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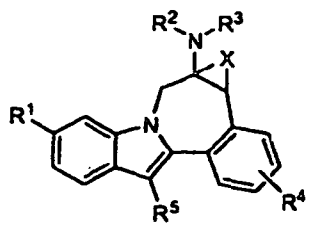
(54) Title: INDOLOBENZAZEPINE DERIVATIVES FOR THE TREATMENT OF HEPATITIS C



(I)

(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.

INDOLOBENZAZEPINE DERIVATIVES FOR THE TREATMENT OF HEPATITIS C

CROSS REFERENCE TO RELATED APPLICATIONS

This application claims the benefit of U.S. provisional applications USSN 60/887,846, filed February 2, 2007 and 60/894,881, filed March 14, 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.

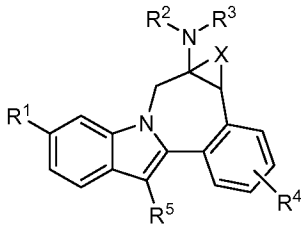
The single strand HCV RNA genome is approximately 9500 nucleotides in length and has a single open reading frame (ORF) encoding a single large polyprotein of about 3000 amino acids. In infected cells, this polyprotein is cleaved at multiple sites by cellular and viral proteases to produce the structural 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^6 or $CONR^7R^8$;

R^2 is COR^{12}, $COCOR^{13}$, $SO_2N(R^{14})(R^{15})$, or SO_2R^{16};

R^3 is hydrogen or alkyl;

R^4 is hydrogen, halo, alkyl, alkenyl, hydroxy, benzyloxy, or alkoxy;

R^5 is cycloalkyl;

R^6 is hydrogen or alkyl;

R^7 is hydrogen, alkyl, $alkylSO_2$, $cycloalkylSO_2$, $haloalkylSO_2$, $(R^9)_2NSO_2$, or $(R^{10})SO_2$;

R^8 is hydrogen or alkyl;

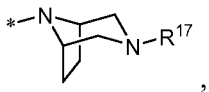
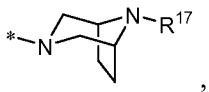
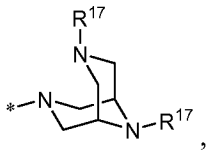
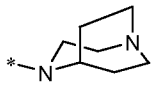
R^9 is hydrogen or alkyl;

R^{10} is azetidinyl, pyrrolidinyl, piperidinyl, N-(R^{11})piperazinyl, morpholinyl, thiomorpholinyl, homopiperidinyl, N-(R^{11})homopiperazinyl, or homomorpholinyl;

R^{11} is hydrogen or alkyl; and

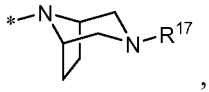
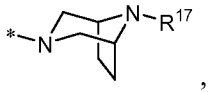
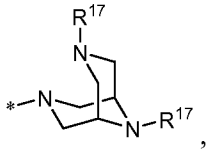
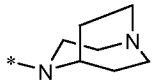
R^{12} is amino, alkylamino, or dialkylamino;

or R^{12} is azetidinyl, pyrrolidinyl, piperidinyl, piperazinyl, morpholinyl, homopiperidinyl, homopiperazinyl, or homomorpholinyl, and is substituted with 0-3 substituents selected from alkyl, alkoxy, and phenyl wherein phenyl is substituted with 0-3 substituents selected from cyano, halo, alkyl, and alkoxy;

or R^{12} is  ,  ,  , or  ;

R^{13} is hydroxy, alkoxy, amino, alkylamino, or dialkylamino;

or R^{13} is azetidinyl, pyrrolidinyl, piperidinyl, piperazinyl, morpholinyl, homopiperidinyl, homopiperazinyl, or homomorpholinyl, and is substituted with 0-3 substituents selected from alkyl, alkoxy, and phenyl wherein phenyl is substituted with 0-3 substituents selected from cyano, halo, alkyl, and alkoxy;

or R^{13} is  ,  ,  , or  ;

R^{14} is hydrogen, or alkyl;

R^{15} is hydrogen or alkyl;

R^{16} is alkyl, cycloalkyl, or haloalkyl;

or R^{16} is azetidinyl, pyrrolidinyl, piperidinyl, piperazinyl, morpholinyl, thiomorpholinyl, homopiperidinyl, homopiperazinyl, or homomorpholinyl, and is substituted with 0-3 substituents selected from alkyl, alkylcarbonyl, alkoxycarbonyl, benzyl, and benzyloxycarbonyl;

or R^{16} is phenyl substituted with 0-3 substituents selected from cyano, halo, alkyl, haloalkyl, alkoxy, and haloalkoxy;

R^{17} is hydrogen, alkyl, cycloalkyl, (cycloalkyl)alkyl, benzyl, alkylcarbonyl, alkoxycarbonyl, benzyloxycarbonyl, alkylSO_2, or pyridinyl; and

X is absent, a bond, or methylene;

or a pharmaceutically acceptable salt thereof.

Another aspect of the invention is a compound of formula I where R^1 is $CONR^7R^8$; R^7 is alkylSO_2, cycloalkylSO_2, haloalkylSO_2, $(R^9)_2NSO_2$, or $(R^{10})SO_2$; and R^8 is hydrogen.

Another aspect of the invention is a compound of formula I where R^2 is COR^{12}.

Another aspect of the invention is a compound of formula I where R^2 is $COCOR^{13}$.

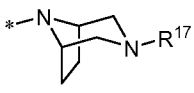
Another aspect of the invention is a compound of formula I where R^2 is $(R^{14})(R^{15})$ or SO_2R^{16}.

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

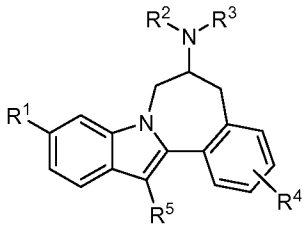
Another aspect of the invention is a compound of formula I where R^4 is hydrogen.

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

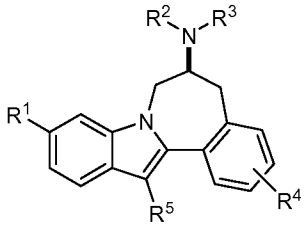
Another aspect of the invention is a compound of formula I where R^5 is cyclohexyl.

Another aspect of the invention is a compound of formula where R^{12} or R^{13} is dimethylamino, pyrrolidinyl, morpholinyl, dimethylmorpholinyl, piperazinyl, trimethylpiperazinyl, or  where R^{17} is alkyl.

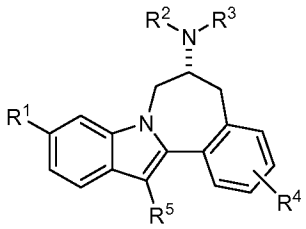
Another aspect of the invention is a compound of formula I where X is absent.



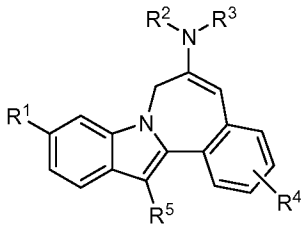
Another aspect of the invention is a compound of formula I where X is absent with the following stereochemistry.



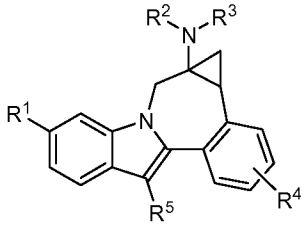
Another aspect of the invention is a compound of formula I where X is absent with the following stereochemistry.



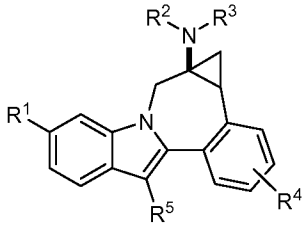
Another aspect of the invention is a compound of formula I where X is a bond .



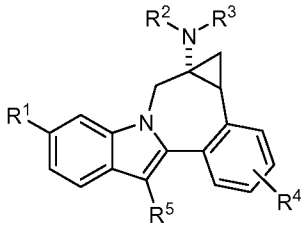
Another aspect of the invention is a compound of formula I where X is methylene.



Another aspect of the invention is a compound of formula I where X is methylene with the following stereochemistry.



Another aspect of the invention is a compound of formula I where X is methylene with the following stereochemistry.



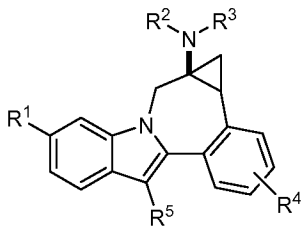
Any scope of a variable, including R^1, R^2, R^3, R^4, R^5, R^6, R^7, R^8, R^9, R^{10}, R^{11}, R^{12}, R^{13}, R^{14}, R^{15}, R^{16}, R^{17} and X, can be used independently with the scope of any other instance of a variable.

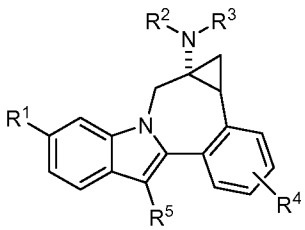
Unless specified otherwise, these terms have the following meanings. "Alkyl" means a straight or branched alkyl group composed of 1 to 6 carbons. "Alkenyl" means a straight or branched alkyl group composed of 2 to 6 carbons with at least one double bond. "Cycloalkyl" means a monocyclic ring system composed of 3 to 7 carbons. "Hydroxyalkyl," "alkoxy" and other terms with a substituted alkyl

moiety include straight and branched isomers composed of 1 to 6 carbon atoms for the alkyl moiety. "Haloalkyl" and "haloalkoxy" include all halogenated isomers from monohalo substituted alkyl to perhalo substituted alkyl. "Aryl" includes carbocyclic and heterocyclic aromatic substituents. Parenthetic and multiparenthetic terms are intended to clarify bonding relationships to those skilled in the art. For example, a term such as ((R)alkyl) means an alkyl substituent further substituted with the substituent R.

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

Some of the compounds of the invention possess asymmetric carbon atoms (for example, the structures 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 known in the art.





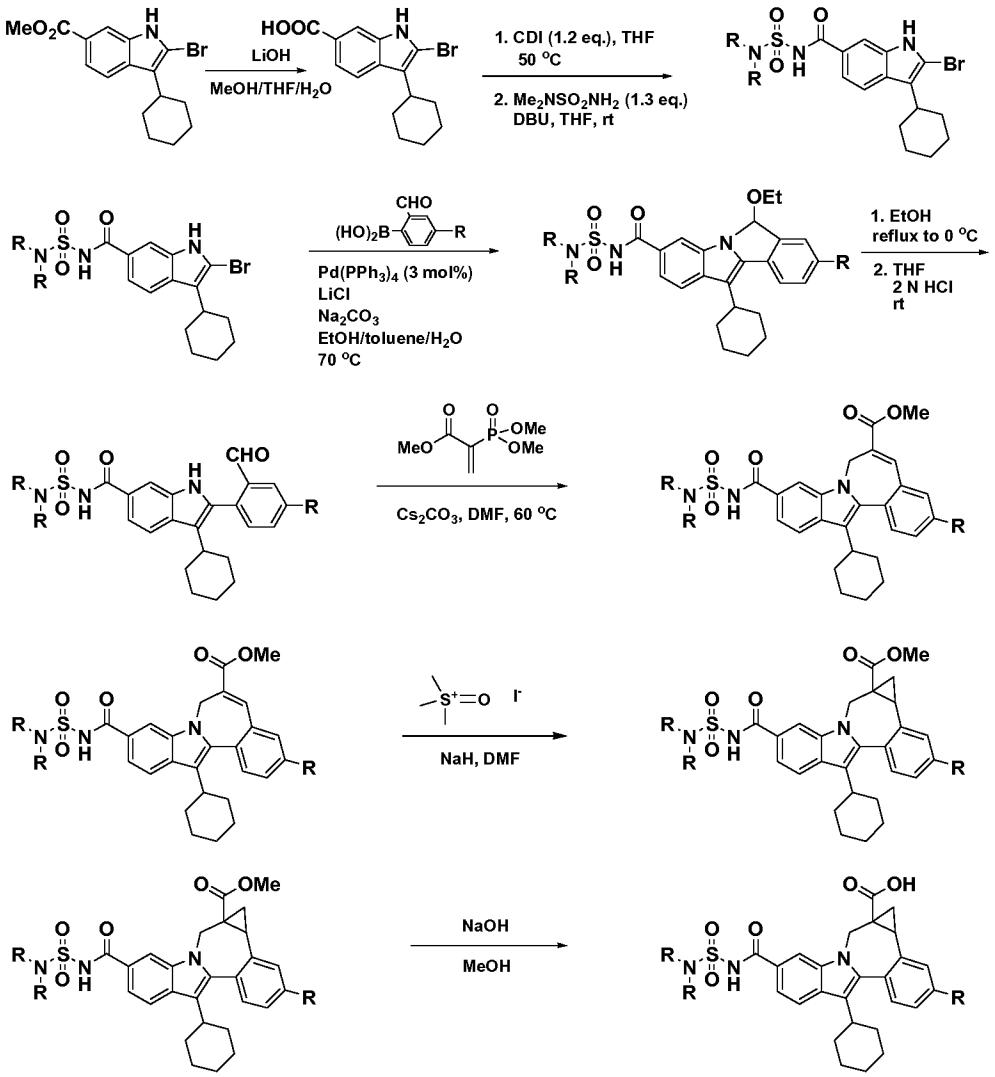
Synthetic Methods

The compounds may be made by methods known in the art including those described below. Some reagents and intermediates are known in the art. Other reagents and intermediates can be made by methods known in the art using commercially available materials. The variables (e.g. numbered "R" substituents) used to describe the synthesis of the compounds are intended only to illustrate how to make and are not to be confused with variables used in the claims or in other sections of the specification. Abbreviations used within the schemes generally follow conventions used in the art.

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

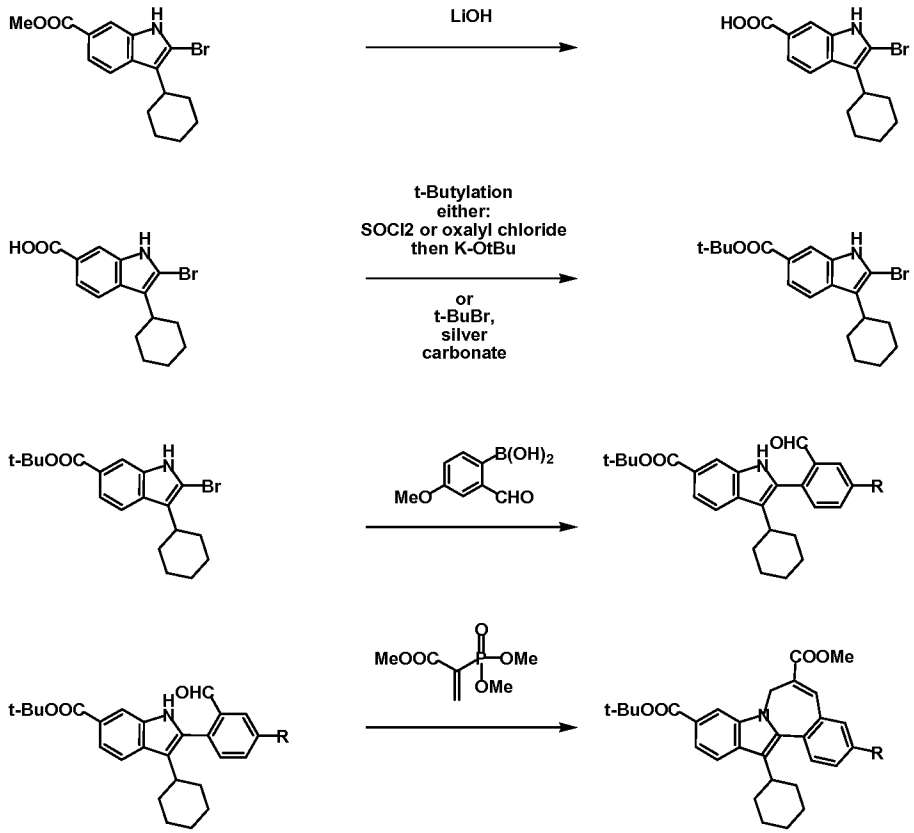
Related fused cyclopropyl ester derivatives can be generated by methods known in the art, including treatment of the indolobenzazepine esters with trimethyl sulfoxonium iodide under strongly basic conditions in DMSO. The residual aliphatic ester moiety in the resultant fused cyclopropanes can be hydrolyzed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

Scheme1.



An intermediate useful for the synthesis of some compounds of the invention involves the preparation of the tert-butyl ester indolobenzazepine shown in Scheme 2.

Scheme 2.

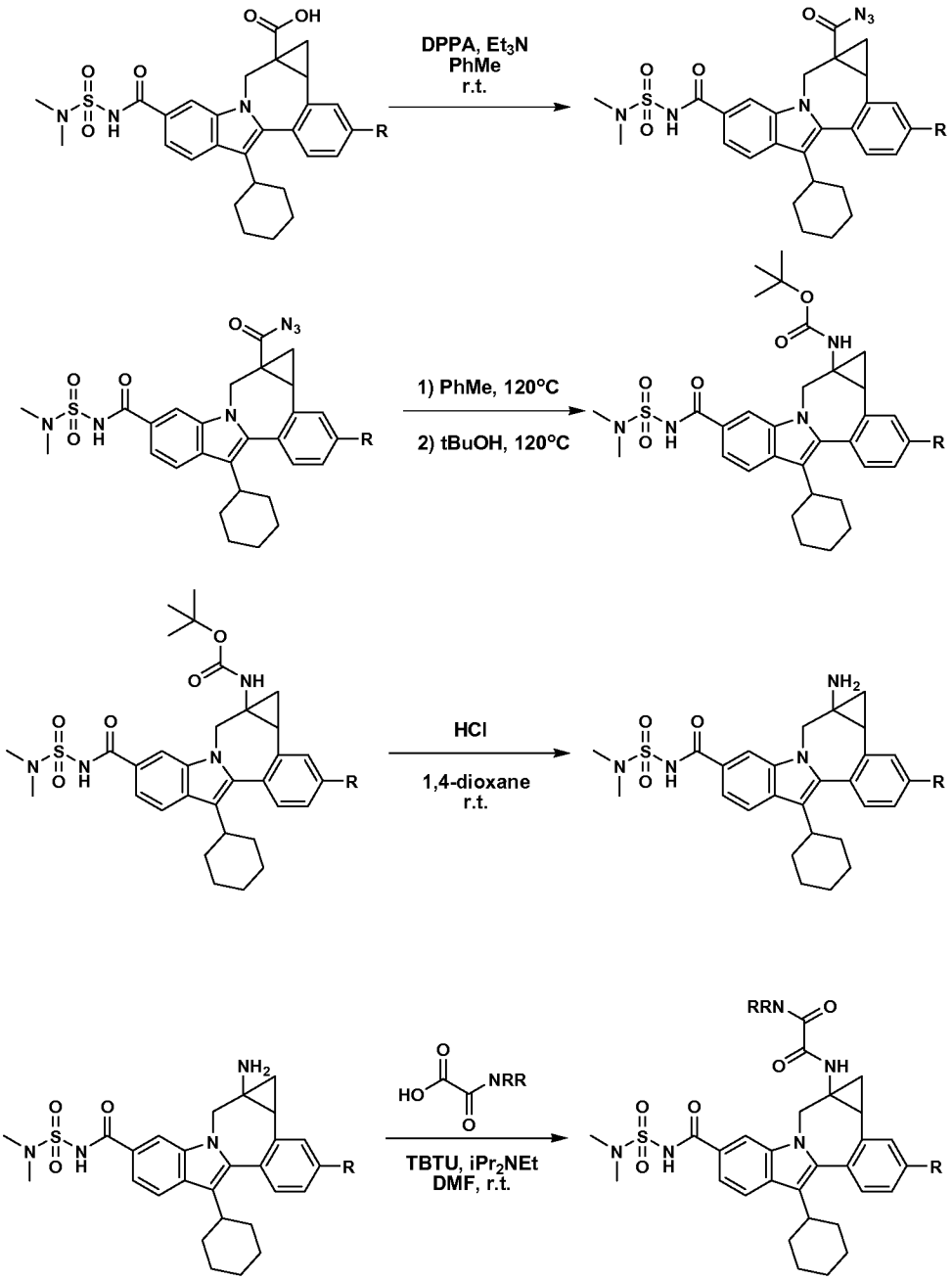


This methodology involves base catalyzed hydrolysis of the indole methyl ester shown, followed by its reaction with either thionyl chloride and potassium tertiary butoxide, or alkylation with silver carbonate and tertiary butyl bromides. The resultant compound can be transformed using chemistry analogous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

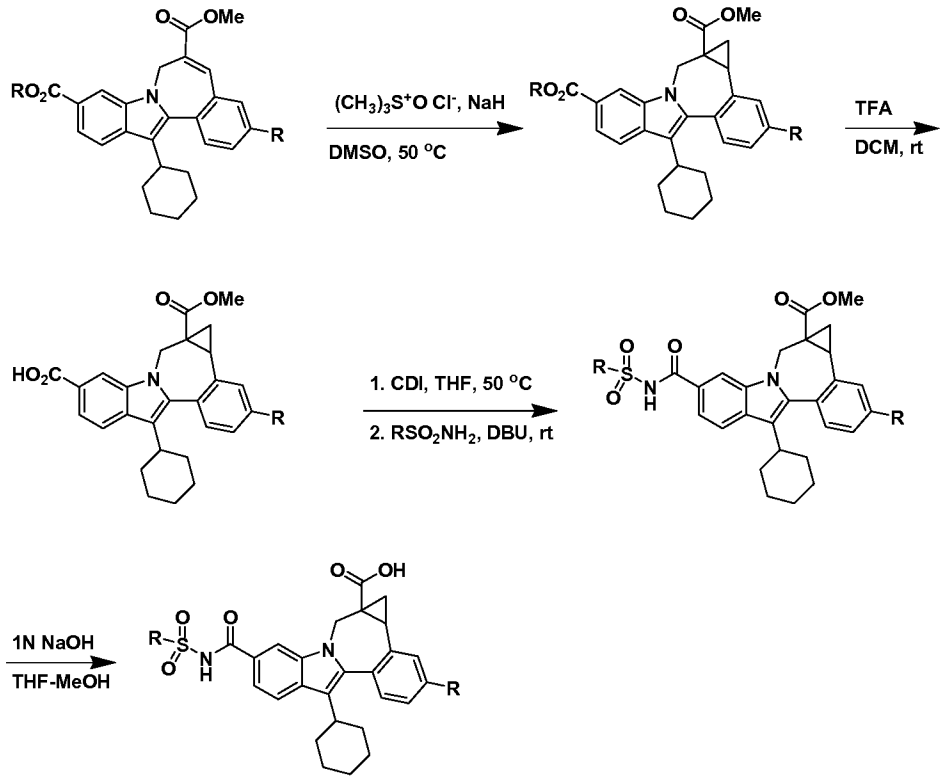
These intermediates are useful in an alternative procedure that can be employed for the preparation of acylsulfamide and acylsulfonamide alkyl-bridged piperazines, as shown in Scheme 4. Cyclopropanation of an intermediate t-butyl ester indolobenzazepine and subsequent cleavage of the t-butyl ester group 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 converted to the amine and then oxamides of this invention as shown below in Scheme 3. For example, coupling of the amine in the final step to the oxamide acid

can use O-(1H-benzotriazol-1-yl)-N,N, N',N'-tetramethyluronium tetrafluoroborate and diisopropyl ethyl amine in DMF can give the oxamides.

Scheme 3.

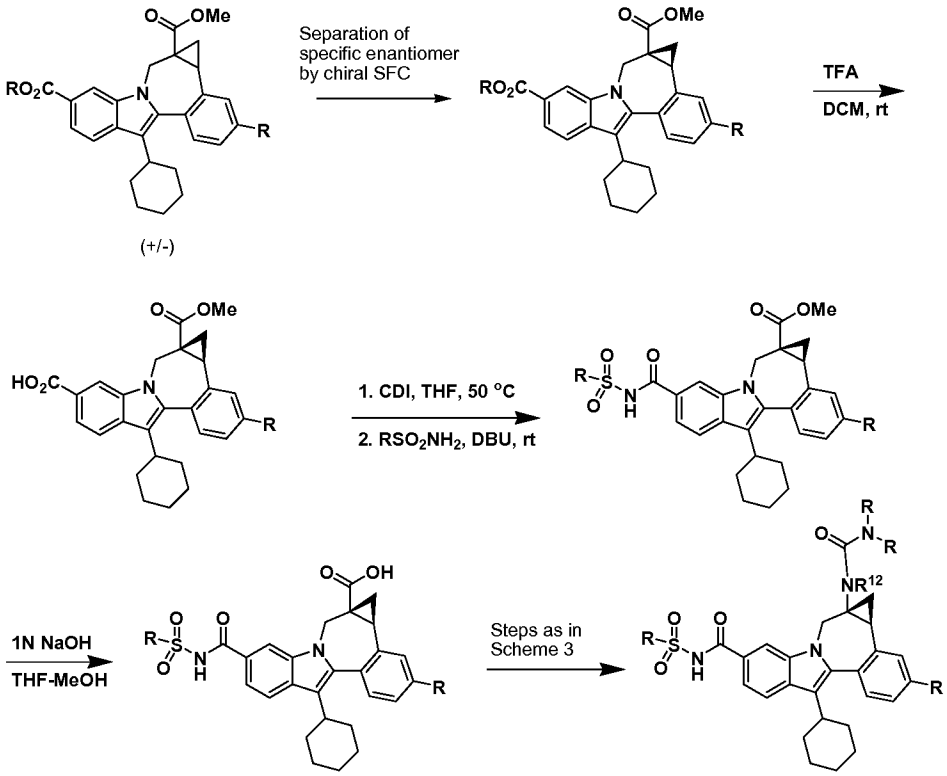


Scheme 4.



Schemes 5 and 6 describe the synthesis and separation of some stereoisomeric mixtures of compounds .

Scheme 5.



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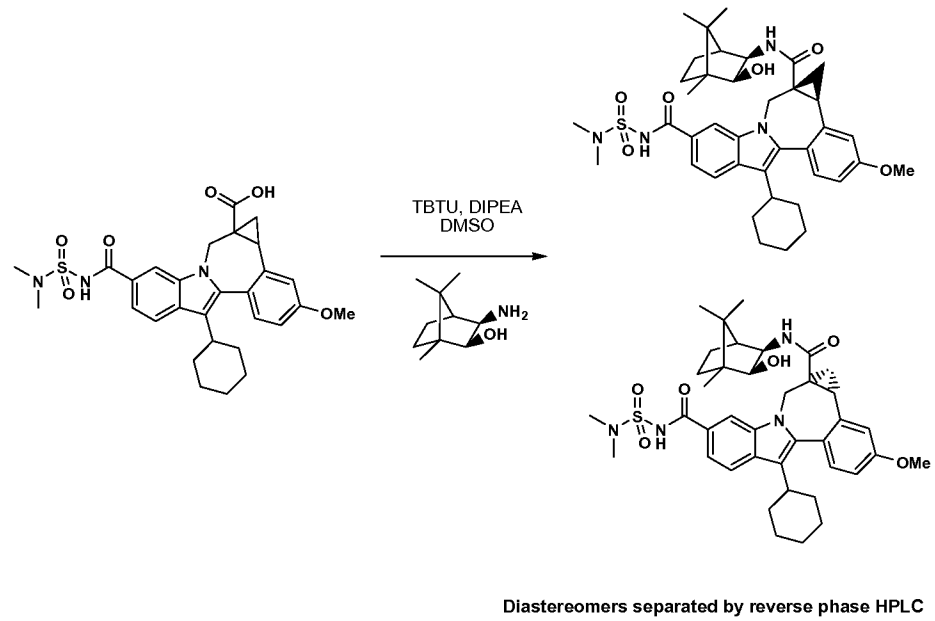
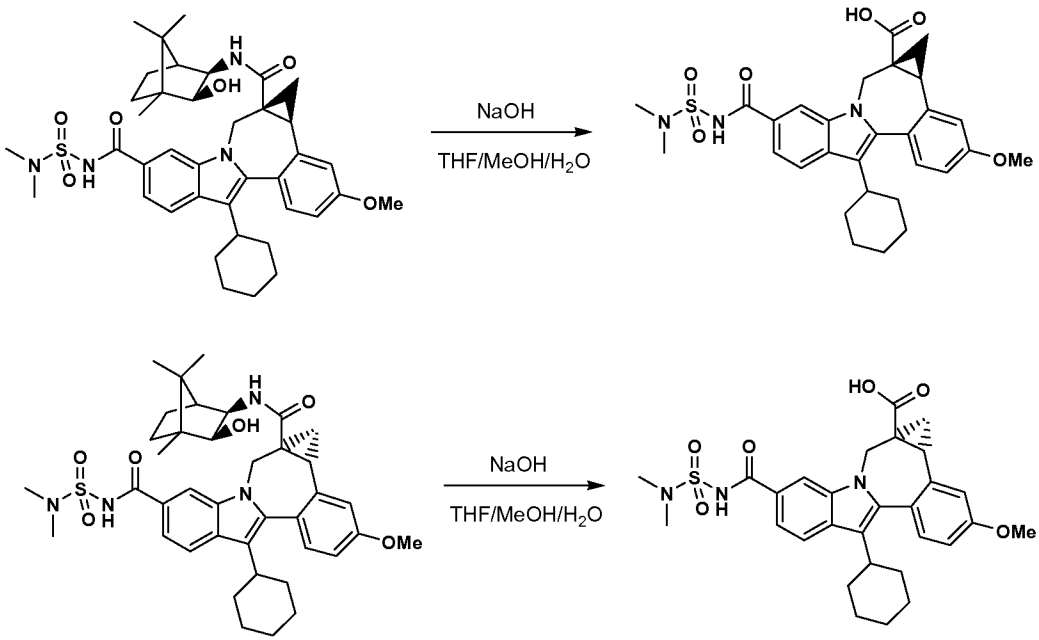
Scheme 6.



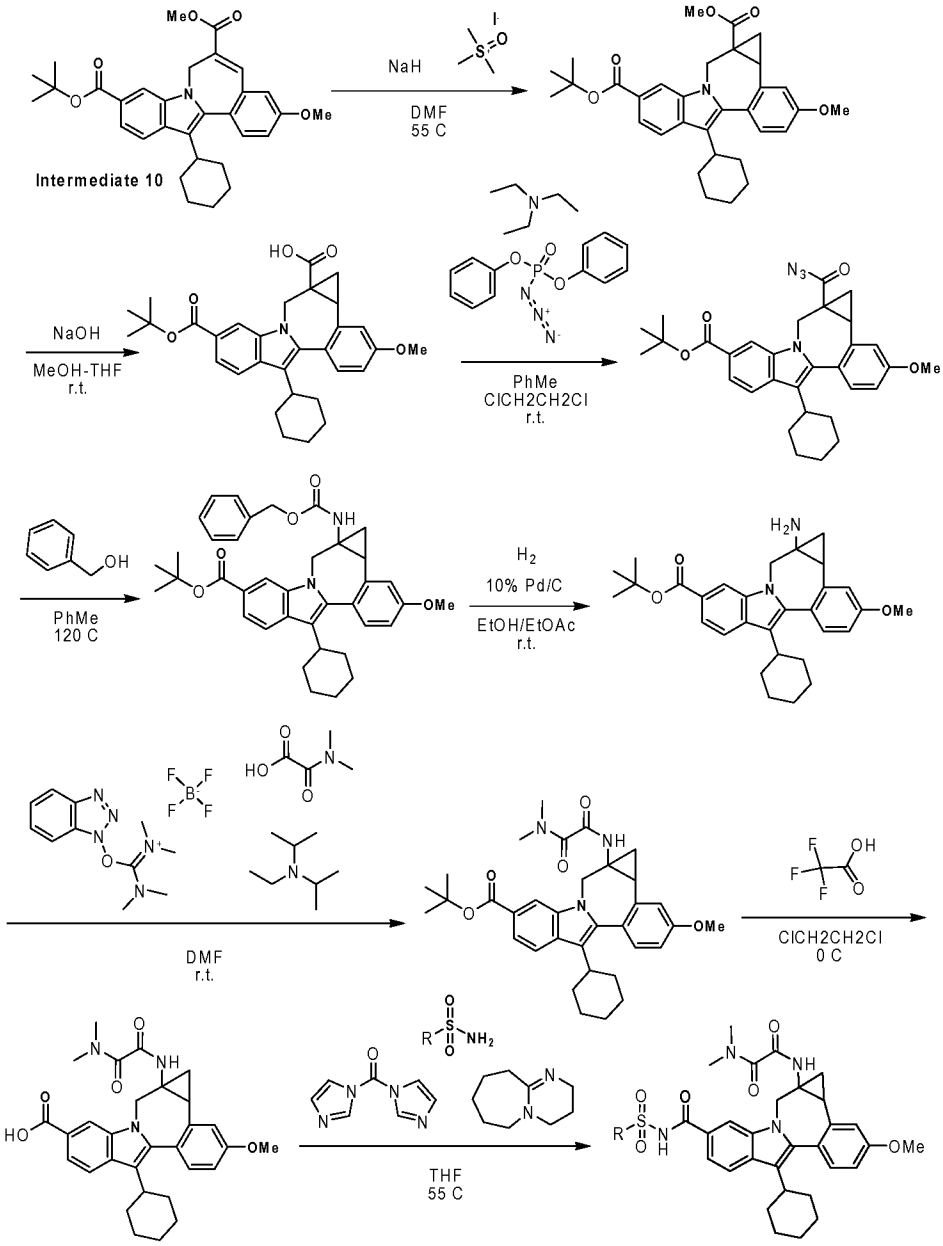
Some diastereomeric amides can be separated using reverse phase HPLC. After hydroysis, the resultant optically active acids can be coupled with bridged piperazine derivatives (Scheme 7). For example, O-(1H-benzotriazol-1-yl)-N,N, N',N'-tetramethyluronium tetrafluoroborate and diisopropyl ethyl amine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

Scheme 7.



Preparation of some indole-C6-acylsulfonamide analogs are illustrated in Scheme 8.

Scheme 8.



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.

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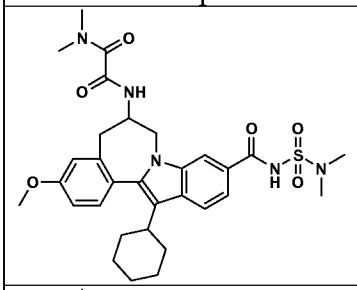
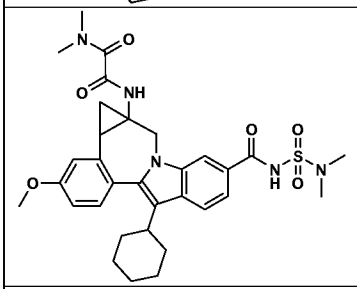
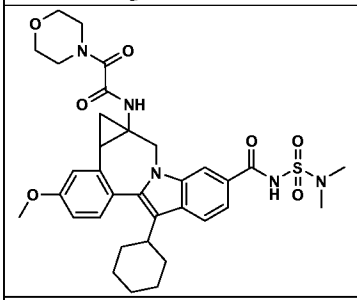
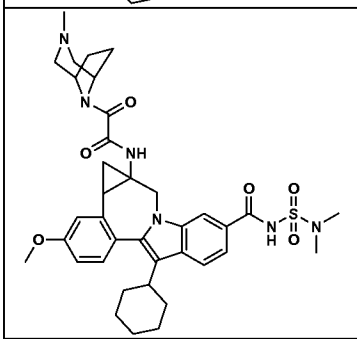
	B	B
	B	B
	B	B
	B	B

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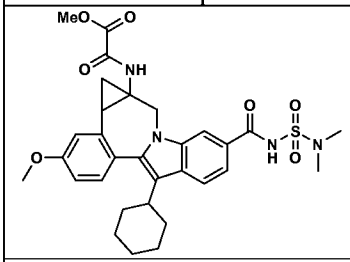
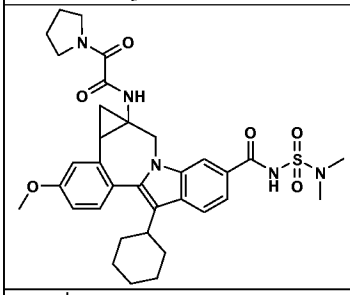
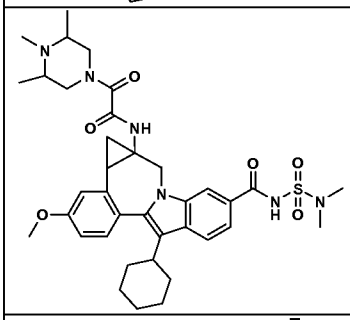
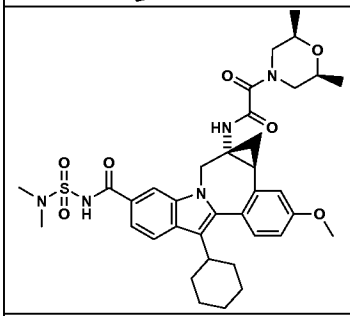
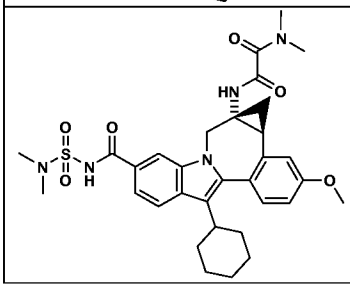
	B	B
	B	B
	B	B
	B	B
	B	B

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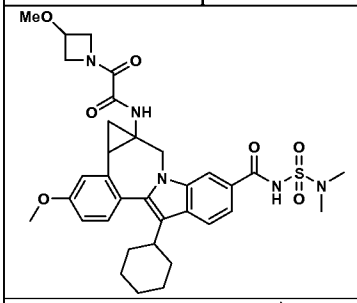
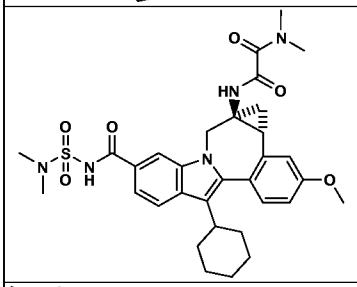
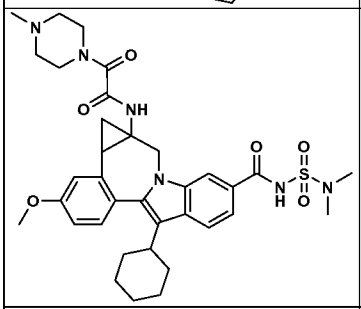
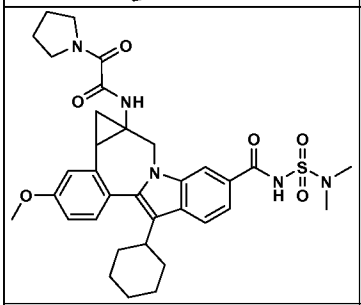
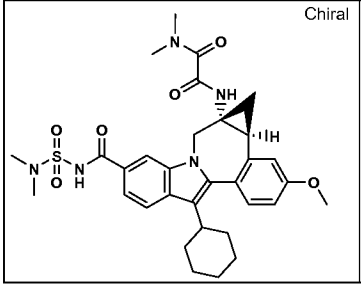
		
	B	B
	B	B
	B	B
Chiral 	B	B

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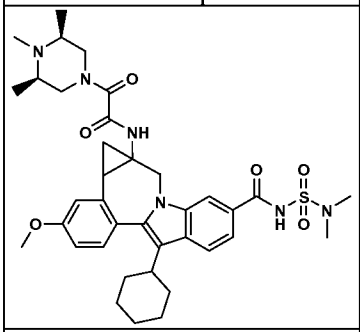
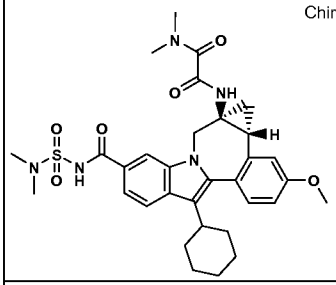
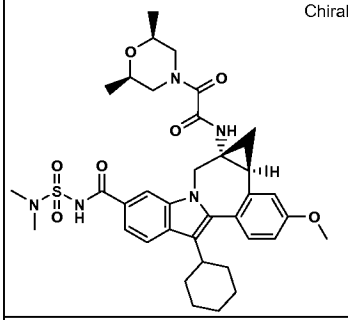
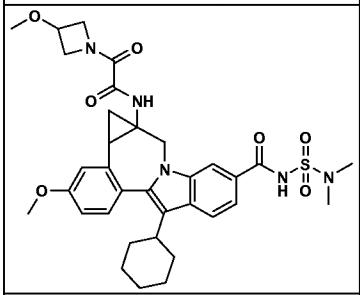
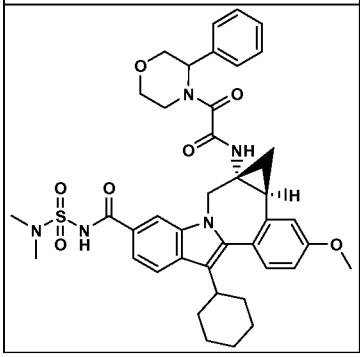
	B	B
Chiral 	B	B
Chiral 	B	B
	B	B
	B	B

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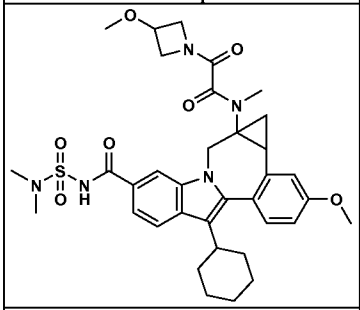
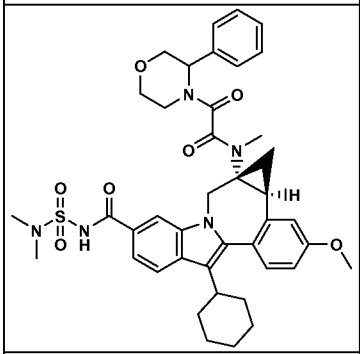
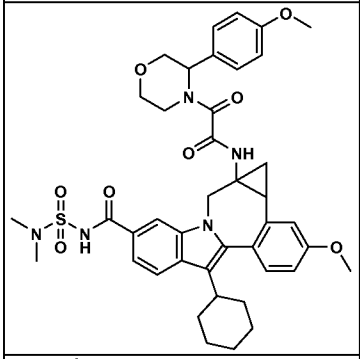
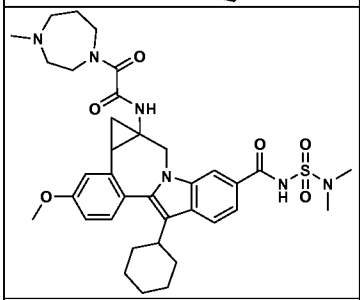
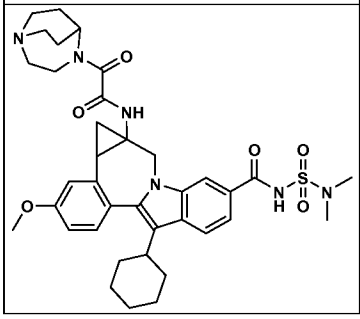
	B	B
	B	B
	B	B
	B	B
	B	B

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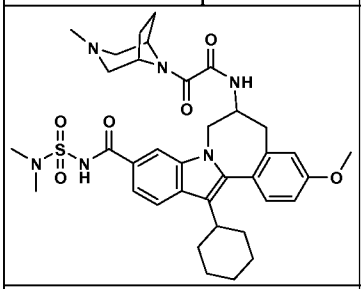
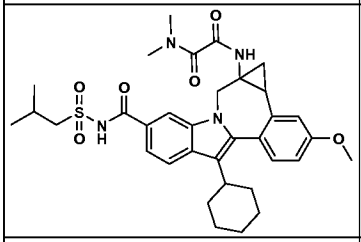
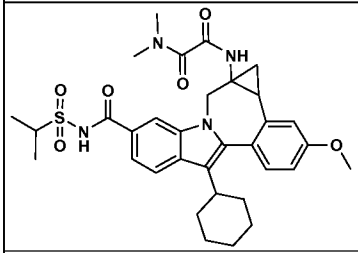
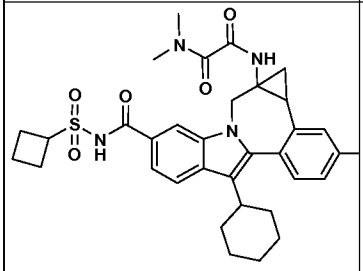
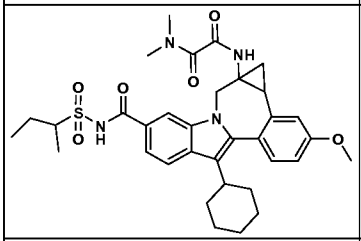
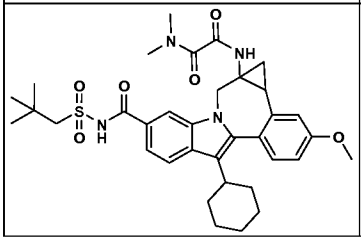
	B	B
		
	B	B
	B	B
	B	B
	B	B

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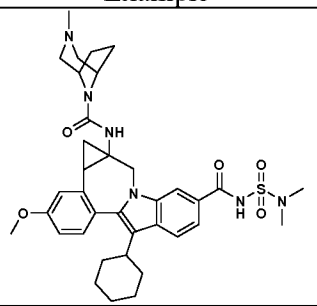
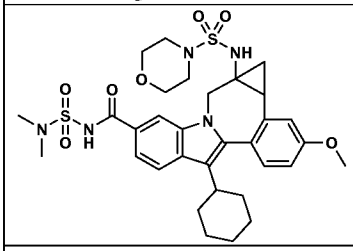
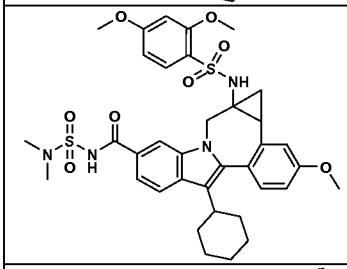
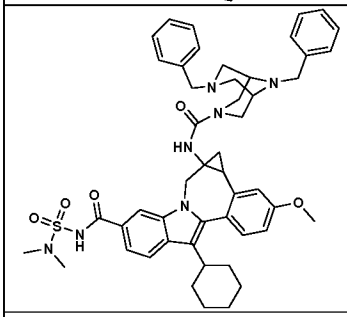
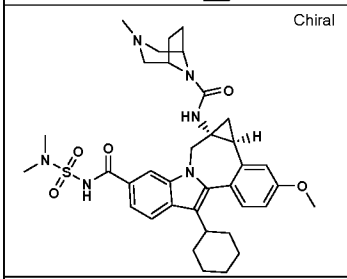
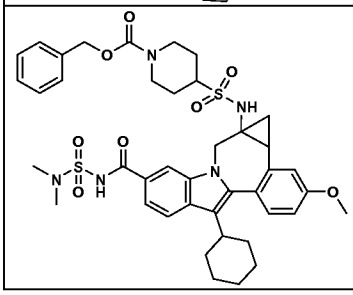
	B	B
	B	B
	B	B
	B	
Chiral 	B	B
	B	B

A>0.5 μM; B 0.001 μM – 0.5 μM; C <0.02 μM but an exact value was not determined; IC_{50} values were determined using the preincubation protocol. EC50 values were determined using the FRET assay.

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 of formula I 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 of formula I 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. Another aspect of the invention is a method of inhibiting the function of the HCV replicon. Another aspect of the invention is a method of inhibiting 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 judgment.

The invention also encompasses methods where the compound is given in combination therapy. That is, the compound can be used in conjunction with, but separately from, other agents useful in treating hepatitis and HCV infection. In these combination methods, the compound will generally be given in a daily dose of 1-100 mg/kg body weight daily in conjunction with other agents. The other agents generally will be given in the amounts used therapeutically. The specific dosing regime, however, will be determined by a physician using sound medical judgement.

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

Table 2.

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

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

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

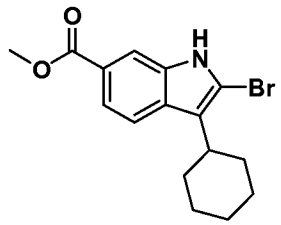
DESCRIPTION OF SPECIFIC EMBODIMENTS

Unless otherwise specified, analytical LCMS data on the following intermediates and examples were acquired using the following columns and conditions. Stop time: Gradient time + 1 minute; Starting conc: 0% B unless otherwise noted; Eluent A: 5% CH_3CN / 95% H_2O with 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. 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.

Intermediate 1

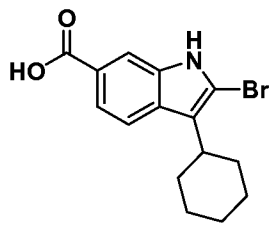


1H-Indole-6-carboxylic acid, 2-bromo-3-cyclohexyl-, methyl ester.

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



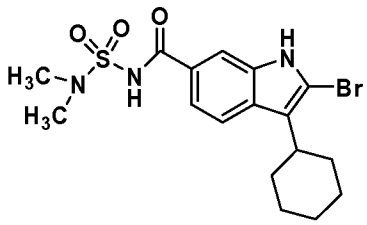
1H-Indole-6-carboxylic acid, 2-bromo-3-cyclohexyl-. A solution of methyl 2-bromo-3-cyclohexyl-1*H*-indole-6-carboxylate (20 g, 60 mmol) and LiOH (3.8 g, 160 mmol) in MeOH/THF/H_2O (1:1:1, 300 mL) was heated at 90 °C for 2h. The reaction mixture was cooled in an ice/H_2O bath, neutralized with 1M HCl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

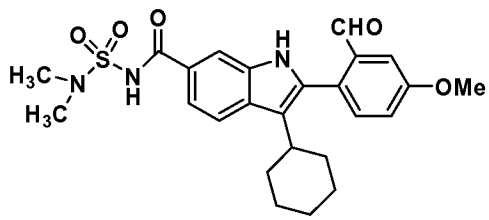


1H-Indole-6-carboxamide, 2-bromo-3-cyclohexyl-N-[(dimethylamino)sulfonyl]-. 1,1'-Carbonyldiimidazole (1.17 g, 7.2 mmol) was added to a stirred solution of 2-bromo-3-cyclohexyl-1H-indole-6-carboxylic acid (2.03 g, 6.3 mmol) in THF (6 mL) at 22 °C. The evolution of CO_2 was instantaneous and when it slowed 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). ^{1}H NMR (300 MHz, DMSO-D6) δ ppm 1.28 - 1.49 (m, 3 H) 1.59 - 2.04 (m, 7 H) 2.74 - 2.82 (m, 1 H) 2.88 (s, 6 H) 7.57 (dd, *J*=8.42, 1.46 Hz, 1 H) 7.74 (d, *J*=8.78 Hz, 1 H) 7.91 (s, 1 H) 11.71 (s, 1 H) 12.08 (s, 1 H).

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

To a 1 L four necked round bottom flask equipped with a mechanical stirrer, a temperature controller, a N2 inlet , and a condenser, under N2, was added 2-bromo-3-cyclohexyl-1*H*-indole-6-carboxylic acid (102.0 g, 0.259 mol) and dry THF (300 mL). After stirring for 10 min, CDI (50.3 g, 0.31 mol) was added portion wise. The reaction mixture was then heated to 50 oC for 2 h. After cooling to 30 oC, *N*,*N*-dimethylaminosulfonamide (41.7 g, 0.336 mol) was added in one portion followed by addition of DBU (54.1 mL, 0.362 mol) drop wise over a period of 1 h. The reaction mixture was then stirred at rt for 20 h. The solvent was removed in vacuo and the residue was partitioned between EtOAc and 1 N HCl (1 : 1, 2 L). The organic layer was separated and the aqueous layer was extracted with EtOAc (500 mL). The combined organic layers were washed with brine (1.5 L) and dried over MgSO4. The solution was filtered and concentrated in vacuo to give the crude product (111.0 g). The crude product was suspended in EtOAc (400 mL) at 60 oC. To the suspension was added heptane (2 L) slowly. The resulting suspension was stirred and cooled to 0 oC. It was then filtered. The filter cake was rinsed with small amount of heptane and house vacuum air dried for 2 days. The product was collected as a white solid (92.0 g, 83%). ^{1}H NMR (MeOD, 300 MHz) δ 7.89 (s, H), 7.77 (d, *J* = 8.4 Hz, 1H), 7.55 (dd, *J* = 8.4 and 1.8 Hz, 1H), 3.01 (s, 6H), 2.73-2.95 (m, 1H), 1.81-2.05 (m, 8H), 1.39-1.50 (m, 2H); m/z 429 (M +H)+.

Intermediate 4



1H-Indole-6-carboxamide, 3-cyclohexyl-N-[(dimethylamino)sulfonyl]-2-(2-formyl-4-methoxyphenyl)-. A mixture of the 2-Bromo-3-cyclohexyl- N-[(dimethylamino)sulfonyl]-1H-indole-6-carboxamide (4.28g, 0.01 mol), 4-methoxy-2-formylphenyl boronic acid (2.7g, 0.015 mol), 2-dicyclohexylphosphino-2',6'-dimethoxy-biphenyl (41 mg, 0.0001 mol), palladium acetate (11.2 mg), and finely

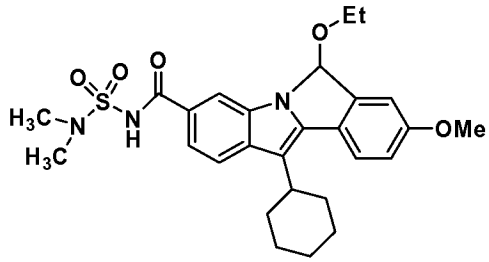
ground potassium carbonate (4.24g, 0.02 mol) in toluene (30 mL) was stirred under reflux and under nitrogen for 30 min, at which time LC/MS analysis showed the reaction to be complete. The reaction mixture was then diluted with ethyl acetate and water, and then acidified with an excess of dilute HCl. The ethyl acetate layer was then collected and washed with dilute HCl, water and brine. The organic solution was then dried (magnesium sulfate), filtered and concentrated to give a gum. The gum was diluted with hexanes (250 ml) and ethyl acetate (25 mL), and the mixture was stirred for 20 hr at 22° C during which time the product was transformed into a bright yellow granular solid (4.8 g) which was used directly without further purification.

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

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

110.4, 109.8, 79.6, 45.9, 37.2(2), 34.7, 32.0(2), 25.9(2), 24.9. LCMS: m/e 482 $(M-H)^-$, ret time 2.56 min, column A, 4 minute gradient.

Intermediate 5

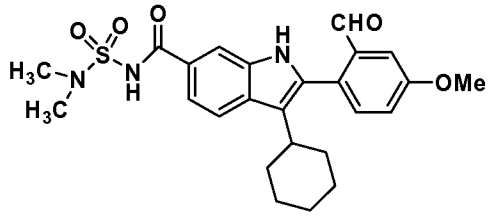


6H-Isoindolo[2,1-a]indole-3-carboxamide, 11-cyclohexyl-N-[(dimethylamino)sulfonyl]-6-ethoxy-8-methoxy-. To a 5 L four necked round bottom flask equipped with a temperature controller, a condenser, a N2 inlet and a mechanical stirrer, was charged toluene (900 mL), EtOH (900 mL), 2-bromo-3-cyclohexyl-*N*-(*N*,*N*-dimethylsulfamoyl)-1*H*-indole-6-carboxamide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

The mother liquid from the trituration was concentrated in vacuo. The residue was refluxed with EtOH (50 mL) for 3 h. The solution was then cooled to

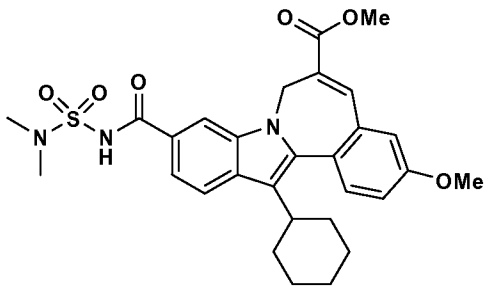
0 °C. The precipitates were filtered and washed with cooled TBME (5 °C) (20 mL). The filter cake was house vacuum air dried to give a further quantity of the title compound as a white solid (16.0 g). HPLC purity, 99%. ^{1}H NMR (CDCl3, 300 MHz) δ 8.75 (s, 1H), 7.96 (s, 1H), 7.73 (d, *J* = 8.4 Hz, 1H), 7.67 (d, *J* = 8.4 Hz, 1H), 7.45 (dd, *J* = 8.4 and 1.4 Hz, 1H), 7.09 (d, *J* = 2.2 Hz, 1H), 6.98 (dd, *J* = 8.4 and 2.2 Hz, 1H), 6.50 (s, 1H), 3.86 (s, 3H), 3.05 (s, 6H), 2.92-3.13 (m, 3H), 1.85-1.93 (m, 7 H), 1.40-1.42 (m, 3H), 1.05 (t, *J* = 7.1 Hz, 3H). m/z 512 (M + H)+.

Intermediate 6



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

Intermediate 7



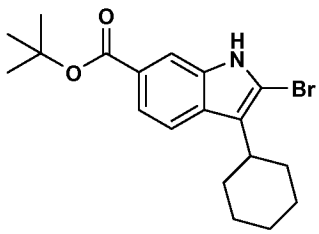
7H-Indolo[2,1-a][2]benzazepine-6-carboxylic acid, 13-cyclohexyl-10-[[[(dimethylamino)sulfonyl]amino]carbonyl]-3-methoxy-, methyl ester. A mixture of the 3-cyclohexyl-N-(N,N-dimethylsulfamoyl)-2-(2-formyl-4-methoxyphenyl)-1H-indole-6-carboxamide (4.8g, 0.01 mol), methyl 2-(dimethoxyphosphoryl)acrylate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

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

A solution of 11-cyclohexyl-N-[(dimethylamino)sulfonyl]-6-hydroxy-8-methoxy-6H-isoindolo[2,1-a]indole-3-carboxamide (cyclic hemiaminal) (63.0 g, 130 mmol), methyl 2-(dimethoxyphosphoryl)acrylate (60 g, 261 mmol), cesium carbonate (106 g, 326 mmol) in DMF (400 mL) was heated at 60 °C (bath temp) for 4.5h. Additional methyl 2-(dimethoxyphosphoryl)acrylate (15 g, 65 mmol) and cesium carbonate (21.2 g, 65 mmol) were added and the reaction was heated at 60 °C overnight then and cooled to rt. The stirring reaction mixture was diluted with H_2O

(1 L), slowly neutralized with 1N aqueous HCl (800 mL), stirred 3h, and then the precipitates were collected by filtration. The solids were triturated with Et2O (800 mL) and dried to yield methyl 7H-indolo[2,1-a][2]benzazepine-6-carboxylic acid, 13-cyclohexyl-10-[[[(dimethylamino)sulfonyl]amino]carbonyl]-3-methoxy-, methyl ester (70.2 g, 127 mmol, 98%) as a yellow solid which was used without further purification. 1HNMR (300 MHz, CDCl3) δ 8.67 (s, 1H), 8.09 (s, 1H), 7.86 (d, J = 8.4 Hz, 1H), 7.80 (s, 1H), 7.50 (d, J = 8.4 Hz, 1H), 7.42 (d, J = 8.8 Hz, 1H), 7.08 (dd, J = 2.6, 8.8 Hz, 1H), 6.98 (d, J = 2.6 Hz, 1H), 5.75 - 5.51 (m, 1H), 4.29 - 4.01 (m, 1H), 3.89 (s, 3H), 3.82 (s, 3H), 3.05 (s, 6H), 2.87 - 2.73 (m, 1H), 2.11 - 1.12 (m, 10H). LCMS: m/e 550 (M-H)-, ret time 3.21 min, column A, 4 minute gradient.

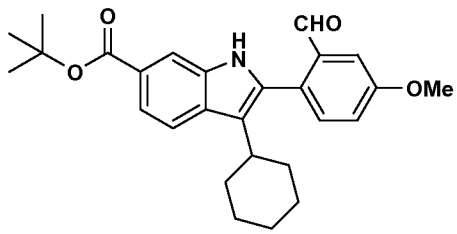
Intermediate 8



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).

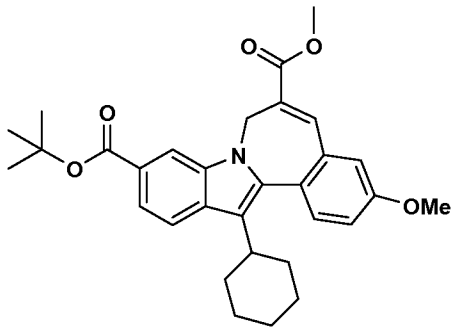
Intermediate 9



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).

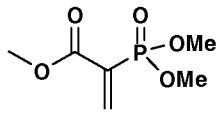
Intermediate 10



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 &

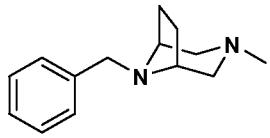
5.65 (two br. peak., 1H each, allylic CH_2), 6.95 (s, 1H, aryl $H_{6'}$), 7.01 (d, 1H, aryl $H_{2'}$), 7.53 (d, J = 8 Hz, 1H, aryl $H_{3'}$), 7.70 (d, J = 4 Hz, 1H, Indole-H_5), 7.84 (s + d, 2H, olefinic H + Indole-H_4), 8.24 (s, 1H, indole – H_7); ^{13}C NMR ($CDCl_3$) (100.0 MHz) δ 166.92, 165.71, 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 11



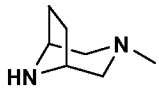
2-Propenoic acid, 2-(dimethoxyphosphinyl)-, methyl ester. To a 5 L four necked round bottom flask equipped with a mechanical stirrer, a condenser, a temperature controller and a N2 inlet , was charged paraformaldehyde (40.5 g, 1.35 mol), MeOH (2 L) and piperidine (2 mL). The reaction mixture was heated 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. ^1H NMR ($CDCl_3$, 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 12



3,8-Diazabicyclo[3.2.1]octane, 3-methyl-8-(phenylmethyl)-. Cis-1-Benzyl-2,5-bis(chloromethyl)pyrrolidine hydrochloride (37.5 g, 0.13 mol) (Prepared as described in Published PCT patent application WO200232902) was suspended in CH_3CN (900 mL) in a 3-neck 5 L round bottom flask fitted with mechanical stirrer, reflux condenser, and thermometer. The stirred suspension was warmed to 50 °C, $NaHCO_3$ (97 g, 1.1 mol) was added, and the suspension was warmed to 70 °C. NaI (50 g, 0.33 mol) was added and stirred at 70 °C for 5 min, at which point an addition funnel was affixed atop the condenser. To the addition funnel was added 48 mL of 40% aqueous $MeNH_2$ (0.55 mol) in 850 mL of CH_3CN, and this solution was added dropwise (rate of addition maintained between 10-15 ml/min). The addition was complete after 75 min, at which point the reaction was cooled to rt., the solids filtered off, and the solvent concentrated to ~800 mL. The reaction was poured into EtOAc (800 mL) and washed with 1 N NaOH (2 x 100 mL). The aqueous phase was re-extracted with EtOAc (2 x 100 mL), the combined organic phases were dried over Na_2SO_4 and concentrated. The resulting residue was introduced on to silica gel (620g) and eluted with 2.8% MeOH/0.4% conc. NH_4OH in $CHCl_3$ (6 L total). Pure fractions were collected from 2 L to 4 L. Concentration yielded 8.76 g (32% yield) of the title compound as a brown oil. 1H NMR (400 MHz, CDCl3) δ ppm 1.79 - 1.87 (m, 2 H) 1.92 - 1.99 (m, 2 H) 2.23 (s, 3 H) 2.27 - 2.37 (m, 2 H) 2.54 - 2.63 (m, 2 H) 3.10 (s, 2 H) 3.52 (s, 2 H) 7.20 - 7.26 (m, 1 H) 7.30 (t, J=7.30 Hz, 2 H) 7.36 - 7.42 (m, 2 H). LC method: Solvent A = 10% MeOH / 90% H2O / 0.1% TFA, Solvent B = 90% MeOH / 10% H2O / 0.1% TFA, Start %B = 0%, Final %B = 100, Flow Rate = 4 ml/min, Gradient time = 2 min, Run time = 3 min, Column: Phenomenex-Luna 10 □m C18 50 mm x 3.0 mm, Rt = 0.23 min; MS: (ES+) m/z (M+H)+ = 217.3. An additional 6.1 g of mixed fractions were obtained from the column (>80% pure by 1H NMR integration).

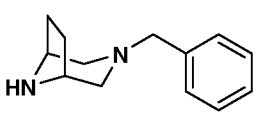
Intermediate 13

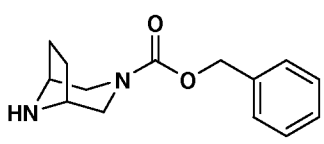


*2HCl

3,8-Diazabicyclo[3.2.1]octane, 3-methyl-, dihydrochloride. N-methyl-N-benzylbicyclodiamine, (14.22g, 65.7mMol) was dissolved in 650ml of methanol and 17ml of 12M aqueous hydrochloric acid was added. The solution was placed in a 2L Parr bottle under nitrogen and 3.66g of 20% palladium hydroxide on carbon added to the reaction. The mixture was placed on a Parr shaker under 60psig of hydrogen for 17hours. The reaction was judged complete by TLC analysis (Silica Gel plate eluted with a 10 parts by volume solution of 2M ammonia in methanol dissolved in 90 parts by volume of chloroform). The reaction was filtered through a plug of ceilite, which was then rinsed sequentially with water and methanol. The combined filtrates were concentrated in vacuuo and methanol and benzene added until a homogenous solution was obtained. 75mL of 2.0M hydrochloric acid in diethyl ether was then added. Volatiles were removed from the product solution in vacuuo. A pale yellow solid was eventually obtained by repeated azetroping of water from the product solution using a methanol / benzene mixture. The solid product, 3-methyl-3,8-diazabicyclo[3.2.1]octane was dried in vacuuo overnight to obtain 11.98g (91%) of a hygroscopic solid. The product was removed from the flask and bottled in a glove bag under nitrogen due to its hygroscopic nature. ^{1}H NMR (500 MHz, DMSO-D6) δ ppm 1.96 - 2.14 (m, 2 H) 2.34 (d, J=8.24 Hz, 2 H) 2.66 (s, 3 H) 3.46 (d, J=11.90 Hz, 2 H) 3.58 (s, 3 H, contains H2O) 4.17 (s, 2 H) 9.92 (s, 1 H) 10.21 (s, 1 H) 11.39 (s, 1H); ^{13}C NMR (126 MHz, DMSO-D6) δ ppm 24.04 (s, 1 C) 43.49 (s, 1 C) 52.50 (s, 1 C) 54.47 (s, 1 C).

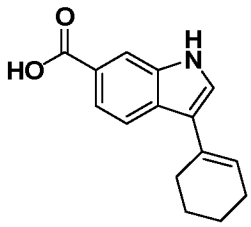
Intermediate 14 and 15





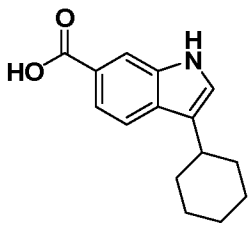
3,8-diazabicyclo[3.2.1]octane-3-carboxylic acid, phenylmethyl ester and 3-(phenylmethyl)-3,8-diazabicyclo[3.2.1]octane. Triethylamine (1.44 mL, 10.363 mmol) was added to a solution of 8-boc-3,8-diaza-bicyclo[3.2.1]ocatane (2.0 g, 9.421 mmol) in CH_2Cl_2 (20 mL), Benzyl chloroformate (1.46 mL, 10.363 mmol) was added dropwise at 0°C and the reaction mixture was stirred at 0°C for 0.5 hr, then allowed to warm to rt. and stirring was continued for 3 days. The reaction mixture was then quenched with water and acidified with 1N HCl solution. The organic layer was separated, washed with brine, dried ($MgSO_4$) and concentrated to give a colorless thick oil as the crude product. 70 mg of this material was then dissolved in 1,2-dichloroethane (2mL) and TFA (0.5 mL) was added. The reaction mixture was stirred at rt. for 2 hr. The solvent and TFA were then evaporated to give a mixture of the two title compounds as a colorless thick oil.

Intermediate 16



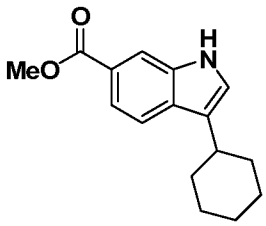
3-Cyclohexenyl-1H-indole-6-carboxylic acid. Cyclohexanone (96 mL, 0.926 mol) was added to a stirred solution of methyl indole-6-carboxylic acid (50.0 g, 0.335 mol) in methanol (920 mL) at 22 °C. Methanolic sodium methoxide (416 mL of 25% w/w, 1.82 mol) was added in portions over 10 minutes. The mixture was stirred at reflux for 18 hours, cooled to room temperature, concentrated, diluted with cold water, and acidified with 36% HCl solution. The resulting precipitate was collected by filtration, washed with cold water, and dried over phosphorous pentoxide (0.1 mm) to provide the the title compound as a tan colored solid (80.9 g, 97.5% yield).

Intermediate 17



3-Cyclohexyl-1H-indole-6-carboxylic acid. 3-Cyclohexenyl-1H-indole-6-carboxylic acid (38 g) was added to a Parr bottle, followed by methanol (100 mL) and THF (100 mL). The bottle was flushed with argon and 10% palladium on carbon (1.2 g) was added. The flask was then evacuated and subsequently refilled with H_2 to a pressure of 55 psi, and the resultant mixture was shaken for18 hours at RT. The catalyst was then removed by filtration through celite. Concentration of the filtrate provided the desired product as a pale purple solid (30.6 g, 79%). ESI-MS *m/z* 244 (MH+).

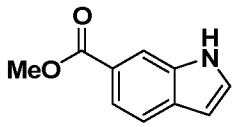
Intermediate 18



Methyl 3-cyclohexyl-1H-indole-6-carboxylate. Thionyl chloride (1 mL) was added to a stirred mixture of 3-cyclohexyl-1H-indole-6-carboxylic acid (30.4 g, 0.125 mol) in methanol (300 mL). The mixture was stirred at reflux for 18 hours, treated with decolorizing carbon, and filtered. The filtrate was concentrated to about 150 mL at which point crystallization occurred. The filtrate was cooled to room temperature and filtered. The solid was washed with cold methanol followed by diethyl ether to provide the desired product as a pale purple solid (22.2 g, 69% yield). ESI-MS *m/z* 258 (MH+); ^{1}H NMR (300 MHz, $CDCl_3$) δ 1.35 (m, 4H), 1.63 (s, 1H),

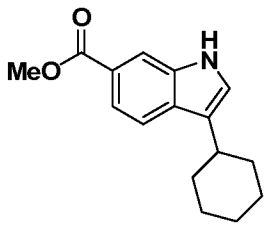
1.78 (m, 3H), 2.06 (d, *J*=8.05 Hz, 2H, 3.90 (m, 1H), 7.08 (d, *J*=1.83 Hz, 1H), 7.62 (s, 1H), 7.65 (s, 1H),7.74 (d, *J*=1.46 Hz, 1H), 7.77 (d, *J*=1.46 Hz, 1H), 8.08 (s, 1H).

Intermediate 19



Methyl 1H-indole-6-carboxylate. An ethereal solution of diazomethane (620 mL) was added slowly to a cooled, (-15 °C) stirred suspension of 6-indole carboxylic acid (45 g, 0.27 mol.) in diethyl ether (250 mL). Upon addition, the reaction mixture was stirred for a further 1h at -15 °C, after which the reaction was quenched by the slow addition of acetic acid (50 mL). The resultant mixture was then concentrated under reduced pressure, and the residue purified using flash chromatography on silica (60 – 120), using MDC as eluant.

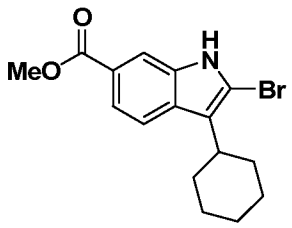
Intermediate 20



Methyl 3-cyclohexyl-1H-indole-6-carboxylate. Cyclohexanone (42.46 mL, 0.40 mol) was added in a single portion to a stirred solution of methyl indole-6-carboxylate (47.8 g, 0.27 m) in dry dichloromethane (500 mL). The reaction mixture was then cooled to 10°C and trifluoroacetic acid (63.13 mL, 0.8 m) was added dropwise followed by triethyl silane (174.5 mL, 1.09 m). Upon addition, the temperature was allowed to rise to rt, after which it was stirred for a further 12 h. Dichloromethane (200 mL) was then added and the reaction mixture was washed successively with with 10% sodium bicarbonate solution and brine. The organic layer dried over sodium sulfate, filtered and concentrated under vacuum. The

resultant residuce was purified by flash chromatography on silica (60 – 120) using hexane – ethyl acetate (9.5:0.5) mixture as eluant. Homogeneous fractions were combined and evaporated to give 60 g of the desired product (85%). Analytical data on this material was consistant with that observed with a sample prepared by the alternative route described above.

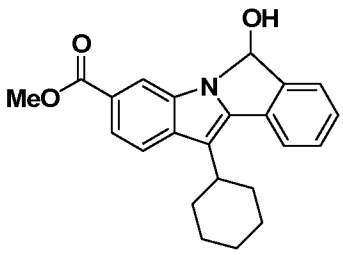
Intermediate 21



Methyl 2-bromo-3-cyclohexyl-2-1H-indole-6-carboxylate. Dry pyridinium tribromide (12.0 g, 38 mmol) was added in one portion to a stirred and cooled (ice/water bath) solution of methyl 3-cyclohexyl-1H-indole-6-carboxylate (7.71 g, 30 mmol) in a mixture of THF (80 mL) and chloroform (80 mL). The flask was removed from the cooling bath and stirring was continued for 2 hours at room temperature. The mixture was sequentially washed with 1M $NaHSO_3$ (2 x 50 mL) and1N HCl (50 mL). It was then dried over anhydrous sodium sulfate, filtered, and concentrated. The concentrate was treated with hexanes and the resulting precipitate was collected by filtration to provide the desired product as an off-white solid (5.8 g, 58%). ^{1}H NMR (300 MHz, $CDCl_3$) δ 1.38 (m, 3H), 1.85 (m, 7H), 2.81 (m, 1H), 7.71 (m, 2H), 8.03 (s, 1H), 8.47 (s, 1H).

The hexane mother liquor was concentrated and the residue was dissolved in hexane/ethyl acetate (5:1). The solution was passed through a pad of silica gel with the same solvents. Concentration of the eluate followed by the addition of hexane (10 mL) resulted in the precipitation of additional product which was collected by filtration to provide 2.8 g (28%) of the desired product.

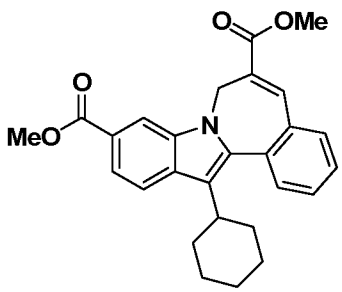
Intermediate 22



Methyl 11-cyclohexyl-6-hydroxy-6H-isoindolo[2,1-a]indole-3-carboxylate.

A stirred mixture of methyl 2-bromo-3-cyclohexyl-1H-indole-6-carboxylate (10.1 g, 30 mmol), 2-formylphenylboronic acid (5.4 g, 36 mmol), LiCl (3.8 g (90 mmol) and Pd $(PPh_3)_4$ (1.6 g, 1.38 mmol) in 1M Na_2CO_3 (40 mL) and 1:1 EtOH-toluene (180 mL) was heated under nitrogen at 85 °C for 3 hours. The reaction mixture was then cooled to RT, and extracted with EtOAc (2X 100 mL). The extracts were washed sequentially with water and brine, then dried ($MgSO_4$), filtered and conventrated in-vacuo to afforded 13.3 g of crude product. This material was triturated with DCM and hexanes to provide pure desired product (7.52 g, 70%). LC-MS: m/e 360 (M-H); 344 $(M-17)^+$. ^{1}H NMR (400 MHz, CHLOROFORM-D) δ ppm 1.33 - 1.60 (m, 4 H) 1.77 - 2.01 (m, 6 H) 2.80 (d, *J*=11.83 Hz, 1 H) 3.02 - 3.18 (m, 1 H) 3.89 (s, 3 H) 6.49 (d, *J*=11.33 Hz, 1 H) 7.34 (t, *J*=7.55 Hz, 1 H) 7.46 (t, *J*=7.55 Hz, 1 H) 7.62 (d, *J*=7.30 Hz, 1 H) 7.66 - 7.74 (m, 2 H) 7.77 (d, *J*=7.81 Hz, 1 H) 8.21 (s, 1 H).

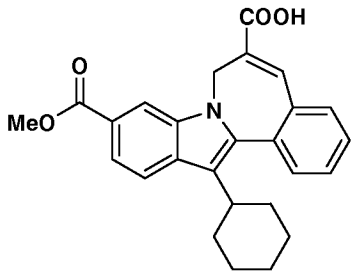
Intermediate 23



Methyl 13-cyclohexyl-6-(methoxycarbonyl)-7H-indolo[2,1-a][2]benzazepine-10-carboxylate. A stirred suspension of methyl 11-cyclohexyl-6-hydroxy-6H-isoindolo[2,1-a]indole-3-carboxylate (3.61 g, 10mmol), Cs_2CO_3 (3.91 g,

12 mmol) and trimethyl 2-phosphonoacetate (2.86g, 14 mmol) in an. DMF (40 mL) was heated at 60 °C under nitrogen for 3 h. The resultant yellow suspension was cooled to rt and water was added with vigorous stirring. A yellow precipitate formed which was collected by filtration. The solid was washed with water, and then air dried overnight to afford the title compound as a yellow powder (4.124g, 96%). LC/MS: m/e 430 (MH^+); ^1H NMR (400 MHz, CHLOROFORM-D) δ ppm 1.30 - 1.46 (m, *J*=14.86 Hz, 2 H) 1.55 (s, 2 H) 1.77 (s, 2 H) 1.85 - 2.18 (m, 4 H) 2.76 - 2.89 (m, 1 H) 3.84 (s, 3 H) 3.95 (s, 3 H) 4.19 (s, 1 H) 5.68 (s, 1 H) 7.38 - 7.63 (m, 4 H) 7.74 (dd, *J*=8.44, 1.39 Hz, 1 H) 7.81 - 7.98 (m, 2 H) 8.29 (d, *J*=1.01 Hz, 1 H).

Intermediate 24



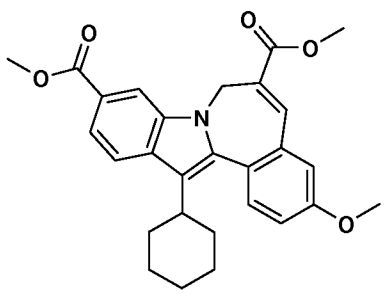
Methyl 13-cyclohexyl-6-(carboxy)-5H-indolo[2,1-a][2]benzazepine-10-carboxylate. Methyl 13-cyclohexyl-6-(methoxycarbonyl)-7H-indolo[2,1-a][2]benzazepine-10-carboxylate (308mg, 0.72mmol) was dissolved in N,N-dimethylformamide (5 mL) and treated with LiOH (173mg, 7.2mmol). The mixture was heated at 50 °C for 4hr, afterwhich the solvent was removed in vacuo. The residue was dissolved in H_2O (5mL) and the resultant mixture was acidified by the addition of a 10% aqueous HCL solution. A precipitate formed which was collected by filtration and air dried to afford the title compound as a bright yellow solid (290mg, 97%). ESI-MS m/z [M+1]=415.

The general methods below were used with the following experimental procedures until indicated otherwise: LCMS data: 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 and D); 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 and D); 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 5.0 mm C18.

To a slurried solution of methyl 2-bromo-3-cyclohexyl-1*H*-indole-6-carboxylate (4.3 g, 13 mmol), 4-methoxy-2-formylphenylboronic acid (3.0 g, 17 mmol) and LiCl (2.2 g, 51 mmol) in EtOH/toluene (1:1, 100 mL) was added $Pd(PPh_3)_4$ (1.4 g, 1.3 mmol) and then 1M Na_2CO_3 (aq.) (32 mL, 32 mmol). The reaction solution was flushed with nitrogen and heated at 100 °C for 3h and cooled to rt. The reaction was concentrated to remove EtOH, diluted with H_2O (200 mL) and extracted with EtOAc (2 x 150 mL). The combined organics were washed with brine (100 mL), dried ($MgSO_4$), filtered and concentrated to dryness. The residue was triturated with CH_2Cl_2 and the solids were collected by filtrated and washed with Et_2O and CH_2Cl_2 to yield methyl 11-cyclohexyl-6-hydroxy-8-methoxy-6*H*-isoindolo[2,1-*a*]indole-3-carboxylate (3.0 g, 8.0 mmol, 63%) as a yellow solid which was used without further purification. LCMS: m/e 374 $(M+H)^+$, ret time 3.09 min, column B, 3 minute gradient.

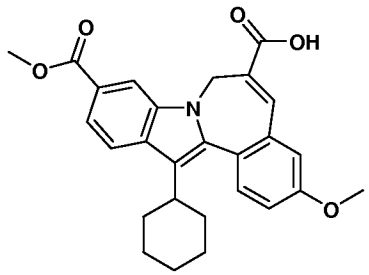
Intermediate 25



A solution of methyl 11-cyclohexyl-6-hydroxy-8-methoxy-6*H*-isoindolo[2,1-*a*]indole-3-carboxylate (2.9 g, 7.4 mmol), methyl 2-(dimethoxyphosphoryl)acrylate

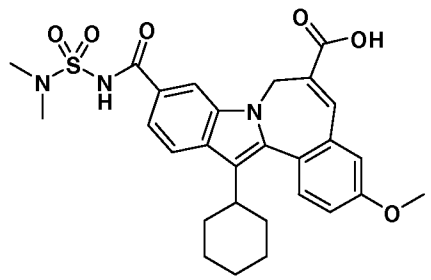
(2.6 g, 11 mmol), cesium carbonate (3.6 g, 11 mmol) in DMF (20 mL) was heated at 60 °C for 2h and cooled to rt. The stirring reaction mixture was diluted with H_2O (50 mL) and the precipitates were collected by filtration to yield dimethyl 13-cyclohexyl-3-methoxy-7*H*-indolo[2,1-*a*][2]benzazepine-6,10-dicarboxylate (3.3 g, 7.1 mmol, 97%) as a yellow solid which was used without further purification. LCMS: m/e 460 $(M+H)^+$, ret time 3.35 min, column B, 3 minute gradient.

Intermediate 26



A solution of tetrabutylammonium hydroxide (1M in MeOH, 2.2 mL, 2.2 mmol) was added to a stirring solution of dimethyl 13-cyclohexyl-3-methoxy-7*H*-indolo[2,1-*a*][2]benzazepine-6,10-dicarboxylate (1.0 g, 2.2 mmol) in THF (75 mL) and stirred at rt overnight. The reaction mixture was concentrated to ~30 mL, diluted with EtOAc (120 mL), washed with 0.5 M HCl (aq.) (2 x 50 mL) and brine (40 mL), dried ($MgSO_4$), filtered and concentrated to dryness to yield methyl 7*H*-indolo[2,1-*a*][2]benzazepine-10-carboxylate, 13-cyclohexyl, 3-methoxy, 6-carboxylic acid (1.0 g, 2.2 mmol, quant.) as a yellow solid which was used without further purification. LCMS: m/e 446 $(M+H)^+$, ret time 1.54 min, column A, 2 minute gradient.

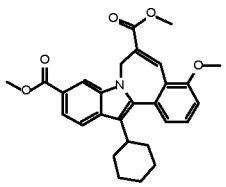
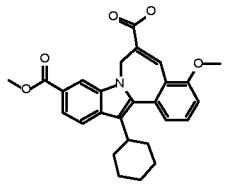
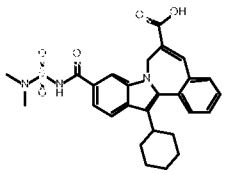
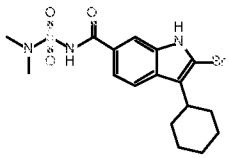
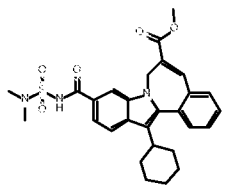
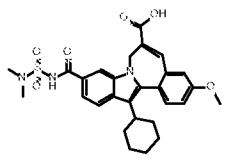
Intermediate 27

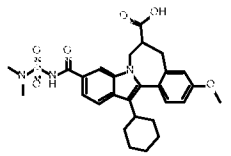


Added 1M NaOH (aq.) (5 mL, 5 mmol) to a solution of methyl 13-cyclohexyl-*N*-[(dimethylamino)sulfonyl]-3-methoxy-7*H*-indolo[2,1-*a*][2]benzazepine-6-carboxylate-10-carboxamide (900 mg, 1.6 mmol) in THF/MeOH (1:1, 14 mL) and heated the reaction mixture in a sealed tube with microwave irradiation at 85 °C for 30 min. The reaction was cooled, neutralized with 1M HCl (aq.) (5 mL, 5.0 mmol) and concentrated to remove organic solvents. The residue was slurried with H_2O and the solids were collected by filtration, flushed with H_2O and dried to yield 13-cyclohexyl-*N*-[(dimethylamino)sulfonyl]-3-methoxy-7*H*-indolo[2,1-*a*][2]benzazepine-10-carboxamide-6-carboxylic acid (807 mg, 1.5 mmol, 92%) as a yellow solid. LCMS: m/e 536 $(M-H)^-$, ret time 2.18 min, column A, 4 minute gradient.

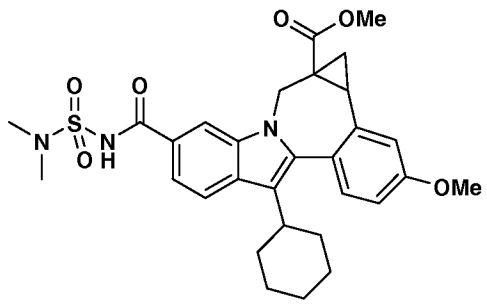
The general methods described below pertain to the experimental data for the compounds in the Table 3. LCMS data: Gradient time: 2min; Flow rate: 4 mL/min; Stop time: Gradient time + 2 minute; Starting conc: 0% B; Eluent A: 10 % MeOH / 90 % H_2O with 0.1% TFA; Eluent B: 90 % MeOH / 10 % H_2O with 0.1% TFA; Column 1: Phenomenex 10µ C18 4.6 x 50 mm.

Table 3.

Compound	Analytical Data
	LCMS: *m/z* 460 (MH^+), ret time 3.05 min
	LCMS: *m/z* 446 (MH^+), ret time 2.89 min
	LCMS: *m/z* 508 (MH^+), ret time 2.08 min
	LCMS: *m/z* 429 (MH^+), ret time 2.34 min
	LCMS: *m/z* 522 (MH^+), ret time 2.49 min
	LCMS: *m/z* 538 (MH^+), ret time 2.13 min

Compound	Analytical Data
	LCMS: *m/z* 540 (MH^+), ret time 2.12 min

Intermediate 28

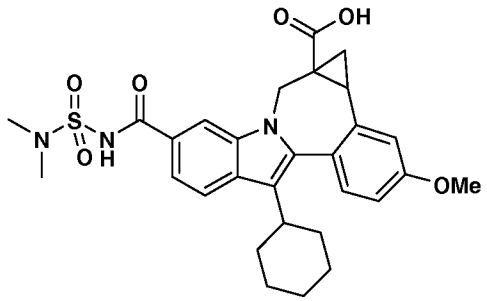


(+/-) Cycloprop[d]indolo[2,1-a][2]benzazepine-5-carboxylic acid, 8-cyclohexyl-1,1a,2,12b-tetrahydro-11-methoxy-1a-[(4-morpholinylcarbonyl)amino]-methyl ester. DMSO (5 mL) was added to a mixture of trimethylsulfoxonium iodide (199 mg, 0.906 mmol) and NaH (38 mg in 60% oil dispersion, 0.953 mmol) in a 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 alternate procedure. To a mixture trimethylsulfoxonium iodide (6.85 g, 31 mmol) in DMSO (35 mL) at r.t. under N2 was added NaH (1.37 g, 34 mmol, 60% in oil) in three portions, and the mixture stirred at r.t. for 40 min. To this mixture was then added a solution of the olefin (7.82 g, 14.2 mmol) in DMSO (35 ml, then 30 ml + 35 ml washing) via a funnel under a stream of N2. The brown mixture was then stirred at 55°C for 2 hr 45 min. The mixture was cooled to r.t., then cooled in an ice-water bath, added slowly hydrochloric acid (150 ml, 1 N) and further diluted with water (100 ml). The yellow precipitates were filtered, washed with hydrochloric acid (50 ml, 1 N) and water (2 x 50 ml), and then dried. The crude material was purified by Biotage Horizon chromatography (0 to 70% EtOAc/Hexane) to give the cyclopropanated product (4.25 g, 53%) as an off white solid. LC/MS were performed by using Shimadzu-VP instrument with UV detection at 220 nm and Waters Micromass. HPLC method: Solvent A = 10% MeOH–90% H_2O–0.1% TFA, Solvent B = 90% MeOH–10%H_2O–0.1% TFA, Start %B = 0, Final %B = 100, Gradient time = 2 min, Stop time = 3 min, Flow Rate = 5 ml/min, Column: Xterra MS C18 S7 3.0 x 50mm; (ES+) m/z $(M+H)^+$ = 566.41, HPLC R_t = 1.985 min. HPLC method: Solvent A = 5% MeCN–95% H_2O–10 mM NH_4OAc, Solvent B = 95% MeCN–5%H_2O–10 mM NH_4OAc, Start %B = 0, Final %B = 100, Gradient time = 2 min, Stop time = 3 min, Flow Rate = 5 ml/min, Column: Phenomenex Lina C18 5um 3.0 x 50mm; (ES+) m/z $(M+H)^+$ = 566.21, HPLC R_t = 1.568 min.

Intermediate 29

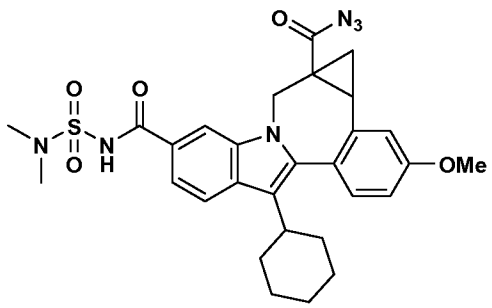


(+/-) Cycloprop[d]indolo[2,1-a][2]benzazepine-1a(2H)-carboxylic acid, 8-cyclohexyl-5-[[[(dimethylamino)sulfonyl]amino]carbonyl]-1,12b-dihydro-11-methoxy-. To a solution of (+/-) Cycloprop[d]indolo[2,1-a][2]benzazepine-5-carboxylic acid, 8-cyclohexyl-1,1a,2,12b-tetrahydro-11-methoxy-1a-[(4-morpholinylcarbonyl)amino]-methyl 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 Prep. 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).

An alternate procedure. To a mixture of Methyl 8-Cyclohexyl-5-((dimethylsulfamoyl)carbamoyl)-11-methoxy-1,12b-dihydrocyclopropa[d]indolo[2,1-a][2]benzazepine-1a(2H)-carboxylate (0.61 g, 1.08 mmol) in a 1:1 mixture of THF/MeOH (4.5 ml/4.5 ml) at r.t. under N2 was added aqueous sodium hydroxide (3.4 ml, 3.4 mmol, 1N), and the mixture was stirred at r.t.

for 6 hr 15 min. The mixture was quenched with hydrochloric acid (4 ml, 4 mmol, 1N), and evaporated to dryness. The residue was added with water (10 ml) and swirled. The semi-solid was filtered and washed with water (2 x 10 ml) to give a solid, which was then dried. The acid product was used without further purification. LC/MS were performed by using Shimadzu-VP instrument with UV detection at 220 nm and Waters Micromass. HPLC method: Solvent A = 10% MeOH–90% H_2O–0.1% TFA, Solvent B = 90% MeOH–10%H_2O–0.1% TFA, Start %B = 0, Final %B = 100, Gradient time = 2 min, Stop time = 3 min, Flow Rate = 5 ml/min, Column: Xterra MS C18 S7 3.0 x 50mm; (ES+) m/z $(M+H)^+$ = 552.07, HPLC R_t = 1.922 min.

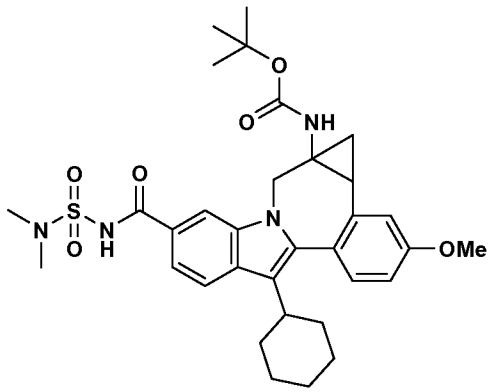
Intermediate 30



8-Cyclohexyl-5-(((dimethylamino)sulfonyl)carbamoyl)-11-methoxy-1,12b-dihydrocyclopropa[d]indolo[2,1-a][2]benzazepine-1a(2H)-carbonyl azide. To a mixture of the acid, 8-cyclohexyl-5-(((dimethylamino)sulfonyl)carbamoyl)-11-methoxy-1,12b-dihydrocyclopropa[d]indolo[2,1-a][2]benzazepine-1a(2H)-carboxylic acid, (1 g, 1.81 mmol) in PhMe (18 ml) at r.t. under N_2 was added triethylamine (0.38 ml, 2.73 mmol), followed by diphenylphosphoryl azide (DPPA) (0.59 ml, 2.73 mmol). The mixture was stirred at r.t. for 2.5 hr. The volatiles were then evaporated and the residue purified by Biotage flash chromatography (gradient elution, 0 to 60% EtOAc/Hexane) to gave the acyl azide, 8-cyclohexyl-5-(((dimethylamino)sulfonyl)carbamoyl)-11-methoxy-1,12b-dihydrocyclopropa[d]indolo[2,1-a][2]benzazepine-1a(2H)-carbonyl azide, (725.4 mg); Analytical HPLC method: Solvent A = 10% MeOH–90% H_2O–0.1% TFA,

Solvent B = 90% MeOH–10%H_2O–0.1% TFA, Start %B = 0, Final %B = 100, Gradient time = 2 min, Flow Rate = 5 ml/min, Column: Xterra MS C18 S7 3.0 x 50mm; LC/MS: (ES+) m/z $(M+H)^+$ = 577.29, HPLC R_t = 2.015 min. Analytical HPLC method: Solvent A = 5% MeCN–95% H_2O–10 mM NH_4OAc, Solvent B = 95% MeCN–5%H_2O–10 mM NH_4OAc, Start %B = 0, Final %B = 100, Gradient time = 2 min, Flow Rate = 5 ml/min, Column: Phenomenex Lina C18 5um 3.0 x 50mm; LC/MS: (ES+) m/z $(M+H)^+$ = 577.18, HPLC R_t = 1.633 min.

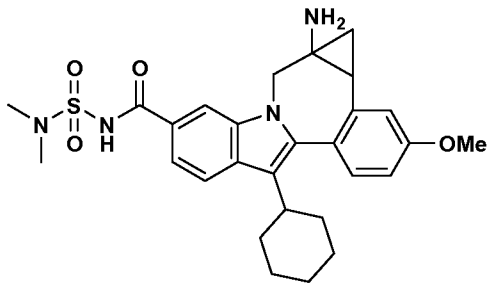
Intermediate 31



1,1-Dimethylethyl (8-cyclohexyl-5-((((dimethylamino)sulfonyl)amino)carbonyl)-11-(methyloxy)-1,12b-dihydrocyclopropa[d]indolo[2,1-a][2]benzazepin-1a(2H)-yl)carbamate. A mixture of the azide, 8-cyclohexyl-5-(((dimethylamino)sulfonyl)carbamoyl)-11-methoxy-1,12*b*-dihydrocyclopropa[*d*]indolo[2,1-*a*][2]benzazepine-1*a*(2*H*)-carbonyl azide, (102 mg) in PhMe (2 ml) under N_2 was stirred at 120°C for 1 hr. 35 min., cooled to r.t. and then concentrated. The residue was added *tert*-butanol (2 ml) and stirred at 120°C for 1 hr. 45 min., and then evaporated. The crude product was purified by flash chromatography (gradient elution 0-60% EtOAc/Hexane) to give 1,1-dimethylethyl (8-cyclohexyl-5-((((dimethylamino)sulfonyl)amino)carbonyl)-11-(methyloxy)-1,12*b*-dihydrocyclopropa[*d*]indolo[2,1-*a*][2]benzazepin-1*a*(2*H*)-yl)carbamate as a pale yellow solid. Analytical HPLC method: Solvent A = 10% MeOH–90% H_2O–0.1% TFA, Solvent B = 90% MeOH–10%H_2O–0.1% TFA, Start %B = 0, Final %B = 100, Gradient time = 2 min, Flow Rate = 5 ml/min, Column:

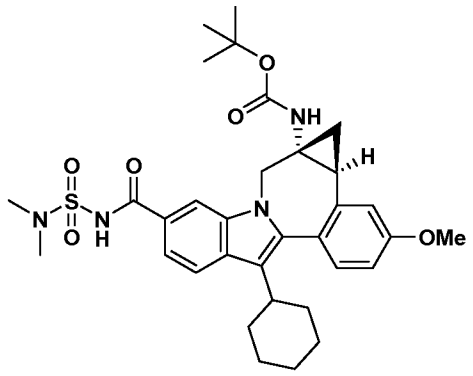
Xterra MS C18 S7 3.0 x 50mm; LC/MS: (ES+) m/z $(M+H)^+$ = 623.45, HPLC R_t = 1.957 min. Analytical HPLC method: Solvent A = 5% MeCN–95% H_2O–10 mM NH_4OAc, Solvent B = 95% MeCN–5%H_2O–10 mM NH_4OAc, Start %B = 0, Final %B = 100, Gradient time = 2 min, Flow Rate = 5 ml/min, Column: Phenomenex Lina C18 5um 3.0 x 50mm; LC/MS: (ES+) m/z $(M+H)^+$ = 623.37, HPLC R_t = 1.628 min.

Intermediate 32



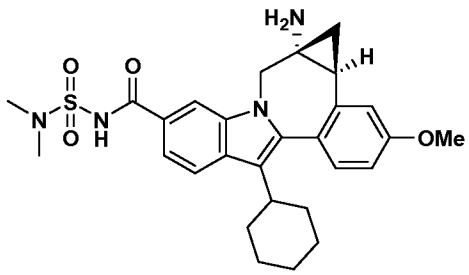
1a-amino-8-cyclohexyl-N-((dimethylamino)sulfonyl)-11-(methyloxy)-1,1a,2,12b-tetrahydrocyclopropa[d]indolo[2,1-a][2]benzazepine-5-carboxamide. To 1,1-dimethylethyl (8-cyclohexyl-5-(((((dimethylamino)sulfonyl)amino)carbonyl)-11-(methyloxy)-1,12*b*-dihydrocyclopropa[*d*]indolo[2,1-*a*][2]benzazepin-1*a*(2*H*)-yl)carbamate (75.3 mg) at r.t. under N_2 was added a solution of HCl in 1,4-dioxane (0.5 ml, 4M). The mixture was stirred for 3 hr. 35 min., evaporated to give the hydrochloride salt of the amine, 1*a*-amino-8-cyclohexyl-*N*-((dimethylamino)sulfonyl)-11-(methyloxy)-1,1*a*,2,12*b*-tetrahydrocyclopropa[*d*]indolo[2,1-*a*][2]benzazepine-5-carboxamide, which was used without further purification. Analytical HPLC method: Solvent A = 10% MeOH–90% H_2O–0.1% TFA, Solvent B = 90% MeOH–10%H_2O–0.1% TFA, Start %B = 0, Final %B = 100, Gradient time = 2 min, Flow Rate = 5 ml/min, Column: Xterra MS C18 S7 3.0 x 50mm; LC/MS: (ES+) m/z $(M+H)^+$ = 523.39, HPLC R_t = 1.632 min.

Intermediate 33



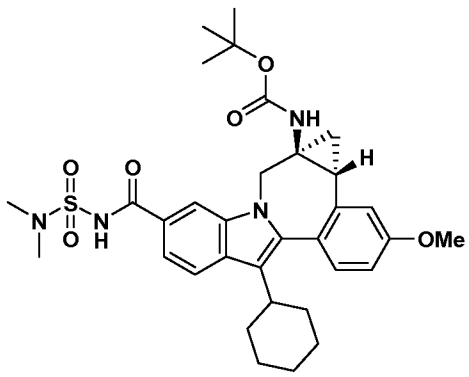
tert-Butyl ((1aR,12bS)-8-cyclohexyl-5-((dimethylsulfamoyl)carbamoyl)-11-methoxy-1,12b-dihydrocyclopropa[d]indolo[2,1-a][2]benzazepin-1a(2H)-yl)carbamate. *tert*-Butyl ((1*aR*,12*bS*)-8-cyclohexyl-5-((dimethylsulfamoyl)carbamoyl)-11-methoxy-1,12*b*-dihydrocyclopropa[*d*]indolo[2,1-*a*][2]benzazepin-1*a*(2*H*)-yl)carbamate was prepared from the corresponding chiral acid, (1a*R*,12*bS*)-8-cyclohexyl-5-((dimethylsulfamoyl)carbamoyl)-11-methoxy-1,12*b*-dihydrocyclopropa[*d*]indolo[2,1-*a*][2]benzazepine-1*a*(2*H*)-carboxylic acid, in a similar manner as described above. Analytical HPLC method: Solvent A = 10% MeOH–90% H_2O–0.1% TFA, Solvent B = 90% MeOH–10%H_2O–0.1% TFA, Start %B = 0, Final %B = 100, Gradient time = 2 min, Flow Rate = 5 ml/min, Column: Xterra MS C18 S7 3.0 x 50mm; LC/MS: (ES+) m/z $(M+H)^+$ = 623.16, HPLC R_t = 1.980 min. Analytical HPLC method: Solvent A = 5% MeCN–95% H_2O–10 mM NH_4OAc, Solvent B = 95% MeCN–5%H_2O–10 mM NH_4OAc, Start %B = 0, Final %B = 100, Gradient time = 2 min, Flow Rate = 5 ml/min, Column: Phenomenex Lina C18 5um 3.0 x 50mm; LC/MS: (ES+) m/z $(M+H)^+$ = 623.48, HPLC R_t = 1.600 min. Average specific rotation = –56.55° (1.29 mg/ml in MeOH; Wavelength 589 nm; 100 mm cell).

Intermediate 34



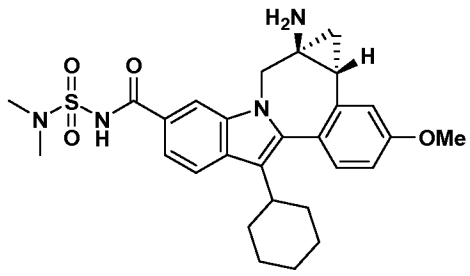
(1aR,12bS)-1a-Amino-8-cyclohexyl-N-(dimethylsulfamoyl)-11-methoxy-1,1a,2,12b-tetrahydrocyclopropa[d]indolo[2,1-a][2]benzazepine-5-carboxamide. The hydrochloride salt of (1*aR*,12*bS*)-1*a*-amino-8-cyclohexyl-*N*-(dimethylsulfamoyl)-11-methoxy-1,1*a*,2,12*b*-tetrahydrocyclopropa[*d*]indolo[2,1-*a*][2]benzazepine-5-carboxamide was prepared from *tert*-butyl ((1*aR*,12*bS*)-8-cyclohexyl-5-((dimethylsulfamoyl)carbamoyl)-11-methoxy-1,12*b*-dihydrocyclopropa[*d*]indolo[2,1-*a*][2]benzazepin-1*a*(2*H*)-yl)carbamate in a similar manner as described above. Analytical HPLC method: Solvent A = 10% MeOH–90% H_2O–0.1% TFA, Solvent B = 90% MeOH–10%H_2O–0.1% TFA, Start %B = 0, Final %B = 100, Gradient time = 2 min, Flow Rate = 5 ml/min, Column: Xterra MS C18 S7 3.0 x 50mm; LC/MS: (ES+) m/z $(M+H)^+$ = 523.26, HPLC R_t = 1.640 min. Average specific rotation = –36.95° (1.19 mg/ml in MeOH; Wavelength 589 nm; 50 mm cell).

Intermediate 35



tert-Butyl ((1aS,12bR)-8-cyclohexyl-5-((dimethylsulfamoyl)carbamoyl)-11-methoxy-1,12b-dihydrocyclopropa[d]indolo[2,1-a][2]benzazepin-1a(2H)-yl)carbamate. *tert*-Butyl ((1*aS*,12*bR*)-8-cyclohexyl-5-((dimethylsulfamoyl)carbamoyl)-11-methoxy-1,12*b*-dihydrocyclopropa[*d*]indolo[2,1-*a*][2]benzazepin-1*a*(2*H*)-yl)carbamate was prepared from the corresponding chiral acid, (1*aS*,12*bR*)-8-cyclohexyl-5-((dimethylsulfamoyl)carbamoyl)-11-methoxy-1,12*b*-dihydrocyclopropa[*d*]indolo[2,1-*a*][2]benzazepine-1*a*(2*H*)-carboxylic acid, in a similar manner as described above. Analytical HPLC method: Solvent A = 10% MeOH–90% H_2O–0.1% TFA, Solvent B = 90% MeOH–10%H_2O–0.1% TFA, Start %B = 0, Final %B = 100, Gradient time = 2 min, Flow Rate = 5 ml/min, Column: Xterra MS C18 S7 3.0 x 50mm; LC/MS: (ES+) m/z $(M+H)^+$ = 623.10, HPLC R_t = 1.935 min. Analytical HPLC method: Solvent A = 5% MeCN–95% H_2O–10 mM NH_4OAc, Solvent B = 95% MeCN–5%H_2O–10 mM NH_4OAc, Start %B = 0, Final %B = 100, Gradient time = 2 min, Flow Rate = 5 ml/min, Column: Phenomenex Lina C18 5um 3.0 x 50mm; LC/MS: (ES–) m/z $(M–H)^+$ = 621.26, HPLC R_t = 1.653 min. Average specific rotation = +56.07° (2.57 mg/ml in MeOH; Wavelength 589 nm; 50 mm cell).

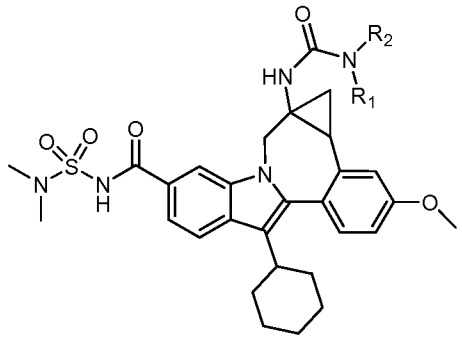
Intermediate 36



(1aS,12bR)-1a-Amino-8-cyclohexyl-N-(dimethylsulfamoyl)-11-methoxy-1,1a,2,12b-tetrahydrocyclopropa[d]indolo[2,1-a][2]benzazepine-5-carboxamide. The hydrochloride salt of (1*aS*,12*bR*)-1a-Amino-8-cyclohexyl-*N*-(dimethylsulfamoyl)-11-methoxy-1,1*a*,2,12*b*-tetrahydrocyclopropa[*d*]indolo[2,1-*a*][2]benzazepine-5-carboxamide was prepared from *tert*-butyl ((1*aS*,12*bR*)-8-

cyclohexyl-5-((dimethylsulfamoyl)carbamoyl)-11-methoxy-1,12*b*-dihydrocyclopropa[*d*]indolo[2,1-*a*][2]benzazepin-1*a*(2*H*)-yl)carbamate in a similar manner as described above. Analytical HPLC method: Solvent A = 10% MeOH–90% H_2O–0.1% TFA, Solvent B = 90% MeOH–10%H_2O–0.1% TFA, Start %B = 0, Final %B = 100, Gradient time = 2 min, Flow Rate = 5 ml/min, Column: Xterra MS C18 S7 3.0 x 50mm; LC/MS: (ES+) m/z $(M+H)^+$ = 523.32, HPLC R_t = 1.603 min.

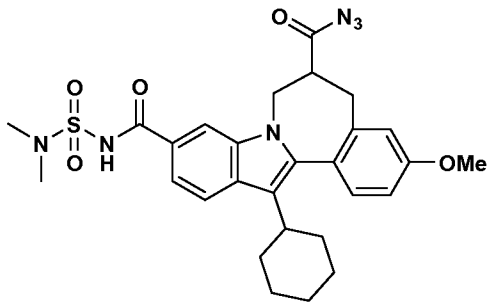
Intermediate 37



General procedure. To 1.0 g of carboxylic acid in a 100 mL round bottom flask (RBF) equipped with a septa under nitrogen, was added 20 mL of dry dichloroethane (DCE). To this solution was then added 1.2 equivalents of Diphenylphosphorylazide (DPPA) in one portion followed by 3 equivalents of triethylamine. The solution was stirred overnight at room temperature. The reaction progress was followed by an analytical Shimadzu LC/MS. The crude mixture was passed through a 24g SiliCycle-Isco™ silica gel cartridge with DCE to give acyl azide as an orange foam after solvent evacuation (50-65% yield). The acyl azide was found to be stable at room temperature in a vacuum desiccator for up to three months. To a 50 mL RBF was added 0.2mmol of acyl azide in 5.0 mL of dry toluene. The mixture was heated in an oil bath at 120°C for 15 minutes then quickly cooled to room temperature. To this mixture was then added 3.0 equivalents of amine, and the flask was returned to the oil bath and heated at 120°C for 60 minutes. The crude reaction mixture was then evacuated to near dryness, taken up in 1.2 mL of methanol and purified using a Shimadzu preparative HPLC employing methanol/water and

0.1% trifluoroacetic acid buffer with a Phenomenex Luna, C18, 21 mm x 100 mm, 10 μm column at a gradient of 40-100% B (where A = 10% HPLC grade methanol/ 0.1% trifluoroacetic acid/ 90% HPLC grade water and B = 90% HPLC grade methanol/ 0.1% trifluoroacetic acid/ 10% HPLC grade water) and a flow rate of 25 mL/min. over 10 minutes with a 5-10 minute hold, to give dimethylamino sulfamide ureas as yellow amorphous solids (35-50% yield). Post-purification LC/MS data was obtained on a Shimadzu analytical LC /Micromass Platform LC (ESI+) at 220nm using the following set of conditions: Column I (Phenomenex 10μm C18, 4.6 x 30mm), Solvent system I (gradient of 0-100%B where A = 10% HPLC grade methanol/ 0.1% trifluoroacetic acid/ 90% HPLC grade water and B = 90% HPLC grade methanol/ 0.1% trifluoroacetic acid/ 10% HPLC grade water), in 2 minutes with a 1 minute hold at a flow rate of 5 mL/minute.

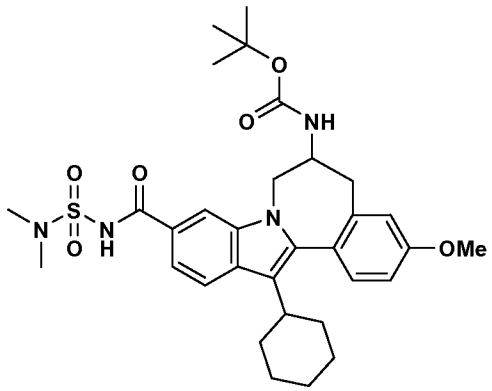
Intermediate 38



13-Cyclohexyl-10-((((dimethylamino)sulfonyl)amino)carbonyl)-3-(methyloxy)-6,7-dihydro-5H-indolo[2,1-a][2]benzazepine-6-carbonyl azide. To a mixture of the acid, 13-cyclohexyl-10-((((dimethylamino)sulfonyl)amino)carbonyl)-3-(methyloxy)-6,7-dihydro-5*H*-indolo[2,1-*a*][2]benzazepine-6-carboxylic acid, (427.2 mg, 0.79 mmol) in a mixture of PhMe/CH_2Cl_2 (6 ml/2 ml) at r.t. under N_2 was added triethylamine (117 mg, 1.16 mmol), followed by diphenylphosphoryl azide (DPPA) (320 mg, 1.16 mmol). The mixture was stirred at r.t. for 4 hr. The volatiles were then evaporated. The residue was titurated with hydrochloric acid (3 x 10 ml, 1N), dried and the crude azide, 13-cyclohexyl-10-((((dimethylamino)sulfonyl)amino)carbonyl)-3-(methyloxy)-6,7-dihydro-5*H*-indolo[2,1-*a*][2]benzazepine-6-carbonyl azide, was used without further purification Analytical HPLC method: Solvent A = 10% MeOH–90% H_2O–0.1% TFA, Solvent B

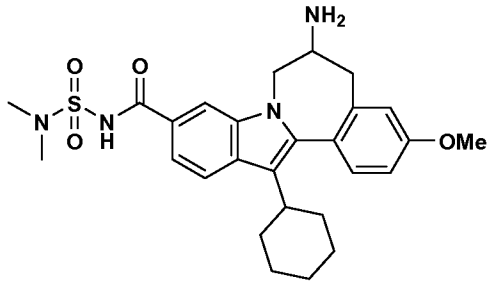
= 90% MeOH–10%H_2O–0.1% TFA, Start %B = 0, Final %B = 100, Gradient time = 2 min, Flow Rate = 5 ml/min, Column: Xterra MS C18 S7 3.0 x 50mm; LC/MS: (ES+) m/z $(M+H)^+$ = 565.21, HPLC R_t = 1.988 min.

Intermediate 39



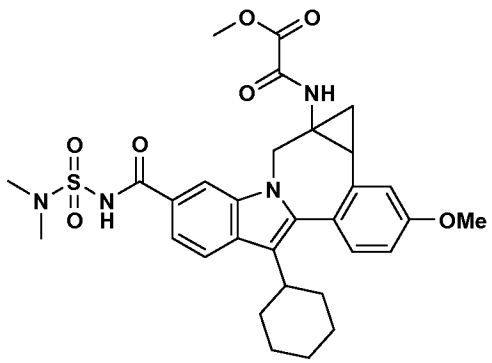
1,1-Dimethylethyl (13-cyclohexyl-10-((((dimethylamino)sulfonyl)amino)carbonyl)-3-(methyloxy)-6,7-dihydro-5H-indolo[2,1-a][2]benzazepin-6-yl)carbamate. A mixture of the crude azide, 13-cyclohexyl-10-((((dimethylamino)sulfonyl)amino)carbonyl)-3-(methyloxy)-6,7-dihydro-5*H*-indolo[2,1-*a*][2]benzazepine-6-carbonyl azide, (about 0.79 mmol) in *tert*-butanol (10 ml) under N_2 in a microwave reaction tube was placed under microwave irradiation in an Emrys Optimizer (*Personal Chemistry*) at 100°C and with the absorption level set to normal for 20 min. The mixture was then evaporated, titurated with water and the residue dried. The residue was then purified by Biotage flash chromatography (gradient elution, 0 to 50% EtOAc/Hexane) to gave 1,1-dimethylethyl (13-cyclohexyl-10-((((dimethylamino)sulfonyl)amino)carbonyl)-3-(methyloxy)-6,7-dihydro-5*H*-indolo[2,1-*a*][2]benzazepin-6-yl)carbamate. Analytical HPLC method: Solvent A = 10% MeOH–90% H_2O–0.1% TFA, Solvent B = 90% MeOH–10%H_2O–0.1% TFA, Start %B = 0, Final %B = 100, Gradient time = 2 min, Flow Rate = 5 ml/min, Column: Xterra MS C18 S7 3.0 x 50mm; LC/MS: (ES+) m/z $(M+Na)^+$ = 633.23, HPLC R_t = 2.018 min.

Intermediate 40



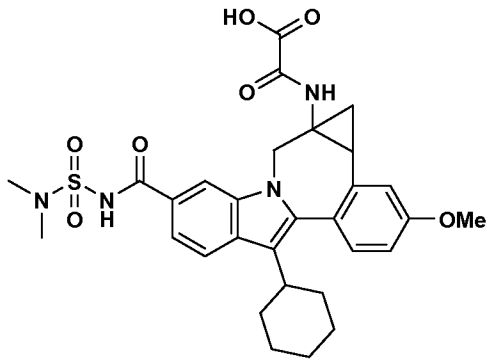
6-Amino-13-cyclohexyl-N-((dimethylamino)sulfonyl)-3-(methyloxy)-6,7-dihydro-5H-indolo[2,1-a][2]benzazepine-10-carboxamide. The hydrochloride salt of 6-amino-13-cyclohexyl-*N*-((dimethylamino)sulfonyl)-3-(methyloxy)-6,7-dihydro-5*H*-indolo[2,1-*a*][2]benzazepine-10-carboxamide was prepared from the deprotection of 1,1-dimethylethyl (13-cyclohexyl-10-((((dimethylamino)sulfonyl)amino)carbonyl)-3-(methyloxy)-6,7-dihydro-5*H*-indolo[2,1-*a*][2]benzazepin-6-yl)carbamate using 4N HCl in 1,4-dioxane. Analytical HPLC method: Solvent A = 10% MeOH–90% H_2O–0.1% TFA, Solvent B = 90% MeOH–10%H_2O–0.1% TFA, Start %B = 0, Final %B = 100, Gradient time = 2 min, Flow Rate = 5 ml/min, Column: Xterra MS C18 S7 3.0 x 50mm; LC/MS: (ES+) m/z $(M+H)^+$ = 511.22, HPLC R_t = 1.658 min.

Example 1



Methyl ((8-cyclohexyl-5-((((dimethylamino)sulfonyl)amino)carbonyl)-11-(methyloxy)-1,12b-dihydrocyclopropa[d]indolo[2,1-a][2]benzazepin-1a(2H)-yl)amino)(oxo)acetate. Methyl ((8-cyclohexyl-5-((((dimethylamino)sulfonyl)amino)carbonyl)-11-(methyloxy)-1,12*b*-dihydrocyclopropa[*d*]indolo[2,1-*a*][2]benzazepin-1*a*(2*H*)-yl)amino)(oxo)acetate was prepared in a similar manner as described using 2-methoxy-2-oxoacetic acid and purified by preparative reverse phase HPLC with separation method: Solvent A = 10% MeOH–90% H_2O–0.1% TFA, Solvent B = 90% MeOH–10%H_2O–0.1% TFA, Start %B = 50, Final %B = 100, Gradient time = 6min, Flow Rate = 30mL/min, Column: Phenomenex-Luna S10 30x50mm,, Fraction Collection: 6.14 – 6.81 min (UV detection at 220 nm); Analytical HPLC method: Solvent A = 10% MeOH–90% H_2O–0.1% TFA, Solvent B = 90% MeOH–10%H_2O–0.1% TFA, Start %B = 0, Final %B = 100, Gradient time = 2 min, Flow Rate = 5 ml/min, Column: Xterra MS C18 S7 3.0 x 50mm; LC/MS: (ES+) m/z $(M+H)^+$ = 609.12, HPLC R_t = 1.845 min. Analytical HPLC method: Solvent A = 5% MeCN–95% H_2O–10 mM NH_4OAc, Solvent B = 95% MeCN–5%H_2O–10 mM NH_4OAc, Start %B = 0, Final %B = 100, Gradient time = 2 min, Flow Rate = 5 ml/min, Column: Phenomenex Lina C18 5um 3.0 x 50mm; LC/MS: (ES+) m/z $(M+H)^+$ = 609.39, HPLC R_t = 1.103 min.

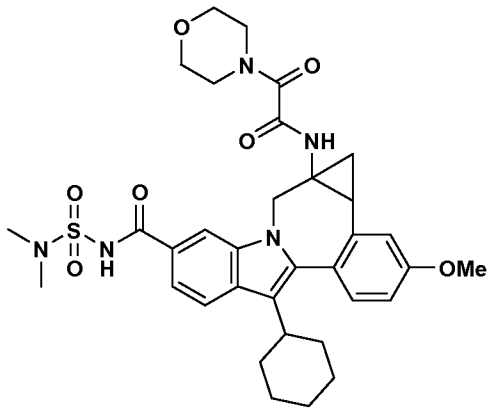
Example 2



((8-Cyclohexyl-5-((((dimethylamino)sulfonyl)amino)carbonyl)-11-(methyloxy)-1,12b-dihydrocyclopropa[d]indolo[2,1-a][2]benzazepin-1a(2H)-yl)amino)(oxo)acetic acid. The acid, ((8-Cyclohexyl-5-

((((dimethylamino)sulfonyl)amino)carbonyl)-11-(methyloxy)-1,12*b*-dihydrocyclopropa[*d*]indolo[2,1-*a*][2]benzazepin-1*a*(2*H*)-yl)amino)(oxo)acetic acid, was obtained from the hydrolysis of Methyl ((8-cyclohexyl-5-((((dimethylamino)sulfonyl)amino)carbonyl)-11-(methyloxy)-1,12*b*-dihydrocyclopropa[*d*]indolo[2,1-*a*][2]benzazepin-1*a*(2*H*)-yl)amino)(oxo)acetate in a 1;1 mixture of MeOH/THF using 1N NaOH. Analytical HPLC method: Solvent A = 10% MeOH–90% H_2O–0.1% TFA, Solvent B = 90% MeOH–10%H_2O–0.1% TFA, Start %B = 0, Final %B = 100, Gradient time = 2 min, Flow Rate = 5 ml/min, Column: Xterra MS C18 S7 3.0 x 50mm; LC/MS: (ES+) m/z $(M+H)^+$ = 595.06, HPLC R_t = 1.832 min.

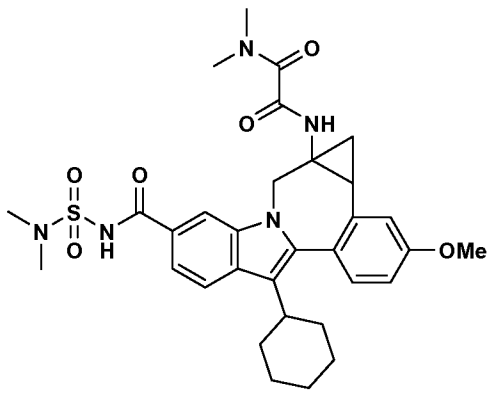
Example 3



8-Cyclohexyl-N-((dimethylamino)sulfonyl)-11-(methyloxy)-1a-((4-morpholinyl(oxo)acetyl)amino)-1,1a,2,12b-tetrahydrocyclopropa[d]indolo[2,1-a][2]benzazepine-5-carboxamide. To the hydrochloride salt of the amine, 1*a*-amino-8-cyclohexyl-*N*-((dimethylamino)sulfonyl)-11-(methyloxy)-1,1*a*,2,12*b*-tetrahydrocyclopropa[*d*]indolo[2,1-*a*][2]benzazepine-5-carboxamide, (40 mg, 71.5 μmol) at r.t. under N_2 was added *O*-benzotriazo-1-yl-*N,N,N',N'*-tetramethyluronium tetrafluoroborate (TBTU, 105.5 mg, 0.33 mmol) and a solution of 2-morpholino-2-oxoacetic acid (17.1 mg, 0.11 mmol) in DMF (1 ml), and then *N,N*-diisopropylethylamine (75 μl, 0.43 mmol). The reaction mixture was stirred at r.t. for 18 hr. 15 min., and then concentrated. The residue was diluted with MeOH (6 ml)

and purified by Shimadzu-VP preparative reverse phase HPLC with separation method: Solvent A = 10% MeOH–90% H_2O–0.1% TFA, Solvent B = 90% MeOH–10%H_2O–0.1% TFA, Start %B = 50, Final %B = 100, Gradient time = 6min, Flow Rate = 30mL/min, Column: Phenomenex-Luna S10 30x50mm, Fraction Collection: 6.10 – 6.77 min (UV detection at 220 nm) to give 8-cyclohexyl-*N*-((dimethylamino)sulfonyl)-11-(methyloxy)-1*a*-((4-morpholinyl(oxo)acetyl)amino)-1,1*a*,2,12*b*-tetrahydrocyclopropa[*d*]indolo[2,1-*a*][2]benzazepine-5-carboxamide; Analytical HPLC method: Solvent A = 10% MeOH–90% H_2O–0.1% TFA, Solvent B = 90% MeOH–10%H_2O–0.1% TFA, Start %B = 0, Final %B = 100, Gradient time = 2 min, Flow Rate = 5 ml/min, Column: Xterra MS C18 S7 3.0 x 50mm; LC/MS: (ES+) m/z $(M+H)^+$ = 664.54, HPLC R_t = 1.837 min. Analytical HPLC method: Solvent A = 5% MeCN–95% H_2O–10 mM NH_4OAc, Solvent B = 95% MeCN–5%H_2O–10 mM NH_4OAc, Start %B = 0, Final %B = 100, Gradient time = 2 min, Flow Rate = 5 ml/min, Column: Phenomenex Lina C18 5um 3.0 x 50mm; LC/MS: (ES+) m/z $(M+H)^+$ = 664.35, HPLC R_t = 1.352 min.

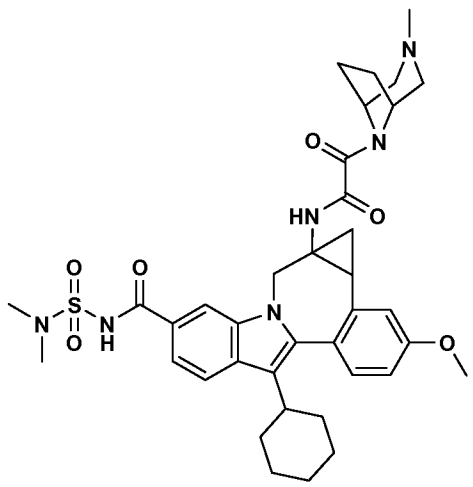
Example 4



N'-(8-Cyclohexyl-5-((((dimethylamino)sulfonyl)amino)carbonyl)-11-(methyloxy)-1,12b-dihydrocyclopropa[d]indolo[2,1-a][2]benzazepin-1a(2H)-yl)-N,N-dimethylethanediamide. *N*'-(8-Cyclohexyl-5-((((dimethylamino)sulfonyl)amino)carbonyl)-11-(methyloxy)-1,12*b*-dihydrocyclopropa[*d*]indolo[2,1-*a*][2]benzazepin-1*a*(2*H*)-yl)-*N*,*N*-

dimethylethanediamide was prepared in a similar manner as described using 2-(dimethylamino)-2-oxoacetic acid and purified by preparative reverse phase HPLC with separation method: Solvent A = 10% MeOH–90% H_2O–0.1% TFA, Solvent B = 90% MeOH–10%H_2O–0.1% TFA, Start %B = 0, Final %B = 100, Gradient time = 6min, Flow Rate = 30mL/min, Column: Xterra Prep MS C18 5u 30x50mm, Fraction Collection: 6.94 – 7.37 min (UV detection at 220 nm); Analytical HPLC method: Solvent A = 10% MeOH–90% H_2O–0.1% TFA, Solvent B = 90% MeOH–10%H_2O–0.1% TFA, Start %B = 0, Final %B = 100, Gradient time = 2 min, Flow Rate = 5 ml/min, Column: Xterra MS C18 S7 3.0 x 50mm; LC/MS: (ES+) m/z $(M+H)^+$ = 622.51, HPLC R_t = 1.855 min. Analytical HPLC method: Solvent A = 5% MeCN–95% H_2O–10 mM NH_4OAc, Solvent B = 95% MeCN–5%H_2O–10 mM NH_4OAc, Start %B = 0, Final %B = 100, Gradient time = 2 min, Flow Rate = 5 ml/min, Column: Phenomenex Lina C18 5um 3.0 x 50mm; LC/MS: (ES+) m/z $(M+H)^+$ = 622.31, HPLC R_t = 1.362 min.

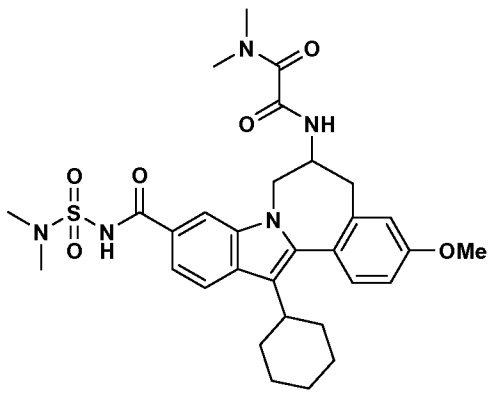
Example 5



8-Cyclohexyl-N-((dimethylamino)sulfonyl)-1a-(((3-methyl-3,8-diazabicyclo[3.2.1]oct-8-yl)(oxo)acetyl)amino)-11-(methyloxy)-1,1a,2,12b-tetrahydrocyclopropa[d]indolo[2,1-a][2]benzazepine-5-carboxamide. 8-Cyclohexyl-*N*-((dimethylamino)sulfonyl)-1*a*-(((3-methyl-3,8-diazabicyclo[3.2.1]oct-8-yl)(oxo)acetyl)amino)-11-(methyloxy)-1,1*a*,2,12*b*-

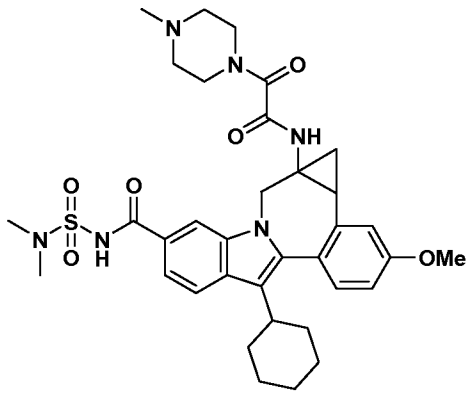
tetrahydrocyclopropa[*d*]indolo[2,1-*a*][2]benzazepine-5-carboxamide was prepared by the coupling of the acid, ((8-cyclohexyl-5-((((dimethylamino)sulfonyl)amino)carbonyl)-11-(methyloxy)-1,12*b*-dihydrocyclopropa[*d*]indolo[2,1-*a*][2]benzazepin-1*a*(2*H*)-yl)amino)(oxo)acetic acid, with 3-methyl-3,8-diazabicyclo[3.2.1]octane dihydrochloride in DMF at r.t. using *N,N*-diisopropylethylamine and TBTU as the coupling reagent. Purification by Shimadzu-VP preparative reverse phase HPLC with separation method: Solvent A = 10% MeOH–90% H_2O–0.1% TFA, Solvent B = 90% MeOH–10%H_2O–0.1% TFA, Start %B = 0, Final %B = 100, Gradient time = 6min, Flow Rate = 30mL/min, Column: Phenomenex-Luna S10 30x50mm, Fraction Collection: 6.55 – 6.72 min (UV detection at 220 nm); Analytical HPLC method: Solvent A = 10% MeOH–90% H_2O–0.1% TFA, Solvent B = 90% MeOH–10%H_2O–0.1% TFA, Start %B = 0, Final %B = 100, Gradient time = 2 min, Flow Rate = 5 ml/min, Column: Xterra MS C18 S7 3.0 x 50mm; LC/MS: (ES+) m/z $(M+H)^+$ = 703.26, HPLC R_t = 1.685 min. Analytical HPLC method: Solvent A = 5% MeCN–95% H_2O–10 mM NH_4OAc, Solvent B = 95% MeCN–5%H_2O–10 mM NH_4OAc, Start %B = 0, Final %B = 100, Gradient time = 2 min, Flow Rate = 5 ml/min, Column: Phenomenex Lina C18 5um 3.0 x 50mm; LC/MS: (ES+) m/z $(M+H)^+$ = 703.53, HPLC R_t = 1.085 min.

Example 6



N'-(13-Cyclohexyl-10-((((dimethylamino)sulfonyl)amino)carbonyl)-3-(methyloxy)-6,7-dihydro-5H-indolo[2,1-a][2]benzazepin-6-yl)-N,N-dimethylethanediamide. *N'*-(13-Cyclohexyl-10-((((dimethylamino)sulfonyl)amino)carbonyl)-3-(methyloxy)-6,7-dihydro-5*H*-indolo[2,1-*a*][2]benzazepin-6-yl)-*N*,*N*-dimethylethanediamide was prepared in an analogous manner as the cyclopropyl analog as described. Analytical HPLC method: Solvent A = 10% MeOH–90% H_2O–0.1% TFA, Solvent B = 90% MeOH–10%H_2O–0.1% TFA, Start %B = 0, Final %B = 100, Gradient time = 2 min, Flow Rate = 5 ml/min, Column: Xterra MS C18 S7 3.0 x 50mm; LC/MS: (ES+) m/z $(M+H)^+$ = 610.47, HPLC R_t = 1.873 min. Analytical HPLC method: Solvent A = 5% MeCN–95% H_2O–10 mM NH_4OAc, Solvent B = 95% MeCN–5%H_2O–10 mM NH_4OAc, Start %B = 0, Final %B = 100, Gradient time = 2 min, Flow Rate = 5 ml/min, Column: Phenomenex Lina C18 5um 3.0 x 50mm; LC/MS: (ES+) m/z $(M+H)^+$ = 610.28, HPLC R_t = 1.427 min.

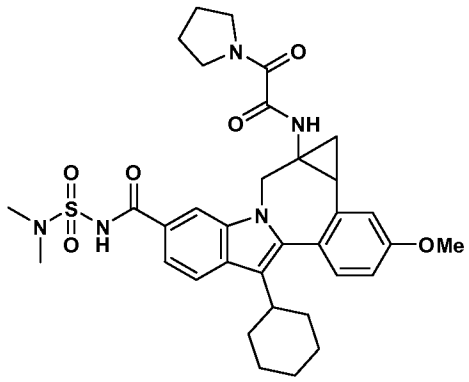
Example 8



8-Cyclohexyl-N-(dimethylsulfamoyl)-11-methoxy-1a-(((4-methyl-1-piperazinyl)(oxo)acetyl)amino)-1,1a,2,12b-tetrahydrocyclopropa[d]indolo[2,1-a][2]benzazepine-5-carboxamide. Prepared as a TFA salt in a similar manner as example 3. Purification by Shimadzu-VP preparative reverse phase HPLC using the separation method: Solvent A = 10% MeOH–90% H_2O–0.1% TFA, Solvent B = 90% MeOH–10%H_2O–0.1% TFA, Start %B = 0, Final %B = 100, Gradient time = 6 min, Stop time = 8 min, Flow Rate = 30 mL/min, Column: Xterra Prep MS C18 5u 30x50mm, UV detection at 220 nm. LC/MS were performed by using Shimadzu-VP

instrument with UV detection at 220 nm and Waters Micromass. HPLC method: Solvent A = 10% MeOH–90% H_2O–0.1% TFA, Solvent B = 90% MeOH–10%H_2O–0.1% TFA, Start %B = 0, Final %B = 100, Gradient time = 2 min, Stop time = 3 min, Flow Rate = 5 ml/min, Column: Xterra MS C18 S7 3.0 x 50mm; (ES+) m/z $(M+H)^+$ = 677.18, HPLC R_t = 1.693 min. HPLC method: Solvent A = 5% MeCN–95% H_2O–10 mM NH_4OAc, Solvent B = 95% MeCN–5%H_2O–10 mM NH_4OAc, Start %B = 0, Final %B = 100, Gradient time = 2 min, Stop time = 3 min, Flow Rate = 5 ml/min, Column: Phenomenex Lina C18 5um 3.0 x 50mm; (ES+) m/z $(M+H)^+$ = 677.64, HPLC R_t = 1.280 min. Analytical HPLC method: Solvent A = 5% MeCN–95% H_2O–0.1% TFA, Solvent B = 95% MeCN–5%H_2O–0.1% TFA, Start %B = 10, Final %B = 100, Gradient time = 10 min, Stop time = 20 min, Flow Rate = 1 ml/min, Column: Waters Sunfire C-18, 4.6 x 150 mm, 3.5 um, R_t = 8.05 min.

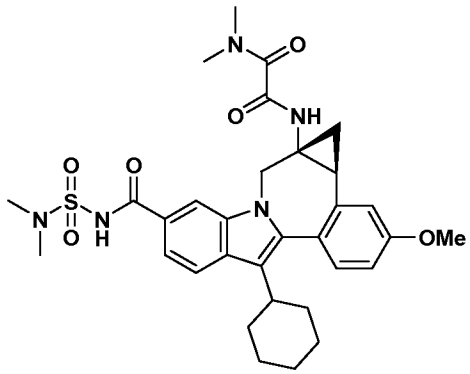
Example 9



8-Cyclohexyl-N-(dimethylsulfamoyl)-11-methoxy-1a-((oxo(1-pyrrolidinyl)acetyl)amino)-1,1a,2,12b-tetrahydrocyclopropa[d]indolo[2,1-a][2]benzazepine-5-carboxamide. Prepared in a similar manner as example 3. Purification by Shimadzu-VP preparative reverse phase HPLC using the separation method: Solvent A = 10% MeOH–90% H_2O–0.1% TFA, Solvent B = 90% MeOH–10%H_2O–0.1% TFA, Start %B = 0, Final %B = 100, Gradient time = 6 min, Stop time = 8 min, Flow Rate = 30 mL/min, Column: Xterra Prep MS C18 5u 30x50mm, UV detection at 220 nm. LC/MS were performed by using Shimadzu-VP instrument with UV detection at 220 nm and Waters Micromass. HPLC method: Solvent A = 10% MeOH–90% H_2O–0.1% TFA, Solvent B = 90%

MeOH–10%H_2O–0.1% TFA, Start %B = 0, Final %B = 100, Gradient time = 2 min, Stop time = 3 min, Flow Rate = 5 ml/min, Column: Xterra MS C18 S7 3.0 x 50mm; (ES+) m/z $(M+H)^+$ = 648.22, HPLC R_t = 1.883 min. HPLC method: Solvent A = 5% MeCN–95% H_2O–10 mM NH_4OAc, Solvent B = 95% MeCN–5%H_2O–10 mM NH_4OAc, Start %B = 0, Final %B = 100, Gradient time = 2 min, Stop time = 3 min, Flow Rate = 5 ml/min, Column: Phenomenex Lina C18 5um 3.0 x 50mm; (ES+) m/z $(M+H)^+$ = 648.58, HPLC R_t = 1.428 min.

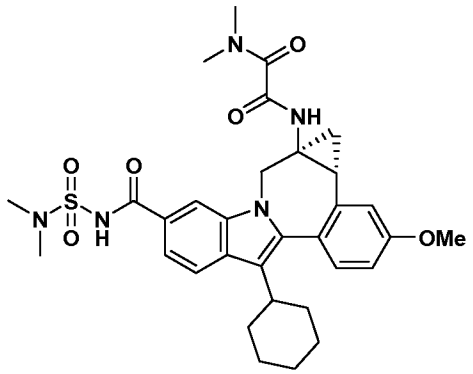
Example 10



N'-((1aR,12bS)-8-Cyclohexyl-5-((dimethylsulfamoyl)carbamoyl)-11-methoxy-1,12b-dihydrocyclopropa[d]indolo[2,1-a][2]benzazepin-1a(2H)-yl)-N,N-dimethylethanediamide. Prepared from the chiral cyclopropyl acid, (1aR,12bS)-8-cyclohexyl-5-((dimethylsulfamoyl)carbamoyl)-11-methoxy-1,12b-dihydrocyclopropa[d]indolo[2,1-a][2]benzazepine-1a(2H)-carboxylic acid, in a similar manner as the racemic, N'-(8-Cyclohexyl-5-((((dimethylamino)sulfonyl)amino)carbonyl)-11-(methyloxy)-1,12b-dihydrocyclopropa[d]indolo[2,1-a][2]benzazepin-1a(2H)-yl)-N,N-dimethylethanediamide. LC/MS were performed by using Shimadzu-VP instrument with UV detection at 220 nm and Waters Micromass. HPLC method: Solvent A = 10% MeOH–90% H_2O–0.1% TFA, Solvent B = 90% MeOH–10%H_2O–0.1% TFA, Start %B = 0, Final %B = 100, Gradient time = 2 min, Stop time = 3 min, Flow Rate = 5 ml/min, Column: Xterra MS C18 S7 3.0 x 50mm; (ES+) m/z $(M+H)^+$ = 622.18, HPLC R_t = 1.860 min. Analytical HPLC were performed by using Shimadzu-VP instrument with UV detection at 254 nm and 256 nm. Analytical HPLC method: Solvent A = 5% MeCN–95% H_2O–0.1% TFA, Solvent B = 95%

MeCN–5%H_2O–0.1% TFA, Start %B = 10, Final %B = 100, Gradient time = 10 min, Stop time = 20 min, Flow Rate = 1 ml/min, Column: Waters Sunfire C-18, 4.6 x 150 mm, 3.5 um, R_t = 11.48 min; Column: Waters Xbridge Phenyl column 4.6 x 150 mm, 3.5 um, R_t = 10.27 min. ^{1}H NMR (500 MHz, CD_3OD, as a mixture of two isomers in about 88:12 ratio) δ major isomer 7.97 (s, 1H), 7.90 (d, J = 8.5, 1H), 7.54 (dd, J = 8.0, 1.5, 1H), 7.33 (d, J = 8.5, 1H), 7.17 (broad d, 1H), 7.02 (dd, J = 8.5, 2.8, 1H), 5.21 (d, J = 15, 1H), 3.90 (s, 3H), 3.57 (d, J = 15.5, 1H), 3.03 (s, 6H), 2.99 (m, 1H), 2.91 (d, J = 2.1, 3H), 2.84 (s, 3H), 2.37 (broad t, 1H), 2.20–1.91 (broad overlapping m, 4H), 1.87–1.75 (broad overlapping m, 2H), 1.70 (broad d, 1H), 1.55–1.42 (broad m, 3H), 1.38 (t, J = 5.8, 1H), 1.36–1.23 (m, 1H). Optical rotation [α] = –37.71, c=1.41 mg/ml (MeOH), 589 nm, 100 mm cell.

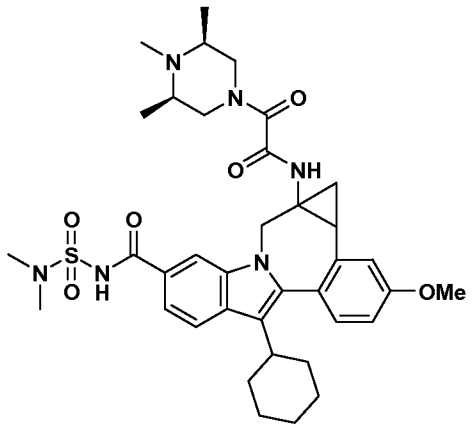
Example 11



N'-((1aS,12bR)-8-Cyclohexyl-5-((dimethylsulfamoyl)carbamoyl)-11-methoxy-1,12b-dihydrocyclopropa[d]indolo[2,1-a][2]benzazepin-1a(2H)-yl)-N,N-dimethylethanediamide. Prepared from the entiopodal chiral cyclopropyl acid, (1aS,12bR)-8-cyclohexyl-5-((dimethylsulfamoyl)carbamoyl)-11-methoxy-1,12b-dihydrocyclopropa[d]indolo[2,1-a][2]benzazepine-1a(2H)-carboxylic acid, in a similar manner as described above. LC/MS were performed by using Shimadzu-VP instrument with UV detection at 220 nm and Waters Micromass. HPLC method: Solvent A = 10% MeOH–90% H_2O–0.1% TFA, Solvent B = 90% MeOH–10%H_2O–0.1% TFA, Start %B = 0, Final %B = 100, Gradient time = 2 min, Stop time = 3 min, Flow Rate = 5 ml/min, Column: Xterra MS C18 S7 3.0 x 50mm;

(ES+) m/z $(M+H)^+$ = 622.49, HPLC R_t = 1.847 min. Analytical HPLC were performed by using Shimadzu-VP instrument with UV detection at 254 nm and 256 nm. Analytical HPLC method: Solvent A = 5% MeCN–95% H_2O–0.1% TFA, Solvent B = 95% MeCN–5%H_2O–0.1% TFA, Start %B = 10, Final %B = 100, Gradient time = 10 min, Stop time = 20 min, Flow Rate = 1 ml/min, Column: Waters Sunfire C-18, 4.6 x 150 mm, 3.5 um, R_t = 11.11 min; Column: Waters Xbridge Phenyl column 4.6 x 150 mm, 3.5 um, R_t = 10.01 min. Optical rotation [α] = +42.39, c=2.57 mg/ml (MeOH), 589 nm, 50 mm cell.

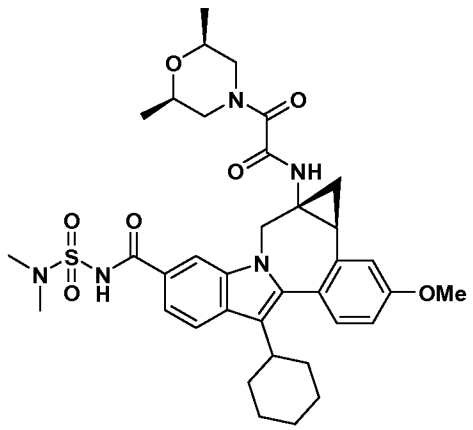
Example 12



8-Cyclohexyl-N-(dimethylsulfamoyl)-11-methoxy-1a-((oxo((3R,5S)-3,4,5-trimethyl-1-piperazinyl)acetyl)amino)-1,1a,2,12b-tetrahydrocyclopropa[d]indolo[2,1-a][2]benzazepine-5-carboxamide. Prepared as a TFA salt in a similar manner as example 5. Purification by Shimadzu-VP preparative reverse phase HPLC using the separation method: Solvent A = 10% MeOH–90% H_2O–0.1% TFA, Solvent B = 90% MeOH–10%H_2O–0.1% TFA, Start %B = 0, Final %B = 100, Gradient time = 6 min, Stop time = 8 min, Flow Rate = 30 mL/min, Column: Xterra Prep MS C18 5u 30x50mm, UV detection at 220 nm. LC/MS were performed by using Shimadzu-VP instrument with UV detection at 220 nm and Waters Micromass. HPLC method: Solvent A = 10% MeOH–90% H_2O–0.1% TFA, Solvent B = 90% MeOH–10%H_2O–0.1% TFA, Start %B = 0, Final %B = 100, Gradient time = 2 min, Stop time = 3 min, Flow Rate = 5 ml/min,

Column: Xterra MS C18 S7 3.0 x 50mm; (ES+) m/z $(M+H)^+$ = 705.18, HPLC R_t = 1.717 min. Analytical HPLC were performed by using Shimadzu-VP instrument with UV detection at 254 nm and 256 nm. Analytical HPLC method: Solvent A = 5% MeCN–95% H_2O–0.1% TFA, Solvent B = 95% MeCN–5%H_2O–0.1% TFA, Start %B = 10, Final %B = 100, Gradient time = 10 min, Stop time = 20 min, Flow Rate = 1 ml/min, Column: Waters Sunfire C-18, 4.6 x 150 mm, 3.5 um, R_t = 8.96 min; Column: Waters Xbridge Phenyl column 4.6 x 150 mm, 3.5 um, R_t = 9.13 min.

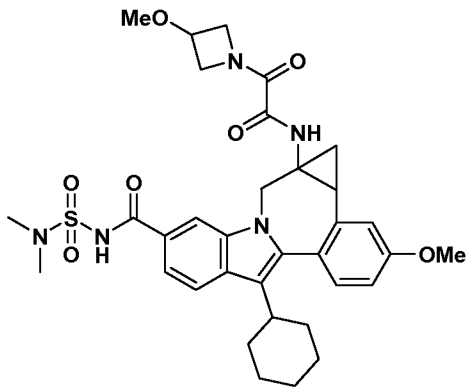
Example 13



(1aR,12bS)-8-Cyclohexyl-1a-(((2,6-cis-dimethyl-4-morpholinyl)(oxo)acetyl)amino)-N-(dimethylsulfamoyl)-11-methoxy-1,1a,2,12b-tetrahydrocyclopropa[d]indolo[2,1-a][2]benzazepine-5-carboxamide. Prepared in a similar manner as described and using 2-(2,6-cis-dimethylmorpholino)-2-oxoacetic acid (prepared from the coupling of 2,6-cis-dimethylmopholine to methyl chlorooxoacetate followed by hydrolysis (1N NaOH, H_2O/MeOH); other non-commercially available 2-oxoacetic acids were prepared similarly). Purification by Shimadzu-VP preparative reverse phase HPLC using the separation method: Solvent A = 10% MeOH–90% H_2O–0.1% TFA, Solvent B = 90% MeOH–10%H_2O–0.1% TFA, Start %B = 0, Final %B = 100, Gradient time = 6 min, Stop time = 8 min, Flow Rate = 30 mL/min, Column: Xterra Prep MS C18 5u 30x50mm, UV detection at 220 nm. LC/MS were performed by using Shimadzu-VP instrument with UV detection at 220 nm and Waters Micromass. HPLC method: Solvent A = 10% MeOH–90% H_2O–0.1% TFA, Solvent B = 90% MeOH–10%H_2O–0.1% TFA, Start %B = 0, Final

%B = 100, Gradient time = 2 min, Stop time = 3 min, Flow Rate = 5 ml/min, Column: Xterra MS C18 S7 3.0 x 50mm; (ES+) m/z $(M+H)^+$ = 692.24, HPLC R_t = 1.908 min. HPLC method: Solvent A = 5% MeCN–95% H_2O–10 mM NH_4OAc, Solvent B = 95% MeCN–5%H_2O–10 mM NH_4OAc, Start %B = 0, Final %B = 100, Gradient time = 2 min, Stop time = 3 min, Flow Rate = 5 ml/min, Column: Phenomenex Lina C18 5um 3.0 x 50mm; (ES+) m/z $(M+H)^+$ = 692.32, HPLC R_t = 1.518 min. Analytical HPLC were performed by using Shimadzu-VP instrument with UV detection at 254 nm and 256 nm. Analytical HPLC method: Solvent A = 5% MeCN–95% H_2O–0.1% TFA, Solvent B = 95% MeCN–5%H_2O–0.1% TFA, Start %B = 10, Final %B = 100, Gradient time = 10 min, Stop time = 20 min, Flow Rate = 1 ml/min, Column: Waters Sunfire C-18, 4.6 x 150 mm, 3.5 um, R_t = 12.27 min; Column: Waters Xbridge Phenyl column 4.6 x 150 mm, 3.5 um, R_t = 10.99 min.

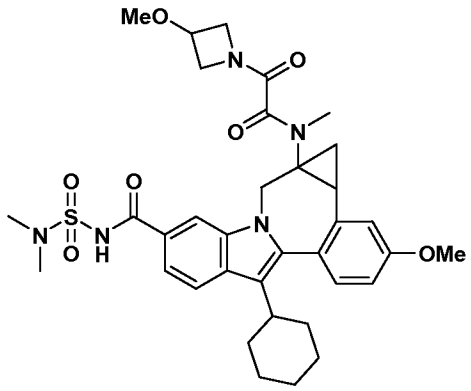
Example 14



8-Cyclohexyl-N-(dimethylsulfamoyl)-11-methoxy-1a-(((3-methoxy-1-azetidinyl)(oxo)acetyl)amino)-1,1a,2,12b-tetrahydrocyclopropa[d]indolo[2,1-a][2]benzazepine-5-carboxamide. Prepared in a similar manner as example 3. Purification by Shimadzu-VP preparative reverse phase HPLC using the separation method: Solvent A = 10% MeOH–90% H_2O–0.1% TFA, Solvent B = 90% MeOH–10%H_2O–0.1% TFA, Start %B = 0, Final %B = 100, Gradient time = 6 min, Stop time = 8 min, Flow Rate = 30 mL/min, Column: Xterra Prep MS C18 5u 30x50mm, UV detection at 220 nm. LC/MS were performed by using Shimadzu-VP

instrument with UV detection at 220 nm and Waters Micromass. HPLC method: Solvent A = 10% MeOH–90% H_2O–0.1% TFA, Solvent B = 90% MeOH–10%H_2O–0.1% TFA, Start %B = 0, Final %B = 100, Gradient time = 2 min, Stop time = 3 min, Flow Rate = 5 ml/min, Column: Xterra MS C18 S7 3.0 x 50mm; (ES+) m/z $(M+H)^+$ = 664.13, HPLC R_t = 1.868 min. HPLC method: Solvent A = 5% MeCN–95% H_2O–10 mM NH_4OAc, Solvent B = 95% MeCN–5%H_2O–10 mM NH_4OAc, Start %B = 0, Final %B = 100, Gradient time = 2 min, Stop time = 3 min, Flow Rate = 5 ml/min, Column: Phenomenex Lina C18 5um 3.0 x 50mm; (ES-) m/z $(M-H)^-$ = 662.28, HPLC R_t = 1.472 min. Analytical HPLC were performed by using Shimadzu-VP instrument with UV detection at 254 nm and 256 nm. Analytical HPLC method: Solvent A = 5% MeCN–95% H_2O–0.1% TFA, Solvent B = 95% MeCN–5%H_2O–0.1% TFA, Start %B = 10, Final %B = 100, Gradient time = 10 min, Stop time = 20 min, Flow Rate = 1 ml/min, Column: Waters Sunfire C-18, 4.6 x 150 mm, 3.5 um, R_t = 11.55 min; Column: Waters Xbridge Phenyl column 4.6 x 150 mm, 3.5 um, R_t = 10.36 min.

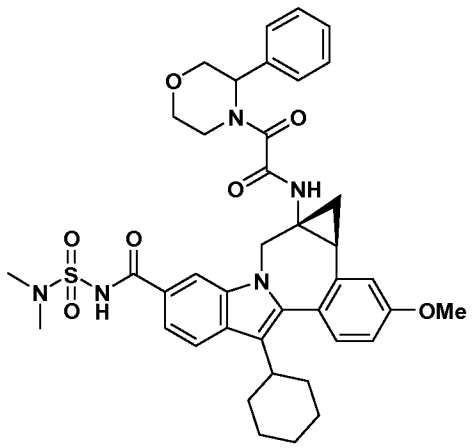
Example 15



8-Cyclohexyl-N-(dimethylsulfamoyl)-11-methoxy-1a-(((3-methoxy-1-azetidinyl)(oxo)acetyl)(methyl)amino)-1,1a,2,12b-tetrahydrocyclopropa[d]indolo[2,1-a][2]benzazepine-5-carboxamide. To a mixture of 8-Cyclohexyl-N-(dimethylsulfamoyl)-11-methoxy-1a-(((3-methoxy-1-azetidinyl)(oxo)acetyl)amino)-1,1a,2,12b-tetrahydrocyclopropa[d]indolo[2,1-

a][2]benzazepine-5-carboxamide (30 mg, 45.2 umol) in DMF (1 ml) at r.t. under N2 was added NaH (9 mg, 225 umol, 60% in oil), and stirred for about 10 min until all the solids dissolved. A solution of MeI (13 mg, 91.6 umol) in DMF (0.2 ml) was then added to the mixture which was then stirred for 2 h. LC/MS indicated complete conversion of the starting material to the product. The mixture was quenched with hydrochloric acid (0.4 ml, 1N), evaporated and then added excess water. The light orange solids were filtered, washed with water (3 x 2 ml) and hexane (3 x 2 ml), and then dried to give the product (22.1 mg, 72%). LC/MS were performed by using Shimadzu-VP instrument with UV detection at 220 nm and Waters Micromass. HPLC method: Solvent A = 10% MeOH–90% H_2O–0.1% TFA, Solvent B = 90% MeOH–10%H_2O–0.1% TFA, Start %B = 0, Final %B = 100, Gradient time = 2 min, Stop time = 3 min, Flow Rate = 5 ml/min, Column: Xterra MS C18 S7 3.0 x 50mm; (ES+) m/z $(M+H)^+$ = 678.14, HPLC R_t = 1.732 min. HPLC method: Solvent A = 5% MeCN–95% H_2O–10 mM NH_4OAc, Solvent B = 95% MeCN–5%H_2O–10 mM NH_4OAc, Start %B = 0, Final %B = 100, Gradient time = 2 min, Stop time = 3 min, Flow Rate = 5 ml/min, Column: Phenomenex Lina C18 5um 3.0 x 50mm; (ES-) m/z $(M-H)^-$ = 676.26, HPLC R_t = 1.463 min. Analytical HPLC were performed by using Shimadzu-VP instrument with UV detection at 254 nm and 256 nm. Analytical HPLC method: Solvent A = 5% MeCN–95% H_2O–0.1% TFA, Solvent B = 95% MeCN–5%H_2O–0.1% TFA, Start %B = 10, Final %B = 100, Gradient time = 10 min, Stop time = 20 min, Flow Rate = 1 ml/min, Column: Waters Sunfire C-18, 4.6 x 150 mm, 3.5 um, R_t = 11.75 min; Column: Waters Xbridge Phenyl column 4.6 x 150 mm, 3.5 um, R_t = 10.44 min.

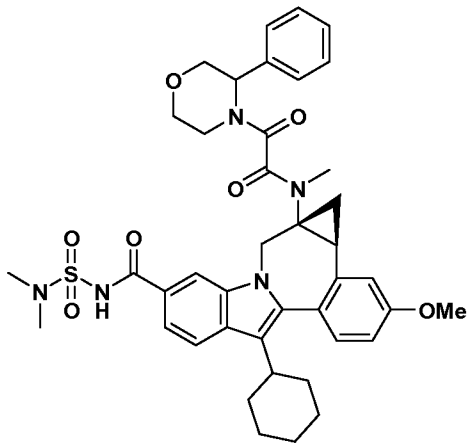
Example 16



(1aR,12bS)-8-Cyclohexyl-N-(dimethylsulfamoyl)-11-methoxy-1a-((oxo(3-phenyl-4-morpholinyl)acetyl)amino)-1,1a,2,12b-tetrahydrocyclopropa[d]indolo[2,1-a][2]benzazepine-5-carboxamide. Prepared in a similar manner as described. Purification by Shimadzu-VP preparative reverse phase HPLC using the separation method: Solvent A = 10% MeOH–90% H_2O–0.1% TFA, Solvent B = 90% MeOH–10%H_2O–0.1% TFA, Start %B = 30, Final %B = 100, Gradient time = 6 min, Stop time = 8 min, Flow Rate = 30 mL/min, Column: Xterra Prep MS C18 5u 30x50mm, UV detection at 220 nm. LC/MS were performed by using Shimadzu-VP instrument with UV detection at 220 nm and Waters Micromass. HPLC method: Solvent A = 10% MeOH–90% H_2O–0.1% TFA, Solvent B = 90% MeOH–10%H_2O–0.1% TFA, Start %B = 0, Final %B = 100, Gradient time = 2 min, Stop time = 3 min, Flow Rate = 5 ml/min, Column: Xterra MS C18 S7 3.0 x 50mm; (ES+) m/z $(M+H)^+$ = 740.01, HPLC R_t = 1.932 min. HPLC method: Solvent A = 5% MeCN–95% H_2O–10 mM NH_4OAc, Solvent B = 95% MeCN–5%H_2O–10 mM NH_4OAc, Start %B = 0, Final %B = 100, Gradient time = 2 min, Stop time = 3 min, Flow Rate = 5 ml/min, Column: Phenomenex Lina C18 5um 3.0 x 50mm; (ES-) m/z $(M-H)^-$ = 738.22, HPLC R_t = 1.588 min. Analytical HPLC were performed by using Shimadzu-VP instrument with UV detection at 254 nm and 256 nm. Analytical HPLC method: Solvent A = 5% MeCN–95% H_2O–0.1% TFA, Solvent B = 95% MeCN–5%H_2O–0.1% TFA, Start %B = 10, Final %B = 100, Gradient time = 10 min,

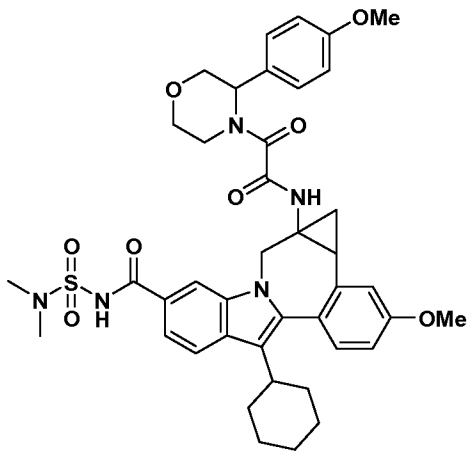
Stop time = 20 min, Flow Rate = 1 ml/min, Column: Waters Sunfire C-18, 4.6 x 150 mm, 3.5 um, R_t = 12.34 min; Column: Waters Xbridge Phenyl column 4.6 x 150 mm, 3.5 um, R_t = 11.14 min.

Example 17



(1aR,12bS)-8-Cyclohexyl-N-(dimethylsulfamoyl)-11-methoxy-1a-(methyl(oxo(3-phenyl-4-morpholinyl)acetyl)amino)-1,1a,2,12b-tetrahydrocyclopropa[d]indolo[2,1-a][2]benzazepine-5-carboxamide. Prepared in a similar manner as described for 8-Cyclohexyl-N-(dimethylsulfamoyl)-11-methoxy-1a-(((3-methoxy-1-azetidinyl)(oxo)acetyl)(methyl)amino)-1,1a,2,12b-tetrahydrocyclopropa[d]indolo[2,1-a][2]benzazepine-5-carboxamide. LC/MS were performed by using Shimadzu-VP instrument with UV detection at 220 nm and Waters Micromass. HPLC method: Solvent A = 10% MeOH–90% H_2O–0.1% TFA, Solvent B = 90% MeOH–10%H_2O–0.1% TFA, Start %B = 0, Final %B = 100, Gradient time = 2 min, Stop time = 3 min, Flow Rate = 5 ml/min, Column: Xterra MS C18 S7 3.0 x 50mm; (ES+) m/z $(M+H)^+$ = 754.14, HPLC R_t = 1.963 min. HPLC method: Solvent A = 5% MeCN–95% H_2O–10 mM NH_4OAc, Solvent B = 95% MeCN–5%H_2O–10 mM NH_4OAc, Start %B = 0, Final %B = 100, Gradient time = 2 min, Stop time = 3 min, Flow Rate = 5 ml/min, Column: Phenomenex Lina C18 5um 3.0 x 50mm; (ES-) m/z $(M-H)^-$ = 752.21, HPLC R_t = 1.633 min.

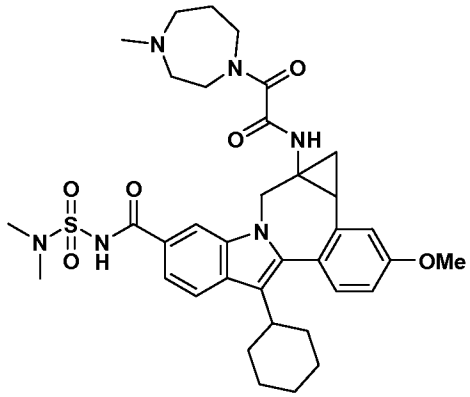
Example 18



8-Cyclohexyl-N-(dimethylsulfamoyl)-11-methoxy-1a-(((3-(4-methoxyphenyl)-4-morpholinyl)(oxo)acetyl)amino)-1,1a,2,12b-tetrahydrocyclopropa[d]indolo[2,1-a][2]benzazepine-5-carboxamide. Prepared in a similar manner as example 3. Purification by Shimadzu-VP preparative reverse phase HPLC using the separation method: Solvent A = 10% MeOH–90% H_2O–0.1% TFA, Solvent B = 90% MeOH–10%H_2O–0.1% TFA, Start %B = 0, Final %B = 100, Gradient time = 6 min, Stop time = 8 min, Flow Rate = 30 mL/min, Column: Xterra Prep MS C18 5u 30x50mm, UV detection at 220 nm. LC/MS were performed by using Shimadzu-VP instrument with UV detection at 220 nm and Waters Micromass. HPLC method: Solvent A = 10% MeOH–90% H_2O–0.1% TFA, Solvent B = 90% MeOH–10%H_2O–0.1% TFA, Start %B = 0, Final %B = 100, Gradient time = 2 min, Stop time = 3 min, Flow Rate = 5 ml/min, Column: Xterra MS C18 S7 3.0 x 50mm; (ES+) m/z $(M+H)^+$ = 770.11, HPLC R_t = 1.905 min. HPLC method: Solvent A = 5% MeCN–95% H_2O–10 mM NH_4OAc, Solvent B = 95% MeCN–5%H_2O–10 mM NH_4OAc, Start %B = 0, Final %B = 100, Gradient time = 2 min, Stop time = 3 min, Flow Rate = 5 ml/min, Column: Phenomenex Lina C18 5um 3.0 x 50mm; (ES-) m/z $(M-H)^-$ = 770.02, HPLC R_t = 1.543 min. Analytical HPLC were performed by using Shimadzu-VP instrument with UV detection at 254 nm and 256 nm. Analytical HPLC method: Solvent A = 5% MeCN–95% H_2O–0.1% TFA, Solvent B = 95% MeCN–5%H_2O–0.1% TFA, Start %B = 10, Final %B = 100, Gradient time = 10 min, Stop time = 20 min, Flow Rate = 1 ml/min, Column: Waters Sunfire C-18, 4.6 x 150

mm, 3.5 um, R_t = 11.83 min; Column: Waters Xbridge Phenyl column 4.6 x 150 mm, 3.5 um, R_t = 10.77 min.

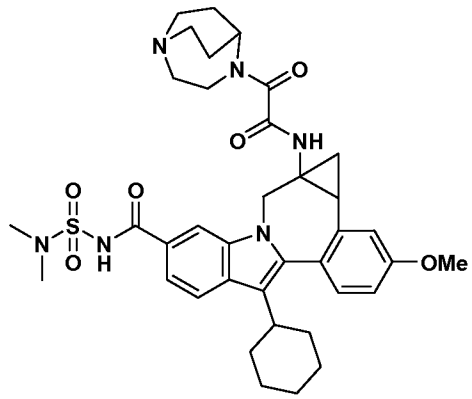
Example 19



8-Cyclohexyl-N-(dimethylsulfamoyl)-11-methoxy-1a-(((4-methyl-1,4-diazepan-1-yl)(oxo)acetyl)amino)-1,1a,2,12b-tetrahydrocyclopropa[d]indolo[2,1-a][2]benzazepine-5-carboxamide. Prepared as a TFA salt in a similar manner as example 3. Purification by Shimadzu-VP preparative reverse phase HPLC using the separation method: Solvent A = 10% MeOH–90% H_2O–0.1% TFA, Solvent B = 90% MeOH–10%H_2O–0.1% TFA, Start %B = 0, Final %B = 100, Gradient time = 6 min, Stop time = 8 min, Flow Rate = 30 mL/min, Column: Xterra Prep MS C18 5u 30x50mm, UV detection at 220 nm. LC/MS were performed by using Shimadzu-VP instrument with UV detection at 220 nm and Waters Micromass. HPLC method: Solvent A = 10% MeOH–90% H_2O–0.1% TFA, Solvent B = 90% MeOH–10%H_2O–0.1% TFA, Start %B = 0, Final %B = 100, Gradient time = 2 min, Stop time = 3 min, Flow Rate = 5 ml/min, Column: Xterra MS C18 S7 3.0 x 50mm; (ES+) m/z $(M+H)^+$ = 691.15, HPLC R_t = 1.678 min. HPLC method: Solvent A = 5% MeCN–95% H_2O–10 mM NH_4OAc, Solvent B = 95% MeCN–5%H_2O–10 mM NH_4OAc, Start %B = 0, Final %B = 100, Gradient time = 2 min, Stop time = 3 min, Flow Rate = 5 ml/min, Column: Phenomenex Lina C18 5um 3.0 x 50mm; (ES+) m/z $(M+H)^+$ = 691.08, HPLC R_t = 1.318 min. Analytical HPLC were performed by using Shimadzu-VP instrument with UV detection at 254 nm and 256 nm. Analytical

HPLC method: Solvent A = 5% MeCN–95% H_2O–0.1% TFA, Solvent B = 95% MeCN–5%H_2O–0.1% TFA, Start %B = 10, Final %B = 100, Gradient time = 10 min, Stop time = 20 min, Flow Rate = 1 ml/min, Column: Waters Sunfire C-18, 4.6 x 150 mm, 3.5 um, R_t = 8.49 min; Column: Waters Xbridge Phenyl column 4.6 x 150 mm, 3.5 um, R_t = 8.66 min.

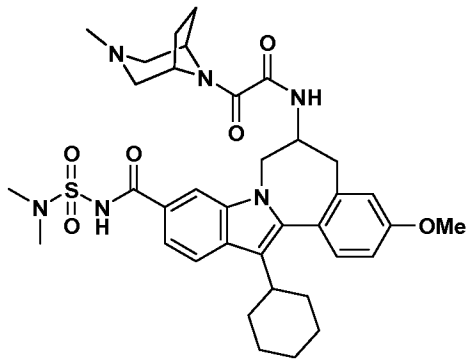
Example 20



8-Cyclohexyl-1a-((1,4-diazabicyclo[3.2.2]non-4-yl(oxo)acetyl)amino)-N-(dimethylsulfamoyl)-11-methoxy-1,1a,2,12b-tetrahydrocyclopropa[d]indolo[2,1-a][2]benzazepine-5-carboxamide. Prepared as a TFA salt in a similar manner as example 3. Purification by Shimadzu-VP preparative reverse phase HPLC using the separation method: Solvent A = 10% MeOH–90% H_2O–0.1% TFA, Solvent B = 90% MeOH–10%H_2O–0.1% TFA, Start %B = 30, Final %B = 100, Gradient time = 6 min, Stop time = 8 min, Flow Rate = 30 mL/min, Column: Xterra Prep MS C18 5u 30x50mm, UV detection at 220 nm. LC/MS were performed by using Shimadzu-VP instrument with UV detection at 220 nm and Waters Micromass. HPLC method: Solvent A = 10% MeOH–90% H_2O–0.1% TFA, Solvent B = 90% MeOH–10%H_2O–0.1% TFA, Start %B = 0, Final %B = 100, Gradient time = 2 min, Stop time = 3 min, Flow Rate = 5 ml/min, Column: Xterra MS C18 S7 3.0 x 50mm; (ES+) m/z $(M+H)^+$ = 703.14, HPLC R_t = 1.673 min. HPLC method: Solvent A = 5% MeCN–95% H_2O–10 mM NH_4OAc, Solvent B = 95% MeCN–5%H_2O–10 mM NH_4OAc, Start %B = 0, Final %B = 100, Gradient time = 2 min, Stop time = 3 min,

Flow Rate = 5 ml/min, Column: Phenomenex Lina C18 5um 3.0 x 50mm; (ES+) m/z $(M+H)^+$ = 703.13, HPLC R_t = 1.283 min. Analytical HPLC were performed by using Shimadzu-VP instrument with UV detection at 254 nm and 256 nm. Analytical HPLC method: Solvent A = 5% MeCN–95% H_2O–0.1% TFA, Solvent B = 95% MeCN–5%H_2O–0.1% TFA, Start %B = 10, Final %B = 100, Gradient time = 10 min, Stop time = 20 min, Flow Rate = 1 ml/min, Column: Waters Sunfire C-18, 4.6 x 150 mm, 3.5 um, R_t = 7.86 min; Column: Waters Xbridge Phenyl column 4.6 x 150 mm, 3.5 um, R_t = 8.54 min.

Example 21



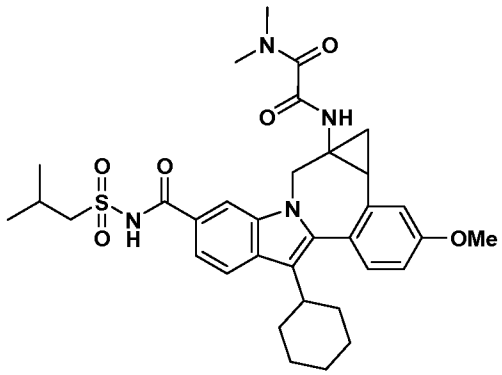
13-Cyclohexyl-N-(dimethylsulfamoyl)-3-methoxy-6-(((3-methyl-3,8-diazabicyclo[3.2.1]oct-8-yl)(oxo)acetyl)amino)-6,7-dihydro-5H-indolo[2,1-a][2]benzazepine-10-carboxamide. Prepared as a TFA salt in a similar manner as described for N'-(13-Cyclohexyl-10-((((dimethylamino)sulfonyl)amino)carbonyl)-3-(methyloxy)-6,7-dihydro-5H-indolo[2,1-a][2]benzazepin-6-yl)-N,N-dimethylethanediamide. Purification by Shimadzu-VP preparative reverse phase HPLC using the separation method: Solvent A = 10% MeOH–90% H_2O–0.1% TFA, Solvent B = 90% MeOH–10%H_2O–0.1% TFA, Start %B = 0, Final %B = 100, Gradient time = 10 min, Stop time = 12 min, Flow Rate = 30 mL/min, Column: Xterra Prep MS C18 5u 30x50mm, UV detection at 220 nm. LC/MS were performed by using Shimadzu-VP instrument with UV detection at 220 nm and Waters Micromass. HPLC method: Solvent A = 10% MeOH–90% H_2O–0.1% TFA, Solvent B = 90% MeOH–10%H_2O–0.1% TFA, Start %B = 0, Final %B = 100, Gradient time

= 2 min, Stop time = 3 min, Flow Rate = 5 ml/min, Column: Xterra MS C18 S7 3.0 x 50mm; (ES+) m/z $(M+H)^+$ = 691.52, HPLC R_t = 1.682 min. HPLC method: Solvent A = 5% MeCN–95% H_2O–10 mM NH_4OAc, Solvent B = 95% MeCN–5%H_2O–10 mM NH_4OAc, Start %B = 0, Final %B = 100, Gradient time = 2 min, Stop time = 3 min, Flow Rate = 5 ml/min, Column: Phenomenex Lina C18 5um 3.0 x 50mm; (ES+) m/z $(M+H)^+$ = 691.50, HPLC R_t = 1.443 min. Analytical HPLC were performed by using Shimadzu-VP instrument with UV detection at 254 nm and 256 nm. Analytical HPLC method: Solvent A = 5% MeCN–95% H_2O–0.1% TFA, Solvent B = 95% MeCN–5%H_2O–0.1% TFA, Start %B = 10, Final %B = 100, Gradient time = 10 min, Stop time = 20 min, Flow Rate = 1 ml/min, Column: Waters Sunfire C-18, 4.6 x 150 mm, 3.5 um, R_t = 8.88 min; Column: Waters Xbridge Phenyl column 4.6 x 150 mm, 3.5 um, R_t = 8.96 min.

The following sulfonamide analogs were prepared from 7H-Indolo[2,1-a][2]benzazepine-6,10-dicarboxylic acid, 13-cyclohexyl-, 10-(1,1-dimethylethyl) 6-methyl ester, according to the Scheme shown above. Purification was performed by using Shimadzu-VP preparative reverse phase HPLC with the separation method: Solvent A = 10% MeOH–90% H_2O–0.1% TFA, Solvent B = 90% MeOH–10%H_2O–0.1% TFA, Start %B = 30 (or 10), Final %B = 100, Gradient time = 10 min, Stop time = 12 min, Flow Rate = 30 mL/min, Column: Xterra Prep MS C18 5u 30x50mm, UV detection at 220 nm. LC/MS were performed by using Shimadzu-VP instrument with UV detection at 220 nm and Waters Micromass, and with HPLC Methods A and B as follows: Method A: Solvent A = 10% MeOH–90% H_2O–0.1% TFA, Solvent B = 90% MeOH–10%H_2O–0.1% TFA, Start %B = 0, Final %B = 100, Gradient time = 2 min, Stop time = 3 min, Flow Rate = 5 ml/min, Column: Xterra MS C18 S7 3.0 x 50mm; Method B: Solvent A = 5% MeCN–95% H_2O–10 mM NH_4OAc, Solvent B = 95% MeCN–5%H_2O–10 mM NH_4OAc, Start %B = 0, Final %B = 100, Gradient time = 2 min, Stop time = 3 min, Flow Rate = 5 ml/min (or 4 ml/min as stated), Column: Phenomenex Lina C18 5um 3.0 x 50mm. Analytical HPLC were performed by using Shimadzu-VP instrument with UV detection at 254 nm and 256 nm. Analytical HPLC method: Solvent A = 5% MeCN–95% H_2O–0.1% TFA, Solvent B = 95% MeCN–5%H_2O–0.1% TFA, Start

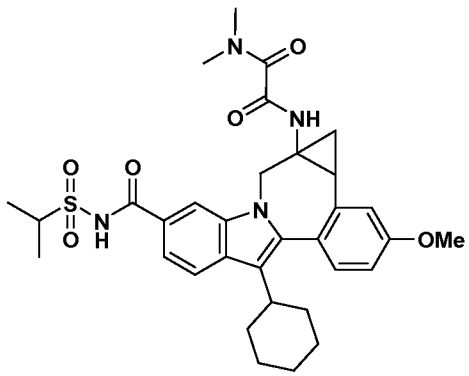
%B = 10, Final %B = 100, Gradient time = 10 min, Stop time = 20 min, Flow Rate = 1 ml/min, Column A: Waters Sunfire C-18, 4.6 x 150 mm, 3.5 um, Column B: Waters Xbridge Phenyl column 4.6 x 150 mm, 3.5 um.

Example 22



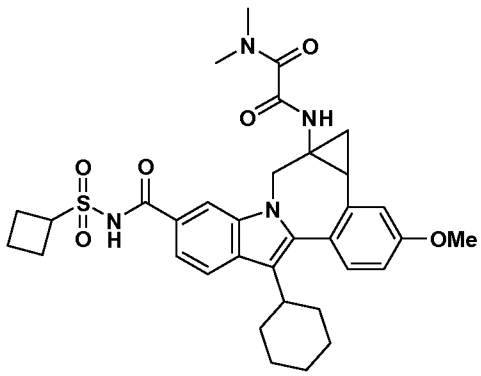
N'-(8-Cyclohexyl-5-((isobutylsulfonyl)carbamoyl)-11-methoxy-1,12b-dihydrocyclopropa[d]indolo[2,1-a][2]benzazepin-1a(2H)-yl)-N,N-dimethylethanediamide. Method A: (ES+) m/z $(M+H)^+$ = 635.40, HPLC R_t = 1.895 min. Method B: (ES+) m/z $(M+H)^+$ = 635.42, HPLC R_t = 1.238 min. Analytical HPLC Column A: R_t = 11.45 min; Column B: R_t = 10.27 min.

Example 23



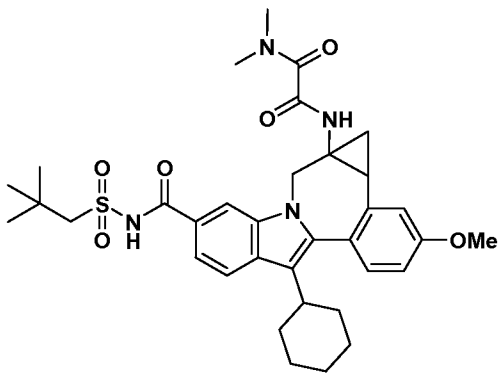
N'-(8-Cyclohexyl-5-((isopropylsulfonyl)carbamoyl)-11-methoxy-1,12b-dihydrocyclopropa[d]indolo[2,1-a][2]benzazepin-1a(2H)-yl)-N,N-dimethylethanediamide. Method A: (ES+) m/z $(M+H)^+$ = 621.31, HPLC R_t = 1.820 min. Method B: (ES+) m/z $(M+H)^+$ = 621.37, HPLC R_t = 1.213 min. Analytical HPLC Column A: R_t = 11.00 min; Column B: R_t = 9.93 min.

Example 24



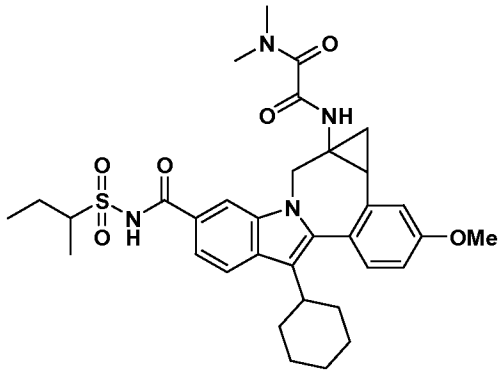
N'-(5-((Cyclobutylsulfonyl)carbamoyl)-8-cyclohexyl-11-methoxy-1,12b-dihydrocyclopropa[d]indolo[2,1-a][2]benzazepin-1a(2H)-yl)-N,N-dimethylethanediamide. Method A: (ES+) m/z $(M+H)^+$ = 633.26, HPLC R_t = 1.857 min. Method B: (ES+) m/z $(M+H)^+$ = 633.41, HPLC R_t = 1.183 min. Analytical HPLC Column A: R_t = 11.35 min; Column B: R_t = 10.18 min.

Example 25



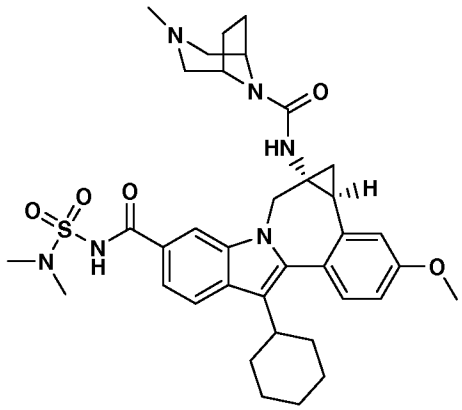
N'-(8-Cyclohexyl-5-(((2,2-dimethylpropyl)sulfonyl)carbamoyl)-11-methoxy-1,12b-dihydrocyclopropa[d]indolo[2,1-a][2]benzazepin-1a(2H)-yl)-N,N-dimethylethanediamide. Method A: (ES+) m/z $(M+H)^+$ = 649.32, HPLC R_t = 1.940 min. Method B: (ES+) m/z $(M+H)^+$ = 649.42, HPLC R_t = 1.348 min (Flow Rate = 4 ml/min). Analytical HPLC Column A: R_t = 11.86 min; Column B: R_t = 10.55 min.

Example 26



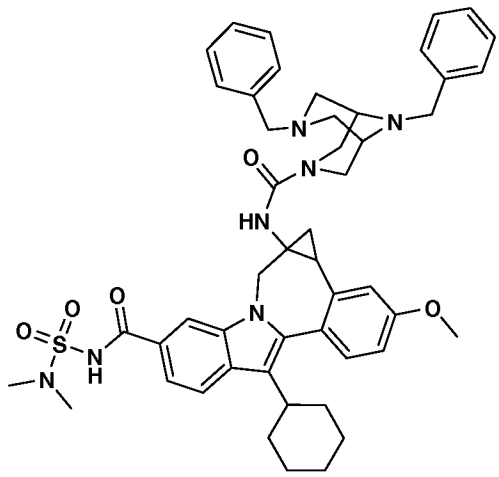
N'-(5-((sec-Butylsulfonyl)carbamoyl)-8-cyclohexyl-11-methoxy-1,12b-dihydrocyclopropa[d]indolo[2,1-a][2]benzazepin-1a(2H)-yl)-N,N-dimethylethanediamide. Method A: (ES+) m/z $(M+H)^+$ = 635.45, HPLC R_t = 1.847 min. Method B: (ES+) m/z $(M+H)^+$ = 635.42, HPLC R_t = 1.218 min (Flow Rate = 4 ml/min). Analytical HPLC Column A: R_t = 11.36 min; Column B: R_t = 10.19 min.

Example 27



(1aR,12bS)-8-Cyclohexyl-N-(dimethylsulfamoyl)-11-methoxy-1a-(((3-methyl-3,8-diazabicyclo[3.2.1]oct-8-yl)carbonyl)amino)-1,1a,2,12b-tetrahydrocyclopropa [d] indolo[2,1-a][2]benzazepine-5-carboxamide. ^{1}H NMR (500 MHz, CD_3OD) δ ppm: 1.19 - 1.28 (m, 3 H), 1.35 - 1.44 (m, 2 H), 1.61 (m, 1 H), 1.71 - 1.80 (m, 5 H), 1.86 - 1.96 (m, 2 H), 1.99 - 2.08 (m, 3 H), 2.23 (m, 1 H), 2.55 (d, J=12.21 Hz, 1 H), 2.73 (s, 3 H), 2.81 - 2.84 (m, 1 H), 2.94 (s, 6 H), 3.13 (d, J=12.21 Hz, 1 H), 3.22 (m, 1 H), 3.33 (d, J=12.21 Hz, 1 H), 3.37 - 3.43 (d, J=14.95 Hz, 1 H), 3.81 (s, 3 H), 4.28 (t, J=6.56 Hz, 2 H), 5.15 (d, J=14.04 Hz, 1 H), 6.94 (dd, J=8.55, 2.44 Hz, 1 H), 7.08 (d, J=2.44 Hz, 1 H), 7.25 (d, J=8.55 Hz, 1 H), 7.48 (dd, J=8.39, 1.53 Hz, 1 H), 7.84 (d, J=8.39 Hz, 1 H), 7.91 (d, J=1.53 Hz, 1 H). LC/MS: m/z 675.18 (MH^+), Rf 1.82 min., 98.0% purity.

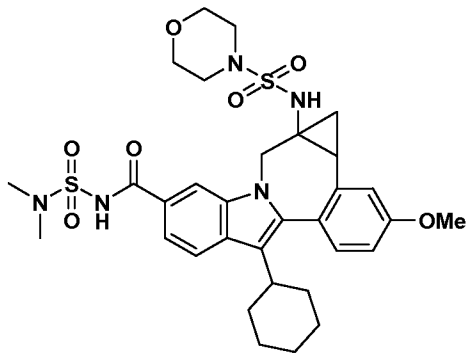
Example 28



8-Cyclohexyl-1a-(((7,9-dibenzyl-3,7,9-triazabicyclo[3.3.1]non-3-yl)carbonyl)amino)-N-(dimethylsulfamoyl)-11-methoxy-1,1a,2,12b-tetrahydrocyclopropa[d]indolo[2,1-a][2]benzazepine-5-carboxamide. ^{1}H NMR (500 MHz, CD_3OD) δ ppm: 0.16 (m, 0.20 H), 0.84 (m, 0.20 H), 1.19 - 1.29 (m, 2.80 H), 1.33 - 1.43 (m, 2.80 H), 1.45 (m, 1 H), 1.64 (m, 1H), 1.75 (m, 2 H), 1.93 (m, 2 H), 2.06 (m, 2 H), 2.24 (m, 0.80 H), 2.31 (m, 0.20 H), 2.64 (m, 2 H), 2.77 (m, 1 H), 2.93 (m, 6 H), 3.11 (m, 2 H), 3.22 (m, 4 H), 3.41 (d, J=14.95 Hz, 1 H), 3.48 (m, 1 H), 3.74 (m, 2 H), 3.83 (m, 3 H), 3.92 (m, 1 H), 5.24 (d, J=14.95 Hz, 1 H), 6.90 (dd, J =8.55, 2.74 Hz, 0.20 H), 6.96 (dd, J =8.55, 2.74 Hz, 0.80 H), 7.09 (d, *J*= 2.74 Hz, 0.20 H), 7.11 (d, *J*= 2.74 Hz, 0.80 H), 7.17 (m, 1 H), 7.22 – 7.29 (m, 9 H), 7.35 (m, 1 H), 7.52 – 7.57 (m, 1 H), 7.82 - 7.87 (m, 1 H), 7.93 (s, 0.80 H), 8.07 (s, 0.20 H). LC/MS: *m/z* 857.12 (MH^+), *Rf* 1.96 min., 94.0% purity.

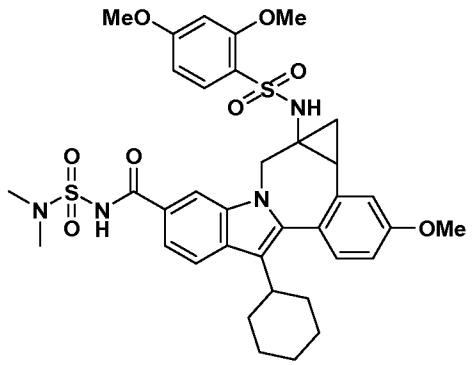
Examples 29-31 use the following procedures. Analytical HPLC and LC/MS were performed by using Shimadzu-VP instrument with UV detection at 220 nm and Waters Micromass.

Example 29



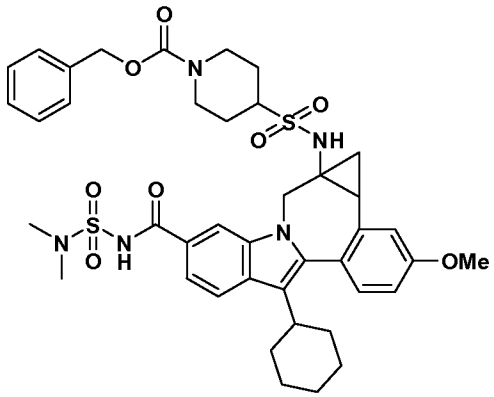
8-Cyclohexyl-N-(dimethylsulfamoyl)-11-methoxy-1a-((4-morpholinylsulfonyl)amino)-1,1a,2,12b-tetrahydrocyclopropa[d]indolo[2,1-a][2]benzazepine-5-carboxamide. To the hydrochloride salt of 1*a*-amino-8-cyclohexyl-*N*-((dimethylamino)sulfonyl)-11-(methyloxy)-1,1*a*,2,12*b*-tetrahydrocyclopropa[*d*]indolo[2,1-*a*][2]benzazepine-5-carboxamide (30 mg, 53.7 μmol) at r.t. under N_2 was added a solution of morpholine-4-sulfonyl chloride (32 mg, 172 μmol) in DMF (1 ml total), and then triethylamine (41 μl, 294 μmol). The mixture was stirred at r.t. for 19.5 h. The mixture was then concentrated, diluted with MeOH and purified by Shimadzu-VP preparative reverse phase HPLC with separation method: Solvent A = 10% MeOH–90% H_2O–0.1% TFA, Solvent B = 90% MeOH–10%H_2O–0.1% TFA, Start %B = 0, Final %B = 100, Gradient time = 6min, Flow Rate = 30mL/min, Column: Xterra Prep MS C18 5u 30x50mm, Fraction Collection: 6.99 – 7.58 min. (UV detection at 220 nm) to give 8-cyclohexyl-*N*-(dimethylsulfamoyl)-11-methoxy-1*a*-((4-morpholinylsulfonyl)amino)-1,1*a*,2,12*b*-tetrahydrocyclopropa[*d*]indolo[2,1-*a*][2]benzazepine-5-carboxamide. Analytical HPLC method: Solvent A = 10% MeOH–90% H_2O–0.1% TFA, Solvent B = 90% MeOH–10%H_2O–0.1% TFA, Start %B = 0, Final %B = 100, Gradient time = 2 min, Flow Rate = 5 ml/min, Column: Xterra MS C18 S7 3.0 x 50mm; LC/MS: (ES+) m/z $(M+H)^+$ = 672.12, HPLC R_t = 1.892 min.

Example 30



8-Cyclohexyl-1a-(((2,4-dimethoxyphenyl)sulfonyl)amino)-N-(dimethylsulfamoyl)-11-methoxy-1,1a,2,12b-tetrahydrocyclopropa[d]indolo[2,1-a][2]benzazepine-5-carboxamide. 8-Cyclohexyl-1*a*-(((2,4-dimethoxyphenyl)sulfonyl)amino)-*N*-(dimethylsulfamoyl)-11-methoxy-1,1*a*,2,12*b*-tetrahydrocyclopropa[*d*]indolo[2,1-*a*][2]benzazepine-5-carboxamide was prepared in a similar manner to 8-cyclohexyl-*N*-(dimethylsulfamoyl)-11-methoxy-1*a*-((4-morpholinylsulfonyl)amino)-1,1*a*,2,12*b*-tetrahydrocyclopropa[*d*]indolo[2,1-*a*][2]benzazepine-5-carboxamide. Purification was performed by Shimadzu-VP preparative reverse phase HPLC with separation method: Solvent A = 10% MeOH–90% H_2O–0.1% TFA, Solvent B = 90% MeOH–10%H_2O–0.1% TFA, Start %B = 0, Final %B = 100, Gradient time = 6min, Flow Rate = 30mL/min, Column: Xterra Prep MS C18 5u 30x50mm, Fraction Collection: 7.06 – 7.66 min. (UV detection at 220 nm). Analytical HPLC method: Solvent A = 10% MeOH–90% H_2O–0.1% TFA, Solvent B = 90% MeOH–10%H_2O–0.1% TFA, Start %B = 0, Final %B = 100, Gradient time = 2 min, Flow Rate = 5 ml/min, Column: Xterra MS C18 S7 3.0 x 50mm; LC/MS: (ES+) m/z $(M+H)^+$ = 723.07, HPLC R_t = 1.948 min. Analytical HPLC method: Solvent A = 5% MeCN–95% H_2O–10 mM NH_4OAc, Solvent B = 95% MeCN–5%H_2O–10 mM NH_4OAc, Start %B = 0, Final %B = 100, Gradient time = 2 min, Flow Rate = 5 ml/min, Column: Phenomenex Lina C18 5um 3.0 x 50mm; LC/MS: (ES+) m/z $(M+H)^+$ = 723.17, HPLC R_t = 1.592 min.

Example 31

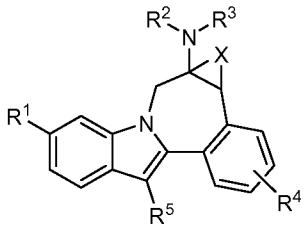


Benzyl 4-((8-cyclohexyl-5-((dimethylsulfamoyl)carbamoyl)-11-methoxy-1,12b-dihydrocyclopropa[d]indolo[2,1-a][2]benzazepin-1a(2H)-yl)sulfamoyl)-1-piperidinecarboxylate. Benzyl 4-((8-cyclohexyl-5-((dimethylsulfamoyl)carbamoyl)-11-methoxy-1,12b-dihydrocyclopropa[d]indolo[2,1-a][2]benzazepin-1a(2H)-yl)sulfamoyl)-1-piperidinecarboxylate was prepared in a similar manner to 8-cyclohexyl-N-(dimethylsulfamoyl)-11-methoxy-1a-((4-morpholinylsulfonyl)amino)-1,1a,2,12b-tetrahydrocyclopropa[d]indolo[2,1-a][2]benzazepine-5-carboxamide. Purification was performed by Shimadzu-VP preparative reverse phase HPLC with separation method: Solvent A = 10% MeOH–90% H_2O–0.1% TFA, Solvent B = 90% MeOH–10%H_2O–0.1% TFA, Start %B = 30, Final %B = 100, Gradient time = 6min, Flow Rate = 30mL/min, Column: Xterra Prep MS C18 5u 30x50mm, Fraction Collection: 7.04 – 7.64 min. (UV detection at 220 nm). Analytical HPLC method: Solvent A = 10% MeOH–90% H_2O–0.1% TFA, Solvent B = 90% MeOH–10%H_2O–0.1% TFA, Start %B = 0, Final %B = 100, Gradient time = 2 min, Flow Rate = 5 ml/min, Column: Xterra MS C18 S7 3.0 x 50mm; LC/MS: (ES+) m/z $(M+H)^+$ = 804.10, HPLC R_t = 1.990 min. Analytical HPLC method: Solvent A = 5% MeCN–95% H_2O–10 mM NH_4OAc, Solvent B = 95% MeCN–5%H_2O–10 mM NH_4OAc, Start %B = 0, Final %B = 100, Gradient time = 2 min, Flow Rate = 5 ml/min, Column: Phenomenex Lina C18 5um 3.0 x 50mm; LC/MS: (ES–) m/z $(M–H)^+$ = 802.27, HPLC R_t = 1.658 min.

CLAIMS

We claim:

1. A compound of formula I



I

where:

R^1 is CO_2R^6 or $CONR^7R^8$;

R^2 is COR^{12}, $COCOR^{13}$, $SO_2N(R^{14})(R^{15})$, or SO_2R^{16};

R^3 is hydrogen or alkyl;

R^4 is hydrogen, halo, alkyl, alkenyl, hydroxy, benzyloxy, or alkoxy;

R^5 is cycloalkyl;

R^6 is hydrogen or alkyl;

R^7 is hydrogen, alkyl, $alkylSO_2$, $cycloalkylSO_2$, $haloalkylSO_2$, $(R^9)_2NSO_2$, or $(R^{10})SO_2$;

R^8 is hydrogen or alkyl;

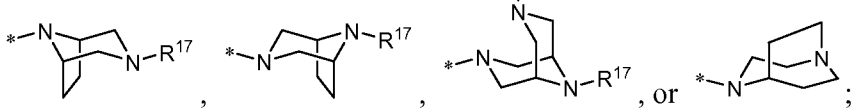
R^9 is hydrogen or alkyl;

R^{10} is azetidinyl, pyrrolidinyl, piperidinyl, N-(R^{11})piperazinyl, morpholinyl, thiomorpholinyl, homopiperidinyl, N-(R^{11})homopiperazinyl, or homomorpholinyl;

R^{11} is hydrogen or alkyl; and

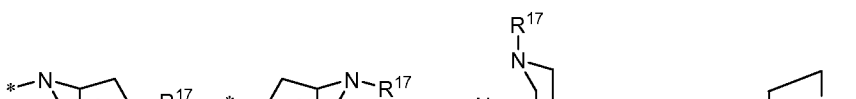
R^{12} is amino, alkylamino, or dialkylamino;

or R^{12} is azetidinyl, pyrrolidinyl, piperidinyl, piperazinyl, morpholinyl, homopiperidinyl, homopiperazinyl, or homomorpholinyl, and is substituted with 0-3 substituents selected from alkyl, alkoxy, and phenyl wherein phenyl is substituted with 0-3 substituents selected from cyano, halo, alkyl, and alkoxy;

or R^{12} is  ;

R^{13} is hydroxy, alkoxy, amino, alkylamino, or dialkylamino;

or R^{13} is azetidinyl, pyrrolidinyl, piperidinyl, piperazinyl, morpholinyl, homopiperidinyl, homopiperazinyl, or homomorpholinyl, and is substituted with 0-3 substituents selected from alkyl, alkoxy, and phenyl wherein phenyl is substituted with 0-3 substituents selected from cyano, halo, alkyl, and alkoxy;

or R^{13} is  ;

R^{14} is hydrogen, or alkyl;

R^{15} is hydrogen or alkyl;

R^{16} is alkyl, cycloalkyl, or haloalkyl;

or R^{16} is azetidinyl, pyrrolidinyl, piperidinyl, piperazinyl, morpholinyl, thiomorpholinyl, homopiperidinyl, homopiperazinyl, or homomorpholinyl, and is substituted with 0-3 substituents selected from alkyl, alkylcarbonyl, alkoxycarbonyl, benzyl, and benzyloxycarbonyl;

or R^{16} is phenyl substituted with 0-3 substituents selected from cyano, halo, alkyl, haloalkyl, alkoxy, and haloalkoxy;

R^{17} is hydrogen, alkyl, cycloalkyl, (cycloalkyl)alkyl, benzyl, alkylcarbonyl, alkoxycarbonyl, benzyloxycarbonyl, alkylSO_2, or pyridinyl; and

X is absent, a bond, or methylene;

or a pharmaceutically acceptable salt thereof.

2. A compound of claim 1 where R^1 is $CONR^7R^8$; R^7 is alkylSO_2, cycloalkylSO_2, haloalkylSO_2, $(R^9)_2NSO_2$, or $(R^{10})SO_2$; and R^8 is hydrogen.

3. A compound of claim 1 where R^2 is COR^{12}.

4. A compound of claim 1 where R^2 is $COCOR^{13}$.

5. A compound of claim 1 where R^2 is $SO_2N(R^{14})(R^{15})$ or SO_2R^{16}.

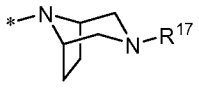
6. A compound of claim 1 where R^3 is hydrogen.

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

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

9. A compound of claim 1 where R^5 is cyclohexyl.

10. A compound of claim 1 where R^{12} or R^{13} is dimethylamino, pyrrolidinyl, morpholinyl, dimethylmorpholinyl, piperazinyl, trimethylpiperazinyl, or



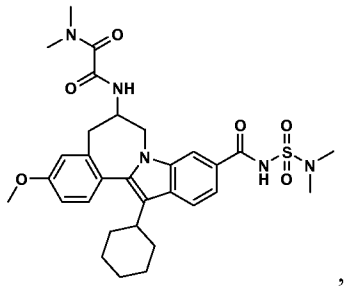
where R^{17} is alkyl.

11. A compound of claim 1 where X is absent.

12. A compound of claim 1 where X is a bond.

13. A compound of claim 1 where X is methylene.

14. A compound of claim 1 selected from the group consisting of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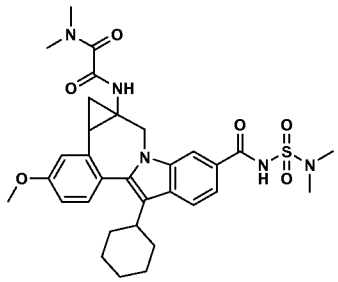
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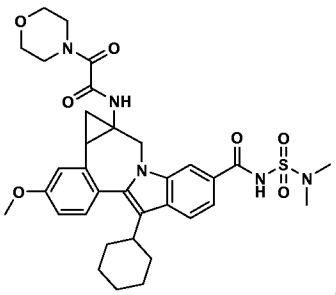
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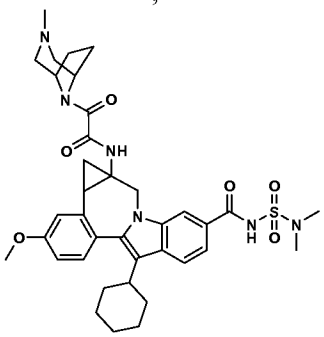
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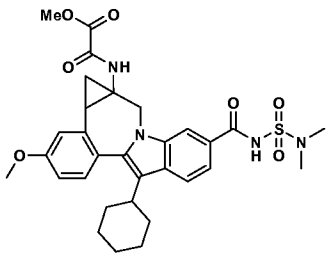
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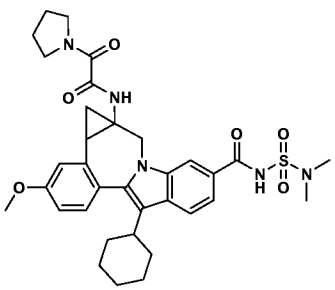
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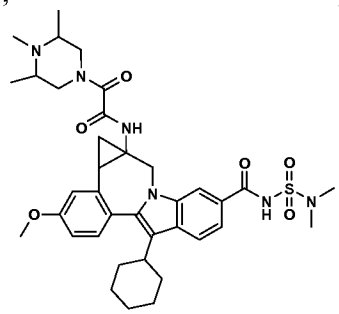
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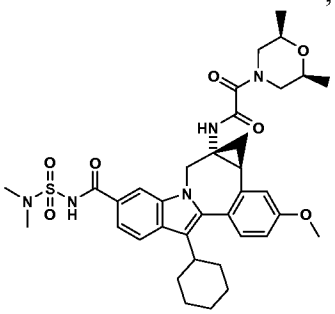
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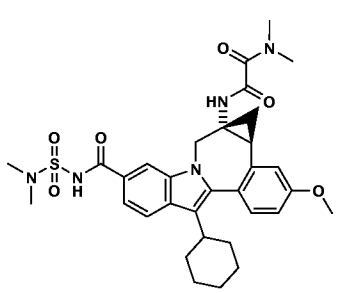
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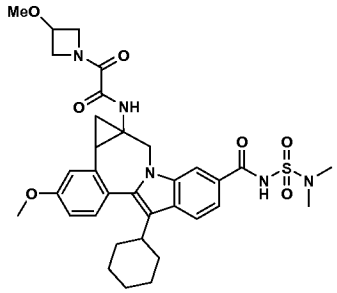
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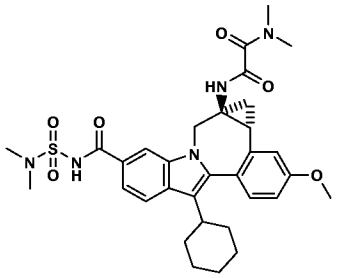
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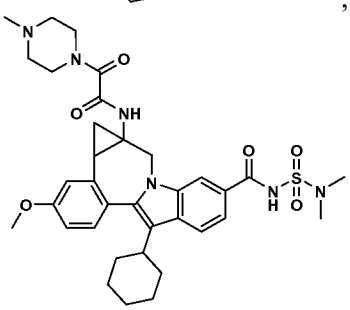
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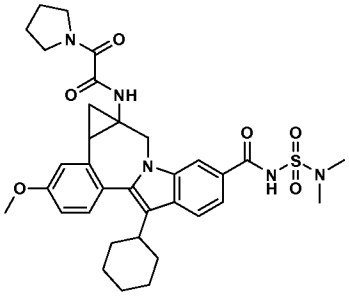
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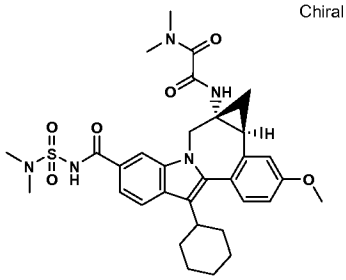
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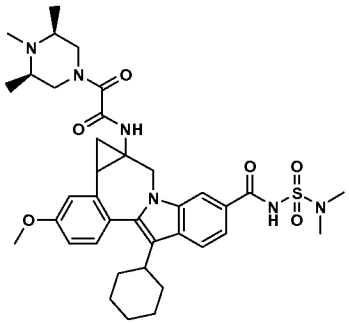
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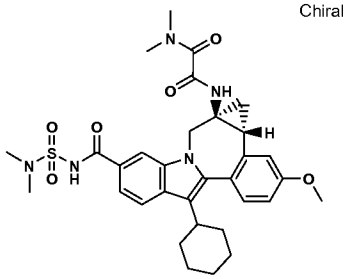
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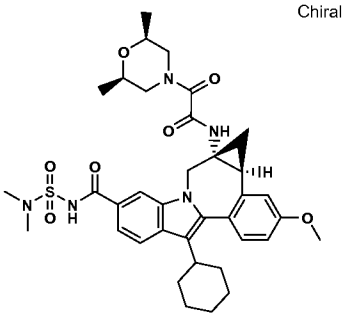
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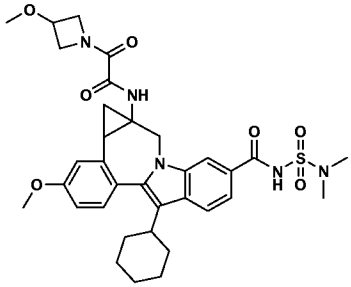
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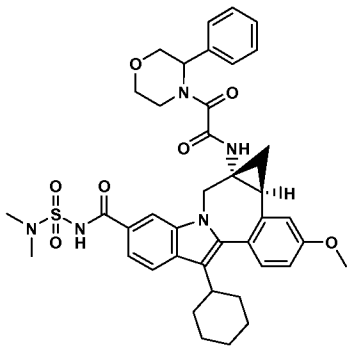
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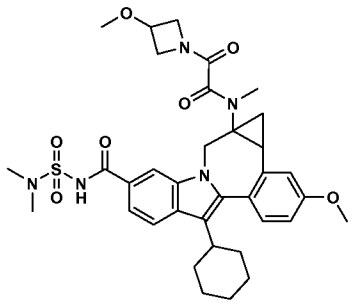
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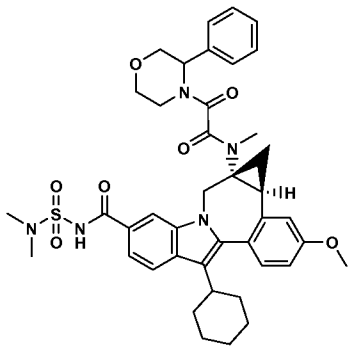
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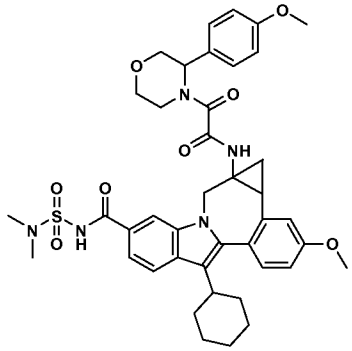
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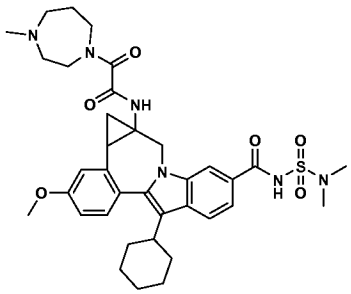
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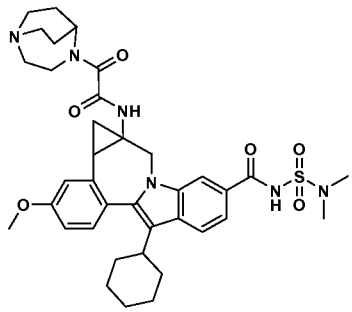
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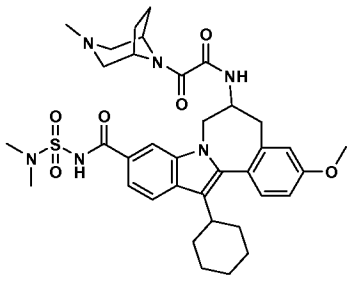
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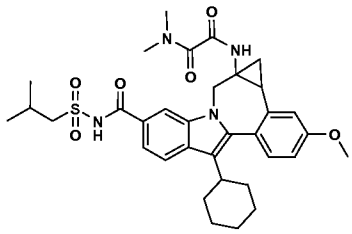
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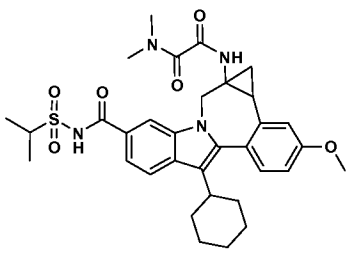
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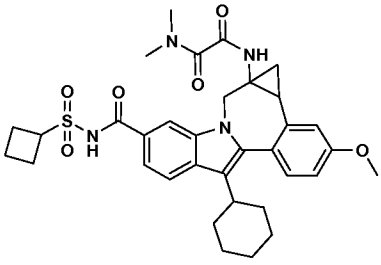
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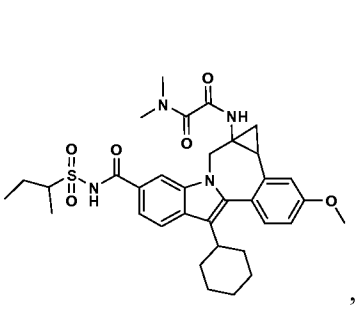
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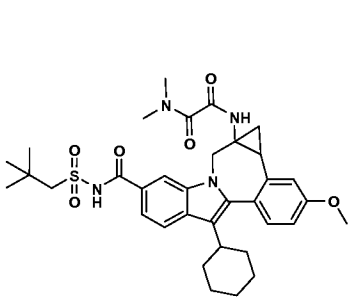
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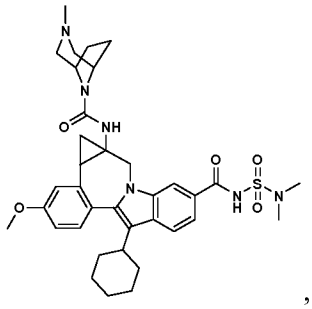
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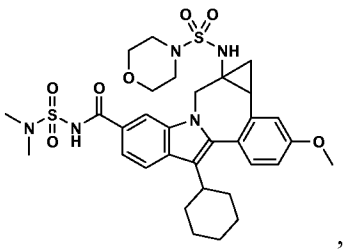
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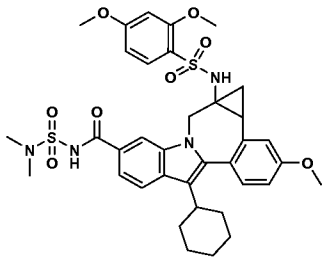
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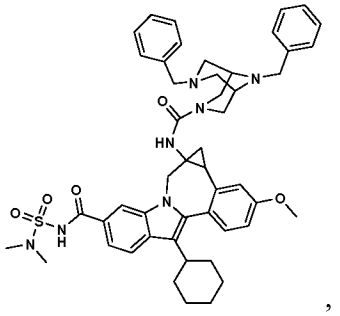
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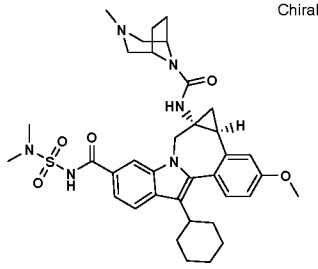
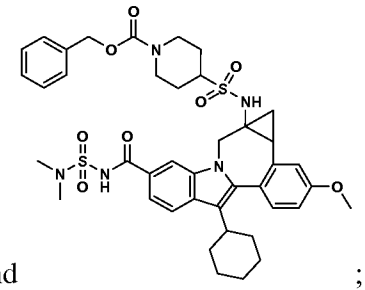
, and ;

or a pharmaceutically acceptable salt thereof.

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

16. The composition of claim 15 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.

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

18. The method of claim 17 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/US2008/052573

A. CLASSIFICATION OF SUBJECT MATTER
INV. C07D487/04 C07D519/00 A61K31/55 A61P31/12

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 A61K A61P

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, CHEM ABS Data

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
P,X	WO 2007/143521 A (SQUIBB BRISTOL MYERS CO [US]; YEUNG KAP-SUN [US]; GRANT-YOUNG KATHARIN) 13 December 2007 (2007-12-13) examples; table 1	1-18
P,X	WO 2007/033175 A (SQUIBB BRISTOL MYERS CO [US]; BERGSTROM CARL P [US]; BENDER JOHN A [US) 22 March 2007 (2007-03-22) examples	1-18
X	WO 2006/046039 A (ANGELETTI P IST RICHERCHE BIO [IT]; ERCOLANI CATERINA [IT]; HABERMANN) 4 May 2006 (2006-05-04) examples	1-18
X	WO 2006/020082 A (SQUIBB BRISTOL MYERS CO [US]; HUDYMA THOMAS W [US]; ZHENG XIAOFAN [US]) 23 February 2006 (2006-02-23) examples	1-18

☐ Further documents are listed in the continuation of Box C.

☒ 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
19 June 2008	03/07/2008

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	Fazzi, Raffaella

INTERNATIONAL SEARCH REPORT

International application No.
PCT/US2008/052573

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 17-18 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/US2008/052573

Patent document cited in search report	Publication date	Patent family member(s)	Publication date
WO 2007143521 A	13-12-2007	US 2007287694 A1	13-12-2007
WO 2007033175 A	22-03-2007	AR 055165 A1	08-08-2007
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