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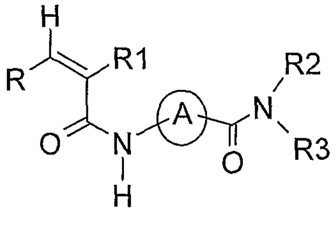
(54) **Title:** STILBENE LIKE COMPOUNDS AS NOVEL HDAC INHIBITORS



(I)

(57) **Abstract:** The present invention relates to novel stilbene like compounds of the general formula (I), their derivatives, analogs, tautomeric forms, stereoisomers, polymorphs, hydrates, solvates, pharmaceutically acceptable salts and compositions, metabolites and prodrugs thereof. The present invention more particularly provides novel stilbene like compounds of the general formula (I). Also included is a method for treatment of cancer, psoriasis, proliferative conditions and conditions mediated by HDAC, in a mammal comprising administering an effective amount of a novel compound of formula (I) as described above.

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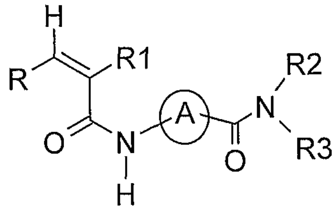
STILBENE LIKE COMPOUNDS AS NOVEL HDAC INHIBITORS

Field of the invention

The present invention relates to novel stilbene like compounds of the general formula (I), their derivatives, analogs, tautomeric forms, stereoisomers, polymorphs, hydrates, solvates, pharmaceutically acceptable salts and compositions metabolites and prodrugs thereof. The present invention more particularly provides novel, stilbene like compounds of the general formula (I).



(I)

The present invention also provides a process for the preparation of the above said novel stilbene like compounds of the formula (I), their derivatives, analogs, stereoisomers, polymorphs, hydrates, solvates, their pharmaceutically acceptable salts and compositions metabolites and prodrugs thereof. .

Background of the invention

The present invention relates to potentially pharmaceutical compositions and in particular to new molecules as active ingredients, that are used in particular as anticancer agents. Compounds of the general formula (I), or pharmaceutically acceptable salts thereof according to the present invention have an ability of inhibiting histone deacetylating enzyme and of inducing differentiation and are useful as therapeutic or ameliorating agent for diseases that are involved in cellular growth such as malignant tumors, autoimmune diseases, skin diseases, infections etc.

The novel stilbene like compounds (1) of the present invention are useful for the treatment cancer, which is one of the leading causes of death in the present society. A great deal of effort has been underway to treat various forms of cancer for decades and until recently. Chemoprevention of cancer is receiving its due share of attention.

Cancer may affect people at all ages, but risk tends to increase with age, due to the fact that DNA damage becomes more apparent in aging DNA. It is one of the principal causes of death in developed countries, more than 11 million people are diagnosed with cancer every year, and it is estimated that there will be 16 million new cases every year by 2020. Cancer causes 7 million deaths every year or 12.5% of deaths worldwide. Cancer is a leading cause of death worldwide particularly affecting major portion of people in industrialized world than in the non-industrialized world. From a total of 58 million deaths worldwide in 2005, cancer accounts for 7.6 million (or 13%) of all deaths. The main types of cancer leading to overall cancer mortality are Lung (1.3 million deaths/year), Stomach (almost 1 million deaths/year), Liver (662,000 deaths/year), Colon (655,000 deaths/year) and Breast (502,000 deaths/year). Deaths from cancer in the world are projected to continue rising, with an estimated 9 million people dying from cancer in 2015 and 11.4 million dying in 2030 (Parkin D etal, 2002)

Every cell constantly faces decisions. Should it divide? Or should it differentiate? Or should it die (Apoptosis)? Proper development and tissue homeostasis rely on the correct balance between division and apoptosis. Too much apoptosis leads to tissue atrophy such as in Alzheimer's disease. Too much proliferation or too little apoptosis leads to cancer. Cancer is a disease of multifactorial origin characterized by uncontrolled division of cells; when the cancer cell faces spatial restrictions, due to uncontrolled proliferation in an organ of the body, the ability of the cell to invade other distinct tissues occurs by a process defined as "Metastasis" the stage in which cancer cells are transported through the bloodstream or lymphatic system.

The most common treatment for easily accessible cancer is surgical removal of diseased tissues and radiation. The choice of treatment for in-accessible tumors is chemotherapy. Also chemotherapy is given as additional insurance for most cancer as it is difficult to access the extent of metastasis.

Most clinically revelant anticancer drugs currently used in the clinic, interfere with cell division and hence are not highly selective to cancer cells and there are potential chances, that chemotherapy can lead to secondary cancers in due course of time. Also the quality of life is hampered in the patients upon chemotherapy, hence there is an unmet medical need for treating cancer patients without affecting the quality of life. (Hill R P et al., 2005 & Kleinsmith, L J, 2006).

The cell cycle deregulation and the molecular basis of cancer cell growth has been thoroughly exploited in the recent years. Inhibition of signal transduction has become a viable and attractive avenue in biomedical cancer research based on the discovery of a large number of somatic mutations in many different types of cancer that lead to deregulated growth signal transduction and subsequent aberrant growth, invasion, tumor-derived angiogenesis and metastasis. Most of the noncytotoxic drugs that have been recently developed include Protein kinase inhibitors such as Gleevec, Iressa and Tarceva, Tyrosine kinase inhibitors like Leflunomide. Glivec™ (STI571), is an inhibitor of the bcr-abl kinase and CML. PKIl 66, on the other hand, is a dual inhibitor of EGF receptor (HER 1) as well as erbB (HER 2). EGF-receptor and PTK787, potent inhibitors of VEGF-receptor 2 (KDR) are able to suppress tumor growth via suppression of tumor angiogenesis and also these agents have entered clinical trials in tumor patients (Alex Matter, M.D., 2002). These types of orally active and relatively well-tolerated compounds can be used in the clinics; either as single agents or in combination with other well established cytotoxic agents.

Cytokines play an important role in the communication between cells of multicellular organisms. Early studies indicate that B cells lineage tend to secrete IL6 in response to host immune defense mechanisms, but in recent decades studies have indicated elevated levels of IL6 in various cancer phenotypes. IL6 promotes survival and proliferation of certain cancerous cell lines through the phosphorylation of STAT3 (Bharti et al., Verma et al., Kerr et al.). Inhibitors of Jak/Stat pathway likely represent potential therapeutic targets for cancer (Catlett Falcone et al., 1999; Alas and Bonavida, 2003; Burdelya et al., 2002)

IL6 has been found to be a growth factor for multiple myeloma cells; anti IL6 antibodies were shown to block myeloma cell proliferation in a leukemic patients (Lkein et al., Blood, 78, (5), pp 1198-1204,1991 and Lu et al., Eur. J. Immunol., 22. 2819 -24,1992). A need exists for a compound that blocks IL6 mediated Stat3 activation at lower concentration and suppresses expression of proto-oncogenes like c-myc, which is over expressed, rearranged or mutated in many malignancies (Hallek et al., 1998; Selvanayagam et al., 1988; Jernberg-Wiklund et al., 1992; Kuehl et al., 1997).

Elevation of inflammatory cytokine levels, particularly IL-6 and TNF-α also appears to be associated with the Cancer-related cachexia, a syndrome involving loss of adipose and skeletal muscle tissue, and one that is not responsive to increased caloric intake. Cachexia may also be related to the role of acute phase proteins. The acute phase response and production of acute phase proteins (e.g., C-reactive protein CRP) are mediated by IL-6. Studies correlate elevated levels of IL-6 elevate acute phase proteins, which, interestingly, are also associated with increased weight loss and decreased survival. Thus, with elevated IL-6 levels, amino acid metabolism is directed away from peripheral tissues to the liver for production of acute phase proteins. This in turn leads to muscle wasting, which is a component of cachexia. Accordingly, the cytokine-induced acute phase response may be a primary component of cancer-related cachexia. Moreover, diminishing or blocking IL-6 activity in animal models attenuates cachexia, further demonstrating the essential role IL-6 plays in the development of this syndrome.

Resveratol, a representation of hydroxystilbene, is a plytoalexin present in grapes and other food products and has received special attention. It is known to possess a variety of biological significances such as cancer chemo-preventive activity, anti-inflammatory activity through inhibition of cyclooxygenase. It also inhibits arachidonate release, MAPK activation, protein kinase and degruanulation of mast cells and is a known antioxidant having anti-cancer as well as anti-diabetic activity. It has been suggested as a potential cancer chemo-preventive agent based on its striking inhibitory effects on cellular events associated with cancer initiation, promotion, and progression. This triphenolic stilbene has also displayed in vitro growth inhibition in a number of human cancer cell lines.

Hypoglycemic activity of a naturally occurring pterostilbene, trans-1-(3,5-dimethoxyphenyl-2-(4-hydroxyphenyl)ethylene, and its isolation from the heartwood of pterocarpus marsupium have been reported by Manickam et al, J.Natu.Prod., 1997, 60:609-610.

NF-IcB that plays an important role in INOS (inducible nitric oxide syntheses) expression is one of the targets of various potential anti-inflammatory agents including Resveratol.

The first isolation of histone deacetylase was described in 1964 from crude nuclear extracts of cells, but the molecular characterization of isoforms of the enzyme has been achieved only recently. Inhibitors of histone deacetylase (HDACs) are zinc hydrolase's responsible for the deacetylation of N-acetyl lysine residues of histone and nonhistone protein substrates. Human HDACs are classified into two distinct classes, the HDACs and sirtuins. The HDACs are devised into two subclasses based on their similarity to yeast histone deacetylases, RPD 3 (class I includes HDAC 1, 2, 3, 8, and 11) and Hda 1 (class II includes HDAC 4, 6, 7, 9, and 10). All of the HDACs have a highly conserved zinc dependent catalytic domain. There is growing evidence that the acetylation state of proteins and thus the HDAC enzyme family plays a crucial role in the modulation of a number of biological processes, including transcription and cell cycle.

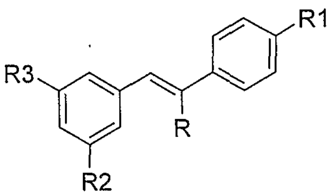
Transcriptional regulation is a major event in cell differentiation, proliferation and apoptosis. Transcriptional activation of a set of genes determines cell destination and for this reason transcription is tightly regulated by a variety of factors. One of its regulatory mechanisms involved in the process is an alteration in the tertiary structure of DNA, which affects transcription factors to their target DNA regiments. Nucleosomal integrity is regulated by the acetylating status of the core histone, with the result being permissiveness to transcription. The acetylating status of the histone is governed by the balance of activities of the histone acetyl transferase (HAT) and histone deacetylase (HDAC). Recently HDAC inhibitors have been found to arrest growth and apoptosis in several types of cancer cells, including colon cancer, t-cell lymphoma and erythroleukemic cells.

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

Several structural classes of HDAC inhibitors have been identified and are reviewed in Marks, P.A. et al., J. Natl. Cancer Inst., 92, (2000), 1210-1215. More specifically WO 98/55449 and US patent 5,369,108 report alkanoyl hydroxamates with HDAC inhibitory activity.

Few prior art references, which disclose the closest compounds, are given here:

I). **US 6624197 Bl** discloses a class of novel diphenylethylenes of the formula I,

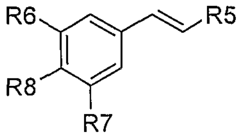


(I)

wherein R is hydrogen or --CO_2Z, Z is hydrogen or a cation; and Ri, R_2 and R3 are each independently H, —OH or —OR_4, wherein R_4 is linear or branched alkyl of 1-12 carbon atoms; with the condition that when R is hydrogen and $R_2 = R_3 =$ -OMe, then

Ri is not —OH. The configuration around the double bond may be E/Z.

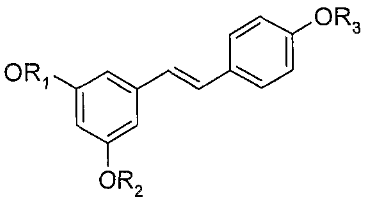
A novel class of styrenes of the formula II is also provided,



(II)

wherein R_5 is hydrogen or methyl; R_6 and R_7 are independently hydrogen or OMe; R_8 is hydrogen or hydroxy. The configuration around the double bond may be E/Z. Pharmaceutical compositions of compounds of the formula I or II are provided for the treatment of diabetes comprising of therapeutically effective amount of the compounds in a physiologically acceptable carrier. A method of treating diabetes is also provided comprising a step of orally administering to a subject suffering from a diabetic condition a therapeutically effective amount of a compound of formula I or II.

II). US 20050038125 discloses the invention related to a method for the treatment and/or prevention of disorders with elevated PGE_2 (such as arthritis, fibromyalgia and pain) and/or LTB_4 levels (such as asthma, allergy, arthritis, fibromyalgia and inflammation), comprising administering to a mammal an effective amount of pterostilbene component (PS .component), a pharmaceutically acceptable salt of PS component or a precursor of PS component, wherein the PS component has the formula 1 as shown below



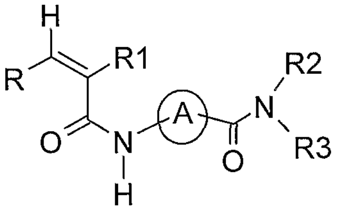
in which R_1, R_2 and R_3 are independently selected from hydrogen, Ci-so hydrocarbyl, Ci-50 substituted hydrocarbyl, C_1-So heterohydrocarbyl, C_1-So substituted heterohydrocarbyl; and wherein at least one of Ri and R_2 is not hydrogen

Objective of the invention

Due to unmet medical needs and also as all of us know, cancer is one of the leading causes of death in the present society, we focused our attention to identify novel small molecule anticancer agents, particularly focusing on HDAC inhibitors. Our sustained efforts have resulted in novel anticancer agents of the formula (I). Histone acetylation and deacetylation play an essential role in modifying chromatin structure and regulating gene expression in eukaryotic cells. Hyper acetylated histones are generally found in transcriptionally active genes and in transcriptionally silent regions of the genome. Key enzymes, which modify histone proteins and thereby regulate gene expression, are histone acetyl transferases (HATs) and histone deacetylases (HDACs). Compounds able to inhibit HDAC activity i.e. HDAC inhibitors such as Trichostatin A (TSA), Trapoxin (TPX), Suberoylanilide hydroxamic acid (SAHA), Sodium butyrate (NaB), Sodium valproate (VPA), Cyclic hydroxamic acid containing peptides (CHAPs), Depsipeptide FK-228 and MS-275 can de-repress these genes, resulting in antiproliferative effects in vitro and anti tumor effects in vivo.

Summary of the invention

The present invention relates to novel stilbene like compounds of the general formula (I),

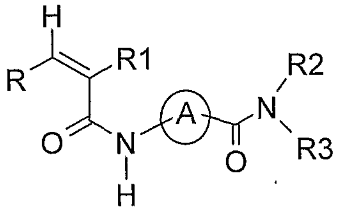


(I)

their derivatives, analogs, tautomeric forms, stereoisomers, polymorphs, solvates, pharmaceutically acceptable salts and compositions, metabolites and prodrugs thereof, wherein A represents $-(CH_2)_n$ which may be optionally substituted or unsubstituted by groups selected from aryl, aralkyl, heteroaryl and the like, which may be further substituted; R and Ri represent optionally substituted or unsubstituted groups selected from aryl, heteroaryl and benzo fused heteroaryl; wherein R_2 and R_3 represent optionally substituted or unsubstituted groups which may be same or different and represents hydrogen,, hydroxy, alkyl, alkoxy, benzyloxy acetyl, cycloalkyl, aryl, heterocyclyl, heteroaryl, benzofused heteroaryl; n is an integer in the range **of** 1 to 8.

Detailed description of the invention

The present invention relates to novel stilbene like compounds of the general formula (I),



(I)

their derivatives, analogs, tautomeric forms, stereoisomers, polymorphs, solvates, pharmaceutically acceptable salts and compositions metabolites and prodrugs thereof, wherein A represents -$(CH_2)_n$ which may be optionally substituted or unsubstituted by groups selected from aryl, arylalkyl, heteroaryl and the like, which may be further substituted, the substitutents may be selected from hydroxy, halogen and the like. .

Suitable groups represented by R and Ri represent aryl groups such as phenyl, naphthyl and the like which may be substituted; heteroaryl groups such as pyridyl, thienyl, furyl, pyrrolyl, oxazolyl, thiazolyl, imidazolyl, isooxazolyl, oxadiazolyl, triazolyl, thiadiazolyl, tetrazolyl, pyrimidinyl, pyrazinyl, pyridazinyl and the like, which may be substituted and benzo fused heteroaryl groups such as quinoline, quinoxaline, acridine, phenazine and the like which may be substituted.

Suitable groups represented by R_2 and R_3 may be selected from hydrogen, hydroxyl, substituted or unsubstituted groups selected from, linear or branched (Q-C_4) alkyl groups such as methyl, ethyl, n-propyl, isopropyl, n-butyl, isobutyl, t-butyl and the like, alkoxy groups such as methoxy, ethoxy, propoxy, n-butoxy, isobutoxy, t-butoxy and the like; benzyloxy; acetyl; benzyloxy acetyl; cycloalkyl groups such as cyclohexyl, cycloheptyl, cyclooctyl and the like; aryl groups such as phenyl, naphthyl and the like; heterocyclyl groups such as pyrrolidinyl, thiazolidinyl, oxazolidinyl, morpholinyl, thiomorpholinyl, piperidinyl, piperazinyl, and the like; heteroaryl groups such as pyridyl, thienyl, furyl, pyrrolyl, oxazolyl, thiazolyl, imidazolyl, isooxazolyl, oxadiazolyl, triazolyl, thiadiazolyl, tetrazolyl, pyrimidinyl, pyrazinyl, pyridazinyl and the like; benzo fused heteroaryl groups such as quinoline, quinoxaline, acridine, phenazine, benzothiazole and the like.

n is an integer in the range of 1 to 8.

When the groups R, Ri, R_2 and R_3 are substituted, the substituents (which may be one or more) may be selected from halogens (fluorine, chlorine, bromine, iodine), hydroxy, nitro, cyano, azido, nitroso, amino, hydrazine, hydroxamate, formyl, alkyl, haloalkyl, haloalkoxy, cycloalkyl, aryl, benzyl, alkoxy, aryloxy, acyl, acyloxy, acyloxyacyl, heterocyclyl, heteroaryl, monoalkylamino, dialkylamino, acylamino, alkoxycarbonyl, aryloxycarbonyl such as methoxy carbonyl, ethoxycarbonyl and the like; alkylsulfonyl, arylsulfonyl, alkylsulfinyl, arylsulfinyl, thioalkyl, arylthio, sulfamoyl, alkoxyalkyl groups and carboxylic acids and its derivatives like esters, hydroxamic acid and hydroxamate these groups may be further substituted by groups such as hydroxy.

Furthermore, whenever the groups R, Ri, R_2 and R_3 represent substituted or unsubstituted 5 to 10 membered ring systems, the rings may be monocyclic or bicyclic, saturated or partially saturated or aromatic containing 1 to 4 heteroatoms selected from O, S and N.

Definitions:

As used throughout the specification and the appended claims the following terms have the following meanings:

The term analog includes a compound, which differs from the parent structure by one or more C, N, O or S atoms. Hence, a compound in which one of the N atoms in the parent structure is replaced by an S atom is an analog of the former.

The term stereoisomer includes isomers that differ from one another in the way the atoms are arranged in space, but whose chemical formulas and structures are otherwise identical. Stereoisomers include enantiomers and diastereoisomers.

The term tautomers include readily interconvertible isomeric forms of a compound in equilibrium. The enol-keto tautomerism is an example.

The term polymorphs include crystallographically distinct forms of compounds with chemically identical structures.

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

The term derivative refers to a compound obtained from a compound according to formula (I), an analog, tautomeric form, stereoisomer, polymorph, hydrate, pharmaceutically acceptable salt or pharmaceutically acceptable solvate thereof, by a simple chemical process converting one or more functional groups, such as, by oxidation, hydrogenation, alkylation, esterification, halogenation, and the like.

Pharmaceutically acceptable salts forming part of this invention include base addition salts such as alkali metal salts like Li, Na, and K salts, alkaline earth metal salts like Ca and Mg, salts of organic bases such as lysine, arginine, guanidine, diethanolamine, α-phenylethylamine, benzylamine, piperidine, morpholine, pyridine, hydroxyethylpyrrolidine, hydroxyethylpiperidine, choline and the like, ammonium or substituted ammonium salts, aluminum salts. 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, benzenesulfonates, ascorbates, glycerophosphates, ketoglutarates and the like.

Pharmaceutically acceptable solvates may be hydrates or comprising of other solvents of crystallization such as alcohols.

Particularly useful compounds according to the present invention include:

1. (2Z)-3-(3,5-Dimethoxy phenyl)-2-(4-fluorophenyl)-N-[6-(2-hydroxybenzyl amine)-6-oxohexyl]acrylamide;

2. (2Z)-3-(3,5-Dimethoxyphenyl)-2-(4-fluorophenyl)-N-[6-(3-hydroxybenzyl amine) -6-oxohexyl] acrylamide;

3. (2Z)-3-(3,5-Dimethoxyphenyl)-2-(4-fluorophenyl)-N-[6-(hydroxyamino)-6-oxohexyljacrylamide;

4. (2Z)-3-(3,5-Dimethoxy phenyl)-2-(4-hydroxyphenyl)-N-[6-(2-aminobenzyl amine)-6-oxohexyl]acrylamide;

5. (2Z)-3-(3,5-Dimethoxyphenyl)-2-(4-hydroxyphenyl)-N-[6-(2-hydroxybenzyl amine) -6-oxohexyl]acrylamide;

6. (2Z)-3-(3,4,5-Trimethoxy phenyl)-2~(4-hydroxyphenyl)-N-[6-(2-hydroxy benzyl amine) -6-oxohexyl]acrylamide;

7. (2Z)-3-(3,4,5-Trimethoxy phenyl)-2-(4-hydroxyphenyl)-N-[6-(N,O dimethyl amine)-6-oxohexyl]acrylamide;

8. [(2Z)-3-(4-Methyl-l,3-thiazol-5-yl)-2-(2-thienyl))-N-[6-(hydroxyamino)-6-oxohexyl] acrylamide;

9. (2Z)-3-(3,5-Dimethoxyphenyl)-2-(4-nitrophenyl)-N-[6-(hydroxyamino)-6-oxohexyl]acrylamide;

10. (2Z)-3-(3-Chloro,4-fluorophenyl)-2-(4-fluorophenyl)-N-[6-(hydroxyamino)-6-oxohexyl]acrylamide;

11. (2Z)-3-(3,5-dimethoxyphenyl)-2-(4-hydroxyphenyl)-N-[6-(hydroxyamino)-6-oxohexyl]acrylamide;

12. (2Z)-3-(4-Methyl-l,3-thiazol-5-yl)-2-(4-chlorophenyl)-N-[6-(hydroxyamino)-6-oxohexyl]acrylamide;

13. (2Z)-3-(5-Bromo-2-thienyl)-2-(4-bromophenyl)-N-[6-(hydroxyamino)-6-oxohexyl]acrylamide;

14. (2Z)-3-(4-Pyridine)-2-(4-fluorophenyl)-N-[6-(hydroxyamino)-6-oxo hexyl] acrylamide;

15. (2Z)-3-(4-Pyridine)-2-(4-fluorophenyl)-N-[6-(4-hydroxy-2-nitrobenzylamine)-6 -oxohexyl] acrylamide;

16. (2Z)-3-(4-Thiomethyl phenyl)-2-(4-fluorophenyl)-N-[6-(hydroxyamine)-6-oxohexyl]acrylamide;

17. (2Z)-3-(4-Thiomethylphenyl)-2-(4-fluorophenyl)-N-[6-(5-nitro-2-thiazole amine)-6-oxohexyl]acrylamide;

18. (2Z)-3-(4-Thiomethylphenyl)-2-(4-fluorophenyl)-N-[6-(N,O dimethylamine)-6-oxohexyl]acrylamide;

19. (2Z)-3-(4-Thiomethylphenyl)-2-(4-fluorophenyl)-N-[6-(5-methyl-2-benzo thiazoleamine)-6-oxohexyl]acrylamide;

20. (2Z)-3-(4-Thiomethylphenyl)-2-(4-fluorophenyl)-N-[6-(2-thiazoleamine)-6-oxohexyljacrylamide;

21. (2Z)-3-(3,4-Difluorophenyl)-2-(4-fluorophenyl)-N-[6-(2-thiazole amine)-6-oxo hexyl]acrylamide;

22. (2Z)-3-(4-Fluoro-3-trifluoromethyl-phenyl)-2-(4-trifluoromethylphenyl)-N-[6-(hydroxyamino)-6-oxohexyl]acrylamide;

23. (2Z)-3-(4-Methylthiazol-5-yl)-2-(4-bromophenyl)-N-[6-(hydroxyamino)-6-oxo hexyljacrylamide;

24. (2Z)-3-(4-Fluoro-3-tri fluoro methylphenyl)-2-(4-nitrophenyl)-N-[6-(hydroxy amino)-6-oxohexyl]acrylamide;

25. (2Z)-3-(2,3,5-Trifluorophenyl)-2-(thiophene-2-yl)-N-[6-(hydroxyamino)-6-oxohexyl]acrylamide;

26. (2Z)-3-(4-Methylthiazol-5-yl)-2-(4-trifluoromethyl phenyl)-N-[6-(hydroxy amino)-6-oxo hexyl]acrylamide;

27. (2Z)-3-(2,3,5-Tri fluorophenyl)-2-(4-nitrophenyl)-N-[6-(hydroxy amino)-6-oxohexyl]acrylamide;

28. (2Z)-3-(3-Chlorophenyl)-2-(4-methoxyphenyl)-N-[6-(hydroxy amino)-6-oxo hexyl]acrylamide;

29. (2Z)-3-(4-Methoxyphenyl)-2-(phenyl)-N-[6-(hydroxy amino)-6-oxo hexyl] acrylamide;

30. (2Z)-3-(2-Nitro phenyl)-2-(4-chlorophenyl)-N-[6-(hydroxyamino)-6-oxohexyl] acrylamide;

31. (2Z)-3-(2-Chloro-4-fluorophenyl)-2-(phenyl)-N-[6-(hydroxyamino)-6-oxohexyl]acrylamide;

32. (2Z)-3-(2,3,4-Trimethoxyphenyl)-2-(4-hydroxyphenyl)-N-[6-(hydroxyamino)-6-oxohexyl]acrylamide;

33. (2Z)-3-(3,5-Dimethoxyphenyl)-2-(4-fluorophenyl)-N-[6-(hydroxy amino)-6-oxo hexyl]acrylamide;

34. (2Z)-3-(3,4-Difluorophenyl)-2-(4-fluorophenyl)-N-[6-(hydroxy amino)-6-oxohexyl]acrylamide;

35. (2Z)-3-(3,4-Difluorophenyl)-2-(4-fluorophenyl)-N-[6-(N,O dimethyl hydroxy amino)-6-oxohexyl]acrylamide;

36. (2Z)-3-(3,4-Difluorophenyl)-2-(4-fluorophenyl)-N-[6-(amino thiazol-2-yl)-6-oxohexyl]acrylamide;

37. (2Z)-3-(5-Chloro-2-furyl)-2-(4-fluorophenyl)-N-[6-(hydroxyamino)-6-oxohexyl]acrylamide;

38. (2Z)-3-(4-Thiomethylphenyl)-2-(4-trifluoromethylphenyl)-N-[6-(hydroxy amino)-6-oxo hexyl]acrylamide;

39. (2Z)-3-(Thiazol-2-yl)-2-(4-trifluoromethylphenyl)-N-[6-(hydroxyamino)-6-oxohexyl]acrylamide;

40. (2Z)-3-(2,3,6-Trifluoro phenyl)-2-(4-methoxyphenyl)-N-[6-(hydroxyamino)-6-oxohexyl]acrylamide;

41. (2Z)-3-(4-Thiomethylphenyl)-2-(4-nitrophenyl)-N-[6-(hydroxyamino)-6-oxo hexyl]acrylamide;

42. (2Z)-3-(3-Chloro-4-fluorophenyl)-2-(4-hydroxyphenyl)-N-[6-(hydroxyamino) -6-oxo hexyljacrylamide;

43. (2Z)-3-(4-Thiomethylphenyl)-2-(thiophene-2-yl)-N-[6-(hydroxyamino)-6-oxo hexyl]acrylamide;

44. (2Z)-3-(5-Chlorothiophen-2-yl)-2-(4-fluorophenyl)-N-[6-(hydroxyamino)-6-oxohexyl]acrylamide;

45. (2Z)-3-(4-Fluoro-3-methylphenyl)-2-(4-fluorophenyl)-N-[6-(hydroxyamino)-6-oxo hexyljacrylamide;

46. (2Z)-3-(4-Hydroxy-3-methoxyphenyl)-2-(4-fluorophenyl)-N-[6-(hydroxy amino) - 6-oxohexyl]acrylamide;

47. (2Z)-3-(4-Trifluoromethylphenyl)-2-(4-fluorophenyl)-N-[6-(hydroxyamino)-6-oxohexyl] aerylamide;

48. (2Z)-3-(3,4,5-Trimethoxyphenyl)-2-(4 fluorophenyl)-N-[6-(hydroxyamino)-6-oxo hexyljacrylamide;

49. *N*-[4-(hydroxyamino)-4-oxobutyl]-6-{[(2Z)- 3-(3, 5 dimethoxyphenyl)-2-(4 nitrophenyl)-acrylamide] }hexanamide;

50. (2Z)-3-(3,4,5-Trimethoxyphenyl)-2-(4-methoxyphenyl)- N-[6-(hydroxy amino)-6-oxo hexyljacrylamide;

51. (2Z)-3-(4-Thio methyl phenyl)-2-(4-fluorophenyl)-N-[6-(O-benzyl hydroxyamino)-6-oxo hexyljacrylamide;

52. *N*-Aetyl-6-{[(2Z)-3-(4-thiomethyl phenyl)-2-(4-fluorophenyl)- acryl amide] }-*N*-hydroxyhexanamide;

53. *N*-Acetyl-6-{[(2Z)-3-(5-chloro-2-turyl)-2-(4-fluorophenyl)- acryl amide] }-*N*-hydroxyhexanamide;

54. N-Hydroxy-2- {[(2Z)-3-(4-thiomethylphenyl)-2-(4-fluorophenyl)-acrylamideJ- 6-oxohexyl]amino}-3-(4-hydroxyphenyl) propanamide;

55. Methyl-2-{[(2Z)-3-(2,3,5,6 tetrafluoro-4-methoxyphenyl)-2-(4-fluorophenyl)-acrylamide] 6-oxohexyl]amino}-3-(4-hydroxyphenyl) propanoate;

56. N-Hydroxy-2-{[(2Z)-3-(2,3,5,6 tetrafluoro-4-methoxyphenyl)-2-(4-fluoro phenyl)-acrylamide]6-oxohexyl]amino}-3-(4-hydroxyphenyl)propanamide;

57. Methyl-2-{[(2Z)-3-(3,4 difluorophenyl)-2-(4-fluorophenyl)- acrylamide] 6-oxohexylJamino}-3-(4-hydroxyphenyl)propanoate;

58. N-hydroxy-2-{[(2Z)-3-(3,4 difluorophenyl)-2-(4-fluorophenyl)- acrylamide] 6-oxohexyl]amino}-3-(4-hydroxyphenyl)propanamide;

59. (2Z)-*N*-(l-(4-hydroxybenzyl)-2-{[4-(hydroxyamino)-4-oxobutyl]amino}-2-oxo ethyl)- 3-(3-fluoro-4-trifluoro methylphenyl)-2-(4-nitrophenyl)- acrylamide;

60. (2Z)-*N*-[2-(hydroxyamino)-l-(4-hydroxybenzyl)-2-oxoethyl]- 3-(4-fluoro-3-trifluoromethyl phenyl)-2-(4-nitrophenyl)-acrylamide;

61. N-Hydroxy-2-{[(2Z)-3-(3,4 dimethoxyphenyl)-2-(4-fluorophenyl)-acrylamide] 6-oxohexyl]amino}-3-(4-hydroxyphenyl)propanamide;

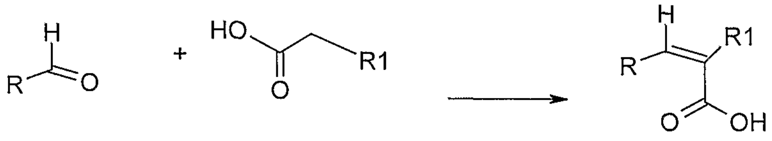
62. (2Z)-*N*-[2-(hydroxyamino)-1-(4-hydroxybenzyl)-2-oxoethyl]-3-(4-methyl thiazol-5-yl)-2-(thiophen-2-yl)-acrylamide;

63. (2Z)-*N*-[2-(Hydroxyamino)-l-(4-hydroxybenzyl)-2-oxoethyl]- 3-(4 methoxy phenyl)-2-(phenyl)-acrylamide;

64. (2Z)-*N*-[2-(hydroxyamino)-l-(4-hydroxybenzyl)-2-oxoethyl]- 3-(3,5 dimethoxyphenyl)-2-(4-hydiOxyphenyl)-acrylamide and

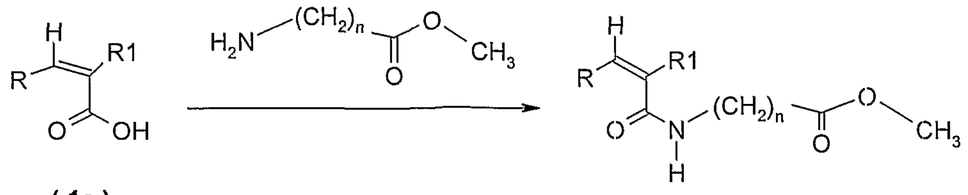
According to another feature of the present invention, there is provided a process as shown in the following scheme, for the preparation of compounds of the formula (I), wherein all the groups are as defined earlier.

A) By condensing the compound of formula (Ia) and the compound of formula (Ib) with Ac_2O to yield a compound of formula (Ic), wherein R and Ri, are as defined earlier.



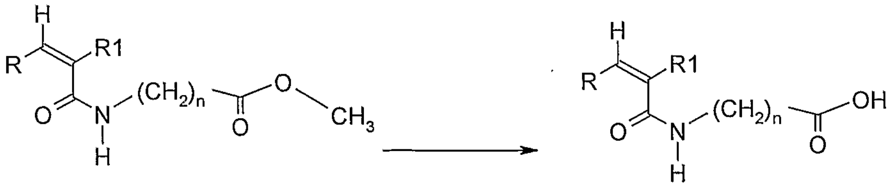
(1a) (1b) (1c)

B) By reacting the compound of the formula (Ic) with an acid activating agent such as BOP, HOBT and the like in the presence of the respective 5-aminocaproic methyl ester to yield the compound of the general formula (Id) wherein R and Ri are as defined earlier.



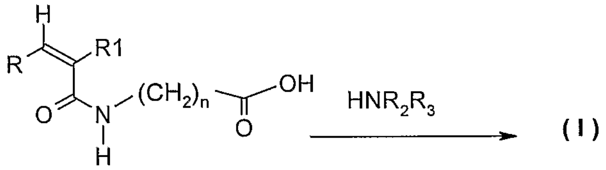
(1c) (1d)

C) By reacting the compound of formula (Id) with a suitable base like LiOH, NaOH and the like to yield the compound of the general formula (Ie) wherein R and Ri are as defined earlier.



(l d l (1e)

D) By reacting the compound of formula (Ie) with an acid activating agent such as BOP, HOBT and the like in the presence of the respective amine HNR_2R_3 to yield the compound of the general formula (I) wherein R, Ri,R2 and R3 are as defined earlier.



(1e)

The compound of the general formula (I) is prepared by **the** following **procedure:**

Step (T): Condensation of the compound of the formula (Ia) and (Ib) with TEA in the presence of a solvent such as Ac_2O, and a base such as triethylamine, diethylamine, pyridine, DMAP and the like, afforded the compound of the formula (Ic), wherein R and Ri are as defined earlier.

Step (II): Condensation of the compound of the formula (Ic) with an acid activating agent such as BOP, HOBT and the like in the presence of the respective 5-aminocaproic methyl ester and base such as triethylamine, diethyl amine, pyridine, DMAP and like, yielded the compound of the general formula (Id), wherein Rand R_1 are as defined earlier.

Step (III): Reaction of the compound of the formula (Id) with a suitable base like LiOH, NaOH and the like, yielded the compound of the general formula (Ie), wherein R and R_1 are as defined earlier

Step (IV): Condensation of the compound of the formula (Ie) with an acid activating agent such as BOP, HOBT and the like in the presence of the respective amine HNR_2R_3, and base such as triethylamine, diethylamine, pyridine, DMAP and the like, yielded the compound of the general formula (I), wherein R, R_1, R_2 and R_3 are as defined earlier

It is appreciated that in any of the above-mentioned reactions, any reactive group in the substrate molecule may be protected according to conventional chemical practice. Suitable protecting groups in any of the above-mentioned reactions are those used conventionally in the art. The methods of formation and removal of such protecting groups are those conventional methods appropriate to the molecule being protected. Protecting groups are removed under conditions, which will not affect the remaining portion of the molecule.

The pharmaceutically acceptable salts are prepared by reacting the compound of formula (I) with 1 to 4 equivalents of a base such as sodium hydroxide, sodium methoxide, sodium hydride, potassium t-butoxide, and calcium hydroxide, magnesium hydroxide and the like, in solvents like ether, THF, methanol, t-butanol, dioxane, isopropanol, ethanol etc. Mixtures of solvents may be used. Organic bases like lysine, arginine, diethanolamine, choline, guanidine and their derivatives etc. may also be used. Alternatively, 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, ascorbic acid, palmitic acid, succinic acid, benzoic acid, benzene sulfonic acid, tartaric acid and the like in solvents like ethyl acetate, ether, alcohols, acetone, THF, dioxane etc. Mixture of solvents may also be used.

It should be noted that compounds of the invention may contain groups that may exist in tautomeric forms, and though one form is named, described, displayed and/or claimed herein, all the tauomeric forms are intended to be inherently included in such name, description, display and/or claim.

The stereoisomers of the compounds can also be made by conducting the reaction in the presence of reagents or catalysts in their single enantiomer form or by resolving the mixture of stereoisomers by conventional methods. Some of the preferred methods include use of microbial resolution, resolving the diastereomeric salts formed with chiral acids such as mandelic acid, camphorsulfonic acid, tartaric acid, lactic acid, and the like wherever applicable or by using chiral bases such as brucine, cinchona alkaloids, their derivatives and the like. Commonly used methods are compiled by Jaques et al in "Enantiomers, Racemates and Resolution" (Wiley Interscience, 1981).

Prodrugs of the compounds of formula (I) are also contemplated by this invention. A prodrug is an active or inactive compound that is modified chemically through *in vivo* physiological action, such as hydrolysis, metabolism and the like, into a compound of this invention following administration of the prodrug to a patient. The suitability and techniques involved in making and using prodrugs are well known by those skilled in the art.

Various polymorphs of the compounds of the general formula (I), forming part of this invention may be prepared by crystallization of the compounds of formula (I) under different conditions. For example, using different commonly used solvents, or their mixtures for recrystallization; crystallizations at different temperatures; various modes of cooling, ranging from very fast to very slow cooling during crystallizations. Heating or melting the compounds followed by cooling gradually or immediately, one can also obtain polymorphs. The presence of polymorphs may be determined by solid probe NMR spectroscopy, IR spectroscopy, differential scanning calorimetry and powder X-ray diffraction or other such techniques.

The present invention also provides a pharmaceutical composition, containing one or more of the compounds of the general formula (I) as defined above, their derivatives, analogs, tautomeric forms, stereoisomers, polymorphs, hydrates, metabolites, prodrugs, pharmaceutically acceptable salts, and pharmaceutically acceptable solvates in combination with the usual pharmaceutically employed carriers, diluents and the like, useful for the treatment and/or prevention of cancer, psoriasis, proliferative conditions, conditions mediated by HDAC and diseases involved in cellular growth such as malignant tumors, autoimmune diseases, skin diseases and infections.

The pharmaceutical composition may be in the forms normally employed, such as tablets, capsules, powders, syrups, solutions, suspensions and the like, may contain flavorants, sweeteners 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. The amount of the active ingredient in the composition may be less than 70% by weight. Such compositions typically contain from 1 to 25%, preferably 1 to 15% by weight of active compound, the remainder of the composition being pharmaceutically acceptable carriers, diluents, excipients or solvents.

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 in the range as described above. Thus, for oral administration, the compounds can be combined with a suitable solid or liquid carrier or diluent to form capsules, tablets, powders, syrups, solutions, suspensions and the like. The pharmaceutical compositions, may, if desired, contain additional components such as flavorants, sweeteners, excipients and the like. For parenteral administration, the compounds can be combined with 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, with intramuscular administration being preferred in humans.

The pharmaceutical compositions of the present invention are effective in treating and/or preventing cancer, psoriasis, proliferative conditions, conditions mediated by HDAC and diseases involved in cellular growth such as malignant tumors, autoimmune diseases, skin diseases and infections. Generally, the effective dose for treating a particular condition in a patient may be readily determined and adjusted by the physician during treatment to alleviate the symptoms or indications of the condition or disease. Generally, a daily dose of active compound in the range of about 0.01 to 1000 mg/kg of body weight is appropriate for administration to obtain effective results. The daily dose may be administered in a single dose or divided into several doses. In some cases, depending upon the individual response, it may be necessary to deviate upwards or downwards from the initially prescribed daily dose. Typical pharmaceutical preparations normally contain from about 0.2 to about 500 mg of active compound of formula I and/or its pharmaceutically active salts or solvates per dose.

While the compounds of the invention can be administered as the sole active pharmaceutical agent, they can also be used in combination with one or more compounds of the invention or other agents. When administered as a combination, the therapeutic agents can be formulated as separate compositions that are given at the same time or different times, or the therapeutic agents can be given as a single composition. Thus compounds of the present invention can be used in the treatment of cancer, psoriasis, as a monotherapy, or also in combination of these HDAC inhibitors with other clinically relevant cytotoxic agents or non-cytotoxic agents.

The term "therapeutically effective amount" or "effective amount" refers to that amount of a compound or mixture of compounds of formula (I) that is sufficient to effect treatment, as defined below, when administered alone or in combination with other therapies to an animal in need of such treatment.

The term "animal" as used herein is meant to include all mammals, and in particular humans. Such animals are also referred to herein as subjects or patients 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.

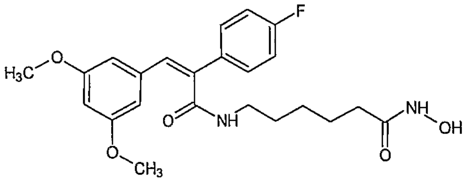
The term "treatment" or "treating" means any treatment of a disease in a mammal, including:

a) Preventing the disease, that is, causing the clinical symptoms of the disease not to develop;
b) Inhibiting the disease, that is, slowing or arresting the development of clinical symptoms; and/or
c) Relieving the disease, that is, causing the regression of clinical symptoms.

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, can make various changes and modifications of the invention to adapt it to various usages and conditions.

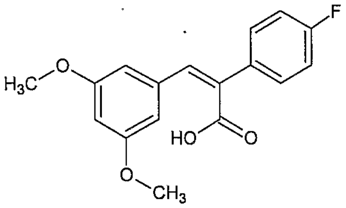
The present invention is provided by **the examples given below, which are provided** by **the** way **of illustration** only, **and** should **not be considered to limit the scope of the invention. Variation and changes, which are obvious to one** skilled **in the art, are intended to be within the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

Example **1:** Synthesis **of** (2Z)-3-(3,5-Dimethoxyphenyl)-2-(4~fluorophenyI)-N-[6-(hydroxyamino)-6-oxohexyI]acrylamide.



Stage 1

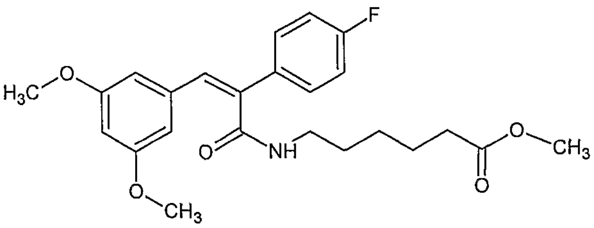
Synthesis **of** (2Z)-3-(3,5-DimethoxyphenyI)-2-(4-fluorophenyl) acrylic **acid.**



A mixture of 4-fluoro phenyl acetic acid (0.928g, 6.02mmol), 3,5 dimethoxybenzaldehyde (Ig, 6.02mmole), Ac_2O (ImI) and triethylamine (0.5ml) was heated at 100^0C for 12 hours. Upon completion (as monitored by TLC using hexane-ethyl acetate (3:2), the reaction mixture was cooled to room temperature and concentrated HCL (5ml) was added. The precipitate was dissolved in CH_2Cl_2 (100ml), washed with 10% aqueous NaOH (3x50ml) and the basic solution was acidified (PH-1) with concentrated HCL. After stirring, the precipitate was collected and dried to get the product (1.5g, 82.87%).

Stage 2

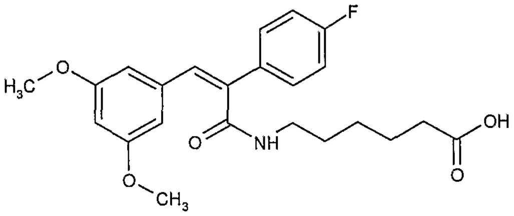
Synthesis **of** Methyl 6~{[(2Z)-3-(3,5-Dimethoxyphenyl)-2-(4-fluorophenyl) **prop-**2-enoyl] **amino} hexonate**



To a suspension of (2Z)-3-(3,5-dimethoxyphenyl)-2-(4-fluorophenyl) acrylic acid (Ig, 3.31mmole) in THF was added 5-aminocaproic acid methyl ester (576mg, 3.97 mmol), BOP reagent (1.75g, 3.97mmol), and HOBT (536mg, 3.97mmol). DIPEA (2.5ml, 9.93mmol) was added drop wise with constant stirring to the above and the reaction mixture was stirred at room temperature overnight. Subsequently the reaction mixture was evaporated to dryness. The residue was dissolved in ethyl acetate and washed successively with IN HCL (3x5OmI), saturated NaHC θ_3 (3x5OmI) and brine solution (3x50ml). The organic layer was dried over Na_2SO_4 and concentrated to give the pure compound (1.1 0Og, 77.46%).

Stage 3

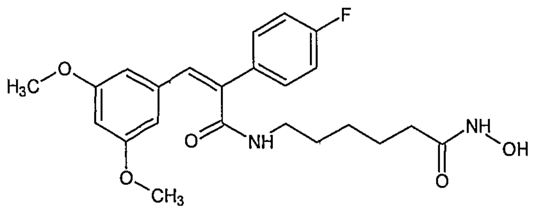
Synthesis **of** 6-{[(2Z)-3-(3,5-Dimethoxyphenyl)-2-(4-fluoroplienyl) prop-2-enoyl] **amino} hexanoic acid**



Methyl 6-{[(2Z)-3-(3,5-dimethoxyphenyl)-2-(4-fluorophenyl) prop-2-enoyl] amino} hexonate (Ig) was hydrolyzed with IM NaOH (5ml) in a mixture of water (2ml) and methanol (15ml), and the mixture was stirred at room temperature overnight. After evaporation of MeOH, the residual aqueous solution was adjusted at PH-3 with IN HCL. The resulting precipitate was filtered and washed with water to give the pure compound (750mg, 77.55%).

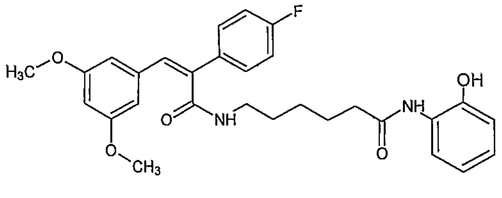
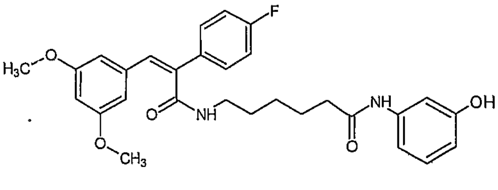
Stage 4

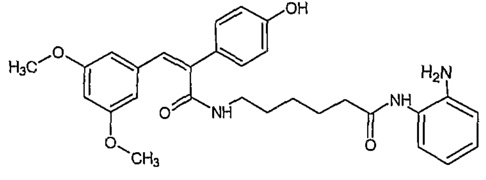
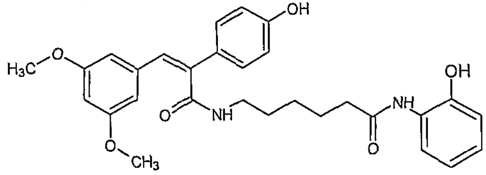
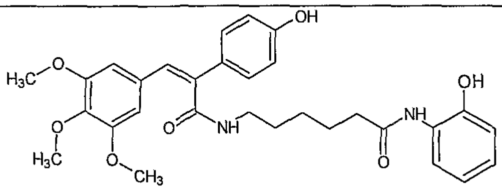
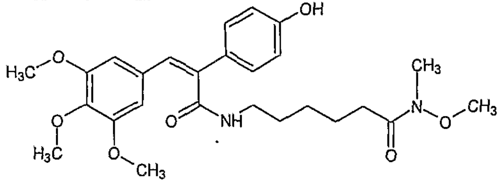
Synthesis of (2Z)-3~(3,5-DimethoxyphenyI)-2-(4-fluorophenyl)-N-[6-(hydroxyamino)-6-oxohexyl]acrylamide

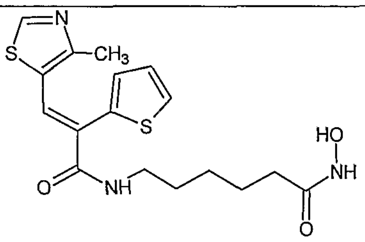
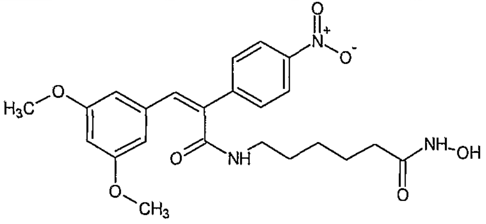
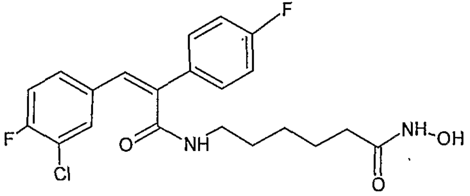
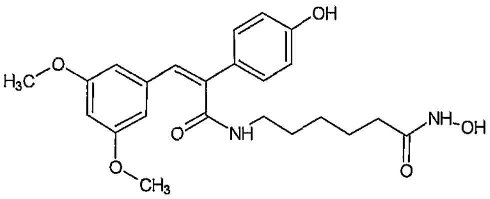
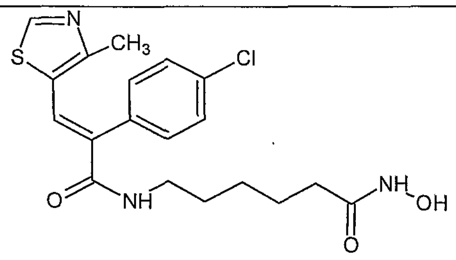


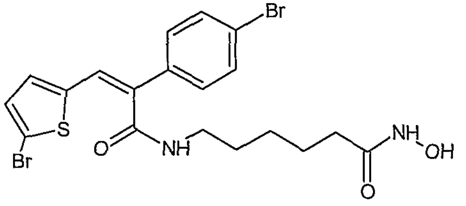
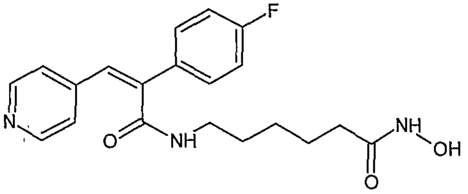
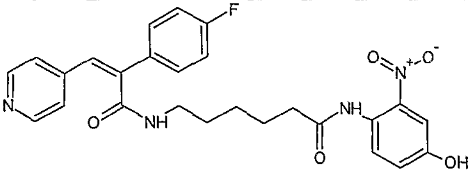
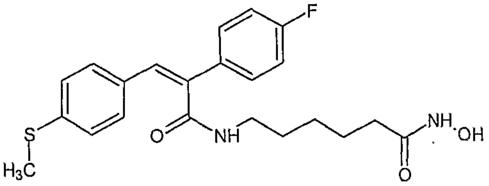
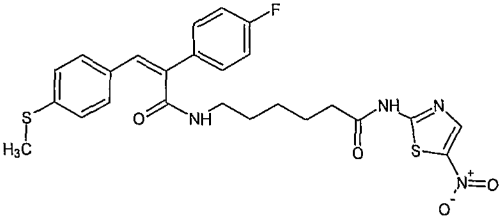
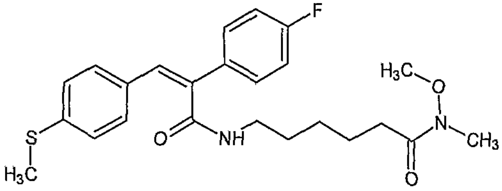
To a suspension of 6-{[(2Z)-3-(3,5-dimethoxyphenyl)-2-(4-fluorophenyl) prop-2-enoyl] amino} hexonic acid (500mg, 1.20mmol) in TBDF was added hydroxylamine hydrochloride (125mg, 1.80mmol), BOP reagent (637.2mg, 1.40mmol), and HOBT (162mg, 1.40mmol). DIPEA (0.55ml, 3.60mmol) was added dropwise with constant stirring to the above, and the reaction mixture was stirred at room temperature overnight. Subsequently the reaction mixture was evaporated to dryness, the residue was dissolved in ethyl acetate and washed successively with IN HCL (3x50ml), saturated NaHCO$_3$ (3x50ml) and brine solution (3x50ml). The organic layer was dried over Na$_2$SO$_4$ and concentrated to give the pure (2Z)-3-(3,5-dimethoxyphenyl)-2-(4-fluorophenyl)-N-[6-(hydroxyamino)-6-oxohexyl] acrylamide (450mg, 86.87%) as an off white solid with m.p.: 104.5 ^{0}C -105 ^{0}C. ^{1}H NMR (DMSO-d$_6$) δ: 1.22(3H,m), 1.46(4H,m), 1.95(2H,t), 3.33(2H,q), 3.53(6H,s), 6.15(2H,s), 6.33(lH,s), 7.23(4H,m), 7.27(lH,s), 7.48(lH,t), 8.66(lH,s), 10.334(lH,s); m/z: (M+H)$^+$ at 431.1

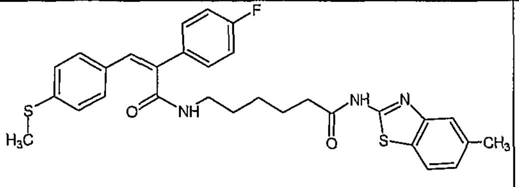
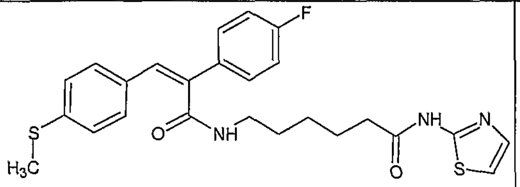
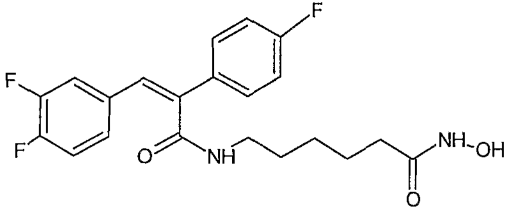
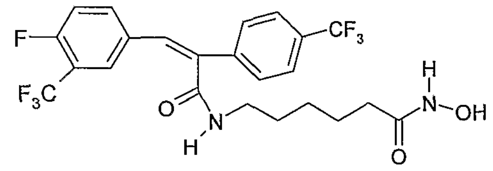
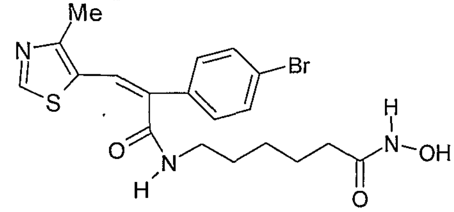
The following compounds were prepared according to the above procedure.

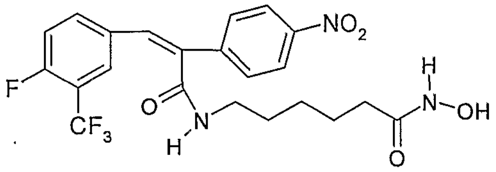
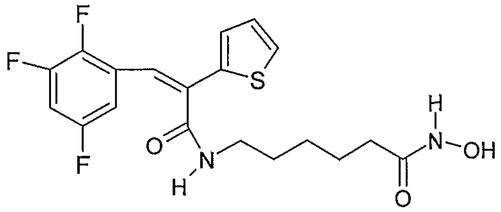
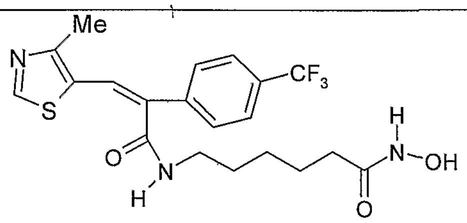
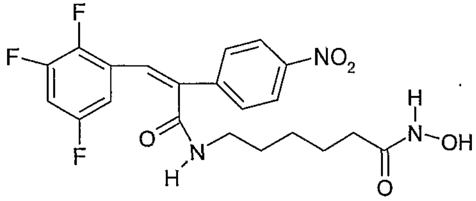
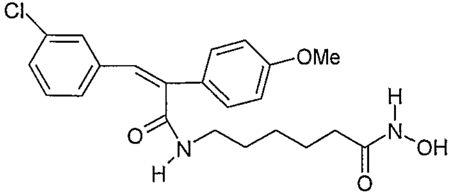
Exp.	**Structure**	Analytical **Data**
2		'HNMR(DMSO-d$_6$) δ: 1.26(3H,m), 1.46 (2H,m), 2.26(2H,t), 3.13(2H,q), 3.35(lH,m) 3.53(6H,s), 6.14(2H,s), 6.33(lH,s), 6.42(lH,q), 6.95(lH,q), 7.03(lH,q), 7.22(5H,m) 7.32(lH,s), 7.48(lH,t), 9.32(lH,s), 9.72(lH,s); m/z: (M+H)$^+$ at 507.2; sticky compound
3		^{1}HNMR (DMSO-d$_6$) δ: 1.46(2H,m), 1.59(2H,m), 2.26(2H,t), 3.13(2H,q), 3.35(2H,m), 3.53(6H,s), 6.14(2H,s), 6.33(lH,s), 6.42(lH,q), 6.90i;iH,q),

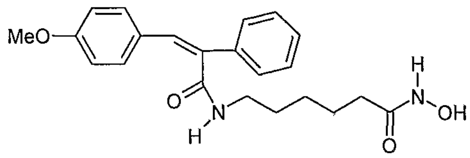
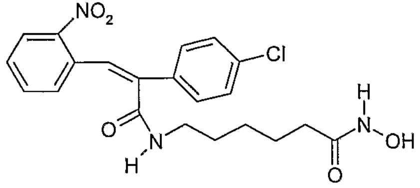
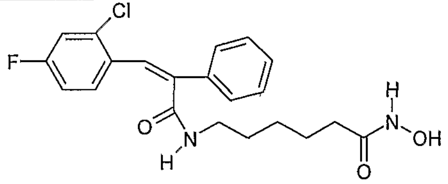
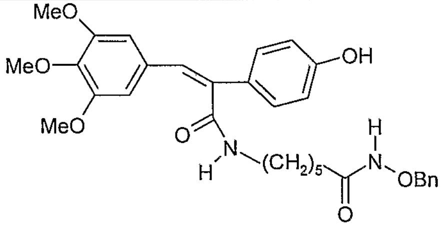
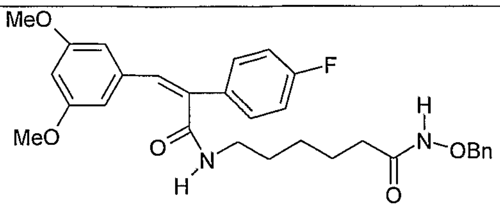
		7.03(1H,t), 7.22(5H,m), 7.32(1H,s), 7.48(1H,t), 9.32(1H,s), 9.72(1H,s); m/z: (M+H)$^+$at 507.2; m.p.: 147.2 -147.7°C
4		^{1}HNMR(DMSO-d$_6$) δ: 1.26(2H,m), 1.44(2H,m), 1.57(2H,m), 2.39(2H,t), 3.13(2H,t), 3.35(4H,m), 3.53(6H,s), 6.19(2H,s), 6.32(1H,s), 6.78(1H,m), 6.83(2H,s), 6.97(1H,d), 7.25(2H,m), 7.67(1H,d) 9.24(1H,s), 9.57(1H,s), 9.72(1H,s); m/z: (M+H)$^+$ at 504.2; m.p: 101.5°C -102°C
5		^{1}HNMR (DMSO-d$_6$) δ: 1.26(2H,m), 1.44(2H,m), 1.57(2H,m), 2.39(2H,t) 3.13(2H,t), 3.35(2H,m), 3.53(6H,s), 6.19(2H,s), 6.32(1H,s), 6.78(1H,m), 6.83(2H,m) 6.97(1H,d), 7.25(2H,m), 7.67(1H,d) 9.24(1H,s), 9.57(2H,s), 9.72(1H,s); m/z: (M+H)$^+$ at 505.2; m.p. 165.2 -165.7°C
6		^{1}HNMR (DMSO-d$_6$) δ: 1.26(2H,m), 1.42(2H,m), 1.59(2H,m), 2.3(2H,m), 3.13(2H,m) 3.35(2H,m), 3.49(6H,s), 3.60(3H, s), 6.34(2H,s), 6.74(1H,t), 6.83(3H,d), 6.99(1H,d), 7.10(1H,t), 7.33(1H,d), 7.67(1H,d), 9.24(1H,s), 9.58(1H,s), 9.72(1H,s); m/z: (M+H)$^+$ at 535.2; m.p.: 182.5°C-183°C
7		^{1}HNMR (DMSO-d$_6$) δ: 1.24(2H,m), 1.41(2H,m), 1.50(2H,m), 2.34(2H,m) 3.08(5H,m), 3.49(6H,s), 3.59(3H,s) 3.64(2H,s), 6.34(2H,s), 6.83(2H,d), 6.99(2H,d), 7.11(1H,t), 7.32(1H,s), 9.59(1H,s); m/z: (M+H)$^+$ at 487.2; m.p.:

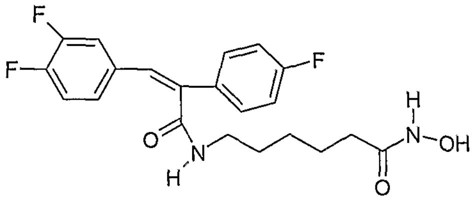
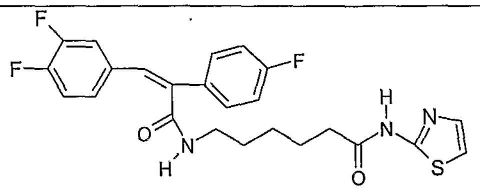
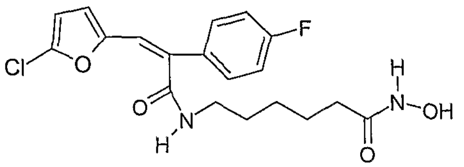
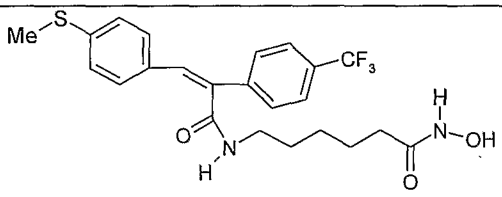
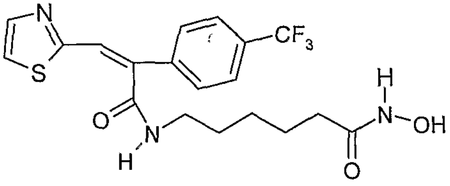
		130.2°C -130.7°C
8		^{1}HNMR (DMSO-d_6) δ: 1.76(4H,m), 1.46(4H,m), 1.94(2H,t), 3.15(2H,q), 7.01(1H,d), 7.21(1H,t), 7.48(1H,t), 7.81(2H,s), 8.66(1H,s), 8.89(1H,s), 10.33(1H,s); m/z: (M+H)$^+$ at 380.0; m.p.: 98.7°C -99.2°C
9		^{1}HNMR (DMSO-d_6) δ: 1.24(2H,m), 1.46(4H,m), 1.98(2H,m), 3.14(2H,q), 3.52(6H,s), 4.16(2H,d), 6.37(1H,d), 7.41(1H,s), 7.45(1H,t), 7.79(2H,t), 8.28(2H,d), 8.89(1H,s), 10.33(1H,s); m/z: (M+H)$^+$ at 458.1
10		^{1}HNMR (DMSO-d_6) δ: 1.23(2H,m), 1.46(4H,m), 1.93(2H,m), 3.13(2H,q), 6.99(1H,d), 7.15(3H,m), 7.28(3H,m) 7.34(1H,s), 7.56(1H,t), 8.99(1H,s), 10.33(1H,s); m/z: (M+H)$^+$at 423.1; m.p.: 163.8°C -164.3°C
11		^{1}HNMR (DMSO-d_6) δ: 1.19(2H,m), 1.40(2H,m), 1.49(2H,m), 1.92(2H,t), 3.09(2H,q) 3.53(6H,s), 6.19(2H,d), 6.32(1H,t), 6.79(2H,d), 6.95(2H,d), 7.22(2H,q), 8.67(1H,s) 9.59(1H,s), 10.33(1H,s); m/z: (M+H)$^+$ at 429.1; m.p.: 144.1°C -144.6°C
12		^{1}HNMR (DMSO-d_6) δ: 1.15(3H,m), 1.18(2H,m), 1.42(2H,m), 1.98(2H,q), 3.08(2H,q), 3.35(2H,m), 7.19(2H,d), 7.38(1H,t), 7.56(2H,d), 7.72(1H,s), 8.66(1H,s), 8.80(1H,s), 10.32(1H,s); m/z: (M+H)$^+$ at 408.0; m.p.: 78.5°C -79°C

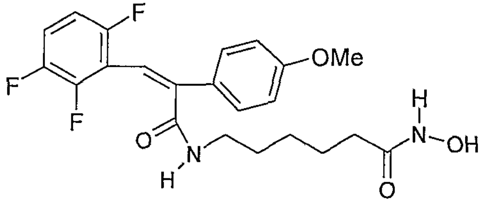
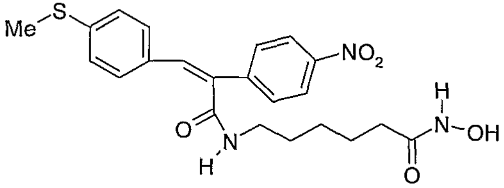
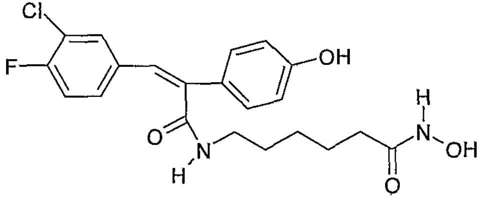
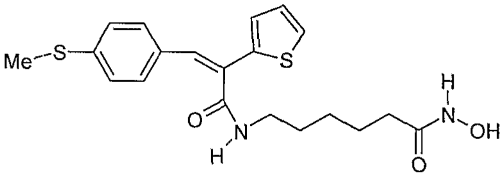
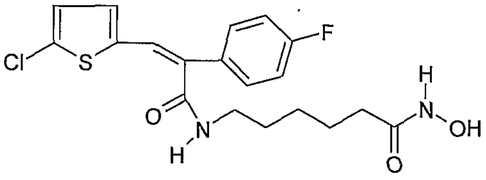
13		^{1}HNMR(DMSO-d_6) δ: 1.15(3H,m), 1.19(2H,m), 1.45(2H,m), 1.91(2H,q), 3.09(2H,q), 7.18(5H,m), 7.69(3H,m), 8.66(1H,s), 10.32(1H,s); m/z:(M+H) at 516.9
14		^{1}HNMR (DMSO-d_6) δ: 1.18(4H,m), 1.57(2H,m), 1.99(2H,S), 2.50(2H,s), 7.42(3H,m), 7.36(1H,s), 7.56(3H,m), 7.98(3H,d), 10.37(1H,s), 1.50(1H,s), 13.64(1H,d); m/z: (M+H)$^+$at 372.1, m.p.101.2°C-105.5°C
15		^{1}HNMR (DMSO-d_6) δ: 1.25(2H,m), 1.34(2H,m), 1.49(2H,m), 1.92(2H,s), 3.17(2H,s), 3.37(2H,m), 5.16(1H,s), 6.75(2H,d), 6.91(2H,d), 7.16(1H,s), 7.19(4H,m), 7.71(1H,d), 8.36(2H,s); m/z: (M+H)$^+$at 493.1
16		^{1}H NMR (DMSO-d_6) δ: 1.20(2H,s), 1.46(4H,m), 1.94(2H,t), 2.41(3H,s), 3.08(2H,t), 6.89(2H,d), 7.06(2H,d), 7.20(4H,m), 7.34(1H,s), 8.66(1H,s), 10.33(1H,s); m/z: (M+H)$^+$at 417.1; m.p.: 168.1°C -170.9°C
17		^{1}HNMR(DMSO-d_6) δ: 1.28(2H,m), 1.45(2H,m), 1.62(2H,m), 2.41(3H,s), 2.50(2H,t), 3.12(2H,t), 6.89(2H,d), 7.06(2H,d), 7.18(4H,m), 7.32(1H,s), 8.61(1H,s), 13.05(1H,s); m/z:(M+H)$^+$at 529.1; m.p.201.4°C-205.9°C
18		^{1}HNMR (DMSO-d_6) δ: 1.27(4H,m), 1.47(4H,m), 2.41(3H,s), 3.07(5H,m), 3.64(3H,s), 6.91(2H,d), 7.06(2H,d), 7.20(4H,m), 7.34(1H,s); m/z: (M+H)$^+$at

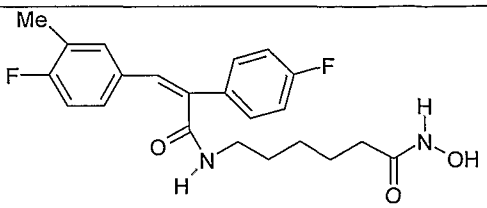
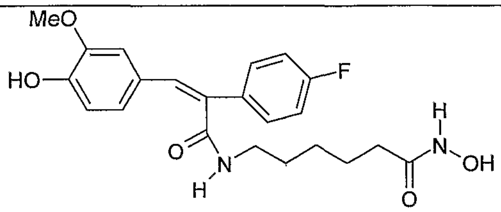
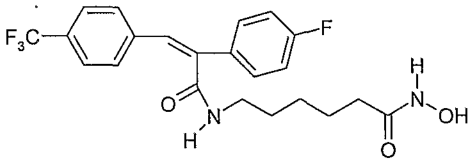
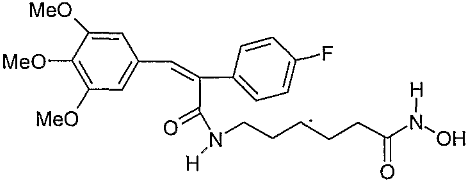
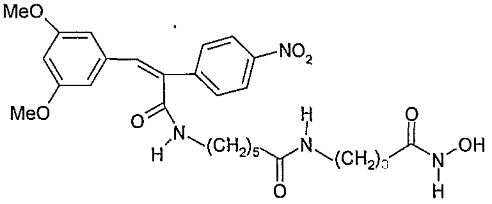
		445.1, m.p.: 205.4°C-209.1°C
19		^{1}HNMR (DMSO-d$_6$) δ: 1.20(2H,m), 1.45(4H,m), 1.94(2H,t), 2.41(3H,s), 3.08(2H,t), 6.87(1H,d), 7.02(1H,d), 7.05(3H,d), 7.20(2H,d), 7.31(2H,s), 7.59(2H,d), 7.73(1H,s); m/z: (M+H)$^+$at 548.1
20		^{1}HNMR (DMSO-d$_6$) δ: 1.26(2H,m), 1.44(2H,m), 1.59(2H,m), 2.42(3H,s), 2.50(2H,s), 3.11(2H,s), 3.36(4H,m), 6.89(4H,d), 7.33(1H,s), 7.44(2H,d), 12.05(1H,s); m/z: (M+H)$^+$ at 484.1; m.p.: 158.1-159.6°C
21		^{1}H NMR (DMSO-d$_6$) δ: 1.20(2H,q), 1.45(4H,m), 1.92(2H,t), 3.12(2H,q), 6.85(1H,s), 6.94(1H,d), 7.20(5H,t), 7.24(1H,s), 7.55(1H,t), 8.65(1H,d), 10.34(1H,s); m/z: (M+H)$^+$ at 407; m.p.: 135.8°C-139.4°C
22		^{1}H NMR (DMSO-d$_6$) δ: 1.19-1.23 (2H,q), 1.42-1.46 (4H,m), 1.91-1.94(2H,t), 2.50 (2H,q), 7.13 (1H,s), 7.22-7.35 (4H,m), 7.50(1H,s), 7.77-7.79 (3H,m), 8.69 (1H,t), 8.65 (1H,s), 10.35 (1H,s); m/z: (M+H)$^+$ at 507.1; m.p.: 95.1-103.6 °C
23		^{1}H NMR (DMSO-d$_6$) δ: 1.17-1.19 (2H,q), 1.38-1.48 (4H,m), 1.90-1.93 (2H,t), 3.08-3.10 (2H,q), 6.85(1H,s), 7.12-7.14 (2H,dd), 7.38-7.40 (1H,s), 7.68-7.70 (2H,dd), 7.72 (1H,d), 8.66 (1H,t), 8.80 (1H,s), 10.33(1H,s); m/z: (M+2)$^+$at 454.1; hygroscopic

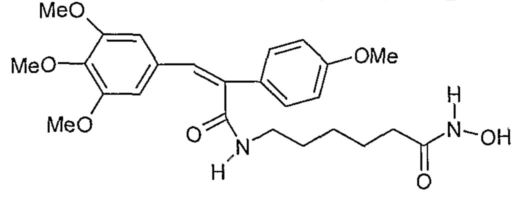
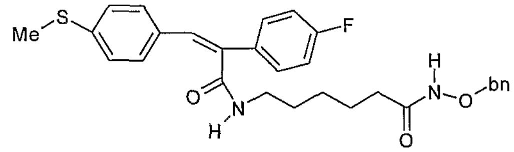
24		^{1}H NMR (DMSO-d_6) δ: 1.24-1.26 (2H,q), 1.44-1.51 (4H,m), 1.92-1.96 (2H,t), 3.13-3.16 (2H,q), 6.66 (1H,s), 6.98 (1H,d), 7.04-7.05 (1H,d), 7.13 (2H,dd), 7.50 (2H,dd), 7.62-7.63 (1H,d), 8.10-8.12 (1H,t), 8.67 (1H,s), 10.34 (1H,s); m/z: $(M+H)^+$at 483.9; m.p.:128.8-134.9 °C
25		^{1}H NMR (DMSO-d_6) δ: 1.21-1.22 (2H,q), 1.40-1.48 (2H,m), 1.91-1.95 (2H,t), 3.10-3.11 (2H,q), 6.99 (1H,m), 7.14-7.56 (7H,m), 7.56 (1H,t), 8.16 (1H,t), 8.90 (1H,s), 10.34(1H,s); m/z: $(M+H)^+$at 412.9; hygroscopic
26		^{1}H NMR (DMSO-d_6) δ: 1.02 (3H, s), 1.17-1.21 (2H,q), 1.39-1.49 (4H,m), 1.90-1.94 (2H,t), 3.10-3.11 (2H,q), 7.41-7.43 (2H,dd), 7.53-7.56 (1H,d), 7.52 (1H,s), 7.84 (2H,dd), 8.67 (1H,s), 8.81 (1H,s), 10.34 (1H,s); m/z: $(M+H)^+$at 441.8; m.p.: 66.1-75.2 °C
27		^{1}H NMR (DMSO-d_6) δ: 1.19-1.23 (2H, q), 1.42-1.46 (4H, m), 1.91-1.94(2H, t), 2.50 (2H, q), 6.57 (1H, s), 7.30-7.47 (4H, m), 8.00 (1H, t), 8.20-8.22 (2H, m), 8.64 (1H, t), 8.68 (1H, s), 10.35 (1H, s); m/z: $(M+H)^+$ at 452.8; hygroscopic
28		^{1}H NMR (DMSO-d_6) δ: 1.19-1.22 (2H,q), 1.41-1.45 (4H,m), 1.91-1.94(2H,t), 2.52 (2H,q), 3.78 (3H, s), 7.13 (1H,s), 6.97-6.99 (4H,m), 7.06-7.08 (2H,dd), 7.24-7.25 (2H,dd), 7.27 (1H,s), 7.47 (1H,s), 8.65 (1H,s), 10.35 (1H,s); m/z: $(M+H)^+$at 417.1; hygroscopic

29		^{1}H NMR (DMSO-d_6) δ: 1.20-1.22 (2H,q), 1.39-1.43 (4H,m), 1.90-1.92(2H,t), 2.50 (2H,q), 3.68 (3H, s), 6.71-6.73 (2H,dd), 6.89-6.91 (2H,dd), 7.15-7.44 (7H,m), 8.67 (1H,s), 10.33 (1H,s); m/z: $(M+H)^+$ at 383.2; m.p.: 117.2-119.6 °C
30		^{1}H NMR (DMSO-d_6) δ: 1.16-1.29 (4H,m), 1.44-1.53 (4H,m), 1.95-2.21 (2H,t), 6.96-6.97 (1H,dd), 6.98-7.03 (2H,dd), 7.31-7.33 (2H,dd), 7.48-7.7.49 (2H, t), 7.58 (1H,s), 7.79-7.80 (1H,m), 8.07-8.09 (1H,m), 8.69 (1H,s), 10.36 (1H,s); m/z: $(M+H)^+$ at 432.1; sticky material
31		^{1}H NMR (DMSO-d_6) δ: 1.34-1.35 (2H,m), 1.53-1.56 (4H,m), 1.61-1.65 (2H,t), 2.07-2.11 (2H,t), 3.35(2H,m), 6.71-6.76 (2H,m), 7.13-7.15 (2H,dd), 7.22-7.24 (1H,dd), 7.34-7.35 (2H, m), 7.57 (1H,s), 7.59 (1H,s), 8.69 (1H,s), 10.36 (1H,s); m/z: $(M+H)^+$ at 405.1; m.p.: 156.2-166.9 °C
32		^{1}H NMR (DMSO-d_6) δ: 1.18-1.19 (2H,m), 1.37-1.47 (4H,m), 1.91-1.93 (2H,t), 3.09-3.10 (2H,t), 3.48 (6H, s), 3.59 (3H, s), 4.77 (2H, s), 6.33 (1H, s), 6.83-6.85 (2H, dd), 6.97-6.99 (2H, dd), 7.10 (1H,t), 7.32-7.36 (6H, m), 9.60 (1H,s), 10.94 (1H,s); m/z: $(M+H)^+$ at 549.2; hygroscopic
33		^{1}H NMR (DMSO-d_6) δ: 1.08-1.26 (2H,m), 1.39-1.48 (4H,m), 1.94-1.98 (2H,t), 3.09-3.11 (2H,t), 3.52 (6H, s), 4.77 (2H, s), 4.79 (1H, s), 6.14-6.15 (2H, d), 6.33 (1H, t), 7.19-7.22 (4H,m), 7.24 (1H,dd), 7.34-7.36 (4H, m), 7.48 (1H,s), 10.94 (1H,s); m/z: $(M+H)^+$

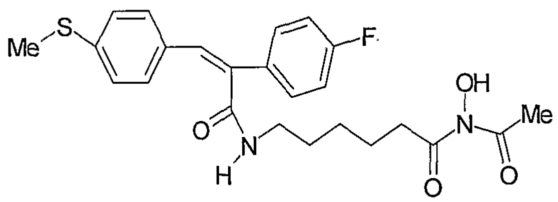
		at 521.2; m.p.: 79.9-86.7 °C
34		^{1}H NMR (DMSO-d6) δ: 1.19-1.24(2H, m), 1.40-1.51 (4H, m), 1.91-1.95 (2H, m), 3.08-3.13 (2H, m), 6.85(1H, s), 6.86-6.96 (1H, m), 7.17-7.34(6H, m) 8.63-6.67 (2H, s), 10.34(1H, s); m/z: $(M+H)^+$ at 407.1; m.p: 135.8-139.4 °C
36		^{1}H NMR (DMSO-d6) δ: 1.24-1.27 (3H, m), 1.43-1.45 (3H,m), 1.57-1.61 (2H, m), 2.40-2.43 (2H, m), 7.20-7.44 (8H, m), 7.45-7.53 (1H, m), 7.55-7.56 (1H, m), 12.05 (2H, s); m/z: $(M+H)^+$at 474.2; m.p.:199.1-202.3 °C
37		^{1}H NMR (DMSO-d6) δ: 1.18-1.19 (2H, m), 1.37-1.48 (4H, m), 1.90-1.93 (2H, m), 3.07-3.09 (2H, m), 5.96-5.97 (1H, m), 6.43-6.44 (1H, m), 7.32-7.34 (5H, m), 8.68 (2H, s), 10.34 (1H, s); m/z: $(M+H)^+$ at 395.1; m.p.: 121.1-127.2 °C
38		^{1}H NMR (DMSO-d6) δ: 1.22-1.25 (2H, m), 1.43-1.52 (4H, m), 1.91-1.95 (2H, m), 2.41 (3H, s), 3.08-3.11 (2H, m), 6.89-6.91 (2H, m), 7.06-7.08 (2H, m), 7.37-7.38 (3H, m), 7.65-7.66 (2H, m), 7.75-7.77 (1H, m), 8.67 (1H, s), 10.34 (1H, s); m/z: $(M+H)^+$at 467.2; m.p.:132.5-133.8 °C
39		^{1}H NMR (DMSO-d6) δ: 1.03-1.04 (2H, m), 1.19-1.22 (2H, m), 1.41-1.50 (4H, m), 3.12-3.59 (2H, m), 7.49-7.51 (2H, m), 7.66-7.67 (1H, m), 7.72 (1H, s), 7.77-7.80 (1H, s), 7.86-7.90 (2H, m), 8.66-8.67 (2H, m), 10.33 (1H, s); m/z: $(M+H)^+$at 428.0; off white sticky solid;

40		^{1}H NMR (DMSO-d6) δ: 1.22-1.25 (2H, m), 1.44-1.50 (4H, m), 1.92-1.96 (2H, m), 3.13 –3.16 (2H, m), 3.31(4H,m), 6.90 (1H, s), 6.96-6.98 (2H, m), 7.05 (1H, s), 7.16-7.18 (1H, m), 7.40-7.41 (1H, m), 7.85 (1H, m), 10.35 (1H, s); m/z: (M+H)$^+$at 437.1; pale brown sticky solid
41		^{1}H NMR (DMSO-d6) δ: 1.22-1.27 (2H, m), 1.43-1.48 (4H, m), 1.91-1.95 (1H, m), 2.20 (1H, s), 2.41 (3H, s), 3.10-3.12 (2H, m), 6.91-6.93 (2H, m), 7.06-7.09 (2H, m), 7.45-7.51 (3H, m), 7.70-7.74 (1H, s), 8.25-8.27 (1H, m), 8.67 (1H, s), 10.34 (1H, s), 12.0 (1H, s); m/z: (M+H)$^+$ at 444.1; m.p.138.2-143.9 °C
42		^{1}H NMR (DMSO-d6) δ: 1.18-1.23 (2H, m), 1.38-1.49 (4H, m), 1.91-1.94 (2H, m), 3.07-3.12 (2H, m), 6.80-6.82 (2H, m), 6.94-6.96 (2H, m), 7.03-7.04 (1H, m), 7.15-7.16 (1H, m), 7.24-7.28 (2H, m), 7.32-7.34 (1H, m), 8.67 (1H, s), 9.88 (1H, s), 10.35 (1H, s); m/z: (M+H)$^+$at 421.1; m.p.100.3-103.9 °C
43		^{1}H NMR (DMSO-d6) δ: 1.20-1.23 (2H, m), 1.41-1.50 (4H, m), 1.91-1.95 (2H, m), 2.44 (3H, s), 3.11-3.15 (2H, m), 6.96 (1H, s), 7.02-7.04 (2H, m), 7.10-7.12 (3H, m), 7.38 (1H, s), 7.59-7.65 (2H, m), 8.78 (1H, s), 10.23 (1H, s); m/z: (M+H)$^+$ at 405.1; m.p.147.1-149.9 °C
44		^{1}H NMR (DMSO-d6) δ: 1.15-1.18 (2H, m), 1.36-1.47 (4H, m), 1.89-1.93 (2H, m), 3.06-3.08 (2H, m), 7.03 (1H, s), 7.17-7.20 (1H, m), 7.23-7.26 (3H, m), 7.34-7.38 (2H, m),

		7.68 (1H, s), 8.68 (1H, s), 10.33 (1H, s); m/z: (M+H)$^+$at 411.1; m.p.181-185.2 °C
45		^{1}H NMR (DMSO-d6) δ: 1.18-1.24 (2H, m), 1.40-1.48 (4H, m), 1.91-1.95 (2H, m), 2.07 (3H, s), 3.08-3.11 (2H, m), 6.74-6.77 (1H, m), 6.93-6.98 (2H, m), 7.16-7.19 (2H, m), 7.22-7.27 (2H, m), 7.34 (1H, s), 7.48 (1H, s), 8.68 (1H, s), 10.34 (1H, s); m/z: (M+H)$^+$ at 411.1; m.p.:161.2-163.1 °C
46		^{1}H NMR (DMSO-d6) δ: 1.18-1.23 (2H, m), 1.38-1.49 (4H, m), 1.90-1.94 (2H, m), 3.08-3.11 (2H, m), 3.32 (3H, s), 6.37 (1H, s), 6.55-6.57 (1H, m), 6.61-6.63 (1H, m), 7.19-7.21 (2H, m), 7.22-7.30 (3H, m), 7.34 (1H, s), 8.67 (1H, s), 9.34 (1H, s), 10.34 (1H, s); m/z: (M+H)$^+$at 417.1;m.p.:162-167 °C
47		^{1}H NMR (DMSO-d6) δ: 1.22-1.24 (2H, m), 1.42-1.50 (4H, m), 1.92-1.95 (2H, m), 3.11-3.12 (2H, m), 7.03-7.09 (4H, m), 7.36-7.38 (2H, m), 7.42 (1H, s), 7.72-7.76 (3H, m), 8.68 (1H, s), 10.35 (1H, s); m/z: (M+H)$^+$at 439.1; m.p.:103-105.2 °C
48		^{1}H NMR (DMSO-d6) δ: 1.20-1.21 (2H, m), 1.39-1.43 (4H, m), 1.91-1.94 (2H, m), 3.09-3.11 (2H, m), 3.34 (6H, s), 3.60 (3H, s), 6.30 (2H, s), 7.21-7.24 (4H, m), 7.29-7.31 (1H, m), 7.38 (1H, s), 8.76 (1H, s), 10.34 (1H, s); m/z: (M+H)$^+$at 461.1; m.p:153-157 °C
49		^{1}H NMR (DMSO-d$_6$) δ: 1.67-1.69 (2H,t), 1.93-2.07 (8H,m), 2.79-2.82 (2H,t), 3.15-3.19 (4H,m), 3.52 (6H,s), 7.47-7.49 (3H,m), 7.55 (1H,s), 7.98-8.00 (2H,dd), 8.25-8.27

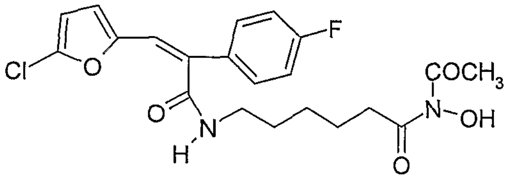
		(2H,dd), 8.69 (1H,s), 10.36 (1H,s), 12.05 (1H,s), 13.63 (1H,s); m/z: $(M+H)^+$ at 501.5; hygroscopic
50		^{1}H NMR (DMSO-d6) δ: 1.19-1.20 (2H, m), 1.38-1.58 (4H, m), 1.90-1.94 (2H, m), 3.09-3.10 (2H, m), 3.47 (6H, s), 3.59 (3H, s), 3.77 (3H, s), 6.32 (2H, s), 7.02-7.04 (2H, m), 7.10-7.12 (2H, m), 7.19 (1H, s), 7.34 (2H, s), 8.56 (1H, s); m/z: $(M+H)^+$at 473.2; Red sticky liquid;
51		^{1}H NMR (DMSO-d6) δ: 1.20-1.25 (2H, m), 1.39-1.48 (4H, m), 1.92-1.94 (2H, m), 2.41 (3H, s), 3.09-3.11 (2H, s), 4.77 (2H, s), 6.88-6.91 (2H, m), 7.04-7.06 (2H, m), 7.18-7.33 (4H, m), 7.35-7.37 (6H, m), 7.44 (1H, s), 10.95 (1H, s); m/z: $(M+H)^+$at 507.1; m.p.:134-136 °C

Example 52: Synthesis **of** 7V-acetyl-6-{[(2Z)-3-(4-thiomethyl phenyl)-2-(4-fluoro phenyl)- acryl **amide]** }-*N*-hydroxyhexanamide.

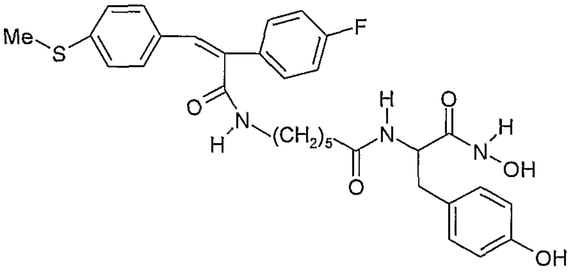


To a solution of (2Z)-3-(4-Thiomethylphenyl)-2-(4-fluorophenyl)-N-[6-(hydroxy amine)-6-oxohexyl]acrylamide (prepared following the similar procedure described for example 1) in dichloromethane (5 mL), pyridine (0.27 mL, 3.96 mmol) was added and cooled to 0 ^{0}C followed by the dropwise addition of acetyl chloride (0.25 mL, 3.6 mmol) and the reaction mixture was stirred for 1 h. The reaction mixture was diluted with dichloromethane (30 mL) and washed with water, the organic layer was dried on anhydrous Na_2SO_4, concentrated and triturated with d.ichloromethane/hexane (1:1) (20 mL) to afford 0.06 g (35 % yield) of the title compound as a colorless sticky mass. ^{1}H NMR (DMSO-d6) δ: 1.23-1.26 (2H, m), 1.40-1.53 (4H, m), 2.08-2.13 (3H, m), 2.50 (3H, m), 2.72-2.88 (2H, m), 3.09-3.11 (2H, m), 6.89-6.91 (2H, m), 7.05-7.07 (2H, m), 7.16-7.26 (4H, m), 7.33 (IH, s), 7.44 (IH, s), 11.35 (IH, s); and m/z: $(M+H)^+$at 437.2

The following compound was prepared according to the above procedure:

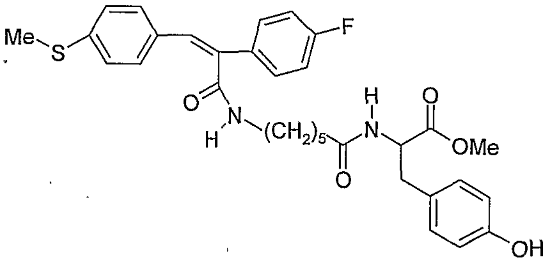
Exp.	Structure	Analytical Data
53		^{1}H NMR (DMSO-CJO) δ: 1.22-1.23 (3H, m), 1.38-1.42 (2H, m), 1.48-1.52 (2H, m), 2.07-2.50 (4H, m), 3.35(2H,m), 5.96-5.97 (IH, m), 6.43-6.44 (IH, m), 7.23-7.35 (5H, m), 10.33 (IH, s), 11.55 (IH, s); m/z: $(M+H)^+$ at 437.2; pale brown sticky liquid

Example 54: Synthesis of $N_r$hydroxy-2-{[(2Z)-3-(4-thiomethyl phenyl)-2-(4-fluoro phenyl)- acryl amide] 6-oxohexyl]amino}-3-(4-hydroxy phenyl) propanamide.



Stage 1

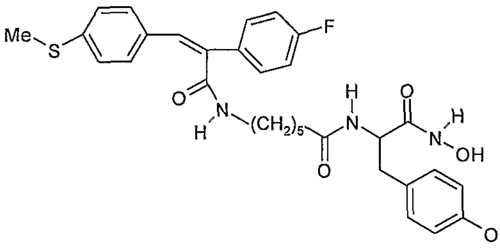
Synthesis of Methyl-2-{[(2Z)-3-(4-thiomethyl phenyl)-2-(4-fluoro phenyl)-acrylamide] 6-oxohexyl]amino}-3-(4-hydroxy phenyl)propanoate.



To a solution of 6-{[(2Z)~3-(4-Thiomethyl phenyl)-2-(4-fluorophenyl) prop-2-enoyl] amino} hexonic acid (0.050 g, 0.12 mmol) (prepared according to the procedure described in example 1 stage 3) in THF (3 mL) was added DIPEA (0.06 mL, 0.37 mmol), BOP (0.065 g, 0.14 mmol), HOBt (0.020 g, 0.14 mmol) followed by the methyl ester of tyrosine (0.029 g, 0.14 mmol). The reaction was stirred at room temperature for 12 hours, THF was removed under reduced pressure, the crude was taken up in EtOAc (25 mL), washed with water, and the organic layer was dried over anhydrous Na_2SO_4, concentrated and purified by silica gel column chromatography using dichloromethane/MeOH (9.8:0.2) to afford Methyl-2-{[(2Z)-3-(4-thiomethyl phenyl)-2-(4-fluoro phenyl)- acrylamide] 6-oxohexyl]amino}-3-(4-hydroxy phenyl)propanoate 0.040 g, 55 % yield as an off-white solid.

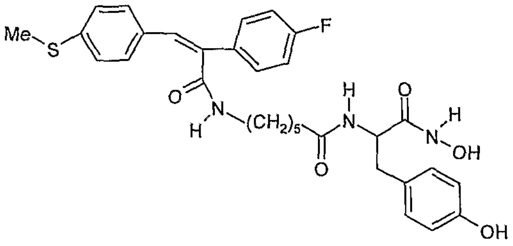
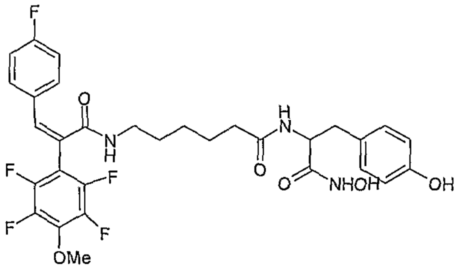
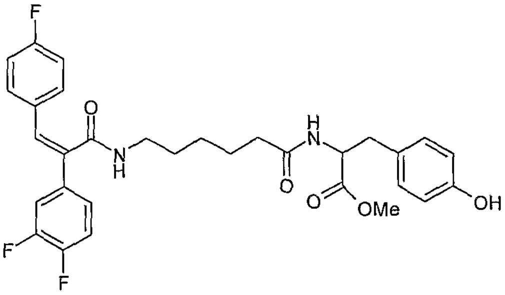
Stage 2

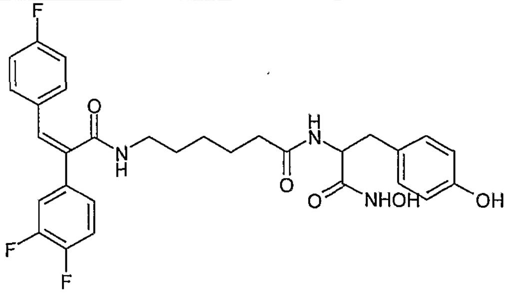
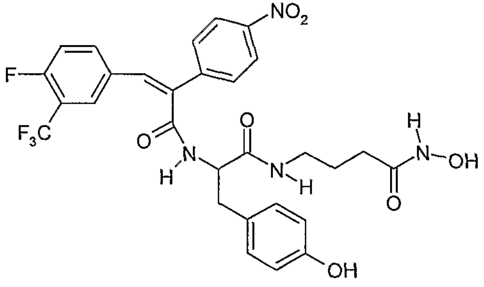
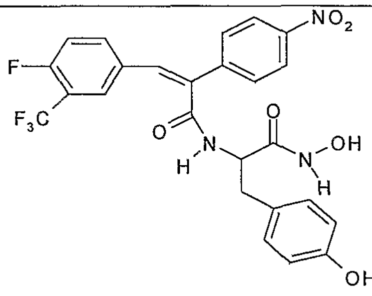
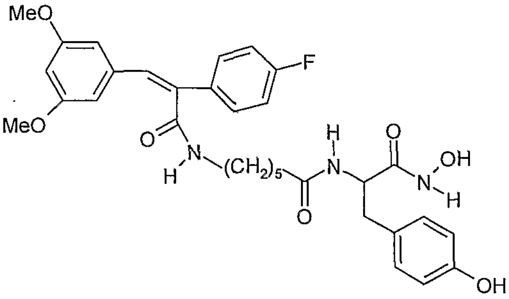
Synthesis **of** N-hydroxy-2-{[(2Z)-3-(4-thiomethyI phenyl)-2-(4-fluoro phenyl)-acryl **amide]** 6-oxohexyl]amino}-3-(4-hydroxy phenyl)propanamide.

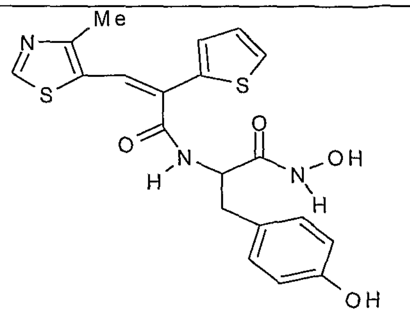
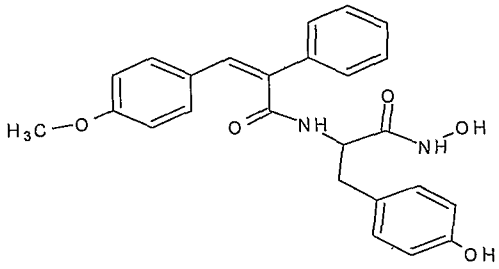
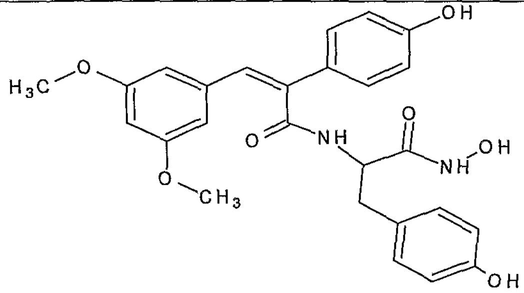


Hydroxylamine hydrochloride (0.086 g, 1.2 mmol) in methanol (2 mL) was mixed with KOH (0.069 g, 1.2 mmol) in methanol (3 mL) at 40 ^{0}C, and cooled to 0^{0}C when a white precipitate was formed which was filtered. The filtrate was immediately added to the Methyl-2-{[(2Z)-3-(4-thiomethyl phenyl)-2-(4-fluoro phenyl)- acrylamide] 6-oxohexyl]amino}-3-(4-hydroxy phenyl)propanoate (0.040 g, 0.06 mmol) followed by the addition of KOH (0.0057 g, 0.13 mmol), and the mixture was stirred at room temperature, for 1 hour. Around 2OmL of water was added and neutralized to a pH of 7 by dilute AcOH. On standing a colorless precipitate started was formed which was filtered, dried and triturated with dichloromethane/hexanes (1:1, 20 mL), to afford the required compound as a pure colorless solid (0.025 g, 62.5 %). ^{1}H NMR (DMSO-d6) δ: 1.02-1.04 (2H, m), 1.10 (IH, s), 1.99-2.01 (2H, m), 2.41 (3H, s), 2.50-2.67 (2H, m), 3.06-3.08 (2H, m), 4.47 (IH, s), 6.02-6.62 (2H, m), 6.89-6.91 (2H, m), 6.97-6.99 (2H, m), 7.05-7.07 (2H, m), 7.18-7.24 (4H, m), 7.34 (4H, s), 7.42 (IH, s), 8.00 (IH, s), 8.82 (IH, s), 9.15 (IH, s), 10.61 (IH, s); and m/z: (M+H)$^+$ at 580.1; **m.p.:142.1-145.4** ^{0}C

The following compounds were prepared according to the above procedure:

Exp.	**Structure**	Analytical **Data**
55		H NMR (DMSO-d6) δ: 1.17-1.19 (2H, m), 1.41-1.44 (4H, m), 2.04-2.08 (2H, m), 2.50 (2H, s), 3.1 1-3.13 (2H, m), 3.57 (3H, s), 4.03 (3H, s), 4.7 (IH, s), 6.63-6.65 (2H, m), 6.95-6.99 (3H, m), 7.12-7.14 (4H, m), 7.97 (IH, s), 8.19-8.20 (IH, s), 9.21 (IH, s); m/z: (M+H)$^+$ at 635.2; white hygroscopic solid
56		^{1}H NMR (DMSO-d6) δ: 1.13-1.15 (2H, m), 1.23 .(2H, s), 1.37-1.43 (4H, m), 2.01-2.05 (2H, m), 3.10-3.12 (2H, m), 4.02 (3H, s), 5.75 (IH, s), 6.61-6.63 (2H, m), 6.95-6.99 (3H, m), 7.12-7.14 (4H, m), 7.95-8.02 (2H, m), 8.80 (IH, s), 9.14 (IH, s), 10.06 (IH, s); m/z: (M+H)$^+$at 636.1; m.p.:162.4-165.2 °C
57		^{1}H NMR (DMSO-d6) δ: 1.14-1.16 (2H, m), 1.24-1.25 (2H, m), 1.37-1.43 (4H, m), 2.03-2.06 (2H, m), 3.06-3.33 (2H, m), 3.57 (3H, s), 4.35 (IH, s), 6.63-6.65 (2H, m), 6.85 (IH, m), 6.92-6.98 (3H, m), 7.17-7.21 (2H, m), 7.23-7.34 (3H, m), 7.51-7.54 (IH, m), 8.17 (IH, s), 8.19 (IH, s), 9.2 (IH, s); m/z: (M+H)$^+$ at 569.1; creamy white hygroscopic solid
58		^{1}H NMR (DMSOd ó) δ: 1.09-1.12 (2H7 m), 1.23-1.29 (2H, m), 1.33-1.39 (4H, m), 2.2-2.03 (2H, m), 3.07-3.08 (2H, m),

		5.39 (1H, s), 6.60-6.62 (2H, m), 6.95-6.99 (1H, m), 7.17-7.28 (3H, m), 7.30 (2H, s), 7.34 (2H, s), 7.51 (2H, s), 7.99 (1H, s), 8.02 (1H, s), 8.81 (1H, s), 9.14 (1H, s), 10.64 (1H, s); m/z: (M+H)$^+$at 570.1; Pale yellow hygroscopic solid
59		^{1}H NMR (DMSO-d_6) δ: 2.66-2.69 (2H,d), 2.85-2.89 (2H,t), 3.49-3.52 (1H,t), 4.21-4.25 (2H,t), 4.31-4.33 (2H, m), 6.65-6.67 (2H, dd), 7.01-7.03 (2H,dd), 7.29-7.37 (2H,m), 7.39-7.42 (3H, m), 7.72-7.74 (2H,m), 8.20-8.22 (2H, dd), 8.51 (1H, s), 9.62 (1H, s), 10.94 (1H,s); m/z: (M+H)$^+$ at 519.2; hygroscopic
60		^{1}H NMR (DMSO-d_6) δ: 2.78-2.86 (2H,m), 4.46 (1H,t), 6.65-6.67 (2H,dd), 7.00-7.02 (2H,dd), 7.28-7.30 (3H, m), 7.35-7.39 (3H, m), 7.99-8.02 (1H,d), 8.20-8.22 (2H,d), 8.91 (2H, s), 9.22 (1H,s), 10.72 (1H,s); m/z: (M+H)$^+$ at 534.0; off white solid hygroscopic
61		^{1}H NMR (DMSO-d_6) δ: 1.14-1.16 (1H,m), 1.17-1.19 (3H,m), 1.22-1.23 (2H,t), 1.39-1.43 (4H,t), 3.09-3.10 (2H,m), 3.53 (6H,s), 4.02-4.04 (1H,t), 6.15 (2H,s), 6.34 (1H,s), 6.98-7.00 (2H, dd), 7.18-7.20 (2H; dd), 7.22-7.27 (4H, m), 7.32-7.35 (1H, s), 7.45 (1H,s), 8.16-8.18 (1H,d), 8.90 (1H, s), 9.20 (1H,s), 10.73 (1H,s); m/z: (M+H)$^+$at 593.2; pale yellow solid hygroscopic

62		^{1}H NMR (DMSO-d$_6$) δ: 2.50 (3H, s), 2.73-2.84 (2H,m), 4.40-4.43 (1H,t), 6.62-6.64 (2H,dd), 6.90-6.96 (3H,m), 7.19-7.20 (1H, m), 7.21-7.22 (1H, dd), 7.71 (1H,s), 7.80-7.82 (1H,d), 8.90 (2H, s), 9.20 (1H,s), 10.73 (1H,s); m/z: $(M+H)^+$ at 430.0; off white solid hygroscopic
63		^{1}H NMR (DMSO-d$_6$) δ: 2.88-2.93 (2H,m), 3.69 (3H, s) 4.54 (1H,t), 6.63-6.65 (2H,dd), 6.73-6.75 (2H,dd), 6.86-6.93 (4H, m), 7.07-7.08 (1H, m), 7.13-7.15 (1H,d), 7.40-7.41 (3H,d), 8.91 (2H, s), 9.22 (1H,s), 10.72 (1H,s); m/z: $(M+H)^+$ at 432.9; hygroscopic
64		^{1}H NMR (DMSO-d$_6$) δ: 2.86-2.91 (2H,m), 3.54 (6H, s) 4.56 (1H,t), 6.20-6.21 (2H,dd), 6.34 (1H,md), 6.63-6.65 (3H, m), 6.77-6.80 (2H, m), 6.86-6.89 (4H,m), 7.18/-7.20 (1H,d), 7.23 (1H, s), 9.26 (1H,s), 9.64 (1H,s); m/z: $(M+H)^+$at 479.9; hygroscopic

Anti-cancer experimental methods

Anti-cancer screen:

Experimental drugs are screened for anti-cancer activity in three cell lines for their GI$_{50}$, TGI and LC$_{50}$ values (using five concentrations for each compound). The cell lines are maintained in DMEM containing 10% fetal bovine serum. 96 well micro titer plates are inoculated with cells in 100 μL for 24h at 37^{0}C, 5% CO2, 95% air and 100% relative humidity. 5000 HCT 116 cells/well, 5000 NCIH 460 cells/well and 5000 U251 cells/well are plated. A separate plate with these cell lines is also inoculated to determine cell viability before the addition of the compounds (To) (See **Table I).**

Addition of experimental drugs:

Following 24-hour incubation, experimental drugs are added to the 96 well plates. Each plate contains one of the above cell lines and the following in triplicate: five different concentrations (0.01, 0.1, 1, 10 and 100 μM) of four different compounds, appropriate dilutions of a cytotoxic standard and control (untreated) wells. Compounds are dissolved in DMSO to make 20 mM stock solutions on the day of drug addition and frozen at -20^{0}C. Serial dilutions of these 20 mM stock solutions are made in complete growth medium such that 100 μL of these drug solutions in medium, of final concentrations equaling 0.01, 0.1, 1, 10 and 100 μM can be added to the cells in triplicate. Standard drugs whose anti-cancer activity has been well documented and which are regularly used are doxorubicin and SAHA. **(See Table I).**

End-point measurement:

For T_0 measurement, 24 hours after seeding the cells, 10 μL of 3-(4,5-Dimethyl-2-thiazolyl)-2,5-diphenyl-2H-tetrazolium (MTT) solution per well is added and incubation carried out for 3 hours at 37°C, 5% CO_2, 95% air and 100% relative humidity, protected from light. Cells incubated with compounds for 48 hours are treated similarly except with the addition of 20μL MTT solution per well and a subsequent incubation under the same conditions. After 3 hours of MTT incubation, well contents are aspirated carefully followed by addition of 150 μL DMSO per well. Plates are agitated to ensure solution of the formazan crystals in DMSO and absorbance read at 570 nm. **(See Table I).**

Calculation of GI$_{50}$, TGI and LC$_{50}$:

Percent growth is calculated for each compound's concentration relative to the control and zero measurement wells (T_0; viability right before compound addition).

If a test well's O.D. value is greater than the T_0 measurement for that cell line

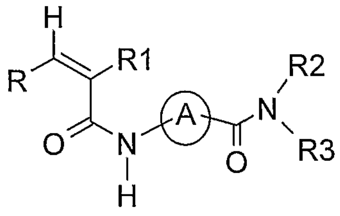
% Growth = (test - zero) / (control - zero) X 100

If a test well's O.D. value is lower than the T_0 measurement for that cell line, then, % Growth = (test - zero) / zero X 100

Plotting % growth versus experimental drug concentration, GI$_{50}$ is the concentration required to decrease % growth by 50%; TGI is the concentration required to decrease % growth by 100% and LC$_{50}$ is the concentration required to decrease % growth by 150%. (See Table I).

We claim:

1. A compound of formula (I),



(I)

derivatives, analogs, tautomeric forms, stereoisomers, polymorphs, solvates, pharmaceutically acceptable salts and compositions, metabolites and prodrugs thereof, wherein A represents $-(CH_2)_H$ which is optionally substituted or unsubstituted by groups selected from aryl, arylalkyl, and heteroaryl, which may be substituted, the substitutents are selected from hydroxy, and halogen;

suitable groups represented by R and Ri represent aryl groups comprising phenyl, and naphthyl, which may be substituted; heteroaryl groups comprising pyridyl, thienyl, furyl, pyrrolyl, oxazolyl, thiazolyl, imidazolyl, isooxazolyl, oxadiazolyl, triazolyl, thiadiazolyl, tetrazolyl, pyrimidinyl, pyrazinyl, and pyridazinyl, which may be substituted; and benzofused heteroaryl groups comprising quinoline, quinoxaline, acridine, and phenazine, which may be substituted;

suitable groups represented by R_2 and R_3 may be selected from hydrogen, hydroxyl, substituted or unsubstituted groups selected from, linear or branched $(C_1$-$C_4)$ alkyl groups comprising methyl, ethyl, n-propyl, isopropyl, n-butyl, isobutyl, and t-butyl, alkoxy groups comprising methoxy, ethoxy, propoxy, n-butoxy, isobutoxy, and t-butoxy; benzyloxy; acetyl; benzyloxy acetyl; cycloalkyl groups comprising cyclohexyl, cycloheptyl, and cyclooctyl; aryl groups comprising phenyl, and naphthyl; heterocyclyl groups comprising pyrrolidinyl, thiazolidinyl, oxazolidinyl, morpholinyl, thiomorpholinyl, piperidinyl, and piperazinyl; heteroaryl groups comprising pyridyl, thienyl, furyl, pyrrolyl, oxazolyl, thiazolyl, imidazolyl, isooxazolyl, oxadiazolyl, triazolyl, thiadiazolyl, tetrazolyl, pyrimidinyl, pyrazinyl, and pyridazinyl; benzofused heteroaryl groups comprising quinoline, quinoxaline, acridine, phenazine, and benzothiazole;

n is an integer in the range of 1 to 8;

when the groups R, R_1, R_2 and R_3 are substituted, the substituents (which are one or more) are selected from halogens comprising fluorine, chlorine, bromine, and iodine, hydroxy, nitro, cyano, azido, nitroso, amino, hydrazine, hydroxamate, formyl, alkyl, haloalkyl, haloalkoxy, cycloalkyl, aryl, benzyl, alkoxy, aryloxy, acyl, acyloxy, acyloxyacyl, heterocyclyl, heteroaryl, monoalkylamino, dialkylamino, acylamino, alkoxycarbonyl, aryloxycarbonyl comprising methoxy carbonyl, ethoxycarbonyl and the like; alkylsulfonyl, arylsulfonyl, alkylsulfinyl, arylsulfmyl, thioalkyl, arylthio, sulfamoyl, alkoxyalkyl groups and carboxylic acids and its derivatives like esters, hydroxamic acid and hydroxamate. In addition the substituents, may be further substituted;

furthermore, whenever the groups R, Ri, R_2 and R_3 represent substituted or unsubstituted 5 to 10 membered ring systems, the rings may be monocyclic or bicyclic, saturated or partially saturated or aromatic containing 1 to 4 heteroatoms selected from O, S and N.

2. The compound of claim 1, selected from a group consisting of:

(2Z)-3-(3,5-Dimethoxyphenyl)-2-(4-fluorophenyl)-N-[6-(2-hydroxybenzyl amine)-6-oxohexyljacrylamide;

(2Z)-3-(3,5-Dimethoxyphenyl)-2-(4-fluorophenyl)-N-[6-(3-hydroxybenzyl amine) -6-oxohexyl] acrylamide;

(2Z)-3-(3,5-Dimethoxyphenyl)-2-(4-fluorophenyl)-N-[6-(hydroxyamino)-6-oxo hexyl]acrylamide;

(2Z)-3-(3,5-Dimethoxyphenyl)-2-(4-hydroxyphenyl)-N-[6-(2-aminobenzyl amine)-6-oxo hexyl] acrylamide;

(2Z)-3-(3,5-Dimethoxyphenyl)-2-(4-hydroxyphenyl)-N-[6-(2-hydroxybenzyl amine) -6-oxohexyl]acrylamide;

(2Z)-3-(3,4,5-Trimethoxyphenyl)-2-(4-hydroxyphenyl)-N-[6-(2-hydroxybenzyl amine) -6-oxohexyl] acrylamide;

(2Z)-3-(3,4,5-Trimethoxyphenyl)-2-(4-hydroxyphenyl)-N-[6-(N,O dimethyl amine)-6-oxohexyl]acrylamide;

(2Z)-3-(4-Methyl-l,3-thiazol-5-yl)-2-(2-thienyl))-N-[6-(hydroxyamino)-6-oxo hexyl] acrylamide;

(2Z)-3-(3,5-Dimethoxyphenyl)-2-(4-nitrophenyl)-N-[6-(hydroxyamino)-6-oxo hexyl]acrylamide;

(2Z)-3-(3-Chloro,4-fluorophenyl)-2-(4-fluorophenyl)-N-[6-(hydroxyamino)-6-oxohexyljacrylamide;

(2Z)-3-(3,5-Dimethoxyphenyl)-2-(4-hydroxyphenyl)-N-[6-(hydroxyamino)-6-oxohexyl]acrylamide;

(2Z)-3-(4-Methyl-l,3-thiazol-5-yl)-2-(4-chlorophenyl)-N-[6-(hydroxyamino)-6-oxohexyljacrylamide;

(2Z)-3-(5-Bromo-2-thienyl)-2-(4-bromophenyl)-N-[6-(hydroxyamino)-6-oxohexyljacrylamide;

(2Z)-3-(4-Pyridine)-2-(4-fluorophenyl)-N-[6-(hydroxy amino)-6-oxo hexyl] acrylamide;

(2Z)-3-(4-Pyridine)-2-(4~fluorophenyl)-N-[6-(4-hydroxy-2-nitrobenzyl amine)-6-oxohexyl] acrylamide;

(2Z)-3-(4-Thiomethylphenyl)-2-(4-fluorophenyl)-N-[6-(hydroxyamine)-6-oxohexyl]acrylamide;

(2Z)-3-(4-Thiomethylphenyl)-2-(4-fluorophenyl)-N-[6-(5-nitro-2-thiazole amine)-6-oxohexyl]acrylamide;

(2Z)-3-(4-Thiomethylphenyl)-2-(4-fluorophenyl)-N-[6-(N,O dimethylamine)-6-oxohexyl] acrylamide;

(2Z)-3-(4-Thiomethylphenyl)-2-(4-fluorophenyl)-N-[6-(5-methyl-2-benzo thiazole amine)-6-oxohexyl]acrylamide;

(2Z)-3-(4-Thiomethylphenyl)-2-(4-fluorophenyl)-N-[6-(2-thiazoleamine)-6-oxohexyl]acrylamide;

(2Z)-3-(3,4-Difluorophenyl)-2-(4-fluorophenyl)-N-[6-(2-thiazoleamine)-6-oxo hexyl]acrylamide;

(2Z)-3-(4-Fluoro-3-trifluoromethyl-phenyl)-2-(4-trifluoromethylphenyl)-N-[6-(hydroxyamino)-6-oxohexyl]acrylamide;

(2Z)-3-(4-Methylthiazol-5-yl)-2-(4-bromophenyl)-N-[6-(hydroxyamino)-6-oxo hexyljacrylamide;

(2Z)-3-(4-Fluoro-3-trifluoromethyl-phenyl)-2-(4-nitrophenyl)-N-[6-(hydroxy amino)-6-oxohexyl]acrylamide;

(2Z)-3-(2,3,5-Trifluoro-phenyl)-2-(thiophene-2-yl)-N-[6-(hydroxyamino)-6-oxo hexyljacrylamide;

(2Z)-3-(4-Methylthiazol-5-yl)-2-(4-trifluoromethylphenyl)-N-[6-(hydroxyamino) -6-oxo hexyljacrylamide;

(2Z)-3-(2,3,5-Trifluoro-phenyl)-2-(4-nitrophenyl)-N-[6-(hydroxyamino)-6-oxo hexyl]acrylamide;

(2Z)-3-(3-Chlorophenyl)-2-(4-methoxyphenyl)-N-[6-(hydroxyamino)-6-oxo hexyl]acrylamide;

(2Z)-3-(4-Methoxyphenyl)-2-(phenyl)-N-[6-(hydroxyamino)-6-oxo hexyl] acryl amide;

(2Z)-3-(2-Nitrophenyl)-2-(4-chlorophenyl)-N-[6-(hydroxyamino)-6-oxohexyl] acrylamide;

(2Z)-3-(2-Chloro-4-fluorophenyl)-2-(phenyl)-N-[6-(hydroxyammo)-6-oxohexyljacrylamide;

(2Z)-3-(2,3,4-Trimethoxyphenyl)-2-(4-hydiOxyphenyl)-N-[6-(hydroxyamino)-6-oxohexyl]acrylamide;

(2Z)-3-(3,5-Dimethoxyphenyl)-2-(4-fluorophenyl)-N-[6-(hydroxyamino)-6-oxo hexyljacrylamide;

(2Z)-3-(3,4-Difluorophenyl)-2-(4-fluorophenyl)-N-[6-(hydroxyamino)-6-oxohexyljacrylamide;

(2Z)-3-(3,4-Difluorophenyl)-2-(4-fluorophenyl)-N-[6-(N,Odimethyl hydroxy amino)-6-oxo hexyl]acrylamlde;

(2Z)-3-(3,4 Difluorophenyl)-2-(4-fluoro phenyl)-N-[6-(amino thiazol-2-yl)-6-oxo hexyl]acrylamide;

(2Z)-3-(5-Chloro-2-furyl)-2-(4-fluorophenyl)-N-[6-(hydroxyamino)-6-oxo hexyljacrylamide;

(2Z)-3-(4-Thiomethylphenyl)-2-(4-trifluoromethylphenyl)-N-[6-(hydroxyamino)-6-oxo hexyljacrylamide;

(2Z)-3-(Thiazol-2-yl)-2-(4-trifluoromethylphenyl)-N-[6-(hydroxyamino)-6-oxo hexyljacrylamide;

(2Z)-3-(2,3,6 Trifluorophenyl)-2-(4-methoxyphenyl)-N-[6-(hydroxyamino)-6-oxo hexyljacrylamide;

(2Z)-3-(4-Thiomethylphenyl)-2-(4-nitrophenyl)-N-[6-(hydroxyamino)-6-oxo hexyljacrylamide;

(2Z)-3-(3-Chloro-4-fluorophenyl)-2-(4-hydroxyphenyl)-N-[6-(hydroxyamino)-6-oxo hexyljacrylamide;

(2Z)-3-(4-Thiomethylphenyl)-2-(thiophene-2-yl)-N-[6-(hydroxyamino)-6-oxo hexyljacrylamide;

(2Z)-3-(5-Chlorothiophen-2-yl)-2-(4-fluorophenyl)-N-[6-(hydroxyamino)-6-oxo hexyl]acrylamide;

(2Z)-3-(4-Fluoro-3-methylphenyl)-2-(4-fluorophenyl)-N-[6-(hydroxyamino)-6-oxo hexyl]acrylamide;

(2Z)-3-(4-Hydroxy-3-methoxyphenyl)-2-(4-fluorophenyl)-N-[6-(hydroxyamino) - 6-oxo hexyljacrylamide;

(2Z)-3-(4-Trifluoromethylphenyl)-2-(4-fluorophenyl)-N-[6-(hydroxyamino)-6-oxo hexyljacrylamide;

(2Z)-3-(3,4,5-Trimethoxyphenyl)-2-(4 fluorophenyl)-N-[6-(hydroxyamino)-6-oxo hexyljacrylamide;

N-[4-(Hydroxyamino)-4-oxobutyl]-6-{[(22)- 3-(3,5 dimethoxyphenyl)-2-(4 nitrophenyl)-acrylamide]}hexanamide;

(2Z)-3-(3,4,5-Trimethoxyphenyl)-2-(4-methoxyphenyl)- N-[6-(hydroxyamino)-6-oxo hexyljacrylamide;

(2Z)-3-(4-Thiomethylphenyl)-2-(4-fluorophenyl)-N-[6-(O-benzyl hydroxyamino)-6-oxo hexyljacrylamide;

N-Acetyl-6-{[(2Z)-3-(4-thiomethylphenyl)-2-(4-fluorophenyl)- acrylamide] }-*N*-hydroxyhexanamide;

N-Acetyl-6-{[(2Z)-3-(5-chloro-2-furyl)-2-(4-fluorophenyl)-acrylamide]}- *N*-hydroxy hexanamide;

N-Hydroxy-2-{[(2Z)-3-(4-thiomethylphenyl)-2-(4-fluorophenyl)-acrylamide]6-oxohexyl]amino}-3-(4-hydroxy phenyl) propanamide;

Methyl-2-{[(2Z)-3-(2,3,5,6 tetrafluoro-4-methoxyphenyl)-2-(4-fluorophenyl)- acryl amide] 6-oxohexyl]amino}-3-(4-hydroxy phenyl) propanoate;

N-Hydroxy-2-{[(2Z)-3-(2,3,5,6 tetrafluoro-4-methoxyphenyl)-2-(4-fluorophenyl)-acrylamide] 6-oxohexyl]amino}-3-(4-hydroxy phenyl)propanamide;

Methyl-2-{[(2Z)-3-(3,4 difluorophenyl)-2-(4-fluorophenyl)- acrylamide] 6-oxohexyl]amino}-3-(4-hydroxy phenyl)propanoate;

N-Hydroxy-2-{[(2Z)-3-(3,4 difluorophenyl)-2-(4-fluorophenyl)- acrylamide] 6-oxohexyl]amino}-3-(4-hydroxy phenyl)propanamide;

(2Z)-*N*-(l-(4-hydroxybenzyl)-2-{[4-(hydroxyamino)-4-oxobutyl]amino}-2-oxo ethyl)- 3-(3-fluoro-4-trifluoro methyl phenyl)-2-(4-nitrophenyl)- acrylamide;

(2Z)-*N*-[2-(hydroxyamino)-l-(4-hydroxybenzyl)-2-oxoethyl]-3-(4-fluoro-3-trifluoromethyl phenyl)-2-(4-nitro phenyl)-acrylamide;

N-Hydroxy-2-{[(2Z)-3-(3,4 dimethoxyphenyl)-2-(4-fluorophenyl)- acrylamide] 6-oxohexyl]amino}-3-(4-hydroxy phenyl)propanaraide;

(2Z)~*N*-[2-(hydroxyamino)- 1-(4-hydroxybenzyl)-2-oxoethyl]- 3-(4-methyl thiazol-5-yl)-2-(thiophen-2-yl)-acrylamide;

(2Z)-*N*-[2-(hydroxyamino)-l-(4-hydroxybenzyl)-2-oxoethyl]- 3-(4 methoxy phenyl)-2-(phenyl)-acrylamide; .

(2Z)-*N*-[2-(hydroxyamino)-l-(4-hydroxybenzyl)-2-oxoethyl]- 3-(3,5 dimethoxy phenyl)-2-(4-hydroxy phenyl)-acrylamide and

3. The pharmaceutical composition comprising a compound of formula (I) according to claim 1, as an active ingredient, along with a pharmaceutically acceptable carrier, diluent, excipient or solvate.

4. The pharmaceutical composition according to claim 3, wherein the pharmaceutical composition is in a tablet, capsule, powder, syrup, solution, aerosol or suspension.

5. The pharmaceutical composition according to claim 3, wherein the amount of the compound of formula (I) in the composition is less than 70 % by weight.

6. The method for modulating the number of biological processes, including transcription, cell cycle and regulating nucleosomal integrity.

7. The method of treating diseases that are involved in cellular growth such as malignant tumors, autoimmune diseases, skin diseases, infections.

8. The method of inhibiting HDAC in a cell comprising treating the said cell with an effective amount of a compound according to claim 1.

9. The method for the treatment of a condition mediated by HDAC comprising administering to a subject suffering from a condition mediated by HDAC a therapeutically effective amount of a compound according to the claim 1.

10. The method for the treatment of psoriasis comprising administering to a subject suffering from psoriasis a therapeutically effective amount of a compound according to claim 1.

11. The method for the treatment of a proliferative condition comprising administering to a subject suffering from a proliferative condition a therapeutically effective amount of a compound according to claim 1, to the mammal in need thereof.

12. The method for the treatment and/or prevention of cancer comprising administering to a subject suffering from cancer a therapeutically effective amount of a compound according to claim 1, to the mammal in need thereof.