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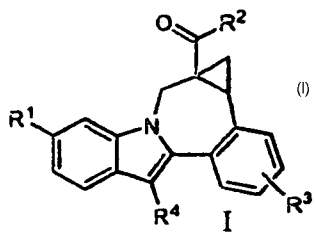

(57) Abstract: The invention encompasses compounds of formula (I) as well as compositions and methods of using the compounds. The compounds have activity against hepatitis C virus (HCV) and are useful in treating those infected with HCV.

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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 60/894884 filed March 14, 2007 and 60/989470 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.

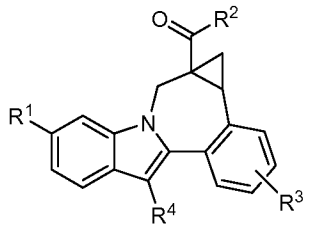
The single strand HCV RNA genome is approximately 9500 nucleotides in length and has a single open reading frame (ORF) encoding a single large polyprotein of about 3000 amino acids. In infected cells, this polyprotein is cleaved at multiple sites by cellular and viral proteases to produce the structural 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 a [4.4.0], [4.3.0] or [3.3.0] bicyclic diamine attached to the carbonyl through one nitrogen, and is substituted with 0-2 R^8 substituents;

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, (cycloalkyl)carbonyl, alkoxycarbonyl, aminocarbonyl, (alkylamino)carbonyl, (dialkylamino)carbonyl, (R^{12})carbonyl, benzyl, or benzyloxycarbonyl;

R^9 is hydrogen or alkyl;

R^{10} is hydrogen or alkyl;

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

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

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 a [4.3.0] or [3.3.0] bicyclic diamine attached to the carbonyl through one nitrogen, and is substituted with 0-2 R^8 substituents;

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, (cycloalkyl)carbonyl, alkoxycarbonyl, aminocarbonyl, (alkylamino)carbonyl, (dialkylamino)carbonyl, (R^{12})carbonyl, benzyl, or benzyloxycarbonyl;

R^9 is hydrogen or alkyl;

R^{10} is hydrogen or alkyl;

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

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

Another aspect of the invention is a compound of formula I where R^1 is $CONR^6R^7$; R^6 is $alkylSO_2$, $cycloalkylSO_2$, $haloalkylSO_2$, $(R^9)(R^{10})NSO_2$, or $(R^{11})SO_2$; and R^7 is hydrogen.

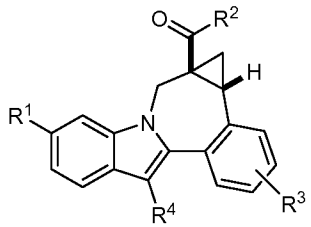
Another aspect of the invention is a compound of formula I where R^3 is hydrogen.

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

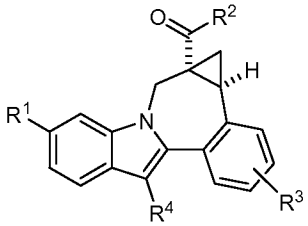
Another aspect of the invention is a compound of formula I where R^4 is cyclohexyl.

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.



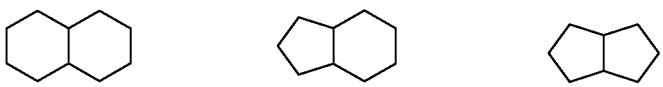
Another aspect of the invention is a compound of formula I according to the following stereochemistry.



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}, and 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.

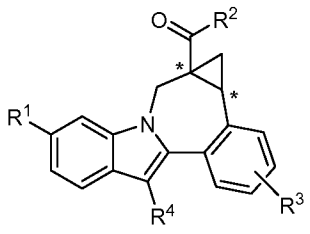
A [4.4.0], [4.3.0] or [3.3.0] bicyclic diamine has one of the ring systems shown where two carbon atoms of the ring system have been replaced with nitrogens.



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. The use of wedges or hashes in the depictions of molecular structures in the following schemes and tables is intended only to indicate relative stereochemistry, and should not be interpreted as implying absolute stereochemical assignments.



Synthetic Methods

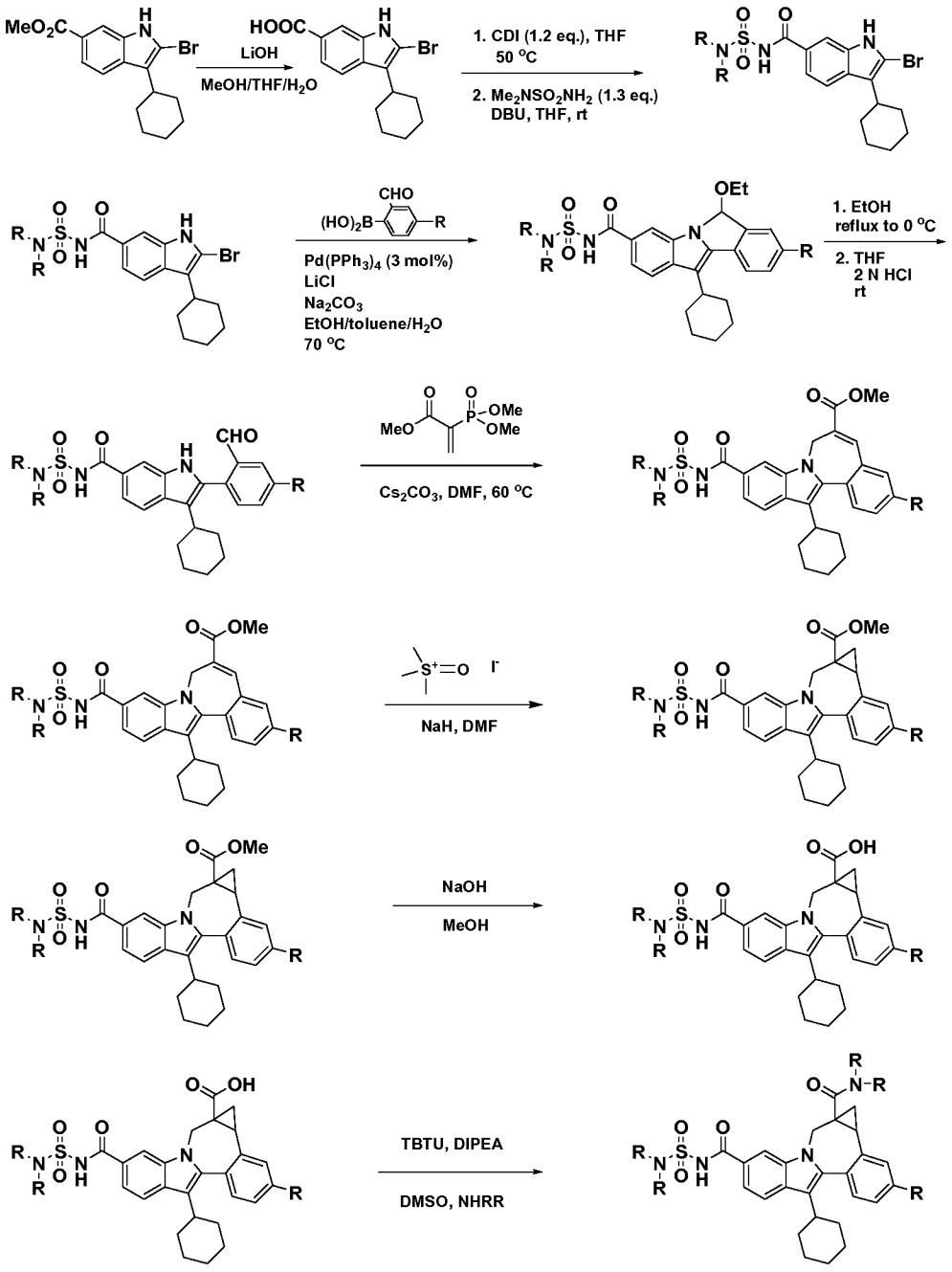
The compounds may be made by methods known in the art including those described below. Some reagents and intermediates are known in the art. Other reagents and intermediates can be made by methods known in the art using readily available materials. The variables (e.g. numbered "R" substituents) used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

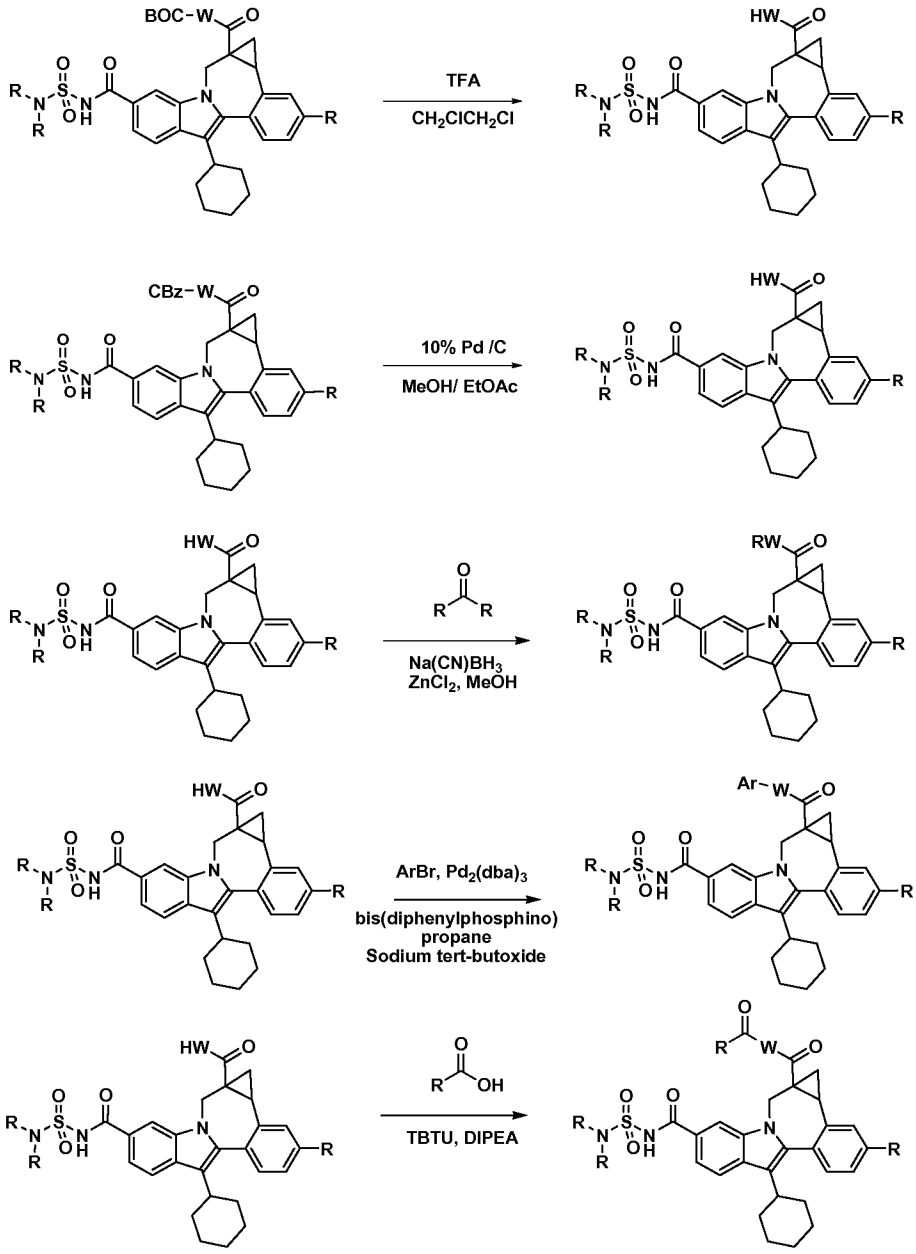
Related fused cyclopropyl ester derivatives can be generated by methods known in the art, including treatment of the indolobenzazepine esters with trimethyl sulfoxonium iodide under strongly basic conditions in DMSO. The residual aliphatic ester moiety in the resultant fused cyclopropanes can be hydrolyzed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

Scheme1.



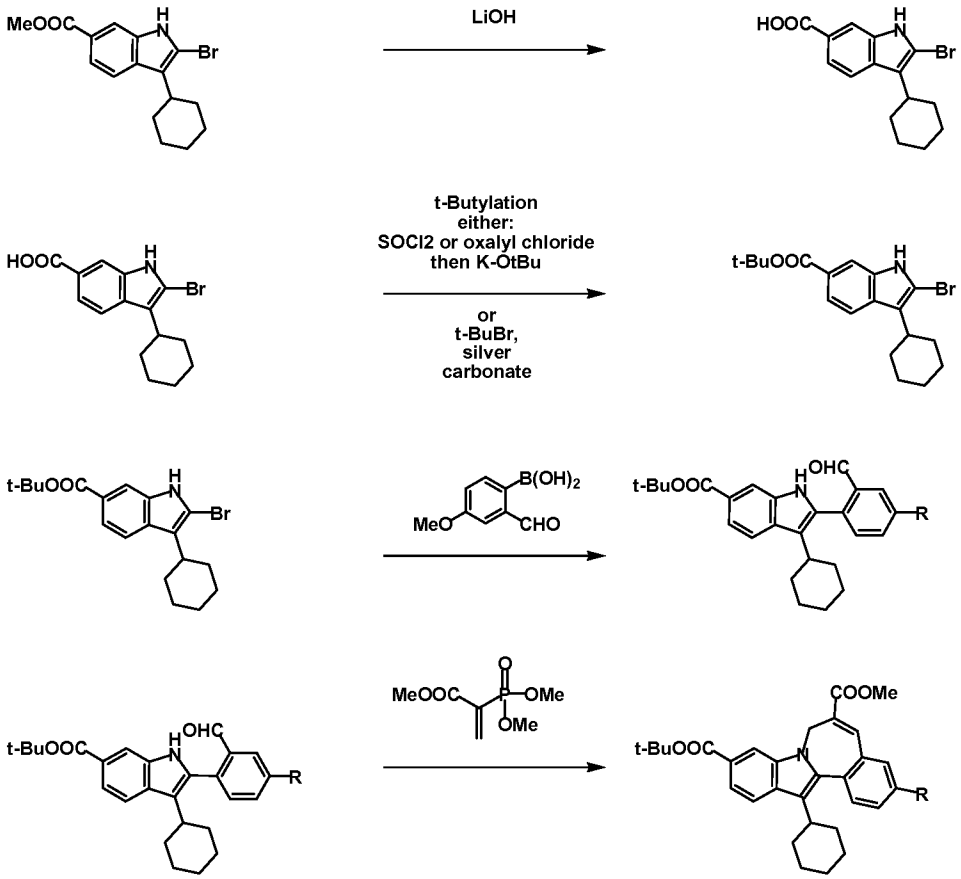
N-protected diamines can also be coupled to the intermediate indolobenzazepine acids and the resultant diamine carboxamides can be deprotected using methods known in the art and derivatized using a variety of synthetic protocols, some illustrative examples of which are shown below (See Scheme 2).

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.

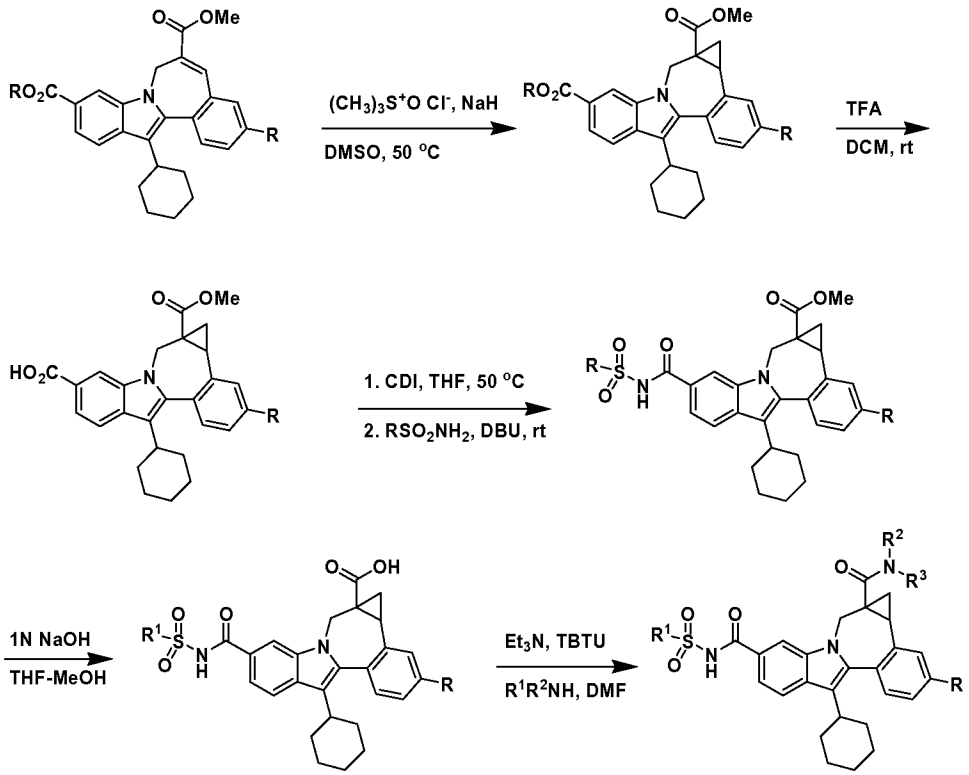


This methodology involves base catalyzed hydrolysis of the indole methyl ester shown, followed by its reaction with either thionyl chloride and potassium tertiary butoxide, or alkylation with silver carbonate and tertiary butyl bromides. The resultant compound can be transformed using chemistry analogous 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-fused 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-fused diamines. For example, O-(1H-benzotriazol-1-yl)-N,N,

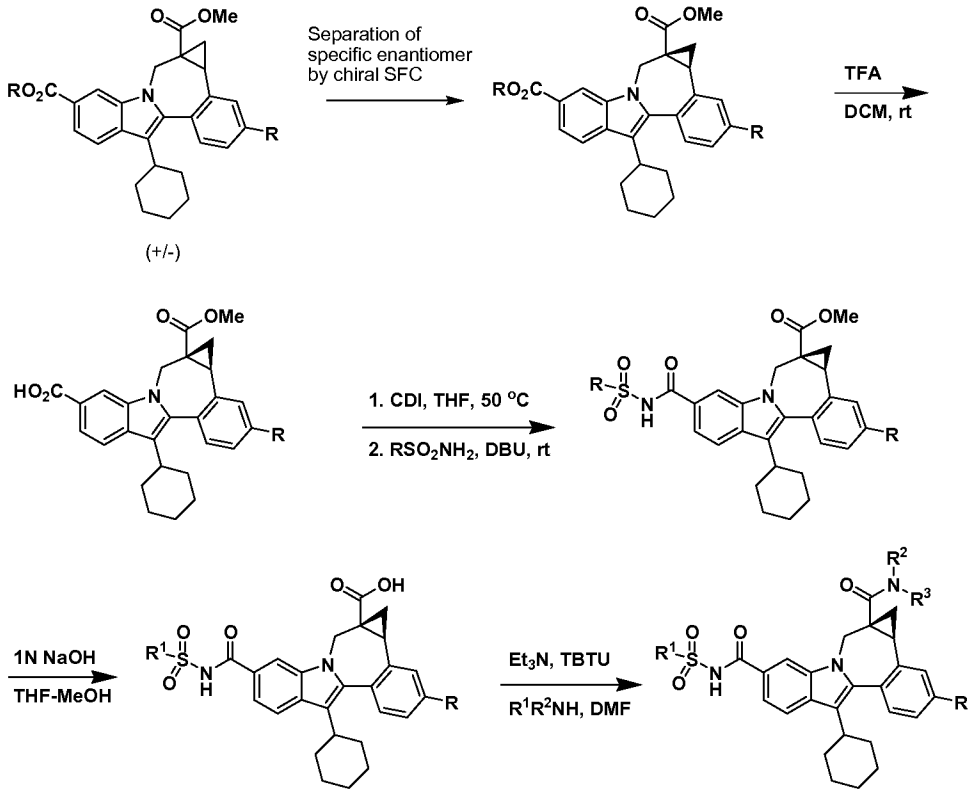
N',N'-tetramethyluronium tetrafluoroborate and diisopropyl ethyl amine in DMSO can give the alkyl fused diamine carboxamides.

Scheme 4.



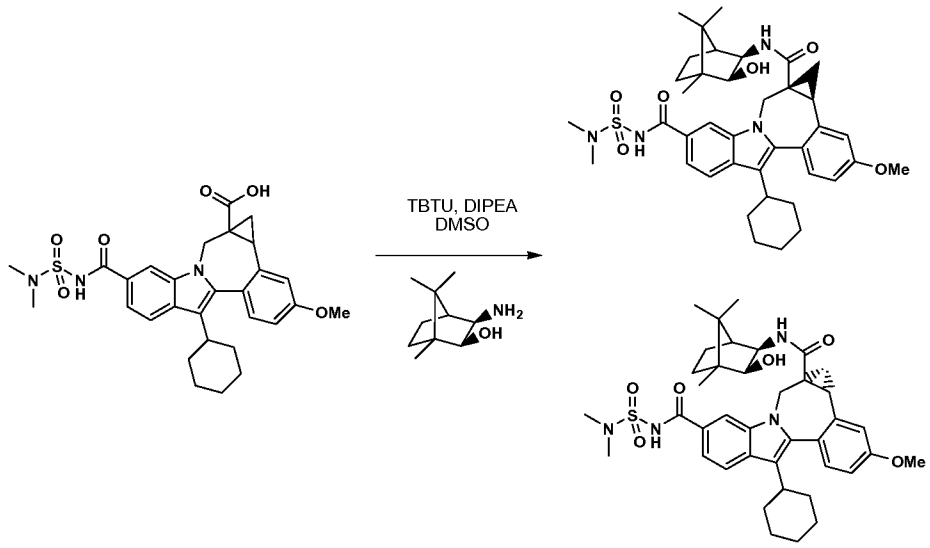
Some examples exist as stereoisomeric mixtures. The invention encompasses all stereoisomers of the compounds. Methods of fractionating stereoisomeric mixtures are well known in the art, and include but are not limited to; preparative chiral supercritical fluid chromatography (SFC) and chiral high performance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

Scheme 5.



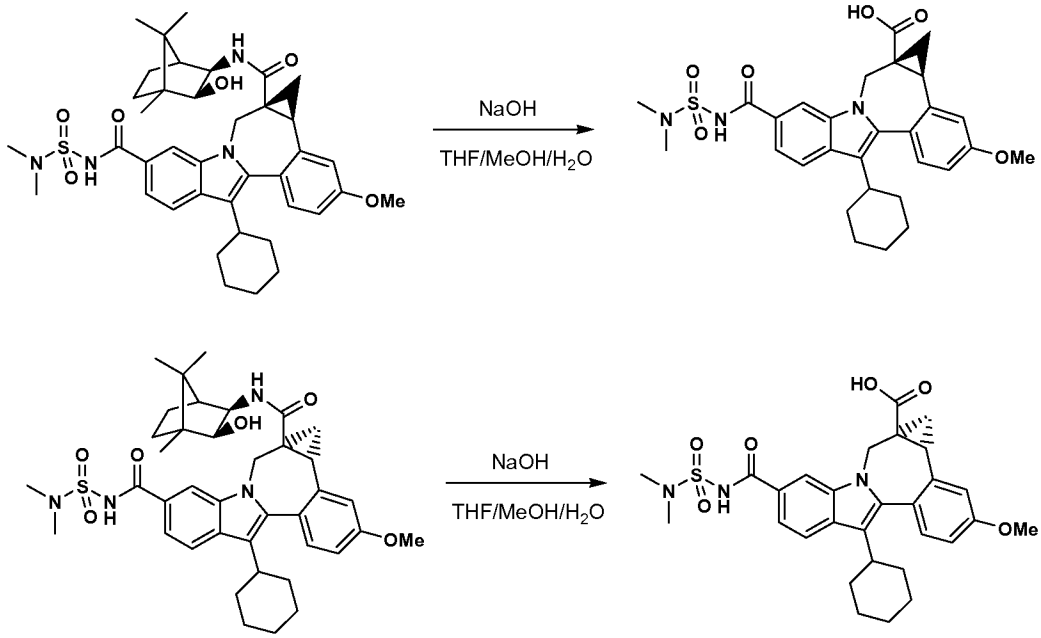
An additional method to achieve such separations involves the preparation of mixtures of diastereomers which can be separated using a variety of methods known in the art. One example of this approach is shown below (Scheme 6).

Scheme 6.



Some diastereomeric amides can be separated using reverse phase HPLC. After hydroysis, the resultant optically active acids can be coupled with fused diamine derivatives (Scheme 6). 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 fused carboxamides. Other standard acid amine coupling methods can also be used to give optically active carboxamides.

Scheme 6.



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.

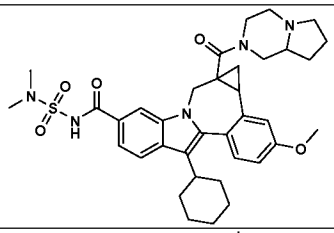
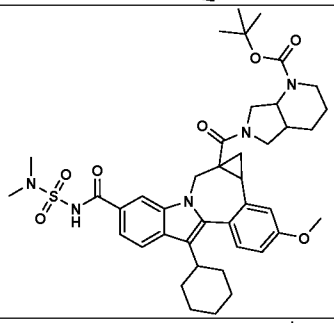
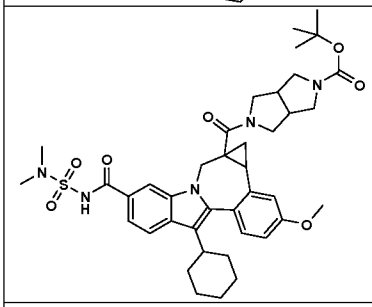
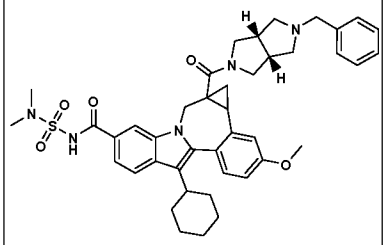
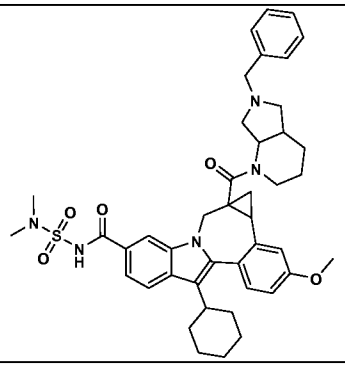
Assays. Subsequent to addition of the test compounds described above (FRET Assay Preparation), at various times the plate was removed and Alamar blue solution (Trek Diagnostics, #00-100) was added to measure cellular toxicity. After

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.

Table 1.

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

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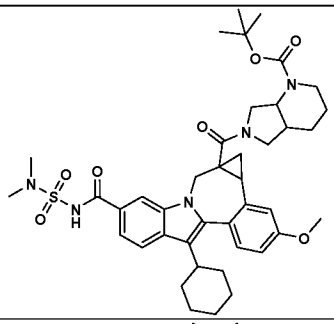
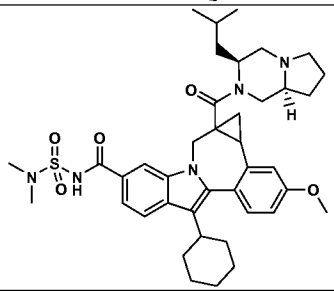
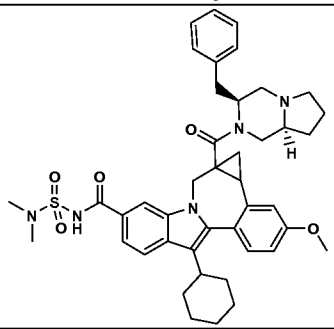
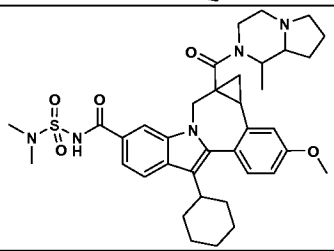
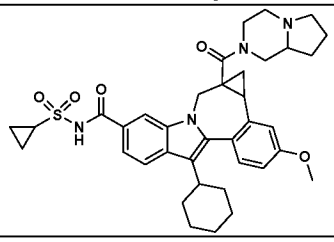
	B	B
	B	B
	B	B
	B	B
	B	B

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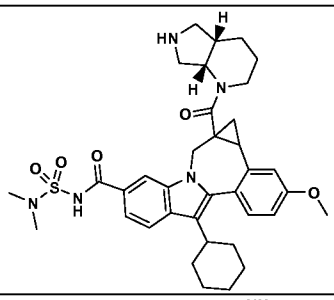
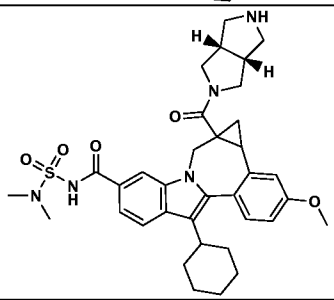
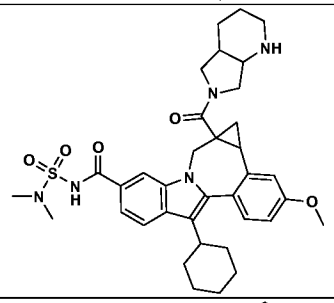
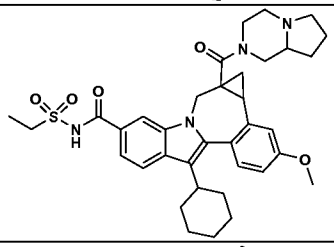
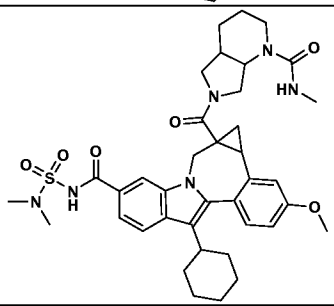
	B	B
	B	B
	B	B
	B	B
	B	B

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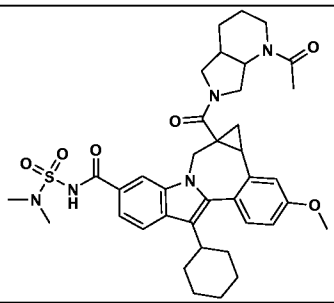
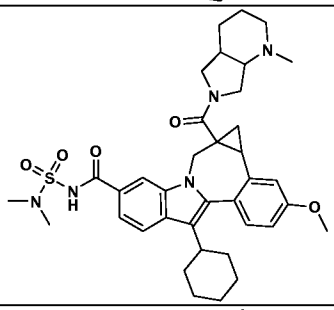
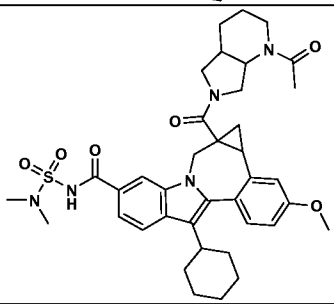
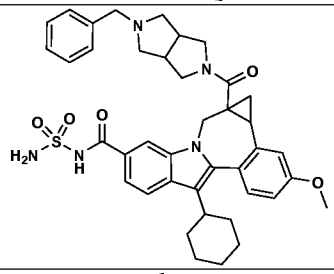
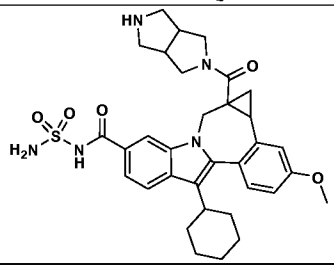
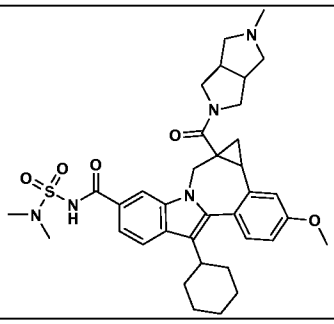
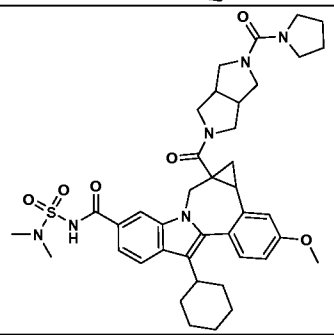
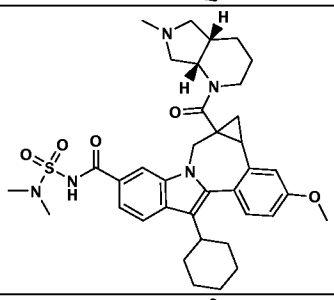
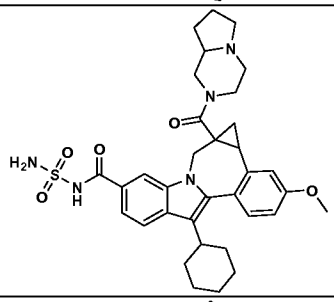
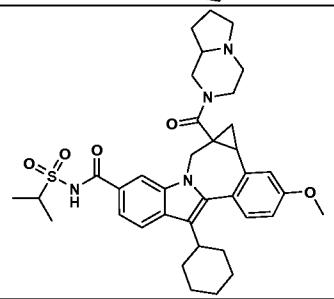
	B	B
	B	B
	B	B
	B	B
	B	A

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

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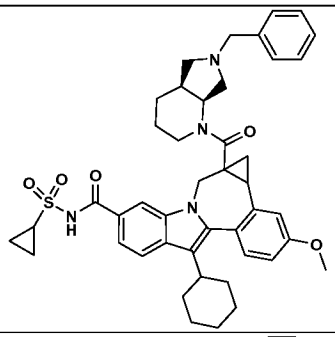
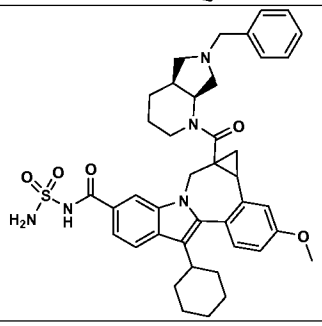
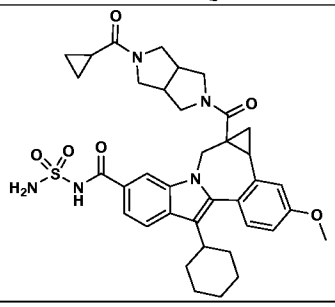
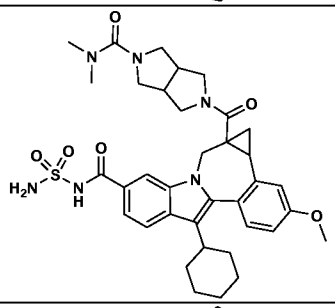
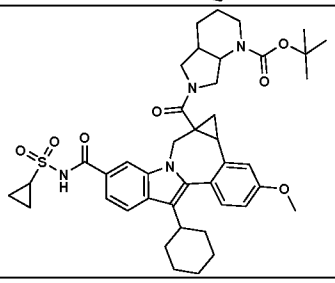
	B	B
	B	B
	B	
	B	
	B	B

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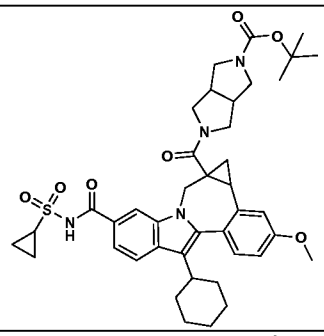
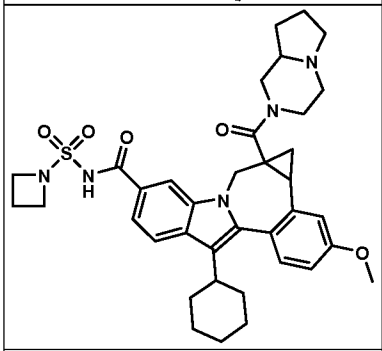
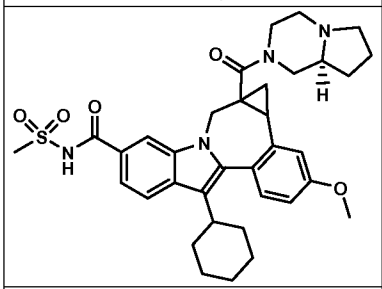
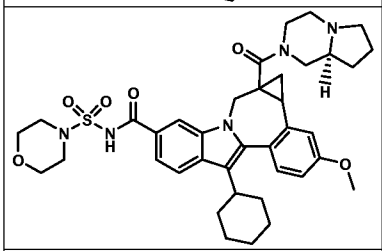
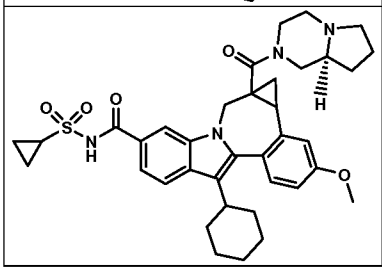
	B	
	B	B
	B	B
	B	B
	B	B

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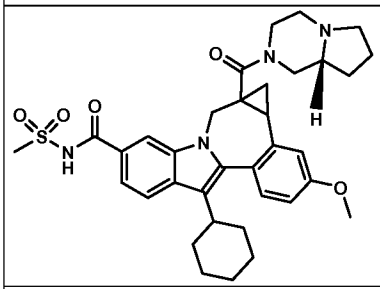
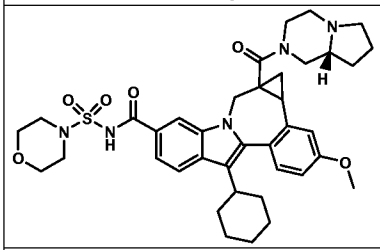
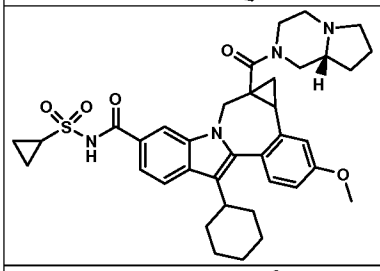
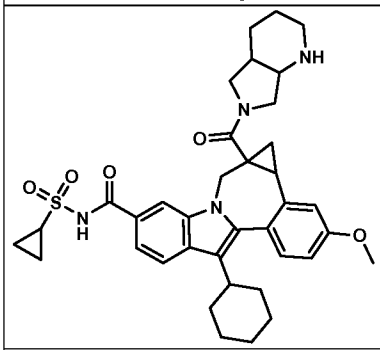
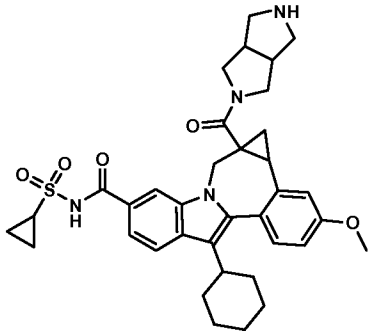
	B	B
	B	B
	B	B
	B	B
	B	F

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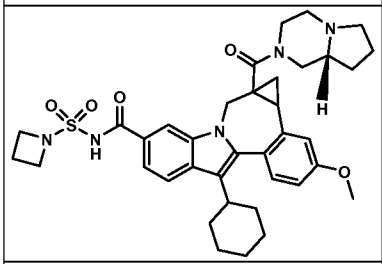
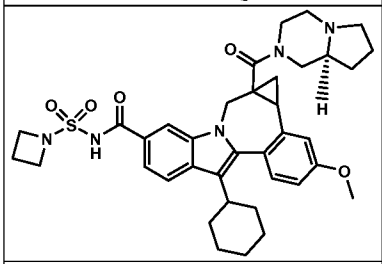
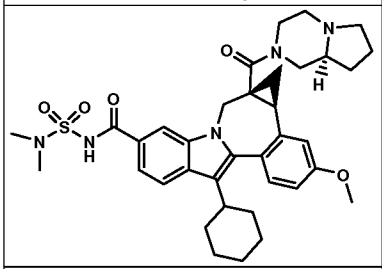
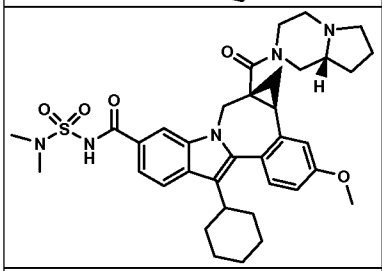
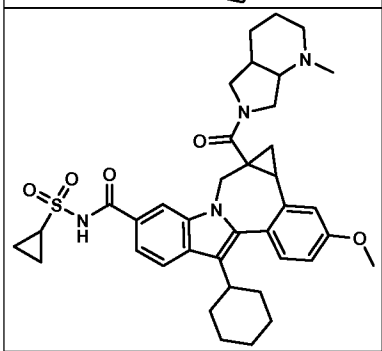
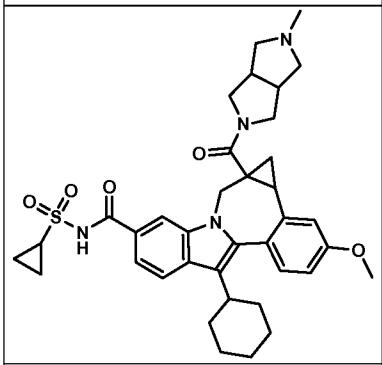
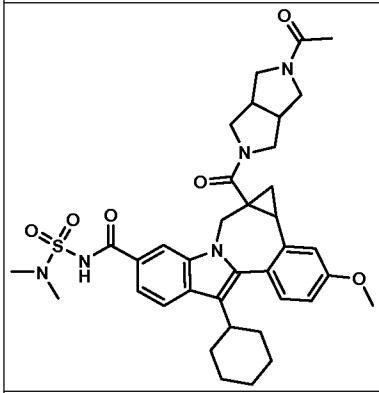
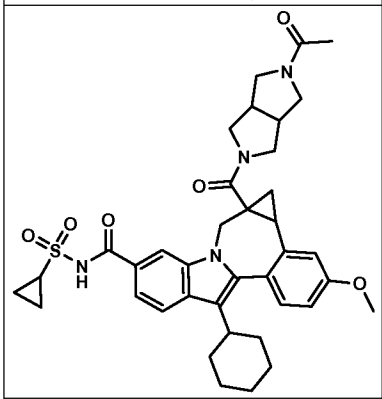
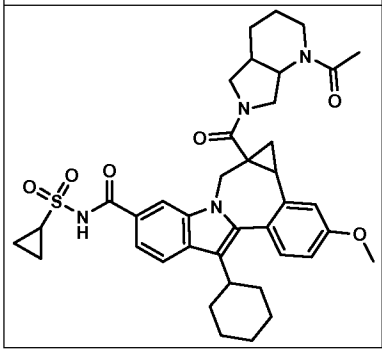
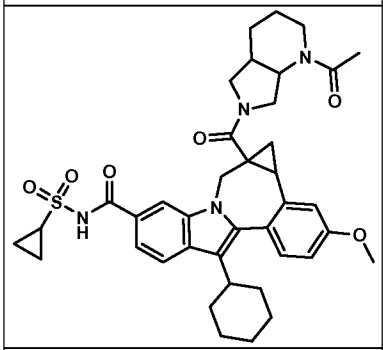
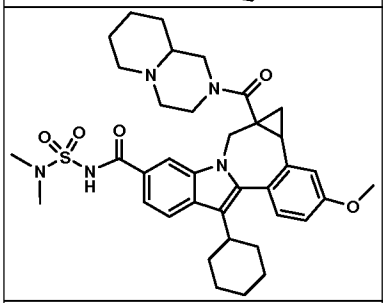
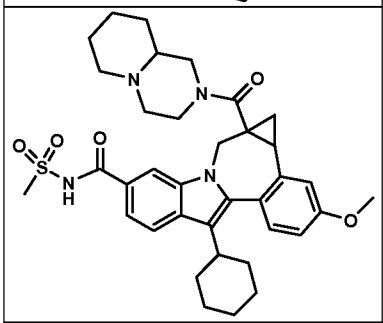
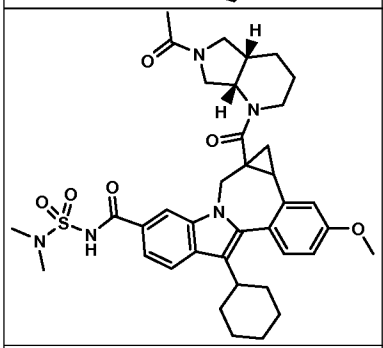
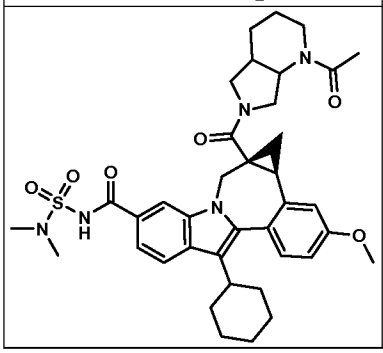
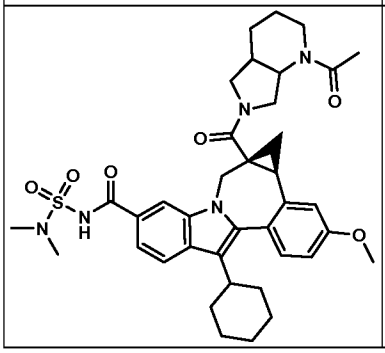
	B	B
	B	B
	B	B
	B	B
	B	B

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

A>0.5 μM; B 0.00458 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; F > 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

Brand Name	Type of Inhibitor or Target	Source Company
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
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

Brand Name	Type of Inhibitor or Target	Source Company
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
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.

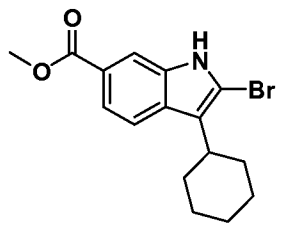
Brand Name	Type of Inhibitor or Target	Source Company
2'C Methyl adenosine	NS5B Replicase Inhibitor	Merck
GS-9132 (ACH-806)	HCV Inhibitor	Achillion / Gilead

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 an artifact of the graphics software, some structures have missing hydrogen atoms.

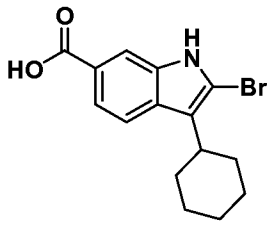
Intermediate 1



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

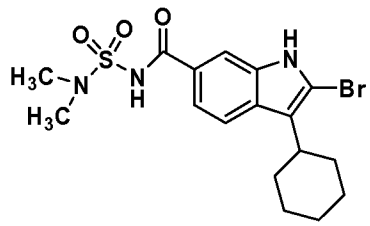


1H-Indole-6-carboxylic acid, 2-bromo-3-cyclohexyl-. A solution of methyl 2-bromo-3-cyclohexyl-1*H*-indole-6-carboxylate (20 g, 60 mmol) and LiOH (3.8 g, 160 mmol) in MeOH/THF/H_2O (1:1:1, 300 mL) was heated at 90 °C for 2h. The reaction mixture was cooled in an ice/H_2O bath, neutralized with 1M HCl (~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



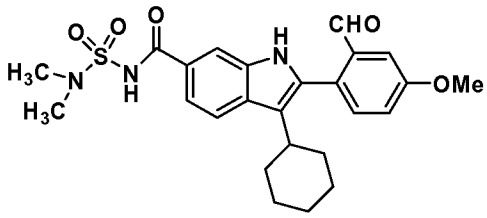
1H-Indole-6-carboxamide, 2-bromo-3-cyclohexyl-N-[(dimethylamino)sulfonyl]-. 1,1'-Carbonyldiimidazole (1.17 g, 7.2 mmol) was added to a stirred solution of 2-bromo-3-cyclohexyl-1H-indole-6-carboxylic acid (2.03 g, 6.3 mmol) in THF (6 mL) at 22 °C. The evolution of CO_2 was instantaneous and when it slowed 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%). ^1H 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



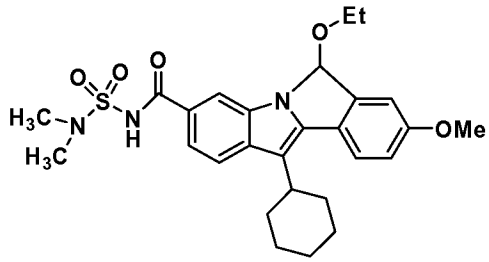
1H-Indole-6-carboxamide, 3-cyclohexyl-N-[(dimethylamino)sulfonyl]-2-(2-formyl-4-methoxyphenyl)-. A mixture of the 2-Bromo-3-cyclohexyl- N-[(dimethylamino)sulfonyl]-1H-indole-6-carboxamide (4.28g, 0.01 mol), 4-methoxy-2-formylphenyl boronic acid (2.7g, 0.015 mol), 2-dicyclohexylphosphino-2',6'-dimethoxy-biphenyl (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

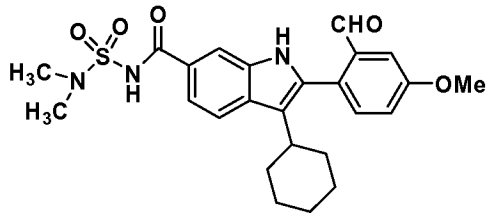


6H-Isoindolo[2,1-a]indole-3-carboxamide, 11-cyclohexyl-N-[(dimethylamino)sulfonyl]-6-ethoxy-8-methoxy-. To a 5 L four necked round bottom flask equipped with a temperature controller, a condenser, a N2 inlet and a mechanical stirrer, was charged toluene (900 mL), EtOH (900 mL), 2-bromo-3-cyclohexyl-*N*-(*N*,*N*-dimethylsulfamoyl)-1*H*-indole-6-carboxamide (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)+.

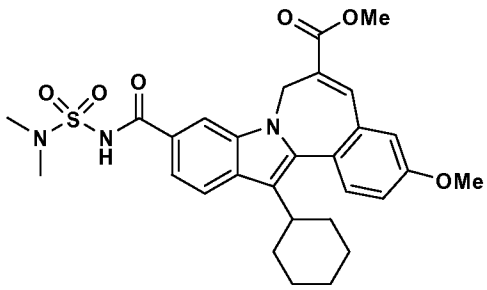
Intermediate 6



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

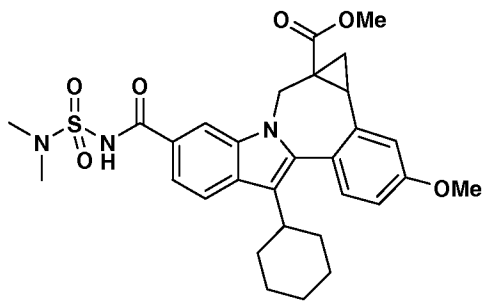


7H-Indolo[2,1-a][2]benzazepine-6-carboxylic acid, 13-cyclohexyl-10-[[[(dimethylamino)sulfonyl]amino]carbonyl]-3-methoxy-, methyl ester. A mixture of the 3-cyclohexyl-N-(N,N-dimethylsulfamoyl)-2-(2-formyl-4-methoxyphenyl)-1H-indole-6-carboxamide (4.8g, 0.01 mol), methyl 2-(dimethoxyphosphoryl)acrylate (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

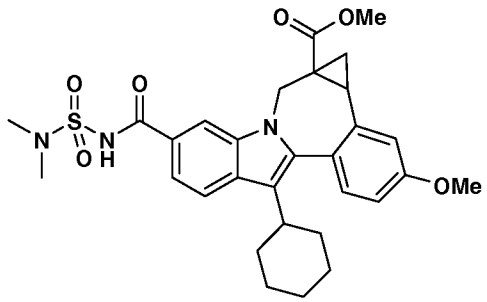
at rt for 0.5 hr. 7H-Indolo[2,1-a][2]benzazepine-6-carboxylic acid, 13-cyclohexyl-10-[[[(dimethylamino)sulfonyl]amino]carbonyl]-3-(methoxy)-, methyl ester (125 mg, 0.227 mmol) was then added and the reaction mixture was stirred at rt. for 3 hr., and then at 50^0C for a further 3 hr. The reaction was 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



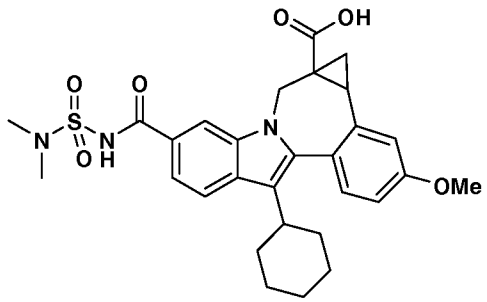
Cycloprop[d]indolo[2,1-a][2]benzazepine-1a(2H)-carboxylic acid, 8-cyclohexyl-5-[[[(dimethylamino)sulfonyl]amino]carbonyl]-1,12b-dihydro-11-methoxy-, methyl ester, (-)-. A sample of (+/-) cycloprop[d]indolo[2,1-a][2]benzazepine-1a(2H)-carboxylic acid, 8-cyclohexyl-5-[[[(dimethylamino)sulfonyl]amino]carbonyl]-1,12b-dihydro-11-methoxy- 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.

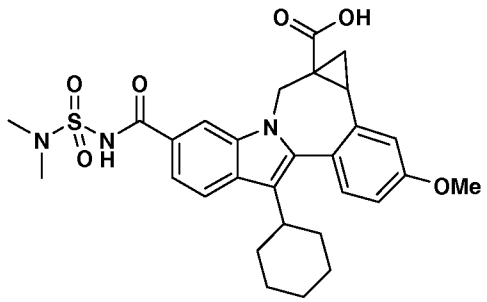
Analytical conditions of ee determination on Thar analytical SFC. Analytical Column: Chiralcel OJ (.46x25cm, 10µl); BPR pressure: 100 bars; Temperature: 35 °C; Flow rate: 3.0 ml/min; Mobile Phase: 15% MeOH/ CH_3CN (1/1) in CO_2; Detector Wavelength: 254 nm; Retention time (min): 4, 6.5.

Intermediate 10



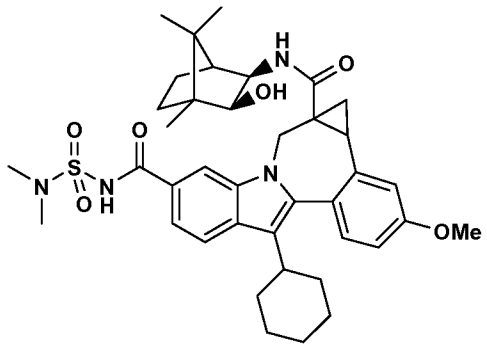
Cycloprop[d]indolo[2,1-a][2]benzazepine-1a(2H)-carboxylic acid, 8-cyclohexyl-5-[[[(dimethylamino)sulfonyl]amino]carbonyl]-1,12b-dihydro-11-methoxy-, (-)-. To a solution of (-) cycloprop[d]indolo[2,1-a][2]benzazepine-1a(2H)-carboxylic acid, 8-cyclohexyl-5-[[[(dimethylamino)sulfonyl]amino]carbonyl]-1,12b-dihydro-11-methoxy-, 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

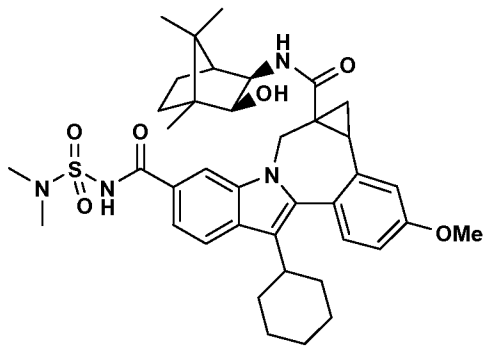


Cycloprop[d]indolo[2,1-a][2]benzazepine-1a,5(2H)-dicarboxamide, 8-cyclohexyl-N^5-[(dimethylamino)sulfonyl]-1,12b-dihydro-N^{1a}-[(2R,3S)-3-hydroxy-4,7,7-trimethylbicyclo[2.2.1]hept-2-yl]-11-methoxy-, (1aR)-[partial]-. TBTU (437 mg, 1.36 mmol) and DIPEA (0.95 mL, 5.436 mmol) were added to a solution of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

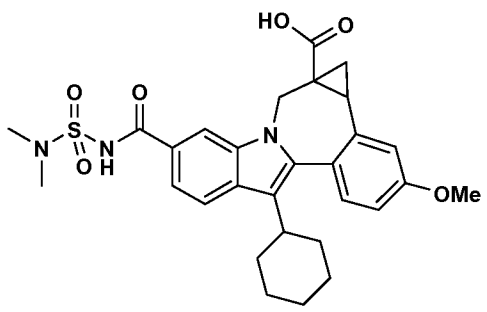


Cycloprop[d]indolo[2,1-a][2]benzazepine-1a,5(2H)-dicarboxamide, 8-cyclohexyl-N^5-[(dimethylamino)sulfonyl]-1,12b-dihydro-N^{1a}-[(2R,3S)-3-hydroxy-4,7,7-trimethylbicyclo[2.2.1]hept-2-yl]-11-methoxy-, (1aS)- [partial]-. TBTU (437 mg, 1.36 mmol) and DIPEA (0.95 mL, 5.436 mmol) were added to a solution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

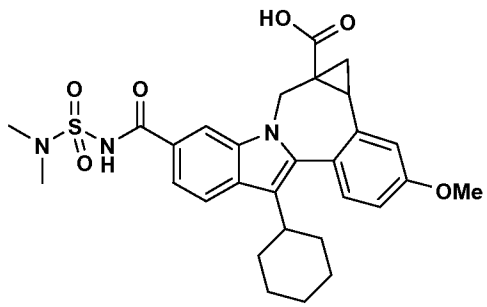
Cycloprop[d]indolo[2,1-a][2]benzazepine-1a,5(2H)-dicarboxamide, 8-cyclohexyl-N^5-[(dimethylamino)sulfonyl]-1,12b-dihydro-N^{1a}-[(2R,3S)-3-hydroxy-4,7,7-trimethylbicyclo[2.2.1]hept-2-yl]-11-methoxy-, (1aS)- [partial]- elutes after cycloprop[d]indolo[2,1-a][2]benzazepine-1a,5(2H)-dicarboxamide, 8-cyclohexyl-N^5-[(dimethylamino)sulfonyl]-1,12b-dihydro-N^{1a}-[(2R,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



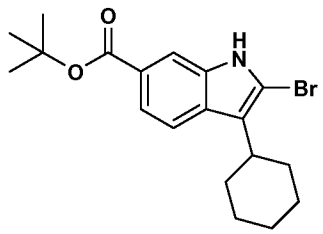
Cycloprop[d]indolo[2,1-a][2]benzazepine-1a(2H)-carboxylic acid, 8-cyclohexyl-5-[[[(dimethylamino)sulfonyl]amino]carbonyl]-1,12b-dihydro-11-methoxy-, (-)-. 10 N NaOH (2.0 mL, 20 mmol) solution and 4 mL of water were added to a solution of cycloprop[d]indolo[2,1-a][2]benzazepine-1a,5(2H)-dicarboxamide, 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).

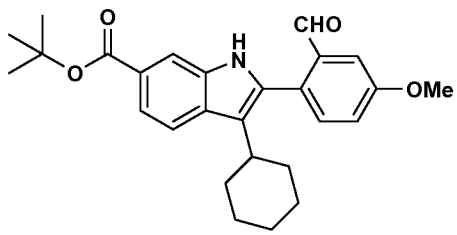
Intermediate 16



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).

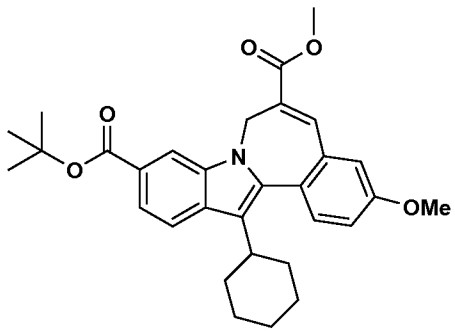
Intermediate 17



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).

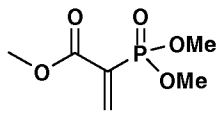
Intermediate 18



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.

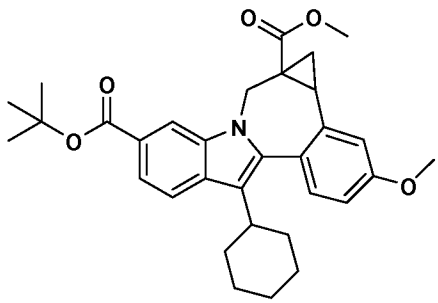
Intermediate 19



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).

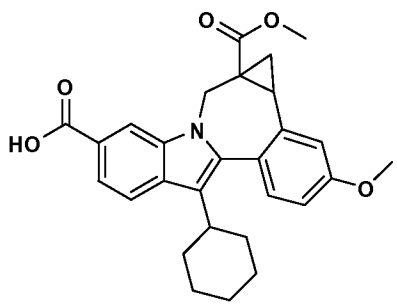
Intermediate 20



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.

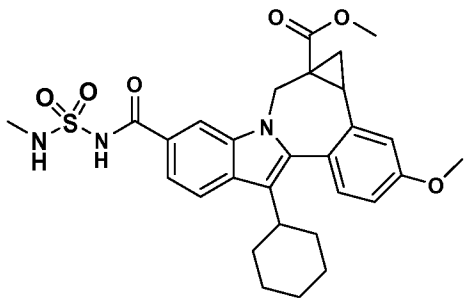
The following procedure is an example of a method to effect the resolution of racemic cycloprop[d]indolo[2,1-a][2]benzazepine-1a,5(2H)-dicarboxylic acid, 8-cyclohexyl-1,12b-dihydro-11-methoxy-, 5-(1,1-dimethylethyl) 1a-methyl ester, (+/-). A sample of cycloprop[d]indolo[2,1-a][2]benzazepine-1a,5(2H)-dicarboxylic 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



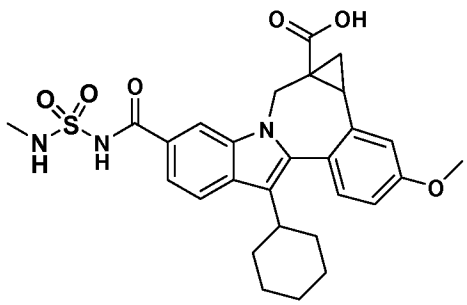
Cycloprop[d]indolo[2,1-a][2]benzazepine-1a,5(2H)-dicarboxylic acid, 8-cyclohexyl-1,12b-dihydro-11-methoxy-, 1a-methyl ester, (+/-)-. TFA (5 mL) was added to a solution of (+/-) 8-Cyclohexyl-1,1a,2,12b-tetrahydro-11-methoxy-1a-(methoxycarbonyl)-cycloprop[d]indolo[2,1-a][2]benzazepine-5-carboxylic acid, 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



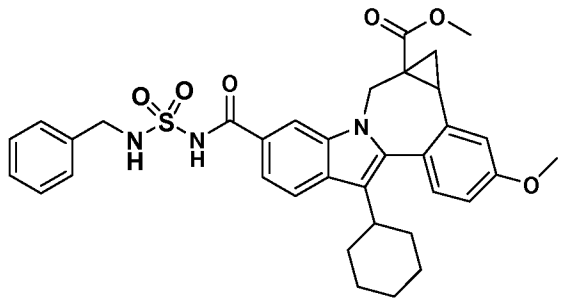
Cycloprop[d]indolo[2,1-a][2]benzazepine-1a(2H)-carboxylic acid, 8-cyclohexyl-1,12b-dihydro-11-methoxy-5-[[[(methylamino)sulfonyl]amino]carbonyl]-, methyl ester. A solution of 8-Cyclohexyl-1,1a,2,12b-tetrahydro-11-methoxy-1a-(methoxycarbonyl)-cycloprop[d]indolo[2,1-a][2]benzazepine-5-carboxylic acid (140 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.

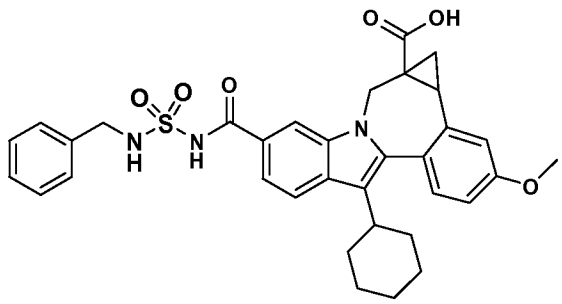
Intermediate 24



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)

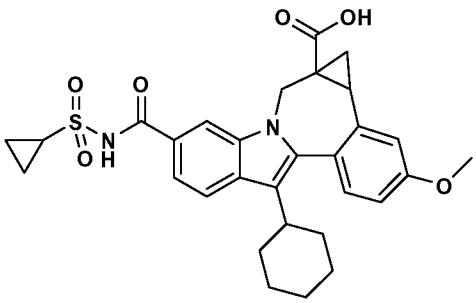
and evaporated in vacuo to provide the title compound as a brown solid. ESI-MS m/e 628 (MH^+).

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

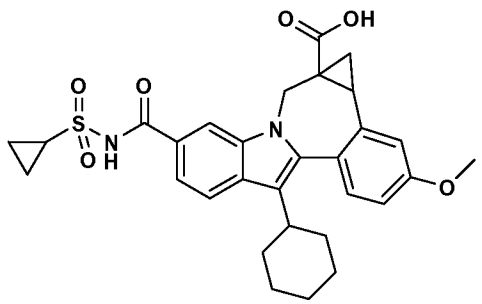


Cycloprop[d]indolo[2,1-a][2]benzazepine-1a(2H)-carboxylic acid, 8-cyclohexyl-5-[[(cyclopropylsulfonyl)amino]carbonyl]-1,12b-dihydro-11-methoxy-, (+/-)-. A mixture of (+/-) 8-cyclohexyl-1,1a,2,12b-tetrahydro-11-methoxy-1a-(methoxycarbonyl)-cycloprop[d]indolo[2,1-a][2]benzazepine-5-carboxylic acid (1 equiv), 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^+). ^{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.

Intermediates 27-38 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

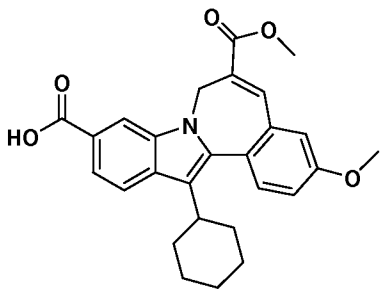
10mM NH_4OAc buffer; Gradient: Linear over 20 min. unless otherwise noted; Starting conc: 15% B unless otherwise noted; Ending conc: 100% B; Eluent A: 5% CH_3CN / 95% H_2O with 10mM NH_4OAc; Eluent B:95% CH_3CN / 5% H_2O with 10mM NH_4OAc; Column: Sunfire Prep C_{18} OBD 5μ 30 x 100 mm; Conditions for 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 27



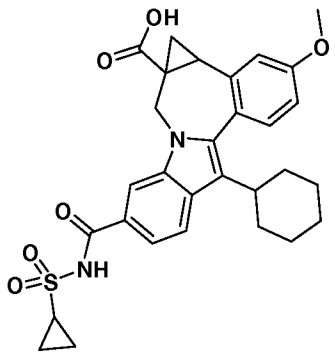
Cycloprop[d]indolo[2,1-a][2]benzazepine-1a(2H)-carboxylic acid, 8-cyclohexyl-5-[[(cyclopropylsulfonyl)amino]carbonyl]-1,12b-dihydro-11-methoxy-, (+/-)-. A mixture of (+/-) 8-cyclohexyl-1,1a,2,12b-tetrahydro-11-methoxy-1a-(methoxycarbonyl)-cycloprop[d]indolo[2,1-a][2]benzazepine-5-carboxylic acid (1 equiv), 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^+). ^{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.

Intermediate 28



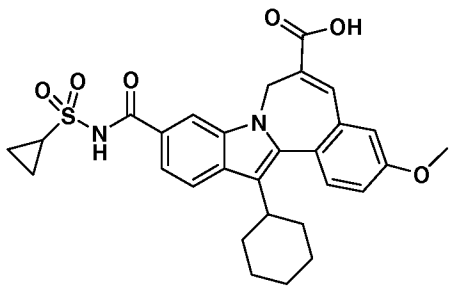
13-Cyclohexyl-3-methoxy-6-(methoxycarbonyl)-7H-indolo[2,1-a][2]benzazepine-10-carboxylic acid. Trifluoroacetic acid (30 mL) was added dropwise to a stirring slurry of 10-tert-butyl 6-methyl 13-cyclohexyl-3-methoxy-7*H*-indolo[2,1-*a*][2]benzazepine-6,10-dicarboxylate (10 g, 20 mmol) in dichloroethane (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 29



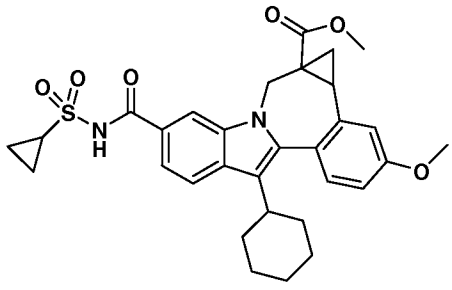
Methyl 13-cyclohexyl-10-((cyclopropylsulfonyl)carbamoyl)-3-methoxy-7H-indolo[2,1-a][2]benzazepine-6-carboxylate. 1,1'-Carbonyldiimidazole (1.82 g, 11.2 mmol) was added to a slurry of 13-cyclohexyl-3-methoxy-6-(methoxycarbonyl)-7*H*-indolo[2,1-*a*][2]benzazepine-10-carboxylic acid (3.85 g, 8.65 mmol) 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 30



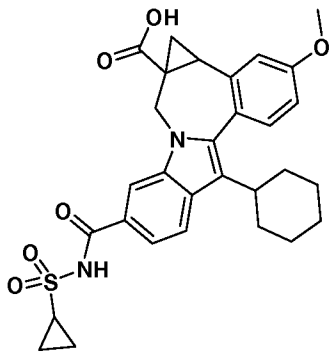
13-Cyclohexyl-10-((cyclopropylsulfonyl)carbamoyl)-3-methoxy-7H-indolo[2,1-a][2]benzazepine-6-carboxylic acid. Methyl 13-cyclohexyl-10-((cyclopropylsulfonyl)carbamoyl)-3-methoxy-7*H*-indolo[2,1-*a*][2]benzazepine-6-carboxylate (1.0 g, 1.8 mmol) was dissolved into MeOH//THF (1:1, 24 mL) and treated with 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 31



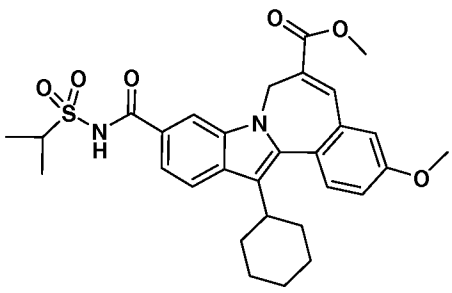
Methyl 8-cyclohexyl-5-((cyclopropylsulfonyl)carbamoyl)-11-methoxy-1,12b-dihydrocyclopropa[d]indolo[2,1-a][2]benzazepine-1a(2H)-carboxylate. To slurry of sodium hydride (60% dispersion in mineral oil, 370 mg, 9.2 mmol) in DMSO (8 mL) stirring under N_2 was added trimethylsulfoxonium iodide (2.03 g, 9.2 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 32



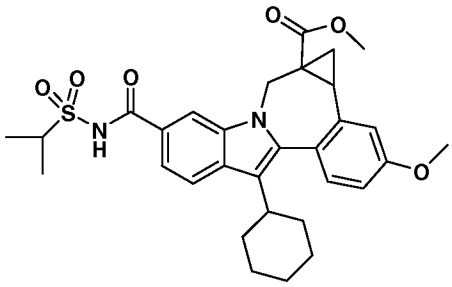
8-Cyclohexyl-5-((cyclopropylsulfonyl)carbamoyl)-11-methoxy-1,12b-dihydrocyclopropa[d]indolo[2,1-a][2]benzazepine-1a(2H)-carboxylic acid. Methyl 8-cyclohexyl-5-((cyclopropylsulfonyl)carbamoyl)-11-methoxy-1,12b-dihydrocyclopropa[*d*]indolo[2,1-*a*][2]benzazepine-1a(2*H*)-carboxylate (1.92 g, 3.41 mmol) 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 33



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.

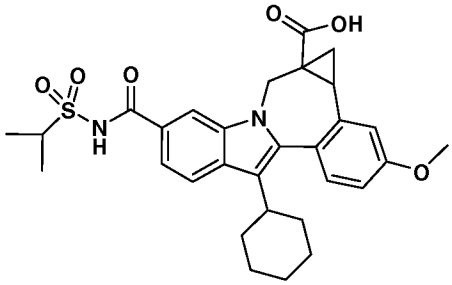
Intermediate 34



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,

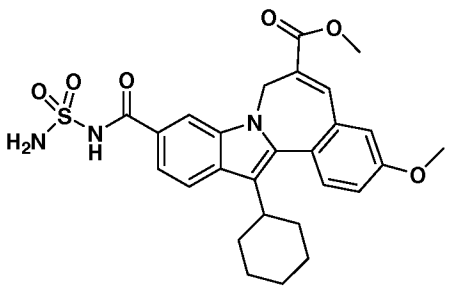
0.4H), 8.20 (d, *J* = 1.5 Hz, 0.6H), 8.39 (s, 0.4H), 8.43 (s, 0.6H). LCMS: m/e 563 $(M-H)^-$, ret time 3.00 min, column A, 4 minute gradient.

Intermediate 35



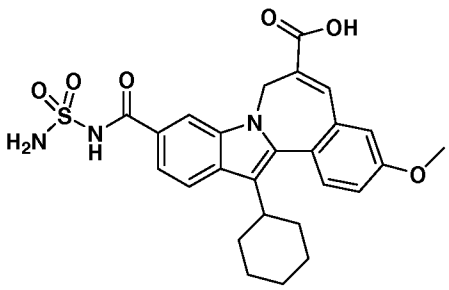
8-Cyclohexyl-5-((isopropylsulfonyl)carbamoyl)-11-methoxy-1,12b-dihydrocyclopropa[d]indolo[2,1-a][2]benzazepine-1a(2H)-carboxylic acid. Methyl 8-cyclohexyl-5-((isopropylsulfonyl)carbamoyl)-11-methoxy-1,12b-dihydrocyclopropa[d]indolo[2,1-*a*][2]benzazepine-1a(2H)-carboxylate (606 mg, 1.07 mmol) was dissolved 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 36



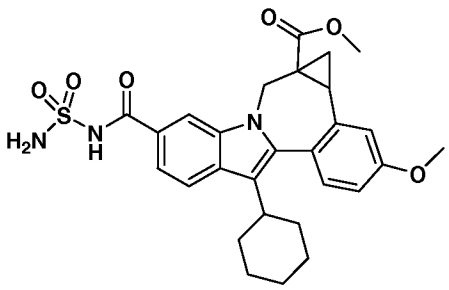
Methyl 10-((aminosulfonyl)carbamoyl)-13-cyclohexyl-3-methoxy-7H-indolo[2,1-a][2]benzazepine-6-carboxylate. 1,1'-Carbonyldiimidazole (1.23 g, 7.60 mmol) was added to a slurry of 13-cyclohexyl-3-methoxy-6-(methoxycarbonyl)-7*H*-indolo[2,1-*a*][2]benzazepine-10-carboxylic acid (2.6 g, 5.8 mmol) in THF (11 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 37



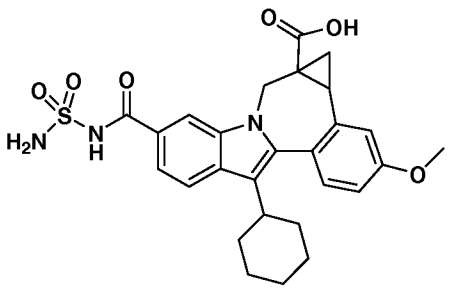
10-((Aminosulfonyl)carbamoyl)-13-cyclohexyl-3-methoxy-7H-indolo[2,1-a][2]benzazepine-6-carboxylic acid. Methyl 10-((aminosulfonyl)carbamoyl)-13-cyclohexyl-3-methoxy-7*H*-indolo[2,1-*a*][2]benzazepine-6-carboxylate (725 mg, 1.39 mmol) was dissolved into MeOH//THF (1:1, 16 mL) and treated with 1M aqueous 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 38



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.

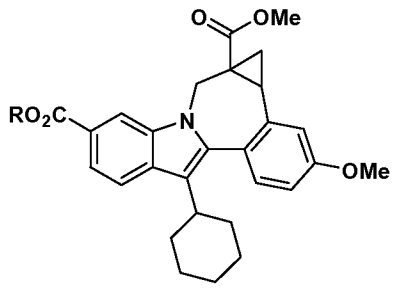
Intermediate 39



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.

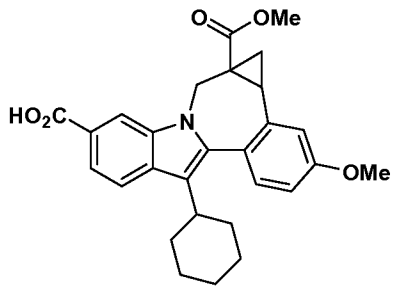
Intermediates 40-44 use the experimental procedures that follow until noted.

Intermediate 40



Dry NaH (96 mg, 4 mmol) was added to a stirred suspension of trimethylsulfoxonium chloride (567 mg, 4.4 mmol) in an. DMSO (10 mL) under nitrogen. The resultant mixture was stirred at rt for 30-45 min and then neat olefin (1.0, 2 mmol) was added in small portions. The suspension was diluted with DMSO (5 mL) and heated at 50 °C for 3-4 h. Reaction mixture was allowed to cool to rt and water was added. Precipitated solid was filtered and washed with water and then air dried overnight to afford 1.15 g of crude product which was purified by flash column chromatography (silica gel, 3% MeOH in DCM), to provide pure desired cyclopropyl compound (0.96 g), as a off-white solid: LC/MS: Retention time 3.816 min; m/e 516 (MH^+). ^1H NMR (400 MHz, $CDCl_3$): The product was observed to exist as inter-converting rotamers.

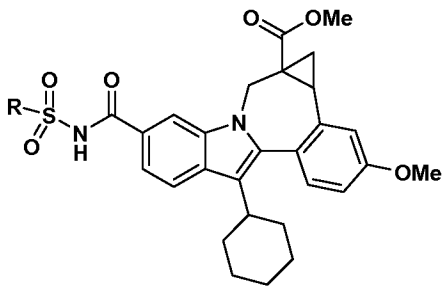
Intermediate 41



The *tert*-butyl ester (515 mg, 1 mmol) and TFA (5 mL) in an. DCM (10 mL) was stirred at rt until hydrolysis is complete (8-12 hr). Excess TFA and DCM were evaporated to dryness to afford desired acid (0.47g, 100%) as a light beige solid.

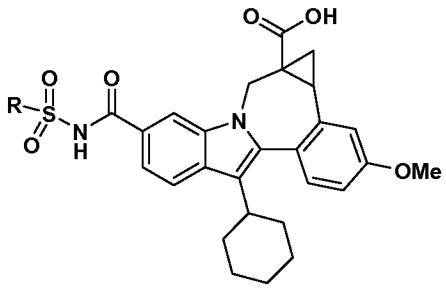
LC/MS: Retention time 2.245 min; m/e 460 (MH^+), . ^1H NMR (400 MHz, $CDCl_3$): The product was observed to exist as inter-converting rotamers.

Intemediate 42



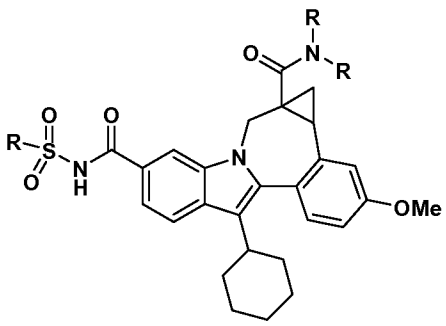
General procedure. A mixture of acid (1 equiv) and carbonyldiimidazole (1.5 equiv) in an. THF was heated at 50 °C for 30 min and allowed to cool to rt. Then 1 equiv of either sulfamide (R = NR_2) or sulfonamide (R = alkyl or aryl) and DBU (2 equiv) were added consecutively. The resultant mixture was stirred at rt overnight. After acidic aqueous workup, isolated crude product was purified by prep. HPLC to afford the product.

Intermediate 43



Methyl ester moiety was hydrolyzed using 1N NaOH in THF-MeOH to provide the corresponding acids.

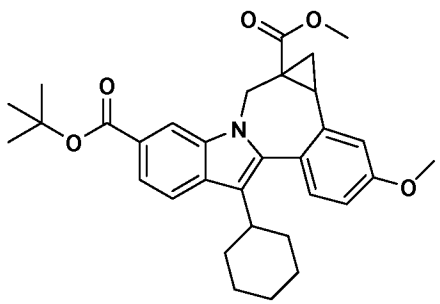
Intermediate 44



Acid derivatives (1 equiv) were combined with corresponding amine (RRNH, 1.2 equiv), triethylamine (2-3 equiv) and TBTU (1.3 equiv) in an. DMF and stirred at rt for 1-2 h until completion of the amide coupling. Isolated crude products were purified by prep. HPLC to provide desired amides.

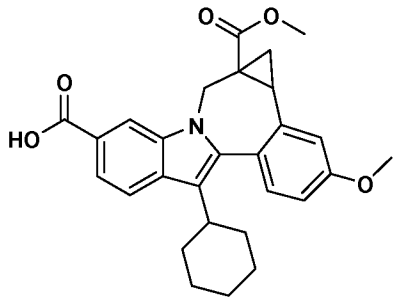
Intermediates 45-49 described below were analyzed by the following LC/MS method: Analysis Conditions: Column: PHENOMENNEX-LUNA 3.0 x 50mm S10; Mobile Phase: (A) 10:90 methanol-water; (B) 90:10 methanol-water; Buffer: 0.1% TFA; Gradient Range: 0-100% B; Gradient Time: 2 min; Flow Rate: 4 mL/min; Analysis Time: 3 min; Detection: Detector 1: UV at 220 nm; Detector 2: MS (ESI+)/

Intermediate 45



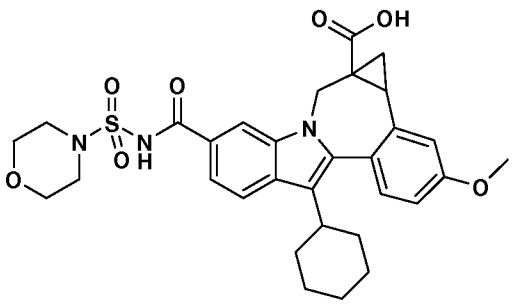
(+/-)-8-Cyclohexyl-1,1a,2,12b-tetrahydro-11-methoxy-1a-(methoxycarbonyl) -cycloprop[d]indolo[2,1-a][2]benzazepine-5-carboxylic acid, tert-butyl ester. LC/MS: Retention time 3.816 min; m/e 516 (MH^+). ^1H NMR (400 MHz, $CDCl_3$): The product was observed to exist as inter-converting rotamers.

Intermediate 46



(+/-)-8-Cyclohexyl-1,1a,2,12b-tetrahydro-11-methoxy-1a-(methoxycarbonyl) -cycloprop[d]indolo[2,1-a][2]benzazepine-5-carboxylic acid. Retention time 2.245 min; m/e 460 (MH^+), . ^1H NMR (400 MHz, $CDCl_3$). The product was observed to exist as inter-converting rotamers.

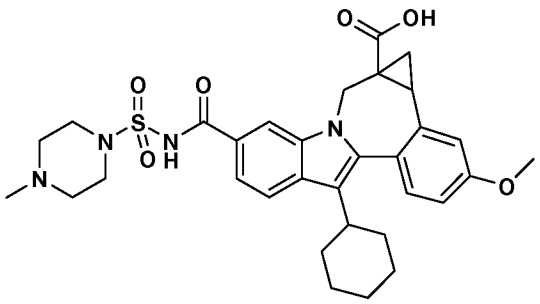
Intermediate 47



(+/-)-8-cyclohexyl-5-(morpholinosulfonylcarbamoyl)-1,1a,2,12b-tetrahydro-11-methoxy-cycloprop[d]indolo[2,1-a][2]benzazepine-1a-carboxylic acid. The product was purified by prep HPLC and isolated as a beige solid. LC/MS: Retention

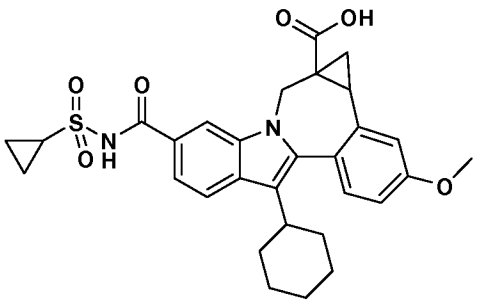
time: 1.968 min; m/e 460 (MH^+). ^1H NMR (400 MHz, $CDCl_3$). The product was observed to exist as inter-converting rotamers.

Intermediate 48



(+/-)-8-cyclohexyl-5-(4-methylpiperazin-1-ylsulfonylcarbamoyl)-1,1a,2,12b-tetrahydro-11-methoxy-cycloprop[d]indolo[2,1-a][2]benzazepine-1a-carboxylic acid. The product was purified by prep HPLC and isolated in mono TFA salt form as a beige solid. LC/MS: Retention time: 1.687 min; m/e 607 (MH^+). ^1H NMR (400 MHz, $CDCl_3$). The product was observed to exist as inter-converting rotamers.

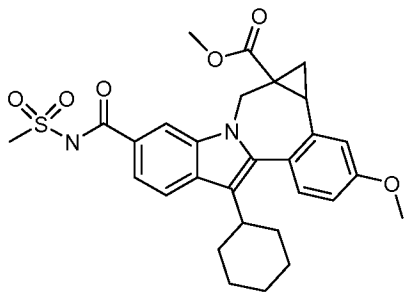
Intermediate 49



(+/-)-8-cyclohexyl-5-(cyclopropylsulfonylcarbamoyl) -1,1a,2,12b-tetrahydro-11-methoxy-cycloprop[d]indolo[2,1-a][2]benzazepine-1a-carboxylic acid. 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.

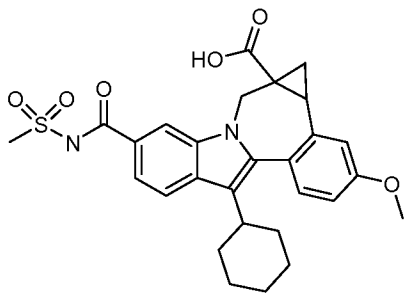
Intermiates 50-60 were analyzed by the following LC/MS method: Start % B: 0; Final % B: 100; Gradient time: 3 min; Stop time: 4 min; Flow rate: 4 ml/min; Wavelenth: 220; Solvent A: 10% MeOH / 90% H_2O / 0.1% Trifluoroacetic Acid; Solvent B: 10% H_2O / 90% MeOH / 0.1% Trifluoroacetic Acid; Column: XBridge 4.6 x 50 mm S5.

Intermediate 50



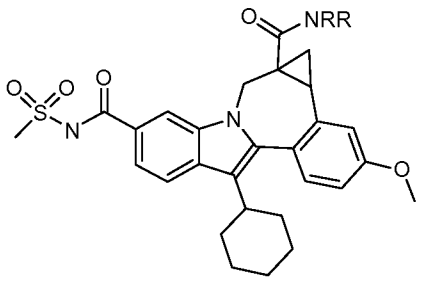
A mixture of the acid (1.3 g, 2.83 mmol) and CDI (0.64 g, 3.97 mmol) in THF (20 mL) was heated at 50 °C for 0.5 h, cooled down and added methylsulfonamide (0.4 g, 4.2 mmol) and DBU (0.264 mL, 1.77 mmol). The mixture was stirred for 20 h and diluted with EtOAc, washed with cold 1N HCl (2x), brine, dried (MgSO4), removed the solvent and purified by flash (Biotage 40 M) to afford the compound 1-2 (1.28 g, 85%) as a pale yellow solid. LC-MS retention time: 3.51; MS m/z 537 (M+H). Compound 1-2 was observed to exist as inter-converting rotamers. The major isomer: ^{1}H NMR (400 MHz, CHLOROFORM-D) δ ppm 1.11 - 2.17 (m, 12 H), 2.84 - 2.98 (m, 2 H), 3.43 (d, *J*=14.86 Hz, 1 H), 3.49 (s, 3 H), 3.55 (s, 3 H), 3.89 (s, 3 H), 5.40 (d, *J*=15.11 Hz, 1 H), 6.91 - 6.96 (m, 1 H), 7.13 (d, *J*=2.52 Hz, 1 H), 7.22 - 7.27 (m, 1 H), 7.39 (dd, *J*=8.31, 1.51 Hz, 1 H), 7.85 (d, *J*=8.81 Hz, 1 H), 8.23 (d, *J*=1.26 Hz, 1 H), 8.75 (s, 1 H).

Intermediate 51



To a solution of the ester (1.28 g, 2.4 mmol) in THF (5 mL) and MeOH (5 mL) was added NaOH (1N, 12 mL, 12 mmol). After being stirred at room temperature for 3 h, the mixture was diluted with EtOAc, washed with cold 1N HCl, brine, dried (MgSO4), and removed the solvent in vacuo to afford the acid as a beige solid (1.20 g, 96%). LC-MS retention time: 3.46; MS m/z 523 (M+H). The acid was observed to exist as inter-converting rotamers (~1/1) ^{1}H NMR (400 MHz, CHLOROFORM-D).

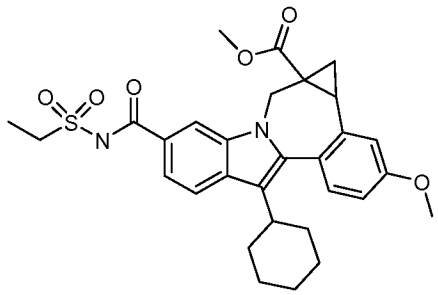
Intermediate 52



Typical general procedure for amine coupling: To a mixture of the acid (0.060g, 0.11 mmol) and a secondary / tertiary amine containing diamine bishydrochloric acid salt (0.034g, 0.17 mmol) in DMC (1.5 mL) was added Et_3N (0.096 mL, 0.69 mmol) and HBTU (0.065g, 0.17 mmol). The mixture was stirred at room temperature for 0.5 h, diluted with MeOH, removed the solvent. The residue was dissolved in methanol, filtered, and purified by prep-HPLC to afford A TFA salt

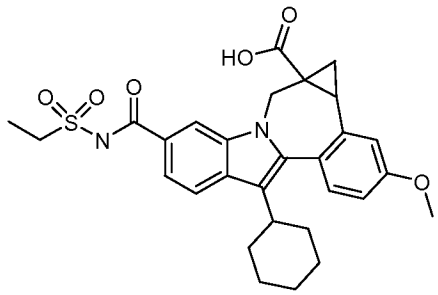
of an amide 1 (0.0378g , 82%) as TFA salt which was characterized by LC-MS and ^{1}H NMR.

Intermediate 53



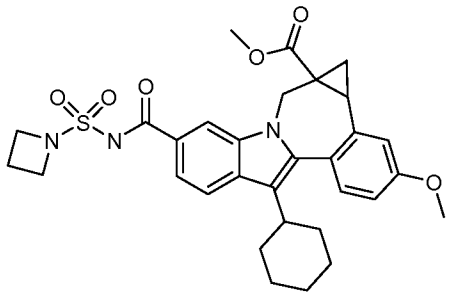
The product was prepared from the the acid (0.47g, 44%). LC-MS retention time: 3.54; MS m/z 551 (M+H).

Intermediate 54



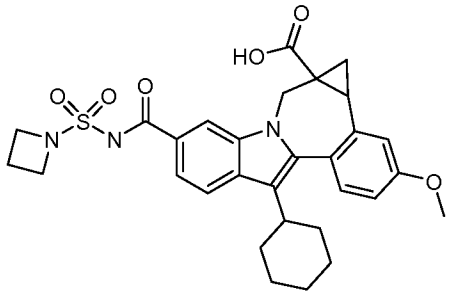
The product was prepared (0.43 g, 94%). LC-MS retention time: 3.49; MS m/z 537 (M+H).

Intermediate 55



The producut was prepared from the acid (0.96g, 59%). LC-MS retention time: 3.58; MS m/z 578 (M+H). compound was observed to exist as inter-converting rotamers (3/4). The major isomer: ^{1}H NMR (400 MHz, CHLOROFORM-D) δ ppm 1.16 - 1.59 (m, 4 H), 1.72 (dd, *J*=9.44, 4.15 Hz, 3 H), 1.88 - 2.12 (m, 4 H), 2.24 - 2.36 (m, 2 H), 2.75 - 2.97 (m, 2 H), 3.44 (d, *J*=14.86 Hz, 1 H), 3.56 (s, 3 H), 3.89 (s, 3 H), 4.09 (d, 1 H), 4.24 - 4.37 (m, 4 H), 5.41 (d, *J*=14.86 Hz, 1 H), 6.92 - 6.96 (m, 1 H), 7.13 (d, *J*=2.01 Hz, 1 H), 7.24 - 7.30 (m, 1 H), 7.39 (dd, *J*=8.31, 1.51 Hz, 1 H), 7.84 - 7.88 (m, 1 H), 8.24 (d, *J*=1.51 Hz, 1 H).

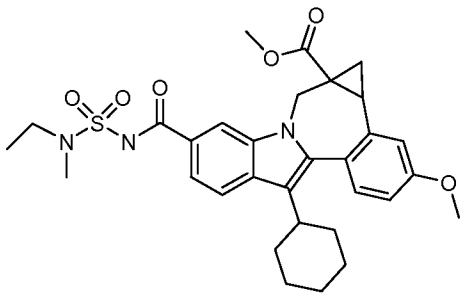
Intermediate 56



The product was prepared (0.93 g, 100%). LC-MS retention time: 3.51; MS m/z 564 (M+H). Compound was observed to exist as inter-converting rotamers (~3/4). The major isomer: ^{1}H NMR (400 MHz) ppm 0.34 - 0.42 (m, 1 H), 1.15 - 2.10 (m, 11 H), 2.22 - 2.38 (m, 2 H), 2.65 - 2.78 (m, 1 H), 2.84 - 2.94 (m, *J*=3.02 Hz, 1 H), 3.84 (s, 3 H), 4.03 (d, *J*=15.11 Hz, 1 H), 4.21 - 4.43 (m, 4 H), 5.34 (d, *J*=14.86 Hz, 1

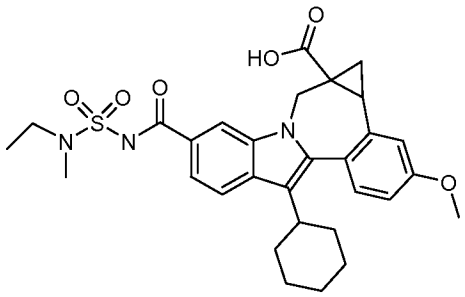
H), 6.87 (dd, *J*=8.56, 2.77 Hz, 1 H), 6.98 (d, *J*=2.52 Hz, 1 H), 7.21 (d, *J*=8.31 Hz, 1 H), 7.69 - 7.75 (m, 1 H), 7.86 - 7.90 (m, 1 H), 8.13 (s, 1 H).

Intermediate 57



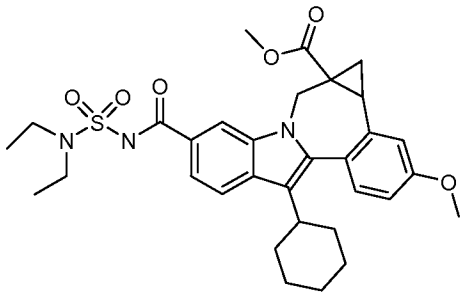
The product was prepared from the acid (0.109 g, 67%). LC-MS retention time: 3.60; MS m/z 580 (M+H). Compound was observed to exist as inter-converting rotamers (~5/4). The major isomer: ^{1}H NMR (400 MHz) ppm 1.16 - 2.09 (m, 14 H), 2.73 - 2.93 (m, 2 H), 3.07 (s, 3 H), 3.31 - 3.52 (m, 3 H), 3.76 (s, 3 H), 3.88 (s, 3 H), 4.05 - 4.10 (m, 1 H), 5.40 (d, *J*=15.11 Hz, 1 H), 6.88 - 6.93 (m, 1 H), 7.13 (d, *J*=2.27 Hz, 1 H), 7.22 - 7.29 (m, 1 H), 7.33 - 7.42 (m, 1 H), 7.82 - 7.86 (m, 1 H), 8.19 (d, *J*=1.51 Hz, 1 H)

Intermediate 58



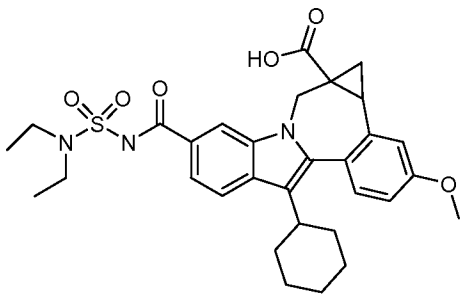
The product was prepared (0.108 g, 100%). LC-MS retention time: 3.55; MS m/z 566 (M+H).

Intermediate 59



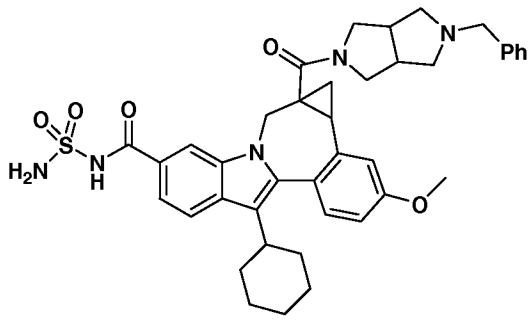
The product was prepared from the acid (0.127 g, 67%). LC-MS retention time: 3.64; MS m/z 594 (M+H). Compound was observed to exist as inter-converting rotamers: ^{1}H NMR (400 MHz) ppm 1.11 - 2.13 (m, 18 H), 2.64 (dd, *J*=10.07, 6.80 Hz, 1 H), 2.84 - 2.96 (m, 1 H), 3.34 - 3.67 (m, 4 H), 3.75 (s, 3 H), 3.88 (s, 3 H), 4.03 - 4.10 (m, 1 H), 5.40 (d, *J*=15.36 Hz, 1 H), 6.90 - 6.95 (m, 1 H), 7.13 (d, *J*=2.01 Hz, 1 H), 7.21 - 7.29 (m, 1 H), 7.33 - 7.39 (m, 1 H), 7.83 (d, *J*=8.06 Hz, 1 H), 8.20 (d, *J*=1.26 Hz, 1 H).

Intermediate 60



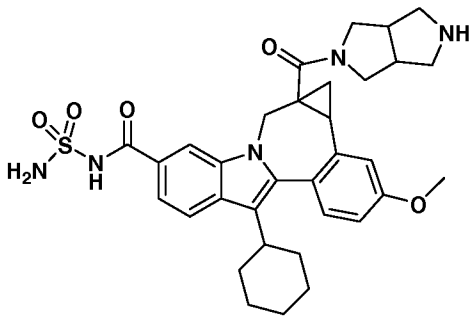
The product was prepared (0.126 g, 100%). LC-MS retention time: 3.57; MS m/z 580 (M+H).

Example 1



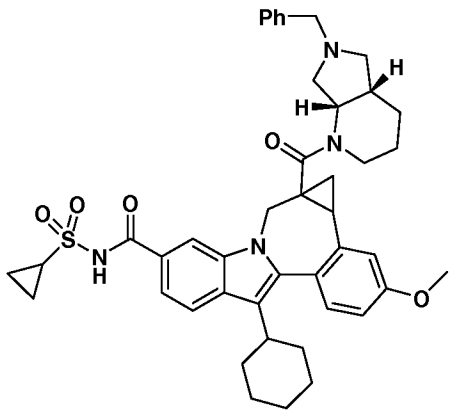
N-(aminosulfonyl)-1a-((5-benzylhexahydropyrrolo[3,4-c]pyrrol-2(1H)-yl)carbonyl)-8-cyclohexyl-11-methoxy-1,1a,2,12b-tetrahydrocyclopropa[d]indolo[2,1-a][2]benzazepine-5-carboxamide. To a stirred solution of 5-((aminosulfonyl)carbamoyl)-8-cyclohexyl-11-methoxy-1,12b-dihydrocyclopropa[d]indolo[2,1-a][2]benzazepine-1a(2H)-carboxylic acid (200 mg, 0.38 mmol), 2-benzyloctahydropyrrolo[3,4-c]pyrrole (100 mg, 0.50 mmol) in DMF (4 mL) was added HATU (190 mg, 0.5 mmol) and triethylamine (0.21 mL). The reaction mixture was stirred at rt for 1h, diluted with H2O (15 mL) and 1M HCl (aq.) (1.6 mL) and the precipitates were collected by filtration. The solids were dissolved into MeOH/DMF, filtered and purified by preparative HPLC (H2O/CH3CN with 10mM NH4OAc buffer) to yield N-(aminosulfonyl)-1a-((5-benzylhexahydropyrrolo[3,4-c]pyrrol-2(1H)-yl)carbonyl)-8-cyclohexyl-11-methoxy-1,1a,2,12b-tetrahydrocyclopropa[d]indolo[2,1-a][2]benzazepine-5-carboxamide (196 mg, 0.28 mmol, 72%) as a white solid. Presents as a ~1:3 mixture of rotamers or atrope isomers. 1HNMR (300 MHz, CD3OD) δ 0.12 - 0.21 (m, 0.25H), 1.03 - 2.21 (m, 13.75H), 2.41 - 3.15 (m, 9H), 3.25 - 3.31 (m, 1H), 3.61 (d, J = 15.0 Hz, 0.75H), 3.55 - 3.72 (m, 2H), 3.88 (s, 0.75H), 3.90 (s, 2.25H), 4.12 (d, J = 15.0 Hz, 0.25H), 4.79 (d, J = 15.0 Hz, 0.25H), 5.13 (d, J = 15.0 Hz, 0.75H), 6.98 (dd, J = 8.4, 2.6 Hz, 0.25H), 7.02 (dd, J = 8.8, 2.6 Hz, 0.75H), 7.20 (d, J = 2.6 Hz, 0.75H), 7.30 (d, J = 8.4 Hz, 0.25H), 7.32 (d, J = 8.8 Hz, 0.75H), 7.34 - 7.44 (m, 5.25H), 7.63 (d, J = 8.4 Hz, 0.75H), 7.65 (d, J = 8.4 Hz, 0.25H), 7.86 (d, J = 8.4 Hz, 0.75H), 7.87 (d, J = 8.4 Hz, 0.25H), 7.99 (s, 0.75H), 8.11 (s, 0.25H). LCMS: m/e 708 (M+H)+, ret time 2.97 min, column B, 4 minute gradient.

Example 2



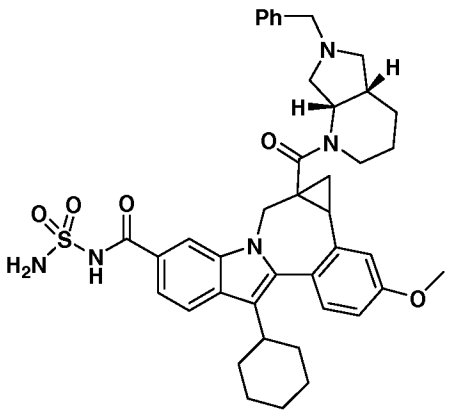
N-(aminosulfonyl)-8-cyclohexyl-1a-(hexahydropyrrolo[3,4-c]pyrrol-2(1H)-ylcarbonyl)-11-methoxy-1,1a,2,12b-tetrahydrocyclopropa[d]indolo[2,1-a][2]benzazepine-5-carboxamide. 10% Pd/C (130 mg, 0.12 mmol) was added to a solution of N-(aminosulfonyl)-1a-((5-benzylhexahydropyrrolo[3,4-c]pyrrol-2(1H)-yl)carbonyl)-8-cyclohexyl-11-methoxy-1,1a,2,12b-tetrahydrocyclopropa[d]indolo[2,1-a][2]benzazepine-5-carboxamide (175 mg, 0.25 mmol) in MeOH/CH2Cl2 (4:1, 50 mL). The reaction solution was vacuum flushed with nitrogen (3X) and then with hydrogen (3X) and shaken on a Parr shaker under 50 psi of hydrogen for 7h. The solution was filtered through celite and concentrated to yield N-(aminosulfonyl)-8-cyclohexyl-1a-(hexahydropyrrolo[3,4-c]pyrrol-2(1H)-ylcarbonyl)-11-methoxy-1,1a,2,12b-tetrahydrocyclopropa[d]indolo[2,1-a][2]benzazepine-5-carboxamide (125 mg, 0.20 mmol, 80%) as a white solid which was used without further purification. Presents as a ~2:3 mixture of rotamers or atrope isomers. 1HNMR (300 MHz, DMSO-d6) δ -0.02 - 0.05 (m, 0.4H), 0.79 - 2.29 (m, 9.6H), 2.45 - 3.77 (m, 12H), 3.85 (s, 1.8H), 3.87 (s, 1.8H), 3.98 - 4.18 (m, 3H), 4.91 (d, J = 15.0 Hz, 0.4H), 5.18 (d, J = 15.0 Hz, 0.6H), 7.02 (dd, J = 8.4, 2.6 Hz, 0.4H), 7.05 (dd, J = 8.8, 2.6 Hz, 0.6H), 7.13 (d, J = 2.6 Hz, 0.6H), 7.23 (d, J = 2.6 Hz, 0.4H), 7.28 (d, J = 8.4 Hz, 1H), 7.60 - 7.70 (m, 1H), 7.79 - 7.89 (m, 1H) 8.16 (s, 0.6H), 8.33 (s, 0.4H). LCMS: m/e 616 (M-H)-, ret time 2.06 min, column A, 4 minute gradient.

Example 3



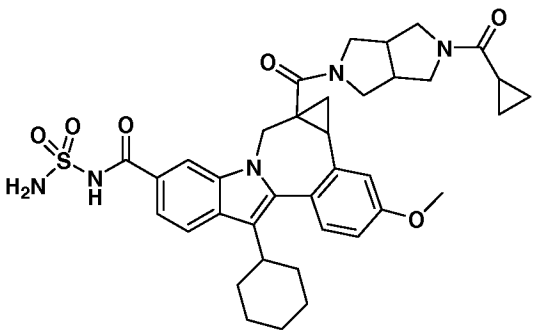
1a-(((4aS,7aS)-6-benzyloctahydro-1H-pyrrolo[3,4-b]pyridin-1-yl)carbonyl)-8-cyclohexyl-N-(cyclopropylsulfonyl)-11-methoxy-1,1a,2,12b-tetrahydrocyclopropa[d]indolo[2,1-a][2]benzazepine-5-carboxamide. To a stirred solution of 8-cyclohexyl-5-((cyclopropylsulfonyl)carbamoyl)-11-methoxy-1,12b-dihydrocyclopropa[d]indolo[2,1-a][2]benzazepine-1a(2H)-carboxylic acid (32 mg, 0.061 mmol), (4aS,7aS)-6-ethyloctahydro-1H-pyrrolo[3,4-b]pyridine (30 mg, 0.10 mmol) and triethylamine (0.05 mL) in DMF (0.5 mL) was added HATU (30 mg, 0.08 mmol). The reaction mixture was stirred at rt for 2h, diluted with MeOH (1 mL), filtered and purified by preparative HPLC (H2O/CH3CN with 10mM NH4OAc buffer) to yield 1a-(((4aS,7aS)-6-benzyloctahydro-1H-pyrrolo[3,4-b]pyridin-1-yl)carbonyl)-8-cyclohexyl-N-(cyclopropylsulfonyl)-11-methoxy-1,1a,2,12b-tetrahydrocyclopropa[d]indolo[2,1-a][2]benzazepine-5-carboxamide (29 mg, 0.04 mmol, 64%) as a light yellow solid. Complex mixture of diastereomers. 1HNMR (300 MHz, CD3OD) δ 0.93 - 2.69 (m, 23H), 2.88 - 3.05 (m, 2H), 3.07 - 3.25 (m, 2H), 3.29 - 3.68 (m, 3H), 3.87 - 3.92 (m, 3H), 4.09 - 4.53 (m, 3H), 4.69 - 4.84 (m, 1H), 5.03 - 5.15 (m, 1H), 7.15 - 7.20 (m, 1H), 7.27 - 7.36 (m, 1H), 7.38 - 7.53 (m, 5H), 7.65 - 7.90 (m, 2H), 8.03 - 8.16 (m, 1H). LCMS: m/e 747 (M+H)+, ret time 3.25 min, column B, 4 minute gradient.

Example 4



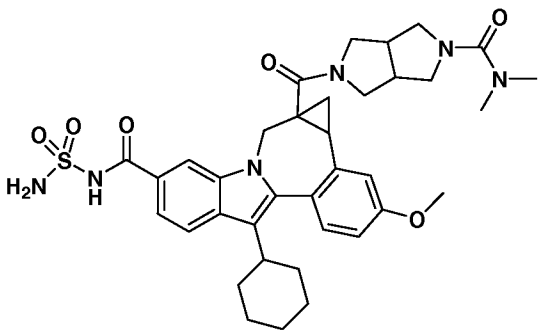
rac-N-(aminosulfonyl)-1a-(((4aR,7aR)-6-benzyloctahydro-1H-pyrrolo[3,4-b]pyridin-1-yl)carbonyl)-8-cyclohexyl-11-methoxy-1,1a,2,12b-tetrahydrocyclopropa[d]indolo[2,1-a][2]benzazepine-5-carboxamide. To a stirred solution of 5-((aminosulfonyl)carbamoyl)-8-cyclohexyl-11-methoxy-1,12b-dihydrocyclopropa[d]indolo[2,1-a][2]benzazepine-1a(2H)-carboxylic acid (32 mg, 0.058 mmol), (4aS,7aS)-6-ethyloctahydro-1H-pyrrolo[3,4-b]pyridine (30 mg, 0.10 mmol) and triethylamine (0.05 mL) in DMF (0.5 mL) was added HATU (30 mg, 0.08 mmol). The reaction mixture was stirred at rt for 2h, diluted with MeOH (1 mL), filtered and purified by preparative HPLC (H2O/CH3CN with 10mM NH4OAc buffer) to yield rac-N-(aminosulfonyl)-1a-(((4aR,7aR)-6-benzyloctahydro-1H-pyrrolo[3,4-b]pyridin-1-yl)carbonyl)-8-cyclohexyl-11-methoxy-1,1a,2,12b-tetrahydrocyclopropa[d]indolo[2,1-a][2]benzazepine-5-carboxamide (20 mg, 0.03 mmol, 48%) as a light yellow solid. Complex mixture of diastereomers. 1HNMR (300 MHz, CD3OD) δ 1.16 - 3.69 (m, 25H), 3.86 - 3.94 (m, 3H), 4.05 - 5.09 (m, 5H), 6.97 - 7.07 (m, 1H), 7.13 - 7.21 (m, 1H), 7.26 - 7.36 (m, 5H), 7.62 - 7.73 (m, 1H), 7.77 - 7.90 (m, 1H), 7.97 - 8.10 (m, 1H). LCMS: m/e 722 (M+H)+, ret time 3.06 min, column B, 4 minute gradient.

Example 5



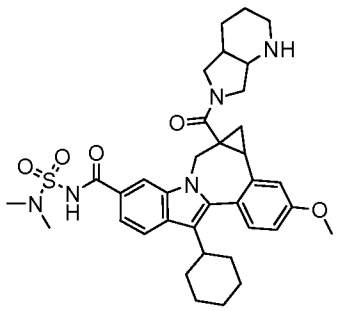
N-(aminosulfonyl)-8-cyclohexyl-1a-((5-(cyclopropylcarbonyl)hexahydropyrrolo[3,4-c]pyrrol-2(1H)-yl)carbonyl)-11-methoxy-1,1a,2,12b-tetrahydrocyclopropa[d]indolo[2,1-a][2]benzazepine-5-carboxamide. To a stirred solution of N-(aminosulfonyl)-8-cyclohexyl-1a-(hexahydropyrrolo[3,4-c]pyrrol-2(1H)-ylcarbonyl)-11-methoxy-1,1a,2,12b-tetrahydrocyclopropa[d]indolo[2,1-a][2]benzazepine-5-carboxamide (28 mg, 0.045 mmol), cyclopropanecarboxylic acid (30 mg, 0.34 mmol) and triethylamine (0.05 mL) in DMF (0.5 mL) was added HATU (30 mg, 0.08 mmol). The reaction mixture was stirred at rt for 1h, diluted with MeOH (1 mL), filtered and purified by preparative HPLC (H2O/CH3CN with 10mM NH4OAc buffer) to yield N-(aminosulfonyl)-8-cyclohexyl-1a-((5-(cyclopropylcarbonyl)hexahydropyrrolo[3,4-c]pyrrol-2(1H)-yl)carbonyl)-11-methoxy-1,1a,2,12b-tetrahydrocyclopropa[d]indolo[2,1-a][2]benzazepine-5-carboxamide (20 mg, 0.03 mmol, 65%) as a white solid. Presents as a complex mixture of rotamers and/or atrope isomers. 1HNMR (300 MHz, CD3OD) δ 0.13 - 0.22 (m, 0.15H), 0.75 - 2.28 (m, 15.85H), 2.50 - 3.86 (m, 13.85H), 3.88 - 3.94 (m, 3H), 4.17 - 4.26 (m, 0.15H), 4.83 - 4.92 (m, 0.15H), 5.10 - 5.23 (m, 0.85H), 6.97 - 7.07 (m, 1H), 7.18 - 7.24 (m, 1H), 7.34 (d, J = 8.8 Hz, 1H), 7.52 - 7.68 (m, 1H), 7.85 - 7.94 (m, 1H) 7.95 - 8.03 (m, 0.85H), 8.12 - 8.19 (m, 0.15H). LCMS: m/e 684 (M-H)-, ret time 2.30 min, column A, 4 minute gradient.

Example 6



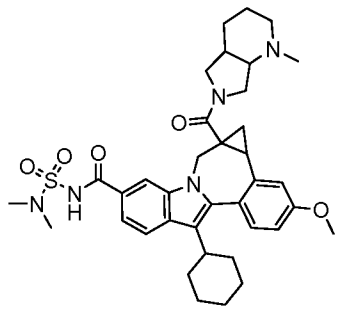
N-(aminosulfonyl)-8-cyclohexyl-1a-((5-(dimethylcarbamoyl)hexahydropyrrolo[3,4-c]pyrrol-2(1H)-yl)carbonyl)-11-methoxy-1,1a,2,12b-tetrahydrocyclopropa[d]indolo[2,1-a][2]benzazepine-5-carboxamide. To a stirred solution of N-(aminosulfonyl)-8-cyclohexyl-1a-(hexahydropyrrolo[3,4-c]pyrrol-2(1H)-ylcarbonyl)-11-methoxy-1,1a,2,12b-tetrahydrocyclopropa[d]indolo[2,1-a][2]benzazepine-5-carboxamide (29 mg, 0.047 mmol) and dimethylcarbamyl chloride (100 mg, 0.80 mmol) in CH2Cl2 (1 mL) was added triethylamine (0.1 mL). The reaction mixture was stirred at rt for 1h and concentrated to dryness. The residue was dissolved into MeOH (1.5 mL), filtered and purified by preparative HPLC (H2O/CH3CN with 10mM NH4OAc buffer) to yield N-(aminosulfonyl)-8-cyclohexyl-1a-((5-(dimethylcarbamoyl)hexahydropyrrolo[3,4-c]pyrrol-2(1H)-yl)carbonyl)-11-methoxy-1,1a,2,12b-tetrahydrocyclopropa[d]indolo[2,1-a][2]benzazepine-5-carboxamide (24 mg, 0.03 mmol, 74%) as a white solid. Presents as a complex mixture of rotamers and/or atrope isomers. 1HNMR (300 MHz, CD3OD) δ 0.16 - 0.23 (m, 0.2H), 1.06 - 3.82 (m, 30.6H), 3.87 - 3.93 (m, 3H), 4.20 (d, J = 15.0 Hz, 0.2H), 4.82 - 4.90 (m, 0.2H), 5.07 - 5.20 (m, 0.8H), 6.95 - 7.06 (m, 1H), 7.16 - 7.26 (m, 1H), 7.29 - 7.36 (m, 1H), 7.58 - 7.70 (m, 1H), 7.84 - 7.93 (m, 1H) 7.95 - 8.06 (m, 0.8H), 8.17 (s, 0.2H). LCMS: m/e 687 (M-H)-, ret time 2.26 min, column A, 4 minute gradient.

Example 7



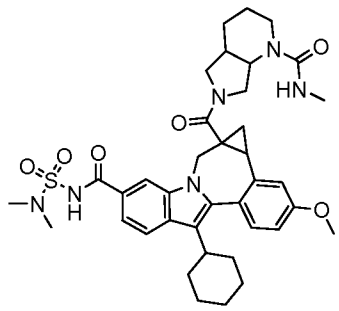
8-cyclohexyl-N-((dimethylamino)sulfonyl)-11-methoxy-1a-(octahydro-6H-pyrrolo[3,4-b]pyridin-6-ylcarbonyl)-1,1a,2,12b-tetrahydrocyclopropa[d]indolo[2,1-a][2]benzazepine-5-carboxamide. To a solution of 8-cyclohexyl-5-(((dimethylamino)sulfonyl)carbamoyl)-11-methoxy-1,12b-dihydrocyclopropa[d]indolo[2,1-a][2]benzazepine-1a(2H)-carboxylic acid (180 mg, 0.33 mmol) and tert-butyl octahydro-1H-pyrrolo[3,4-b]pyridine-1-carboxylate (90 mg, 0.40 mmol) in DMF (3 mL) and TEA (0.2 mL) was added HATU (162 mg, 0.43 mmol) as solid. The reaction was stirred at rt for 4h and then diluted with aq HCl (1.0N, 1.4 mL) and H2O (5 mL) while stirring. The off-white precipitate was collected via filtration, washed with H2O and dried to yield a crude intermediate as yellow solid. The crude intermediate (300 mg) was dissolved into CH2Cl2 (3 mL) with TFA (1 mL) and the reaction mixture was stirred at rt for 2 h. The volatile organic solvents was evaporated under vacuum and the yellow residue was purified by prep HPLC (H2O/MeOH with 0.1% TFA buffer) to yield 8-cyclohexyl-N-((dimethylamino)sulfonyl)-11-methoxy-1a-(octahydro-6H-pyrrolo[3,4-b]pyridin-6-ylcarbonyl)-1,1a,2,12b-tetrahydrocyclopropa[d]indolo[2,1-a][2]benzazepine-5-carboxamide (205 mg, 0.31 mmol, 94%) as a bright yellow solid. Presents as a 1:2 mixture of rotamers or atrope isomers. 1H NMR (300 MHz, MeOD) δ ppm 8.04 - 8.28 (m, 0.33H), 7.82 - 8.02 (m, 1.67H), 7.51 - 7.66 (m, 1H), 7.28 - 7.40 (m, 1H), 7.20 (s, 1H), 6.95 - 7.09 (m, 1H), 5.06 - 5.24 (m, 0.67H), 4.87 - 5.02 (m, 0.33H), 3.91 (s, 3H), 3.02 (s, 6H), 2.45 - 4.40 (m, 11H), 1.05 - 2.40 (m, 16.67H), 0.06 - 0.32 (m, 0.33H). LCMS: m/e 660 (M+H)+, Column C, Gradient time: 2 min, ret time 1.91 min.

Example 8



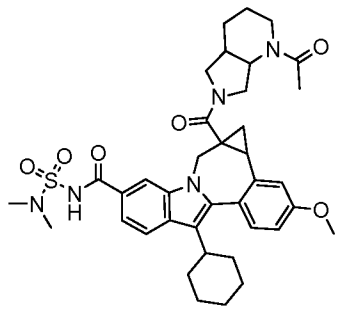
8-cyclohexyl-N-((dimethylamino)sulfonyl)-11-methoxy-1a-((1-methyloctahydro-6H-pyrrolo[3,4-b]pyridin-6-yl)carbonyl)-1,1a,2,12b-tetrahydrocyclopropa[d]indolo[2,1-a][2]benzazepine-5-carboxamide. To a solution of 8-cyclohexyl-N-((dimethylamino)sulfonyl)-11-methoxy-1a-(octahydro-6H-pyrrolo[3,4-b]pyridin-6-ylcarbonyl)-1,1a,2,12b-tetrahydrocyclopropa[d]indolo[2,1-a][2]benzazepine-5-carboxamide (50 mg, 0.076 mmol) in MeOH (1 mL) was added formaldehyde (37% in H2O, 0.03 mL) followed by sodium cyanotrihydroborate (24 mg, 0.38 mmol). The reaction mixture was stirred at rt for 2h, diluted with DMF and MeOH and purified by prep HPLC (H2O/MeOH with 0.1% TFA buffer) to yield 8-cyclohexyl-N-((dimethylamino)sulfonyl)-11-methoxy-1a-((1-methyloctahydro-6H-pyrrolo[3,4-b]pyridin-6-yl)carbonyl)-1,1a,2,12b-tetrahydrocyclopropa[d]indolo[2,1-a][2]benzazepine-5-carboxamide (43 mg, 0.064 mmol, 84%) as a bright yellow solid. 1H NMR (300 MHz, MeOD) δ ppm 8.05 - 8.30 (m, 0.25H), 7.83 - 8.04 (m, 1.75H), 7.53 - 7.66 (m, 1H), 7.29 - 7.39 (m, J = 8.42 Hz, 1H), 7.20 (s, 1H), 6.96 - 7.09 (m, 1H), 5.04 - 5.27 (m, 0.75H), 4.86 - 5.03 (m, 0.25H), 3.91 (s, 3H), 3.03 (s, 6H), 2.47 - 4.32 (m, 13H), 0.96 - 2.43 (m, 16.75H), 0.03 - 0.31 (m, 0.25H). LCMS: m/e 674 (M+H)+, Column C, Gradient time: 2 min, ret time 1.89 min.

Example 9



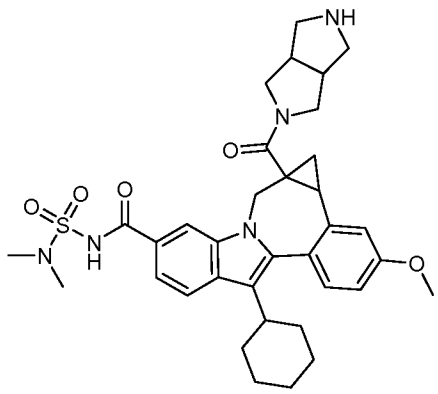
8-cyclohexyl-N-((dimethylamino)sulfonyl)-11-methoxy-1a-((1-(methylcarbamoyl)octahydro-6H-pyrrolo[3,4-b]pyridin-6-yl)carbonyl)-1,1a,2,12b-tetrahydrocyclopropa[d]indolo[2,1-a][2]benzazepine-5-carboxamide. To a solution of 8-cyclohexyl-N-((dimethylamino)sulfonyl)-11-methoxy-1a-(octahydro-6H-pyrrolo[3,4-b]pyridin-6-ylcarbonyl)-1,1a,2,12b-tetrahydrocyclopropa[d]indolo[2,1-a][2]benzazepine-5-carboxamide (50 mg, 0.076 mmol) in CH2Cl2 (1 mL) was added isocyanatomethane (13 mg, 0.23 mmol). The reaction mixture was stirred at rt for 16h and concentrated to dryness. The residue was dissolved into DMF and MeOH and purified by prep HPLC (H2O/MeOH with 0.1% TFA buffer) to yield 8-cyclohexyl-N-((dimethylamino)sulfonyl)-11-methoxy-1a-((1-(methylcarbamoyl)octahydro-6H-pyrrolo[3,4-b]pyridin-6-yl)carbonyl)-1,1a,2,12b-tetrahydrocyclopropa[d]indolo[2,1-a][2]benzazepine-5-carboxamide (20 mg, 0.028 mmol, 37%) as a yellow solid. 1H NMR (300 MHz, MeOD) δ ppm 8.11 - 8.16 (m, 0.2H), 7.85 - 8.00 (m, 1.8H), 7.53 - 7.66 (m, J=8.4, 1.5 Hz, 1H), 7.27 - 7.38 (m, 1H), 7.18 - 7.24 (m, J=2.6 Hz, 1H), 7.06 - 6.96 (m, J=8.4, 2.6 Hz, 1H), 5.20 (d, J=15.0 Hz, 0.8H), 4.75 - 4.92 (m, 0.2H), 4.34 - 4.53 (m, 0.8H), 4.17 (d, J=15.0 Hz, 0.2H), 3.91 (s, 3H), 3.02 (s, 6H), 2.79 - 3.86 (m, 8H), 2.77 (s, 1H), 2.68 (s, 2H), 2.35 - 2.50 (m, 0.5H), 0.98 - 2.33 (m, 16.5H), 0.54 - 0.67 (m, 0.5H), -0.64 - -0.47 (m, 0.5H). LCMS: m/e 717 (M+H)+, Column C, Gradient time: 2 min, ret time 2.15 min.

Example 10



1a-((1-acetyloctahydro-6H-pyrrolo[3,4-b]pyridin-6-yl)carbonyl)-8-cyclohexyl-N-((dimethylamino)sulfonyl)-11-methoxy-1,1a,2,12b-tetrahydrocyclopropa[d]indolo[2,1-a][2]benzazepine-5-carboxamide. To a solution of 8-cyclohexyl-N-((dimethylamino)sulfonyl)-11-methoxy-1a-(octahydro-6H-pyrrolo[3,4-b]pyridin-6-ylcarbonyl)-1,1a,2,12b-tetrahydrocyclopropa[d]indolo[2,1-a][2]benzazepine-5-carboxamide (40 mg, 0.061 mmol) and glacial acetic acid (37 mg, 0.62 mmol) in DMF (1 mL) and TEA (0.13 mL) was added HATU (116 mg, 0.31 mmol). The reaction mixture was stirred at rt for 16h, diluted with DMF and MeOH and purified by prep HPLC (H2O/MeOH with 0.1% TFA buffer) to yield two sets of products: Racemate pair A (first eluting product), 1a-((1-acetyloctahydro-6H-pyrrolo[3,4-b]pyridin-6-yl)carbonyl)-8-cyclohexyl-N-((dimethylamino)sulfonyl)-11-methoxy-1,1a,2,12b-tetrahydrocyclopropa[d]indolo[2,1-a][2]benzazepine-5-carboxamide (13 mg, 0.018 mmol, 30%) as yellow solid. 1H NMR (300 MHz, MeOD) δ ppm 7.86 - 8.15 (m, 2H), 7.55 - 7.72 (m, J=8.4, 1.5 Hz, 1H), 7.29 - 7.38 (m, J=8.4, 1H), 7.17 - 7.26 (m, 1H), 6.98 - 7.08 (m, J=8.4 Hz, 1H), 5.09 - 5.22 (m, J=15.4 Hz, 1H), 4.65 - 4.79 (m, 0.6H), 4.22 - 4.36 (m, 0.4H), 3.91 (s, 3H), 3.03 (s, 6H), 2.80 - 4.17 (m, 8H), 1.96 (s, 1.2H), 1.95 (s, 1.8H), 0.95 - 2.27 (m, 17.4H), -0.24 - -0.04 (m, 0.6H). LCMS: m/e 702 (M+H)+, Column C, Gradient time: 2 min, ret time 2.08 min. Racemate pair B (second eluting product), 1a-((1-acetyloctahydro-6H-pyrrolo[3,4-b]pyridin-6-yl)carbonyl)-8-cyclohexyl-N-((dimethylamino)sulfonyl)-11-methoxy-1,1a,2,12b-tetrahydrocyclopropa[d]indolo[2,1-a][2]benzazepine-5-carboxamide (16 mg, 0.023 mmol, 38%) as yellow solid. LCMS: m/e 702 (M+H)+, Column C, Gradient time: 2 min, ret time 2.14 min.

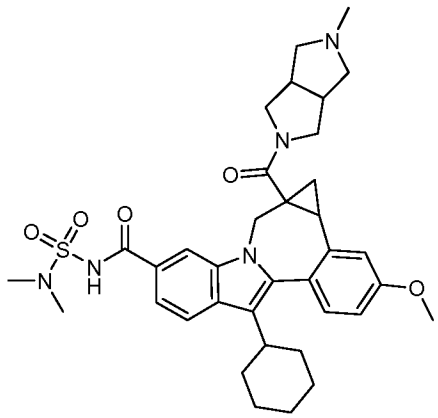
Example 11



rac-8-cyclohexyl-N-((dimethylamino)sulfonyl)-1a-((3aR,6aS)-hexahydropyrrolo[3,4-c]pyrrol-2(1H)-ylcarbonyl)-11-methoxy-1,1a,2,12b-tetrahydrocyclopropa[d]indolo[2,1-a][2]benzazepine-5-carboxamide. To a solution of 8-cyclohexyl-5-(((dimethylamino)sulfonyl)carbamoyl)-11-methoxy-1,12b-dihydrocyclopropa[d]indolo[2,1-a][2]benzazepine-1a(2H)-carboxylic acid (180 mg, 0.33 mmol) and 2-benzyloctahydropyrrolo[3,4-c]pyrrole (80 mg, 0.40 mmol) in DMF (3 mL) and TEA (0.2 mL) was added HATU (162 mg, 0.43 mmol) as a solid. The reaction mixture was stirred at rt for 4h, then aq HCl (1.0N, 1.4 mL) and H2O (5 mL) were added under stirring. The resulting off-white precipitate was collected via filtration, washed with H2O and dried to yield crude intermediate as a yellow solid. This crude intermediate (296 mg) was dissolved into MeOH/EtOAc/95% EtOH to this solution 10% Pd-C (catalytic) was added. The mixture was vigorously shaken under H2 (50 psi) at rt for 1 day, then filtered through Celite. The filtrate was concentrate down, purified by prep HPLC (H2O/MeOH with 0.1% TFA buffer) to yield rac-8-cyclohexyl-N-((dimethylamino)sulfonyl)-1a-((3aR,6aS)-hexahydropyrrolo[3,4-c]pyrrol-2(1H)-ylcarbonyl)-11-methoxy-1,1a,2,12b-tetrahydrocyclopropa[d]indolo[2,1-a][2]benzazepine-5-carboxamide (163 mg, 0.25 mmol, 77%) as a bright yellow solid. Presents as a 2:7 mixture of rotamers or atrope isomers. 1H NMR (300 MHz, MeOD) δ ppm 8.12 (br s, 0.22H), 7.99 (br s, 0.78H), 7.93 (d, J=8.4 Hz, 0.78H), 7.91 (d, J=8.4 Hz, 0.22H), 7.62 (dd, J=8.4, 1.5 Hz, 0.22H), 7.60 (dd, J=8.4, 1.5 Hz, 0.78H), 7.33 (d, J=8.4 Hz, 0.78H), 7.32 (d, J=8.4 Hz, 0.22H), 7.17 - 7.22 (m, 1H), 7.03 (dd, J=8.4, 2.6 Hz, 0.78H), 7.00 (dd, J=8.4, 2.6 Hz, 0.22H),

5.15 (d, J=15.4 Hz, 0.78H), 4.84 -4.90 (m, 0.22H), 4.20 (d, J=15.4 Hz, 0.22H), 3.92 (s, 0.66H) 3.90 (s, 2.34H), 3.62 (d, J=15.4 Hz, 0.78H), 3.03 (s, 6H), 2.51 - 4.03 (m, 12H), 1.06 - 2.21 (m, 11.78H), 0.13 - 0.19 (m, 0.22H). LCMS: m/e 646 (M+H)+, Column C, Gradient time: 2 min, ret time 1.88 min.

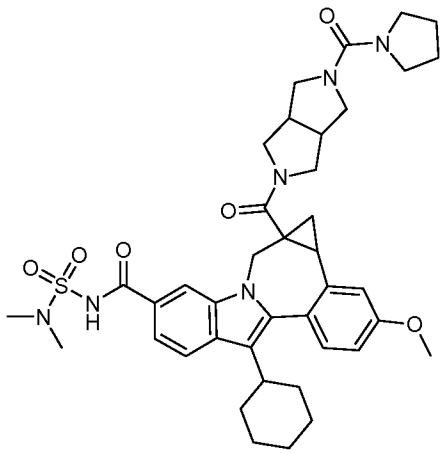
Example 12



8-cyclohexyl-N-((dimethylamino)sulfonyl)-11-methoxy-1a-((5-methylhexahydropyrrolo[3,4-c]pyrrol-2(1H)-yl)carbonyl)-1,1a,2,12b-tetrahydrocyclopropa[d]indolo[2,1-a][2]benzazepine-5-carboxamide. To a solution of rac-8-cyclohexyl-N-((dimethylamino)sulfonyl)-1a-((3aR,6aS)-hexahydropyrrolo[3,4-c]pyrrol-2(1H)-ylcarbonyl)-11-methoxy-1,1a,2,12b-tetrahydrocyclopropa[d]indolo[2,1-a][2]benzazepine-5-carboxamide (40 mg, 0.062 mmol) in MeOH (1 mL) and formaldehyde (37% in H2O, 0.03 mL) was added sodium cyanotrihydroborate (24 mg, 0.38 mmol). The reaction mixture was stirred at rt for 2h, diluted with DMF and MeOH and purified by prep HPLC (H2O/MeOH with 0.1% TFA buffer) to yield 8-cyclohexyl-N-((dimethylamino)sulfonyl)-11-methoxy-1a-((5-methylhexahydropyrrolo[3,4-c]pyrrol-2(1H)-yl)carbonyl)-1,1a,2,12b-tetrahydrocyclopropa[d]indolo[2,1-a][2]benzazepine-5-carboxamide (34 mg, 0.052 mmol, 83%) as a bright yellow solid. Presents as a 1:4 mixture of rotamers or atrope isomers. 1H NMR (300 MHz, MeOD) δ ppm 7.85 - 8.20 (m, 2H), 7.61 (br d, J=8.4 Hz, 1H), 7.27 - 7.38 (m, 1H), 7.13 - 7.23 (m, 1H), 6.95 - 7.08 (m, 1H), 5.18 (d, J=15.0 Hz, 0.8H), 4.93 (d, J=15.0 Hz, 0.2H), 4.21 (d, J=15.4 Hz, 0.2H),

3.92 (s, 0.6H), 3.91 (s, 2.4H), 3.66 (d, J=15.4 Hz, 0.8H), 3.04 (s, 1.2H), 3.03 (s, 4.8H), 2.46 - 4.20 (m, 15H), 1.04 - 2.25 (m, 11.8H), 0.15 - 0.25 (m, 0.2H). LCMS: m/e 660 (M+H)+, Column C, Gradient time: 2 min, ret time 1.86 min.

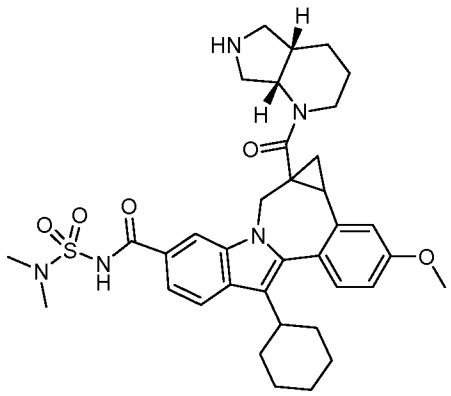
Example 13



8-cyclohexyl-N-((dimethylamino)sulfonyl)-11-methoxy-1a-((5-(1-pyrrolidinylcarbonyl)hexahydropyrrolo[3,4-c]pyrrol-2(1H)-yl)carbonyl)-1,1a,2,12b-tetrahydrocyclopropa[d]indolo[2,1-a][2]benzazepine-5-carboxamide. To a solution of rac-8-cyclohexyl-N-((dimethylamino)sulfonyl)-1a-((3aR,6aS)-hexahydropyrrolo[3,4-c]pyrrol-2(1H)-ylcarbonyl)-11-methoxy-1,1a,2,12b-tetrahydrocyclopropa[d]indolo[2,1-a][2]benzazepine-5-carboxamide (40 mg, 0.062 mmol) in THF (1 mL), pyrrolidine-1-carbonyl chloride (0.02 mL) was added dropwise, followed by the addition of TEA (0.04 mL). The reaction was stirred at rt for 16h, diluted with DMF and MeOH and purified by prep HPLC (H2O/MeOH with 0.1% TFA buffer) to yield 8-cyclohexyl-N-((dimethylamino)sulfonyl)-11-methoxy-1a-((5-(1-pyrrolidinylcarbonyl)hexahydropyrrolo[3,4-c]pyrrol-2(1H)-yl)carbonyl)-1,1a,2,12b-tetrahydrocyclopropa[d]indolo[2,1-a][2]benzazepine-5-carboxamide (31 mg, 0.042 mmol, 67%) as a yellow solid. Presents as a 1:4 mixture of rotamers or atrope isomers. 1H NMR (300 MHz, MeOD) δ ppm 8.14 (s, 0.2H), 7.84 - 8.03 (m, 1.8H), 7.51 - 7.65 (m, 1H), 7.33 (d, J=8.8 Hz, 1H), 7.20 (d, J=2.6 Hz, 0.8H), 7.19 (d, J=2.6 Hz, 0.2H), 7.03 (dd, J=8.8, 2.6 Hz, 0.8H), 6.99 (dd, J=8.8, 2.6 Hz, 0.2H), 5.13 (d, J=15.4 Hz, 0.8H), 4.80 - 4.91 (m, 0.2H), 4.22 (d, J=15.0 Hz, 0.2H), 4.00 (s, 1.6H),

3.91 (s, 0.6H), 3.90 (s, 2.4H), 3.02 (s, 1.2H), 3.01 (s, 4.8H), 1.70 - 3.83 (m, 25.2H), 1.08 - 1.64 (m, 5.8H), 0.10 - 0.18 (m, 0.2H). LCMS: m/e 743 (M+H)+, Column C, Gradient time: 2 min, ret time 2.19 min.

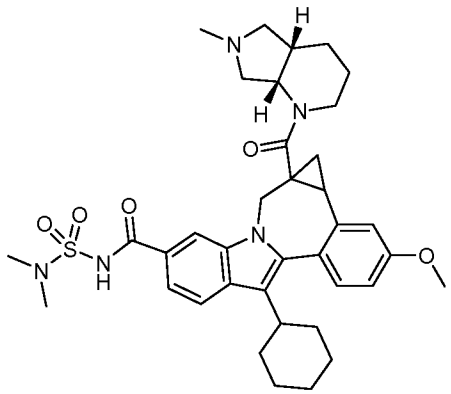
Example 14



rac-8-cyclohexyl-N-((dimethylamino)sulfonyl)-11-methoxy-1a-((4aR,7aR)-octahydro-1H-pyrrolo[3,4-b]pyridin-1-ylcarbonyl)-1,1a,2,12b-tetrahydrocyclopropa[d]indolo[2,1-a][2]benzazepine-5-carboxamide. To a solution of 8-cyclohexyl-5-(((dimethylamino)sulfonyl)carbamoyl)-11-methoxy-1,12b-dihydrocyclopropa[d]indolo[2,1-a][2]benzazepine-1a(2H)-carboxylic acid (180 mg, 0.33 mmol) and rac-(4aS,7aS)-6-benzyloctahydro-1H-pyrrolo[3,4-b]pyridine dihydrochloride (114 mg, 0.40 mmol) in DMF (3 mL) and TEA (0.2 mL) was added HATU (162 mg, 0.43 mmol). The reaction was stirred at rt for 2h, then aq HCl (1.0N, 1.3 mL) and H2O (5 mL) were added under stirring. The precipitate was collected via filtration, washed with H2O and dried to yield crude intermediate as an orange solid. This crude intermediate (270 mg) was dissolved in MeOH/EtOAc/95% EtOH and to this solution 10 %Pd-C (catalytic) was added. The mixture was vigorously shaken under H2 (50 psi) at rt for 16h and then filtered through Celite. The filtrate was concentrated, and the residue was purified by prep HPLC (H2O/MeOH with 0.1% TFA buffer) to yield rac-8-cyclohexyl-N-((dimethylamino)sulfonyl)-11-methoxy-1a-((4aR,7aR)-octahydro-1H-pyrrolo[3,4-b]pyridin-1-ylcarbonyl)-1,1a,2,12b-tetrahydrocyclopropa[d]indolo[2,1-a][2]benzazepine-5-carboxamide (142 mg, 0.22 mmol, 66%) as a bright yellow solid. Presents as a 1:4 mixture of rotamers or atrope

isomers. 1H NMR (300 MHz, MeOD) δ ppm 7.85 - 8.12 (m, 2H), 7.52 - 7.65 (m, 1H), 7.30 - 7.38 (m, 1H), 7.16 - 7.23 (m, 1H), 6.99 - 7.08 (m, 1H), 3.92 (s, 0.6H), 3.89 - 3.92 (m, 2.4H), 3.04 (s, 2H), 3.03 (s, 4H), 2.40 - 5.18 (m, 12H), 0.98 -2.25 (m, 15.8H), 0.15 - 0.27 (m, 0.2H). LCMS: m/e 660 (M+H)+, Column C, Gradient time: 2 min, ret time 1.92 min.

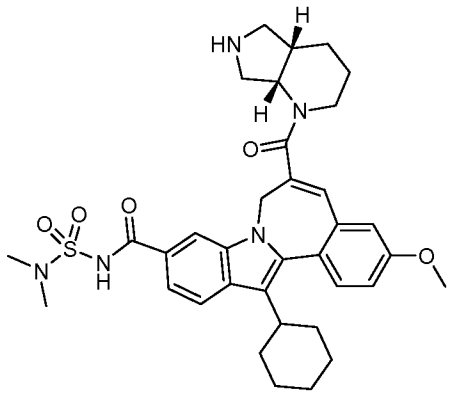
Example 15



rac-8-cyclohexyl-N-((dimethylamino)sulfonyl)-11-methoxy-1a-(((4aR,7aR)-6-methyloctahydro-1H-pyrrolo[3,4-b]pyridin-1-yl)carbonyl)-1,1a,2,12b-tetrahydrocyclopropa[d]indolo[2,1-a][2]benzazepine-5-carboxamide. To a solution of rac-8-cyclohexyl-N-((dimethylamino)sulfonyl)-11-methoxy-1a-((4aR,7aR)-octahydro-1H-pyrrolo[3,4-b]pyridin-1-ylcarbonyl)-1,1a,2,12b-tetrahydrocyclopropa[d]indolo[2,1-a][2]benzazepine-5-carboxamide (40 mg, 0.061 mmol) and formaldehyde (37% in H2O, 0.03 mL) in MeOH (1 mL) was added sodium cyanotrihydroborate (24 mg, 0.38 mmol). The reaction was stirred at rt for 2h, diluted with DMF and MeOH and purified by prep HPLC (H2O/MeOH with 0.1% TFA buffer) to yield rac-8-cyclohexyl-N-((dimethylamino)sulfonyl)-11-methoxy-1a-(((4aR,7aR)-6-methyloctahydro-1H-pyrrolo[3,4-b]pyridin-1-yl)carbonyl)-1,1a,2,12b-tetrahydrocyclopropa[d]indolo[2,1-a][2]benzazepine-5-carboxamide (36 mg, 0.053 mmol, 88%) as a bright yellow solid. Presents as a 1:9 mixture of rotamers or atrope isomers. 1H NMR (300 MHz, MeOD) δ ppm 7.84 - 8.12 (m, 2H), 7.51 - 7.65 (m, 1H), 7.29 - 7.40 (m, 1H), 7.16 - 7.23 (m, 1H), 6.99 - 7.09 (m, 1H), 3.89 - 3.93 (m, 3H), 3.02 - 3.06 (m, 6H), 2.23 - 5.33 (m, 15H), 1.01 -

2.22 (m, 15.9H), 0.15 - 0.26 (m, 0.1H). LCMS: m/e 674 (M+H)+, Column C, Gradient time: 2 min, ret time 1.92 min.

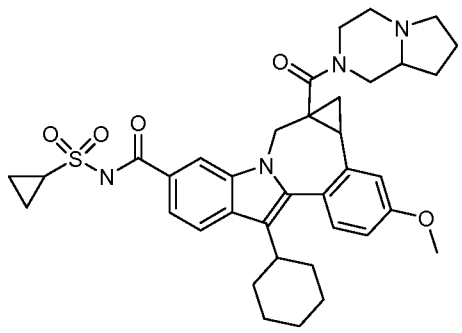
Example 16



13-cyclohexyl-N-((dimethylamino)sulfonyl)-3-methoxy-6-((4aS,7aS)-octahydro-1H-pyrrolo[3,4-b]pyridin-1-ylcarbonyl)-7H-indolo[2,1-a][2]benzazepine-10-carboxamide. To a solution of 13-cyclohexyl-10-(((dimethylamino)sulfonyl)carbamoyl)-3-methoxy-7H-indolo[2,1-a][2]benzazepine-6-carboxylic acid (178 mg, 0.33 mmol) and (4aS,7aS)-6-benzyloctahydro-1H-pyrrolo[3,4-b]pyridine dihydrochloride (114 mg, 0.40 mmol) in DMF (3 mL) and TEA (0.2 mL) was added HATU (162 mg, 0.43 mmol). The reaction was stirred at rt for 2 h, then aq HCl (1.0N, 1.3 mL) and H2O (5 mL) were added under stirring. The resulting precipitate was collected via filtration, washed with H2O and dried to yield crude intermediate as an orange solid. This crude intermediate (260 mg) was dissolved into MeOH/EtOAc/95% EtOH and to this solution 10% Pd-C (catalytic) was added. The mixture was vigorously shaken under H2 (50 psi) at rt for 16h, then filtered through Celite. The filtrate was concentrated and the residue was purified by prep HPLC (H2O/MeOH with 0.1% TFA buffer) to yield 13-cyclohexyl-N-((dimethylamino)sulfonyl)-3-methoxy-6-((4aS,7aS)-octahydro-1H-pyrrolo[3,4-b]pyridin-1-ylcarbonyl)-7H-indolo[2,1-a][2]benzazepine-10-carboxamide (129 mg, 0.20 mmol, 61%) as a yellow solid. 1H NMR (300 MHz, MeOD) δ ppm 8.11 (s, 1H), 7.93 (d, J=8.8 Hz, 1H), 7.59 (dd, J=8.4, 1.5 Hz, 1H), 7.58 (d, J=8.8 Hz, 1H), 7.18 (dd, J=8.8, 2.6 Hz, 1H), 7.03 - 7.11 (m, 1H), 6.91 - 7.00 (m, 1H), 4.99 - 5.22 (m,

1H), 4.24 - 4.54 (m, 1H), 3.93 (s, 3H), 3.03 (s, 6H), 2.75 - 4.02 (m, 8H), 1.12 - 2.47 (m, 16H). LCMS: m/e 646 (M+H)+, Column C, Gradient time: 2 min, ret time 1.93 min.

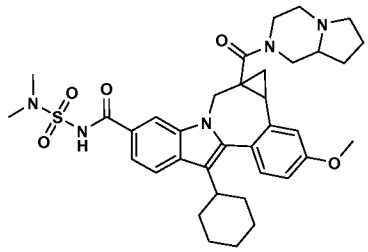
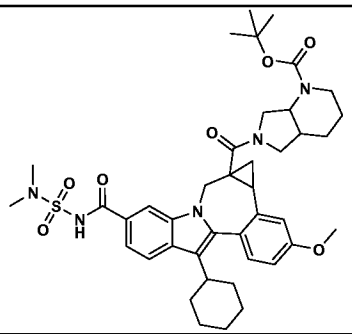
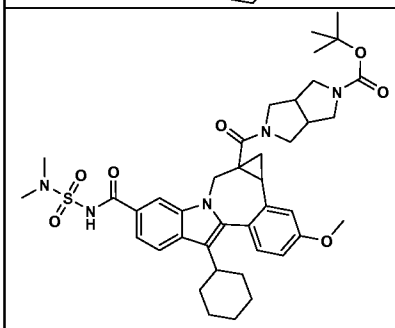
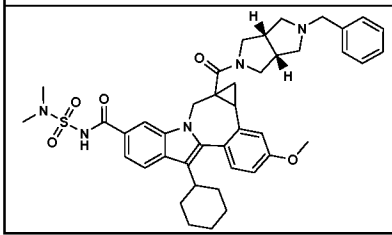
Example 17

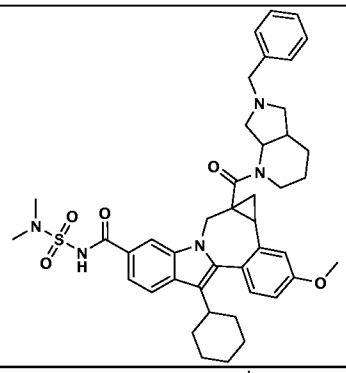
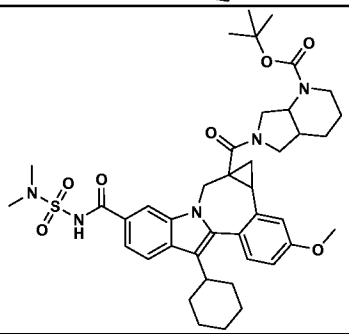
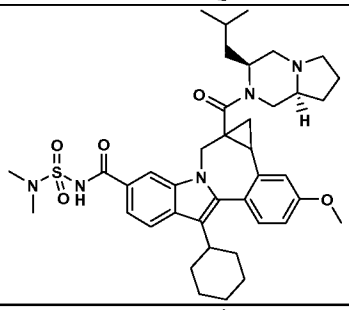
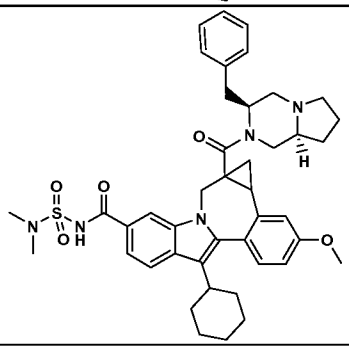


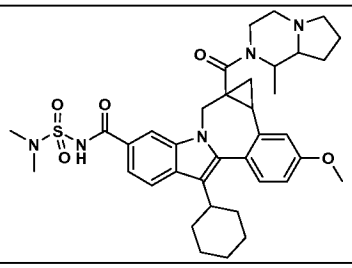
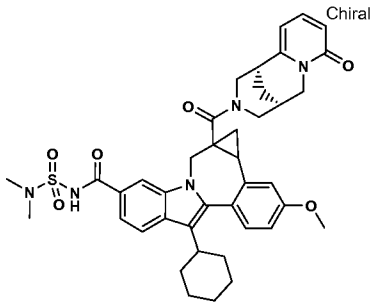
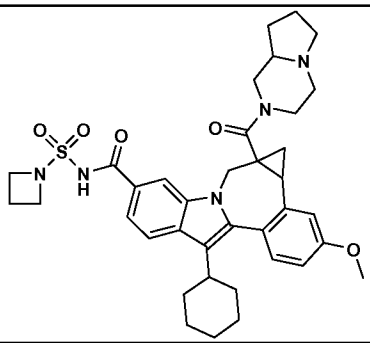
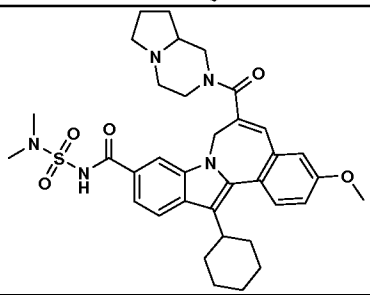
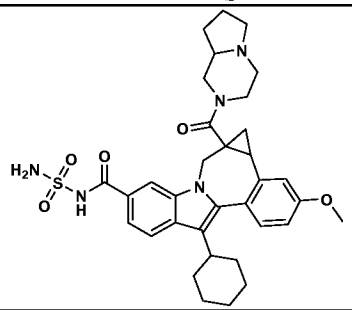
(+/-) 8-cyclohexyl-N-(cyclopropylsulfonyl)-1,1a,2,12b-tetrahydro-11-methoxy-1a-(1-(hexahydropyrrolo[1,2-a]pyrazin-2(1H)-yl))-8-carbonyl)-cycloprop[d]indolo[2,1-a][2]benzazepine-5-carboxamide. A TFA salt of the product was prepared in similar method from acid 7-1 (0.062g, 0.11 mmol), in similar method as described in 1-1 (0.063 g, 73%). LC-MS retention time: 3.05; MS m/z 657 (M+H). The product was analyzed by the 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.

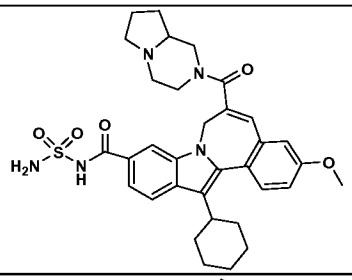
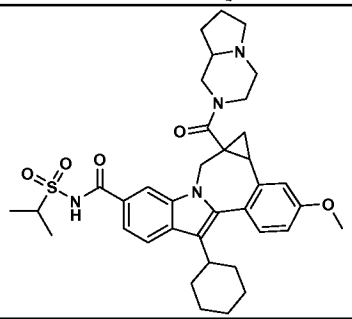
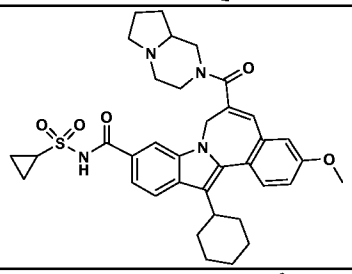
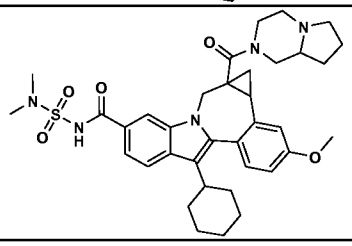
The general procedures below pertain to the experimental procedures that follow until noted. The acid (0.055 mmol, 1 eq.) was dissolved in dried DMF and followed by adding HATU (0.083 mmol, 1.5 eq.) and DIPEA(0.083. 1.5 eq.). The solution was stirred for 2 minutes and added into pre-weighted amine (0.083 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

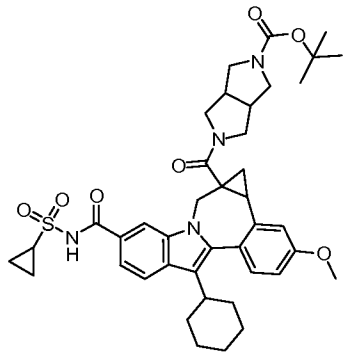
C: Column: Waters x-Bidge C18 150x4.6mm 5 micron; mobile phase: water, 10 mM NH_4OH, ACN; Method D: Column: Waters Xbridge 2.1x50mm 5 um C18; mobile phase: water, 10 mM NH_4OH, ACN.

Structure	HPLC Ret. Time [min]	HPLC Purity [%]	MS Reported Mass	HPLC Method
	4.89	100	660.4	Method A
	5.07	100	760.39	Method A
	5.16	95.3	746.42	Method A
	5.42	100	736.42	Method A

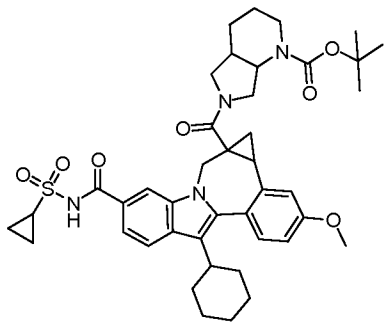
Structure	HPLC Ret. Time [min]	HPLC Purity [%]	MS Reported Mass	HPLC Method
	5.94	100	750.45	Method A
	5.38	100	760.42	Method A
	8.88	100	716.41	Method B
	8.87	100	750.4	Method B

Structure	HPLC Ret. Time [min]	HPLC Purity [%]	MS Reported Mass	HPLC Method
	7.22	96.4	674.34	Method B
	6.11	100	724.33	Method B
	8.3	98.1	672.23	Method C
	2.65	98.2	646.75	Method E
	2.33	100	631.79	Method D

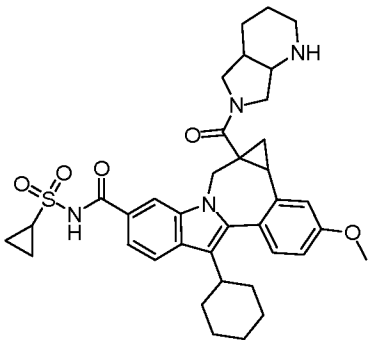
Structure	HPLC Ret. Time [min]	HPLC Purity [%]	MS Reported Mass	HPLC Method
	7.61	100	618.14	Method D
	6.26	100	659.22	Method D
	2.26	100	642.76	Method D
	2.43	100.0	660.41	Method D



tert-Butyl 5-((8-cyclohexyl-5-((cyclopropylsulfonyl)carbamoyl)-11-methoxy-1,12b-dihydrocyclopropa[d]indolo[2,1-a][2]benzazepin-1a(2H)-yl)carbonyl)hexahydropyrrolo[3,4-c]pyrrole-2(1H)-carboxylate. HATU (270 mg, 0.71 mmol) was added to a stirring solution of 8-cyclohexyl-5-((cyclopropylsulfonyl)carbamoyl)-11-methoxy-1,12b-dihydrocyclopropa[d]indolo[2,1-a][2]benzazepine-1a(2H)-carboxylic acid (300 mg, 0.55 mmol)and tert-butyl hexahydropyrrolo[3,4-c]pyrrole-2(1H)-carboxylate (140 mg, 0.66 mmol) in DMF (5 mL) and TEA (0.3 mL) and the reaction was stirred at rt for 1 h. H2O (10 mL) was added to the reaction mixture and the resulting white precipitate was collected by filtration, rinsed with water and dried to yield a crude yellow solid (476 mg). H2O was added drop wise to a clear solution of this crude material dissolved into MeOH and the resulting white precipitate was collected by filtration, rinsed with 1:1 MeOH/H2O, dried to yield tert-butyl 5-((8-cyclohexyl-5-((cyclopropylsulfonyl)carbamoyl)-11-methoxy-1,12b-dihydrocyclopropa[d]indolo[2,1-a][2]benzazepin-1a(2H)-yl)carbonyl)hexahydropyrrolo[3,4-c]pyrrole-2(1H)-carboxylate (212 mg, 0.29 mmol, 52%) as a white solid. The compound was isolated as a mixture of enantiomers and presents as a 1:4 mixture of rotamers or atrope isomers. 1H NMR (300 MHz, CD3OD) ppm δ 8.15 - 8.08 (m, 0.2H), 8.00 - 7.82 (m, 1.8H), 7.69 - 7.51 (m, 1H), 7.33 (d, J = 8.8 Hz, 1H), 7.23 - 7.16 (m, 1H), 7.07 - 6.97 (m, 1H), 5.11 (d, J = 15.4 Hz, 0.8H), 4.25 - 4.14 (m, 0.2H), 3.92 (s, 0.6H), 3.90 (s, 2.4H), 3.81 - 0.73 (m, 38.8H), 0.17 - 0.06 (m, 0.2H). LCMS : m/e = 743 (M+H)+, retention time = 2.24 min, (Column = (2)phenomenex 4.6x50mmC18 10um, Solvent A = 10% MeOH - 90% H20 - 0.1% TFA, Solvent B = 90% MeOH - 10% H2O - 0.1% TFA Start % B = 0, Final % B = 100, Gradient Time = 2 min, Hold time = 1 min, Flow Rate = 5 mL /min).

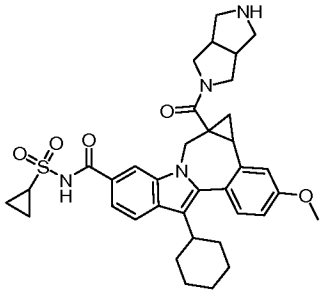


tert-Butyl 6-((8-cyclohexyl-5-((cyclopropylsulfonyl)carbamoyl)-11-methoxy-1,12b-dihydrocyclopropa[d]indolo[2,1-a][2]benzazepin-1a(2H)-yl)carbonyl)octahydro-1H-pyrrolo[3,4-b]pyridine-1-carboxylate. HATU (180 mg, 0.47 mmol) was added to a stirring solution of 8-cyclohexyl-5-((cyclopropylsulfonyl)carbamoyl)-11-methoxy-1,12b-dihydrocyclopropa[d]indolo[2,1-a][2]benzazepine-1a(2H)-carboxylic acid (200 mg, 0.36 mmol) and tert-butyl octahydro-1H-pyrrolo[3,4-b]pyridine-1-carboxylate (100 mg, 0.44 mmol) in DMF (4 mL) and TEA (0.2 mL) and the reaction was stirred at rt for 1 h. H2O (10 mL) was added to the mixture and the resulting white precipitate was collected by filtration, rinsed with water and dried to yield a crude yellow solid (285 mg). This crude was then triturated with 1:1 MeOH/H2O and dried to yield tert-butyl 6-((8-cyclohexyl-5-((cyclopropylsulfonyl)carbamoyl)-11-methoxy-1,12b-dihydrocyclopropa[d]indolo[2,1-a][2]benzazepin-1a(2H)-yl)carbonyl)octahydro-1H-pyrrolo[3,4-b]pyridine-1-carboxylate (257 mg, 0.34 mmol, 95%) as a white solid. The compound was isolated as a mixture of four stereoisomers. 1H NMR (300 MHz, CD3OD) δ ppm 8.16 - 7.84 (m, 2H), 7.70 - 7.52 (m, 1H), 7.36 - 7.25 (m, 1H), 7.25 - 7.14 (m, 1H), 7.06 - 6.93 (m, 1H), 5.28 - 5.04 (m, 0.8H), 4.56 - 4.25 (m, 1H), 4.09 - 3.94 (m, 0.2H), 3.91 (s, 3H), 3.83 - 2.70 (m, 7H), 2.43 - 0.54 (m, 32.8H), -0.17 - -0.37 (m, 0.2H). LCMS: m/e = 757 (M+H)+, retention time = 2.28 min (Column = (2)phenomenex 4.6x50mmC18 10um, Solvent A = 10% MeOH - 90% H20 - 0.1% TFA, Solvent B = 90% MeOH - 10% H2O - 0.1% TFA, Start % B = 0, Final % B = 100, Gradient Time = 2 min, Hold time = 1 min, Flow Rate = 5 mL /min).



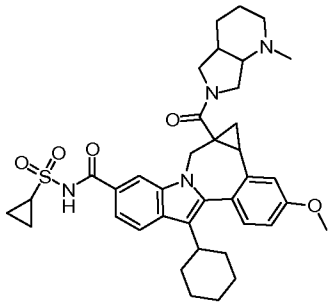
8-Cyclohexyl-N-(cyclopropylsulfonyl)-11-methoxy-1a-(octahydro-6H-pyrrolo[3,4-b]pyridin-6-ylcarbonyl)-1,1a,2,12b-tetrahydrocyclopropa[d]indolo[2,1-a][2]benzazepine-5-carboxamide. TFA (1.0 mL , 13 mmol) was added to a stirring solution of tert-butyl 6-((8-cyclohexyl-5-((cyclopropylsulfonyl)carbamoyl)-11-methoxy-1,12b-dihydrocyclopropa[d]indolo[2,1-a][2]benzazepin-1a(2H)-yl)carbonyl)octahydro-1H-pyrrolo[3,4-b]pyridine-1-carboxylate 87 (231 mg, 0.305 mmol) in CH2Cl2 (3 mL) and the reaction was stirred at rt for 2 h. The reaction mixture was concentrated under vacuum and the residue was triturated with Et2O to yield crude 8-cyclohexyl-N-(cyclopropylsulfonyl)-11-methoxy-1a-(octahydro-6H-pyrrolo[3,4-b]pyridin-6-ylcarbonyl)-1,1a,2,12b-tetrahydrocyclopropa[d]indolo[2,1-a][2]benzazepine-5-carboxamide xTFA (257 mg) as a yellow solid, which was used without further purification. A portion (16 mg, 6.2%) of this crude product was purified by preparative HPLC (H2O/MeOH with 0.1% TFA buffer) to yield product 8-cyclohexyl-N-(cyclopropylsulfonyl)-11-methoxy-1a-(octahydro-6H-pyrrolo[3,4-b]pyridin-6-ylcarbonyl)-1,1a,2,12b-tetrahydrocyclopropa[d]indolo[2,1-a][2]benzazepine-5-carboxamide (11.7 mg, 0.018 mmol, 95%) as a white solid. The compound was isolated as a mixture of four stereoisomers. 1H NMR (300 MHz, CD3OD) δ ppm 8.24 (s, 0.1H), 8.12 (s, 0.2H), 8.04 - 7.86 (m, 1.7H), 7.68 - 7.53 (m, 1H), 7.40 - 7.29 (m, 1H), 7.21 (s, 1H), 7.10 - 6.96 (m, 1H), 5.23 - 4.82 (m, 1H), 4.44 - 2.46 (m, 12H), 3.92, 3.91 (s, s, 3H), 2.43 - 1.03 (m, 20.7H), 0.85 - 0.67 (m, 0.1H), 0.33 - 0.11 (m, 0.2H). LCMS: m/e = 657 (M+H)+, retention time = 3.38 min (Column = (2)phenomenex 4.6x50mmC18 10um, Solvent A = 10% MeOH - 90% H20 - 0.1% TFA, Solvent B = 90% MeOH - 10% H2O - 0.1% TFA, Start % B = 0,

Final % B = 100, Gradient Time = 4 min, Hold time = 1 min, Flow Rate = 4 mL /min).



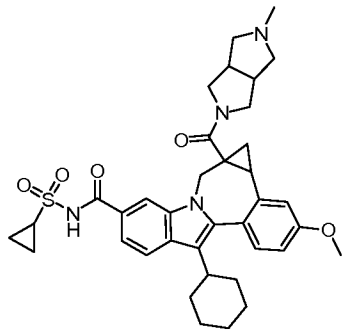
8-Cyclohexyl-*N*-(cyclopropylsulfonyl)-1a-(hexahydropyrrolo[3,4-*c*]pyrrol-2(1*H*)-ylcarbonyl)-11-methoxy-1,1a,2,12b-tetrahydrocyclopropa[*d*]indolo[2,1-*a*][2]benzazepine-5-carboxamide. TFA (1.0 mL , 13 mmol) was added to a stirring solution of *tert*-butyl 5-((8-cyclohexyl-5-((cyclopropylsulfonyl)carbamoyl)-11-methoxy-1,12b-dihydrocyclopropa[*d*]indolo[2,1-*a*][2]benzazepin-1a(2*H*)-yl)carbonyl)hexahydropyrrolo[3,4-*c*]pyrrole-2(1*H*)-carboxylate (203 mg, 0.273 mmol) in CH_2Cl_2 (3 mL) and the mixture was stirred at rt for 2 h. The reaction mixture was concentrated and the residue was triturated with Et_2O to yield crude 8-cyclohexyl-*N*-(cyclopropylsulfonyl)-1a-(hexahydropyrrolo[3,4-*c*]pyrrol-2(1*H*)-ylcarbonyl)-11-methoxy-1,1a,2,12b-tetrahydrocyclopropa[*d*]indolo[2,1-*a*][2]benzazepine-5-carboxamide xTFA (240 mg, 0.373 mmol) as a yellow solid which was used without further purification. A portion of the crude material (26 mg, 11%) was purified by preparative HPLC (H_2O-MeOH with 0.1% TFA buffer) to yield 8-cyclohexyl-*N*-(cyclopropylsulfonyl)-1a-(hexahydropyrrolo[3,4-*c*]pyrrol-2(1*H*)-ylcarbonyl)-11-methoxy-1,1a,2,12b-tetrahydrocyclopropa[*d*]indolo[2,1-*a*][2]benzazepine-5-carboxamide (13.9 mg, 0.022 mmol, 74%) as a white solid. The compound was isolated as a mixture of enantiomers and presents as a 1:4 mixture of rotamers or atrope isomers. ^{1}H NMR (300 MHz, CD_3OD) δ ppm 8.16 - 8.11 (m, 0.2H), 8.01 (br s, 0.8H), 7.96 - 7.87 (m, 1H), 7.65 - 7.55 (m, 1H), 7.37 - 7.28 (m, 1H), 7.22 - 7.16 (m, 1H), 7.07 - 6.97 (m, 1H), 5.16 (d, *J* = 15.4 Hz, 0.8H), 4.25 - 4.16 (m, 0.2H), 4.01 - 2.47 (m, 14H), 3.92 (s, 0.6H), 3.91 (s, 2.4H), 2.23 - 1.06 (m, 16.8H), 0.22 - 0.10 (m, 0.2H). LCMS: m/e = 643 $(M+H)^+$, retention time = 3.30 min

(Column = (2)phenomenex 4.6x50mmC18 10um, Solvent A = 10% MeOH - 90% H_20 - 0.1% TFA, Solvent B = 90% MeOH - 10% H_2O - 0.1% TFA, Start % B = 0, Final % B = 100, Gradient Time = 4 min, Hold time = 1 min, Flow Rate = 4 mL /min).

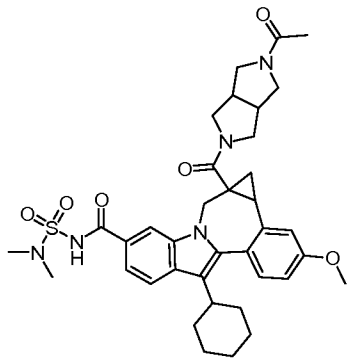


8-Cyclohexyl-*N*-(cyclopropylsulfonyl)-11-methoxy-1a-((1-methyloctahydro-6*H*-pyrrolo[3,4-b]pyridin-6-yl)carbonyl)-1,1a,2,12b-tetrahydrocyclopropa[*d*]indolo[2,1-*a*][2]benzazepine-5-carboxamide. Sodium cyanoborohydride (19.13 mg, 0.304 mmol) was added to a stirring solution of 8-cyclohexyl-*N*-(cyclopropylsulfonyl)-11-methoxy-1a-(octahydro-6*H*-pyrrolo[3,4-b]pyridin-6-ylcarbonyl)-1,1a,2,12b-tetrahydrocyclopropa[*d*]indolo[2,1-*a*][2]benzazepine-5-carboxamide (40 mg, 0.061 mmol) and formaldehyde (0.025 mL , 0.30 mmol) in MeOH (1 mL) and the reaction was stirred at rt for 2 h. The reaction mixture was diluted with MeOH and DMF, and purified by preparative HPLC (H_2O-MeOH with 0.1% TFA buffer) to yield product 8-cyclohexyl-*N*-(cyclopropylsulfonyl)-11-methoxy-1a-((1-methyloctahydro-6*H*-pyrrolo[3,4-b]pyridin-6-yl)carbonyl)-1,1a,2,12b-tetrahydrocyclopropa[*d*]indolo[2,1-*a*][2]benzazepine-5-carboxamide (21.8 mg, 0.032 mmol, 53 % yield) as an off white solid. The compound was isolated as a mixture of four stereoisomers. ^{1}H NMR (300 MHz, CD_3OD) δ ppm 8.29 - 8.04 (m, 0.3H), 8.04 - 7.85 (m, 1.7H), 7.66 - 7.54 (m, 1H), 7.38 - 7.27 (m, 1H), 7.20 (d, *J* = 2.2 Hz, 1H), 7.08 - 6.97 (m, 1H), 5.23 -5.07 (m, 0.7H), 4.99 - 4.83 (m, 0.3H), 4.45 - 2.46 (m, 15H), 3.91 (s, 3H), 2.25 - 0.98 (m, 19.7H), 0.31 - 0.05 (m, 0.3H). LCMS: m/e = 671 $(M+H)^+$, retention time = 3.37 min (Column = (2)phenomenex 4.6x50mmC18 10um, Solvent A = 10% MeOH - 90% H20 - 0.1% TFA, Solvent B = 90% MeOH - 10% H2O - 0.1% TFA, Start % B = 0,

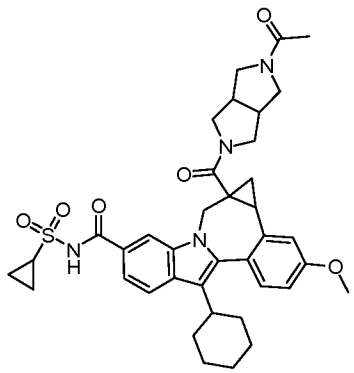
Final % B = 100 Gradient Time = 4 min, Hold time = 1 min, Flow Rate = 4 mL /min).



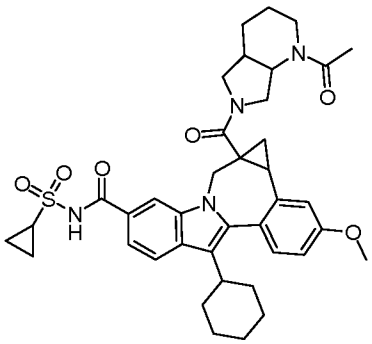
8-Cyclohexyl-*N*-(cyclopropylsulfonyl)-11-methoxy-1a-((5-methylhexahydropyrrolo[3,4-*c*]pyrrol-2(1*H*)-yl)carbonyl)-1,1a,2,12b-tetrahydrocyclopropa[*d*]indolo[2,1-*a*][2]benzazepine-5-carboxamide. Sodium cyanoborohydride (20 mg, 0.31 mmol) was added to a stirring solution of 8-cyclohexyl-*N*-(cyclopropylsulfonyl)-1a-(hexahydropyrrolo[3,4-*c*]pyrrol-2(1*H*)-ylcarbonyl)-11-methoxy-1,1a,2,12b-tetrahydrocyclopropa[*d*]indolo[2,1-*a*][2]benzazepine-5-carboxamide (40 mg, 0.062 mmol) and formaldehyde (0.023 mL, 0.31 mmol) in MeOH (1 mL) and the reaction mixture was stirred at rt for 2 h. The reaction was diluted with MeOH and DMF, and purified by preparative HPLC (H_2O-MeOH with 0.1% TFA buffer) to yield 8-cyclohexyl-*N*-(cyclopropylsulfonyl)-11-methoxy-1a-((5-methylhexahydropyrrolo[3,4-*c*]pyrrol-2(1*H*)-yl)carbonyl)-1,1a,2,12b-tetrahydrocyclopropa[*d*]indolo[2,1-*a*][2]benzazepine-5-carboxamide (23.9 mg, 0.036 mmol, 59% yield) as an off white solid. The compound was isolated as a mixture of enantiomers and presents as a 1:4 mixture of rotamers or atrope isomers. ^{1}H NMR (300 MHz, CD_3OD) δ ppm 8.09 - 8.22 (m, 0.2H), 8.01 (s, 0.8H), 7.87 - 7.99 (m, 1H), 7.62 (d, *J* = 8.78 Hz, 1H), 7.37 - 7.28 (m, 1H), 7.23 - 7.17 (m, 1H), 7.07 - 6.96 (m, 1H), 5.15 (d, *J* = 15.37 Hz, 0.8H), 4.97 - 4.82 (m, 0.2H), 4.24 - 2.44 (m, 17H), 3.92, 3.90 (s, s, 3H), 2.21 - 1.01 (m, 15.8H), 0.23 - 0.12 (m, 0.2H). LCMS : m/e = 657 $(M+H)^+$, retention time = 3.31 min (Column = (2)phenomenex 4.6x50mmC18 10um, Solvent A = 10% MeOH - 90% H20 - 0.1% TFA, Solvent B = 90% MeOH - 10% H2O - 0.1% TFA, Start % B = 0, Final % B = 100, Gradient Time = 4 min, Hold time = 1 min, Flow Rate = 4 mL /min).



1a-((5-Acetylhexahydropyrrolo[3,4-*c*]pyrrol-2(1*H*)-yl)carbonyl)-8-cyclohexyl-*N*-(dimethylsulfamoyl)-11-methoxy-1,1a,2,12b-tetrahydrocyclopropa[*d*]indolo[2,1-*a*][2]benzazepine-5-carboxamide. HATU (46 mg, 0.12 mmol) was added to a stirring solution of *rac*-8-cyclohexyl-*N*-((dimethylamino)sulfonyl)-1a-((3a*R*,6a*S*)-hexahydropyrrolo[3,4-*c*]pyrrol-2(1*H*)-ylcarbonyl)-11-methoxy-1,1a,2,12b-tetrahydrocyclopropa[*d*]indolo[2,1-*a*][2]benzazepine-5-carboxamide (60 mg, 0.093 mmol) and acetic acid (7 µl, 0.1 mmol) in DMF (1 mL) and TEA (0.05 mL , 0.4 mmol) and the reaction was stirred at rt for 2 h. The reaction mixture was diluted with MeOH, and purified by preparative HPLC (H_2O-MeOH with 0.1% TFA buffer) to yield 1a-((5-acetylhexahydropyrrolo[3,4-*c*]pyrrol-2(1*H*)-yl)carbonyl)-8-cyclohexyl-*N*-(dimethylsulfamoyl)-11-methoxy-1,1a,2,12b-tetrahydrocyclopropa[*d*]indolo[2,1-*a*][2]benzazepine-5-carboxamide (45 mg, 0.065 mmol, 70 % yield) as a white solid. The compound was isolated as a mixture of enantiomers and presents as a ~1:6 mixture of rotamers or atrope isomers. ^{1}H NMR (300 MHz, CD_3OD) δ ppm 8.10 (s, 0.15H), 8.00 - 7.84 (m, 1.85H), 7.63 - 7.53 (m, 1H), 7.31 (d, *J* = 8.4 Hz, 1H), 7.23 - 7.15 (m, 1H), 7.05 - 6.95 (m, 1H), 5.19 - 5.04 (m, 0.85H), 4.92 - 4.74 (m, 0.15H), 4.29 - 2.46 (m, 12H), 3.91 (s, 0.45H) 3.90 (s, 2.55H), 3.01 (s, 6H), 2.24 - 1.06 (m, 15.85H), 0.18 - -0.05 (m, 0.15H). LCMS: m/e = 688 $(M+H)^+$, retention time = 2.05 min (Column = (2)phenomenex 4.6x50mmC18 10um, Solvent A = 10% MeOH - 90% H_20 - 0.1% TFA, Solvent B = 90% MeOH - 10% H_2O - 0.1% TFA, Start % B = 0, Final % B = 100 Gradient Time = 2 min, Hold time 1 min, Flow Rate = 5 mL /min).

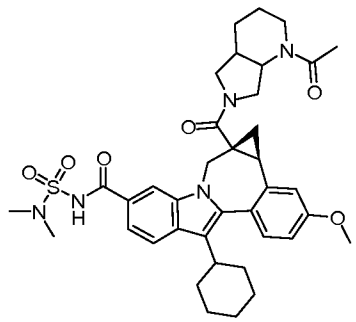


1a-((5-Acetylhexahydropyrrolo[3,4-*c*]pyrrol-2(1*H*)-yl)carbonyl)-8-cyclohexyl-*N*-(cyclopropylsulfonyl)-11-methoxy-1,1a,2,12b-tetrahydrocyclopropa[*d*]indolo[2,1-*a*][2]benzazepine-5-carboxamide. HATU (54mg, 0.14 mmol) was added to a stirring solution of 8-cyclohexyl-*N*-(cyclopropylsulfonyl)-1a-(hexahydropyrrolo[3,4-*c*]pyrrol-2(1*H*)-ylcarbonyl)-11-methoxy-1,1a,2,12b-tetrahydrocyclopropa[*d*]indolo[2,1-*a*][2]benzazepine-5-carboxamide (70 mg, 0.11 mmol) and acetic acid (8.0 µl, 0.14 mmol) in DMF (1 mL) and TEA (0.06 mL , 0.4 mmol) and the reaction was stirred at rt for 2 h. The reaction mixture was diluted with MeOH, and purified by preparative HPLC (H_2O-MeOH with 0.1% TFA buffer) to yield product 1a-((5-acetylhexahydropyrrolo[3,4-*c*]pyrrol-2(1*H*)-yl)carbonyl)-8-cyclohexyl-*N*-(cyclopropylsulfonyl)-11-methoxy-1,1a,2,12b-tetrahydrocyclopropa[*d*]indolo[2,1-*a*][2]benzazepine-5-carboxamide (49.5 mg, 0.072 mmol, 66 % yield) as a white solid. The compound was isolated as a mixture of enantiomers and presents as a 1:6 mixture of rotamers or atrope isomers. ^{1}H NMR (300 MHz, CD_3OD) δ ppm 8.11 (s, 0.15H), 7.96 (s, 0.85H), 7.94 - 7.84 (m, 1H), 7.64 - 7.54 (m, 1H), 7.35 - 7.21 (m, 1H), 7.23 - 7.17 (m, 1H), 7.07 - 6.96 (m, 1H), 5.11 (dd, *J* = 15.0, 5.9 Hz, 0.85H), 4.90 - 4.75 (m, 0.15H), 4.25 - 2.42 (m, 12H), 3.91 (s, 0.45H), 3.90 (s, 2.55H), 2.27 - 1.06 (m, 20.85H), 0.18 - 0.07 (m, 0.15H). LCMS: m/e = 685 $(M+H)^+$, retention time = 2.05 min (Column = (2)phenomenex 4.6x50mmC18 10um, Solvent A = 10% MeOH - 90% H20 - 0.1% TFA, Solvent B = 90% MeOH - 10% H2O - 0.1% TFA, Start % B = 0, Final % B = 100, Gradient Time = 2 min, Hold time = 1 min, Flow Rate = 5 mL /min).



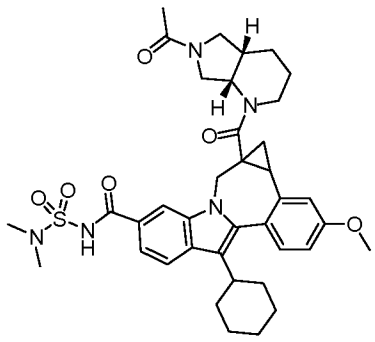
1a-((1-Acetyloctahydro-6*H*-pyrrolo[3,4-b]pyridin-6-yl)carbonyl)-8-cyclohexyl-*N*-(cyclopropylsulfonyl)-11-methoxy-1,1a,2,12b-tetrahydrocyclopropa[*d*]indolo[2,1-*a*][2]benzazepine-5-carboxamide. HATU (53 mg, 0.14 mmol) was added to a stirring solution of 8-cyclohexyl-*N*-(cyclopropylsulfonyl)-11-methoxy-1a-(octahydro-6*H*-pyrrolo[3,4-b]pyridin-6-ylcarbonyl)-1,1a,2,12b-tetrahydrocyclopropa[*d*]indolo[2,1-*a*][2]benzazepine-5-carboxamide (70 mg, 0.11 mmol) and acetic acid (8 µl, 0.14 mmol) in DMF (1 mL) and TEA (0.06 mL , 0.4 mmol) and the reaction was stirred at rt for 2 h. The reaction mixture was diluted with MeOH, and purified by preparative HPLC (H_2O-MeOH with 0.1% TFA buffer) to yield the first eluting racemic diastereomer of 1a-((1-acetyloctahydro-6*H*-pyrrolo[3,4-b]pyridin-6-yl)carbonyl)-8-cyclohexyl-*N*-(cyclopropylsulfonyl)-11-methoxy-1,1a,2,12b-tetrahydrocyclopropa[*d*]indolo[2,1-*a*][2]benzazepine-5-carboxamide (17.5 mg, 0.025 mmol, 24 % yield) as a light yellow solid and the second eluting racemic diastereomer (24.5 mg, 0.035 mmol, 33 % yield) as a light yellow solid. First eluting racemic diastereomer: Presents as a ~1:5 mixture of rotamers or atrope isomers. ^{1}H NMR (300 MHz, CD_3OD) δ ppm 8.10 (s, 0.84H), 8.05 - 7.83 (m, 1.16H), 7.73 -7.51 (m, 1H), 7.37 - 7.27 (m, 1H), 7.25 - 7.15 (m, 1H), 7.07 - 3.95 (m, 1H), 5.22 - 5.01 (m, 1H), 4.82 - 4.61 (m, 0.84H), 4.37 - 3.97 (m, 1.16H), 3.92 (s, 0.48H), 3.91 (s, 2.52H), 3.84 - 2.77 (m, 7H), 2.30 - 0.93 (m, 25.16H), 0.25 - -0.26 (m, 0.84H). LCMS: m/e = 699 $(M+H)^+$, retention time = 3.72 min (Column: phenomenex 4.6x50mmC18 10um, Solvent A = 10% MeOH - 90% H20 - 0.1% TFA, Solvent B = 90% MeOH - 10% H2O - 0.1% TFA, Wavelength = 220, Flow Rate = 4 mL /min, Gradient Time = 4 min, Start % B = 0, Final % B = 100, Stop time = 5 min). Second eluting racemic diastereomer: Presents

as a ~1:5 mixture of rotamers or atrope isomers. ^{1}H NMR (300 MHz, CD_3OD) δ ppm 8.15 - 8.09 (m, 0.15H), 8.02 - 7.85 (m, 1.85H), 7.67 - 7.53 (m, 1H), 7.37 - 7.26 (m, 1H), 7.24 - 7.16 (m, 1H), 7.07 - 6.95 (m, 1H), 5.19 (d, *J* = 15.00 Hz, 0.85H), 4.79 - 3.97 (m, 1.15H), 3.91 (s, 3H), 3.86 - 2.52 (m, 9H), 2.46 - -0.67 (m, 25H). LCMS: m/e = 699 $(M+H)^+$, retention time = 3.85 min (Column: phenomenex 4.6x50mmC18 10um, Solvent A = 10% MeOH - 90% H20 - 0.1% TFA, Solvent B = 90% MeOH - 10% H2O - 0.1% TFA, Wavelength = 220, Flow Rate = 4 mL /min, Gradient Time = 4 min, Start % B = 0, Final % B = 100, Stop time = 5 min).

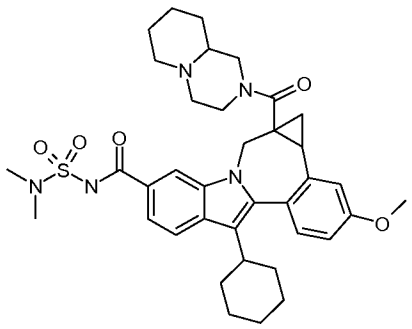


(1a*R*,12b*S*)-1a-((1-Acetyloctahydro-6*H*-pyrrolo[3,4-*b*]pyridin-6-yl)carbonyl)-8-cyclohexyl-*N*-((dimethylamino)sulfonyl)-11-methoxy-1,1a,2,12b-tetrahydrocyclopropa[*d*]indolo[2,1-*a*][2]benzazepine-5-carboxamide. HATU (143 mg, 0.377 mmol) was added to a stirring solution of (1a*R*,12b*S*)-8-cyclohexyl-*N*-((dimethylamino)sulfonyl)-11-methoxy-1a-(octahydro-6*H*-pyrrolo[3,4-*b*]pyridin-6-ylcarbonyl)-1,1a,2,12b-tetrahydrocyclopropa[*d*]indolo[2,1-*a*][2]benzazepine-5-carboxamide (160 mg, 0.290 mmol) and *tert*-butyl octahydro-1*H*-pyrrolo[3,4-*b*]pyridine-1-carboxylate (85 mg, 0.377 mmol) in DMF (3 mL) and TEA (0.16 mL , 1.2 mmol) and the reaction was stirred at rt for 3h. The reaction mixture was diluted with H_2O (5 mL) and aq HCl (1.0N, 1.2 mL) and extracted with EtOAc (15 mL). The organic layer was washed with aq HCl (8 mL) and brine (10 mL), dried ($MgSO_4$) and concentrated a yellow solid (299 mg). TFA (1 mL , 12.98 mmol) was added to a solution of this solid (220 mg, 74%) in CH_2Cl_2 (3 mL) and the mixture was stirred at rt for 0.5 h. The reaction was concentrated under vacuum and the residue was dissolved into EtOAc. The solution was treated with aq $NaHCO_3$ and the resulting white precipitate collected by filtration, rinsed with EtOAc, H_2O and CH_2Cl_2, and

dried to yield an off white solid (172 mg). HATU (143 mg, 0.376 mmol) was added to a stirring suspension of this off-white solid (172 mg, 100%) and acetic acid (0.03 mL , 0.5 mmol) in DMF (5 mL) and TEA (0.2 mL , 1.4 mmol) and the reaction was stirred at rt for2 h. The reaction mixture was diluted with MeOH, and purified by preparative HPLC (H_2O-MeOH with 0.1% TFA buffer) to yield the first eluting diastereomer of (1a*R*,12b*S*)-1a-((1-Acetyloctahydro-6*H*-pyrrolo[3,4-*b*]pyridin-6-yl)carbonyl)-8-cyclohexyl-*N*-((dimethylamino)sulfonyl)-11-methoxy-1,1a,2,12b-tetrahydrocyclopropa[*d*]indolo[2,1-*a*][2]benzazepine-5-carboxamide (84 mg, 0.120 mmol, 46% yield) as a light yellow solid and the second eluting diastereomer (84 mg, 0.120 mmol, 46% yield) as a light yellow solid. Each compound was isolated as a single enantiomer. First eluting diastereomer (single enantiomer): Presents as a ~1:6 mixture of rotamers or atrope isomers. ^{1}H NMR (300 MHz, CD_3OD) δ ppm 8.10 (s, 0.85H), 8.02 - 7.84 (m, 1.15H), 7.70 - 7.51 (m, 1H), 7.37 - 7.27 (m, 1H), 7.25 - 7.14 (m, 1H), 7.06 - 6.94 (m, 1H), 5.21 - 5.00 (m, 1H), 4.84 - 4.62 (m, 1H), 4.47 - 2.74 (m, 8H), 3.92 (s, 0.45H), 3.90 (s, 2.55H), 3.02 (s, 6H), 2.30 - 0.92 (m, 20.15H), 0.22 - -0.24 (m, 0.85H). LCMS: m/e = 702 $(M+H)^+$ retention time = 3.69 min (Column = (2)phenomenex 4.6x50mmC18 10um, Solvent A = 10% MeOH - 90% H_20 - 0.1% TFA, Solvent B = 90% MeOH - 10% H_2O - 0.1% TFA, Start % B = 0, Final % B = 100 Gradient Time = 4 min, Hold time = 1 min, Flow Rate = 4 mL /min). Second eluting diastereomer (single enantiomer): ^{1}H NMR (300 MHz, CD_3OD) δ ppm 8.16 - 7.86 (m, 2H), 7.67 - 7.54 (m, 1H), 7.38 - 7.28 (m, 1H), 7.24 - 7.18 (m, 1H), 7.08 - 6.95 (m, 1H), 5.22 (d, *J* = 15.0 Hz, 1H), 5.00 - 4.68 (m, 1H), 4.56 - 2.58 (m, 8H), 3.91 (s, 3H), 3.03 (s, 6H), 2.39 - -0.70 (m, 21H). LCMS: m/e = 702 $(M+H)^+$ retention time = 3.81 min (Column = (2)phenomenex 4.6x50mmC18 10um Solvent A = 10% MeOH - 90% H_20 - 0.1% TFA, Solvent B = 90% MeOH - 10% H_2O - 0.1% TFA, Start % B = 0, Final % B = 100 Gradient Time = 4 min, Hold time = 1 min, Flow Rate = 4 mL /min.

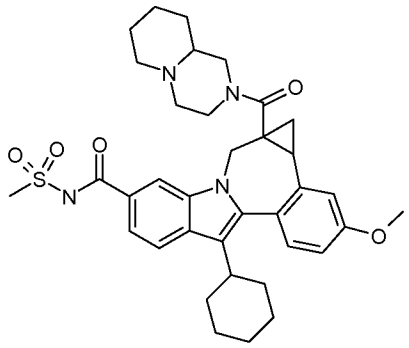


1a-(((4a*S*,7a*S*)-6-Acetyloctahydro-1*H*-pyrrolo[3,4-b]pyridin-1-yl)carbonyl)-8-cyclohexyl-*N*-(dimethylsulfamoyl)-11-methoxy-1,1a,2,12b-tetrahydrocyclopropa[*d*]indolo[2,1-*a*][2]benzazepine-5-carboxamide. HATU (37.5 mg, 0.099 mmol) was added to a stirring solution of *rac*-8-cyclohexyl-*N*-((dimethylamino)sulfonyl)-11-methoxy-1a-((4a*R*,7a*R*)-octahydro-1*H*-pyrrolo[3,4-*b*]pyridin-1-ylcarbonyl)-1,1a,2,12b-tetrahydrocyclopropa[*d*]indolo[2,1-*a*][2]benzazepine-5-carboxamide (50 mg, 0.076 mmol) and acetic acid (0.01 mL , 0.2 mmol) in DMF (1 mL) and TEA (0.05 mL , 0.4 mmol) and the reaction was stirred at rt for 1 h. The reaction mixture was diluted with MeOH, and purified by preparative HPLC (H_2O-MeOH with 0.1% TFA buffer) to yield product 1a-(((4a*S*,7a*S*)-6-acetyloctahydro-1*H*-pyrrolo[3,4-b]pyridin-1-yl)carbonyl)-8-cyclohexyl-*N*-(dimethylsulfamoyl)-11-methoxy-1,1a,2,12b-tetrahydrocyclopropa[*d*]indolo[2,1-*a*][2]benzazepine-5-carboxamide (35 mg, 0.050 mmol, 66 % yield) as a light yellow solid. The compound was isolated as a mixture of diastereomers and presents as a 1:3 mixture of rotamers or atrope isomers. ^1H NMR (300 MHz, CD_3OD) δ ppm 8.11 - 8.05 (m, 0.25H), 8.03 - 7.84 (m, 1.75H), 7.66 - 7.52 (m, 1H), 7.36 - 7.27 (m, 1H), 7.22 - 7.13 (m, 1H), 7.06 - 6.96 (m, 1H), 5.14 - 4.61 (m, 2H), 4.20 - 2.45 (m, 16H), 3.91 (s, 0.75H), 3.90 (s, 2.25H), 2.25 - 0.98 (m, 18.75H), 0.27 - 0.13 (m, 0.25H). LCMS: m/e = 702 $(M+H)^+$, retention time = 3.88 min (Column = (2)phenomenex 4.6x50mmC18 10um Solvent A = 10% MeOH - 90% H_20 - 0.1% TFA, Solvent B = 90% MeOH - 10% H_2O - 0.1% TFA, Start % B = 0, Final % B = 100 Gradient Time = 4 min, Hold time = 1 min, Flow Rate = 4 mL /min).



8-Cyclohexyl-*N*-(dimethylsulfamoyl)-11-methoxy-1a-(octahydro-2*H*-pyrido[1,2-*a*]pyrazin-2-ylcarbonyl)-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 acid (40 mg, 0.073 mmol) and octahydro-1*H*-pyrido[1,2-*a*]pyrazine (20 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-(octahydro-2*H*-pyrido[1,2-*a*]pyrazin-2-ylcarbonyl)-1,1a,2,12b-tetrahydrocyclopropa[*d*]indolo[2,1-*a*][2]benzazepine-5-carboxamide (38.5 mg, 0.057 mmol, 79% yield) as an off-white solid. The compound was isolated as a mixture of four stereoisomers. Partial (aromatic protons) ^{1}HNMR (300 MHz, $CDCl_3$) δ 6.86 - 7.10 (m, 2H), 7.26 (d, J = 8.8 Hz, 0.6H), 7.27 (d, J = 8.8 Hz, 0.4H), 7.43 - 7.64 (m, 1H), 7.83 (d, J = 8.8 Hz, 0.4H), 7.84 (d, J = 8.4 Hz, 0.6H), 7.96 (br s, 0.4H), 7.99 (br s, 0.6H). LC-MS retention time: 2.97 min; m/z 672 (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

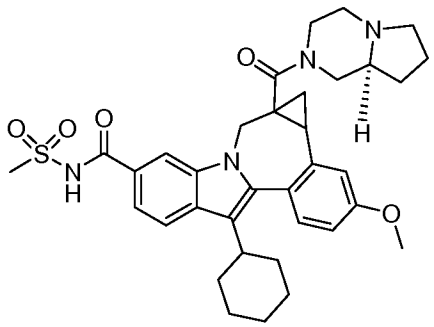
was 5% H_2O / 95% acetonitrile / 10 mM ammonium acetate. MS data was determined using a Micromass Platform for LC in electrospray mode.



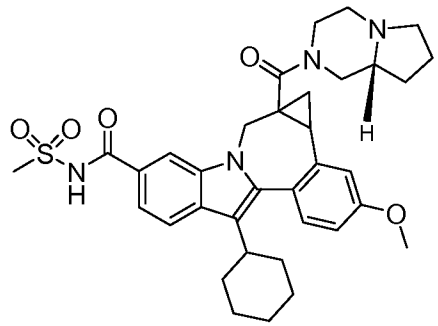
8-Cyclohexyl-11-methoxy-*N*-(methylsulfonyl)-1a-(octahydro-2*H*-pyrido[1,2-*a*]pyrazin-2-ylcarbonyl)-1,1a,2,12b-tetrahydrocyclopropa[*d*]indolo[2,1-*a*][2]benzazepine-5-carboxamide. HATU (38 mg, 0.10 mmol) was added to a stirring solution of acid (40 mg, 0.077 mmol) and octahydro-1H-pyrido[1,2-a]pyrazine (21 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-(octahydro-2*H*-pyrido[1,2-*a*]pyrazin-2-ylcarbonyl)-1,1a,2,12b-tetrahydrocyclopropa[*d*]indolo[2,1-*a*][2]benzazepine-5-carboxamide (36.2 mg, 0.056 mmol, 73% yield) as a white solid. The compound was isolated as a mixture of four stereoisomers. Presents as a ~1:3 mixture of rotamers or atrope isomers and ~1:1 mixture of diastereomers. Partial ^{1}HNMR (300 MHz, $CDCl_3$) δ 3.36 (s, 3H), 3.84 (s, 0.75H), 3.84 (s, 2.25H), 6.81 - 7.09 (m, 2H), 7.15 - 7.29 (m, 1H), 7.46 - 7.78 (m, 1.2H), 7.83 (d, J = 8.4 Hz, 0.38H), 7.84 (d, J = 8.4 Hz, 0.38H), 7.97 (br s , 0.75H), 8.01 (br s, 0.25H). LC-MS retention time: 2.22 min; m/z 643 (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.

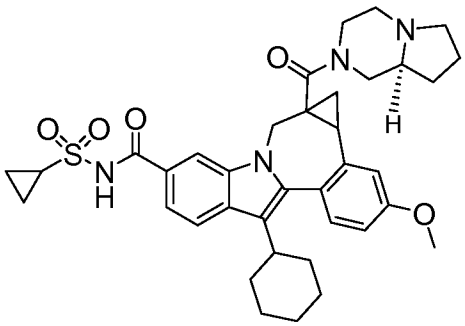
All compounds in the following examples were analyzed by following LCMS methods until noted: LCMS method 1: Start % B: 0, Final % B: 100; Gradient time: 3 min; Stop time: 4 min; Flow rate: 4 ml/min; Wavelenth: 220; Solvent A: 10% MeOH / 90% H_2O / 0.1% Trifluoroacetic Acid; Solvent B: 10% H_2O / 90% MeOH / 0.1% Trifluoroacetic Acid; Column: XBridge 4.6 x 50 mm S5; LCMS method 2: LC-MS retention time: 4.163; MS m/z 516 (M+H). Start % B: 0, Final % B: 100; Gradient time: 3 min; Stop time: 5 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.



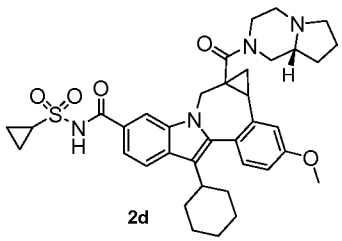
(+/-)-8-cyclohexyl-N-methylsulfonyl-1,1a,2,12b-tetrahydro-11-methoxy-1a-((S)-octahydropyrrolo[1,2-a]pyrazine-1-carbonyl)cycloprop[d]indolo[2,1-a][2]benzazepine-5-carboxamide. The product was purified by Prep HPLC and isolated as TFA salt. LC-MS retention time:2.961 ; MS m/z (M+H) 631.



(+/-)-8-cyclohexyl-N-methylsulfonyl-1,1a,2,12b-tetrahydro-11-methoxy-1a-((R)-octahydropyrrolo[1,2-a]pyrazine-1-carbonyl)cycloprop[d]indolo[2,1-a][2]benzazepine-5-carboxamide. The product was prepared from the acid and (R)-octahydropyrrolo[1,2-a]pyrazine and purified by Prep HPLC and isolated as TFA salt. LC-MS retention time:2.958 ; MS m/z (M+H) 631.

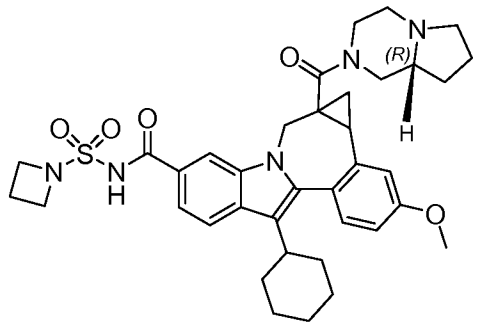


(+/-)-8-cyclohexyl-N-(cyclopropylsulfonyl)-1,1a,2,12b-tetrahydro-11-methoxy-1a-((S)-octahydropyrrolo[1,2-a]pyrazine-1-carbonyl)cycloprop[d]indolo[2,1-a][2]benzazepine-5-carboxamide. The product was prepared from the acid and (S)-octahydropyrrolo[1,2-a]pyrazine and purified by Prep HPLC and isolated as TFA salt. LC-MS retention time: 3.028; MS m/z (M+H) 657.

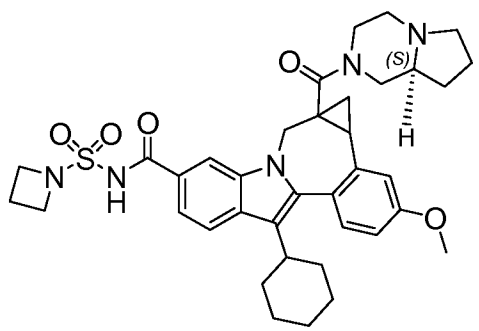


2d

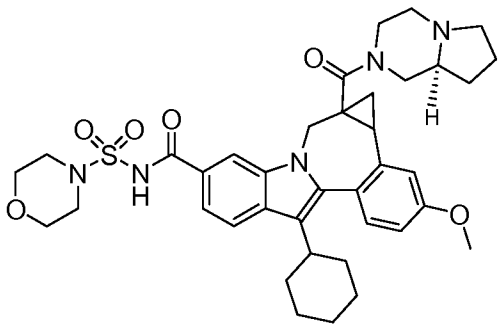
(+/-)-8-cyclohexyl-N-(cyclopropylsulfonyl)-1,1a,2,12b-tetrahydro-11-methoxy-1a-((R)-octahydropyrrolo[1,2-a]pyrazine-1-carbonyl)cycloprop[d]indolo[2,1-a][2]benzazepine-5-carboxamide. The product was prepared from the acid and (R)-octahydropyrrolo[1,2-a]pyrazine and purified by Prep HPLC and isolated as TFA salt. LC-MS retention time: 3.035 min; MS m/z (M+H) 657.



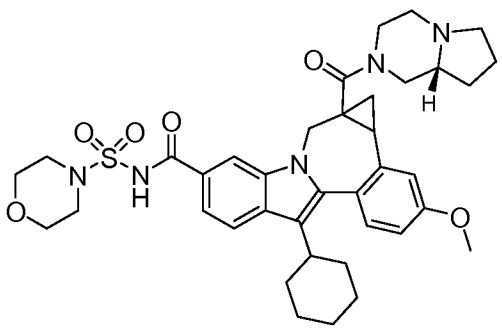
(+/-)-8-cyclohexyl-N-(azetidin-1-ylsulfonyl)-1,1a,2,12b-tetrahydro-11-methoxy-1a-[(R)-octahydropyrrolo[1,2-a]pyrazine-1-carbonyl]cycloprop[d]indolo[2,1-a][2]benzazepine-5-carboxamide. The product was prepared from the acid and (R)-octahydropyrrolo[1,2-a]pyrazine and purified by Prep HPLC and isolated as TFA salt. LC-MS retention time: 3.048 min; MS m/z (M+H) 672. The product was observed to exist as inter-converting rotamers by 1H NMR (400 MHz, CHLOROFORM-d) δ ppm 1.13 - 1.64 (m, 7 H) 1.68 - 1.87 (m, 3 H) 1.88 - 2.14 (m, 6 H) 2.28 (d, J=7.30 Hz, 3 H) 2.43 - 2.76 (m, 8 H) 2.84 - 3.03 (m, 1 H) 3.10 - 3.32 (m, 1 H) 3.44 - 3.79 (m, 2 H) 3.89 (s, 3 H) 4.27 (dd, J=14.48, 7.18 Hz, 5 H) 5.02 - 5.21 (m, 0 H) 6.91 - 7.00 (m, 1 H) 7.04 - 7.14 (m, 1 H) 7.26 - 7.32 (m, 1 H) 7.90 (d, J=8.81 Hz, 2 H).



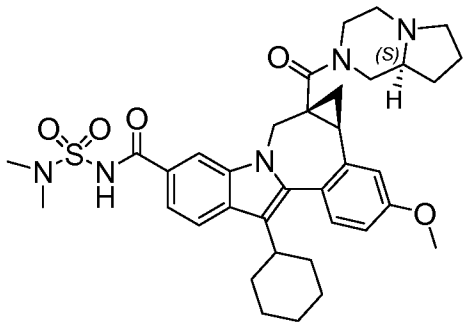
(+/-)-8-cyclohexyl-N-(azetidin-1-ylsulfonyl)-1,1a,2,12b-tetrahydro-11-methoxy-1a-[(S)-octahydropyrrolo[1,2-a]pyrazine-1-carbonyl]cycloprop[d]indolo[2,1-a][2]benzazepine-5-carboxamide. The product was prepared from the acide and (S)-octahydropyrrolo[1,2-a]pyrazine and purified by Prep HPLC and isolated as TFA salt. LC-MS retention time 3.110 min; MS m/z (M+H) 672. The product was observed to exist as inter-converting rotamers by 1H NMR (400 MHz, CHLOROFORM-d) δ ppm 1.12 - 1.60 (m, 7 H) 1.67 - 1.86 (m, 3 H) 1.87 - 2.13 (m, 5 H) 2.18 - 2.36 (m, 3 H) 2.55 - 2.70 (m, 1 H) 2.84 - 2.99 (m, 2 H) 3.08 - 3.32 (m, 1 H) 3.56 - 3.75 (m, 2 H) 3.89 (s, 3 H) 3.92 - 4.39 (m, 9 H) 4.67 - 4.81 (m, 1 H) 5.01 - 5.26 (m, 1 H) 6.89 - 7.02 (m, 1 H) 7.03 - 7.14 (m, 1 H) 7.28 - 7.37 (m, 1 H) 7.40 - 7.76 (m, 1 H) 7.81 - 8.04 (m, 2 H).



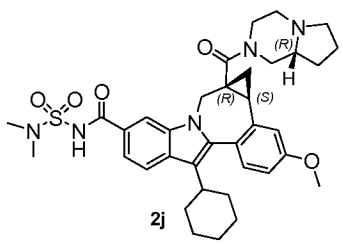
(+/-)-8-cyclohexyl-N--(morpholinosulfonyl)-1,1a,2,12b-tetrahydro-11-methoxy-1a-((S)-octahydropyrrolo[1,2-a]pyrazine-1-carbonyl)cycloprop[d]indolo[2,1-a][2]benzazepine-5-carboxamide. The product was prepared from compound the acid and (S)-octahydropyrrolo[1,2-a]pyrazine and purified by Prep HPLC and isolated as TFA salt. LC-MS retention time: 3.056 min; MS m/z (M+H) 702.



(+/-)-8-cyclohexyl-N-(morpholinosulfonyl)-1,1a,2,12b-tetrahydro-11-methoxy-1a-[(R)-octahydropyrrolo[1,2-a]pyrazine-1-carbonyl]cycloprop[d]indolo[2,1-a][2]benzazepine-5-carboxamide. The product was prepared from the acid and (R)-octahydropyrrolo[1,2-a]pyrazine and purified by Prep HPLC and isolated as TFA salt. LCMS method 1: LC-MS retention time: 3.048; MS m/z (M+H) 702.



8-cyclohexyl-N-(N,N-dimethylsulfamoyl)-1,1a,2,12b-tetrahydro-11-methoxy-1a-[(S)-octahydropyrrolo[1,2-a]pyrazine-1-carbonyl]cycloprop[d]indolo[2,1-a][2]benzazepine-5-carboxamide. The product was prepared from the acid and (S)-octahydropyrrolo[1,2-a]pyrazine and purified by Prep HPLC and isolated as TFA salt. LC-MS retention time 3.051 min; MS m/z (M+H) 660. The product was observed to exist as inter-converting rotamers by 1H NMR (400 MHz, CHLOROFORM-d) δ ppm 1.15 - 1.62 (m, 7 H) 1.62 - 1.88 (m, 3 H) 1.86 - 2.33 (m, 8 H) 2.45 - 2.81 (m, 2 H) 2.82 - 2.99 (m, 2 H) 3.02 (s, 6 H) 3.07 - 3.79 (m, 4 H) 3.89 (s, 3 H) 4.01 - 4.93 (m, 2 H) 5.13 (d, J=15.11 Hz, 0 H) 6.96 (dd, J=8.56, 2.52 Hz, 1 H) 7.03 - 7.13 (m, 1 H) 7.26 - 7.32 (m, 1 H) 7.69 (br. s., 1 H) 7.81 - 8.01 (m, 2 H).



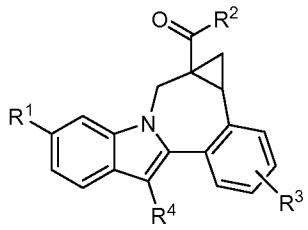
2j

8-cyclohexyl-N-(N,N-dimethylsulfamoyl)-1,1a,2,12b-tetrahydro-11-methoxy-1a-[(R)-octahydropyrrolo[1,2-a]pyrazine-1-carbonyl]cycloprop[d]indolo[2,1-a][2]benzazepine-5-carboxamide. The product was prepared from the acid and (R)-octahydropyrrolo[1,2-a]pyrazine and purified by Prep HPLC and isolated as TFA salt. LC-MS retention time: 3.015 min; MS m/z (M+H) 660. The product was observed to exist as inter-converting rotamers by 1H NMR (400 MHz, CHLOROFORM-d) δ ppm 0.97 - 1.65 (m, 7 H) 1.68 - 1.84 (m, 3 H) 1.86 - 2.34 (m, 8 H) 2.36 - 2.99 (m, 6 H) 3.04 (s, 6 H) 3.18 (dd, 1 H) 3.38 - 3.58 (m, 1 H) 3.69 (d, J=15.11 Hz, 1 H) 3.89 (s, 3 H) 4.00 - 4.19 (m, 0 H) 4.63 - 4.90 (m, 1 H) 5.01 - 5.25 (m, 1 H) 6.97 (dd, J=8.69, 2.64 Hz, 1 H) 7.10 (d, J=2.52 Hz, 1 H) 7.29 (d, J=8.56 Hz, 1 H) 7.57 (br. s., 1 H) 7.90 (dd, J=18.51, 8.44 Hz, 2 H).

CLAIMS

We claim:

1. A compound of formula I



I

where:

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

R^2 is a [4.4.0], [4.3.0] or [3.3.0] bicyclic diamine attached to the carbonyl through one nitrogen, and is substituted with 0-2 R^8 substituents;

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, (cycloalkyl)carbonyl, alkoxycarbonyl, aminocarbonyl, (alkylamino)carbonyl, (dialkylamino)carbonyl, (R^{12})carbonyl, benzyl, or benzyloxycarbonyl;

R^9 is hydrogen or alkyl;

R^{10} is hydrogen or alkyl;

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

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

or a pharmaceutically acceptable salt thereof.

2. A compound of claim 1 where R^1 is $CONR^6R^7$; R^6 is $alkylSO_2$, $cycloalkylSO_2$, $haloalkylSO_2$, $(R^9)(R^{10})NSO_2$, or $(R^{11})SO_2$; and R^7 is hydrogen.

3. A compound of claim 1 where R^2 is a [4.3.0] or [3.3.0] bicyclic diamine attached to the carbonyl through one nitrogen, and is substituted with 0-2 R^8 substituents.

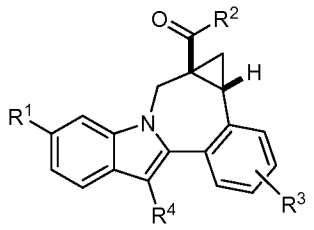
4. A compound of claim 1 where R^3 is hydrogen.

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

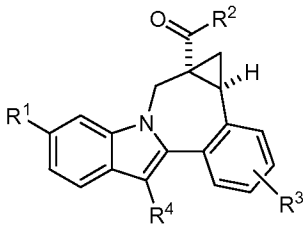
6. A compound of claim 1 where R^4 is cyclohexyl.

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

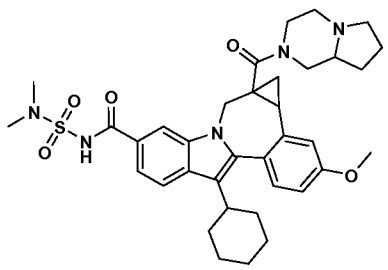
8. A compound of claim 1 according to the following stereochemistry.



9. A compound of claim 1 according to the following stereochemistry.



10. A compound of claim 1 selected from the group consisting of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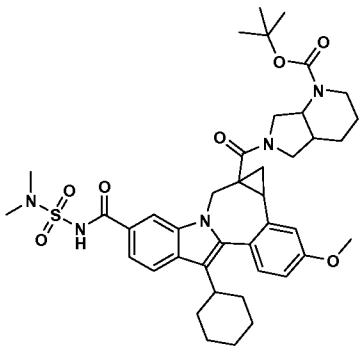
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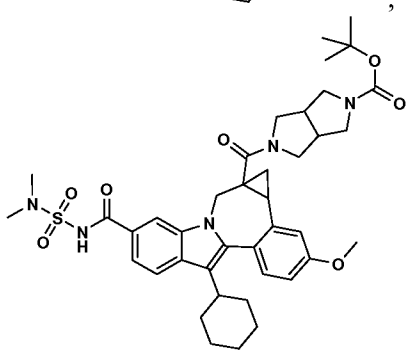
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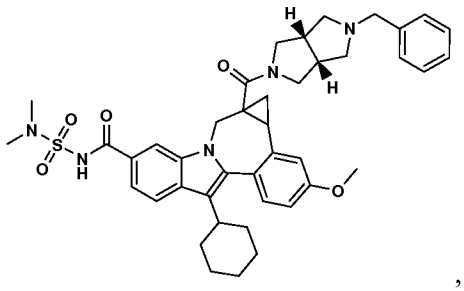
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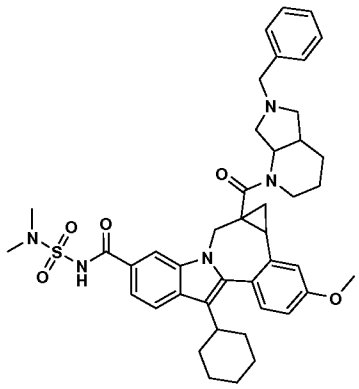
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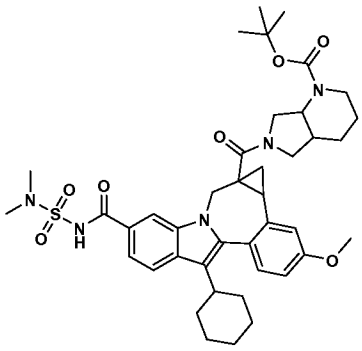
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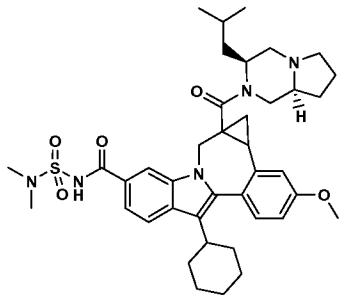
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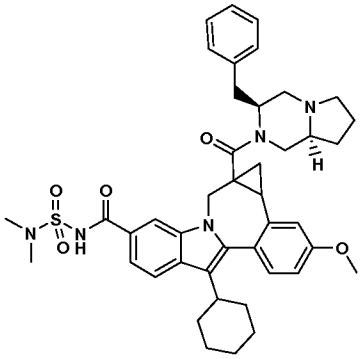
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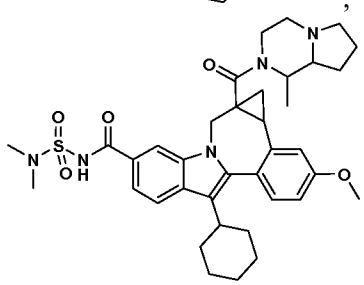
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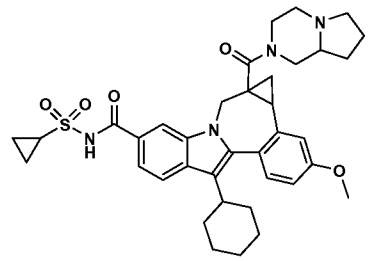
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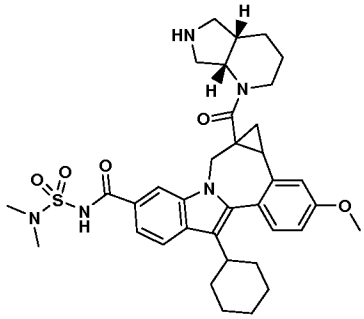
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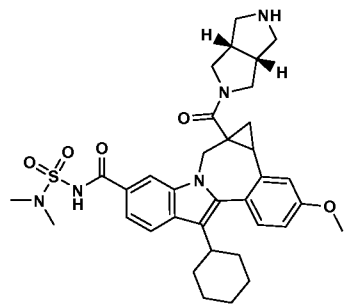
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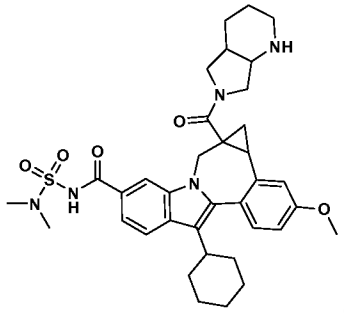
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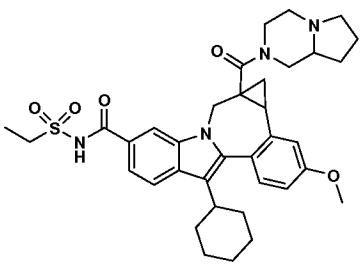
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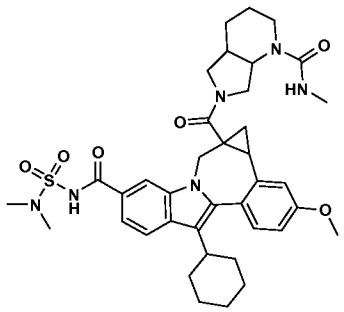
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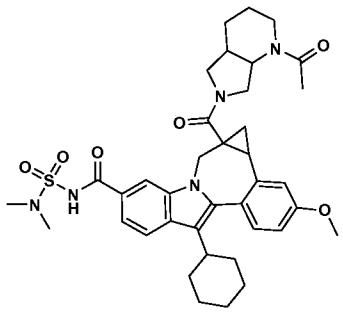
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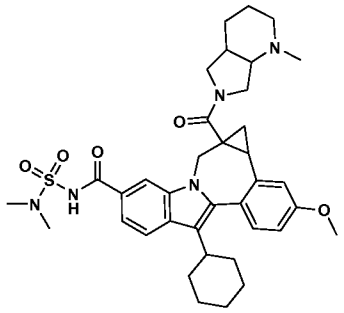
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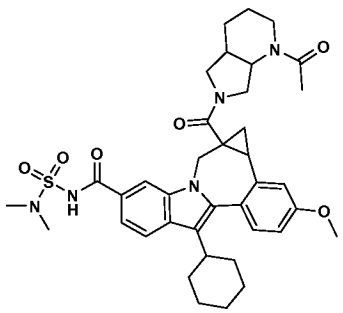
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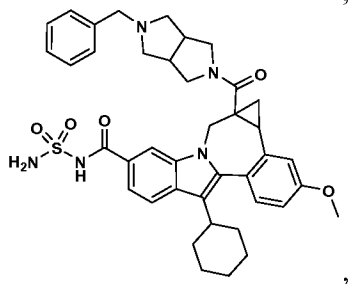
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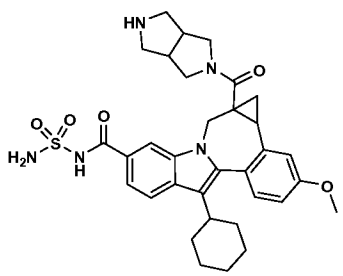
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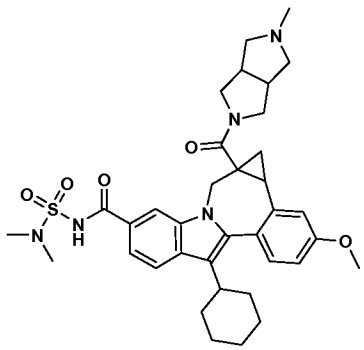
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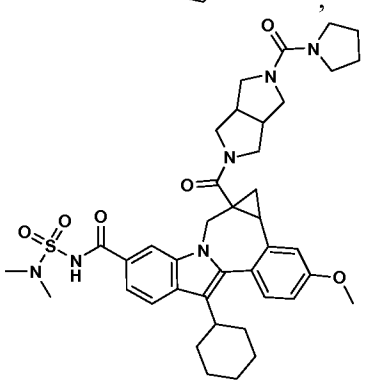
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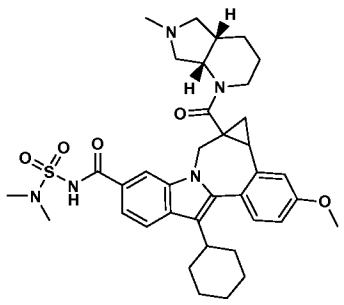
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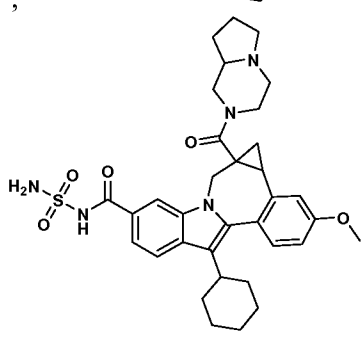
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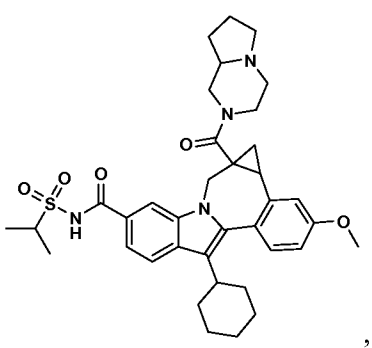
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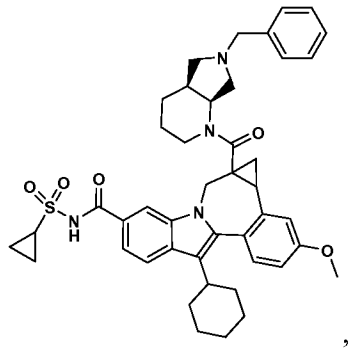
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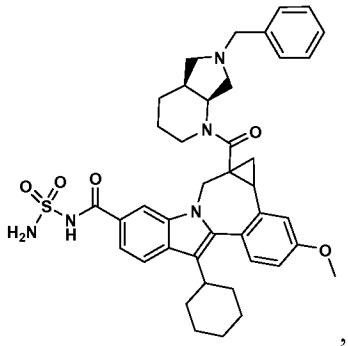
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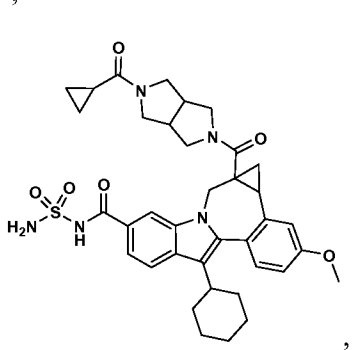
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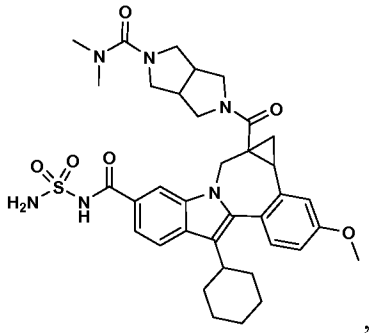
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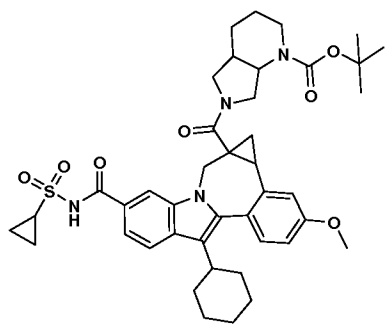
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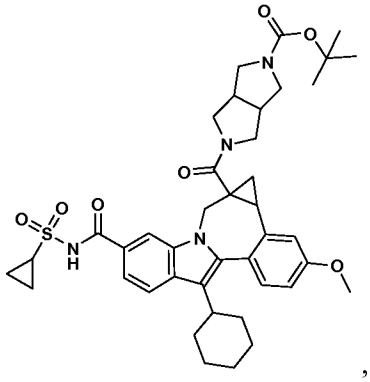
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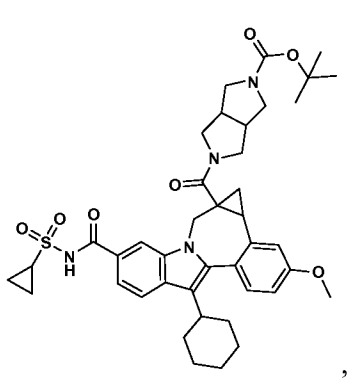
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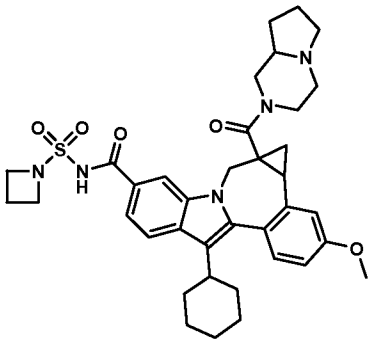
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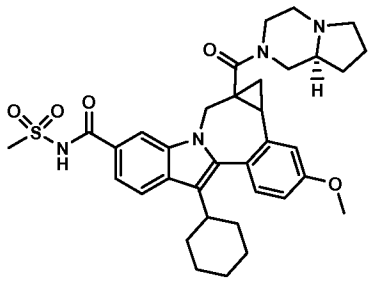
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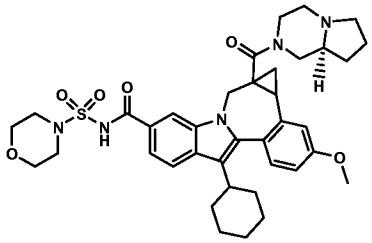
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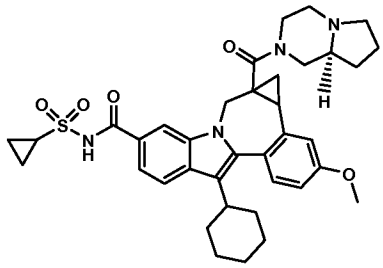
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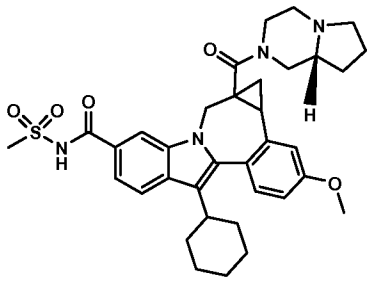
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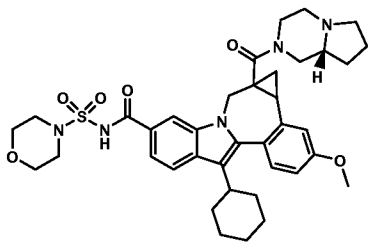
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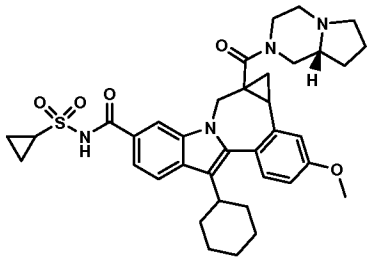
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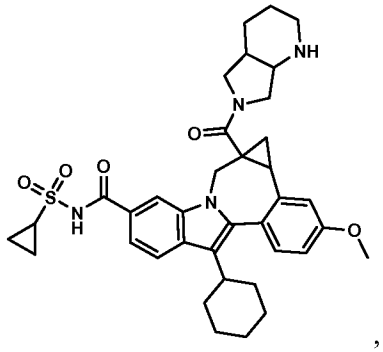
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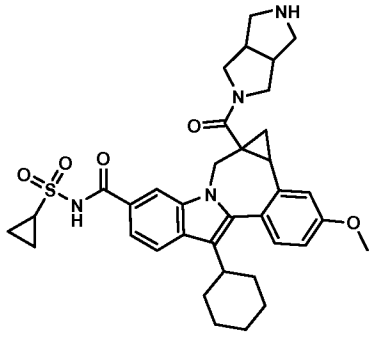
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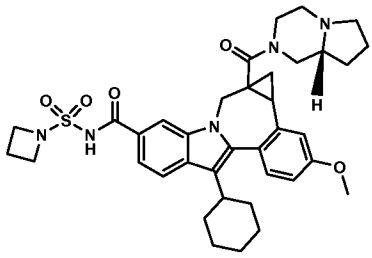
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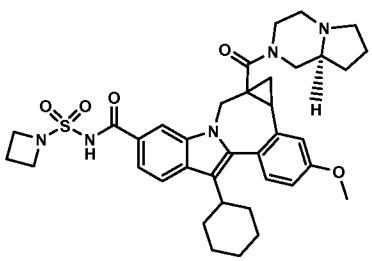
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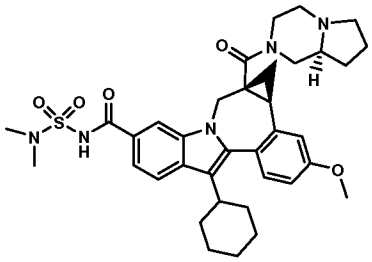
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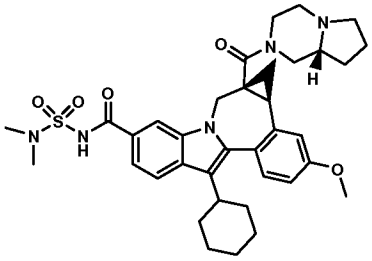
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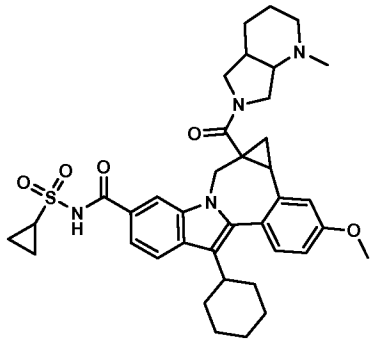
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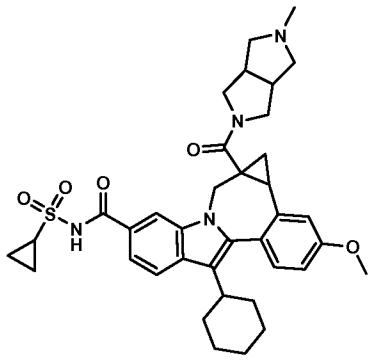
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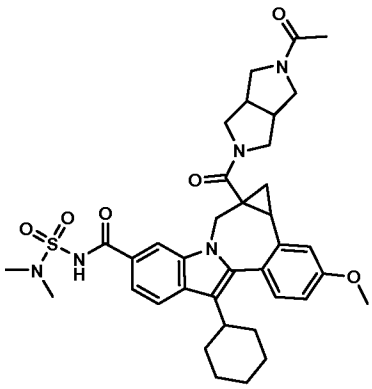
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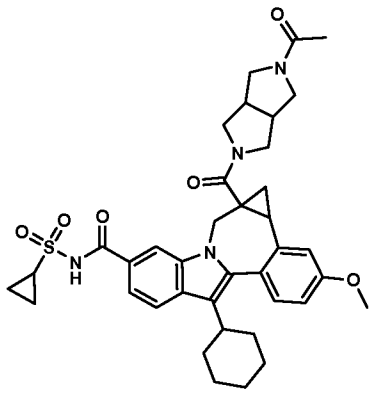
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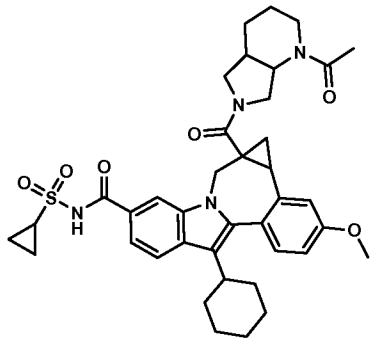
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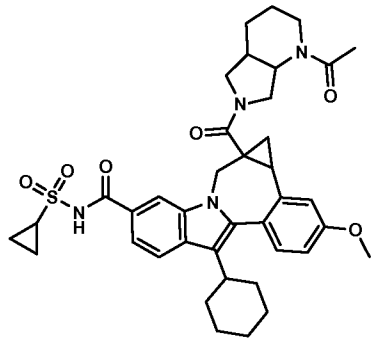
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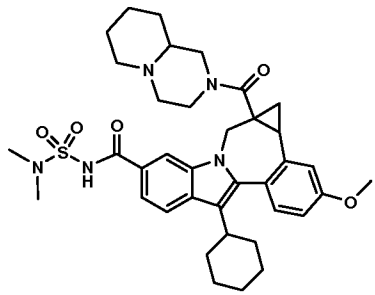
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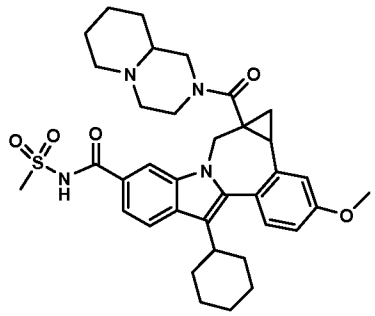
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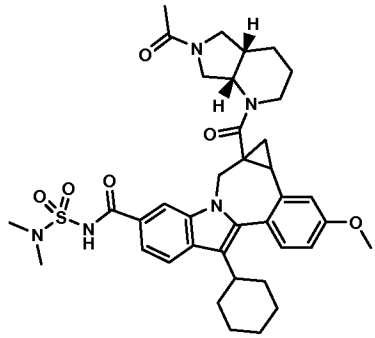
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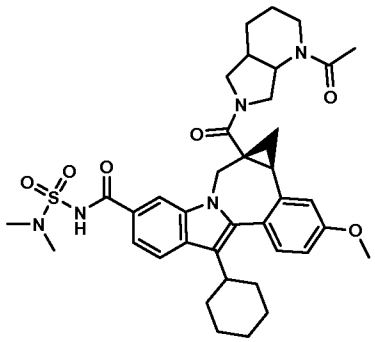
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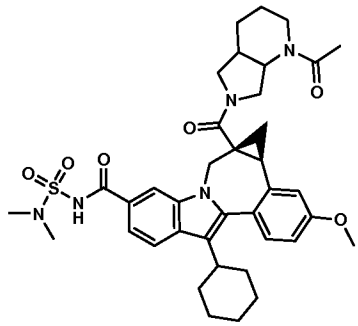
;

or a pharmaceutically acceptable salt thereof.

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

12. The composition of claim 11 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.

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

14. The method of claim 13 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.

INTERNATIONAL SEARCH REPORT

International application No
PCT/US2008/056766

A. CLASSIFICATION OF SUBJECT MATTER
INV. C07D487/04 A61P31/12 A61K31/55

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)
C07D

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)
EPO-Internal, WPI Data, BEILSTEIN Data, BIOSIS

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
P,Y	WO 2007/136982 A (SQUIBB BRISTOL MYERS CO [US]; BENDER JOHN A [US]; DING MIN [US]; GENTL) 29 November 2007 (2007-11-29) page 1, line 1 - page 2, line 28 page 20 - page 29; table 1 claim 1 -----	1-14
P,Y	WO 2007/140109 A (SQUIBB BRISTOL MYERS CO [US]; GENTLES ROBERT G [US]; HEWAWASAM PIYASEN) 6 December 2007 (2007-12-06) page 1, line 1 - page 2, line 28 page 15 - page 18; table 1 claim 1 ----- -/--	1-14

[X] Further documents are listed in the continuation of Box C.

[X] See patent family annex.

* Special categories of cited documents :

"A" document defining the general state of the art which is not considered to be of particular relevance

"E" earlier document but published on or after the international filing date

"L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)

"O" document referring to an oral disclosure, use, exhibition or other means

"P" document published prior to the international filing date but later than the priority date claimed

"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention

"X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone

"Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art.

"&" document member of the same patent family

Date of the actual completion of the international search	Date of mailing of the international search report
11 June 2008	24/06/2008

Name and mailing address of the ISA/	Authorized officer
European Patent Office, P.B. 5818 Patentlaan 2 NL - 2280 HV Rijswijk Tel. (+31-70) 340-2040, Tx. 31 651 epo nl, Fax: (+31-70) 340-3016	Bissmire, Stewart

INTERNATIONAL SEARCH REPORT

International application No
PCT/US2008/056766

C(Continuation). DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
P,Y	WO 2007/143521 A (SQUIBB BRISTOL MYERS CO [US]; YEUNG KAP-SUN [US]; GRANT-YOUNG KATHARIN) 13 December 2007 (2007-12-13) page 1, line 1 - page 2, line 27 page 21 - page 23; table 1 claim 1	1-14
A	WO 2006/020082 A (SQUIBB BRISTOL MYERS CO [US]; HUDYMA THOMAS W [US]; ZHENG XIAOFAN [US]) 23 February 2006 (2006-02-23) the whole document	1-14
A	WO 2006/046030 A (ANGELETTI P IST RICHERCHE BIO [IT]; CONTE IMMACOLATA [IT]; ERCOLANI CA) 4 May 2006 (2006-05-04) the whole document	1-14

INTERNATIONAL SEARCH REPORT

International application No.
PCT/US2008/056766

Box No. II Observations where certain claims were found unsearchable (Continuation of item 2 of first sheet)

This international search report has not been established in respect of certain claims under Article 17(2)(a) for the following reasons:

1. [X] Claims Nos.: –
because they relate to subject matter not required to be searched by this Authority, namely:

Although claims 13 and 14 are directed to a method of treatment of the human/animal body, the search has been carried out and based on the alleged effects of the compound/composition.

2. [ ] Claims Nos.:
because they relate to parts of the international application that do not comply with the prescribed requirements to such an extent that no meaningful international search can be carried out, specifically:

3. [ ] Claims Nos.:
because they are dependent claims and are not drafted in accordance with the second and third sentences of Rule 6.4(a).

Box No. III Observations where unity of invention is lacking (Continuation of item 3 of first sheet)

This International Searching Authority found multiple inventions in this international application, as follows:

1. [ ] As all required additional search fees were timely paid by the applicant, this international search report covers allsearchable claims.

2. [ ] As all searchable claims could be searched without effort justifying an additional fees, this Authority did not invite payment of additional fees.

3. [ ] As only some of the required additional search fees were timely paid by the applicant, this international search reportcovers only those claims for which fees were paid, specifically claims Nos.:

4. [ ] No required additional search fees were timely paid by the applicant. Consequently, this international search report is restricted to the invention first mentioned in the claims; it is covered by claims Nos.:

Remark on Protest

[ ] The additional search fees were accompanied by the applicant's protest and, where applicable, the payment of a protest fee.

[ ] The additional search fees were accompanied by the applicant's protest but the applicable protest fee was not paid within the time limit specified in the invitation.

[ ] No protest accompanied the payment of additional search fees.

INTERNATIONAL SEARCH REPORT

Information on patent family members

International application No
PCT/US2008/056766

Patent document cited in search report	Publication date	Patent family member(s)	Publication date
WO 2007136982 A	29-11-2007	US 2007270405 A1	22-11-2007
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		EP 1807397 A2	18-07-2007
		WO 2006046039 A2	04-05-2006
		KR 20070068427 A	29-06-2007