(12) STANDARD PATENT (11) Application No. **AU 2004205372 B2**
(19) AUSTRALIAN PATENT OFFICE

(54) Title
Hydroxamic acid compounds comprising an ester or ketone linkage as HDAC inhibitors

(51) International Patent Classification(s)
C07C 259/10 (2006.01) ***A61P 35/00*** (2006.01)

(21) Application No: **2004205372** (22) Date of Filing: **2004.01.19**

(87) WIPO No: **WO04/065354**

(30) Priority Data

(31) Number	(32) Date	(33) Country
60/440,616	**2003.01.17**	**US**

(43) Publication Date: **2004.08.05**
(44) Accepted Journal Date: **2011.02.24**

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(12) INTERNATIONAL APPLICATION PUBLISHED UNDER THE PATENT COOPERATION TREATY (PCT)

(19) World Intellectual Property Organization
International Bureau

(43) International Publication Date
5 August 2004 (05.08.2004)

PCT

(10) International Publication Number
WO 2004/065354 A1

(51) International Patent Classification[7]: C07C 259/10, A61K 31/166, A61P 35/00

(21) International Application Number: PCT/GB2004/000147

(22) International Filing Date: 19 January 2004 (19.01.2004)

(25) Filing Language: English

(26) Publication Language: English

(30) Priority Data:
60/440,616 17 January 2003 (17.01.2003) US

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(81) Designated States *(unless otherwise indicated, for every kind of national protection available)*: AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BW, BY, BZ, CA, CH, CN, CO, CR, CU, CZ, DE, DK, DM, DZ, EC, EE, EG, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NA, NI, NO, NZ, OM, PG, PH, PL, PT, RO, RU, SC, SD, SE, SG, SK, SL, SY, TJ, TM, TN, TR, TT, TZ, UA, UG, US, UZ, VC, VN, YU, ZA, ZM, ZW.

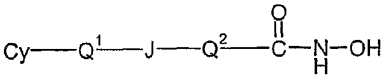
(84) Designated States *(unless otherwise indicated, for every kind of regional protection available)*: ARIPO (BW, GH, GM, KE, LS, MW, MZ, SD, SL, SZ, TZ, UG, ZM, ZW), Eurasian (AM, AZ, BY, KG, KZ, MD, RU, TJ, TM), European (AT, BE, BG, CH, CY, CZ, DE, DK, EE, ES, FI, FR, GB, GR, HU, IE, IT, LU, MC, NL, PT, RO, SE, SI, SK, TR), OAPI (BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, ML, MR, NE, SN, TD, TG).

Declaration under Rule 4.17:
— *of inventorship (Rule 4.17(iv)) for US only*

Published:
— *with international search report*

For two-letter codes and other abbreviations, refer to the "Guidance Notes on Codes and Abbreviations" appearing at the beginning of each regular issue of the PCT Gazette.

(54) Title: CARBAMIC ACID COMPOUNDS COMPRISING AN ESTER OR KETONE LINKAGE AS HDAC INHIBITORS



(I)

(57) Abstract: This invention pertains to certain carbamic acid compounds of the formula (I), which inhibit HDAC (histone deacetylase) activity: wherein: J is a linking functional group and is independently: -O-C(=O)- or -C(=O)-O- or - C(=O)-; Cy is a cyclyl group and is independently: C_{3-20}carbocyclyl, C_{3-20}heterocyclyl, or C_{5-20}aryl; and is optionally substituted; Q^1 is a cyclyl leader group, and is independently a divalent bidentate group obtained by removing two hydrogen atoms from a ring carbon atom of a saturated monocyclic hydrocarbon having from 4 to 7 ring atoms, or by removing two hydrogen atoms from a ring carbon atom of saturated monocyclic heterocyclic compound having from 4 to 7 ring atoms including 1 nitrogen ring atom or 1 oxygen ring atom; and is optionally substituted; Q^2 is an acid leader group, and is independently: C_{1-8}alkylene; and is optionally substituted; or: Q^2 is an acid leader group, and is independently: C_{5-20}arylene; C_{5-20}arylene-C_{1-7}alkylene; C_{1-7}alkylene-C_{5-20}arylene; or C_{1-7}alkylene-C_{5-20}arylene-C_{1-7}alkylene; and is optionally substituted; and pharmaceutically acceptable salts, solvates, amides, esters, ethers, chemically protected forms, and prodrugs thereof. The present invention also pertains to pharmaceutical compositions comprising such compounds, and the use of such compounds and compositions, both *in vitro* and *in vivo,* to inhibit HDAC,and in the treatment of conditions mediated by HDAC, cancer, proliferative conditions, psoriasis, etc.

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HYDROXAMIC ACID COMPOUNDS COMPRISING AN ESTER OR KETONE LINKAGE AS HDAC INHIBITORS

RELATED APPLICATION

This application is related to (and where permitted by law, claims priority to) U.S. Provisional Application Number 60/440,616 filed 17 January 2003, the contents of which are incorporated herein by reference in their entirety.

TECHNICAL FIELD

This invention pertains generally to the field of biologically active compounds, and more specifically to certain hydroxamic acid compounds which inhibit HDAC (histone deacetylase) activity. The present invention also pertains to pharmaceutical compositions comprising such compounds, and the use of such compounds and compositions, both *in vitro* and *in vivo*, to inhibit HDAC, and in the treatment of conditions mediated by HDAC, cancer, proliferative conditions, psoriasis, etc.

BACKGROUND

Throughout this specification, including any claims which follow, unless the context requires otherwise, the word "comprise," and variations such as "comprises" and "comprising," will be understood to imply the inclusion of a stated integer or step or group of integers or steps, but not the exclusion of any other integer or step or group of integers or steps.

It must be noted that, as used in the specification and any appended claims, the singular forms "a," "an," and "the" include plural referents unless the context clearly dictates otherwise. Thus, for example, reference to "a pharmaceutical carrier" includes mixtures of two or more such carriers, and the like.

Ranges are often expressed herein as from "about" one particular value, and/or to "about" another particular value. When such a range is expressed, another embodiment includes from the one particular value and/or to the other particular value. Similarly, when values

are expressed as approximations, by the use of the antecedent "about," it will be understood that the particular value forms another embodiment.

Any discussion of documents, acts, materials, devices, articles or the like which has been included in the present specification is not to be taken as an admission that any or all of these matters form part of the prior art base or were common general knowledge in the field relevant to the present invention as it existed before the priority date of each claim of this application.

DNA in eukaryotic cells is tightly complexed with proteins (histones) to form chromatin. Histones are small, positively charged proteins which are rich in basic amino acids (positively charged at physiological pH), which contact the phosphate groups (negatively charged at physiological pH) of DNA. There are five main classes of histones, H1, H2A, H2B, H3, and H4. The amino acid sequences of histones H2A, H2B, H3, and H4 show remarkable conservation between species, whereas H1 varies somewhat, and in some cases is replaced by another histone, e.g., H5. Four pairs of each of H2A, H2B, H3, and H4 together form a disk-shaped octomeric protein core, around which DNA (about 140 base pairs) is wound to form a nucleosome. Individual nucleosomes are connected by short stretches of linker DNA associated with another histone molecule (e.g., H1, or in certain cases, H5) to form a structure resembling a beaded string, which is itself arranged in a helical stack, known as a solenoid.

The majority of histones are synthesised during the S phase of the cell cycle, and newly synthesised histones quickly enter the nucleus to become associated with DNA. Within minutes of its synthesis, new DNA becomes associated with histones in nucleosomal structures.

A small fraction of histones, more specifically, the amino side chains thereof, are enzymatically modified by post-translational addition of methyl, acetyl, or phosphate groups, neutralising the positive charge of the side chain, or converting it to a negative charge. For example, lysine and arginine groups may be methylated, lysine groups may be acetylated, and serine groups may be phosphorylated. For lysine, the $-(CH_2)_4-NH_2$ sidechain may be acetylated, for example by an acetyltransferase enzyme, to give the amide $-(CH_2)_4-NHC(=O)CH_3$. Methylation, acetylation, and phosphorylation of amino termini of histones which extend from the nucleosomal core affects chromatin structure and gene expression. (See, for example, Spencer and Davie, 1999).

Acetylation and deacetylation of histones is associated with transcriptional events leading to cell proliferation and/or differentiation. Regulation of the function of transcription factors is also mediated through acetylation. Recent reviews of histone deacetylation include Kouzarides, 1999 and Pazin et al., 1997.

The correlation between the acetylation status of histones and the transcription of genes has been known for over 30 years (see, for example, Howe et al., 1999). Certain enzymes, specifically acetylases (e.g., histone acetyltransferase, HAT) and deacetylases (e.g., histone deacetylase, HDAC), which regulate the acetylation state of histones have been identified in many organisms and have been implicated in the regulation of numerous genes, confirming the link between acetylation and transcription. See, for example, Davie, 1998. In general, histone acetylation correlates with transcriptional activation, whereas histone deacetylation is associated with gene repression.

A growing number of histone deacetylases (HDACs) have been identified (see, for example, Ng and Bird, 2000). The first deacetylase, HDAC1, was identified in 1996 (see, for example, Tauton et al., 1996). Subsequently, two other nuclear mammalian deacetylases were found, HDAC2 and HDAC3 (see, for example, Yang et al., 1996, 1997, and Emiliani et al., 1998). See also, Grozinger et al., 1999; Kao et al., 2000; and Van den Wyngaert et al., 2000.

Eleven (11) human HDACs have been cloned so far:

HDAC1 (Genbank Accession No. NP_004955)
HDAC2 (Genbank Accession No. NP_001518)
HDAC3 (Genbank Accession No. O15379)
HDAC4 (Genbank Accession No. AAD29046)
HDAC5 (Genbank Accession No. NP_005465)
HDAC6 (Genbank Accession No. NP_006035)
HDAC7 (Genbank Accession No. AAF63491)
HDAC8 (Genbank Accession No. AAF73428)
HDAC9 (Genbank Accession No. AAK66821)
HDAC10 (Genbank Accession No. AAK 84023)
HDAC11 (Genbank Accession No. NM_024827)

These eleven human HDACs fall in two distinct classes: HDACs 1, 2, 3 and 8 are in class I, and HDACs 4, 5, 6, 7, 9, 10 and 11 are in class II.

There are a number of histone deacetylases in yeast, including the following:

RPD3 (Genbank Accession No. NP_014069)
HDA1 (Genbank Accession No. P53973)
HOS1 (Genbank Accession No. Q12214)

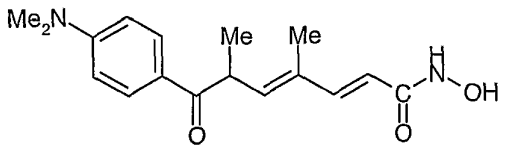
HOS2 (Genbank Accession No. P53096)
HOS3 (Genbank Accession No. Q02959)

There are also numerous plant deacetylases, for example, HD2, in Zea mays (Genbank Accession No. AF254073_1).

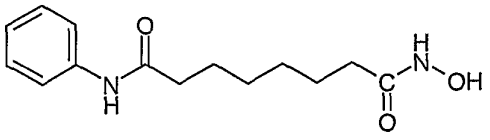
HDACs function as part of large multiprotein complexes, which are tethered to the promoter and repress transcription. Well characterised transcriptional repressors such as Mad (Laherty et al., 1997), pRb (Brehm et al., 1998), nuclear receptors (Wong et al., 1998) and YY1 (Yang et al., 1997) associate with HDAC complexes to exert their repressor function.

The study of inhibitors of histone deacetylases indicates that these enzymes play an important role in cell proliferation and differentiation. The inhibitor Trichostatin A (TSA) (Yoshida et al., 1990a) causes cell cycle arrest at both G1 and G2 phases (Yoshida and Beppu, 1988), reverts the transformed phenotype of different cell lines, and induces differentiation of Friend leukaemia cells and others (Yoshida et al., 1990b). TSA (and SAHA) have been reported to inhibit cell growth, induce terminal differentiation, and prevent the formation of tumours in mice (Finnin et al., 1999).

Trichostatin A (TSA)



Suberoylanilide Hydroxamic Acid (SAHA)



Cell cycle arrest by TSA correlates with an increased expression of gelsolin (Hoshikawa et al., 1994), an actin regulatory protein that is down regulated in malignant breast cancer (Mielnicki et al., 1999). Similar effects on cell cycle and differentiation have been observed with a number of deacetylase inhibitors (Kim et al., 1999).

Trichostatin A has also been reported to be useful in the treatment of fibrosis, e.g., liver fibrosis and liver cirrhosis. See, e.g., Geerts et al., 1998.

Recently, certain compounds that induce differentiation have been reported to inhibit histone deacetylases. Several experimental antitumour compounds, such as trichostatin A (TSA), trapoxin, suberoylanilide hydroxamic acid (SAHA), and phenylbutyrate have been reported to act, at least in part, by inhibiting histone deacetylase (see, e.g., Yoshida et al., 1990; Richon et al., 1998; Kijima et al., 1993). Additionally, diallyl sulfide and related molecules (see, e.g., Lea et al., 1999), oxamflatin (see, e.g., Kim et al., 1999; Sonoda et al., 1996), MS-27-275, a synthetic benzamide derivative (see, e.g., Saito et al., 1999; Suzuki et al., 1999; note that MS-27-275 was later re-named as MS-275), butyrate derivatives (see, e.g., Lea and Tulsyan, 1995), FR901228 (see, e.g., Nokajima et al., 1998), depudecin (see, e.g., Kwon et al., 1998), and m-carboxycinnamic acid bishydroxamide (see, e.g., Richon et al., 1998) have been reported to inhibit histone deacetylases. *In vitro*, some of these compounds are reported to inhibit the growth of fibroblast cells by causing cell cycle arrest in the G1 and G2 phases, and can lead to the terminal differentiation and loss of transforming potential of a variety of transformed cell lines (see, e.g., Richon et al, 1996; Kim et al., 1999; Yoshida et al., 1995; Yoshida & Beppu, 1988). *In vivo*, phenybutyrate is reported to be effective in the treatment of acute promyelocytic leukemia in conjunction with retinoic acid (see, e.g., Warrell et al., 1998). SAHA is reported to be effective in preventing the formation of mammary tumours in rats, and lung tumours in mice (see, e.g., Desai et al., 1999).

The clear involvement of HDACs in the control of cell proliferation and differentiation suggests that aberrant HDAC activity may play a role in cancer. The most direct demonstration that deacetylases contribute to cancer development comes from the analysis of different acute promyelocytic leukemias (APL). In most APL patients, a translocation of chromosomes 15 and 17 (t(15;17)) results in the expression of a fusion protein containing the N-terminal portion of PML gene product linked to most of RARα (retinoic acid receptor). In some cases, a different translocation (t(11;17)) causes the fusion between the zinc finger protein PLZF and RARα. In the absence of ligand, the wild type RARα represses target genes by tethering HDAC repressor complexes to the promoter DNA. During normal hematopoiesis, retinoic acid (RA) binds RARα and displaces the repressor complex, allowing expression of genes implicated in myeloid differentiation. The RARα fusion proteins occurring in APL patients are no longer responsive to physiological levels of RA and they interfere with the expression of the RA-

inducible genes that promote myeloid differentiation. This results in a clonal expansion of promyelocytic cells and development of leukaemia. *In vitro* experiments have shown that TSA is capable of restoring RA-responsiveness to the fusion RARα proteins and of allowing myeloid differentiation. These results establish a link between HDACs and oncogenesis and suggest that HDACs are potential targets for pharmaceutical intervention in APL patients. (See, for example, Kitamura et al., 2000; David et al., 1998; Lin et al., 1998).

Furthermore, different lines of evidence suggest that HDACs may be important therapeutic targets in other types of cancer. Cell lines derived from many different cancers (prostate, colorectal, breast, neuronal, hepatic) are induced to differentiate by HDAC inhibitors (Yoshida and Horinouchi, 1999). A number of HDAC inhibitors have been studied in animal models of cancer. They reduce tumour growth and prolong the lifespan of mice bearing different types of transplanted tumours, including melanoma, leukaemia, colon, lung and gastric carcinomas, etc. (Ueda et al., 1994; Kim et al., 1999).

Psoriasis is a common chronic disfiguring skin disease which is characterised by well-demarcated, red, hardened scaly plaques: these may be limited or widespread. The prevalence rate of psoriasis is approximately 2%, i.e., 12.5 million sufferers in the triad countries (US/Europe/Japan). While the disease is rarely fatal, it clearly has serious detrimental effects upon the quality of life of the patient: this is further compounded by the lack of effective therapies. Present treatments are either ineffective, cosmetically unacceptable, or possess undesired side effects. There is therefore a large unmet clinical need for effective and safe drugs for this condition.

Psoriasis is a disease of complex etiology. Whilst there is clearly a genetic component, with a number of gene loci being involved, there are also undefined environmental triggers. Whatever the ultimate cause of psoriasis, at the cellular level, it is characterised by local T-cell mediated inflammation, by keratinocyte hyperproliferation, and by localised angiogenesis. These are all processes in which histone deacetylases have been implicated (see, e.g., Saunders et al., 1999; Bernhard et al, 1999; Takahashi et al, 1996; Kim et al , 2001). Therefore HDAC inhibitors may be of use in therapy for psoriasis. Candidate drugs may be screened, for example, using proliferation assays with T-cells and/or keratinocytes.

Thus, one aim of the present invention is the provision of compounds which are potent inhibitors of histone deacetylases (HDACs). There is a pressing need for such compounds, particularly for use as antiproliferatives, for example, anti-cancer agents, agents for the treatment of psoriasis, etc.

Such molecules desirably have one or more of the following properties and/or effects:

(a) easily gain access to and act upon tumour cells;

(b) down-regulate HDAC activity;

(c) inhibit the formation of HDAC complexes;

(d) inhibit the interactions of HDAC complexes;

(e) inhibit tumour cell proliferation;

(e) promote tumour cell apoptosis;

(f) inhibit tumour growth; and,

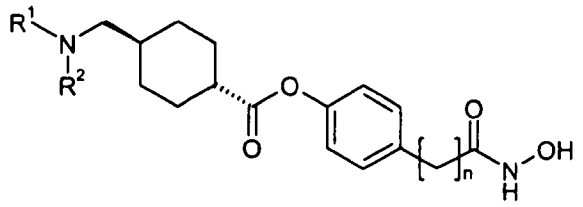
(g) complement the activity of traditional chemotherapeutic agents.

A number of hydroxamic acid compounds have been described.

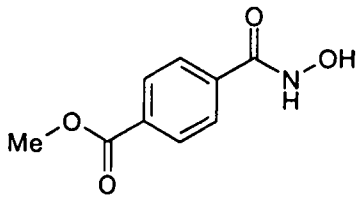
Certain classes of hydroxamic acid compounds which inhibit HDAC are described in Watkins et al., 2002a, 2002b, and 2002c.

Esters

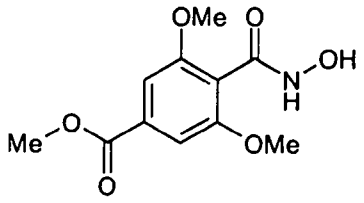
Takahashi et al., 1992, describe several compounds of the following formula, where n is 0, 1, or 2, which apparently have activity as an anti-ulcer agent (see page 6, right hand column; page 8, middle; table on pages 10-12, compounds 6-12, 14, and 22-24).



Suzuki and Oya, 1974, and Fujii et al., 1982, describe the following compound (CAS Registry No. 52134-35-7), which apparently is used as an intermediate in the synthesis of derivatives of para-aminobenzoic acid.



Kompis and Wick, 1977, describe the following compound (CAS Registry No. 65566-10-1), which apparently is used as an intermediate in the synthesis of analogues of the bactericidal agent trimethoprim.



SUMMARY OF THE INVENTION

One aspect of the invention pertains to active hydroxamic acid compounds, as described herein.

Another aspect of the invention pertains to active compounds, as described herein, which inhibit HDAC activity.

Another aspect of the invention pertains to active compounds, as described herein, which treat conditions which are known to be mediated by HDAC, or which are known to be treated by HDAC inhibitors (such as, e.g., trichostatin A).

Another aspect of the invention pertains to active compounds, as described herein, which (a) regulate (e.g., inhibit) cell proliferation; (b) inhibit cell cycle progression; (c) promote apoptosis; or (d) a combination of one or more of these.

Another aspect of the invention pertains to active compounds, as described herein, which are anti-HDAC agents, and which treat a condition mediated by HDAC.

Another aspect of the invention pertains to active compounds, as described herein, which are anticancer agents, and which treat cancer.

Another aspect of the invention pertains to active compounds, as described herein, which are antiproliferative agents, and which treat a proliferative condition.

Another aspect of the invention pertains to active compounds, as described herein, which are antipsoriasis agents, and which treat psoriasis.

Another aspect of the present invention pertains to a composition comprising a compound, as described herein, and a carrier.

Another aspect of the present invention pertains to a composition comprising a compound, as described herein, and a pharmaceutically acceptable carrier.

Another aspect of the present invention pertains to methods of inhibiting HDAC in a cell, comprising contacting said cell with an effective amount of an active compound, as described herein, whether *in vitro* or *in vivo*.

Another aspect of the present invention pertains to methods of (a) regulating (e.g., inhibiting) cell proliferation; (b) inhibiting cell cycle progression; (c) promoting apoptosis; or (d) a combination of one or more of these, comprising contacting a cell with an effective amount of an active compound, as described herein, whether *in vitro* or *in vivo*.

Another aspect of the present invention pertains to methods of treating a condition which is known to be mediated by HDAC, or which is known to be treated by HDAC inhibitors (such as, e.g., trichostatin A), comprising administering to a subject in need of treatment a therapeutically-effective amount of an active compound, as described herein.

Another aspect of the present invention pertains to methods of treating cancer, comprising administering to a subject in need of treatment a therapeutically-effective amount of an active compound, as described herein.

Another aspect of the present invention pertains to methods of treating a proliferative condition comprising administering to a subject in need of treatment a therapeutically-effective amount of an active compound, as described herein.

Another aspect of the present invention pertains to methods of treating psoriasis comprising administering to a subject in need of treatment a therapeutically-effective amount of an active compound, as described herein.

Another aspect of the present invention pertains to an active compound, as described herein, for use in a method of treatment of the human or animal body by therapy.

Another aspect of the present invention pertains to use of an active compound, as described herein, for the manufacture of a medicament for use in the treatment of a condition mediated by HDAC, a condition known to be treated by HDAC inhibitors (such as, e.g., trichostatin A), cancer, a proliferative condition, psoriasis, or other condition as described herein.

Another aspect of the present invention pertains to a kit comprising (a) the active compound, preferably provided as a pharmaceutical composition and in a suitable container and/or with suitable packaging; and (b) instructions for use, for example, written instructions on how to administer the active compound.

Another aspect of the present invention pertains to compounds *obtainable* by a method of synthesis as described herein, or a method comprising a method of synthesis as described herein.

Another aspect of the present invention pertains to compounds *obtained* by a method of synthesis as described herein, or a method comprising a method of synthesis as described herein.

Another aspect of the present invention pertains to novel intermediates, as described herein, which are suitable for use in the methods of synthesis described herein.

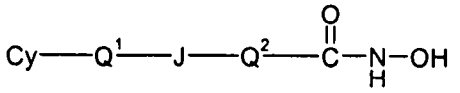
Another aspect of the present invention pertains to the use of such novel intermediates, as described herein, in the methods of synthesis described herein.

As will be appreciated by one of skill in the art, features and preferred embodiments of one aspect of the invention will also pertain to other aspects of the invention.

DETAILED DESCRIPTION OF THE INVENTION

Compounds

In one aspect, the present invention pertains to hydroxamic acid compounds of the following formula and pharmaceutically acceptable salts and solvates thereof:



wherein:

J is independently selected from:

-O-C(=O)-, -C(=O)-O-, and -C(=O)-;

Cy is independently selected from:

C_{3-20}carbocyclyl, C_{3-20}heterocyclyl, and C_{5-20}aryl;

and is optionally substituted with one or more substituents independently selected from:

(1) -C(=O)OR^1, wherein R^1 is independently C_{1-7}alkyl as defined in (7);
(2) -C(=O)NR^2R^3, wherein each of R^2 and R^3 is independently -H or C_{1-7}alkyl as defined in (7);
(3) -C(=O)R^4, wherein R^4 is independently C_{1-7}alkyl as defined in (7) or C_{5-20}aryl as defined in (8);
(4) -F, -Cl, -Br, -I;
(5) -OH;
(6) -OR^5, wherein R^5 is independently C_{1-7}alkyl as defined in (7) or C_{5-20}aryl as defined in (8);
(7) C_{1-7}alkyl, halo-C_{1-7}alkyl, amino-C_{1-7}alkyl, carboxy-C_{1-7}alkyl, hydroxy-C_{1-7}alkyl, C_{1-7}alkoxy-C_{1-7}alkyl, or C_{5-20}aryl-C_{1-7}alkyl;
(8) C_{5-20}aryl, substituted C_{5-20}aryl;
(9) -SO_2R^7, wherein R^7 is independently C_{1-7}alkyl as defined in (7) or C_{5-20}aryl as defined in (8); and
(10) -$SO_2NR^8R^9$, wherein each of R^8 and R^9 is independently -H or C_{1-7}alkyl as defined in (7);

Q^1 is independently a divalent bidentate group obtained by removing two hydrogen atoms from a ring carbon atom of a saturated monocyclic hydrocarbon having from 4 to 7 ring atoms, or by removing two hydrogen

atoms from a ring carbon atom of saturated monocyclic heterocyclic compound having from 4 to 7 ring atoms including 1 nitrogen ring atom or 1 oxygen ring atom; and is optionally substituted with one or more substituents independently selected from: -F, -Cl, -Br, -I, -OH, -OMe, -OEt, -O(iPr), -Ph, -C(=O)Me, $-NH_2$, $-NMe_2$, $-NEt_2$, morpholino, $-CONH_2$, $-CONMe_2$, -NHCOMe, and =O;;

Q^2 is independently selected from:

C_{1-8}alkylene;

C_{5-20}arylene;

C_{5-20}arylene-C_{1-7}alkylene;

C_{1-7}alkylene-C_{5-6}arylene; or,

C_{1-7}alkylene-C_{5-6}arylene-C_{1-7}alkylene;

and is optionally substituted with one or more substituents independently selected from: -F, -Cl, -Br, -I, -OH, -OMe, -OEt, -O(iPr), -Ph, -C(=O)Me, $-NH_2$, $-NMe_2$, $-NEt_2$, morpholino, $-CONH_2$, $-CONMe_2$, -NHCOMe, $-NO_2$, and =O; and wherein, if a substituent is on an arylene group, it may additionally be selected from: -Me, -Et, -iPr, -tBu, and $-CF_3$.;

In preferred embodiments, the hydroxamic acid group, -C(=O)NHOH, is unmodified (e.g., is not an ester).

Note that each of the groups -Q^1-Cy and -Q^2-C(=O)NHOH is a monovalent and monodentate species; and that is it not intended that these groups be linked, other than via the group J.

For the avoidance of doubt, it is not intended that the group, J, be part of another functional group. For example, when J is a ketone group, it is not intended that is be part of an ester, an amide, a urea, a carbamate, a carbonate, etc. For example, when J is an ester group, it is not intended that it be part of a carbamate, a carbonate, etc. Q^1 and Q^2, and optional substituents thereon, are selected accordingly.

The Linking Functional Group, J

The linking functional group, J, is -O-C(=O)- or -C(=O)-O- or -C(=O)-.

In one embodiment, J is -O-C(=O)- or -C(=O)-O- (also referred to herein as an "ester" group). Ester groups have a C atom, a carbonyl O atom, and a chain O atom.

In one embodiment, J is -O-C(=O)-
(also referred to herein as a "reverse ester group").

In one embodiment, J is -C(=O)-O-
(also referred to herein as a "forward ester group").

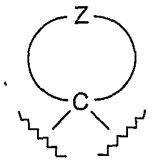
In one embodiment, J is -C(=O)- (also referred to herein as a "ketone" group). Ketone groups have a C atom and a carbonyl O atom.

The Cyclyl Leader Group, Q^1

The cyclyl leader group, Q^1, is independently a divalent bidentate group obtained by removing two hydrogen atoms from a ring carbon atom of a saturated monocyclic

hydrocarbon having from 4 to 7 ring atoms, or by removing two hydrogen atoms from a ring carbon atom of saturated monocyclic heterocyclic compound having from 4 to 7 ring atoms including 1 nitrogen ring atom or 1 oxygen ring atom; and is optionally substituted.

In one embodiment, Q^1 is independently a group of the formula;



wherein:
the ring independently has from 4 to 7 ring atoms;
Z is independently $-CH_2-$, $-N(R^N)-$ or -O-;
R^N, if present, is independently as defined below; and
Q^1 is optionally further substituted.

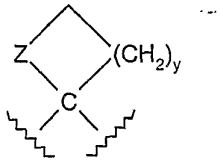
In one embodiment, the ring independently has 4, 5, 6, or 7 ring atoms.
In one embodiment, the ring independently has 5, 6, or 7 ring atoms.
In one embodiment, the ring independently has 5 or 6 ring atoms.
In one embodiment, the ring independently has 5 ring atoms.
In one embodiment, the ring independently has 6 ring atoms.

In one embodiment, Z is independently $-CH_2-$, $-N(R^N)-$ or -O-.
In one embodiment, Z is independently $-CH_2-$ or $-N(R^N)-$.
In one embodiment, Z is independently $-CH_2-$ or -O-;
In one embodiment, Z is independently $-N(R^N)-$ or -O-.
In one embodiment, Z is independently $-CH_2-$.
In one embodiment, Z is independently $-N(R^N)-$.
In one embodiment, Z is independently -O-.

In one embodiment, the ring independently has 5 or 6 ring atoms; and Z is independently $-CH_2-$ or $-N(R^N)-$.

In one embodiment, Z is independently adjacent to the carbon atom which links Cy and J.

In one embodiment, Q^1 is independently a group of the formula;



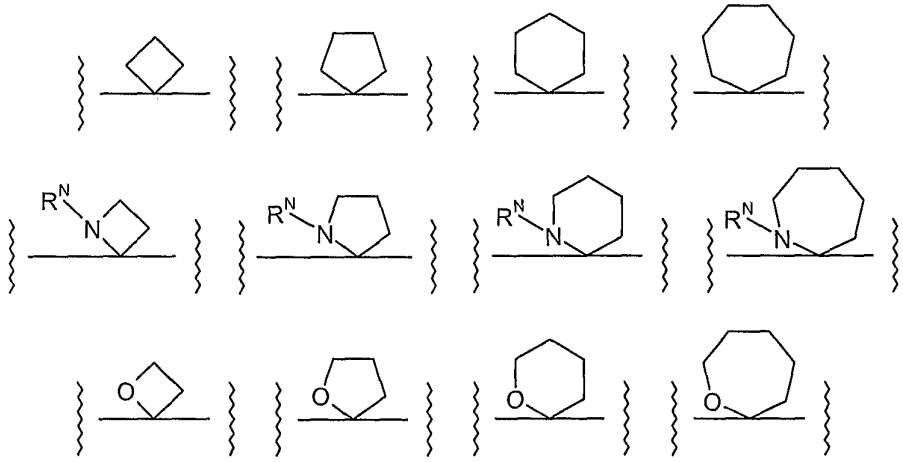
wherein:

y is independently 1, 2, 3, or 4;

Z is as defined above; and,

Q^1 is optionally further substituted.

Examples of such groups include:



In one embodiment, y is independently 1, 2, 3, or 4.

In one embodiment, y is independently 2, 3, or 4.

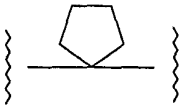
In one embodiment, y is independently 2 or 3.

In one embodiment, y is independently 2.

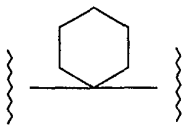
In one embodiment, y is independently 3.

In one embodiment, y is independently 2 or 3; and Z is independently $-CH_2-$ or $-N(R^N)-$.

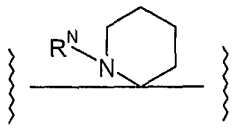
In one embodiment, y is independently 2; and Z is independently $-CH_2-$. Examples of such groups include:



In one embodiment, y is independently 3; and Z is independently -CH_2-. Examples of such groups include:



In one embodiment, y is independently 3; and Z is independently -$N(R^N)$-. Examples of such groups include:



The Nitrogen Substituent, R^N

The nitrogen substituent, R^N, if present, is independently selected from: -H; C_{1-7}alkyl (including, e.g., C_{5-20}aryl-C_{1-7}alkyl); C_{3-20}heterocyclyl; and C_{5-20}aryl.

In one embodiment, R^N, if present, is independently selected from: -H; C_{1-7}alkyl (including, e.g., C_{5-20}aryl-C_{1-7}alkyl); and C_{5-20}aryl.

In one embodiment, R^N, if present, is independently selected from: -H and C_{1-7}alkyl (including, e.g., C_{5-20}aryl-C_{1-7}alkyl).

In one embodiment, R^N, if present, is independently selected from: -H and C_{5-20}aryl.

In one embodiment, R^N, if present, is independently selected from: -H, -Me, -Et, -Ph, and -CH_2-Ph.

In one embodiment, R^N, if present is independently -H.

The Cyclyl Leader Group, Q^1: Substituents

In one embodiment, Q^1 is independently substituted or unsubstituted.

In one embodiment, Q^1 is independently substituted.
In one embodiment, Q^1 is independently unsubstituted.

Note that it is not intended that the nitrogen substituent, R^N, if present, be considered when determining if Q^1 is substituted or unsubstituted.

Examples of substituents on Q^1 include, but are not limited to, those described under the heading "Substituents" below.

Further examples of substituents Q^1 include, but are not limited to, those described under the heading "The Cyclyl Group, Cy: Substituents" below.

In one embodiment, substituents on Q^1, if present, are independently selected from: halo, hydroxy, ether (e.g., C_{1-7}alkoxy), C_{5-20}aryl, acyl, amino, amido, acylamido, and oxo. Where a substituent is on an arylene group (e.g., phenylene), it may additionally be selected from: C_{1-7}alkyl, including substituted C_{1-7}alkyl.

In one embodiment, substituents on Q^1, if present, are independently selected from: -F, -Cl, -Br, -I, -OH, -OMe, -OEt, -O(iPr), -Ph, -C(=O)Me, $-NH_2$, $-NMe_2$, $-NEt_2$, morpholino, $-CONH_2$, $-CONMe_2$, -NHCOMe, and =O. Where a substituent is on an arylene group (e.g., phenylene), it may additionally be selected from: -Me, -Et, -iPr, -tBu, $-CF_3$.

Assigning the Cyclyl Group, Cy

If, within the group $-Q^1$-Cy, there is a plurality of candidate groups satisfying the definition of Cy (referred to as candidate Cy groups), then the candidate Cy group which is furthest from the C atom of the group, J, is identified as Cy (and referred to as "the relevant Cy group").

In this context, distance (e.g., further, furthest) is measured as the number of chain atoms in the shortest continuous chain linking the groups (i.e., linking Cy with the C atom of the group J).

If there is a plurality of furthest candidate Cy groups, then the one (including any substituents) with the largest molecular weight is the relevant one.

If there is a plurality of furthest heaviest candidate Cy groups, then the one (excluding any substituents) with the most annular heteroatoms is the relevant one.

If there is a plurality of furthest heaviest candidate Cy groups with the most annular heteroatoms, then the one with an IUPAC name which alphabetically precedes the other(s), is the relevant one.

The Cyclyl Group, Cy

Cy is independently: C_{3-20}carbocyclyl, C_{3-20}heterocyclyl, or C_{5-20}aryl; and is optionally substituted.

Examples of substituents on Cy are discussed below.

The Cyclyl Group, Cy: Carbocyclyl

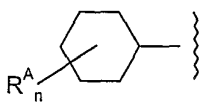
In one embodiment, Cy is independently C_{3-20}carbocyclyl; and is optionally substituted.

In one embodiment, Cy is independently monocyclic C_{3-7}carbocyclyl, and is optionally substituted.

In one embodiment, Cy is independently monocyclic C_{5-6}carbocyclyl, and is optionally substituted.

In one embodiment, Cy is independently C_{3-20}carbocyclyl derived from one of the following: cyclopropane, cyclobutane, cyclopentane, cyclohexane, cyclopentene, cyclohexene, norbornane, adamantane, cyclopentanone, and cyclohexanone; and is optionally substituted.

In one embodiment, Cy is independently an optionally substituted cyclohexyl group of the formula:



wherein n is independently an integer from 0 to 11, and each R^A is independently a substituent as defined herein (see under the heading "The Cyclyl Group, Cy: Substituents").

The Cyclyl Group, Cy: Heterocyclyl

In one embodiment, Cy is independently C_{3-20}heterocyclyl; and is optionally substituted.

In one embodiment, Cy is independently monocyclic C_{3-7}heterocyclyl, and is optionally substituted.

In one embodiment, Cy is independently monocyclic C_{5-6}heterocyclyl, and is optionally substituted.

In one embodiment, Cy is independently C_{3-20}heterocyclyl derived from one of the following: piperidine, azepine, tetrahydropyran, morpholine, azetidine, piperazine, imidazoline, piperazinedione, and oxazolinone; and is optionally substituted.

The Cyclyl Group, Cy: Aryl

In one embodiment, Cy is independently C_{5-20}aryl; and is optionally substituted.

In one embodiment, Cy is independently C_{5-20}carboaryl or C_{5-20}heteroaryl; and is optionally substituted.

In one embodiment, Cy is independently C_{5-20}heteroaryl; and is optionally substituted. In one embodiment, Cy is monocyclic C_{5-20}heteroaryl; and is optionally substituted. In one embodiment, Cy is monocyclic C_{5-6}heteroaryl; and is optionally substituted.

In one embodiment, Cy is independently C_{5-20}carboaryl; and is optionally substituted. In one embodiment, Cy is monocyclic C_{5-20}carboaryl; and is optionally substituted. In one embodiment, Cy is monocyclic C_{5-6}carboaryl; and is optionally substituted. In one embodiment, Cy is phenyl; and is optionally substituted.

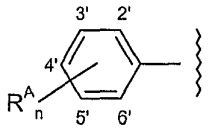
In one embodiment, Cy is independently C_{5-20}aryl derived from one of the following: benzene, pyridine, furan, indole, pyrrole, imidazole, naphthalene, quinoline,

benzimidazole, benzothiofuran, fluorene, acridine, and carbazole; and is optionally substituted.

In one embodiment, Cy is independently C_{5-20}aryl derived from benzene and is optionally substituted.

The Cyclyl Group, Cy: Phenyl

In one embodiment, Cy is independently an optionally substituted phenyl group of the formula:



wherein n is independently an integer from 0 to 5, and each R^A is independently a substituent as defined herein (see under the heading "The Cyclyl Group, Cy: Substituents").

In one embodiment, n is an integer from 0 to 5.
In one embodiment, n is an integer from 0 to 4.
In one embodiment, n is an integer from 0 to 3.
In one embodiment, n is an integer from 0 to 2.
In one embodiment, n is 0 or 1.
In one embodiment, n is an integer from 1 to 5.
In one embodiment, n is an integer from 1 to 4.
In one embodiment, n is an integer from 1 to 3.
In one embodiment, n is 1 or 2.
In one embodiment, n is 5.
In one embodiment, n is 4.
In one embodiment, n is 3.
In one embodiment, n is 2.
In one embodiment, n is 1.
In one embodiment, n is 0.

If the phenyl group has less than the full complement of ring substituents, R^A, they may be arranged in any combination. For example, if n is 1, R^A may be in the 2'-, 3'-, 4'-, 5'-, or 6'-position. Similarly, if n is 2, the two R^A groups may be in, for example, the 2',3'-, 2',4'-,

2',5'-, 2',6'-, 3',4'-, or 3',5'-positions. If n is 3, the three R^A groups may be in, for example, the 2',3',4'-, 2',3',5'-, 2',3',6'-, or 3',4',5'-positions.

In one embodiment, n is 0.

In one embodiment, n is 1, and the R^A group is in the 4'-position.

In one embodiment, n is 2, and one R^A group is in the 4'-position, and the other R^A group is in the 2'-position.

In one embodiment, n is 2, and one R^A group is in the 4'-position, and the other R^A group is in the 3'-position.

The Cyclyl Group, Cy: Substituents

Examples of substituents on Cy (e.g., R^A), include, but are not limited to, those described under the heading "Substituents" below.

Further examples of substituents on Cy (e.g., R^A), include, but are not limited to, those described below.

In one embodiment, each of the substituents on Cy (e.g., each R^A), is independently selected from:

(1) ester;
(2) amido;
(3) acyl;
(4) halo;
(5) hydroxy;
(6) ether;
(7) C_{1-7}alkyl, including substituted C_{1-7}alkyl;
(8) C_{5-20}aryl, including substituted C_{5-20}aryl;
(9) sulfonyl;
(10) sulfonamido.

In one embodiment, each of the substituents on Cy (e.g., each R^A), is independently selected from:

(1) -C(=O)OR^1, wherein R^1 is independently C_{1-7}alkyl as defined in (7);

(2) -C(=O)NR^{2}R^3, wherein each of R^2 and R^3 is independently -H or C_{1-7}alkyl as defined in (7);

(3) -C(=O)R^4, wherein R^4 is independently C_{1-7}alkyl as defined in (7) or C_{5-20}aryl as defined in (8);

(4) -F, -Cl, -Br, -I;

(5) -OH;

(6) -OR^5, wherein R^5 is independently C_{1-7}alkyl as defined in (7) or C_{5-20}aryl as defined in (8);

(7) C_{1-7}alkyl, including substituted C_{1-7}alkyl, e.g.,

halo-C_{1-7}alkyl;

amino-C_{1-7}alkyl (e.g., -$(CH_2)_w$-amino);

carboxy-C_{1-7}alkyl (e.g., -$(CH_2)_w$-COOH);

hydroxy-C_{1-7}alkyl (e.g., -$(CH_2)_w$-OH);

C_{1-7}alkoxy-C_{1-7}alkyl (e.g., -$(CH_2)_w$-O-C_{1-7}alkyl);

C_{5-20}aryl-C_{1-7}alkyl;

wherein w is 1, 2, 3, or 4;

(8) C_{5-20}aryl, including substituted C_{5-20}aryl;

(9) -SO_2R^7, wherein R^7 is independently C_{1-7}alkyl as defined in (7) or C_{5-20}aryl as defined in (8);

(10) -SO_2NR^{8}R^9, wherein each of R^8 and R^9 is independently -H or C_{1-7}alkyl as defined in (7);

In one embodiment, each of the substituents on Cy (e.g., each R^A), is independently selected from:

(1) -C(=O)OMe, -C(=O)OEt, -C(=O)O(Pr), -C(=O)O(iPr), -C(=O)O(nBu), -C(=O)O(sBu), -C(=O)O(iBu), -C(=O)O(tBu), -C(=O)O(nPe);

-C(=O)OCH$_2$CH$_2$OH, -C(=O)OCH$_2$CH$_2$OMe, -C(=O)OCH$_2$CH$_2$OEt;

(2) -(C=O)NH$_2$, -(C=O)NMe$_2$, -(C=O)NEt$_2$, -(C=O)N(iPr)$_2$, -(C=O)N(CH$_2$CH$_2$OH)$_2$;

(3) -(C=O)Me, -(C=O)Et, -(C=O)-cHex, -(C=O)Ph;

(4) -F, -Cl, -Br, -I;

(5) -OH;

(6) -OMe, -OEt, -O(iPr), -O(tBu), -OPh;

-OCF$_3$, -OCH$_2$CF$_3$;

-OCH$_2$CH$_2$OH, -OCH$_2$CH$_2$OMe, -OCH$_2$CH$_2$OEt;

-OCH$_2$CH$_2$NH$_2$, -OCH$_2$CH$_2$NMe$_2$, -OCH$_2$CH$_2$N(iPr)$_2$;

-OPh, -OPh-Me, -OPh-OH, -OPh-OMe, O-Ph-F, -OPh-Cl, -OPh-Br, -OPh-I;

(7) -Me, -Et, -nPr, -iPr, -nBu, -iBu, -sBu, -tBu, -nPe;

$-CF_3$, $-CH_2CF_3$;

$-CH_2CH_2OH$, $-CH_2CH_2OMe$, $-CH_2CH_2OEt$;

$-CH_2CH_2NH_2$, $-CH_2CH_2NMe_2$, $-CH_2CH_2N(iPr)_2$;

$-CH_2$-Ph;

(8) -Ph, -Ph-Me, -Ph-OH, -Ph-OMe, -Ph-F, -Ph-Cl, -Ph-Br, -Ph-I;

(9) $-SO_2Me$, $-SO_2Et$, $-SO_2Ph$;

(10) $-SO_2NH_2$, $-SO_2NMe_2$, $-SO_2NEt_2$.

In one embodiment, each of the substituents on Cy (e.g., each R^A), is independently selected from:

-C(=O)OMe, -OMe, -C(=O)Me, $-SO_2Me$, $-SO_2NMe_2$, $-C(=O)NH_2$, $-OCF_3$, and $-CH_2CH_2OH$.

The Acid Leader Group, Q^2

The acid leader group, Q^2, is independently:

C_{1-8}alkylene;
and is optionally substituted;

or:

C_{5-6}arylene;
C_{5-6}arylene-C_{1-7}alkylene;
C_{1-7}alkylene-C_{5-6}arylene; or,
C_{1-7}alkylene-C_{5-6}arylene-C_{1-7}alkylene;
and is optionally substituted;

In one embodiment, the acid leader group, Q^2, is independently:

C_{1-8}alkylene;
and is optionally substituted;

In one embodiment, the acid leader group, Q^2, is independently:

C_{5-6}arylene;
C_{5-6}arylene-C_{1-7}alkylene;

C_{1-7}alkylene-C_{5-6}arylene;

C_{1-7}alkylene-C_{5-6}arylene-C_{1-7}alkylene; or,

and is optionally substituted;

In one embodiment, the acid leader group, Q^2, is independently:

C_{5-6}arylene;

and is optionally substituted;

In one embodiment, the acid leader group, Q^2, is independently:

C_{5-6}arylene-C_{1-7}alkylene;

C_{1-7}alkylene-C_{5-6}arylene;

C_{1-7}alkylene-C_{5-6}arylene-C_{1-7}alkylene; or,

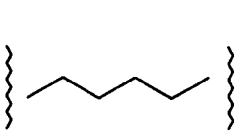
and is optionally substituted;

Again, for the avoidance of doubt, it is not intended that the group, J, be part of another functional group. Q^1 and Q^2, and optional substituents thereon, are selected accordingly.

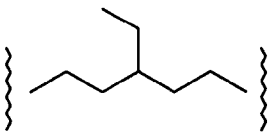
The Acid Leader Group, Q^2: Backbone Length

The acid leader group, Q^2, has a backbone length, as determined by the number of chain atoms in the shortest continuous chain of atoms linking J and the hydroxamic acid group, -C(=O)NHOH.

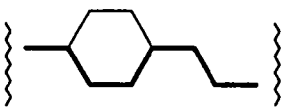
If Q^2 is alkylene, Q^2 necessarily has a backbone of at least 1 atom. Some examples are shown below.



backbone length = 4

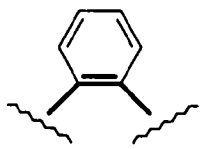


backbone length = 5

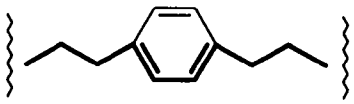


backbone length = 6

If Q^2 is arylene, arylene-alkylene, alkylene-arylene, alkylene-arylene-alkylene, Q^2 necessarily has a backbone of at least 2 atoms. Some examples are shown below.



backbone length = 2



backbone length = 8

Without wishing to be bound to any particular theory, it is believed that Q^2 groups with shorter backbone lengths prevent or reduce the interaction of the hydroxamic acid group (-C(=O)NHOH) with HDAC (or its complexes), and thereby reduce the compound's activity as an HDAC inhibitor.

In one embodiment, Q^2 independently has a backbone of at least 3 atoms.
In one embodiment, Q^2 independently has a backbone of at least 4 atoms.
In one embodiment, Q^2 independently has a backbone of at least 5 atoms.
In one embodiment, Q^2 independently has a backbone of at least 6 atoms.

In one embodiment, Q^2 independently has a backbone of:
from 3 to 8 atoms;
from 3 to 7 atoms;
from 3 to 6 atoms; or,
from 3 to 5 atoms.

In one embodiment, Q^2 independently has a backbone of:
from 4 to 8 atoms;
from 4 to 7 atoms;
from 4 to 6 atoms; or,
from 4 to 5 atoms.

In one embodiment, Q^2 independently has a backbone of:
from 5 to 8 atoms; or
from 5 to 7 atoms; or
from 5 to 6 atoms.

In one embodiment, Q^2 independently has a backbone of from 5 to 6 atoms.

In one embodiment, Q^2 independently has a backbone of 3 atoms.

In one embodiment, Q^2 independently has a backbone of 4 atoms.
In one embodiment, Q^2 independently has a backbone of 5 atoms.
In one embodiment, Q^2 independently has a backbone of 6 atoms.
In one embodiment, Q^2 independently has a backbone of 7 atoms.
In one embodiment, Q^2 independently has a backbone of 8 atoms.

In one embodiment, the Q^2 backbone is independently a carbon backbone.

In one embodiment, the backbone of "atoms" is a backbone of "carbon atoms."

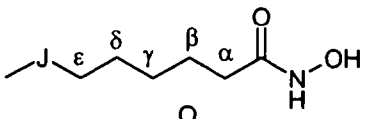
Note that, for embodiments which are characterised by, or further characterised by, a backbone length limitation, corresponding changes in the description of that embodiment may be implicit. For example, for an embodiment wherein (a) Q^2 is a partially unsaturated C_{2-8}alkylene group and (b) Q^2 has a backbone of 4 carbon atoms, the term "C_{2-8}alkylene" group is necessarily, and implicitly, interpreted as "C_{4-8}alkylene."

The Acid Leader Group, Q^2: Substitution

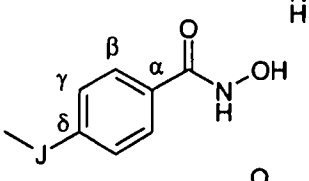
In one embodiment, Q^2 is independently unsubstituted or substituted.
In one embodiment, Q^2 is independently substituted.
In one embodiment, Q^2 is independently unsubstituted.

The backbone atoms of the acid leader group, Q^2, which link J and the hydroxamic acid group (-C(=O)NHOH), are denoted α, β, γ, δ, etc., starting with the backbone atom adjacent to the hydroxamic acid group. Some examples are illustrated below.

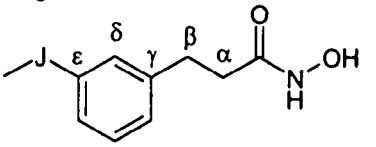
Q^2 is alkylene



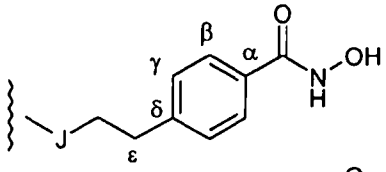
Q^2 is arylene



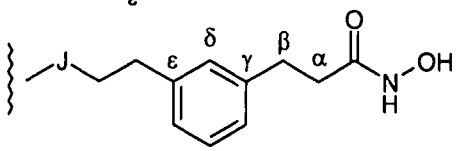
Q^2 is arylene-alkylene



Q^2 is alkylene-arylene



Q^2 is alkylene-arylene-alkylene

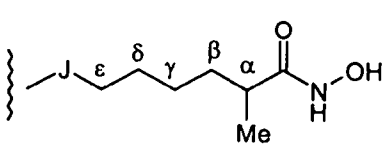


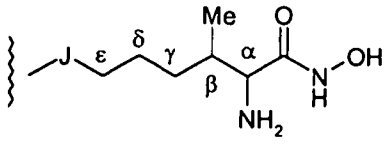
Without wishing to be bound to any particular theory, it is believed that groups (e.g., substituents), particularly bulky groups (e.g., substituents), at the α-position, or at either or both of the α- and β -positions, prevent or reduce the interaction of the hydroxamic acid group (-C(=O)NHOH) with HDAC (or its complexes), and thereby reduce the compound's activity as an HDAC inhibitor.

In one embodiment, Q^2 is, additionally, unsubstituted at the α-position.

In one embodiment, Q^2 is, additionally, unsubstituted at the α-position and unsubstituted at the β-position.

Note that, in some embodiments, Q^2 may have a non-linear alkylene group (for example, a branched alkylene) adjacent to the hydroxamic acid group. An example, wherein Q^2 is a branched saturated C_6-alkylene, having a methyl group at the α-position, is shown below. Although there is a group (i.e., a methyl group) at the α-position, such compounds are "unsubstituted" at the α-position, because the α-methyl group itself is considered to be part of the unsubstituted Q^2. Another example, wherein Q^2 is a branched saturated C_6-alkylene, having an amino group at the α-position and a methyl group at the β-position, is shown below; such compounds are "α-substituted, β-unsubstituted."





In one embodiment, in which Q^2 is a group as defined herein (e.g., C_{1-8}alkylene, C_{5-6}arylene-C_{1-7}alkylene, C_{1-7}alkylene-C_{5-6}arylene-C_{1-7}alkylene) having an alkylene group adjacent to the hydroxamic acid group:

(a) Q^2 is, additionally, unsubstituted at the α-position and/or:

(b) that adjacent alkylene group has a $-CH_2-$ or =CH- group adjacent to the hydroxamic acid group (that is, at the α-position) and/or:
(c) that adjacent alkylene group has a $-CH_2-$ group adjacent to the hydroxamic acid group (that is, at the α-position) and/or:
(d) that adjacent alkylene group has a =CH- group adjacent to the hydroxamic acid group (that is, at the α-position).

In one embodiment, in which Q^2 is a group as defined herein (e.g., C_{1-8}alkylene, C_{5-6}arylene-C_{1-7}alkylene, C_{1-7}alkylene-C_{5-6}arylene-C_{1-7}alkylene) having an alkylene group adjacent to the hydroxamic acid group:
(a) Q^2 is, additionally, unsubstituted at the α-position and unsubstituted at the β -position and/or:
(b) that adjacent alkylene group has a $-CH_2CH_2-$, -CH=CH-, or $-C\equiv C-$ group adjacent to the hydroxamic acid group (that is, at the α,β-position) and/or:
(c) that adjacent alkylene group has a $-CH_2CH_2-$ or -CH=CH- group adjacent to the hydroxamic acid group (that is, at the α,β-position) and/or:
(d) that adjacent alkylene group has a $-CH_2CH_2-$ group adjacent to the hydroxamic acid group (that is, at the α,β-position) and/or:
(e) that adjacent alkylene group has a -CH=CH- group adjacent to the hydroxamic acid group (that is, at the α,β-position).

Again, for the avoidance of doubt, it is <u>not</u> intended that the group, J, be part of another functional group. Q^1 and Q^2, and optional substituents thereon, are selected accordingly.

<u>The Acid Leader Group, Q^2: Substituents</u>

In one embodiment, Q^2 is independently substituted or unsubstituted.
In one embodiment, Q^2 is independently substituted.
In one embodiment, Q^2 is independently unsubstituted.

Examples of substituents on Q^2 (e.g., R^8), include, but are not limited to, those described under the heading "Substituents" below.

Further examples of substituents Q^2 (e.g., R^8), include, but are not limited to, those described under the heading "The Cyclyl Group, Cy: Substituents" above.

In one embodiment, substituents on Q^2 (e.g., R^B), if present, are independently selected from: halo, hydroxy, ether (e.g., C_{1-7}alkoxy), C_{5-20}aryl, acyl, amino, amido, acylamido, nitro, and oxo. Where a substituent is on an arylene group (e.g., phenylene), it may additionally be selected from: C_{1-7}alkyl, including substituted C_{1-7}alkyl.

In one embodiment, substituents on Q^2 (e.g., R^B), if present, are independently selected from: -F, -Cl, -Br, -I, -OH, -OMe, -OEt, -O(iPr), -Ph, -C(=O)Me, $-NH_2$, $-NMe_2$, $-NEt_2$, morpholino, $-CONH_2$, $-CONMe_2$, -NHCOMe, $-NO_2$, and =O. Where a substituent is on an arylene group (e.g., phenylene), it may additionally be selected from: -Me, -Et, -iPr, -tBu, $-CF_3$.

The Acid Leader Group, Q^2: Alkylene

In one embodiment, the acid leader group, Q^2, is independently C_{1-8}alkylene, and is optionally substituted.

In one embodiment, Q^2 is independently:
(a) a saturated C_{1-7}alkylene group; or:
(b) a partially unsaturated C_{2-7}alkylene group; or:
(c) an aliphatic C_{1-7}alkylene group; or:
(d) a linear C_{1-7}alkylene group; or:
(e) a branched C_{2-7}alkylene group; or:
(f) a saturated aliphatic C_{1-7}alkylene group; or:
(g) a saturated linear C_{1-7}alkylene group; or:
(h) a saturated branched C_{2-7}alkylene group; or:
(i) a partially unsaturated aliphatic C_{2-7}alkylene group; or:
(j) a partially unsaturated linear C_{2-7}alkylene group; or:
(k) a partially unsaturated branched C_{2-7}alkylene group;
and is optionally substituted.

In one embodiment, Q^2 additionally has a backbone length as described above under the heading "The Acid Leader Group, Q^2: Backbone Length."

Note that, for embodiments excluding, e.g., certain backbone lengths, absence of adjacent carbon-carbon double bonds, etc., it is to be understood that the corresponding

species listed below are similarly excluded from the respective embodiments discussed below.

In one embodiment, Q^2 is independently selected from:

$-CH_2-$, $-(CH_2)_2-$, $-(CH_2)_3-$, $-(CH_2)_4-$, $-(CH_2)_5-$, $-(CH_2)_6-$, $-(CH_2)_7-$, $-(CH_2)_8-$;

$-CH(CH_3)-$;
$-CH(CH_3)CH_2-$, $-CH_2CH(CH_3)-$;
$-CH(CH_3)CH_2CH_2-$, $-CH_2CH(CH_3)CH_2-$, $-CH_2CH_2CH(CH_3)-$;
$-CH(CH_3)CH_2CH_2CH_2-$, $-CH_2CH(CH_3)CH_2CH_2-$, $-CH_2CH_2CH(CH_3)CH_2-$, $-CH_2CH_2CH_2CH(CH_3)-$;
$-CH(CH_3)CH_2CH_2CH_2CH_2-$, $-CH_2CH(CH_3)CH_2CH_2CH_2-$, $-CH_2CH_2CH(CH_3)CH_2CH_2-$, $-CH_2CH_2CH_2CH(CH_3)CH_2-$, $-CH_2CH_2CH_2CH_2CH(CH_3)-$, $-CH(CH_3)CH_2CH_2CH_2CH(CH_3)-$;

$-CH(CH_2CH_3)-$;
$-CH(CH_2CH_3)CH_2-$, $-CH_2CH(CH_2CH_3)-$;
$-CH(CH_2CH_3)CH_2CH_2-$, $-CH_2CH(CH_2CH_3)CH_2-$, $-CH_2CH_2CH(CH_2CH_3)-$;
$-CH(CH_2CH_3)CH_2CH_2CH_2-$, $-CH_2CH(CH_2CH_3)CH_2CH_2-$, $-CH_2CH_2CH(CH_2CH_3)CH_2-$, $-CH_2CH_2CH_2CH(CH_2CH_3)-$;
$-CH(CH_2CH_3)CH_2CH_2CH_2CH_2-$, $-CH_2CH(CH_2CH_3)CH_2CH_2CH_2-$, $-CH_2CH_2CH(CH_2CH_3)CH_2CH_2-$, $-CH_2CH_2CH_2CH(CH_2CH_3)CH_2-$, $-CH_2CH_2CH_2CH_2CH(CH_2CH_3)-$;

$-CH=CH-$;
$-CH=CHCH_2-$, $-CH_2CH=CH-$;
$-CH=CHCH_2CH_2-$, $-CH_2CH=CHCH_2-$, $-CH_2CH_2CH=CH-$;
$-CH=CHCH_2CH_2CH_2-$, $-CH_2CH=CHCH_2CH_2-$, $-CH_2CH_2CH=CHCH_2-$, $-CH_2CH_2CH_2CH=CH-$;
$-CH=CHCH_2CH_2CH_2CH_2-$, $-CH_2CH=CHCH_2CH_2CH_2-$, $-CH_2CH_2CH=CHCH_2CH_2-$, $-CH_2CH_2CH_2CH=CHCH_2-$, $-CH_2CH_2CH_2CH_2CH=CH-$;

$-C(CH_3)=CH-$, $-CH=C(CH_3)-$;
$-C(CH_3)=CHCH_2-$, $-CH=C(CH_3)CH_2-$, $-CH=CHCH(CH_3)-$;
$-CH(CH_3)CH=CH-$, $-CH_2C(CH_3)=CH-$, $-CH_2CH=C(CH_3)-$;

-CH=CHCH=CH-;

-CH=CHCH=CHCH$_2$-, -CH$_2$CH=CHCH=CH-, -CH=CHCH$_2$CH=CH-;

-CH=CHCH=CHCH$_2$CH$_2$-, -CH=CHCH$_2$CH=CHCH$_2$-, -CH=CHCH$_2$CH$_2$CH=CH-, -CH$_2$CH=CHCH=CHCH$_2$-, -CH$_2$CH=CHCH$_2$CH=CH-, -CH$_2$CH$_2$CH=CHCH=CH-;

-C(CH$_3$)=CHCH=CH-, -CH=C(CH$_3$)CH=CH-, -CH=CHC(CH$_3$)=CH-, -CH=CHCH=C(CH$_3$)-;

-C C-;

-C CCH$_2$-, -CH$_2$C C-; -C CCH(CH$_3$)-, -CH(CH$_3$)C C-;

-C CCH$_2$CH$_2$-, -CH$_2$C CCH$_2$-, -CH$_2$CH$_2$C C-;

-C CCH(CH$_3$)CH$_2$-, -C CCH$_2$CH(CH$_3$)-;

-CH(CH$_3$)C CCH$_2$-, -CH$_2$C CCH(CH$_3$)-;

-CH(CH$_3$)CH$_2$C C-, -CH$_2$CH(CH$_3$)C C-;

-C CCH=CH-, -CH=CHC C-, -C CC C-;

-C CCH$_2$CH$_2$CH$_2$-, -CH$_2$CH$_2$CH$_2$C C-;

-C CCH$_2$CH$_2$CH$_2$CH$_2$-, -CH$_2$CH$_2$CH$_2$CH$_2$C C-;

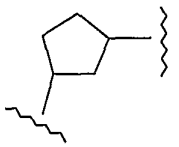
-C CCH=CHCH=CH-, -CH=CHC C-CH=CH-, -CH=CHCH=CHC C-;

-C(CH$_3$)=CHC C-, -CH=C(CH$_3$)C C-, -C CC(CH$_3$)=CH-, -C CCH=C(CH$_3$)-

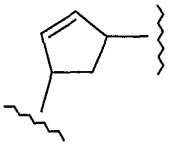
cyclopentylene cyclopentenylene;

cyclohexylene, cyclohexenylene, cyclohexadienylene;

(cyclopent-1,3-ylene)

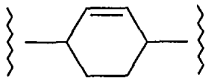


(4-cyclopenten-1,3-ylene)



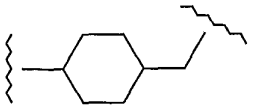
(cyclohex-1,4-ylene)

(2-cyclohexen-1,4-ylene)

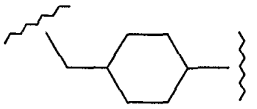


(2,5-cyclohexadien-1,4-ylene)

(cyclohex-1,4-ylene-methylene)



(methylene-cyclohex-1,4-ylene)



In one preferred embodiment, Q^2 is independently selected from:

$-(CH_2)_5-$;

$-(CH_2)_6-$;

$-(CH_2)_7-$;

$-(CH_2)_8-$;

$-CH(CH_3)CH_2CH_2CH_2CH_2-$;

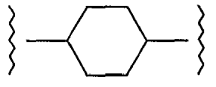
$-CH_2CH_2CH_2CH_2CH(CH_3)-$;

$-CH_2CH_2CH(CH_3)CH_2CH_2-$;

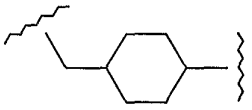
$-CH(CH_3)CH_2CH_2CH_2CH(CH_3)-$;

$-CH_2CH_2CH_2CH=CH-$;

$-CH_2CH_2CH_2CH_2CH=CH-$;



and



.

In one preferred embodiment, Q^2 is independently selected from:

$-(CH_2)_5-$;

$-(CH_2)_6-$;

$-(CH_2)_7-$;

$-(CH_2)_8-$;

$-CH(CH_3)CH_2CH_2CH_2CH_2-$;

$-CH_2CH_2CH_2CH_2CH(CH_3)-$;

$-CH_2CH_2CH_2CH=CH-$; and,

$-CH_2CH_2CH_2CH_2CH=CH-$.

In one preferred embodiment, Q^2 is independently selected from:

$-(CH_2)_5-$;

$-(CH_2)_6-$;

$-(CH_2)_7-$; and

$-(CH_2)_8-$.

The Acid Leader Group, Q^2: Arylene

In one embodiment, the acid leader group, Q^2, is independently C_{5-6}arylene, and is optionally substituted.

In one embodiment, Q^2 is independently C_{5-6}arylene; and is optionally substituted.
In one embodiment, Q^2 is independently phenylene; and is optionally substituted.

In one embodiment, Q^2 additionally has a backbone length as described above under the heading "The Acid Leader Group, Q^2: Backbone Length."

The Acid Leader Group, Q^2:
Alkylene-Arylene, Arylene-Alkylene, and Alkylene-Arylene-Alkylene

In one preferred embodiment, the acid leader group, Q^2, is independently:

C_{5-6}arylene-C_{1-7}alkylene;

C_{1-7}alkylene-C_{5-6}arylene; or,

C_{1-7}alkylene-C_{5-6}arylene-C_{1-7}alkylene;

and is optionally substituted.

In one preferred embodiment, Q^2 is independently:

phenylene-C_{1-7}alkylene;

C_{1-7}alkylene-phenylene; or,

C_{1-7}alkylene-phenylene-C_{1-7}alkylene;
and is optionally substituted.

In one embodiment, Q^2 is independently C_{1-7}alkylene-C_{5-6}arylene; and is optionally substituted.
In one embodiment, Q^2 is independently C_{1-7}alkylene-phenylene; and is optionally substituted.

In one embodiment, Q^2 is independently C_{5-6}arylene-C_{1-7}alkylene; and is optionally substituted.
In one embodiment, Q^2 is independently phenylene-C_{1-7}alkylene; and is optionally substituted.

In one embodiment, Q^2 is independently C_{1-7}alkylene-C_{5-6}arylene-C_{1-7}alkylene; and is optionally substituted.
In one embodiment, Q^2 is independently C_{1-7}alkylene-phenylene-C_{1-7}alkylene; and is optionally substituted.

In one embodiment, in the above arylene-alkylene, alkylene-arylene, and alkylene-arylene-alkylene groups, each alkylene group is independently:
(a) a saturated C_{1-7}alkylene group; or:
(b) a partially unsaturated C_{2-7}alkylene group; or:
(c) an aliphatic C_{1-7}alkylene group; or:
(d) a linear C_{1-7}alkylene group; or:
(e) a branched C_{2-7}alkylene group; or:
(f) a saturated aliphatic C_{1-7}alkylene group; or:
(g) a saturated linear C_{1-7}alkylene group; or:
(h) a saturated branched C_{2-7}alkylene group; or:
(i) a partially unsaturated aliphatic C_{2-7}alkylene group; or:
(j) a partially unsaturated linear C_{2-7}alkylene group; or:

(k) a partially unsaturated branched C_{2-7}alkylene group;

and is optionally substituted.

In one embodiment, Q^2 additionally has a backbone length as described above under the heading "The Acid Leader Group, Q^2: Backbone Length."

In one embodiment, in the above arylene-alkylene, alkylene-arylene, and alkylene-arylene-alkylene groups, each alkylene group is independently selected from:

$-CH_2-$, $-(CH_2)_2-$, $-(CH_2)_3-$, $-(CH_2)_4-$, $-(CH_2)_5-$, $-(CH_2)_6-$,

$-CH_2-CH=CH-$; and,

$-CH_2-CH=CH-CH=CH-$.

In one embodiment, each alkylene group is independently selected from:

$-CH_2-$, $-CH_2CH_2-$, and $-CH_2-CH=CH-$.

In one embodiment, each alkylene group is independently selected from:

$-CH_2-$ and $-CH_2CH_2-$.

Again, for the avoidance of doubt, it is not intended that the group, J, be part of another functional group. Q^2, and optional substituents thereon, are selected accordingly.

The Acid Leader Group, Q^2: Certain Phenylene-Containing Embodiments

In one embodiment, Q^2 is independently:

phenylene;

and is optionally substituted.

In one embodiment, Q^2 is independently:

methylene-phenylene;

ethylene-phenylene;

and is optionally substituted.

In one embodiment, Q^2 is independently:

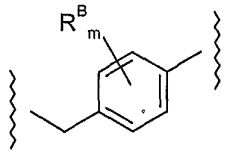
phenylene-methylene;

phenylene-ethylene; or,

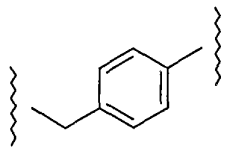
phenylene-ethenylene (also known as phenylene-vinylene);

and is optionally substituted.

In one embodiment, Q^2 is independently methylene-phenylene; and is optionally substituted (wherein R^B and m are as defined below):



In one embodiment, Q^2 is independently unsubstituted methylene-phenylene:



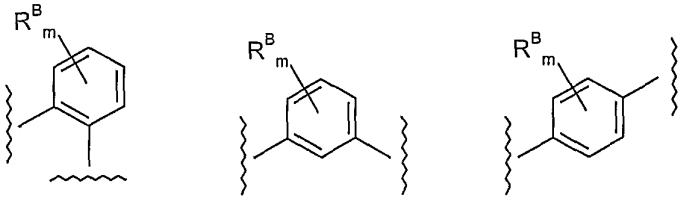
In one embodiment, Q^2 is independently:

methylene-phenylene-methylene;
methylene-phenylene-ethylene;
methylene-phenylene-ethenylene;

ethylene-phenylene-methylene;
ethylene-phenylene-ethylene;
ethylene-phenylene-ethenylene;

and is optionally substituted.

In the above phenylene, phenylene-alkylene, alkylene-phenylene, and alkylene-phenylene-alkylene groups, the phenylene linkage may be ortho (i.e., 1,2-), meta (i.e., 1,3-), or para (i.e., 1,4-), and the phenylene group is optionally substituted with from 1 to 4 substituents, R^B:



In one embodiment, the phenylene linkage is meta or para.
In one embodiment, the phenylene linkage is meta.
In one embodiment, the phenylene linkage is para.

In one embodiment, m is an integer from 0 to 4.
In one embodiment, m is an integer from 0 to 3.
In one embodiment, m is an integer from 0 to 2.
In one embodiment, m is 0 or 1.
In one embodiment, m is an integer from 1 to 4.
In one embodiment, m is an integer from 1 to 3.
In one embodiment, m is 1 or 2.
In one embodiment, m is 4.
In one embodiment, m is 3.
In one embodiment, m is 2.
In one embodiment, m is 1.
In one embodiment, m is 0.

Each substituent, R^B, is independently as defined above under the heading "The Acid Leader Group, Q^2: Substituents."

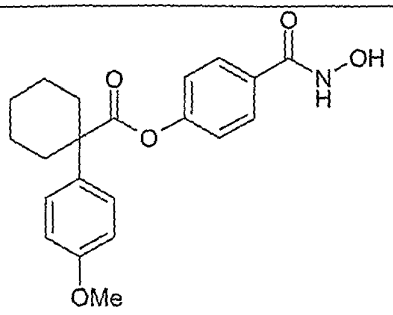
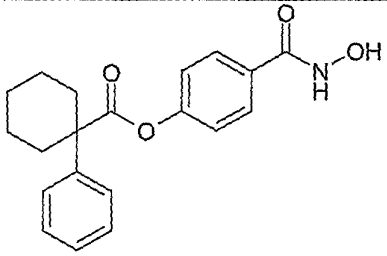
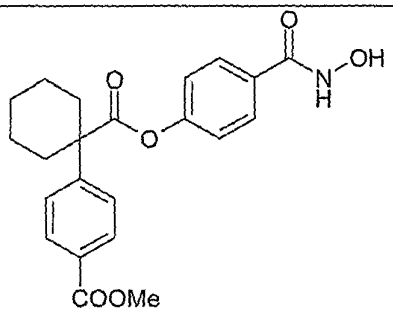
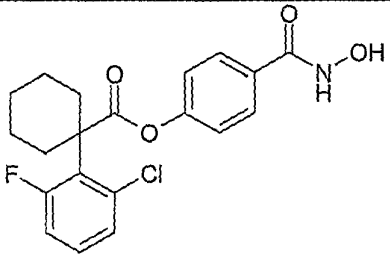
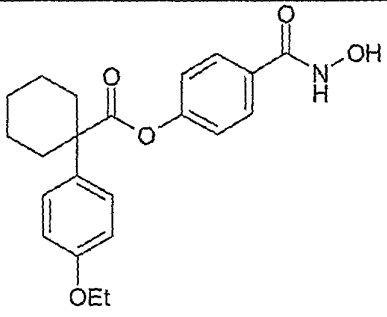
In one embodiment, the phenylene group is substituted or unsubstituted.
In one embodiment, the phenylene group is substituted.
In one embodiment, the phenylene group is unsubstituted.

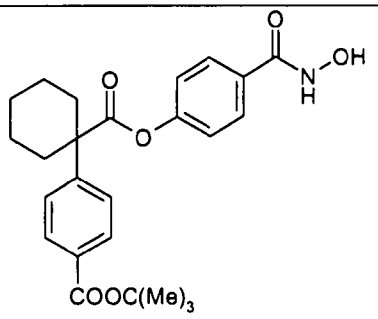
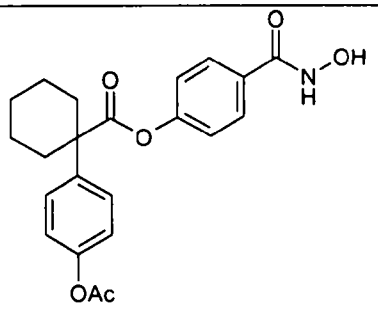
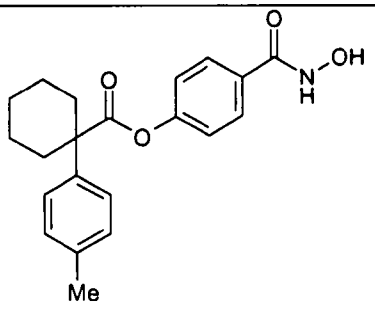
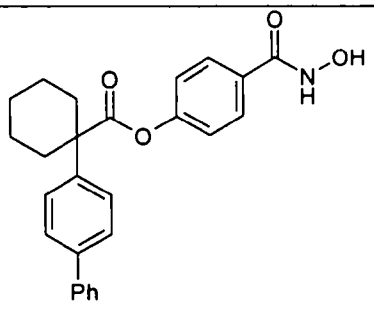
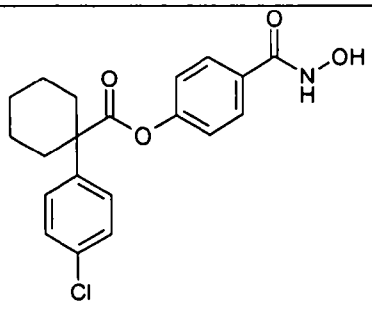
Examples of Specific Embodiments: Esters

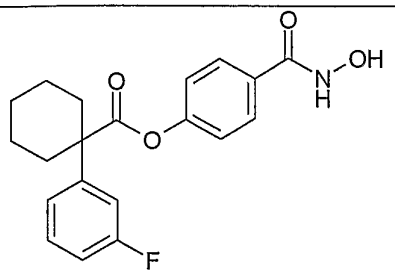
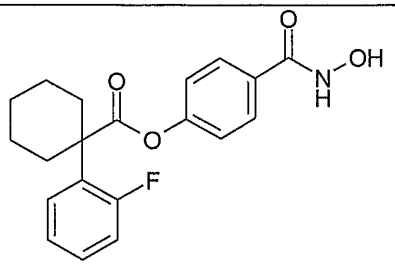
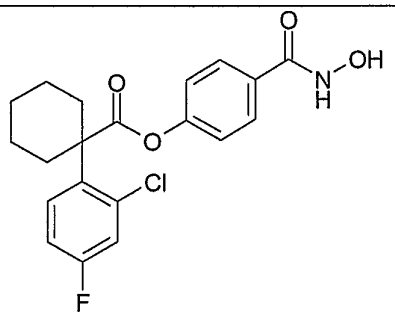
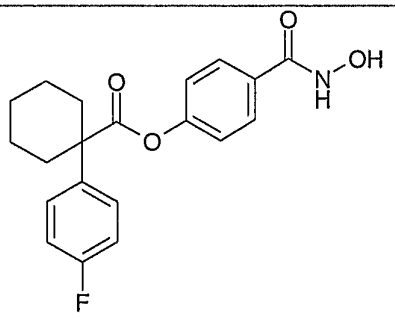
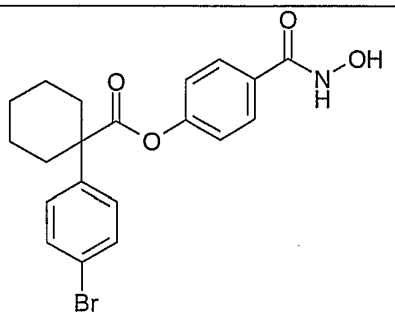
In one preferred embodiment:

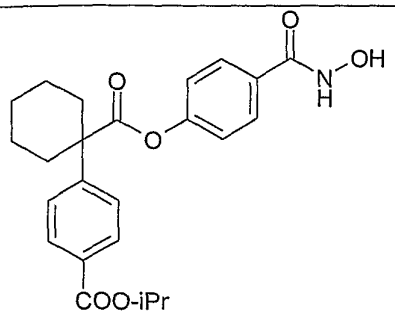
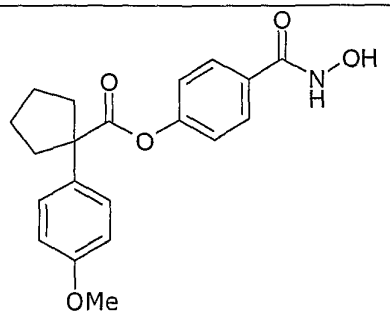
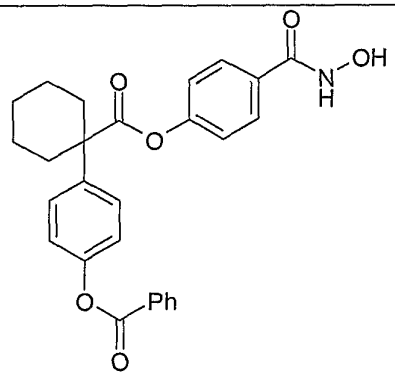
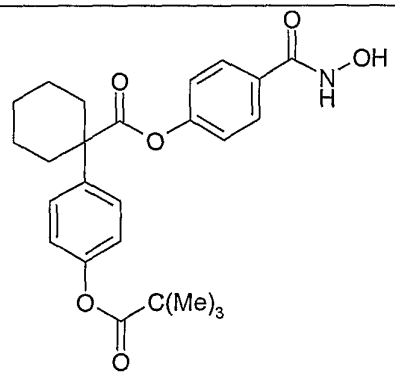
J is -C(=O)O- ("forward ester");
Q^1 is as defined above;
Q^2 is unsubstituted para-phenylene; and,
Cy is optionally substituted phenyl, as defined above.

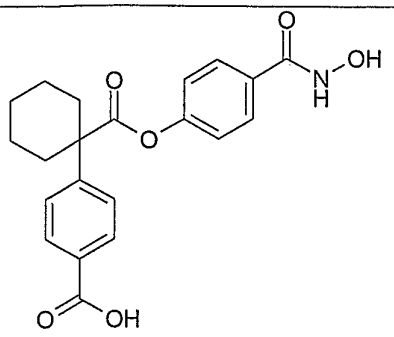
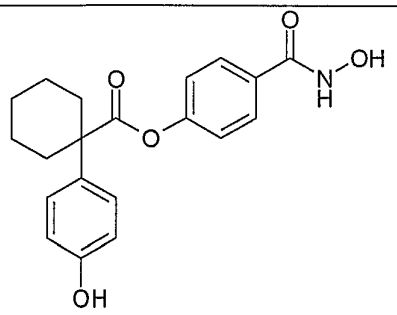
Some individual embodiments of the present invention include the following compounds.

1		PX118478
2		PX118479
3		PX118480
4		PX119101
5		PX118925

6		PX118926
7		PX118959
8		PX118966
9		PX119058
10		PX119059

11		PX119061
12		PX119062
13		PX119064
14		PX119065
15		PX119084

16		PX119100
17		PX119063
18		PX119085
19		PX119086

20		PX119102
21		PX119103

Examples of Specific Embodiments: Ketones

In one preferred embodiment:

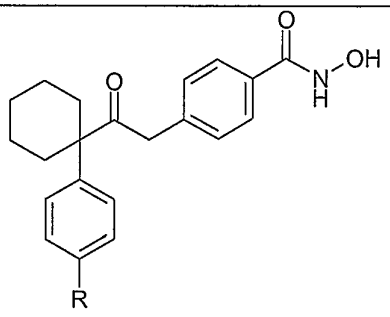
J is -C(=O)- ("ketone");

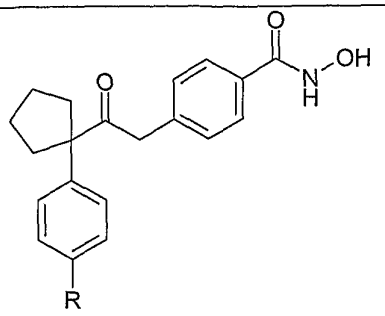
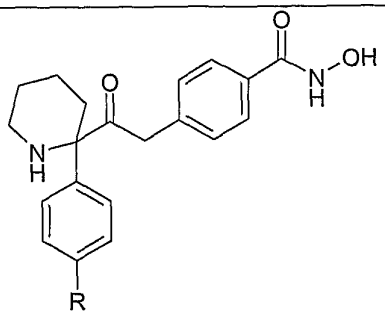
Q^1 is as defined above;

Q^2 is unsubstituted para-methylene-phenylene; and,

Cy is optionally substituted phenyl, as defined above.

Some individual embodiments of the present invention include the following compounds.

1		

2		
3		

Chemical Terms

The term "carbo," "carbyl," "hydrocarbo," and "hydrocarbyl," as used herein, pertain to compounds and/or groups which have only carbon and hydrogen atoms (but see "carbocyclic" below).

The term "hetero," as used herein, pertains to compounds and/or groups which have at least one heteroatom, for example, multivalent heteroatoms (which are also suitable as ring heteroatoms) such as boron, silicon, nitrogen, phosphorus, oxygen, sulfur, and selenium (more commonly nitrogen, oxygen, and sulfur) and monovalent heteroatoms, such as fluorine, chlorine, bromine, and iodine.

The term "saturated," as used herein, pertains to compounds and/or groups which do not have any carbon-carbon double bonds or carbon-carbon triple bonds.

The term "unsaturated," as used herein, pertains to compounds and/or groups which have at least one carbon-carbon double bond or carbon-carbon triple bond.

The term "aliphatic," as used herein, pertains to compounds and/or groups which are linear or branched, but not cyclic (also known as "acyclic" or "open-chain" groups).

The term "ring," as used herein, pertains to a closed ring of from 3 to 10 covalently linked atoms, more preferably 3 to 8 covalently linked atoms, yet more preferably 5 to 6 covalently linked atoms. A ring may be an alicyclic ring or an aromatic ring. The term "alicyclic ring," as used herein, pertains to a ring which is not an aromatic ring.

The term "carbocyclic ring," as used herein, pertains to a ring wherein all of the ring atoms are carbon atoms.

The term "carboaromatic ring," as used herein, pertains to an aromatic ring wherein all of the ring atoms are carbon atoms.

The term "heterocyclic ring," as used herein, pertains to a ring wherein at least one of the ring atoms is a multivalent ring heteroatom, for example, nitrogen, phosphorus, silicon, oxygen, or sulfur, though more commonly nitrogen, oxygen, or sulfur. Preferably, the heterocyclic ring has from 1 to 4 heteroatoms.

The term "cyclic compound," as used herein, pertains to a compound which has at least one ring. The term "cyclyl," as used herein, pertains to a monovalent moiety obtained by removing a hydrogen atom from a ring atom of a cyclic compound.

Where a cyclic compound has two or more rings, they may be fused (e.g., as in naphthalene), bridged (e.g., as in norbornane), spiro (e.g., as in spiro[3.3]heptane), or a combination thereof. Cyclic compounds with one ring may be referred to as "monocyclic" or "mononuclear," whereas cyclic compounds with two or more rings may be referred to as "polycyclic" or "polynuclear."

The term "carbocyclic compound," as used herein, pertains to a cyclic compound which has only carbocyclic ring(s).

The term "heterocyclic compound," as used herein, pertains to a cyclic compound which has at least one heterocyclic ring.

The term "aromatic compound," as used herein, pertains to a cyclic compound which has at least one aromatic ring.

The term "carboaromatic compound," as used herein, pertains to a cyclic compound which has only carboaromatic ring(s).

The term "heteroaromatic compound," as used herein, pertains to a cyclic compound which has at least one heteroaromatic ring.

The term "monodentate substituents," as used herein, pertains to substituents which have one point of covalent attachment.

The term "monovalent monodentate substituents," as used herein, pertains to substituents which have one point of covalent attachment, via a single bond. Examples of such substituents include halo, hydroxy, and alkyl.

The term "multivalent monodentate substituents," as used herein, pertains to substituents which have one point of covalent attachment, but through a double bond or triple bond. Examples of such substituents include oxo, imino, alkylidene, and alklidyne.

The term "bidentate substituents," as used herein, pertains to substituents which have two points of covalent attachment, and which act as a linking group between two other moieties. Examples of such substituents include alkylene and arylene.

Substituents

The phrase "optionally substituted," as used herein, pertains to a parent group which may be unsubstituted or which may be substituted.

Unless otherwise specified, the term "substituted," as used herein, pertains to a parent group which bears one or more substituents. The term "substituent" is used herein in the conventional sense and refers to a chemical moiety which is covalently attached to, appended to, or if appropriate, fused to, a parent group. A wide variety of substituents are well known, and methods for their formation and introduction into a variety of parent groups are also well known.

The substituents are described in more detail below.

Alkyl: The term "alkyl," as used herein, pertains to a monovalent moiety obtained by removing a hydrogen atom from a carbon atom of a hydrocarbon compound having from 1 to 20 carbon atoms (unless otherwise specified), which may be aliphatic or alicyclic, and which may be saturated, partially unsaturated, or fully unsaturated. Thus, the term "alkyl" includes the sub-classes alkenyl, alkynyl, cycloalkyl, etc., discussed below.

In this context, the prefixes (e.g., C_{1-4}, C_{1-7}, C_{1-20}, C_{2-7}, C_{3-7}, etc.) denote the number of carbon atoms, or range of number of carbon atoms. For example, the term "C_{1-4}alkyl," as used herein, pertains to an alkyl group having from 1 to 4 carbon atoms. Examples of groups of alkyl groups include C_{1-4}alkyl ("lower alkyl"), C_{1-7}alkyl, and C_{1-20}alkyl.

Examples of (unsubstituted) saturated alkyl groups include, but are not limited to, methyl (C_1), ethyl (C_2), propyl (C_3), butyl (C_4), pentyl (C_5), hexyl (C_6), heptyl (C_7), octyl (C_8), nonyl (C_9), decyl (C_{10}), undecyl (C_{11}), dodecyl (C_{12}), tridecyl (C_{13}), tetradecyl (C_{14}), pentadecyl (C_{15}), and eicodecyl (C_{20}).

Examples of (unsubstituted) saturated linear alkyl groups include, but are not limited to, methyl (C_1), ethyl (C_2), n-propyl (C_3), n-butyl (C_4), n-pentyl (amyl) (C_5), n-hexyl (C_6), and n-heptyl (C_7).

Examples of (unsubstituted) saturated branched alkyl groups include iso-propyl (C_3), iso-butyl (C_4), sec-butyl (C_4), tert-butyl (C_4), iso-pentyl (C_5), and neo-pentyl (C_5).

Cycloalkyl: The term "cycloalkyl," as used herein, pertains to an alkyl group which is also a cyclyl group; that is, a monovalent moiety obtained by removing a hydrogen atom from an alicyclic ring atom of a cyclic hydrocarbon (carbocyclic) compound, which moiety has from 3 to 20 ring atoms (unless otherwise specified). Preferably, each ring has from 3 to 7 ring atoms.

Examples of (unsubstituted) saturated cylcoalkyl groups include, but are not limited to, those derived from: cyclopropane (C_3), cyclobutane (C_4), cyclopentane (C_5), cyclohexane (C_6), cycloheptane (C_7), norbornane (C_7), norpinane (C_7), norcarane (C_7), adamantane (C_{10}), and decalin (decahydronaphthalene) (C_{10}).

Examples of (substituted) saturated cycloalkyl groups, which are also referred to herein as "alkyl-cycloalkyl" groups, include, but are not limited to, methylcyclopropyl,

dimethylcyclopropyl, methylcyclobutyl, dimethylcyclobutyl, methylcyclopentyl, dimethylcyclopentyl, methylcyclohexyl, and dimethylcyclohexyl, menthane, thujane, carane, pinane, bornane, norcarane, and camphene.

Examples of (substituted) unsaturated cyclic alkenyl groups, which are also referred to herein as "alkyl-cycloalkenyl" groups, include, but are not limited to, methylcyclopropenyl, dimethylcyclopropenyl, methylcyclobutenyl, dimethylcyclobutenyl, methylcyclopentenyl, dimethylcyclopentenyl, methylcyclohexenyl, and dimethylcyclohexenyl.

Examples of (substituted) cycloalkyl groups, with one or more other rings fused to the parent cycloalkyl group, include, but are not limited to, those derived from: indene (C_9), indan (e.g., 2,3-dihydro-1H-indene) (C_9), tetraline (1,2,3,4-tetrahydronaphthalene (C_{10}), acenaphthene (C_{12}), fluorene (C_{13}), phenalene (C_{13}), acephenanthrene (C_{15}), aceanthrene (C_{16}). For example, 2H-inden-2-yl is a C_5cycloalkyl group with a substituent (phenyl) fused thereto.

Alkenyl: The term "alkenyl," as used herein, pertains to an alkyl group having one or more carbon-carbon double bonds. Examples of groups of alkenyl groups include C_{2-4}alkenyl, C_{2-7}alkenyl, C_{2-20}alkenyl.

Examples of (unsubstituted) unsaturated alkenyl groups include, but are not limited to, ethenyl (vinyl, -CH=CH_2), 1-propenyl (-CH=CH-CH_3), 2-propenyl (allyl, -CH-CH=CH_2), isopropenyl (-C(CH_3)=CH_2), butenyl (C_4), pentenyl (C_5), and hexenyl (C_6).

Examples of (unsubstituted) unsaturated cyclic alkenyl groups, which are also referred to herein as "cycloalkenyl" groups, include, but are not limited to, cyclopropenyl (C_3), cyclobutenyl (C_4), cyclopentenyl (C_5), and cyclohexenyl (C_6).

Alkynyl: The term "alkynyl," as used herein, pertains to an alkyl group having one or more carbon-carbon triple bonds. Examples of groups of alkynyl groups include C_{2-4}alkynyl, C_{2-7}alkynyl, C_{2-20}alkynyl.

Examples of (unsubstituted) unsaturated alkynyl groups include, but are not limited to, ethynyl (ethinyl, -C CH) and 2-propynyl (propargyl, -CH_2-C CH).

Alkylidene: The term "alkylidene," as used herein, pertains to a divalent monodentate moiety obtained by removing two hydrogen atoms from a carbon atom of a hydrocarbon compound having from 1 to 20 carbon atoms (unless otherwise specified), which may be aliphatic or alicyclic, or a combination thereof, and which may be saturated, partially unsaturated, or fully unsaturated. Examples of groups of alkylidene groups include C_{1-4}alkylidene, C_{1-7}alkylidene, C_{1-20}alkylidene.

Examples of alkylidene groups include, but are not limited to, methylidene (=CH_2), ethylidene (=CH-CH_3), vinylidene (=C=CH_2), and isopropylidene (=$C(CH_3)_2$). An example of a substituted alkylidene is benzylidene (=CH-Ph).

Alkylidyne: The term "alkylidyne," as used herein, pertains to a trivalent monodentate moiety obtained by removing three hydrogen atoms from a carbon atom of a hydrocarbon compound having from 1 to 20 carbon atoms (unless otherwise specified), which may be aliphatic or alicyclic, or a combination thereof, and which may be saturated, partially unsaturated, or fully unsaturated. Examples of groups of alkylidyne groups include C_{1-4}alkylidyne, C_{1-7}alkylidyne, C_{1-20}alkylidyne.

Examples of alkylidyne groups include, but are not limited to, methylidyne (CH) and ethylidyne (C-CH_3).

Carbocyclyl: The term "carbocyclyl," as used herein, pertains to a monovalent moiety obtained by removing a hydrogen atom from a ring atom of a carbocyclic compound, which moiety has from 3 to 20 ring atoms (unless otherwise specified). Preferably, each ring has from 3 to 7 ring atoms.

In this context, the prefixes (e.g., C_{3-20}, C_{3-7}, C_{5-6}, etc.) denote the number of ring atoms, or range of number of ring atoms. For example, the term "C_{5-6}carbocyclyl," as used herein, pertains to a carbocyclyl group having 5 or 6 ring atoms. Examples of groups of carbocyclyl groups include C_{3-20}carbocyclyl, C_{3-10}carbocyclyl, C_{5-10}carbocyclyl, C_{3-7}carbocyclyl, and C_{5-7}carbocyclyl.

Examples of carbocyclic groups include, but are not limited to, those described above as cycloalkyl groups; and those described below as carboaryl groups.

Heterocyclyl: The term "heterocyclyl," as used herein, pertains to a monovalent moiety obtained by removing a hydrogen atom from a ring atom of a heterocyclic compound, which moiety has from 3 to 20 ring atoms (unless otherwise specified), of which from 1 to 10 are ring heteroatoms. Preferably, each ring has from 3 to 7 ring atoms, of which from 1 to 4 are ring heteroatoms.

In this context, the prefixes (e.g., C_{3-20}, C_{3-7}, C_{5-6}, etc.) denote the number of ring atoms, or range of number of ring atoms, whether carbon atoms or heteroatoms. For example, the term "C_{5-6}heterocyclyl," as used herein, pertains to a heterocyclyl group having 5 or 6 ring atoms. Examples of groups of heterocyclyl groups include C_{3-20}heterocyclyl, C_{3-7}heterocyclyl, C_{5-7}heterocyclyl, and C_{5-6}heterocyclyl.

Examples of (non-aromatic) monocyclic heterocyclyl groups include, but are not limited to, those derived from:

N_1: aziridine (C_3), azetidine (C_4), pyrrolidine (tetrahydropyrrole) (C_5), pyrroline (e.g., 3-pyrroline, 2,5-dihydropyrrole) (C_5), 2H-pyrrole or 3H-pyrrole (isopyrrole, isoazole) (C_5), piperidine (C_6), dihydropyridine (C_6), tetrahydropyridine (C_6), azepine (C_7);

O_1: oxirane (C_3), oxetane (C_4), oxolane (tetrahydrofuran) (C_5), oxole (dihydrofuran) (C_5), oxane (tetrahydropyran) (C_6), dihydropyran (C_6), pyran (C_6), oxepin (C_7);

S_1: thiirane (C_3), thietane (C_4), thiolane (tetrahydrothiophene) (C_5), thiane (tetrahydrothiopyran) (C_6), thiepane (C_7);

O_2: dioxolane (C_5), dioxane (C_6), and dioxepane (C_7);

O_3: trioxane (C_6);

N_2: imidazolidine (C_5), pyrazolidine (diazolidine) (C_5), imidazoline (C_5), pyrazoline (dihydropyrazole) (C_5), piperazine (C_6);

N_1O_1: tetrahydrooxazole (C_5), dihydrooxazole (C_5), tetrahydroisoxazole (C_5), dihydroisoxazole (C_5), morpholine (C_6), tetrahydrooxazine (C_6), dihydrooxazine (C_6), oxazine (C_6);

N_1S_1: thiazoline (C_5), thiazolidine (C_5), thiomorpholine (C_6);

N_2O_1: oxadiazine (C_6);

O_1S_1: oxathiole (C_5) and oxathiane (thioxane) (C_6); and,

$N_1O_1S_1$: oxathiazine (C_6).

Examples of substituted (non-aromatic) monocyclic heterocyclyl groups include saccharides, in cyclic form, for example, furanoses (C_5), such as arabinofuranose, lyxofuranose, ribofuranose, and xylofuranse, and pyranoses (C_6), such as allopyranose, altropyranose, glucopyranose, mannopyranose, gulopyranose, idopyranose, galactopyranose, and talopyranose.

Examples of heterocyclyl groups which are also heteroaryl groups are described below with aryl groups.

Aryl: The term "aryl," as used herein, pertains to a monovalent moiety obtained by removing a hydrogen atom from an aromatic ring atom of an aromatic compound, which moiety has from 3 to 20 ring atoms (unless otherwise specified). Preferably, each ring has from 5 to 7 ring atoms.

In this context, the prefixes (e.g., C_{3-20}, C_{5-7}, C_{5-6}, etc.) denote the number of ring atoms, or range of number of ring atoms, whether carbon atoms or heteroatoms. For example, the term "C_{5-6}aryl," as used herein, pertains to an aryl group having 5 or 6 ring atoms. Examples of groups of aryl groups include C_{3-20}aryl, C_{3-12}aryl, C_{5-12}aryl, C_{5-7}aryl, and C_{5-6}aryl.

The ring atoms may be all carbon atoms, as in "carboaryl groups" (e.g., C_{5-20}carboaryl).

Examples of carboaryl groups include, but are not limited to, those derived from benzene (i.e., phenyl) (C_6), naphthalene (C_{10}), azulene (C_{10}), anthracene (C_{14}), phenanthrene (C_{14}), naphthacene (C_{18}), and pyrene (C_{16}).

Examples of aryl groups which comprise fused rings, at least one of which is an aromatic ring, include, but are not limited to, groups derived from indene (C_9), isoindene (C_9), and fluorene (C_{13}).

Alternatively, the ring atoms may include one or more heteroatoms, as in "heteroaryl groups" (e.g., C_{5-20}heteroaryl).

Examples of monocyclic heteroaryl groups include, but are not limited to, those derived from:

N_1: pyrrole (azole) (C_5), pyridine (azine) (C_6);

O_1: furan (oxole) (C_5);

S_1: thiophene (thiole) (C_5);

N_1O_1: oxazole (C_5), isoxazole (C_5), isoxazine (C_6);

N_2O_1: oxadiazole (furazan) (C_5);

N_3O_1: oxatriazole (C_5);

N_1S_1: thiazole (C_5), isothiazole (C_5);

N_2: imidazole (1,3-diazole) (C_5), pyrazole (1,2-diazole) (C_5), pyridazine (1,2-diazine) (C_6), pyrimidine (1,3-diazine) (C_6) (e.g., cytosine, thymine, uracil), pyrazine (1,4-diazine) (C_6);

N_3: triazole (C_5), triazine (C_6); and,

N_4: tetrazole (C_5).

Examples of heterocyclic groups (some of which are also heteroaryl groups) which comprise fused rings, include, but are not limited to:

C_9heterocyclic groups (with 2 fused rings) derived from benzofuran (O_1), isobenzofuran (O_1), indole (N_1), isoindole (N_1), indolizine (N_1), indoline (N_1), isoindoline (N_1), purine (N_4) (e.g., adenine, guanine), benzimidazole (N_2), indazole (N_2), benzoxazole (N_1O_1), benzisoxazole (N_1O_1), benzodioxole (O_2), benzofurazan (N_2O_1), benzotriazole (N_3), benzothiofuran (S_1), benzothiazole (N_1S_1), benzothiadiazole (N_2S);

C_{10}heterocyclic groups (with 2 fused rings) derived from chromene (O_1), isochromene (O_1), chroman (O_1), isochroman (O_1), benzodioxan (O_2), quinoline (N_1), isoquinoline (N_1), quinolizine (N_1), benzoxazine (N_1O_1), benzodiazine (N_2), pyridopyridine (N_2), quinoxaline (N_2), quinazoline (N_2), cinnoline (N_2), phthalazine (N_2), naphthyridine (N_2), pteridine (N_4);

C_{13}heterocyclic groups (with 3 fused rings) derived from carbazole (N_1), dibenzofuran (O_1), dibenzothiophene (S_1), carboline (N_2), perimidine (N_2), pyridoindole (N_2); and,

C_{14}heterocyclic groups (with 3 fused rings) derived from acridine (N_1), xanthene (O_1), thioxanthene (S_1), oxanthrene (O_2), phenoxathiin (O_1S_1), phenazine (N_2), phenoxazine (N_1O_1), phenothiazine (N_1S_1), thianthrene (S_2), phenanthridine (N_1), phenanthroline (N_2), phenazine (N_2).

Heterocyclic groups (including heteroaryl groups) which have a nitrogen ring atom in the form of an -NH- group may be N-substituted, that is, as -NR-. For example, pyrrole may be N-methyl substituted, to give N-methypyrrole. Examples of N-substituents include, but are not limited to C_{1-7}alkyl, C_{3-20}heterocyclyl, C_{5-20}aryl, and acyl groups.

Heterocyclic groups (including heteroaryl groups) which have a nitrogen ring atom in the form of an -N= group may be substituted in the form of an N-oxide, that is, as -N(O)= (also denoted $-N^+(O^-)=$). For example, quinoline may be substituted to give quinoline N-oxide; pyridine to give pyridine N-oxide; benzofurazan to give benzofurazan N-oxide (also known as benzofuroxan).

Cyclic groups may additionally bear one or more oxo (=O) groups on ring carbon atoms. Monocyclic examples of such groups include, but are not limited to, those derived from:
C_5: cyclopentanone, cyclopentenone, cyclopentadienone;
C_6: cyclohexanone, cyclohexenone, cyclohexadienone;
O_1: furanone (C_5), pyrone (C_6);
N_1: pyrrolidone (pyrrolidinone) (C_5), piperidinone (piperidone) (C_6), piperidinedione (C_6);
N_2: imidazolidone (imidazolidinone) (C_5), pyrazolone (pyrazolinone) (C_5), piperazinone (C_6), piperazinedione (C_6), pyridazinone (C_6), pyrimidinone (C_6) (e.g., cytosine), pyrimidinedione (C_6) (e.g., thymine, uracil), barbituric acid (C_6);
N_1S_1: thiazolone (C_5), isothiazolone (C_5);
N_1O_1: oxazolinone (C_5).

Polycyclic examples of such groups include, but are not limited to, those derived from:
C_9: indenedione;
C_{10}: tetralone, decalone;
C_{14}: anthrone, phenanthrone;
N_1: oxindole (C_9);
O_1: benzopyrone (e.g., coumarin, isocoumarin, chromone) (C_{10});
N_1O_1: benzoxazolinone (C_9), benzoxazolinone (C_{10});
N_2: quinazolinedione (C_{10});

N_4: purinone (C_9) (e.g., guanine).

Still more examples of cyclic groups which bear one or more oxo (=O) groups on ring carbon atoms include, but are not limited to, those derived from:

cyclic anhydrides (-C(=O)-O-C(=O)- in a ring), including but not limited to maleic anhydride (C_5), succinic anhydride (C_5), and glutaric anhydride (C_6);

cyclic carbonates (-O-C(=O)-O- in a ring), such as ethylene carbonate (C_5) and 1,2-propylene carbonate (C_5);

imides (-C(=O)-NR-C(=O)- in a ring), including but not limited to, succinimide (C_5), maleimide (C_5), phthalimide, and glutarimide (C_6);

lactones (cyclic esters, -O-C(=O)- in a ring), including, but not limited to, β-propiolactone, γ-butyrolactone, δ-valerolactone (2-piperidone), and ε-caprolactone;

lactams (cyclic amides, -NR-C(=O)- in a ring), including, but not limited to, β-propiolactam (C_4), γ-butyrolactam (2-pyrrolidone) (C_5), δ-valerolactam (C_6), and ε-caprolactam (C_7);

cyclic carbamates (-O-C(=O)-NR- in a ring), such as 2-oxazolidone (C_5);

cyclic ureas (-NR-C(=O)-NR- in a ring), such as 2-imidazolidone (C_5) and pyrimidine-2,4-dione (e.g., thymine, uracil) (C_6).

The above alkyl, alkylidene, alkylidyne, heterocyclyl, and aryl groups, whether alone or part of another substituent, may themselves optionally be substituted with one or more groups selected from themselves and the additional substituents listed below.

Hydrogen: -H. Note that if the substituent at a particular position is hydrogen, it may be convenient to refer to the compound as being "unsubstituted" at that position.

Halo: -F, -Cl, -Br, and -I.

Hydroxy: -OH.

Ether: -OR, wherein R is an ether substituent, for example, a C_{1-7}alkyl group (also referred to as a C_{1-7}alkoxy group, discussed below), a C_{3-20}heterocyclyl group (also referred to as a C_{3-20}heterocyclyloxy group), or a C_{5-20}aryl group (also referred to as a C_{5-20}aryloxy group), preferably a C_{1-7}alkyl group.

C_{1-7}alkoxy: -OR, wherein R is a C_{1-7}alkyl group. Examples of C_{1-7}alkoxy groups include, but are not limited to, -OMe (methoxy), -OEt (ethoxy), -O(nPr) (n-propoxy), -O(iPr) (isopropoxy), -O(nBu) (n-butoxy), -O(sBu) (sec-butoxy), -O(iBu) (isobutoxy), and -O(tBu) (tert-butoxy).

Acetal: $-CH(OR^1)(OR^2)$, wherein R^1 and R^2 are independently acetal substituents, for example, a C_{1-7}alkyl group, a C_{3-20}heterocyclyl group, or a C_{5-20}aryl group, preferably a C_{1-7}alkyl group, or, in the case of a "cyclic" acetal group, R^1 and R^2, taken together with the two oxygen atoms to which they are attached, and the carbon atoms to which they are attached, form a heterocyclic ring having from 4 to 8 ring atoms. Examples of acetal groups include, but are not limited to, $-CH(OMe)_2$, $-CH(OEt)_2$, and -CH(OMe)(OEt).

Hemiacetal: $-CH(OH)(OR^1)$, wherein R^1 is a hemiacetal substituent, for example, a C_{1-7}alkyl group, a C_{3-20}heterocyclyl group, or a C_{5-20}aryl group, preferably a C_{1-7}alkyl group. Examples of hemiacetal groups include, but are not limited to, -CH(OH)(OMe) and -CH(OH)(OEt).

Ketal: $-CR(OR^1)(OR^2)$, where R^1 and R^2 are as defined for acetals, and R is a ketal substituent other than hydrogen, for example, a C_{1-7}alkyl group, a C_{3-20}heterocyclyl group, or a C_{5-20}aryl group, preferably a C_{1-7}alkyl group. Examples ketal groups include, but are not limited to, $-C(Me)(OMe)_2$, $-C(Me)(OEt)_2$, -C(Me)(OMe)(OEt), $-C(Et)(OMe)_2$, $-C(Et)(OEt)_2$, and -C(Et)(OMe)(OEt).

Hemiketal: $-CR(OH)(OR^1)$, where R^1 is as defined for hemiacetals, and R is a hemiketal substituent other than hydrogen, for example, a C_{1-7}alkyl group, a C_{3-20}heterocyclyl group, or a C_{5-20}aryl group, preferably a C_{1-7}alkyl group. Examples of hemiacetal groups include, but are not limited to, -C(Me)(OH)(OMe), -C(Et)(OH)(OMe), -C(Me)(OH)(OEt), and -C(Et)(OH)(OEt).

Oxo (keto, -one): =O.

Thione (thioketone): =S.

Imino (imine): =NR, wherein R is an imino substituent, for example, hydrogen, C_{1-7}alkyl group, a C_{3-20}heterocyclyl group, or a C_{5-20}aryl group, preferably hydrogen or a C_{1-7}alkyl

group. Examples of ester groups include, but are not limited to, =NH, =NMe, =NEt, and =NPh.

Formyl (carbaldehyde, carboxaldehyde): -C(=O)H.

Acyl (keto): -C(=O)R, wherein R is an acyl substituent, for example, a C_{1-7}alkyl group (also referred to as C_{1-7}alkylacyl or C_{1-7}alkanoyl), a C_{3-20}heterocyclyl group (also referred to as C_{3-20}heterocyclylacyl), or a C_{5-20}aryl group (also referred to as C_{5-20}arylacyl), preferably a C_{1-7}alkyl group. Examples of acyl groups include, but are not limited to, -C(=O)CH_3 (acetyl), -C(=O)CH_2CH_3 (propionyl), -C(=O)$C(CH_3)_3$ (t-butyryl), and -C(=O)Ph (benzoyl, phenone).

Acylhalide (haloformyl, halocarbonyl): -C(=O)X, wherein X is -F, -Cl, -Br, or -I, preferably -Cl, -Br, or -I.

Carboxy (carboxylic acid): -C(=O)OH.

Thiocarboxy (thiocarboxylic acid): -C(=S)SH.

Thiolocarboxy (thiolocarboxylic acid): -C(=O)SH.

Thionocarboxy (thionocarboxylic acid): -C(=S)OH.

Imidic acid: -C(=NH)OH.

Hydroxamic acid: -C(=O)NHOH.

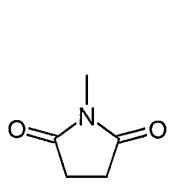
Ester (carboxylate, carboxylic acid ester, oxycarbonyl): -C(=O)OR, wherein R is an ester substituent, for example, a C_{1-7}alkyl group, a C_{3-20}heterocyclyl group, or a C_{5-20}aryl group, preferably a C_{1-7}alkyl group. Examples of ester groups include, but are not limited to, -C(=O)OCH_3, -C(=O)OCH_2CH_3, -C(=O)$OC(CH_3)_3$, and -C(=O)OPh.

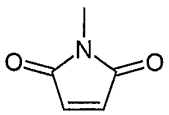
Acyloxy (reverse ester): -OC(=O)R, wherein R is an acyloxy substituent, for example, a C_{1-7}alkyl group, a C_{3-20}heterocyclyl group, or a C_{5-20}aryl group, preferably a C_{1-7}alkyl group. Examples of acyloxy groups include, but are not limited to, -OC(=O)CH_3 (acetoxy), -OC(=O)CH_2CH_3, -OC(=O)$C(CH_3)_3$, -OC(=O)Ph, and -OC(=O)CH_2Ph.

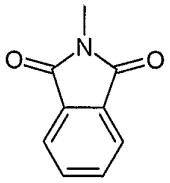
Oxycarboyloxy: -OC(=O)OR, wherein R is an ester substituent, for example, a C_{1-7}alkyl group, a C_{3-20}heterocyclyl group, or a C_{5-20}aryl group, preferably a C_{1-7}alkyl group. Examples of ester groups include, but are not limited to, $-OC(=O)OCH_3$, $-OC(=O)OCH_2CH_3$, $-OC(=O)OC(CH_3)_3$, and -OC(=O)OPh.

Amido (carbamoyl, carbamyl, aminocarbonyl, carboxamide): $-C(=O)NR^1R^2$, wherein R^1 and R^2 are independently amino substituents, as defined for amino groups. Examples of amido groups include, but are not limited to, $-C(=O)NH_2$, $-C(=O)NHCH_3$, $-C(=O)N(CH_3)_2$, $-C(=O)NHCH_2CH_3$, and $-C(=O)N(CH_2CH_3)_2$, as well as amido groups in which R^1 and R^2, together with the nitrogen atom to which they are attached, form a heterocyclic structure as in, for example, piperidinocarbonyl, morpholinocarbonyl, thiomorpholinocarbonyl, and piperazinocarbonyl.

Acylamido (acylamino): $-NR^1C(=O)R^2$, wherein R^1 is an amide substituent, for example, hydrogen, a C_{1-7}alkyl group, a C_{3-20}heterocyclyl group, or a C_{5-20}aryl group, preferably hydrogen or a C_{1-7}alkyl group, and R^2 is an acyl substituent, for example, a C_{1-7}alkyl group, a C_{3-20}heterocyclyl group, or a C_{5-20}aryl group, preferably hydrogen or a C_{1-7}alkyl group. Examples of acylamide groups include, but are not limited to, $-NHC(=O)CH_3$, $-NHC(=O)CH_2CH_3$, and -NHC(=O)Ph. R^1 and R^2 may together form a cyclic structure, as in, for example, succinimidyl, maleimidyl, and phthalimidyl:


succinimidyl


maleimidyl


phthalimidyl

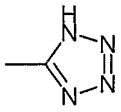
Aminocarbonyloxy: $-OC(=O)NR^1R^2$, wherein R^1 and R^2 are independently amino substituents, as defined for amino groups. Examples of aminocarbonyloxy groups include, but are not limited to, $-OC(=O)NH_2$, -OC(=O)NHMe, $-OC(=O)NMe_2$, and $-OC(=O)NEt_2$.

Thioamido (thiocarbamyl): $-C(=S)NR^1R^2$, wherein R^1 and R^2 are independently amino substituents, as defined for amino groups. Examples of amido groups include, but are not limited to, $-C(=S)NH_2$, $-C(=S)NHCH_3$, $-C(=S)N(CH_3)_2$, and $-C(=S)NHCH_2CH_3$.

Ureido: $-N(R^1)CONR^2R^3$ wherein R^2 and R^3 are independently amino substituents, as defined for amino groups, and R1 is a ureido substituent, for example, hydrogen, a C_{1-7}alkyl group, a C_{3-20}heterocyclyl group, or a C_{5-20}aryl group, preferably hydrogen or a C_{1-7}alkyl group. Examples of ureido groups include, but are not limited to, $-NHCONH_2$, -NHCONHMe, -NHCONHEt, $-NHCONMe_2$, $-NHCONEt_2$, $-NMeCONH_2$, -NMeCONHMe, -NMeCONHEt, $-NMeCONMe_2$, and $-NMeCONEt_2$.

Guanidino: $-NH-C(=NH)NH_2$.

Tetrazolyl: a five membered aromatic ring having four nitrogen atoms and one carbon atom,



Amino: $-NR^1R^2$, wherein R^1 and R^2 are independently amino substituents, for example, hydrogen, a C_{1-7}alkyl group (also referred to as C_{1-7}alkylamino or di-C_{1-7}alkylamino), a C_{3-20}heterocyclyl group, or a C_{5-20}aryl group, preferably H or a C_{1-7}alkyl group, or, in the case of a "cyclic" amino group, R^1 and R^2, taken together with the nitrogen atom to which they are attached, form a heterocyclic ring having from 4 to 8 ring atoms. Amino groups may be primary ($-NH_2$), secondary ($-NHR^1$), or tertiary ($-NHR^1R^2$), and in cationic form, may be quaternary ($-^+NR^1R^2R^3$). Examples of amino groups include, but are not limited to, $-NH_2$, $-NHCH_3$, $-NHC(CH_3)_2$, $-N(CH_3)_2$, $-N(CH_2CH_3)_2$, and -NHPh. Examples of cyclic amino groups include, but are not limited to, aziridino, azetidino, pyrrolidino, piperidino, piperazino, morpholino, and thiomorpholino.

Imino: =NR, wherein R is an imino substituent, for example, for example, hydrogen, a C_{1-7}alkyl group, a C_{3-20}heterocyclyl group, or a C_{5-20}aryl group, preferably H or a C_{1-7}alkyl group. Examples of imino groups include, but are not limited to, =NH, =NMe, and =NEt.

Amidine (amidino): $-C(=NR)NR_2$, wherein each R is an amidine substituent, for example, hydrogen, a C_{1-7}alkyl group, a C_{3-20}heterocyclyl group, or a C_{5-20}aryl group, preferably H or a C_{1-7}alkyl group. Examples of amidine groups include, but are not limited to, $-C(=NH)NH_2$, $-C(=NH)NMe_2$, and $-C(=NMe)NMe_2$.

Nitro: $-NO_2$.

Cyano (nitrile, carbonitrile): -CN.

Isocyano: -NC.

Cyanato: -OCN.

Isocyanato: -NCO.

Isothiocyano (isothiocyanato): -NCS.

Sulfhydryl (thiol, mercapto): -SH.

Thioether (sulfide): -SR, wherein R is a thioether substituent, for example, a C_{1-7}alkyl group (also referred to as a C_{1-7}alkylthio group), a C_{3-20}heterocyclyl group, or a C_{5-20}aryl group, preferably a C_{1-7}alkyl group. Examples of C_{1-7}alkylthio groups include, but are not limited to, $-SCH_3$ and $-SCH_2CH_3$.

Disulfide: -SS-R, wherein R is a disulfide substituent, for example, a C_{1-7}alkyl group, a C_{3-20}heterocyclyl group, or a C_{5-20}aryl group, preferably a C_{1-7}alkyl group (also referred to herein as C_{1-7}alkyl disulfide). Examples of C_{1-7}alkyl disulfide groups include, but are not limited to, $-SSCH_3$ and $-SSCH_2CH_3$.

Sulfine (sulfinyl, sulfoxide): -S(=O)R, wherein R is a sulfine substituent, for example, a C_{1-7}alkyl group, a C_{3-20}heterocyclyl group, or a C_{5-20}aryl group, preferably a C_{1-7}alkyl group. Examples of sulfine groups include, but are not limited to, $-S(=O)CH_3$ and $-S(=O)CH_2CH_3$.

Sulfone (sulfonyl): $-S(=O)_2R$, wherein R is a sulfone substituent, for example, a C_{1-7}alkyl group, a C_{3-20}heterocyclyl group, or a C_{5-20}aryl group, preferably a C_{1-7}alkyl group, including, for example, a fluorinated or perfluorinated C_{1-7}alkyl group. Examples of sulfone groups include, but are not limited to, $-S(=O)_2CH_3$ (methanesulfonyl, mesyl), $-S(=O)_2CF_3$ (triflyl), $-S(=O)_2CH_2CH_3$ (esyl), $-S(=O)_2C_4F_9$ (nonaflyl), $-S(=O)_2CH_2CF_3$ (tresyl), $-S(=O)_2CH_2CH_2NH_2$ (tauryl), $-S(=O)_2Ph$ (phenylsulfonyl, besyl), 4-methylphenylsulfonyl (tosyl), 4-chlorophenylsulfonyl (closyl), 4-bromophenylsulfonyl (brosyl), 4-nitrophenyl (nosyl), 2-naphthalenesulfonate (napsyl), and 5-dimethylamino-naphthalen-1-ylsulfonate (dansyl).

Sulfinic acid (sulfino): -S(=O)OH, $-SO_2H$.

Sulfonic acid (sulfo): -S(=O)$_2$OH, $-SO_3H$.

Sulfinate (sulfinic acid ester): -S(=O)OR; wherein R is a sulfinate substituent, for example, a C_{1-7}alkyl group, a C_{3-20}heterocyclyl group, or a C_{5-20}aryl group, preferably a C_{1-7}alkyl group. Examples of sulfinate groups include, but are not limited to, $-S(=O)OCH_3$ (methoxysulfinyl; methyl sulfinate) and $-S(=O)OCH_2CH_3$ (ethoxysulfinyl; ethyl sulfinate).

Sulfonate (sulfonic acid ester): -S(=O)$_2$OR, wherein R is a sulfonate substituent, for example, a C_{1-7}alkyl group, a C_{3-20}heterocyclyl group, or a C_{5-20}aryl group, preferably a C_{1-7}alkyl group. Examples of sulfonate groups include, but are not limited to, $-S(=O)_2OCH_3$ (methoxysulfonyl; methyl sulfonate) and $-S(=O)_2OCH_2CH_3$ (ethoxysulfonyl; ethyl sulfonate).

Sulfinyloxy: -OS(=O)R, wherein R is a sulfinyloxy substituent, for example, a C_{1-7}alkyl group, a C_{3-20}heterocyclyl group, or a C_{5-20}aryl group, preferably a C_{1-7}alkyl group. Examples of sulfinyloxy groups include, but are not limited to, $-OS(=O)CH_3$ and $-OS(=O)CH_2CH_3$.

Sulfonyloxy: -OS(=O)$_2$R, wherein R is a sulfonyloxy substituent, for example, a C_{1-7}alkyl group, a C_{3-20}heterocyclyl group, or a C_{5-20}aryl group, preferably a C_{1-7}alkyl group. Examples of sulfonyloxy groups include, but are not limited to, $-OS(=O)_2CH_3$ (mesylate) and $-OS(=O)_2CH_2CH_3$ (esylate).

Sulfate: -OS(=O)$_2$OR; wherein R is a sulfate substituent, for example, a C_{1-7}alkyl group, a C_{3-20}heterocyclyl group, or a C_{5-20}aryl group, preferably a C_{1-7}alkyl group. Examples of sulfate groups include, but are not limited to, $-OS(=O)_2OCH_3$ and $-SO(=O)_2OCH_2CH_3$.

Sulfamyl (sulfamoyl; sulfinic acid amide; sulfinamide): $-S(=O)NR^1R^2$, wherein R^1 and R^2 are independently amino substituents, as defined for amino groups. Examples of sulfamyl groups include, but are not limited to, $-S(=O)NH_2$, $-S(=O)NH(CH_3)$, $-S(=O)N(CH_3)_2$, $-S(=O)NH(CH_2CH_3)$, $-S(=O)N(CH_2CH_3)_2$, and -S(=O)NHPh.

Sulfonamido (sulfinamoyl; sulfonic acid amide; sulfonamide): $-S(=O)_2NR^1R^2$, wherein R^1 and R^2 are independently amino substituents, as defined for amino groups. Examples of sulfonamido groups include, but are not limited to, $-S(=O)_2NH_2$, $-S(=O)_2NH(CH_3)$, $-S(=O)_2N(CH_3)_2$, $-S(=O)_2NH(CH_2CH_3)$, $-S(=O)_2N(CH_2CH_3)_2$, and $-S(=O)_2NHPh$.

Sulfamino: $-NR^1S(=O)_2OH$, wherein R^1 is an amino substituent, as defined for amino groups. Examples of sulfamino groups include, but are not limited to, $-NHS(=O)_2OH$ and $-N(CH_3)S(=O)_2OH$.

Sulfonamino: $-NR^1S(=O)_2R$, wherein R^1 is an amino substituent, as defined for amino groups, and R is a sulfonamino substituent, for example, a C_{1-7}alkyl group, a C_{3-20}heterocyclyl group, or a C_{5-20}aryl group, preferably a C_{1-7}alkyl group. Examples of sulfonamino groups include, but are not limited to, $-NHS(=O)_2CH_3$ and $-N(CH_3)S(=O)_2C_6H_5$.

Sulfinamino: $-NR^1S(=O)R$, wherein R^1 is an amino substituent, as defined for amino groups, and R is a sulfinamino substituent, for example, a C_{1-7}alkyl group, a C_{3-20}heterocyclyl group, or a C_{5-20}aryl group, preferably a C_{1-7}alkyl group. Examples of sulfinamino groups include, but are not limited to, $-NHS(=O)CH_3$ and $-N(CH_3)S(=O)C_6H_5$.

In many cases, substituents may themselves be substituted. For example, a C_{1-7}alkyl group may be substituted with, for example, hydroxy (also referred to as a C_{1-7}hydroxyalkyl group), C_{1-7}alkoxy (also referred to as a C_{1-7}alkoxyalkyl group), amino (also referred to as a C_{1-7}aminoalkyl group), halo (also referred to as a C_{1-7}haloalkyl group), carboxy (also referred to as a C_{1-7}carboxyalkyl group), and C_{5-20}aryl (also referred to as a C_{5-20}aryl-C_{1-7}alkyl group).

Similarly, a C_{5-20}aryl group may be substituted with, for example, hydroxy (also referred to as a C_{5-20}hydroxyaryl group), halo (also referred to as a C_{5-20}haloaryl group), amino (also referred to as a C_{5-20}aminoaryl group, e.g., as in aniline), C_{1-7}alkyl (also referred to as a C_{1-7}alkyl-C_{5-20}aryl group, e.g., as in toluene), and C_{1-7}alkoxy (also referred to as a C_{1-7}alkoxy-C_{5-20}aryl group, e.g., as in anisole).

These and other specific examples of such substituted-substituents are described below.

Hydroxy-C_{1-7}alkyl: The term " hydroxy-C_{1-7}alkyl," as used herein, pertains to a C_{1-7}alkyl group in which at least one hydrogen atom (e.g., 1, 2, 3) has been replaced with a hydroxy group. Examples of such groups include, but are not limited to, $-CH_2OH$, $-CH_2CH_2OH$, and $-CH(OH)CH_2OH$.

Halo-C_{1-7}alkyl group: The term " halo-C_{1-7}alkyl," as used herein, pertains to a C_{1-7}alkyl group in which at least one hydrogen atom (e.g., 1, 2, 3) has been replaced with a halogen atom (e.g., F, Cl, Br, I). If more than one hydrogen atom has been replaced with a halogen atom, the halogen atoms may independently be the same or different. Every hydrogen atom may be replaced with a halogen atom, in which case the group may conveniently be referred to as a C_{1-7}perhaloalkyl group." Examples of such groups include, but are not limited to, $-CF_3$, $-CHF_2$, $-CH_2F$, $-CCl_3$, $-CBr_3$, $-CH_2CH_2F$, $-CH_2CHF_2$, and $-CH_2CF_3$.

Amino-C_{1-7}alkyl: The term " amino-C_{1-7}alkyl," as used herein, pertains to a C_{1-7}alkyl group in which at least one hydrogen atom (e.g., 1, 2, 3) has been replaced with an amino group. Examples of such groups include, but are not limited to, $-CH_2NH_2$, $-CH_2CH_2NH_2$, and $-CH_2CH_2N(CH_3)_2$.

Carboxy-C_{1-7}alkyl: The term "carboxy-C_{1-7}alkyl," as used herein, pertains to a C_{1-7}alkyl group in which at least one hydrogen atom (e.g., 1, 2, 3) has been replaced with a carboxy group. Examples of such groups include, but are not limited to, $-CH_2COOH$ and $-CH_2CH_2COOH$.

C_{1-7}alkoxy-C_{1-7}alkyl: The term "C_{1-7}alkoxy-C_{1-7}alkyl," as used herein, pertains to a C_{1-7}alkyl group in which at least one hydrogen atom (e.g., 1, 2, 3) has been replaced with a C_{1-7}alkoxy group. Examples of such groups include, but are not limited to, $-CH_2OCH_3$, $-CH_2CH_2OCH_3$, and ,$-CH_2CH_2OCH_2CH_3$

C_{5-20}aryl-C_{1-7}alkyl: The term "C_{5-20}aryl-C_{1-7}alkyl," as used herein, pertains to a C_{1-7}alkyl group in which at least one hydrogen atom (e.g., 1, 2, 3) has been replaced with a C_{5-20}aryl group. Examples of such groups include, but are not limited to, benzyl (phenylmethyl, $PhCH_2$-), benzhydryl (Ph_2CH-), trityl (triphenylmethyl, Ph_3C-), phenethyl (phenylethyl, Ph-CH_2CH_2-), styryl (Ph-CH=CH-), cinnamyl (Ph-CH=CH-CH_2-).

Hydroxy-C_{5-20}aryl: The term " hydroxy-C_{5-20}aryl," as used herein, pertains to a C_{5-20}aryl group in which at least one hydrogen atom (e.g., 1, 2, 3) has been substituted with an hydroxy group. Examples of such groups include, but are not limited to, those derived from: phenol, naphthol, pyrocatechol, resorcinol, hydroquinone, pyrogallol, phloroglucinol.

Halo-C_{5-20}aryl: The term "halo-C_{5-20}aryl," as used herein, pertains to a C_{5-20}aryl group in which at least one hydrogen atom (e.g., 1, 2, 3) has been substituted with a halo (e.g., F, Cl, Br, I) group. Examples of such groups include, but are not limited to, halophenyl (e.g., fluorophenyl, chlorophenyl, bromophenyl, or iodophenyl, whether ortho-, meta-, or para-substituted), dihalophenyl, trihalophenyl, tetrahalophenyl, and pentahalophenyl.

C_{1-7}alkyl-C_{5-20}aryl: The term "C_{1-7}alkyl-C_{5-20}aryl," as used herein, pertains to a C_{5-20}aryl group in which at least one hydrogen atom (e.g., 1, 2, 3) has been substituted with a C_{1-7}alkyl group. Examples of such groups include, but are not limited to, tolyl (from toluene), xylyl (from xylene), mesityl (from mesitylene), and cumenyl (or cumyl, from cumene), and duryl (from durene).

Hydroxy-C_{1-7}alkoxy: -OR, wherein R is a hydroxy-C_{1-7}alkyl group. Examples of hydroxy-C_{1-7}alkoxy groups include, but are not limited to, $-OCH_2OH$, $-OCH_2CH_2OH$, and $-OCH_2CH_2CH_2OH$.

Halo-C_{1-7}alkoxy: -OR, wherein R is a halo-C_{1-7}alkyl group. Examples of halo-C_{1-7}alkoxy groups include, but are not limited to, $-OCF_3$, $-OCHF_2$, $-OCH_2F$, $-OCCl_3$, $-OCBr_3$, $-OCH_2CH_2F$, $-OCH_2CHF_2$, and $-OCH_2CF_3$.

Carboxy-C_{1-7}alkoxy: -OR, wherein R is a carboxy-C_{1-7}alkyl group. Examples of carboxy-C_{1-7}alkoxy groups include, but are not limited to, $-OCH_2COOH$, $-OCH_2CH_2COOH$, and $-OCH_2CH_2CH_2COOH$.

C_{1-7}alkoxy-C_{1-7}alkoxy: -OR, wherein R is a C_{1-7}alkoxy-C_{1-7}alkyl group. Examples of C_{1-7}alkoxy-C_{1-7}alkoxy groups include, but are not limited to, $-OCH_2OCH_3$, $-OCH_2CH_2OCH_3$, and $-OCH_2CH_2OCH_2CH_3$.

C_{5-20}aryl-C_{1-7}alkoxy: -OR, wherein R is a C_{5-20}aryl-C_{1-7}alkyl group. Examples of such groups include, but are not limited to, benzyloxy, benzhydryloxy, trityloxy, phenethoxy, styryloxy, and cimmamyloxy.

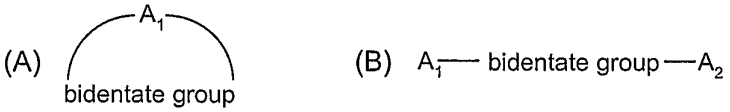
C_{1-7}alkyl-C_{5-20}aryloxy: -OR, wherein R is a C_{1-7}alkyl-C_{5-20}aryl group. Examples of such groups include, but are not limited to, tolyloxy, xylyloxy, mesityloxy, cumenyloxy, and duryloxy.

Amino-C_{1-7}alkyl-amino: The term "amino-C_{1-7}alkyl-amino," as used herein, pertains to an amino group, $-NR^1R^2$, in which one of the substituents, R^1 or R^2, is itself a amino-C_{1-7}alkyl group ($-C_{1-7}$alkyl-NR^3R^4). The amino-C_{1-7}alkylamino group may be represented, for example, by the formula $-NR^1-C_{1-7}$alkyl-NR^3R^4. Examples of such groups include, but are not limited to, groups of the formula $-NR^1(CH_2)_nNR^1R^2$, where n is 1 to 6 (for example, $-NHCH_2NH_2$, $-NH(CH_2)_2NH_2$, $-NH(CH_2)_3NH_2$, $-NH(CH_2)_4NH_2$, $-NH(CH_2)_5NH_2$, $-NH(CH_2)_6NH_2$), $-NHCH_2NH(Me)$, $-NH(CH_2)_2NH(Me)$, $-NH(CH_2)_3NH(Me)$, $-NH(CH_2)_4NH(Me)$, $-NH(CH_2)_5NH(Me)$, $-NH(CH_2)_6NH(Me)$, $-NHCH_2NH(Et)$, $-NH(CH_2)_2NH(Et)$, $-NH(CH_2)_3NH(Et)$, $-NH(CH_2)_4NH(Et)$, $-NH(CH_2)_5NH(Et)$, and $-NH(CH_2)_6NH(Et)$.

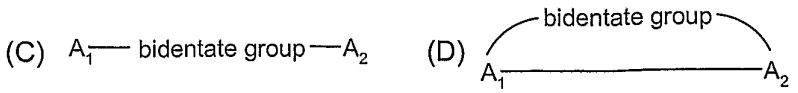
Bidentate Substituents

The term "bidentate substituents," as used herein, pertains to substituents which have two points of covalent attachment, and which act as a linking group between two other moieties.

In some cases (A), a bidentate substituent is covalently bound to a single atom. In some cases (B), a bidentate substituent is covalently bound to two different atoms, and so serves as a linking group therebetween.



Within (B), in some cases (C), a bidentate substituent is covalently bound to two different atoms, which themselves are not otherwise covalently linked (directly, or via intermediate groups). In some cases (D), a bidentate substituent is covalently bound to two different atoms, which themselves are already covalently linked (directly, or via intermediate groups); in such cases, a cyclic structure results. In some cases, the bidentate group is covalently bound to vicinal atoms, that is, adjacent atoms, in the parent group.



In some cases (A and D), the bidentate group, together with the atom(s) to which it is attached (and any intervening atoms, if present) form an additional cyclic structure. In this way, the bidentate substituent may give rise to a cyclic or polycyclic (e.g., fused, bridged, spiro) structure, which may be aromatic.

Examples of bidentate groups include, but are not limited to, C_{1-7}alkylene groups, C_{3-20}heterocyclylene groups, and C_{5-20}arylene groups, and substituted forms thereof.

Alkylene

Alkylene: The term "alkylene," as used herein, pertains to a bidentate moiety obtained by removing two hydrogen atoms, either both from the same carbon atom, or one from each of two different carbon atoms, of a hydrocarbon compound having from 1 to 20 carbon atoms (unless otherwise specified), which may be aliphatic or alicyclic, and which may be saturated, partially unsaturated, or fully unsaturated. Thus, the term "alkylene" includes the sub-classes alkenylene, alkynylene, cycloalkylene, etc., discussed below.

In this context, the prefixes (e.g., C_{1-4}, C_{1-7}, C_{1-20}, C_{2-7}, C_{3-7}, etc.) denote the number of carbon atoms, or range of number of carbon atoms. For example, the term "C_{1-4}alkylene," as used herein, pertains to an alkylene group having from 1 to 4 carbon atoms. Examples of groups of alkylene groups include C_{1-4}alkylene ("lower alkylene"), C_{1-7}alkylene, and C_{1-20}alkylene.

Examples of linear saturated C_{1-7}alkylene groups include, but are not limited to, $-(CH_2)_n-$ where n is an integer from 1 to 7, for example, $-CH_2-$ (methylene), $-CH_2CH_2-$ (ethylene), $-CH_2CH_2CH_2-$ (propylene), and $-CH_2CH_2CH_2CH_2-$ (butylene).

Examples of branched saturated C_{2-7}alkylene groups include, but are not limited to, $-CH(CH_3)-$, $-CH(CH_3)CH_2-$, $-CH(CH_3)CH_2CH_2-$, $-CH(CH_3)CH_2CH_2CH_2-$, $-CH_2CH(CH_3)CH_2-$, $-CH_2CH(CH_3)CH_2CH_2-$, $-CH(CH_2CH_3)-$, $-CH(CH_2CH_3)CH_2-$, and $-CH_2CH(CH_2CH_3)CH_2-$.

Examples of linear partially unsaturated C_{2-7}alkylene groups include, but is not limited to, -CH=CH- (vinylene), -CH=CH-CH_2-, -CH=CH-CH_2-CH_2-, -CH=CH-CH_2-CH_2-CH_2-, -CH=CH-CH=CH-, -CH=CH-CH=CH-CH_2-, -CH=CH-CH=CH-CH_2-CH_2-, -CH=CH-CH_2-CH=CH-, and -CH=CH-CH_2-CH_2-CH=CH-.

Examples of branched partially unsaturated C_{2-7}alkylene groups include, but is not limited to, -C(CH_3)=CH-, -C(CH_3)=CH-CH_2-, and -CH=CH-CH(CH_3)-.

Examples of alicyclic saturated C_{3-7}alkylene groups include, but are not limited to, cyclopentylene (e.g., cyclopent-1,3-ylene), and cyclohexylene (e.g., cyclohex-1,4-ylene).

Examples of alicyclic partially unsaturated C_{3-7}alkylene groups include, but are not limited to, cyclopentenylene (e.g., 4-cyclopenten-1,3-ylene), cyclohexenylene (e.g., 2-cyclohexen-1,4-ylene; 3-cyclohexen-1,2-ylene; 2,5-cyclohexadien-1,4-ylene).

Arylene

Arylene: The term "arylene," as used herein, pertains to a bidentate moiety obtained by removing two hydrogen atoms, one from each of two different aromatic ring atoms of an aromatic compound, which moiety has from 3 to 20 ring atoms (unless otherwise specified). Preferably, each ring has from 5 to 7 ring atoms.

In this context, the prefixes (e.g., C_{3-20}, C_{5-7}, C_{5-6}, etc.) denote the number of ring atoms, or range of number of ring atoms, whether carbon atoms or heteroatoms. For example, the term "C_{5-6}arylene," as used herein, pertains to an arylene group having 5 or 6 ring atoms. Examples of groups of arylene groups include C_{3-20}arylene, C_{3-12}arylene, C_{5-12}arylene, C_{5-7}arylene, and C_{5-6}arylene.

The ring atoms may be all carbon atoms, as in "carboarylene groups" (e.g., C_{5-20}carboarylene).

Alternatively, the ring atoms may include one or more heteroatoms, as in "heteroarylene groups" (e.g., C_{5-20}heteroarylene).

Examples of C_{5-20}arylene groups which do not have ring heteroatoms (i.e., C_{5-20}carboarylene groups) include, but are not limited to, those derived from the compounds discussed above in regard to carboaryl groups.

Examples of C_{5-20}heteroarylene groups include, but are not limited to, those derived from the compounds discussed above in regard to heteroaryl groups.

Includes Other Forms

Unless otherwise specified, included in the above are the well known ionic, salt, solvate, and protected forms of these substituents. For example, a reference to carboxylic acid (-COOH) also includes the anionic (carboxylate) form ($-COO^-$), a salt or solvate thereof, as well as conventional protected forms. Similarly, a reference to an amino group includes the protonated form ($-N^+HR^1R^2$), a salt or solvate of the amino group, for example, a hydrochloride salt, as well as conventional protected forms of an amino group. Similarly, a reference to a hydroxyl group also includes the anionic form ($-O^-$), a salt or solvate thereof, as well as conventional protected forms.

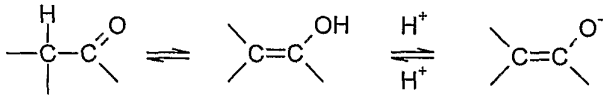
Isomers, Salts, Solvates, Protected Forms, and Prodrugs

Certain compounds may exist in one or more particular geometric, optical, enantiomeric, diasteriomeric, epimeric, atropic, stereoisomeric, tautomeric, conformational, or anomeric forms, including but not limited to, cis- and trans-forms; E- and Z-forms; c-, t-, and r-forms; endo- and exo-forms; R-, S-, and meso-forms; D- and L-forms; d- and l-forms; (+) and (-) forms; keto-, enol-, and enolate-forms; syn- and anti-forms; synclinal- and anticlinal-forms; α- and β-forms; axial and equatorial forms; boat-, chair-, twist-, envelope-, and halfchair-forms; and combinations thereof, hereinafter collectively referred to as "isomers" (or "isomeric forms").

Note that, except as discussed below for tautomeric forms, specifically excluded from the term "isomers," as used herein, are structural (or constitutional) isomers (i.e., isomers which differ in the connections between atoms rather than merely by the position of atoms in space). For example, a reference to a methoxy group, $-OCH_3$, is not to be construed as a reference to its structural isomer, a hydroxymethyl group, $-CH_2OH$. Similarly, a reference to ortho-chlorophenyl is not to be construed as a reference to its structural isomer, meta-chlorophenyl. However, a reference to a class of structures may well

include structurally isomeric forms falling within that class (e.g., C_{1-7}alkyl includes n-propyl and iso-propyl; butyl includes n-, iso-, sec-, and tert-butyl; methoxyphenyl includes ortho-, meta-, and para-methoxyphenyl).

The above exclusion does not pertain to tautomeric forms, for example, keto-, enol-, and enolate-forms, as in, for example, the following tautomeric pairs: keto/enol (illustrated below), imine/enamine, amide/imino alcohol, amidine/amidine, nitroso/oxime, thioketone/enethiol, N-nitroso/hyroxyazo, and nitro/aci-nitro.



keto enol enolate

Note that specifically included in the term "isomer" are compounds with one or more isotopic substitutions. For example, H may be in any isotopic form, including ^{1}H, ^{2}H (D), and ^{3}H (T); C may be in any isotopic form, including ^{12}C, ^{13}C, and ^{14}C; O may be in any isotopic form, including ^{16}O and ^{18}O; and the like.

Unless otherwise specified, a reference to a particular compound includes all such isomeric forms, including (wholly or partially) racemic and other mixtures thereof. Methods for the preparation (e.g., asymmetric synthesis) and separation (e.g., fractional crystallisation and chromatographic means) of such isomeric forms are either known in the art or are readily obtained by adapting the methods taught herein, or known methods, in a known manner.

Unless otherwise specified, a reference to a particular compound also includes ionic, salt, solvate, and protected forms of thereof, for example, as discussed below.

It may be convenient or desirable to prepare, purify, and/or handle a corresponding salt of the active compound, for example, a pharmaceutically-acceptable salt. Examples of pharmaceutically acceptable salts are discussed in Berge et al., 1977, "Pharmaceutically Acceptable Salts," J. Pharm. Sci., Vol. 66, pp. 1-19.

For example, if the compound is anionic, or has a functional group which may be anionic (e.g., -COOH may be $-COO^{-}$), then a salt may be formed with a suitable cation. Examples of suitable inorganic cations include, but are not limited to, alkali metal ions such as Na^{+}

and K^+, alkaline earth cations such as Ca^{2+} and Mg^{2+}, and other cations such as Al^{+3}. Examples of suitable organic cations include, but are not limited to, ammonium ion (i.e., NH_4^+) and substituted ammonium ions (e.g., NH_3R^+, $NH_2R_2^+$, NHR_3^+, NR_4^+). Examples of some suitable substituted ammonium ions are those derived from: ethylamine, diethylamine, dicyclohexylamine, triethylamine, butylamine, ethylenediamine, ethanolamine, diethanolamine, piperazine, benzylamine, phenylbenzylamine, choline, meglumine, and tromethamine, as well as amino acids, such as lysine and arginine. An example of a common quaternary ammonium ion is $N(CH_3)_4^+$.

If the compound is cationic, or has a functional group which may be cationic (e.g., $-NH_2$ may be $-NH_3^+$), then a salt may be formed with a suitable anion. Examples of suitable inorganic anions include, but are not limited to, those derived from the following inorganic acids: hydrochloric, hydrobromic, hydroiodic, sulfuric, sulfurous, nitric, nitrous, phosphoric, and phosphorous.

Examples of suitable organic anions include, but are not limited to, those derived from the following organic acids: 2-acetyoxybenzoic, acetic, ascorbic, aspartic, benzoic, camphorsulfonic, cinnamic, citric, edetic, ethanedisulfonic, ethanesulfonic, fumaric, glucheptonic, gluconic, glutamic, glycolic, hydroxymaleic, hydroxynaphthalene carboxylic, isethionic, lactic, lactobionic, lauric, maleic, malic, methanesulfonic, mucic, oleic, oxalic, palmitic, pamoic, pantothenic, phenylacetic, phenylsulfonic, propionic, pyruvic, salicylic, stearic, succinic, sulfanilic, tartaric, toluenesulfonic, and valeric. Examples of suitable polymeric organic anions include, but are not limited to, those derived from the following polymeric acids: tannic acid, carboxymethyl cellulose.

It may be convenient or desirable to prepare, purify, and/or handle a corresponding solvate of the active compound. The term "solvate" is used herein in the conventional sense to refer to a complex of solute (e.g., active compound, salt of active compound) and solvent. If the solvent is water, the solvate may be conveniently referred to as a hydrate, for example, a mono-hydrate, a di-hydrate, a tri-hydrate, etc.

It may be convenient or desirable to prepare, purify, and/or handle the active compound in a chemically protected form. The term "chemically protected form" is used herein in the conventional chemical sense and pertains to a compound in which one or more reactive functional groups are protected from undesirable chemical reactions under specified conditions (e.g., pH, temperature, radiation, solvent, and the like). In practice, well known

chemical methods are employed to reversibly render unreactive a functional group, which otherwise would be reactive, under specified conditions. In a chemically protected form, one or more reactive functional groups are in the form of a protected or protecting group (also known as a masked or masking group or a blocked or blocking group). By protecting a reactive functional group, reactions involving other unprotected reactive functional groups can be performed, without affecting the protected group; the protecting group may be removed, usually in a subsequent step, without substantially affecting the remainder of the molecule. See, for example, Protective Groups in Organic Synthesis (T. Green and P. Wuts; 3rd Edition; John Wiley and Sons, 1999).

A wide variety of such "protecting," "blocking," or "masking" methods are widely used and well known in organic synthesis. For example, a compound which has two nonequivalent reactive functional groups, both of which would be reactive under specified conditions, may be derivatized to render one of the functional groups "protected," and therefore unreactive, under the specified conditions; so protected, the compound may be used as a reactant which has effectively only one reactive functional group. After the desired reaction (involving the other functional group) is complete, the protected group may be "deprotected" to return it to its original functionality.

For example, a hydroxy group may be protected as an ether (-OR) or an ester (-OC(=O)R), for example, as: a t-butyl ether; a benzyl, benzhydryl (diphenylmethyl), or trityl (triphenylmethyl) ether; a trimethylsilyl or t-butyldimethylsilyl ether; or an acetyl ester (-OC(=O)CH_3, -OAc).

For example, an aldehyde or ketone group may be protected as an acetal (R-CH$(OR)_2$) or ketal ($R_2C(OR)_2$), respectively, in which the carbonyl group (>C=O) is converted to a diether (>C$(OR)_2$), by reaction with, for example, a primary alcohol. The aldehyde or ketone group is readily regenerated by hydrolysis using a large excess of water in the presence of acid.

For example, an amine group may be protected, for example, as an amide (-NRCO-R) or a urethane (-NRCO-OR), for example, as: a methyl amide (-NHCO-CH_3); a benzyloxy amide (-NHCO-$OCH_2C_6H_5$, -NH-Cbz); as a t-butoxy amide (-NHCO-$OC(CH_3)_3$, -NH-Boc); a 2-biphenyl-2-propoxy amide (-NHCO-$OC(CH_3)_2C_6H_4C_6H_5$, -NH-Bpoc), as a 9-fluorenylmethoxy amide (-NH-Fmoc), as a 6-nitroveratryloxy amide (-NH-Nvoc), as a 2-trimethylsilylethyloxy amide (-NH-Teoc), as a 2,2,2-trichloroethyloxy amide (-NH-Troc),

as an allyloxy amide (-NH-Alloc), as a 2(-phenylsulphonyl)ethyloxy amide (-NH-Psec); or, in suitable cases (e.g., cyclic amines), as a nitroxide radical (>N-O•).

For example, a carboxylic acid group may be protected as an ester for example, as: an C_{1-7}alkyl ester (e.g., a methyl ester; a t-butyl ester); a C_{1-7}haloalkyl ester (e.g., a C_{1-7}trihaloalkyl ester); a triC_{1-7}alkylsilyl-C_{1-7}alkyl ester; or a C_{5-20}aryl-C_{1-7}alkyl ester (e.g., a benzyl ester; a nitrobenzyl ester); or as an amide, for example, as a methyl amide.

For example, a thiol group may be protected as a thioether (-SR), for example, as: a benzyl thioether; an acetamidomethyl ether (-S-CH_2NHC(=O)CH_3).

It may be convenient or desirable to prepare, purify, and/or handle the active compound in the form of a prodrug. The term "prodrug," as used herein, pertains to a compound which, when metabolised (e.g., in vivo), yields the desired active compound. Typically, the prodrug is inactive, or less active than the active compound, but may provide advantageous handling, administration, or metabolic properties.

For example, some prodrugs are esters of the active compound (e.g., a physiologically acceptable metabolically labile ester). During metabolism, the ester group (-C(=O)OR) is cleaved to yield the active drug. Such esters may be formed by esterification, for example, of any of the carboxylic acid groups (-C(=O)OH) in the parent compound, with, where appropriate, prior protection of any other reactive groups present in the parent compound, followed by deprotection if required.

Examples of such metabolically labile esters include those of the formula -C(=O)OR wherein R is:
C_{1-7}alkyl (e.g., -Me, -Et, -nPr, -iPr, -nBu, -sBu, -iBu, -tBu);
C_{1-7}aminoalkyl (e.g., aminoethyl; 2-(N,N-diethylamino)ethyl; 2-(4-morpholino)ethyl); and
acyloxy-C_{1-7}alkyl
(e.g., acyloxymethyl;
acyloxyethyl;
pivaloyloxymethyl;
acetoxymethyl;
1-acetoxyethyl;
1-(1-methoxy-1-methyl)ethyl-carbonxyloxyethyl;
1-(benzoyloxy)ethyl; isopropoxy-carbonyloxymethyl;

1-isopropoxy-carbonyloxyethyl; cyclohexyl-carbonyloxymethyl;
1-cyclohexyl-carbonyloxyethyl;
cyclohexyloxy-carbonyloxymethyl;
1-cyclohexyloxy-carbonyloxyethyl;
(4-tetrahydropyranyloxy) carbonyloxymethyl;
1-(4-tetrahydropyranyloxy)carbonyloxyethyl;
(4-tetrahydropyranyl)carbonyloxymethyl; and
1-(4-tetrahydropyranyl)carbonyloxyethyl).

Also, some prodrugs are activated enzymatically to yield the active compound, or a compound which, upon further chemical reaction, yields the active compound (for example, as in ADEPT, GDEPT, LIDEPT, etc.). For example, the prodrug may be a sugar derivative or other glycoside conjugate, or may be an amino acid ester derivative.

Acronyms

For convenience, many chemical moieties are represented using well known abbreviations, including but not limited to, methyl (Me), ethyl (Et), n-propyl (nPr), iso-propyl (iPr), n-butyl (nBu), sec-butyl (sBu), iso-butyl (iBu), tert-butyl (tBu), n-hexyl (nHex), cyclohexyl (cHex), phenyl (Ph), biphenyl (biPh), benzyl (Bn), naphthyl (naph), methoxy (MeO), ethoxy (EtO), benzoyl (Bz), and acetyl (Ac).

For convenience, many chemical compounds are represented using well known abbreviations, including but not limited to, methanol (MeOH), ethanol (EtOH), iso-propanol (i-PrOH), methyl ethyl ketone (MEK), ether or diethyl ether (Et_2O), acetic acid (AcOH), dichloromethane (methylene chloride, DCM), acetonitrile (ACN), trifluoroacetic acid (TFA), dimethylformamide (DMF), tetrahydrofuran (THF), and dimethylsulfoxide (DMSO).

Synthesis

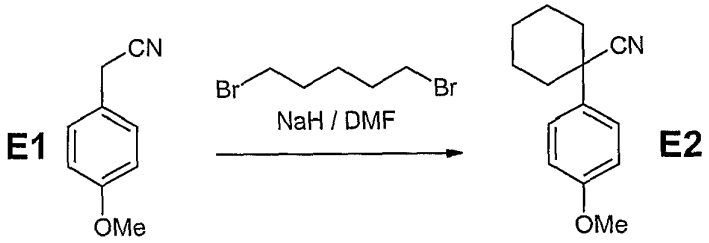
Methods for the chemical synthesis of compounds of the present invention are described herein. These methods may be modified and/or adapted in known ways in order to facilitate the synthesis of additional compounds within the scope of the present invention.

The compounds of the present invention may be prepared, for example, by the methods described herein, or by adapting these or other well known methods in well known ways.

Synthesis: Esters

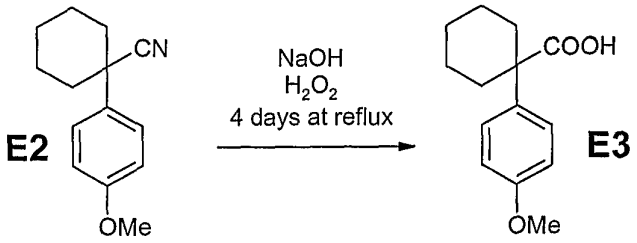
In one approach, a desired nitrile may be prepared from a simpler nitrile, for example, by reaction with a halide, e.g., 1,5-dibromopentane and e.g., NaH in dimethylformamide (DMF). An example of such a method is illustrated in the following scheme.

Scheme 1



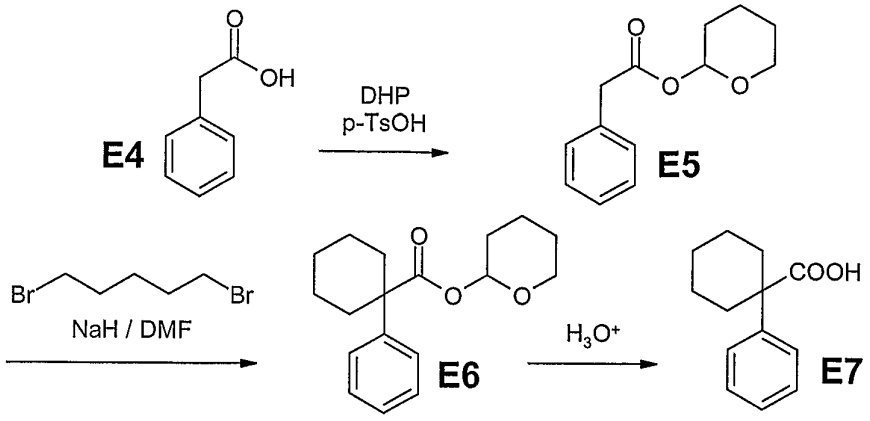
The corresponding carboxylic acid then prepared from the nitrile, for example, by reaction with NaOH and H_2O_2. An example of such a method is illustrated in the following scheme.

Scheme 2



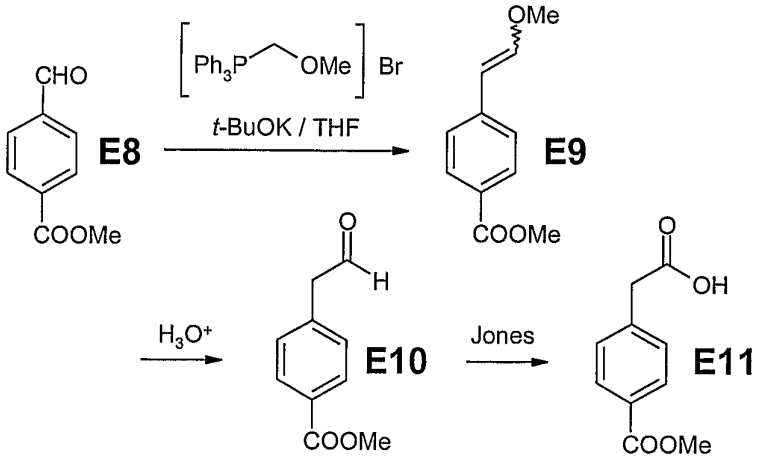
In another approach, a suitable carboxylic acid may be prepared, for example, from a simpler carboxylic acid, for example, by first protecting the carboxylic acid and then by reaction with a halide, e.g., 1,5-dibromopentane and e.g., NaH in dimethylformamide (DMF), followed by deprotection, e.g., by strong acid. An example of such a method is illustrated in the following scheme.

Scheme 3



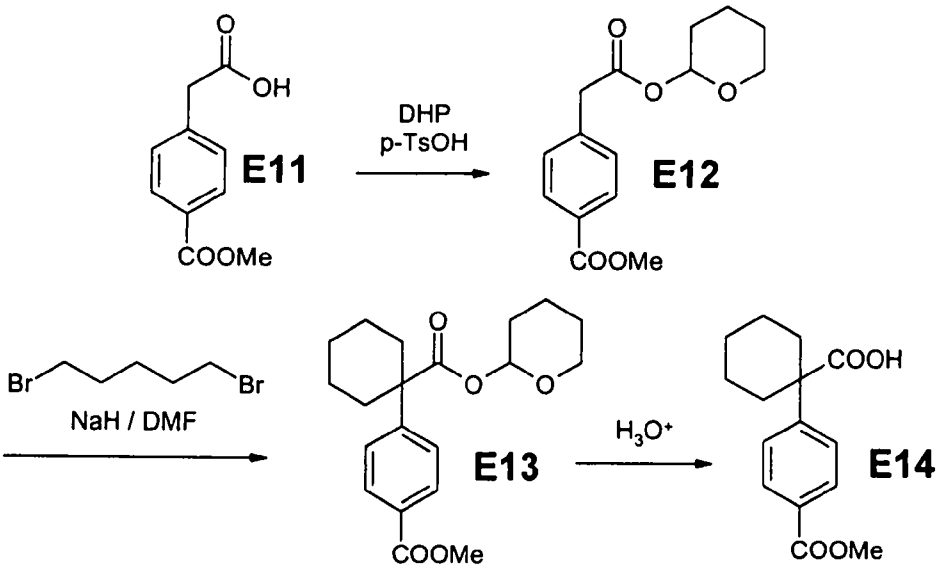
In another approach, a suitable carboxylic acid may be prepared, for example, from a corresponding aldehyde. For example, the carboxylic acid group of 4-carboxybenzaldehyde is protected, for example, as a tert-butyl ester, by reaction with N,N-dimethylformamide-di-tert-butyl acetal. The aldehyde group is then converted to a methoxy-vinyl (enol ether) group, for example, by reaction with (2-hydroxyethyl)triphenylphosphonium bromide and potassium tert-butoxide in tetrahydrofuran. The methoxy-vinyl (enol-ether) group is then converted to an aldehyde group, by acid hydrolysis. The aldehyde group is then converted to a carboxylic acid group, by reaction with Jones reagent. An example of such a method is illustrated in the following scheme.

Scheme 4



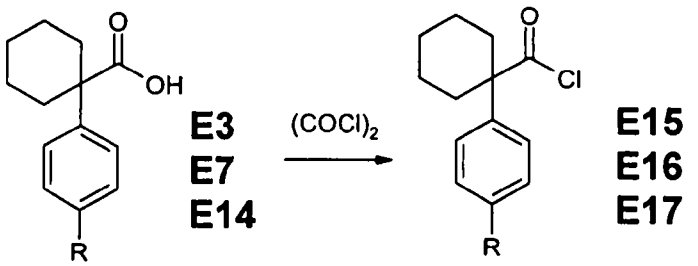
The resulting carboxylic acid is then further derivatised, in a method analogous to that described earlier. An example of such a method is illustrated in the following scheme.

Scheme 5



The carboxylic acid is then converted to the corresponding acyl halide, e.g., acyl chloride, by reaction with, e.g., $(COCl)_2$. An example of such a method is illustrated in the following scheme.

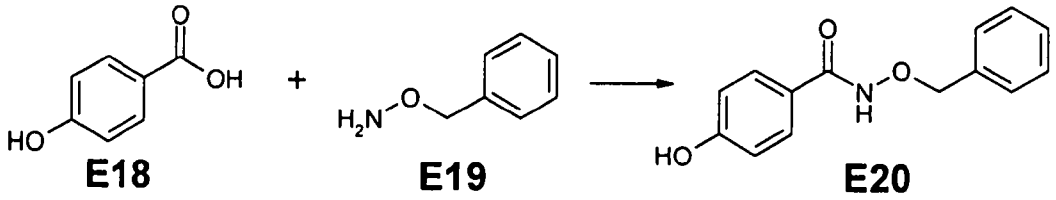
Scheme 6



Separately, a suitable protected hydroxamic acid compound, also having a hydroxy group, is prepared, for example, by reaction of a suitable carboxylic acid, for example, para-hydroxy benzoic acid, with a suitable O-substituted hydroxlyamine, such as O-benzylhydroxylamine, in the presence of a suitable base, for exampe, dimethylaminopyridine. An example of such a method is illustrated in the following scheme.

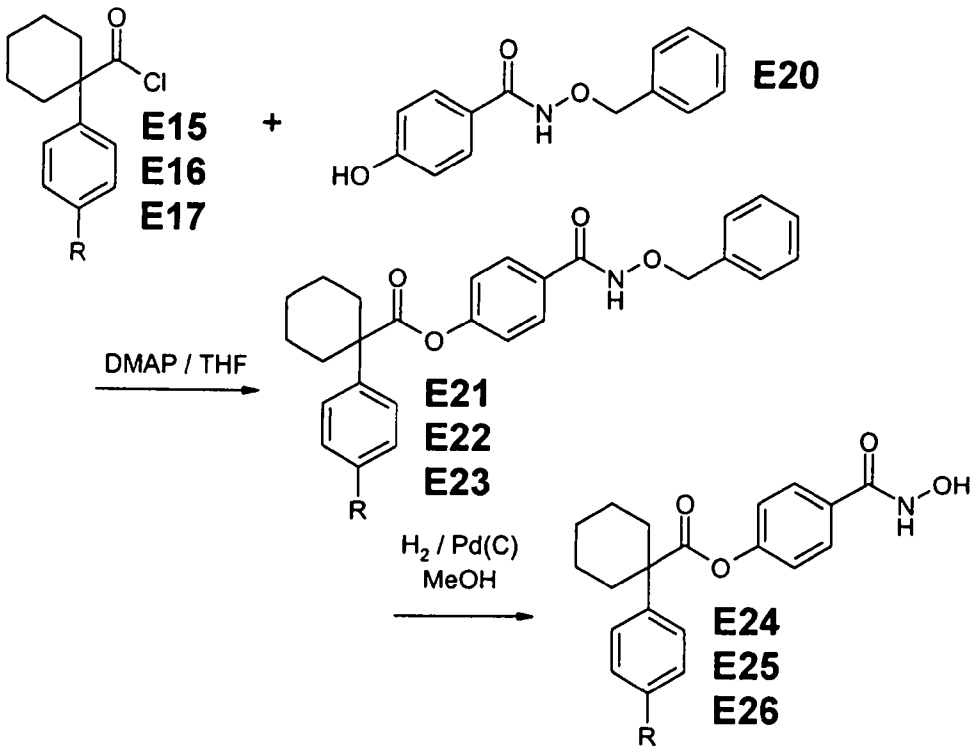
2004205372 24 Dec 2010

Scheme 7



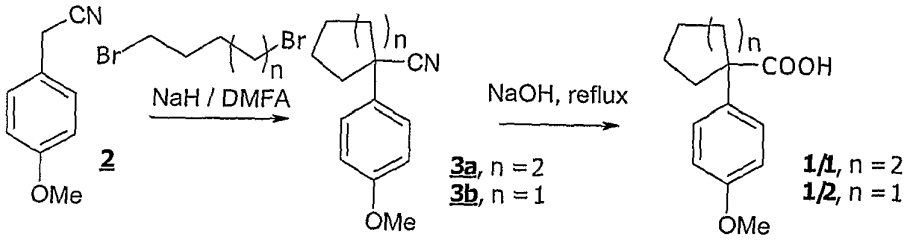
Finally, the acyl halide is then reacted with the protected hydroxamic acid, to give the corresponding conjugate, and the carboxamic acid ester is then deprotected, e.g., with H_2 and Pd(C), to give the corresponding carboxamic acid. An example of such a method is illustrated in the following scheme.

Scheme 8

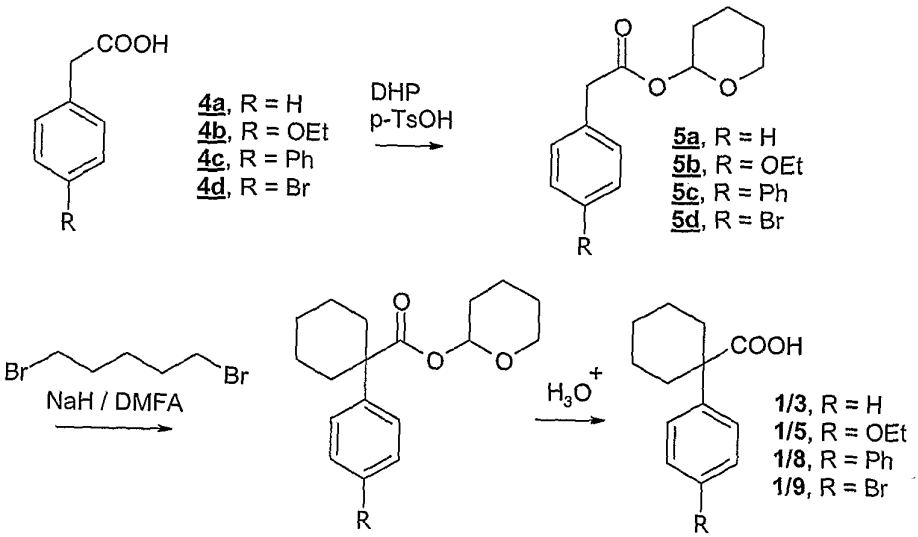


Several additional methods for the synthesis of compounds of the present invention are illustrated by the following schemes.

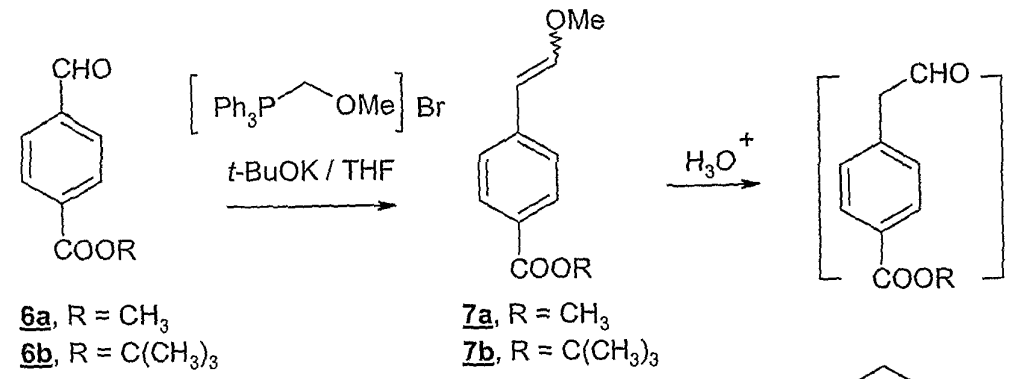
Scheme 9



Scheme 10

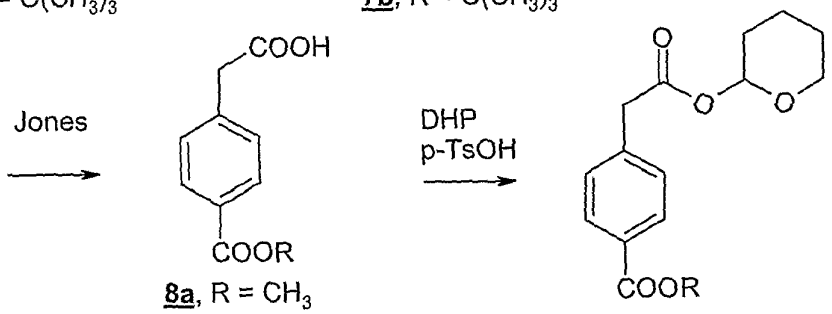


Scheme 11

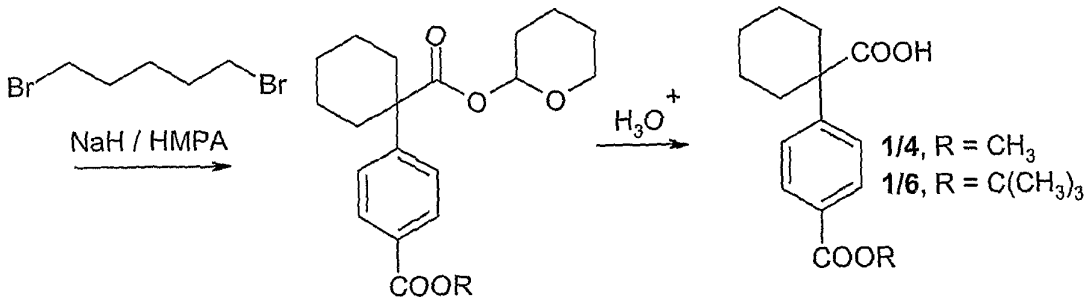


6a, R = CH_3
6b, R = $C(CH_3)_3$

7a, R = CH_3
7b, R = $C(CH_3)_3$

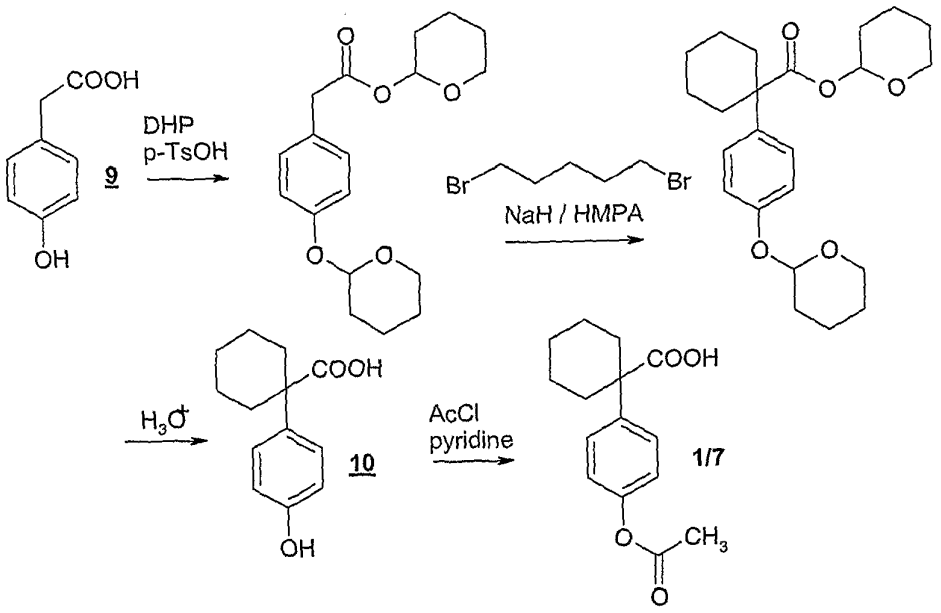


8a, R = CH_3
8b, R = $C(CH_3)_3$

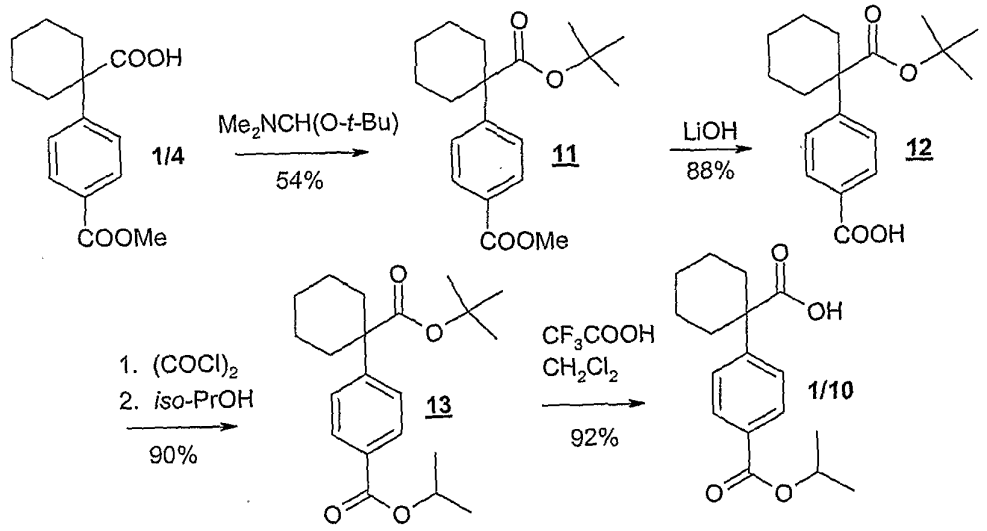


1/4, R = CH_3
1/6, R = $C(CH_3)_3$

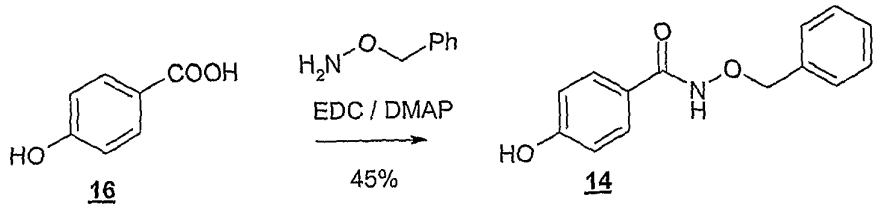
Scheme 12



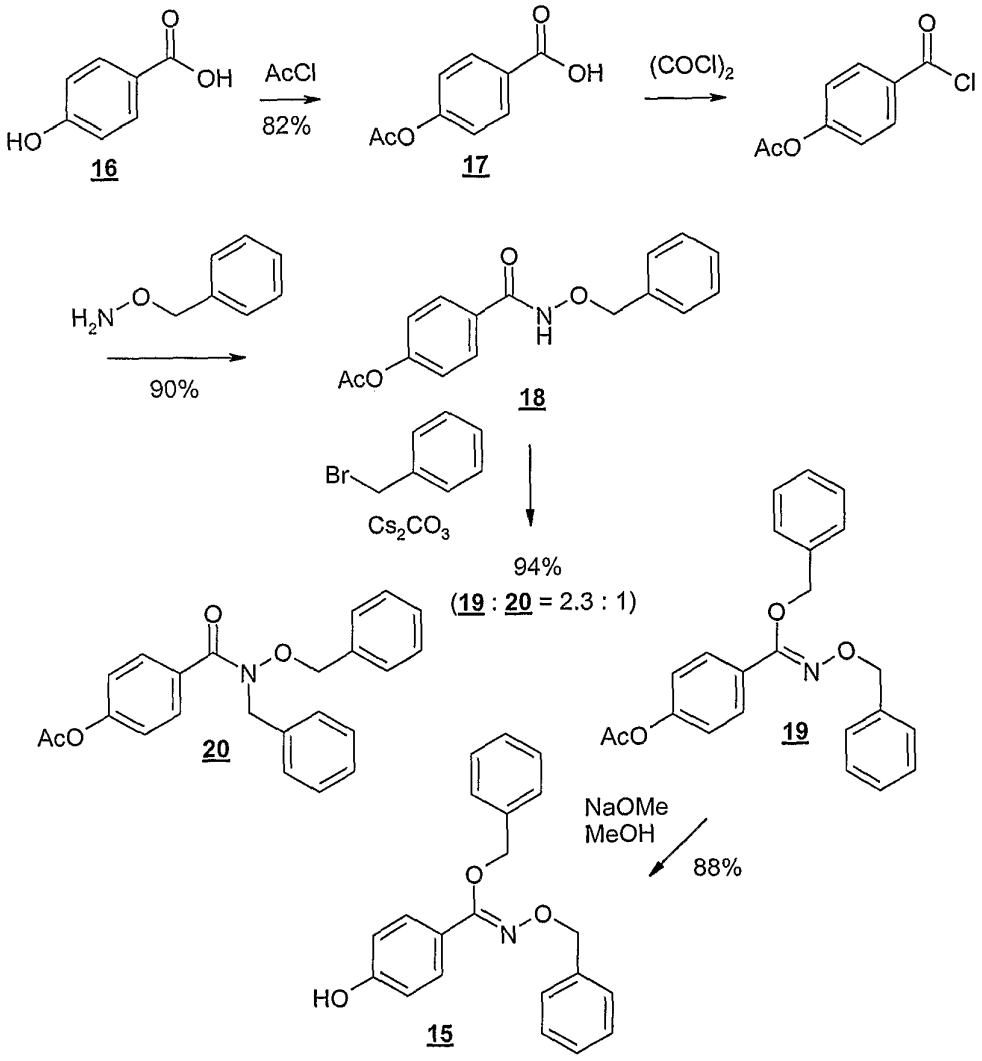
Scheme 13



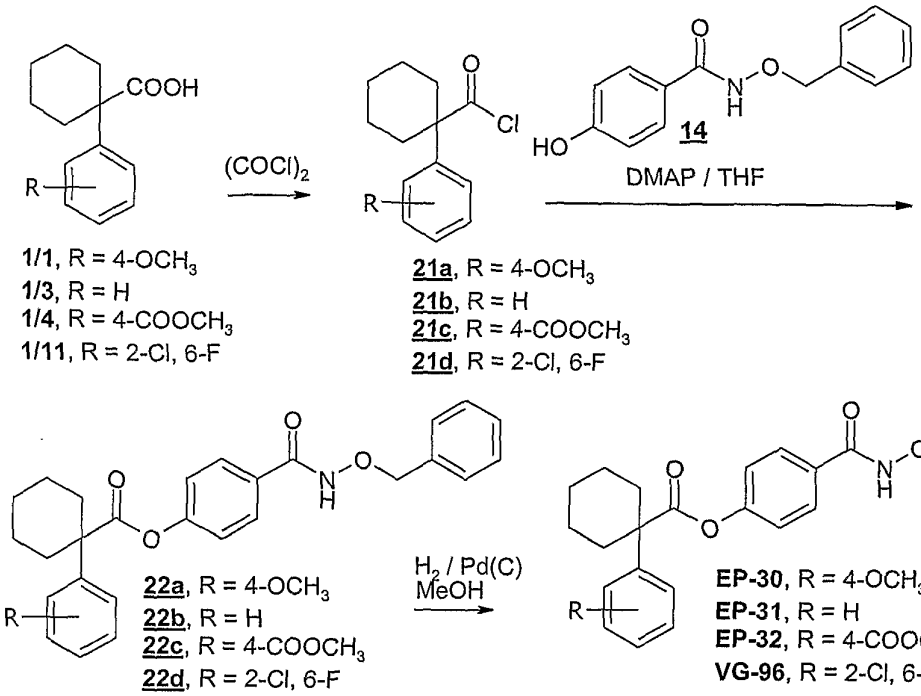
Scheme 14



Scheme 15


HO
OH
O
16
AcCl
82%
AcO
OH
O
17
(COCl)2
AcO
Cl
O
H2N
O
90%
AcO
N
H
O
O
18
Br
Cs2CO3
94%
(19 : 20 = 2.3 : 1)
AcO
N
O
O
20
AcO
O
N
O
19
NaOMe
MeOH
88%
HO
O
N
O
15

Scheme 16



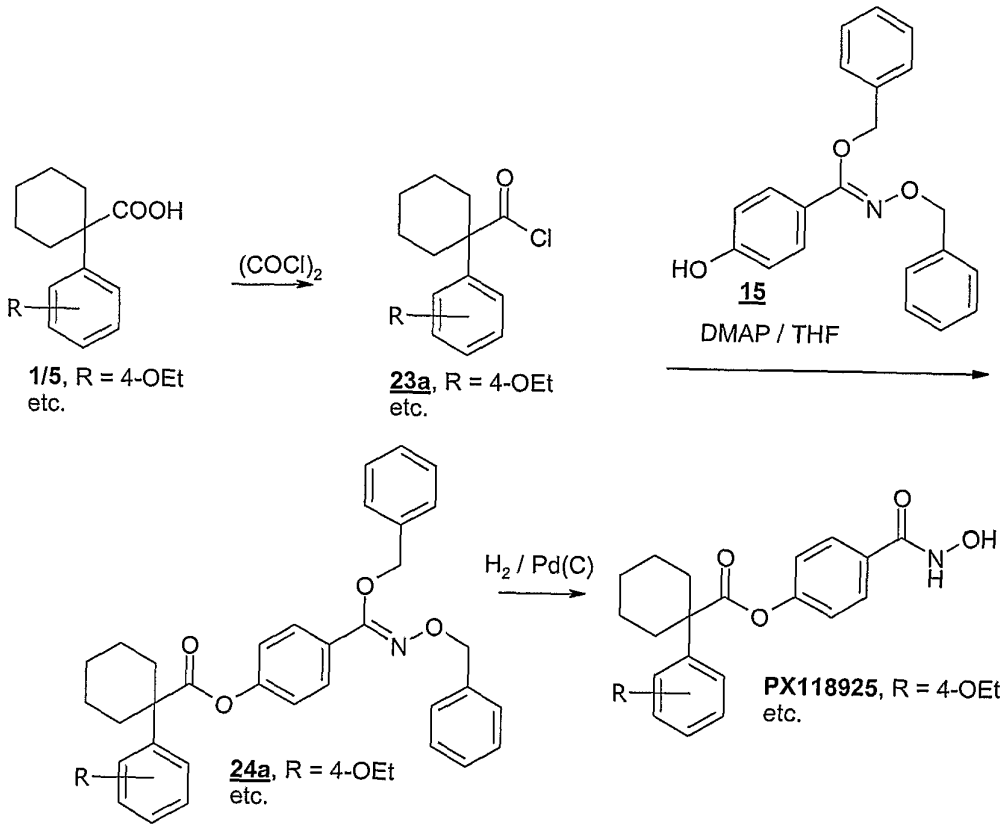
1/1, R = 4-OCH_3
1/3, R = H
1/4, R = 4-$COOCH_3$
1/11, R = 2-Cl, 6-F

21a, R = 4-OCH_3
21b, R = H
21c, R = 4-$COOCH_3$
21d, R = 2-Cl, 6-F

22a, R = 4-OCH_3
22b, R = H
22c, R = 4-$COOCH_3$
22d, R = 2-Cl, 6-F

EP-30, R = 4-OCH_3
EP-31, R = H
EP-32, R = 4-$COOCH_3$
VG-96, R = 2-Cl, 6-F

Scheme 17



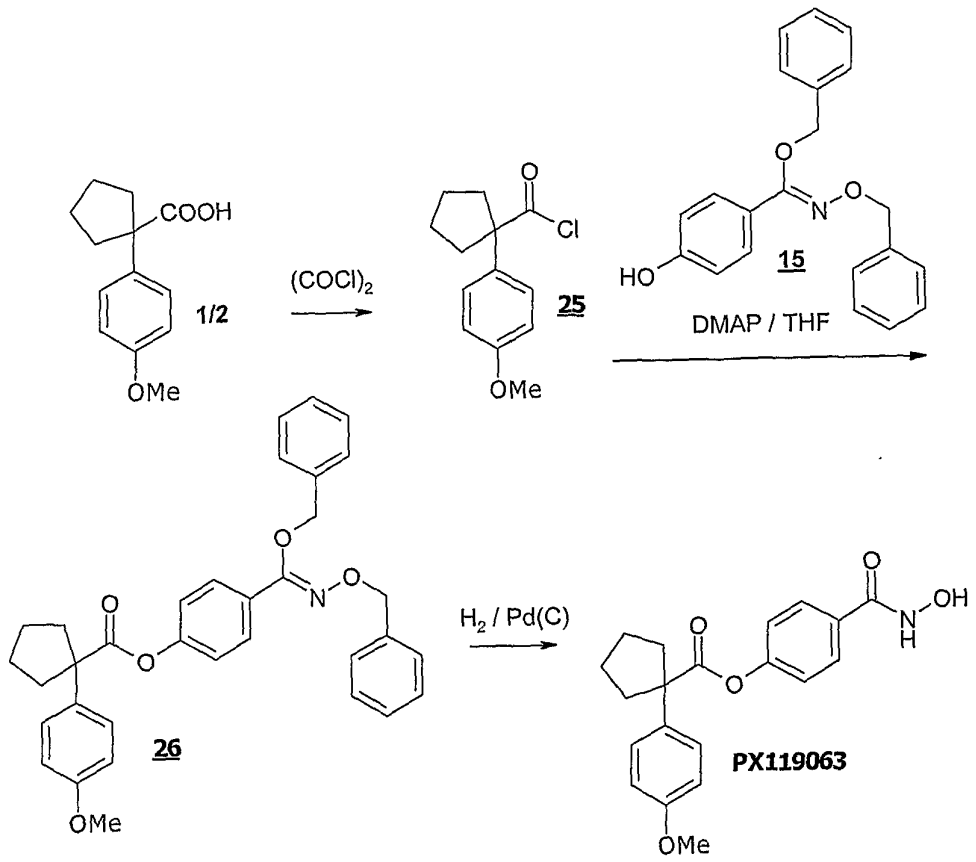
1/5, R = 4-OEt
etc.

23a, R = 4-OEt
etc.

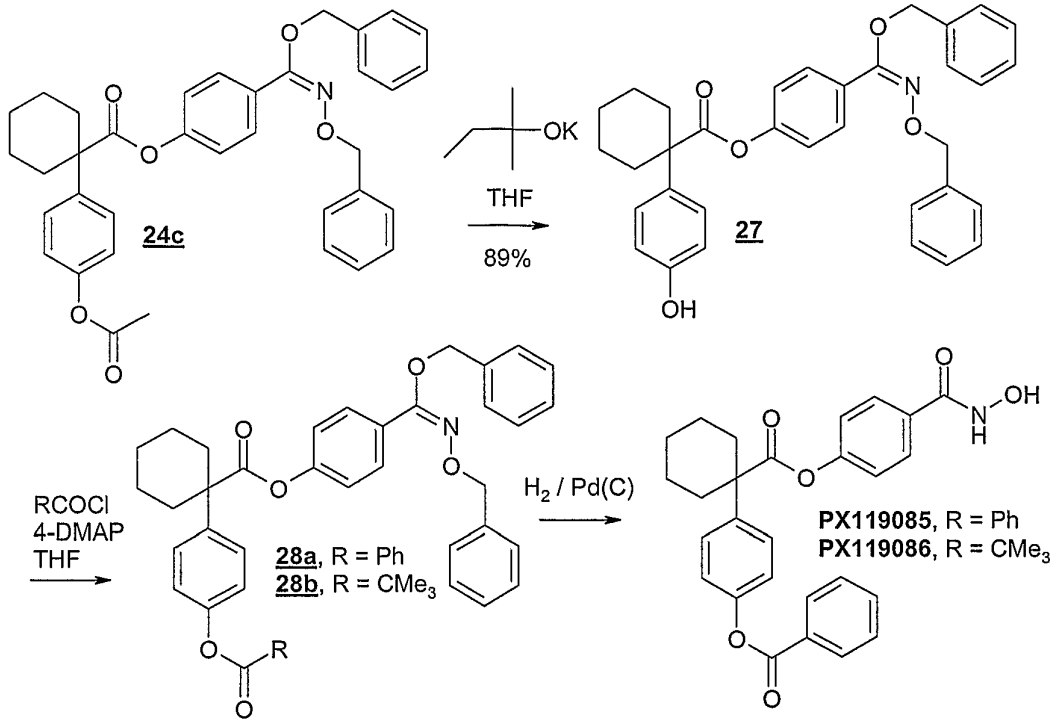
24a, R = 4-OEt
etc.

PX118925, R = 4-OEt
etc.

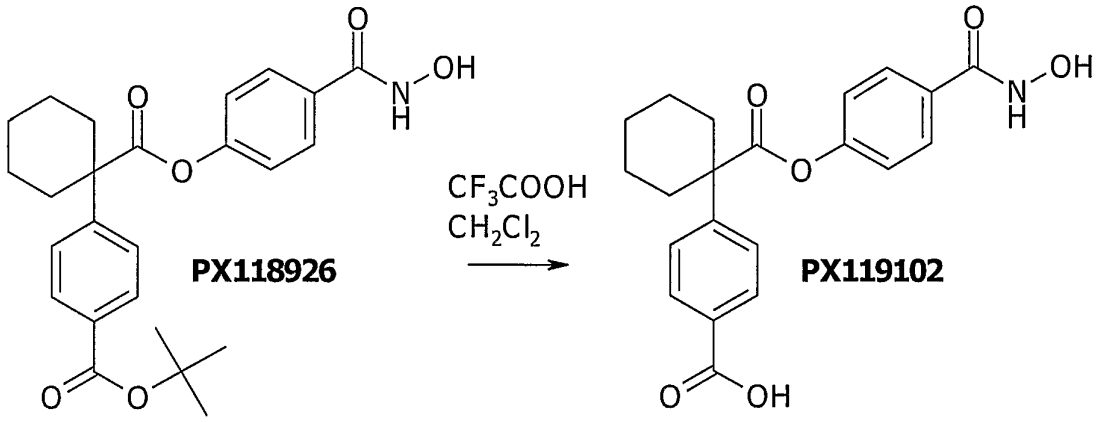
Scheme 18


COOH
1/2
OMe
(COCl)2
Cl
25
OMe
HO
15
DMAP / THF
26
OMe
H2 / Pd(C)
OH
PX119063
OMe

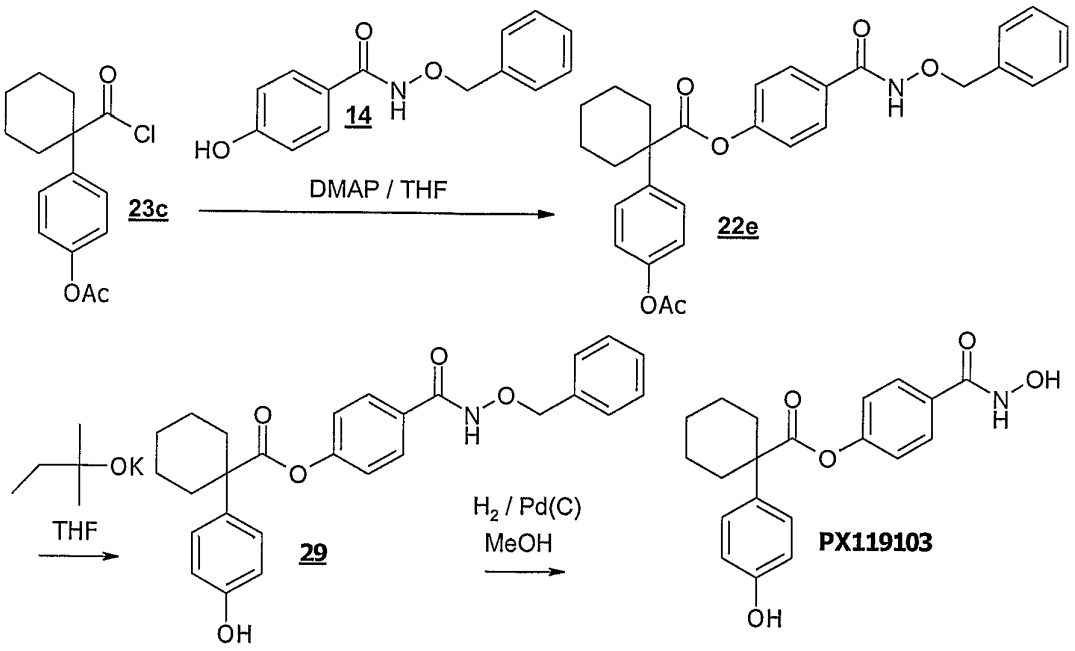
Scheme 19



Scheme 20



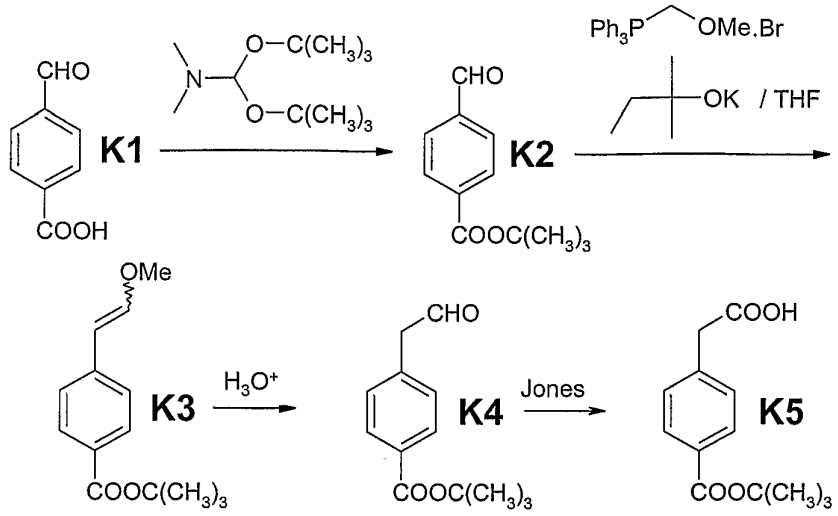
Scheme 21



Synthesis: Ketones

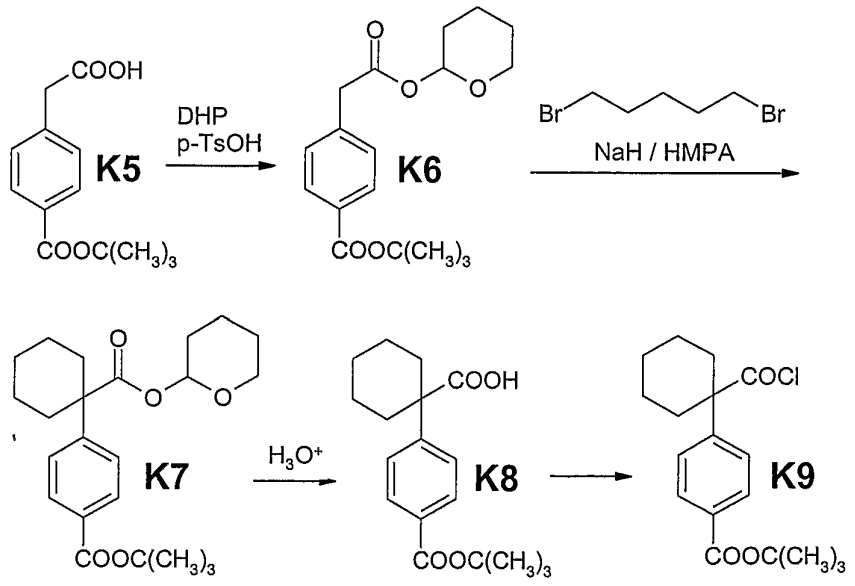
In one method, the carboxylic acid group of 4-carboxybenzaldehyde is protected, for example, as a tert-butyl ester, by reaction with N,N-dimethylformamide-di-tert-butyl acetal. The aldehyde group is then converted to a methoxy-vinyl (enol ether) group, for example, by reaction with (2-hydroxyethyl)triphenylphosphonium bromide and potassium tert-pentoxide in tetrahydrofuran. The methoxy-vinyl (enol-ether) group is then converted to an aldehyde group, by acid hydrolysis. The aldehyde group is then converted to a carboxylic acid group, by reaction with Jones reagent. An example of such a method is illustrated in the following scheme.

Scheme 22



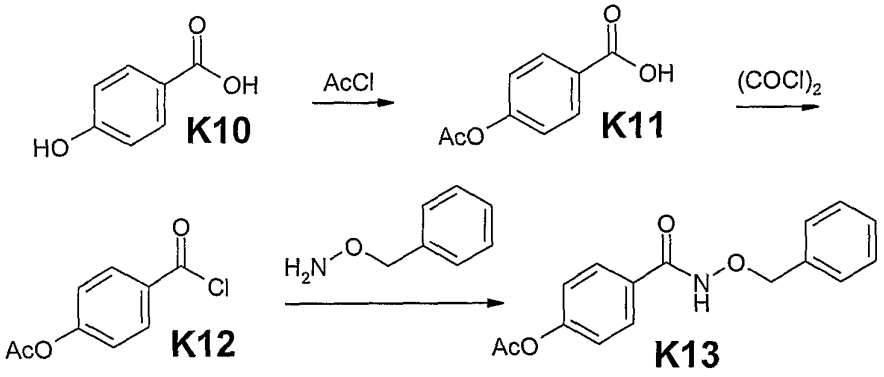
The carboxylic acid is then protected, for example, by reaction with 3,4-dihydro-2H-pyran, in the presence of para-toluene sulfonic acid. The protected compound is then reacted with, for example, 1,5-dibromopentane and sodium hydride in hexamethylphosphoramide (HMPA), to introduce a 1,1-cyclohexylene group. Similar reagents may be used to introduce other cylcic groups. The carboxylic acid ester is deprotected, for example, by acid hydrolysis. The carboxylic acid group is then converted to an acid chloride, for example, by reaction with oxalyl chloride. This acid chloride is used in a later step (see below). An example of such a method is illustrated in the following scheme.

Scheme 23



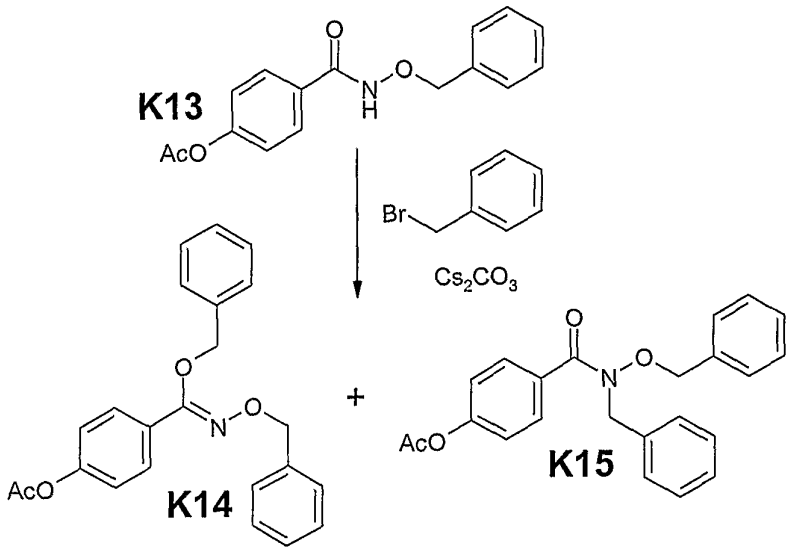
Separately, the hydroxy group of para-hydroxy benzoic acid is converted to an acetoxy group, for example, by reaction with acetyl chloride. The carboxylic acid group is then converted to an acid chloride group, for example, by reaction with oxalyl chloride. The acid chloride is then converted to an O-benzylhydroxamic acid ester, for example, by reaction with O-benzylhydroxylamine hydrochloride. An example of such a method is illustrated in the following scheme.

Scheme 24



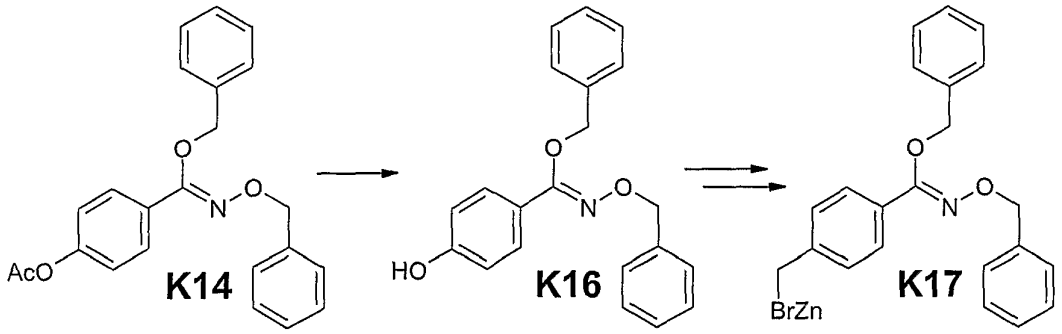
The O-benzylhydroxamic acid is then reacted with benzylbromide and cesium carbonate, to yield a mixture of products: an imidic acid ester and an N,O-dibenzyl hydroxamic acid. An example of such a method is illustrated in the following scheme.

Scheme 25



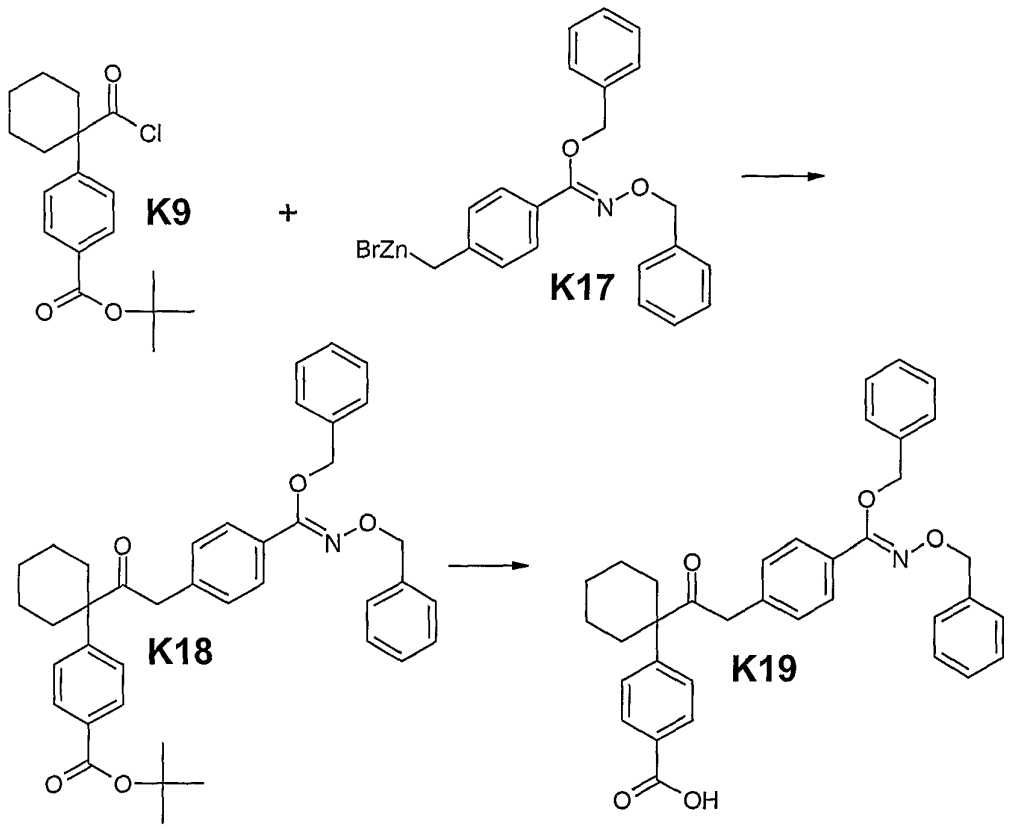
The imidic acid ester is then deprotected, for example, by reaction with sodium methylate (sodium methoxide), to remove the acetoxy group and expose hydroxy group. The hydroxy compound is then converted to a metal bromide, for example, a zinc bromide. An example of such a method is illustrated in the following scheme.

Scheme 26



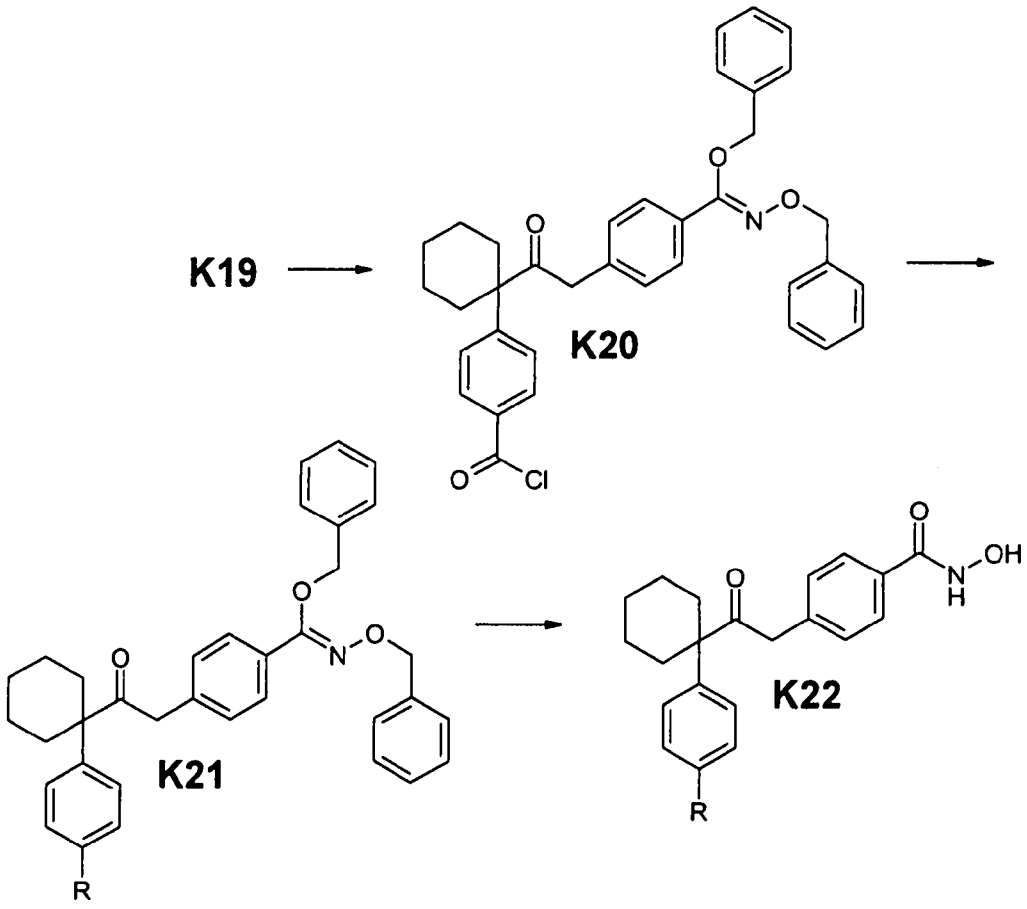
The zinc bromide compound is then reacted with the acid chloride (see above) to form the conjugate product. The carboxylic acid ester is then deprotected to expose the carboxylic acid. An example of such a method is illustrated in the following scheme.

Scheme 27



The carboxylic acid compound is then converted to any one of a number of alternatives. For example, it may be converted to an acid halide, for example, an acid chloride, for example, by reaction with oxalyl chloride, and then converted to, for example, an ester, an amide, a ketone, etc., by reaction, for example, with an alcohol, an amine, a metal organic derivative, etc. Finally, the hydroxamic acid is deprotected, to expose the hydroxamic acid, for example, by reaction with H_2 and Pd(C). An example of such a method is illustrated in the following scheme.

Scheme 28



Use

The present invention provides active compounds, specifically, active hydroxamic acids, as described herein.

The term "active," as used herein, specifically includes both compounds with intrinsic activity (drugs) as well as prodrugs of such compounds, which prodrugs may themselves exhibit little or no intrinsic activity.

The present invention also provides active compounds which inhibit HDAC activity.

The present invention also provides methods of inhibiting HDAC in a cell, comprising contacting said cell with an effective amount of an active compound. Such a method may be practised *in vitro* or *in vivo*. In one embodiment, the method is performed *in vitro*. In

one embodiment, the method is performed *in vivo*. Preferably, the active compound is provided in the form of a pharmaceutically acceptable composition.

The term "inhibiting HDAC," as used herein, includes: inhibiting HDAC activity; inhibiting the formation of HDAC complexes; and inhibiting the activity of HDAC complexes.

One of ordinary skill in the art is readily able to determine whether or not a candidate compound inhibits HDAC activity. For example, one assay which may conveniently be used in order to assess the HDAC inhibition offered by a particular compound is described in the examples below.

The present invention also provides active compounds which (a) regulate (e.g., inhibit) cell proliferation; (b) inhibit cell cycle progression; (c) promote apoptosis; or (d) a combination of one or more of these.

Thus, the present invention also provides methods of (a) regulating (e.g., inhibiting) cell proliferation; (b) inhibiting cell cycle progression; (c) promoting apoptosis; or (d) a combination of one or more of these, *in vitro* or *in vivo,* comprising contacting a cell with an effective amount of an active compound, as described herein.

One of ordinary skill in the art is readily able to determine whether or not a candidate compound regulate (e.g., inhibit) cell proliferation, etc. For example, assays which may conveniently be used to assess the activity offered by a particular compound are described in the examples below.

For example, a sample of cells (e.g., from a tumour) may be grown *in vitro* and an active compound brought into contact with said cells, and the effect of the compound on those cells observed. As an example of "effect," the morphological status of the cells (e.g., alive or dead, etc.) may be determined. Where the active compound is found to exert an influence on the cells, this may be used as a prognostic or diagnostic marker of the efficacy of the compound in methods of treating a patient carrying cells of the same cellular type.

Methods of Treatment, Etc.

The invention further provides methods of treatment, comprising administering to a subject in need of treatment a therapeutically-effective amount of an active compound, preferably in the form of a pharmaceutical composition.

The invention further provides active compounds for use in a method of treatment of the human or animal body by therapy, for example, in the treatment of a condition mediated by HDAC, a condition known to be treated by HDAC inhibitors (such as, e.g., trichostatin A), cancer, a proliferative condition, or other condition as described herein.

The invention further provides the use of an active compound for the manufacture of a medicament, for example, for the treatment of a condition mediated by HDAC, a condition known to be treated by HDAC inhibitors (such as, e.g., trichostatin A), cancer, a proliferative condition, or other condition as described herein.

Treatment

The term "treatment," as used herein in the context of treating a condition, pertains generally to treatment and therapy, whether of a human or an animal (e.g., in veterinary applications), in which some desired therapeutic effect is achieved, for example, the inhibition of the progress of the condition, and includes a reduction in the rate of progress, a halt in the rate of progress, amelioration of the condition, and cure of the condition. Treatment as a prophylactic measure (i.e., prophylaxis) is also included.

The term "therapeutically-effective amount," as used herein, pertains to that amount of an active compound, or a material, composition or dosage form comprising an active compound, which is effective for producing some desired therapeutic effect, commensurate with a reasonable benefit/risk ratio.

The term "treatment" includes combination treatments and therapies, in which two or more treatments or therapies are combined, for example, sequentially or simultaneously. Examples of treatments and therapies include, but are not limited to, chemotherapy (the administration of active agents, including, e.g., drugs, antibodies (e.g., as in immunotherapy), prodrugs (e.g., as in photodynamic therapy, GDEPT, ADEPT, etc.); surgery; radiation therapy; and gene therapy.

Active compounds may also be used, as described above, in combination therapies, that is, in conjunction with other agents, for example, cytotoxic agents.

Anti-HDAC Applications

The present invention also provides active compounds which are anti-HDAC agents, and which treat a condition mediated by HDAC.

The term "a condition mediated by HDAC," as used herein pertains to a condition in which HDAC and/or the action of HDAC is important or necessary, e.g., for the onset, progress, expression, etc. of that condition, or a condition which is known to be treated by HDAC inhibitors (such as, e.g., trichostatin A).

Examples of such conditions include, but are not limited to, the following:

Cancer (see, e.g., Vigushin et al., 2001).

Psoriasis (see, e.g., Iavarone et al., 1999).

Fibroproliferative disorders (e.g., liver fibrosis) (see, e.g., Niki et al., 1999; Corneil et al., 1998).

Smooth muscle proliferative disorder (e.g., atherosclerosis, restenosis) (see, e.g., Kimura et al., 1994).

Neurodegenative diseases (e.g., Alzheimer's, Parkinson's, Huntington's chorea, amyotropic lateral sclerosis, spino-cerebellar degeneration) (see, e.g., Kuusisto et al., 2001).

Inflammatory disease (e.g., osteoarthritis, rheumatoid arthritis) (see, e.g., Dangond et al., 1998; Takahashi et al., 1996).

Diseases involving angiogenesis (e.g., cancer, rheumatoid arthritis, psoriasis, diabetic retinopathy) (see, e.g., Kim et al., 2001).

Haematopoietic disorders (e.g., anaemia, sickle cell anaemia, thalassaeimia) (see, e.g., McCaffrey et al., 1997).

Fungal infection (see, e.g., Bernstein et al., 2000; Tsuji et al., 1976).

Parasitic infection (e.g., malaria, trypanosomiasis, helminthiasis, protozoal infections (see, e.g., Andrews et al., 2000).

Bacterial infection (see, e.g., Onishi et al., 1996).

Viral infection (see, e.g., Chang et al., 2000).

Conditions treatable by immune modulation (e.g., multiple sclerosis, autoimmune diabetes, lupus, atopic dermatitis, allergies, asthma, allergic rhinitis, inflammatory bowel disease; and for improving grafting of transplants) (see, e.g., Dangond et al., 1998; Takahashi et al., 1996).

One of ordinary skill in the art is readily able to determine whether or not a candidate compound treats a condition mediated by HDAC for any particular cell type. For example, assays which may conveniently be used to assess the activity offered by a particular compound are described in the examples below.

Anticancer Applications

The present invention also provides active compounds which are anticancer agents, and treat cancer.

Thus, the present invention also provides methods of treating cancer, comprising administering to a subject in need of treatment a therapeutically-effective amount of an active compound, as described herein, preferably in the form of a pharmaceutical composition.

One of ordinary skill in the art is readily able to determine whether or not a candidate compound treats a cancerous condition for any particular cell type. For example, assays which may conveniently be used to assess the activity offered by a particular compound are described in the examples below.

The term "anticancer agent" as used herein, pertains to a compound which treats a cancer (i.e., a compound which is useful in the treatment of a cancer). The anti-cancer effect may arise through one or more mechanisms, including but not limited to, the regulation of cell proliferation, the inhibition of cell cycle progression, the inhibition of angiogenesis (the formation of new blood vessels), the inhibition of metastasis (the spread of a tumour from its origin), the inhibition of invasion (the spread of tumour cells into neighbouring normal structures), or the promotion of apoptosis (programmed cell death). Exampes of cancers are discussed below.

Antiproliferative Applications

The present invention also provides active compounds which are antiproliferative agents. The term "antiproliferative agent" as used herein, pertain to a compound which treats a proliferative condition (i.e., a compound which is useful in the treatment of a proliferative condition).

Thus, the present invention also provides methods of treating a proliferative condition, comprising administering to a subject in need of treatment a therapeutically-effective amount of an active compound, as described herein, preferably in the form of a pharmaceutical composition.

One of ordinary skill in the art is readily able to determine whether or not a candidate compound treats a proliferative condition for any particular cell type. For example, assays which may conveniently be used to assess the activity offered by a particular compound are described in the examples below.

The terms "cell proliferation," "proliferative condition," "proliferative disorder," and "proliferative disease," are used interchangeably herein and pertain to an unwanted or uncontrolled cellular proliferation of excessive or abnormal cells which is undesired, such as, neoplastic or hyperplastic growth, whether *in vitro* or *in vivo*.

Examples of proliferative conditions include, but are not limited to, benign, pre-malignant, and malignant cellular proliferation, including but not limited to, neoplasms and tumours (e.g., histocytoma, glioma, astrocyoma, osteoma), cancers (e.g., lung cancer, small cell lung cancer, gastrointestinal cancer, bowel cancer, colon cancer, breast carcinoma,

ovarian carcinoma, prostate cancer, testicular cancer, liver cancer, kidney cancer, bladder cancer, pancreas cancer, brain cancer, sarcoma, osteosarcoma, Kaposi's sarcoma, melanoma), leukemias, psoriasis, bone diseases, fibroproliferative disorders (e.g., of connective tissues), and atherosclerosis.

Any type of cell may be treated, including but not limited to, lung, gastrointestinal (including, e.g., bowel, colon), breast (mammary), ovarian, prostate, liver (hepatic), kidney (renal), bladder, pancreas, brain, and skin.

Additional Uses

Active compounds may also be used as cell culture additives to inhibit HDAC, for example, in order to regulate (e.g., inhibit) cell proliferation *in vitro*.

Active compounds may also be used as part of an *in vitro* assay, for example, in order to determine whether a candidate host is likely to benefit from treatment with the compound in question.

Active compounds may also be used as a standard, for example, in an assay, in order to identify other active compounds, other HDAC inhibitors, other anticancer agents, other antiproliferative agents, etc.

The compounds of the present invention may also be used in methods of improving protein production by cultured cells (see, e.g., Furukawa et al., 1998).

Routes of Administration

The active compound or pharmaceutical composition comprising the active compound may be administered to a subject by any convenient route of administration, whether systemically/ peripherally or topically (i.e., at the site of desired action).

Routes of administration include, but are not limited to, oral (e.g, by ingestion); buccal; sublingual; transdermal (including, e.g., by a patch, plaster, etc.); transmucosal (including, e.g., by a patch, plaster, etc.); intranasal (e.g., by nasal spray); ocular (e.g., by eyedrops); pulmonary (e.g., by inhalation or insufflation therapy using, e.g., via an aerosol, e.g., through the mouth or nose); rectal (e.g., by suppository or enema); vaginal (e.g., by

pessary); parenteral, for example, by injection, including subcutaneous, intradermal, intramuscular, intravenous, intraarterial, intracardiac, intrathecal, intraspinal, intracapsular, subcapsular, intraorbital, intraperitoneal, intratracheal, subcuticular, intraarticular, subarachnoid, and intrasternal; by implant of a depot or reservoir, for example, subcutaneously or intramuscularly.

The Subject

The subject may be a prokaryote (e.g., bacteria) or a eukaryote (e.g., protoctista, fungi, plants, animals).

The subject may be an animal, a mammal, a placental mammal, a marsupial (e.g., kangaroo, wombat), a monotreme (e.g., duckbilled platypus), a rodent (e.g., a guinea pig, a hamster, a rat, a mouse), murine (e.g., a mouse), a lagomorph (e.g., a rabbit), avian (e.g., a bird), canine (e.g., a dog), feline (e.g., a cat), equine (e.g., a horse), porcine (e.g., a pig), ovine (e.g., a sheep), bovine (e.g., a cow), a primate, simian (e.g., a monkey or ape), a monkey (e.g., marmoset, baboon), an ape (e.g., gorilla, chimpanzee, orangutang, gibbon), or a human.

Furthermore, the subject may be any of its forms of development, for example, a spore, a seed, an egg, a larva, a pupa, or a foetus.

In one embodiment, the subject is a human.

Formulations

While it is possible for the active compound to be used (e.g., administered) alone, it is often preferable to present it as a formulation.

Thus, one aspect of the present invention pertains to a composition comprising a compound, as described herein, and a carrier.

In one embodiment, the composition is a pharmaceutical composition (e.g., formulation, preparation, medicament) comprising a compound, as described herein, and a pharmaceutically acceptable carrier.

In one embodiment, the composition is a pharmaceutical composition comprising at least one compound, as described herein, together with one or more other pharmaceutically acceptable ingredients well known to those skilled in the art, including, but not limited to, pharmaceutically acceptable carriers, diluents, excipients, adjuvants, fillers, buffers, preservatives, anti-oxidants, lubricants, stabilisers, solubilisers, surfactants (e.g., wetting agents), masking agents, colouring agents, flavouring agents, and sweetening agents.

In one embodiment, the composition further comprises other active agents, for example, other therapeutic or prophylactic agents.

Suitable carriers, diluents, excipients, etc. can be found in standard pharmaceutical texts. See, for example, Handbook of Pharmaceutical Additives, 2nd Edition (eds. M. Ash and I. Ash), 2001 (Synapse Information Resources, Inc., Endicott, New York, USA), Remington's Pharmaceutical Sciences, 18th edition, Mack Publishing Company, Easton, Pa., 1990; and Handbook of Pharmaceutical Excipients, 2nd edition, 1994.

Another aspect of the present invention pertains to methods of making a pharmaceutical composition comprising admixing at least one active compound, as defined above, together with one or more other pharmaceutically acceptable ingredients well known to those skilled in the art, e.g., carriers, diluents, excipients, etc. If formulated as discrete units (e.g., tablets, etc.), each unit contains a predetermined amount (dosage) of the active compound.

The term "pharmaceutically acceptable" as used herein pertains to compounds, ingredients, materials, compositions, dosage forms, etc., which are, within the scope of sound medical judgment, suitable for use in contact with the tissues of the subject in question (e.g., human) without excessive toxicity, irritation, allergic response, or other problem or complication, commensurate with a reasonable benefit/risk ratio. Each carrier, diluent, excipient, etc. must also be "acceptable" in the sense of being compatible with the other ingredients of the formulation.

The formulations may be prepared by any methods well known in the art of pharmacy. Such methods include the step of bringing into association the active compound with a carrier which constitutes one or more accessory ingredients. In general, the formulations are prepared by uniformly and intimately bringing into association the active compound

with carriers (e.g., liquid carriers, finely divided solid carrier, etc.), and then shaping the product, if necessary.

The formulation may be prepared to provide for rapid or slow release; immediate, delayed, timed, or sustained release; or a combination thereof.

Formulations may suitably be in the form of liquids, solutions (e.g., aqueous, non-aqueous), suspensions (e.g., aqueous, non-aqueous), emulsions (e.g., oil-in-water, water-in-oil), elixirs, syrups, electuaries, mouthwashes, drops, tablets (including, e.g., coated tablets), granules, powders, lozenges, pastilles, capsules (including, e.g., hard and soft gelatin capsules), cachets, pills, ampoules, boluses, suppositories, pessaries, tinctures, gels, pastes, ointments, creams, lotions, oils, foams, sprays, mists, or aerosols.

Formulations may suitably be provided as a patch, adhesive plaster, bandage, dressing, or the like which is impregnated with one or more active compounds and optionally one or more other pharmaceutically acceptable ingredients, including, for example, penetration, permeation, and absorption enhancers. Formulations may also suitably be provided in a the form of a depot or reservoir.

The active compound may be dissolved in, suspended in, or admixed with one or more other pharmaceutically acceptable ingredients. The active compound may be presented in a liposome or other microparticulate which is designed to target the active compound, for example, to blood components or one or more organs.

Formulations suitable for oral administration (e.g, by ingestion) include liquids, solutions (e.g., aqueous, non-aqueous), suspensions (e.g., aqueous, non-aqueous), emulsions (e.g., oil-in-water, water-in-oil), elixirs, syrups, electuaries, tablets, granules, powders, capsules, cachets, pills, ampoules, boluses.

Formulations suitable for buccal administration include mouthwashes, lozenges, pastilles, as well as patches, adhesive plasters, depots, and reservoirs. Lozenges typically comprise the active compound in a flavored basis, usually sucrose and acacia or tragacanth. Pastilles typically comprise the active compound in an inert matrix, such as gelatin and glycerin, or sucrose and acacia. Mouthwashes typically comprise the active compound in a suitable liquid carrier.

Formulations suitable for sublingual administration include tablets, lozenges, pastilles, capsules, and pills.

Formulations suitable for oral transmucosal administration include liquids, solutions (e.g., aqueous, non-aqueous), suspensions (e.g., aqueous, non-aqueous), emulsions (e.g., oil-in-water, water-in-oil), mouthwashes, lozenges, pastilles, as well as patches, adhesive plasters, depots, and reservoirs.

Formulations suitable for non-oral transmucosal administration include liquids, solutions (e.g., aqueous, non-aqueous), suspensions (e.g., aqueous, non-aqueous), emulsions (e.g., oil-in-water, water-in-oil), suppositories, pessaries, gels, pastes, ointments, creams, lotions, oils, as well as patches, adhesive plasters, depots, and reservoirs.

Formulations suitable for transdermal administration include gels, pastes, ointments, creams, lotions, and oils, as well as patches, adhesive plasters, bandages, dressings, depots, and reservoirs.

Tablets may be made by conventional means, e.g., compression or molding, optionally with one or more accessory ingredients. Compressed tablets may be prepared by compressing in a suitable machine the active compound in a free-flowing form such as a powder or granules, optionally mixed with one or more binders (e.g., povidone, gelatin, acacia, sorbitol, tragacanth, hydroxypropylmethyl cellulose); fillers or diluents (e.g., lactose, microcrystalline cellulose, calcium hydrogen phosphate); lubricants (e.g., magnesium stearate, talc, silica); disintegrants (*e.g.*, sodium starch glycolate, cross-linked povidone, cross-linked sodium carboxymethyl cellulose); surface-active or dispersing or wetting agents (e.g., sodium lauryl sulfate); preservatives (e.g., methyl p-hydroxybenzoate, propyl p-hydroxybenzoate, sorbic acid); flavours, flavour enhancing agents, and sweeteners. Molded tablets may be made by molding in a suitable machine a mixture of the powdered compound moistened with an inert liquid diluent. The tablets may optionally be coated or scored and may be formulated so as to provide slow or controlled release of the active compound therein using, for example, hydroxypropylmethyl cellulose in varying proportions to provide the desired release profile. Tablets may optionally be provided with a coating, for example, to affect release, for example an enteric coating, to provide release in parts of the gut other than the stomach.

Ointments are typically prepared from the active compound and a paraffinic or a water-miscible ointment base.

Creams are typically prepared from the active compound and an oil-in-water cream base. If desired, the aqueous phase of the cream base may include, for example, at least about 30% w/w of a polyhydric alcohol, i.e., an alcohol having two or more hydroxyl groups such as propylene glycol, butane-1,3-diol, mannitol, sorbitol, glycerol and polyethylene glycol and mixtures thereof. The topical formulations may desirably include a compound which enhances absorption or penetration of the active compound through the skin or other affected areas. Examples of such dermal penetration enhancers include dimethylsulfoxide and related analogues.

Emulsions are typically prepared from the active compound and an oily phase, which may optionally comprise merely an emulsifier (otherwise known as an emulgent), or it may comprises a mixture of at least one emulsifier with a fat or an oil or with both a fat and an oil. Preferably, a hydrophilic emulsifier is included together with a lipophilic emulsifier which acts as a stabiliser. It is also preferred to include both an oil and a fat. Together, the emulsifier(s) with or without stabiliser(s) make up the so-called emulsifying wax, and the wax together with the oil and/or fat make up the so-called emulsifying ointment base which forms the oily dispersed phase of the cream formulations.

Suitable emulgents and emulsion stabilisers include Tween 60, Span 80, cetostearyl alcohol, myristyl alcohol, glyceryl monostearate and sodium lauryl sulphate. The choice of suitable oils or fats for the formulation is based on achieving the desired cosmetic properties, since the solubility of the active compound in most oils likely to be used in pharmaceutical emulsion formulations may be very low. Thus the cream should preferably be a non-greasy, non-staining and washable product with suitable consistency to avoid leakage from tubes or other containers. Straight or branched chain, mono- or dibasic alkyl esters such as di-isoadipate, isocetyl stearate, propylene glycol diester of coconut fatty acids, isopropyl myristate, decyl oleate, isopropyl palmitate, butyl stearate, 2-ethylhexyl palmitate or a blend of branched chain esters known as Crodamol CAP may be used, the last three being preferred esters. These may be used alone or in combination depending on the properties required. Alternatively, high melting point lipids such as white soft paraffin and/or liquid paraffin or other mineral oils can be used.

Formulations suitable for intranasal administration, where the carrier is a liquid, include, for example, nasal spray, nasal drops, or by aerosol administration by nebuliser, include aqueous or oily solutions of the active compound.

Formulations suitable for intranasal administration, where the carrier is a solid, include, for example, those presented as a coarse powder having a particle size, for example, in the range of about 20 to about 500 microns which is administered in the manner in which snuff is taken, i.e., by rapid inhalation through the nasal passage from a container of the powder held close up to the nose.

Formulations suitable for pulmonary administration (e.g., by inhalation or insufflation therapy) include those presented as an aerosol spray from a pressurised pack, with the use of a suitable propellant, such as dichlorodifluoromethane, trichlorofluoromethane, dichoro-tetrafluoroethane, carbon dioxide, or other suitable gases.

Formulations suitable for ocular administration include eye drops wherein the active compound is dissolved or suspended in a suitable carrier, especially an aqueous solvent for the active compound.

Formulations suitable for rectal administration may be presented as a suppository with a suitable base comprising, for example, natural or hardened oils, waxes, fats, semi-liquid or liquid polyols, for example, cocoa butter or a salicylate; or as a solution or suspension for treatment by enema.

Formulations suitable for vaginal administration may be presented as pessaries, tampons, creams, gels, pastes, foams or spray formulations containing in addition to the active compound, such carriers as are known in the art to be appropriate.

Formulations suitable for parenteral administration (e.g., by injection), include aqueous or non-aqueous, isotonic, pyrogen-free, sterile liquids (e.g., solutions, suspensions), in which the active compound is dissolved, suspended, or otherwise provided (e.g., in a liposome or other microparticulate). Such liquids may additional contain other pharmaceutically acceptable ingredients, such as anti-oxidants, buffers, preservatives, stabilisers, bacteriostats, suspending agents, thickening agents, and solutes which render the formulation isotonic with the blood (or other relevant bodily fluid) of the intended recipient. Examples of excipients include, for example, water, alcohols, polyols, glycerol, vegetable

oils, and the like. Examples of suitable isotonic carriers for use in such formulations include Sodium Chloride Injection, Ringer's Solution, or Lactated Ringer's Injection. Typically, the concentration of the active compound in the liquid is from about 1 ng/ml to about 10 µg/ml, for example from about 10 ng/ml to about 1 µg/ml. The formulations may be presented in unit-dose or multi-dose sealed containers, for example, ampoules and vials, and may be stored in a freeze-dried (lyophilised) condition requiring only the addition of the sterile liquid carrier, for example water for injections, immediately prior to use. Extemporaneous injection solutions and suspensions may be prepared from sterile powders, granules, and tablets.

Dosage

It will be appreciated by one of skill in the art that appropriate dosages of the active compounds, and compositions comprising the active compounds, can vary from patient to patient. Determining the optimal dosage will generally involve the balancing of the level of therapeutic benefit against any risk or deleterious side effects. The selected dosage level will depend on a variety of factors including, but not limited to, the activity of the particular compound, the route of administration, the time of administration, the rate of excretion of the compound, the duration of the treatment, other drugs, compounds, and/or materials used in combination, the severity of the condition, and the species, sex, age, weight, condition, general health, and prior medical history of the patient. The amount of compound and route of administration will ultimately be at the discretion of the physician, veterinarian, or clinician, although generally the dosage will be selected to achieve local concentrations at the site of action which achieve the desired effect without causing substantial harmful or deleterious side-effects.

Administration can be effected in one dose, continuously or intermittently (e.g., in divided doses at appropriate intervals) throughout the course of treatment. Methods of determining the most effective means and dosage of administration are well known to those of skill in the art and will vary with the formulation used for therapy, the purpose of the therapy, the target cell(s) being treated, and the subject being treated. Single or multiple administrations can be carried out with the dose level and pattern being selected by the treating physician, veterinarian, or clinician.

In general, a suitable dose of the active compound is in the range of about 0.1 to about 250 mg per kilogram body weight of the subject per day. Where the active compound is a

salt, an ester, an amide, a prodrug, or the like, the amount administered is calculated on the basis of the parent compound and so the actual weight to be used is increased proportionately.

Kits

One aspect of the invention pertains to a kit comprising (a) the active ingredient, preferably provided in a suitable container and/or with suitable packaging; and (b) instructions for use, for example, written instructions on how to administer the active compound, etc.

The written instructions may also include a list of indications for which the active ingredient is a suitable treatment.

EXAMPLES

The following are examples are provided solely to illustrate the present invention and are not intended to limit the scope of the invention, as described herein.

General

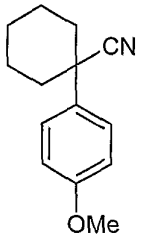
^{1}H NMR spectra were recorded at ambient temperature with WH-90/DS or Mercury 200 (Varian) spectrometers. The HPLC measurements were performed on a Gilson Model 302 system equipped with a spectrophotometer. Elemental analyses were obtained with a Carlo Erba EA 1108 instrument. Melting points were measured on a "Boëtius" micro melting point apparatus and are uncorrected. Silicagel, 0.035-0.070 mm, (Acros) was employed for column chromatography. All the solvents were purified before use by routine techniques. To isolate reaction products the solvents were removed by evaporation using a vacuum rotary evaporator, the water bath temperature not exceeding 40°C.

Various reagents were purchased from Sigma-Aldrich (The Old Brickyard, New Road, Gillingham, Dorset, UK), Acros Organics (Janssens Pharmaceuticalaan 3A, 2440 Geel, Belgium), and Fluka (Industriestr. 25, 9470 Buchs, Switzerland).

The following reagents were prepared according to procedures described in literature: 2.46 N potassium 2-methyl-2-butanolate solution in tetrahydrofuran (Tedesco, R.; Fiaschi, R.; Napolitano, E. *Synthesis* 1995, 1493), *tert*-butyl 4-formylbenzoate (**6b**) (Pritchard, G.J. et al *J.Med.Chem.* 2001, *44*, 1491).

Example 1

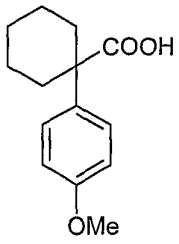
1-(4-Methoxyphenyl)cyclohexanecarbonitrile (**E2**)



To a solution of 4-methoxyphenylacetonitrile (**E1**) (1.002 g, 6.8 mmol) and 1,5-dibromopentane (1.886 g, 8.2 mmol) in dry dimethylformamide (15 ml) at ice bath temperature slowly (ca. 2-3 minutes) a 60% suspension of NaH in mineral oil (0.579 g, 14.4 mmol) was added. The obtained reaction mixture was stirred for 15 minutes at ice bath temperature and for 1.5 hours at room temperature, then the contents were poured into benzene (75 ml). The mixture was successively washed with water (3 x 75 ml), brine (25 ml), and dried (Na_2SO_4). The solvent was evaporated and the residue was chromatographed on silicagel (50 g) with petroleum ether-ethyl acetate (5:1) as eluent to give the title compound (0.924 g, 63%) as a white solid. ^1H NMR ($CDCl_3$, HMDSO) δ: 1.00-2.28 (10H, m); 3.81 (3H, s); 6.90 (2H, d, J=9.0 Hz); 7.40 (2H, d, J=9.0 Hz).

Example 2

1-(4-Methoxyphenyl)cyclohexanecarboxylic acid (**E3**)

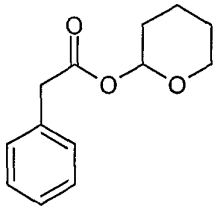


A solution of 1-(4-methoxyphenyl)cyclohexanecarbonitrile (**E2**) (1.092 g, 5.07 mmol) in dioxane (6 ml) to a mixture of 2 M NaOH in water (150 ml) and 30% H_2O_2 in water (7.5 ml) was added and the resultant suspension was stirred under reflux for 4 days. The pH of the reaction medium was brought to pH 1 with conc. HCl (ca. 30 ml) and the obtained

mixture was extracted with ethyl acetate (4 x 80 ml). The combined organic extract was washed with brine (50 ml) and dried (Na_2SO_4). The solvent was evaporated and the residue was chromatographed on silicagel (50 g) with benzene-ethyl acetate-acetic acid (9:1:0.15) as eluent affording the title compound (0.844 g, 71%) as a white solid. ^1H NMR ($CDCl_3$, HMDSO) δ: 1.05-1.91 (8H, m); 2.16-2.61 (2H, m); 3.76 (3H, s); 6.86 (2H, d, J=9.0 Hz); 7.34 (2H, d, J=9.0 Hz); 11.26 (1H, br s).

Example 3

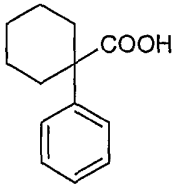
Tetrahydro-2H-pyran-2-yl 2-phenylacetate (**E5**)



To a saturated solution of anhydrous p-toluenesulphonic acid in dry dichloromethane (25 ml), phenylacetic acid (**E4**) (0.581 g, 4.26 mmol) and 3,4-dihydro-2H-pyran (3 ml, 32.9 mmol) were successively added, and the resultant solution was stirred for 1 hour at room temperature. To the reaction mixture, triethylamine (1 ml, 7.2 mmol) was added, and the volatiles were evaporated. The crude title compound was obtained and was immediately utilized in the next step of the synthesis.

Example 4

1-Phenylcyclohexanecarboxylic acid (**E7**)

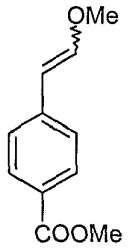


The crude tetrahydro-2H-pyran-2-yl 2-phenylacetate (**E5**) (0.581 g, 4.26 mmol)) and 1,5-dibromopentane (1.474 g, 6.41 mmol) were dissolved in dry hexamethylphosphoric triamide (6 ml) and the mixture was cooled in an ice bath. To the cooled solution 60% suspension of NaH in mineral oil (0.507 g, 12.67 mmol) was added and the reaction mixture was stirred at ice bath temperature for 15 minutes and at room temperature for 5 hours. The reaction mixture was diluted with dioxane (20 ml) and water (15 ml), and the pH of the reaction medium was brought to pH 1 with conc. HCl (3 ml). The reaction mixture was stirred for 20 minutes and poured into ethyl acetate (75 ml). The organic

layer was washed with a mixture of 2 N HCl and brine, 1:1 (2 x 50 ml), brine (50 ml), and dried (Na_2SO_4). The solvents were evaporated and the residue was chromatographed on silicagel (50 g) with benzene-ethyl acetate-acetic acid (9:1:0.1) as eluent to give a crude product. The product was re-chromatographed on silicagel (50 g) with petroleum ether-ethyl acetate-acetic acid (8:2:0.1) as eluent to give the title compound (0.414 g, 47% based on **E4**) as a white solid. ^{1}H NMR ($CDCl_3$, HMDSO) δ: 1.04-2.01 (8H, m); 2.19-2.62 (2H, m); 7.09-7.55 (5H, m), 10.29 (1H, br s).

Example 5

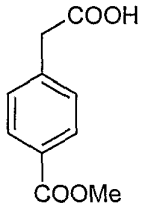
Methyl 4-(2-methoxyethenyl)benzoate (**E9**)



To a suspension of (methoxymethyl)triphenylphosphonium chloride (6.366 g, 18.5 mmol) in dry tetrahydrofuran (50 ml) under argon atmosphere at -78°C slowly (ca. for 5 minutes) a 2.46 N solution of potassium tert-butoxide in tetrahydrofuran (8.2 ml, 20.2 mmol) was added and the reaction mixture was stirred at this temperature for 1 hour. A solution of methyl 4-formylbenzoate (**E8**) (2.531 g, 15.4 mmol) in tetrahydrofuran (10 ml) was added to the reaction mixture and the resultant suspension was stirred at -78°C for 30 minutes. The cooling bath was removed and the reaction was stirred for 30 minutes allowing to warm up to room temperature. The reaction mixture was partitioned between benzene (150 ml) and water (150 ml), and the organic layer was washed successively with water (150 ml), brine (50 ml), and dried (Na_2SO_4). The solvent was evaporated and the residue was chromatographed on silicagel (100 g) with toluene-triethylamine (100:0.25) as eluent to give the title compound (2.696 g, 91%) as a mixture of E and Z isomers (ca. 95:5). (E)-(**E9**): ^{1}H NMR ($CDCl_3$, HMDSO) δ: 3.67 (3H, s); 3.86 (3H, s); 5.81 (1H, d, J=13.5 Hz); 7.14 (1H, d, J=13.5 Hz); 7.25 (2H, d, J=8.5 Hz); 7.89 (2H, d, J=8.5 Hz). A small additional singlet at 3.80 ppm and 2 doublets at 5.23 (d, J=7.6 Hz); 6.22 ppm (d, J=7.6 Hz) in the ^{1}H NMR spectrum of **E9** was attributed to minor amounts (ca. 5%) of (Z)-(**E9**) isomer present in the product.

Example 6

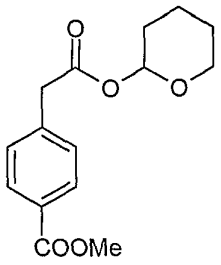
2-[4-(Methoxycarbonyl)phenyl]acetic acid (**E11**)



To a solution of methyl 4-(2-methoxyethenyl)benzoate (**E9**) (2.41 g, 12.5 mmol) in dioxane (50 ml) 1N water solution of HCl (40 ml) was added and the resultant mixture was stirred at room temperature for 12 hours. The reaction mixture was extracted with ethyl acetate (3 x 50 ml), the organic extracts were combined, washed with brine (2 x 30 ml), and dried (Na_2SO_4). The solvents were evaporated, the residue was dissolved in acetone (70 ml) and cooled to -50°C. To the cold solution at this temperature slowly (ca. for 5 minutes) 2.67 M Jones reagent (CrO_3/H_2SO_4; 7.5 ml, 20.0 mmol) was added and the obtained mixture was stirred at -40 to -50°C for 1 hour and at -30°C for 20 minutes. Isopropyl alcohol (2 ml) was added to the reaction mixture and the cooling bath was removed allowing the reaction to warm up for 10 minutes. The mixture was poured into water (150) and extracted with ethyl acetate (3 x 100 ml). The organic layers were combined, washed with brine (2 x 50), and dried (Na_2SO_4). The solvent was evaporated and the residue was dissolved in a small amount of hot dioxane (1-2 ml). Addition of petroleum ether (4-6 ml) caused the formation of a precipitate. The mixture was filtered and the precipitate was washed with dioxane-petroleum ether (1:4). The filtrate was evaporated and the precipitate formation procedure was repeated as described above. Then the filtrate was evaporated and the residue was chromatographed on silicagel (100 g) with petroleum ether-dioxane-acetic acid (2.5:7.5:0.1) to give the title compound (0.681 g, 28%) as a white solid. ^{1}H NMR ($CDCl_3$, HMDSO) δ: 3.68 (2H, s); 3.89 (3H, s); 7.33 (2H, d, J=8.2 Hz); 7.97 (2H, d, J=8.2 Hz); 10.82 (1H, br s).

Example 7

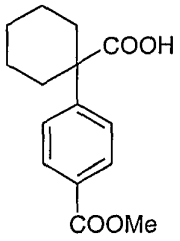
Methyl 4-[2-oxo-2-(tetrahydro-2H-pyran-2-yloxy)ethyl]benzoate (**E12**)



To a saturated solution of anhydrous p-toluenesulphonic acid in dry dichloromethane (35 ml) successively 2-[4-(methoxycarbonyl)phenyl]acetic acid (**E11**) (0.671 g, 3.45 mmol) and 3,4-dihydro-2H-pyran (3 ml, 32.9 mmol) were added, and the resultant solution was stirred for 45 minutes at room temperature. To the reaction mixture triethylamine (1 ml, 7.2 mmol) was added and the volatiles were evaporated. The obtained crude title product (1.64 g) was immediately utilized in the next step of the synthesis.

Example 8

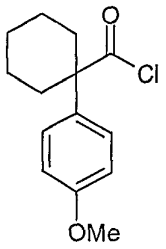
1-[4-(Methoxycarbonyl)phenyl]cyclohexanecarboxylic acid (**E14**)



The crude methyl 4-[2-oxo-2-(tetrahydro-2H-pyran-2-yl-oxy)ethyl]benzoate (**E12**) (1.64 g) (0.671 g, 3.45 mmol)) and 1,5-dibromopentane (1.200 g, 5.21 mmol) were dissolved in dry hexamethylphosphoric triamide (6 ml) and the mixture was cooled in an ice bath. To the cooled solution, a 60% suspension of NaH in mineral oil (0.425 g, 10.62 mmol) was added and the reaction mixture was stirred at ice bath temperature for 15 minutes and 1.5 hours at room temperature. The reaction mixture was diluted with dioxane (20 ml) and water (15 ml), and the pH of the medium was brought to pH 1 with conc. HCl (3 ml). The reaction mixture was stirred for 20 minutes and poured into ethyl acetate (100 ml). The organic layer was washed with 2N HCl (2 x 50 ml), brine (50 ml), and dried (Na_2SO_4). The solvents were evaporated and the residue was chromatographed on silicagel (50 g) with toluene-ethyl acetate-acetic acid (8:2:0.1) as eluent to give the title compound (0.621 g, 68.5% based on **E11**) as a white solid. ^{1}H NMR ($CDCl_3$, HMDSO) δ: 0.94-2.09 (8H, m); 2.25-2.65 (2H, m); 3.88 (3H, s); 7.49 (2H, d, J=8.6 Hz); 7.96 (2H, d, J=8.6 Hz); 10.07 (1H, br s).

Example 9

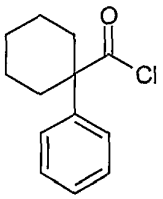
1-(4-Methoxyphenyl)cyclohexanecarbonyl chloride (**E15**)



To a solution of 1-(4-methoxyphenyl)-cyclohexanecarboxylic acid (**E3**) (0.075 g, 0.32 mmol) in dry dichloromethane (2 ml) under argon atmosphere at ice bath temperature oxalyl chloride (0.327 g, 2.57 mmol) and one drop of dimethylformamide were added. The reaction mixture was stirred at room temperature for 15 minutes and at 40°C for one hour, then concentrated under reduced pressure to give crude title product (0.082 g, ca. 100%). The crude product was immediately utilized in the next step of the synthesis without further purification.

Example 10

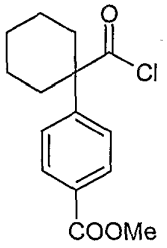
1-Phenylcyclohexanecarbonyl chloride (**E16**)



To a solution of 1-phenylcyclohexanecarboxylic acid (**E7**) (0.095 g, 0.46 mmol) in dry dichloromethane (3 ml) under argon atmosphere at ice bath temperature oxalyl chloride (0.468 g, 3.68 mmol) and one drop of dimethylformamide were added. The reaction mixture was stirred at room temperature for 15 minutes and at 40°C for one hour, then concentrated under reduced pressure to give crude title compound (0.105 g, ca. 100%). The crude product was immediately utilized in the next step of the synthesis without further purification.

Example 11

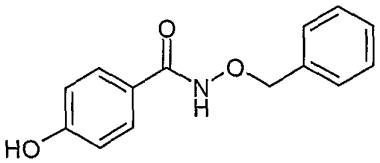
Methyl 4-[1-(chlorocarbonyl)cyclohexyl]benzoate (**E17**)



To a solution of 1-[4-(methoxycarbonyl)phenyl]-cyclohexanecarboxylic acid (**E14**) (0.174 g, 0.66 mmol) in dry dichloromethane (4 ml) under argon atmosphere at ice bath temperature oxalyl chloride (0.648 g, 5.10 mmol) and one drop of dimethylformamide were added. The reaction mixture was stirred at room temperature for 15 minutes and at 40°C for one hour, then concentrated under reduced pressure to give crude title compound (0.187 g, ca. 100%). The crude product was immediately utilized in the next step of the synthesis without further purification.

Example 12

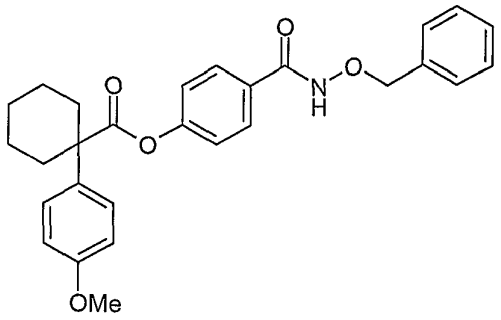
N-(Benzyloxy)-4-hydroxybenzamide (**E20**)



To a mixture of 4-hydroxybenzoic acid (**E18**) (0.424 g, 3.07 mmol), O-benzylhydroxylamine hydrochloride (**E19**) (0.490 g, 3.07 mmol), and 4-dimethylaminopyridine (0.414 g, 3.39 mmol) in dichloromethane (30 ml) under argon atmosphere, 1-(3-dimethylaminopropyl)-3-ethylcarbodiimide hydrochloride (0.643 g, 3.35 mmol) was added and the resultant mixture was stirred at room temperature for 5 hours. The reaction mixture was poured into a mixture of saturated NaH_2PO_4 (30 ml) and water (70 ml), and extracted with ethyl acetate (2 x 75 ml). The extract was washed with a mixture of saturated NaH_2PO_4 (15 ml) and water (35 ml), brine (50 ml), and dried ($MgSO_4$). The solvent was evaporated and the residue was chromatographed on silicagel (50 g) with benzene-ethyl acetate-acetic acid (75:25:1, 100 ml) and benzene-ethyl acetate-acetic acid (50:50:1, 300 ml) as eluents to give the title compound (0.338 g, 45%) as a white solid. ^{1}H NMR (DMSO-d_6, HMDSO), δ: 4.88 (2H, s); 6.79 (2H, d, J=8.8 Hz); 7.23-7.55 (5H, m); 7.59 (2H, d, J=8.8 Hz); 10.02 (1H, br s); 11.48 (1H, s).

Example 13

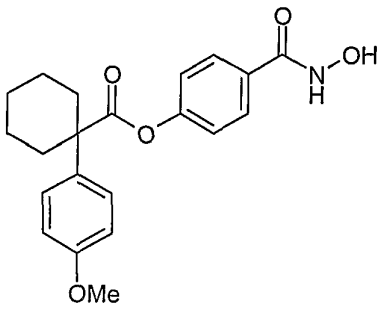
4-{[(Benzyloxy)amino]carbonyl}phenyl 1-(4-methoxyphenyl)cyclohexanecarboxylate (**E21**)



To a solution of N-(benzyloxy)-4-hydroxybenzamide (**E20**) (0.078 g, 0.32 mmol) and 4-dimethylaminopyridine (0.047 g, 0.38 mmol) in tetrahydrofuran (2 ml) under argon atmosphere at ice bath temperature a solution of 1-(4-methoxyphenyl) cyclohexanecarbonyl chloride (**E15**) (0.082 g, obtained in the preceding step of the synthesis) in tetrahydrofuran (2 ml) was added. The resultant white suspension was stirred at room temperature overnight and poured into ethyl acetate (80 ml). The ethyl acetate extract was washed with water (50 ml), brine (30 ml), and dried (Na_2SO_4). The solvent was evaporated and the residue was dissolved in a small amount of benzene (0.5-1 ml). The precipitated solid was filtered off, the filtrate was evaporated and chromatographed on silicagel (10 g) with benzene-ethyl acetate (9:1) as eluent affording the title compound (0.077 g, 52% based on **E3**) as a white solid. ^{1}H NMR (DMSO-d_6, HMDSO), δ: 1.07-2.01 (8H, m); 2.21-2.61 (2H, m, overlapped with a signal of DMSO); 3.75 (3H, s); 4.92 (2H, s); 6.97 (2H, d, J=8.5 Hz); 7.04 (2H, d, J=8.2 Hz); 7.23-7.54 (7H, m); 7.76 (2H, d, J=8.5 Hz); 11.77 (1H, s).

Example 14

4-[(Hydroxyamino)carbonyl]phenyl 1-(4-methoxyphenyl)-cyclohexanecarboxylate (**E24**) (**PX118478**)

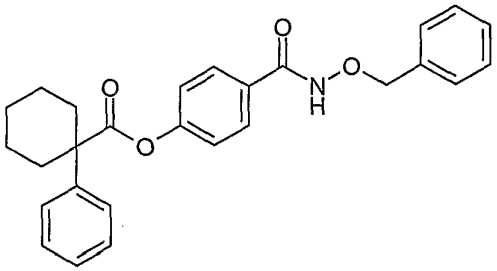


A mixture of 4-{[(benzyloxy)amino]carbonyl}phenyl 1-(4-methoxyphenyl) cyclohexanecarboxylate (**E21**) (0.072 g, 0.16 mmol) and 5% palladium on activated

carbon (0.054 g) in methanol (1 ml) was hydrogenated at room temperature for 45 minutes. The black suspension was filtered, the catalyst was washed with methanol (3 x 1 ml), and the filtrate was evaporated to give a white solid. The solid was suspended in diethyl ether (3 ml) and the mixture was intensively stirred overnight. The solid was filtered, washed with diethyl ether (1 ml), and dried in vacuum to give the title compound (0.037 g, 64%) as white crystals, m.p. 127-129°C. ^{1}H NMR (DMSO-d_6, HMDSO), δ: 1.18-1.90 (8H, m); 2.36-2.65 (2H, m, overlapped with a signal of DMSO); 3.76 (3H, s); 6.97 (2H, d, J=8.6 Hz); 7.01 (2H, d, J=8.8 Hz); 7.40 (2H, d, J=8.8 Hz); 7.77 (2H, d, J=8.6 Hz); 9.07 (1H, br s); 11.23 (1H, br s). HPLC analysis on Symmetry C_8 column: impurities 2.2 % (column size 3.9 x 150 mm; mobile phase acetonitrile - 0.1M phosphate buffer (pH 2.5), 60:40; detector UV 230 nm; sample concentration 0.3 mg/ml; flow rate 1.0 ml/min). Anal. Calcd for $C_{21}H_{23}NO_5$ * 0.3 H_2O, %: C 67.29, H 6.35, N 3.74. Found, %: C 67.29, H 6.23, N 3.76.

Example 15

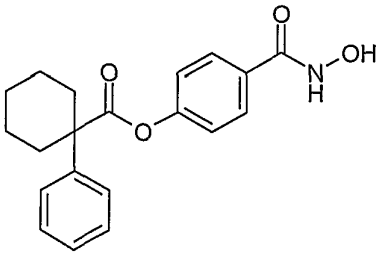
4-{[(Benzyloxy)amino]carbonyl}phenyl 1-phenylcyclohexanecarboxylate (**E22**)



To a solution of N-(benzyloxy)-4-hydroxybenzamide (**E20**) (0.100 g, 0.41 mmol) and 4-dimethylaminopyridine (0.056 g, 0.46 mmol) in tetrahydrofuran (4 ml) under argon atmosphere at ice bath temperature a solution of 1-phenylcyclohexanecarbonyl chloride (**E16**) (0.105 g, obtained in the preceding step of the synthesis) in tetrahydrofuran (2 ml) was added. The resultant white suspension was stirred at room temperature overnight and poured into ethyl acetate (100 ml). The ethyl acetate extract was washed with water (50 ml), brine (30 ml), and dried (Na_2SO_4). The solvent was evaporated and the residue was chromatographed on silicagel (10 g) with benzene-ethyl acetate (9:1) as eluent affording the title compound (0.057 g, 32% based on **E20**) as a white solid. ^{1}H NMR (DMSO-d_6, HMDSO), δ: 1.05-2.01 (8H, m); 2.23-2.61 (2H, m, overlapped with a signal of DMSO); 4.92 (2H, s); 7.06 (2H, d, J=8.6 Hz); 7.25-7.59 (10H, m); 7.77 (2H, m); 11.78 (1H, s).

Example 16

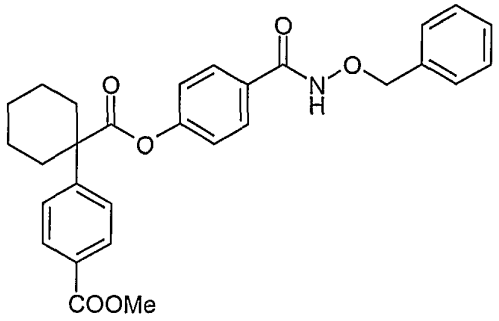
4-[(Hydroxyamino)carbonyl]phenyl 1-phenylcyclohexanecarboxylate (**E25**) (**PX118479**)



A mixture of 4-{[(benzyloxy)amino]carbonyl}phenyl 1-phenylcyclohexane-carboxylate (**E22**) (0.054 g, 0.125 mmol) and 5% palladium on activated carbon (0.038 g) in methanol (1 ml) was hydrogenated at room temperature for 45 minutes. The black suspension was filtered, the catalyst was washed with methanol (3 x 1 ml), and the filtrate was evaporated and dried in vacuum to give the title compound (0.038 g, 89%) as white crystals, m.p. 142-144°C. ^{1}H NMR (DMSO-d_6, HMDSO) δ: 1.16-1.94 (8H, m); 2.35-2.64 (2H, m, overlapped with a signal of DMSO); 7.02 (2H, d, J=8.7 Hz); 7.26-7.54 (5H, m); 7.77 (2H, d, J=8.7 Hz); 9.06 (1H, s); 11.24 (1H, br s). HPLC analysis on Symmetry C_8 column: impurities 2% (column size 3.9 x 150 mm; mobile phase acetonitrile - 0.1M phosphate buffer (pH 2.5), 50:50; detector UV 230 nm; sample concentration 0.5 mg/ml; flow rate 1.1 ml/min). Anal. Calcd for $C_{20}H_{21}NO_4 * 0.4\ H_2O$, %: C 69.31, H 6.34, N 4.04. Found, %: C 69.36, H 6.24, N 3.97.

Example 17

Methyl 4-{1-[(4-{[(benzyloxy)amino]carbonyl}phenoxy) carbonyl]cyclohexyl}benzoate (**E23**)

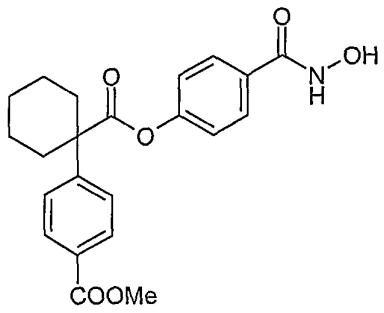


To a solution of N-(benzyloxy)-4-hydroxybenzamide (**E20**) (0.150 g, 0.61 mmol) and 4-dimethylaminopyridine (0.083 g, 0.68 mmol) in tetrahydrofuran (6 ml) under argon atmosphere at ice bath temperature a solution of methyl 4-[1-(chlorocarbonyl)cyclohexyl]benzoate (**E17**) (0.187 g, obtained in the preceding step of the

synthesis) in tetrahydrofuran (2 ml) was added. The resultant white suspension was stirred at room temperature overnight and poured into ethyl acetate (150 ml). The ethyl acetate extract was washed with water (70 ml), brine (30 ml), and dried (Na_2SO_4). The solvent was evaporated and the residue was twice chromatographed on silicagel (10 g) with petroleum ether-ethyl acetate (8:2) and (7:3) as eluents affording the title compound (0.066 g, 22% based upon **E20**) as a white solid. ^{1}H NMR (DMSO-d_6, HMDSO), δ: 1.05-2.03 (8H, m); 2.25-2.69 (2H, m, overlapped with a signal of DMSO); 3.85 (3H, s); 4.92 (2H, s); 7.07 (2H, d, J=8.6 Hz); 7.29-7.52 (5H, m); 7.65 (2H, d, J=8.3 Hz); 7.77 (2H, d, J=8.6 Hz); 8.02 (2H, d, J=8.3 Hz); 11.79 (1H, br s).

Example 18

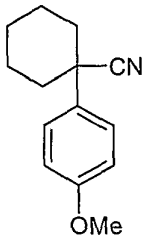
Methyl 4-[1-({4-[(hydroxyamino)carbonyl]phenoxy}carbonyl)-cyclohexyl]benzoate (**E26**) (**PX118480**)



A mixture of methyl 4-{1-[(4-{[(benzyloxy)amino]carbonyl}phenoxy)carbonyl] cyclohexyl}-benzoate (**E23**) (0.063 g, 0.129 mmol) and 5% palladium on activated carbon (0.026 g) in methanol (1 ml) was hydrogenated at room temperature for 50 minutes. The black suspension was filtered, the catalyst was washed with methanol (3 x 1 ml), and the filtrate was evaporated to give a viscous oil. The oil was converted to white crystals by stirring in diethyl ether (3 ml) overnight. The solid was filtered, washed with diethyl ether (0.5 ml), and dried in vacuum to give the title compound (0.033 g, 64%) as white crystals, m.p. 129-131°C. ^{1}H NMR (DMSO-d_6, HMDSO) δ: 1.13-1.99 (8H, m); 2.35-2.58 (2H, m, overlapped with a signal of DMSO); 3.86 (3H, s); 7.05 (2H, d, J=8.6 Hz); 7.65 (2H, d, J=8.4 Hz); 7.77 (2H, d, J=8.6 Hz); 8.01 (2H, d, J=8.4 Hz); 9.07 (1H, s); 11.25 (1H, s). HPLC analysis on Symmetry C_8 column: impurities 2.5 % (column size 3.9 x 150 mm; mobile phase acetonitrile – 0.1M phosphate buffer (pH 2.5), 60:40; detector UV 254 nm; sample concentration 0.5 mg/ml; flow rate 1.0 ml/min). Anal. Calcd for $C_{22}H_{23}NO_6 * 0.35$ H_2O, %: C 65.45, H 5.92, N 3.47. Found, %: C 65.17, H 5.76, N 3.49.

Example 19

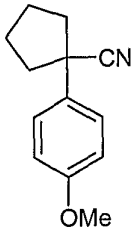
1-(4-Methoxyphenyl)cyclohexanecarbonitrile (**3a**)



To a solution of 4-methoxyphenylacetonitrile (**2**) (1.002 g, 6.8 mmol) and 1,5-dibromopentane (1.886 g, 8.2 mmol) in dry dimethylformamide (15 ml) at ice bath temperature slowly (ca. 2-3 min.) a 60% suspension of NaH in mineral oil (0.579 g, 14.4 mmol) was added. The obtained reaction mixture was stirred for 15 minutes at ice bath temperature and for 1.5 hours at room temperature, then the content was poured into benzene (75 ml). The mixture was successively washed with water (3 x 75 ml), brine (25 ml), and dried (Na_2SO_4). The solvent was evaporated and the residue was chromatographed on silica gel (50 g) with petroleum ether-ethyl acetate (5:1) as eluent to give the title compound (0.924 g, 63%) as a white solid. ^{1}H NMR ($CDCl_3$, HMDSO) δ: 1.00-2.28 (10H, m); 3.81 (3H, s); 6.90 (2H, d, J=9.0 Hz); 7.40 (2H, d, J=9.0 Hz).

Example 20

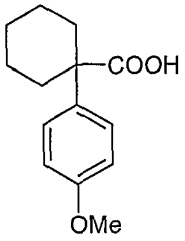
1-(4-Methoxyphenyl)cyclopentanecarbonitrile (**3b**)



The title compound was obtained from 4-methoxyphenylacetonitrile (**2**) and 1,4-dibromobutane by the method of the previous example, yield 80%. ^{1}H NMR ($CDCl_3$, HMDSO) δ: 1.61-2.68 (8H, m); 3.79 (3H, s); 6.89 (2H, d, J=9.2 Hz); 7.34 (2H, d, J=9.2 Hz).

Example 21

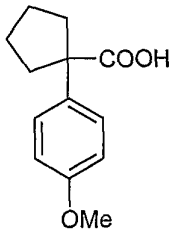
1-(4-Methoxyphenyl)cyclohexanecarboxylic acid (**1/1**)



A solution of 1-(4-methoxyphenyl)cyclohexanecarbonitrile (**6**) (1.092 g, 5.07 mmol) in dioxane (6 ml) was added to a mixture of 2M NaOH in water (150 ml) and 30% H_2O_2 in water (7.5 ml) was added and the resultant suspension was stirred under reflux for 4 days. The pH of the reaction medium was brought to pH 1 with conc. HCl (ca. 30 ml) and the obtained mixture was extracted with ethyl acetate (4 x 80 ml). The combined organic extract was washed with brine (50 ml) and dried (Na_2SO_4). The solvent was evaporated and the residue was chromatographed on silica gel (50 g) with benzene-ethyl acetate-acetic acid (9:1:0.15) as eluent affording the title compound (0.844 g, 71%) as a white solid. ^{1}H NMR ($CDCl_3$, HMDSO) δ: 1.05-1.91 (8H, m); 2.16-2.61 (2H, m); 3.76 (3H, s); 6.86 (2H, d, J=9.0 Hz); 7.34 (2H, d, J=9.0 Hz); 11.26 (1H, br s).

Example 22

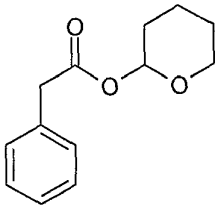
1-(4-Methoxyphenyl)-cyclopentanecarboxylic acid (**1/2**)



The title compound was obtained from 1-(4-methoxyphenyl)cyclohexanecarbonitrile (**3b**) by the method of the previous example, yield 64%. ^{1}H NMR ($CDCl_3$, HMDSO) δ: 1.48-2.14 (6H, m); 2.37-2.82 (2H, m); 3.76 (3H, s); 6.84 (2H, d, J=9.0 Hz); 7.28 (2H, d, J=9.0 Hz); 9.12 (1H, br s).

Example 23

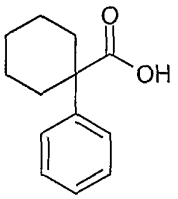
Tetrahydro-2H-pyran-2-yl 2-phenylacetate (**5a**)



To a saturated solution of anhydrous p-toluenesulphonic acid in dry dichloromethane (25 ml) successively phenylacetic acid (**4a**) (0.581 g, 4.26 mmol) and 3,4-dihydro-2H-pyran (3 ml, 32.9 mmol) were added, and the resultant solution was stirred at room temperature until the starting material **4a** disappeared (ca. 1 hour). To the reaction mixture triethylamine (1 ml, 7.2 mmol) was added and the volatiles were evaporated. The obtained crude tetrahydro-2H-pyran-2-yl 2-phenylacetate (**5a**) was immediately utilized in the next step of the synthesis.

Example 24

1-Phenylcyclohexanecarboxylic acid (**1/3**)

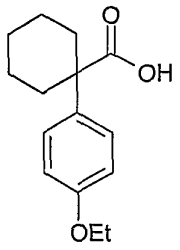


The crude tetrahydro-2H-pyran-2-yl 2-phenylacetate (**5a**) and 1,5-dibromopentane (1.474 g, 6.41 mmol) were dissolved in dry hexamethylphosphoric triamide (6 ml) and the mixture was cooled in an ice bath. To the cooled solution 60% suspension of NaH in mineral oil (0.507 g, 12.67 mmol) was added and the reaction mixture was stirred at ice bath temperature for 15 minutes and at room temperature for 5 hours. The reaction mixture was diluted with dioxane (20 ml) and water (15 ml), and the pH of the reaction medium was brought to pH 1 with conc. HCl (3 ml). The reaction mixture was stirred for 20 minutes and poured into ethyl acetate (75 ml). The organic layer was washed with a mixture of 2 N HCl and brine, 1:1 (2 x 50 ml), brine (50 ml), and dried (Na_2SO_4). The solvents were evaporated and the residue was chromatographed on silica gel (50 g) with benzene-ethyl acetate-acetic acid (9:1:0.1) as eluent to give a crude product. The product was re-chromatographed on silica gel (50 g) with petroleum ether-ethyl acetate-acetic acid (8:2:0.1) as eluent to give the title compound (0.414 g, 47% based on **4a**) as a

white solid. ^{1}H NMR ($CDCl_3$, HMDSO) δ: 1.04-2.01 (8H, m); 2.19-2.62 (2H, m); 7.09-7.55 (5H, m), 10.29 (1H, br s).

Example 25

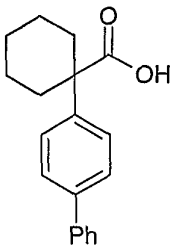
1-(4-ethoxyphenyl)cyclohexanecarboxylic acid (**1/5**),



The title compound was obtained in a manner analogous to that for 1-Phenylcyclohexanecarboxylic acid (**1/3**) starting with (4-ethoxyphenyl)acetic acid (**4b**), via tetrahydro-2H-pyran-2-yl 2-(4-ethoxyphenyl)acetate (**5b**). The crude product **1/5** was chromatographed on silica gel with toluene-ethyl acetate-acetic acid (9:1:0.1) as eluent to give 1-(4-ethoxyphenyl)cyclohexanecarboxylic acid (**1/5**) in 40% yield. ^{1}H NMR ($CDCl_3$, HMDSO) δ: ^{1}H NMR ($CDCl_3$, HMDSO) δ: 1.17-2.08 (8H, m); 1.34 (3H, t, J=7.0 Hz); 2.26-2.63 (2H, m); 4.02 (2H, q, J=7.0 Hz); 6.88 (2H, d, J=8.8 Hz); 7.36 (2H, d, J=8.8 Hz); 10.09 (1H, br s).

Example 26

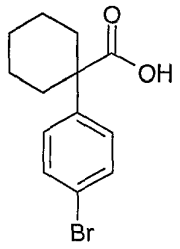
1-[1,1'-biphenyl]-4-ylcyclohexanecarboxylic acid (**1/8**),



The title compound was obtained in a manner analogous to that for 1-Phenylcyclohexanecarboxylic acid (**1/3**) starting with (1,1'-biphenyl)acetic acid (**4c**), via tetrahydro-2H-pyran-2-yl 2-(1,1'-biphenyl)acetate (**5c**). The crude product **1/8** was chromatographed on silica gel with toluene-ethyl acetate-acetic acid (9:1:0.1) as eluent to give 1-[1,1'-biphenyl]-4-ylcyclohexanecarboxylic acid (**1/8**) in 25% yield. ^{1}H NMR ($CDCl_3$, HMDSO) δ: 1.01-2.08 (8H, m); 2.23-2.67 (2H, m); 7.14-7.79 (9H, m); 10.21 (1H, br s).

Example 27

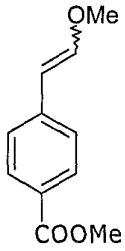
1-(4-bromophenyl)-cyclohexanecarboxylic acid (**1/9**)



The title compound was obtained in a manner analogous to that for 1-Phenylcyclohexanecarboxylic acid (**1/3**) starting with (4-bromophenyl)acetic acid (**4d**), via tetrahydro-2H-pyran-2-yl 2-(4-bromophenyl)acetate (**5d**). The crude product **1/9** was chromatographed on silica gel with petroleum ether-dioxane-acetic acid (85:15:2) and petroleum ether-tert-butylmethyl ether-acetic acid (8:2:0.1) as eluents to give 1-(4-bromophenyl)cyclohexanecarboxylic acid (**1/9**) in 25% yield. ^{1}H NMR ($CDCl_3$, HMDSO) δ: 1.17-1.92 (8H, m); 2.28-2.59 (2H, m); 7.33 (2H, d, J=8.8 Hz); 7.47 (2H, d, J=8.8 Hz); 10.34 (1H, br s).

Example 28

Methyl 4-(2-methoxyethenyl)benzoate (**7a**)

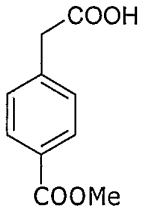


To a suspension of methoxymethyltriphenylphosphonium chloride (6.366 g, 18.5 mmol) in dry tetrahydrofuran (50 ml) under argon atmosphere at -78°C slowly (ca. for 5 minutes) a 2.46 N solution of potassium tert-butoxide in tetrahydrofuran (8.2 ml, 20.2 mmol) was added and the reaction mixture was stirred at this temperature for 1 hour. A solution of methyl 4-formylbenzoate (**6a**) (2.531 g, 15.4 mmol) in tetrahydrofuran (10 ml) was added to the reaction mixture and the resultant suspension was stirred at -78°C for 30 minutes. The cooling bath was removed and the reaction mixture was stirred for 30 minutes allowing warming up to room temperature. The mixture was partitioned between benzene (150 ml) and water (150 ml), and the organic layer was washed successively with water (150 ml), brine (50 ml), and dried (Na_2SO_4). The solvent was evaporated and the residue was chromatographed on silica gel (100 g) with toluene-triethylamine (100:0.25) as eluent

to give the title compound (2.696 g, 91%) as a mixture of E and Z isomers (ca. 95:5). (E)-(**7a**): ^{1}H NMR ($CDCl_3$, HMDSO) δ: 3.67 (3H, s); 3.86 (3H, s); 5.81 (1H, d, J=13.5 Hz); 7.14 (1H, d, J=13.5 Hz); 7.25 (2H, d, J=8.5 Hz); 7.89 (2H, d, J=8.5 Hz). A small additional singlet at 3.80 ppm and 2 doublets at 5.23 (d, J=7.6 Hz); 6.22 ppm (d, J=7.6 Hz) in the ^{1}H NMR spectrum of **7a** was attributed to minor amounts (ca. 5%) of (Z)-(**7a**) isomer present in the product.

Example 29

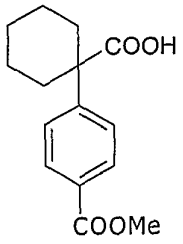
2-[4-(Methoxycarbonyl)phenyl]acetic acid (**8a**)



To a solution of methyl 4-(2-methoxyethenyl)benzoate (**7a**) (2.41 g, 12.5 mmol) in dioxane (50 ml), 1N water solution of HCl (40 ml) was added and the resultant mixture was stirred at room temperature for 12 hours. The reaction mixture was extracted with ethyl acetate (3 x 50 ml), the organic extracts were combined, washed with brine (2 x 30 ml), and dried (Na_2SO_4). The solvents were evaporated and the residue was dissolved in acetone (70 ml), and cooled to -50°C. To the cold solution at this temperature slowly (ca. for 5 minutes) 2.67 M Jones reagent (7.5 ml, 20.0 mmol) was added and the obtained mixture was stirred at -40 to -50°C for 1 hour and at -30°C for 20 minutes. Isopropyl alcohol (2 ml) was added to the reaction mixture and the cooling bath was removed allowing the reaction to warm up for 10 minutes. The mixture was poured into water (150) and extracted with ethyl acetate (3 x 100 ml). The organic layers were combined, washed with brine (2 x 50), and dried (Na_2SO_4). The solvent was evaporated and the residue was dissolved in a small amount of hot dioxane (1-2 ml). Addition of petroleum ether (4-6 ml) caused the formation of a precipitate. The mixture was filtered and the precipitate was washed with dioxane-petroleum ether (1:4). The filtrate was evaporated and the precipitate formation procedure was repeated as described above. Then the filtrate was evaporated and the residue was chromatographed on silica gel (100 g) with petroleum ether-dioxane-acetic acid (2.5:7.5:0.1) to give the title compound (0.681 g, 28%) as a white solid. ^{1}H NMR ($CDCl_3$, HMDSO) δ: 3.68 (2H, s); 3.89 (3H, s); 7.33 (2H, d, J=8.2 Hz); 7.97 (2H, d, J=8.2 Hz); 10.82 (1H, br s).

Example 30

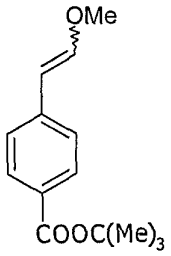
1-[4-(Methoxycarbonyl)phenyl]cyclohexanecarboxylic acid (**1/4**)



The title compound was obtained from 2-[4-(methoxycarbonyl)phenyl]acetic acid (**8a**) by the method described above for tetrahydro-2H-pyran-2-yl 2-phenylacetate (**5a**) and 1-phenylcyclohexanecarboxylic acid (**1/3**). The crude product **1/4** was chromatographed on silica gel with toluene-ethyl acetate-acetic acid (8:2:0.1) as eluent to give 1-[4-(methoxycarbonyl)phenyl]-cyclohexanecarboxylic acid (**1/4**) in 68% yield (on **8a**) as a white solid. ^{1}H NMR ($CDCl_3$, HMDSO) δ: 0.94-2.09 (8H, m); 2.25-2.65 (2H, m); 3.88 (3H, s); 7.49 (2H, d, J=8.6 Hz); 7.96 (2H, d, J=8.6 Hz); 10.07 (1H, br s).

Example 31

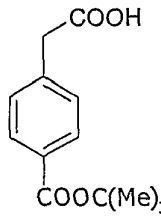
tert-Butyl 4-(2-methoxyethenyl)benzoate (**7b**)



The title compound was obtained from tert-butyl 4-formylbenzoate (**6b**) and methoxymethyltriphenylphosphonium chloride by a method analogous to that described above for methyl 4-(2-methoxyethenyl)benzoate (**7a**), in 94% yield as a mixture of E and Z isomers (ca. 3:2). (E)-(**7b**): ^{1}H NMR ($CDCl_3$, HMDSO) δ: 1.57 (9H, s); 3.70 (3H, s); 5.83 (1H, d, J=13.5 Hz); 7.14(1H, d, J=13.5 Hz); 7.26 (2H, d, J=8.8 Hz); 7.87 (2H, d, J=8.8 Hz). (Z)-(**7b**): ^{1}H NMR ($CDCl_3$, HMDSO) δ: 1.57 (9H, s); 3.81 (3H, s); 5.26 (1H, d, J=7.5 Hz); 6.23(1H, d, J=7.5 Hz); 7.60 (2H, d, J=8.4 Hz); 7.89 (2H, d, J=8.4 Hz).

Example 32

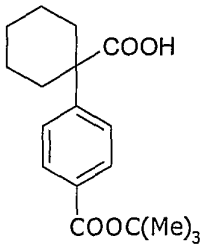
2-[4-(tert-Butoxycarbonyl)phenyl]acetic acid (**8b**)



The title compound was obtained from tert-butyl 4-(2-methoxyethenyl)benzoate (**7b**) by a method analogous to that described above for 2-[4-(methoxycarbonyl)phenyl]acetic acid (**8a**), in 55% yield. ^{1}H NMR ($CDCl_3$, HMDSO) δ: 1.58 (9H, s); 3.69 (2H, s); 7.34 (2H, d, J=8.2 Hz); 7.96 (2H, d, J=8.2 Hz); 10.12 (1H, br s).

Example 33

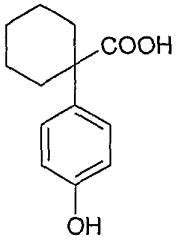
1-[4-(tert-Butoxycarbonyl)phenyl]cyclohexanecarboxylic acid (**1/6**)



The title compound was obtained from 2-[4-(tert-butoxycarbonyl)phenyl]acetic acid (**8b**) by a method analogous to that described above for 1-[4-(methoxycarbonyl)phenyl] cyclohexanecarboxylic acid (**1/4**). The crude product **1/6** was chromatographed on silica gel with petroleum ether-dioxane-acetic acid (85:15:1) as eluent to give 1-[4-(tert-butoxycarbonyl) phenyl]-cyclohexanecarboxylic acid (**1/6**) in 27% yield. ^{1}H NMR ($CDCl_3$, HMDSO) δ: 1.16-1.99 (8H, m); 1.57 (9H, s); 2.22-2.61 (2H, m); 7.51 (2H, d, J=8.4 Hz); 7.96 (2H, d, J=8.4 Hz); 10.30 (1H, br s).

Example 34

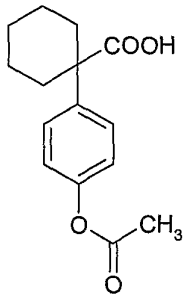
1-(4-Hydroxyphenyl)cyclohexanecarboxylic acid (**10**)



The title compound was obtained from 2-[4-(hydroxy)phenyl]acetic acid (**9**) by the method analogous to that described for 1-phenylcyclohexanecarboxylic acid (**1/3**). The crude product **10** was chromatographed on silica gel with toluene-ethyl acetate-acetic acid (9:1:0.1) as eluent to give 1-(4-hydroxyphenyl) cyclohexanecarboxylic acid (**10**). A thorough purification of the material was performed in a next step of the synthesis.

Example 35

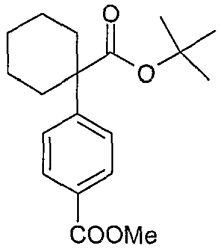
1-[4-(Acetyloxy)phenyl]cyclohexanecarboxylic acid (**1/7**)



To a solution of 1-(4-hydroxyphenyl)cyclohexanecarboxylic acid (**10**) (1.264 g crude material, obtained from 1.000 g (6.57 mmol) of **9**) in pyridine (5 ml) under argon atmosphere at 0°C acetyl chloride (0.541 g, 7.61 mmol) slowly (ca. over 10 minutes) was added and the mixture was stirred for 15 minutes at this temperature. The ice bath was removed and the reaction mixture was stirred at ambient temperature for 3 hours, then the content was poured into ice water (30 ml) and the pH of the medium was brought to 1-2 by adding conc.HCl. The mixture was extracted with ethyl acetate (2 x 40 ml), the organic extract was washed successively with water (30 ml), brine (15 ml), and dried (Na_2SO_4). The solvent was evaporated, the residue was dissolved in toluene and chromatographed on silica gel (100 g) with petroleum ether-dioxane-acetic acid (8:2:0.1) as eluent affording the title compound (0.406 g, 23.5% based on **9**) as a white solid. ^1H NMR ($CDCl_3$, HMDSO) δ: 1.06-1.98 (8H, m); 2.28 (3H, s); 2.30-2.63 (2H, m); 7.09 (2H, d, J=8.6 Hz); 7.46 (2H, d, J=8.6 Hz); 10.49 (1H, br s).

Example 36

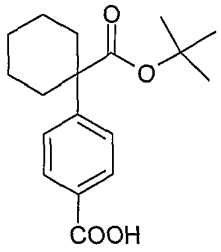
Methyl 4-[1-(tert-butoxycarbonyl)cyclohexyl]benzoate (**11**)



To a stirred solution of 1-[4-(methoxycarbonyl)phenyl]cyclohexanecarboxylic acid (**1/4**) (0.413 g, 1.57 mmol) in refluxing benzene (5 ml), N,N-dimethylformamide di-tert-butyl acetal (1.5 ml, 6.25 mmol) was added over 15 minutes. The reaction mixture was refluxed for 3 hours, then allowed to cool and diluted with benzene (50 ml). The obtained solution was washed successively with water (25 ml), brine (15 ml), and dried (Na_2SO_4). The solvent was evaporated and the residue was chromatographed on silica gel (30 g) with toluene as eluent to give the title compound (0.273 g, 54%). ^{1}H NMR ($CDCl_3$, HMDSO) δ: 1.04-2.09 (8H, m); 1.34 (9H, s); 2.22-2.60 (2H, m); 3.89 (3H, s); 7.48 (2H, d, J=8.4 Hz); 7.99 (2H, d, J=8.4 Hz).

Example 37

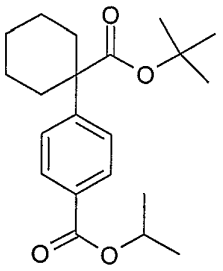
4-[1-(tert-Butoxycarbonyl)cyclohexyl]benzoic acid (**12**)



To a solution of methyl 4-[1-(tert-butoxycarbonyl)cyclohexyl]benzoate (**11**) (0.273 g, 0.86 mmol) in tetrahydrofuran (5 ml) was added 0.63 N LiOH water solution (3 ml, 1.89 mmol) and the resultant suspension was stirred at ambient temperature for 5 days. The reaction mixture was diluted with water (20 ml) and saturated NaH_2PO_4 (5 ml), and the obtained suspension was extracted with ethyl acetate (2 x 30 ml). The extract was washed with brine (15 ml), dried (Na_2SO_4), and the solvent was removed in vacuo. The residue was chromatographed on silica gel with toluene-ethyl acetate-acetic acid (8:2:01) as eluent to give the title compound (0.231 g, 88%) as a white solid. ^{1}H NMR ($CDCl_3$, HMDSO) δ: 1.07-1.91 (8H, m); 1.35 (9H, s); 2.20-2.63 (2H, m); 7.52 (2H, d, J=8.5 Hz); 8.06 (2H, d, J=8.5 Hz); 11.20 (1H, br s).

Example 38

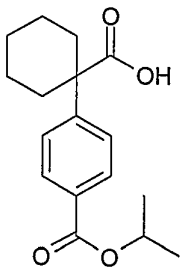
Isopropyl 4-[1-(tert-butoxycarbonyl)cyclohexyl]benzoate (**13**)



To a solution of 4-[1-(tert-butoxycarbonyl)cyclohexyl]benzoic acid (**12**) (0.219 g, 0.72 mmol) in dichloromethane (5 ml) under argon atmosphere at ice bath temperature oxalyl chloride (0.3 ml, 3.44 mmol) and a drop of dimethylformamide were added. The reaction mixture was stirred at ambient temperature for 15 minutes and at 40°C for 1 hour, then the volatiles were evaporated and the residue was dried in vacuo. The residue (0.247 g) was dissolved in tetrahydrofuran (4 ml) and 4-dimethylaminopyridine (0.176 g, 1.43 mmol) and isopropanol (0.35 ml, 4.57 mmol) were added to the resulting solution. The mixture was stirred overnight, supplemented with benzene (50 ml), successively washed with water (30 ml), brine (20 ml), and dried (Na_2SO_4). The solvents were evaporated and the residue was chromatographed on silica gel with toluene-ethyl acetate (97:3) as eluent to give the title compound (0.226 g, 91%) as an oil. ^{1}H NMR ($CDCl_3$, HMDSO) δ: 1.01-1.87 (8H, m); 1.34 (6H, d, J=6.5 Hz); 1.34 (9H, s); 2.17-2.61 (2H, m); 5.23 (1H, sept, J=6.5 Hz); 7.46 (2H, d, J=8.8 Hz); 7.98 (2H, d, J=8.8 Hz).

Example 39

1-[4-(Isopropoxycarbonyl)phenyl]cyclohexanecarboxylic acid (**1/10**)

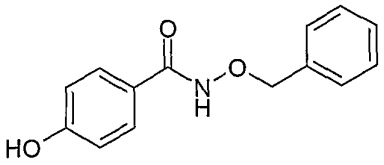


To a solution of isopropyl 4-[1-(tert-butoxycarbonyl)cyclohexyl]benzoate (**13**) (0.136 g, 0.39 mmol) in dichloromethane (1.5 ml) was added trifluoroacetic acid (0.5 ml) and the mixture was stirred at ambient temperature under argon atmosphere for 2.5 hours. The volatiles were evaporated and the residue was chromatographed on silica gel with

toluene-dioxane-acetic acid (95:5:1) as eluent to give the title compound (0.105 g, 92%). ^{1}H NMR ($CDCl_3$, HMDSO) δ: 1.04-2.03 (8H, m); 1.33 (6H, d, J=6.5 Hz); 2.26-2.63 (2H, m); 5.24 (1H, sept, J=6.5 Hz); 7.51 (2H, d, J=8.7 Hz); 8.01 (2H, d, J=8.7 Hz); 10.34 (1H, br s).

Example 40

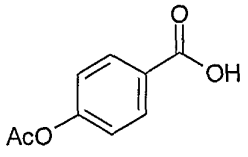
N-(Benzyloxy)-4-hydroxybenzamide (**14**)



To a mixture of 4-hydroxybenzoic acid (**16**) (0.424 g, 3.07 mmol), O-benzylhydroxylamine hydrochloride (0.490 g, 3.07 mmol), and 4-dimethylaminopyridine (0.414 g, 3.39 mmol) in dichloromethane (30 ml) under argon atmosphere 1-(3-dimethylaminopropyl)-3-ethylcarbodiimide hydrochloride (0.643 g, 3.35 mmol) was added and the resultant mixture was stirred at room temperature for 5 hours. The reaction mixture was poured into a mixture of saturated NaH_2PO_4 (30 ml) and water (70 ml), and extracted with ethyl acetate (2 x 75 ml). The extract was washed with a mixture of saturated NaH_2PO_4 (15 ml) and water (35 ml), brine (50 ml), and dried ($MgSO_4$). The solvent was evaporated and the residue was chromatographed on silica gel (50 g) with benzene-ethyl acetate-acetic acid (75:25:1, 100 ml) and benzene-ethyl acetate-acetic acid (50:50:1, 300 ml) as eluents to give the title compound (0.338 g, 45%) as a white solid. ^{1}H NMR (DMSO-d_6, HMDSO), δ: 4.88 (2H, s); 6.79 (2H, d, J=8.8 Hz); 7.23-7.55 (5H, m); 7.59 (2H, d, J=8.8 Hz); 10.02 (1H, br s); 11.48 (1H, s).

Example 41

4-(Acetyloxy)benzoic acid (**17**)

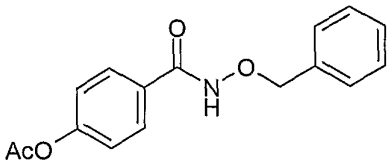


To a mixture of 4-hydroxybenzoic acid (**16**) (20.0 g, 144.8 mmol) and pyridine (60 ml, 742 mmol) at 0°C was added acetyl chloride (12 ml, 169 mol) over 5 minutes. The resulting mixture was stirred at ice bath temperature for 30 minutes and for 1 hour at room temperature. The mixture was poured into ice water (500 ml) and the pH of the medium was brought to 1-2 by adding conc. HCl (ca. 40 ml). The precipitate was filtered, washed

with water (100 ml), and dried (Na_2SO_4). The obtained solid material was crystallized from methanol-water (1:1) (200 ml) affording the title compound (21.485 g, 82.3%) as white crystals, m.p. 181-183°C. ^1H NMR ($CDCl_3$, HMDSO) δ: 2.32 (3H, s); 7.22 (2H, d, J=8.2 Hz); 8.16 (2H, d, J=8.2 Hz); 10.50 (1H, br s).

Example 42

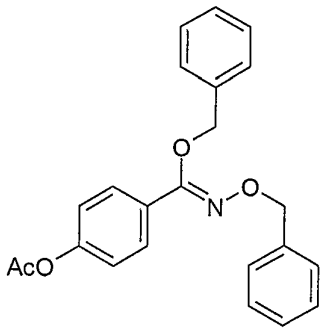
4-{[(Benzyloxy)amino]carbonyl}phenyl acetate (**18**)



To a suspension of 4-(acetyloxy)benzoic acid (**17**) (10.0 g, 55.5 mmol) in dichloromethane (200 ml) oxalyl chloride (15 ml, 172 mmol) and dimethylformamide (0.1 ml) were added. The reaction mixture was stirred at ambient temperature for 30 minutes and at reflux temperature for 1 hour. The volatiles were evaporated in vacuo, the residue was dissolved in benzene (100 ml) and the solvent was evaporated again. The procedure was repeated several times until the poignant smell disappeared after drying in vacuo. The viscous oil was dissolved in tetrahydrofuran (100 ml) and this solution slowly over 10 minutes was added to a prearranged mixture consisting of saturated $NaHCO_3$ solution (100 ml), solid $NaHCO_3$ (11 g), O-benzylhydroxylamine hydrochloride (9.90 g, 62 mmol), and tetrahydrofuran (150 ml). The resulting mixture was stirred at ambient temperature for 1 hour and the volume of the reaction mixture was decreased ca. twice by evaporating the mixture on vacuum rotary evaporator. The residue was extracted with ethyl acetate (3 x 100 ml), the combined organic extracts were successively washed with 2N HCl (100 ml), water (100 ml), brine (100 ml), and dried (Na_2SO_4). The solvents were evaporated and the residue was crystallized from toluene to give the title compound (14.275 g, 90%) as white crystals, m.p. 120-122°C. ^1H NMR ($CDCl_3$, HMDSO) δ: 2.30 (3H, s); 5.02 (2H, s); 7.14 (2H, d, J=8.6 Hz); 7.26-7.54 (5H, m); 7.69 (2H, d, J=8.6 Hz); 8.56 (1H, br s).

Example 43

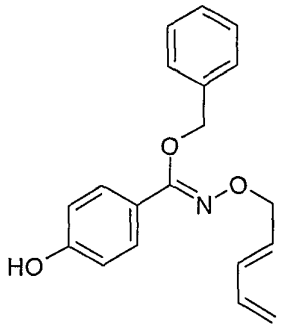
4-{(Benzyloxy)[(benzyloxy)imino]methyl}phenyl acetate (**19**)



To a solution of 4-{[(benzyloxy)amino]carbonyl}phenyl acetate (**18**) (2.000 g, 7.0 mmol) and benzyl bromide (3.59 g, 21.0 mmol) in hexamethylphosphoric triamide (10 ml) Cs_2CO_3 (2.51 g, 7.7 mmol) was added and the reaction mixture was stirred at ambient temperature for 24 hours. The mixture was diluted with benzene (50 ml) and washed successively with water (2 x 30 ml), 2N HCl (30 ml), water (2 x 30 ml), brine (30 ml), and dried (Na_2SO_4). The solvent was evaporated and the residue was chromatographed on silica gel (100 g) with petroleum ether-benzene (1:1) and benzene-ethyl acetate (9:1) as eluents to give 4-{(benzyloxy)[(benzyloxy)imino]methyl}phenyl acetate (**19**) (1.743 g, 66%) as an oil, R_f 0.83 (toluene-ethyl acetate, 9:1), and 4-{[benzyl(benzyloxy)amino]-carbonyl}phenyl acetate (**20**) (0.744 g, 28%) as a white solid, R_f 0.48 (toluene-ethyl acetate, 9:1). (**19**): ^{1}H NMR (DMSO-d_6, HMDSO) δ: 2.24 (3H, s); 5.12 (2H, s); 5.32 (2H, s); 7.17 (2H, d, J=8.7 Hz); 7.25-7.54 (10H, m); 7.66 (2H, d, J=8.7 Hz). GC-MS, m/z (%): 375 (0.2), 268 (0.3), 253 (1), 227 (0.6), 211 (1.3), 196 (0.5), 180 (2.3), 163 (19.5), 121 (36), 107 (5.2), 91 (100), 77 (6), 65 (16). IR (film, cm^{-1}): 1758, 1616, 1578, 1507. (**20**): ^{1}H NMR (DMSO-d_6, HMDSO) δ: 2.28 (3H, s); 4.72 (2H, s); 4.99 (2H, s); 6.88-7.10 (2H, m); 7.12-7.50 (8H, m); 7.22 (2H, d, J=8.0 Hz); 7.63 (2H, d, J=8.0 Hz). GC-MS, m/z (%):269 (36), 227 (27), 121 (100), 106 (25), 91 (46) , 77 (14), 65 (26). IR (nujol, cm^{-1}): 1756, 1663, 1604, 1578, 1507.

Example 44

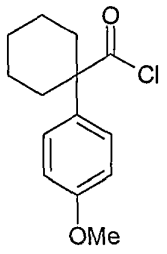
Benzyl N-(benzyloxy)-4-hydroxybenzenecarboximidoate (**15**)



To a solution of 4-{(benzyloxy)[(benzyloxy)imino]methyl}phenyl acetate (**19**) (1.671 g, 4.45 mmol) in dry methanol (30 ml) 3.43 N sodium methoxide solution in methanol (1.3 ml, 4.46 mmol) was added and the reaction mixture was stirred at ambient temperature until the starting material disappeared (ca. 1 hour). The mixture was poured into a mixture of water (60 ml) and saturated NaH_2PO_4 (30 ml), and extracted with ethyl acetate (2 x 25 ml). The extract was washed with brine (30 ml) and dried (Na_2SO_4). The solvent was evaporated and the residue was chromatographed on silicagel (50 g) with benzene-ethyl acetate (9:1) as eluent to give benzyl N-(benzyloxy)-4-hydroxybenzenecarboximidoate (**15**) (1.428 g, 96%) as an interchangeable mixture (2D TLC) of 2 isomers with R_f 0.62 and R_f 0.49 (toluene-ethyl acetate, 9:1). Major (less polar) isomer of **15**: ^{1}H NMR (DMSO-d_6, HMDSO) δ: 4.99 (2H, s); 5.09 (2H, s); 6.80 (2H, d, J=8.7 Hz); 7.27-7.53 (10H, m); 7.67 (2H, d, J=8.7 Hz); 9.96 (1H, s). Minor (more polar) isomer of **15**: ^{1}H NMR (DMSO-d_6, HMDSO) δ: 5.06 (2H, s); 5.24 (2H, s); 6.75 (2H, d, J=8.6 Hz); 7.27-7.53 (10H, m); 7.67 (2H, d, J=8.6 Hz); 9.84 (1H, s).

Example 45

1-(4-Methoxyphenyl)cyclohexanecarbonyl chloride (**21a**)

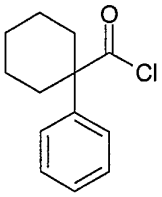


To a solution of 1-(4-methoxyphenyl)-cyclohexanecarboxylic acid (**1/1**) (0.075 g, 0.32 mmol) in dry dichloromethane (2 ml) under argon atmosphere at ice bath temperature oxalyl chloride (0.327 g, 2.57 mmol) and one drop of dimethylformamide

were added. The reaction mixture was stirred at room temperature for 15 minutes and at 40°C for 1 hour, then concentrated under reduced pressure to give crude title compound (0.082 g, ca. 100%). The crude product was immediately utilized in the next step of the synthesis without further purification.

Example 46

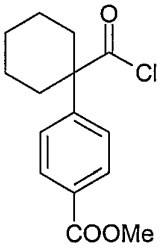
1-Phenylcyclohexanecarbonyl chloride (**21b**)



The title compound was obtained from 1-phenylcyclohexanecarboxylic acid (**1/1**) by a method analogous to that of the previous example, in ca. 100% yield. The crude product was immediately utilized in the next step of the synthesis without further purification.

Example 47

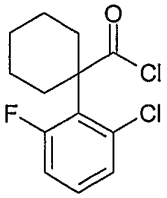
Methyl 4-[1-(chlorocarbonyl)cyclohexyl]benzoate (**21c**)



The title compound was obtained from 1-[4-(methoxycarbonyl)phenyl]-cyclohexanecarboxylic acid (**1/4**) by a method analogous to that of the previous example, in ca. 100% yield. The crude product was immediately utilized in the next step of the synthesis without further purification.

Example 48

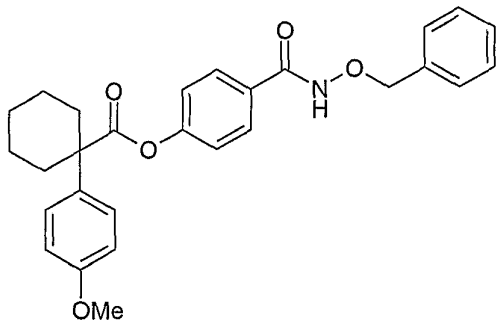
1-(2-Chloro-6-fluorophenyl)cyclohexanecarbonyl chloride (**21d**)



The title compound was obtained from 1-(2-chloro-6-fluorophenyl)cyclohexanecarboxylic acid (**1/11**) by a method analogous to that of the previous example, in ca. 100% yield. The crude product was immediately utilized in the next step of the synthesis without further purification.

Example 49

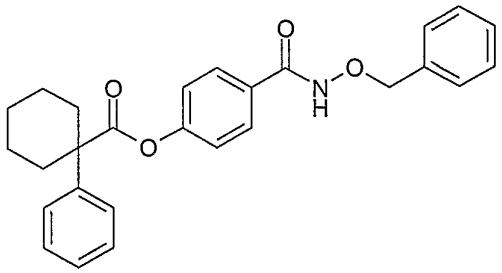
4-{[(Benzyloxy)amino]carbonyl}phenyl 1-(4-methoxyphenyl)cyclohexanecarboxylate (**22a**)



To a solution of N-(benzyloxy)-4-hydroxybenzamide (**14**) (0.078 g, 0.32 mmol) and 4-dimethylaminopyridine (0.047 g, 0.38 mmol) in tetrahydrofuran (2 ml) under argon atmosphere at ice bath temperature a solution of 1-(4-methoxyphenyl) cyclohexanecarbonyl chloride (**21a**) (0.082 g, obtained in the preceding step of the synthesis) in tetrahydrofuran (2 ml) was added. The resultant white suspension was stirred at room temperature overnight and poured into ethyl acetate (80 ml). The ethyl acetate extract was washed with water (50 ml), brine (30 ml), and dried (Na_2SO_4). The solvent was evaporated and the residue was dissolved in a small amount of benzene (0.5-1 ml). The precipitated solid was filtered off, the filtrate was evaporated and chromatographed on silicagel (10 g) with benzene-ethyl acetate (9:1) as eluent affording the title compound (0.077 g, 52% based on **1/1**) as a white solid. ^{1}H NMR (DMSO-d_6, HMDSO) δ: 1.07-2.01 (8H, m); 2.21-2.61 (2H, m, overlapped with a signal of DMSO); 3.75 (3H, s); 4.92 (2H, s); 6.97 (2H, d, J=8.5 Hz); 7.04 (2H, d, J=8.2 Hz); 7.23-7.54 (7H, m); 7.76 (2H, d, J=8.5 Hz); 11.77 (1H, s).

Example 50

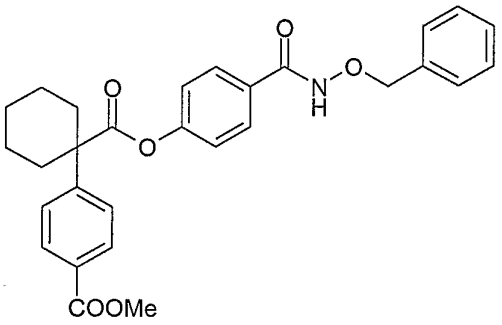
4-{[(Benzyloxy)amino]carbonyl}phenyl 1-phenylcyclohexanecarboxylate (**22b**)



The title compound was obtained from N-(benzyloxy)-4-hydroxybenzamide (**14**) and 1-phenylcyclohexanecarbonyl chloride (**21b**) by a method analogous to that of the previous example, in 32% yield (on **14**) as a white solid. ^{1}H NMR (DMSO-d_6, HMDSO) δ: 1.05-2.01 (8H, m); 2.23-2.61 (2H, m, overlapped with a signal of DMSO); 4.92 (2H, s); 7.06 (2H, d, J=8.6 Hz); 7.25-7.59 (10H, m); 7.77 (2H, m); 11.78 (1H, s).

Example 51

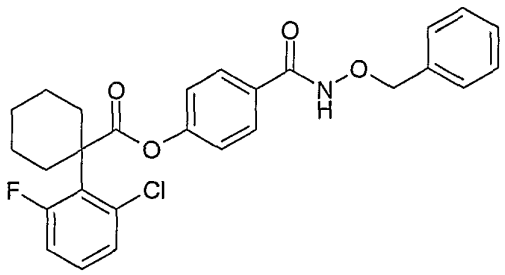
Methyl 4-{1-[(4-{[(benzyloxy)amino]carbonyl}phenoxy)carbonyl]cyclohexyl}benzoate (**22c**)



The title compound was obtained from N-(benzyloxy)-4-hydroxybenzamide (**14**) and methyl 4-[1-(chlorocarbonyl)cyclohexyl]benzoate (**21c**) by a method analogous to that of the previous example, in 22% yield (on **14**) as a white solid. ^{1}H NMR (DMSO-d_6, HMDSO) δ: 1.05-2.03 (8H, m); 2.25-2.69 (2H, m, overlapped with a signal of DMSO); 3.85 (3H, s); 4.92 (2H, s); 7.07 (2H, d, J=8.6 Hz); 7.29-7.52 (5H, m); 7.65 (2H, d, J=8.3 Hz); 7.77 (2H, d, J=8.6 Hz); 8.02 (2H, d, J=8.3 Hz); 11.79 (1H, br s).

Example 52

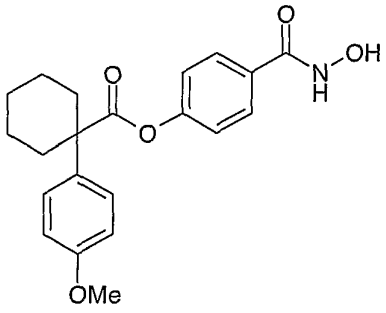
4-{[(Benzyloxy)amino]carbonyl}phenyl 1-(2-chloro-6-fluorophenyl)cyclohexanecarboxylate (**22d**)



The title compound was obtained from N-(benzyloxy)-4-hydroxybenzamide (**14**) and 1-(2-chloro-6-fluorophenyl)cyclohexanecarbonyl chloride (**21d**) by a method analogous to that of the previous example, in 44% yield (on **14**). ^{1}H NMR ($CDCl_3$, HMDSO) δ: 1.17-2.02 (6H, m); 2.20-2.60 (4H, m); 4.99 (2H, s); 6.83-7.78 (3H, m); 7.07 (2H, d, J=8.4 Hz); 7.37 (5H, s); 7.63 (2H, d, J=8.4 Hz); 8.38 (1H, br s).

Example 53

4-[(Hydroxyamino)carbonyl]phenyl 1-(4-methoxyphenyl)-cyclohexanecarboxylate (**PX118478**)

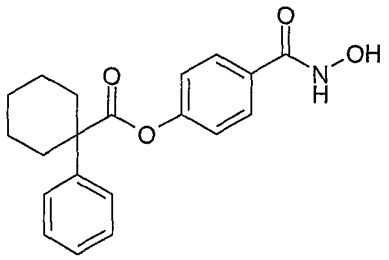


A mixture of 4-{[(benzyloxy)amino]carbonyl}phenyl 1-(4-methoxyphenyl) cyclohexanecarboxylate (**22a**) (0.072 g, 0.16 mmol) and 5% palladium on activated carbon (0.054 g) in methanol (1 ml) was hydrogenated at room temperature until the starting material disappeared (ca. 45 minutes). The black suspension was filtered, the catalyst was washed with methanol (3 x 1 ml), and the filtrate was evaporated to give a white solid. The solid was suspended in diethyl ether (3 ml) and the mixture was intensively stirred overnight. The solid was filtered, washed with diethyl ether (1 ml), and dried in vacuum to give the title compound (0.037 g, 64%) as white crystals, m.p. 127-129°C. ^{1}H NMR (DMSO-d_6, HMDSO) δ: 1.18-1.90 (8H, m); 2.36-2.65 (2H, m, overlapped with a signal of DMSO); 3.76 (3H, s); 6.97 (2H, d, J=8.6 Hz); 7.01 (2H, d, J=8.8 Hz); 7.40

(2H, d, J=8.8 Hz); 7.77 (2H, d, J=8.6 Hz); 9.07 (1H, br s); 11.23 (1H, br s). HPLC analysis on Symmetry C_8 column: impurities 2.2 % (column size 3.9 x 150 mm; mobile phase acetonitrile - 0.1M phosphate buffer (pH 2.5), 60:40; detector UV 230 nm; sample concentration 0.3 mg/ml; flow rate 1.0 ml/min). Anal. Calcd for $C_{21}H_{23}NO_5 * 0.3\ H_2O$, %: C 67.29, H 6.35, N 3.74. Found, %: C 67.29, H 6.23, N 3.76.

Example 54

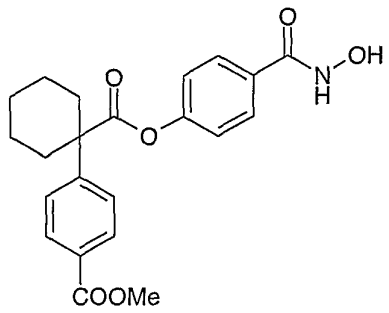
4-[(Hydroxyamino)carbonyl]phenyl 1-phenylcyclohexanecarboxylate (**PX118479**)



The title compound was obtained from 4-{[(benzyloxy)amino]carbonyl}phenyl 1-phenylcyclohexanecarboxylate (**22b**) by a method analogous to that of the previous example, in 89% yield as white crystals, m.p. 142-144°C. ^{1}H NMR (DMSO-d_6, HMDSO) δ: 1.16-1.94 (8H, m); 2.35-2.64 (2H, m, overlapped with a signal of DMSO); 7.02 (2H, d, J=8.7 Hz); 7.26-7.54 (5H, m); 7.77 (2H, d, J=8.7 Hz); 9.06 (1H, s); 11.24 (1H, br s). HPLC analysis on Symmetry C_8 column: impurities 2% (column size 3.9 x 150 mm; mobile phase acetonitrile – 0.1M phosphate buffer (pH 2.5), 50:50; detector UV 230 nm; sample concentration 0.5 mg/ml; flow rate 1.1 ml/min). Anal. Calcd for $C_{20}H_{21}NO_4 * 0.4\ H_2O$, %: C 69.31, H 6.34, N 4.04. Found, %: C 69.36, H 6.24, N 3.97.

Example 55

Methyl 4-[1-({4-[(hydroxyamino)carbonyl]phenoxy}carbonyl)-cyclohexyl]benzoate (**PX118480**)

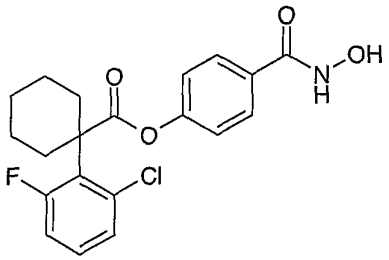


The title compound was obtained from methyl 4-{1-[(4-{[(benzyloxy)amino]carbonyl} phenoxy)carbonyl]cyclohexyl}-benzoate (**22c**) by a method analogous to that of the

previous example, in 64% yield as white crystals, m.p. 129-131°C. ^{1}H NMR (DMSO-d_6, HMDSO) δ: 1.13-1.99 (8H, m); 2.35-2.58 (2H, m, overlapped with a signal of DMSO); 3.86 (3H, s); 7.05 (2H, d, J=8.6 Hz); 7.65 (2H, d, J=8.4 Hz); 7.77 (2H, d, J=8.6 Hz); 8.01 (2H, d, J=8.4 Hz); 9.07 (1H, s); 11.25 (1H, s). HPLC analysis on Symmetry C_8 column: impurities 2.5 % (column size 3.9 x 150 mm; mobile phase acetonitrile – 0.1M phosphate buffer (pH 2.5), 60:40; detector UV 254 nm; sample concentration 0.5 mg/ml; flow rate 1.0 ml/min). Anal. Calcd for $C_{22}H_{23}NO_6 * 0.35\ H_2O$, %: C 65.45, H 5.92, N 3.47. Found, %: C 65.17, H 5.76, N 3.49.

Example 56

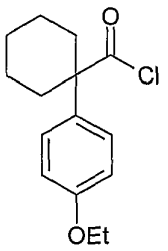
4-[(Hydroxyamino)carbonyl]phenyl 1-(2-chloro-6-fluorophenyl)-cyclohexanecarboxylate (**PX119101**)



The title compound was obtained from methyl 4-{[(benzyloxy)amino]carbonyl}phenyl 1-(2-chloro-6-fluorophenyl)cyclohexanecarboxylate (**22d**) by a method analogous to that of the previous example. The crude product after filtration and evaporation of methanol was chromatographed on silica gel with chloroform-methanol (95:5) as eluent and crystallized from dichloromethane-petroleum ether (1:3) at -18°C to give the compound **PX119101** in 45% yield, m.p. 101-102°C. ^{1}H NMR (DMSO-d_6, HMDSO) δ: 1.10-1.92 (6H, m); 2.27-2.60 (4H, m, overlapped with a signal of DMSO); 7.13 (2H, d, J=8.4 Hz); 7.07-7.80 (3H, m); 7.80 (2H, d, J=8.4 Hz); 9.08 (1H, s); 11.26 (1H, s). HPLC analysis on Omnispher C_{18} column: impurities 1% (column size 4.6 x 150 mm; mobile phase acetonitrile – 0.1M phosphate buffer (pH 2.5), 60:40; detector UV 210 nm; sample concentration 1.0 mg/ml; flow rate 1.0 ml/min). Anal. Calcd for $C_{20}H_{19}ClFNO_4$, %: C 61.31, H 4.89, N 3.57. Found, %: C 61.22, H 4.86, N 3.41.

Example 57

1-(4-Ethoxyphenyl)cyclohexanecarbonyl chloride (**23a**)



The title compound was obtained from 1-(4-ethoxyphenyl)cyclohexanecarboxylic acid (**1/5**) by a method analogous to that described for 1-(4-methoxyphenyl)cyclohexanecarbonyl chloride (**21a**), in ca. 100% yield. The crude product was immediately utilized in the next step of the synthesis without further purification.

Example 58

tert-Butyl 4-[1-(chlorocarbonyl)cyclohexyl]benzoate (**23b**)

The title compound was obtained from 1-[4-(tert-butoxycarbonyl)phenyl] cyclohexanecarboxylic acid (**1/12**) by a method analogous to that described for the previous example, in ca. 100% yield. The crude product was immediately utilized in the next step of the synthesis without further purification.

Example 59

1-(4-Acetoxyphenyl)cyclohexanecarbonyl chloride (**23c**)

The title compound was obtained from 1-(4-acetoxyphenyl)cyclohexanecarboxylic acid (**1/7**) by a method analogous to that described the previous example, in ca. 100% yield. The crude product was immediately utilized in the next step of the synthesis without further purification.

Example 60

1-(4-Methylphenyl)cyclohexanecarbonyl chloride (**23d**)

The title compound was obtained from 1-(4-methylphenyl)cyclohexanecarboxylic acid (**1/13**) by a method analogous to that described for the previous example, in ca. 100% yield. The crude product was immediately utilized in the next step of the synthesis without further purification.

Example 61

1-[1,1'-Biphenyl]-4-ylcyclohexanecarbonyl chloride (**23e**)

The title compound was obtained from 1-[1,1'-biphenyl]-4-ylcyclohexanecarboxylic acid (**1/14**) by a method analogous to that described for the previous example, in ca. 100% yield. The crude product was immediately utilized in the next step of the synthesis without further purification.

Example 62

1-(4-Chlorophenyl)cyclohexanecarbonyl chloride (**23f**)

The title compound was obtained from 1-(4-chlorophenyl)cyclohexanecarboxylic acid (**1/15**) by a method analogous to that described for the previous example, in ca. 100% yield. The crude product was immediately utilized in the next step of the synthesis without further purification.

Example 63

1-(3-Fluorophenyl)cyclohexanecarbonyl chloride (**23g**)

The title compound was obtained from 1-(3-fluorophenyl)cyclohexanecarboxylic acid (**1/16**) by a method analogous to that described for the previous example, in ca. 100% yield. The crude product was immediately utilized in the next step of the synthesis without further purification.

Example 64

1-(2-Fluorophenyl)cyclohexanecarbonyl chloride (**23h**)

The title compound was obtained from 1-(2-fluorophenyl)cyclohexanecarboxylic acid (**1/17**) by a method analogous to that described the previous example, in ca. 100% yield. The crude product was immediately utilized in the next step of the synthesis without further purification.

Example 65

1-(2-Chloro-4-fluorophenyl)cyclohexanecarbonyl chloride (**23i**)

The title compound was obtained from 1-(2-chloro-4-fluorophenyl)cyclohexanecarboxylic acid (**1/18**) by a method analogous to that described the previous example, in ca. 100% yield. The crude product was immediately utilized in the next step of the synthesis without further purification.

Example 66

1-(4-Fluorophenyl)cyclohexanecarbonyl chloride (**23j**)

The title compound was obtained from 1-(4-fluorophenyl)cyclohexanecarboxylic acid (**1/19**) by a method analogous to that described for the previous example, in ca. 100% yield. The crude product was immediately utilized in the next step of the synthesis without further purification.

Example 67

1-(4-Bromophenyl)cyclohexanecarbonyl chloride (**23k**)

The title compound was obtained from 1-(4-bromophenyl)cyclohexanecarboxylic acid (**1/9**) by a method analogous to that described for the previous example, in ca. 100% yield. The crude product was immediately utilized in the next step of the synthesis without further purification.

Example 68

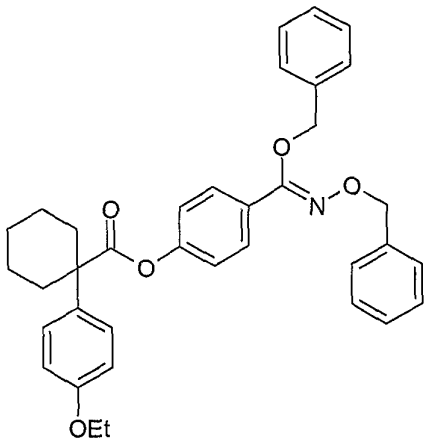
Isopropyl 4-[1-(chlorocarbonyl)cyclohexyl]benzoate (**23l**)

The title compound was obtained from 1-[4-(isopropoxycarbonyl)phenyl] cyclohexanecarboxylic acid (**1/10**) by a method analogous to that described for the previous example, in ca. 100% yield. The crude product was immediately utilized in the next step of the synthesis without further purification.

Example 69

4-{(Benzyloxy)[(benzyloxy)imino]methyl}phenyl 1-(4-ethoxyphenyl)cyclohexanecarboxylate

(**24a**)



The title compound was obtained from benzyl N-(benzyloxy)-4-hydroxybenzenecarboximidoate (**15**) and 1-(4-ethoxyphenyl)cyclohexanecarbonyl chloride (**23a**) by a method analogous to that described for 4-{[(Benzyloxy)amino]carbonyl}phenyl 1-(4-methoxyphenyl)cyclohexanecarboxylate (**22a**), in 68% yield (on **1/5**) in a form of 2 individual (slow equilibrium of interchange) isomers (87:13). Major (less polar) isomer of **24a**: ^{1}H NMR ($CDCl_3$, HMDSO) δ: 1.17-1.92 (8H, m); 1.39 (3H, t, J=7.0 Hz); 2.05-2.77 (2H, m); 4.03 (2H, q, J=7.0 Hz); 5.01 (2H, s); 5.12 (2H, s); 6.92 (2H, d, J=8.8 Hz); 6.94 (2H, d, J=8.8 Hz); 7.32 (10H, s); 7.42 (2H, d, J=8.8 Hz); 7.84 (2H, d, J=8.8 Hz). Minor (more polar) isomer of **24a**: ^{1}H NMR ($CDCl_3$, HMDSO) δ: 1.10-1.91 (8H, m); 1.39 (3H, t, J=7.0 Hz); 2.10-2.73 (2H, m); 4.03 (2H, q, J=7.0 Hz); 5.12 (2H, s); 5.30 (2H, s); 6.89 (2H, d, J=8.8 Hz); 6.91 (2H, d, J=8.8 Hz); 7.32-7.51 (12H, m); 7.63 (2H, d, J=8.8 H

Example 70

tert-Butyl 4-{1-[(4-{(benzyloxy)[(benzyloxy)imino]methyl}phenoxy)carbonyl]cyclohexyl}benzoate (**24b**)

The title compound was obtained from benzyl N-(benzyloxy)-4-hydroxybenzenecarboximidoate (**15**) and tert-butyl 4-[1-(chlorocarbonyl) cyclohexyl]benzoate (**23b**) by a method analogous to that described for the previous example, in 76% yield (on **1/12**). ^{1}H NMR ($CDCl_3$, HMDSO) δ: 1.15-1.92 (8H, m); 1.57

(9H, s); 2.25-2.77 (2H, m); 5.00 (2H, s); 5.12 (2H, s); 6.93 (2H, d, J=8.2 Hz); 7.21-7.47 (10H, m); 7.56 (2H, d, J=8.5 Hz); 7.80 (2H, d, J=8.2 Hz); 8.00 (2H, d, J=8.5 Hz).

Example 71

4-{(Benzyloxy)[(benzyloxy)imino]methyl}phenyl 1-[4-(acetyloxy)phenyl]cyclohexanecarboxylate (**24c**)

The title compound was obtained from benzyl N-(benzyloxy)-4-hydroxybenzenecarboximidoate (**15**) and 1-(4-acetoxyphenyl)cyclohexanecarbonyl chloride (**23c**) by a method analogous to that described for the previous example, in 95% (on **1/7**). ^{1}H NMR ($CDCl_3$, HMDSO) δ: 1.21-1.88 (8H, m); 2.23 (3H, s); 2.32-2.68 (2H, m); 4.88 (2H, s); 5.00 (2H, s); 6.78 (2H, d, J=8.8 Hz); 6.94 (2H, d, J=8.8 Hz); 7.01-7.28 (10H, m); 7.32 (2H, d, J=8.8 Hz); 7.66 (2H, d, J=8.8 Hz).

Example 72

4-{(Benzyloxy)[(benzyloxy)imino]methyl}phenyl 1-(4-methylphenyl)cyclohexanecarboxylate

(**24d**)

The title compound was obtained from benzyl N-(benzyloxy)-4-hydroxybenzenecarboximidoate (**15**) and 1-(4-methylphenyl)cyclohexanecarbonyl chloride (**23d**) by a method analogous to that described for the previous example, in 51% (on **1/13**) as a mixture of 2 isomers (76:24). Major (less polar) isomer of **24d**: ^{1}H NMR ($CDCl_3$, HMDSO) δ: 1.19-2.01 (8H, m); 2.12-2.74 (2H, m); 2.30 (3H, s); 4.97 (2H, s); 5.10 (2H, s); 6.93 (2H, d, J=8.8 Hz); 7.03-7.56 (14H, m); 7.82 (2H, d, J=8.8 Hz). Minor (more polar) isomer of **24d**: ^{1}H NMR ($CDCl_3$, HMDSO) δ: 1.18-2.08 (8H, m); 2.17-2.79 (2H, m); 2.32 (3H, s); 5.11 (2H, s); 5.28 (2H, s); 6.88 (2H, d, J=9.0 Hz); 7.04-7.56 (14H, m); 7.64 (2H, d, J=9.0 Hz).

Example 73

4-{(Benzyloxy)[(benzyloxy)imino]methyl}phenyl 1-[1,1'-biphenyl]-4-ylcyclohexanecarboxylate

(**24e**)

The title compound was obtained from benzyl N-(benzyloxy)-4-hydroxybenzenecarboximidoate (**15**) and 1-[1,1'-biphenyl]-4-ylcyclohexanecarbonyl

chloride (**23e**) by a method analogous to that described for the previous example, in 73% yield (on **1/14**). ^{1}H NMR ($CDCl_3$, HMDSO) δ: 1.06-2.10 (8H, m); 2.41-2.88 (2H, m); 4.99 (2H, s); 5.11 (2H, s); 6.96 (2H, d, J=8.8 Hz); 7.14-7.74 (19H, m); 7.79 (2H, d, J=8.8 Hz).

Example 74

4-{(Benzyloxy)[(benzyloxy)imino]methyl}phenyl 1-(4-chorophenyl)cyclohexanecarboxylate (**24f**)

The title compound was obtained from benzyl N-(benzyloxy)-4-hydroxybenzenecarboximidoate (**15**) and 1-(4-chlorophenyl)cyclohexanecarbonyl chloride (**23f**) by a method analogous to that described for the previous example, in 70% yield (on **1/15**) as a mixture of 2 isomers (92:8). Major isomer of **24f**: ^{1}H NMR ($CDCl_3$, HMDSO) δ: 1.14-1.98 (8H, m); 2.31-2.78 (2H, m); 4.99 (2H, s); 5.11 (2H, s); 6.90 (2H, d, J=8.8 Hz); 7.09-7.53 (14H, m); 7.80 (2H, d, J=8.8 Hz).

Example 75

4-{(Benzyloxy)[(benzyloxy)imino]methyl}phenyl 1-(3-fluorophenyl)cyclohexanecarboxylate (**24g**)

The title compound was obtained from benzyl N-(benzyloxy)-4-hydroxybenzenecarboximidoate (**15**) and 1-(3-fluorophenyl)cyclohexanecarbonyl chloride (**23g**) by a method analogous to that described for the previous example, in 66% yield (on **1/16**) as a mixture of 2 isomers (93:7). Major isomer of **24g**: ^{1}H NMR ($CDCl_3$, HMDSO) δ: 1.08-1.97 (8H, m); 2.30-2.78 (2H, m); 5.00 (2H, s); 5.12 (2H, s); 6.79-7.52(14H, m); 6.94 (2H, d, J=8.8 Hz); 7.83 (2H, d, J=8.8 Hz).

Example 76

4-{(Benzyloxy)[(benzyloxy)imino]methyl}phenyl 1-(2-fluorophenyl)cyclohexanecarboxylate (**24h**)

The title compound was obtained from benzyl N-(benzyloxy)-4-hydroxybenzenecarboximidoate (**15**) and 1-(2-fluorophenyl)cyclohexanecarbonyl chloride (**23h**) by a method analogous to that described for the previous example, in 66% yield (on **1/17**) as a mixture of 2 isomers (98:2). Major isomer of **24h**: ^{1}H NMR ($CDCl_3$, HMDSO) δ: 1.10-2.12 (8H, m); 2.25-2.67 (2H, m); 4.99 (2H, s); 5.11 (2H, s); 6.90-7.61 (14H, m); 7.00 (2H, d, J=8.8 Hz); 7.82 (2H, d, J=8.8 Hz).

Example 77

4-{(Benzyloxy)[(benzyloxy)imino]methyl}phenyl 1-(2-chloro-4-fluorophenyl)cyclohexanecarboxylate (**24i**)

The title compound was obtained from benzyl N-(benzyloxy)-4-hydroxybenzenecarboximidoate (**15**) and 1-(2-chloro-4-fluorophenyl)cyclohexanecarbonyl chloride (**23i**) by a method analogous to that described for the previous example, in 85% yield (on **1/18**) as a mixture of 2 isomers (98:2). Major isomer of **24i**: ^{1}H NMR ($CDCl_3$, HMDSO) δ: 1.10-2.18 (8H, m); 2.18-2.71 (2H, m); 5.00 (2H, s); 5.12 (2H, s); 6.74-7.63 (13H, m); 7.00 (2H, d, J=8.8 Hz); 7.82 (2H, d, J=8.8 Hz).

Example 78

4-{(Benzyloxy)[(benzyloxy)imino]methyl}phenyl 1-(4-fluorophenyl-)cyclohexanecarboxylate (**24j**)

The title compound was obtained from benzyl N-(benzyloxy)-4-hydroxybenzenecarboximidoate (**15**) and 1-(4-fluorophenyl)cyclohexanecarbonyl chloride (**23j**) by a method analogous to that described for the previous example, in 90% yield (on **1/19**) as a mixture of 2 isomers (98:2). Major isomer of **24j**: ^{1}H NMR ($CDCl_3$, HMDSO) δ: 1.05-1.95 (8H, m); 2.31-2.77 (2H, m); 4.99 (2H, s); 5.11 (2H, s); 6.70-7.58 (14H, m); 6.89 (2H, d, J=8.8 Hz); 7.81 (2H, d, J=8.8 Hz).

Example 79

4-{(Benzyloxy)[(benzyloxy)imino]methyl}phenyl 1-(4-bromophenyl)cyclohexanecarboxylate (**24k**)

The title compound was obtained from benzyl N-(benzyloxy)-4-hydroxybenzenecarboximidoate (**15**) and 1-(4-bromophenyl)cyclohexanecarbonyl chloride (**23k**) by a method analogous to that described for the previous example, in 90% yield (on **1/9**) as a mixture of 2 isomers (81:19). Major (less polar) isomer of **24k**: ^{1}H NMR ($CDCl_3$, HMDSO) δ: 1.17-1.97 (8H, m); 2.39-2.73 (2H, m); 5.01 (2H, s); 5.12 (2H, s); 6.92 (2H, d, J=8.5 Hz); 7.26-7.50 (10H, m); 7.36 (2H, d, J=8.8 Hz); 7.48 (2H, d, J=8.8 Hz); 7.82 (2H, d, J=8.5 Hz). Minor (more polar) isomer of **24k**: ^{1}H NMR ($CDCl_3$, HMDSO) δ: 1.12-1.92 (8H, m); 2.28-2.65 (2H, m); 5.12 (2H, s); 5.29 (2H, s); 6.86 (2H, d, J=8.5 Hz); 7.14-7.42 (12H, m); 7.49 (2H, d, J=8.8 Hz); 7.62 (2H, d, J=8.5 Hz)

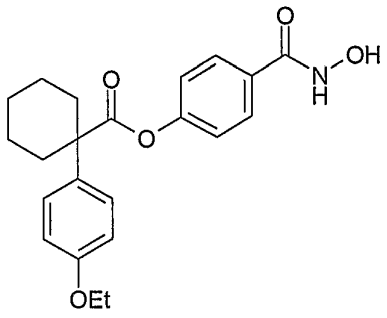
Example 80

Isopropyl 4-{1-[(4-{(benzyloxy)[(benzyloxy)imino]methyl}phenoxy)carbonyl]cyclohexyl}benzoate (**24l**)

The title compound was obtained from benzyl N-(benzyloxy)-4-hydroxybenzenecarboximidoate (**15**) and isopropyl 4-[1-(chlorocarbonyl)cyclohexyl]benzoate (**23l**) by a method analogous to that described for the previous example, in 94% yield (on **1/10**) as a mixture of 2 isomers (96:4). Major (less polar) isomer of **24l**: ^{1}H NMR ($CDCl_3$, HMDSO) δ: 1.14-1.93 (8H, m); 1.34 (6H, d, J=6.5 Hz); 2.39-2.79 (2H, m); 5.00 (2H, s); 5.12 (2H, s); 5.25 (1H, sept, J=6.5 Hz); 6.91 (2H, d, J=8.0 Hz); 7.31 (5H, s); 7.34 (5H, m); 7.55 (2H, d, J=8.4 Hz); 7.81 (2H, d, J=8.0 Hz); 8.03 (2H, d, J=8.4 Hz). Minor (more polar) isomer of **24l**: ^{1}H NMR ($CDCl_3$, HMDSO) δ: 1.03-2.13 (8H, m); 1.34 (6H, d, J=6.0 Hz); 2.33-2.80 (2H, m); 4.94-5.40 (1H, m); 5.12 (2H, s); 5.30 (2H, s); 6.85 (2H, d, J=8.2 Hz); 7.21-7.47 (10H, m); 7.55 (2H, d, J=8.5 Hz); 7.63 (2H, d, J=8.2 Hz); 8.04 (2H, d, J=8.5 Hz).

Example 81

4-[(Hydroxyamino)carbonyl]phenyl 1-(4-ethoxyphenyl)-cyclohexanecarboxylate (**PX118925**)

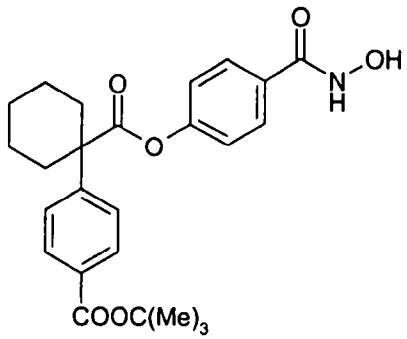


The title compound was obtained from 4-{(benzyloxy)[(benzyloxy)imino]methyl}phenyl 1-(4-ethoxyphenyl)cyclohexane-carboxylate (**24a**) by a method analogous to that described for 4-[(hydroxyamino)carbonyl]phenyl 1-(4-methoxyphenyl)-cyclohexanecarboxylate (**PX118478**). After filtration of the catalyst and evaporation of methanol the crude product was crystallized from diethyl ether to give the title compound in 31% yield, m.p. 140-143°C. ^{1}H NMR (DMSO-d_6, HMDSO) δ: 1.23-1.85 (8H, m); 1.32 (3H, t, J=6.8 Hz); 2.34-2.55 (2H, m, overlapped with a signal of DMSO); 4.01 (2H, q, J=6.8 Hz); 6.95 (2H, d, J=8.8 Hz); 7.00 (2H, d, J=8.6 Hz); 7.38 (2H, d, J=8.8 Hz); 7.76 (2H, d, J=8.6 Hz); 9.05 (1H, s); 11.23 (1H, s). HPLC analysis on Kromasil 100 C_{18} column: impurities 4% (column

size 4.6 x 150 mm; mobile phase acetonitrile – 0.1M phosphate buffer (pH 2.5), 60:40; detector UV 230 nm; sample concentration 1.0 mg/ml; flow rate 1.5 ml/min). Anal. Calcd for $C_{22}H_{25}NO_5$, %: C 68.91, H 6.57, N 3.65. Found, %: C 68.85, H 6.57, N 3.67.

Example 82

tert-Butyl 4-[1-({4-[(hydroxyamino)carbonyl]phenoxy}-carbonyl)cyclohexyl]benzoate (**PX118926**)

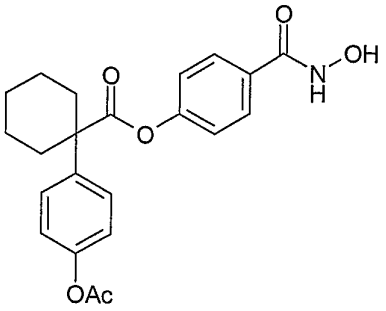


The title compound was obtained from tert-butyl 4-{1-[(4-{(benzyloxy)[(benzyloxy)imino] methyl}phenoxy)carbonyl]-cyclohexyl}benzoate (**24b**) by a method analogous to that described for the previous example, using methanol-dioxane (2:1) as a solvent. After filtration of the catalyst and evaporation of methanol-dioxane mixture the crude product was crystallized from dichloromethane-petroleum ether (1:1) to give the title compound in 75% yield, m.p. 143-147°C (dec.). ^{1}H NMR ($CDCl_3$, HMDSO) δ: 1.23-1.94 (8H, m); 1.59 (9H, s); 2.51-2.68 (2H, m); 6.98 (2H, d, J=8.0 Hz); 7.53 (2H, d, J=8.4 Hz); 7.69 (2H, d, J=8.0 Hz); 7.75 (1H, br s); 7.99 (2H, d, J=8.4 Hz); 8.73 (1H, br s). HPLC analysis on Alltima C_{18} column: impurities 3.5% (column size 4.6 x 150 mm; mobile phase acetonitrile – 0.1M phosphate buffer (pH 2.5), 70:30; detector UV 230 nm; sample concentration 0.5 mg/ml; flow rate 1.2 ml/min; column temperature 40°C). Anal. Calcd for $C_{25}H_{29}NO_6 * 0.2$ H_2O containing 2% of inorganic impurities, %: C 66.41, H 6.55, N 3.10. Found, %: C 66.44, H 6.58, N 3.06.

Example 83

4-[(Hydroxyamino)carbonyl]phenyl 1-[4-(acetyloxy)phenyl]-cyclohexanecarboxylate

(**PX118959**)

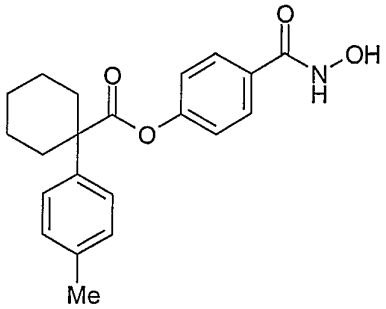


The title compound was obtained from 4-{(benzyloxy)[(benzyloxy)imino]methyl}phenyl 1-[4-(acetyloxy)phenyl]-cyclohexanecarboxylate (**24c**) by a method analogous to that described for the previous example, using methanol-dioxane (2:1) as a solvent. After filtration of the catalyst and evaporation of methanol-dioxane the crude product was chromatographed on silica gel with petroleum ether-ethyl acetate (1:1) and chloroform-methanol (98:2) as eluents and crystallized from diethyl ether to give the title compound in 50% yield, m.p. 69°C. ^{1}H NMR (DMSO-d_6, HMDSO) δ: 1.22-1.91 (8H, m); 2.27 (3H, s); 2.33-2.62 (2H, m, overlapped with a signal of DMSO); 7.04 (2H, d, J=8.5 Hz); 7.17 (2H, d, J=8.6 Hz); 7.52 (2H, d, J=8.6 Hz); 7.78 (2H, d, J=8.5 Hz); 9.05 (1H, d, J=1.6 Hz); 11.24 (1H, s). HPLC analysis on Zorbax SB-C_{18} column: impurities 7% [the compound contained ca. 5% of a deacetylated analogue (i.e. 4-[(hydroxyamino)carbonyl]phenyl 1-[4-(hydroxy)phenyl]-cyclohexanecarboxylate) as a major impurity] (column size 4.6 x 150 mm; mobile phase acetonitrile – 0.1% H_3PO_4, gradient 10 min from 1:1 to 100:0; detector UV 230 nm; sample concentration 0.5 mg/ml; flow rate 1.5 ml/min). Anal. Calcd for $C_{22}H_{23}NO_6 * 0.5\ H_2O$, %: C 65.01, H 5.95, N 3.45. Found, %: C 64.88, H 5.88, N 3.16.

Example 84

4-[(Hydroxyamino)carbonyl]phenyl 1-(4-methylphenyl)-cyclohexanecarboxylate

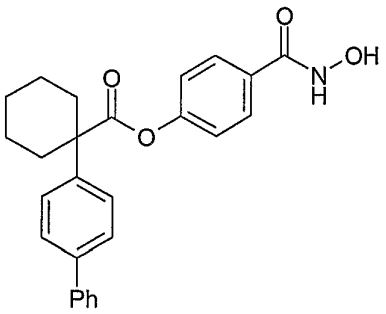
(**PX118966**)



The title compound was obtained from 4-{(benzyloxy)[(benzyloxy)imino]methyl}phenyl 1-(4-methylphenyl)cyclohexane-carboxylate (**24d**) by a method analogous to that described for the previous example, using methanol-dioxane (2:1) as a solvent. After filtration of the catalyst and evaporation of methanol-dioxane the crude product was chromatographed on silica gel with chloroform-methanol (96:4) as eluent to give the title compound in 28% yield, m.p. 59-60°C. ^{1}H NMR (DMSO-d_6, HMDSO) δ: 1.22-1.91 (8H, m); 2.27 (3H, s); 2.33-2.62 (2H, m, overlapped with a signal of DMSO); 7.04 (2H, d, J=8.5 Hz); 7.17 (2H, d, J=8.6 Hz); 7.52 (2H, d, J=8.6 Hz); 7.78 (2H, d, J=8.5 Hz); 9.05 (1H, d, J=1.6 Hz); 11.24 (1H, s). HPLC analysis on Alltima C_{18} column: impurities 1% (column size 4.6 x 150 mm; mobile phase acetonitrile – 0.1M phosphate buffer (pH 2.5), 70:30; detector UV 215 nm; sample concentration 1.0 mg/ml; flow rate 1.0 ml/min). Anal. Calcd for $C_{21}H_{23}NO_4 * 0.5$ H_2O, %: C 69.60, H 6.67, N 3.86. Found, %: C 69.91, H 6.65, N 3.62.

Example 85

4-[(Hydroxyamino)carbonyl]phenyl 1-[1,1'-biphenyl]-4-yl-cyclohexanecarboxylate (**PX119058**)



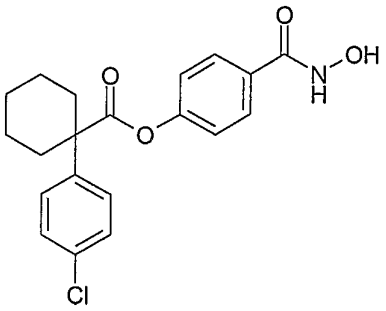
The title compound was obtained from 4-{(benzyloxy)[(benzyloxy)imino] methyl}phenyl 1-[1,1'-biphenyl]-4-ylcyclohexanecarboxylate (**24e**) by a method analogous to that described for the previous example, using dioxane as a solvent. After filtration of the catalyst and evaporation of the solvent the crude product was chromatographed on silica gel with chloroform-methanol (96:4) as eluent to give the title compound in 76% yield, foam. ^{1}H NMR (DMSO-d_6, HMDSO) δ: 1.18-1.98 (8H, m); 2.43-2.64 (2H, m, overlapped with a signal of DMSO); 7.07 (2H, d, J=8.7 Hz); 7.37 (1H, t, J=7.1 Hz); 7.48 (2H, t, J=7.3 Hz); 7.58 (2H, d, J=8.4 Hz); 7.69 (2H, d, J=8.0 Hz); 7.73 (2H, d, J=8.4 Hz); 7.78 (2H, d, J=8.7 Hz); 9.06 (1H, s); 11.24 (1H, s). HPLC analysis on Omnispher C_{18} column: impurities 1.5% (column size 4.6 x 150 mm; mobile phase acetonitrile – 0.1M phosphate buffer (pH 2.5), 60:40; detector UV 220 nm; sample concentration 1.0 mg/ml; flow rate 1.5 ml/min).

Anal. Calcd for $C_{26}H_{25}NO_4 * 0.4$ MeOH $*$ 0.1 EtOAc), %: C 73.64, H 6.32, N 3.20. Found, %: C 73.54, H 6.11, N 3.19.

Example 86

4-[(Hydroxyamino)carbonyl]phenyl 1-(4-chlorophenyl)-cyclohexanecarboxylate

(**PX119059**)

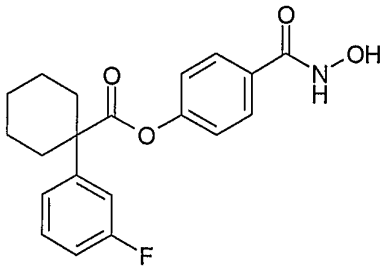


The title compound was obtained from 4-{(benzyloxy)[(benzyloxy)imino] methyl}phenyl 1-(4-chlorophenyl)cyclohexane-carboxylate (**24f**) by a method analogous to that described for the previous example, using dioxane as a solvent. After filtration of the catalyst and evaporation of the solvent the crude product was crystallized from diethyl ether to give the title compound in 58% yield, m.p. 145-146°C. ^{1}H NMR (DMSO-d_6, HMDSO) δ: 1.20-1.95 (8H, m); 2.37-2.58 (2H, m, overlapped with a signal of DMSO); 7.04 (2H, d, J=8.5 Hz); 7.48 (2H, d, J=9.0 Hz); 7.51 (2H, d, J=9.0 Hz); 7.78 (2H, d, J=8.5 Hz); 9.07 (1H, s); 11.25 (1H, s). HPLC analysis on Alltima C_{18} column: impurities 3% (column size 4.6 x 150 mm; mobile phase acetonitrile – 0.1M phosphate buffer (pH 2.5), 55:45; detector UV 254 nm; sample concentration 1.0 mg/ml; flow rate 1.5 ml/min). Anal. Calcd for $C_{20}H_{20}ClNO_4$, %: C 64.26, H 5.39, N 3.75. Found, %: C 63.91, H 5.36, N 3.70.

Example 87

4-[(Hydroxyamino)carbonyl]phenyl 1-(3-fluorophenyl)-cyclohexanecarboxylate

(**PX119061**)

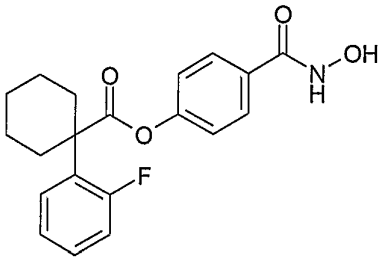


The title compound was obtained from 4-{(benzyloxy)[(benzyloxy)imino] methyl}phenyl 1-(3-fluorophenyl)cyclohexane-carboxylate (**24g**) by a method analogous to that described for the previous example, using dioxane as a solvent. After filtration of the catalyst and evaporation of the solvent the crude product was washed with diethyl ether to give the pure title compound in 61% yield, m.p. 150-151°C. ^{1}H NMR (DMSO-d_6, HMDSO)δ: 1.15-1.95 (8H, m); 2.39-2.57 (2H, m, overlapped with a signal of DMSO); 7.04 (2H, d, J=8.6 Hz); 7.17 (1H, ddt, J=0.9, 2.7 and 8.4 Hz); 7.29 (1H, dt, J=8.0 and 2.2 Hz); 7.30-7.37 (1H, m); 7.48 (1H, dt, J=6.4 and 8.3 Hz); 7.78 (2H, d, J=8.6 Hz); 9.05 (1H, s); 11.23 (1H, br s). HPLC analysis on Alltima C_{18} column: impurities 1% (column size 4.6 x 150 mm; mobile phase acetonitrile – 0.1M phosphate buffer (pH 2.5), 50:50; detector UV 215 nm; sample concentration 1.0 mg/ml; flow rate 1.5 ml/min). Anal. Calcd for $C_{20}H_{20}FNO_4$, %: C 67.22, H 5.64, N 3.92. Found, %: C 66.67, H 5.65, N 3.85

Example 88

4-[(Hydroxyamino)carbonyl]phenyl 1-(2-fluorophenyl)-cyclohexanecarboxylate

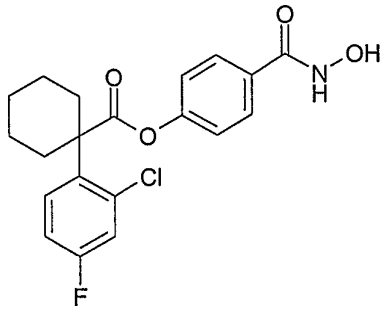
(**PX119062**)



The title compound was obtained from 4-{(benzyloxy)[(benzyloxy)imino] methyl}phenyl 1-(2-fluorophenyl)cyclohexane-carboxylate (**24h**) by a method analogous to that described for the previous example, using dioxane as a solvent. After filtration of the catalyst and evaporation of the solvent the crude product was chromatographed on silica gel with chloroform-methanol (96:4) as eluent and crystallized from diethyl ether to give the title compound in 93% yield, m.p. 125-126°C. ^{1}H NMR (DMSO-d_6, HMDSO) δ: 1.26-1.55 (1H, m); 1.56-2.14 (7H, m); 2.26-2.48 (2H, m); 7.05 (2H, d, J=8.5 Hz); 7.17-7.47 (3H, m); 7.60 (1H, dt, J=2.1 and 8.0 Hz); 7.79 (2H, d, J=8.5 Hz); 9.06 (1H, s); 11.24 (1H, s). HPLC analysis on Omnispher 5 C_{18} column: impurities 1% (column size 4.6 x 150 mm; mobile phase acetonitrile – 0.1M phosphate buffer (pH 2.5), 55:45; detector UV 215 nm; sample concentration 1.0 mg/ml; flow rate 1.5 ml/min). Anal. Calcd for $C_{20}H_{20}FNO_4$, %: C 67.22, H 5.64, N 3.92. Found, %: C 67.15, H 5.57, N 3.84.

Example 89

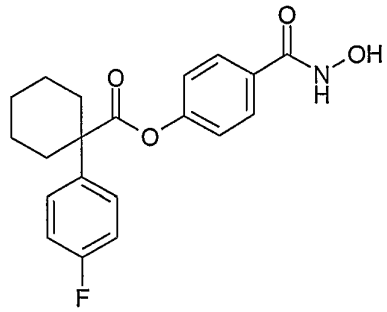
4-[(Hydroxyamino)carbonyl]phenyl 1-(2-chloro-4-fluorophenyl)-cyclohexanecarboxylate (**PX119064**)



The title compound was obtained from 4-{(benzyloxy)[(benzyloxy)imino] methyl}phenyl 1-(2-chloro-4-fluorophenyl)cyclohexane-carboxylate (**24i**) by a method analogous to that described for the previous example, using dioxane as a solvent. After filtration of the catalyst and evaporation of the solvent the crude product was crystallized from diethyl ether to give the title compound in 53% yield, m.p. 164-165°C. ^{1}H NMR (DMSO-d_6, HMDSO) δ: 1.28-1.52 (1H, m); 1.52-2.11 (7H, m); 2.34-2.60 (2H, m, overlapped with a signal of DMSO); 7.09 (2H, d, J=8.6 Hz); 7.29 (1H, ddd, J=2.8, 8,1 and 8.9 Hz); 7.50 (1H, dd, J=2.8 and 8.6 Hz); 7.73 (1H, dd, J=6.1 and 8.9 Hz); 7.78 (2H, d, J=8.6 Hz); 9.05 (1H, s); 11.23 (1H, s). HPLC analysis on Alltima C18 column: impurities 2% (column size 4.6 x 150 mm; mobile phase acetonitrile – 0.1M phosphate buffer (pH 2.5), 50:50; detector UV 215 nm; sample concentration 1.0 mg/ml; flow rate 1.5 ml/min). Anal. Calcd for $C_{20}H_{19}ClFNO_4$, %: C 61.31, H 4.89, N 3.57. Found, %: C 61.31, H 4.99, N 3.37.

Example 90

4-[(Hydroxyamino)carbonyl]phenyl 1-(4-fluorophenyl)-cyclohexanecarboxylate (**PX119065**)

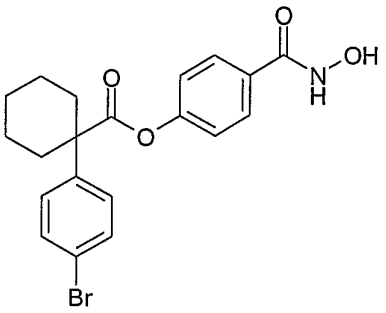


The title compound was obtained from 4-{(benzyloxy)[(benzyloxy)imino] methyl}phenyl 1-(4-fluorophenyl)cyclohexane-carboxylate (**24j**) by a method analogous to that described for the previous example, using dioxane as a solvent. After filtration of the catalyst and

evaporation of the solvent the crude product was crystallized from diethyl ether to give the title compound in 86% yield, m.p. 150-151°C. ^{1}H NMR (DMSO-d_6, HMDSO) δ: 1.16-1.94 (8H, m); 2.39-2.61 (2H, m, overlapped with a signal of DMSO); 7.03 (2H, d, J=8.5 Hz); 7.24 (2H, t, J=8.9 Hz); 7.53 (2H, dd, J=5.4 and 8.9 Hz); 7.78 (2H, d, J=8.5 Hz); 9.06 (1H, s); 11.24 (1H, s). HPLC analysis on Alltima C18 column: impurities 1% (column size 4.6 x 150 mm; mobile phase acetonitrile – 0.1M phosphate buffer (pH 2.5), 50:50; detector UV 215 nm; sample concentration 1.0 mg/ml; flow rate 1.5 ml/min). Anal. Calcd for $C_{20}H_{20}FNO_4$, %: C 67.22, H 5.64, N 3.92. Found, %: C 66.89, H 5.66, N 3.92.

Example 91

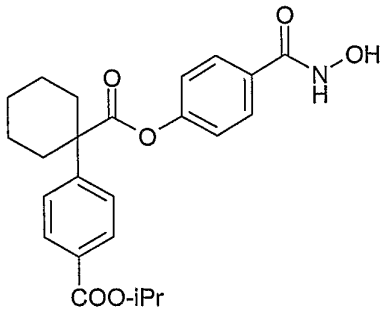
4-[(Hydroxyamino)carbonyl]phenyl 1-(4-bromophenyl)-cyclohexanecarboxylate (**PX119084**)



The title compound was obtained from 4-{(benzyloxy)[(benzyloxy)imino] methyl}phenyl 1-(4-bromophenyl)cyclohexane-carboxylate (**24k**) by a method analogous to that described for the previous example, using methanol-dioxane (2:1) as a solvent. After filtration of the catalyst and evaporation of methanol-dioxane the crude product was chromatographed on silica gel with petroleum ether-ethyl acetate (3:2) as eluent to give the title compound in 46% yield, foam. According to analytical data (^{1}H NMR, elemental analysis) the product contained ca. 12-15% of the debrominated analogue, i.e., 4-[(hydroxyamino)carbonyl]-phenyl 1-phenylcyclohexanecarboxylate (**PX118479**) as an impurity. ^{1}H NMR (DMSO-d_6, HMDSO) δ: 1.16-1.94 (8H, m); 2.34-2.56 (2H, m, overlapped with a signal of DMSO); 7.04 (2H, d, J=8.6 Hz); 7.45 (2H, d, J=8.6 Hz); 7.61 (2H, d, J=8.6 Hz); 7.77 (2H, d, J=8.6 Hz); 9.05 (1H, s); 11.24 (1H, s). HPLC analysis on Chromolith Performance RP-18 C column: impurities 13% (column size 3.9 x 150 mm; mobile phase acetonitrile – 0.1% H_3PO_4, 60:40; detector UV 254 nm; sample concentration 0.5 mg/ml; flow rate 2 ml/min). Anal. Calcd for $C_{20}H_{20}BrNO_4 * 0.12\ C_{20}H_{21}NO_4$, %: C 58.61, H 4.94, N 3.35. Found, %: C 58.59, H 4.87, N 3.42.

Example 92

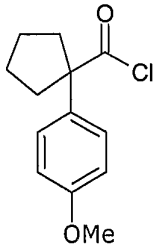
Isopropyl 4-[1-({4-[(hydroxyamino)carbonyl]phenoxy}-carbonyl)cyclohexyl]benzoate (**PX119100**)



The title compound was obtained from isopropyl 4-{1-[(4-{(benzyloxy)[(benzyloxy) imino]methyl}phenoxy)carbonyl]-cyclohexyl}benzoate (**24l**) by a method analogous to that described for the previous example, using methanol-dioxane (2:1) as a solvent. After filtration of the catalyst and evaporation of methanol-dioxane the crude product was chromatographed on silica gel with chloroform-methanol (96:4) as eluent to give the title compound in 44% yield, foam. ^{1}H NMR (DMSO-d_6, HMDSO) δ: 1.09-1.98 (8H, m); 1.32 (6H, d, J=6.2 Hz); 2.38-2.60 (2H, m, overlapped with a signal of DMSO); 5.14 (1H, septet, J=6.2 Hz); 7.06 (2H, d, J=8.4 Hz); 7.65 (2H, d, J=8.4 Hz); 7.77 (2H, d, J=8.4 Hz); 8.00 (2H, d, J=8.4 Hz); 9.07 (1H, s); 11.25 (1H, s). HPLC analysis on Chromolith RP-18C column: impurities 6.6% (column size 4.6 x 100 mm; mobile phase acetonitrile – 0.1% H_3PO_4, 70:30; detector UV 254 nm; sample concentration 1 mg/ml; flow rate 1 ml/min). Anal. Calcd for $C_{24}H_{27}NO_6 * 0.4\ H_2O$, %: C 66.62, H 6.48, N 3.24. Found, %: C 66.77, H 6.36, N 3.03.

Example 93

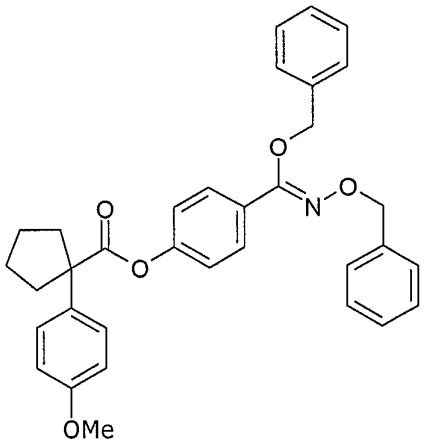
1-(4-Methoxyphenyl)cyclopentanecarbonyl chloride (**25**)



The title compound was obtained from 1-(4-methoxyphenyl) cyclopentanecarboxylic acid (**1/2**) by a method analogous to that described for 1-(4-methoxyphenyl) cyclohexanecarbonyl chloride (**21a**), in ca. 100% yield. The crude product was immediately utilized in the next step of the synthesis without further purification.

Example 94

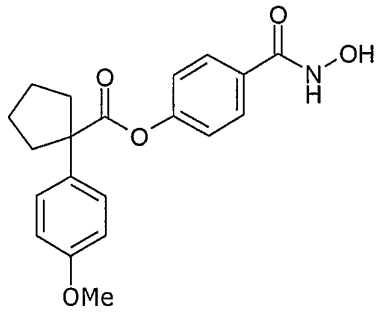
4-{(Benzyloxy)[(benzyloxy)imino]methyl}phenyl 1-(4-methoxyphenyl) cyclopentanecarboxylate (**26**)



The title compound was obtained from benzyl N-(benzyloxy)-4-hydroxybenzenecarboximidoate (**15**) and 1-(4-methoxyphenyl) cyclopentanecarbonyl chloride (**25**) by a method analogous to that described for 4-{[(benzyloxy)amino]carbonyl} phenyl 1-(4-methoxyphenyl) cyclohexanecarboxylate (**22a**), in 65% yield (on **1/2**) as a mixture of 2 isomers (94:6). Major (less polar) isomer of **26**: ^{1}H NMR ($CDCl_3$, HMDSO) δ: 1.50-2.19 (6H, m); 2.51-2.92 (2H, m); 3.78 (3H, s); 4.99 (2H, s); 5.11 (2H, s); 6.86 (2H, d, J=8.8 Hz); 6.89 (2H, d, J=8.8 Hz); 7.17-7.47 (12H, m); 7.79 (2H, d, J=8.8 Hz).

Example 95

4-[(Hydroxyamino)carbonyl]phenyl 1-(4-methoxyphenyl)-cyclopentanecarboxylate (**PX119063**)

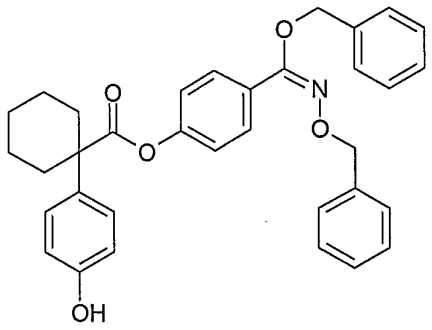


The title compound was obtained from 4-{(benzyloxy)[(benzyloxy)imino] methyl}phenyl 1-(4-methoxyphenyl)-cyclopentanecarboxylate (**26**) by a method analogous to that described for 4-[(Hydroxyamino)carbonyl]phenyl 1-(4-methoxyphenyl)-cyclohexanecarboxylate (**PX118478**), using dioxane as a solvent. After filtration of the

catalyst and evaporation of the solvent the crude product was washed with diethyl ether to give the title compound in 78% yield as crystals, m.p. 143-144°C. ^{1}H NMR (DMSO-d_6, HMDSO) δ: 1.61-1.86 (4H, m); 1.86-2.08 (2H, m); 2.54-2.74 (2H, m); 3.75 (3H, s); 6.95 (2H, d, J=8.7 Hz); 7.01 (2H, d, J=8.5 Hz); 7.38 (2H, d, J=8.7 Hz); 7.75 (2H, d, J=8.5 Hz); 9.04 (1H, s); 11.22 (1H, s). HPLC analysis on Alltima C_{18} column: impurities 2% (column size 4.6 x 150 mm; mobile phase acetonitrile – 0.1M phosphate buffer (pH 2.5), 50:50; detector UV 230 nm; sample concentration 1.0 mg/ml; flow rate 1.5 ml/min). Anal. Calcd for $C_{20}H_{21}NO_5$ * 0.1 EtOAc, %: C 67.28, H 6.03, N 3.85. Found, %: C 67.00, H 5.96, N 3.78.

Example 96

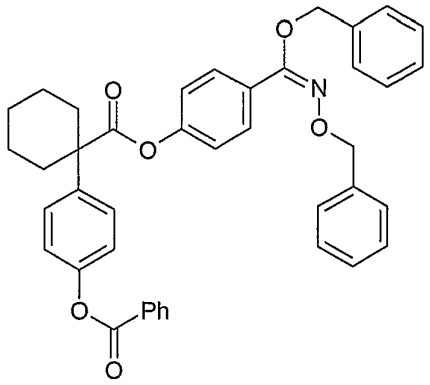
4-{(Benzyloxy)[(benzyloxy)imino]methyl}phenyl 1-(4-hydroxyphenyl) cyclohexanecarboxylate (**27**)



To a solution of 4-{(benzyloxy)[(benzyloxy)imino]methyl}-phenyl 1-[4-(acetyloxy)phenyl]-cyclohexanecarboxylate (**24c**) (0.429 g, 0.74 mmol) in tetrahydrofuran (5 ml) under argon atmosphere at ice bath temperature 2.46 N potassium 2-methyl-2-butanolate solution in tetrahydrofuran (0.32 ml, 0.79 mmol) slowly (ca. over 3 minutes) was added and the reaction mixture was stirred at this temperature for 1.5 hours. The mixture was poured into a mixture of ice water (30 ml) and saturated NaH_2PO_4 solution (5 ml), extracted with benzene (2 x 25 ml), the organic extract was washed with brine (15 ml), and dried (Na_2SO_4). The solvent was evaporated and the residue was chromatographed on silica gel (25 g) with toluene-ethyl acetate (95:5) as eluent to give the title compound (0.354 g, 89%) as a mixture of 2 isomers. The prevailing isomer of **27**: ^{1}H NMR ($CDCl_3$, HMDSO) δ: 1.12-1.97 (8H, m); 2.29-2.74 (2H, m); 4.97 (2H, s); 5.08 (2H, s); 6.75 (2H, d, J=8.8 Hz); 6.88 (2H, d, J=8.8 Hz); 7.21-7.49 (12H, m); 7.79 (2H, d, J=8.8 Hz).

Example 97

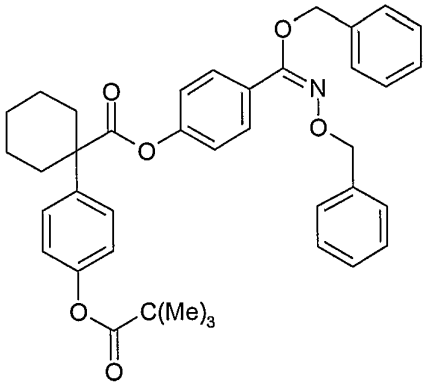
4-{1-[(4-{(Benzyloxy)[(benzyloxy)imino]methyl}phenoxy)carbonyl]cyclohexyl}phenyl benzoate (**28a**)



To a solution of 4-{(benzyloxy)[(benzyloxy)imino]methyl}phenyl 1-(4-hydroxyphenyl)-cyclohexanecarboxylate (**27**) (0.189 g, 0.35 mmol) and benzoyl chloride (0.049 ml, 0.42 mmol) in tetrahydrofuran (4 ml) under argon atmosphere at ice bath temperature 4-dimethylaminopyridine (0.052 g, 0.42 mmol) was added. The resulting mixture was stirred at room temperature until the starting material **27** disappeared (ca. 2 hours) and then supplemented with benzene (25 ml). The obtained mixture was washed successively with water (25 ml), brine (15 ml), and dried (Na_2SO_4). The solvents were evaporated and the residue was chromatographed on silica gel with petroleum ether-toluene (1:2) as eluent to give the title compound as a mixture of 2 isomers (7:3). ^{1}H NMR ($CDCl_3$, HMDSO) δ: 1.15-1.91 (8H, m); 2.41-2.72 (2H, m); 5.02 (2H· 0.7, s); 5.06 (2H· 0.3, s); 5.12 (2H· 0.7, s); 5.16 (2H· 0.3, s); 6.94 (2H· 0.7, d, J=8.8 Hz); 7.27-7.42 (12H+2H· 0.3, m); 7.45-7.69 (5H, m); 7.84 (2H· 0.7, d, J=8.8 Hz); 7.94 (2H· 0.3, d, J=8.8 Hz); 8.15-8.24 (2H, m).

Example 98

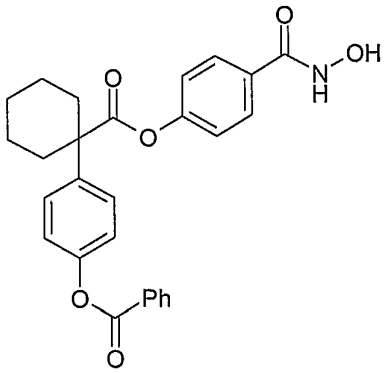
4-{(Benzyloxy)[(benzyloxy)imino]methyl}phenyl 1-{4-[(2,2-dimethylpropanoyl)oxy]phenyl}-cyclohexanecarboxylate (**28b**)



The title compound was obtained from 4-{(benzyloxy)[(benzyloxy)imino] methyl}phenyl 1-(4-hydroxyphenyl)cyclohexanecarboxylate (**27**) and pivaloyl chloride by a method analogous to that described for the previous example, in 67% yield as a mixture of 2 isomers (2:1). ^{1}H NMR (200 MHz, $CDCl_3$, HMDSO) δ: 1.22-1.86 (8H, m); 1.33 (9H· 0.33, s); 1.34 (9H· 0.66, s); 2.49-2.68 (2H, m); 5.01 (2H· 0.66, s); 5.03 (2H· 0.33, s); 5.12 (2H· 0.66, s); 5.14 (2H· 0.33, s); 6.91 (2H· 0.33, d, J=8.8 Hz); 7.06 (2H· 0.66, d, J=8.8 Hz); 7.22-7.41 (12H+2H· 0.33, m); 7.48 (2H· 0.66, d, J=8.8 Hz); 7.82 (2H· 0.66, d, J=8.6 Hz); 7.87 (2H· 0.33, d, J=8.8 Hz).

Example 99

4-[1-({4-[(Hydroxyamino)carbonyl]phenoxy}carbonyl)cyclohexyl]-phenyl benzoate (**PX119085**)

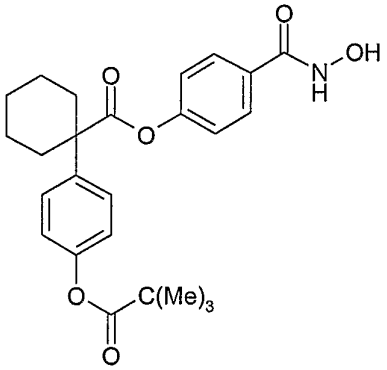


The title compound was obtained from 4-{1-[(4-{(benzyloxy)[(benzyloxy)imino] methyl} phenoxy)carbonyl]-cyclohexyl}phenyl benzoate (**28a**) by a method analogous to that described for 4-[(hydroxyamino)carbonyl]phenyl 1-(4-methoxyphenyl)-cyclohexanecarboxylate (**PX118478**), using methanol-dioxane (2:1) as a solvent. After

filtration of the catalyst and evaporation of methanol-dioxane the crude product was chromatographed on silica gel with chloroform-methanol (9:1) as eluent to give the title compound in 19% yield, m.p. 114-115°C. ^{1}H NMR (DMSO-d_6, HMDSO) δ: 1.18-1.97 (8H, m); 2.33-2.69 (2H, m, overlapped with a signal of DMSO); 7.08 (2H, d, J=8.5 Hz); 7.36 (2H, d, J=8.6 Hz); 7.55-7.69 (4H, m); 7.72-7.85 (3H, m); 8.15 (2H, d, J=7.8 Hz); 9.16 (1H, br s); 11.31 (1H, br s). HPLC analysis on Omnispher 5 C_{18} column: impurities 4% (column size 4.6 x 150 mm; mobile phase acetonitrile – 0.1M phosphate buffer (pH 2.5), 60:40; detector UV 215 nm; sample concentration 1.0 mg/ml; flow rate 1.5 ml/min). Anal. Calcd for $C_{27}H_{25}NO_6 * 0.5\ H_2O$, %: C 69.22, H 5.59, N 2.99. Found, %: C 69.28, H 5.46, N 2.79.

Example 100

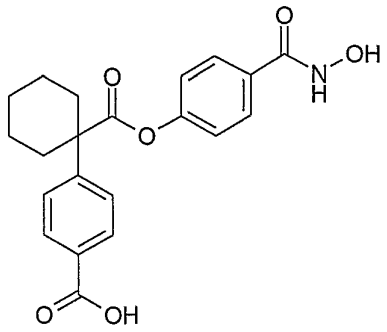
4-[(Hydroxyamino)carbonyl]phenyl 1-{4-[(2,2-dimethylpropanoyl)oxy]-phenyl}-cyclohexane-carboxylate (**PX119086**)



The title compound was obtained from 4-{(benzyloxy)[(benzyloxy)imino] methyl}phenyl 1-{4-[(2,2-dimethylpropanoyl)oxy]phenyl}-cyclohexanecarboxylate (**28b**) by a method analogous to that described for the previous example, using methanol-dioxane (2:1) as a solvent. After filtration of the catalyst and evaporation of methanol-dioxane the crude product was chromatographed on silica gel with chloroform-methanol (9:1) as eluent to give the title compound in 26% yield, m.p. 124-125°C. ^{1}H NMR (DMSO-d_6, HMDSO) δ: 1.13-1.96 (8H, m); 1.30 (9H, s); 2.41-2.58 (2H, m, overlapped with a signal of DMSO); 7.04 (2H, d, J=8.7 Hz); 7.15 (2H, d, J=8.6 Hz); 7.53 (2H, d, J=8.7 Hz); 7.78 (2H, d, J=8.6 Hz); 9.06 (1H, d, J=1.5 Hz); 11.24 (1H, d, J=1.2 Hz). HPLC analysis on Omnispher 5 C_{18} column: impurities 4.5% (column size 4.6 x 150 mm; mobile phase acetonitrile – 0.1M phosphate buffer (pH 2.5), 60:40; detector UV 215 nm; sample concentration 1.0 mg/ml; flow rate 1.5 ml/min). Anal. Calcd for $C_{25}H_{29}NO_6$, %: C 68.32, H 6.65, N 3.19. Found, %: C 67.86, H 6.61, N 3.18.

Example 101

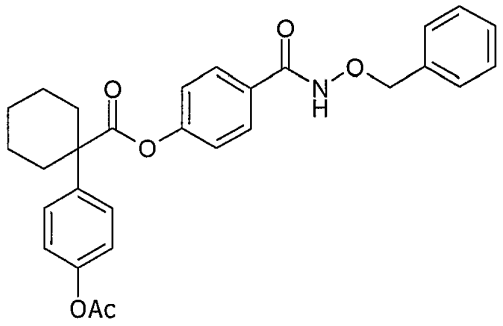
4-[1-({4-[(Hydroxyamino)carbonyl]phenoxy}carbonyl)cyclohexyl]-benzoic acid (**PX119102**)



A mixture of tert-butyl 4-[1-({4-[(hydroxyamino)carbonyl]phenoxy}-carbonyl)cyclohexyl]-benzoate (**PX118926**) (0.12 g, 0.27 mmol), dichloromethane (4 ml), and trifluoroacetic acid (1 ml) was stirred under argon atmosphere at room temperature until the starting material disappeared (ca. 2 hours). The mixture was supplemented with ethyl acetate (150 ml), the obtained solution was washed successively with water (2 x 100 ml), brine (50 ml), and dried (Na_2SO_4). The solvents were evaporated and the residue was chromatographed on silica gel with chloroform-isopropanol (9:1) as eluent to give the title compound in 48% yield as crystals, m.p. 169-170°C. ^{1}H NMR (DMSO-d_6, HMDSO) δ: 1.18-2.05 (8H, m); 2.34-2.69 (2H, m, overlapped with a signal of DMSO); 7.05 (2H, d, J=8.5 Hz); 7.62 (2H, d, J=8.4 Hz); 7.78 (2H, d, J=8.5 Hz); 7.99 (2H, d, J=8.4 Hz); 9.09 (1H, br s); 11.26 (1H, br s). HPLC analysis on Chromasil 100 C_{18} column: impurities 5% (column size 4.6 x 150 mm; mobile phase acetonitrile – 0.1M phosphate buffer (pH 2.5), 60:40; detector UV 254 nm; sample concentration 1.0 mg/ml; flow rate 1.5 ml/min). Anal. Calcd for $C_{21}H_{21}NO_6$ * 0.25 H_2O, %: C 65.02, H 5.59, N 3.61. Found, %: C 64.88, H 5.49, N 3.45.

Example 102

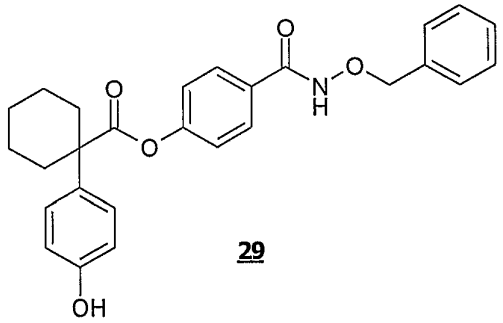
4-{[(Benzyloxy)amino]carbonyl}phenyl 1-[4-(acetyloxy)phenyl]cyclohexanecarboxylate (**22e**)



The title compound was obtained from N-(benzyloxy)-4-hydroxybenzamide (**14**) and 1-(4-acetoxyphenyl)cyclohexane-carbonyl chloride (**23c**) by the method of Example 7 in 55% yield (based on **1/7**). ^{1}H NMR ($CDCl_3$, HMDSO) δ: 1.03-2.08 (8H, m); 2.28 (3H, s); 2.37-2.79 (2H, m); 5.00 (2H, s); 6.94 (2H, d, J=8.4 Hz); 7.09 (2H, d, J=8.8 Hz); 7.38 (5H, s); 7.46 (2H, d, J=8.4 Hz); 7.60 (2H, d, J=8.4 Hz); 8.42 (1H, br s).

Example 103

4-{[(Benzyloxy)amino]carbonyl}phenyl 1-(4-hydroxyphenyl)cyclohexanecarboxylate (**29**)

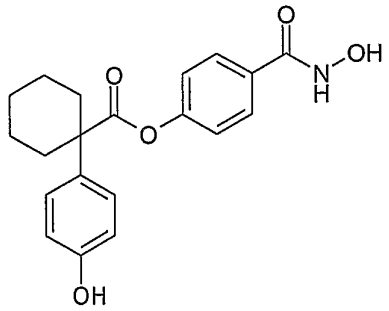


29

The title compound was obtained from 4-{[(benzyloxy)amino]carbonyl}phenyl 1-[4-(acetyloxy)phenyl]cyclohexane-carboxylate (**22e**) and potassium 2-methyl-2-butanolate by the method of Example 9 in 65% yield. ^{1}H NMR (DMSO-d_6, HMDSO) δ: 1.14-1.93 (8H, m); 2.30-2.63 (2H, m, overlapped with a signal of DMSO); 4.90 (2H, s); 6.78 (2H, d, J=8.8 Hz); 7.02 (2H, d, J=8.8 Hz); 7.26 (2H, d, J=8.8 Hz); 7.27-7.55 (5H, m); 7.74 (2H, d, J=8.8 Hz); 9.40 (1H, br s); 11.58 (1H, br s).

Example 104

4-[(Hydroxyamino)carbonyl]phenyl 1-(4-hydroxyphenyl)-cyclohexanecarboxylate (**PX119103**)



The title compound was obtained from 4-{[(benzyloxy)amino]carbonyl}phenyl 1-(4-hydroxyphenyl)cyclohexane-carboxylate (**29**) by the method of Example 8 using methanol-dioxane (2:1) as a solvent. After filtration of the catalyst and evaporation of

methanol-dioxane the crude product was crystallized from diethyl ether to give the title compound in 77% yield, m.p. 93-94°C. ^{1}H NMR (DMSO-d_6, HMDSO) δ: 1.18-2.05 (8H, m); 2.34-2.69 (2H, m, overlapped with a signal of DMSO); 7.05 (2H, d, J=8.5 Hz); 7.62 (2H, d, J=8.4 Hz); 7.78 (2H, d, J=8.5 Hz); 7.99 (2H, d, J=8.4 Hz); 9.09 (1H, br s); 11.26 (1H, br s). HPLC analysis on Chromasil 100 C_{18} column: impurities 5% (column size 4.6 x 150 mm; mobile phase acetonitrile – 0.1M phosphate buffer (pH 2.5), 60:40; detector UV 254 nm; sample concentration 1.0 mg/ml; flow rate 1.5 ml/min). Anal. Calcd for $C_{20}H_{21}NO_5 * 0.5\ H_2O * 0.8\ Et_2O$, %: C 65.77, H 7.14, N 3.31. Found, %: C 65.86, H 7.11, N 3.15.

Biological Activity

Candidate compounds were assessed for their ability to inhibit deacetylase activity (biochemical assays) and to inhibit cell proliferation (cell-based antiproliferation assays), as described below.

Primary Assay (1): Deacetylase Activity

Briefly, this assay relies on the release of radioactive acetate from a radioactively labelled histone fragment by the action of HDAC enzyme. Test compounds, which inhibit HDAC, reduce the yield of radioactive acetate. Signal (e.g., scintillation counts) measured in the presence and absence of a test compound provide an indication of that compound's ability to inhibit HDAC activity. Decreased activity indicates increased inhibition by the test compound.

The histone fragment was an N-terminal sequence from histone H4, and it was labelled with radioactively labelled acetyl groups using tritiated acetylcoenzyme A (coA) in conjunction with an enzyme which is the histone acetyltransferase domain of the transcriptional coactivator p300. 0.33 mg of peptide H4 (the N-terminal 20 amino acids of histone H4, synthesized using conventional methods) were incubated with His6-tagged p300 histone acetyltransferase domain (amino acids 1195-1673, expressed in *E. coli* strain BLR(DE3)pLysS (Novagen, Cat. No. 69451-3) and 3H-acetyl coA (10 µL of 3.95 Ci/mmol; from Amersham) in a total volume of 300 µL of HAT buffer (50 mM TrisCl pH 8, 5% glycerol, 50 mM KCl, 0.1 mM ethylenediaminetetraacetic acid (EDTA), 1 mM dithiothreitol (DTT) and 1 mM 4-(2-aminoethyl)-benzenesulfonylfluoride (AEBSF)). The mixture was incubated at 30°C for 45 minutes after which the His-p300 was removed using nickel-trinitriloacetic acid agarose (Qiagen, Cat No. 30210). The acetylated peptide

was then separated from free acetyl coA by size exclusion chromatography on Sephadex G-15 (Sigma G-15-120), using distilled H_2O as the mobile phase.

After purification of the radiolabelled histone fragment, it was incubated with a source of HDAC (e.g., an extract of HeLa cells (a rich source of HDAC), recombinantly produced HDAC1 or HDAC2) and any released acetate was extracted into an organic phase and quantitatively determined using scintillation counting. By including a test compound with the source of HDAC, that compound's ability to inhibit the HDAC was determined.

Primary Assay (2): Deacetylase Activity: Fluorescent Assay

Alternatively, the activity of the compounds as HDAC inhibitors was determined using a commercially available fluorescent assay kit: (Fluor de Lys™, BioMol Research Labs, Inc., Plymouth Meeting, USA). HeLa extract was incubated for 1 hour at 37°C in assay buffer (25 mM HEPES, 137 mM NaCl, 2.7 mM KCl, 1 mM $MgCl_2$, pH 8.0) with 15 μM acetylated substrate in the presence of test compound (HDAC inhibitor). The extent of deacetylation was determined by the addition of 50 μL of a 1-in-500 dilution of Developer, and measurement of the fluorescence (excitation 355 nm, emission 460 nm), according to the instructions provided with the kit.

Extensive comparative studies have shown that Primary Assay (1) and Primary Assay (2), discussed above, yield equivalent results. Primary Assay results reported herein are (a) exclusively from (1); (b) exclusively from (2); or (c) from both (1) and (2).

HeLa Cell Extract

The HeLa cell extract was made from HeLa cells (ATCC Ref. No. CCL-2) by freeze-thawing three times in 60 mM TrisCl pH 8.0, 450 mM NaCl, 30% glycerol. Two cell volumes of extraction buffer were used, and particulate material was centrifuged out (20800 g, 4°C, 10 minutes). The supernatant extract having deacetylase activity was aliquotted and frozen for storage.

Recombinantly Produced HDAC1 and HDAC2

Recombinant plasmids were prepared as follows.

Full length human HDAC1 was cloned by PCR using a λgt11 Jurkat cDNA library (Clontech-HL5012b). The amplified fragment was inserted into the EcoRI-SalI sites of pFlag-CTC vector (Sigma-E5394), in frame with the Flag tag. A second PCR was carried out in order to amplify a fragment containing the HDAC1 sequence fused to the Flag tag. The resulting fragment was subcloned into the EcoRI-Sac1 sites of the baculovirus transfer vector pAcHTL-C (Pharmingen-21466P).

Full length mouse HDAC2 was subcloned into pAcHLT-A baculovirus transfer vector (Pharmingen-21464P) by PCR amplification of the EcoRI-Sac1 fragment from a HDAC2-pFlag-CTC construct.

Recombinant protein expression and purification was performed as follows.

HDAC1 and HDAC2 recombinant baculoviruses were constructed using BaculoGold Transfection Kit (Pharmingen-554740). Transfer vectors were co-transfected into SF9 insect cells (Pharmingen-21300C). Amplification of recombinant viruses was performed according to the Pharmingen Instruction Manual. SF9 cells were maintained in serum-free SF900 medium (Gibco 10902-096).

For protein production, $2x10^7$ cells were infected with the appropriate recombinant virus for 3 days. Cells were then harvested and spun at 3,000 rpm for 5 minutes. They were then washed twice in PBS and resuspended in 2 pellet volumes of lysis buffer (25 mM HEPES pH 7.9, 0.1 mM EDTA, 400 mM KCl, 10% glycerol, 0.1% NP-40, 1 mM AEBSF). Resuspended cells were frozen on dry ice and thawed at 37°C 3 times and centrifuged for 10 minutes at 14,000 rpm. The supernatant was collected and incubated with 300 µl of 50% Ni-NTA agarose bead slurry (Qiagen-30210). Incubation was carried out at 4°C for 1 hour on a rotating wheel. The slurry was then centrifuged at 500 g for 5 minutes. Beads were washed twice in 1 ml of wash buffer (25 mM HEPES pH7.9, 0.1 mM EDTA, 150 mM KCl, 10% glycerol, 0.1% NP-40, 1 mM AEBSF). Protein was eluted 3 times in 300 µl elution buffer (25 mM HEPES pH 7.9, 0.1 mM EDTA, 250 mM KCl, 10% glycerol, 0.1% NP-40, 1 mM AEBSF) containing increasing concentrations of imidazole: 0.2 M, 0.5 M

and 1 M. Each elution was performed for 5 minutes at room temperature. Eluted protein was kept in 50% glycerol at -70°C.

Assay Method

A source of HDAC (e.g., 2 µL of crude HeLa extract, 5 µL of HDAC1 or HDAC2; in elution buffer, as above) was incubated with 3 µL of radioactively labelled peptide along with appropriate dilutions of candidate compounds (1.5 µL) in a total volume of 150 µL of buffer (20 mM Tris pH 7.4, 10% glycerol). The reaction was carried out at 37°C for one hour, after which the reaction was stopped by adding 20 µL of 1 M HCl / 0.4 M sodium acetate. Then, 750 µL of ethyl acetate was added, the samples vortexed and, after centrifugation (14000 rpm, 5 minutes), 600 µL from the upper phase were transferred to a vial containing 3 mL of scintillation liquid (UltimaGold, Packard, Cat. No. 6013329). Radioactivity was measured using a Tri-Carb 2100TR Liquid Scintillation Analyzer (Packard).

Percent activity (% activity) for each test compound was calculated as:

$$\% \text{ activity} = \{ (S^C - B) / (S^\circ - B) \} \times 100$$

wherein S^C denotes signal measured in the presence of enzyme and the compound being tested, S° denotes signal measured in the presence of enzyme but in the absence of the compound being tested, and B denotes the background signal measured in the absence of both enzyme and compound being tested. The IC50 corresponds to the concentration which achieves 50% activity.

IC50 data for several compounds of the present invention, as determined using this assay, are also shown in Table 1, below.

Measurement of cell viability in the presence of increasing concentration of test compound at different time points is used to assess both cytotoxicity and the effect of the compound on cell proliferation.

Secondary Assay: Cell Proliferation

Compounds with HDAC inhibition activity, as determined using the primary assay, were subsequently evaluated using secondary cell-based assays. The following cell lines were used:

HeLa - Human cervical adenocarcinoma cell line (ATCC ref. No. CCL-2).

K11 – HPV E7 transformed human keratinocyte line provided by Pidder Jansen-Duerr, Institut für Biomedizinische Alternsforschung, Innsbruck, Austria.

NHEK-Ad – Primary human adult keratinocyte line (Cambrex Corp., East Rutherford, NJ, USA).

JURKAT – Human T-cell line (ATCC no. TIB-152).

Assay Method

Cells were cultured, exposed to candidate compounds, and incubated for a time, and the number of viable cells was then assessed using the Cell Proliferation Reagent WST-1 from Boehringer Mannheim (Cat. No. 1 644 807), described below.

Cells were plated in 96-well plates at 3-10x10^3 cells/well in 100 µL of culture medium. The following day, different concentrations of candidate compounds were added and the cells incubated at 37°C for 48 hours. Subsequently, 10 µL/well of WST-1 reagent was added and the cells reincubated for 1 hour. After the incubation time, absorbance was measured.

WST-1 is a tetrazolium salt which is cleaved to formazan dye by cellular enzymes. An expansion in the number of viable cells results in an increase in the overall activity of mitochondrial dehydrogenases in the sample. This augmentation in the enzyme activity leads to an increase in the amount of formazan dye formed, which directly correlates to the number of metabolically active cells in the culture. The formazan dye produced is quantified by a scanning multiwell spectrophotometer by measuring the absorbance of the dye solution at 450 nm wavelength (reference wavelength 690 nm).

Percent activity (% activity) in reducing the number of viable cells was calculated for each test compound as:

$$\% \text{ activity} = \{ (S^C - B) / (S^\circ - B) \} \times 100$$

wherein S^C denotes signal measured in the presence of the compound being tested, S° denotes signal measured in the absence of the compound being tested, and B denotes the background signal measured in blank wells containing medium only. The IC50 corresponds to the concentration which achieves 50% activity. IC50 values were calculated using the software package Prism 3.0 (GraphPad Software Inc., San Diego, CA) , setting top value at 100 and bottom value at 0.

IC50 data for several compounds of the present invention, as determined using this assay, are also shown in Table 2, below.

Measurement of cell viability in the presence of increasing concentration of test compound at different time points is used to assess both cytotoxicity and the effect of the compound on cell proliferation.

Biological Data

IC50 (or percent activity) data for several compounds of the present invention, as determined using the assays described above are summarised in Table 1 and Table 2, below.

Table 1
Biochemical Assay Data

Compound		HDAC Inhibition (IC50 unless otherwise specified)		
No.	Ref.	HeLa	HDAC1	HDAC2
	TSA	5 nM	15 nM	17 nM
	SAHA	189 nM	-	-
1	PX118478	23 nM	-	-
2	PX118479	52 nM	-	-
3	PX118480	25 nM	-	-
4	PX119063	85 nM	-	-

Table 2
Cell-Based Antiproliferation Assay Data

Compound		Cell Proliferation Inhibition WST-1 (IC50 unless otherwise specified)			
No.	Ref.	HeLa	K11	NHEK-AD	Jurkat
	TSA	350 nM	0.38 μM	0.2 μM	42 nM
	Oxamflatin	-	4.82 μM	3.53 μM	170 nM
	MS-275	-	9.16 μM	3.1 μM	365 nM
	SAHA	-	6.82 μM	5.37μM	750 nM
1	PX118478	4.6 μM	13.6 μM	-	500 nM
2	PX118479	13.7 μM	21.3 μM	-	1.25 μM
3	PX118480	7.9 μM	1.65 μM	-	780 nM
4	PX119063	4.9 μM	-	-	-

* * *

The foregoing has described the principles, preferred embodiments, and modes of operation of the present invention. However, the invention should not be construed as limited to the particular embodiments discussed. Instead, the above-described embodiments should be regarded as illustrative rather than restrictive, and it should be appreciated that variations may be made in those embodiments by workers skilled in the art without departing from the scope of the present invention as defined by the appended claims.

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A number of patents and publications are cited herein in order to more fully describe and disclose the invention and the state of the art to which the invention pertains. Full citations for these references are provided herein. Each of these references is incorporated herein by reference in its entirety into the present disclosure.

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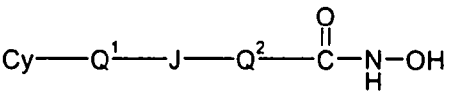
CLAIMS

1. A compound selected from compounds of the following formula and pharmaceutically acceptable salts and solvates thereof:



wherein:

J is independently selected from:

-C(=O)-,

-O-C(=O)-, and

-C(=O)-O-;

Cy is independently selected from:

C_{3-20}carbocyclyl,

C_{3-20}heterocyclyl, and

C_{5-20}aryl;

and is optionally substituted with one or more substituents independently selected from:

(1) -C(=O)OR^1, wherein R^1 is independently C_{1-7}alkyl as defined in (7);

(2) -C(=O)NR^2R^3, wherein each of R^2 and R^3 is independently -H or C_{1-7}alkyl as defined in (7);

(3) -C(=O)R^4, wherein R^4 is independently C_{1-7}alkyl as defined in (7) or C_{5-20}aryl as defined in (8);

(4) -F, -Cl, -Br, -I;

(5) -OH;

(6) -OR^5, wherein R^5 is independently C_{1-7}alkyl as defined in (7) or C_{5-20}aryl as defined in (8);

(7) C_{1-7}alkyl, halo-C_{1-7}alkyl, amino-C_{1-7}alkyl, carboxy-C_{1-7}alkyl, hydroxy-C_{1-7}alkyl, C_{1-7}alkoxy-C_{1-7}alkyl, or C_{5-20}aryl-C_{1-7}alkyl;

(8) C_{5-20}aryl, substituted C_{5-20}aryl;

(9) -SO_2R^7, wherein R^7 is independently C_{1-7}alkyl as defined in (7) or C_{5-20}aryl as defined in (8); and

(10) -$SO_2NR^8R^9$, wherein each of R^8 and R^9 is independently -H or C_{1-7}alkyl as defined in (7);

Q^1 is independently a divalent bidentate group obtained by removing two hydrogen atoms from a ring carbon atom of a saturated monocyclic hydrocarbon having from 4 to 7 ring atoms, or by removing two hydrogen atoms from a ring carbon atom of saturated monocyclic heterocyclic compound having from 4 to 7 ring atoms including 1 nitrogen ring atom or 1 oxygen ring atom;
and is optionally substituted with one or more substituents independently selected from: -F, -Cl, -Br, -I, -OH, -OMe, -OEt, -O(iPr), -Ph, -C(=O)Me, $-NH_2$, $-NMe_2$, $-NEt_2$, morpholino, $-CONH_2$, $-CONMe_2$, -NHCOMe, and =O;

Q^2 is independently selected from:

C_{1-8}alkylene,

C_{5-6}arylene,

C_{5-6}arylene-C_{1-7}alkylene,

C_{1-7}alkylene-C_{5-6}arylene, and

C_{1-7}alkylene-C_{5-6}arylene-C_{1-7}alkylene;

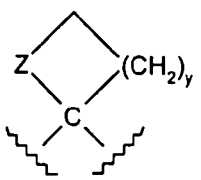
and is optionally substituted with one or more substituents independently selected from: -F, -Cl, -Br, -I, -OH, -OMe, -OEt, -O(iPr), -Ph, -C(=O)Me, $-NH_2$, $-NMe_2$, $-NEt_2$, morpholino, $-CONH_2$, $-CONMe_2$, -NHCOMe, $-NO_2$, and =O; and wherein, if a substituent is on an arylene group, it may additionally be selected from: -Me, -Et, -iPr, -tBu, and $-CF_3$.

2. A compound according to claim 1, wherein J is -O-C(=O)-.

3. A compound according to claim 1, wherein J is -C(=O)-O-.

4. A compound according to claim 1, wherein J is -C(=O)-.

5. A compound according to any one of claims 1 to 4, wherein Q^1 is independently a group of the formula:



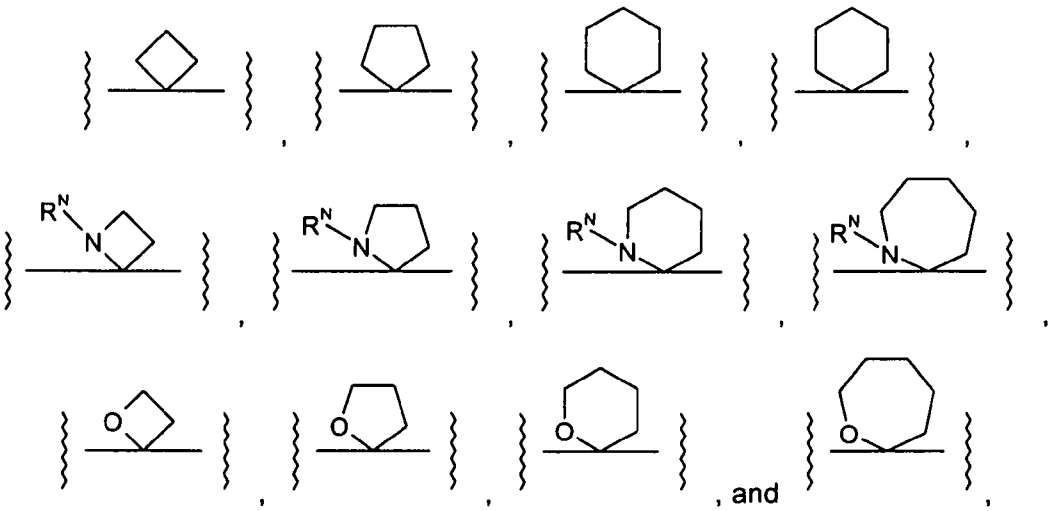
wherein:

Z is independently $-CH_2-$, $-N(R^N)-$ or -O-;

R^N, if present, is independently -H, C_{1-7}alkyl, C_{5-20}aryl-C_{1-7}alkyl; and

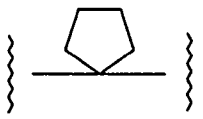
y is independently 1, 2, 3, or 4.

6. A compound according to any one of claims 1 to 4, wherein Q^1 is independently selected from:

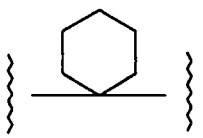


wherein R^N is independently -H, C_{1-7}alkyl, C_{5-20}aryl-C_{1-7}alkyl.

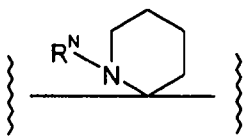
7. A compound according to any one of claims 1 to 4, wherein Q^1 is independently:



8. A compound according to any one of claims 1 to 4, wherein Q^1 is independently:



9. A compound according to any one of claims 1 to 4, wherein Q^1 is independently:



wherein R^N is independently -H, C_{1-7}alkyl, C_{5-20}aryl-C_{1-7}alkyl.

10. A compound according to any one of claims 5, 6, and 9, wherein R^N is independently selected from: -H, -Me, -Et, -Ph, and -CH_2-Ph.

11. A compound according to any one of claims 5, 6, and 9, wherein R^N is independently -H.

12. A compound according to any one of claims 1 to 11, wherein Q^2 is independently C_{5-6}arylene; and is optionally substituted with one or more substituents independently selected from: -F, -Cl, -Br, -I, -OH, -OMe, -OEt, -O(iPr), -Ph, -C(=O)Me, $-NH_2$, $-NMe_2$, $-NEt_2$, morpholino, $-CONH_2$, $-CONMe_2$, -NHCOMe, $-NO_2$, =O, -Me, -Et, -iPr, -tBu, and $-CF_3$.

13. A compound according to any one of claims 1 to 11, wherein Q^2 is independently phenylene; and is optionally substituted with one or more substituents independently selected from: -F, -Cl, -Br, -I, -OH, -OMe, -OEt, -O(iPr), -Ph, -C(=O)Me, $-NH_2$, $-NMe_2$, $-NEt_2$, morpholino, $-CONH_2$, $-CONMe_2$, -NHCOMe, $-NO_2$, =O, -Me, -Et, -iPr, -tBu, and $-CF_3$.

14. A compound according to claim 13, wherein the phenylene linkage is meta.

15. A compound according to claim 13, wherein the phenylene linkage is para.

16. A compound according to any one of claims 12 to 15, wherein Q^2 is unsubstituted.

17. A compound according to any one of claims 1 to 11, wherein Q^2 is independently selected from:

C_{5-6}arylene-C_{1-7}alkylene,

C_{1-7}alkylene-C_{5-6}arylene, and

C_{1-7}alkylene-C_{5-6}arylene-C_{1-7}alkylene;

and is optionally substituted with one or more substituents independently selected from: -F, -Cl, -Br, -I, -OH, -OMe, -OEt, -O(iPr), -Ph, -C(=O)Me, $-NH_2$, $-NMe_2$, $-NEt_2$, morpholino, $-CONH_2$, $-CONMe_2$, -NHCOMe, $-NO_2$, and =O; and wherein, if a substituent is on an arylene group, it may additionally be selected from: -Me, -Et, -iPr, -tBu, and $-CF_3$.

18. A compound according to any one of claims 1 to 11, wherein Q^2 is independently selected from:

phenylene-C_{1-7}alkylene,

C_{1-7}alkylene-phenylene, and

C_{1-7}alkylene-phenylene-C_{1-7}alkylene;

and is optionally substituted with one or more substituents independently selected from: -F, -Cl, -Br, -I, -OH, -OMe, -OEt, -O(iPr), -Ph, -C(=O)Me, $-NH_2$, $-NMe_2$, $-NEt_2$, morpholino, $-CONH_2$, $-CONMe_2$, -NHCOMe, $-NO_2$, and =O; and wherein, if a substituent is on a phenylene group, it may additionally be selected from: -Me, -Et, -iPr, -tBu, and $-CF_3$.

19. A compound according to claim 17 or 18, wherein Q^2 is unsubstituted.

20. A compound according to any one of claims 1 to 11, wherein Q^2 is independently selected from: methylene-phenylene and ethylene-phenylene.

21. A compound according to any one of claims 1 to 11, wherein Q^2 is independently selected from: $-(CH_2)_5-$, $-(CH_2)_6-$, $-(CH_2)_7-$, and $-(CH_2)_8-$.

22. A compound according to any one of claims 1 to 21, wherein Cy is independently selected from: C_{5-20}carboaryl and C_{5-20}heteroaryl; and is optionally substituted with one or more substituents independently selected from:

(1) $-C(=O)OR^1$, wherein R^1 is independently C_{1-7}alkyl as defined in (7);

(2) $-C(=O)NR^2R^3$, wherein each of R^2 and R^3 is independently -H or C_{1-7}alkyl as defined in (7);

(3) $-C(=O)R^4$, wherein R^4 is independently C_{1-7}alkyl as defined in (7) or C_{5-20}aryl as defined in (8);

(4) -F, -Cl, -Br, -I;

(5) -OH;

(6) $-OR^5$, wherein R^5 is independently C_{1-7}alkyl as defined in (7) or C_{5-20}aryl as defined in (8);

(7) C_{1-7}alkyl, halo-C_{1-7}alkyl, amino-C_{1-7}alkyl, carboxy-C_{1-7}alkyl, hydroxy-C_{1-7}alkyl, C_{1-7}alkoxy-C_{1-7}alkyl, or C_{5-20}aryl-C_{1-7}alkyl;

(8) C_{5-20}aryl, substituted C_{5-20}aryl;

(9) $-SO_2R^7$, wherein R^7 is independently C_{1-7}alkyl as defined in (7) or C_{5-20}aryl as defined in (8); and

(10) $-SO_2NR^8R^9$, wherein each of R^8 and R^9 is independently -H or C_{1-7}alkyl as defined in (7).

23. A compound according to any one of claims 1 to 21, wherein Cy is independently selected from: phenyl, pyridyl, furanyl, indolyl, pyrrolyl, imidazolyl, naphthyl, quinolinyl, benzimidazolyl, benzothiofuranyl, fluorenyl, acridinyl, and carbazolyl; and is optionally substituted with one or more substituents independently selected from:

(1) $-C(=O)OR^1$, wherein R^1 is independently C_{1-7}alkyl as defined in (7);

(2) $-C(=O)NR^2R^3$, wherein each of R^2 and R^3 is independently -H or C_{1-7}alkyl as defined in (7);

(3) $-C(=O)R^4$, wherein R^4 is independently C_{1-7}alkyl as defined in (7) or C_{5-20}aryl as defined in (8);

(4) -F, -Cl, -Br, -I;

(5) -OH;

(6) $-OR^5$, wherein R^5 is independently C_{1-7}alkyl as defined in (7) or C_{5-20}aryl as defined in (8);

(7) C_{1-7}alkyl, halo-C_{1-7}alkyl, amino-C_{1-7}alkyl, carboxy-C_{1-7}alkyl, hydroxy-C_{1-7}alkyl, C_{1-7}alkoxy-C_{1-7}alkyl, or C_{5-20}aryl-C_{1-7}alkyl;

(8) C_{5-20}aryl, substituted C_{5-20}aryl;

(9) $-SO_2R^7$, wherein R^7 is independently C_{1-7}alkyl as defined in (7) or C_{5-20}aryl as defined in (8); and

(10) $-SO_2NR^8R^9$, wherein each of R^8 and R^9 is independently -H or C_{1-7}alkyl as defined in (7).

24. A compound according to any one of claims 1 to 21, wherein Cy is independently phenyl, and is optionally substituted with one or more substituents independently selected from:

(1) $-C(=O)OR^1$, wherein R^1 is independently C_{1-7}alkyl as defined in (7);

(2) $-C(=O)NR^2R^3$, wherein each of R^2 and R^3 is independently -H or C_{1-7}alkyl as defined in (7);

(3) $-C(=O)R^4$, wherein R^4 is independently C_{1-7}alkyl as defined in (7) or C_{5-20}aryl as defined in (8);

(4) -F, -Cl, -Br, -I;

(5) -OH;

(6) -OR^5, wherein R^5 is independently C_{1-7}alkyl as defined in (7) or C_{5-20}aryl as defined in (8);

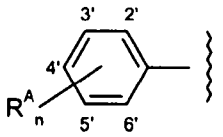
(7) C_{1-7}alkyl, halo-C_{1-7}alkyl, amino-C_{1-7}alkyl, carboxy-C_{1-7}alkyl, hydroxy-C_{1-7}alkyl, C_{1-7}alkoxy-C_{1-7}alkyl, or C_{5-20}aryl-C_{1-7}alkyl;

(8) C_{5-20}aryl, substituted C_{5-20}aryl;

(9) -SO_2R^7, wherein R^7 is independently C_{1-7}alkyl as defined in (7) or C_{5-20}aryl as defined in (8); and

(10) -$SO_2NR^8R^9$, wherein each of R^8 and R^9 is independently -H or C_{1-7}alkyl as defined in (7).

25. A compound according to any one of claims 1 to 21, wherein Cy is independently an optionally substituted phenyl group of the formula:



wherein n is independently an integer from 0 to 5, and

each R^A is independently a substituent selected from:

(1) -$C(=O)OR^1$, wherein R^1 is independently C_{1-7}alkyl as defined in (7);

(2) -$C(=O)NR^2R^3$, wherein each of R^2 and R^3 is independently -H or C_{1-7}alkyl as defined in (7);

(3) -$C(=O)R^4$, wherein R^4 is independently C_{1-7}alkyl as defined in (7) or C_{5-20}aryl as defined in (8);

(4) -F, -Cl, -Br, -I;

(5) -OH;

(6) -OR^5, wherein R^5 is independently C_{1-7}alkyl as defined in (7) or C_{5-20}aryl as defined in (8);

(7) C_{1-7}alkyl, halo-C_{1-7}alkyl, amino-C_{1-7}alkyl, carboxy-C_{1-7}alkyl, hydroxy-C_{1-7}alkyl, C_{1-7}alkoxy-C_{1-7}alkyl, or C_{5-20}aryl-C_{1-7}alkyl;

(8) C_{5-20}aryl, substituted C_{5-20}aryl;

(9) -SO_2R^7, wherein R^7 is independently C_{1-7}alkyl as defined in (7) or C_{5-20}aryl as defined in (8); and

(10) -$SO_2NR^8R^9$, wherein each of R^8 and R^9 is independently -H or C_{1-7}alkyl as defined in (7).

26. A compound according to claim 25, wherein n is 0.

27. A compound according to claim 25, wherein n is 1, and the R^A group is in the 4'-position.

28. A compound according to claim 25, wherein n is 2, and one R^A group is in the 4'-position, and the other R^A group is in the 2'-position.

29. A compound according to claim 25, wherein n is 2, and one R^A group is in the 4'-position, and the other R^A group is in the 3'-position.

30. A compound according to any one of claims 1 to 29, wherein each of the optional substituents on Cy is independently selected from:

(1) -C(=O)OMe, -C(=O)OEt, -C(=O)O(Pr), -C(=O)O(iPr), -C(=O)O(nBu), -C(=O)O(sBu), -C(=O)O(iBu), -C(=O)O(tBu), -C(=O)O(nPe), -C(=O)OCH_2CH_2OH, -C(=O)OCH_2CH_2OMe, -C(=O)OCH_2CH_2OEt;

(2) -(C=O)NH_2, -(C=O)NMe_2, -(C=O)NEt_2, -(C=O)$N(iPr)_2$, -(C=O)$N(CH_2CH_2OH)_2$;

(3) -(C=O)Me, -(C=O)Et, -(C=O)-cHex, -(C=O)Ph;

(4) -F, -Cl, -Br, -I;

(5) -OH;

(6) -OMe, -OEt, -O(iPr), -O(tBu), -OPh, -OCF_3, -OCH_2CF_3, -OCH_2CH_2OH, -OCH_2CH_2OMe, -OCH_2CH_2OEt, -$OCH_2CH_2NH_2$, -$OCH_2CH_2NMe_2$, -$OCH_2CH_2N(iPr)_2$, -OPh, -OPh-Me, -OPh-OH, -OPh-OMe, O-Ph-F, -OPh-Cl, -OPh-Br, -OPh-I;

(7) -Me, -Et, -nPr, -iPr, -nBu, -iBu, -sBu, -tBu, -nPe, -CF_3, -CH_2CF_3; -CH_2CH_2OH, -CH_2CH_2OMe, -CH_2CH_2OEt, -$CH_2CH_2NH_2$, -$CH_2CH_2NMe_2$, -$CH_2CH_2N(iPr)_2$, -CH_2-Ph;

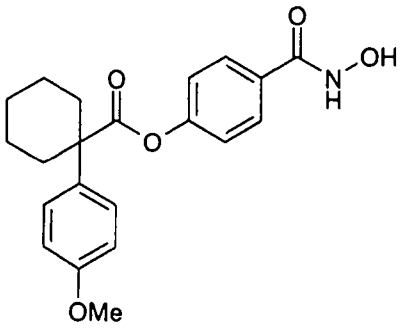
(8) -Ph, -Ph-Me, -Ph-OH, -Ph-OMe, -Ph-F, -Ph-Cl, -Ph-Br, -Ph-I;

(9) -SO_2Me, -SO_2Et, -SO_2Ph; and

(10) -SO_2NH_2, -SO_2NMe_2, -SO_2NEt_2.

31. A compound according to any one of claims 1 to 29, wherein each of the optional substituents on Cy is independently selected from: -C(=O)OMe, -OMe, -C(=O)Me, -SO_2Me, -SO_2NMe_2, -C(=O)NH_2, -OCF_3, and -CH_2CH_2OH.

32. A compound according to claim 1, selected from the following compounds, and pharmaceutically acceptable salts and solvates thereof:



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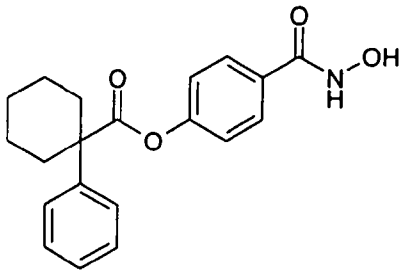

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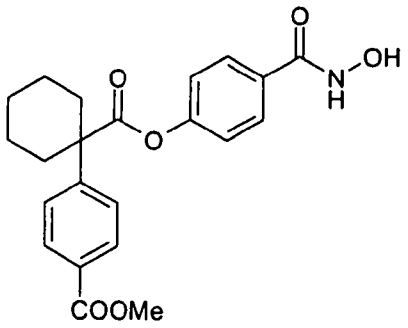

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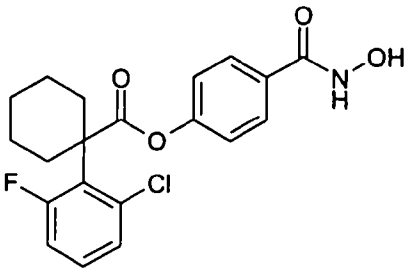

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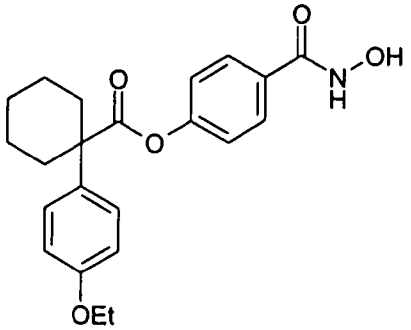

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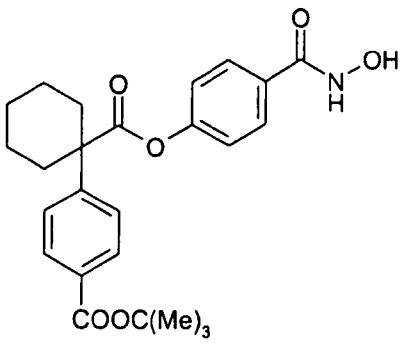

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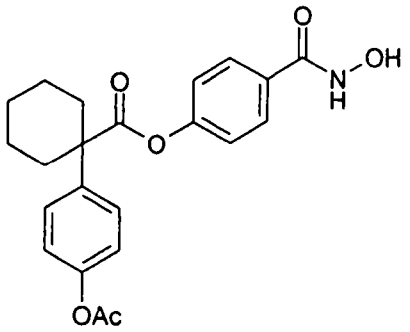

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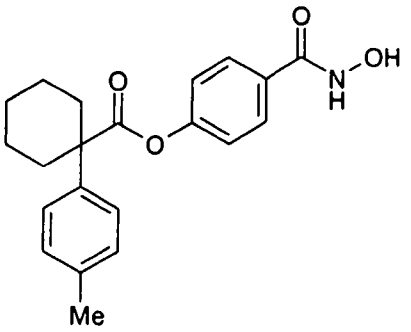

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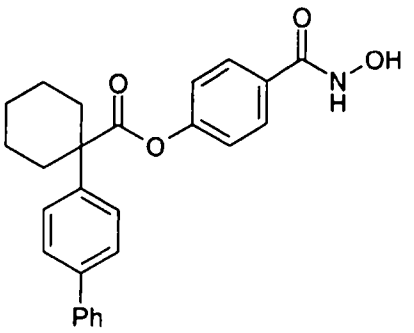

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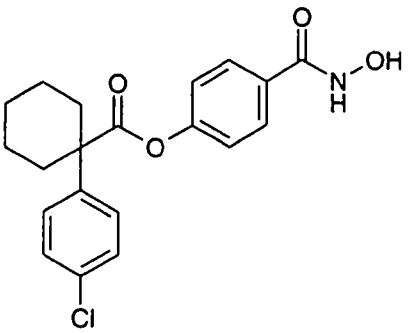

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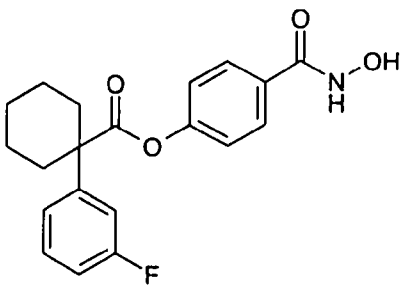

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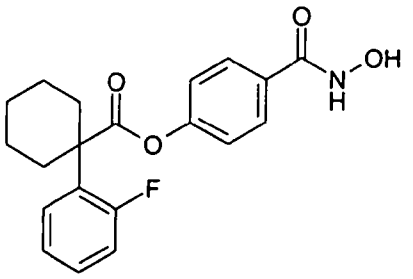

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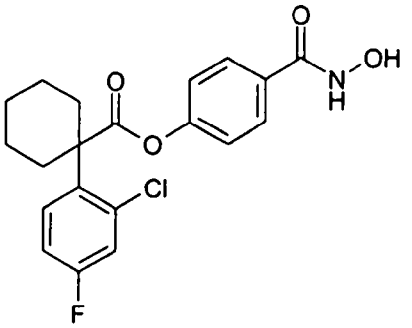

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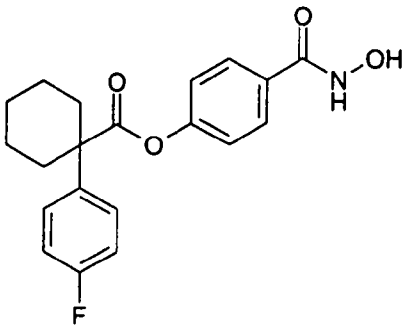

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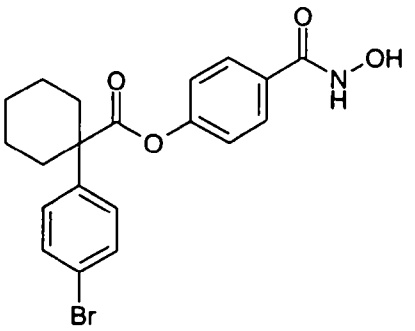

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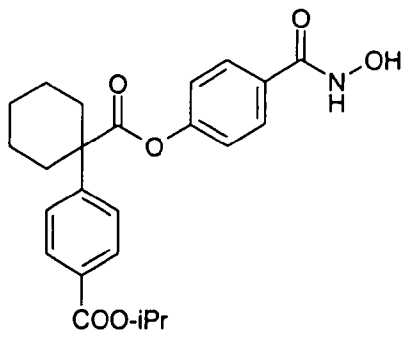

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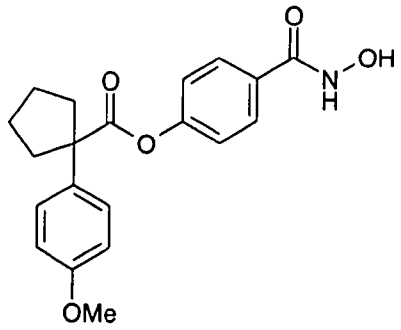

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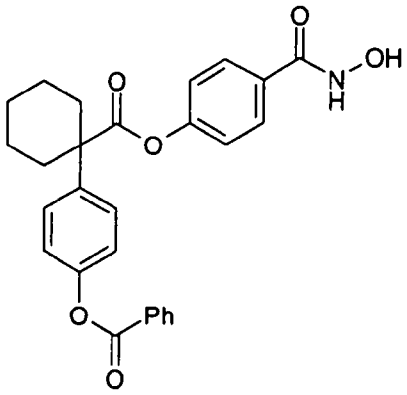

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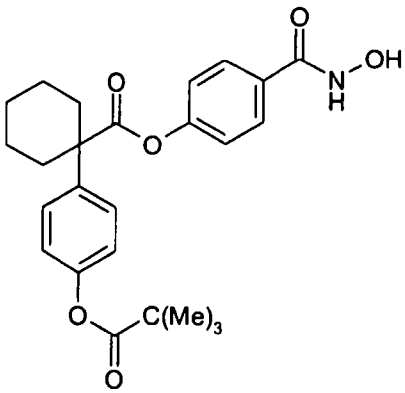

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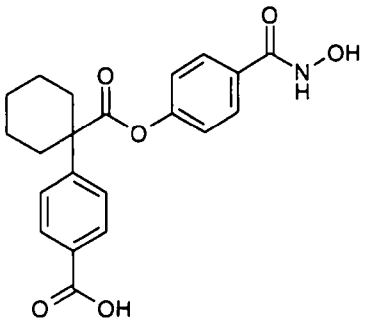
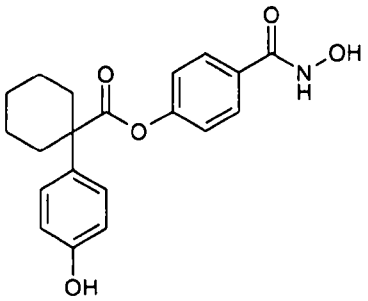


(PX119102), and



(PX119103).

33. A composition comprising a compound according to any one of claims 1 to 32 and a pharmaceutically acceptable carrier.

34. Use of a compound according to any one of claims 1 to 32 for the manufacture of a medicament for the treatment of a condition mediated by HDAC.

35. Use of a compound according to any one of claims 1 to 32 for the manufacture of a medicament for the treatment of:

cancer;

psoriasis;

a fibroproliferative disorder; liver fibrosis;

smooth muscle proliferative disorder; atherosclerosis; restenosis;

a neurodegenative disease; Alzheimer's; Parkinson's; Huntington's chorea; amyotropic lateral sclerosis; spino-cerebellar degeneration;

an inflammatory disease; osteoarthritis; rheumatoid arthritis;

a diseases involving angiogenesis; rheumatoid arthritis; diabetic retinopathy;

a haematopoietic disorder; anaemia; sickle cell anaemia; thalassaeimia;

a fungal infection;

a parasitic infection; malaria; trypanosomiasis; helminthiasis; a protozoal infection;
a bacterial infection;
a viral infection;
multiple sclerosis; autoimmune diabetes; lupus; atopic dermatitis; an allergy; asthma; allergic rhinitis; or inflammatory bowel disease.

36. Use of a compound according to any one of claims 1 to 32 for the manufacture of a medicament for the treatment of a proliferative condition.

37. Use of a compound according to any one of claims 1 to 32 for the manufacture of a medicament for the treatment of cancer.

38. Use of a compound according to any one of claims 1 to 32 for the manufacture of a medicament for the treatment of psoriasis.

39. A method of treating a condition mediated by HDAC comprising administering to a subject in need of treatment a therapeutically-effective amount of a compound according to any one of claims 1 to 32.

40. A method of treating:
cancer;
psoriasis;
a fibroproliferative disorder; liver fibrosis;
smooth muscle proliferative disorder; atherosclerosis; restenosis;
a neurodegenative disease; Alzheimer's; Parkinson's; Huntington's chorea; amyotropic lateral sclerosis; spino-cerebellar degeneration;
an inflammatory disease; osteoarthritis; rheumatoid arthritis;
a diseases involving angiogenesis; rheumatoid arthritis; diabetic retinopathy;
a haematopoietic disorder; anaemia; sickle cell anaemia; thalassaeimia;
a fungal infection;
a parasitic infection; malaria; trypanosomiasis; helminthiasis; a protozoal infection;
a bacterial infection;
a viral infection;

multiple sclerosis; autoimmune diabetes; lupus; atopic dermatitis; an allergy; asthma; allergic rhinitis; or inflammatory bowel disease; comprising administering to a subject in need of treatment a therapeutically-effective amount of a compound according to any one of claims 1 to 32.

41. A method of treating a proliferative condition comprising administering to a subject in need of treatment a therapeutically-effective amount of a compound according to any one of claims 1 to 32.

42. A method of treating cancer comprising administering to a subject in need of treatment a therapeutically-effective amount of a compound according to any one of claims 1 to 32.

43. A method of treating psoriasis comprising administering to a subject in need of treatment a therapeutically-effective amount of a compound according to any one of claims 1 to 32.

44. A method of inhibiting HDAC in a cell, in vitro, comprising contacting said cell with an effective amount of a compound according to any one of claims 1 to 32.

45. A method of inhibiting HDAC in a cell as substantially hereinbefore described with reference to the assays as described in relation to compounds PX118478, PX118479, PX118480, PX119063.

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