

2,4,5-TRIPHENYL IMIDAZOLINE DERIVATIVES AS INHIBITORS OF THE INTERACTION BETWEEN P53 AND MDM2 PROTEINS FOR USE AS ANTICANCER AGENTS

The protein 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**, 50, 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.

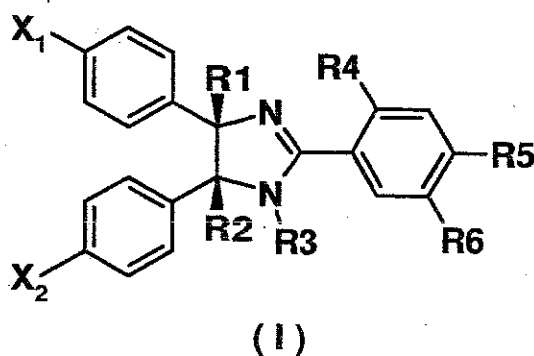
EP 363 061 to Matsumoto reports imidazoline derivatives useful as immunomodulators. The compounds were indicated to have low toxicity. Treatment and/or prevention of rheumatoid arthritis, multiple sclerosis, systemic lupus, erythemathodes, and rheumatic fever were implicated. WO 00/78725 to Choueiry *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.

US 6,617,346 B1 (issued September 9, 2003), US 6,734,302 B2 (issued May 11, 2004), US20040259884A1 (published December 23, 2004), US20040259867A1 (published December 23, 2004), US20050282803A1 (published December 22, 2005) and US20050288287A1 (published December 29, 2005) disclose related cis-imidazolines.

The present invention provides chiral 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 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 mechanism of action. These compounds can be potent and selective anticancer agents.

5 According to a first aspect, there is provided at least one compound of formula I



wherein

X_1 and X_2 are halogen, acetylene, cyano, trifluoromethyl or nitro;

10

R^1 and R^2 are selected from the group consisting of -H, -CH₃, -CH₂CH₃, -CH₂OH and -CH₂OCH₃ with the proviso that R^1 and R^2 are not both hydrogen;

R^3 is -H or -C(=O)-R⁷;

15

and where R^6 is hydrogen then

R^4 is -OCH₃, -OCH₂CH₃, -OCH₂CH₂F, -OCH₂CH₂OCH₃, or -OCH(CH₃)₂;

R^5 is

-H

20

-halogen,

-CH₃,

-CF₃,

-OCH₃,

-C(CH₃)₂,

25

-cyclopropyl,

-cyano,

-C(CH₃)₃,

-C(CH₃)₂OR (where R is -H, -CH₃ or -CH₂CH₃),

- C(CH₃)₂CH-OR (where R is -H, -CH₃, -CH(CH₃)₂, -CH₂CH₂OH or -CH₂CH₂OCH₃),
- C(CH₃)₂CN,
- C(CH₃)₂COR (where R is -CH₃),
- 5 -C(CH₃)₂COOR (where R is -H, -CH₃, -CH₂CH₃ or -CH(CH₃)₂),
- C(CH₃)₂CONR^aR^b (where R^a is -H or -CH₃ and R^b = -H or -CH₃),
- SR (where R is -CH₃ or -CH₂CH₃), or
- SO₂R (where R is -CH₃, -CH₂CH₃, 1-pyrrolidine, -NH-*tert*-butyl or -N(CH₃)₂);

10 and where R⁶ is not hydrogen then

R⁴ is -OCH₃, -OCH₂CH₃, -OCH₂CH₂F, -OCH₂CH₂OCH₃, or -OCH(CH₃)₂;

R⁵ is hydrogen, -Cl, -OCH₃, *tert*-butyl or -N(CH₃)₂;

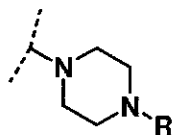
R⁶ is -Cl, cyclopropyl, -SO₂R (where R is -CH₃, -CH₂CH₃, 1-pyrrolidine, -NH-*tert*-butyl, -NH₂, or -N(CH₃)₂);

15

and R⁷ is selected from the group consisting of

- i) -CH₃, -CH(CH₃)₂, -CH₂CH(CH₃)₂, cyclopropyl, cyclobutyl, -CH₂CH₂Ph, 2-furanyl, phenyl, or phenyl substituted by chloro, -OCH₃ or cyano,
- 20 ii) 4-morpholinyl, 1-piperidinyl, 4-thiomorpholinyl, or 4-thiomorpholinyl-1,1-dioxide,
- iii) -NR^c₂ (wherein R^c is hydrogen, -CH₃, -CH₂CH₃, -CH₂CH₂OH, -CH₂CH₂OCH₃, or -CH₂CH(OH)CH₂OH),

25 iv) a substituted piperazine of the formula



wherein R is selected from the group consisting of

- 30 a) hydrogen,
- b) lower alkyl,
- c) -CH(CH₃)₂,

- d) $-\text{CH}(\text{CH}_2\text{CH}_3)_2$,
 e) cyclopentyl,
 f) $-\text{CH}_2\text{CH}(\text{OH})\text{CH}_3$,
 5 g) $-\text{CH}_2\text{CF}_3$,
 h) $-\text{CH}_2\text{CH}(\text{OH})\text{CF}_3$,
 i) $-\text{CH}_2\text{C}(\text{CH}_3)_2\text{OH}$,
 j) $-\text{CH}_2$ -[4-N-methylpiperidiny],
- 10 k) $-\text{CH}_2\text{CH}_2\text{R}^d$ (wherein R^d is $-\text{OH}$, $-\text{OCH}_3$, $-\text{OCH}_2\text{CH}_2\text{OH}$, $-\text{OCH}_2\text{CH}_2\text{OCH}_3$, $-\text{CN}$, $-\text{CF}_3$, $-\text{SO}_2\text{CH}_3$, $-\text{SO}_2\text{NH}_2$, $-\text{SO}_2\text{N}(\text{CH}_3)_2$, $-\text{CONH}_2$, $-\text{CON}(\text{CH}_3)_2$, $-\text{NH}_2$, $-\text{NHCOCH}_3$, $-\text{NHSO}_2\text{CH}_3$, $-\text{N}(\text{CH}_3)_2$, $-\text{N}(\text{CH}_2\text{CH}_3)_2$, $-\text{N}(\text{CH}_2\text{CH}_2\text{CH}_3)_2$, 1-pyrrolidinyl, 1-piperidinyl, 4-morpholinyl, 2-isothiazolidinyl-1,1-dioxide, or 2-tetrahydrofuran),
- 15 l) $-\text{CH}_2\text{CH}_2\text{CH}_2\text{R}^e$ (wherein R^e is $-\text{OH}$, $-\text{OCH}_3$, $-\text{SO}_2\text{CH}_3$, $-\text{SO}_2\text{CH}_2\text{CH}_3$, $-\text{SO}_2\text{N}(\text{CH}_3)_2$, $-\text{CN}$, $-\text{N}(\text{CH}_3)_2$, $-\text{N}(\text{CH}_2\text{CH}_2\text{CH}_3)_2$, 1-imidazolyl, 1-pyrrolidinyl, 1-piperidinyl, 4-morpholinyl, $-\text{COOCH}_3$, $-\text{COOCH}_2\text{CH}_3$, $-\text{COOC}(\text{CH}_3)_3$, $-\text{CON}(\text{CH}_3)_2$, $-\text{CO-R}^f$ (wherein R^f is $-\text{CH}_3$, $-\text{CH}_2\text{CH}_3$, cyclopropyl, phenyl, 2-thienyl, 3-thienyl, 2-furanyl, 3-furanyl), $-\text{COCH}_2\text{-R}^g$ (wherein R^g is H , $-\text{NHCH}_2\text{CH}_2\text{OH}$,
 20 $-\text{NHCH}_2\text{CH}_2\text{OCH}_3$, $-\text{NHCH}_2\text{CH}_2\text{N}(\text{CH}_3)_2$, 1-piperidinyl, 1-(piperidinyl-4-methanol), 4-morpholinyl, or $-\text{N}(\text{CH}_3)$ -(3-(1-methylpyrrolidinyl))),
- m) $-\text{CH}_2\text{-CO-R}^h$ (wherein R^h is $-\text{OCH}_3$, $-\text{OCH}_2\text{CH}_3$, $-\text{NH}_2$, $-\text{NHCH}_2\text{CH}(\text{CH}_3)_2$, $-\text{NHCH}_2\text{CF}_3$, $-\text{NH-cyclopropyl}$, $-\text{NH-tert-butyl}$, $-\text{NHCH}_2\text{CH}_2\text{CH}_2\text{OH}$, $-\text{N}(\text{CH}_3)_2$,
 25 $-\text{N}(\text{CH}_2\text{CH}_3)_2$, $-\text{N}(\text{CH}_2\text{CH}_2\text{OH})_2$, $-\text{N}(\text{CH}_2\text{CH}_2\text{OCH}_3)_2$, $-\text{N}(\text{CH}_3)\text{CH}_2\text{CH}_2\text{OH}$, $-\text{N}(\text{CH}_3)\text{CH}_2\text{CH}_2\text{OCH}_3$, $-\text{NHCH}_2\text{CH}_2\text{OCH}_3$, 1-pyrrolidinyl, 1-piperidinyl, 1-(piperidinyl-4-methanol), 1-(piperidinyl-3-carboxamide), 4-morpholinyl, 4-thiomorpholinyl, 4-thiomorpholinyl-1,1-dioxide, 1-piperazinyl, 1-(4-acetylpiperazinyl), 1-(3-oxopiperazinyl),
 30
- n) $-\text{SO}_2\text{R}^i$ (wherein R^i is $-\text{CH}_3$, $-\text{CH}_2\text{CH}_3$, $-\text{CH}(\text{CH}_3)_2$, phenyl, 4-methylphenyl, 4-propylphenyl, $-\text{CF}_3$, 2-thienyl, 3-thienyl, $-\text{NH}_2$, $-\text{NHCH}_3$, $-\text{N}(\text{CH}_3)_2$, $-\text{NHCH}_2\text{CH}_2\text{OCH}_3$, $-\text{N}(\text{CH}_2\text{CH}_2\text{OCH}_3)_2$, 1-pyrrolidinyl, 1-piperidinyl, 4-morpholinyl, 1-piperazyl-4-ethanol, 1-(4-acetylpiperazinyl), 1-(3-oxopiperazinyl)),

o) -COR^j (wherein R^j is -CH₃, -CH₂CH₃, -CH(CH₃)₂, 2-tetrahydrofuranyl, 2-thienyl, 3-thienyl, -NH₂, -NHCH₃, -N(CH₃)₂, 1-pyrrolidinyl, 1-piperidinyl, 4-morpholinyl, 1-piperazinyl-4-ethanol, 1-(4-acetylpiperazinyl), or 1-(3-oxopiperazinyl)),

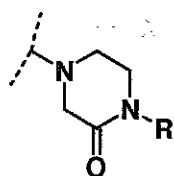
p) 4-tetrahydro-2H-thiopyranyl-1,1-dioxide,

q) 4-piperidinyl-1-acetyl,

r) 4-piperidinyl-1-dimethylcarboxamide, and

s) 3-tetrahydro-thiophenyl-1,1-dioxide;

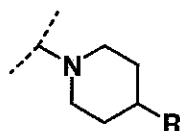
v) a substituted oxopiperazine of the formula



wherein R is -H, -CH₃, -CH₂CH₃, -CH₂CH₂CH₃, -CH₂CH₂OH, or -CH₂CH₂OCH₃;

and

vi) a substituted piperidine of the formula



wherein R is -H, -COOCH₃, -COOCH₂CH₃, -CONH₂, -OH, -CH₂OH, -CH₂CH₂OH, -CH₂-N(CH₂CH₃)₂, -CH₂-(1-piperazinyl), -CH₂-(1-(3-oxopiperazinyl)), -NH₂, -NHCOCH₃, -NHCOCH₂NH₂, -NHCOCH₂NHCH₃, -NHCOCH₂N(CH₃)₂, -NHCOCH₂N(CH₂CH₂OH)₂, -NHCOCH₂N(CH₂CH₂OCH₃)₂, -NHCOCH₂NHCH₂CH₂OH, -NHCOCH₂-(1-(4-acetylpiperazinyl)), -NHCOCH₂-(1-(3-oxopiperazinyl)), -NHCOCH₂-(1-piperidinecarboxamide), -NHCOCH₂-(N,N-diethyl-1-piperidinylcarboxamide), -NHCOCH₂-(1-(3-hydroxypiperidinyl)), -NHCOCH₂-(1-(piperidinyl-4-methanol)), -NHCON(CH₃)₂, -NHCSNHCH₃,

-NHCSNHPH, -NHCH₂CONH₂, 1-pyrrolidinyl, 1-piperidinyl, 1-(4-methylpiperazinyl), or 4-morpholinyl;

and the pharmaceutically acceptable salts and esters thereof.

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More preferred compounds are those wherein X₁ and X₂ are -Cl.

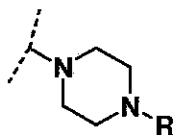
More preferred compounds are those wherein R³ is -C(=O)-R⁷.

- 10 More preferred compounds are those wherein R⁶ is hydrogen; R⁴ is -OCH₃, -OCH₂CH₃, or -OCH(CH₃)₂; and R⁵ is -C(CH₃)₃, -C(CH₃)₂OR (where R is -H or -CH₃), -C(CH₃)₂CH-OR (where R is -H or -CH₃), -C(CH₃)₂CN, -C(CH₃)₂COR (where R is -CH₃), -SO₂R (where R is -CH₃, 1-pyrrolidine, -NH-*tert*-butyl or N(CH₃)₂).

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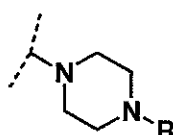
Also preferred compounds are those wherein R⁴ is -OCH₃, -OCH₂CH₃, or -OCH(CH₃)₂; R⁵ is -Cl; and R⁶ is -SO₂R (where R is -CH₃, 1-pyrrolidine, -NH-*tert*-butyl, -NH₂, or -N(CH₃)₂).

20

More preferred compounds are those wherein R⁷ is  wherein R is -CH₂COR^h.

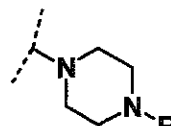
Yet more preferred compounds are those where R^h is 4-morpholinyl,

- 25 1-pyrrolidinyl, 1-piperidinyl, -NH₂, or -N(CH₃)₂.

More preferred compounds are those wherein R⁷ is  wherein R is -CH₂CH₂CH₂R^e.

Yet more preferred compounds are those wherein R^e is $-\text{SO}_2\text{CH}_3$ or $-\text{SO}_2\text{CH}_2\text{CH}_3$.

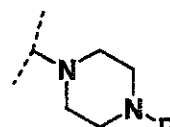
5 More preferred compounds are those wherein R^7 is $-\text{CH}_2\text{CH}_2\text{R}^d$.



wherein R is

Yet more preferred compounds are those wherein R^d is $-\text{SO}_2\text{CH}_3$, $-\text{NHSO}_2\text{CH}_3$, $-\text{NHCOCH}_3$, or $-\text{CF}_3$.

10 More preferred compounds are those wherein R^7 is 4-tetrahydro-2H-thiopyranyl-1,1-dioxide.



wherein R is

As a further embodiment of the disclosure there are provided the compounds of formula I, wherein

15 X_1 and X_2 are $-\text{Cl}$;

R^1 and R^2 are selected from the group consisting of $-\text{H}$, $-\text{CH}_3$, $-\text{CH}_2\text{CH}_3$, $-\text{CH}_2\text{OH}$ and $-\text{CH}_2\text{OCH}_3$ with the proviso that R^1 and R^2 are not both hydrogen;

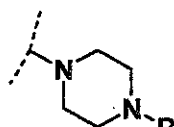
R^3 is $-\text{C}(\text{O})-\text{R}^7$;

20 R^4 is $-\text{OCH}_3$, $-\text{OCH}_2\text{CH}_3$, or $-\text{OCH}(\text{CH}_3)_2$;

R^5 is $-\text{C}(\text{CH}_3)_3$, $-\text{C}(\text{CH}_3)_2\text{OR}$ (where R is $-\text{H}$ or $-\text{CH}_3$), $-\text{C}(\text{CH}_3)_2\text{CH-OR}$ (where R is $-\text{H}$ or $-\text{CH}_3$), $-\text{C}(\text{CH}_3)_2\text{CN}$, $-\text{C}(\text{CH}_3)_2\text{COR}$ (where R is $-\text{CH}_3$), $-\text{SO}_2\text{R}$ (where R is $-\text{CH}_3$, 1-pyrrolidine, $-\text{NH-tert-butyl}$ or $-\text{N}(\text{CH}_3)_2$);

25 R^6 is hydrogen;

R^7 is is $-\text{CHCOR}^h$;



R^h is 4-morpholinyl, 1-pyrrolidinyl, 1-piperidinyl, $-NH_2$, or $-N(CH_3)_2$; and pharmaceutically acceptable salts and esters thereof.

5 As yet another embodiment of the disclosure there are provided the compounds of formula I, wherein

X_1 and X_2 are $-Cl$;

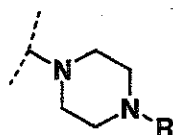
R^1 and R^2 are selected from the group consisting of $-H$, $-CH_3$, $-CH_2CH_3$, $-CH_2OH$ and $-CH_2OCH_3$ with the proviso that R^1 and R^2 are not both hydrogen;

R^3 is $-C(O)-R^7$;

R^4 is $-OCH_3$, $-OCH_2CH_3$, or $-OCH(CH_3)_2$;

R^5 is $-C(CH_3)_3$, $-C(CH_3)_2OR$ (where R is $-H$ or $-CH_3$), $-C(CH_3)_2CH-OR$ (where R is $-H$ or $-CH_3$), $-C(CH_3)_2CN$, $-C(CH_3)_2COR$ (where R is $-CH_3$), $-SO_2R$ (where R is $-CH_3$, 1-pyrrolidine, $-NH$ -*tert*-butyl or $-N(CH_3)_2$);

R^6 is hydrogen;

R^7 is is  (wherein R is $-CH_2CH_2CH_2R^e$);

R^e is $-SO_2CH_3$ or $-SO_2CH_2CH_3$; and

pharmaceutically acceptable salts and esters thereof.

As yet another embodiment of the disclosure there are provided the compounds of formula I, wherein

X_1 and X_2 are $-Cl$;

R^1 and R^2 are selected from the group consisting of $-H$, $-CH_3$, $-CH_2CH_3$, $-CH_2OH$ and $-CH_2OCH_3$ with the proviso that R^1 and R^2 are not both hydrogen;

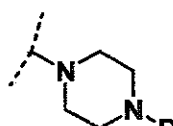
R^3 is $-C(O)-R^7$;

R^4 is $-OCH_3$, $-OCH_2CH_3$, or $-OCH(CH_3)_2$;

R^5 is $-C(CH_3)_3$, $-C(CH_3)_2OR$ (where R is $-H$ or $-CH_3$), $-C(CH_3)_2CH-OR$ (where R is $-H$ or $-CH_3$), $-C(CH_3)_2CN$, $-C(CH_3)_2COR$ (where

R is -CH₃), -SO₂R (where R is -CH₃, 1-pyrrolidine, -NH-*tert*-butyl or -N(CH₃)₂);

R⁶ is hydrogen;

R⁷ is  (wherein R is -CH₂CH₂R^d);

5 R^d is -SO₂CH₃, -NHSO₂CH₃, -NHCOCH₃, or -CF₃; and

pharmaceutically acceptable salts and esters thereof.

10 As yet another embodiment of the disclosure there are provided the compounds of formula I, wherein

X₁ and X₂ are -Cl;

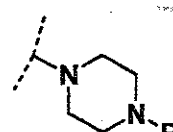
R¹ and R² are selected from the group consisting of -H, -CH₃, -CH₂CH₃, -CH₂OH and -CH₂OCH₃ with the proviso that R¹ and R² are not both hydrogen;

15 R³ is -C(O)-R⁷;

R⁴ is -OCH₃, -OCH₂CH₃, or -OCH(CH₃)₂;

R⁵ is -Cl;

R⁶ is -SO₂R (wherein R is -CH₃, 1-pyrrolidine, -NH-*tert*-butyl, -NH₂, or -N(CH₃)₂);

20 R⁷ is  (wherein R is -CHCOR^h);

R^h is 4-morpholinyl, 1-pyrrolidinyl, 1-piperidinyl, -NH₂, or -N(CH₃)₂;

and

pharmaceutically acceptable salts and esters thereof.

25 As yet another embodiment of the disclosure there are provided the compounds of formula I, wherein

X₁ and X₂ are -Cl;

R¹ and R² are selected from the group consisting of -H, -CH₃, -CH₂CH₃,

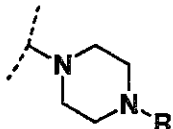
-CH₂OH and -CH₂OCH₃ with the proviso that R¹ and R² are not both hydrogen;

R³ is -C(O)-R⁷;

R⁴ is -OCH₃, -OCH₂CH₃, or -OCH(CH₃)₂;

5 R⁵ is -Cl;

R⁶ is -SO₂R (wherein R is -CH₃, 1-pyrrolidine, -NH-*tert*-butyl, -NH₂, or -N(CH₃)₂);

R⁷ is  (wherein R is -CH₂CH₂CH₂R^e);

R^e is -SO₂CH₃ or -SO₂CH₂CH₃; and

10

pharmaceutically acceptable salts and esters thereof.

As still another embodiment of the disclosure there are provided the compounds of formula I, wherein

15 X₁ and X₂ are -Cl;

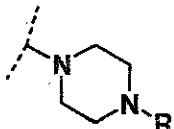
R¹ and R² are selected from the group consisting of -H, -CH₃, -CH₂CH₃, -CH₂OH and -CH₂OCH₃ with the proviso that R¹ and R² are not both hydrogen;

R³ is -C(O)-R⁷;

20 R⁴ is -OCH₃, -OCH₂CH₃, or -OCH(CH₃)₂;

R⁵ is -Cl;

R⁶ is -SO₂R (wherein R is -CH₃, 1-pyrrolidine, -NH-*tert*-butyl, -NH₂, or -N(CH₃)₂);

R⁷ is  (wherein R is -CH₂CH₂R^d);

25 R^d is -SO₂CH₃, -NHSO₂CH₃, -NHCOCH₃, or -CF₃; and

pharmaceutically acceptable salts and esters thereof.

Especially preferred compounds are from the group consisting of:

- 5 *rac*-(4S*,5R*)-4,5-Bis(4-chlorophenyl)-2-(4-(*tert*-butyl)-2-ethoxy-phenyl)-4,5-dimethyl-4,5-dihydro-1H-imidazole,
- (4S, 5R)-4,5-Bis(4-chlorophenyl)-2-(4-(*tert*-butyl)-2-ethoxy-phenyl)-4,5-dimethyl-4,5-dihydro-1H-imidazole-1-carbonyl chloride,
- (4S, 5R)-4-[[4-[[4,5-Bis(4-chlorophenyl)-2-[4-(*tert*-butyl)-2-ethoxy-phenyl]-4,5-dimethyl-4,5-dihydro-1H-imidazol-1-yl]carbonyl]-1-piperazinyl]acetyl]-morpholine,
- 10 (4S, 5R)-4-[[4-[[4,5-bis(4-chlorophenyl)-2-[4-(*tert*-butyl)-2-ethoxy-phenyl]-4,5-dimethyl-4,5-dihydro-1H-imidazol-1-yl]carbonyl]-1-piperidine,
- (4S, 5R)-1-[[4-[[4,5-bis(4-chlorophenyl)-2-[4-(*tert*-butyl)-2-ethoxy-phenyl]-4,5-dimethyl-4,5-dihydro-1H-imidazol-1-yl]]-carbonyl]-4-[3-(methylsulfonyl)propyl]-piperazine,
- 15 (4S, 5R)-1-[[4-[[4,5-bis(4-chlorophenyl)-2-[4-(*tert*-butyl)-2-ethoxy-phenyl]-4,5-dimethyl-4,5-dihydro-1H-imidazol-1-yl]]-carbonyl]-4-[3,3,3-trifluoropropyl]-piperazine,
- 2-4-[(4S,5R)-2-(4-*tert*-Butyl-2-ethoxy-phenyl)-4,5-bis-(4-chloro-phenyl)-4,5-dimethyl-4,5-dihydro-imidazole-1-carbonyl]-piperazin-1-yl}-acetamide,
- 20 2-4-[(4S,5R)-2-(4-*tert*-Butyl-2-ethoxy-phenyl)-4,5-bis-(4-chloro-phenyl)-4,5-dimethyl-4,5-dihydro-imidazole-1-carbonyl]-piperazin-1-yl}-1-pyrrolidin-1-yl-ethanone,
- N-(2-{4-[(4S,5R)-2-(4-*tert*-Butyl-2-ethoxy-phenyl)-4,5-bis-(4-chloro-phenyl)-4,5-dimethyl-4,5-dihydro-imidazole-1-carbonyl]-piperazin-1-yl}-ethyl)-acetamide,
- 25 N-(2-{4-[(4S,5R)-2-(4-*tert*-Butyl-2-ethoxy-phenyl)-4,5-bis-(4-chloro-phenyl)-4,5-dimethyl-4,5-dihydro-imidazole-1-carbonyl]-piperazin-1-yl}-ethyl)-methanesulfonamide,
- [(4S,5R)-2-(4-*tert*-Butyl-2-ethoxy-phenyl)-4,5-bis-(4-chloro-phenyl)-4,5-dimethyl-4,5-dihydro-imidazol-1-yl]-[4-(2-hydroxy-ethyl)-piperazin-1-yl]-methanone,

(S)-4-[(4S,5R)-2-(4-*tert*-Butyl-2-ethoxy-phenyl)-4,5-bis-(4-chloro-phenyl)-4,5-dimethyl-4,5-dihydro-imidazole-1-carbonyl]-1-methyl-piperazine-2-carboxylic acid methyl ester,

5 5-[(4S,5R)-4,5-Bis-(4-chloro-phenyl)-1-[4-(3-methanesulfonyl-propyl)-piperazine-1-carbonyl]-4,5-dimethyl-4,5-dihydro-1H-imidazol-2-yl]-2-*tert*-butyl-4-ethoxy-N,N-dimethyl-benzenesulfonamide,

rac-2-{4-[(4S*,5R*)-4,5-Bis-(4-chloro-phenyl)-4,5-dimethyl-4,5-dihydro-1H-imidazol-2-yl]-3-ethoxy-phenyl}-2-methyl-propionitrile,

10 2-(4-{(4S,5R)-4,5-Bis-(4-chloro-phenyl)-1-[4-(3-methanesulfonyl-propyl)-piperazine-1-carbonyl]-4,5-dimethyl-4,5-dihydro-1H-imidazol-2-yl}-3-ethoxy-phenyl)-2-methyl-propionitrile,

N-[2-(4-{(4S,5R)-4,5-Bis-(4-chloro-phenyl)-2-[4-(cyano-dimethyl-methyl)-2-ethoxy-phenyl]-4,5-dimethyl-4,5-dihydro-imidazole-1-carbonyl]-piperazin-1-yl)-ethyl]-methanesulfonamide,

15 N-[2-(4-{(4S,5R)-4,5-Bis-(4-chloro-phenyl)-2-[4-(cyano-dimethyl-methyl)-2-ethoxy-phenyl]-4,5-dimethyl-4,5-dihydro-imidazole-1-carbonyl]-piperazin-1-yl)-ethyl]-acetamide,

20 2-(4-{(4S,5R)-4,5-Bis-(4-chloro-phenyl)-1-[4-(2-hydroxy-ethyl)-piperazine-1-carbonyl]-4,5-dimethyl-4,5-dihydro-1H-imidazol-2-yl}-3-ethoxy-phenyl)-2-methyl-propionitrile,

2-(4-{(4S,5R)-4,5-Bis-(4-chloro-phenyl)-1-[4-(1,1-dioxo-tetrahydro-2H-thiopyran-4-yl)-piperazine-1-carbonyl]-4,5-dimethyl-4,5-dihydro-1H-imidazol-2-yl}-3-ethoxy-phenyl)-2-methyl-propionitrile,

25 2-(4-{(4S,5R)-4,5-Bis-(4-chloro-phenyl)-2-[4-(cyano-dimethyl-methyl)-2-ethoxy-phenyl]-4,5-dimethyl-4,5-dihydro-imidazole-1-carbonyl]-piperazin-1-yl)-acetamide,

2-[4-((4S,5R)-4,5-Bis-(4-chloro-phenyl)-1-[4-[2-(1,1-dioxo-isothiazolidin-2-yl)-ethyl]-piperazine-1-carbonyl]-4,5-dimethyl-4,5-dihydro-1H-imidazol-2-yl)-3-ethoxy-phenyl]-2-methyl-propionitrile,

30 2-(4-{(4S,5R)-4,5-Bis-(4-chloro-phenyl)-4,5-dimethyl-1-[4-(2-oxo-2-pyrrolidin-1-yl-ethyl)-piperazine-1-carbonyl]-4,5-dihydro-1H-imidazol-2-yl}-3-ethoxy-phenyl)-2-methyl-propionitrile,

2-{4-[(4S,5R)-1-[4-(1-Acetyl-piperidin-4-yl)-piperazine-1-carbonyl]-4,5-bis-(4-chloro-phenyl)-4,5-dimethyl-4,5-dihydro-1H-imidazol-2-yl]-3-ethoxy-phenyl}-2-methyl-propionitrile,

4-(4-{(4S,5R)-4,5-Bis-(4-chloro-phenyl)-2-[4-(cyano-dimethyl-methyl)-2-ethoxy-phenyl]-4,5-dimethyl-4,5-dihydro-imidazole-1-carbonyl}-piperazin-1-yl)-piperidine-1-carboxylic acid isopropylamide,

rac-(4S*,5R*)-4,5-Bis-(4-chloro-phenyl)-2-[2-ethoxy-4-(pyrrolidine-1-sulfonyl)-phenyl]-4,5-dimethyl-4,5-dihydro-1H-imidazole,

rac-(4S*,5R*)-4-[(4,5-Bis-(4-chloro-phenyl)-4,5-dimethyl-4,5-dihydro-1H-imidazol-2-yl)-N-*tert*-butyl-3-ethoxy-benzenesulfonamide,

{(4S,5R)-4,5-Bis-(4-chloro-phenyl)-2-[2-ethoxy-4-(pyrrolidine-1-sulfonyl)-phenyl]-4,5-dimethyl-4,5-dihydro-imidazol-1-yl}-[4-(3-methanesulfonyl-propyl)-piperazin-1-yl]-methanone,

2-(4-{(4S,5R)-4,5-Bis-(4-chloro-phenyl)-2-[2-ethoxy-4-(pyrrolidine-1-sulfonyl)-phenyl]-4,5-dimethyl-4,5-dihydro-imidazole-1-carbonyl}-piperazin-1-yl)-acetamide,

2-(4-{(4S,5R)-4,5-Bis-(4-chloro-phenyl)-2-[2-ethoxy-4-(pyrrolidine-1-sulfonyl)-phenyl]-4,5-dimethyl-4,5-dihydro-imidazole-1-carbonyl}-piperazin-1-yl)-1-pyrrolidin-1-yl-ethanone,

N-[2-(4-{(4S,5R)-4,5-Bis-(4-chloro-phenyl)-2-[2-ethoxy-4-(pyrrolidine-1-sulfonyl)-phenyl]-4,5-dimethyl-4,5-dihydro-imidazole-1-carbonyl}-piperazin-1-yl)-ethyl]-methanesulfonamide,

N-[2-(4-{(4S,5R)-4,5-Bis-(4-chloro-phenyl)-2-[2-ethoxy-4-(pyrrolidine-1-sulfonyl)-phenyl]-4,5-dimethyl-4,5-dihydro-imidazole-1-carbonyl}-piperazin-1-yl)-ethyl]-acetamide,

{(4S,5R)-4,5-Bis-(4-chloro-phenyl)-2-[2-ethoxy-4-(pyrrolidine-1-sulfonyl)-phenyl]-4,5-dimethyl-4,5-dihydro-imidazol-1-yl}-[4-(2-hydroxy-ethyl)-piperazin-1-yl]-methanone,

4-{(4S,5R)-4,5-Bis-(4-chloro-phenyl)-1-[4-(3-methanesulfonyl-propyl)-piperazine-1-carbonyl]-4,5-dimethyl-4,5-dihydro-1H-imidazol-2-yl}-N-*tert*-butyl-3-ethoxy-benzenesulfonamide,

- 2-{4-[(4S,5R)-2-(4-*tert*-Butylsulfamoyl-2-ethoxy-phenyl)-4,5-bis-(4-chloro-phenyl)-4,5-dimethyl-4,5-dihydro-imidazole-1-carbonyl]-piperazin-1-yl}-acetamide,
rac-(4S*,5R*)-5-[4,5-Bis-(4-chlorophenyl)-4,5-dimethyl-4,5-dihydro-1H-imidazol-2-yl]-N-*tert*-butyl-2-chloro-4-ethoxybenzenesulfonamide,
- 5 5-{(4S,5R)-4,5-Bis-(4-chloro-phenyl)-1-[4-(3-methanesulfonyl-propyl)-piperazine-1-carbonyl]-4,5-dimethyl-4,5-dihydro-1H-imidazol-2-yl}-N-*tert*-butyl-2-chloro-4-ethoxy-benzenesulfonamide,
 5-{(4S,5R)-4,5-Bis-(4-chlorophenyl)-1-[4-(2-methanesulfonylaminoethyl)piperazine-1-carbonyl]-4,5-dimethyl-4,5-dihydro-1H-imidazol-2-yl}-N-*tert*-butyl-2-chloro-4-ethoxybenzenesulfonamide,
- 10 N-{(4S,5R)-(2-{4-[2-(5-*tert*-Butylsulfamoyl-4-chloro-2-ethoxyphenyl)-4,5-bis-(4-chlorophenyl)-4,5-dimethyl-4,5-dihydroimidazole-1-carbonyl]-piperazin-1-yl}ethyl)acetamide,
 5-{(4S,5R)-4,5-Bis-(4-chlorophenyl)-1-[4-(2-hydroxyethyl)piperazine-1-carbonyl]-4,5-dimethyl-4,5-dihydro-1H-imidazol-2-yl}-N-*tert*-butyl-2-chloro-4-ethoxybenzenesulfonamide,
- 15 5-{(4S,5R)-4,5-Bis-(4-chlorophenyl)-4,5-dimethyl-1-[4-(2-oxo-2-pyrrolidin-1-ylethyl)-piperazine-1-carbonyl]-4,5-dihydro-1H-imidazol-2-yl}-N-*tert*-butyl-2-chloro-4-ethoxybenzenesulfonamide,
- 20 2-{4-[(4S,5R)-2-(5-*tert*-Butylsulfamoyl-4-chloro-2-ethoxyphenyl)-4,5-bis-(4-chlorophenyl)-4,5-dimethyl-4,5-dihydroimidazole-1-carbonyl]-piperazin-1-yl}-acetamide,
 (S)-4-[(4S,5R)-2-(5-*tert*-Butylsulfamoyl-4-chloro-2-ethoxyphenyl)-4,5-bis-(4-chlorophenyl)-4,5-dimethyl-4,5-dihydroimidazole-1-carbonyl]-1-methylpiperazine-2-carboxylic acid methyl ester,
- 25 *rac*-(4S*,5R*)-2-[4-Chloro-2-ethoxy-5-(pyrrolidine-1-sulfonyl)phenyl]-4,5-bis-(4-chlorophenyl)-4,5-dimethyl-4,5-dihydro-1H-imidazole,
 5-{(4S,5R)-2-[4-Chloro-2-ethoxy-5-(pyrrolidine-1-sulfonyl)phenyl]-4,5-bis-(4-chloro-phenyl)-4,5-dimethyl-4,5-dihydroimidazol-1-yl}-[4-(3-methanesulfonylpropyl)-piperazin-1-yl]methanone,
- 30

rac-(4S*,5R*)-4,5-Bis-(4-chlorophenyl)-2-[2-ethoxy-4-methoxy-5-(pyrrolidine-1-sulfonyl)phenyl]-4,5-dimethyl-4,5-dihydro-1H-imidazole,

{(4S,5R)-4,5-Bis-(4-chlorophenyl)-2-[2-ethoxy-4-methoxy-5-(pyrrolidine-1-sulfonyl)-phenyl]-4,5-dimethyl-4,5-dihydroimidazol-1-yl}-[4-(3-

5 methanesulfonylpropyl)-piperazin-1-yl]methanone,

rac-(4S*,5R*)-2-(4-Chloro-2-ethoxy-5-methanesulfonylphenyl)-4,5-bis-(4-chlorophenyl)-4,5-dimethyl-4,5-dihydro-1H-imidazole,

[(4S,5R)-2-(4-Chloro-2-ethoxy-5-methanesulfonyl-phenyl)-4,5-bis-(4-chlorophenyl)-4,5-dimethyl-4,5-dihydroimidazol-1-yl]-[4-(3-

10 methanesulfonylpropyl)-piperazin-1-yl]methanone,

rac-(4S*,5R*)-4,5-Bis-(4-chlorophenyl)-2-[2-ethoxy-5-(pyrrolidine-1-sulfonyl)phenyl]-4,5-dimethyl-4,5-dihydro-1H-imidazole,

{(4S,5R)-4,5-Bis-(4-chlorophenyl)-2-[2-ethoxy-5-(pyrrolidine-1-sulfonyl)phenyl]-4,5-dimethyl-4,5-dihydroimidazol-1-yl}-[4-(3-methanesulfonylpropyl)-piperazin-1-

15 yl]methanone,

rac-4-[(4S*,5R*)-4,5-Bis-(4-chloro-phenyl)-4,5-dimethyl-4,5-dihydro-1H-imidazol-2-yl]-3-ethoxy-benzonitrile,

4-[(4S,5R)-4,5-Bis-(4-chlorophenyl)-1-[4-(3-methanesulfonylpropyl)-piperazine-1-carbonyl]-4,5-dimethyl-4,5-dihydro-1H-imidazol-2-yl]-3-ethoxybenzonitrile,

20 [(4S,5R)-2-(4-tert-Butyl-2-ethoxy-phenyl)-4,5-bis-(4-chloro-phenyl)-4,5-dimethyl-4,5-dihydro-imidazol-1-yl]-piperazin-1-yl-methanone,

1-[4-[(4S,5R)-2-(4-tert-Butyl-2-ethoxy-phenyl)-4,5-bis-(4-chloro-phenyl)-4,5-dimethyl-4,5-dihydro-imidazole-1-carbonyl]-piperazin-1-yl]-ethanone ,

25 N-tert-Butyl-2-[4-[(4S,5R)-2-(4-tert-butyl-2-ethoxy-phenyl)-4,5-bis-(4-chloro-phenyl)-4,5-dimethyl-4,5-dihydro-imidazole-1-carbonyl]-piperazin-1-yl]-acetamide,

rac-(4S*,5R*)-2-(4-Bromo-2-ethoxy-phenyl)-4,5-bis-(4-chloro-phenyl)-4,5-dimethyl-4,5-dihydro-1H-imidazole,

rac-(4S*,5R*)-2-(4-Bromo-2-ethoxy-phenyl)-4,5-bis-(4-chloro-phenyl)-4,5-dimethyl-4,5-dihydro-imidazol-1-yl]-[4-(3-methanesulfonyl-propyl)-piperazin-1-yl]-

30 methanone,

rac-2-{4-[(4S*,5R*)-4,5-Bis-(4-chloro-phenyl)-4,5-dimethyl-4,5-dihydro-1*H*-imidazol-2-yl]-3-ethoxy-phenyl}-propan-2-ol,

[(4S,5R)-4,5-Bis-(4-chloro-phenyl)-2-(2-ethoxy-phenyl)-4,5-dimethyl-4,5-dihydro-imidazol-1-yl]-[4-(3-methanesulfonyl-propyl)-piperazin-1-yl]-methanone,

5 2-{4-[(4S,5R)-4,5-Bis-(4-chloro-phenyl)-2-(2-ethoxy-phenyl)-4,5-dimethyl-4,5-dihydro-imidazole-1-carbonyl]-piperazin-1-yl}-acetamide,

{(4S,5R)-4,5-Bis-(4-chloro-phenyl)-2-[2-ethoxy-4-(1-hydroxy-1-methyl-ethyl)-phenyl]-4,5-dimethyl-4,5-dihydro-imidazol-1-yl}-[4-(3-methanesulfonyl-propyl)-piperazin-1-yl]-methanone,

10 2-(4-{(4S,5R)-4,5-Bis-(4-chloro-phenyl)-2-[2-ethoxy-4-(1-hydroxy-1-methyl-ethyl)-phenyl]-4,5-dimethyl-4,5-dihydro-imidazole-1-carbonyl}-piperazin-1-yl)-acetamide,

{(4S,5R)-4,5-Bis-(4-chloro-phenyl)-2-[2-ethoxy-4-(1-hydroxy-1-methyl-ethyl)-phenyl]-4,5-dimethyl-4,5-dihydro-imidazol-1-yl}-[4-(2-hydroxy-ethyl)-piperazin-1-yl]-methanone ,

2-(4-{(4S,5R)-4,5-Bis-(4-chloro-phenyl)-2-[2-ethoxy-4-(1-hydroxy-1-methyl-ethyl)-phenyl]-4,5-dimethyl-4,5-dihydro-imidazole-1-carbonyl}-piperazin-1-yl)-1-pyrrolidin-1-yl-ethanone,

20 N-[2-(4-{(4S,5R)-4,5-Bis-(4-chloro-phenyl)-2-[2-ethoxy-4-(1-hydroxy-1-methyl-ethyl)-phenyl]-4,5-dimethyl-4,5-dihydro-imidazole-1-carbonyl}-piperazin-1-yl)-ethyl]-acetamide,

N-[2-(4-{(4S,5R)-4,5-Bis-(4-chloro-phenyl)-2-[2-ethoxy-4-(1-hydroxy-1-methyl-ethyl)-phenyl]-4,5-dimethyl-4,5-dihydro-imidazole-1-carbonyl}-piperazin-1-yl)-ethyl]-methanesulfonamide,

25 {(4S,5R)-4,5-Bis-(4-chloro-phenyl)-2-[2-ethoxy-4-(1-hydroxy-1-methyl-ethyl)-phenyl]-4,5-dimethyl-4,5-dihydro-imidazol-1-yl}-[4-(1,1-dioxo-tetrahydro-2*H*-thiopyran-4-yl)-piperazin-1-yl]-methanone,

rac-(4S*,5R*)-4,5-Bis-(4-chloro-phenyl)-2-(2-isopropoxy-4-methoxy-phenyl)-4,5-dimethyl-4,5-dihydro-1*H*-imidazole,

rac-(4S*,5R*)-4,5-Bis-(4-chloro-phenyl)-2-(2-isopropoxy-4-methoxy-phenyl)-4,5-dimethyl-4,5-dihydro-imidazol-1-yl]-[4-(3-methanesulfonyl-propyl)-piperazin-1-yl]-methanone,

5 *rac*-2-[4-[(4S*,5R*)-4,5-Bis-(4-chloro-phenyl)-2-(2-isopropoxy-4-methoxy-phenyl)-4,5-dimethyl-4,5-dihydro-imidazole-1-carbonyl]-piperazin-1-yl]-acetamide,

rac-2-[4-[(4S*,5R*)-4,5-Bis-(4-chloro-phenyl)-2-(2-isopropoxy-4-methoxy-phenyl)-4,5-dimethyl-4,5-dihydro-imidazole-1-carbonyl]-piperazin-1-yl]-1-morpholin-4-yl-ethanone,

10 *rac*-4-[(4S*,5R*)-4,5-Bis-(4-chloro-phenyl)-2-(2-isopropoxy-4-methoxy-phenyl)-4,5-dimethyl-4,5-dihydro-imidazole-1-carbonyl]-piperazin-2-one,

rac-[(4S*,5R*)-4,5-Bis-(4-chloro-phenyl)-2-(2-isopropoxy-4-methoxy-phenyl)-4,5-dimethyl-4,5-dihydro-imidazol-1-yl]-[4-(2-methanesulfonyl-ethyl)-piperazin-1-yl]-methanone,

15 *rac*-(4S*,5R*)-4,5-Bis-(4-chloro-phenyl)-2-[2-ethoxy-4-(1-methoxy-1-methyl-ethyl)-phenyl]-4,5-dimethyl-4,5-dihydro-1*H*-imidazole,

2-(4-[(4S,5R)-4,5-Bis-(4-chloro-phenyl)-2-[2-ethoxy-4-(1-methoxy-1-methyl-ethyl)-phenyl]-4,5-dimethyl-4,5-dihydro-imidazole-1-carbonyl]-piperazin-1-yl)-acetamide,

20 {*rac*-(4S*,5R*)-4,5-Bis-(4-chloro-phenyl)-2-[2-ethoxy-4-(1-methoxy-1-methyl-ethyl)-phenyl]-4,5-dimethyl-4,5-dihydro-imidazol-1-yl]-[4-(3-methanesulfonyl-propyl)-piperazin-1-yl]-methanone,

{(4S,5R)-4,5-Bis-(4-chloro-phenyl)-2-[2-ethoxy-4-(1-methoxy-1-methyl-ethyl)-phenyl]-4,5-dimethyl-4,5-dihydro-imidazol-1-yl]-[4-(1,1-dioxo-tetrahydro-2*H*-thiopyran-4-yl)-piperazin-1-yl]-methanone,

25 *rac*-1-[(4S*,5R*)-2-(4-tert-Butyl-2-ethoxy-phenyl)-4,5-bis-(4-chloro-phenyl)-4,5-dimethyl-4,5-dihydro-imidazol-1-yl]-ethanone,

1-[(4S,5R)-2-(4-tert-Butyl-2-ethoxy-phenyl)-4,5-bis-(4-chloro-phenyl)-4,5-dimethyl-4,5-dihydro-imidazol-1-yl]-2-methyl-propan-1-one,

30 [(4S,5R)-2-(4-tert-Butyl-2-ethoxy-phenyl)-4,5-bis-(4-chloro-phenyl)-4,5-dimethyl-4,5-dihydro-imidazol-1-yl]-cyclopropyl-methanone,

- [(4S,5R)-2-(4-*tert*-Butyl-2-ethoxy-phenyl)-4,5-bis-(4-chloro-phenyl)-4,5-dimethyl-4,5-dihydro-imidazol-1-yl]-cyclobutyl-methanone,
- 1-[(4S,5R)-2-(4-*tert*-Butyl-2-ethoxy-phenyl)-4,5-bis-(4-chloro-phenyl)-4,5-dimethyl-4,5-dihydro-imidazol-1-yl]-3-methyl-butan-1-one,
- 5 1-[(4S,5R)-2-(4-*tert*-Butyl-2-ethoxy-phenyl)-4,5-bis-(4-chloro-phenyl)-4,5-dimethyl-4,5-dihydro-imidazol-1-yl]-3-phenyl-propan-1-one,
- 4-[(4S,5R)-2-(4-*tert*-Butyl-2-ethoxy-phenyl)-4,5-bis-(4-chloro-phenyl)-4,5-dimethyl-4,5-dihydro-imidazole-1-carbonyl]-benzonitrile,
- 10 [(4S,5R)-2-(4-*tert*-Butyl-2-ethoxy-phenyl)-4,5-bis-(4-chloro-phenyl)-4,5-dimethyl-4,5-dihydro-imidazol-1-yl]-furan-2-yl-methanone,
- [(4S,5R)-2-(4-*tert*-Butyl-2-ethoxy-phenyl)-4,5-bis-(4-chloro-phenyl)-4,5-dimethyl-4,5-dihydro-imidazol-1-yl]-phenyl-methanone,
- rac*-[(4S*,5R*)-2-(4-*tert*-Butyl-2-ethoxy-phenyl)-4,5-bis-(4-chloro-phenyl)-4,5-dimethyl-4,5-dihydro-imidazol-1-yl]-(4-methoxy-phenyl)-methanone,
- 15 *rac*-[(4S*,5R*)-2-(4-*tert*-Butyl-2-ethoxy-phenyl)-4,5-bis-(4-chloro-phenyl)-4,5-dimethyl-4,5-dihydro-imidazol-1-yl]-(4-chloro-phenyl)-methanone,
- rac*-(4S*,5R*)-2-(4-*tert*-Butyl-5-chloro-2-ethoxy-phenyl)-4,5-bis-(4-chloro-phenyl)-4,5-dimethyl-4,5-dihydro-1*H*-imidazole,
- 20 [(4S,5R)-2-(4-*tert*-Butyl-5-chloro-2-ethoxy-phenyl)-4,5-bis-(4-chloro-phenyl)-4,5-dimethyl-4,5-dihydro-imidazol-1-yl]-[4-(3-methanesulfonyl-propyl)-piperazin-1-yl]-methanone,
- 2-{4-[(4S,5R)-2-(4-*tert*-Butyl-5-chloro-2-ethoxy-phenyl)-4,5-bis-(4-chloro-phenyl)-4,5-dimethyl-4,5-dihydro-imidazole-1-carbonyl]-piperazin-1-yl}-acetamide,
- rac*-(2-{4-[4S*,5R*)-2-(4-*tert*-Butyl-5-chloro-2-ethoxy-phenyl)-4,5-bis-(4-chloro-phenyl)-4,5-dimethyl-4,5-dihydro-imidazole-1-carbonyl]-piperazin-1-yl}-1-morpholin-4-yl)-ethanone,
- 25 *rac*-[(4S*,5R*)-2-(4-*tert*-Butyl-5-chloro-2-ethoxy-phenyl)-4,5-bis-(4-chloro-phenyl)-4,5-dimethyl-4,5-dihydro-imidazol-1-yl]-(4-dimethylamino-piperidin-1-yl)-methanone,

rac-[(4S*,5R*)-2-(4-tert-Butyl-5-chloro-2-ethoxy-phenyl)-4,5-bis-(4-chloro-phenyl)-4,5-dimethyl-4,5-dihydro-imidazol-1-yl]-(4-pyrrolidin-1-yl-piperidin-1-yl)-methanone,

5 *rac*-[1,4']Bipiperidiny-1'-yl-[(4S*,5R*)-2-(4-tert-butyl-5-chloro-2-ethoxy-phenyl)-4,5-bis-(4-chloro-phenyl)-4,5-dimethyl-4,5-dihydro-imidazol-1-yl]-methanone ,

rac-{1-[(4S*,5R*)-2-(4-tert-Butyl-5-chloro-2-ethoxy-phenyl)-4,5-bis-(4-chloro-phenyl)-4,5-dimethyl-4,5-dihydro-imidazole-1-carbonyl]-piperidin-4-yl}-carbamic acid tert-butyl ester,

10 *rac*-(4S*,5R*)-4,5-Bis-(4-chloro-phenyl)-2-(2-ethoxy-4-trifluoromethyl-phenyl)-4,5-dimethyl-4,5-dihydro-1*H*-imidazole,

rac-4-[(4S*,5R*)-4,5-Bis-(4-chloro-phenyl)-2-(2-ethoxy-4-trifluoromethyl-phenyl)-4,5-dimethyl-4,5-dihydro-imidazole-1-carbonyl]-piperazin-2-one,

rac-1-{4-[(4S*,5R*)-4,5-Bis-(4-chloro-phenyl)-2-(2-ethoxy-4-trifluoromethyl-phenyl)-4,5-dimethyl-4,5-dihydro-imidazole-1-carbonyl]-piperazin-1-yl}-ethanone,

15 [(4S,5R)-4,5-Bis-(4-chloro-phenyl)-2-(2-ethoxy-4-trifluoromethyl-phenyl)-4,5-dimethyl-4,5-dihydro-imidazol-1-yl]-[4-(3-methanesulfonyl-propyl)-piperazin-1-yl]-methanone,

20 *rac*-2-{4-[(4S*,5R*)-4,5-Bis-(4-chloro-phenyl)-2-(2-ethoxy-4-trifluoromethyl-phenyl)-4,5-dimethyl-4,5-dihydro-imidazole-1-carbonyl]-piperazin-1-yl}-1-morpholin-4-yl-ethanone,

rac-(4S*,5R*)-4,5-Bis-(4-chloro-phenyl)-2-(2-ethoxy-4-trifluoromethyl-phenyl)-4,5-dimethyl-4,5-dihydro-imidazol-1-yl]-(4-ethanesulfonyl-piperazin-1-yl)-methanone,

25 *rac*-(4S*,5R*)-4,5-Bis-(4-chloro-phenyl)-2-(2-ethoxy-4-trifluoromethyl-phenyl)-4,5-dimethyl-4,5-dihydro-imidazole-1-carboxylic acid (1-methanesulfonyl-piperidin-4-yl)-amide,

rac-[(4S*,5R*)-4,5-Bis-(4-chloro-phenyl)-2-(2-ethoxy-4-trifluoromethyl-phenyl)-4,5-dimethyl-4,5-dihydro-imidazol-1-yl]-[4-(4-methyl-piperazin-1-yl)-piperidin-1-yl]-methanone,

30 *rac*-[(4S*,5R*)-4,5-Bis-(4-chloro-phenyl)-2-(2-ethoxy-4-trifluoromethyl-phenyl)-4,5-dimethyl-4,5-dihydro-imidazol-1-yl]-(4-morpholin-4-yl-piperidin-1-yl)-methanone,

rac-[(4S*,5R*)-4,5-Bis-(4-chloro-phenyl)-2-(2-ethoxy-4-trifluoromethyl-phenyl)-4,5-dimethyl-4,5-dihydro-imidazol-1-yl]-(4-hydroxy-piperidin-1-yl)-methanone,

rac-[(4S*,5R*)-4,5-Bis-(4-chloro-phenyl)-2-(2-ethoxy-4-trifluoromethyl-phenyl)-4,5-dimethyl-4,5-dihydro-imidazol-1-yl]-(4-hydroxymethyl-piperidin-1-yl)-

5 methanone,

rac-[(4S*,5R*)-4,5-Bis-(4-chloro-phenyl)-2-(2-ethoxy-4-trifluoromethyl-phenyl)-4,5-dimethyl-4,5-dihydro-imidazol-1-yl]-[4-(2-hydroxy-ethyl)-piperidin-1-yl]-methanone,

rac-1-[(4S*,5R*)-4,5-Bis-(4-chloro-phenyl)-2-(2-ethoxy-4-trifluoromethyl-phenyl)-4,5-dimethyl-4,5-dihydro-imidazole-1-carbonyl]-piperidine-4-carboxylic acid
10 amide,

rac-(4S*,5R*)-4,5-Bis-(4-chloro-phenyl)-2-(2-ethoxy-4-trifluoromethyl-phenyl)-4,5-dimethyl-4,5-dihydro-imidazole-1-carboxylic acid bis-(2-hydroxy-ethyl)-amide,

rac-(4S*,5R*)-4,5-Bis-(4-chloro-phenyl)-2-(2-ethoxy-4-trifluoromethyl-phenyl)-4,5-
15 dimethyl-4,5-dihydro-imidazole-1-carboxylic acid (2,3-dihydroxy-propyl)-amide,
3-{4-[4,5-Bis-(4-chloro-phenyl)-4,5-dimethyl-4,5-dihydro-1H-imidazol-2-yl]-3-ethoxy-phenyl}-3-methyl-butan-2-one,

3-(4-{4,5-Bis-(4-chloro-phenyl)-1-[4-(3-methanesulfonyl-propyl)-piperazine-1-carbonyl]-4,5-dimethyl-4,5-dihydro-1H-imidazol-2-yl}-3-ethoxy-phenyl)-3-methyl-
20 butan-2-one,

3-(4-{(4S,5R)-4,5-Bis-(4-chloro-phenyl)-1-[4-(1,1-dioxo-tetrahydro-2H-thiopyran-4-yl)-piperazine-1-carbonyl]-4,5-dimethyl-4,5-dihydro-1H-imidazol-2-yl}-3-ethoxy-phenyl)-3-methyl-butan-2-one,

2-(4-{(4S,5R)-4,5-Bis-(4-chloro-phenyl)-2-[4-(1,1-dimethyl-2-oxo-propyl)-2-ethoxy-phenyl]-4,5-dimethyl-4,5-dihydro-imidazole-1-carbonyl}-piperazin-1-yl)-
25 acetamid,

rac-(4S*,5R*)-2-(4-*tert*-Butyl-2-isopropoxy-phenyl)-4,5-bis-(4-chloro-phenyl)-4,5-dimethyl-4,5-dihydro-1H-imidazole,

rac-1-{4-[(4S*,5R*)-2-(4-*tert*-Butyl-2-isopropoxy-phenyl)-4,5-bis-(4-chloro-phenyl)-4,5-dimethyl-4,5-dihydro-imidazole-1-carbonyl]-piperazin-1-yl}-ethanone,
30

rac-[(4S*,5R*)-2-(4-tert-Butyl-2-isopropoxy-phenyl)-4,5-bis-(4-chloro-phenyl)-4,5-dimethyl-4,5-dihydro-imidazol-1-yl]-(4-isopropyl-piperazin-1-yl)-methanone,

rac-4-{4-[(4S*,5R*)-2-(4-tert-Butyl-2-isopropoxy-phenyl)-4,5-bis-(4-chloro-phenyl)-4,5-dimethyl-4,5-dihydro-imidazole-1-carbonyl]-piperazin-1-yl}-

5 butyronitrile,

rac-[(4S*,5R*)-2-(4-tert-Butyl-2-isopropoxy-phenyl)-4,5-bis-(4-chloro-phenyl)-4,5-dimethyl-4,5-dihydro-imidazol-1-yl]-[4-(3-methoxy-propyl)-piperazin-1-yl]-methanone,

10 *rac*-[(4S*,5R*)-2-(4-tert-Butyl-2-isopropoxy-phenyl)-4,5-bis-(4-chloro-phenyl)-4,5-dimethyl-4,5-dihydro-imidazol-1-yl]-[4-(2-morpholin-4-yl-ethyl)-piperazin-1-yl]-methanone,

rac-[(4S*,5R*)-2-(4-tert-Butyl-2-isopropoxy-phenyl)-4,5-bis-(4-chloro-phenyl)-4,5-dimethyl-4,5-dihydro-imidazol-1-yl]-[4-(tetrahydro-furan-2-ylmethyl)-piperazin-1-yl]-methanone,

15 *rac*-[(4S*,5R*)-2-(4-tert-Butyl-2-isopropoxy-phenyl)-4,5-bis-(4-chloro-phenyl)-4,5-dimethyl-4,5-dihydro-imidazol-1-yl]-(hexahydro-pyrrolo[1,2-a]pyrazin-2-yl)-methanone,

rac-[(4S*,5R*)-2-(4-tert-Butyl-2-isopropoxy-phenyl)-4,5-bis-(4-chloro-phenyl)-4,5-dimethyl-4,5-dihydro-imidazol-1-yl]-(octahydro-pyrido[1,2-a]pyrazin-2-yl)-

20 methanone,

rac-(4S*,5R*)-2-(4-tert-Butyl-2-isopropoxy-phenyl)-4,5-bis-(4-chloro-phenyl)-4,5-dimethyl-4,5-dihydro-imidazole-1-carboxylic acid bis-(2-methoxy-ethyl)-amide,

rac-[(4S*,5R*)-2-(4-tert-Butyl-2-isopropoxy-phenyl)-4,5-bis-(4-chloro-phenyl)-4,5-dimethyl-4,5-dihydro-imidazol-1-yl]-[4-(2-methoxy-ethyl)-piperazin-1-yl]-

25 methanone,

[(4S,5R)-2-(4-tert-Butyl-2-isopropoxy-phenyl)-4,5-bis-(4-chloro-phenyl)-4,5-dimethyl-4,5-dihydro-imidazol-1-yl]-[4-(3-methanesulfonyl-propyl)-piperazin-1-yl]-methanone,

30 [(4S,5R)-4,5-Bis-(4-chloro-phenyl)-2-(2-ethoxy-4-isopropyl-phenyl)-4,5-dimethyl-4,5-dihydro-imidazol-1-yl]-[4-(3-methanesulfonyl-propyl)-piperazin-1-yl]-methanone,

- [(4S,5R)-2-(5-tert-Butyl-2-ethoxy-phenyl)-4,5-bis-(4-chloro-phenyl)-4,5-dimethyl-4,5-dihydro-imidazol-1-yl]-[4-(3-methanesulfonyl-propyl)-piperazin-1-yl]-methanone,
- 5 [(4S,5R)-4,5-Bis-(4-chloro-phenyl)-2-(2-ethoxy-5-methanesulfonyl-phenyl)-4,5-dimethyl-4,5-dihydro-imidazol-1-yl]-[4-(3-methanesulfonyl-propyl)-piperazin-1-yl]-methanone,
- [(4S,5R)-4,5-Bis-(4-chloro-phenyl)-2-(2-ethoxy-4-methanesulfonyl-phenyl)-4,5-dimethyl-4,5-dihydro-imidazol-1-yl]-[4-(3-methanesulfonyl-propyl)-piperazin-1-yl]-methanone,
- 10 [(4S,5R)-4,5-Bis-(4-chloro-phenyl)-2-(4-cyclopropyl-2-ethoxy-phenyl)-4,5-dimethyl-4,5-dihydro-imidazol-1-yl]-[4-(3-methanesulfonyl-propyl)-piperazin-1-yl]-methanone,
- [(4S,5R)-4,5-Bis-(4-chloro-phenyl)-2-(5-cyclopropyl-2-ethoxy-phenyl)-4,5-dimethyl-4,5-dihydro-imidazol-1-yl]-[4-(3-methanesulfonyl-propyl)-piperazin-1-yl]-methanone,
- 15 [(4S,5R)-4,5-Bis-(4-chloro-phenyl)-2-(4-ethanesulfonyl-2-ethoxy-phenyl)-4,5-dimethyl-4,5-dihydro-imidazol-1-yl]-[4-(3-methanesulfonyl-propyl)-piperazin-1-yl]-methanone,
- [(4S,5R)-2-(4-tert-Butyl-2-ethoxy-phenyl)-4,5-bis-(4-chloro-phenyl)-4,5-diethyl-4,5-dihydro-imidazol-1-yl]-[4-(3-methanesulfonyl-propyl)-piperazin-1-yl]-methanone,
- 20 [(4S,5R)-4,5-Bis-(4-chloro-phenyl)-2-(2-ethoxy-4-ethylsulfonyl-phenyl)-4,5-dimethyl-4,5-dihydro-imidazol-1-yl]-[4-(3-methanesulfonyl-propyl)-piperazin-1-yl]-methanone,
- 25 [(4S,5R)-2-(4-tert-Butyl-2-methoxy-phenyl)-4,5-bis-(4-chloro-phenyl)-4,5-dimethyl-4,5-dihydro-imidazol-1-yl]-[4-(3-methanesulfonyl-propyl)-piperazin-1-yl]-methanone,
- [(4S,5R)-2-(4-Chloro-2-ethoxy-5-methanesulfonyl-phenyl)-4,5-bis-(4-chloro-phenyl)-4,5-dimethyl-4,5-dihydro-imidazol-1-yl]-[4-(1,1-dioxo-tetrahydro-2H-thiopyran-4-yl)-piperazin-1-yl]-methanone,
- 30

[(4S,5R)-2-(4-*tert*-Butyl-2-ethoxy-phenyl)-4,5-bis-(4-chloro-phenyl)-4,5-dimethyl-4,5-dihydro-imidazol-1-yl]-[4-(1,1-dioxo-tetrahydro-thiophen-3-yl)-piperazin-1-yl]-methanone,

5 [(4S,5R)-2-(4-*tert*-Butyl-2-ethoxy-phenyl)-4,5-bis-(4-chloro-phenyl)-4,5-dimethyl-4,5-dihydro-imidazol-1-yl]-[4-(3-ethanesulfonyl-propyl)-piperazin-1-yl]-methanone,
2-(4-[(4S,5R)-4,5-Bis-(4-chloro-phenyl)-1-[4-(3-ethanesulfonyl-propyl)-piperazine-1-carbonyl]-4,5-dimethyl-4,5-dihydro-1H-imidazol-2-yl]-3-ethoxy-phenyl)-2-methyl-propionitrile,

10 (4S,5R)-2-(4-*tert*-Butyl-2-ethoxy-phenyl)-4,5-bis-(4-chloro-phenyl)-4-methyl-4,5-dihydro-1*H*-imidazole,

[(4S,5R)-2-(4-*tert*-Butyl-2-ethoxy-phenyl)-4,5-bis-(4-chloro-phenyl)-4-methyl-4,5-dihydro-imidazol-1-yl]-piperazin-1-yl-methanone,

[(4S,5R)-2-(4-*tert*-Butyl-2-ethoxy-phenyl)-4,5-bis-(4-chloro-phenyl)-4-methyl-4,5-dihydro-imidazol-1-yl]-piperazin-1-yl-methanone,

15 1-[(4S,5R)-2-(4-*tert*-Butyl-2-ethoxy-phenyl)-4,5-bis-(4-chloro-phenyl)-4-methyl-4,5-dihydro-imidazole-1-carbonyl]-piperidine-4-carboxylic acid amide,

1-{4-[(4S,5R)-2-(4-*tert*-Butyl-2-ethoxy-phenyl)-4,5-bis-(4-chloro-phenyl)-4-methyl-4,5-dihydro-imidazole-1-carbonyl]-piperazin-1-yl}-ethanone,

20 *rac*-(4S*,5R*)-2-(4-*tert*-Butyl-2-ethoxy-phenyl)-4,5-bis-(4-chloro-phenyl)-4-methyl-4,5-dihydro-imidazole-1-carboxylic acid (2-dimethylamino-ethyl)-amide,

rac-4-[(4S*,5R*)-2-(4-*tert*-Butyl-2-ethoxy-phenyl)-4,5-bis-(4-chloro-phenyl)-4-methyl-4,5-dihydro-imidazole-1-carbonyl]-piperazin-2-one,

25 *rac*-2-{4-[(4S,5R)-2-(4-*tert*-Butyl-2-ethoxy-phenyl)-4,5-bis-(4-chloro-phenyl)-4-methyl-4,5-dihydro-imidazole-1-carbonyl]-piperazin-1-yl}-1-morpholin-4-yl-ethanone,

rac-[(4S,5R)-2-(4-*tert*-Butyl-2-ethoxy-phenyl)-4,5-bis-(4-chloro-phenyl)-4-methyl-4,5-dihydro-imidazol-1-yl]-(4-methanesulfonyl-piperazin-1-yl)-methanone,

30 *rac*-2-{4-[(4S*,5R*)-2-(4-*tert*-Butyl-2-ethoxy-phenyl)-4,5-bis-(4-chloro-phenyl)-4-methyl-4,5-dihydro-imidazole-1-carbonyl]-piperazin-1-yl}-1-pyrrolidin-1-yl-ethanone,

rac-[(4S*,5R*)-2-(4-*tert*-Butyl-2-ethoxy-phenyl)-4,5-bis-(4-chloro-phenyl)-4-methyl-4,5-dihydro-imidazol-1-yl]-[4-(tetrahydro-furan-2-carbonyl)-piperazin-1-yl]-methanone,

5 *rac*-4-[(4S*,5R*)-2-(4-*tert*-Butyl-2-ethoxy-phenyl)-4,5-bis-(4-chloro-phenyl)-4-methyl-4,5-dihydro-imidazole-1-carbonyl]-piperazine-1-carboxylic acid dimethylamide,

rac-2-{4-[(4S*,5R*)-2-(4-*tert*-Butyl-2-ethoxy-phenyl)-4,5-bis-(4-chloro-phenyl)-4-methyl-4,5-dihydro-imidazole-1-carbonyl]-piperazin-1-yl}-acetamide,

10 *rac*-2-{4-[(4S*,5R*)-4,5-Bis-(4-chloro-phenyl)-2-(2-isopropoxy-4-methoxy-phenyl)-4-methyl-4,5-dihydro-imidazole-1-carbonyl]-piperazin-1-yl}-1-pyrrolidin-1-yl-ethanone,

rac-4-[(4S*,5R*)-4,5-Bis-(4-chloro-phenyl)-2-(2-isopropoxy-4-methoxy-phenyl)-4-methyl-4,5-dihydro-imidazole-1-carbonyl]-piperazin-2-one,

15 *rac*-2-{4-[(4S*,5R*)-4,5-Bis-(4-chloro-phenyl)-2-(2-isopropoxy-4-methoxy-phenyl)-4-methyl-4,5-dihydro-imidazole-1-carbonyl]-piperazin-1-yl}-1-morpholin-4-yl-ethanone,

rac-[(4S*,5R*)-4,5-Bis-(4-chloro-phenyl)-2-(2-isopropoxy-4-methoxy-phenyl)-4-methyl-4,5-dihydro-imidazol-1-yl]-(4-methanesulfonyl-piperazin-1-yl)-methanone,

20 *rac*-1-{4-[(4S*,5R*)-4,5-Bis-(4-chloro-phenyl)-2-(2-isopropoxy-4-methoxy-phenyl)-4-methyl-4,5-dihydro-imidazole-1-carbonyl]-piperazin-1-yl}-ethanone,

rac-[(4S*,5R*)-4,5-Bis-(4-chloro-phenyl)-2-(2-isopropoxy-4-methoxy-phenyl)-4-methyl-4,5-dihydro-imidazol-1-yl]-[4-(tetrahydro-furan-2-carbonyl)-piperazin-1-yl]-methanone,

25 *rac*-2-{4-[(4S*,5R*)-4,5-Bis-(4-chloro-phenyl)-2-(2-isopropoxy-4-methoxy-phenyl)-4-methyl-4,5-dihydro-imidazole-1-carbonyl]-piperazin-1-yl}-acetamide,

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

30 *rac*-[(4S*,5R*)-4,5-Bis-(4-chloro-phenyl)-2-(2-isopropoxy-4-methoxy-phenyl)-4-methyl-4,5-dihydro-imidazol-1-yl]-[4-(3-methanesulfonyl-propyl)-piperazin-1-yl]-methanone,

rac-[(4S*,5R*)-4,5-Bis-(4-chloro-phenyl)-2-(2-isopropoxy-4-methoxy-phenyl)-4-methyl-4,5-dihydro-imidazol-1-yl]-piperazin-1-yl-methanone,

rac-(4S*,5R*)-4,5-Bis-(4-chloro-phenyl)-2-(2-isopropoxy-4-methoxy-phenyl)-4-methyl-4,5-dihydro-imidazole-1-carboxylic acid (2-dimethylamino-ethyl)-amide,

5 *rac*-1-[(4S*,5R*)-4,5-Bis-(4-chloro-phenyl)-2-(2-isopropoxy-4-methoxy-phenyl)-4-methyl-4,5-dihydro-imidazole-1-carbonyl]-piperidine-4-carboxylic acid amide,

rac-4-[(4S*,5R*)-2-(4-*tert*-Butyl-2-ethoxy-phenyl)-4,5-bis-(4-chloro-phenyl)-4-ethyl-4,5-dihydro-imidazole-1-carbonyl]-piperazin-2-one,

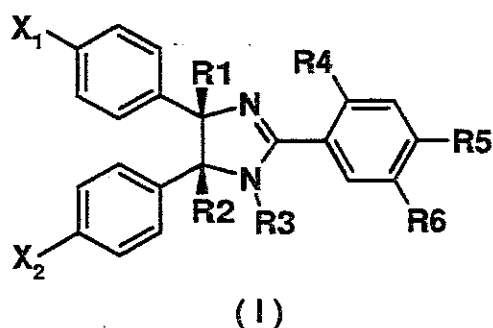
10 *rac*-1-[(4S*,5R*)-2-(4-*tert*-Butyl-2-ethoxy-phenyl)-4,5-bis-(4-chloro-phenyl)-4-ethyl-4,5-dihydro-imidazole-1-carbonyl]-piperidine-4-carboxylic acid amide,

rac[(4S*,5R*)-4,5-Bis-(4-chloro-phenyl)-4-ethyl-2-(2-isopropoxy-4-methoxy-phenyl)-4,5-dihydro-imidazol-1-yl]-[4-(tetrahydro-furan-2-carbonyl)-piperazin-1-yl]-methanone,

15 *rac*-2-[4-[(4S*,5R*)-4,5-Bis-(4-chloro-phenyl)-4-ethyl-2-(2-isopropoxy-4-methoxy-phenyl)-4,5-dihydro-imidazole-1-carbonyl]-piperazin-1-yl]-1-morpholin-4-yl-ethanone and

rac-4-[(4S*,5R*)-4,5-Bis-(4-chloro-phenyl)-4-ethyl-2-(2-isopropoxy-4-methoxy-phenyl)-4,5-dihydro-imidazole-1-carbonyl]-piperazine-1-carboxylic acid dimethylamide.

According to a second aspect, there is provided a pharmaceutical composition comprising a compound of the formula



5

wherein X_1 and X_2 are halogen, acetylene, cyano, trifluoromethyl or nitro;

R^1 and R^2 are selected from the group consisting of -H, -CH₃, -CH₂CH₃, -CH₂OH and -CH₂OCH₃ with the proviso that R^1 and R^2 are not both hydrogen;

R^3 is -H or -C(=O)- R^7 ;

10

and where R^6 is hydrogen then

R^4 is -OCH₃, -OCH₂CH₃, -OCH₂CH₂F, -OCH₂CH₂OCH₃, or -OCH(CH₃)₂;

R^5 is

-H

15 -halogen,

-CH₃,

-CF₃,

-OCH₃,

-C(CH₃)₂,

20 -cyclopropyl,

-cyano,

-C(CH₃)₃,

-C(CH₃)₂OR (where R is -H, -CH₃ or -CH₂CH₃),

-C(CH₃)₂CH-OR (where R is -H, -CH₃, -CH(CH₃)₂, -CH₂CH₂OH or

25

-CH₂CH₂OCH₃),

-C(CH₃)₂CN,

-C(CH₃)₂COR (where R is -CH₃),

-C(CH₃)₂COOR (where R is -H, -CH₃, -CH₂CH₃ or -CH(CH₃)₂),

-C(CH₃)₂CONR^aR^b (where R^a is -H or -CH₃ and R^b = -H or -CH₃),
 -SR (where R is -CH₃ or -CH₂CH₃), or
 -SO₂R (where R is -CH₃, -CH₂CH₃, 1-pyrrolidine, NH-*tert*-butyl or N(CH₃)₂);

5 and where R⁶ is not hydrogen then

R⁴ is -OCH₃, -OCH₂CH₃, -OCH₂CH₂F, -OCH₂CH₂OCH₃, or -OCH(CH₃)₂;

R⁵ is hydrogen, -Cl, -OCH₃, *tert*-butyl or -N(CH₃)₂;

R⁶ is -Cl, cyclopropyl, -SO₂R (where R is -CH₃, -CH₂CH₃, 1-pyrrolidine, -NH-*tert*-butyl, -NH₂, or -N(CH₃)₂);

10

and R⁷ is selected from the group consisting of

i) -CH₃, -CH(CH₃)₂, -CH₂CH(CH₃)₂, cyclopropyl, cyclobutyl, -CH₂CH₂Ph, 2-furanyl, phenyl, or phenyl substituted by chloro, -OCH₃ or cyano,

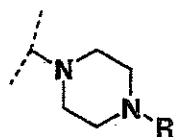
15

ii) 4-morpholinyl, 1-piperidinyl, 4-thiomorpholinyl, or 4-thiomorpholinyl-1,1-dioxide,

iii) -NR^c₂ (wherein R^c is hydrogen, -CH₃, -CH₂CH₃, -CH₂CH₂OH, -CH₂CH₂OCH₃, or -CH₂CH(OH)CH₂OH),

20

iv) a substituted piperazine of the formula



wherein R is selected from the group consisting of

25

a) hydrogen,

b) lower alkyl,

c) -CH(CH₃)₂,

d) -CH(CH₂CH₃)₂,

e) cyclopentyl,

30

f) -CH₂CH(OH)CH₃,

g) -CH₂CF₃,

h) -CH₂CH(OH)CF₃,

i) $-\text{CH}_2\text{C}(\text{CH}_3)_2\text{OH}$,

j) $-\text{CH}_2$ -[4-N-methylpiperidiny],

5 k) $-\text{CH}_2\text{CH}_2\text{R}^d$ (wherein R^d is $-\text{OH}$, $-\text{OCH}_3$, $-\text{OCH}_2\text{CH}_2\text{OH}$, $-\text{OCH}_2\text{CH}_2\text{OCH}_3$, $-\text{CN}$,
 $-\text{CF}_3$, $-\text{SO}_2\text{CH}_3$, $-\text{SO}_2\text{NH}_2$, $-\text{SO}_2\text{N}(\text{CH}_3)_2$, $-\text{CONH}_2$, $-\text{CON}(\text{CH}_3)_2$, $-\text{NH}_2$, $-\text{NHCOCH}_3$,
 $-\text{NHSO}_2\text{CH}_3$, $-\text{N}(\text{CH}_3)_2$, $-\text{N}(\text{CH}_2\text{CH}_3)_2$, $-\text{N}(\text{CH}_2\text{CH}_2\text{CH}_3)_2$, 1-pyrrolidiny, 1-
piperidiny, 4-morpholiny, 2-isothiazolidiny-1,1-dioxide, or 2-tetrahydrofurany),

10 l) $-\text{CH}_2\text{CH}_2\text{CH}_2\text{R}^e$ (wherein R^e is $-\text{OH}$, $-\text{OCH}_3$, $-\text{SO}_2\text{CH}_3$, $-\text{SO}_2\text{CH}_2\text{CH}_3$,
 $-\text{SO}_2\text{N}(\text{CH}_3)_2$, $-\text{CN}$, $-\text{N}(\text{CH}_3)_2$, $-\text{N}(\text{CH}_2\text{CH}_2\text{CH}_3)_2$, 1-imidazoyl, 1-pyrrolidiny,
1-piperidiny, 4-morpholiny, $-\text{COOCH}_3$, $-\text{COOCH}_2\text{CH}_3$, $-\text{COOC}(\text{CH}_3)_3$,
 $-\text{CON}(\text{CH}_3)_2$, $-\text{CO}-\text{R}^f$ (wherein R^f is $-\text{CH}_3$, $-\text{CH}_2\text{CH}_3$, cyclopropyl, phenyl, 2-thienyl,
3-thienyl, 2-furany, 3-furany), $-\text{COCH}_2-\text{R}^g$ (wherein R^g is $-\text{H}$, $-\text{NHCH}_2\text{CH}_2\text{OH}$,
 $-\text{NHCH}_2\text{CH}_2\text{OCH}_3$, $-\text{NHCH}_2\text{CH}_2\text{N}(\text{CH}_3)_2$, 1-piperidiny, 1-(piperidiny-4-methanol),
15 4-morpholiny, or $-\text{N}(\text{CH}_3)$ -(3-(1-methylpyrrolidiny))),

m) $-\text{CH}_2-\text{CO}-\text{R}^h$ (wherein R^h is $-\text{OCH}_3$, OCH_2CH_3 , $-\text{NH}_2$, $-\text{NHCH}_2\text{CH}(\text{CH}_3)_2$,
 $-\text{NHCH}_2\text{CF}_3$, $-\text{NH}$ -cyclopropyl, $-\text{NH}$ -*tert*-butyl, $-\text{NHCH}_2\text{CH}_2\text{CH}_2\text{OH}$, $-\text{N}(\text{CH}_3)_2$,
 $-\text{N}(\text{CH}_2\text{CH}_3)_2$, $-\text{N}(\text{CH}_2\text{CH}_2\text{OH})_2$, $-\text{N}(\text{CH}_2\text{CH}_2\text{OCH}_3)_2$, $-\text{N}(\text{CH}_3)\text{CH}_2\text{CH}_2\text{OH}$,
20 $-\text{N}(\text{CH}_3)\text{CH}_2\text{CH}_2\text{OCH}_3$, $-\text{NHCH}_2\text{CH}_2\text{OCH}_3$, 1-pyrrolidiny, 1-piperidiny, 1-
(piperidiny-4-methanol), 1-(piperidiny-3-carboxamide), 4-morpholiny, 4-
thiomorpholiny, 4-thiomorpholiny-1,1-dioxide, 1-piperaziny, 1-(4-
acetylpiperaziny), 1-(3-oxopiperaziny),

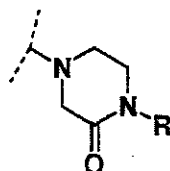
25 n) $-\text{SO}_2\text{R}^i$ (wherein R^i is $-\text{CH}_3$, $-\text{CH}_2\text{CH}_3$, $-\text{CH}(\text{CH}_3)_2$, phenyl, 4-methylphenyl, 4-
propylphenyl, $-\text{CF}_3$, 2-thienyl, 3-thienyl, $-\text{NH}_2$, $-\text{NHCH}_3$, $-\text{N}(\text{CH}_3)_2$,
 $-\text{NHCH}_2\text{CH}_2\text{OCH}_3$, $-\text{N}(\text{CH}_2\text{CH}_2\text{OCH}_3)_2$, 1-pyrrolidiny, 1-piperidiny, 4-morpholiny,
1-piperazyl-4-ethanol, 1-(4-acetylpiperaziny), 1-(3-oxopiperaziny)),

30 o) $-\text{COR}^j$ (wherein R^j is $-\text{CH}_3$, $-\text{CH}_2\text{CH}_3$, $-\text{CH}(\text{CH}_3)_2$, 2-tetrahydrofurany, 2-thienyl,
3-thienyl, $-\text{NH}_2$, $-\text{NHCH}_3$, $-\text{N}(\text{CH}_3)_2$, 1-pyrrolidiny, 1-piperidiny, 4-morpholiny, 1-
piperaziny-4-ethanol, 1-(4-acetylpiperaziny), or 1-(3-oxopiperaziny)),

p) 4-tetrahydro-2H-thiopyrany-1,1-dioxide,

- q) 4-piperidiny-1-acetyl,
- r) 4-piperidiny-1-dimethylcarboxamide, and
- s) 3-tetrahydro-thiophenyl-1,1-dioxide;

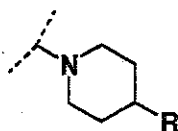
5 v) a substituted oxopiperazine of the formula



wherein R is H, -CH₃, -CH₂CH₃, -CH₂CH₂CH₃, -CH₂CH₂OH, or -CH₂CH₂OCH₃;

10 and

vi) a substituted piperidine of the formula



- 15 wherein R is H, -COOCH₃, -COOCH₂CH₃, -CONH₂, -OH, -CH₂OH, -CH₂CH₂OH, -CH₂-N(CH₂CH₃)₂, -CH₂-(1-piperaziny), -CH₂-(1-(3-oxopiperaziny)), -NH₂, -NHCOCH₃, -NHCOCH₂NH₂, -NHCOCH₂NHCH₃, -NHCOCH₂N(CH₃)₂, -NHCOCH₂N(CH₂CH₂OH)₂, -NHCOCH₂N(CH₂CH₂OCH₃)₂, -NHCOCH₂NHCH₂CH₂OH, -NHCOCH₂-(1-(4-acetyl-piperaziny)), -NHCOCH₂-(1-(3-oxopiperaziny)), -NHCOCH₂-(1-piperidinecarboxamide), -NHCOCH₂-(N,N-diethyl-1-piperidiny)carboxamide, -NHCOCH₂-(1-(3-hydroxypiperidiny)), -NHCOCH₂-(1-(piperidiny-4-methanol)), -NHCON(CH₃)₂, -NHCSNHCH₃, -NHCSNHPh, -NHCH₂CONH₂, 1-pyrrolidiny, 1-piperidiny, 1-(4-methylpiperaziny), or 4-morpholiny;
- 20 and the pharmaceutically acceptable salts and esters thereof together with a pharmaceutically acceptable excipient.
- 25

According to a third aspect, there is provided the pharmaceutical composition of the second aspect for the treatment or control of cancer, in particular solid tumors, more particularly breast, colon, lung and prostate tumors.

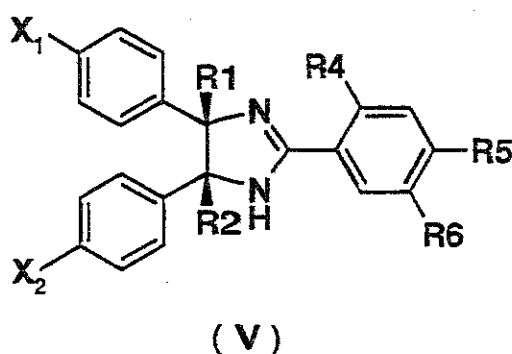
5 According to a fourth aspect, there is provided a compound as defined above for the use as medicament.

According to a fifth aspect, there is provided a compound as defined above for the treatment or control of cancer, in particular solid tumors, more particularly
10 breast, colon, lung and prostate tumors.

According to a sixth aspect, there is provided the use of a compound as defined above for the manufacture of medicaments for the treatment or control of cancer, in particular solid tumors, more particularly breast, colon, lung and
15 prostate tumors.

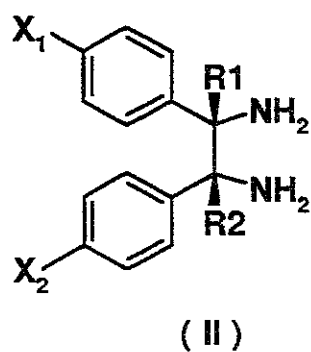
According to a seventh aspect, there is provided the process for the synthesis of a compound of formula (I) according to the first aspect, whereby

20 a) an imidazoline of formula (V), thus a compound of formula (I) with R³ being hydrogen,

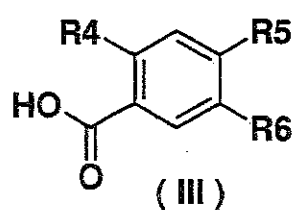


25 is obtained either by

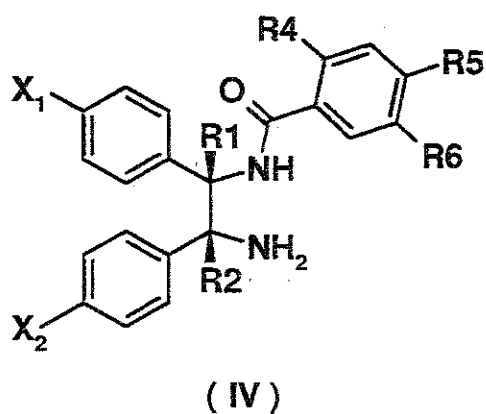
i) condensation of a tetrasubstituted 1,2-diamine of formula (II)



with an aromatic acid of formula (III)



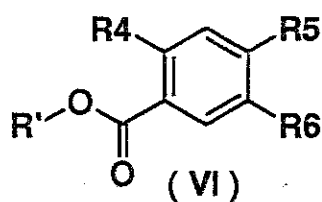
to form a monoamide derivative of formula (IV)



followed by cyclodehydration to give a compound of formula (V)

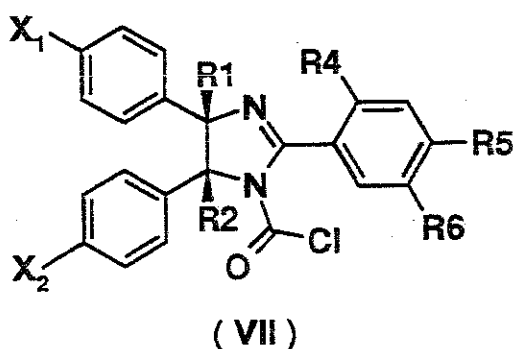
or

ii) by reaction of a tetrasubstituted 1,2-diamine of formula (II) as shown under i) above with an aromatic ester of formula (VI)



in the presence of a trialkyl aluminum to also give an imidazoline of formula (V); and

b) said compound of formula (V) is reacted with phosgene to form a carbamoyl chloride of formula (VII)



which is then reacted with primary or secondary amines to form the corresponding compound of formula (I) wherein R³ is different from hydrogen; and

c) said compound of formula (I) is, if desired, turned into a pharmaceutically acceptable salt; and

all substituents have the meanings given in the first aspect.

The term "alkyl" refers to straight- or branched-chain saturated hydrocarbon groups having from 1 to about 20 carbon atoms, preferably 1 to 12, more preferably 1 to about 7 carbon atoms. In certain embodiments, alkyl substituents may be lower alkyl substituents. The term "lower alkyl" refers to alkyl groups having from 1 to 6 carbon atoms, and in certain embodiments from 1 to 4 carbon atoms. Examples of alkyl groups include, but are not limited to, methyl, ethyl, n-propyl, i-propyl, n-butyl, s-butyl, t-butyl, n-pentyl, and s-pentyl.

As used herein, "cycloalkyl" is intended to refer to any stable monocyclic or polycyclic system which consists of carbon atoms only, any ring of which being saturated. Preferably such cycloalkyls are 3 to 14-membered, more preferably 3 to 10-membered, mono- or bicyclic systems. Examples of cycloalkyls include, but

are not limited to, cyclopropyl, cyclobutyl, cyclopentyl, cyclohexyl, cycloheptyl, adamantyl, cyclooctyl, bicycloalkyls, including bicyclooctanes such as [2.2.2]bicyclooctane or [3.3.0]bicyclooctane, bicyclononanes such as [4.3.0]bicyclononane, and bicyclodecanes such as [4.4.0]bicyclodecane (decalin),
5 or spiro compounds.

The term "halogen" as used in the definitions means fluorine, chlorine, bromine, or iodine, preferably fluorine and chlorine.

10 "Alkoxy, alkoxyl or lower alkoxy" refers to any of the above lower alkyl groups attached to an oxygen atom. Typical lower alkoxy groups include methoxy, ethoxy, isopropoxy or propoxy, butyloxy and the like. Further included within the meaning of alkoxy are multiple alkoxy side chains, *e.g.* ethoxy ethoxy, methoxy ethoxy, methoxy ethoxy ethoxy and the like and substituted alkoxy side
15 chains, *e.g.*, dimethylamino ethoxy, diethylamino ethoxy, dimethoxy-phosphoryl methoxy and the like.

The compounds of formula I as well as their salts that have at least one asymmetric carbon atom may be present as racemic mixtures or different
20 stereoisomers. The various isomers can be isolated by known separation methods, *e.g.*, chromatography.

Compounds disclosed herein and covered by formula I above may exhibit tautomerism or structural isomerism. It is intended that the invention
25 encompasses any tautomeric or structural isomeric form of these compounds, or mixtures of such forms, and is not limited to any one tautomeric or structural isomeric form depicted in formula I above.

The compounds of the present invention are useful in the treatment or control of
30 cell proliferative disorders, in particular oncological disorders. These compounds and formulations containing said compounds may be useful in the treatment or control of solid tumors, such as, for example, breast, colon, lung and prostate tumors.

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 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 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 administration, it may be given as continuous infusion.

Formulations of the present invention include those suitable for oral, nasal, topical (including buccal and sublingual), rectal, vaginal and/or parenteral administration. The formulations may conveniently be presented in unit dosage form and may be prepared by any methods well known in the art of pharmacy. The amount of active ingredient which can be combined with a carrier material to produce a single dosage form will vary depending upon the host being treated, as well as the particular mode of administration. The amount of active ingredient which can be combined with a carrier material to produce a single dosage form will generally be that amount of a formula I compound which produces a therapeutic effect. Generally, out of one hundred percent, this amount will range from about 1 percent to about ninety-nine percent of active ingredient, preferably from about 5 percent to about 70 percent, most preferably from about 10 percent to about 30 percent.

Methods of preparing these formulations or compositions include the step of bringing into association a compound of the present invention with the carrier and, optionally, one or more accessory ingredients. In general, the formulations

are prepared by uniformly and intimately bringing into association a compound of the present invention with liquid carriers, or finely divided solid carriers, or both, and then, if necessary, shaping the product.

- 5 Formulations of the invention suitable for oral administration may be in the form of capsules, cachets, sachets, pills, tablets, lozenges (using a flavored basis, usually sucrose and acacia or tragacanth), powders, granules, or as a solution or a suspension in an aqueous or non-aqueous liquid, or as an oil-in-water or water-in-oil liquid emulsion, or as an elixir or syrup, or as pastilles (using an inert
- 10 base, such as gelatin and glycerin, or sucrose and acacia) and/or as mouth washes and the like, each containing a predetermined amount of a compound of the present invention as an active ingredient. A compound of the present invention may also be administered as a bolus, electuary or paste.

15

"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.*,

25 Textbook of Drug Design and Development (2d Ed. 1996) at pp. 152-191.

30

"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, 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 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" means that the substitution can occur at one or more positions and, unless otherwise indicated, that the substituents at each substitution 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.

Compounds of the present invention as exemplified advantageously show IC₅₀s from about 1 nM to about 1000 nM.

25 The present invention also provides pharmaceutical compositions comprising at least one compound of formula I, or a pharmaceutically acceptable salt or ester thereof, and a pharmaceutically acceptable carrier or excipient.

The general methods for the preparation of compounds of formula (I) are given in schemes 1, 2, 3 and 4 wherein, unless explicitly otherwise stated, all substituents (X₁, X₂, R¹, R², R³, R⁴, R⁵ and R⁶) have the meanings given above.

5

Briefly, the process involves the formation of imidazoline (V) either by condensation of a tetrasubstituted 1,2-diamine (II) with an aromatic acid (III.) to form a monoamide derivative (IV) followed by cyclodehydration (method 1, scheme 1), or by reaction of a tetrasubstituted 1,2-diamine (II) with an aromatic ester (VI) in the presence of a trialkyl aluminum (method 2, scheme 2).

10

The imidazoline (V) is reacted with phosgene to form carbamoyl chloride (VII) which is then reacted with amines of the general formula RaRbNH to form the corresponding urea derivatives of formula (I), thus those derivatives wherein R³ is a group –C(O)-R⁷, and R⁷ has a meaning according to paragraphs ii) to vi) as defined above (route (A) of scheme 3).

15

The imidazoline (V) can also be reacted with acid chlorides of formula (VIII) in the presence of a base such as triethylamine to form the corresponding amide derivatives of formula (I), thus those derivatives wherein R³ is a group –C(O)-R⁷, and R⁷ has a meaning according to paragraph i) as defined above (route (B) of scheme 3).

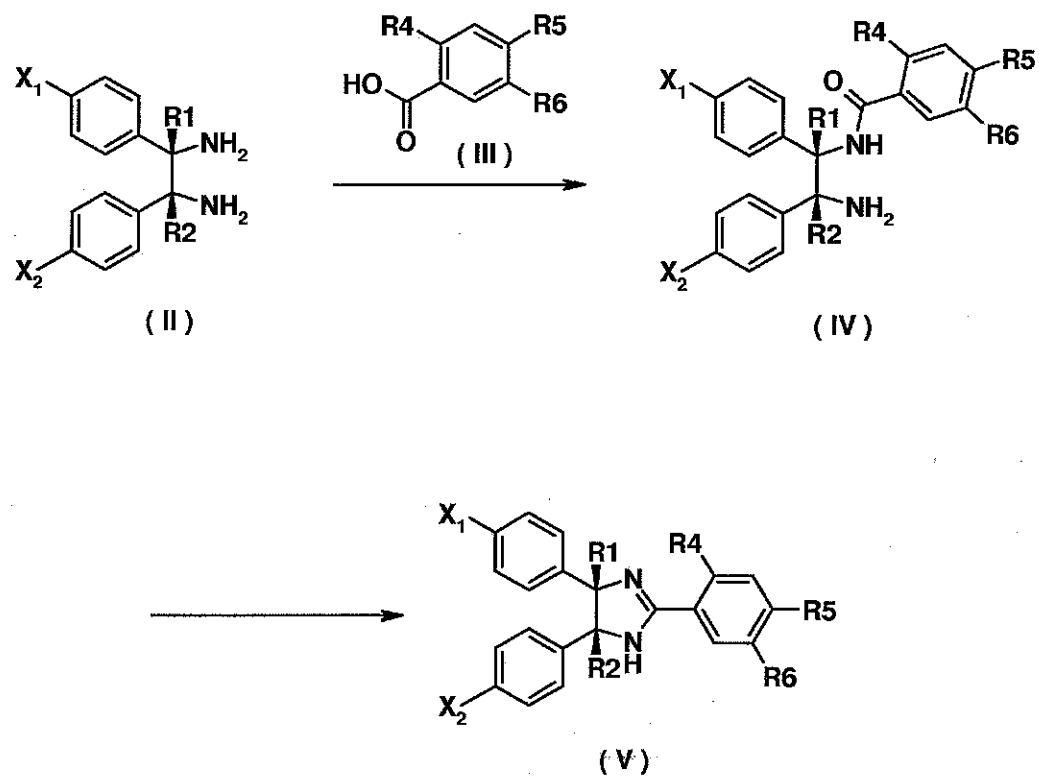
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The absolute stereochemistry of the active enantiomer of (I) is determined based on the crystal structure of its complex with human MDM2 (see Vassilev, L. *et al. Science* **2004**, 303, 844-848).

25

Preparation of imidazolines

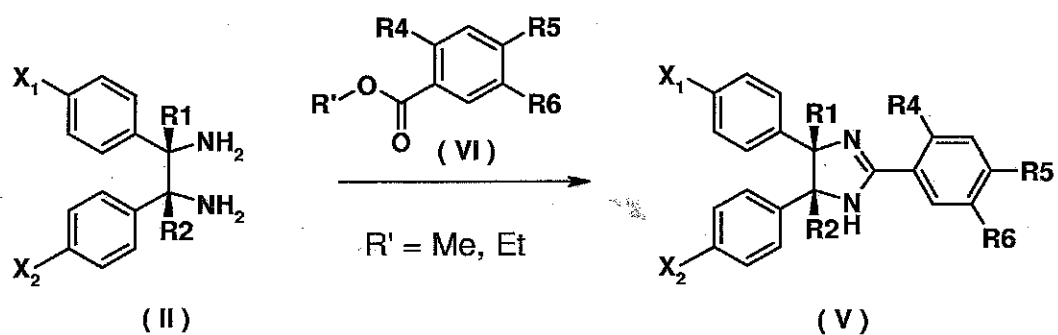
Method 1: diamines with acids



5

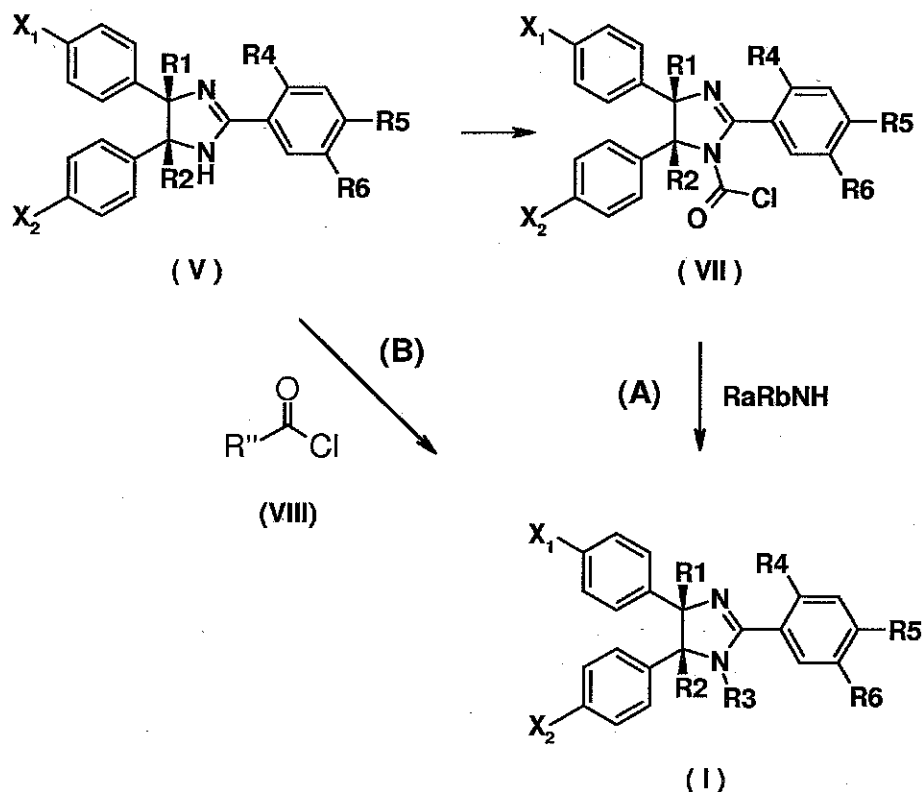
Scheme 1

Method 2: diamines with esters



10

Scheme 2

Derivatization of the imidazolines

Scheme 3

The group RaRbNH in scheme 3 means a primary or secondary (also cyclic) amine according to the definitions of R⁷, paragraphs ii) to vi), respectively.

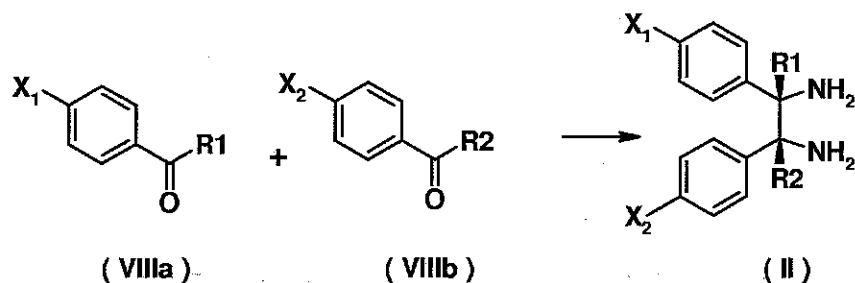
- 10 The group R'' in formula (VIII) of scheme 3 is a group according to item i) of R⁷ as defined above.

Preparation of diamine intermediates

- 15 The diamine intermediates were prepared either by the reductive coupling of imines via the process described by Volckaerts [B. Bracke, E. Volckaerts, A. T. H. Lenstra, H. J. Geise, H. J., Bulletin des Societes Chimiques Belges, 1990, 99, 797-801.] (method 3) or by the reaction of 1,2,5-thiadiazole 1,1-dioxides

with Grignard reagents via a process described by Pansare [S. V. Pansare, A. N. Rai, S. N. Kate, Synlett, 1998, 623-624] (method 4).

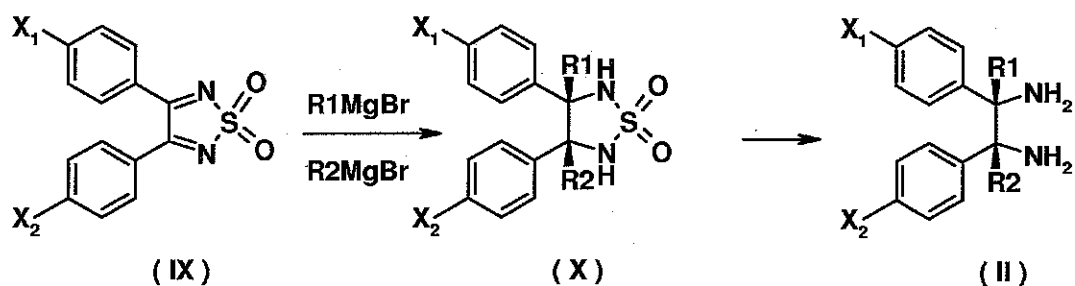
Method 3:



5

Scheme 4

Method 4:



10

Scheme 5

The following examples and references are provided to aid the understanding of the present invention, the true scope of which is set forth in the appended claims.

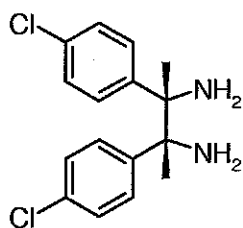
15

General: In the examples temperatures are indicated in degrees C. For mass spectral data, values are given as the MH^+/Z ion obtained in the positive mode, electrospray measured on a Micromass Platform II mass spectrometer.

5

Example 1

meso-2,3-bis-(4-chlorophenyl)-2,3-butanediamine



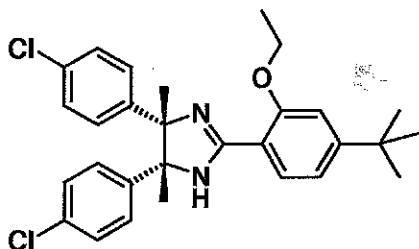
10

A mixture of 15.0 g (97.3 mmol) of titanium trichloride and 480 mL of tetrahydrofuran under an argon atmosphere was cooled to -15 °C and then 48.64 mL of a 1 M solution of lithium aluminum hydride in tetrahydrofuran was added dropwise. The mixture was stirred for 10 min, then heated to reflux for 1 h. The mixture was cooled to room temperature and solutions of 50 mL of ammonia in 192 mL of tetrahydrofuran and 15.04 g (97.3 mmol) of 4-chloroacetophenone in 240 mL of tetrahydrofuran were added simultaneously over 40 min. The mixture was stirred overnight at room temperature, then cooled to 0 °C and acidified by addition of 2 M hydrochloric acid. The aqueous phase was extracted with dichloromethane, then made basic by the addition of 2 M sodium hydroxide solution and extracted with dichloromethane. The latter dichloromethane phase was dried over anhydrous sodium sulfate, filtered and concentrated under reduced pressure to give 4.64 g of 2,3-bis-(4-chlorophenyl)-2,3-butanediamine as a mixture of *meso* and *dl*-isomers. This material was used without further purification in subsequent reactions.

25

Example 2

rac-(4S*,5R*)-4,5-Bis(4-chlorophenyl)-2-(4-(*tert*-butyl)-2-ethoxy-phenyl)-4,5-dimethyl-4,5-dihydro-1H-imidazole.

**Method 1:**

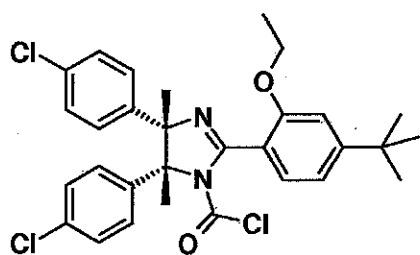
A mixture of *meso*-2,3-bis-(4-chlorophenyl)-2,3-butanediamine (70 mg, 0.226 mmol, example 1) and triethylamine (62 μ L, 0.226 mmol) in 2 mL of dichloromethane was reacted with 0.225 mmol of 4-(*tert*-butyl)-2-ethoxy-benzoyl chloride (prepared from the reaction of 0.225 mmol of 4-(*tert*-butyl)-2-ethoxy-benzoic acid and 0.34 mmol of oxalyl chloride) for 30 min at room temperature. The mixture was partitioned between 10% sodium bicarbonate solution and dichloromethane. The dichloromethane extract was washed with water, dried over anhydrous sodium sulfate, filtered and concentrated under reduced pressure to give the crude amide mixture. Purification by chromatography on silica gel, eluting with hexane-ethyl acetate (3:1) provided 20 mg of *N*-[2-amino-1,2-bis-(4-chloro-phenyl)-1-methyl-propyl]-4-(*tert*-butyl)-2-ethoxy-benzamide. The intermediate was refluxed under argon with 0.5 mg of toluenesulfonic acid monohydrate and 7 mL of toluene for 3.5 h, then cooled, taken up in ethyl acetate and washed successively with saturated sodium bicarbonate, water and brine. The ethyl acetate layer was dried over anhydrous sodium sulfate, filtered, and concentrated under reduced pressure. Purification by chromatography on silica gel, eluting with ethyl acetate, followed by ethyl acetate-methanol (95:5) provided 9.5 mg of *rac*-(4S*,5R*)-4,5-bis(4-chlorophenyl)-2-(4-(*tert*-butyl)-2-ethoxy-phenyl)-4,5-dimethyl-4,5-dihydro-1H-imidazole. LR-MS: 495.0 [(M+H)⁺]

Method 2:

A solution of *meso*-2,3-bis-(4-chlorophenyl)-2,3-butanediamine (2.5 g, 8.08 mmol, example 1) in 100 mL of toluene was added to a solution of trimethylaluminum (4 mL, 2M solution in toluene, Aldrich) in 24 mL of toluene at 0 °C. The mixture was stirred 10 min at 0 °C, 20 min at room temperature and then 4-(*tert*-butyl)-2-ethoxy-benzoic acid methyl ester (2.1 g, 8.9 mmol) in 10 mL of toluene was added. The mixture was heated to reflux for 2.5 h then cooled to 0 °C and quenched by the dropwise addition of saturated potassium sodium tartrate solution. The mixture was extracted with ethyl acetate and the ethyl acetate layer washed successively with 10% sodium bicarbonate solution and brine, then dried over anhydrous sodium sulfate, filtered and concentrated under reduced pressure. Purification by chromatography on silica gel, eluting with hexane-ethyl acetate (1:1) provided 710 mg of *rac*-(4*S**,5*R**)-4,5-bis(4-chlorophenyl)-2-(4-(*tert*-butyl)-2-ethoxy-phenyl)-4,5-dimethyl-4,5-dihydro-1*H*-imidazole. LR-MS: 495.0 [(M+H)⁺]

Example 3

rac-(4*S**,5*R**)-4,5-Bis(4-chlorophenyl)-2-(4-(*tert*-butyl)-2-ethoxy-phenyl)-4,5-dimethyl-4,5-dihydro-1*H*-imidazole-1-carbonyl chloride

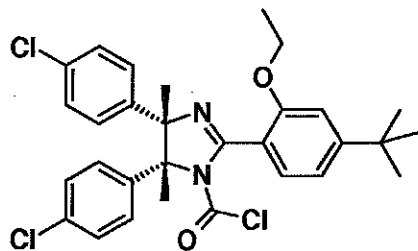


To a solution of *rac*-(4*S**,5*R**)-4,5-bis(4-chlorophenyl)-2-(4-(*tert*-butyl)-2-ethoxy-phenyl)-4,5-dimethyl-4,5-dihydro-1*H*-imidazole (710 mg, 1.43 mmol, example 2) and triethylamine (400 μ L, 2.86 mmol) in 12 mL of dichloromethane at 0 °C was added 1.13 mL of 1.9 M phosgene in toluene solution (Fluka). After stirring for 30 min the mixture was taken up in dichloromethane and washed with water, dried over anhydrous sodium sulfate, filtered and concentrated under reduced pressure. Purification by chromatography on silica gel, eluting with

hexane-ethyl acetate (4:1) provided 689 mg of *rac*-(4*S**,4*R**)-4,5-bis(4-chlorophenyl)-2-(4-(*tert*-butyl)-2-ethoxy-phenyl)-4,5-dimethyl-4,5-dihydro-1*H*-imidazole-1-carbonyl chloride as a white solid.

5 **Example 4**

(4*S*, 4*R*)-4,5-Bis(4-chlorophenyl)-2-(4-(*tert*-butyl)-2-ethoxy-phenyl)-4,5-dimethyl-4,5-dihydro-1*H*-imidazole-1-carbonyl chloride

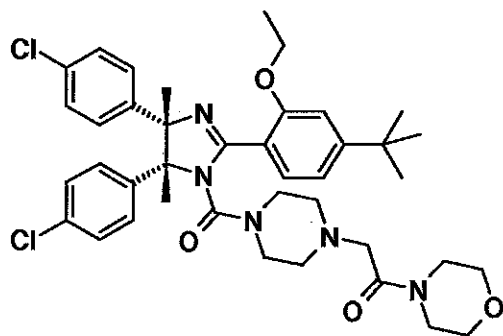


10 Chiral separation of *rac*-(4*S**,4*R**)-4,5-bis(4-chlorophenyl)-2-(4-(*tert*-butyl)-2-ethoxy-phenyl)-4,5-dimethyl-4,5-dihydro-1*H*-imidazole-1-carbonyl chloride (example 4) by supercritical fluid chromatography (Berger Instrument Multi-Gram II, Daicel ChiralPak OD-H 3 x 25 cm, 35 °C at 100 bar, eluting with 15% acetonitrile in carbon dioxide) gave the title compound.

15

Example 5

(4*S*, 4*R*)-4-[[4-[[4,5-Bis(4-chlorophenyl)-2-[4-(*tert*-butyl)-2-ethoxy-phenyl]-4,5-dimethyl-4,5-dihydro-1*H*-imidazol-1-yl]carbonyl]-1-piperazinyl]acetyl]-morpholine



20

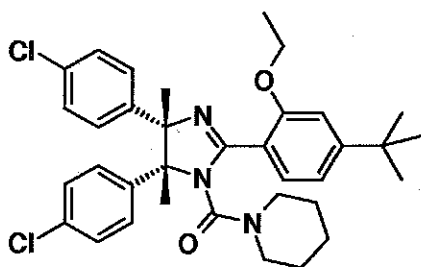
To a solution of *rac*-(4*S**,4*R**)-4,5-bis(4-chlorophenyl)-2-(4-(*tert*-butyl)-2-ethoxy-phenyl)-4,5-dimethyl-4,5-dihydro-1*H*-imidazole-1-carbonyl chloride (50 mg, 0.09 mmol, example 4) in 5 mL of dichloromethane at 0 °C were added triethylamine (165 μ L, 1.186 mmol) and 4-(1-piperazinylacetyl)-morpholine (20

mg (0.097 mmol, Oakwood Products). The mixture was allowed to react for 20 h and then taken up in dichloromethane and washed successively with 10% sodium bicarbonate and water. The dichloromethane phase was dried over anhydrous sodium sulfate, filtered and concentrated under reduced pressure.

- 5 Purification by chromatography on silica gel eluting with ethyl acetate-methanol (95:5) provided 55.4 mg of *rac*-(4S*,5R*)-4-[[4-[[4,5-bis(4-chlorophenyl)-2-[4-(*tert*-butyl)-2-ethoxy-phenyl]-4,5-dimethyl-4,5-dihydro-1H-imidazol-1-yl]carbonyl]-1-piperazinyl]acetyl]-morpholine. Separation of the enantiomers by chiral HPLC gave 24 mg of (4S, 5R)- 4-[[4-[[4,5-bis(4-chlorophenyl)-2-[4-(*tert*-butyl)-2-ethoxy-phenyl]-4,5-dimethyl-4,5-dihydro-1H-imidazol-1-yl]carbonyl]-1-piperazinyl]acetyl]-morpholine. HR-MS (ES, *m/z*) calculated for C₄₀H₅₀N₅O₄Cl₂ [(M+H)⁺] 734.3235, observed 734.3237.

Example 6

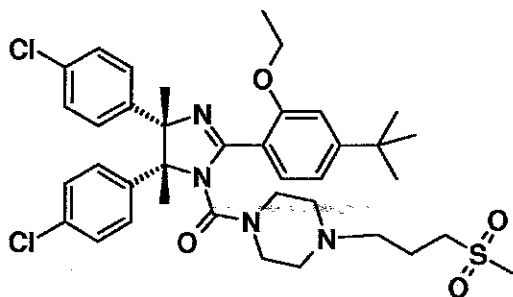
- 15 (4S, 5R)- 4-[[4-[[4,5-bis(4-chlorophenyl)-2-[4-(*tert*-butyl)-2-ethoxy-phenyl]-4,5-dimethyl-4,5-dihydro-1H-imidazol-1-yl]carbonyl]-1-piperidine



- In a manner analogous to the method described in example 5, *rac*-(4S*,5R*)-4,5-bis(4-chlorophenyl)-2-[4-(*tert*-butyl)-2-ethoxy-phenyl]-4,5-dimethyl-4,5-dihydro-1H-imidazole-1-carbonyl chloride (50 mg, 0.09 mmol) was reacted with piperidine (Aldrich) to give 24 mg of the title compound after chiral separation. HR-MS (ES, *m/z*) calculated for C₃₅H₄₂N₃O₂Cl₂ [(M+H)⁺] 606.2649, observed 606.2650.

Example 7

(4S, 5R)- 1-[[4-[[4,5-bis(4-chlorophenyl)-2-[4-(*tert*-butyl)-2-ethoxy-phenyl]-4,5-dimethyl-4,5-dihydro-1H-imidazol-1-yl]-carbonyl]- 4-[3-(methylsulfonyl)propyl]-piperazine

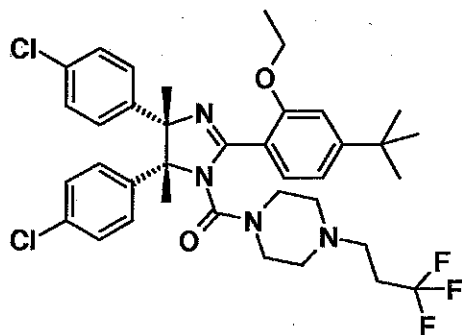


In a manner analogous to the method described in example 5, *rac*-
 (4*S**,5*R**)-4,5-bis(4-chlorophenyl)-2-(4-(*tert*-butyl)-2-ethoxy-phenyl)-4,5-dimethyl-
 4,5-dihydro-1*H*-imidazole-1-carbonyl chloride (50 mg, 0.09 mmol) was reacted
 5 with 4-[3-(methylsulfonyl)propyl]-piperazine (0.09 mmol, prepared as described in
 Fotouhi, N. *et al.* WO 2005110996) to give 24 mg of the title compound after
 chiral separation. HR-MS (ES, *m/z*) calculated for C₃₈H₄₉N₄O₄SCl₂ [(*M*+*H*)⁺]
 727.2846, observed 727.2846.

10

Example 8

(4*S*, 5*R*)- 1-[[4-[[4,5-bis(4-chlorophenyl)-2-[4-(*tert*-butyl)-2-ethoxy-phenyl]-4,5-
 dimethyl-4,5-dihydro-1*H*-imidazol-1-yl]]-carbonyl]- 4-[3,3,3-trifluoropropyl]-
 piperazine

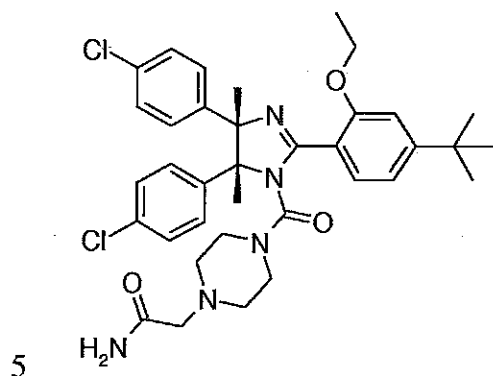


15

In a manner analogous to the method described in example 5, *rac*-
 (4*S**,5*R**)-4,5-bis(4-chlorophenyl)-2-(4-(*tert*-butyl)-2-ethoxy-phenyl)-4,5-dimethyl-
 4,5-dihydro-1*H*-imidazole-1-carbonyl chloride (50 mg, 0.09 mmol) was reacted
 20 with 4-[3-(methylsulfonyl)-propyl]-piperazine (0.09 mmol, prepared as described
 in Fotouhi, N. *et al.* WO 2005110996) to give 38 mg of the title compound after
 chiral separation. HR-MS (ES, *m/z*) calculated for C₃₇H₄₄N₄O₂F₃Cl₂ [(*M*+*H*)⁺]
 727.2846, observed 727.2846.

Example 9

2-{4-[(4S,5R)-2-(4-*tert*-Butyl-2-ethoxy-phenyl)-4,5-bis-(4-chloro-phenyl)-4,5-dimethyl-4,5-dihydro-imidazole-1-carbonyl]-piperazin-1-yl}-acetamide



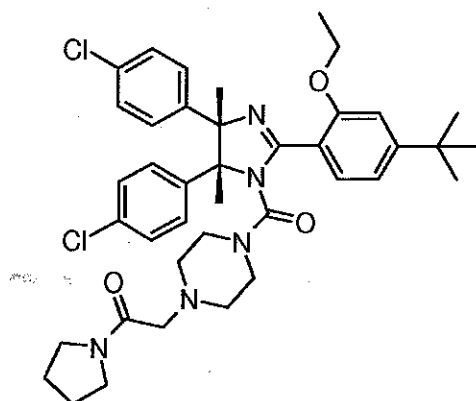
In a manner analogous to the method described in example 5, (4S,5R)-2-(4-*tert*-butyl-2-ethoxy-phenyl)-4,5-bis-(4-chloro-phenyl)-4,5-dimethyl-4,5-dihydro-imidazole-1-carbonyl chloride (example 4) was reacted with 2-piperazin-1-yl-acetamide dihydrochloride (Matrix Scientific) to give the title compound. HR-MS (ES, m/z) calculated for $C_{36}H_{44}N_5O_3Cl_2$ $[(M+H)^+]$ 664.2816, observed 664.2810.

10

Example 10

2-{4-[(4S,5R)-2-(4-*tert*-Butyl-2-ethoxy-phenyl)-4,5-bis-(4-chloro-phenyl)-4,5-dimethyl-4,5-dihydro-imidazole-1-carbonyl]-piperazin-1-yl}-1-pyrrolidin-1-yl-ethanone

15



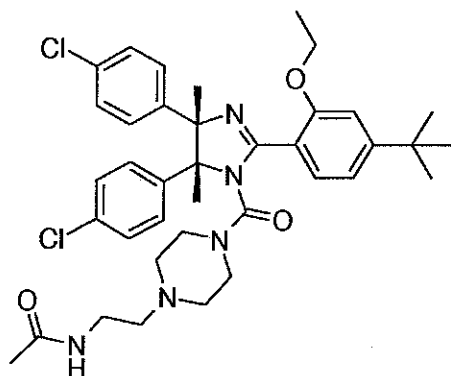
In a manner analogous to the method described in example 5, (4S,5R)-2-(4-*tert*-butyl-2-ethoxy-phenyl)-4,5-bis-(4-chloro-phenyl)-4,5-dimethyl-4,5-dihydro-imidazole-1-carbonyl chloride (example 4) was reacted with 2-piperazin-1-yl-1-

20

pyrrolidin-1-yl-ethanone (Aldrich) to give the title compound. HR-MS (ES, m/z) calculated for $C_{40}H_{50}N_5O_3Cl_2$ $[(M+H)^+]$ 718.3285, observed 718.3286.

Example 11

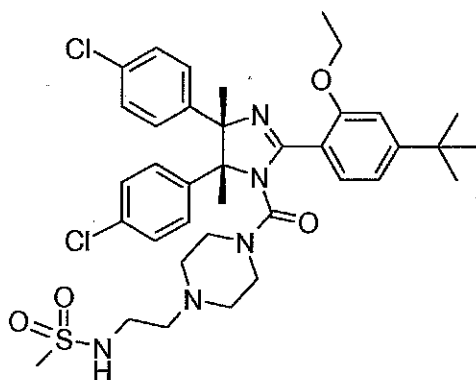
- 5 N-(2-{4-[(4S,5R)-2-(4-*tert*-Butyl-2-ethoxy-phenyl)-4,5-bis-(4-chloro-phenyl)-4,5-dimethyl-4,5-dihydro-imidazole-1-carbonyl]-piperazin-1-yl}-ethyl)-acetamide



- 10 In a manner analogous to the method described in example 5, (4S,5R)-2-(4-*tert*-butyl-2-ethoxy-phenyl)-4,5-bis-(4-chloro-phenyl)-4,5-dimethyl-4,5-dihydro-imidazole-1-carbonyl chloride (example 4) was reacted with N-(2-piperazin-1-yl-ethyl)-acetamide dihydrochloride (prepared as described in Fotouhi, N. *et al.* WO 2005110996) to give the title compound. HR-MS (ES, m/z) calculated for $C_{38}H_{48}N_5O_3Cl_2$ $[(M+H)^+]$ 692.3129, observed 692.3125.

Example 12

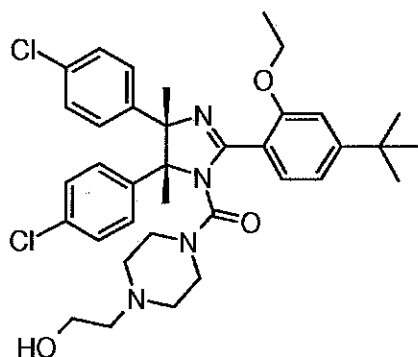
- 15 N-(2-{4-[(4S,5R)-2-(4-*tert*-Butyl-2-ethoxy-phenyl)-4,5-bis-(4-chloro-phenyl)-4,5-dimethyl-4,5-dihydro-imidazole-1-carbonyl]-piperazin-1-yl}-ethyl)-methanesulfonamide



In a manner analogous to the method described in example 5, (4S,5R)-2-(4-*tert*-butyl-2-ethoxy-phenyl)-4,5-bis-(4-chloro-phenyl)-4,5-dimethyl-4,5-dihydro-imidazole-1-carbonyl chloride (example 4) was reacted with N-(2-piperazin-1-yl-ethyl)-methanesulfonamide dihydrochloride (prepared as described in Fotouhi, N. *et al.* WO 2005110996) to give the title compound. HR-MS (ES, *m/z*) calculated for C₃₇H₄₈N₅O₄SCl₂ [(M+H)⁺] 782.2799, observed 782.2787.

Example 13

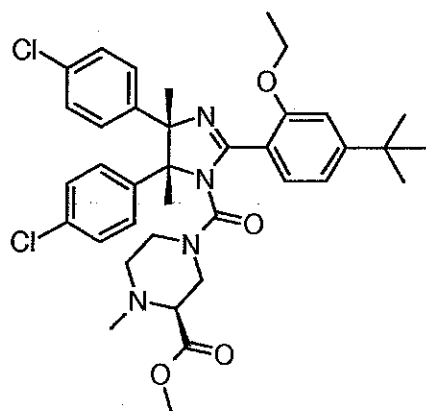
[(4S,5R)-2-(4-*tert*-Butyl-2-ethoxy-phenyl)-4,5-bis-(4-chloro-phenyl)-4,5-dimethyl-4,5-dihydro-imidazol-1-yl]-[4-(2-hydroxy-ethyl)-piperazin-1-yl]-methanone



In a manner analogous to the method described in example 5, (4S,5R)-2-(4-*tert*-butyl-2-ethoxy-phenyl)-4,5-bis-(4-chloro-phenyl)-4,5-dimethyl-4,5-dihydro-imidazole-1-carbonyl chloride (example 4) was reacted with 2-piperazin-1-yl-ethanol (Chemical Dynamics) to give the title compound. HR-MS (ES, *m/z*) calculated for C₃₆H₄₅N₄O₃Cl₂ [(M+H)⁺] 651.2863, observed 651.2863.

Example 14

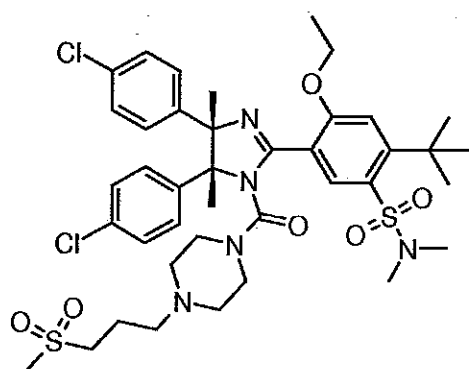
(S)-4-[(4S,5R)-2-(4-*tert*-Butyl-2-ethoxy-phenyl)-4,5-bis-(4-chloro-phenyl)-4,5-dimethyl-4,5-dihydro-imidazole-1-carbonyl]-1-methyl-piperazine-2-carboxylic acid methyl ester



In a manner analogous to the method described in example 5, (4S,5R)-2-(4-*tert*-butyl-2-ethoxy-phenyl)-4,5-bis-(4-chloro-phenyl)-4,5-dimethyl-4,5-dihydroimidazole-1-carbonyl chloride (example 4) was reacted with (S)-1-methyl-piperazine-2-carboxylic acid methyl ester (Aldrich) to give the title compound. HR-MS (ES, m/z) calculated for $C_{37}H_{45}N_4O_4Cl_2$ $[(M+H)^+]$ 679.2813, observed 679.2805.

10 **Example 15**

5-[(4S,5R)-4,5-Bis-(4-chloro-phenyl)-1-[4-(3-methanesulfonyl-propyl)-piperazine-1-carbonyl]-4,5-dimethyl-4,5-dihydro-1H-imidazol-2-yl]-2-*tert*-butyl-4-ethoxy-N,N-dimethyl-benzenesulfonamide



15

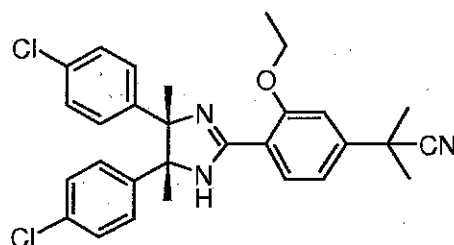
In a manner analogous to the method described in example 2, *meso*-2,3-bis-(4-chlorophenyl)-2,3-butanediamine (example 1) was reacted with 4-*tert*-butyl-5-dimethylsulfamoyl-2-ethoxy-benzoic acid methyl ester (prepared in an analogous manner as described in example 43) in the presence of trimethylaluminum to give *rac*-5-[(4S*,5R*)-4,5-bis-(4-chloro-phenyl)-4,5-

dimethyl-4,5-dihydro-1H-imidazol-2-yl]-2-*tert*-butyl-4-ethoxy-N,N-dimethyl-benzenesulfonamide.

In a manner analogous to the method described in example 3, *rac*-5-[(4*S**,5*R**)-4,5-bis-(4-chloro-phenyl)-4,5-dimethyl-4,5-dihydro-1H-imidazol-2-yl]-2-*tert*-butyl-4-ethoxy-N,N-dimethyl-benzenesulfonamide was reacted with phosgene in the presence of triethylamine to give *rac*-(4*S**,5*R**)-2-(4-*tert*-butyl-5-dimethylsulfamoyl-2-ethoxy-phenyl)-4,5-bis-(4-chloro-phenyl)-4,5-dimethyl-4,5-dihydro-imidazole-1-carbonyl chloride. The carbamoyl chloride was then reacted with 1-(3-methanesulfonyl-propyl)-piperazine dihydrochloride (prepared as described in Fotouhi, N. *et al.* WO 2005110996) in the presence of triethylamine to give the title compound as a racemic mixture. The enantiomers were then separated by supercritical fluid chromatography (Berger Instrument Multi-Gram II, Daicel ChiralPak OD-H 3 x 25 cm, 35 °C at 100 bar, eluting with 30% methanol in carbon dioxide). HR-MS (ES, *m/z*) calculated for C₄₀H₅₃N₅O₆S₂Cl₂ [(M+H)⁺] 834.2887, observed 834.2878.

Example 16

rac-2-{4-[(4*S**,5*R**)-4,5-Bis-(4-chloro-phenyl)-4,5-dimethyl-4,5-dihydro-1H-imidazol-2-yl]-3-ethoxy-phenyl}-2-methyl-propionitrile



20

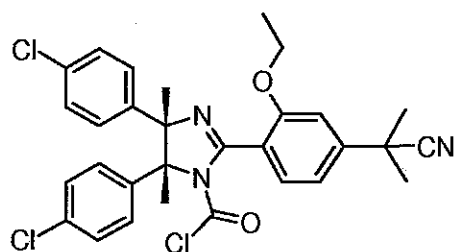
In a manner analogous to the method described in example 2, *meso*-2,3-bis-(4-chlorophenyl)-2,3-butanediamine was reacted with 4-(cyanodimethylmethyl)-2-ethoxybenzoic acid methyl ester (prepared as described in Fotouhi, N. *et al.* WO 2005110996) in the presence of trimethylaluminum to give the title compound. LR-MS: 506.0 [(M+H)⁺]

25

Example 17

rac-(4*S**,5*R**)-4,5-Bis-(4-chloro-phenyl)-2-[4-(cyano-dimethyl-methyl)-2-ethoxy-phenyl]-4,5-dimethyl-4,5-dihydro-imidazole-1-carbonyl chloride

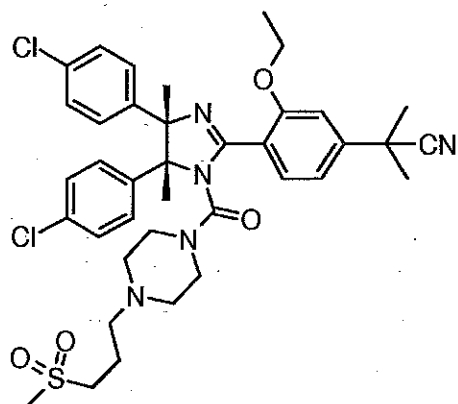
30



In a manner analogous to the method described in example 3, 2-[4-[*rac*-
(4*S**,5*R**)-4,5-bis-(4-chloro-phenyl)-4,5-dimethyl-4,5-dihydro-1*H*-imidazol-2-yl]-3-
ethoxy-phenyl]-2-methyl-propionitrile (example 17) was reacted with phosgene in
the presence of triethylamine to give the title compound.

Example 18

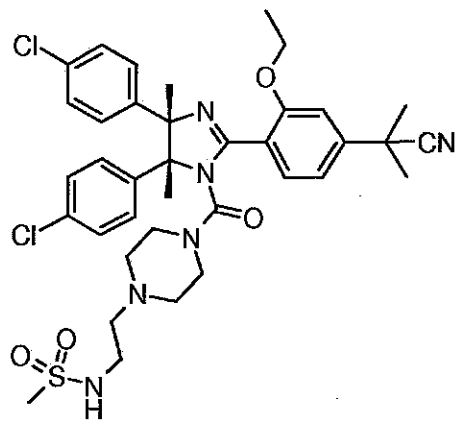
2-(4-[(4*S*,5*R*)-4,5-Bis-(4-chloro-phenyl)-1-[4-(3-methanesulfonyl-propyl)-
piperazine-1-carbonyl]-4,5-dimethyl-4,5-dihydro-1*H*-imidazol-2-yl]-3-ethoxy-
phenyl)-2-methyl-propionitrile



In a manner analogous to the method described in example 5, *rac*-
(4*S**,5*R**)-4,5-bis-(4-chloro-phenyl)-2-[4-(cyano-dimethyl-methyl)-2-ethoxy-
phenyl]-4,5-dimethyl-4,5-dihydro-imidazole-1-carbonyl chloride was reacted with
1-(3-methanesulfonyl-propyl)-piperazine dihydrochloride (prepared as described
in Fotouhi, N. *et al.* WO 2005110996) to give the title compound as a racemic
mixture. The enantiomers were then separated by supercritical fluid
chromatography (Berger Instrument Multi-Gram II, Daicel ChiralPak OD-H 3 x 25
cm, 35 °C at 100 bar, eluting with 35% methanol in carbon dioxide). LR-MS:
738.0 [(M+H)⁺]

Example 19

N-[2-(4-((4S,5R)-4,5-Bis-(4-chloro-phenyl)-2-[4-(cyano-dimethyl-methyl)-2-ethoxy-phenyl]-4,5-dimethyl-4,5-dihydro-imidazole-1-carbonyl)-piperazin-1-yl)-ethyl]-methanesulfonamide



5

In a manner analogous to the method described in example 5, *rac*-(4S*,5R*)-4,5-bis-(4-chloro-phenyl)-2-[4-(cyano-dimethyl-methyl)-2-ethoxy-phenyl]-4,5-dimethyl-4,5-dihydro-imidazole-1-carbonyl chloride was reacted with

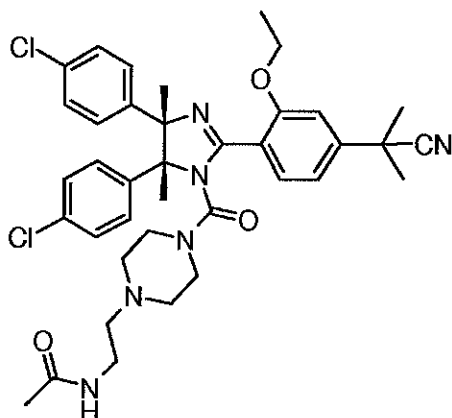
10 N-(2-piperazin-1-yl-ethyl)-methanesulfonamide dihydrochloride (prepared as described in Fotouhi, N. *et al.* WO 2005110996) to give the title compound as a racemic mixture. The enantiomers were then separated by supercritical fluid chromatography (Berger Instrument Multi-Gram II, Daicel ChiralPak OD-H 3 x 25 cm, 35 °C at 100 bar, eluting with 35% methanol in carbon dioxide). LR-MS:

15 739.3 [(M+H)⁺]

Example 20

N-[2-(4-((4S,5R)-4,5-Bis-(4-chloro-phenyl)-2-[4-(cyano-dimethyl-methyl)-2-ethoxy-phenyl]-4,5-dimethyl-4,5-dihydro-imidazole-1-carbonyl)-piperazin-1-yl)-ethyl]-acetamide

20



In a manner analogous to the method described in example 5, *rac*-(4*S**,5*R**)-4,5-bis-(4-chloro-phenyl)-2-[4-(cyano-dimethyl-methyl)-2-ethoxy-phenyl]-4,5-dimethyl-4,5-dihydro-imidazole-1-carbonyl chloride was reacted with

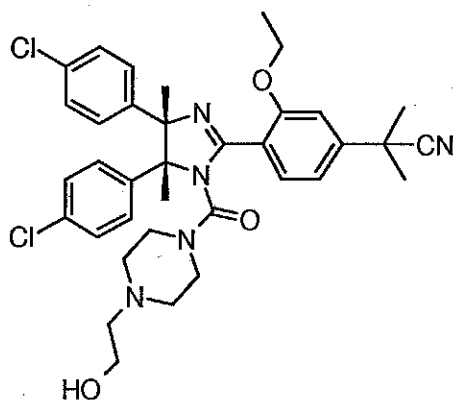
5 N-(2-piperazin-1-yl-ethyl)-acetamide dihydrochloride (prepared as described in Fotouhi, N. *et al.* WO 2005110996) to give the title compound as a racemic mixture. The enantiomers were then separated by supercritical fluid chromatography (Berger Instrument Multi-Gram II, Daicel ChiralPak OD-H 3 x 25 cm, 35 °C at 100 bar, eluting with 35% methanol in carbon dioxide). LR-MS:

10 703.3 [(M+H)⁺]

Example 21

2-(4-{(4*S*,5*R*)-4,5-Bis-(4-chloro-phenyl)-1-[4-(2-hydroxy-ethyl)-piperazine-1-carbonyl]-4,5-dimethyl-4,5-dihydro-1*H*-imidazol-2-yl}-3-ethoxy-phenyl)-2-methyl-propionitrile

15



In a manner analogous to the method described in example 5, *rac*-(4*S**,5*R**)-4,5-bis-(4-chloro-phenyl)-2-[4-(cyano-dimethyl-methyl)-2-ethoxy-phenyl]-4,5-dimethyl-4,5-dihydro-imidazole-1-carbonyl chloride was reacted with

20

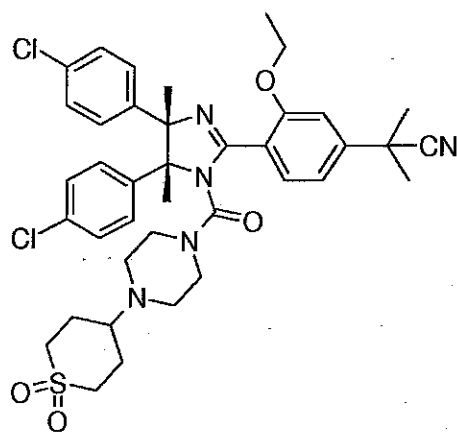
2-piperazin-1-yl-ethanol (Chemical Dynamics) to give the title compound as a racemic mixture. The enantiomers were then separated by supercritical fluid chromatography (Berger Instrument Multi-Gram II, Daicel ChiralPak OD-H 3 x 25 cm, 35 °C at 100 bar, eluting with 35% methanol in carbon dioxide). LR-MS:

5 662.2 [(M+H)⁺]

Example 22

2-(4-((4S,5R)-4,5-Bis-(4-chloro-phenyl)-1-[4-(1,1-dioxo-tetrahydro-2H-thiopyran-4-yl)-piperazine-1-carbonyl]-4,5-dimethyl-4,5-dihydro-1H-imidazol-2-yl)-3-ethoxy-phenyl)-2-methyl-propionitrile

10



To a stirred solution of tetrahydrothiopyran-4-one (5.30 g, 43.1 mmol, Aldrich) in 50 mL of ethyl acetate was added dropwise 32% peracetic acid (24 g, 110 mmol) at a rate to avoid reflux. After the addition, the mixture was cooled to room temperature and the solid filtered to give 1,1-dioxo-tetrahydro-thiopyran-4-one as a white solid (5.69 g, 89%).

15

Tetrahydro-4H-thiopyran-4-one (6 g, 40.5 mmol) was dissolved in 1,2-dichloroethane (250 mL) with some help of heating. When the temperature goes back to room temperature, 1-Boc-piperazine (7.62 g, 41 mmol), sodium triacetoxyborohydride (17.01 g, 56.7 mmol) were added followed by glacial acetic acid (2.4 g, 41 mmol). The reaction mixture was stirred at room temperature overnight. It was quenched with water, and the layers were separated. The aqueous layer was extracted with 1,2-dichloroethane (3 x 20 mL). The combined organic extracts were dried over sodium sulfate, filtered and

20

25

concentrated to give a white solid. The white solid was purified by flash chromatography (ISCO machine, silica gel, eluting with 2-7% methanol-ethyl acetate in a period of 30 min) to give 4-(1,1-dioxo-tetrahydro-2H-thiopyran-4-yl)-piperazine-1-carboxylic acid *tert*-butyl ester as a white solid (9.3 g, 69%). LR-

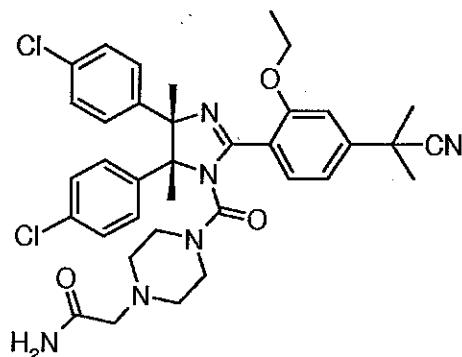
5 MS: 334 [(M+H)⁺]

To a stirred solution of 4-(1,1-dioxo-tetrahydro-2H-thiopyran-4-yl)-piperazine-1-carboxylic acid *tert*-butyl ester (8.02 g, 25 mmol) in methanol at 45 °C (150 mL) was added 4 N hydrochloric acid in 1,4-dioxane (100 mmol, 25 mL, Aldrich). The mixture was stirred at 45 °C for 7 h until thin layer
10 chromatography (5% methanol in ethyl acetate) indicated that the reaction was complete. The solvent was removed under reduced pressure to give 1-(1,1-dioxo-tetrahydro-2H-thiopyran-4-yl)-piperazine dihydrochloride as a white solid (7.24 g, 99.5%). LR-MS: 218 [(M+H)⁺]

In a manner analogous to the method described in example 5, *rac*-
15 (4S*,5R*)-4,5-bis-(4-chloro-phenyl)-2-[4-(cyano-dimethyl-methyl)-2-ethoxy-phenyl]-4,5-dimethyl-4,5-dihydro-imidazole-1-carbonyl chloride was reacted with 1-(1,1-dioxo-tetrahydro-2H-thiopyran-4-yl)-piperazine dihydrochloride to give the title compound as a racemic mixture. The enantiomers were then separated by supercritical fluid chromatography (Berger Instrument Multi-Gram II,
20 Daicel ChiralPak OD-H 3 x 25 cm, 35 °C at 100 bar, eluting with 35% methanol in carbon dioxide). LR-MS: 749.63 [(M+H)⁺]

Example 23

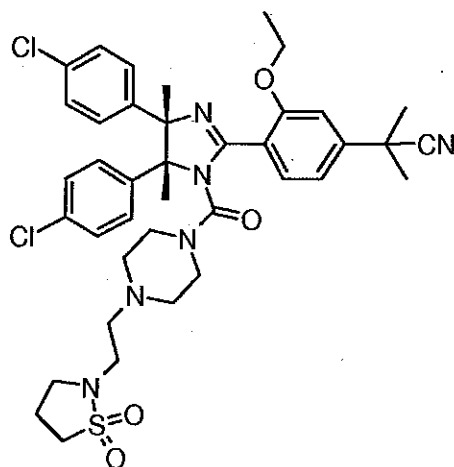
2-(4-((4S,5R)-4,5-Bis-(4-chloro-phenyl)-2-[4-(cyano-dimethyl-methyl)-2-ethoxy-phenyl]-4,5-dimethyl-4,5-dihydro-imidazole-1-carbonyl)-piperazin-1-yl)-acetamide
25



In a manner analogous to the method described in example 5, *rac*-
 (4*S**,5*R**)-4,5-bis-(4-chloro-phenyl)-2-[4-(cyano-dimethyl-methyl)-2-ethoxy-
 phenyl]-4,5-dimethyl-4,5-dihydro-imidazole-1-carbonyl chloride was reacted
 with 2-piperazin-1-yl-acetamide dihydrochloride (Matrix Scientific) to give the title
 5 compound as a racemic mixture. The enantiomers were then separated by
 supercritical fluid chromatography (Berger Instrument Multi-Gram II, Daicel
 ChiralPak OD-H 3 x 25 cm, 35 °C at 100 bar, eluting with 35% methanol in
 carbon dioxide). LR-MS: 675.2 [(M+H)⁺]

10 **Example 24**

2-[4-((4*S*,5*R*)-4,5-Bis-(4-chloro-phenyl)-1-{4-[2-(1,1-dioxo-isothiazolidin-2-yl)-
 ethyl]-piperazine-1-carbonyl]-4,5-dimethyl-4,5-dihydro-1*H*-imidazol-2-yl)-3-
 ethoxy-phenyl]-2-methyl-propionitrile



15

To a stirred solution of 1-Boc-4-(2-aminoethyl)-piperazine (1.26 g, 6.8
 mmol, Aldrich) and triethylamine (1 mL) in tetrahydrofuran (10 mL), 3-chloro-
 propylsulfonyl chloride (0.68 mL, 6.94 mmol, Aldrich) was added slowly at room
 temperature. The mixture was stirred for 30 min at room temperature and the
 20 reaction was quenched with water. It was extracted with ethyl acetate and the
 extracts were combined and dried over anhydrous sodium sulfate. The solids
 were filtered off, and the filtrate was concentrated *in vacuo* to give 4-[2-(3-chloro-
 propane-1-sulfonylamino)-ethyl]-piperazine-1-carboxylic acid *tert*-butyl ester. It
 was taken in tetrahydrofuran (20 mL), and cesium carbonate (500 mg) sodium
 25 iodide (80 mg) were added and the mixture was stirred at reflux overnight. The
 mixture was cooled to room temperature and poured into water. It was extracted

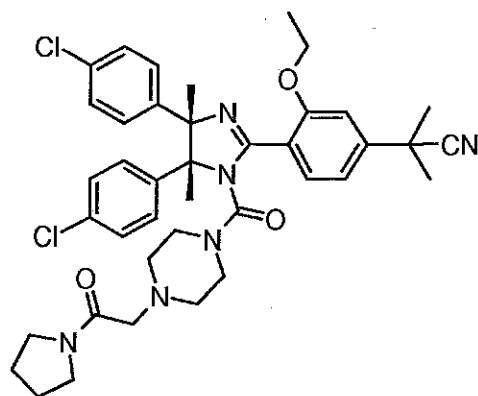
with ethyl acetate (3 x 15 mL), and the extracts were combined and dried over anhydrous sodium sulfate. The solids were filtered off, and the filtrate was concentrated *in vacuo* to give 2.01 g of 4-[2-(1,1-dioxo-isothiazolidin-2-yl)-ethyl]-piperazine-1-carboxylic acid *tert*-butyl ester as a solid. LR-MS: 334 [(M+H)⁺]

- 5 4-[2-(1,1-Dioxo-isothiazolidin-2-yl)-ethyl]-piperazine-1-carboxylic acid *tert*-butyl ester (2.01 g) was treated with 30% trifluoroacetic acid in dichloromethane (10 mL), and the mixture was stirred at room temperature for 30 min. The mixture was concentrated *in vacuo* to give 2.46 g of 1-[2-(1,1-dioxo-isothiazolidin-2-yl)-ethyl]-piperazine trifluoroacetate as a solid. LR-MS: 234
10 [(M+H)⁺]

- In a manner analogous to the method described in example 5, *rac*-(4S*,5R*)-4,5-bis-(4-chloro-phenyl)-2-[4-(cyano-dimethyl-methyl)-2-ethoxy-phenyl]-4,5-dimethyl-4,5-dihydro-imidazole-1-carbonyl chloride was reacted with
15 1-[2-(1,1-dioxo-isothiazolidin-2-yl)-ethyl]-piperazine trifluoroacetate to give the title compound as a racemic mixture. The enantiomers were then separated by supercritical fluid chromatography (Berger Instrument Multi-Gram II, Daicel ChiralPak OD-H 3 x 25 cm, 35 °C at 100 bar, eluting with 35% methanol in carbon dioxide). LR-MS: 765.0 [(M+H)⁺]

20 **Example 25**

2-(4-[(4S,5R)-4,5-Bis-(4-chloro-phenyl)-4,5-dimethyl-1-[4-(2-oxo-2-pyrrolidin-1-yl-ethyl)-piperazine-1-carbonyl]-4,5-dihydro-1H-imidazol-2-yl]-3-ethoxy-phenyl)-2-methyl-propionitrile



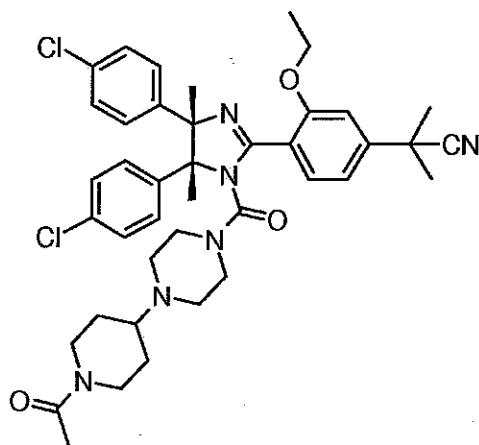
- 25 In a manner analogous to the method described in example 5, *rac*-(4S*,5R*)-4,5-bis-(4-chloro-phenyl)-2-[4-(cyano-dimethyl-methyl)-2-ethoxy-phenyl]-4,5-dimethyl-4,5-dihydro-imidazole-1-carbonyl chloride was reacted with

2-piperazin-1-yl-1-pyrrolidin-1-yl-ethanone (Aldrich) to give the title compound as a racemic mixture. The enantiomers were then separated by supercritical fluid chromatography (Berger Instrument Multi-Gram II, Daicel ChiralPak OD-H 3 x 25 cm, 35 °C at 100 bar, eluting with 20% methanol in carbon dioxide). LR-MS:

5 729.4 [(M+H)⁺]

Example 26

2-{4-[(4S,5R)-1-[4-(1-Acetyl-piperidin-4-yl)-piperazine-1-carbonyl]-4,5-bis-(4-chloro-phenyl)-4,5-dimethyl-4,5-dihydro-1H-imidazol-2-yl]-3-ethoxy-phenyl}-2-methyl-propionitrile



N-*tert*-butoxycarbonyl-piperazine (1.86 g, 10 mmol, Lancaster), N-Fmoc-4-oxo-piperidine (3.21 g, 10 mmol, Aldrich) and titanium(IV) isopropoxide (3.72 mL, Aldrich) were combined, and the mixture was stirred at room temperature for 1 h. Then ethyl alcohol (10 mL) was added followed by sodium cyanoborohydride (0.47 g, 7.48 mmol, Aldrich), and the mixture was stirred overnight. Water (2 mL) was added and the mixture was filtered. The solid was washed with ethyl alcohol and the filtrate was combined. The solvent was removed under reduced pressure and the residue was purified by flash chromatography (ISCO machine, silica gel, eluting with 20% ethyl acetate in hexane for a period of 30 min) to give 4-(1-Fmoc-piperidin-4-yl)-piperazine-1-carboxylic acid *tert*-butyl ester as a white foam (1.02 g).

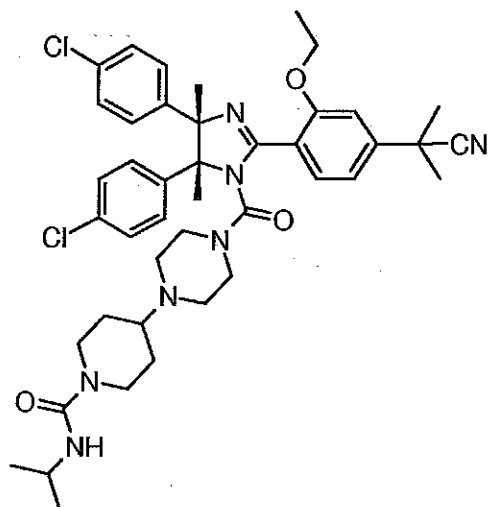
25 4-(1-Fmoc-piperidin-4-yl)-piperazine-1-carboxylic acid *tert*-butyl ester (0.3 g, 0.61 mmol) was stirred with 20% piperidine in methylene chloride for 40 min.

The mixture was concentrated to dryness to give 4-piperidin-4-yl-piperazine-1-carboxylic acid *tert*-butyl ester. It was then dissolved in tetrahydrofuran (5 mL), and triethylamine (308 mg, 3.05 mmol) and acetic anhydride (86 mg, 0.9 mmol) were added, respectively. After the reaction mixture was stirred for 2 h, water and ethyl acetate were added. The layers were separated, and the aqueous layer was extracted with ethyl acetate. The combined organic extracts were dried over anhydrous sodium sulfate. The solids were filtered off, and the filtrate was concentrated to give 4-(1-acetyl-piperidin-4-yl)-piperazine-1-carboxylic acid *tert*-butyl ester. It was dissolved in methylene chloride (7 mL), cooled with an ice bath and trifluoroacetic acid was added. The reaction mixture was stirred for 30 min, and the solvent was removed. The residue was triturated with diethyl ether and the solvent was removed to give 1-(4-piperazin-1-yl-piperidin-1-yl)-ethanone trifluoroacetate as a light-yellow foam (151 mg, 76%). LR-MS: 212 [(M+H)⁺]

In a manner analogous to the method described in example 5, *rac*-(4S*,5R*)-4,5-bis-(4-chloro-phenyl)-2-[4-(cyano-dimethyl-methyl)-2-ethoxy-phenyl]-4,5-dimethyl-4,5-dihydro-imidazole-1-carbonyl chloride was reacted with 1-(4-piperazin-1-yl-piperidin-1-yl)-ethanone trifluoroacetate to give the title compound as a racemic mixture. The enantiomers were then separated by supercritical fluid chromatography (Berger Instrument Multi-Gram II, Daicel ChiralPak OD-H 3 x 25 cm, 35 °C at 100 bar, eluting with 35% methanol in carbon dioxide). LR-MS: 743.4 [(M+H)⁺]

Example 27

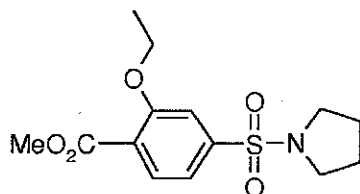
4-(4-[(4S,5R)-4,5-Bis-(4-chloro-phenyl)-2-[4-(cyano-dimethyl-methyl)-2-ethoxy-phenyl]-4,5-dimethyl-4,5-dihydro-imidazole-1-carbonyl]-piperazin-1-yl)-piperidine-1-carboxylic acid isopropylamide



To a solution of 4-piperidin-4-yl-piperazine-1-carboxylic acid *tert*-butyl ester (108 mg, 0.4 mmol, example 27) in dichloromethane (2 mL) was added isopropyl isocyanate. The mixture was stirred for 1 h and quenched with water. After aqueous workup with water and dichloromethane, the organic layers was dried over anhydrous magnesium sulfate. The solids were filtered off, and the filtrate was concentrated to give 4-(1-isopropylcarbamoyl-piperidin-4-yl)-piperazine-1-carboxylic acid *tert*-butyl ester as a viscous oil.

In a manner analogous to the method described in example 27, 4-(1-isopropylcarbamoyl-piperidin-4-yl)-piperazine-1-carboxylic acid *tert*-butyl ester was treated with trifluoroacetic acid to give 4-piperazin-1-yl-piperidine-1-carboxylic acid isopropylamide trifluoroacetate as a yellow solid. LR-MS: 255 [(M+H)⁺]

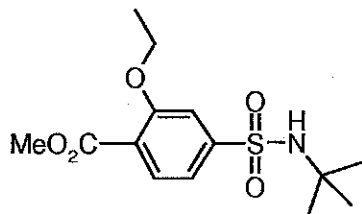
In a manner analogous to the method described in example 5, *rac*-(4S*,5R*)-4,5-bis-(4-chloro-phenyl)-2-[4-(cyano-dimethyl-methyl)-2-ethoxy-phenyl]-4,5-dimethyl-4,5-dihydro-imidazole-1-carbonyl chloride was reacted with 4-piperazin-1-yl-piperidine-1-carboxylic acid isopropylamide trifluoroacetate to give the title compound as a racemic mixture. The enantiomers were then separated by supercritical fluid chromatography (Berger Instrument Multi-Gram II, Daicel ChiralPak OD-H 3 x 25 cm, 35 °C at 100 bar, eluting with 30% methanol in carbon dioxide). LR-MS: 786.0 [(M+H)⁺]

Example 28**2-Ethoxy-4-(pyrrolidine-1-sulfonyl)-benzoic acid methyl ester**

- 5 2-Ethoxy-4-thiol-benzoic acid (1.6 g, 8.08 mmol, prepared according to Robertson, D. *et al. J. Med. Chem.* **1985**, 28, 717-727) was taken up in methanol (80 mL) and cooled to 0 °C. Thionyl chloride (1.2 mL, 16.2 mmol) was added slowly. The reaction mixture was allowed to warm slowly to room temperature and stirred overnight. Evaporation of the solvents afforded a mixture of sulfide and disulfide methyl ester (1.9 g, 100%) as yellow oil, which was used without further purification. This crude sulfide/disulfide ester was taken up in acetic acid and cooled to 0 °C. A small amount of toluene was added to the reaction mixture to prevent the reaction mixture from freezing. Chlorine gas (Cl₂) was bubbled into the reaction mixture until thin layer chromatography (50% ethyl acetate in hexanes) showed consumption of starting material. Argon gas (Ar) was bubbled into the reaction mixture to remove excess chlorine. The reaction mixture was concentrated to dryness *in vacuo* to give quantitative yield of the methyl 4-chlorosulfonyl-2-ethoxy-benzoate. It was taken up in anhydrous methylene chloride (50 mL) and cooled to 0 °C. Triethylamine (8.5 mL, 62 mmol) and pyrrolidine (2.7 mL, 32.3 mmol) were added. The reaction mixture was allowed to slowly warm to room temperature and stirred at room temperature for 16 h. The reaction mixture was washed with water, dried over magnesium sulfate and concentrated. Purification of the crude residue by flash column chromatography (40 g of silica gel, eluting with 15-30% ethyl acetate in hexanes) gave -ethoxy-4-(pyrrolidine-1-sulfonyl)-benzoic acid methyl ester. HR-MS (ES, *m/z*) calculated for C₁₄H₂₀NO₅ [(M+H)⁺] 314.1057, observed 314.1056.
- 10
- 15
- 20
- 25

Example 29

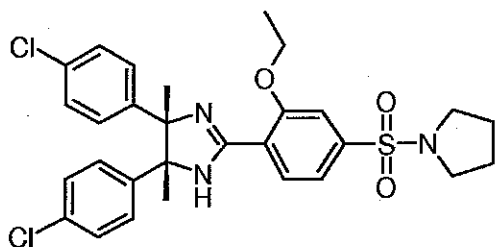
4-*tert*-Butylsulfamoyl-2-ethoxy-benzoic acid methyl ester



- 5 In a manner analogous to the method described in example 29, methyl 4-chlorosulfonyl-2-ethoxy-benzoate was reacted with *tert*-butylamine to give 4-*tert*-butylsulfamoyl-2-ethoxy-benzoic acid methyl ester.

Example 30

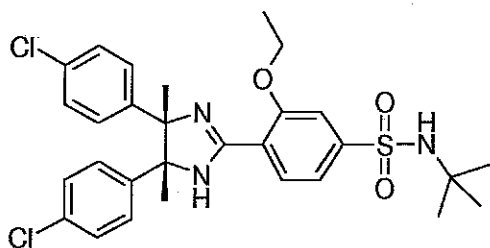
- 10 *rac*-(4*S*^{*},5*R*^{*})-4,5-Bis-(4-chloro-phenyl)-2-[2-ethoxy-4-(pyrrolidine-1-sulfonyl)-phenyl]-4,5-dimethyl-4,5-dihydro-1*H*-imidazole



- 15 In a manner analogous to the method described in example 2, *meso*-2,3-bis-(4-chlorophenyl)-2,3-butanediamine was reacted with 2-ethoxy-4-(pyrrolidine-1-sulfonyl)-benzoic acid methyl ester in the presence of trimethylaluminum to give the title compound. HR-MS (ES, *m/z*) calculated for C₂₉H₃₂N₃O₃SCl₂ [(*M*+*H*)⁺] 572.1536, observed 572.1534.

20 **Example 31**

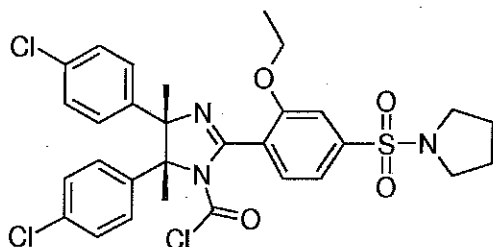
rac-(4*S*^{*},5*R*^{*})-4-[(4,5-Bis-(4-chloro-phenyl)-4,5-dimethyl-4,5-dihydro-1*H*-imidazol-2-yl]-*N*-*tert*-butyl-3-ethoxy-benzenesulfonamide



In a manner analogous to the method described in example 2, *meso*-2,3-bis-(4-chlorophenyl)-2,3-butanedi-amine was reacted with 4-*tert*-butylsulfonyl-2-ethoxy-benzoic acid methyl ester in the presence of trimethylaluminum to give the title compound. HR-MS (ES, m/z) calculated for $C_{29}H_{34}N_3O_3SCl_2$ [(M+H)⁺] 574.1693, observed 574.1589.

Example 32

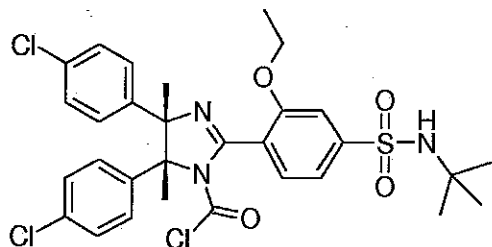
10 *rac*-(4S*,5R*)-4,5-Bis-(4-chloro-phenyl)-2-[2-ethoxy-4-(pyrrolidine-1-sulfonyl)-phenyl]-4,5-dimethyl-4,5-dihydro-imidazole-1-carbonyl chloride



In a manner analogous to the method described in example 3, *rac*-(4S*,5R*)-4,5-bis-(4-chloro-phenyl)-2-[2-ethoxy-4-(pyrrolidine-1-sulfonyl)-phenyl]-4,5-dimethyl-4,5-dihydro-1H-imidazole (example 31) was reacted with phosgene in the presence of triethylamine to give the title compound.

Example 33

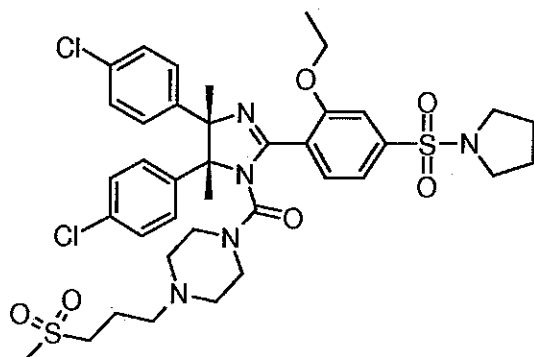
20 *rac*-(4S*,5R*)-2-(4-*tert*-Butylsulfonyl-2-ethoxy-phenyl)-4,5-bis-(4-chloro-phenyl)-4,5-dimethyl-4,5-dihydro-imidazole-1-carbonyl chloride



In a manner analogous to the method described in example 3, *rac*-
 (4S*,5R*)-4-[(4,5-Bis-(4-chloro-phenyl)-4,5-dimethyl-4,5-dihydro-1H-imidazol-2-yl]-N-*tert*-butyl-3-ethoxy-benzenesulfonamide (example 32) was reacted with
 5 phosgene in the presence of triethylamine to give the title compound.

Example 34

{(4S,5R)-4,5-Bis-(4-chloro-phenyl)-2-[2-ethoxy-4-(pyrrolidine-1-sulfonyl)-phenyl]-
 10 4,5-dimethyl-4,5-dihydro-imidazol-1-yl]-[4-(3-methanesulfonyl-propyl)-piperazin-
 1-yl]-methanone

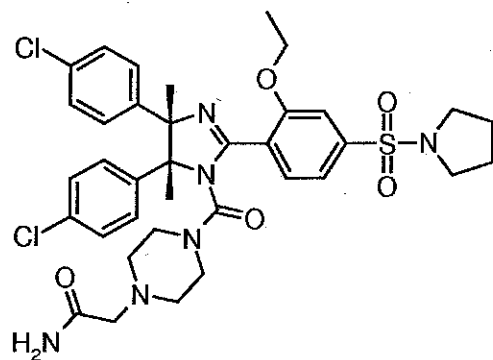


In a manner analogous to the method described in example 5, *rac*-
 15 (4S*,5R*)-4,5-bis-(4-chloro-phenyl)-2-[2-ethoxy-4-(pyrrolidine-1-sulfonyl)-phenyl]-
 4,5-dimethyl-4,5-dihydro-imidazole-1-carbonyl chloride was reacted with 1-(3-
 methanesulfonyl-propyl)-piperazine dihydrochloride (prepared as described in
 Fotouhi, N. *et al.* WO 2005110996) to give the title compound as a racemic
 mixture. The enantiomers were then separated by supercritical fluid
 20 chromatography (Berger Instrument Multi-Gram II, Daicel ChiralPak OD-H 3 x 25
 cm, 35 °C at 100 bar, eluting with 25% methanol in carbon dioxide). HR-MS

(ES, m/z) calculated for $C_{38}H_{47}N_6O_5S_2Cl_2$ $[(M+H)^+]$ 804.2418, observed 804.2413.

Example 35

- 5 2-(4-((4S,5R)-4,5-Bis-(4-chloro-phenyl)-2-[2-ethoxy-4-(pyrrolidine-1-sulfonyl)-phenyl]-4,5-dimethyl-4,5-dihydro-imidazole-1-carbonyl)-piperazin-1-yl)-acetamide

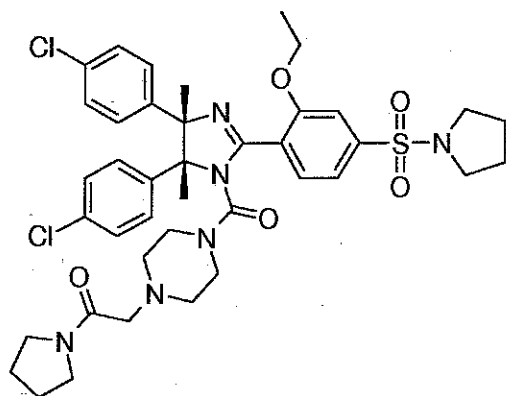


- In a manner analogous to the method described in example 5, *rac*-
 10 (4S*,5R*)-4,5-bis-(4-chloro-phenyl)-2-[2-ethoxy-4-(pyrrolidine-1-sulfonyl)-phenyl]-4,5-dimethyl-4,5-dihydro-imidazole-1-carbonyl chloride was reacted with 2-piperazin-1-yl-acetamide dihydrochloride (Matrix Scientific) to give the title compound as a racemic mixture. The enantiomers were then separated by supercritical fluid chromatography (Berger Instrument Multi-Gram II, Daicel
 15 ChiralPak OD-H 3 x 25 cm, 35 °C at 100 bar, eluting with 25% of 1:1 ethanol/acetonitrile in carbon dioxide).

HR-MS (ES, m/z) calculated for $C_{36}H_{42}N_6O_5SCl_2$ $[(M+H)^+]$ 741.2387, observed 741.2379.

20 Example 36

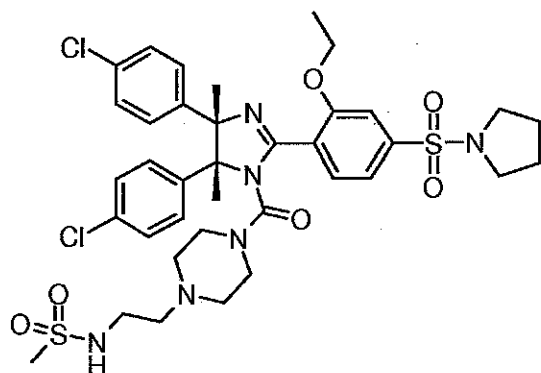
2-(4-((4S,5R)-4,5-Bis-(4-chloro-phenyl)-2-[2-ethoxy-4-(pyrrolidine-1-sulfonyl)-phenyl]-4,5-dimethyl-4,5-dihydro-imidazole-1-carbonyl)-piperazin-1-yl)-1-pyrrolidin-1-yl-ethanone



In a manner analogous to the method described in example 5, *rac*-
 (4S*,5R*)-4,5-bis-(4-chloro-phenyl)-2-[2-ethoxy-4-(pyrrolidine-1-sulfonyl)-phenyl]-
 4,5-dimethyl-4,5-dihydro-imidazole-1-carbonyl chloride was reacted with 2-
 5 piperazin-1-yl-1-pyrrolidin-1-yl-ethanone (Aldrich) to give the title compound as a
 racemic mixture. The enantiomers were then separated by supercritical fluid
 chromatography (Berger Instrument Multi-Gram II, Daicel ChiralPak OD-H 3 x 25
 cm, 35 °C at 100 bar, eluting with 30% of 1:1 ethanol/acetonitrile in carbon
 10 dioxide). HR-MS (ES, m/z) calculated for $C_{40}H_{48}N_6O_5SCl_2$ $[(M+H)^+]$ 795.2857,
 observed 795.2851.

Example 37

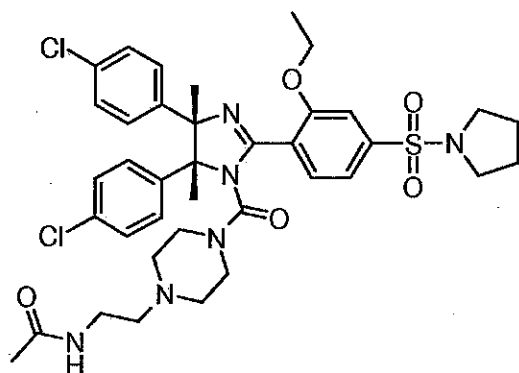
N-[2-(4-{(4S,5R)-4,5-Bis-(4-chloro-phenyl)-2-[2-ethoxy-4-(pyrrolidine-1-sulfonyl)-
 15 phenyl]-4,5-dimethyl-4,5-dihydro-imidazole-1-carbonyl}-piperazin-1-yl)-ethyl]-
 methanesulfonamide



In a manner analogous to the method described in example 5, *rac*-(4*S**,5*R**)-4,5-bis-(4-chloro-phenyl)-2-[2-ethoxy-4-(pyrrolidine-1-sulfonyl)-phenyl]-4,5-dimethyl-4,5-dihydro-imidazole-1-carbonyl chloride was reacted with N-(2-piperazin-1-yl-ethyl)-methanesulfonamide dihydrochloride (prepared as described in Fotouhi, N. *et al.* WO 2005110996) to give the title compound as a racemic mixture. The enantiomers were then separated by supercritical fluid chromatography (Berger Instrument Multi-Gram II, Daicel ChiralPak OD-H 3 x 25 cm, 35 °C at 100 bar, eluting with 35% methanol in carbon dioxide). HR-MS (ES, *m/z*) calculated for C₃₇H₄₆N₆O₆S₂Cl₂ [(M+H)⁺] 805.2370, observed 805.2372.

Example 38

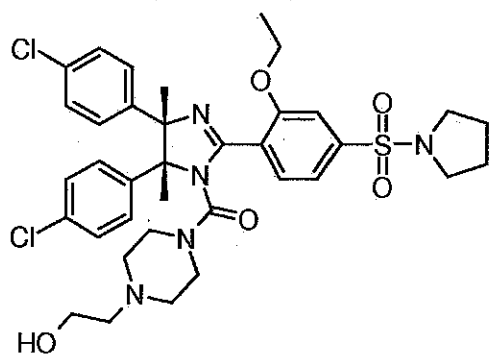
N-[2-(4-((4*S*,5*R*)-4,5-Bis-(4-chloro-phenyl)-2-[2-ethoxy-4-(pyrrolidine-1-sulfonyl)-phenyl]-4,5-dimethyl-4,5-dihydro-imidazole-1-carbonyl)-piperazin-1-yl)-ethyl]-acetamide



In a manner analogous to the method described in example 5, *rac*-(4*S**,5*R**)-4,5-bis-(4-chloro-phenyl)-2-[2-ethoxy-4-(pyrrolidine-1-sulfonyl)-phenyl]-4,5-dimethyl-4,5-dihydro-imidazole-1-carbonyl chloride was reacted with N-(2-piperazin-1-yl-ethyl)-acetamide dihydrochloride (prepared as described in Fotouhi, N. *et al.* WO 2005110996) to give the title compound as a racemic mixture. The enantiomers were then separated by supercritical fluid chromatography (Berger Instrument Multi-Gram II, Daicel ChiralPak OD-H 3 x 25 cm, 35 °C at 100 bar, eluting with 25% methanol in carbon dioxide). HR-MS (ES, *m/z*) calculated for C₃₈H₄₆N₆O₅SCl₂ [(M+H)⁺] 769.2700, observed 769.2697.

Example 39

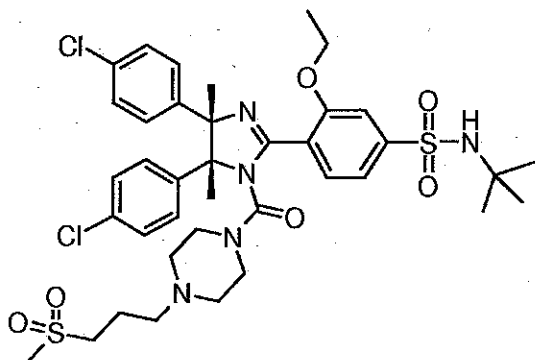
{(4S,5R)-4,5-Bis-(4-chloro-phenyl)-2-[2-ethoxy-4-(pyrrolidine-1-sulfonyl)-phenyl]-4,5-dimethyl-4,5-dihydro-imidazol-1-yl]-[4-(2-hydroxy-ethyl)-piperazin-1-yl]-methanone



In a manner analogous to the method described in example 5, *rac*-(4S*,5R*)-4,5-bis-(4-chloro-phenyl)-2-[2-ethoxy-4-(pyrrolidine-1-sulfonyl)-phenyl]-4,5-dimethyl-4,5-dihydro-imidazole-1-carbonyl chloride was reacted with 2-piperazin-1-yl-ethanol (Chemical Dynamics) to give the title compound as a racemic mixture. The enantiomers were then separated by supercritical fluid chromatography (Berger Instrument Multi-Gram II, Daicel ChiralPak OD-H 3 x 25 cm, 35 °C at 100 bar, eluting with 30% methanol in carbon dioxide). HR-MS (ES, *m/z*) calculated for C₃₆H₄₃N₅O₅SCl₂ [(M+H)⁺] 728.2435, observed 728.2431.

Example 40

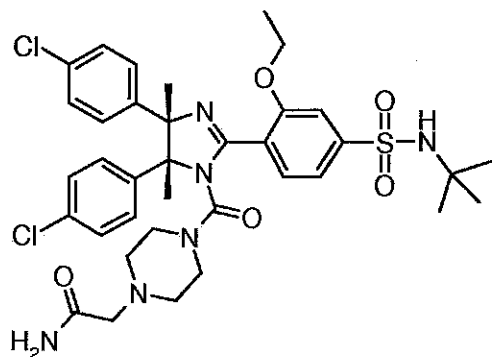
4-{(4S,5R)-4,5-Bis-(4-chloro-phenyl)-1-[4-(3-methanesulfonyl-propyl)-piperazine-1-carbonyl]-4,5-dimethyl-4,5-dihydro-1H-imidazol-2-yl}-N-*tert*-butyl-3-ethoxy-benzenesulfonamide



In a manner analogous to the method described in example 5, *rac*-
 (4S*,5R*)-2-(4-*tert*-butylsulfamoyl-2-ethoxy-phenyl)-4,5-bis-(4-chloro-phenyl)-4,5-
 5 dimethyl-4,5-dihydro-imidazole-1-carbonyl chloride was reacted with 1-(3-
 methanesulfonyl-propyl)-piperazine dihydrochloride (prepared as described in
 Fotouhi, N. *et al.* WO 2005110996) to give the title compound as a racemic
 mixture. The enantiomers were then separated by supercritical fluid
 chromatography (Berger Instrument Multi-Gram II, Daicel ChiralPak OD-H 3 x 25
 10 cm, 35 °C at 100 bar, eluting with 35% methanol in carbon dioxide). HR-MS
 (ES, *m/z*) calculated for C₃₈H₄₉N₅O₆S₂Cl₂ [(M+H)⁺] 806.2574, observed
 806.2579.

Example 41

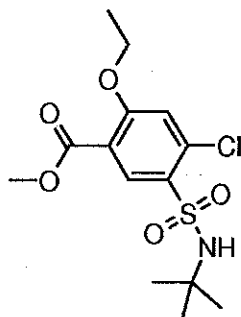
15 2-[4-[(4S,5R)-2-(4-*tert*-Butylsulfamoyl-2-ethoxy-phenyl)-4,5-bis-(4-chloro-phenyl)-
 4,5-dimethyl-4,5-dihydro-imidazole-1-carbonyl]-piperazin-1-yl]-acetamide



In a manner analogous to the method described in example 5, *rac*-(4S*,5R*)-2-(4-*tert*-butylsulfamoyl-2-ethoxy-phenyl)-4,5-bis-(4-chloro-phenyl)-4,5-dimethyl-4,5-dihydro-imidazole-1-carbonyl chloride was reacted with 2-piperazin-1-yl-acetamide dihydrochloride (Matrix Scientific) to give the title compound as a racemic mixture. The enantiomers were then separated by supercritical fluid chromatography (Berger Instrument Multi-Gram II, Daicel ChiralPak OD-H 3 x 25 cm, 35 °C at 100 bar, eluting with 35% methanol in carbon dioxide). HR-MS (ES, *m/z*) calculated for C₃₆H₄₄N₆O₅SCl₂ [(M+H)⁺] 743.2544, observed 743.2538.

10 **Example 42**

5-*tert*-Butylsulfamoyl-4-chloro-2-ethoxybenzoic acid methyl ester



4-Chlorosalicylic acid (15 g, Aldrich, 87.5 mmol) and ethyl iodide (35.7 g, 230 mmol) were dissolved in dimethylformamide (400 mL) and the solution was cooled to 0 °C (acetone-ice bath) with good paddle stirring. Sodium hydride (10.5 g, Aldrich, 50% in oil, 220 mmol) was added in two portions. Cooling was removed after 10 min and the reaction warmed slowly to 30 °C at which point heating was increased to 50-60 °C for 2 h. The reaction was cooled and poured into ice water and extracted into dichloromethane (3 x 500 mL). The organic layer was washed with water (2 x 500 mL), washed with brine, dried over magnesium sulfate and evaporated to dryness to give 4-chloro-2-ethoxybenzoic acid ethyl ester.

4-Chloro-2-ethoxybenzoic acid ethyl ester (~18 g) was suspended in ethanol (500 mL). This was treated with potassium hydroxide (200 mL, 2 M solution) and refluxed for 1 h. The reaction was cooled and poured into cold aqueous hydrochloric acid (300 mL, 3 M solution) and extracted into dichloromethane (3 x 500 mL). The dichloromethane was washed with water (500 mL) and dried over

magnesium sulfate and evaporated to dryness to give 4-chloro-2-ethoxy-benzoic acid as a solid.

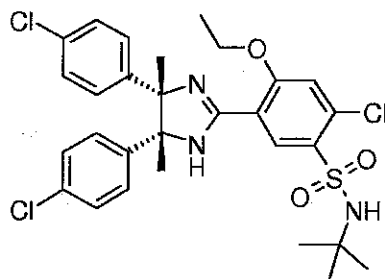
4-Chloro-2-ethoxybenzoic acid (9.4 g, 47 mmol) was added in several portions to cold chlorosulfonic acid (55 mL, Aldrich) stirring at 0-10 °C, and the resulting solution was heated at ~60 °C for 2 h. The resulting dark solution was poured into ice (800 g), and then 500 mL of dichloromethane was added. After stirring for 15 min, the layers were separated and the aqueous layer was extracted with 200 mL of dichloromethane. The organic layers were washed in turn with brine, combined, dried over magnesium sulfate, filtered, and concentrated at room temperature. Crystallization from ether/hexane gave 3.4 g of 4-chloro-5-chlorosulfonyl-2-ethoxybenzoic acid.

A solution of 4-chloro-6-chlorosulfonyl-2-ethoxybenzoic acid (1.0 g, 3.34 mmol) and *tert*-butyl amine (2.0 mL) in 20 mL of tetrahydrofuran was refluxed for 4 h and concentrated. The residue in water was acidified and extracted with ether, the extract was washed with water, brine, dried over magnesium sulfate, filtered and evaporated. Precipitation from ether/hexane provided 0.8 g of crude 5-*tert*-butylsulfamoyl-4-chloro-2-ethoxybenzoic acid.

5-*tert*-Butylsulfamoyl-4-chloro-2-ethoxybenzoic acid (0.8 g, 24 mmol) in 10 mL of tetrahydrofuran was treated with diazomethane (15 mL, ~2-3 M in ether, prepared from N-methyl-N-nitroso-p-toluenesulfonamide, Aldrich) at room temperature and stirred for 0.5 h. The mixture was concentrated, and the residue was purified by flash chromatography (silica gel, eluting with 20% ethyl acetate in hexane) to give 0.45 g of 5-*tert*-butylsulfamoyl-4-chloro-2-ethoxybenzoic acid methyl ester as a solid.

Example 43

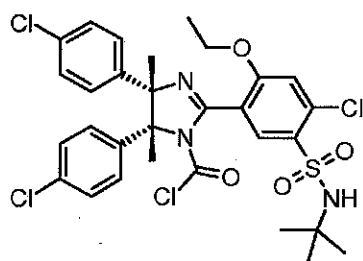
rac-(4S*,5R*)-5-[4,5-Bis-(4-chlorophenyl)-4,5-dimethyl-4,5-dihydro-1H-imidazol-2-yl]-N-*tert*-butyl-2-chloro-4-ethoxybenzenesulfonamide



In a manner analogous to the method described in example 2, *meso*-2,3-bis-(4-chlorophenyl)-2,3-butanediol (example 1) was reacted with 5-*tert*-butylsulfamoyl-4-chloro-2-ethoxybenzoic acid methyl ester (example 43) in the presence of trimethylaluminum to give the title compound. HR-MS (ES, *m/z*) calculated for C₂₉H₃₃N₃O₃SCl₃ [(M+H)⁺] 608.1303, observed 608.1300.

Example 44

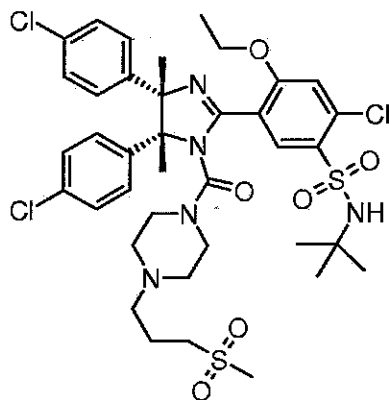
rac-(4*S**,5*R**)-2-(5-*tert*-Butylsulfamoyl-4-chloro-2-ethoxyphenyl)-4,5-bis-(4-chlorophenyl)-4,5-dimethyl-4,5-dihydroimidazole-1-carbonyl chloride



In a manner analogous to the method described in example 3, *rac*-(4*S**,5*R**)-5-[4,5-bis-(4-chlorophenyl)-4,5-dimethyl-4,5-dihydro-1*H*-imidazol-2-yl]-*N*-*tert*-butyl-2-chloro-4-ethoxybenzenesulfonamide (example 44) was reacted with phosgene in the presence of triethylamine to give the title compound.

Example 45

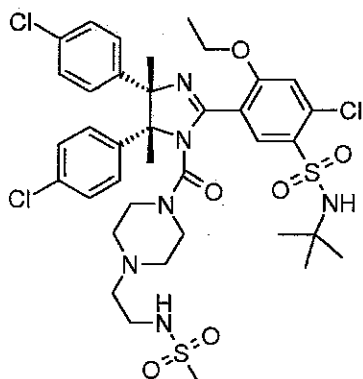
5-[(4*S*,5*R*)-4,5-Bis-(4-chloro-phenyl)-1-[4-(3-methanesulfonyl-propyl)-piperazine-1-carbonyl]-4,5-dimethyl-4,5-dihydro-1*H*-imidazol-2-yl]-*N*-*tert*-butyl-2-chloro-4-ethoxy-benzenesulfonamide



- In a manner analogous to the method described in example 5, *rac*-(4S*,5R*)-2-(5-*tert*-butylsulfonyl-4-chloro-2-ethoxy-phenyl)-4,5-bis-(4-chloro-phenyl)-4,5-dimethyl-4,5-dihydro-imidazole-1-carbonyl chloride (260 mg, 0.39 mmol, example 5) and triethylamine (350 mg, 3.34 mmol) in methylene chloride (10 mL) was treated with 1-(3-methanesulfonyl-propyl)-piperazine dihydrochloride (110 mg, 0.39 mmol, prepared as described in Fotouhi, N. *et al.* WO 2005110996) to give the title compound as a racemic mixture. The enantiomers were then separated by supercritical fluid chromatography (Berger Instrument Multi-Gram II, Daicel ChiralPak OD-H 3 x 25 cm, 35 °C at 100 bar, eluting with 30% methanol in carbon dioxide). HR-MS (ES, *m/z*) calculated for C₃₈H₄₉N₅O₆S₂Cl₃ [(M+H)⁺] 840.2185, observed 840.2179

Example 46

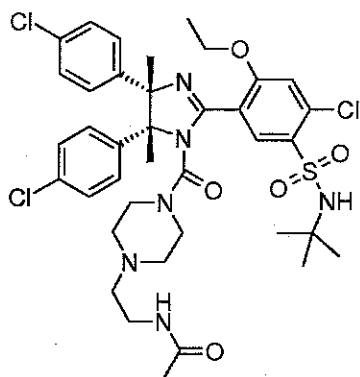
- 15 5-[(4S,5R)-4,5-Bis-(4-chlorophenyl)-1-[4-(2-methanesulfonylaminoethyl)piperazine-1-carbonyl]-4,5-dimethyl-4,5-dihydro-1H-imidazol-2-yl]-N-*tert*-butyl-2-chloro-4-ethoxybenzenesulfonamide



In a manner analogous to the method described in example 5, *rac*-(4S*,5R*)-2-(5-*tert*-butylsulfamoyl-4-chloro-2-ethoxy-phenyl)-4,5-bis-(4-chloro-phenyl)-4,5-dimethyl-4,5-dihydro-imidazole-1-carbonyl chloride (example 45) was reacted with N-(2-piperazin-1-yl-ethyl)-methanesulfonamide dihydrochloride (prepared as described in Fotouhi, N. *et al.* WO 2005110996) to give the title compound as a racemic mixture. The enantiomers were then separated by supercritical fluid chromatography (Berger Instrument Multi-Gram II, Daicel ChiralPak OD-H 3 x 25 cm, 35 °C at 100 bar, eluting with 35% methanol in carbon dioxide). HR-MS (ES, *m/z*) calculated for C₃₇H₄₈N₆O₆S₂Cl₃ [(M+H)⁺] 841.2137, observed 841.2129.

Example 47

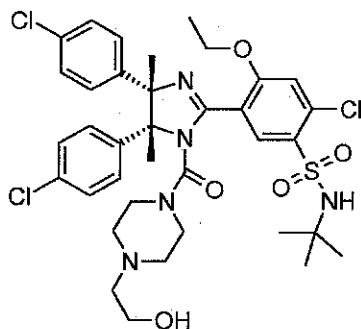
N-((4S,5R)-(2-{4-[2-(5-*tert*-Butylsulfamoyl-4-chloro-2-ethoxyphenyl)-4,5-bis-(4-chlorophenyl)-4,5-dimethyl-4,5-dihydroimidazole-1-carbonyl]-piperazin-1-yl}ethyl)acetamide



In a manner analogous to the method described in example 5, *rac*-(4S*,5R*)-2-(5-*tert*-butylsulfamoyl-4-chloro-2-ethoxy-phenyl)-4,5-bis-(4-chloro-phenyl)-4,5-dimethyl-4,5-dihydro-imidazole-1-carbonyl chloride (example 45) was reacted with N-(2-piperazin-1-yl-ethyl)-acetamide dihydrochloride (prepared as described in Fotouhi, N. *et al.* WO 2005110996) to give the title compound as a racemic mixture. The enantiomers were then separated by supercritical fluid chromatography (Berger Instrument Multi-Gram II, Daicel ChiralPak OD-H 3 x 25 cm, 35 °C at 100 bar, eluting with 25% methanol in carbon dioxide). HR-MS (ES, *m/z*) calculated for C₃₇H₄₈N₆O₅SCl₃ [(M+H)⁺] 805.2460, observed 805.2467.

Example 48

5-[(4S,5R)-4,5-bis-(4-chlorophenyl)-1-[4-(2-hydroxyethyl)piperazine-1-carbonyl]-4,5-dimethyl-4,5-dihydro-1H-imidazol-2-yl]-N-*tert*-butyl-2-chloro-4-ethoxybenzenesulfonamide



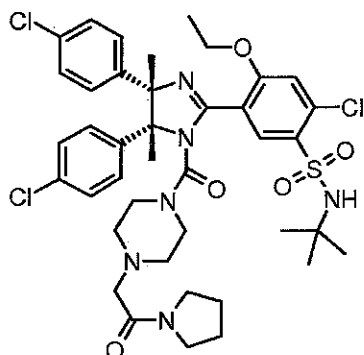
5

In a manner analogous to the method described in example 5, *rac*-(4S*,5R*)-2-(5-*tert*-butylsulfamoyl-4-chloro-2-ethoxy-phenyl)-4,5-bis-(4-chloro-phenyl)-4,5-dimethyl-4,5-dihydro-imidazole-1-carbonyl chloride (example 45) was reacted with 2-piperazin-1-yl-ethanol (Chemical Dynamics) to give the title compound as a racemic mixture. The enantiomers were then separated by supercritical fluid chromatography (Berger Instrument Multi-Gram II, Daicel ChiralPak OD-H 3 x 25 cm, 35 °C at 100 bar, eluting with 25% methanol in carbon dioxide). HR-MS (ES; *m/z*) calculated for C₃₆H₄₅N₅O₅SCl₃ [(M+H)⁺] 764.2202, observed 764.2198.

15

Example 49

5-[(4S,5R)-4,5-bis-(4-chlorophenyl)-4,5-dimethyl-1-[4-(2-oxo-2-pyrrolidin-1-yl-ethyl)-piperazine-1-carbonyl]-4,5-dihydro-1H-imidazol-2-yl]-N-*tert*-butyl-2-chloro-4-ethoxybenzenesulfonamide

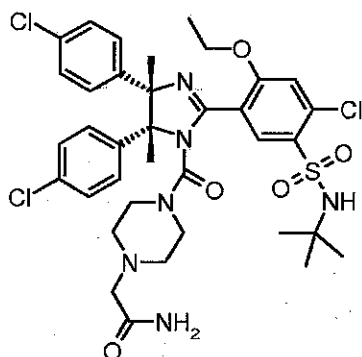


20

In a manner analogous to the method described in example 5, *rac*-(4*S**,5*R**)-2-(5-*tert*-butylsulfamoyl-4-chloro-2-ethoxy-phenyl)-4,5-bis-(4-chloro-phenyl)-4,5-dimethyl-4,5-dihydro-imidazole-1-carbonyl chloride (example 45) was reacted with 2-piperazin-1-yl-1-pyrrolidin-1-yl-ethanone (Aldrich) to give the title compound as a racemic mixture. The enantiomers were then separated by supercritical fluid chromatography (Berger Instrument Multi-Gram II, Daicel ChiralPak OJ-H 3 x 25 cm, 35 °C at 100 bar, eluting with 15% methanol in carbon dioxide). HR-MS (ES, *m/z*) calculated for C₄₀H₅₀N₆O₅SCl₃ [(M+H)⁺] 831.2624, observed 831.2625.

Example 50

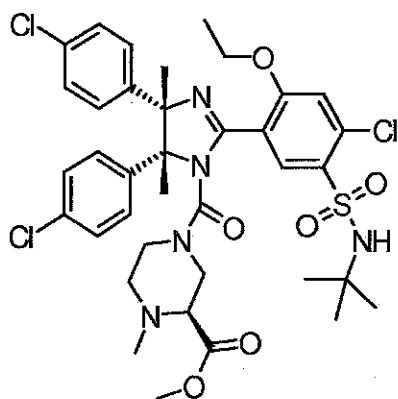
2-{4-[(4*S*,5*R*)-2-(5-*tert*-Butylsulfamoyl-4-chloro-2-ethoxyphenyl)-4,5-bis-(4-chlorophenyl)-4,5-dimethyl-4,5-dihydroimidazole-1-carbonyl]-piperazin-1-yl}-acetamide



In a manner analogous to the method described in example 5, *rac*-(4*S**,5*R**)-2-(5-*tert*-butylsulfamoyl-4-chloro-2-ethoxy-phenyl)-4,5-bis-(4-chloro-phenyl)-4,5-dimethyl-4,5-dihydro-imidazole-1-carbonyl chloride (example 45) was reacted with 2-piperazin-1-yl-acetamide dihydrochloride (Matrix Scientific) to give the title compound as a racemic mixture. The enantiomers were then separated by supercritical fluid chromatography (Berger Instrument Multi-Gram II, Daicel ChiralPak OD-H 3 x 25 cm, 35 °C at 100 bar, eluting with 25% of 1:1 acetonitrile/ethanol in carbon dioxide). HR-MS (ES, *m/z*) calculated for C₃₆H₄₄N₆O₅SCl₃ [(M+H)⁺] 777.2154, observed 777.2146.

Example 51

(S)-4-[(4S,5R)-2-(5-*tert*-Butylsulfamoyl-4-chloro-2-ethoxyphenyl)-4,5-bis-(4-chlorophenyl)-4,5-dimethyl-4,5-dihydroimidazole-1-carbonyl]-1-methylpiperazine-2-carboxylic acid methyl ester

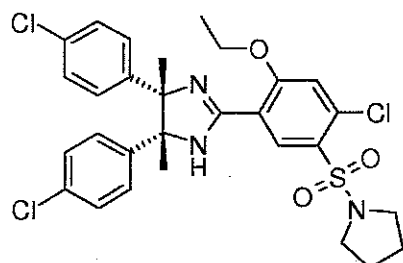


In a manner analogous to the method described in example 5, *rac*-(4S*,5R*)-2-(5-*tert*-butylsulfamoyl-4-chloro-2-ethoxy-phenyl)-4,5-bis-(4-chloro-phenyl)-4,5-dimethyl-4,5-dihydro-imidazole-1-carbonyl chloride (example 45) was reacted with (S)-1-methyl-piperazine-2-carboxylic acid methyl ester to give the title compound as a racemic mixture. The enantiomers were then separated by supercritical fluid chromatography (Berger Instrument Multi-Gram II, Daicel ChiralPak OD-H 3 x 25 cm, 35 °C at 100 bar, eluting with 25% methanol in carbon dioxide). HR-MS (ES, *m/z*) calculated for C₃₇H₄₅N₅O₆SCl₃ [(M+H)⁺]

792.2151, observed 792.2148.

Example 52

rac-(4S*,5R*)-2-[4-Chloro-2-ethoxy-5-(pyrrolidine-1-sulfonyl)phenyl]-4,5-bis-(4-chlorophenyl)-4,5-dimethyl-4,5-dihydro-1H-imidazole

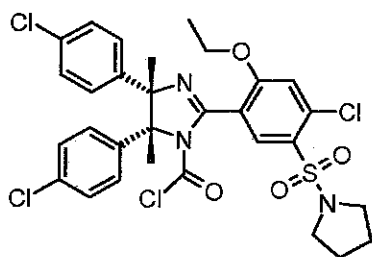


In a manner analogous to the method described in example 2, *meso*-2,3-bis-(4-chlorophenyl)-2,3-butanediamine (example 1) was reacted with 4-chloro-2-ethoxy-5-(pyrrolidine-1-sulfonyl)benzoic acid methyl ester (prepared in an analogous manner as described in example 43) in the presence of

5 trimethylaluminum to give the title compound. HR-MS (ES, m/z) calculated for $C_{29}H_{33}N_3O_3SCl_3$ $[(M+H)^+]$ 608.1303, observed 608.1300.

Example 53

10 *rac*-(4*S**,5*R**)-[-2-[4-Chloro-2-ethoxy-5-(pyrrolidine-1-sulfonyl)phenyl]-4,5-bis-(4-chlorophenyl)-4,5-dimethyl-4,5-dihydroimidazole-1-carbonyl chloride

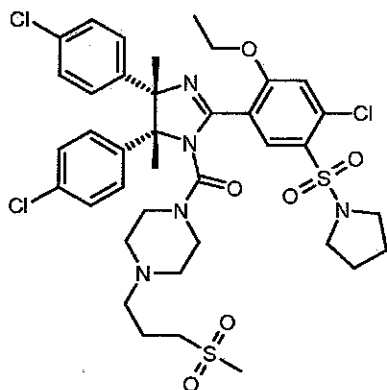


In a manner analogous to the method described in example 3, *rac*-(4*S**,5*R**)-2-[4-chloro-2-ethoxy-5-(pyrrolidine-1-sulfonyl)phenyl]-4,5-bis-(4-chlorophenyl)-4,5-

15 dimethyl-4,5-dihydro-1*H*-imidazole (example 53) was reacted with phosgene in the presence of triethylamine to give the title compound.

Example 54

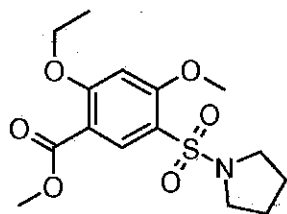
20 5-[(4*S*, 5*R*)-2-[4-Chloro-2-ethoxy-5-(pyrrolidine-1-sulfonyl)phenyl]-4,5-bis-(4-chloro-phenyl)-4,5-dimethyl-4,5-dihydroimidazol-1-yl]-[4-(3-methanesulfonylpropyl)-piperazin-1-yl]methanone



In a manner analogous to the method described in example 5, *rac*-(4S*,5R*)-2-[4-chloro-2-ethoxy-5-(pyrrolidine-1-sulfonyl)-phenyl]-4,5-bis-(4-chloro-phenyl)-4,5-dimethyl-4,5-dihydro-imidazole-1-carbonyl chloride (example 54) was reacted
 5 with 1-(3-methanesulfonyl-propyl)-piperazine dihydrochloride (prepared as described in Fotouhi, N. *et al.* WO 2005110996) to give the title compound as a racemic mixture. The enantiomers were then separated by supercritical fluid chromatography (Berger Instrument Multi-Gram II, Daicel ChiralPak OD-H 3 x 25 cm, 35 °C at 100 bar, eluting with 35% methanol in carbon dioxide). HR-MS
 10 (ES, *m/z*) calculated for C₃₈H₄₇N₅O₆S₂Cl₃ [(M+H)⁺] 838.2028, observed 838.2025.

Example 55

2-Ethoxy-4-methoxy-5-(pyrrolidine-1-sulfonyl)benzoic acid methyl ester



15

4-Methoxysalicylic acid (10 g, 59 mmol, Aldrich) and ethyl iodide (23.2 g, 150 mmol, Aldrich) were dissolved in dimethylformamide (300 mL) and the solution was cooled to 0 °C (ice bath) with good paddle stirring. Sodium hydride (6.2 g, 130 mmol, 50% in mineral oil, Aldrich) was added in two portions. The ice bath
 20 was removed after 10 min, and the reaction was warmed slowly to 30 °C at which point heating was applied to increase the temperature to 50-60 °C. After 2 h, the reaction was cooled and poured into ice water and extracted into

dichloromethane (2 x 500 mL). The organic layer was washed with water (2 x 500 mL), brine and dried over anhydrous magnesium sulfate. The solids were filtered off, and the filtrate was evaporated to dryness to give 2-ethoxy-4-methoxybenzoic acid ethyl ester.

- 5 2-Ethoxy-4-methoxybenzoic acid ethyl ester (13 g, 58 mmol) was suspended in ethanol (150 mL). This was treated with potassium hydroxide (40 mL, ~4 M) and refluxed for 1 h. The reaction was cooled and poured into cold aqueous hydrochloric acid (300 mL, 2 M) and extracted into dichloromethane (3 x 200 mL). The organic layers were washed with brine and dried over anhydrous
10 magnesium sulfate. The solids were filtered off, and the filtrate was evaporated to dryness to give 2-ethoxy-4-methoxybenzoic acid (9.5 g, white solid).

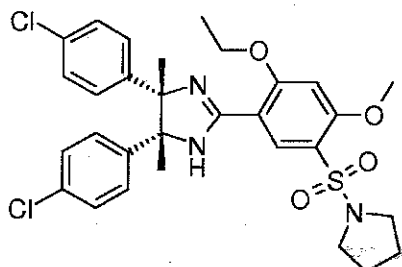
- 2-Ethoxy-4-methoxybenzoic acid (9.5 g, 48.5 mmol) was added in portions to cold chlorosulfonic acid (60 mL, Aldrich) stirring at -3 to 0 °C (ice-acetone bath) over 15 min and warmed slowly to room temperature and heated to 60-65 °C for
15 40 min. The resulting dark solution was carefully poured with stirring into a large excess of ice and then 500 mL of dichloromethane was added. After stirring for 15 min, the layers were separated and the aqueous layer was extracted with dichloromethane (3 x 250 mL). The organic layers were washed with brine and dried over anhydrous magnesium sulfate. The solids were filtered off, and the
20 filtrate was evaporated to a low volume. This was triturated with ether/hexane and filtered to give 5-chlorosulfonyl-2-ethoxy-4-methoxybenzoic acid as a colorless solid (13.4 g, 94%).

- A solution of 5-chlorosulfonyl-2-ethoxy-4-methoxybenzoic acid (13 g, 44 mmol) in tetrahydrofuran was cooled to 5 °C and treated with excess diazomethane in
25 ether solution (prepared from N-methyl-N-nitroso-p-toluenesulfonamide, Aldrich) and stirred for 10 min. Solvent and excess diazomethane was removed by rotary evaporation. The resulting residue was dissolved in dichloromethane and filtered through a plug of silica gel and evaporated. The solids were triturated with ether/hexane to give 13 g of 5-chlorosulfonyl-2-ethoxy-4-methoxy-benzoic acid
30 methyl ester as a colorless solid.

In a manner analogous to the method described in example 33, 5-chlorosulfonyl-2-ethoxy-4-methoxy-benzoic acid methyl ester was reacted with pyrrolidine to give the title compound.

Example 56

rac-(4S*,5R*)-4,5-Bis-(4-chlorophenyl)-2-[2-ethoxy-4-methoxy-5-(pyrrolidine-1-sulfonyl)phenyl]-4,5-dimethyl-4,5-dihydro-1H-imidazole



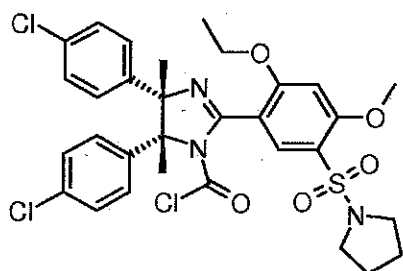
5

In a manner analogous to the method described in example 2, *meso*-2,3-bis-(4-chlorophenyl)-2,3-butanediamine was reacted with 2-ethoxy-4-methoxy-5-(pyrrolidine-1-sulfonyl)benzoic acid methyl ester in the presence of trimethylaluminum to give the title compound. LR-MS: 602 (M+H)⁺.

10

Example 57

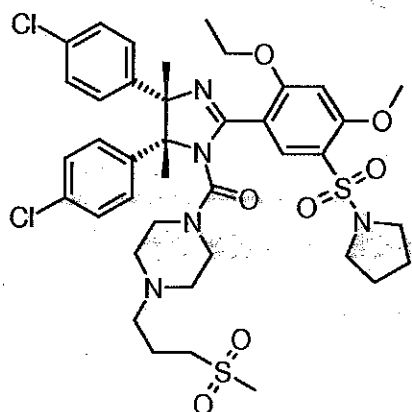
rac-(4S*,5R*)-4,5-Bis-(4-chlorophenyl)-2-[2-ethoxy-4-methoxy-5-(pyrrolidine-1-sulfonyl)-phenyl]-4,5-dimethyl-4,5-dihydroimidazole-1-carbonyl chloride



15 In a manner analogous to the method described in example 3, *rac*-(4S*,5R*)-4,5-bis-(4-chlorophenyl)-2-[2-ethoxy-4-methoxy-5-(pyrrolidine-1-sulfonyl)phenyl]-4,5-dimethyl-4,5-dihydro-1H-imidazole was reacted with phosgene in the presence of triethylamine to give the title compound.

Example 58

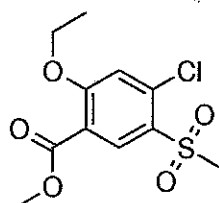
{{(4S,5R)-4,5-Bis-(4-chlorophenyl)-2-[2-ethoxy-4-methoxy-5-(pyrrolidine-1-sulfonyl)-phenyl]-4,5-dimethyl-4,5-dihydroimidazol-1-yl}-[4-(3-methanesulfonylpropyl)-piperazin-1-yl]methanone



In a manner analogous to the method described in example 5, *rac*-(4S*,5R*)-4,5-bis-(4-chlorophenyl)-2-[2-ethoxy-4-methoxy-5-(pyrrolidine-1-sulfonyl)-phenyl]-4,5-dimethyl-4,5-dihydroimidazole-1-carbonyl chloride was reacted with 1-(3-methanesulfonyl-propyl)-piperazine dihydrochloride (prepared as described in Fotouhi, N. *et al.* WO 2005110996) to give the title compound as a racemic mixture. The enantiomers were then separated by supercritical fluid chromatography (Berger Instrument Multi-Gram II, Daicel ChiralPak OD-H 3 x 25 cm, 35 °C at 100 bar, eluting with 30% methanol in carbon dioxide). HR-MS (ES, *m/z*) calculated for C₃₉H₅₀N₅O₇S₂Cl₂ [(M+H)⁺] 834.2523, observed 834.2524.

Example 59

4-Chloro-2-ethoxy-5-methanesulfonyl-benzoic acid methyl ester

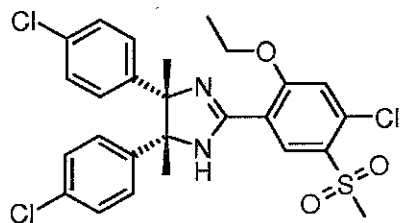


To a solution of sodium bicarbonate (5.0 g, 60 mmol) and sodium sulfite (2.4 g, 19 mmol) in water (25 mL) at 70-75 °C was treated with 4-chloro-5-chlorosulfonyl-2-ethoxy-benzoic acid (6.2 g, 21 mmol, example 43) in portions according to the procedure described by Imamura, S. *et al. (Bioorg. Med. Chem.* 5 **2005**, 13, 397-416). After 1 h at 75 °C, chloroacetic acid (3.0 g, 32 mmol) was carefully added in three portions followed by a solution of aqueous sodium hydroxide (1.28 g, 32 mmol/4 mL water) and stirred at 100 °C for 16 h. This was cooled and poured into 2N hydrochloric acid (100 mL) and extracted with ethyl acetate (2x) The organic extracts were washed with brine, dried over magnesium sulfate, filtered, and concentrated at room temperature to a low volume. This 10 was triturated with ether and filtered to give 4-chloro-2-ethoxy-5-methanesulfonyl-benzoic acid methyl ester as a colorless solid (5.2 g, 89%).

A solution of 4-chloro-2-ethoxy-5-methanesulfonylbenzoic acid (2.5 g, 9.0 15 mmol) in tetrahydrofuran was cooled to 5 °C and treated with excess diazomethane in ether solution (prepared from N-methyl-N-nitroso-p-toluenesulfonamide, Aldrich) and stirred for 10 min. Solvent and excess diazomethane was removed by rotary evaporation. The resulting residue was dissolved in dichloromethane and filtered through a plug of silica gel and 20 evaporated. The solids were triturated with ether/hexane to give 4-chloro-2-ethoxy-5-methanesulfonyl-benzoic acid methyl ester (2.1 g, colorless solids).

Example 60

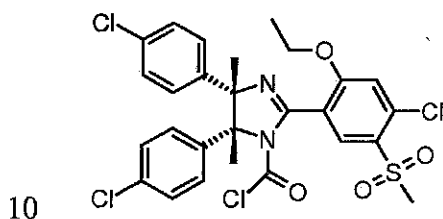
rac-(4S*,5R*)-2-(4-Chloro-2-ethoxy-5-methanesulfonylphenyl)4,5-bis-(4-chlorophenyl)4,5-dimethyl-4,5-dihydro-1H-imidazole 25



In a manner analogous to the method described in example 2, *meso*-2,3-bis-(4-chlorophenyl)-2,3-butanediamine was reacted with 4-chloro-2-ethoxy-5-methanesulfonyl-benzoic acid methyl ester in the presence of trimethylaluminum to give the title compound. HR-MS (ES, m/z) calculated for $C_{26}H_{26}N_2O_3SCl_3$ [(M+H)⁺] 551.0724, observed 551.0721.

Example 61

rac-(4S*,5R*)-2-(4-Chloro-2-ethoxy-5-methanesulfonyl-phenyl)-4,5-bis-(4-chlorophenyl)-4,5-dimethyl-4,5-dihydro-imidazole-1-carbonyl chloride



10

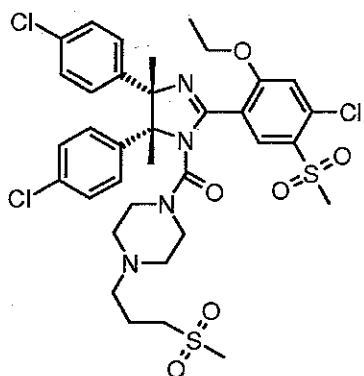
In a manner analogous to the method described in example 3, *rac*-(4S*,5R*)-2-(4-chloro-2-ethoxy-5-methanesulfonyl-phenyl)-4,5-bis-(4-chlorophenyl)-4,5-dimethyl-4,5-dihydro-1H-imidazole was reacted with phosgene in the presence of triethylamine to give the title compound.

15

Example 62

[(4S,5R)-2-(4-Chloro-2-ethoxy-5-methanesulfonyl-phenyl)-4,5-bis-(4-chlorophenyl)-4,5-dimethyl-4,5-dihydroimidazol-1-yl]-[4-(3-methanesulfonylpropyl)-piperazin-1-yl]methanone

20

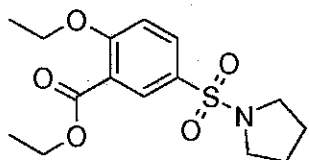


- In a manner analogous to the method described in example 5, 2-(4-chloro-2-ethoxy-5-methanesulfonylphenyl)-4,5-bis-(4-chlorophenyl)-4,5-dimethyl-4,5-dihydroimidazole-1-carbonyl chloride was reacted with 1-(3-methanesulfonylpropyl)-piperazine dihydrochloride (prepared as described in Fotouhi, N. *et al.* WO 2005110996) to give the title compound as a racemic mixture. The enantiomers were then separated by supercritical fluid chromatography (Berger Instrument Multi-Gram II, Daicel ChiralPak OD-H 3 x 25 cm, 35 °C at 100 bar, eluting with 30% of 1:1 ethanol/acetonitrile in carbon dioxide). HR-MS (ES, *m/z*) calculated for C₃₅H₄₂N₄O₆S₂Cl₃ [(M+H)⁺] 783.1606, observed 783.1596

10

Example 63

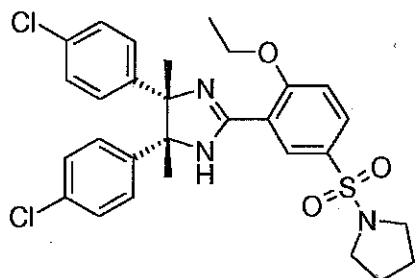
2-Ethoxy-5-(pyrrolidine-1-sulfonyl)benzoic acid ethyl ester



- A solution of 5-chlorosulfonyl-2-hydroxybenzoic acid (0.52 g, 2.0 mmol, Matrix Scientific) in tetrahydrofuran (10 mL) was treated with pyrrolidine (1.5 g, 21 mmol) and refluxed for 2 h. This was cooled and poured into dilute aqueous hydrochloric acid and extracted into dichloromethane (2 x 50 mL). The combined extracts were washed with brine, dried over magnesium sulfate, filtered, and concentrated to give a solid. This was triturated with ether to give 2-hydroxy-5-(pyrrolidine-1-sulfonyl)benzoic acid as a solid. It was then converted to 2-ethoxy-5-(pyrrolidine-1-sulfonyl)benzoic acid ethyl ester in a manner analogous to the method described in example 33.

Example 64

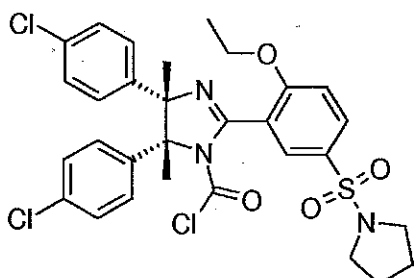
rac-(4S*,5R*)-4,5-Bis-(4-chlorophenyl)-2-[2-ethoxy-5-(pyrrolidine-1-sulfonyl)phenyl]-4,5-dimethyl-4,5-dihydro-1H-imidazole



In a manner analogous to the method described in example 2, *meso*-2,3-bis-(4-chlorophenyl)-2,3-butanediamine was reacted with 2-ethoxy-5-(pyrrolidine-1-sulfonyl)benzoic acid ethyl ester in the presence of trimethylaluminum to give the title compound.

Example 65

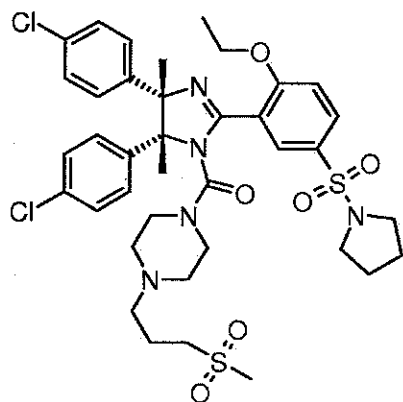
rac-(4*S*^{*},5*R*^{*})-4,5-Bis-(4-chlorophenyl)-2-[2-ethoxy-5-(pyrrolidine-1-sulfonyl)phenyl]-4,5-dimethyl-4,5-dihydroimidazole-1-carbonyl chloride



In a manner analogous to the method described in example 3, *rac*-(4*S*^{*},5*R*^{*})-4,5-bis-(4-chlorophenyl)-2-[2-ethoxy-5-(pyrrolidine-1-sulfonyl)phenyl]-4,5-dimethyl-4,5-dihydro-1*H*-imidazole was reacted with phosgene in the presence of triethylamine to give the title compound.

Example 66

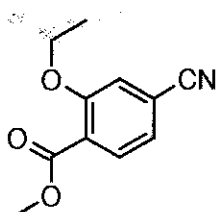
{(4*S*,5*R*)-4,5-Bis-(4-chlorophenyl)-2-[2-ethoxy-5-(pyrrolidine-1-sulfonyl)phenyl]-4,5-dimethyl-4,5-dihydroimidazol-1-yl}-[4-(3-methanesulfonylpropyl)-piperazin-1-yl]methanone



- In a manner analogous to the method described in example 5, *rac*-(4S*,5R*)-4,5-bis-(4-chloro-phenyl)-2-[2-ethoxy-5-(pyrrolidine-1-sulfonyl)-phenyl]-4,5-dimethyl-4,5-dihydro-imidazole-1-carbonyl chloride was reacted with 1-(3-methanesulfonyl-propyl)-piperazine dihydrochloride (prepared as described in Fotouhi, N. *et al.* WO 2005110996) to give the title compound as a racemic mixture. The enantiomers were then separated by supercritical fluid chromatography (Berger Instrument Multi-Gram II, Daicel ChiralPak OD-H 3 x 25 cm, 35 °C at 100 bar, eluting with 35% methanol in carbon dioxide). HR-MS (ES, *m/z*) calculated for C₃₈H₄₈N₅O₆S₂Cl₂ [(M+H)⁺] 804.2418, observed 804.2413

Example 67

4-Cyano-2-ethoxybenzoic acid methyl ester



15

- 2-Ethoxy-4-nitrobenzoic acid (20 g, 94 mmol, Aldrich) was suspended in ethanol (170 mL) and combined with a saturated aqueous solution of ammonium chloride (100 mL). As this was rapidly stirred, iron dust (13.3 g, 239 mmol) was added in portions. The temperature was raised to 80 °C for 1 h. The cooled suspension was filtered through Celite, and the cake washed with dichloromethane (150 mL). The filtrate was diluted with dichloromethane and washed with brine, dried over magnesium sulfate, filtered and evaporated. A brown solid was triturated with

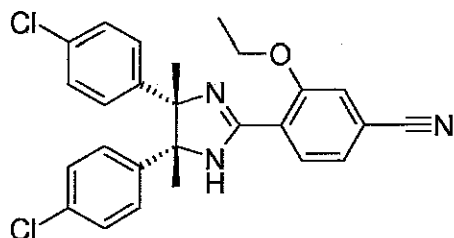
dichloromethane and filtered to give 15 g of 4-amino-2-ethoxybenzoic acid (88%).

A suspension 4-amino-2-ethoxybenzoic acid (20 g, 110 mmol) in 2N hydrochloric acid (200 mL) was well stirred with ice bath cooling. To this was
5 added sodium nitrite (7.68 g, 111 mmol) in 22 mL of water. After stirring for 5 min, solid sodium carbonate was added to adjust the pH to 9-10. Separately, copper chloride (14.2 g, 143 mmol) in 200 mL water was slowly added to a solution of sodium cyanide ((18.28 g, 371 mmol) in 200 mL water at 0-5 °C and stirred for 2 h. The cold nitrite solution was added slowly to the cyanide solution
10 and stirred at 0-5 °C for 15 min, followed by 25 °C for 2 h. This was filtered and the aqueous solution was adjusted to pH 2 with concentrated hydrochloric acid. This was extracted with ethyl acetate (4 L). The organic extracts were washed with brine and dried over anhydrous magnesium sulfate. The solids were filtered off, and the filtrate was concentrated to give 19 g of crude 4-cyano-2-
15 ethoxybenzoic acid.

Crude 4-cyano-2-ethoxybenzoic acid (19 g) was dissolved in a mixture of benzene (446 mL) and methanol (111 mL). At 0 °C, (trimethylsilyl)diazomethane (76 mL, 2.0 M in ether, Aldrich) was added slowly and then at room temperature. Solvent was removed, and the residue was purified by flash chromatography
20 (silica gel, eluting with 25% ethyl acetate in hexane) to give 4-cyano-2-ethoxybenzoic acid methyl ester as a solid (15.5 g, 74%).

Example 68

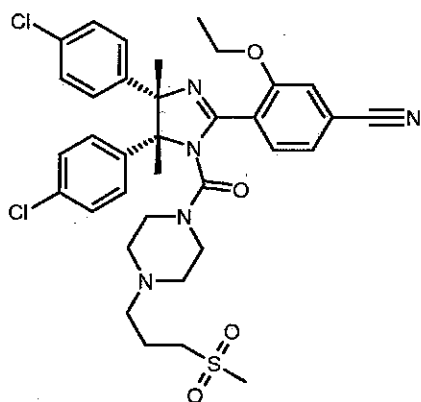
rac-4-[(4S*,5R*)-4,5-Bis-(4-chloro-phenyl)-4,5-dimethyl-4,5-dihydro-1*H*-imidazol-
25 2-yl]-3-ethoxy-benzonitrile



In dry toluene (6 mL) was added trimethylaluminum (0.7 mL, 0.14 mmol, 2.0 M in toluene, Aldrich). At 0 °C, *meso*-2,3-bis-(4-chlorophenyl)-butane-2,3-diamine (0.28 g, 0.091 mmol) in toluene (7 mL) was added over 10 min. This was warmed to room temperature for 1 h. 4-Cyano-2-ethoxybenzoic acid methyl ester (0.34 g, 0.166 mmol) suspended in toluene (6 mL) was added and the mixture was raised to reflux for 16 h. The reaction was cooled and 3 mL of Rochelle salt was added and stirred for 2 h. The reaction was diluted with ethyl acetate (20 mL) and stirred for 10 min. The organic layer was separated, dried over magnesium sulfate, filtered and evaporated. Purification of the residue by flash chromatography (silica gel, eluting with 20-50% ethyl acetate /hexane) gave 250 mg of the title compound.

Example 69

4-[(4*S*,5*R*)-4,5-Bis-(4-chlorophenyl)-1-[4-(3-methanesulfonylpropyl)-piperazine-1-carbonyl]-4,5-dimethyl-4,5-dihydro-1*H*-imidazol-2-yl]-3-ethoxybenzonitrile



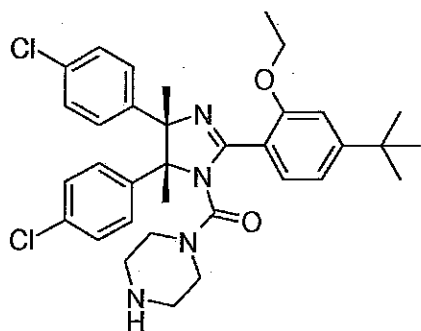
A solution of *rac*-4-[(4*S*^{*},5*R*^{*})-4,5-bis-(4-chloro-phenyl)-4,5-dimethyl-4,5-dihydro-1*H*-imidazol-2-yl]-3-ethoxy-benzonitrile (190 mg, 0.31 mmol) in dichloromethane was cooled to 0 °C and treated with phosgene (2.5 mL, 0.47 mmol, 1.9 M in toluene) and triethylamine (0.66 g, 0.65 mmol). After 1 h, the reaction was charged with the same quantities of phosgene and triethylamine. After an additional 1 h at 0 °C, the reaction was worked up in ice water and dichloromethane. The organic layer was dried over anhydrous magnesium sulfate, filtered and evaporated to give an oil. It was purified by a short plug of silica gel (eluting with 20% ethyl acetate /hexane) to give *rac*-(4*S*^{*},5*R*^{*})-4,5-bis-

(4-chloro-phenyl)-2-(4-cyano-2-ethoxy-phenyl)-4,5-dimethyl-4,5-dihydro-imidazole-1-carbonyl chloride.

A solution of *rac*-(4S*,5R*)-4,5-bis-(4-chloro-phenyl)-2-(4-cyano-2-ethoxy-phenyl)-4,5-dimethyl-4,5-dihydro-imidazole-1-carbonyl chloride (~175 mg, 0.26 mmol) in dichloromethane (10 mL) and triethylamine (0.35 g, 3.34 mmol) at 0 °C was treated with 1-(3-methanesulfonylpropyl)piperazine (0.11 g, 0.39 mmol, prepared as described in Fotouhi, N. *et al.* WO 2005110996) for 0.5 h. The reaction was washed with cold water, dried over anhydrous magnesium sulfate, filtered and evaporated to give a solid. Trituration with ether and filtration gave the title compound as a racemic mixture. The enantiomers were then separated by supercritical fluid chromatography (Berger Instrument Multi-Gram II, Daicel ChiralPak OD-H 3 x 25 cm, 35 °C at 100 bar, eluting with 35% methanol in carbon dioxide). HR-MS (ES, *m/z*) calculated for C₃₅H₄₀N₅O₄SCl₂ [(M+H)⁺] 696.2173, observed 696.2167.

Example 70

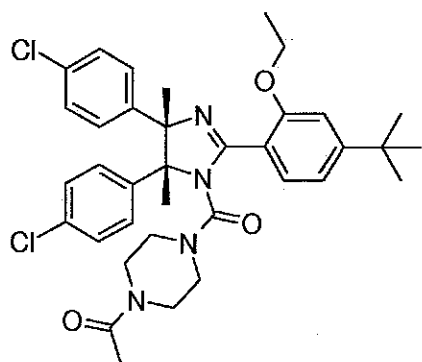
[(4S,5R)-2-(4-*tert*-Butyl-2-ethoxy-phenyl)-4,5-bis-(4-chloro-phenyl)-4,5-dimethyl-4,5-dihydro-imidazol-1-yl]-piperazin-1-yl-methanone



In a manner analogous to the method described in example 5, (4S,5R)-2-(4-*tert*-butyl-2-ethoxy-phenyl)-4,5-bis-(4-chloro-phenyl)-4,5-dimethyl-4,5-dihydro-imidazole-1-carbonyl chloride (example 4) was reacted with piperazine (Aldrich) to give the title compound. HR-MS (ES, *m/z*) calculated for C₃₄H₄₁N₄O₂Cl₂ [(M+H)⁺] 607.2601, observed 607.2603.

Example 71

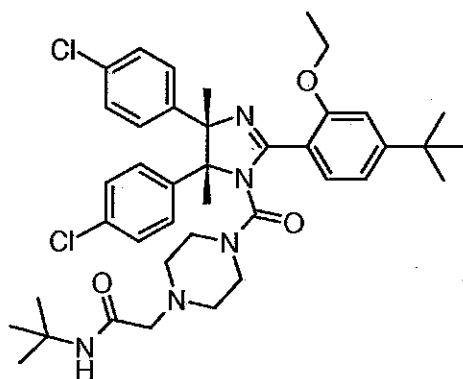
1-{4-[(4S,5R)-2-(4-*tert*-Butyl-2-ethoxy-phenyl)-4,5-bis-(4-chloro-phenyl)-4,5-dimethyl-4,5-dihydro-imidazole-1-carbonyl]-piperazin-1-yl}-ethanone



In a manner analogous to the method described in example 5, (4S,5R)-2-(4-*tert*-butyl-2-ethoxy-phenyl)-4,5-bis-(4-chloro-phenyl)-4,5-dimethyl-4,5-dihydro-
 5 imidazole-1-carbonyl chloride (example 4) was reacted with 1-acetyl-piperazine (Aldrich) to give the title compound. LR-MS: 649.2 [(M+H)⁺]

Example 72

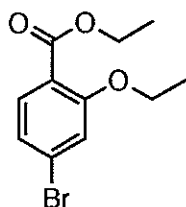
N-tert-Butyl-2-{4-[(4S,5R)-2-(4-*tert*-butyl-2-ethoxy-phenyl)-4,5-bis-(4-chloro-phenyl)-4,5-dimethyl-4,5-dihydro-imidazole-1-carbonyl]-piperazin-1-yl}-acetamide
 10



In a manner analogous to the method described in example 5, (4S,5R)-2-(4-*tert*-butyl-2-ethoxy-phenyl)-4,5-bis-(4-chloro-phenyl)-4,5-dimethyl-4,5-dihydro-
 15 imidazole-1-carbonyl chloride (example 4) was reacted with *N-tert*-butyl-2-piperazin-1-yl-acetamide (Enamine-BB) to give the title compound.

Example 73

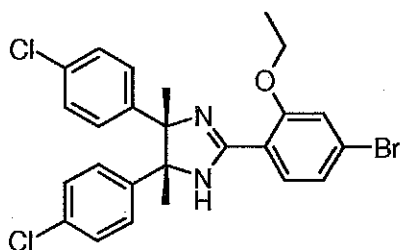
20 4-Bromo-2-ethoxy-benzoic acid ethyl ester



Sodium (1.815 g, 78.9 mmol, Aldrich) was cut into small pieces and added to ethanol (100 mL). After all the pieces were dissolved, the clear solution was added to a solution of ethyl 4-bromo-2-fluoro-benzoate (13 g, 52.6 mmol) in ethanol (20 mL) cooled to 0 °C. The ice bath was then removed and the mixture was stirred at room temperature for 12 h. The reaction mixture was concentrated *in vacuo*, and the residue was taken in water and 20% ethyl acetate-hexane. The organic layer was washed with saturated solution of sodium bicarbonate, brine, and dried over anhydrous sodium sulfate. The solids were filtered off, and the filtrate was concentrated *in vacuo*. Purification of the crude residue by flash chromatography (120 g of silica gel, eluting with 10-15% ethyl acetate in hexane) gave 4-bromo-2-ethoxy-benzoic acid ethyl ester as white solids (11.020 g, 77%).

Example 74

- 15 *rac*-(4*S**,5*R**)-2-(4-Bromo-2-ethoxy-phenyl)-4,5-bis-(4-chloro-phenyl)-4,5-dimethyl-4,5-dihydro-1*H*-imidazole

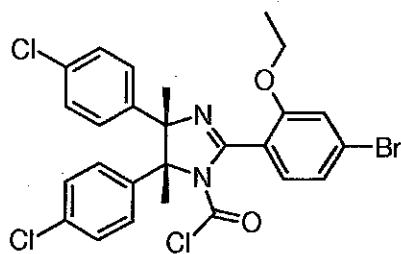


- 20 To a solution of meso-2,3-bis-(4-chlorophenyl)-2,3-butanediamine (3 g, example 1) in toluene cooled to 0 °C was added dropwise 2 M solution of trimethylaluminum in toluene (5.33 mL, 10.66 mmol). After the addition, the mixture was stirred at 0 °C for 15 min then the ice bath was removed. After 30 min, the mixture was warmed up to 80-100 °C for about 30 min before being
- 25 slowly cooled down to room temperature. At room temperature, a solution of 4-bromo-2-ethoxy-benzoic acid ethyl ester (3.18 g, 11.64 mmol) in toluene (10 mL) was added, and the yellow reaction mixture was heated at reflux for 48 h. Upon

cooling to room temperature, 1 M Rochelle solution (~20 mL) and ethyl acetate (~50 mL) were added. The biphasic mixture was stirred rigorously at room temperature for 3 h. The layers were separated and the aqueous layer was extracted with ethyl acetate (1 x 100 mL). The combined organic layers were washed with saturated solution of sodium bicarbonate (1 x 20 mL), brine (1 x 20 mL), dried over anhydrous sodium sulfate. The solids were filtered off and the filtrate was concentrated to dryness. Purification of the crude residue by flash chromatography (120 g of silica gel, eluting with 5-10%, 20%, 40% then 80% ethyl acetate in hexane) gave the title compound as light yellow foam (3.25 g, 65%). HR-MS (ES, m/z) calculated for $C_{25}H_{24}N_2OCl_2Br$ $[(M+H)^+]$ 517.0444, observed 517.0443.

Example 75

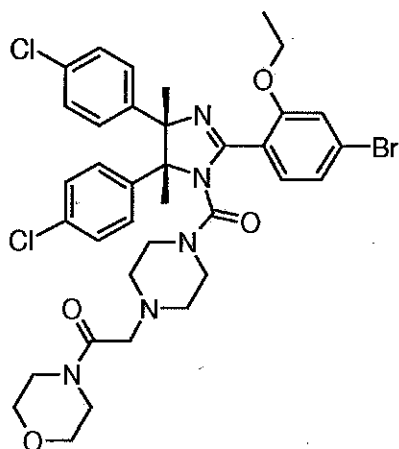
rac-(4S*,5R*)-2-(4-Bromo-2-ethoxy-phenyl)-4,5-bis-(4-chloro-phenyl)-4,5-dimethyl-4,5-dihydro-imidazole-1-carbonyl chloride



In a manner analogous to the method described in example 3, *rac*-(4S*,5R*)-2-(4-bromo-2-ethoxy-phenyl)-4,5-bis-(4-chloro-phenyl)-4,5-dimethyl-4,5-dihydro-1H-imidazole was reacted with phosgene in the presence of triethylamine to give the title compound.

Example 76

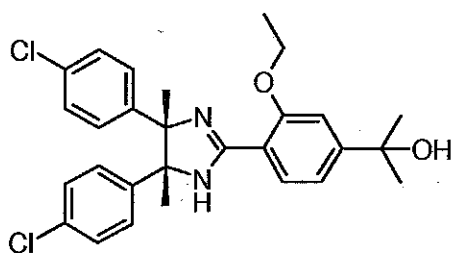
rac-(4S*,5R*)-2-(4-Bromo-2-ethoxy-phenyl)-4,5-bis-(4-chloro-phenyl)-4,5-dimethyl-4,5-dihydro-imidazol-1-yl]-[4-(3-methanesulfonyl-propyl)-piperazin-1-yl]-methanone



- In a manner analogous to the method described in example 5, *rac*-(4S*,5R*)-2-(4-bromo-2-ethoxy-phenyl)-4,5-bis-(4-chloro-phenyl)-4,5-dimethyl-4,5-dihydro-imidazole-1-carbonyl chloride was reacted with 1-(3-methanesulfonyl-propyl)-
- 5 piperazine dihydrochloride (prepared as described in Fotouhi, N. *et al.* WO 2005110996) to give the title compound. HR-MS (ES, *m/z*) calculated for C₃₆H₄₁N₅O₄Cl₂Br [(M+H)⁺] 756.1714, observed 756.1720.

Example 77

- 10 *rac*-2-{4-[(4S*,5R*)-4,5-Bis-(4-chloro-phenyl)-4,5-dimethyl-4,5-dihydro-1*H*-imidazol-2-yl]-3-ethoxy-phenyl}-propan-2-ol



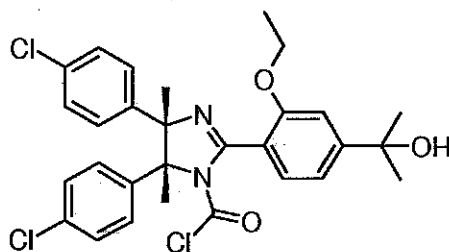
- To a solution of *n*-butyllithium (11.6 mL, 28.95 mmol, 2.5 M solution in hexane, Aldrich) in tetrahydrofuran (50 mL) at -78 °C was added dropwise a solution of
- 15 *rac*-(4S*,5R*)-2-(4-bromo-2-ethoxy-phenyl)-4,5-bis-(4-chloro-phenyl)-4,5-dimethyl-4,5-dihydro-1*H*-imidazole (1.5 g, 2.894 mmol, example 74) in tetrahydrofuran (50 mL). The brown reaction mixture was stirred at -78 °C for 15 min then acetone (2.12 mL, 28.94 mmol) was added dropwise. The color turned
- 20 yellow at the end of addition. The reaction mixture was stirred at -78 °C for 30 min then quenched with water. The ice bath was removed to let the reaction

warmed up to room temperature. The reaction was worked up with water and ethyl acetate. The organic layers were washed with brine and dried over anhydrous sodium sulfate. The solids were filtered off and the filtrate was concentrated to give a yellow residue. Purification of the crude residue by flash chromatography (120 g of silica gel, eluting with 100% ethyl acetate, 2-5% methanol in ethyl acetate) to give the title compound (702 mg, 49%). HR-MS (ES, m/z) calculated for $C_{28}H_{31}N_2O_2Cl_2$ $[(M+H)^+]$ 497.1757, observed 497.1758.

A small amount of the side product, *rac*-(4S*,5R*)-4,5-bis-(4-chloro-phenyl)-2-(2-ethoxy-phenyl)-4,5-dimethyl-4,5-dihydro-1*H*-imidazole, was also obtained (187 mg, 15%). HR-MS (ES, m/z) calculated for $C_{25}H_{25}N_2OCl_2$ $[(M+H)^+]$ 439.1339, observed 439.1339.

Example 78

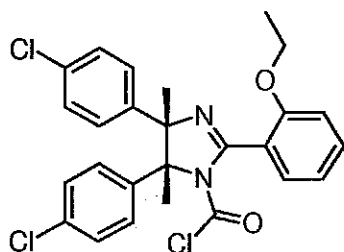
rac-(4S*,5R*)-4,5-Bis-(4-chloro-phenyl)-2-[2-ethoxy-4-(1-hydroxy-1-methyl-ethyl)-phenyl]-4,5-dimethyl-4,5-dihydro-imidazole-1-carbonyl chloride



In a manner analogous to the method described in example 3, *rac*-2-{4-[(4S*,5R*)-4,5-bis-(4-chloro-phenyl)-4,5-dimethyl-4,5-dihydro-1*H*-imidazol-2-yl]-3-ethoxy-phenyl}-propan-2-ol was reacted with phosgene in the presence of triethylamine to give the title compound.

Example 79

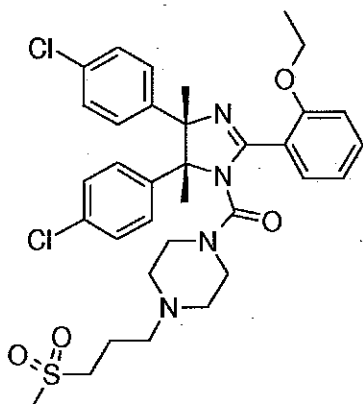
rac-(4S*,5R*)-4,5-Bis-(4-chloro-phenyl)-2-(2-ethoxy-phenyl)-4,5-dimethyl-4,5-dihydro-imidazole-1-carbonyl chloride



In a manner analogous to the method described in example 3, *rac*-(4S*,5R*)-4,5-bis-(4-chloro-phenyl)-2-(2-ethoxy-phenyl)-4,5-dimethyl-4,5-dihydro-1H-imidazole
 5 was reacted with phosgene in the presence of triethylamine to give the title compound.

Example 80

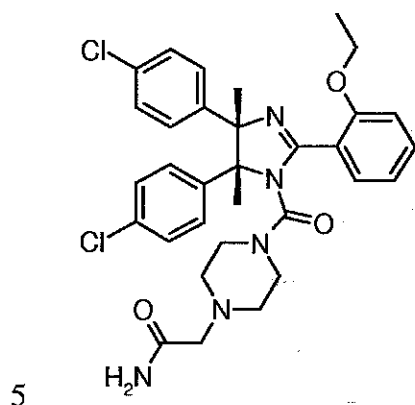
[(4S,5R)-4,5-Bis-(4-chloro-phenyl)-2-(2-ethoxy-phenyl)-4,5-dimethyl-4,5-dihydro-imidazol-1-yl]-[4-(3-methanesulfonyl-propyl)-piperazin-1-yl]-methanone
 10



In a manner analogous to the method described in example 5, *rac*-(4S*,5R*)-4,5-bis-(4-chloro-phenyl)-2-(2-ethoxy-phenyl)-4,5-dimethyl-4,5-dihydro-imidazole-1-carbonyl chloride was reacted with 1-(3-methanesulfonyl-propyl)-piperazine
 15 dihydrochloride (prepared as described in Fotouhi, N. *et al.* WO 2005110996) to give the title compound as a racemic mixture. The enantiomers were then separated by supercritical fluid chromatography (Berger Instrument Multi-Gram II, Daicel ChiralPak OD-H 3 x 25 cm, 35 °C at 100 bar, eluting with 25% of 1:1
 20 ethanol/acetonitrile in carbon dioxide). HR-MS (ES, *m/z*) calculated for C₃₄H₄₁N₄O₄SCl₂ [(M+H)⁺] 671.2220, observed 671.2218.

Example 81

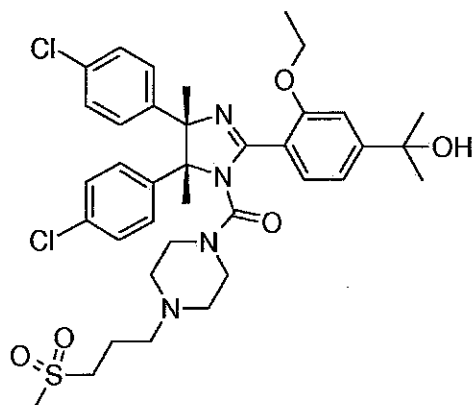
2-{4-[(4S,5R)-4,5-Bis-(4-chloro-phenyl)-2-(2-ethoxy-phenyl)-4,5-dimethyl-4,5-dihydro-imidazole-1-carbonyl]-piperazin-1-yl}-acetamide



- In a manner analogous to the method described in example 5, *rac*-(4S*,5R*)-4,5-bis-(4-chloro-phenyl)-2-(2-ethoxy-phenyl)-4,5-dimethyl-4,5-dihydro-imidazole-1-carbonyl chloride was reacted with 2-piperazin-1-yl-acetamide dihydrochloride (Matrix Scientific) to give the title compound as a racemic mixture. The enantiomers were then separated by supercritical fluid chromatography (Berger Instrument Multi-Gram II, Daicel ChiralPak OD-H 3 x 25 cm, 35 °C at 100 bar, eluting with 35% of 1:1 ethanol/acetonitrile in carbon dioxide). HR-MS (ES, *m/z*) calculated for C₃₂H₃₆N₅O₃Cl₂ [(M+H)⁺] 608.2190, observed 608.2190.
- 10

15 **Example 82**

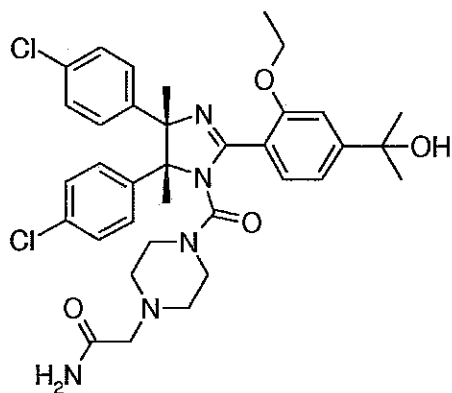
{(4S,5R)-4,5-Bis-(4-chloro-phenyl)-2-[2-ethoxy-4-(1-hydroxy-1-methyl-ethyl)-phenyl]-4,5-dimethyl-4,5-dihydro-imidazol-1-yl}-[4-(3-methanesulfonyl-propyl)-piperazin-1-yl]-methanone



- In a manner analogous to the method described in example 5, *rac*-(4*S**,5*R**)-4,5-bis-(4-chloro-phenyl)-2-[2-ethoxy-4-(1-hydroxy-1-methyl-ethyl)-phenyl]-4,5-dimethyl-4,5-dihydro-imidazole-1-carbonyl chloride was reacted with 1-(3-methanesulfonyl-propyl)-piperazine dihydrochloride (prepared as described in Fotouhi, N. *et al.* WO 2005110996) to give the title compound as a racemic mixture. The enantiomers were then separated by supercritical fluid chromatography (Berger Instrument Multi-Gram II, Daicel ChiralPak OD-H 3 x 25 cm, 35 °C at 100 bar, eluting with 35% of 1:1 ethanol/acetonitrile in carbon dioxide). HR-MS (ES, *m/z*) calculated for C₃₇H₄₇N₄O₅SCl₂ [(*M*+*H*)⁺] 729.2639, observed 729.2634.

Example 83

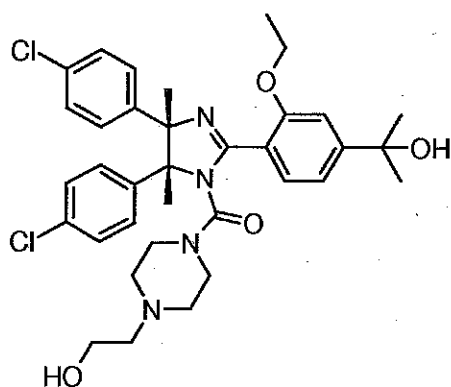
- 2-(4-((4*S*,5*R*)-4,5-Bis-(4-chloro-phenyl)-2-[2-ethoxy-4-(1-hydroxy-1-methyl-ethyl)-phenyl]-4,5-dimethyl-4,5-dihydro-imidazole-1-carbonyl)-piperazin-1-yl)-acetamide



In a manner analogous to the method described in example 5, *rac*-(4S*,5R*)-4,5-bis-(4-chloro-phenyl)-2-[2-ethoxy-4-(1-hydroxy-1-methyl-ethyl)-phenyl]-4,5-dimethyl-4,5-dihydro-imidazole-1-carbonyl chloride was reacted with 2-piperazin-1-yl-acetamide dihydrochloride (Matrix Scientific) to give the title compound as a racemic mixture. The enantiomers were then separated by supercritical fluid chromatography (Berger Instrument Multi-Gram II, Daicel ChiralPak OD-H 3 x 25 cm, 35 °C at 100 bar, eluting with 45% of 1:1 ethanol/acetonitrile in carbon dioxide). HR-MS (ES, *m/z*) calculated for C₃₅H₄₂N₅O₄Cl₂ [(M+H)⁺] 666.2609, observed 666.2606.

Example 84

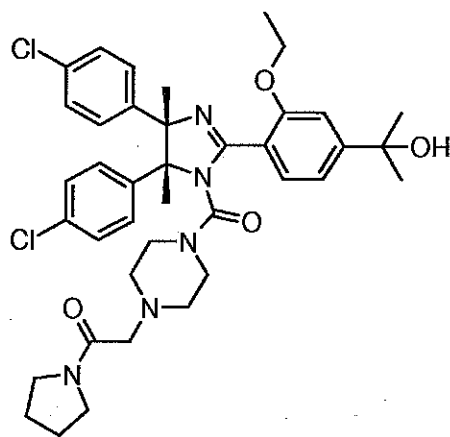
{{(4S,5R)-4,5-Bis-(4-chloro-phenyl)-2-[2-ethoxy-4-(1-hydroxy-1-methyl-ethyl)-phenyl]-4,5-dimethyl-4,5-dihydro-imidazol-1-yl}-[4-(2-hydroxy-ethyl)-piperazin-1-yl]-methanone



In a manner analogous to the method described in example 5, *rac*-(4S*,5R*)-4,5-bis-(4-chloro-phenyl)-2-[2-ethoxy-4-(1-hydroxy-1-methyl-ethyl)-phenyl]-4,5-dimethyl-4,5-dihydro-imidazole-1-carbonyl chloride was reacted with 2-piperazin-1-yl-ethanol (Chemical Dynamics) to give the title compound as a racemic mixture. The enantiomers were then separated by supercritical fluid chromatography (Berger Instrument Multi-Gram II, Daicel ChiralPak OD-H 3 x 25 cm, 35 °C at 100 bar, eluting with 30% methanol in carbon dioxide). HR-MS (ES, *m/z*) calculated for C₃₅H₄₃N₄O₄Cl₂ [(M+H)⁺] 653.2656, observed 653.2657.

Example 85

2-(4-((4S,5R)-4,5-Bis-(4-chloro-phenyl)-2-[2-ethoxy-4-(1-hydroxy-1-methyl-ethyl)-phenyl]-4,5-dimethyl-4,5-dihydro-imidazole-1-carbonyl)-piperazin-1-yl)-1-pyrrolidin-1-yl-ethanone



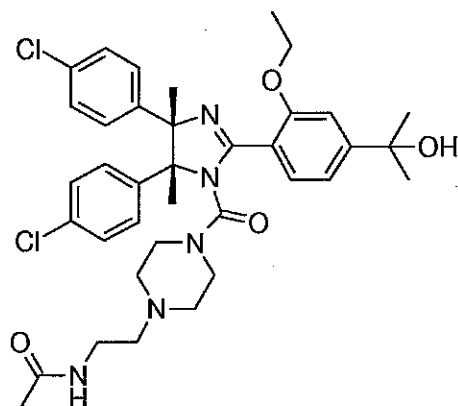
5

In a manner analogous to the method described in example 5, *rac*-(4S*,5R*)-4,5-bis-(4-chloro-phenyl)-2-[2-ethoxy-4-(1-hydroxy-1-methyl-ethyl)-phenyl]-4,5-dimethyl-4,5-dihydro-imidazole-1-carbonyl chloride was reacted with 2-piperazin-1-yl-1-pyrrolidin-1-yl-ethanone (Aldrich) to give the title compound as a racemic mixture. The enantiomers were then separated by supercritical fluid chromatography (Berger Instrument Multi-Gram II, Daicel ChiralPak OD-H 3 x 25 cm, 35 °C at 100 bar, eluting with 25% methanol in carbon dioxide). HR-MS (ES, *m/z*) calculated for C₃₉H₄₈N₅O₄Cl₂ [(M+H)⁺] 720.3078, observed 720.3072.

15

Example 86

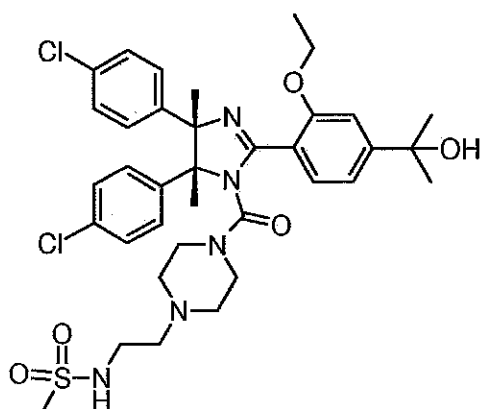
N-[2-(4-((4S,5R)-4,5-Bis-(4-chloro-phenyl)-2-[2-ethoxy-4-(1-hydroxy-1-methyl-ethyl)-phenyl]-4,5-dimethyl-4,5-dihydro-imidazole-1-carbonyl)-piperazin-1-yl)-ethyl]-acetamide



In a manner analogous to the method described in example 5, *rac*-(4*S**,5*R**)-4,5-bis-(4-chloro-phenyl)-2-[2-ethoxy-4-(1-hydroxy-1-methyl-ethyl)-phenyl]-4,5-dimethyl-4,5-dihydro-imidazole-1-carbonyl chloride was reacted with N-(2-piperazin-1-yl-ethyl)-acetamide dihydrochloride (prepared as described in Fotouhi, N. *et al.* WO 2005110996) to give the title compound as a racemic mixture. The enantiomers were then separated by supercritical fluid chromatography (Berger Instrument Multi-Gram II, Daicel ChiralPak OD-H 3 x 25 cm, 35 °C at 100 bar, eluting with 30% methanol in carbon dioxide). HR-MS (ES, *m/z*) calculated for C₃₇H₄₆N₅O₄Cl₂ [(M+H)⁺] 694.2922, observed 694.2918.

Example 87

N-[2-(4-((4*S*,5*R*)-4,5-Bis-(4-chloro-phenyl)-2-[2-ethoxy-4-(1-hydroxy-1-methyl-ethyl)-phenyl]-4,5-dimethyl-4,5-dihydro-imidazole-1-carbonyl)-piperazin-1-yl)-ethyl]-methanesulfonamide

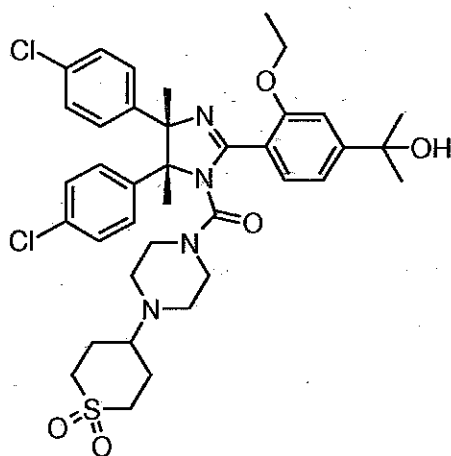


In a manner analogous to the method described in example 5, *rac*-(4S*,5R*)-4,5-bis-(4-chloro-phenyl)-2-[2-ethoxy-4-(1-hydroxy-1-methyl-ethyl)-phenyl]-4,5-dimethyl-4,5-dihydro-imidazole-1-carbonyl chloride was reacted with N-(2-piperazin-1-yl-ethyl)-methanesulfonamide dihydrochloride (prepared as described in Fotouhi, N. *et al.* WO 2005110996) to give the title compound as a racemic mixture. The enantiomers were then separated by supercritical fluid chromatography (Berger Instrument Multi-Gram II, Daicel ChiralPak OD-H 3 x 25 cm, 35 °C at 100 bar, eluting with 30% methanol in carbon dioxide). HR-MS (ES, *m/z*) calculated for C₃₆H₄₅N₅O₅SCl₂ [(M+H)⁺] 730.2591, observed 730.2585.

10

Example 88

{(4S,5R)-4,5-Bis-(4-chloro-phenyl)-2-[2-ethoxy-4-(1-hydroxy-1-methyl-ethyl)-phenyl]-4,5-dimethyl-4,5-dihydro-imidazol-1-yl}-[4-(1,1-dioxo-tetrahydro-2H-thiopyran-4-yl)-piperazin-1-yl]-methanone.



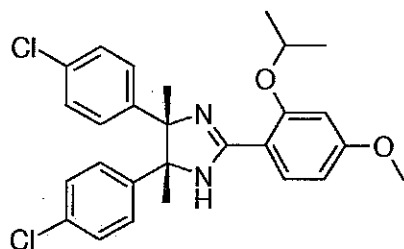
15

In a manner analogous to the method described in example 5, *rac*-(4S*,5R*)-4,5-bis-(4-chloro-phenyl)-2-[2-ethoxy-4-(1-hydroxy-1-methyl-ethyl)-phenyl]-4,5-dimethyl-4,5-dihydro-imidazole-1-carbonyl chloride was reacted with 1-(1,1-dioxo-tetrahydro-2H-thiopyran-4-yl)-piperazine dihydrochloride (example 22) to give the title compound as a racemic mixture. The enantiomers were then separated by supercritical fluid chromatography (Berger Instrument Multi-Gram II, Daicel ChiralPak OD-H 3 x 25 cm, 35 °C at 100 bar, eluting with 35% of 1:1

ethanol/acetonitrile in carbon dioxide). HR-MS (ES, m/z) calculated for $C_{38}H_{47}N_4O_5SCl_2$ $[(M+H)^+]$ 741.2639, observed 741.2637.

Example 89

- 5 *rac*-(4S*,5R*)-4,5-Bis-(4-chloro-phenyl)-2-(2-isopropoxy-4-methoxy-phenyl)-4,5-dimethyl-4,5-dihydro-1*H*-imidazole

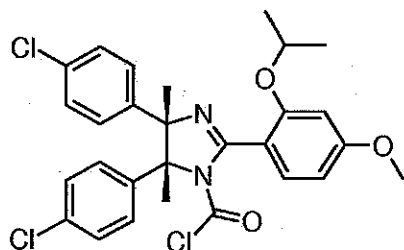


In a manner analogous to the method described in example 2, meso-2,3-bis-(4-chlorophenyl)-2,3-butanediamine was reacted with 2-isopropoxy-4-

- 10 methoxybenzoic acid methyl ester (prepared in a manner analogous to the method described in example 56) in the presence of trimethylaluminum to give the title compound. HR-MS (ES, m/z) calculated for $C_{29}H_{34}N_3O_3SCl_2$ $[(M+H)^+]$ 574.1693, observed 574.1589.

15 Example 90

rac-(4S*,5R*)-4,5-Bis-(4-chloro-phenyl)-2-(2-isopropoxy-4-methoxy-phenyl)-4,5-dimethyl-4,5-dihydro-imidazole-1-carbonyl chloride

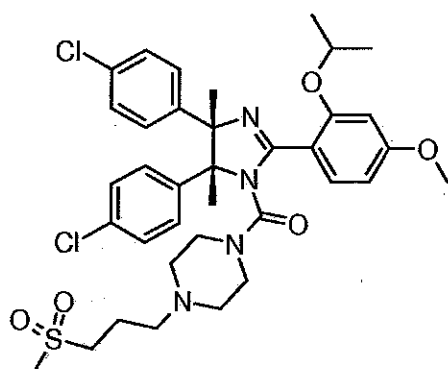


- 20 In a manner analogous to the method described in example 3, *rac*-(4S*,5R*)-4,5-Bis-(4-chloro-phenyl)-2-(2-isopropoxy-4-methoxy-phenyl)-4,5-dimethyl-4,5-

dihydro-1*H*-imidazole was reacted with phosgene in the presence of triethylamine to give the title compound.

Example 91

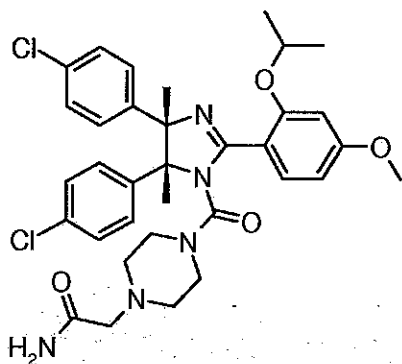
- 5 *rac*-(4*S*^{*},5*R*^{*})-4,5-Bis-(4-chloro-phenyl)-2-(2-isopropoxy-4-methoxy-phenyl)-4,5-dimethyl-4,5-dihydro-imidazol-1-yl]-[4-(3-methanesulfonyl-propyl)-piperazin-1-yl]-methanone



- 10 In a manner analogous to the method described in example 5, *rac*-(4*S*^{*},5*R*^{*})-4,5-bis-(4-chloro-phenyl)-2-(2-isopropoxy-4-methoxy-phenyl)-4,5-dimethyl-4,5-dihydro-imidazole-1-carbonyl chloride was reacted with 1-(3-methanesulfonyl-propyl)-piperazine dihydrochloride (prepared as described in Fotouhi, N. *et al.* WO 2005110996) to give the title compound. HR-MS (ES, *m/z*) calculated for
- 15 C₃₆H₄₅N₄O₅SCl₂ [(M+H)⁺] 715.2482, observed 715.2485.

Example 92

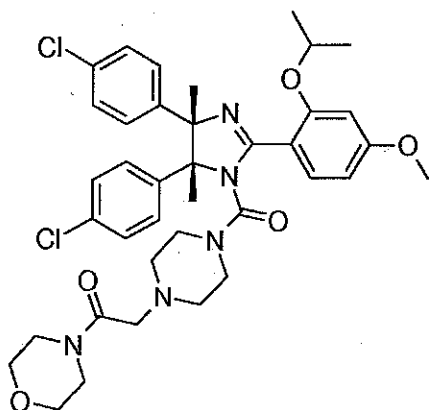
rac-2-{4-[(4*S*^{*},5*R*^{*})-4,5-Bis-(4-chloro-phenyl)-2-(2-isopropoxy-4-methoxy-phenyl)-4,5-dimethyl-4,5-dihydro-imidazole-1-carbonyl]-piperazin-1-yl}-acetamide



In a manner analogous to the method described in example 5, *rac*-(4S*,5R*)-4,5-bis-(4-chloro-phenyl)-2-(2-isopropoxy-4-methoxy-phenyl)-4,5-dimethyl-4,5-dihydro-imidazole-1-carbonyl chloride was reacted with 2-piperazin-1-yl-acetamide dihydrochloride (Matrix Scientific) to give the title compound. HR-MS (ES, *m/z*) calculated for C₃₄H₄₀N₅O₄Cl₂ [(M+H)⁺] 652.2452, observed 652.2451.

Example 93

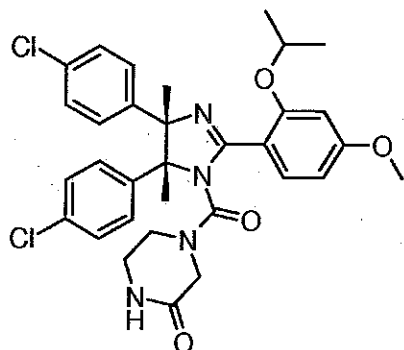
rac-2-{4-[(4S*,5R*)-4,5-Bis-(4-chloro-phenyl)-2-(2-isopropoxy-4-methoxy-phenyl)-4,5-dimethyl-4,5-dihydro-imidazole-1-carbonyl]-piperazin-1-yl}-1-morpholin-4-yl-ethanone



In a manner analogous to the method described in example 5, *rac*-(4S*,5R*)-4,5-bis-(4-chloro-phenyl)-2-(2-isopropoxy-4-methoxy-phenyl)-4,5-dimethyl-4,5-dihydro-imidazole-1-carbonyl chloride was reacted with 1-morpholin-4-yl-2-piperazin-1-yl-ethanone (Oakwood Products) to give the title compound. HR-MS (ES, *m/z*) calculated for C₃₈H₄₆N₅O₅Cl₂ [(M+H)⁺] 722.2871, observed 722.2874.

Example 94

rac-4-[(4S*,5R*)-4,5-Bis-(4-chloro-phenyl)-2-(2-isopropoxy-4-methoxy-phenyl)-4,5-dimethyl-4,5-dihydro-imidazole-1-carbonyl]-piperazin-2-one

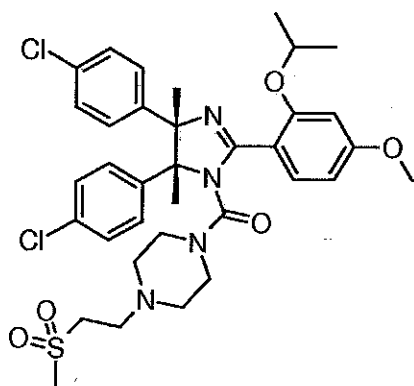


- 5 In a manner analogous to the method described in example 5, *rac*-(4S*,5R*)-4,5-bis-(4-chloro-phenyl)-2-(2-isopropoxy-4-methoxy-phenyl)-4,5-dimethyl-4,5-dihydro-imidazole-1-carbonyl chloride was reacted with 2-piperazinone (Avocado Organics) to give the title compound. HR-MS (ES, *m/z*) calculated for C₃₂H₃₅N₄O₄Cl₂ [(M+H)⁺] 609.2030, observed 609.2025.

10

Example 95

rac-[(4S*,5R*)-4,5-Bis-(4-chloro-phenyl)-2-(2-isopropoxy-4-methoxy-phenyl)-4,5-dimethyl-4,5-dihydro-imidazol-1-yl]-[4-(2-methanesulfonyl-ethyl)-piperazin-1-yl]-methanone



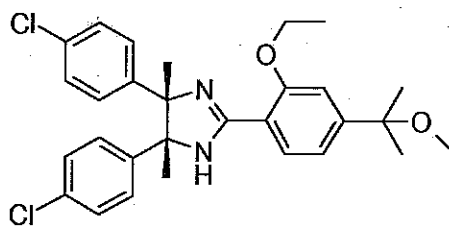
15

In a manner analogous to the method described in example 5, *rac*-(4S*,5R*)-4,5-bis-(4-chloro-phenyl)-2-(2-isopropoxy-4-methoxy-phenyl)-4,5-dimethyl-4,5-dihydro-imidazole-1-carbonyl chloride was reacted with 1-(2-methanesulfonyl-

ethyl)-piperazine (prepared as described in Fotouhi, N. *et al.* WO 2005110996) to give the title compound. HR-MS (ES, *m/z*) calculated for C₃₅H₄₃N₄O₅SCl₂ [(M+H)⁺] 701.2326, observed 701.2325.

5 **Example 96**

rac-(4S*,5R*)-4,5-Bis-(4-chloro-phenyl)-2-[2-ethoxy-4-(1-methoxy-1-methyl-ethyl)-phenyl]-4,5-dimethyl-4,5-dihydro-1*H*-imidazole



To a solution of 1-bromo-3-ethoxy-benzene (20 g, 99.473 mmol) in anhydrous tetrahydrofuran (300 mL) cooled to -78 °C was added 2.5 M n-butyllithium in hexane (39.8 mL, 99.473 mmol, Aldrich) The reaction mixture was stirred at -78 °C for 5 min then acetone (43.8 mL, 596.838 mmol) was added. After 30 min at -78 °C, the ice bath was removed and saturated solution of ammonium chloride was added to quench the reaction. The product was extracted with ethyl acetate (2 x 150 mL). The combined organic layers were washed with brine (1 x 50 mL) and dried over anhydrous sodium sulfate. The solids were filtered off, and the filtrate was concentrated *in vacuo*. Purification of the crude residue by flash chromatography (silica gel, eluting with 15-25% ethyl acetate in hexane) gave the 2-(3-ethoxy-phenyl)-propan-2-ol as clear oil (10.930 g, 61%).

Sodium hydride (3.261 g, 81.54 mmol, 60% in mineral oil, Aldrich) was washed twice with hexane, and tetrahydrofuran (60 mL) was added. To this suspension was added 2-(3-ethoxy-phenyl)-propan-2-ol (4.9 g, 27.18 mmol). The mixture was stirred at 45 °C for 1.5 h until the bubbling subsided. It was cooled down to 0 °C and iodomethane (5.08 mL, 81.54 mmol, Aldrich) was added. After 4 h of stirring at room temperature, another portion of iodomethane (5.08 mL, 81.54 mmol) was added. The mixture was stirred at room temperature for 4 d then quenched at 0 °C with cold 20% solution of ammonium chloride. The product was extracted with ethyl acetate (2 x 1 L). The organic extracts were washed with brine and dried over anhydrous sodium sulfate. The solids

were filtered off, and the filtrate was concentrated *in vacuo* to give 1-ethoxy-3-(1-methoxy-1-methyl-ethyl)-benzene (5.15 g, 97%).

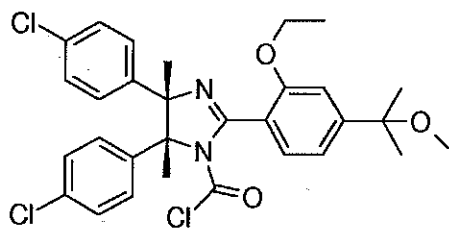
To a solution of 1-ethoxy-3-(1-methoxy-1-methyl-ethyl)-benzene (5.15 g, 26.51 mmol) in acetonitrile (60 mL) were added N-iodosuccinimide (8.349 g, 37.11 mmol) and trifluoroacetic acid (1.02 mL, 13.26 mmol). The mixture was stirred at room temperature overnight. It was then concentrated *in vacuo* and the residue was taken in ethyl acetate. After washing with saturated solution of sodium bicarbonate, water and brine, the organic layer was dried over anhydrous sodium sulfate. The solids were filtered off, and the filtrate was concentrated *in vacuo* to give 9.39 g of 2-ethoxy-1-iodo-4-(1-methoxy-1-methyl-ethyl)-benzene as light brown oil.

Diisopropylethylamine (10.15 mL, 58.10 mmol) was added to a solution of 2-ethoxy-1-iodo-4-(1-methoxy-1-methyl-ethyl)-benzene (9.3 g, 29.05 mmol) in methanol (60 mL). Argon was bubbling through the mixture for 30 min and palladium (II) acetate (653 mg, 2.91 mmol) was added. The reaction flask was flushed with carbon monoxide several times then stirred at 60 °C for 18 h under a pressure of carbon monoxide (40 psi). The reaction mixture was concentrated and the residue was taken in ethyl acetate. It was washed with water, brine and dried over anhydrous sodium sulfate and concentrated. Purification of the crude residue by flash chromatography (silica gel, eluting with 10-30% ethyl acetate in hexane over 30 min) gave 2-ethoxy-4-(1-methoxy-1-methyl-ethyl)-benzoic acid methyl ester (2.81 g).

In a manner analogous to the method described in example 2, meso-2,3-bis-(4-chlorophenyl)-2,3-butanedi-amine was reacted with 2-ethoxy-4-(1-methoxy-1-methyl-ethyl)-benzoic acid methyl ester in the presence of trimethylaluminum to give the title compound.

Example 97

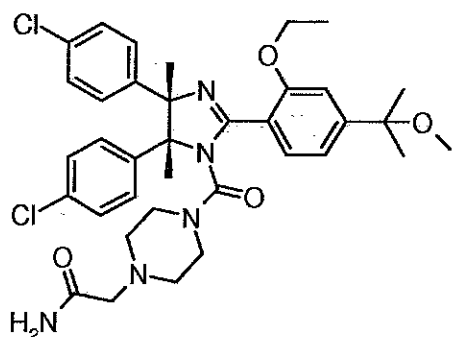
rac-(4S*,5R*)-4,5-Bis-(4-chloro-phenyl)-2-[2-ethoxy-4-(1-methoxy-1-methyl-ethyl)-phenyl]-4,5-dimethyl-4,5-dihydro-imidazole-1-carbonyl chloride



In a manner analogous to the method described in example 3, *rac*-(4S*,5R*)-4,5-bis-(4-chloro-phenyl)-2-[2-ethoxy-4-(1-methoxy-1-methyl-ethyl)-phenyl]-4,5-dimethyl-4,5-dihydro-1*H*-imidazole was reacted with phosgene in the presence of triethylamine to give the title compound.

Example 98

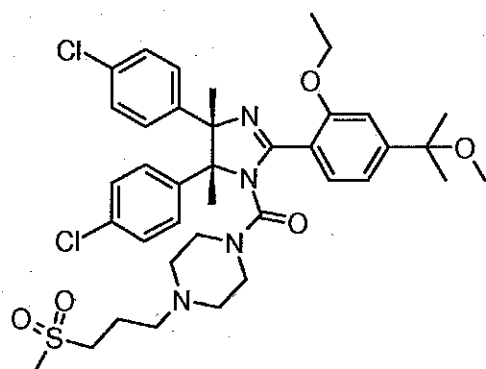
2-(4-((4S,5R)-4,5-Bis-(4-chloro-phenyl)-2-[2-ethoxy-4-(1-methoxy-1-methyl-ethyl)-phenyl]-4,5-dimethyl-4,5-dihydro-imidazole-1-carbonyl)-piperazin-1-yl)-acetamide



In a manner analogous to the method described in example 5, 4,5-Bis-(4-chloro-phenyl)-2-[2-ethoxy-4-(1-methoxy-1-methyl-ethyl)-phenyl]-4,5-dimethyl-4,5-dihydro-imidazole-1-carbonyl chloride was reacted with 2-piperazin-1-yl-acetamide dihydrochloride (Matrix Scientific) to give the title compound as a racemic mixture. The enantiomers were then separated by supercritical fluid chromatography (Berger Instrument Multi-Gram II, Daicel ChiralPak OD-H 3 x 25 cm, 35 °C at 100 bar, eluting with 30% methanol in carbon dioxide). HR-MS (ES, *m/z*) calculated for C₃₆H₄₄N₅O₄Cl₂ [(M+H)⁺] 680.2765, observed 680.2767.

Example 99

{*rac*-(4*S**,5*R**)-4,5-Bis-(4-chloro-phenyl)-2-[2-ethoxy-4-(1-methoxy-1-methyl-ethyl)-phenyl]-4,5-dimethyl-4,5-dihydro-imidazol-1-yl]-[4-(3-methanesulfonyl-propyl)-piperazin-1-yl]-methanone



5

In a manner analogous to the method described in example 5, 4,5-bis-(4-chloro-phenyl)-2-[2-ethoxy-4-(1-methoxy-1-methyl-ethyl)-phenyl]-4,5-dimethyl-4,5-dihydro-imidazole-1-carbonyl chloride was reacted with 1-(3-methanesulfonyl-propyl)-piperazine dihydrochloride (prepared as described in Fotouhi, N. *et al.*

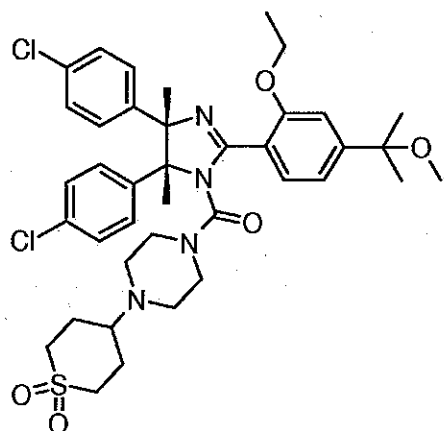
10 WO 2005110996) to give the title compound as a racemic mixture. The enantiomers were then separated by supercritical fluid chromatography (Berger Instrument Multi-Gram II, Daicel ChiralPak OD-H 3 x 25 cm, 35 °C at 100 bar, eluting with 30% methanol in carbon dioxide). HR-MS (ES, *m/z*) calculated for C₃₈H₄₉N₄O₅SCl₂ [(M+H)⁺] 743.2795, observed 743.2795.

15

Example 100

{(4*S*,5*R*)-4,5-Bis-(4-chloro-phenyl)-2-[2-ethoxy-4-(1-methoxy-1-methyl-ethyl)-phenyl]-4,5-dimethyl-4,5-dihydro-imidazol-1-yl]-[4-(1,1-dioxo-tetrahydro-2H-thiopyran-4-yl)-piperazin-1-yl]-methanone

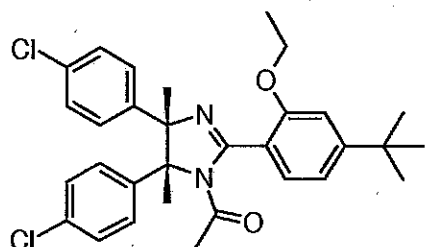
20



In a manner analogous to the method described in example 5, 4,5-bis-(4-chloro-phenyl)-2-[2-ethoxy-4-(1-methoxy-1-methyl-ethyl)-phenyl]-4,5-dimethyl-4,5-dihydro-imidazole-1-carbonyl chloride was reacted with 1-(1,1-dioxo-tetrahydro-2H-thiopyran-4-yl)-piperazine dihydrochloride (example 22) to give the title compound as a racemic mixture. The enantiomers were then separated by supercritical fluid chromatography (Berger Instrument Multi-Gram II, Daicel ChiralPak OD-H 3 x 25 cm, 35 °C at 100 bar, eluting with 35% methanol in carbon dioxide). HR-MS (ES, m/z) calculated for $C_{39}H_{49}N_4O_5SCl_2$ [(M+H)⁺]
 755.2795, observed 755.2792.

Example 101

rac-1-[(4S*,5R*)-2-(4-*tert*-Butyl-2-ethoxy-phenyl)-4,5-bis-(4-chloro-phenyl)-4,5-dimethyl-4,5-dihydro-imidazol-1-yl]-ethanone



15

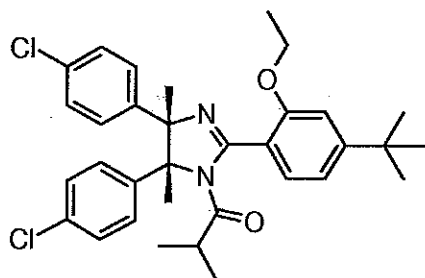
To a solution of *rac*-(4S*,5R*)-2-(4-*tert*-butyl-2-ethoxy-phenyl)-4,5-bis-(4-chloro-phenyl)-4,5-dimethyl-4,5-dihydro-1H-imidazole (70 mg, 0.13 mmol, example 2) and triethylamine (92 μ L, 0.65 mmol) in methylene chloride (3 mL) was added acetyl chloride (59 μ L, Aldrich). The reaction mixture was stirred at room
 temperature overnight then concentrated. Purification of the crude residue by

20

flash chromatography (12 g of silica gel, eluting with 5-30% ethyl acetate in hexane) gave the title compound (56.1 mg, 80%). HR-MS (ES, m/z) calculated for $C_{31}H_{34}N_2O_2Cl_2$ $[(M+H)^+]$ 537.2070, observed 537.2068.

5 **Example 102**

1-[(4S,5R)-2-(4-*tert*-Butyl-2-ethoxy-phenyl)-4,5-bis-(4-chloro-phenyl)-4,5-dimethyl-4,5-dihydro-imidazol-1-yl]-2-methyl-propan-1-one

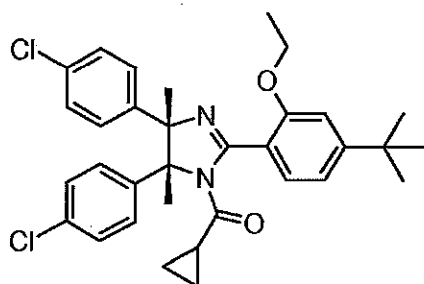


- 10 In a manner analogous to the method described in example 5, *rac*-(4S*,5R*)-2-(4-*tert*-butyl-2-ethoxy-phenyl)-4,5-bis-(4-chloro-phenyl)-4,5-dimethyl-4,5-dihydro-1H-imidazole was reacted with isobutyryl chloride (Aldrich) to give the title compound. HR-MS (ES, m/z) calculated for $C_{33}H_{37}N_2O_2Cl_2$ $[(M+H)^+]$ 565.2383, observed 565.2384.

15

Example 103

[(4S,5R)-2-(4-*tert*-Butyl-2-ethoxy-phenyl)-4,5-bis-(4-chloro-phenyl)-4,5-dimethyl-4,5-dihydro-imidazol-1-yl]-cyclopropyl-methanone



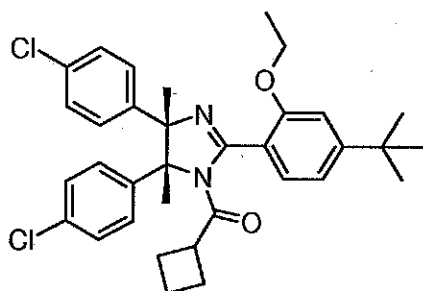
20

In a manner analogous to the method described in example 5, *rac*-(4S*,5R*)-2-(4-*tert*-butyl-2-ethoxy-phenyl)-4,5-bis-(4-chloro-phenyl)-4,5-dimethyl-4,5-dihydro-1H-imidazole was reacted with cyclopropanecarbonyl chloride (Aldrich) to give

the title compound. HR-MS (ES, m/z) calculated for $C_{33}H_{37}N_2O_2Cl_2$ $[(M+H)^+]$ 563.2227, observed 563.2224.

Example 104

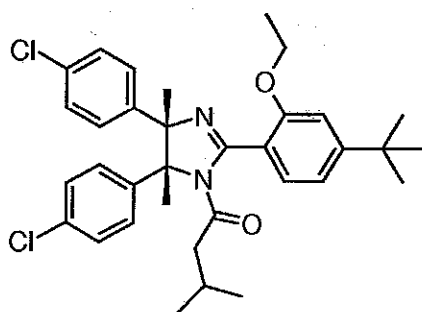
- 5 [(4*S*,5*R*)-2-(4-*tert*-Butyl-2-ethoxy-phenyl)-4,5-bis-(4-chloro-phenyl)-4,5-dimethyl-4,5-dihydro-imidazol-1-yl]-cyclobutyl-methanone



- 10 In a manner analogous to the method described in example 5, *rac*-(4*S*^{*},5*R*^{*})-2-(4-*tert*-butyl-2-ethoxy-phenyl)-4,5-bis-(4-chloro-phenyl)-4,5-dimethyl-4,5-dihydro-1*H*-imidazole was reacted with cyclobutanecarbonyl chloride (Aldrich) to give the title compound. HR-MS (ES, m/z) calculated for $C_{34}H_{39}N_2O_2Cl_2$ $[(M+H)^+]$ 577.2383, observed 577.2382.

15 Example 105

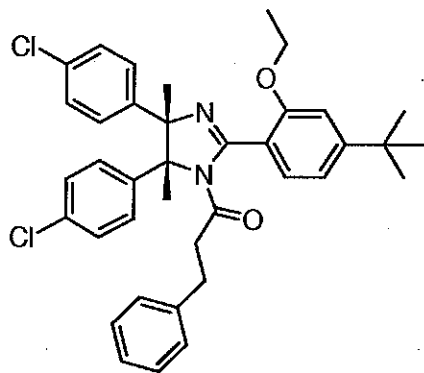
- 1-[(4*S*,5*R*)-2-(4-*tert*-Butyl-2-ethoxy-phenyl)-4,5-bis-(4-chloro-phenyl)-4,5-dimethyl-4,5-dihydro-imidazol-1-yl]-3-methyl-butan-1-one



- 20 In a manner analogous to the method described in example 5, *rac*-(4*S*^{*},5*R*^{*})-2-(4-*tert*-butyl-2-ethoxy-phenyl)-4,5-bis-(4-chloro-phenyl)-4,5-dimethyl-4,5-dihydro-1*H*-imidazole was reacted with 3-methyl-butyryl chloride (Aldrich) to give the title compound. HR-MS (ES, m/z) calculated for $C_{34}H_{41}N_2O_2Cl_2$ $[(M+H)^+]$ 579.2540, observed 579.2543.

Example 106

1-[(4S,5R)-2-(4-*tert*-Butyl-2-ethoxy-phenyl)-4,5-bis-(4-chloro-phenyl)-4,5-dimethyl-4,5-dihydro-imidazol-1-yl]-3-phenyl-propan-1-one



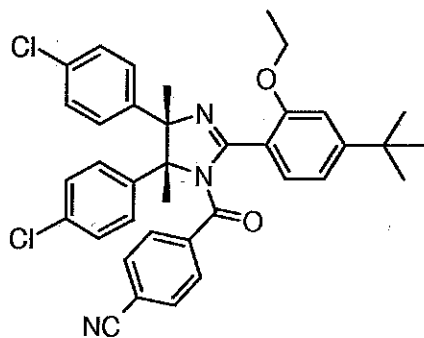
5

In a manner analogous to the method described in example 5, *rac*-(4S*,5R*)-2-(4-*tert*-butyl-2-ethoxy-phenyl)-4,5-bis-(4-chloro-phenyl)-4,5-dimethyl-4,5-dihydro-1H-imidazole was reacted with 3-phenyl-propionyl chloride (Aldrich) to give the title compound. HR-MS (ES, *m/z*) calculated for C₃₈H₄₁N₂O₂Cl₂ [(M+H)⁺]

10 627.2540, observed 627.2541.

Example 107

4-[(4S,5R)-2-(4-*tert*-Butyl-2-ethoxy-phenyl)-4,5-bis-(4-chloro-phenyl)-4,5-dimethyl-4,5-dihydro-imidazole-1-carbonyl]-benzonitrile



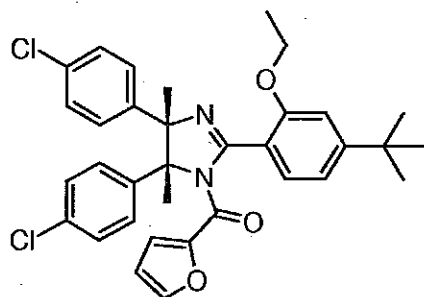
15

In a manner analogous to the method described in example 5, *rac*-(4S*,5R*)-2-(4-*tert*-butyl-2-ethoxy-phenyl)-4,5-bis-(4-chloro-phenyl)-4,5-dimethyl-4,5-dihydro-1H-imidazole was reacted with 4-cyano-benzoyl chloride (Aldrich) to give the title compound. HR-MS (ES, *m/z*) calculated for C₃₇H₃₆N₃O₂Cl₂ [(M+H)⁺] 624.2179, observed 624.2177.

20

Example 108

[(4S,5R)-2-(4-*tert*-Butyl-2-ethoxy-phenyl)-4,5-bis-(4-chloro-phenyl)-4,5-dimethyl-4,5-dihydro-imidazol-1-yl]-furan-2-yl-methanone



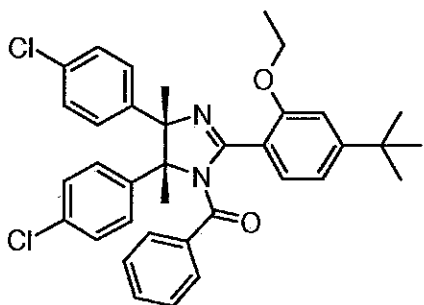
5

In a manner analogous to the method described in example 5, *rac*-(4S*,5R*)-2-(4-*tert*-butyl-2-ethoxy-phenyl)-4,5-bis-(4-chloro-phenyl)-4,5-dimethyl-4,5-dihydro-1H-imidazole was reacted with furan-2-carbonyl chloride (Aldrich) to give the title compound. HR-MS (ES, *m/z*) calculated for C₃₄H₃₅N₂O₃Cl₂ [(M+H)⁺] 589.2019, observed 589.2017.

10

Example 109

[(4S,5R)-2-(4-*tert*-Butyl-2-ethoxy-phenyl)-4,5-bis-(4-chloro-phenyl)-4,5-dimethyl-4,5-dihydro-imidazol-1-yl]-phenyl-methanone



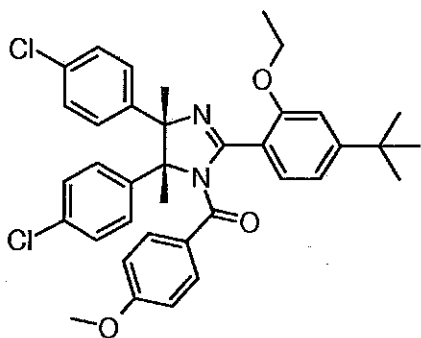
15

In a manner analogous to the method described in example 5, *rac*-(4S*,5R*)-2-(4-*tert*-butyl-2-ethoxy-phenyl)-4,5-bis-(4-chloro-phenyl)-4,5-dimethyl-4,5-dihydro-1H-imidazole was reacted with benzoyl chloride (Aldrich) to give the title compound. HR-MS (ES, *m/z*) calculated for C₃₆H₃₇N₂O₂Cl₂ [(M+H)⁺] 599.2227, observed 599.2223.

20

Example 108

rac-[(4*S**,5*R**)-2-(4-*tert*-Butyl-2-ethoxy-phenyl)-4,5-bis-(4-chloro-phenyl)-4,5-dimethyl-4,5-dihydro-imidazol-1-yl]-(4-methoxy-phenyl)-methanone



5

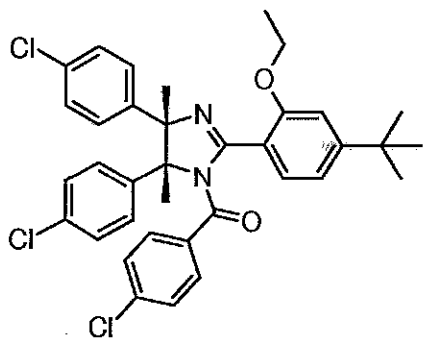
In a manner analogous to the method described in example 5, *rac*-(4*S**,5*R**)-2-(4-*tert*-butyl-2-ethoxy-phenyl)-4,5-bis-(4-chloro-phenyl)-4,5-dimethyl-4,5-dihydro-1*H*-imidazole was reacted with 4-methoxybenzoyl chloride (Aldrich) to give the title compound. HR-MS (ES, *m/z*) calculated for C₃₇H₃₉N₂O₃Cl₂ [(*M*+*H*)⁺] 629.2332, observed 629.2337.

10

Example 111

rac-[(4*S**,5*R**)-2-(4-*tert*-Butyl-2-ethoxy-phenyl)-4,5-bis-(4-chloro-phenyl)-4,5-dimethyl-4,5-dihydro-imidazol-1-yl]-(4-chloro-phenyl)-methanone

15



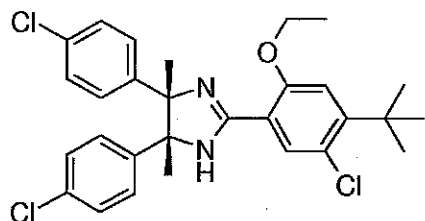
20

In a manner analogous to the method described in example 5, *rac*-(4*S**,5*R**)-2-(4-*tert*-butyl-2-ethoxy-phenyl)-4,5-bis-(4-chloro-phenyl)-4,5-dimethyl-4,5-dihydro-1*H*-imidazole was reacted with 4-chlorobenzoyl chloride (Aldrich) to give the title compound. HR-MS (ES, *m/z*) calculated for C₃₆H₃₆N₂O₃Cl₃ [(*M*+*H*)⁺] 633.1837, observed 633.1838.

Example 112

rac-(4S*,5R*)-2-(4-*tert*-Butyl-5-chloro-2-ethoxy-phenyl)-4,5-bis-(4-chloro-phenyl)-4,5-dimethyl-4,5-dihydro-1*H*-imidazole

5

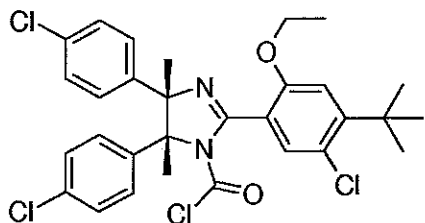


In a manner analogous to the method described in example 2, meso-2,3-bis-(4-chlorophenyl)-2,3-butanediamine was reacted with 4-*tert*-butyl-5-chloro-2-ethoxybenzoic acid methyl ester (prepared as described in Fotouhi, N. *et al.* WO 2005110996) in the presence of trimethylaluminum to give the title compound.

10

Example 113

rac-(4S*,5R*)-4,5-Bis-(4-chloro-phenyl)-2-[2-ethoxy-4-(1-methoxy-1-methyl-ethyl)-phenyl]-4,5-dimethyl-4,5-dihydro-imidazole-1-carbonyl chloride

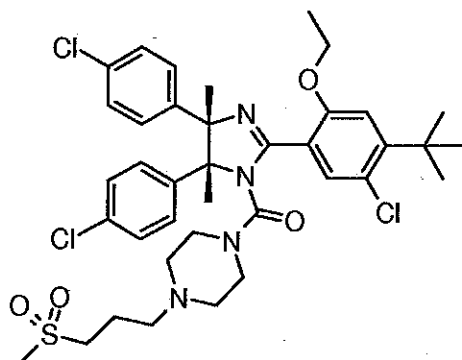


15

In a manner analogous to the method described in example 3, *rac*-(4S*,5R*)-4,5-bis-(4-chloro-phenyl)-2-[2-ethoxy-4-(1-methoxy-1-methyl-ethyl)-phenyl]-4,5-dimethyl-4,5-dihydro-1*H*-imidazole was reacted with phosgene in the presence of triethylamine to give the title compound.

Example 114

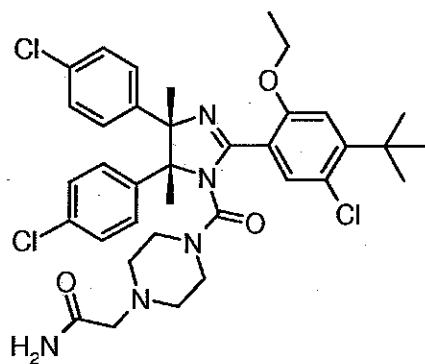
5 [(4S,5R)-2-(4-*tert*-Butyl-5-chloro-2-ethoxy-phenyl)-4,5-bis-(4-chloro-phenyl)-4,5-dimethyl-4,5-dihydro-imidazol-1-yl]-[4-(3-methanesulfonyl-propyl)-piperazin-1-yl]-methanone



In a manner analogous to the method described in example 5, *rac*-(4S*,5R*)-2-(4-*tert*-butyl-5-chloro-2-ethoxy-phenyl)-4,5-bis-(4-chloro-phenyl)-4,5-dimethyl-4,5-dihydro-1H-imidazole was reacted with 1-(3-methanesulfonyl-propyl)-piperazine dihydrochloride (prepared as described in Fotouhi, N. *et al.* WO 2005110996) to give the racemic *rac*-(4S*,5R*)-2-(4-*tert*-butyl-5-chloro-2-ethoxy-phenyl)-4,5-bis-(4-chloro-phenyl)-4,5-dimethyl-4,5-dihydro-imidazol-1-yl]-[4-(3-methanesulfonyl-propyl)-piperazin-1-yl]-methanone. Chiral separation of the enantiomers by supercritical fluid chromatography (Berger Instrument Multi-Gram II, Daicel ChiralPak OD-H 3 x 25 cm, 35 °C at 100 bar, eluting with 25% methanol in carbon dioxide) gave the title compound. HR-MS (ES, *m/z*) calculated for C₃₈H₄₈N₄O₄SCl₃ [(M+H)⁺] 761.2457, observed 761.2460.

20 **Example 115**

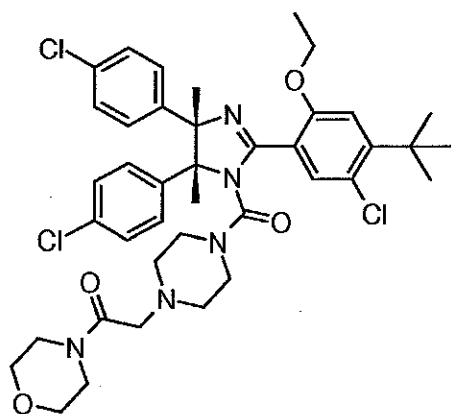
2-[4-[(4S,5R)-2-(4-*tert*-Butyl-5-chloro-2-ethoxy-phenyl)-4,5-bis-(4-chloro-phenyl)-4,5-dimethyl-4,5-dihydro-imidazole-1-carbonyl]-piperazin-1-yl]-acetamide



- In a manner analogous to the method described in example 5, *rac*-(4S*,5R*)-2-(4-*tert*-butyl-5-chloro-2-ethoxy-phenyl)-4,5-bis-(4-chloro-phenyl)-4,5-dimethyl-4,5-dihydro-1H-imidazole was reacted with 2-piperazin-1-yl-acetamide dihydrochloride (Matrix Scientific) to give the racemic 2-*rac*-{4-[(4S*,5R*)-2-(4-*tert*-butyl-5-chloro-2-ethoxy-phenyl)-4,5-bis-(4-chloro-phenyl)-4,5-dimethyl-4,5-dihydro-imidazole-1-carbonyl]-piperazin-1-yl}-acetamide. Chiral separation of the enantiomers by supercritical fluid chromatography (Berger Instrument Multi-Gram II, Daicel ChiralPak OD-H 3 x 25 cm, 35 °C at 100 bar, eluting with 25% methanol in carbon dioxide) gave the title compound. HR-MS (ES, *m/z*) calculated for C₃₆H₄₃N₅O₃Cl₃ [(M+H)⁺] 698.2426, observed 698.2431.

Example 116

- 15 *rac*-(2-{4-[(4S*,5R*)-2-(4-*tert*-Butyl-5-chloro-2-ethoxy-phenyl)-4,5-bis-(4-chloro-phenyl)-4,5-dimethyl-4,5-dihydro-imidazole-1-carbonyl]-piperazin-1-yl}-1-morpholin-4-yl-ethanone

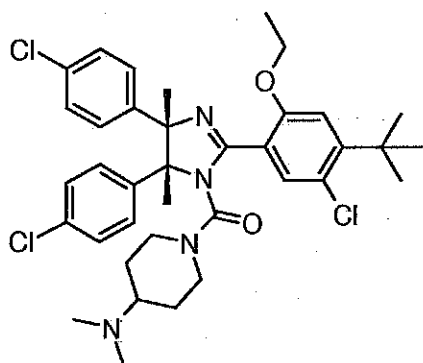


- 20 In a manner analogous to the method described in example 5, *rac*-(4S*,5R*)-2-(4-*tert*-butyl-5-chloro-2-ethoxy-phenyl)-4,5-bis-(4-chloro-phenyl)-4,5-dimethyl-4,5-

dihydro-1H-imidazole was reacted with 1-morpholin-4-yl-2-piperazin-1-yl-ethanone (Oakwood Products) to give the title compound. HR-MS (ES, m/z) calculated for $C_{40}H_{49}N_5O_4Cl_3$ $[(M+H)^+]$ 768.2845, observed 768.2845.

5 **Example 117**

rac-[(4*S**,5*R**)-2-(4-*tert*-Butyl-5-chloro-2-ethoxy-phenyl)-4,5-bis-(4-chloro-phenyl)-4,5-dimethyl-4,5-dihydro-imidazol-1-yl]-(4-dimethylamino-piperidin-1-yl)-methanone



10

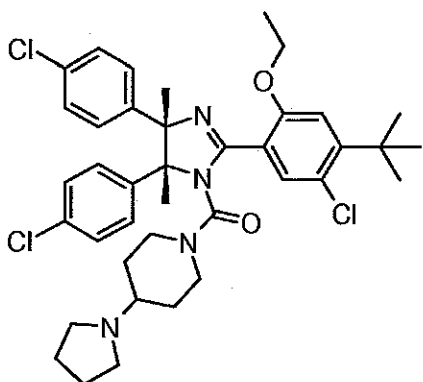
In a manner analogous to the method described in example 5, *rac*-(4*S**,5*R**)-2-(4-*tert*-butyl-5-chloro-2-ethoxy-phenyl)-4,5-bis-(4-chloro-phenyl)-4,5-dimethyl-4,5-dihydro-1H-imidazole was reacted with dimethyl-piperidin-4-yl-amine (Aldrich) to give the title compound. HR-MS (ES, m/z) calculated for $C_{37}H_{46}N_4O_2Cl_3$ $[(M+H)^+]$

15 683.2681, observed 683.2681.

Example 118

rac-[(4*S**,5*R**)-2-(4-*tert*-Butyl-5-chloro-2-ethoxy-phenyl)-4,5-bis-(4-chloro-phenyl)-4,5-dimethyl-4,5-dihydro-imidazol-1-yl]-(4-pyrrolidin-1-yl-piperidin-1-yl)-methanone

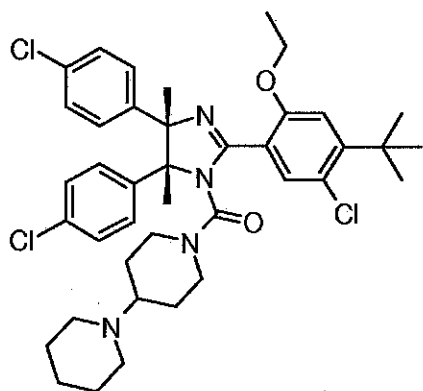
20



In a manner analogous to the method described in example 5, *rac*-(4S*,5R*)-2-(4-*tert*-butyl-5-chloro-2-ethoxy-phenyl)-4,5-bis-(4-chloro-phenyl)-4,5-dimethyl-4,5-dihydro-1H-imidazole was reacted with 4-pyrrolidin-1-yl-piperidine (Aldrich) to give the title compound. HR-MS (ES, *m/z*) calculated for C₃₉H₄₈N₄O₂Cl₃ [(M+H)⁺] 709.2838, observed 709.2836.

Example 119

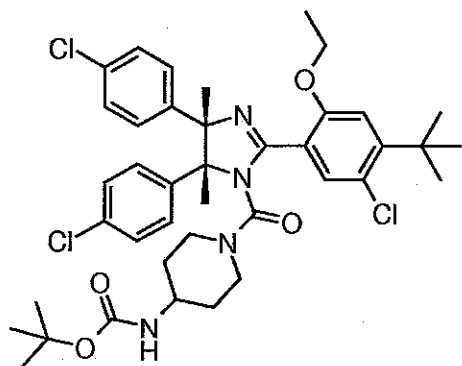
rac-[1,4']Bipiperidiny-1'-yl-[(4S*,5R*)-2-(4-*tert*-butyl-5-chloro-2-ethoxy-phenyl)-4,5-bis-(4-chloro-phenyl)-4,5-dimethyl-4,5-dihydro-imidazol-1-yl]-methanone



In a manner analogous to the method described in example 5, *rac*-(4S*,5R*)-2-(4-*tert*-butyl-5-chloro-2-ethoxy-phenyl)-4,5-bis-(4-chloro-phenyl)-4,5-dimethyl-4,5-dihydro-1H-imidazole was reacted with [1,4']bipiperidiny (Aldrich) to give the title compound. HR-MS (ES, *m/z*) calculated for C₄₀H₅₀N₄O₂Cl₃ [(M+H)⁺] 723.2994, observed 723.2997.

Example 120

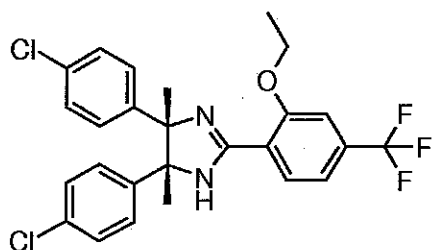
rac-{1-[(4S*,5R*)-2-(4-*tert*-Butyl-5-chloro-2-ethoxy-phenyl)-4,5-bis-(4-chloro-phenyl)-4,5-dimethyl-4,5-dihydro-imidazole-1-carbonyl]-piperidin-4-yl}-carbamic acid *tert*-butyl ester



In a manner analogous to the method described in example 5, *rac*-(4S*,5R*)-2-(4-*tert*-butyl-5-chloro-2-ethoxy-phenyl)-4,5-bis-(4-chloro-phenyl)-4,5-dimethyl-4,5-dihydro-1H-imidazole was reacted with piperidin-4-yl-carbamic acid *tert*-butyl ester (Aldrich) to give the title compound. HR-MS (ES, *m/z*) calculated for C₄₀H₅₀N₄O₄Cl₃ [(M+H)⁺] 755.2892, observed 755.2895.

Example 121

10 *rac*-(4S*,5R*)-4,5-Bis-(4-chloro-phenyl)-2-(2-ethoxy-4-trifluoromethyl-phenyl)-4,5-dimethyl-4,5-dihydro-1H-imidazole



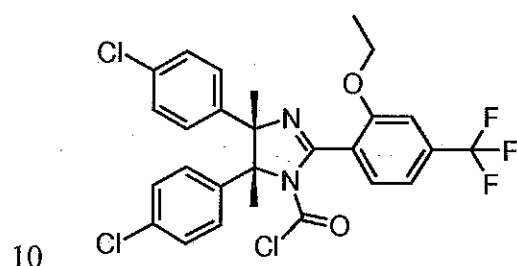
To a solution of 2-hydroxy-4-trifluoromethyl-benzoic acid (5 g, 24.258 mmol, Matrix Scientific) in ethanol (50 mL) were added potassium carbonate (8.38 g, 60.645 mmol) and ethyl iodide (7.68 mL, 97.032 mmol). The reaction mixture was heated at gentle reflux for 4 h then concentrated *in vacuo*. The residue was taken in petroleum ether and water, and the layers were separated. The product was extracted with petroleum ether (1x). The organic layers were washed with brine (1x), dried over anhydrous sodium sulfate, filtered and concentrated. Purification of the crude residue by flash chromatography (40g of silica gel, eluting with 10% ethyl acetate in hexane) gave 2-ethoxy-4-trifluoromethyl-benzoic acid ethyl ester as colorless oil (4.68 g, 74%).

In a manner analogous to the method described in example 2, meso-2,3-bis-(4-chlorophenyl)-2,3-butanediamine was reacted with 2-ethoxy-4-trifluoromethyl-benzoic acid ethyl ester in the presence of trimethylaluminum to give the title compound. HR-MS (ES, m/z) calculated for $C_{26}H_{24}N_2OF_3Cl_2$

5 $[(M+H)^+]$ 507.1213, observed 507.1207.

Example 122

rac-(4*S**,5*R**)-4,5-Bis-(4-chloro-phenyl)-2-(2-ethoxy-4-trifluoromethyl-phenyl)-4,5-dimethyl-4,5-dihydro-imidazole-1-carbonyl chloride

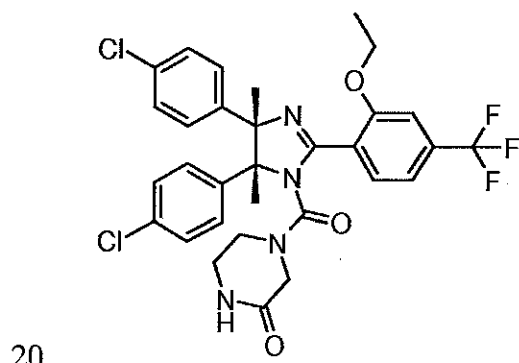


In a manner analogous to the method described in example 3, *rac*-(4*S**,5*R**)-4,5-bis-(4-chloro-phenyl)-2-(2-ethoxy-4-trifluoromethyl-phenyl)-4,5-dimethyl-4,5-dihydro-1*H*-imidazole was reacted with phosgene in the presence of

15 triethylamine to give the title compound.

Example 123

rac-4-[(4*S**,5*R**)-4,5-Bis-(4-chloro-phenyl)-2-(2-ethoxy-4-trifluoromethyl-phenyl)-4,5-dimethyl-4,5-dihydro-imidazole-1-carbonyl]-piperazin-2-one

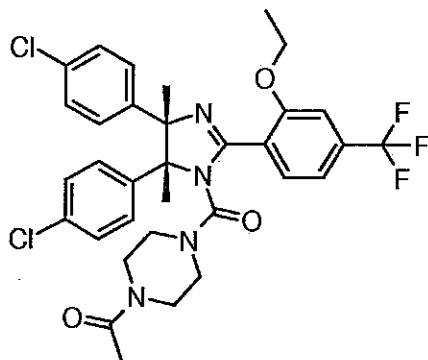


In a manner analogous to the method described in example 5, *rac*-(4*S**,5*R**)-4,5-bis-(4-chloro-phenyl)-2-(2-ethoxy-4-trifluoromethyl-phenyl)-4,5-dimethyl-4,5-

dihydro-imidazole-1-carbonyl chloride was reacted with 2-piperazinone (Avocado Organics) to give the title compound. HR-MS (ES, m/z) calculated for $C_{31}H_{30}N_4O_3F_3Cl_2$ $[(M+H)^+]$ 633.1642, observed 633.1638.

5 **Example 124**

rac-1-{4-[(4*S**,5*R**)-4,5-Bis-(4-chloro-phenyl)-2-(2-ethoxy-4-trifluoromethyl-phenyl)-4,5-dimethyl-4,5-dihydro-imidazole-1-carbonyl]-piperazin-1-yl}-ethanone

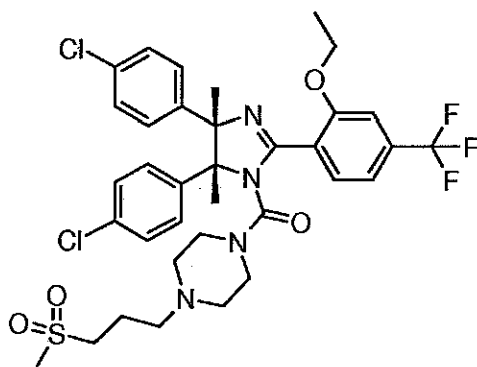


- 10 In a manner analogous to the method described in example 5, *rac*-(4*S**,5*R**)-4,5-bis-(4-chloro-phenyl)-2-(2-ethoxy-4-trifluoromethyl-phenyl)-4,5-dimethyl-4,5-dihydro-imidazole-1-carbonyl chloride was reacted with 1-acetyl-piperazine (Aldrich) to give the title compound. HR-MS (ES, m/z) calculated for $C_{33}H_{34}N_4O_3F_3Cl_2$ $[(M+H)^+]$ 661.1955, observed 661.1947.

15

Example 125

[(4*S*,5*R*)-4,5-Bis-(4-chloro-phenyl)-2-(2-ethoxy-4-trifluoromethyl-phenyl)-4,5-dimethyl-4,5-dihydro-imidazol-1-yl]-[4-(3-methanesulfonyl-propyl)-piperazin-1-yl]-methanone

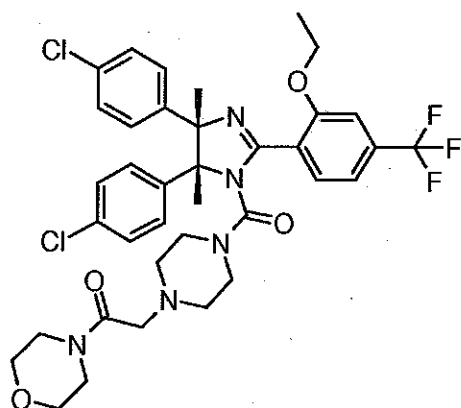


20

In a manner analogous to the method described in example 5, *rac*-(4S*,5R*)-4,5-bis-(4-chloro-phenyl)-2-(2-ethoxy-4-trifluoromethyl-phenyl)-4,5-dimethyl-4,5-dihydro-imidazole-1-carbonyl chloride was reacted with 1-(3-methanesulfonyl-propyl)-piperazine dihydrochloride (prepared as described in Fotouhi, N. *et al.* WO 2005110996) to give the racemic *rac*-(4S*,5R*)-4,5-bis-(4-chloro-phenyl)-2-(2-ethoxy-4-trifluoromethyl-phenyl)-4,5-dimethyl-4,5-dihydro-imidazol-1-yl]-[4-(3-methanesulfonyl-propyl)-piperazin-1-yl]-methanone. Chiral separation of the enantiomers by supercritical fluid chromatography (Berger Instrument Multi-Gram II, Daicel ChiralPak OD-H 3 x 25 cm, 35 °C at 100 bar, eluting with 25% methanol in carbon dioxide) gave the title compound. HR-MS (ES, *m/z*) calculated for C₃₅H₄₀N₄O₄SF₃Cl₂ [(M+H)⁺] 739.2094, observed 739.2094.

Example 126

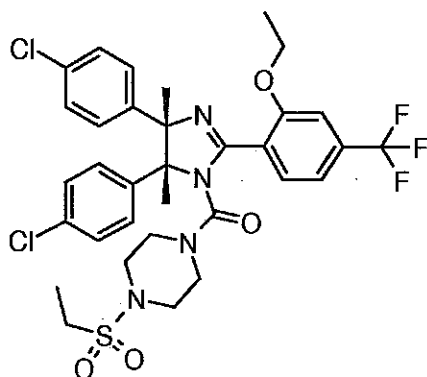
rac-2-{4-[(4S*,5R*)-4,5-Bis-(4-chloro-phenyl)-2-(2-ethoxy-4-trifluoromethyl-phenyl)-4,5-dimethyl-4,5-dihydro-imidazole-1-carbonyl]-piperazin-1-yl}-1-morpholin-4-yl-ethanone



In a manner analogous to the method described in example 5, *rac*-(4S*,5R*)-4,5-bis-(4-chloro-phenyl)-2-(2-ethoxy-4-trifluoromethyl-phenyl)-4,5-dimethyl-4,5-dihydro-imidazole-1-carbonyl chloride was reacted with 1-morpholin-4-yl-2-piperazin-1-yl-ethanone (Oakwood Products) to give the title compound. HR-MS (ES, *m/z*) calculated for C₃₇H₄₁N₅O₄F₃Cl₂ [(M+H)⁺] 746.2482, observed 746.2483.

Example 127

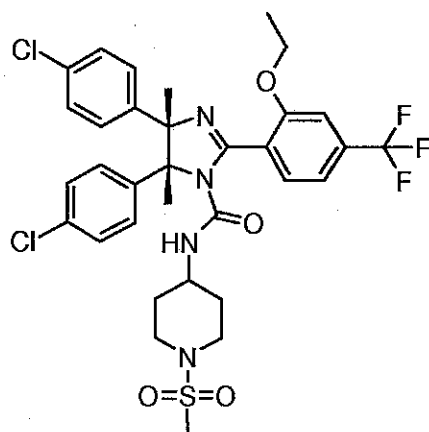
rac-(4S*,5R*)-4,5-Bis-(4-chloro-phenyl)-2-(2-ethoxy-4-trifluoromethyl-phenyl)-4,5-dimethyl-4,5-dihydro-imidazol-1-yl]-[4-(4-ethanesulfonyl-piperazin-1-yl)-methanone



- In a manner analogous to the method described in example 5, *rac*-(4S*,5R*)-4,5-bis-(4-chloro-phenyl)-2-(2-ethoxy-4-trifluoromethyl-phenyl)-4,5-dimethyl-4,5-dihydro-imidazole-1-carbonyl chloride was reacted with 1-ethanesulfonyl-piperazine (Aldrich) to give the title compound. HR-MS (ES, *m/z*) calculated for $C_{33}H_{36}N_4O_4SF_3Cl_2$ [(M+H)⁺] 711.1781, observed 711.1786.

Example 128

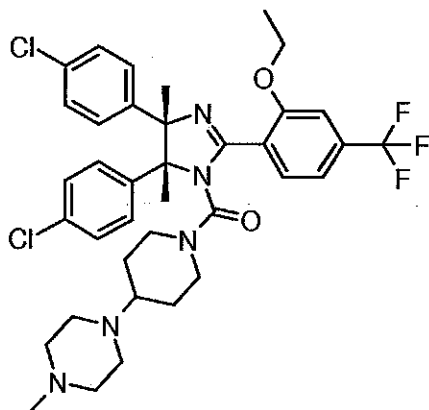
- 10 *rac*-(4S*,5R*)-4,5-Bis-(4-chloro-phenyl)-2-(2-ethoxy-4-trifluoromethyl-phenyl)-4,5-dimethyl-4,5-dihydro-imidazole-1-carboxylic acid (1-methanesulfonyl-piperidin-4-yl)-amide



- 15 In a manner analogous to the method described in example 5, *rac*-(4S*,5R*)-4,5-bis-(4-chloro-phenyl)-2-(2-ethoxy-4-trifluoromethyl-phenyl)-4,5-dimethyl-4,5-dihydro-imidazole-1-carbonyl chloride was reacted with 1-methanesulfonyl-piperidin-4-ylamine (prepared as described by Bartkovitz, D. J. *et al.* WO2004069139) to give the title compound. HR-MS (ES, *m/z*) calculated for $C_{33}H_{36}N_4O_4SF_3Cl_2$ [(M+H)⁺] 711.1781, observed 711.1778.
- 20

Example 129

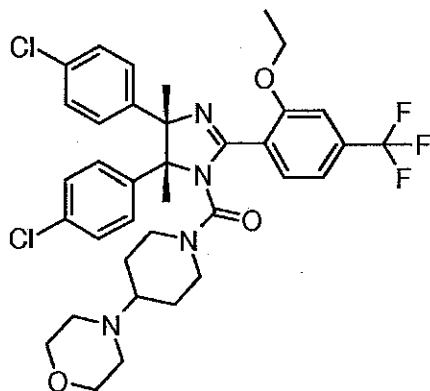
rac-[(4*S**,5*R**)-4,5-Bis-(4-chloro-phenyl)-2-(2-ethoxy-4-trifluoromethyl-phenyl)-4,5-dimethyl-4,5-dihydro-imidazol-1-yl]-[4-(4-methyl-piperazin-1-yl)-piperidin-1-yl]-methanone



In a manner analogous to the method described in example 5, *rac*-(4*S**,5*R**)-4,5-bis-(4-chloro-phenyl)-2-(2-ethoxy-4-trifluoromethyl-phenyl)-4,5-dimethyl-4,5-dihydro-imidazole-1-carbonyl chloride was reacted with 1-methyl-4-piperidin-4-yl-piperazine (Oakwood Products) to give the title compound. HR-MS (ES, *m/z*) calculated for C₃₇H₄₃N₅O₂F₃Cl₂ [(*M*+*H*)⁺] 716.2741, observed 716.2746.

Example 130

rac-[(4*S**,5*R**)-4,5-Bis-(4-chloro-phenyl)-2-(2-ethoxy-4-trifluoromethyl-phenyl)-4,5-dimethyl-4,5-dihydro-imidazol-1-yl]-(4-morpholin-4-yl-piperidin-1-yl)-methanone

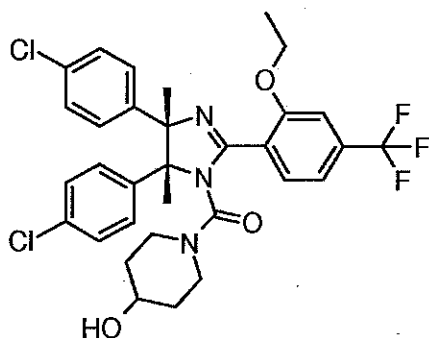


In a manner analogous to the method described in example 5, *rac*-(4S*,5R*)-4,5-bis-(4-chloro-phenyl)-2-(2-ethoxy-4-trifluoromethyl-phenyl)-4,5-dimethyl-4,5-dihydro-imidazole-1-carbonyl chloride was reacted with 4-piperidin-4-yl-morpholine (Aldrich) to give the title compound. HR-MS (ES, *m/z*) calculated for

5 $C_{36}H_{40}N_4O_3F_3Cl_2$ [(M+H)⁺] 703.2424, observed 703.2419.

Example 131

rac-[(4S*,5R*)-4,5-Bis-(4-chloro-phenyl)-2-(2-ethoxy-4-trifluoromethyl-phenyl)-4,5-dimethyl-4,5-dihydro-imidazol-1-yl]-(4-hydroxy-piperidin-1-yl)-methanone



10

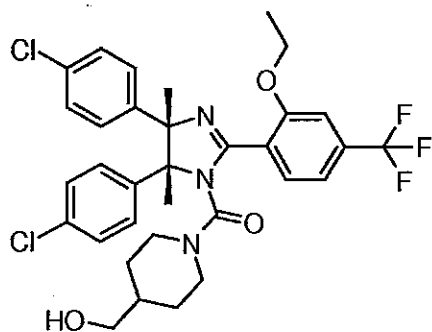
In a manner analogous to the method described in example 5, *rac*-(4S*,5R*)-4,5-bis-(4-chloro-phenyl)-2-(2-ethoxy-4-trifluoromethyl-phenyl)-4,5-dimethyl-4,5-dihydro-imidazole-1-carbonyl chloride was reacted with 4-hydroxy-piperidine

15 (Aldrich) to give the title compound. HR-MS (ES, *m/z*) calculated for $C_{32}H_{33}N_3O_3F_3Cl_2$ [(M+H)⁺] 634.1846, observed 634.1846.

Example 132

rac-[(4S*,5R*)-4,5-Bis-(4-chloro-phenyl)-2-(2-ethoxy-4-trifluoromethyl-phenyl)-4,5-dimethyl-4,5-dihydro-imidazol-1-yl]-(4-hydroxymethyl-piperidin-1-yl)-methanone

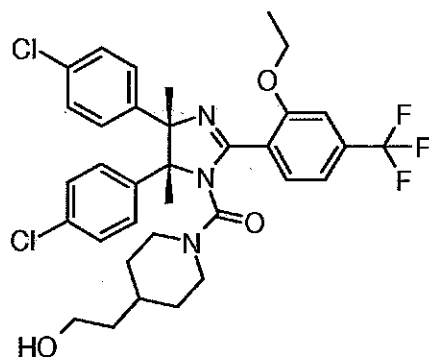
20



- In a manner analogous to the method described in example 5, *rac*-(4S*,5R*)-4,5-bis-(4-chloro-phenyl)-2-(2-ethoxy-4-trifluoromethyl-phenyl)-4,5-dimethyl-4,5-dihydro-imidazole-1-carbonyl chloride was reacted with piperidin-4-yl-methanol (Lancaster) to give the title compound. HR-MS (ES, *m/z*) calculated for
- 5 $C_{33}H_{35}N_4O_3F_3Cl_2$ [(M+H)⁺] 648.2002, observed 648.2006.

Example 133

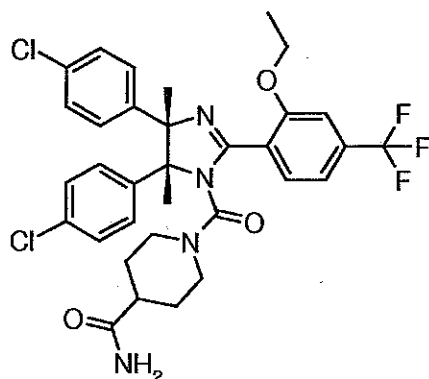
- rac*-[(4S*,5R*)-4,5-Bis-(4-chloro-phenyl)-2-(2-ethoxy-4-trifluoromethyl-phenyl)-4,5-dimethyl-4,5-dihydro-imidazol-1-yl]-[4-(2-hydroxy-ethyl)-piperidin-1-yl]-
- 10 methanone



- In a manner analogous to the method described in example 5, *rac*-(4S*,5R*)-4,5-bis-(4-chloro-phenyl)-2-(2-ethoxy-4-trifluoromethyl-phenyl)-4,5-dimethyl-4,5-
- 15 dihydro-imidazole-1-carbonyl chloride was reacted with piperidin-4-yl-ethanol (Aldrich) to give the title compound. HR-MS (ES, *m/z*) calculated for
- $C_{34}H_{37}N_3O_3F_3Cl_2$ [(M+H)⁺] 662.2159, observed 662.2158.

Example 134

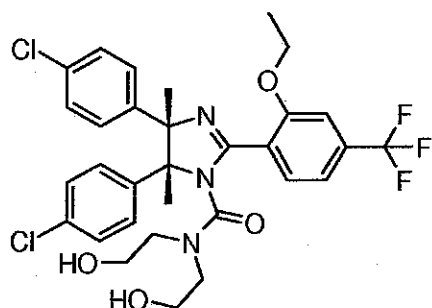
- 20 *rac*-1-[(4S*,5R*)-4,5-Bis-(4-chloro-phenyl)-2-(2-ethoxy-4-trifluoromethyl-phenyl)-4,5-dimethyl-4,5-dihydro-imidazole-1-carbonyl]-piperidine-4-carboxylic acid amide



In a manner analogous to the method described in example 5, *rac*-(4S*,5R*)-4,5-bis-(4-chloro-phenyl)-2-(2-ethoxy-4-trifluoromethyl-phenyl)-4,5-dimethyl-4,5-dihydro-imidazole-1-carboxylic acid bis-(2-hydroxy-ethyl)-amide (isonipecotamide, Aldrich) to give the title compound. HR-MS (ES, *m/z*) calculated for C₃₃H₃₄N₄O₃F₃Cl₂ [(M+H)⁺] 661.1955, observed 662.1955.

Example 135

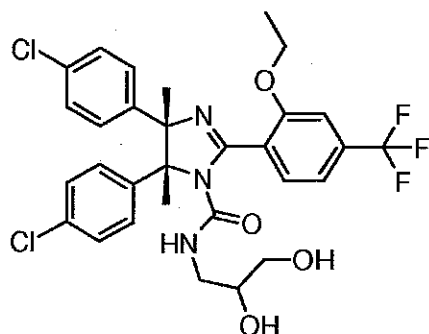
10 *rac*-(4S*,5R*)-4,5-Bis-(4-chloro-phenyl)-2-(2-ethoxy-4-trifluoromethyl-phenyl)-4,5-dimethyl-4,5-dihydro-imidazole-1-carboxylic acid bis-(2-hydroxy-ethyl)-amide



15 In a manner analogous to the method described in example 5, *rac*-(4S*,5R*)-4,5-bis-(4-chloro-phenyl)-2-(2-ethoxy-4-trifluoromethyl-phenyl)-4,5-dimethyl-4,5-dihydro-imidazole-1-carboxylic acid bis-(2-hydroxyethyl)-amine (Sigma) to give the title compound. HR-MS (ES, *m/z*) calculated for C₃₁H₃₃N₃O₄F₃Cl₂ [(M+H)⁺] 638.1795, observed 638.1797.

20 Example 136

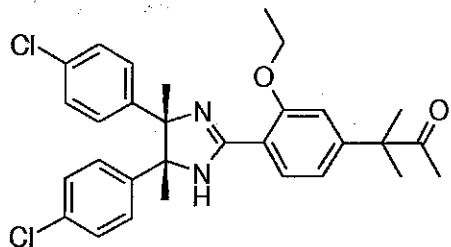
rac-(4S*,5R*)-4,5-Bis-(4-chloro-phenyl)-2-(2-ethoxy-4-trifluoromethyl-phenyl)-4,5-dimethyl-4,5-dihydro-imidazole-1-carboxylic acid (2,3-dihydroxy-propyl)-amide



In a manner analogous to the method described in example 5, *rac*-(4*S**,5*R**)-4,5-bis-(4-chloro-phenyl)-2-(2-ethoxy-4-trifluoromethyl-phenyl)-4,5-dimethyl-4,5-dihydro-imidazole-1-carbonyl chloride was reacted with 3-amino-propane-1,2-diol (Aldrich) to give the title compound as a mixture of diastereomers. HR-MS (ES, *m/z*) calculated for C₃₀H₃₁N₃O₄F₃Cl₂ [(M+H)⁺] 624.1638, observed 624.1641.

Example 137

3-{4-[4,5-Bis-(4-chloro-phenyl)-4,5-dimethyl-4,5-dihydro-1H-imidazol-2-yl]-3-ethoxy-phenyl}-3-methyl-butan-2-one



Sodium hydride (3.65 g, 91.347 mmol, 60% in mineral oil, Aldrich) was added to a round bottom flask and washed with hexane. Tetrahydrofuran (80 mL) was then added. To a suspension of sodium hydride in tetrahydrofuran cooled to 0 °C was added a solution of 1-(3-methoxy-phenyl)-propan-2-one (6 g, 36.539 mmol, Lancaster) in 1 mL of tetrahydrofuran. The ice bath was removed, and the mixture was stirred at room temperature for 30 min. Methyl iodide (6.82 mL, 109.6 mmol, Aldrich) was added at 0 °C, and the mixture was stirred at room temperature for 48 h. The reaction was quenched with saturated solution of ammonium chloride and taken in water and ethyl acetate. The product was extracted with ethyl acetate (1x). The organic layers were washed with brine (1x), dried over anhydrous sodium sulfate and concentrated. The residue was purified

by flash column chromatography (40 g of silica gel, eluting with 3-5% ethyl acetate in hexane) to give 3-(3-methoxy-phenyl)-3-methyl-butan-2-one as clear oil (6.603 g, 94%).

To a solution of 3-(3-methoxy-phenyl)-3-methyl-butan-2-one (6.570 g, 34.172 mmol) in methylene chloride (100 mL) cooled to -78 °C was added boron tribromide (102 mL, 1 M solution in methylene chloride, Aldrich). The mixture was stirred at -78 °C for 1 h, warmed up to 0 °C for 1 h then put in the freezer (-20 °C) for 72 h. At 0 °C, water was added to quench the excess boron tribromide (CAUTION: Violent reaction). The product was extracted with petroleum ether. The organic layers were washed with brine, dried over anhydrous sodium sulfate and concentrated. The crude residue was purified by flash chromatography (40 g of silica gel, eluting with 5-20% ethyl acetate in hexane) to give 3-(3-hydroxy-phenyl)-3-methyl-butan-2-one as a yellow oil (5 g, 82%).

The mixture of 3-(3-hydroxy-phenyl)-3-methyl-butan-2-one (3.4 g, 19.08 mmol), diisopropylamine (16.7 mL, 95.4 mmol) and ethyl iodide (6.2 mL, 76.32 mmol) in 60 mL of ethanol was heated at refluxed overnight. Thin layer chromatography still showed starting material. Potassium carbonate (9 g) was added, and the mixture was heated at reflux for 12 h. It was concentrated *in vacuo*, and the residue was taken in ethyl acetate. After being washed with water and brine, the organic layer was dried over anhydrous sodium sulfate. The solids were filtered off, and the filtrate was concentrated to give 3.727g of 3-(3-ethoxy-phenyl)-3-methyl-butan-2-one as light brown oil. It was used without further purification.

To a solution of 3-(3-ethoxy-phenyl)-3-methyl-butan-2-one (3.720 g, 18.03 mmol) in acetonitrile (40 mL) was added N-iodosuccinimide (5.679 g, 25.24 mmol) and trifluoroacetic acid (0.7 mL, 9.02 mmol) with stirring under argon. The reaction mixture was stirred at room temperature for 10 min then at 50 °C for 1 h. Upon cooling to room temperature, it was diluted with 10% ethyl acetate in hexane and filtered through a bed of Celite and silica gel. The filtrate was washed with water (1x), saturated solution of sodium bicarbonate (1x), 5% solution of sodium thiosulfate (1x), brine (1x), dried over anhydrous sodium sulfate and concentrated *in vacuo*. Purification of the crude residue by flash chromatography (330 g of silica gel, eluting with 30% ethyl acetate in hexane

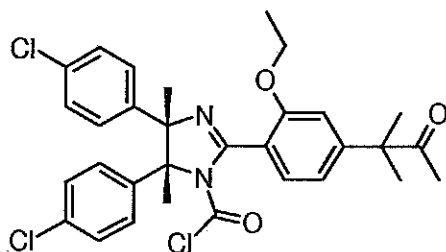
over 30 min) gave 4.83 g of 3-(3-ethoxy-4-iodo-phenyl)-3-methyl-butan-2-one as off-white solid.

To a dry pressure tube were added with stirring anhydrous acetonitrile (10 mL), 3-(3-ethoxy-4-iodo-phenyl)-3-methyl-butan-2-one (450 mg, 1.35 mmol),
5 diphenylpropylphosphine (77 mg, 0.34 mmol) and triethylamine (470 μ L, 3.37 mmol), respectively. Argon was bubbled through the solution for 10 min then palladium acetate (76 mg, 0.34 mmol) was added. The system was evacuated under high vacuum and refilled with carbon monoxide (40 psi). After 10 min, trihexylsilane (960 μ L, 2.7 mmol) was added. The system was recharged with
10 carbon monoxide (60 psi) and stirred at 60 °C overnight. The reaction mixture was concentrated *in vacuo*, and the residue was taken in ethyl acetate. It was filtered through a short silica gel plug. The filtrate was washed with water (2x), brine (1x), dried over anhydrous sodium sulfate. The solids were filtered off, and the filtrate was concentrated *in vacuo*. The crude residue was purified by flash
15 chromatography (80 g of silica gel, eluting with 10-30% ethyl acetate in hexane over a period of 35 min) to give 150 mg of 4-(1,1-dimethyl-2-oxo-propyl)-2-ethoxy-benzaldehyde.

To a solution of 4-(1,1-dimethyl-2-oxo-propyl)-2-ethoxy-benzaldehyde (145 mg, 0.62 mmol) in anhydrous 1,2-dichloroethane (2 mL) cooled to 0 °C was
20 added *meso*-2,3-bis-(4-chlorophenyl)-2,3-butanediamine (191 mg, 0.62 mmol). The mixture was stirred at room temperature for 4 d. N-bromosuccinimide (x mg, x mmol) was added at 0 °C and the mixture was stirred at room temperature for 1.5 h. Saturated solution of sodium carbonate was added to make it basic, and the product was extracted with ethyl acetate. The organic layers were dried over
25 anhydrous sodium sulfate and concentrated *in vacuo*. The crude residue was purified by flash chromatography (45 g of silica gel, eluting with 0-30% ethyl acetate in hexane over a period of 25 min) to give 217 mg of the title product as light yellow solid.

30 **Example 138**

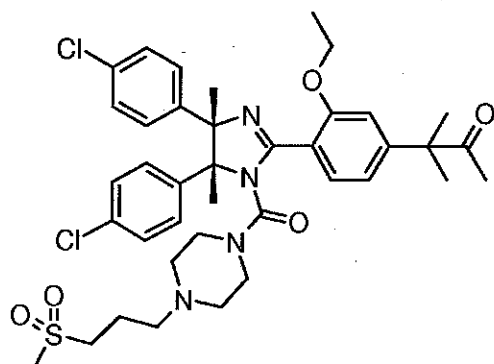
rac-(4S*,5R*)-4,5-Bis-(4-chloro-phenyl)-2-[4-(1,1-dimethyl-2-oxo-propyl)-2-ethoxy-phenyl]-4,5-dimethyl-4,5-dihydro-imidazole-1-carbonyl chloride



In a manner analogous to the method described in example 3, 3-(4-[4,5-bis-(4-chloro-phenyl)-4,5-dimethyl-4,5-dihydro-1H-imidazol-2-yl]-3-ethoxy-phenyl)-3-methyl-butan-2-one was reacted with phosgene in the presence of triethylamine to give the title compound.

Example 139

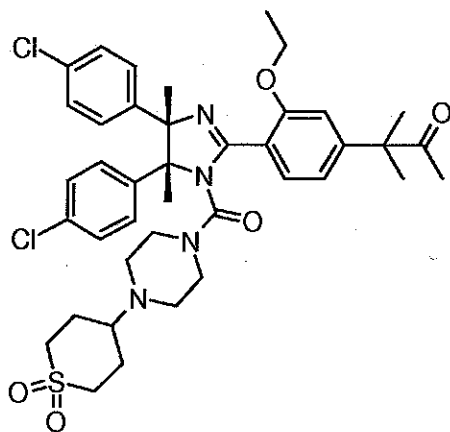
3-(4-[4,5-Bis-(4-chloro-phenyl)-1-[4-(3-methanesulfonyl-propyl)-piperazine-1-carbonyl]-4,5-dimethyl-4,5-dihydro-1H-imidazol-2-yl]-3-ethoxy-phenyl)-3-methyl-butan-2-one



In a manner analogous to the method described in example 5, *rac*-(4S*,5R*)-4,5-bis-(4-chloro-phenyl)-2-[4-(1,1-dimethyl-2-oxo-propyl)-2-ethoxy-phenyl]-4,5-dimethyl-4,5-dihydro-imidazole-1-carbonyl chloride was reacted with 1-(3-methanesulfonyl-propyl)-piperazine dihydrochloride (prepared as described in Fotouhi, N. *et al.* WO 2005110996) to give the title product as a racemic mixture. The enantiomers were then separated by supercritical fluid chromatography (Berger Instrument Multi-Gram II, Daicel ChiralPak OD-H 3 x 25 cm, 35 °C at 100 bar, eluting with 25% methanol in carbon dioxide). HR-MS (ES, *m/z*) calculated for C₃₉H₄₉N₄O₅SCl₂ [(M+H)⁺] 775.2795, observed 775.2795.

Example 140

3-(4-((4S,5R)-4,5-Bis-(4-chloro-phenyl)-1-[4-(1,1-dioxo-tetrahydro-2H-thiopyran-4-yl)-piperazine-1-carbonyl]-4,5-dimethyl-4,5-dihydro-1H-imidazol-2-yl)-3-ethoxy-phenyl)-3-methyl-butan-2-one

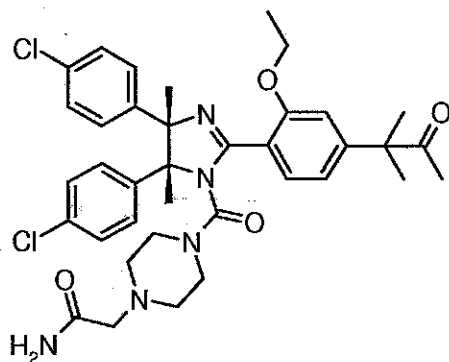


5

In a manner analogous to the method described in example 5, *rac*-(4S*,5R*)-4,5-bis-(4-chloro-phenyl)-2-[4-(1,1-dimethyl-2-oxo-propyl)-2-ethoxy-phenyl]-4,5-dimethyl-4,5-dihydro-imidazole-1-carbonyl chloride was reacted with 1-(1,1-dioxo-tetrahydro-2H-thiopyran-4-yl)-piperazine dihydrochloride (example 22) to give the title product as a racemic mixture. The enantiomers were then separated by supercritical fluid chromatography (Berger Instrument Multi-Gram II, Daicel ChiralPak OD-H 3 x 25 cm, 35 °C at 100 bar, eluting with 35% methanol in carbon dioxide). HR-MS (ES, *m/z*) calculated for C₄₀H₄₉N₄O₅SCl₂ [(M+H)⁺]
 10
 15 767.2795, observed 767.2790.

Example 141

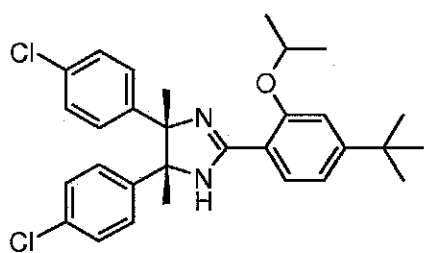
2-(4-((4S,5R)-4,5-Bis-(4-chloro-phenyl)-2-[4-(1,1-dimethyl-2-oxo-propyl)-2-ethoxy-phenyl]-4,5-dimethyl-4,5-dihydro-imidazole-1-carbonyl)-piperazin-1-yl)-acetamide
 20



In a manner analogous to the method described in example 5, *rac*-(4S*,5R*)-4,5-bis-(4-chloro-phenyl)-2-[4-(1,1-dimethyl-2-oxo-propyl)-2-ethoxy-phenyl]-4,5-dimethyl-4,5-dihydro-imidazole-1-carbonyl chloride was reacted with 2-piperazin-1-yl-acetamide dihydrochloride (Matrix Scientific) to give the title product as a racemic mixture. The enantiomers were then separated by supercritical fluid chromatography (Berger Instrument Multi-Gram II, Daicel ChiralPak OD-H 3 x 25 cm, 35 °C at 100 bar, eluting with 30% methanol in carbon dioxide). HR-MS (ES, *m/z*) calculated for C₃₇H₄₄N₅O₄Cl₂ [(M+H)⁺] 692.2765, observed 692.2762.

Example 142

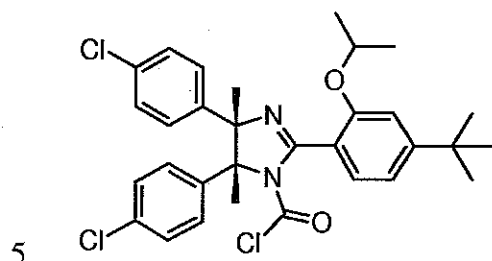
rac-(4S*,5R*)-2-(4-*tert*-Butyl-2-isopropoxy-phenyl)-4,5-bis-(4-chloro-phenyl)-4,5-dimethyl-4,5-dihydro-1*H*-imidazole



In a manner analogous to the method described in example 2, meso-2,3-bis-(4-chlorophenyl)-2,3-butanediamine was reacted with 4-*tert*-butyl-2-isopropoxy-benzoic acid methyl ester (prepared from 3-*tert*-butyl-phenol and isopropyl iodide as described in Fotouhi, N. *et al.* WO 2005110996) in the presence of trimethylaluminum to give the title compound. HR-MS (ES, *m/z*) calculated for C₃₀H₃₅N₂OCl₂ [(M+H)⁺] 509.2121, observed 509.2121.

Example 143

rac-(4S*,5R*)-2-(4-*tert*-Butyl-2-isopropoxy-phenyl)-4,5-bis-(4-chloro-phenyl)-4,5-dimethyl-4,5-dihydro-imidazole-1-carbonyl chloride

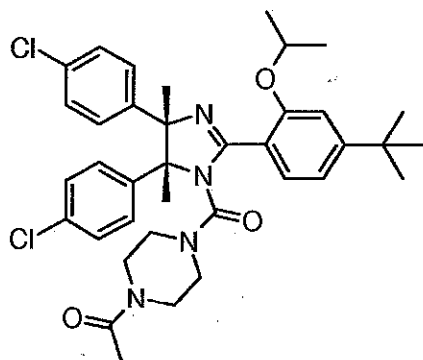


In a manner analogous to the method described in example 3, *rac*-(4S*,5R*)-2-(4-*tert*-butyl-2-isopropoxy-phenyl)-4,5-bis-(4-chloro-phenyl)-4,5-dimethyl-4,5-dihydro-1*H*-imidazole was reacted with phosgene in the presence of triethylamine to give the title compound.

10

Example 144

rac-1-{4-[(4S*,5R*)-2-(4-*tert*-Butyl-2-isopropoxy-phenyl)-4,5-bis-(4-chloro-phenyl)-4,5-dimethyl-4,5-dihydro-imidazole-1-carbonyl]-piperazin-1-yl}-ethanone

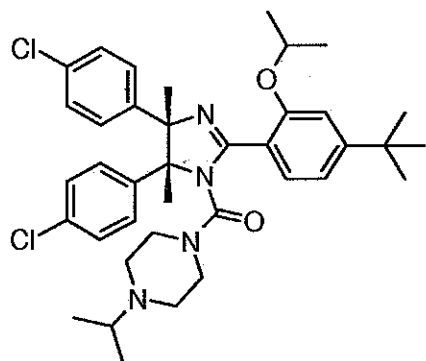


In a manner analogous to the method described in example 5, *rac*-(4S*,5R*)-2-(4-*tert*-butyl-2-isopropoxy-phenyl)-4,5-bis-(4-chloro-phenyl)-4,5-dimethyl-4,5-dihydro-imidazole-1-carbonyl chloride was reacted with 1-acetyl-piperazine (Aldrich) to give the title compound. HR-MS (ES, *m/z*) calculated for C₃₇H₅₅N₄O₃Cl₂ [(M+H)⁺] 663.2863, observed 663.2857.

20

Example 145

rac-[(4S*,5R*)-2-(4-*tert*-Butyl-2-isopropoxy-phenyl)-4,5-bis-(4-chloro-phenyl)-4,5-dimethyl-4,5-dihydro-imidazol-1-yl]-(4-isopropyl-piperazin-1-yl)-methanone

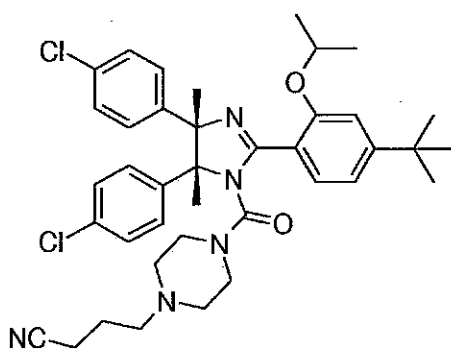


- 5 In a manner analogous to the method described in example 5, *rac*-(4S*,5R*)-2-(4-*tert*-butyl-2-isopropoxy-phenyl)-4,5-bis-(4-chloro-phenyl)-4,5-dimethyl-4,5-dihydro-imidazole-1-carbonyl chloride was reacted with 1-isopropyl-piperazine (Aldrich) to give the title compound. HR-MS (ES, *m/z*) calculated for C₃₈H₄₉N₄O₂Cl₂ [(M+H)⁺] 663.3227, observed 663.3228.

10

Example 146

rac-4-{4-[(4S*,5R*)-2-(4-*tert*-Butyl-2-isopropoxy-phenyl)-4,5-bis-(4-chloro-phenyl)-4,5-dimethyl-4,5-dihydro-imidazole-1-carbonyl]-piperazin-1-yl}-butyronitrile

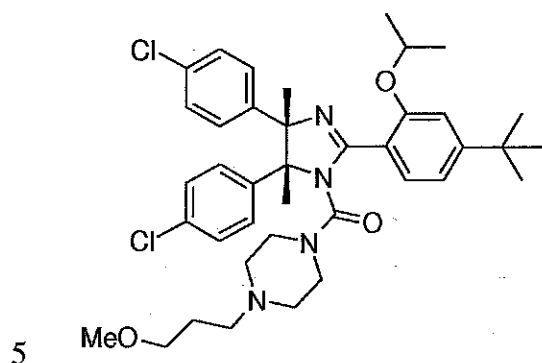


15

- In a manner analogous to the method described in example 5, *rac*-(4S*,5R*)-2-(4-*tert*-butyl-2-isopropoxy-phenyl)-4,5-bis-(4-chloro-phenyl)-4,5-dimethyl-4,5-dihydro-imidazole-1-carbonyl chloride was reacted with 4-piperazin-1-yl-
20 butyronitrile (Aldrich) to give the title compound. HR-MS (ES, *m/z*) calculated for C₃₉H₄₈N₅O₂Cl₂ [(M+H)⁺] 688.3180, observed 688.3186.

Example 147

rac-[(4*S*^{*},5*R*^{*})-2-(4-*tert*-Butyl-2-isopropoxy-phenyl)-4,5-bis-(4-chloro-phenyl)-4,5-dimethyl-4,5-dihydro-imidazol-1-yl]-[4-(3-methoxy-propyl)-piperazin-1-yl]-methanone



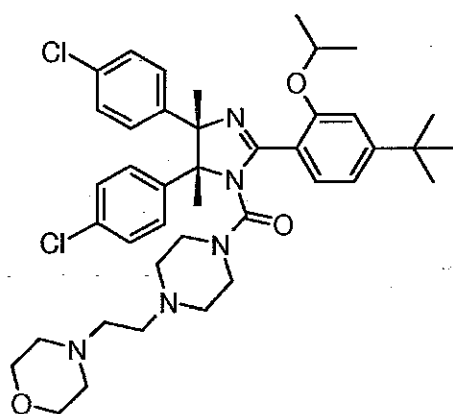
In a manner analogous to the method described in example 5, *rac*-(4*S*^{*},5*R*^{*})-2-(4-*tert*-butyl-2-isopropoxy-phenyl)-4,5-bis-(4-chloro-phenyl)-4,5-dimethyl-4,5-dihydro-imidazole-1-carbonyl chloride was reacted with 1-(3-methoxy-propyl)-piperazine (Aldrich) to give the title compound. HR-MS (ES, *m/z*) calculated for C₃₉H₅₁N₄O₃Cl₂ [(*M*+*H*)⁺] 693.3333, observed 693.3334.

10

Example 148

rac-[(4*S*^{*},5*R*^{*})-2-(4-*tert*-Butyl-2-isopropoxy-phenyl)-4,5-bis-(4-chloro-phenyl)-4,5-dimethyl-4,5-dihydro-imidazol-1-yl]-[4-(2-morpholin-4-yl-ethyl)-piperazin-1-yl]-methanone

15



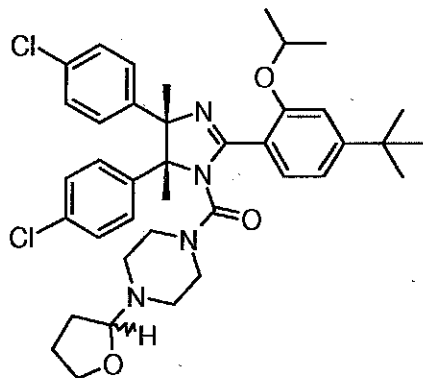
In a manner analogous to the method described in example 5, *rac*-(4*S*^{*},5*R*^{*})-2-(4-*tert*-butyl-2-isopropoxy-phenyl)-4,5-bis-(4-chloro-phenyl)-4,5-dimethyl-4,5-dihydro-imidazole-1-carbonyl chloride was reacted with 4-(2-piperazin-1-yl-ethyl)-

20

morpholine (Aldrich) to give the title compound. HR-MS (ES, m/z) calculated for $C_{41}H_{54}N_5O_3Cl_2$ $[(M+H)^+]$ 734.3598, observed 734.3600.

Example 149

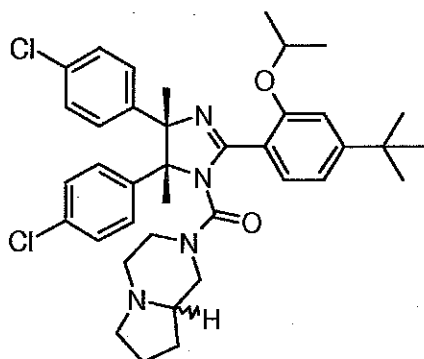
- 5 *rac*-[(4*S**,5*R**)-2-(4-*tert*-Butyl-2-isopropoxy-phenyl)-4,5-bis-(4-chloro-phenyl)-4,5-dimethyl-4,5-dihydro-imidazol-1-yl]-[4-(tetrahydro-furan-2-ylmethyl)-piperazin-1-yl]-methanone



- 10 In a manner analogous to the method described in example 5, *rac*-(4*S**,5*R**)-2-(4-*tert*-butyl-2-isopropoxy-phenyl)-4,5-bis-(4-chloro-phenyl)-4,5-dimethyl-4,5-dihydro-imidazole-1-carbonyl chloride was reacted with 1-(tetrahydro-furan-2-ylmethyl)-piperazine (Aldrich) to give the title compound as a mixture of diastereomers. HR-MS (ES, m/z) calculated for $C_{40}H_{51}N_4O_3Cl_2$ $[(M+H)^+]$
- 15 705.3333, observed 705.3332.

Example 150

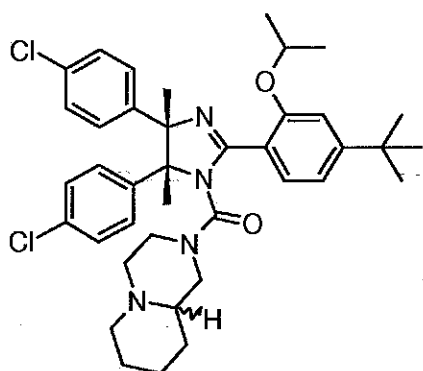
- rac*-[(4*S**,5*R**)-2-(4-*tert*-Butyl-2-isopropoxy-phenyl)-4,5-bis-(4-chloro-phenyl)-4,5-dimethyl-4,5-dihydro-imidazol-1-yl]-(hexahydro-pyrrolo[1,2-*a*]pyrazin-2-yl)-
- 20 methanone



In a manner analogous to the method described in example 5, *rac*-(4S*,5R*)-2-(4-*tert*-butyl-2-isopropoxy-phenyl)-4,5-bis-(4-chloro-phenyl)-4,5-dimethyl-4,5-dihydro-imidazole-1-carbonyl chloride was reacted with octahydro-pyrrolo[1,2-
 5 a]pyrazine (Aldrich) to give the title compound. HR-MS (ES, *m/z*) calculated for C₃₈H₄₇N₄O₃Cl₂ [(M+H)⁺] 661.3071, observed 661.3073.

Example 151

rac-[(4S*,5R*)-2-(4-*tert*-Butyl-2-isopropoxy-phenyl)-4,5-bis-(4-chloro-phenyl)-4,5-dimethyl-4,5-dihydro-imidazol-1-yl]-(octahydro-pyrido[1,2-a]pyrazin-2-yl)-
 10 methanone

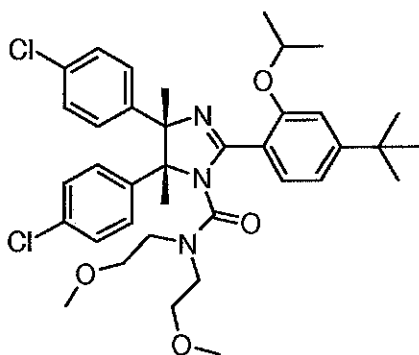


In a manner analogous to the method described in example 5, *rac*-(4S*,5R*)-2-(4-*tert*-butyl-2-isopropoxy-phenyl)-4,5-bis-(4-chloro-phenyl)-4,5-dimethyl-4,5-dihydro-imidazole-1-carbonyl chloride was reacted with octahydro-pyrido[1,2-
 15 a]pyrazine (Aldrich) to give the title compound as a mixture of diastereomers. HR-MS (ES, *m/z*) calculated for C₃₉H₄₉N₄O₂Cl₂ [(M+H)⁺] 675.3227, observed 675.3224.

20

Example 152

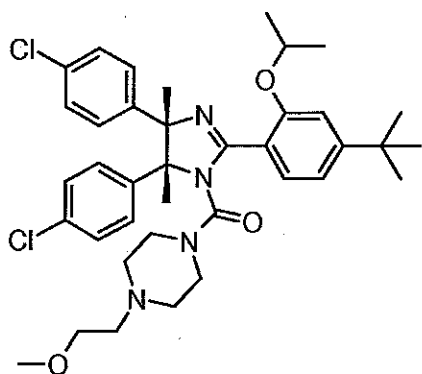
rac-(4S*,5R*)-2-(4-*tert*-Butyl-2-isopropoxy-phenyl)-4,5-bis-(4-chloro-phenyl)-4,5-dimethyl-4,5-dihydro-imidazole-1-carboxylic acid bis-(2-methoxy-ethyl)-amide



- In a manner analogous to the method described in example 5, *rac*-(4*S*^{*},5*R*^{*})-2-(4-*tert*-butyl-2-isopropoxy-phenyl)-4,5-bis-(4-chloro-phenyl)-4,5-dimethyl-4,5-dihydro-imidazole-1-carbonyl chloride was reacted with bis-(2-methoxyethyl)-amine (Aldrich) to give the title compound. HR-MS (ES, *m/z*) calculated for C₃₇H₄₉N₄O₅SCl₂ [(M+H)⁺] 668.3017, observed 668.3010.

Example 153

- 10 *rac*-[(4*S*^{*},5*R*^{*})-2-(4-*tert*-Butyl-2-isopropoxy-phenyl)-4,5-bis-(4-chloro-phenyl)-4,5-dimethyl-4,5-dihydro-imidazol-1-yl]-[4-(2-methoxy-ethyl)-piperazin-1-yl]-methanone

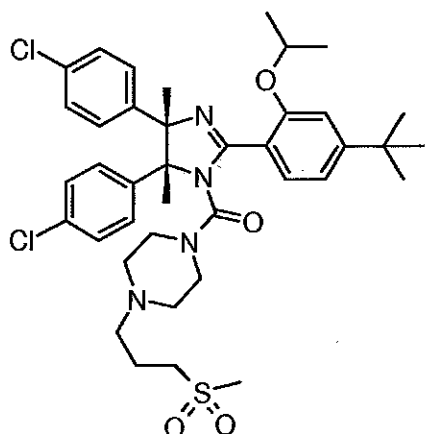


- 15 In a manner analogous to the method described in example 5, *rac*-(4*S*^{*},5*R*^{*})-2-(4-*tert*-butyl-2-isopropoxy-phenyl)-4,5-bis-(4-chloro-phenyl)-4,5-dimethyl-4,5-dihydro-imidazole-1-carbonyl chloride was reacted with 1-(2-methoxy-ethyl)-piperazine (Aldrich) to give the title compound. HR-MS (ES, *m/z*) calculated for C₃₈H₄₉N₄O₃Cl₂ [(M+H)⁺] 679.3176, observed 679.3180.

20

Example 154

[(4S,5R)-2-(4-*tert*-Butyl-2-isopropoxy-phenyl)-4,5-bis-(4-chloro-phenyl)-4,5-dimethyl-4,5-dihydro-imidazol-1-yl]-[4-(3-methanesulfonyl-propyl)-piperazin-1-yl]-methanone



5

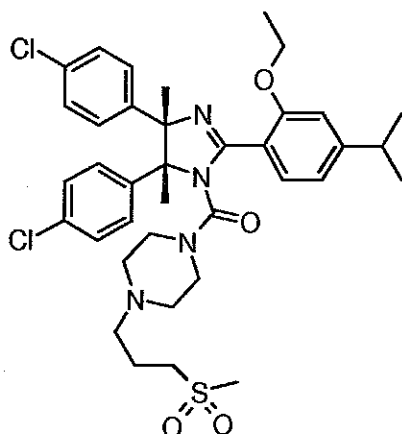
In a manner analogous to the method described in example 5, *rac*-(4S*,5R*)-2-(4-*tert*-butyl-2-isopropoxy-phenyl)-4,5-bis-(4-chloro-phenyl)-4,5-dimethyl-4,5-dihydro-imidazole-1-carbonyl chloride was reacted with 1-(3-methanesulfonyl-propyl)-piperazine dihydrochloride (prepared as described in Fotouhi, N. *et al.* WO 2005110996) to give the title compound as a racemic mixture. The enantiomers were separated by supercritical fluid chromatography (Berger Instrument Multi-Gram II, Daicel ChiralPak OD-H 3 x 25 cm, 35 °C at 100 bar, eluting with 25% isopropanol in carbon dioxide) gave the title compound. HR-MS (ES, *m/z*) calculated for C₃₉H₅₁N₄O₄SCl₂ [(M+H)⁺] 741.3003, observed 741.2998.

15

Example 155

[(4S,5R)-4,5-Bis-(4-chloro-phenyl)-2-(2-ethoxy-4-isopropyl-phenyl)-4,5-dimethyl-4,5-dihydro-imidazol-1-yl]-[4-(3-methanesulfonyl-propyl)-piperazin-1-yl]-methanone

20



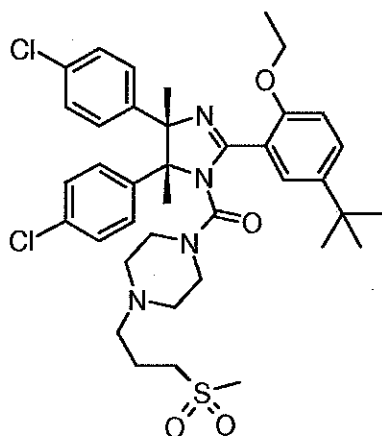
rac-(4S*,5R*)-4,5-Bis-(4-chloro-phenyl)-2-(2-ethoxy-4-isopropyl-phenyl)-4,5-dimethyl-4,5-dihydro-1*H*-imidazole was prepared from 2-ethoxy-4-isopropyl-benzoyl chloride (prepared from 2-hydroxy-4-isopropyl-benzoic acid in 3 steps) and *meso*-2,3-bis-(4-chlorophenyl)-2,3-butanediamine (example 1) in an analogous manner as described in example 2 (method 1).

rac-(4S*,5R*)-4,5-Bis-(4-chloro-phenyl)-2-(2-ethoxy-4-isopropyl-phenyl)-4,5-dimethyl-4,5-dihydro-1*H*-imidazole was reacted with phosgene in the presence of triethylamine to give the corresponding carbamoyl chloride.

In a manner analogous to the method described in example 5, *rac*-(4S*,5R*)-4,5-bis-(4-chloro-phenyl)-2-(2-ethoxy-4-isopropyl-phenyl)-4,5-dimethyl-4,5-dihydro-imidazole-1-carbonyl chloride was reacted with 1-(3-methanesulfonyl-propyl)-piperazine dihydrochloride (prepared as described in Fotouhi, N. *et al.* WO 2005110996) to give the title compound as a racemic mixture. The enantiomers were separated by supercritical fluid chromatography (Berger Instrument Multi-Gram II, Daicel ChiralPak OJ-H 3 x 25 cm, 35 °C at 100 bar, eluting with 15% of 1:1 ethanol/acetonitrile in carbon dioxide) gave the title compound. HR-MS (ES, *m/z*) calculated for C₃₇H₄₇N₄O₄SCl₂ [(M+H)⁺] 713.2690, observed 713.2692.

Example 156

[(4S,5R)-2-(5-*tert*-Butyl-2-ethoxy-phenyl)-4,5-bis-(4-chloro-phenyl)-4,5-dimethyl-4,5-dihydro-imidazol-1-yl]-[4-(3-methanesulfonyl-propyl)-piperazin-1-yl]-methanone



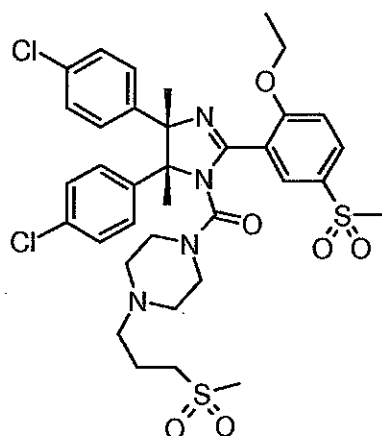
rac-(4*S**,5*R**)-2-(5-*tert*-butyl-2-ethoxy-phenyl)-4,5-bis-(4-chloro-phenyl)-4,5-dimethyl-4,5-dihydro-1*H*-imidazole was prepared from 5-*tert*-butyl-2-ethoxy-benzoyl chloride (prepared from 5-*tert*-butyl-2-hydroxy-benzoic acid) and *meso*-2,3-bis-(4-chlorophenyl)-2,3-butanediamine (example 1) in an analogous manner as described in example 2 (method 1).

rac-(4*S**,5*R**)-2-(5-*tert*-butyl-2-ethoxy-phenyl)-4,5-bis-(4-chloro-phenyl)-4,5-dimethyl-4,5-dihydro-1*H*-imidazole was reacted with phosgene in the presence of triethylamine to give the corresponding carbamoyl chloride.

In a manner analogous to the method described in example 5, *rac*-(4*S**,5*R**)-2-(5-*tert*-butyl-2-ethoxy-phenyl)-4,5-bis-(4-chloro-phenyl)-4,5-dimethyl-4,5-dihydro-imidazole-1-carbonyl chloride was reacted with 1-(3-methanesulfonyl-propyl)-piperazine dihydrochloride (prepared as described in Fotouhi, N. *et al.* WO 2005110996) to give the title compound as a racemic mixture. The enantiomers were separated by supercritical fluid chromatography (Berger Instrument Multi-Gram II, Daicel ChiralPak OD-H 3 x 25 cm, 35 °C at 100 bar, eluting with 20% of 1:1 ethanol/acetonitrile in carbon dioxide) gave the title compound. HR-MS (ES, *m/z*) calculated for C₃₈H₄₉N₄O₄SCl₂ [(*M*+*H*)⁺] 727.2846, observed 727.2847.

Example 157

[(4*S*,5*R*)-4,5-Bis-(4-chloro-phenyl)-2-(2-ethoxy-5-methanesulfonyl-phenyl)-4,5-dimethyl-4,5-dihydro-imidazol-1-yl]-[4-(3-methanesulfonyl-propyl)-piperazin-1-yl]-methanone



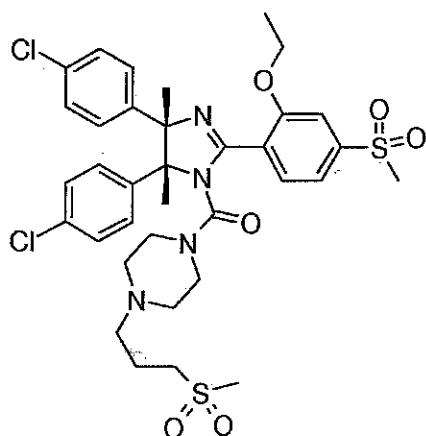
rac-(4S*,5R*)-4,5-bis-(4-chloro-phenyl)-2-(2-ethoxy-5-methanesulfonyl-phenyl)-4,5-dimethyl-4,5-dihydro-1H-imidazole was prepared from 2-ethoxy-5-methanesulfonyl-benzoyl chloride (prepared from 2-ethoxy-benzoic acid in an analogous as described in example 59) and *meso*-2,3-bis-(4-chlorophenyl)-2,3-butanediamine (example 1) in an analogous manner as described in example 2 (method 1).

rac-(4S*,5R*)-4,5-bis-(4-chloro-phenyl)-2-(2-ethoxy-5-methanesulfonyl-phenyl)-4,5-dimethyl-4,5-dihydro-1H-imidazole was reacted with phosgene in the presence of triethylamine to give the corresponding carbamoyl chloride.

In a manner analogous to the method described in example 5, *rac*-(4S*,5R*)-4,5-bis-(4-chloro-phenyl)-2-(2-ethoxy-5-methanesulfonyl-phenyl)-4,5-dimethyl-4,5-dihydro-imidazole-1-carbonyl chloride was reacted with 1-(3-methanesulfonyl-propyl)-piperazine dihydrochloride (prepared as described in Fotouhi, N. *et al.* WO 2005110996) to give the title compound as a racemic mixture. The enantiomers were separated by supercritical fluid chromatography (Berger Instrument Multi-Gram II, Daicel ChiralPak OD-H 3 x 25 cm, 35 °C at 100 bar, eluting with 25% of 1:1 ethanol/acetonitrile in carbon dioxide) gave the title compound. HR-MS (ES, *m/z*) calculated for C₃₅H₄₃N₄O₆S₂Cl₂ [(M+H)⁺] 749.1996, observed 749.1991.

Example 158

[(4S,5R)-4,5-Bis-(4-chloro-phenyl)-2-(2-ethoxy-4-methanesulfonyl-phenyl)-4,5-dimethyl-4,5-dihydro-imidazol-1-yl]-[4-(3-methanesulfonyl-propyl)-piperazin-1-yl]-methanone



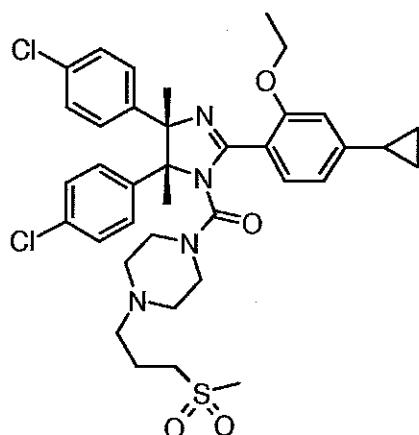
rac-(4S*,5R*)-4,5-Bis-(4-chloro-phenyl)-2-(2-ethoxy-4-methanesulfonyl-phenyl)-4,5-dimethyl-4,5-dihydro-1H-imidazole was prepared from 2-ethoxy-4-methanesulfonyl-benzoyl chloride (prepared from ethyl 2-ethoxy-4-fluorobenzoate and sodium thiomethoxide in 4 steps) and *meso*-2,3-bis-(4-chlorophenyl)-2,3-butanediamine (example 1) in an analogous manner as described in example 2 (method 1).

rac-(4S*,5R*)-4,5-Bis-(4-chloro-phenyl)-2-(2-ethoxy-4-methanesulfonyl-phenyl)-4,5-dimethyl-4,5-dihydro-1H-imidazole was reacted with phosgene in the presence of triethylamine to give the corresponding carbamoyl chloride.

In a manner analogous to the method described in example 5, *rac*-(4S*,5R*)-4,5-bis-(4-chloro-phenyl)-2-(2-ethoxy-4-methanesulfonyl-phenyl)-4,5-dimethyl-4,5-dihydro-imidazole-1-carbonyl chloride was reacted with 1-(3-methanesulfonyl-propyl)-piperazine dihydrochloride (prepared as described in Fotouhi, N. *et al.* WO 2005110996) to give the title compound as a racemic mixture. The enantiomers were separated by supercritical fluid chromatography (Berger Instrument Multi-Gram II, Daicel ChiralPak OD-H 3 x 25 cm, 35 °C at 100 bar, eluting with 30% methanol in carbon dioxide) gave the title compound. HR-MS (ES, *m/z*) calculated for C₃₅H₄₃N₄O₆S₂Cl₂ [(M+H)⁺] 749.1996, observed 749.1995.

Example 159

[(4S,5R)-4,5-Bis-(4-chloro-phenyl)-2-(4-cyclopropyl-2-ethoxy-phenyl)-4,5-dimethyl-4,5-dihydro-imidazol-1-yl]-[4-(3-methanesulfonyl-propyl)-piperazin-1-yl]-methanone



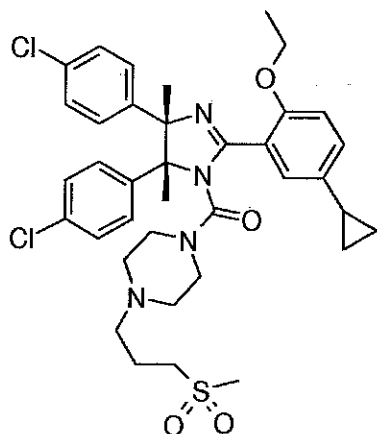
5 *rac*-(4S*,5R*)-4,5-Bis-(4-chloro-phenyl)-2-(4-cyclopropyl-2-ethoxy-phenyl)-4,5-dimethyl-4,5-dihydro-1H-imidazole was prepared from 4-cyclopropyl-2-ethoxy-benzoyl chloride (prepared from 4-bromo-2-hydroxy-benzoic acid by alkylation with iodoethane, Suzuki coupling with cyclopropyl boronic acid, then saponification and conversion to the chloride) and *meso*-2,3-bis-(4-chlorophenyl)-2,3-butanediamine (example 1) in an analogous manner as described in example 2 (method 1).

10 *rac*-(4S*,5R*)-4,5-Bis-(4-chloro-phenyl)-2-(4-cyclopropyl-2-ethoxy-phenyl)-4,5-dimethyl-4,5-dihydro-1H-imidazole was reacted with phosgene in the presence of triethylamine to give the corresponding carbamoyl chloride.

In a manner analogous to the method described in example 5, *rac*-(4S*,5R*)-4,5-bis-(4-chloro-phenyl)-2-(4-cyclopropyl-2-ethoxy-phenyl)-4,5-dimethyl-4,5-dihydro-imidazole-1-carbamoyl chloride was reacted with 1-(3-methanesulfonyl-propyl)-piperazine dihydrochloride (prepared as described in Fotouhi, N. *et al.* WO 2005110996) to give the title compound as a racemic mixture. The enantiomers were separated by supercritical fluid chromatography (Berger Instrument Multi-Gram II, Daicel ChiralPak OD-H 3 x 25 cm, 35 °C at
 15 100 bar, eluting with 30% methanol in carbon dioxide) gave the title compound. HR-MS (ES, *m/z*) calculated for C₃₇H₄₄N₄O₄SCl₂ [(M+H)⁺] 711.2533, observed 711.2533.
 20

Example 160

[(4S,5R)-4,5-Bis-(4-chloro-phenyl)-2-(5-cyclopropyl-2-ethoxy-phenyl)-4,5-dimethyl-4,5-dihydro-imidazol-1-yl]-[4-(3-methanesulfonyl-propyl)-piperazin-1-yl]-methanone



rac-(4S*,5R*)-4,5-Bis-(4-chloro-phenyl)-2-(5-cyclopropyl-2-ethoxy-phenyl)-4,5-dimethyl-4,5-dihydro-1H-imidazole was prepared from 5-cyclopropyl-2-ethoxybenzoyl chloride (prepared from 5-bromo-2-hydroxy-benzoic acid by alkylation with iodoethane, Suzuki coupling with cyclopropyl boronic acid, then saponification and conversion to the chloride) and *meso*-2,3-bis-(4-chlorophenyl)-2,3-butanediamine (example 1) in an analogous manner as described in example 2 (method 1).

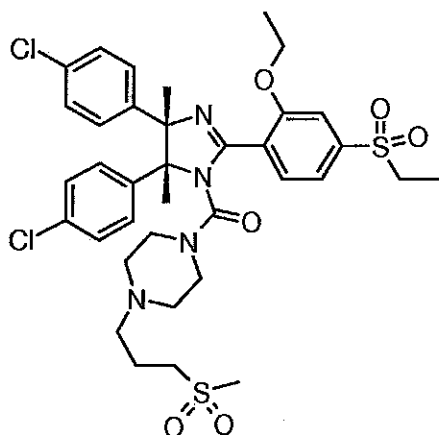
rac-(4S*,5R*)-4,5-Bis-(4-chloro-phenyl)-2-(5-cyclopropyl-2-ethoxy-phenyl)-4,5-dimethyl-4,5-dihydro-1H-imidazole was reacted with phosgene in the presence of triethylamine to give the corresponding carbamoyl chloride.

In a manner analogous to the method described in example 5, *rac*-(4S*,5R*)-4,5-bis-(4-chloro-phenyl)-2-(5-cyclopropyl-2-ethoxy-phenyl)-4,5-dimethyl-4,5-dihydro-imidazole-1-carbonyl chloride was reacted with 1-(3-methanesulfonyl-propyl)-piperazine dihydrochloride (prepared as described in Fotouhi, N. *et al.* WO 2005110996) to give the title compound as a racemic mixture. The enantiomers were separated by supercritical fluid chromatography (Berger Instrument Multi-Gram II, Daicel ChiralPak OD-H 3 x 25 cm, 35 °C at 100 bar, eluting with 30% isopropanol in carbon dioxide) gave the title compound.

HR-MS (ES, m/z) calculated for $C_{37}H_{44}N_4O_4SCl_2$ $[(M+H)^+]$ 711.2533, observed 711.2536.

Example 161

- 5 [(4S,5R)-4,5-Bis-(4-chloro-phenyl)-2-(4-ethanesulfonyl-2-ethoxy-phenyl)-4,5-dimethyl-4,5-dihydro-imidazol-1-yl]-[4-(3-methanesulfonyl-propyl)-piperazin-1-yl]-methanone



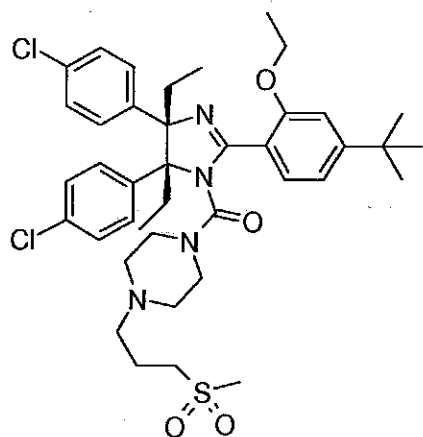
- 10 *rac*-(4S*,5R*)-4,5-bis-(4-chloro-phenyl)-2-(4-ethanesulfonyl-2-ethoxy-phenyl)-4,5-dimethyl-4,5-dihydro-1H-imidazole was prepared from 4-ethanesulfonyl-2-ethoxy-benzoyl chloride (prepared from ethyl 2-ethoxy-4-fluoro-benzoate and sodium ethanethiolate) and *meso*-2,3-bis-(4-chlorophenyl)-2,3-butanediamine (example 1) in an analogous manner as described in example 2 (method 1).

- 15 *rac*-(4S*,5R*)-4,5-bis-(4-chloro-phenyl)-2-(4-ethanesulfonyl-2-ethoxy-phenyl)-4,5-dimethyl-4,5-dihydro-1H-imidazole was reacted with phosgene in the presence of triethylamine to give the corresponding carbamoyl chloride.

- In a manner analogous to the method described in example 5, *rac*-(4S*,5R*)-4,5-bis-(4-chloro-phenyl)-2-(4-ethanesulfonyl-2-ethoxy-phenyl)-4,5-dimethyl-4,5-dihydro-imidazole-1-carbonyl chloride was reacted with 1-(3-methanesulfonyl-propyl)-piperazine dihydrochloride (prepared as described in Fotouhi, N. *et al.* WO 2005110996) to give the title compound as a racemic mixture. The enantiomers were separated by supercritical fluid chromatography (Berger Instrument Multi-Gram II, Daicel ChiralPak OD-H 3 x 25 cm, 35 °C at 100 bar, eluting with 30% methanol in carbon dioxide) gave the title compound.
- 25 HR-MS (ES, m/z) calculated for $C_{36}H_{53}N_4O_4SCl_2$ $[(M+H)^+]$ 763.2152, observed 763.2150.

Example 162

[(4S,5R)-2-(4-*tert*-Butyl-2-ethoxy-phenyl)-4,5-bis-(4-chloro-phenyl)-4,5-diethyl-4,5-dihydro-imidazol-1-yl]-[4-(3-methanesulfonyl-propyl)-piperazin-1-yl]-methanone



1-(4-Chlorophenyl)propan-1-one (8.4 g, 50 mmol) was combined with hydroxylamine hydrochloride (4.0 g, 58 mmol), pyridine (4.6 g, 58 mmol), and ethanol (75 mL). The mixture was refluxed for 3 h. Solvent was evaporated and the residue diluted with water and extracted into diethyl ether/hexane (1:1). The organic extracts were washed with water, brine, and dried over anhydrous magnesium sulfate. Crystallization from cold hexane gave 5.0 g of 1-(4-chlorophenyl)propan-1-one oxime.

1-(4-Chlorophenyl)propan-1-one oxime (5.0 g, 27.3 mmol) was dissolved in acetonitrile (200 mL) and zinc dust (8.8 g, 136 mmol) was added. With mechanical stirring at -15 °C methanesulfonic acid (13 g, 136 mmol) was added over 0.5 hr. Stirring was continued at room temperature for 16 h. Water (100 mL) was added with stirring and the mixture was filtered through Celite. Volatiles were evaporated and the aqueous portion was diluted with 3 N sodium hydroxide (100 mL). The mixture was extracted with diethyl ether (2 x). The organic extracts were washed with water, brine, dried over anhydrous magnesium sulfate and concentrated. The crude residue was partially purified by flash chromatography to give ~2 g of a mixture of the *threo* and *erythro* isomers (8:1 ratio). Crystallization from diethyl ether/ hexane gave pure *threo* isomer (1.4 g)

and crystallization of the mother liquors gave *erythro*-3,4-bis-(4-chlorophenyl)hexane-3,4-diamine (310 mg, 90% purity).

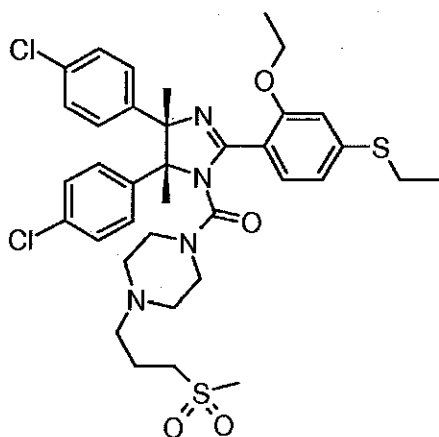
rac-(4*S**,5*R**)-2-(4-*tert*-Butyl-2-ethoxy-phenyl)-4,5-bis-(4-chloro-phenyl)-4,5-diethyl-4,5-dihydro-1*H*-imidazole was prepared from 4-*tert*-butyl-2-ethoxy-benzoyl chloride and *meso*-3,4-bis-(4-chloro-phenyl)-hexane-3,4-diamine in an analogous manner as described in example 2 (method 1).

rac-(4*S**,5*R**)-2-(4-*tert*-Butyl-2-ethoxy-phenyl)-4,5-bis-(4-chloro-phenyl)-4,5-diethyl-4,5-dihydro-1*H*-imidazole was reacted with phosgene in the presence of triethylamine to give the corresponding carbamoyl chloride.

In a manner analogous to the method described in example 5, the carbamoyl chloride was reacted with 1-(3-methanesulfonyl-propyl)-piperazine dihydrochloride (prepared as described in Fotouhi, N. *et al.* WO 2005110996) to give the title compound as a racemic mixture. The enantiomers were separated by supercritical fluid chromatography (Berger Instrument Multi-Gram II, Daicel ChiralPak OD-H 3 x 25 cm, 35 °C at 100 bar, eluting with 25% isopropanol in carbon dioxide) gave the title compound. HR-MS (ES, *m/z*) calculated for C₄₀H₅₃N₄O₄SCl₂ [(*M*+*H*)⁺] 755.3159, observed 755.3157.

Example 163

[(4*S*,5*R*)-4,5-Bis-(4-chloro-phenyl)-2-(2-ethoxy-4-ethylsulfanyl-phenyl)-4,5-dimethyl-4,5-dihydro-imidazol-1-yl]-[4-(3-methanesulfonyl-propyl)-piperazin-1-yl]-methanone



rac-(4*S**,5*R**)-4,5-bis-(4-chloro-phenyl)-2-(2-ethoxy-4-ethylsulfanyl-phenyl)-4,5-dimethyl-4,5-dihydro-1*H*-imidazole was prepared from 2-ethoxy-4-ethylsulfanyl-

benzoyl chloride (prepared from ethyl 2-ethoxy-4-fluoro-benzoate and sodium ethanethiolate) and *meso*-2,3-bis-(4-chlorophenyl)-2,3-butanediamine (example 1) in an analogous manner as described in example 2 (method 1).

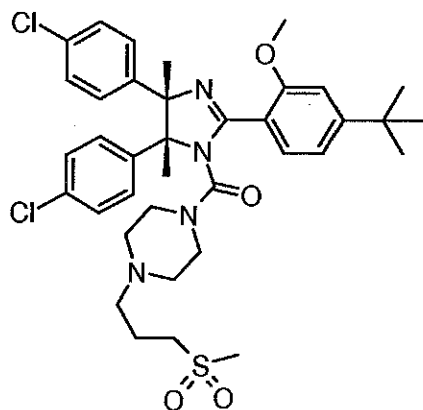
rac-(4*S**,5*R**)-4,5-bis-(4-chloro-phenyl)-2-(2-ethoxy-4-ethylsulfanyl-phenyl)-4,5-dimethyl-4,5-dihydro-1*H*-imidazole was reacted with phosgene in the presence of triethylamine to give the corresponding carbamoyl chloride.

In a manner analogous to the method described in example 5, *rac*-(4*S**,5*R**)-4,5-bis-(4-chloro-phenyl)-2-(2-ethoxy-4-ethylsulfanyl-phenyl)-4,5-dimethyl-4,5-dihydro-imidazole-1-carbonyl chloride was reacted with 1-(3-methanesulfonyl-propyl)-piperazine dihydrochloride (prepared as described in Fotouhi, N. *et al.* WO 2005110996) to give the title compound as a racemic mixture. The enantiomers were separated by supercritical fluid chromatography (Berger Instrument Multi-Gram II, Daicel ChiralPak OD-H 3 x 25 cm, 35 °C at 100 bar, eluting with 35% methanol in carbon dioxide) gave the title compound.

HR-MS (ES, *m/z*) calculated for C₃₆H₄₅N₄O₄S₂Cl₂ [(*M*+*H*)⁺] 731.2254, observed 731.2259.

Example 164

[(4*S*,5*R*)-2-(4-*tert*-Butyl-2-methoxy-phenyl)-4,5-bis-(4-chloro-phenyl)-4,5-dimethyl-4,5-dihydro-imidazol-1-yl]-[4-(3-methanesulfonyl-propyl)-piperazin-1-yl]-methanone



rac-(4*S**,5*R**)-2-(4-*tert*-butyl-2-methoxy-phenyl)-4,5-bis-(4-chloro-phenyl)-4,5-dimethyl-4,5-dihydro-1*H*-imidazole was prepared from 4-*tert*-butyl-2-methoxy-benzoyl chloride (prepared from 4-*tert*-butyl-2-hydroxy-benzoic acid) and *meso*-

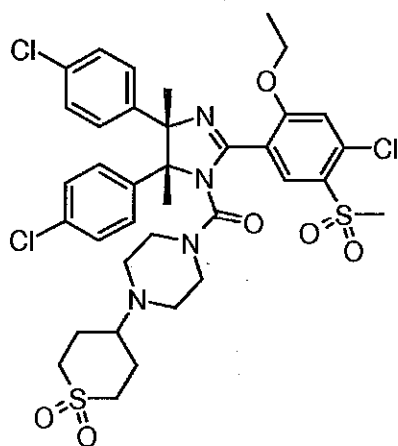
2,3-bis-(4-chlorophenyl)-2,3-butanediamine (example 1) in an analogous manner as described in example 2 (method 1).

rac-(4S*,5R*)-2-(4-*tert*-butyl-2-methoxy-phenyl)-4,5-bis-(4-chloro-phenyl)-4,5-dimethyl-4,5-dihydro-1H-imidazole was reacted with phosgene in the presence of triethylamine to give the corresponding carbamoyl chloride.

In a manner analogous to the method described in example 5, *rac*-(4S*,5R*)-2-(4-*tert*-butyl-2-methoxy-phenyl)-4,5-bis-(4-chloro-phenyl)-4,5-dimethyl-4,5-dihydro-imidazole-1-carbonyl chloride was reacted with 1-(3-methanesulfonyl-propyl)-piperazine dihydrochloride (prepared as described in Fotouhi, N. *et al.* WO 2005110996) to give the title compound as a racemic mixture. The enantiomers were separated by supercritical fluid chromatography (Berger Instrument Multi-Gram II, Daicel ChiralPak OD-H 3 x 25 cm, 35 °C at 100 bar, eluting with 35% methanol in carbon dioxide) gave the title compound. HR-MS (ES, *m/z*) calculated for C₃₇H₄₇N₄O₄SCl₂ [(M+H)⁺] 713.2690, observed 713.2690.

Example 165

[(4S,5R)-2-(4-Chloro-2-ethoxy-5-methanesulfonyl-phenyl)-4,5-bis-(4-chloro-phenyl)-4,5-dimethyl-4,5-dihydro-imidazol-1-yl]-[4-(1,1-dioxo-tetrahydro-2H-thiopyran-4-yl)-piperazin-1-yl]-methanone

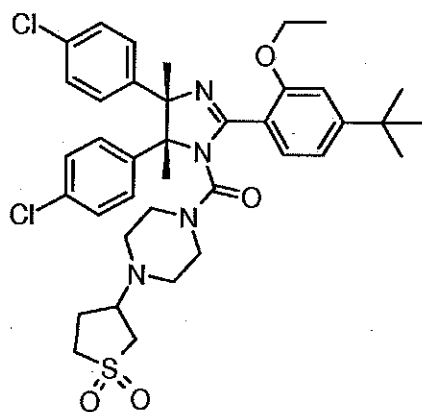


In a manner analogous to the method described in example 5, *rac*-(4S*,5R*)-2-(4-chloro-2-ethoxy-5-methanesulfonyl-phenyl)-4,5-bis-(4-chloro-phenyl)-4,5-dimethyl-4,5-dihydro-imidazole-1-carbonyl chloride (example 61) was reacted with 1-(1,1-dioxo-tetrahydro-2H-thiopyran-4-yl)-piperazine dihydrochloride

(example 22) to give the title compound as a racemic mixture. The enantiomers were separated by supercritical fluid chromatography (Berger Instrument Multi-Gram II, Regis Technologies Whelk-01 3 x 25 cm, 35 °C at 100 bar, eluting with 40% methanol in carbon dioxide) gave the title compound. HR-MS (ES, m/z) calculated for $C_{36}H_{42}N_4O_6S_2Cl_3$ [(M+H)⁺] 795.1606, observed 795.1605.

Example 166

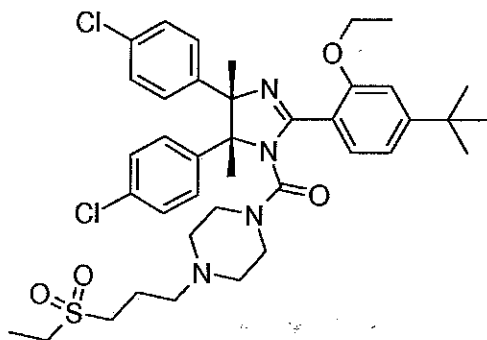
[(4S,5R)-2-(4-*tert*-Butyl-2-ethoxy-phenyl)-4,5-bis-(4-chloro-phenyl)-4,5-dimethyl-4,5-dihydro-imidazol-1-yl]-[4-(1,1-dioxo-tetrahydro-thiophen-3-yl)-piperazin-1-yl]-methanone



In a manner analogous to the method described in example 5, *rac*-(4S*,5R*)-2-(4-*tert*-butyl-2-ethoxy-phenyl)-4,5-bis-(4-chloro-phenyl)-4,5-dimethyl-4,5-dihydro-1*H*-imidazole was reacted with 1-(1,1-dioxo-tetrahydro-thiophen-3-yl)-piperazine (Enamine-BB) to give the title compound as a racemic mixture. The enantiomers were separated by supercritical fluid chromatography (Berger Instrument Multi-Gram II, Daicel ChiralPak OJ-H 3 x 25 cm, 35 °C at 100 bar, eluting with 20% isopropanol in carbon dioxide) gave the title compound as a mixture of diastereomers. HR-MS (ES, m/z) calculated for $C_{38}H_{46}N_4O_4SCl_2$ [(M+H)⁺] 725.2690, observed 725.2692.

Example 167

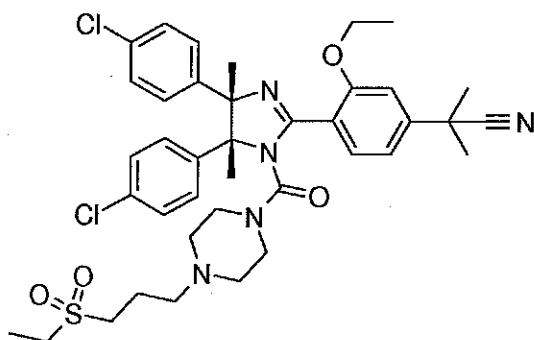
[(4S,5R)-2-(4-*tert*-Butyl-2-ethoxy-phenyl)-4,5-bis-(4-chloro-phenyl)-4,5-dimethyl-4,5-dihydro-imidazol-1-yl]-[4-(3-ethanesulfonyl-propyl)-piperazin-1-yl]-methanone



In a manner analogous to the method described in example 5, (4S,5R)-2-(4-*tert*-butyl-2-ethoxy-phenyl)-4,5-bis-(4-chloro-phenyl)-4,5-dimethyl-4,5-dihydro-1*H*-imidazole (example 4) was reacted with 1-(3-ethanesulfonyl-propyl)-piperazine dihydrochloride (prepared from 3-ethylsulfanyl-propan-1-ol in an analogous manner as the method described for 1-(3-methanesulfonyl-propyl)-piperazine dihydrochloride) to give the title compound. HR-MS (ES, *m/z*) calculated for $C_{39}H_{51}N_4O_4S$ [(M+H)⁺] 741.3003, observed 741.2998.

Example 168

2-(4-((4S,5R)-4,5-Bis-(4-chloro-phenyl)-1-[4-(3-ethanesulfonyl-propyl)-piperazine-1-carbonyl]-4,5-dimethyl-4,5-dihydro-1*H*-imidazol-2-yl]-3-ethoxy-phenyl)-2-methyl-propionitrile

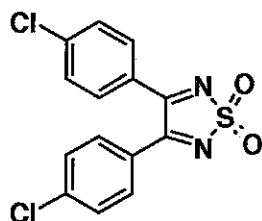


The enantiomers of *rac*-(4*S*^{*},5*R*^{*})-4,5-bis-(4-chloro-phenyl)-2-[4-(cyano-dimethyl-methyl)-2-ethoxy-phenyl]-4,5-dimethyl-4,5-dihydro-imidazole-1-carbonyl chloride (example 17) were separated by supercritical fluid chromatography (Berger Instrument Multi-Gram II, Daicel ChiralPak OD-H 3 x 25 cm, 35 °C at 100 bar, eluting with 18% acetonitrile in carbon dioxide).

In a manner analogous to the method described in example 5, (4S,5R)-4,5-bis-(4-chloro-phenyl)-2-[4-(cyano-dimethyl-methyl)-2-ethoxy-phenyl]-4,5-dimethyl-4,5-dihydro-imidazole-1-carbonyl chloride was reacted with 1-(3-ethanesulfonyl-propyl)-piperazine dihydrochloride (example 167) to give the title compound. HR-MS (ES, m/z) calculated for $C_{38}H_{48}N_5O_4SCl_2$ $[(M+H)^+]$ 752.2799, observed 752.2799.

Example 169

3,4-bis(4-chlorophenyl)-1,2,5-thiadiazole-1,1-dioxide



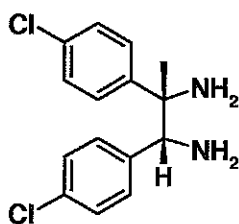
To a solution of 4-chlorobenzaldehyde (240 g, 1.707 mol) in 144 mL of methanol was added 2.40 g of potassium cyanide in 4.8 mL water over 6 min. The mixture was refluxed for another 50 min (mixture became deep red), cooled, then concentrated under reduced pressure. The red residue was taken up in 1500 mL of hexane-ethyl acetate (1:1), and washed successively with water (1 x 150 mL), 20% sodium bisulfite (6 x 150 mL), brine (1 x 150 mL) and dried over anhydrous sodium sulfate. After filtration and concentration under reduced pressure, the product was boiled in 400 mL of hexane to remove small amounts of 4-chlorobenzaldehyde. The mixture was cooled and the white solid was collected by suction filtration to give 183.94 g of 4,4'-dichlorobenzoin (76%). This procedure was adapted from Lutz *et al. J. Am. Chem. Soc.* **1949**, 71, 478.

To a solution of 4,4'-dichlorobenzoin (183.94 g, 0.645 mol) in 1400 mL of ethyl acetate was added 109.785 g (0.687 mole) of bromine over 2 min. The mixture was stirred for 1.5 h during which time the dark bromine color lightened, and crystals came out of solution (use of mechanical stirrer is recommended). The mixture was cooled in ice bath for 10 min, and the solids were collected by suction filtration and washed with 800 mL of diethyl ether to give 149.01 g of 4,4'-dichlorobenzil as yellow crystals (81%).

A mixture of 4,4'-dichlorobenzil (55.824 g, 0.20 mol), sulfamide (24.028 g, 0.25 mol), triethylamine (8.36 mL, 0.06 mol) and absolute ethanol (1200 mL) was refluxed under argon for 18 h, then ~ 600 mL was distilled out and the remainder of the volatiles removed under reduced pressure. LC-MS indicated incomplete
5 reaction, therefore additional amounts of sulfamide (4.806 g, 0.05 mol), triethylamine (8.36 mL, 0.06 mol) and absolute ethanol (1200 mL) were added. The mixture was refluxed under argon for 22 h. About 600 mL of the volatiles was distilled out and the remainder was removed under reduced pressure. Additional acetonitrile was added and the mixture was again concentrated under
10 reduced pressure. The residue was taken up in 1000 mL of ethyl acetate, washed successively with saturated sodium bicarbonate (1 x 250 mL), water (3 x 250 mL), brine (1 x 250 mL). The organic layer was dried over anhydrous sodium sulfate, filtered and concentrated under reduced pressure. The residue was evaporated again with acetonitrile, and then taken in 450 mL of diethyl ether
15 and stirred for 30 min. The solids were collected by suction filtration to give 56.14 g of 3,4-bis-(4-chlorophenyl)-1,2,5-thiadiazole-1,1-dioxide as a tan solid (82%).

Example 170

20 *rac*-(1R*,2S*)-1,2-Bis-(4-chloro-phenyl)-propane-1,2-diamine



A solution of 5.0 g (14.7 mmol) of 3,4-bis-(4-chlorophenyl)-1,2,5-thiadiazole-1,1-dioxide in 55 mL of anhydrous tetrahydrofuran, under argon was cooled to 0 °C
25 and then 12.9 mL of a 1.4 M solution (1:3 tetrahydrofuran-toluene) of methyl magnesium bromide was added dropwise over 5 min. The mixture was stirred for 35 min and then poured onto 100 g of ice plus 55 mL of 1 M hydrochloric acid. The mixture was taken up in 1000 mL of ethyl acetate, and the organic layer was
30 washed with brine and then dried over anhydrous sodium sulfate. After filtration

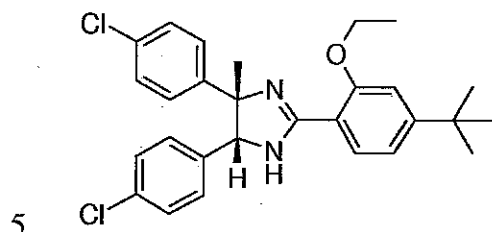
and concentration under reduced pressure, 5.38 g of 2,3-dihydro-3-methyl-3,4-bis(4-chlorophenyl)-1,2,5-thiadiazole-1,1-dioxide was obtained. This material was used directly in the next step without further purification.

To a solution of 3,4-bis-(4-chloro-phenyl)-3-methyl-2,3-dihydro-[1,2,5]-thiadiazole 1,1-dioxide (5.38 g, 15.1 mmol) in 91 mL of ethanol cooled to 0 °C was added sodium borohydride (0.30 g, 61 mmol) portionwise over 7 min. After stirring at 0 °C for another 45 min, the mixture was allowed to warm to room temperature and stirred for 3.5 h. The reaction was then cooled to 0 °C and quenched by dropwise addition of 1 M hydrochloric acid (38 mL). The reaction mixture was taken up in 500 mL of ethyl acetate then washed with water (300 mL) and brine (300 mL), dried over anhydrous sodium sulfate and concentrated. The crude residue was purified by flash column chromatography (silica gel, eluting with 3:1 heptane-ethyl acetate) to give *rac*-(3R*,4S*)-3,4-bis(4-chlorophenyl)-3-methyl-1,2,5-thiadiazolidine-1,1-dioxide (4.3 g).

A suspension of *rac*-(3R*,4S*)-3,4-bis(4-chlorophenyl)-3-methyl-1,2,5-thiadiazolidine-1,1-dioxide (3.71 g, 10.4 mmol) and phenol (4.86 g, 52 mmol) in 48% hydrobromic acid (13.56 mL) and acetic acid (46.44 mL) was stirred at 130 °C for 40 min (reaction progress monitored by TLC), then allowed to cool to room temperature. The crude reaction mixture was partitioned between ethyl acetate and water, and the aqueous phase washed twice with ethyl acetate. The aqueous phase was then made basic by the slow addition of solid sodium hydroxide (60 g; **CARE!** Exothermic) and extracted with diethyl ether (3 x 500 mL). The combined ethereal extracts were washed with 2M sodium hydroxide (100 mL), then dried over anhydrous sodium sulfate (with a few pellets of solid sodium hydroxide) and evaporated to give the title compound (1.56 g). This material was carried forward to the next step without any further purification.

Example 171

(4S,5R)-2-(4-*tert*-Butyl-2-ethoxy-phenyl)-4,5-bis-(4-chloro-phenyl)-4-methyl-4,5-dihydro-1*H*-imidazole



In a manner analogous to the method described in example 2, *rac*-(1*R*^{*},2*S*^{*})-1,2-bis-(4-chloro-phenyl)-propane-1,2-diamine was reacted with 4-*tert*-butyl-2-ethoxy-benzoic acid methyl ester (prepared as described in Fotouhi, N. *et al.* WO 2005110996) in the presence of trimethylaluminum to give the title compound as a racemic mixture.

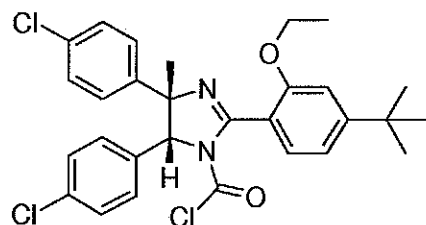
10

The enantiomers were separated by supercritical fluid chromatography (Berger Instrument Multi-Gram II, Daicel ChiralPak OD-H 3 x 25 cm, 35 °C at 100 bar, eluting with 25% methanol and 0.2% isopropylamine in carbon dioxide) to give (4*S*,5*R*)-2-(4-*tert*-butyl-2-ethoxy-phenyl)-4,5-bis-(4-chloro-phenyl)-4-methyl-4,5-dihydro-1*H*-imidazole. HR-MS (ES, *m/z*) calculated for C₂₈H₃₁N₂OCl₂ [(*M*+*H*)⁺] 481.1808, observed 481.1801.

15

Example 172

20 *rac*-(4*S*^{*},5*R*^{*})-2-(4-*tert*-Butyl-2-ethoxy-phenyl)-4,5-bis-(4-chloro-phenyl)-4-methyl-4,5-dihydro-imidazole-1-carbonyl chloride

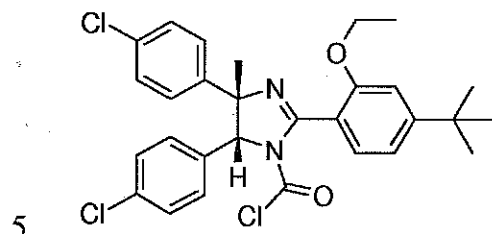


In a manner analogous to the method described in example 3, *rac*-(4*S*^{*},5*R*^{*})-2-(4-*tert*-butyl-2-ethoxy-phenyl)-4,5-bis-(4-chloro-phenyl)-4-methyl-4,5-dihydro-1*H*-imidazole was reacted with phosgene in the presence of triethylamine to give the title compound.

25

Example 173

(4S,5R)-2-(4-*tert*-Butyl-2-ethoxy-phenyl)-4,5-bis-(4-chloro-phenyl)-4-methyl-4,5-dihydro-imidazole-1-carbonyl chloride

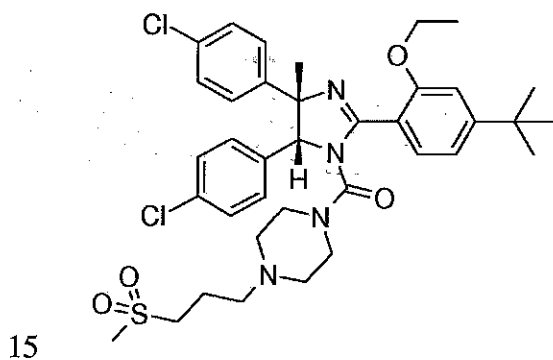


In a manner analogous to the method described in example 3, (4S,5R)-2-(4-*tert*-butyl-2-ethoxy-phenyl)-4,5-bis-(4-chloro-phenyl)-4-methyl-4,5-dihydro-1*H*-imidazole was reacted with phosgene in the presence of triethylamine to give the title compound.

10

Example 174

[(4S,5R)-2-(4-*tert*-Butyl-2-ethoxy-phenyl)-4,5-bis-(4-chloro-phenyl)-4-methyl-4,5-dihydro-imidazol-1-yl]-piperazin-1-yl-methanone

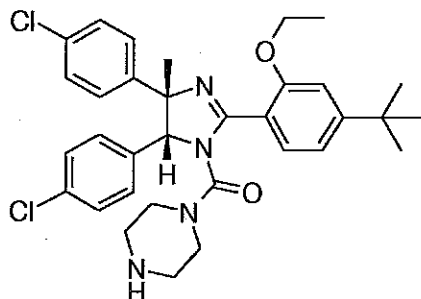


In a manner analogous to the method described in example 5, (4S,5R)-2-(4-*tert*-butyl-2-ethoxy-phenyl)-4,5-bis-(4-chloro-phenyl)-4-methyl-4,5-dihydro-imidazole-1-carbonyl chloride was reacted with 1-(3-methanesulfonyl-propyl)-piperazine dihydrochloride (prepared as described in Fotouhi, N. *et al.* WO 2005110996) to give the title compound. HR-MS (ES, *m/z*) calculated for C₃₇H₄₇N₄O₄SCl₂ [(M+H)⁺] 713.2690, observed 713.2687.

20

Example 175

[(4S,5R)-2-(4-*tert*-Butyl-2-ethoxy-phenyl)-4,5-bis-(4-chloro-phenyl)-4-methyl-4,5-dihydro-imidazol-1-yl]-piperazin-1-yl-methanone

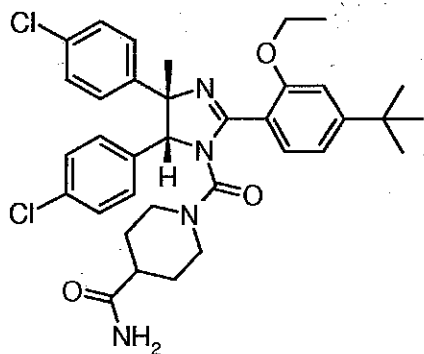


In a manner analogous to the method described in example 5, (4S,5R)-2-(4-*tert*-butyl-2-ethoxy-phenyl)-4,5-bis-(4-chloro-phenyl)-4-methyl-4,5-dihydro-imidazole-1-carbonyl chloride was reacted with piperazine (Aldrich) to give the title compound. LC-MS: 593.2 [(M+H)⁺]

10

Example 176

1-[(4S,5R)-2-(4-*tert*-Butyl-2-ethoxy-phenyl)-4,5-bis-(4-chloro-phenyl)-4-methyl-4,5-dihydro-imidazole-1-carbonyl]-piperidine-4-carboxylic acid amide

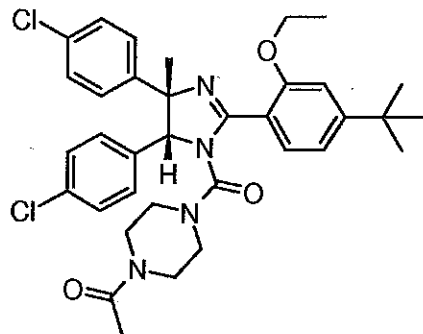


In a manner analogous to the method described in example 5, (4S,5R)-2-(4-*tert*-butyl-2-ethoxy-phenyl)-4,5-bis-(4-chloro-phenyl)-4-methyl-4,5-dihydro-imidazole-1-carbonyl chloride was reacted with 1-piperidin-4-yl-ethanone (Aldrich) to give the title compound. LC-MS: 635.2 [(M+H)⁺]

20

Example 177

1-{4-[(4S,5R)-2-(4-*tert*-Butyl-2-ethoxy-phenyl)-4,5-bis-(4-chloro-phenyl)-4-methyl-4,5-dihydro-imidazole-1-carbonyl]-piperazin-1-yl}-ethanone



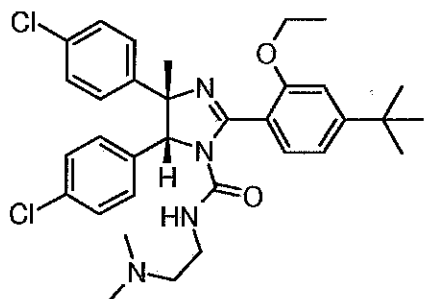
5

In a manner analogous to the method described in example 5, (4S,5R)-2-(4-*tert*-butyl-2-ethoxy-phenyl)-4,5-bis-(4-chloro-phenyl)-4-methyl-4,5-dihydro-imidazole-1-carbonyl chloride was reacted with 1-acetyl-piperazine (Aldrich) to give the title compound. LC-MS: 635.2 [(M+H)⁺]

10

Example 178

rac-(4S*,5R*)-2-(4-*tert*-Butyl-2-ethoxy-phenyl)-4,5-bis-(4-chloro-phenyl)-4-methyl-4,5-dihydro-imidazole-1-carboxylic acid (2-dimethylamino-ethyl)-amide



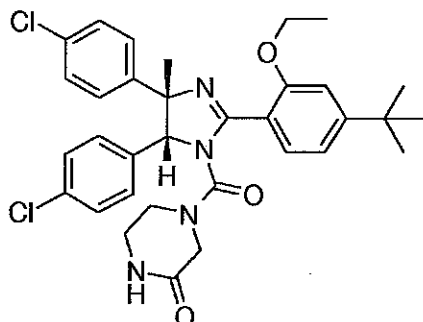
15

In a manner analogous to the method described in example 5, *rac*-(4S*,5R*)-2-(4-*tert*-butyl-2-ethoxy-phenyl)-4,5-bis-(4-chloro-phenyl)-4-methyl-4,5-dihydro-imidazole-1-carbonyl chloride was reacted with N,N-dimethyl-1,2-ethanediamine (Aldrich) to give the title compound. LC-MS: 595.2 [(M+H)⁺]

20

Example 179

rac-4-[(4S*,5R*)-2-(4-*tert*-Butyl-2-ethoxy-phenyl)-4,5-bis-(4-chloro-phenyl)-4-methyl-4,5-dihydro-imidazole-1-carbonyl]-piperazin-2-one



5

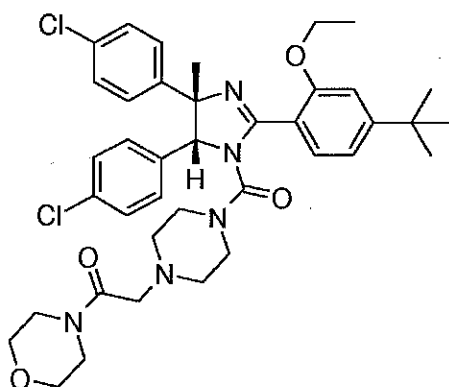
In a manner analogous to the method described in example 5, *rac*-(4S*,5R*)-2-(4-*tert*-butyl-2-ethoxy-phenyl)-4,5-bis-(4-chloro-phenyl)-4-methyl-4,5-dihydro-imidazole-1-carbonyl chloride was reacted with 2-piperazinone (Avocado

10 Organics) to give the title compound. LC-MS: 607.2 [(M+H)⁺]

Example 180

rac-2-{4-[(4S*,5R*)-2-(4-*tert*-Butyl-2-ethoxy-phenyl)-4,5-bis-(4-chloro-phenyl)-4-methyl-4,5-dihydro-imidazole-1-carbonyl]-piperazin-1-yl}-1-morpholin-4-yl-ethanone

15



In a manner analogous to the method described in example 5, *rac*-(4S*,5R*)-2-(4-*tert*-butyl-2-ethoxy-phenyl)-4,5-bis-(4-chloro-phenyl)-4-methyl-4,5-dihydro-imidazole-1-carbonyl chloride was reacted with 1-morpholin-4-yl-2-piperazin-1-yl-

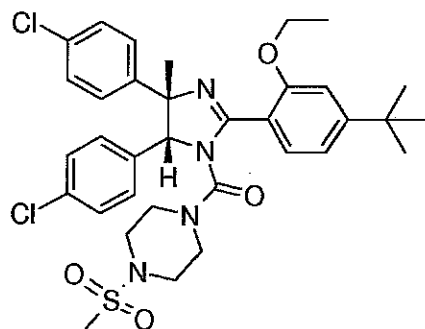
20

ethanone (Oakwood Products) to give the title compound. LC-MS: 720.3

$[(M+H)^+]$

Example 181

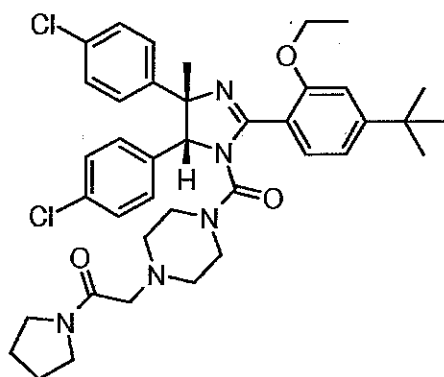
- 5 *rac*-[(4S*,5R*)-2-(4-*tert*-Butyl-2-ethoxy-phenyl)-4,5-bis-(4-chloro-phenyl)-4-methyl-4,5-dihydro-imidazol-1-yl]-(4-methanesulfonyl-piperazin-1-yl)-methanone



- 10 In a manner analogous to the method described in example 5, *rac*-(4S*,5R*)-2-(4-*tert*-butyl-2-ethoxy-phenyl)-4,5-bis-(4-chloro-phenyl)-4-methyl-4,5-dihydro-imidazole-1-carbonyl chloride was reacted with 1-methylsulfonyl-piperazine (Aldrich) to give the title compound. LC-MS: 671.2 $[(M+H)^+]$

Example 182

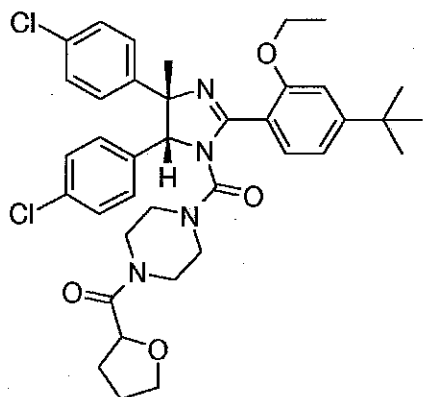
- 15 *rac*-2-{4-[(4S*,5R*)-2-(4-*tert*-Butyl-2-ethoxy-phenyl)-4,5-bis-(4-chloro-phenyl)-4-methyl-4,5-dihydro-imidazole-1-carbonyl]-piperazin-1-yl}-1-pyrrolidin-1-yl-ethanone



In a manner analogous to the method described in example 5, *rac*-(4S*,5R*)-2-(4-*tert*-butyl-2-ethoxy-phenyl)-4,5-bis-(4-chloro-phenyl)-4-methyl-4,5-dihydro-imidazole-1-carbonyl chloride was reacted with 2-piperazin-1-yl-1-pyrrolidin-1-yl-ethanone (Aldrich) to give the title compound. LC-MS: 704.3 [(M+H)⁺]

Example 183

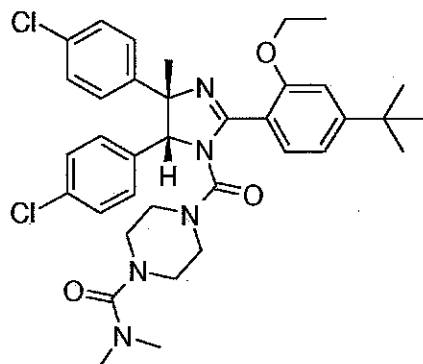
rac-(4S*,5R*)-2-(4-*tert*-Butyl-2-ethoxy-phenyl)-4,5-bis-(4-chloro-phenyl)-4-methyl-4,5-dihydro-imidazol-1-yl]-[4-(tetrahydro-furan-2-carbonyl)-piperazin-1-yl]-methanone



In a manner analogous to the method described in example 5, *rac*-(4S*,5R*)-2-(4-*tert*-butyl-2-ethoxy-phenyl)-4,5-bis-(4-chloro-phenyl)-4-methyl-4,5-dihydro-imidazole-1-carbonyl chloride was reacted with piperazin-1-yl-(tetrahydro-furan-2-yl)-methanone (Aldrich) to give the title compound. LC-MS: 691.3 [(M+H)⁺]

Example 184

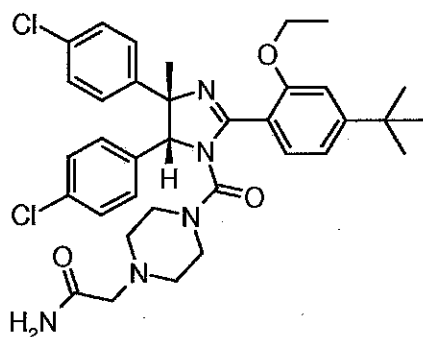
rac-4-[(4S*,5R*)-2-(4-*tert*-Butyl-2-ethoxy-phenyl)-4,5-bis-(4-chloro-phenyl)-4-methyl-4,5-dihydro-imidazole-1-carbonyl]-piperazine-1-carboxylic acid dimethylamide



In a manner analogous to the method described in example 5, *rac*-(4S*,5R*)-2-(4-*tert*-butyl-2-ethoxy-phenyl)-4,5-bis-(4-chloro-phenyl)-4-methyl-4,5-dihydro-imidazole-1-carbonyl chloride was reacted with piperazine-1-carboxylic acid dimethylamide (Aldrich) to give the title compound. LC-MS: 664.3 [(M+H)⁺]

Example 185

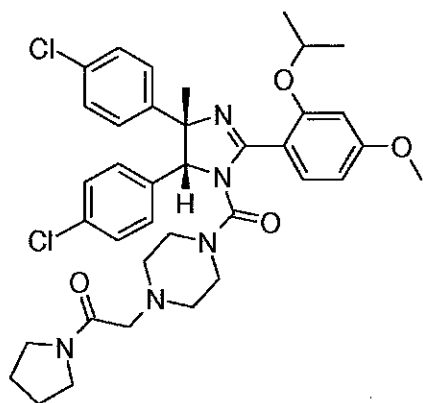
rac-2-{4-[(4S*,5R*)-2-(4-*tert*-Butyl-2-ethoxy-phenyl)-4,5-bis-(4-chloro-phenyl)-4-methyl-4,5-dihydro-imidazole-1-carbonyl]-piperazin-1-yl}-acetamide



In a manner analogous to the method described in example 5, *rac*-(4S*,5R*)-2-(4-*tert*-butyl-2-ethoxy-phenyl)-4,5-bis-(4-chloro-phenyl)-4-methyl-4,5-dihydro-imidazole-1-carbonyl chloride was reacted with 2-piperazin-1-yl-acetamide dihydrochloride (Matrix Scientific) to give the title compound. LC-MS: 650.3 [(M+H)⁺]

Example 186

rac-2-[4-[(4*S**,5*R**)-4,5-Bis-(4-chloro-phenyl)-2-(2-isopropoxy-4-methoxy-phenyl)-4-methyl-4,5-dihydro-imidazole-1-carbonyl]-piperazin-1-yl]-1-pyrrolidin-1-yl-ethanone

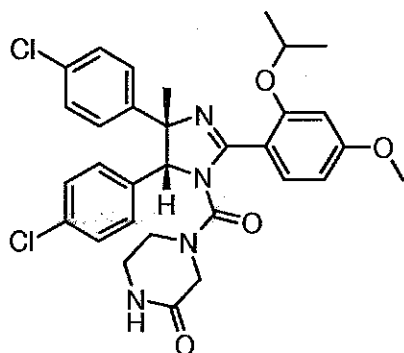


rac-2-[4-[(4*S**,5*R**)-4,5-Bis-(4-chloro-phenyl)-2-(2-isopropoxy-4-methoxy-phenyl)-4-methyl-4,5-dihydro-1*H*-imidazole was prepared from *rac*-(1*R**,2*S**)-1,2-bis-(4-chloro-phenyl)-propane-1,2-diamine and methyl 2-isopropoxy-4-methoxy-benzoate in the presence of trimethylaluminum using the procedure as described in example 2. It was then reacted with phosgene in the presence of triethylamine to give *rac*-(4*S**,5*R**)-4,5-bis-(4-chloro-phenyl)-2-(2-isopropoxy-4-methoxy-phenyl)-4-methyl-4,5-dihydro-imidazole-1-carbonyl chloride (example 3).

In a manner analogous to the method described in example 5, *rac*-(4*S**,5*R**)-4,5-bis-(4-chloro-phenyl)-2-(2-isopropoxy-4-methoxy-phenyl)-4-methyl-4,5-dihydro-imidazole-1-carbonyl chloride was reacted with 2-piperazin-1-yl-1-pyrrolidin-1-yl-ethanone (Aldrich) to give the title compound. LC-MS: 692.3 [(*M*+*H*)⁺]

Example 187

rac-4-[(4*S**,5*R**)-4,5-Bis-(4-chloro-phenyl)-2-(2-isopropoxy-4-methoxy-phenyl)-4-methyl-4,5-dihydro-imidazole-1-carbonyl]-piperazin-2-one

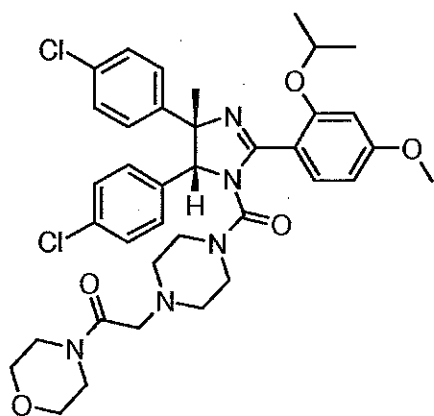


rac-(4S*,5R*)-4,5-Bis-(4-chloro-phenyl)-2-(2-isopropoxy-4-methoxy-phenyl)-4-methyl-4,5-dihydro-1*H*-imidazole was prepared from *rac*-(1R*,2S*)-1,2-bis-(4-chloro-phenyl)-propane-1,2-diamine and methyl 2-isopropoxy-4-methoxy-benzoate in the presence of trimethylaluminum using the procedure as described in example 2. It was then reacted with phosgene in the presence of triethylamine to give *rac*-(4S*,5R*)-4,5-bis-(4-chloro-phenyl)-2-(2-isopropoxy-4-methoxy-phenyl)-4-methyl-4,5-dihydro-imidazole-1-carbonyl chloride (example 3).

In a manner analogous to the method described in example 5, *rac*-(4S*,5R*)-4,5-bis-(4-chloro-phenyl)-2-(2-isopropoxy-4-methoxy-phenyl)-4-methyl-4,5-dihydro-imidazole-1-carbonyl chloride was reacted with 2-piperazinone (Avocado Organics) to give the title compound. LC-MS: 595.2 [(M+H)⁺]

Example 188

rac-2-{4-[(4S*,5R*)-4,5-Bis-(4-chloro-phenyl)-2-(2-isopropoxy-4-methoxy-phenyl)-4-methyl-4,5-dihydro-imidazole-1-carbonyl]-piperazin-1-yl}-1-morpholin-4-yl-ethanone

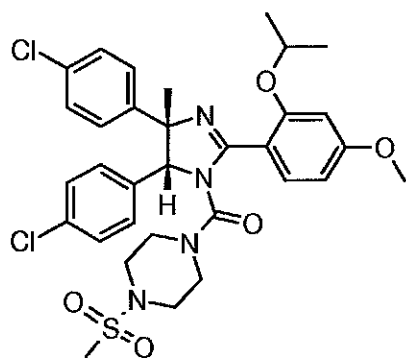


In a manner analogous to the method described in example 5, *rac*-(4S*,5R*)-4,5-bis-(4-chloro-phenyl)-2-(2-isopropoxy-4-methoxy-phenyl)-4-methyl-4,5-dihydro-imidazole-1-carbonyl chloride was reacted with 1-morpholin-4-yl-2-piperazin-1-yl-ethanone (Oakwood Products) to give the title compound. LC-MS: 708.3

5 [(M+H)⁺]

Example 189

rac-[(4S*,5R*)-4,5-Bis-(4-chloro-phenyl)-2-(2-isopropoxy-4-methoxy-phenyl)-4-methyl-4,5-dihydro-imidazol-1-yl]-(4-methanesulfonyl-piperazin-1-yl)-methanone



10

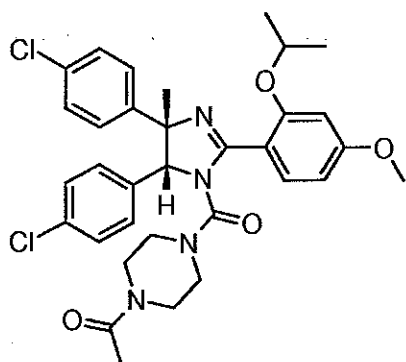
In a manner analogous to the method described in example 5, *rac*-(4S*,5R*)-4,5-bis-(4-chloro-phenyl)-2-(2-isopropoxy-4-methoxy-phenyl)-4-methyl-4,5-dihydro-imidazole-1-carbonyl chloride was reacted with 1-methylsulfonyl-piperazine

15 (Aldrich) to give the title compound. LC-MS: 659.2 [(M+H)⁺]

Example 190

rac-1-{4-[(4S*,5R*)-4,5-Bis-(4-chloro-phenyl)-2-(2-isopropoxy-4-methoxy-phenyl)-4-methyl-4,5-dihydro-imidazole-1-carbonyl]-piperazin-1-yl}-ethanone

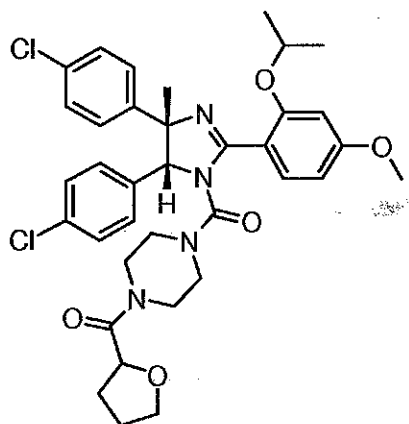
20



In a manner analogous to the method described in example 5, *rac*-(4S*,5R*)-4,5-bis-(4-chloro-phenyl)-2-(2-isopropoxy-4-methoxy-phenyl)-4-methyl-4,5-dihydro-imidazole-1-carbonyl chloride was reacted with 1-acetyl-piperazine (Aldrich) to give the title compound. LC-MS: 623.2 [(M+H)⁺]

Example 191

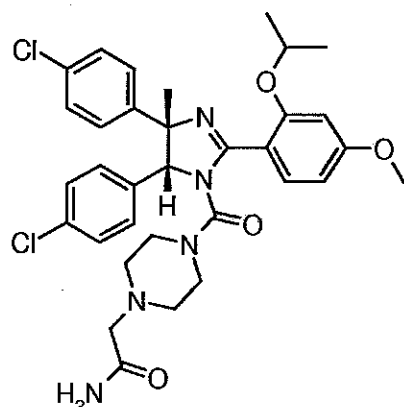
rac-[(4S*,5R*)-4,5-Bis-(4-chloro-phenyl)-2-(2-isopropoxy-4-methoxy-phenyl)-4-methyl-4,5-dihydro-imidazol-1-yl]-[4-(tetrahydro-furan-2-carbonyl)-piperazin-1-yl]-methanone



In a manner analogous to the method described in example 5, *rac*-(4S*,5R*)-4,5-bis-(4-chloro-phenyl)-2-(2-isopropoxy-4-methoxy-phenyl)-4-methyl-4,5-dihydro-imidazole-1-carbonyl chloride was reacted with piperazin-1-yl-(tetrahydro-furan-2-yl)-methanone (Aldrich) to give the title compound. LC-MS: 679.2 [(M+H)⁺]

Example 192

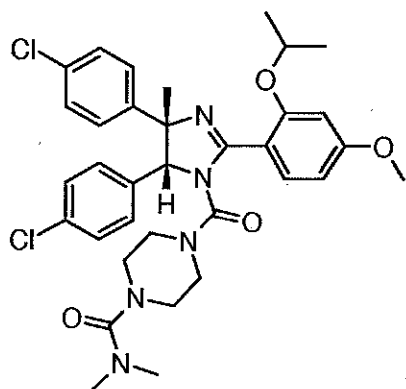
rac-2-{4-[(4S*,5R*)-4,5-Bis-(4-chloro-phenyl)-2-(2-isopropoxy-4-methoxy-phenyl)-4-methyl-4,5-dihydro-imidazole-1-carbonyl]-piperazin-1-yl}-acetamide



In a manner analogous to the method described in example 5, *rac*-(4S*,5R*)-4,5-bis-(4-chloro-phenyl)-2-(2-isopropoxy-4-methoxy-phenyl)-4-methyl-4,5-dihydro-imidazole-1-carbonyl chloride was reacted with 2-piperazin-1-yl-acetamide dihydrochloride (Matrix Scientific) to give the title compound. LC-MS: 638.2 [(M+H)⁺]

Example 193

10 *rac*-4-[(4S*,5R*)-4,5-Bis-(4-chloro-phenyl)-2-(2-isopropoxy-4-methoxy-phenyl)-4-methyl-4,5-dihydro-imidazole-1-carbonyl]-piperazine-1-carboxylic acid dimethylamide



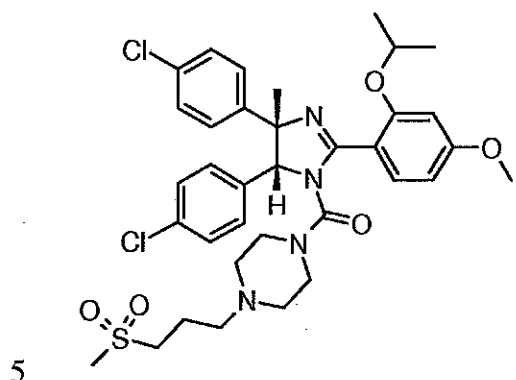
15

In a manner analogous to the method described in example 5, *rac*-(4S*,5R*)-4,5-bis-(4-chloro-phenyl)-2-(2-isopropoxy-4-methoxy-phenyl)-4-methyl-4,5-dihydro-imidazole-1-carbonyl chloride was reacted with piperazine-1-carboxylic acid dimethylamide (Aldrich) to give the title compound. LC-MS: 652.2 [(M+H)⁺]

20

Example 194

rac-[(4S*,5R*)-4,5-Bis-(4-chloro-phenyl)-2-(2-isopropoxy-4-methoxy-phenyl)-4-methyl-4,5-dihydro-imidazol-1-yl]-[4-(3-methanesulfonyl-propyl)-piperazin-1-yl]-methanone



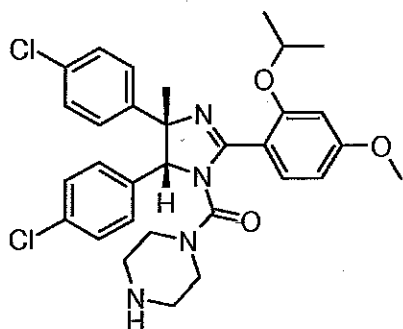
In a manner analogous to the method described in example 5, *rac*-(4S*,5R*)-4,5-bis-(4-chloro-phenyl)-2-(2-isopropoxy-4-methoxy-phenyl)-4-methyl-4,5-dihydro-imidazole-1-carbonyl chloride was reacted with 1-(3-methanesulfonyl-propyl)-piperazine dihydrochloride (prepared as described in Fotouhi, N. *et al.* WO 2005110996) to give the title compound. LC-MS: 701.2 [(M+H)⁺]

10

Example 195

rac-[(4S*,5R*)-4,5-Bis-(4-chloro-phenyl)-2-(2-isopropoxy-4-methoxy-phenyl)-4-methyl-4,5-dihydro-imidazol-1-yl]-piperazin-1-yl-methanone

15

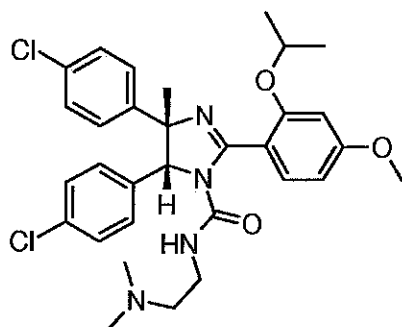


In a manner analogous to the method described in example 5, *rac*-(4S*,5R*)-4,5-bis-(4-chloro-phenyl)-2-(2-isopropoxy-4-methoxy-phenyl)-4-methyl-4,5-dihydro-imidazole-1-carbonyl chloride was reacted with piperazine (Aldrich) to give the title compound. LC-MS: 581.2 [(M+H)⁺]

20

Example 196

rac-(4S*,5R*)-4,5-Bis-(4-chloro-phenyl)-2-(2-isopropoxy-4-methoxy-phenyl)-4-methyl-4,5-dihydro-imidazole-1-carboxylic acid (2-dimethylamino-ethyl)-amide



5

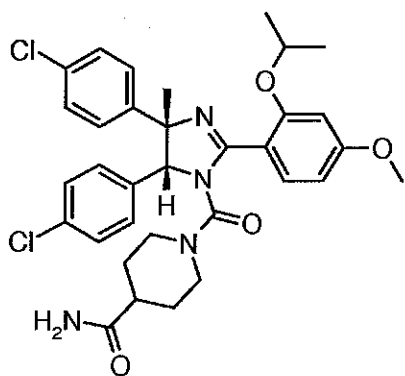
In a manner analogous to the method described in example 5, *rac*-(4S*,5R*)-4,5-bis-(4-chloro-phenyl)-2-(2-isopropoxy-4-methoxy-phenyl)-4-methyl-4,5-dihydro-imidazole-1-carbonyl chloride was reacted with N,N-dimethyl-1,2-ethanediamine (Aldrich) to give the title compound. LC-MS: 583.2 [(M+H)⁺]

10

Example 197

rac-1-[(4S*,5R*)-4,5-Bis-(4-chloro-phenyl)-2-(2-isopropoxy-4-methoxy-phenyl)-4-methyl-4,5-dihydro-imidazole-1-carbonyl]-piperidine-4-carboxylic acid amide

15

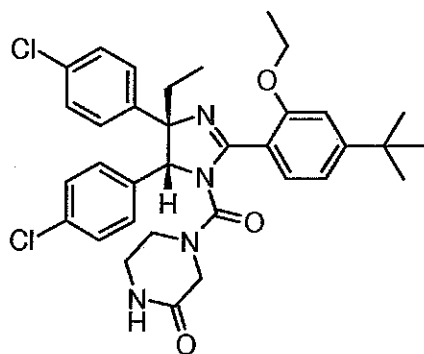


In a manner analogous to the method described in example 5, *rac*-(4S*,5R*)-4,5-bis-(4-chloro-phenyl)-2-(2-isopropoxy-4-methoxy-phenyl)-4-methyl-4,5-dihydro-imidazole-1-carbonyl chloride was reacted with 1-piperidin-4-yl-ethanone (Aldrich) to give the title compound. LC-MS: 623.3 [(M+H)⁺]

20

Example 198

rac-4-[(4*S**,5*R**)-2-(4-*tert*-Butyl-2-ethoxy-phenyl)-4,5-bis-(4-chloro-phenyl)-4-ethyl-4,5-dihydro-imidazole-1-carbonyl]-piperazin-2-one

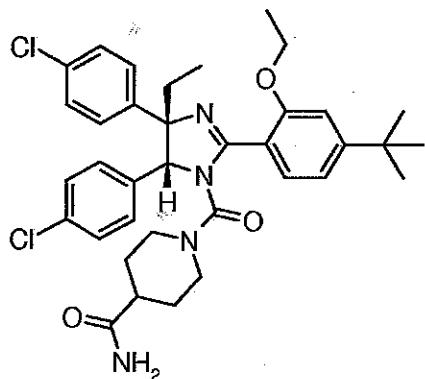


rac-(4*S**,5*R**)-2-(4-*tert*-butyl-2-ethoxy-phenyl)-4,5-bis-(4-chloro-phenyl)-4-ethyl-4,5-dihydro-1*H*-imidazole was prepared from *rac*-(1*R**,2*S**)-1,2-bis-(4-chloro-phenyl)-butane-1,2-diamine (prepared from 3,4-bis-aryl-1,2,5-thiadiazole-1,1-dioxide and ethylmagnesium bromide as described in example 170) and methyl 2-isopropoxy-4-methoxy-benzoate in the presence of trimethylaluminum using the procedure as described in example 2. It was then reacted with phosgene in the presence of triethylamine to give *rac*-(4*S**,5*R**)-2-(4-*tert*-butyl-2-ethoxy-phenyl)-4,5-bis-(4-chloro-phenyl)-4-ethyl-4,5-dihydro-imidazole-1-carbonyl chloride.

In a manner analogous to the method described in example 5, *rac*-(4*S**,5*R**)-2-(4-*tert*-butyl-2-ethoxy-phenyl)-4,5-bis-(4-chloro-phenyl)-4-ethyl-4,5-dihydro-imidazole-1-carbonyl chloride was reacted with 2-piperazinone (Avocado Organics) to give the title compound. LC-MS: 621.2 [(M+H)⁺]

Example 199

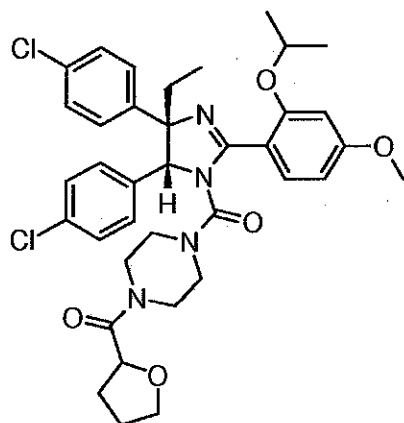
rac-1-[(4*S**,5*R**)-2-(4-*tert*-Butyl-2-ethoxy-phenyl)-4,5-bis-(4-chloro-phenyl)-4-ethyl-4,5-dihydro-imidazole-1-carbonyl]-piperidine-4-carboxylic acid amide



- In a manner analogous to the method described in example 5, *rac*-(4*S**,5*R**)-2-(4-*tert*-butyl-2-ethoxy-phenyl)-4,5-bis-(4-chloro-phenyl)-4-ethyl-4,5-dihydro-imidazole-1-carbonyl chloride was reacted with 1-piperidin-4-yl-ethanone (Aldrich) to give the title compound. LC-MS: 649.3 [(M+H)⁺]

Example 200

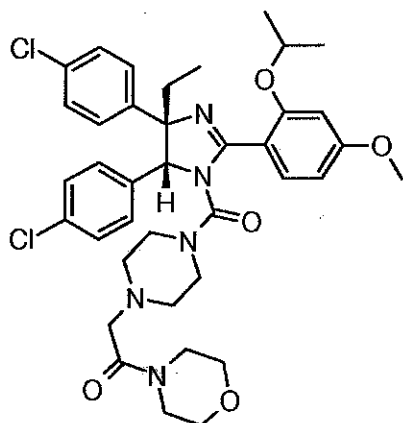
- rac*-[(4*S**,5*R**)-4,5-Bis-(4-chloro-phenyl)-4-ethyl-2-(2-isopropoxy-4-methoxy-phenyl)-4,5-dihydro-imidazol-1-yl]-[4-(tetrahydro-furan-2-carbonyl)-piperazin-1-yl]-methanone



- In a manner analogous to the method described in example 5, *rac*-(4*S**,5*R**)-4,5-bis-(4-chloro-phenyl)-4-ethyl-2-(2-isopropoxy-4-methoxy-phenyl)-4,5-dihydro-imidazole-1-carbonyl chloride was reacted with piperazin-1-yl-(tetrahydro-furan-2-yl)-methanone (Aldrich) to give the title compound. LC-MS: 693.3 [(M+H)⁺]

Example 201

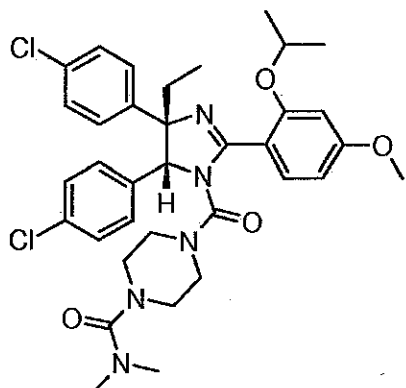
5 *rac*-2-[4-[(4S*,5R*)-4,5-Bis-(4-chloro-phenyl)-4-ethyl-2-(2-isopropoxy-4-methoxy-phenyl)-4,5-dihydro-imidazole-1-carbonyl]-piperazin-1-yl}-1-morpholin-4-yl-ethanone



In a manner analogous to the method described in example 5, *rac*-(4S*,5R*)-4,5-bis-(4-chloro-phenyl)-4-ethyl-2-(2-isopropoxy-4-methoxy-phenyl)-4,5-dihydro-10 imidazole-1-carbonyl chloride was reacted with 1-morpholin-4-yl-2-piperazin-1-yl-ethanone (Oakwood Products) to give the title compound. LC-MS: 722.3 [(M+H)⁺]

Example 202

15 *rac*-4-[(4S*,5R*)-4,5-Bis-(4-chloro-phenyl)-4-ethyl-2-(2-isopropoxy-4-methoxy-phenyl)-4,5-dihydro-imidazole-1-carbonyl]-piperazine-1-carboxylic acid dimethylamide



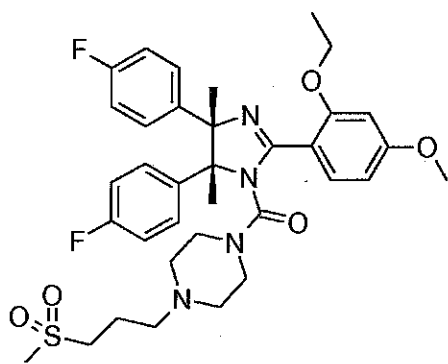
In a manner analogous to the method described in example 5, *rac*-(4S*,5R*)-4,5-bis-(4-chloro-phenyl)-4-ethyl-2-(2-isopropoxy-4-methoxy-phenyl)-4,5-dihydro-imidazole-1-carbonyl chloride was reacted with piperazine-1-carboxylic acid dimethylamide (Aldrich) to give the title compound. LC-MS: 666.3 [(M+H)⁺]

5

Example 203

[(4S,5R)-2-(4-*tert*-Butyl-2-ethoxy-phenyl)-4,5-bis-(4-fluoro-phenyl)-4,5-dimethyl-4,5-dihydro-imidazol-1-yl]-[4-(3-methanesulfonyl-propyl)-piperazin-1-yl]-methanone

10



meso-2,3-bis-(4-fluorophenyl)-2,3-butanediamine was prepared from 4,4'-difluorobenzil in an analogous manner as described in examples 169 and 170. It was then reacted with 2-ethoxy-benzoyl chloride using the procedure as described in example 2 (method 1) to give *rac*-(4S*, 5R*)-2-(4-*tert*-butyl-2-ethoxy-phenyl)-4,5-bis-(4-fluoro-phenyl)-4,5-dimethyl-4,5-dihydro-1H-imidazole.

15

20

rac-(4S*, 5R*)-2-(4-*tert*-Butyl-2-ethoxy-phenyl)-4,5-bis-(4-fluoro-phenyl)-4,5-dimethyl-4,5-dihydro-1H-imidazole was then reacted with phosgene in the presence of triethylamine to give *rac*-(4S*, 5R*)-2-(4-*tert*-butyl-2-ethoxy-phenyl)-4,5-bis-(4-fluoro-phenyl)-4,5-dimethyl-4,5-dihydro-imidazole-1-carbonyl chloride.

25

In a manner analogous to the method described in example 5, *rac*-(4S*, 5R*)-2-(4-*tert*-butyl-2-ethoxy-phenyl)-4,5-bis-(4-fluoro-phenyl)-4,5-dimethyl-4,5-dihydro-imidazole-1-carbonyl chloride was reacted with 1-(3-methanesulfonyl-propyl)-piperazine dihydrochloride (prepared as described in Fotouhi, N. *et al.* WO 2005110996) to give the title compound as a racemic mixture. The enantiomers were separated by supercritical fluid chromatography (Berger Instrument Multi-Gram II, Daicel ChiralPak OD-H 3 x 25 cm, 35 °C at 100 bar,

eluting with 30% methanol in carbon dioxide) gave the title compound. HR-MS (ES, m/z) calculated for $C_{38}H_{49}N_4O_4SF_2 [(M+H)^+]$ 695.3437, observed 695.3433.

Example 204

5

In Vitro Activity Assay

The ability of the compounds to inhibit the interaction between p53 and MDM2 proteins was measured by an HTRF (homogeneous time-resolved
10 fluorescence) assay in which recombinant GST-tagged MDM2 binds to a peptide that resembles the MDM2-interacting region of p53 (Lane *et al.*). Binding of GST-MDM2 protein and p53-peptide (biotinylated on its N-terminal end) is registered by the FRET (fluorescence resonance energy transfer) between Europium (Eu)-labeled anti-GST antibody and streptavidin-conjugated
15 Allophycocyanin (APC).

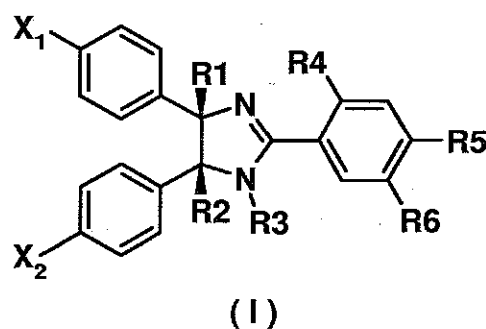
Test is performed in black flat-bottom 384-well plates (Costar) in a total volume of 40 μ L containing: 90 nM biotinylate peptide, 160 ng/mL GST-MDM2, 20 nM streptavidin-APC (PerkinElmerWallac), 2 nM Eu-labeled anti-GST-antibody
20 (PerkinElmerWallac), 0.2% bovine serum albumin (BSA), 1 mM dithiothreitol (DTT) and 20 mM Tris-borate saline (TBS) buffer as follows: Add 10 μ L of GST-MDM2 (640 ng/mL working solution) in reaction buffer to each well. Add 10 μ L diluted compounds (1:5 dilution in reaction buffer) to each well, mix by shaking. Add 20 μ L biotinylated p53 peptide (180 nM working solution) in
25 reaction buffer to each well and mix on shaker. Incubate at 37°C for 1 h. Add 20 μ L streptavidin-APC and Eu-anti-GST antibody mixture (6 nM Eu-anti-GST and 60 nM streptavidin-APC working solution) in TBS buffer with 0.2% BSA, shake at room temperature for 30 minutes and read using a TRF-capable plate reader at 665 and 615 nm (Victor 5, Perkin ElmerWallac). If not specified, the
30 reagents were purchased from Sigma Chemical Co.

IC₅₀s showing biological activity that applies to compounds of the subject matter of this invention ranges from about 1 nM to about 1000 nM. Specific data for some examples are as follows:

Example	IC ₅₀ (μM)
5	0.019
6	0.344
8	0.046
35	0.017
177	0.107
190	0.048

Claims:

1. A compound of the formula



wherein

X_1 and X_2 are halogen, acetylene, cyano, trifluoromethyl or nitro;

10 R^1 and R^2 are selected from the group consisting of -H, -CH₃, -CH₂CH₃, -CH₂OH and -CH₂OCH₃ with the proviso that R^1 and R^2 are not both hydrogen;

R^3 is -H or -C(=O)-R⁷;

15 and where R^6 is hydrogen then

R^4 is -OCH₃, -OCH₂CH₃, -OCH₂CH₂F, -OCH₂CH₂OCH₃, or -OCH(CH₃)₂;

R^5 is

-H

20 -halogen,

-CH₃,

-CF₃,

-OCH₃,

-C(CH₃)₂,

25 -cyclopropyl,

-cyano,

-C(CH₃)₃,

-C(CH₃)₂OR (where R is -H, -CH₃ or -CH₂CH₃),

- C(CH₃)₂CH-OR (where R is -H, -CH₃, -CH(CH₃)₂, -CH₂CH₂OH or -CH₂CH₂OCH₃),
- C(CH₃)₂CN,
- C(CH₃)₂COR (where R is -CH₃),
- 5 -C(CH₃)₂COOR (where R is -H, -CH₃, -CH₂CH₃ or -CH(CH₃)₂),
- C(CH₃)₂CONR^aR^b (where R^a is -H or -CH₃ and R^b = -H or -CH₃),
- SR (where R is -CH₃ or -CH₂CH₃), or
- SO₂R (where R is -CH₃, -CH₂CH₃, 1-pyrrolidine, -NH-*tert*-butyl or -N(CH₃)₂);

10 and where R⁶ is not hydrogen then

R⁴ is -OCH₃, -OCH₂CH₃, -OCH₂CH₂F, -OCH₂CH₂OCH₃, or -OCH(CH₃)₂;

R⁵ is hydrogen, -Cl, -OCH₃, *tert*-butyl or -N(CH₃)₂;

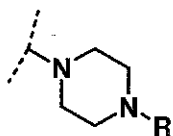
R⁶ is -Cl, cyclopropyl, -SO₂R (where R is -CH₃, -CH₂CH₃, 1-pyrrolidine, -NH-*tert*-butyl, -NH₂, or -N(CH₃)₂);

15

and R⁷ is selected from the group consisting of

- i) -CH₃, -CH(CH₃)₂, -CH₂CH(CH₃)₂, cyclopropyl, cyclobutyl, -CH₂CH₂Ph, 2-furanyl, phenyl, or phenyl substituted by chloro, -OCH₃ or cyano,
- 20 ii) 4-morpholinyl, 1-piperidinyl, 4-thiomorpholinyl, or 4-thiomorpholinyl-1,1-dioxide,
- iii) -NR^c₂ (wherein R^c is hydrogen, -CH₃, -CH₂CH₃, -CH₂CH₂OH, -CH₂CH₂OCH₃, or -CH₂CH(OH)CH₂OH),

25 iv) a substituted piperazine of the formula



wherein R is selected from the group consisting of

- 30 a) hydrogen,
- b) lower alkyl,
- c) -CH(CH₃)₂,

- d) $-\text{CH}(\text{CH}_2\text{CH}_3)_2$,
 e) cyclopentyl,
 f) $-\text{CH}_2\text{CH}(\text{OH})\text{CH}_3$,
 5 g) $-\text{CH}_2\text{CF}_3$,
 h) $-\text{CH}_2\text{CH}(\text{OH})\text{CF}_3$,
 i) $-\text{CH}_2\text{C}(\text{CH}_3)_2\text{OH}$,
 j) $-\text{CH}_2-[4\text{-N-methylpiperidinyl}]$,
- 10 k) $-\text{CH}_2\text{CH}_2\text{R}^d$ (wherein R^d is $-\text{OH}$, $-\text{OCH}_3$, $-\text{OCH}_2\text{CH}_2\text{OH}$, $-\text{OCH}_2\text{CH}_2\text{OCH}_3$, $-\text{CN}$, $-\text{CF}_3$, $-\text{SO}_2\text{CH}_3$, $-\text{SO}_2\text{NH}_2$, $-\text{SO}_2\text{N}(\text{CH}_3)_2$, $-\text{CONH}_2$, $-\text{CON}(\text{CH}_3)_2$, $-\text{NH}_2$, $-\text{NHCOCH}_3$, $-\text{NHSO}_2\text{CH}_3$, $-\text{N}(\text{CH}_3)_2$, $-\text{N}(\text{CH}_2\text{CH}_3)_2$, $-\text{N}(\text{CH}_2\text{CH}_2\text{CH}_3)_2$, 1-pyrrolidinyl, 1-piperidinyl, 4-morpholinyl, 2-isothiazolidinyl-1,1-dioxide, or 2-tetrahydrofuranyl),
- 15 l) $-\text{CH}_2\text{CH}_2\text{CH}_2\text{R}^e$ (wherein R^e is $-\text{OH}$, $-\text{OCH}_3$, $-\text{SO}_2\text{CH}_3$, $-\text{SO}_2\text{CH}_2\text{CH}_3$, $-\text{SO}_2\text{N}(\text{CH}_3)_2$, $-\text{CN}$, $-\text{N}(\text{CH}_3)_2$, $-\text{N}(\text{CH}_2\text{CH}_2\text{CH}_3)_2$, 1-imidazolyl, 1-pyrrolidinyl, 1-piperidinyl, 4-morpholinyl, $-\text{COOCH}_3$, $-\text{COOCH}_2\text{CH}_3$, $-\text{COOC}(\text{CH}_3)_3$, $-\text{CON}(\text{CH}_3)_2$, $-\text{CO-R}^f$ (wherein R^f is $-\text{CH}_3$, $-\text{CH}_2\text{CH}_3$, cyclopropyl, phenyl, 2-thienyl, 3-thienyl, 2-furanyl, 3-furanyl), $-\text{COCH}_2\text{-R}^g$ (wherein R^g is H , $-\text{NHCH}_2\text{CH}_2\text{OH}$,
 20 $-\text{NHCH}_2\text{CH}_2\text{OCH}_3$, $-\text{NHCH}_2\text{CH}_2\text{N}(\text{CH}_3)_2$, 1-piperidinyl, 1-(piperidinyl-4-methanol), 4-morpholinyl, or $-\text{N}(\text{CH}_3)-(3-(1\text{-methylpyrrolidinyl}))$),
- m) $-\text{CH}_2\text{-CO-R}^h$ (wherein R^h is $-\text{OCH}_3$, $-\text{OCH}_2\text{CH}_3$, $-\text{NH}_2$, $-\text{NHCH}_2\text{CH}(\text{CH}_3)_2$, $-\text{NHCH}_2\text{CF}_3$, $-\text{NH-cyclopropyl}$, $-\text{NH-tert-butyl}$, $-\text{NHCH}_2\text{CH}_2\text{CH}_2\text{OH}$, $-\text{N}(\text{CH}_3)_2$,
 25 $-\text{N}(\text{CH}_2\text{CH}_3)_2$, $-\text{N}(\text{CH}_2\text{CH}_2\text{OH})_2$, $-\text{N}(\text{CH}_2\text{CH}_2\text{OCH}_3)_2$, $-\text{N}(\text{CH}_3)\text{CH}_2\text{CH}_2\text{OH}$, $-\text{N}(\text{CH}_3)\text{CH}_2\text{CH}_2\text{OCH}_3$, $-\text{NHCH}_2\text{CH}_2\text{OCH}_3$, 1-pyrrolidinyl, 1-piperidinyl, 1-(piperidinyl-4-methanol), 1-(piperidinyl-3-carboxamide), 4-morpholinyl, 4-thiomorpholinyl, 4-thiomorpholinyl-1,1-dioxide, 1-piperazinyl, 1-(4-acetylpiperazinyl), 1-(3-oxopiperazinyl),
 30
- n) $-\text{SO}_2\text{R}^i$ (wherein R^i is $-\text{CH}_3$, $-\text{CH}_2\text{CH}_3$, $-\text{CH}(\text{CH}_3)_2$, phenyl, 4-methylphenyl, 4-propylphenyl, $-\text{CF}_3$, 2-thienyl, 3-thienyl, $-\text{NH}_2$, $-\text{NHCH}_3$, $-\text{N}(\text{CH}_3)_2$, $-\text{NHCH}_2\text{CH}_2\text{OCH}_3$, $-\text{N}(\text{CH}_2\text{CH}_2\text{OCH}_3)_2$, 1-pyrrolidinyl, 1-piperidinyl, 4-morpholinyl, 1-piperazyl-4-ethanol, 1-(4-acetylpiperazinyl), 1-(3-oxopiperazinyl)),

o) -COR^j (wherein R^j is -CH₃, -CH₂CH₃, -CH(CH₃)₂, 2-tetrahydrofuranyl, 2-thienyl, 3-thienyl, -NH₂, -NHCH₃, -N(CH₃)₂, 1-pyrrolidinyl, 1-piperidinyl, 4-morpholinyl, 1-piperazinyl-4-ethanol, 1-(4-acetylpiperazinyl), or 1-(3-oxopiperazinyl)),

5

p) 4-tetrahydro-2H-thiopyranyl-1,1-dioxide,

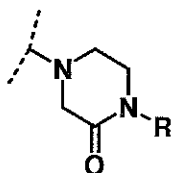
q) 4-piperidinyl-1-acetyl,

r) 4-piperidinyl-1-dimethylcarboxamide, and

s) 3-tetrahydro-thiophenyl-1,1-dioxide;

10

v) a substituted oxopiperazine of the formula

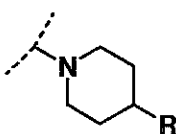


wherein R is -H, -CH₃, -CH₂CH₃, -CH₂CH₂CH₃, -CH₂CH₂OH, or -CH₂CH₂OCH₃;

15

and

vi) a substituted piperidine of the formula



20

wherein R is -H, -COOCH₃, -COOCH₂CH₃, -CONH₂, -OH, -CH₂OH, -CH₂CH₂OH, -CH₂-N(CH₂CH₃)₂, -CH₂-(1-piperazinyl), -CH₂-(1-(3-oxopiperazinyl)), -NH₂, -NHCOCH₃, -NHCOCH₂NH₂, -NHCOCH₂NHCH₃, -NHCOCH₂N(CH₃)₂, -NHCOCH₂N(CH₂CH₂OH)₂, -NHCOCH₂N(CH₂CH₂OCH₃)₂, -NHCOCH₂NHCH₂CH₂OH, -NHCOCH₂-(1-(4-acetylpiperazinyl)), -NHCOCH₂-(1-(3-oxopiperazinyl)), -NHCOCH₂-(1-piperidinecarboxamide), -NHCOCH₂-(N,N-diethyl-1-piperidinylcarboxamide), -NHCOCH₂-(1-(3-hydroxypiperidinyl)), -NHCOCH₂-(1-(piperidinyl-4-methanol)), -NHCON(CH₃)₂, -NHCSNHCH₃,

25

-NHCSNHPH, -NHCH₂CONH₂, 1-pyrrolidinyl, 1-piperidinyl, 1-(4-methylpiperazinyl), or 4-morpholinyl;

and the pharmaceutically acceptable salts and esters thereof.

5

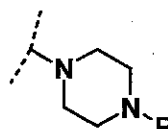
2. Compound of claim 1 wherein X₁ and X₂ are -Cl.

3. Compound of claim 2 wherein R³ is -C(=O)-R⁷.

10 4. Compound of claim 3 where R⁶ is hydrogen; R⁴ is -OCH₃, -OCH₂CH₃, or -OCH(CH₃)₂; and R⁵ is -C(CH₃)₃, -C(CH₃)₂OR (where R is -H or -CH₃), -C(CH₃)₂CH-OR (where R is -H or -CH₃), -C(CH₃)₂CN, -C(CH₃)₂COR (where R is -CH₃), -SO₂R (where R is -CH₃, 1-pyrrolidine, -NH-*tert*-butyl or -N(CH₃)₂).

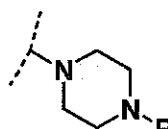
15 5. The compound of claim 3 where R⁴ is -OCH₃, -OCH₂CH₃, or -OCH(CH₃)₂; R⁵ is -Cl; and R⁶ is -SO₂R (where R is -CH₃, 1-pyrrolidine, -NH-*tert*-butyl, -NH₂, or -N(CH₃)₂).

20 6. The compound of claim 3 wherein R⁷ is -CHCOR^h.

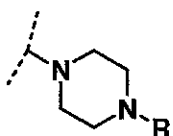


7. The compound of claim 6 wherein R^h is 4-morpholinyl, 1-pyrrolidinyl, 1-piperidinyl, -NH₂, or -N(CH₃)₂.

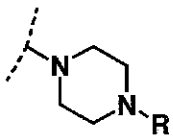
25 8. The compound of claim 3 wherein R⁷ is -CH₂CH₂CH₂R^e.



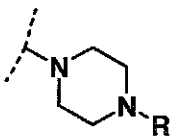
9. The compound of claim 8 wherein R^e is -SO₂CH₃ or -SO₂CH₂CH₃.

10. The compound of claim 3 wherein R^7 is  and wherein R is $-\text{CH}_2\text{CH}_2\text{R}^d$.

11. The compound of claim 10 wherein R^d is $-\text{SO}_2\text{CH}_3$, $-\text{NHSO}_2\text{CH}_3$,
5 $-\text{NHCOCH}_3$, or $-\text{CF}_3$.

12. The compound of claim 3 wherein R^7 is  and R is 4-tetrahydro-2H-thiopyran-1,1-dioxide.

13. The compound of claim 1, wherein
10 X_1 and X_2 are $-\text{Cl}$;
 R^3 is $-\text{C}(\text{O})-\text{R}^7$;
 R^4 is $-\text{OCH}_3$, $-\text{OCH}_2\text{CH}_3$, or $-\text{OCH}(\text{CH}_3)_2$;
 R^5 is $-\text{C}(\text{CH}_3)_3$, $-\text{C}(\text{CH}_3)_2\text{OR}$ (where R is $-\text{H}$ or $-\text{CH}_3$), $-\text{C}(\text{CH}_3)_2$
15 $\text{CH}-\text{OR}$ (where R is $-\text{H}$ or $-\text{CH}_3$), $-\text{C}(\text{CH}_3)_2\text{CN}$, $-\text{C}(\text{CH}_3)_2\text{COR}$ (where
R is $-\text{CH}_3$), $-\text{SO}_2\text{R}$ (where R is $-\text{CH}_3$, 1-pyrrolidine, $-\text{NH-tert-butyl}$ or
 $-\text{N}(\text{CH}_3)_2$);
 R^6 is hydrogen;

R^7 is  (wherein R is $-\text{CHCOR}^h$);
 R^h is 4-morpholinyl, 1-pyrrolidinyl, 1-piperidinyl, $-\text{NH}_2$, or $-\text{N}(\text{CH}_3)_2$;

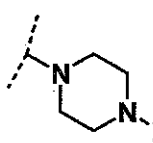
20 and

R^1 and R^2 have the meanings given in claim 1; and
pharmaceutically acceptable salts and esters thereof.

14. The compound of claim 1, wherein
25 X_1 and X_2 are $-\text{Cl}$;
 R^3 is $-\text{C}(\text{O})-\text{R}^7$;
 R^4 is $-\text{OCH}_3$, $-\text{OCH}_2\text{CH}_3$, or $-\text{OCH}(\text{CH}_3)_2$;

R^5 is $-C(CH_3)_3$, $-C(CH_3)_2OR$ (where R is $-H$ or $-CH_3$), $-C(CH_3)_2CH-OR$ (where R is $-H$ or $-CH_3$), $-C(CH_3)_2CN$, $-C(CH_3)_2COR$ (where R is $-CH_3$), $-SO_2R$ (where R is $-CH_3$, 1-pyrrolidine, $-NH$ -*tert*-butyl or $-N(CH_3)_2$);

5 R^6 is hydrogen;

R^7 is  (wherein R is $-CH_2CH_2CH_2R^e$);

R^e is $-SO_2CH_3$ or $-SO_2CH_2CH_3$; and

10 R^1 and R^2 have the meanings given in claim 1; and
pharmaceutically acceptable salts and esters thereof.

15. The compound of claim 1, wherein

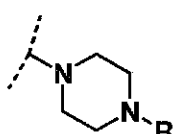
X_1 and X_2 are $-Cl$;

R^3 is $-C(O)-R^7$;

15 R^4 is $-OCH_3$, $-OCH_2CH_3$, or $-OCH(CH_3)_2$;

R^5 is $-C(CH_3)_3$, $-C(CH_3)_2OR$ (where R is $-H$ or $-CH_3$), $-C(CH_3)_2CH-OR$ (where R is $-H$ or $-CH_3$), $-C(CH_3)_2CN$, $-C(CH_3)_2COR$ (where R is $-CH_3$), $-SO_2R$ (where R is $-CH_3$, 1-pyrrolidine, $-NH$ -*tert*-butyl or $-N(CH_3)_2$);

20 R^6 is hydrogen;

R^7 is  (wherein R is $-CH_2CH_2R^d$);

R^d is $-SO_2CH_3$, $-NH SO_2CH_3$, $-NHCOCH_3$, or $-CF_3$; and

25 R^1 and R^2 have the meanings given in claim 1; and
pharmaceutically acceptable salts and esters thereof.

16. The compound of claim 1, wherein

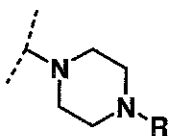
X_1 and X_2 are $-Cl$;

R^3 is $-C(O)-R^7$;

R^4 is $-OCH_3$, $-OCH_2CH_3$, or $-OCH(CH_3)_2$;

R^5 is $-Cl$;

R^6 is $-SO_2R$ (wherein R is $-CH_3$, 1-pyrrolidine, $-NH$ -*tert*-butyl, $-NH_2$, or $-N(CH_3)_2$);

5 R^7 is is  (wherein R is $-CHCOR^h$);

R^h is 4-morpholinyl, 1-pyrrolidinyl, 1-piperidinyl, $-NH_2$, or $-N(CH_3)_2$;

and

R^1 and R^2 have the meanings given in claim 1; and

pharmaceutically acceptable salts and esters thereof.

10

17. The compound of claim 1, wherein

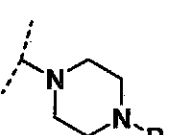
X_1 and X_2 are $-Cl$;

R^3 is $-C(O)-R^7$;

R^4 is $-OCH_3$, $-OCH_2CH_3$, or $-OCH(CH_3)_2$;

15 R^5 is $-Cl$;

R^6 is $-SO_2R$ (wherein R is $-CH_3$, 1-pyrrolidine, $-NH$ -*tert*-butyl, $-NH_2$, or $-N(CH_3)_2$);

R^7 is is  (wherein R is $-CH_2CH_2CH_2R^e$);

R^e is $-SO_2CH_3$ or $-SO_2CH_2CH_3$; and

20

R^1 and R^2 have the meanings given in claim 1; and

pharmaceutically acceptable salts and esters thereof.

18. The compound of claim 1, wherein

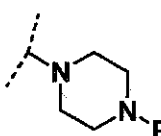
25 X_1 and X_2 are $-Cl$;

R^3 is $-C(O)-R^7$;

R^4 is $-OCH_3$, $-OCH_2CH_3$, or $-OCH(CH_3)_2$;

R^5 is $-Cl$;

R^6 is $-\text{SO}_2\text{R}$ (wherein R is $-\text{CH}_3$, 1-pyrrolidine, $-\text{NH-tert-butyl}$, $-\text{NH}_2$, or $-\text{N}(\text{CH}_3)_2$);

R^7 is  (wherein R is $-\text{CH}_2\text{CH}_2\text{R}^d$);

R^d is $-\text{SO}_2\text{CH}_3$, $-\text{NHSO}_2\text{CH}_3$, $-\text{NHCOCH}_3$, or $-\text{CF}_3$; and

5

R^1 and R^2 have the meanings given in claim 1; and
pharmaceutically acceptable salts and esters thereof.

19. A compound of claim 1 selected from the group consisting of:

- 10 *rac*-(4S*,5R*)-4,5-Bis(4-chlorophenyl)-2-(4-(*tert*-butyl)-2-ethoxy-phenyl)-4,5-dimethyl-4,5-dihydro-1H-imidazole,
- (4S, 5R)-4-[[4-[[4,5-Bis(4-chlorophenyl)-2-[4-(*tert*-butyl)-2-ethoxy-phenyl]-4,5-dimethyl-4,5-dihydro-1H-imidazol-1-yl]carbonyl]-1-piperazinyl]acetyl]-morpholine,
- (4S, 5R)- 4-[[4-[[4,5-bis(4-chlorophenyl)-2-[4-(*tert*-butyl)-2-ethoxy-phenyl]-4,5-
- 15 dimethyl-4,5-dihydro-1H-imidazol-1-yl]carbonyl]-1-piperidine,
- (4S, 5R)- 1-[[4-[[4,5-bis(4-chlorophenyl)-2-[4-(*tert*-butyl)-2-ethoxy-phenyl]-4,5-dimethyl-4,5-dihydro-1H-imidazol-1-yl]]-carbonyl]- 4-[3-(methylsulfonyl)propyl]-piperazine,
- (4S, 5R)- 1-[[4-[[4,5-bis(4-chlorophenyl)-2-[4-(*tert*-butyl)-2-ethoxy-phenyl]-4,5-
- 20 dimethyl-4,5-dihydro-1H-imidazol-1-yl]]-carbonyl]- 4-[3,3,3-trifluoropropyl]-piperazine,
- 2-{4-[(4S,5R)-2-(4-*tert*-Butyl-2-ethoxy-phenyl)-4,5-bis-(4-chloro-phenyl)-4,5-dimethyl-4,5-dihydro-imidazole-1-carbonyl]-piperazin-1-yl}-acetamide,
- 2-{4-[(4S,5R)-2-(4-*tert*-Butyl-2-ethoxy-phenyl)-4,5-bis-(4-chloro-phenyl)-4,5-
- 25 dimethyl-4,5-dihydro-imidazole-1-carbonyl]-piperazin-1-yl}-1-pyrrolidin-1-yl-ethanone and
- N-(2-{4-[(4S,5R)-2-(4-*tert*-Butyl-2-ethoxy-phenyl)-4,5-bis-(4-chloro-phenyl)-4,5-dimethyl-4,5-dihydro-imidazole-1-carbonyl]-piperazin-1-yl}-ethyl)-acetamide.

20. A compound of claim 1 selected from the group consisting of
- N-(2-{4-[(4S,5R)-2-(4-*tert*-Butyl-2-ethoxy-phenyl)-4,5-bis-(4-chloro-phenyl)-4,5-dimethyl-4,5-dihydro-imidazole-1-carbonyl]-piperazin-1-yl}-ethyl)-methanesulfonamide,
- 5 [(4S,5R)-2-(4-*tert*-Butyl-2-ethoxy-phenyl)-4,5-bis-(4-chloro-phenyl)-4,5-dimethyl-4,5-dihydro-imidazol-1-yl]-[4-(2-hydroxy-ethyl)-piperazin-1-yl]-methanone,
- (S)-4-[(4S,5R)-2-(4-*tert*-Butyl-2-ethoxy-phenyl)-4,5-bis-(4-chloro-phenyl)-4,5-dimethyl-4,5-dihydro-imidazole-1-carbonyl]-1-methyl-piperazine-2-carboxylic acid methyl ester,
- 10 5-[(4S,5R)-4,5-Bis-(4-chloro-phenyl)-1-[4-(3-methanesulfonyl-propyl)-piperazine-1-carbonyl]-4,5-dimethyl-4,5-dihydro-1H-imidazol-2-yl]-2-*tert*-butyl-4-ethoxy-N,N-dimethyl-benzenesulfonamide,
- rac*-2-{4-[(4S*,5R*)-4,5-Bis-(4-chloro-phenyl)-4,5-dimethyl-4,5-dihydro-1H-imidazol-2-yl]-3-ethoxy-phenyl}-2-methyl-propionitrile,
- 15 2-(4-{(4S,5R)-4,5-Bis-(4-chloro-phenyl)-1-[4-(3-methanesulfonyl-propyl)-piperazine-1-carbonyl]-4,5-dimethyl-4,5-dihydro-1H-imidazol-2-yl}-3-ethoxy-phenyl)-2-methyl-propionitrile,
- N-[2-(4-{(4S,5R)-4,5-Bis-(4-chloro-phenyl)-2-[4-(cyano-dimethyl-methyl)-2-ethoxy-phenyl]-4,5-dimethyl-4,5-dihydro-imidazole-1-carbonyl]-piperazin-1-yl)-ethyl]-methanesulfonamide,
- 20 N-[2-(4-{(4S,5R)-4,5-Bis-(4-chloro-phenyl)-2-[4-(cyano-dimethyl-methyl)-2-ethoxy-phenyl]-4,5-dimethyl-4,5-dihydro-imidazole-1-carbonyl]-piperazin-1-yl)-ethyl]-acetamide and
- 25 2-(4-{(4S,5R)-4,5-Bis-(4-chloro-phenyl)-1-[4-(2-hydroxy-ethyl)-piperazine-1-carbonyl]-4,5-dimethyl-4,5-dihydro-1H-imidazol-2-yl}-3-ethoxy-phenyl)-2-methyl-propionitrile.

21. A compound of claim 1 selected from the group consisting of

2-(4-((4S,5R)-4,5-Bis-(4-chloro-phenyl)-1-[4-(1,1-dioxo-tetrahydro-2H-thiopyran-4-yl)-piperazine-1-carbonyl]-4,5-dimethyl-4,5-dihydro-1H-imidazol-2-yl)-3-ethoxy-phenyl)-2-methyl-propionitrile,

2-(4-((4S,5R)-4,5-Bis-(4-chloro-phenyl)-2-[4-(cyano-dimethyl-methyl)-2-ethoxy-phenyl]-4,5-dimethyl-4,5-dihydro-imidazole-1-carbonyl]-piperazin-1-yl)-acetamide,

2-[4-((4S,5R)-4,5-Bis-(4-chloro-phenyl)-1-[4-[2-(1,1-dioxo-isothiazolidin-2-yl)-ethyl]-piperazine-1-carbonyl]-4,5-dimethyl-4,5-dihydro-1H-imidazol-2-yl)-3-ethoxy-phenyl]-2-methyl-propionitrile,

2-(4-((4S,5R)-4,5-Bis-(4-chloro-phenyl)-4,5-dimethyl-1-[4-(2-oxo-2-pyrrolidin-1-yl-ethyl)-piperazine-1-carbonyl]-4,5-dihydro-1H-imidazol-2-yl)-3-ethoxy-phenyl)-2-methyl-propionitrile,

2-{4-[(4S,5R)-1-[4-(1-Acetyl-piperidin-4-yl)-piperazine-1-carbonyl]-4,5-bis-(4-chloro-phenyl)-4,5-dimethyl-4,5-dihydro-1H-imidazol-2-yl]-3-ethoxy-phenyl}-2-methyl-propionitrile,

4-(4-((4S,5R)-4,5-Bis-(4-chloro-phenyl)-2-[4-(cyano-dimethyl-methyl)-2-ethoxy-phenyl]-4,5-dimethyl-4,5-dihydro-imidazole-1-carbonyl]-piperazin-1-yl)-piperidine-1-carboxylic acid isopropylamide,

rac-(4S*,5R*)-4,5-Bis-(4-chloro-phenyl)-2-[2-ethoxy-4-(pyrrolidine-1-sulfonyl)-phenyl]-4,5-dimethyl-4,5-dihydro-1H-imidazole and

rac-(4S*,5R*)-4-[(4,5-Bis-(4-chloro-phenyl)-4,5-dimethyl-4,5-dihydro-1H-imidazol-2-yl]-N-*tert*-butyl-3-ethoxy-benzenesulfonamide..

22. A compound of claim 1 selected from the group consisting of

{(4S,5R)-4,5-Bis-(4-chloro-phenyl)-2-[2-ethoxy-4-(pyrrolidine-1-sulfonyl)-phenyl]-4,5-dimethyl-4,5-dihydro-imidazol-1-yl}-[4-(3-methanesulfonyl-propyl)-piperazin-1-yl]-methanone,

2-(4-((4S,5R)-4,5-Bis-(4-chloro-phenyl)-2-[2-ethoxy-4-(pyrrolidine-1-sulfonyl)-phenyl]-4,5-dimethyl-4,5-dihydro-imidazole-1-carbonyl)-piperazin-1-yl)-acetamide,

5 2-(4-((4S,5R)-4,5-Bis-(4-chloro-phenyl)-2-[2-ethoxy-4-(pyrrolidine-1-sulfonyl)-phenyl]-4,5-dimethyl-4,5-dihydro-imidazole-1-carbonyl)-piperazin-1-yl)-1-pyrrolidin-1-yl-ethanone,

N-[2-(4-((4S,5R)-4,5-Bis-(4-chloro-phenyl)-2-[2-ethoxy-4-(pyrrolidine-1-sulfonyl)-phenyl]-4,5-dimethyl-4,5-dihydro-imidazole-1-carbonyl)-piperazin-1-yl)-ethyl]-methanesulfonamide,

10 N-[2-(4-((4S,5R)-4,5-Bis-(4-chloro-phenyl)-2-[2-ethoxy-4-(pyrrolidine-1-sulfonyl)-phenyl]-4,5-dimethyl-4,5-dihydro-imidazole-1-carbonyl)-piperazin-1-yl)-ethyl]-acetamide,

15 {(4S,5R)-4,5-Bis-(4-chloro-phenyl)-2-[2-ethoxy-4-(pyrrolidine-1-sulfonyl)-phenyl]-4,5-dimethyl-4,5-dihydro-imidazol-1-yl}-[4-(2-hydroxy-ethyl)-piperazin-1-yl]-methanone,

4-((4S,5R)-4,5-Bis-(4-chloro-phenyl)-1-[4-(3-methanesulfonyl-propyl)-piperazine-1-carbonyl]-4,5-dimethyl-4,5-dihydro-1H-imidazol-2-yl)-N-*tert*-butyl-3-ethoxy-benzenesulfonamide,

20 2-{4-[(4S,5R)-2-(4-*tert*-Butylsulfamoyl-2-ethoxy-phenyl)-4,5-bis-(4-chloro-phenyl)-4,5-dimethyl-4,5-dihydro-imidazole-1-carbonyl]-piperazin-1-yl}-acetamide ,

rac-(4S*,5R*)-5-[4,5-Bis-(4-chlorophenyl)-4,5-dimethyl-4,5-dihydro-1H-imidazol-2-yl]-N-*tert*-butyl-2-chloro-4-ethoxybenzenesulfonamide and

25 5-((4S,5R)-4,5-Bis-(4-chloro-phenyl)-1-[4-(3-methanesulfonyl-propyl)-piperazine-1-carbonyl]-4,5-dimethyl-4,5-dihydro-1H-imidazol-2-yl)-N-*tert*-butyl-2-chloro-4-ethoxy-benzenesulfonamide.

23. A compound of claim 1 selected from the group consisting of

5-((4S,5R)-4,5-Bis-(4-chlorophenyl)-1-[4-(2-methanesulfonylaminoethyl)piperazine-1-carbonyl]-4,5-dimethyl-4,5-dihydro-1H-imidazol-2-yl)-N-*tert*-butyl-2-chloro-4-ethoxybenzenesulfonamide,

30

N-[(4S,5R)-2-{4-[2-(5-*tert*-Butylsulfamoyl)-4-chloro-2-ethoxyphenyl]-4,5-bis-(4-chlorophenyl)-4,5-dimethyl-4,5-dihydroimidazole-1-carbonyl]-piperazin-1-yl}ethyl)acetamide,

5 5-[(4S,5R)-4,5-Bis-(4-chlorophenyl)-1-[4-(2-hydroxyethyl)piperazine-1-carbonyl]-4,5-dimethyl-4,5-dihydro-1H-imidazol-2-yl]-N-*tert*-butyl-2-chloro-4-ethoxybenzenesulfonamide,

5-[(4S,5R)-4,5-Bis-(4-chlorophenyl)-4,5-dimethyl-1-[4-(2-oxo-2-pyrrolidin-1-yl-ethyl)-piperazine-1-carbonyl]-4,5-dihydro-1H-imidazol-2-yl]-N-*tert*-butyl-2-chloro-4-ethoxybenzenesulfonamide,

10 2-{4-[(4S,5R)-2-(5-*tert*-Butylsulfamoyl)-4-chloro-2-ethoxyphenyl]-4,5-bis-(4-chlorophenyl)-4,5-dimethyl-4,5-dihydroimidazole-1-carbonyl]-piperazin-1-yl}-acetamide,

(S)-4-[(4S,5R)-2-(5-*tert*-Butylsulfamoyl)-4-chloro-2-ethoxyphenyl]-4,5-bis-(4-chlorophenyl)-4,5-dimethyl-4,5-dihydroimidazole-1-carbonyl]-1-methylpiperazine-15 2-carboxylic acid methyl ester,

rac-(4S*,5R*)-2-[4-Chloro-2-ethoxy-5-(pyrrolidine-1-sulfonyl)phenyl]-4,5-bis-(4-chlorophenyl)-4,5-dimethyl-4,5-dihydro-1H-imidazole,

5-[(4S,5R)-2-[4-Chloro-2-ethoxy-5-(pyrrolidine-1-sulfonyl)phenyl]-4,5-bis-(4-chlorophenyl)-4,5-dimethyl-4,5-dihydroimidazol-1-yl]-[4-(3-methanesulfonylpropyl)-piperazin-1-yl]methanone and

rac-(4S*,5R*)-4,5-Bis-(4-chlorophenyl)-2-[2-ethoxy-4-methoxy-5-(pyrrolidine-1-sulfonyl)phenyl]-4,5-dimethyl-4,5-dihydro-1H-imidazole.

24. A compound of claim 1 selected from the group consisting of

25. {(4S,5R)-4,5-Bis-(4-chlorophenyl)-2-[2-ethoxy-4-methoxy-5-(pyrrolidine-1-sulfonyl)-phenyl]-4,5-dimethyl-4,5-dihydroimidazol-1-yl}-[4-(3-methanesulfonylpropyl)-piperazin-1-yl]methanone,

rac-(4S*,5R*)-2-(4-Chloro-2-ethoxy-5-methanesulfonylphenyl)-4,5-bis-(4-chlorophenyl)-4,5-dimethyl-4,5-dihydro-1H-imidazole,

[(4S,5R)-2-(4-Chloro-2-ethoxy-5-methanesulfonyl-phenyl)-4,5-bis-(4-chlorophenyl)-4,5-dimethyl-4,5-dihydroimidazol-1-yl]-[4-(3-methanesulfonylpropyl)-piperazin-1-yl]methanone,

5 *rac*-(4S*,5R*)-4,5-Bis-(4-chlorophenyl)-2-[2-ethoxy-5-(pyrrolidine-1-sulfonyl)phenyl]-4,5-dimethyl-4,5-dihydro-1H-imidazole,

{(4S,5R)-4,5-Bis-(4-chlorophenyl)-2-[2-ethoxy-5-(pyrrolidine-1-sulfonyl)phenyl]-4,5-dimethyl-4,5-dihydroimidazol-1-yl}-[4-(3-methanesulfonylpropyl)-piperazin-1-yl]methanone,

10 *rac*-4-[(4S*,5R*)-4,5-Bis-(4-chloro-phenyl)-4,5-dimethyl-4,5-dihydro-1H-imidazol-2-yl]-3-ethoxy-benzonitrile and

4-[(4S,5R)-4,5-Bis-(4-chlorophenyl)-1-[4-(3-methanesulfonylpropyl)-piperazine-1-carbonyl]-4,5-dimethyl-4,5-dihydro-1H-imidazol-2-yl]-3-ethoxybenzonitrile.

25. A compound of claim 1 selected from the group consisting of

15 [(4S,5R)-2-(4-*tert*-Butyl-2-ethoxy-phenyl)-4,5-bis-(4-chloro-phenyl)-4,5-dimethyl-4,5-dihydro-imidazol-1-yl]-piperazin-1-yl-methanone,

1-{4-[(4S,5R)-2-(4-*tert*-Butyl-2-ethoxy-phenyl)-4,5-bis-(4-chloro-phenyl)-4,5-dimethyl-4,5-dihydro-imidazole-1-carbonyl]-piperazin-1-yl}-ethanone ,

20 *N-tert*-Butyl-2-{4-[(4S,5R)-2-(4-*tert*-butyl-2-ethoxy-phenyl)-4,5-bis-(4-chloro-phenyl)-4,5-dimethyl-4,5-dihydro-imidazole-1-carbonyl]-piperazin-1-yl}-acetamide ,

rac-(4S*,5R*)-2-(4-Bromo-2-ethoxy-phenyl)-4,5-bis-(4-chloro-phenyl)-4,5-dimethyl-4,5-dihydro-1H-imidazole,

25 *rac*-(4S*,5R*)-2-(4-Bromo-2-ethoxy-phenyl)-4,5-bis-(4-chloro-phenyl)-4,5-dimethyl-4,5-dihydro-imidazol-1-yl]-[4-(3-methanesulfonyl-propyl)-piperazin-1-yl]-methanone,

rac-2-{4-[(4S*,5R*)-4,5-Bis-(4-chloro-phenyl)-4,5-dimethyl-4,5-dihydro-1H-imidazol-2-yl]-3-ethoxy-phenyl}-propan-2-ol and

30 [(4S,5R)-4,5-Bis-(4-chloro-phenyl)-2-(2-ethoxy-phenyl)-4,5-dimethyl-4,5-dihydro-imidazol-1-yl]-[4-(3-methanesulfonyl-propyl)-piperazin-1-yl]-methanone .

26. A compound of claim 1 selected from the group consisting of
- 2-{4-[(4S,5R)-4,5-Bis-(4-chloro-phenyl)-2-(2-ethoxy-phenyl)-4,5-dimethyl-4,5-dihydro-imidazole-1-carbonyl]-piperazin-1-yl}-acetamide,
- 5 {(4S,5R)-4,5-Bis-(4-chloro-phenyl)-2-[2-ethoxy-4-(1-hydroxy-1-methyl-ethyl)-phenyl]-4,5-dimethyl-4,5-dihydro-imidazol-1-yl}-[4-(3-methanesulfonyl-propyl)-piperazin-1-yl]-methanone,
- 2-(4-{(4S,5R)-4,5-Bis-(4-chloro-phenyl)-2-[2-ethoxy-4-(1-hydroxy-1-methyl-ethyl)-phenyl]-4,5-dimethyl-4,5-dihydro-imidazole-1-carbonyl}-piperazin-1-yl)-acetamide,
- 10 {(4S,5R)-4,5-Bis-(4-chloro-phenyl)-2-[2-ethoxy-4-(1-hydroxy-1-methyl-ethyl)-phenyl]-4,5-dimethyl-4,5-dihydro-imidazol-1-yl}-[4-(2-hydroxy-ethyl)-piperazin-1-yl]-methanone ,
- 2-(4-{(4S,5R)-4,5-Bis-(4-chloro-phenyl)-2-[2-ethoxy-4-(1-hydroxy-1-methyl-ethyl)-phenyl]-4,5-dimethyl-4,5-dihydro-imidazole-1-carbonyl}-piperazin-1-yl)-1-pyrrolidin-1-yl-ethanone,
- 15 N-[2-(4-{(4S,5R)-4,5-Bis-(4-chloro-phenyl)-2-[2-ethoxy-4-(1-hydroxy-1-methyl-ethyl)-phenyl]-4,5-dimethyl-4,5-dihydro-imidazole-1-carbonyl}-piperazin-1-yl)-ethyl]-acetamide,
- 20 N-[2-(4-{(4S,5R)-4,5-Bis-(4-chloro-phenyl)-2-[2-ethoxy-4-(1-hydroxy-1-methyl-ethyl)-phenyl]-4,5-dimethyl-4,5-dihydro-imidazole-1-carbonyl}-piperazin-1-yl)-ethyl]-methanesulfonamide,
- {(4S,5R)-4,5-Bis-(4-chloro-phenyl)-2-[2-ethoxy-4-(1-hydroxy-1-methyl-ethyl)-phenyl]-4,5-dimethyl-4,5-dihydro-imidazol-1-yl}-[4-(1,1-dioxo-tetrahydro-2H-thiopyran-4-yl)-piperazin-1-yl]-methanone,
- 25 *rac*-(4S*,5R*)-4,5-Bis-(4-chloro-phenyl)-2-(2-isopropoxy-4-methoxy-phenyl)-4,5-dimethyl-4,5-dihydro-1*H*-imidazole.

27. A compound of claim 1 selected from the group consisting of

rac-(4S*,5R*)-4,5-Bis-(4-chloro-phenyl)-2-(2-isopropoxy-4-methoxy-phenyl)-4,5-dimethyl-4,5-dihydro-imidazol-1-yl]-[4-(3-methanesulfonyl-propyl)-piperazin-1-yl]-methanone,

rac-2-{4-[(4S*,5R*)-4,5-Bis-(4-chloro-phenyl)-2-(2-isopropoxy-4-methoxy-phenyl)-4,5-dimethyl-4,5-dihydro-imidazole-1-carbonyl]-piperazin-1-yl}-acetamide,

rac-2-{4-[(4S*,5R*)-4,5-Bis-(4-chloro-phenyl)-2-(2-isopropoxy-4-methoxy-phenyl)-4,5-dimethyl-4,5-dihydro-imidazole-1-carbonyl]-piperazin-1-yl}-1-morpholin-4-yl-ethanone,

rac-4-[(4S*,5R*)-4,5-Bis-(4-chloro-phenyl)-2-(2-isopropoxy-4-methoxy-phenyl)-4,5-dimethyl-4,5-dihydro-imidazole-1-carbonyl]-piperazin-2-one,

rac-[(4S*,5R*)-4,5-Bis-(4-chloro-phenyl)-2-(2-isopropoxy-4-methoxy-phenyl)-4,5-dimethyl-4,5-dihydro-imidazol-1-yl]-[4-(2-methanesulfonyl-ethyl)-piperazin-1-yl]-methanone,

rac-(4S*,5R*)-4,5-Bis-(4-chloro-phenyl)-2-[2-ethoxy-4-(1-methoxy-1-methyl-ethyl)-phenyl]-4,5-dimethyl-4,5-dihydro-1*H*-imidazole,

2-(4-{(4S,5R)-4,5-Bis-(4-chloro-phenyl)-2-[2-ethoxy-4-(1-methoxy-1-methyl-ethyl)-phenyl]-4,5-dimethyl-4,5-dihydro-imidazole-1-carbonyl}-piperazin-1-yl)-acetamide,

{*rac*-(4S*,5R*)-4,5-Bis-(4-chloro-phenyl)-2-[2-ethoxy-4-(1-methoxy-1-methyl-ethyl)-phenyl]-4,5-dimethyl-4,5-dihydro-imidazol-1-yl}-[4-(3-methanesulfonyl-propyl)-piperazin-1-yl]-methanone and

{(4S,5R)-4,5-Bis-(4-chloro-phenyl)-2-[2-ethoxy-4-(1-methoxy-1-methyl-ethyl)-phenyl]-4,5-dimethyl-4,5-dihydro-imidazol-1-yl}-[4-(1,1-dioxo-tetrahydro-2*H*-thiopyran-4-yl)-piperazin-1-yl]-methanone.

28. A compound of claim 1 selected from the group consisting of

rac-1-[(4S*,5R*)-2-(4-*tert*-Butyl-2-ethoxy-phenyl)-4,5-bis-(4-chloro-phenyl)-4,5-dimethyl-4,5-dihydro-imidazol-1-yl]-ethanone,

5 1-[(4S,5R)-2-(4-*tert*-Butyl-2-ethoxy-phenyl)-4,5-bis-(4-chloro-phenyl)-4,5-dimethyl-4,5-dihydro-imidazol-1-yl]-2-methyl-propan-1-one,

[(4S,5R)-2-(4-*tert*-Butyl-2-ethoxy-phenyl)-4,5-bis-(4-chloro-phenyl)-4,5-dimethyl-4,5-dihydro-imidazol-1-yl]-cyclopropyl-methanone,

10 [(4S,5R)-2-(4-*tert*-Butyl-2-ethoxy-phenyl)-4,5-bis-(4-chloro-phenyl)-4,5-dimethyl-4,5-dihydro-imidazol-1-yl]-cyclobutyl-methanone,

1-[(4S,5R)-2-(4-*tert*-Butyl-2-ethoxy-phenyl)-4,5-bis-(4-chloro-phenyl)-4,5-dimethyl-4,5-dihydro-imidazol-1-yl]-3-methyl-butan-1-one,

1-[(4S,5R)-2-(4-*tert*-Butyl-2-ethoxy-phenyl)-4,5-bis-(4-chloro-phenyl)-4,5-dimethyl-4,5-dihydro-imidazol-1-yl]-3-phenyl-propan-1-one,

15 4-[(4S,5R)-2-(4-*tert*-Butyl-2-ethoxy-phenyl)-4,5-bis-(4-chloro-phenyl)-4,5-dimethyl-4,5-dihydro-imidazole-1-carbonyl]-benzonitrile,

[(4S,5R)-2-(4-*tert*-Butyl-2-ethoxy-phenyl)-4,5-bis-(4-chloro-phenyl)-4,5-dimethyl-4,5-dihydro-imidazol-1-yl]-furan-2-yl-methanone,

20 [(4S,5R)-2-(4-*tert*-Butyl-2-ethoxy-phenyl)-4,5-bis-(4-chloro-phenyl)-4,5-dimethyl-4,5-dihydro-imidazol-1-yl]-phenyl-methanone and

rac-[(4S*,5R*)-2-(4-*tert*-Butyl-2-ethoxy-phenyl)-4,5-bis-(4-chloro-phenyl)-4,5-dimethyl-4,5-dihydro-imidazol-1-yl]-(4-methoxy-phenyl)-methanone.

29. A compound of claim 1 selected from the group consisting of

25 *rac*-[(4S*,5R*)-2-(4-*tert*-Butyl-2-ethoxy-phenyl)-4,5-bis-(4-chloro-phenyl)-4,5-dimethyl-4,5-dihydro-imidazol-1-yl]-(4-chloro-phenyl)-methanone,

rac-(4S*,5R*)-2-(4-*tert*-Butyl-5-chloro-2-ethoxy-phenyl)-4,5-bis-(4-chloro-phenyl)-4,5-dimethyl-4,5-dihydro-1*H*-imidazole,

[(4S,5R)-2-(4-*tert*-Butyl-5-chloro-2-ethoxy-phenyl)-4,5-bis-(4-chloro-phenyl)-4,5-dimethyl-4,5-dihydro-imidazol-1-yl]-[4-(3-methanesulfonyl-propyl)-piperazin-1-yl]-methanone,

2-{4-[(4S,5R)-2-(4-*tert*-Butyl-5-chloro-2-ethoxy-phenyl)-4,5-bis-(4-chloro-phenyl)-4,5-dimethyl-4,5-dihydro-imidazole-1-carbonyl]-piperazin-1-yl}-acetamide,

rac-(2-{4-[4S*,5R*]-2-(4-*tert*-Butyl-5-chloro-2-ethoxy-phenyl)-4,5-bis-(4-chloro-phenyl)-4,5-dimethyl-4,5-dihydro-imidazole-1-carbonyl]-piperazin-1-yl}-1-morpholin-4-yl)-ethanone,

rac-[(4S*,5R*)-2-(4-*tert*-Butyl-5-chloro-2-ethoxy-phenyl)-4,5-bis-(4-chloro-phenyl)-4,5-dimethyl-4,5-dihydro-imidazol-1-yl]-(4-dimethylamino-piperidin-1-yl)-methanone,

rac-[(4S*,5R*)-2-(4-*tert*-Butyl-5-chloro-2-ethoxy-phenyl)-4,5-bis-(4-chloro-phenyl)-4,5-dimethyl-4,5-dihydro-imidazol-1-yl]-(4-pyrrolidin-1-yl-piperidin-1-yl)-methanone,

rac-[1,4']Bipiperidiny-1'-yl-[(4S*,5R*)-2-(4-*tert*-butyl-5-chloro-2-ethoxy-phenyl)-4,5-bis-(4-chloro-phenyl)-4,5-dimethyl-4,5-dihydro-imidazol-1-yl]-methanone and *rac*-{1-[(4S*,5R*)-2-(4-*tert*-Butyl-5-chloro-2-ethoxy-phenyl)-4,5-bis-(4-chloro-phenyl)-4,5-dimethyl-4,5-dihydro-imidazole-1-carbonyl]-piperidin-4-yl}-carbamic acid *tert*-butyl ester.

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30. A compound of claim 1 selected from the group consisting of

rac-(4S*,5R*)-4,5-Bis-(4-chloro-phenyl)-2-(2-ethoxy-4-trifluoromethyl-phenyl)-4,5-dimethyl-4,5-dihydro-1*H*-imidazole,

rac-4-[(4S*,5R*)-4,5-Bis-(4-chloro-phenyl)-2-(2-ethoxy-4-trifluoromethyl-phenyl)-4,5-dimethyl-4,5-dihydro-imidazole-1-carbonyl]-piperazin-2-one,

rac-1-{4-[(4S*,5R*)-4,5-Bis-(4-chloro-phenyl)-2-(2-ethoxy-4-trifluoromethyl-phenyl)-4,5-dimethyl-4,5-dihydro-imidazole-1-carbonyl]-piperazin-1-yl}-ethanone,

[(4S,5R)-4,5-Bis-(4-chloro-phenyl)-2-(2-ethoxy-4-trifluoromethyl-phenyl)-4,5-dimethyl-4,5-dihydro-imidazol-1-yl]-[4-(3-methanesulfonyl-propyl)-piperazin-1-yl]-methanone,

rac-2-{4-[(4S*,5R*)-4,5-Bis-(4-chloro-phenyl)-2-(2-ethoxy-4-trifluoromethyl-phenyl)-4,5-dimethyl-4,5-dihydro-imidazole-1-carbonyl]-piperazin-1-yl}-1-morpholin-4-yl-ethanone,

5 *rac*-(4S*,5R*)-4,5-Bis-(4-chloro-phenyl)-2-(2-ethoxy-4-trifluoromethyl-phenyl)-4,5-dimethyl-4,5-dihydro-imidazol-1-yl]-(4-ethanesulfonyl-piperazin-1-yl)-methanone,

rac-(4S*,5R*)-4,5-Bis-(4-chloro-phenyl)-2-(2-ethoxy-4-trifluoromethyl-phenyl)-4,5-dimethyl-4,5-dihydro-imidazole-1-carboxylic acid (1-methanesulfonyl-piperidin-4-yl)-amide,

10 *rac*-[(4S*,5R*)-4,5-Bis-(4-chloro-phenyl)-2-(2-ethoxy-4-trifluoromethyl-phenyl)-4,5-dimethyl-4,5-dihydro-imidazol-1-yl]-[4-(4-methyl-piperazin-1-yl)-piperidin-1-yl]-methanone and

rac-[(4S*,5R*)-4,5-Bis-(4-chloro-phenyl)-2-(2-ethoxy-4-trifluoromethyl-phenyl)-4,5-dimethyl-4,5-dihydro-imidazol-1-yl]-(4-morpholin-4-yl-piperidin-1-yl)-methanone.

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31. A compound of claim 1 selected from the group consisting of

rac-[(4S*,5R*)-4,5-Bis-(4-chloro-phenyl)-2-(2-ethoxy-4-trifluoromethyl-phenyl)-4,5-dimethyl-4,5-dihydro-imidazol-1-yl]-(4-hydroxy-piperidin-1-yl)-methanone,

20 *rac*-[(4S*,5R*)-4,5-Bis-(4-chloro-phenyl)-2-(2-ethoxy-4-trifluoromethyl-phenyl)-4,5-dimethyl-4,5-dihydro-imidazol-1-yl]-(4-hydroxymethyl-piperidin-1-yl)-methanone,

rac-[(4S*,5R*)-4,5-Bis-(4-chloro-phenyl)-2-(2-ethoxy-4-trifluoromethyl-phenyl)-4,5-dimethyl-4,5-dihydro-imidazol-1-yl]-[4-(2-hydroxy-ethyl)-piperidin-1-yl]-methanone,

25 *rac*-1-[(4S*,5R*)-4,5-Bis-(4-chloro-phenyl)-2-(2-ethoxy-4-trifluoromethyl-phenyl)-4,5-dimethyl-4,5-dihydro-imidazole-1-carbonyl]-piperidine-4-carboxylic acid amide,

rac-(4S*,5R*)-4,5-Bis-(4-chloro-phenyl)-2-(2-ethoxy-4-trifluoromethyl-phenyl)-4,5-dimethyl-4,5-dihydro-imidazole-1-carboxylic acid bis-(2-hydroxy-ethyl)-amide,

- rac*-(4S*,5R*)-4,5-Bis-(4-chloro-phenyl)-2-(2-ethoxy-4-trifluoromethyl-phenyl)-4,5-dimethyl-4,5-dihydro-imidazole-1-carboxylic acid (2,3-dihydroxy-propyl)-amide,
 3-{4-[4,5-Bis-(4-chloro-phenyl)-4,5-dimethyl-4,5-dihydro-1H-imidazol-2-yl]-3-ethoxy-phenyl}-3-methyl-butan-2-one,
 5 3-(4-{4,5-Bis-(4-chloro-phenyl)-1-[4-(3-methanesulfonyl-propyl)-piperazine-1-carbonyl]-4,5-dimethyl-4,5-dihydro-1H-imidazol-2-yl}-3-ethoxy-phenyl)-3-methyl-butan-2-one and
 3-(4-{(4S,5R)-4,5-Bis-(4-chloro-phenyl)-1-[4-(1,1-dioxo-tetrahydro-2H-thiopyran-4-yl)-piperazine-1-carbonyl]-4,5-dimethyl-4,5-dihydro-1H-imidazol-2-yl}-3-ethoxy-phenyl)-3-methyl-butan-2-one.
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32. A compound of claim 1 selected from the group consisting of

- 2-(4-{(4S,5R)-4,5-Bis-(4-chloro-phenyl)-2-[4-(1,1-dimethyl-2-oxo-propyl)-2-ethoxy-phenyl]-4,5-dimethyl-4,5-dihydro-imidazole-1-carbonyl}-piperazin-1-yl)-acetamid,
 15 *rac*-(4S*,5R*)-2-(4-*tert*-Butyl-2-isopropoxy-phenyl)-4,5-bis-(4-chloro-phenyl)-4,5-dimethyl-4,5-dihydro-1H-imidazole,
rac-1-{4-[(4S*,5R*)-2-(4-*tert*-Butyl-2-isopropoxy-phenyl)-4,5-bis-(4-chloro-phenyl)-4,5-dimethyl-4,5-dihydro-imidazole-1-carbonyl]-piperazin-1-yl}-ethanone,
 20 *rac*-[(4S*,5R*)-2-(4-*tert*-Butyl-2-isopropoxy-phenyl)-4,5-bis-(4-chloro-phenyl)-4,5-dimethyl-4,5-dihydro-imidazol-1-yl]-(4-isopropyl-piperazin-1-yl)-methanone,
rac-4-{4-[(4S*,5R*)-2-(4-*tert*-Butyl-2-isopropoxy-phenyl)-4,5-bis-(4-chloro-phenyl)-4,5-dimethyl-4,5-dihydro-imidazole-1-carbonyl]-piperazin-1-yl}-butyronitrile,
 25 *rac*-[(4S*,5R*)-2-(4-*tert*-Butyl-2-isopropoxy-phenyl)-4,5-bis-(4-chloro-phenyl)-4,5-dimethyl-4,5-dihydro-imidazol-1-yl]-[4-(3-methoxy-propyl)-piperazin-1-yl]-methanone,
rac-[(4S*,5R*)-2-(4-*tert*-Butyl-2-isopropoxy-phenyl)-4,5-bis-(4-chloro-phenyl)-4,5-dimethyl-4,5-dihydro-imidazol-1-yl]-[4-(2-morpholin-4-yl-ethyl)-piperazin-1-yl]-methanone,
 30

rac-[(4S*,5R*)-2-(4-*tert*-Butyl-2-isopropoxy-phenyl)-4,5-bis-(4-chloro-phenyl)-4,5-dimethyl-4,5-dihydro-imidazol-1-yl]-[4-(tetrahydro-furan-2-ylmethyl)-piperazin-1-yl]-methanone and

rac-[(4S*,5R*)-2-(4-*tert*-Butyl-2-isopropoxy-phenyl)-4,5-bis-(4-chloro-phenyl)-4,5-dimethyl-4,5-dihydro-imidazol-1-yl]-(hexahydro-pyrrolo[1,2-a]pyrazin-2-yl)-methanone.

33. A compound of claim 1 selected from the group consisting of

rac-[(4S*,5R*)-2-(4-*tert*-Butyl-2-isopropoxy-phenyl)-4,5-bis-(4-chloro-phenyl)-4,5-dimethyl-4,5-dihydro-imidazol-1-yl]-(octahydro-pyrido[1,2-a]pyrazin-2-yl)-methanone,

rac-(4S*,5R*)-2-(4-*tert*-Butyl-2-isopropoxy-phenyl)-4,5-bis-(4-chloro-phenyl)-4,5-dimethyl-4,5-dihydro-imidazole-1-carboxylic acid bis-(2-methoxy-ethyl)-amide,

rac-[(4S*,5R*)-2-(4-*tert*-Butyl-2-isopropoxy-phenyl)-4,5-bis-(4-chloro-phenyl)-4,5-dimethyl-4,5-dihydro-imidazol-1-yl]-[4-(2-methoxy-ethyl)-piperazin-1-yl]-methanone,

[(4S,5R)-2-(4-*tert*-Butyl-2-isopropoxy-phenyl)-4,5-bis-(4-chloro-phenyl)-4,5-dimethyl-4,5-dihydro-imidazol-1-yl]-[4-(3-methanesulfonyl-propyl)-piperazin-1-yl]-methanone,

[(4S,5R)-4,5-Bis-(4-chloro-phenyl)-2-(2-ethoxy-4-isopropyl-phenyl)-4,5-dimethyl-4,5-dihydro-imidazol-1-yl]-[4-(3-methanesulfonyl-propyl)-piperazin-1-yl]-methanone,

[(4S,5R)-2-(5-*tert*-Butyl-2-ethoxy-phenyl)-4,5-bis-(4-chloro-phenyl)-4,5-dimethyl-4,5-dihydro-imidazol-1-yl]-[4-(3-methanesulfonyl-propyl)-piperazin-1-yl]-methanone,

[(4S,5R)-4,5-Bis-(4-chloro-phenyl)-2-(2-ethoxy-5-methanesulfonyl-phenyl)-4,5-dimethyl-4,5-dihydro-imidazol-1-yl]-[4-(3-methanesulfonyl-propyl)-piperazin-1-yl]-methanone,

[(4S,5R)-4,5-Bis-(4-chloro-phenyl)-2-(2-ethoxy-4-methanesulfonyl-phenyl)-4,5-dimethyl-4,5-dihydro-imidazol-1-yl]-[4-(3-methanesulfonyl-propyl)-piperazin-1-yl]-methanone,

[(4S,5R)-4,5-Bis-(4-chloro-phenyl)-2-(4-cyclopropyl-2-ethoxy-phenyl)-4,5-dimethyl-4,5-dihydro-imidazol-1-yl]-[4-(3-methanesulfonyl-propyl)-piperazin-1-yl]-methanone, and

5 [(4S,5R)-4,5-Bis-(4-chloro-phenyl)-2-(5-cyclopropyl-2-ethoxy-phenyl)-4,5-dimethyl-4,5-dihydro-imidazol-1-yl]-[4-(3-methanesulfonyl-propyl)-piperazin-1-yl]-methanone.

34. A compound of claim1 selected from the group consisting of

10 [(4S,5R)-4,5-Bis-(4-chloro-phenyl)-2-(4-ethanesulfonyl-2-ethoxy-phenyl)-4,5-dimethyl-4,5-dihydro-imidazol-1-yl]-[4-(3-methanesulfonyl-propyl)-piperazin-1-yl]-methanone,

[(4S,5R)-2-(4-*tert*-Butyl-2-ethoxy-phenyl)-4,5-bis-(4-chloro-phenyl)-4,5-diethyl-4,5-dihydro-imidazol-1-yl]-[4-(3-methanesulfonyl-propyl)-piperazin-1-yl]-methanone,

15 [(4S,5R)-4,5-Bis-(4-chloro-phenyl)-2-(2-ethoxy-4-ethylsulfanyl-phenyl)-4,5-dimethyl-4,5-dihydro-imidazol-1-yl]-[4-(3-methanesulfonyl-propyl)-piperazin-1-yl]-methanone,

20 [(4S,5R)-2-(4-*tert*-Butyl-2-methoxy-phenyl)-4,5-bis-(4-chloro-phenyl)-4,5-dimethyl-4,5-dihydro-imidazol-1-yl]-[4-(3-methanesulfonyl-propyl)-piperazin-1-yl]-methanone,

[(4S,5R)-2-(4-Chloro-2-ethoxy-5-methanesulfonyl-phenyl)-4,5-bis-(4-chloro-phenyl)-4,5-dimethyl-4,5-dihydro-imidazol-1-yl]-[4-(1,1-dioxo-tetrahydro-2H-thiopyran-4-yl)-piperazin-1-yl]-methanone,

25 [(4S,5R)-2-(4-*tert*-Butyl-2-ethoxy-phenyl)-4,5-bis-(4-chloro-phenyl)-4,5-dimethyl-4,5-dihydro-imidazol-1-yl]-[4-(1,1-dioxo-tetrahydro-thiophen-3-yl)-piperazin-1-yl]-methanone,

[(4S,5R)-2-(4-*tert*-Butyl-2-ethoxy-phenyl)-4,5-bis-(4-chloro-phenyl)-4,5-dimethyl-4,5-dihydro-imidazol-1-yl]-[4-(3-ethanesulfonyl-propyl)-piperazin-1-yl]-methanone,

30 2-(4-[(4S,5R)-4,5-Bis-(4-chloro-phenyl)-1-[4-(3-ethanesulfonyl-propyl)-piperazine-1-carbonyl]-4,5-dimethyl-4,5-dihydro-1H-imidazol-2-yl]-3-ethoxy-phenyl)-2-methyl-propionitrile,

(4S,5R)-2-(4-*tert*-Butyl-2-ethoxy-phenyl)-4,5-bis-(4-chloro-phenyl)-4-methyl-4,5-dihydro-1*H*-imidazole.

35. A compound of claim 1 selected from the group consisting of

- 5 [(4S,5R)-2-(4-*tert*-Butyl-2-ethoxy-phenyl)-4,5-bis-(4-chloro-phenyl)-4-methyl-4,5-dihydro-imidazol-1-yl]-piperazin-1-yl-methanone,
[(4S,5R)-2-(4-*tert*-Butyl-2-ethoxy-phenyl)-4,5-bis-(4-chloro-phenyl)-4-methyl-4,5-dihydro-imidazol-1-yl]-piperazin-1-yl-methanone,
1-[(4S,5R)-2-(4-*tert*-Butyl-2-ethoxy-phenyl)-4,5-bis-(4-chloro-phenyl)-4-methyl-
10 4,5-dihydro-imidazole-1-carbonyl]-piperidine-4-carboxylic acid amide,
1-{4-[(4S,5R)-2-(4-*tert*-Butyl-2-ethoxy-phenyl)-4,5-bis-(4-chloro-phenyl)-4-methyl-4,5-dihydro-imidazole-1-carbonyl]-piperazin-1-yl}-ethanone,
rac-(4S*,5R*)-2-(4-*tert*-Butyl-2-ethoxy-phenyl)-4,5-bis-(4-chloro-phenyl)-4-methyl-4,5-dihydro-imidazole-1-carboxylic acid (2-dimethylamino-ethyl)-amide,
15 *rac*-4-[(4S*,5R*)-2-(4-*tert*-Butyl-2-ethoxy-phenyl)-4,5-bis-(4-chloro-phenyl)-4-methyl-4,5-dihydro-imidazole-1-carbonyl]-piperazin-2-one,
rac-2-{4-[(4S,5R)-2-(4-*tert*-Butyl-2-ethoxy-phenyl)-4,5-bis-(4-chloro-phenyl)-4-methyl-4,5-dihydro-imidazole-1-carbonyl]-piperazin-1-yl}-1-morpholin-4-yl-ethanone,
20 *rac*-[(4S,5R)-2-(4-*tert*-Butyl-2-ethoxy-phenyl)-4,5-bis-(4-chloro-phenyl)-4-methyl-4,5-dihydro-imidazol-1-yl]-(4-methanesulfonyl-piperazin-1-yl)-methanone,
rac-2-{4-[(4S*,5R*)-2-(4-*tert*-Butyl-2-ethoxy-phenyl)-4,5-bis-(4-chloro-phenyl)-4-methyl-4,5-dihydro-imidazole-1-carbonyl]-piperazin-1-yl}-1-pyrrolidin-1-yl-ethanone, and
25 *rac*-[(4S*,5R*)-2-(4-*tert*-Butyl-2-ethoxy-phenyl)-4,5-bis-(4-chloro-phenyl)-4-methyl-4,5-dihydro-imidazol-1-yl]-[4-(tetrahydro-furan-2-carbonyl)-piperazin-1-yl]-methanone.

36. A compound of claim 1 selected from the group consisting of
- rac*-4-[(4S*,5R*)-2-(4-*tert*-Butyl-2-ethoxy-phenyl)-4,5-bis-(4-chloro-phenyl)-4-methyl-4,5-dihydro-imidazole-1-carbonyl]-piperazine-1-carboxylic acid
- 5 dimethylamide,
- rac*-2-{4-[(4S*,5R*)-2-(4-*tert*-Butyl-2-ethoxy-phenyl)-4,5-bis-(4-chloro-phenyl)-4-methyl-4,5-dihydro-imidazole-1-carbonyl]-piperazin-1-yl}-acetamide,
- rac*-2-{4-[(4S*,5R*)-4,5-Bis-(4-chloro-phenyl)-2-(2-isopropoxy-4-methoxy-phenyl)-4-methyl-4,5-dihydro-imidazole-1-carbonyl]-piperazin-1-yl}-1-pyrrolidin-1-yl-
- 10 ethanone,
- rac*-4-[(4S*,5R*)-4,5-Bis-(4-chloro-phenyl)-2-(2-isopropoxy-4-methoxy-phenyl)-4-methyl-4,5-dihydro-imidazole-1-carbonyl]-piperazin-2-one,
- rac*-2-{4-[(4S*,5R*)-4,5-Bis-(4-chloro-phenyl)-2-(2-isopropoxy-4-methoxy-phenyl)-4-methyl-4,5-dihydro-imidazole-1-carbonyl]-piperazin-1-yl}-1-morpholin-4-yl-
- 15 ethanone,
- rac*-[(4S*,5R*)-4,5-Bis-(4-chloro-phenyl)-2-(2-isopropoxy-4-methoxy-phenyl)-4-methyl-4,5-dihydro-imidazol-1-yl]-(4-methanesulfonyl-piperazin-1-yl)-methanone,
- rac*-1-{4-[(4S*,5R*)-4,5-Bis-(4-chloro-phenyl)-2-(2-isopropoxy-4-methoxy-phenyl)-4-methyl-4,5-dihydro-imidazole-1-carbonyl]-piperazin-1-yl}-ethanone,
- 20 *rac*-[(4S*,5R*)-4,5-Bis-(4-chloro-phenyl)-2-(2-isopropoxy-4-methoxy-phenyl)-4-methyl-4,5-dihydro-imidazol-1-yl]-[4-(tetrahydro-furan-2-carbonyl)-piperazin-1-yl]-methanone,
- rac*-2-{4-[(4S*,5R*)-4,5-Bis-(4-chloro-phenyl)-2-(2-isopropoxy-4-methoxy-phenyl)-4-methyl-4,5-dihydro-imidazole-1-carbonyl]-piperazin-1-yl}-acetamide and
- 25 *rac*-4-[(4S*,5R*)-4,5-Bis-(4-chloro-phenyl)-2-(2-isopropoxy-4-methoxy-phenyl)-4-methyl-4,5-dihydro-imidazole-1-carbonyl]-piperazine-1-carboxylic acid dimethylamide.

37. A compound of claim 1 selected from the group consisting of

rac-[(4S*,5R*)-4,5-Bis-(4-chloro-phenyl)-2-(2-isopropoxy-4-methoxy-phenyl)-4-methyl-4,5-dihydro-imidazol-1-yl]-[4-(3-methanesulfonyl-propyl)-piperazin-1-yl]-methanone,

rac-[(4S*,5R*)-4,5-Bis-(4-chloro-phenyl)-2-(2-isopropoxy-4-methoxy-phenyl)-4-methyl-4,5-dihydro-imidazol-1-yl]-piperazin-1-yl-methanone,

rac-(4S*,5R*)-4,5-Bis-(4-chloro-phenyl)-2-(2-isopropoxy-4-methoxy-phenyl)-4-methyl-4,5-dihydro-imidazole-1-carboxylic acid (2-dimethylamino-ethyl)-amide,

10 *rac*-1-[(4S*,5R*)-4,5-Bis-(4-chloro-phenyl)-2-(2-isopropoxy-4-methoxy-phenyl)-4-methyl-4,5-dihydro-imidazole-1-carbonyl]-piperidine-4-carboxylic acid amide,

rac-4-[(4S*,5R*)-2-(4-*tert*-Butyl-2-ethoxy-phenyl)-4,5-bis-(4-chloro-phenyl)-4-ethyl-4,5-dihydro-imidazole-1-carbonyl]-piperazin-2-one,

15 *rac*-1-[(4S*,5R*)-2-(4-*tert*-Butyl-2-ethoxy-phenyl)-4,5-bis-(4-chloro-phenyl)-4-ethyl-4,5-dihydro-imidazole-1-carbonyl]-piperidine-4-carboxylic acid amide,

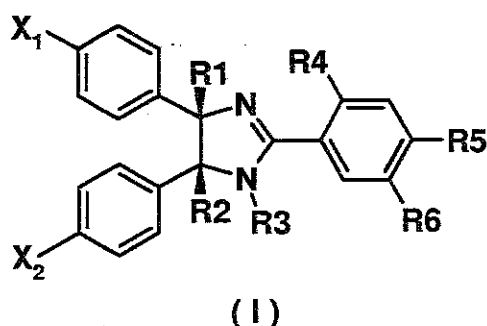
rac-[(4S*,5R*)-4,5-Bis-(4-chloro-phenyl)-4-ethyl-2-(2-isopropoxy-4-methoxy-phenyl)-4,5-dihydro-imidazol-1-yl]-[4-(tetrahydro-furan-2-carbonyl)-piperazin-1-yl]-methanone,

20 *rac*-2-{4-[(4S*,5R*)-4,5-Bis-(4-chloro-phenyl)-4-ethyl-2-(2-isopropoxy-4-methoxy-phenyl)-4,5-dihydro-imidazole-1-carbonyl]-piperazin-1-yl}-1-morpholin-4-yl-ethanone and

rac-4-[(4S*,5R*)-4,5-Bis-(4-chloro-phenyl)-4-ethyl-2-(2-isopropoxy-4-methoxy-phenyl)-4,5-dihydro-imidazole-1-carbonyl]-piperazine-1-carboxylic acid dimethylamide.

25

38. A pharmaceutical composition comprising a compound of the formula



5

wherein X_1 and X_2 are halogen, acetylene, cyano, trifluoromethyl or nitro;

R^1 and R^2 are selected from the group consisting of -H, -CH₃, -CH₂CH₃, -CH₂OH and -CH₂OCH₃ with the proviso that R^1 and R^2 are not both hydrogen;

R^3 is -H or -C(=O)-R⁷;

10

and where R^6 is hydrogen then

R^4 is -OCH₃, -OCH₂CH₃, -OCH₂CH₂F, -OCH₂CH₂OCH₃, or -OCH(CH₃)₂;

R^5 is

-H

15

-halogen,

-CH₃,

-CF₃,

-OCH₃,

-C(CH₃)₂,

20

-cyclopropyl,

-cyano,

-C(CH₃)₃,

-C(CH₃)₂OR (where R is -H, -CH₃ or -CH₂CH₃),

-C(CH₃)₂CH-OR (where R is -H, -CH₃, -CH(CH₃)₂, -CH₂CH₂OH or

25

-CH₂CH₂OCH₃),

-C(CH₃)₂CN,

-C(CH₃)₂COR (where R is -CH₃),

-C(CH₃)₂COOR (where R is -H, -CH₃, -CH₂CH₃ or -CH(CH₃)₂),

-C(CH₃)₂CONR^aR^b (where R^a is -H or -CH₃ and R^b = -H or -CH₃),
 -SR (where R is -CH₃ or -CH₂CH₃), or
 -SO₂R (where R is -CH₃, -CH₂CH₃, 1-pyrrolidine, NH-*tert*-butyl or N(CH₃)₂);

5 and where R⁶ is not hydrogen then

R⁴ is -OCH₃, -OCH₂CH₃, -OCH₂CH₂F, -OCH₂CH₂OCH₃, or -OCH(CH₃)₂;

R⁵ is hydrogen, -Cl, -OCH₃, *tert*-butyl or -N(CH₃)₂;

R⁶ is -Cl, cyclopropyl, -SO₂R (where R is -CH₃, -CH₂CH₃, 1-pyrrolidine, -NH-*tert*-butyl, -NH₂, or -N(CH₃)₂);

10

and R⁷ is selected from the group consisting of

i) -CH₃, -CH(CH₃)₂, -CH₂CH(CH₃)₂, cyclopropyl, cyclobutyl, -CH₂CH₂Ph, 2-furanyl, phenyl, or phenyl substituted by chloro, -OCH₃ or cyano,

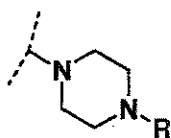
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ii) 4-morpholinyl, 1-piperidinyl, 4-thiomorpholinyl, or 4-thiomorpholinyl-1,1-dioxide,

iii) -NR^c₂ (wherein R^c is hydrogen, -CH₃, -CH₂CH₃, -CH₂CH₂OH, -CH₂CH₂OCH₃, or -CH₂CH(OH)CH₂OH),

20

iv) a substituted piperazine of the formula



wherein R is selected from the group consisting of

25

a) hydrogen,

b) lower alkyl,

c) -CH(CH₃)₂,

d) -CH(CH₂CH₃)₂,

e) cyclopentyl,

30

f) -CH₂CH(OH)CH₃,

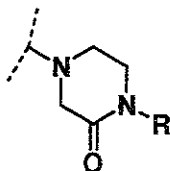
g) -CH₂CF₃,

h) -CH₂CH(OH)CF₃,

- i) $-\text{CH}_2\text{C}(\text{CH}_3)_2\text{OH}$,
 j) $-\text{CH}_2-[4\text{-N-methylpiperidinyl}]$,
- k) $-\text{CH}_2\text{CH}_2\text{R}^d$ (wherein R^d is $-\text{OH}$, $-\text{OCH}_3$, $-\text{OCH}_2\text{CH}_2\text{OH}$, $-\text{OCH}_2\text{CH}_2\text{OCH}_3$, $-\text{CN}$,
 5 $-\text{CF}_3$, $-\text{SO}_2\text{CH}_3$, $-\text{SO}_2\text{NH}_2$, $-\text{SO}_2\text{N}(\text{CH}_3)_2$, $-\text{CONH}_2$, $-\text{CON}(\text{CH}_3)_2$, $-\text{NH}_2$, $-\text{NHCOCH}_3$,
 $-\text{NHSO}_2\text{CH}_3$, $-\text{N}(\text{CH}_3)_2$, $-\text{N}(\text{CH}_2\text{CH}_3)_2$, $-\text{N}(\text{CH}_2\text{CH}_2\text{CH}_3)_2$, 1-pyrrolidinyl, 1-
 piperidinyl, 4-morpholinyl, 2-isothiazolidinyl-1,1-dioxide, or 2-tetrahydrofuranyl),
- l) $-\text{CH}_2\text{CH}_2\text{CH}_2\text{R}^e$ (wherein R^e is $-\text{OH}$, $-\text{OCH}_3$, $-\text{SO}_2\text{CH}_3$, $-\text{SO}_2\text{CH}_2\text{CH}_3$,
 10 $-\text{SO}_2\text{N}(\text{CH}_3)_2$, $-\text{CN}$, $-\text{N}(\text{CH}_3)_2$, $-\text{N}(\text{CH}_2\text{CH}_2\text{CH}_3)_2$, 1-imidazolyl, 1-pyrrolidinyl,
 1-piperidinyl, 4-morpholinyl, $-\text{COOCH}_3$, $-\text{COOCH}_2\text{CH}_3$, $-\text{COOC}(\text{CH}_3)_3$,
 $-\text{CON}(\text{CH}_3)_2$, $-\text{CO}-\text{R}^f$ (wherein R^f is $-\text{CH}_3$, $-\text{CH}_2\text{CH}_3$, cyclopropyl, phenyl, 2-thienyl,
 3-thienyl, 2-furanyl, 3-furanyl), $-\text{COCH}_2-\text{R}^g$ (wherein R^g is $-\text{H}$, $-\text{NHCH}_2\text{CH}_2\text{OH}$,
 $-\text{NHCH}_2\text{CH}_2\text{OCH}_3$, $-\text{NHCH}_2\text{CH}_2\text{N}(\text{CH}_3)_2$, 1-piperidinyl, 1-(piperidinyl-4-methanol),
 15 4-morpholinyl, or $-\text{N}(\text{CH}_3)-(3-(1\text{-methylpyrrolidinyl}))$),
- m) $-\text{CH}_2-\text{CO}-\text{R}^h$ (wherein R^h is $-\text{OCH}_3$, OCH_2CH_3 , $-\text{NH}_2$, $-\text{NHCH}_2\text{CH}(\text{CH}_3)_2$,
 $-\text{NHCH}_2\text{CF}_3$, $-\text{NH-cyclopropyl}$, $-\text{NH-tert-butyl}$, $-\text{NHCH}_2\text{CH}_2\text{CH}_2\text{OH}$, $-\text{N}(\text{CH}_3)_2$,
 $-\text{N}(\text{CH}_2\text{CH}_3)_2$, $-\text{N}(\text{CH}_2\text{CH}_2\text{OH})_2$, $-\text{N}(\text{CH}_2\text{CH}_2\text{OCH}_3)_2$, $-\text{N}(\text{CH}_3)\text{CH}_2\text{CH}_2\text{OH}$,
 20 $-\text{N}(\text{CH}_3)\text{CH}_2\text{CH}_2\text{OCH}_3$, $-\text{NHCH}_2\text{CH}_2\text{OCH}_3$, 1-pyrrolidinyl, 1-piperidinyl, 1-
 (piperidinyl-4-methanol), 1-(piperidinyl-3-carboxamide), 4-morpholinyl, 4-
 thiomorpholinyl, 4-thiomorpholinyl-1,1-dioxide, 1-piperazinyl, 1-(4-
 acetylpiperazinyl), 1-(3-oxopiperazinyl),
- 25 n) $-\text{SO}_2\text{R}^i$ (wherein R^i is $-\text{CH}_3$, $-\text{CH}_2\text{CH}_3$, $-\text{CH}(\text{CH}_3)_2$, phenyl, 4-methylphenyl, 4-
 propylphenyl, $-\text{CF}_3$, 2-thienyl, 3-thienyl, $-\text{NH}_2$, $-\text{NHCH}_3$, $-\text{N}(\text{CH}_3)_2$,
 $-\text{NHCH}_2\text{CH}_2\text{OCH}_3$, $-\text{N}(\text{CH}_2\text{CH}_2\text{OCH}_3)_2$, 1-pyrrolidinyl, 1-piperidinyl, 4-morpholinyl,
 1-piperazyl-4-ethanol, 1-(4-acetylpiperazinyl), 1-(3-oxopiperazinyl)),
- 30 o) $-\text{COR}^j$ (wherein R^j is $-\text{CH}_3$, $-\text{CH}_2\text{CH}_3$, $-\text{CH}(\text{CH}_3)_2$, 2-tetrahydrofuranyl, 2-thienyl,
 3-thienyl, $-\text{NH}_2$, $-\text{NHCH}_3$, $-\text{N}(\text{CH}_3)_2$, 1-pyrrolidinyl, 1-piperidinyl, 4-morpholinyl, 1-
 piperazinyl-4-ethanol, 1-(4-acetylpiperazinyl), or 1-(3-oxopiperazinyl)),
- p) 4-tetrahydro-2H-thiopyranyl-1,1-dioxide,

- q) 4-piperidiny-1-acetyl,
- r) 4-piperidiny-1-dimethylcarboxamide, and
- s) 3-tetrahydro-thiophenyl-1,1-dioxide;

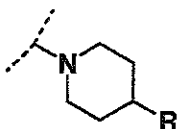
- 5 v) a substituted oxopiperazine of the formula



wherein R is H, -CH₃, -CH₂CH₃, -CH₂CH₂CH₃, -CH₂CH₂OH, or -CH₂CH₂OCH₃;

- 10 and

- vi) a substituted piperidine of the formula



- 15 wherein R is H, -COOCH₃, -COOCH₂CH₃, -CONH₂, -OH, -CH₂OH, -CH₂CH₂OH, -CH₂-N(CH₂CH₃)₂, -CH₂-(1-piperazinyl), -CH₂-(1-(3-oxopiperazinyl)), -NH₂, -NHCOCH₃, -NHCOCH₂NH₂, -NHCOCH₂NHCH₃, -NHCOCH₂N(CH₃)₂, -NHCOCH₂N(CH₂CH₂OH)₂, -NHCOCH₂N(CH₂CH₂OCH₃)₂, -NHCOCH₂NHCH₂CH₂OH, -NHCOCH₂-(1-(4-acetylpiperazinyl)), -NHCOCH₂-(1-(3-oxopiperazinyl)), -NHCOCH₂-(1-piperidinecarboxamide), -NHCOCH₂-(N,N-diethyl-1-piperidiny-carboxamide), -NHCOCH₂-(1-(3-hydroxypiperidiny-yl)), -NHCOCH₂-(1-(piperidiny-4-methanol)), -NHCON(CH₃)₂, -NHCSNHCH₃, -NHCSNHPh, -NHCH₂CONH₂, 1-pyrrolidiny, 1-piperidiny, 1-(4-methylpiperazinyl), or 4-morpholiny;
- 20 and the pharmaceutically acceptable salts and esters thereof together with a pharmaceutically acceptable excipient.
- 25

39. The pharmaceutical composition of claim 38 for the treatment or control of cancer, in particular solid tumors, more particularly breast, colon, lung and prostate tumors.

5 40. A compound of any one of claims 1 to 37 for the use as medicament.

41. A compound according to any one of claims 1 to 37 for the treatment or control of cancer, in particular solid tumors, more particularly breast, colon, lung and prostate tumors.

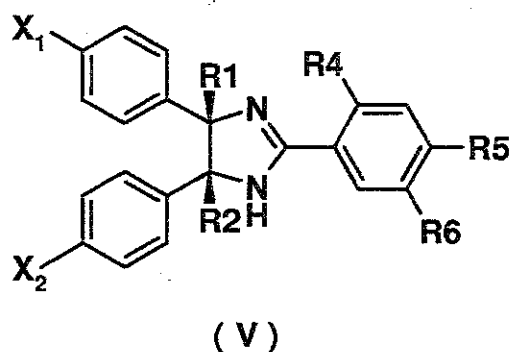
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42. The use of a compound of any one of claims 1 to 37 for the manufacture of medicaments for the treatment or control of cancer, in particular solid tumors, more particularly breast, colon, lung and prostate tumors.

15 43. The process for the synthesis of a compound of formula (I) according to claim 1, whereby

a) an imidazoline of formula (V), thus a compound of formula (I) with R^3 being hydrogen,

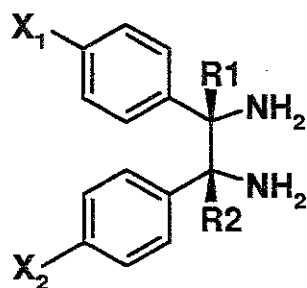
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is obtained either by

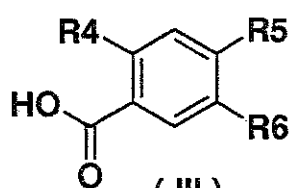
i) condensation of a tetrasubstituted 1,2-diamine of formula (II)

25



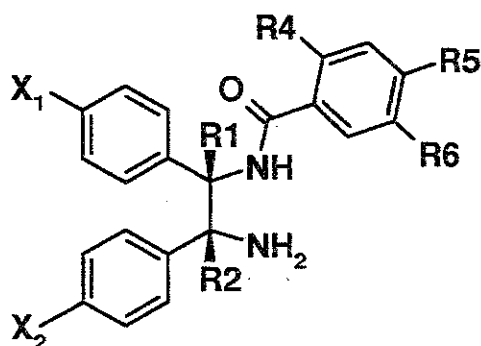
(II)

with an aromatic acid of formula (III)



(III)

to form a monoamide derivative of formula (IV)

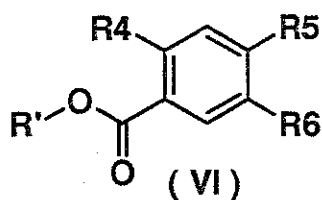


(IV)

followed by cyclodehydration to give a compound of formula (V)

or

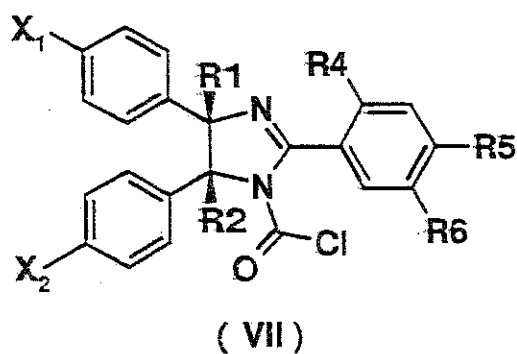
ii) by reaction of a tetrasubstituted 1,2-diamine of formula (II) as shown under i) above with an aromatic ester of formula (VI)



(VI)

in the presence of a trialkyl aluminum to also give an imidazoline of formula (V); and

- 5 b) said compound of formula (V) is reacted with phosgene to form a carbamoyl chloride of formula (VII)



- 10 which is then reacted with primary or secondary amines to form the corresponding compound of formula (I) wherein R³ is different from hydrogen; and

- 15 c) said compound of formula (I) is, if desired, turned into a pharmaceutically acceptable salt; and

all substituents have the meanings given in claim 1.