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Title: HISTONE DEACETYLASE INHIBITORS

Abstract: Provided herein are isoform selective histone deacetylase inhibitors of the formula (I), their derivatives, analogs, tautomeric forms, stereoisomers, polymorphs, hydrates, metabolites, prodrugs, solvates, pharmaceutically acceptable salts and compositions thereof. These compounds are isoform selective inhibitors of HDACs and are useful as a therapeutic or ameliorating agent for diseases that are involved in cellular growth such as cancer, malignant tumors, autoimmune diseases, skin diseases, fungal infections, protozoal infections, HIV, inflammation and CNS disorders.

Declarations under Rule 4.17:
— of inventorship (Rule 4.17(iv))
— with international search report (Art. 21(3))
— before the expiration of the time limit for amending the claims and to be republished in the event of receipt of amendments (Rule 48.2(h))
HISTONE DEACYTYLASE INHIBITORS

FIELD
Described herein are compounds as isoform selective histone deacytylase inhibitors, their derivatives, analogs, tautomeric forms, stereoisomers, geometrical isomers, diastereomers, polymorphs, hydrates, solvates, pharmaceutically acceptable salts, metabolites, intermediates and prodrugs thereof, the preparation of these compounds, the pharmaceutical compositions comprising these compounds and the use of these compounds for treating various diseases.

BACKGROUND
Transcriptional regulation is a major event in cell differentiation, proliferation and apoptosis. Particularly the regulations of transcription factor are thought to involve by changes in the structure of chromatin. Changing the affinity of histone proteins for coiled DNA in the nucleosome alters the structure of chromatin. Hypoacetylated histones are believed to have greater affinity to the DNA and form a tightly bound DNA-histone complex and render the DNA inaccessible to transcriptional regulation. The acetylating status of the histone is governed by the balancing activities of the histone acetyl transferase (HAT) and histone deacytylase (HDAC). The post translational modifications of protein play a critical role in regulating cellular function. Human HDACs are classified into two distinct classes, the HDACs and sirtuins. The HDACs are further divided into two subclasses based on their similarity to yeast histone deacytylases, Rpd3 (class I includes HDAC 1, 2, 3, 8 and 11) and Hdal (class II includes HDAC 4, 5, 6, 7, 9 and 10). Biochemically all of these HDACs have a highly conserved zinc dependent catalytic domain, while Class-III (SIRT1-7) are dependent on nicotinamide adenine dinucleotide (NAD+) (Langley B., et al., Current Drug Targets-CNS & Neurological Disorders, 2005, 4, 41-50).

Given that the apoptosis is a crucial function for cancer progression, HDAC inhibitors are promising reagents for cancer therapy as effective inducers of apoptosis.

Suberoylanilide hydroxamic acid (SAHA) was launched as an antitumor agent for treating cutaneous T-cell lymphoma (CTCL) and another HDAC inhibitor, Istodax was also approved by Food and Drug Administration (FDA) for the treatment of CTCL. Some of the other HDAC inhibitors in clinical trials are Entinostat (MS-275), Belinostat (PXD101), Resminostat (4SC-201), Mocetinostat (MGCD0103), Panobinostat (LBH589), Sodium butyrate (NaB), Sodium valproate (VPA), Cyclic...

In new role, HDAC inhibitors were shown to have both pro- and anti-inflammatory effects in a wide range of inflammation relevant cell types. These inhibitors have shown promising effects in animal models in variety of inflammatory diseases such as arthritis, inflammatory bowel disease, septic shock, granuloma, airways inflammation and asthma. ITF2357 is found to reduce the production of pro-inflammatory cytokines in vitro and systemic inflammation in vivo (Halili M.A., et al., Current Topics in Medicinal Chemistry, 2009, 9, 309-319; Bonfils C., et al., Expert Opinion on Drug Discovery, 2008, 3, 1041-1065).


Most of the above mentioned compounds are pan-HDAC inhibitors. At present, isoform selective HDAC inhibitors are gaining importance in treating various diseases such as inflammation, CNS disorders etc., since these might have better toxicological profile and more disease specific (Butler K.V., et al., Current Pharmaceutical Design, 2008, 14, 505-528; Hahnen E., et al., Expert Opinion on Investigational Drugs, 2008, 17(2), 169-184).

Although the molecular mechanistics of the HDAC isoforms are not so clear, HDAC1 mostly involves in cancer related problems/diseases. The over-expression of HDAC1 mediates the reduction in the expression of p53 and pVHL (von Hippel Lindau protein), which results in the over-expression of HIF-Iα and its transcriptional target Vascular endothelial growth factor (VEGF). The same was reversed by the use of the HDACi Trichostatin-A (TSA) both in vitro and in vivo (Ellis L., et al.,
**Pharmaceuticals**, 2010, 3, 2441-2469). Some of the examples of HDAC1 selective inhibitors are trapoxin-A, SB-429201, MS275 and MGCD0103.

HDAC3 is another isoform which is involved in inflammatory diseases (Zhu H., et al., *Journal of Biological Chemistry*, 2010, 285, 9429-9436) and CNS disorders. Triazol-4-ylphenyl bearing benzamide compounds are found to be HDAC3 selective inhibitors (He R., et al., *Journal of Medicinal Chemistry*, 2010, 53, 1347-1356). Repligen Corporation disclosed the SAR and HDAC3 activity of the compounds including pimelic acid derivatives as HDAC inhibitors (WO2010028193A1). Recently in 2010, Repligen Corporation received orphan drug approval for their HDAC3 isoform selective compound (RG2833) to treat Friedreich's ataxia.

HDAC6, which is a cytoplasmic enzyme that mediates wide range of cellular functions including microtubule-dependent trafficking and signalling, ubiquitin level sensing, regulation of chaperone levels and responses to oxidative stress. Over expression of HDAC6 has been identified in a variety of cancer cell lines and mouse tumor models. The up-regulation of HDAC6 in diverse tumors and cell lines are widely investigated (Aldana-Masangkay G.I., et al., *Journal of Biomedicine and Biotechnology*, 2011, ID875824, 1-10). The misfolded protein clearance by formation of aggresomes and autophagy with the help of ubiquitin-binding HDAC6 looks promising for developing small isoform selective molecules for treating cancer. Due to the multiple role of HDAC6, it can have potential utility when used alone or in combination with other chemotherapeutic drugs. The proteasome inhibitor, Velcade® (bortezomib) from Millennium Pharmaceuticals is a known drug for treating many types of cancers and it was found that the combination of Velcade® with HDAC6 selective inhibitor tubacin shows synergic effect in multiple myeloma cells (Hideshima T., et al., *Proceedings of the National Academy of Sciences*, 2005, 102(24), 8567-8572). Acyetlon Pharmaceuticals disclosed US20110300134A1 with HDAC6 selective inhibitors, interesting to note that one of its isoform selective molecules ACY-1215 shows interesting results in multiple myeloma when treated in combination with bortezomib (Santo L., et al., *Blood*, 2011, *Inpress*).

Inhibition of HDAC6 can promote survival and regeneration of neurons. Consistent with a cytoplasmic localization, the biological effects of HDAC6 inhibition appear transcription independent. Specifically, the selective inhibition of HDAC6 avoids cell death associated with pan-HDAC inhibition due to their toxicity toward a
host of CNS cell types. These findings define HDAC6 as a potential non-toxic therapeutic target for ameliorating CNS injury characterized by oxidative stress induced neurodegeneration and insufficient axonal regeneration (Rivieccio M.A., et al., *Proceedings of the National Academy of Sciences*, 2009, 106(46), 19599-19604).


Another important isoform HDAC8, which belongs to Class-I family, have clinical relevance in neuroblastoma biology, a highly malignant embryonal childhood cancer (Oehme I., et al., *Expert Opinion on Investigational Drugs*, 2009, 18(11), 1605-1617). Linkerless hydroxamic acids are found to be HDAC8 isoform selective (Butler K.V., et al., *Current Pharmaceutical Design*, 2008, 14, 505-528).

WO2005108367A1 discloses the compounds for treatment of neurodegenerative diseases,

\[
\begin{align*}
\text{Y} & \text{N} \quad \text{O} \quad \text{NH} \quad \text{OH} \\
\end{align*}
\]


WO2006010749A2 and WO2007082874A1 discloses following compounds, which have histone deacetylase inhibiting enzymatic activity,

\[
\begin{align*}
\text{HO} & \text{N} \quad \text{O} \quad \text{N} \quad \text{R} \quad \text{R} \quad \text{R} \\
\end{align*}
\]

There is a widespread need for the isoform or class specific HDAC inhibitors which possess higher potency and fewer side effects compared to the pan HDAC inhibitors.
OBJECTIVE

There are still huge unmet medical needs for treating various cancers viz. liquid or solid tumours such as cancer of colon, pancreas, breast etc. One objective herein is to provide compound of the formula (I), their derivatives, analogs, tautomeric forms, stereoisomers, geometrical isomers, diastereomers, polymorphs, hydrates, solvates, pharmaceutically acceptable salts, metabolites, intermediates and prodrugs thereof for the treatment of various cancers viz. liquid or solid tumours such as cancer of colon, pancreas, breast, etc.

Another objective herein is to provide a method of preventing or treating proliferative diseases or cancers.

Yet another objective herein is to provide a method of preventing or treating CNS disorders including but not limited to Huntington's disease, Parkinson's disease, Alzheimer's disease, Friedreich's ataxia and stroke by administering a therapeutic amount of compound of the formula (I).

Herein another objective is to provide a method of preventing or treating immune & inflammatory conditions.

Another objective herein is to provide a pharmaceutical composition containing compounds described herein.

Another objective herein is to provide a process for the preparation of compounds described herein.

Another object of the present invention is to provide a compound of potent isoform selective/pan HDAC inhibitor; and/or an improved method for inhibiting HDACs in a cell; and/or an improved method for the treatment of a condition mediated by HDACs; and/or a method of treatment and/or prevention of proliferative condition or cancer; and/or a method of treatment and/or prevention of inflammatory disorders; and/or a method of treatment and/or prevention of neurodegenerative disorders; and/or a method of treatment and/or prevention of cancer induced bone pain; or at least to provide the public with a useful choice.

SUMMARY

Described herein is the compound of formula (I),

\[
\text{CONH}_R \quad (I)
\]
its derivatives, analogs, tautomeric forms, stereoisomers, geometrical isomers, diastereomers, polymorphs, hydrates, solvates, pharmaceutically acceptable salts, metabolites, intermediates and prodrugs thereof.

wherein A represents \( \text{Ar} \), \( \text{Ar}^1 \), \( \text{Ar}^2 \) or \( \text{Ar}^3 \).

5 \( \text{Ar} \) represents substituted or unsubstituted groups selected from \((\text{C}_6\text{-C}_{14})\text{aryl}, 5-15 \text{membered heterocyclyl and 5-15 membered heteroaryl};\)

5 \( \text{Ar}^1 \) represents optionally substituted groups selected from \((\text{C}_6\text{-C}_{14})\text{aryl}, 5-15 \text{membered heterocyclyl and 5-15 membered heteroaryl};\)

5 \( \text{Ar}^2 \) represents substituted or unsubstituted groups selected from \((\text{C}_1\text{-C}_6)\text{arylene, (C}_6\text{-C}_{14}\text{aryl or 5-15 membered heteroarylene};}\)

5 B represents hydrogen, \(-\text{COOR}^1\), \(-\text{CONR}^1\text{R}^2\), \(-\text{CH}_2\text{NR}^1\text{R}^2\), \(-\text{CH}_2\text{OR}^1\), \(-\text{CH}_2\text{OCONR}^1\text{R}^2\), \(-\text{CH}_2\text{NR}^1\text{C}^0\text{R}^2\), substituted or unsubstituted groups selected from \((\text{C}_1\text{-C}_6)\text{alkyl, (C}_2\text{-C}_6\text{alkenyl, (C}_2\text{-C}_{14}\text{alkynyl, (C}_6\text{-C}_{14}\text{aryl and (C}_3\text{-C}_2\text{cycloalkyl;}})\text{aryl});}\)

5 B represents hydrogen, \(-\text{COOR}^1\), \(-\text{CONR}^1\text{R}^2\), \(-\text{CH}_2\text{NR}^1\text{R}^2\), \(-\text{CH}_2\text{OR}^1\), \(-\text{CH}_2\text{OCONR}^1\text{R}^2\), \(-\text{CH}_2\text{NR}^1\text{C}^0\text{R}^2\), substituted or unsubstituted groups selected from \((\text{C}_1\text{-C}_6)\text{alkyl, (C}_2\text{-C}_6\text{alkenyl, (C}_2\text{-C}_{14}\text{alkynyl, (C}_6\text{-C}_{14}\text{aryl and (C}_3\text{-C}_2\text{cycloalkyl;}})\text{aryl});}\)

5 D represents hydrogen, \(-\text{COOR}^1\), \(-\text{CONR}^1\text{R}^2\), \(-\text{CH}_2\text{NR}^1\text{R}^2\), \(-\text{CH}_2\text{OR}^1\), \(-\text{CH}_2\text{OCONR}^1\text{R}^2\), \(-\text{CH}_2\text{NR}^1\text{C}^0\text{R}^2\), substituted or unsubstituted groups selected from \((\text{C}_1\text{-C}_6)\text{alkyl, (C}_2\text{-C}_6)\text{alkenyl, (C}_2\text{-C}_{14}\text{alkynyl, (C}_6\text{-C}_{14}\text{aryl and (C}_3\text{-C}_2\text{cycloalkyl;}})\text{aryl});\)

5 R^1 represents hydrogen, substituted or unsubstituted groups selected from \((\text{C}_1\text{-C}_6)\text{alkyl, (C}_3\text{-C}_{12})\text{cycloalkyl, 5-15 membered heterocyclyl, (C}_6\text{-C}_{14})\text{aryl, (C}_6\text{-C}_{14})\text{aryl(C}_1\text{-C}_6)\text{alkyl, (C}_6\text{-C}_{14})\text{aryl(C}_2\text{-C}_6)\text{alkenyl, (C}_6\text{-C}_{14})\text{aryl(C}_2\text{-C}_{14})\text{alkynyl, 5-15 membered heteroaryl, 5-15 membered heteroaryl(C}_1\text{-C}_6)\text{alkyl, 5-15 membered heteroaryl(C}_2\text{-C}_6)\text{alkenyl and 5-15 membered heteroaryl(C}_2\text{-C}_{14})\text{alkynyl;}})\text{aryl);}\)

5 R^2 represents hydrogen, substituted or unsubstituted groups selected from \((\text{C}_1\text{-C}_6)\text{alkyl, (C}_2\text{-C}_{14})\text{alkenyl, (C}_2\text{-C}_{14})\text{alkynyl, (C}_3\text{-C}_2)\text{cycloalkyl, 5-15 membered heterocyclyl, (C}_6\text{-C}_{14})\text{aryl, (C}_6\text{-C}_{14})\text{aryl(C}_1\text{-C}_6)\text{alkyl, (C}_6\text{-C}_{14})\text{aryl(C}_2\text{-C}_6)\text{alkenyl, (C}_6\text{-C}_{14})\text{aryl(C}_2\text{-C}_{14})\text{alkynyl, 5-15 membered heteroaryl, 5-15 membered heteroaryl(C}_1\text{-C}_6)\text{alkyl, 5-15 membered heteroaryl(C}_2\text{-C}_6)\text{alkenyl and 5-15 membered heteroaryl(C}_2\text{-C}_{14})\text{alkynyl;}})\text{aryl);}\)

5 C\text{alkynyl;
or R¹ and R² combine together to form substituted or unsubstituted 3-7
membered ring having 0-3 heteroatoms selected from O, S and N;
when one of B¹ or D is hydrogen or unsubstituted alkyl, the other is neither of
hydrogen nor of unsubstituted alkyl;
X represents a bond, -CO-, -SO₂-, -CS-, -CH₂-, -CONR³-, -CONR³CH₂-,
-CH₂OCO-, -CONR³CO-, -CH₂NR³CO-, -CH₂NR³- or -CH₂NR³CH₂⁻; wherein R³
represents hydrogen or substituted or unsubstituted groups selected from (C₁-C₆)alkyl
and (C₃-C₅)cycloalkyl;

represents substituted or unsubstituted groups selected from

W, W¹, W², W³ and W⁴ independently represent C or N;
W⁵ represents O, S or N; W⁶ represents C or N;
ring Q¹ is a substituted or unsubstituted 4 to 8 membered heterocyclyl ring;
R⁴ represents hydrogen, halogen, hydroxy, nitro, amino, cyano or substituted or
unsubstituted (C₁-C₆)alkyl, amino(C₁-C₆)alkyl, halo(C₁-C₆)alkyl, (C₁-C₆)alkoxy and
halo(C₁-C₆)alkoxy;
R represents -OH, ortho substituted aniline or substituted or unsubstituted
group selected from aminoaryl and hydroxyaryl;
when the groups are substituted, the substituents are one or more, selected from
halogens, hydroxy, nitro, cyano, azido, nitroso, oxo (=O), thiooxo (=S), amino,
hydrazino, formyl, (C₁-C₆)alkyl, halo(C₁-C₆)alkyl, (C₁-C₆)alkoxy, halo(C₁-C₆)alkoxy,
(C₆-C₁₄)aryllalkoxy, (C₃-C₁₂)cycloalkyl, (C₃-C₁₄)cycloalkyloxy, (C₆-C₁₄)aryl,
(C₆-C₁₄)aryloxy, 5-15 membered heterocyclyl, 5-15 membered heteroaryl,
(C₁-C₁₄)alkylamino, -SONR⁻R⁻, -SO₂NR⁻R⁻, -SR⁻, -S⁻, -S⁻R⁻, -SO₂R⁻, -COOR⁻, -C(0)R⁻, \(-C(S)R⁻, -C(0)NR⁻R⁻, -C(S)NR⁻R⁻, -NR⁻C(0)NR⁻R⁻, -NR⁻C(S)NR⁻R⁻, -NR⁻R⁻, -NR⁻C(0)R⁻, -NR⁻C(S)R⁻, -OR⁻, -OR⁻C(0)OR⁻, -OC(0)NR⁻R⁻, -OC(0)OR⁻, -R⁻NR⁻R⁻, -R⁻OR⁻, \) wherein R⁻, R⁻ and R⁻ in each of the above groups represent hydrogen, optionally substituted
groups selected from (C₁-C₆)alkyl, (C₁-C₆)alkylen, (C₃-C₁₂)cycloalkyl, (C₆-C₁₄)aryl,
(C₆-C₁₄)aryl(C₁-C₆)alkyl, 5-15 membered heterocyclyl, 5-15 membered heteroaryl and
5-15 membered heteroaryl(C\(-\)C\(\)alkyl; \(R^a\), \(R^b\) or \(R^c\) can also combine to form a substituted or unsubstituted 3-10 membered heterocyclic ring including spiro-fused heterocyclic ring having 0-3 heteroatoms; the substituents are optionally further substituted by one or more substituents.

In another aspect, provided herein is the compound of formula (I) for use in the inhibition of histone deacetylase enzyme.

In yet another aspect, provided herein is the method of inhibiting the histone deacetylase enzyme comprising administering therapeutically effective amount of compound of formula (I).

In yet another aspect, described herein is the pharmaceutical composition comprising compound of formula (I).

In yet another aspect, described herein is the process for the preparation of the compound of formula (I).

In yet another aspect, described herein is the compound of formula (I) for use in the treatment of proliferative conditions or cancer.

In yet another aspect, described herein is the compound of formula (I), for use in the treatment of proliferative conditions or cancer in combination with other clinically relevant cytotoxic agents or non-cytotoxic agents or radiation or monoclonal antibodies.

In yet another aspect, described herein is the compound of formula (I) for use in the treatment of proliferative conditions or cancer selected from lung cancer, non-small-cell lung cancer (NSCLC), small cell lung cancer (SCLC), colon cancer, fibrosarcoma, kidney cancer, lymphoma, leukemia, skin cancer, pancreatic cancer, breast cancer, prostate cancer, bone cancer, oral cancer, multiple myeloma, brain cancer, head and neck cancer, ovarian cancer, gastric cancer, liver cancer, cervical cancer, solid tumors, cutaneous T-cell lymphoma (CTCL), acute myeloid leukemia, chronic lymphocytic leukemia and acute lymphoblastic leukemia.

In yet another aspect, described herein is the compound of formula (I) for use in the treatment of inflammatory diseases and autoimmune diseases.

In yet another aspect, described herein is the compound of formula (I) for use in the treatment of the inflammatory diseases, comprising rheumatoid arthritis, inflammatory bowel disease, psoriasis, dermatitis, granuloma, uveitis, chronic
obstructive pulmonary disease (COPD), ulcerative colitis, Crohn's disease, multiple sclerosis and sepsis.

In yet another aspect, described herein is the compound of formula (I) for use in the treatment of neurodegenerative disorders selected from Huntington's disease, Alzheimer's disease, Parkinson's disease, Friedreich's ataxia and stroke.

In other aspect, the compound of formula (I) described herein is efficiently transported across the blood brain barrier (BBB).

In yet another aspect, described herein is the compound of formula (I) for use in the treatment of central nervous system (CNS) disorders.

In another aspect, described herein is the compound of formula (I) for use in inhibiting HDAC.

DETAILED DESCRIPTION

Described herein is the compound of formula (I), its derivatives, analogs, tautomeric forms, stereoisomers, geometrical isomers, diastereomers, polymorphs, hydrates, solvates, pharmaceutically acceptable salts, metabolites, intermediates and prodrugs thereof.

\[
\begin{align*}
A & \quad X \quad P \quad CONH \quad R \\
& \quad B \quad A^1 \quad A^2 \quad A^3
\end{align*}
\]

In one embodiment, A represents \( \text{Ar} \); 
In another embodiment, A represents \( \text{Ar}^{1} \); 
Preferably, Ar represents substituted or unsubstituted groups selected from \((C_6-C_{14})\text{aryll or } 5-15 \text{membered heteroaryll;}

In one embodiment, Ar represents substituted or unsubstituted \((C_6-C_{14})\text{aryl;}

In another embodiment, Ar represents substituted or unsubstituted 5-15 membered heterocycyl or 5-15 membered heteroaryl;

Preferably, X represents \(-\text{CO-, -CH}_2-, -\text{CONR}^3-, -\text{CONR}^3\text{CH}_2-, -\text{SO}_2-\) or \(-\text{NR}^3\text{CO-;}

More preferably, X represents \(-\text{CO-, -CH}_2-, -\text{CONR}^3-\) or \(-\text{CONR}^3\text{CH}_2-\);
In one embodiment, X represents -CO- or -CH₂⁻;

In another embodiment, X represents -CO-, -CONR⁻, -NR⁻CO- or -CONR⁻CH₂⁻;

More preferably, ring Q¹ represents piperidinyl, piperazinyl, pyrrolidinyl or azepanyl;

Preferably, the group is selected from,

More preferably, the group is selected from,

In another embodiment, the group is selected from,

Preferably, R represents OH, or halo substituted;
More Preferably, R represents OH or

More preferably, Ar represents phenyl, naphthyl, benzo[d][1,3]dioxolyl, indolyl, pyridyl, quinolinyl or thieryl;

More preferably, Ar\textsuperscript{1} represents phenyl, naphthyl, benzo[d][1,3]dioxolyl, indolyl, pyridyl, quinolinyl or thieryl;

Most preferred X represents -CO-, -CH\textsubscript{2}-, -CONH- or -CONHCH\textsubscript{2}-. In one embodiment, described herein is the compound of formula (IA),

\[
A^a \xrightarrow{X^a} p^1 \xrightarrow{CONH} R^a \quad (IA)
\]

wherein:

\[A^a\] represents \[
\begin{array}{c}
\text{Ar}^a \\
\text{Ar}^a\text{a} \\
\text{Ar}^a\text{b}
\end{array}
\];

\[\text{Ar}^a\text{ represents substituted or unsubstituted groups selected from } (C_6 - C_{10})\text{aryl, 5-10 membered heterocyclyl and 5-10 membered heteroaryl}; \]

\[\text{Ar}^a\text{ represents optionally substituted groups selected from } (C_{6-9})\text{aryl, 5-10 membered heterocyclyl and 5-10 membered heteroaryl}; \]

\[\text{Ar}^a\text{ represents substituted or unsubstituted groups selected from } (C_6-C_{10})\text{arylene and 5-10 membered heteroarylene}; \]

\[\text{B}^a\text{ represents hydrogen, substituted or unsubstituted groups selected from } (C_1-C_5)\text{alkyl and } (C_3-C_6)\text{cycloalkyl}; \]

\[\text{B}^a\text{ represents hydrogen, -CONR}^\text{1a}R^a, \text{substituted or unsubstituted groups selected from } (C_1-C_5)\text{alkyl and } (C_3-C_6)\text{cycloalkyl}; \]

\[\text{D}^a\text{ represents hydrogen, -COOR}^\text{1a}, -CONR^\text{1a}R^a, \text{substituted or unsubstituted groups selected from } (C_1-C_5)\text{alkyl, } (C_2-C_6)\text{alkenyl, } (C_2-C_6)\text{alkynyl, } (C_6-C_{10})\text{aryl and } (C_3-C_6)\text{cycloalkyl}; \]

\[\text{when one of } B^\text{1a} \text{ or } D^a \text{ is hydrogen or unsubstituted alkyl, the other is neither of } \]

\[\text{hydrogen nor of unsubstituted alkyl}; \]

\[\text{R}^\text{1a}\text{ represents hydrogen, substituted or unsubstituted groups selected from } (C_1-C_5)\text{alkyl and } (C_3-C_6)\text{cycloalkyl}; \]

\[\text{R}^a\text{ represents hydrogen, substituted or unsubstituted groups selected from } (C_1-C_5)\text{alkyl and } (C_3-C_6)\text{cycloalkyl}; \]
or \( R^{1a} \) and \( R^{2a} \) combine together to form substituted or unsubstituted 3-7 membered ring having 0-3 heteroatoms selected from O, S and N;

\( X^a \) represents a bond, \(-\text{CO}-\), \(-\text{CH}_2-\), \(-\text{CONR}^{3a}-\), \(-\text{CONR}^{3a}\text{CH}_2-\) or \(-\text{CH}_2\text{NR}^{3a}-\);

\( R^{3a} \) represents hydrogen, \((\text{C}_6-\text{C}_6)\text{alkyl or (C}_3-\text{C}_6)\text{cycloalkyl}\);

\( \text{p}^1 \)

wherein:

\( T \) represents C, S or O; \( W^1b \) represents C, S or O; \( W^2b \) represents C or O;

\( a \) is an integer selected from 1 and 2;

\( \text{b at each occurrence is independently selected from an integer 0 and 1;} \)

"-----" represents single or double bond;

\( R^4 \) represents hydrogen, halogen, hydroxy, nitro, amino, cyano or substituted or unsubstituted groups selected from \((\text{C}_1-\text{C}_6)\text{alkyl, amino(C}_1-\text{C}_6)\text{alkyl, halo(C}_1-\text{C}_6)\text{alkyl, (C}_6-\text{C}_6)\text{alkoxy and halo(Ci-Ce)alkoxy;}\)

\( R^x \) represents OH or

wherein the substituents are one or more groups, selected from halogens, hydroxy, nitro, cyano, amino, formyl, \((\text{Ci-Ce})\text{alkyl, halo(\text{Ci-Ce})alkyl, (\text{Ci-Ce})alkoxy, halo(\text{Ci-Ce})alkoxy, (\text{C}_6-\text{C}_14)\text{arylalkoxy, (C}_3-\text{C}_12)\text{cycloalkyloxy, (C}_6-\text{C}_14)\text{aryl, (C}_6-\text{C}_14)\text{arylalkyloxy, (\text{C}_6-\text{C}_14)alkylamino, \text{COOR}^a, -\text{C}(0)R^b, -\text{C}(0)NR^aR^b, -\text{NR}^a\text{C}(0)NR^bR^c, -\text{NR}^a\text{C}(\text{S})NR^bR^c, -\text{N}(R^a)\text{SOR}^b, -\text{N}(R^b)\text{SO}_2R^b, -\text{NR}^a\text{C}(0)\text{OR}^b, -\text{NR}^a\text{R}^b, -\text{NR}^a\text{C}(0)R^b, -\text{NR}^a\text{C}(\text{S})R^b, -\text{SONR}^a\text{R}^b, -\text{SO}_2\text{NR}^a\text{R}^b, -\text{OR}^a, -\text{SR}^a, -\text{SOR}^a \) and \(-\text{SOR}^a \), wherein \( R^a \), \( R^b \) and \( R^c \) in each of the above groups represent hydrogen, optionally substituted groups selected from \((\text{Ci-Ce})\text{alkyl, (C}_3-\text{C}_12)\text{cycloalkyl, (C}_6-\text{C}_14)\text{aryl, the substituents are optionally further substituted by one or more substituents as defined above.}\)

In one embodiment, \( A^a \) represents \( \text{Ar}^a \text{Ar}^b \);
In another embodiment, A represents
Preferably, Ar<sup>2a</sup> represents (C<sub>6</sub>-C<sub>i</sub>)arylene;
In one embodiment, described herein is the compound of formula (IA), derived
from compound of formula (I).

Preferably, π represents
In some embodiments described herein are the compounds of formula (II),

wherein:
T represents C, O, S or N;
W<sup>1a</sup> represents C, O, S or N;
W<sup>2a</sup> represents C or N;
a is an integer selected from 1 and 2;
b at each occurrence is independently selected from integer 0 and 1;
"------" represents single or double bond;

R<sup>x</sup> represents OH or
wherein the terms A, X, R<sup>4</sup> are as defined earlier.
In some embodiments described herein are the compounds of formula (II),
derived from compound of formula (I).

In certain other embodiments, provided herein are the compound of formula

(III);

W<sup>3a</sup> represents C or N;
wherein the groups, A, X, R<sup>4</sup> and R<sup>x</sup> are as defined earlier.
In certain other embodiments, provided herein are the compound of formula

(III), derived from compound of formula (I).
In some other embodiments, described herein is the compound of formula (Ila), (lib), (lie), (lid), (He), (Ilf) or (Ilg);

In some other embodiments, described herein is the compound of formula (Ila), (lib), (lie), (lid), (He), (Ilf) or (Ilg), derived from compound of formula (I).

In some embodiments, the hydrogen atom in -CH-, -CH₂-, -NH-, optionally be replaced with the groups, not limited to, halogen, hydroxy, nitro, cyano, amino, formyl, substituted or unsubstituted groups selected from (C₁-C₆)alkyl, halo(Q-C₆)alkyl, (C₁-C₆)alkoxy, halo(C₁-C₆)alkoxy, (C₆-C₁₄)aryloxy, (C₃-C₂) cycloalkyl, (C₆-C₁₄)aryl, (C₆-C₁₄)aryloxy and the like. The -CH₂- groups can be alkylene chain such as -CH₂-, -CH₂-CH₂-, -CH₂-CH₂-CH₂-, -CH₂-CH(CH₃)-, -CH₂-CH(CH₃)-CH₂- and the like.

In yet another embodiment, the ☐ or ☐ can have zero, one or more substituents.

The term "(C₁-C₆)alkyl" refers to straight or branched aliphatic hydrocarbon groups having the specified number of carbon atoms, which are attached to the rest of the molecule by a single atom, which may be optionally substituted by one or more substituents. Examples include, without limitation, methyl, ethyl, isopropyl, n-propyl, n-butyl, isobutyl, t-butyl, pentyl and hexyl.

The term "(C₆-C₁₄)alkylene" refers to a diradical of a branched or unbranched saturated hydrocarbon chain, which may be optionally substituted by one or more...
substituents. Examples include, without limitation, methylene, ethylene, isopropylene, 
n-propylene, n-butylene, isobutylene, t-butylene, pentylene and hexylene.

The term "(C6-Ci4)aryl" refers to aromatic radicals having 6 to 14 carbon 
atoms, which may be optionally substituted by one or more substituents. Typically, 
"(C6-Ci4)aryl" moiety is (C6-C10)aryl. Examples include, without limitation, phenyl, 
naphthyl, indanyl and biphenyl.

The term "5-15 membered heterocyclyl", refers to a stable 5 to 15 membered 
ring radical, which consists of carbon atoms and one to five heteroatoms selected from 
nitrogen, phosphorus, oxygen and sulfur. For purposes of this invention the 
heterocyclic ring radical may be monocyclic, bicyclic, tricyclic or polycyclic 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. The heterocyclyl ring radical may be attached to the main 
structure at any heteroatom or carbon atom that results in the creation of a stable 
structure, which may be optionally substituted by one or more substituents. Typically, 
"5-15 membered heterocyclyl" moiety includes 5-10 membered heterocyclyl. 
Preferably "5-15 membered heterocyclyl" moiety includes 4-8 membered heterocyclyl.

Examples include, without limitation, azetidinyl, acridinyl, benzodioxolyl, 
benzo[d][1,3]dioxolyl, benzodioxanyl, benzofuranyl, carbazolyl, cinnolinyl, 
dioxolanyl, indolizinyl, naphthyridinyl, perhydroazepinyl, phenazinyl, phenothiazinyl, 
phenoazinyl, phthalazinyl, pteridinyl, purinyl, quinazolinyl, quinoxalinyl, quinolinyl, 
isouquinolinyl, tetrazolyl,imidazolyl, tetrahydroisquinolinyl, piperidinyl, piperazinyl, 
homopiperazinyl, 2-oxoazepinyl, azepinyl, pyrrolyl, 4-piperidonyl, pyrrolidinyl, 
pyridinyl, pyrimidinyl, oxazolyl, oxazolinyl, oxazolidinyl, triazolyl, isoxazolyl, 
isoxazolidinyl, thiazolyl, thiazolinyl, thiazolidinyl, isothiazolyl, quinuclidinyl, 
isothiazolidinyl, indolyl, isoindolyl, indolinyl, isoindolinyl, octahydroindolyl, 
octahydroisoindolyl, quinolyl, isoquinolinyl, decahydroisoquinolyl, benzimidazolyl, 
thiazole, benzopyranyl, benzothiazolyl, benzoxazolyl, thiényl, morpholinyl, 
thiomorpholinyl, thiomorpholinyl sulfoxide, furyl, tetrahydrofuryl, tetrahydropyranyl, 
chromanyl and isochromanyl.

Preferably, 5-15 membered heterocyclyl are selected from 
benzo[d][1,3]dioxolyl, benzothiazolyl, benzoxazolyl, thiényl, furyl, pyrrolyl, thiazolyl,
indolyl, isoindolyl, morpholinyl, quinolyl, isoquinolyl, oxazolyl, pyridinyl and pyrimidinyl.

The term "5-15 membered heteroaryl" refers to an aromatic heterocyclyl ring radical as defined above. The heteroaryl ring radical may be attached to the main structure at any heteroatom or carbon atom that results in the creation of stable structure. Typically, "5-15 membered heteroaryl" moiety is 5-10 membered heteroaryl.

The term "(C₆-Ci₄)arylene" or "5-15 membered heteroarylene" refers to bivalent aryl or heteroaryl respectively. Examples of "arylene" include, without limitation, phenylene, naphthylene and indylene. Examples of heteroarylene include, without limitation, benzo[d][1,3]dioxolylene, benzothiazolylene, benzoazolylene, thienylene, furylene, pyrrolylene, thiazolylene, indolylene, isoindolylene, morpholinylene, quinolylene, isoquinolylene, oxazolylene, pyridinylene and pyrimidinylene.

The term "(C₃-Ci₂)cycloalkyl" refers to non-aromatic mono or polycyclic ring system of about 3 to 12 carbon atoms, which may be optionally substituted by one or more substituents. The polycyclic ring denotes hydrocarbon systems containing two or more ring systems with one or more ring carbon atoms in common i.e. a spiro, fused or bridged structures. Typically, "(C₅-Ci₂)cycloalkyl" moiety is "(C₆-Ci₆)cycloalkyl". Examples include, without limitation, cyclopropyl, cyclobutyl, cyclopentyl, cyclohexyl, cyclooctyl, perhydronaphthyl, adamantyl, homo adamantyl, noradamantyl and norbornyl groups, bridged cyclic groups and spirobicyclic groups e.g spiro [4.4] non-2-yl.

The term "(C₁-C₆)alkoxy" refers to an alkyl group attached via an oxygen linkage to the rest of the molecule, which may be optionally substituted by one or more substituents. Examples include, without limitation, -OCH₃, -OC₂H₅ and -OC3H₇.

The term "(C₁-C₆)alkylamino" refers to an alkyl group as defined above attached via amino linkage to the rest of the molecule, which may be optionally substituted by one or more substituents. Preferred alkylamino groups include, without limitation -NHCH₃, -N(CH₃)₂ and -NHCH₂CH₃.

The term "(C₂-C₆)alkenyl" refers to an aliphatic hydrocarbon group containing a carbon-carbon double bond and which may be straight or branched chain having about 2 to 6 carbon atoms, which may be optionally substituted by one or more
substituents. Examples include, without limitation, ethenyl, 1-propenyl, 2-propenyl, iso-propenyl, 2-methyl-1-propenyl, 1-butenyl, 2-butenyl and pentenyl.

The term "(C2-C6)alkynyl" refers to a straight or branched hydrocarbyl radicals having at least one carbon-carbon triple bond and having in the range of 2-6 carbon atoms, which may be optionally substituted by one or more substituents. Examples include, without limitation, ethynyl, propynyl, butynyl and pentynyl.

The term "halogen" refers to fluorine, chlorine, bromine and iodine.

The term "halo(C1-C6)alkyl" refers to halogen group attached via an alkyl linkage to the rest of the molecule, which may be optionally substituted by one or more substituents. Examples include, without limitation, -CH₂C₁, -C₂H₄C₁, trifluoromethyl, tribromomethyl and trichloromethyl.

The term "halo(C₁-C₆)alkoxy" refers to a group resulting from the replacement of one or more hydrogen atoms from an alkoxy group with one or more halogen atoms, which can be the same or different, which may be optionally substituted by one or more substituents. Examples include, without limitation, chloromethoxy, chloroethoxy, trifluoromethoxy, trifluoroethoxy and trichloromethoxy.

The term "(C₆-C₄)aryl(C₁-C₆)alkoxy" refers to an alkoxy group attached to aryl substituent, which may be substituted by one or more substituents. Preferred arylalkoxy groups include, without limitation, benzyloxy and phenylethoxy.

The term "(C₃-C₅)cycloalkyloxy" refers to a cycloalkyl group attached via an oxygen linkage to the rest of the molecule, which may be substituted. Examples include, without limitation -O-cyclopropyl, -O-cyclobutyl, -O-cyclopentyl and -O-cyclohexyl.

The term "amino(C₁-C₆)alkyl" refers to an amino group attached via alkyl linkage to the rest of the molecule, which may be optionally substituted by one or more substituents. Examples include, without limitation -CH₂NH₂, -CH₂CH₂NH₂, -CH₂NHCH₃ and -CH₂N(CH₃)₂.

The term "(C₆-C₄)aryl(C₁-C₆)alkyl" refers to an aryl group directly bonded to an alkyl group, which may be optionally substituted by one or more substituents. Examples, include, without limitation, -CH₂C₆H₅ and -C₂H₄C₆H₅.

The term "(C₆-C₄)aryl(C₂-C₆)alkenyl" refers to an aryl group directly bonded to an alkenyl group, which may be optionally substituted by one or more substituents. Examples, include, without limitation, -C₂H₂C₆H₅ and -C₃H₅C₆H₅.
The term "(C6-Ci4)aryl(C2-C6)alkynyl" refers to an aryl group directly bonded to an alkynyl group, which may be optionally substituted by one or more substituents. Examples include, without limitation, -C2H5 and -C3H7.

The term "5-15 membered heteroaryl(Ci-C6)alkyl" refers to a heteroaryl group directly bonded to an alkyl group, which may be optionally substituted by one or more substituents. Examples include, without limitation, -CH2-pyridinyl and -C2H4-furyl.

The term "5-15 membered heteroaryl(C2-C6)alkenyl" refers to a heteroaryl group directly bonded to an alkenyl group, which may be optionally substituted by one or more substituents. Examples include, without limitation, -C2H2-pyridinyl and -C3H5-furyl.

The term "5-15 membered heteroaryl(C2-C6)alkynyl" refers to a heteroaryl group directly bonded to an alkynyl group, which may be optionally substituted by one or more substituents. Examples include, without limitation, -C2-pyridinyl and -C3H2-furyl.

The term "aminoaryl" refers to aryl group substituted with amino group.

The term "hydroxyaryl" refers to aryl group substituted with hydroxy group.

The term substituents as given here refers to one or more groups selected from hydroxy, nitro, cyano, azido, nitroso, oxo (=O), thioxy (=S), amino, hydrazino, formyl, (Ci-C6)alkyl, halo(C1-C6)alkyl, (C1-C6)alkoxy, halo(Ci-C6)alkoxy, (C6-Ci4)arylamino, (C5-Ci2)cycloalkyl, (C3-Ci2)cycloalkyloxy, (C6-Ci4)arylyl, (C6-Ci4)aryloxy, 5-15 membered heterocyclyl, 5-15 membered heteroaryl, (Ci-C6)alkylamino, -COOR, -C(0)R, -C(0)NR, -N(R)SO2Rb, -N(R)SO2R, -NRbC(0)OR, -NRbRb, -NRbC(0)R, -NRbC(S)R, -SONRR, -SO2NRbR, -SR, -SOR, and -S02R, wherein R, Rb and Rb in each of the above groups represent hydrogen, optionally substituted groups selected from (C1-C6)alkyl, (C5-Ci4)cycloalkyl, (C6-Ci4)aryl, (C6-Ci4)alkyl(C1-C6)alkyl, 5-15 membered heterocyclyl, 5-15 membered heteroaryl and 5-15 membered heteroaryl(Ci-C6)alkyl. Rb, Rb or Rb can also combine to form a substituted or unsubstituted 3-10 membered heterocyclic rings including spiro-fused heterocyclic ring having 0-3 heteroatoms; the substituents are optionally further substituted by one or more substituents as defined above.

Preferably, term substituents as given here refers to one or more groups selected from halogens, hydroxy, nitro, cyano, amino, formyl, (C1-C6)alkyl, halo(C1-C6)alkyl, (C1-C6)alkoxy, (C5-Ci4)aryl, (C5-Ci4)aryloxy, (d-C6)alkylamino, -COOR,
-C(0)NR \textsuperscript{a}R \textsuperscript{b}, -SR \textsuperscript{a}, -SOR \textsuperscript{a} and -S0 \textsubscript{2}R \textsuperscript{a}, wherein R \textsuperscript{a}, R \textsuperscript{b} or R \textsuperscript{c} in each of the above groups represent hydrogen, optionally substituted groups selected from (Ci-C\textsubscript{6})alkyl, (\textsubscript{c3} -C\textsubscript{2})cycloalkyl, (\textsubscript{c6} -C\textsubscript{14})aryl; the substituents are optionally further substituted by one or more substituents as defined above.

The compounds described herein can be either E or Z geometrical isomers and in some cases mixtures can also be present. In cases where two or more double bonds are present in formula (I), then it can give rise to more than two geometrical isomers and in these cases the invention is said to cover all the isomers.

It is understood that included in the family of compounds of Formula (I) are isomeric forms including diastereomers, enantiomers, tautomers, and geometrical isomers in "E" or "Z" configuration or a mixture of E and Z isomers. It is also understood that some isomeric form such as diastereomers, enantiomers and geometrical isomers can be separated by physical and/or chemical methods by those skilled in the art.

The stereoisomers are isomers that differ in the arrangement of their atoms in space. Compounds disclosed herein may exist as single stereoisomers, racemates and/or mixtures of enantiomers and/or diastereomers. All such single stereoisomers, racemates and mixtures thereof are intended to be within the scope of the subject matter described.

The term "solvates" includes combinations of solvent molecules with molecules or ions of the solute compound.

The term "derivatives" refers to a chemical compound or molecule made from a parent compound by one or more chemical reactions such as, by oxidation, hydrogenation, alkylation, esterification, halogenation and the like.

The term "tautomer" refers to one of two or more structural isomers which exist in equilibrium and which are readily converted from one isomeric form to another.

The term "metabolite" refers to compounds that result from a metabolic process either by breakdown or modifications of parent compound through phase I or phase II metabolism. Examples of metabolism on the compounds of the present invention include addition of -OH, hydrolysis and cleavage.

The term "analog" refers to a chemical compound that is structurally similar to another compound but differs slightly in the replacement of one atom by an atom of a different element or in the presence of a particular functional group, or the replacement
of one functional group by another functional group. An analog is a compound that is similar or comparable in function and appearance, but not in structure or origin to the reference compound.

The pharmaceutical composition may be in the forms normally employed, such as tablets, capsules, powders, syrups, solutions, cream, suspensions, aerosols, and the like, may contain flavorants, sweeteners, excipients etc. in suitable solid or liquid carriers or diluents, or in suitable sterile media to form injectable solutions or suspensions. The compositions may be prepared by processes known in the art. Suitable pharmaceutically acceptable carriers include solid fillers or diluents and sterile aqueous or organic solutions. The active compound will be present in such pharmaceutical compositions in the amounts sufficient to provide the desired dosage. Suitable routes of administration, includes, not limited to, oral, transdermal, rectal, nasal, topical, sublingual, intrathecal, intra-articular, intracisternal, intravaginal, ophthalmic, epidural, intracerebral, intracerebroventricular, intravesical, intravitreal, intracavernous intrauterine transmucosal or parenteral administration such as subcutaneous, intramuscular, intravenous, intraperitoneal and intradermal routes. For parenteral administration, the compounds can be combined with a sterile aqueous or organic media to form injectable solutions or suspensions. For example, solutions in sesame or peanut oil, aqueous propylene glycol and the like can be used, as well as aqueous solutions of water-soluble pharmaceutically acceptable acid addition salts or alkali or alkaline earth metal salts of the compounds. The injectable solutions prepared in this manner can then be, administered intravenously, intraperitoneally, subcutaneously or intramuscularly.

The phrase "pharmaceutically acceptable" refers to compounds or compositions that are physiologically tolerable and do not typically produce allergic or similar untoward reaction, including but not limited to gastric upset or dizziness when administered to mammal.

Pharmaceutically acceptable salts forming part of this invention include salts derived from inorganic bases such as Li, Na, K, Ca, Mg, Fe, Cu, Al, Zn and Mn salts; salts of organic bases such as N, N'-diacetylenediamine, glucamine, triethylamine, choline, dicyclohexylamine, benzylamine, trialkylamine, thiamine, guanidine, diethanolamine, a-phenylethylamine, piperidine, morpholine, pyridine, hydroxyethylpyrrolidine, hydroxyethylpiperidine, ammonium, substituted ammonium...
salts and the like. Salts also include amino acid salts such as glycine, alanine, cystine, cysteine, lysine, arginine, phenylalanine, guanidine, etc. Salts may include acid addition salts where appropriate which are sulphates, nitrates, phosphates, perchlorates, borates, hydrohalides, acetates, tartrates, maleates, citrates, succinates, palmoates, methanesulphonates, tosylates, benzoates, salicylates, hydroxynaphthoates, benzenesulphonates, ascorbates, glycerophosphates, ketoglutarates and the like.

The term "prodrugs" as used herein refers to any pharmacologically inactive or less active compound which, when metabolized or chemically transformed by a mammalian system is converted into a pharmacologically active compound of formula (I) of the present invention. For example, some of the prodrugs are esters of the compound of formula (I), during metabolism the ester group is cleaved to form the active compound of formula (I). A general overview of prodrug is provided in H Surya Prakash Rao, Resonance, 2003, 8, 19-27.

The compounds described herein can also be prepared in any solid or liquid physical form, for example the compound can be in a crystalline form, in amorphous form and have any particle size. Furthermore, the compound particles may be micronized or nanoized, or may be agglomerated, or in the form of particulate granules, powders, oils, oily suspensions or any other form of solid or liquid physical forms.

The compounds described herein may also exhibit polymorphism. This invention further includes different polymorphs of the compounds of the present invention. The term polymorph refers to a particular crystalline state of a substance, having particular physical properties such as X-ray diffraction, IR spectra, melting point and the like.

The term "histone deacetylase inhibitor" or "inhibitor of histone deacetylase" is used to identify a compound, which is capable of interacting with a histone deacetylase and inhibiting its activity, more particularly its enzymatic activity. Inhibiting histone deacetylase enzymatic activity means reducing the ability of a histone deacetylase to remove an acetyl group from a histone. Preferably, such inhibition is specific, i.e. the histone deacetylase inhibitor reduces the ability of histone deacetylase to remove an acetyl group from a histone at a concentration that is lower than the concentration of the inhibitor that is required to produce some other, unrelated biological effect.
The terms "histone deacetylase" and "HDAC" are intended to refer to any one of a family of enzymes that remove acetyl groups from the ε-amino groups of lysine residues at the N-terminus of a histone. Unless otherwise indicated by context, the term "histone" is meant to refer to any histone protein, including HI, H2A, H2B, H3, H4 and H5, from any species. Human HDAC proteins or gene products include but are not limited to, HDAC-1, HDAC-2, HDAC-3, HDAC-4, HDAC-5, HDAC-6, HDAC-7, HDAC-8, HDAC-9, HDAC-10 and HDAC-11. The histone deacetylase can also be derived from a protozoal or fungal source.

The term "isoform selective-specific HDAC inhibitors" are one which affects a single HDAC isoform and the term "class selective-specific HDAC inhibitors" are one which affects several isoforms within a single class.

The compounds described herein are used in the treatment or prevention of cancer. The cancer includes solid tumors or hematologic malignancies. Examples include, without limitation, multiple myeloma, lung cancer, breast cancer, prostate cancer, colon cancer and fibrosarcoma.

The present invention provides a method of treatment of a disorder caused by, associated with or accompanied by disruptions of cell proliferation and/or angiogenesis including administration of a therapeutically effective amount of a compound of formula (I).

In another aspect, described herein is the use of the compound of formula (I) for treating cancer, without limitation, tumors, sarcomas, lymphomas, carcinomas, leukemias, myelomas and melanomas.

The present invention provides a method of treatment of a disorder, disease or condition that can be treated by the inhibition of HDAC enzymes including administration of therapeutically effective amount of compound of formula (I).

Various proliferative diseases include, for example, a tumor disease and/or metastasis. In certain embodiment, the proliferative disease may furthermore be a hyperproliferative condition such as leukemia, fibrosis, angiogenesis, psoriasis, atherosclerosis and smooth muscle proliferation in the blood vessels, such as stenosis or restenosis following angioplasty.

In yet another embodiment, the compounds described herein are selectively toxic or toxic to rapidly proliferating cells than to normal cells, including, for example, human cancer cells, e.g. cancerous tumors, the compounds have significant
antiproliferative effects and promotes differentiation, e.g., cell cycle arrest and apoptosis. In addition, the compounds induce p21, cyclin-CDK interacting protein, which includes either apoptosis or G1 arrest in variety of cell lines.

A method of treatment and/or prevention of inflammatory diseases which are mediated by HDAC's comprising rheumatoid arthritis (RA), inflammatory bowel disease (IBD), pelvic inflammatory disease (PID), human airway diseases such as asthma and chronic obstructive pulmonary disease (COPD), cancer-induced bone pain (CIBP), atherosclerosis, endometriosis, granuloma, sepsis, multiple sclerosis, organ transplant rejection and other systemic inflammatory diseases, comprising administrating to a subject suffering from the inflammatory diseases, a therapeutically effective amount of a compound of formula (I) (Bonfils C et al., Expert Opinion on Drug Discovery, 2008, 3, 1041-1065).

A method of treatment and/or prevention of neurodegenerative disorders/CNS disorders including but not limited to Huntingtons's disease, Alzheimer's disease, Parkinson's disease, Friedreich's ataxia, stroke, spinal muscle atrophy, anxiety, traumatic brain injury, cerebral palsy, schizophrenia, spinocerebellar ataxia, Rett syndrome, fragile X disease, seizure disorders, depression, unipolar depression, bipolar disorder, amyotrophic lateral sclerosis, ischemia, Rubinstein-taybi syndrome, AIDS dementia, dementia, Korsakoff's syndrome, brain cancers, Wilson disease, Tay-Sach's disease, Tourette's disease, epilepsy and the like comprising administrating to a subject suffering from the CNS disorder, a therapeutically effective amount of a compound of formula (I).

A method of treatment and/or prevention of CIBP, comprising administrating to a subject suffering from such a disorder, a therapeutically effective dose of compound of formula (I).

The present invention provides a method of treatment of various fungal diseases by the inhibition of fungal HDAC enzymes, comprising administration of therapeutically effective amount of compound of formula (I).

Further, the present invention also provides a method of treatment and/or prevention of human immunovirus (HIV) latent disease, comprising, administrating a therapeutically effective amount of a compound of formula (I). (Kelly Huber et al., Journal of Biological Chemistry, 2011, 286(25), 22211-22218).
In another aspect, the compounds described herein are also used for the treatment and/or prevention of protozoal infections such as malaria by inhibiting protozoal HDAC, comprising administering therapeutically effective amount of compound of formula (I).

Compounds disclosed herein are also used to treat Gaucher disease by inhibiting HDAC enzyme.

The term "therapeutically effective amount" or "effective amount" is an amount sufficient to effect beneficial or desired results. An effective amount can be administered in one or more administrations. An effective amount is typically sufficient to palliate, ameliorate, stabilize, reverse, slow or delay the progression of the disease state.

In another aspect, the compound may be administered in combination therapy by combining the compound of formula (I) with one or more separate agents, not limited to targets such as HDAC, DNA methyltransferase, heat shock proteins (e.g. HSP90), kinase, matrix metalloproteinases, proteasome inhibitors, topoisomerase I inhibitors, topoisomerase II inhibitors or other known HDAC inhibitors.

"Combination therapy" includes the administration of the subject compounds in further combination with other biologically active ingredients (such as, but are not limited to, different antineoplastic agent) and non-drug therapies (such as, but are not limited to, surgery or radiation treatment). The compounds described herein can be used in combination with other pharmaceutically active compounds, preferably, which will enhance the effect of the compounds of the invention. The compounds can be administered simultaneously or sequentially to the other drug therapy.

The term "cytotoxic agents" are those which possesses a specific destructive action on certain cells or that may be genotoxic, oncogenic, mutagenic, teratogenic, or hazardous to cells in any way and includes most anti-cancer drugs substances. It acts by killing the cell or inhibiting the growth or proliferation of cells.

The term "non-cytotoxic agents" are substances that can be employed in treatment of cancers, which are more often cytostatic than cytotoxic (no tumor regression but inhibition of tumor progression). Examples include but not limited to tyrosine kinase inhibitors, angiogenesis inhibitors etc.,

In other aspect, the compound of formula (I) described herein may be co-administered with the other cytotoxic agents/non-cytotoxic agents, selected from but
not limited to, bortezomib, disulfiram, salinosporamide A and carfilzomib, afatinib, 
axitinib, bevacizumab, cetuximab, crizotinib, dasatinib, erlotinib, fostamatinib, 
gefitinib, imatinib, lapatinib, lenvatinib, mubritinib, nilotinib, panitumumab, 
pazopanib, pegaptanib, ranibizumab, ruxolitinib, sorafenib, sunitinib, trastuzumab, 
vandetanib and vemurafenib, raloxifene, tamoxifen and related analogs, docetaxel, 
paclitaxel and related analogs.

In another aspect, the subject compounds may be combined with the antineoplastic agents (e.g. small molecules, monoclonal antibodies, antisense RNA and fusion proteins) that inhibit one or more biological targets. Such combination may enhance therapeutic efficacy over the efficacy achieved by any of the agents alone and may prevent or delay the appearance of resistant variants.

In another aspect, described herein is inhibiting HDAC6, in a biological sample includes in vitro, in vivo, ex vivo, cell cultures, blood and other body fluids.

The term "subject" as used herein refers to animals including, not limited to mammals, and in particular humans, in need of treatment. The therapeutically effective amount will vary depending upon the subject and disease condition being treated, the weight and age of the subject, the severity of the disease condition, the particular compound of formula (I) chosen, the dosing regimen to be followed, timing of administration, the manner of administration and the like, all of which can readily be determined by one of ordinary skill in the art.

The term "transported across the blood-brain barrier" refers to targeting moiety that is able to cross the BBB. The permeability will be determined by the BBB uptake parameters like $K_p$, $K_{pu}$ etc.

The term "prophylaxis" or "prevention" means preventing the disease, i.e, causing the clinical symptoms of the disease not to develop.

The term "treatment" or "treating" mean any treatment of a disease in a mammal, including: (a) Inhibiting the disease, i.e, slowing or arresting the development of clinical symptoms; and/or (b) Relieving the disease, i.e, causing the regression of clinical symptoms. A beneficial outcome of the treatment may include, but not limited to either a decrease in the severity of systems or delay in the onset of symptoms or a substantial reversal of the symptom or condition.

The term "compound(s) for use" as used herein embrace any one or more of the following: (1) use of compound(s), (2) method of use of compound(s), (3) use in the
treatment of, (4) the use for the manufacture of pharmaceutical composition / medicament for treatment/treating or (5) method of treatment / treating/ preventing / reducing / inhibiting comprising administering an effective amount of the active compound to a subject in need thereof.

The present invention is provided by the examples given below, which are provided by way of illustration only, and should not be construed to limit the scope of the invention. Variation and changes, that are obvious to one skilled in the art, are intended to be within the scope and nature of the invention.

A term once described, the same meaning applies for it, throughout the patent.

Particularly useful compounds include:

1. 2-(2,3-Diphenylacryloyl)-N-hydroxy-1,2,3,4-tetrahydroisoquinoline-7-carboxamide;
2. 2-(3-(4-Fluorophenyl)-2-(4-fluorophenyl)acryloyl)-N-hydroxy-1,2,3,4-tetrahydroisoquinoline-7-carboxamide;
3. 2-(3-(3,4-Dimethoxyphenyl)-2-(4-fluorophenyl)acryloyl)-N-hydroxy-1,2,3,4-tetrahydroisoquinoline-7-carboxamide;
4. 2-(2-(2,4-Difluorophenyl)-3-phenylacryloyl)-N-hydroxy-1,2,3,4-tetrahydroisoquinoline-7-carboxamide;
5. 2-(2-(4-Fluorophenyl)-3-(4-methoxyphenyl)acryloyl)-N-hydroxy-1,2,3,4-tetrahydroisoquinoline-7-carboxamide;
6. 2-(2-(4-Fluorophenyl)-3-phenylacryloyl)-N-hydroxy-1,2,3,4-tetrahydroisoquinoline-7-carboxamide;
7. 2-(3-(3,4-Difluorophenyl)-2-(4-methoxyphenyl)acryloyl)-N-hydroxy-1,2,3,4-tetrahydroisoquinoline-7-carboxamide;
8. 2-(3-(2,4-Difluorophenyl)-2-(4-fluorophenyl)acryloyl)-N-hydroxy-1,2,3,4-tetrahydroisoquinoline-7-carboxamide;
9. 2-(3-(4-Fluoro-3-methoxyphenyl)-2-(4-fluorophenyl)acryloyl)-N-hydroxy-1,2,3,4-tetrahydroisoquinoline-7-carboxamide;
10. 2-(3-(3,4-Dimethoxyphenyl)-2-p-tolylacryloyl)-N-hydroxy-1,2,3,4-tetrahydroisoquinoline-7-carboxamide;
11. 2-(3-(3,4-Dimethoxyphenyl)-2-p-tolylacryloyl)-N-hydroxy-1,2,3,4-tetrahydroisoquinoline-7-carboxamide;
12. 2-(3-(3,4-Dimethoxyphenyl)-2-phenylacryloyl)-N-hydroxy-1,2,3,4-tetrahydroisoquinoline-7-carboxamide;
13. N-Hydroxy-2-(3-(4-(methylthio)phenyl)-2-ethyltolylacryloyl)-1,2,3,4-tetrahydroisoquinoline-7-carboxamide;
14. 2-(3-(3,4-Dimethoxyphenyl)-2-(2-fluorophenyl)acryloyl)-N-hydroxy-1,2,3,4-tetrahydroisoquinoline-7-carboxamide;
15. 2-(2-(3,4-Dimethoxyphenyl)-3-(3-fluorophenyl)acryloyl)-N-hydroxy-1,2,3,4-tetrahydroisoquinoline-7-carboxamide;
16. 2-(2,3-6w(3,4-Dimethoxyphenyl)acryloyl)-N-hydroxy-1,2,3,4-tetrahydroisoquinoline-7-carboxamide;
17. 2-(2-(Benzo[d][1,3]dioxol-5-yl)-3-(4-fluorophenyl)acryloyl)-N-hydroxy-1,2,3,4-tetrahydroisoquinoline-7-carboxamide;
18. 2-(2-(4-Fluorophenyl)-3-(3-phenoxyphenyl)acryloyl)-N-hydroxy-1,2,3,4-tetrahydroisoquinoline-7-carboxamide;
19. 2-(2-(3-Chlorophenyl)-3-phenylacryloyl)-N-hydroxy-1,2,3,4-tetrahydroisoquinoline-7-carboxamide;
20. 2-(2-(3-Fluorophenyl)-3-phenylacryloyl)-N-hydroxy-1,2,3,4-tetrahydroisoquinoline-7-carboxamide;
21. 2-(2-(2-Fluorophenyl)-3-phenylacryloyl)-N-hydroxy-1,2,3,4-tetrahydroisoquinoline-7-carboxamide;
22. 2-(2-(2-Chloro-4-fluorophenyl)-3-phenylacryloyl)-N-hydroxy-1,2,3,4-tetrahydroisoquinoline-7-carboxamide;
23. N-Hydroxy-2-(3-phenyl-2-ethyltolylacryloyl)-1,2,3,4-tetrahydroisoquinoline-7-carboxamide;
24. 2-(3-(4-Fluorophenyl)-2-phenylacryloyl)-N-hydroxy-1,2,3,4-tetrahydroisoquinoline-7-carboxamide;
25. 2-(2-(4-Fluorophenyl)-3-(thiophen-2-yl)acryloyl)-N-hydroxy-1,2,3,4-tetrahydroisoquinoline-7-carboxamide;
26. 2-(3-(2,4-Dimethoxyphenyl)-2-(3-fluorophenyl)acryloyl)-N-hydroxy-1,2,3,4-tetrahydroisoquinoline-7-carboxamide;
27. 2-(3-(4-Chlorophenyl)-2-phenylacryloyl)-N-hydroxy-1,2,3,4-tetrahydroisoquinoline-7-carboxamide;
28. 2-(2-(2-Chlorophenyl)-3-phenylacryloyl)-N-hydroxy-1,2,3,4-tetrahydroisoquinoline-7-carboxamide;
29. 2-(3-(2,4-Dimethoxyphenyl)-2-(4-fluorophenyl)acryloyl)-N-hydroxy-1,2,3,4-tetrahydroisoquinoline-7-carboxamide;
30. N-Hydroxy-2-(2-(naphthalen-2-yl)-3-phenylacryloyl)-1,2,3,4-tetrahydroisoquinoline-7-carboxamide;
31. 2-(2-(4-(N,N-Dimethylamino)phenyl)-3-phenylacryloyl)-N-hydroxy-1,2,3,4-tetrahydroisoquinoline-7-carboxamide;
32. N-Hydroxy-2-(3-(4-methoxyphenyl)-2-phenylacryloyl)-1,2,3,4-tetrahydroisoquinoline-7-carboxamide;
33. 2-(2,3-Ox(4-Methoxyphenyl)acryloyl)-N-hydroxy-1,2,3,4-tetrahydroisoquinoline-7-carboxamide;
34. 2-(3-(2-Fluorophenyl)-2-(4-fluorophenyl)acryloyl)-N-hydroxy-1,2,3,4-tetrahydroisoquinoline-7-carboxamide;
35. 2-(2-(4-Fluorophenyl)-3-(5-methylthiophen-2-yl)acryloyl)-N-hydroxy-1,2,3,4-tetrahydroisoquinoline-7-carboxamide;
36. 2-(2-(4-Fluorophenyl)-3-(3-nitrophenyl)acryloyl)-N-hydroxy-1,2,3,4-tetrahydroisoquinoline-7-carboxamide;
37. 2-(3-(3,4-Dimethoxyphenyl)-2-(thiophen-2-yl)acryloyl)-N-hydroxy-1,2,3,4-tetrahydroisoquinoline-7-carboxamide;
38. 2-(2-(2-Chlorophenyl)-3-(4-fluorophenyl)acryloyl)-N-hydroxy-1,2,3,4-tetrahydroisoquinoline-7-carboxamide;
39. 2-(3-(4-Chlorophenyl)-2-(4-fluorophenyl)acryloyl)-N-hydroxy-1,2,3,4-tetrahydroisoquinoline-7-carboxamide;
40. N-Hydroxy-2-(3-(4-methoxyphenyl)-2-p-tolylacryloyl)-1,2,3,4-tetrahydroisoquinoline-7-carboxamide;
41. 2-(2-(2-Chlorophenyl)-3-(4-chlorophenyl)acryloyl)-N-hydroxy-1,2,3,4-tetrahydroisoquinoline-7-carboxamide;
42. 5-(2-(4-Fluorophenyl)-3-phenylacryloyl)-N-hydroxy-4,5,6,7-tetrahydrothieno[3,2-c]pyridine-2-carboxamide;
43. 5-(2-(3-Fluorophenyl)-3-phenylacryloyl)-N-hydroxy-4,5,6,7-tetrahydrothieno[3,2-c]pyridine-2-carboxamide;
44. 2-(2-(4-Fluorophenyl)-3-(3,4,5-trimethoxyphenyl)acryloyl)-N-hydroxy-1,2,3,4-tetrahydroisoquinoline-7-carboxamide;

45. 2-(2-(4-Fluorophenyl)-3-(pyridin-3-yl)acryloyl)-N-hydroxy-1,2,3,4-tetrahydroisoquinoline-7-carboxamide;

46. 2-(2-(4-Fluorophenyl)-3-(pyridin-4-yl)acryloyl)-N-hydroxy-1,2,3,4-tetrahydroisoquinoline-7-carboxamide;

47. 4-(2-(4-Fluorophenyl)-3-(7-(hydroxycarbamoyl)-3,4-dihydroisoquinolin-2(1H)-yl)-3-oxoprop-1-eryl)benzoic acid;

48. 2-(2-(2-Chlorophenyl)-3-(4-methoxyphenyl)acryloyl)-N-hydroxy-1,2,3,4-tetrahydroisoquinoline-7-carboxamide;

49. 2-(3-(3,4-Difluorophenyl)-2-phenylacryloyl)-N-hydroxy-1,2,3,4-tetrahydroisoquinoline-7-carboxamide;

50. 2-(3-(3,4-Difluorophenyl)-2-/?-tolylacryloyl)-N-hydroxy-1,2,3,4-tetrahydroisoquinoline-7-carboxamide;

51. 2-(2-(4-Chlorophenyl)-3-phenylacryloyl)-N-hydroxy-1,2,3,4-tetrahydroisoquinoline-7-carboxamide;

52. 1-(2,3-Diphenylacryloyl)-N-hydroxyindoline-5-carboxamide;

53. 5-(2,3-Diphenylacryloyl)-N-hydroxy-4,5,6,7-tetrahydrothieno[3,2-c]pyridine-2-carboxamide;

54. 2-(2-(4-Fluorophenyl)-3-(4-(methylthio)phenyl)acryloyl)-N-hydroxy-1,2,3,4-tetrahydroisoquinoline-7-carboxamide;

55. 1-(2-(4-Fluorophenyl)-3-phenylacryloyl)-N-hydroxyindoline-5-carboxamide;

56. 2-(2,3-Di/?-tolylacryloyl)-N-hydroxy-1,2,3,4-tetrahydroisoquinoline-7-carboxamide;

57. N-Hydroxy-2-(2-phenyl-3-p-tolylacryloyl)-1,2,3,4-tetrahydroisoquinoline-7-carboxamide;

58. N-Hydroxy-2-(3-phenyl-2-(4-(trifluoromethyl)phenyl)acryloyl)-1,2,3,4-tetrahydroisoquinoline-7-carboxamide;

59. 2-(4-(3-(Cyclopropylamino)-3-oxo-2-phenylprop-1-ethyl)benzoyl)-N-hydroxy-1,2,3,4-tetrahydroisoquinoline-7-carboxamide;

60. 2-(2-(4-Chlorophenyl)-3-(thiophen-2-yl)acryloyl)-N-hydroxy-1,2,3,4-tetrahydroisoquinoline-7-carboxamide;
61. \(2-(2,3\text{-Diphenylacryloyl})-N\text{-hydroxy-2,3,4,5-tetrahydro-1H-benzo[c]azepine-8-carboxamide;}\)

62. \(2-(3-(2\text{-Aminophenyl})-2-(4\text{-fluorophenyl})acryloyl)-N\text{-hydroxy-1,2,3,4-tetrahydroisoquinoline-7-carboxamide;}\)

63. \(2-(2-(2\text{-Chlorophenyl})-3\text{-thiophen-2-yl)acryloyl})-N\text{-hydroxy-1,2,3,4-tetrahydroisoquinoline-7-carboxamide;}\)

64. \(2-(2-(2\text{-Fluorophenyl})-3\text{-thiophen-2-yl)acryloyl})-N\text{-hydroxy-1,2,3,4-tetrahydroisoquinoline-7-carboxamide;}\)

65. \(2-(3-(4\text{-Chlorophenyl})-2-(4\text{-fluorophenyl})acryloyl)-N\text{-hydroxy-2,3,4,5-tetrahydro-1H-benzo[c]azepine-8-carboxamide;}\)

66. \(2-(2-(3\text{-Chlorophenyl})-3-(4\text{-fluorophenyl})acryloyl)-N\text{-hydroxy-2,3,4,5-tetrahydro-1H-benzo[c]azepine-8-carboxamide;}\)

67. \(2-(4-(3\text{-Cyclopropylamino})-2-(4\text{-fluorophenyl})-3\text{-oxoprop-1-enyl)benzoyl})-N\text{-hydroxy-1,2,3,4-tetrahydroisoquinoline-7-carboxamide;}\)

68. \(2-(2-(3\text{-Chlorophenyl})-3\text{-phenylacryloyl})-N\text{-hydroxy-2,3,4,5-tetrahydro-1H-benzo[c]azepine-8-carboxamide;}\)

69. \(N\text{-Hydroxy-2-(2-phenyl-3-(thiophen-2-yl)acryloyl)-1,2,3,4-tetrahydroisoquinoline-7-carboxamide;}\)

70. \(2-(2,3\text{-Di(thiophen-2-yl)acryloyl})-N\text{-hydroxy-1,2,3,4-tetrahydroisoquinoline-7-carboxamide;}\)

71. \(N\text{-Hydroxy-2-(2-(4\text{-methoxyphenyl})-3-(thiophen-2-yl)acryloyl)-1,2,3,4-tetrahydroisoquinoline-7-carboxamide;}\)

72. \(N\text{-Hydroxy-2-(3-(thiophen-2-yl)-2-/\text{-tolylacryloyl)-1,2,3,4-tetrahydroisoquinoline-7-carboxamide;}\)

73. \(2-(3-(3\text{-Fluorophenyl})-2\text{-phenylacryloyl})-N\text{-hydroxy-1,2,3,4-tetrahydroisoquinoline-7-carboxamide;}\)

74. \(N\text{-Hydroxy-2-(3-phenyl-2-/w-tolylacryloyl)-1,2,3,4-tetrahydroisoquinoline-7-carboxamide;}\)

75. \(2-(3-(3\text{-Fluorophenyl})-2/d-p-tolylacryloyl)-N\text{-hydroxy-1,2,3,4-tetrahydroisoquinoline-7-carboxamide;}\)

76. \(N\text{-Hydroxy-2-(2-(3\text{-methoxyphenyl})-3-phenylacryloyl)-1,2,3,4-tetrahydroisoquinoline-7-carboxamide;}\)

77. \(1-(2-(3\text{-Fluorophenyl})-3-phenylacryloyl)-N\text{-hydroxyindoline-6-carboxamide;}\)
78. \(N\text{-Hydroxy-2-(2-(4-methoxyphenyl)-3-phenylacryloyl)-1,2,3,4-tetrahydroisoquinoline-7-carboxamide;}\)
79. \(2-(2-(3,4-Dimethoxyphenyl)-3-phenylacryloyl)\text{-}N\text{-hydroxy-1,2,3,4-tetrahydroisoquinoline-7-carboxamide;}\)
80. \(2-(3-(4-Fluorophenyl)-2-(3-methoxyphenyl)acryloyl)\text{-}N\text{-hydroxy-1,2,3,4-tetrahydroisoquinoline-7-carboxamide;}\)
81. \(1-(3-(4-Chlorophenyl)-2-(4-fluorophenyl)acryloyl)\text{-}N\text{-hydroxyindoline-5-carboxamide;}\)
82. \(1-(2-(3-Chlorophenyl)-3-(4-fluorophenyl)acryloyl)\text{-}N\text{-hydroxyindoline-5-carboxamide;}\)
83. \(3-(3-(3-Fluorophenyl)-2-p-tolylacryloyl)\text{-}N\text{-hydroxyindoline-5-carboxamide;}\)
84. \(N\text{-Hydroxy-1-(3-phenyl-2-m-tolylacryloyl)indoline-5-carboxamide;}\)
85. \(1-(3-(4-Fluorophenyl)-2-phenylacryloyl)\text{-}N\text{-hydroxyindoline-5-carboxamide;}\)
86. \(5-(3-(4-Fluorophenyl)-2-phenylacryloyl)\text{-}N\text{-hydroxy-4,5,6,7-tetrahydrothieno[3,2-c]pyridine-2-carboxamide;}\)
87. \(N\text{-Hydroxy-5-(3-phenyl-2-p-tolylacryloyl)-4,5,6,7-tetrahydrothieno[3,2-c]pyridine-2-carboxamide;}\)
88. \(5-(3-(3-Fluorophenyl)-2-p-tolylacryloyl)\text{-}N\text{-hydroxy-4,5,6,7-tetrahydrothieno[3,2-c]pyridine-2-carboxamide;}\)
89. \(N\text{-Hydroxy-2-(2-(3-chlorophenyl)-3-(quinolin-4-yl)acryloyl)-1,2,3,4-tetrahydroisoquinoline-7-carboxamide;}\)
90. \(5-(2-(4-Fluorophenyl)-3-(1H-indol-3-yl)acryloyl)\text{-}N\text{-hydroxy-4,5,6,7-tetrahydrothieno[3,2-c]pyridine-2-carboxamide;}\)
91. \(1-(2-(4-Fluorophenyl)-3-(1H-indol-3-yl)acryloyl)\text{-}N\text{-hydroxy-1,2,3,4-tetrahydroisoquinoline-7-carboxamide;}\)
92. \(5-(3-(4-Fluorophenyl)-2-(1H-indol-3-yl)acryloyl)\text{-}N\text{-hydroxy-4,5,6,7-tetrahydroisoxazolo[4,5-c]pyridine-3-carboxamide;}\)
93. \(5-(2-(4-Fluorophenyl)-3-(pyridin-4-yl)acryloyl)\text{-}N\text{-hydroxy-4,5,6,7-tetrahydroisoxazolo[4,5-c]pyridine-3-carboxamide;}\)
94. \(5-(3-(4-Fluorophenyl)-2-phenylacryloyl)\text{-}N\text{-hydroxy-4,5,6,7-tetrahydroisoxazolo[4,5-c]pyridine-3-carboxamide;}\)
95. \(N\text{-Hydroxy-5-(2-(4-methoxyphenyl)-3-(thiophen-2-yl)acryloyl)-4,5,6,7-tetrahydroisoxazolo[4,5-c]pyridine-3-carboxamide;}\)
96. 5-(2-(4-Fluorophenyl)-3-phenylacryloyl)-N-hydroxy-4,5,6,7-tetrahydroisoxazolo[4,5-c]pyridine-3-carboxamide;
97. 5-(2,3-Diphenylacryloyl)-N-hydroxy-4,5,6,7-tetrahydroisoxazolo[4,5-c]pyridine-3-carboxamide;
98. N-Hydroxy-5-(3-phenyl-2-(thiophen-2-yl)acryloyl)-4,5,6,7-tetrahydrothieno[3,2-c]pyridine-2-carboxamide;
99. N-Hydroxy-5-(2-(4-methoxyphenyl)-3-(thiophen-2-yl)acryloyl)-4,5,6,7-tetrahydrothieno[3,2-c]pyridine-2-carboxamide;
100. 5-(2-(4-Fluorophenyl)-3-(pyridin-4-yl)acryloyl)-N-hydroxy-4,5,6,7-tetrahydrothieno[3,2-c]pyridine-2-carboxamide;
101. 2-(3-(4-Fluorophenyl)-2-phenylacryloyl)-N-hydroxy-1,2,3,4-tetrahydroisoquinoline-6-carboxamide;
102. 2-(3-(4-Fluorophenyl)-2-phenylacryloyl)-N-hydroxy-1,2,3,4-tetrahydroisoquinoline-8-carboxamide;
103. 5-(2-(4-Fluorophenyl)-3-phenylacryloyl)-N-hydroxy-4,5,6,7-tetrahydrofuro[3,2-c]pyridine-2-carboxamide;
104. N-Hydroxy-1-(3-phenyl-2-(thiophen-2-yl)acryloyl)indoline-4-carboxamide;
105. 2-(2-(4-Fluorophenyl)-3-phenylacryloyl)-N-hydroxy-1,2,3,4-tetrahydroisoquinoline-6-carboxamide;
106. 2-(2-(4-Fluorophenyl)-3-phenylacryloyl)-N-hydroxy-1,2,3,4-tetrahydroisoquinoline-8-carboxamide;
107. 1-(3-(4-Fluorophenyl)-2-phenylacryloyl)-N-hydroxyindoline-6-carboxamide;
108. 1-(2-(4-Fluorophenyl)-3-phenylacryloyl)-N-hydroxyindoline-6-carboxamide;
109. 1-(2-(2-Chlorophenyl)-3-phenylacryloyl)-N-hydroxyindoline-6-carboxamide;
110. N-Hydroxy-1-(2-(4-methoxyphenyl)-3-(thiophen-2-yl)acryloyl)indoline-4-carboxamide;
111. 1-(3-(4-Fluorophenyl)-2-phenylacryloyl)-N-hydroxyindoline-4-carboxamide;
112. 1-(2-(4-Fluorophenyl)-3-(pyridin-4-yl)acryloyl)-N-hydroxyindoline-4-carboxamide;
113. N-Hydroxy-1-(3-(pyridin-4-yl)-2-(thiophen-2-yl)acryloyl)indoline-4-carboxamide;
114. N-Hydroxy-1-(3-phenyl-2-(thiophen-2-yl)acryloyl)indoline-6-carboxamide;
115. 1-(2-(4-Fluorophenyl)-3-(pyridin-4-yl)acryloyl)-N-hydroxyindoline-6-carboxamide;
116. 2-(4-(3-(3,4-Dimethoxyphenyl)-2-(4-fluorophenyl)acryloyl)piperazin-1-yl)-N-hydroxypyrimidine-5-carboxamide;
117. 2-(4-(3-(3,4-Dimethoxyphenyl)-2-(phenyl)acryloyl)piperazin-1-yl)-N-hydroxypyrimidine-5-carboxamide;
118. 2-(4-(3-(3,4-Dimethoxyphenyl)-2-(3-fluorophenyl)acryloyl)piperazin-1-yl)-N-hydroxypyrimidine-5-carboxamide;
119. 2-(4-(3-(3,4-Dimethoxyphenyl)-2-(thiophen-2-yl)acryloyl)piperazin-1-yl)-N-hydroxypyrimidine-5-carboxamide;
120. 2-(4-(3-(3,4-Dimethoxyphenyl)-2-(pyridin-3-yl)acryloyl)piperazin-1-yl)-N-hydroxypyrimidine-5-carboxamide;
121. 2-(4-(3-(Phenyl)-2-(4-fluorophenyl)acryloyl)piperazin-1-yl)-N-hydroxypyrimidine-5-carboxamide;
122. 2-(4-(3-(3,4-Methylenedioxyphenyl)-2-(phenyl)acryloyl)piperazin-1-yl)-N-hydroxypyrimidine-5-carboxamide;
123. 2-(4-(3-(3,4-Difluorophenyl)-2-(4-methoxyphenyl)acryloyl)piperazin-1-yl)-N-hydroxypyrimidine-5-carboxamide;
124. 2-(4-(3-(3-Fluorophenyl)-2-(4-fluorophenyl)acryloyl)piperazin-1-yl)-N-hydroxypyrimidine-5-carboxamide;
125. 2-(4-(3-(3,4-Fluoro-3-methoxyphenyl)-2-(4-fluorophenyl)acryloyl)piperazin-1-yl)-N-hydroxypyrimidine-5-carboxamide;
126. 2-(4-(3-(3,4-Dimethoxyphenyl)-2-(2-fluorophenyl)acryloyl)piperazin-1-yl)-N-hydroxypyrimidine-5-carboxamide;
127. 2-(4-(3-(4-Methylthiophenyl)-2-(phenyl)acryloyl)piperazin-1-yl)-N-hydroxypyrimidine-5-carboxamide;
128. 2-(4-(3-(3,4-Difluorophenyl)-2-(4-methoxyphenyl)acryloyl)piperazin-1-yl)-N-hydroxypyrimidine-5-carboxamide;
129. 2-(4-(3-(Pyridin-3-yl)-2-(pyridin-3-yl)acryloyl)piperazin-1-yl)-N-hydroxypyrimidine-5-carboxamide;
130. 2-(4-(3-(4-Fluorophenyl)-2-(indol-3-yl)acryloyl)piperazin-1-yl)-N-hydroxypyrimidine-5-carboxamide;
131. 2-(4-(3-(3,4-Dimethoxyphenyl)-2-(indol-3-yl)acryloyl)piperazin-1-yl)-N-hydroxypyrimidine-5-carboxamide;
132. 2-(4-(3-(4-Methylthiophenyl)-2-(4-tolyl)acryloyl)piperazin-1-yl)-N-hydroxypyrimidine-5-carboxamide;
133. 2-(4-(3-(4-Fluorophenyl)-2-(4-methoxyphenyl)acryloyl)piperazin-1-yl)-N-hydroxypyrimidine-5-carboxamide;
134. 2-(4-(3-(Pyridin-3-yl)-2-(4-fluorophenyl)acryloyl)piperazin-1-yl)-N-hydroxypyrimidine-5-carboxamide;
135. 2-(4-(3-(3,4-Dimethoxyphenyl)-2-(3-chlorophenyl)acryloyl)piperazin-1-yl)-N-hydroxypyrimidine-5-carboxamide;
136. 2-(4-(2,3-Diphenylacryloyl)piperazin-1-yl)-N-hydroxypyrimidine-5-carboxamide;
137. 2-(4-(3-(3,4-Dimethoxyphenyl)-2-(3-methoxyphenyl)acryloyl)piperazin-1-yl)-N-hydroxypyrimidine-5-carboxamide;
138. 2-(4-(3-(4-Fluorophenyl)-2-(3,4-dimethoxyphenyl)acryloyl)piperazin-1-yl)-N-hydroxypyrimidine-5-carboxamide;
139. 2-(4-(3-(4-Fluorophenyl)-2-(3,4-methylenedioxyphenyl)acryloyl)piperazin-1-yl)-N-hydroxypyrimidine-5-carboxamide;
140. 2-(4-(3-(4-Fluorophenyl)-2-(3-fluorophenyl)acryloyl)piperazin-1-yl)-N-hydroxypyrimidine-5-carboxamide;
141. 2-(4-(3-(3,4-Methylenedioxyphenyl)-2-(4-fluorophenyl)acrylamido)piperidin-1-yl)-N-hydroxypyrimidine-5-carboxamide;
142. 2-(4-(3-(3,4-Methylenedioxyphenyl)-2-(3-fluorophenyl)acryloyl)piperazin-1-yl)-N-hydroxypyrimidine-5-carboxamide;
143. 2-(4-(3-(3-Fluorophenyl)-2-(4-dimethoxyphenyl)acryloyl)piperazin-1-yl)-N-hydroxypyrimidine-5-carboxamide;
144. 2-(4-(3-(3-Fluorophenyl)-2-(3,4-dimethoxyphenyl)acrylamido)piperidin-1-yl)-N-hydroxypyrimidine-5-carboxamide;
145. 2-(4-(3-(Phenyl)-2-(4-dimethoxyphenyl)acrylamido)piperidin-1-yl)-N-hydroxypyrimidine-5-carboxamide;
146. 2-(4-(3-(4-Fluorophenyl)-2-(3,4-dimethoxyphenyl)acrylamido)piperidin-1-yl)-N-hydroxypyrimidine-5-carboxamide;
147. 2-(4-((3-(3,4-Dimethoxyphenyl)-2-(3-fluorophenyl)acrylamido)methyl)piperidin-1-yl)-N-hydroxypyrimidine-5-carboxamide;
148. 2-(4-(4-(3-(Cyclopropylamino)-2-(4-fluorophenyl)-3-oxoprop-1-enyl)benzoyl)piperazin-1-yl)-N-hydroxypyrimidine-5-carboxamide;
149. 2-(4-(4-(3-(Cyclopropylamino)-2-(3,4-dimethoxyphenyl)-3-oxoprop-1-enyl)benzoyl)piperazin-1-yl)-N-hydroxypyrimidine-5-carboxamide;
150. 2-(4-(4-(3-(Cyclopropylamino)-2-(p-tolyl)-3-oxoprop-1-enyl)benzoyl)piperazin-1-yl)-N-hydroxypyrimidine-5-carboxamide;
151. 2-(4-(4-(3-(Cyclopropylamino)-2-(phenyl)-3-oxoprop-1-enyl)benzoyl)piperazin-1-yl)-N-hydroxypyrimidine-5-carboxamide;
152. 2-(4-(4-(3-(N,N-Dimethylamino)-2-(4-fluorophenyl)-3-oxoprop-1-enyl)benzoyl)piperazin-1-yl)-N-hydroxypyrimidine-5-carboxamide;
153. 2-(2-(4-Fluorophenyl)-3-phenylallyl)-N-hydroxy-1,2,3,4-tetrahydroisoquinoline-7-carboxamide;
154. N-(2-Aminophenyl)-2-(2,3-diphenylacryloyl)-1,2,3,4-tetrahydroisoquinoline-7-carboxamide;
155. N-(2-Aminophenyl)-2-(2-(3-fluorophenyl)-3-phenylacryloyl)-1,2,3,4-tetrahydroisoquinoline-7-carboxamide;
156. N-(2-Aminophenyl)-2-(2-(2-phenyl-3-(thiophen-2-yl)acryloyl)-1,2,3,4-tetrahydroisoquinoline-7-carboxamide;
157. 1-(2-(4-Fluorophenyl)-3-phenylacryloyl)-N-hydroxy-1,2,3,4-tetrahydroquinoline-6-carboxamide;
158. 1-(2-(4-Fluorophenyl)-3-(pyridin-4-yl)acryloyl)-N-hydroxy-1,2,3,4-tetrahydroquinoline-6-carboxamide;
159. 1-(2-(4-Fluorophenyl)-3-(pyridin-4-yl)acryloyl)-N-hydroxy-1,2,3,4-tetrahydroquinoline-6-carboxamide; and
160. 1-(2-(4-Fluorophenyl)-3-(pyridin-4-yl)acryloyl)-N-hydroxy-2-methyl-1,2,3,4-tetrahydroquinoline-6-carboxamide;
163. 1-(3-(4-Fluorophenyl)-2-phenylacryloyl)-N-hydroxy-2-methyl-1,2,3,4-tetrahydroquinoline-6-carboxamide.

There is also provided the process for the preparation of compounds of the formula (1) using General Scheme-1, wherein all the groups are as defined earlier.

General scheme-1:

![Diagram]

The said process for the preparation of compound of formula (1) comprises the steps of:

A) Coupling of compound of formula (1a), (where Y is a carboxylic acid) with compound of formula (lb) using appropriate peptide coupling reagents viz. 1-(3-dimethylaminopropyl)-3-ethylcarbodiimide hydrochloride (EDCI), benzotriazol-1-yl-oxytripyrrolidinophosphonium hexafluorophosphate (Py-BOP), etc. and 1-hydroxybenzotriazole (HOBT) in presence of an organic base such as triethylamine (TEA) or \( \text{N,N-diisopropylethylamine (DIEA)} \) and the like, to yield the compound of formula (2).

B) Coupling of compound of formula (1a), (where Y is an aldehyde) with compound of formula (lb) gives the Schiff’s base which on reduction using various reducing agents such as \( \text{NaBH}_4 \), \( \text{NaB}_3\text{CN} \), and the like, gives compound of formula (2).

C) Reacting a compound of formula (1a), (where Y is sulfonylchloride) with compound of formula (lb) in the presence of an organic base such as TEA or DIEA and the like, to yield the compound of formula (2).

D) The reaction between compound of formula (1a), (where Y is -CH\(_2\)OH) and compound of formula (lb) in the presence of carbodiimidazole and a base to yield the compound of formula (2).
E) Hydrolyzing the compound of formula (2) with an inorganic base such as 
LiOH, NaOH, KOH and the like to give the corresponding acid (3). Coupling 
the acid (3) with respective amine RNH₂ to yield the compound of the general 
formula (I) or reacting the compound of formula (2) with NH₂R and an 
inorganic base to give the compound of formula (I).

The pharmaceutically acceptable salts of the compounds of formula (I) are also 
prepared. Acid addition salts are prepared by treatment with acids such as 
hydrochloric acid, hydrobromic acid, nitric acid, sulfuric acid, phosphoric acid, p-
toluenesulfonic acid, methanesulfonic acid, acetic acid, citric acid, maleic acid, 
salicylic acid, hydroxynaphthoic acid, fumaric acid, ascorbic acid, palmitic acid, 
succinic acid, benzoic acid, benzenesulfonic acid, tartaric acid and the like in solvents 
like ethyl acetate, ether, alcohols, acetone, tetrahydrofuran (THF), dioxane, etc. 
Mixture of solvents may also be used.

The examples given below are provided by the way of illustration only and 
therefore should not be construed to limit the scope of the invention.

Experimental Procedures:

**Synthesis of Intermediates:**

Intermediate 1: 1,2,3,4-Tetrahydroisoquinoline-7-carboxylic acid methyl ester

\[ \text{Step A: 4-Cyanomethyl-benzoic acid methyl ester} \]

To a solution of trimethylsilyl cyanide (TMSCN, 12 mL, 96 mmol), tetra-\( n \)-butylammonium fluoride (TBAF, 25 g, 96 mmol) was added portion wise over a period 
of 30 minutes and stirred for another 30 minutes. 4-Bromethyl benzoic acid methyl 
ester (20 g, 87.3 mmol) dissolved in acetonitrile (100 mL) was added drop wise over a 
period of 30 minutes, the reaction temperature was increased to 80 °C and stirring 
continued for another 30 minutes. On completion of the reaction, solvent was distilled 
out under reduced pressure, the crude material obtained was purified by column 
chromatography to give the pure title compound (10 g, Yield 68.7 %).

Step B: Methyl 4-(2-aminoethyl)benzoate hydrochloride salt

To a solution of 4-cyanomethylbenzoic acid methyl ester (10 g, 48.3 mmol) in 
THF (150 mL) was added 50 mL of methanolic.HCl and 5% Pd/C (3 g). The mixture 
was stirred under hydrogen atmosphere for 2 hours, filtered and washed with hot
methanol (500 mL). The filtrate was concentrated under reduced pressure. The crude product obtained was added with dichloromethane (20 mL) and sonicated for 10 minutes. The resulting solid was filtered and dried under vacuum to give the title compound as a white solid (5.0 g, Yield 57.87 %).

Step C: Methyl 4-[2-(2,2,2-trifluoroacetylamino)ethyl]-benzoate

Methyl 4-(2-aminoethyl)benzoate (10 g, 55.86 mmol) was added portion wise to the well stirred trifluoroacetic anhydride (50 mL). The reaction mixture was stirred at room temperature for 3 hours. On completion of the reaction, the reaction mixture was poured into 100 mL of ice water and stirred for 30 minutes. The resulting solid was filtered, washed with hexane and dried under vacuum to give the pure compound (10 g, Yield 65.10 %).

Step D: Methyl 2-(2,2,2-trifluoroacetyl)-1,2,3,4-tetrahydroisoquinoline-7-carboxylate

Methyl 4-[2-(2,2,2-trifluoroacetylamino)ethyl]benzoate (4.5 g, 16.36 mmol) was stirred at room temperature with paraformaldehyde (2.4 g, 81.8 mmol) and cone. H2SO4 (38 mL) for 1 hour. The clear solution was added to cold water (100 mL) and extracted with ethyl acetate (2 x 100 mL). The organic layer was washed with 50 mL of saturated sodium bicarbonate solution, water (200 mL) and dried over anhydrous sodium sulphate. The filtrate was concentrated under vacuum to give the title compound (2.0 g, Yield 42.46 %).

Step E: Methyl 1,2,3,4-tetrahydroisoquinoline-7-carboxylate

Methyl 2-(2,2,2-trifluoroacetyl)-1,2,3,4-tetrahydroisoquinoline-7-carboxylate (2 g, 6.9 mmol) was added to potassium carbonate (1.4 g, 10.4 mmol), methanol (5 mL), water (2 mL) and stirred at room temperature for 3 hours. Methanol was removed from the reaction mixture and water (100 mL) was added, extracted with ethyl acetate (100 mL), followed by washing with water (100 mL). The organic layer was dried over anhydrous sodium sulphate and evaporated under reduced pressure to get colourless solid (0.8 g Yield 60.6 %). 1H NMR (DMSO-d6) 6(ppm): 2.74-2.76 (2H, t, -CH2), 2.78-2.79 (2H, brs, -CH2), 3.81 (2H, s, -CH2), 4.1 (3H, s, -OCH3), 5.02 (1H, brs, -NH), 7.14 (1H, d, -Ar-H), 7.71-7.74 (2H, m, Ar-H); MS m/z: 192.1 (M+).

By following the above procedure, 1,2,3,4-tetrahydroisoquinoline-6-carboxylic acid methyl ester and 1,2,3,4-tetrahydroisoquinoline-8-carboxylic acid methyl ester were prepared.

Intermediate 2: Ethyl 4,5,6,7-tetrahydrofuro[3,2-c]pyridine-2-carboxylate
Step A: tert-Butyl 4-chloro-3-formyl-5,6-dihydropyridine-1(2H)-carboxylate

POCl3 (3.49 mL, 37.7 mmol) in DMF (4.87 mL, 62.8 mmol) was stirred at 0 °C for 15 minutes, tert-butyl-4-oxopiperidine-1-carboxylate (5 g, 25.1 mmol) was added and the stirring was continued at room temperature for 2 hours. The reaction mixture was quenched with water and extracted with dichloromethane (DCM) (2 x 100 mL). The organic layer was separated, dried over anhydrous Na2SO4 and concentrated under reduced pressure to afford crude product (4.9 g, Yield 81%).

Step B: 5-tert-Butyl 2-ethyl 6,7-dihydrofuro[3,2-c]pyridine-2,5(4H)-dicarboxylate

To a solution of ethyl glycolate (2.07 mL, 19.9 mmol) in THF was added sodium hydride (1.19 g, 49.9 mmol) at 0 °C and stirred at room temperature for 1 hour. tert-Butyl 4-chloro-3-formyl-5,6-dihydropyridine-1(2 H)-carboxylate dissolved in THF was added at 0 °C, refluxed the reaction mixture for 2 hours. The reaction mixture was quenched with water and extracted with ethyl acetate (2 x 100 mL). The organic layer was separated, dried over anhydrous Na2SO4 and concentrated under reduced pressure to afford crude product, which on purification by column chromatography yields the title compound (0.75 g, Yield 15%).

Step C: Ethyl 4,5,6,7-tetrahydrofuro[3,2-c]pyridine-2-carboxylate

To a solution of 5-tert-Butyl 2-ethyl 6,7-dihydrofuro[3,2-c]pyridine-2,5(4 H)-dicarboxylate (0.5 g, 1.7 mmol) in DCM was added trifluoroacetic acid (TFA) (0.13 mL, 1.7 mmol) at 0-5 °C. After the completion of addition, the reaction mixture was allowed to stir for 6 hours. The excess solvent and reagents were evaporated under reduced pressure. The crude product was triturated with hexane to afford the title compound as TFA salt (0.5 g, Yield 95%). H NMR (DMSO-d6) 5(ppm): 1.36 (3H, t, -CH3), 2.77 (2H, brs, -CH2), 3.74 (2H, brs, -CH2), 4.32-4.38 (4H, m, -CH2), 5.02 (1H, brs, -NH), 7.02 (1H, s, Ar-H); MS m/z: 196.1 (M+).

Intermediate 3: Ethyl 4,5,6,7-tetrahydrothieno[3,2-c]pyridine-2-carboxylate

Step A: 5-tert-butyl 2-ethyl 6,7-dihydrothieno[3,2-c]pyridine-2,5(4H)-dicarboxylate
To a solution of tert-Butyl 4-chloro-5-formyl-3,6-dihydropyridine-1(2 H)-carboxylate (10 g, 40.9 mmol) in DCM was added triethylamine (11.8 mL, 81.8 mmol) and ethyl mercaptoacetate (7.8 g, 65.4 mmol) at room temperature. The reaction mixture was refluxed for 2 hours, quenched with water and extracted with ethyl acetate (2 x 100 mL). The organic layer was separated, dried over anhydrous Na₂SO₄ and concentrated under reduced pressure to afford the crude product. The crude product obtained on purification by column chromatography affords the title compound. (4.0 g, Yield 35%).

Step B: Ethyl 4,5,6,7-tetrahydrothieno[3,2-c]pyridine-2-carboxylate

To a solution of 5-tert-Butyl 2-ethyl 6,7-dihydrothieno[3,2-c]pyridine-2,5(4 H)-dicarboxylate (1.0 g, 3.2 mmol) in DCM was added TFA (0.5 mL, 6.4 mmol) at 0-5 °C and the reaction mixture was stirred for 3 hours. Excess solvent and reagents were evaporated under reduced pressure. Crude product on purification by column chromatography with n-hexane/ethyl acetate solvent mixture afforded the title compound (0.333 g, Yield 49 %). ³¹H NMR (DMSO-d₆) 5(ppm): 1.35 (3H, t, -CH₃), 2.85 (2H, t, -CH₂), 3.17 (2H, brs, -CH₂), 3.93 (2H, s, -CH₂), 4.32 (2H, q, -OCH₂), 7.45 (1H, s, Ar-H); MS m/z: 212.1 (M+1).

Intermediate 4: 4,5,6,7-Tetrahydroisoxazolo[5,4-c]pyridine-3-carboxylicacid ethylester

Step A: Ethyl (2)-(hydroxyimino)acetate

Ethyl glyoxylate in toluene (10 mL, 195.9 mmol) was added drop wise to ethanol (12.5 mL) at 25 °C for 30 minutes. Aqueous hydroxylamine (13.5 g, 391.81 mmol) was added at the same temperature and reaction mixture was stirred for another 30 minutes. Reaction was quenched with water and extracted with ethyl acetate (2x 150 mL). Organic layer was separated and washed with brine solution, dried over anhydrous sodium sulphate and concentrated under reduced pressure to afford crude product (7.0 g, Yield 61.13 %).

Step B: Ethyl (2)-(chloro(hydroxyimino))acetate

To a solution of N-chlorosuccinimide (8.23 g, 123.2 mmol) in DMF was added ethyl (2)-(hydroxyimino)acetate (7.00 g, 123.2 mmol) at 0-5 °C. The reaction mixture was stirred at room temperature for 12 hours. Reaction was quenched with water and
extracted with ethyl acetate (2x 150 mL). Organic layer was separated, dried over anhydrous sodium sulphate and concentrated under reduced pressure to afford crude product (6.95 g, Yield 74.73 %).

Step C: tert-Butyl 4-(pyrrolidin-1-yl)-5,6-dihydropyridine-l(2H)-carboxylate

To a solution of N-Boc piperidone (10.0 g, 50.25 mmol) in toluene (120 mL), was added p-toluenesulphonic acid (PTSA, 0.95 g, 5.02 mmol) and pyrrolidine (4.5 mL, 55.27 mmol) at 25 °C. The reaction mixture was refluxed at 120 °C for 2 hours in presence of Dean-Stark apparatus. Solvents were then removed under reduced pressure to get the crude product (11.5 g, Yield 90.83 %).

Step D: 5-tert-Butyl 3-ethyl 7a-(pyrrolidin-1-yl)-3a,4,7,7a-tetrahydroisoxazolo[4,5-c]pyridine-3,5(6H)-dicarboxylate

To ethyl (2)-chloro(hydroxyimino)acetate (6.89 g, 91.26 mmol) in DCM was added TEA (9.5 mL, 136.91 mmol) drop wise at 0-5 °C, followed by tert-butyl 4-(pyrrolidin-1-yl)-5,6-dihydropyridine-l(2H)-carboxylate (6.75 g, 45.63 mmol) and stirred for 12 hours. Reaction was quenched with citric acid and extracted with ethyl acetate (2x 150 mL). The organic layer was separated, dried over anhydrous Na₂S0₄ and concentrated under reduced pressure to afford crude product. On column purification using hexane/ethyl acetate solvent mixture yielded the title product (5.02 g, Yield 60.03 %).

Step E: Ethyl 4,5,6,7-tetrahydroisoxazolo[4,5-c]pyridine-3-carboxylate

5-tert-Butyl 3-ethyl 7a-(pyrrolidin-1-yl)-3a,4,7,7a-tetrahydroisoxazolo[4,5-c]pyridine-3,5(6H)-dicarboxylate (5 g, 27.24 mmol) was dissolved in DCM and TFA (3.15 mL, 81.74 mmol) was added. The reaction mixture was refluxed for 2 hours, quenched with aqueous sodium bicarbonate solution and extracted with ethyl acetate (2x 150 mL). The organic layer was separated, dried over anhydrous Na₂S0₄ and concentrated under reduced pressure to afford the crude product. Further it was column purified using DCM/methanol solvent mixture to yield the title product as its TFA salt (1 g, Yield 37.73 %). ¹H NMR (DMSO-d₆) (ppm): 1.32 (3H, t, -CH₃), 2.75 (2H, t, -CH₂), 3.05 (2H, brs, -CH₂), 3.73 (2H, s, -CH₂), 4.31 (2H, q, -OCH₂); MS m/z: 197.0 (M+1).

Intermediate 5: 2,3-Dihydro-lH-indole-5-carboxylic acid methyl ester
Methyl indole-5-carboxylate (1 g, 11.4 mmol) dissolved in glacial acetic acid (10 mL) was stirred at room temperature for 10 minutes. To this sodium cyanoborohydride (1.8 g, 28 mmol) was added slowly and the stirring continued for 1 hour. On completion of reaction, it was quenched by the addition of saturated sodium bicarbonate solution (150 mL) and extracted with ethyl acetate (2 x 100 mL). The organic layer was separated, dried over anhydrous Na$_2$SO$_4$ and concentrated under reduced pressure to get the title product (0.65 g, Yield 65%).

$^1$H NMR (DMSO-d$_6$) 6(ppm): 3.23 (2H, t, -CH$_2$), 3.61 (2H, t, -CH$_2$), 4.0 (3H, s, -OCH$_3$), 6.8 (1H, d, Ar-H), 7.6-7.65 (2H, m, Ar-H), 8.45 (1H, brs, -NH); MS m/z: 178.1 (M+1).

By following the above procedure, 2,3-Dihydro-IH-indole-6-carboxylic acid methyl ester and 2,3-Dihydro-IH-indole-4-carboxylic acid methyl ester were prepared.

Intermediate 6: Methyl 2,3,4,5-tetrahydro-IH-benzo[c]azepine-8-carboxylate

Step A: (E)-3-(4-(methoxycarbonyl)phenyl)acrylic acid
Methyl 4-formyl benzoate (5.0 g, 30.5 mmol), malonic acid (9.5 g, 91.5 mmol) and piperidine (0.5 mL, mmol) were added to a solution of pyridine (30 mL) and refluxed at 100 °C for 4 hours. The reaction mixture was cooled, neutralised with concentrated HCl and filtered to obtain the crude product (4.5 g, Yield 59%).

Step B: (E)-Methyl 4-(3-amino-3-oxoprop-1-enyl)benzoate
(E)-3-(4-(Methoxycarbonyl)phenyl)acrylic acid (1.5g, 7.28 mmol) was dissolved in dichloromethane (5 mL) and cooled to 0 °C. Thionyl chloride (2.1 mL, 29.12 mmol) was added drop wise and the reaction mixture was allowed to stir at room temperature for 1 hour. Excess solvent and reagents were removed under reduced pressure. The residue was dissolved in diethyl ether and added drop wise to aqueous ammonia (20 mL). The resultant precipitate was filtered, washed with excess water and dried to get the title compound (0.9 g, Yield 60.1%).

Step C: (E)-Methyl 4-(2-cyanovinyl)benzoate
(E)-Methyl 4-(3-amino-3-oxoprop-1-enyl)benzoate (1.0 g, 4.8 mmol) was dissolved in THF (50 mL). To this triethylamine (2.56 mL, 18.4 mmol) was added and cooled to 0 °C. Trifluoro acetic anhydride (1.2 mL, 8.8 mmol) was added slowly to the reaction mixture and stirred at room temperature for 1 hour. The reaction mixture was poured into ice mixture and the resultant precipitate was filtered which was further purified by silica column chromatography eluting with acetone/hexane solvent mixture to get the title compound (0.35 g, Yield 38.5 %).

Step D: Methyl 4-(3-aminopropyl)benzoate

(E)-Methyl 4-(2-cyanovinyl)benzoate (1.0 g, 5.34 mmol) taken in methanol (50 mL). To this raney nickel (0.1 g) was added, followed by the addition of sodium borohydride (0.79 g, 21.39 mmol). The reaction mixture was stirred at room temperature for 1 hour and filtered. The filtrate was acidified with concentrated HCl and the resultant solid was filtered and dried to get the title compound (0.4 g, Yield 32.8 %).

Step E: Methyl 4-(3-(2,2,2-trifluoroacetamido)propyl)benzoate

Methyl 4-(3-aminopropyl)benzoate (10 g, 43.66 mmol) was added portion wise to the well stirred trifluoroacetic anhydride (30 mL). This was further stirred for 3 hours at room temperature. The reaction mixture was poured into 100 mL of ice cold water and stirred for another 30 minutes. The resulting solid was filtered, washed with hexane and dried under vacuum to get the title compound (9 g, Yield 71.3 %).

Step F: Methyl 2-(2,2,2-trifluoroacetyl)-2,3,4,5-tetrahydro-IH-benzo[c]azepine-8-carboxylate

Methyl 4-(3-(2,2,2-trifluoroacetamido)propyl)benzoate (5.0 g, 18.18 mmol) was stirred at room temperature with paraformaldehyde (2.1 g, 72.7 mmol), acetic acid (25 mL) and cone. H₂SO₄ (38 mL) for 18 hours. The clear solution was added to cold water (100 mL) and extracted with ethyl acetate (2 x 100 mL). The organic layer was washed with 50 mL of saturated sodium bicarbonate solution, water (200 mL) and dried over anhydrous sodium sulphate, concentrated under vacuum to get the title compound (3.0 g, Yield 52.5 %).

Step G: Methyl 2,3,4,5-tetrahydro-IH-benzo[c]azepine-8-carboxylate

Methyl 2-(2,2,2-trifluoroacetyl)-2,3,4,5-tetrahydro-IH-benzo[c]azepine-8-carboxylate (3 g, 9.9 mmol) was dissolved in methanol (20 mL) and added to potassium carbonate (4.18 g, 29.9 mmol) and water (2 mL) and then stirred at room
temperature for 3 hours. Methanol was removed from the reaction mixture and water (100 mL) was added, extracted with ethyl acetate (100 mL), followed by washing with water (100 mL). The organic layer was dried over anhydrous sodium sulphate and evaporated under reduced pressure to get colourless solid (1.23 g, Yield 60.6 %).

$^1$H NMR (DMSO-de) 5(ppm): 1.52 (2H, m, -CH$_2$), 2.73-2.75 (2H, t, -CH$_2$), 2.76-2.77 (2H, brs, -CH$_2$), 3.8 (2H, s, -OCH$_3$), 4.01 (3H, s, -OCH$_3$), 5.4 (1H, brs, -NH), 7.12 (1H, d, -Ar-H), 7.71-7.74 (2H, m, Ar-H); MS m/z: 205.9 (M+1).

Intermediate 7: Ethyl 2-(piperazin-1-yl)pyrimidine-5-carboxylate

Step A: Ethyl 2-(methylthio)pyrimidine-5-carboxylate

Ethyl 4-chloro-2- methylthiopyrimidine-5- carboxylate (5.0 g, 21.4 mmol) and magnesium oxide (0.9 g, 21.4 mmol) was added to methanol (200 mL) in par-shaker vessel. Dry 10% Pd/C (5 g) was added and the flask was evacuated, purged with nitrogen and the contents allowed to react under 50 psi pressure hydrogen for 6 hours. The system was evacuated and purged with nitrogen. After dilution with methanol the solution was filtered through a pad of celite. The filter cake was washed with methanol and the filtrate was evaporated to get the crude material. Further on column purification using hexane/ethyl acetate solvent mixture yielded the title compound (2.2 g, Yield 52 %).

Step B: Ethyl 2-(methylsulfonyl)pyrimidine-5-carboxylate

Ethyl 2-(methylthio)pyrimidine-5-carboxylate (2.2 g, 11 mmol) was dissolved in DCM at 0 °C and stirred at room temperature for 15 minutes, followed by addition of /w-chloroperbenzoic acid (mCPBA) (5.75 g, 33 mmol). The reaction mixture was stirred for 1 hour. Saturated NaHCO$_3$ solution was added to reaction mass and extracted with DCM. The organic layer was washed with water, brine solution and dried over an anhydrous Na$_2$SO$_4$. The solvent was evaporated to get the title compound (2.0 g, Yield 75 %).

Step C: Ethyl 2-(4-(tert-butoxycarbonyl)piperazin-1-yl)pyrimidine-5-carboxylate
Ethyl 2-(methylsulfonyl)pyrimidine-5-carboxylate (2 g, 8.6 mmol) was dissolved in 10 mL of DMSO. Boc protected piperazine (4.04 g, 21.7 mmol) was added to this and heated to 75-85 °C for an hour. The reaction mass was cooled to room temperature, quenched with water and extracted with DCM (2 x 100 mL). The organic layer was washed with water, brine solution, dried over anhydrous sodium sulphate and concentrated under reduced pressure. The crude product was further purified by column chromatography using DCM/MeOH solvent mixture to get the pure title product (2 g, Yield 68%).

Step D: Ethyl 2-(piperazin-1-yl)pyrimidine-5-carboxylate

Ethyl 2-(4-(tert-butoxycarbonyl)piperazin-1-yl)pyrimidine-5-carboxylate (2 g, 5.9 mmol) was dissolved in DCM and TFA (7.3 mL, 95 mmol) was added at 0 °C, and stirred for 10 minutes. Solvent was evaporated completely and diethyl ether was added drop wise. The solid thrown was filtered to get the pure title compound as its TFA salt (1.6 g, Yield 57 %). 1H NMR (DMSO-d6) 5(ppm): 1.32 (3H, t, -CH3), 3.51 (4H, brs, -CH2), 3.67 (4H, s, -CH2), 4.31 (2H, q, -OCH2), 8.64 (2H, brs, Ar-H); MS m/z: 237.1 (M+1).

By following the above procedure, ethyl 2-(4-aminopiperidin-1-yl)pyrimidine-5-carboxylate and ethyl 2-(4-(aminomethyl)piperidin-1-yl)pyrimidine-5-carboxylate were prepared.

Example 1: 2-(2,3-Diphenylacryloyl)-N-hydroxy-1,2,3,4-tetrahydroisoquinoline-7-carboxamide

Step-I: Methyl 2-(2,3-Diphenylacryloyl)-1,2,3,4-tetrahydroisoquinoline-7-carboxylate

To a solution of 2,3-Diphenylacrylic acid (0.900 g, 4.0 mmol) in 1 mL of N,N-dimethylformamide (DMF) was added DIEA (2 mL, 12 mmol), EDCI (1.5 g, 8 mmol), HOBT (0.216 g, 1.6 mmol) and finally methyl 1,2,3,4-tetrahydroisoquinoline-7-
carboxylate (0.925 g, 4.8 mmol). The reaction mixture was stirred at room temperature for 3 hours and cold water was added (50 mL), extracted with ethyl acetate (100 mL). The organic layer was washed with 50 mL of water, 50 mL of brine solution, dried over anhydrous sodium sulphate and the solvent was evaporated under reduced pressure. The crude product was subjected to column chromatography on silica gel using hexane, ethyl acetate solvent system to get the title compound as solid. The resulting solid was further washed with methanol, filtered and dried under vacuum (0.850 g, Yield 53.52 %).

Step-II: 2-(2,3-Diphenylacryloyl)-N-hydroxy-1,2,3,4-tetrahydroisoquinoline-7-carboxamide

Hydroxylamine hydrochloride (0.633 g, 9.0 mmol) in methanol (5 mL) was mixed with potassium hydroxide (0.500 g, 9.0 mmol) in methanol (5 mL) at 0 °C. The resulting white precipitate was filtered and the filtrate was immediately added to a round bottom flask containing Methyl 2-(2,3-diphenylacryloyl)-1,2,3,4-tetrahydroisoquinoline-7-carboxylate (0.200 g, 0.5 mmol). The reaction mixture was stirred at room temperature for 2 hours. Methanol was evaporated under reduced pressure and diluted with ice-cold water (100 mL). The pH of the reaction mixture was adjusted to 8 using dilute acetic acid and kept in refrigerator at 10 °C for 2 hours. The resulting solid was filtered to afford the title compound as colourless solid (0.080 g, Yield 40.20 %).

\[ ^{1}H \text{ NMR (DMSO-}d_{6}) \] 5(ppm): 2.67-2.68 (2H, m, -CH\_2), 3.79 (2H, t, -CH\_2), 4.73 (2H, brs, -CH\_2), 6.79 (1H, s, =CH), 7.12 (2H, d, Ar-H), 7.20-7.22 (4H, m, Ar-H), 7.30-7.33 (5H, m, Ar-H), 7.53-7.60 (2H, m, Ar-H), 9.0 (1H, s, -OH), 11.14 (1H, s, -NH); MS m/z: 399.1 (M+).

The following compounds were prepared according to the procedure given in Example 1:

<table>
<thead>
<tr>
<th>Ex.</th>
<th>Structure</th>
<th>Analytical Data</th>
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<tbody>
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<td>2</td>
<td><img src="image" alt="Structure" /></td>
<td>[ ^{1}H \text{ NMR (DMSO-}d_{6}) ] 5(ppm): 2.74-2.84 (2H, m, -CH_2), 3.79 (2H, t, -CH_2), 4.73 (2H, brs, -CH_2), 6.8 (1H, s, =CH), 7.07-7.11 (2H, m, Ar-H), 7.14-7.18 (3H, m, Ar-H), 7.21-7.23 (2H, m, Ar-H), 7.31-7.35 (2H, m, Ar-H), 7.53-7.55 (1H, d, Ar-H), 7.6 (1H, s, Ar-H), 9.01 (1H, s, -OH), 11.14 (1H, s, -NH); MS m/z: 435.1 (M+).</td>
</tr>
</tbody>
</table>
$^1$H NMR (DMSO-$d_6$) $\delta$ (ppm): 2.74 (2H, brs, -CH$_2$), 3.44 (3H, s, -OCH$_3$), 3.71 (3H, s, -OCH$_3$), 3.79 (2H, s, -CH$_2$), 4.71 (2H, brs, -CH$_2$), 6.63 (1H, s, =CH), 6.72-6.74 (2H, m, Ar-H), 6.83-6.85 (1H, d, Ar-H), 7.17-7.14 (1H, m, Ar-H), 7.22-7.24 (2H, t, Ar-H), 7.35-7.39 (2H, t, Ar-H), 7.53-7.55 (2H, m, Ar-H); MS m/z: 477.1 (M+1).

$^1$H NMR (DMSO-de) $\delta$ (ppm): 2.66 (2H, brs, -CH$_2$), 3.73-3.77 (2H, s, -CH$_2$), 4.75 (2H, s, -CH$_2$), 6.66-6.73 (1H, s, =CH), 6.91-6.96 (1H, m, Ar-H), 7.02-7.07 (1H, m, Ar-H), 7.22-7.24 (4H, m, Ar-H), 7.53-7.61 (2H, m, Ar-H), 9.02 (1H, s, -OH), 11.15 (1H, s, -NH); MS m/z: 435.1 (M+1).

$^1$H NMR (DMSO-$d_6$) 5(ppm): 2.67-2.84 (2H, s, -CH$_2$), 3.44 (3H, s, -OCH$_3$), 3.75 (2H, s, -CH$_2$), 4.72 (2H, s, -CH$_2$), 6.69 (1H, s, =CH), 6.91 (2H, brs, Ar-H), 7.00-7.07 (1H, m, Ar-H), 7.17-7.21 (5H, m, Ar-H), 7.53-7.6 (2H, m, Ar-H), 9.0 (1H, s, -OH), 11.14 (1H, s, -NH); MS m/z: 447.1 (M+1).

$^1$H NMR (DMSO-$d_6$) 6(ppm): 2.67-2.84 (2H, m, -CH$_2$), 3.77-3.80 (2H, t, -CH$_2$), 4.73 (2H, s, -CH$_2$), 6.78 (1H, s, =CH), 7.04-7.09 (2H, t, Ar-H), 7.14-7.21 (3H, m, Ar-H), 7.28-7.34 (5H, m, Ar-H), 7.53-7.59 (2H, m, Ar-H), 9.01 (1H, s, -OH), 11.14 (1H, s, -NH); MS m/z: 417.1 (M+1).

$^1$H NMR (DMSO-$d_6$) 7(ppm): 2.69 (2H, brs, -CH$_2$), 3.75 (3H, s, -OCH$_3$), 3.76 (2H, s, -CH$_2$), 4.72 (2H, s, -CH$_2$), 6.68 (1H, s, =CH), 6.93-6.99 (3H, m, Ar-H), 7.13-7.21 (4H, m, Ar-H), 7.28-7.33 (1H, m, Ar-H), 7.53-7.6 (2H, m, Ar-H), 9.0 (1H, s, -OH), 11.14 (1H, s, -NH); MS m/z: 465.1 (M+1).
| 8 | \(^1^H\) NMR (DMSO-d<sub>6</sub>) δ(ppm): 2.70-2.87 (2H, brs, -CH<sub>2</sub>), 3.78 (2H, s, -CH<sub>2</sub>), 4.75 (2H, brs, -CH<sub>2</sub>), 6.67-6.74 (1H, s, -CH), 6.94-6.99 (1H, m, Ar-H), 7.04-7.1 (1H, m, Ar-H), 7.15-7.17 (2H, m, Ar-H), 7.20-7.23 (2H, m, Ar-H), 7.26-7.28 (3H, m, Ar-H), 7.53-7.55 (2H, d, Ar-H), 7.61 (1H, s, Ar-H), 9.02 (1H, s, -OH), 11.15 (1H, s, -NH); MS m/z: 453.1 (M+1). |
| 9 | \(^1^H\) NMR (DMSO-d<sub>6</sub>) δ(ppm): 2.75 (2H, brs, -CH<sub>2</sub>), 3.57 (3H, s, -OCH<sub>3</sub>), 3.8 (2H, s, -CH<sub>2</sub>), 4.73 (2H, s, -CH<sub>2</sub>), 6.72-6.73 (2H, m, =CH & Ar-H), 6.77 (1H, d, Ar-H), 7.07-7.12 (1H, m, Ar-H), 7.22-7.24 (3H, m, Ar-H), 7.35-7.38 (2H, m, Ar-H), 7.54-7.56 (1H, d, Ar-H), 7.6 (1H, s, Ar-H), 9.01 (1H, s, -OH), 11.15 (1H, s, -NH); MS m/z: 465.1 (M+1). |
| 10 | \(^1^H\) NMR (DMSO-d<sub>6</sub>) δ(ppm): 2.29 (3H, s, -CH<sub>3</sub>), 2.68-2.84 (2H, brs, -CH<sub>2</sub>), 3.75-3.78 (2H, t, -CH<sub>2</sub>), 4.72 (2H, s, -CH<sub>2</sub>), 6.68 (1H, s, =CH), 7.05-7.1 (2H, t, Ar-H), 7.16-7.20 (7H, m, Ar-H), 7.53-7.6 (2H, m, Ar-H), 9.02 (1H, s, -OH), 11.15 (1H, s, -NH); MS m/z: 431.1 (M+1). |
| 11 | \(^1^H\) NMR (DMSO-d<sub>6</sub>) δ(ppm): 2.32 (3H, s, -CH<sub>3</sub>), 2.71 (2H, brs, -CH<sub>2</sub>), 3.42 (3H, s, -OCH<sub>3</sub>), 3.70 (3H, s, -OCH<sub>3</sub>), 3.77-3.79 (2H, brs, -CH<sub>2</sub>), 4.72 (2H, s, -CH<sub>2</sub>), 6.65 (2H, s, =CH & Ar-H), 6.73-6.75 (1H, d, Ar-H), 6.81-6.83 (1H, d, Ar-H), 7.20-7.22 (5H, m, Ar-H), 7.53-7.58 (2H, m, Ar-H), 9.02 (1H, s, -OH), 11.15 (1H, s, -NH); MS m/z: 473.1 (M+1). |
| 12 | \(^1^H\) NMR (DMSO-d<sub>6</sub>) δ(ppm): 2.73-2.88 (2H, brs, -CH<sub>2</sub>), 3.32 (3H, s, -OCH<sub>3</sub>), 3.70 (3H, s, -OCH<sub>3</sub>), 3.8 (2H, s, -CH<sub>2</sub>), 4.74 (2H, s, -CH<sub>2</sub>), 6.55 (1H, s, =CH), 6.69 (1H, s, Ar-H), 6.74-6.76 (1H, d, Ar-H), 6.81-6.83 (1H, d, Ar-H), 7.15-7.17 (1H, d, Ar-H), 7.33-7.44 (3H, m, Ar-H), 7.39-7.4 (2H, m, Ar-H), 7.53-7.55 (1H, d, Ar-H), 7.59 (1H, s,
| 13 | Ar-H), 9.02 (1H, s, -OH), 11.16 (1H, s, -NH); MS m/z: 459.1 (M+1). |
| 14 | \(^1\)H NMR (DMSO-d$_6$) δ(ppm): 2.29 (3H, s, -CH$_3$), 2.43 (3H, s, -SCH$_3$), 2.67-2.83 (2H, brs, -CH$_2$), 3.75-3.78 (2H, t, -CH$_2$), 4.72 (2H, s, -CH$_2$), 6.67 (1H, s, =CH), 7.09 (4H, m, Ar-H), 7.18 (5H, s, Ar-H), 7.53-7.62 (2H, m, Ar-H), 9.05 (1H, s, -OH), 11.17 (1H, s, -NH); MS m/z: 459.1 (M+1). |
| 15 | \(^1\)H NMR (DMSO-d$_6$) δ(ppm): 2.79 (2H, s, -CH$_2$), 3.33 (3H, s, -OCH$_3$), 3.72 (3H, s, -OCH$_3$), 3.82 (2H, s, -CH$_2$), 4.76 (2H, brs, -CH$_2$), 6.61 (1H, s, =CH), 6.75-6.77 (1H, d, Ar-H), 6.83-6.85 (1H, d, Ar-H), 6.92 (1H, s, Ar-H), 7.21-7.35 (3H, m, Ar-H), 7.35-7.42 (2H, m, Ar-H), 7.55-7.57 (2H, m, Ar-H), 9.02 (1H, s, -OH), 11.16 (1H, s, -NH); MS m/z: 477.1 (M+1). |
| 16 | \(^1\)H NMR (DMSO-d$_6$) δ(ppm): 2.69-2.85 (2H, s, -CH$_2$), 3.35 (3H, s, -OCH$_3$), 3.72 (3H, s, -OCH$_3$), 3.75 (2H, s, -CH$_2$), 4.76 (2H, s, -CH$_2$), 6.64 (1H, s, =CH), 6.78-6.83 (2H, m, Ar-H), 6.96-7.08 (4H, m, Ar-H), 7.16-7.18 (1H, s, Ar-H), 7.26-7.32 (1H, m, Ar-H), 7.53-7.60 (2H, m, Ar-H); MS m/z: 477.1 (M+1). |
| 17 | \(^1\)H NMR (DMSO-d$_6$) δ(ppm): 2.67-2.84 (2H, s, -CH$_2$), 3.76-3.78 (2H, t, -CH$_2$), 4.72 (2H, s, -CH$_2$), 5.75 (2H, s, -CH$_2$), 6.7 (1H, s, =CH), 6.76-6.79 (2H, m, Ar-H), 6.89
| 18 | \( ^1H \) NMR (DMSO-d_{6}) (ppm): 2.71-2.83 (2H, s, -CH\(_2\)), 3.77 (2H, brs, -CH\(_2\)), 4.7 (2H, s, -CH\(_2\)), 6.61 (IH, s, =CH), 6.78 (IH, s, Ar-H), 6.84-6.86 (2H, d, Ar-H), 6.91-6.92 (IH, s, Ar-H), 6.95-6.97 (IH, d, Ar-H), 7.09-7.13 (2H, m, Ar-H), 7.2-7.22 (3H, d, Ar-H), 7.25-7.34 (5H, m, Ar-H), 7.53-7.54 (IH, m, Ar-H), 9.0 (IH, s, -OH), 11.13 (IH, s, -NH); MS m/z: 461.1 (M+1). |
| 19 | \( ^1H \) NMR (DMSO-d_{6}) (ppm): 2.79 (2H, m, -CH\(_2\)), 4.02-4.03 (2H, t, -CH\(_2\)), 4.74 (2H, s, -CH\(_2\)), 6.85 (IH, s, =CH), 7.12-7.13 (2H, m, Ar-H), 7.21-7.27 (5H, m, Ar-H), 7.34 (IH, s, Ar-H), 7.39 (2H, s, Ar-H), 7.54-7.56 (IH, d, Ar-H), 7.61 (IH, s, Ar-H); MS m/z: 433 (M+1). |
| 20 | \( ^1H \) NMR (DMSO-d_{6}) (ppm): 2.76-2.85 (2H, brs, -CH\(_2\)), 3.81 (2H, s, -CH\(_2\)), 4.74 (2H, s, -CH\(_2\)), 6.85 (IH, s, =CH), 7.09-7.14 (5H, m, Ar-H), 7.22-7.27 (4H, m, Ar-H), 7.39 (IH, s, Ar-H), 7.56 (IH, s, Ar-H), 7.61 (IH, s, Ar-H), 9.01 (IH, s, -OH), 11.15 (IH, s, -NH); MS m/z: 417.1 (M+1). |
| 21 | \( ^1H \) NMR (DMSO-d_{6}) (ppm): 2.77 (2H, brs, -CH\(_2\)), 3.82 (2H, s, -CH\(_2\)), 4.73 (2H, s, -CH\(_2\)), 7.0 (IH, s, =CH), 7.11-7.13 (2H, m, Ar-H), 7.23-7.25 (6H, m, Ar-H), 7.33-7.40 (2H, m, Ar-H), 7.54-7.59 (2H, m, Ar-H), 9.01 (IH, s, -OH), 11.15 (IH, s, -NH); MS m/z: 417.1 (M+1). |
| 22 | \( ^1H \) NMR (DMSO-d_{6}) (ppm): 2.88 (2H, brs, -CH\(_2\)), 3.94 (2H, s, -CH\(_2\)), 4.77 (2H, s, -CH\(_2\)), 7.06-7.07 (IH, s, =CH), 7.08-7.09 (IH, m, Ar-H), 7.25-7.26 (5H, m, Ar-H), 7.32 (2H, m, Ar-H), 7.51 (IH, s, Ar-H), 7.56-7.58 (2H, m, Ar-H), 9.01 (IH, s, -OH), 11.14 (IH, s, -NH); MS m/z: 449 (M+1). |
| 23 | ![Image of 23](image.png) | ¹H NMR (DMSO-d₆) 5(ppm): 2.29 (3H, s, -CH₃), 2.68-2.84 (2H, brs, -CH₂), 3.75-3.78 (2H, t, -CH₂), 4.72 (2H, s, -CH₂), 6.73 (IH, s, =CH), 7.13-7.15 (6H, m, Ar-H), 7.21-7.23 (4H, m, Ar-H), 7.53-7.55 (IH, m, Ar-H), 7.61 (IH, m, Ar-H), 9.01 (IH, s, -OH), 11.14 (1H, s, -NH); MS m/z: 413 (M+). |
| 24 | ![Image of 24](image.png) | ¹H NMR (DMSO-d₆) 5(ppm): 2.67-2.84 (2H, brs, -CH₂), 3.77-3.80 (2H, t, -CH₂), 4.73 (2H, s, -CH₂), 6.78 (IH, s, =CH), 7.04-7.09 (2H, t, Ar-H), 7.14-7.21 (3H, m, Ar-H), 7.28-7.29 (2H, m, Ar-H), 7.34 (3H, brs, Ar-H), 7.53-7.59 (2H, m, Ar-H), 9.01 (IH, s, -OH), 11.14 (1H, s, -NH); MS m/z: 417.1 (M+). |
| 25 | ![Image of 25](image.png) | ¹H NMR (DMSO-d₆) 5(ppm): 2.70-2.85 (2H, d, -CH₂), 3.83 (2H, brs, -CH₂), 4.76 (2H, s, -CH₂), 6.97-6.99 (IH, s, =CH), 7.07 (IH, s, Ar-H), 7.18-7.22 (2H, m, Ar-H), 7.26-7.3 (2H, t, Ar-H), 7.41-7.42 (IH, d, Ar-H), 7.46-7.49 (2H, m, Ar-H), 7.54-7.56 (IH, d, Ar-H), 7.61 (IH, s, Ar-H), 9.0 (IH, s, -OH), 11.13 (1H, s, -NH); MS m/z: 423.1 (M+). |
| 26 | ![Image of 26](image.png) | ¹H NMR (DMSO-d₆) 6(ppm): 2.7-2.85 (2H, d, -CH₂), 3.55 (3H, s, -OCH₃), 3.75 (5H, s, -OCH₃ & -CH₂), 4.75 (2H, brs, -CH₂), 6.7 (IH, s, =CH), 6.83 (2H, s, Ar-H), 6.94-7.08 (4H, m, Ar-H), 7.18 (IH, brs, Ar-H), 7.26-7.32 (IH, q, Ar-H), 7.53-7.59 (2H, m, Ar-H); MS m/z: 477.1 (M+). |
| 27 | ![Image of 27](image.png) | ¹H NMR (DMSO-d₆) 5(ppm): 2.86-2.87 (2H, t, -CH₂), 3.92 (2H, brs, -CH₂), 4.74-5.02 (2H, m, -CH₂), 7.04-7.06 (3H, m, =CH & Ar-H), 7.17-7.26 (4H, m, Ar-H), 7.3-7.33 (2H, m, Ar-H), 7.36-7.41 (IH, m, Ar-H), 7.43-7.58 (3H, m, Ar-H), 8.99 (IH, s, -OH), 11.11 (1H, brs, -NH); MS m/z: 433.1 (M+). |
| 28 | \[
\text{HNMR (DMSO-d}_6\text{) 5 (ppm): 2.86-2.87 (2H, t, -CH}_2\text{), 3.92 (2H, brs, -CH}_2\text{), 4.74-5.01 (2H, brs, -CH}_2\text{), 7.04-7.06 (3H, m, =CH & Ar-H), 7.2-7.24 (4H, m, Ar-H), 7.26-7.33 (2H, m, Ar-H), 7.36-7.39 (IH, m, Ar-H), 7.47 (IH, brs, Ar-H), 7.56-7.58 (2H, d, Ar-H), 9.0 (IH, s, OH), 11.13 (IH, s, -NH); MS m/z: 433 (M+1).}
\] |
| 29 | \[
\text{HNMR (DMSO-d}_6\text{) 5 (ppm): 2.67-2.79 (2H, brs, -CH}_2\text{), 3.37 (3H, s, -OCH}_3\text{), 3.72 (3H, s, -OCH}_3\text{), 3.81-3.89 (2H, brs, -CH}_2\text{), 6.62 (IH, s, =CH), 6.75-6.77 (IH, d, Ar-H), 6.84-6.86 (IH, d, Ar-H), 6.92 (IH, s, Ar-H), 7.16-7.24 (3H, m, Ar-H), 7.37-7.41 (2H, m, Ar-H), 7.68-7.7 (2H, m, Ar-H), 9.04 (IH, brs, -OH), 11.15 (IH, brs, -NH); MS m/z: 477.1 (M+1).}
\] |
| 30 | \[
\text{HNMR (DMSO-d}_6\text{) 6 (ppm): 2.67-2.85 (2H, brs, -CH}_2\text{), 3.82 (2H, s, -CH}_2\text{), 4.75 (2H, s, -CH}_2\text{), 6.82 (IH, s, =CH), 7.15-7.2 (3H, m, Ar-H), 7.37-7.39 (3H, m, Ar-H), 7.51 (IH, m, Ar-H), 7.53-7.59 (4H, m, Ar-H), 7.88 (4H, m, Ar-H), 9.01 (IH, s, -OH), 11.1 (IH, s, -NH); MS m/z: 442.2 (M+1).}
\] |
| 31 | \[
\text{HNMR (DMSO-d}_6\text{) 5 (ppm): 2.67 (2H, brs, -CH}_2\text{), 2.89-2.93 (6H, s, -CH}_3\text{), 3.7-3.76 (2H, s, -CH}_2\text{), 4.71 (2H, s, -CH}_2\text{), 6.49-6.65 (3H, m, Ar-H & =CH), 7.06-7.08 (2H, m, Ar-H), 7.17-7.25 (6H, m, Ar-H), 7.48-7.6 (2H, m, Ar-H), 9.06 (IH, s, -OH), 11.11 (IH, s, -NH); MS m/z: 429.48 (M+1).}
\] |
| 32 | \[
\text{HNMR (DMSO-d}_6\text{) 5 (ppm): 2.68 (2H, brs, -CH}_2\text{), 3.70 (3H, s, -OCH}_3\text{), 3.77 (2H, s, -CH}_2\text{), 4.73 (2H, s, -CH}_2\text{), 6.70 (IH, s, =CH), 6.79 (2H, brs, Ar-H), 7.04-7.06 (2H, t, Ar-H), 7.19-7.21 (IH, d, Ar-H), 7.29-7.34 (5H, m, Ar-H), 7.53-7.58 (2H, m, Ar-H), 9.0 (IH, s, -OH), 11.14 (IH, s, -NH); MS m/z: 429.48 (M+1).}
\]
1H NMR (DMSO-d6) δ (ppm): 2.67 (2H, brs, -CH2), 3.71 (3H, s, -OCH3), 3.74 (3H, s, -OCH3), 3.76 (2H, s, -CH2), 4.71 (2H, s, -CH2), 6.61 (1H, s, =CH), 6.78 (2H, d, Ar-H), 6.90-6.92 (2H, d, Ar-H), 7.08-7.10 (2H, d, Ar-H), 7.20-7.22 (3H, d, Ar-H), 7.53-7.58 (2H, m, Ar-H), 9.0 (1H, s, -OH), 11.14 (1H, s, -NH); MS m/z: 459.2 (M+1).

1H NMR (DMSO-d6) δ (ppm): 2.71-2.87 (2H, m, -CH2), 3.79 (2H, s, -CH2), 4.76 (2H, s, -CH2), 6.78 (1H, s, =CH), 7.03-7.04 (2H, m, Ar-H), 7.17-7.19 (3H, m, Ar-H), 7.21-7.28 (4H, m, Ar-H), 7.55-7.61 (2H, m, Ar-H), 9.0 (1H, s, -OH), 11.16 (1H, s, -NH); MS m/z: 435.1 (M+1).

1H NMR (DMSO-d6) δ (ppm): 2.29 (3H, s, -CH3), 2.79 (2H, brs, -CH2), 3.81 (2H, s, -CH2), 4.74 (2H, s, -CH2), 6.68-6.69 (1H, s, =CH), 6.97 (1H, s, Ar-H), 7.02-7.03 (1H, d, Ar-H), 7.21-7.23 (1H, d, Ar-H), 7.23-7.25 (2H, d, Ar-H), 7.44-7.47 (2H, d, Ar-H), 7.53-7.55 (1H, s, Ar-H), 7.60 (1H, s, Ar-H), 9.03 (1H, s, -OH), 11.15 (1H, s, -NH); MS m/z: 437.1 (M+1).

1H NMR (DMSO-d6) δ (ppm): 2.67-2.84 (2H, m, -CH2), 3.81 (2H, s, -CH2), 4.7-4.82 (2H, d, -CH2), 6.81-6.97 (2H, d, =CH & Ar-H), 7.16-7.37 (6H, m, Ar-H), 7.53-7.59 (3H, m, Ar-H), 7.99-8.07 (1H, d, Ar-H); MS m/z: 462.1 (M+1).

1H NMR (DMSO-d6) δ (ppm): 2.83 (2H, s, -CH2), 3.33 (3H, s, -OCH3), 3.55 (3H, s, -OCH3), 4.01-4.03 (2H, d, -CH2), 4.75 (2H, brs, -CH2), 6.7 (1H, s, =CH), 6.83-6.9 (3H, d, Ar-H), 7.04 (2H, s, Ar-H), 7.23-7.25 (1H, d, Ar-H), 7.54-7.61 (3H, m, Ar-H), 9.02 (1H, s, -OH), 11.15 (1H, s, -NH); MS m/z: 465.1 (M+1).
<p>| 38 | NMR (DMSO-d&lt;sub&gt;6&lt;/sub&gt;) 6(ppm): 2.85 (2H, s, -CH&lt;sub&gt;2&lt;/sub&gt;), 3.92 (2H, brs, -CH&lt;sub&gt;2&lt;/sub&gt;), 4.73 (2H, brs, -CH&lt;sub&gt;2&lt;/sub&gt;), 7.08-7.10 (5H, m, =CH &amp; Ar-H), 7.23-7.25 (2H, m, Ar-H), 7.31-7.39 (3H, m, Ar-H), 7.48 (1H, s, Ar-H), 7.55-7.57 (1H, m, Ar-H), 9.00 (1H, s, -OH), 11.14 (1H, s, -NH); MS m/z: 451.0 (M+). |
| 39 | NMR (DMSO-d&lt;sub&gt;6&lt;/sub&gt;) 6(ppm): 2.67-2.85 (2H, m, -CH&lt;sub&gt;2&lt;/sub&gt;), 3.77-3.80 (2H, t, -CH&lt;sub&gt;2&lt;/sub&gt;), 4.73 (2H, brs, -CH&lt;sub&gt;2&lt;/sub&gt;), 6.6 (1H, s, =CH), 7.12-7.14 (2H, d, Ar-H), 7.21-7.23 (3H, m, Ar-H), 7.30-7.32 (4H, d, Ar-H), 7.53-7.60 (2H, d, Ar-H), 9.00 (1H, s, -OH), 11.13 (1H, s, -NH); MS m/z: 451.0 (M+). |
| 40 | NMR (DMSO-d&lt;sub&gt;6&lt;/sub&gt;) 6(ppm): 2.29 (3H, s, -CH&lt;sub&gt;3&lt;/sub&gt;), 2.67 (2H, brs, -CH&lt;sub&gt;2&lt;/sub&gt;), 3.71 (3H, s, -OCH&lt;sub&gt;3&lt;/sub&gt;), 3.74-3.77 (2H, s, -CH&lt;sub&gt;2&lt;/sub&gt;), 4.71 (2H, s, -CH&lt;sub&gt;2&lt;/sub&gt;), 6.65 (1H, s, =CH), 6.77-6.80 (2H, d, Ar-H), 7.07-7.09 (2H, d, Ar-H), 7.18-7.21 (5H, m, Ar-H), 7.53-7.58 (2H, d, Ar-H), 9.0 (1H, s, -OH), 11.14 (1H, s, -NH); MS m/z: 443.1 (M+). |
| 41 | NMR (DMSO-d&lt;sub&gt;6&lt;/sub&gt;) 6(ppm): 2.85 (2H, t, -CH&lt;sub&gt;2&lt;/sub&gt;), 3.92 (2H, brs, -CH&lt;sub&gt;2&lt;/sub&gt;), 4.73 (2H, brs, -CH&lt;sub&gt;2&lt;/sub&gt;), 7.04-7.07 (3H, m, =CH, Ar-H), 7.23-7.48 (6H, m, Ar-H), 7.55-7.57 (3H, m, Ar-H), 8.99 (1H, s, -OH), 11.14 (1H, s, -NH); MS m/z: 469 (M+). |
| 42 | NMR (DMSO-d&lt;sub&gt;6&lt;/sub&gt;) 5(ppm): 2.67-2.76 (2H, t, -CH&lt;sub&gt;2&lt;/sub&gt;), 3.87 (2H, s, -CH&lt;sub&gt;2&lt;/sub&gt;), 4.60 (2H, s, -CH&lt;sub&gt;2&lt;/sub&gt;), 6.85 (1H, s, =CH), 7.11-7.14 (4H, m, Ar-H), 7.24-7.25 (3H, s, Ar-H), 7.40 (3H, s, Ar-H), 9.10 (1H, s, -OH), 11.13 (1H, s, -NH); MS m/z: 423.0 (M+). |
| 43 | NMR (DMSO-d&lt;sub&gt;6&lt;/sub&gt;) 5(ppm): 2.67-2.73 (2H, m, -CH&lt;sub&gt;2&lt;/sub&gt;), 3.84-3.87 (2H, m, -CH&lt;sub&gt;2&lt;/sub&gt;), 4.60 (2H, s, -CH&lt;sub&gt;2&lt;/sub&gt;), 6.8 (1H, s, =CH), 7.11-7.13 (2H, d, Ar-H), 7.2-7.4 (8H, m, Ar-H), 9.08 (1H, s, -OH), 11.13 (1H, s, -NH); MS m/z: 423.0 |
| 44 | $^1$H NMR (DMSO-d$_6$) 5(ppm): 2.79 (2H, t, -CH$_2$), 3.31 (3H, s, -OCH$_3$), 3.33 (3H, s, -OCH$_3$), 3.62 (3H, s, -OCH$_3$), 3.78 (2H, brs, -CH$_2$), 4.73 (2H, brs, -CH$_2$), 6.44 (2H, s =CH &amp; Ar-H), 7.2-7.27 (3H, m, Ar-H), 7.38-7.42 (2H, m, Ar-H), 7.53-7.56 (2H, d, Ar-H), 7.6 (IH, s, Ar-H), 9.00 (IH, s, -OH), 11.14 (IH, s, -NH); MS m/z: 507.1 (M$^+$). |
| 45 | $^1$H NMR (DMSO-d$_6$) 5(ppm): 2.75-2.85 (2H, t, -CH$_2$), 3.82 (2H, brs, -CH$_2$), 4.74-4.82 (2H, d, -CH$_2$), 6.79-6.84 (IH, d, =CH), 7.05-7.06 (2H, m, Ar-H), 7.22-7.24 (3H, d, Ar-H), 7.36 (2H, s, Ar-H), 7.54-7.56 (IH, d, Ar-H), 7.56-7.62 (IH, s, Ar-H), 8.34-8.44 (2H, d, Ar-H), 9.02 (IH, s, -OH), 11.17 (IH, s, -NH); MS m/z: 418.1 (M$^+$). |
| 46 | $^1$H NMR (DMSO-de) 6(ppm): 2.7-2.87 (2H, t, -CH$_2$), 3.8 (2H, brs, -CH$_2$), 4.75-4.79 (2H, d, -CH$_2$), 6.75-6.81 (IH, d, =CH), 7.05-7.06 (2H, m, Ar-H), 7.22-7.24 (3H, d, Ar-H), 7.36 (2H, s, Ar-H), 7.54-7.56 (IH, d, Ar-H), 7.56-7.62 (IH, s, Ar-H), 8.43-8.44 (2H, d, Ar-H), 9.02 (IH, s, -OH), 11.17 (IH, s, -NH); MS m/z: 418.1 (M$^+$). |
| 47 | $^1$H NMR (DMSO-d$_6$) 6(ppm): 2.73-2.86 (2H, t, -CH$_2$), 3.80 (2H, s, -CH$_2$), 4.73 (2H, s, -CH$_2$), 6.85 (IH, s, =CH), 7.16-7.23 (4H, m, Ar-H), 7.33-7.35 (3H, m, Ar-H), 7.49-7.55 (2H, m, Ar-H), 7.71-7.73 (2H, d, Ar-H), 7.91 (IH, s, -COOH) 9.0 (IH, s, -OH), 11.14 (IH, s, -NH); MS m/z: 461(M$^+$). |
| 48 | $^1$H NMR (DMSO-de) 5(ppm): 2.85 (2H, brs, -CH$_2$), 3.71 (3H, s, -OCH$_3$), 3.89 (2H, brs, -CH$_2$), 4.80 (2H, brs, -CH$_2$), 6.78-6.80 (2H, d, =CH &amp; Ar-H) 6.97-6.99 (3H, d, Ar-H), 7.23-7.25 (IH, d, Ar-H), 7.29-7.38 (3H, m, Ar-H), 7.48-7.50 (IH, d, Ar-H) 7.55-7.57 (2H, d, Ar-H), 8.99 (IH, s, -OH), 11.14 (IH, s, -NH); MS m/z: 463.0 |</p>
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<td>2.70 (2H, m, -CH$_2$), 3.79 (2H, s, -CH$_2$), 4.72 (2H, s, -CH$_2$), 6.78 (IH, s, =CH), 6.97 (IH, d, Ar-H), 7.08-7.12 (IH, t, Ar-H), 7.20-7.22 (IH, d, Ar-H), 7.28-7.30 (3H, m, Ar-H), 7.32-7.38 (3H, m, Ar-H) 7.53-7.55 (IH, d, Ar-H), 7.60 (IH, s, Ar-H), 9.02 (IH, s, -OH); MS m/z: 435.1 (M+).</td>
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<td>3.1-3.15 (2H, t, -CH$_2$), 4.08-4.13 (2H, t, -CH$_2$), 7.0 (IH, s, =CH), 7.14-7.16 (2H, d, Ar-H), 7.15-7.25 (3H, dd, Ar-H), 7.31-7.4 (5H, m, Ar-H), 7.62-7.65 (2H, d, Ar-H), 8.0 (IH, brs, Ar-H), 8.95 (IH, s, -OH), 11.11 (IH, s, -NH); MS m/z: 385.1 (M+).</td>
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$^1$H NMR (DMSO-d$_6$) $\delta$ (ppm): 2.43 (3H, s, -SCH$_3$), 2.67-2.84 (2H, t, -CH$_2$), 3.78 (2H, s, -CH$_2$), 4.73 (2H, s, -CH$_2$), 6.69 (IH, s, =CH), 7.03-7.05 (2H, d, Ar-H), 7.10-7.12 (2H, d, Ar-H), 7.21-7.23 (3H, m, Ar-H), 7.32-7.36 (2H, m, Ar-H), 7.53-7.59 (2H, m, Ar-H) 9.0 (IH, s, -OH), 11.13 (IH, s, -NH); MS m/z: 463.0 (M+).

$^1$H NMR (DMSO-d$_6$) $\delta$ (ppm): 3.14 (2H, brs, -CH$_2$), 4.13 (2H, brs, -CH$_2$), 7.02 (IH, s, =CH), 7.15-7.36 (8H, m, Ar-H), 7.25-7.27 (IH, d, Ar-H), 7.64 (2H, brs, Ar-H), 8.0 (IH, brs, Ar-H); MS m/z: 403.1 (M+).

$^1$H NMR (DMSO-de) $\delta$ (ppm): 2.24 (6H, s, -CH$_3$), 2.67-2.83 (2H, t, -CH$_2$), 3.78 (2H, s, -CH$_2$), 4.73 (2H, s, -CH$_2$), 6.67 (IH, s, =CH), 7.03 (4H, s, Ar-H), 7.16-7.22 (5H, m, Ar-H), 7.53-7.58 (2H, m, Ar-H), 9.01 (IH, s, -OH), 11.14 (IH, s, -NH); MS m/z: 427.1 (M+).

$^1$H NMR (DMSO-d$_6$) $\delta$ (ppm): 2.23 (3H, s, -CH$_3$), 2.67-2.83 (2H, t, -CH$_2$), 3.78 (2H, s, -CH$_2$), 4.73 (2H, s, -CH$_2$), 6.73 (IH, s, =CH), 7.01 (4H, s, Ar-H), 7.21-7.33 (6H, m, Ar-H), 7.53-7.59 (2H, m, Ar-H), 9.02 (IH, s, -OH), 11.13 (IH, s, -NH); MS m/z: 413.1 (M+).

$^1$H NMR (DMSO-de) $\delta$ (ppm): 2.78 (2H, brs, -CH$_2$), 3.82 (2H, s, -CH$_2$), 4.74 (2H, s, -CH$_2$), 6.93 (IH, s, =CH), 7.1-7.13 (2H, m, Ar-H), 7.22-7.25 (4H, m, Ar-H), 7.51-7.61 (4H, m, Ar-H), 7.51 (2H, brs, Ar-H), 9.01 (IH, s, -OH), 11.15 (IH, s, -NH); MS m/z: 467.1 (M+).

$^1$H NMR (DMSO-de) $\delta$ (ppm): 0.51-0.53 (2H, t, -CH$_2$), 0.62-0.66 (2H, t, -CH$_2$), 2.75 (IH, m, -CH), 2.85 (2H, s, -CH$_2$), 3.80 (2H, t, -CH$_2$), 4.74-4.73 (2H, d, -CH$_2$), 7.05-7.07 (2H, d, =CH & Ar-H), 7.16-7.18 (2H, m, Ar-H), 7.22-7.26 (4H, m, Ar-H), 7.37-7.39 (3H, d, Ar-H), 7.53-7.61 (2H, d, Ar-H), 7.78-7.79 (IH, d, Ar-H), 8.99 (IH, s, -OH), 11.14 (IH, s, -NH); MS m/z: 482.1 (M+).
<p>| 60 |  NMR (DMSO-d$_6$) 5(ppm): 2.81 (2H, t, -CH$_2$), 3.83 (2H, s, -CH$_2$), 4.75 (2H, s, -CH$_2$), 6.68-6.69 (IH, d, =CH), 6.98-6.99 (IH, d, Ar-H), 7.00 (2H, s, Ar-H), 7.21-7.24 (2H, d, Ar-H), 7.42-7.45 (IH, m, Ar-H), 7.47 (2H, d, Ar-H), 7.53-7.54 (IH, m, Ar-H), 7.56-7.61 (IH, m, Ar-H), 9.03 (IH, s, -OH), 11.15 (IH, s, -NH); MS m/z: 439.1 (M+). |
| 61 |  NMR (DMSO-d$_6$) 6(ppm): 1.55-1.77 (2H, d, -CH$_2$), 2.95 (2H, t, -CH$_2$), 3.84 (2H, s, -CH$_2$), 4.63 (2H, brs, -CH$_2$), 6.53 (IH, s, =CH), 6.96-7.15 (4H, m, Ar-H), 7.16-7.20 (5H, m, Ar-H), 7.22-7.28 (3H, m, Ar-H), 8.99 (IH, s, -OH), 11.19 (IH, s, -NH); MS m/z: 413.1 (M+). |
| 62 |  NMR (DMSO-d$_6$) 5(ppm): 2.66-2.67 (2H, d, -CH$_2$), 2.73 (2H, s, -CH$_2$), 4.73 (2H, s, -CH$_2$), 5.19 (2H, s, -NH$_2$), 6.27-6.30 (IH, t, Ar-H), 6.58 (IH, s, =CH), 6.66-6.68 (IH, d, Ar-H), 6.75 (IH, s, =CH), 6.89-6.90 (IH, t, Ar-H), 7.11 (2H, brs, Ar-H), 7.20-7.24 (3H, m, Ar-H), 7.53-7.55 (IH, d, Ar-H), 7.60 (IH, s, Ar-H), 9.01 (IH, s, -OH), 11.14 (IH, s, -NH); MS m/z: 432.0 (M+). |
| 63 |  NMR (DMSO-d$_6$) 6(ppm): 2.84 (2H, brs, -CH$_2$), 3.91 (2H, brs, -CH$_2$), 4.79 (2H, brs, -CH$_2$), 7.00-7.04 (IH, t, Ar-H), 7.11-7.13 (IH, d, =CH), 7.27 (IH, m, Ar-H), 7.33 (IH, m, Ar-H), 7.44-7.48 (4H, m, Ar-H), 7.53-7.55 (3H, m, Ar-H) 9.02 (IH, s, -OH), 11.15 (IH, s, -NH); MS m/z: 439.9 (M+). |
| 64 |  NMR (DMSO-d$_6$) 5(ppm): 2.78-2.81 (2H, t, -CH$_2$), 3.82 (2H, s, -CH$_2$), 4.74 (2H, brs, -CH$_2$), 7.00-7.02 (IH, t, Ar-H), 7.15-7.17 (IH, d, =CH), 7.25-7.31 (4H, m, Ar-H), 7.41-7.43 (IH, m, Ar-H), 7.45-7.50 (2H, m, Ar-H), 7.54-7.55 (2H, m, Ar-H) 9.02 (IH, s, -OH), 11.15 (IH, s, -NH); MS m/z: 423.1 (M+). |</p>
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<td>74</td>
<td><img src="image" alt="Structure 74" /></td>
<td>2.24 (3H, s, -CH$_3$), 2.67-2.71 (2H, t, -CH$_2$), 3.79 (2H, s, -CH$_2$), 4.74 (2H, s, -CH$_2$), 6.74 (IH, s, =CH) 7.06-7.12 (6H, m, Ar-H), 7.16-7.21 (4H, m, Ar-H), 7.53-7.58 (2H, m, Ar-H), 9.01 (IH, s, -OH), 11.13 (IH, s, -NH); MS m/z: 413.0 (M+1).</td>
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<td>75</td>
<td>76</td>
<td>77</td>
<td>78</td>
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<td><img src="" alt="Image" /></td>
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<tr>
<td><strong>H NMR (DMSO-d_6)</strong> δ (ppm): 2.30 (3H, s, -CH₃), 2.70-2.84 (2H, d, -CH₂), 3.75-3.78 (2H, t, -CH₂), 4.72 (2H, s, -CH₂), 6.74 (1H, s, =CH), 6.91-6.93 (1H, d, Ar-H), 6.97-6.99 (1H, d, Ar-H), 7.04-7.07 (1H, t, Ar-H), 7.18 (5H, brs, Ar-H), 7.24-7.30 (1H, q, Ar-H), 7.53-7.55 (1H, d, Ar-H), 7.60 (1H, s, Ar-H), 9.0 (1H, s, -OH), 11.14 (1H, s, -NH); MS m/z: 431.0 (M+1).</td>
<td><strong>H NMR (DMSO-d_6)</strong> δ (ppm): 2.71-2.84 (2H, t, -CH₂), 3.58 (3H, s, -OCH₃), 3.64 (2H, s, -CH₂), 4.72 (2H, s, -CH₂), 6.77-6.84 (4H, m, =CH &amp; Ar-H), 7.14-7.15 (2H, m, Ar-H), 7.16-7.23 (5H, m, Ar-H), 7.53-7.55 (1H, d, Ar-H), 7.59 (1H, s, Ar-H), 9.0 (1H, s, -OH), 11.14 (1H, s, -NH); MS m/z: 428.9 (M+1).</td>
<td><strong>H NMR (DMSO-d_6)</strong> δ (ppm): 3.12-3.16 (2H, t, -CH₂), 4.15-4.19 (2H, t, -CH₂), 7.09 (1H, s, =CH), 7.14-7.21 (5H, m, Ar-H), 7.25-7.27 (3H, t, Ar-H), 7.39-7.45 (1H, m, Ar-H), 7.62-7.65 (2H, d, Ar-H), 7.8 (1H, brs, Ar-H), 8.96 (1H, s, -OH), 11.12 (1H, s, -NH); MS m/z: 402.9 (M+1).</td>
<td><strong>H NMR (DMSO-d_6)</strong> δ (ppm): 2.67-2.84 (2H, t, -CH₂), 3.49 (3H, s, -OCH₃), 3.76 (2H, s, -CH₂), 4.73 (2H, s, -CH₂), 6.65 (1H, brs, =CH), 6.7 (2H, d, Ar-H), 7.15-7.17 (2H, d, Ar-H), 7.19-7.26 (6H, m, Ar-H), 7.53-7.55 (1H, d, Ar-H), 7.6 (1H, s, Ar-H), 9.0 (1H, s, -OH), 11.15 (1H, s, -NH); MS m/z: 428.9 (M+1).</td>
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<td></td>
<td>Chemical Structure</td>
<td>NMR Data (DMSO-d$_6$) δ (ppm)</td>
<td>MS m/z (M+1)</td>
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<tr>
<td>80</td>
<td><img src="image1" alt="Chemical Structure" /></td>
<td>1H NMR: 2.72-2.84 (2H, t, -CH$_2$), 3.66-3.79 (5H, s, -CH$_2$ &amp; -OCH$_3$), 4.72 (2H, s, -CH$_2$), 6.77-6.83 (4H, m, =CH &amp; Ar-H), 7.06-7.10 (2H, m, Ar-H), 7.17-7.22 (4H, m, Ar-H), 7.53-7.55 (1H, d, Ar-H), 7.59 (1H, s, Ar-H), 9.0 (1H, s, -OH), 11.14 (1H, s, -NH); MS m/z: 446.9 (M+1).</td>
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<tr>
<td>81</td>
<td><img src="image2" alt="Chemical Structure" /></td>
<td>1H NMR: 3.14-3.16 (2H, t, -CH$_2$), 4.16-4.20 (2H, t, -CH$_2$), 7.10-7.18 (5H, m, =CH &amp; Ar-H), 7.27-7.29 (1H, d, Ar-H), 7.38-7.42 (3H, m, Ar-H), 7.62-7.65 (2H, d, Ar-H), 7.99 (1H, s, Ar-H), 8.96 (1H, s, -OH), 11.13 (1H, s, -NH); MS m/z: 436.9 (M+1).</td>
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<tr>
<td>82</td>
<td><img src="image3" alt="Chemical Structure" /></td>
<td>1H NMR: 3.10-3.14 (2H, t, -CH$_2$), 4.09-4.13 (2H, t, -CH$_2$), 7.02 (1H, s, =CH), 7.13-7.16 (2H, d, Ar-H), 7.20-7.24 (2H, t, Ar-H), 7.33-7.38 (4H, m, Ar-H), 7.61-7.64 (2H, d, Ar-H), 7.99 (1H, s, Ar-H), 8.96 (1H, s, -OH), 11.12 (1H, s, -NH); MS m/z: 436.2 (M+1).</td>
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<tr>
<td>83</td>
<td><img src="image4" alt="Chemical Structure" /></td>
<td>1H NMR: 2.30 (3H, s, -CH$_3$), 3.09-3.13 (2H, t, -CH$_2$), 4.05-4.09 (2H, t, -CH$_2$), 6.92-6.95 (2H, d, =CH &amp; Ar-H), 6.99-7.01 (1H, d, Ar-H), 7.05-7.10 (1H, t, Ar-H), 7.18-7.23 (4H, m, Ar-H), 7.27-7.32 (1H, q, Ar-H), 7.62-7.64 (2H, d, Ar-H), 8.01 (1H, s, Ar-H), 8.94 (1H, s, -OH), 11.11 (1H, s, -NH); MS m/z: 417.0 (M+1).</td>
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<tr>
<td>84</td>
<td><img src="image5" alt="Chemical Structure" /></td>
<td>1H NMR: 2.25 (3H, s, -CH$_3$), 3.10-3.14 (2H, t, -CH$_2$), 4.09-4.13 (2H, t, -CH$_2$), 6.97 (1H, s, =CH), 7.08-7.10 (1H, d, Ar-H), 7.16 (4H, s, Ar-H), 7.23 (4H, s, Ar-H), 7.61 (2H, m, Ar-H), 7.64 (1H, s, Ar-H), 8.94 (1H, s, -OH), 11.11 (1H, s, -NH); MS m/z: 399 (M+1).</td>
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<tr>
<td>Number</td>
<td>Structure</td>
<td>NMR (DMSO-d$_6$) 6(ppm):</td>
<td>Additional Information</td>
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<tr>
<td>85</td>
<td><img src="image" alt="Structure 85" /></td>
<td>3.10-3.14 (2H, t, -CH$_2$), 4.08-4.12 (2H, t, -CH$_2$), 7.01 (IH, s, =CH), 7.07-7.12 (2H, m, Ar-H), 7.18-7.2 (2H, m, Ar-H), 7.32-7.34 (2H, m, Ar-H), 7.36-7.41 (3H, d, Ar-H), 7.62-7.64 (2H, d, Ar-H), 8.0 (IH, s, Ar-H), 8.98 (IH, s, -OH), 11.13 (IH, s, -NH); MS m/z: 403.2 (M+1).</td>
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<tr>
<td>86</td>
<td><img src="image" alt="Structure 86" /></td>
<td>2.67 (2H, brs, -CH$_2$), 3.84 (2H, s, -CH$_2$), 4.59 (2H, s, -CH$_2$), 6.79 (IH, s, =CH), 7.05-7.16 (4H, m, Ar-H), 7.29-7.36 (6H, d, Ar-H), 9.08 (IH, s, -OH), 11.13 (IH, s, -NH); MS m/z: 422.9 (M+1).</td>
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<tr>
<td>87</td>
<td><img src="image" alt="Structure 87" /></td>
<td>2.3 (3H, s, -CH$_3$), 2.67 (2H, brs, -CH$_2$), 3.83 (2H, s, -CH$_2$), 4.59 (2H, s, -CH$_2$), 6.73 (IH, s, =CH), 7.16-7.21 (6H, d, Ar-H), 7.31 (3H, s, Ar-H), 7.31 (IH, s, Ar-H), 9.08 (IH, s, -OH), 11.13 (IH, s, -NH); MS m/z: 419 (M+1).</td>
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<tr>
<td>88</td>
<td><img src="image" alt="Structure 88" /></td>
<td>2.31 (3H, s, -CH$_3$), 2.69 (2H, brs, -CH$_2$), 3.82 (2H, s, -CH$_2$), 4.59 (2H, s, -CH$_2$), 6.74 (IH, s, =CH), 6.91-6.98 (2H, m, Ar-H), 7.02 (IH, d, Ar-H), 7.04-7.07 (4H, m, Ar-H), 7.19-7.29 (IH, m, Ar-H), 7.39 (IH, brs, Ar-H), 9.08 (IH, s, -OH), 11.13 (IH, s, -NH); MS m/z: 436.9 (M+1).</td>
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<tr>
<td>89</td>
<td><img src="image" alt="Structure 89" /></td>
<td>2.84-2.93 (2H, t, -CH$_2$), 3.88 (2H, s, -CH$_2$), 4.82-4.90 (2H, d, -CH$_2$), 7.07-7.12 (2H, m, =CH &amp; Ar-H), 7.22-7.35 (6H, m, Ar-H), 7.48 (IH, s, Ar-H) 7.56-7.58 (3H, d, Ar-H), 7.66-7.68 (2H, m, Ar-H), 7.79-7.83 (IH, t, Ar-H), 9.01 (IH, s, -OH), 11.15 (IH, s, -NH); MS m/z: 483.1 (M+1).</td>
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<tr>
<td>90</td>
<td><img src="image" alt="Structure 90" /></td>
<td>2.76-2.95 (2H, d, -CH$_2$), 3.89 (2H, s, -CH$_2$), 4.63-4.85 (2H, t, -CH$_2$), 6.78 (IH, s, =CH), 6.98-7.14 (2H, m, Ar-H), 7.18-7.26 (2H, m, Ar-H), 7.35-7.47 (3H, m, Ar-H), 7.56-7.61 (2H, brs, Ar-H), 11.13 (IH, s, -NH); MS m/z: 436.9 (M+1).</td>
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<td>7.88-7.93 (1H, m, Ar-H), 9.1 (1H, s, -OH) 11.13 (1H, s, -NH), 11.34 (1H, s, -NH); MS m/z: 461.9 (M+1).</td>
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<tr>
<td>91</td>
<td>(^1)H NMR (DMSO-d&lt;sub&gt;6&lt;/sub&gt;) δ (ppm): 2.88 (2H, m, -CH&lt;sub&gt;2&lt;/sub&gt;), 3.64-3.76 (2H, d, -CH&lt;sub&gt;2&lt;/sub&gt;), 4.59-4.69 (2H, t, -CH&lt;sub&gt;2&lt;/sub&gt;), 6.63-6.70 (1H, d, =CH), 6.82-6.86 (1H, m, Ar-H), 6.92-7.05 (5H, m, Ar-H), 7.25 (2H, s, Ar-H), 7.37 (2H, d, Ar-H), 7.57-7.62 (2H, m, Ar-H), 11.44 (1H, s, -NH); MS m/z: 456.1 (M+1).</td>
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<tr>
<td>92</td>
<td>(^1)H NMR (DMSO-d&lt;sub&gt;6&lt;/sub&gt;) δ (ppm): 2.66 (2H, brs, -CH&lt;sub&gt;2&lt;/sub&gt;), 3.72 (2H, brs, -CH&lt;sub&gt;2&lt;/sub&gt;), 4.60 (2H, brs, -CH&lt;sub&gt;2&lt;/sub&gt;), 6.75 (1H, s, =CH), 6.84 (1H, s, Ar-H), 6.91-6.93 (1H, m, Ar-H), 6.97-7.06 (3H, m, Ar-H), 7.26 (2H, brs, Ar-H), 7.39 (2H, brs, Ar-H), 9.41 (1H, s, -OH), 11.41 (1H, s, -NH) 11.58 (1H, s, -NH); MS m/z: 447.2 (M+1).</td>
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<tr>
<td>93</td>
<td>(^1)H NMR (DMSO-d&lt;sub&gt;6&lt;/sub&gt;) δ (ppm): 2.67-2.69 (2H, m, -CH&lt;sub&gt;2&lt;/sub&gt;), 3.82 (2H, s, -CH&lt;sub&gt;2&lt;/sub&gt;), 4.49-4.63 (2H, d, -CH&lt;sub&gt;2&lt;/sub&gt;), 6.81 (1H, s, =CH), 7.03-7.16 (2H, m, Ar-H), 7.18 (2H, s, Ar-H), 7.29-7.35 (4H, m, Ar-H), 8.58 (1H, s, -OH), 11.01 (1H, s, -NH); MS m/z: 409 (M+1).</td>
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<td>94</td>
<td>(^1)H NMR (DMSO-d&lt;sub&gt;6&lt;/sub&gt;) δ (ppm): 2.67-2.69 (2H, m, -CH&lt;sub&gt;2&lt;/sub&gt;), 3.82 (2H, s, -CH&lt;sub&gt;2&lt;/sub&gt;), 4.49-4.63 (2H, d, -CH&lt;sub&gt;2&lt;/sub&gt;), 6.81 (1H, s, =CH), 7.04-7.16 (5H, m, Ar-H), 7.30-7.35 (4H, m, Ar-H), 8.58 (1H, s, -OH), 11.01 (1H, s, -NH); MS m/z: 408 (M+1).</td>
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<tr>
<td>95</td>
<td>(^1)H NMR (DMSO-d&lt;sub&gt;6&lt;/sub&gt;) δ (ppm): 2.64 (2H, brs, -CH&lt;sub&gt;2&lt;/sub&gt;), 3.78 (3H, s, -OCH&lt;sub&gt;3&lt;/sub&gt;), 3.83 (2H, s, -CH&lt;sub&gt;2&lt;/sub&gt;), 4.50 (2H, brs, -CH&lt;sub&gt;2&lt;/sub&gt;), 6.95-7.01 (3H, m, =CH &amp; Ar-H), 7.19 (1H, s, Ar-H), 7.30 (2H, brs, Ar-H), 7.37-7.38 (2H, d, Ar-H), 8.61 (1H, s, -OH), 11.05 (1H, s, -NH); MS m/z: 426.1 (M+1).</td>
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<tr>
<td>96</td>
<td>( ^1H ) NMR (DMSO-d&lt;sub&gt;6&lt;/sub&gt;) ( \delta ) (ppm): 2.60-2.74 (2H, m, -CH&lt;sub&gt;2&lt;/sub&gt;), 3.83 (2H, s, -CH&lt;sub&gt;2&lt;/sub&gt;), 4.49-4.63 (2H, d, -CH&lt;sub&gt;2&lt;/sub&gt;), 6.82 (1H, s, -CH), 7.12-7.24 (8H, m, Ar-H), 7.33 (1H, s, Ar-H), 8.59 (1H, s, -OH), 11.03 (1H, s, -NH); MS m/z: 408.2 (M+1).</td>
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<tr>
<td>97</td>
<td>( ^1H ) NMR (DMSO-d&lt;sub&gt;6&lt;/sub&gt;) ( \delta ) (ppm): 2.67 (2H, m, -CH&lt;sub&gt;2&lt;/sub&gt;), 3.82 (2H, brs, -CH&lt;sub&gt;2&lt;/sub&gt;), 4.49-4.65 (2H, d, -CH&lt;sub&gt;2&lt;/sub&gt;), 6.81 (1H, s, -CH), 7.09-7.13 (2H, brs, Ar-H), 7.20-7.21 (4H, m, Ar-H), 7.24-7.34 (4H, m, Ar-H), 8.60 (1H, s, -OH), 11.05 (1H, s, -NH); MS m/z: 390.4 (M+1).</td>
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<tr>
<td>98</td>
<td>( ^1H ) NMR (DMSO-d&lt;sub&gt;6&lt;/sub&gt;) ( \delta ) (ppm): 2.67-2.80 (2H, t, -CH&lt;sub&gt;2&lt;/sub&gt;), 3.81-3.89 (2H, d, -CH&lt;sub&gt;2&lt;/sub&gt;), 4.54-4.62 (2H, d, -CH&lt;sub&gt;2&lt;/sub&gt;), 6.69-6.79 (1H, m, =CH), 7.00 (2H, s, Ar-H), 7.31 (5H, brs, Ar-H), 7.48-7.52 (1H, m, Ar-H), 8.68 (1H, s, -OH), 11.05 (1H, s, -NH); MS m/z: 396.1 (M+1).</td>
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<tr>
<td>99</td>
<td>( ^1H ) NMR (DMSO-d&lt;sub&gt;6&lt;/sub&gt;) ( \delta ) (ppm): 2.75 (2H, brs, -CH&lt;sub&gt;2&lt;/sub&gt;), 3.79, (3H, s, -OCH&lt;sub&gt;3&lt;/sub&gt;), 3.86 (2H, s, -CH&lt;sub&gt;2&lt;/sub&gt;), 4.58 (2H, s, -CH&lt;sub&gt;2&lt;/sub&gt;), 6.95-7.01 (4H, m, =CH &amp; Ar-H), 7.19 (1H, s, Ar-H), 7.32-7.34 (3H, d, Ar-H), 7.38-7.39 (1H, d, Ar-H), 9.09 (1H, s, -OH), 11.07 (1H, s, -NH); MS m/z: 441.2 (M+1).</td>
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<tr>
<td>100</td>
<td>( ^1H ) NMR (DMSO-d&lt;sub&gt;6&lt;/sub&gt;) ( \delta ) (ppm): 2.71-2.74 (2H, m, -CH&lt;sub&gt;2&lt;/sub&gt;), 3.85 (2H, brs, -CH&lt;sub&gt;2&lt;/sub&gt;), 4.59 (2H, brs, -CH&lt;sub&gt;2&lt;/sub&gt;), 6.81 (1H, s, -CH), 7.05-7.06 (2H, d, Ar-H), 7.21-7.36 (5H, m, Ar-H), 8.42-8.44 (2H, d, Ar-H), 8.66 (1H, s, -OH), 10.03 (1H, s, -NH); MS m/z: 424.0 (M+1).</td>
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<tr>
<td>101</td>
<td>( ^1H ) NMR (DMSO-d&lt;sub&gt;6&lt;/sub&gt;) ( \delta ) (ppm): 2.69-2.85 (2H, t, -CH&lt;sub&gt;2&lt;/sub&gt;), 3.80 (2H, brs, -CH&lt;sub&gt;2&lt;/sub&gt;), 4.74 (2H, brs, -CH&lt;sub&gt;2&lt;/sub&gt;), 6.8 (1H, brs, -CH), 7.05-7.09 (2H, t, Ar-H), 7.16 (2H, s, Ar-H), 7.3-7.36 (6H, d, Ar-H), 7.55 (2H, s, Ar-H), 9.01 (1H, s, -OH), 11.17 (1H, s, -NH); MS m/z: 417.1 (M+1).</td>
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<tr>
<td>No.</td>
<td>Structure</td>
<td>NMR Data</td>
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<tr>
<td>102</td>
<td><img src="image1.png" alt="Structure 1" /></td>
<td>$^1$H NMR (DMSO-d$_6$) $\delta$(ppm): 2.67 (2H, brs, -CH$_2$), 3.77 (2H, brs, -CH$_2$), 4.79 (2H, brs, -CH$_2$), 6.79 (1H, brs, =CH), 7.06-7.35 (12H, m, Ar-H), 9.2 (1H, s, -OH), 10.96 (1H, s, -NH); MS m/z: 417.1 (M+1).</td>
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<tr>
<td>103</td>
<td><img src="image2.png" alt="Structure 2" /></td>
<td>$^1$H NMR (DMSO-d$_6$) $\delta$(ppm): 2.67 (2H, brs, -CH$_2$), 3.89 (2H, brs, -CH$_2$), 4.48 (2H, brs, -CH$_2$), 6.81 (1H, s, =CH), 6.99 (1H, s, Ar-H), 7.12-7.31 (9H, m, Ar-H), 9.03 (1H, s, -OH), 11.08 (1H, s, -NH); MS m/z: 407.1 (M+1).</td>
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<tr>
<td>104</td>
<td><img src="image3.png" alt="Structure 3" /></td>
<td>$^1$H NMR (DMSO-d$_6$) $\delta$(ppm): 3.27-3.33 (2H, t, -CH$_2$), 4.1-4.15 (2H, t, -CH$_2$), 6.94 (1H, s, =CH), 7.0-7.53 (11H, m, Ar-H), 9.07 (1H, s, -OH), 11.07 (1H, s, -NH); MS m/z: 391.1 (M+1).</td>
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<tr>
<td>105</td>
<td><img src="image4.png" alt="Structure 4" /></td>
<td>$^1$H NMR (DMSO-d$_6$) $\delta$(ppm): 2.74 (2H, brs, -CH$_2$), 3.81 (2H, brs, -CH$_2$), 4.75 (2H, brs, -CH$_2$), 6.79 (1H, brs, =CH), 7.12-7.54 (12H, m, Ar-H), 8.99 (1H, brs, -OH), 10.13 (1H, s, -NH); MS m/z: 417.0 (M+1).</td>
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<tr>
<td>106</td>
<td><img src="image5.png" alt="Structure 5" /></td>
<td>$^1$H NMR (DMSO-d$_6$) $\delta$(ppm): 2.67-2.71 (2H, t, -CH$_2$), 3.79 (2H, brs, -CH$_2$), 4.79 (2H, brs, -CH$_2$), 6.79 (1H, brs, =CH), 7.11-7.31 (12H, m, Ar-H), 9.18 (1H, s, -OH), 10.96 (1H, s, -NH); MS m/z: 417.1 (M+1).</td>
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<tr>
<td>107</td>
<td><img src="image6.png" alt="Structure 6" /></td>
<td>$^1$H NMR (DMSO-d$_6$) $\delta$(ppm): 3.1-3.15 (2H, t, -CH$_2$), 4.01-4.12 (2H, t, -CH$_2$), 6.98 (1H, s, =CH), 7.07-7.57 (12H, m, Ar-H), 8.42 (1H, s, -OH), 8.98 (1H, s, -NH); MS m/z: 403.1 (M+1).</td>
<td></td>
</tr>
<tr>
<td>108</td>
<td><img src="image7.png" alt="Structure 7" /></td>
<td>$^1$H NMR (DMSO-d$_6$) $\delta$(ppm): 3.11-3.16 (2H, t, -CH$_2$), 4.09-4.14 (2H, t, -CH$_2$), 7.01 (1H, s, =CH), 7.14-7.51 (12H, m, Ar-H), 8.98 (1H, s, -OH), 11.17 (1H, s, -NH); MS m/z: 403.1 (M+1).</td>
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</tr>
<tr>
<td>No.</td>
<td>Structure</td>
<td>¹H NMR (DMSO-d₆) δ(ppm):</td>
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</tr>
<tr>
<td>-----</td>
<td>-----------</td>
<td>--------------------------</td>
<td>---</td>
</tr>
<tr>
<td>109</td>
<td><img src="image" alt="Structure 109" /></td>
<td>3.27-3.32 (2H, t, -CH₂), 4.27-4.31 (2H, t, -CH₂), 7.07 (2H, s, -CH &amp; Ar-H), 7.08-7.43 (9H, m, Ar-H), 7.53-7.55 (1H, d, Ar-H), 8.03-8.06 (1H, d, Ar-H), 9.07 (1H, s, -OH), 11.01 (1H, s, -NH);</td>
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<tr>
<td>110</td>
<td><img src="image" alt="Structure 110" /></td>
<td>3.23-3.28 (2H, t, -CH₂), 3.79 (3H, s, -OCH₃), 4.05-4.1 (2H, t, -CH₂), 6.98-7.03 (3H, m, -CH &amp; Ar-H), 7.17-7.25 (4H, m, Ar-H), 7.35-7.38 (2H, d, Ar-H), 7.43-7.44 (1H, d, Ar-H), 8.06-8.08 (1H, d, Ar-H), 9.04 (1H, s, -OH), 10.99 (1H, s, -NH);</td>
<td></td>
</tr>
<tr>
<td>111</td>
<td><img src="image" alt="Structure 111" /></td>
<td>3.24-3.29 (2H, t, -CH₂), 4.06-4.1 (2H, t, -CH₂), 6.99 (2H, s, -CH &amp; Ar-H), 7.06-7.40 (10H, s, Ar-H), 8.13 (1H, brs, Ar-H), 9.05 (1H, s, -OH), 11.00 (1H, s, -NH);</td>
<td></td>
</tr>
<tr>
<td>112</td>
<td><img src="image" alt="Structure 112" /></td>
<td>3.27-3.31 (2H, t, -CH₂), 4.09-4.13 (2H, t, -CH₂), 7.00 (1H, s, -CH), 7.06-7.08 (2H, d, Ar-H), 7.21-7.27 (6H, m, Ar-H), 7.35-7.39 (2H, dd, Ar-H), 8.14 (1H, brs, Ar-H), 9.15 (1H, brs, -OH), 11.02 (1H, brs, -NH);</td>
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<tr>
<td>113</td>
<td><img src="image" alt="Structure 113" /></td>
<td>3.29 (2H, t, -CH₂), 4.03 (2H, brs, -CH₂), 6.85-6.92 (2H, m, -CH &amp; Ar-H), 7.20-7.56 (6H, m, Ar-H), 8.17 (1H, brs, Ar-H), 8.47 (2H, d, Ar-H), 9.09 (1H, s, -OH), 11.07 (1H, s, -NH);</td>
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</tr>
<tr>
<td>114</td>
<td><img src="image" alt="Structure 114" /></td>
<td>3.1-3.15 (2H, t, -CH₂), 4.07-4.11 (2H, t, -CH₂), 6.98 (1H, s, -CH), 7.07-7.11 (2H, m, Ar-H), 7.17-7.2 (2H, m, Ar-H), 7.28-7.40 (6H, m, Ar-H), 8.42 (1H, brs, Ar-H), 8.98 (1H, s, -OH), 11.17 (1H, s, -NH);</td>
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1H NMR (DMSO-d$_6$) $\delta$(ppm): 3.27-3.32 (2H, t, -CH$_2$), 4.09-4.13 (2H, t, -CH$_2$), 7.00 (1H, s, =CH), 7.06-7.08 (2H, d, Ar-H), 7.21-7.27 (4H, m, Ar-H), 7.35-7.39 (2H, m, Ar-H), 8.14 (1H, brs, Ar-H), 8.45-8.47 (2H, d, Ar-H), 9.09 (1H, s, -OH), 11.07 (1H, s, -NH); MS m/z: 404.1 (M+1).

1H NMR (DMSO-d$_6$) $\delta$(ppm): 3.45 (3H, s, -OCH$_3$), 3.67 (4H, brs, -NCH$_2$), 3.72 (3H, s, -OCH$_3$), 3.81 (4H, brs, -NCH$_2$), 6.62 (1H, s, Ar-H), 6.70-6.74 (2H, m, Ar-H & =CH), 7.21-7.25 (2H, dd, Ar-H), 7.32-7.39 (2H, dd, Ar-H), 8.70 (2H, s, Ar-H), 9.02 (1H, s, -OH), 11.1 (1H, s, -NH). MS m/z: 508.1 (M+1).

1H NMR (DMSO-d$_6$) $\delta$(ppm): 3.42 (3H, s, -OCH$_3$), 3.67 (4H, brs, -NCH$_2$), 3.71 (3H, s, -OCH$_3$), 3.80 (4H, brs, -NCH$_2$), 6.59 (1H, s, Ar-H), 6.68 (1H, s, =CH), 6.74-6.84 (2H, dd, Ar-H), 7.30-7.42 (5H, m, Ar-H), 8.69 (2H, s, Ar-H), 9.04 (1H, s, -OH), 11.1 (1H, s, -NH). MS m/z: 490.2 (M+1).

1H NMR (DMSO-d$_6$) $\delta$(ppm): 3.44 (3H, s, -OCH$_3$), 3.67 (4H, brs, -NCH$_2$), 3.72 (3H, s, -OCH$_3$), 3.81 (4H, brs, -NCH$_2$), 6.59 (1H, d, Ar-H), 6.70 (1H, s, =CH), 6.71-6.86 (2H, dd, Ar-H), 7.21-7.26 (2H, t, Ar-H), 7.35-7.39 (2H, m, Ar-H), 8.70 (2H, s, Ar-H), 9.04 (1H, s, -OH), 11.1 (1H, s, -NH). MS m/z: 508.1 (M+1).

1H NMR (DMSO-d$_6$) $\delta$(ppm): 3.56 (3H, s, -OCH$_3$), 3.66 (4H, brs, -NCH$_2$), 3.75 (3H, s, -OCH$_3$), 3.92 (4H, brs, -NCH$_2$), 6.69 (1H, s, Ar-H), 6.82 (1H, s, =CH), 6.86-6.82 (2H, m, Ar-H), 7.03-7.06 (2H, m, Ar-H), 7.54-7.56 (1H, m, Ar-H), 8.68 (2H, s, Ar-H). MS m/z: 496.1 (M+1).
<p>| 120 | 1H NMR (DMSO-d$_6$) δ (ppm): 3.43 (3H, s, -OCH$_3$), 3.71 (4H, brs, -NCH$_2$), 3.72 (3H, s, -OCH$_3$), 3.84 (4H, brs, -NCH$_2$), 6.60 (1H, s, Ar-H), 6.71-6.73 (1H, d, Ar-H), 6.84 (1H, s, =CH), 6.86 (1H, s, Ar-H), 7.42-7.45 (1H, t, Ar-H), 7.75-7.77 (1H, d, Ar-H), 8.48 (1H, s, Ar-H), 8.52-8.54 (1H, d, Ar-H), 8.70 (2H, s, Ar-H), 9.04 (1H, s, -OH), 11.1 (1H, s, -NH). MS m/z: 491.2 (M+1). |
| 121 | 1H NMR (DMSO-d$_6$) δ (ppm): 3.80 (8H, m, -NCH$_2$), 6.78 (1H, s, =CH), 7.11-7.13 (2H, m, Ar-H), 7.18-7.27 (5H, m, Ar-H), 7.32-7.35 (2H, m, Ar-H), 8.57-8.67 (2H, brs, Ar-H). MS m/z: 448.1 (M+1). |
| 122 | 1H NMR (DMSO-d$_6$) δ (ppm): 3.66 (4H, s, -NCH$_2$), 3.79 (4H, s, -NCH$_2$), 5.96 (2H, s, -OCH$_2$), 6.50 (1H, s, =CH), 6.67 (1H, s, Ar-H), 6.71-6.73 (1H, d, Ar-H), 6.80-6.82 (1H, d, Ar-H), 7.30-7.32 (2H, d, Ar-H), 7.34-7.41 (3H, m, Ar-H), 8.69 (2H, s, Ar-H), 9.05 (1H, brs, -NH), 11.11 (1H, brs, -OH) MS m/z: 474.1(M+1). |
| 123 | 1H NMR (DMSO-d$_6$) δ (ppm): 3.70 (4H, s, -NCH$_2$), 3.84 (4H, s, -NCH$_2$), 6.92 (1H, s, =CH), 7.08-7.11 (1H, m, Ar-H), 7.13-7.17 (3H, m, Ar-H), 7.40-7.43 (1H, m, Ar-H), 7.71-7.73 (1H, d, Ar-H), 8.44 (1H, s, Ar-H), 8.52-8.54 (1H, d, Ar-H), 8.70 (2H, s, Ar-H), 9.06 (1H, brs, -NH), 11.12 (1H, brs, OH). MS m/z: 449.1 (M+1). |
| 124 | 1H NMR (DMSO-d$_6$) δ (ppm): 3.51 (4H, s, -NCH$_2$), 3.66 (4H, s, -NCH$_2$), 6.79 (1H, s, =CH), 6.88-6.90 (1H, d, Ar-H), 6.94-6.96 (1H, d, Ar-H), 7.04-7.09 (1H, t, Ar-H), 7.20-7.24 (2H, t, Ar-H), 7.26-7.30 (1H, m, Ar-H), 7.32-7.36 (2H, m, Ar-H), 8.67 (2H, s, Ar-H), MS m/z: 466.1 (M+1). |
| 125 | 1H NMR (DMSO-d$_6$) δ (ppm): 3.57 (3H, s, -OCH$_3$), 3.68 (4H, brs, -NCH$_2$), 3.82 (4H, brs, -NCH$_2$), 6.69-6.73 (1H, m, Ar-H), 6.76 (1H, s, =CH), 6.84-6.85 (1H, d, Ar-H), |
| 126 | 7.08-7.13 (1H, m, Ar-H), 7.22-7.26 (2H, m, Ar-H), 7.35-7.38 (2H, m, Ar-H), 8.70 (2H, s, -NCH₃), 9.04 (1H, s, -OH), 11.01 (1H, s, -NH). MS m/z: 496.1 (M+1). |
| 127 | ¹H NMR (DMSO-d₆) δ(ppm): 3.45 (3H, s, -OCH₃), 3.84 (3H, s, -OCH₃), 3.72 (8H, s, -NCH₃), 6.69 (1H, s, =CH), 6.75-6.77 (1H, m, Ar-H), 6.85-6.87 (1H, m, Ar-H), 6.89 (1H, s, Ar-H), 7.24-7.29 (2H, m, Ar-H), 7.36-7.44 (2H, m, Ar-H), 8.71 (2H, s, Ar-H), 9.04 (1H, s, -OH), 11.11 (1H, s, -NH). MS m/z: 508.1 (M+1). |
| 128 | ¹H NMR (DMSO-d₆) δ(ppm): 2.43 (3H, s, -SCH₃), 3.66 (8H, s, -NCH₃), 6.71 (1H, s, =CH), 7.04-7.06 (2H, d, Ar-H), 7.09-7.11 (2H, d, Ar-H), 7.30-7.32 (2H, m, Ar-H), 7.36-7.38 (3H, m, Ar-H), 8.68 (2H, s, Ar-H), 8.98 (1H, s, -OH), 11.11 (1H, s, -NH). MS m/z: 476.1 (M+1). |
| 129 | ¹H NMR (DMSO-d₆) δ(ppm): 3.65-3.74 (8H, s, -NCH₃), 3.84 (3H, s, -OCH₃), 6.67 (1H, s, =CH), 6.94-6.96 (2H, s, Ar-H), 6.99 (1H, s, Ar-H), 7.14-7.15 (1H, m, Ar-H), 7.21-7.23 (2H, d, Ar-H), 7.32-7.34 (1H, m, Ar-H), 8.69 (2H, s, Ar-H), 9.04 (1H, s, -OH), 11.11 (1H, s, -NH). MS m/z: 496.1 (M+1). |
| 130 | ¹H NMR (DMSO-d₆) δ(ppm): 3.59-3.87 (8H, brs, -NCH₃), 6.75 (1H, s, =CH), 6.90-6.94 (1H, m, Ar-H), 7.03-7.15 (4H, m, Ar-H), 7.24-7.34 (2H, m, Ar-H), 7.44-7.46 (2H, m, Ar-H), 8.74 (2H, s, Ar-H), 11.46 (1H, s, -NH). MS m/z: 487.1 (M+1). |
| 131 | <img src="image1" alt="Molecular Structure" /> | (^1)H NMR (DMSO-d6) δ(ppm): 3.08 (3H, s, -OCH3), 3.59 (3H, s, -OCH3), 3.69-3.80 (8H, m, -NCH2), 6.67 (1H, s, =CH), 6.72 (1H, s, Ar-H), 6.79-6.81 (1H, m, Ar-H), 6.86-6.90 (2H, m, Ar-H), 7.02-7.10 (2H, m, Ar-H), 7.41-7.43 (2H, m, Ar-H), 8.69 (2H, s, Ar-H), 11.37 (1H, s, -NH). MS m/z: 529.1 (M+1). |
| 132 | <img src="image2" alt="Molecular Structure" /> | (^1)H NMR (DMSO-d6) δ(ppm): 2.30 (3H, s, -CH3), 2.43 (3H, s, -SCH3), 3.62-3.79 (8H, m, -NCH2), 6.65 (1H, s, =CH), 7.06 (2H, s, Ar-H), 7.08-7.11 (2H, m, Ar-H), 7.18 (4H, s, Ar-H), 8.68 (2H, s, Ar-H), 9.01 (1H, s, -OH), 11.13 (1H, s, -NH). MS m/z: 490.1 (M+1). |
| 133 | <img src="image3" alt="Molecular Structure" /> | (^1)H NMR (DMSO-d6) δ(ppm): 3.63 (4H, s, -NCH2), 3.75 (3H, s, -OCH3), 3.81 (4H, s, -NCH2), 6.67 (1H, s, =CH), 6.92-6.93 (2H, d, Ar-H), 7.06-7.10 (2H, d, Ar-H), 7.19-7.21 (4H, d, Ar-H), 8.68 (2H, s, Ar-H), 8.98 (1H, s, -OH), 11.16 (1H, s, -NH). MS m/z: 478.1 (M+1). |
| 134 | <img src="image4" alt="Molecular Structure" /> | (^1)H NMR (DMSO-d6) δ(ppm): 3.68 (4H, s, -NCH2), 3.79-3.85 (4H, d, -NCH2), 6.82 (1H, s, =CH), 7.21-7.28 (3H, m, Ar-H), 7.33-7.37 (2H, m, Ar-H), 7.42-7.44 (1H, m, Ar-H), 8.33 (1H, s, Ar-H), 8.39-8.40 (1H, d, Ar-H), 8.69 (2H, s, Ar-H), 9.05 (1H, s, -OH), 11.13 (1H, s, -NH). MS m/z: 449.1 (M+1). |
| 135 | <img src="image5" alt="Molecular Structure" /> | (^1)H NMR (DMSO-d6) δ(ppm): 3.45 (3H, s, -OCH3), 3.70 (3H, s, -OCH3), 3.73 (4H, m, -NCH2), 3.85 (4H, m, -NCH2), 6.63 (1H, s, =CH), 6.75-6.76 (2H, m, Ar-H), 6.87-6.89 (1H, s, Ar-H), 7.32-7.34 (1H, m, Ar-H), 7.41-7.43 (1H, m, Ar-H), 7.45-7.48 (2H, m, Ar-H), 8.72 (2H, s, Ar-H), 9.06 (1H, s, -OH), 11.12 (1H, s, -NH). MS m/z: 525.1 (M+1). |
| 136 | <img src="image6" alt="Molecular Structure" /> | (^1)H NMR (DMSO-d6) δ(ppm): 3.67-3.81 (6H, brs, -NCH2), 3.89 (2H, s, -NCH2), 6.71 (1H, s, =CH), 7.12-7.14 (2H, m, Ar-H), 7.22-7.24 (3H, m, Ar-H), 7.29-7.32 |</p>
<table>
<thead>
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<th>No.</th>
<th>Compound Structure</th>
<th>NMR Data (DMSO-d$_6$) δ (ppm):</th>
<th>MS m/z:</th>
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<td><img src="image1.png" alt="Compound Structure" /></td>
<td>$^1$H NMR (DMSO-d$_6$) δ (ppm): 3.38-3.42 (3H, brs, -OCH$_3$), 3.67 (3H, s, -OCH$_3$), 3.71-3.73 (8H, t, -NCH$_2$), 3.80 (3H, s, -OCH$_3$) 6.66-6.67 (2H, m, Ar-H &amp; -CH), 6.75-6.78 (1H, m, Ar-H), 6.81-6.89 (2H, m, Ar-H), 6.92-6.96 (2H, m, Ar-H), 7.21 (1H, s, Ar-H), 8.69 (2H, s, Ar-H), 9.04 (1H, s, -OH), 11.12 (1H, s, -NH).</td>
<td>430.1 (M+1).</td>
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<td><img src="image2.png" alt="Compound Structure" /></td>
<td>$^1$H NMR (DMSO-d$_6$) δ (ppm): 3.45 (3H, s, -OCH$_3$), 3.60 (4H, s, -NCH$_2$) 3.70-(4H, s, -NCH$_2$), 3.81 (3H, s, -OCH$_3$), 6.74 (1H, s, -CH), 6.85-6.89 (2H, t, Ar-H), 6.98-7.01 (1H, d, Ar-H), 7.23-7.25 (1H, d, Ar-H), 7.30-7.32 (4H, m, Ar-H), 8.75 (2H, s, Ar-H), 9.09 (1H, s, -OH), 11.16 (1H, s, -NH).</td>
<td>520.1 (M+1).</td>
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<td><img src="image3.png" alt="Compound Structure" /></td>
<td>$^1$H NMR (DMSO-d$_6$) δ (ppm): 3.60-3.70 (5H, m, -CH$_2$), 3.81-3.88 (3H, m, -CH$_2$), 6.09 (2H, s, -OCH$_3$), 6.74 (1H, s, -CH), 6.82-6.85 (2H, t, Ar-H), 6.91-6.99 (1H, d, Ar-H), 7.17-7.19 (2H, t, Ar-H), 7.24-7.31 (2H, m, Ar-H), 8.71-8.75 (2H, s, Ar-H), 9.09 (1H, s, -OH), 11.16 (1H, s, -NH).</td>
<td>492.1 (M+1).</td>
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<td>$^1$H NMR (DMSO-d$_6$) δ (ppm): 3.65-3.79 (8H, d, -NCH$_2$), 6.81(1H, s, -CH), 7.06-7.08 (2H, m, Ar-H), 7.10(3H, m, Ar-H), 7.15-7.20 (2H, m, Ar-H), 7.38-7.44 (1H, m, Ar-H), 8.65-8.67 (2H, s, Ar-H),</td>
<td>466.1 (M+1).</td>
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<td>141</td>
<td><img src="image5.png" alt="Compound Structure" /></td>
<td>$^1$H NMR (DMSO-d$_6$) δ (ppm): 3.66 (4H, s, -NCH$_2$), 3.80 (4H, s, -NCH$_2$), 5.97 (2H, s, -OCH$_3$), 6.52 (1H, s, -CH), 6.69-6.71 (2H, m, Ar-H), 6.82-6.84 (1H, d, Ar-H), 7.20-7.25 (2H, t, Ar-H), 7.33-7.36 (2H, m, Ar-H), 8.69 (2H, s, -Ar-H), 9.03(1H, brs, -NH), 11.10 (1H, brs, -OH).</td>
<td>492.1 (M+1).</td>
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<td>142</td>
<td>$^1$H NMR (DMSO-d$_6$) δ (ppm): 3.65 (4H, s, -NCH$_2$), 3.80 (4H, s, -NCH$_2$), 5.97 (2H, s, -OCH$_3$), 6.51 (1H, s, =CH), 6.69-6.71 (2H, d, Ar-H), 6.82-6.84 (1H, d, Ar-H), 7.20-7.25 (2H, t, Ar-H), 7.33-7.36 (2H, m, Ar-H), 8.69 (2H, s, Ar-H), 9.04 (1H, brs, -NH), 11.11 (1H, brs, -OH). MS m/z: 492.1 (M+1).</td>
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<td>143</td>
<td>$^1$H NMR (DMSO-d$_6$) δ (ppm): 3.58 (3H, s, -OCH$_3$), 3.75 (3H, s, -OCH$_3$), 3.64 (4H, s, -NCH$_2$), 3.72 (2H, s, -NCH$_2$), 3.85 (2H, s, -NCH$_2$), 6.69 (1H, s, =CH), 6.82-6.83 (1H, m, Ar-H), 6.86-6.88 (1H, m, Ar-H), 6.96 (2H, m, Ar-H), 7.05-7.12 (2H, m, Ar-H), 7.31-7.37 (1H, m, Ar-H), 8.69 (2H, s, Ar-H), 9.06 (1H, s, -OH), 11.09 (1H, s, -NH). MS m/z: 508.1 (M+1).</td>
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<td>144</td>
<td>$^1$H NMR (DMSO-d$_6$) δ (ppm): 1.30-1.33 (2H, d, -CH$_2$), 1.77-1.79 (2H, d, -NCH$_2$), 2.99-3.05 (2H, t, -CH$_2$), 3.37 (3H, s, -OCH$_3$), 3.69-3.78 (3H, s, OCH$_3$), 4.02 (1H, m, -CH$_2$), 4.53-4.62 (2H, d, -CH$_2$), 6.45 (1H, s, =CH), 6.68-6.70 (1H, d, -NH), 6.81-6.83 (1H, d, Ar-H), 6.99-7.02 (2H, m, Ar-H), 7.18-7.22 (1H, m, Ar-H), 7.33 (1H, s, Ar-H), 7.42-7.51 (2H, m, Ar-H), 8.60-8.65 (2H, brs, Ar-H); MS m/z: 522.1 (M+1).</td>
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<td>$^1$H NMR (DMSO-d$_6$) δ (ppm): 1.17-1.18 (2H, m, -CH$_2$), 1.42-1.47 (2H, m, -NCH$_2$), 3.07-3.13 (2H, s, -CH$_2$), 3.76 (3H, s, -OCH$_3$), 3.60 (3H, s, -OCH$_3$), 4.00-4.06 (1H, m, -NCH$_2$), 4.00-4.06 (2H, s, -NCH$_2$), 6.71-6.67 (2H, m, Ar-H &amp; =CH), 6.95-6.93 (1H, d, NH), 7.04-7.06 (2H, m, Ar-H), 7.19-7.22 (3H, m, Ar-H), 7.29-7.33 (2H, m, Ar-H), 8.66 (2H, s, Ar-H), 9.00 (1H, s, -OH), 11.06 (1H, s, -NH); MS m/z: 504.1 (M+1).</td>
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| 146 | $^1$H NMR (DMSO-d$_6$) δ (ppm): 1.40-1.44 (2H, m, CH$_2$), 1.75-1.78 (2H, m, -NCH$_2$), 2.99-3.04 (2H, t, -CH$_2$), 3.39 (3H, s, -OCH$_3$), 3.70 (3H, s, -OCH$_3$) 4.00 (1H, m, -
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<td>NCH₂, 4.58-4.62 (2H, d, -NCH₂), 6.43-6.44 (1H, d, Ar-H), 6.66-6.68 (1H, d, Ar-H), 6.81-6.83 (1H, d, Ar-H), 7.19-7.27 (4H, m, Ar-H), 7.31 (1H, s, =CH), 7.42-7.44 (1H, d, -NH), 8.59 (2H, s, Ar-H); MS m/z: 522.1 (M+1).</td>
<td></td>
<td></td>
</tr>
<tr>
<td>148</td>
<td>¹H NMR (DMSO-d₆) δ(ppm): 1.07-1.09 (2H, m, -CH₂), 1.68-1.73 (2H, m, -CH₂), 2.89-2.95 (2H, t, -NCH₂), 3.04-3.06 (2H, t, -NCH₂), 3.37 (3H, s, OCH₃), 3.71 (3H, s, OCH₃), 4.67-4.70 (2H, d, -NCH₂), 6.44 (1H, s, Ar-H), 6.69-6.71 (1H, m, Ar-H), 6.83-6.85 (1H, m, Ar-H), 7.03-7.05 (2H, m, Ar-H), 7.23-7.25 (1H, t, -NH), 7.41 (1H, s, =CH), 7.47-7.50 (2H, m, Ar-H), 8.65 (2H, s, Ar-H), 8.99 (1H, s, -OH); MS m/z: 536.2 (M+1).</td>
<td></td>
<td></td>
</tr>
<tr>
<td>149</td>
<td>¹H NMR (DMSO-d₆) δ(ppm): 0.52-0.53 (2H, m, -CH₂), 0.62-0.67 (2H, m, -CH₂), 2.73-2.77 (1H, m, -CH), 3.65 (4H, brs, -NCH₂), 3.84 (4H, brs, -NCH₂), 7.05-7.07 (2H, d, Ar-H), 7.17-7.20 (4H, m, Ar-H), 7.21-7.30 (3H, m, Ar-H &amp; =CH), 7.83-7.85 (1H, d, -NH), 8.69 (2H, s, Ar-H), 9.03 (1H, s, -OH); MS m/z: 531.2 (M+1).</td>
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<td></td>
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<tr>
<td>150</td>
<td>¹H NMR (DMSO-d₆) δ(ppm): 0.62-0.64 (2H, m, -CH₂), 0.64-0.66 (2H, m, -CH₂), 2.73-2.77 (1H, m, -CH), 3.39-3.43 (2H, d, -CH₂), 3.62-3.64 (2H, d, -CH₂), 3.79-3.83 (4H, m, -NCH₂), 3.37 (3H, s, -OMe), 3.7-3.8 (3H, s, -OCH₃), 6.68-6.70 (2H, t, Ar-H), 6.96-6.98 (1H, d, =CH), 7.11-7.13 (2H, d, Ar-H), 7.27-7.29 (3H, d Ar-H), 7.56-7.57 (1H, s, -NH), 8.65-8.69 (2H, brs, Ar-H), 9.03 (1H, s, -OH); MS m/z: 573.2 (M+1).</td>
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<tr>
<td>150</td>
<td>¹H NMR (DMSO-d₆) δ(ppm): 0.48-0.51 (2H, m, -CH₂), 0.61-0.65 (2H, m, -CH₂), 2.33 (3H, s, -CH₃), 2.73-2.76 (1H, m, -CH), 3.31-3.33 (2H, m, -NCH₂), 3.65 (2H, brs, -NCH₂), 3.84 (4H, brs, -NCH₂) 7.04-7.09 (4H, m, Ar-</td>
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</tbody>
</table>
Example 154: 2-(2-(4-Fluorophenyl)-3-phenylallyl)-N-hydroxy-1,2,3,4-tetrahydroisoquinoline-7-carboxamide

Step A: 2-(4-Fluorophenyl)-3-phenylprop-2-en-1-ol

To a solution of 2-(4-Fluorophenyl)-3-phenylacrylic acid (1.5 g, 6.1 mmol) in THF (10 mL) was added triethylamine (1 mL, 7.4 mmol), followed by the addition of
ethyl chloroformate (0.8 g, 7.4 mmol) in THF (5 mL) over a period of 30 minutes at 0 °C. The stirring was continued at same temperature. On completion of the reaction sodium borohydride (0.28 g, 7.4 mmol) was added slowly. Methanol (30 mL) was added to the reaction mixture stirred at room temperature for 1 hour. Cold water (100 mL) was added and the mixture extracted with ethyl acetate (2 x 200 mL). The organic layer was washed with 50 mL of brine solution, dried over anhydrous sodium sulphate and concentrated under vacuum to get the crude material. This was further purified by column chromatography using n-hexane and ethyl acetate solvent mixture to get the pure title compound (0.5 g, 36%).

Step B: 2-(4-fluorophenyl)-3-phenylallyl methanesulfonate

To a solution of 2-(4-fluorophenyl)-3-phenylprop-2-en-1-ol (0.5 g, 4.3 mmol) in DCM (10 mL), triethylamine (0.6 mL, 4.4 mmol was added, followed by the slow addition of methanesulfonyl chloride (0.2 mL, 2.6 mmol) at 0-5 °C. The reaction mixture was slowly warmed to room temperature and stirring continued for 1 hour. The reaction was quenched with water and extracted with DCM. The organic layer was washed with 10% cone. HCl solution, water, followed by saturated sodium bicarbonate solution. The organic layer was dried over sodium sulphate and concentrated under reduced pressure to get the crude title product (0.4 g, 61%).

Step C: Methyl 2-(2-(4-fluorophenyl)-3-phenylallyl)-1,2,3,4-tetrahydroisoquinoline-7-carboxylate

To a solution of 2-(4-fluorophenyl)-3-phenylallyl methanesulfonate (0.4 g, 1.3 mmol) in DMF (10 mL) was added K$_2$CO$_3$ (0.53 g, 3.9 mmol) followed by methyl 1,2,3,4-tetrahydroisoquinoline-7-carboxylate (0.25 g, 1.3 mmol) and the reaction mixture was stirred at room temperature for 4 hours. To this cold water (100 mL) was added and extracted with ethyl acetate (2 x 100 mL). The organic layer was washed with brine solution, dried over anhydrous sodium sulphate, and concentrated under vacuum to get the crude product, which was further purified by column chromatography using n-hexane and ethyl acetate solvent mixture to get the pure title compound (0.35 g, Yield 57%).

Step D: 2-(2-(4-Fluorophenyl)-3-phenylallyl)-N-hydroxy-1,2,3,4-tetrahydroisoquinoline-7-carboxamide

According to procedure given in example 1, step II, Methyl 2-(2-(4-fluorophenyl)-3-phenylallyl)-1,2,3,4-tetrahydroisoquinoline-7-carboxylate was
converted to title compound (0.2 g, 57%). H NMR (DMSO-d$_6$) 6(ppm): 2.74-2.76 (2H, t, -CH$_2$), 2.78-2.79 (2H, d, -CH$_2$), 3.48 (2H, s, -CH$_2$), 3.64 (2H, s, -CH$_2$), 6.72 (1H, s, =CH), 6.96-6.97 (2H, d, Ar-H), 7.1 1-7.17 (6H, m, Ar-H), 7.24-7.28 (2H, m, Ar-H), 7.46-7.51 (2H, m, Ar-H), 8.97 (1H, s, -OH), 11.1 (1H, s, -NH); MS m/z: 474.1 (M+l).

Example 155: N-(2-Aminophenyl)-2-(2,3-diphenylacryloyl)-1,2,3,4-tetrahydro isoquinoline-7-carboxamide

Step-I: 2-(2,3-Diphenylacryloyl)-1,2,3,4-tetrahydroisoquinoline-7-carboxylic acid

To a solution of 2-(2,3-Diphenylacryloyl)-1,2,3,4-tetrahydroisoquinoline-7-carboxylic acid methyl ester (0.300 g, 0.7 mmol) in methanol (15 mL) was added aqueous LiOH (0.090 g, 3.7 mmol in 2 mL of water) solution. The reaction mixture was stirred at room temperature for 4 hours and diluted with 100 mL of cold water. The pH of the reaction mixture was adjusted to 2 with dilute aqueous HCl and allowed to stand at 4 °C for 30 minutes. The resulting precipitate was filtered and dried under vacuum to give the pure title compound as a colourless solid (0.250 g, Yield 87.10%).

Step-II: N-(2-Aminophenyl)-2-(2,3-diphenylacryloyl)-1,2,3,4-tetrahydroisoquinoline-7-carboxamide

To a solution of 2-(2,3-Diphenylacryloyl)-1,2,3,4-tetrahydroisoquinoline-7-carboxylic acid (0.200 g, 0.52 mmol) in DMF (5 mL) was added EDCI (0.198 g, 1.04 mmol), HOBt (0.028 g, 0.20 mmol), (9-phenylenediamine (0.109 g, 1.04 mmol), followed by DIEA (0.259 mL, 1.56 mmol). The reaction mixture was stirred for 3 hours at room temperature and added to cold water (50 mL) and extracted with ethyl acetate (2 x 150 mL). The organic layer was washed with water (2 x 80 mL), brine solution (1 x 100 mL), dried over anhydrous Na$_2$SO$_4$ and concentrated to give crude compound. The crude yellow coloured compound was triturated with diethyl ether (20 mL) to afford the pure title compound as a colourless solid (0.080 g, yield 32.65%).

$^1$H NMR (DMSO-de) 5(ppm): 2.67-2.73 (2H, m, -CH$_2$), 3.82 (2H, t, -CH$_2$), 4.79 (4H, d, -CH$_2$ & NH$_2$), 6.57 (1H, s, =CH), 6.76-6.78 (2H, m, Ar-H), 6.94-6.98 (1H, m, Ar-H), 7.14-7.21 (6H, m, Ar-H), 7.31-7.34 (6H, m, Ar-H), 7.76-7.85 (2H, m, Ar-H), 9.59 (1H, s, -NH); MS m/z: 474.1 (M+l).
The following compounds were prepared according to the procedure given in Example 155.

<table>
<thead>
<tr>
<th>Ex.</th>
<th>Structure</th>
<th>Analytical Data</th>
</tr>
</thead>
<tbody>
<tr>
<td>156</td>
<td><img src="image1.png" alt="Structure 1" /></td>
<td>^1H NMR (DMSO-d$_6$) δ(ppm): 2.80-2.88 (2H, d, -CH$_2$), 3.84 (2H, brs, -CH$_2$), 4.79 (2H, s, -CH$_2$), 4.89 (2H, s, -NH$_2$), 6.57-6.61 (1H, t, =CH), 6.76-6.78 (1H, d, Ar-H), 6.86 (1H, brs, Ar-H), 6.94-6.98 (1H, t, Ar-H), 7.10-7.15 (6H, m, Ar-H), 7.24-7.30 (4H, m, Ar-H), 7.40 (1H, brs, Ar-H), 7.77-7.79 (1H, d, Ar-H), 7.86 (1H, s, Ar-H), 9.59 (1H, s, -NH); MS m/z: 492.0 (M+1).</td>
</tr>
<tr>
<td>157</td>
<td><img src="image2.png" alt="Structure 2" /></td>
<td>^1H NMR (DMSO-d$_6$) δ(ppm): 2.88 (2H, s, -CH$_2$), 3.85 (2H, brs, -CH$_2$), 4.79 (2H, brs, -CH$_2$), 4.9 (2H, s, -NH$_2$), 6.57-6.61 (1H, t, =CH), 6.76-6.78 (1H, d, Ar-H), 6.86 (1H, brs, Ar-H), 6.94-6.98 (2H, m, Ar-H), 7.06 (1H, s, Ar-H), 7.14-7.19 (2H, m, Ar-H), 7.27-7.29 (1H, d, Ar-H), 7.38-7.44 (6H, m, Ar-H), 7.76-7.78 (1H, d, Ar-H), 7.86 (1H, s, Ar-H), 9.6 (1H, s, -NH); MS m/z: 480.1 (M+1).</td>
</tr>
</tbody>
</table>

Comparative Examples:

<table>
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<tr>
<th>Example</th>
<th>HDAC6 IC$_{50}$</th>
</tr>
</thead>
<tbody>
<tr>
<td>AA</td>
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</tr>
<tr>
<td>AB</td>
<td>~1 μM</td>
</tr>
</tbody>
</table>

HDAC assay and other experimental methods

HDAC 1 & 6 Assays:

The Histone Deacetylase (HDAC) inhibitory activity of molecules to specific isoforms (rhHDAC1 or rhHDAC6) were assayed with Boc-Lys (q-Ac)-AMC substrate, (Bachem 1-1875) which has been previously described as a small-molecule screening method for HDAC enzymes in vitro. The total HDAC assay volume was 100 μL and the assay components were diluted in HDAC buffer (50 mM Tris-HCl, 137 mM NaCl, 2.7 mM KCl and 2 mM MgCl$_2$, pH 8.0). The reaction was carried out in black 96-well
plates (Nunc). In brief, the HDAC assay mixture contained HDAC substrate (37.5 µM, 40 µL), rhHDAC1 or rhHDAC6 enzymes (final concentration 30 µL, diluted to 10 µL final volumes) and inhibitor (2X, the required assay concentration, diluted to 50 µL final volume). For HDAC1 inhibitory activity, the assay components were incubated at 37 °C for 3 Hours, whereas for HDAC6 the components were incubated for 1 hour. Positive control termed as total activity (TA) contained all the above components except the inhibitor. The negative control or blank contained neither enzyme nor inhibitor. In each case inhibitor volumes were replaced with an equivalent volume of buffer. Following incubation, the reaction was quenched with the addition of 100 µL of trypsin (10 mg/mL) stop solution containing 2 µM Trichostatin A (TSA). The plates were incubated for 15 minutes at 37 °C to allow the fluorescence signal to develop. The fluorescent signal was detected by fluorometer (GeminiXS; Molecular Devices) at 360 nm excitation, 460 nm emission, and cut off at 435 nm for both rhHDAC1 and for rhHDAC6. The IC50 values of the test compounds (disclosed herein) were computed by analyzing dose-response inhibition curves (Graph Pad prism, 4) (Bonfils C., et al., *Clinical Cancer Research*, 2008, 14, 3441 - 3449).

As detailed above, some of the test compounds were screened for HDAC6 enzyme inhibitory activity. The compounds whose IC50 values in the range of less than 1 nM to 50 nM are 1, 4, 5, 6, 7, 8, 9, 10, 12, 11, 14, 17, 19, 20, 21, 22, 23, 24, 25, 29, 32, 43, 44, 45, 46, 48, 49, 52, 53, 54, 55, 59, 62, 64, 69, 70, 71, 72, 76, 77, 78, 80, 85, 87, 88, 28, 86, 152 and 153.

A few of the compounds showed greater than 2000 fold selectivity for HDAC6 over HDAC1. In another embodiment some of the compounds showed greater than 1000 fold selectivity for HDAC6 over HDAC1. Several compounds have greater than 100 fold selectivity for HDAC6 over HDAC1.

**Anticancer Activity:**

**Cell Viability screening:**

The test compounds were screened in ten cancer cell lines for cell viability using Sulforhodamine B (SRB) cell viability assay (Vichai V., et al., *Nature Protocols*, 2006, 1(3), 1112-1116) and CCK8 assay. The cell lines - MCF7 and MDA MB231 (human breast cancer cell lines), NCIH460 (human lung cancer cell line), HCT116 (human colon cancer cell line), PC3 (human prostate cancer cell line), HT1080 (human fibrosarcoma cell line) were maintained in Dulbecco’s modified eagle's medium
(DMEM) and the multiple myeloma cell lines (U266B1, RPMI8226, NCIH929 & MM.IS) were maintained in RPMI 1640 medium containing 10 % foetal bovine serum. 96-well microtiter plates were inoculated with cells in 50 µL of cell culture media (6 x 10^4 cells/mL) for 24 hours at 37 °C, 5 % CO₂, 95 % air and 100 % relative humidity. Separate plate with these cell lines was also inoculated to determine cell viability before the addition of the test compounds (T₀). For multiple myeloma cell lines, drug addition can be performed immediately after seeding of cells.

**Addition of experimental drugs:**

Following 24 hours incubation, test compounds were added to the plates in triplicates with appropriate dilutions along with the cytotoxic standard and control (untreated) wells. Test compounds were dissolved in dimethyl sulfoxide (DMSO) to prepare 100 mM stock solutions on the day of drug addition and serial dilutions were carried out in complete growth medium at 5x strength such that 50 µL added to wells gave final concentrations of 0.0064, 0.032, 0.16, 0.8, 4, 20 and 100 µM in the well. The plates were then incubated for 72 hours at 37 °C, 5 % CO₂, 95 % air and 100 % relative humidity.

**End-point measurement:**

For T₀ measurement (24 hours after seeding the cells) 100 µL of ice-cold trichloroacetic acid (TCA) was added to all the wells to precipitate proteins. The plates were incubated at 4 °C for 60 minutes. The plates were washed 4 times under running tap water taking care not to dislodge the cells with a direct stream of water. The plates were tapped dry and 50 µL of 0.057 % (w/v in 1 % acetic acid) SRB solution was added to each well. The plates were incubated at room temperature for 30 minutes in dark and then rinsed four times with 200 µM 1 % acetic acid to remove unbound dye. The plates were blot dried on a paper towel. 200 µL of 10 mM Tris base was added to each well. The plates were kept on a shaker to solubilise the protein bound dye and absorbance was measured at 530 nm in a spectrophotometer. The plates treated with test compounds for 72 hours were also processed in an identical manner.

**CCK8 assay for multiple myeloma:**

For T₀ measurement, 10 µL of CCK8 was added to each of the wells and kept in the incubator for 90 minutes and absorbance was measured at 450 nm. The plates containing cells that were treated for 72 hours were also processed in an identical manner.
Calculation of GI50, TGI and LC50:
Percent growth (PG) was calculated relative to the control and zero measurement wells (T0) as follows.

\[
PG = \frac{OD_{530\text{test}} - OD_{530\text{T}_0}}{OD_{530\text{control}} - OD_{530\text{T}_0}} \times 100 \quad \text{(If OD}_{530\text{test}} > OD_{530\text{T}_0})
\]

\[
PG = \frac{OD_{530\text{test}} - OD_{530\text{T}_0}}{OD_{530\text{T}_0}} \times 100 \quad \text{(If OD}_{530\text{test}} < OD_{530\text{T}_0}).
\]

PG values were plotted against drug concentration to derive the following:

1. GI50: the concentration required to decrease PG by 50 % vs control

As detailed above, some of the compounds were screened for cell viability. The results obtained were tabulated in Table 1.

<table>
<thead>
<tr>
<th>Ex</th>
<th>Human Myeloma Cells</th>
<th>Human Prostate Cancer</th>
<th>Human Breast cancer</th>
<th>Human Colon cancer</th>
<th>Lung cancer</th>
<th>Prostate Cancer</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>GI50</td>
<td>GI50</td>
<td>GI50</td>
<td>Gliso</td>
<td>GI50</td>
<td>GIso</td>
</tr>
<tr>
<td>1</td>
<td>16.68</td>
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<td>57.7</td>
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</tr>
<tr>
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<td>18.95</td>
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</tr>
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<td>-</td>
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<tr>
<td>10</td>
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<td>-</td>
<td>3.4</td>
<td>-</td>
</tr>
<tr>
<td>19</td>
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</tr>
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<td>53</td>
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<td>1.1</td>
</tr>
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<td>5</td>
<td>1.66</td>
<td>-</td>
<td>1.2</td>
<td>6.7</td>
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<tr>
<td>55</td>
<td>0.92</td>
<td>0.9</td>
<td>1.33</td>
<td>-</td>
<td>1.1</td>
<td>7.6</td>
</tr>
</tbody>
</table>
CNS Protection: Measurement of cytotoxicity by using LDH Assay:

PC-12 (pheochromocytoma), a semi suspension cells were seeded in Poly-D Lysine coated plate and incubated overnight at 37 °C and 5% C02. After 24 hours, the cells were treated with test compounds along with 3-Nitropropionic acid and kept for 48 hours incubation at 37 °C, 5% C02. Lactate dehydrogenase (LDH) in the cell supernatant was estimated using an LDH kit for cytotoxicity (Roche, Cat. No.11644793001). To determine the LDH activity of supematants, 100 μL reaction mixture was added to each well and incubated for 30 minutes at 25 °C and the absorbance of the samples measured at 490 nm. The results obtained were tabulated below.

Table 2: CNS Protection

<table>
<thead>
<tr>
<th>Ex</th>
<th>PC12 Neuroprotection</th>
<th>Ex</th>
<th>PC12 Neuroprotection</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>36.6% @ 1 μM</td>
<td>14</td>
<td>100% @ 1 μM</td>
</tr>
<tr>
<td>4</td>
<td>77% @ 10 μM</td>
<td>19</td>
<td>77.8% @ 1 μM</td>
</tr>
<tr>
<td>5</td>
<td>77.3% @ 10 μM</td>
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<td>80.9% @ 1 μM</td>
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<td>68.7% @ 10 μM</td>
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<td>56.0% @ 1 μM</td>
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<td>38 % @ 1 μM</td>
</tr>
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<td>9</td>
<td>67.2% @ 1 μM</td>
<td>32</td>
<td>55 % @ 1 μM</td>
</tr>
<tr>
<td>10</td>
<td>100% @ 1 μM</td>
<td></td>
<td></td>
</tr>
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</table>
RAW 264.7 (Macrophages) - TNF-a protocol:
RAW 264.7 cells were seeded in a 24 well plate and incubated for 48 hours. After 48 hours, the cells were treated with various concentrations of the test compounds for 24 hours followed by lipopolysaccharide (LPS) stimulation (10 ng/mL) for 3 hours. TNF-a in the cell supernatant was estimated using an ELISA kit (R&D Systems) as per manufacturer's instructions.

RAW 264.7 (Macrophages) - IL-6 protocol:
RAW 264.7 cells were seeded in a 24 well plate and incubated for 48 hours. After 48 hours the cells were treated with various concentrations of the test compounds for 24 hours followed by LPS stimulation (100 ng/mL) for 3 hours. IL-6 in the cell supernatant was estimated using an ELISA kit (R&D Systems) as per manufacturer's instructions.

THP1 (Macrophages) - TNF-a protocol:
THP1 cells were seeded in a 24 well plate along with phorbol myristate acetate (PMA) (32 nM) and incubated for 24 hours. After 24 hours, the media were changed and cells were incubated for another 24 hours. Then cells were treated with various concentrations of the test compounds for 24 hours followed by LPS stimulation (10 ng/mL) for 4 hours. TNF-a in the cell supernatant was estimated using an ELISA kit (R&D Systems) as per manufacturer's instructions.

THP1 (Macrophages) - IL-6 protocol:
THP1 cells were seeded in 24 well plates along with PMA (32 nM) and incubated for 24 hours. After 24 hours media were changed and cells were incubated for another 24 hours. Then cells were treated with various concentrations of the test compounds for 24 hours followed by LPS stimulation (100 ng/mL) for 8 hours. IL-6 in the cell supernatant was estimated using an ELISA kit (R&D Systems) as per manufacturer's instructions.

In vitro metabolic stability in liver microsomes:
Metabolic stability is defined as the percentage of parent compound lost over time in the presence of liver microsomes, liver S9, or hepatocytes, depending on the goal of the assay. By understanding the metabolic stability of compounds early in discovery, compounds can be ranked for further studies, and the potential for a drug candidate to fail in development as a result of pharmacokinetic reasons may be reduced.
The stock solutions of test compound were prepared using DMSO or water. Incubation of reaction mixture including cryopreserved mouse or human liver microsomes (1 mg/mL), test compound (50 µM), and nicotinamide adenine dinucleotide phosphate (NADPH) for different time points, e.g. 10, 15, 30, and 60 minutes or single time points, e.g. 60 minutes. Reaction is started by the addition of NADPH and stopped either immediately or after 60 minutes for screening assay or at 5, 15, 30 and 60 minutes for a more precise estimate of clearance by addition of ice-cold acetonitrile, followed by sample preparation. Determination of loss of parent compound (compared to zero time point control and/or no NADPH-control) was done using HPLC or LC-MS methods. Metabolism was expressed as percentage of test compound metabolized after a certain time. A marker reaction and marker substrate (e.g. testosterone) was employed as quality criteria of the metabolic capability of the microsomes. (Rodrigues, A.D., et al. Biochemical Pharmacology, 1994, 48(12): 2147-2156). Metabolic stability was expressed as % metabolism of the compound after 30 minutes of incubation in the presence of active microsomes. Compound that had a % metabolism less than 30 % were defined as highly stable. Compound that had a metabolism between 30 % and 60 % were defined as moderately stable and compounds that showed a % metabolism higher than 60 % were defined as less stable. Some of the test compounds were found to be moderately stable.

Protein binding assay:

Dialysis membranes (Cellulose acetate membranes with 12,000-14,000 molecular weight cut-off) were charged by serially wetting in distilled water and distilled water containing 20 % ethanol for 60 and 20 minutes, respectively. Charged dialysis membranes were rinsed with distilled water three times and stored in isotonic sodium phosphate buffer until use. The 96-well dialysis apparatus was assembled by following the manufacturers instructions using the charged membranes. 0.15 mL of sodium phosphate buffer (pH 7.4) was placed on the dialysate side of each well and 0.15 mL of plasma spiked with the test compound (predetermined concentrations) on the other side, and the plate was completely sealed with adhesive membrane and incubated in a shaking dry incubator preset at 100 rpm at 37 °C to equilibrate for 8 hours (as determined previously). All samples were incubated in triplicates at predetermined concentrations. At the end of equilibration time, the volume of plasma and the buffer was measured for each well. 80 µL of plasma and the buffer was diluted
with an equal volume of acetonitrile and centrifuged for 10 minutes to precipitate the proteins. The supernatant was analyzed using HPLC. The test compound shows moderate plasma protein binding.

**Pharmacokinetics and BBB permeability studies of test compounds:**

Three separate sets of mice were administered orally with the test compounds at dose level of 50 mg/kg to check for its oral availability. Sample collection was staggered such that each time point resulted in n=3 to allow for minimal sampling volumes from each animal. Blood was collected at the specified time points post dosing using retro orbital bleeding method. Plasma was separated from the blood by centrifugation at 9,000 g for five minutes and processed by protein precipitation method using acidified organic solvent (0.1 % formic acid in acetonitrile). The processed samples were analyzed by the HPLC method. Following single oral administration of 50 mg/kg, some of test compounds were orally available with a C_{max} of around 0.35 mg/L and the concentration was observed up to 1.5 hours.

In addition, the test compounds were administered to separate sets of two animals for each time point at 15 mg/kg dose intravenously to check for its blood-brain barrier permeability. Cerebrospinal fluid (CSF) was collected by direct cisterna-magna (CM) puncture at the specified time points from anesthetized rats.

Following CSF collection, blood was collected immediately from same animal using retro orbital bleeding method in heparinized microfuge tubes. Plasma was separated from the blood by centrifugation at 9,000 g for five minutes. Following blood collection, animals were sacrificed and brain samples were isolated and collected in labelled microfuge tubes. Brain samples were homogenized with phosphate buffered saline buffer (pH-7.4). Plasma and brain homogenate samples were processed by protein precipitation method using organic solvent (acetonitrile) and CSF samples were injected directly into HPLC.

**Maximum tolerated dose determination:**

Maximum tolerated dose determination was carried out using 6-7 weeks old female severe combined immunodeficient (SCID) mice. The mice were housed in individually ventilated cages (IVC), maintained in 12 hours light dark cycle with standard laboratory chow diet and water *ad libitum* in controlled room temperature (22 ± 3 °C) and humidity (50 ± 20 %). The animals were grouped based on body weight and treated with test compound at 50 mg/kg i.p for seven days. After the treatment
period, the animals were observed for 14 days, during which body weight and clinical symptoms were recorded. Mean changes in body weight was calculated as compared to the control. On the day of termination, the animals were sacrificed using CO₂ asphyxiation and gross pathological examination carried out. Organs of interest were collected and subjected to histopathological analysis.

**Xenograft Study:**

The experiment was carried out using 6-7 weeks old female SCID mice. The mice were housed in IVC, maintained in 12 hours light dark cycle with standard laboratory chow diet and water *ad libitum* in controlled room temperature (22 ± 3 °C) and humidity (50 ± 20 %). Tumors rose from cells obtained from ATCC, USA and maintained *in vivo* by subcutaneous (s.c.) passage of tumor fragments (-30 mg) in healthy mice according to standard reporting procedures. Each experimental group included 6-8 mice bearing s.c tumors. Tumors were implanted into the auxiliary region using precision trochar and tumor growth was monitored by measuring diameters with a vernier caliper. Tumor volume (TV) was calculated according to the formula:

\[ TV = \frac{L \times W^2}{2} \]

L and W are the longest diameter and shortest diameter of the tumor respectively.

The compound treatment started when tumors were palpable (-100 mm³). Test compound was administered by per oral or by intra peritoneal once daily for a period of 21 days. Control mice were administered with vehicle at equivalent volume. Tumor size was measured twice a week and body weight taken daily prior to dosing. Parameters such as survival, change in the tumor volume, body weight and clinical symptoms were observed and recorded. Test compound efficacy was assessed by calculating tumor volume with respect to vehicle control

\[ \frac{T/C}{\%} = (\frac{1 - TV_{treatment}}{TV_{control}}) \times 100 \]

On day of termination, the animals were sacrificed and gross pathological examination was carried out. Tumor samples, organs of interest were collected and subjected to histopathological analysis and Target modulations. The tumor bearing animals (RPMI-8226 Xenograft) treated with test compound showed reduction in tumor volume as compared to untreated control.
**In vivo Inhibitory activity in Atopic Dermatitis Model**

Oxazolone induced dermatitis in mice was performed using the protocol described in Tamura T., et al., *European Journal of Pharmacology*, 2005, 524, 149-154. Balb/C mice were acclimatized to laboratory conditions five to seven days prior to the start of the experiment. They were randomly distributed to various groups based on body weight. The abdomen of animals was shaved using a small animal clipper. All the animals were sensitized with 15% oxazolone by application to the clipped abdomen (20 µL) 7 days before challenge. On 7th day, the animals were challenged with 2% oxazolone at the ears (20 µL per ear). Test compounds were applied over the ears of sensitized mice 30 minutes before and 4 hours after challenge. Before challenge (0 hour) and again post-challenge at 4 and 24 hours, the ear thickness was measured using a thickness gauge. Animals were sacrificed after 24 hours and ears collected by punch biopsy for ear weight and histopathology. Percent reduction in the ear thickness and ear weight was calculated using the following equation.

\[
\frac{\text{Ear thickness in Oxazolone group} - \text{Ear thickness in Treatment group}}{\text{Ear thickness in Oxazolone group} - \text{Ear thickness in Vehicle group}} \times 100
\]

\[
\frac{\text{Ear weight in Oxazolone group} - \text{Ear weight in Treatment group}}{\text{Ear weight in Oxazolone group} - \text{Ear weight in Vehicle group}} \times 100
\]

<table>
<thead>
<tr>
<th>Ex</th>
<th>Dose (µg/ear)</th>
<th>Oxazolone induced dermatitis % inhibition</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td>Ear Weight (24 hours)</td>
</tr>
<tr>
<td>7</td>
<td>500</td>
<td>26.74</td>
</tr>
<tr>
<td>23</td>
<td>500</td>
<td>47.14</td>
</tr>
<tr>
<td>151</td>
<td>500</td>
<td>26.30</td>
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From the foregoing description, one skilled in the art can easily ascertain the essential characteristics of this invention, and without departing from the spirit and scope thereof, make various changes and modifications of the invention to adapt it to various usages and conditions.
We claim:

1. A compound of formula (I),

   \[
   A - X - P - \text{CONH} - R \tag{I}
   \]

   their derivatives, analogs, tautomeric forms, stereoisomers, geometrical
   isomers, diastereomers, polymorphs, hydrates, solvates, pharmaceutically acceptable
   salts, metabolites, intermediates and prodrugs thereof;

   wherein A represents

   \[
   \begin{array}{c}
   \text{Ar} \\
   \text{Ar}^1 \\
   \text{Ar}^2
   \end{array}
   \]

   Ar represents substituted or unsubstituted groups selected from (C6-Cu)aryl, 5-
   15 membered heterocyclyl and 5-15 membered heteroaryl;

   Ar\(^1\) represents optionally substituted groups selected from (C6-Ci4)aryl, 5-15
   membered heterocyclyl and 5-15 membered heteroaryl;

   Ar\(^2\) represents substituted or unsubstituted groups selected from (C1-
   C6)alkylene, (C6-Ci4)arylene and 5-15 membered heteroarylene;

   B represents hydrogen, -COOR \(^1\), -CONR'\(^R\) \(^2\), -CHZNR'\(^R\) \(^2\), -CH\(^2\)OR',

   \(-\text{CH}_2\text{OCOR}'\(^R\) \(^2\), -\text{CH}^2\text{N}^\text{R} \(^R\) \(^2\), -\text{CH}_2\text{OR}'\(^R\) \(^2\), -\text{CH}_2\text{N}^\text{R} \(^R\) \(^2\)

   or substituted or unsubstituted groups selected from

   (Ci-C6)alkyl, (C2-C6)alkenyl, (C2-C6)alkynyl, (C6-Ci4)aryl and (C3-Ci2)cycloalkyl;

   B \(^1\) represents hydrogen, -COOR \(^1\), -CONR'\(^R\) \(^2\), -CH\(^2\)N\(^R\) \(^2\), -CH\(^2\)OR',

   -CH\(^2\)\text{OCOR}'\(^R\) \(^2\), -CH\(^2\)\text{N}^\text{R} \(^R\) \(^2\), -CH\(^2\)\text{OR}'\(^R\) \(^2\), -CH\(^2\)\text{N}^\text{R} \(^R\) \(^2\)

   or substituted or unsubstituted groups selected from

   (Ci-C6)alkyl, (C2-C6)alkenyl, (C2-C6)alkynyl, (C6-Ci4)aryl and (C3-Ci2)cycloalkyl;

   D represents hydrogen, -COOR \(^1\), -CONR'\(^R\) \(^2\), -CH\(^2\)N\(^R\) \(^R\) \(^R\), -CH\(^2\)OR',

   -CH\(^2\)\text{OCOR}'\(^R\) \(^R\), -CH\(^2\)\text{N}^\text{R} \(^R\) \(^R\), -CH\(^2\)\text{OR}'\(^R\) \(^R\), -CH\(^2\)\text{N}^\text{R} \(^R\) \(^R\)

   or substituted or unsubstituted groups selected from

   (C1-C6)alkyl, (C2-C6)alkenyl, (C2-C6)alkynyl, (C6-Ci4)aryl and (C3-Ci2)cycloalkyl;

   R\(^1\) represents hydrogen or substituted or unsubstituted groups selected from

   (Ci-C6)alkyl, (C3-Ci2)cycloalkyl, 5-15 membered heterocyclyl, (C6-Ci4)aryl, (C6-
   Ci4)aryl(Ci-C6)alkenyl, (C6-Ci4)alkynyl, (C6-Ci4)aryl(C2-C6)alkynyl, 5-15
   membered heteroaryl, 5-15 membered heteroaryl(C1-C6)alkenyl and 5-15 membered heteroaryl(C2-Ce)alkynyl;

   R\(^2\) represents hydrogen or substituted or unsubstituted groups selected from

   (Ci-C6)alkyl, (C2-C6)alkenyl, (C2-C6)alkynyl, (C3-Ci2)cycloalkyl, 5-15 membered

heterocyclyl, (C₆-C₁₄)aryl, (C₆-C₁₄)aryl(Cᵢ-C₆)alkyl, (C₆-C₁₄)aryl(C₂-C₆)alkenyl, (C₆-
C₁₄)aryl(C₂-C₆)alkynyl, 5-15 membered heteroaryl, 5-15 membered heteroaryl(C₁-
C₆)alkyl, 5-15 membered heteroaryl(C₂-C₆)alkynyl; or R¹ and R² combine together to form substituted or unsubstituted 3-7
membered ring having 0-3 heteroatoms selected from O, S and N;
when one of B¹ or D is hydrogen or unsubstituted alkyl, the other is neither of hydrogen nor of unsubstituted alkyl;

X represents a bond, -CO-, -SO₂-, -CS-, -CH₂-, -CONR³-, -CONR³CH₂₂,

-CH₂OOC-, -CONR³CO₂-, -CH₂NR³CO₂-, -CH₂NR³- or -CH₂NR³CH₂₂; wherein R³
represents hydrogen, (C₁-C₆)alkyl or (C₃-C₅)cycloalkyl;

P represents substituted or unsubstituted groups selected from,

\[ \begin{align*}
W, & \quad W¹, \quad W², \quad W³ \text{ and } W⁴ \text{ independently represents C or N;} \\
W⁵ \text{ represents O, S or N; } W⁶ \text{ represents C or N;} \\
\text{ring } Q¹ \text{ is substituted or unsubstituted } 4 \text{ to } 8 \text{ membered heterocyclyl ring;} \\
R⁴ \text{ represents hydrogen, halogen, hydroxy, nitro, amino, cyano or substituted or unsubstituted (Cᵢ-C₆)alkyl, amino(Cᵢ-C₆)alkyl, halo(Cᵢ-C₆)alkyl, (Cᵢ-C₆)alkoxy and halo(C₁-C₆)alkoxy;} \\
R \text{ represents -OH, ortho substituted aniline or substituted or unsubstituted group selected from aminoaryl and hydroxyaryl;}

\text{when the groups are substituted, the substituents are one or more groups,}
\text{selected from halogens, hydroxy, nitro, cyano, azido, nitroso, oxo (=O), thiooxy (=S),}
\text{amino, hydrazino, formyl, (C₁-C₆)alkyl, halo(C₁-C₆)alkyl, (CrC₆)alkoxy, halo(C₁-
C₆)alkoxy, (C₆-C₁₄)arylalkoxy, (C₃-C₅)cycloalkyl, (C₃-C₅)cycloalkyloxy, (C₆-
C₁₄)aryl, (C₆-C₁₄)arylalkoxy, 5-15 membered heterocyclyl, 5-15 membered heteroaryl,}
\text{(Cᵢ-C₆)alkylamino, -SONR⁺R⁺b, -SO₂NR⁺R⁺b, -SR⁺a, -SOR⁺a, -SO₂⁺R⁺a,}
\text{-COOR⁺a, -C(ₒ)R⁺b, -C(S)R⁺a, -C(ₒ)NR⁺R⁺b, -C(S)NR⁺R⁺b, -NR⁺R⁺C(ₒ)NR⁺R⁺c,}
\text{-NR⁺C(S)NR⁺R⁺c, -N(R⁺a)SOR⁺b, -N(R⁺a)SO₂⁺R⁺b, -NR⁺C(ₒ)OR⁺b, -NR⁺R⁺b,}
\text{-NR⁺C(ₒ)R⁺b, -NR⁺C(S)R⁺b, -OR⁺a, -OR⁺C(ₒ)OR⁺b, -OC(ₒ)NR⁺R⁺b, -OC(ₒ)R⁺a,}
\text{-R⁺NR⁺R⁺c and -R⁺aOR⁺b, wherein R⁺a,}
R^b and R^c in each of the above groups independently represents hydrogen or optionally substituted groups selected from (Ci-Ce)alkyl, (Ci-C_6)alkylene, (C_3-C_2)cycloalkyl, (C_6-C_4)aryl, (C_6-C_4)aryl(C_1-C_6)alkyl, 5-15 membered heterocyclyl, 5-15 membered heteroaryl and 5-15 membered heteroaryl(C_1-C_6)alkyl; or R^a, R^b or R^c can also combine to form a substituted or unsubstituted 3-10 membered heterocyclic ring including spiro-fused heterocyclic ring having 0-3 heteroatoms; the substituents are optionally further substituted by one or more substituents.

2. A compound of formula (I) as claimed in claim 1, wherein the compound is selected from the compound of formula (IA),

```
A^a -> X^a -> p^1 -> CONH -> R^x (IA)
```

their derivatives, analogs, tautomeric forms, stereoisomers, geometrical isomers, diastereomers, polymorphs, hydrates, solvates, pharmaceutically acceptable salts, metabolites, intermediates and prodrugs thereof;

wherein:

- A^a represents substituted or unsubstituted groups selected from (Ce-Cio)aryl, 5-10 membered heterocyclyl and 5-10 membered heteroaryl;
- Ar^1 represents optionally substituted groups selected from (C_6-Cio)aryl, 5-10 membered heterocyclyl and 5-10 membered heteroaryl;
- Ar^2 represents substituted or unsubstituted groups selected from (C_6-Cio)arylene and 5-10 membered heteroarylene;
- B^a represents hydrogen or substituted or unsubstituted groups selected from (C_1-C_6)alkyl and (C_3-C_6)cycloalkyl;
- B^1 represents hydrogen, -CONR^1R^2 or substituted or unsubstituted groups selected from (Ci-C_6)alkyl and (C_3-C_6)cycloalkyl;
- D^a represents hydrogen, -COOR^1, -CONR^1R^2 or substituted or unsubstituted groups selected from (Ci-C_6)alkyl, (C_2-C_6)alkenyl, (C_2-C_6)alkynyl, (C_6-Cio)aryl and (C_3-C_6)cycloalkyl;

when one of B^1 or D^a is hydrogen or unsubstituted alkyl, the other is neither of hydrogen nor of unsubstituted alkyl;
R$^{1a}$ represents hydrogen or substituted or unsubstituted groups selected from 
(C$_{1^{-}}$C$_{6}$)alkyl and (C$_{3^{-}}$C$_{6}$)cycloalkyl;

R$^{2a}$ represents hydrogen or substituted or unsubstituted groups selected from 
(Ci-C$_{6}$)alkyl and (C$_{3^{-}}$C$_{6}$)cycloalkyl;
or R$^{1a}$ and R$^{2a}$ combine together to form substituted or unsubstituted 3-7 
membered ring having 0-3 heteroatoms selected from O, S and N;

X$^{a}$ represents a bond, -CO-, -CH$_{2}$-, -CONR$_{3a}$-, -CONR$_{3}^{3a}$CH$_{2}$- or -CH$_{2}$NR$_{3a}$;

R$^{3a}$ represents hydrogen, (Ci-C$_{6}$)alkyl or (C$_{3^{-}}$C$_{6}$)cycloalkyl;

$^{[p]}$ represents 

T represents C, S, O or N; W$^{1b}$ represents C, S, O or N; W$^{2b}$ represents C or N;

W$^{3b}$ represents C or N;
a is an integer selected from 1 and 2;
b at each occurrence is independently selected from an integer 0 and 1;

"----" represents single or double bond;

R$^{d}$ represents hydrogen, halogen, hydroxy, nitro, amino, cyano or substituted or 
unsubstituted (Ci-C$_{6}$)alkyl, amino(Ci-C$_{6}$)alkyl, halo(Ci-C$_{6}$)alkyl, (Ci-C$_{6}$)alkoxy and 
halo(Ci-C$_{6}$)alkoxy;

R$^{s}$ represents OH or

wherein the substituents are one or more groups, selected from halogens, hydroxy, 
nitro, cyano, amino, formyl, (Ci-Ce)alkyl, halo(Ci-C$_{6}$)alkyl, (Ci-Ce)alkoxy, (C$_{6^{-}}$
C$_{14}$)aryl, (C$_{6^-}$C$_{4}$)aryloxy, (Q-Ce$^{i}$kylamino, -COOR$^{a}$, -C(0)NR$_{a}$R$_{b}$, -SR$_{a}$, -SOR$_{a}$ and 
-S0$_{2}$$^{a}$R$_{a}$, wherein R$^{a}$, R$^{b}$ or R$^{s}$ in each of the above groups independently 
represents hydrogen or optionally substituted groups selected from (C$_{1}$-C$_{6}$)alkyl,
(C$_{3^{-}}$C$_{4}$)cycloalkyl and (C$_{6^-}$C$_{4}$)aryl; the substituents are optionally further substituted 
by one or more substituents.

3. The compound of formula (I) as claimed in claim 1, selected from the group 
consisting of:

2-(2,3-Diphenylacryloyl)-N-hydroxy-1,2,3,4-tetrahydroisoquinoline-7-
carboxamide;
2-(3-(4-Fluorophenyl)-2-(4-fluorophenyl)acryloyl)-N-hydroxy-1,2,3,4-tetrahydroisoquinoline-7-carboxamide;
2-(3-(3,4-Dimethoxyphenyl)-2-(4-fluorophenyl)acryloyl)-N-hydroxy-1,2,3,4-tetrahydroisoquinoline-7-carboxamide;
2-(2-(2,4-Difluorophenyl)-3-phenylacryloyl)-N-hydroxy-1,2,3,4-tetrahydroisoquinoline-7-carboxamide;
2-(2-(4-Fluorophenyl)-3-(4-methoxyphenyl)acryloyl)-N-hydroxy-1,2,3,4-tetrahydroisoquinoline-7-carboxamide;
2-(2-(4-Fluorophenyl)-3-(4-p-tolylacryloyl))-N-hydroxy-1,2,3,4-tetrahydroisoquinoline-7-carboxamide;
2-(3-(3,4-Dimethoxyphenyl)-2-(4-methoxyphenyl)acryloyl)-N-hydroxy-1,2,3,4-tetrahydroisoquinoline-7-carboxamide;
2-(2-(3,4-Dimethoxyphenyl)-3-(3-fluorophenyl)acryloyl)-N-hydroxy-1,2,3,4-tetrahydroisoquinoline-7-carboxamide;
2-(2,3-Z,3s-(3,4-Dimethoxyphenyl)acryloyl)-N-hydroxy-1,2,3,4-tetrahydroisoquinoline-7-carboxamide;
2-(2-(Benzo[d][1,3]dioxol-5-yl)-3-(4-fluorophenyl)acryloyl)-N-hydroxy-1,2,3,4-tetrahydroisoquinoline-7-carboxamide;
2-(2-(4-Fluorophenyl)-3-(3-phenoxyphenyl)acryloyl)-N-hydroxy-l, 2,3,4-tetrahydroisoquinoline-7-carboxamide;
2-(2-(3-Chlorophenyl)-3-phenylacryloyl)-N-hydroxy-1,2,3,4-tetrahydroisoquinoline-7-carboxamide;
2-(2-(3-Fluorophenyl)-3-phenylacryloyl)-N-hydroxy-1,2,3,4-tetrahydroisoquinoline-7-carboxamide;
2-(2-(2-Fluorophenyl)-3-phenylacryloyl)-N-hydroxy-1,2,3,4-tetrahydroisoquinoline-7-carboxamide;
2-(2-(2-Chloro-4-fluorophenyl)-3-phenylacryloyl)-N-hydroxy-1,2,3,4-tetrahydroisoquinoline-7-carboxamide;
N-Hydroxy-2-(3-phenyl-2-p-tolylacryloyl)-1,2,3,4-tetrahydroisoquinoline-7-carboxamide;
2-(3-(4-Fluorophenyl)-2-phenylacryloyl)-N-hydroxy-1,2,3,4-tetrahydroisoquinoline-7-carboxamide;
2-(2-(4-Fluorophenyl)-3-(thiophen-2-yl)acryloyl)-N-hydroxy-1,2,3,4-tetrahydroisoquinoline-7-carboxamide;
2-(3-(2,4-Dimethoxyphenyl)-2-(3-fluorophenyl)acryloyl)-N-hydroxy-1,2,3,4-tetrahydroisoquinoline-7-carboxamide;
2-(3-(4-Chlorophenyl)-2-phenylacryloyl)-N-hydroxy-1,2,3,4-tetrahydroisoquinoline-7-carboxamide;
2-(2-(2-Chlorophenyl)-3-phenylacryloyl)-N-hydroxy-1,2,3,4-tetrahydroisoquinoline-7-carboxamide;
2-(3-(2,4-Dimethoxyphenyl)-2-(4-fluorophenyl)acryloyl)-N-hydroxy-1,2,3,4-tetrahydroisoquinoline-7-carboxamide;
N-Hydroxy-2-(2-(naphthalen-2-yl)-3-phenylacryloyl)-1,2,3,4-tetrahydroisoquinoline-7-carboxamide;
2-(2-(4-(N,N-Dimethylamino)phenyl)-3-phenylacryloyl)-N-hydroxy-1,2,3,4-tetrahydroisoquinoline-7-carboxamide;
N-Hydroxy-2-(3-(4-methoxyphenyl)-2-phenylacryloyl)-1,2,3,4-tetrahydroisoquinoline-7-carboxamide;
2-(2,3-6w(4-Methoxyphenyl)acryloyl)-N-hydroxy-1,2,3,4-tetrahydroisoquinoline-7-carboxamide;
2-(3-(2-Fluorophenyl)-2-(4-fluorophenyl)acryloyl)-N-hydroxy-1,2,3,4-tetrahydroisoquinoline-7-carboxamide;
2-(2-(4-Fluorophenyl)-3-(5-methylthiophen-2-yl)acryloyl)-N-hydroxy-1,2,3,4-tetrahydroisoquinoline-7-carboxamide;
2-(2-(4-Fluorophenyl)-3-(3-nitrophenyl)acryloyl)-N-hydroxy-1,2,3,4-tetrahydroisoquinoline-7-carboxamide;
2-(3-(3,4-Dimethoxyphenyl)-2-(thiophen-2-yl)acryloyl)-N-hydroxy-1,2,3,4-tetrahydroisoquinoline-7-carboxamide;
2-(2-(2-Chlorophenyl)-3-(4-fluorophenyl)acryloyl)-N-hydroxy-1,2,3,4-tetrahydroisoquinoline-7-carboxamide;
N-Hydroxy-2-(3-(4-methoxyphenyl)-2^-tolylacryloyl)-1,2,3,4-tetrahydroisoquinoline-7-carboxamide;
5-(2-(4-Fluorophenyl)-3-phenylacryloyl)-N-hydroxy-4,5,6,7-tetrahydrothieno[3,2-c]pyridine-2-carboxamide;
5-(2-(3-Fluorophenyl)-3-phenylacryloyl)-N-hydroxy-4,5,6,7-tetrahydrothieno[3,2-c]pyridine-2-carboxamide;
2-(2-(4-Fluorophenyl)-3-(7-(hydroxycarbamoyl)-3,4-dihydroisoquinolin-2(1H)-yl)-3-oxoprop-1-enyl)benzoic acid;
2-(2-(2-Chlorophenyl)-3-(4-methoxyphenyl)acryloyl)-N-hydroxy-1,2,3,4-tetrahydroisoquinoline-7-carboxamide;
2-(3-(3,4-Difluorophenyl)-2-phenylacryloyl)-N-hydroxy-1,2,3,4-tetrahydroisoquinoline-7-carboxamide;
2-(3-(3,4-Difluorophenyl)-2-p-tolylacryloyl)-N-hydroxy-1,2,3,4-tetrahydroisoquinoline-7-carboxamide;
2-(2-(4-Chlorophenyl)-3-phenylacryloyl)-N-hydroxy-1,2,3,4-tetrahydroisoquinoline-7-carboxamide;
1-(2,3-Diphenylacryloyl)-N-hydroxyindoline-5-carboxamide;
5-(2,3-Diphenylacryloyl)-N-hydroxy-4,5,6,7-tetrahydrothieno[3,2-c]pyridine-2-carboxamide;
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4. A pharmaceutical composition comprising a compound of formula (I), according to claim 1, 2 or 3, as an active ingredient, along with a pharmaceutically acceptable carrier.

5. The compound of formula (I) as claimed in claim 1, 2 or 3, wherein the said compound is efficiently transported across the blood-brain barrier.

6. The compound of formula (I) as claimed in claim 1, 2 or 3, for use in inhibiting HDAC in a cell.
7. The compound of formula (I) as claimed in claim 1, 2 or 3, for use in the treatment of a condition mediated by HDAC.

8. The compound of formula (I) as claimed in claim 1, 2 or 3, for use in the treatment of proliferative conditions or cancer.

9. The compound of formula (I) as claimed in claim 1, 2 or 3, for use in the treatment of proliferative conditions or cancer in combination with other clinically relevant cytotoxic agents or non-cytotoxic agents or radiation or monoclonal antibodies.

10. The compound of formula (I) for use as claimed in claim 7 or 8, wherein the diseases are selected from lung cancer, non-small-cell lung cancer, small cell lung cancer, colon cancer, fibrosarcoma, kidney cancer, lymphoma, leukemia, skin cancer, pancreatic cancer, breast cancer, prostate cancer, bone cancer, oral cancer, multiple myeloma, brain cancer, head and neck cancer, ovarian cancer, gastric cancer, liver cancer, cervical cancer, solid tumors, cutaneous T-cell lymphoma, acute myeloid leukemia, chronic lymphocytic leukemia and acute lymphoblastic leukemia.

11. The compound of formula (I) as claimed in claim 1, 2 or 3, for use in the treatment of inflammatory diseases or autoimmune diseases.

12. The compound of formula (I) for use as claimed in claim 11, wherein the inflammatory diseases are selected from rheumatoid arthritis, inflammatory bowel disease, psoriasis, dermatitis, granuloma, uveitis, chronic obstructive pulmonary disease (COPD), ulcerative colitis, Crohn's disease, multiple sclerosis and sepsis.

13. The compound of formula (I) as claimed in claim 1, 2 or 3, for use in the treatment of Central Nervous System disorders.

14. The compound of formula (I) as claimed in claim 1, 2 or 3, for use in the treatment of neurodegenerative disorders selected from Huntington's disease, Alzheimer's disease, Friedrich's ataxia, stroke and Parkinson's disease.

15. The compound of formula (I) as claimed in claim 1, 2 or 3, for inhibiting HDAC6 in a cell.

16. The compound of formula (I) as claimed in claim 1, 2 or 3, for inhibiting HDAC6 in a subject.

17. The compound of formula (I) as claimed in claim 1, 2 or 3, for use in the treatment of malaria, fungal and HIV infections.
INTERNATIONAL SEARCH REPORT

International application No
PCT/IN2012/00147

A. CLASSIFICATION OF SUBJECT MATTER
A61K31/4725 A61K31/5Q6 A61K31/55 C07D217/Q6 C07D495/04
C07D401/06 C07D209/08 C07D223/16 C07D409/06 C07D491/04

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)
A61K C07D

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

Electronic data base consulted during the international search (name of data base and, where practicable, search terms used)
EPO-Internal

C. DOCUMENTS CONSIDERED TO BE RELEVANT

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<td>WO 2009/053808 A2 (ORCHID RES LAB LTD [IN] ; RAJAGOPAL SRIDHARAN [IN] ; KACHHADIA VI RENDRA) 30 April 1 2009 (2009- 04-30) Hi stone acetyl ase inhi bi tors of general formul a (I), in claim 1, parti ally encompassing the compounds of general formul a 1 and of claim 3 of the present applicati on, and the r use to treat relevant di seases: see cl aim 1, compound of examples 1-166; in parti cul ar compound 105 (page 69), and experiments i n tables 1 and 2 in pages 98-105, cl aims ----- */ -.</td>
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Further documents are listed in the continuation of Box C. See patent family annex.

* Special categories of cited documents:
  * "A" document defining the general state of the art which is not considered to be of particular relevance
  * "E" earlier application or patent but published on or after the international filing date
  * "L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)
  * "O" document referring to an oral disclosure, use, exhibition or other means
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"Z" document member of the same patent family

Date of the actual completion of the international search
17 July 2012

Date of mailing of the international search report
08/08/2012

Name and mailing address of the ISA/
European Patent Office, P.B. 5818 Patentlaan 2
NL-2280 HV Rijswijk
tel. (+31-70) 340-2040,
Fax: (+31-70) 340-3016

Authorized officer
Veronese, Andrea
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