Title: NOVEL CARBOXAMIDE DERIVATIVES AS HIV INHIBITORS

Abstract: The present invention relates to carboxamide derivatives of Formula (I), where B1, B2, X, L, n, R, R1, R2, Z1, Z2, R3 and R4 are as defined in the claims, as compounds and compositions for inhibiting Human Immunodeficiency Virus (HIV) and for processing making the compounds.
NOVEL CARBOXAMIDE DERIVATIVES AS HIV INHIBITORS

This application claims the benefit of Indian Provisional Patent Application Nos. 2830/CHE/2009 filed on 17th November 2009, which is incorporated herein by reference.

Field of the Invention

The present invention relates to novel carboxamide derivatives as novel compounds and compositions for inhibiting Human Immunodeficiency Virus (HIV) and process for making the compounds.

Background of the Invention

HIV-1 infection remains a major medical problem, with an estimated 40 million people infected worldwide. The number of cases of HIV and AIDS (acquired immunodeficiency syndrome) has risen rapidly. In 2005, approximately 5.0 million new infections were reported, and 3.2 million people died from AIDS.

HPV protease inhibitors are one important class of therapeutic agents for inhibition and treatment of HIV infection. Several protease inhibitors like saquinavir, ritonavir, indinavir, nelfinavir, amprenavir, lopinavir, fosamprenavir and atazanavir have been approved as drugs for treatment of HIV infection. There is a continuing need for novel HIV inhibitors that are very potent and effective against resistant strains of HIV. Therefore, novel anti-HIV agents exhibiting distinct resistance patterns, and favorable pharmacokinetic as well as safety profiles are needed to provide more treatment options.

Structurally related compounds of this invention were explored for their therapeutic activities by several publications, include for example, WO 02/083657, WO 03/076413, WO 03/97616 and WO 2004/014371 disclosed broad-spectrum substituted benzisoxazole sulfonamide HIV protease inhibitors; WO 2007/02172 and WO 2008/118849 disclosed HIV-1 protease inhibitors; WO 2008/013834 discloses bisfuranyl protease inhibitors; WO 2008/133734 discloses method and compositions for treating HIV infections; US 5968942, US 5578606, US 5843946 and US 6060476 disclosed alpha and beta amino acid hydroxyethylamino sulfonamides useful as retroviral protease inhibitors; WO 00/47551 and WO 00/076961 disclosed inhibitors of aspartyl protease; US 5585397, WO 95/24385, WO 99/33815, WO 99/65870 and US 5783701 disclosed sulfonamide inhibitors of aspartyl protease; WO 96/33184 and US 5723490 disclosed THF-containing

However no patent or publication in the literature has reported the specific compounds or their anti HIV activity of the present invention. This observation is of practical importance in synthesizing the compounds of the present invention and screening them for their anti-HIV activity, for the discovery of the new drugs.

**Summary of the Invention**

The present invention relates to compounds of the formula (I)

![Formula (I)](image)

or a pharmaceutically acceptable salt, prodrug or stereoisomer there of, wherein,

- $B_1$ and $B_2$ are independently can be selected from O, CO, C ($R^a$)$_2$, or NR$_2$;
- X can be a bond, -0-, -0(C(R$_c$)$_2$)$_m$-, or - (C($R^c$)$_2$)$_m$O-;
- L can be a bond, -(CH$_2$)$_m$-, -N $R^d$-, or substituted or unsubstituted phenylene;
- n can be an integer 0-4;
- m can be an integer 0-3;
- R can be H, substituted or unsubstituted alkyl, substituted or unsubstituted cycloalkyl, substituted or unsubstituted aryl, substituted or unsubstituted heteroaryl, or substituted or unsubstituted heterocyclyl, and preferably R can be substituted by $R$;
- $R_1$ can be H, substituted or unsubstituted alkyl or substituted or unsubstituted cycloalkyl;
- $R_2$ can be H, substituted or unsubstituted alkyl, substituted or unsubstituted cycloalkyl, substituted or unsubstituted aryl, or substituted or unsubstituted heterocyclyl;
Zi and Z₂ are independently selected from a bond or NR² and provided that when NR₁ is directly connected to S₀₂R₂ then both Z₁ and Z₂ are absent;

Rᵢ and Zi are together attached with N atom to form a cyclic ring which can be mono cyclic ring, bicyclic ring or tricyclic ring and preferably they can be selected from

\[ \text{R}^\text{X}, \text{R}^\text{Y} \text{ are independently selected from H, halogen, substituted or unsubstituted alkyl, or R}^\text{X} \text{ and R}^\text{Y} \text{ are together attached with ring C atom to form C}_{3-6} \text{ cyclic ring or } C_{3-6} \text{ heterocyclic ring;} \]

\[ \text{R}^\text{A}, \text{R}^\text{B}, \text{R}^\text{C}, \text{ and R}^\text{D} \text{ are independently selected from H, substituted or unsubstituted alkyl, substituted or unsubstituted aryl, substituted or unsubstituted cycloalkyl, substituted or unsubstituted heterocyclyl, and preferably R}^\text{A}, \text{R}^\text{B}, \text{R}^\text{C}, \text{ and R}^\text{D} \text{ can be substituted by R}^\text{'} \text{;} \]

\[ \text{R}^\text{'} \text{ can be H, OH, halogen, NR}^\text{''}, \text{C(0)} \text{R}^\text{''}, \text{C(0)NR}^\text{''} \text{ substituted or unsubstituted alkyl, substituted or unsubstituted alkoxy, substituted or unsubstituted alkyloxy, or substituted or unsubstituted heterocyclyloxy;} \]

\[ \text{R}^\text{''} \text{ can be H, substituted or unsubstituted alkyl, substituted or unsubstituted amino, substituted or unsubstituted aryl, substituted or unsubstituted cycloalkyl, or substituted or unsubstituted heterocyclyl.} \]

The present invention also provides the process for making the compounds of formula (I).

The present invention further provides a pharmaceutical composition comprising a therapeutically effective amount of a compound or combination of compounds of the present invention, or a pharmaceutically acceptable salt form, stereoisomer and a pharmaceutically acceptable carrier.

Pharmaceutically acceptable salts of the compounds of the formula (I) are also contemplated. Likewise, pharmaceutically acceptable solvates, including hydrates, of the compounds of the formula (I) are contemplated.
It should be understood that the formula (I) structurally encompasses all stereoisomers, including enantiomers and diastereomers, which may be contemplated from the chemical structure of the genus described herein.

Also contemplated are prodrugs of the compounds of the formula (I), including ester prodrugs.

According to one embodiment, there is provided a compound of formula (I), wherein X is -0-.

According to one embodiment, there is provided a compound of formula (I), wherein X is a bond.

According to one embodiment, there is provided a compound of formula (I), wherein X is - (CR₂)ₘO- wherein m is 1 or 2.

According to one embodiment, there is provided a compound of formula (I), wherein R is H.

According to one embodiment, there is provided a compound of formula (I), wherein R is substituted or unsubstituted alkyl.

According to one embodiment, there is provided a compound of formula (I), wherein R is substituted or unsubstituted hetero aryl.

According to one embodiment, there is provided a compound of formula (I), wherein Bi is O or CH₂.

According to one embodiment, there is provided a compound of formula (I), wherein B₂ is O, CO or CH₂.

According to one embodiment, there is provided a compound of formula (I), wherein L is CH₂.

According to one embodiment, there is provided a compound of formula (I), wherein L is substituted or unsubstituted phenylene.

According to one embodiment, there is provided a compound of formula (I), wherein R₂ is substituted or unsubstituted phenyl.

According to one embodiment, there is provided a compound of formula (I), wherein R₁ is substituted or unsubstituted alkyl.

According to one embodiment, there is provided a compound of formula (I), wherein R₁ is substituted or unsubstituted cycloalkyl.

According to one embodiment, there is provided a compound of formula (I), wherein Rₓ and Rᵧ are selected from H, methyl or fluorine and Rₓ and Rᵧ are together attached with ring C atom to form C₃₋₆ hetero cyclic ring.
According to one embodiment, there is provided a compound of formula (I), wherein \( n \) is 0, 1 or 2.

Accordingly, one aspect of the present invention provides compounds of formula (IA):

\[
\text{Formula (IA)}
\]

wherein,

- \( B_1 \) and \( B_2 \) are independently selected from \( O, CO, C(\text{R}_1)_2, \) or \( NR^b; \)
- \( X \) can be a bond, \(-O-, -0((CR)_{2})_mO-,\) or \( -((CR^c)_{2})_mO-; \)
- \( L \) can be a bond, \(-((CH_2)_{m})-, -N \text{R}_d-,\) or substituted or unsubstituted phenylene;
- \( n \) can be an integer 0-4;
- \( m \) can be an integer 0-3;
- \( R \) can be \( H, \) substituted or unsubstituted alkyl, substituted or unsubstituted cycloalkyl, substituted or unsubstituted aryl, substituted or unsubstituted heteroaryl, or substituted or unsubstituted heterocyclyl, and preferably \( R \) can be substituted by \( \text{R'}; \)
- \( R_i \) can be \( H, \) substituted or unsubstituted alkyl, or substituted or unsubstituted cycloalkyl;
- \( R_2 \) can be \( H, \) substituted or unsubstituted alkyl, substituted or unsubstituted cycloalkyl, substituted or unsubstituted aryl, or substituted or unsubstituted heterocyclyl;
- \( R^a, R^b, R^c, \) and \( R^d \) are independently selected from \( \text{H}, \) halogen, substituted or unsubstituted alkyl, or \( \text{R}^a \) and \( \text{R}^b \) are together attached with ring \( C \) atom to form \( C_{3-6} \) cyclic ring or \( C_{3,6} \) heterocyclic ring;
- \( R^a, R^b, R^c, \) and \( R^d \) are independently selected from \( \text{H}, \) substituted or unsubstituted alkyl, substituted or unsubstituted aryl, substituted or unsubstituted cycloalkyl, substituted or unsubstituted heterocyclyl, and preferably \( R^a, R^b, R^c, \) and \( R^d \) can be substituted by \( \text{R'}; \)
- \( \text{R'} \) can be \( \text{H}, \text{OH}, \) halogen, \( \text{NR}^\prime, \text{C}(0)_{2}R^\prime, \text{C}(0)\text{NR}^\prime \) substituted or unsubstituted alkyl, substituted or unsubstituted alkoxy, substituted or unsubstituted...
alkyl, substituted or unsubstituted cycloalkyloxy, or substituted or unsubstituted heterocyclyloxy;

R" can be H, substituted or unsubstituted alkyl, substituted or unsubstituted amino, substituted or unsubstituted aryl, substituted or unsubstituted cycloalkyl, or substituted or unsubstituted heterocyclyl.

Accordingly, one aspect of the present invention provides compounds of formula (IB):

\[
\begin{align*}
&\text{Formula (IB)} \\
&\text{B_1 and B_2 are independent and can be selected from O, CO, C (R^3)_2, or NR^b;} \\
&X\text{ can be a bond, }-0-, -0(CR^c)_2-, \text{ or } - (CR^c)_2 O-; \\
&L\text{ can be a bond, }-(CH_2)_m-, -N R^d-, \text{ or substituted or unsubstituted phenylene; } \\
&n\text{ can be an integer 0-4; } \\
&m\text{ can be an integer 0-3; } \\
&R\text{ can be H, substituted or unsubstituted alkyl, substituted or unsubstituted cycloalkyl, substituted or unsubstituted aryl, substituted or unsubstituted heteroaryl, or substituted or unsubstituted heterocyclyl, and preferably R can be substituted by } R'; \\
&R_2\text{ can be H, substituted or unsubstituted alkyl, substituted or unsubstituted cycloalkyl, substituted or unsubstituted aryl, or substituted or unsubstituted heterocyclyl; } \\
&Z_2\text{ can be a bond or NR^b;} \\
\end{align*}
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can be mono cyclic ring, bicyclic ring or bridged ring and preferably they can be selected from

\[
\begin{align*}
\text{from}
\end{align*}
\]
R₁, and R² are independently can be H, halogen, substituted or unsubstituted alkyl, or R₁ and R² are together attached with ring C atom to form C₃-6 cyclic ring or C₃-6 heterocyclic ring;

R₃, R₄, R⁵, and R⁶ are independently selected from H, substituted or unsubstituted alkyl, substituted or unsubstituted aryl, substituted or unsubstituted cycloalkyl, substituted or unsubstituted heterocyclyl, and preferably R₃, R⁴, R⁵, and R⁶ can be substituted by R¹;

R¹ can be H, OH, halogen, NR"², C(0)₂R", C(0)NR"² substituted or unsubstituted alkyl, substituted or unsubstituted alkoxy, substituted or unsubstituted alkyl, substituted or unsubstituted cycloalkyloxy, or substituted or unsubstituted heterocyclyloxy;

R"² can be H, substituted or unsubstituted alkyl, substituted or unsubstituted amino, substituted or unsubstituted aryl, substituted or unsubstituted cycloalkyl, or substituted or unsubstituted heterocyclyl.

Below are the representative compounds, which are illustrative in nature only and are not intended to limit to the scope of the invention (Nomenclature has been generated from Chem. Draw Ultra 11.0 version):

N-((2S,3R)-3-hydroxy-4-(N-isobutyl-4-nitrophenylsulfonamido)-l-phenylbutan-2-yl)-2-((S)-tetrahydrofuran-3-yloxy)acetamide (Compound 1),

N-((2S,3R)-4-(4-amino-N-isobutylphenylsulfonamido)-3-hydroxy-l-phenylbutan-2-yl)-2-((S)-tetrahydrofuran-3-yloxy)acetamide (Compound 2),

N-((2S,3R)-3-hydroxy-4-(N-isobutyl-4-methoxyphenylsulfonamido)-l-phenylbutan-2-yl)-2-(tetrahydrofuran-3-yloxy)acetamide (Compound 3),

N-((2S,3R)-3-hydroxy-4-(N-isobutyl-4-methylphenylsulfonamido)-l-phenylbutan-2-yl)-2-(tetrahydrofuran-3-yloxy)acetamide (Compound 4),

N-((2S,3R)-4-(3-chloro-4-fluoro-N-isobutylphenylsulfonamido)-3-hydroxy-l-phenylbutan-2-yl)-2-(tetrahydrofuran-3-yloxy)acetamide (Compound 5),

1-ethyl-N-((2S,3R)-3-hydroxy-4-(N-isobutyl-4-nitrophenylsulfonamido)-l-phenylbutan-2-yl)cyclopentanecarboxamide (Compound 6),

N-((2S,3R)-4-(4-amino-N-isobutylphenylsulfonamido)-3-hydroxy-l-phenylbutan-2-yl)-1-ethylcyclopentanecarboxamide (Compound 7),
1-ethyl-N-((2S,3R)-3-hydroxy-4-(N-isobutyl-4-methoxyphenylsulfonamido)-1-phenylbutan-2-yl)cyclopentanecarboxamide (Compound 8),

N-((2S,3R)-4-(3-chloro-4-fluoro-N-isobutylphenylsulfonamido)-3-hydroxy-1-phenylbutan-2-yl)-1-ethylcyclopentanecarboxamide (Compound 9),

1-ethyl-N-((2S,3R)-3-hydroxy-4-(N-isobutyl-4-methylphenylsulfonamido)-1-phenylbutan-2-yl)cyclohexanecarboxamide (Compound 10),

1-ethyl-N-((2S,3R)-3-hydroxy-4-(N-isobutyl-4-methoxyphenylsulfonamido)-1-phenylbutan-2-yl)cyclohexanecarboxamide (Compound 11),

N-((2S,3R)-4-(3-chloro-4-fluoro-N-isobutylphenylsulfonamido)-3-hydroxy-1-phenylbutan-2-yl)-1-ethylcyclohexanecarboxamide (Compound 12),

1-ethyl-N-((2S,3R)-3-hydroxy-4-(N-isobutyl-4-nitrophenylsulfonamido)-1-phenylbutan-2-yl)cyclohexanecarboxamide (Compound 13),

N-((2S,3R)-4-(4-amino-N-isobutylphenylsulfonamido)-3-hydroxy-1-phenylbutan-2-yl)-1-ethylcyclohexanecarboxamide (Compound 14),

1-ethyl-N-((2S,3R)-4-(4-fluoro-N-isobutylphenylsulfonamido)-3-hydroxy-1-phenylbutan-2-yl)cyclohexanecarboxamide (Compound 15),

N-((2S,3R)-4-(3,4-difluoro-N-isobutylphenylsulfonamido)-3-hydroxy-1-phenylbutan-2-yl)-1-ethylcyclohexanecarboxamide (Compound 16),

1-ethyl-N-((2S,3R)-3-hydroxy-4-(3-(4-methoxyphenylsulfonamido)-8-azabicyclo[3.2.1]octan-8-yl)-1-phenylbutan-2-yl)cyclopentanecarboxamide (Compound 17A),

1-(2-ethoxyethyl)-N-((2S,3R)-3-hydroxy-4-(3-(3-(4-methoxyphenylsulfonamido)-8-azabicyclo[3.2.1]octan-8-yl)-1-phenylbutan-2-yl)cyclopentanecarboxamide (Compound 17B),

N-((2S,3R)-4-(4-amino-N-isobutylphenylsulfonamido)-3-hydroxy-1-phenylbutan-2-yl)-3,3-difluorocyclopentanecarboxamide (Compound 18),

3,3-difluoro-N-((2S,3R)-3-hydroxy-4-(N-isobutyl-4-methoxyphenylsulfonamido)-1-phenylbutan-2-yl)cyclopentanecarboxamide (Compound 19),

N-((2S,3R)-4-(3-chloro-4-fluoro-N-isobutylphenylsulfonamido)-3-hydroxy-1-phenylbutan-2-yl)-2-(1-(pyridin-2-yl)cyclohexyl)acetamide (Compound 20),
N-((2S,3R)-3-hydroxy-4-(N-isobutyl-4-methoxyphenylsulfonamido)-l-phenylbutan-2-yl)-2-((1-pyridin-2-yl)cyclohexyl)acetamide (Compound 21),
N-((2S,3R)-3-hydroxy-4-(N-isobutyl-4-methylphenylsulfonamido)-l-phenylbutan-2-yl)-2-((1-pyridin-2-yl)cyclohexyl)acetamide (Compound 22),
N-((2S,3R)-3-hydroxy-4-(N-isobutyl-4-nitrophenylsulfonamido)-l-phenylbutan-2-yl)-2-((1-pyridin-2-yl)cyclohexyl)acetamide (Compound 23),
N-((2S,3R)-4-(4-amino-N-isobutylphenylsulfonamido)-3-hydroxy-l-phenylbutan-2-yl)-2-((1-pyridin-2-yl)cyclohexyl)acetamide (Compound 24),
2-(4,4-difluoro-1-(pyridin-2-yl)cyclohexyl)-N-((2S,3R)-3-hydroxy-4-(N-isobutyl-4-methoxyphenylsulfonamido)-l-phenylbutan-2-yl)acetamide (Compound 25),
N-((2S,3R)-4-(4-fluoro-N-isobutylphenylsulfonamido)-3-hydroxy-l-phenylbutan-2-yl)-1-(methoxymethyl)cyclopentanecarboxamide (Compound 26),
N-((2S,3R)-4-(3-chloro-4-fluoro-N-isobutylphenylsulfonamido)-3-hydroxy-l-phenylbutan-2-yl)-1-(methoxymethyl)cyclopentanecarboxamide (Compound 27),
N-((2S,3R)-3-hydroxy-4-(N-isobutyl-4-methoxyphenylsulfonamido)-l-phenylbutan-2-yl)-1-(methoxymethyl)cyclopentanecarboxamide (Compound 28),
N-((2S,3R)-3-hydroxy-4-(N-isobutyl-4-methoxyphenylsulfonamido)-l-phenylbutan-2-yl)-1-(methoxymethyl)cyclopentanecarboxamide (Compound 29),
N-((2S,3R)-3-hydroxy-4-(N-isobutyl-4-nitrophenylsulfonamido)-1-phenylbutan-2-yl)-1-(methoxymethyl)cyclopentanecarboxamide (Compound 30),
N-((2S,3R)-3-hydroxy-4-(N-isobutyl-4-nitrophenylsulfonamido)-1-phenylbutan-2-yl)-1-(methoxymethyl)cyclopentanecarboxamide (Compound 31),
N-((2S,3R)-3-hydroxy-4-(N-isobutyl-4-nitrophenylsulfonamido)-1-phenylbutan-2-yl)-2-(((S)-tetrahydrofuran-3-yloxy)benzamide (Compound 32),
N-((2S,3R)-4-(4-amino-N-isobutylphenylsulfonamido)-3-hydroxy-l-phenylbutan-2-yl)-2-(((S)-tetrahydrofuran-3-yloxy)benzamide (Compound 33),
N-((2S,3R)-3-hydroxy-4-(N-isobutyl-4-methoxyphenylsulfonamido)-l-phenylbutan-2-yl)-2-(((S)-tetrahydrofuran-3-yloxy)benzamide (Compound 34),
N-((2S,3R)-4-(3-chloro-4-fluoro-N-isobutylphenylsulfonamido)-3-hydroxy-l-phenylbutan-2-yl)-2-(((S)-tetrahydrofuran-3-yloxy)benzamide (Compound 35),
3-chloro-N-((2S,3R)-3-hydroxy-4-(N-isobutyl-4-methoxyphenylsulfonamido)-1-phenylbutan-2-yl)-5-(((S)-tetrahydrofuran-3-yloxy)benzamide (Compound 36).
3-chloro-N-((2S,3R)-3-hydroxy-4-(N-isobutyl-4-nitrophenylsulfonamido)-l-phenylbutan-2-yl)-5-((S)-tetrahydrofuran-3-yloxy)benzamide (Compound 37),
N-((2S,3R)-4-(4-amino-N-isobutylphenylsulfonamido)-3-hydroxy-l-phenylbutan-2-yl)-3-chloro-5-((S)-tetrahydrofuran-3-yloxy)benzamide (Compound 38),
N-((2S,3R)-3-hydroxy-4-(3-chloro-4-fluoro-N-isobutylphenylsulfonamido)-l-phenylbutan-2-yl)-4-methyl-2-((S)-tetrahydrofuran-3-yloxy)benzamide (Compound 39),
N-((2S,3R)-4-(3-chloro-4-fluoro-N-isobutylphenylsulfonamido)-3-hydroxy-l-phenylbutan-2-yl)-4-methyl-2-((S)-tetrahydrofuran-3-yloxy)benzamide (Compound 40),
N-((2S,3R)-4-(3-chloro-4-fluoro-N-isobutylphenylsulfonamido)-3-hydroxy-l-phenylbutan-2-yl)-2-((S)-tetrahydrofuran-3-yloxy)benzamide (Compound 41),
N-((2S,3R)-3-hydroxy-4-(N-isobutyl-4-methoxyphenylsulfonamido)-l-phenylbutan-2-yl)-2-((S)-tetrahydrofuran-3-yloxy)benzamide (Compound 42),
N-((2S,3R)-4-(4-amino-N-isobutylphenylsulfonamido)-3-hydroxy-l-phenylbutan-2-yl)-2-((S)-tetrahydrofuran-3-yloxy)benzamide (Compound 43),
4-fluoro-N-((2S,3R)-3-hydroxy-4-(N-isobutyl-4-methoxyphenylsulfonamido)-l-phenylbutan-2-yl)-2-((S)-tetrahydrofuran-3-yloxy)benzamide (Compound 44),
N-((2S,3R)-4-(3-chloro-4-fluoro-N-isobutylphenylsulfonamido)-3-hydroxy-l-phenylbutan-2-yl)-2-(4-((S)-tetrahydrofuran-3-yloxy)phenyl)acetamide (Compound 45),
N-((2S,3R)-3-hydroxy-4-(N-isobutyl-4-methoxyphenylsulfonamido)-l-phenylbutan-2-yl)-2-(4-((S)-tetrahydrofuran-3-yloxy)phenyl)acetamide (Compound 46),
N-((2S,3R)-4-(4-amino-N-isobutylphenylsulfonamido)-3-hydroxy-l-phenylbutan-2-yl)-2-(4-((S)-tetrahydrofuran-3-yloxy)phenyl)acetamide (Compound 47),
N-((2S,3R)-3-hydroxy-4-(N-isobutyl-4-methoxyphenylsulfonamido)-l-phenylbutan-2-yl)-2-(4-((S)-tetrahydrofuran-3-yloxy)phenyl)acetamide (Compound 48),
1-(2-ethoxyethyl)-N-((2S,3R)-3-hydroxy-4-(N-isobutyl-4-methoxyphenylsulfonamido)-1-phenylbutan-2-yl)cyclopentanecarboxamide (Compound 49),

N-((2S,3R)-4-(4-amino-N-isobutylphenylsulfonamido)-3-hydroxy-l-phenylbutan-2-yl)-l-(2-ethoxyethyl)cyclopentanecarboxamide (Compound 50),

(N-((2S,3R)-3-hydroxy-4-(N-isobutyl-4-methoxyphenylsulfonamido)-l-phenylbutan-2-yl)-2-ethyl-N-((2S,3S)-3-hydroxy-4-(N-isobutyl-4-nitrophenylsulfonamido)-l-phenylbutan-2-yl) tetrahydrofuran-2-carboxamide (Compound 52A),

N-((2S,3R)-4-(4-amino-N-isobutylphenylsulfonamido)-3-hydroxy-l-phenylbutan-2-yl)-2-ethyltetrahydrofuran-2-carboxamide (Compound 52B),

N-((2S,3R)-3-hydroxy-4-(N-isobutyl-4-methoxyphenylsulfonamido)-l-phenylbutan-2-yl)-2-(1-ethylcyclopentyl)methyl (2S,3R)-3-hydroxy-4-(N-isobutyl-4-methoxyphenylsulfonamido)-l-phenylbutan-2-ylcarbamate (Compound 53),

N-((2S,3R)-3-hydroxy-4-(N-isobutyl-4-methoxyphenylsulfonamido)-l-phenylbutan-2-yl)-2-(S)-tetrahydrofuran-3-yloxy)propanamide (Compound 54),

N-((2S,3R)-3-hydroxy-4-(N-isobutyl-4-methoxyphenylsulfonamido)-l-phenylbutan-2-yl)-1-oxaspiro[4.4]nonane-7-carboxamide (Compound 55),

N-((2S,3R)-4-(3-chloro-4-fluoro-N-isobutylphenylsulfonamido)-3-hydroxy-l-phenylbutan-2-yl)-1-oxaspiro[4.4]nonane-7-carboxamide (Compound 56),

N-((2S,3R)-4-(4-amino-N-isobutylphenylsulfonamido)-3-hydroxy-l-phenylbutan-2-yl)-l-oxaspiro[4.4]nonane-7-carboxamide (Compound 57),

N-((2S,3R)-4-(4-fluoro-N-isobutylphenylsulfonamido)-2-((S)-tetrahydrofuran-3-yloxy)acetamide (Compound 60),

(2-ethyltetrahydrofuran-2-yl)methyl (2S,3R)-3-hydroxy-4-(N-isobutyl-4-methoxyphenylsulfonamido)-l-phenylbutan-2-ylcarbamate (Compound 61),

1-(2-ethoxyethyl)-N-((2S)-3-hydroxy-4-((IR,5S)-3-(4-methoxyphenylsulfonamido)-8-azabicyclo[3.2.1]octan-8-yl)-1-phenylbutan-2-yl)cyclopentanecarboxamide (Compound 62).
N-((2S,3S)-3-hydroxy-4-(N-isobutyl-4-methoxyphenylsulfonamido)-1-phenylbutan-2-yl)- 1-(methoxymethyl)cyclopentanecarboxamide (Compound 63),
4,4-dimethyl-2-oxotetrahydrofuran-3-yl (2R,3S)-4-(4-amino-N-isobutylphenylsulfonamido)-3-hydroxy-1-phenylbutan-2-ylcarbamate (Compound 64),
4,4-dimethyl-2-oxotetrahydrofuran-3-yl (2R,3S)-4-(N-cyclopentyl-4-methoxyphenylsulfonamido)-3-hydroxy-1-phenylbutan-2-ylcarbamate (Compound 65),
(R)-4,4-dimethyl-2-oxotetrahydrofuran-3-yl (2S,3R)-3-hydroxy-4-(4-(2R,3S)-4-amino-N-isobutylphenylsulfonamido)piperidin-1-yl)-1-phenylbutan-2-ylcarbamate (Compound 66),
(R)-tetrahydrofuran-3-yl (2S,3R)-3-hydroxy-4-(4-(2R,3S)-4-amino-N-isobutylphenylsulfonamido)piperidin-1-yl)-1-phenylbutan-2-ylcarbamate (Compound 67),
1-ethyl-N-((2S,3R)-3-hydroxy-4-(4-(2R,3S)-4-amino-N-isobutylphenylsulfonamido)piperidin-1-yl)-1-phenylbutan-2-yl)cyclopentanecarboxamide (Compound 68),
(R)-tetrahydrofuran-3-yl (2S)-3-hydroxy-4-((IR,5S)-3-(4-methoxyphenylsulfonamido)-8-azabicyclo[3.2.1]octan-8-yl)-1-phenylbutan-2-ylcarbamate (Compound 69),
N-((2S)-3-hydroxy-4-((IR,5S)-3-(4-methoxyphenylsulfonamido)-8-azabicyclo[3.2.1]octan-8-yl)-1-phenylbutan-2-yl)- 1-(methoxymethyl)cyclopentanecarboxamide (Compound 70),
N-((2S,3S)-3-hydroxy-4-(N-isobutyl-4-methoxyphenylsulfonamido)-1-phenylbutan-2-yl)- 1-(methoxymethyl)cyclopentanecarboxamide (Compound 71),
Example 73: Preparation of (3-ethyloxetan-3-yl)
Methyl (2S)-3-hydroxy-4-(N-isobutyl-4-nitrophenylsulfonamido)-1-phenylbutan-2-ylcarbamate (Compound 72),
(3-ethyloxetan-3-yl) methyl (2S)-4-(4-amino-N-isobutylphenylsulfonamido)-3-hydroxy-1-phenylbutan-2-ylcarbamate (Compound 73),
(3-methyloxetan-3-yl)methyl (2S,3R)-4-(4-amino-N-isobutylphenylsulfonamido)-3-hydroxy-1-phenylbutan-2-ylcarbamate (Compound 74).
(2-ethyltetrahydrofuran-2-yl)methyl (2S,3R)-4-(4-amino-N-isobutylphenylsulfonamido)-3-hydroxy-1-phenylbutan-2-ylcarbamate (Compound 75),

(2S)-3-hydroxy-4-(N-isobutyl-4-methoxyphenylsulfonamido)-1-phenylbutan-2-yl 2-((R)-tetrahydrofuran-3-yloxy)acetate (Compound 76),

N-((2S)-4-(N-(2-(1H-indol-2-yl)ethyl)-4-aminophenylsulfonamido)-3-hydroxy-1-phenylbutan-2-yl) 1-(methoxymethyl)cyclopentanecarboxamide (Compound 77),

N-((2S)-4-(4-amino-N-cyclopentylphenylsulfonamido)-3-hydroxy-1-phenylbutan-2-yl)-1-ethylcyclopentanecarboxamide (Compound 78),

N-((2S)-4-(4-amino-N-cyclopentylphenylsulfonamido)-3-hydroxy-1-phenylbutan-2-yl)-1-ethylcyclopentanecarboxamide (Compound 79),

(N-((2S,3R)-4-(4-amino-N-isobutylphenylsulfonamido)-3-hydroxy-1-phenylbutan-2-yl)-3-methyl-5-(tetrahydrofuran-3-yloxy)benzamide (Compound 81),

N-((2R,3S)-4-(N-cyclopentyl-4-methoxyphenylsulfonamido)-3-hydroxy-1-phenylbutan-2-yl)-1-(methoxymethyl)cyclopentanecarboxamide (Compound 82),

N-((2R,3S)-4-(N-cyclopentyl-4-methoxyphenylsulfonamido)-3-hydroxy-1-phenylbutan-2-yl)-1-ethylcyclopentanecarboxamide (Compound 83), or pharmaceutically acceptable salts, solvates, stereo isomers, including hydrates and prodrugs of compounds are also contemplated.

The compounds and pharmaceutical compositions described herein are useful in the treatment of diseases, conditions and/or disorders mediated by, for example, viral infections, more particularly for treating HIV infection.

The present invention further provides a method of treating a disease, condition and/or disorder mediated by, for example, viral infections, more particularly HIV infection in a subject in need thereof by administering to the subject one or more compounds described herein in an amount effective to treat that infection.

**Detailed Description of the Invention**

The present invention relates to novel carboxamide compounds and, a composition for inhibiting Human Immunodeficiency Virus (HIV) and process for making the compounds.
The following definitions apply to the terms as used herein:

The terms "halogen" or "halo" includes fluorine, chlorine, bromine, or iodine.

The term "alkyl" refers to a straight or branched hydrocarbon chain radical consisting solely of carbon and hydrogen atoms, containing no unsaturation, having from one to eight carbon atoms, and which is attached to the rest of the molecule by a single bond, e.g., methyl, ethyl, n-propyl, 1-methylethyl (isopropyl), n-butyl, n-pentyl, and 1,1-dimethylethyl (t-butyl).

The term "alkenyl" refers to an aliphatic hydrocarbon group containing a carbon-carbon double bond and which may be a straight or branched chain having from 2 to about 10 carbon atoms, e.g., ethenyl, 1-propenyl, 2-propenyl (allyl), isopropenyl, 2-methyl-1-propenyl, 1-butenyl, and 2-butenyl.

The term "haloalkyl" is used to denote a group comprised of an alkyl group substituted with halogen atom, where alkyl group is as defined above and halogen is used to denote fluorine, chlorine, bromine or iodine, an example of such group is trifluoromethyl, difluoromethyl.

The term "acyl group" is used to denote a linear or branched aliphatic acyl group (preferably a C_{1-4} alkanoyl group) or an aromatic acyl group, which contains 2 to 10 carbon atoms. Examples include an acetyl group, a propionyl group, a pivaloyl group, a butyryl group, an isobutyryl group, a valeryl group and a benzoyl group, with an acetyl group being preferred.

The term "alkoxy group" is used to denote a linear or branched alkoxy group containing 1 to 6 carbon atoms. Preferred are C_{1-4} alkoxy groups including a methoxy group, an ethoxy group, a propoxy group, an isopropoxy group, an n-butoxy group, an isobutoxy group and a tert-butoxy group.

The term "alkoxycarbonyl group" is used to denote a structure composed of a linear or branched C_{1-5} alkoxy group and a carbonyl group. Preferred are C_{2-5} alkoxy carbonyl groups including a methoxycarbonyl group, an ethoxycarbonyl group, a propoxycarbonyl group, an isopropoxycarbonyl group and a butoxycarbonyl group. Among them, a methoxycarbonyl group is preferred.

The term "cycloalkyl" denotes a non-aromatic mono or multicyclic ring system of from 3 to about 12 carbon atoms, such as cyclopropyl, cyclobutyl, cyclopentyl, and cyclohexyl. Examples of multicyclic cycloalkyl groups include,
but are not limited to, perhydronaphthyl, adamantyi and norbornyl groups, bridged cyclic groups and spirobicyclic groups, e.g., spiro (4,4) non-2-yl.

The term "cycloalkylalkyl" refers to a cyclic ring-containing radical having from 3 to about 8 carbon atoms directly attached to an alkyl group. The cycloalkylalkyl group may be attached to the main structure at any carbon atom in the alkyl group that results in the creation of a stable structure. Non-limiting examples of such groups include cyclopropylmethyl, cyclobutylethyl, and cyclopentylethyl.

The term "cycloalkenyl" refers to a cyclic ring-containing radical having from 3 to about 8 carbon atoms with at least one carbon-carbon double bond, such as cyclopropenyl, cyclobutenyl, and cyclopentenyl.

The term "cyclalkyloxy" group is used to denote a cyclic ring-containing radical having from 3 to about 8 carbon atoms directly attached to an Oxygen atom. The cycloalkyloxy group may be attached to the main structure at Oxygen atom that results in the creation of a stable structure. Non-limiting examples of such groups include cyclopropyloxy, cyclobutyloxy, and cyclopentyloxy.

The term "aryl" refers to an aromatic radical having from 6 to 14 carbon atoms such as phenyl, naphthyl, tetrahydroanaphthyl, indanyl, and biphenyl.

The term "arylalkyl" refers to an aryl group as defined above directly bonded to an alkyl group as defined above, e.g., -CH2C6H5 and -C2H5C6H5.

"Substituted" refers to 1-3 substituents on the same position or on different positions with the same groups or different groups.

"Alkynyl" refers to alkynyl groups having from 2 to 6 carbon atoms and having at least one alkynyl saturation, for example acetylenyl, and propargyl.

"Carbonyloxy" refers to a group such as -C(0)O.

"Sulfonyl", "sulfonyloxy" refers to the groups -S02R6, where R6 is selected from the groups consisting of alkyl, aryl, heteroaryl, heterocyclyl.

The terms "heterocyclyl" and "heterocyclic ring" refer to a stable 3- to 15-membered ring radical which consists of carbon atoms and from one to five heteroatoms selected from nitrogen, phosphorus, oxygen and sulfur. For purposes of this invention, the heterocyclic ring radical may be a monocyclic, bicyclic or tricyclic ring system, which may include fused, bridged or spiro ring systems, and the nitrogen, phosphorus, carbon, oxygen or sulfur atoms in the heterocyclic ring radical may be optionally oxidized to various oxidation states. In addition, the
nitrogen atom may be optionally quaternized; and the ring radical may be partially or fully saturated (i.e., heterocyclic or heteroaryl). Examples of such heterocyclic ring radicals include, but are not limited to, azetidinyl, acridinyl, carbazolyl, cinnolinyl, indolizinyl, naphthyridinyl, perhydroazepinyl, phenazinyl, phenothiazinyl, phenoxyazinyl, phthalazinyl, pyridyl,pteridinyl, purinyl, quinazolyl, quinoxalinyl, quinolinyl, isoquinolinyl, tetrazolyl, imidazolyl, tetrahydroisouinolyl, piperidinyl, piperezinyl, 2-oxoazepinyl, 2-oxoazepinyl, 2-oxopyrrolidinyl, 2-oxoazepinyl, azepinyl, pyrrolyl, 4-piperidonyl, pyrrolidinyl, pyrazinyl, pyrimidinyl, pyridazinyl, oxazolyl, oxazolynyl, oxazolidinyl, triazolyl, thiazolyl, isoxazolyl, isoxazolidinyl, mo\(\text{THO}\)holinyl, thiazolyl, thiazolinyl, thiazolindinyl, isoazolyl, quinclidinyl, isothiazolindinyl, indolyl, isoindolyl, indolynyl, isoindolynyl, octahydroindolyl, octahydroisoindolyl, quinolyl, isoquinolnyl, decahydroisoquinol, benzimidazolyl, thiadiazolyl, benzothiazolyl, benzooxazolyl, furyl, tetrahydrofuryl, tetrahydrofuryl, thienyl, benzothienyl, thiamorpholinyl, thiamorpholynyl sulfoxide, thiamorpholynyl sulfone, dioxaphospholanyl, oxadiazolyl. The heterocyclic ring radical may be attached to the main structure at any heteroatom or carbon atom that results in the creation of a stable structure.

The term "heterocyclalkyl" refers to a heterocyclic ring radical directly bonded to an alkyl group. The heterocyclalkyl radical may be attached to the main structure at any carbon atom in the alkyl group that results in the creation of a stable structure.

The term "heterocyclaloxy group" is used to denote a heterocyclic ring-containing radical having from 3 to about 8 carbon atoms directly attached to an Oxygen atom. The heterocyclaloxy group may be attached to the main structure at Oxygen atom that results in the creation of a stable structure. Non-limiting examples of such groups include tetrahydrofuryl, pyrrolidinyl, and piperidinyl.

The term "heteroaryl" refers to an aromatic heterocyclic ring radical. The heteroaryl ring radical may be attached to the main structure at any heteroatom or carbon atom that results in the creation of a stable structure.

The term "heteroarylalkyl" refers to a heteroaryl ring radical directly bonded to an alkyl group. The heteroarylalkyl radical may be attached to the main structure at any carbon atom in the alkyl group that results in the creation of a stable structure.

Unless otherwise specified, the term "substituted" as used herein refers to substitution with any one or any combination of the following substituents: hydroxy,
halogen, carboxyl, cyano, nitro, oxo (=0), thio (=S), substituted or unsubstituted alkyl, haloalkyl, substituted or unsubstituted alkoxy, substituted or unsubstituted alkenyl, substituted or unsubstituted alkynyl, substituted or unsubstituted arylalkyl, substituted or unsubstituted aryl, substituted or unsubstituted arylalkyl, substituted or unsubstituted cycloalkyl, substituted or unsubstituted cycloalkenylalkyl, substituted or unsubstituted cycloalkenyl, substituted or unsubstituted amino, substituted or unsubstituted aryl, substituted or unsubstituted heteroaryl, substituted or unsubstituted heterocyclylalkyl ring, substituted or unsubstituted heteroarylalkyl, substituted or unsubstituted heterocyclic ring, substituted or unsubstituted guanidine, COOR \ -C(0)R \ -C(S)R^x, -C(0)NR^xR^y, -C(0)ONR^xR^y, -NR^xCONR^yR^z, -N(R^x)SOR^y, -N(R^x)S0\_2R^y, -(=N-N(R^x)R^y), -NR^xC(0)OR^y, -NR^xR^y, -NR^xC(0)R^y, -NR^xC(S)R^y, -NR^xC(S)NR^yR^z, -SONR^xR^y, -S0\_2NR^xR^y, -OR^x, -OR^xC(0)NR^yR^z, -OR^xC(0)OR^y, -OC(0)R^x, -OC(0)NR^xR^y, -R^xNR^yC(0)R^z, -R^xOR^y, -R^xC(0)OR^y, -R^xC(0)NR^yR^z, -R^xC(0)R^y, -R^xOC(0)R^y, -SR^x, -SOR^x, -S0\_2R^x, and -ON0\_2, wherein R^x, R^y and R^z are independently selected from hydrogen, substituted or unsubstituted alkyl, haloalkyl, substituted or unsubstituted alkoxy, substituted or unsubstituted alkenyl, substituted or unsubstituted alkynyl, substituted or unsubstituted aryl, substituted or unsubstituted arylalkyl, substituted or unsubstituted cycloalkyl, substituted or unsubstituted cycloalkenyl, substituted or unsubstituted amino, substituted or unsubstituted aryl, substituted or unsubstituted heteroaryl, substituted or unsubstituted heterocyclylalkyl ring, substituted or unsubstituted heteroarylalkyl, or substituted or unsubstituted heterocyclic ring. The substituents in the aforementioned "substituted" groups cannot be further substituted. For example, when the substituent on "substituted alkyl" is "substituted aryl", the substituent on "substituted aryl" cannot be "substituted alkenyl".

The term "prodrug" means a compound that is transformed in vivo to yield a compound of Formula (I) (1A) or (IB) or a pharmaceutically acceptable salt, hydrate or solvate of the compound. The transformation may occur by various mechanisms, such as through hydrolysis in blood. A discussion of the use of prodrugs is provided by T. Higuchi and W. Stella, "Pro-drugs as Novel Delivery Systems," Vol. 14 of the A.C.S. Symposium, and in Bioreversible Carriers in Drug Design, ed. Edward B. Roche, American Pharmaceutical Association and Pergamon Press, 1987.

The term "treating" or "treatment" of a state, disease, disorder or condition includes:
(1) preventing or delaying the appearance of clinical symptoms of the state, disease, disorder or condition developing in a subject that may be afflicted with or predisposed to the state, disease, disorder or condition but does not yet experience or display clinical or subclinical symptoms of the state, disease, disorder or condition;

(2) inhibiting the state, disease, disorder or condition, i.e., arresting or reducing the development of the state, disease, disorder or condition or at least one clinical or subclinical symptom thereof; or

(3) relieving the state, disease, disorder or condition, i.e., causing regression of the state, disease, disorder or condition or at least one of its clinical or subclinical symptoms.

The benefit to a subject receiving treatment is either statistically significant or at least perceptible to the subject or to the physician.

The term "subject" includes, for example, mammals (especially humans), and other animals,

A "therapeutically effective amount" means, for example, the amount of a compound that, when administered to a subject for treating a state, disease, disorder or condition, is sufficient to effect such treatment. The "therapeutically effective amount" will vary depending on the compound, the state, disease, disorder or condition and its severity and the age, weight, physical condition and responsiveness of the subject receiving treatment.

The compound of the invention may form salts. Non-limiting examples of pharmaceutically acceptable salts forming part of the invention include salts derived from inorganic/organic acids or bases and amino acids salts. Certain compounds of the invention are capable of existing in stereoisomeric forms (e.g. diastereomers and enantiomers). With respect to the overall compounds described by the Formula (I), Formula (IA) or Formula (IB), the invention extends to these stereoisomeric forms and to mixtures thereof. To the extent prior art teaches synthesis or separation of particular stereoisomers, the different stereoisomeric forms of the invention may be separated from one another by the method known in the art, or a given isomer may be obtained by stereospecific or asymmetric synthesis. Tautomeric forms and mixtures of compounds described herein are also contemplated.

Pharmaceutically acceptable solvates includes, for example, hydrates and other solvents of crystallization (such as alcohols). The compounds of the present
invention may form solvates with low molecular weight solvents by methods known in the art.

**Pharmaceutical Compositions**

The pharmaceutical compositions provided in the invention include at least one compound described herein and at least one pharmaceutically acceptable excipient (such as a pharmaceutically acceptable carrier or diluent). Preferably, the contemplated pharmaceutical compositions include a compound(s) described herein in an amount sufficient to treat viral infection in a subject.

The subjects contemplated include, for example, a living cell and a mammal, including human beings. The compound of the present invention may be associated with a pharmaceutically acceptable excipient (such as a carrier or a diluent) or be diluted by a carrier.

Examples of suitable carriers include, but are not limited to, water, salt solutions, alcohols, polyethylene glycols, polyhydroxyethoxylated castor oil, peanut oil, olive oil, gelatin, lactose, terra alba, sucrose, dextrin, magnesium carbonate, sugar, cyclodextrin, amylose, magnesium stearate, talc, gelatin, agar, pectin, acacia, stearic acid or lower alkyl ethers of cellulose, silicic acid, fatty acids, fatty acid amines, fatty acid monoglycerides and diglycerides, pentaerythritol fatty acid esters, polyoxyethylene, hydroxymethylcellulose and polyvinylpyrrolidone.

The carrier or diluent may include a sustained release material, such as, for example, glycercyl monostearate or glycercyl distearate, alone or mixed with a wax.

The pharmaceutical composition may also include one or more pharmaceutically acceptable auxiliary agents, wetting agents, emulsifying agents, suspending agents, preserving agents, salts for influencing osmotic pressure, buffers, sweetening agents, flavoring agents, colorants, or any combination of the foregoing. The pharmaceutical composition of the invention may be formulated so as to provide quick, sustained, or delayed release of the active ingredient after administration to the subject by employing procedures known in the art.

The pharmaceutical compositions described herein may be prepared, e.g., as described in *Remington: The Science and Practice of Pharmacy*, 20th Ed., 2003 (Lippincott Williams & Wilkins).

The pharmaceutical compositions may be, for example, capsules, tablets, aerosols, solutions, suspensions or products for topical application.
The route of administration may be any route which effectively transports the active compound to the appropriate or desired site of action. Suitable routes of administration include, but are not limited to, oral, nasal, pulmonary, buccal, subdermal, intradermal, transdermal, parenteral, rectal, depot, subcutaneous, intravenous, intraurethral, intramuscular, intranasal, ophthalmic (such as with an ophthalmic solution) or topical (such as with a topical ointment). The oral route is preferred.

Solid oral formulations include, but are not limited to, tablets, capsules (soft or hard gelatin), dragees (containing the active ingredient in powder or pellet form), troches and lozenges. Tablets, dragees, or capsules having talc and/or a carbohydrate carrier or binder or the like are particularly suitable for oral application. Preferable carriers for tablets, dragees, or capsules include lactose, cornstarch, and/or potato starch. A syrup or elixir can be used in cases where a sweetened vehicle can be employed.

A typical tablet that may be prepared by conventional tabletting techniques may contain: (1) Core: Active compound (as free compound or salt thereof), colloidal silicon dioxide (Aerosil®), microcrystalline cellulose (Avicel®), modified cellulose gum (Ac-Di-Sol®), and magnesium stearate; (2) Coating: HPMC, Mywacett 9-40 T and acetylated monoglyceride.

Liquid formulations include, but are not limited to, syrups, emulsions, soft gelatin and sterile injectable liquids, such as aqueous or non-aqueous liquid suspensions or solutions.

For parenteral application, particularly suitable are injectable solutions or suspensions, preferably aqueous solutions with the active compound dissolved in polyhydroxylated castor oil.

Methods of screening

Anti HIV activity and cytotoxicity of compounds of present invention can be measured in parallel by following the methods published in the literature.

The cytotoxic effect of compounds can be analyzed by measuring the proliferation of cells using the 3-(4,5-Dimethylthiazol-2-yl)-2,5-diphenyl tetrazlium bromide (MTT) staining. Cells (5 x 10^3 cells /well) will be incubated in in 96 well plates in the presence or absence of compounds. At the end of treatment, 20µl of MTT (5mg/ml in PBS) will be added to each well and incubated for an additional 4 hours at 37°C. The purple -blue MTT formazan precipitate will be dissolved in a
triplex reagent containing 10% SDS, 5% isobutanol and 10 mmol/lit HCl. The activity of mitochondria, reflecting cellular growth and viability, will be evaluated by measuring the optical density at 570 nm on micro titer plate.

Action of compounds on replication of HIV in Sup-T1 cells can be determined by the method published by Roda Rani et al., 2006 (Archives of Biochemistry and Biophysics, Volume 456, Issue 1, 1 December 2006, Pages 79-92).

Briefly, 1x10⁶ Sup-T1 cells with 100% cell viability will be seeded in RPMI 1640, 0.1% FBS four 12 well plates. Increasing concentrations of Epap-1 peptides will be added to the cells and will be infected with HIV1 each at final concentration of virus equivalent to 2 ngof p24 per ml. The infected cells will be incubated at 37 C and 5% C02 incubator for 2 hours. After 2hrs the cells will be pelleted at 350 g for 10 min, supernatant will be discarded and cell will be held with RPMI 1640 containing 10% FBS. The cells will be resuspended in the same medium with increasing concentrations of Epap-1 peptides and will be incubated for 96 hours. The cells will be supplemented with peptides at every 24 hours. The supematants will be collected after 96 hours and analyzed using P24 antigen capture assay kit (SAIC Fredrick). The infection in the absence of Epap-1 will be considered to be 0% inhibition Azidothymidine (AZT) will be taken as positive control.

Action of compound on virus entry and quantification of virus entered can be done in terms of GFP expression by the following the methods published J. Virol. 72, 6988 (1998) by in Cecilia et al., and Analytical Biochemistry Volume 360, Issue 2, 15 January 2007, Pages 315-317 (Dyavar S. and Debashis Mitra).

Briefly, Cells will be seeded in to wells of 24 well plates 1 day prior to the experiment. The cells will be transfected with Tat-reporter. The virus inoculum will be adjusted to 1,000-4,000 TCID 50/ ml in assay medium (DMEM,10%FCS,glutamine and antibiotics ),50 μl aliquots will be incubated with serial dilutions of compounds (50 μl ) for 1hr at 37 C. The reporter expression will be quantified at appropriate time calculated inhibitory doses referrers to the concentration of these agents in this preincubation mixture.


Methods of Treatment

The present invention provides compounds and pharmaceutical formulations thereof that are useful in the treatment of diseases, conditions and/or disorders mediated by viral infections. The connection between therapeutic effect and antiviral is illustrated. For example, PCT publication Nos. WO 01/07646, WO 01/65957, or WO 03/037908; US publication Nos. US 4,598,095 or US 2002/0068757; EP publication Nos. EP0989862 or EP 0724650; Bioorganic & Medicinal Chemistry Letters, 16, (6), 1712-1715, 2006; and references cited therein, all of which are incorporated herein by reference in their entirety and for the purpose stated.

The invention further provides a method of treating a disease, condition and/or disorder mediated by viral infections in a subject in need thereof by administering to the subject a therapeutically effective amount of a compound or a pharmaceutical composition of the present invention.

Diseases, conditions, and/or disorders that are mediated by viral infections are believed to include, but are not limited to, HIV infection, a retroviral infection genetically related to HIV, AIDS, or inflammatory disease,
The compounds of the present invention can obtain more advantageous effects than additive effects in the prevention or treatment of the above diseases when using suitably in combination with the above drugs. Also, the administration dose can be decreased in comparison with administration of either drug alone, or adverse effects of co administrated drugs other than antiviral can be avoided or declined.

Methods of Preparation

Procedures for preparing the compounds of formula (I) are set forth below. It should be noted that the general procedure is shown as it relates to preparation of compounds having unspecified stereochemistry. However, the same procedure is applicable to prepare compounds with specific stereo chemistry. For example, where in the absolute stereochemistry about the hydroxyl group is designated as (R) and carbon substituted with benzyl group is (S). However, such procedures are generally applicable to those compounds of opposite configurations or of same configurations at the different carbon centers for example, where the stereochemistry about hydroxyl is (S) and carbon substituted with benzyl group is (R). In addition the compounds having the (R) stereochemistry can be utilized to produce those having (S) stereo chemistry. For example, a compound having the (R) stereochemistry can be inverted to the (S) stereochemistry using well known methods.

The compounds described herein may be prepared by techniques known in the art. In addition, the compounds described herein may be prepared by following the reaction sequence as depicted in Scheme-1. Further, in the following schemes, where specific bases, acids, reagents, solvents, coupling agents, etc., are mentioned, it is understood that other bases, acids, reagents, solvents, coupling agents etc., known in the art may also be used and are therefore included within the present invention. Variations in reaction conditions, for example, temperature and/or duration of the reaction, which may be used as known in the art, are also within the scope of the present invention. All the stereo isomers of the compounds in these schemes, unless otherwise specified, are also encompassed within the scope of this invention.
The compounds of present invention represented by formula (I) can be prepared by using the following general procedure as described in Scheme 1. Methods for conversion of vicinal diol to an epoxide are well established, and can be prepared by modifying the reported procedures (Tetrahedron Lett. 1995, 36, 3019-3022; Angew. Chem. Int. Ed. Engl. 1986, 25, 835-839; Bioorg. Med. Chem. Lett. 1996, 6, 1117-1122). Practical process for this transformation was reported in Organic Process Research & Development 2002, 6, 323-328. Stereoselective synthesis of anti-N-protected 3-amino-1,2-epoxides are described in J. Org. Chem. 2009, 74, 5975-5982. (2S,3S)-1,2-epoxy-3-amino-4-phenylbutane was prepared subjecting (2S, 3S)-halo-2-hydroxy-3-amino-4-phenylbutane derivatives to ring closure under alkaline conditions as described in WO 96/17821 and Journal of Organic Chemistry, Volume 59, 365, 1994.

Appropriate cycloalkyl carboxylic acid of compounds formula 1 can be converted to corresponding esters of compounds of formula 3 by reacting with alcohol of compounds of formula 2. The esters of compounds of formula 3 can reacted with halides of compounds of formula 4 [RI (where in R is alkyl, aryl, heteroaryl, or aralkyl)] to give the compounds of formula 5 in the presence of LDA/THF solution at around -70 °C, the temperature then may be allowed to rise slowly to room temperature. The compounds of formula 5 can be converted to the
intermediates of acid compounds of formula 6 by ester hydrolysis in the presence of a basic medium such as, for example, solutions of lithium hydroxide, sodium or potassium hydroxide or the like.

Also the intermediates of formula 6 (wherein R is H, X=O- or 0 (CR2)m-.

L=(CH2)m or (CH)mR) can be synthesized by reacting appropriate cycloalkyl-hydroxy compounds with a halo substituted compounds of hal-L-COOEt in the presence of base, for example, potassium or cesium carbonate or the like in a solvent such as acetone, acetonitrile, dimethyl formamide or the like.

The N-protected amino epoxide compounds of of formula 7 with specific stereochemistry are commercially available or can be prepared by known methods (Fassler A et al. in Bioorg. Med. Chem. Lett., 1993, 3, 2837-2842). All four possible stereoisomers can be separated according to the authors by chiracel OD analytical column. The N-protected amino epoxide compounds of formula 7 can be reacted with the amino compounds of formula (RN2(H)Z1)H (8) to give the N-protected amino alcohol compounds of formula 9 in presence of a suitable solvent like protic or non protic such as, isopropanol, methanol, ethanol or the like or ether such as, foe example tetrahydrofuran, dioxane or the like or toluene, dimethyl formamide, dimethylsulfoxide, or mixtures thereof in the conditions, for example, over a wide range of temperatures (from about 10-100 °C) or at a temperature which the solvent begins to reflux. The N-protected amino alcohol compounds of formula 9 can be reacted with the compounds of sulfonyl chloride (R2SO2Cl) of formula 10 to give the sulfonamide compounds of formula 11 in presence of acid scavengers, for example, triethylamine, pyridine or the like in the suitable solvent, for example methylene chloride, tetrahydrofuran or the like. The sulfonamide compounds of formula 11 can be deprotected into the amine compounds of formula 12 under the conditions which should not affect the remaining part of the molecule except BOC protected Nitrogen. These methods are well known in the literature, for example, acid hydrolysis or the like. In acid hydrolysis, acid can be organic or in-organic acid, for example, HCl, trifluoroacetic acid or the like in a suitable solvent, for example, dioxane, methylenechloride, ethylacetate or the like.

Finally, the intermediates of formula 6 can be reacted with the free amine of compounds of formula 12 to give the final compounds of formula (I), either by converting intermediates of formula 6 to acid chloride in the solvent, such as methylene chloride or the like by using one of the halogenating agent such as,
thionyl chloride or the like or an activating agent such as, DSC or the like either at room temperature or refluxing temperature of the solvent.

In other methods, the compounds of formula (I) can be synthesized by reacting the compounds of formula 6 with the compounds of formula 12 in the presence of coupling reagent for example, 1-hydroxybenzotrazolehydrate(HOBT), 0-benzotrazol-1-yl-N,N,N',N'-tetramethyluroniumhexafluorophosphate(HBTU), O-benzotrazol-1-yl-N,N,N',N'-tetramethyluronium tetrafluoroborate(TBTU), bis(2-oxo-3-oxazolidenyl)phosphenic chloride(BOPCl), benzotrazol-1-yloxytris(dimefhylamino)phosphonium hexafluorophosphate (BOP) and a base for example, triethylamine, diisopropylethylamine, sodiumcarbonate, potassiumcarbonate, or the like in the solvents, for example, ethylactate, dichloromethane, acetonitnle, tetrahydrofuran, dioxane or mixtures thereof with conditions at about room temperature by stirring for a period of about 30 minutes to about 72 hours.

**Experimental**

The present invention is further illustrated by the following examples, which are not to be construed in any way as imposing limitations upon the scope of this disclosure, but rather are intended to be illustrative only.

**Intermediates**

Intermediate 1: Preparation of 1-ethylcyclohexanecarboxylic acid:

![Chemical Structure](image)

**Step 1: Synthesis of ethyl cyclohexanecarboxylate:**

To a cyclohexanecarboxylic acid (about 10 g) in ethanol (150 ml), sulphuric acid (about 8.64 ml) was added and the reaction was refluxed about for 6 hours at about 80°C. Upon completion of the reaction (monitored by TLC), ethanol was evaporated under reduced pressure. The residue was washed with water, neutralized with sat. NaHCO₃ and extracted with DCM then the organic layer was dried over Na₂SO₄ and concentrated under reduced pressure. The resulting residue was purified
by silica gel column chromatography using 5% ethyl acetate in hexane as eluent to furnish the title compound (12 g) as a light yellow liquid. $^1$H NMR (300 MHz, CDCl$_3$): 1.22-1.26 (m, 6H); 1.40-1.51 (m, 2H); 1.55-1.98 (m, 5H); 2.23-2.31 (m, 1H); 4.07-4.14 (m, 2H); ES Mass: (100%), [M+1] 157.

Step 2: Synthesis of ethyl 1-ethylcyclohexanecarboxylate:

Di-isopropyl amine (about 6.5 ml) in dry THF (25 ml) was cooled to -10 °C then n-butyl lithium (about 23 ml) was added to this mixture, slowly drop wise under nitrogen atmosphere at about -10 °C for about 45 minutes. Reaction mixture was cooled to about -75°C. Ethyl cyclohexanecarboxylate (step 1, about 5g in 30 ml THF) was added and stirred the reaction at same temp for about 30 minutes, then increased the reaction temperature to -35 °C and stirred for 45 minutes and again cooled to about -75°C then ethyl chloride (about 4.4 ml in 20 ml THF) was added drop wise and the reaction was slowly allowed to return to room temperature and stirred for about 12 hours. After completion of the reaction (monitored by TLC), reaction mixture was quenched with saturated ammonium chloride and extracted with ethyl acetate. The organic layer was washed with sat. NaHCO$_3$, followed by brine sol, dried over Na$_2$SO$_4$ and concentrated under reduced pressure. The residue was purified by silica gel column chromatography using 5% ethyl acetate in hexane as eluent to furnish the title compound (2.2 g) as light yellow colour liquid. $^1$H NMR (300 MHz, CDCl$_3$): 0.77-0.82 (m, 3H); 1.16-1.39 (m, 8H); 1.45-1.65 (m, 5H); 2.04-2.09 (m, 2H); 4.11-4.18 (m, 2H); ES Mass: (100%), [M+1] 185.

Step 3: Synthesis of 1-ethylcyclohexanecarboxylic acid:

To a stirred solution of ethyl 1-ethylcyclohexanecarboxylate (step 2, about 3.0 g) in ethanol, potassium hydroxide (about 2.9 g) was added and refluxed for 6 hours at 80 °C. Completion of the reaction (monitored by TLC), reaction mixture was evaporated under reduced pressure. The residue was taken in water, acidified with aq HC1 and extracted with ethyl acetate. The organic layer was washed with water, followed by brine the organic layer dried over Na$_2$SO$_4$ and concentrated under reduced pressure. The residue was purified by silica gel column chromatography
using 5% ethyl acetate in hexane as eluent to furnish the title compound (2 g) as a light yellow liquid. 1H NMR (300 MHz, CDCl3): 1.07-1.52 (m, 8H); 1.55-1.94 (m, 7H); 12.02 (s, 1H); ES Mass: (100%), [M+H] 157.

5 Intermediate-2: Preparation of (S)-2-(tetrahydrofuran-3-yl)oxy)acetic acid:

Step 1: Synthesis of ethyl 2-((S)-tetrahydrofuran-3-yl)oxy)acetate:

Sodium hydride (4 g) was taken in THF (75 ml) and cooled to 0°C, to this (S)-tetrahydrofuran-3-ol (about 5 g) was added and stirred for about 1 hour at 0°C, then ethyl 2-bromoacetate (about 10.1 ml) was added drop wise at 0°C and the reaction was allowed to return to room temperature, and the stirring was continued for 12 hours. Completion of the reaction monitored by TLC then reaction mixture was quenched with water and extracted with ethyl acetate, the organic layer was dried over Na2SO4 and concentrated under reduced pressure. The residue was purified by silica gel column chromatography using 5% ethyl acetate in hexane as eluent to furnish the title compound (4 g) as a light yellow liquid. 1H NMR 300 MHz in CDCl3: 1.25-1.30 (t, 3H); 2.01-2.05 (m, 2H); 3.78-3.86 (m, 4H); 4.07 (s, 2H); 4.17-4.24 (m, 3H); MASS (M+Na): 197.

Step 2: Synthesis of (S)-2-(tetrahydrofuran-3-yl)oxy)acetic acid:

To a ethyl 2-((S)-tetrahydrofuran-3-yl)oxy)acetate (step 1, about 4 g) in Aq MEOH, potassium hydroxide (about 3.8 g) was added and refluxed for about 6 hours at about 80°C. Completion of the reaction monitored by TLC, reaction temperature was evaporated under reduced pressure, the residue was taken in water and acidified with aq HCl and extracted with ethyl acetate then the organic layer was washed with water, brine, dried over Na2SO4 and concentrated under reduced pressure. The residue was purified by silica gel column chromatography using 5% ethyl acetate in hexane as eluent to furnish the title compound (2 g) as a light yellow liquid. 1H NMR
300 MHz in DMSO: 1.87-1.93 (m, 2H); 3.59-3.72 (m, 4H); 4.00 (s, 2H); 4.18-4.20 (m, 1H); 12.63 (bs, 1H).

Intermediate 3A: Synthesis of ethylcyclopentanecarboxylic acid:

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\text{OH}
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\text{Step 1: Synthesis of ethyl cyclopentanecarboxylate:}

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\text{O}
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To a cyclopentanecarboxylic acid (about 10 g) in ethanol (150 ml), sulphuric acid (about 10 ml) was added and refluxed for about 6 hours at 80 °C. Completion of the reaction was monitored by TLC, ethanol was evaporated under reduced pressure, the residue was taken in water, neutralized with saturated NaHCO₃ and extracted with DCM, and the organic layer was dried over Na₂SO₄ and concentrated under reduced pressure. The residue was purified by silica gel column chromatography using 5% ethyl acetate in hexane as eluent to furnish the title compound (12 g) as a light yellow liquid. §H NMR (300 MHz, CDC1₃): 1.22-1.27 (m, 3H); 1.57-1.87 (m, 8H); 2.65-2.76 (m, 1H); 4.08-4.15 (m, 2H); ES Mass: [M+1] 143 (100%).

\text{Step 2: Synthesis of ethyl 1-ethylcyclopentanecarboxylate:}

\[
\text{O}
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Di-isopropyl amine (6.5 ml) was taken in dry THF (about 25 ml) and cooled to -10°C, to this n-butyl lithium (about 23 ml) was added drop wise under nitrogen atmosphere and maintain the reaction temperature at about -10 °C for about 45 minutes, after that the reaction mixture was cooled to about -75 °C, ethyl cyclopentanecarboxylate (step 1, about 5 g in 30 ml THF) was added and stirred at same temperature for about 30 minutes then increase the reaction temperature to about -35 °C and stirred for about 45 minutes and again the reaction was cooled to about -75°C, then ethyl chloride (about 4.4 ml in 20 ml THF) was added drop wise.
Slowly the reaction was allowed to return to room temperature and stirred for about 12 hours. Completion of the reaction was monitored by TLC, the reaction mixture was quenched with sat ammonium chloride and extracted with ethyl acetate, the organic layer was washed with saturated NaHCO$_3$, brine solution, dried over Na$_2$SO$_4$ and concentrated under reduced pressure. The resulting residue was purified by silica gel column chromatography using 3% ethyl acetate in hexane as eluent to furnish the title compound (2.2 g) as light yellow colour liquid. $^1$H NMR (300 MHz, CDCl$_3$): 0.80-0.85 (m, 3H); 1.22- 1.27 (m, 3H); 1.41-1.70 (m, 9H); 2.05-2.12 (m, 2H); 4.09-4.16 (m, 2H); ES Mass: [M+1] 171 (100%).

**Step 3: Synthesis of 1-ethylcyclopentanecarboxylic acid:**

To a stirred solution of ethyl 1-ethylcyclopentanecarboxylate (step2, about 3.0 g) in ethanol, potassium hydroxide (about 2.9 g) was added and refluxed for about 6 hours at about 80 °C. Completion of the reaction (monitored by TLC), reaction mixture was evaporated under reduced pressure. The residue was taken in water, acidified with aq HCl and extracted with ethyl acetate. The organic layer was washed with water, followed by brine the organic layer dried over Na$_2$SO$_4$ and concentrated under reduced pressure. The residue was purified by silica gel column chromatography using 5% ethyl acetate in hexane as eluent to furnish the title compound (2 g) as a light yellow liquid. $^1$H NMR (300 MHz, CDCl$_3$): 0.76-0.81 (m, 3H); 1.35- 1.59 (m, 8H); 1.94-2.02 (m, 2H); 12.01 (s, 1H); ES Mass: [M+1] 143 (100%).

Intermediate 3B: Synthesis of 1-(methoxymethyl)cyclopentanecarboxylic acid:

**Step 1: Synthesis of ethyl 1-(methoxymethyl) cyclopentanecarboxylate:**
Di-isopropyl amine (about 6.5 ml) was taken in dry THF (25 ml) and cooled the contents to -10 °C and to this mixture, n-butyl lithium (about 23 ml) was added slowly drop wise under nitrogen atmosphere at -10 °C, after reaction mixture was cooled to about -75°C then ethyl cyclopentanecarboxylate (Intermediate 3A-step 1, about 5g in 30 ml THF) was added and the reaction was stirred at the same temp for about 30 minutes, then increase the reaction temperature to about -35 °C and stirred for about 45 minutes and again cooled to about -75°C then bromo(methoxy)methane (about 4.3 ml in 20 ml THF) was added drop wise and slowly allowed the reaction to room temperature and stirred for 12 hours. After completion of the reaction (monitored by TLC), reaction mixture was quenched with saturated ammonium chloride and extracted with ethyl acetate. The organic layer was washed with sat. NaHCO₃ followed by brine sol, dried over Na₂SO₄ and concentrated under reduced pressure. The residue was purified by silica gel column chromatography using 3% ethyl acetate in hexane as eluent to furnish the title compound (2.2 g) as light yellow colour liquid. 

\[ ^1H \text{NMR (300 MHz, CDCl}_3\text{): 1.23- 127 (m, 3H); 1.56- 1.66 (m, 6H); 2.03- 2.08(m, 2H); 3.33 (s, 3H); 3.45 (s, 2H); 4.12-4.19 (m, 2H); ES Mass (M+Na): 209.} \]

**Step 2: Synthesis of 1-(methoxymethyl)cyclopentanecarboxylic acid:**

To a stirred solution of ethyl 1-(methoxymethyl) cyclopentanecarboxylate (step 1, about 3.0 g) in ethanol, potassium hydroxide (about 2.6 g) was added and refluxed for 6 hours at 80 °C. Completion of the reaction (monitored by TLC), reaction mixture was evaporated under reduced pressure. The residue was taken in water, acidified with aq HCl and extracted with ethyl acetate. The organic layer was washed with water, followed by brine. The organic layer was dried over Na₂SO₄ and concentrated under reduced pressure. The residue was purified by silica gel column chromatography using 5% ethyl acetate in hexane as eluent to furnish the title compound (2 g) as a light yellow liquid. 

\[ ^1H \text{NMR (300 MHz, DMSO-D6): 1.46-1.56 (m, 6H); 1.87- 1.91 (m, 2H); 3.20 (s, 3H); 3.36 (s, 2H); 12.12 (bs, 1H).} \]
Intermediate 3C: Synthesis of 1-(2-ethoxyethyl)cyclopentanecarboxylic acid:

Step 1: Synthesis of ethyl 1-(2-ethoxyethyl)cyclopentanecarboxylate:

Di-isopropyl amine (about 6.5 ml) in dry THF (25 ml) was cooled to -10 °C and to this mixture, n-butyl lithium (about 23 ml) was added slowly drop wise under nitrogen atmosphere at about -10 °C for about 45 minutes, after that reaction mixture was cooled to -75°C then ethyl cyclopentanecarboxylate (step 1, about 5g in 30 ml THF) was added and stirred the reaction at same temp for about 30 minutes, then increased the reaction temperature to -35 °C and stirred for about 45 minutes and again cooled to about -75°C. Then, 1-ethoxy-2-iodoethane (about 4.3 ml in 20 ml THF) was added drop wise and slowly allowed the reaction temperature to rise to room temperature and stirred for about 12 hours at this temperature. After completion of the reaction (monitored by TLC), reaction mixture was quenched with saturated ammonium chloride and extracted with ethyl acetate. The organic layer was washed with sat. NaHCO₃ followed by brine solution, dried over Na₂SO₄ and concentrated under reduced pressure. The residue was purified by silica gel column chromatography using 3% ethyl acetate in hexane as eluent to furnish the title compound (2.2 g) as light yellow colour liquid. ¹H NMR (300 MHz, CDCl₃): 1.14-1.27 (m, 6H); 1.49-1.64 (m, 6H); 1.92-1.95 (m, 2H); 2.08-2.14 (m, 2H); 3.35-3.45 (m, 4H); 4.07-4.15 (m, 2H).

Step 2: Synthesis of 1-(2-ethoxyethyl)cyclopentanecarboxylic acid:
To a stirred solution of ethyl l-(2-ethoxyethyl)cyclopentanecarboxylate (step 1, about 3.0 g) in ethanol, potassium hydroxide (about 2.6 g) was added and refluxed for about 6 hours at about 80 °C. Completion of the reaction (monitored by TLC), reaction mixture was evaporated under reduced pressure. The residue was taken in water, acidified with aqueous HCl and extracted with ethyl acetate. The organic layer was washed with water, followed by brine. The organic layer was dried over Na₂SO₄ and concentrated under reduced pressure. The residue was purified by silica gel column chromatography using 5% ethyl acetate in hexane as eluent to furnish the title compound (2 g) as a light yellow liquid. 1H NMR (300 MHz, DMSO-D₆): 1.14-1.19 (m, 3H); 1.54-1.67 (m, 6H); 1.93-1.98 (m, 2H); 2.11-2.17 (m, 2H); 3.42-3.49 (m, 4H); 12.12 (bs, 1H).

Intermediate 4: Preparation of 2-(1-(pyridin-2-yl)cyclohexyl)acetic acid:

Step 1: Synthesis of ethyl 2-cyano-2-cyclohexylideneacetate:

To cyclohexanone (about 10.0 g) in toluene (about 200 ml), ethyl 2-cyanoacetate (about 5.7 g) was added followed by 1 drop of acetic acid and catalytic amount of ammonium acetate. Reaction mixture was azeotropically refluxed for about 24 hours at about 120°C. Completion of the reaction was monitored by TLC, reaction temperature was evaporated under reduced pressure then the residue was taken in water, neutralized with saturated NaHCO₃ and extracted with DCM, the organic layer was dried over Na₂SO₄ and concentrated under reduced pressure. The residue was purified by silica gel column chromatography using 5% ethyl acetate in hexane as eluent to furnish the title compound (0.8 g) as a light yellow liquid and proceeded to next step.
Step 2: Synthesis of ethyl 2-cyano-2-(1-(pyridin-2-yl)cyclohexyl)acetate:

To a stirred solution of butyl sulfide (about 72 ml) in dry THF Cuprous iodide (about 60 g) was added under nitrogen atmosphere and cooled to about -40 °C in a separate flask. In a different flask a solution of n-BuLi in dry THF was cooled to about -78°C, to this 2-bromo pyridine (about 66 ml) was added and stirred the mixture to result in dark red mixture then this was transferred to the above flask via cannula, the mixture was stirred for about 30 minutes at about 0 °C prior to the addition of ethyl 2-cyano-2-cyclohexylideneacetate (step 1) in dry THF. Now the reaction mixture was slowly warm to about 25 °C and stirred for about 20 hours. Completion of the reaction was monitored by TLC, reaction mixture was quenched with saturated ammonium chloride solution and extracted with ethyl acetate, dried over Na₂SO₄ and concentrated under reduced pressure. The resulting residue was purified by silica gel column chromatography using 4% ethyl acetate in hexane as eluent to furnish the title compound (0.8 g) as a yellow liquid. 

NMR (300 MHz, CDCl₃): 1.05-1.10 (m, 3H); 1.35 (s, 2H); 1.60-1.61 (m, 4H); 1.68-1.87 (m, 2H); 2.57-2.64 (m, 2H); 3.84 (s, 1H); 3.97-4.02 (m, 2H); 7.16-7.20 (m, 1H); 7.26-7.42 (m, 1H); 7.66-7.21 (m, 1H); 8.60-8.61 (m, 1H); ES Mass: (100%), [M] 273.

Step 3: Synthesis of 2-(1-(pyridin-2-yl)cyclohexyl)acetonitrile:

To a ethyl 2-cyano-2-(1-(pyridin-2-yl)cyclohexyl)acetate (step 2, about 2.0 g) in DMSO (about 50 ml), sodium chloride (about 2 g) was added and heated at 80 °C for 16 hours. Completion of the reaction was monitored by TLC, solvent was evaporated under reduced pressure. The resulting residue was taken in water, extracted with DCM, dried over Na₂SO₄ and concentrated under reduced pressure. The residue was purified by silica gel column chromatography using 20% ethyl acetate in hexane as eluent to furnish the title compound (0.8 g) as a yellow liquid.
Step 4: Synthesis of 2-(1-(pyridin-2-yl)cyclohexyl)acetic acid:

To a stirred solution of 2-(1-(pyridin-2-yl)cyclohexyl)acetonitrile (step 3, about 5 g) in ethylene glycol (about 100 ml) potassium hydroxide (about 4.1 g) was added and refluxed for about 24 hours at 180 °C. Completion of the reaction was monitored by TLC. The reaction mixture was evaporated under reduced pressure. The resulting residue was taken in 150 ml of water and acidified with 5 % citric acid, extracted with 5 % MeOH in DCM, washed with water, brine, the organic layer was dried over Na$_2$SO$_4$ and concentrated under reduced pressure. The residue was purified by silica gel column chromatography using 5% ethyl acetate in hexane as eluent to furnish the title compound (2.3 g) as a light brown solid. $^1$H NMR (300 MHz, DMSO): 1.27-1.36 (m, 7H); 1.38-1.50 (m, 2H); 1.68-1.76 (m, 2H); 2.12-2.55 (m, 2H); 7-14-7.18 (m, 1H); 7.38-7.41 (d, J=9Hz, 1H); 7.68-7.73 (m, 1H); 8.50-8.52 (m, 1H); 11.80 (s, 1H); ES Mass: (100%), [M+Na] 242.

Intermediate 5A: Synthesis of (S)-2-(tetrahydrofuran-3-yloxy)benzoic acid:

Step 1: Synthesis of methyl 2-hydroxybenzoate:

To a 2-hydroxybenzoic acid (about 10 g) in methanol (about 150 ml) sulphuric acid (about 7.8 ml) was added and refluxed for about 6 hours at about 80 °C. Completion of the reaction was monitored by TLC then reaction temperature was evaporated under reduced pressure. The resulting residue was taken in water, neutralized with saturated NaHCO$_3$ and extracted with DCM, the organic layer was dried over Na$_2$SO$_4$ and concentrated under reduced pressure. The residue was
purified by silica gel column chromatography using 5% ethyl acetate in hexane as eluent to furnish the title compound (12 g) as a light yellow liquid. $^1$H NMR (300 MHz, CDCl$_3$): 3.9 (s, 3H); 6.86-7.00 (m, 2H); 7.43-7.85 (m, 2H); 10.78 (s, 1H); ES Mass: (100%), [M+1] 153.

Step 2: Synthesis of (s)-tetrahydrofuran-3-yl 4-methylbenzenesulfonate:

To a stirred solution of (s)-tetrahydrofuran-3-ol (about 2.0 g, 22.7 mmol) in DCM (30 ml) triethylamine (about 9.5 ml, 68.1 mmol) was added at room temperature and cooled to about 0 °C, after ten minutes 4-methylbenzene-1-sulfinothioic chloride (step 1, about 3.7 ml) was added and stirred for about 6 hours. Completion of the reaction was monitored by TLC, reaction mixture was neutralized with saturated NaHCO$_3$ and extracted with DCM, the organic layer was dried over Na$_2$SO$_4$ and concentrated under reduced pressure. The residue was purified by silica gel column chromatography using 5% ethyl acetate in hexane as eluent to furnish the title compound (3.5 g) as light yellow liquid. $^1$H NMR (300 MHz, CDCl$_3$): 2.05-2.12 (m, 2H); 2.46 (s, 3H); 3.77-3.93 (m, 4H); 5.09-5.14 (m, 1H); 7.34-7.81 (m, 4H); ES Mass: (100%), [M+1] 243.

Step 3: Synthesis of (S)-methyl 2-(tetrahydrofuran-3-yloxy)benzoate:

To a stirred solution of methyl 2-hydroxybenzoate (about 2.0 g, 22.7 mmol) in DCM (50 ml) cesium carbonate (about 2.4 g) was added at room temperature and cooled to about 0 °C, after ten minutes (S)-tetrahydrofuran-3-yl 4-methylbenzenesulfonate (step 2, 1.59 g) was added and stirred at room temperature for about 6 hours. Completion of the reaction was monitored by TLC, the reaction mixture was quenched with water and extracted with DCM, the organic layer was dried over Na$_2$SO$_4$ and concentrated under reduced pressure to furnish the title...
compound (0.6 g) as a light yellow liquid. $^1$H NMR (300 MHz, CDCl$_3$): 1.63-2.24 (m, 2H); 2.46 (s, 1H); 3.88-4.05 (m, 6H); 4.98-5.00 (m, 1H); 6.88-7.47 (m, 4H); ES Mass: (100%), [M+Na] 245.

Step 4: Synthesis of (S)-2-(tetrahydrofuran-3-yloxy)benzoic acid:

To a (S)-methyl 2-(tetrahydrofuran-3-yloxy)benzoate (step 3, about 3 g) in MeOH (100 ml) potassium hydroxide (about 2.9 g) was added and refluxed for about 6 hours at about 80 °C. Completion of the reaction was monitored by TLC. Then reaction mixture was evaporated under reduced pressure. The resulting residue was taken in water and acidified with aq HCl, extracted with ethyl acetate, the organic layer was washed with water, brine, dried over Na$_2$SO$_4$ and concentrated under reduced pressure. The residue was purified by silica gel column chromatography using 5% ethyl acetate in hexane as eluent to furnish the title compound (2 g) as a light yellow liquid. $^1$H NMR (300 MHz, DMSO): 1.90-1.98 (m, 2H); 2.15-2.22 (m, 1H); 3.73-3.93 (m, 6H); 5.07-5.09 (m, 1H); 6.97-7.62 (m, 4H); 12.46 (bs, 1H); ES Mass: (100%), [M+Na] 231.

Intermediate 5 B: Synthesis of (S)-2-(4-(tetrahydrofuran-3-yloxy)phenyl)acetic acid:

Step 1: Synthesis of methyl 2-(4-hydroxyphenyl)acetate:

To a 2-(4-hydroxyphenyl)acetic acid (about 10 g) in methanol (about 150 ml) sulphuric acid (about 7.8 ml) was added and refluxed for about 6 hours at about 80 °C. Completion of the reaction was monitored by TLC. Then reaction temperature was evaporated under reduced pressure. The resulting residue was taken in water, neutralized with saturated NaHCO$_3$ and extracted with DCM. The organic layer was dried over Na$_2$SO$_4$ and concentrated under reduced pressure. The residue was purified by silica gel column chromatography using 5% ethyl acetate in hexane as eluent to furnish the title compound (12 g) as a light yellow liquid. $^1$H NMR (300 MHz, CDCl$_3$): 3.9 (s, 3H); 6.86-7.00 (m, 2H); 7.43-7.85 (m, 2H); 10.78 (s, 1H); ES Mass: (100%), [M+I] 169.
Step 2: Synthesis of (S)-methyl 2-(4-(tetrahydrofuran-3-yl)oxy)phenyl)acetate:

To a stirred solution of methyl 2-(4-hydroxyphenyl)acetate (0.5 g, 3.012 mmol) in DCM (50 ml) cesium carbonate (2.4 g) was added at room temperature and cooled to 0 °C, after ten minutes (S)-tetrahydrofuran-3-yl 4-methylbenzenesulfonate (0.72 g) was added and stirred the reaction at room temperature for about 6 hours. Completion of the reaction was monitored by TLC, the reaction mixture was quenched with water and extracted with DCM, the organic layer was dried over Na₂SO₄ and concentrated under reduced pressure to furnish the title compound (0.6 g) as a light yellow liquid. ¹H NMR (300 MHz, CDCl₃): 1.32-1.41 (m, 1H); 2.14-2.19 (m, 2H); 3.54-3.56 (d, J=6 Hz, 2H); 3.69 (s, 3H); 3.89-3.99 (m, 4H); 4.89-4.91 (m, 1H); 6.80-7.20 (m, 4H); ES Mass: (100%), [M+Na] 265.

Step 3: Synthesis of (S)-2-(4-(tetrahydrofuran-3-yl)oxy)phenyl)acetic acid:

To (S)-methyl 2-(4-(tetrahydrofuran-3-yl)oxy)phenyl)acetate (step 2, about 10 g) in ethanol (about 150 ml) sulphuric acid (about 7.8 ml) was added and refluxed for about 6 hours at about 80 °C. Completion of the reaction monitored by TLC then reaction temperature was evaporated under reduced pressure. The resulting residue was taken in water, neutralized with saturated NaHCO₃ and extracted with DCM, the organic layer dried over Na₂SO₄ and concentrated under reduced pressure. The residue was purified by silica gel column chromatography using 5% ethyl acetate in hexane as eluent to furnish the title compound (12 g) as a light yellow. ¹H NMR (300 MHz, CDCl₃): 1.32-1.41 (m, 1H); 2.14-2.19 (m, 2H); 3.54-3.56 (d, J=6 Hz, 2H); 3.89-3.99 (m, 4H); 4.89-4.91 (m, 1H); 6.80-7.20 (m, 4H); ES Mass: (100%), [M+H] 223.

Intermediate-6: Synthesis of N-((2R,3S)-3-amino-2-hydroxy-4-phenylbutyl)-N-isobutyl-4-nitrobenzenesulfonamide:
Step 1: Synthesis of tert-butyl (2S,3R)-3-hydroxy-4-(isobutylamino)-l-phenylbutan-2-ylcarbamate:

2-methylpropan-l-amine (19 ml) was added to tert-butyl (S)-l-((S)-oxiran-2-yl)-2-phenylethylcarbamate (about 10.0 g) in isopropyl alcohol (about 150 ml) and refluxed for about 6 hours at about 80°C. Completion of the reaction was monitored by TLC, then the reaction mixture was evaporated under reduced pressure. The resulting residue was taken in 150 ml ethyl acetate, the organic layer was washed with water, brine, dried over Na$_2$SO$_4$ and concentrated under reduced pressure. The obtained solid was washed with pentane to get the title compound (12.0 g) as a white solid. 'HNMR (300 MHz in CDCl$_3$): 0.90-0.92 (m, 6H); 1.35 (s, 9H); 1.69-1.73 (m, 1H); 2.4-2.69 (m, 4H); 2.8-3.02 (m, 2H); 3.4-3.80 (m, 2H); 4.69-4.72 (d, j=9 Hz, 1H); 7.21-7.29 (m, 5H); MASS (M+l) 337.

Step 2: Synthesis of tert-butyl (2S,3R)-3-hydroxy-4-(N-isobutyl-4-nitrophenylsulfonamido)-l-phenylbutan-2-ylcarbamate:

To a stirred solution of tert-butyl (2S,3R)-3-hydroxy-4-(isobutylamino)-l-phenylbutan-2-ylcarbamate (Step 1, about 5 g) in DCM (about 75 ml) triethylamine (about 6.2 ml) was added and the reaction was cooled to about 0°C then 4-nitrobenzene-l-sulfonyl chloride (about 3.9 g) was added and stirred at room temperature for about 12 hours. Completion of reaction was monitored by TLC, then the reaction mixture was diluted with DCM, the organic layer was washed with saturated NaHCO$_3$, brine, dried over Na$_2$SO$_4$ and concentrated under reduced pressure. The residue was purified by silica gel column chromatography using 5% ethyl acetate in hexane as eluent to furnish the title compound (3 g) as a white solid. 'HNMR (300 MHz in CDCl$_3$): 0.86-0.89 (m, 6H); 1.35 (s, 9H); 1.69-1.73 (m, 1H);
2.97-3.20 (m, 6H); 3.75-3.80 (m, 2H); 4.69-4.67 (d, j=7.5Hz, 1H); 7.22-7.31 (m, 5H); 7.94-8.30 (m, 4H); MASS (M+1): 522.

**Step 3: Synthesis of N-((2R,3S)-3-amino-2-hydroxy-4-phenylbutyl)-N-isobutyl-4-nitrobenzenesulfonamide:**

To a stirred solution of tert-butyl (2S,3R)-3-hydroxy-4-(N-isobutyl-4-nitrophenoxy)sulfonamido)-1-phenylbutan-2-ylcarbamate (Step 2, about 2 g, 3.83 mmol) in DCM (20 ml) Trifluoroacetic acid (about 1.4 ml, 19.1 mmol) was added at about 0°C and stirred for about 1 hour then the reaction was allowed to room temperature and stirred for about 6 hours. Completion of the reaction was monitored by TLC. The reaction mixture was neutralized with saturated NaHCO₃ and extracted with DCM, the organic layer was dried over Na₂S(¾ and concentrated under reduced pressure. The residue was purified by silica gel column chromatography using 30% ethyl acetate in hexane as eluent to furnish the title compound D (1.2 g) as a white solid. 'HNMR (300 MHz in CDCl₃): 0.86-0.89 (m, 6H); 1.69-1.73 (m, 1H); 2.97-3.20 (m, 6H); 3.75-3.80 (m, 2H); 4.69-4.67 (d, j=7.5Hz, 1H); 7.22-7.31 (m, 5H); 7.94-8.30 (m, 4H); MASS (M+1): 422.

**Intermediated: Preparation of N-((1R,5S)-8-((2R,3S)-3-amino-2-hydroxy-4-phenylbutyl)-8-azabicyclo[3.2.1]octan-3-yl)-4-methoxybenzenesulfonamide:**

(1R,5S)-8-benzyl-8-azabicyclo[3.2.1]octan-3-amine (about 1.0 g) in DCM (75 ml) triethylamine (about 1.4 ml) was added and cooled to about 0°C, to this mixture 4-methoxybenzene-1-sulfonyl chloride (about 1.0 g) was added and allowed the reaction to reach room temperature, stirred for about 12 hours. Completion of the reaction was monitored by TLC, the reaction mixture was diluted with DCM and the organic layer was washed with saturated NaHCO₃ followed by brine solution. Then
the organic layer was dried over Na₂SO₄ and concentrated under reduced pressure. The resulting residue was purified by silica gel column chromatography using 5% ethyl acetate in hexane as eluent to furnish the title compound (1.4 g) as a white solid. 'HNMR 300 MHz in CDCl₃: 1.50-1.57 (m, 6H), 1.97- 2.00 (m, 3H), 2.80-2.83 (d, J= 9Hz, 1H), 3.12- 3.14 (m, 2H), 3.47 (s, 3H), 3.86 (s, 3H), 4.39- 4.41 (d, J= 6Hz, 1H), 6.94-6.97 (m, 2H), 7.20- 7.33 (m, 5H), 7.78- 7.81 (m, 2H); MASS (M+1): 387.

**Step 2: Synthesis of N-((IR,5S)-8-azabicyclo[3.2.1]octan-3-yl)-4-methoxybenzenesulfonamide:**

N-((IR,5S)-8-benzyl-8-azabicyclo[3.2.1]octan-3-yl)-4-methoxybenzenesulfonamide (step 1, about 1 g) in ethyl acetate (25 ml) palladium on carbon (about 0.3 g) was added and stirred under H₂ atmosphere (about 60 psi) for 6 hours. Completion of the reaction was monitored by TLC. The reaction mixture was filtered through celite bed and the filtrate was evaporated. The resulting residue was purified by silica gel column chromatography using 5% ethyl acetate in hexane as eluent to furnish the title compound (0.5 g) as a white solid. 'HNMR 300 MHz in CDCl₃: 1.50-1.57 (m, 6H), 1.97- 2.00 (m, 3H), 3.47 (s, 3H), 3.86 (s, 3H), 4.39- 4.41 (d, J=6Hz, 1H), 6.94-6.97 (m, 2H), 7.78- 7.81 (m, 2H); MASS (M+1): 292.

**Step 3: Synthesis of tert-butyl (2S,3R)-3-hydroxy-4-((IR,5S)-3-(4-methoxyphenylsulfonamido)-8-azabicyclo[3.2.1]octan-8-yl)-1-phenylbutan-2-ylcarbamate:**

To a tert-butyl (S)-1-((S)-oxiran-2-yl)-2-phenylethylcarbamate (about 1.0 g) in isopropyl alcohol (50 ml) N-((IR,5S)-8-azabicyclo[3.2.1]octan-3-yl)-4-methoxybenzenesulfonamide (Step 2, 2.25 g) was added followed by triethyl amine (1.2 ml) was added and refluxed for about 6 hours at 80 °C. Completion of the
reaction was monitored by TLC, then the reaction mixture was evaporated under reduced pressure. The residue was taken in 150 ml ethyl acetate, the organic layer was washed with water followed by brine, the organic layer was dried over Na₂SO₄ and concentrated under reduced pressure. Obtained solid was washed with pentane to get the title compound (1.4 g). 'HNMR 300 MHz in CDCl₃: 1.32 (s, 9H), 1.43-1.65 (m, 9H), 2.19-2.26 (m, 1H), 2.48-2.51 (d, J=9Hz, 1H), 2.80-2.97 (m, 4H), 3.44-3.76 (m, 4H), 3.88 (s, 3H), 4.58-4.61 (d, J=9Hz, 1H), 6.95-6.98 (m, 2H), 7.20-7.30 (m, 5H), 7.78-7.81 (d, J= 9Hz, 2H); MASS (M+1): 560.

**Step 4: Synthesis of N-((IR,5S)-8-((2R,3S)-3-amino-2-hydroxy-4-phenylbutyl)-8-azabicyclo[3.2.1]octan-3-yl)-4-methoxybenzenesulfonamide:**

To a stirred solution of tert-butyl (2S,3R)-3-hydroxy-4-((IR,5S)-3-(4-methoxyphenylsulfonamido)-8-azabicyclo[3.2.1]octan-8-yl)-1-phenylbutan-2-ylcarbamate (Step 3, 1.4 g, 2.50 mmol) in DCM trifluoroacetic acid (about 1.4 ml, 12.2 mmol) was added at about 0 °C and stirred for about 1 hour, then reaction was allowed to rise to room temperature and stirred for about 6 hours. Completion of the reaction was monitored by TLC. The reaction mixture was neutralized with saturated NaHCO₃, extracted with dichloromethane; the organic layer was dried over Na₂SO₄ and concentrated under reduced pressure. The residue was purified by silica gel column chromatography using 30% ethyl acetate in hexane as eluent to furnish the title compound (0.8 g) as a white solid. 'HNMR 300 MHz in CDCl₃: 1.43-1.65 (m, 9H), 2.19-2.26 (m, 1H), 2.48-2.51 (d, J=9Hz, 1H), 2.80-2.97 (m, 4H), 3.44-3.76 (m, 4H), 3.88 (s, 3H), 4.58-4.61 (d, J=9Hz, 1H), 6.95-6.98 (m, 2H), 7.20-7.30 (m, 5H), 7.78-7.81 (d, J= 9Hz, 2H); MASS (M+1): 460.

**Intermediate 8: Preparation of 2-((R)-tetrahydrofuran-3-yloxy)propanoic acid:**

**Step 1: synthesis of ethyl 2-((S)-tetrahydrofuran-3-yloxy)propanoate:**
To a stirred solution of sodium hydride (about 1.5 g) in THF (25 ml) and cooled to about 0°C, (S)-tetrahydrofuran-3-ol (about 1 g) was added and stirred at about 0°C for about 1 hour, then ethyl 2-bromopropanoate (about 1.7 ml) was added dropwise at about 0°C and allow the reaction to room temperature for about 12 hrs.

Completion of the reaction monitored by TLC, the reaction mixture was quenched with water and extracted with ethyl acetate, the organic layer was dried over Na₂SO₄ and concentrated under reduced pressure. The residue was purified by silica gel column chromatography using 5% ethyl acetate in hexane as eluent to furnish the title compound (0.75 g) as a light yellow liquid. ¹HNMR 300 MHz in CDCl₃: 1.91 (s, 3H); 3.64-3.71 (m, 4H); 4.01 (s, 2H); 4.19-4.20 (m, 1H); 12.41 (s, 1H); MASS (M+Na); 211.

**Step 2: synthesis of 2-((R)-tetrahydrofuran-3-yloxy)propanoic acid:**

ethyl 2-((S)-tetrahydrofuran-3-yloxy)propanoate (step 1, about 0.9 g) in aq MeOH potassium hydroxide (about 0.8 g) was added and refluxed for about 6 hours at about 80°C. Completion of the reaction monitored by TLC, reaction temperature was evaporated under reduced pressure. The residue was taken in 150 ml water and acidified with aqueous HCl and extracted with ethyl acetate, the organic layer was washed with water followed by brine, the organic layer was dried over Na₂SO₄ and concentrated under reduced pressure. The residue was purified by silica gel column chromatography using 5% ethyl acetate in hexane as eluent to furnish the title compound (0.5 g) as a light yellow liquid. ¹HNMR 300 MHz in DMSO: 1.45-1.47 (s, 3H); 1.98-2.1 (m, 3H); 3.76-3.98 (m, 4H); 4.04-4.28 (m, 2H); 12.41 (s, 1H); MASS (M+Na); 183.

**Intermediate 9: Preparation of 1-oxaspiro[4.4]nonane-7-carboxylic acid:**

![Diagram of 1-oxaspiro[4.4]nonane-7-carboxylic acid]

HO₂C
Step 1: Synthesis of benzyl 3-oxocyclopentanecarboxylate:

A stirred solution of 3-oxocyclopentanecarboxylic acid (about 5 g, 39.06 mmol) in DMF (40 ml) at about 0 °C benzyl bromide (about 5.13 ml, 42.96 mmol) and cesium carbonate (about 4.63 g, 14.06 mmol) were added and allowed to stir at room temperature for about 90 minutes. After completion of the reaction (monitored by TLC), the reaction mixture was diluted with ethyl acetate (400 ml) and washed with water, brine and dried over Na₂SO₄, the solvent was evaporated and combined with another batch (5.0 g) with same quantity and purified by silica gel column chromatography (100-200 mesh, Elution: 5 % EtOAc in Hexane) to afford the title compound as a liquid. Wt: 12.7 g; Yield: 75 %; ¹H NMR: (300 MHz, CDCl₃): δ 7.38-7.36 (m, 5H), 5.18 (s, 2H), 3.14-3.25 (m, 1H), 2.53-2.16 (m, 6H).

Step 2: Synthesis of benzyl 3-allyl-3-hydroxycyclopentanecarboxylate:

A stirred solution of benzyl 3-oxocyclopentanecarboxylate (step 1, about 4.0 g, 18.39 mmol) in dry DCM (20 ml) at about 0 °C TiCL, (about 2.0 ml, 18.34 mmol) was added, after five minutes allyltrimethylsilane (about 11.7 ml, 73.39 mmol) was added slowly and allowed to stir at room temperature for about 3 hours. After completion of the reaction (monitored by TLC), the reaction was quenched with water, extracted with EtOAc (200 ml x 2) and the organic layers were washed with brine, dried with Na₂SO₄ and the solvent was evaporated. The resulting crude was combined with another batch (8.7 g) and purified by silica gel column chromatography (100-200 Mesh, Elution: 8-10 % EtOAc in Hexane) to afford the title compound as a pale yellow liquid. Wt: 5.0 g; Yield: 33 %; ¹H NMR: (300 MHz, CDCl₃): δ 7.36-7.34 (m, 5H), 5.96-5.86 (m, 1H), 5.15-5.14 (m, 4H), 2.98-2.93, 2.68 (brm, 1H), 2.37-2.34 (m, 2H), 2.10-1.65 (m, 4H), 1.65-1.62 (m, 2H); Mass: [M+Na]⁺: 283(100%), [M+H]⁺: 261(18%).
Step 3: Synthesis of benzyl 3-hydroxy-3-(3-hydroxypropyl)cyclopentanecarboxylate:

A stirred solution of benzyl 3-allyl-3-hydroxycyclopentanecarboxylate (Step 2, about 3.0 g, 11.53 mmol) in dry THF (8 ml) at about 0 °C BH₃ : THF (23.07 ml, 23.07 mmol) was added and stirred at room temperature for about 3 hours. After completion of the reaction (monitored by TLC), NaOH (2N, 10 ml) flowed by H₂O₂ (11.5 ml) were added, after about 30 minutes (monitored by TLC) the reaction mixture was diluted with EtOAc (200ml) and washed with brine. The organic layer was dried with Na₂S₀₄ and the solvent was evaporated under reduced pressure, the resulted crude combined with another batch (1 g) and purified by Silica gel column chromatography (100-200 mesh, Elution: 35-40 % EtOAc in Hexane) to afford the title compound as a liquid. Wt: 2.0 g; Yield: 47.6 %; ¹H NMR: (300 MHz, CDC₁₃): δ 7.38-7.36 (m, 5H), 5.14 (s, 2H), 3.67 (m, 2H), 3.02-2.98 (m, 1H), 2.08-2.02 (m, 3H), 1.91-1.83 (m, 2H), 1.76-1.59 (m, 5H); Mass: [M+Na]⁺: 301 (100%).

Step 4: Synthesis of benzyl 1-oxaspiro[4.4]nonane-7-carboxylate:

A stirred solution of benzyl 3-hydroxy-3-(3-hydroxypropyl)cyclopentanecarboxylate (step 3, about 1.0 g, 3.59 mmol) in dry DCM (8 ml) at 0 °C triethylamine (about 1.24 ml, 8.99 mmol) was added followed by methanesulfonyl chloride (0.33 ml, 4.30 mmol) and stirred at room temperature, after about 30 minutes the reaction mixture was stirred at reflux temperature for about 10 hours. After completion of the reaction (monitored by TLC), the reaction mixture was diluted with EtOAc (150 ml) and washed with brine. The organic layer was dried with Na₂S₀₄ and the solvent was evaporated under reduced pressure, the resulting crude combined with another batch (0.9 g) purified by Silica gel column chromatography (100-200 mesh, Elution: 2-2.5% EtOAc in Hexane) to afford the
title compound as a liquid. Wt: 0.9 g; Yield: 50%; \textsuperscript{1}H NMR: (300 MHz, \textit{CDCl}_3): \delta
7.36-7.34 (m, 5H), 5.14 (d, J = 2.1 Hz, 2H), 3.80 (t, J = 6.9 Hz, 2H), 2.88-2.82 (m, 1H), 2.19-2.10 (m, 2H), 1.97-1.89 (m, 5H), 1.81-1.76 (m, 2H), 1.64-1.58 (m, 1H); Mass: [M+Na\textsuperscript{+}]: 283 (100%), [M+H\textsuperscript{+}]: 261 (30%).

Step 5: Synthesis of 1-oxaspiro[4.4]nonane-7-carboxylic acid:

A stirred solution of benzy l 1-oxaspiro[4.4]nonane-7-carboxylate (step 4, about 1.35 g, 5.19 mmol) in EtOAc (8 ml) 10 % palladium on carbon (about 0.020 g) was added at room temperature and the reaction mixture was stirred under H\textsubscript{2} gas atmosphere at room temperature for about 3 hours. After completion of the reaction (monitored by TLC), the reaction mixture was filtered through celite bed and the obtained filtrate concentrated under reduced pressure to afford the title compound as a liquid. Wt: 0.8 g; Yield: 90%; \textsuperscript{1}H NMR: (300 MHz, \textit{CDCl}_3): 3.88-3.84 (m, 2H), 2.98-3.01 (m, 1H), 2.14-1.83 (m, 9H), 1.65-1.61 (m, 1H); Mass: [M+Na\textsuperscript{+}]: 193 (100%).

Intermediate 10: Preparation of 2-ethyltetrahydrofuran-2-carboxylic acid:

Step 1: Synthesis of ethyl tetrahydrofuran-2-carboxylate:

To a stirred solution of tetrahydrofuran-2-carboxylic acid (about 10 g) in ethanol (150 ml), sulfuric acid (about 10 ml) was added and refluxed for 6 hours at 80 °C. Completion of the reaction was monitored by TLC, reaction mixture was evaporated under reduced pressure, the residue was taken in water, neutralized with saturated NaHCO\textsubscript{3} and extracted with DCM, the organic layer was dried over Na\textsubscript{2}SO\textsubscript{4} and concentrated under reduced pressure. The residue was purified by silica gel column chromatography using 5% ethyl acetate in hexane as eluent to furnish the title compound (12 g) as a light yellow liquid. \textsuperscript{1}H NMR (300 MHz, \textit{CDCl}_3): 1.22-1.27 (m, 3H); 1.57- 1.87 (m, 8H); 2.65-2.76 (m, 1H); 4.08-4.15 (m, 2H); ES Mass: [M+I\textsuperscript{+}] 143 (100%).
Step 2: Synthesis of ethyl 2-ethyltetrahydrofuran-2-carboxylate:

A stirred solution of Diisopropylamine (about 6.5 ml) in dry THF (25 ml) was cooled to about -10 °C and to this n-butyl lithium (23 ml) was added drop wise under nitrogen atmosphere and maintain the same temperature for about 45 minutes then cooled to the reaction mixture about -75°C for about 15 minutes then ethyl tetrahydrofuran-2-carboxylate (step 1, about 5 g in 30 ml THF) was added and stirred the reaction at same temperature for about 30 minutes. Increased the reaction temperature to about -35 °C and stirred for 45 minutes then again cooled the reaction to about -75°C then ethyl iodide (5.2 ml in 20 ml THF) was added drop wise and the reaction temperature was slowly allowed to reach room temperature and stirred the reaction mixture at room temperature for about 12 hours. Completion of the reaction was monitored by TLC, the reaction mixture was quenched with saturated ammonium chloride and extracted with ethyl acetate, the organic layer was washed with saturated NaHCO₃ followed by brine solution, the organic layer was dried over Na₂SO₄ and concentrated under reduced pressure. The residue was purified by silica gel column chromatography using 3% ethyl acetate in hexane as eluent to furnish the title compound as light yellow colour liquid. ¹H NMR (300 MHz, CDC₃): 1.40-1.44 (m, 3H); 1.77-1.87 (m, 6H); 1.88-1.96 (m, 4H); 4.78-4.85 (m, 2H); ES Mass: [M+1] 173 (100%).

Step 3: Synthesis of 2-ethyltetrahydrofuran-2-carboxylic acid:

To a stirred solution of ethyl 2-ethyltetrahydrofuran-2-carboxylate (step 2, about 3 g) in ethanol (25 ml) potassium hydroxide (about 2.6 g) was added and refluxed for about 6 hours at about 80 °C. Completion of the reaction was monitored by TLC, reaction mixture was evaporated under reduced pressure, the residue was taken in 150 ml of water and acidified with aqueous HCl and extracted with ethyl acetate, the organic layer was washed with water followed by brine, the organic layer was dried over Na₂SO₄ and concentrated under reduced pressure. The residue was purified by silica gel column chromatography using 5% ethyl acetate in hexane as eluent to furnish the title compound (2 g) as a light yellow liquid. ¹H NMR (300
Examples

Example 1: Preparation of N-((2S,3R)-3-hydroxy-4-(N-isobutyl-4-nitrophenylsulfonamido)-1-phenylbutan-2-yl)-2-((S)-tetrahydrofuran-3-yloxy)acetamide:

To a stirred solution of (S)-2-(tetrahydrofuran-3-yloxy)acetic acid (Intermediate 2, about 0.5 g) in DCM, N-((2R,3S)-3-amino-2-hydroxy-4-phenylbutyl)-N-isobutyl-4-nitrobenzenesulfonamide (Intermediate 6, about 1.4 g) was added followed by 1-Ethyl-3-(3-Dimethylaminopropyl)carbodiimide (about 1.3 g) and Hydroxybenzotrazole (about 0.7 g) were added at room temperature and stirred for about 16 hours. Completion of the reaction was monitored by TLC. Reaction mixture was quenched with water and extracted with DCM. The organic layer was washed with sat. NaHCO₃ followed by brine solution, dried over Na₂SO₄ and concentrated under reduced pressure. The residue was purified by silica gel column chromatography using 15% ethyl acetate in hexane as eluent to furnish the title compound (0.8 g) as a yellow solid. ¹H NMR (300 MHz, CDCl₃): δ 0.86-0.89 (m, 6H); 1.85-1.90 (m, 3H); 2.89-3.10 (m, 4H); 3.15-3.25 (m, 2H); 3.68-4.01 (m, 8H); 6.71-6.74 (d, J= 9Hz, 1H); 7.19-7.31 (m, 5H); 7.95-7.98 (d, J= 12Hz, 2H); 8.33-8.36 (d, J= 9Hz, 2H); ES Mass: (100%), [M+H] 550; HPLC: 97.8%.

Example 2: N-((2S,3R)-4-(4-amino-N-isobutylphenylsulfonamido)-3-hydroxy-1-phenylbutan-2-yl)-2-((S)-tetrahydrofuran-3-yloxy)acetamide:

To a stirred solution of N-((2S,3R)-3-hydroxy-4-(N-isobutyl-4-nitrophenylsulfonamido)-1-phenylbutan-2-yl)-2-((S)-tetrahydrofuran-3-yloxy)acetamide (Example 1, about 0.8 g) in ethanol (2.5 ml) tinchloride (2.3 g) was
added and refluxed for about 6 hours at about 80 °C. Completion of the reaction monitored by TLC, the reaction mixture was evaporated under reduced pressure, the residue was taken in water, neutralized with saturated NaHCO₃ and extracted with DCM, the organic layer was dried over Na₂SO₄ and concentrated under reduced pressure. The residue was purified by silica gel column chromatography using 5% ethyl acetate in hexane as eluent to furnish the title compound (5 g) as a white solid.

$^1$H NMR (300 MHz, CDCl₃): δ 0.89-0.91 (m, 6H); 1.25-1.48 (m, 2H); 1.81-1.95 (m, 3H); 2.81-3.06 (m, 6H); 3.81-3.89 (m, 2H); 3.97-4.16 (m, 9H); 6.66-6.69 (m, 2H); 7.24-7.29 (m, 5H); 7.53-7.56 (d, J = 8.7 Hz, 2H); ES Mass: (100%), [M+Na] 542; HPLC: 95.3%.

Similarly, the following compounds have been prepared by the above procedure using corresponding intermediates:

Example 3: N-((2S,3R)-3-hydroxy-4-(N-isobutyl-4-methoxyphenylsulfonamido)-1-phenylbutan-2-yl)-2-(tetrahydrofuran-3-yl)oxacylamide:

Yield: 0.8 g as a yellow solid. $^1$H NMR (300 MHz, CDCl₃): δ 0.85-0.90 (m, 6H); 1.88-1.96 (m, 3H); 2.84-3.08 (m, 6H); 3.70-3.73 (m, 5H); 3.74 (s, 3H); 3.81-4.24 (m, 4H); 6.71-6.72 (d, J = 9 Hz, 1H); 6.98-7.01 (d, J = 9 Hz, 2H); 7.21-7.74 (m, 7H); MASS (M+Na): 557; HPLC Purity: 96%.

Example 4: N-((2S,3R)-3-hydroxy-4-(N-isobutyl-4-methylphenylsulfonamido)-1-phenylbutan-2-yl)-2-(tetrahydrofuran-3-yl)oxacylamide:

Yield: 0.8 g as a yellow solid. $^1$H NMR (300 MHz, CDCl₃): δ 0.85-0.90 (m, 6H); 1.80-2.01 (m, 3H); 2.43 (s, 3H); 2.84-3.08 (m, 6H); 3.70-4.25 (m, 10H); 6.69-6.72 (d, J = 9 Hz, 1H); 7.21-7.32 (m, 5H); 7.64-7.66 (d, J = 6 Hz, 2H); ES Mass: (100%), [M+Na] 519; HPLC: 99.9%.
Example 5: N-((2S,3R)-4-(3-chloro-4-fluoro-N-isobutylphenylsulfonamido)-3-hydroxy-1-phenylbutan-2-yl)-2-(tetrahydrofuran-3-yloxy)acetamide:

Yield: 0.8 g as a yellow solid. $^1$H NMR (300 MHz, CDCl$_3$): $\delta$ 0.87-0.89 (m, 6H); 1.89-2.05 (m, 2H); 2.92-3.15 (m, 6H); 3.69-4.1 (m, 9H); 6.72 - 6.75 (d, J= 9Hz, 1H); 7.21-7.33 (m, 6H); 7.65 - 7.68 (m, 1H); 7.85 -7.89 (m, 1H); ES Mass: (100%), [M+Na] 579; HPLC: 96.1%.

Example 6: l-ethyl-N-((2S,3R)-3-hydroxy-4-(N-isobutyl-4-nitrophenylsulfonamido)-1-phenylbutan-2-yl)cyclopentanecarboxamide:

To a stirred solution of 1-ethylcyclopentanecarboxylic acid (Intermediate 3A, about 2.0 g, 14 mmol) in DCM (50 ml) thionyl chloride (about 3.2 ml, 42 mmol) was added at room temperature and refluxed for about 6 hours at about 40°C. Completion of the reaction was monitored by TLC and reaction mixture was concentrated under reduced pressure. The residue was taken in 15 ml DCM and kept under N2 atmosphere.

To a stirred solution of N-((2R,3S)-3-amino-2-hydroxy-4-phenylbutyl)-N-isobutyl-4-nitrobenzenesulfonamide (Intermediate 6, about 5.9 g, 14 mmol) in 50 ml DCM triethylamine (about 5.8 ml, 42 mmol) was added at about 0°C and stirred for about 15 minutes then this above prepared compound was taken in DCM (15 ml) and the reaction was stirred at room temperature for about 8 hours, and the completion of the reaction was monitored by TLC. Reaction mixture was neutralized with saturated NaHCO$_3$ and extracted with DCM, dried over Na$_2$SO$_4$ and concentrated under reduced pressure. The residue was purified by silica gel column chromatography using 5% ethyl acetate in hexane as eluent to furnish the title compound (5 g) as a white solid. $^1$H NMR (300 MHz, CDCl$_3$): 0.58 -0.63 (m, 3H); 0.86-0.90 (m, 6H); 1.34-1.50 (m, 7H); 1.53-1.78 (m, 2H); 2.80-4.60 (m, 9H); 5.66-
5.68 (d, $J=6$ Hz, IH); 7.24-7.32 (m, 5H); 7.95-7.98 (m, IH); 8.34-8.36 (m, IH); ES Mass: [M+Na] 568 (100%); HPLC: 98.3%.

Example 7: N-((2S,3R)-4-(4-amino-N-isobutylphenylsulfonamido)-3-hydroxy-l-phenylbutan-2-yl)-l-ethylcyclopentanecarboxamide:

Yield: 0.8 g as an off white solid. $^1$H NMR (300 MHz, CDCl$_3$): $\delta$ 0.6-0.76 (m, 3H); 0.89-0.91 (m, 6H); 1.43-1.48 (m, 6H); 1.75-1.93 (m, 3H); 2.86-2.90 (m, 2H); 3.00-3.07 (m, 3H); 3.19-3.26 (m, IH); 3.84-3.86 (m, IH); 4.13 (s, 2H); 4.23-4.56 (m, 2H); 5.80-5.82 (d, $J=7.8$ Hz, IH); 6.68-6.71 (d, $J=8.7$ Hz, 2H); 7.2-7.5 (m, 7H); ES Mass: [M+Na] 538 (100%); [M+Na] 553 (80%); HPLC: 97.5%.

Example 8: l-ethyl-N-((2S,3R)-3-hydroxy-4-(N-isobutyl-4-methoxyphenylsulfonamido)-l-phenylbutan-2-yl)cyclopentanecarboxamide:

Yield: 1 g as a white solid. $^1$H NMR (300 MHz, CDCl$_3$): 0.60-0.65 (m, 3H); 0.89-0.91 (m, 6H); 1.43-1.47 (m, 5H); 1.73-1.80 (m, 4H); 2.88-3.07 (m, 5H); 3.22-3.23 (m, 6H); 3.89 (s, 3H); 4.58-4.59 (m, IH); 5.77-5.79 (m, IH); 6.98-7.01 (m, 2H); 7.24-7.32 (m, 5H); 7.71-7.74 (m, 2H); ES Mass: [M+Na] 553 (100%); HPLC: 98.8%.

Example 9: N-((2S,3R)-4-(3-chloro-4-fluoro-N-isobutylphenylsulfonamido)-3-hydroxy-l-phenylbutan-2-yl)-l-ethylcyclopentanecarboxamide:

Yield: 5 g as a white solid. $^1$H NMR (300 MHz, CDCl$_3$): 0.61-0.70 (m, 3H); 0.87-0.91 (m, 7H); 1.37-1.54 (m, 6H); 1.73-1.77 (m, 3H); 2.90-3.07 (m, 6H); 3.27-3.28 (m, IH); 3.83-3.84 (m, IH); 4.60-4.61 (m, IH); 5.71-5.74 (m, IH); 7.22-7.33 (m,
Example 10: l-ethyl-N-((2S,3R)-3-hydroxy-4-(N-isobutyl-4-methylphenylsulfonamido)-1-phenylbutan-2-yl)cyclohexanecarboxamide:

Yield: 5 g as a white solid. $^1$H NMR (300 MHz, CDCl$_3$): $\delta$ 0.50 -0.60 (m, 3H); 0.88-0.90 (m, 6H); 1.10-1.50 (m, 10H); 1.80-1.94 (m, 1H); 2.45 (s, 3H); 2.89-3.10 (m, 4H); 3.25-3.35 (m, 1H); 3.85-3.90 (m, 1H); 4.25-4.35 (m, 1H); 4.62 (s, 1H); 5.88-5.91 (d, J=9Hz, 1H); 7.20 - 7.32 (m, 7H); 7.65-7.67 (d, J=6Hz, 2H); ES Mass: (100%), [M+Na] 575; HPLC: 98.8%.

Example 11: l-ethyl-N-((2S,3R)-3-hydroxy-4-(N-isobutyl-4-methoxyphenylsulfonamido)-1-phenylbutan-2-yl)cyclohexanecarboxamide:

Yield: 5 g as a white solid. $^1$H NMR (300 MHz, CDCl$_3$): $\delta$ 0.50 -0.60 (m, 3H); 0.88-0.90 (m, 6H); 1.10-1.50 (m, 10H); 1.71 -2.00 (m, 3H); 2.85-3.20 (m, 5H); 3.25-3.35 (m, 1H); 3.85-3.90 (m, 1H); 4.15-4.25 (m, 1H); 4.67-4.69 (d, J=6Hz, 1H); 7.20 - 7.32 (m, 5H); 7.96 - 7.99 (d, J=9Hz, 2H); 8.33-8.36 (d, J=9Hz, 2H); ES Mass: (100%), [M+Na] 589; HPLC: 97.7%.

Example 12: N-((2S,3R)-4-(3-chloro-4-fluoro-N-isobutylphenylsulfonamido)-3-hydroxy-1-phenylbutan-2-yl)-l-ethylcyclohexanecarboxamide:

Yield: 5 g as a white solid. $^1$H NMR (300 MHz, CDCl$_3$): $\delta$ 0.50 -0.60 (m, 3H); 0.88-0.90 (m, 6H); 1.10-1.50 (m, 10H); 1.71 -2.00 (m, 3H); 2.85-3.20 (m, 5H); 3.25-3.35
Example 13: l-ethyl-N-((2S,3R)-3-hydroxy-4-(N-isobutyl-4-nitrophenylsulfonamido)-1-phenylbutan-2-yl)cyclohexanecarboxamide:

Yield: 5 g as a white solid. $^1$H NMR (300 MHz, CDCl$_3$): $\delta$ 0.50 - 0.60 (m, 3H); 0.88 - 0.90 (m, 6H); 1.10 - 1.50 (m, 10H); 1.71 - 2.00 (m, 3H); 2.85 - 3.20 (m, 5H); 3.25 - 3.35 (m, 1H); 3.85 - 3.90 (m, 1H); 4.15 - 4.25 (m, 1H); 4.67 - 4.69 (d, J = 6 Hz, 1H); 5.75 - 5.77 (d, J = 6 Hz, 1H); 7.20 - 7.32 (m, 5H); 7.96 - 7.99 (d, J = 9 Hz, 2H); 8.33 - 8.36 (d, J = 9 Hz, 2H); ES Mass: (100%), [M+Na] 589; HPLC: 97.6%.

Example 14: N-((2S,3R)-4-(4-amino-N-isobutylphenylsulfonamido)-3-hydroxy-1-phenylbutan-2-yl)-1-ethylcyclohexanecarboxamide:

Yield: 0.8 g as a yellow solid. $^1$H NMR (300 MHz, CDCl$_3$): $\delta$ 0.54 - 0.59 (m, 3H); 0.85 - 0.90 (m, 6H); 1.14 - 1.50 (m, 12H); 1.80 - 1.94 (m, 3H); 2.85 - 3.09 (m, 5H); 3.19 - 3.20 (m, 1H); 3.84 - 3.91 (m, 1H); 4.13 - 4.39 (m, 3H); 4.59 - 4.60 (d, J = 3 Hz, 1H); 5.90 - 5.92 (d, J = 6 Hz, 1H); 6.66 - 6.69 (d, J = 9 Hz, 2H); 7.20 - 7.28 (m, 5H); 7.53 - 7.56 (d, J = 9 Hz, 2H); ES Mass: (100%), [M+Na] 552; HPLC: 95.1%.

Example 15: l-ethyl-N-((2S,3R)-4-(4-fluoro-N-isobutylphenylsulfonamido)-3-hydroxy-1-phenylbutan-2-yl)cyclohexanecarboxamide:
Yield: 5 g as a white solid. $^1$H NMR (300 MHz, CDCl$_3$): $\delta$ 0.54-0.59 (m, 3H); 0.87-.90 (m, 6H); 1.14 -1.50 (m, 10H); 1.80 -2.00 (m, 3H); 2.85 -3.09 (m, 6H); 3.25-3.35 (m, IH); 3.84- 3.88 (m, IH); 4.23 -4.33 (m, IH); 4.59- 4.60 (d, J= 3Hz, IH); 5.83-5.84 (d, J= 6Hz, IH); 7.20 - 7.30 (m, 7H); 7.78 - 7.82 (m, 2H); Mass: (100%), [M+1] 533; HPLC: 97.3%.

Example 16: N-((2S,3R)-4-(3,4-difluoro-N-isobutylphenylsulphonamido)-3-hydroxy-l-phenylbutan-2-yl)-l-ethylcyclohexanecarboxamide:

$^1$H NMR (300 MHz, CDCl$_3$): 0.56-0.58 (t, J=6 Hz, 3H), 0.82-0.88 (m, 4H), 1.25 (m, 3H), 1.35-1.385 (m, 3H), 1.87-1.91 (m, 4H), 3.30-3.11 (m, 5H), 3.50-3.52 (d, J=4.5Hz, 2H), 3.87 (s, IH), 4.23-4.25 (m, IH), 4.65-4.66 (d, J=4.5Hz, IH), 5.82-5.84 (d, J=6.6Hz, IH), 6.96-7.92 (m, 9H); ES Mass: (100%), [M+Na] 573; HPLC purity: 92.1%.

Example 17A: Preparation of l-ethyl-N-((2S,3R)-3-hydroxy-4-(3-(4-methoxyphenylsulphonamido)-8-azabicvclor3.2.1octan-8-yl)-l-phenylbutan-2-vDcyclopentanecarboxamide:

ES Mass: [M+1] 584 (20%).

Example 17 B: l-(2-ethoxyethylVN-((2S,3R)-3-hydroxy-4-(3-(4-methoxyphenylsulphonamido)-8-azabicyclo[3.2.1]octan-8-yl)-l-phenylbutan-2-vl)cyclopentanecarboxamide:
Example 18: N-((2S,3R)-4-(4-amino-N-isobutylphenylsulfonamido)-3-hydroxy-1-phenylbutan-2-yl)-3,3-difluorocyclopentanecarboxamide:

![Chemical structure]

\[\text{IR (KBr): 3383, 2955, 2054, 1597, 1498, 1260, 1153, 1095, 1024, 836, 563; ES Mass: [M+Na] 546 (100%); HPLC purity: 99.3%}.\]

Example 19: 3,3-difluoro-N-((2S,3R)-3-hydroxy-4-(N-isobutyl-4-methoxyphenylsulfonamido)-1-phenylbutan-2-yl)cyclopentanecarboxamide:

![Chemical structure]

\[\text{IR (KBr): 3586, 2932, 1664, 1556, 1482, 1380, 1260, 1155, 1095, 1029, 837; ES Mass: [M+Na] 557.5 (70%); HPLC purity: 95%}.\]

Example 20: Preparation of N-((2S,3R)-4-(3-chloro-4-fluoro-N-isobutylphenylsulfonamido)-3-hydroxy-1-phenylbutan-2-yl)-2-(1-(pyridin-2-yl)cyclohexyldacetamide:

![Chemical structure]
To a stirred solution of 2-(1-(pyridin-2-yl)cyclohexyl)acetic acid (Intermediate 4, about 0.5 g) in DCM (25 ml) N-((2R,3S)-3-amino-2-hydroxy-4-phenylbutyl)-3-chloro-4-fluoro-N-isobutylbenzenesulfonamide (about 1.3 g) was added followed by 1-Ethyl-3-(3-Dimethylaminopropyl)carbodiimide (about 1.3 g) and hydroxybenzotriazole (about 0.7 g) were added at room temperature and stirred for about 16 hours then completion of the reaction monitored by TLC. Reaction mixture was quenched with water and extracted with DCM, washed with saturated NaHCO₃ followed by brine solution, dried over Na₂SO₄ and concentrated under reduced pressure. The residue was purified by silica gel column chromatography using 15% ethyl acetate in hexane as eluent to furnish the title compound (0.8 g) as a yellow solid. ¹H NMR (300 MHz, CDC₁₃): 0.85-0.99 (m, 6H); 1.6-1.61 (m, 4H); 2.02-2.06 (m, 4H); 2.68-2.78 (m, 11H); 2.89-2.93 (m, 8H); 3.63-3.66 (m, 1H); 3.96-3.98 (m, 2H); 6.43-6.45 (d, J=7.2Hz, 1H); 7.08-8.49 (m, 12H); ES Mass: (100%), [M+I] 630; HPLC: 93.01%.

Similarly, the following compounds have been prepared by the above procedures using corresponding intermediates:

Example 21: N-((2S,3R)-3-hydroxy-4-(N-isobutyl-4-methoxyphenylsulfonamido)-1-phenylbutan-2-yl)-2-(1-(pyridin-2-yl)cyclohexyl)acetamide:

Yield: 0.8 g as a yellow solid. ¹H NMR (300 MHz, CDC₁₃) 0.73-0.75 (m, 6H); 1.42-1.45 (m, 6H); 2.13-2.17 (m, 1H); 2.47-2.48 (m, 2H); 2.69-3.06 (m, 7H); 3.85 (s, 3H); 4.24-4.28 (m, 1H); 4.79-4.82 (m, 1H); 6.30-6.33 (d, J=9.6Hz, 1H); 6.92-7.60 (m, 11H); 8.46-8.52 (m, 2H); ES Mass: (100%), [M]607; HPLC: 98.3%.

Example 22: N-((2S,3R)-3-hydroxy-4-(N-isobutyl-4-methylphenylsulfonamido)-1-phenylbutan-2-yl)-2-(1-(pyridin-2-yl)cyclohexyl)acetamide:
Yield: 0.8 g as a yellow solid. $^1$H NMR (300 MHz, CDCl$_3$): 0.82-0.87 (m, 6H); 1.50-1.61 (m, 13H); 1.75-1.78 (d, J=7.2Hz, 2H); 2.59 (s, 3H); 2.81-2.94 (m, 8H); 3.60-3.63 (m, 2H); 3.96-3.99 (m, 2H); 4.21 (s, 1H); 7.07-7.11 (d, J=11.4Hz, 1H); 7.20-7.63 (m, 10H); 8.45-8.47 (m, 1H); ES Mass: (100%), [M+Na] 592; HPLC: 95%.

Example 23: N-f(2S,3R)-3-hydroxy-4-(N-isobutyl-4-nitrophenylsulfonaniido)-1-phenylbutan-2-yl)-2-(1-(pyridin-2-y1)cyclohexyl)acetamide:

Yield: 0.8 g as a yellow solid. $^1$H NMR (300 MHz, CDCl$_3$): 0.82-0.87 (m, 6H); 1.34-1.37 (m, 4H); 1.67-1.79 (m, 2H); 1.99 (m, 2H); 2.58 (s, 2H); 2.72-2.91 (m, 6H); 3.61-3.62 (m, J=3 Hz, IH); 4.1-4.17 (m, 3H); 6.25-6.67 (m, 3H); 7.07-7.60 (m, 10H); 8.461-8.464 (m, 1H); ES Mass: (100%), [M+Na] 645.

Example 24: N-((2S,3R)-4-(4-amino-N-isobutylphenylsulfonamido)-3-hydroxy-1-phenylbutan-2-yl)-2-(1-(pyridin-2-y1)cyclohexyl)acetamide:

Yield: 0.8 g as a yellow solid. $^1$H NMR (300 MHz, CDCl$_3$): 0.82-0.87 (m, 6H); 1.34-1.37 (m, 4H); 1.67-1.79 (m, 2H); 1.99 (m, 2H); 2.58 (s, 2H); 2.72-2.91 (m, 6H); 3.61-3.62 (m, J=3 Hz, IH); 4.1-4.17 (m, 3H); 6.25-6.67 (m, 3H); 7.07-7.60 (m, 10H); 8.461-8.464 (m, 1H); ES Mass: (100%), [M+Na] 645; HPLC: 99.7%.

Example 25: 2-(4,4-difluoro-1-(pyridin-2-y1)cyclohexyn-N-(2S,3R)-3-hydroxy-4-(N-isobutyl-4-methoxyphenylsulfonamido)-1-phenylbutan-2-yl)acetamide:
Yield: 0.06 g as a light yellow solid. $^1$H NMR (300 MHz, CDCl$_3$): $\delta$ 0.83 -0.88 (m, 6H); 1.70 - 1.81 (m, 4H); 2.49 - 2.66 (m, 4H); 2.74 - 2.90 (m, 8H); 3.87 (s, 3H); 3.99 - 4.03 (m, 2H); 6.94 - 6.95 (m, 1H); 6.97 - 6.98 (m, 2H); 7.06 - 7.22 (m, 7H); 7.22 - 7.69 (m, 3H); 8.51 - 8.53 (d, J= 6 Hz, 1H); Mass: 666[M+Na]; HPLC: 96.25%.

Example 26: N-((2S3R)-4-(4-fluoro-N-isobutylphenylsulfonamido)-3-hydroxy-l-phenylbutan-2-yl)-2-(1-(pyridin-2-yl)cyclohexyl)acetamide:

![Chemical Structure]

$^{1}$H NMR (300 MHz, CDC$_1$$_3$): 0.82 - 0.86 (m, 6H), 1.25 - 1.61 (m, 11H), 2.61 - 2.99 (m, 8H), 3.62 - 3.64 (d, J= 3.9 Hz, 1H), 4.22 - 4.24 (d, J= 3.9 Hz, 2H), 7.07 - 7.31 (m, 9H), 7.60 - 7.63 (m, 1H), 7.73 - 7.78 (m, 2H), 8.45 - 8.46 (m, 1H); ES Mass: (100%), [M+l] 596; HPLC purity: 98.36%.

Example 27: Preparation of N-((2S,3R)-4-(3-chloro-4-fluoro-N-isobutylphenylsulfonamido)-3-hydroxy-l-phenylbutan-2-yl)-(methoxymethyl)cyclopentanecarboxamide:

To a stirred solution of l-(methoxymethyl)cyclopentanecarboxylic acid (Intermediate 3B, about 0.5 g) in DCM (25 ml) N-((2R,3S)-3-amino-2-hydroxy-4-phenylbutyl)-3-chloro-4-fluoro-N-isobutylbenzenesulfonamide (about 1.4 g) was added followed by l-Ethyl-3-(3-Dimethylaminopropyl)carbodiimide (about 1.3 g) and hydroxybenzotriazole (about 0.7 g) were added at room temperature and stirred for about 16 hours then completion of the reaction monitored by TLC. The reaction mixture was quenched with water and extracted with DCM, washed with saturated NaHCO$_3$ followed by brine solution, dried over Na$_2$SO$_4$ and concentrated under reduced pressure. The residue was purified by silica gel column chromatography using 15% ethyl acetate in hexane as eluent to furnish the title compound (0.8 g) as a yellow solid. $^{1}$H NMR (300 MHz, DMSO-D$_6$): $\delta$ 0.804 - 0.84 (m, 6H); 1.25 - 1.34 (m,
Similarly, the following compounds have been prepared by the above procedure using corresponding intermediates:

**Example 28:** N-((2S,3R)-4-(4-amino-N-isobutylphenylsulfonamido)-3-hydroxy-1-phenylbutan-2-yl)-1-(methoxymethyl)cyclopentanecarboxamide:

![Chemical structure](image)

Yield: 0.78 g as a white solid. $^1$H NMR (300 MHz, CDCl$_3$): 0.85-0.95 (m, 6H); 1.4-1.91 (m, 8H); 2.84-3.25 (m, 10H); 3.75-3.78 (m, 1H); 4.12 (s, 3H); 4.57-4.58 (d, J=3 Hz, 1H); 6.66-6.69 (d, J=9 Hz, 2H); 6.97-7.00 (d, J=3 Hz, 1H); 7.15-7.35 (m, 5H); 7.55-7.58 (d, J=9 Hz, 2H); Mass (M+Na$^+$): 554.

**Example 29:** N-((2S,3R)-3-hydroxy-4-(N-isobutyl-4-methoxyphenylsulfonamido)-1-phenylbutan-2-yl)-1-(methoxymethyl)cyclopentanecarboxamide:

![Chemical structure](image)

Yield: 0.8 g as a yellow solid. $^1$H NMR (300 MHz, CDCl$_3$): 0.90-0.87 (m, 6H), 1.45-1.41 (m, 4H), 1.86-1.80 (m, 3H), 2.90-2.88 (m, 2H), 3.10-3.02 (m, 5H), 3.17 (s, 3H), 3.49-3.45 (m, 1H), 3.79-3.76 (m, 1H), 3.87 (s, 3H), 4.14-4.09 (m, 1H), 4.56-4.55 (d, J=3 Hz), 7.00-6.96 (m, 3H), 7.29-7.20 (m, 5H), 7.74-7.72 (m, 2H); Mass: (100%), [M+1]$: 546$; HPLC: 97.7%.

**Example 30:** N-((2S,3R)-4-(3-chloro-4-fluoro-N-isobutylphenylsulfonamido)-3-hydroxy-1-phenylbutan-2-yl)-1-(methoxymethyl)cyclopentanecarboxamide:
Yield: 0.8 g as a yellow solid. ¹H NMR (300 MHz, DMSO-D₆): δ 0.804 -0.84 (m, 6H); 1.25-1.34 (m, 7H); 1.63-1.94 (m, 2H); 2.60-2.64 (m, 1H); 2.87-2.93 (m, 1H); 3.03-3.21 (m, 7H); 3.21-3.85 (m, 2H); 4.99-5.02 (d, J=9 Htz, 1H); 7.16-7.21 (m, 5H); 7.62-8.00 (m, 3H); Mass: (100%), [M]; 569; HPLC: 98.6%.

Example 31: N-((2S,3R)-3-hydroxy-4-(N-isobutyl-4-nitrophenylsulfonamido)-1-phenylbutan-2-yl)-l-(methoxymethyl)cyclopentanecarboxamide:

Example 32: N-((2S,3R)-3-hydroxy-4-(N-isobutyl-4-nitrophenylsulfonamido)-1-phenylbutan-2-yl)-2-((R)-tetrahydrofurari-3-yloxy)benzamide:

To a stirred solution of (S)-2-(tetrahydrofuran-3-yloxy)benzoic acid (intermediate 5A, about 0.5 g) in DCM (25 ml) N-((2R,3S)-3-amino-2-hydroxy-4-phenylbutyl)-N-isobutyl-4-nitrobenzenesulfonamide (Intermediate 6, about 1.3 g) was added followed by 1-Ethyl-3-(3-Dimethylaminopropyl)carbodiimide (about 1.3 g) and Hydroxybenzotriazole (0.7 g) were added at room temperature and stirred for about 16 hours then completion of the reaction was monitored by TLC. The reaction mixture was quenched with water and extracted with DCM, washed with saturated
NaHCO₃ followed by brine solution, dried over Na₂SO₄ and concentrated under reduced pressure. The residue was purified by silica gel column chromatography using 15% ethyl acetate in hexane as eluent to furnish the title compound (0.8 g) as a yellow solid. ¹H NMR (300 MHz, CDCl₃): 0.86-0.89 (m, 6H); 2.08-2.22 (m, 2H); 2.84-2.87 (m, 4H); 3.00-3.25 (m, 6H); 3.80-3.96 (m, 6H); 4.21-4.23 (d, J=6Hz, 2H); 5.06-5.07 (d, J=3Hz, 1H); 6.90-6.93 (d, J=9Hz, 1H); 7.09-8.26 (m, 11H); ES Mass: (100%), [M+Na] 634; HPLC: 95.0%.

Similarly, the following compounds have been prepared by the above procedure using corresponding intermediates:

Example 33: N-((2S,3R)-4-(4-amino-N-isobutylphenylsulfonamido)-3-hydroxy-1-phenylbutan-2-yl)-2-((R)-tetrahydrofuran-3-yl)oxy)benzamide:

Yield: 0.8 g as a yellow solid. ¹H NMR (300 MHz, CDCl₃): 0.82-0.87 (m, 6H); 2.08-2.22 (m, 2H); 2.84-2.87 (m, 4H); 3.05-3.11 (m, 4H); 3.82-3.91 (m, 5H); 4.09 (s, 2H); 4.22-4.23 (d, J=3Hz, 1H); 4.38-4.42 (m, 1H); 5.02-5.02 (d, J=1.5Hz, 1H); 6.60-6.63 (d, J=9Hz, 2H); 6.83-6.86 (d, J=9Hz, 1H); 7.07-8.20 (m, 12H); ES Mass: (100%), [M+Na] 604; HPLC: 95.0%.

Example 34: N-((2S,3R)-3-hydroxy-4-(N-isobutyl-4-methoxyphenylsulfonamido)-1-phenylbutan-2-yl)-2-((R)-tetrahydrofuran-3-yl)oxy)benzamide:

Yield: 0.8 g as a yellow solid. ¹H NMR (300 MHz, CDCl₃): 0.82-0.87 (m, 6H); 1.26 (s, 1H); 2.02 (s, 3H); 2.85-3.06 (m, 3H); 3.07-3.09 (m, 1H); 3.09-3.11 (m, 4H); 3.83-3.90 (m, 6H); 3.91-3.919 (s, 1H); 3.98-4.00 (d, J=6Hz, 1H); 5.03-5.05 (m, 1H); 6.85-6.93 (m, 5H); 7.08-8.20 (m, 7H); ES Mass: (100%), [M+Na] 597; HPLC: 98.6%.
Example 35: N-((2S,3R)-4-(3-chloro-4-fluoro-N-isobutylphenylsulfonamido)-3-hydroxy-l-phenylbutan-2-yl)-2-((R)-tetrahydrofuran-3-yloxy)benzamide:

Yield: 0.8 g) as a yellow solid. $^1$H NMR (300 MHz, CDC$_1$$_3$): 0.86-0.87 (m, 6H); 1.6 (s, IH); 2.34 (m, 3H); 2.91 (m, IH); 2.93 (m, IH); 3.04-3.17 (m, 6H); 3.83-3.89 (m, 5H); 3.99 (s, IH); 4.22-4.23 (d, J=3Hz, IH); 5.05-5.06 (d, J=3Hz, IH); 6.88-6.91 (d, J=9Hz, IH); 7.07-7.22 (m, 6H); 7.41-7.44 (m, IH); 7.62-8.19 (m, 4H); ES Mass: (100%), [M+I] 619; HPLC: 99.5%.

Example 36: 3-chloro-N-((2S,3R)-3-hydroxy-4-(N-isobutyl-4-methoxyphenylsulfonamido)-l-phenylbutan-2-yl)-5-((R)-tetrahydrofuran-3-yloxy)benzamide:

Yield: 0.8 g as a yellow solid. $^1$H NMR (300 MHz, CDC$_1$$_3$): 0.83-0.90 (m, 6H); 1.82-2.26 (m, 3H); 2.82-3.12 (m, 6H); 3.84 (s, 3H); 3.87-4.14 (m, 7H); 5.00-5.01 (d, J=3Hz, 1H); 6.85-7.30 (m, 8H); 6.82-8.29 (m, 12H); ES Mass: (100%), [M+Na] 653; HPLC: 99.6%.

Example 37: 3-chloro-N-((2S,3R)-3-hydroxy-4-(N-isobutyl-4-nitrophenylsulfonamido)-l-phenylbutan-2-yl)-5-((S)-tetrahydrofuran-3-yloxy)benzamide:

Yield: 0.8 g as a yellow solid. $^1$H NMR (300 MHz, CDC$_1$$_3$): 0.83-0.90 (m, 6H); 1.91-2.97 (m, 3H); 3.00-3.25 (m, 6H); 3.83-3.99 (m, 6H); 4.13-4.15 (d, J=6Hz, 1H); 5.04-5.07 (m, 1H); 6.92-8.29 (m, 12H); ES Mass: (100%), [M+Na] 668; HPLC: 99.6%.
Example 38: N-((2S,3R)-4-(4-amino-N-isobutylphenylsulfonamido)-3-hydroxy-1-phenylbutan-2-yl)-3-chloro-5-((R)-tetrahydrofuran-3-yloxy)benzamide:

Yield: 0.06 g as a light yellow solid. $^1$H NMR (300 MHz, CDCl$_3$): 0.83-0.90 (m, 6H); 2.02-2.28 (m,6H) ÷ 2.79-3.12 (m,6H) 3.84-3.92 (m,5H) 4.11-4.18 (m,3H) 5.00-5.01 (d, J= 3Hz,1H); 6.62-6.65(d, j=9 Hz,1H) ;6.84-7.52 (m,9H) ;8.05-8.09 (m,2H); ES Mass: (100%), [M+Na]638; HPLC: 95.1%.

Example 39: N-((2S,3R)-3-hydroxy-4-(N-isobutyl-4-methoxyphenylsulfonamido)-1-phenylbutan-2-yl)-4-methyl-2-((R)-tetrahydrofuran-3-yloxy)benzamide:

$^1$H NMR (300 MHz, CDCl$_3$): 0.85-0.94 (m, 6H), 1.27-1.32 (m, 1H), 1.61 (m, 1H), 2.21 (m, 3H), 2.39 (s, 3H), 2.86-3.12 (m, 6H), 3.80-3.90 (m, 8H), 4.29-4.30 (d, J=3.3 Hz, 2H), 5.03-5.04 (m, 1H), 6.67-8.18 (m, 12H); ES Mass: (100%), [M+Na] 633; HPLC purity: 96.2%.

Example 40: N-((2S,3R)-4-(3-chloro-4-fluoro-N-isobutylphenylsulfonamido)-3-hydroxy-1-phenylbutan-2-yl)-4-methyl-2-((R)-tetrahydrofuran-3-yloxy)benzamide:

$^1$H NMR (300 MHz, CDCl$_3$): 0.86-0.88 (m, 6H), 1.89 (m, 1H), 2.03 (m, 1H), 2.20 (m, 1H), 2.38 (s, 3H), 3.01-3.18 (m, 6H), 3.82-3.98 (m, 5H), 4.33-4.37 (m, 2H), 5.03-5.05 (m, 1H), 6.68-8.13 (m, 11H); ES Mass: (100%), [M+Na] 655; HPLC purity: 99.73%.

Example 41: N-((2S,3R)-4-(3-chloro-4-fluoro-N-isobutylphenylsulfonamido)-3-hydroxy-1-phenylbutan-2-yl)-2-((R)-tetrahydrofuran-3-yloxy)benzamide:
Example 42: N-((2S,3R)-3-hydroxy-4-(N-isobutyl-4-methoxyphenylsulfonamido)-1-phenylbutan-2-yl)-2-((R)-tetrahydrofuran-3-yloxy)benzamide:

\[ ^1H \text{ NMR (300 MHz, CDCl}_3\] : 0.86-0.88 (m, 6H), 1.61 (m, IH), 2.34 (m, IH), 2.91-2.93 (m, 2H), 3.04-3.17 (m, 6H), 3.83-3.89 (m, 5H), 3.99 (m, IH), 4.22-4.23 (d, J=4.3 Hz, IH), 5.05-5.06 (d, J=1.5 Hz, IH), 6.88-6.91 (d, J=8.1 Hz, IH), 7.07-7.22 (m, 6H), 7.41-7.44 (m, IH), 7.62-8.19 (m, 4H); ES Mass: (100%), [M+Na] 641, [M+I] 619 (80%); HPLC purity: 99.5%.

Example 43: N-((2S,3R)-4-(4-amino-N-isobutylphenylsulfonamido)-3-hydroxy-1-phenylbutan-2-yl)-2-((R)-tetrahydrofuran-3-yloxy)benzamide:

\[ ^1H \text{ NMR (300 MHz, CDCl}_3\] : 0.82-0.87 (m, 6H), 1.60 (m, IH), 2.03 (m, 3H), 2.84-2.98 (m, 2H), 3.07-3.09 (m, IH), 3.1-3.12 (m, 4H), 3.40-3.83 (m, 6H), 3.91-3.92 (s, IH), 3.98-4.00 (d, J=4.5 Hz, IH), 5.03-5.05 (m, IH), 6.85-6.93 (m, 5H), 7.08-7.10 (m, 3H), 7.18-7.43 (m, 5H), 7.68-7.69 (d, J=3 Hz, 2H), 8.14-8.20 (m, 2H); ES Mass: [M+I] 597 (100%); HPLC purity: 98.60%.
Example 44: 4-fluoro-N-((2S,3R)-3-hydroxy-4-(N-isobutyl-4-methoxyphenylsulfonamido)-l-phenylbutan-2-yl)-2-((R)-tetrahydrofuran-3-yloxy)benzamide:

\[
\begin{align*}
^1H \text{ NMR (300 MHz, CDCl}_3\):} & \quad 0.88-0.92 (m, 6H), \quad 1.83-2.26 (m, 3H), \quad 2.82-3.07 (m, 6H), \quad 3.86 (s, 3H), \quad 3.97-4.41 (m, 5H), \quad 4.97 (s, 1H), \quad 6.55-6.60 (m, 1H), \quad 6.67-7.68 (m, 9H), \quad 8.05-8.19 (m, 4H); \quad \text{ES Mass: [M+1]615(100%); HPLC purity: 98.9%}. 
\end{align*}
\]

Example 45: N-((2S,3R)-4-(3-chloro-4-fluoro-N-isobutylphenylsulfonamido)-3-hydroxy-l-phenylbutan-2-yl)-2-(4-((R)-tetrahydrofuran-3-yloxy)phenyl)acetamide:

\[
\begin{align*}
^1H \text{ NMR (300 MHz, CDCl}_3\):} & \quad 0.86-0.93 (m, 6H), \quad 1.27-1.61 (m, 3H), \quad 2.87-2.94 (m, 5H), \quad 3.40 (s, 1H), \quad 4.00-4.32 (m, 6H), \quad 4.91-4.93 (m, 1H), \quad 5.33-5.56 (d, J=6.7Hz, 1H), \quad 6.77-7.32 (m, 6H), \quad 7.64-7.84 (m, 6H); \quad \text{ES Mass: [M+Na] 655 (100%); HPLC purity: 94.3%}. 
\end{align*}
\]

Example 46: N-((2S,3R)-3-hydroxy-4-(N-isobutyl-4-methoxyphenylsulfonamido)-l-phenylbutan-2-yl)-2-(4-((R)-tetrahydrofuran-3-yloxy)phenyl)acetamide:

\[
\begin{align*}
^1H \text{ NMR (300 MHz, CDCl}_3\):} & \quad 0.85-0.87 (m, 6H), \quad 1.62-2.21 (m, 3H), \quad 2.28-2.92 (m, 6H), \quad 3.72 (s, 1H), \quad 3.91-4.91 (m, 8H), \quad 4.89-4.91 (m, 1H), \quad 5.54-5.56 (d, J=8.1Hz, 1H), \quad 6.75-6.78 (d, J=8.7Hz, 2H), \quad 6.87-7.23 (m, 9H), \quad 7.67-7.70 (d, J=9Hz, 2H); \quad \text{ES Mass: [M+1] 611 (100%); HPLC purity: 99.5%}. 
\end{align*}
\]

Example 47: N-((2S,3R)-4-(4-amino-N-isobutylphenylsulfonamido)-3-hydroxy-l-phenylbutan-2-yl)-2-(4-((R)-tetrahydrofuran-3-yloxy)phenyl)acetamide:
Example 48: N-((2S,3R)-3-hydroxy-4-(N-isobutyl-4-methoxyphenylsulfonamido)-1-phenylbutan-2-yl)-2-(4-((S)-tetrahydrofuran-3-yloxy)phenyl)acetamide:

\[
\text{H NMR (300 MHz, CDC13): 0.85-0.88 (m, 6H), 2.18-3.05 (m, 6H), 3.36 (s, 2H), 3.91-4.02 (m, 4H), 4.16 (s, 3H), 4.32-4.33 (d, J=4.5Hz, 2H), 4.89-4.91 (d, J=2.4Hz, 3H), 5.52-5.58 (d, J=18Hz, 1H), 6.65-6.69 (m, 4H), 6.75-6.78 (d, J=8.7Hz, 2H), 6.90-7.21 (m, 6H); ES Mass: [M+Na] 618 (100%); HPLC purity: 95.7%}
\]

Example 49: Preparation of l-(2-ethoxyethyl)-N-((2S,3R)-3-hydroxy-4-(N-isobutyl-4-methoxyphenylsulfonamido)-1-phenylbutan-2-yl)cyclopentanecarboxamide:

To a stirred solution of l-(2-ethoxyethyl)cyclopentanecarboxylic acid (Intermediate 3C, about 0.20 g) in DCM (25 ml), N-((2R,3S)-3-amino-2-hydroxy-4-phenylbutyl)-N-isobutyl-4-methoxybenzenesulfonamide (about 0.43 g) was added and stirred at room temperature followed by l-Ethyl-3-(3-dimethylaminopropyl)carbodiimide (about 0.41 g) and hydroxybenzotriazole (about 0.21 g) were added at room temperature and stirred for about 16 hours then completion of the reaction monitored by TLC. The reaction mixture was quenched with water and extracted with DCM, washed with saturated NaHCO\textsubscript{3} followed by brine solution, dried over Na\textsubscript{2}SO\textsubscript{4} and concentrated under reduced pressure. The residue was purified by silica gel column chromatography using 15% ethyl acetate.
in hexane as eluent to furnish the title compound (0.10 g) as a light yellow solid. 

\[ ^1 \text{H NMR (300 MHz, CDCl}_3\]:} \delta 0.88-0.90 (m, 6H); 1.11-1.15 (m, 3H); 1.39-1.56 (m, 7H); 1.72-1.86 (m, 6H); 2.87-2.88 (m, 2H); 2.87-2.97 (m, 3H); 3.00-3.36 (m, 5H); 3.87 (s, 3H); 4.44-4.46 (m, 1H); 6.96-6.97 (d, J = 3Hz, 1H); 6.99-7.71 (m, 7H); 7.72-7.73 (d, J = 3Hz, 2H); Mass: 597[M+Na]; HPLC: 95.1%.

Similarly, the following compounds have been prepared by the above procedure using corresponding intermediates:

Example 50: N-((2S,3R)-4-(4-amino-N-isobutylphenylsulfonamido)-3-hydroxy-1-phenylbutan-2-vD-1-(2-ethoxyethyl)cvclopentanecarboxamide:

Yield: 0.10 g as a white solid. 

\[ ^1 \text{H NMR (300 MHz, CDCl}_3\]:} \delta 0.88-0.90 (m, 6H); 1.11-1.16 (m, 3H); 1.42-1.87 (m, 12 H); 2.85-2.87 (d, J = 6Hz, 2H); 2.97-3.00 (m, 6H); 3.02-3.04 (d, J = 6Hz, 2H); 3.16-3.23 (m, 2H); 3.85-3.86 (d, J = 3Hz, 1H); 4.18-4.20 (m, 1H); 4.22-4.44 (m, 1H); 6.25-6.27 (d, J = 6Hz, 1H); 6.66-6.69 (d, J = 9Hz, 2H); 7.20-7.29 (m, 5H); 7.54-7.57 (d, J = 9Hz, 2H); Mass: 582[M+Na]; HPLC: 92.1%.

Example 51: (l-(2-ethoxyethyl)cvclopentyl)methyl (2S,3R)-3-hydroxy-4-(N-isobutyl-4-methoxyphenylsulfonamido)-1-phenylbutan-2-yIcarbamate:

Yield: 0.15 g as a light yellow solid. 

\[ ^1 \text{H NMR (300 MHz, CDCl}_3\]:} \delta 0.85-0.92 (m, 6H); 1.15-1.19 (m, 3H); 1.37-1.38 (m, 5H); 1.79-1.87 (m, 2H); 2.81 (s, 3H); 2.91-2.94 (m, 4H); 3.01-3.05 (m, 5H); 3.36-3.45 (m, 4H); 3.76 (s, 3H); 3.83-3.88 (m, 1H); 4.80-4.82 (d, J = 6Hz, 1H); 6.96-6.99 (d, J = 9Hz, 2H); 7.20-7.23 (m, 5H); 7.69-7.72 (d, J = 9Hz, 2H); Mass: 627[M+Na]; HPLC: 95.8%.
Example 52A: Preparation of 2-ethyl-N-((2S,3S)-3-hydroxy-4-(N-isobutyl-4-nitrophenylsulfonamido)-1-phenylbutan-2-yl) tetrahydrofuran-2-carboxamide:

To a stirred solution of 2-ethyltetrahydrofuran-2-carboxylic acid (Intermediate 10, about 0.5 g) in DCM N-((2S,3S)-3-amino-2-hydroxy-4-phenylbutyl)-N-isobutyl-4-nitrobenzenesulfonamide (1.3 g) was added followed by 1-Ethyl-3-(3-Dimethylaminopropyl)carbodiimide (about 1.3 g) and Hydroxybenzotriazole (about 0.7 g) were added at room temperature and stirred for about 16 hours. Completion of the reaction was monitored by TLC. The reaction mixture was quenched with water and extracted with DCM. The organic layer was washed with sat. NaHCO₃ followed by brine solution, dried over Na₂SO₄ and concentrated under reduced pressure. The residue was purified by silica gel column chromatography using 15% ethyl acetate in hexane as eluent to furnish the title compound (0.8 g) as a yellow solid. \(^1\)H NMR (300 MHz, CDCl₃): \(\delta 0.58-0.63\) (m, 3H); 0.77-0.94 (m, 6H); 1.42 (m, 1H); 1.74-1.86 (m, 4H); 2.84-2.99 (m, 4H); 3.10-3.19 (m, 2H); 3.76-3.79 (m, 2H); 4.18-4.64 (m, 2H); 7.20-7.28 (m, 5H); 7.96-7.97 (d, \(j=2.1\) Hz, 2H); 8.34-8.35 (d, \(j=1.8\) Hz, 2H); ES Mass: 547 (100%), [M+Na] 570; HPLC: 96.0%.

Example 52B: Preparation of N-((2S,3R)-4-(4-amino-N-isobutylphenylsulfonamido)-3-hydroxy-1-phenylbutan-2-yl)-2-ethyltetrahydrofuran-2-carboxamide:

\(^1\)H NMR (300 MHz, CDCl₃): 0.55-0.60 (m, 3H), 0.76-0.78 (m, 6H), 0.80-0.93 (m, 1H), 1.24-1.288 (m, 1H), 1.61-1.66 (m, 3H), 1.77-1.85 (m, 1H), 2.05 (m, 1H), 2.83-2.98 (m, 3H), 3.88-4.20 (m, 4H), 6.66-6.69 (d, \(j=9\) Hz, 2H), 7.19-7.58 (m, 7H); ES Mass: 517 (100%), [M+H] 518; HPLC: 96.2%.
Example 53: 2-ethyl-N-((2S,3R)-3-hydroxy-4-(N-isobutyl-4-methoxyphenylsulfonamido)-l-phenylbutan-2-yl)tetrahydrofuran-2-carboxamide:

Yield: 0.8 g as a yellow solid. $^1$H NMR (300 MHz, CDCl$_3$):  δ : 0.56-0.61 (m,3H); 0.77-0.94(m,6H); 1.42(m,1H); 1.74-1.86(m,4H); 2.84-2.99(m,4H); 3.10-3.19(m,2H); 3.76-3.79(m,2H); 3.87(s,1H); 4.18-4.64(m,2H); 6.96-6.99(m,2H); 7.20-7.28(m,5H); 7.72-7.74(m,2H); ES Mass: 532. (100%), [M+Na] 555; HPLC: 96.0%.

Example 54: N-((2S3R)-3-hydroxy-4-(N-isobutyl-4-methoxyphenylsulfonamido)-l-phenylbutan-2-vl)-2-((S)-tetrahydrofuran-3-yloxy)propanamide:

To a stirred solution of 2-((S)-tetrahydrofuran-3-yloxy)propanoic acid (about 0.30 g) in DCM (25 ml) N-((2R,3S)-3-amino-2-hydroxy-4-phenylbutyl)-N-isobutyl-4-methoxybenzenesulfonamide (about 0.70 g) was added and stirred at room temperature followed by 1-Ethyl-3-(3-Dimethylaminopropyl)carbodiimide (about 0.72 g) and hydroxybenzotriazole (about 0.38 g) were added at room temperature and stirred for about 16 hours then completion of the reaction was monitored by TLC. The reaction mixture was quenched with water and extracted with DCM, washed with saturated NaHCO$_3$ followed by brine solution, dried over Na$_2$SO$_4$ and concentrated under reduced pressure. The residue was purified by silica gel column chromatography using 15% ethyl acetate in hexane as eluent to furnish the title compound (0.10 g) as a light yellow solid. (0.8g) as a yellow solid. $^1$H NMR (300 MHz, CDCl$_3$): 0.83-0.90 (m, 6H), 1.19-1.29 (m, 4H), 1.63-1.91 (m, 3H), 2.87-3.11 (m, 5H), 3.49-4.88 (m, 7H), 4.15-4.38 (m, 3H), 6.96-6.99 (m, 2H), 7.00-7.28 (m, 5H), 7.68-7.74 (m, 2H); ES Mass: (100%), [M+Na] 571; HPLC: 98.6%.

Example 55: (l-ethylcyclopentyl)methyl (2S,3R)-3-hydroxy-4-(N-isobutyl-4-methoxyphenylsulfonamido)-l-phenylbutan-2-ylcarbamate:

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Example 56: N-((2S,3R)-4-(3-chloro-4-fluoro-N-isobutylphenylsulfonamido)-3-hydroxy-1-phenylbutan-2-yl)-1-oxaspiro[4.4]nonane-7-carboxamide:

\[ \text{H NMR (300 MHz, CDCl}_3\text{)}: 0.75-0.87 (m, 6H), 0.88-0.92 (m, 3H), 1.25-1.32 (m, 8H), 1.55 (s, 3H), 2.78-3.10 (m, 7H), 3.76-3.93 (m, 6H), 4.76-4.78 (d, J=6Hz, 1H), 6.91-7.00 (d, J=3Hz, 2H), 7.20 (s, 5H), 7.70-7.73 (d, J=9Hz, 2H); ES Mass: (100%), [M+Na] 583; HPLC purity: 94.2%.

Example 57: N-((2S,3R)-3-hydroxy-4-(N-isobutyl-4-methoxyphenylsulfonamido)-1-phenylbutan-2-yl)-1-oxaspiro[4.4]nonane-7-carboxamide:

\[ \text{H NMR (300 MHz, CDCl}_3\text{): 0.85-0.91 (m, 6H), 1.69-1.88 (m, 13H), 2.84-2.95 (m, 4H), 3.03-3.09 (m, 3H), 3.55-4.61 (m, 9H), 6.96-6.98 (d, J=6Hz, 2H), 7.19-7.28 (m, 5H), 7.71-7.74 (d, J=9Hz, 2H); ES Mass: [M+Na] 581 (100%); HPLC purity: 96.4%.

Example 58: N-((2S,3R)-3-hydroxy-4-(N-isobutyl-4-methylphenylsulfonamido)-1-phenylbutan-2-yl)-1-oxaspiro[4.4]nonane-7-carboxamide:
Example 59: N-((2S,3R)-4-(4-amino-N-isobutylphenylsulfonamido)-3-hydroxy-1-phenylbutan-2-yl)-1-oxaspiro4.41nonane-7-carboxamide:

![Chemical Structure Image]

$^1$H NMR (300 MHz, DMSO-D6): 0.77-0.85 (m, 6H), 1.94-1.96 (m, 1H), 2.25 (s, 3H), 2.80-2.86 (m, 2H), 3.06-3.14 (m, 4H), 3.72-3.74 (d, J=6.3Hz, 1H), 4.09-4.11 (d, J=7.5Hz, 1H), 5.26-5.28 (d, J=6.9Hz, 1H), 6.66-6.71 (m, 2H), 7.10-7.19 (m, 6H), 7.24-7.50 (m, 1H), 7.73-8.52 (m, 3H); ES Mass: [M+1] 543 (100%); HPLC purity: 93.4%.

Example 60: N-((2S,3R)-4-(4-fluoro-N-isobutylphenylsulfonamido)-3-hydroxy-1-phenylbutan-2-yl)-2-((S)-tetrahydrofuran-3-yloxy)acetamide:

$^1$H NMR (300 MHz, CDCl3): 0.84-0.92 (m, 6H), 1.52-2.11 (m, 11H), 2.85-3.03 (m, 7H), 3.55-3.70 (m, 3H), 4.09-4.60 (m, 4H), 6.66-6.69 (d, J=9Hz, 2H), 7.24-7.27 (m, 5H), 7.54-7.57 (d, J=9Hz, 2H), 7.73-8.52 (m, 3H); ES Mass: [M+1] 566 (100%); HPLC purity: 95.5%.

Example 61: (2-ethyltetrahydrofuran-2-yl)methyl (2S,3R)-3-hydroxy-4-(N-isobutyl-4-methoxyphenylsulfonamido)-1-phenylbutan-2-ylcarbamate:

$^1$H NMR (300 MHz, CDCl3): 0.75-0.87 (m, 6H), 1.12 (s, 3H), 1.45-1.66 (m, 8H), 2.05-2.97 (m, 5H), 3.02-3.15 (m, 5H), 3.87 (s, 3H), 6.96-6.99 (d, J=9Hz, 1H), 7.23-
7.69 (m, 6H), 7.70-7.72 (d, J=9Hz, 2H); ES Mass: [M+Na] 585 (100%); HPLC purity: 97.1%.

Similarly, the following compounds have been prepared by the above procedures using corresponding intermediates:

Example 62: 1-(2-ethoxyethyl)-N-((2S)-3-hydroxy-4-((1R,5S)-3-(4-methoxyphenylsulfonamido)-8-azabicyclo[3.2.1]octan-8-yl)-1-phenylbutan-2-yl)cyclopentanecarboxamide:

IR cm⁻¹: 3383, 2955, 2054, 1597, 1498, 1260, 1153, 1095, 1024, 836, 563

¹H NMR (300 MHz, CDCl₃): δ 1.12-1.16 (m, 3H); 1.43-1.45 (m, 8H); 1.73-1.79 (m, 6H); 1.81-1.84 (d, J=9Hz, 3H); 2.09 (m, 2H); 2.28 (m, 2H); 2.74 (m, 3H); 2.86-2.88 (m, 4H); 3.13-3.39 (m, 2H); 3.559 (s, 3H); 4.13-4.14 (d, J=3Hz, 2H); 6.38 (s, 1H); 6.97-7.00 (d, J=9Hz, 2H); 7.22-7.27 (m, 5H); 7.83-7.86 (d, J=9Hz, 2H); ES Mass: 627 (100%), [M+H] 628; HPLC: 95.2%.

Example 63: N-((2S,3S)-3-hydroxy-4-(N-isobutyl-4-methoxyphenylsulfonamido)-1-phenylbutan-2-yl)cyclopentanecarboxamide:

¹H NMR (300 MHz, CDCl₃): 1.25-1.27 (m, 2H); 1.43-1.45 (m, 9H); 1.49-1.51 (m, 3H); 1.77-1.85 (m, 3H); 2.97-3.00 (m, 2H); 3.02-3.07 (m, 4H); 3.11-3.21 (m, 4H); 3.78-3.80 (m, 1H); 3.87 (s, 3H); 4.14-4.19 (m, 2H); 4.40-4.41 (m, 1H); 6.94-7.01 (m, 3H); 7.20-7.22 (m, 2H); 7.28-7.31 (m, 2H); 7.74-7.76 (d, J=8 Hz, 2H); Mass: 581 [M+Na]; HPLC: 95.63%.

Example 64: 4,4-dimethyl-2-oxotetrahydrofuran-3-yl (2R,3S)-4-(4-amino-N-isobutylphenylsulfonamido)-3-hydroxy-1-phenylbutan-2-ylcarbamate:
Example 65: 4,4-dimethyl-2-oxotetrahydrofuran-3-yl (2R,3S)-4-(N-cyclopentyl-4-methoxyphenylsulfonamido)-3-hydroxy-1-phenylbutan-2-ylcarbamate:

\[ \text{NMR (300 MHz, CDC13): } 0.90-0.92 \text{ (m, 12H); 1.79-1.93 (m, 2H); 2.83-2.87 (m, 2H); 3.07-3.14 (m, 2H); 3.25-3.30 (m, IH); 3.41-3.44 (m, IH); 3.83-3.84 (m, 3H); 4.14-4.27 (m, 3H); 6.68-6.71 (d, J=9 Hz, 2H); 7.21-7.24 (m, 5H); 7.57-7.60 (d, J=9 Hz, 2H); Mass: 547; [M+Na] 550; HPLC: 97.24\%.

Example 66: (R)-4,4-dimethyl-2-oxotetrahydrofuran-3-yl (2S,3R)-3-hydroxy-4-(4-(4-methoxyphenylsulfonamido)piperidin-1-yl)-1-phenylbutan-2-ylcarbamate:

\[ \text{NMR (300 MHz, CDC13): } 1.14 \text{ (s, 6H); 1.41-1.47 (m, 4H); 1.50-1.56 (m, 4H); 1.75-2.02 (m, 5H); 2.31-2.83 (m, 5H); 3.18-3.42 (m, 5H); 3.60-3.67 (m, 2H); 3.88 (s, 3H); 4.15-4.45 (m, 3H); 6.96-6.99 (d, J= 3Hz, 2H); 7.14-7.22 (m, 5H); 7.79-7.82 (d, J=3Hz, 2H); ES Mass: 589 (100\%), [M+Na] 612; HPLC: 98.29\%.

Example 67: (R)-tetrahydrofuran-3-yl (2S,3R)-3-hydroxy-4-(4-(4-methoxyphenylsulfonamido)piperidin-1-yl)-1-phenylbutan-2-ylcarbamate:
IR cm⁻¹: 3388, 2946, 1702, 1498, 1329, 1259, 1157, 1025, 835, 576. ¹H NMR (300 MHz, CDCl₃): 1.39-1.49 (m, 3H); 1.76-1.80 (m, 3H); 1.90-1.99 (m, 4H); 2.032-829 (m, 7H); 3.15-3.17 (d, J=6Hz, 1H); 3.59-3.84 (m, J=6Hz, 6H); 3.88 (s, 3H); 4.40-4.43 (d, J=9Hz, 1H); 4.74-5-12 (m, 2H); 6.96-6.99 (m, 2H); 7.18-7.80 (m, 5H); 7.81-7.82 (d, J=3Hz, 2H); Mass: 547.[M+Na].100% 570; HPLC: 98.6%.

Example 68: l-ethyl-N-((2S,3R)-3-hydroxy-4-(4-(4-methoxyphenylsulfonamido)piperidin-1-yl)-1-phenylbutan-2-yl)cyclopentanecarboxamide:

¹H NMR (300 MHz, CDCl₃): δ 0.57-0.62 (m, 3H); 0.85-0.88 (m, 2H); 1.26-1.39 (m, 10H); 1.40-1.56 (m, 11H); 1.73-1.98 (m, 9H); 2.02-2.43 (m, 1H); 3.48 (s, 3H); 4.19-5.50 (m, 2H); 5.52-6.99 (m, 6H); 7.18-7.19 (d, j=3Hz, 1H); 7.81-7.82 (d, j=3Hz); ES Mass: 557 (100%), [M+1] 558; HPLC: 96.1%.

Example 69: (R)-tetrahydrofuran-3-yl(2S)-3-hydroxy-4-((IR,5S)-3-(4-methoxyphenylsulfonamido)-8-azabicyclo[3.2.1]octan-8-yl)-1-phenylbutan-2-yl)cyclopentanecarboxamide:

¹H NMR (300 MHz, CDCl₃): 1.76-1.79 (m, 6H); 2.02-2.05 (m, 5H); 2.60-3.06 (m, 5H); 3.56-3.59 (d, j=9Hz, 3H); 3.73-3.87 (m, 5H); 4.06 (s, 3H); 5.08-5.11 (d, j=9Hz, 2H); 6.95-6.98 (d, j=9Hz); 7.19-7.29 (m, 5H); 7.80-7.83 (d, j=9Hz, 2H); Mass: 573.[M+1].100% 574; HPLC: 94.5%.

Example 70: N-((2SV3-hydroxy-4-((IR,5S)-3-(4-methoxyphenylsulfonamido)8-azabicyclo[3.2.1]octan-8-yl)-1-phenylbutan-2-yl)carboxamide:
Example 71: N-((2S,3S)-3-hydroxy-4-(N-isobutyl-4-methoxyphenylsulfonamido)-1-
phenylbutan-2-yl)-1-(methoxymethyl)cyclopentanecarboxamide:

1H NMR (300 MHz, CDCl3): δ 1.25-1.27 (m, 2H); 1.43-1.45 (m, 9H); 1.49-1.51 (m, 3H); 1.77-1.85 (m, 3H); 2.97-3.00 (m, 2H); 3.02-3.07 (m, 4H); 3.11-3.21 (m, 4H); 3.78-3.80 (m, 1H); 3.87 (s, 3H); 4.14-4.19 (m, 2H); 4.40-4.41 (m, 1H); 6.94-7.01 (m, 3H); 7.20-7.22 (m, 2H); 7.28-7.31 (m, 2H); 7.74-7.76 (d, J=8.7 Hz, 2H); Mass: 581[M+Na]; HPLC: 95.63%.

Example 72: Preparation of (3-ethyloxetan-3-yl)
methyl (2S)-3-hydroxy4-(N-isobutyl-4-nitrophenylsulfonamido)-1-phenylbutan-2-
ylcarbamate:

To a stirred solution of 2,5-dioxopyrrolidin-l-yl (3-ethyloxetan-3-yl)methyl carbonate (0.125 g , 0.297, mmol) in 4 ml DCM was added N-((2S,3S)-3-amino-2-
hydroxy-4-phenylbutyl)-N-isobutyl-4-nitrobenzenesulfonamide (0.113 g ,0.385 mm) followed by triethyl amine (0.05 ml ) were added at room temperature and stirred for 6 hours. TLC showed completion of reaction. Reaction mixture was quenched with water and extracted with DCM then the organic layer was washed with saturated NaHCO3 followed by brine solution. The organic layer was dried over
Na₂SO₄ and concentrated under reduced pressure. The residue was purified by silica gel column chromatography using 15% ethyl acetate in hexane as eluent to furnish the title compound (0.15 g) as a light yellow solid. ¹H NMR (300 MHz, CDCl₃): 0.82-0.87(s,6H); 0.90-0.92(s,3H); 1.25-1.29(m,1H); 2.72-2.79(m,1H); 2.88-3.11(m,5H); 4.93-4.96(d,J=9Hz,1H); 6.66-6.69(d,J=9Hz,2H); 7.22-7.31(m,5H); 7.52-7.55(d,J=9Hz,2H); Mass: 564. [M+1].100%.

Example 73: (3-ethyloxetan-3-yl) methyl (2S)-4-(4-amino-N-isobutylphenylsulfonamido)-3-hydroxy-1-phenylbutan-2-ylcarbamate:

Nitro group of Compound 72 upon reduction gave the title compound.

[Chemical structure image]

IR cm⁻¹: 3369, 2962, 1708, 1597, 1316, 1149, 772, 552. ¹H NMR (300 MHz, CDCl₃): 0.82-0.87 (s, 6H); 0.90-0.92 (s, 3H); 1.25-1.29 (m, 1H); 2.72-2.79 (m, 1H); 2.88-3.11 (m, 5H); 4.93-4.96 (d, J=9Hz, 1H); 6.66-6.69 (d, J=9Hz, 2H); 7.22-7.31 (m, 5H); 7.52-7.55 (d, J=9Hz, 2H); Mass: 519 [M+Na] 100% 534.

Similarly, the following compound has been prepared by the above procedure using corresponding intermediates:

Example 74: (3-methyloxetan-3-yl)methyl (2S,3R)-4-(4-amino-N-isobutylphenylsulfonamido)-3-hydroxy-1-phenylbutan-2-ylcarbamate:

[Chemical structure image]

IR cm⁻¹: 3369, 2962, 1708, 1597, 1316, 1149, 772, 552. ¹H NMR (300 MHz, CDCl₃): 0.82-0.87 (s, 6H); 0.90-0.92 (s, 3H); 1.25-1.29 (m, 1H); 2.72-2.79 (m, 1H); 2.88-3.11 (m, 5H); 4.93-4.96 (d, J=9Hz, 1H); 6.66-6.69 (d, J=9Hz, 2H); 7.22-7.31 (m, 5H); 7.52-7.55 (d, J=9Hz, 2H); Mass: 519 [M+Na] 100% 542.

Similarly, the following compounds have been prepared by corresponding procedures in the above using their corresponding intermediates:
Example 75: (2-ethyltetrahydrofuran-2-yl)methyl (2S,3R)-4-(4-amino-N-isobutylphenylsulfonamido)-3-hydroxy-1-phenylbutan-2-ylcarbamate:

\[
\text{\begin{figure}[h]
\centering
\includegraphics[width=0.5\textwidth]{example75}
\end{figure}}
\]

HPLC: 95.2%; MASS: 547 [M+Na] 100% 570; IR Cm': In (KBR): 3373, 2929, 1728, 1597, 1316, 1149, 1033, 773, 552; \(^1\)H NMR (300MHz, CDCl3): 0.82-0.87 (S, 6H); 0.90-0.92 (s, 3H); 1.28-1.49 (M, 3H); 1.62-1.86 (M, 6H); 2.70-2.78 (m, 1H); 2.86-3.12 (M, 4H); 3.70-3.80 (M, 4H); 3.84-3.94 (M, 4H); 4.85-4.87 (d, J=6Hz, 1H); 6.66-6.69 (d, J=9Hz, 2H); 7.21-7.28 (m, 4H); 7.52-7.55 (d, J=9Hz, 2H);

Example 76: (2S)-3-hydroxy-4-(N-isobutyl-4-methoxyphenylsulfonamido)-1-phenylbutan-2-yl 2-((R)-tetrahydrofuran-3-yloxy)acetate:

\[
\text{\begin{figure}[h]
\centering
\includegraphics[width=0.5\textwidth]{example76}
\end{figure}}
\]

HPLC: 95.9%; MASS: (534) [ M+Na]-557; \(^1\)H NMR (300MHz, CDCl3): 0.878-0.923 (M, 6H); 1.884-1.969 (M, 3H); 2.862-3.01 1 (M, 6H); 3.710-4.246 (M, 12H); 6.714-6.740 (M, IH); 6.984-7.747 (M, 9H).

Example 77: N-((2S)-4-(4-amino-N-cyclopentylphenylsulfonamido)-3-hydroxy-1-phenylbutan-2-yl)-1-(methoxymethyl)cyclopentanecarboxamide:

\[
\text{\begin{figure}[h]
\centering
\includegraphics[width=0.5\textwidth]{example77}
\end{figure}}
\]

HPLC: 98.43%; ES MASS: 618; ( 100%), [M+Na] 641; IR Cm': in (KBr): 3380, 2938, 1596, 1315, 1148, 742, 526; \(^1\)H NMR (300MHz, CDCl3): 1.44-1.50 (m, 3H); 1.78-1.88 (m, 3H); 2.91-3.16 (m, 10H); 3.28-3.43 (m, 3H); 3.78 (s, IH); 409 (s, 3H); 4.48 (s, IH); 6.63-6.66 (d, J=9Hz, 2H); 7.05-7.37 (m, 10H); 7.57-7.60 (d, J=9Hz, 2H); 8.04 (s, IH).

Example 78: N-((2S)-4-(4-amino-N-cyclopentylphenylsulfonamido)-3-hydroxy-1-phenylbutan-2-yl)-1-ethylcyclopentanecarboxamide:
HPLC: 97.13%; Mass: 527, [M+Na] 550; $^1$H NMR (300MHz, CDCL3): 0.61-0.65 (m, 3H); 1.18-1.77 (m, 16H); 2.95-2.99 (m, 2H); 3.11-3.12 (m, IH); 3.21-3.22 (m, 2H); 3.85-3.89 (m, IH); 4.07-4.40 (m, 5H); 5.84-5.87 (m, IH); 6.67-6.69 (d, J=4.5 Hz, 2H); 7.19-7.29 (m, 5H); 7.55-7.57 (d, J=4.8 Hz, 2H).

Example 79: N-((2S)-4-(N-cyclopentyl-4-methoxyphenylsulfonamido)-3-hydroxy-1-phenylbutan-2-yl)-1-(2-ethoxyethyl)cyclopentanecarboxamide:

HPLC: 90.36%; MASS: 586; [M+Na] 609; $^1$H NMR (300MHz, CDCL3): 1.18-1.26 (m, 4H); 1.40-1.47 (m, 8H); 1.71-1.76 (m, 8H); 1.79-1.83 (m, 4H); 2.98-3.08 (m, 3H); 3.11-3.13 (m, 2H); 3.13-3.22 (m, 2H); 3.88 (s, 3H); 4.12-4.31 (m, 2H); 5.30 (s, IH); 6.28-6.31 (m, 2H); 6.95-6.98 (d, J=9Hz, 2H); 7.21-7.23 (m, 5H); 7.73-7.76 (d, J=9Hz, 2H).

Example 80: (R)-4,4-dimethyl-2-oxotetrahydrofuran-3-y1 (2R)-3-hydroxy-4-(N-isobutyl-4-methoxyphenylsulfonamido)-1-phenylbutan-2-ylcarbamate:

HPLC: 94.43%; MASS: 562 [M+Na] 585; $^1$H NMR (300MHz, CDCL3): 0.85-0.90 (m, 6H); 0.91-0.92 (m, 6H); 1.42-1.94 (m, 3H); 2.86-2.89 (m, 2H); 3.08-3.11 (m, IH); 3.16-3.18 (m, IH); 3.21-3.28 (m, IH); 3.30-3.44 (m, 3H); 3.88 (s, 3H); 4.27 (m, 2H); 4.49-4.56 (m, IH); 6.98-6.99 (d, J=3Hz, 2H); 7.00-7.25 (m, 5H); 7.73-7.76 (d, J=9Hz, 2H).

Example 81: N-((2S,3R)-4-(4-amino-N-isobutylphenylsulfonamido)-3-hydroxy-1-phenylbutan-2-yl)-3-methyl-5-(tetrahydrofuran-3-yloxy)benzamide:
HPLC: 97.6%; ES MASS: 595 (100%), [M+Na]618; $^1$H NMR (300MHz, CDCl3):
0.83-0.90 (m, 6H); 1.84-2.23 (m, 3H); 2.38 (s, 3H); 2.82-3.1 (m, 6H); 3.82-3.99 (m, 5H); 4.00-4.40 (m, 5H); 6.63-6.66 (d, J=9Hz, 3H); 6.88-7.30 (m, 7H); 7.53-7.55 (d, J=6Hz, 1H); 8.04-8.06 (d, J=6Hz, 1H).

Example 82: N-((2R,3S)-4-(N-cyclopentyl-4-methoxyphenylsulfonamido)-3-hydroxy-1-phenylbutan-2-yl)-1-(methoxymethyl)cyclopentanecarboxamide:

HPLC: 95.63%; MASS: 581 [M+Na]; $^1$H NMR (300MHz, CDCl3):
1.25-1.27 (m, 2H); 1.43-1.45 (m, 9H); 1.49-1.51 (m, 3H); 1.77-1.85 (m, 3H); 2.97-3.00 (m, 2H); 3.02-3.07 (m, 4H); 3.11-3.21 (M, 4H); 3.78-3.80 (m, 3H); 3.87 (s, 3H); 4.14-4.19 (m, 2H); 4.40-4.41 (m, 1H); 6.94-7.01 (m, 3H); 7.20-7.22 (M, 2H); 7.28-7.31 (m, 2H); 7.74-7.76 (d, J=8Hz, 2H).

Example 83: N-((2R,3S)-4-(N-cyclopentyl-4-methoxyphenylsulfonamido)-3-hydroxy-1-phenylbutan-2-yl)-1-ethylcyclopentanecarboxamide:

HPLC: 99.36%; MASS: 565 [M+Na]; $^1$H NMR (300MHz, CDCl3):
0.61-0.66 (m, 3H); 1.41-1.14 (m, 2H); 1.43-1.45 (m, 6H); 1.48-1.50 (m, 6H); 1.50 (m, 6H); 1.76-1.81 (m, 2H); 2.96-3.08 (m, 3H); 3.18-3.25 (m, 1H); 3.88 (s, 3H); 4.12-4.17 (m, 1H); 4.26-4.32 (m, 1H); 4.38-4.39 (m, 1H); 5.82-5.85 (d, J=8Hz, 1H); 6.95-6.98 (d, J=8Hz, 2H); 7.18-7.36 (m, 5H); 7.72-7.75 (d, J=8Hz, 2H).
Pharmacological activity

Example 84: ANTIVIRAL ASSAY:

MT2 cells were infected with HrV-1 strain 92HT599 (10 TCID 50/30000 cells). The infected cells were plated at the concentration of -30000 cells per well in 96 well plate. Test compound was added to the microplate in defined format with the final concentration of DMSO (vehicle) not more than 1%. Incubation was carried out in a CO2 incubator for 96 hours for viral infection. At the end of incubation period an aliquot from each well was taken for p24 estimation. The quantitation of p24 is an index for antiviral activity of the compound. Percent inhibition was calculated with reference to control values (vehicle controls).

P-24 estimation was carried out using advance biosciences kit per the procedure detailed by supplier.

Compound Preparation:

10 mM stock was made by dissolving test compound in DMSO. Subsequent dilutions were made with DMSO to make necessary working stocks (100X).

Cytotoxicity assay:

For cytotoxicity assay the same amount of MT-2 cells as in antivirus without HrV-1 virus was added to the cytotoxicity plates. The cytotoxicity was measured using MTT reagent in parallel with P24 estimation. The percent viability is calculated in comparison with vehicle control.

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HIV inhibitory concentration 50 (IC50) against different HIV strains and Cytotoxic concentration 50 (CC50) against corresponding cell lines:
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Although the invention herein has been described with reference to particular embodiments, it is to be understood that these embodiments are merely illustrative of the principles and applications of the present invention. It is therefore to be understood that numerous modifications may be made to the illustrative embodiments and that other arrangements may be devised without departing from the spirit and scope of the present invention as described above.
All publications and patent applications cited in this application are herein incorporated by reference to the same extent as if each individual publication or patent application was specifically and individually indicated to be incorporated herein by reference.
WE CLAIM:

1. A compound of the formula (I):

   \[ \text{Formula (I)} \]

   wherein,

   - \( B_1 \) and \( B_2 \) are independently selected from \( \text{O}, \text{CO}, \text{C} (\text{Ra})_2 \), or \( \text{NR}^b \);
   - \( X \) is a bond, \(-\text{O}^-, -\text{G}(\text{C}(\text{R}^c))_2^m^-\), or \(- -\text{(C}(\text{R}^c)_2)_m^-\);
   - \( L \) is a bond, \(-\text{(CH}_2)_m^-\), \(-\text{N} \text{R}^d^-, \) or substituted or unsubstituted phenylene;
   - \( n \) is an integer 0-4;
   - \( m \) is an integer 0-3;
   - \( R \) is H, substituted or unsubstituted alkyl, substituted or unsubstituted cycloalkyl, substituted or unsubstituted aryl, substituted or unsubstituted heteroaryl, or substituted or unsubstituted heterocyclyl, and preferably \( R \) can be substituted by \( \text{R}^* \);
   - \( R^1 \) is H, substituted or unsubstituted alkyl or substituted or unsubstituted cycloalkyl;
   - \( R^2 \) is H, substituted or unsubstituted alkyl, substituted or unsubstituted cycloalkyl, substituted or unsubstituted aryl, or substituted or unsubstituted heterocyclyl;
   - \( Z_1 \) and \( Z_2 \) are independently selected from a bond or \( \text{NR}^b \) and provided that when \( \text{NR}_1 \) is directly connected to \( \text{SO}_2 \text{R}_2 \) then both \( Z_1 \) and \( Z_2 \) are absent;
   - \( R^i \) and \( Z^i \) are together attached with \( \text{N} \) atom to form a cyclic ring which is monocyclic ring, bicyclic ring or bridged ring and are selected from

\[ \text{Diagram} \]
R\(^x\), and R\(^y\) are independently selected from H, halogen, and substituted or unsubstituted alkyl, or R\(^x\) and R\(^y\) are together attached with ring C atom to form C\(_{3-6}\) cyclic ring or C\(_{3-6}\) heterocyclic ring;

R\(^a\), R\(^b\), R\(^c\), and R\(^d\) are independently selected from H, substituted or unsubstituted alkyl, substituted or unsubstituted aryl, substituted or unsubstituted cycloalkyl, and substituted or unsubstituted heterocycl, and preferably R\(^a\), R\(^b\), R\(^c\), and R\(^d\) can be substituted by R\(^i\);

R\(^i\) is H, OH, halogen, NR\(n\), C(0)\(_{2}\)R\(^n\), C(0)NR\(n\) substituted or unsubstituted alkyl, substituted or unsubstituted alkoxy, substituted or unsubstituted alkyl, substituted or unsubstituted cycloalkyloxy, or substituted or unsubstituted heterocyclyloxy;

R\(^n\) is H, substituted or unsubstituted alkyl, substituted or unsubstituted amino, substituted or unsubstituted aryl, substituted or unsubstituted cycloalkyl, or substituted or unsubstituted heterocyclyl, an analog thereof, a pharmaceutically acceptable salt thereof, a pharmaceutically acceptable solvate thereof, a pharmaceutically acceptable hydrate thereof, an N-oxide thereof, a tautomer thereof, a regioisomer thereof, a stereoisomer thereof, a prodrug thereof or a polymorph thereof.

2. A compound of the formula (IA):

![Formula (IA)](image_url)

wherein,

B\(_1\) and B\(_2\) are independently selected from O, CO, C (R\(^a\))\(_2\), or NR\(^b\);

X is a bond, -0-, -0(R(C(R\(^c\))\(_2\))\(_m\)-, or - (C(R\(^a\))\(_2\))\(_m\)O-;

L is a bond, -(CH\(_2\))\(_m\)-, -N R\(^d\)-, or substituted or unsubstituted phenylene;

n is an integer 0-4;

m is an integer 0-3;
R is H, substituted or unsubstituted alkyl, substituted or unsubstituted cycloalkyl, substituted or unsubstituted aryl, substituted or unsubstituted heteroaryl, or substituted or unsubstituted heterocyclyl, and preferably R can be substituted by R';

Ri is H, substituted or unsubstituted alkyl, or substituted or unsubstituted cycloalkyl;

R2 is H, substituted or unsubstituted alkyl, substituted or unsubstituted cycloalkyl, substituted or unsubstituted aryl, or substituted or unsubstituted heterocyclyl;

R, and R are independently selected from H, halogen, and substituted or unsubstituted alkyl, or R and R are together attached with ring C atom to form C3-6 cyclic ring or C3-6 heterocyclic ring;

R, R, R, and R are independently selected from H, substituted or unsubstituted alkyl, substituted or unsubstituted aryl, substituted or unsubstituted cycloalkyl, and substituted or unsubstituted heterocyclyl, and preferably R, R, R, and R can be substituted by R';

R' is H, OH, halogen, NR", C(0)"R", C(0)NR" substituted or unsubstituted alkyl, substituted or unsubstituted alkoxy, substituted or unsubstituted alkyl, substituted or unsubstituted cycloalkyloxy, or substituted or unsubstituted heterocyclyloxy;

R" is H, substituted or unsubstituted alkyl, substituted or unsubstituted amino, substituted or unsubstituted aryl, substituted or unsubstituted cycloalkyl, or substituted or unsubstituted heterocyclyl, an analog thereof, a pharmaceutically acceptable salt thereof, a pharmaceutically acceptable solvate thereof, a pharmaceutically acceptable hydrate thereof, an N-oxide thereof, a tautomer thereof, a regioisomer thereof, a stereoisomer thereof, a prodrug thereof or a polymorph thereof.

3. A compound of the formula (IB):
B, and $B_2$ are independently selected from O, CO, C$(R^a)_2$, or NR$^b$;
X is a bond, -0-, -0(C(R$^c$))$_m$-, or - (C(R$^c$))$_m$O-;
L is a bond, -(CH$_2$)$_m$-, -N R$^d$, or substituted or unsubstituted phenylene;
n is an integer 0-4;
m is an integer 0-3;
R is H, substituted or unsubstituted alkyl, substituted or unsubstituted cycloalkyl,
substituted or unsubstituted aryl, substituted or unsubstituted heteroaryl or substituted or
unsubstituted heterocycl and preferably R can be substituted by R$'$;
$R_2$ is H, substituted or unsubstituted alkyl, substituted or unsubstituted cycloalkyl,
substituted or unsubstituted aryl, or substituted or unsubstituted heterocycl;
$Z_2$ is a bond or NR$^b$;

is mono cyclic ring, bicyclic ring or bridged ring and preferably they
can be selected from

$R^a$, and $R^y$ are independently selected from H, halogen, and substituted or
unsubstituted alkyl, or $R^a$ and $R^y$ are together attached with ring C atom to form $C_{3-6}$
cyclic ring or $C_{3-6}$ heterocyclic ring;
$R^a$, $R^b$, $R^c$, and $R^d$ are independently selected from H, substituted or unsubstituted
alkyl, substituted or unsubstituted aryl, substituted or unsubstituted cycloalkyl, and
substituted or unsubstituted heterocycl, and preferably $R^a$, $R^b$, $R^c$, and $R^d$ can be
substituted by R$'$;
R$'$ is H, OH, halogen, NR$''$, C(0)$_2$R$''$, C(0)NR$''$ substituted or unsubstituted alkyl,
substituted or unsubstituted alkoxy, substituted or unsubstituted alkyl, substituted or
unsubstituted cycloalkyloxy, or substituted or unsubstituted heterocyclloxy;
R$''$ is H, substituted or unsubstituted alkyl, substituted or unsubstituted amino,
substituted or unsubstituted aryl, substituted or unsubstituted cycloalkyl, or substituted or
unsubstituted heterocycl, an analog thereof, a pharmaceutically acceptable salt thereof,
a pharmaceutically acceptable solvate thereof, a pharmaceutically acceptable hydrate
thereof, an N-oxide thereof, a tautomer thereof, a regioisomer thereof, a stereoisomer thereof, a prodrug thereof or a polymorph thereof.

4. A compound selected from the group consisting of:

\[
\begin{align*}
&N-((2S,3R)-3\text{-hydroxy}-4-(N\text{-isobutyl-4-nitrophenylsulfonamido})-l\text{-phenylbutan-2-yl})-2-((S)\text{-tetrahydrofuran-3-yloxy})acetamide \text{ (Compound 1),} \\
&N-((2S,3R)-4-(4\text{-amino-N\text{-isobutylphenylsulfonamido})-3\text{-hydroxy-l-phenylbutan-2-yl})-2-((S)\text{-tetrahydrofuran-3-yloxy})acetamide \text{ (Compound 2),} \\
&N-((2S,3R)-3\text{-hydroxy}-4-(N\text{-isobutyl-4-methoxyphenylsulfonamido})-l\text{-phenylbutan-2-yl})-2-(tetrahydrofuran-3-yloxy)acetamide \text{ (Compound 3),} \\
&N-((2S,3R)-3\text{-hydroxy}-4-(N\text{-isobutyl-4-methylphenylsulfonamido})-l\text{-phenylbutan-2-yl})-2-(tetrahydrofuran-3-yloxy)acetamide \text{ (Compound 4),} \\
&1\text{-ethyl-N-((2S,3R)-3\text{-hydroxy}-4-(N\text{-isobutyl-4-nitrophenylsulfonamido})-l\text{-phenylbutan-2-yl})cyclopentanecarboxamide \text{ (Compound 6),} \\
&N-((2S,3R)-4-(4\text{-amino-N\text{-isobutylphenylsulfonamido})-3\text{-hydroxy-l-phenylbutan-2-yl})-l\text{-ethylcyclopentanecarboxamide \text{ (Compound 7),} \\
&1\text{-ethyl-N-((2S,3R)-3\text{-hydroxy}-4-(N\text{-isobutyl-4-methoxyphenylsulfonamido})-l\text{-phenylbutan-2-yl})cyclopentanecarboxamide \text{ (Compound 8),} \\
&N-((2S,3R)-4-(3\text{-chloro-4-fluoro-N\text{-isobutylphenylsulfonamido})-3\text{-hydroxy-l-phenylbutan-2-yl})-l\text{-ethylcyclopentanecarboxamide \text{ (Compound 9),} \\
&1\text{-ethyl-N-((2S,3R)-3\text{-hydroxy}-4-(N\text{-isobutyl-4-methylphenylsulfonamido})-l\text{-phenylbutan-2-yl})cyclohexanecarboxamide \text{ (Compound 10),} \\
&1\text{-ethyl-N-((2S,3R)-3\text{-hydroxy}-4-(N\text{-isobutyl-4-methoxyphenylsulfonamido})-l\text{-phenylbutan-2-yl})cyclohexanecarboxamide \text{ (Compound 11),} \\
&N-((2S,3R)-4-(3\text{-chloro-4-fluoro-N\text{-isobutylphenylsulfonamido})-3\text{-hydroxy-l-phenylbutan-2-yl})-l\text{-ethylcyclohexanecarboxamide \text{ (Compound 12),} \\
&1\text{-ethyl-N-((2S,3R)-3\text{-hydroxy}-4-(N\text{-isobutyl-4-nitrophenylsulfonamido})-l\text{-phenylbutan-2-yl})cyclohexanecarboxamide \text{ (Compound 13),}
\end{align*}
\]
N-((2S,3R)-4-(4-amino-N-isobutylphenylsulfonylamido)-3-hydroxy-1-phenylbutan-2-yl)-l-ethylcyclohexanecarboxamide (Compound 14),
1-ethyl-N-((2S,3R)-4-(4-fluoro-N-isobutylphenylsulfonylamido)-3-hydroxy-1-phenylbutan-2-yl)cyclohexanecarboxamide (Compound 15),
N-((2S,3R)-4-(3,4-difluoro-N-isobutylphenylsulfonylamido)-3-hydroxy-1-phenylbutan-2-yl)-l-ethylcyclohexanecarboxamide (Compound 16),
1-ethyl-N-((2S,3R)-3-hydroxy-4-(3-(4-methoxyphenylsulfonylamido)-8-azabicyclo[3.2.1]octan-8-yl)-1-phenylbutan-2-yl)cyclopentanecarboxamide (Compound 17A),
1-(2-ethoxyethyl)-N-((2S,3R)-3-hydroxy-4-(3-(4-methoxyphenylsulfonylamido)-1-phenylbutan-2-yl)cyclopentanecarboxamide (Compound 17B),
N-((2S,3R)-4-(4-amino-N-isobutylphenylsulfonylamido)-3-hydroxy-1-phenylbutan-2-yl)-3,3-difluorocyclopentanecarboxamide (Compound 18),
3,3-difluoro-N-((2S,3R)-3-hydroxy-4-(N-isobutyl-4-methoxyphenylsulfonylamido)-1-phenylbutan-2-yl)cyclopentanecarboxamide (Compound 19),
N-((2S,3R)-4-(3-chloro-4-fluoro-N-isobutylphenylsulfonylamido)-3-hydroxy-1-phenylbutan-2-yl)-2-(1-(pyridin-2-yl)cyclohexyl)acetamide (Compound 20),
N-((2S,3R)-3-hydroxy-4-(N-isobutyl-4-methoxyphenylsulfonylamido)-1-phenylbutan-2-yl)-2-(1-(pyridin-2-yl)cyclohexyl)acetamide (Compound 21),
N-((2S,3R)-3-hydroxy-4-(N-isobutyl-4-methylphenylsulfonylamido)-1-phenylbutan-2-yl)-2-(1-(pyridin-2-yl)cyclohexyl)acetamide (Compound 22),
N-((2S,3R)-3-hydroxy-4-(N-isobutyl-4-nitrophenylsulfonylamido)-1-phenylbutan-2-yl)-2-(1-(pyridin-2-yl)cyclohexyl)acetamide (Compound 23),
N-((2S,3R)-4-(4-amino-N-isobutylphenylsulfonylamido)-3-hydroxy-1-phenylbutan-2-yl)-2-(1-(pyridin-2-yl)cyclohexyl)acetamide (Compound 24),
2-(4,4-difluoro-1-(pyridin-2-yl)cyclohexyl)-N-((2S,3R)-3-hydroxy-4-(N-isobutyl-4-methoxyphenylsulfonylamido)-1-phenylbutan-2-yl)acetamide (Compound 25),
N-((2S,3R)-4-(4-fluoro-N-isobutylphenylsulfonylamido)-3-hydroxy-1-phenylbutan-2-yl)-2-(1-(pyridin-2-yl)cyclohexyl)acetamide (Compound 26),
N-((2S,3R)-4-(3-chloro-4-fluoro-N-isobutylphenylsulfonamido)-3-hydroxy-l-phenylbutan-2-yl)-1-(methoxymethyl)cyclopentanecarboxamide (Compound 27),
N-((2S,3R)-4-(4-amino-N-isobutylphenylsulfonamido)-3-hydroxy-l-phenylbutan-2-yl)-1-(methoxymethyl)cyclopentanecarboxamide (Compound 28),
N-((2S,3R)-3-hydroxy-4-(N-isobutyl-4-methoxyphenylsulfonamido)-l-phenylbutan-2-yl)-1-(methoxymethyl)cyclopentanecarboxamide (Compound 29),
N-((2S,3R)-4-(3-chloro-4-fluoro-N-isobutylphenylsulfonamido)-3-hydroxy-l-phenylbutan-2-yl)-1-(methoxymethyl)cyclopentanecarboxamide (Compound 30),
N-((2S,3R)-3-hydroxy-4-(N-isobutyl-4-nitrophenylsulfonamido)-l-phenylbutan-2-yl)-1-(methoxymethyl)cyclopentanecarboxamide (Compound 31),
N-((2S,3R)-3-hydroxy-4-(N-isobutyl-4-nitrophenylsulfonamido)-l-phenylbutan-2-yl)-2-((S)-tetrahydrofuran-3-yloxy)benzamide (Compound 32),
N-((2S,3R)-4-(4-amino-N-isobutylphenylsulfonamido)-3-hydroxy-l-phenylbutan-2-yl)-2-((S)-tetrahydrofuran-3-yloxy)benzamide (Compound 33),
N-((2S,3R)-3-hydroxy-4-(N-isobutyl-4-methoxyphenylsulfonamido)-l-phenylbutan-2-yl)-2-((S)-tetrahydrofuran-3-yloxy)benzamide (Compound 34),
N-((2S,3R)-4-(3-chloro-4-fluoro-N-isobutylphenylsulfonamido)-3-hydroxy-l-phenylbutan-2-yl)-2-((S)-tetrahydrofuran-3-yloxy)benzamide (Compound 35),
3-chloro-N-((2S,3R)-3-hydroxy-4-(N-isobutyl-4-methoxyphenylsulfonamido)-l-phenylbutan-2-yl)-5-((S)-tetrahydrofuran-3-yloxy)benzamide (Compound 36),
3-chloro-N-((2S,3R)-3-hydroxy-4-(N-isobutyl-4-nitrophenylsulfonamido)-l-phenylbutan-2-yl)-5-((S)-tetrahydrofuran-3-yloxy)benzamide (Compound 37),
N-((2S,3R)-4-(4-amino-N-isobutylphenylsulfonamido)-3-hydroxy-l-phenylbutan-2-yl)-3-chloro-5-((S)-tetrahydrofuran-3-yloxy)benzamide (Compound 38),
N-((2S,3R)-3-hydroxy-4-(N-isobutyl-4-methoxyphenylsulfonamido)-l-phenylbutan-2-yl)-4-methyl-2-((S)-tetrahydrofuran-3-yloxy)benzamide (Compound 39),
N-((2S,3R)-4-(3-chloro-4-fluoro-N-isobutylphenylsulfonamido)-3-hydroxy-l-phenylbutan-2-yl)-4-methyl-2-((S)-tetrahydrofuran-3-yloxy)benzamide (Compound 40),
N-((2S,3R)-4-(3-chloro-4-fluoro-N-isobutylphenylsulfonamido)-3-hydroxy-l-phenylbutan-2-yl)-2-((S)-tetrahydrofuran-3-yloxy)benzamide (Compound 41).
N-((2S,3R)-3-hydroxy-4-(N-isobutyl-4-methoxyphenylsulfonamido)-1-phenylbutan-2-yl)-2-((S)-tetrahydrofuran-3-yloxy)benzamide (Compound 42),
N-((2S,3R)-4-(4-amino-N-isobutylphenylsulfonamido)-3-hydroxy-1-phenylbutan-2-yl)-2-((S)-tetrahydrofuran-3-yloxy)benzamide (Compound 43),
4-fluoro-N-((2S,3R)-3-hydroxy-4-(N-isobutyl-4-methoxyphenylsulfonamido)-1-phenylbutan-2-yl)-2-((S)-tetrahydrofuran-3-yloxy)benzamide (Compound 44),
N-((2S,3R)-4-(3-chloro-4-fluoro-N-isobutylphenylsulfonamido)-3-hydroxy-1-phenylbutan-2-yl)-2-((4-((S)-tetrahydrofuran-3-yloxy)phenyl)acetamide (Compound 45),
N-((2S,3R)-3-hydroxy-4-(N-isobutyl-4-methoxyphenylsulfonamido)-1-phenylbutan-2-yl)-2-((4-((S)-tetrahydrofuran-3-yloxy)phenyl)acetamide (Compound 46),
N-((2S,3R)-4-(4-amino-N-isobutylphenylsulfonamido)-3-hydroxy-1-phenylbutan-2-yl)-2-((4-((S)-tetrahydrofuran-3-yloxy)phenyl)acetamide (Compound 47),
N-((2S,3R)-3-hydroxy-4-(N-isobutyl-4-methoxyphenylsulfonamido)-1-phenylbutan-2-yl)-2-((4-((S)-tetrahydrofuran-3-yloxy)phenyl)acetamide (Compound 48),
1-(2-ethoxyethyl)-N-((2S,3R)-3-hydroxy-4-(N-isobutyl-4-methoxyphenylsulfonamido)-1-phenylbutan-2-yl)cyclopentanecarboxamide (Compound 49),
N-((2S,3R)-4-(4-amino-N-isobutylphenylsulfonamido)-3-hydroxy-1-phenylbutan-2-yl)-l-(2-ethoxyethyl)cyclopentanecarboxamide (Compound 50),
(1-(2-ethoxyethyl)cyclopentyl)methyl (2S,3R)-3-hydroxy-4-(N-isobutyl-4-methoxyphenylsulfonamido)-1-phenylbutan-2-ylcarbamate (Compound 51),
2-ethyl-N-((2S,3S)-3-hydroxy-4-(N-isobutyl-4-nitrophenylsulfonamido)-1-phenylbutan-2-yl) tetrahydrofuran-2-carboxamide (Compound 52A),
N-((2S,3R)-4-(4-amino-N-isobutylphenylsulfonamido)-3-hydroxy-1-phenylbutan-2-yl)-2-ethyltetrahydrofuran-2-carboxamide (Compound 52B),
2-ethyl-N-((2S,3R)-3-hydroxy-4-(N-isobutyl-4-methoxyphenylsulfonamido)-1-phenylbutan-2-yl) tetrahydrofuran-2-carboxamide (Compound 53),
N-((2S,3R)-3-hydroxy-4-(N-isobutyl-4-methoxyphenylsulfonamido)-1-phenylbutan-2-yl)-2-((S)-tetrahydrofuran-3-yloxy)propanamide (Compound 54),
(1-ethylcyclopentyl)methyl (2S,3R)-3-hydroxy-4-(N-isobutyl-4-methoxyphenylsulfonamido)-1-phenylbutan-2-ylcarbamate (Compound 55),
N-((2S,3R)-4-(3-chloro-4-fluoro-N-isobutylphenylsulfonamido)-3-hydroxy-1-phenylbutan-2-yl)-1-oxaspiro[4.4]nonane-7-carboxamide (Compound 56),
N-((2S,3R)-3-hydroxy-4-(N-isobutyl-4-methoxyphenylsulfonamido)-1-phenylbutan-2-yl)-1-oxaspiro[4.4]nonane-7-carboxamide (Compound 57),
N-((2S,3R)-3-hydroxy-4-(N-isobutyl-4-methylphenylsulfonamido)-1-phenylbutan-2-yl)-1-oxaspiro[4.4]nonane-7-carboxamide (Compound 58),
N-((2S,3R)-4-(4-amino-N-isobutylphenylsulfonamido)-3-hydroxy-1-phenylbutan-2-yl)-1-oxaspiro[4.4]nonane-7-carboxamide (Compound 59),
N-((2S,3R)-4-(4-fluoro-N-isobutylphenylsulfonamido)-3-hydroxy-1-phenylbutan-2-yl)-2-((S)-tetrahydrofuran-3-yl)oxy)acetamide (Compound 60),
(2-ethyltetrahydrofuran-2-yl)methyl (2S,3R)-3-hydroxy-4-(N-isobutyl-4-methoxyphenylsulfonamido)-1-phenylbutan-2-ylcarbamate (Compound 61),
1-(2-ethoxyethyl)-N-((2S)-3-hydroxy-4-((1R,5S)-3-(4-methoxyphenylsulfonamido)-8-azabicyclo[3.2.1]octan-8-yl)-1-phenylbutan-2-yl)cyclopentanecarboxamide (Compound 62),
N-((2S,3S)-3-hydroxy-4-(N-isobutyl-4-methoxyphenylsulfonamido)-1-phenylbutan-2-yl)-1-(methoxymethyl)cyclopentanecarboxamide (Compound 63),
4,4-dimethyl-2-oxotetrahydrofuran-3-yl (2R,3S)-4-(4-amino-N-isobutylphenylsulfonamido)-3-hydroxy-1-phenylbutan-2-ylcarbamate (Compound 64),
4,4-dimethyl-2-oxotetrahydrofuran-3-yl (2R,3S)-4-(N-cyclopentyl-4-methoxyphenylsulfonamido)-3-hydroxy-1-phenylbutan-2-ylcarbamate (Compound 65),
(R)-4,4-dimethyl-2-oxotetrahydrofuran-3-yl (2S,3R)-3-hydroxy-4-(4-(4-methoxyphenylsulfonamido)piperidin-1-yl)-1-phenylbutan-2-ylcarbamate (Compound 66),
(R)-tetrahydrofuran-3-yl (2S,3R)-3-hydroxy-4-(4-(4-methoxyphenylsulfonamido)piperidin-1-yl)-1-phenylbutan-2-ylcarbamate (Compound 67),
1-ethyl-N-((2S,3R)-3-hydroxy-4-(4-(4-methoxyphenylsulfonamido)piperidin-1-yl)-1-phenylbutan-2-yl)cyclopentanecarboxamide (Compound 68),
(R)-tetrahydrofuran-3-yl (2S)-3-hydroxy-4-((IR,5S)-3-(4-methoxyphenylsulfonamido)-8-azabicyclo[3.2.1]octan-8-yl)-l-phenylbutan-2-ylcarbamate (Compound 69),
5
N-((2S)-3-hydroxy-4-((IR,5S)-3-(4-methoxyphenylsulfonamido)-8-azabicyclo[3.2.1]octan-8-yl)-l-phenylbutan-2-yl)-1-(methoxymethyl)cyclopentanecarboxamide (Compound 70),
N-((2S,3S)-3-hydroxy-4-(N-isobutyl-4-methoxyphenylsulfonamido)-l-phenylbutan-2-yl)-1-(methoxymethyl)cyclopentanecarboxamide (Compound 71),

Example 73: Preparation of (3-ethyloxetan-3-yl)

10 Methyl (2S)-3-hydroxy-4-(N-isobutyl-4-nitrophenylsulfonamido)-l-phenylbutan-2-ylcarbamate (Compound 72),
(3-ethyloxetan-3-yl) methyl (2S)-4-(4-amino-N-isobutylphenylsulfonamido)-3hydroxy-l-phenylbutan-2-ylcarbamate (Compound 73),
(3-methylxetan-3-yl)methyl (2S,3R)-4-(4-amino-N-isobutylphenylsulfonamido) -3hydroxy-l-phenylbutan-2-ylcarbamate (Compound 74),
(2-ethyltetrahydrofuran-2-yl)methyl (2S,3R)-4-(4-amino-N-isobutylphenylsulfonamido)-3-hydroxy-l-phenylbutan-2-ylcarbamate (Compound 75),
(2S)-3-hydroxy-4-(N-isobutyl-4-methoxyphenylsulfonamido)-1-phenylbutan-2-yl 2-((R)-tetrahydrofuran-3-yloxy)acetate (Compound 76),

20 N-((2S)-4-(N-(2-(1H-indol-2-yl)ethyl)-4-aminophenylsulfonamido)-3-hydroxy-1-phenylbutan-2-yl)-1-(methoxymethyl)cyclopentanecarboxamide (Compound 77),
N-((2S)-4-(4-amino-N-cyclopentylphenylsulfonamido)-3-hydroxy-l-phenylbutan-2-yl)-1-ethylcyclopentanecarboxamide (Compound 78),
N-((2S)-4-(N-cyclopentyl-4-methoxyphenylsulfonamido)-3-hydroxy-l-phenylbutan-2-yl)-l-(methoxymethyl)cyclopentanecarboxamide (Compound 79),

25 (R)-4,4-dimethyl-2-oxotetrahydrofuran-3-yl (2R)-3-hydroxy-4-(N-isobutyl-4-methoxyphenylsulfonamido)-1-phenylbutan-2-ylcarbamate (Compound 80),
N-((2S,3R)-4-(4-amino-N-isobutylphenylsulfonamido)-3-hydroxy-l-phenylbutan-2-yl)-3-methyl-5-(tetrahydrofuran-3-yloxy)benzamide (Compound 81),
N-((2R,3S)-4-(N-cyclopentyl-4-methoxyphenylsulfonamido)-3-hydroxy-l-phenylbutan-2-yl)-1-(methoxymethyl)cyclopentanecarboxamide (Compound 82),
N-((2R,3S)-4-(N-cyclopentyl-4-methoxyphenylsulfonamido)-3-hydroxy-l-phenylbutan-2-yl)-l-ethylcyclopentanecarboxamide (Compound 83), and pharmaceutically acceptable salts thereof.

5. A pharmaceutical composition comprising a compound according to any one of claims 1-4 and a pharmaceutically acceptable excipient.

6. The pharmaceutical composition according to claim 5, wherein the pharmaceutically acceptable excipient is a carrier or diluent.

7. A method for preventing, ameliorating or treating a viral mediated disease, disorder or syndrome in a subject in need thereof comprising administering to the subject a therapeutically effective amount of a compound according to any one of claims 1-4.

8. The method according to claim 7, wherein the viral mediated disease, disorder or syndrome is selected from the group consisting of HIV infection, HBV, HCV, a retroviral infection genetically related to AIDS, respiratory disorders, adult respiratory distress syndrome (ARDS), and inflammatory disease.

9. A method of treating HIV in a subject in need thereof comprising administering to the subject a therapeutically effective amount of a compound according to any one of claims 1-4.

10. A method for preventing, ameliorating or treating a viral mediated disease, disorder or syndrome in a subject in need thereof comprising administering to the subject a therapeutically effective amount of a compound according to claim 5.

11. The method according to claim 10, wherein the viral mediated disease, disorder or syndrome is selected from the group consisting of HIV infection, HBV, HCV, a retroviral infection genetically related to AIDS, respiratory disorders, adult respiratory distress syndrome (ARDS), and inflammatory disease.
INTERNATIONAL SEARCH REPORT

A. CLASSIFICATION OF SUBJECT MATTER

INV. C07C311/18 C07C311/29 C07C311/41 C07D209/14 C07D213/56
C07D305/06 C07D307/12 C07D307/20 C07D307/24 C07D307/33
C07D307/94 C07D451/04 A61K31/18 A61P31/18

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)
C07C 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, CHEM ABS Data

C. DOCUMENTS CONSIDERED TO BE RELEVANT

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Date of the actual completion of the international search
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Name and mailing address of the ISA:
European Patent Office, P.B. 5018 Patentlaan 2
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Fax: (+31-70) 340-3016

Authorized officer

English, Russell

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<td>A. K. GHOSH, ET AL.: &quot;Structure-based design of non-peptidde HIV protease inhibitors to combat drug resistance&quot;</td>
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