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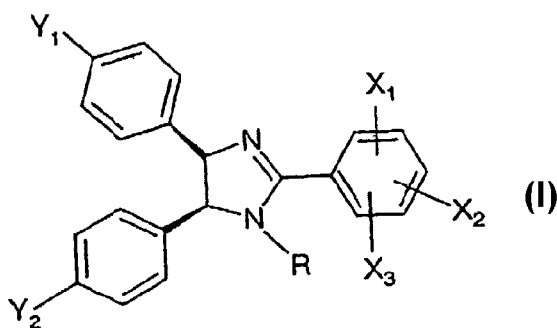
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(54) Title: CIS-2,4,5- TRIPHENYL-IMIDAZOLINES AND THEIR USE IN THE TREATMENT OF TUMORS

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(57) Abstract: The present invention provides compounds according to formula I and formula II and pharmaceutically acceptable salts and esters thereof, having the designations provided herein and which inhibit the interaction of MDM2 protein with a p53-like peptide and have antiproliferative activity. Formula (I).

CIS-2,4,5-TRIPHENYL-IMIDAZOLINES AND THEIR USE IN THE TREATMENT OF TUMORS

p53 is a tumor suppresser protein that plays a central role in protection against development of cancer. It guards cellular integrity and prevents the propagation of permanently damaged clones of cells by the induction of growth arrest or apoptosis. At the molecular level, p53 is a transcription factor that can activate a panel of genes implicated in the regulation of cell cycle and apoptosis. p53 is a potent cell cycle inhibitor which is tightly regulated by MDM2 at the cellular level. MDM2 and p53 form a feedback control loop. MDM2 can bind p53 and inhibit its ability to transactivate p53-regulated genes. In addition, MDM2 mediates the ubiquitin-dependent degradation of p53. p53 can activate the expression of the MDM2 gene, thus raising the cellular level of MDM2 protein. This feedback control loop insures that both MDM2 and p53 are kept at a low level in normal proliferating cells. MDM2 is also a cofactor for E2F, which plays a central role in cell cycle regulation.

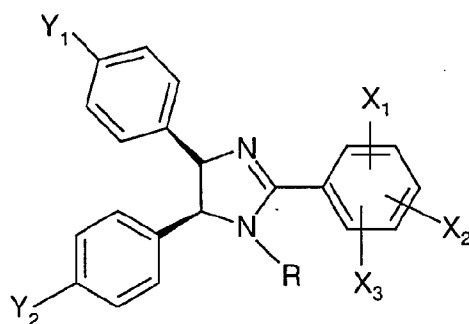
The ratio of MDM2 to p53 (E2F) is dysregulated in many cancers. Frequently occurring molecular defects in the p16INK4/p19ARF locus, for instance, have been shown to affect MDM2 protein degradation. Inhibition of MDM2-p53 interaction in tumor cells with wild-type p53 should lead to accumulation of p53, cell cycle arrest and/or apoptosis. MDM2 antagonists, therefore, can offer a novel approach to cancer therapy as single agents or in combination with a broad spectrum of other antitumor therapies. The feasibility of this strategy has been shown by the use of different macromolecular tools for inhibition of MDM2-p53 interaction (e.g. antibodies, antisense oligonucleotides, peptides). MDM2 also binds E2F through a conserved binding region as p53 and activates E2F-dependent transcription of cyclin A, suggesting that MDM2 antagonists might have effects in p53 mutant cells.

Wells et al. J. Org. Chem., 1972, 37, 2158-2161, report synthesis of imidazolines. Hunter et al., Can. J. Chem., 1972, Vol. 50, pgs. 669-77, report the preparation of amarine and isoamarine compounds which had previously been studied for chemiluminescence (McCapra et al. Photochem. and Photobiol. 1965, 4, 1111-1121). Zupanc et al. Bull. Soc. Chem. & Tech. (Yugoslavia) 1980-81, 27/28, 71-80, report the use of triaryl imidazolines as starting materials in the preparation of EDTA derivatives. EP 363 061 to Matsumoto

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reports imidazoline derivatives useful as immunomodulators. The compounds were indicated to have low toxicity. Treatment and/or prevention of rheumatoid arthritis, multiple sclerosis, systemic lupus, erythemathodes, and rheumatic fever were implicated. WO 00/78725 to Choueiry et al. report a method for making substituted amidine compounds, and indicate that imidazoline-type compounds may be useful in the treatment of diabetes or related diseases involving impaired glucose disposal.

The present invention provides at least a compound of formula I



and the pharmaceutically acceptable salts and esters thereof, wherein

R is -C=OR₁, wherein

R₁ is selected from C₁-C₆ alkyl, -C=CHCOOH, -NHCH₂CH₂R₂, -

N(CH₂CH₂OH)CH₂CH₂OH, -N(CH₃)CH₂CH₂NCH₃, -

N(CH₃)CH₂CH₂N(CH₃)CH₃, saturated 4-, 5- and 6-membered rings, and

saturated and unsaturated 5- and 6- membered rings containing at least one

hetero atom wherein the hetero atom is selected from S, N and O and being

optionally substituted with a group selected from C₁-C₆ alkyl, -C=O-R₅, -OH,

C₁-C₆ alkyl optionally substituted with hydroxy, C₁-C₆ alkyl optionally

substituted with -NH₂, N- C₁-C₆ alkyl, -SO₂CH₃, =O, -CH₂C=OCH₃, and 5-

and 6-membered saturated rings containing at least one hetero atom selected

from S, N and O, wherein

R₅ is selected from H, C₁-C₆ alkyl, -NH₂, -N- C₁-C₆ alkyl, C₁-C₆ alkyl optionally

substituted with hydroxy, and C₁-C₆ alkyl optionally substituted with NH₂,

R₂ is selected from -N(CH₃)CH₃, -NCH₂CH₂NH₂, -NH₂, morpholinyl and

piperazinyl,

X₁, X₂ and X₃ are independently selected from -OH, C₁-C₂ alkyl, C₁-C₆

alkoxy, -Cl, -Br, -F, -CH₂OCH₃, and -CH₂OCH₂CH₃, or one of X₁, X₂ or X₃

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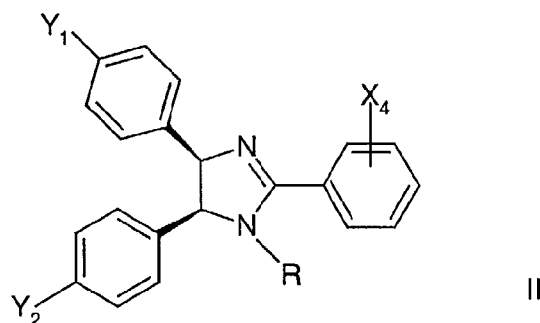
is H and the other two are independently selected from hydroxy, C₁-C₆ alkyl, C₁-C₆ alkoxy, Cl, Br, F, -CF₃, -CH₂OCH₃, -CH₂OCH₂CH₃, -OCH₂CH₂R₃, -OCH₂CF₃, and -OR₄, or one of X₁, X₂ or X₃ is H and the other two taken together with the two carbon atoms and the bonds between them from the benzene ring to which they are optionally substituted form a 5- or 6-membered saturated ring that contains at least one hetero atom selected from S, N, and O, wherein

R₃ is selected from -F, -OCH₃, -N(CH₃)CH₃, -Cl, -Br, unsaturated 5- and 6-membered rings containing at least one hetero atom wherein the hetero atom is selected from S, N and O,

R₄ is a 3- to 5- membered saturated ring and

Y₁ and Y₂ are each independently selected from -Cl, -Br, -NO₂, -C=N, and -C=CH.

The present invention also provides at least one compound of formula II



and the pharmaceutically acceptable salts and esters thereof, wherein

R is -C=OR₁,

R₁ is selected from C₁-C₆ alkyl, saturated 5- and 6-membered rings, saturated 5- and 6-membered rings containing at least one hetero atom wherein the hetero atom is selected from S, N and O and being optionally substituted with a group selected from C₁-C₂ alkyl, C₁-C₃ alcohol, -N(CH₃)CH₃, -C=OCH₃, and 5- and 6-membered rings containing at least one hetero atom wherein the hetero atom is selected from S, N, and O,

X₄ is selected from C₁-C₂ alkyl, C₁-C₆ alkoxy, fluoroethoxy, -Cl, -Br, -F, -OCH₂C=OOQ, -O- C₁-C₆ alkyl, -OCH₂-cyclopropyl, -CH₂OCH₂-phenyl, saturated and unsaturated 5- and 6-membered rings, saturated and unsaturated 5- and 6-membered rings containing at least one hetero atom wherein the hetero atom is selected from S, N and O, wherein

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Q is selected from H, and C₁-C₆ alkyl,

Y1 and Y2 are independently selected from -Cl, -Br, -NO₂, -C=N and -C=H,

with the proviso that where Y1 and Y2 are both -Cl, and R1 is -CH₃ or phenyl, then X4 is not -Cl.

- 5 It is another object of the present invention to provide pharmaceutical composition containing these compounds, and the use of those compounds in the medical therapy, especially in treatment of tumor.

A still further object of the present invention is to provide a process for the preparation of those compounds.

- 10 The present invention provides cis-imidazolines which are small molecule inhibitors of the MDM2-p53 interaction. In cell-free and cell-based assays, compounds of the present invention are shown to inhibit the interaction of MDM2 protein with a p53-like peptide with a potency that is approximately 100 fold greater than a p53-derived peptide. In cell-based assays, these compounds demonstrate mechanistic activity. Incubation of
15 cancer cells with wild-type p53 leads to accumulation of p53 protein, induction of p53-regulated p21 gene, and cell cycle arrest in G1 and G2 phase, resulting in potent antiproliferative activity against wild-type p53 cells in vitro. In contrast, these activities were not observed in cancer cells with mutant p53 at comparable compound concentrations. Therefore, the activity of MDM2 antagonists is likely linked to its
20 mechanism of action. These compounds can be potent and selective anticancer agents.

Unless otherwise indicated, the following definitions are set forth to illustrate and define the meaning and scope of the various terms used to describe the present invention herein.

- "Effective amount" means an amount that is effective to prevent, alleviate or
25 ameliorate symptoms of disease or prolong the survival of the subject being treated.

"Halogen" means fluorine, chlorine, bromine or iodine.

"Hetero atom" means an atom selected from N, O and S.

- "IC₅₀" refers to the concentration of a particular compound required to inhibit 50% of a specific measured activity. IC₅₀ can be measured, inter alia, as is described
30 subsequently.

"Alkyl" denotes a straight-chained or branched saturated aliphatic hydrocarbon. "Lower alkyl" groups denote C₁-C₆ alkyl groups and include methyl, ethyl, propyl, isopropyl, butyl, t-butyl, 2-butyl, pentyl, hexyl, and the like. Generally, lower alkyl is preferably C₁-C₄ alkyl, and more preferably C₁-C₃ alkyl.

5 "Alkoxy" denotes -O-alkyl. "Lower alkoxy" denotes -O- C₁-C₆ alkyl.

The term "saturated 4-, 5- and 6-membered ring" for R₁ preferably refers to cyclopentyl and cyclohexyl.

The term "saturated and unsaturated 5- and 6-membered rings containing at least one hetero atom selected from S, N and O" for R₁ preferably refers to saturated and
10 unsaturated ring systems like morpholinyl, piperazinyl, piperidinyl, thiophenyl, isoxazolyl, furanyl and piperazinyl, more preferably piperazinyl.

The term "unsaturated 5- and 6-membered rings containing at least one hetero atom" for R₃ preferably means imidazolyl.

The term "3- to 5-membered saturated ring" for R₄ preferably means an aliphatic
15 ring, e.g. cyclopentyl.

"Pharmaceutically acceptable ester" refers to a conventionally esterified compound of formula I having a carboxyl group, which esters retain the biological effectiveness and properties of the compounds of formula I and are cleaved in vivo (in the organism) to the corresponding active carboxylic acid.

20 Information concerning esters and the use of esters for the delivery of pharmaceutical compounds is available in Design of Prodrugs. Bundgaard H ed. (Elsevier, 1985). See also, H. Ansel et. al., Pharmaceutical Dosage Forms and Drug Delivery Systems (6th Ed. 1995) at pp. 108-109; Krogsgaard-Larsen, et. al., Textbook of Drug Design and Development (2d Ed. 1996) at pp. 152-191.

25 "Pharmaceutically acceptable salt" refers to conventional acid-addition salts or base-addition salts that retain the biological effectiveness and properties of the compounds of the present invention and are formed from suitable non-toxic organic or inorganic acids or organic or inorganic bases. Sample acid-addition salts include those derived from inorganic acids such as hydrochloric acid, hydrobromic acid, hydroiodic acid, sulfuric acid,
30 sulfamic acid, phosphoric acid and nitric acid, and those derived from organic acids such

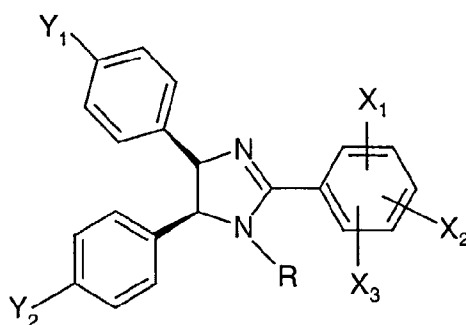
as p-toluenesulfonic acid, salicylic acid, methanesulfonic acid, oxalic acid, succinic acid, citric acid, malic acid, lactic acid, fumaric acid, and the like. Sample base-addition salts include those derived from ammonium, potassium, sodium and, quaternary ammonium hydroxides, such as for example, tetramethylammonium hydroxide. Chemical
 5 modification of a pharmaceutical compound (i.e. drug) into a salt is a technique well known to pharmaceutical chemists to obtain improved physical and chemical stability, hygroscopicity, flowability and solubility of compounds. See, e.g., H. Ansel et. al., Pharmaceutical Dosage Forms and Drug Delivery Systems (6th Ed. 1995) at pp. 196 and 1456-1457.

10 "Pharmaceutically acceptable," such as pharmaceutically acceptable carrier, excipient, etc., means pharmacologically acceptable and substantially non-toxic to the subject to which the particular compound is administered.

"Substituted," as in substituted alkyl, means that the substitution can occur at one or more positions and, unless otherwise indicated, that the substituents at each substitution
 15 site are independently selected from the specified options.

"Therapeutically effective amount" means an amount of at least one designated compound, that significantly inhibits proliferation and/or prevents differentiation of a human tumor cell, including human tumor cell lines.

The present invention concerns compounds of formula I



20

and the pharmaceutically acceptable salts and esters thereof, wherein

R is -C(=O)R₁, wherein

R₁ is selected from C₁-C₆ alkyl, -C(=CH₂)COOH, -NHCH₂CH₂R₂, -
 N(CH₂CH₂OH)CH₂CH₂OH, -N(CH₃)CH₂CH₂NCH₃, -

- N(CH₃)CH₂CH₂N(CH₃)CH₃, saturated 4-, 5- and 6-membered rings, and
 saturated and unsaturated 5- and 6- membered rings containing at least one
 hetero atom wherein the hetero atom is selected from S, N and O and being
 optionally substituted with a group selected from C₁-C₆ alkyl, -C=O-R₅, -OH,
 5 C₁-C₆ alkyl optionally substituted with hydroxy, C₁-C₆ alkyl optionally
 substituted with -NH₂, N- C₁-C₆ alkyl, -SO₂CH₃, =O, -CH₂C=OCH₃, and 5-
 and 6-membered saturated rings containing at least one hetero atom selected
 from S, N and O, wherein
 R₅ is selected from H, C₁-C₆ alkyl, -NH₂, -N- C₁-C₆ alkyl, C₁-C₆ alkyl optionally
 10 substituted with hydroxy, and C₁-C₆ alkyl optionally substituted with NH₂,
 R₂ is selected from -N(CH₃)CH₃, -NCH₂CH₂NH₂, -NH₂, morpholinyl and
 piperazinyl,
 X₁, X₂ and X₃ are independently selected from -OH, C₁-C₂ alkyl, C₁-C₆
 alkoxy, -Cl, -Br, -F, -CH₂OCH₃, and -CH₂OCH₂CH₃, or one of X₁, X₂ or X₃
 15 is H and the other two are independently selected from hydroxy, C₁-C₆ alkyl,
 C₁-C₆ alkoxy, Cl, Br, F, -CF₃, -CH₂OCH₃, -CH₂OCH₂CH₃, -OCH₂CH₂R₃, -
 OCH₂CF₃, and -OR₄, or one of X₁, X₂ or X₃ is H and the other two taken
 together with the two carbon atoms and the bonds between them from the
 benzene ring to which they are optionally substituted form a 5- or 6-membered
 20 saturated ring that contains at least one hetero atom selected from S, N, and O,
 wherein
 R₃ is selected from -F, -OCH₃, -N(CH₃)CH₃, -Cl, -Br, unsaturated 5- and 6-
 membered rings containing at least one hetero atom wherein the hetero atom
 is selected from S, N and O,
 25 R₄ is a 3- to 5- membered saturated ring and
 Y₁ and Y₂ are each independently selected from -Cl, -Br, -NO₂, -C=N, and -C=CH.

In a preferred embodiment, the invention comprises compounds of formula I
 wherein Y₁ and Y₂ are each independently selected from -Cl and -Br.

- In another preferred embodiment, the present invention concerns compounds of
 30 formula I, wherein R₁ is selected from morpholinyl, piperazinyl, piperadinyl, cyclopentyl,
 cyclohexyl, thiophenyl, isoxazolyl, and furanyl, piperazinyl substituted with at least one
 group selected from C₁-C₃ alkyl, -C₁-C₂ alkoxy, -C=OCH₃, -SO₂CH₃, -C=O, -OH,

-CH₂NH₂, -C=OCH₂NH₂, -C=OCH₂OH, -C=OC(OH)CH₂OH, -CH₂C(OH)-CH₂OH, -C=ON(CH₂-)₂, -C=ONH₂, and -C=ON(CH₃)CH₃, -C=OCH(CH₃)₂, -CH₂C=OCH₃, -CH₂CH(OH)CH₃, -CH(CH₃)CH(OH)CH₃ and -CH₂CH₂OH.

In a further preferred embodiment, the present invention concerns compounds of formula I, wherein one of X₁, X₂ and X₃ is H and the other two are independently selected from hydroxy, C₁-C₅ alkoxy, Cl, Br, F, -CH₂OCH₃, -CH₂OCH₂CH₃, C₁-C₂ alkyl, -OCH₂CH₂R₃ and -OR₄, wherein R₃ is selected from -F, -OCH₃, -N(CH₃)CH₃, unsaturated 5-membered rings containing at least one hetero atom wherein the hetero atom is selected from S, N and O, and wherein R₄ is cyclopentyl, more preferably, R₃ is imidazolyl, or one of X₁, X₂ or X₃ is H and the other two taken together with the two carbon atoms and the bonds between them from the benzene ring to which they are substituted form a 5-membered saturated ring that contains at least one hetero atom selected from S, N and O.

Preferably, when one of X₁, X₂ or X₃ is H, the other two are independently selected from -OCH₃ and -CH₂OCH₂CH₃.

More preferably, when one of X₁, X₂ or X₃ is H, one or both of the other two is -O-C₁ alkyl, -O-C₂ alkyl or -O-C₃ alkyl.

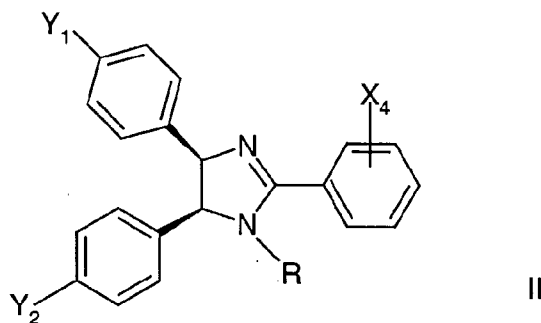
Another embodiment of the present invention concerns compounds of formula I, wherein X₃ is H and X₁ and X₂ together with the two carbon atoms and the bonds between them from the benzene ring to they are substituted form a 6-membered saturated ring that contains one hetero atom which is O.

Another embodiment of the present invention concerns compounds of formula I, wherein one of the groups X₁, X₂ or X₃ is H at meta position, the group at ortho position is selected from C₁-C₅ alkoxy and -OCH₂CF₃, and the group at para position is lower alkoxy. Preferably, X₁, X₂ or X₃ group at ortho position is selected from ethoxy, isopropoxy and -OCH₂CF₃, and the group at para position is selected from methoxy and ethoxy. In this preferred embodiment, R₁ is selected from piperazinyl and substituted piperazinyl.

One embodiment of the present invention concerns compounds of formula I wherein one of the groups X₁, X₂ or X₃ is H at meta position, the group at the ortho

position is C₁-C₆ alkoxy and the group at the para position is -Cl, -Br or -F, or one of the groups X₁, X₂ or X₃ is H at para position, and the two other groups at ortho position are C₁-C₆ alkoxy and the group at meta position is -Cl, -Br or -F.

Another embodiment of the present invention concerns compound of formula II



5

and the pharmaceutically acceptable salts and esters thereof, wherein

R is -C=OR₁,

R₁ is selected from C₁-C₆ alkyl, saturated 5- and 6-membered rings, saturated 5- and 6-

membered rings containing at least one hetero atom wherein the hetero atom is
 10 selected from S, N and O and being optionally substituted with a group selected from
 C₁-C₂ alkyl, C₁-C₃ alcohol, -N(CH₃)CH₃, -C=OCH₃, and 5- and 6-membered
 rings containing at least one hetero atom wherein the hetero atom is selected from S,
 N, and O,

X₄ is selected from C₁-C₂ alkyl, C₁-C₆ alkoxy, fluoroethoxy, -Cl, -Br, -F, -OCH₂C=OOQ,

15 -O- C₁-C₆ alkyl, -OCH₂-cyclopropyl, -CH₂OCH₂-phenyl, saturated and
 unsaturated 5- and 6-membered rings, saturated and unsaturated 5- and 6-
 membered rings containing at least one hetero atom wherein the hetero atom is
 selected from S, N and O, wherein

Q is selected from H, and C₁-C₆ alkyl,

20 Y₁ and Y₂ are independently selected from -Cl, -Br, -NO₂, -C= N and -C=H,

with the proviso that where Y₁ and Y₂ are both -Cl, and R₁ is -CH₃ or phenyl, then
 X₄ is not -Cl.

In a preferred embodiment, the present invention concerns compounds of formula
 II, wherein X₄ is selected from -CH₃, C₁-C₆ alkoxy, -Cl, -Br, -OCH₂C=OOQ, phenyl and

pyrrolidinyl, more preferably, X4 is selected from -CH₃, C₁-C₆ alkoxy, -OCH₂C=OOQ, phenyl and pyrrolidinyl, wherein Q is H or -CH₂CH₃.

Another preferred embodiment of the present invention concerns compounds of formula II, wherein R1 is selected from -CH(CH₃)CH₃, piperazinyl, piperazinyl
5 substituted with a group selected from -CH₃, -CH₂CH₂OH, and -C=OCH₃, piperadinyl, and piperadinyl substituted with a group selected from -pyrrolidinyl, piperadinyl, and -N(CH₃)CH₃.

More preferably, C₁-C₆ alkyl in the compounds of formula II is selected from C₁ alkyl, C₂ alkyl and C₃ alkyl.

10 More preferably, the present invention concerns compounds of formula II wherein Y1 and Y2 are independently selected from -Cl and -Br.

Another preferred embodiment of the present invention concerns compounds of formula I, wherein X4 is C₁-C₆ alkoxy at ortho position, more preferably, the C₁-C₆ alkoxy is selected from ethoxy, isopropoxy and 2-fluoroethoxy. In this preferred
15 embodiment R1 is selected from piperazinyl and substituted piperazinyl.

The present invention concerns compounds of formula I, selected from the group of:

- a) 1-[4,5-Bis-(4-chloro-phenyl)-2-(2,4-dimethoxy-phenyl)-4,5-dihydro-imidazol-1-yl]-2-methyl-propan-1-one;
- b) 1-[4,5-Bis-(4-chloro-phenyl)-2-(2,4-dimethoxy-phenyl)-4,5-dihydro-imidazol-1-yl] ethanone;
- c) 1-[4,5-Bis-(4-chloro-phenyl)-2-(2,4-dimethoxy-phenyl)-4,5-dihydro-imidazol-1-yl]-2,2-dimethyl-propan-1-one;
- d) [4,5-Bis-(4-chloro-phenyl)-2-(2,4-dimethoxy-phenyl)-4,5-dihydro-imidazol-1-yl]-cyclopentyl-methanone;
- 25 e) [4,5-Bis-(4-chloro-phenyl)-2-(2,4-dimethoxy-phenyl)-4,5-dihydro-imidazol-1-yl]-cyclohexyl-methanone;
- f) [4,5-Bis-(4-chloro-phenyl)-2-(2,4-dimethoxy-phenyl)-4,5-dihydro-imidazol-1-yl]-thiophen-2-yl-methanone;
- g) [4,5-Bis-(4-chloro-phenyl)-2-(2,4-dimethoxy-phenyl)-4,5-dihydro-imidazol-1-yl]-isoxazol-5-yl-methanone;
- 30

- h) [4,5-Bis-(4-chloro-phenyl)-2-(2,4-dimethoxy-phenyl)-4,5-dihydro-imidazol-1-yl]-furan-2-yl-methanone;
- i) 1-[4,5-Bis-(4-chloro-phenyl)-2-(2,3-dimethoxy-phenyl)-4,5-dihydro-imidazol-1-yl]-2-methyl-propan-1-one;
- 5 j) [4,5-Bis-(4-chloro-phenyl)-2-(2,4-dimethoxy-phenyl)-4,5-dihydro-imidazol-1-yl]-(4-methyl-piperazin-1-yl)-methanone;
- k) [4,5-Bis-(4-chloro-phenyl)-2-(2,4-dimethoxy-phenyl)-4,5-dihydro-imidazol-1-yl]-piperazin-1-yl-methanone;
- l) [4,5-Bis-(4-chloro-phenyl)-2-(2-fluoro-6-methoxy-phenyl)-4,5-dihydro-imidazol-1-yl]-[4-(2-hydroxy-ethyl)-piperazin-1-yl]-methanone;
- 10 m) 1-{4-[4,5-Bis-(4-bromo-phenyl)-2-(2,4-dimethoxy-phenyl)-4,5-dihydro-imidazole-1-carbonyl]-piperazin-1-yl}-ethanone;
- n) [4,5-Bis-(4-bromo-phenyl)-2-(2,4-dimethoxy-phenyl)-4,5-dihydro-imidazol-1-yl]-[4-(2-hydroxy-ethyl)-piperazin-1-yl]-methanone;
- 15 o) [4,5-Bis-(4-chloro-phenyl)-2-(2-isopropoxy-4-methoxy-phenyl)-4,5-dihydro-imidazol-1-yl]-[4-(2-hydroxy-ethyl)-piperazin-1-yl]-methanone hydrochloride;
- p) [4,5-Bis-(4-chloro-phenyl)-2-(2-ethoxy-4-methoxy-phenyl)-4,5-dihydro-imidazol-1-yl]-(4-methanesulfonyl-piperazin-1-yl)-methanone;
- 20 q) [4,5-Bis-(4-chloro-phenyl)-2-(2-ethoxy-4-methoxy-phenyl)-4,5-dihydro-imidazol-1-yl]-[4-(2-hydroxy-ethyl)-piperazin-1-yl]-methanone;
- r) [4,5-Bis-(4-chloro-phenyl)-2-(2-ethoxy-4-methoxy-phenyl)-4,5-dihydro-imidazol-1-yl]-morpholin-4-yl-methanone;
- s) [4,5-Bis-(4-chloro-phenyl)-2-(2-ethoxy-4-methoxy-phenyl)-4,5-dihydro-imidazol-1-yl]-(4-methyl-piperazin-1-yl)-methanone;
- 25 t) 1-{4-[4,5-Bis-(4-chloro-phenyl)-2-(2-ethoxy-4-methoxy-phenyl)-4,5-dihydro-imidazole-1-carbonyl]-piperazin-1-yl}-ethanone;
- u) 4-[4,5-Bis-(4-chloro-phenyl)-2-(2-ethoxy-4-methoxy-phenyl)-4,5-dihydro-imidazole-1-carbonyl]-piperazin-2-one;
- 30 v) [4,5-Bis-(4-chloro-phenyl)-2-(2-isopropoxy-4-methoxy-phenyl)-4,5-dihydro-imidazol-1-yl]-piperazin-1-yl-methanone;
- w) 1-{4-[4,5-Bis-(4-chloro-phenyl)-2-(2-isopropoxy-4-methoxy-phenyl)-4,5-dihydro-imidazole-1-carbonyl]-piperazin-1-yl}-ethanone;
- x) [4,5-Bis-(4-chloro-phenyl)-2-(2-isopropoxy-4-methoxy-phenyl)-4,5-dihydro-imidazol-1-yl]-(4-methanesulfonyl-piperazin-1-yl)-methanone;
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- y) [4,5-Bis-(4-chloro-phenyl)-2-(2-isopropoxy-4-methoxy-phenyl)-4,5-dihydro-imidazol-1-yl]-(2,5-dimethyl-piperazin-1-yl)-methanone;
- z) 4,5-Bis-(4-chloro-phenyl)-2-(2-isopropoxy-4-methoxy-phenyl)-4,5-dihydro-imidazole-1-carboxylic acid bis-(2-hydroxy-ethyl)-amide;
- 5 aa) [4,5-Bis-(4-chloro-phenyl)-2-(2-isopropoxy-4-methoxy-phenyl)-4,5-dihydro-imidazol-1-yl]-(4-ethyl-piperazin-1-yl)-methanone;
- bb) [1,4']Bipiperidinyl-1'-yl-[4,5-bis-(4-chloro-phenyl)-2-(2-isopropoxy-4-methoxy-phenyl)-4,5-dihydro-imidazol-1-yl]-methanone;
- cc) [4,5-Bis-(4-chloro-phenyl)-2-(2-isopropoxy-4-methoxy-phenyl)-4,5-dihydro-imidazol-1-yl]-(4-pyrrolidin-1-yl-piperidin-1-yl)-methanone;
- 10 dd) [4,5-Bis-(4-chloro-phenyl)-2-(2-isopropoxy-4-methoxy-phenyl)-4,5-dihydro-imidazol-1-yl]-(4-dimethylamino-piperidin-1-yl)-methanone;
- ee) [4,5-Bis-(4-chloro-phenyl)-2-(2-isopropoxy-4-methoxy-phenyl)-4,5-dihydro-imidazol-1-yl]-morpholin-4-yl-methanone;
- 15 ff) [4,5-Bis-(4-chloro-phenyl)-2-(2-isopropoxy-4-methoxy-phenyl)-4,5-dihydro-imidazol-1-yl]-(4-isopropyl-piperazin-1-yl)-methanone;
- gg) 4-[4,5-Bis-(4-chloro-phenyl)-2-(2-isopropoxy-4-methoxy-phenyl)-4,5-dihydro-imidazole-1-carbonyl]-piperazin-2-one;
- hh) [4,5-Bis-(4-chloro-phenyl)-2-(2-isopropoxy-4-methoxy-phenyl)-4,5-dihydro-imidazol-1-yl]-(4-hydroxymethyl-piperidin-1-yl)-methanone;
- 20 ii) [4,5-Bis-(4-chloro-phenyl)-2-(2-isopropoxy-4-methoxy-phenyl)-4,5-dihydro-imidazol-1-yl]-[4-(2-hydroxy-ethyl)-piperidin-1-yl]-methanone;
- jj) [4,5-Bis-(4-chloro-phenyl)-2-(2-isopropoxy-4-methoxy-phenyl)-4,5-dihydro-imidazol-1-yl]-(3-methyl-piperazin-1-yl)-methanone;
- 25 kk) 1-{4-[4,5-Bis-(4-chloro-phenyl)-2-(2-isopropoxy-4-methoxy-phenyl)-4,5-dihydro-imidazole-1-carbonyl]-2-methyl-piperazin-1-yl}-ethanone;
- ll) [4,5-Bis-(4-chloro-phenyl)-2-(2-isopropoxy-4-methoxy-phenyl)-4,5-dihydro-imidazol-1-yl]-(4-methanesulfonyl-3-methyl-piperazin-1-yl)-methanone;
- mm) [4,5-Bis-(4-chloro-phenyl)-2-(2-isopropoxy-4-methoxy-phenyl)-4,5-dihydro-imidazol-1-yl]-(4-hydroxy-piperidin-1-yl)-methanone;
- 30 nn) (4-Aminomethyl-piperidin-1-yl)-[4,5-bis-(4-chloro-phenyl)-2-(2-isopropoxy-4-methoxy-phenyl)-4,5-dihydro-imidazol-1-yl]-methanone;
- oo) [4,5-Bis-(4-bromo-phenyl)-2-(2-ethoxy-4-methoxy-phenyl)-4,5-dihydro-imidazol-1-yl]-[4-(2-hydroxy-ethyl)-piperazin-1-yl]-methanone;

- pp) [4,5-Bis-(4-bromo-phenyl)-2-(2-ethoxy-4-methoxy-phenyl)-4,5-dihydro-imidazol-1-yl]-piperazin-1-yl-methanone;
- qq) [4,5-Bis-(4-bromo-phenyl)-2-(2-ethoxy-4-methoxy-phenyl)-4,5-dihydro-imidazol-1-yl]-(4-methanesulfonyl-piperazin-1-yl)-methanone;
- 5 rr) 1-[4-[4,5-Bis-(4-bromo-phenyl)-2-(2-ethoxy-4-methoxy-phenyl)-4,5-dihydro-imidazole-1-carbonyl]-piperazin-1-yl}-ethanone;
- ss) [4,5-Bis-(4-bromo-phenyl)-2-(2-ethoxy-4-methoxy-phenyl)-4,5-dihydro-imidazol-1-yl]-(4-methyl-piperazin-1-yl)-methanone;
- tt) 4-[4,5-Bis-(4-bromo-phenyl)-2-(2-ethoxy-4-methoxy-phenyl)-4,5-dihydro-imidazole-1-carbonyl]-piperazine-1-carbaldehyde;
- 10 uu) [4,5-Bis-(4-bromo-phenyl)-2-(2-ethoxy-4-methoxy-phenyl)-4,5-dihydro-imidazol-1-yl]-(4-pyrrolidin-1-yl-piperidin-1-yl)-methanone;
- vv) [4,5-Bis-(4-bromo-phenyl)-2-(2-ethoxy-4-methoxy-phenyl)-4,5-dihydro-imidazol-1-yl]-(4-dimethylamino-piperidin-1-yl)-methanone;
- 15 ww) [4,5-Bis-(4-bromo-phenyl)-2-(2-ethoxy-4-methoxy-phenyl)-4,5-dihydro-imidazol-1-yl]-(4-isopropyl-piperazin-1-yl)-methanone;
- xx) 4-[4,5-Bis-(4-bromo-phenyl)-2-(2-ethoxy-4-methoxy-phenyl)-4,5-dihydro-imidazole-1-carbonyl]-piperazin-2-one; and
- yy) [4,5-Bis-(4-bromo-phenyl)-2-(2-isopropoxy-4-methoxy-phenyl)-4,5-dihydro-imidazol-1-yl]-piperazin-1-yl-methanone.
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In another embodiment, the present invention concerns compounds of formula I, selected from the group of:

- a) 1-[4-[4,5-Bis-(4-bromo-phenyl)-2-(2-isopropoxy-4-methoxy-phenyl)-4,5-dihydro-imidazole-1-carbonyl]-piperazin-1-yl}-ethanone;
- 25 b) [4,5-Bis-(4-bromo-phenyl)-2-(2-isopropoxy-4-methoxy-phenyl)-4,5-dihydro-imidazol-1-yl]-(4-methanesulfonyl-piperazin-1-yl)-methanone;
- c) [4,5-Bis-(4-bromo-phenyl)-2-(2-isopropoxy-4-methoxy-phenyl)-4,5-dihydro-imidazol-1-yl]-(4-methyl-piperazin-1-yl)-methanone;
- d) [4,5-Bis-(4-bromo-phenyl)-2-(2-isopropoxy-4-methoxy-phenyl)-4,5-dihydro-imidazol-1-yl]-morpholin-4-yl-methanone;
- 30 e) [1,4']Bipiperidiny-1'-yl-[4,5-bis-(4-bromo-phenyl)-2-(2-isopropoxy-4-methoxy-phenyl)-4,5-dihydro-imidazol-1-yl]-methanone;
- f) [4,5-Bis-(4-bromo-phenyl)-2-(2-isopropoxy-4-methoxy-phenyl)-4,5-dihydro-imidazol-1-yl]-(4-ethyl-piperazin-1-yl)-methanone;

- g) 4-[4,5-Bis-(4-bromo-phenyl)-2-(2-isopropoxy-4-methoxy-phenyl)-4,5-dihydro-imidazole-1-carbonyl]-piperazin-2-one;
- h) [4,5-Bis-(4-cyano-phenyl)-2-(2-isopropoxy-4-methoxy-phenyl)-4,5-dihydro-imidazol-1-yl]-piperazin-1-yl-methanone;
- 5 i) 1-(4-{4,5-Bis-(4-chloro-phenyl)-2-[4-methoxy-2-(2-methoxy-ethoxy)-phenyl]-4,5-dihydro-imidazole-1-carbonyl}-piperazin-1-yl)-ethanone;
- j) 1-(4-{4,5-Bis-(4-chloro-phenyl)-2-[2-(2-fluoro-ethoxy)-4-methoxy-phenyl]-4,5-dihydro-imidazole-1-carbonyl}-piperazin-1-yl)-ethanone;
- k) 4-[4,5-Bis-(4-chloro-phenyl)-2-[2-(2-fluoro-ethoxy)-4-methoxy-phenyl]-4,5-dihydro-imidazole-1-carbonyl]-piperazin-2-one;
- 10 l) [4,5-Bis-(4-chloro-phenyl)-2-(2-ethoxy-4-methoxy-phenyl)-4,5-dihydro-imidazol-1-yl]-piperazin-1-yl-methanone hydrochloride;
- m) 4,5-Bis-(4-chloro-phenyl)-2-(2-ethoxy-4-methoxy-phenyl)-4,5-dihydro-imidazole-1-carboxylic acid methyl-(2-methylamino-ethyl)-amide, trifluoroacetic acid salt;
- 15 n) 4,5-Bis-(4-chloro-phenyl)-2-(2-ethoxy-4-methoxy-phenyl)-4,5-dihydro-imidazole-1-carboxylic acid (2-dimethylamino-ethyl)-methyl-amide, trifluoroacetic acid salt;
- o) 4,5-Bis-(4-chloro-phenyl)-2-(2-ethoxy-4-methoxy-phenyl)-4,5-dihydro-imidazole-1-carboxylic acid (2-dimethylamino-ethyl)-amide, trifluoroacetic acid salt;
- 20 p) 4,5-Bis-(4-chloro-phenyl)-2-(2-ethoxy-4-methoxy-phenyl)-4,5-dihydro-imidazole-1-carboxylic acid (2-amino-ethyl)-amide, trifluoroacetic acid salt;
- q) [4,5-Bis-(4-chloro-phenyl)-2-(2-ethoxy-4-methoxy-phenyl)-4,5-dihydro-imidazol-1-yl]-(4-pyrrolidin-1-yl-piperidin-1-yl)-methanone hydrochloride;
- 25 r) [4,5-Bis-(4-chloro-phenyl)-2-(4-methoxy-2-propoxy-phenyl)-4,5-dihydro-imidazol-1-yl]-piperazin-1-yl-methanone, trifluoroacetic acid salt;
- s) [4,5-Bis-(4-chloro-phenyl)-2-(2-isopropoxy-4-methoxy-phenyl)-4,5-dihydro-imidazol-1-yl]-(4-methyl-piperazin-1-yl)-methanone hydrochloride;
- 30 t) 4,5-Bis-(4-chloro-phenyl)-2-(2-isopropoxy-4-methoxy-phenyl)-4,5-dihydro-imidazole-1-carboxylic acid (2-morpholin-4-yl-ethyl)-amide hydrochloride;
- u) 4,5-Bis-(4-chloro-phenyl)-2-(2-isopropoxy-4-methoxy-phenyl)-4,5-dihydro-imidazole-1-carboxylic acid (2-piperazin-1-yl-ethyl)-amide hydrochloride;
- v) [4,5-Bis-(4-chloro-phenyl)-2-(2-isobutoxy-4-methoxy-phenyl)-4,5-dihydro-imidazol-1-yl]-piperazin-1-yl-methanone hydrochloride;
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- w) [4,5-Bis-(4-chloro-phenyl)-2-(2-isopropoxy-4-methoxy-phenyl)-4,5-dihydro-imidazol-1-yl]-(3-methyl-piperazin-1-yl)-methanone hydrochloride;
- x) {4,5-Bis-(4-chloro-phenyl)-2-[4-methoxy-2-(2-methoxy-ethoxy)-phenyl]-4,5-dihydro-imidazol-1-yl}-piperazin-1-yl-methanone, trifluoroacetic acid salt;
- 5 y) {4,5-Bis-(4-chloro-phenyl)-2-[2-(2-fluoro-ethoxy)-4-methoxy-phenyl]-4,5-dihydro-imidazol-1-yl}-piperazin-1-yl-methanone;
- z) {4,5-Bis-(4-chloro-phenyl)-2-[2-(2-fluoro-ethoxy)-4-methoxy-phenyl]-4,5-dihydro-imidazol-1-yl}-(4-pyrrolidin-1-yl-piperidin-1-yl)-methanone hydrochloride;
- 10 aa) 2-Amino-1-{4-[4,5-bis-(4-chloro-phenyl)-2-(2-isopropoxy-4-methoxy-phenyl)-4,5-dihydro-imidazole-1-carbonyl]-piperazin-1-yl}-ethanone;
- bb) 1-{4-[4,5-Bis-(4-chloro-phenyl)-2-(2-isopropoxy-4-methoxy-phenyl)-4,5-dihydro-imidazole-1-carbonyl]-piperazin-1-yl}-2-hydroxy-ethanone;
- cc) 1-{4-[4,5-Bis-(4-chloro-phenyl)-2-(2-isopropoxy-4-methoxy-phenyl)-4,5-dihydro-imidazole-1-carbonyl]-piperazin-1-yl}-2,3-dihydroxy-propan-1-one;
- 15 dd) [4,5-Bis-(4-chloro-phenyl)-2-(2-isopropoxy-4-methoxy-phenyl)-4,5-dihydro-imidazol-1-yl]-[4-(2,3-dihydroxy-propyl)-piperazin-1-yl]-methanone;
- ee) 4-[4,5-Bis-(4-chloro-phenyl)-2-(2-isopropoxy-4-methoxy-phenyl)-4,5-dihydro-imidazole-1-carbonyl]-piperazine-1-carboxylic acid dimethylamide;
- 20 ff) 4-[4,5-Bis-(4-chloro-phenyl)-2-(2-isopropoxy-4-methoxy-phenyl)-4,5-dihydro-imidazole-1-carbonyl]-piperazine-1-carboxylic acid amide;
- gg) [4,5-Bis-(4-chloro-phenyl)-2-(2,4-diethoxy-phenyl)-4,5-dihydro-imidazol-1-yl]-piperazin-1-yl-methanone;
- hh) [4,5-Bis-(4-chloro-phenyl)-2-(2,4-diethoxy-phenyl)-4,5-dihydro-imidazol-1-yl] morpholin-4-yl-methanone;
- 25 ii) [4,5-Bis-(4-chloro-phenyl)-2-(2,4-diethoxy-phenyl)-4,5-dihydro-imidazol-1-yl]-[4-(2-hydroxy-ethyl)-piperazin-1-yl]-methanone;
- jj) [4,5-Bis-(4-chloro-phenyl)-2-(2,4-diethoxy-phenyl)-4,5-dihydro-imidazol-1-yl]-(4-methyl-piperazin-1-yl)-methanone;
- 30 kk) 1-{4-[4,5-Bis-(4-chloro-phenyl)-2-(2,4-diethoxy-phenyl)-4,5-dihydro-imidazole-1-carbonyl]-piperazin-1-yl}-ethanone;
- ll) [4,5-Bis-(4-chloro-phenyl)-2-(2,4-diethoxy-phenyl)-4,5-dihydro-imidazol-1-yl]-(4-methanesulfonyl-piperazin-1-yl)-methanone;
- mm) [4,5-Bis-(4-chloro-phenyl)-2-(2,4-diethoxy-phenyl)-4,5-dihydro-imidazol-1-yl]-(4-pyrrolidin-1-yl-piperidin-1-yl)-methanone;
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- nn) [4,5-Bis-(4-bromo-phenyl)-2-(2,4-diethoxy-phenyl)-4,5-dihydro-imidazol-1-yl]-(4-methyl-piperazin-1-yl)-methanone;
- oo) [4,5-Bis-(4-bromo-phenyl)-2-(2,4-diethoxy-phenyl)-4,5-dihydro-imidazol-1-yl]-(4-ethyl-piperazin-1-yl)-methanone;
- 5 pp) [4,5-Bis-(4-bromo-phenyl)-2-(2,4-diethoxy-phenyl)-4,5-dihydro-imidazol-1-yl]-morpholin-4-yl-methanone;
- qq) 4-[4,5-Bis-(4-chloro-phenyl)-2-(2,4-diethoxy-phenyl)-4,5-dihydro-imidazole-1-carbonyl]-piperazine-1-carboxylic acid amide;
- rr) 4-[4,5-Bis-(4-chloro-phenyl)-2-(2,4-diethoxy-phenyl)-4,5-dihydro-imidazole-1-carbonyl]-piperazine-1-carboxylic acid dimethylamide;
- 10 ss) [4,5-Bis-(4-chloro-phenyl)-2-(4-dimethylamino-2-ethoxy-phenyl)-4,5-dihydro-imidazol-1-yl]-piperazin-1-yl-methanone;
- tt) [4,5-Bis-(4-chloro-phenyl)-2-(2-ethoxy-4-ethyl-phenyl)-4,5-dihydro-imidazol-1-yl]-piperazin-1-yl-methanone;
- 15 uu) [4,5-Bis-(4-chloro-phenyl)-2-(2-ethoxy-4-methyl-phenyl)-4,5-dihydro-imidazol-1-yl]-piperazin-1-yl-methanone;
- vv) [4,5-Bis-(4-chloro-phenyl)-2-(4-ethyl-2-isopropoxy-phenyl)-4,5-dihydro-imidazol-1-yl]-piperazin-1-yl-methanone;
- ww) [4,5-Bis-(4-chloro-phenyl)-2-(2-isopropoxy-4-methyl-phenyl)-4,5-dihydro-imidazol-1-yl]-piperazin-1-yl-methanone;
- 20 xx) 1-{4-[4,5-Bis-(4-chloro-phenyl)-2-(4-dimethylamino-2-ethoxy-phenyl)-4,5-dihydro-imidazole-1-carbonyl]-piperazin-1-yl}-ethanone; and
- yy) [4,5-Bis-(4-chloro-phenyl)-2-(2-ethoxy-5-methyl-phenyl)-4,5-dihydro-imidazol-1-yl]-piperazin-1-yl-methanone, trifluoroacetic acid salt.

25 In another embodiment, the present invention concerns compounds of formula I, selected from the group of:

- a) [4,5-Bis-(4-chloro-phenyl)-2-(2-ethoxy-4-fluoro-phenyl)-4,5-dihydro-imidazol-1-yl]-(4-pyrrolidin-1-yl-piperidin-1-yl)-methanone;
- b) [4,5-Bis-(4-chloro-phenyl)-2-(2-ethoxy-4-fluoro-phenyl)-4,5-dihydro-imidazol-1-yl]-(4-dimethylamino-piperidin-1-yl)-methanone;
- 30 c) [4,5-Bis-(4-chloro-phenyl)-2-(2-ethoxy-4-fluoro-phenyl)-4,5-dihydro-imidazol-1-yl]-piperazin-1-yl-methanone;
- d) [4,5-Bis-(4-chloro-phenyl)-2-(4-fluoro-2-isopropoxy-phenyl)-4,5-dihydro-imidazol-1-yl]-(4-pyrrolidin-1-yl-piperidin-1-yl)-methanone;

- e) [4,5-Bis-(4-chloro-phenyl)-2-(4-fluoro-2-isopropoxy-phenyl)-4,5-dihydro-imidazol-1-yl]-(4-dimethylamino-piperidin-1-yl)-methanone;
- f) [4,5-Bis-(4-chloro-phenyl)-2-(4-fluoro-2-isopropoxy-phenyl)-4,5-dihydro-imidazol-1-yl]-(4-methyl-piperazin-1-yl)-methanone;
- 5 g) [4,5-Bis-(4-chloro-phenyl)-2-(4-fluoro-2-isopropoxy-phenyl)-4,5-dihydro-imidazol-1-yl]-piperazin-1-yl-methanone;
- h) [4,5-Bis-(4-chloro-phenyl)-2-(4-fluoro-2-isopropoxy-phenyl)-4,5-dihydro-imidazol-1-yl]-(4-methanesulfonyl-piperazin-1-yl)-methanone;
- i) 4-[4,5-Bis-(4-chloro-phenyl)-2-(4-fluoro-2-isopropoxy-phenyl)-4,5-dihydro-
10 imidazole-1-carbonyl]-piperazin-2-one;
- j) [4,5-Bis-(4-chloro-phenyl)-2-chroman-8-yl-4,5-dihydro-imidazol-1-yl]-piperazin-1-yl-methanone;
- k) 4-[4,5-Bis-(4-bromo-phenyl)-2-(2-ethoxy-4-fluoro-phenyl)-4,5-dihydro-imidazole-1-carbonyl]-piperazin-2-one;
- 15 l) [4,5-Bis-(4-bromo-phenyl)-2-(2-ethoxy-4-fluoro-phenyl)-4,5-dihydro-imidazol-1-yl]-morpholin-4-yl-methanone;
- m) [4,5-Bis-(4-bromo-phenyl)-2-(2-ethoxy-4-fluoro-phenyl)-4,5-dihydro-imidazol-1-yl]-(4-pyrrolidin-1-yl-piperidin-1-yl)-methanone;
- n) [4,5-Bis-(4-bromo-phenyl)-2-(2-ethoxy-4-fluoro-phenyl)-4,5-dihydro-
20 imidazol-1-yl]-(4-dimethylamino-piperidin-1-yl)-methanone;
- o) [4,5-Bis-(4-bromo-phenyl)-2-(2-ethoxy-4-fluoro-phenyl)-4,5-dihydro-imidazol-1-yl]-piperazin-1-yl-methanone;
- p) [4,5-Bis-(4-chloro-phenyl)-2-(2-cyclopentyloxy-4-methoxy-phenyl)-4,5-dihydro-imidazol-1-yl]-piperazin-1-yl-methanone;
- 25 q) {4,5-Bis-(4-chloro-phenyl)-2-[2-(2-dimethylamino-ethoxy)-4-methoxy-phenyl]-4,5-dihydro-imidazol-1-yl}-piperazin-1-yl-methanone;
- r) {4,5-Bis-(4-chloro-phenyl)-2-[2-(2-imidazol-1-yl-ethoxy)-4-methoxy-phenyl]-4,5-dihydro-imidazol-1-yl}-piperazin-1-yl-methanone;
- s) [2-(4-Chloro-2-ethoxy-phenyl)-4,5-bis-(4-chloro-phenyl)-4,5-dihydro-
30 imidazol-1-yl]-piperazin-1-yl-methanone hydrochloride;
- t) [2-(4-Chloro-2-ethoxy-phenyl)-4,5-bis-(4-chloro-phenyl)-4,5-dihydro-imidazol-1-yl]-(4-methyl-piperazin-1-yl)-methanone hydrochloride;
- u) [2-(4-Chloro-2-ethoxy-phenyl)-4,5-bis-(4-chloro-phenyl)-4,5-dihydro-imidazol-1-yl]-(4-pyrrolidin-1-yl-piperidin-1-yl)-methanone hydrochloride;

- v) [2-(4-Chloro-2-ethoxy-phenyl)-4,5-bis-(4-chloro-phenyl)-4,5-dihydro-imidazol-1-yl]-morpholin-4-yl-methanone;
- w) 1-{4-[2-(4-Chloro-2-ethoxy-phenyl)-4,5-bis-(4-chloro-phenyl)-4,5-dihydro-imidazole-1-carbonyl]-piperazin-1-yl}-ethanone;
- 5 x) [2-(4-Chloro-2-ethoxy-phenyl)-4,5-bis-(4-chloro-phenyl)-4,5-dihydro-imidazol-1-yl]-[4-(2-hydroxy-ethyl)-piperazin-1-yl]-methanone hydrochloride;
- y) 4-[2-(4-Chloro-2-ethoxy-phenyl)-4,5-bis-(4-chloro-phenyl)-4,5-dihydro-imidazole-1-carbonyl]-piperazin-2-one;
- 10 z) [4,5-Bis-(4-chloro-phenyl)-2-(4-ethoxy-2-isopropoxy-phenyl)-4,5-dihydro-imidazol-1-yl]-piperazin-1-yl-methanone;
- aa) [4,5-Bis-(4-chloro-phenyl)-2-(2-ethoxy-5-methoxy-phenyl)-4,5-dihydro-imidazol-1-yl]-piperazin-1-yl-methanone, trifluoroacetic acid salt;
- bb) [4,5-Bis-(4-chloro-phenyl)-2-(2-ethoxy-5-methoxy-phenyl)-4,5-dihydro-imidazol-1-yl]-(4-methanesulfonyl-piperazin-1-yl)-methanone;
- 15 cc) [4,5-Bis-(4-chloro-phenyl)-2-(2-ethoxy-5-methoxy-phenyl)-4,5-dihydro-imidazol-1-yl]-[4-(2-hydroxy-ethyl)-piperazin-1-yl]-methanone hydrochloride;
- dd) [4,5-Bis-(4-chloro-phenyl)-2-(2,5-diethoxy-phenyl)-4,5-dihydro-imidazol-1-yl]-piperazin-1-yl-methanone hydrochloride;
- 20 ee) [4,5-Bis-(4-chloro-phenyl)-2-(2,5-diethoxy-phenyl)-4,5-dihydro-imidazol-1-yl]-(4-methanesulfonyl-piperazin-1-yl)-methanone;
- ff) [4,5-Bis-(4-chloro-phenyl)-2-(4-ethoxy-2-isopropoxy-phenyl)-4,5-dihydro-imidazol-1-yl]-[4-(2-hydroxy-ethyl)-piperazin-1-yl]-methanone;
- 25 gg) 4-[4,5-Bis-(4-chloro-phenyl)-2-(4-ethoxy-2-isopropoxy-phenyl)-4,5-dihydro-imidazole-1-carbonyl]-piperazin-2-one;
- hh) [4,5-Bis-(4-chloro-phenyl)-2-(5-ethoxy-2-isopropoxy-phenyl)-4,5-dihydro-imidazol-1-yl]-piperazin-1-yl-methanone;
- ii) [4,5-Bis-(4-chloro-phenyl)-2-(5-ethoxy-2-isopropoxy-phenyl)-4,5-dihydro-imidazol-1-yl]-(4-methanesulfonyl-piperazin-1-yl)-methanone;
- 30 jj) [4,5-Bis-(4-chloro-phenyl)-2-(5-ethoxy-2-isopropoxy-phenyl)-4,5-dihydro-imidazol-1-yl]-[4-(2-hydroxy-ethyl)-piperazin-1-yl]-methanone hydrochloride;
- kk) 1-{4-[4,5-Bis-(4-chloro-phenyl)-2-(4-ethoxy-2-isopropoxy-phenyl)-4,5-dihydro-imidazole-1-carbonyl]-piperazin-1-yl}-ethanone;
- 35

- ll) 1-{4-[4,5-Bis-(4-chloro-phenyl)-2-(5-ethoxy-2-isopropoxy-phenyl)-4,5-dihydro-imidazole-1-carbonyl]-piperazin-1-yl}-ethanone;
- mm) [4,5-Bis-(4-chloro-phenyl)-2-(4-ethoxy-2-isopropoxy-phenyl)-4,5-dihydro-imidazol-1-yl]-(4-pyrrolidin-1-yl-piperidin-1-yl)-methanone;
- 5 nn) [4,5-Bis-(4-chloro-phenyl)-2-(2-isopropoxy-5-methoxy-phenyl)-4,5-dihydro-imidazol-1-yl]-piperazin-1-yl-methanone, trifluoroacetic acid salt;
- oo) [4,5-Bis-(4-chloro-phenyl)-2-(2,4-diisopropoxy-phenyl)-4,5-dihydro-imidazol-1-yl]-piperazin-1-yl-methanone;
- pp) [4,5-Bis-(4-chloro-phenyl)-2-(2,5-diisopropoxy-phenyl)-4,5-dihydro-imidazol-1-yl]-piperazin-1-yl-methanone hydrochloride;
- 10 qq) 1-[4,5-Bis-(4-chloro-phenyl)-2-(2-methoxy-5-morpholin-4-yl-methyl-phenyl)-4,5-dihydro-imidazol-1-yl]-2-methyl-propan-1-one;
- rr) 1-[4,5-Bis-(4-chloro-phenyl)-2-(3-hydroxymethyl-5-methoxy-phenyl)-4,5-dihydro-imidazol-1-yl]-2-methyl-propan-1-one;
- 15 ss) 1-[4,5-Bis-(4-chloro-phenyl)-2-(3-hydroxymethyl-5-methoxymethyl-phenyl)-4,5-dihydro-imidazol-1-yl]-ethanone;
- tt) 1-[4,5-Bis-(4-chloro-phenyl)-2-(3-methoxy-5-methoxymethyl-phenyl)-4,5-dihydro-imidazol-1-yl]-2-methyl-propan-1-one;
- uu) 3-[4,5-Bis-(4-chloro-phenyl)-1-isobutyryl-4,5-dihydro-1H-imidazol-2-yl]-5-methoxymethyl-benzoic acid;
- 20 vv) 1-[4,5-Bis-(4-chloro-phenyl)-2-(5-ethoxymethyl-2,4-dimethoxy-phenyl)-4,5-dihydro-imidazol-1-yl]-2-methyl-propan-1-one;
- ww) [4,5-Bis-(4-chloro-phenyl)-2-(2-ethoxy-6-methoxy-phenyl)-4,5-dihydro-imidazol-1-yl]-piperazin-1-yl-methanone; and
- 25 xx) [4,5-bis-(4-chloro-phenyl)-2-(5-ethoxymethyl-2,4-dimethoxy-phenyl)-4,5-dihydro-imidazol-1-yl]-piperazin-1-yl-methanone.

In a further embodiment, the present invention concerns compounds of formula I selected from the group of:

- 30 a) [4,5-Bis-(4-chloro-phenyl)-2-(2-isopropoxy-4-methoxy-phenyl)-4,5-dihydro-imidazol-1-yl]-[4-(2-hydroxy-propyl)-piperazin-1-yl]-methanone;
- b) [4,5-Bis-(4-chloro-phenyl)-2-(2-isopropoxy-4-methoxy-phenyl)-4,5-dihydro-imidazol-1-yl]-threo[4-(2-hydroxy-1-methyl-propyl)-piperazin-1-yl]-methanone;

- c) [4,5-Bis-(4-chloro-phenyl)-2-(2-isopropoxy-4-methoxy-phenyl)-4,5-dihydro-imidazol-1-yl]-erythro[4-(2-hydroxy-1-methyl-propyl)-piperazin-1-yl]-methanone;
- d) 1-[4-[4,5-Bis-(4-chloro-phenyl)-2-(2-isopropoxy-4-methoxy-phenyl)-4,5-dihydro-imidazole-1-carbonyl]-piperazin-1-yl]-propan-2-one;
- e) [4,5-Bis-(4-chloro-phenyl)-2-(2-isopropoxy-4-methoxy-phenyl)-4,5-dihydro-imidazol-1-yl]-[1,4]diazepan-1-yl-methanone;
- f) 4-[4,5-Bis-(4-chloro-phenyl)-2-(2-isopropoxy-4-methoxy-phenyl)-4,5-dihydro-imidazole-1-carbonyl]-1-methyl-piperazin-2-one;
- g) 1-[4-[4,5-Bis-(4-chloro-phenyl)-2-(2-isopropoxy-4-methoxy-phenyl)-4,5-dihydro-imidazole-1-carbonyl]-piperazin-1-yl]-2-methyl-propan-1-one;
- h) 4-[4,5-Bis-(4-chloro-phenyl)-2-(2-isopropoxy-4-methoxy-phenyl)-4,5-dihydro-imidazole-1-carbonyl]-piperazine-1-carbaldehyde;
- i) 4-[4,5-Bis-(4-chloro-phenyl)-2-[4-methoxy-2-(2,2,2-trifluoro-ethoxy)-phenyl]-4,5-dihydro-imidazole-1-carbonyl]-piperazin-2-one;
- j) 4-[4,5-Bis-(4-bromo-phenyl)-2-[4-methoxy-2-(2,2,2-trifluoro-ethoxy)-phenyl]-4,5-dihydro-imidazole-1-carbonyl]-piperazin-2-one;
- k) [4,5-Bis-(4-ethynyl-phenyl)-2-(2-isopropoxy-4-methoxy-phenyl)-4,5-dihydro-imidazol-1-yl]-(4-pyrrolidin-1-yl-piperidin-1-yl)-methanone;
- l) 1-[4-[2-(5-Chloro-2-isopropoxy-phenyl)-4,5-bis-(4-chloro-phenyl)-4,5-dihydro-imidazole-1-carbonyl]-piperazin-1-yl]-ethanone; and
- m) [5-(4-Chloro-phenyl)-4-(4-ethynyl-phenyl)-2-(2-isopropoxy-4-methoxy-phenyl)-4,5-dihydro-imidazol-1-yl]-(4-pyrrolidin-1-yl-piperidin-1-yl)-methanone.

In another embodiment, the present invention concerns compounds of formula II selected from the group consisting of:

- a) 1-[4,5-Bis-(4-chloro-phenyl)-2-(2-methoxy-phenyl)-4,5-dihydro-imidazol-1-yl]-2-methyl-propan-1-one;
- b) 1-[4,5-Bis-(4-chloro-phenyl)-2-p-tolyl-4,5-dihydro-imidazol-1-yl]-ethanone;
- c) {4-[4,5-Bis-(4-chloro-phenyl)-1-isobutyryl-4,5-dihydro-1H-imidazol-2-yl]-phenoxy}-acetic acid ethyl ester;
- d) {4-[4,5-Bis-(4-chloro-phenyl)-1-isobutyryl-4,5-dihydro-1H-imidazol-2-yl]-phenoxy}-acetic acid;

- e) 2-Methyl-1-[2,4,5-tris-(4-chloro-phenyl)-4,5-dihydro-imidazol-1-yl]-propan-1-one;
- f) 1-[4,5-Bis-(4-chloro-phenyl)-2-(4-methoxy-phenyl)-4,5-dihydro-imidazol-1-yl]-ethanone;
- 5 g) [2-(2-Chloro-phenyl)-4,5-bis-(4-chloro-phenyl)-4,5-dihydro-imidazol-1-yl]-piperazin-1-yl-methanone;
- h) [2-(3-Bromo-phenyl)-4,5-bis-(4-chloro-phenyl)-4,5-dihydro-imidazol-1-yl]-piperazin-1-yl-methanone;
- i) [2-Biphenyl-3-yl-4,5-bis-(4-chloro-phenyl)-4,5-dihydro-imidazol-1-yl]-(4-methyl-piperazin-1-yl)-methanone;
- 10 j) [4,5-Bis-(4-chloro-phenyl)-2-(3-pyrrolidin-1-yl-phenyl)-4,5-dihydro-imidazol-1-yl]-piperazin-1-yl-methanone;
- k) [4,5-Bis-(4-bromo-phenyl)-2-(2-methoxy-phenyl)-4,5-dihydro-imidazol-1-yl]-[4-(2-hydroxy-ethyl)-piperazin-1-yl]-methanone;
- 15 l) 1-[5-(4-Chloro-phenyl)-2-(4-methoxy-phenyl)-4-(4-nitro-phenyl)-4,5-dihydro-imidazol-1-yl]-2-methyl-propan-1-one;
- m) 1-[4-(4-chloro-phenyl)-2-(4-methoxy-phenyl)-5-(4-nitro-phenyl)-4,5-dihydro-imidazol-1-yl]-2-methyl-propan-1-one;
- n) 1-[4,5-Bis-(4-chloro-phenyl)-2-(2-isopropoxy-phenyl)-4,5-dihydro-imidazol-1-yl]-2-methyl-propan-1-one;
- 20 o) [4,5-Bis-(4-chloro-phenyl)-2-(2-isopropoxy-phenyl)-4,5-dihydro-imidazol-1-yl]-(4-pyrrolidin-1-yl-piperidin-1-yl)-methanone;
- p) [4,5-Bis-(4-chloro-phenyl)-2-(2-isopropoxy-phenyl)-4,5-dihydro-imidazol-1-yl]-piperazin-1-yl-methanone;
- 25 q) [4,5-Bis-(4-chloro-phenyl)-2-(2-isopropoxy-phenyl)-4,5-dihydro-imidazol-1-yl]-(4-dimethylamino-piperidin-1-yl)-methanone;
- r) [1,4']Bipiperidinyl-1'-yl-[4,5-bis-(4-chloro-phenyl)-2-(2-isopropoxy-phenyl)-4,5-dihydro-imidazol-1-yl]-methanone;
- s) [4,5-Bis-(4-chloro-phenyl)-2-(2-isopropoxy-phenyl)-4,5-dihydro-imidazol-1-yl]-[4-(2-hydroxy-ethyl)-piperazin-1-yl]-methanone;
- 30 t) [4,5-Bis-(4-chloro-phenyl)-2-[2-(2-methyl-butoxy)-phenyl]-4,5-dihydro-imidazol-1-yl]-piperazin-1-yl-methanone;
- u) [4,5-Bis-(4-chloro-phenyl)-2-(2-pentyloxy-phenyl)-4,5-dihydro-imidazol-1-yl]-piperazin-1-yl-methanone;

- v) [4,5-Bis-(4-chloro-phenyl)-2-(3-ethoxy-phenyl)-4,5-dihydro-imidazol-1-yl]-piperazin-1-yl-methanone, trifluoroacetic acid salt;
- w) [4,5-Bis-(4-chloro-phenyl)-2-(3-isopropoxy-phenyl)-4,5-dihydro-imidazol-1-yl]-piperazin-1-yl-methanone, trifluoroacetic acid salt;
- 5 x) 1-{4-[4,5-Bis-(4-bromo-phenyl)-2-(2-ethoxy-phenyl)-4,5-dihydro-imidazole-1-carbonyl]-piperazin-1-yl}-ethanone;
- y) [4,5-Bis-(4-bromo-phenyl)-2-(2-ethoxy-phenyl)-4,5-dihydro-imidazol-1-yl]-[4-(2-hydroxy-ethyl)-piperazin-1-yl]-methanone;
- 10 z) 1-{4-[4,5-Bis-(4-bromo-phenyl)-2-(2-isopropoxy-phenyl)-4,5-dihydro-imidazole-1-carbonyl]-piperazin-1-yl}-ethanone; and
- aa) [4,5-Bis-(4-bromo-phenyl)-2-(2-isopropoxy-phenyl)-4,5-dihydro-imidazol-1-yl]-[4-(2-hydroxy-ethyl)-piperazin-1-yl]-methanone.

The compounds according to the present invention show strong anti-tumor activity against various tumor cell lines. This anti-tumor activity indicates that compounds of the present invention and pharmaceutically acceptable salts thereof can be anti-tumor agents.

One embodiment of the present invention is also a pharmaceutical composition comprising a compound according to the invention as an active ingredient and a pharmaceutical acceptable carrier. Preferably, the pharmaceutical composition according to the invention is suitable for oral or parenteral administration.

20 The pharmaceutical compositions may be administered orally, for example in the form of tablets, coated tablets, dragées, hard or soft gelatine capsules, solutions, emulsions or suspensions. Administration can also be carried out rectally, for example using suppositories; locally or percutaneously, for example using ointments, creams, gels or solutions; or parenterally, for example using injectable solutions.

25 For the preparation of tablets, coated tablets, dragées or hard gelatine capsules the compounds of the present invention may be admixed with pharmaceutically inert, inorganic or organic excipients. Examples of suitable excipients for tablets, dragées or hard gelatine capsules include lactose, maize starch or derivatives thereof, talc or stearic acid or salts thereof.

30 Suitable excipients for use with soft gelatine capsules include for example vegetable oils, waxes, fats, semi-solid or liquid polyols etc.; according to the nature of the active

ingredients it may however be the case that no excipient is needed at all for soft gelatine capsules.

For the preparation of solutions and syrups, excipients which may be used include for example water, polyols, saccharose, invert sugar and glucose.

- 5 For injectable solutions, excipients which may be used include for example water, alcohols, polyols, glycerine, and vegetable oils.

For suppositories, and local or percutaneous application, excipients which may be used include for example natural or hardened oils, waxes, fats and semi-solid or liquid polyols.

- 10 The pharmaceutical compositions may also contain preserving agents, solubilising agents, stabilising agents, wetting agents, emulsifiers, sweeteners, colorants, odorants, salts for the variation of osmotic pressure, buffers, coating agents or antioxidants. They may also contain other therapeutically valuable agents.

- In summary, a pharmaceutical formulation for oral administration may be granule,
15 tablet, sugar coated tablet, capsule, pill, suspension or emulsion, which for parenteral injection, for example, intravenously, intramuscularly or subcutaneously, may be used in the form of a sterile aqueous solution which may contain other substances, for example, salts or glucose to make the solution isotonic. The anti-tumor agent can also be administered in the form of a suppository or pessary, or they may be applied topically in
20 the form of a lotion, solution, cream, ointment or dusting powder.

The present invention concerns also the use of compound as above described for the preparation of a medicament, more preferably a medicament for the treatment or control of cell proliferative disorders, most preferably, a medicament for the treatment or control of cancer.

- 25 For example, they are useful in treating or controlling of breast, colon, lung or prostate tumors.

- A further embodiment of the present invention concerns a method for treating a cell proliferative disorder comprising administering to a patient in need thereof a therapeutically effective amount of a compound according to the present invention. More
30 preferably the method according to the invention concerns a method wherein the cell

proliferative disorder is cancer and most preferably a method wherein the cancer is breast, colon, lung or prostate tumors.

Finally the present invention concerns the compounds of formula I and the compounds of formula II for use in therapy.

- 5 Compounds of the present invention as exemplified advantageously show IC₅₀s from about 70 nM to about 100 nM.

A therapeutically effective amount of a compound in accordance with this invention means an amount of compound that is effective to prevent, alleviate or ameliorate symptoms of disease or prolong the survival of the subject being treated. Determination of
10 a therapeutically effective amount is within the skill in the art.

The therapeutically effective amount or dosage of a compound according to this invention can vary within wide limits and may be determined in a manner known in the art. Such dosage will be adjusted to the individual requirements in each particular case including the specific compound(s) being administered, the route of administration, the
15 condition being treated, as well as the patient being treated. In general, in the case of oral or parenteral administration to adult humans weighing approximately 70 Kg, a daily dosage of about 10 mg to about 10,000 mg, preferably from about 200 mg to about 1,000 mg, should be appropriate, although the upper limit may be exceeded when indicated. The daily dosage can be administered as a single dose or in divided doses, or for parenteral
20 administration, it may be given as continuous infusion.

The compounds of the present invention can be prepared according to the following Schemes in accordance to the process provided. Starting compounds are known in the art or are commercially available. The following definitions are provided as applicable to the synthesis schemes:

- 25 V₁, V₂, V₃, V₄, V₅ are each independently selected from Hydrogen, -OR₆, -SR₇, -NR₈VR₉, -CONVR₈VR₉, -COOR₁₀, halogen, nitro, trifluoromethyl, C₁-C₆ alkyl, which optionally may be substituted by V₁₁, and cycloalkyl;

V₁, V₂ together may form part of a heterocycle with one or more heteroatoms, which optionally may be substituted by V₁₀.

V2, V3 together may form part of a heterocycle with one or more heteroatoms, which optionally may be substituted by V10.

Y1, Y2 are each independently selected from -Cl, -Br, nitro, cyano; and -C=CH.

V, is selected from COV12 and CONV13V14,

5 V6 is selected from the group of hydrogen, C₁-C₆ alkyl, which optionally may be substituted by V11, and cycloalkyl;

V7 is selected from the group of hydrogen, and C₁-C₆ alkyl;

V8, V9 are each independently selected from the group of hydrogen, C₁-C₆ alkyl, and cycloalkyl;

10 V8, V9 together may form part of a heterocycle with one or more heteroatoms;

V10 is selected from the group of hydrogen, C₁-C₆ alkyl, and cycloalkyl;

V11 is selected from the group of -CONV8V9, -NV8V9, -COOV10, aryl, halogen, C₁-C₆ alkoxy, morpholinyl, and heterocycles;

15 V12 is selected from the group of hydrogen, C₁-C₆ alkyl, cycloalkyl, aryl, heterocycle, and heteroaryl;

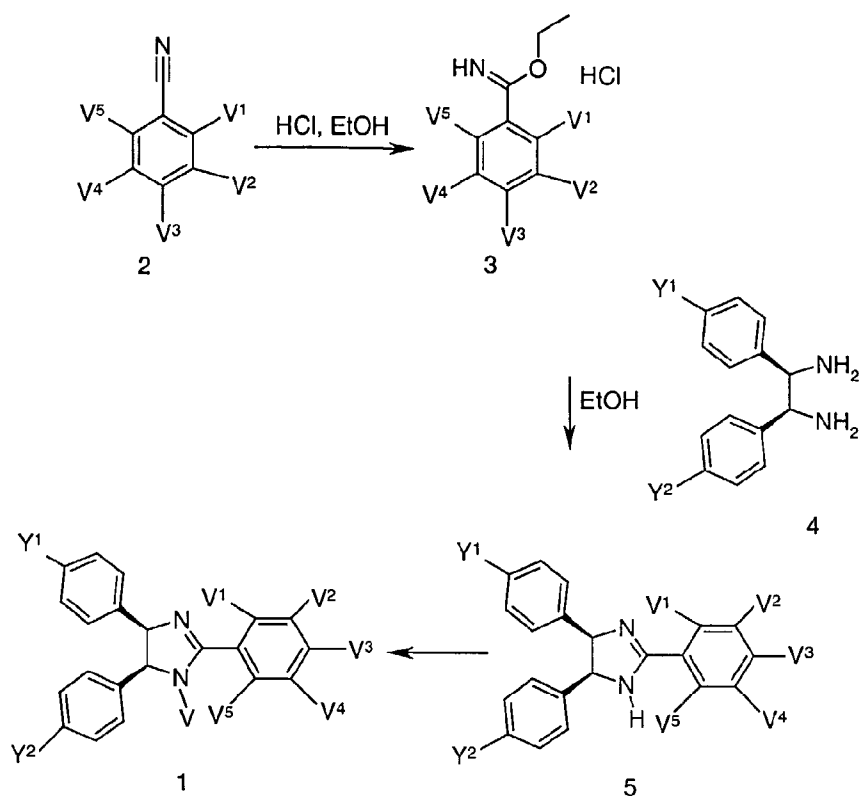
V13 and V14 are independently selected from the group of C₁-C₆ alkyl, cycloalkyl, C₁-C₄ alkyl substituted by V11; or

20 V13 and V14 together may form part of a heterocycle such as morpholine, piperidine, pyrrolidine and piperazine; The piperazine may be substituted by C₁-C₆ alkyl, hydroxyalkyl, acyl, acyl substituted with hydroxy and amino, alkylsulfonyl, CONH₂, CONV8V9, keto, hydroxy;

The piperidine may be substituted by dialkyl amine, pyrrolidine, or piperidine.

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Scheme I



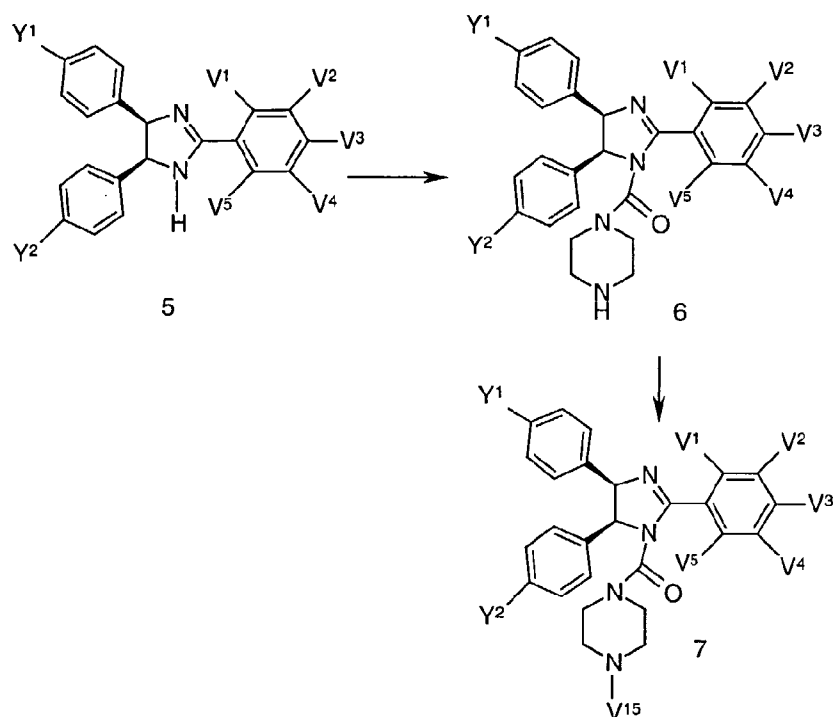
A compound of formula 2, a known compound or a compound prepared by known methods, is converted to a compound of formula 3 using hydrogen chloride gas in ethanol over a period of several hours to several weeks. A formula of compound 3 is then reacted with a compound of formula 4 in a solvent such as ethanol, at a temperature of 60 to 100°C to afford a compound of formula 5.

When V is COV12, a compound of formula 5 is reacted with a compound of formula ClCOV12 (a known compound or a compound prepared by known methods) at 0°C to 25°C in the presence a base such as triethylamine to give a compound of formula 1.

When V is CONV13V14(providing that NHV13V14 is a known compound or a compound prepared by known methods), a compound of formula 5 is reacted with phosgene at 0°C in the presence of triethylamine followed by the treatment of a compound of formula HNV13V14 to afford a compound of formula 1.

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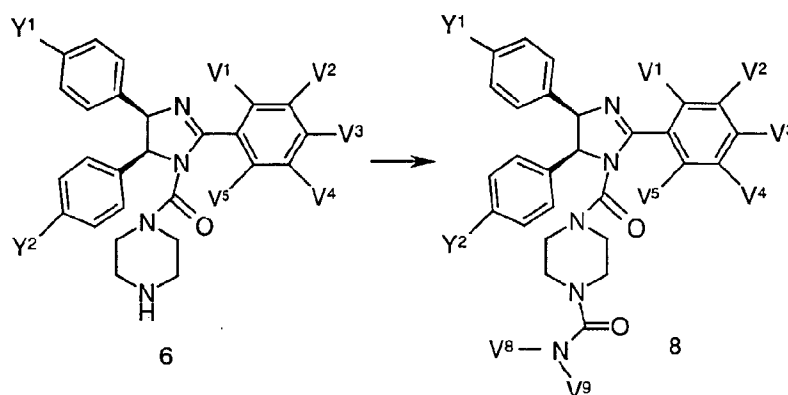
Scheme II



As set forth in Scheme II, when V¹⁵ substituted piperazines are not commercially available (V¹⁵ may be acyl, acyl substituted with hydroxyl, amino, protected amino and sulfonyl), a compound of formula 7 is prepared as follows: a compound of formula 5 is reacted with phosgene and triethylamine followed by the treatment of piperazine to afford a compound of formula 6. A compound of 6 is reacted with V¹⁵X to give a compound of formula 7.

As set forth in Scheme III, a compound of formula 8 can be prepared from a compound of formula 6 by the reaction of phosgene and triethylamine followed by the treatment of NHV⁸V⁹, a known compound or a compound prepared by known methods.

Scheme III

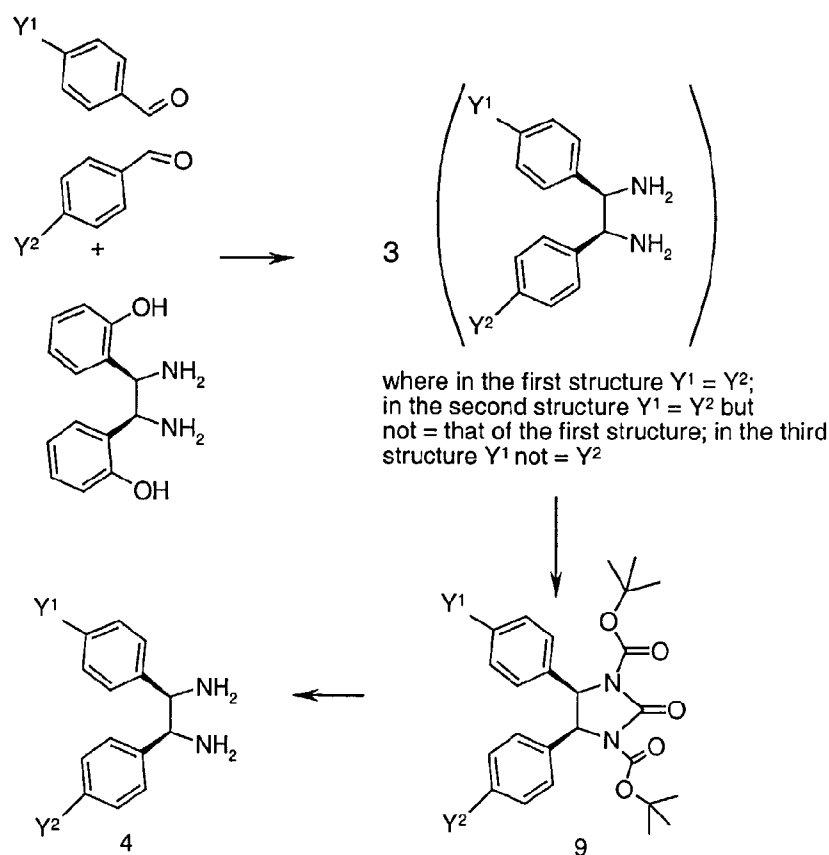


The meso-1,2-diamine of formula 4 ($Y1 = Y2$) can be prepared according to the literature procedures (see Jennerwein, M. et al. Cancer Res. Clin. Oncol. 1988, 114, 347-58; Vogtle, F.; Goldschmitt, E. Chem. Ber. 1976, 109, 1-40).

If it is desired to prepare a compound of formula 4 wherein $Y1 \neq Y2$, modifications to the existing procedure can be made. An equal molar mixture of the benzaldehydes and meso-1,2-bis-(2-hydroxy-phenyl)-ethane-1,2-diamine can be used to afford a mixture of 1,2-diamines (Scheme IV). Knölker, H. J., et al. Tetrahedron Letters 1998, 39, p. 9407. It was then reacted with di-*t*-butyldicarbonate in the presence of dimethylaminopyridine to give a compound of formula 9 after HPLC purification. Compound 9 is then converted to a compound of formula 4 by the treatment of hydrobromic acid in hot acetic acid.

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Scheme IV

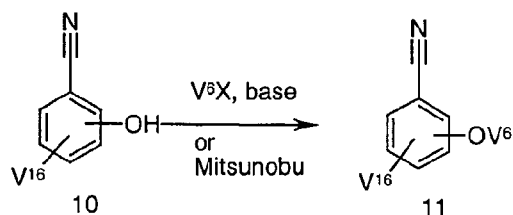


If it is desired to prepare a compound of formula 2 which is not commercially available, many synthetic methods known in the art can be employed. Suitable processes
 5 for synthesizing these benzonitriles are provided in the examples. Following schemes illustrate some of these methods.

A compound of formula 11 (V16 can be any suitable group such as V1, V2, V3, V4, or V5) can be prepared by alkylation of a compound of formula 10 with V6X (X = Cl, Br, I) using conventional methods (scheme V). The phenoxide anion is generated by a base
 10 such as cesium carbonate or potassium carbonate. The reaction typically is carried out in refluxing acetone. V6 can also be introduced using Mitsunobu reaction (see for example, Hughes, D. L. Org. React. 1992, 42, 335-656).

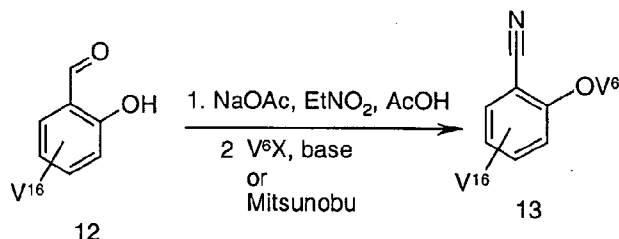
- 30 -

Scheme V



A compound of formula 12 (V16 can be any suitable group such as V1, V2, V3, V4, or V5) can be converted into the benzonitrile 13 using literature procedures (Karmarkar, S. N; Kelkar, S. L.; Wadia, M. S. Synthesis 1985, 510-512; Bergeron, R. J. et al. J. Med. Chem. 1999, 42, 95-108). V group can then be introduced using V6X (X = Cl, Br, I) or Mitsunobu reaction to give the benzonitrile 13 (scheme VI).

Scheme VI

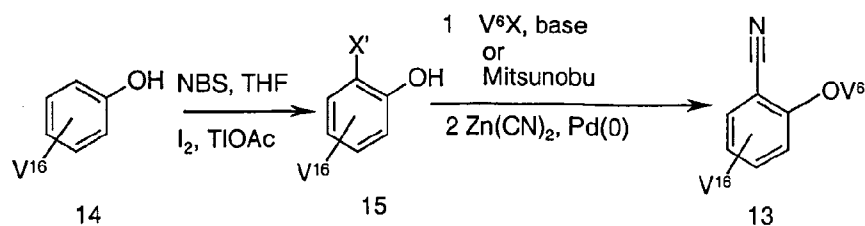


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A compound of formula 15 can be prepared by bromination or iodination of phenol 14 (Scheme VII), (V16 can be any suitable group such as V1, V2, V3, V4, or V5). Reaction conditions such as N-bromosuccinamide/tetrahydrofuran or iodine/thallium(I) acetate can be utilized (see for example, Carreno, M. C.; Garcia Ruano, J. L.; Sanz, G.; Toledo, M. A.; Urbano, A. Synlett 1997, 1241-1242; Cambie, R. C.; Rutledge, P. S.; Smith-Palmer, T.; Woodgate, P. D. J. Chem. Soc., Perkin Trans. 1 1976, 1161-4). V5 group can then be introduced using V6X (X = Cl, Br, I) or Mitsunobu reaction. Methods of converting aromatic halides to the corresponding nitriles are known in the art (see for example, Okano, T.; Iwahara, M.; Kiji, J., Synlett 1998, 243). Cyanation of the halide 15 (X' = Br, I) can be accomplished using zinc cyanide with a catalyst such as tetrakis(triphenylphosphine)palladium (0). Solvents such dimethylformamide can be used and the reaction temperature is between 80-110 °C.

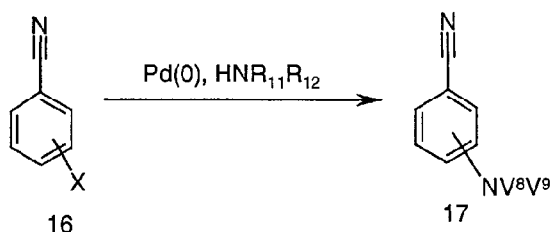
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Scheme VII



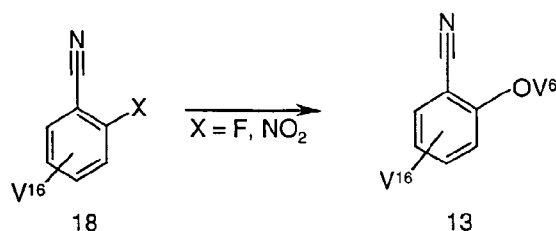
In scheme VIII, amination of aromatic halide 16 using HNV7V8 and palladium catalyst can be utilized to provide the benzonitrile of formula 17 (see for example, Harris, M. C.; Geis, O.; Buchwald, S. L. J. Org. Chem. 1999, 64, 6019).

Scheme VIII



A compound of formula 13 (V16 can be any suitable group such as V1, V2, V3, V4, or V5) can be prepared by nucleophilic substitution of 2-halobenzonitrile 18 (scheme IX). (see for example, X = F: Wells, K. M.; Shi, Y.-J.; Lynch, J. E.; Humphrey, G. R.; Volante, R. P.; Reider, P. J. Tetrahedron Lett. 1996, 37, 6439-6442; X = NO₂: Harrison, C. R.; Lett, R. M.; McCann, S. F.; Shapiro, R.; Stevenson, T. M. WO 92/03421, 1992).

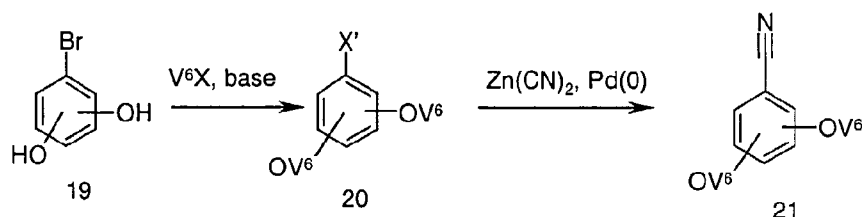
Scheme IX



To prepare the benzonitrile of formula 21 wherein V1, V2, V3, V4, or V5 = OV6, sequential alkylation of the diol 19 with suitable V6X (X = Cl, Br, I) are used. The bromides 20 are then converted to the nitriles 21 using zinc cyanide and Pd(0) catalyst (scheme X).

5

Scheme X



Certain of the following Examples refer to Examples provided in U.S. Provisional application Serial No. 60/341,729. The Examples of these Provisional applications are incorporated herein by reference.

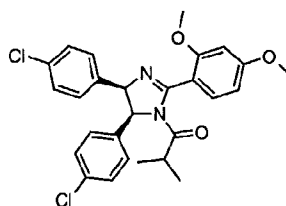
- 10 The present invention encompasses the following Examples. For structural formulas shown, it is understood that oxygen and nitrogen atoms with available elections have a hydrogen bound thereto, as indicated by compound name. The following examples illustrate the preferred methods for the preparation of the compounds of the present invention, which are not intended to limit the scope of the invention thereto.

15

EXAMPLES

Example 1

1-[4,5-Bis-(4-chloro-phenyl)-2-(2,4-dimethoxy-phenyl)-4,5-dihydro-imidazol-1-yl]-2-methyl-propan-1-one



5

Hydrogen chloride gas was passed through a solution of 2, 4-dimethoxy-benzonitrile (5.20 g, 32 mmol) in anhydrous ethanol (200 mL) at 0 °C. After 7 h, hydrogen chloride gas was stopped and the reaction mixture was stirred at room temperature overnight. The solvent was removed and the residue was triturated in diethyl ether to afford ethyl 2,4-dimethoxy-benzimidate hydrochloride (4.5 g, 57%). It was used without further purification.

A solution of meso-1,2-bis-(4-chloro-phenyl)-ethane-1,2-diamine (1.21 g, 4.30 mmol, prepared according to the procedure described by Jennerwein, M. et al. Cancer Res. Clin. Oncol. 1988, 114, 347-8; Vogtle, F.; Goldschmitt, E. Chem. Ber. 1976, 109, 1-40) and ethyl 2,4-dimethoxy-benzimidate hydrochloride (1.58 g, 6.43 mmol) in ethanol (30 mL) was heated at reflux for 16 h. The reaction mixture was basified with sodium bicarbonate solution (10 mL) and extracted with ethyl acetate. The organic extracts were washed with brine and dried over anhydrous sodium sulfate. The solids were then filtered off, and the filtrate was concentrated in vacuo. Purification of the crude residue by flash chromatography (Biotage system, KP-Sil™ 32-63µm, 60 Å silica gel) eluting with 2-6% methanol in methylene chloride yielded 4,5-bis-(4-chloro-phenyl)-2-(2, 4-dimethoxy-phenyl)-4,5-dihydro-1H-imidazole (1.10 g, 60%).

Isobutryl chloride (19 µL, 0.18 mmol) was added to a solution of triethylamine (25 µL, 0.18 mmol) and 4,5-bis-(4-chloro-phenyl)-2-(2, 4-dimethoxy-phenyl)-4,5-dihydro-1H-imidazole (70 mg, 0.164 mmol). The reaction mixture was stirred at room temperature for 2 h. It was diluted with methylene chloride and washed with water and brine, and dried over sodium sulfate. The solvents were removed under reduced pressure

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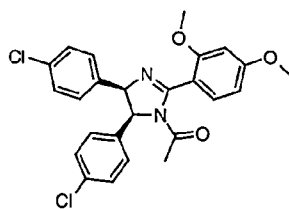
and chromatography of the residue over silica gel using 0.5-1% methanol in methylene chloride gave 1-[4,5-bis-(4-chloro-phenyl)-2-(2,4-dimethoxy-phenyl)-4,5-dihydro-imidazol-1-yl]-2-methyl-propan-1-one. HR-MS (EI, m/z) calculated for C₂₇H₂₆N₂O₃Cl₂ (M⁺) 496.1320, observed 496.1319.

5

Example 2

In a similar manner as described in example 1, the following compounds were prepared.

- a) 1-[4,5-Bis-(4-chloro-phenyl)-2-(2,4-dimethoxy-phenyl)-4,5-dihydro-imidazol-1-yl] ethanone. HR-MS (EI, m/z) calculated for C₂₅H₂₂N₂O₃Cl₂ (M⁺) 468.1007, observed 468.1020



- b) 1-[4,5-Bis-(4-chloro-phenyl)-2-(2,4-dimethoxy-phenyl)-4,5-dihydro-imidazol-1-yl]-2,2-dimethyl-propan-1-one. HR-MS (EI, m/z) calculated for C₂₈H₂₈N₂O₃Cl₂ (M⁺) 510.1477, observed 510.1476.

- c) [4,5-Bis-(4-chloro-phenyl)-2-(2,4-dimethoxy-phenyl)-4,5-dihydro-imidazol-1-yl]-cyclopentyl-methanone. HR-MS (EI, m/z) calculated for C₂₉H₂₈N₂O₃Cl₂ (M⁺) 522.1477, observed 522.1470.

- d) [4,5-Bis-(4-chloro-phenyl)-2-(2,4-dimethoxy-phenyl)-4,5-dihydro-imidazol-1-yl]-cyclohexyl-methanone. HR-MS (EI, m/z) calculated for C₃₀H₃₀N₂O₃Cl₂ (M⁺) 536.1633, observed 536.1633.

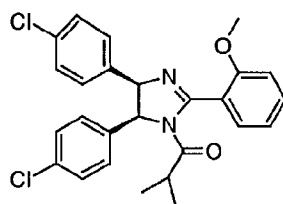
- e) [4,5-Bis-(4-chloro-phenyl)-2-(2,4-dimethoxy-phenyl)-4,5-dihydro-imidazol-1-yl]-thiophen-2-yl-methanone. HR-MS (EI, m/z) calculated for C₂₈H₂₀N₂O₃Cl₂S [(M-2H)⁺] 534.0572, observed 534.0566.

20

f)[4,5-Bis-(4-chloro-phenyl)-2-(2,4-dimethoxy-phenyl)-4,5-dihydro-imidazol-1-yl]-isoxazol-5-yl-methanone. HR-MS (EI, m/z) calculated for C₂₇H₂₁N₃O₄Cl₂ (M+) 521.0909, observed 521.0892.

g)[4,5-Bis-(4-chloro-phenyl)-2-(2,4-dimethoxy-phenyl)-4,5-dihydro-imidazol-1-yl]-furan-2-yl-methanone. HR-MS (EI, m/z) calculated for C₂₈H₂₀N₂O₄Cl₂ [(M-2H)+] 518.0800, observed 518.0802.

h)1-[4,5-Bis-(4-chloro-phenyl)-2-(2-methoxy-phenyl)-4,5-dihydro-imidazol-1-yl]-2-methyl-propan-1-one. HR-MS (EI, m/z) calculated for C₂₆H₂₅N₂O₂Cl₂ [(M+H)+] 467.1289, observed 467.1295



10

i)1-[4,5-Bis-(4-chloro-phenyl)-2-p-tolyl-4,5-dihydro-imidazol-1-yl]-ethanone. HR-MS (EI, m/z) calculated for C₂₄H₂₀N₂OCl₂ (M+) 422.0953, observed 422.0950.

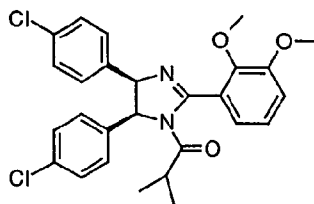
j){4-[4,5-Bis-(4-chloro-phenyl)-1-isobutyryl-4,5-dihydro-1H-imidazol-2-yl]-phenoxy}-acetic acid ethyl ester. HR-MS (ES, m/z) calculated for C₂₉H₂₉N₂O₄Cl₂ [(M+H)+] 539.1499, observed 539.1506. The starting ethyl (4-cyano-phenoxy)-acetate was prepared from 4-hydroxy-benzonitrile and ethyl bromoacetate as described in Kirkiacharian, S.; Goma, J. R. et al. Ann. Pharm. Fr. 1989, 47, 16-23.

k){4-[4,5-Bis-(4-chloro-phenyl)-1-isobutyryl-4,5-dihydro-1H-imidazol-2-yl]-phenoxy}-acetic acid was prepared by hydrolysis of {4-[4,5-bis-(4-chloro-phenyl)-1-isobutyryl-4,5-dihydro-1H-imidazol-2-yl]-phenoxy}-acetic acid ethyl ester. HR-MS (ES, m/z) calculated for C₂₇H₂₅N₂O₄Cl₂ (M+) 511.1186, observed 511.1191.

l)2-Methyl-1-[2,4,5-tris-(4-chloro-phenyl)-4,5-dihydro-imidazol-1-yl]-propan-1-one. HR-MS (FAB, m/z) calculated for C₂₅H₂₂N₂OCl₃ [(M+H)+] 471.0797, observed 471.0814.

20

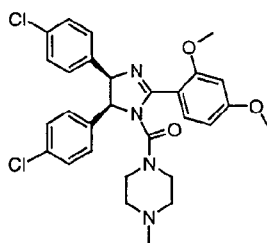
m) 1-[4,5-Bis-(4-chloro-phenyl)-2-(4-methoxy-phenyl)-4,5-dihydro-imidazol-1-yl]-ethanone. HR-MS (FAB, m/z) calculated for C₂₄H₂₁N₂O₂Cl₂ [(M+H)⁺] 439.0980, observed 439.0967.



5 n) 1-[4,5-Bis-(4-chloro-phenyl)-2-(2,3-dimethoxy-phenyl)-4,5-dihydro-imidazol-1-yl]-2-methyl-propan-1-one. HR-MS (ES, m/z) calculated for C₂₇H₂₇N₂O₃Cl₂ [(M+H)⁺] 497.1393, observed 497.1398

Example 3

10 [4,5-Bis-(4-chloro-phenyl)-2-(2,4-dimethoxy-phenyl)-4,5-dihydro-imidazol-1-yl]-(4-methyl-piperazin-1-yl)-methanone



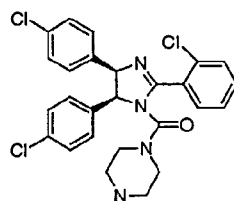
Phosgene (1.31 mL, 2.53 mmol, 1.93 M in toluene) was added dropwise to a cooled (0 °C) mixture of triethylamine (0.37 mL, 2.64 mmol) and 4,5-bis-(4-chloro-phenyl)-2-(2,4-dimethoxy phenyl)-4,5-dihydro-1H-imidazole (225 mg, 0.53 mmol, example 1) in THF (5 mL). The reaction mixture was stirred for 2.5 h and evaporated. The residue was kept under high vacuum for 30 min and was redissolved in methylene chloride (10 mL). The slurry was added dropwise to a solution of N-methylpiperazine (1.05 g, 10.48 mmol) in methylene chloride (5 mL). After 1 h, the reaction was worked up with aqueous sodium bicarbonate and extracted with methylene chloride. The organic extracts were washed with water and brine, and dried over sodium sulfate. Evaporation of the solvents and chromatography of the residue over silica gel using 1-4% methanol in methylene chloride

gave 4,5-bis-(4-chloro-phenyl)-2-(2,4-dimethoxy-phenyl)-4,5-dihydro-imidazol-1-yl]-(4-methyl-piperazin-1-yl)-methanone. HR-MS (ES, m/z) calculated for C₂₉H₃₁N₄O₃Cl₂ [(M+H)+] 553.1768, observed 553.1773.

5 Example 4

In a similar manner as described in example 1 and 3, the following compounds were prepared.

- a)[2-(2-Chloro-phenyl)-4,5-bis-(4-chloro-phenyl)-4,5-dihydro-imidazol-1-yl]-piperazin-1-yl-methanone. HR-MS (ES, m/z) calculated for C₂₆H₂₄N₄OCl₃ [(M+H)+]
10 513.1009, observed 513.1013



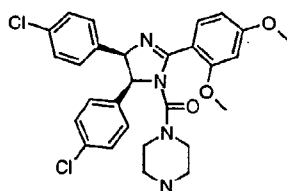
- b)[2-(3-Bromo-phenyl)-4,5-bis-(4-chloro-phenyl)-4,5-dihydro-imidazol-1-yl]-piperazin-1-yl-methanone. HR-MS (ES, m/z) calculated for C₂₆H₂₄N₄OCl₂Br [(M+H)+] 557.0505, observed 557.0506.

- 15 c)[2-Biphenyl-3-yl-4,5-bis-(4-chloro-phenyl)-4,5-dihydro-imidazol-1-yl]-(4-methyl-piperazin-1-yl)-methanone. HR-MS (ES, m/z) calculated for C₃₃H₃₁N₄OCl₂ [(M+H)+] 569.1870, observed 569.1875.

- d)[4,5-Bis-(4-chloro-phenyl)-2-(3-pyrrolidin-1-yl-phenyl)-4,5-dihydro-imidazol-1-yl]-piperazin-1-yl-methanone was synthesized from 3-pyrrolidinobenzonitrile (described
20 in the previous patent). HR-MS (ES, m/z) calculated for C₃₀H₃₂N₅OCl₂ [(M+H)+] 548.1979, observed 548.1980.

- e)[4,5-Bis-(4-chloro-phenyl)-2-(2,4-dimethoxy-phenyl)-4,5-dihydro-imidazol-1-yl]-piperazin-1-yl-methanone. HR-MS (ES, m/z) calculated for C₂₈H₂₉N₄O₃Cl₂ [(M+H)+] 539.1610 observed 539.1613

- 38 -

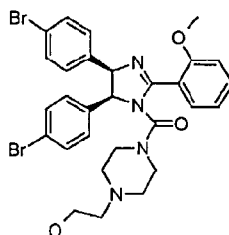


f) [4,5-Bis-(4-chloro-phenyl)-2-(2-fluoro-6-methoxy-phenyl)-4,5-dihydro-imidazol-1-yl]-[4-(2-hydroxy-ethyl)-piperazin-1-yl]-methanone. HR-MS (ES, m/z) calculated for $C_{29}H_{30}N_4O_3FCl_2$ [(M+H)+] 571.1674, observed 571.1678.

- 5 g) 1-[4-[4,5-Bis-(4-bromo-phenyl)-2-(2,4-dimethoxy-phenyl)-4,5-dihydro-imidazole-1-carbonyl]-piperazin-1-yl]-ethanone. HR-MS (ES, m/z) calculated for $C_{30}H_{31}N_4O_4Br_2$ [(M+H)+] 669.0707, observed 669.0710.

- h) [4,5-Bis-(4-bromo-phenyl)-2-(2,4-dimethoxy-phenyl)-4,5-dihydro-imidazol-1-yl]-[4-(2-hydroxy-ethyl)-piperazin-1-yl]-methanone. HR-MS (ES, m/z) calculated for
10 $C_{30}H_{33}N_4O_4Br_2$ [(M+H)+] 671.0863, observed 671.0870.

i) [4,5-Bis-(4-bromo-phenyl)-2-(2-methoxy-phenyl)-4,5-dihydro-imidazol-1-yl]-[4-(2-hydroxy-ethyl)-piperazin-1-yl]-methanone. HR-MS (ES, m/z) calculated for $C_{29}H_{31}N_4O_3Br_2$ [(M+H)+] 641.0758, observed 641.0765



15

Example 5

1-[5-(4-chloro-phenyl)-2-(4-methoxy-phenyl)-4-(4-nitro-phenyl)-4,5-dihydro-imidazol-1-yl]-2-methyl-propan-1-one and 1-[4-(4-Chloro-phenyl)-2-(4-methoxy-phenyl)-5-(4-nitro-phenyl)-4,5-dihydro-imidazol-1-yl]-2-methyl-propan-1-one

- 20 To a solution of meso-1,2-bis-(2-hydroxy-phenyl)-ethane-1,2-diamine (5.38 g, 22 mmol, prepared according to the procedure described by Vogtle, F.; Goldschmitt, E.

Chem. Ber. 1976, 109, 1-40) in acetonitrile (50 mL) were added 4-nitrobenzaldehyde (3.33 g, 22 mmol) and 4-chlorobenzaldehyde (3.31 g, 23.5 mmol). The reaction mixture was heated at gentle reflux for 12 h. Upon cooling to room temperature, the solvent was removed in vacuo. The residue was suspended in 3 N sulfuric acid and the reaction mixture was heated at reflux for 2 h. Upon cooling to room temperature, the salicylaldehyde by-product was removed by extraction with diethyl ether (1 x 10 mL). The clear aqueous layer was neutralized with 5% sodium hydroxide solution to precipitate out the diamine product (pH >9). Crude 1-(4-chloro-phenyl)-2-(4-nitro-phenyl)-ethane-1,2-diamine (4.61 g) was collected by filtration, washed with water, and dried under vacuum overnight.

Di-t-butylidicarbonate (6.77 g, 31 mmol) was added to a solution of crude 1-(4-chloro-phenyl)-2-(4-nitro-phenyl)-ethane-1,2-diamine (2.92 g) in acetonitrile (100 mL) in an ice-bath. Dimethylaminopyridine (122 mg, 1 mmol) was added and the ice-bath was removed. After 1 h, more dimethylaminopyridine (122 mg, 1 mmol) was added. After a few minutes, the mixture was warmed up to 50 °C over 10 min. Evaporation of the solvents and reversed phase HPLC purification of the crude mixture gave 4-(4-chloro-phenyl)-5-(4-nitro-phenyl)-2-oxo-cyclopentane-1,3-dicarboxylic acid di-tert-butyl ester (1.19 g).

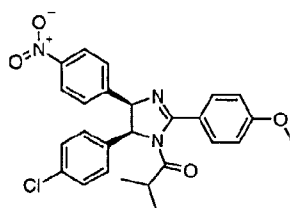
A mixture of 4-(4-chloro-phenyl)-5-(4-nitro-phenyl)-2-oxo-cyclopentane-1,3-dicarboxylic acid di-tert-butyl ester (1.0 g, 2.0 mmol) in hydrobromic acid (4.37 mL, 48%) and acetic acid (3.21 mL) was heated at reflux overnight. After cooling to room temperature, water was added. The mixture was washed with diethyl ether and then basified with 10 N NaOH. The aqueous layers were extracted with methylene chloride. The organic extracts were washed with brine, dried over magnesium sulfate and evaporated to give 1-(4-chloro-phenyl)-2-(4-nitro-phenyl)-ethane-1,2-diamine (464 mg, 80%).

To a solution of 1-(4-chloro-phenyl)-2-(4-nitro-phenyl)-ethane-1,2-diamine (200 mg, 0.685 mmol) and ethyl 4-methoxy-benzimidate hydrochloride (148 mg, 0.686 mmol) in ethanol (5 mL) was added triethylamine (0.11 mL, 0.79 mmol). The reaction mixture was heated at reflux for 12 h. The solvent was removed to give a clear oil. It was then taken in methylene chloride (2 mL) and aqueous sodium carbonate. The product was extracted with methylene chloride (2 x 20 mL). The organic layers were washed with brine (1 x 5 mL), dried (Na₂SO₄) and concentrated. Purification of the crude residue by Biotage

flash chromatography eluting with 70% ethyl acetate in hexanes gave 4-(4-chloro-phenyl)-2-(4-methoxy-phenyl)-5-(4-nitro-phenyl)-4,5-dihydro-1H-imidazole (103 mg, 37%).

Isobutyryl chloride (32 μ L, 0.30 mmol) was added to a solution of triethylamine (71 μ L, 0.51 mmol) and 4-(4-chloro-phenyl)-2-(4-methoxy-phenyl)-5-(4-nitro-phenyl)-4,5-dihydro-1H-imidazole (103 mg, 0.25 mmol). The reaction mixture was stirred at room temperature for 2 h and it was then diluted with methylene chloride and aqueous sodium. The organic layer was washed with water and brine, and dried over sodium sulfate. The solvents were removed under reduced pressure and chromatography of the residue over silica gel using 10-40% ethyl acetate in hexanes gave 2 products:

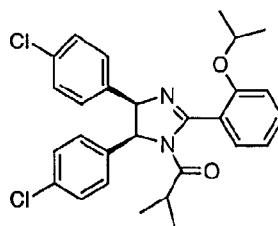
- 10 a) 1-[5-(4-Chloro-phenyl)-2-(4-methoxy-phenyl)-4-(4-nitro-phenyl)-4,5-dihydro-imidazol-1-yl]-2-methyl-propan-1-one (48 mg, 40%). HR-MS (ES, m/z) calculated for $C_{26}H_{25}N_3O_4Cl$ [(M+H)+] 478.1528, observed 478.1533



- 15 b) 1-[4-(4-chloro-phenyl)-2-(4-methoxy-phenyl)-5-(4-nitro-phenyl)-4,5-dihydro-imidazol-1-yl]-2-methyl-propan-1-one (31 mg, 26%). HR-MS (ES, m/z) calculated for $C_{26}H_{25}N_3O_4Cl$ [(M+H)+] 478.1528, observed 478.1533.

Example 6

- 20 1-[4,5-Bis-(4-chloro-phenyl)-2-(2-isopropoxy-phenyl)-4,5-dihydro-imidazol-1-yl]-2-methyl-propan-1-one



A mixture of 2-cyanophenol (5.0 g, 42 mmol), cesium carbonate (27.1 g, 82.9 mmol) and 2-iodopropane (7.63 mL, 76 mmol) in acetone (80 mL) was heated at 60 °C with vigorous stirring. After 45 min, the gray brown mixture was decanted and the acetone layer was concentrated in vacuo. Water was added to dissolve the solid, and the mixture
5 was extracted with diethyl ether (3 x 200 mL). The organic layers were washed with water, 1 N ammonium hydroxide and brine, and dried over anhydrous sodium sulfate. The solids were then filtered off, and the filtrate was concentrated in vacuo. Purification of the crude residue by flash chromatography (Biotage system, KP-Sil™ 32-63µm, 60 Å silica gel) eluting with 5% ethyl acetate in hexanes yielded 2-isopropoxy-benzonitrile (6.6 g, 97%) as
10 a colorless liquid.

Hydrogen chloride gas was passed through a solution of 2-isopropoxy-benzonitrile (6.6 g, 40.9 mmol) in anhydrous ethanol (75mL) at 0 °C in a pressure tube. After 30 min , hydrogen chloride gas was stopped. The reaction vessel was sealed and stirred at room temperature for 3 d. The pressure was released only after the tube has been cooled to 0 °C.
15 The solvent was removed to give a pale yellow oil (10.1 g). It was triturated in diethyl ether (100 mL) to afford a white solid. Ethyl 2-isopropoxy-benzimidate hydrochloride (9.17 g, 92%) was collected by filtration, washed with diethyl ether (3 x 25 mL), and dried in vacuo. It was used without further purification.

To a solution of triethylamine (0.88 mL, 6.26 mmol) in ethanol (3.5 mL) were added
20 meso-1,2-bis-(4-chloro-phenyl)-ethane-1,2-diamine (0.80 g, 2.85 mmol, prepared according to the procedure described by Vogtle, F.; Goldschmitt, E. Chem. Ber. 1976, 109, 1-40) and ethyl 2-isopropoxy-benzimidate hydrochloride (0.86 g, 3.52 mmol) . The reaction mixture was refluxed overnight. After cooled to room temperture, the reaction mixture was diluted with methylene chloride washed with with 1 N HCl and 5% aqueous
25 sodium bicarbonate. The organic layer was washed with brine and dried over anhydrous sodium sulfate. Evaporation of the solvents and chromatography of the residue over silica gel using 2% methanol in methylene chloride gave 4,5-bis-(4-chloro-phenyl)-2-(2-isopropoxy-phenyl)-4,5-dihydro-1H-imidazole (0.86 g, 71%).

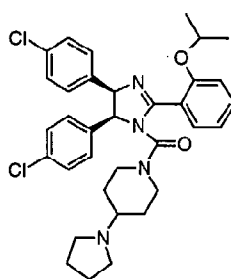
Isobutyryl chloride (8.1 µL, 0.077 mmol) was added to a solution of triethylamine
30 (10.8 µL, 0.077 mmol) and 4,5-bis-(4-chloro-phenyl)-2-(2-isopropoxy-phenyl)-4,5-dihydro-1H-imidazole (30 mg, 0.071 mmol) in methylene chloride (3 mL). The reaction mixture was stirred at room temperature for 3 h. It was then diluted with methylene chloride and washed with water and brine, and dried over sodium sulfate. The solvents

were remove under reduced pressure and chromatography of the residue over silica gel using 25% ethyl acetate in hexanes gave 1-[4,5-bis-(4-chloro-phenyl)-2-(2-isopropoxy-phenyl)-4,5-dihydro-imidazol-1-yl]-2-methyl-propan-1-one. HR-MS (ES, m/z) calculated for C₂₈H₂₉N₂O₂Cl₂ [(M+H)+] 495.1601, observed 495.1606.

5

Example 7

[4,5-Bis-(4-chloro-phenyl)-2-(2-isopropoxy-phenyl)-4,5-dihydro-imidazol-1-yl]-(4-pyrrolidin-1-yl-piperidin-1-yl)-methanone



10 Phosgene (2.95 mL, 5.69 mmol, 1.93 M in toluene) was added dropwise to a cooled mixture of triethylamine (1.3 mL, 9.4 mmol) and 4,5-bis-(4-chloro-phenyl)-2-(2-isopropoxy-phenyl)-4,5-dihydro-1H-imidazole (0.80 g, 1.88 mmol, example 6) in methylene chloride (15 mL) at 0 °C. The reaction mixture was stirred for 30 min at 0 °C and evaporated. The residue was kept under high vacuum for 30 min. Chromatography of
15 the residue over silica gel using 60-80% methylene chloride in hexanes gave 4,5-bis-(4-chloro-phenyl)-2-(2-isopropoxy-phenyl)-4,5-dihydro-imidazole-1-carbonyl chloride (0.71 g, 77%)

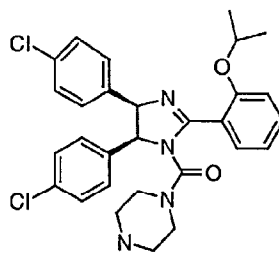
4,5-Bis-(4-chloro-phenyl)-2-(2-isopropoxy-phenyl)-4,5-dihydro-imidazole-1-carbonyl chloride (200 mg, 0.41 mmol) was added a solution of triethylamine (0.23 mL,
20 1.64 mmol) and 4-(1-pyrrolidinyl)-piperidine (0.11 g, 0.70 mmol) in methylene chloride (8 mL) at 0 °C over 15 min. After 30 min, the reaction was worked up with water. The mixture was extracted with methylene chloride and washed with water and brine. The organic extracts were dried over sodium sulfate and evaporated. Chromatography of the residue over silica gel using 1-2% methanol in methylene chloride gave [4,5-bis-(4-chloro-
25 phenyl)-2-(2-isopropoxy-phenyl)-4,5-dihydro-imidazol-1-yl]-(4-pyrrolidin-1-yl-

piperidin-1-yl)-methanone (0.18 g, 72%) as an off-white foam. HR-MS (ES, m/z) calculated for $C_{34}H_{39}N_4O_2Cl_2$ [(M+H)+] 605.2445, observed 605.2448

Example 8

5 In a similar manner as described in examples 6 and 7, the following compounds were prepared.

a) [4,5-Bis-(4-chloro-phenyl)-2-(2-isopropoxy-phenyl)-4,5-dihydro-imidazol-1-yl]-piperazin-1-yl-methanone. HR-MS (ES, m/z) calculated for $C_{29}H_{31}N_4O_2Cl_2$ [(M+H)+] 537.1819, observed 537.1828



10

b) [4,5-Bis-(4-chloro-phenyl)-2-(2-isopropoxy-phenyl)-4,5-dihydro-imidazol-1-yl]-(4-dimethylamino-piperidin-1-yl)-methanone. HR-MS (ES, m/z) calculated for $C_{32}H_{37}N_4O_2Cl_2$ [(M+H)+] 579.2288, observed 579.2293.

15 c) [1,4']Bipiperidinyl-1'-yl-[4,5-bis-(4-chloro-phenyl)-2-(2-isopropoxy-phenyl)-4,5-dihydro-imidazol-1-yl]-methanone. HR-MS (ES, m/z) calculated for $C_{35}H_{41}N_4O_2Cl_2$ [(M+H)+] 619.2601, observed 619.2606.

d) [4,5-Bis-(4-chloro-phenyl)-2-(2-isopropoxy-phenyl)-4,5-dihydro-imidazol-1-yl]-[4-(2-hydroxy-ethyl)-piperazin-1-yl]-methanone. HR-MS (ES, m/z) calculated for
20 $C_{31}H_{35}N_4O_3Cl_2$ [(M+H)+] 581.2081, observed 581.2082.

e) {4,5-Bis-(4-chloro-phenyl)-2-[2-(2-methyl-butoxy)-phenyl]-4,5-dihydro-imidazol-1-yl}-piperazin-1-yl-methanone. HR-MS (ES, m/z) calculated for $C_{31}H_{35}N_4O_2Cl_2$ [(M+H)+] 565.2132, observed 565.2140.

f)[4,5-Bis-(4-chloro-phenyl)-2-(2-pentyloxy-phenyl)-4,5-dihydro-imidazol-1-yl]-piperazin-1-yl-methanone. HR-MS (ES, m/z) calculated for C₃₁H₃₅N₄O₂Cl₂ [(M+H)+] 565.2132, observed 565.2138.

g)[4,5-Bis-(4-chloro-phenyl)-2-(3-ethoxy-phenyl)-4,5-dihydro-imidazol-1-yl]-piperazin-1-yl-methanone, trifluoroacetic acid salt. HR-MS (ES, m/z) calculated for C₂₈H₂₉N₄O₂Cl₂ [(M+H)+] 523.1662, observed 523.1666.

h)[4,5-Bis-(4-chloro-phenyl)-2-(3-isopropoxy-phenyl)-4,5-dihydro-imidazol-1-yl]-piperazin-1-yl-methanone, trifluoroacetic acid salt. HR-MS (ES, m/z) calculated for C₂₉H₃₁N₄O₂Cl₂ [(M+H)+] 537.1819, observed 537.1824.

i)1-[4-[4,5-Bis-(4-bromo-phenyl)-2-(2-ethoxy-phenyl)-4,5-dihydro-imidazole-1-carbonyl]-piperazin-1-yl]-ethanone. HR-MS (ES, m/z) calculated for C₃₀H₃₁N₄O₃Br₂ [(M+H)+] 653.0758, observed 653.0771.

j)[4,5-Bis-(4-bromo-phenyl)-2-(2-ethoxy-phenyl)-4,5-dihydro-imidazol-1-yl]-[4-(2-hydroxy-ethyl)-piperazin-1-yl]-methanone. HR-MS (ES, m/z) calculated for C₃₀H₃₃N₄O₃Br₂ [(M+H)+] 655.0914, observed 655.0928.

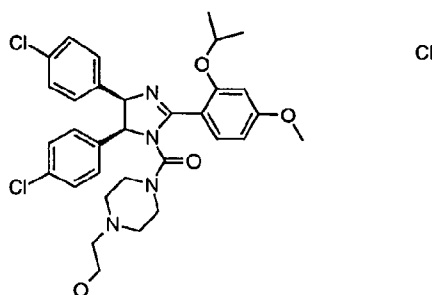
k)1-[4-[4,5-Bis-(4-bromo-phenyl)-2-(2-isopropoxy-phenyl)-4,5-dihydro-imidazole-1-carbonyl]-piperazin-1-yl]-ethanone. HR-MS (ES, m/z) calculated for C₃₁H₃₃N₄O₃Br₂ [(M+H)+] 667.0914, observed 667.0920.

l)[4,5-Bis-(4-bromo-phenyl)-2-(2-isopropoxy-phenyl)-4,5-dihydro-imidazol-1-yl]-[4-(2-hydroxy-ethyl)-piperazin-1-yl]-methanone. HR-MS (ES, m/z) calculated for C₃₁H₃₅N₄O₃Br₂ [(M+H)+] 669.1071, observed 669.1069.

Example 9

[4,5-Bis-(4-chloro-phenyl)-2-(2-isopropoxy-4-methoxy-phenyl)-4,5-dihydro-imidazol-1-yl]-[4-(2-hydroxy-ethyl)-piperazin-1-yl]-methanone hydrochloride

- 45 -



A mixture of 2-hydroxy-4-methoxybenzaldehyde (25.0 g, 164 mmol), sodium acetate (26.4 g, 322 mmol), nitroethane (23 g, 307 mmol) in acetic acid (45 mL) was heated at reflux for 6 h. The mixture was then cooled to room temperature and poured onto ice water. The solids were filtered off, washed with water and dried. Recrystallization of the crude solid in ethyl acetate gave 2-hydroxy-4-methoxy-benzonitrile as a brown solid (15.9 g, 65%).

Cesium carbonate (51.5 g, 158 mmol) was added to a solution of 2-hydroxy-4-methoxybenzonitrile (11.8 g, 79 mmol) in acetone (100 mL). 2-Iodopropane (12.5 mL, 125 mmol) was added. The mixture was heated at reflux for 3 h. Water was added and the mixture was extracted with diethyl ether (4 x 100 mL). The combined organic extracts were washed with diluted ammonium hydroxide, brine and dried (MgSO₄). Evaporation of the solvents and chromatography of the residue over silica gel using 5% diethyl ether in hexanes gave 2-isopropoxy-4-methoxybenzonitrile (13.2 g, 87%).

Hydrogen chloride gas was passed through a solution of 2-isopropoxy-4-methoxybenzonitrile (13.2 g, 69 mmol) in absolute ethanol (200 mL) in a pressure tube for 1 h at -10 °C. The tube was sealed and stirred at room temperature for 7 d. The tube was cooled to -10 °C and more ethanol (100 mL) was added. Hydrogen chloride gas was passed through it for additional 30 min at -10 °C. The tube was resealed and stirred at room temperature for 7 d. Evaporation of the solvents and trituration of the residue in diethyl ether gave ethyl 2-isopropoxy-4-methoxy-benzimidate hydrochloride as a white solid (17.5 g, 99%). It was used without further purification.

A mixture of ethyl 2-isopropoxy-4-methoxy-benzimidate hydrochloride (8.21 g, 30 mmol), meso-1,2-bis-(4-chloro-phenyl)-ethane-1,2-diamine (7.59 g, 27 mmol, prepared according to the procedure described by Vogtle, F.; Goldschmitt, E. Chem. Ber. 1976, 109, 1-40) and triethylamine (8.35 mL, 60 mmol) in ethanol (200 mL) was heated at reflux for 24 h. Additional ethyl 2-isopropoxy-4-methoxy-benzimidate hydrochloride (1.64 g, 6

mmol) was added and the reaction mixture was heated at reflux for another 24 h. Aqueous sodium bicarbonate was added and it was extracted with methylene chloride (3 x). The combined organic extracts were washed with water and brine, and dried over sodium sulfate. Chromatography of the residue over silica gel using 0.5-2% methanol in methylene chloride followed by recrystallization using diethyl ether in pentane gave 4,5-bis-(4-chloro-phenyl)-2-(2-isopropoxy-4-methoxy-phenyl)-4,5-dihydro-1H-imidazole (9 g, 73%).

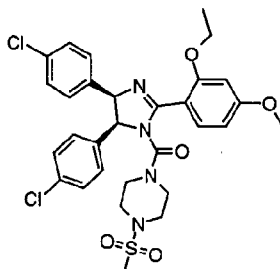
Phosgene (12 mL, 23 mmol, 1.93 M in toluene) was added dropwise to a mixture of triethylamine (3.75 mL, 26.9 mmol) and 4,5-bis-(4-chloro-phenyl)-2-(2-isopropoxy-4-methoxy-phenyl)-4,5-dihydro-1H-imidazole (3.50 g, 7.69 mmol) in methylene chloride (80 mL) at 0 °C. The reaction mixture was stirred for 30 min at 0 °C and evaporated. The residue was kept under high vacuum for 30 min. Methylene chloride (50 mL) was added to the residue and the solution was added dropwise to a solution of 2-piperazin-1-yl-ethanol (10 g) in methylene chloride (200 mL) at 0 °C over 15 min. After 30 min, the reaction was worked up with water. The mixture was extracted with methylene chloride and washed with water and brine. The organic extracts were dried over sodium sulfate and evaporated. Chromatography of the residue over silica gel using 1-2% methanol in methylene chloride gave [4,5-bis-(4-chloro-phenyl)-2-(2-isopropoxy-4-methoxy-phenyl)-4,5-dihydro-imidazol-1-yl]-[4-(2-hydroxy-ethyl)-piperazin-1-yl]-methanone as a light yellow foam (4.07 g, 87%).

[4,5-Bis-(4-chloro-phenyl)-2-(2-isopropoxy-4-methoxy-phenyl)-4,5-dihydro-imidazol-1-yl]-[4-(2-hydroxy-ethyl)-piperazin-1-yl]-methanone (2.20 g, 3.60 mmol) was dissolved in dilute hydrochloric acid (0.23 N, 20 mL). The light yellow solution was filtered and lyophilized to give [4,5-bis-(4-chloro-phenyl)-2-(2-isopropoxy-4-methoxy-phenyl)-4,5-dihydro-imidazol-1-yl]-[4-(2-hydroxy-ethyl)-piperazin-1-yl]-methanone hydrochloride as a off-white powder (2.26 g, 97%). HR-MS (ES, m/z) calculated for C₃₂H₃₇N₄O₄Cl₂ [(M+H)+] 611.2187, observed 611.2195.

Example 10

In a similar manner as described in example 9, the following compounds were prepared.

a)[4,5-Bis-(4-chloro-phenyl)-2-(2-ethoxy-4-methoxy-phenyl)-4,5-dihydro-imidazol-1-yl]-(4-methanesulfonyl-piperazin-1-yl)-methanone. HR-MS (ES, m/z) calculated for C₃₀H₃₃N₄O₅SCl₂ [(M+H)+] 631.1543, observed 631.1549



5 b)[4,5-Bis-(4-chloro-phenyl)-2-(2-ethoxy-4-methoxy-phenyl)-4,5-dihydro-imidazol-1-yl]-[4-(2-hydroxy-ethyl)-piperazin-1-yl]-methanone. HR-MS (ES, m/z) calculated for C₃₁H₃₅N₄O₄Cl₂ [(M+H)+] 597.2030, observed 597.2038.

c)[4,5-Bis-(4-chloro-phenyl)-2-(2-ethoxy-4-methoxy-phenyl)-4,5-dihydro-imidazol-1-yl]-morpholin-4-yl-methanone. HR-MS (m/z) calculated for C₂₉H₃₀N₃O₄Cl₂
10 [(M+H)+] 554.1608, observed 554.1614

d)[4,5-Bis-(4-chloro-phenyl)-2-(2-ethoxy-4-methoxy-phenyl)-4,5-dihydro-imidazol-1-yl]-(4-methyl-piperazin-1-yl)-methanone. HR-MS (ES, m/z) calculated for C₃₀H₃₃N₄O₃Cl₂ [(M+H)+] 567.1924, observed 567.1929.

e)1-[4-[4,5-Bis-(4-chloro-phenyl)-2-(2-ethoxy-4-methoxy-phenyl)-4,5-dihydro-
15 imidazole-1-carbonyl]-piperazin-1-yl]-ethanone. HR-MS (ES, m/z) calculated for C₃₁H₃₃N₄O₄Cl₂ [(M+H)+] 595.1874, observed 595.1882.

f)4-[4,5-Bis-(4-chloro-phenyl)-2-(2-ethoxy-4-methoxy-phenyl)-4,5-dihydro-imidazole-1-carbonyl]-piperazin-2-one. HR-MS (ES, m/z) calculated for C₂₉H₂₉N₄O₄Cl₂ [(M+H)+] 567.1561, observed 567.1571.

20 g)[4,5-Bis-(4-chloro-phenyl)-2-(2-isopropoxy-4-methoxy-phenyl)-4,5-dihydro-imidazol-1-yl]-piperazin-1-yl-methanone. HR-MS (ES, m/z) calculated for C₃₀H₃₃N₄O₃Cl₂ [(M+H)+] 567.1924, observed 567.1927.

h) 1-[4-[4,5-Bis-(4-chloro-phenyl)-2-(2-isopropoxy-4-methoxy-phenyl)-4,5-dihydro-imidazole-1-carbonyl]-piperazin-1-yl]-ethanone. HR-MS (ES, m/z) calculated for $C_{32}H_{35}N_4O_4Cl_2$ [(M+H)+] 609.2030, observed 609.2036.

i) [4,5-Bis-(4-chloro-phenyl)-2-(2-isopropoxy-4-methoxy-phenyl)-4,5-dihydro-imidazol-1-yl]-(4-methanesulfonyl-piperazin-1-yl)-methanone was prepared by sulfonylation of [4,5-bis-(4-chloro-phenyl)-2-(2-isopropoxy-4-methoxy-phenyl)-4,5-dihydro-imidazol-1-yl]-piperazin-1-yl-methanone (example 10 g). HR-MS (ES, m/z) calculated for $C_{31}H_{35}N_4O_5S$ [(M+H)+] 645.1700, observed 645.1710.

j) [4,5-Bis-(4-chloro-phenyl)-2-(2-isopropoxy-4-methoxy-phenyl)-4,5-dihydro-imidazol-1-yl]-(2,5-dimethyl-piperazin-1-yl)-methanone. HR-MS (ES, m/z) calculated for $C_{32}H_{37}N_4O_3Cl_2$ [(M+H)+] 595.2237, observed 595.2240.

k) 4,5-Bis-(4-chloro-phenyl)-2-(2-isopropoxy-4-methoxy-phenyl)-4,5-dihydro-imidazole-1-carboxylic acid bis-(2-hydroxy-ethyl)-amide. HR-MS (ES, m/z) calculated for $C_{30}H_{34}N_3O_5Cl_2$ [(M+H)+] 586.1870, observed 586.1878.

l) [4,5-Bis-(4-chloro-phenyl)-2-(2-isopropoxy-4-methoxy-phenyl)-4,5-dihydro-imidazol-1-yl]-(4-ethyl-piperazin-1-yl)-methanone. HR-MS (ES, m/z) calculated for $C_{32}H_{37}N_4O_3Cl_2$ [(M+H)+] 595.2237, observed 595.2241.

m) [1,4'-Bipiperidinyl-1'-yl]-[4,5-bis-(4-chloro-phenyl)-2-(2-isopropoxy-4-methoxy-phenyl)-4,5-dihydro-imidazol-1-yl]-methanone. HR-MS (ES, m/z) calculated for $C_{36}H_{43}N_4O_3Cl_2$ [(M+H)+] 649.2707, observed 649.2712.

n) [4,5-Bis-(4-chloro-phenyl)-2-(2-isopropoxy-4-methoxy-phenyl)-4,5-dihydro-imidazol-1-yl]-(4-pyrrolidin-1-yl-piperidin-1-yl)-methanone. HR-MS (ES, m/z) calculated for $C_{35}H_{41}N_4O_3Cl_2$ [(M+H)+] 635.2550, observed 635.2559.

o) [4,5-Bis-(4-chloro-phenyl)-2-(2-isopropoxy-4-methoxy-phenyl)-4,5-dihydro-imidazol-1-yl]-(4-dimethylamino-piperidin-1-yl)-methanone. HR-MS (ES, m/z) calculated for $C_{33}H_{39}N_4O_3Cl_2$ [(M+H)+] 609.2394, observed 609.2395.

p) [4,5-Bis-(4-chloro-phenyl)-2-(2-isopropoxy-4-methoxy-phenyl)-4,5-dihydro-imidazol-1-yl]-morpholin-4-yl-methanone. HR-MS (ES, m/z) calculated for $C_{30}H_{32}N_3O_4Cl_2$ [(M+H)+] 568.1765, observed 568.1768.

q) [4,5-Bis-(4-chloro-phenyl)-2-(2-isopropoxy-4-methoxy-phenyl)-4,5-dihydro-imidazol-1-yl]-(4-isopropyl-piperazin-1-yl)-methanone. HR-MS (ES, m/z) calculated for C₃₃H₃₉N₄O₃Cl₂ [(M+H)+] 609.2394, observed 609.2395. The N-isopropyl piperazine used in the synthesis of above compound was prepared according to the procedure
5 described in Renau, Thomas E.; Sanchez, Joseph P. et al. J. Med. Chem. 1996, 39, 729-35.

r) 4-[4,5-Bis-(4-chloro-phenyl)-2-(2-isopropoxy-4-methoxy-phenyl)-4,5-dihydro-imidazole-1-carbonyl]-piperazin-2-one. HR-MS (ES, m/z) calculated for C₃₀H₃₁N₄O₄Cl₂ [(M+H)+] 581.1717, observed 581.1723.

s) [4,5-Bis-(4-chloro-phenyl)-2-(2-isopropoxy-4-methoxy-phenyl)-4,5-dihydro-imidazol-1-yl]-(4-hydroxymethyl-piperidin-1-yl)-methanone. HR-MS (ES, m/z)
10 calculated for C₃₂H₃₆N₃O₄Cl₂ [(M+H)+] 596.2078, observed 596.2081.

t) [4,5-Bis-(4-chloro-phenyl)-2-(2-isopropoxy-4-methoxy-phenyl)-4,5-dihydro-imidazol-1-yl]-[4-(2-hydroxy-ethyl)-piperidin-1-yl]-methanone. HR-MS (ES, m/z) calculated for C₃₃H₃₈N₃O₄Cl₂ [(M+H)+] 610.2234, observed 610.2236.

15 u) [4,5-Bis-(4-chloro-phenyl)-2-(2-isopropoxy-4-methoxy-phenyl)-4,5-dihydro-imidazol-1-yl]-(3-methyl-piperazin-1-yl)-methanone. HR-MS (ES, m/z) calculated for C₃₁H₃₅N₄O₃Cl₂ [(M+H)+] 581.2081, observed 581.2081.

v) 1-[4-[4,5-Bis-(4-chloro-phenyl)-2-(2-isopropoxy-4-methoxy-phenyl)-4,5-dihydro-imidazole-1-carbonyl]-2-methyl-piperazin-1-yl]-ethanone. HR-MS (ES, m/z)
20 calculated for C₃₃H₃₇N₄O₄Cl₂ [(M+H)+] 623.2187, observed 623.2190.

w) [4,5-Bis-(4-chloro-phenyl)-2-(2-isopropoxy-4-methoxy-phenyl)-4,5-dihydro-imidazol-1-yl]-(4-methanesulfonyl-3-methyl-piperazin-1-yl)-methanone was prepared by sulfonylation of [4,5-bis-(4-chloro-phenyl)-2-(2-isopropoxy-4-methoxy-phenyl)-4,5-dihydro-imidazol-1-yl]-(3-methyl-piperazin-1-yl)-methanone (example 10u). HR-MS
25 (ES, m/z) calculated for C₃₂H₃₇N₄O₅Cl₂ [(M+H)+] 659.1856, observed 659.1856.

x) [4,5-Bis-(4-chloro-phenyl)-2-(2-isopropoxy-4-methoxy-phenyl)-4,5-dihydro-imidazol-1-yl]-(4-hydroxy-piperidin-1-yl)-methanone. HR-MS (ES, m/z) calculated for C₃₁H₃₄N₃O₄Cl₂ [(M+H)+] 582.1921, observed 582.1926.

y)(4-Aminomethyl-piperidin-1-yl)-[4,5-bis-(4-chloro-phenyl)-2-(2-isopropoxy-4-methoxy-phenyl)-4,5-dihydro-imidazol-1-yl]-methanone. HR-MS (ES, m/z) calculated for C₃₂H₃₇N₄O₃Cl₂ [(M+H)+] 595.2237, observed 595.2243.

z)[4,5-Bis-(4-bromo-phenyl)-2-(2-ethoxy-4-methoxy-phenyl)-4,5-dihydro-imidazol-1-yl]-[4-(2-hydroxy-ethyl)-piperazin-1-yl]-methanone. HR-MS (ES, m/z) calculated for C₃₁H₃₅N₄O₄Br₂ [(M+H)+] 685.1020, observed 685.1031.

aa)[4,5-Bis-(4-bromo-phenyl)-2-(2-ethoxy-4-methoxy-phenyl)-4,5-dihydro-imidazol-1-yl]-piperazin-1-yl-methanone. HR-MS (ES, m/z) calculated for C₂₉H₃₁N₄O₃Br₂ [(M+H)+] 641.0758, observed 641.0762.

bb)[4,5-Bis-(4-bromo-phenyl)-2-(2-ethoxy-4-methoxy-phenyl)-4,5-dihydro-imidazol-1-yl]-[4-(methanesulfonyl-piperazin-1-yl)-methanone was prepared by sulfonylation of [4,5-bis-(4-bromo-phenyl)-2-(2-ethoxy-4-methoxy-phenyl)-4,5-dihydro-imidazol-1-yl]-piperazin-1-yl-methanone (example 10 aa) using the method known in the art. HR-MS (ES, m/z) calculated for C₃₀H₃₃N₄O₅Br₂ [(M+H)+] 719.0533, observed 719.0540.

cc)1-[4-[4,5-Bis-(4-bromo-phenyl)-2-(2-ethoxy-4-methoxy-phenyl)-4,5-dihydro-imidazole-1-carbonyl]-piperazin-1-yl]-ethanone. HR-MS (ES, m/z) calculated for C₃₁H₃₃N₄O₄Br₂ [(M+H)+] 683.0863, observed 683.0866.

dd)[4,5-Bis-(4-bromo-phenyl)-2-(2-ethoxy-4-methoxy-phenyl)-4,5-dihydro-imidazol-1-yl]-[4-methyl-piperazin-1-yl]-methanone. HR-MS (ES, m/z) calculated for C₃₀H₃₃N₄O₃Br₂ [(M+H)+] 655.0914, observed 655.0917.

ee)4-[4,5-Bis-(4-bromo-phenyl)-2-(2-ethoxy-4-methoxy-phenyl)-4,5-dihydro-imidazole-1-carbonyl]-piperazine-1-carbaldehyde. HR-MS (ES, m/z) calculated for C₃₀H₃₁N₄O₄Br₂ [(M+H)+] 669.0707, observed 669.0713.

ff)[4,5-Bis-(4-bromo-phenyl)-2-(2-ethoxy-4-methoxy-phenyl)-4,5-dihydro-imidazol-1-yl]-[4-pyrrolidin-1-yl-piperidin-1-yl]-methanone. HR-MS (ES, m/z) calculated for C₃₄H₃₉N₄O₃Br₂ [(M+H)+] 709.1384, observed 709.1401.

gg)[4,5-Bis-(4-bromo-phenyl)-2-(2-ethoxy-4-methoxy-phenyl)-4,5-dihydro-imidazol-1-yl]-[4-dimethylamino-piperidin-1-yl]-methanone. HR-MS (ES, m/z) calculated for C₃₂H₃₇N₄O₃Br₂ [(M+H)+] 683.1227, observed 683.1250.

hh)[4,5-Bis-(4-bromo-phenyl)-2-(2-ethoxy-4-methoxy-phenyl)-4,5-dihydro-imidazol-1-yl]-(4-isopropyl-piperazin-1-yl)-methanone. HR-MS (ES, m/z) calculated for $C_{32}H_{37}N_4O_3Br_2$ [(M+H)+] 683.1227, observed 683.1231.

5 ii)4-[4,5-Bis-(4-bromo-phenyl)-2-(2-ethoxy-4-methoxy-phenyl)-4,5-dihydro-imidazole-1-carbonyl]-piperazin-2-one. HR-MS (ES, m/z) calculated for $C_{29}H_{29}N_4O_4Br_2$ [(M+H)+] 655.0550, observed 655.0557.

jj)[4,5-Bis-(4-bromo-phenyl)-2-(2-isopropoxy-4-methoxy-phenyl)-4,5-dihydro-imidazol-1-yl]-piperazin-1-yl-methanone. HR-MS (ES, m/z) calculated for $C_{30}H_{33}N_4O_3Br_2$ [(M+H)+] 655.0914, observed 655.0918

10 kk)1-{4-[4,5-Bis-(4-bromo-phenyl)-2-(2-isopropoxy-4-methoxy-phenyl)-4,5-dihydro-imidazole-1-carbonyl]-piperazin-1-yl}-ethanone. HR-MS (ES, m/z) calculated for $C_{32}H_{35}N_4O_4Br_2$ [(M+H)+] 697.1020 observed 697.1028.

ll)[4,5-Bis-(4-bromo-phenyl)-2-(2-isopropoxy-4-methoxy-phenyl)-4,5-dihydro-imidazol-1-yl]-(4-methanesulfonyl-piperazin-1-yl)-methanone was prepared by
15 sulfonylation of [4,5-bis-(4-bromo-phenyl)-2-(2-isopropoxy-4-methoxy-phenyl)-4,5-dihydro-imidazol-1-yl]-piperazin-1-yl-methanone (example 10 jj) using the method known in the art. HR-MS (ES, m/z) calculated for $C_{31}H_{35}N_4O_5SBr_2$ [(M+H)+] 733.0690, observed 733.0696.

mm)[4,5-Bis-(4-bromo-phenyl)-2-(2-isopropoxy-4-methoxy-phenyl)-4,5-dihydro-
20 imidazol-1-yl]-(4-methyl-piperazin-1-yl)-methanone. HR-MS (ES, m/z) calculated for $C_{31}H_{35}N_4O_3Br_2$ [(M+H)+] 669.1071, observed 669.1078.

nn)[4,5-Bis-(4-bromo-phenyl)-2-(2-isopropoxy-4-methoxy-phenyl)-4,5-dihydro-imidazol-1-yl]-morpholin-4-yl-methanone. HR-MS (ES, m/z) calculated for $C_{30}H_{32}N_3O_4Br_2$ [(M+H)+] 656.0754, observed 656.0762.

25 oo)[1,4']Bipiperidiny-1'-yl-[4,5-bis-(4-bromo-phenyl)-2-(2-isopropoxy-4-methoxy-phenyl)-4,5-dihydro-imidazol-1-yl]-methanone. HR-MS (ES, m/z) calculated for $C_{36}H_{43}N_4O_3Br_2$ [(M+H)+] 737.1697, observed 737.1707.

pp)[4,5-Bis-(4-bromo-phenyl)-2-(2-isopropoxy-4-methoxy-phenyl)-4,5-dihydro-imidazol-1-yl]-(4-ethyl-piperazin-1-yl)-methanone. HR-MS (ES, m/z) calculated for
30 $C_{32}H_{37}N_4O_3Br_2$ [(M+H)+] 683.1227, observed 683.1232.

qq) 4-[4,5-Bis-(4-bromo-phenyl)-2-(2-isopropoxy-4-methoxy-phenyl)-4,5-dihydro-imidazole-1-carbonyl]-piperazin-2-one. HR-MS (ES, m/z) calculated for $C_{30}H_{31}N_4O_4Br_2$ [(M+H)+] 669.0707, observed 669.0718.

rr) [4,5-Bis-(4-cyano-phenyl)-2-(2-isopropoxy-4-methoxy-phenyl)-4,5-dihydro-imidazol-1-yl]-piperazin-1-yl-methanone. HR-MS (ES, m/z) calculated for $C_{32}H_{33}N_6O_3$ [(M+H)+] 549.2609, observed 549.2614

ss) 1-(4-{4,5-Bis-(4-chloro-phenyl)-2-[4-methoxy-2-(2-methoxy-ethoxy)-phenyl]-4,5-dihydro-imidazole-1-carbonyl}-piperazin-1-yl)-ethanone. HR-MS (ES, m/z) calculated for $C_{32}H_{35}N_4O_5Cl_2$ [(M+H)+] 625.1979, observed 625.1987.

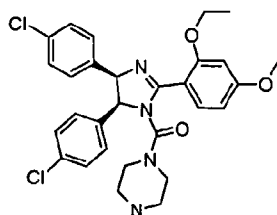
tt) 1-(4-{4,5-Bis-(4-chloro-phenyl)-2-[2-(2-fluoro-ethoxy)-4-methoxy-phenyl]-4,5-dihydro-imidazole-1-carbonyl}-piperazin-1-yl)-ethanone. HR-MS (ES, m/z) calculated for $C_{31}H_{32}N_4O_4FCl_2$ [(M+H)+] 613.1779, observed 613.1775.

uu) 4-{4,5-Bis-(4-chloro-phenyl)-2-[2-(2-fluoro-ethoxy)-4-methoxy-phenyl]-4,5-dihydro-imidazole-1-carbonyl}-piperazin-2-one. HR-MS (ES, m/z) calculated for $C_{29}H_{28}N_4O_4FCl_2$ [(M+H)+] 585.1466, observed 585.1475.

Example 11

In a similar manner as described in example 9, the following compounds were prepared.

a) [4,5-Bis-(4-chloro-phenyl)-2-(2-ethoxy-4-methoxy-phenyl)-4,5-dihydro-imidazol-1-yl]-piperazin-1-yl-methanone hydrochloride. HR-MS (ES, m/z) calculated for $C_{29}H_{31}N_4O_3Cl_2$ [(M+H)+] 553.1768, observed 553.1773



Cl

- b) 4,5-Bis-(4-chloro-phenyl)-2-(2-ethoxy-4-methoxy-phenyl)-4,5-dihydro-imidazole-1-carboxylic acid methyl-(2-methylamino-ethyl)-amide, trifluoroacetic acid salt. HR-MS (ES, m/z) calculated for C₂₉H₃₃N₄O₃Cl₂ [(M+H)+] 555.1924, observed 555.1929.
- 5 c) 4,5-Bis-(4-chloro-phenyl)-2-(2-ethoxy-4-methoxy-phenyl)-4,5-dihydro-imidazole-1-carboxylic acid (2-dimethylamino-ethyl)-methyl-amide, trifluoroacetic acid salt. HR-MS (ES, m/z) calculated for C₃₀H₃₅N₄O₃Cl₂ [(M+H)+] 569.2081, observed 569.2085.
- d) 4,5-Bis-(4-chloro-phenyl)-2-(2-ethoxy-4-methoxy-phenyl)-4,5-dihydro-
10 imidazole-1-carboxylic acid (2-dimethylamino-ethyl)-amide, trifluoroacetic acid salt. HR-MS (ES, m/z) calculated for C₂₉H₃₃N₄O₃Cl₂ [(M+H)+] 555.1924, observed 555.1940.
- e) 4,5-Bis-(4-chloro-phenyl)-2-(2-ethoxy-4-methoxy-phenyl)-4,5-dihydro-imidazole-1-carboxylic acid (2-amino-ethyl)-amide, trifluoroacetic acid salt. HR-MS (m/z) calculated for C₂₇H₂₉N₄O₃Cl₂ [(M+H)+] 527.1611, observed 527.1621.
- 15 f) [4,5-Bis-(4-chloro-phenyl)-2-(2-ethoxy-4-methoxy-phenyl)-4,5-dihydro-imidazol-1-yl]-(4-pyrrolidin-1-yl-piperidin-1-yl)-methanone hydrochloride. HR-MS (ES, m/z) calculated for C₃₄H₃₉N₄O₃Cl₂ [(M+H)+] 621.2394, observed 621.2400.
- g) [4,5-Bis-(4-chloro-phenyl)-2-(4-methoxy-2-propoxy-phenyl)-4,5-dihydro-imidazol-1-yl]-piperazin-1-yl-methanone, trifluoroacetic acid salt. HR-MS (ES, m/z)
20 calculated for C₃₀H₃₃N₄O₃Cl₂ [(M+H)+] 567.1924, observed 567.1932.
- h) [4,5-Bis-(4-chloro-phenyl)-2-(2-isopropoxy-4-methoxy-phenyl)-4,5-dihydro-imidazol-1-yl]-(4-methyl-piperazin-1-yl)-methanone hydrochloride. HR-MS (ES, m/z) calculated for C₃₁H₃₅N₄O₃Cl₂ [(M+H)+] 581.2081, observed 581.2086.
- i) 4,5-Bis-(4-chloro-phenyl)-2-(2-isopropoxy-4-methoxy-phenyl)-4,5-dihydro-
25 imidazole-1-carboxylic acid (2-morpholin-4-yl-ethyl)-amide hydrochloride. HR-MS (ES, m/z) calculated for C₃₂H₃₇N₄O₄Cl₂ [(M+H)+] 611.2187, observed 611.2197.
- j) 4,5-Bis-(4-chloro-phenyl)-2-(2-isopropoxy-4-methoxy-phenyl)-4,5-dihydro-imidazole-1-carboxylic acid (2-piperazin-1-yl-ethyl)-amide hydrochloride. HR-MS (ES, m/z) calculated for C₃₂H₃₈N₅O₃Cl₂ [(M+H)+] 610.2346, observed 610.2348.

k) [4,5-Bis-(4-chloro-phenyl)-2-(2-isobutoxy-4-methoxy-phenyl)-4,5-dihydro-imidazol-1-yl]-piperazin-1-yl-methanone hydrochloride. HR-MS (ES, m/z) calculated for $C_{31}H_{35}N_4O_3Cl_2$ [(M+H)+] 581.2081, observed 581.2081.

l) [4,5-Bis-(4-chloro-phenyl)-2-(2-isopropoxy-4-methoxy-phenyl)-4,5-dihydro-imidazol-1-yl]-(3-methyl-piperazin-1-yl)-methanone hydrochloride. HR-MS (ES, m/z) calculated for $C_{31}H_{35}N_4O_3Cl_2$ [(M+H)+] 581.2081, observed 581.2084.

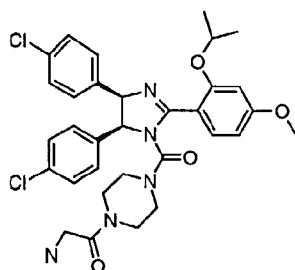
m) {4,5-Bis-(4-chloro-phenyl)-2-[4-methoxy-2-(2-methoxy-ethoxy)-phenyl]-4,5-dihydro-imidazol-1-yl}-piperazin-1-yl-methanone, trifluoroacetic acid salt. HR-MS (ES, m/z) calculated for $C_{30}H_{33}N_4O_4Cl_2$ [(M+H)+] 583.1874, observed 583.1875.

n) {4,5-Bis-(4-chloro-phenyl)-2-[2-(2-fluoro-ethoxy)-4-methoxy-phenyl]-4,5-dihydro-imidazol-1-yl}-piperazin-1-yl-methanone. HR-MS (ES, m/z) calculated for $C_{29}H_{30}N_4O_3FCl_2$ [(M+H)+] 571.1674, observed 571.1676.

o) {4,5-Bis-(4-chloro-phenyl)-2-[2-(2-fluoro-ethoxy)-4-methoxy-phenyl]-4,5-dihydro-imidazol-1-yl}-(4-pyrrolidin-1-yl-piperidin-1-yl)-methanone hydrochloride. HR-MS (ES, m/z) calculated for $C_{34}H_{38}N_4O_3FCl_2$ [(M+H)+] 639.2300, observed 639.2303.

Example 12

2-Amino-1-{4-[4,5-bis-(4-chloro-phenyl)-2-(2-isopropoxy-4-methoxy-phenyl)-4,5-dihydro-imidazole-1-carbonyl]-piperazin-1-yl}-ethanone



[4,5-Bis-(4-chloro-phenyl)-2-(2-isopropoxy-4-methoxy-phenyl)-4,5-dihydro-imidazol-1-yl]-piperazin-1-yl-methanone (52 mg, 0.092 mmol, example 10) was added to a solution of N-(t-butoxycarbonyl)glycine (21 mg, 0.119 mmol) in THF (12 mL), followed

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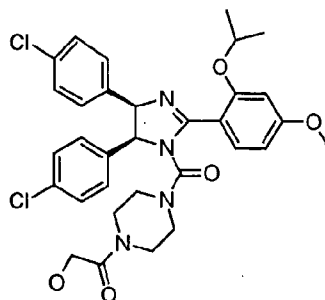
by diisopropyl carbodiimide (19.7 μ L, 0.125 mmol). After 3 h, the reaction mixture was concentrated and diluted with methylene chloride. The mixture was washed with aqueous sodium carbonate, water and brine, and dried over sodium sulfate. Evaporation of the solvents and chromatography of the residue over silica using 1-2 % methanol in methylene chloride gave (2-{4-[4,5-bis-(4-chloro-phenyl)-2-(2-isopropoxy-4-methoxy-phenyl)-4,5-dihydro-imidazole-1-carbonyl]-piperazin-1-yl}-2-oxo-ethyl)-carbamic acid tert-butyl ester (54 mg, 81%).

Trifluoroacetic acid (2 mL, 26 mmol) was added to a solution of (2-{4-[4,5-bis-(4-chloro-phenyl)-2-(2-isopropoxy-4-methoxy-phenyl)-4,5-dihydro-imidazole-1-carbonyl]-piperazin-1-yl}-2-oxo-ethyl)-carbamic acid tert-butyl ester (40 mg, 0.054 mmol) in methylene chloride (6 mL). The reaction mixture was stirred for 2.5 h and diluted with methylene chloride. The mixture was washed aqueous sodium carbonate, water and brine, and dried over sodium sulfate. Evaporation of the solvents and chromatography of the residue over silica gel with 5-10% methanol in methylene chloride gave 2-amino-1-{4-[4,5-bis-(4-chloro-phenyl)-2-(2-isopropoxy-4-methoxy-phenyl)-4,5-dihydro-imidazole-1-carbonyl]-piperazin-1-yl}-ethanone (22 mg, 65%). HR-MS (ES, m/z) calculated for $C_{32}H_{36}N_5O_4Cl_2$ [(M+H)+] 624.2139, observed 624.2147.

Example 13

In a similar manner as described in example 12, the following compounds were prepared.

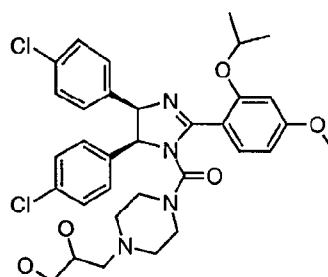
a) 1-{4-[4,5-Bis-(4-chloro-phenyl)-2-(2-isopropoxy-4-methoxy-phenyl)-4,5-dihydro-imidazole-1-carbonyl]-piperazin-1-yl}-2-hydroxy-ethanone. HR-MS (ES, m/z) calculated for $C_{32}H_{35}N_4O_5Cl_2$ [(M+H)+] 625.1979, observed 625.1984



b) 1-[4-[4,5-Bis-(4-chloro-phenyl)-2-(2-isopropoxy-4-methoxy-phenyl)-4,5-dihydro-imidazole-1-carbonyl]-piperazin-1-yl]-2,3-dihydroxy-propan-1-one. HR-MS (ES, m/z) calculated for C₃₃H₃₇N₄O₆Cl₂ [(M+H)+] 655.2085, observed 655.2090.

5 Example 14

[4,5-Bis-(4-chloro-phenyl)-2-(2-isopropoxy-4-methoxy-phenyl)-4,5-dihydro-imidazol-1-yl]-[4-(2,3-dihydroxy-propyl)-piperazin-1-yl]-methanone

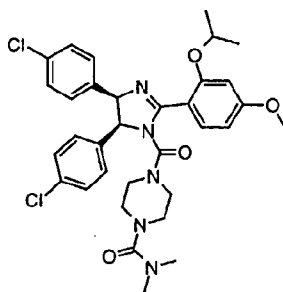


[4,5-Bis-(4-chloro-phenyl)-2-(2-isopropoxy-4-methoxy-phenyl)-4,5-dihydro-imidazol-1-yl]-piperazin-1-yl-methanone (50 mg, 0.088 mmol, example 10 g) was dissolved in anhydrous methanol (10 mL). Glycidol (0.15 mL, 2.26 mmol) was added and the reaction was heated at 40 °C for 20 h. The mixture was cooled to room temperature and concentrated in vacuo. Chromatography of the residue over silica gel using 1-6% methanol in methylene chloride gave [4,5-bis-(4-chloro-phenyl)-2-(2-isopropoxy-4-methoxy-phenyl)-4,5-dihydro-imidazol-1-yl]-[4-(2,3-dihydroxy-propyl)-piperazin-1-yl]-methanone (25 mg, 44%). HR-MS (ES, m/z) calculated for C₃₃H₃₉N₄O₅Cl₂ [(M+H)+] 641.2292, observed 641.2300.

Example 15

4-[4,5-Bis-(4-chloro-phenyl)-2-(2-isopropoxy-4-methoxy-phenyl)-4,5-dihydro-imidazole-1-carbonyl]-piperazine-1-carboxylic acid dimethylamide

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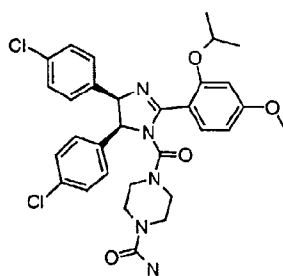


Phosgene (0.26 mL, 0.5 mmol, 1.93 M in toluene) was added to a solution of 4,5-bis-(4-chloro-phenyl)-2-(2-isopropoxy-4-methoxy-phenyl)-4,5-dihydro-imidazol-1-yl]-piperazin-1-yl-methanone (60 mg, 0.11 mmol, example 10 g) and triethylamine (97 μ L, 0.70 mmol) in methylene chloride (10 mL). The reaction mixture was stirred for 1 h. The solvents were evaporated and the residue was dried under high vacuum for 30 min. The residue was redissolved in methylene chloride (10 mL). Dimethylamine (0.993 mL, 1.986 mmol, 2 M in THF) was added and the reaction mixture was stirred overnight. The mixture was washed with brine and the aqueous layer was extracted with methylene chloride. The combined organic extracts were dried (MgSO_4) and evaporated. Purification of the residue using reversed phase HPLC gave 4-[4,5-bis-(4-chloro-phenyl)-2-(2-isopropoxy-4-methoxy-phenyl)-4,5-dihydro-imidazole-1-carbonyl]-piperazine-1-carboxylic acid dimethylamide (48 mg, 68%). HR-MS (ES, m/z) calculated for $\text{C}_{33}\text{H}_{38}\text{N}_5\text{O}_4\text{Cl}_2$ [(M+H)+] 638.2296, observed 638.2299.

15

Example 16

4-[4,5-Bis-(4-chloro-phenyl)-2-(2-isopropoxy-4-methoxy-phenyl)-4,5-dihydro-imidazole-1-carbonyl]-piperazine-1-carboxylic acid amide

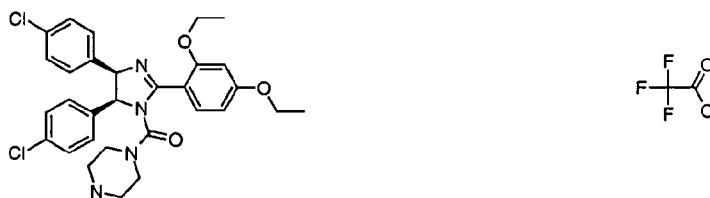


20

The named compound was prepared in a similar manner as described in example 15.
HR-MS (m/z) calculated for C₃₁H₃₄N₅O₄Cl₂ [(M+H)+] 610.1983, observed 610.1985.

Example 17

- 5 [4,5-Bis-(4-chloro-phenyl)-2-(2,4-diethoxy-phenyl)-4,5-dihydro-imidazol-1-yl]-
piperazin-1-yl-methanone trifluoroacetate salt



- A mixture of 2,4-diethoxybenzaldehyde (5.0 g, 25.7 mmol), sodium acetate (4.23 g, 51.6 mmol), nitroethane (3.86 g, 51.4 mmol) in acetic acid (7 mL) was heated at reflux for
10 6 h. The mixture was then cooled and poured onto ice-water. The solids were filtered off, washed with water and dried. Chromatography of the residue over silica gel using 2-5% ethyl acetate in hexanes followed recrystallization in ethyl acetate gave 2, 4-diethoxybenzonitrile (1.86 g, 38%).

- Hydrogen chloride gas was passed through a solution of 2,4-diethoxybenzonitrile
15 (1.86 g, 9.7 mmol) in absolute ethanol (20 mL) in a pressure tube for 1 h at -10 °C. The tube was sealed and stirred at room temperature for 12 d. Evaporation of the solvents and trituration of the residue in diethyl ether gave ethyl 2, 4-diethoxy-benzimidate hydrochloride (2.53 g, 95%).

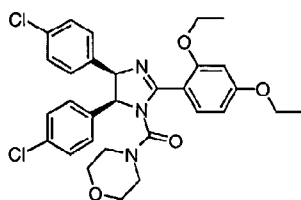
- A mixture of ethyl 2, 4-diethoxy-benzimidate hydrochloride (0.76 g, 2.79 mmol),
20 meso-1,2-bis-(4-chloro-phenyl)-ethane-1,2-diamine (0.65 mg, 2.327 mmol, prepared according to the procedure described by Vogtle, F.; Goldschmitt, E. Chem. Ber. 1976, 109, 1-40) and triethylamine (0.489 mL, 3.49 mmol) in ethanol (10 mL) was heated at reflux for 4 h. The solvent was removed to give a yellow paste. Aqueous sodium bicarbonate was added and it was extracted with methylene chloride. The combined organic extracts were
25 washed with water and brine, and dried over sodium sulfate. Chromatography of the residue over silica gel with 70% ethyl acetate-hexane gave 4,5-bis-(4-chloro-phenyl)-2-(2,4-diethoxy-phenyl)-4,5-dihydro-1H-imidazole (0.50 g, 47%).

Phosgene (0.558 mL, 1.1 mmol, 1.93 M in toluene) was added dropwise to a mixture of triethylamine (0.216 mL, 1.54 mmol) and 4,5-bis-(4-chloro-phenyl)-2-(2,4-diethoxy-phenyl)-4,5-dihydro-1H-imidazole (0.10 g, 0.22 mmol) in methylene chloride (10 mL) at 0 °C. The reaction mixture was stirred for 1 h at 0 °C and evaporated. The residue was kept
5 under high vacuum for 30 min. Methylene chloride (5 mL) was added to the residue and the solution was added dropwise to a solution of piperazine (0.38 g, 4.4 mmol) in methylene chloride (5 mL) at 0 °C over 15 min. After 1 h, the reaction was worked up with aqueous sodium bicarbonate. The mixture was extracted with methylene chloride and washed with water and brine. The organic extracts were dried over sodium sulfate and
10 evaporated. Purification using HPLC gave [4,5-Bis-(4-chloro-phenyl)-2-(2,4-diethoxy-phenyl)-4,5-dihydro-imidazol-1-yl]-piperazin-1-yl-methanone, trifluoroacetic acid salt (4.07 g, 87%). HR-MS (ES, m/z) calculated for C₃₀H₃₃N₄O₃Cl₂ [(M+H)+] 567.1924, observed 567.1928.

15 Example 18

In a similar manner as described in example 17 the following compounds were prepared.

a) [4,5-Bis-(4-chloro-phenyl)-2-(2,4-diethoxy-phenyl)-4,5-dihydro-imidazol-1-yl]-morpholin-4-yl-methanone. HR-MS (ES, m/z) calculated for C₃₀H₃₂N₃O₄Cl₂
20 [(M+H)+] 568.1765, observed 568.1766



b) [4,5-Bis-(4-chloro-phenyl)-2-(2,4-diethoxy-phenyl)-4,5-dihydro-imidazol-1-yl]-[4-(2-hydroxy-ethyl)-piperazin-1-yl]-methanone. HR-MS (ES, m/z) calculated for C₃₂H₃₇N₄O₄Cl₂ [(M+H)+] 611.2187, observed 611.2203.

25 c) [4,5-Bis-(4-chloro-phenyl)-2-(2,4-diethoxy-phenyl)-4,5-dihydro-imidazol-1-yl]-(4-methyl-piperazin-1-yl)-methanone. HR-MS (ES, m/z) calculated for C₃₁H₃₅N₄O₃Cl₂ [(M+H)+] 581.2081, observed 581.2087.

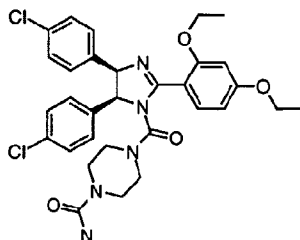
- d) 1-{4-[4,5-Bis-(4-chloro-phenyl)-2-(2,4-diethoxy-phenyl)-4,5-dihydro-imidazole-1-carbonyl]-piperazin-1-yl}-ethanone. HR-MS (ES, m/z) calculated for C₃₂H₃₅N₄O₄Cl₂ [(M+H)+] 609.2030, observed 609.2035.
- e) [4,5-Bis-(4-chloro-phenyl)-2-(2,4-diethoxy-phenyl)-4,5-dihydro-imidazol-1-yl]-
5 (4-methanesulfonyl-piperazin-1-yl)-methanone was prepared by sulfonylation of [4,5-bis-(4-chloro-phenyl)-2-(2,4-diethoxy-phenyl)-4,5-dihydro-imidazol-1-yl]-piperazin-1-yl-methanone (example 17). HR-MS (ES, m/z) calculated for C₃₁H₃₅N₄O₅SCl₂ [(M+H)+] 645.1700, observed 645.1704.
- f) [4,5-Bis-(4-chloro-phenyl)-2-(2,4-diethoxy-phenyl)-4,5-dihydro-imidazol-1-yl]-
10 (4-pyrrolidin-1-yl-piperidin-1-yl)-methanone. HR-MS (ES, m/z) calculated for C₃₅H₄₁N₄O₃Cl₂ [(M+H)+] 635.2550, observed 635.2561.
- g) [4,5-Bis-(4-bromo-phenyl)-2-(2,4-diethoxy-phenyl)-4,5-dihydro-imidazol-1-yl]-
(4-methyl-piperazin-1-yl)-methanone. HR-MS (ES, m/z) calculated for C₃₁H₃₅N₄O₃Br₂ [(M+H)+] 669.1071, observed 669.1074.
- 15 h) [4,5-Bis-(4-bromo-phenyl)-2-(2,4-diethoxy-phenyl)-4,5-dihydro-imidazol-1-yl]-
(4-ethyl-piperazin-1-yl)-methanone. HR-MS (ES, m/z) calculated for C₃₂H₃₇N₄O₃Br₂ [(M+H)+] 683.1227, observed 683.1228.
- i) [4,5-Bis-(4-bromo-phenyl)-2-(2,4-diethoxy-phenyl)-4,5-dihydro-imidazol-1-yl]-
morpholin-4-yl-methanone. HR-MS (ES, m/z) calculated for C₃₀H₃₂N₃O₄Br₂
20 [(M+H)+] 656.0754, observed 656.0760.

Example 19

In a similar manner as described in example 15, the following compounds were prepared from [4,5-bis-(4-chloro-phenyl)-2-(2,4-diethoxy-phenyl)-4,5-dihydro-imidazol-
25 1-yl]-piperazin-1-yl-methanone (example 17).

a) 4-[4,5-Bis-(4-chloro-phenyl)-2-(2,4-diethoxy-phenyl)-4,5-dihydro-imidazole-1-carbonyl]-piperazine-1-carboxylic acid amide. HR-MS (ES, m/z) calculated for C₃₁H₃₄N₅O₄Cl₂ [(M+H)+] 610.1983, observed 610.1983

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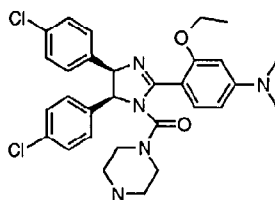


b) 4-[4,5-Bis-(4-chloro-phenyl)-2-(2,4-diethoxy-phenyl)-4,5-dihydro-imidazole-1-carbonyl]-piperazine-1-carboxylic acid dimethylamide. HR-MS (ES, m/z) calculated for $C_{33}H_{38}N_5O_4Cl_2$ [(M+H)+] 638.2296, observed 638.2297.

5

Example 20

[4,5-Bis-(4-chloro-phenyl)-2-(4-dimethylamino-2-ethoxy-phenyl)-4,5-dihydro-imidazol-1-yl]-piperazin-1-yl-methanone



10 Iodine (6.35 g, 25 mmol) in methylene chloride (300 mL) was added dropwise over 3 h to a stirred suspension of thallium(I) acetate (7.90 g, 30 mmol) and 3-dimethylaminophenol (3.43 g, 25 mmol) in methylene chloride (300 mL). The resulting mixture was stirred at room temperature for 24 h and filtered. Evaporation of the solvents and chromatography of the residue over silica gel using 0-5% diethyl ether in hexanes gave
15 5-dimethylamino-2-iodophenol (2.35 g, 36%).

A mixture of 5-dimethylaminol-2-iodophenol (0.90 g, 3.42 mmol), cesium carbonate (2.79 g, 8.55 mmol) and iodoethane (0.81 mL, 10 mmol) in acetone (5 mL) was heated at reflux for 2 h. The reaction mixture was cooled to room temperature and water was added. The mixture was extracted with diethyl ether (3 x). The combined organic extracts were
20 washed with brine, dried over magnesium sulfate and evaporated. Chromatography of the residue over silica gel using hexanes gave N, N-dimethyl-2-ethoxy-4-iodo-aniline (0.75 g, 76%).

N, N-dimethyl-2-ethoxy-4-iodo-aniline (0.75 g, 2.58 mmol) was dissolved in DMF (4 mL). Zinc cyanide (0.18 g, 1.54 mmol) was added. Argon was passed through the mixture for 10 min. Tetrakis(triphenylphosphine)palladium (148 mg, 0.13 mmol) was added and the mixture was heated at 110 °C for 24 h. The reaction mixture was cooled and
5 poured into water. The mixture was extracted with ethyl acetate, washed with brine and dried over magnesium sulfate. Evaporation of the solvents and chromatography of the residue over silica gel using 20% ethyl acetate in hexanes gave N, N-dimethyl-2-ethoxy-4-cyano-aniline (187 mg, 38%).

Hydrogen chloride gas was passed through a solution of N, N-dimethyl-2-ethoxy-4-
10 cyano-aniline (0.185 g, 0.97 mmol) in ethanol (5 mL) at 0 °C for 30 min. The pressure tube was sealed and stirred for 2 d at room temperature. The tube was cooled to 0 °C before the pressure was released. Evaporation of the solvents and trituration of the residue in diethyl ether gave ethyl 4-(N,N-dimethylamino)-2-ethoxy-benzimidate hydrochloride as a white powder (0.25 g, 95%).

Triethylamine (0.28 mL, 2.0 mmol) was added to a mixture of 4-(N,N-dimethylamino)-2-ethoxy-benzimidate hydrochloride (250 mg, 0.92 mmol) and meso-1,2-bis-(4-chloro-phenyl)-ethane-1,2-diamine (190 mg, 0.68 mmol, prepared according to the procedure described by Vogtle, F.; Goldschmitt, E. Chem. Ber. 1976, 109, 1-40) in ethanol (5 mL). The mixture was heated at reflux overnight. The reaction was worked up with
20 aqueous sodium bicarbonate and extracted with methylene chloride. The organic extracts were washed with brine and dried over sodium sulfate. Evaporation of the solvents and chromatography of the residue over silica gel using 10-30% methanol in methylene chloride gave {4-[4,5-bis-(4-chloro-phenyl)-4,5-dihydro-1H-imidazol-2-yl]-3-ethoxy-phenyl}-dimethyl-amine as a white foam (0.18 g, 59%).

Phosgene (0.47 mL, 0.91 mmol, 1.93 M in toluene) was added to a stirred solution of {4-[4,5-bis-(4-chloro-phenyl)-4,5-dihydro-1H-imidazol-2-yl]-3-ethoxy-phenyl}-dimethyl-amine (83 mg, 0.18 mmol) and triethylamine (0.14 mL, 1 mmol) in THF (3 mL) at 0 °C over a period of 5 min. The mixture was stirred for 1 h and evaporated. The residue was dissolved in methylene chloride (2 mL) and added dropwise to a stirred solution of
30 piperazine (0.239 g, 2.77 mmol) in methylene chloride (2 mL) at room temperature for 1 h. The mixture was diluted with aqueous sodium bicarbonate and extracted with methylene chloride. The organic extracts were washed with brine and dried over sodium sulfate. Evaporation of the solvents and chromatography of the residue over silica gel using 0-10%

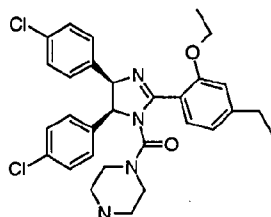
methanol in methylene chloride gave [4,5-bis-(4-chloro-phenyl)-2-(4-dimethylamino-2-ethoxy-phenyl)-4,5-dihydro-imidazol-1-yl]-piperazin-1-yl-methanone as a white foam (68 mg, 66%). HR-MS (ES, m/z) calculated for C₃₀H₃₄N₅O₂Cl₂ [(M+H)+] 566.2084, observed 566.2088.

5

Example 21

In a similar manner as described in example 20 the following compounds were prepared.

- a) [4,5-Bis-(4-chloro-phenyl)-2-(2-ethoxy-4-ethyl-phenyl)-4,5-dihydro-imidazol-1-yl]-piperazin-1-yl-methanone. HR-MS (ES, m/z) calculated for C₃₀H₃₃N₄O₂Cl₂ [(M+H)+] 551.1975, observed 551.1984



- b) [4,5-Bis-(4-chloro-phenyl)-2-(2-ethoxy-4-methyl-phenyl)-4,5-dihydro-imidazol-1-yl]-piperazin-1-yl-methanone. HR-MS (ES, m/z) calculated for C₂₉H₃₁N₄O₂Cl₂ [(M+H)+] 537.1819, observed 537.1824.

- c) [4,5-Bis-(4-chloro-phenyl)-2-(4-ethyl-2-isopropoxy-phenyl)-4,5-dihydro-imidazol-1-yl]-piperazin-1-yl-methanone. HR-MS (ES, m/z) calculated for C₃₁H₃₅N₄O₂Cl₂ [(M+H)+] 565.2132, observed 565.2135.

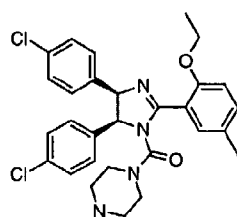
- d) [4,5-Bis-(4-chloro-phenyl)-2-(2-isopropoxy-4-methyl-phenyl)-4,5-dihydro-imidazol-1-yl]-piperazin-1-yl-methanone. HR-MS (ES, m/z) calculated for C₃₀H₃₃N₄O₂Cl₂ [(M+H)+] 551.1975, observed 551.1980.

- e) 1-{4-[4,5-Bis-(4-chloro-phenyl)-2-(4-dimethylamino-2-ethoxy-phenyl)-4,5-dihydro-imidazole-1-carbonyl]-piperazin-1-yl}-ethanone. HR-MS (ES, m/z) calculated for C₃₂H₃₆N₅O₃Cl₂ [(M+H)+] 608.2190, observed 608.2201.

Example 22

In a similar manner as described in example 20, the following compounds were prepared.

- 5 a) [4,5-Bis-(4-chloro-phenyl)-2-(2-ethoxy-5-methyl-phenyl)-4,5-dihydro-imidazol-1-yl]-piperazin-1-yl-methanone, trifluoroacetic acid salt. HR-MS (ES, m/z) calculated for $C_{32}H_{31}N_4O_2Cl_2$ [(M+H)+] 537.1819, observed 537.1826



- 10 b) [4,5-Bis-(4-chloro-phenyl)-2-(2-ethoxy-4-fluoro-phenyl)-4,5-dihydro-imidazol-1-yl]-(4-pyrrolidin-1-yl-piperidin-1-yl)-methanone. HR-MS (ES, m/z) calculated for $C_{33}H_{36}N_4O_2Cl_2F$ [(M+H)+] 609.2194, observed 609.2204.

c) [4,5-Bis-(4-chloro-phenyl)-2-(2-ethoxy-4-fluoro-phenyl)-4,5-dihydro-imidazol-1-yl]-(4-dimethylamino-piperidin-1-yl)-methanone. HR-MS (ES, m/z) calculated for $C_{31}H_{34}N_4O_2Cl_2F$ [(M+H)+] 583.2038, observed 583.2041.

- 15 d) [4,5-Bis-(4-chloro-phenyl)-2-(2-ethoxy-4-fluoro-phenyl)-4,5-dihydro-imidazol-1-yl]-piperazin-1-yl-methanone. HR-MS (ES, m/z) calculated for $C_{28}H_{28}N_4O_2Cl_2F$ [(M+H)+] 541.1568, observed 541.1571.

- 20 e) [4,5-Bis-(4-chloro-phenyl)-2-(4-fluoro-2-isopropoxy-phenyl)-4,5-dihydro-imidazol-1-yl]-(4-pyrrolidin-1-yl-piperidin-1-yl)-methanone. HR-MS (ES, m/z) calculated for $C_{34}H_{38}N_4O_2FCl_2$ [(M+H)+] 623.2351, observed 623.2360.

f) [4,5-Bis-(4-chloro-phenyl)-2-(4-fluoro-2-isopropoxy-phenyl)-4,5-dihydro-imidazol-1-yl]-(4-dimethylamino-piperidin-1-yl)-methanone. HR-MS (ES, m/z) calculated for $C_{32}H_{36}N_4O_2FCl_2$ [(M+H)+] 597.2194, observed 597.2197.

g)[4,5-Bis-(4-chloro-phenyl)-2-(4-fluoro-2-isopropoxy-phenyl)-4,5-dihydro-imidazol-1-yl]-(4-methyl-piperazin-1-yl)-methanone. HR-MS (ES, m/z) calculated for $C_{30}H_{32}N_4O_2FCl_2$ [(M+H)+] 569.1881, observed 569.1887.

h)[4,5-Bis-(4-chloro-phenyl)-2-(4-fluoro-2-isopropoxy-phenyl)-4,5-dihydro-imidazol-1-yl]-piperazin-1-yl-methanone. HR-MS (ES, m/z) calculated for $C_{29}H_{30}N_4O_2FCl_2$ [(M+H)+] 551.1725, observed 551.1726.

i)[4,5-Bis-(4-chloro-phenyl)-2-(4-fluoro-2-isopropoxy-phenyl)-4,5-dihydro-imidazol-1-yl]-(4-methanesulfonyl-piperazin-1-yl)-methanone. HR-MS (ES, m/z) calculated for $C_{30}H_{32}N_4O_4SFCl_2$ [(M+H)+] 633.1500, observed 633.1506.

10 j)4-[4,5-Bis-(4-chloro-phenyl)-2-(4-fluoro-2-isopropoxy-phenyl)-4,5-dihydro-imidazole-1-carbonyl]-piperazin-2-one. HR-MS (ES, m/z) calculated for $C_{29}H_{28}N_4O_3FCl_2$ [(M+H)+] 569.1517, observed 569.1529.

k)[4,5-Bis-(4-chloro-phenyl)-2-chroman-8-yl-4,5-dihydro-imidazol-1-yl]-piperazin-1-yl-methanone was prepared from 8-bromo-chroman (prepared from 2,6-dibromo-phenol using the procedure reported by Thomas, G. H. et al. Tetrahedron Lett. 1998, 39, 2219-22). HR-MS (ES, m/z) calculated for $C_{29}H_{29}N_4O_2Cl_2$ [(M+H)+] 535.1662, observed 535.1672.

l)4-[4,5-Bis-(4-bromo-phenyl)-2-(2-ethoxy-4-fluoro-phenyl)-4,5-dihydro-imidazole-1-carbonyl]-piperazin-2-one. HR-MS (ES, m/z) calculated for $C_{28}H_{26}N_4O_3FBr_2$ [(M+H)+] 643.0350, observed 643.0349.

m)[4,5-Bis-(4-bromo-phenyl)-2-(2-ethoxy-4-fluoro-phenyl)-4,5-dihydro-imidazol-1-yl]-morpholin-4-yl-methanone. HR-MS (ES, m/z) calculated for $C_{28}H_{27}N_3O_3FCl_2$ [(M+H)+] 630.0398, observed 630.0414.

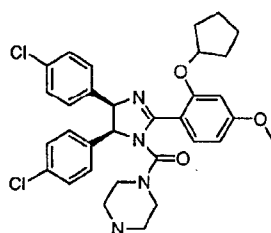
25 n)[4,5-Bis-(4-bromo-phenyl)-2-(2-ethoxy-4-fluoro-phenyl)-4,5-dihydro-imidazol-1-yl]-(4-pyrrolidin-1-yl-piperidin-1-yl)-methanone. HR-MS (ES, m/z) calculated for $C_{33}H_{36}N_4O_2FBr_2$ [(M+H)+] 697.1184, observed 697.1188.

o)[4,5-Bis-(4-bromo-phenyl)-2-(2-ethoxy-4-fluoro-phenyl)-4,5-dihydro-imidazol-1-yl]-(4-dimethylamino-piperidin-1-yl)-methanone. HR-MS (ES, m/z) calculated for $C_{31}H_{34}N_4O_2FBr_2$ [(M+H)+] 671.1027, observed 671.1036.

p)[4,5-Bis-(4-bromo-phenyl)-2-(2-ethoxy-4-fluoro-phenyl)-4,5-dihydro-imidazol-1-yl]-piperazin-1-yl-methanone. HR-MS (ES, m/z) calculated for C₂₈H₂₈N₄O₂FBr₂ [(M+H)+] 629.0558, observed 629.0569.

5 Example 23

[4,5-Bis-(4-chloro-phenyl)-2-(2-cyclopentyloxy-4-methoxy-phenyl)-4,5-dihydro-imidazol-1-yl]-piperazin-1-yl-methanone



To a solution of 2-hydroxy-4-methoxy-benzonitrile (90 mg, 0.60 mmol, example 9),
10 cyclopentanol (55 mg, 0.64 mmol) and triphenylphosphine (167 mg, 0.64 mmol) in THF
(3 mL) at -78 °C was added diethyl azodicarboxylate (0.16 mL, 0.860 mmol, 85%). The
cooling bath was removed and the reaction was allowed to warm up to room temperature
over 1.5 h. The reaction mixture was concentrated in vacuo, and purification of the
residue by flash chromatography (Biotage system, KP-Sil™ 32-63 µm, 60 Å silica gel)
15 eluting with 0-8% diethyl ether in hexanes yielded 2-cyclopentyloxy-4-methoxy-
benzonitrile as a clear liquid (125 mg, 90%).

Hydrogen chloride gas was passed through a solution of 2-cyclopentyloxy-4-
methoxy-benzonitrile (0.12 g, 0.55 mmol) in absolute ethanol (15 mL) in a pressure tube
for 1 h at 0 °C. The tube was sealed and stirred at room temperature for 3 d. Evaporation
20 of the solvents and trituration of the residue in diethyl ether gave ethyl 2-cyclopentyloxy-4-
methoxy -benzimidate hydrochloride (0.17 g, 100%).

A mixture of ethyl 2-cyclopentyloxy-4-methoxy -benzimidate hydrochloride (0.16 g,
0.57 mmol), meso-1,2-bis-(4-chloro-phenyl)-ethane-1,2-diamine (0.17 g, 0.56 mmol,
prepared according to the procedure described by Vogtle, F.; Goldschmitt, E. Chem. Ber.
25 1976, 109, 1-40) in ethanol (2 mL) was heated at reflux for 18 h. The solvent was removed
to give a yellow paste. Aqueous sodium bicarbonate was added and it was extracted with

methylene chloride. The combined organic extracts were washed with water and brine, and dried over sodium sulfate. Chromatography of the residue over silica gel with 0-5% methanol in methylene chloride gave 4,5-bis-(4-chloro-phenyl)-2-(2-cyclopentyloxy-4-methoxy-phenyl)-4,5-dihydro-1H-imidazole.

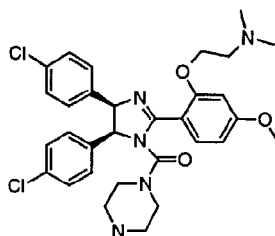
- 5 Phosgene (0.48 mL, 0.925 mmol, 1.93 M in toluene) was added dropwise to a mixture of triethylamine (0.14 mL, 1.0 mmol) and 4,5-bis-(4-chloro-phenyl)-2-(2-cyclopentyloxy-4-methoxy-phenyl)-4,5-dihydro-1H-imidazole (89 mg, 0.185 mmol) in THF (2 mL) at 0 °C. The reaction mixture was stirred for 1 h at 0 °C and evaporated. The residue was kept under high vacuum for 30 min. Methylene chloride (2 mL) was added to
- 10 the residue and the solution was added dropwise to a solution of piperazine (0.24 g, 2.78 mmol) in methylene chloride (2 mL) at 0 °C. After 1 h, the reaction was worked up with aqueous sodium bicarbonate. The mixture was extracted with methylene chloride and washed with water and brine. The organic layer was extracted with 0.5 N HCl (2 x 50 mL). The combined aqueous layers were cooled to 0 °C and basified using 2 N NaOH. The
- 15 mixture was extracted with methylene chloride (3 x 50 mL). The organic extracts were dried over sodium sulfate and evaporated. Flash chromatography of the residue over silica gel using 3-6 % methanol in methylene chloride gave [4,5-Bis-(4-chloro-phenyl)-2-(2-cyclopentyloxy-4-methoxy-phenyl)-4,5-dihydro-imidazol-1-yl]-piperazin-1-yl-methanone (89 mg, 81%). HR-MS (ES, m/z) calculated for C₃₂H₃₅N₄O₃Cl₂ [(M+H)+] 593.2081,
- 20 observed 593.2084.

Example 24

In a similar manner as described in example 23 and example 9, the following compounds were prepared.

- 25 a) {4,5-Bis-(4-chloro-phenyl)-2-[2-(2-dimethylamino-ethoxy)-4-methoxy-phenyl]-4,5-dihydro-imidazol-1-yl}-piperazin-1-yl-methanone. HR-MS (ES, m/z) calculated for C₃₁H₃₆N₅O₃Cl₂ [(M+H)+] 596.2190, observed 596.2196

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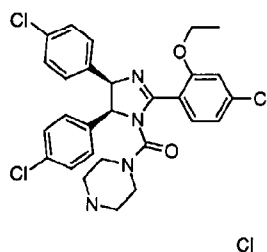


b) {4,5-Bis-(4-chloro-phenyl)-2-[2-(2-imidazol-1-yl-ethoxy)-4-methoxy-phenyl]-4,5-dihydro-imidazol-1-yl}-piperazin-1-yl-methanone. HR-MS (ES, m/z) calculated for $C_{32}H_{33}N_6O_3Cl_2$ [(M+H)+] 619.1986, observed 619.1988.

5

Example 25

[2-(4-Chloro-2-ethoxy-phenyl)-4,5-bis-(4-chloro-phenyl)-4,5-dihydro-imidazol-1-yl]-piperazin-1-yl-methanone hydrochloride



10 To a solution of 4-chloro-2-fluorobenzonitrile (1.0 g, 6.428 mmol) in ethanol (10 mL) were added sodium ethoxide solution (4.8 mL, 12.86 mmol, 21% wt in ethanol). The reaction mixture was heated at gently reflux for 12 h. The solvent was removed and the residue was partitioned between water (10 mL) and diethyl ether (20 mL). The layers were separated and the product was extracted with diethyl ether (20 mL). The organic layers
15 were washed with brine (5 mL) and dried over anhydrous sodium sulfate. The solids were filtered off and the filtrate was concentrated in vacuo. Purification of the residue by flash chromatography (Biotage system, KP-Sil™ 32-63 μ m, 60 Å silica gel) eluting with 5% ethyl acetate in hexanes yielded 4-chloro-2-ethoxybenzonitrile (0.67 g, 57%).

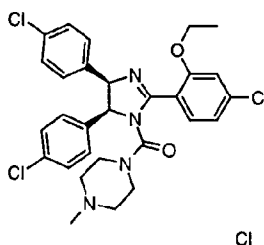
20 [2-(4-Chloro-2-ethoxy-phenyl)-4,5-bis-(4-chloro-phenyl)-4,5-dihydro-imidazol-1-yl]-piperazin-1-yl-methanone hydrochloride was prepared from 4-chloro-2-ethoxy-

benzonitrile in a similar manner as described in example 23. HR-MS (ES, m/z) calculated for C₂₈H₂₈N₄O₂Cl₃ [(M+H)+] 557.1273, observed 557.1277.

Example 26

5 In a similar manner as described in example 23 and example 25, the following compounds were prepared.

a) [2-(4-Chloro-2-ethoxy-phenyl)-4,5-bis-(4-chloro-phenyl)-4,5-dihydro-imidazol-1-yl]-(4-methyl-piperazin-1-yl)-methanone hydrochloride. HR-MS (ES, m/z) calculated for C₂₉H₃₀N₄O₂Cl₂ [(M+H)+] 571.1429, observed 571.1438



b) [2-(4-Chloro-2-ethoxy-phenyl)-4,5-bis-(4-chloro-phenyl)-4,5-dihydro-imidazol-1-yl]-(4-pyrrolidin-1-yl-piperidin-1-yl)-methanone hydrochloride. HR-MS (ES, m/z) calculated for C₃₃H₃₆N₄O₂Cl₃ [(M+H)+] 625.1899, observed 625.1908.

c) [2-(4-Chloro-2-ethoxy-phenyl)-4,5-bis-(4-chloro-phenyl)-4,5-dihydro-imidazol-1-yl]-morpholin-4-yl-methanone. HR-MS (ES, m/z) calculated for C₂₈H₂₇N₃O₃Cl₃ [(M+H)+] 558.1113, observed 558.1118.

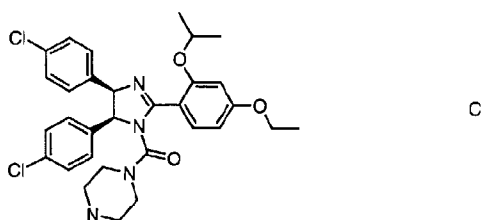
d) 1-{4-[2-(4-Chloro-2-ethoxy-phenyl)-4,5-bis-(4-chloro-phenyl)-4,5-dihydro-imidazole-1-carbonyl]-piperazin-1-yl}-ethanone. HR-MS (ES, m/z) calculated for C₃₀H₃₀N₄O₃Cl₃ [(M+H)+] 599.1378, observed 599.1388.

e) [2-(4-Chloro-2-ethoxy-phenyl)-4,5-bis-(4-chloro-phenyl)-4,5-dihydro-imidazol-1-yl]-[4-(2-hydroxy-ethyl)-piperazin-1-yl]-methanone hydrochloride. HR-MS (ES, m/z) calculated for C₃₀H₃₂N₄O₃Cl₃ [(M+H)+] 601.1535, observed 601.1543.

f) 4-[2-(4-Chloro-2-ethoxy-phenyl)-4,5-bis-(4-chloro-phenyl)-4,5-dihydro-imidazole-1-carbonyl]-piperazin-2-one. HR-MS (ES, m/z) calculated for $C_{28}H_{26}N_4O_3Cl_3$ [(M+H)+] 571.1065, observed 571.1071.

5 Example 27

[4,5-Bis-(4-chloro-phenyl)-2-(4-ethoxy-2-isopropoxy-phenyl)-4,5-dihydro-imidazol-1-yl]-piperazin-1-yl-methanone



To a solution of 4-bromo-benzene-1,3-diol (1.50 g, 7.94 mmol) in acetone (10 mL)
10 were added potassium carbonate (1.1 g, 7.94 mmol) and 2-iodopropane (1.58 mL, 15.87 mmol). The reaction mixture was heated at gentle reflux for 12 h. The solvent was removed to give a white paste. It was then taken in diethyl ether (50 mL). The white solids were filtered off and the filtrate was concentrated. Purification of the residue by Biotage flash chromatography eluting with 10% ethyl acetate in hexanes gave 4-bromo-3-isopropoxy-phenol (0.77 g, 42%).
15

To a solution of 4-bromo-3-isopropoxy-phenol (0.50 g, 2.16 mmol) in acetone (3 mL) were added potassium carbonate (0.30 g, 2.16 mmol) and ethyl iodide (0.35 mL, 4.33 mmol). The reaction mixture was heated at gentle reflux for 12 h. The solvent was removed to give a white paste. It was then taken in diethyl ether (50 mL). The white solids
20 were filtered off and the filtrate was concentrated. Purification of the residue by Biotage flash chromatography eluting with 10% ethyl acetate in hexanes gave 1-bromo-4-ethoxy-2-isopropoxy-benzene (0.48 g, 86%).

To a solution of 1-bromo-4-ethoxy-2-isopropoxy-benzene (0.48 g, 1.85 mmol) in DMF (5 mL) was added zinc cyanide (217 mg, 1.85 mmol). The reaction was degassed by
25 passing argon through the mixture for 2 h before tetrakis(triphenylphosphine)-palladium (0) (0.21 g, 0.185 mmol) was added. The reaction mixture was heated at 100-105 °C under

argon for 12 h. The reaction mixture was taken up in diethyl ether (50 mL) and saturated sodium bicarbonate solution (5 mL). The product was extracted with diethyl ether (2 x 30 mL). The organic layers were washed with water (1 x 10 mL) and brine (1 x 10 mL), dried (sodium sulfate) and concentrated. Purification of the crude by Biotage flash
5 chromatography eluting with 10-15% ethyl acetate in hexanes gave 4-ethoxy-2-isopropoxy-benzonitrile as a clear oil (0.31 g, 81%).

Hydrogen chloride gas was passed through a solution of 4-ethoxy-2-isopropoxy-benzonitrile (0.30 g, 1.46 mmol) in absolute ethanol (100 mL) in a pressure tube for 45 min at 0 °C. The tube was sealed and stirred at room temperature for 4 d. The pressure
10 was released only after the tube is cooled to 0 °C. Evaporation of the solvents and trituration of the residue in diethyl ether gave ethyl 4-ethoxy-2-isopropoxy-benzimidate hydrochloride which was used without further purification.

A mixture of crude ethyl 4-ethoxy-2-isopropoxy-benzimidate hydrochloride and meso-1,2-bis-(4-chloro-phenyl)-ethane-1,2-diamine (0.41 g, 1.46 mmol, prepared
15 according to the procedure described by Vogtle, F.; Goldschmitt, E. Chem. Ber. 1976, 109, 1-40) and triethylamine (0.205 mL, 1.46 mmol) in ethanol (25 mL) was heated at reflux for 3 h. The solvent was removed to give a yellow paste. Aqueous sodium bicarbonate was added and it was extracted with methylene chloride. The combined organic extracts were washed with water and brine, and dried over sodium sulfate. Chromatography of the
20 residue over silica gel with 70% ethyl acetate-hexane gave 4,5-bis-(4-chloro-phenyl)-2-(4-ethoxy-2-isopropoxy-phenyl)-4,5-dihydro-1H-imidazole (0.50 g, 47%).

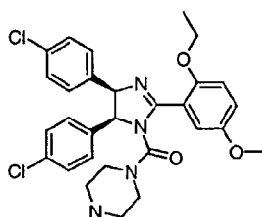
Phosgene (0.325 mL, 0.64 mmol, 1.93 M in toluene) was added dropwise to a mixture of triethylamine (0.126 mL, 0.896 mmol) and 4,5-bis-(4-chloro-phenyl)-2-(4-ethoxy-2-isopropoxy-phenyl)-4,5-dihydro-1H-imidazole (60 mg, 0.128 mmol) in
25 methylene chloride (5 mL) at 0 °C. The reaction mixture was stirred for 30 min at 0 °C and evaporated. The residue was kept under high vacuum for 30 min. Methylene chloride (5 mL) was added to the residue and the solution was added dropwise to a solution of piperazine (0.22 mg, 2.56 mmol) in methylene chloride (5 mL) at 0 °C over 15 min. After 1 h, the reaction was worked up with aqueous sodium bicarbonate. The mixture was
30 extracted with methylene chloride and washed with water and brine. The organic extracts were dried over sodium sulfate and evaporated. Purification using reverse phase HPLC gave [4,5-bis-(4-chloro-phenyl)-2-(4-ethoxy-2-isopropoxy-phenyl)-4,5-dihydro-imidazol-

1-yl]-piperazin-1-yl-methanone (6.5 mg, 8%). HR-MS (ES, m/z) calculated for $C_{31}H_{35}N_4O_3Cl_2 [(M+H)^+]$ 581.2081, observed 581.2086.

Example 28

5 In a similar manner as described in example 27 the following compounds were prepared.

a) [4,5-Bis-(4-chloro-phenyl)-2-(2-ethoxy-5-methoxy-phenyl)-4,5-dihydro-imidazol-1-yl]-piperazin-1-yl-methanone, trifluoroacetic acid salt. HR-MS (ES, m/z)
10 calculated for $C_{29}H_{31}N_4O_3Cl_2 [(M+H)^+]$ 553.1768, observed 553.1776



b) [4,5-Bis-(4-chloro-phenyl)-2-(2-ethoxy-5-methoxy-phenyl)-4,5-dihydro-imidazol-1-yl]-(4-methanesulfonyl-piperazin-1-yl)-methanone was prepared by sulfonylation of [4,5-bis-(4-chloro-phenyl)-2-(2-ethoxy-5-methoxy-phenyl)-4,5-dihydro-
15 imidazol-1-yl]-piperazin-1-yl-methanone (example 28a). HR-MS (ES, m/z) calculated for $C_{30}H_{33}N_4O_5S_2Cl_2 [(M+H)^+]$ 631.1543, observed 631.1548.

c) [4,5-Bis-(4-chloro-phenyl)-2-(2-ethoxy-5-methoxy-phenyl)-4,5-dihydro-imidazol-1-yl]-[4-(2-hydroxy-ethyl)-piperazin-1-yl]-methanone hydrochloride. HR-MS (ES, m/z) calculated for $C_{31}H_{35}N_4O_4Cl_2 [(M+H)^+]$ 597.2030, observed 597.2037.

20 d) [4,5-Bis-(4-chloro-phenyl)-2-(2,5-diethoxy-phenyl)-4,5-dihydro-imidazol-1-yl]-piperazin-1-yl-methanone hydrochloride. HR-MS (ES, m/z) calculated for $C_{30}H_{33}N_4O_3Cl_2 [(M+H)^+]$ 567.1924, observed 567.1928.

e) [4,5-Bis-(4-chloro-phenyl)-2-(2,5-diethoxy-phenyl)-4,5-dihydro-imidazol-1-yl]-(4-methanesulfonyl-piperazin-1-yl)-methanone was prepared by sulfonylation of [4,5-bis-

(4-chloro-phenyl)-2-(2,5-diethoxy-phenyl)-4,5-dihydro-imidazol-1-yl]-piperazin-1-yl-methanone (example 28d). HR-MS (ES, m/z) calculated for C₃₁H₃₅N₄O₅SCl₂ [(M+H)+] 645.1700, observed 645.1714.

f)[4,5-Bis-(4-chloro-phenyl)-2-(4-ethoxy-2-isopropoxy-phenyl)-4,5-dihydro-imidazol-1-yl]-[4-(2-hydroxy-ethyl)-piperazin-1-yl]-methanone. HR-MS (ES, m/z) calculated for C₃₃H₃₉N₄O₄Cl₂ [(M+H)+] 625.2343, observed 625.2350.

g)4-[4,5-Bis-(4-chloro-phenyl)-2-(4-ethoxy-2-isopropoxy-phenyl)-4,5-dihydro-imidazole-1-carbonyl]-piperazin-2-one. HR-MS (ES, m/z) calculated for C₃₁H₃₃N₄O₄Cl₂ [(M+H)+] 595.1874, observed 595.1879.

h)[4,5-Bis-(4-chloro-phenyl)-2-(5-ethoxy-2-isopropoxy-phenyl)-4,5-dihydro-imidazol-1-yl]-piperazin-1-yl-methanone. HR-MS (ES, m/z) calculated for C₃₁H₃₅N₄O₃Cl₂ [(M+H)+] 581.2081, observed 581.2088.

i)[4,5-Bis-(4-chloro-phenyl)-2-(5-ethoxy-2-isopropoxy-phenyl)-4,5-dihydro-imidazol-1-yl]-[4-methanesulfonyl-piperazin-1-yl]-methanone was prepared by sulfonylation of [4,5-bis-(4-chloro-phenyl)-2-(5-ethoxy-2-isopropoxy-phenyl)-4,5-dihydro-imidazol-1-yl]-piperazin-1-yl-methanone (example 28 h). HR-MS (ES, m/z) calculated for C₃₂H₃₇N₄O₅SCl₂ [(M+H)+] 659.1856, observed 659.1864.

j)[4,5-Bis-(4-chloro-phenyl)-2-(5-ethoxy-2-isopropoxy-phenyl)-4,5-dihydro-imidazol-1-yl]-[4-(2-hydroxy-ethyl)-piperazin-1-yl]-methanone hydrochloride. HR-MS (ES, m/z) calculated for C₃₃H₃₉N₄O₄Cl₂ [(M+H)+] 625.2343, observed 625.2352.

k)1-[4-[4,5-Bis-(4-chloro-phenyl)-2-(4-ethoxy-2-isopropoxy-phenyl)-4,5-dihydro-imidazole-1-carbonyl]-piperazin-1-yl]-ethanone. HR-MS (ES, m/z) calculated for C₃₃H₃₇N₄O₄Cl₂ [(M+H)+] 623.2187, observed 623.2194.

l)1-[4-[4,5-Bis-(4-chloro-phenyl)-2-(5-ethoxy-2-isopropoxy-phenyl)-4,5-dihydro-imidazole-1-carbonyl]-piperazin-1-yl]-ethanone. HR-MS (ES, m/z) calculated for C₃₃H₃₇N₄O₄Cl₂ [(M+H)+] 623.2187, observed 623.2195.

m)[4,5-Bis-(4-chloro-phenyl)-2-(4-ethoxy-2-isopropoxy-phenyl)-4,5-dihydro-imidazol-1-yl]-[4-pyrrolidin-1-yl-piperidin-1-yl]-methanone. HR-MS (ES, m/z) calculated for C₃₆H₄₃N₄O₃Cl₂ [(M+H)+] 649.2707, observed 649.2717.

n)[4,5-Bis-(4-chloro-phenyl)-2-(2-isopropoxy-5-methoxy-phenyl)-4,5-dihydro-imidazol-1-yl]-piperazin-1-yl-methanone, trifluoroacetic acid salt. HR-MS (ES, m/z) calculated for C₃₀H₃₃N₄O₃Cl₂ [(M+H)+] 567.1924, observed 567.1929.

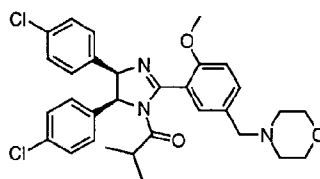
o)[4,5-Bis-(4-chloro-phenyl)-2-(2,4-diisopropoxy-phenyl)-4,5-dihydro-imidazol-1-yl]-piperazin-1-yl-methanone. HR-MS (ES, m/z) calculated for C₃₂H₃₇N₄O₃Cl₂ [(M+H)+] 595.2237, observed 595.2244.

p)[4,5-Bis-(4-chloro-phenyl)-2-(2,5-diisopropoxy-phenyl)-4,5-dihydro-imidazol-1-yl]-piperazin-1-yl-methanone hydrochloride. HR-MS (ES, m/z) calculated for C₃₂H₃₇N₄O₃Cl₂ [(M+H)+] 595.2237, observed 595.2243.

10

Example 29

1-[4,5-Bis-(4-chloro-phenyl)-2-(2-methoxy-5-morpholin-4-yl-methyl-phenyl)-4,5-dihydro-imidazol-1-yl]-2-methyl-propan-1-one

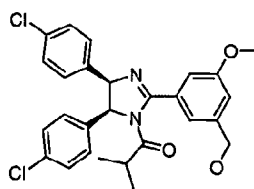


15 To a solution of 4-{3-[4,5-bis-(4-chloro-phenyl)-4,5-dihydro-1H-imidazol-2-yl]-4-methoxy-benzyl}-morpholine (100 mg, 0.20 mmol, as in the U.S. Provisional applications incorporated by reference herein, Example 31) in methylene chloride (10 mL) were sequentially added triethylamine (0.10 mL, 0.712 mmol) and isobutyryl chloride (42 mL, 0.392 mmol). The reaction mixture was stirred for 12 h. The solvents were removed under
20 reduced pressure. Saturated sodium bicarbonate (2 mL) and methylene chloride (20 mL) were added and the layers were separated. The aqueous layer was extracted with methylene chloride (1 x 100 mL). The combined organic extracts were evaporated. Purification of the crude residue by Biotage flash chromatography eluting with 0-5% methanol in ethyl acetate gave 1-[4,5-bis-(4-chloro-phenyl)-2-(2-methoxy-5-morpholin-4-ylmethyl-phenyl)-4,5-dihydro-imidazol-1-yl]-2-methyl-propan-1-one. HR-MS (ES, m/z) calculated
25 for C₃₁H₃₄N₃O₃Cl₂ [(M+H)+] 566.1972, observed 566.1977.

Example 30

In an analogous manner as described in example 29, the following compounds were prepared.

- a) 1-[4,5-Bis-(4-chloro-phenyl)-2-(3-hydroxymethyl-5-methoxy-phenyl)-4,5-dihydro-imidazol-1-yl]-2-methyl-propan-1-one from {3-[4,5-bis-(4-chloro-phenyl)-4,5-dihydro-1H-imidazol-2-yl]-5-methoxy-phenyl}-methanol, as in the U.S. Provisional applications incorporated by reference herein, Example 33. HR-MS (ES, m/z) calculated for C₂₇H₂₇N₂O₃Cl₂ [(M+H)+] 497.1393, observed 497.1402



- b) 1-[4,5-Bis-(4-chloro-phenyl)-2-(3-hydroxymethyl-5-methoxymethyl-phenyl)-4,5-dihydro-imidazol-1-yl]-ethanone from sodium {3-[4,5-bis-(4-chloro-phenyl)-4,5-dihydro-1H-imidazol-2-yl]-5-methoxymethyl-phenyl}-methanol, as in the U.S. Provisional applications incorporated by reference herein, Example 35. HR-MS (EI, m/z) calculated for C₂₆H₂₄N₂O₃Cl₂ (M+) 482.1164, observed 482.1161.

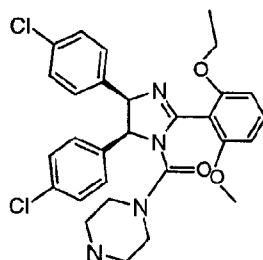
- c) 1-[4,5-Bis-(4-chloro-phenyl)-2-(3-methoxy-5-methoxymethyl-phenyl)-4,5-dihydro-imidazol-1-yl]-2-methyl-propan-1-one from 4,5-bis-(4-chloro-phenyl)-2-(3-methoxy-5-methoxymethyl-phenyl)-4,5-dihydro-1H-imidazole, as in the U.S. Provisional applications incorporated by reference herein, Example 34, HR-MS (m/z) calculated for C₂₈H₂₉N₂O₃Cl₂ [(M+H)+] 511.1550, observed 511.1556.

- d) 3-[4,5-Bis-(4-chloro-phenyl)-1-isobutyryl-4,5-dihydro-1H-imidazol-2-yl]-5-methoxymethyl-benzoic acid from 3-[4,5-bis-(4-chloro-phenyl)-4,5-dihydro-1H-imidazol-2-yl]-5-methoxymethyl-benzoate, as in the U.S. Provisional applications incorporated by reference herein, Example 40, HR-MS (ES, m/z) calculated for C₂₈H₂₇N₂O₄Cl₂ [(M+H)+] 525.1343, observed 525.1347.

- e) 1-[4,5-Bis-(4-chloro-phenyl)-2-(5-ethoxymethyl-2,4-dimethoxy-phenyl)-4,5-dihydro-imidazol-1-yl]-2-methyl-propan-1-one from 4,5-Bis-(4-chloro-phenyl)-2-(5-ethoxymethyl-2,4-dimethoxy-phenyl)-4,5-dihydro-1H-imidazole as in the U.S. Provisional applications incorporated by reference herein, Example 32,

Example 31

[4,5-Bis-(4-chloro-phenyl)-2-(2-ethoxy-6-methoxy-phenyl)-4,5-dihydro-imidazol-1-yl]-piperazin-1-yl-methanone

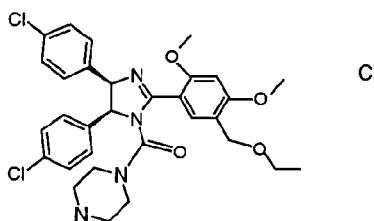


5

Phosgene (0.147 mL, 0.283 mmol, 1.93 M in toluene) was added to a stirred solution of 4,5-bis-(4-chloro-phenyl)-2-(2-ethoxy-6-methoxy-phenyl)-4,5-dihydro-1H-imidazole (described in previous patent) (25 mg, 0.0566 mmol) and triethylamine (39 mL, 0.283 mmol) in THF (2 mL) at 0 °C over a period of 5 min. The mixture was stirred for 3 h and
10 evaporated. The residue was dissolved in methylene chloride (2 mL) and added dropwise to a stirred solution of piperazine (24 mg, 0.283 mmol) in methylene chloride (2 mL) at room temperature for 3 h. The mixture was diluted with aqueous sodium bicarbonate and extracted with methylene chloride. The organic extracts were washed with brine and dried over sodium sulfate. Evaporation of the solvents and chromatography of the residue over
15 silica gel using 0-10% methanol in methylene chloride gave [4,5-bis-(4-chloro-phenyl)-2-(2-ethoxy-6-methoxy-phenyl)-4,5-dihydro-imidazol-1-yl]-piperazin-1-yl-methanone (19 mg, 61%). HR-MS (ES, m/z) calculated for C₂₉H₃₁N₄O₃Cl₂ [(M+H)+] 553.1768, observed 553.1770.

Example 32

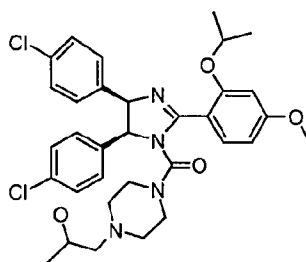
[4,5-bis-(4-chloro-phenyl)-2-(5-ethoxymethyl-2,4-dimethoxy-phenyl)-4,5-dihydro-imidazol-1-yl]-piperazin-1-yl-methanone



- 5 In a similar manner as described in example 31, the named compound was prepared from 4,5-bis-(4-chloro-phenyl)-2-(5-ethoxymethyl-2,4-dimethoxy-phenyl)-4,5-dihydro-1H-imidazole (described in previous patent). HR-MS (ES, m/z) calculated for $C_{31}H_{35}N_4O_4Cl_2$ [(M+H)+] 597.2030, observed 597.2034.

10 Example 33

[4,5-Bis-(4-chloro-phenyl)-2-(2-isopropoxy-4-methoxy-phenyl)-4,5-dihydro-imidazol-1-yl]-[4-(2-hydroxy-propyl)-piperazin-1-yl]-methanone

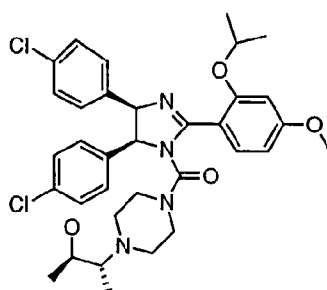


- 15 The compound was prepared by the treatment of [4,5-bis-(4-chloro-phenyl)-2-(2-isopropoxy-4-methoxy-phenyl)-4,5-dihydro-imidazol-1-yl]-piperazin-1-yl-methanone (example 10g) with propylene oxide in methanol for 7 h at 45°C in a sealed tube. HR-MS (ES, m/z) calculated for $C_{33}H_{38}N_4O_4Cl_2$ [(M+H)+] 625.2343, observed 625.2350.

Example 34

In a similar manner as described in examples 33, the following compounds were prepared.

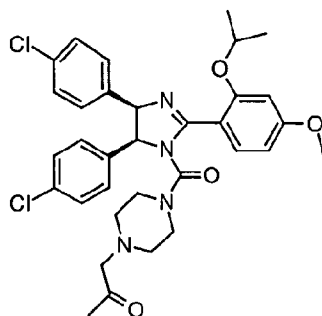
- a) [4,5-Bis-(4-chloro-phenyl)-2-(2-isopropoxy-4-methoxy-phenyl)-4,5-dihydro-imidazol-1-yl]-threo[4-(2-hydroxy-1-methyl-propyl)-piperazin-1-yl]-methanone. HR-MS (ES, m/z) calculated for C₃₄H₄₀N₄O₄Cl₂ [(M+H)+] 639.2500, observed 639.2508.



- b) [4,5-Bis-(4-chloro-phenyl)-2-(2-isopropoxy-4-methoxy-phenyl)-4,5-dihydro-imidazol-1-yl]-erythro[4-(2-hydroxy-1-methyl-propyl)-piperazin-1-yl]-methanone. HR-MS (ES, m/z) calculated for C₃₄H₄₀N₄O₄Cl₂ [(M+H)+] 639.2500, observed 639.2507.

Example 35

1-{4-[4,5-Bis-(4-chloro-phenyl)-2-(2-isopropoxy-4-methoxy-phenyl)-4,5-dihydro-imidazole-1-carbonyl]-piperazin-1-yl}-propan-2-one



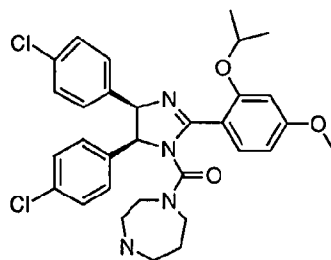
The compound was prepared by the treatment of [4,5-bis-(4-chloro-phenyl)-2-(2-isopropoxy-4-methoxy-phenyl)-4,5-dihydro-imidazol-1-yl]-piperazin-1-yl-methanone

(example 10g) with chloroacetone and triethylamine at 40°C overnight. HR-MS (ES, m/z) calculated for C₃₃H₃₆N₄O₄Cl₂ [(M+H)+] 623.2187, observed 623.2194.

Example 36

5 In a similar manner as described in examples 9, the following compounds were prepared.

a) [4,5-Bis-(4-chloro-phenyl)-2-(2-isopropoxy-4-methoxy-phenyl)-4,5-dihydro-imidazol-1-yl]-[1,4]diazepan-1-yl-methanone. HR-MS (ES, m/z) calculated for C₃₁H₃₄N₄O₃Cl₂ [(M+H)+] 581.2081, observed 581.2086.



b) 4-[4,5-Bis-(4-chloro-phenyl)-2-(2-isopropoxy-4-methoxy-phenyl)-4,5-dihydro-imidazole-1-carbonyl]-1-methyl-piperazin-2-one. HR-MS (ES, m/z) calculated for C₃₁H₃₂N₄O₄Cl₂ [(M+H)+] 595.1874, observed 595.1880.

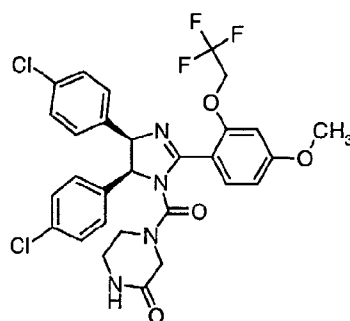
c) 1-{4-[4,5-Bis-(4-chloro-phenyl)-2-(2-isopropoxy-4-methoxy-phenyl)-4,5-dihydro-imidazole-1-carbonyl]-piperazin-1-yl}-2-methyl-propan-1-one. HR-MS (ES, m/z) calculated for C₃₄H₃₈N₄O₄Cl₂ [(M+H)+] 637.2343, observed 637.2348.

d) 4-[4,5-Bis-(4-chloro-phenyl)-2-(2-isopropoxy-4-methoxy-phenyl)-4,5-dihydro-imidazole-1-carbonyl]-piperazine-1-carbaldehyde. HR-MS (ES, m/z) calculated for C₃₁H₃₂N₄O₄Cl₂ [(M+H)+] 595.1874, observed 595.1882.

Example 37

In a similar manner as described in example 9, the following compounds were prepared:

- a) 4-{4,5-Bis-(4-chloro-phenyl)-2-[4-methoxy-2-(2,2,2-trifluoro-ethoxy)-phenyl]-4,5-dihydro-imidazole-1-carbonyl}-piperazin-2-one



The compound was prepared from 4,5-bis-(4-chloro-phenyl)-2-[4-methoxy-2-(2,2,2-trifluoro-ethoxy)-phenyl]-4,5-dihydro-1H-imidazole, as in the U.S. Provisional applications incorporated by reference herein, example 47a. HR-MS (ES, m/z) calculated for C₂₉H₂₅N₄O₄F₃Cl₂ [(M+H)+] 621.1278, observed 621.1285.

- b) 4-{4,5-Bis-(4-bromo-phenyl)-2-[4-methoxy-2-(2,2,2-trifluoro-ethoxy)-phenyl]-4,5-dihydro-imidazole-1-carbonyl}-piperazin-2-one from 4,5-bis-(4-bromo-phenyl)-2-[4-methoxy-2-(2,2,2-trifluoro-ethoxy)-phenyl]-4,5-dihydro-1H-imidazole, as in the U.S. Provisional applications incorporated by reference herein, example 47b. HR-MS (ES, m/z) calculated for C₂₉H₂₅N₄O₄F₃Br₂ [(M+H)+] 709.0268, observed 709.0280.

- c) [4,5-Bis-(4-ethynyl-phenyl)-2-(2-isopropoxy-4-methoxy-phenyl)-4,5-dihydro-imidazol-1-yl]-(4-pyrrolidin-1-yl-piperidin-1-yl)-methanone from 4,5-bis-(4-ethynyl-phenyl)-2-(2-isopropoxy-4-methoxy-phenyl)-4,5-dihydro-1H-imidazole, as in the U.S. Provisional applications incorporated by reference herein, example 47d. HR-MS (ES, m/z) calculated for C₂₉H₂₅N₄O₄F₃Br₂ [(M+H)+] 615.3330, observed 615.3319.

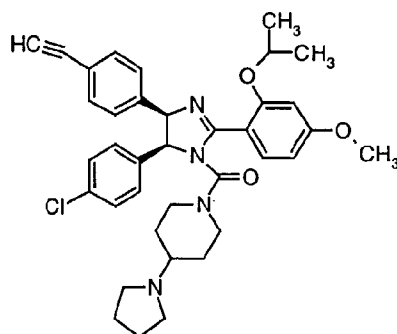
- d) 1-{4-[2-(5-Chloro-2-isopropoxy-phenyl)-4,5-bis-(4-chloro-phenyl)-4,5-dihydro-imidazole-1-carbonyl]-piperazin-1-yl}-ethanone from 2-(5-Chloro-2-isopropoxy-phenyl)-4,5-bis-(4-chloro-phenyl)-4,5-dihydro-1H-imidazole, as in the U.S. Provisional

applications incorporated by reference herein, example 46. HR-MS (ES, m/z) calculated for $C_{31}H_{31}N_3O_3Cl_3$ [(M+H)+] 613.1535, observed 613.1543.

Example 38

5 In a similar manner as described in examples 3, the following compounds were prepared from 4-(4-chloro-phenyl)-5-(4-ethynyl-phenyl)-2-(2-isopropoxy-4-methoxy-phenyl)-4,5-dihydro-1H-imidazole, as in the U.S. Provisional applications incorporated by reference herein, example 47e:

a) [5-(4-Chloro-phenyl)-4-(4-ethynyl-phenyl)-2-(2-isopropoxy-4-methoxy-phenyl)-
10 4,5-dihydro-imidazol-1-yl]-(4-pyrrolidin-1-yl-piperidin-1-yl)-methanone. HR-MS (ES, m/z) calculated for $C_{37}H_{41}N_4O_3Cl$ [(M+H)+] 625.2940, observed 625.2943.



b) 4-{4,5-Bis-(4-bromo-phenyl)-2-[4-methoxy-2-(2,2,2-trifluoro-ethoxy)-phenyl]-
4,5-dihydro-imidazole-1-carbonyl]-piperazin-2-one [4-(4-Chloro-phenyl)-5-(4-ethynyl-
15 phenyl)-2-(2-isopropoxy-4-methoxy-phenyl)-4,5-dihydro-imidazol-1-yl]-(4-pyrrolidin-1-yl-piperidin-1-yl)-methanone. HR-MS (ES, m/z) calculated for $C_{37}H_{41}N_4O_3Cl$ [(M+H)+] 625.2940, observed 625.2943.

Example 39

In Vitro Activity Assay

The ability of the compounds to inhibit the interaction between p53 and MDM2 proteins was measured by an ELISA (Enzyme-Linked Immuno Sorbent Assay) in which
5 recombinant GST-tagged MDM2 binds to a peptide that resembles the MDM2-interacting region of p53 (Böttger et al., J. Mol. Bio. 1997, Vol. 269, pgs. 744-756). This peptide is immobilized to the surface of a 96 well plate via N-terminal biotin which binds to streptavidin-coated wells. MDM2 is added to each well in the presence of anti-MDM2 mouse monoclonal antibody (SMP-14, Santa Cruz Biotech). After removal of the
10 unbound MDM2 protein, a peroxidase-linked secondary antibody (anti-mouse IgG, Roche Molecular Biochemicals) and the amount of peptide-bound MDM2 is determined colorimetrically by the addition of a peroxidase substrate (MTB Microwell Peroxidase Substrate System, Kirkegaard & Perry Labs).

Test plates were prepared by coating with streptavidin (5 mg/ml in PBS) for 2 hours
15 followed by a PBS (phosphate-buffered saline) wash and overnight blocking with 150 ml of blocking buffer containing 2 mg/ml bovine serum albumin (Sigma) and 0.05% Tween 20 (Sigma) in PBS at 40C. Biotinylated peptide (1 mM) is added to each well in 50 ml of blocking buffer and washed extensively after 1 h incubation. Test compounds were diluted in a separate 96 well plate and added in triplicate to a compound incubation plate
20 containing a mix of the MDM2 protein and anti-MDM2 antibody. After 20 min incubation, the content of the plate is transferred to the test plate and incubated for an additional 1 hour. The secondary anti-mouse IgG antibody is added to the test plate preceeded and followed by a triple wash with 0.05% Tween 20 in PBS. Finally, peroxidase substrate is added to each well and the absorption was read using a plate reader (MR7000,
25 Dynatech) at 450nm. The inhibitory activity of the test compounds was measured as a percentage of the bound MDM2 in treated vs. untreated wells and IC50 was calculated.

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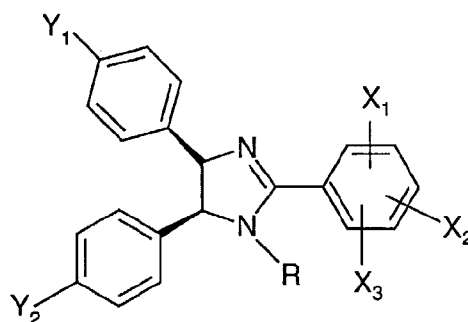
- 82A -

Throughout this specification and the claims which follow, unless the context requires otherwise, the word "comprise", and variations such as "comprises" or "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.

The reference in this specification to any prior publication (or information derived from it), or to any matter which is known, is not, and should not be taken as an acknowledgment or admission or any form of suggestion that that prior publication (or information derived from it) or known matter forms part of the common general knowledge in the field of endeavour to which this specification relates.

CLAIMS

1. A compound of formula I



I

5 and the pharmaceutically acceptable salts and esters thereof, wherein

R is -C=OR1, wherein

R1 is selected from C₁-C₆ alkyl, -C=CHCOOH, -NHCH₂CH₂R₂, -

N(CH₂CH₂OH)CH₂CH₂OH, -N(CH₃)CH₂CH₂NCH₃, -

N(CH₃)CH₂CH₂N(CH₃)CH₃, saturated 4-, 5- and 6-membered rings, and

10 saturated and unsaturated 5- and 6- membered rings containing at least one hetero atom wherein the hetero atom is selected from S, N and O and being optionally substituted with a group selected from C₁-C₆ alkyl, -C=O-R₅, -OH, C₁-C₆ alkyl optionally substituted with hydroxy, C₁-C₆ alkyl optionally substituted with -NH₂, -N-C₁-C₆ alkyl, -SO₂CH₃, =O, -CH₂C=OCH₃, and 5-
15 and 6-membered saturated rings containing at least one hetero atom selected from S, N and O, wherein

R₅ is selected from H, C₁-C₆ alkyl, -NH₂, -N- C₁-C₆ alkyl, C₁-C₆ alkyl optionally substituted with hydroxy, and C₁-C₆ alkyl optionally substituted with NH₂,

R₂ is selected from -N(CH₃)CH₃, -NCH₂CH₂NH₂, -NH₂, morpholinyl and
20 piperazinyl,

X₁, X₂ and X₃ are independently selected from -OH, C₁-C₂ alkyl, C₁-C₆ alkoxy, -Cl, -Br, -F, -CH₂OCH₃, and -CH₂OCH₂CH₃, or one of X₁, X₂ or X₃ is H and the other two are independently selected from hydroxy, C₁-C₆ alkyl, C₁-C₆ alkoxy, Cl, Br, F, -CF₃, -CH₂OCH₃, -CH₂OCH₂CH₃, -OCH₂CH₂R₃, -

OCH₂CF₃, and -OR₄, or one of X₁, X₂ or X₃ is H and the other two taken together with the two carbon atoms and the bonds between them from the benzene ring to which they are optionally substituted form a 5- or 6-membered saturated ring that contains at least one hetero atom selected from S, N, and O,
 5 wherein

R₃ is selected from -F, -OCH₃, -N(CH₃)CH₃, -Cl, -Br, unsaturated 5- and 6-membered rings containing at least one hetero atom wherein the hetero atom is selected from S, N and O,

R₄ is a 3- to 5- membered saturated ring and

10 Y₁ and Y₂ are each independently selected from -Cl, -Br, -NO₂, -C=N, and -C=CH.

2. The compound according to claim 1, wherein Y₁ and Y₂ are each independently selected from -Cl and -Br.

15 3. The compound according to claim 1, wherein R₁ is selected from morpholinyl, piperazinyl, piperadinyl, cyclopentyl, cyclohexyl, thiophenyl, isoxazolyl, and furanyl, piperazinyl substituted with at least one group selected from C₁-C₃ alkyl, -C₁-C₂ alkoxy, -C=OCH₃, -SO₂CH₃, -C=O, -OH, -CH₂NH₂, -C=OCH₂NH₂, -C=OCH₂OH, -C=OC(OH)CH₂OH, -CH₂C(OH)-CH₂OH, -C=ON(CH₂-)₂,
 20 -C=ONH₂, and -C=ON(CH₃)CH₃, -C=OCH(CH₃)₂, -CH₂C=OCH₃, -CH₂CH(OH)CH₃, -CH(CH₃)CH(OH)CH₃ and -CH₂CH₂OH.

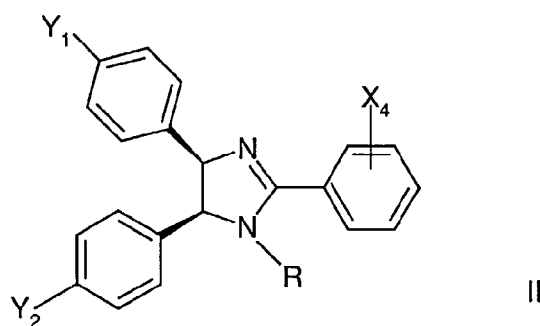
4. The compound according to claim 1, wherein one of X₁, X₂ and X₃ is H and the other two are independently selected from hydroxy, C₁-C₆ alkoxy, Cl, Br, F,
 25 -CH₂OCH₃, -CH₂OCH₂CH₃, C₁-C₂ alkyl, -OCH₂CH₂R₃ and -OR₄, wherein R₃ is selected from -F, -OCH₃, -N(CH₃)CH₃, unsaturated 5-membered rings containing at least one hetero atom wherein the hetero atom is selected from S, N and O, and wherein R₄ is cyclopentyl, or one of X₁, X₂ or X₃ is H and the other two taken together with the two carbon atoms and the bonds between them from the benzene

ring to which they are substituted form a 5- membered saturated ring that contains at least one hetero atom selected from S, N and O.

5. The compound according to claim 4, wherein one of X1, X2 or X3 is H, the other
5 two are independently selected from $-\text{OCH}_3$ and $-\text{CH}_2\text{OCH}_2\text{CH}_3$.
6. The compound according to claim 4, wherein one of X1, X2 or X3 is H, and one or both of the other two is $-\text{O}-\text{C}_1$ alkyl, $-\text{O}-\text{C}_2$ alkyl or $-\text{O}-\text{C}_3$ alkyl.
- 10 7. The compound according to claim 4, wherein R3 is imidazolyl.
8. The compound according to claim 1, wherein X3 is H and X1 and X2 together with the two carbon atoms and the bonds between them from the benzene ring to they are substituted form a 6-membered saturated ring that contains one hetero atom which
15 is O.
9. The compound according to claim 1, wherein one of the groups X1, X2 or X3 is H at meta position, the group at ortho position is selected from C_1-C_6 alkoxy and $-\text{OCH}_2\text{CF}_3$, and the group at para position is C_1-C_6 alkoxy.
20
10. The compound according to claim 9, wherein the X1, X2 or X3 group at ortho position is selected from ethoxy, isopropoxy and $-\text{OCH}_2\text{CF}_3$, and the group at para position is selected from methoxy and ethoxy.
- 25 11. The compound according to claim 10, wherein R1 is selected from piperazinyl and substituted piperazinyl.

12. The compound according to claim 1, wherein one of the groups X1, X2 or X3 is H at meta position, the group at the ortho position is C₁-C₆ alkoxy and the group at the para position is -Cl, -Br or -F, or one of the groups X1, X2 or X3 is H at para position, and the two other groups at ortho position are C₁-C₆ alkoxy and the group at meta position is -Cl, -Br or -F.

13. A compound of formula II



- 10 and the pharmaceutically acceptable salts and esters thereof, wherein
 R is -C=OR₁,
 R₁ is selected from C₁-C₆ alkyl, saturated 5- and 6-membered rings, saturated 5- and 6-membered rings containing at least one hetero atom wherein the hetero atom is selected from S, N and O and being optionally substituted with a group selected from C₁-C₂ alkyl, C₁-C₃ alcohol, -N(CH₃)CH₃, -C=OCH₃, and 5- and 6-membered rings containing at least one hetero atom wherein the hetero atom is selected from S, N, and O,
 X₄ is selected from C₁-C₂ alkyl, C₁-C₆ alkoxy, fluoroethoxy, -Cl, -Br, -F, -OCH₂C=OOQ, -O- C₁-C₆ alkyl, -OCH₂-cyclopropyl, -CH₂OCH₂-phenyl, saturated and unsaturated 5- and 6-membered rings, saturated and unsaturated 5- and 6-membered rings containing at least one hetero atom wherein the hetero atom is selected from S, N and O, wherein
 Q is selected from H, and C₁-C₆ alkyl,
 Y₁ and Y₂ are independently selected from -Cl, -Br, -NO₂, -C=N and -C=H,

with the proviso that where Y1 and Y2 are both -Cl, and R1 is -CH₃ or phenyl, then X4 is not -Cl.

14. The compound according to claim 13, wherein X4 is selected from -CH₃, C₁-C₅
5 alkoxy, -Cl, -Br, -OCH₂C=OOQ, phenyl and pyrrolidinyl,
wherein Q is H or -CH₂CH₃.
15. The compound according to claim 14, wherein X4 is selected from -CH₃, C₁-C₆
alkoxy, -OCH₂C=OOQ, phenyl and pyrrolidinyl, wherein Q is H or -CH₂CH₃.
- 10
16. The compound according to claim 13, wherein R1 is selected from -CH(CH₃)CH₃,
piperazinyl, piperazinyl substituted with a group selected from -CH₃, -CH₂CH₂OH,
and -C=OCH₃, piperadinyl, and piperadinyl substituted with a group selected from -
pyrrolidinyl, piperadinyl, and -N(CH₃)CH₃.
- 15
17. The compound according to claim 13, wherein C₁-C₆ alkyl is selected from C₁ alkyl,
C₂ alkyl and C₃ alkyl.
18. The compound according to claim 13, wherein Y1 and Y2 are independently selected
20 from -Cl and -Br.
19. The compound according to claim 18, wherein X4 is C₁-C₆ alkoxy at ortho position.

20. The compound according to claim 19, wherein the C₁-C₆ alkoxy is selected from ethoxy, isopropoxy and 2-fluoroethoxy.
21. The compound according to claim 20, wherein R₁ is selected from piperazinyl and substituted piperazinyl.
22. The compound according to claim 1, selected from the group of:
- a) 1-[4,5-Bis-(4-chloro-phenyl)-2-(2,4-dimethoxy-phenyl)-4,5-dihydro-imidazol-1-yl]-2-methyl-propan-1-one;
 - b) 1-[4,5-Bis-(4-chloro-phenyl)-2-(2,4-dimethoxy-phenyl)-4,5-dihydro-imidazol-1-yl] ethanone;
 - c) 1-[4,5-Bis-(4-chloro-phenyl)-2-(2,4-dimethoxy-phenyl)-4,5-dihydro-imidazol-1-yl]-2,2-dimethyl-propan-1-one;
 - d) [4,5-Bis-(4-chloro-phenyl)-2-(2,4-dimethoxy-phenyl)-4,5-dihydro-imidazol-1-yl]-cyclopentyl-methanone;
 - e) [4,5-Bis-(4-chloro-phenyl)-2-(2,4-dimethoxy-phenyl)-4,5-dihydro-imidazol-1-yl]-cyclohexyl-methanone;
 - f) [4,5-Bis-(4-chloro-phenyl)-2-(2,4-dimethoxy-phenyl)-4,5-dihydro-imidazol-1-yl]-thiophen-2-yl-methanone;
 - g) [4,5-Bis-(4-chloro-phenyl)-2-(2,4-dimethoxy-phenyl)-4,5-dihydro-imidazol-1-yl]-isoxazol-5-yl-methanone;
 - h) [4,5-Bis-(4-chloro-phenyl)-2-(2,4-dimethoxy-phenyl)-4,5-dihydro-imidazol-1-yl]-furan-2-yl-methanone;
 - i) 1-[4,5-Bis-(4-chloro-phenyl)-2-(2,3-dimethoxy-phenyl)-4,5-dihydro-imidazol-1-yl]-2-methyl-propan-1-one;

- j) [4,5-Bis-(4-chloro-phenyl)-2-(2,4-dimethoxy-phenyl)-4,5-dihydro-imidazol-1-yl]-(4-methyl-piperazin-1-yl)-methanone;
- k) [4,5-Bis-(4-chloro-phenyl)-2-(2,4-dimethoxy-phenyl)-4,5-dihydro-imidazol-1-yl]-piperazin-1-yl-methanone;
- 5 l) [4,5-Bis-(4-chloro-phenyl)-2-(2-fluoro-6-methoxy-phenyl)-4,5-dihydro-imidazol-1-yl]-[4-(2-hydroxy-ethyl)-piperazin-1-yl]-methanone;
- m) 1-{4-[4,5-Bis-(4-bromo-phenyl)-2-(2,4-dimethoxy-phenyl)-4,5-dihydro-imidazole-1-carbonyl]-piperazin-1-yl}-ethanone;
- 10 n) [4,5-Bis-(4-bromo-phenyl)-2-(2,4-dimethoxy-phenyl)-4,5-dihydro-imidazol-1-yl]-[4-(2-hydroxy-ethyl)-piperazin-1-yl]-methanone;
- o) [4,5-Bis-(4-chloro-phenyl)-2-(2-isopropoxy-4-methoxy-phenyl)-4,5-dihydro-imidazol-1-yl]-[4-(2-hydroxy-ethyl)-piperazin-1-yl]-methanone hydrochloride;
- 15 p) [4,5-Bis-(4-chloro-phenyl)-2-(2-ethoxy-4-methoxy-phenyl)-4,5-dihydro-imidazol-1-yl]-(4-methanesulfonyl-piperazin-1-yl)-methanone;
- q) [4,5-Bis-(4-chloro-phenyl)-2-(2-ethoxy-4-methoxy-phenyl)-4,5-dihydro-imidazol-1-yl]-[4-(2-hydroxy-ethyl)-piperazin-1-yl]-methanone;
- r) [4,5-Bis-(4-chloro-phenyl)-2-(2-ethoxy-4-methoxy-phenyl)-4,5-dihydro-imidazol-1-yl]-morpholin-4-yl-methanone;
- 20 s) [4,5-Bis-(4-chloro-phenyl)-2-(2-ethoxy-4-methoxy-phenyl)-4,5-dihydro-imidazol-1-yl]-(4-methyl-piperazin-1-yl)-methanone;
- t) 1-{4-[4,5-Bis-(4-chloro-phenyl)-2-(2-ethoxy-4-methoxy-phenyl)-4,5-dihydro-imidazole-1-carbonyl]-piperazin-1-yl}-ethanone;
- 25 u) 4-[4,5-Bis-(4-chloro-phenyl)-2-(2-ethoxy-4-methoxy-phenyl)-4,5-dihydro-imidazole-1-carbonyl]-piperazin-2-one;
- v) [4,5-Bis-(4-chloro-phenyl)-2-(2-isopropoxy-4-methoxy-phenyl)-4,5-dihydro-imidazol-1-yl]-piperazin-1-yl-methanone;

- w) 1-{4-[4,5-Bis-(4-chloro-phenyl)-2-(2-isopropoxy-4-methoxy-phenyl)-4,5-dihydro-imidazole-1-carbonyl]-piperazin-1-yl}-ethanone;
- x) [4,5-Bis-(4-chloro-phenyl)-2-(2-isopropoxy-4-methoxy-phenyl)-4,5-dihydro-imidazol-1-yl]-(4-methanesulfonyl-piperazin-1-yl)-methanone;
- 5 y) [4,5-Bis-(4-chloro-phenyl)-2-(2-isopropoxy-4-methoxy-phenyl)-4,5-dihydro-imidazol-1-yl]-(2,5-dimethyl-piperazin-1-yl)-methanone;
- z) 4,5-Bis-(4-chloro-phenyl)-2-(2-isopropoxy-4-methoxy-phenyl)-4,5-dihydro-imidazole-1-carboxylic acid bis-(2-hydroxy-ethyl)-amide;
- 10 aa) [4,5-Bis-(4-chloro-phenyl)-2-(2-isopropoxy-4-methoxy-phenyl)-4,5-dihydro-imidazol-1-yl]-(4-ethyl-piperazin-1-yl)-methanone;
- bb) [1,4']Bipiperidinyl-1'-yl-[4,5-bis-(4-chloro-phenyl)-2-(2-isopropoxy-4-methoxy-phenyl)-4,5-dihydro-imidazol-1-yl]-methanone;
- cc) [4,5-Bis-(4-chloro-phenyl)-2-(2-isopropoxy-4-methoxy-phenyl)-4,5-dihydro-imidazol-1-yl]-(4-pyrrolidin-1-yl-piperidin-1-yl)-methanone;
- 15 dd) [4,5-Bis-(4-chloro-phenyl)-2-(2-isopropoxy-4-methoxy-phenyl)-4,5-dihydro-imidazol-1-yl]-(4-dimethylamino-piperidin-1-yl)-methanone;
- ee) [4,5-Bis-(4-chloro-phenyl)-2-(2-isopropoxy-4-methoxy-phenyl)-4,5-dihydro-imidazol-1-yl]-morpholin-4-yl-methanone;
- 20 ff) [4,5-Bis-(4-chloro-phenyl)-2-(2-isopropoxy-4-methoxy-phenyl)-4,5-dihydro-imidazol-1-yl]-(4-isopropyl-piperazin-1-yl)-methanone;
- gg) 4-[4,5-Bis-(4-chloro-phenyl)-2-(2-isopropoxy-4-methoxy-phenyl)-4,5-dihydro-imidazole-1-carbonyl]-piperazin-2-one;
- hh) [4,5-Bis-(4-chloro-phenyl)-2-(2-isopropoxy-4-methoxy-phenyl)-4,5-dihydro-imidazol-1-yl]-(4-hydroxymethyl-piperidin-1-yl)-methanone;
- 25 ii) [4,5-Bis-(4-chloro-phenyl)-2-(2-isopropoxy-4-methoxy-phenyl)-4,5-dihydro-imidazol-1-yl]-[4-(2-hydroxy-ethyl)-piperidin-1-yl]-methanone;

- jj) [4,5-Bis-(4-chloro-phenyl)-2-(2-isopropoxy-4-methoxy-phenyl)-4,5-dihydro-imidazol-1-yl]-(3-methyl-piperazin-1-yl)-methanone;
- kk) 1-{4-[4,5-Bis-(4-chloro-phenyl)-2-(2-isopropoxy-4-methoxy-phenyl)-4,5-dihydro-imidazole-1-carbonyl]-2-methyl-piperazin-1-yl}-ethanone;
- 5 ll) [4,5-Bis-(4-chloro-phenyl)-2-(2-isopropoxy-4-methoxy-phenyl)-4,5-dihydro-imidazol-1-yl]-(4-methanesulfonyl-3-methyl-piperazin-1-yl)-methanone;
- mm) [4,5-Bis-(4-chloro-phenyl)-2-(2-isopropoxy-4-methoxy-phenyl)-4,5-dihydro-imidazol-1-yl]-(4-hydroxy-piperidin-1-yl)-methanone;
- nn) (4-Aminomethyl-piperidin-1-yl)-[4,5-bis-(4-chloro-phenyl)-2-(2-isopropoxy-4-methoxy-phenyl)-4,5-dihydro-imidazol-1-yl]-methanone;
- 10 oo) [4,5-Bis-(4-bromo-phenyl)-2-(2-ethoxy-4-methoxy-phenyl)-4,5-dihydro-imidazol-1-yl]-(4-(2-hydroxy-ethyl)-piperazin-1-yl)-methanone;
- pp) [4,5-Bis-(4-bromo-phenyl)-2-(2-ethoxy-4-methoxy-phenyl)-4,5-dihydro-imidazol-1-yl]-piperazin-1-yl-methanone;
- 15 qq) [4,5-Bis-(4-bromo-phenyl)-2-(2-ethoxy-4-methoxy-phenyl)-4,5-dihydro-imidazol-1-yl]-(4-methanesulfonyl-piperazin-1-yl)-methanone;
- rr) 1-{4-[4,5-Bis-(4-bromo-phenyl)-2-(2-ethoxy-4-methoxy-phenyl)-4,5-dihydro-imidazole-1-carbonyl]-piperazin-1-yl}-ethanone;
- ss) [4,5-Bis-(4-bromo-phenyl)-2-(2-ethoxy-4-methoxy-phenyl)-4,5-dihydro-imidazol-1-yl]-(4-methyl-piperazin-1-yl)-methanone;
- 20 tt) 4-[4,5-Bis-(4-bromo-phenyl)-2-(2-ethoxy-4-methoxy-phenyl)-4,5-dihydro-imidazole-1-carbonyl]-piperazine-1-carbaldehyde;
- uu) [4,5-Bis-(4-bromo-phenyl)-2-(2-ethoxy-4-methoxy-phenyl)-4,5-dihydro-imidazol-1-yl]-(4-pyrrolidin-1-yl-piperidin-1-yl)-methanone;
- 25 vv) [4,5-Bis-(4-bromo-phenyl)-2-(2-ethoxy-4-methoxy-phenyl)-4,5-dihydro-imidazol-1-yl]-(4-dimethylamino-piperidin-1-yl)-methanone;

- ww) [4,5-Bis-(4-bromo-phenyl)-2-(2-ethoxy-4-methoxy-phenyl)-4,5-dihydro-imidazol-1-yl]-(4-isopropyl-piperazin-1-yl)-methanone;
- xx) 4-[4,5-Bis-(4-bromo-phenyl)-2-(2-ethoxy-4-methoxy-phenyl)-4,5-dihydro-imidazole-1-carbonyl]-piperazin-2-one; and
- 5 yy) [4,5-Bis-(4-bromo-phenyl)-2-(2-isopropoxy-4-methoxy-phenyl)-4,5-dihydro-imidazol-1-yl]-piperazin-1-yl-methanone.
23. The compound according to claim 1, selected from the group of:
- 10 a) 1-[4-[4,5-Bis-(4-bromo-phenyl)-2-(2-isopropoxy-4-methoxy-phenyl)-4,5-dihydro-imidazole-1-carbonyl]-piperazin-1-yl]-ethanone;
- b) [4,5-Bis-(4-bromo-phenyl)-2-(2-isopropoxy-4-methoxy-phenyl)-4,5-dihydro-imidazol-1-yl]-(4-methanesulfonyl-piperazin-1-yl)-methanone;
- c) [4,5-Bis-(4-bromo-phenyl)-2-(2-isopropoxy-4-methoxy-phenyl)-4,5-dihydro-imidazol-1-yl]-(4-methyl-piperazin-1-yl)-methanone;
- 15 d) [4,5-Bis-(4-bromo-phenyl)-2-(2-isopropoxy-4-methoxy-phenyl)-4,5-dihydro-imidazol-1-yl]-morpholin-4-yl-methanone;
- e) [1,4']Bipiperidinyl-1'-yl-[4,5-bis-(4-bromo-phenyl)-2-(2-isopropoxy-4-methoxy-phenyl)-4,5-dihydro-imidazol-1-yl]-methanone;
- 20 f) [4,5-Bis-(4-bromo-phenyl)-2-(2-isopropoxy-4-methoxy-phenyl)-4,5-dihydro-imidazol-1-yl]-(4-ethyl-piperazin-1-yl)-methanone;
- g) 4-[4,5-Bis-(4-bromo-phenyl)-2-(2-isopropoxy-4-methoxy-phenyl)-4,5-dihydro-imidazole-1-carbonyl]-piperazin-2-one;
- h) [4,5-Bis-(4-cyano-phenyl)-2-(2-isopropoxy-4-methoxy-phenyl)-4,5-dihydro-imidazol-1-yl]-piperazin-1-yl-methanone;
- 25 i) 1-(4-{4,5-Bis-(4-chloro-phenyl)-2-[4-methoxy-2-(2-methoxy-ethoxy)-phenyl]-4,5-dihydro-imidazole-1-carbonyl}-piperazin-1-yl)-ethanone;

- j) 1-(4-{4,5-Bis-(4-chloro-phenyl)-2-[2-(2-fluoro-ethoxy)-4-methoxy-phenyl]-4,5-dihydro-imidazole-1-carbonyl}-piperazin-1-yl)-ethanone;
- k) 4-{4,5-Bis-(4-chloro-phenyl)-2-[2-(2-fluoro-ethoxy)-4-methoxy-phenyl]-4,5-dihydro-imidazole-1-carbonyl}-piperazin-2-one;
- 5 l) [4,5-Bis-(4-chloro-phenyl)-2-(2-ethoxy-4-methoxy-phenyl)-4,5-dihydro-imidazol-1-yl]-piperazin-1-yl-methanone hydrochloride;
- m) 4,5-Bis-(4-chloro-phenyl)-2-(2-ethoxy-4-methoxy-phenyl)-4,5-dihydro-imidazole-1-carboxylic acid methyl-(2-methylamino-ethyl)-amide, trifluoroacetic acid salt;
- 10 n) 4,5-Bis-(4-chloro-phenyl)-2-(2-ethoxy-4-methoxy-phenyl)-4,5-dihydro-imidazole-1-carboxylic acid (2-dimethylamino-ethyl)-methyl-amide, trifluoroacetic acid salt;
- o) 4,5-Bis-(4-chloro-phenyl)-2-(2-ethoxy-4-methoxy-phenyl)-4,5-dihydro-imidazole-1-carboxylic acid (2-dimethylamino-ethyl)-amide, trifluoroacetic acid salt;
- 15 p) 4,5-Bis-(4-chloro-phenyl)-2-(2-ethoxy-4-methoxy-phenyl)-4,5-dihydro-imidazole-1-carboxylic acid (2-amino-ethyl)-amide, trifluoroacetic acid salt;
- q) [4,5-Bis-(4-chloro-phenyl)-2-(2-ethoxy-4-methoxy-phenyl)-4,5-dihydro-imidazol-1-yl]-(4-pyrrolidin-1-yl-piperidin-1-yl)-methanone hydrochloride;
- 20 r) [4,5-Bis-(4-chloro-phenyl)-2-(4-methoxy-2-propoxy-phenyl)-4,5-dihydro-imidazol-1-yl]-piperazin-1-yl-methanone, trifluoroacetic acid salt;
- s) [4,5-Bis-(4-chloro-phenyl)-2-(2-isopropoxy-4-methoxy-phenyl)-4,5-dihydro-imidazol-1-yl]-(4-methyl-piperazin-1-yl)-methanone hydrochloride;
- t) 4,5-Bis-(4-chloro-phenyl)-2-(2-isopropoxy-4-methoxy-phenyl)-4,5-dihydro-imidazole-1-carboxylic acid (2-morpholin-4-yl-ethyl)-amide hydrochloride;
- 25 u) 4,5-Bis-(4-chloro-phenyl)-2-(2-isopropoxy-4-methoxy-phenyl)-4,5-dihydro-imidazole-1-carboxylic acid (2-piperazin-1-yl-ethyl)-amide hydrochloride;

- v) [4,5-Bis-(4-chloro-phenyl)-2-(2-isobutoxy-4-methoxy-phenyl)-4,5-dihydro-imidazol-1-yl]-piperazin-1-yl-methanone hydrochloride;
- w) [4,5-Bis-(4-chloro-phenyl)-2-(2-isopropoxy-4-methoxy-phenyl)-4,5-dihydro-imidazol-1-yl]-(3-methyl-piperazin-1-yl)-methanone hydrochloride;
- 5 x) {4,5-Bis-(4-chloro-phenyl)-2-[4-methoxy-2-(2-methoxy-ethoxy)-phenyl]-4,5-dihydro-imidazol-1-yl}-piperazin-1-yl-methanone, trifluoroacetic acid salt;
- y) {4,5-Bis-(4-chloro-phenyl)-2-[2-(2-fluoro-ethoxy)-4-methoxy-phenyl]-4,5-dihydro-imidazol-1-yl}-piperazin-1-yl-methanone;
- z) {4,5-Bis-(4-chloro-phenyl)-2-[2-(2-fluoro-ethoxy)-4-methoxy-phenyl]-4,5-dihydro-imidazol-1-yl}-(4-pyrrolidin-1-yl-piperidin-1-yl)-methanone hydrochloride;
- 10 aa) 2-Amino-1-{4-[4,5-bis-(4-chloro-phenyl)-2-(2-isopropoxy-4-methoxy-phenyl)-4,5-dihydro-imidazole-1-carbonyl]-piperazin-1-yl}-ethanone;
- bb) 1-{4-[4,5-Bis-(4-chloro-phenyl)-2-(2-isopropoxy-4-methoxy-phenyl)-4,5-dihydro-imidazole-1-carbonyl]-piperazin-1-yl}-2-hydroxy-ethanone;
- 15 cc) 1-{4-[4,5-Bis-(4-chloro-phenyl)-2-(2-isopropoxy-4-methoxy-phenyl)-4,5-dihydro-imidazole-1-carbonyl]-piperazin-1-yl}-2,3-dihydroxy-propan-1-one;
- dd) [4,5-Bis-(4-chloro-phenyl)-2-(2-isopropoxy-4-methoxy-phenyl)-4,5-dihydro-imidazol-1-yl]-[4-(2,3-dihydroxy-propyl)-piperazin-1-yl]-methanone;
- 20 ee) 4-[4,5-Bis-(4-chloro-phenyl)-2-(2-isopropoxy-4-methoxy-phenyl)-4,5-dihydro-imidazole-1-carbonyl]-piperazine-1-carboxylic acid dimethylamide;
- ff) 4-[4,5-Bis-(4-chloro-phenyl)-2-(2-isopropoxy-4-methoxy-phenyl)-4,5-dihydro-imidazole-1-carbonyl]-piperazine-1-carboxylic acid amide;
- gg) [4,5-Bis-(4-chloro-phenyl)-2-(2,4-diethoxy-phenyl)-4,5-dihydro-imidazol-1-yl]-piperazin-1-yl-methanone;
- 25 hh) [4,5-Bis-(4-chloro-phenyl)-2-(2,4-diethoxy-phenyl)-4,5-dihydro-imidazol-1-yl] morpholin-4-yl-methanone;

- ii) [4,5-Bis-(4-chloro-phenyl)-2-(2,4-diethoxy-phenyl)-4,5-dihydro-imidazol-1-yl]-[4-(2-hydroxy-ethyl)-piperazin-1-yl]-methanone;
- jj) [4,5-Bis-(4-chloro-phenyl)-2-(2,4-diethoxy-phenyl)-4,5-dihydro-imidazol-1-yl]-[4-methyl-piperazin-1-yl]-methanone;
- 5 kk) 1-[4-[4,5-Bis-(4-chloro-phenyl)-2-(2,4-diethoxy-phenyl)-4,5-dihydro-imidazole-1-carbonyl]-piperazin-1-yl]-ethanone;
- ll) [4,5-Bis-(4-chloro-phenyl)-2-(2,4-diethoxy-phenyl)-4,5-dihydro-imidazol-1-yl]-[4-methanesulfonyl-piperazin-1-yl]-methanone;
- mm) [4,5-Bis-(4-chloro-phenyl)-2-(2,4-diethoxy-phenyl)-4,5-dihydro-imidazol-1-yl]-[4-pyrrolidin-1-yl-piperidin-1-yl]-methanone;
- 10 nn) [4,5-Bis-(4-bromo-phenyl)-2-(2,4-diethoxy-phenyl)-4,5-dihydro-imidazol-1-yl]-[4-methyl-piperazin-1-yl]-methanone;
- oo) [4,5-Bis-(4-bromo-phenyl)-2-(2,4-diethoxy-phenyl)-4,5-dihydro-imidazol-1-yl]-[4-ethyl-piperazin-1-yl]-methanone;
- 15 pp) [4,5-Bis-(4-bromo-phenyl)-2-(2,4-diethoxy-phenyl)-4,5-dihydro-imidazol-1-yl]-morpholin-4-yl-methanone;
- qq) 4-[4,5-Bis-(4-chloro-phenyl)-2-(2,4-diethoxy-phenyl)-4,5-dihydro-imidazole-1-carbonyl]-piperazine-1-carboxylic acid amide;
- rr) 4-[4,5-Bis-(4-chloro-phenyl)-2-(2,4-diethoxy-phenyl)-4,5-dihydro-imidazole-1-carbonyl]-piperazine-1-carboxylic acid dimethylamide;
- 20 ss) [4,5-Bis-(4-chloro-phenyl)-2-(4-dimethylamino-2-ethoxy-phenyl)-4,5-dihydro-imidazol-1-yl]-piperazin-1-yl-methanone;
- tt) [4,5-Bis-(4-chloro-phenyl)-2-(2-ethoxy-4-ethyl-phenyl)-4,5-dihydro-imidazol-1-yl]-piperazin-1-yl-methanone;
- 25 uu) [4,5-Bis-(4-chloro-phenyl)-2-(2-ethoxy-4-methyl-phenyl)-4,5-dihydro-imidazol-1-yl]-piperazin-1-yl-methanone;

- vv) [4,5-Bis-(4-chloro-phenyl)-2-(4-ethyl-2-isopropoxy-phenyl)-4,5-dihydro-imidazol-1-yl]-piperazin-1-yl-methanone;
- ww) [4,5-Bis-(4-chloro-phenyl)-2-(2-isopropoxy-4-methyl-phenyl)-4,5-dihydro-imidazol-1-yl]-piperazin-1-yl-methanone;
- 5 xx) 1-{4-[4,5-Bis-(4-chloro-phenyl)-2-(4-dimethylamino-2-ethoxy-phenyl)-4,5-dihydro-imidazole-1-carbonyl]-piperazin-1-yl}-ethanone; and
- yy) [4,5-Bis-(4-chloro-phenyl)-2-(2-ethoxy-5-methyl-phenyl)-4,5-dihydro-imidazol-1-yl]-piperazin-1-yl-methanone, trifluoroacetic acid salt.
- 10 24. The compound according to claim 1, selected from the group of:
- a) [4,5-Bis-(4-chloro-phenyl)-2-(2-ethoxy-4-fluoro-phenyl)-4,5-dihydro-imidazol-1-yl]-(4-pyrrolidin-1-yl-piperidin-1-yl)-methanone;
- b) [4,5-Bis-(4-chloro-phenyl)-2-(2-ethoxy-4-fluoro-phenyl)-4,5-dihydro-imidazol-1-yl]-(4-dimethylamino-piperidin-1-yl)-methanone;
- 15 c) [4,5-Bis-(4-chloro-phenyl)-2-(2-ethoxy-4-fluoro-phenyl)-4,5-dihydro-imidazol-1-yl]-piperazin-1-yl-methanone;
- d) [4,5-Bis-(4-chloro-phenyl)-2-(4-fluoro-2-isopropoxy-phenyl)-4,5-dihydro-imidazol-1-yl]-(4-pyrrolidin-1-yl-piperidin-1-yl)-methanone;
- e) [4,5-Bis-(4-chloro-phenyl)-2-(4-fluoro-2-isopropoxy-phenyl)-4,5-dihydro-imidazol-1-yl]-(4-dimethylamino-piperidin-1-yl)-methanone;
- 20 f) [4,5-Bis-(4-chloro-phenyl)-2-(4-fluoro-2-isopropoxy-phenyl)-4,5-dihydro-imidazol-1-yl]-(4-methyl-piperazin-1-yl)-methanone;
- g) [4,5-Bis-(4-chloro-phenyl)-2-(4-fluoro-2-isopropoxy-phenyl)-4,5-dihydro-imidazol-1-yl]-piperazin-1-yl-methanone;
- 25 h) [4,5-Bis-(4-chloro-phenyl)-2-(4-fluoro-2-isopropoxy-phenyl)-4,5-dihydro-imidazol-1-yl]-(4-methanesulfonyl-piperazin-1-yl)-methanone;

- i) 4-[4,5-Bis-(4-chloro-phenyl)-2-(4-fluoro-2-isopropoxy-phenyl)-4,5-dihydro-imidazole-1-carbonyl]-piperazin-2-one;
- j) [4,5-Bis-(4-chloro-phenyl)-2-chroman-8-yl-4,5-dihydro-imidazol-1-yl]-piperazin-1-yl-methanone;
- 5 k) 4-[4,5-Bis-(4-bromo-phenyl)-2-(2-ethoxy-4-fluoro-phenyl)-4,5-dihydro-imidazole-1-carbonyl]-piperazin-2-one;
- l) [4,5-Bis-(4-bromo-phenyl)-2-(2-ethoxy-4-fluoro-phenyl)-4,5-dihydro-imidazol-1-yl]-morpholin-4-yl-methanone;
- 10 m) [4,5-Bis-(4-bromo-phenyl)-2-(2-ethoxy-4-fluoro-phenyl)-4,5-dihydro-imidazol-1-yl]-(4-pyrrolidin-1-yl-piperidin-1-yl)-methanone;
- n) [4,5-Bis-(4-bromo-phenyl)-2-(2-ethoxy-4-fluoro-phenyl)-4,5-dihydro-imidazol-1-yl]-(4-dimethylamino-piperidin-1-yl)-methanone;
- o) [4,5-Bis-(4-bromo-phenyl)-2-(2-ethoxy-4-fluoro-phenyl)-4,5-dihydro-imidazol-1-yl]-piperazin-1-yl-methanone;
- 15 p) [4,5-Bis-(4-chloro-phenyl)-2-(2-cyclopentyloxy-4-methoxy-phenyl)-4,5-dihydro-imidazol-1-yl]-piperazin-1-yl-methanone;
- q) {4,5-Bis-(4-chloro-phenyl)-2-[2-(2-dimethylamino-ethoxy)-4-methoxy-phenyl]-4,5-dihydro-imidazol-1-yl}-piperazin-1-yl-methanone;
- 20 r) {4,5-Bis-(4-chloro-phenyl)-2-[2-(2-imidazol-1-yl-ethoxy)-4-methoxy-phenyl]-4,5-dihydro-imidazol-1-yl}-piperazin-1-yl-methanone;
- s) [2-(4-Chloro-2-ethoxy-phenyl)-4,5-bis-(4-chloro-phenyl)-4,5-dihydro-imidazol-1-yl]-piperazin-1-yl-methanone hydrochloride;
- t) [2-(4-Chloro-2-ethoxy-phenyl)-4,5-bis-(4-chloro-phenyl)-4,5-dihydro-imidazol-1-yl]-(4-methyl-piperazin-1-yl)-methanone hydrochloride;
- 25 u) [2-(4-Chloro-2-ethoxy-phenyl)-4,5-bis-(4-chloro-phenyl)-4,5-dihydro-imidazol-1-yl]-(4-pyrrolidin-1-yl-piperidin-1-yl)-methanone hydrochloride;

- v) [2-(4-Chloro-2-ethoxy-phenyl)-4,5-bis-(4-chloro-phenyl)-4,5-dihydro-imidazol-1-yl]-morpholin-4-yl-methanone;
- w) 1-{4-[2-(4-Chloro-2-ethoxy-phenyl)-4,5-bis-(4-chloro-phenyl)-4,5-dihydro-imidazole-1-carbonyl]-piperazin-1-yl}-ethanone;
- 5 x) [2-(4-Chloro-2-ethoxy-phenyl)-4,5-bis-(4-chloro-phenyl)-4,5-dihydro-imidazol-1-yl]-[4-(2-hydroxy-ethyl)-piperazin-1-yl]-methanone hydrochloride;
- y) 4-[2-(4-Chloro-2-ethoxy-phenyl)-4,5-bis-(4-chloro-phenyl)-4,5-dihydro-imidazole-1-carbonyl]-piperazin-2-one;
- 10 z) [4,5-Bis-(4-chloro-phenyl)-2-(4-ethoxy-2-isopropoxy-phenyl)-4,5-dihydro-imidazol-1-yl]-piperazin-1-yl-methanone;
- aa) [4,5-Bis-(4-chloro-phenyl)-2-(2-ethoxy-5-methoxy-phenyl)-4,5-dihydro-imidazol-1-yl]-piperazin-1-yl-methanone, trifluoroacetic acid salt;
- bb) [4,5-Bis-(4-chloro-phenyl)-2-(2-ethoxy-5-methoxy-phenyl)-4,5-dihydro-imidazol-1-yl]-[4-methanesulfonyl-piperazin-1-yl]-methanone;
- 15 cc) [4,5-Bis-(4-chloro-phenyl)-2-(2-ethoxy-5-methoxy-phenyl)-4,5-dihydro-imidazol-1-yl]-[4-(2-hydroxy-ethyl)-piperazin-1-yl]-methanone hydrochloride;
- dd) [4,5-Bis-(4-chloro-phenyl)-2-(2,5-diethoxy-phenyl)-4,5-dihydro-imidazol-1-yl]-piperazin-1-yl-methanone hydrochloride;
- 20 ee) [4,5-Bis-(4-chloro-phenyl)-2-(2,5-diethoxy-phenyl)-4,5-dihydro-imidazol-1-yl]-[4-methanesulfonyl-piperazin-1-yl]-methanone;
- ff) [4,5-Bis-(4-chloro-phenyl)-2-(4-ethoxy-2-isopropoxy-phenyl)-4,5-dihydro-imidazol-1-yl]-[4-(2-hydroxy-ethyl)-piperazin-1-yl]-methanone;
- 25 gg) 4-[4,5-Bis-(4-chloro-phenyl)-2-(4-ethoxy-2-isopropoxy-phenyl)-4,5-dihydro-imidazole-1-carbonyl]-piperazin-2-one;
- hh) [4,5-Bis-(4-chloro-phenyl)-2-(5-ethoxy-2-isopropoxy-phenyl)-4,5-dihydro-imidazol-1-yl]-piperazin-1-yl-methanone;

- ii) [4,5-Bis-(4-chloro-phenyl)-2-(5-ethoxy-2-isopropoxy-phenyl)-4,5-dihydro-imidazol-1-yl]-(4-methanesulfonyl-piperazin-1-yl)-methanone;
- jj) [4,5-Bis-(4-chloro-phenyl)-2-(5-ethoxy-2-isopropoxy-phenyl)-4,5-dihydro-imidazol-1-yl]-[4-(2-hydroxy-ethyl)-piperazin-1-yl]-methanone
5 hydrochloride;
- kk) 1-[4-[4,5-Bis-(4-chloro-phenyl)-2-(4-ethoxy-2-isopropoxy-phenyl)-4,5-dihydro-imidazole-1-carbonyl]-piperazin-1-yl]-ethanone;
- ll) 1-[4-[4,5-Bis-(4-chloro-phenyl)-2-(5-ethoxy-2-isopropoxy-phenyl)-4,5-dihydro-imidazole-1-carbonyl]-piperazin-1-yl]-ethanone;
- 10 mm) [4,5-Bis-(4-chloro-phenyl)-2-(4-ethoxy-2-isopropoxy-phenyl)-4,5-dihydro-imidazol-1-yl]-(4-pyrrolidin-1-yl-piperidin-1-yl)-methanone;
- nn) [4,5-Bis-(4-chloro-phenyl)-2-(2-isopropoxy-5-methoxy-phenyl)-4,5-dihydro-imidazol-1-yl]-piperazin-1-yl-methanone, trifluoroacetic acid salt;
- oo) [4,5-Bis-(4-chloro-phenyl)-2-(2,4-diisopropoxy-phenyl)-4,5-dihydro-imidazol-1-yl]-piperazin-1-yl-methanone;
15
- pp) [4,5-Bis-(4-chloro-phenyl)-2-(2,5-diisopropoxy-phenyl)-4,5-dihydro-imidazol-1-yl]-piperazin-1-yl-methanone hydrochloride;
- qq) 1-[4,5-Bis-(4-chloro-phenyl)-2-(2-methoxy-5-morpholin-4-yl-methyl-phenyl)-4,5-dihydro-imidazol-1-yl]-2-methyl-propan-1-one;
- 20 rr) 1-[4,5-Bis-(4-chloro-phenyl)-2-(3-hydroxymethyl-5-methoxy-phenyl)-4,5-dihydro-imidazol-1-yl]-2-methyl-propan-1-one;
- ss) 1-[4,5-Bis-(4-chloro-phenyl)-2-(3-hydroxymethyl-5-methoxymethyl-phenyl)-4,5-dihydro-imidazol-1-yl]-ethanone;
- tt) 1-[4,5-Bis-(4-chloro-phenyl)-2-(3-methoxy-5-methoxymethyl-phenyl)-4,5-dihydro-imidazol-1-yl]-2-methyl-propan-1-one;
25
- uu) 3-[4,5-Bis-(4-chloro-phenyl)-1-isobutyryl-4,5-dihydro-1H-imidazol-2-yl]-5-methoxymethyl-benzoic acid;

- vv) 1-[4,5-Bis-(4-chloro-phenyl)-2-(5-ethoxymethyl-2,4-dimethoxy-phenyl)-4,5-dihydro-imidazol-1-yl]-2-methyl-propan-1-one;
- ww) [4,5-Bis-(4-chloro-phenyl)-2-(2-ethoxy-6-methoxy-phenyl)-4,5-dihydro-imidazol-1-yl]-piperazin-1-yl-methanone; and
- 5 xx) [4,5-bis-(4-chloro-phenyl)-2-(5-ethoxymethyl-2,4-dimethoxy-phenyl)-4,5-dihydro-imidazol-1-yl]-piperazin-1-yl-methanone.
25. The compound according to claim 1, selected from the group of:
- 10 a) [4,5-Bis-(4-chloro-phenyl)-2-(2-isopropoxy-4-methoxy-phenyl)-4,5-dihydro-imidazol-1-yl]-[4-(2-hydroxy-propyl)-piperazin-1-yl]-methanone;
- b) [4,5-Bis-(4-chloro-phenyl)-2-(2-isopropoxy-4-methoxy-phenyl)-4,5-dihydro-imidazol-1-yl]-threo[4-(2-hydroxy-1-methyl-propyl)-piperazin-1-yl]-methanone;
- 15 c) [4,5-Bis-(4-chloro-phenyl)-2-(2-isopropoxy-4-methoxy-phenyl)-4,5-dihydro-imidazol-1-yl]-erythro[4-(2-hydroxy-1-methyl-propyl)-piperazin-1-yl]-methanone;
- d) 1-{4-[4,5-Bis-(4-chloro-phenyl)-2-(2-isopropoxy-4-methoxy-phenyl)-4,5-dihydro-imidazole-1-carbonyl]-piperazin-1-yl}-propan-2-one;
- 20 e) [4,5-Bis-(4-chloro-phenyl)-2-(2-isopropoxy-4-methoxy-phenyl)-4,5-dihydro-imidazol-1-yl]-[1,4]diazepan-1-yl-methanone;
- f) 4-[4,5-Bis-(4-chloro-phenyl)-2-(2-isopropoxy-4-methoxy-phenyl)-4,5-dihydro-imidazole-1-carbonyl]-1-methyl-piperazin-2-one;
- g) 1-{4-[4,5-Bis-(4-chloro-phenyl)-2-(2-isopropoxy-4-methoxy-phenyl)-4,5-dihydro-imidazole-1-carbonyl]-piperazin-1-yl}-2-methyl-propan-1-one;
- 25 h) 4-[4,5-Bis-(4-chloro-phenyl)-2-(2-isopropoxy-4-methoxy-phenyl)-4,5-dihydro-imidazole-1-carbonyl]-piperazine-1-carbaldehyde;

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- i) 4-[4,5-Bis-(4-chloro-phenyl)-2-[4-methoxy-2-(2,2,2-trifluoro-ethoxy)-phenyl]-4,5-dihydro-imidazole-1-carbonyl]-piperazin-2-one;
- j) 4-[4,5-Bis-(4-bromo-phenyl)-2-[4-methoxy-2-(2,2,2-trifluoro-ethoxy)-phenyl]-4,5-dihydro-imidazole-1-carbonyl]-piperazin-2-one;
- 5 k) [4,5-Bis-(4-ethynyl-phenyl)-2-(2-isopropoxy-4-methoxy-phenyl)-4,5-dihydro-imidazol-1-yl]-(4-pyrrolidin-1-yl-piperidin-1-yl)-methanone;
- l) 1-[4-[2-(5-Chloro-2-isopropoxy-phenyl)-4,5-bis-(4-chloro-phenyl)-4,5-dihydro-imidazole-1-carbonyl]-piperazin-1-yl]-ethanone; and
- 10 m) [5-(4-Chloro-phenyl)-4-(4-ethynyl-phenyl)-2-(2-isopropoxy-4-methoxy-phenyl)-4,5-dihydro-imidazol-1-yl]-(4-pyrrolidin-1-yl-piperidin-1-yl)-methanone.
26. The compound according to claim 13, selected from the group of:
- 15 a) 1-[4,5-Bis-(4-chloro-phenyl)-2-(2-methoxy-phenyl)-4,5-dihydro-imidazol-1-yl]-2-methyl-propan-1-one;
- b) 1-[4,5-Bis-(4-chloro-phenyl)-2-p-tolyl-4,5-dihydro-imidazol-1-yl]-ethanone;
- c) {4-[4,5-Bis-(4-chloro-phenyl)-1-isobutyryl-4,5-dihydro-1H-imidazol-2-yl]-phenoxy}-acetic acid ethyl ester;
- 20 d) {4-[4,5-Bis-(4-chloro-phenyl)-1-isobutyryl-4,5-dihydro-1H-imidazol-2-yl]-phenoxy}-acetic acid;
- e) 2-Methyl-1-[2,4,5-tris-(4-chloro-phenyl)-4,5-dihydro-imidazol-1-yl]-propan-1-one;
- f) 1-[4,5-Bis-(4-chloro-phenyl)-2-(4-methoxy-phenyl)-4,5-dihydro-imidazol-1-yl]-ethanone;
- 25 g) [2-(2-Chloro-phenyl)-4,5-bis-(4-chloro-phenyl)-4,5-dihydro-imidazol-1-yl]-piperazin-1-yl-methanone;

- h) [2-(3-Bromo-phenyl)-4,5-bis-(4-chloro-phenyl)-4,5-dihydro-imidazol-1-yl]-piperazin-1-yl-methanone;
- i) [2-Biphenyl-3-yl-4,5-bis-(4-chloro-phenyl)-4,5-dihydro-imidazol-1-yl]-(4-methyl-piperazin-1-yl)-methanone;
- 5 j) [4,5-Bis-(4-chloro-phenyl)-2-(3-pyrrolidin-1-yl-phenyl)-4,5-dihydro-imidazol-1-yl]-piperazin-1-yl-methanone;
- k) [4,5-Bis-(4-bromo-phenyl)-2-(2-methoxy-phenyl)-4,5-dihydro-imidazol-1-yl]-[4-(2-hydroxy-ethyl)-piperazin-1-yl]-methanone;
- 10 l) 1-[5-(4-Chloro-phenyl)-2-(4-methoxy-phenyl)-4-(4-nitro-phenyl)-4,5-dihydro-imidazol-1-yl]-2-methyl-propan-1-one;
- m) 1-[4-(4-chloro-phenyl)-2-(4-methoxy-phenyl)-5-(4-nitro-phenyl)-4,5-dihydro-imidazol-1-yl]-2-methyl-propan-1-one;
- n) 1-[4,5-Bis-(4-chloro-phenyl)-2-(2-isopropoxy-phenyl)-4,5-dihydro-imidazol-1-yl]-2-methyl-propan-1-one;
- 15 o) [4,5-Bis-(4-chloro-phenyl)-2-(2-isopropoxy-phenyl)-4,5-dihydro-imidazol-1-yl]-(4-pyrrolidin-1-yl-piperidin-1-yl)-methanone;
- p) [4,5-Bis-(4-chloro-phenyl)-2-(2-isopropoxy-phenyl)-4,5-dihydro-imidazol-1-yl]-piperazin-1-yl-methanone;
- 20 q) [4,5-Bis-(4-chloro-phenyl)-2-(2-isopropoxy-phenyl)-4,5-dihydro-imidazol-1-yl]-(4-dimethylamino-piperidin-1-yl)-methanone;
- r) [1,4']Bipiperidiny-1'-yl-[4,5-bis-(4-chloro-phenyl)-2-(2-isopropoxy-phenyl)-4,5-dihydro-imidazol-1-yl]-methanone;
- s) [4,5-Bis-(4-chloro-phenyl)-2-(2-isopropoxy-phenyl)-4,5-dihydro-imidazol-1-yl]-[4-(2-hydroxy-ethyl)-piperazin-1-yl]-methanone;
- 25 t) {4,5-Bis-(4-chloro-phenyl)-2-[2-(2-methyl-butoxy)-phenyl]-4,5-dihydro-imidazol-1-yl}-piperazin-1-yl-methanone;

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- u) [4,5-Bis-(4-chloro-phenyl)-2-(2-pentyloxy-phenyl)-4,5-dihydro-imidazol-1-yl]-piperazin-1-yl-methanone;
- v) [4,5-Bis-(4-chloro-phenyl)-2-(3-ethoxy-phenyl)-4,5-dihydro-imidazol-1-yl]-piperazin-1-yl-methanone, trifluoroacetic acid salt;
- 5 w) [4,5-Bis-(4-chloro-phenyl)-2-(3-isopropoxy-phenyl)-4,5-dihydro-imidazol-1-yl]-piperazin-1-yl-methanone, trifluoroacetic acid salt;
- x) 1-{4-[4,5-Bis-(4-bromo-phenyl)-2-(2-ethoxy-phenyl)-4,5-dihydro-imidazole-1-carbonyl]-piperazin-1-yl}-ethanone;
- 10 y) [4,5-Bis-(4-bromo-phenyl)-2-(2-ethoxy-phenyl)-4,5-dihydro-imidazol-1-yl]-[4-(2-hydroxy-ethyl)-piperazin-1-yl]-methanone;
- z) 1-{4-[4,5-Bis-(4-bromo-phenyl)-2-(2-isopropoxy-phenyl)-4,5-dihydro-imidazole-1-carbonyl]-piperazin-1-yl}-ethanone; and
- aa) [4,5-Bis-(4-bromo-phenyl)-2-(2-isopropoxy-phenyl)-4,5-dihydro-imidazol-1-yl]-[4-(2-hydroxy-ethyl)-piperazin-1-yl]-methanone.
- 15 27. A pharmaceutical composition comprising a compound according to any one of claims 1 to 26 as an active ingredient and a pharmaceutical acceptable carrier.
28. The pharmaceutical composition according to claim 27 which is suitable for oral or parenteral administration.
29. A use of compound as defined in any one of claims 1 to 26 for the preparation of a
20 medicament.
30. The use according to claim 29 for the preparation of a medicament for the treatment or control of cell proliferative disorders.
31. The use according to claim 29 and/or 30 for the treatment or control of cancer.
32. The use according to any one of claims 29 to 31 for the treatment or control of
25 breast, colon, lung or prostate tumors.

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33. A method for treating a cell proliferative disorder comprising administering to a patient in need thereof a therapeutically effective amount of a compound according to any one of claims 1 to 26.
- 5 34. The method according to claim 33 wherein the cell proliferative disorder is cancer.
35. The method according to claim 34 wherein the cancer is breast, colon, lung or prostate tumors.
- 10 36. A compound of any one of claims 1 to 26 for use in therapy.
37. A process for the preparation of a compound according to any one of claim 1 to 26 as depicted in scheme I to X.
- 15 38. A compound of formula I or II as defined herein and substantially as herein described with reference to the Examples.