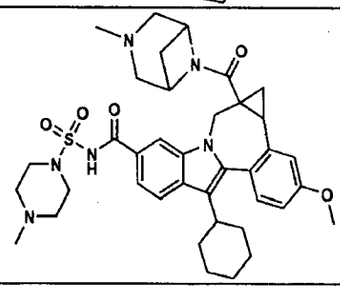
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Estructura	IC_{50}	EC_{50}
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	B	B
	B	B
	B	B
	B	B
	B	B

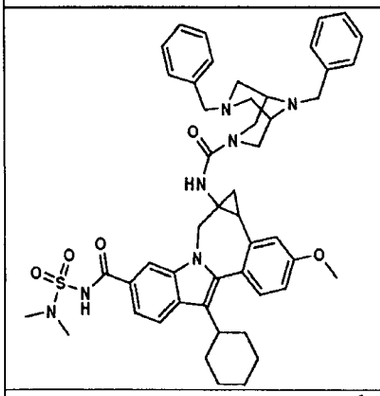
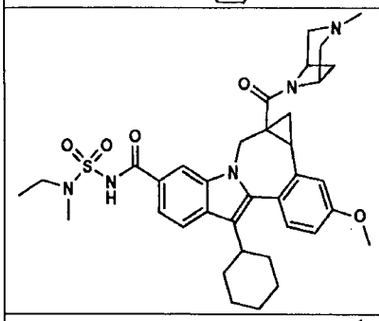
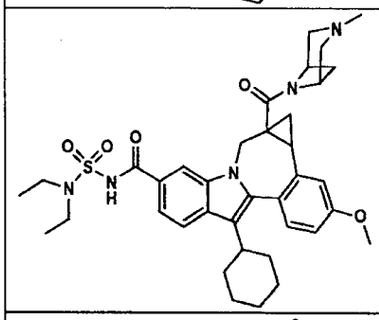
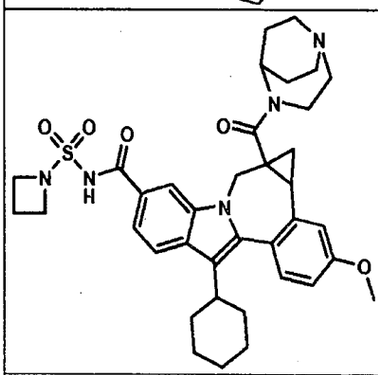
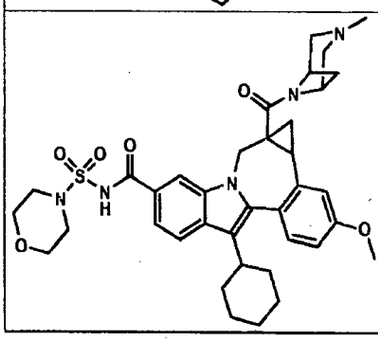
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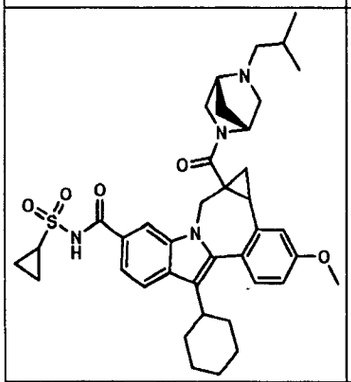
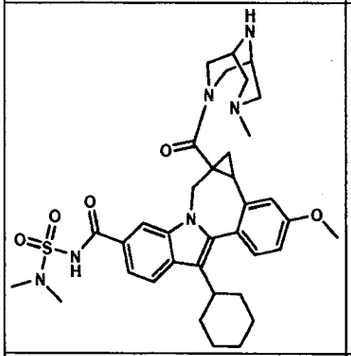
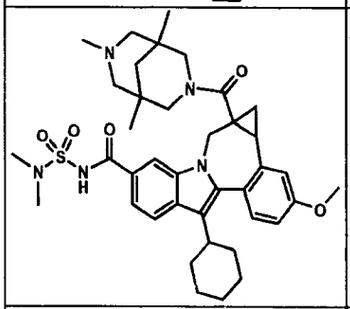
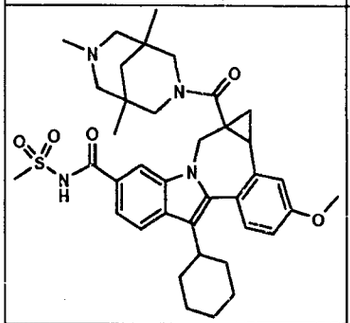
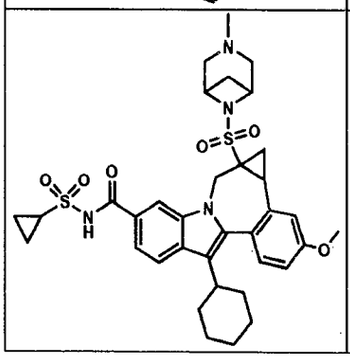
Estructura	IC_{50}	EC_{50}
	B	B
	B	B
 Quiral	B	B
	B	B
	B	B

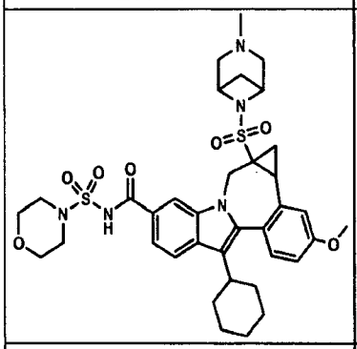
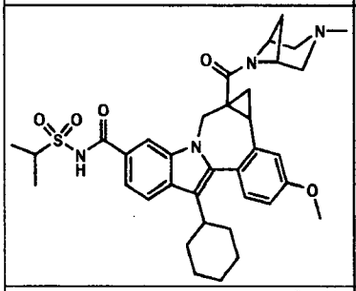
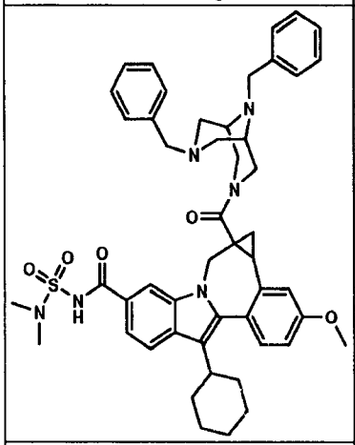
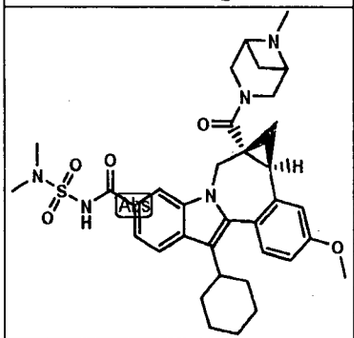
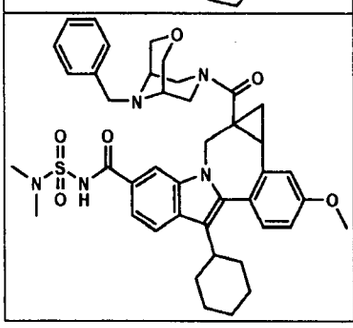
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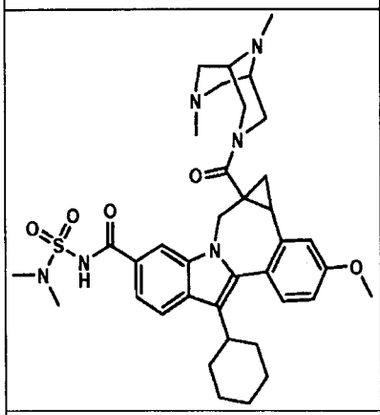
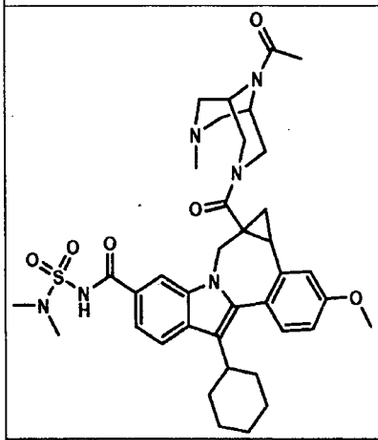
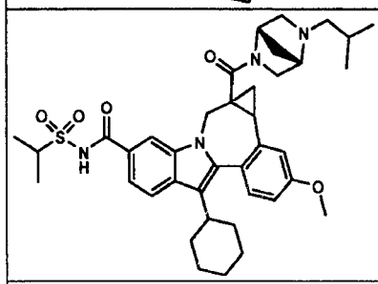
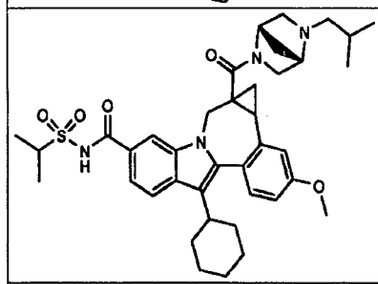
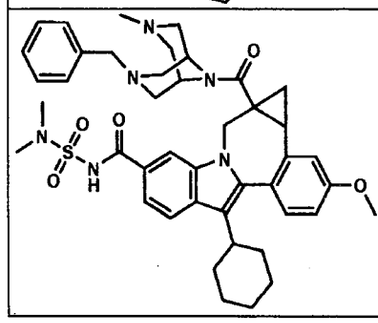
Estructura	IC_{50}	EC_{50}
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	C	B
 Quiral	B	
	B	B
	B	B

000250

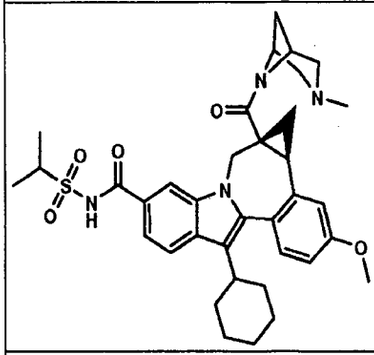
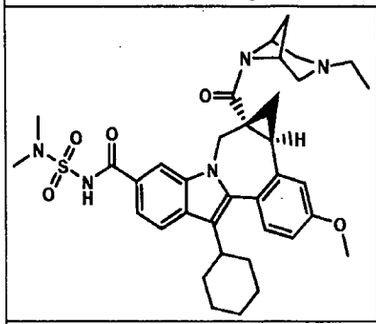
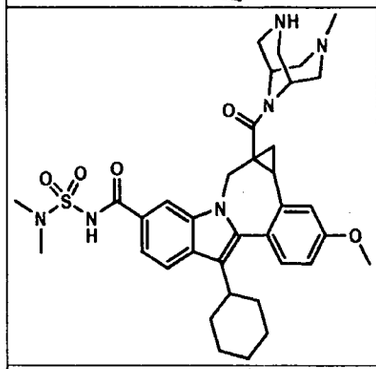
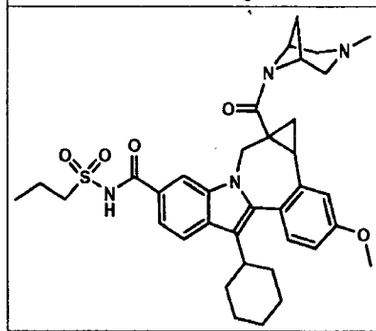
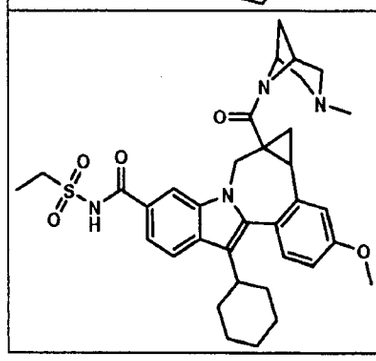
Estructura	IC_{50}	EC_{50}
	G	
	B	B
	B	B
	B	B
	B	B

Estructura	IC_{50}	EC_{50}
	B	B
	B	B
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	B	B
	B	B

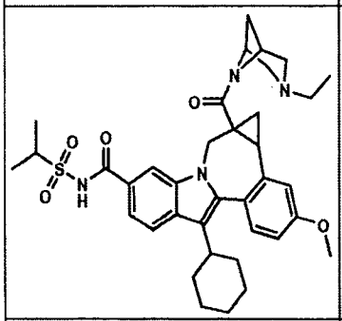
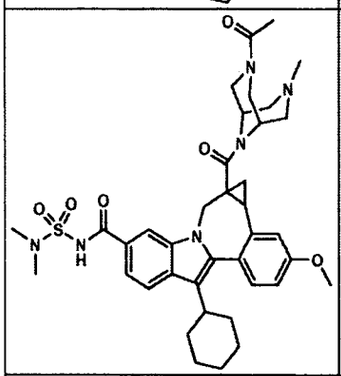
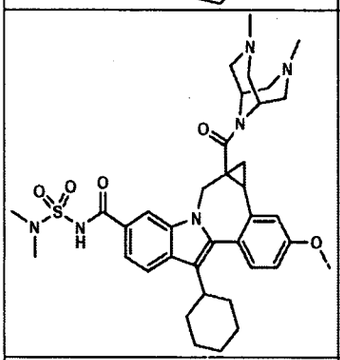
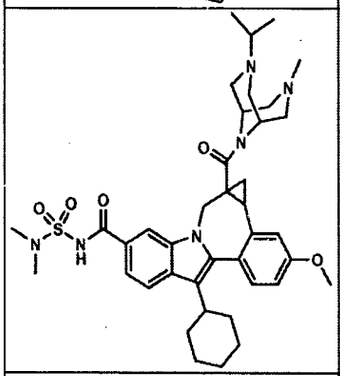
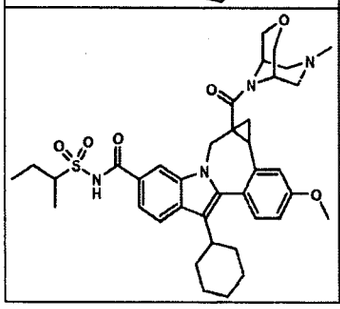
Estructura	IC_{50}	EC_{50}
	B	B
	B	B
	B	G
	B	B
	B	B

Estructura	IC_{50}	EC_{50}
	B	B
	B	B
	B	B
	B	B
	B	B

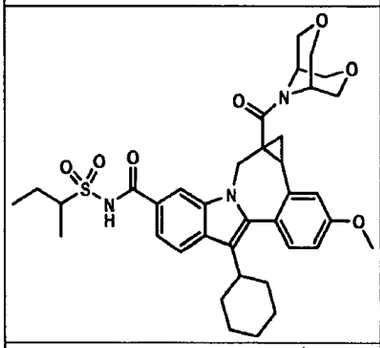
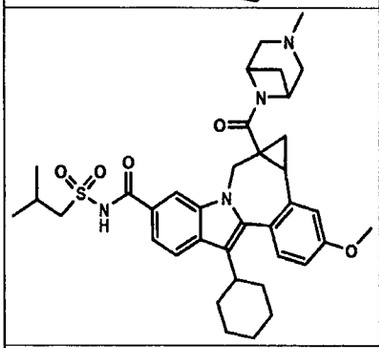
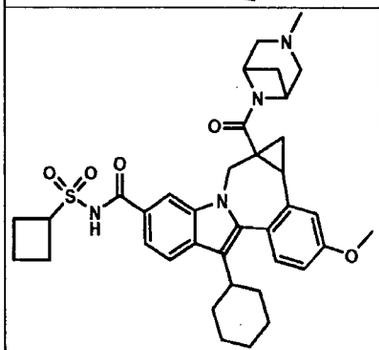
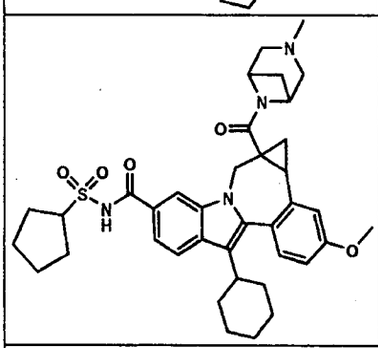
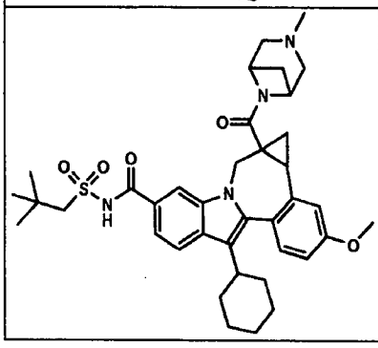
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Estructura	IC_{50}	EC_{50}
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	B	B
	B	
	B	B
		

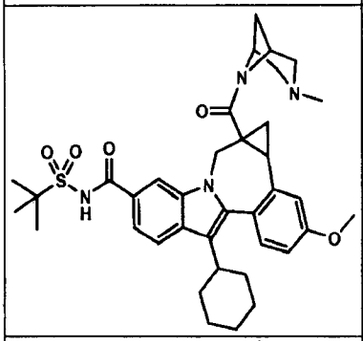
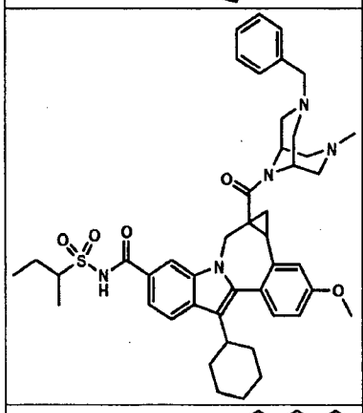
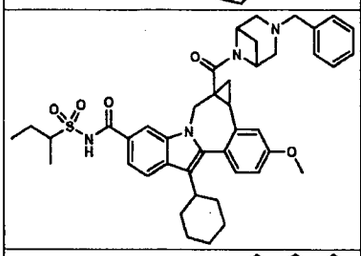
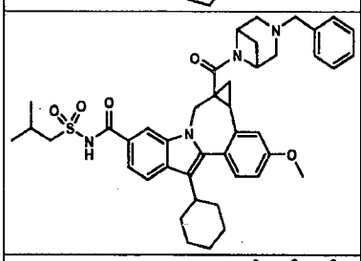
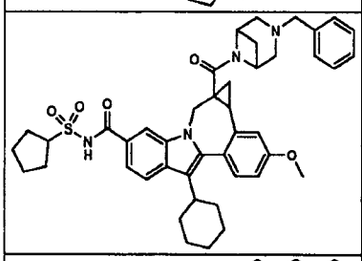
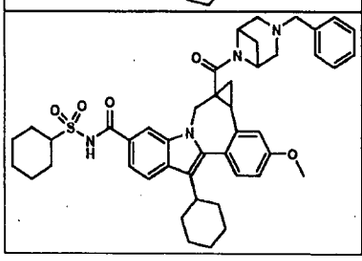
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Estructura	IC_{50}	EC_{50}
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	B	B
	B	B
	B	B
	B	

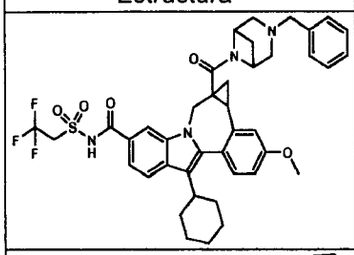
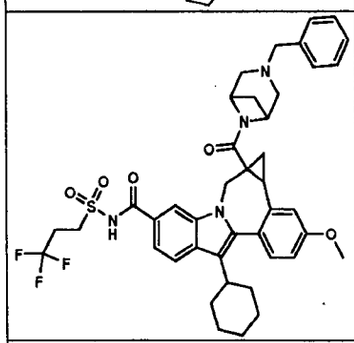
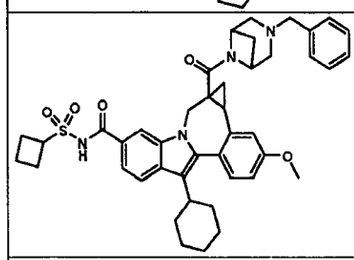
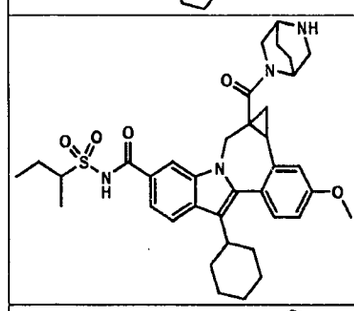
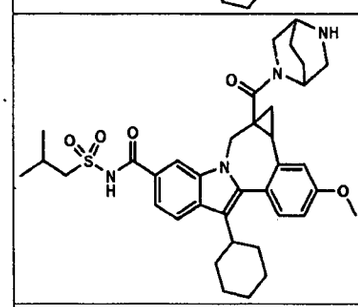
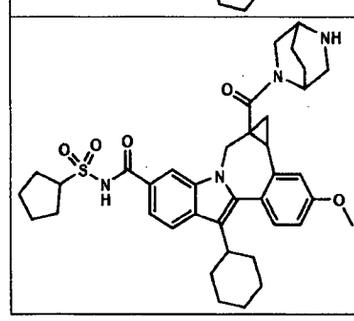
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Estructura	IC_{50}	EC_{50}
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	B	B
	B	B
	B	B
	B	B

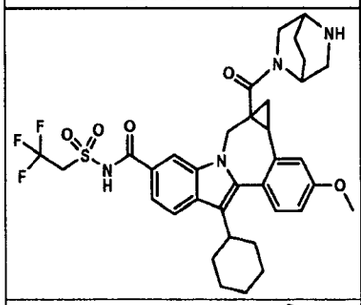
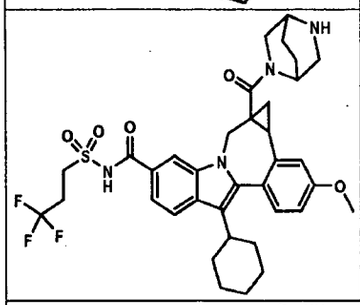
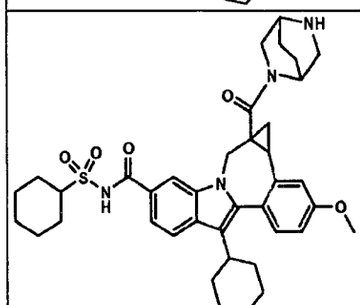
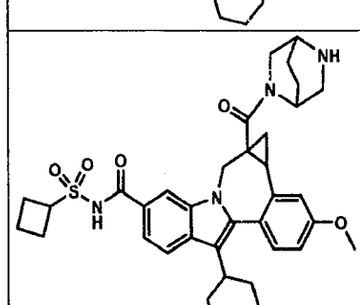
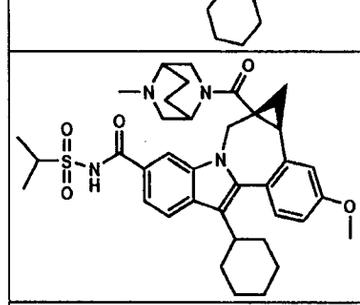
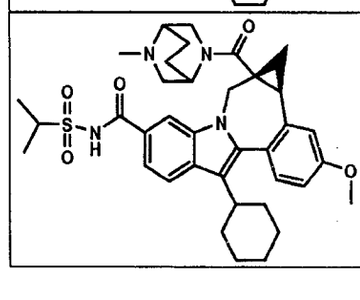
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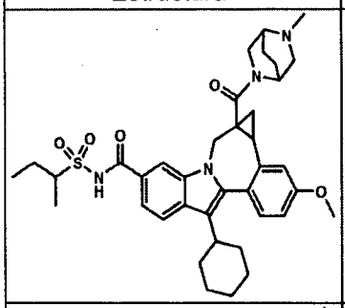
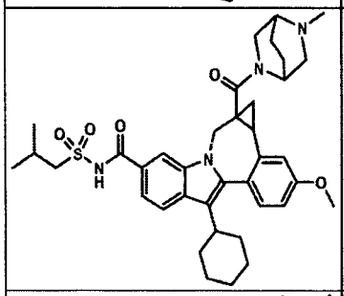
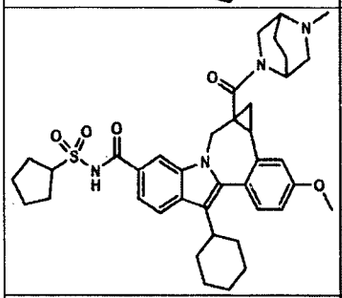
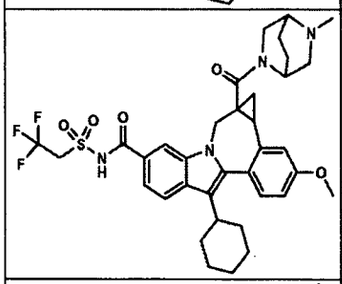
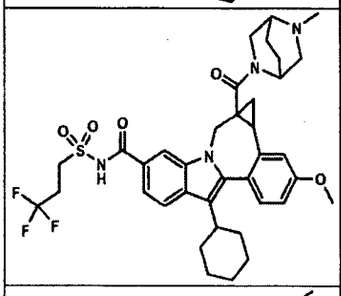
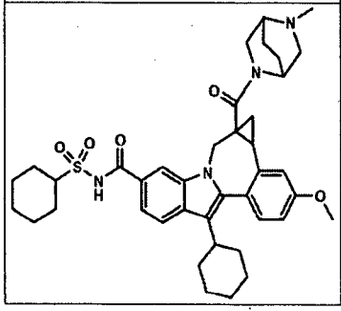
Estructura	IC_{50}	EC_{50}
	B	B
	B	B
	B	B
	B	B
	B	B
	B	G

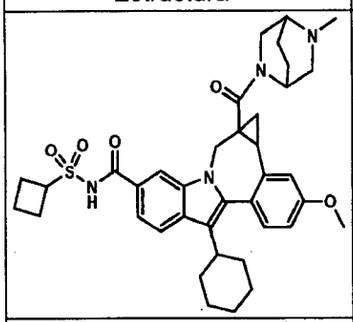
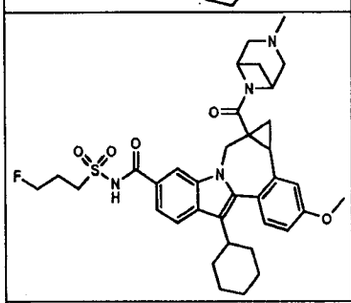
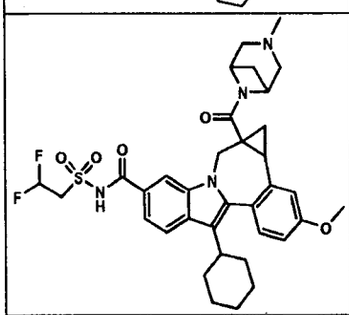
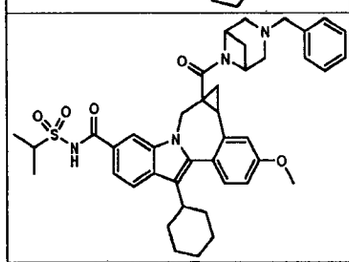
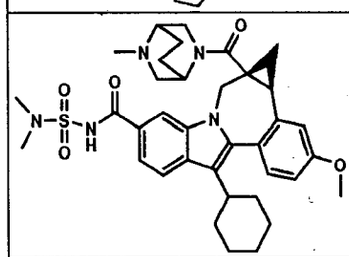
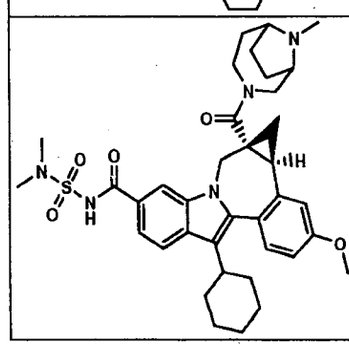
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Estructura	IC_{50}	EC_{50}
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	B	G
	B	G
	B	G
	B	H
	B	H

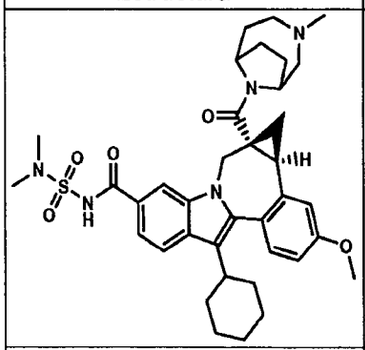
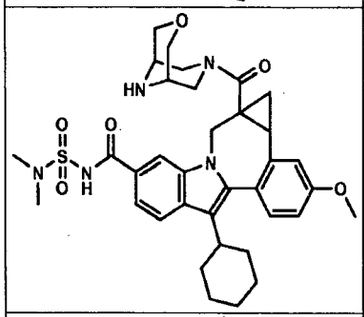
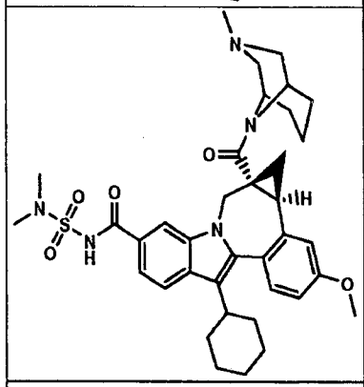
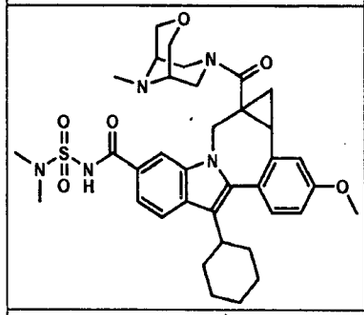
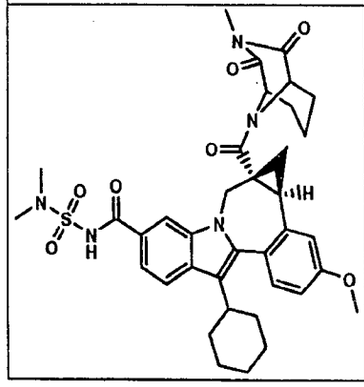
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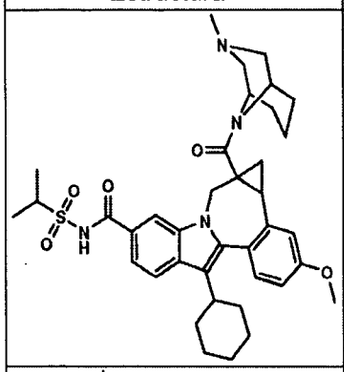
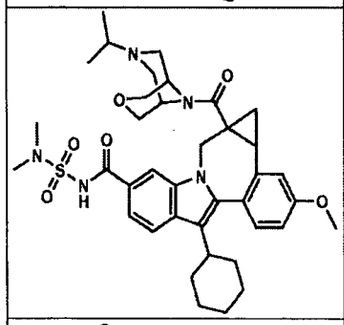
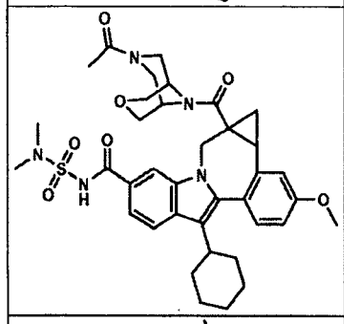
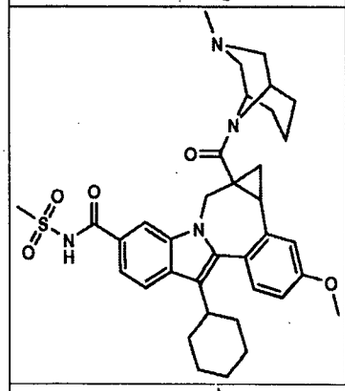
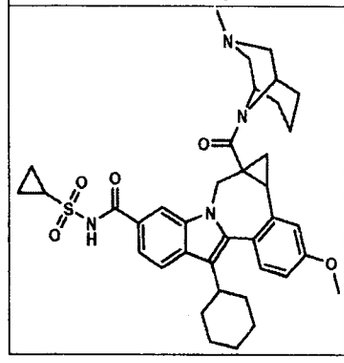
Estructura	IC_{50}	EC_{50}
	B	H
	B	H
	B	H
	B	B
		B
		B

Estructura	IC_{50}	EC_{50}
		
		
		
		
		
		

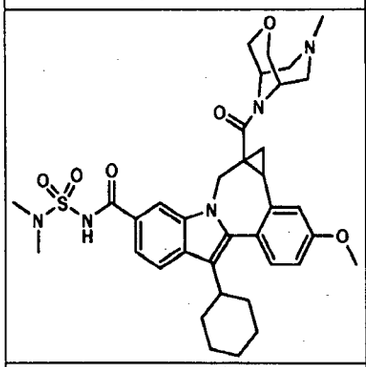
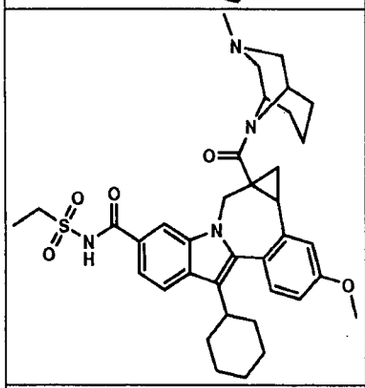
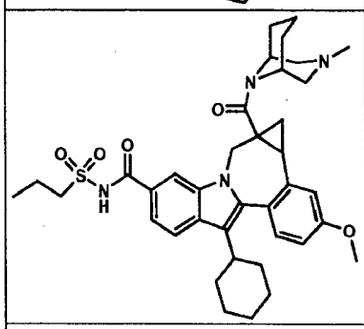
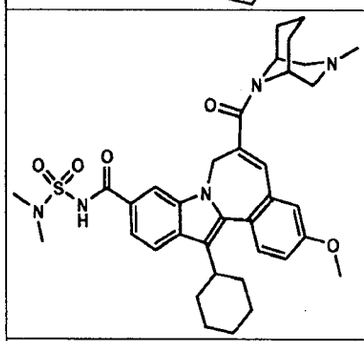
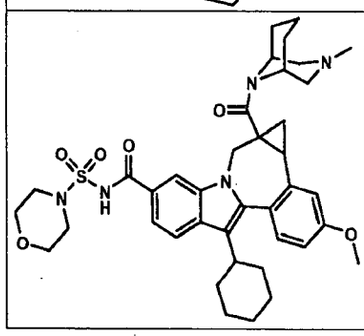
Estructura	IC_{50}	EC_{50}
		
	B	B
	B	B
	B	B
	B	B
	B	B

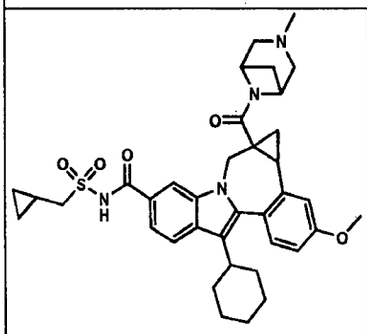
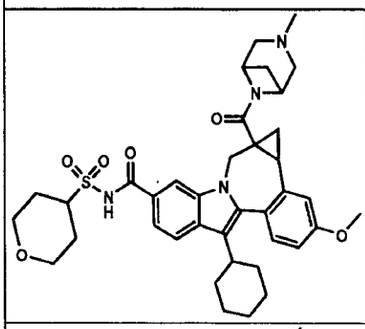
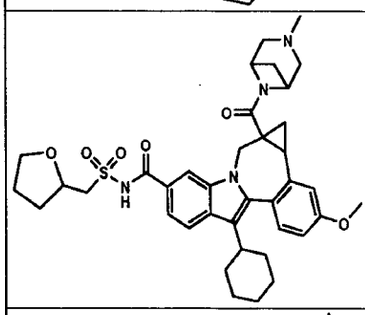
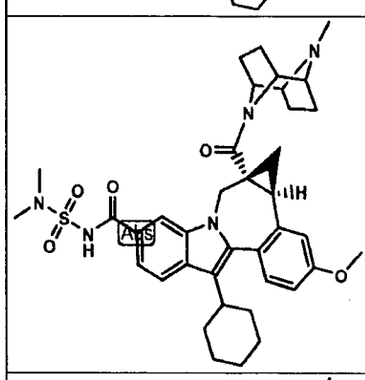
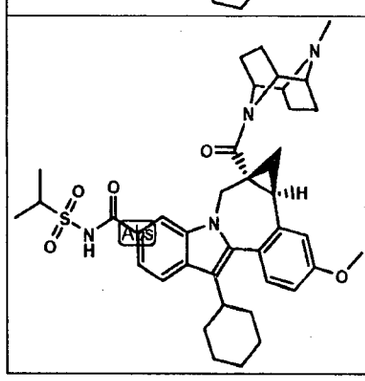
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Estructura	IC_{50}	EC_{50}
		
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	B	B
	B	B
	B	B

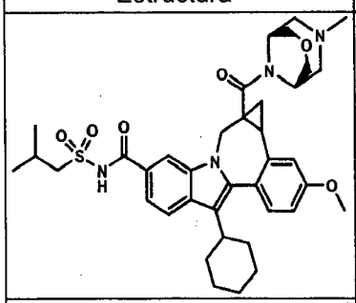
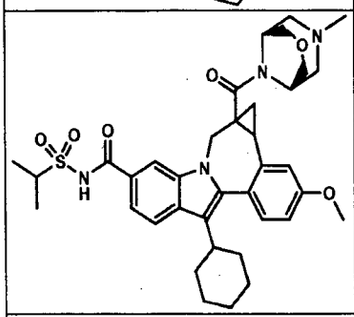
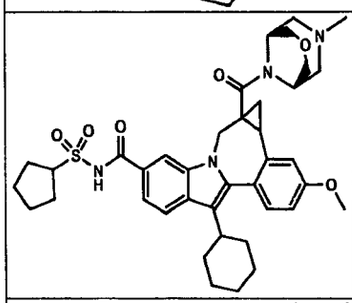
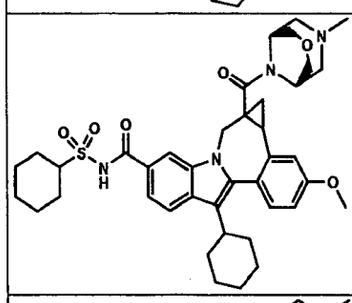
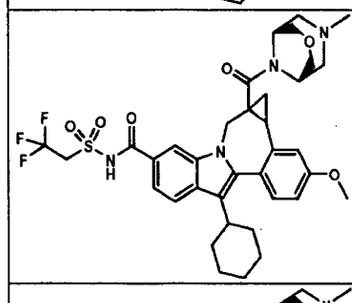
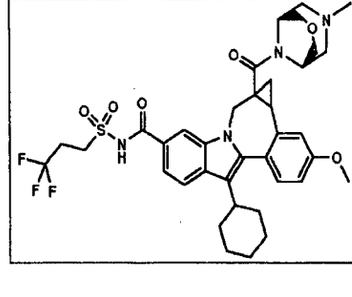
Estructura	IC_{50}	EC_{50}
	B	B
	B	B
	B	B
	B	B
	B	B

000264

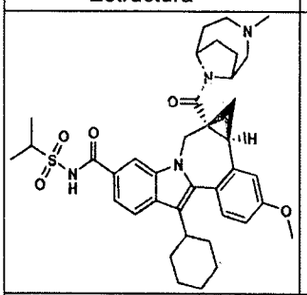
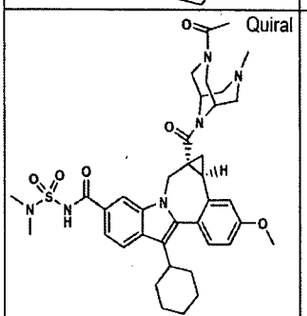
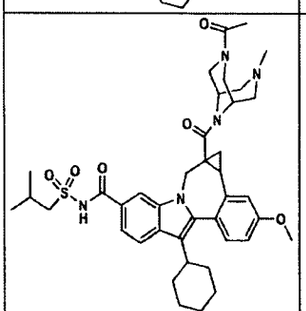
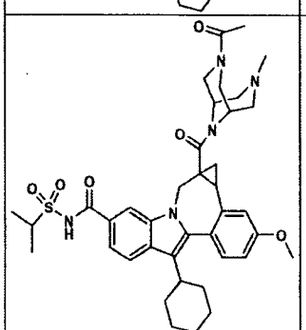
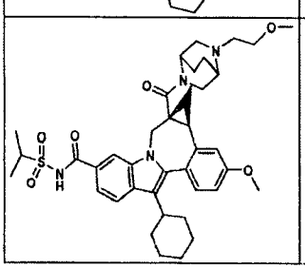
Estructura	IC_{50}	EC_{50}
	B	B
	B	B
	B	B
	B	B
	B	B

Estructura	IC_{50}	EC_{50}
	B	B
	B	B
	B	B
	B	B
	B	B

000266

Estructura	IC_{50}	EC_{50}
	B	B
	B	B
	B	B
	B	B
	B	B
	B	B

000267

Estructura	IC_{50}	EC_{50}
	B	B
 Quiral	B	B
		
		
	B	B

A>0.5 µM; B 0.0024 µM - 0.5 µM; C <0.02 µM pero un valor exacto no se determinó; D>0.04 µM pero un valor exacto no se determió; E<0.07 µM pero un valor exacot no se determinó; G >0.5 µM hasta 5.0µM; H>1.0 µM pero un valor exacto no se determinó.

000268

Composiciones farmacéuticas y métodos de tratamiento

Los compuestos demuestran actividad contra NS5B del VHC y pueden ser útiles en el tratamiento del VHC y la infección por VHC. Por lo tanto, otro aspecto de la invención es una composición que comprende un compuesto, o una sal farmacéuticamente aceptable del mismo, y un portador farmacéuticamente aceptable.

Otro aspecto de la invención es una composición que comprende además un compuesto que tiene actividad anti-VHC.

Otro aspecto de la invención es una composición donde el compuesto que tiene actividad anti-VHC es un interferón. Otro aspecto de la invención es donde el interferón se selecciona del interferón alfa 2B, interferón alfa pegilado, interferón de consenso, interferón alfa 2A, e interferón tau de linfoblastoide.

Otro aspecto de la invención es una composición donde el compuesto que tiene actividad anti-VHC es una ciclosporina. Otro aspecto de la invención es donde la ciclosporina es ciclosporina A.

Otro aspecto de la invención es una composición donde el compuesto que tiene actividad anti-VHC se selecciona del grupo que consiste de interleucina 2, interleucina 6, interleucina 12, un compuesto que aumenta el desarrollo de una respuesta de célula T auxiliar tipo 1, ARN de interferencia, ARN anti-sentido, Imiqimod, ribavirina, un inhibidor de deshidrogenasa

000269

de 5'-monofosfto, amantadina, y rimantadina.

Otro aspecto de la invención es una composición donde el compuesto que tiene actividad anti-VHC es efectivo para inhibir la función de un objetivo seleccionado de metaloproteasa del VHC, serina proteasa del VHC, polimerasa del VHC, helicasa del VHC, proteína NS4B del VHC, entrada del VHC, ensamble del VHC, salida del VHC, proteína NS5A VHC, IMPDH, y un análogo de nucleósido para el tratamiento de una infección por VHC.

Otro aspecto de la invención es una composición que comprende un compuesto, o una sal farmacéuticamente aceptable del mismo, un portador farmacéuticamente aceptable, un interferón y ribavirina.

Otro aspecto de la invención es un método para inhibir la función del replicón del VHC que comprende poner en contactyo el replicón del VHC con un compuesto o una sal farmacéuticamente aceptable del mismo.

Otro aspecto de la invención es un método para inhibir la función de la proteína NS5B del VHC que comprende poner en contacto la proteína NS5B del VHC con un compuesto o una sal farmacéuticamente aceptable del mismo.

Otro aspecto de la invención es un método para tratar una infección por VHC en un paciente que comprende administrar al paciente una cantidad terapéuticamente efectiva de un compuesto o una sal farmacéuticamente aceptable del mismo. En

000270

otra modalidad el compuesto es efectivo para inhibir la función del replicón del VHC. En otra modalidad el compuesto es efectivo para inhibir la función de la proteína NS5B del VHC.

Otro aspecto de la invención es un método para tratar una infección por VHC en un paciente que comprende administrar al paciente una cantidad terapéuticamente efectiva de un compuesto, o una sal farmacéuticamente aceptable del mismo, en conjunto con (previo a, después de, o concurrentemente con) otro compuesto que tiene actividad anti-VHC.

Otro aspecto de la invención es el método donde el otro compuesto que tiene actividad anti-VHC es un interferón.

Otro aspecto de la invención es el método donde el interferón se selecciona de interferón alfa 2B, interferón alfa pegilado, interferón de consenso, interferón alfa 2A, e interferón tau de linfoblastoide.

Otro aspecto de la invención es el método donde el otro compuesto que tiene actividad anti-VHC es una ciclosporina.

Otro aspecto de la invención es el método donde la ciclosporina es ciclosporina A.

Otro aspecto de la invención es el método donde el otro compuesto que tiene actividad anti-VHC se selecciona de interleucina 2, interleucina 6, interleucina 12, un compuesto que aumenta el desarrollo de una respuesta de célula T auxiliar tipo 1, ARN de interfernecia, ARN anti-sentido,

000271

Imiqimod, ribavirina, un inhibidor de inosina 5'-monofosfato deshidrogenasa, amantadina, y rimantadina.

Otro aspecto de la invención es el método donde el otro compuesto que tiene actividad anti-VHC es efectivo para inhibir la función de un objetivo seleccionado del grupo que consiste de metaloproteasa del VHC, serina proteasa del VHC, polimerasa del VHC, helicasa del VHC, proteína NS4B del VHC, entrada del VHC, ensamble del VHC, salida del VHC, proteína NS5A del VHC, IMPDH, y un análogo de nucleósido para el tratamiento de una infección por VHC.

Otro aspecto de la invención es el método donde el otro compuesto que tiene actividad anti-VHC es efectivo para inhibir la función del objetivo en el ciclo de vida del VHC diferente al de la proteína NS5B del VHC.

"Terapéuticamente efectiva" significa la cantidad de agente requerido para proporcionar un beneficio al paciente significativo como se entiende por los médicos en el campo de hepatitis y la infección por VHC.

"Paciente" significa una persona infectada con el virus del VHC y es adecuada para terapia como se entiende por los médicos en el campo de la hepatitis y la infección por VHC.

"Tratamiento," "terapia," "régimen," "infección por VHC," y términos relacionados se usan como se entiende por los médicos en el campo de la hepatitis y la infección por VHC.

Los compuestos de esta invención se dan generalmente como

composiciones farmacéuticas que comprenden de una cantidad terapéuticamente efectiva de un compuesto o su sal farmacéuticamente aceptable y un portador farmacéuticamente aceptable y pueden contener excipientes convencionales. Una cantidad terapéuticamente efectiva es aquella que se necesita para proporcionar un beneficio al paciente significante. Los portadores farmacéuticamente aceptables son aquellos portadores convencionalmente conocidos que tienen perfiles de seguridad aceptables. Las composiciones abarcan todas las fromas sólidas y líquidas comunes incluyendo cápsulas, comprimidos, pastillas, y polvos así como suspensiones líquidas, jarabes, elíxeres, y soluciones. Las composiciones se hacen usando técnicas de formulación comunes, y excipientes convencionales (tales como agentes de enlace y humectantes) y vehículos (tales como agua y alcoholes) se usan generalmente para las composiciones.

Las composiciones sólidas se formulan normalmente en unidades de dosificación y composiciones que proporcionan desde alrededor de 1 hasta 1000 mg del ingrediente activo por dosis se prefieren. Algunos ejemplos de dosificaciones son 1 mg, 10 mg, 100 mg, 250 mg, 500 mg, y 1000 mg. Generalmente, otros agentes se presentarán en un rango de unidad similar a los agentes de tal clase usada clínicamente. Típicamente, esto es 0.25-1000 mg/unidad.

Las composiciones líquidas están usualmente en rangos de

unidad de dosificación. Generalmente, la composición líquida estará en un rango de dosificación unitaria de 1-100 mg/mL. Algunos ejemplos de dosificaciones son 1 mg/mL, 10 mg/mL, 25 mg/mL, 50 mg/mL, y 100 mg/mL. Generalmente, otros agentes estarán presentes en un rango de unidad similar a los agentes de tal clase usada clínicamente. Típicamente, esto es 1-100 mg/mL.

La invención abarca todos los modos convencionales de administración; son preferidos los métodos orales y parenterales. Generalmente, el régimen de dosificación será similar a otros agentes usados clínicamente. Típicamente, la dosis diaria será 1-100 mg/kg de peso corporal diario. Generalmente, más compuesto se requiere oralmente y menos parenteralmente. El régimen de dosificación específico, sin embargo, se determinará por un médico usando el juicio médico sólido.

La invención también abarca métodos donde el compuesto se da en terapia de combinación. Esto es, el compuesto puede usarse en conjunto con, pero separadamente de, otros agentes útiles en el tratamiento de hepatitis y la infección por VHC. En estos métodos de combinación, el compuesto generalmente se dará en una dosis diaria de 1-100 mg/kg de peso corporal diario en conjunto con otros agentes. Los otros agentes generalmente se darán en las cantidades usadas terapéuticamente. El régimen de dosificación especíifico, sin

embargo, se determinará por un médico usando el juicio médico sólido.

Algunos ejemplos de los compuestos adecuados para las composiciones y métodos se enlistan en la Tabla 2.

Tabla 2.

Nombre comercial	Tipo de inhibidor u objetivo	Compañía fuente
Omega IFN	INF-α	Intarcia Therapeutics
BILN-2061	Inhibidor de serina proteasa	Boehringer Ingelheim Pharma KG, Ingelheim, Alemania
Summetrel	Antivírico	Endo Pharmaceuticals Holdings Inc., Chadds Ford, PA
Roferon A	IFN-α2a	F. Hoffmann-La Roche LTD, Basel, Suiza
Pegasys	IFN-α2a PEGilado	F. Hoffmann-La Roche LTD, Basel, Suiza
Pegasys y Ribavirina	IFN-α2a/ribavirina PEGilada	F. Hoffmann-La Roche LTD, Basel, Suiza
Wellferon	IFN-αn1 de linfoblastoide	GlaxoSmithKline plc, Uxbridge, RU
Albuferon-α	IFN-α2b de albúmina	Human Genome Sciences Inc., Rockville, MD
Levovirina	Ribavirina	ICN Pharmaceuticals, Costa Mesa, CA
IDN-6556	Inhibidor de caspasa	Idun Pharmaceuticals Inc., San Diego, CA
IP-501	Antifibrótico	Indevus Pharmaceuticals Inc., Lexington, MA

000275

Nombre comercial	Tipo de inhibidor u objetivo	Compañía fuente
Actimmune	INF-γ	InterMune Inc., Brisbane, CA
Infergen A	Alfacon-1 IFN	InterMune Pharmaceuticals Inc., Brisbane, CA
ISIS 14803	Antisentido	ISIS Pharmaceuticals Inc., Carlsbad, CA/Elan Pharmaceuticals Inc., New York, NY
JTK-003	Inhibidor de RdRp	Japan Tobacco Inc., Tokyo, Japón
Pegasys y Ceplene	Modulador de IFN-α2a/inmune PEGilado	Maxim Pharmaceuticals Inc., San Diego, CA
Ceplene	Modulador inmune	Maxim Pharmaceuticals Inc., San Diego, CA
Civacir	Inmunosupresor IgG del VHC	Nabi Biopharmaceuticals Inc., Boca Raton, FL
Intron A y Zadaxin	IFN-α2b/α1-timosina	RegeneRx Biopharmaceuticals Inc., Bethesda, MD/SciClone Pharmaceuticals Inc., San Mateo, CA
Levovirin	Inhibidor de IMPDH	Ribapharm Inc., Costa Mesa, CA
Viramidine	Profármaco de ribavirina	Ribapharm Inc., Costa Mesa, CA
Heptazyme	Ribozima	Ribozyme Pharmaceuticals Inc., Boulder, CO
Intron A	IFN-α2b	Schering-Plough Corporation, Kenilworth, NJ
PEG-Intron	IFN-α2b PEGilado	Schering-Plough Corporation, Kenilworth, NJ
Rebetron	IFN-α2b/ribavirina	Schering-Plough Corporation, Kenilworth, NJ

Nombre comercial	Tipo de inhibidor u objetivo	Compañía fuente
Ribavirin	Ribavirina	Schering-Plough Corporation, Kenilworth, NJ
PEG-Intron/ Ribavirin	IFN-α2b/ribavirina PEGilada	Schering-Plough Corporation, Kenilworth, NJ
Zadazim	Modulador inmune	SciClone, Pharmaceuticals Inc., San Mateo, CA
Rebif	IFN-β1a	Serono, Geneva, Suiza
IFN-β y EMZ701	IFN-β y EMZ701	Transition Therapeutics Inc., Ontario, Canadá
Batabulin (T67)	Inhibidor de β-tubulina	Tularik Inc., South San Francisco, CA
Merimepodib (VX-497)	Inhibidor de IMPDH	Vertex Pharmaceuticals Inc., Cambridge, MA
Telaprevir (VX-950, LY-570310)	Inhibidor de NS3 serina proteasa	Vertex Pharmaceuticals Inc., Cambridge, MA/Eli Lilly y Co. Inc., Indianapolis, IN
Omniferon	IFN-α natural	Viragen Inc., Plantation, FL
XTL-6865 (XTL-002)	Anticuerpo monoclonal	XTL Biopharmaceuticals Ltd., Rehovot, Isreal
HCV-796	Inhibidor de la replicasa NS5B	Wyeth/Viropharma
NM-283	Inhibidor de la replicasa NS5B	Idenix / Novartis
GL-59728	Inhibidor de la replicasa NS5B	Gene Labs / Novartis
GL-60667	Inhibidor de la replicasa NS5B	Gene Labs / Novartis
2'C MeA	Inhibidor de la replicasa NS5B	Gilead
PSI 6130	Inhibidor de la replicasa NS5B	Roche
R1626	Inhibidor de la replicasa NS5B	Roche
SCH 503034	Inhibidor de la serina proteasa	Schering Plough

000277

Nombre comercial	Tipo de inhibidor u objetivo	Compañía fuente
NIM811	Inhibidor de ciclofilina	Novartis
Suvus	Azul de metileno	Bioenvision
Multiferon	IFN de larga duración	Viragen/Valentis
Actilon (CPG10101)	Agonista TLR9	Coley
Interferon-β	Interferón-β-1a	Serono
Zadaxin	Inmunomodulador	Sciclone
Pyrazolopyrimidine compounds and salts from WO-2005047288 26 may 2005	Inhibidor del VHC	Arrow Therapeutics Ltd.
2'C methyl adenosine	Inhibidor de la replicasa NS5B	Merck
GS-9132 (ACH-806)	Inhibidor del VHC	Achillion/Gilead

Descripción Detallada de la Invención

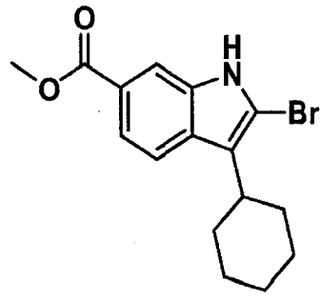
A menos que se especifique de otra manera, los datos CLEM analíticos en los siguientes Compuesto intermedios y ejemplos se adquirieron usando las siguientes columnas y condiciones. Tiempo de paro: Tiempo de gradiente + 1 minuto; Cono de inicio: B al 0% a menos que se anote de otra manera; Eluyente A: CH_3CN al 5%/H_2O al 95% con NH_4OAc al 10 mM (para las columnas A, D y E); MeOH al 10%/H_2O al 90% con TFA al 0.1% (para las columnas B y C); Eluyente B: CH_3CN al 95%/H_2O al 5% con NH_4OAc al 10 mM (para las columnas A, D y E); MeOH al 90%/H_2O al 10% con TFA al 0.1% (para las columnas B y C); Columna A: Phenomenex 10µ 4.6 x 50 mm C18; Columna B:

000278

Phenomenex C18 10µ 3.0 x 50 mm; Columna C: Phenomenex 4.6 x 50 mm C18 10µ; Columna D: Phenomenex Lina C18 5µ 3.0 x 50 mm; Columna E: Phenomenex 5µ 4.6 x 50 mm C18.

Como artefacto del software usado, algunas estructuras químicas tienen algunos átomos de hidrógeno omitidos.

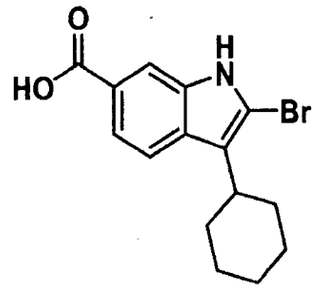
Compuesto Intermedio 1



Acido 1H-indol-6-carboxílico, 2-bromo-3-ciclohexilo, éster de metilo. El tribromuro de piridinio recientemente recristalizado (recristalización de AcOH caliente (5 mL por 1 g), enjuagado con AcOH frío y secado bajo alto vacío sobre KOH) se agregó en porciones (durante 10 min.) a una solución agitada de 3-ciclohexil-1H-indol-6-carboxilato de metilo (60 g, 233 mmol) (preparada usando los procedimientos descritos en WO2004/065367) en $CHCl_3$/THF (1:1, 1.25 L) a 2°C. La solución de reacción se agitó a 0-5°C durante 2.5h, y se lava con $NaHSO_3$ acuoso saturado (1 L), HCl 1 N (1 L) y salmuera (1 L). La capa orgánica se secó ($MgSO_4$) y se concentra. El aceite rojo resultante se diluyó con Et_2O y se concentra. El sólido rosa resultante se disolvió en Et_2O (200 mL) tratado con hexanos (300 mL) y se concentra pacialmente. Los sólidos se rerecolectaron por filtración y se enjuagan con hexanos. El

lícor madre se concentró hasta secarse y el procedimiento se repite. Los sólidos se combinaron para proporcionar ácido 1H-indol-6-carboxílico, 2-bromo-3-ciclohexilo, éster de metilo (64 g, 190 mmol, 82%) como un sólido rosa suave, el cual se usó sin purificación adicional. 1HRMN (300 MHz, $CDCl_3$) δ 8.47 (br s, 1H), 8.03 (d, J = 1.4 Hz, 1H), 7.74 (dd, J = 1.4, 8.8 Hz, 1H), 7.69 (d, J = 8.8 Hz, 1H), 3.92 (s, 3H), 2.82 (tt, J = 3.7, 11.7 Hz, 1H), 1.98 - 1.72 (m, 7H), 1.50 - 1.27 (m, 3H). 13CRMN (75 MHz, CDCl3) δ 168.2, 135.6, 130.2, 123.1, 120.8, 120.3, 118.7, 112.8, 110.7, 52.1, 37.0, 32.2(2), 27.0(2), 26.1. CLEM: m/e 334 $(M-H)^+$, tiempo de retención 3.34 min, columna A, gradiente de 4 minutos.

Compuesto Intermedio 2



Acido 1H-indol-6-carboxílico, 2-bromo-3-ciclohexilo. Una solución de 2-bromo-3-ciclohexil-1H-indol-6-carboxilato de metilo (20 g, 60 mmol) y LiOH (3.8 g, 160 mmol) en MeOH/THF/H_2O (1:1:1, 300 mL) se calentó a 90°C durante 2h. La mezcla de reacción se enfrió en un baño de hielo/H_2O, se neutraliza con HCl 1M (~160 mL) diluida con H_2O (250 mL) y se agita durante 1h a temperatura ambiente. Los precipitados se

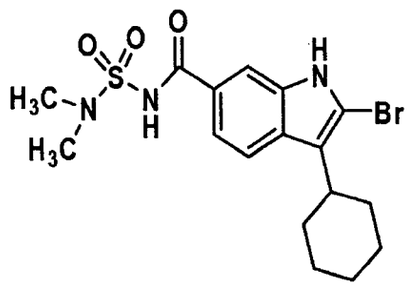
000280

rerecolectaron por filtración se enjuagan con H_2O y se secan para proporcionar ácido 1H-indol-6-carboxílico, 2-bromo-3-ciclohexilo (cant.) el cual se usó sin purificación adicional.

Un procedimiento alternativo que puede usarse para proporcionar ácido 1H-indol-6-carboxílico, 2-bromo-3-ciclohexilo se describe a continuación:

Una solución de 2-bromo-3-ciclohexil-1H-indol-6-carboxilato de metil (117 g, 349 mmol) y $LiOH.H_2O$ (26.4 g, 629 mmol) en MeOH/THF/H2O (1:1:1, 1.8 L) se calentó a reflujo durante 3h. La mezcla de reacción se enfrió en un baño de hielo/H_2O hasta ~2°C, se neutraliza con HCl 1M (~650 mL) (se agrega a tal velocidad que la temperatura no excede 5°C), diluida con H2O (1 L) y se agita mientras de calienta hasta temperatura ambiente. Los precipitados se rerecolectaron por filtración se enjuagan con H_2O y se secan para proporcionar el solvato mono THF del ácido 1H-indol-6-carboxílico, 2-bromo-3-ciclohexilo (135.5 g, 345 mmol, 99%) como un sólido amarillo, el cual se usó sin purificación adicional. 1HRMN (300 MHz, $CDCl_3$) δ 11.01 (br s, 1H), 8.77 (s, 1H), 8.07 (d, J = 1.5 Hz, 1H), 7.82 (dd, J = 1.5, 8.8 Hz, 1H), 7.72 (d, J = 8.8 Hz, 1H), 3.84 - 3.74 (m, 4H), 2.89 (m, 1H), 1.98 - 1.72 (m, HH), 1.50 - 1.24 (m, 3H). 13CRMN (75 MHz, CDC13) δ 172.7, 135.5, 130.7, 122.3, 120.9(2), 118.8, 113.3, 111.1, 67.9(2), 37.0, 32.2(2), 27.0(2), 26.1, 25.5(2). CLEM: m/e 320 $(M-H)^-$, tiempo de retención 2.21 min, columna A, gradiente de 4 minutos.

Compuesto Intermedio 3



1H-indol-6-carboxamida, 2-bromo-3-ciclohexil-N-[(dimetilamino)sulfonilo]. El 1,1'-carbonildiimidazol (1.17 g, 7.2 mmol) se agregó a una solución agitada de ácido 2-bromo-3-ciclohexil-1H-indol-6-carboxílico (2.03 g, 6.3 mmol) en THF (6 mL) a 22°C. La evolución de CO_2 fue instantánea y cuando fue lenta la solución se calentó a 50°C durante 1 hr y luego se enfría hasta 22°C. La N,N-dimetilsulfamida (0.94 g, 7.56 mmol) se agregó seguido por la adición gota a gota de una solución de DBU (1.34 g ,8.8 mmol) en THF (4 mL). Se continuó agitando durante 24 hr. La mezcla se dividió entre acetato de etilo y HCl diluido. La capa de acetato de etilo se lavó con agua seguido por salmuera y se seca sobre Na_2SO_4. El extracto se concentró hasta secarse para dejar el producto del título como una espuma quebradiza amarillo pálido, (2.0 g, 74 %, >90% de pureza, estimado de RMN). 1H RMN (300 MHz, DMSO-D6) δ ppm 1.28 - 1.49 (m, 3 H) 1.59 - 2.04 (m, 7 H) 2.74 - 2.82 (m, 1 H) 2.88 (s, 6 H) 7.57 (dd, J=8.42, 1.46 Hz, 1 H) 7.74 (d, J=8.78 Hz, 1 H) 7.91 (s, 1 H) 11.71 (s, 1 H) 12.08 (s, 1 H).

Un método alternativo para la preparación de 1H-indol-6-carboxamida, 2-bromo-3-ciclohexil-N-[(dimetilamino)sulfonilo]

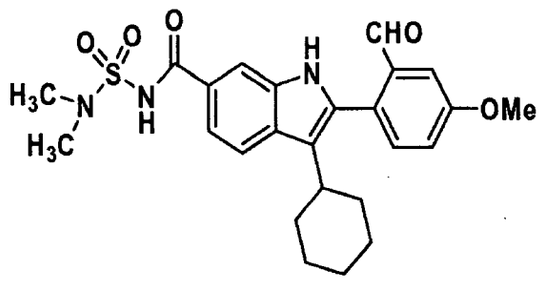
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se describe a continuación.

A un matraz de fondo redondo de cuatro cuellos de 1 L equipado con un agitador mecanico, un controlador de temperatura, una entrada N2, y un condensador, bajo N2, se agregó ácido 2-bromo-3-ciclohexil-1H-indol-6-carboxílico (102.0 g, 0.259 mol) y THF seco (300 mL). Después de agitar durante 10 min, CDI (50.3 g, 0.31 mol) se agregó en porciones. La mezcla de reacción luego se calentó hasta 50°C durante 2 h. Despues se enfría hasta 30°C, la N,N-dimetilaminosulfonamida (41.7 g, 0.336 mol) se agregó en una porción seguido por la adición de DBU (54.1 mL, 0.362 mol) gota a gota durante un periodo de 1 h. La mezcla de reacción luego se agitó a temperatura ambiente durante 20 h. El solvente se removió in vacuo y el residuo se dividió entre EtOAc y HCl 1 N (1:1, 2 L). La capa orgánica se separó y la capa acuosa se extrajo con EtOAc (500 mL). Las capas orgánicas combinadas se lavaron con salmuera (1.5 L) y se secan sobre MgSO4. La solución se filtró y se concentró in vacuo para dar el producto crudo (111.0 g). El producto crudo se suspendió en EtOAc (400 mL) a 60°C. A la suspensión se agregó heptano (2 L) lentamente. La suspensión resultante se agitó y enfrió hasta 0°C. Luego se filtró. La torta de filtración se enjuagó con cantidad pequeña de heptano y se seca con aire al vacío alojado durante 2 días. El producto se recolectó como un sólido blanco (92.0 g, 83%). ^{1}H RMN (MeOD, 300 MHz) δ 7.89 (s, H), 7.77 (d, J= 8.4 Hz, 1H),

7.55 (dd, J= 8.4 y 1.8 Hz, 1H), 3.01 (s, 6H), 2.73-2.95 (m, 1H), 1.81-2.05 (m, 8H), 1.39-1.50 (m, 2H); m/z 429 $(M + H)^+$.

Compuesto Intermedio 4



1H-indol-6-carboxamida, 3-ciclohexil-N-[(dimetilamino)sulfonil]-2-(2-formil-4-metoxifenilo). Una mezcla de la N-[(dimetilamino)sulfonil]-1H-indol-6-carboxamida de 2-Bromo-3-ciclohexilo (4.28 g, 0.01 mol), ácido 4-metoxi-2-formilfenil borónico (2.7 g, 0.015 mol), 2-diciclohexilfosfino-2',6'-dimetoxi-bifenilo (41 mg, 0.0001 mol), acetato de paladio (11.2 mg), y carbonato de potasio finamente molido (4.24 g, 0.02 mol) en tolueno (30 mL) se agitó bajo reflujo y bajo nitrógeno durante 30 min, en cuyo tiempo el análisis CL/EM muestra que la reacción se ha completado. La mezcla de reacción luego se diluyó con acetato de etilo y agua, y luego se hace ácida con un exceso de HCl diluido. La capa de acetato de etilo luego se recolectó y se lava con HCl dluido, agua y salmuera. La solución orgánica luego se secó (sulfato de magnesio), se filtra y se concentra para dar una goma. La goma se diluyó con hexanos (250 ml) y acetato de etilo (25 mL), y la mezcla se agitó durante 20 hr a 22°C durante cuyo tiempo el producto se transformó en un

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sólido granular amarillo brillante (4.8 g) el cual se usó directamente sin purificación adicional.

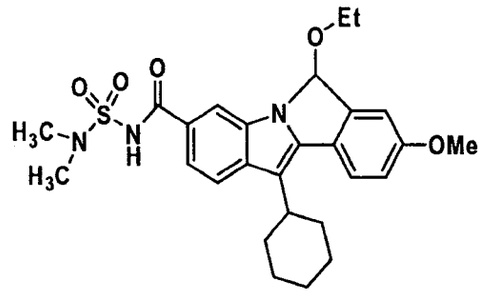
Un procedimiento alternativo para la preparación de 1H-indol-6-carboxamida, 3-ciclohexil-N-[(dimetilamino)sulfonil]-2-(2-formil-4-metoxifenilo) se proporciona a continuación:

A una solución en mezcla espesa de 2-bromo-3-ciclohexil-N-[(dimetilamino)sulfonil]-indol-6-carboxamida (54.0 g, 126 mmol), ácido 4-metoxi-2-formilfenilborónico (29.5 g, 164 mmol) y LiCl (13.3 g, 315 mmol) en EtOH/tolueno (1:1, 1 L) se agregó una solución de Na_2CO_3 (40.1 g, 379 mmol) en agua (380 mL). La mezcla de reacción se agitó 10 min. y luego Pd(PPh3)4 (11.3 g, 10.0 mmol) se agregó. La solución de reacción se enjuagó con nitrógeno y calentó a 70°C (monitoreo interno) durante la noche y luego se enfría hasta temperatura ambiente. La reacción se diluyó con EtOAc (1 L) y EtOH (100 mL), se lava cuidadosamente con HCl acuoso 1N (1 L) y salmuera (500 mL), se seca (MgSO4), se filtra y se concentra. Los sólidos residuales se agitaron con Et2O (600 mL) durante 1h y se recolectan por filtración para proporcionar 1H-indol-6-carboxamida, 3-ciclohexil-N-[(dimetilamino)sulfonil]-2-(2-formil-4-metoxifenilo) (52.8g, 109 mmol, 87%) como un polvo amarillo el cual se usó sin purificación adicional. 1HRMN (300 MHz, d6-DMSO) δ 11.66 (s, 1H), 8.17 (s, 1H), 7.75 (d, J = 8.4 Hz, 1H), 7.74 (d, J = 8.4 Hz, 1H), 7.59 (dd, J = 1.4, 8.4 Hz, 1H), 7.23 - 7.16 (m, 2H), 7.08 (dd, J = 2.6, 8.4 Hz, 1H), 6.54 (d, J =

000285

8.8 Hz, 1H), 3.86 (s, 3H), 3.22 - 3.08 (m, 1H), 2.91 (s, 6H), 2.00 - 1.74 (m, 7H), 1.60 - 1.38 (m, 3H). 13CRMN (75 MHz, CDCl3) δ 165.7, 158.8, 147.2, 139.1, 134.3, 132.0, 123.4, 122.0, 119.2, 118.2, 114.8, 112.3, 110.4, 109.8, 79.6, 45.9, 37.2(2), 34.7, 32.0(2), 25.9(2), 24.9. CLEM: m/e 482 $(M-H)^-$, tiempo de retención 2.56 min, columna A, gradiente de 4 minutos.

Compuesto Intermedio 5



6H-isoindol[2,1-a]indol-3-carboxamida, 11-ciclohexil-N-[(dimetilamino)sulfonil]-6-etoxi-8-metoxi. A un matraz de fondo redondo de cuatro cuellos de 5 L equipado con un controlador de temperatura, un condensador, una entrada N2 y un agitador mecánico, se cargó tolueno (900 mL), EtOH (900 mL), 2-bromo-3-ciclohexil-N-(N,N-dimetilsulfamoil)-1H-indol-6-carboxamida (90 g, 0.21 mol), ácido 2-formil-4-metoxifenilborónico (49.2 g, 0.273 mol) y LiCl (22.1 g, 0.525 mol). La solución resultante se burbujeó con N_2 durante 15 mins. Una solución de Na_2CO_3 (66.8 g, 0.63 mol) en H_2O (675 mL) se agregó y la mezcla de reacción se burbujeó con N_2 durante otros (10 mins). $Pd(PPh_3)_4$ (7.0 g, 6.3 mmol) se agregó y la mezcla de

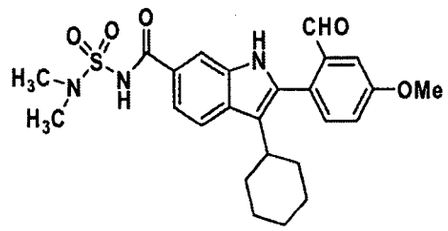
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reacción se calentó hasta 70°C durante 20 h. Después de enfriarse hasta 35°C, una solución de HCl 1 N (1.5 L) se agregó lentamente. La mezcla resultante se transfirió a un embudo de separación de 6 L y se extrae con EtOAc (2 X 1.5 L). Los extractos orgánicos combinados se lavaron con salmuera (2 L), se secan sobre MgSO4, se filtran y se concentran in vacuo para dar un sólido amarillo, el cual se trituró con EtOAc al 20% en hexano (450 mL, 50°C hasta 0°C) para dar 3-ciclohexil-N-(N,N-dimetilsulfamoil)-2-(2-formil-4-metoxifenil)-1H-indol-6-carboxamida (65.9 g) como un sólido amarillo. Pureza HPLC, 98%.

El lícor madre de la trituración se concentró in vacuo. El residuo se puso a reflujo con EtOH (50 mL) durante 3 h. La solución luego se enfrió hasta 0°C. Los precipitados se filtraron y se lavaron con TBME enfriado (5°C) (20 mL). La torta filtro se secó con aire al vacío alojado para dar una cantidad adicional del compuesto del título como un sólido blanco (16.0 g). Pureza HPLC, 99%. ^{1}H RMN (CDCl3, 300 MHz) δ 8.75 (s, 1H), 7.96 (s, 1H), 7.73 (d, J= 8.4 Hz, 1H), 7.67 (d, J= 8.4 Hz, 1H), 7.45 (dd, J= 8.4 y 1.4 Hz, 1H), 7.09 (d, J= 2.2 Hz, 1H), 6.98 (dd, J= 8.4 y 2.2 Hz, 1H), 6.50 (s, 1H), 3.86 (s, 3H), 3.05 (s, 6H), 2.92-3.13 (m, 3H), 1.85-1.93 (m, 7 H), 1.40-1.42 (m, 3H), 1.05 (t, J= 7.1 Hz, 3H). m/z 512 $(M + H)^+$.

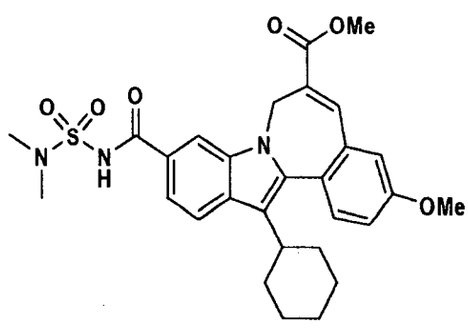
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Compuesto Intermedio 6



1H-indol-6-carboxamida, 3-ciclohexil-N-[(dimetilamino)sulfonil]-2-(2-formil-4-metoxifenilo). La 11-ciclohexil-N-(N,N-dimetilsulfamoil)-6-etoxi-8-metoxi-6H-isoindol[2,1-a]indol-3-carboxamida se disolvió en THF (75 mL). A la solución se agregó una solución de HCl 2 N (300 mL). La mezcla se agitó vigorosamente bajo N2 a temperatura ambiente durante 16 h. La suspensión resultante se filtró y se lavó con TBME enfriado (2 X 30 mL). La torta filtro se secó con aire al vacío durante la noche para dar el compuesto del título como un sólido amarillo. Pureza HPLC, 99% ^{1}H RMN (DMSO-d6, 300 MHz) δ 11.65 (s, 1H), 8.16 (s, 1H), 7.76 (d, J= 5.9 Hz, 1H), 7.73 (d, J= 5.9 Hz, 1H), 7.58 (dd, J= 8.5 y 1.5 Hz, 1H), 7.17-7.20 (m, 2H), 7.08 (dd, J = 8.5 y 1.4 Hz, 1H), 6.55 (d, J= 8.6 Hz, 1H), 3.86 (s, 3H), 3.14-3.18 (m, 1H), 2.91 (s, 6H), 1.75-1.99 (m, 7H), 1.48-1.60 (m, 3H); m/z 484 (M + H)+.

Compuesto intermedio 7



000288

Acido 7H-indol[2,1-a][2]benzazepin-6-carboxílico, 13-ciclohexil-10-[[[(dimetilamino)sulfonil]amino]carbonil]-3-metoxi, éster de metilo. Una mezcla de la 3-ciclohexil-N-(N,N-dimetilsulfamoil)-2-(2-formil-4-metoxifenil)-1H-indol-6-carboxamida (4.8g, 0.01 mol), 2-(dimetoxifosforil)acrilato de metilo (9.7 g, 0.02 mol) y carbonato de cesio (7.1 g, 0.02 mol) en DMF (28 mL) se agitó durante 20 hr en una temperatura de baño de aceite de 55°C. La mezcla se vació en agua con hielo y se hizo ácida con HCl diluido para precipitar el producto crudo. El sólido se recolectó, se secó y procesó por cromatografía instantánea en SiO_2 (110 g) usando una solución de acetato de etilo y cloruro de metileno (1:10) que contiene ácido acético al 2%. Las fracciones homogéneas se combinaron y evaporaron para proporcionar el compuesto del título como un sólido amarillo pálido (3.9g, 71% de rendimiento). EM: 552 (M=H+).

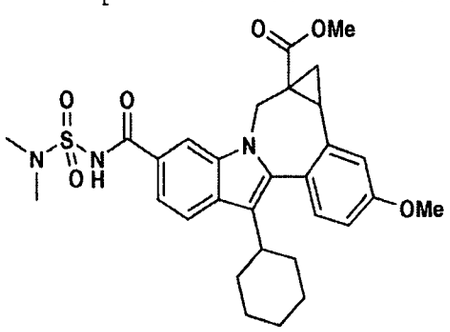
Un procedimiento alternativo para la preparación de ácido 7H-indol[2,1-a][2]benzazepin-6-carboxílico, 13-ciclohexil-10-[[[(dimetilamino)sulfonil]amino]carbonil]-3-metoxi, éster de metilo se proporciona a continuación.

Una solución de 11-ciclohexil-N-[(dimetilamino)sulfonil]-6-hidroxi-8-metoxi-6H-isoindol[2,1-a]indol-3-carboxamida (hemiaminal cíclico) (63.0 g, 130 mmol), 2-(dimetoxifosforil)acrilato de metilo (60 g, 261 mmol), carbonato de cesio (106 g, 326 mmol) en DMF (400 mL) se

000289

calentó a 60°C (temperatura del baño) durante 4.5h. El 2-(dimetoxifosforil)acrilato de metilo adicional (15 g, 65 mmol) y carbonato de cesio (21.2 g, 65 mmol) se agregaron y la reacción se calentó entonces a 60°C durante la noche y se enfrío a temperatura ambiente. La mezcla de reacción agitada se diluyó con H_2O (1 L), lentamente se neutraliza con HCl acuoso 1N (800 mL), se agita 3h, y luego los precipitados se rerecolectaron por filtración. Los sólidos se trituraron con Et2O (800 mL) y se secan para proporcionar ácido 7H-indol[2,1-a][2]benzazepin-6-carboxílico de metilo, 13-ciclohexil-10-[[[(dimetilamino)sulfonil]amino]carbonil]-3-metoxi, éster de metilo (70.2 g, 127 mmol, 98%) como un sólido amarillo el cual se usó sin purificación adicional. 1HRMN (300 MHz, CDCl3) δ 8.67 (s, 1H), 8.09 (s, 1H), 7.86 (d, J = 8.4 Hz, 1H), 7.80 (s, 1H), 7.50 (d, J = 8.4 Hz, 1H), 7.42 (d, J = 8.8 Hz, 1H), 7.08 (dd, J = 2.6, 8.8 Hz, 1H), 6.98 (d, J = 2.6 Hz, 1H), 5.75 - 5.51 (m, 1H), 4.29 - 4.01 (m, 1H), 3.89 (s, 3H), 3.82 (s, 3H), 3.05 (s, 6H), 2.87 - 2.73 (m, 1H), 2.11 - 1.12 (m, 10H). CLEM: m/e 550 (M-H)-, tiempo de retención 3.21 min, columna A, gradiente de 4 minutos.

Compuesto intermedio 8



000290

Acido cicloprop[d]indol[2,1-a][2]benzazepin-1a(2H)-carboxílico, 8-ciclohexil-5-[[[(dimetilamino)sulfonil]amino]carbonil]-1,12b-dihidro-11-metoxi, éster de metilo, (+/-)-. DMSO (5 mL) se agregó a una mezcla de yoduro de trimetilsulfoxonio (199 mg, 0.906 mmol) y NaH (38 mg en dispersión de aceite al 60%, 0.953 mmol) en un matraz de fondo redondo. La mezcla de reacción se agitó a temperatura ambiente durante 0.5 hr. El ácido 7H-indol[2,1-a][2]benzazepin-6-carboxílico, 13-ciclohexil-10-[[[(dimetilamino)sulfonil]amino]carbonil]-3-(metoxi)-, éster de metilo (125 mg, 0.227 mmol) luego se agregó y la mezcla de reacción se agitó a temperatura ambiente durante 3 hr., y luego a 50°C durante unas 3 hr adicionales. La reacción luego se apagó con agua y se hizo ácida con solución de HCl 1N. El producto crudo luego se precipita como un sólido amarillo ligero que se recolectó por filtración y se seca con aire, (106 mg, 83% de rendimiento). 6 mg de este material luego se purificó por HPLC preparativa para proporcionar el compuesto del título como un sólido amarillo ligero (1.8 mg). EM m/z 566 (MH^+), Tiempo de retención: 3.850 min. 1H RMN (500 MHz, MeOD) δ ppm 0.28 (m, 0.36 H) 1.19 - 2.20 (m, 11.64 H) 2.70 - 3.02 (m, 2 H) 3.03 (s, 2.16 H) 3.05 (s, 3.84 H) 3.49 (d, J=15.26 Hz, 0.64 H) 3.54 (s, 1.92 H) 3.83 (s, 1.08 H) 3.91 (s, 3 H) 4.08 (d, J=15.26 Hz, 0.36 H) 5.29 (d, J=15.26 Hz, 0.36 H) 5.50 (d, J=14.95 Hz, 0.64 H) 6.98 - 7.06 (m, 1 H) 7.16 (d, J=2.44

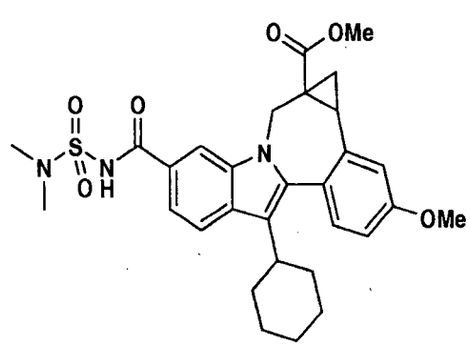
Hz, 0.36 H) 7.23 (d, J=2.44 Hz, 0.64 H) 7.30 (d, J=8.55 Hz, 0.64 H) 7.34 (d, J=8.55 Hz, 0.36 H) 7.56 (dd, J=8.55, 1.53 Hz, 0.64 H) 7.63 (dd, J=8.55, 1.53 Hz, 0.36 H) 7.88 (d, J=8.55 Hz, 0.64 H) 7.91 (d, J=8.55 Hz, 0.36 H) 8.12 (s, 0.36 H) 8.33 (d, J=1.53 Hz, 0.64 H).

Un procedimiento alternativo para la preparación de los compuestos del título se proporciona a continuación.

A un matraz de fondo redondo de 1 L, de cuatro cuellos, secado a la flama equipado con un agitador mecánico, entrada de N2 y un termómetro, bajo N2, se cargó hidruro de sodio (95%) (3.09 g, 129.2 mmol) y DMF seco (200 mL). Con agitación vigorosa, el yoduro de trimetilsulfoxonio (32.5 g, 147.3 mmol) en porciones durante cuyo tiempo la temperatura se eleva hasta 30°C. Despues de agitar durante 30 mins, una solución de ácido 7H-indol[2,1-a][2]benzazepin-6-carboxílico, 13-ciclohexil-10-[[[(dimetilamino)sulfonil]amino]carbonil]-3-(metoxi), éster de metilo (33.8 g, 61.3 mmol) en DMF seco (70 mL) se agregó rápidamente. La mezcla de reacción se agitó debajo de 30°C durante 30 mins y luego se vacia en una solución fría con hielo de HCl 1 N (130 mL) en H2O (2 L) en porciones. Después la suspensión resultante se agitó mecánicamente durante 1 h, los precipitados se filtraron y la torta filtro se lavó con H2O (100 mL). La torta filtro se dividió entre EtOAc y HCl 0.5 N (1:1, 4 L). La fase orgánica se separó, se lavó con H2O (1 L) y salmuera (1 L), se secó sobre $MgSO_4$, se filtró y se

concentró in vacuo. El residuo se disolvió en EtOAc (150 mL), y la solución se filtró a través de una almohadilla de gel de sílice (300 g en hexano) y se enjuagan con EtOAc al 50% en hexano (5 L). El filtrado se concentró in vacuo para dar un sólido ligeramente amarillo que se trituró con EtOAc al 10% en TBME (220 mL) desde 50°C hasta 0°C para dar ácido ciclopropa[d]indol[2,1-a][2]benzazepin-1a(2H)-carboxílico, 8-ciclohexil-5-[[[(dimetilamino)sulfonil]amino]carbonil]-1,12b-dihidro-11-metoxi, éster de metilo, (+/-)- como un sólido blanco (26.1 g, 75% de rendimiento). Pureza HPLC, 100%. ^{1}H RMN (DMSO-d_6, 300 MHz) δ 11.61 (s, 1H), 8.47 (s, 0.5H), 8.25 (s, 0.5H), 7.81-7.88 (m, 1H), 7.57-7.63 (m, 1H), 7.23-7.29 (m, 2H), 7.01-7.07 (m, 1H), 5.43 (d, J = 15.0 Hz, 0.5H), 5.22 (d, J = 15 Hz, 0.5H), 4.04 (dd, J = 15.4 y 6.6 Hz, 0.5H), 3.83 (s, 3H), 3.75 (s, 1H), 3.08-3.47 (m, 0.5H), 3.29 (s, 3H), 2.73-2.92 (m, 8H), 1.11-1.99 (m, 10.5H), 0.20 (m, 0.5H); m/z 566 $(M + H)^+$.

Compuesto intermedio 9



Acido cicloprop[d]indol[2,1-a][2]benzazepin-1a(2H)-carboxílico, 8-ciclohexil-5-[[[(dimetilamino)sulfonil]amino]carbonil]-1,12b-dihidro-11-metoxi, éster de metilo, (-)-. Una muestra de (+/-) ácido cicloprop[d]indol[2,1-a][2]benzazepin-1a(2H)-carboxílico, 8-ciclohexil-5-[[[(dimetilamino)sulfonil]amino]carbonil]-1,12b-dihidro-11-metoxi-éster de metilo se disolvió en EtOH/CH_3CN 1/1 + DEA al 0.5% en una concentración de 50 mg/ml. [La adición de DEA asegura el compuesto restante en la solución durante el proceso de inyección]. Esta solución luego se inyectó en un SFC preparativo Thar SFC-350 bajo las condiciones mostradas a continuación.

Condiciones preparativas en Thar SFC-350: Columna: Chiralcel OJ-H 5x25 cm; fase móvil: MeOH/CH3CN al 25% (1/1) en CO2; presión (bar): 100; velocidad de flujo (ml/ min): 240; concentración de la solución (mg/ml): 50; cantidad de inyección (ml): 4.5-5; tiempo de ciclo (min/inj): 6.5-7; Temperatura (°C): 45; desempeño (g/hr): ~2; longitud de onda del detector (nm): 254.

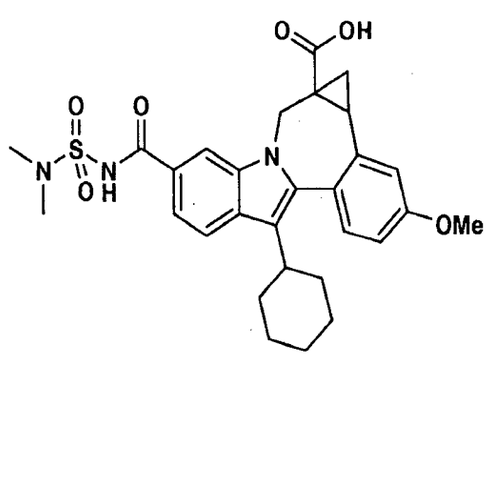
A partir de 371.4 g del material de partida racémico, un total de 177.3 g del segundo isómero (-) eluido deseado se obtuvo, que contiene ~1 Meq de dietilamina. Este material se purificó usando el siguiente procedimiento. La mezcla (24.7 g) se disuelve en diclorometano (800 mL)) se lavó secuencialmente con; HCl 0.5 N (1 x 400 mL, 1 x 240 mL), H_2O (2 x 240 mL), y

000294

salmuera (2 x 240 mL). La capa orgánica luego se secó (Na_2SO_4 anh.), se filtró y evaporó para dar 22.33 g de (ácido cicloprop[d]indol[2,1-a][2]benzazepin-1a(2H)-carboxílico, 8-ciclohexil-5-[[[(dimetilamino)sulfonil]amino]carbonil]-1,12b-dihidro-11-metoxi, éster de metilo, (-)- como un sólido amarillo (92% de recuperación). HPLC[1]> 99% (Tr 2.38 min); CL/EM (ES^+) 566.51 (M+H, 100); $[\alpha]_D^{25C}$ - 194.64° (c 1.03, MeOH). Análisis calculado para $C_{30}H_{35}N_3O_6S \cdot 0.33H_2O$: C, 63.04; H, 6.29; N, 7.35; S, 5.61; H_2O, 1.04. Encontrado: C, 63.07; H, 6.01; N, 7.24; S, 5.58; H_2O, 1.03. La RMN muestra la ausencia de Et_2NH. El EE de este material se determinó para ser >99% usando el siguiente procedimiento HPLC analítico.

Condiciones analíticas de la determinación ee en SFC analitici Thar. Columna analítica: Chiralcel OJ (.46x25cm, lOμl); presión BPR: 100 bars; Temperatura: 35°C; Velocidad de flujo: 3.0 ml/min; Fase móvil: MeOH/CH_3CN al 15% (1/1) en CO2; Longitud de onda del detector: 254 nm; Tiempo de retención (min): 4, 6.5.

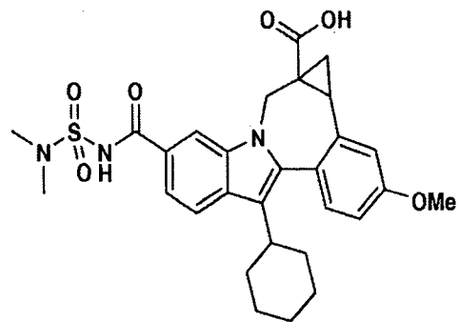
Compuesto intermedio 10



Acido cicloprop[d]indol[2,1-a][2]benzazepin-1a(2H)-carboxílico, 8-ciclohexil-5-[[[(dimetilamino)sulfonil]amino]carbonil]-1,12b-dihidro-11-metoxi-, (-)-. A una solución de (-) ácido cicloprop[d]indol[2,1-a][2]benzazepin-1a(2H)-carboxílico, 8-ciclohexil-5-[[[(dimetilamino)sulfonil]amino]carbonil]-1,12b-dihidro-11-metoxi-, éster de metilo (22.33 g, 39.5 mmol) en MeOH (300 mL) se agregó NaOH 1 N (120 mL) lentamente durante 20 min., mientras se mantiene la temperatura de la reacción <30°C. La mezcla se agitó a temperatura ambiente bajo N_2 durante 18 h. la HPLC indica que la reacción se completó. A la solución de reacción se agregó HCl 1 N (130 mL). Después de que se completó la adición, el pH de la mezcla de reacción fue alrededor de 2. El metanol en la mezcla de reacción se evaporó. Agua (300 mL) se agregó a la mezcla que luego se extrajo con CH_2Cl_2 (1 x 600 mL, 1 x 200 mL). Los extractos combinados se lavaron con H_2O (2 x 300 mL), salmuera (2 x 300 mL), se secaron (Na_2SO_4) y evaporaron para dar 20.82 g (96% de rendimiento) del compuesto del título como un sólido amarillo. Condiciones HPLC columna: Phenomenoex Synergi Polar-RP 4 um 4.6 x 50 mm; UV: 220 nm; tiempo del gradiente: 4 min; velocidad de flujo: 4 mL/min, B al 75 - 100%; solvente A: MeOH al 10%/H_2O al 90% con H_3PO_4 al 0.2%, solvente B: MeOH al 90%/H_2O al 10% con H_3PO_4 al 0.2%. HPLC > 99% (Tr 1.80 min.) CL/EM (ES^+) 552.25 (M+H, 100); $[\alpha]_D^{25C}$ - 166.99° (c 1.00,

MeOH). Análisis GC: CH_2Cl_2 al 4.94%; Análisis calculado para $C_{29}H_{33}N_3O_6S \cdot 0.16\ H_2O \cdot 0.35\ CH_2Cl_2$: C, 60.37; H, 5.87; N, 7.20; S, 5.49; H_2O, 0.49; CH_2Cl_2, 5.02. Encontrado: C, 59.95; H, 5.89; N, 7.03; S, 5.38; H_2O, 0.47; CH_2Cl_2, 4.94.

Compuesto intermedio 11

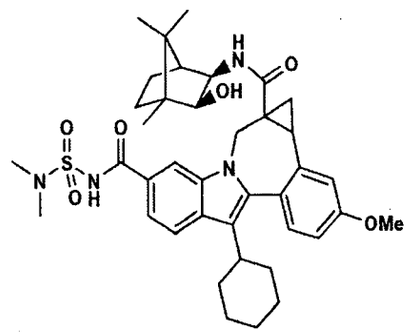


Acido ciclopropa[d]indol[2,1-a][2]benzazepin-1a(2H)-carboxílico, 8-ciclohexil-5-[[[(dimetilamino)sulfonil]amino]carbonil]-1,12b-dihidro-11-metoxi, (+/-)-. A una solución de (+/-) ácido ciclopropa[d]indol[2,1-a][2]benzazepin-1a(2H)-carboxílico, 8-ciclohexil-5-[[[(dimetilamino)sulfonil]amino]carbonil]-1,12b-dihidro-11-metoxi, éster de metilo (100 mg, 0.177 mmol) en mezcla de THF/Metanol (2.0 mL/2.0 mL), solución NaOH 2N (1.0 mL) se agregó. La mezcla de reacción se calentó a 90°C bajo condiciones de microondas durante 5 min. Luego se concentró, hizo ácida con solución HCl 1N y se extrajo con acetato de etilo (2X20 mL). Las capas orgánicas se combinaron, se secaron ($MgSO_4$), se filtraron y se concentraron. El residuo se purificó por HPLC preparativa para proporcionar el producto deseado como un sólido amarillo ligero, (59 mg, 60% de rendimiento). EM m/z

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552 (MH^+), Tiempo de retención: 3.850 min. ^1H RMN (300 MHz, MeOD) δ ppm 0.25 (m, 0.38 H) 1.14 - 2.22 (m, 11.62 H) 2.69 - 2.98 (m, 2 H) 3.02 (s, 2.28 H) 3.02 (s, 3.72 H) 3.41 (d, J=15.00 Hz, 0.62 H) 3.88 (s, 3 H) 4.01 (d, J=15.00 Hz, 0.38 H) 5.26 (d, J=15.00 Hz, 0.38 H) 5.45 (d, J=14.64 Hz, 0.62 H) 6.94 - 7.02 (m, 1 H) 7.13 (d, J=2.56 Hz, 0.38 H) 7.21 (d, J=2.20 Hz, 0.62 H) 7.26 (d, J=8.42 Hz, 0.62 H) 7.30 (d, J=8.78 Hz, 0.38 H) 7.53 (dd, J=8.42, 1.46 Hz, 0.62 H) 7.61 (dd, J=8.60, 1.65 Hz, 0.38 H) 7.85 (d, J=8.42 Hz, 0.62 H) 7.89 (d, J=8.42 Hz, 0.38 H) 8.10 (s, 0.38 H) 8.28 (d, J=1.46 Hz, 0.62 H).

Compuesto intermedio 12



Ciclopropa[d]indol[2,1-a][2]benzazepin-1a,5(2H)-dicarboxamida, 8-ciclohexil-N^5-[(dimetilamino)sulfonil]-1,12b-dihidro-N^{1a}-[(2R,3S)-3-hidroxi-4,7,7-trimetilbiciclo[2.2.1]hept-2-il]-11-metoxi, (1aR)-[parcial]-.

TBTU (437 mg, 1.36 mmol) y DIPEA (0.95 mL, 5.436 mmol) se agregaron a una solución de (+/-) ácido ciclopropa[d]indol[2,1-a][2]benzazepin-1a(2H)-carboxílico, 8-ciclohexil-5-[[[(dimetilamino)sulfonil]amino]carbonil]-1,12b-dihidro-11-metoxi (500 mg, 0.906 mmol) en DMSO (20.0 mL). La mezcla de

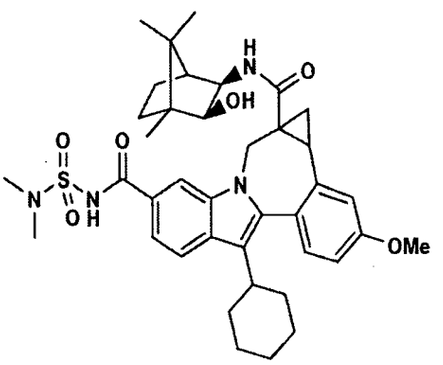
reacción se agitó a temperatura ambiente durante 15 min. ,El (2S,3R)-3-Amino-1,7,7-trimetilbiciclo[2.2.1]heptan-2-ol (280 mg, 1.36mmol) luego se agregó y la mezcla de reacción se agitó a temperatura ambiente durante la noche. La mezcla de reacción se apagó con agua y se hizo ácida con solución HCl 1N. Un sólido café separado el cual se recolectó por filtración. Este material luego se fraccionó por HPLC preparativa bajo las siguientes condiciones. Columna: Waters Sunfire 19mm x 100mm; Solvente A: CH3CN al 10%-H2O al 90%-TFA al 0.1%; Solvente B: CH3CN al 90%-H2O al 10%-TFA al 0.1%; Programa: Inicio con solvente B al 65%, tiempo de espera inicial durante 5 min, luego incrementa gradualmente hasta 90% del solvente B en 30 min con velocidad de flujo 25 mL/min. Carga: 50-60 mg/corrida.

La ciclopropa[d]indol[2,1-a][2]benzazepin-1a,5(2H)-dicarboxamida, 8-ciclohexil-N^5-[(dimetilamino)sulfonil]-1,12b-dihidro-N^{1a}-[(2R,3S)-3-hidroxi-4,7,7-trimetilbiciclo[2.2.1]hept-2-il]-11-metoxi, (1aR)- [parcial]- se eluye antes ciclopropa[d]indol[2,1-a][2]benzazepin-1a,5(2H)-dicarboxamida, 8-ciclohexil-N^5-[(dimetilamino)sulfonil]-1,12b-dihidro-N^{1a}-[(2R,3S)-3-hidroxi-4,7,7-trimetilbiciclo[2.2.1]hept-2-il]-11-metoxi, (1aS)- [parcial]- bajo las condiciones HPLC descritas arriba. El producto obtenido como un sólido amarillo ligero, 230 mg, 36% de rendimiento). EM m/ 703(MH^+), Tiempo de retención: 3.936 min. 1H RMN (500 MHz, MeOD) δ ppm 0.14 - 0.24 (m, 2.64 H) 0.51 (s, 2.46 H) 0.72 - 2.21 (m, 20.9 H) 2.49 (m, 0.18 H) 2.62

000299

(m, 0.82 H) 2.85 (m, 0.18 H) 2.96 (m, 0.82 H) 3.03 (s, 6 H) 3.39 (m, 0.82 H) 3.49 - 3.58 (m, 1.64 H) 3.71 - 3.80 (m, 0.36 H) 3.90 (s, 3 H) 4.17 (d, J=14.65 Hz, 0.18 H) 5.06 (d, J=14.65 Hz, 0.18 H) 5.37 (d, J=14.95 Hz, 0.82 H) 6.73 (d, J=5.49 Hz, 0.82 H) 6.98 - 7.05 (m, 1 H) 7.08 (d, J=4.58 Hz, 0.18 H) 7.10 (d, J=2.44 Hz, 0.18 H) 7.21 (d, J=2.44 Hz, 0.82 H) 7.31 (d, J=8.55 Hz, 0.82 H) 7.34 (d, J=8.55 Hz, 0.18 H) 7.59 - 7.64 (m, 1 H) 7.87 - 7.93 (m, 1 H) 7.99 (s, 0.18 H) 8.09 (d, J =1.22 Hz, 0.82 H).

Compuesto intermedio 13



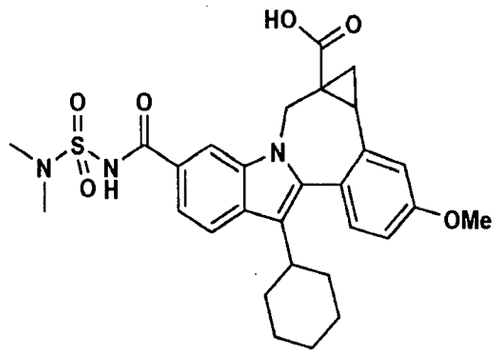
Cicloprop[d]indol[2,1-a][2]benzazepin-1a,5(2H)-dicarboxamida, 8-ciclohexil-N^5-[(dimetilamino)sulfonil]-1,12b-dihidro-N^{1a}-[(2R,3S)-3-hidroxi-4,7,7-trimetilbiciclo[2.2.1]hept-2-il]-11-metoxi-, (1aS)-[parcial]-. TBTU (437 mg, 1.36 mmol) y DIPEA (0.95 mL, 5.436 mmol) se agregaron a una solución de (+/-) ácido cicloprop[d]indol[2,1-a][2]benzazepin-1a(2H)-carboxílico, 8-ciclohexil-5-[[[(dimetilamino)sulfonil]amino]carbonil]-1,12b-dihidro-11-metoxi (500 mg, 0.906 mmol) en DMSO (20.0 mL). La mezcla de reacción se agitó a temperatura ambiente durante 15 min. Luego (2S,3R)-3-amino-1,7,7-trimetilbiciclo[2.2.1]heptan-2-ol (280

mg, 1.36 mmol) se agregó, y la mezcla de reacción se agitó a temperatura ambiente durante la noche. La mezcla de reacción se apagó con agua y luego se hizo ácida con solución de HCl 1N. Un sólido color café separado el cual se recolectó por filtración. Este material luego se fraccionó por HPLC preparativa bajo las siguientes condiciones. Columna: Waters Sunfire 19mm x 100mm; Solvente A: CH3CN al 10%-H2O al 90%-TFA al 0.1%; Solvente B: CH3CN al 90%-H2O al 10%-TFA al 0.1%; Programa: inicia con 65% del solvente B, tiempo de espera inicial durante 5 min, luego se incrementa gradualmente hasta 90% del solvente B en 30 min con velocidad de flujo 25 mL/min. carga: 50-60 mg/corrida.

La ciclopropa[d]indol[2,1-a][2]benzazepin-1a,5(2H)-dicarboxamida, 8-ciclohexil-N^5-[(dimetilamino)sulfonil]-1,12b-dihidro-N^{1a}-[(2R,3S)-3-hidroxi-4,7,7-trimetilbiciclo[2.2.1]hept-2-il]-11-metoxi, (1aS)-[parcial] se eluye después ciclopropa[d]indol[2,1-a][2]benzazepin-1a,5(2H)-dicarboxamida, 8-ciclohexil-N^5-[(dimetilamino)sulfonil]-1,12b-dihidro-N^{1a}-[(2R,3S)-3-hidroxi-4,7,7-trimetilbiciclo[2.2.1]hept-2-il]-11-metoxi, (1aR)-[parcial]- bajo las condiciones HPLC descritas arriba. El producto se obtiene como un sólido amarillo ligero, 215 mg, 34% de rendimiento). EM m/ 703 (MH^+), Tiempo de retención: 4.038 min. ^{1}H RMN (500 MHz, MeOD) δ ppm 0.20 (m, 0.38 H) 0.75 (s, 1.86 H) 0.76 (s, 1.86 H) 0.84 (s, 1.86 H) 0.85 (s, 1.14 H) 0.89 - 2.18

(m, 18.9 H) 2.52 (m, 0.38 H) 2.70 (m, 0.62 H) 2.85 (m, 0.38 H) 2.97 (m, 0.62 H) 3.03 (s, 2.28 H) 3.04 (s, 3.72 H) 3.33 - 3.39 (m, 0.62 H) 3.43 - 3.51 (m, 1.24 H) 3.73 - 3.77 (m, 0.38 H) 3.78 - 3.84 (m, 0.38 H) 3.90 (s, 1.86 H) 3.90 (s, 1.14 H) 4.14 (d, J=14.65 Hz, 0.38 H) 5.11 (d, J=14.65 Hz, 0.38 H) 5.44 (d, J=15.26 Hz, 0.62 H) 6.68 (d, J=4.88 Hz, 0.62 H) 6.96 - 7.03 (m, 1 H) 7.07 (d, J=5.19 Hz, 0.38 H) 7.12 (d, J=2.44 Hz, 0.38 H) 7.23 (d, J=2.14 Hz, 0.62 H) 7.27 (d, J=8.54 Hz, 0.62 H) 7.33 (d, J=8.54 Hz, 0.38 H) 7.55 (dd, J=8.39, 1.68 Hz, 0.62 H) 7.62 (dd, J=8.55, 1.53 Hz, 0.38 H) 7.87 (d, J=8.54 Hz, 0.62 H) 7.91 (d, J=8.55 Hz, 0.38 H) 8.08 (d, J=1.22 Hz, 0.38 H) 8.10 (d, J=1.22 Hz, 0.62 H).

Compuesto intermedio 14



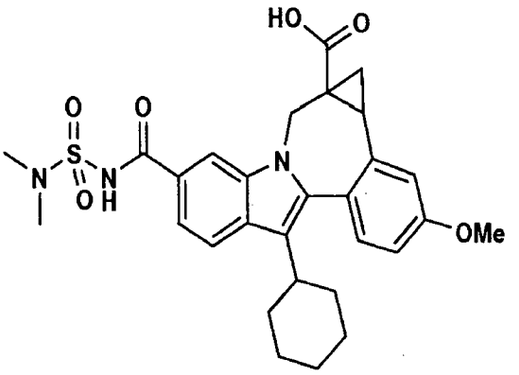
Acido ciclopropl[d]indol[2,1-a][2]benzazepin-1a(2H)-carboxílico, 8-ciclohexil-5-[[[(dimetilamino)sulfonil]amino]carbonil]-1,12b-dihidro-11-metoxi, (-)-. La solución de NaOH 10 N (2.0 mL, 20 mmol) y 4 mL de agua se agregaron a una solución de ciclopropl[d]indol[2,1-a][2]benzazepin-1a,5(2H)-dicarboxamida, 8-ciclohexil-N^5-[(dimetilamino)sulfonil]-1,12b-dihidro-N^{1a}-[(2R,3S)-3-hidroxi-

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4,7,7-trimetilbiciclo[2.2.1]hept-2-il]-11-metoxi, (1aR)-[parcial]- (160 mg, 0.228 mmol) en THF/MeOH (7 mL/7 mL). La mezcla de reacción se calentó a 120°C bajo condiciones de microondas durante 1 hr. Luego se concentró, se hizo ácida con solución de HCl concentrado y se extrajo con acetato de etilo dos veces (2X 30 mL). Las capas orgánicas se combinaron, se secaron ($MgSO_4$), se filtraron y se concentraron in vacuo hasta un aceite anaranjado. El producto crudo luego se purificó por columa HPLC preparativa para proporcionar el producto como un sólido amarillo ligero, (80 mg, 64% de rendimiento). Una rotación específica promedio -130.85°; Solvente MeOH; longitud de onda 589 nm; 50 cm. de célula EM m/ 552 (MH^+), Tiempo de retención: 3.760 min. 1H RMN (500 MHz, MeOD) δ ppm 0.27 (m, 0.38 H) 1.14 - 2.22 (m, 11.62 H) 2.76 (m, 0.38 H) 2.80 - 2.92 (m, 1 H) 2.92 - 3.09 (m, 6.62 H) 3.45 (d, J=14.95 Hz, 0.62 H) 3.90 (s, 1.86 H) 3.91 (s, 1.14 H) 4.04 (d, J=15.26 Hz, 0.38 H) 5.28 (d, J=15.26 Hz, 0.38 H) 5.47 (d, J=15.26 Hz, 0.62 H) 6.95 - 7.05 (m, 1 H) 7.15 (d, J=2.75 Hz, 0.38 H) 7.23 (d, J=1.83 Hz, 0.62 H) 7.28 (d, J=8.55 Hz, 0.62 H) 7.33 (d, J=8.54 Hz, 0.38 H) 7.54 (dd, J=8.39, 1.68 Hz, 0.62 H) 7.63 (dd, J=8.55, 1.53 Hz, 0.38 H) 7.86 (d, J=8.55 Hz, 0.62 H) 7.91 (d, J=8.55 Hz, 0.38 H) 8.11 (d, J=1.22 Hz, 0.62 H) 8.29 (d, J=1.22 Hz, 0.38 H).

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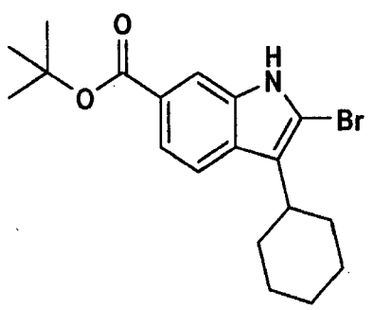
Compuesto intermedio 15



Acido cicloprop[d]indol[2,1-a][2]benzazepin-1a(2H)-carboxílico, 8-ciclohexil-5-[[[(dimetilamino)sulfonil]amino]carbonil]-1,12b-dihidro-11-metoxi-, (+)-. Una solución NaOH 10 N (1.8 mL, 18 mmol) y 4 mL de agua se agregaron a una solución de cicloprop[d]indol[2,1-a][2]benzazepin-1a,5(2H)-dicarboxamida, 8-ciclohexil-N^5-[(dimetilamino)sulfonil]-1,12b-dihidro-N^{1a}-[(2R,3S)-3-hidroxi-4,7,7-trimetilbiciclo[2.2.1]hept-2-il]-11-metoxi-, (1aS)-[parcial]- (130 mg, 0.185 mmol) en bTHF/MeOH (7 mL/7 mL). La mezcla de reacción se calentó a 120°C bajo condiciones de microondas durante 1 hr. Se concentró, se hizo ácida con solución de HCl concentrado y se extrajo con acetato de etilo dos veces (2X 30 mL). Las capas orgánicas se combinaron, se secaron ($MgSO_4$), se filtraron y se concentraron in vacuo para dar un aceite anaranjado. El producto crudo luego se purificó por columna HPLC preparativa para proporcionar el producto como un sólido amarillo ligero, (68 mg, 67% de rendimiento). Rotación específica promedio + 174.73°; Solvente MeOH; longitud de onda 589 nm; 50 cm célula EM m/ 552 (MH^+), Tiempo

de retención: 3.773 min. 1H RMN (500 MHz, MeOD) δ ppm 0.27 (m, 0.38 H) 1.14 - 2.22 (m, 11.62 H) 2.76 (m, 0.38 H) 2.80 - 2.92 (m, 1 H) 2.92 - 3.09 (m, 6.62 H) 3.45 (d, J=14.95 Hz, 0.62 H) 3.90 (s, 1.86 H) 3.91 (s, 1.14 H) 4.04 (d, J=15.26 Hz, 0.38 H) 5.28 (d, J=15.26 Hz, 0.38 H) 5.47 (d, J=15.26 Hz, 0.62 H) 6.95 - 7.05 (m, 1 H) 7.15 (d, J=2.75 Hz, 0.38 H) 7.23 (d, J=1.83 Hz, 0.62 H) 7.28 (d, J=8.55 Hz, 0.62 H) 7.33 (d, J=8.54 Hz, 0.38 H) 7.54 (dd, J=8.39, 1.68 Hz, 0.62 H) 7.63 (dd, J=8.55, 1.53 Hz, 0.38 H) 7.86 (d, J=8.55 Hz, 0.62 H) 7.91 (d, J=8.55 Hz, 0.38 H) 8.11 (d, J=I.22 Hz, 0.62 H) 8.29 (d, J=1.22 Hz, 0.38 H).

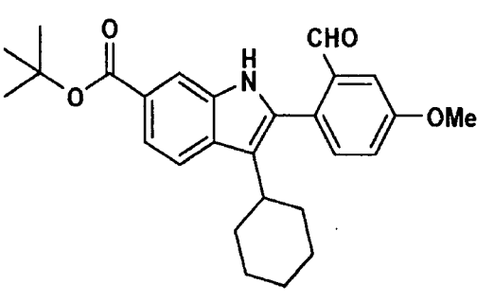
Compuesto intermedio 16



Acido 1H-indol-6-carboxílico, 2-bromo-3-ciclohexilo, éster de 1,1-dimetiletilo. A una solución mecánicamente agitada de ácido 2-bromo-3-ciclohexil-1H-indol-6-carboxílico (80 g, 0.24 m) en dicloruro de metileno seco (1.2 L) y THF (100 mL) se agregaron tamices moleculares activados (4A, 80 g) y carbonato de plata (275 g, 0.99 m). La mezcla de reacción se enfrió hasta 0°C y bromuro de t-Butilo (142 g, 1.04 m) se agregó gota a gota. La mezcla se agitó durante la noche a temperatura ambiente y se observó por CCD (Hexano- acetato de

etilo 80:20, $_{Rf}$ (Producto) = 0.7). Si cualquier ácido de bromo se dejó sin conversión, un 10% adicional de carbonato de plata se agregó y se continuó agitando durante unas 2 - 4 h adicionales. Al terminar, la mezcla de reacción se filtró a través de un lecho delgado de celite. El filtrado se lavó con dicloruro de metileno (500 mL). Los filtrados combinados se concentraron in-vacuo, y el producto crudo así obtenido se purificó por cromatografía en gel de sílice: (malla 230 - 400, eluida con un gradiente de acetato de etilo en éter de pet al 0 - 2%). Las fracciones homogéneas se combinaron y evaporaron bajo presión reducida para dar 80 g (85%) del compuesto del título. HPLC: 90.1% (TR = 6.56 min), Columna: C18 BDS, (50X4.6mm), Fase móvil: Gradiente de TFA al 0.1% en agua: ACN (30 → 100 → 30), velocidad de flujo 0.8 mL / min. CLEM: 99.8% (TR = 4.44 min), Columna: Geneis, C18 50X4.6 mm Fase móvil: Gradiente de ácido fórmico al 0.1% en agua: ACN (70 → 95 → 70), velocidad de flujo: 0.8 mL / min; M - 1 = 376.5; ^{1}H RMN $CDCl_3$) (400 MHz) δ 1.37 - 1.40 (m, 3H, Hexilo cíclico), 1.62 (s, 9H, t-Bu), 1.80 - 1.94 (dos conjuntos de m, 3H, y 4H respectivamente, parte hexilo cicl.), 2.81 (m, 1H, CH de hexilo cicl.- bencílico), 7.70 - 7.75 (m, 2H, Indol-H_{4y5}), 8.04 (s, 1H, Indol-H_7), 8.52 (s, 1H, Indol-NH).

Compuesto intermedio 17



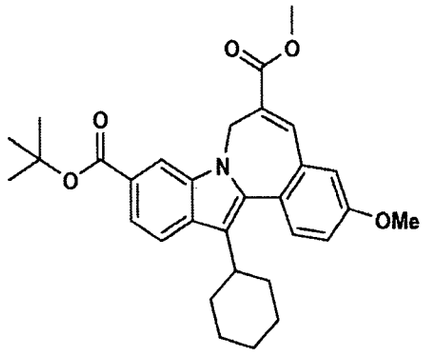
000306

Acido 1H-indol-6-carboxílico, 3-ciclohexil-2-(2-formil-4-metoxifenilo), éster de 1,1-dimetiletilo. El 2-bromo-3-ciclohexil-1H-indol-6-carboxilato de tert-Butilo (72 g, 0.19 m) se disolvió en una mezcla 1:1 de tolueno y etanol (720 mL) y se desgasificó. LiCl (23.9 g, 0.51 m) luego se agregó, seguido por carbonato de sodio (720 mL, solución 1.0 M desgasificada separadamente,) y Pd-tetraquis (13.1 g, 0.011 m). Después de agitar durante 0.25 h, el ácido 2-formil-4-metoxifenilborónico (41.1 g, 0.22 m) se agregó y la mezcla de reacción se calentó hasta 85°C durante 4 h. La reacción luego se observó por CCD, (Hexano-acetato de etilo 80:20, R_f (Producto) = 0.55). Al terminar, la mezcla de reacción se enfrió hasta temperatura ambiente y agua (1.0 L) se agregó seguido por acetato de etilo (1.0 L). La capa orgánica se lavó con salmuera, y se secó y se concentró bajo vacío para proporcionar el compuesto del título como un sólido amarillo. Rendimiento 75 g (74%). HPLC: 99.7% (TR = 6.30 min), Columna: C18 BDS (4.6 X 50 mm), SC-307, Fase móvil: Gradiente de TFA al 0.1% en agua: ACN (30 → 100 → 30), velocidad de flujo 0.8 mL/min. CLEM : 98.0% (TR = 5.28 min), Columna: Geneis, C18 (50X4.6 mm), Fase móvil: Gradiente de ácido fórmico al 0.1% en agua: ACN (70 → 95 → 70), velocidad de flujo: 0.8 mL / min; M - 1 = 432.2; ^{1}H RMN (DMSO-d_6) (400 MHz) δ 1.40 - 1.48 (m, 3H, hexilo cicl.), 1.57 (s, 9H, t-Bu), 1.84 - 1.90 (m, 7H, parte hexilo cicl.), 3.09 (m, 1H, CH de hexilo cicl. - bencílico), 3.84 (s, 3H, OCH_3), 6.55 (d, J = 4 Hz, 1H,

000307

arilo $H_{2'}$), 7.06 (d, 1H, arilo $H_{3'}$), 7.08 (s, 1H, arilo $H_{6'}$), 7.23 (d, 1H, Indol-H_5), 7.53 (d, J = 8 Hz, 1H, Indole-H_4), 7.70 - 7.75 (m, 2H, NH + Indol-H_7), 8.06 (s, 1H, CHO).

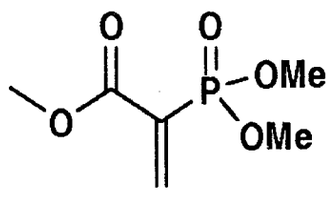
Compuesto intermedio 18



Acido 7H-Indol[2,1-a][2]benzazepin-6,10-dicarboxílico, 13-ciclohexilo, éster de 10-(1,1-dimetiletil) 6-metilo. El 3-ciclohexil-2-(2-formil-4-metoxifenil)-1H-indol-6-carboxilato de tert-butilo (62.5 g, 0.144 m) se disolvió en DMF seco (1.2 L) y se agitó inmediatamente. El carbonato de cesio (84 g, 0.17 m) y 2-(dimetoxifosforil)acrilato de metilo (GC puro al 65-70%, 56.2 g, 0.18 m) luego se agregaron y la mezcla de reacción se calentó hasta 65°C durante 4h, y la reacción se observó por CCD (Hexano-acetato de etilo 80:20, R_f (Producto) = 0.7). Al terminar, la mezcla se enfrió hasta temperatura ambiente, luego se apagó con agua (1.0 L). Un sólido amarillo se precipita, el cual se recolectó por filtración y se seca con aire. Este material luego se hizo mezcla espesa en metanol, se filtró, y se secó bajo vacío para dar el producto como un polvo amarillo, (70 g, 90%). HPLC: 99.1% (TR = 6.45 min), Columna: C18 BDS (4.6 X 50 mm), Fase móvil: Gradiente de TFA al 0.1% en agua: ACN (30

→ 100 → 30), velocidad de flujo 0.8 mL / min. CLEM: 100% (TR = 7.00 min), Columna: Geneis, C18 (50X4.6 mm), Fase móvil: Gradiente de ácido fórmico al 0.1% en agua: ACN (70 → 95 → 70), velocidad de flujo: 0.8 mL / min; M + 1 = 502.2; ^{1}H RMN ($CDCl_3$) (400 MHz) δ 1.10 - 1.30 (m, 3H, hexilo cicl.), 1.64 (s, 9H, t-Bu), 1.77 - 2.07 (m, 7H, parte hexilo cicl.), 2.80 (m, 1H, CH de hexilo cicl. - bencílico), 3.84 (s, 3H, OCH_3), 3.93 (s, 3H, $COOCH_3$), 4.15 y 5.65 (dos picos amplios., 1H cada uno, CH_2 alílico), 6.95 (s, 1H, arilo $H_{6'}$), 7.01 (d, 1H, arilo $H_{2'}$), 7.53 (d, J = 8 Hz, 1H, arilo $H_{3'}$), 7.70 (d, J = 4 Hz, 1H, Indol-H_5), 7.84 (s + d, 2H, H olefínico + Indol-H_4), 8.24 (s, 1H, indol - H_7); ^{13}C RMN ($CDCl_3$) (100.0 MHz) δ 166.92, 165.71, 158.96, 142.28, 136.47, 13.50, 134.61, 132.43, 132.01, 129.73, 124.78, 124.68, 120.33, 119.39, 119.04, 115.62, 115.05, 111.27, 80.27, 55.49, 52.50, 39.09, 36.81, 33.40, 28.38, 27.15, 26.28.

Compuesto intermedio 19

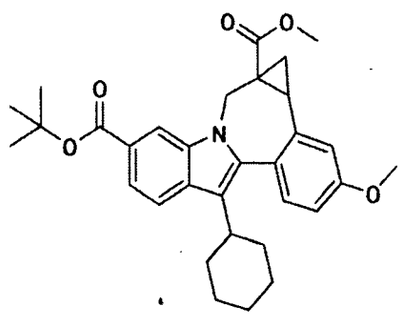


Acido 2-Propenoico, 2-(dimetoxifosfinilo), éster de metilo. A un matraz de fondo redondo de cuatro cuellos de 5 L equipado con un agitador mecánico, un condensador, un controlador de temperatura y una entrada N2, se cargó paraformaldehído (40.5 g, 1.35 mol), MeOH (2 L) y piperidina (2 mL). La mezcla de reacción se calentó hasta reflujo bajo N2

000309

durante 3 h. Después se enfría hasta 50°C, 2-(dimetoxifosforil)acetato (150 g, 0.824 mol) se agregó en una porción. La mezcla de reacción se continuó hasta reflujo durante 18 h. Después se enfría hasta temperatura ambiente, la solución de reacción se concentró in vacuo para dar un aceite incoloro transparente. El aceite anterior se disolvió en tolueno seco (1 L) en un matraz de fondo redondo de cuatro cuellos de 3 L equipado con un controlador de temperatura, una entrada de N2, un agitador magnético y un aparato Dean-Stark. A la solución se agregó $TsOH.H_2O$ (5.2 g). La mezcla de reacción luego se puso a reflujo azeotropicamente para remover el metanol durante 18 h. Después se enfría hasta temperatura ambiente, la solución se concentró in vacuo para dar un aceite amarillo el cual se destiló al vacío a 150 - 155°C /0.2 mm de Hg para proporcionar el producto como un aceite incoloro (135.0 g). Pureza, 90% con base en 1H RMN. ^1H RMN (CDCl3, 300 MHz) δ 7.0 (dd, J= 42.4 y 1.5 Hz, 1H), 6.73 (dd, J= 20.5 y 1.8 Hz, 1H), 3.80 (s, 6H), 3.76 (s, 3H).

Compuesto intermedio 20



000310

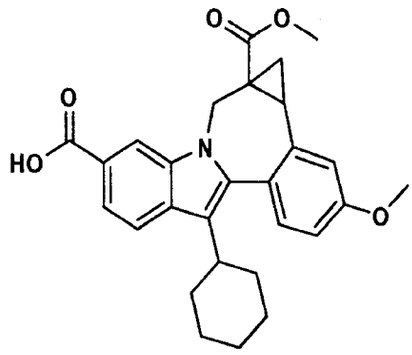
Acido cicloprop[d]indol[2,1-a][2]benzazepin-1a,5(2H)-dicarboxílico, 8-ciclohexil-1,12b-dihidro-11-metoxi, éster de 5-(1,1-dimetiletil) 1a-metil, (+/-). El hidruro de sodio (96 mg, 4 mmol) se agregó a una suspensión agitada de cloruro de trimetilsulfoxonio (567 mg, 4.4 mmol) en DMSO anhidro (10 mL) bajo nitrógeno. La mezcla resultante se agitó a temperatura ambiente durante 30-45 min y luego ácido 7H-indol[2,1-a][2]benzazepin-6,10-dicarboxílico puro, 13-ciclohexil-3-metoxi, éster de 10-(1,1-dimetiletil) 6-metilo (1.0, 2 mmol) se agregó en pequeñas porciones. La suspensión se diluyó con DMSO (5 mL) y se calentó a 50°C durante 3-4 h. La mezcla de reacción se se dejó enfriar hasta temperatura ambiente y agua se agregó. Un sólido se separa, el cual se recolectó por filtración y se lava con agua y luego se seca con aire durante la noche para proporcionar 1.15 g del producto crudo. Este material se purificó por cromatografía de columna instantánea (gel de sílice, MeOH al 3% en DCM) para proporcionar el compuesto del título puro (0.96 g): CL/EM: Tiempo de retención 3.816 min; m/e 516 (MH^+). ^1H RMN (400 MHz, CDCI3): Se observó que el producto existe como rotámeros de interconversión, como lo evidencia el espectro RMN del compuesto.

El siguiente procedimiento es un ejemplo de un método para efectuar la resolución de ácido cicloprop[d]indol[2,1-a][2]benzazepin-1a,5(2H)-dicarboxílico racémico, 8-ciclohexil-1,12b-dihidro-11-metoxi, éster de 5-(1,1-dimetiletil) 1a-

000311

metilo, (+/-). Una muestra de ácido cicloprop[d]indol[2,1-a][2]benzazepin-1a,5(2H)-dicarboxílico, 8-ciclohexil-1,12b-dihidro-11-metoxi, éster 5-(1,1-dimetiletil) 1a-metilo, (+/-)- se disolvió en una mezcla de isopropanol y acetonitrilo (8:2) para dar una concentración final de 20 mg/mL. Esta mezcla se inyectó en un sistema de cromatografía SFC quiral preparativo usando las siguientes condiciones: columna Chiralcel OJ-H, 4.6 x 250 mm, 5µm; Fase móvil: MeOH al 8% en CO2; Temp: 35°C; Velocidad de flujo: 2 mL/min durante 16 min; UV monitoreado @ 260nm; Inyección: 5µL de ~20.0 mg/mL en IPA: ACN (8:2).

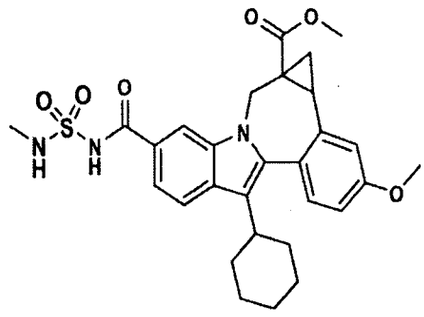
Compuesto intermedio 21



Acido cicloprop[d]indol[2,1-a][2]benzazepin-1a,5(2H)-dicarboxílico, 8-ciclohexil-1,12b-dihidro-11-metoxi, éster 1a-metilo, (+/-)-. TFA (5 mL) se agregó a una solución de (+/-) ácido 8-ciclohexil-1,1a,2,12b-tetrahidro-11-metoxi-1a-(metoxicarbonil)-cicloprop[d]indol[2,1-a][2]benzazepin-5-carboxílico, éster de tert-butilo (515 mg, 1 mmol) en DCM anhidro (10 mL). La solución resultante se agitó a temperatura ambiente durante aproximadamente 8 hasta 12 hr. La reacción luego se evaporó hasta secarse para proporcionar el compuesto

del título (0.47g, 100%). CL/EM: Tiempo de retención 2.245 min; m/e 460 (MH^+). ^1H RMN (400 MHz, $CDCl_3$): del espectro RMN de los compuestos, el producto se observó para existir como una mezcla de de rotámeros interconvertidos.

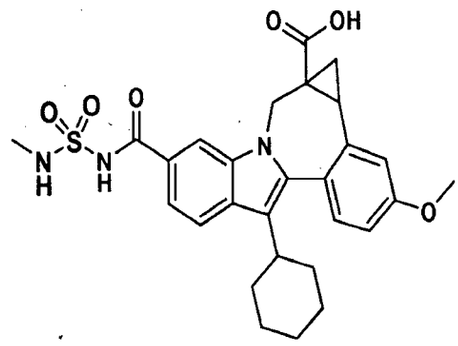
Compuesto intermedio 22



Acido cicloprop[d]indol[2,1-a][2]benzazepin-1a(2H)-carboxílico, 8-ciclohexil-1,12b-dihidro-11-metoxi-5-[[[(metilamino)sulfonil]amino]carbonilo], éster de metilo. Una solución de ácido 8-ciclohexil-1,1a,2,12b-tetrahidro-11-metoxi-1a-(metoxicarbonil)-cicloprop[d]indol[2,1-a][2]benzazepin-5-carboxílico (140 mg, 0.31 mmol) y CDI (64 mg, 0.40 mmol) en THF (3 mL) se agitó durante 1 hr a 60°C. La N-metilsulfamida (68 mg, 0.62 mmol) y DBU (71.6 mg, 0.47 mmol) se agregaron y la mezcla se agitó a 60°C durante la noche. La reacción luego se vació en agua fría, se hizo ácida con ácido clorhídrico diluido y se extrajo en acetato de etilo. Los extractos se lavaron secuencialmente con ácido clorhídrico diluido (0.1 N), y salmuera, y luego se secaron (sulfato de sodio anhidro), se filtraron y se evaporaron para proporcionar el compuesto del título como un sólido café. ESI-EM m/e 552 (MH+). Este material se usó sin purificación adicional.

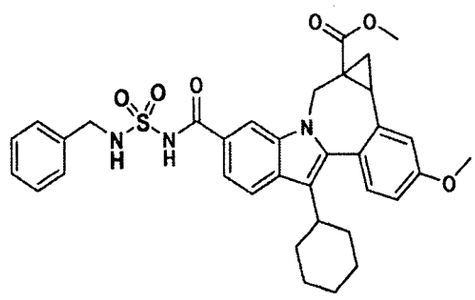
000313

Compuesto intermedio 23



Acido cicloprop[d]indol[2,1-a][2]benzazepin-1a(2H)-carboxílico, 8-ciclohexil-1,12b-dihidro-11-metoxi-5-[[[(metilamino)sulfonil]amino]carbonilo]-. El ácido cicloprop[d]indol[2,1-a][2]benzazepin-1a(2H)-carboxílico, 8-ciclohexil-5-[[[(metilamino)sulfonil]amino]carbonil]-1,12b-dihidro-11-metoxi, éster de metilo se disolvió en THF, mezcla de MeOH (2 mL,2 mL). NaOH 2.5 M (ac.) (1.2 mL, 3 mmol) luego se agregó y la reacción se agitó a 22°C durante 2 hr. La solución luego se neutralizó con HCl 1M (ac.) (3 mL) y se concentró para remover los solventes orgánicos. El residuo se hizo mezcla espesa con H_2O y los sólidos se rerecolectaron por filtración, se lavaron con H_2O y se secaron para proporcionar el compuesto del título (160 mg, 0.30 mmol). ESI-EM m/e 538 (MH^+). Este material se usó sin purificación adicional.

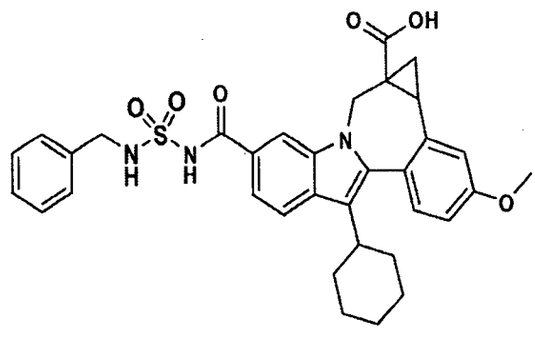
Compuesto intermedio 24



000314

Acido cicloprop[d]indol[2,1-a][2]benzazepin-1a(2H)-carboxílico, 8-ciclohexil-5-[[[(bencilamino)sulfonil]amino]carbonil]-1,12b-dihidro-11-(metoxi)-12-(metoxi), éster de metilo, (+/-)-. Una solución de (+/-) ácido 8-ciclohexil-1,1a,2,12b-tetrahidro-11-metoxi-1a-(metoxicarbonil)-cicloprop[d]indol[2,1-a][2]benzazepin-5-carboxílico (200 mg, 0.44 mmol) y CDI (92 mg, 0.57 mmol) en THF (5 mL) se agitó durante 1 hr a 60°C. La N-bencilsulfamida (164 mg, 0.88 mmol) y DBU (100 mg, 0.66 mmol) luego se agregaron y la mezcla resultante se agitó a 60°C durante la noche. La reacción luego se vació en agua fría, se hizo ácida con ácido clorhídrico diluido y se extrajo en acetato de etilo. La fase orgánica se lavó en ácido clorhídrico (0.1 N), salmuera y se secó (sodio sulfato) y evaporó in vacuo para proporcionar el compuesto del título como un sólido café. ESI-EM m/e 628 (MH^+).

Compuesto intermedio 25

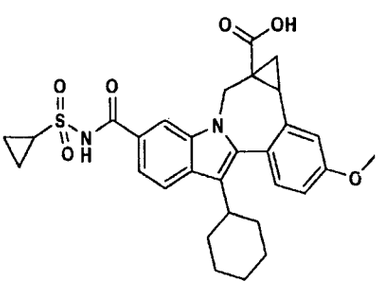


Acido Cicloprop[d]indol[2,1-a][2]benzazepin-1a(2H)-carboxílico, 8-ciclohexil-1,12b-dihidro-11-metoxi-5-[[[[(fenilmetil)amino]sulfonil]amino]carbonilo]-, (+/-)-. El compuesto del título se preparó usando un procedimiento

000315

similar al que se describe para ácido cicloprop[d]indol[2,1-a][2]benzazepin-1a(2H)-carboxílico, el ácido 8-ciclohexil-5-[[[(metilamino)sulfonil]amino]carbonil]-1,12b-dihidro-11-metoxi-cicloprop[d]indol[2,1-a][2]benzazepin-1a(2H)-carboxílico partiendo de (+/-) ácido 8-ciclohexil-1,1a,2,12b-tetrahidro-11-metoxi-1a-(metoxicarbonil)-cicloprop[d]indol[2,1-a][2]benzazepin-5-carboxílico. ESI-EM m/e 613 (MH+), 1H RMN (500 MHz, MeOD) δ ppm 1.22 - 2.20 (m, 13 H) 3.27 - 3.31 (m, 1 H) 3.47 (d, J=14.95 Hz, 0.6 H) 3.92 (d, J=2.44 Hz, 3 H) 4.04 (d, 0.4 H) 4.31 (d, J=2.75 Hz, 2 H) 5.24 (d, 0.4 H) 5.48 (d, 0.6 H) 7.02 (d, 1 H) 7.17 (d, J=2.75 Hz, 1 H) 7.19 - 7.35 (m, 5 H) 7.39 (t, J=7.48 Hz, 2 H) 7.45 - 7.52 (m, 1 H) 7.80 (d, J=I.53 Hz, 0.4 H) 7.85 (dd, J=8.39, 6.87 Hz, 1 H) 8.22 (d, J=1.53 Hz, 0.6 H).

Compuesto intermedio 26



ácido Cicloprop[d]indol[2,1-a][2]benzazepin-1a(2H)-carboxílico, 8-ciclohexil-5-[[(ciclopropilsulfonil)amino]carbonil]-1,12b-dihidro-11-metoxi-, (+/-)-. Una mezcla de ácido (+/-) 8-ciclohexil-1,1a,2,12b-tetrahidro-11-metoxi-1a-(metoxicarbonil)-

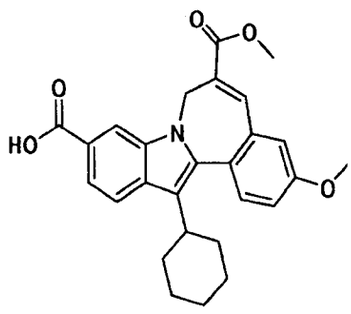
ciclopropl[d]indol[2,1-a][2]benzazepin-5-carboxílico (1 equiv), y carbonildiimidazol (1.5 equiv) en THF anhidro se calentó a 50°C durante 30 min y se dejó enfriar a temperatura ambiente. Luego 1 equiv de ciclopropansulfonamida y 1,8-diazabiciclo[5.4.0]undec-7-eno (2 equiv) se agregaron consecutivamente. La mezcla resultante se agitó a temperatura ambiente durante la noche. Después de preparar el ácido acuoso, el producto crudo aislado se purificó por HPLC prep. El éster Compuesto intermedio luego se hidrolizó usando NaOH 1N en THF-MeOH para proporcionar el compuesto del título. CL/EM: Tiempo de retención: 2.030 min; m/e 549 (MH^+). ^1H NMR (400 MHz, $CDCl_3$): El producto se observó que existe como rotámeros de Interconversión, como lo evidencia el espectro RMN de los compuestos.

Los compuesto intermedios 26bis-37 usan los procedimientos experimentales que siguen hasta que se indique lo contrario. Datos CLEM: Tiempo detenido: Tiempo de gradiente + 1 minuto; Conc. inicial: B al 0% a menos de que se indique lo contrario; Conc. final: B al 100% a menos de que se indique lo contrario; Eluyente A: CH_3CN al 5%/H_2O al 95% con NH_4Ac 10 mM (para las columnas A, D y E); MeOH al 10%/H_2O al 90% con TFA al 0.1% (para las columnas B y C); Eluyente B: CH_3CN al 95%/H_2O al 5% con NH_4Ac 10 mM (para las columnas A, D y E); MeOH al 90%/H_2O al 10% con TFA al 0.1% (para las columnas B y C); Columna A: Phenomenex 10µ 4.6 x 50 mm C18; Columna B:

000317

Phenomenex C18 10µ 3.0 x 50 mm; Columna C: Phenomenex 4.6 x 50 mm C18 10µ; Columna D: Phenomenex Luna C18 5µ 3.0 x 50 mm; Columna E: Phenomenex 5µ 4.6 x 50 mm C18; Datos de HPLC preparativo: Condiciones para H_2O/CH_3CN con solución amortiguadora de NH_4Ac 10 mM; Gradiente: Lineal durante 20 min. a menos de que se indique lo contrario; Conc. inicial: B al 15% a menos de que se indique lo contrario; Conc. final: B al 100%; Eluyente A: CH_3CN al 5%/H_2O al 95% con NH_4Ac 10 mM; Eluyente B: CH_3CN al 95%/H_2O al 5% con NH_4Ac 10 mM; Columna: Sunfire Prep C_{18} OBD 5µ 30 x 100 mm; Condiciones para H_2O/MeOH con solución amortiguadora TFA al 0.1%; Gradiente: Lineal durante 20 min. a menos de que se indique lo contrario; Conc. inicial: B al 30% a menos de que se indique lo contrario; Conc. final: B al 100%; Eluyente A: MeOH al 10%/H_2O al 90% con TFA al 0.1%; Eluyente B: MeOH al 90%/H_2O al 10% con TFA al 0.1%; Columna: phenomenex 21 x 100 mm C18 H_2O.

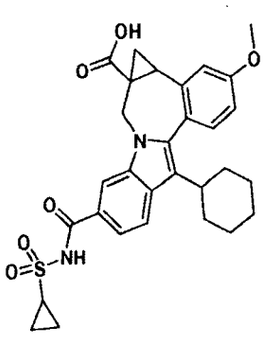
Compuesto intermedio 26 bis



ácido 13-Ciclohexil-3-metoxi-6-(metoxicarbonil)-7H-indol[2,1-a][2]benzazepin-10-carboxílico. El ácido Trifluoroacético (30 mL) se agregó gota a gota a una mezcla

espesa agitada de 6-metil 13-ciclohexil-3-metoxi-7H-indol[2,1-a][2]benzazepin-6,10-dicarboxilato de 10-tert-butilo (10 g, 20 mmol) en dicloroetano (30 mL) bajo N_2. La solución verde oscura clara se agitó a temperatura ambiente durante 2.5h, concentró hasta secarse y agitó con EtOAc (100 mL) durante la noche. Los sólidos se recolectaron por filtración, lavaron con EtOAc y Et_2O para proporcionar el ácido 13-ciclohexil-3-metoxi-6-(metoxicarbonil)-7H-indol[2,1-a][2]benzazepin-10-carboxílico (8.35 g, 18.8 mmol, 94%) como un sólido amarillo el cual se usó sin purificación adicional. 1H RMN (300 MHz, CDCl3) δ 1.13 - 2.16 (m, 10H), 2.74 - 2.88 (m, 1H), 3.84 (s, 3H), 3.89 (s, 3H), 4.06 - 4.29 (m, 1H), 5.54 - 5.76 (m, 1H), 6.98 (d, J = 2.6 Hz, 1H), 7.08 (dd, J= 8.4, 2.6 Hz, 1H), 7.52 (d, J= 8.4 Hz, 1H), 7.78 (dd, J= 8.8, 1.1 Hz, 1H), 7.80 (s, 1H), 7.86 (d, J= 8.8 Hz, 1H), 8.34 (d, J= 1.1Hz, 1H). CLEM: m/e 446 $(M+H)^+$, tiempo de retención 3.21 min, Columna B, 4 gradiente de minuto.

Compuesto intermedio 27

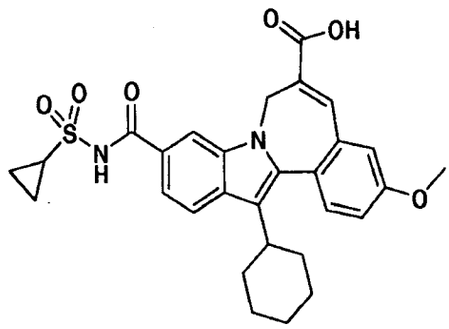


13-ciclohexil-10-((ciclopropilsulfonil)carbamoil)-3-metoxi-7H-indol[2,1-a][2]benzazepin-6-carboxilato de metilo. El 1,1'-Carbonildiimidazol (1.82 g, 11.2 mmol) se agregó a una mezcla

espesa de ácido 13-ciclohexil-3-metoxi-6-(metoxicarbonil)-7H-indol[2,1-a][2]benzazepin-10-carboxílico (3.85 g, 8.65 mmol) en THF (15 mL). La mezcla de reacción se calentó a 60°C durante 1.5h, enfrió a temperatura ambiente, trató con ciclopropansulfonamida (1.36 g, 11.2 mmol), agitó 10 min y luego trató con la adición gota a gota de una solución de DBU (2.0 mL, 13 mmol) en THF (3 mL). La mezcla de reacción se agitó a temperatura ambiente durante la noche, diluyó con EtOAc (100 mL) y lavó con H_2O (~30 mL), HCl 1N (ac.) (2 x 50 mL) y salmuera (~30 mL). Las capas acuosas combinadas se extrajeron con EtOAc (100 mL) y la capa orgánica se lavó con HCl 1N (ac.) (~50 mL). Las capas orgánicas combinadas se lavaron con salmuera (~30 mL), secaron ($MgSO_4$), filtraron y concentraron. El residuo se agitó con Et_2O (~100 mL) durante 2h y los sólidos se recolectaron por filtración, enjugaron con Et_2O y secaron para proporcionar 13-ciclohexil-10-((ciclopropilsulfonil)carbamoil)-3-metoxi-7H-indol[2,1-a][2]benzazepin-6-carboxilato de metilo (4.24 g, 7.73 mmol, 89%) como un sólido amarillo pálido el cual se usó sin purificación adicional. ^1H RMN (300 MHz, $CDCl_3$) δ 1.08 - 2.13 (m, 14H), 2.73 - 2.87 (m, 1H), 3.13 - 3.24 (m, 1H), 3.82 (s, 3H), 3.89 (s, 3H), 4.04 - 4.27 (m, 1H), 5.50 - 5.71 (m, 1H), 6.98 (d, J= 2.6 Hz, 1H), 7.08 (dd, J= 8.8, 2.6 Hz, 1H), 7.44 (dd, J= 8.4, 1.1 Hz, 1H), 7.50 (d, J= 8.8 Hz, 1H), 7.80 (s, 1H), 7.86 (d, J= 8.4 Hz, 1H), 8.11 (br s, 1H), 8.78 (br s, 1H). CLEM: m/e 549

(M+H)+, tiempo de retención 3.79 min, Columna B, 4 gradiente de minuto.

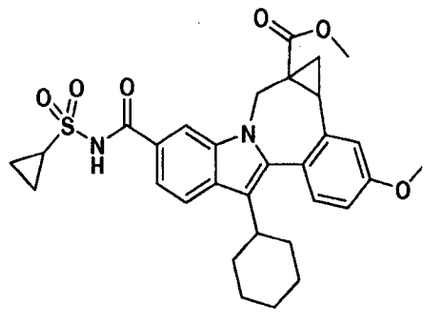
Compuesto intermedio 28



ácido 13-Ciclohexil-10-((ciclopropilsulfonil)carbamoil)-3-metoxi-7H-indol[2,1-a][2]benzazepin-6-carboxílico. El 13-ciclohexil-10-((ciclopropilsulfonil)carbamoil)-3-metoxi-7H-indol[2,1-a][2]benzazepin-6-carboxilato de metilo (1.0 g, 1.8 mmol) se disolvió en MeOH//THF (1:1, 24 mL) y trató con NaOH acuoso 1M (5 mL). La mezcla de reacción se agitó y calentó a 60°C durante 1.5h y enfrió a temperatura ambiente. La solución clara se neutralizó con HCl acuoso 1M (5 mL) y concentró para remover los solventes orgánicos. Los sólidos resultantes se recolectaron por filtración, lavaron con H_2O y secaron bajo vacío para proporcionar el ácido 13-ciclohexil-10-((ciclopropilsulfonil)carbamoil)-3-metoxi-7H-indol[2,1-a][2]benzazepin-6-carboxílico (1.0 g, 1.7 mmol, 94%) como un sólido amarillo brillante (con 0.75 equiv. de THF) el cual se usó sin purificación adicional. ^{1}HRMN (300 MHz, CD_3OD) δ 1.11 - 2.24 (m, 17H, 3H de THF), 2.81 - 2.96

(m, 1H), 3.17 - 3.28 (m, 1H), 3.69 - 3.79 (m, 3H, de THF), 3.94 (s, 3H), 4.07 - 4.33 (m, 1H), 5.55 - 5.81 (m, 1H), 7.14 - 7.24 (m, 2H), 7.55 - 7.64 (m, 2H), 7.88 - 7.94 (m, 2H), 8.20 (br s, 1H). CLEM: m/e 535 $(M+H)^+$, tiempo de retención 3.73 min, Columna B, 4 gradiente de minuto.

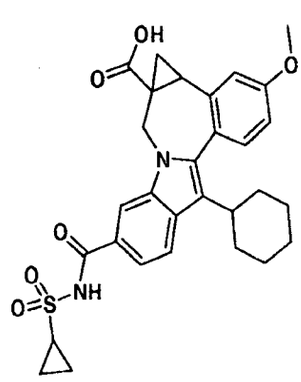
Compuesto intermedio 29



8-ciclohexil-5-((ciclopropilsulfonil)carbamoil)-11-metoxi-1,12b-dihidrociclopropa[d]indol[2,1-a][2]benzazepin-1a(2H)-carboxilato de metilo. A una mezcla espesa de hidruro de sodio (dispersión en aceite mineral al 60%, 370 mg, 9.2 mmol) en DMSO (8 mL) agitada bajo N_2, se agregó yoduro de trimetilsulfoxonio (2.03 g, 9.2 mmol). La mezcla de reacción se agitó durante 45 min y luego 13-ciclohexil-10-((ciclopropilsulfonil)carbamoil)-3-metoxi-7H-indol[2,1-a][2]benzazepin-6-carboxilato de metilo (2.2 g, 4.0 mmol) en DMSO (5 mL) se agregó (el matraz se enjuaga con DMSO (2 x 3 mL)). La mezcla de reacción se agitó 1h, vació en HCl 0.25 N (100 mL), y extrajo con EtOAc (150 mL). La capa orgánica se lavó con salmuera (20 mL) y las capas acuosas combinadas se extrajeron con EtOAc (100 mL). Las capas orgánicas combinadas

se lavaron con salmuera (~20 mL), secaron ($MgSO_4$), filtraron y concentraron hasta secarse. El residuo se agitó con EtOAc/Et_2O (1:3, 50 mL) y los sólidos se removieron por filtración. El licor madre se concentró y secó bajo alto vacío para proporcionar el 8-ciclohexil-5-((ciclopropilsulfonil)carbamoil)-11-metoxi-1,12b-dihidrociclopropa[(i]indol[2,1-a][2]benzazepin-1a(2H)-carboxilato de metilo (1.92 g, 3.4 mmol, 85%) como un sólido amarillo el cual se usó sin purificación adicional. Se presenta como una mezcla de rotámeros o isómeros atropos ~2:1. ^{1}HRMN (300 MHz, CD_3OD) δ 0.19 - 0.26 (m, 0.4H), 0.78 - 2.19 (m, 15.6H), 2.64 - 3.02 (m, 2H), 3.16 - 3.28 (m, 1H), 3.41 (d, J= 15.0 Hz, 0.6H), 3.51 (s, 1.8H), 3.80 (s, 1.2H), 3.88 (s, 3H), 4.00 (d, J= 15.0 Hz, 0.4H), 5.22 (d, J= 15.0 Hz, 0.4H), 5.42 (d, J= 15.0 Hz, 0.6H), 6.93 - 7.01 (m, 1H), 7.12 (d, J= 2.6 Hz, 0.4H), 7.19 (d, J= 2.6 Hz, 0.6H); 7.25 (d, J= 8.8 Hz, 0.6H), 7.29 (d, J= 8.8 Hz, 0.4H), 7.55 (dd, J= 8.8, 1.5 Hz, 0.6H), 7.63 (dd, J = 8.8, 1.5 Hz, 0.4H), 7.85 (d, J= 8.8 Hz, 0.6H), 7.88 (d, J= 8.8 Hz, 0.4H), 8.08 (d, J= 1.5 Hz, 0.4H), 8.31 (d, J= 1.5 Hz, 0.6H). CLEM: m/e 563 $(M+H)^+$, tiempo de retención 3.75 min, Columna B, 4 gradiente de minuto.

Compuesto intermedio 30

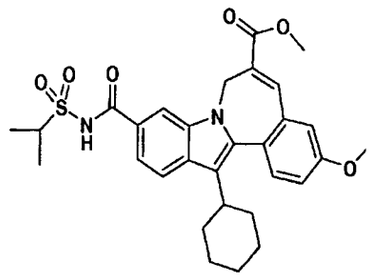


ácido 8-Ciclohexil-5-((ciclopropilsulfonil)carbamoil)-11-metoxi-1,12b-dihidrociclopropa[d]indol[2,1-a][2]benzazepin-1a(2H)-carboxílico. El 8-ciclohexil-5-((ciclopropilsulfonil)carbamoil)-11-metoxi-1,12b-dihidrociclopropa[d]indol[2,1-a][2]benzazepin-1a(2H)-carboxilato de metilo (1.92 g, 3.41 mmol) se disolvió en MeOH//THF (1:1, 40 mL) y trató con NaOH acuoso 1M (8 mL). La mezcla de reacción se agitó y calentó a 60°C durante 2h y enfrió a temperatura ambiente. La solución clara se neutralizó con HCl acuoso 1M (8 mL) y concentró para remover los solventes orgánicos. Los sólidos resultantes se recolectaron por filtración, lavaron con H_2O y secaron bajo vacío para proporcionar el ácido 8-ciclohexil-5-((ciclopropilsulfonil)carbamoil)-11-metoxi-1,12b-dihidrociclopropa[d]indol[2,1-a][2]benzazepin-1a(2H)-carboxílico (1.66 g, 3.03 mmol, 89%) como un polvo amarillo el cual se usó sin purificación adicional. Se presenta como una mezcla de rotámeros o isómeros atropos 1:1. ^{1}HRMN (300 MHz, CDCI3) δ 0.32 (t, J= 6.2 Hz, 0.5H), 0.71 - 2.12 (m, 15.5H), 2.61 - 2.94 (m, 2H), 3.16 - 3.27 (m, 1H), 3.41 (d, J= 15.0 Hz, 0.5H), 3.82 (s, 1.5H), 3.86 (s, 1.5H), 3.99 (d, J= 15.0 Hz, 0.5H), 5.28 (d, J= 15.0 Hz, 0.5H), 5.49 (d, J= 15.0 Hz, 0.5H), 6.85 (dd, J= 8.4, 2.6 Hz, 0.5H), 6.91 (dd, J= 8.4, 2.6 Hz, 0.5H), 6.96 (d, J= 2.6 Hz, 0.5H), 7.08 (d, J = 2.6 Hz, 0.5H), 7.19 (d, J= 8.4 Hz, 0.5H), 7.24 (d, J= 8.4 Hz, 0.5H), 7.61 (d,

000324

J = 8.4 Hz, 0.5H), 7.67 (d, J= 8.4 Hz, 0.5H), 7.83 (d, J= 8.4 Hz, 0.5H), 7.85 (d, J= 8.4 Hz, 0.5H), 8.06 (s, 0.5H), 8.35 (s, 0.5H), 9.31 - 10.35 (m, 1H). CLEM: m/e 547 $(M-H)^-$, tiempo de retención 2.06 min, Columna A, 4 gradiente de minuto.

Compuesto intermedio 31

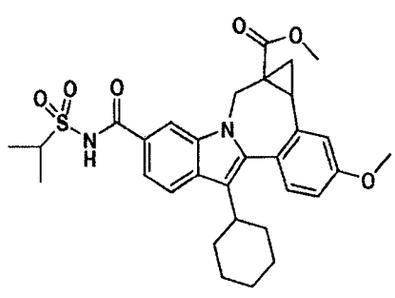


13-ciclohexil-10-((isopropilsulfonil)carbamoil)-3-metoxi-7H-indol[2,1-a][2]benzazepin-6-carboxilato de metilo. El 1,1'-Carbonildiimidazol (262 mg, 1.62 mmol) se agregó a una mezcla espesa de ácido 13-ciclohexil-3-metoxi-6-(metoxicarbonil)-7H-indol[2,1-a][2]benzazepin-10-carboxílico (603 mg, 1.36 mmol) en THF (3 mL). La mezcla de reacción se calentó a 60°C durante 1.5h, enfrió a temperatura ambiente, trató con propano-2-sulfonamida (200 mg, 1.62 mmol), agitó 10 min y luego se trató con la adición gota a gota de una solución de DBU (0.27 mL, 1.8 mmol) en THF (0.75 mL). La mezcla de reacción se agitó a temperatura ambiente durante la noche, diluyó con EtOAc (15 mL) y lavó con H_2O (~5 mL), HCl 1N (ac.) (2 x 10 mL) y salmuera (~5 mL). Las capas acuosas combinadas se extrajeron con EtOAc (15 mL) y la capa orgánica se lavó con HCl 1N (ac.) (~10 mL). Las capas orgánicas combinadas se lavaron con

000375

salmuera (~5 mL), secaron ($MgSO_4$), filtraron y concentraron. El residuo se agitó con Et_2O (~15 mL) durante 2h y los sólidos se recolectaron por filtración, enjuagaron con Et_2O y secaron para proporcionar el 13-ciclohexil-10-((isopropilsulfonil)carbamoil)-3-metoxi-7H-indol[2,1-a][2]benzazepin-6-carboxilato de metilo (640 mg, 1.2 mmol, 85%) como un sólido amarillo brillante el cual se usó sin purificación adicional. ^{1}HRMN (300 MHz, $CDCl_3$) δ 1.12 - 2.13 (m, 10H), 1.47 (d, J= 7.0 Hz, 6H), 2.73 - 2.86 (m, 1H), 3.82 (s, 3H), 3.89 (s, 3H), 4.06 - 4.26 (m, 1H), 4.09 (septeto, J= 7.0 Hz, 1H), 5.51 - 5.71 (m, 1H), 6.98 (d, J= 2.6 Hz, 1H), 7.08 (dd, J= 8.4, 2.6 Hz, 1H), 7.44 (dd, J= 8.4, 1.5 Hz, 1H), 7.50 (d, J= 8.4 Hz, 1H), 7.80 (s, 1H), 7.87 (d, J= 8.4 Hz, 1H), 8.10 (d, J= 1.5 Hz, 1H), 8.57 (s, 1H). CLEM: m/e 551 $(M+H)^+$, tiempo de retención 3.87 min, Columna B, 4 gradiente de minuto.

Compuesto intermedio 32



8-ciclohexil-5-((isopropilsulfonil)carbamoil)-11-metoxi-1,12b-dihidrociclopropa[d]indol[2,1-a][2]benzazepin-1a(2H)-carboxilato de metilo. A una mezcla espesa de hidruro de sodio

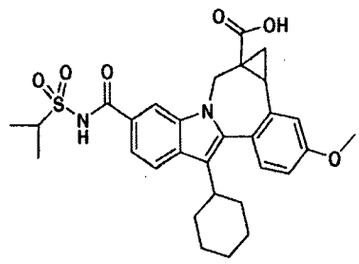
000326

(dispersión en aceite mineral al 60%, 97 mg, 2.4 mmol) en DMSO (2 mL) agitada bajo N_2, se agregó yoduro de trimetilsulfoxonio (530 g, 2.4 mmol). La mezcla de reacción se agitó durante 45 min y luego 13-ciclohexil-10-((isopropilsulfonil)carbamoil)-3-metoxi-7H-indol[2,1-a][2]benzazepin-6-carboxilato de metilo (578 g, 1.05 mmol) en DMSO (1.5 mL) se agregó (el matraz se enjuaga con DMSO (2 x 0.75 mL)). La mezcla de reacción se agitó 1h, vació en HCl 0.25 N (25 mL), y extrajo con EtOAc (40 mL). La capa orgánica se lavó con salmuera (10 ml) y las capas acuosas combinadas se extrajeron con EtOAc (25 mL). Las capas orgánicas combinadas se lavaron con salmuera (~10 mL), secaron ($MgSO_4$), filtraron y concentraron hasta secarse. El residuo se agitó con EtOAc/Et_2O (1:4, 10 mL) y los sólidos se removieron por filtración. El licor madre se concentró y secó bajo alto vacío para proporcionar 8-ciclohexil-5-((isopropilsulfonil)carbamoil)-11-metoxi-1,12b-dihidrociclopropa[d]indol[2,1-a][2]benzazepin-1a(2H)-carboxilato de metilo (620 mg, 1.0 mmol, cant.) como un sólido amarillo el cual se usó sin purificación adicional. Se presenta como una mezcla de rotámeros o isómeros atropos ~2:1. ^{1}HRMN (300 MHz, $CDCl_3$) δ 0.32 - 0.39 (m, 0.4H), 0.77 - 2.09 (m, 17.6H), 2.60 - 2.96 (m, 2H), 3.41 (d, J= 15.0 Hz, 0.6H), 3.53 (s, 1.8H), 3.79 (s, 1.2H), 3.87 (s, 3H), 4.02 - 4.14 (m, 1.4H), 5.14 (d, J= 15.0 Hz, 0.4H), 5.39 (d, J= 15.0 Hz, 0.6H), 6.89 (dd, J= 8.4, 2.6 Hz, 0.4H), 6.91 (dd, J= 8.4,

000327

2.6 Hz, 0.6H), 7.00 (d, J= 2.6 Hz, 0.4H), 7.11 (d, J= 2.6 Hz, 0.6H), 7.23 (d, J= 8.4 Hz, 0.6H), 7.25 (d, J= 8.4 Hz, 0.4H), 7.38 (dd, J= 8.4, 1.5 Hz, 0.6H), 7.43 (dd, J= 8.4, 1.5 Hz, 0.4H), 7.83 (d, J= 8.4 Hz, 0.6H), 7.86 (d, J= 8.4 Hz, 0.4H), 7.96 (d, J= 1.5 Hz, 0.4H), 8.20 (d, J= 1.5 Hz, 0.6H), 8.39 (s, 0.4H), 8.43 (s, 0.6H). CLEM: m/e 563 $(M-H)^-$, tiempo de retención 3.00 min, Columna A, 4 gradiente de minuto.

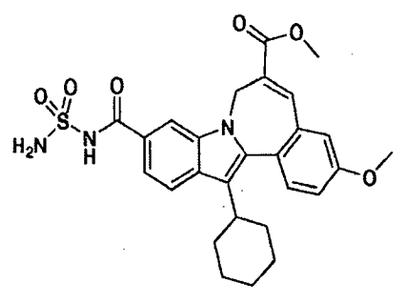
Compuesto intermedio 33



ácido 8-Ciclohexil-5-((isopropilsulfonil)carbamoil)-11-metoxi-1,12b-dihidrociclopropa[d]indol[2,1-a][2]benzazepin-1a(2H)-carboxílico. El 8-ciclohexil-5-((isopropilsulfonil)carbamoil)-11-metoxi-1,12b-dihidrociclopropa[d]indol[2,1-a][2]benzazepin-1a(2H)-carboxilato de metilo (606 mg, 1.07 mmol) se disolvió en MeOH//THF (1:1, 14 mL) y trató con NaOH acuoso 1M (2.5 mL). La mezcla de reacción se agitó y calentó a 60°C durante 2h y enfrió a temperatura ambiente. La solución clara se neutralizó con HCl acuoso 1M (2.5 mL) y concentró para remover los solventes orgánicos. El residuo se agitó con H_2O (10 mL) durante la noche y los sólidos resultantes se recolectaron por filtración, lavaron con H_2O y secaron bajo vacío para

proporcionar el ácido 8-ciclohexil-5-((isopropilsulfonil)carbamoil)-11-metoxi-1,12b-dihidrociclopropa[d]indol[2,1-a][2]benzazepin-1a(2H)-carboxílico (530 mg, 0.96 mmol, 90%) como un sólido amarillo brillante el cual se usó sin purificación adicional. Se presenta como una mezcla de rotámeros o isómeros atropos ~2:1. ^{1}HRMN (300 MHz, CD_3OD) δ 0.23 - 0.30 (m, 0.4H), 0.80 - 2.24 (m, 17.6H), 2.70 - 3.11 (m, 2H), 3.46 (d, J= 15.0 Hz, 0.6H), 3.95 (s, 3H), 3.93 - 4.10 (m, 1.4H), 5.29 (d, J= 15.0 Hz, 0.4H), 5.48 (d, J= 15.0 Hz, 0.6H), 6.98 - 7.05 (m, 1H), 7.16 (d, J= 2.6 Hz, 0.4H), 7.23 (d, J= 2.6 Hz, 0.6H), 7.29 (d, J= 8.8 Hz, 0.6H), 7.33 (d, J= 8.8 Hz, 0.4H), 7.56 (dd, J= 8.8, 1.5 Hz, 0.6H), 7.64 (dd, J= 8.4, 1.5 Hz, 0.4H), 7.87 (d, J = 8.8 Hz, 0.6H), 7.92 (d, J= 8.4 Hz, 0.4H), 8.13 (d, J= 1.5 Hz, 0.4H), 8.31 (d, J = 1.5 Hz, 0.6H). CLEM: m/e 551 $(M+H)^+$, tiempo de retención 3.74 min, Columna B, 4 gradiente de minuto.

Compuesto intermedio 34



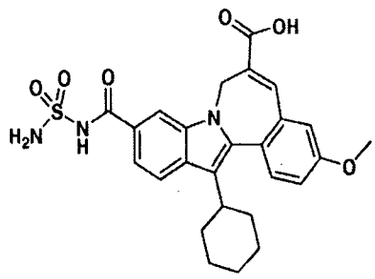
10-((aminosulfonil)carbamoil)-13-ciclohexil-3-metoxi-7H-indol[2,1-a][2]benzazepin-6-carboxilato de metilo. El 1,1'-

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Carbonildiimidazol (1.23 g, 7.60 mmol) se agregó a una mezcla espesa del ácido 13-ciclohexil-3-metoxi-6-(metoxicarbonil)-7H-indol[2,1-a][2]benzazepin-10-carboxílico (2.6 g, 5.8 mmol) en THF (11 mL). La mezcla de reacción se calentó a 60°C durante 1.5h, enfrió a temperatura ambiente, trató con sulfamida (1.12 g, 11.7 mmol), agitó 10 min y luego trató con la adición gota a gota de una solución de DBU (1.8 mL, 11.7 mmol) en THF (3 mL). La mezcla de reacción se agitó a temperatura ambiente durante 3h, diluyó con EtOAc (80 mL) y CH_2Cl_2 (100 mL) y concentró hasta secarse. El residuo se diluyó con CH_2Cl_2 (100 mL) y lavó con HCl 1N (ac.) (2 x 100 mL). Las capas acuosas combinadas se extrajeron con CH_2Cl_2 (100 mL) y las capas orgánicas combinadas se lavaron con ½ salmuera saturada (~50 mL), secaron ($MgSO_4$), filtraron y concentraron. El residuo se agitó con Et_2O (~75 mL) durante 1h y los sólidos se recolectaron por filtración, enjuagaron con Et_2O y secaron para proporcionar el 10-((aminosulfonil)carbamoil)-13-ciclohexil-3-metoxi-7H-indol[2,1-a][2]benzazepin-6-carboxilato de metilo (2.8 g, 5.3 mmol, 91%) como un sólido amarillo brillante el cual se usó sin purificación adicional. ^{1}HRMN (300 MHz, $CDCl_3$) δ 1.08 - 2.10 (m, 10H), 2.71 - 2.84 (m, 1H), 3.79 (s, 3H), 3.89 (s, 3H), 4.00 - 4.18 (m, 1H), 5.50 - 5.64 (m, 1H), 5.68 (s, 2H), 6.97 (d, J = 2.6 Hz, 1H), 7.07 (dd, J = 8.8, 2.6 Hz, 1H), 7.46 (dd, J = 8.4, 1.5 Hz, 1H), 7.49 (d, J = 8.8 Hz, 1H), 7.78 (s, 1H), 7.82 (d, J = 8.4 Hz, 1H), 8.10 (br

s, 1H), 9.49 (s, 1H). CLEM: m/e 524 $(M+H)^+$, tiempo de retención 3.60 min, Columna B, 4 gradiente de minuto.

Compuesto intermedio 35

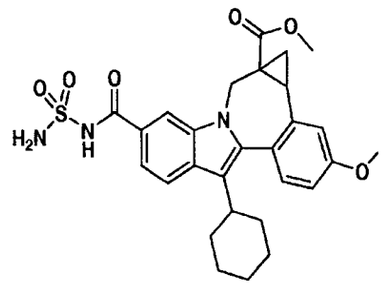


ácido 10-((Aminosulfonil)carbamoil)-13-ciclohexil-3-metoxi-7H-indol[2,1-a][2]benzazepin-6-carboxílico. El 10-((aminosulfonil)carbamoil)-13-ciclohexil-3-metoxi-7H-indol[2,1-a][2]benzazepin-6-carboxilato de metilo (725 mg, 1.39 mmol) se disolvió en MeOH//THF (1:1, 16 mL) y trató con NaOH acuoso 1M (3 mL). La mezcla de reacción se agitó y calentó a 60°C durante 0.5h y enfrió a temperatura ambiente. La solución de reacción se diluyó con $MeOH/H_2O$ (2:1, 15 mL), neutralizó con HCl acuoso 1M (3 mL) y concentró para remover los solventes orgánicos. Los sólidos resultantes se recolectaron por filtración, lavaron con H_2O y secaron bajo vacío para proporcionar el ácido 10-((aminosulfonil)carbamoil)-13-ciclohexil-3-metoxi-7H-indol[2,1-a][2]benzazepin-6-carboxílico (650 g, 1.3 mmol, 92%) como un sólido amarillo brillante el cual se usó sin purificación adicional. ^{1}HRMN (300 MHz, $CDCl_3$) δ 1.16 - 2.22 (m, 10H), 2.82 - 2.96 (m, 1H), 3.94 (s, 3H), 4.07 - 4.29 (m,

000331

1H), 5.57 - 5.80 (m, 1H), 7.14 - 7.23 (m, 2H), 7.55 - 7.63 (m, 2H), 7.88 - 7.94 (m 2H), 8.18 (s, 1H). CLEM: m/e 510 (M+H)+, tiempo de retención 2.85 min, Columna B, 4 gradiente de minuto.

Compuesto intermedio 36

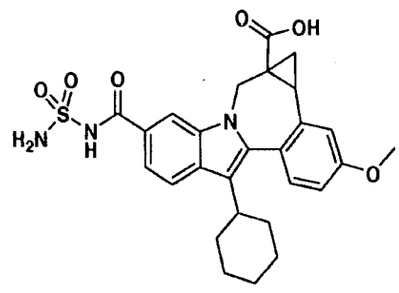


5-((aminosulfonil)carbamoil)-8-ciclohexil-11-metoxi-1,12b-dihidrociclopropa[d]indol[2,1-a][2]benzazepin-1a(2H)-carboxilato de metilo. A una mezcla espesa de hidruro de sodio (dispersión en aceite mineral al 60%, 350 mg, 8.8 mmol) en DMSO (8 mL) agitada bajo N_2, se agregó yoduro de trimetilsulfoxonio (1.93 g, 8.8 mmol) en tres porciones. La mezcla de reacción se agitó durante 0.5h y luego 10-((aminosulfonil)carbamoil)-13-ciclohexil-3-metoxi-7H-indol[2,1-a][2]benzazepin-6-carboxilato de metilo (2.0 g, 3.8 mmol) en DMSO (8 mL) se agregó (el matraz se enjuaga con DMSO (2 x 2 mL)). La mezcla de reacción se agitó 1h, vació en HCl 0.25 N (100 mL), y diluyó con CH_2Cl_2 (100 mL). La solución se filtró para colectar los sólidos, y la capa orgánica del licor madre se separó y concentró hasta secarse. El residuo se disolvió en EtOAc (~150 mL) se lavó con H_2O (~50 mL) y

000332

salmuera (~50 mL), secó ($MgSO_4$), filtró y concentró hasta secarse. El residuo se agitó con EtOAc/Et_2O (4:1, 50 mL) y los sólidos se recolectaron por filtración y lavaron con EtOAc. Estos sólidos se combinaron con los sólidos colectados inicialmente para proporcionar el 5-((aminosulfonil)carbamoil)-8-ciclohexil-11-metoxi-1,12b-dihidrociclopropa[d]indol[2,1-a][2]benzazepin-1a(2H)-carboxilato de metilo (1.39 g, 2.6 mmol, 68%) como un sólido color canela el cual se usó sin purificación adicional. Se presenta como una mezcla de rotámeros o isómeros atropos 1:1. ^{1}HRMN (300 MHz, DMSO-d_6) δ 0.13 - 0.21 (m, 0.5H), 1.06 - 2.12 (m, 11.5H), 2.64 - 2.94 (m, 2H), 3.46 (s, 1.5H), 3.49 (d, J = 15.0 Hz, 0.5H), 3.75 (s, 1.5H), 3.85 (s, 3H), 4.02 (d, J= 15.0 Hz, 0.5H), 5.21 (d, J = 15.0 Hz, 0.5H), 5.42 (d, J= 15.0 Hz, 0.5H), 6.99 - 7.09 (m, 1H), 7.17 - 7.31 (m, 1H), 7.41 (s, 0.5H), 7.43 (s, 0.5H), 7.66 - 7.56 (m, 1H), 7.82 (d, J= 8.4 Hz, 0.5H), 7.87 (d, J= 8.8 Hz, 0.5H), 8.25 (s, 0.5H), 8.47 (s, 0.5H), 11.62 (s, 0.5H), 11.69 (s, 0.5H). CLEM: m/e 538 $(M+H)^+$, tiempo de retención 3.56 min, Columna B, 4 gradiente de minuto.

Compuesto intermedio 37

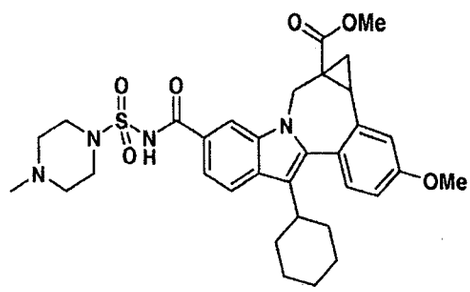


ácido 5-((Aminosulfonil)carbamoil)-8-ciclohexil-11-metoxi-1,12b-dihidrociclopropa[d]indol[2,1-a][2]benzazepin-1a(2H)-carboxílico. El 5-((aminosulfonil)carbamoil)-8-ciclohexil-11-metoxi-1,12b-dihidrociclopropa[d]indol[2,1-a][2]benzazepin-1a(2H)-carboxilato de metilo (1.1 mg, 2.0 mmol) se disolvió en MeOH//THF (1:1, 24 mL) y trató con NaOH acuoso 1M (5 mL). La mezcla de reacción se agitó y calentó a 60°C durante 2h y enfrió a temperatura ambiente. La solución clara se neutralizó con HCl acuoso 1M (5 mL) y concentró para remover los solventes orgánicos. El residuo se agitó con H_2O (10 mL) durante 1 h y los sólidos resultantes se recolectaron por filtración, lavaron con H_2O y secaron bajo vacío para proporcionar el ácido 5-((aminosulfonil)carbamoil)-8-ciclohexil-11-metoxi-1,12b-dihidrociclopropa[(i]indol[2,1-a][2]benzazepin-1a(2H)-carboxílico (1.05 mg, 2.0 mmol, 98%) como un sólido amarillo ligero el cual se usó sin purificación adicional. Se presenta como una mezcla de rotámeros o isómeros atropos 1:1. ^{1}HRMN (300 MHz, DMSO-d6) δ 0.08 - 0.17 (m, 0.5H), 0.79 - 2.13 (m, 11.5H), 2.65 - 2.94 (m, 2H), 3.44 (d, J= 14.6 Hz, 0.5H), 3.85 (s, 3H), 3.96 (d, J= 14.6 Hz, 0.5H), 5.20 (d, J= 14.6 Hz, 0.5H), 5.40 (d, J= 14.6 Hz, 0.5H), 6.98 - 7.08 (m, 1H), 7.17 - 7.46 (m, 4H), 7.58 (d, J= 8.1 Hz, 0.5H), 7.62 (d, J= 8.1 Hz, 0.5H), 7.81 (d, J= 8.8 Hz, 0.5H), 7.87 (d, J= 8.8 Hz, 0.5H), 8.25 (s, 0.5H), 8.44 (s, 0.5H), 11.48 - 13.19

(m, 2H). CLEM: m/e 524 (M+H)+, tiempo de retención 3.51 min, Columna B, 4 gradiente de minuto.

El compuesto intermedio 38 se analizó por el siguiente método CL/EM: Columna: PHENOMENNEX-LUNA 3.0 x 50mm S10; Fase móvil: (A) metanol-agua 10:90; (B) metanol-agua 90:10; Solución amortiguadora: TFA al 0.1%; Rango de gradiente: B al 0-100%; Tiempo de gradiente: 2 min; Relación de flujo: 4 mL/min; Tiempo de análisis: 3 min; Detección: Detector 1: UV a 220 nm; Detector 2: EM (ESI+).

Compuesto intermedio 38



(+/-)-8-Ciclohexil-N-4-(4-metilpiperazin-1-ilsulfonil)-1,1a,2,12b-tetrahidro-11-metoxi-1a-(metoxicarbonil)ciclopropa[d]indol[2,1-a][2]benzazepin-5-carboxamida. A una solución agitada de ácido (1.15 g, 2.5 mmol) en THF an. (5 mL), CDI puro (0.61 g, 3.75 mmol) se agregó y la mezcla se calentó a 50°C durante 30 min. Luego al reactivo la amina y DBU se agregaron y la mezcla resultante se agitó a temperatura ambiente durante la noche. La reacción se apagó con NH_4Cl sat. y luego extrajo con EtOAc (2X50 mL). La capa orgánica se lavó con agua y luego se secó (Na2SO4). El

producto crudo se purificó por cromatografía de columna instantánea (gel de sílice, MeOH al 8-10% en DCM) para proporcionar el producto (1.03 g, 66%) como un sólido beige. CL/EM: Tiempo de retención: 2.913 min; m/e 621 (MH+). El producto se observó que existe como rotámeros de Interconversión por 1H RMN (400 MHz, CLOROFORMO-D): δ ppm 0.31 - 0.41 (m, 1 H), 1.16 - 1.28 (m, 2 H), 1.29 - 1.48 (m, 2 H), 1.50 - 1.61 (m, 1 H), 1.63 - 1.84 (m, 3 H), 1.85 - 2.10 (m, 6 H), 2.28 - 2.39 (m, 3 H), 2.38 - 2.50 (m, 1 H), 2.51 - 2.61 (m, 4 H), 2.61 - 2.82 (m, 1 H), 2.82 - 2.96 (m, 1 H), 3.36 - 3.48 (m, 1 H), 3.50 - 3.62 (m, 3 H), 3.77 - 3.92 (m, 3 H), 5.10 - 5.44 (m, 1 H), 6.69 (s, 1 H), 6.86 - 7.04 (m, 1 H), 7.08 - 7.15 (m, 1 H), 7.21 - 7.28 (m, 1 H), 7.33 - 7.55 (m, 1 H), 7.77 - 7.88 (m, 1 H), 7.94 - 8.25 (m, 1 H).

El Compuesto intermedio 39 y los Ejemplos 1-11 emplean los procedimientos experimentales que siguen hasta que se indica lo contrario. Método HPLC: Método A: % inicial B= 0; % final B= 100; Tiempo de gradiente= 3 min; Relación de flujo= 4 ml/min; Longitud de onda= 220; Solvente A= MeOH al 10%-H_2O al 90%-TFA al 0.1%; Solvente B= MeOH al 90%-H_2O al 10%-TFA al 0.1%; Columna: Peneomenex-Luna 3.0 x 50 mm S10; Método B: % inicial B= 0; % final B= 100; Tiempo de gradiente= 3 min; Relación de flujo= 4 ml/min; Longitud de onda= 220; Solvente A= acetonitrilo al 5%-H_2O al 95%-acetato de amonio 10 Mm; Solvente B= acetonitrilo al 95%-H_2O al 5%-acetato de amonio 10 Mm; Columna= Phenomenex-Luna

3.0 x 50 mm S10. Los compuestos para los cuales los datos CL/EM se obtuvieron con el método B se observaron. A menos de que se indique el CL/EM se obtuvo usando el Método A.

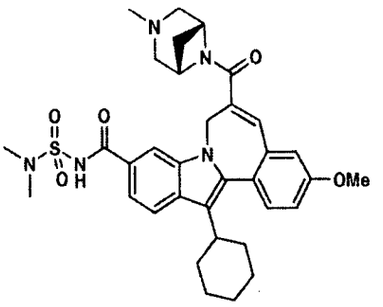
Compuesto intermedio 39



(1R,5S)-3-metil-3,6-diazabiciclo[3.1.1]heptano. A una solución de 3,6-diazabiciclo[3.1.1]heptano-6-carboxilato de (1R,5S)-tert-butilo (1.0 g, 5.04 mmol) en MeOH (25 mL), se agregaron paraformaldehído (0.227 g, 7.57 mmol) y cloruro de zinc (1.03 g, 7.57 mmol). Luego cianoborohidruro de sodio (0.475 g, 7.57 mmol) se agregó en porciones. La mezcla de reacción se agitó a temperatura ambiente durante la noche. Luego el sólido insoluble se filtró y el filtrado se concentró. El residuo participó entre solución de $NaHCO_3$ al 10% y acetato de etilo (2X50 mL). Las capas orgánicas se combinaron, secaron ($MgSO_4$) y concentraron para dar un aceite incoloro. Este luego se disolvió en CH_2Cl_2 (10 mL) y TFA (2.5 mL) se agregó. La mezcla de reacción se agitó a temperatura ambiente durante la noche. El TFA y el solvente se evaporaron para dar un sólido blanco como producto final como sal diTFA. (1.14 g, 66% de rendimiento). EM m/113 (MH^+). ^1H RMN (500 MHz, MeOD) δ ppm 2.25 (d, J=11.90 Hz, 1 H) 3.01 - 3.06 (m, 3 H) 3.08 - 3.18 (m, 1 H) 3.80 (d, J=13.73 Hz, 2 H) 4.13 (d, J=14.34 Hz, 2 H) 4.47 (d, J=6.10 Hz, 2 H).

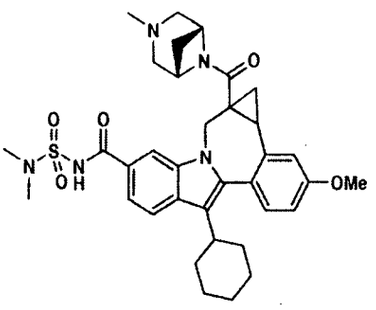
000337

Ejemplo 1



7H-Indol[2,1-a][2]benzazepin-10-carboxamida,13-ciclohexil-N-[(dimetilamino)sulfonil]-3-metoxi-6-[[(1R,5S)-3-metil-3,6-diazabiciclo[3.1.1]hept-6-il]carbonilo]-. EM m/z 632(MH+), Tiempo de retención: 2.510 min. ^{1}H RMN (500 MHz, MeOD) δ ppm 1.12 - 1.61 (m, 4 H) 1.65 - 2.22 (m, 7 H) 2.28 - 3.09 (m, 12 H) 3.51 - 3.88 (m, 3 H) 3.95 (s, 3 H) 4.20 (d, J=13.42 Hz, 1 H) 4.63 (s, br, 2 H) 5.51 (d, J=13.43 Hz, 1 H) 7.17 - 7.25 (m, 2 H) 7.43 (s, 1 H) 7.54 - 7.62 (m, 2 H) 7.93 (d, J=8.24 Hz, 1 H) 8.18 (s, 1 H).

Ejemplo 2

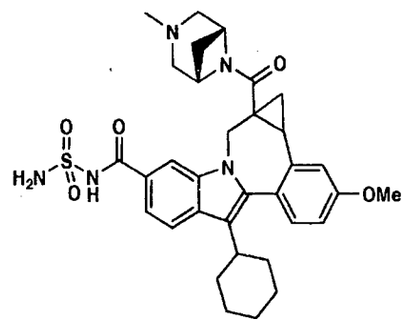


Cicloprop[d]indol[2,1-a][2]benzazepin-5-carboxamida, 8-ciclohexil-N-[(dimetilamino)sulfonil]-1,1a,2,12b-tetrahidro-11-metoxi-1a-[[(1R,5S)-3-metil-3,6-diazabiciclo[3.31]hept-6-il]carbonilo]-. EM m/z 644(MH+), Tiempo de retención: 2.057 min (Método B). ^{1}H RMN (500 MHz, MeOD) δ ppm 0.14 (m, 0.2 H) 1.12 -

000338

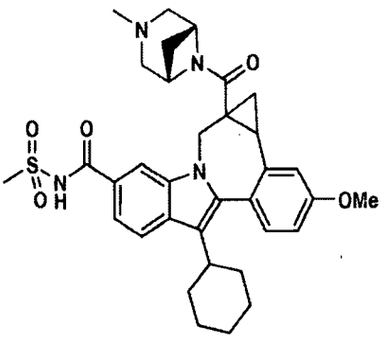
2.19 (m, 14.8 H) 2.39 - 3.08 (m, 12 H) 3.44 - 3.95 (m, 7.4 H) 4.15 (d, J=14.65 Hz, 0.2 H) 4.57 (s, br, 0.4 H) 5.01 (d, J=14.65 Hz, 0.2 H) 5.31 (s, br, 0.8 H) 6.98 - 7.04 (m, 1 H) 7.19 (s, 1 H) 7.30 (d, J=8.55 Hz, 0.8 H) 7.33 (d, J=8.55 Hz, 0.2 H) 7.59 (d, J=8.24 Hz, 1 H) 7.88 (d, J=8.55 Hz, 0.2 H) 7.93 (d, J=8.54 Hz, 0.8 H) 8.08 (s, 0.2 H) 8.10 (s, 0.8 H).

Ejemplo 3



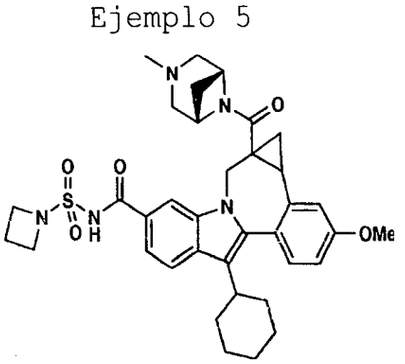
Ciclopropa[d]indol[2,1-a][2]benzazepin-5-carboxamida, N-(aminosulfonil)-8-ciclohexil-1,1a,2,12b-tetrahidro-11-metoxi-1a-[[(1R,5S)-3-metil-3,6-diazabiciclo[3.31]hept-6-il]carbonilo]-. EM m/z 618(MH+), Tiempo de retención: 2.292 min. ^{1}H RMN (500 MHz, MeOD) δ ppm 0.18 (m, 0.17 H) 1.20 - 2.23 (m, 14.83 H) 2.55 - 3. 3.99 (m, 13.49 H) 4.19 (d, J=14.95 Hz, 0.17 H) 4.62 (s, br, 0.34 H) 5.05 (d, J=14.65 Hz, 0.17 H) 5.35 (s, br, 0.83 H) 7.01 - 7.09 (m, 1 H) 7.21 - 7.27 (m, 1 H) 7.30 - 7.38 (m, 1 H) 7.60 - 7.69 (m, 1 H) 7.91 (d, J=8.55 Hz, 0.17 H) 7.97 (d, J=8.55 Hz, 0.83 H) 8.12 (s, 0.17 H) 8.15 (s, 0.83 H).

Ejemplo 4



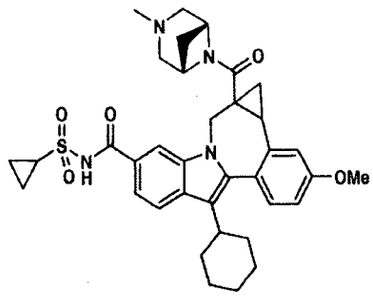
Cicloprop[d]indol[2,1-a][2]benzazepin-5-carboxamida, 8-ciclohexil-1,1a,2,12b-tetrahidro-11-metoxi-1a-[[(1R,5S)-3-metil-3,6-diazabiciclo[3.1.1]hept-6-il]carbonil]-N-(metilsulfonilo)-. EM m/z 617(MH+), Tiempo de retención: 2.383 min. ^{1}H RMN (500 MHz, MeOD) δ ppm 0.18 (m, 0.19 H) 1.17 - 2.25 (m, 14.81 H) 2.54 - 4.04 (m, 16.43 H) 4.19 (d, J=14.65 Hz, 0.19 H) 4.62 (s, br, 0.38 H) 5.06 (d, J=14.34 Hz, 0.19 H) 5.35 (s, br, 0.81 H) 7.01 - 7.10 (m, 1 H) 7.22 - 7.25 (m, 1 H) 7.32 - 7.39 (m, 1 H) 7.60 - 7.68 (m, 1 H) 7.93 (d, J=8.55 Hz, 0.19 H) 7.98 (d, J=8.55 Hz, 0.81 H) 8.14 (s, 0.19 H) 8.17 (s, 0.81 H).

Ejemplo 5



Cicloprop[d]indol[2,1-a][2]benzazepin-5-carboxamida, N-(1-azetidinilsulfonil)-8-ciclohexil-1,1a,2,12b-tetrahidro-11-metoxi-1a-[[(1R,5S)-3-metil-3,6-diazabiciclo[3.31]hept-6-il]carbonilo]-. EM m/z 658 (MH^+), Tiempo de retención: 2.467 min. ^1H RMN (500 MHz, MeOD) δ ppm 0.20 (m, 0.18 H) 1.18 - 2.23 (m, 14.82 H) 2.24 - 2.37 (m, 2 H) 2.53 - 3.99 (m, 13.46 H) 4.16 - 4.30 (m, 4.18 H) 4.62 (s, br, 0.36 H) 5.07 (d, J=14.65 Hz, 0.18 H) 5.36 (s, br, 0.82 H) 7.02 - 7.10 (m, 1 H) 7.22-7.25 (m, 1 H) 7.31 - 7.39 (m, 1 H) 7.66 (d, J=8.24 Hz, 1 H) 7.94 (d, J=8.55 Hz, 0.18 H) 7.99 (d, J=8.55 Hz, 0.82 H) 8.15 (s, 0.18 H) 8.19 (s, 0.82 H).

Ejemplo 6

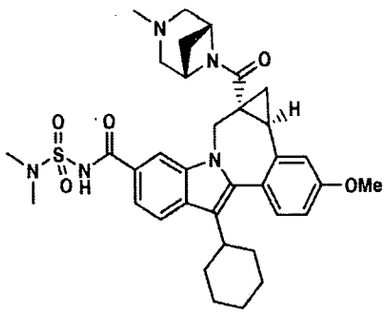


Cicloprop[d]indol[2,1-a][2]benzazepin-5-carboxamida, 8-ciclohexil-N-(ciclopropilsulfonil)-1,1a,2,12b-tetrahidro-11-metoxi-1a-[[(1R,5S)-3-metil-3,6-diazabiciclo[3.31]hept-6-il]carbonilo]-. EM m/z 643(MH+), Tiempo de retención: 2.438 min. ^1H RMN (500 MHz, MeOD) δ ppm 0.14 - 0.23 (m, 0.16 H) 1.11 - 2.25 (m, 18.84 H) 2.51 - 4.01 (m, 14.52 H) 4.19 (d, J=14.95 Hz, 0.16 H) 4.62 (s, br, 0.32 H) 5.06 (d, J=14.95 Hz, 0.16H) 5.37 (s, br, 0.84 H) 7.00 - 7.11 (m, 1 H) 7.19 - 7.27 (m, 1 H)

000341

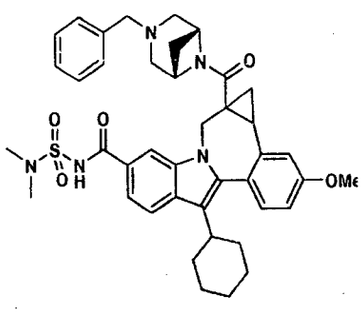
7.32 - 7.41 (m, 1 H) 7.60 - 7.69 (m, 1 H) 7.94 (d, J=8.55 Hz, 0.16 H) 7.99 (d, J=8.55 Hz, 0.84 H) 8.13 (s, 0.16 H) 8.17 (s, 0.84 H).

Ejemplo 7



Cicloprop[d]indol[2,1-a][2]benzazepin-5-carboxamida, 8-ciclohexil-N-[(dimetilamino)sulfonil]-1,1a,2,12b-tetrahidro-11-metoxi-1a-[[(1R,5S)-3-metil-3,6-diazabiciclo[3.31]hept-6-il]carbonilo]-, (1aR,12bS)-. EM m/z 644 (MH^+), Tiempo de retención: 2.175 min (Método B). ^1H RMN (500 MHz, MeOD) δ ppm 0.14 (m, 0.2 H) 1.12 - 2.19 (m, 14.8 H) 2.39 - 3.08 (m, 12 H) 3.44 - 3.95 (m, 7.4 H) 4.15 (d, J=14.65 Hz, 0.2 H) 4.57 (s, br, 0.4 H) 5.01 (d, J=14.65 Hz, 0.2 H) 5.31 (s, br, 0.8 H) 6.98 - 7.04 (m, 1 H) 7.19 (s, 1 H) 7.30 (d, J=8.55 Hz, 0.8 H) 7.33 (d, J=8.55 Hz, 0.2 H) 7.59 (d, J=8.24 Hz, 1 H) 7.88 (d, J=8.55 Hz, 0.2 H) 7.93 (d, J=8.54 Hz, 0.8 H) 8.08 (s, 0.2 H) 8.10 (s, 0.8 H).

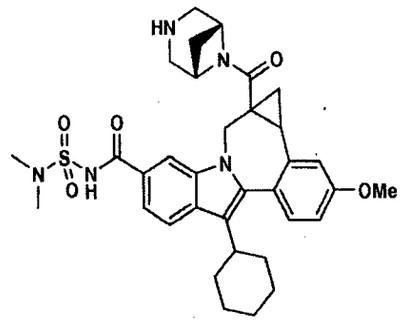
Ejemplo 8



Cicloprop[d]indol[2,1-a][2]benzazepin-5-carboxamida, 8-ciclohexil-N-[(dimetilamino)sulfonil]-1,1a,2,12b-tetrahidro-11-metoxi-1a-[[(1R,5S)-3-(fenilmetil)-3,6-diazabiciclo[3.1.1]hept-6-il]carbonilo]-. A una solución de ácido cicloprop[d]indol[2,1-a][2]benzazepin-1a(2H)-carboxílico, 8-ciclohexil-5-[[[(dimetilamino)sulfonil]amino]carbonil]-1,12b-dihidro-11-metoxi- (300 mg, 0.544 mmol) en DMSO (10 mL), TBTU (262 mg, 0.816 mmol) y DIPEA (0.47 mL, 2.72 mmol) se agregaron. La mezcla de reacción se agitó a temperatura ambiente durante 15 min. Luego (1R,5S)-3-bencil-3,6-diazabiciclo[3.1.1]heptano (154 mg, 0. 816 mmol) se agregó y la mezcla de reacción se agitó a temperatura ambiente durante la noche. Luego se concentró y el residuo se purificó por la columna HPLC prep. para dar un sólido amarillo ligero como producto final. (373 mg, 82% de rendimiento). EM m/z 722(MH+), Tiempo de retención: 3.500 min (Método B). ^{1}H RMN (500 MHz, MeOD) δ ppm 0.13 (m, 0.24 H) 1.14 - 2.25 (m, 14.76 H) 2.49 - 4.03 (m, 18.28 H) 4.13 (d, J=14.65 Hz, 0.24 H) 4.45 - 4.66 (m, 0.48 H) 4.98 (d, J=14.95 Hz, 0.24 H) 5.36 (s, br, 0.76 H) 7.03 (dd, J=8.39, 2.59 Hz, 1 H) 7.16 - 7.64 (m, 8 H) 7.90 (d, J=8.54 Hz, 0.24 H) 7.92 (d, J=8.55 Hz, 0.76 H) 8.08 (s, 0.24 H) 8.19 (s, br, 0.76 H).

000343

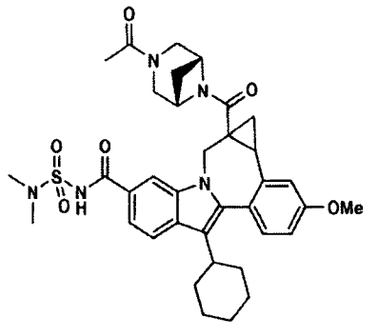
Ejemplo 9



Cicloprop[d]indol[2,1-a][2]benzazepin-5-carboxamida, 8-ciclohexil-1a-[(1R,5S)-3,6-diazabiciclo[3.1.1]hept-6-ilcarbonil]-N-[(dimetilamino)sulfonil]-1,1a,2,12b-tetrahidro-11-metoxi-. A una solución de cicloprop[d]indol[2,1-a][2]benzazepin-5-carboxamida, 8-ciclohexil-N-[(dimetilamino)sulfonil]-1,1a,2,12b-tetrahidro-11-metoxi-1a-[[(1R,5S)-3-(fenilmetil)-3,6-diazabiciclo[3.1.1]hept-6-il]carbonilo]- (60 mg, 0.072 mmol) en etanol (5 mL), $Pd(OH)_2$ (60 mg) y Solución HCl 1N (0.072 mL, 0.072 mmol) se agregaron. La mezcla de reacción se agitó bajo un hidrogenador a 30-40 psi (2.109-2.812 kg/cm^2) durante 6 hr. El catalizador se filtró del celite y el filtrado se concentró para dar un sólido amarillento como producto crudo. Luego se purificó por Columna de HPLC prep. para dar un sólido amarillo ligero como producto final como sal TFA. (42 mg, 78% de rendimiento). EM m/z 632 (MH^+), Tiempo de retención: 1.795 min (Método B). ^1H RMN (500 MHz, MeOD) δ ppm 0.17 (m, 0.26 H) 1.15 - 2.25 (m, 14.74 H) 2.45 - 4.01 (m, 16.22 H) 4.20 (d, J=14.34 Hz, 0.26

H) 4.57 (s, br, 0.52 H) 5.00 - 5.04 (m, 0.26 H) 5.23 (d, J=14.95 Hz, 0.74 H) 7.01 - 7.09 (m, 1 H) 7.22 (s, 1 H) 7.33 (d, J=8.55 Hz, 0.74 H) 7.36 (d, J=8.54 Hz, 0.26 H) 7.63 (dd, J=8.55, 1.53 Hz, 1 H) 7.89 - 7.98 (m, 1 H) 8.14 (s, 1 H).

Ejemplo 10

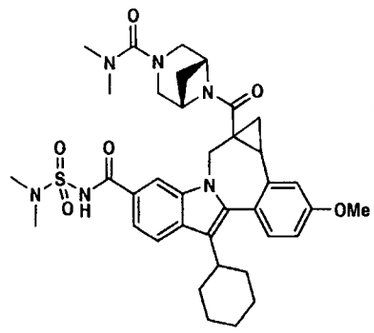


Cicloprop[d]indol[2,1-a][2]benzazepin-5-carboxamida, 1a-[[(1R,5S)-3-acetil-3,6-diazabiciclo[3.1.1]hept-6-il]carbonil]-8-ciclohexil-N-[(dimetilamino)sulfonil]-1,1a,2,12b-tetrahidro-11-metoxi-. A una solución de ácido acético (0.002 mL, 0.040 mmol) en DMSO (1.0 mL), TBTU (16.1 mg, 0.050 mmol) y DIPEA (0.029 mL, 0.128 mmol) se agregaron. La mezcla de reacción se agitó a temperatura ambiente durante 10 min. Luego cicloprop[d]indol[2,1-a][2]benzazepin-5-carboxamida, 8-ciclohexil-1a-[(1R,5S)-3,6-diazabiciclo[3.1.1]hept-6-ilcarbonil]-N-[(dimetilamino)sulfonil]-1,1a,2,12b-tetrahidro-11-metoxi- (25 mg, 0.0335 mmol) se agregó. La mezcla de reacción luego se agitó a temperatura ambiente durante la noche. Luego se

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purificó por Columna de HPLC prep. Las fracciones se recolectaron y concentraron para dar un sólido amarillo ligero como producto final. (16.5 mg, 73% de rendimiento). EM m/z 674(MH+), Tiempo de retención: 2.718 min. ^{1}H RMN (500 MHz, MeOD) δ ppm 0.09 (m, 0.3 H) 0.49 - 2.28 (m, 17.7 H) 2.31 - 4.52 (m, 16.4 H) 4.66 - 5.43 (m, 1.6 H) 6.92 - 7.05 (m, 1 H) 7.06 - 7.21 (m, 1 H) 7.25 - 7.35 (m, 1 H) 7.45 - 7.69 (m, 1 H) 7.76 - 8.00 (m, 1 H) 8.02 - 8.16 (m, 1 H).

Ejemplo 11



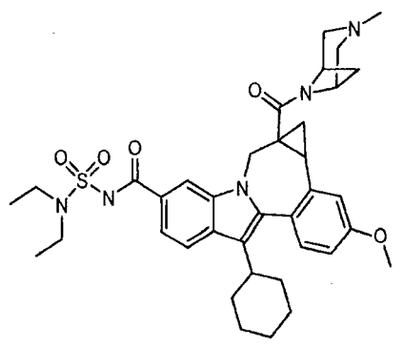
Ciclopropa[d]indol[2,1-a][2]benzazepin-5-carboxamida, 8-ciclohexil-1a-[[(1R,5S)-3-[(dimetilamino)carbonil]-3,6-diazabiciclo[3.1.1]hept-6-il]carbonil]-N-[(dimetilamino)sulfonil]-1,1a,2,12b-tetrahidro-11-metoxi-. A una solución de ciclopropa[d]indol[2,1-a][2]benzazepin-5-carboxamida, 8-ciclohexil-1a-[(1R,5S)-3,6-diazabiciclo[3.1.1]hept-6-ilcarbonil]-N-[(dimetilamino)sulfonil]-1,1a,2,12b-tetrahidro-11-metoxi- (50 mg, 0.067 mmol) en CH2Cl2 (3 mL), DIPEA (0.052 mL, 0.3 mmol) y cloruro de dimetilcarbami (0.009 mL, 0.1 mmol) se agregaron. La mezcla de reacción se agitó a temperatura ambiente durante

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la noche. Luego se concentró y el residuo se purificó por Columna de HPLC prep. Las fracciones se recolectaron y concentraron para dar un sólido amarillo como producto final. (18.5 mg, 39% de rendimiento). EM m/z 703 (MH^+), Tiempo de retención: 2.771 min. ^1H RMN (500 MHz, MeOD) δ ppm 0.08 (m, 0.4 H) 0.53 - 2.22 (m, 14.6 H) 2.29 - 4.43 (m, 22.2 H) 4.55-5.46 (m, 1.8 H) 6.93 - 7.04 (m, 1 H) 7.16 (d, J=2.44 Hz, 0.4 H) 7.19 (d, J=2.45 Hz, 0.6 H) 7.25 - 7.34 (m, 1 H) 7.44 - 7.70 (m, 1 H) 7.76 - 7.99 (m, 1 H) 8.00 - 8.16 (m, 0.6 H) 8.42 (s, br, 0.4 H).

Los Ejemplos 12 - 16 usan los procedimientos experimentales que siguen hasta que se indique lo contrario. Todos los compuestos descritos a continuación se analizaron por seguir el método CL/EM: % inicial B: 0; % final B: 100; Tiempo de gradiente: 3 min; Tiempo detenido: 4 min; Relación de flujo: 4 ml/min; Longitud de onda: 220; Solvente A: MeOH al 10%/H_2O al 90%/ácido trifluoroacético al 0.1%; Solvente B: H_2O al 10%/MeOH al 90%/ácido trifluoroacético al 0.1%; Columna: XBridge 4.6 x 50 mm S5.

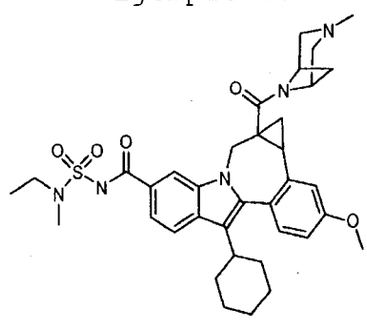
Ejemplo 12



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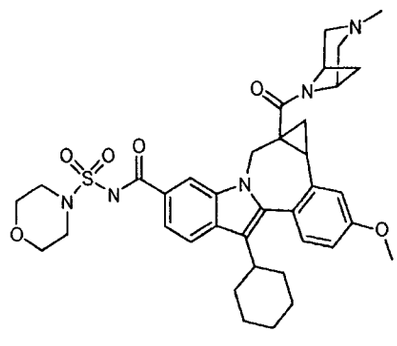
(+/-)-8-Ciclohexil-N-(N,N-dietilaminosulfonil)-1,1a,2,12b-tetrahidro-11-metoxi-1a-(1-(3-metil-3,6-diazabiciclo[3.1.1]heptan-6-il))-8-carbonil)-cicloprop[d]indol[2,1-a][2]benzazepin-5-carboxamida. A una mezcla del compuesto ácido (0.050g, 0.86 mmol) y bis(2,2,2-trifluoroacetato) de 3-metil-3,6-diazabiciclo[3.1.1]heptano (44.0 mg, 0.129 mmol) en CH2Cl2 (1.5 ml) se agregó TEA (0.120 ml, 0.863 mmol) y HBTU (49.0 mg, 0.129 mmol) y agitó a temperatura ambiente durante 80 min, diluyó con MeOH, removió el solvente. El residuo se disolvió en metanol, y purificó por HPLC prep. para proporcionar una sal TFA del compuesto 1 (0.0296 g, 45%). Tiempo de retención CL-EM: 3.150; EM m/z 674 (M+H)]. 1H RMN (400 MHz, CLOROFORMO-D): δ ppm 1.12 - 1.57 (m, 7 H) 1.23 (t, J=7.18 Hz, 6 H) 1.81 (s, 2 H) 1.87 - 2.17 (m, 5 H) 2.64 - 2.79 (m, 1 H) 2.83 - 3.02 (m, 2 H) 3.10 - 3.23 (m, J=7.30, 4.78 Hz, 1 H) 3.32 - 5.34 (m, 7 H) 3.54 (q, J=7.05 Hz, 4 H) 3.90 (s, 3 H) 4.36 (s, 1 H) 5.39 - 5.64 (m, 1 H) 6.97 (dd, J=8.56, 2.77 Hz, 1 H) 7.12 (d, J=2.52 Hz, 1 H) 7.22 - 7.32 (m, 1 H) 7.47 (d, J=8.31 Hz, 1 H) 7.86 - 7.90 (m, 1 H) 8.11 (s, 1H).

Ejemplo 13



(+/-)-8-Ciclohexil-N-(N-metil-N-etilaminosulfonil)-1,1a,2,12b-tetrahidro-11-metoxi-1a-(1-(3-metil-3,6-diazabiciclo[3.1.1]heptan-6-il))-8-carbonil)-ciclopropa[d]indol[2,1-a] [2]benzazepin-5-carboxamida. Se preparó una sal TFA del producto a partir del ácido (0.0294 g, 55%). Tiempo de retención CL-EM: 3.066; EM m/z 660(M+H). 1H RMN (400 MHz, CLOROFORMO-d): δ ppm 1.20 - 1.26 (m, 3 H) 1.25 - 1.56 (m, 6 H) 1.81 (s, 3 H) 1.88 - 2.12 (m, 5 H) 2.63 - 2.78 (m, 1 H) 3.06 (s, 3 H) 3.10 - 3.22 (m, J=7.18, 5.16 Hz, 1 H) 3.42 - 3.50 (m, 5 H) 3.55 - 3.76 (m, 1 H) 3.90 (s, 3 H) 3.93 - 4.40 (m, 5 H) 4.33 - 4.39 (m, 1 H) 5.38 - 5.53 (m, 1 H) 6.97 (dd, J=8.69, 2.64 Hz, 1 H) 7.12 (d, J=2.52 Hz, 1 H) 7.24 - 7.32 (m, 1 H) 7.49 (d, J=8.31 Hz, 1 H) 7.85 - 7.90 (m, 1 H) 8.12 (s, 1 H).

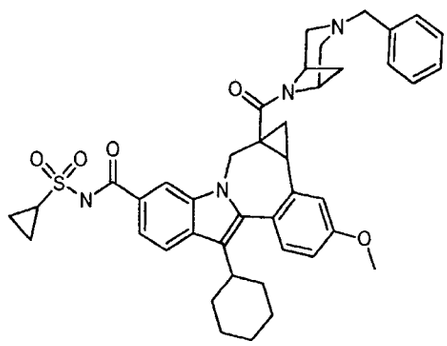
Ejemplo 14



(+/-)-8-Ciclohexil-N-(morfolinosulfonil)-1,1a,2,12b-tetrahidro-11-metoxi-1a-(1-(3-metil-3,6-diazabiciclo[3.1.1]heptan-6-il))-8-carbonil)-ciclopropa[d]indol[2,1-a][2]benzazepin-5-carboxamida. Se preparó una sal TFA del producto (0.0323 g, 48%). Tiempo de

retención CL-EM: 2.955; EM m/z (M+H) 688. 1H RMN (400 MHz, CLOROFORMO-d): δ ppm 1.18 - 1.56 (m, 6 H) 1.81 (t, J=12.84 Hz, 3 H) 1.87 - 2.13 (m, 5 H) 2.62 - 2.78 (m, 1 H) 2.80 - 2.89 (m, J=18.51, 4.66 Hz, 1 H) 2.90 - 3.01 (m, 1 H) 3.08 - 3.20 (m, 1 H) 3.40 - 3.55 (m, 6 H) 3.56 - 3.69 (m, 1 H) 3.71 - 4.31 (m, 4 H) 3.73 - 3.79 (m, 4 H) 3.89 (s, 3 H) 4.31 - 4.41 (m, 1 H) 5.35 - 5.56 (m, 1 H) 6.97 (dd, J=8.69, 2.64 Hz, 1 H) 7.11 (d, J=2.27 Hz, 1 H) 7.20 - 7.33 (m, 1 H) 7.46 - 7.56 (m, 1 H) 7.87 (d, J=8.56 Hz, 1 H) 8.12 (s, 1 H).

Ejemplo 15

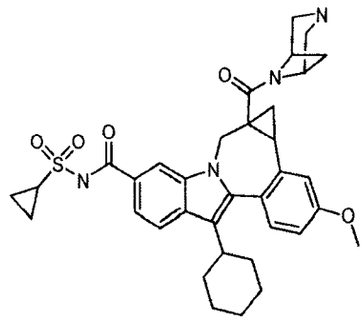


(+/-)-8-Ciclohexil-N-(ciclopropilsulfonil)-1,1a,2,12b-tetrahidro-11-metoxi-1a-(1-(3-bencil-3,6-diazabiciclo[3.1.1]heptan-6-il))-8-carbonil)-ciclopropa[d]indol[2,1-a][2]benzazepin-5-carboxamida.

Se preparó una sal TFA del producto (0.056 g, 71%). Tiempo de retención CL-EM: 3.11; EM m/z 719 (M+H). ^{1}H RMN (400 MHz, CLOROFORMO-d): δ ppm 1.02 - 1.60 (m, 9 1.69 - 2.17 (m, 9 2.48 - 3.03 (m, 3 3.06 - 3.34 (m, 3 3.46 (d, J=13.35 Hz, 1 3.62 - 4.06 (m, 4 3.90 (s, 3

4.28 - 4.68 (m, 2 6.88 - 7.02 (m, 2 7.13 (d, J=2.27 Hz, 2 7.23 - 7.30 (m, 1 7.35 (d, J=5.04 Hz, 2 7.38 - 7.54 (m, 2 7.87 (d, J=8.31 Hz, 1 8.32 (s, 1 H).

Ejemplo 16

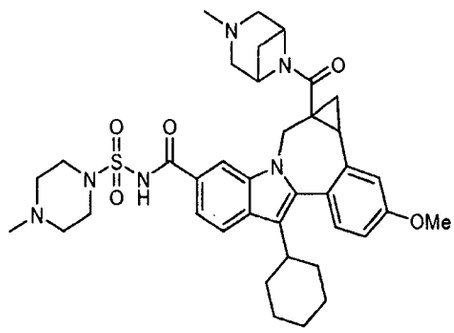


(+/-) 8-Ciclohexil-N-(ciclopropilsulfonil)-1,1a,2,12b-tetrahidro-11-metoxi-1a-(1-(3,6-diazabiciclo[3.1.1]heptan-6-il))-8-carbonil)-ciclopropa[d]indol[2,1-a][2]benzazepin-5-carboxamida. Una mezcla del compuesto de bencilo (0.052g, 0.072 mmol) y Pd/C (p/p 10%, 0.05g), en MeOH (8 mL) se desgasificó y agitó bajo un globo de H_2 durante la noche. Se filtra el sólido y remueve el solvente para proporcionar el producto como un sólido amarillo (0.042g, 93%) en la forma de sal TFA. Tiempo de retención CL-EM: 2.976; EM m/z 629 (M+H). ^{1}H RMN (400 MHz, CLOROFORMO-d): δ ppm 0.99 - 2.13 (m, 18 2.38 - 2.51 (m, 1 2.71 - 3.76 (m, 7 3.88 (s, 3 4.09 - 4.26 (m, J= 11.08 Hz, 1 4.50 (d, J=31.73 Hz, 1 4.90 (d, J=14.86 Hz, 1 6.89 - 6.98 (m, 1 7.05 (d, J=2.01 Hz, 1 7.21 - 7.31 (m, 1 7.69 (d, J=7.81 Hz, 1 7.82 - 7.92 (m, J=8.31 Hz, 1 8.24 - 8.33 (m, 1 H).

009351

El ejemplo 17 se analizó por el siguiente método CL/EM: Columna: PHENOMENNEX-LUNA 3.0 x 50mm S10; Fase móvil:(A) 10:90 metanol-agua; (B) 90:10 metanol-agua; Solución amortiguadora: TFA al 0.1%; Rango de gradiente: B al 0-100%; Tiempo de gradiente: 2 min; Relación de flujo: 4 mL/min; Tiempo de análisis: 3 min; Detección: Detector 1: UV a 220 nm; Detector 2: EM (ESI+).

Ejemplo 17

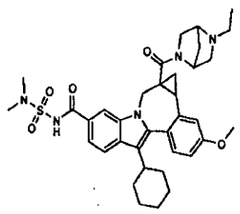
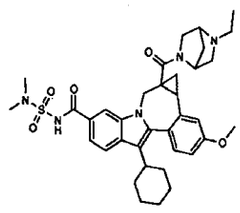
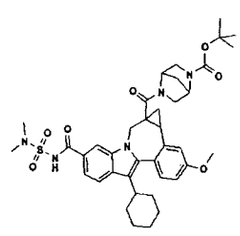
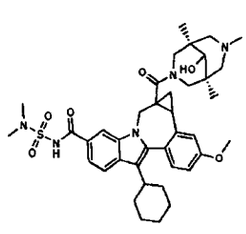
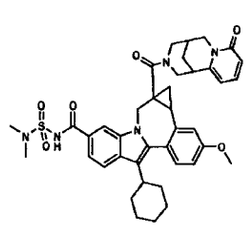
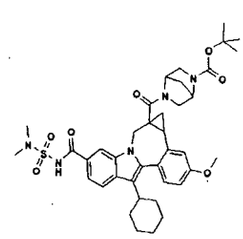


(+/-)-8-Ciclohexil-N-4-(4-metilpiperazin-1-ilsulfonil)-1,1a,2,12b-tetrahidro-11-metoxi-1a-(3-metil-3,6-diazabiciclo[3.1.1]heptano-6-carbonil)cicloprop[d]indol[2,1-a][2]benzazepin-5-carboxamida. El material de partida se hidrolizó con NaOH 1N en THF-MeOH para proporcionar el ácido correspondiente en rendimiento cuantitativo. El ácido se acopló con amina usando TBTU y TEA para proporcionar la amida la cual se purifica por HPLC preparativa de fase inversa y se aísla en forma de sal bis-TFA como un sólido beige. CL/EM: Tiempo de

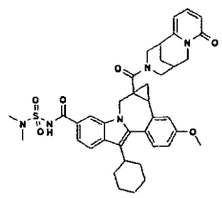
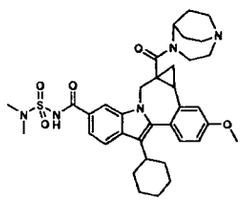
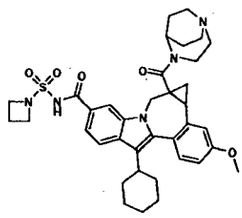
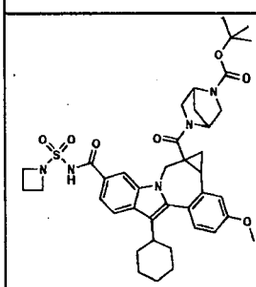
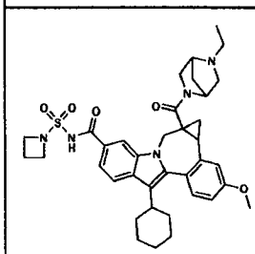
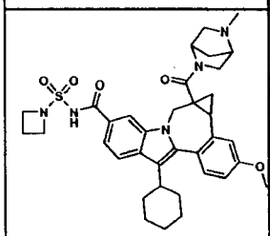
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retención: 1.562 min; m/e 701 (MH+). El producto se observó que existe como rotámeros de Interconversión por 1H RMN (500 MHz, CLOROFORMO-D): δ ppm 1.14 - 1.52 (m, 7 H), 1.70 - 2.11 (m, 9 H), 2.75 - 3.11 (m, 10 H), 3.11 - 3.23 (m, J=7.17, 4.73 Hz, 1 H), 3.38 - 3.74 (m, 7 H), 3.89 (s, 3 H), 4.09 (s, 3 H), 4.28 - 4.75 (m, 1 H), 6.88 - 7.05 (m, 1 H), 7.07 - 7.16 (m, 1 H), 7.20 - 7.32 (m, 1 H), 7.50 - 7.66 (m, 1 H), 7.75 - 7.93 (m, 1 H), 8.05 - 8.26 (m, 1 H).

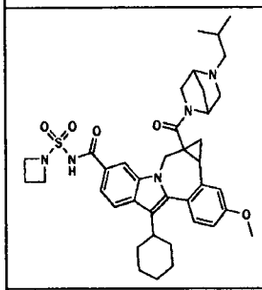
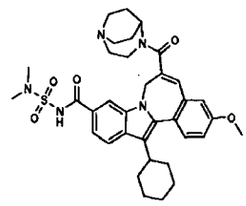
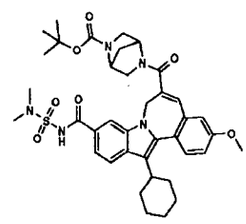
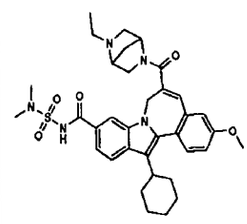
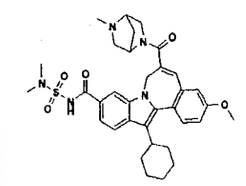
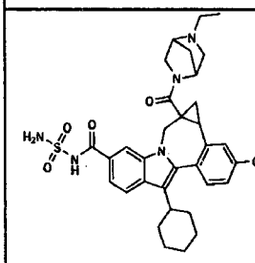
Los procedimientos generales a continuación pertenecen a los procedimientos experimentales que se señalaron. El ácido (0.055 mmol, 1 eq.) se disolvió en DMF seco y se siguió por agregar HATU (0.083 mmol, 1.5 eq.) y DIPEA (0.083. 1.5 eq.). La solución se agitó durante 2 minutos y agregó en amina pre-pesada (0.083 mmol, 1.5 eq.) a temperatura ambiente. La mezcla se agitó 14 h y purificó por HPLC preparativa. Métodos de gradiente HPLC: Método A: Columna: Agilent SB CN4.6x100mm 3.5 um; Fase móvil: agua, NH_4OH 10 mM, ACN; Método B: Columna: Phenomenex Gemini 4.6x100mm 5 um C18; Fase móvil: agua, NH_4OH 10 mM, ACN; Método C: Columna: Aguas x-Bidge C18 150x4.6mm 5 micron; Fase móvil: agua, NH_4OH 10 mM, ACN; Método D: Columna: Waters Xbridge 2.1x50mm 5 um C18; Fase móvil: agua, NH_4OH 10 mM, ACN.

Estructura	Tiempo de Ret. HPLC [min]	Pureza HPLC [%]	Masa reportada EM	Método HPLC
	4.92	90.5	660.4	Método A
	2.11	100	660.39	Método D
	5.06	92.5	732.4	Método A
	5.32	100	718.43	Método A
	5.86	98.3	724.33	Método B
	7.79	99.4	732.33	Método B

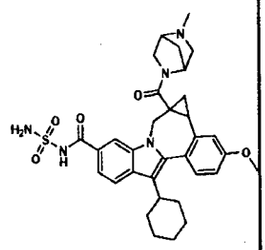
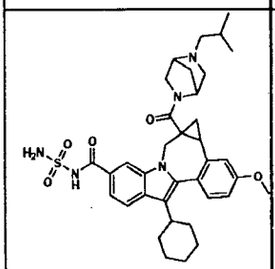
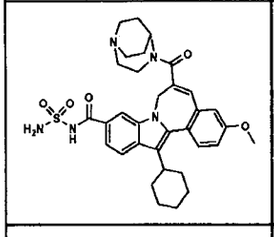
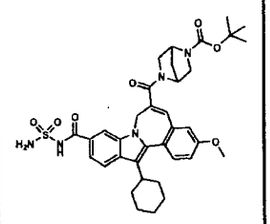
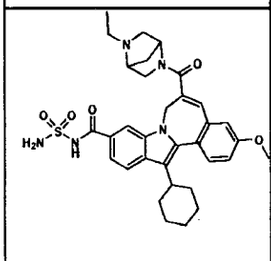
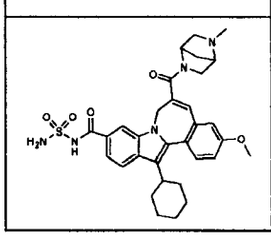
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Estructura	Tiempo de Ret. HPLC [min]	Pureza HPLC [%]	Masa reportada EM	Método HPLC
	6.11	100	724.33	Método B
	5.01	100	660.34	Método B
	7.5	98.4	672.22	Método C
	9.6	99.3	744.22	Método C
	7.6	90.3	672.28	Método C
	7.41	93.6	658.23	Método C

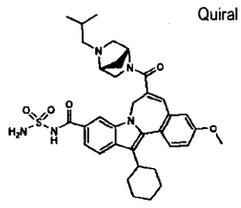
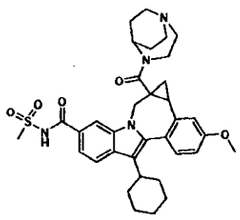
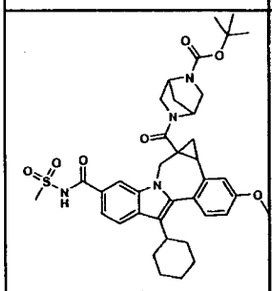
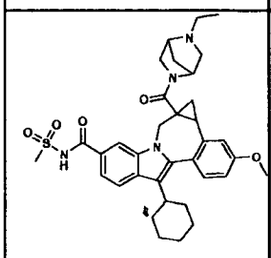
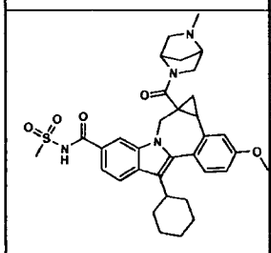
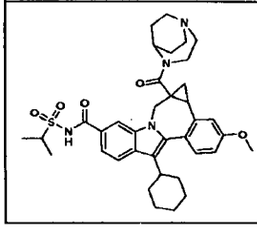
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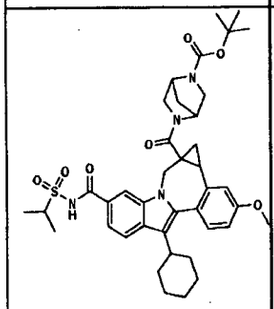
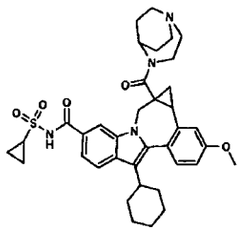
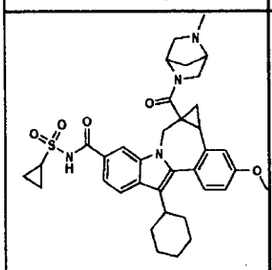
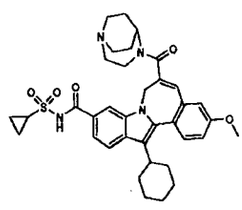
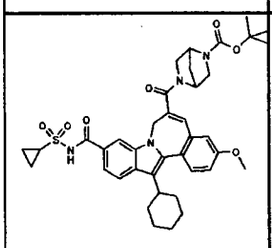
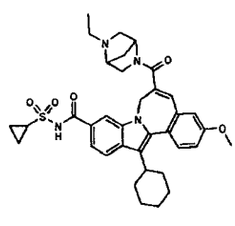
Estructura	Tiempo de Ret. HPLC [min]	Pureza HPLC [%]	Masa reportada EM	Método HPLC
	8.91	97	700.22	Método C
	2.46	100	646.74	Método D
	3.31	97	718.6	Método D
	2.38	100	646.73	Método D
	2.39	100	632.74	Método D
	1.94	96.4	631.8	Método D

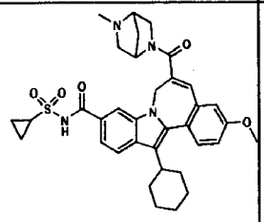
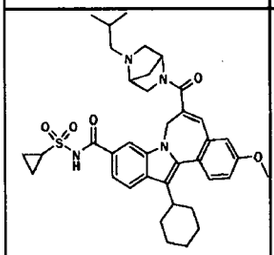
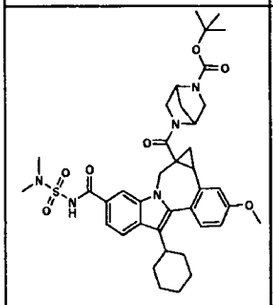
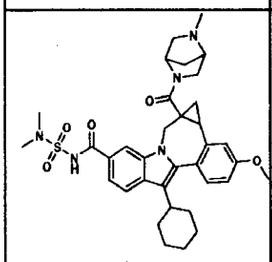
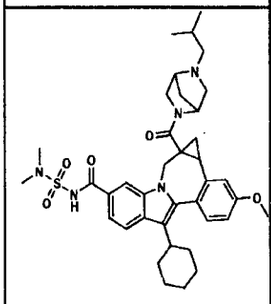
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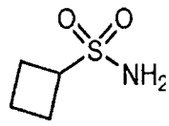
Estructura	Tiempo de Ret. HPLC [min]	Pureza HPLC [%]	Masa reportada EM	Método HPLC
	2.06	100	617.84	Método D
	2.47	91.7	660.75	Método D
	6.99	93	618.12	Método D
	9.35	93.9	690.11	Método D
	7.16	100	618.12	Método D
	7.01	100	604.13	Método D

000357

Estructura	Tiempo de Ret. HPLC [min]	Pureza HPLC [%]	Masa reportada EM	Método HPLC
 Quiral	8.34	100	646.16	Método D
	2.05	96.3	631.39	Método D
	2.53	100	703.42	Método D
	1.96	90.6	631.38	Método D
	1.93	97.3	617.36	Método D
	7.28	100	659.2	Método D

Estructura	Tiempo de Ret. HPLC [min]	Pureza HPLC [%]	Masa reportada EM	Método HPLC
	7.02	100	731.07	Método D
	2.06	93.3	657.37	Método D
	2.17	93.2	643.35	Método D
	2.08	100	642.78	Método D
	2.95	100	714.66	Método D
	2.17	100	642.77	Método D

Estructura	Tiempo de Ret. HPLC [min]	Pureza HPLC [%]	Masa reportada EM	Método HPLC
	2.48	100	628.79	Método D
	2.39	100	670.71	Método D
	3.12	100.0	732.44	Método D
	2.10	100.0	646.39	Método D
	2.71	98.5	688.44	Método D

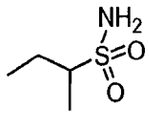


000360

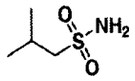
A un RBF de 250 ml equipado con una barra de agitación se agregó bromociclobutano (3.49 mL, 37.0 mmol) y 70 mL de dietil éter. El matraz se enfrió a -78°C (baño de acetona/hielo seco). A esta solución luego se agregó, por medio de una jeringa, 2.0eq. de una solución 1.7M de tert-butilitio (43.6 mL, 74.1 mmol). La mezcla se agitó durante 60 minutos, luego se transfirió por medio de una cánula en un matraz de 500 ml que contiene cloruro de sulfurilo (6.00 mL, 74.1 mmol) en 30mL de dietiléter a -78°C. La suspensión se calentó a temperatura ambiente durante la noche. La mezcla blanca se diluyó con 40mL de dietiléter, filtró y colocó a un lado. Un RBF de 500 ml de 3 cuellos equipado con una barra de agitación y THF seco (10 mL) se enfrió a -65°C con la ayuda de un baño de hielo seco/isopropanol y amonio gaseoso se añadió lentamente en el matraz. Cloruro de ciclobutanosulfonilo previamente sintetizado (5.2g, 33.6 mmol) luego se goteó por medio de una jeringa (mezcla cruda en ~200 mL de éter/THF). El rocío de gas de amonio se continuó durante 5 minutos adicionales. La mezcla se mantuvo a -65°C durante 4 horas luego se permitió calentar lentamente a temperatura ambiente. La mezcla de reacción se filtró y lavó con 100mL de THF. El solvente se evaporó para dar 2.1g de la sulfonamida deseada (46% de rendimiento) como

000361

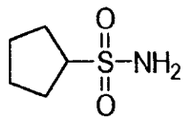
un sólido aceitoso amarillo pálido. ^{1}H RMN (500 MHz, DMSO-D6): δ ppm 1.81 - 1.89 (m, 2 H), 2.16 - 2.22 (m, 2 H), 2.23 - 2.31 (m, 2 H), 3.66 - 3.74 (m, 1 H), 6.68 (s, 2 H).



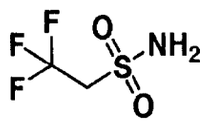
^{1}H RMN (500 MHz, DMSO-D6): δ ppm 0.94 (m, 3 H), 1.20 (m, 3 H), 1.30 - 1.45 (m, 1 H), 1.90 (m, 1 H), 2.76 (m, 1 H), 6.59 (s, 2 H).



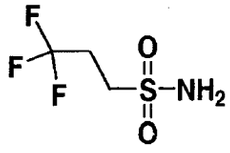
^{1}H RMN (500 MHz, DMSO-D6): δ ppm 1.02 (d, J= 6.95 Hz, 6 H), 2.11 (m, 1 H), 2.86 (d, J= 6.22 Hz, 2 H), 6.71 (s, 2 H).



^{1}H RMN (500 MHz, DMSO-D6): δ ppm 1.51 - 1.66 (m, 4 H), 1.86 (m, 4 H), 3.37 (m, 1 H), 6.65 (s, 2 H).

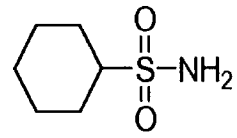


^{1}H RMN (500 MHz, DMSO-D6): δ ppm 4.24 (m, 2 H), 7.46 (s, 2 H).

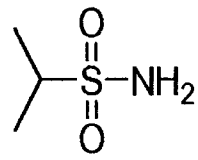


^{1}H RMN (500 MHz, DMSO-D6): δ ppm 2.70 (m, 2H), 3.20 (m, 2

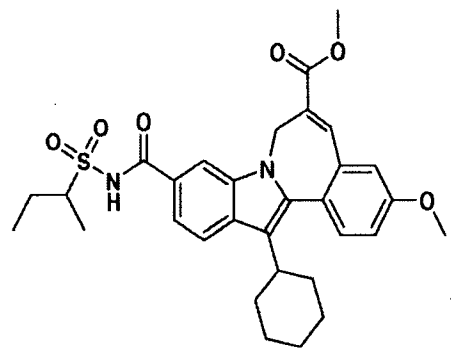
H), 7.01 (s, 2 H). 000362



^{1}H RMN (500 MHz, DMSO-D6): δ ppm 1.07 - 1.17 (m, 1H), 1.22 - 1.38 (m, 4H), 1.62 (m, 1H), 1.78 (m, 2H), 2.05 (m, 2H), 2.68 - 2.77 (m, 1 H), 6.57 (s, 2 H).



^{1}H RMN (300 MHz, DMSO-D6): δ ppm 1.22 (d, J=6.59 Hz, 6 H), 3.00 (m, 1 H), 6.59 (s, 2 H).

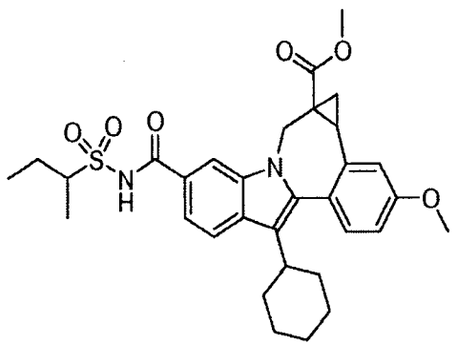


10-((sec-butilsulfonil)carbamoil)-13-ciclohexil-3-metoxi-7H-indol[2,1-a][2]benzazepin-6-carboxilato de metilo. En un matraz de fondo redondo de 100 ml (RBF) se agregó ácido carboxílico **1** (575 mg, 1.291 mmol) y 1,1'-carbonildiimidazol (460 mg, 2.84 mmol) en THF (15 mL) para dar una solución amarilla. La mezcla se agitó a temperatura ambiente bajo nitrógeno durante 1 hora luego calentó a 70°C, en un baño de aceite, durante 90 minutos. La mezcla se enfrió y sulfonamida

000363

de sec-butilo (921 mg, 6.71 mmol) en 4 mL de THF se agregó junto con DBU puro (0.389 mL, 2.58 mmol). El RBF se regresó al baño de aceite y calentó durante la noche a 70°C. La mezcla de reacción se transfirió a un embudo de separación, diluyó con 100mL de DCM, lavó x3 con 100 mL de HCl 0.5 M, luego con 100 mL de H_2O, y finalmente NaCl saturado. La mezcla orgánica se secó sobre MgSO4, filtró y concentró para dar 713 mgs de la acilsulfonamida deseada 2 como un sólido amarillo (96% de rendimiento) la cual se colocó bajo vacío durante la noche. Los Datos CL se registraron en un equipo de cromatografía líquida Shimadzu CL-10AS con una columna Phenomenex-Luna 10µ, C18, 4.6x30mm, usando un detector SPD-10AV UV-Vis en un detector de longitud de onda de 220 nM. Las condiciones de elución emplean una relación de flujo de 5 ml/min., un gradiente de solvente A al 100%/solvente B al 0% a solvente A al 0%/solvente B al 100%, un tiempo de gradiente de 2 min., un tiempo de espera de 1 min., y un tiempo de análisis de 3 min. Donde el solvente A fue 10% de MeOH/90% de H2O/0.1% de ácido trifluoroacético y el solvente B fue 10% de H2O/90% de MeOH/0.1% de ácido trifluoroacético. Los datos EM se determinaron usando una plataforma de micromasa para CL en el modo de electro-rocío. 1H RMN (500 MHz, CD3OD): δ ppm 0.84 - 0.92 (m, 3 H), 1.03 (t, J=7.32 Hz, 3 H), 1.23 (m, 1 H), 1.28 - 1.44 (m, 7 H), 1.58 (m, 1 H), 1.72 (m, 2 H), 1.85 (m, 1 H), 1.95 - 2.07 (m, 3 H), 2.17 (m, 1 H), 2.78 (m, 1 H), 3.69 (m, 2

H), 3.83 - 3.91 (m, 3 H), 7.02 (s, 1 H), 7.11 (m, 1 H), 7.47 (d, J = 7.63 Hz, 1 H), 7.74 (m, 3 H), 8.25 (s, 1 H). CL/EM: m/z 565.22, Rf 2.192 min., 97.5% de pureza.



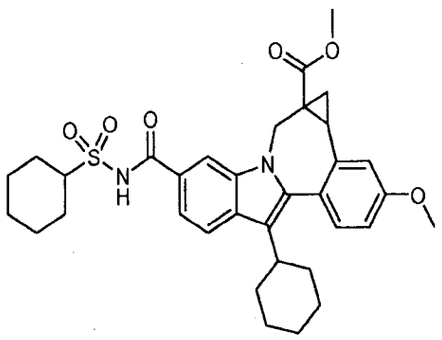
5-((sec-butilsulfonil)carbamoil)-8-ciclohexil-11-metoxi-1,12b-dihidro ciclopropa[d]indol[2,1-a][2]benzazepin-1a(2H)-carboxilato de metilo. A 63.1 mgs de NaH al 95% en 5 mL de DMF seco en un RBF de 100 mL se agregó 629 mgs de yoduro de trimetilsuloxonio a temperatura ambiente. La mezcla se agitó a temperatura ambiente bajo nitrógeno durante 30 minutos. Una solución del Compuesto intermedio 9 (en 7 mL de DMF) se agregó por medio de una jeringa y la reacción se agitó durante 15 - 20 minutos. La mezcla de reacción se enfrió rápidamente a 0°C con un baño de hielo, 1 mL de HCl 1M se agregó seguido por 60 mL de agua con hielo. La mezcla heterogénea se agitó durante 30 minutos. La mezcla se filtró y el sólido amarillo se lavó con agua con hielo. El sólido se tomó hasta en metanol/DCM al 2% y se purificó usando un Biotage Horizon MPLC empleando una columna 40+M con un gradiente de solvente de metanol/DCM al 2% hasta metanol/DCM al 10%. 450mgs (62% de rendimiento) del compuesto se obtuvo como un sólido amarillo después de la

006365

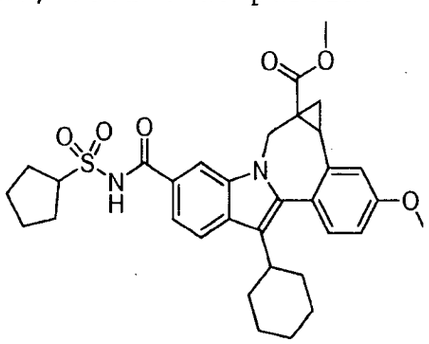
evaporación del solvente. Los Datos CL se registraron en un equipo de cromatografía líquida Shimadzu CL-10AS con una columna Phenomenex-Luna 10µ, C18, 4.6x30mm, usando un detector SPD-10AV UV-Vis en un detector de longitud de onda de 220nM. Las condiciones de elución emplean una relación de flujo de 5 ml/min., un gradiente de solvente A al 100%/solvente B al 0% a solvente A al 0%/solvente B al 100%, un tiempo de gradiente de 2 min., un tiempo de espera de 1 min., y un tiempo de análisis de 3 min. Donde el solvente A fue 10% de MeOH/90% de H2O/0.1% de ácido trifluoroacético y el solvente B fue 10% de H2O/90% de MeOH/0.1% de ácido trifluoroacético. Los datos EM se determinaron usando una plataforma de micromasa para CL en el modo de electro-rocío. 1H RMN (300 MHz, CD3OD): δ ppm 0.19 (m, 0.35 H), 1.03 - 1.14 (m, 3 H), 1.19 - 1.34 (m, 2.65 H), 1.43 (m, 5 H), 1.55 - 1.66 (m, 2 H), 1.74 (m, 2 H), 1.89 - 1.94 (m, 2 H), 1.99 - 2.14 (m, 3 H), 2.64 - 2.95 (m, 2 H), 3.35 (d, J=15.00 Hz, 0.65 H), 3.48 (m, 2 H), 3.67 - 3.81 (m, 2 H), 3.85 (s, 3 H), 3.90 - 3.98 (m, 0.35 H), 5.17 (m, 0.35 H), 5.36 (m, 0.65 H), 6.91 - 6.98 (m, 1 H), 7.09 (m, 0.35 H), 7.16 (m, 0.65 H), 7.19 - 7.27 (m, 1 H), 7.52 - 7.65 (m, 1 H), 7.83 (m, 1 H), 8.09 (s, 0.35 H), 8.29 (s, 0.65 H). CL/EM: m/z 579.31, Rf 2.167 min. 95.2 %

000366

de pureza.

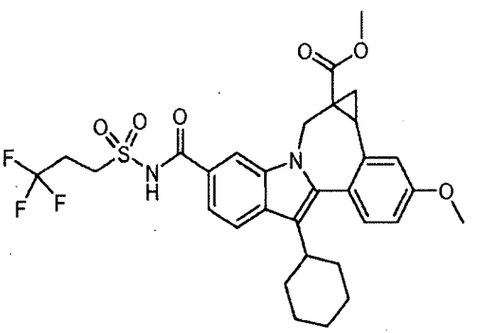


8-ciclohexil-5-((ciclohexilsulfonil)carbamoil)-11-metoxi-1,12b-dihidrociclo propa[d]indol[2,1-a][2]benzazepin-1a(2H)-carboxilato de metilo. 1H RMN (300 MHz, CD3OD): δ ppm 0.23 (m, 0.35 H), 1.14 - 1.53 (m, 10 H), 1.60 - 1.79 (m, 3 H), 1.91 (m, 3 H), 2.09 (m, 1.65 H), 2.18 (m, 3 H), 2.81 - 2.98 (m, 3 H), 3.41 - 3.46 (m, 0.65 H), 3.50 (m, 2 H), 3.71 - 3.79 (m, 2 H), 3.88 (s, 3 H), 3.99 - 4.04 (m, 0.35 H), 5.25 (m, 0.35 H), 5.45 (m, 0.65 H), 6.97 - 7.02 (m, 1 H), 7.13 (m, 0.35 H), 7.21 (m, 0.65 H), 7.26 - 7.32 (m, 1 H), 7.55 - 7.65 (m, 1 H), 7.85 - 7.92 (m, 1 H), 8.11 (s, 0.35 H), 8.32 (s, 0.65 H). CL/EM: m/z 605.42, Rf 2.223 min., 99.2 % de pureza.



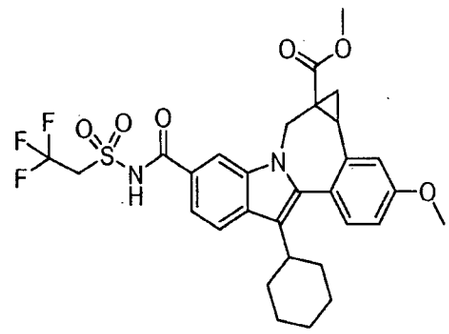
8-ciclohexil-5-((ciclopentilsulfonil)carbamoil)-11-metoxi-1,12b-dihidrociclo propa[d]indol[2,1-a][2]benzazepin-1a(2H)-carboxilato de metilo. 1H RMN (300 MHz, CD3OD): δ ppm

0.23 (m, 0.35 H), 1.27 (m, 2.65 H), 1.39 (m, 2 H), 1.60 - 1.79 (m, 7 H), 1.91 - 2.19 (m, 8 H), 2.67 - 2.97 (m, 2 H), 3.47 (m, 0.65 H), 3.50 (m, 3 H), 3.78 - 3.87 (m, 3 H), 4.10 (m, 0.35 H), 4.29 (m, 1 H), 5.22 (m, 0.35 H), 5.43 (m, 0.65 H), 6.98 - 7.02 (m, 1 H), 7.14 (m, 0.35 H), 7.21 (m, 0.65 H), 7.26 - 7.32 (m, 1 H), 7.55 - 7.65 (m, 1 H), 7.85 - 7.91 (m, 1 H), 8.10 (s, 0.35 H), 8.32 (s, 0.65 H). CL/EM: m/z 591.33, Rf 2.200 min., 100 % de pureza.

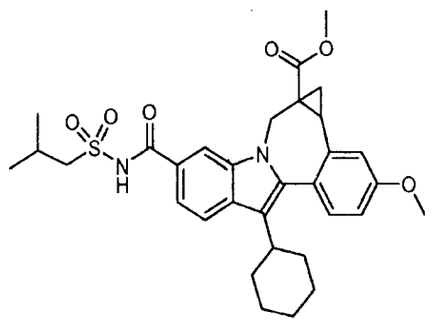


8-ciclohexil-11-metoxi-5-(((3,3,3-trifluoropropil)sulfonil)carbamoil)-1,12b-dihidrociclopropa[d]indol[2,1-a][2]benzazepin-1a(2H)-carboxilato de metilo. 1H RMN (300 MHz, CD3OD): δ ppm 0.19 (m, 0.35 H), 1.25 (m, 1.65 H), 1.41 (m, 2 H), 1.65 (m, 1 H), 1.76 (m, 2 H), 1.94 (m, 2 H), 2.04 (m, 1 H), 2.61 - 2.84 (m, 6 H), 2.88 - 2.96 (m, 1 H), 3.35 - 3.40 (m, 0.65 H), 3.48 (m, 2 H), 3.80 (m, 2 H), 3.86 (m, 3 H), 3.89 - 3.98 (m, 0.35 H), 5.18 (m, 0.35 H), 5.38 (m, 0.65 H), 6.96 - 7.01 (m, 1 H), 7.13 (m, 0.35 H), 7.20 (m, 0.65 H), 7.24 - 7.30 (m, 1 H), 7.58 - 7.69 (m, 1 H), 7.84 - 7.90 (m, 1 H), 8.13 (s, 0.35 H), 8.34 (s, 0.65 H). CL/EM: m/z 619.32, Rf 2.188 min., 99.5 % de

pureza.



8-ciclohexil-11-metoxi-5-(((2,2,2-trifluoroetil)sulfonil)carbamoil)-1,12b-dihidro ciclopropa[d]indol[2,1-a][2]benzazepin-1a(2H)-carboxilato de metilo. 1H RMN (300 MHz, CD3OD): δ ppm 0.13 (m, 0.35 H), 1.18 (m, 1.65 H), 1.38 (m, 2 H), 1.57 - 1.62 (m, 2 H), 1.73 (m, 2 H), 1.87 (m, 2 H), 1.96 - 2.05 (m, 1 H), 2.60 - 2.90 (m, 1.35 H), 3.17 - 3.22 (m, 0.65 H), 3.45 (m, 2 H), 3.74 (m, 1 H), 3.84 (m, 2 H), 4.04 - 4.10 (m, 3 H), 4.38 - 4.53 (m, 2 H), 5.06 (m, 0.35 H), 5.18 (m, 0.65 H), 6.90 - 6.96 (m, 1 H), 7.06 (m, 0.35 H), 7.13 (m, 0.65 H), 7.16 - 7.22 (m, 1 H), 7.63 (m, 0.65 H), 7.70 - 7.80 (m, 1.35 H), 8.14 (s, 0.35 H), 8.33 (s, 0.65 H). CL/EM: m/z 605.29, Rf 2.178 min., 96.5 % de pureza.

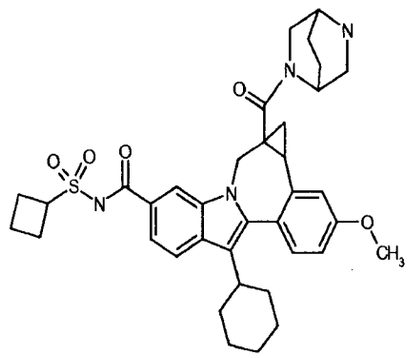


8-ciclohexil-5-((isobutilsulfonil)carbamoil)-11-metoxi-1,12b-dihidrociclopropa[d]indol[2,1-a][2]benzazepin-1a(2H)-carboxilato de metilo. 1H RMN (300

MHz, CD3OD): δ ppm 0.17 (m, 0.35 H), 1.09 (m, 6 H), 1.22 (m, 1.65 H), 1.38 (m, 2 H), 1.49 - 1.60 (m, 1 H), 1.73 (m, 2 H), 1.87 (m, 2 H), 1.96 - 2.05 (m, 2 H), 2.15 - 2.39 (m, 1 H), 2.61 - 2.87 (m, 2 H), 2.96 (d, J = 6.22 Hz, 2 H), 3.19 (m, 2 H), 3.43 (m, 2 H), 3.70 (m, 2 H), 3.84 (m, 2 H), 5.06 - 5.11 (m, 1 H), 6.90 - 6.95 (m, 1 H), 7.05 - 7.11 (m, 1 H), 7.16 - 7.23 (m, 1 H), 7.67 - 782 (m, 2 H), 8.20 (s, 0.35 H), 8.39 (s, 0.65 H). CL/EM: m/z 579.30, Rf 2.190 min., 96.2% de pureza.

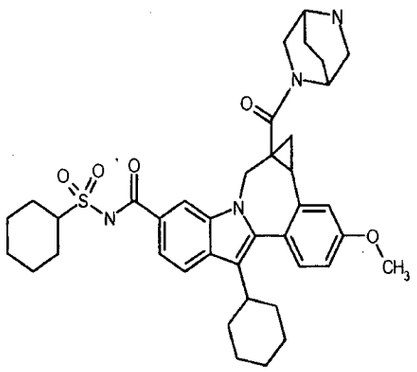
Procedimiento general para la transformación de ésteres de la fórmula I a amidas correspondientes. En un matraz de fondo redondo de 100 ml se agregó hidróxido de sodio 1N (3 eq., 1.583 ml, 1.583 mmol) y éster ponteado **1** (1 eq., 0.528 mmol) en metanol (4.00 ml) y THF (4.00 ml) para dar una solución amarilla. La mezcla se agitó durante 3 horas a temperatura ambiente. 3 equivalentes de HCl 1N luego se agregó, el producto se diluye con acetato de etilo luego extrajo, lavó con salmuera y secó sobre $MgSO_4$. La filtración y evaporación posterior de los volátiles dio los ácidos carboxílicos 2 en un rendimiento cuantitativo cercano. A una solución 0.10 mmol de ácido carboxílico **2** en 1 mL de N,N-Dimetilformamida anhidro (DMF) en un vial de 2 dram equipado con un Teflon™ alineado a la tapa de rosca se agregó 0.3 mmol (3 eq.) de Tetrafluoroborato de 2-(1H-Benzotriazol-1-il)-1,1,3,3,-Tetrametiluronio (TBTU)

en 1.0 mL de DMF anhidro seguido por la adición de 0.2 mmol (2 eq.) de amina 1 en 1.0 mL de DMF anhidro y 0.4 mmol de N,N-diisopropiletilamina pura. La reacción se agitó en un mezclador VWR Vortex-Genie 2 durante la noche a temperatura ambiente. Los volúmenes de la reacción luego se redujeron en un Savant Speedvac y los productos crudos se tomaron en 1.2 mL de metanol y purificaron usando HPLC preparativa Shimadzu empleando metanol/agua y solución amortiguadora de ácido trifluoroacético al 0.1% con una columna Phenomenex Luna, Cl 8, 30 mm x 100 mm, 10 µm en un gradiente de B al 40-100% y una relación de flujo de 40 mL/min. durante 10 minutos con una espera de 5-10 minutos, para dar las carboxamidas 4 como sólidos amorfos amarillos (65% - 70% de rendimiento). Los datos CL/EM de post-purificación se obtuvieron en una CL analítica Shimadzu/Plataforma de micromasa CL (ESI+) a 220nm usando el siguiente conjunto de condiciones: Columna I (Phenomenex 10µm C18, 4.6 x 30mm), Sistema del solvente I (gradiente de B al 0-100% donde B = metanol grado HPLC al 90%/ácido trifluoroacético al 0.1%/agua grado HPLC al 10%), en 2 minutos con un 1 minuto de espera en una relación de flujo de 5 mL/minuto.

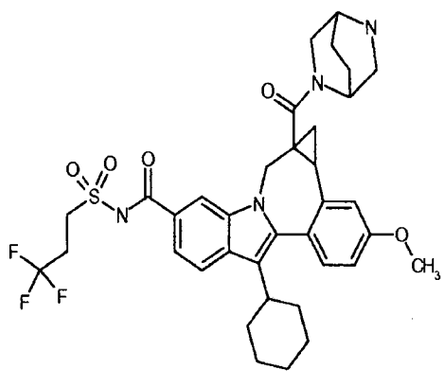


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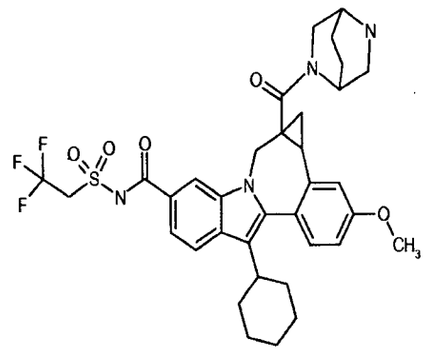
N-(ciclobutilsulfonil)-8-ciclohexil-1a-(2,5-diazabiciclo[2.2.2]oct-2-ilcarbonil)-11-metoxi-1,1a,2,12b-tetrahidrociclopropa[d]indol[2,1-a][2]benzazepin-5-carboxamida. CL/EM: m/z 657.51, Rf 1.783 min., 96.5 % de pureza.



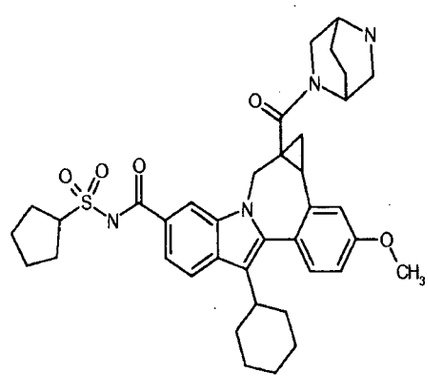
8-Ciclohexil-N-(ciclohexilsulfonil)-1a-(2,5-diazabiciclo[2.2.2]oct-2-ilcarbonil)-11-metoxi-1,1a,2,12b-tetrahidrociclopropa[d]indol[2,1-a][2]benzazepin-5-carboxamida. CL/EM: m/z 685.52, Rf 1.872 min., 99.3 % de pureza.



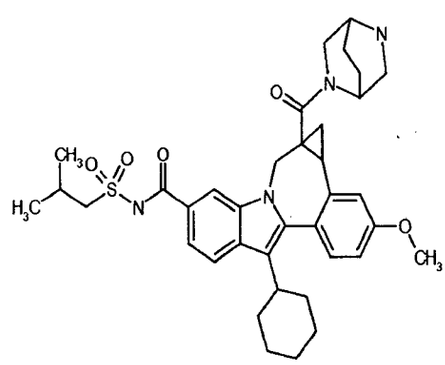
8-Ciclohexil-1a-(2,5-diazabiciclo[2.2.2]oct-2-ilcarbonil)-11-metoxi-N-((3,3,3-trifluoropropil)sulfonil)-1,1a,2,12b-tetrahidrociclopropa[d]indol[2,1-a][2]benzazepin-5-carboxamida. CL/EM: m/z 699.49, Rf 1.793 min., 98.0 % de pureza.



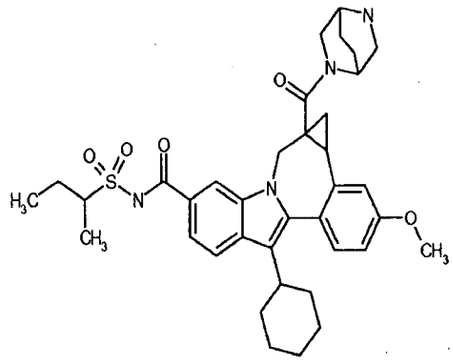
8-Ciclohexil-1a-(2,5-diazabiciclo[2.2.2]oct-2-ilcarbonil)-11-metoxi-N-((2,2,2-trifluoroetil)sulfonil)-1,1a,2,12b-tetrahidrociclopropa[d]indol[2,1-a][2]benzazepin-5-carboxamida. CL/EM: m/z 685.45, Rf 1.778 min., 96.5 % de pureza.



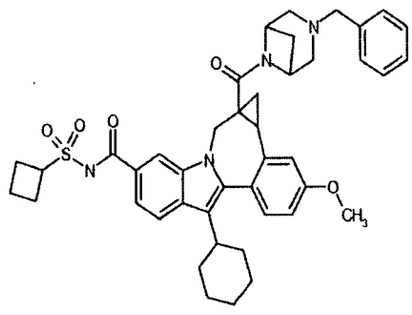
8-Ciclohexil-N-(ciclopentilsulfonil)-1a-(2,5-diazabiciclo[2.2.2]oct-2-ilcarbonil)-11-metoxi-1,1a,2,12b-tetrahidrociclopropa[d]indol[2,1-a][2]benzazepin-5-carboxamida. CL/EM: m/z 671.51, Rf 1.833 min., 99.3 % de pureza.



8-Ciclohexil-1a-(2,5-diazabiciclo[2.2.2]oct-2-ilcarbonil)-N-(isobutilsulfonil)-11-metoxi-1,1a,2,12b-tetrahidrociclopropa[d]indol[2,1-a][2]benzazepin-5-carboxamida. CL/EM: m/z 659.52, Rf 1.808 min., 98.1 % de pureza.

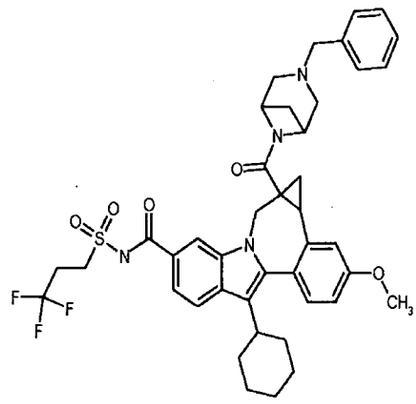


N-(sec-butilsulfonil)-8-ciclohexil-1a-(2,5-diazabiciclo[2.2.2]oct-2-ilcarbonil)-11-metoxi-1,1a,2,12b-tetrahidrociclopropa[d]indol[2,1-a][2]benzazepin-5-carboxamida. CL/EM: m/z 659.52, Rf 1.805 min., 98.2 % de pureza.



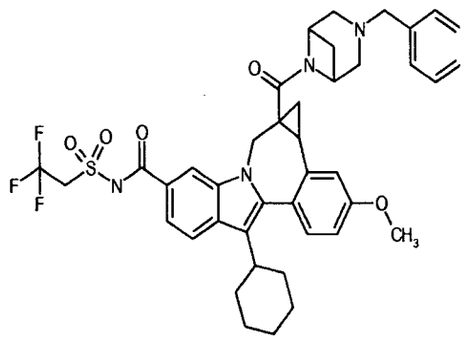
1a-((3-Bencil-3,6-diazabiciclo[3.1.1]hept-6-il)carbonil)-N-(ciclobutilsulfonil)-8-ciclohexil-11-metoxi-1,1a,2,12b-tetrahidrociclopropa[d]indol[2,1-a][2]benzazepin-5-carboxamida. 1H RMN (300 MHz, CD3OD): δ ppm 0.16 (m, 0.35 H), 1.27 - 1.37 (m, 2 H), 1.41 (m, I H), 1.45 (m, 1.65 H), 1.62 (m, 1 H), 2.05 (m, 2 H), 2.06 - 2.15 (m, 7 H) 2.39 (m, 2 H),

2.59 - 2.68 (m, 2 H), 2.81 - 2.90 (m, 1 H), 3.02 (m, 1 H), 3.19 (m, 1 H), 3.36 - 3.45 (m, 1 H), 3.47 (m, 1 H), 3.53 (m, 1 H), 3.62 (m, 1 H), 3.90 - 3.97 (m, 3 H), 4.15 - 4.33 (m, 1 H), 4.50 (m, 1 H), 4.59 (m, 1 H), 4.77 (m, 2 H), 5.39 (m, 2 H), 7.06 (dd, J=8.55, 2.44 Hz, 1 H), 7.24 (d, J=2.44 Hz, 1 H), 7.32 - 7.41 (m, 2 H), 7.45 - 7.52 (m, 3 H), 7.55 - 7.64 (m, 2 H), 7.92 - 8.00 (m, 1 H), 8.21 (m, 1 H). CL/EM: m/z 733.48, Rf 1.833 min., 98.5 % de pureza.

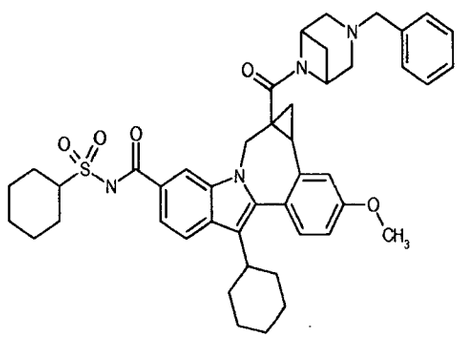


1a-((3-Bencil-3,6-diazabiciclo[3.1.1]hept-6-il)carbonil)-8-ciclohexil-11-metoxi-N-((3,3,3-trifluoropropil)sulfonil)-1,1a,2,12b-tetrahidrociclopropa[d]indol[2,1-a][2]benzazepin-5-carboxamida. 1H RMN (500 MHz, CD3OD): δ ppm 0.16 (m, 0.35 H), 1.28 - 1.37 (m, 3 H), 1.41 (m, 1.65 H), 1.47 (m, 2 H), 1.70 (m, 1 H), 1.83 (m, 2 H), 1.98 - 2.14 (m, 5 H), 2.59 (m, 1 H), 2.78 - 2.86 (m, 4 H), 3.03 (m, 1 H), 3.16 - 3.24 (m, 1 H), 3.44 - 3.58 (m, 2 H), 3.85 - 3.96 (m, 6 H), 4.18 (m, 1 H), 4.47 (m, 1 H), 5.47 (m 7.07 (m, 1 H), 7.20 - 7.26 (m, 1 H), 7.32 - 7.39 (m, 2 H), 7.46 (m, 3 H), 7.59 - 7.67 (m, 2 H),

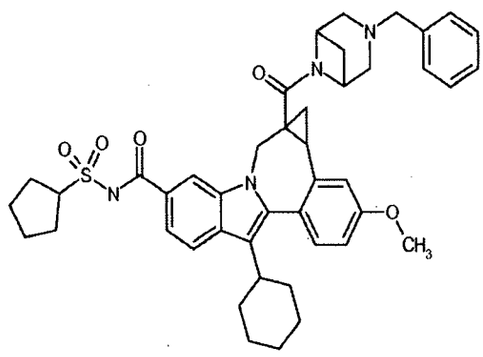
7.94 - 7.98 (m, 1 H), 8.15 - 8.29 (m, 1 H). CL/EM: m/z 775.45, Rf 1.888 min., 95.7 % de pureza.



1a-((3-Bencil-3,6-diazabiciclo[3.1.1]hept-6-il)carbonil)-8-ciclohexil-11-metoxi-N-((2,2,2-trifluoroetil)sulfonil)-1,1a,2,12b-tetrahidrociclopropa[d]indol[2,1-a][2]benzazepin-5-carboxamida. 1H RMN (300 MHz1 CD3OD): δ ppm 0.10 (m, 0.35 H), 1.28 (m, 2 H), 1.35 (m, 3 H), 1.51 (m, 0.65 H), 1.68 - 1.84 (m, 3 H), 1.87 - 2.10 (m, 5 H), 2.53 (m, 1 H), 2.71 - 2.86 (m, 1 H), 2.89 - 3.04 (m, 1 H), 3.43 - 3.58 (m, 3 H), 3.67 - 3.80 (m, 1 H), 3.87 (s, 3 H), 4.13 (m, 1 H), 4.32 (m, 1 H), 4.49 - 4.74 (m, 3 H), 4.90 - 5.04 (m, 1 H), 5.30 (m, 1 H), 7.00 (m, 1 H), 7.15 - 7.23 (m, 1 H), 7.25 - 7.33 (m, 2 H), 7.36 - 7.46 (m, 3 H), 7.48 - 7.61 (m, 2 H), 7.89 (m, 1 H), 8.09 - 8.18 (m, 1 H). CL/EM: m/z 761.47, Rf 1.850 min., 97.0 % de pureza.

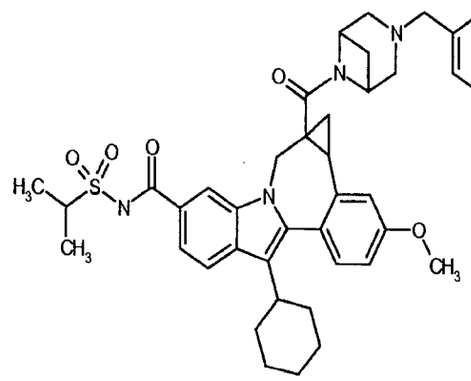


1a-((3-Bencil-3,6-diazabiciclo[3.1.1]hept-6-il)carbonil)-8-ciclohexil-N-(ciclohexilsulfonil)-11-metoxi-1,1a,2,12b-tetrahidrociclopropa[d]indol[2,1-a][2]benzazepin-5-carboxamida. 1H RMN (500 MHz, CD3OD): δ ppm 0.14 (m, 0.35 H), 1.21 - 1.48 (m, 9.65 H), 1.63 (m, 3 H), 1.68 (m, 1 H), 1.80 (m, 3 H), 1.93 (m, 4 H), 1.98 - 2.08 - 2.17 (m, 5 H), 2.60 - 2.87 (m, 1 H), 2.99 (m, 1 H), 3.18 (m, 1 H), 3.44 (m, 1 H), 3.55 (m, 2 H), 3.68 - 3.77 (m, 2 H), 3.86 - 3.94 (m, 3 H), 4.16 (m, 1 H), 4.58 (m, 1 H), 5.36 (m, 1 H), 7.04 (dd, J=8.55, 2.75 Hz, 1 H), 7.18 - 7.27 (m, 1 H), 7.30 - 7.38 (m, 2 H), 7.42 - 7.50 (m, 3 H), 7.53 - 7.60 (m, 2 H), 7.92 (m, 1 H), 8.12 - 8.22 (m, 1 H). CL/EM: m/z 761.54, Rf 1.922 min., 98.6 % de pureza.

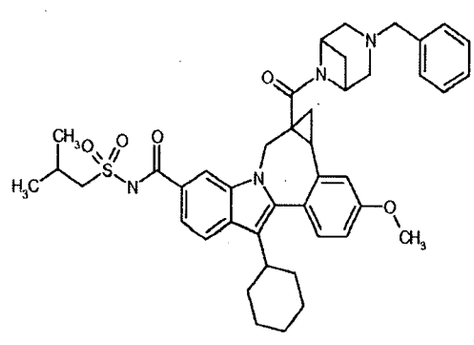


1a-((3-Bencil-3,6-diazabiciclo[3.1.1]hept-6-il)carbonil)-8-ciclohexil-N-(ciclopentilsulfonil)-11-metoxi-1,1a,2,12b-tetrahidrociclopropa[d]indol[2,1-a][2]benzazepin-5-carboxamida. 1H RMN (500 MHz, CD3OD): δ ppm 0.012 (m, 0.35), 1.33 (m, 2 H), 1.39 (m, 1.65 H), 1.45 (m, 3 H), 1.65 (m, 1 H), 1.79 (m, 3 H), 1.83 (m, 4 H), 1.91 (m, 2 H), 1.94 - 2.14 (m, 6 H), 2.58 - 2.89 (m, 2 H), 2.99 (m, 2 H), 3.16 (m, 1 H), 3.36 (m, 2 H), 3.40 - 3.56 (m, 2 H), 3.89 (m, 3 H), 4.30 (m, 1 H),

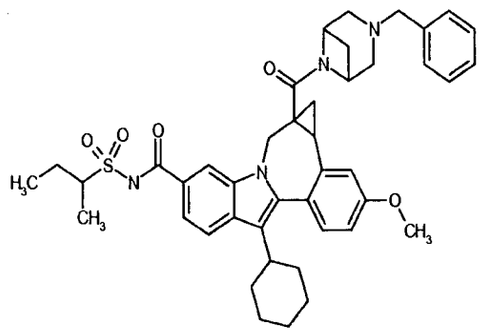
4.50 (m, 1 H), 5.38 (m, 1 H), 7.04 (dd, J=8.39, 2.59 Hz, 1 H), 7.18 - 7.22 (m, 1 H), 7.32 - 7.37 (m, 2 H), 7.44 (m, 3 H), 7.57 (m, 2 H), 7.91 - 7.95 (m, 1 H), 8.10 - 8.21 (m, 1 H). CL/EM: m/z 747.50, Rf 1.868 min., 96.3 % de pureza.



1a-((3-Bencil-3,6-diazabiciclo[3.1.1]hept-6-il)carbonil)-8-ciclohexil-N-(isopropilsulfonil)-11-metoxi-1,1a,2,12b-tetrahidrociclopropa[d]indol[2,1-a][2]benzazepin-5-carboxamida. 1H RMN (300 MHz, CD3OD): δ ppm 0.12 (m, 0.35 H), 1.34 (m, 6.65 H), 1.43 (m, 6 H), 1.59 (m, 1 H), 1.79 (m, 3 H), 1.97 (m, 5 H), 2.56 - 2.85 (m, 1 H), 2.92 - 3.07 (m, 1 H), 3.45 - 3.60 (m, 3 H), 3.85 (m, 1 H), 3.88 - 4.00 (m, 6 H), 4.52 (m, 1 H), 5.32 (m, 1 H), 7.03 (dd, J=8.78, 2.56 Hz, 1 H), 7.17 - 7.23 (m, 1 H), 7.29 - 7.36 (m, 2 H), 7.41 - 7.49 (m, 3 H), 7.51 - 7.65 (m, 2 H), 7.88 - 7.96 (m, 1 H), 8.08 - 8.19 (m, 1 H). CL/EM: m/z 721.50, Rf 1.828 min., 97.0 % de pureza.



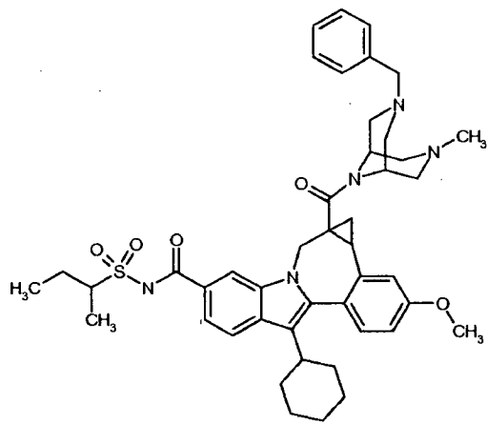
1a-((3-Bencil-3,6-diazabiciclo[3.1.1]hept-6-il)carbonil)-8-ciclohexil-N-(isobutilsulfonil)-11-metoxi-1,1a,2,12b-tetrahidrociclopropa[d]indol[2,1-a][2]benzazepin-5-carboxamida. 1H RMN (500 MHz, CD3OD): δ ppm 0.14 (m, 0.35 H), 1.13 (m, 6.65 H), 1.23 (m, 1 H), 1.26 - 1.35 (m, 2 H), 1.39 (m, 2 H), 1.42 (m, 2 H), 1.59 (m, 1 H), 1.81 (m, 2 H), 1.95 (m, 2 H), 2.02 (m, 1 H), 2.12 (m, 2 H), 2.27 - 2.36 (m, 2 H), 2.87 (m, 1 H), 3.01 (m, 1 H), 3.13 - 3.22 (m, 1 H), 3.39 - 3.44 (m, 2 H), 3.47 - 3.53 (m, 3 H), 3.88 - 3.95 (m, 4 H), 4.58 (m, 1 H), 5.36 (m, 1 H), 7.04 (dd, J=8.55, 2.44 Hz, 1 H), 7.17 - 7.24 (m, 1 H), 7.30 - 7.38 (m, 2 H), 7.45 (m, 3 H), 7.55 - 7.64 (m, 2 H), 7.92 - 8.00 (m, 1 H), 8.10 - 8.21 (m, 1 H). CL/EM: m/z 735.51, Rf 1.895 min., 95.0 % de pureza.



1a-((3-Bencil-3,6-diazabiciclo[3.1.1]hept-6-il)carbonil)-N-(sec-butilsulfonil)-8-ciclohexil-11-metoxi-1,1a,2,12b-tetrahidrociclopropa[d]indol[2,1-a][2]benzazepin-5-carboxamida. 1H RMN (300 MHz, CD3OD): δ ppm θ.13 (m, 0.35 H), 1.01 - 1.13 (m, 3.65 H), 1.21 (m, 3 H), 1.30 - 1.45 (m, 6 H),

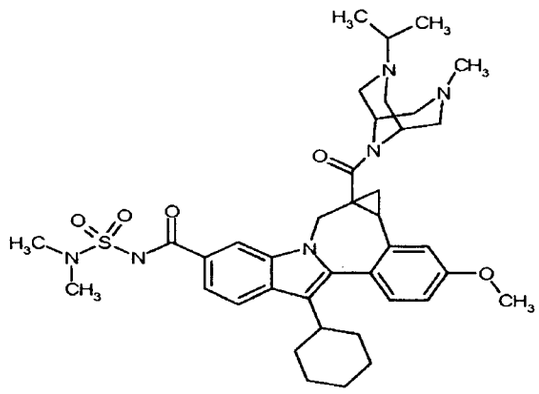
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1.50 - 1.80 (m, 6 H), 1.80 - 2.12 (m, 4 H), 2.57 - 2.86 (m, 2 H), 3.00 (m, 1 H), 3.55 (m, 3 H), 3.76 (m, 2 H), 3.84 - 3.94 (m, 3 H), 4.11 (m, 2 H), 4.56 (m, 1 H), 5.36 (m, 1 H), 7.03 - 7.09 (m, 1 H), 7.23 (m, 1 H), 7.27 - 7.40 (m, 3 H), 7.45 -7.86 (m, 4 H), 7.92 - 8.00 (m, 1 H), 8.13 - 8.23 (m, 1 H). CL/EM: m/z 735.60, Rf 1.865 min., 95.2 % de pureza.

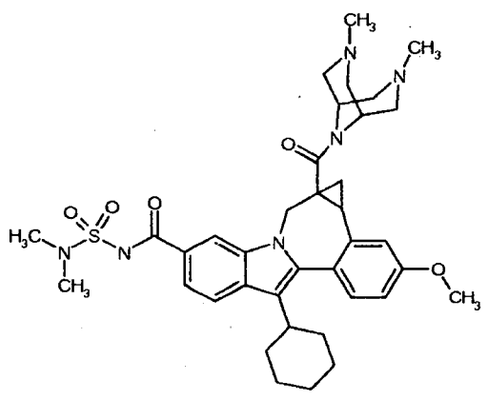


1a-((3-Bencil-7-metil-3,7,9-triazabiciclo[3.3.1]non-9-il)carbonil)-N-(sec-butilsulfonil)-8-ciclohexil-11-metoxi-1,1a,2,12b-tetrahidrociclopropa[d]indol[2,1-a][2]benzazepin-5-carboxamida. 1H RMN (300 MHz, CD3OD): δ ppm 0.20 (m, 0.20 H), 1.06 - 1.14 (m, 3 H), 1.20 - 1.36 (m, 2.80 H), 1.42 (m, 6 H), 1.72 (m, 4 H), 1.98 - 2.13 (m, 6 H), 2.62 (m, 2 H), 2.85 (m, 4 H), 3.15 (m, 1 H), 3.52 (m, 2 H), 3.63 (m, 2 H), 3.76 (m, 2 H), 3.87 (m, 4 H), 4.11 (m, 1 H), 4.38 (m, 1 H), 4.55 (m, 1 H), 5.06 (m, 1 H), 6.97 - 7.05 (m, 1 H), 7.11 - 7.17 (m, 1 H), 7.27 - 7.42 (m, 5 H), 7.59 (m, 2 H), 7.90 (m, 1 H), 8.01 - 8.09 (m, 1 H).

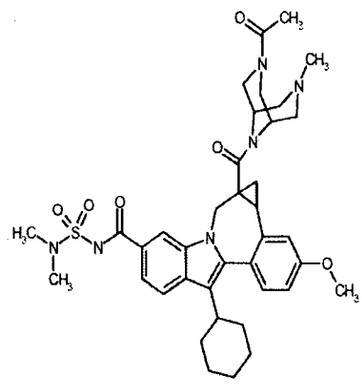
CL/EM: m/z 779.48, Rf 1.897 min., 95.3 % de pureza.



8-Ciclohexil-N-(dimetilsulfamoil)-1a-((3-isopropil-7-metil-3,7,9-triazabiciclo[3.3.1]non-9-il)carbonil)-11-metoxi-1,1a,2,12b-tetrahidrociclopropa[d]indol[2,1-a][2]benzazepin-5-carboxamida. 1H RMN (300 MHz, CD3OD): δ ppm 0.19 (m, 0.35 H), 1.12 (m, 3.65 H), 1.20 - 1.35 (m, 4 H), 1.39 (m, 2 H), 1.45 - 1.58 (m, 2 H), 1.64 (m, 2 H), 1.78 (m, 3 H), 2.00 (m, 6 H), 2.61 (m, 3 H), 2.74 - 2.90 (m, 2 H), 2.90 - 3.05 (m, 6 H), 3.48 (m, 1 H), 3.61 (m, 2 H), 3.84 - 3.91 (m, 4 H), 4.15 (m, 1 H), 4.45 (m, 1 H), 5.07 (m, 1 H), 7.01 (m, 1 H), 7.11 - 7.20 (m, 1 H), 7.26 - 7.35 (m, 1 H), 7.50 - 7.63 (m, 1 H), 7.88 (m, 1 H), 8.00 - 8.09 (m, 1 H). CL/EM: m/z 717.52, Rf 1.762 min., 97.8% de pureza.

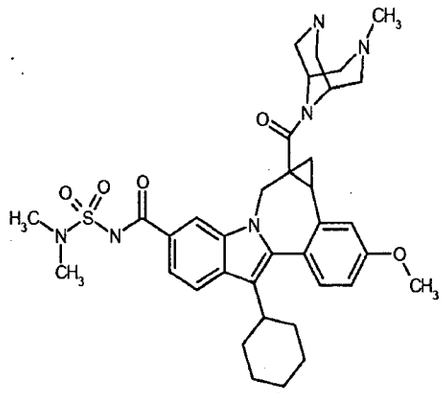


8-Ciclohexil-N-(dimetilsulfamoil)-1a-((3,7-dimetil-3,7,9-triazabiciclo[3.3.1]non-9-il)carbonil)-11-metoxi-1,1a,2,12b-tetrahidrociclopropa[d]indol[2,1-a][2]benzazepin-5-carboxamida. 1H RMN (300 MHz, CD3OD): δ ppm 0.24 (m, 0.20 H), 1.24 - 1.38 (m, 2.80 H), 1.45 (m, 4 H), 1.56 (m, 1 H), 1.83 (m, 2 H), 2.04 (m, 4 H), 2.65 (m, 1 H), 2.82 - 2.91 (m, 1 H), 2.93 - 3.05 (m, 9 H), 3.17 (m, 3 H), 3.49 (m, 1 H), 3.64 (m, 2 H), 3.78 (m, 1 H), 3.86 - 3.95 (m, 4 H), 4.03 (m, 1 H), 4.18 (m, 1 H), 4.37 (m, 1 H), 4.51 (m, 1 H), 5.08 (d, J=15.37 Hz, 1 H), 6.99 - 7.07 (m, 1 H), 7.13 - 7.22 (m, 1 H), 7.29 - 7.37 (m, 1 H), 7.51 - 7.63 (m, 1 H), 7.89 (m, 1 H), 7.99 - 8.10 (m, 1 H). CL/EM: m/z 689.50, Rf 1.813 min., 98.3 % de pureza.

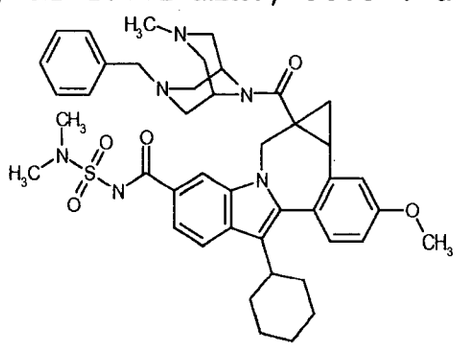


1a-((3-Acetil-7-metil-3,7,9-triazabiciclo[3.3.1]non-9-il)carbonil)-8-ciclohexil-N-(dimetilsulfamoil)-11-metoxi-1,1a,2,12b-tetrahidrociclopropa[d]indol[2,1-a][2]benzazepin-5-carboxamida. 1H RMN (300 MHz, CD3OD): δ ppm 0.51 (m, 0.20 H), 1.68 (m, 4.80 H), 1.98 (m, 2 H), 2.12 (m, 2 H), 2.41 (m, 7 H), 2.98 (m, 1 H), 3.19 (m, 2 H), 3.56 - 3.65 (m, 13 H), 3.94 - 4.10 (m, 2 H), 4.14 - 4.29 (m, 4 H), 4.95 (m, 2 H), 5.40 (m, 1

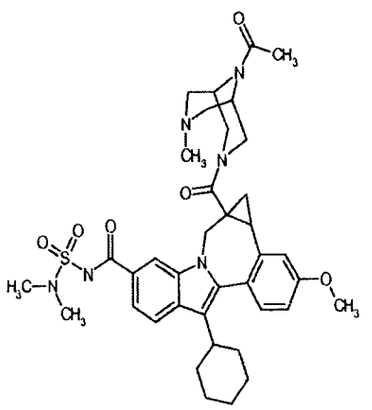
H), 7.35 (m, 1 H), 7.47 - 7.53 (m, 1 H), 7.60 - 7.67 (m, 1 H), 7.85 (m, 1 H), 8.16 - 8.25 (m, 1 H), 8.36 (s, 1 H). CL/EM: m/z 717.47, Rf 1.710 min., 97.1 % de pureza.



8-Ciclohexil-N-(dimetilsulfamoil)-11-metoxi-1a-((3-metil-3,7,9-triazabiciclo[3.3.1]non-9-il)carbonil)-1,1a,2,12b-tetrahidrociclopropa[d]indol[2,1-a][2]benzazepin-5-carboxamida. 1H RMN (300 MHz, CD3OD): δ ppm 0.20 (m, 0.20 H), 1.24 - 1.36 (m, 1.80 H), 1.45 (m, 2 H), 1.55 (m, 3 H), 1.64 (m, 1 H), 1.80 (m, 1 H) 1.86 (m, 2 H) 2.08 (m, 6 H), 2.36 (m, 1 H), 2.48 (m, 1 H), 2.62 (m, 2 H), 2.86 (m, 1 H), 3.00 (m, 3 H), 3.16 (m, 1 H), 3.45 (m, 2 H) 3.66 (m, 4 H), 3.85 - 3.96 (m, 3 H), 4.18 (m, 1 H), 4.34 (m, 1 H), 4.46 (m, 1 H), 5.05 (m, 1 H), 7.01 (m, 1 H), 7.13 - 7.20 (m, 1 H), 7.32 (m, 1 H), 7.52 - 7.61 (m, 1 H), 7.89 (m, 1 H), 8.00 - 8.07 (m, 1 H). CL/EM: m/z 675.37, Rf 1.772 min., 95.3 % de pureza.

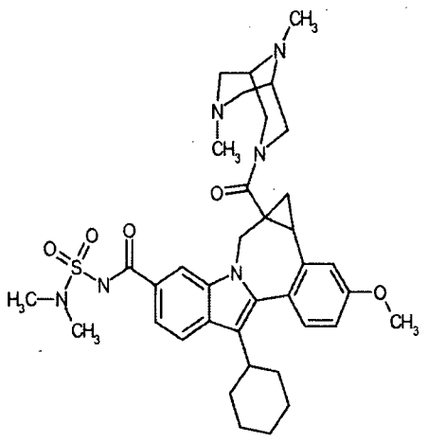


1a-((3-Bencil-7-metil-3,7,9-triazabiciclo[3.3.1]non-9-il)carbonil)-8-ciclohexil-N-(dimetilsulfamoil)-11-metoxi-1,1a,2,12b-tetrahidrociclopropa[d]indol[2,1-a][2]benzazepin-5-carboxamida. 1H RMN (300 MHz, CD3OD): δ ppm 0.20 (m, 0.20 H), 1.32 (m, 2.80 H), 1.43 (m, 4 H), 1.77 (m, 2 H), 2.01 (m, 5 H), 2.59 - 2.72 (m, 2 H), 2.78 (m, 1 H), 2.87 (m, 1 H), 2.90 - 3.05 (m, 8 H), 3.25 (m, 2 H), 3.59 (m, 4 H), 3.75 (m, 1 H), 3.84 - 3.93 (m, 3 H), 4.15 (m, 1 H), 4.38 (m, 1 H), 4.56 (m, 1 H), 5.08 (d, J=15.00 Hz, 1 H), 6.97 - 7.04 (m, 1 H), 7.07 - 7.17 (m, 1 H), 7.28 - 7.42 (m, 6 H), 7.53 - 7.61 (m, 1 H), 7.85 - 7.92 (m, 1 H), 7.99 - 8.13 (m, 1 H). CL/EM: m/z 765.45, Rf 1.840 min., 99.7 % de pureza.

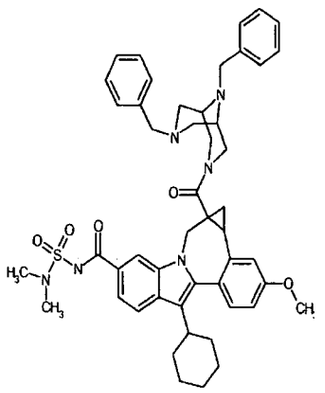


1a-((9-Acetil-7-metil-3,7,9-triazabiciclo[3.3.1]non-3-il)carbonil)-8-ciclohexil-N-(dimetilsulfamoil)-11-metoxi-1,1a,2,12b-tetrahidrociclopropa[d]indol[2,1-a][2]benzazepin-5-carboxamida. 1H RMN (300 MHz, CD3OD): δ ppm 0.20 (m, 0.35 H), 1.01 - 1.30 (m, 0.65 H), 1.38 (m, 5 H), 1.79 (m, 3 H), 1.93 - 2.21 (m, 13 H), 2.62 (m, 1 H), 2.82 (m, 2 H), 2.99 (s, 6 H), 3.56

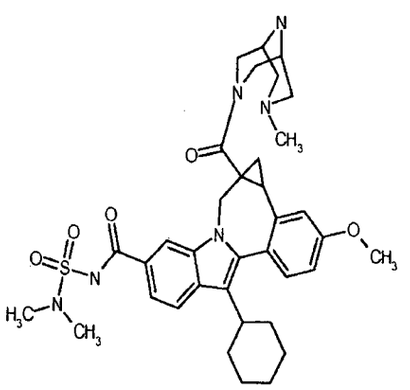
(m, 1 H), 3.90 (m, 3 H), 4.04 - 4.18 (m, 3 H), 4.53 (m, 1 H), 4.63 (m, 1 H), 4.99 (m, 1 H), 6.95 - 7.01 (m, 1 H), 7.19 (m, 1 H), 7.31 (m, 1 H), 7.50 - 7.60 (m, 1 H), 7.80 (m, 1 H), 7.88 - 8.07 (m, 1 H). CL/EM: m/z 717.92, Rf 1.760 min., 97.6 % de pureza.



8-Ciclohexil-N-(dimetilsulfamoil)-1a-((7,9-dimetil-3,7,9-triazabiciclo[3.3.1]non-3-il)carbonil)-11-metoxi-1,1a,2,12b-tetrahidrociclopropa[d]indol[2,1-a][2]benzazepin-5-carboxamida. 1H RMN (300 MHz, CD3OD): δ ppm 0.24 (m, 0.35 H), 1.24 (m, 0.65 H), 1.29 - 1.49 (m, 5 H), 1.62 (m, 1 H), 1.79 (m, 2 H), 1.98 (m, 4 H), 2.42 (m, 1 H), 2.53 (m, 1 H), 2.62 (m, 1 H), 2.75 (m, 1 H), 2.87 (m, 2 H), 2.93 - 3.07 (m, 8 H), 3.12 - 3.22 (m, 2 H), 3.42 (m, 2 H), 3.51 - 3.66 (m, 1 H), 3.88 (m, 3 H), 4.13 (m, 3 H), 4.27 (m, 1 H), 4.60 (m, 1 H), 5.00 (m, 1 H), 6.97 - 7.04 (m, 1 H), 7.14 - 7.20 (m, 1 H), 7.31 (m, 1 H), 7.49 - 7.61 (m, 1 H), 7.81 - 7.92 (m, 1.65 H), 8.06 (m, 0.35 H). CL/EM: m/z 689.86, Rf 1.785 min., 96.2 % de pureza.



8-Ciclohexil-1a-((7,9-dibencil-3,7,9-triazabiciclo[3.3.1]non-3-il)carbonil)-N-(dimetilsulfamoil)-11-metoxi-1,1a,2,12b-tetrahidrociclopropa[d]indol[2,1-a][2]benzazepin-5-carboxamida. 1H RMN (500 MHz, CD3OD): δ ppm 0.22 (m, 0.25 H), 0.90 (m, 1 H), 1.19 - 1.28 (m, 1.75 H), 1.38 - 1.46 (m, 3 H), 1.76 (m, 3 H), 1.95 (m, 2 H), 2.00 (m, 2 H), 2.07 (m, 2 H), 2.54 (m, 1 H), 2.86 (m, 1 H), 2.99 (m, 9 H), 3.16 (m, 1 H), 3.43 (m, 1 H), 3.47 (m, 3 H), 3.84 - 3.91 (m, 4 H), 4.01 - 4.09 (m, 2 H), 4.75 (m, 1 H), 4.99 (d, J=15.26 Hz, 1 H), 6.94 - 7.02 (m, 1 H), 7.08 - 7.17 (m, 1 H), 7.27 - 7.56 (m, 11 H), 7.70 (m, 1 H), 7.86 - 8.07(m, 2 H). CL/EM: m/z 842.66, Rf 2.010 min., 98.0 % de pureza.



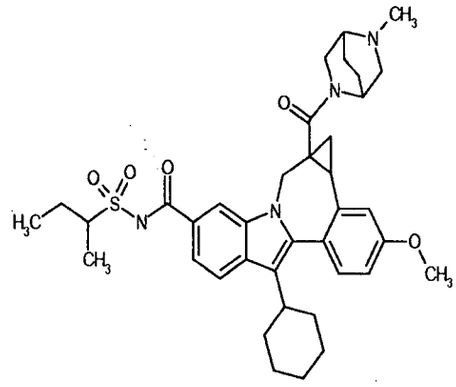
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8-Ciclohexil-N-(dimetilsulfamoil)-11-metoxi-1a-((7-metil-3,7,9-triazabiciclo[3.3.1]non-3-il)carbonil)-1,1a,2,12b-tetrahidrociclopropa[d]indol[2,1-a][2]benzazepin-5-carboxamida. 1H RMN (500 MHz, CD3OD): δ ppm 0.23 (m, 0.30 H), 1.07 -1.29 (m, 0.70 H), 1.36 - 1.45 (m, 5 H), 1.60 (m, 1 H), 1.73 - 1.82 (m, 2 H), 1.90 - 2.07 (m, 4 H), 2.17 (m, 1 H), 2.35 (m, 1 H), 2.54 - 2.70 (m, 3 H), 2.86 (m, 1 H), 3.00 (m, 8 H), 3.20 (m, 2 H), 3.59 (m, 1 H), 3.71 - 3.80 (m, 1 H), 3.84 - 3.91 (m, 3 H), 4.14 m, 1 H), 4.43 (m, 1 H), 4.65 (m, 1 H), 4.98 (m, 1 H), 6.98 - 7.01 (m, 1 H), 7.15 - 7.20 (m, 1 H), 7.28 - 7.32 (m, 1 H), 7.50 - 7.60 (m, 1 H), 7.85 - 8.05 (m, 2 H). CL/EM: m/z 675.61, Rf 1.783 min., 98.7 % de pureza.

Procedimiento general para alquilación reductiva. A un vial de 2 dram se agregó 0.05 mmol de carboxamida de piperidina en 600 µL de metanol y 60 µL de agua, junto con 1.0 eq. de 1H-benzo[d][1,2,3]triazol, 2.0 eq. de formaldehído acuoso y 2.0 equivalentes de trietilamina pura. Los viales se taparon y agitaron durante la noche a temperatura ambiente en un agitador orbital. Las mezclas de reacción luego se diluyeron con 2mL de metanol y borohidruro de sodio seco se agregó lentamente (2 eq). Cuando la efervescencia cesó, los viales se volvieron a tapar y calentaron a 65°C con agitación en un bloque de secado durante ~90min. Después del regreso a temperatura ambiente los productos crudos se purificaron usando HPLC preparativa Shimadzu empleando

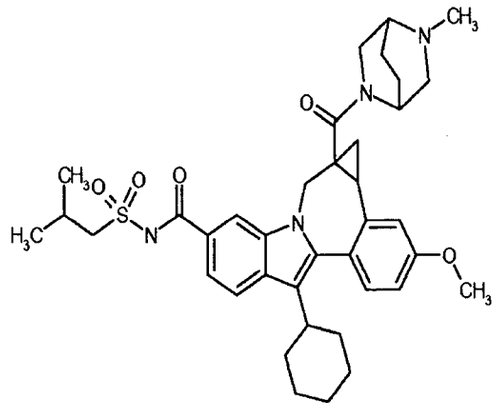
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metanol/agua/Solución amortiguadora TFA al 0.1% donde el solvente A fue 10% de MeOH/90% de H2O/0.1% de ácido trifluoroacético y el solvente B fue 10% de H2O/90% de MeOH/0.1% de ácido trifluoroacético con una columna Phenomenex-Luna 10u C18 30x100mm en un gradiente de B al 30-100% y una relación de flujo de 40 mL/min. Durante 10 minutos con una espera de 8 minutos. Los productos se evaporaron hasta secarse durante la noche en un Savant Speedvac que proporciona las metilpiperidinas como sólidos amorfos amarillos (63% de rendimiento promedio).



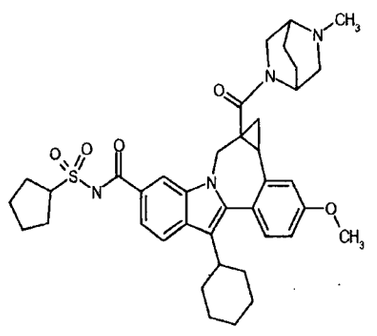
Ciclopropl[d]indol[2,1-a][2]benzazepin-5-carboxamida, 8-ciclohexil-1,1a,2,12b-tetrahidro-11-metoxi-1a-[(5-metil-2,5-diazabiciclo[2.2.2]oct-2-il)carbonil]-N-[(1-metilpropil)sulfonil]-. 1H RMN (500 MHz, CD3OD): δ ppm 0.13 (m, 0.20 H), 0.98 - 1.14 (m, 3 H), 1.17 - 1.35 (m, 1.80 H), 1.35 - 1.59 (m, 7 H), 1.60 - 1.73 (m, 2 H), 1.72 - 1.85 (m, 2 H), 1.87 - 2.16 (m, 6 H), 2.20 - 2.45 (m, 1 H), 2.56 (m, 1 H), 2.73 - 2.92 (m, 3 H), 2.97 - 3.17 (m, 3 H), 3.27 - 3.35 (m, 1H), 3.45 - 3.69 (m, 2 H), 3.69 - 3.81 (m, 2 H), 3.83 - 3.94 (m, 3 H), 3.93 - 4.20 (m, 1 H), 4.16 - 4.52 (m, 1 H), 4.92 - 5.26 (m, 1

H), 6.97 - 7.04 (m, 1 H), 7.18 (m, 1 H), 7.26 - 7.31 (m, 1 H), 7.47 - 7.61 (m, 1 H), 7.85 - 7.91 (m, 1 H), 7.93 - 8.17 (m, 1 H). CL/EM: m/z 673.35, Rf 1.823 min., 98.4 % de pureza.

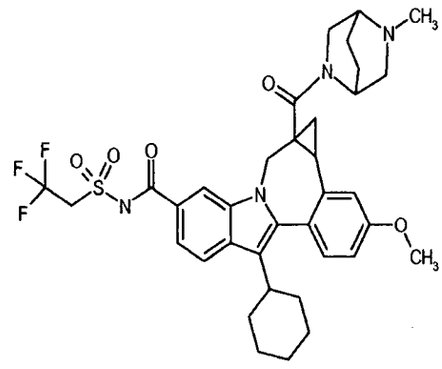


Ciclopropa[d]indol[2,1-a][2]benzazepin-5-carboxamida, 8-ciclohexil-1,1a,2,12b-tetrahidro-11-metoxi-1a-[(5-metil-2,5-diazabiciclo[2.2.2]oct-2-il)carbonil]-N-[(2-metilpropil)sulfonil]-.

1H RMN (500 MHz, CD3OD): δ ppm 0.13 (m, 0.20 H), 1.14 (d, J=6.71 Hz, 6 H), 1.24 - 1.32 (m, 1.80 H), 1.39 - 1.49 (m, 4 H), 1.50 (m, 1 H), 1.80 (m, 3 H), 1.93 - 2.08 (m, 5 H), 2.31 (m, 2 H), 2.52 (m, 1 H), 2.88 (m, 2 H), 2.97 (m, 2 H), 3.10 (m, 1 H), 3.33 (m, 1 H), 3.49 (m, 2 H), 3.67 (m, 3 H), 3.82 - 3.90 (m, 3 H), 4.03 (m, 1 H), 4.32 (m, 1 H), 5.05 (m, 1 H), 7.01 (m, 1 H), 7.21 (m, 1 H), 7.26 - 7.34 (m, 1 H), 7.55 - 7.64 (m, 1 H), 7.90 (m, 1 H), 7.93 - 8.02 (m, 1 H). CL/EM: m/z 673.45, Rf 1.827 min., 98.5 % de pureza.

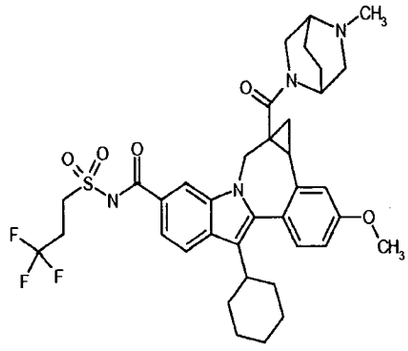


Cicloprop[d]indol[2,1-a][2]benzazepin-5-carboxamida, 8-ciclohexil-N-(ciclopentilsulfonil)-1,1a,2,12b-tetrahidro-11-metoxi-1a-[(5-metil-2,5-diazabiciclo[2.2.2]oct-2-il)carbonil]-. 1H RMN (500 MHz, CD3OD): δ ppm 0.13 (m, 0.20 H), 1.17 - 1.32 (m, 2 H), 1.39 - 1.48 (m, 3.80 H), 1.65 - 1.75 (m, 3 H), 1.76 - 1.85 (m, 4 H), 1.90 - 2.17 (m, 9 H), 2.40 (m, 1 H), 2.57 (m, 2 H), 2.83 - 2.92 (m, 2 H), 2.92 - 3.01 (m, 3 H), 3.34 (m, 1 H), 3.62 (m, 3 H), 3.82 - 3.90 (m, 3 H), 4.02 (m, 1 H), 4.22 - 4.31 (m, 2 H), 5.02 (m, 1 H), 7.00 (m, 1 H), 7.17 (m, 1 H), 7.27 - 7.32 (m, 1 H), 7.52 - 7.61 (m, 1 H), 7.84 - 8.20 (m, 2 H). CL/EM: m/z 685.47, Rf 1.827 min., 99.2 % de pureza.

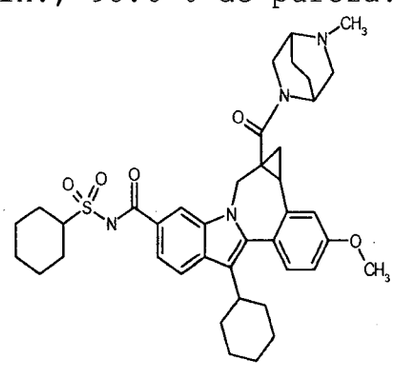


Cicloprop[d]indol[2,1-a][2]benzazepin-5-carboxamida, 8-ciclohexil-1,1a,2,12b-tetrahidro-11-metoxi-1a-[(5-metil-2,5-diazabiciclo[2.2.2]oct-2-il)carbonil]-N-[(2,2,2-trifluoroetil)sulfonil]-. 1H RMN (500 MHz, CD3OD): δ ppm 0.15 (m, 0.20 H), 1.23 - 1.32 (m, 3 H), 1.39 - 1.49 (m, 3.80 H), 1.80 (m, 3 H), 1.94 - 2.30 (m, 4 H), 2.69 (m, 1 H), 2.84 - 2.93 (m, 2 H), 2.94 - 3.03 (m, 2 H), 3.14 - 3.21 (m, 2 H), 3.34 (m, 1 H), 3.58 (m, 2 H), 3.70 (m, 2 H), 3.75 (m 1 H), 3.85 - 3.91 (m, 3 H), 4.10 (m, 1 H), 4.36 (m, 1 H),

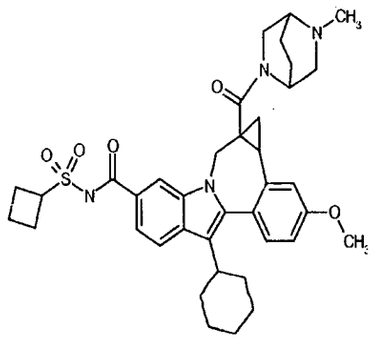
4.61 - 4.70 (m, 1 H), 5.08 (m, 1 H), 6.98 - 7.07 (m, 1 H), 7.15 - 7.24 (m, 1 H), 7.32 (m, 1 H), 7.47 - 7.64 (m, 1 H), 7.85 - 7.96 (m, 1 H), 8.02 (m, 1 H). CL/EM: m/z 699.25, Rf 1.813 min., 98.3 % de pureza.



Ciclopropa[d]indol[2,1-a][2]benzazepin-5-carboxamida, 8-ciclohexil-1,1a,2,12b-tetrahidro-11-metoxi-1a-[(5-metil-2,5-diazabiciclo[2.2.2]oct-2-il)carbonil]-N-[(3,3,3-trifluoropropil)sulfonil]-. 1H RMN (500 MHz, CD3OD): δ ppm 0.12 (m, 0.20 H), 1.06 - 1.33 (m, 2 H), 1.36 - 1.70 (m, 4.80 H), 1.78 (m, 2 H), 1.93 - 2.09 (m, 5 H), 2.30 (m, 1 H), 2.56 (m, 2 H), 2.7 - 3.19 (m, 7 H), 3.34 (m, 1 H), 3.59 (m, 3 H), 3.88 (m, 5 H), 4.02 (m, 1 H), 4.28 (m, 1 H), 5.04 (m, 1 H), 7.00 - 7.07 (m, 1 H), 7.17 - 7.22 (m, 1 H), 7.23 - 7.34 (m, 1 H), 7.54 - 7.64 (m, 1 H), 7.84 - 8.02 (m, 2 H). CL/EM: m/z 713.30, Rf 1.818 min., 98.6 % de pureza.

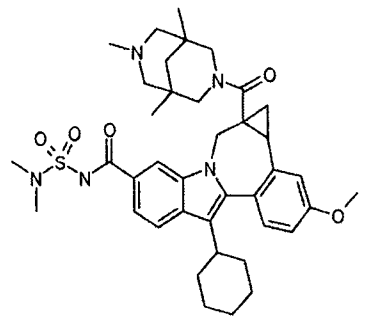


Cicloprop[d]indol[2,1-a][2]benzazepin-5-carboxamida, 8-ciclohexil-N-(ciclohexilsulfonil)-1,1a,2,12b-tetrahidro-11-metoxi-1a-[(5-metil-2,5-diazabiciclo[2.2.2]oct-2-il)carbonil]-. 1H RMN (500 MHz, CD3OD): δ ppm 0.19 (m, 0.20 H), 1.14 - 1.50 (m, 8.80 H), 1.66 (m, 3 H), 1.80 (m, 3 H), 1.96 (m, 3 H), 2.01 - 2.20 (m, 6 H), 2.40 (m, 1 H), 2.61 (m, 2 H), 2.89 (m, 2 H), 3.00 (m, 3 H), 3.37 (m, 1 H), 3.73 (m, 4 H), 3.91 (m, 3 H), 4.06 (m, 1 H), 4.32 (m, 1 H), 5.09 (m, 1 H), 7.02 - 7.08 (m, 1 H), 7.21 - 7.24 (m, 1 H), 7.33 (m, 1 H), 7.56 - 7.66 (m, 1 H), 7.88 8.02 (m, 2 H). CL/EM: m/z 699.46, Rf 1.895 min., 100% de pureza.



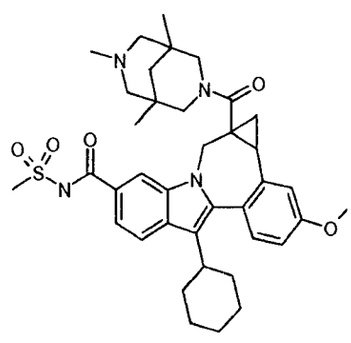
Cicloprop[d]indol[2,1-a][2]benzazepin-5-carboxamida, N-(ciclobutilsulfonil)-8-ciclohexil-1,1a,2,12b-tetrahidro-11-metoxi-1a-[(5-metil-2,5-diazabiciclo[2.2.2]oct-2-il)carbonil]-. 1H RMN (500 MHz, CD3OD): δ ppm 0.12 (m, 0.20 H), 1.21 - 1.31 (m, 3 H), 1.38 - 1.61 (m, 4.80 H), 1.99 (m, 3 H), 1.73 - 1.82 (m, 3 H), 1.90 - 2.09 (m, 4 H), 2.31 - 2.40 (m, 3 H), 2.54 - 2.63 (m, 3 H), 2.90 (m, 1 H), 2.93 - 3.17 (m, 4 H), 3.55 (m, 3 H), 3.89 (m, 3 H), 4.00 (m, 1 H), 4.29 (m, 1 H), 4.50 - 4.59 (m, 1 H), 5.05 (m, 1 H), 7.04 (m, 1 H), 7.20 (m, 1 H), 7.29 -

7.33 (m, 1 H), 7.54 - 7.61 (m, 1 H), 7.88 - 8.09 (m, 2 H). CL/EM: m/z 671.34, Rf 1.886 min., 100% de pureza.



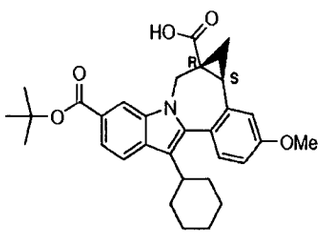
8-Ciclohexil-N-(dimetilsulfamoil)-11-metoxi-1a-((1,5,7-trimetil-3,7-diazabiciclo[3.3.1]non-3-il)carbonil)-1,1a,2,12b-tetrahidrociclopropa[d]indol[2,1-a][2]benzazepin-5-carboxamida. El HATU (36 mg, 0.094 mmol) se agregó a una solución agitada del ácido de partida (40 mg, 0.073 mmol) y 1,3,5-trimetil-3,7-diazabiciclo[3.3.1]nonano (25 mg, 0.15 mmol) en DMF (0.5 mL) y TEA (0.06 mL, 0.4 mmol) y la reacción se agitó a temperatura ambiente durante 1h. La mezcla de reacción se diluyó con MeOH (~1 mL), filtró y purificó por HPLC preparativa (Xterra Prep EM C18 5u 30 x 100 mm, Eluyente A: acetonitrilo al 5%/agua con acetato de amonio 10 mM, Eluyente B: acetonitrilo al 95%/agua con acetato de amonio 10 mM, Relación de flujo: 42 mL/min, gradiente lineal desde eluyente B al 15% a eluyente B al 100% durante 15 min) para proporcionar la 8-ciclohexil-N-(dimetilsulfamoil)-11-metoxi-1a-((1,5,7-trimetil-3,7-diazabiciclo[3.3.1]non-3-il)carbonil)-1,1a,2,12b-tetrahidrociclopropa[d]indol[2,1-a][2]benzazepin-5-carboxamida (37.5 mg, 0.053 mmol, 74% de rendimiento) como un

sólido blanco opaco. El compuesto se aisló como una mezcla de enantiómeros. Se presenta como una mezcla 1:1 de rotámeros o isómeros átropos. ^{1}H RMN (300 MHz, $CDCl_3$) δ 0.17 - 3.20 (m, 31H), 3.02 (s, 6H), 3.77 - 5.05 (m, 4H), 3.87 (s, 3H), 6.84 - 6.95 (m, 1H), 6.99 - 7.11 (m, 1H), 7.26 (d, J = 8.8 Hz, 1H), 7.42 - 8.01 (m, 1.5H), 7.85 (d, J= 8.4 Hz, 1H), 8.04 (br s, 0.5H). Tiempo de retención CL-EM: 3.45 min; m/z 700 (MH-). Los Datos CL se registraron en un equipo de cromatografía líquida Shimadzu CL-10AS con una columna Phenomenex-Luna 10u C18 4.6x50mm usando un detector SPD-10AV UV-Vis en un detector de longitud de onda de 220nM. Las condiciones de elución emplean una relación de flujo de 5 mL/min, un gradiente de solvente A al 100%/solvente B al 0% a solvente A al 0%/solvente B al 100%, un tiempo de gradiente de 4 min, un tiempo de espera de 1 min, y un tiempo de análisis de 5 min donde el solvente A fue acetonitrilo al 5%/H2O al 59%/acetato de amonio 10 mM y el solvente B fue H2O al 5%/acetonitrilo al 95%/acetato de amonio 10 mM. Los datos EM se determinaron usando una plataforma de micromasa para CL en el modo de electro-rocío.



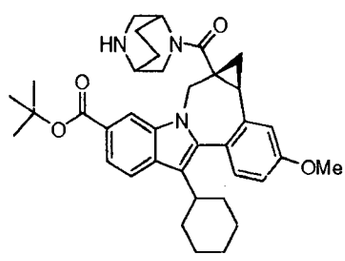
8-Ciclohexil-11-metoxi-N-(metilsulfonil)-1a-((1,5,7-trimetil-3,7-diazabiciclo[3.3.1]non-3-il)carbonil)-1,1a,2,12b-tetrahidrociclopropa[d]indol[2,1-a][2]benzazepin-5-carboxamida. El HATU (38 mg, 0.10 mmol) se agregó a una solución agitada del ácido de partida (40 mg, 0.077 mmol) y 1,3,5-trimetil-3,7-diazabiciclo[3.3.1]nonano (26 mg, 0.15 mmol) en DMF (0.5 mL) y TEA (0.06 mL, 0.4 mmol) y la reacción se agitó a temperatura ambiente durante 3h. La mezcla de reacción se diluyó con MeOH (~1 mL), filtró y purificó por HPLC preparativa (Xterra Prep EM C1 8 5u 30 x 100 mm, Eluyente A: acetonitrilo al 5%/agua con acetato de amonio 10 mM, Eluyente B: acetonitrilo al 95%/agua con acetato de amonio 10 mM, Relación de flujo: 42 mL/min, gradiente lineal desde el eluyente B al 15% a eluyente B al 100% durante 15 min) para proporcionar la 8-ciclohexil-11-metoxi-N-(metilsulfonil)-1a-((1,5,7-trimetil-3,7-diazabiciclo[3.3.1]non-3-il)carbonil)-1,1a,2,12b-tetrahidrociclopropa[d]indol[2,1-a][2]benzazepin-5-carboxamida (40.2 mg, 0.060 mmol, 78% de rendimiento) como un sólido blanco. El compuesto se aisló como una mezcla de enantiómeros. 1H RMN (300 MHz, CDCl3) δ ppm 0.07 - 3.15 (m, 24H), 3.40 (s, 3H), 3.46 - 4.12 (m, 3H), 3.87 (s, 3H), 4.34 - 5.05 (m, 3H), 6.85 - 6.96 (m, 1H), 6.99 - 7.12 (m, 1H), 7.24 - 7.33 (m, 1H), 7.49 - 7.65 (m, 1H), 7.80 - 7.90 (m, 1H), 7.92 - 8.08 (m, 1H). Tiempo de retención CL-EM: 2.43 min; m/z 671 (MH-). Los Datos CL se registraron en un equipo de

cromatografía líquida Shimadzu CL-10AS con una columna Phenomenex-Luna 10u C18 4.6x50mm usando un detector SPD-10AV UV-Vis en un detector de longitud de onda de 220nM. Las condiciones de elución emplean una relación de flujo de 5 mL/min, un gradiente de solvente A al 100%/solvente B al 0% a solvente A al 0%/solvente B al 100%, un tiempo de gradiente de 4 min, un tiempo de espera de 1 min, y un tiempo de análisis de 5 min donde el solvente A fue acetonitrilo al 5%/H2O al 59%/acetato de amonio 10 mM y el solvente B fue H2O al 5%/acetonitrilo al 95%/acetato de amonio 10 mM. Los datos EM se determinaron usando una plataforma de micromasa para CL en el modo de electro-rocío.



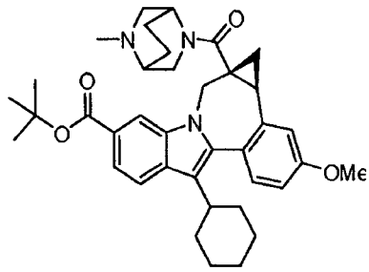
ácido (1aR,12bS)-5-(tert-butoxicarbonil)-8-ciclohexil-11-metoxi-1,12b-dihidrociclopropa[d]indol[2,1-a][2]benzazepin-1a(2H)-carboxílico. El hidróxido de sodio (1M ac., 31 mL) se agregó a una solución fría (0°C, baño de hielo) que contiene 1a-etil (1aR,12bS)-8-ciclohexil-11-metoxi-1,12b-dihidrociclopropa[d]indol[2,1-a][2]benzazepin-1a,5(2H)-dicarboxilato de 5-tert-butilo (4.0 g, 7.76 mmol), THF (35 mL), y metanol (35 mL). Después de 20 min, la solución se removió del baño de enfriamiento y mantuvo a temperatura

ambiente durante 3h. La solución se enfrió nuevamente (0°C, baño de hielo) y el pH se redujo hasta de bajo de 4 por la adición lenta de HCL 1N (ac., 33mL). La mezcla se extrajo inmediatamente con acetato de etilo (2 x 30 mL). Las porciones orgánicas combinadas se lavaron con salmuera, (20 mL), secaron (sulfato de magnesio), filtraron y concentraron para proporcionar un sólido blanco el cual se usó sin purificación adicional en la siguiente etapa. CLEM: Tiempo de retención: 3.162 min. Los Datos CL se registraron en un equipo de cromatografía líquida Shimadzu CL-10AS con una columna Phenomenex-Luna 10u C18 4.6x50mm usando un detector SPD-10AV UV-Vis en un detector de longitud de onda de 220nM. Las condiciones de elución emplean una relación de flujo de 4 mL/min, un gradiente de solvente A al 100%/solvente B al 0% a solvente A al 0%/solvente B al 100%, un tiempo de gradiente de 4 min, un tiempo de espera de 1 min, y un tiempo de análisis de 5 min donde el solvente A fue CH_3CN al 5%/H_2O al 59%/acetato de amonio 10 mM y el solvente B fue H_2O al 5%/CH_3CN al 95%/acetato de amonio 10 mM. Los datos EM se determinaron usando una plataforma de micromasa para CL en el modo de electro-rocío, m/z 502(MH+).



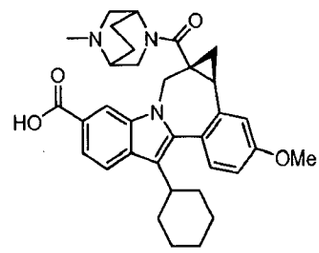
(1aR,12bS)-8-ciclohexil-1a-(2,5-diazabiciclo[2.2.2]oct-2-ilcarbonil)-11-metoxi-1,1a,2,12b-tetrahidrociclopropa[d]indol[2,1-a][2]benzazepin-5-carboxilato de Tert-butilo. El TBTU (691 mg, 2.15 mmol) se agregó en una porción en una solución fría (0°C, baño de hielo) que contiene el ácido (1aR,12bS)-5-(tert-butoxicarbonil)-8-ciclohexil-11-metoxi-1,12b-dihidrociclopropa[d]indol[2,1-a][2]benzazepin-1a(2H)-carboxílico (900 mg, 1.79 mmol), DIEA (1.88 mL, 10.77 mmol), diclorohidrato de 2,5-diazabiciclo[2.2.2]octano (1:1) ((498 mg, 2.69 mmol), (H. Newman, J. Het. Chem. 449 (1974); P.E. Thompson, J. B. Zeigler, J. W. McCaIl, J. Med. Chem., 17 ', 481 (1974)), y dichlorometano (36 mL). La solución se mantuvo durante 1.5 h y diluyó con diclorometano adicional (20 mL). La solución se lavó con agua (3 x 20 mL), lavó con salmuera (15 mL), secó (sulfato de magnesio), filtró y concentró para proporcionar un residuo blanco pegajoso el cual se trituró con n-pentano (2 x 20 mL) para proporcionar un sólido blanco el cual se usó sin purificación adicional en la siguiente etapa. CLEM: tiempo de retención 3.841 min. Los Datos CL se registraron en un equipo de cromatografía líquida Shimadzu CL-10AS con una columna Phenomenex-Luna 10u C18 4.6x50mm usando un detector SPD-10AV UV-Vis en un detector de longitud de onda de 220nM. Las condiciones de elución emplean una relación de flujo de 4 mL/min, un gradiente de solvente A al 100%/solvente B al 0% a solvente A al 0%/solvente B al

100%, un tiempo de gradiente de 4 min, un tiempo de espera de 1 min, y un tiempo de análisis de 5 min donde el solvente A fue CH3CN al 5%/H_2O al 59%/acetato de amonio 10 mM y el solvente B fue H_2O al 5%/CH_3CN al 95%/acetato de amonio 10 mM. Los datos EM se determinaron usando una plataforma de micromasa para CL en el modo de electro-rocío., m/z 596(MH+).



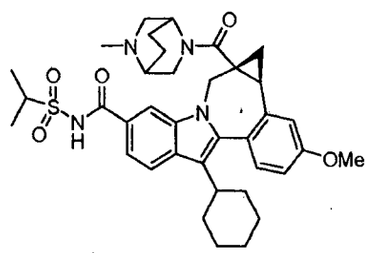
(1aR,12bS)-8-ciclohexil-11-metoxi-1a-((5-metil-2,5-diazabiciclo[2.2.2]oct-2-il)carbonil)-1,1a,2,12b-tetrahidrociclopropa[d]indol[2,1-a][2]benzazepin-5-carboxilato de Tert-butilo. Una suspensión que contiene (1aR,12bS)-8-ciclohexil-1a-(2,5-diazabiciclo[2.2.2]oct-2-ilcarbonil)-11-metoxi-1,1a,2,12b-tetrahidrociclopropa[d]indol[2,1-a][2]benzazepin-5-carboxilato de tert-butilo (904 mg, 1.51 mmol), formaldehído (37% en agua, 40 mL, 531 mmol), paladio en carbono al 10% (323 mg, 0.303 mmol Pd), y etanol (76 mL) se agitó bajo un globo de gas de hidrógeno durante 26 hrs. La mezcla se filtró a través de celite y el filtrado se concentró hasta secarse. El sólido resultante se trituró con n-pentano (2 x 25 mL) y se usó sin purificación adicional. CLEM: tiempo de retención 4.123 min. Los Datos CL se registraron en un

equipo de cromatografía líquida Shimadzu CL-10AS con una columna Phenomenex-Luna 10u C18 4.6x50mm usando un detector SPD-10AV UV-Vis en un detector de longitud de onda de 220nM. Las condiciones de elución emplean una relación de flujo de 4 mL/min, un gradiente de solvente A al 100%/solvente B al 0% a solvente A al 0%/solvente B al 100%, un tiempo de gradiente de 4 min, un tiempo de espera de 1 min, y un tiempo de análisis de 5 min donde el solvente A fue CH_3CN al 5%/H_2O al 59%/acetato de amonio 10 mM y el solvente B fue H_2O al 5%/CH_3CN al 95%/acetato de amonio 10 mM. Los datos EM se determinaron usando una plataforma de micromasa para CL en el modo de electro-rocío, m/z 610 (MH+).



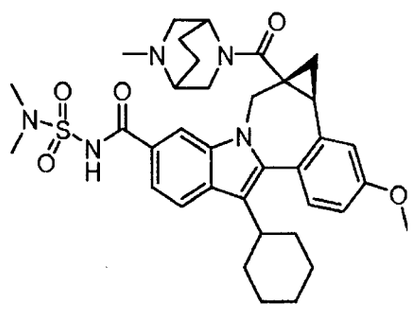
ácido (1aR,12bS)-8-ciclohexil-11-metoxi-1a-((5-metil-2,5-diazabiciclo[2.2.2]oct-2-il)carbonil)-1,1a,2,12b-tetrahidrociclopropa[d]indol[2,1-a][2]benzazepin-5-carboxílico. El TFA (11.6 mL, 1.164 mmol) se agregó a una solución que contiene (1aR,12bS)-8-ciclohexil-11-metoxi-1a-((5-metil-2,5-diazabiciclo[2.2.2]oct-2-il)carbonil)-1,1a,2,12b-tetrahidrociclopropa[d]indol[2,1-a][2]benzazepin-5-carboxilato de tert-butilo (710 mg, 1.164 mmol) y DCM (11.6 mL). La solución se mantuvo a temperatura ambiente durante 3 h

y luego concentró hasta secarse. El residuo resultante se cargó con 1:1 metanol/agua (20 mL) y el pH se incrementa arriba de 8 por la adición lenta de bicarbonato de sodio acuoso, saturado (10 mL). La solución se concentró para remover metanol y extrajo con diclorometano (6 x 10mL). Las porciones orgánicas combinadas se lavaron con salmuera (20 mL), secaron (sulfato de magnesio), filtraron y concentraron para proporcionar un sólido amarillo el cual se usó sin purificación adicional. El CL/EM mostró diaestereómeros separados bajo condiciones básicas en tiempos de retención de 2.047 min y 2.178 min. Los Datos CL se registraron en un equipo de cromatografía líquida Shimadzu CL-10AS con una columna Phenomenex-Luna 10u C18 4.6x50mm usando una detector SPD-10AV UV-Vis en un detector de longitud de onda de 220nM. Las condiciones de elución emplean una relación de flujo de 4 mL/min, un gradiente de solvente A al 100%/solvente B al 0% a solvente A al 0%/solvente B al 100%, un tiempo de gradiente de 4 min, un tiempo de espera de 1 min, y un tiempo de análisis de 5 min donde el solvente A fue CH_3CN al 5%/H_2O al 59%/acetato de amonio 10 mM y el solvente B fue H_2O al 5%/CH_3CN al 95%/acetato de amonio 10 mM. Los datos EM se determinaron usando una plataforma de micromasa para CL en el modo de electro-rocío.; m/z 554 (MH+).



(1aR,12bS)-8-ciclohexil-N-(isopropilsulfonil)-11-metoxi-1a-((5-metil-2,5-diazabiciclo[2.2.2]oct-2-il)carbonil)-1,1a,2,12b-tetrahidrociclopropa[d]indol[2,1-a][2]benzazepin-5-carboxamida. El EDCI (208 mg, 1.084 mmol) se agregó a temperatura ambiente, en una porción, a una solución que contiene ácido (1aR,12bS)-8-ciclohexil-11-metoxi-1a-((5-metil-2,5-diazabiciclo[2.2.2]oct-2-il)carbonil)-1,1a,2,12b-tetrahidrociclopropa[d]indol[2,1-a][2]benzazepin-5-carboxílico (300 mg, 0.542 mmol), DMAP (50 mg, 0.406 mmol), 2-isopropil sulfonamida (100 mg, 0.813 mmol), y diclorometano (6 mL). La solución se mantuvo a temperatura ambiente durante 24 h, diluyó con diclorometano adicional (20 mL), lavó con bicarbonato de sodio acuoso saturado (2 x 20 mL), lavó con agua (20 mL), secó (sulfato de magnesio), filtró y concentró. El residuo amarillo resultante se purificó por HPLC preparativa de fase inversa bajo condiciones básicas usando una columna Phenomenex, luna, 10 micron, 30 x 100 mm. Esto separa dos diaestereómeros, cada uno como un sólido blanco. El CL/EM mostró diaestereómeros separados bajo condiciones básicas en tiempos de retención de 2.160 min y 2.292 min. Los Datos CL se registraron en un equipo de cromatografía líquida Shimadzu CL-10AS con una columna Phenomenex-Luna 10u C18 4.6x50mm usando un detector SPD-10AV UV-Vis en un detector de longitud de onda de 220nM. Las condiciones de elución emplean una relación de flujo de 4 mL/min, un gradiente de solvente A

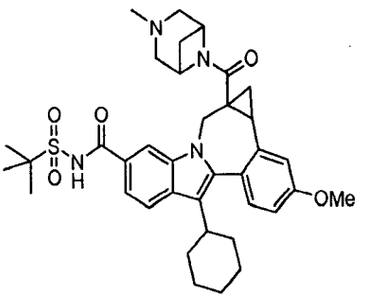
al 100%/solvente B al 0% a solvente A al 0%/solvente B al 100%, un tiempo de gradiente de 4 min, un tiempo de espera de 1 min, y un tiempo de análisis de 5 min donde el solvente A fue CH_3CN al 5%/H_2O al 59%/acetato de amonio 10 mM y el solvente B fue H_2O al 5%/CH_3CN al 95%/acetato de amonio 10 mM. Los datos EM se determinaron usando una plataforma de micromasa para CL en el modo de electro-rocío m/z 659 (MH+).



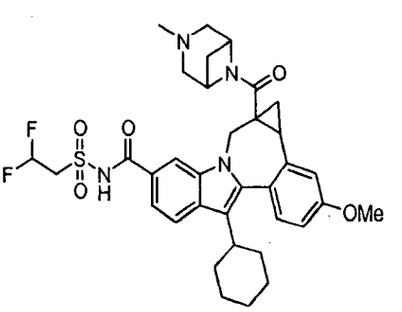
(1aR,12bS)-8-ciclohexil-N-(dimetilsulfamoil)-11-metoxi-1a-((5-metil-2,5-diazabiciclo[2.2.2]oct-2-il)carbonil)-1,1a,2,12b-tetrahidrociclopropa[d]indol[2,1-a][2]benzazepin-5-carboxamida. El compuesto del título se preparó a partir de ácido (1aR,12bS)-8-ciclohexil-11-metoxi-1a-((5-metil-2,5-diazabiciclo[2.2.2]oct-2-il)carbonil)-1,1a,2,12b-tetrahidrociclopropa[d]indol[2,1-a][2]benzazepin-5-carboxílico bajo condiciones similares a aquellas descritas por la (1aR,12bS)-8-ciclohexil-N-(isopropilsulfonil)-11-metoxi-1a-((5-metil-2,5-diazabiciclo[2.2.2]oct-2-il)carbonil)-1,1a,2,12b-tetrahidrociclopropa[d]indol[2,1-a][2]benzazepin-5-carboxamida. El residuo amarillo resultante se purificó por HPLC preparativa de fase inversa bajo condiciones básicas

usando una columna Phenomenex, luna, 10 micron, 30 x 100 mm. Esto separa dos diaestereómeros, cada uno como un sólido blanco. El CL/EM mostró diaestereómeros separados bajo condiciones básicas en tiempo de retención de 2.285 min y 2.437 min. Los Datos CL se registraron en un equipo de cromatografía líquida Shimadzu CL-10AS con una columna Phenomenex-Luna 10u C18 4.6x50mm usando detector SPD-10AV UV-Vis en un detector de longitud de onda de 220nM. Las condiciones de elución emplean una relación de flujo de 4 mL/min, un gradiente de solvente A al 100%/solvente B al 0% a solvente A al 0%/solvente B al 100%, un tiempo de gradiente de 4 min, un tiempo de espera de 1 min, y un tiempo de análisis de 5 min donde el solvente A fue CH_3CN al 5%/H_2O al 59%/acetato de amonio 10 mM y el solvente B fue H_2O al 5%/CH_3CN al 95%/acetato de amonio 10 mM. Los datos EM se determinaron usando una plataforma de micromasa para CL en el modo de electro-rocío.; m/z 660 (MH+).

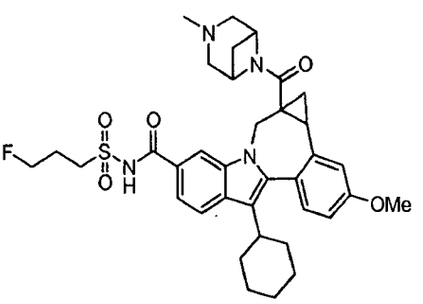
Los compuestos descritos en los siguientes procedimientos se analizaron por usar el siguiente método CL/EM: Condiciones de análisis: Columna: PHENOMENNEX- LUNA 3.0 x 50mm S 10; Fase móvil: (A) 10:90 metanol-agua; (B) 90:10 metanol-agua; Solución amortiguadora: TFA al 0.1%; Rango de gradiente: B al 0-100%; Tiempo de gradiente: 2 min; Relación de flujo: 4 mL/min; Tiempo de análisis: 3 min; Detección: Detector 1: UV a 220 nm; Detector 2: EM (ESI+).



(+/-)-8-ciclohexil-N-(tert-butilsulfonil)-1,1a,2,12b-tetrahidro-11-metoxi-1a-(3-metil-3,6-diazabiciclo[3.1.1]heptano-6-carbonil)cicloprop[d]indol[2,1-a][2]benzazepin-5-carboxamida. El producto se purificó por HPLC prep. y aisló como un sólido beige en una forma de sal mono TFA. CL/EM: Tiempo de retención: 1.867 min; m/e 659 (MH+). El producto se observó que existe como rotámeros de Interconversión por 1H RMN (400 MHz, CLOROFORMO-D) δ ppm 1.09 - 1.69 (m, 16 H), 1.81 (s, 3 H), 2.01 (s, 5 H), 2.70 (s, 1 H), 2.95 (d, J=3.53 Hz, 2 H), 3.17 (s, 1 H), 3.24 - 3.77 (m, 6 H), 3.87 - 3.98 (m, 3 H), 4.07 (s, 1 H), 4.38 (s, 1 H), 5.44 (s, 1 H), 6.98 (dd, J=8.56, 2.52 Hz, 1 H), 7.12 (d, J=2.52 Hz, 1 H), 7.19 - 7.37 (m, 1 H), 7.57 (d, J=8.31 Hz, 1 H), 7.89 (d, J=8.31 Hz, 1 H), 8.11 (s, 1 H).

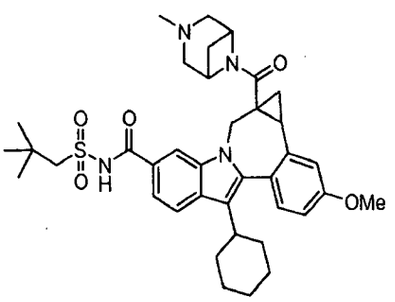


(+/-)-8-ciclohexil-N-(2,2-difluoroetilsulfonil)-1,1a,2,12b-tetrahidro-11-metoxi-1a-(3-metil-3,6-diazabiciclo[3.1.1]heptano-6-carbonil)cicloprop[d]indol[2,1-a][2]benzazepin-5-carboxamida. El producto se purificó por HPLC prep. y aisló como un sólido beige en una forma de sal mono TFA. CL/EM: Tiempo de retención: 1.837 min; m/e 667 (MH+). El producto se observó que existe como rotámeros de Interconversión por 1H RMN (400 MHz, CLOROFORMO-D) δ ppm 0.73 - 1.59 (m, 6 H), 1.59 - 2.11 (m, 14 H), 2.59 - 2.87 (m, 1 H), 2.87 - 3.22 (m, 2 H), 3.26 - 3.65 (m, 3 H), 3.78 - 3.94 (m, 3 H), 3.98 - 4.46 (m, 3 H), 5.29 - 5.55 (m, 1 H), 6.08 - 6.48 (m, 1 H), 6.89 - 7.06 (m, 1 H), 7.04 - 7.19 (m, J=2.77 Hz, 1 H), 7.18 - 7.34 (m, 1 H), 7.60 - 7.77 (m, J=9.82 Hz, 1 H), 7.84 - 7.98 (m, J=8.56 Hz, 1 H), 8.01 - 8.12 (m, 1 H).



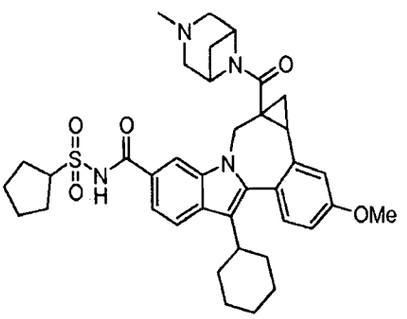
(+/-)-8-ciclohexil-N-(3-fluoropropilsulfonil)-1,1a,2,12b-tetrahidro-11-metoxi-1a-(3-metil-3,6-diazabiciclo[3.1.1]heptano-6-carbonil)cicloprop[d]indol[2,1-a][2]benzazepin-5-carboxamida. El producto se purificó por HPLC prep. y aisló como un sólido beige en una forma de sal mono TFA. CL/EM: Tiempo de retención: 1.811 min; m/e 663

(MH+). El producto se observó que existe como rotámeros de Interconversión por 1H RMN (400 MHz, CLOROFORMO-D) δ ppm 0.71 - 0.97 (m, 1 H), 1.09 - 1.59 (m, 5 H), 1.68 - 2.11 (m, J=74.28 Hz, 6 H), 2.16 - 2.49 (m, 2 H), 2.60 - 3.31 (m, 8 H), 3.35 - 3.56 (m, 4 H), 3.68 - 3.82 (m, 4 H), 3.84 - 3.95 (m, 3 H), 4.30 - 4.43 (m, 1 H), 4.46 - 4.56 (m, 1 H), 4.57 - 4.73 (m, 1 H), 5.31 - 5.57 (m, 1 H), 6.87 - 7.04 (m, J=8.56, 2.52 Hz, 1 H), 7.04 - 7.19 (m, J=2.27 Hz, 1 H), 7.18 - 7.34 (m, 1 H), 7.57 - 7.74 (m, J=8.81 Hz, 1 H), 7.80 - 7.95 (m, J=8.69, 8.69 Hz, 1 H), 8.04 - 8.19 (m, 1 H).



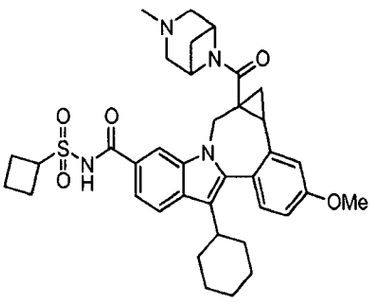
(+/-)-8-ciclohexil-N-(neopentilsulfonil)-1,1a,2,12b-tetrahidro-11-metoxi-1a-(3-metil-3,6-diazabiciclo[3.1.1]heptano-6-carbonil)cicloprop[d]indol[2,1-a][2]benzazepin-5-carboxamida. El producto se purificó por HPLC prep. y aisló como un sólido beige en una forma de sal mono TFA. CL/EM: Tiempo de retención: 1.935 min; m/e 673 (MH+). El producto se observó que existe como rotámeros de Interconversión por 1H RMN (500 MHz, CLOROFORMO-D) δ ppm 0.26 - 1.01 (m, 2 H), 0.97 - 1.65 (m, 14 H), 1.65 - 2.31 (m, 7 H), 2.50 - 3.35 (m, 9 H), 3.31 - 3.71 (m, 4 H), 3.80 - 3.95 (m, 3

H), 3.93 - 4.45 (m, 1 H), 4.44 - 5.01 (m, 1 H), 5.31 - 5.58 (m, 1 H), 6.87 - 7.06 (m, 1 H), 7.01 - 7.20 (m, J=2.14 Hz, 1 H), 7.16 - 7.34 (m, 1 H), 7.43 - 7.72 (m, J=8.24 Hz, 1 H), 7.80 - 8.00 (m, J=8.39, 8.39 Hz, 1 H), 8.01 - 8.20 (m, 1 H).

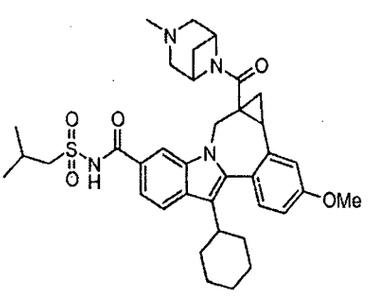


(+/-)-8-ciclohexil-N-(ciclopentilsulfonil)-1,1a,2,12b-tetrahidro-11-metoxi-1a-(3-metil-3,6-diazabiciclo[3.1.1]heptano-6-carbonil)cicloprop[d]indol[2,1-a][2]benzazepin-5-carboxamida. El producto se purificó por HPLC prep. y aisló como un sólido beige en una forma de sal mono TFA. CL/EM: Tiempo de retención: 1.895 min; m/e 671 (MH+). El producto se observó que existe como rotámeros de Interconversión por 1H RMN (500 MHz, CLOROFORMO-D) δ ppm 0.32 - 0.96 (m, 1 H), 1.17 - 1.60 (m, 5 H), 1.62 - 2.33 (m, 8 H), 2.38 - 2.82 (m, 10 H), 2.77 - 3.27 (m, 5 H), 3.32 - 3.75 (m, 3 H), 3.82 - 3.98 (m, 3 H), 3.93 - 4.22 (m, 1 H), 4.25 - 4.45 (m, 2 H), 4.50 - 4.90 (m, 1 H), 5.28 - 5.58 (m, 1 H), 6.90 - 7.05 (m, 1 H), 7.04 - 7.18 (m, 1 H), 7.17 - 7.37 (m, 1 H), 7.39 - 7.69 (m, 1 H), 7.72 - 7.96 (m, 1 H),

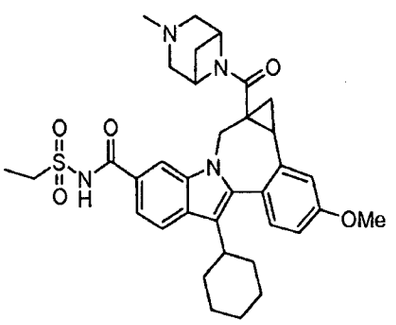
8.05 - 8.32 (m, 1 H).ppm.



(+/-)-8-ciclohexil-N-(ciclobutilsulfonil)-1,1a,2,12b-tetrahidro-11-metoxi-1a-(3-metil-3,6-diazabiciclo[3.1.1]heptano-6-carbonil)cicloprop[d]indol[2,1-a][2]benzazepin-5-carboxamida. El producto se purificó por HPLC prep. y aisló como un sólido beige en una forma de sal mono TFA. CL/EM: Tiempo de retención: 1.850 min; m/e 657 (MH+). El producto se observó que existe como rotámeros de Interconversión por 1H RMN (500 MHz, CLOROFORMO-D) δ ppm 1.07 - 1.67 (m, 6 H), 1.71 - 2.17 (m, 7 H), 2.27 - 2.53 (m, 3 H), 2.51 - 3.31 (m, 11 H), 3.31 - 3.78 (m, 4 H), 3.80 - 3.95 (m, 3 H), 3.95 - 4.25 (m, J=53.41 Hz, 1 H), 4.26 - 4.48 (m, 1 H), 4.49 - 4.72 (m, 1 H), 5.33 - 5.63 (m, 1 H), 6.87 - 7.05 (m, 1 H), 7.05 - 7.19 (m, J=2.44 Hz, 1 H), 7.18 - 7.36 (m, 1 H), 7.52 - 7.80 (m, 1 H), 7.81 - 7.96 (m, 1 H), 8.04 - 8.36 (m, 1 H).

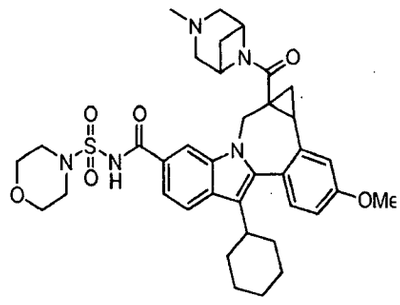


(+/-)-8-ciclohexil-N-(isobutilsulfonil)-1,1a,2,12b-tetrahidro-11-metoxi-1a-(3-metil-3,6-diazabiciclo[3.1.1]heptano-6-carbonil)cicloprop[d]indol[2,1-a][2]benzazepin-5-carboxamida. El producto se purificó por HPLC prep. y aisló como un sólido beige en una forma de sal mono TFA. CL/EM: Tiempo de retención: 1.935 min; m/e 659 (MH+). El producto se observó que existe como rotámeros de Interconversión por 1H RMN (500 MHz, CLOROFORMO-D) δ ppm 0.29 - 0.93 (m, J=272.84 Hz, 1 H), 1.07 - 1.19 (m, J=6.71, 6.71 Hz, 4 H), 1.17 - 1.66 (m, 7 H), 1.70 - 2.21 (m, 7 H), 2.25 - 2.55 (m, 2 H), 2.58 - 3.25 (m, 4 H), 3.29 - 3.75 (m, 8 H), 3.81 - 3.96 (m, 3 H), 3.94 - 4.27 (m, 1 H), 4.28 - 4.47 (m, 1 H), 4.52 - 4.97 (m, 1 H), 5.31 - 5.59 (m, 1 H), 6.87 - 7.05 (m, 1 H), 7.04 - 7.18 (m, J=1.83 Hz, 1 H), 7.18 - 7.34 (m, 1 H), 7.52 - 7.78 (m, 1 H), 7.81 - 7.97 (m, 1 H), 8.10 - 8.36 (m, 1 H).



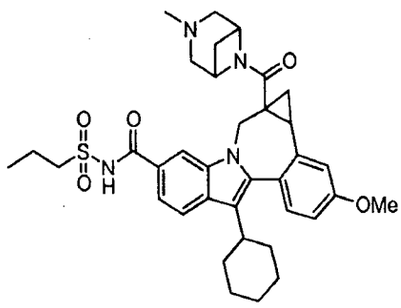
(+/-)-8-ciclohexil-N-(etilsulfonil)-1,1a,2,12b-tetrahidro-11-metoxi-1a-(3-metil-3,6-diazabiciclo[3.1.1]heptano-6-carbonil)cicloprop[d]indol[2,1-a][2]benzazepin-5-carboxamida. El producto se purificó por HPLC prep. y aisló como un sólido beige en una forma de sal

mono TFA. CL/EM: Tiempo de retención: 1.778 min; m/e 631 (MH+). El producto se observó que existe como rotámeros de Interconversión por 1H RMN (400 MHz, CLOROFORMO-D) δ ppm 0.30 - 0.97 (m, J=222.34 Hz, 1 H), 1.09 - 1.64 (m, 8 H), 1.66 - 2.24 (m, 6 H), 2.54 - 3.21 (m, 4 H), 3.21 - 3.76 (m, 10 H), 3.81 - 3.95 (m, 3 H), 3.92 - 4.26 (m, 1 H), 4.28 - 4.50 (m, 1 H), 4.51 - 5.01 (m, J=126.15 Hz, 1 H), 5.23 - 5.57 (m, 1 H), 6.90 - 7.02 (m, 1 H), 7.05 - 7.18 (m, J=2.52 Hz, 1 H), 7.19 - 7.35 (m, 1 H), 7.57 - 7.71 (m, J=8.31 Hz, 1 H), 7.80 - 7.99 (m, J=7.81, 7.81 Hz, 1 H), 8.02 - 8.22 (m, 1 H).



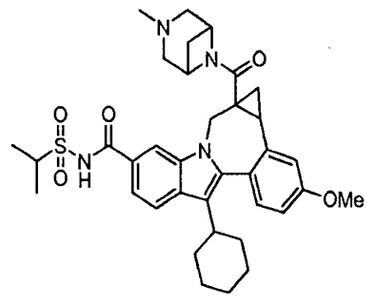
(+/-)-8-ciclohexil-N-(morfolinosulfonil)-1,1a,2,12b-tetrahidro-11-metoxi-1a-(3-metil-3,6-diazabiciclo[3.1.1]heptano-6-carbonil)ciclopropa[d]indol[2,1-a][2]benzazepin-5-carboxamida. El producto se purificó por HPLC prep. y aisló como un sólido beige en una forma de sal mono TFA. CL/EM: Tiempo de retención: 1.847 min; m/e 688 (MH+). El producto se observó que existe como rotámeros de Interconversión por 1H RMN (400 MHz, CLOROFORMO-D) δ ppm 0.32 - 1.06 (m, 1 H), 1.13 - 1.67 (m, 6 H), 1.67 - 2.13 (m, 6 H), 2.14 - 2.78 (m, 9 H), 2.80 - 3.27 (m, 3 H), 3.36 - 3.70 (m, 5

H), 3.69 - 3.84 (m, J=4.28 Hz, 3 H), 3.84 - 3.93 (m, 3 H), 3.93 - 4.17 (m, 1 H), 4.25 - 4.49 (m, 1 H), 4.50 - 4.93 (m, J=112.56 Hz, 1 H), 5.26 - 5.54 (m, 1 H), 6.90 - 7.05 (m, J=8.44, 2.64 Hz, 1 H), 7.05 - 7.19 (m, J=2.52 Hz, 1 H), 7.17 - 7.34 (m, 1 H), 7.50 - 7.65 (m, 1 H), 7.79 - 7.95 (m, 1 H), 8.02 - 8.15 (m, 1 H).



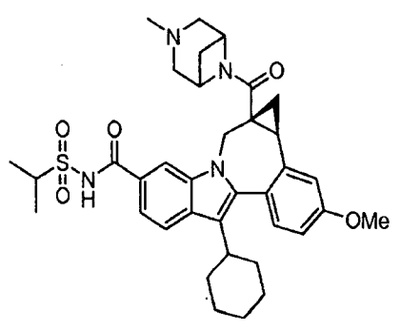
(+/-)-8-ciclohexil-N-(propilsulfonil)-1,1a,2,12b-tetrahidro-11-metoxi-1a-(3-metil-3,6-diazabiciclo[3.1.1]heptano-6-carbonil)cicloprop[d]indol[2,1-a][2]benzazepin-5-carboxamida. El producto se purificó por HPLC prep. y aisló como un sólido beige en una forma de sal mono TFA. CL/EM: Tiempo de retención: 1.888 min; m/e 645 (MH+). El producto se observó que existe como rotámeros de Interconversión por 1H RMN (400 MHz, CLOROFORMO-D) δ ppm 0.27 - 0.88 (m, 1 H), 0.97 - 1.15 (m, J=7.64, 7.64, 7.64 Hz, 3 H), 1.14 - 1.62 (m, 4 H), 1.69 - 2.23 (m, 8 H), 2.53 - 3.22 (m, 5 H), 3.22 - 3.79 (m, 10 H), 3.81 - 3.94 (m, 3 H), 3.94 - 4.25 (m, 1 H), 4.26 - 4.51 (m, 1 H), 4.53 - 4.97 (m, 1 H), 5.25 - 5.54 (m, 1 H), 6.89 - 7.05 (m, 1 H), 7.06 - 7.18 (m, J=2.27 Hz, 1 H), 7.19 - 7.33 (m, 1 H), 7.51 - 7.71 (m, J=8.31 Hz, 1

H), 7.79 - 7.95 (m, 1 H), 8.05 - 8.22 (m, 1 H).

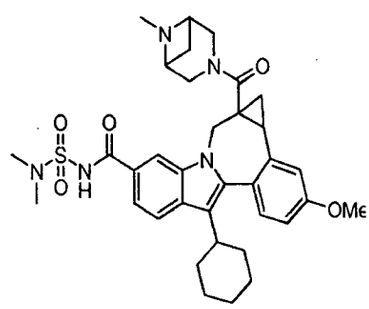


(+/-)-8-ciclohexil-N-(isopropilsulfonil)-1,1a,2,12b-tetrahidro-11-metoxi-1a-(3-metil-3,6-diazabiciclo[3.1.1]heptano-6-carbonil)cicloprop[d]indol[2,1-a][2]benzazepin-5-carboxamida.

El producto se purificó por HPLC prep. y aisló como un sólido beige en una forma de sal mono TFA. CL/EM: Tiempo de retención: 1.871 min; m/e 645 (MH+). El producto se observó que existe como rotámeros de Interconversión por 1H RMN (400 MHz, CLOROFORMO-D) δ ppm 1.05 - 1.57 (m, 9 H), 1.69 - 2.08 (m, J=79.57 Hz, 4 H), 2.08 - 2.42 (m, 9 H), 2.58 - 3.25 (m, 5 H), 3.35 - 3.75 (m, 4 H), 3.82 - 3.95 (m, 3 H), 3.95 - 4.18 (m, 2 H), 4.26 - 4.45 (m, 1 H), 5.26 - 5.52 (m, 1 H), 6.89 - 7.03 (m, J=8.18, 2.90 Hz, 1 H), 7.04 - 7.17 (m, J=2.27 Hz, 1 H), 7.21 - 7.34 (m, 1 H), 7.49 - 7.68 (m, J=34.75 Hz, 1 H), 7.81 - 7.96 (m, J=8.56 Hz, 1 H), 8.05 - 8.19 (m, 1 H).

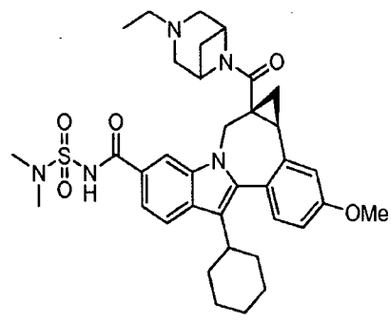


8-ciclohexil-N-(isopropilsulfonil)-1,1a,2,12b-tetrahidro-11-metoxi-1a-(3-metil-3,6-diazabiciclo[3.1.1]heptano-6-carbonil)cicloprop[d]indol[2,1-a][2]benzazepin-5-carboxamida. El producto se purificó por HPLC prep. y aisló como un sólido beige en una forma de sal mono TFA. CL/EM: Tiempo de retención: 1.855 min; m/e 645 (MH+). El producto se observó que existe como rotámeros de Interconversión por 1H RMN (400 MHz, CLOROFORMO-D) δ ppm 1.11 - 1.62 (m, 11 H), 1.68 - 2.16 (m, J=74.53 Hz, 6 H), 2.42 - 2.82 (m, 7 H), 2.78 - 3.23 (m, 4 H), 3.38 - 3.68 (m, 4 H), 3.81 - 3.94 (m, 3 H), 3.95 - 4.16 (m, 1 H), 4.55 - 4.92 (m, J=94.43 Hz, 1 H), 5.34 - 5.54 (m, 1 H), 6.87 - 7.04 (m, J=8.81, 2.27 Hz, 1 H), 7.04 - 7.19 (m, J=2.27 Hz, 1 H), 7.20 - 7.33 (m, 1 H), 7.50 - 7.67 (m, 1 H), 7.82 - 7.97 (m, J=8.31 Hz, 1 H), 8.05 - 8.23 (m, 1 H).



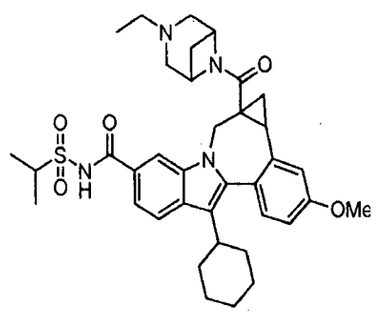
(+/-)-8-ciclohexil-N-(N,N-dimetilsulfamoil)-1,1a,2,12b-tetrahidro-11-metoxi-1a-(6-metil-3,6-diazabiciclo[3.1.1]heptano-3-carbonil)cicloprop[d]indol[2,1-a][2]benzazepin-5-carboxamida. El producto se purificó por HPLC prep. y aisló como un sólido beige en una forma de sal mono TFA. CL/EM: Tiempo de retención: 1.545 min; m/e 646

(MH+). El producto se observó que existe como rotámeros de Interconversión por 1H RMN (400 MHz, CLOROFORMO-D) δ ppm 0.38 - 1.08 (m, 1 H), 1.09 - 1.64 (m, 5 H), 1.66 - 2.21 (m, 6 H), 2.40 - 2.68 (m, J=50.86 Hz, 1 H), 2.75 - 3.04 (m, 11 H), 3.07 - 3.32 (m, 3 H), 3.47 - 3.84 (m, 2 H), 3.82 - 3.97 (m, 3 H), 3.98 - 4.37 (m, 2 H), 4.74 - 5.17 (m, 1 H), 5.22 - 5.70 (m, 2 H), 6.85 - 7.06 (m, 1 H), 7.04 - 7.19 (m, 1 H), 7.21 - 7.38 (m, 1 H), 7.47 - 7.85 (m, 1 H), 7.85 - 7.99 (m, 1 H), 8.26 - 8.71 (m, 1 H).



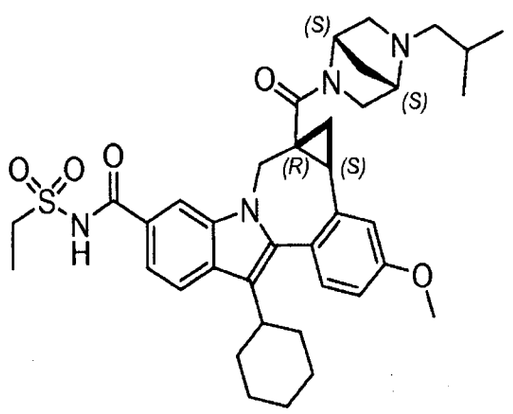
8-ciclohexil-N-(N,N-dimetilsulfamoil)-1,1a,2,12b-tetrahidro-11-metoxi-1a-(3-etil-3,6-diazabiciclo[3.1.1]heptano-6-carbonil)cicloprop[d]indol[2,1-a][2]benzazepin-5-carboxamida. El producto se purificó por HPLC prep. y aisló como un sólido beige en una forma de sal mono TFA. CL/EM: Tiempo de retención: 1.823 min; m/e 660 (MH+). El producto se observó que existe como rotámeros de Interconversión por 1H RMN (400 MHz, CLOROFORMO-D) δ ppm 0.74 - 1.04 (m, J=19.89 Hz, 2 H), 1.09 - 1.60 (m, 6 H), 1.65 - 2.19 (m, 6 H), 2.61 - 3.22 (m, 14 H), 3.25 - 3.75 (m, 4 H), 3.82 - 3.95 (m, 3 H), 3.94 - 4.28 (m, 1 H), 4.27 - 4.46 (m, 1 H),

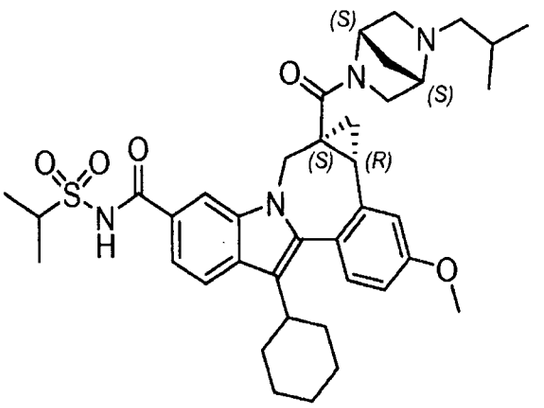
4.43 - 4.95 (m, 1 H), 5.33 - 5.60 (m, 1 H), 6.83 - 7.04 (m, 1 H), 7.05 - 7.18 (m, J=2.52 Hz, 1 H), 7.18 - 7.35 (m, 1 H), 7.47 - 7.65 (m, 1 H), 7.81 - 7.96 (m, 1 H), 8.03 - 8.21 (m, 1 H).



(+/-)-8-ciclohexil-N-(isopropilsulfonil)-1,1a,2,12b-tetrahidro-11-metoxi-1a-(3-etil-3,6-diazabiciclo[3.1.1]heptano-6-carbonil)cicloprop[d]indol[2,1-a][2]benzazepin-5-carboxamida. El producto se purificó por HPLC prep. y aisló como un sólido beige en una forma de sal mono TFA. CL/EM: Tiempo de retención: 1.863 min; m/e 659 (MH+). El producto se observó que existe como rotámeros de Interconversión por 1H RMN (400 MHz, CLOROFORMO-D) δ ppm 0.70 - 1.09 (m, 3 H), 1.10 - 1.63 (m, 11 H), 1.69 - 2.12 (m, 5 H), 2.57 - 3.05 (m, J=4.28 Hz, 9 H), 3.04 - 3.24 (m, 1 H), 3.26 - 3.76 (m, 4 H), 3.80 - 3.95 (m, 3 H), 3.96 - 4.24 (m, 2 H), 4.27 - 4.48 (m, 1 H), 5.34 - 5.56 (m, 1 H), 6.87 - 7.04 (m, J=8.56, 2.52 Hz, 1 H), 7.04 - 7.19 (m, J=2.52 Hz, 1 H), 7.18 - 7.35 (m, 1 H), 7.54 - 7.71 (m, J=8.56 Hz, 1

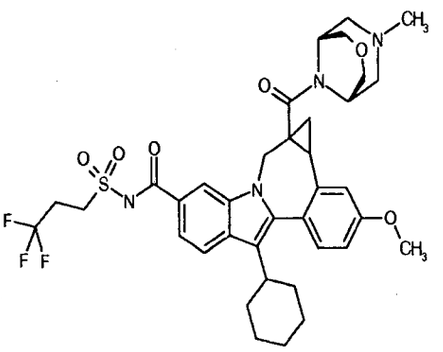
H), 7.81 - 7.94 (m, J=9.06, 9.06 Hz, 1 H), 8.03 - 8.18 (m, 1 H).





8-ciclohexil-N-(isopropilsulfonil)-1,1a,2,12b-tetrahidro-11-metoxi-1a-[(1S,4S)-5-isobutil-2,5-diazabiciclo[2.2.1]heptano-2-carbonil]cicloprop[d]indol[2,1-a][2]benzazepin-5-carboxamida. Etapa 1: A una mezcla de compuesto ácido (50 mg, 0.091 mmol) y (1S,4S)-2-isobutil-2,5-diazabiciclo[2.2.1]heptano, 2TFA (52 mg, 0.136 mmol) en diclorometano (1.5 ml) se agregó TEA (0.127 ml, 0.908 mmol) y HBTU (48 mg, 0.127 mmol). La mezcla se agitó a temperatura ambiente durante 2 h. Se diluye con MeOH (1 ml), se remueven los solventes, el residuo se disolvió en MeOH, filtró y purificó por HPLC prep. y aisló como sales TFA para proporcionar los productos (0.0094 g, 26%) y (0.0099 g, 27%). Primer pico: Tiempo de retención CL-EM: 3.138; EM m/z (M+H) 687; se observa que existen como rotámeros de Interconversión 1H RMN (400 MHz, CLOROFORMO-d) δ ppm 0.93 (6 H, m), 1.35 (10 H, m), 1.74 (11 H, m), 2.45 (1 H, br. s.), 2.80 (4 H, m), 3.14

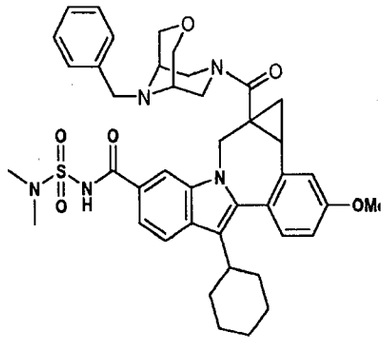
(2 H, br. s.), 3.64 (3 H, m), 3.90 (3 H, s), 3.98 (1 H, m), 4.15 (1 H, br. s.), 5.20 (1 H, d, J=15.11 Hz), 6.98 (1 H, dd, J=8.44, 2.64 Hz), 7.11 (1 H, d, J=2.01 Hz), 7.28 (1 H, m), 7.82 (1 H, br. s.), 7.96 (1 H, d, J=8.31 Hz), 8.53 (1 H, br. s.). Segundo pico: Tiempo de retención CL-EM: 3.170; EM m/z (M+H) 687; se observa que existen como rotámeros de Interconversión por 1H RMN.



8-Ciclohexil-11-metoxi-1a-(((1R,5S)-7-metil-3-oxa-7,9-diazabiciclo[3.3.1]non-9-il)carbonil)-N-((3,3,3-trifluoropropil)sulfonil)-1,1a,2,12b-tetrahidrociclopropa[d]indol[2,1-a][2]benzazepin-5-carboxamida. 1H RMN (300 MHz, CD3OD): δ ppm 0.20 (m, 0.35 H), 1.21 (m, 1 H), 1.35 (m, 1.65 H), 1.45 (m, 2H), 1.58 (m, 2 H), 1.79 (m, 2 H), 1.91 - 2.07 (m, 4 H), 2.62 (m, 1 H), 2.74 - 2.90 (m, 4 H), 2.90 - 3.06 (m, 3 H), 3.34 (m, 1 H), 3.62 (d, J=15.37 Hz, 2 H), 3.72 (m, 1 H), 3.80 - 3.93 (m, 6 H), 4.00 (m, 2 H), 4.15 (d, J=15.00 Hz, 1 H), 4.38 (m, 2 H), 4.90 - 5.09 (m, 1 H), 7.02 (m, 1 H), 7.12 - 7.20 (m, 1 H), 7.27 - 7.33 (m, 1 H), 7.53 - 7.63 (m, 1 H), 7.89 (m, 1 H), 8.04 - 8.11 (m, 1 H). CL/EM: m/z 729.42, Rf 1.793 min., 95.7 % de

000418

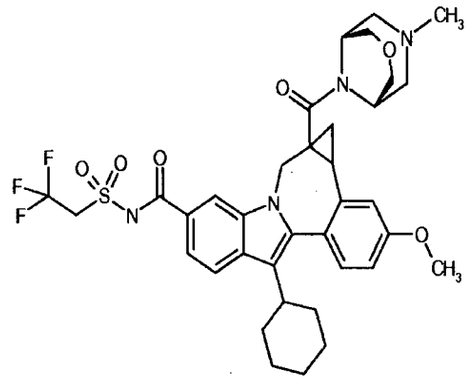
pureza.



Cicloprop[d]indol[2,1-a][2]benzazepin-5-carboxamida, 8-ciclohexil-N-[(dimetilamino)sulfonil]-1,1a,2,12b-tetrahidro-11-metoxi-1a-[[9-(fenilmetil)-3-oxa-7,9-diazabiciclo[3.31]non-7-il]carbonilo]-. Se preparó a partir del acoplamiento entre el ácido racémico y clorohidrato de 9-Bencil-3-oxa-7,9-diazabiciclo[3.3.1]nonano en una manera similar como se describe arriba. La purificación por HPLC de fase inversa preparativa Shimadzu-VP usando el método de separación: Solvente A = MeOH al 10%-H_2O al 90%-TFA al 0.1%, Solvente B = MeOH al 90%-H_2O al 10%-TFA al 0.1%, Inicio %B = 30, Final %B = 100, Tiempo de gradiente = 10 min, Relación de flujo = 30mL/min, Columna: Xterra Prep EM Cl 8 5u 30x50mm, Colección de fracción: 8.31 - 8.91 min. (Detección UV a 220 nm); CL/EM se realizaron por usar el instrumento Shimadzu con Detección UV a 220 nm y Micromasa Waters. Método HPLC: Solvente A = MeOH al 10%-H_2O al 90%-TFA al 0.1%, Solvente B = MeOH al 90%-H_2O al 10%-TFA al 0.1%, Inicio %B = 0, Final %B = 100, Tiempo de gradiente = 2 min, Relación de flujo = 5 ml/min, Columna: Xterra EM C18 S7 3.0 x 50mm; (ES+) m/z (M+H)+ = 752.91, HPLC

000419

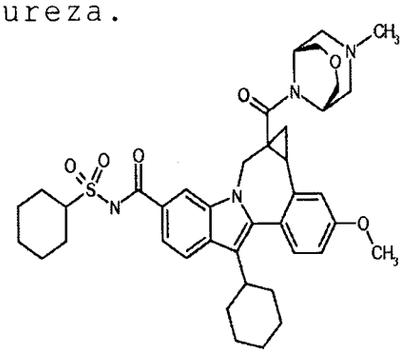
t.r. = 1.752 min. Método HPLC: Solvente A = MeCN al 5%-H_2O al 59%-NH_4OAc 10 mM, Solvente B = MeCN al 95%-H_2O al 5%-NH_4OAc 10 mM, Inicio %B = 0, Final %B = 100, Tiempo de gradiente = 2 min, Relación de flujo = 5 ml/min, Columna: Phenomenex Lina C18 5um 3.0 x 50mm; (ES+) m/z $(M+H)^+$ = 752.48, HPLC T.r. = 1.633 min.



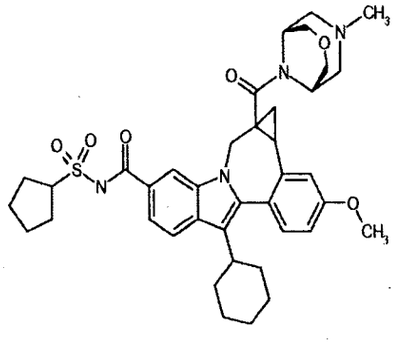
8-Ciclohexil-11-metoxi-1a-(((1R,5S)-7-metil-3-oxa-7,9-diazabiciclo[3.3.1]non-9-il)carbonil)-N-((2,2,2-trifluoroetil)sulfonil)-1,1a,2,12b-tetrahidrociclopropa[d]indol[2,1-a][2]benzazepin-5-carboxamida. 1H RMN (300 MHz, CD3OD): δ ppm 0.22 (m, 0.35 H), 1.19 (m, 1 H), 1.25 - 1.41 (m, 2 H), 1.44 (m, 2 H), 1.58 (m, 1.65 H), 1.79 (m, 2 H), 1.92 - 2.04 (m, 4 H), 2.63 (m, 2 H), 2.86 (m, 2 H), 2.90 - 3.04 (m, 2 H), 3.60 (m, 2 H), 3.66 (m, 1 H), 3.85 - 3.98 (m, 6 H), 4.16 (m, 1 H), 4.27 - 4.42 (m, 2 H), 4.67 (m, 2 H), 5.08 (d, J=15.00 Hz, 1 H), 6.98 - 7.06 (m, 1 H), 7.13 - 7.21 (m, 1 H), 7.27 - 7.35 (m, 1 H), 7.53 - 7.64 (m, 1 H), 7.90 (m, 1 H), 8.04 - 8.13 (m, 1 H). CL/EM: m/z 715.41, Rf 1.783

000420

min., 98.0% de pureza.



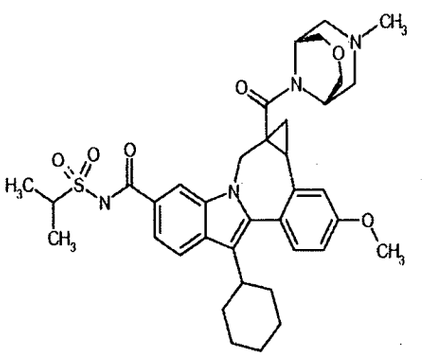
8-Ciclohexil-N-(ciclohexilsulfonil)-11-metoxi-1a-(((1R,5S)-7-metil-3-oxa-7,9-diazabiciclo[3.3.1]non-9-il)carbonil)-1,1a,2,12b-tetrahidrociclopropa[d]indol[2,1-a][2]benzazepin-5-carboxamida. 1H RMN (300 MHz, CD3OD): δ ppm 0.24 (m, 0.35 H), 1.31 - 1.52 (m, 7.65 H), 1.59 - 1.74 (m, 4 H), 1.80 (m, 3 H), 1.95 (m, 4 H), 2.11 (m, 2 H), 2.21 (m, 2 H), 2.68 (m, 2 H), 2.89 (m, 2 H), 2.97 (m, 2 H), 3.64 - 3.79 (m, 4 H), 3.83 - 3.98 (m, 4 H), 4.10 (m, 3 H), 4.41 (m, 2 H), 5.12 (d, J=15.37 Hz, 1 H), 7.05 (m,1 H), 7.16 - 7.25 (m, 1 H), 7.34 (m, 1 H), 7.56 - 7.69 (m, 1 H), 7.93 (m, 1 H), 8.04 - 8.19 (m, 1 H). CL/EM: m/z 715.51, Rf 1.840 min., 97.1 % de pureza.



8-Ciclohexil-N-(ciclopentilsulfonil)-11-metoxi-1a-(((1R,5S)-7-metil-3-oxa-7,9-diazabiciclo[3.3.1]non-9-il)carbonil)-1,1a,2,12b-tetrahidrociclopropa[d]indol[2,1-a][2]benzazepin-5-carboxamida. 1H RMN (300 MHz, CD3OD): δ ppm 0.21 (m, 0.35 H), 1.15 - 1.26 (m, 1.65 H) 1.32 - 1.37 (m, 1

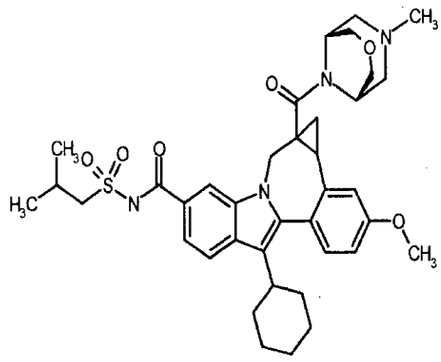
000421

H), 1.41 (m, 2 H), 1.58 (m, 1 H), 1.69 - 1.74 (m, 3 H), 1.76 - 1.86 (m, 4 H), 2.00 - 2.16 (m, 8 H), 2.63 (m, 1 H), 2.86 - 3.06 (m, 5 H), 3.63 (m, 3 H), 3.81 - 3.95 (m, 5 H), 4.01 (m, 1 H), 4.16 (m, 1 H), 4.23 - 4.38 (m, 3 H), 4.84 - 5.10 (m, 1 H), 6.95 - 7.06 (m, 1 H), 7.12 - 7.22(m, 1 H), 7.26 - 7.34 (m, 1 H), 7.52 - 7.62 (m, 1 H), 7.83 - 7.93 (m, 1 H), 8.01 - 8.09 (m, 1 H). CL/EM: m/z 701.49, Rf 1.778 min., 97.0 % de pureza.

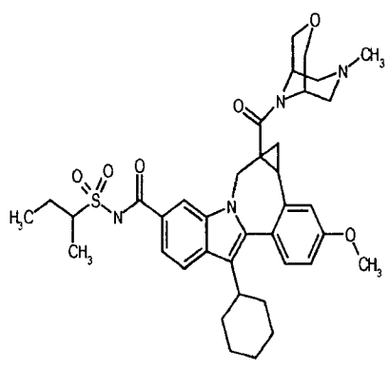


8-ciclohexil-N-(isopropilsulfonil)-11-metoxi-1a-(((1R,5S)-7-metil-3-oxa-7,9-diazabiciclo[3.3.1]non-9-il)carbonil)-1,1a,2,12b-tetrahidrociclopropa[d]indol[2,1-a][2]benzazepin-5-carboxamida. 1H RMN (300 MHz, CD3OD): δ ppm 0.19 (m, 0.35 H), 1.28 (m, 1.65 H), 1.31 - 1.38 (m, 1 H), 1.38 - 1.48 (m, 6 H), 1.57 (m, 2 H), 1.78 (m, 2 H), 1.91 - 2.09 (m, 4 H), 2.64 (m, 1 H), 2.81 (m, 1 H), 2.89 - 3.02 (m, 4 H), 3.64 (m, 4 H), 3.85 - 3.99 (m, 7 H), 4.01 (m, 2 H), 4.37 (m, 2 H), 4.85 - 5.08 (m, 1 H), 7.02 - 7.07 (m, 1 H), 7.17 - 7.22 (m, 1 H), 7.32 - 7.36 (m, 1 H), 7.57 - 7.64 (m, 1 H), 7.90 - 7.94 (m, 1 H), 8.05 - 8.10 (m, 1 H). CL/EM: m/z 675.44, Rf 1.743 min., 97.2 % de pureza.

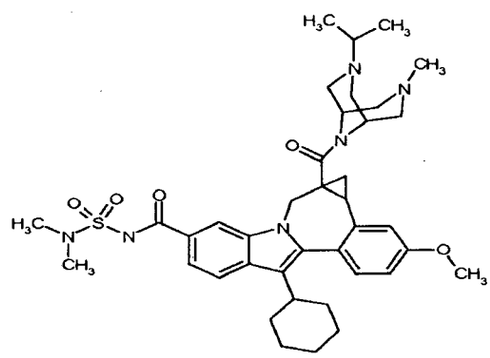
000422



8-Ciclohexil-N-(isobutilsulfonil)-11-metoxi-1a-(((1R,5S)-7-metil-3-oxa-7,9-diazabiciclo[3.3.1]non-9-il)carbonil)-1,1a,2,12b-tetrahidrociclopropa[d]indol[2,1-a][2]benzazepin-5-carboxamida. 1H RMN (300 MHz, CD3OD): 0.19 (m, 0.35), 1.07 (td, J=7.50, 2.56 Hz, 3 H), 1.23 - 1.37 (m, 2.65 H), 1.37 - 1.49 (m, 5 H), 1.57 - 1.68 (m, 2 H), 1.70 - 1.82 (m, 3 H), 1.94 - 2.13 (m, 6 H), 2.61 (m, 2 H), 2.85 (m, 1 H), 2.89 - 3.03 (m, 3 H), 3.10 - 3.24 (m, 1 H), 3.61 (d, J=15.37 Hz, 1 H), 3.67 - 3.82 (m, 3 H), 3.83 - 3.91 (m, 3 H), 3.96 (m, 1 H), 4.15 (m, 1 H), 4.37 (m, 2 H), 4.90 - 5.08 (m, 1 H), 6.97 - 7.04 (m, 1 H), 7.13 (d, J=2.56 Hz, 0.35 H), 7.17 (d, J=2.56 Hz, 0.65 H), 7.26 - 7.33 (m, 1 H), 7.53 - 7.60 (m, 1 H), 7.84 - 7.92 (m, 1 H), 8.02 - 8.07 (s, 1 H). CL/EM: m/z 689.49, Rf 1.788 min., 97.0 % de pureza.



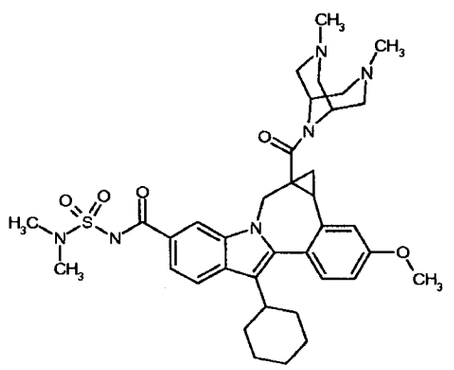
N-(sec-butilsulfonil)-8-ciclohexil-11-metoxi-1a-((7-metil-3-oxa-7,9-diazabiciclo[3.3.1]non-9-il)carbonil)-1,1a,2,12b-tetrahidrociclopropa[d]indol[2,1-a][2]benzazepin-5-carboxamida. 1H RMN (300 MHz, CD3OD): δ ppm 0.21 (m, 0.20 H), 1.09 (m, 3 H), 1.30 (m, 1.80 H), 1.44 (m, 7 H), 1.56 - 1.79 (m, 5 H), 1.72 - 2.12 (m, 5 H), 2.65 (m, 1 H), 2.97 (m, 5 H), 3.63 (d, J=15.37 Hz, 1 H), 3.69 - 3.83 (m, 3 H), 3.84 - 3.97 (m, 4 H), 4.14 (m, 2 H), 4.39 (m, 2 H), 5.07 (m, 1 H), 6.98 - 7.06 (m, 1 H), 7.14 - 7.21 (m, 1 H), 7.28 - 7.34 (m, 1 H), 7.53 - 7.63 (m, 1 H), 7.85 - 7.93 (m, 1 H), 8.02 - 8.11 (m, 1 H). CL/EM: m/z 689.46, Rf 1.797 min., 96.0 % de pureza.



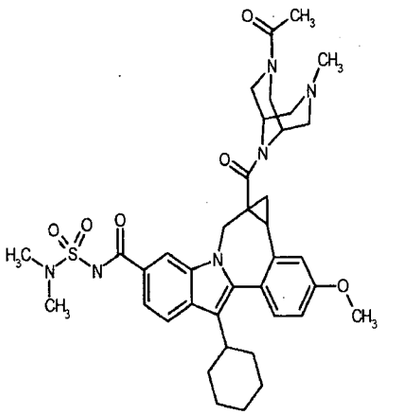
8-Ciclohexil-N-(dimetilsulfamoil)-1a-((3-isopropil-7-metil-3,7,9-triazabiciclo[3.3.1]non-9-il)carbonil)-11-metoxi-1,1a,2,12b-tetrahidrociclopropa[d]indol[2,1-a][2]benzazepin-5-carboxamida. 1H RMN (300 MHz, CD3OD): δ ppm 0.19 (m, 0.35 H), 1.12 (m, 3.65 H), 1.20 - 1.35 (m, 4 H), 1.39 (m, 2 H), 1.45 - 1.58 (m, 2 H), 1.64 (m, 2 H), 1.78 (m, 3 H), 2.00 (m, 6 H), 2.61 (m, 3 H), 2.74 - 2.90 (m, 2 H), 2.90 - 3.05 (m, 6 H), 3.48

000424

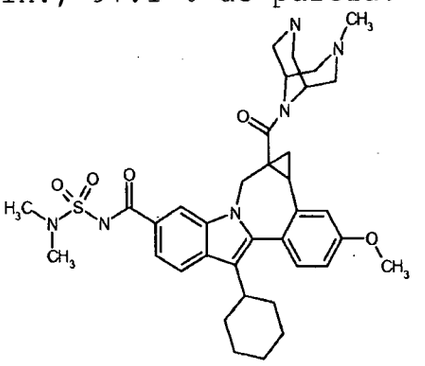
(m, 1 H), 3.61 (m, 2 H), 3.84 - 3.91 (m, 4 H), 4.15 (m, 1 H), 4.45 (m, 1 H), 5.07 (m, 1 H), 7.01 (m, 1 H), 7.11 - 7.20 (m, 1 H), 7.26 - 7.35 (m, 1 H), 7.50 - 7.63 (m, 1 H), 7.88 (m, 1 H), 8.00 - 8.09 (m, 1 H). CL/EM: m/z 717.52, Rf 1.762 min., 97.8% de pureza.



8-Ciclohexil-N-(dimetilsulfamoil)-1a-((3,7-dimetil-3,7,9-triazabiciclo[3.3.1]non-9-il)carbonil)-11-metoxi-1,1a,2,12b-tetrahidrociclopropa[d]indol[2,1-a][2]benzazepin-5-carboxamida. 1H RMN (300 MHz, CD3OD): δ ppm 0.24 (m, 0.20 H), 1.24 - 1.38 (m, 2.80 H), 1.45 (m, 4 H), 1.56 (m, 1 H), 1.83 (m, 2 H), 2.04 (m, 4 H), 2.65 (m, 1 H), 2.82 - 2.91 (m, 1 H), 2.93 - 3.05 (m, 9 H), 3.17 (m, 3 H), 3.49 (m, 1 H), 3.64 (m, 2 H), 3.78 (m, 1 H), 3.86 - 3.95 (m, 4 H), 4.03 (m, 1 H), 4.18 (m, 1 H), 4.37 (m, 1 H), 4.51 (m, 1 H), 5.08 (d, J=15.37 Hz, 1 H), 6.99 - 7.07 (m, 1 H), 7.13 - 7.22 (m, 1 H), 7.29 - 7.37 (m, 1 H), 7.51 - 7.63 (m, 1 H), 7.89 (m, 1 H), 7.99 - 8.10 (m, 1 H). CL/EM: m/z 689.50, Rf 1.813 min., 98.3 % de pureza.

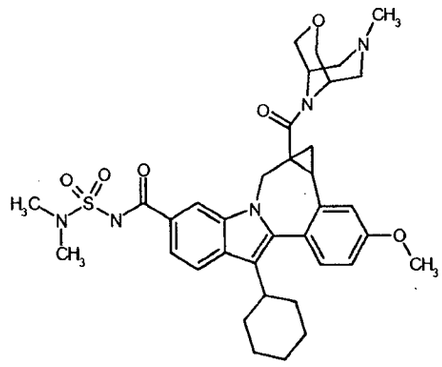


1a-((3-Acetil-7-metil-3,7,9-triazabiciclo[3.3.1]non-9-il)carbonil)-8-ciclohexil-N-(dimetilsulfamoil)-11-metoxi-1,1a,2,12b-tetrahidrociclopropa[d]indol[2,1-a][2]benzazepin-5-carboxamida. 1H RMN (300 MHz, CD3OD): δ ppm 0.51 (m, 0.20 H), 1.68 (m, 4.80 H), 1.98 (m, 2 H), 2.12 (m, 2 H), 2.41 (m, 7 H), 2.98 (m, 1 H), 3.19 (m, 2 H), 3.56 - 3.65 (m, 13 H), 3.94 - 4.10 (m, 2 H), 4.14 - 4.29 (m, 4 H), 4.95 (m, 2 H), 5.40 (m, 1 H), 7.35 (m, 1 H), 7.47 - 7.53 (m, 1 H), 7.60 - 7.67 (m, 1 H), 7.85 (m, 1 H), 8.16 - 8.25 (m, 1 H), 8.36 (s, 1 H). CL/EM: m/z 717.47, Rf 1.710 min., 97.1 % de pureza.



8-Ciclohexil-N-(dimetilsulfamoil)-11-metoxi-1a-((3-metil-3,7,9-triazabiciclo[3.3.1]non-9-il)carbonil)-1,1a,2,12b-tetrahidrociclopropa[d]indol[2,1-a][2]benzazepin-5-carboxamida. 1H RMN (300 MHz, CD3OD): δ ppm 0.20 (m, 0.20 H),

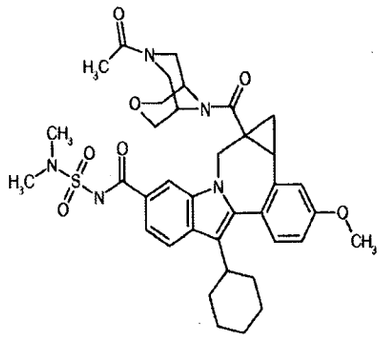
1.24 - 1.36 (m, 1.80 H), 1.45 (m, 2 H), 1.55 (m, 3 H), 1.64 (m, 1 H), 1.80 (m, 1 H) 1.86 (m, 2 H) 2.08 (m, 6 H), 2.36 (m, 1 H), 2.48 (m, 1 H), 2.62 (m, 2 H), 2.86 (m, 1 H), 3.00 (m, 3 H), 3.16 (m, 1 H), 3.45 (m, 2 H) 3.66 (m, 4 H), 3.85 - 3.96 (m, 3 H), 4.18 (m, 1 H), 4.34 (m, 1 H), 4.46 (m, 1 H), 5.05 (m, 1 H), 7.01 (m, 1 H), 7.13 - 7.20 (m, 1 H), 7.32 (m, 1 H), 7.52 - 7.61 (m, 1 H), 7.89 (m, 1 H), 8.00 - 8.07 (m, 1 H). CL/EM: m/z 675.37, Rf 1.772 min., 95.3 % de pureza.



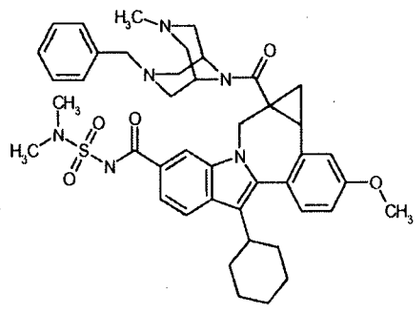
8-Ciclohexil-N-(dimetilsulfamoil)-11-metoxi-1a-((7-metil-3-oxa-7,9-diazabiciclo[3.3.1]non-9-il)carbonil)-1,1a,2,12b-tetrahidrociclopropa[d]indol[2,1-a][2]benzazepin-5-carboxamida.

1H RMN (300 MHz, CD3OD): δ ppm 0.22 (m, 0.20 H), 1.30 - 1.38 (m, 1.80 H), 1.44 (m, 2 H), 1.56 (m, 2 H), 1.70 (m, 1 H), 1.80 (m, 2 H), 2.02 (m, 4 H), 2.66 (m, 1 H), 2.86 (m, 2 H), 2.92 - 3.07 (m, 9 H), 3.66 (m, 3 H), 3.81 - 3.94 (m, 4 H), 4.02 (m, 2 H), 4.17 (m, 1 H), 4.36 (m, 2 H), 5.10 (m, 1 H), 7.03 (m, 1 H), 7.13 - 7.22 (m, 1 H), 7.32 (m, 1 H), 7.56 (m, 1 H), 7.86 - 7.95 (m, 1 H), 8.01 - 8.11 (m, 1 H). CL/EM: m/z 676.40, Rf 1.703 min., 98.2 % de pureza.

000427



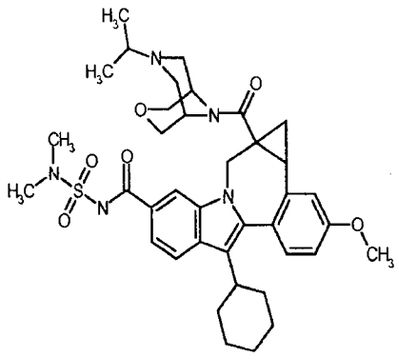
1a-((7-Acetil-3-oxa-7,9-diazabiciclo[3.3.1]non-9-il)carbonil)-8-ciclohexil-N-(dimetilsulfamoil)-11-metoxi-1,1a,2,12b-tetrahidrociclopropa[d]indol[2,1-a][2]benzazepin-5-carboxamida. 1H RMN (500 MHz, CD3OD): δ ppm 0.17 (m, 0.25 H), 1.12 (m, 0.75 H), 1.33 (m, 2 H), 1.51 (m, 3 H), 1.70 (m, 1 H), 1.80 (m, 2 H), 2.00 - 2.15 (m, 7 H), 2.55 - 2.65 (m, 1 H), 2.85 (m, 1 H), 2.94 - 3.02 (m, 6 H), 3.16 (m, 1 H), 3.34 (m, 1 H), 3.63 (m, 1 H), 3.75 (m, 1 H), 3.88 (m, 3 H), 4.12 (m, 3 H), 4.26 (m, 1 H), 4.78 (m, 1 H), 4.90 (m, 1 H), 5.06 (m, 1 H), 6.96 - 7.03 (m, 1 H), 7.11 - 7.20 (m, 1 H), 7.26 - 7.34 (m, 1 H), 7.51 - 7.57 (m, 1 H), 7.84 - 7.91 (m, 1 H), 8.04 - 8.12 (s, 1 H). CL/EM: m/z 704.34, Rf 1.938 min., 98.1 % de pureza.



1a-((3-Bencil-7-metil-3,7,9-triazabiciclo[3.3.1]non-9-il)carbonil)-8-ciclohexil-N-(dimetilsulfamoil)-11-metoxi-1,1a,2,12b-tetrahidrociclopropa[d]indol[2,1-a][2]benzazepin-5-carboxamida. 1H RMN (300 MHz, CD3OD): δ ppm 0.20 (m, 0.20 H),

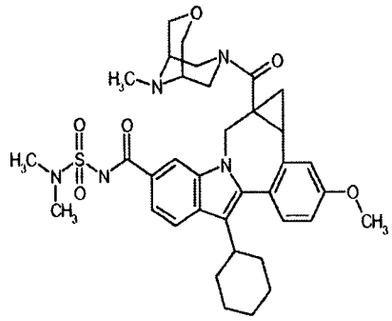
000428

1.32 (m, 2.80 H), 1.43 (m, 4 H), 1.77 (m, 2 H), 2.01 (m, 5 H), 2.59 - 2.72 (m, 2 H), 2.78 (m, 1 H), 2.87 (m, 1 H), 2.90 - 3.05 (m, 8 H), 3.25 (m, 2 H), 3.59 (m, 4 H), 3.75 (m, 1 H), 3.84 - 3.93 (m, 3 H), 4.15 (m, 1 H), 4.38 (m, 1 H), 4.56 (m, 1 H), 5.08 (d, J=15.00 Hz, 1 H), 6.97 - 7.04 (m, 1 H), 7.07 - 7.17 (m, 1 H), 7.28 - 7.42 (m, 6 H), 7.53 - 7.61 (m, 1 H), 7.85 - 7.92 (m, 1 H), 7.99 - 8.13 (m, 1 H). CL/EM: m/z 765.45, Rf 1.840 min., 99.7 % de pureza.

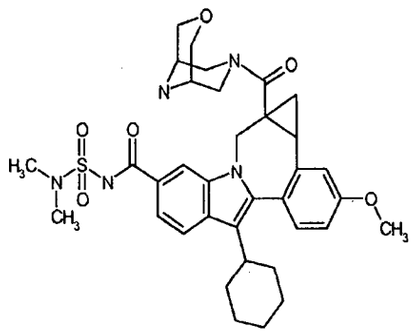


8-Ciclohexil-N-(dimetilsulfamoil)-1a-((7-isopropil-3-oxa-7,9-diazabiciclo[3.3.1]non-9-il)carbonil)-11-metoxi-1,1a,2,12b-tetrahidrociclopropa[d]indol[2,1-a][2]benzazepin-5-carboxamida. 1H RMN (500 MHz, CD3OD): δ ppm 0.24 (m, 0.25 H), 1.23 (m, 0.75 H), 1.36 (m, 2 H), 1.38(m, 1 H), 1.49 (m, 6 H), 1.61 (m, 1 H), 1.70 (m, 1 H), 1.84 (m, 2 H), 1.96 - 2.14 (m, 4 H), 2.64 - 2.71 (m, 1 H), 2.89 (m, 1 H), 2.98 - 3.07 (m, 6 H), 3.20 (m, 1 H), 3.29 (m, 2 H), 3.37 (m, 1 H), 3.41 (m, 1 H), 3.50 (m, 1 H), 3.69 (m, 1 H), 3.92 (m, 4 H), 4.00 (m, 2 H), 4.18 (m, 1 H), 4.43 (m, 1 H), 5.14 (m, 1 H), 7.05 (m, 1 H), 7.16 - 7.24 (m, 1 H), 7.35 (m, 1 H), 7.55 - 7.64 (m, 1 H), 7.93(m, 1 H), 8.05 - 8.12 (m, 1 H). CL/EM: m/z 704.40, Rf

1.755 min., 99.2 % de pureza.

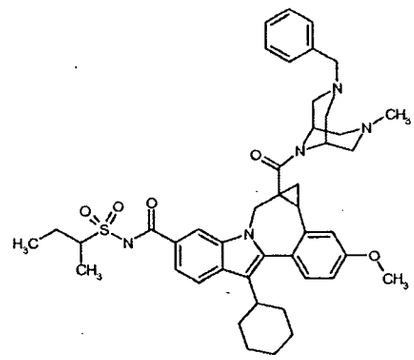


8-ciclohexil-N-(dimetilsulfamoil)-11-metoxi-1a-((9-metil-3-oxa-7,9-diazabiciclo[3.3.1]non-7-il)carbonil)-1,1a,2,12b-tetrahidrociclopropa[d]indol[2,1-a][2]benzazepin-5-carboxamida. 1H RMN (300 MHz, CD3OD): δ ppm 0.24 (m, 0.25 H), 1.32 (m, 1.75 H), 1.43 (m, 4 H), 1.78 (m, 3 H), 1.98 (m, 4 H), 2.55 (m, 1 H), 2.77 - 2.90 (m, 1 H), 3.00 (s, 6 H), 3.11 - 3.26 (m, 4 H), 3.55 (m, 3 H), 3.88 (m, 3 H), 4.13 (m, 4 H), 4.54 (m, 2 H), 5.00 (d, J=15.00 Hz, 1 H), 7.00 (dd, J=8.42, 2.56 Hz, 1 H), 7.16 (m, 1 H), 7.21 - 7.33 (m, 1 H), 7.49 - 7.60 (m, 1 H), 7.81 - 7.88 (m, 1 H), 7.91 - 8.06 (m, 1 H). CL/EM: m/z 676.35, Rf 1.747 min., 98.2 % de pureza.



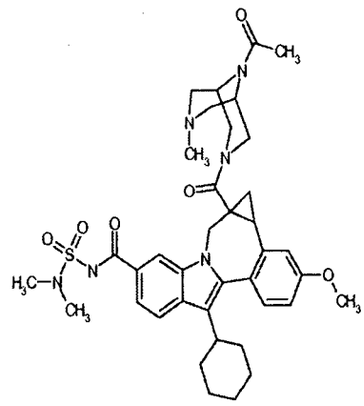
8-Ciclohexil-N-(dimetilsulfamoil)-11-metoxi-1a-(3-oxa-7,9-diazabiciclo[3.3.1]non-7-ilcarbonil)-1,1a,2,12b-tetrahidrociclopropa[d]indol[2,1-a][2]benzazepin-5-carboxamida. 1H RMN (300 MHz, CD3OD): δ ppm 0.25 (m, 0.20 H), 1.08 - 1.32 (m, 1.80 H), 1.44 (m, 4 H), 1.78 (m, 3 H), 1.99

(m, 4 H), 2.57 (m, 1 H), 2.77 (m, 1 H), 2.90 - 3.02 (m, 7 H), 3.62 (m, 3 H), 3.85 - 3.94 (m, 3 H), 4.00 - 4.15 (m, 4 H), 4.57 (m, 2 H), 5.00 (d, J=15.37 Hz, 1 H), 7.00 (dd, J=8.60, 2.38 Hz, 1 H), 7.17 (d, J=2.38 Hz, 1 H), 7.24 - 7.34 (m, 1 H), 7.50 - 7.61 (m, 1 H), 7.82 - 8.06 (m, 2 H). CL/EM: m/z 662.46, Rf 1.760 min., 98.2 % de pureza.

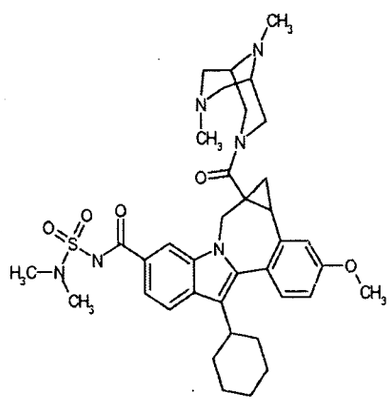


1a-((3-Bencil-7-metil-3,7,9-triazabiciclo[3.3.1]non-9-il)carbonil)-N-(sec-butilsulfonil)-8-ciclohexil-11-metoxi-1,1a,2,12b-tetrahidrociclopropa[d]indol[2,1-a][2]benzazepin-5-carboxamida. 1H RMN (300 MHz, CD3OD): δ ppm 0.20 (m, 0.20 H), 1.06 - 1.14 (m, 3 H), 1.20 - 1.36 (m, 2.80 H), 1.42 (m, 6 H), 1.72 (m, 4 H), 1.98 - 2.13 (m, 6 H), 2.62 (m, 2 H), 2.85 (m, 4 H), 3.15 (m, 1 H), 3.52 (m, 2 H), 3.63 (m, 2 H), 3.76 (m, 2 H), 3.87 (m, 4 H), 4.11 (m, 1 H), 4.38 (m, 1 H), 4.55 (m, 1 H), 5.06 (m, 1 H), 6.97 - 7.05 (m, 1 H), 7.11 - 7.17 (m, 1 H), 7.27 - 7.42 (m, 5 H), 7.59 (m, 2 H), 7.90 (m, 1 H), 8.01 - 8.09 (m, 1 H). CL/EM: m/z 779.48, Rf 1.897 min., 95.3

% de pureza.

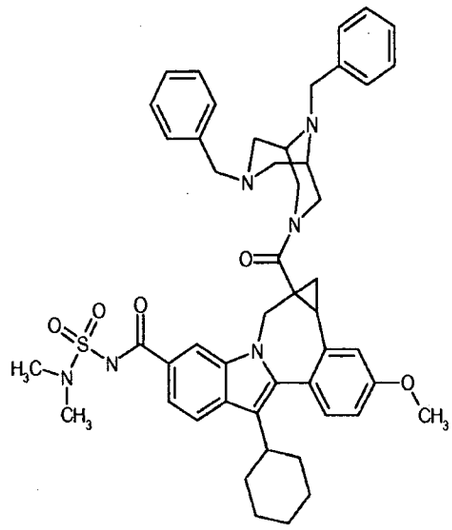


1a-((9-Acetil-7-metil-3,7,9-triazabiciclo[3.3.1]non-3-il)carbonil)-8-ciclohexil-N-(dimetilsulfamoil)-11-metoxi-1,1a,2,12b-tetrahidrociclopropa[d]indol[2,1-a][2]benzazepin-5-carboxamida. 1H RMN (300 MHz, CD3OD): δ ppm 0.20 (m, 0.35 H), 1.01 - 1.30 (m, 0.65 H), 1.38 (m, 5 H), 1.79 (m, 3 H), 1.93 - 2.21 (m, 13 H), 2.62 (m, 1 H), 2.82 (m, 2 H), 2.99 (s, 6 H), 3.56 (m, 1 H), 3.90 (m, 3 H), 4.04 - 4.18 (m, 3 H), 4.53 (m, 1 H), 4.63 (m, 1 H), 4.99 (m, 1 H), 6.95 - 7.01 (m, 1 H), 7.19 (m, 1 H), 7.31 (m, 1 H), 7.50 - 7.60 (m, 1 H), 7.80 (m, 1 H), 7.88 - 8.07 (m, 1 H). CL/EM: m/z 717.92, Rf 1.760 min., 97.6 % de pureza.



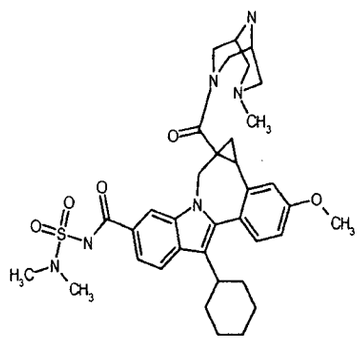
000432

8-Ciclohexil-N-(dimetilsulfamoil)-1a-((7,9-dimetil-3,7,9-triazabiciclo[3.3.1]non-3-il)carbonil)-11-metoxi-1,1a,2,12b-tetrahidrociclopropa[d]indol[2,1-a][2]benzazepin-5-carboxamida. 1H RMN (300 MHz, CD3OD): δ ppm 0.24 (m, 0.35 H), 1.24 (m, 0.65 H), 1.29 - 1.49 (m, 5 H), 1.62 (m, 1 H), 1.79 (m, 2 H), 1.98 (m, 4 H), 2.42 (m, 1 H), 2.53 (m, 1 H), 2.62 (m, 1 H), 2.75 (m, 1 H), 2.87 (m, 2 H), 2.93 - 3.07 (m, 8 H), 3.12 - 3.22 (m, 2 H), 3.42 (m, 2 H), 3.51 - 3.66 (m, 1 H), 3.88 (m, 3 H), 4.13 (m, 3 H), 4.27 (m, 1 H), 4.60 (m, 1 H), 5.00 (m, 1 H), 6.97 - 7.04 (m, 1 H), 7.14 - 7.20 (m, 1 H), 7.31 (m, 1 H), 7.49 - 7.61 (m, 1 H), 7.81 - 7.92 (m, 1.65 H), 8.06 (m, 0.35 H). CL/EM: m/z 689.86, Rf 1.785 min., 96.2 % de pureza.



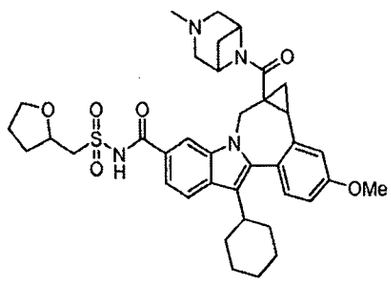
8-Ciclohexil-1a-((7,9-dibencil-3,7,9-triazabiciclo[3.3.1]non-3-il)carbonil)-N-(dimetilsulfamoil)-11-metoxi-1,1a,2,12b-tetrahidrociclopropa[d]indol[2,1-a][2]benzazepin-5-carboxamida. 1H RMN (500 MHz, CD3OD): δ ppm 0.22 (m, 0.25 H), 0.90 (m, 1 H), 1.19 - 1.28 (m, 1.75 H), 1.38

- 1.46 (m, 3 H), 1.76 (m, 3 H), 1.95 (m, 2 H), 2.00 (m, 2 H), 2.07 (m, 2 H), 2.54 (m, 1 H), 2.86 (m, 1 H), 2.99 (m, 9 H), 3.16 (m, 1 H), 3.43 (m, 1 H), 3.47 (m, 3 H), 3.84 - 3.91 (m, 4 H), 4.01 - 4.09 (m, 2 H), 4.75 (m, 1 H), 4.99 (d, J=15.26 Hz, 1 H), 6.94 - 7.02 (m, 1 H), 7.08 - 7.17 (m, 1 H), 7.27 - 7.56 (m, 11 H), 7.70 (m, 1 H), 7.86 - 8.07(m, 2 H). CL/EM: m/z 842.66, Rf 2.010 min., 98.0 % de pureza.



8-Ciclohexil-N-(dimetilsulfamoil)-11-metoxi-1a-((7-metil-3,7,9-triazabiciclo[3.3.1]non-3-il)carbonil)-1,1a,2,12b-tetrahidrociclopropa[d]indol[2,1-a][2]benzazepin-5-carboxamida. 1H RMN (500 MHz, CD3OD): δ ppm 0.23 (m, 0.30 H), 1.07 -1.29 (m, 0.70 H), 1.36 - 1.45 (m, 5 H), 1.60 (m, 1 H), 1.73 - 1.82 (m, 2 H), 1.90 - 2.07 (m, 4 H), 2.17 (m, 1 H), 2.35 (m, 1 H), 2.54 - 2.70 (m, 3 H), 2.86 (m, 1 H), 3.00 (m, 8 H), 3.20 (m, 2 H), 3.59 (m, 1 H), 3.71 - 3.80 (m, 1 H), 3.84 - 3.91 (m, 3 H), 4.14 m, 1 H), 4.43 (m, 1 H), 4.65 (m, 1 H), 4.98 (m, 1 H), 6.98 - 7.01 (m, 1 H), 7.15 - 7.20 (m, 1 H), 7.28 - 7.32 (m, 1 H), 7.50 - 7.60 (m, 1 H), 7.85 - 8.05 (m, 2 H). CL/EM: m/z 675.61, Rf 1.783 min., 98.7 % de pureza.

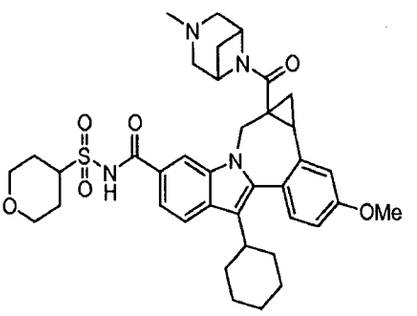
Todos los compuestos descritos en los procedimientos y ejemplos que siguen se analizaron usando el siguiente método CL/EM a menos que se note: Condiciones de análisis: Columna: PHENOMENNEX-LUNA 3.0 x 50mm S10; Fase móvil: (A) 10:90 metanol-agua; (B) 90:10 metanol-agua; Solución amortiguadora: TFA al 0.1%; Rango de gradiente: 0-100% B; Tiempo de gradiente: 2 min; Relación de flujo: 4 mL/min; Tiempo de análisis: 3 min; Detección: Detector 1: UV a 220 nm; Detector 2: EM (ESI+).



8-ciclohexil-N-((tetrahidrofuran-2-il)metilsulfonil)-1,1a,2,12b-tetrahidro-11-metoxi-1a-(3-metil-3,6-diazabiciclo[3.1.1]heptano-6-carbonil)ciclopropa[d]indol[2,1-a][2]benzazepin-5-carboxamida. El producto se purificó por HPLC prep. y aisló como una mezcla de diaestereómeros en una forma de sal mono TFA. CL/EM: Tiempo de retención: 1.832 min; m/e 687 (MH+). El producto se observó que existe como rotámeros de Interconversión por 1H RMN (400 MHz, CLOROFORMO-D) δ ppm 1.07 - 1.58 (m, 6 H), 1.61 - 2.10 (m, 6 H), 2.11 - 2.51 (m, 8 H), 2.58 - 2.88 (m, 2 H), 2.89 - 3.04 (m, 2 H), 3.06 - 3.25 (m, 1 H), 3.38 - 3.82 (m, 7 H), 3.83 - 3.97 (m, 5

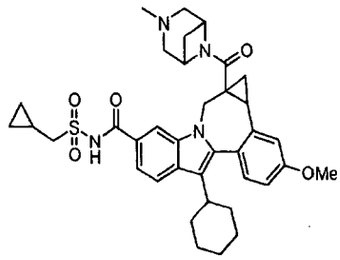
000435

H), 4.31 - 4.52 (m, J=25.94 Hz, 2 H), 5.34 - 5.57 (m, 1 H), 6.91 - 7.02 (m, J=8.69, 2.64 Hz, 1 H), 7.05 - 7.18 (m, J=2.52 Hz, 1 H), 7.21 - 7.35 (m, 1 H), 7.54 - 7.69 (m, 1 H), 7.79 - 7.98 (m, 1 H), 8.04 - 8.23 (m, 1 H).



(+/-)-8-ciclohexil-N-(tetrahidro-2H-piran-4-ilsulfonil)-1,1a,2,12b-tetrahidro-11-metoxi-1a-(3-metil-3,6-diazabiciclo[3.1.1]heptano-6-carbonil)ciclopropa[d]indol[2,1-a][2]benzazepin-5-carboxamida. El producto se purificó por HPLC prep. y aisló como un sólido beige en una forma de sal mono TFA. CL/EM: Tiempo de retención: 1.810 min; m/e 687 (MH+). El producto se observó que existe como rotámeros de Interconversión por 1H RMN (400 MHz, CLOROFORMO-D) δ ppm 1.08 - 1.63 (m, 7 H), 1.72 - 1.86 (m, 2 H), 1.88 - 2.15 (m, 7 H), 2.15 - 2.60 (m, 7 H), 2.60 - 3.19 (m, 4 H), 3.34 - 3.52 (m, 3 H), 3.52 - 3.68 (m, 1 H), 3.83 - 3.94 (m, 3 H), 3.97 - 4.20 (m, 4 H), 4.28 - 4.49 (m, 1 H), 5.33 - 5.56 (m, 1 H), 6.87 - 7.04 (m, J=8.56, 2.77 Hz, 1 H), 7.05 - 7.17 (m, J=2.52 Hz, 1 H), 7.24 - 7.35 (m, 1 H), 7.55 - 7.73 (m, J=8.31 Hz, 1 H), 7.81 - 7.96 (m, J=8.56 Hz, 1 H), 8.02 - 8.21 (m, 1

H).

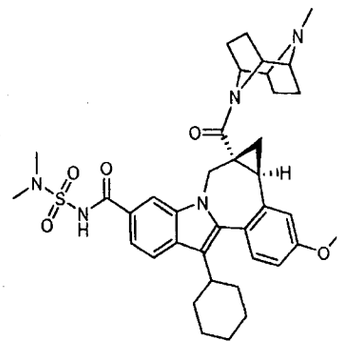


(+/-)-8-ciclohexil-N-(ciclopropilmetilsulfonil)-1,1a,2,12b-tetrahidro-11-metoxi-1a-(3-metil-3,6-diazabiciclo[3.1.1]heptano-6-carbonil)cicloprop[d]indol[2,1-a][2]benzazepin-5-carboxamida. El producto se purificó por HPLC prep. y aisló como un sólido beige en una forma de sal mono TFA. CL/EM: Tiempo de retención: 1.848 min; m/e 657 (MH+). El producto se observó que existe como rotámeros de Interconversión por 1H RMN (400 MHz, CLOROFORMO-D) δ ppm 0.29 - 0.48 (m, 2 H), 0.59 - 0.78 (m, 2 H), 1.10 - 1.61 (m, 6 H), 1.68 - 2.19 (m, J=81.58 Hz, 6 H), 2.21 - 2.78 (m, 10 H), 2.79 - 3.28 (m, 2 H), 3.31 - 3.72 (m, 4 H), 3.78 - 3.97 (m, 3 H), 3.97 - 4.70 (m, 2 H), 5.33 - 5.59 (m, 1 H), 6.86 - 7.04 (m, J=8.56, 2.52 Hz, 1 H), 7.05 - 7.18 (m, J=2.27 Hz, 1 H), 7.18 - 7.37 (m, 1 H), 7.47 - 7.70 (m, 1 H), 7.79 - 8.01 (m, 1 H), 8.03 - 8.35 (m, 1 H).

9-metil-9,10-diazatriciclo[4.2.1.$1^{2,5}$]decano. A una solución fría (0°C) de 9-Bencil-9,10-diazatriciclo[4.2.1.$1^{2,5}$]decano (J. Med. Chem. 2000, 43, 2115-2123) y TEA en DMF anhidro (1-2 ml) se agregó MeI. La mezcla se permitió calentar a temperatura ambiente y agitó durante 2-3 h.

000437

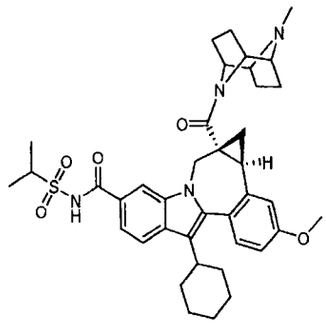
La mezcla rxn se evaporó hasta secarse y dividió entre éter y $NaHCO_3$ sat. y la capa de éter se separó, lavó con salmuera y secó (Na2SO4). La evaporación del éter proporciona el 9-Bencil-10-metil-9,10-diazatriciclo[4.2.1.$1^{2,5}$]decano como un aceite café ligero. Una suspensión agitada de 9-Bencil-10-metil-9,10-diazatriciclo[4.2.1.$1^{2,5}$]decano en EtOH que contiene HCl conc. (0.5 ml) y Pd-C al 10% se hidrogenó bajo un globo de presión de hidrógeno durante la noche. La suspensión se filtró y al filtrado se agregó tolueno seco (10-15 ml) y evaporó hasta secarse para proporcionar el 9-metil-9,10-diazatriciclo[4.2.1.12'5]decano y se aísla como sal bis-HCl.



8-ciclohexil-N-(N,N-dimetilsulfamoil)-1,1a,2,12b-tetrahidro-ì1-metoxi-1a-(9-metil-9,10-diazatriciclo[4.2.1.$1^{2,5}$]decano-10-carbonil)cicloprop[d]indol[2,1-a][2]benzazepin-5-carboxamida.

El tetrafluoroborato de 2-(1H-enzotriazol-1-il)-1,1,3,3-tetrametiluronio (12.52 mg, 0.039 mmol) se agregó a una solución agitada de ácido (17 mg, 0.03 mmol), 9-metil-9,10-diazatriciclo[4.2.1.$1^{2,5}$]decano (9 mg, 0.036 mmol) y TEA (0.025 ml, 0.180 mmol) en DCM anhidro (1 ml). La mezcla se agita a

temperatura ambiente durante la noche y luego evapora hasta secarse. El producto crudo se purificó por HPLC prep. de fase inversa para proporcionar el producto y se aísla como sal mono TFA: CL/EM: Tiempo de retención: 2.810 min; m/e 686 (MH+). El producto se observó que existe como rotámeros de Interconversión por 1H RMN (400 MHz, CLOROFORMO-D) δ ppm 0.18 - 0.35 (m, J=6.17, 6.17 Hz, 1 H), 1.10 - 1.28 (m, 2 H), 1.30 - 1.43 (m, 3 H), 1.43 - 1.61 (m, J=24.93 Hz, 1 H), 1.69 - 1.85 (m, 2 H), 1.83 - 2.08 (m, 4 H), 2.10 - 2.34 (m, 2 H), 2.37 - 2.55 (m, 2 H), 2.58 - 2.72 (m, 2 H), 2.73 - 2.94 (m, 3 H), 2.95 - 3.08 (m, 6 H), 3.37 - 3.61 (m, 3 H), 3.65 - 3.81 (m, J=18.63 Hz, 2 H), 3.82 - 3.94 (m, J=3.02 Hz, 3 H), 3.94 - 4.06 (m, J=14.60 Hz, 1 H), 4.09 - 4.25 (m, J=14.10 Hz, 1 H), 4.34 - 4.63 (m, 1 H), 4.73 - 4.88 (m, 1 H), 5.15 - 5.27 (m, 1 H), 6.91 - 6.99 (m, 1 H), 6.97 - 7.14 (m, 1 H), 7.26 - 7.35 (m, 1 H), 7.46 - 7.55 (m, J=9.32, 9.32 Hz, 1 H), 7.83 - 7.90 (m, J=8.18, 8.18 Hz, 1 H), 7.90 - 8.00 (m, 1 H).

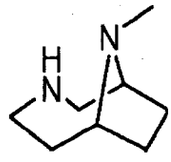


8-ciclohexil-N-(isopropilsulfonil)-1,1a,2,12b-tetrahidro-11-metoxi-1a-(9-metil-9,10-diazatriciclo[4.2.1.1^{2,5}]decano-10-carbonil)cicloprop[d]indol[2,1-a][2]benzazepin-5-carboxamida.

El tetrafluoroborato de 2-(1H-benzotriazol-1-il)-1,1,3,3-

000439

tetrametiluronio puro (12.52 mg, 0.039 mmol) se agregó a una solución agitada de ácido (17 mg, 0.03 mmol), 9-metil-9,10-diazatriciclo[4.2.1.$1^{2,5}$]decano (9 mg, 0.036 mmol) y TEA (0.025 ml, 0.180 mmol) en DCM anhidro (1 ml). La mezcla se agita a temperatura ambiente durante la noche y luego se evapora hasta secarse. El producto crudo se purificó por HPLC prep. de fase inversa para proporcionar el producto y aíslo como sal mono TFA: CL/EM: Tiempo de retención: 2.855 min; m/e 685 (MH+). El producto se observó que existe como rotámeros de Interconversión por 1H RMN (400 MHz, CLOROFORMO-D) δ ppm 0.16 - 0.36 (m, 1 H), 1.03 - 1.28 (m, 2 H), 1.29 - 1.57 (m, 8 H), 1.65 - 1.85 (m, 2 H), 1.84 - 2.06 (m, 4 H), 2.09 - 2.33 (m, 2 H), 2.36 - 2.54 (m, 1 H), 2.59 - 2.79 (m, 2 H), 2.80 - 2.89 (m, 2 H), 2.89 - 3.20 (m, 2 H), 3.41 - 3.63 (m, 3 H), 3.62 - 3.82 (m, 4 H), 3.83 - 3.93 (m, J=3.78 Hz, 3 H), 3.96 - 4.09 (m, 2 H), 4.10 - 4.25 (m, J=14.60 Hz, 1 H), 4.43 - 4.56 (m, 1 H), 4.71 - 4.85 (m, 1 H), 5.12 - 5.26 (m, 1 H), 6.91 - 6.98 (m, 1 H), 6.97 - 7.12 (m, 1 H), 7.27 - 7.34 (m, 1 H), 7.49 - 7.58 (m, J=8.31 Hz, 1 H), 7.84 - 7.90 (m, J=8.44, 6.17 Hz, 1 H), 7.90 - 7.99 (m, 1 H).



9-metil-3,9-diazabiciclo[4.2.1]nonano. El 9-Metil-3,9-diazabiciclo[4.2.1]nonano (J. Org. Chem., 1960, 637). H_2SO_4

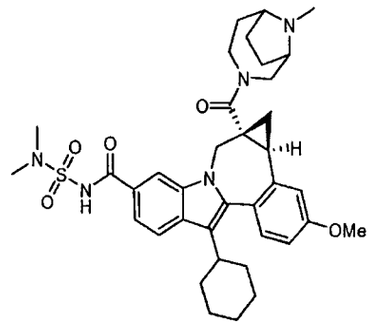
000440

Conc. (6.25 ml, 0.117 mol) se agregó gota a gota a una solución fría agitada (-5°C) de 8-metil-8-azabiciclo[3.2.1]octan-3-ona (2.78 g, 0.02 mol) en $CHCl_3$ (25 ml) mientras se mantiene la temperatura de bajo de 15°C. Después de enfriarse a 0-5°C, azida de sodio puro (2.60 g, 0.040 mol) se agregó en pequeñas porciones mientras se mantiene el contenedor a temperatura de bajo de 35°C. La mezcla se agita a temperatura ambiente durante 2h y luego calienta a 50°C durante 2 h. La mezcla rxn se vació en hielo y neutralizó con Na_2CO_3 y luego basificó con NaOH al 50%. La capa orgánica se separó y la capa ac. se vuelve a extraer con $CHCl_3$ (2x25 ml). Las capas orgánicas combinadas se lavaron con agua (10 ml), salmuera y secaron (MgSO4). La evaporación de $CHCl_3$ dio la 9-metil-3,9-diazabiciclo[4.2.1]nonan-4-ona como un sólido blanco opaco (1.15 g, 37%). 1H RMN (400 MHz, CLOROFORMO-D) d ppm 1.67 - 1.75 (m, 1 H) 1.77 - 1.85 (m, 1 H) 2.05 - 2.16 (m, 2 H) 2.42 (s, 3 H) 2.46 (ddd, J=16.05, 6.23, 2.14 Hz, 1 H) 2.80 - 2.90 (m, 2 H) 3.17 (t, J=6.42 Hz, 1 H) 3.24 (t, J=6.30 Hz, 1 H) 3.60 (d, J=14.60 Hz, 1 H) 5.90 (s, 1 H).

El LAH puro (0.5 g, 13.17 mmol) se agregó en porciones pequeñas a una solución agitada de 9-metil-3,9-diazabiciclo[4.2.1]nonan-4-ona (1.0 g, 6.48 mmol) en THF (40 ml) y la mezcla se calentó a reflujo bajo nitrógeno durante 3-4 h. La mezcla de reacción se enfrió en un baño de hielo y apagó por la adición consecutiva de agua (0.5 ml), NaOH al 15% (1.5

000461

ml) y agua (0.5 ml) y luego agitó durante 30 min. El aluminato de sodio precipitado se filtró completamente y el filtrado se secó sobre $MgSO_4$, filtró y evaporó hasta secarse para proporcionar el 9-metil-3,9-diazabiciclo[4.2.1]nonano como un aceite amarillo ligero. 1H RMN (400 MHz, CLOROFORMO-D) δ ppm 1.08 - 1.67 (m, 4 H) 1.74 - 1.92 (m, 1 H) 2.01 - 2.31 (m, 2 H) 2.41 - 2.46 (m, 3 H) 2.66 (dd, J=13.09, 2.01 Hz, 1 H) 2.77 - 3.00 (m, 2 H) 3.07 - 3.36 (m, 2 H) 3.50 - 4.06 (m, 1 H).

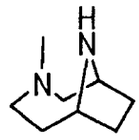


8-ciclohexil-N-(N,N-dimetilsulfamoil)-1,1a,2,12b-tetrahidro-11-metoxi-1a-(9-metil-3,9-diazabiciclo[4.2.1]nonano-3-carbonil)cicloprop[d]indol[2,1-a][2]benzazepin-5-carboxamida.

El tetrafluoroborato de 2-(1H-benzotriazol-1-il)-1,1,3,3-tetrametiluronio puro (22 mg, 0.069 mmol) se agregó a una solución agitada de ácido (28 mg, 0.051 mmol), 9-metil-3,9-diazabiciclo[4.2.1]nonano (15 mg, 0.102 mmol) y TEA (0.021 ml, 0.152 mmol) en DCM anhidro (1 ml). La mezcla se agita a temperatura ambiente durante 30-45 min y luego evapora hasta secarse. El producto crudo se purificó por HPLC prep. de fase inversa para proporcionar el producto como una mezcla de

000442

diaestereómeros y se aísla en la sal mono TFA: CL/EM: Tiempo de retención: 1.788 min; m/e 674 (MH+). El producto se observó que existe como rotámeros de Interconversión por 1H RMN (400 MHz, CLOROFORMO-D) δ ppm 0.22 - 0.50 (m, 1 H), 1.13 - 1.46 (m, J=54.89 Hz, 4 H), 1.46 - 1.61 (m, 1 H), 1.63 - 1.84 (m, 3 H), 1.85 - 2.22 (m, 5 H), 2.28 - 2.69 (m, 7 H), 2.69 - 2.98 (m, 4 H), 2.98 - 3.12 (m, 6 H), 3.43 - 3.56 (m, 1 H), 3.55 - 3.82 (m, 2 H), 3.84 - 3.91 (m, J=4.28 Hz, 3 H), 3.92 - 4.08 (m, 2 H), 4.10 - 4.24 (m, 1 H), 4.64 - 5.10 (m, J=132.95 Hz, 1 H), 6.87 - 7.00 (m, 1 H), 7.01 - 7.12 (m, 1 H), 7.27 - 7.35 (m, 1 H), 7.40 - 7.63 (m, 1 H), 7.82 - 7.93 (m, 2 H).



3-metil-3,9-diazabiciclo[4.2.1]nonano. El 3-Metil-3,9-diazabiciclo[4.2.1]nonano se preparó por seguir el procedimiento descrito en la referencia: J. Org. Chem., 1960, 637. El H_2SO_4 conc. (3.25 ml, 0.061 mol) se agregó gota a gota a una solución fría agitada (-5°C) de 8-Bencil-8-azabiciclo[3.2.1]octan-3-ona (2.153 g, 0.01 mol) en $CHCl_3$ (15 ml) mientras se mantiene la temperatura de bajo de 15°C. Después de enfriarse a 0-5°C, azida de sodio puro (1.30 g, 0.020 mol) se agregó en porciones pequeñas mientras se mantiene la temperatura del contenedor de bajo de 35°C. La mezcla se agitó a temperatura ambiente durante la noche y luego calentó a

000443

50°C durante 2 h. La mezcla rxn se vació en hielo y neutralizó con Na_2CO_3 y luego basificó con NaOH al 50%. La capa orgánica se separa y luego la capa ac. se vuelve a extraer con $CHCl_3$ (2x25 ml). Las capas orgánicas combinadas se lavaron con agua (10 ml), salmuera y secaron (MgSO4). La evaporación de CHCl3 dio la 9-Bencil-3,9-diazabiciclo[4.2.1]nonan-4-ona como un semi-sólido beige. CL/EM: m/e 231 (MH+).

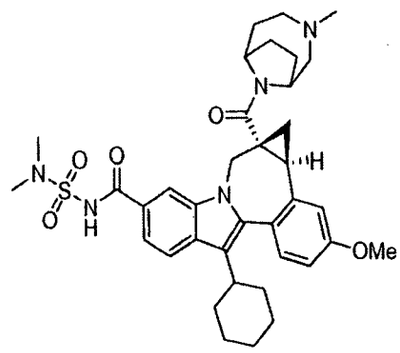
El LAH puro (0.4 g, 10.54 mmol) se agregó en porciones pequeñas a una solución agitada de 9-Bencil-3,9-diazabiciclo[4.2.1]nonan-4-ona (1.2 g, 5.21 mmol) en THF (40 ml) y la mezcla se agitó bajo nitrógeno durante la noche. La mezcla de reacción se enfrió en un baño de hielo y apagó por la adición consecutiva de agua (0.4 ml), NaOH al 15% (1.2 ml) y agua (0.4 ml) y luego agitó durante 30 min. El aluminato de sodio precipitado se filtró completamente y el filtrado se secó sobre MgSO4, filtró y evaporó hasta secarse para proporcionar el 9-Bencil-3,9-diazabiciclo[4.2.1]nonano como un aceite amarillo ligero. CL/EM: m/e 217 (MH+).

El yodometano puro (0.173 ml, 2.77 mmol) se agregó gota a gota a una solución agitada de 9-Bencil-3,9-diazabiciclo[4.2.1]nonano (0.4 g, 1.849 mmol) y TEA (2.58 ml, 18.49 mmol) en THF (5 ml). La suspensión resultante se agitó a temperatura ambiente durante 3 hrs y diluyó con éter y luego filtró. El filtrado se evaporó hasta secarse para proporcionar el 9-Bencil-3-metil-3,9-diazabiciclo[4.2.1]nonano como un

000444

aceite amarillo ligero. CL/EM: m/e 231 (MH+).

El formiato de amonio puro (2 g, 31.7 mmol) se agregó a una suspensión agitada de 9-Bencil-3-metil-3,9-diazabiciclo[4.2.1]nonano (250 mg, 1.085 mmol) y Pd-C al 10% (150 mg, 0.141 mmol) en etanol abs. (50 ml). La mezcla se calentó a reflujo durante 2-3 h. La suspensión se filtró y al filtrado TFA (0.5 ml) se agregó y evaporó hasta secarse para proporcionar el 3-metil-3,9-diazabiciclo[4.2.1]nonano y aíslo como la sal bis-TFA. CL/EM: m/e 141 (MH+).



8-ciclohexil-N-(N,N-dimetilsulfamoil)-1,1a,2,12b-tetrahidro-11-metoxi-1a-(3-metil-3,9-diazabiciclo[4.2.1]nonano-9-carbonil)cicloprop[d]indol[2,1-a][2]benzazepin-5-carboxamida. El tetrafluoroborato de 2-(1H-benzotriazol-1-il)-1,1,3,3-tetrametiluronio puro (22 mg, 0.069 mmol) se agregó a una solución agitada de ácido (28 mg, 0.051 mmol), 3-metil-3,9-diazabiciclo[4.2.1]nonano, 2TFA (37.4 mg, 0.102 mmol) y TEA (0.035 ml, 0.254 mmol) en DCM anhidro (1 ml). La mezcla se agita a temperatura ambiente durante 30-45 min y luego evapora hasta secarse. El producto crudo se purificó por HPLC prep. de fase inversa para proporcionar el

producto como una mezcla de diaestereómeros y se aísla en la sal mono TFA: CL/EM: Tiempo de retención: 1.830 min; m/e 674 (MH+). El producto se observó que existe como rotámeros de Interconversión por 1H RMN (500 MHz, CLOROFORMO-D) δ ppm 0.09 - 0.66 (m, 1 H), 0.72 - 1.14 (m, 1 H), 1.13 - 1.47 (m, 5 H), 1.48 - 1.65 (m, 1 H), 1.65 - 1.83 (m, 3 H), 1.83 - 2.14 (m, 4 H), 2.14 - 2.40 (m, 2 H), 2.38 - 2.69 (m, 2 H), 2.70 - 2.87 (m, 3 H), 2.86 - 3.08 (m, 6 H), 3.09 - 3.42 (m, 2 H), 3.43 - 3.55 (m, 1 H), 3.56 - 3.73 (m, J=16.48 Hz, 1 H), 3.74 - 3.98 (m, 4 H), 3.95 - 4.26 (m, 1 H), 4.22 - 4.61 (m, 2 H), 4.61 - 4.87 (m, J=35.10 Hz, 1 H), 4.95 - 5.21 (m, J=64.39 Hz, 1 H), 6.86 - 7.01 (m, 1 H), 7.02 - 7.14 (m, 1 H), 7.25 - 7.34 (m, 1 H), 7.34 - 7.58 (m, 1 H), 7.78 - 8.00 (m, 2 H).

Los siguientes compuestos se analizaron por el siguiente método hasta anotar: Condiciones de análisis: Columna: PHENOMENNEX-LUNA 3.0 x 50mm S10; Fase móvil: (A) 10:90 metanol-agua; (B) 90:10 metanol-agua; Solución amortiguadora: TFA al 0.1%; Rango de gradiente: B al 0-100%; Tiempo de gradiente: 2 min; Relación de flujo: 4 mL/min; Tiempo de análisis: 3 min; Detección: Detector 1: UV a 220 nm; Detector 2: EM (ESI+).

Procedimiento general para la preparación de 3-alquilo-3,9-diazabiciclo[3.3.1]nonano. Una suspensión de ácido piridin-2,6-dicarboxílico (6.68 g, 40.0 mmol) y óxido de platino (IV) (0.23 g, 1.013 mmol) en ácido acético (200 ml) se

000446

hidrogenó en un agitador Parr bajo 50 psi (3.515 kg/cm^2) de presión de hidrógeno durante 4-5 h. La suspensión se filtró y el filtrado se hizo ácido con HCl conc. (50 ml) al clorohidrato del ácido piperidin-2,6-dicarboxílico como un sólido blanco (5.9 g, 70%). CLEM: m/e 174 (MH+).

A una solución fría (0-5°C) de clorohidrato del ácido piperidina-2,6-dicarboxílico (1.05 g, 5.01 mmol) en NaOH 1N (10.02 mL, 10.02 mmol) cloroformiato de bencilo (1.430 mL, 10.02 mmol) se agregó a una relación que mantiene la temperatura de la reacción, de bajo de 5°C. La mezcla de reacción se permitió calentar a temperatura ambiente y agitó durante la noche. El exceso de cloroformiato de bencilo se removió por lavar la mezcla rxn con éter (2X10 ml). La capa acuosa se enfrió en un baño de hielo y se hizo ácida con HCl 6N (4 ml) y el precipitado blanco se extrajo con EtOAc (2X25 ml), secó (MgSO4), evaporó para proporcionar el ácido 1-(benciloxicarbonil)-piperidina-2,6-dicarboxílico como un sólido blanco (1.35 g, 88%). CLEM: m/e 264 (M-CO2H)+.

El anhídrido acético puro (0.453 ml, 4.80 mmol) se agregó a una suspensión agitada de ácido 1-(benciloxicarbonil)piperidin-2,6-dicarboxílico (1.23 g, 4.00 mmol) en tolueno (20 ml) y la mezcla se calentó a reflujo durante 1 h. La solución clara resultante se evaporó hasta secarse para proporcionar el anhídrido correspondiente como un aceite viscoso incoloro (1.2 g, 100%). Una solución THF de

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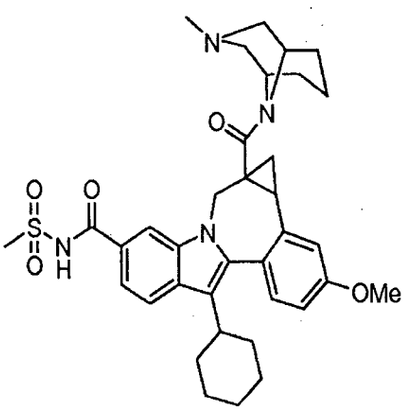
metilamina (5.00 ml, 10.01 mmol) y TEA (0.558 ml, 4.00 mmol) se agregaron a una solución fría (-20°C) del anhídrido crudo en THF an. (4 ml) y la mezcla se permitió calentar a temperatura ambiente y agitó durante 1-2 h. El rxn se diluyó con éter (25 ml) y HCl 2N (10 ml) se agregó y la capa orgánica separada se lavó con agua, salmuera y secó (MgSO4). La evaporación de los solventes dio un aceite viscoso (1.13 g) el cual se disolvió en tolueno an. (10 ml) y trató con anhídrido acético (0.453 ml, 4.80 mmol). La mezcla se calentó a reflujo durante 2 h y luego se evaporó hasta secarse para proporcionar un aceite (1.32 g) el cual se purificó por cromatografía de columna instantánea (gel de sílice, MeOH al 3% en DCM) para proporcionar el 3-metil-2,4-dioxo-3,9-diazabiciclo[3.3.1]nonano-9-carboxilato de bencilo como un aceite incoloro (0.805 g, 66.5%). CL/EM: m/e 303 (MH+).

Una suspensión agitada de 3-metil-2,4-dioxo-3,9-diazabiciclo[3.3.1]nonano-9-carboxilato de bencilo (742 mg, 2.454 mmol) y Pd-C al 10% (100 mg) en acetato de etilo (40 ml) se hidrogenó bajo un globo de presión de hidrógeno durante la noche. La suspensión se filtró para remover el catalizador y el filtrado se evaporó hasta secarse para proporcionar la 3-metil-3,9-diazabiciclo[3.3.1]nonano-2,4-diona como un sólido blanco (377 mg). EM: m/e 169 (MH+).

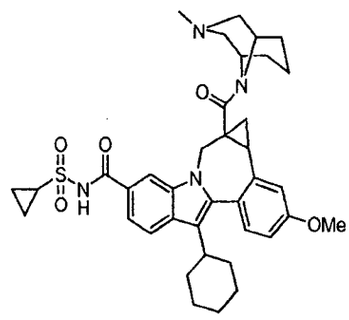
A una suspensión fría agitada (0-5°C) de LAH (205 mg, 5.40 mmol) en THF an. (15 ml) una solución de 3-metil-3,9-

diazabiciclo[3.3.1]nonano-2,4-diona (375 mg) en THF (5 ml) se agregó y la mezcla se calentó a reflujo durante 1-2 h. El rxn se enfrió en un baño de hielo y apagó por la adición de agua (0.2 ml), NaOH al 15% (0.6 ml) y agua (0.2 ml) y la suspensión se agitó vigorosamente y filtró y secó sobre Na2SO4. La evaporación de los solventes dio el aceite café ligero el cual se disolvió en éter y trató con HCl 1N en éter para proporcionar el 3-metil-3,9-diazabiciclo[3.3.1]nonano y se aísla como sal bis-HCl. EM: m/e 141 (MH+). 1H RMN (500 MHz, CD3OD): δ ppm 1.34-1.59 (5H, m), 2.02-2.32 (6H, m), 2.57-2.97 (4H, m).

Procedimiento general para la preparación de amidas a partir de los ácidos correspondientes por medio de acoplar la amida usando el 3-metil-3,9-diazabiciclo[3.3.1]nonano. Una mezcla del ácido (1 eq), amina (1.2-1.5 eq), TBTU (1.3 eq) y TEA (4 eq) en DCM anhidro se agitó durante 1-2 h a temperatura ambiente para proporcionar la amida las cuales se purificaron por HPLC preparativa de fase inversa y aislaron como sal TFA.

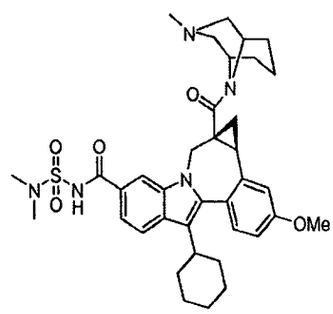


(+/-)-8-ciclohexil-N-(metilsulfonil)-1,1a,2,12b-tetrahidro-11-metoxi-1a-(3-metil-3,9-diazabiciclo[3.3.1]nonano-9-carbonil)cicloprop[d]indol[2,1-a][2]benzazepin-5-carboxamida. El producto se purificó por HPLC prep. y aisló como un sólido beige. CL/EM: Tiempo de retención: 2.776 min; m/e 645 (MH+). El producto se observó que existe como rotámeros de Interconversión por 1H RMN (400 MHz, CLOROFORMO-D) δ ppm 0.17 - 0.49 (m, 1 H), 1.06 - 1.48 (m, 5 H), 1.48 - 2.16 (m, J=80.83 Hz, 10 H), 2.19 - 2.45 (m, 1 H), 2.48 - 3.17 (m, 10 H), 3.32 - 3.53 (m, 3 H), 3.54 - 3.76 (m, J=15.36 Hz, 2 H), 3.77 - 4.04 (m, 4 H), 4.54 - 4.77 (m, 1 H), 4.81 - 5.27 (m, J=119.61 Hz, 1 H), 6.86 - 7.05 (m, 1 H), 7.03 - 7.16 (m, J=2.52 Hz, 1 H), 7.19 - 7.34 (m, 1 H), 7.48 - 7.75 (m, 1 H), 7.80 - 8.16 (m, 2 H).



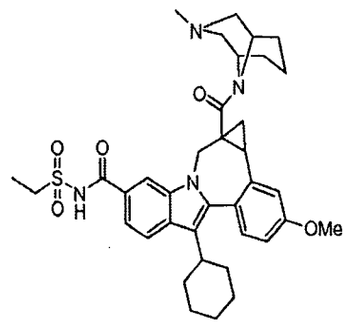
(+/-)-8-ciclohexil-N-(ciclopropilsulfonil)-1,1a,2,12b-tetrahidro-11-metoxi-1a-(3-metil-3,9-diazabiciclo[3.31]nonano-9-carbonil)cicloprop[d]indol[2,1-a][2]benzazepin-5-carboxamida. El producto se purificó por HPLC prep. y aisló como un sólido beige. CL/EM: Tiempo de retención: 2.846 min; m/e 671 (MH+). El producto se observó que existe como

rotámeros de Interconversión por 1H RMN (400 MHz, CLOROFORMO-D) δ ppm 1.04 - 1.57 (m, 6 H), 1.60 - 1.86 (m, J=44.57 Hz, 4 H), 1.85 - 2.29 (m, 18 H), 2.49 - 3.26 (m, 4 H), 3.52 - 3.74 (m, J=14.60 Hz, 2 H), 3.80 - 3.99 (m, 4 H), 4.54 - 4.77 (m, 1 H), 4.97 - 5.31 (m, 1 H), 6.88 - 7.04 (m, 1 H), 7.06 - 7.18 (m, J=2.77 Hz, 1 H), 7.18 - 7.35 (m, 2 H), 7.81 - 8.01 (m, 2 H).

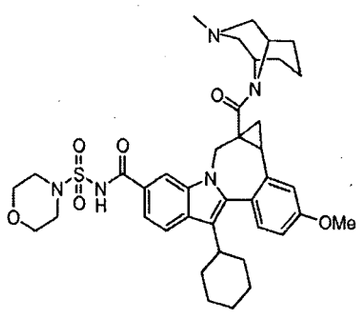


8-ciclohexil-N-(N,N-dimetilsulfamoil)-1,1a,2,12b-tetrahidro-11-metoxi-1a-(3-metil-3,9-diazabiciclo[3.3.1]nonano-9-carbonil)cicloprop[d]indol[2,1-a][2]benzazepin-5-carboxamida. El producto se purificó por HPLC prep. y aisló como un sólido beige. CL/EM: Tiempo de retención: 2.890 min; m/e 674 (MH+). El producto se observó que existe como rotámeros de Interconversión por 1H RMN (400 MHz, CLOROFORMO-D) δ ppm 1.01 - 1.59 (m, 7 H), 1.58 - 2.36 (m, 9 H), 2.37 - 3.30 (m, 15 H), 3.42 - 3.74 (m, 2 H), 3.77 - 3.93 (m, J=3.02 Hz, 4 H), 3.93 - 4.22 (m, 1 H), 4.55 - 4.73 (m, 1 H), 4.71 - 5.20 (m, 1 H), 6.85 - 7.04 (m, 1 H), 7.02 - 7.17 (m, J=2.27 Hz, 1 H), 7.16 - 7.34 (m, 1 H), 7.41 - 7.66 (m, 1

H), 7.76 - 8.15 (m, 2 H).

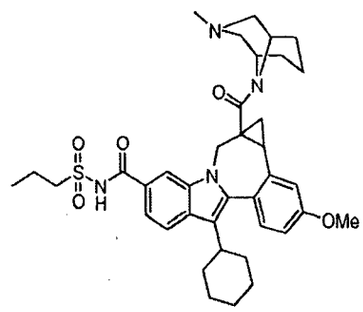


(+/-)-8-ciclohexil-N-(etilsulfonil)-1,1a,2,12b-tetrahidro-11-metoxi-1a-(3-metil-3,9-diazabiciclo[3.31]nonano-9-carbonil)cicloprop[d]indol[2,1-a][2]benzazepin-5-carboxamida. El producto se purificó por HPLC prep. y aisló como un sólido beige. CL/EM: Tiempo de retención: 2.846 min; m/e 659 (MH+). El producto se observó que existe como rotámeros de Interconversión por 1H RMN (400 MHz, CLOROFORMO-D) δ ppm 0.14 - 0.52 (m, 1 H), 1.10 - 1.49 (m, 7 H), 1.48 - 2.19 (m, 11 H), 2.18 - 2.39 (m, 1 H), 2.50 - 3.21 (m, 5 H), 3.28 - 3.75 (m, 7 H), 3.83 - 3.92 (m, 4 H), 3.92 - 4.34 (m, 2 H), 4.53 - 4.79 (m, 1 H), 4.86 - 5.24 (m, J=82.59 Hz, 1 H), 6.91 - 7.02 (m, 1 H), 7.08 - 7.15 (m, J=2.52 Hz, 1 H), 7.26 - 7.33 (m, 1 H), 7.48 - 7.73 (m, J=76.80 Hz, 1 H), 7.87 - 7.96 (m, J=8.56 Hz, 1 H), 7.96 - 8.17 (m, 1 H).



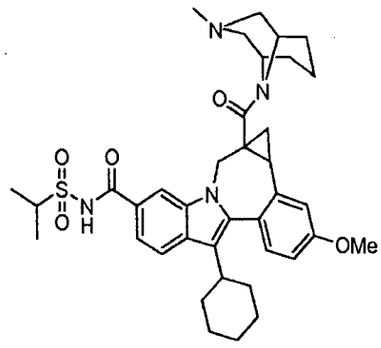
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(+/-)-8-ciclohexil-N-(morfolinosulfonil)-1,1a,2,12b-tetrahidro-11-metoxi-1a-(3-metil-3,9-diazabiciclo[3.31]nonano-9-carbonil)cicloprop[d]indol[2,1-a][2]benzazepin-5-carboxamida. El producto se purificó por HPLC prep. y aisló como un sólido beige. CL/EM: Tiempo de retención: 2.828 min; m/e 716 (MH+). El producto se observó que existe como rotámeros de Interconversión por 1H RMN (400 MHz, CLOROFORMO-D) δ ppm 0.14 - 0.57 (m, 1 H), 1.01 - 1.47 (m, 6 H), 1.47 - 1.88 (m, 6 H), 1.87 - 2.21 (m, 7 H), 2.24 - 3.13 (m, 11 H), 3.38 - 3.56 (m, 4 H), 3.57 - 3.69 (m, J=15.11 Hz, 2 H), 3.84 - 3.94 (m, 4 H), 4.56 - 4.74 (m, 1 H), 4.76 - 5.25 (m, 1 H), 6.93 - 7.03 (m, 1 H), 7.07 - 7.15 (m, J=2.52 Hz, 1 H), 7.29 (d, J=8.56 Hz, 1 H), 7.49 - 7.71 (m, 1 H), 7.84 - 8.00 (m, 2 H).



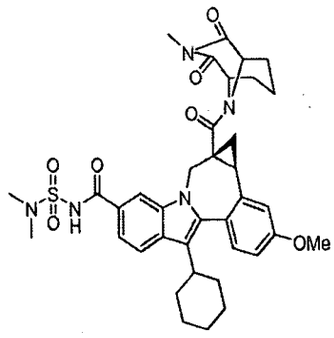
(+/-)-8-ciclohexil-N-(propilsulfonil)-1,1a,2,12b-tetrahidro-11-metoxi-1a-(3-metil-3,9-diazabiciclo[3.31]nonano-9-carbonil)cicloprop[d]indol[2,1-a][2]benzazepin-5-carboxamida. El producto se purificó por HPLC prep. y aisló como un sólido beige. CL/EM: Tiempo de retención: 2.918 min; m/e 673 (MH+). El producto se observó que existe como

rotámeros de Interconversión por 1H RMN (400 MHz, CLOROFORMO-D) δ ppm 0.12 - 0.53 (m, 1 H), 0.76 - 1.14 (m, 4 H), 1.14 - 1.52 (m, 5 H), 1.49 - 2.16 (m, 12 H), 2.20 - 2.46 (m, 1 H), 2.48 - 3.05 (m, 4 H), 3.05 - 3.71 (m, 9 H), 3.82 - 4.01 (m, 4 H), 4.55 - 4.79 (m, 1 H), 4.82 - 5.22 (m, J=86.12 Hz, 1 H), 6.91 - 7.02 (m, 1 H), 7.07 - 7.15 (m, J=2.52 Hz, 1 H), 7.26 - 7.33 (m, 1 H), 7.56 - 7.76 (m, 1 H), 7.85 - 7.96 (m, J=8.56 Hz, 1 H), 7.95 - 8.19 (m, 1 H).

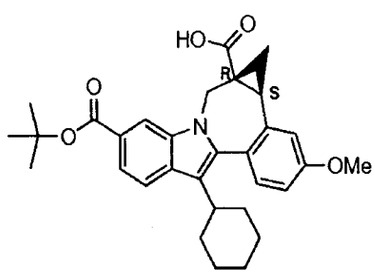


(+/-)-8-ciclohexil-N-(isopropilsulfonil)-1,1a,2,12b-tetrahidro-11-metoxi-1a-(3-metil-3,9-diazabiciclo[3.3.1]nonano-9-carbonil)cicloprop[d]indol[2,1-a][2]benzazepin-5-carboxamida. El producto se purificó por HPLC prep. y aisló como un sólido beige. CL/EM: Tiempo de retención: 3.120 min; m/e 673 (MH+). El producto se observó que existe como rotámeros de Interconversión por 1H RMN (400 MHz, CLOROFORMO-D) δ ppm 0.14 - 0.53 (m, 1 H), 1.12 - 1.51 (m, 9 H), 1.50 - 2.19 (m, 12 H), 2.20 - 2.46 (m, 1 H), 2.48 - 3.27 (m, 8 H), 3.40 - 3.70 (m, 3 H), 3.81 - 3.95 (m, 4 H), 3.93 - 4.12 (m, J=22.66 Hz, 1 H), 4.52 - 4.76 (m, 1 H), 4.79 - 5.24 (m, J=105.76 Hz, 1 H), 6.91 - 7.03 (m, 1 H), 7.07 - 7.14 (m,

J=2.52 Hz, 1 H), 7.26 - 7.32 (m, J=8.56 Hz, 1 H), 7.51 - 7.70 (m, 1 H), 7.85 - 8.00 (m, J=8.56 Hz, 2 H).



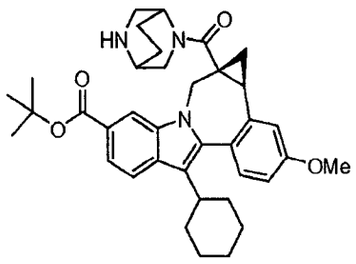
(+/-)-8-ciclohexil-N-(N,N-dimetilsulfamoil)-1,1a,2,12b-tetrahidro-11-metoxi-1a-(3-metil-2,4-dioxo-3,9-diazabiciclo[3.3.1]nonano-9-carbonil)ciclopropa[d]indol[2,1-a][2]benzazepin-5-carboxamida. El producto se purificó por HPLC prep. y aisló como un sólido beige. CL/EM: Tiempo de retención: 3.306 min; m/e 702 (MH+). El producto se observó que existe como rotámeros de Interconversión por 1H RMN (500 MHz, CLOROFORMO-D) δ ppm 0.29 - 0.77 (m, 1 H), 0.98 - 1.64 (m, 4 H), 1.64 - 2.23 (m, 9 H), 2.44 - 2.97 (m, 2 H), 2.98 - 3.16 (m, 9 H), 3.31 - 3.67 (m, 6 H), 3.79 - 3.96 (m, 4 H), 3.96 - 4.54 (m, 1 H), 5.03 - 5.52 (m, 1 H), 6.83 - 6.96 (m, 1 H), 6.97 - 7.14 (m, 1 H), 7.17 - 7.33 (m, 1 H), 7.44 - 7.71 (m, 1 H), 7.73 - 7.90 (m, 1 H), 7.90 - 8.30 (m, 1 H).



ácido (1aR,12bS)-5-(tert-butoxicarbonil)-8-ciclohexil-11-metoxi-1,12b-dihidrociclopropa[d]indol[2,1-a][2]benzazepin-1a(2H)-carboxílico. El hidróxido de sodio (1M ac., 31 mL) se agregó a una solución fría (0°C, baño de hielo) que contiene 1a-etil(1aR,12bS)-8-ciclohexil-11-metoxi-1,12b-dihidrociclopropa[d]indol[2,1-a][2]benzazepin-1a,5(2H)-dicarboxilato de 5-tert-butilo (4.0 g, 7.76 mmol), THF (35 mL), y metanol (35 mL). Después de 20 min, la solución se removió del baño de enfriamiento y mantuvo a temperatura ambiente durante 3h. La solución se enfrió nuevamente (0°C, baño de hielo) y el pH se redujo hasta de bajo de 4 por la adición lenta de HCl 1N (ac., 33mL). La mezcla se extrajo inmediatamente con acetato de etilo (2 x 30 mL). Las porciones orgánicas combinadas se lavaron con salmuera, (20 mL), secaron (sulfato de magnesio), filtraron y concentraron para proporcionar un sólido blanco el cual se usó sin purificación adicional en la siguiente etapa. CLEM: Tiempo de retención: 3.162 min. Los Datos CL se registraron en un equipo de cromatografía líquida Shimadzu CL-10AS con una columna Phenomenex-Luna 10u C18 4.6x50mm usando un detector SPD-10AV UV-Vis en un detector de longitud de onda de 220nM. Las condiciones de elución emplean una relación de flujo de 4 mL/min, un gradiente de solvente A al 100%/solvente B al 0% a solvente A al 0%/solvente B al 100%, un tiempo de gradiente de 4 min, un tiempo de espera de 1 min, y un tiempo de análisis

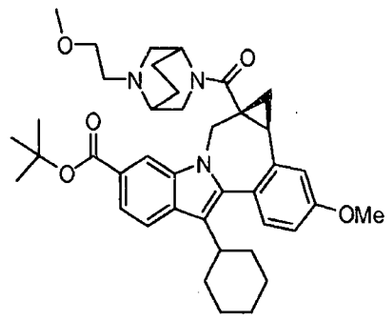
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de 5 min donde el solvente A fue CH_3CN al 5%/H_2O al 59%/acetato de amonio 10 mM y el solvente B fue H_2O al 5%/CH_3CN al 95%/acetato de amonio 10 mM. Los datos EM se determinaron usando una plataforma de micromasa para CL en el modo de electro-rocío, m/z 502(MH+).



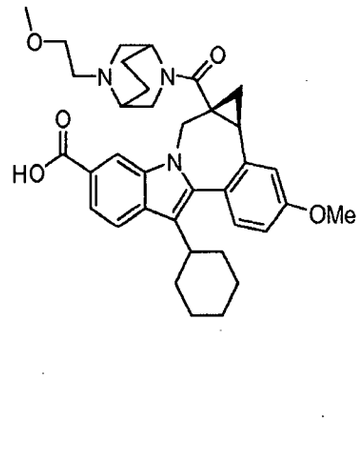
(1aR,12bS)-8-ciclohexil-1a-(2,5-diazabiciclo[2.2.2]oct-2-ilcarbonil)-11-metoxi-1,1a,2,12b-tetrahidrociclopropa[d]indol[2,1-a][2]benzazepin-5-carboxilato de Tert-butilo. El TBTU (691 mg, 2.15 mmol) se agregó en una porción en una solución fría (0°C, baño de hielo) que contiene ácido (1aR,12bS)-5-(tert-butoxicarbonil)-8-ciclohexil-11-metoxi-1,12b-dihidrociclopropa[d]indol[2,1-a][2]benzazepin-1a(2H)-carboxílico (900 mg, 1.79 mmol), DIEA (1.88 mL, 10.77 mmol), diclorohidrato de 2,5-diazabiciclo[2.2.2]octano (1:1) ((498 mg, 2.69 mmol), (H. Newman, J. Het. Chem. 449 (1974); P.E. Thompson, J. B. Zeigler, J. W. McCall, J. Med. Chem., 17, 481 (1974)), y diclorometano (36 mL). La solución se mantuvo durante 1.5 h y diluyó con diclorometano adicional (20 mL). La solución se lavó con agua (3 x 20 mL), lavó con salmuera (15 mL), secó (sulfato de magnesio), filtró y concentró para proporcionar un residuo blanco pegajoso el cual se trituró con

n-pentano (2 x 20 mL) para proporcionar un sólido blanco el cual se usó sin purificación adicional en la siguiente etapa. CLEM: tiempo de retención 3.841 min. Los Datos CL se registraron en un equipo de cromatografía líquida Shimadzu CL-10AS con una columna Phenomenex-Luna 10u C18 4.6x50mm usando un detector SPD-10AV UV-Vis en un detector de longitud de onda de 220nM. Las condiciones de elución emplean una relación de flujo de 4 mL/min, un gradiente de solvente A al 100%/solvente B al 0% a solvente A al 0%/solvente B al 100%, un tiempo de gradiente de 4 min, un tiempo de espera de 1 min, y un tiempo de análisis de 5 min donde el solvente A fue CH_3CN al 5%/H_2O al 59%/acetato de amonio 10 mM y el solvente B fue H_2O al 5%/CH_3CN al 95%/acetato de amonio 10 mM. Los datos EM se determinaron usando una plataforma de micromasa para CL en el modo de electro-rocío, m/z 596(MH+).



(1aR,12bS)-8-ciclohexil-11-metoxi-1a-((5-(2-metoxietil)-2,5-diazabiciclo[2.2.2]oct-2-il)carbonil)-1,1a,2,12b-tetrahidrociclopropa[d]indol[2,1-a][2]benzazepin-5-carboxilato de Tert-butilo. Una suspensión que contiene (1aR,12bS)-8-ciclohexil-1a-(2,5-diazabiciclo[2.2.2]oct-2-ilcarbonil)-11-

metoxi-1,1a,2,12b-tetrahidrociclopropa[d]indol[2,1-a][2]benzazepin-5-carboxilato de tert-butilo (400 mg, 0.671 mmol), 1-bromo-2-metoxietano (373 mg, 2.69 mmol), carbonato de potasio (978 mg, 6.71 mmol), y THF (7.0 mL) se agitó con rigor a 70°C durante 20 hrs. La mezcla se filtró y el filtrado se concentró hasta secarse. El sólido resultante se trituró con n-pentano (2 x 5 mL) y se usó sin purificación adicional. CLEM: tiempo de retención 4.073 min. Los Datos CL se registraron en un equipo de cromatografía líquida Shimadzu CL-10AS con una columna Phenomenex-Luna 10u C18 4.6x50mm usando un detector SPD-10AV UV-Vis en un detector de longitud de onda de 220nM. Las condiciones de elución emplean una relación de flujo de 4 mL/min, un gradiente de solvente A al 100%/solvente B al 0% a solvente A al 0%/solvente B al 100%, un tiempo de gradiente de 4 min, un tiempo de espera de 1 min, y un tiempo de análisis de 5 min donde el solvente A fue CH_3CN al 5%/H_2O al 59%/acetato de amonio 10 mM y el solvente B fue H_2O al 5%/CH_3CN al 95%/acetato de amonio 10 mM. Los datos EM se determinaron usando una plataforma de micromasa para CL en el modo de electro-rocío, m/z 654 (MH+).

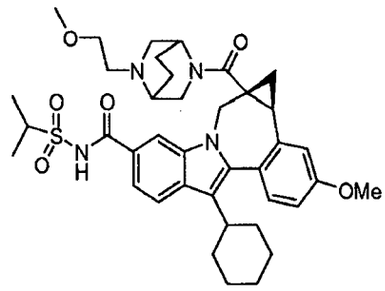


000459

ácido (1aR,12bS)-8-ciclohexil-11-metoxi-1a-((5-metil-2,5-diazabiciclo[2.2.2]oct-2-il)carbonil)-1,1a,2,12b-tetrahidrociclopropa[d]indol[2,1-a][2]benzazepin-5-carboxílico.

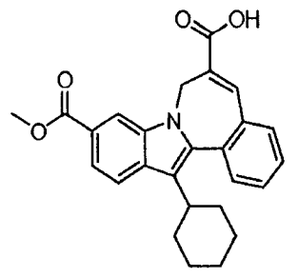
El TFA (8.4 mL) se agregó a una solución que contiene (1aR,12bS)-8-ciclohexil-11-metoxi-1a-((5-metil-2,5-diazabiciclo[2.2.2]oct-2-il)carbonil)-1,1a,2,12b-tetrahidrociclopropa[d]indol[2,1-a][2]benzazepin-5-carboxilato de tert-butilo (550 mg, 0.841 mmol) y DCM (8.4 mL). La solución se mantuvo a temperatura ambiente durante 3 h y luego concentró hasta secarse. El residuo resultante se cargó con 1:1 metanol/agua (20 mL) y el pH se incrementa arriba de 8 por la adición lenta de bicarbonato de sodio acuoso, saturado (10 mL). La solución se concentró para remover el metanol y extrajo con diclorometano (6 x 10mL). Las porciones orgánicas combinadas se lavaron con salmuera (20 mL), secaron (sulfato de magnesio), filtraron y concentraron para proporcionar un sólido amarillo ligero el cual se usó sin purificación adicional. El CL/EM mostró picos translapados en tiempo de retención de 2.385 min. Los Datos CL se registraron en un equipo de cromatografía líquida Shimadzu CL-10AS con una Phenomenex-Luna 10u C18 4.6x50mm usando un detector SPD-10AV UV-Vis en un detector de longitud de onda de 220nM. Las condiciones de elución emplean una relación de flujo de 4 mL/min, un gradiente de solvente A al 100%/solvente B al 0% a solvente A al 0%/solvente B al 100%, un tiempo de gradiente de 4 min, un tiempo de espera de 1 min,

y un tiempo de análisis de 5 min donde el solvente A fue CH_3CN al 5%/H_2O al 59%/acetato de amonio 10 mM y el solvente B fue H_2O al 5%/CH_3CN al 95%/acetato de amonio 10 mM. Los datos EM se determinaron usando una plataforma de micromasa para CL en el modo de electro-rocío.; m/z 598 (MH+).



(1aR,12bS)-8-ciclohexil-N-(isopropilsulfonil)-11-metoxi-1a-((5-(2-metoxietil)-2,5-diazabiciclo[2.2.2]oct-2-il)carbonil)-1,1a,2,12b-tetrahidrociclopropa[d]indol[2,1-a][2]benzazepin-5-carboxamida. El EDCI (178 mg, 928 mmol) se agregó a temperatura ambiente, en una porción, a una solución que contiene ácido (1aR,12bS)-8-ciclohexil-11-metoxi-1a-((5-(2-metoxietil)-2,5-diazabiciclo[2.2.2]oct-2-il)carbonil)-1,1a,2,12b-tetrahidrociclopropa[d]indol[2,1-a][2]benzazepin-5-carboxílico (378 mg, 0.619 mmol), DMAP (38 mg, 0.309 mmol), 2-isopropil sulfonamida (191 mg, 1.547 mmol), y diclorometano (7 mL). La solución se mantuvo a temperatura ambiente durante 24 h, diluyó con diclorometano adicional (20 mL), lavó con bicarbonato de sodio acuoso saturado (2 x 20 mL), lavó con agua (20 mL), secó (sulfato de magnesio), filtró y concentró. El residuo amarillo ligero resultante se purificó por HPLC

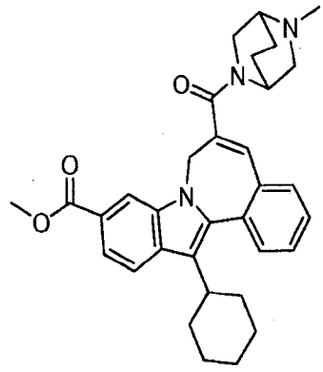
preparativa de fase inversa bajo condiciones básicas usando una columna Phenomenex, luna, 10 micron, 30 x 100 mm. Los diaestereómeros no se separaron bajo estas condiciones. El producto fue un sólido blanco. El CL/EM mostró diaestereómeros separados como picos translapados en tiempos de retención de 2.288 min y 2.372 min. Los Datos CL se registraron en un equipo de cromatografía líquida Shimadzu CL-10AS con una columna Phenomenex-Luna 10u C18 4.6x50mm usando un detector SPD-10AV UV-Vis en un detector de longitud de onda de 220nM. Las condiciones de elución emplean una relación de flujo de 4 mL/min, un gradiente de solvente A al 100%/solvente B al 0% hasta solvente A al 0%/solvente B al 100%, un tiempo de gradiente de 4 min, un tiempo de espera de 1 min, y un tiempo de análisis de 5 min donde el solvente A fue CH_3CN al 5%/H_2O al 59%/acetato de amonio 10 mM y el solvente B fue H_2O al 5%/CH_3CN al 95%/acetato de amonio 10 mM. Los datos EM se determinaron usando una plataforma de micromasa para CL en el modo de electro-rocío m/z 703 (MH+).



ácido 13-ciclohexil-10-(metoxicarbonil)-7H-indol[2,1-a][2]benzazepin-6-carboxílico. El hidroxido de tetrabutilamonio (9.1 mL, solución al 40% en agua) se agregó gota a gota a una

solución fría (0°C, baño de hielo) que contiene 13-ciclohexil-7H-indol[2,1-a][2]benzazepin-6,10-dicarboxilato de dimetilo (Preparado como se describe en la Publicación de Solicitud de Patente de E.U.A US20070184024 A1, Compuesto intermedio 9) y THF (463 mL). La solución se mantuvo con enfriamiento continúo durante 50 min. y luego se concentró hasta un volumen de alrededor de 50 mL. La solución resultante se diluyó con acetato de etilo (250 mL), lavó con HCl ac. (0.5 N, 3 x 150 mL), lavó con salmuera (150 mL), secó (sulfato de magnesio), filtró y concentró para proporcionar un sólido amarillo. CLEM: Tiempo de retención: 1.698 min. Los Datos CL se registraron en un equipo de cromatografía líquida Shimadzu CL-10AS con una columna Phenomenex-Luna 10u C18 4.6x50mm usando un detector SPD-10AV UV-Vis en un detector de longitud de onda de 220nM. Las condiciones de elución emplean una relación de flujo de 4 mL/min, un gradiente de solvente A al 100%/solvente B al 0% a solvente A al 0%/solvente B al 100%, un tiempo de gradiente de 4 min, un tiempo de espera de 1 min, y un tiempo de análisis de 5 min donde el solvente A fue CH_3CN al 5%/H_2O al 59%/acetato de amonio 10 mM y el solvente B fue H_2O al 5%/CH_3CN al 95%/acetato de amonio 10 mM. Los datos EM se determinaron usando una plataforma de micromasa para CL en el modo de electro-rocío: m/z 416(MH+). 1H RMN (300 MHz, DMSO-D6) δ ppm: 12.97 (s, 1 H), 8.17 (m, 1 H), 7.91 (m, 2 H), 7.63 (m, 5 H), 5.56 (s, 1 H), 4.51 (m, 1 H), 3.89 (m, 3 H), 2.80 (m, 1 H), 1.99 (m, 6 H),

1.30 (m, 4 H).

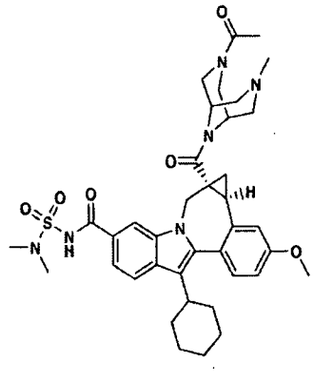


Se prepara a partir del ácido de arriba por medio de acoplamiento estándar entre el ácido y diamina y luego mutilación reductiva de diamina. El acoplamiento de la N-monometil diamina podría utilizarse. La ciclopropanación estándar, esterhidrólisis, y acoplamiento del ácido a una sulfamida o sulfonamida apropiada como se detalla en los procedimientos y esquemas de reacción podría proporcionar los compuestos finales la invención. Las etapas restantes podrían realizarse en el orden descrito o la esterhidrólisis y el acoplamiento a la sulfonamida o sulfamida podría realizarse previo a la ciclopropanación. 1H RMN (500 MHz, CD_3OD): δ ppm 0.92-2.69 (series de múltiplos, 19 H), 2.90- 3.19, (series de múltiplos, 3 H), 3.41-3.85 (series de múltiplos, 3 H), 3.96-3.98 (m, 2 H), (m, 1 H), 4.37 - 4.45 (m, 1 H), 5.19-5.28 (m, 1H), 6.98 (m, 0.7 H), 7.17 (m, 0.3 H), 6.98 - 7.07 (m, 1 H), 7.56 - 7.58 (m, 3 H), 7.64-7.65 (m, 1 H), 7.73 - 7.75 (m, 1 H), 7.92 - 7.94 (m, 1 H), 8.23 (m, 1 H). CLEM: tiempo de retención 4.008 min. Los Datos CL se registraron en un equipo de cromatografía líquida Shimadzu CL-10AS con una columna

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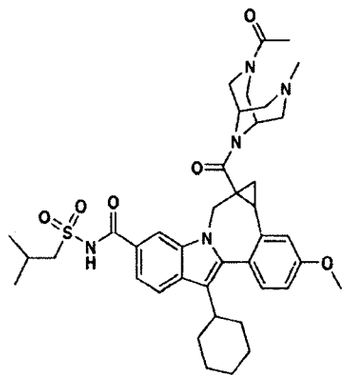
Phenomenex-Luna 10u C18 4.6x50mm usando un detector SPD-10AV UV-Vis en un detector de longitud de onda de 220nM. Las condiciones de elución emplean una relación de flujo de 4 mL/min, un gradiente de solvente A al 100%/solvente B al 0% a solvente A al 0%/solvente B al 100%, un tiempo de gradiente de 4 min, un tiempo de espera de 1 min, y un tiempo de análisis de 5 min donde el solvente A fue CH_3CN al 5%/H_2O al 59%/acetato de amonio 10 mM y el solvente B fue H_2O al 5%/CH_3CN al 95%/acetato de amonio 10 mM. Los datos EM se determinaron usando una plataforma de micromasa para CL en el modo de electro-rocío, m/z 524(MH+).

Los siguientes compuestos se prepararon usando los procedimientos análogos a aquellos descritos arriba.



1a-((3-Acetil-7-metil-3,7,9-triazabiciclo[3.3.1]non-9-il)carbonil)-8-ciclohexil-N-(dimetilsulfamoil)-11-metoxi-1,1a,2,12b-tetrahidrociclopropa[d]indol[2,1-a][2]benzazepin-5-carboxamida, (1aR, 12bS). 1H RMN (500 MHz, CD3OD): δ ppm 0.21 (m, 0.25 H), 1.19 - 1.33 (m, 1 H), 1.43 (m, 3 H), 1.70 (m, 1.75 H), 1.80 (m, 2 H), 1.95 (m, 2 H), 2.25 (m, 5 H), 2.64 (m, 1 H), 2.83 (m, 2 H), 3.01 (m, 9 H), 3.16 (m, 1 H),

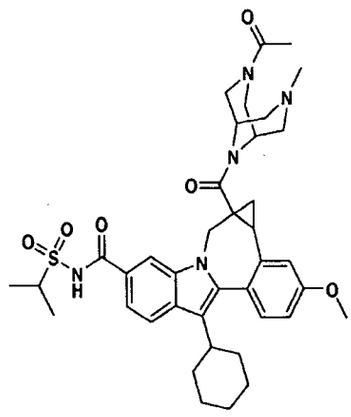
3.39 (m, 1 H), 3.44 (m, 1 H), 3.74 (m, 3 H), 3.91 (m, 4 H), 4.19 (m, 0.25 H), 5.54 (m, 2 H), 5.00 (m, 1.75 H), 7.03 (m, 1 H), 7.18 (m, 1 H), 7.28 (d, J = 8.55, 0.75 H), 7.34 (d, J = 8.55, 0.25 H), 7.53 (m, 0.75 H), 7.60 (m, 0.25 H), 7.86 (d, J = 8.24, 0.75 H), 7.91 (d, J = 8.24, 0.25 H), 8.05 (m, 1 H). CL/EM: m/z 717.43, Rf 1.705 min., 97.7 % de pureza. Los Datos CL se registraron en un equipo de cromatografía líquida Shimadzu CL-10AS con una columna Phenomenex-Luna 10µ, C18, 4.6 x 30mm, usando un detector SPD-10AV UV-Vis en un detector de longitud de onda de 220nM. Las condiciones de elución emplean una relación de flujo de 5 ml/min., un gradiente de solvente A al 100%/solvente B al 0% a solvente A al 0%/solvente B al 100%, un tiempo de gradiente de 2 min., un tiempo de espera de 1 min., y un tiempo de análisis de 3 min. donde el solvente A fue 10% de MeOH/90% de H2O/0.1% de ácido trifluoroacético y el solvente B fue 10% de H2O/90% de MeOH/0.1% de ácido trifluoroacético. Los datos EM se determinaron usando una plataforma de micromasa para CL en el modo de electro-rocío.



000466

1a-((3-Acetil-7-metil-3,7,9-triazabiciclo[3.3.1]non-9-il)carbonil)-8-ciclohexil-N-(isobutilsulfonil)-11-metoxi-1,1a,2,12b-tetrahidrociclopropa[d]indol[2,1-a][2]benzazepin-5-carboxamida. 1H RMN (300 MHz, CD3OD): δ ppm 0.20 (m, 0.25 H), 1.14 (m, 6 H), 1.36 (m, 4 H), 1.64 (m, 1 H), 1.78 (m, 2.75 H), 1.99 (m, 4 H), 2.29 (m, 4 H), 2.63 (m, 2 H), 2.84 (m, 4 H), 2.97 (m, 3 H), 3.18 (m, 1 H), 3.47 (m, 2 H), 3.66 (m, 2 H), 3.88 (m, 4 H), 4.19 (m, 1 H), 4.50 (m, 2 H), 5.05 (m, 1 H), 7.01 (m, 1 H), 7.17 (m, 1 H), 7.29 (m, 1 H), 7.51 - 7.61 (m, 1 H), 7.88 (m, 1 H), 7.96 - 8.06 (m, 1 H). CL/EM: m/z 730.30, Rf 1.787 min., 96.0 % de pureza. Los Datos CL se registraron en un equipo de cromatografía líquida Shimadzu CL-10AS con una columna Phenomenex-Luna 10µ, C18, 4.6 x 30mm, usando un detector SPD-10AV UV-Vis en un detector de longitud de onda de 220nM. Las condiciones de elución emplean una relación de flujo de 5 ml/min., un gradiente de solvente A al 100%/solvente B al 0% a solvente A al 0%/solvente B al 100%, un tiempo de gradiente de 2 min., un tiempo de espera de 1 min., y un tiempo de análisis de 3 min. donde el solvente A fue 10% de MeOH/90% de H2O/0.1% de ácido trifluoroacético y el solvente B fue 10% de H2O/90% de MeOH/0.1% de ácido trifluoroacético. Los datos EM se determinaron usando una plataforma de micromasa para

CL en el modo de electro-rocío.



1a-((3-Acetil-7-metil-3,7,9-triazabiciclo[3.3.1]non-9-il)carbonil)-8-ciclohexil-N-(isopropilsulfonil)-11-metoxi-1,1a,2,12b-tetrahidrociclopropa[d]indol[2,1-a][2]benzazepin-5-carboxamida. 1H RMN (300 MHz, CD3OD): δ ppm 0.20 (m, 0.25 H), 0.98 (m, 2 H), 1.13 (m, 1 H), 1.24 - 1.49 (m, 9 H), 1.65 (m, 0.75 H), 1.83 (m, 2 H), 2.04 (m, 4 H), 2.50 (m, 4 H), 2.67 (m, 1 H), 2.83 (m, 1 H), 2.88 (m, 3 H), 3.01 (m, 3 H), 3.10 (m, 1 H), 3.17 (m, 2 H), 3.72 (m, 2 H), 3.92 (m, 3 H), 3.98 (m, 1 H), 4.50 (m, 1 H), 5.03 (m, 1 H), 7.06 (m, 1 H), 7.21 (m, 1 H), 7.35 (m, 1 H), 7.57 - 7.70 (m, 1 H), 7.92 (m, 1 H), 8.00 - 8.09 (m, 1 H). CL/EM: m/z 716.23, Rf 1.740 min., 98.0 % de pureza. Los Datos CL se registraron en un equipo de cromatografía líquida Shimadzu CL-10AS con una columna Phenomenex-Luna 10µ, C 18, 4.6 x 30mm, usando un detector SPD-10AV UV-Vis en un detector de longitud de onda de 220nM. Las condiciones de elución emplean una relación de flujo de 5 ml/min., un gradiente de solvente A al 100%/solvente B al 0% a

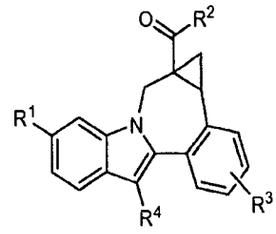
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solvente A al 0%/solvente B al 100%, un tiempo de gradiente de 2 min., un tiempo de espera de 1 min., y un tiempo de análisis de 3 min. donde el solvente A fue 10% de MeOH/90% de H2O/0.1% de ácido trifluoroacético y el solvente B fue 10% de H2O/90% de MeOH/0.1% de ácido trifluoroacético. Los datos EM se determinaron usando una plataforma de micromasa para CL en el modo de electro-rocío.

000469

REIVINDICACIONES

1. Un compuesto de la fórmula I

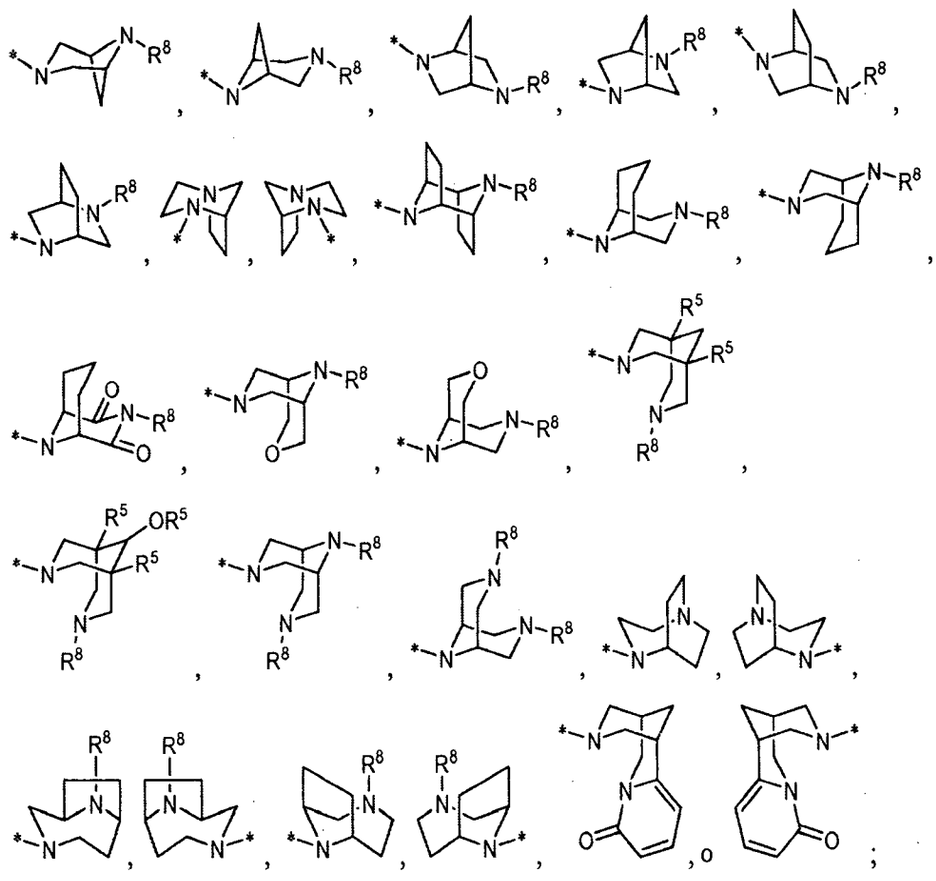


I

caracterizado porque:

R^1 es CO_2R^5 o $CONR^6R^7$;

R^2 es



R^3 es hidrógeno, halo, alquilo, alquenilo, hidroxi, benciloxi, o alcoxi;

R^4 es cicloalquilo;

R^5 es hidrógeno o alquilo;

R^6 es hidrógeno, alquilo, alquiloSO_2, alqueniloSO$_2$, cicloalquiloSO$_2$, (cicloalquilo)alquiloSO$_2$, haloalquiloSO$_2$, $(R^9)(R^{10})NSO_2$, o $(R^{11})SO_2$;

R^7 es hidrógeno o alquilo;

R^8 es hidrógeno, alquilo, cicloalquilo, (cicloalquilo)alquilo, hidroxialquilo, alcoxialquilo, alquilcarbonilo, cicloalquilcarbonilo, haloalquilcarbonilo, alcoxicarbonilo, alquiloSO_2, cicloalquiloSO$_2$, haloalquiloSO$_2$, aminocarbonilo, (alquilamino)carbonilo, (dialquilamino)carbonilo, bencilo, benciloxicarbonilo, o piridinilo;

R^9 es hidrógeno o alquilo;

R^{10} es hidrógeno o alquilo;

R^{11} es azetidinilo, pirrolidinilo, piperidinilo, N-(R^{12})piperazinilo, morfolinilo, tiomorfolinilo, homopiperidinilo, homomorfolinilo, tetrahidrofuranilo, tetrahidropiranilo, (tetrahidrofuranil)alquilo, o (tetrahidropiranil)alquilo; y

R^{12} es hidrógeno o alquilo;

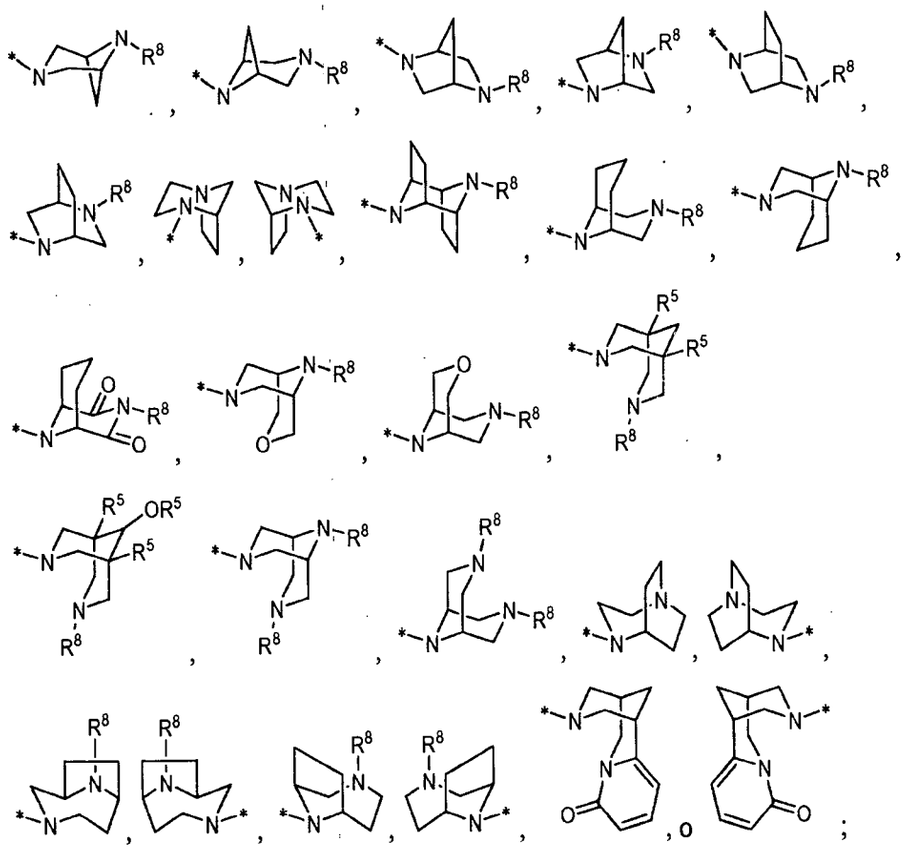
o una sal farmacéuticamente aceptable del mismo.

2. El compuesto de conformidad con la reivindicación 1, caracterizado porque

R^1 es CO_2R^5 o $CONR^6R^7$;

R^2 es

000471



R^3 es hidrógeno, halo, alquilo, alquenilo, hidroxi, benciloxi, o alcoxi;

R^4 es cicloalquilo;

R^5 es hidrógeno o alquilo;

R^6 es hidrógeno, alquilo, alquiloSO_2, alqueniloSO_2, cicloalquiloSO_2, (cicloalquilo)alquiloSO_2, haloalquiloSO_2, $(R^9)(R^{10})NSO_2$, o $(R^{11})SO_2$;

R^7 es hidrógeno o alquilo;

R^8 es hidrógeno, alquilo, cicloalquilo, (cicloalquilo)alquilo, alquilcarbonilo, cicloalquilcarbonilo, haloalquilcarbonilo, alcoxicarbonilo, alquiloSO_2, cicloalquiloSO_2, haloalquiloSO_2, aminocarbonilo, (alquilamino)carbonilo, (dialquilamino)carbonilo,

bencilo, benciloxicarbonilo, o piridinilo;

R^9 es hidrógeno o alquilo;

R^{10} es hidrógeno o alquilo;

R^{11} es azetidinilo, pirrolidinilo, piperidinilo, N-(R^{12})piperazinilo, morfolinilo, tiomorfolinilo, homopiperidinilo, homomorfolinilo, tetrahidrofuranilo, tetrahidropiranilo, (tetrahidrofuranil)alquilo, o (tetrahidropiranil)alquilo; y

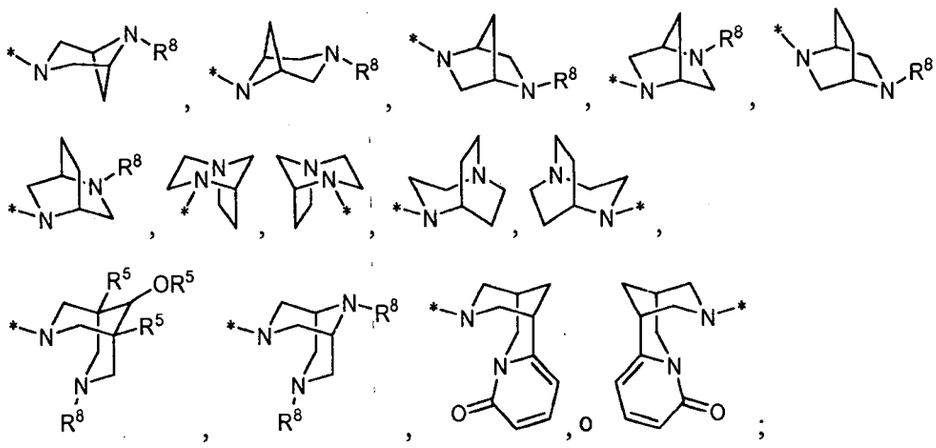
R^{12} es hidrógeno o alquilo;

o una sal farmacéuticamente aceptable del mismo.

3. El compuesto de conformidad con la reivindicación 1, caracterizado porque

R^1 es CO_2R^5 o $CONR^6R^7$;

R^2 es



R^3 es hidrógeno, halo, alquilo, alquenilo, hidroxi, benciloxi, o alcoxi;

R^4 es cicloalquilo;

R^5 es hidrógeno o alquilo;

R^6 es hidrógeno, alquilo, alquiloSO_2, cicloalquiloSO_2, haloalquiloSO_2, (R^9)(R^{10})NSO_2, o (R^{11})SO_2;

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R^7 es hidrógeno o alquilo;

R^8 es hidrógeno, alquilo, cicloalquilo, (cicloalquilo)alquilo, alquilcarbonilo, cicloalquilcarbonilo, haloalquilcarbonilo, alcoxicarbonilo, alquiloSO_2, cicloalquiloSO_2, haloalquiloSO_2, aminocarbonilo, (alquilamino)carbonilo, (dialquilamino)carbonilo, bencilo, benciloxicarbonilo, o piridinilo;

R^9 es hidrógeno o alquilo;

R^{10} es hidrógeno o alquilo;

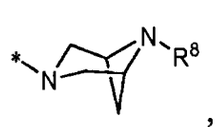
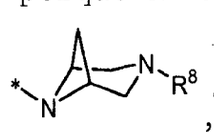
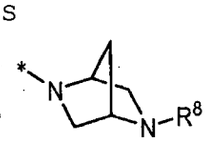
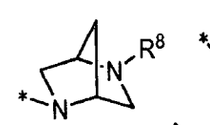
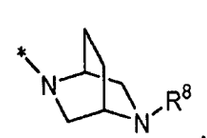
R^{11} es azetidinilo, pirrolidinilo, piperidinilo, N-(R^{12})piperazinilo, morfolinilo, tiomorfolinilo, homopiperidinilo, o homomorfolinilo; y

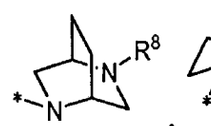
R^{12} es hidrógeno o alquilo;

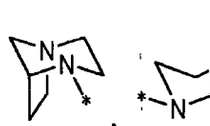
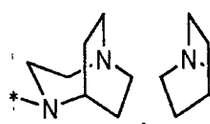
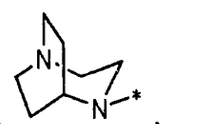
o una sal farmacéuticamente aceptable del mismo.

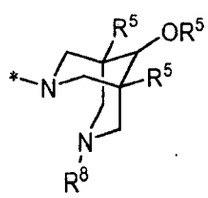
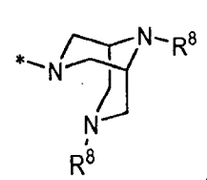
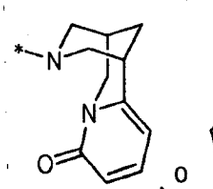
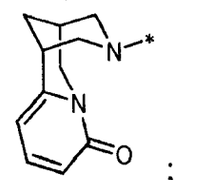
4. El compuesto de conformidad con la reivindicación 1, caracterizado porque R^1 es $CONR^6R^7$; R^6 es alquiloSO_2, cicloalquiloSO_2, haloalquiloSO_2, $(R^9)_2NSO_2$, o $(R^{10})SO_2$; y R^7 es hidrógeno.

5. El compuesto de conformidad con la reivindicación 1, caracterizado porque R^2 es


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R^{11} es azetidinilo, pirrolidinilo, piperidinilo, N-(R^{12})piperazinilo, morfolinilo, tiomorfolinilo, homopiperidinilo, o homomorfolinilo.

6. El compuesto de conformidad con la reivindicación 1, caracterizado porque R^3 es hidrógeno.

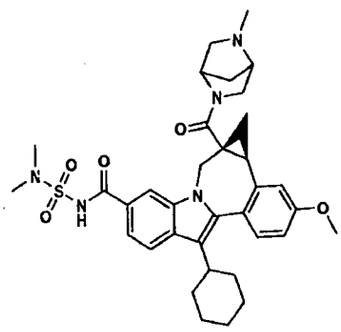
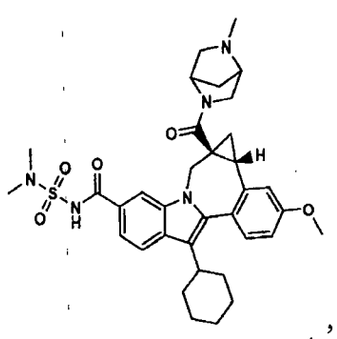
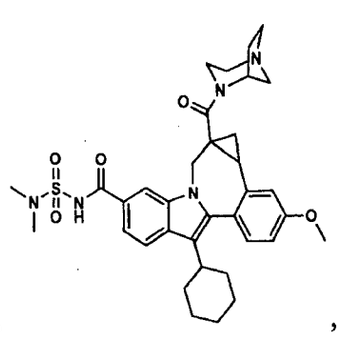
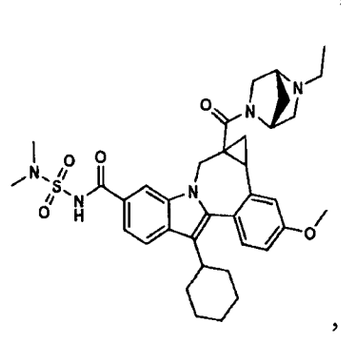
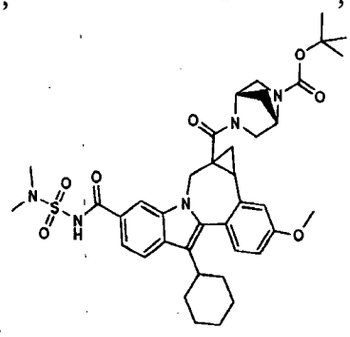
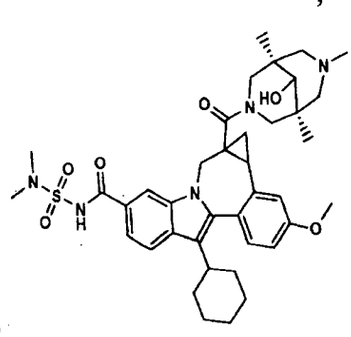
7. El compuesto de conformidad con la reivindicación 1, caracterizado porque R^3 es metoxi.

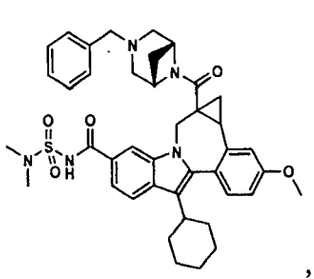
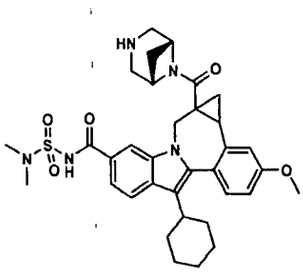
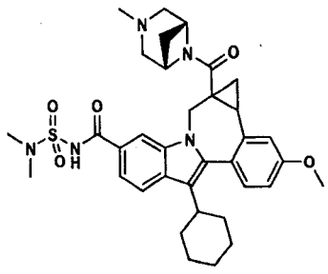
8. El compuesto de conformidad con la reivindicación 1, caracterizado porque R^4 es ciclohexilo.

9. El compuesto de conformidad con la reivindicación 1, caracterizado porque R^6 es $(R^9)(R^{10})NSO_2$ o $(R^{11})SO_2$.

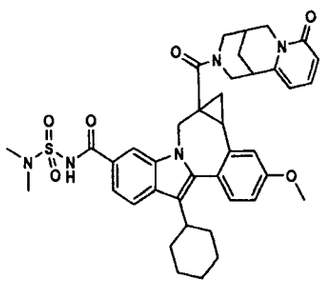
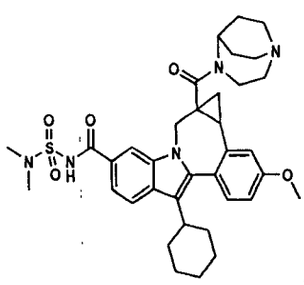
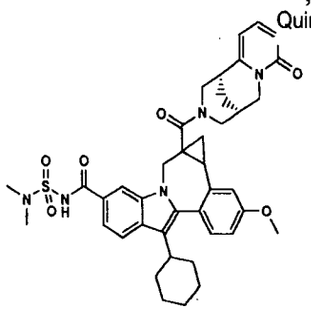
10. El compuesto de conformidad con la reivindicación 1, caracterizado porque R^8 es alquilo o alcoxialquilo.

11. El compuesto de conformidad con la reivindicación 1, caracterizado porque se selecciona del grupo que consiste de

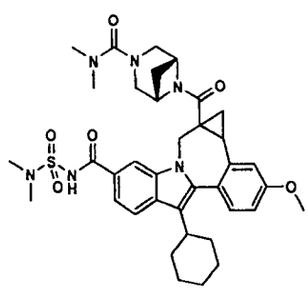
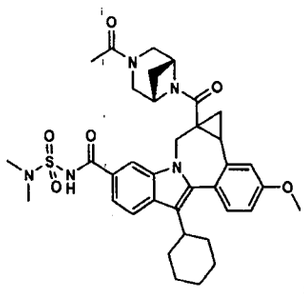
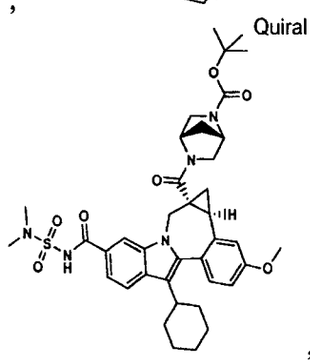

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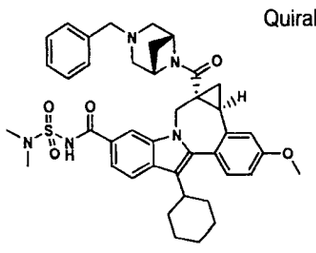
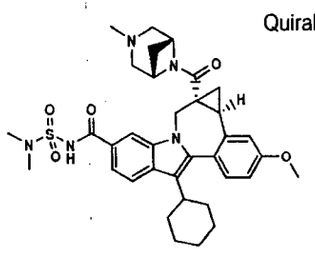
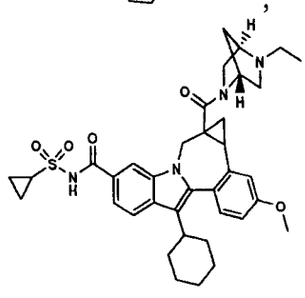

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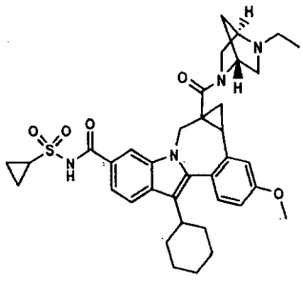
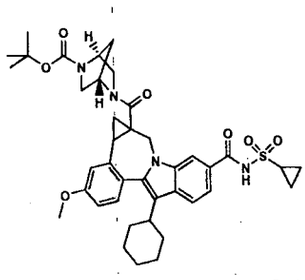
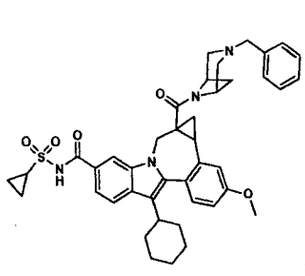
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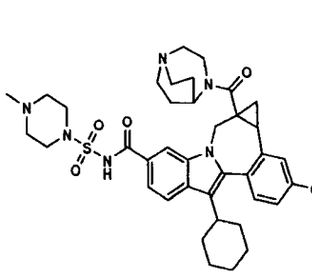
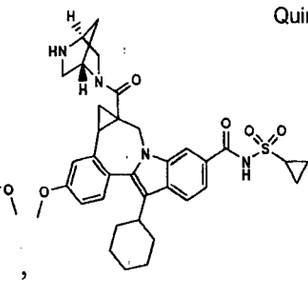
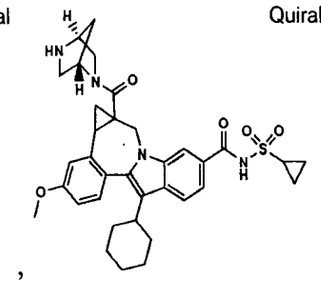

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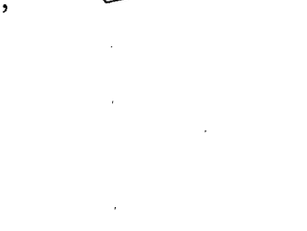

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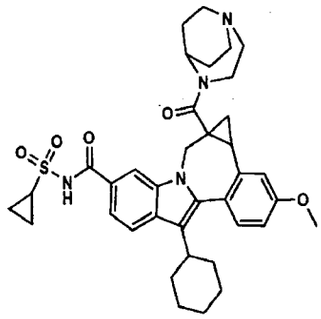
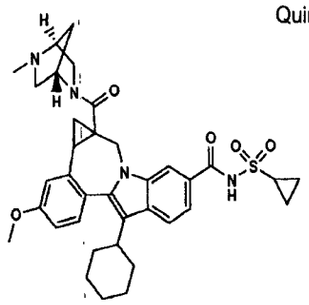
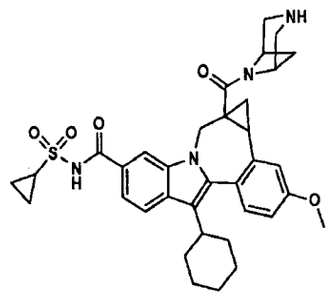
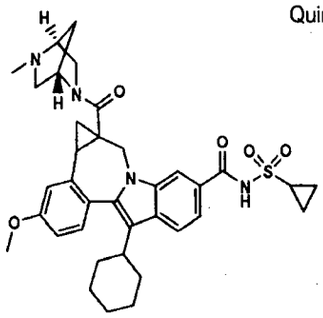
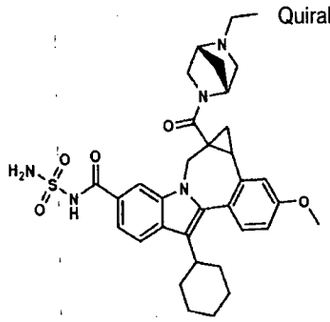
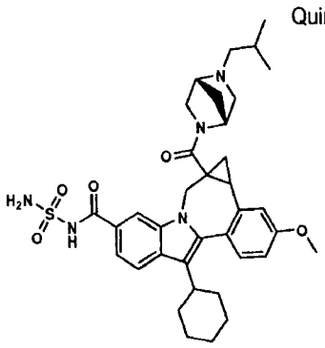
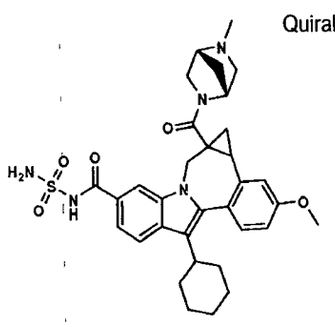
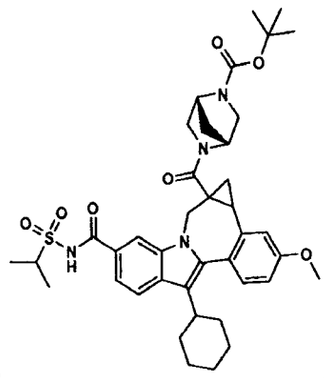
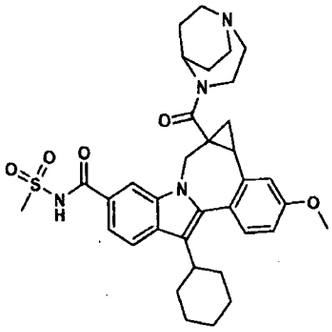
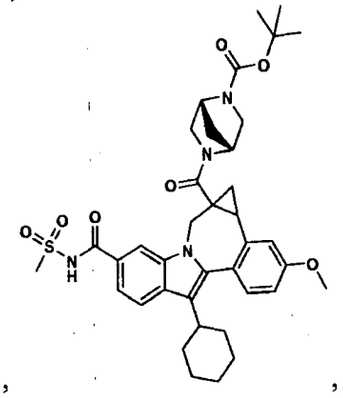
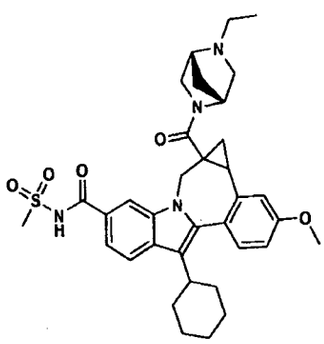
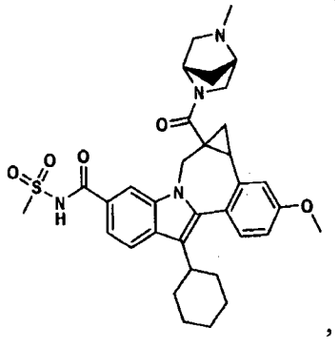

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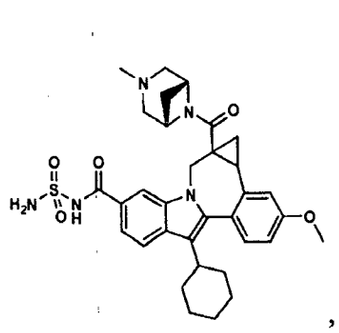
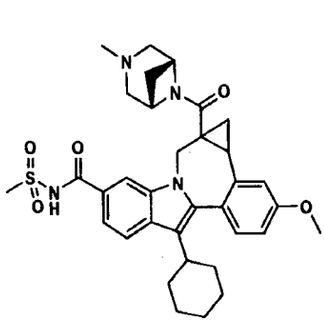
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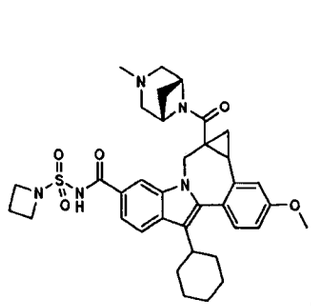
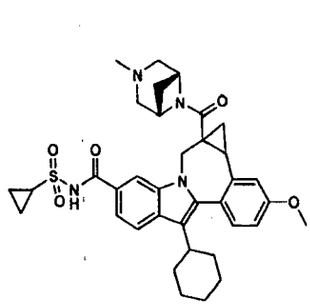
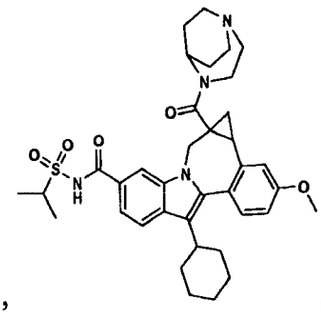
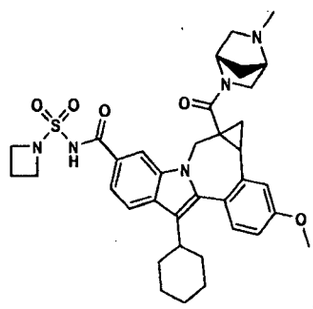
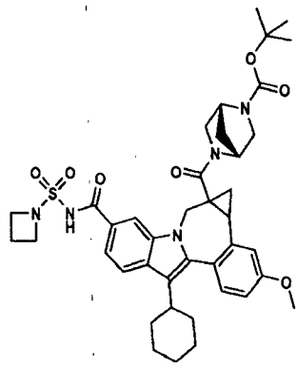
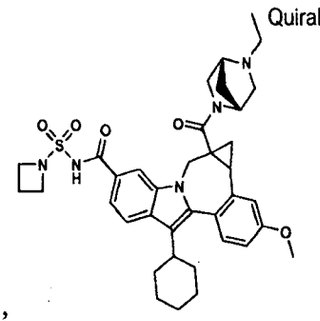
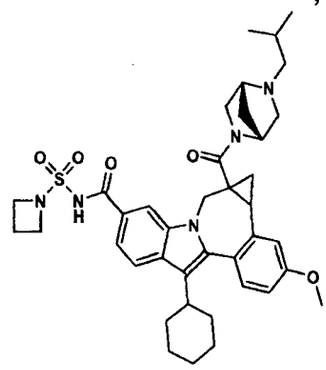
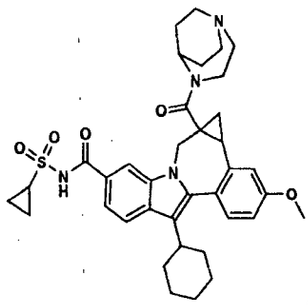
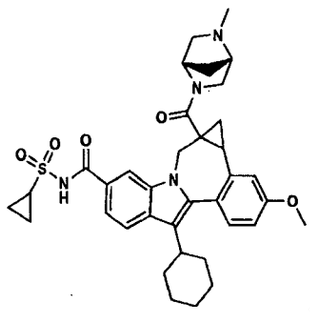
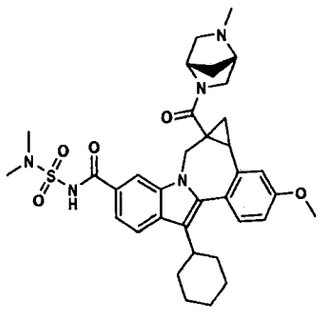
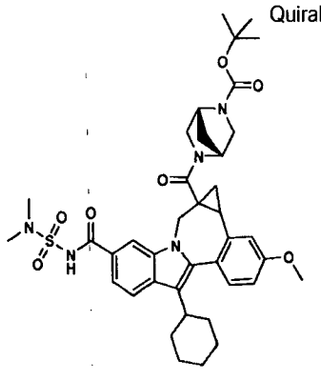
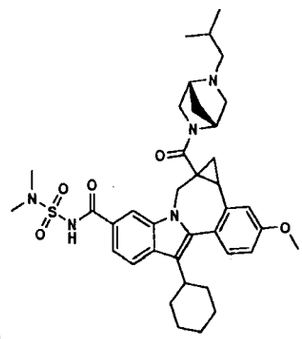
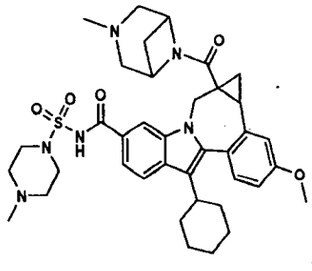
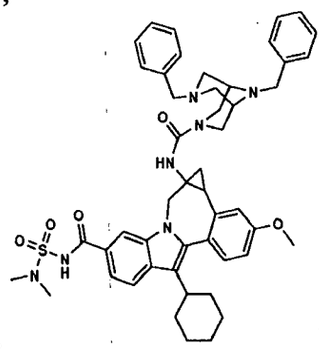
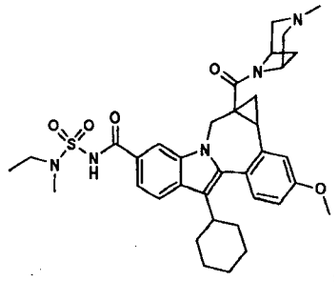
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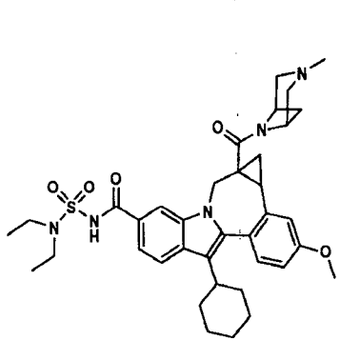

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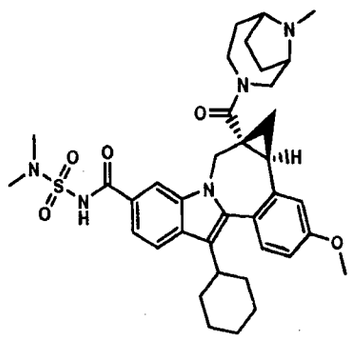
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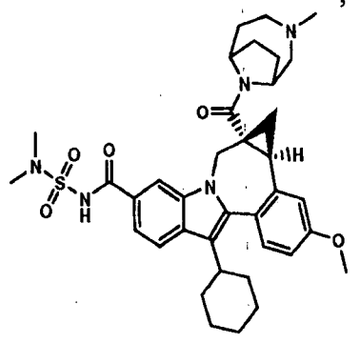
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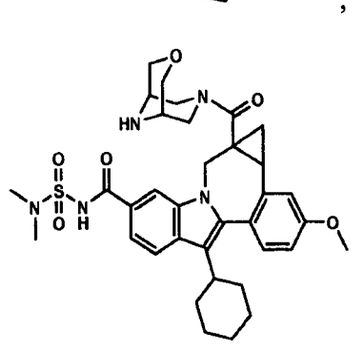
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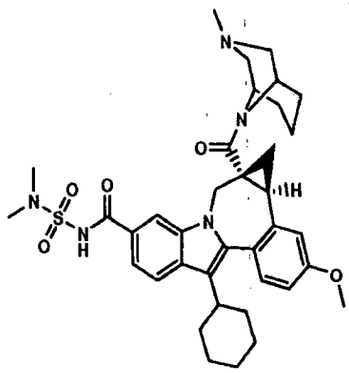

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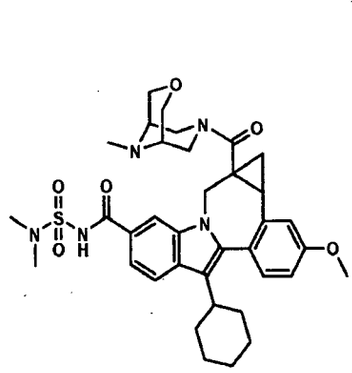


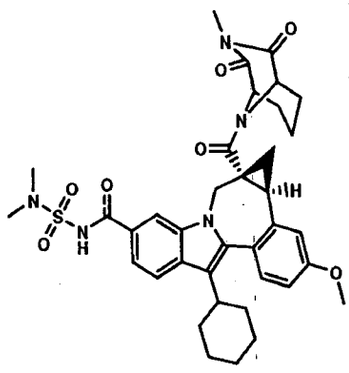


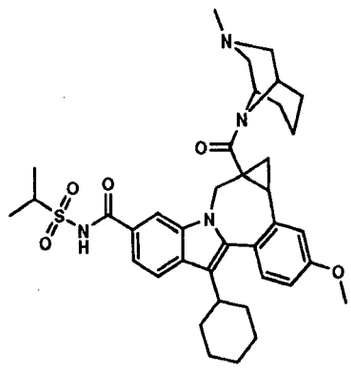


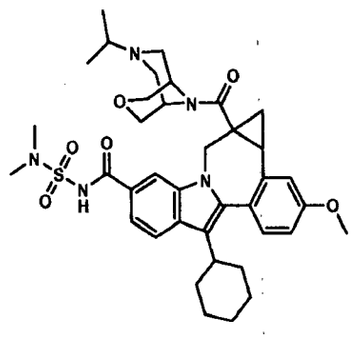


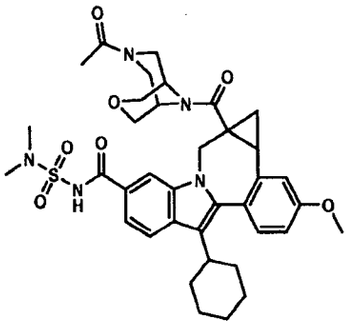


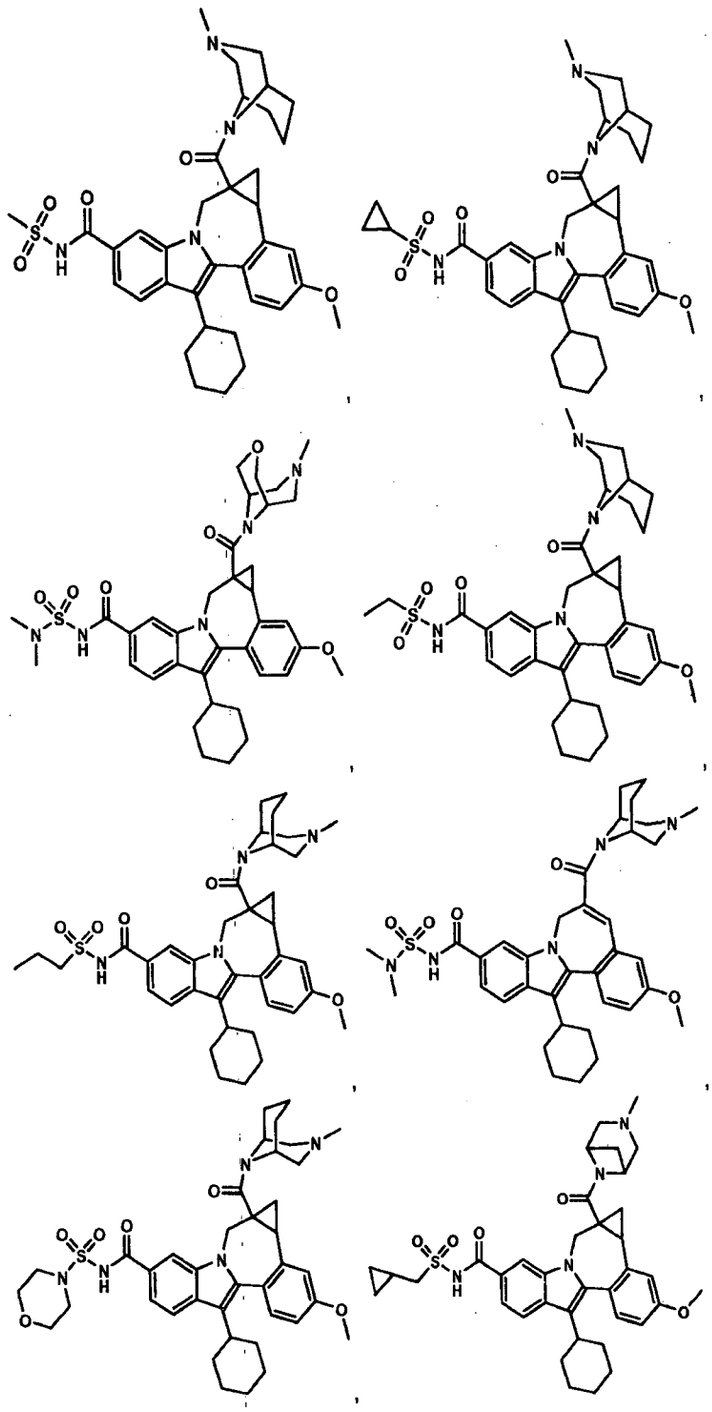


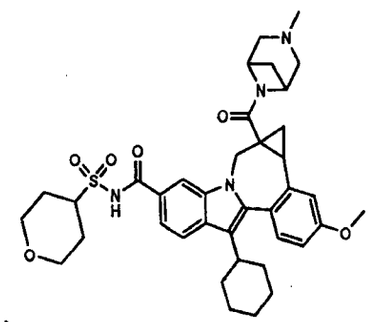
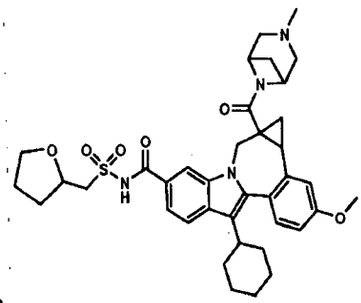


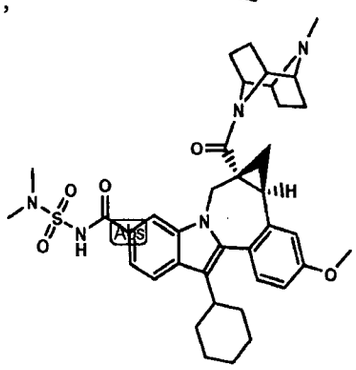
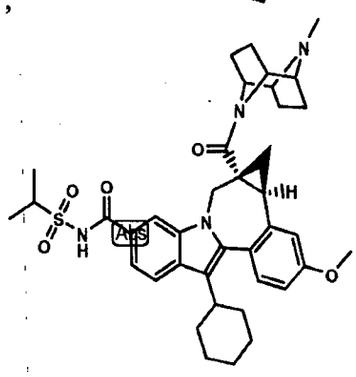


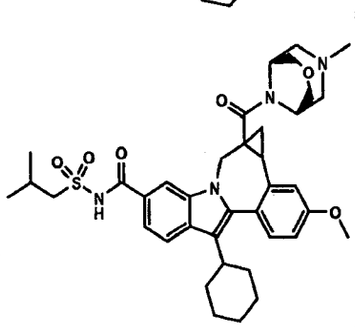
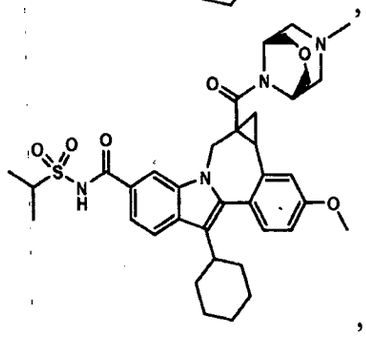


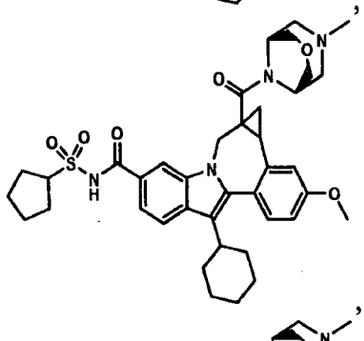
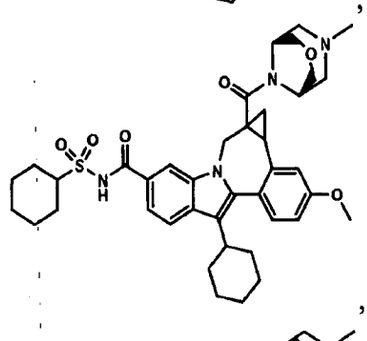


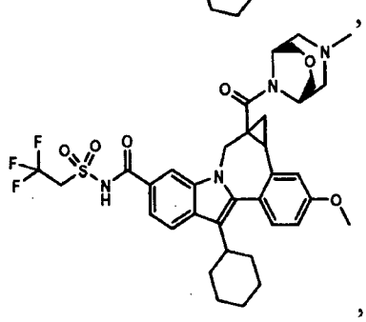
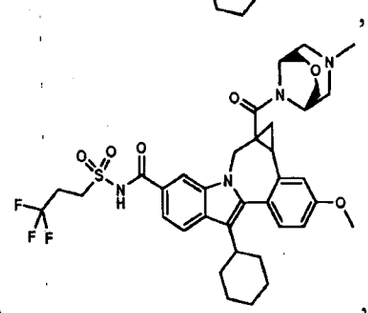
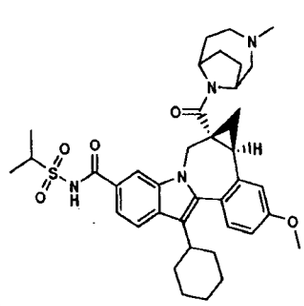



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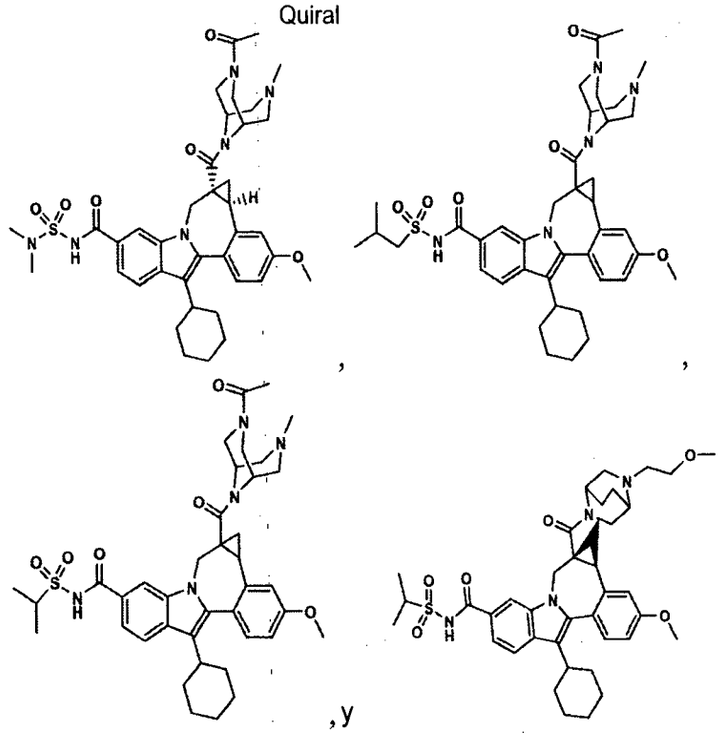

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o una sal farmacéuticamente aceptable del mismo.

12. Una composición caracterizada porque comprende el compuesto de conformidad con la reivindicación 1, o una sal farmacéuticamente aceptable del mismo y un portador farmacéuticamente aceptable.

13. La composición de conformidad con la reivindicación 12, caracterizada además porque comprende al menos un compuesto adicional que tiene beneficios terapéuticos para el VHC en donde el compuesto se selecciona del grupo que consiste de interferones, cicloesporinas, interleucias, inhibidores de metaloproteasa VHC, inhibidores de serina proteasa del VHC, inhibidores de polimerasa del VHC, inhibidores de helicasa del VHC, inhibidores de la proteína del VHC NS4B, inhibidores de entrada del VHC, inhibidores del ensamble del VHC, inhibidores

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de salida del VHC, inhibidores de la proteína del VHC NS5A, inhibidores de la proteína del VHC NS5B e inhibidores del replicón del VHC.

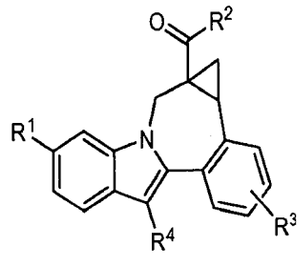
14. Un método para tratar la infección de hepatitis C, caracterizado porque comprende administrar una cantidad terapéuticamente efectiva del compuesto de conformidad con la reivindicación 1 a un paciente.

15. El método de conformidad con la reivindicación 14, caracterizado además porque comprende administrar al menos un compuesto adicional que tiene beneficios terapéuticos para el VHC, en donde el compuesto se selecciona del grupo que consiste de interferones, cicloesporinas, interleucias, inhibidores de metaloproteasa del VHC, inhibidores de serina proteasa del VHC, inhibidores de polimerasa del VHC, inhibidores de helicasa del VHC, inhibidores de la proteína HCV NS4B, inhibidores de entrada de del VHC, inhibidores del ensamble del VHC, inhibidores de salida del VHC, inhibidores de la proteína del VHC NS5A, inhibidores de la proteína del VHC NS5B e inhibidores del replicón del VHC.

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RESUMEN DE LA INVENCION

La invención abarca los compuestos de la fórmula I, incluyendo sales farmacéuticamente aceptables,



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así como composiciones y métodos de uso de estos compuestos. Los compuestos tienen actividad contra el virus de hepatitis C (VHC) y son útiles en tratar a aquéllos infectados con el VHC.

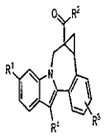
Industria y Comercio
SUPERINTENDENCIA

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

(21) N° de solicitud:	(51) Int Cl: C07D 487; A61K 31/55 ; A61P 31/12
22) Fecha de solicitud:	(71)Solicitante(s) BRISTOL-MYERS SQUIBB COMPANY
(30) Prioridad (31) ***No.*** 32) ***Fecha*** (33) ***País*** 60/894,887 14.03.2007 US 60/989,474 21.11.2007 US	(72) Inventor(es) GENTLES, Robert G.; ZHENG, Xiaofan; Y OTROS
	(74) Apoderado: **ALVARO CORREA ORDOÑEZ**
(85) Fecha limite inicio fase nacional: 14.10.2009 (86) Datos relativos a la presentación de la solicitud PCT Fecha de presentación de la solicitud: 05.03.2008 No. de solicitud PCT/US2008/055893	(87) Publicación internacional Fecha: 18.09.2008 N° publicación: WO/2008/112473
(54) Titulo: COMPUESTOS PARA EL TRATAMIENTO DE HEPATITIS C	

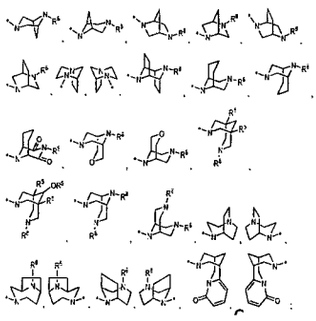
Reivindicación(es):

1. Un compuesto de la fórmula I



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caracterizado porque:
R1 es CO2R5 o CONR6R7;
R2 es



R3 es hidrógeno, halo, alquilo, alquenilo, hidroxi, benciloxi, o alcoxi;
R4 es cicloalquilo;
R5 es hidrógeno o alquilo;
R6 es hidrógeno, alquilo, alquiloSO2, alqueniloSO2, cicloalquiloSO2, (cicloalquilo)alquiloSO2, haloalquiloSO2, (R9)(R10)NSO2, o (R11)SO2;
R7 es hidrógeno o alquilo;
R8 es hidrógeno, alquilo, cicloalquilo, (cicloalquilo)alquilo, hidroxialquilo, alcoxialquilo, alquilcarbonilo, cicloalquilcarbonilo, haloalquilcarbonilo, alcoxicarbonilo, alquiloSO2, cicloalquiloSO2, haloalquiloSO2, aminocarbonilo, (alquilamino)carbonilo, (dialquilamino)carbonilo, bencilo, benciloxicarbonilo, o piridinilo;
R9 es hidrógeno o alquilo;
R10 es hidrógeno o alquilo;
R11 es azetidinilo, pirrolidinilo, piperidinilo, N-(R12)piperazinilo, morfolinilo, tiomorfolinilo, homopiperidinilo, homomorfolinilo, tetrahidrofuranilo, tetrahidropiranilo, (tetrahidrofuranil)alquilo, o (tetrahidropiranil)alquilo; y
R12 es hidrógeno o alquilo;
o una sal farmacéuticamente aceptable del mismo.

485

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

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

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

(51) Clasificación Internacional : C07D 487; A61K 31/55 ; A61P 31/12

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

(72) Inventor(es) GENTLES, Robert G.; ZHENG, Xiaofan; DING, Mm; TU, Yong; HAN, Ying; HEWAWASAM, Piyasena; KADOW, John F.; BENDER, John A.; YEUNG, Kap-sun; GRANT-YOUNG, Katharine A.; HUDYMA, Thomas W.

(74) Apoderado: ALVARO CORREA ORDOÑEZ

(30) Prioridad	(31) *No. Prioridad*	32) *Fecha*	(33) *País*
	60/894,887	14.03.2007	US
	60/989,474	21.11.2007	US

(85) Fecha inicio fase nacional: 14.10.2009

(86) Datos relativos a la presentación de la solicitud PCT
Fecha de presentación de la solicitud: 05.03.2008
No. de solicitud PCT/US2008/055893

(87) Publicación internacional
Fecha: 18.09.2008
N° publicación: WO/2008/112473

(54) Titulo: COMPUESTOS PARA EL TRATAMIENTO DE HEPATITIS C

Industria y Comercio
SUPERINTENDENCIA

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

SUPERINTENDENCIA PATENTE DE INVENCION ___ PCT X MODELO DE UTILIDAD ___ DISEÑO INDUSTRIAL ___

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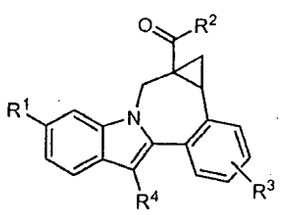
(74) Apoderado: ALVARO CORREA ORDOÑEZ

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(31) *No. Prioridad*	32) *Fecha*	(33) *País*
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60/989,474	21.11.2007	US

(85) Fecha límite inicio fase nacional: 14.10.2009
(86) Datos relativos a la presentación de la solic. PCT
Fecha de presentación de la solicitud:05.03.2008
No. de solicitud PCT/US2008/055893

(87) Publicación internacional:
Fecha: 18.09.2008
No. Publicación : WO/2008/112473



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(54) Titulo: COMPUESTOS PARA EL TRATAMIENTO DE HEPATITIS C

(57) Resumen: La invención abarca los compuestos de la fórmula I, incluyendo sales farmacéuticamente aceptables, así como composiciones y métodos de uso de estos compuestos. Los compuestos tienen actividad contra el virus de hepatitis C (VHC) y son útiles en tratar a aquéllos infectados con el VHC.

NIT : 800176089-2

2009/009 487

RECIBO OFICIAL DE CAJA : 9 - 48,664
FECHA : JULIO 6 DE 2009

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

DEPOSITANTE	TIPO PAGO	BANCO	CUENTA	No. PAGO	FECHA PGO	Vr. PAGO
BAKER & MCKENZIE	RECIBO DE CAJA			48090	03/07/2009	85,400,500.00

***** 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	540,000.00
		TOTAL : $	540,000.00

SON: QUINIENTOS CUARENTA MIL PESOS

RESPONSABLE : _____

RECIBO DE CAJA APLICADO AL ASUNTO No.

SUPERINTENDENCIA DE INDUSTRIA Y COMERCIO

No. 09-097263- -00000-0000

Fecha: 2009-09-10 15:53:08 Dep. 2020 NUECREACIONE
Tra. 11 PATENTEIYII Eve: 378 FASENACIONALI
Act. 411 PRESENTACION Folios: 487

Industria y Comercio

SUPERINTENDENCIA

Delegatura de Propiedad Industrial
División de Nuevas Creaciones

REQUISITOS NECESARIOS PARA PRESENTACIÓN Y AGILIZACIÓN DEL TRAMITE

	USUARIO	RADICADOR
PATENTE DE INVENCIÓN (X) MODELO DE UTILIDAD ( )	( )	(X)
-Indicación de que se solicita la concesión de una patente.	(X)	(X)
-Datos de identificación del solicitante o de la persona que se presenta la solicitud.	(X)	(X)
-Descripción de la invención.	(X)	(X)
-Dibujos de ser estos pertinentes.	(X)	(X)
-Comprobante de Pago de las tasas establecidas.	(X)	(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 se 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 Diseño Industrial.	( )	( )
-Datos de identificación del solicitante o de la persona que se presenta la solicitud.	( )	( )
-Representación gráfica del Esquema Trazado.	( )	( )
-Comprobante de Pago de las tasas establecidas.	( )	( )
COMPLETA ( ) INCOMPLETA		

Firma Responsable: _____

Fecha: _____

SUPERINTENDENCIA DE INDUSTRIA Y COMERCIO

No. 09-097263- -00000-0000

Fecha: 2009-09-10 15:53:08 Dep. 2020 NUECREACIONI
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REPUBLICA DE COLOMBIA
SUPERINTENDENCIA DE INDUSTRIA Y COMERCIO

Bogotá,
2020

Doctor(a)
CORREA ORDOÑEZ ALVARO
Apoderado(a) y/o Representante de
BRISTOL - MYERS SQUIBB COMPANY

REFERENCIA	Radicación No.	9 97263
	Solicitud internacional	PCT/US2008/055893
	Fecha inicio fase nacional	14/10/2009
	Trámite	11
	Evento	378
	Actuación	430
	Oficio No.	11590

Como resultado del examen de forma, realizado con fundamento en el artículo 38 de la Decisión 486 de la Comisión de la Comunidad Andina, artículo 27 del Tratado de Cooperación en Materia de Patentes (PCT), regla 51 bis del Reglamento y Circular Única de la Superintendencia de Industria y Comercio, se le comunica que:

1. La solicitud no contiene la copia del documento en que consta la cesión del derecho a la patente del inventor al solicitante o a su causante, conforme a lo establecido por el artículo 26 literal k) de la Decisión 486 de la Comisión de la Comunidad Andina. Cuando se trate de documentos otorgados en el extranjero, estos deberán legalizarse de conformidad con lo dispuesto por los artículos 259 y 260 del Código de Procedimiento Civil. Cuando se trate de las declaraciones a que hace referencia la Regla 4.17 ii) del Tratado de Cooperación en Materia de Patentes PCT., el alcance de las tales declaraciones se determinará según indiquen claramente una cesión de derechos del inventor al solicitante o su causante, de conformidad con lo dispuesto en el numeral 5.2.15 del Capítulo Quinto, Título X de la Circular Única de Superintendencia de Industria y Comercio.

En cumplimiento de lo dispuesto por el artículo 39 de la Decisión 486, se le requiere para que dentro del término de dos meses siguientes a la fecha de notificación del presente oficio, complete los requisitos anteriormente enunciados. En caso de no dar cumplimiento al presente requerimiento, la solicitud se considerará abandonada y perderá su prelación.

Notifíquese el presente oficio conforme a lo dispuesto en el numeral 5.2, literal e), del capítulo quinto del título primero de la Circular Unica No.10 de 2001.

ALIX CARMENZA CESPEDES DE VERGEL
Jefe de la división de Nuevas Creaciones

El anterior requerimiento fue notificado por fijación en lista de fecha 16 OCT. 2009
adpa11