(54) Titre : DERIVES DE TYROSYLE ET LEUR UTILISATION COMME MODULATEURS DU RECEPTEUR P2X7
(54) Title: TYROSYL DERIVATIVES AND THEIR USE AS P2X7 RECEPTOR MODULATORS

(57) Abrégé/Abstract:
The present invention relates to tyrosyl derivatives and their pharmaceutically acceptable salts; compositions thereof and methods of preparing the compounds are also described. The compounds are useful in the treatment of diseases in mammals that are mediated by the action of the P2X7 receptor.
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TYROSYL DERIVATIVES AND THEIR USE AS P2X7 RECEPTOR MODULATORS

BACKGROUND OF THE INVENTION

[0001] The present invention relates generally to the field of purinergic P2 receptors. More particularly, the present invention relates to novel purinergic P2X receptor compounds and production thereof. In further detail, the present invention relates to compounds, their intermediates, and enantiomers of both which have P2X receptor subtype 7 (P2X7) binding inhibition activity, and are useful for preventing and/or treating diseases associated with adenosine 5'-triphosphate or other natural or synthetic nucleotides.

[0002] P2 receptors have been generally categorized as either metabotropic nucleotide receptors or inotropic receptors for extracellular nucleotides. Metabotropic nucleotide receptors (usually designated P2Y or P2Yn, where "n" is a subscript integer indicating subtype) are believed to differ from inotropic receptors (usually designated P2X or P2Xn) in that they are based on a different fundamental means of transmembrane signal transduction: P2Y receptors operate through a G protein-coupled system, while P2X receptors are ligand-gated ion channels. The ligand for these P2X receptors is ATP, and/or other natural nucleotides, for example, ADP, UTP, UDP, and/or synthetic nucleotides, for example 2-methylthioATP.

[0003] A therapeutic role for P2 receptors has been suggested, for example, for cystic fibrosis (Boucher et al. (1995) in: Belardinelli et al. (eds) Adenosine and Adenine Nucleotides: From Molecular Biology to Integrative Physiology (Kluwer Acad., Norwell Mass.) pp 525-532), diabetes (Loubatieres-Mariani et al. (1995) in: Belardinelli et al. (eds), supra, pp 337-345), immune and

Native P2X receptors form rapidly activated, nonselective cationic channels that are activated by ATP. Rat P2X₁ and rat P2X₂ have equal permeability to Na⁺ and K⁺ but significantly less to Cs⁺. The channels formed by the P2X receptors generally have high Ca²⁺ permeability. The cloned rat P2X₁, P2X₂ and P2X₄ receptors exhibit the same permeability for Ca²⁺ observed with native receptors. However, the mechanism by which P2X receptors form an ionic pore or bind ATP is not known.

A variety of tissues and cell types, including epithelial, immune, muscle and neuronal, express at least one form of P2X receptor. The widespread distribution of P2X₄ receptors in the rat central nervous system suggests a role for P2X₄-mediated events in the central nervous system. However, study of the role of individual P2X receptors is hampered by the lack of receptor subtype-specific agonists and antagonists. For example, one agonist useful for studying ATP-gated channels is α, β methylene ATP (meATP). However, the P2X receptors display differential sensitivity to the agonist with P2X₁ and P2X₂ being meATP-sensitive and insensitive, respectively. Furthermore, binding of meATP to P2X receptors does not always result in channel opening. The predominant forms of P2X receptors in the rat brain, P2X₄ and P2X₆ receptors, cannot be blocked by suramin or PPADS. These two forms of the P2X receptor are also not activated by meATP and are, thus, intractable to study with currently available pharmacological tools.

The functional properties of the P2X₁,₆ receptors are fundamentally similar to those of the other two ionotropic receptors, the nicotinic and excitatory amino acid receptors, and are then relatively impermeable to cations that are more than about 200 D.
One of the most interesting members of the ionotropic P2X family is the P2X₇ receptor. Di Virgilio, F., et. al. (1998) Cell Death and Differentiation 5:191; Di Virgilio, F., et. al. (1995) Immunology Today 16:524. The P2X₇ ionic channel differs strikingly from these channels and it is formed by the aggregation of an unknown number of subunits each 595 amino acids (AA) long (200 AA longer than the other six P2X receptor), and upon stimulation by high concentrations of extracellular ATP generates a nonselective membrane pore of variable size (3-5 nm) and permeable to hydrophilic molecules with molecular weight up to 900 Dalton. Suprenant, A., et. al. (1996) Science 272:735.

Selective activation of the P2X₇ receptor in mycobacterial-infected cells may provide a new therapy for tuberculosis, as well as an effective anticancer agent for many tumors that are rich in P2X₇ receptor. This receptor is mainly, if not exclusively, expressed by mononuclear phagocytes, where it mediates cytotoxic responses, cytokine release and cell fusion. Di Virgilio, F., et. al., (1998) Drug Dev. Res.45:207; Falzoni, S., et. al. (1995) J. Clin. Invest. 95:1207. Activation of the P2X₇ receptor in macrophages and microglial cells causes a large and rapid release of mature interleukin-1β in response to lipopolysaccaride (LPS) stimulation.

IL-1β is of prime importance in the induction of the immune responses, including facilitating response to antigens, synthesis of prostaglandins, proliferation of fibroblasts, blood neutrophils, and inducing the synthesis of other cytokines. Due to likely involvement in immunomodulation and in the inflammatory reaction, it would be of the most importance to develop selective P2X₇ antagonists.
[0011] Human macrophages have proven very useful for the evaluation of P2X7 agonists and antagonists. Compound KN62 (1-N, 0-(bis(1,5-isoquinolinesulfonyle)-N-methyl-L-tyrosyl)-4-phenylpiperazine) is one of the most potent antagonists for the P2X7 receptor with complete inhibition at the concentration of 500 nM. Gargett, C.E. et. al. (1997) B. J. Pharmacol. 120:1483. KN62 is a specific cell-permeable inhibitor of the autophosphorylation of Ca²⁺/calmodulin-dependent protein kinase II (CaMK II) and may be useful as a pharmacological tool for evaluating the role of CaMK II. Hidaka, H. et. al. (1992) Ann. Rev. Pharmacol. Toxicol., 32:377 (1992).

[0012] CaMK II is one of the important kinases whose response seems to be mediated by calmodulin, and that is proposed as a regulator for the synthesis and vesicular release of neurotransmitters. The same compound KN62 significantly inhibited both stimulated catecholamine release and secretory function via the direct blockade of activated Ca²⁺ influx. Maurer, J.A. et. al. (1996) J. Neurochem 66:105. KN62, at non-cytotoxic concentration (2 μM), enhanced etoposide (VP-16) cytotoxicity in Adriamycin-resistant cells (HL-60) and this is due to enhancement (from 2-to4-fold) of VP-16 induced topoisomerase II-mediated DNA cleavable complex formation. Kawamura, K., et. al. (1996) Biochem Pharmacol. 12:1903. The DNA damage induced by VP-16 in the presence of KN62 resulted in the rapid introduction of apoptosis and depletion of cell in "S phase" of the cell cycle.

[0013] Thus, what is needed is specific agonists and antagonists for the P2X7 receptor subtype and, in particular, agents that will be effective in vivo, useful in the treatment of patients, as well as methods for identifying the P2X7 receptor-specific agonist and antagonist compounds.
BRIEF SUMMARY OF THE INVENTION

[0014] The present invention comprises various novel compounds, their intermediates, their pharmaceutically acceptable salts, methods of treatment of medical conditions and methods for identifying receptors in mammals.

[0015] It is an object of the present invention to provide novel compounds, their intermediates, and their pharmaceutically acceptable salts.

[0016] It is another object of the invention to provide ligands selective for the P2X7 receptor that have a broader therapeutic index than those currently available.

[0017] It is a further object of the invention to provide P2X7 receptor antagonists.

[0018] It is a further object of the invention to provide compounds having activity as anti-inflammatories.

[0019] It is yet another object of the invention to provide compounds having activity that enhance endocrine function and hormonal modulation.

[0020] It is a further object of the invention to provide compounds useful in modulating or inhibiting the immune response.

[0021] It is another object of the invention to provide compounds having activity which will induce apoptosis either when administered singly or in combination with other agents.

[0022] Additional objects and advantages of the present invention will be apparent in the following detailed description read in conjunction with the accompanying table, and figures.
BRIEF DESCRIPTION OF THE DRAWINGS

[0023] Figure 1 illustrates the general synthesis procedure for compounds of formula I.

[0024] Figure 2 illustrates the general synthesis procedure for compounds of formula II.

[0025] Figure 3 illustrates the general synthesis procedure for compounds of formula III.

[0026] Figure 4 illustrates the general synthesis procedure for compounds of formula IV.

[0027] Table 1 illustrates the IC50 values for compounds toward inhibiting calcium influx in human monocytes in the presence of 1 mM ATP.

DETAILED DESCRIPTION OF THE INVENTION

[0028] The inventors have synthesized and evaluated the antagonist activities of a series of P2X7 receptor ligands.

The general structure of the compounds of the present invention are illustrated in Formulas I, II, III, and IV:
ula I

wherein $R_1$ and $R_2$ are independently hydrogen, C1-C4 alkyl, C1-C4 alkoxy, halogen, cyano, nitro, amino, or C1-C4 acyl;

$R_3$, $R_4$, $R_5$, $R_6$, $R_7$, and $R_8$ are independently CH or nitrogen;

$R_9$ is independently hydrogen or methyl;

$R_{10}$ is independently carbonyl or (CH$_2$)$_n$; where $n$ is 0, 1, 2, 3, or 4;

$R_{11}$ is independently nitrogen or CH;

$R_{12}$ is independently nitrogen or CH;

$X_1$ and $X_2$ are independently halogen or tritium; and

$X_3$ is N or CH.
wherein $R_1$ is hydrogen, C1-C4 alkyl, C1-C4 alkoxy, C1-C4 acyl, halogen, cyano, nitro, amino, alkylamino, or dialkylamino; $X_1$ and $X_2$ are independently hydrogen, deuterium, tritium, or halogen; $R_9$ is methyl or hydrogen.

wherein $R_1$ and $R_2$ are independently hydrogen, C1-C4 alkyl, C1-C4 alkoxy, C1-C4 acyl, halogen, cyano, nitro, amino, alkylamino or dialkylamino; $R_9$ is hydrogen or methyl; $X_1$ and $X_2$ are independently hydrogen, deuterium, tritium, or halogen; and $X_3$ is independently nitrogen or CH.
Formula IV

wherein $R_1$ and $R_2$ are independently hydrogen, C1-C4 alkyl, C1-C4 alkoxy, halogen, cyano, nitro, or amino;

$R_3$, $R_4$, $R_5$, $R_6$, $R_7$, and $R_8$ are independently CH or nitrogen;

$n$ is 0,1,2,3,4; and

with the proviso that when $n$ is 0 either $R_1$ or $R_2$ is not hydrogen.

[0029] Figure 1 illustrates the synthetic process for the formation of the compounds of Formula I and their intermediates. In summary, these compounds are prepared from an N-Boc-protected-tyrosine derivative. These amino-protected precursors are converted to the activated 1-hydroxy-1,2,3-benzotriazole (HOBt) esters with HOBt and EDC and coupled with the appropriate substituted-aryl, aralkyl, heteroaryl, or heteroaralkyl-piperazines or piperidines to afford the requisite amides in good yields. The phenolic anion of the tyrosyl-moiety compounds (generated in situ with sodium hydride) is converted to the corresponding heteroarylsulfonyl ester by treatment with a dichloromethane (CH$_2$Cl$_2$) solution of the requisite heteroarylsulfonyl chloride. Removal of the amine protecting tert-butyloxycarbonyl (Boc) group is conveniently effected with trifluoroacetic acid (TFA) in a CH$_2$Cl$_2$ solution to
provide the corresponding free amine. This intermediate is then coupled with an excess of the desired heteroarylsulfonyl chloride to provide the desired sulphonamides in acceptable yields.

[0030] Figure 2 illustrates the synthetic process for the formation of the compounds of Formula II and their intermediates. In summary, these compounds are prepared from an N-Boc-protected-tyrosine derivative. These amino-protected precursors are converted to the activated 1-hydroxy-1,2,3-benzotriazole (HOBt) esters with HOBt and EDC and coupled with the appropriate 3,4-dihydro-1H-pyrazino[1,2-a]indole to afford the requisite amides in good yields. The phenolic anion of the tyrosyl-moiety compounds (generated in situ with sodium hydride) is converted to the corresponding isoquinolinesulfonyl ester by treatment with a dichloromethane (CH2Cl2) solution of the requisite isoquinolinesulfonyl chloride. Removal of the amine protecting tert-butylxycarbonyl (Boc) group is conveniently effected with trifluoroacetic acid (TFA) in a CH2Cl2 solution to provide the corresponding free amine. This intermediate is then coupled with an excess of the desired isoquinolinesulfonyl chloride to provide the desired sulphonamides in acceptable yields.

[0031] Figure 3 illustrates the synthetic scheme followed in the preparation of compounds of Formula III and their intermediates. These compounds are prepared from an appropriately substituted N-Boc-protected-tyrosine. These precursors are converted to the activated 1-hydroxy-1, 2,3-benzotriazole (HOBt) esters with HOBt and EDC and coupled with the desired substituted-N-aryl piperazinones to provide the requisite amides in good yields. The phenolic anion of the tyrosyl-moiety compounds (generated in situ with sodium hydride)
is converted to the corresponding 3-pyridinesulfonyl ester by treatment with a
dichloromethane (CH₂Cl₂) solution of the requisite 3-pyridinesulfonyl chloride.
Removal of the amine protecting tert-butyloxycarbonyl (Boc) group is
conveniently effected with trifluoroacetic acid (TFA) in a CH₂Cl₂ solution to
provide the corresponding free amine. This intermediate is then coupled with
a excess of 3-pyridinesulfonyl chloride to provide the target products in
acceptable yields.

[0032] Figure 4 illustrates the synthetic process for the formation of the
compounds of Formula IV and their intermediates. In summary, these
compounds are prepared from an N-Boc-protected-tyrosine derivative. These
amino-protected precursors are converted to the activated 1-hydroxy-1,2,3-
benzotriazole (HOBt) esters with HOBt and EDC and coupled with the
appropriate substituted-N-arylpirperazines or substituted-N-aralkylpirperazines,
affording the requisite amides in good yields. The phenolic anion of the tyrosyl-
moiety compounds (generated in situ with sodium hydride) is converted to the
corresponding heteroarylsulfonyl ester by treatment with a dichloromethane
(CH₂Cl₂) solution of the requisite heteroarylsulfonyl chloride. Removal of the
amine protecting tert-butyloxycarbonyl (Boc) group is conveniently effected
with trifluoroacetic acid (TFA) in a CH₂Cl₂ solution to provide the
corresponding free amine. This intermediate is then coupled with a excess of
the desired heteroarylsulfonyl chloride to provide the desired sulphonamides in
acceptable yields.

[0033] Where the plural form is used for compounds, and salts, this is taken to
mean also a single compound or salt. Any asymmetric carbon atoms may be
present in the (R)-, (S)- or (R, S) configuration. Substituents at a double bond
or a ring may be present in cis- (Z) or trans (E) form. The compounds may thus be present as mixtures of isomers or as pure isomers. In cases wherein compounds may exist in tautomeric forms, each tautomeric form is contemplated as being included within this invention whether existing in equilibrium or predominantly in one form.

[0034] Certain of the compounds of the present invention are sufficiently basic, (e.g., amino derivatives) or acidic (e.g., carboxylic acid derivatives) to form salts. Pharmaceutically acceptable salts of the compounds of formulas I are within the scope of the present invention. As will be understood by those skilled in the art, pharmaceutically acceptable salts include, but are not limited, to salts with inorganic acids such as hydrochloride, sulfate, phosphate, hydrobromide, and nitrate or salts with an organic acid such as malate, maleate, fumarate, tartrate, succinate, citrate, acetate, lactate, methanesulfonate, p-toluenesulfonate, palmoate, salicylate, and stearate. Other acids such as oxalic, while not in themselves pharmaceutically acceptable, may be useful as intermediates in obtaining the compounds of the invention and their pharmaceutical salts.

[0035] Compounds with particularly significant IC\textsubscript{50} values would be useful for the identification and labeling of P2X receptors in mammals. This would make them useful as diagnostic agents for P2X receptors.

[0036] The compounds and their intermediates are formed in the following steps:

Step a. General Procedure for the synthesis of compounds B₅.
[0037] General procedure (A) for the synthesis of compounds Bᵢ of Figure 1. To a solution of Aᵢ (1 mmole) in dry DMF (5 mL) cooled at 0°C was added EDC (211 mg, 1.1 mmol, 1.1 equiv.), HOBt (1.1 mmol) and the suitable N-substituted piperazine (1.1 mmol). This mixture was stirred for 18 h and then concentrated *in vacuo*. The residue was dissolved in EtOAc (10 mL), washed with water (5 mL) and then with brine (5 mL). The organic layer was dried (Na₂SO₄) and concentrated *in vacuo*. The residue purified by column chromatography furnished the derivatives Bᵢ.

[0038] 1-[(S)-N-tert-butyloxy carbonyl-N-methyl-tyrosyl]-4-(benzyl)-piperazine. Following the general procedure (A), this product was obtained as a white solid (yield >95%); m.p.=104-106°C, [α]D =-63.7, c=0.91% in CHCl₃. 1H-NMR (CDCl₃) : 1.36 (s, 9H), 2.28 (m, 4H), 2.79 (s, 3H), 2.83 (s, 2H), 2.89 (dd, J=16.7 and 7.3 Hz, 2H), 3.49 (m, 4H), 5.21 (t, J=7.3 Hz, 1H), 5.85 (s, 1H), 6.72 (d, J=8.3 Hz, 2H), 7.05 (d, J=8.3 Hz, 2H), 7.20 (m, 5H).

[0039] 1-[(S)-N-tert-butyloxy carbonyl-N-methyl-tyrosyl]-4-(phenethyl)-piperazine. Following the general procedure (A), this product was obtained as a white solid (yield 46%); m.p.=147-150°C, [α]D=-46.8, c=1.5% in CH₂Cl₂. 1H-NMR (CDCl₃) : 1.37 (s, 9H), 2.38 (m, 4H), 2.58 (m, 2H), 2.75 (m, 2H), 2.81 (s, 3H), 2.89 (dd, J=14.1 and 8.3 Hz, 2H), 3.49 (m, 4H), 5.21 (t, J=8.3 Hz, 1H), 5.49 (s, 1H), 6.70 (d, J=8.3 Hz, 2H), 7.00 (d, J=8.3 Hz, 2H), 7.23 (m, 5H).

[0040] 1-[(S)-N-tert-butyloxy carbonyl-N-methyl-tyrosyl]-4-(4-fluorophenyl)-piperazine. Following the general procedure (A), this product was obtained as a white solid (yield 94%); m.p.=67-69°C, [α]D=-85.4, c=1.29% in CHCl₃. 1H-NMR (CDCl₃) : 1.34 (s, 9H), 2.78 (s, 3H), 2.89 (dd, J=16.7 and
7.3 Hz, 2H), 3.07 (m, 4H), 3.50 (m, 4H), 5.21 (t, J=7.3 Hz, 1H), 5.85 (s, 1H), 6.86 (m, 8H).

[0041] 1-[(S)-N-tert-butyloxy carbonyl-N-methyl-tyrosyl]-4-(4-chlorophenyl)-piperazine. Following the general procedure (A), this product was obtained as a white solid (yield 78%); m.p.=73-75°C, [ ]=-77, c=0.76% in CHCl₃. 1H-NMR (CDCl₃) : 1.39 (s, 9H), 1.56 (m, 2H), 2.89 (s, 3H), 2.95 (m, 4H), 3.54 (m, 4H), 5.25 (t, J=7.2 Hz, 1H), 6.78 (m, 3H), 7.02 (d, J=8.4 Hz, 1H), 7.09 (d, J=8.2 Hz, 2H), 7.22 (m, 2H), 9.46 (s, 1H).

[0042] 1-[(S)-N-tert-butyloxy carbonyl-N-methyl-tyrosyl]-4-(4-iodophenyl)-piperazine. Following the general procedure (A), this product was obtained as a yellow solid (yield 92%); m.p.=73-75°C, [ ]=-65.4, c=1.02% in CHCl₃. 1H-NMR (CDCl₃) : 1.38 (s, 9H), 2.82 (s, 3H), 2.93 (dd, J=14.6 and 7.2 Hz, 2H), 3.12 (m, 4H), 5.31 (m, 4H), 5.24 (t, J=7.2 Hz, 1H), 5.82 (s, 1H), 6.61 (d, J=8.8 Hz, 2H), 6.72 (d, J=8.4 Hz, 2H), 7.10 (d, J=8.4 Hz, 2H), 7.52 (d, J=8.8 Hz, 2H).

[0043] 1-[(S)-N-tert-butyloxy carbonyl-N-methyl-tyrosyl]-4-(p-toly)-piperazine. Following the general procedure (A), this product was obtained as a foam oil (yield 93%); [ ]=-83.3, c=1.34% in CHCl₃. 1H-NMR (CDCl₃) : 1.38 (s, 9H), 2.27 (s, 3H), 2.81 (s, 3H), 2.86 (dd, J=14 and 7.6 Hz, 2H), 3.42 (m, 4H), 3.54 (m, 4H), 5.26 (t, J=7 Hz, 1H), 6.80 (m, 4H), 7.06 (m, 4H), 9.5 (s, 1H).

[0044] 1-[(S)-N-tert-butyloxy carbonyl-N-methyl-tyrosyl]-4-(4-methoxyphenyl)-piperazine. Following the general procedure (A), this product was obtained as a foam yellow solid (yield 99%); [ ]=-63.3, c=1.1% in CHCl₃. 1H-NMR (CDCl₃) : 1.38 (s, 9H), 2.82 (s, 3H), 2.87 (m, 6H), 3.52 (m,
4H), 3.77 (s, 3H), 5.26 (t, J=7.2 Hz, 1H), 6.71 (d, J=8.4 Hz, 2H), 6.84 (m, 2H), 7.02 (d, J=8.6 Hz, 2H), 7.10 (d, J=8.6 Hz, 2H), 9.46 (s, 1H).

1-[(S)-N-tert-butyloxycarbonyl-N-methyl-tyrosyl]-4-(4-nitrophenyl)piperazine. Following the general procedure (A), this product was obtained as a yellow solid (yield 88%); m.p.=211-213°C, [\(\alpha\)]=-66.7, c=1.02% in CHCl₃. 1H-NMR (CDCl₃) : 1.39 (s, 9H), 2.74 (dd, J=14 and 7.6 Hz, 2H), 2.84 (s, 3H), 3.34 (m, 4H), 3.56 (m, 4H), 5.25 (t, J=7.2 Hz, 1H), 6.71 (d, J=3.4 Hz, 2H), 6.76 (d, J=3.4 Hz, 2H), 7.12 (d, J=8.4 Hz, 2H), 8.12 (d, J=9.2 Hz, 2H), 9.5 (s, 1H).

1-[(S)-N-tert-butyloxycarbonyl-N-methyl-tyrosyl]-4-(4-cyanophenyl)piperazine. Following the general procedure (A), this product was obtained as a oil (yield 76%); [\(\alpha\)]=-49.7, c=1.47% in CHCl₃. 1H-NMR (CDCl₃) : 1.39 (s, 9H), 1.56 (m, 2H), 2.84 (s, 3H), 3.10 (m, 4H), 3.52 (m, 4H), 5.31 (t, J=7.2 Hz, 1H), 6.73 (d, J=8.6 Hz, 2H), 6.79 (d, J=9.2 Hz, 2H), 7.11 (d, J=8.2 Hz, 2H), 7.48 (d, J=8.8 Hz, 2H), 9.46 (s, 1H).

1-[(S)-N-tert-butyloxycarbonyl-N-methyl-tyrosyl]-4-(4-acetylphenyl)piperazine. Following the general procedure (A), this product was obtained as a yellow solid (yield); m.p.=°C, [\(\alpha\)]=.1H-NMR (CDCl₃) : 1.34 (s, 9H), 2.53 (s, 3H), 2.84 (s, 3H), 2.93 (dd, J=14.8 and 7.3 Hz, 2H), 3.42 (m, 4H), 3.54 (m, 4H), 5.26 (t, J=7.3 Hz, 1H), 5.91 (s, 1H), 6.77 (m, J=8 Hz, 4H), 7.10 (d, J=8 Hz, 2H), 7.87 (d, J=8 Hz, 2H).

1-[(S)-N-tert-butyloxycarbonyl-N-methyl-tyrosyl]-4-(4-fluorobenzyl)piperazine. Following the general procedure (A), this product was obtained as a brown oil (yield 78%); [\(\alpha\)]=-62.2, c=0.49% in CHCl₃. 1H-NMR (CDCl₃) : 1.37 (s, 9H), 2.37 (m, 4H), 2.84 (s, 5H), 2.94 (m, 1H), 3.11 (m,
1H), 3.53 (m, 4H), 4.57 (m, 1H), 5.16 (t, J=7.3 Hz, 1H), 6.78 (d, J=8.1 Hz, 2H),
7.00 (m, J=8.4 Hz, 4H), 7.21 (d, J=8.2 Hz, 2H).

[0049] 1-[(S)-N-tert-butyloxycarbonyl-N-methyl-tyrosyl]-4-(4-
fluorobenzoyl)-piperazine. Following the general procedure (A), this product
was obtained as a white oil (yield 97%); [ ]=−10.6, c=1.18% in CH2Cl2. 1H-
NMR (CDCl3) : 1.38 (s, 9H), 2.85 (s, 3H), 3.00 (m, 2H), 3.50 (m, 8H), 4.57 (m,
1H), 5.16 (m, 1H), 6.73 (d, J=8.3 Hz, 2H), 7.08 (m, 4H), 7.38 (d, J=8.2 Hz,
2H).

[0050] 1-[(S)-N-tert-butyloxycarbonyl-N-methyl-tyrosyl]-4-(4-nitrobenzyl)-
piperazine. Following the general procedure (A), this product was obtained as
a brown oil (yield 78%); [ ]=−30, c=0.46% in CHCl3. 1H-NMR (CDCl3) : 1.35
(s, 9H), 2.35 (m, 4H), 2.82 (s, 2H), 2.89 (m, 2H), 2.96 (s, 3H), 3.51 (m, 4H),
4.88 (m, 1H), 5.19 (m, 1H), 6.75 (d, J=8.5 Hz, 2H), 7.05 (d, J=8.5 Hz, 2H), 7.46
(d, J=8.3 Hz, 2H), 8.14 (d, J=8.3 Hz, 2H).

[0051] 1-[(S)-N-tert-butyloxycarbonyl-N-methyl-tyrosyl]-4-(2-
fluorophenyl)-piperazine. Following the general procedure (A), this product
was obtained as a white solid (yield 78%); m.p.=73-75°C, [ ]=−77, c=0.76% in
CHCl3. 1H-NMR (CDCl3) : 1.38 (s, 9H), 2.84 (s, 3H), 2.94 (m, 4H), 3.11 (dd,
J=13.8 and 7.6 Hz, 2H), 3.58 (m, 4H), 5.26 (t, J=7.2 Hz, 1H), 6.76 (m, 3H),
7.01 (m, 5H), 9.46 (s, 1H).

[0052] 1-[(S)-N-tert-butyloxycarbonyl-N-methyl-tyrosyl]-4-(2-
chlorophenyl)-piperazine. Following the general procedure (A), this product
was obtained as a white solid (yield >95%); m.p.=70-72°C, [ ]=−70.3, c=1.15%
in CHCl3. 1H-NMR (CDCl3) : 1.38 (s, 9H), 2.84 (s, 3H), 2.91 (m, 6H), 3.71
(m, 4H), 5.25 (t, J=7.2 Hz, 1H), 5.82 (s, 1H), 6.74 (m, 2H), 7.04 (m, 5H), 7.34 (d, J=9.2 Hz, 1H).

[0053] 1-[(S)-N-tert-butyloxycarbonyl-N-methyl-tyrosyl]-4-(o-tolyl)-piperazine. Following the general procedure (A), this product was obtained as a white solid (yield 95%); m.p.=80-82°C, [ ]=−66.7, c=1.9% in CHCl₃. 1H-NMR (CDCl₃) : 1.38 (s, 9H), 2.28 (s, 3H), 2.74 (m, 6H), 2.86 (s, 3H), 3.65 (m, 4H), 5.26 (t, J=7.2 Hz, 1H), 6.01 (s, 1H), 6.74 (m, 2H), 7.10 (m, 6H).

[0054] 1-[(S)-N-tert-butyloxycarbonyl-N-methyl-tyrosyl]-4-(2-methoxyphenyl)-piperazine. Following the general procedure (A), this product was obtained as a white solid (yield >95%); m.p.=153-155°C, [ ]=−126.9, c=0.93% in CHCl₃. 1H-NMR (CDCl₃) : 1.38 (s, 9H), 2.83 (s, 3H), 2.93 (m, 6H), 3.64 (m, 4H), 3.86 (s, 3H), 5.27 (t, J=7.2 Hz, 1H), 5.82 (s, 1H), 6.72 (m, 3H), 6.89 (m, 2H), 7.06 (m, 3H).

[0055] 1-[(S)-N-tert-butyloxycarbonyl-N-methyl-tyrosyl]-4-(3-chlorophenyl)-piperazine. Following the general procedure (A), this product was obtained as a yellow solid (yield 93%); m.p.=60-62°C, [ ]=−72, c=0.88% in CHCl₃. 1H-NMR (CDCl₃) : 1.36 (s, 9H), 2.83 (s, 3H), 2.99 (m, 6H), 3.52 (m, 4H), 5.26 (t, J=7.2 Hz, 1H), 6.76 (m, 4H), 7.12 (m, 4H), 9.46 (s, 1H).

[0056] 1-[(S)-N-tert-butyloxycarbonyl-N-methyl-tyrosyl]-4-(3-trifluoromethyl-phenyl)-piperazine (27). Following the general procedure (A), this product was obtained as a yellow solid (yield 78%); m.p.=102-104°C, [ ]=−63.4, c=0.8% in CHCl₃. 1H-NMR (CDCl₃) : 1.39 (s, 9H), 2.83 (s, 3H), 3.04 (m, 6H), 3.56 (m, 4H), 5.25 (t, J=7.2 Hz, 1H), 5.82 (s, 1H), 6.73 (d, J=8.3 Hz, 2H), 7.02 (m, 3H), 7.10 (d, J=8.3 Hz, 2H), 7.35 (m, 1H).
[0057] 1-[(S)-N-tert-butyloxycarbonyl-N-methyl-tyrosyl]-4-(2,3-dimethylphenyl)-piperazine. Following the general procedure (A), this product was obtained as a oil (yield 91%); [ ]=−20.3, c=0.7% in CH₂Cl₂. 1H-NMR (CDCl₃) : 1.44 (s, 9H), 2.18 (s, 3H), 2.26 (s, 3H), 2.85 (s, 3H), 2.93 (m, 6H), 3.65 (m, 4H), 5.25 (t, J=7.2 Hz, 1H), 5.82 (s, 1H), 6.76 (m, 3H), 6.94 (m, 1H), 7.06 (m, 3H).

[0058] 1-[(S)-N-tert-butyloxycarbonyl-N-methyl-tyrosyl]-4-(3,4-dichlorophenyl)-piperazine Following the general procedure (A), this product was obtained as a white solid (yield 85%); m.p.=77-78°C, [ ]=−71.4, c=0.42% in CHCl₃. 1H-NMR (CDCl₃) : 1.39 (s, 9H), 2.84 (s, 3H), 2.99 (m, 6H), 3.56 (m, 4H), 5.25 (t, J=7.2 Hz, 1H), 6.75 (m, 2H), 6.88 (m, 1H), 7.08 (m, 2H), 7.26 (m, 2H), 9.46 (s, 1H).

[0059] 1-[(S)-N-tert-butyloxycarbonyl-N-methyl-tyrosyl]-4-(pyridin-2-yl)-piperazine. Following the general procedure (A), this product was obtained as a white oil (yield 89%); [ ]=−57.1, c=0.7% in CH₂Cl₂. 1H-NMR (CDCl₃) : 1.39 (s, 9H), 2.83 (s, 3H), 2.97 (m, J=7.6 Hz, 1H), 3.50 (m, 9H), 4.95 (m, 1H), 5.26 (t, J=7.5 Hz, 1H), 6.66 (m, J= 8.6 Hz, 4H), 7.05 (m, J= 8.3 Hz, 2H), 7.49 (m, 1H), 8.18 (m, 1H).

[0060] 1-[(S)-N-tert-butyloxycarbonyl-N-methyl-tyrosyl]-4-(pyrimidin-2-yl)-piperazine. Following the general procedure (A), this product was obtained as a white solid (yield 91%); m.p.=109-111°C, [ ]=−54.5, c=0.27% in CH₂Cl₂. 1H-NMR (CDCl₃) : 1.38 (s, 9H), 2.83 (s, 3H), 3.02 (m, 2H), 3.53 (m, 5H), 3.88 (m, 3H), 4.92 (m, 1H), 5.26 (t, J=7.5 Hz, 1H), 6.53 (m, 1H), 6.72 (m, 2H), 7.09 (m, J=8.3 Hz, 2H), 8.32 (m, 1H).
[0061] 1-[(S)-N-tert-butyloxycarbonyl-N-methyl-tyrosyl]-4-(benzyl)-piperidine. Following the general procedure (A), this product was obtained as a white solid (yield >95%); m.p.=70-72°C, [α]=−61.7, c=0.46% in CH₂Cl₂. 1H-NMR (CDCl₃): 1.39 (s, 9H), 1.62 (m, 5H), 2.50 (m, 3H), 2.86 (m, J=12.6 and 6.8 Hz, 6H), 3.95 (m, 1H), 4.58 (m, 1H), 5.21 (t, J=6.8 Hz, 1H), 5.85 (s, 1H), 6.72 (m, J=7.5 Hz, 2H), 7.10 (m, 4H), 7.25 (m, 3H).

[0062] 1-[(S)-N-tert-butyloxycarbonyl-tyrosyl]-4-(4-fluorophenyl)-piperazin. Following the general procedure (A), this product was obtained as a foam yellow oil (yield 87%); [α]=+7.0, c=0.43% in CH₂Cl₂. 1H-NMR (CDCl₃): 1.43 (s, 9H), 2.93 (m, 6H), 3.57 (m, 4H), 4.82 (t, J=8.6 Hz, 1H), 5.45 (s, 1H), 6.75 (m, 4H), 6.93 (d, J=8.4 Hz, 2H), 7.04 (d, J=8.4 Hz, 2H).

[0063] 1-[(S)-N-tert-butyloxycarbonyl-tyrosyl]-4-(o-tolyl)-piperazin. Following the general procedure (A), this product was obtained as a white solid (yield 94%); m.p.=80-82°C, [α]=+14.9, c=1.03% in CH₂Cl₂. 1H-NMR (CDCl₃): 1.43 (s, 9H), 2.26 (s, 3H), 2.31 (m, 1H), 2.69 (m, 3H), 2.92 (d, J=6.9 Hz, 2H), 3.29 (m, 1H), 3.46 (m, 1H), 3.69 (m, 2H), 4.85 (dd, J=15.7 and 7.3 Hz, 1H), 5.47 (d, J=8.6 Hz, 1H), 6.20 (s, 1H), 6.74 (d, J=8.4 Hz, 2H), 6.86 (d, J=7.7 Hz, 1H), 7.03 (m, J=8.4 Hz, 3H), 7.15 (t, J=7.4 Hz, 2H).

[0064] 2-(3,4-Dihydro-1H-pyrazino[1,2-a]indol-2-yl)-1-(4-hydroxy-benzyl)-2-oxo-ethyl]-carbamic acid tert-butyl ester. Following the general procedure (A) this product was obtained. m.p. 85-87°C; [α] = -4.1, c=0.9% in CHCl₃; 1H-NMR (CDCl₃): d 1.44 (s, 9H), 2.90 (t, J=4 Hz, 2H), 3.52 (m, 1H), 3.81 (m, 3H), .4.43 (m, 1H), 4.86 (m, 2H), 5.43 (d, J=10.8 Hz, 1H), 5.65 (s,
1H), 6.1 (s, 1H), 6.54 (d, J=6.8 Hz, 2H), 6.96 (dd, J=8.2 and 5.8 Hz, 2H), 7.129 (m, 3H), 7.56 (d, J=8.0 Hz, 1H).

[0065] **[2-(3,4-Dihydro-1H-pyrazino[1,2-a]indol-2-yl)-1-(4-hydroxy-benzyl)-2-oxo-ethyl]-methyl-carbamic acid tert-butyl ester.** Following the general procedure (A) this product was obtained. m.p. 130-132°C; [α] = -9.47, c=0.35% in CHCl3; 1H-NMR (CDCl3): d 1.42 (s, 9H), 2.71 (s, 3H), 2.82 (t, J=4.0 Hz, 2H), 3.96 (m, 4H), 4.43 (m, 1H), 4.84 (m, 2H), 5.33 (d, J=10.6 Hz, 1H), 5.43 (t, J=7.2 Hz, 1H), 6.34 (dd, J=12.2 and 7.2 Hz, 1H), 6.64 (m, 1H), 7.15 (m, 5H), 7.57 (d, J=8.2 Hz, 1H).

[0066] **[2-(8-Fluoro-3,4-dihydro-1H-pyrazino[1,2-a]indol-2-yl)-1-(4-hydroxy-benzyl)-2-oxo-ethyl]-methyl-carbamic acid tert-butyl ester.**

Following the general procedure (A) this product was obtained. m.p. 65-67°C; [α] = -79.3, c=1% in CHCl3; 1H-NMR (CDCl3): d 1.41 (s, 9H), 2.84 (s, 3H), 2.96 (m, 2H), 4.15 (m, 4H), 4.84 (t, J=14.6 Hz, 1H), 5.02 (t, J=14.6 Hz, 1H), 5.37 (d, J=8.6 Hz, 1H), 5.53 (d, J=6.2 Hz, 1H), 6.26 (dd, J=12.0 and 7.2 Hz, 1H), 6.73 (m, 2H), 7.13 (m, 5H).

[0067] **General procedure (B) for the synthesis of compounds C1.** To a suspension of NaH (24 mg of 55-65% oil suspension, 0.6 mmol, 1.2 equiv.) in dry THF (5 mL) was added B1 (0.5 mmol, 1 equiv.). After 10', the isoquinoline sulfonyl chloride (1 mmole, 2 equiv.) dissolved in dry DCM (2 mL) was added. This mixture was stirred for 18 h at rt. and then concentrated in vacuo. The residue was dissolved in a mixture of EtOAc (10 mL) and a saturated aqueous NaHCO3 (5 mL). After the layers were separated, the organic layer was dried
concentrated in vacuo and the residue purified by column chromatography yielded the derivatives C.

[0068] 1-[(S)-O-isoquinolinesulfonfyl-N-tert-butyloxy carbonyl-N-methyl-tyrosyl]-4-(benzyl)-piperazine. Following the general procedure (B), this product was obtained as a yellow oil (yield 90%); [ ] = -64.4, c=1.15% in CHCl3. 1H-NMR (CDCl3) : 1.31 (s, 9H), 2.72 (m, 4H), 2.90 (m, 2H), 3.48 (m, 7H), 3.70 (m, 2H), 5.15 (t, J=7 Hz, 1H), 6.76 (m, J=8.6 Hz, 3H), 7.05 (m, J=8.6 Hz, 3H), 7.28 (m, 3H), 7.63 (m, 1H), 8.27 (m, J=7.8 Hz, 2H), 8.54 (d, J=6.1 Hz, 1H), 8.79 (d, J=6.1 Hz, 1H), 9.42 (s, 1H).

[0069] 1-[(S)-O-isoquinolinesulfonfyl-N-tert-butyloxy carbonyl-N-methyl-tyrosyl]-4-(phenethyl)-piperazine. Following the general procedure (B), this product was obtained as a white solid (yield 82%); m.p.=58-60°C, [ ] = -33.8, c=0.73% in CH2Cl2. 1H-NMR (CDCl3) : 1.39 (s, 9H), 2.05 (s, 1H), 2.17 (s, 1H), 2.39 (m, 3H), 2.57 (m, 3H), 2.72 (m, 4H), 2.87 (m, 2H), 3.36 (m, 2H), 3.51 (m, 1H), 5.15 (t, J=7 Hz, 1H), 6.77 (m, 2H), 7.03 (d, J=8.3 Hz, 2H), 7.18 (m, 3H), 7.25 (m, 2H), 7.59 (m, J=8.0 Hz, 1H), 8.25 (m, J=5.8 Hz, 2H), 8.53 (d, J=6.2 Hz, 1H), 8.79 (d, J=6.2 Hz, 1H), 9.42 (s, 1H).

[0070] 1-[(S)-O-isoquinolinesulfonfyl-N-tert-butyloxy carbonyl-N-methyl-tyrosyl]-4-(4-fluorophenyl)-piperazine. Following the general procedure (B), this product was obtained as a oil (yield 85%); [ ] = -54.1, c=1.31% in CHCl3. 1H-NMR (CDCl3) : 1.33 (s, 9H), 2.73 (s, 3H), 2.91 (m, 6H), 3.51 (m, 4H), 5.17 (t, J=7.2 Hz, 1H), 6.77 (m, J=8.6 Hz, 4H), 7.01 (m, J=8.6 Hz, 4H), 7.62 (dd, J=7.6 Hz, 1H), 8.26 (m, J=7.6, 2H), 8.52 (d, J=6.1 Hz, 1H), 8.79 (d, J=6.1 Hz, 1H), 9.40 (s, 1H).
[0071] 1-[(S)-O-isoquinolinesulfonyl-N-tert-butyloxy carbonyl-N-methyl-tyrosyl]-4-(4-chlorophenyl)-piperazine. Following the general procedure (B), this product was obtained as a white liquid (yield 86%); [α]D=−68.4, c=1% in CHCl₃. 1H-NMR (CDCl₃): 1.33 (s, 9H), 1.57 (m, 2H), 2.74 (s, 3H), 3.09 (m, 4H), 3.48 (m, 4H), 5.22 (t, J=7 Hz, 1H), 6.77 (m, 4H), 7.10 (t, J=8.6 Hz, 2H), 7.23 (m, 2H), 7.61 (t, J=8.6 Hz, 1H), 8.25 (dd, J=6.6 and 6.2 Hz, 2H), 8.54 (d, J=6.2 Hz, 1H), 8.80 (d, J=6.2 Hz, 1H), 9.41 (s, 1H).

[0072] 1-[(S)-O-isoquinolinesulfonyl-N-tert-butyloxy carbonyl-N-methyl-tyrosyl]-4-(4-iodophenyl)-piperazine. Following the general procedure (B), this product was obtained as a foam yellow oil (yield >95%); [α]D=−48.8, c=1.22% in CHCl₃. 1H-NMR (CDCl₃): 1.34 (s, 9H), 2.73 (s, 3H), 2.98 (m, 6H), 3.51 (m, 4H), 5.21 (t, J=7 Hz, 1H), 6.64 (d, J=8.8, 2H), 6.76 (t, J=8.6, 2H), 7.09 (t, J=8.6, 2H), 7.53 (d, J=8.8, 2H), 7.61 (m, J=7.2 Hz, 1H), 8.25 (m, J=7.2 Hz, 2H), 8.53 (d, J=6.1 Hz, 1H), 8.80 (d, J=6.1 Hz, 1H), 9.41 (s, 1H).

[0073] 1-[(S)-O-isoquinolinesulfonyl-N-tert-butyloxy carbonyl-N-methyl-tyrosyl]-4-(p-tolyl)piperazine. Following the general procedure (B), this product was obtained as a yellow oil (yield 90%); [α]D=−10.9, c=1.34 % in CHCl₃. 1H-NMR (CDCl₃): 1.33 (s, 9H), 2.05 (s, 3H), 2.74 (s, 3H), 2.82 (m, 2H), 3.04 (m, 4H), 3.51 (m, 4H), 5.22 (t, J=7.2 Hz, 1H), 6.79 (t, J=8.4 Hz, 4H), 7.09 (d, J=8.4 Hz, 4H), 7.61 (t, J=7.6 Hz, 1H), 8.26 (m, 2H), 8.53 (d, J=6 Hz, 1H), 8.80 (d, J=6 Hz, 1H), 9.41 (s, 1H).

[0074] 1-[(S)-O-isoquinolinesulfonyl-N-tert-butyloxy carbonyl-N-methyl-tyrosyl]-4-(4-methoxyphenyl)-piperazine. Following the general procedure (B), this product was obtained as a yellow oil (yield 82%); [α]D=−63.3, c=1.1% in
CHCl₃. 1H-NMR (CDCl₃): 1.33 (s, 9H), 1.57 (m, 2H), 2.73 (s, 3H), 2.96 (m, 4H), 3.51 (m, 4H), 3.76 (s, 3H), 5.21 (t, J=7 Hz, 1H), 6.82 (m, 4H), 7.10 (t, J=8.6 Hz, 2H), 7.23 (m, 2H), 7.61 (t, J=8.6 Hz, 1H), 8.25 (dd, J=6.6 and 6.2 Hz, 2H), 8.54 (d, J=6.2 Hz, 1H), 8.78 (d, J=6.2 Hz, 1H), 9.42 (s, 1H).

[0075] 1-[(S)-O-isoquinonesulfonyl-N-tert-butyloxy carbonyl-N-methyl-tyrosyl]-4-(4-nitrophenyl)-piperazine. Following the general procedure (B), this product was obtained as a yellow solid (yield 79%); m.p.=46-47°C, [α]D = 58.71, c=1.01% in CHCl₃. 1H-NMR (CDCl₃): 1.34 (s, 9H), 2.83 (dd, J=14 and 6.4 Hz, 2H), 2.95 (s, 3H), 3.44 (m, 4H), 3.56 (m, 4H), 5.19 (t, J=7.2 Hz, 1H), 6.79 (dd, J=7.2 and 3.6 Hz, 4H), 7.10 (d, J=8.6 Hz, 2H), 7.61 (t, J=7.8 Hz, 1H), 8.11 (d, J=7.4 Hz, 2H), 8.25 (t, J=8.8 Hz, 2H), 8.51 (d, J=6.2 Hz, 1H), 8.80 (d, J=6.2 Hz, 1H), 9.51 (s, 1H).

[0076] 1-[(S)-O-isoquinonesulfonyl-N-tert-butyloxy carbonyl-N-methyl-tyrosyl]-4-(4-cyanophenyl)-piperazine. Following the general procedure (B), this product was obtained as a foal yellow oil (yield <95%); [α]D = +4.21, c=1.4% in CHCl₃. 1H-NMR (CDCl₃): 1.34 (s, 9H), 2.74 (s, 3H), 3.09 (m, 6H), 3.49 (m, 4H), 5.22 (t, J=7 Hz, 1H), 6.79 (t, J=8.6 Hz, 4H), 7.11 (t, J=8.4 Hz, 3H), 7.51 (d, J=8.6 Hz, 1H), 7.63 (t, J=7.6 Hz, 1H), 8.26 (dd, J=6.8 and 4.4 Hz, 2H), 8.51 (d, J=6 Hz, 1H), 8.80 (d, J=6 Hz, 1H), 9.41 (s, 1H).

[0077] 1-[(S)-O-isoquinonesulfonyl-N-tert-butyloxy carbonyl-N-methyl-tyrosyl]-4-(4-acetylphenyl)-piperazine. Following the general procedure (B), this product was obtained as a oil (yield >95%); [α]D = -51.82, c=1.2% in CHCl₃. 1H-NMR (CDCl₃): 1.35 (s, 9H), 2.53 (s, 3H), 2.74 (s, 3H), 3.49 (m, 10H), 5.19 (t, J=7.2 Hz, 1H), 6.77 (m, J=8.6, 2H), 6.84 (m, J=8.9 Hz, 2H), 7.10 (t,
J=8.6 Hz, 2H), 7.62 (t, 1H), 7.89 (d, J=8.9 Hz, 2H), 8.28 (m, J=6.2 Hz, 2H), 8.51 (d, J=6.2 Hz, 1H), 8.80 (d, J=6.2 Hz, 1H), 9.42 (s, 1H).

[0078] 1-[(S)-O-isoquinolinesulfonyl-N-tert-butyloxy carbonyl-N-methyl-tyrosyl]-4-(4-fluorobenzyl)-piperazine. Following the general procedure (B), this product was obtained as a brown oil (yield 77%); [ ]=–38.9, c=0.66% in CHCl₃. 1H-NMR (CDCl₃) : 1.32 (s, 9H), 2.72 (s, 3H), 2.90 (m, 3H), 3.50 (m, 7H), 3.73 (m, 2H), 5.15 (t, J=7 Hz, 1H), 6.78 (t, J=8.6 Hz, 2H), 7.03 (m, J=8.6 Hz, 4H), 7.25 (m, J=6.6 Hz, 2H), 7.64 (m, 1H), 8.28 (d, J=7.8 Hz, 2H), 8.54 (d, J=6.1 Hz, 2H), 8.81 (d, J=6.2 Hz, 1H), 9.42 (s, 1H).

[0079] 1-[(S)-O-isoquinolinesulfonyl-N-tert-butyloxy carbonyl-N-methyl-tyrosyl]-4-(4-fluorobenzoyl)-piperazine. Following the general procedure (B), this product was obtained as a white oil (yield >95%); [ ]=–27.4, c=0.74% in CH₂Cl₂. 1H-NMR (CDCl₃) : 1.35 (s, 9H), 1.62 (m, 5H), 2.50 (m, 3H), 2.72 (s, 3H), 2.90 (m, 3H), 3.90 (m, 1H), 4.50 (m, 1H), 5.12 (t, J=6.2 Hz, 1H), 6.76 (d, J=8.4 Hz, 2H), 7.08 (m, J=8.6 Hz, 4H), 7.23 (m, 3H), 7.67 (m, 1H), 8.27 (m, J=6.0 Hz, 2H), 8.54 (d, J=6.1 Hz, 1H), 8.80 (d, J=6.0 Hz, 1H), 9.42 (s, 1H).

[0080] 1-[(S)-O-isoquinolinesulfonyl-N-tert-butyloxy carbonyl-N-methyl-tyrosyl]-4-(4-nitrobenzyl)-piperazine. Following the general procedure (B), this product was obtained as a yellow oil (yield 54%); [ ]=–44.5, c=0.44% in CH₃OH. 1H-NMR (CDCl₃) : 1.30 (s, 9H), 2.73 (m, 4H), 2.90 (m, 2H), 3.50 (m, 7H), 3.70 (m, 2H), 5.15 (t, J=7 Hz, 1H), 6.79 (t, J=8.3 Hz, 2H), 7.06 (t, J=8.5 Hz, 2H), 7.49 (d, J=8.3 Hz, 2H), 7.65 (t, J=7.7 Hz, 1H), 8.18 (d, J=8.3 Hz, 2H), 8.29 (d, J=7.7 Hz, 2H), 8.54 (d, J=6.0 Hz, 1H), 8.80 (d, J=6.1 Hz, 1H), 9.42 (s, 1H).
[0081] 1-[(S)-O-isoquinolinesulfonyl-N-tert-butyloxy carbonyl-N-methyl-tyrosyl]-4-(2-fluorophenyl)-piperazine. Following the general procedure (B), this product was obtained as a yellow oil (yield >95%); [ ]-44.23, c=1.04% in CHCl₃. 1H-NMR (CDCl₃) : 1.34 (s, 9H), 2.75 (s, 3H), 2.92 (m, 6H), 3.52 (m, 4H), 5.22 (t, J=7 Hz, 1H), 6.79 (m, 5H), 7.14 (m, 4H), 7.62 (t, J=7.6 Hz, 1H), 8.26 (t, J=7.2 Hz, 1H), 8.53 (t, J=6 Hz, 1H), 8.82 (d, J=6 Hz, 1H), 9.41 (s, 1H).

[0082] [(S)-O-isoquinolinesulfonyl-N-tert-butyloxy carbonyl-N-methyl-tyrosyl]-4-(2-chlorophenyl)-piperazine. Following the general procedure (B), this product was obtained as a oil (yield >95%); [ ]-40.6, c=1.23 % in CHCl₃. 1H-NMR (CDCl₃) : 1.34 (s, 9H), 2.76 (s, 3H), 2.88 (m, 6H), 3.62 (m, 4H), 5.19 (t, J=7 Hz, 1H), 6.79 (t, J=8.6, 2H), 7.05 (m, J=6.2 and 8.6, 4H), 7.22 (d, J=6.2 Hz, 1H), 7.37 (d, J=7.9 Hz, 1H), 7.64 (t, 1H), 8.28 (t, J=7, 2H), 8.57 (d, J=6.1 Hz, 1H), 8.80 (d, J=6.1 Hz, 1H), 9.44 (s, 1H).

[0083] 1-[(S)-O-Preparation of isoquinolinesulfonflyl-N-tert-butyloxy carbonyl-N-methyl-tyrosyl]-4-(o-tolyl)-piperazine. Following the general procedure (B), this product was obtained as a yellow oil (yield 72%); [ ]-47.0, c=1.27% in CHCl₃. 1H-NMR (CDCl₃) : 1.38 (s, 9H), 2.28 (s, 3H), 2.74 (m, 6H), 2.86 (s, 3H), 3.65 (m, 4H), 5.26 (t, J=7.2 Hz, 1H), 6.81 (t, J=9.0 and 8.4 Hz, 3H), 7.02 (m, J=8.9 and 8.5 Hz, 3H), 7.18 (t, J=7.4 Hz, 2H), 7.72 (t, J=7.7 Hz, 1H), 8.27 (m, J=8.4 and 6.1 Hz, 2H), 8.54 (d, J=6 Hz, 1H), 8.82 (d, J=6 Hz, 1H), 9.43 (s, 1H).

[0084] 1-[(S)-O-isoquinolinesulfonflyl-N-tert-butyloxy carbonyl-N-methyl-tyrosyl]-4-(2-methoxyphenyl)-piperazine Following the general procedure (B), this product was obtained as a yellow oil (yield 64%); [ ]=-61.0,
c=1.54% in CHCl₃. 1H-NMR (CDCl₃) : 1.34 (s, 9H), 2.75 (s, 3H), 2.91 (m, 6H), 3.51 (m, 4H), 3.87 (s, 3H), 5.20 (t, J=7 Hz, 1H), 6.76 (d, J=8.5, 2H), 6.83 (m, J=6.6, 3H), 7.06 (m, J=8.5, 3H), 7.61 (m, J=6.6 Hz, 1H), 8.27 (m, 2H), 8.54 (d, J=6 Hz, 1H), 8.81 (d, J=6 Hz, 1H), 9.42 (s, 1H).

[0085] 1-[(S)-O-isooquinolinesulfonyl-N-tert-butyloxycarbonyl-N-methyl-tyrosyl]-4-(3-chlorophenyl)-piperazine. Following the general procedure (B), this product was obtained as a foam yellow oil (yield >95%); m.p. = 79-81°C, [ ] = -42.2, c=0.62% in CHCl₃. 1H-NMR (CDCl₃) : 1.35 (s, 9H), 2.73 (s, 3H), 2.92 (m, 6H), 3.51 (m, 4H), 5.21 (t, J=7 Hz, 1H), 6.79 (m, 5H), 7.14 (m, 4H), 7.61 (t, J=7.2 Hz, 1H), 8.26 (t, J=7.2 Hz, 1H), 8.53 (d, J=6.2 Hz, 1H), 8.80 (d, J=4.2 Hz, 1H), 9.41 (s, 1H).

[0086] 1-[(S)-O-isooquinolinesulfonyl-N-tert-butyloxycarbonyl-N-methyl-tyrosyl]-4-(3-trifluoromethylphenyl)-piperazine. Following the general procedure (B), this product was obtained as a white solid (yield 75%); m.p.=74-76°C, [ ] = -48.9, c=0.76% in CHCl₃. 1H-NMR (CDCl₃) : 1.35 (s, 9H), 2.74 (s, 3H), 3.01 (m, 6H), 3.65 (m, 4H), 5.20 (t, J=7 Hz, 1H), 6.79 (m, J=8.6 Hz, 2H), 7.08 (m, J=8.6 Hz, 5H), 7.37 (t, J=7.8 Hz, 1H), 7.66 (m, J=7.8 Hz, 1H), 8.29 (dd, J=8.1 and 4.6 Hz, 2H), 8.58 (d, J=6.1 Hz, 1H), 8.81 (d, J=6.1 Hz, 1H), 9.44 (s, 1H).

[0087] 1-[(S)-O-isooquinolinesulfonyl-N-tert-butyloxycarbonyl-N-methyl-tyrosyl]-4-(2,3-dimethylphenyl)-piperazine. Following the general procedure (B), this product was obtained as a yellow oil (yield 44%); [ ] = -70, c=0.2% in CH₂Cl₂. 1H-NMR (CDCl₃) : 1.39 (s, 9H), 2.21 (s, 3H), 2.27 (s, 3H), 2.76 (s, 3H), 2.82 (m, 6H), 3.58 (m, 4H), 5.20 (t, J=7 Hz, 1H), 6.80 (m, J=8.3 Hz, 3H),
6.95 (m, 1H), 7.08 (m, J=8.4 Hz, 3H), 7.66 (m, 1H), 8.26 (m, J=8.4, 2H), 8.55 (d, J=6.1 Hz, 1H), 8.81 (d, J=6.1 Hz, 1H), 9.41 (s, 1H).

[0088] 1-[(S)-O-isoquinolinesulfonfyl-N-tert-butyloxy carbonyl-N-methyl-tyrosyl-4-(3,4-dichlorophenyl)-piperazine. Following the general procedure (B), this product was obtained as a yellow solid (yield 52%); m.p. =85-87°C, [α]D =+12, c=0.5 % in CHCl₃. 1H-NMR (CDCl₃) : 1.34 (s, 9H), 2.73 (s, 3H), 2.92 (m, 6H), 3.51 (m, 4H), 5.19 (t, J=7 Hz, 1H), 6.74 (m, 2H), 6.90 (s, 1H), 7.10 (d, J=7.4 Hz, 1H), 7.32 (d, J=7.4 Hz, 1H), 7.63 (t, J=7.6 Hz, 1H), 8.26 (dd, J=7 and 3.6 Hz, 1H), 8.54 (t, J=6 Hz, 1H), 8.81 (d, J=6 Hz, 1H), 9.42 (s, 1H).

[0089] 1-[(S)-O-isoquinolinesulfonfyl-N-tert-butyloxy carbonyl-N-methyl-tyrosyl]-4-(pyridin-2-yl)-piperazine. Following the general procedure (B), this product was obtained as a white solid (yield 90%); m.p. =56-58°C, [α]D =-59.3, c=0.43% in CH₂Cl₂. 1H-NMR (CDCl₃) : 1.35 (s, 9H), 2.75 (s, 3H), 3.00 (m, 1H), 3.45 (m, 8H), 3.85 (m, 1H), 5.19 (t, J=7 Hz, 1H), 6.69 (m, J=8.4 Hz, 4H), 7.07 (t, J=8.4 Hz, 2H), 7.51 (t, J=6.6 Hz, 1H), 7.62 (m, 1H), 8.23 (m, J=7.1 Hz, 3H), 8.53 (d, J=6.1 Hz, 1H), 8.89 (d, J=6.2 Hz, 1H), 9.41 (s, 1H).

[0090] 1-[(S)-O-isoquinolinesulfonfyl-N-tert-butyloxy carbonyl-N-methyl-tyrosyl]-4-(pyrimidin-2-yl)-piperazine]. Following the general procedure (B), this product was obtained as a white solid (yield 80%); m.p. =104-106°C, [α]D =-48.6, c=0.37% in CH₂Cl₂. 1H-NMR (CDCl₃) : 1.35 (s, 9H), 2.76 (s, 3H), 3.00 (m, 2H), 3.53 (m, 5H), 3.85 (m, 3H), 5.19 (t, J=7 Hz, 1H), 6.54 (m, 1H), 6.78 (t, J=8.4 Hz, 2H), 7.08 (t, J=8.4 Hz, 2H), 7.63 (m, 1H), 8.29 (m, 4H), 8.53 (d, J=6.1 Hz, 1H), 8.81 (d, J=6.2 Hz, 1H), 9.42 (s, 1H).
[0091] 1-[(S)-O-isoquinolinesulfonyl-N-tert-butyloxy carbonyl-N-methyl-tyrosyl]-4-(benzyl)-piperidine. Following the general procedure (B), this product was obtained as a white solid (yield 90%); m.p.=100-102°C, [ \textgreek{a} ]=-39.3, c=0.4% in CH₂Cl₂. 1H-NMR (CDCl₃) : 1.31 (s, 9H), 2.72 (m, 4H), 2.90 (m, 2H), 3.48 (m, 7H), 3.70 (m, 2H), 5.15 (t, J=7 Hz, 1H), 6.76 (m, J=8.6 Hz, 3H), 7.05 (m, J=8.6 Hz, 3H), 7.28 (m, 3H), 7.63 (m, 1H), 8.27 (m, J=7.8 Hz, 2H), 8.54 (d, J=6.1 Hz, 1H), 8.79 (d, J=6.1 Hz, 1H), 9.42 (s, 1H).

[0092] 1-[(S)-O-isoquinolinesulfonyl-N-tert-butyloxy carbonyl-tyrosyl]-4-(4-fluoro-phenyl)-piperazine. Following the general procedure (B), this product was obtained as a white solid (yield 79%); m.p.=87-89°C, [ \textgreek{a} ]=-1.6, c=0.63 % in CH₂Cl₂. 1H-NMR (CDCl₃) : 1.39 (s, 9H), 2.65 (m, 1H), 2.92 (m, 6H), 3.43 (m, 2H), 3.78 (m, 1H), 4.76 (m, 1H), 5.33 (d, 1H), 6.82 (m, 4H), 7.01 (m, 4H), 7.54 (t, J=7.6 Hz, 1H), 8.22 (dd, J=7.5 and 8.2 Hz, 2H), 8.53 (d, J=6.1 Hz, 1H), 8.80 (d, J=6.1 Hz, 1H), 9.41 (s, 1H).

[0093] 1-[(S)-O-isoquinolinesulfonyl-N-tert-butyloxy carbonyl-tyrosyl]-4-(o-tolyl)-piperazine. Following the general procedure (B), this product was obtained as a white solid (yield 73%); m.p.=73-75°C, [ \textgreek{a} ]=+22.5, c=1.3% in CH₂Cl₂. 1H-NMR (CDCl₃) : 1.39 (s, 9H), 2.27 (s, 3H), 2.42 (m, 1H), 2.75 (m, 3H), 2.91 (d, J=6.7 Hz, 2H), 3.15 (m, 1H), 3.51 (m, 3H), 4.80 (m, 1H), 5.37 (d, J=8.5 Hz, 1H), 6.80 (d, J=8.5 Hz, 2H), 6.90 (d, J=7.8 Hz, 1H), 7.05 (t, J=8.4 Hz, 3H), 7.18 (t, J=7.3 Hz, 2H), 7.54 (t, J=7.8, 1H), 8.22 (dd, J=8.2 and 7.3 Hz, 2H), 8.54 (d, J=6.2 Hz, 1H), 8.81 (d, J=6 Hz, 1H), 9.41 (s, 1H).

[0094] General procedure for removal the Boc protecting group from compounds Cₖ. The ester Cₖ (1.5 mmol) was stirred at rt. in a mixture of
TFA/CH₂Cl₂ (1:1, 5 mL) for 3 h. The volatiles were removed in vacuo and the residue was diluted with 5% aqueous NaHCO₃ (5 mL). The aqueous mixture was extracted with CH₂Cl₂ (3x5 mL) and the combined organic extracts were dried (Na₂SO₄) and concentrated in vacuo. The residue obtained was used for the next reaction without any purification.

[0095] General procedure (C) for the synthesis of compounds Dᵣ. To a stirred solution of the appropriate free amine (0.5 mmol) in dry DCM (5 mL) were added Et₃N (70 L, 0.5 mmol, 1 equiv.) and then dropwise isoquinolinesulfonyle chloride (1 mmole, 2 equiv.) dissolved in DCM (3 mL), under cooling with ice. The reaction mixture obtained was allowed to slowly warm up to rt. and stirred for 18 h. After this time, the mixture was diluted with DCM (5 mL) and washed with a saturated aqueous NaHCO₃ (2 mL), water (5 mL) and brine (5 mL). After the layers were separated, the organic layer was dried (Na₂SO₄) and concentrated in vacuo. The residue obtained, subjected to purification by column chromatography, furnished the appropriate product Dᵣ.

[0096] Preparation of 1-[(S)-N,O-bis-(isoquinolinesulfonyl)-N-methyl-tyrosyl]-4-(benzyl)piperazin. Following the general procedure (C), this product was obtained as a yellow solid (yield 35%); m.p.=92-94°C, [ ]=-33.8, c=0.95% in CHCl₃. 1H-NMR (CDCl₃) : 1.95 (m, 1H), 2.16 (m, 1H), 2.25 (t, J=4.7 Hz, 2H), 2.49 (dd, J=12.4 and 4.6 Hz, 1H), 3.04 (m, 4H), 3.19 (dd, J=10.3 Hz, 2H), 3.40 (m, 4H), 5.06 (dd, J=10.3 and 4.5 Hz, 1H), 6.76 (d, J= 8.6 Hz, 2H), 6.95 (d, J=8.6 Hz, 2H), 7.27 (m, 5H), 7.59 (t, J=7.8 Hz, 1H), 7.88 (t, J=7.6 Hz, 1H), 8.25 (m, J= 8.2 and 7.7 Hz, 4H), 8.39 (d, J=6.1 Hz, 1H), 8.56
(d, J=6.2 Hz, 1H), 8.66 (d, J=6.2 Hz, 1H), 8.83 (d, J=6.1 Hz, 1H), 9.35 (s, 1H),
9.43 (s, 1H).

[0097] 1-[(S)-N,O-bis-(isoquinolinesulfonyl)-N-methyl-tyrosyl]-4-
(phenethyl)-piperazine. Following the general procedure (C), this product was
obtained as a yellow solid (yield 25%); m.p.=98-100°C, [ ]+33.2, c=0.84% in
CH₂Cl₂. 1H-NMR (CDCl₃) : 1.94 (m, 6H), 2.47 (m, 2H), 2.73 (m, 5H), 3.04
(m, 4H), 4.31 (m, 1H), 6.12 (m, 1H), 6.63 (d, J= 8.5 Hz, 2H), 6.86 (d, J=8.5 Hz,
2H), 7.22 (m, 5H), 7.62 (dt, J=7.8 Hz, 2H), 8.23 (m, 5H), 8.51 (d, J=6 Hz, 1H),
8.68 (d, J=6.2 Hz, 1H), 8.80 (d, J=6.2 Hz, 1H), 9.32 (s, 1H), 9.41 (s, 1H).

[0098] 1-[(S)-N,O-bis-(isoquinolinesulfonyl)-N-methyl-tyrosyl]-4-(4-
fluorophenyl)-piperazine. Following the general procedure (C), this product
was obtained as a yellow solid (yield 38%); m.p.=110-112°C, [ ]=-56.6, c=0.45%
in CHCl₃. 1H-NMR (CDCl₃) : 2.42 (dd, J=12.6 and 6.2 Hz, 1H), 2.63 (m,
1H), 2.89 (m, 2H), 3.03 (s, 3H), 3.25 (dd, J=12.6 Hz, 2H) 3.55 (m, 4H), 5.12
(dd, J=12 and 6.2 Hz, 1H), 6.80 (m, J=8.5 Hz, 4H), 6.99 (m, J=8.5 Hz, 4H),
7.55 (t, J=7.9 Hz, 1H), 7.71 (t, J=7.9 Hz, 1H), 8.25 (m, J=8 Hz, 4H), 8.42 (d,
J=6.3 Hz, 1H), 8.52 (d, J=6.3 Hz, 1H), 8.68 (d, J=6.3 Hz, 1H), 8.81 (d, J=6.3
Hz, 1H), 9.36 (s, 1H), 9.41 (s, 1H).

[0099] 1-[(S)-N,O-bis-(isoquinolinesulfonyl)-N-methyl-tyrosyl]-4-(4-
chlorophenyl)-piperazine. Following the general procedure (C), this product
was obtained as a yellow oil (yield 61%); [ ]=-43.4, c=0.89% in CHCl₃. 1H-
NMR (CDCl₃) : 2.44 (dd, J=12.6 and 6.2 Hz, 2H), 2.92 (m, 4H), 3.00 (s, 3H),
3.57 (m, 4H), 5.11 (dd, J=6.6 and 6.2 Hz, 1H), 6.76 (d, J=8.6 Hz, 4H), 6.95 (d,
J=8.6 Hz, 2H), 7.23 (d, J=6.6 Hz, 1H), 7.54 (d, J=8 Hz, 1H), 7.70 (t, J=7.8 Hz,
1H), 8.23 (m, 4H), 8.41 (d, J=6 Hz, 1H), 8.49 (d, J=6 Hz, 1H), 8.67 (d, J=6.2 Hz, 1H), 8.80 (d, J=6 Hz, 1H), 9.35 (s, 1H), 9.41 (s, 1H).

[00100] 1-[(S)-N,O-bis-(isoquinolinesulfonyl)-N-methyl-tyrosyl]-4-(4-iodophenyl)-piperazine. Following the general procedure (C), this product was obtained as a yellow solid (yield 44%); m.p.=95-97°C, [ ]=−46.0, c=0.73% in CHCl₃. 1H-NMR (CDCl₃) : 2.42 (dd, J=12.6 and 6.2 Hz, 1H), 2.63 (m, 1H), 2.99 (m, 5H), 3.22 (m, 2H), 3.55(m, 4H), 5.11 (dd, J=13.6 and 6 Hz, 1H), 6.63 (d, J=8.9 Hz, 2H), 6.77 (d, J=8.4 Hz, 2H), 6.96 (d, J=8.4 Hz, 2H), 7.54 (m, J=8.8 and 7.8 Hz, 3H), 7.71 (t, J=7.8 Hz, 1H), 8.24 (m, J=7.6 Hz, 4H), 8.42 (d, J=6.3 Hz, 1H), 8.50 (d, J=6.1 Hz, 1H), 8.68 (d, J=6.1 Hz, 1H), 8.81 (d, J=6.1 Hz, 1H), 9.36 (s, 1H), 9.41 (s, 1H).

[00101] 1-[(S)-N,O-bis-(isoquinolinesulfonyl)-N-methyl-tyrosyl]-4-(p-tolyl)-piperazine. Following the general procedure, this product was obtained as a foam yellow oil (yield 58%); m.p.=70-72°C, [ ]=−41.5, c=0.45% in CHCl₃. 1H-NMR (CDCl₃) : 2.28 (s, 3H), 2.89 (m, 2H), 3.04 (s, 3H), 3.21 (m, 4H), 3.49 (m, 4H), 5.14.(dd, J=12 and 6.2 Hz, 1H), 6.77 (dd, J=6.2 and 3 Hz, 2H), 6.96 (d, J=8.6 Hz, 2H), 7.09 (d, J=8.4 Hz, 2H), 7.49 (t, J=7.8 Hz, 1H), 7.70 (t, J=7.8 Hz, 1H), 8.13 (d, J=7.4 Hz, 2H), 8.17 (t, J=8.8 Hz, 2H), 8.24 (t, J=7.8 Hz, 1H), 8.31 (d, J=7.2 Hz, 1H), 8.41 (d, J=6 Hz, 1H), 8.51 (d, J=6.2 Hz, 1H), 8.68 (d, J=6.2 Hz, 1H), 8.81 (d, J=6 Hz, 1H), 9.35 (s, 1H), 9.40 (s, 1H).

[00102] 1-[(S)-N,O-bis-(isoquinolinesulfonyl)-N-methyl-tyrosyl]-4-(4-methoxyphenyl)-piperazine. Following the general procedure (C), this product was obtained as a white solid (yield 47%); m.p.=85-87°C, [ ]=−48.4, c=0.94% in CHCl₃. 1H-NMR (CDCl₃) : 2.48 (dd, J=12 and 4.4 Hz, 2H), 2.83
(m, 4H), 3.16 (s, 3H), 3.52 (m, 4H), 3.77 (s, 3H), 5.11 (dd, J=6.6 and 6.2 Hz, 1H), 6.76 (m, 6H), 6.96 (d, J=8.4 Hz, 2H), 7.51 (d, J=8 Hz, 1H), 7.69 (t, J=8 Hz, 1H), 8.23 (m, 4H), 8.41 (d, J=6.2 Hz, 1H), 8.51 (d, J=6.2 Hz, 1H), 8.67 (d, J=6.2 Hz, 1H), 8.80 (d, J=6.2 Hz, 1H), 9.35 (s, 1H), 9.40 (s, 1H).

[00103] 1-[(S)-N,O-bis(isoquinolinesulfonyl)-N-methyl-tyrosyl]-4-(4-nitrophenyl)-piperazine. Following the general procedure (C), this product was obtained as a yellow solid (yield 76%); m.p.=77-79°C, [α] D =–86, c=1.02% in CHCl₃. 1H-NMR (CDCl₃): 2.34 (dd, J=14 and 6.2 Hz, 2H), 3.01 (s, 3H), 3.28 (m, 4H), 3.64 (m, 4H), 5.19 (dd, J=13.8 and 6.2 Hz, 1H), 6.78 (d, J=5.2 Hz, 2H), 6.81 (d, J=5.6 Hz, 2H), 6.98 (d, J=8.6 Hz, 2H), 7.59 (t, J=7.8 Hz, 1H), 7.73 (t, J=7.8 Hz, 1H), 8.13 (d, J=7.4 Hz, 2H), 8.17 (d, J=7.4 Hz, 2H), 8.20 (t, J=8.8 Hz, 1H), 8.23 (t, J=8.8 Hz, 1H), 8.44 (d, J=6.2 Hz, 1H), 8.50 (d, J=6.2 Hz, 1H), 8.68 (d, J=6.2 Hz, 1H), 8.80 (d, J=6 Hz, 1H), 9.37 (s, 1H), 9.42 (s, 1H).

[00104] 1-[(S)-N,O-bis(isoquinolinesulfonyl)-N-methyl-tyrosyl]-4-(4-cyanophenyl)-piperazine. Following the general procedure (C), this product was obtained as a yellow solid (yield 58%); m.p.=125-127°C, [α] D =–67.2, c=0.75% in CHCl₃. 1H-NMR (CDCl₃): 2.17 (dd, J=12.6 and 6.2 Hz, 2H), 3.00 (s, 3H), 3.17 (m, 4H), 3.69 (m, 4H), 5.11 (dd, J=6.6 and 6 Hz, 1H), 6.80 (m, 4H), 6.97 (d, J=6.8 Hz, 2H), 7.52 (d, J=8.6 Hz, 1H), 7.58 (t, J=7.6 Hz, 1H), 7.72 (t, J=7.8 Hz, 1H), 8.30 (m, 4H), 8.41 (d, J=6 Hz, 1H), 8.49 (d, J=6 Hz, 1H), 8.67 (d, J=6.2 Hz, 1H), 8.81 (d, J=6 Hz, 1H), 9.37 (s, 1H), 9.42 (s, 1H).

[00105] 1-[(S)-N,O-bis(isoquinolinesulfonyl)-N-methyl-tyrosyl]-4-(4-acetylphenyl)-piperazine. Following the general procedure (C), this product was obtained as a yellow solid (yield 43%); m.p.=82-84°C, [α] D =–56.9, c=1.12%
in CHCl₃. 1H-NMR (CDCl₃) : 2.42 (dd, J=12.6 and 6.2 Hz, 1H), 2.53 (s, 3H),
2.90 (m, 1H), 3.02 (s, 3H), 3.21 (m, 5H), 3.63 (m, 3H), 5.14 (dd, J=12 and 6.2
Hz, 1H), 6.79 (t, J=8.5, 4H), 6.95 (d, J=8.5 Hz, 2H), 7.52 (t, J=7.8 Hz, 1H), 7.71
(t, J=7.8 Hz, 1H), 7.89 (d, J=8.9 Hz, 2H), 8.24 (m, J=7.4 Hz, 4H), 8.41 (d,
J=6.1 Hz, 1H), 8.49 (d, J=6.2 Hz, 1H), 8.68 (d, J=6.2 Hz, 1H), 8.79 (d, J=6.1
Hz, 1H), 9.35 (s, 1H), 9.39 (s, 1H).

[00106] Preparation of 1-[(S)-N,O-bis-(isoquinolinesulfonyl)-N-
methyl-tyrosyl]-4-(4-fluorobenzyl)-piperazine. Following the general
procedure (C), this product was obtained as a yellow solid (yield 10%);
m.p.=103-105°C, [ ]=−21.5, c=0.72% in CHCl₃. 1H-NMR (CDCl₃) : 1.95 (m,
1H), 2.24 (m, 3H), 2.49 (dd, J=12.4 and 4.6 Hz, 1H), 3.04 (m, 4H), 3.14 (m,
2H), 3.38 (m, 4H), 5.06 (dd, J=10.3 and 4.5 Hz, 1H), 6.78 (d, J= 8.4 Hz, 2H),
6.99 (m, J=8.4 Hz, 4H), 7.22 (m, 2H), 7.66 (dt, J=7.8 Hz, 2H), 8.25 (m, 4H),
8.39 (d, J=6.2 Hz, 1H), 8.56 (d, J=6 Hz, 1H), 8.66 (d, J=6.3 Hz, 1H), 8.83 (d,
J=6.2 Hz, 1H), 9.36 (s, 1H), 9.44 (s, 1H).

[00107] 1-[(S)-N,O-bis-(isoquinolinesulfonyl)-N-methyl-tyrosyl]-4-(4-
fluorobenzoyl)-piperazine. Following the general procedure (C), this product
was obtained as a yellow solid (yield 18%); m.p.=124-126°C, [ ]=−37.8,
c=0.82% in CH₂Cl₂. 1H-NMR (CDCl₃) : 2.49 (m, 1H), 2.79 (m, 1H), 3.03 (s,
3H), 3.28 (m, 6H), 3.57 (m, 2H), 5.07 (dd, J=10.9 and 4.3 Hz, 1H), 6.79 (d, J= 8.4 Hz, 2H), 6.97 (d, J=8.5 Hz, 2H), 7.12 (t, J=8.6 Hz, 2H), 7.44 (m, 2H), 7.72
(t, J=7.9 Hz, 2H), 8.31 (m, 5H), 8.54 (d, J=5.9 Hz, 1H), 8.68 (d, J=6 Hz, 1H),
8.84 (d, J=6 Hz, 1H), 9.38 (s, 1H), 9.45 (s, 1H).
[00108] 1-\[(S)-N,O-bis-(isoquinolinesulfonyl)-N-methyl-tyrosyl\]-4-(4-nitrobenzyl)-piperazine. Following the general procedure (C), this product was obtained as a yellow solid (yield 40%); m.p.=145-147°C, \( \delta \)=28.4, c=0.37% in CHCl\(_3\). 1H-NMR (CDCl\(_3\)) : 1.95 (m, 1H), 2.27 (m, 3H), 2.49 (dd, J=12.4 and 4.6 Hz, 1H), 2.02 (m, 4H), 3.21 (dd, J=10.3 Hz, 2H), 3.49 (m, 4H), 5.12 (dd, J=10.3 and 4.5 Hz, 1H), 6.82 (d, J=8.4 Hz, 2H), 6.97 (d, J=8.6 Hz, 2H), 7.48 (d, J=8.4 Hz, 2H), 7.68 (m, J=8.3 Hz, 2H), 8.18 (d, J=8.6 Hz, 3H), 8.30 (m, J=7.5 Hz, 3H), 8.40 (d, J=6 Hz, 1H), 8.55 (d, J=6.2 Hz, 1H), 8.67 (d, J=6 Hz, 1H), 8.83 (d, J=6.3 Hz, 1H), 9.37 (s, 1H), 9.45 (s, 1H).

[00109] 1-\[(S)-N,O-bis-(isoquinolinesulfonyl)-N-methyl-tyrosyl\]-4-(2-fluorophenyl)-piperazine. Following the general procedure (C), this product was obtained as a yellow solid (yield 76%); m.p.=133-135°C, \( \delta \)=58.4, c=0.44% in CHCl\(_3\). 1H-NMR (CDCl\(_3\)) : 2.49 (m, 2H), 3.06 (s, 3H), 3.22 (m, 4H), 3.63 (m, 4H), 5.11 (dd, J=13.6 and 6 Hz, 1H), 6.79 (m, 4H), 7.00 (m, 4H), 7.57 (t, J=8.2 Hz, 1H), 7.70 (t, J=7.8 Hz, 1H), 8.25 (m, 4H), 8.41 (d, J=6.2 Hz, 1H), 8.52 (d, J=6.2 Hz, 1H), 8.67 (d, J=6.2 Hz, 1H), 8.81 (d, J=6.2 Hz, 1H), 9.36 (s, 1H), 9.42 (s, 1H).

[00110] 1-\[(S)-N,O-bis-(isoquinolinesulfonyl)-N-methyl-tyrosyl\]-4-(2-chlorophenyl)-piperazine. Following the general procedure (C), this product was obtained as a yellow solid (yield 58%); m.p.=84-86°C, \( \delta \)=39.2, c=0.92% in CHCl\(_3\). 1H-NMR (CDCl\(_3\)) : 2.48 (m, J=12.4 and 4.6 Hz, 2H), 2.83 (m, 2H), 3.07 (s, 3H), 3.23 (t, J=10.4 Hz, 2H), 3.58 (m, 4H), 5.12 (dd, J=10.3 and 4.5 Hz, 1H), 6.77 (d, J=8.6 Hz, 2H), 6.97 (m, J=8.6 Hz, 4H), 7.23 (d, J=7.8 Hz, 1H), 7.38 (d, J=8.8 Hz, 1H), 7.58 (t, J=7.8 Hz, 1H), 7.71 (t, J=7.7 Hz, 1H), 8.25
(m, J=8.3 and 7.4 Hz, 4H), 8.42 (d, J=6.2 Hz, 1H), 8.54 (d, J=6 Hz, 1H), 8.68 (d, J=5.9 Hz, 1H), 8.82 (d, J=6.2 Hz, 1H), 9.37 (s, 1H), 9.43 (s, 1H).

[00111] 1-[(S)-N,O-bis-(isoquinolinesulfonyl)-N-methyl-tyrosyl]-4-(o-tolyl)-piperazine. Following the general procedure (C), this product was obtained as a yellow solid (yield 58%); m.p.=84-86°C, [ ]<sub>D</sub>=-39.2, c=0.92% in CHCl₃. 1H-NMR (CDCl₃): 2.28 (s, 3H), 2.35 (m, 1H), 2.49 (dd, J=12.4 and 4.6 Hz, 1H), 2.68 (m, 2H), 3.06 (s, 3H), 3.30 (m, 2H), 3.58 (m, 4H), 5.12 (dd, J=10.3 and 4.5 Hz, 1H), 6.81 (t, J= 9.0 and 8.4 Hz, 3H), 7.02 (m, J=8.9 and 8.5 Hz, 3H), 7.18 (t, J=7.4 Hz, 2H), 7.56 (t, J=7.7 Hz, 1H), 7.72 (t, J=7.7 Hz, 1H), 8.27 (m, J=8.4 and 6.1 Hz, 4H), 8.42 (d, J=6.2 Hz, 1H), 8.54 (d, J=6 Hz, 1H), 8.68 (d, J=6.2 Hz, 1H), 8.82 (d, J=6 Hz, 1H), 9.37 (s, 1H), 9.43 (s, 1H).

[00112] 1-[(S)-N,O-bis-(isoquinolinesulfonyl)-N-methyl-tyrosyl]-4-(2-methoxyphenyl)-piperazine. Following the general procedure (C), this product was obtained as a yellow solid (yield 10%); m.p.=85-87°C, [ ]<sub>D</sub>=-29.8, c=0.45% in CHCl₃. 1H-NMR (CDCl₃): 2.51 (dd, J=12.6 and 6.2 Hz, 1H), 2.62 (m, 1H), 2.87 (m, 2H), 3.07 (s, 3H), 3.22 (m, 2H), 3.56 (m, 4H), 3.87 (s, 3H), 5.15 (dd, J=13.6 and 6 Hz, 1H), 6.76 (d, J=8.6 Hz, 2H), 6.97 (m, J=7.9 Hz, 4H), 7.30 (m, 1H), 7.63 (m, 3H), 8.11 (d, J=8.1 Hz, 1H), 8.27 (m, J=7.3 Hz, 3H), 8.44 (m, 1H), 8.54 (d, J=6 Hz, 1H), 8.75 (m, 2H), 9.40 (m, 2H).

[00113] 1-[(S)-N,O-bis-(isoquinolinesulfonyl)-N-methyl-tyrosyl]-4-(3-chlorophenyl)-piperazine. Following the general procedure (C), this product was obtained as a yellow solid (yield 67%); m.p.=138-140°C, [ ]<sub>D</sub>=-58.8, c=0.6% in CHCl₃. 1H-NMR (CDCl₃): 2.42 (m, 2H), 2.99 (s, 3H), 3.22 (m, 4H), 3.59 (m, 4H), 5.12 (dd, J=12 and 6.2 Hz, 1H), 6.79 (m, 4H), 6.89 (m, 3H), 7.21 (t,
J=8 Hz, 1H), 7.54 (t, J=8 Hz, 1H), 7.72 (t, J=8 Hz, 1H), 8.26 (m, 4H), 8.42 (d, J=6.2 Hz, 1H), 8.51 (d, J=6.2 Hz, 1H), 8.68 (d, J=6.2 Hz, 1H), 8.81 (d, J=6.2 Hz, 1H), 9.37 (s, 1H), 9.42 (s, 1H).

1-{[S]-N,O-bis-(isoquinolinesulfonfyl)-N-methyl-tyrosyl}-4-{3-trifluoromethylphenyl}-piperazine. Following the general procedure (C), this product was obtained as a yellow solid (yield 20%); m.p.=81-83°C, [ ]=-61.5, c=0.4% in CHCl3. 1H-NMR (CDCl3) : 2.48 (dd, J=12 and 4.4 Hz, 1H), 2.75 (m, 1H), 2.93 (m, 5H), 3.30 (m, 2H), 3.62 (m, 4H), 5.11 (dd, J=6.6 and 6.2 Hz, 1H), 6.78 (d, J=8.6 Hz, 2H), 6.99 (m, J=8.6 Hz, 4H), 7.15 (d, J=7.8 Hz, 1H), 7.40 (t, J=8.8 Hz, 1H), 7.55 (t, J=7.8 Hz, 1H), 7.72 (t, J=7.7 Hz, 1H), 8.23 (m, 4H), 8.43 (d, J=6 Hz, 1H), 8.51 (d, J=6.3 Hz, 1H), 8.68 (d, J=6.4 Hz 1H), 8.80 (d, J=6 Hz 1H), 9.36 (s, 1H), 9.41 (s, 1H).

1-{[S]-N,O-bis-(isoquinolinesulfonfyl)-N-methyl-tyrosyl}-4-{(2,3-dimethylphenyl)}-piperazine. Following the general procedure (C), this product was obtained as a brown solid (yield 21%); m.p.=174-176°C, [ ]=-17.5, c=1.91% in CH2Cl2. 1H-NMR (CDCl3) : 2.19 (s, 3H), 2.27 (s, 3H), 2.49 (dd, J=12.4 and 4.6 Hz, 1H), 2.68 (m, 3H), 3.06 (s, 3H), 3.25 (m, 2H), 3.58 (m, 4H), 5.12 (dd, J=10.3 and 4.5 Hz, 1H), 6.76 (m, J=8.7 Hz, 3H), 7.03 (m, J=8.7 Hz, 4H), 7.56 (t, J=7.7 Hz, 1H), 7.71 (t, J=7.7 Hz, 1H), 8.26 (m, J=7 Hz, 4H), 8.44 (d, J=6.1 Hz, 1H), 8.54 (d, J=6.2 Hz, 1H), 8.68 (d, J=6.2 Hz, 1H), 8.82 (d, J=6 Hz, 1H), 9.36 (s, 1H), 9.42 (s, 1H).

1-{[S]-N,O-bis-(isoquinolinesulfonfyl)-N-methyl-tyrosyl}-4-{(3,4-dichlorophenyl)}-piperazine. Following the general procedure (C), this product was obtained as a yellow solid (yield 64%); m.p.=130-132°C, [ ]=-
73.4, c=0.44% in CHCl₃. 1H-NMR (CDCl₃) : 2.96 (m, 2H), 3.02 (s, 3H), 3.41 (m, 4H), 3.63 (m, 4H), 5.16 (dd, J=13.6 and 6 Hz, 1H), 6.80 (m, 4H), 6.94 (t, J=8.4 Hz, 3H), 7.57 (t, J=8 Hz, 1H), 7.72 (t, J=6 Hz, 1H), 8.22 (m, 4H), 8.44 (d, J=6 Hz, 1H), 8.52 (d, J=6 Hz, 1H), 8.66 (d, J=6 Hz, 1H), 8.81 (d, J=6 Hz, 1H), 9.37 (s, 1H), 9.42 (s, 1H).

[00117] 1-[(S)-N,O-bis-(isoquinolinesulfonyl)-N-methyl-tyrosyl]-4-(pyridin-2-yl)-piperazine. Following the general procedure (C), this product was obtained as a yellow solid (yield 48%); m.p.=183-185°C, [α] = -55.8, c=0.41% in CH₂Cl₂. 1H-NMR (CDCl₃) : 2.46 (dd, J=12.7 and 4.3 Hz, 1H), 2.91 (m, 1H), 3.05 (s, 3H), 3.21 (m, J=10.6 Hz, 3H), 3.42 (m, 3H), 5.09 (dd, J=10.4 and 4.4 Hz, 1H), 6.60 (d, J=8.6 Hz, 1H), 6.70 (m, J=8.4 Hz, 3H), 6.96 (d, J=8.4 Hz, 2H), 7.53 (m, 2H), 7.70 (t, J=7.8 Hz, 1H), 8.12 (d, J=7.3 Hz, 1H), 8.22 (m, 3H), 8.30 (d, J=7.3 Hz, 1H), 8.41 (d, J=6.2 Hz, 1H), 8.51 (d, J=6.2 Hz, 1H), 8.67 (d, J=6.3 Hz, 1H), 8.80 (d, J=6.1 Hz, 1H), 9.35 (s, 1H), 9.40 (s, 1H).

[00118] 1-[(S)-N,O-bis-(isoquinolinesulfonyl)-N-methyl-tyrosyl]-4-(pyrimidin-2-yl)-piperazine. Following the general procedure (C), this product was obtained as a yellow solid (yield 32%); m.p.=187-189°C, [α] = -54.6, c=0.76% in CH₂Cl₂. 1H-NMR (CDCl₃) : 2.46 (dd, J=12.7 and 4.3 Hz, 1H), 3.00 (m, 1H), 3.06 (s, 3H), 3.41 (m, J=10.4 Hz, 6H), 3.80 (m, 2H), 5.09 (dd, J=10.4 and 4.4 Hz, 1H), 6.56 (t, J=8.6 Hz, 1H), 6.74 (d, J=8.5 Hz, 2H), 6.96 (d, J=8.5 Hz, 2H), 7.57 (t, J=7.8 Hz, 1H), 7.70 (t, J=7.8 Hz, 1H), 8.21 (m, J=7.6 Hz, 4H), 8.33 (m, 2H), 8.40 (d, J=6.3 Hz, 1H), 8.52 (d, J=6.1 Hz, 1H), 8.67 (d, J=6 Hz, 1H), 8.82 (d, J=6 Hz, 1H), 9.35 (s, 1H), 9.41 (s, 1H).
[00119] 1-[(S)-N,O-bis-(isoquinolinesulfonyl)-N-methyl-tyrosyl]-4-(benzyl)-piperidine. Following the general procedure (C), this product was obtained as a yellow solid (yield 35%); m.p.=131-133°C, [α]D=-24, c=0.42% in CH2Cl2. 1H-NMR (CDCl3) : 1.50 (m, 2H), 2.39 (m, 6H), 2.70 (m, 1H), 3.04 (s, 3H), 3.25 (m, 2H), 3.80 (m, 1H), 4.40 (m, 1H), 5.10 (m, 1H), 6.73 (m, 1H), 6.88 (d, J=8.6 Hz, 2H), 7.05 (m, 3H), 7.24 (m, 3H), 7.68 (m, 2H), 8.26 (m, 4H), 8.41 (d, J=6.1 Hz, 1H), 8.56 (d, J=6.2 Hz, 1H), 8.68 (d, J=6.2 Hz, 1H), 8.82 (d, J=6 Hz, 1H), 9.35 (s, 1H), 9.43 (s, 1H).

[00120] 1-[(S)-N,O-bis-(isoquinolinesulfonyl)tyrosyl]-4-(4-fluorophenyl)-piperazine. Following the general procedure (C), this product was obtained as a yellow solid (yield 50%); m.p.=145-147°C, [α]D=+47.7, c=0.62 % in CH2Cl2. 1H-NMR (CDCl3) : 2.22 (m, 2H), 2.50 (m, 4H), 3.06 (m, 3H), 3.25 (m, 1H), 4.35 (m, 1H) 5.99 (d, 1H), 6.65 (d, J=8.4 Hz, 2H), 6.78 (m, 2H), 6.88 (d, J=8.5 Hz, 2H), 6.99 (t, J=8.5 Hz, 2H), 7.58 (m, 2H), 8.16 (t, J=8 Hz, 2H), 8.27 (t, J=6.5 Hz, 3H), 8.51 (d, J=6.3 Hz, 1H), 8.70 (d, J=6.3 Hz, 1H), 8.82 (d, J=6 Hz, 1H), 9.30 (s, 1H), 9.41 (s, 1H).

[00121] 1-[(S)-N,O-bis-(isoquinolinesulfonyl)-tyrosyl]-4-(o-tolyl)-piperazine. Following the general procedure (C), this product was obtained as a yellow solid (yield 88%); m.p.=132-134°C, [α]D=+80.3, c=1% in CH2Cl2. 1H-NMR (CDCl3) : 2.24 (s, 3H), 2.36 (m, 3H), 2.54 (m, 1H), 2.80 (d, J=7.2 Hz, 2H), 2.93 (m, 1H), 3.06 (m, 1H), 3.25 (m, 2H), 4.35 (m, J=7.5 Hz, 1H), 6.09 (d, J=9.1 Hz, 1H), 6.4 (d, J=8.3 Hz, 2H), 6.85 (m, J=8.6 and 7.8 Hz, 3H), 7.03 (t, J=7.4 Hz, 1H), 7.18 (m, 2H), 7.55 (t, J=7.9 Hz, 1H), 7.63 (t, J=7.7 Hz, 1H), 8.24 (m, J=7.5 Hz, 5H), 8.52 (d, J=6 Hz, 1H), 8.69 (d, J=6.2 Hz, 1H), 8.82 (d, J=6 Hz, 2H), 9.33 (s, 1H), 9.41 (s, 1H).
[00122] Preparation of 1-[(S)-N,O-bis (isoquinolinesulfonyl)-N-methyl-tyrosyl]-4-(4-amino-phenyl)-piperazine. Following the general procedure (C), this product was obtained as a yellow solid (yield 45%);
m.p.=80-82°C, [γ]=−48.4 c=0.90% in CHCl3. 1H-NMR (CDCl3): 2.48 (m, 2H), 2.83 (m, 4H), 3.16 (s, 3H), 3.52 (m, 4H), 4.00 (m, 2H), 5.11 (dd, J=6.6 and 6.2 Hz, 1H), 6.28 (d, J=8.3 Hz, 2H), 6.34 (d, J=8.3 Hz, 2H), 6.76 (d, J=8.4 Hz, 2H), 6.96 (d, J=8.4 Hz, 2H), 7.51 (d, J=8 Hz, 1H), 7.69 (t, J=8 Hz, 1H), 8.23 (m, 4H), 8.41 (d, J=6.2 Hz, 1H), 8.51 (d, J=6.2 Hz, 1H), 8.67 (d, J=6.2 Hz, 1H), 8.80 (d, J=6.2 Hz, 1H), 9.35 (s, 1H), 9.40 (s, 1H).

[00123] 1,2,3,4-Tetrahydro-2-[(S)-N,O-bis(isoquinolinesulfonyl)-tyrosyl]-1,4-pyrazino[1,2-a]indole. Following the general procedure C this product was obtained. m.p. 83-85°C; [α] = +8.0, c=0.5% in CHCl3; 1H-NMR (CDCl3): d 2.86 (m, 5H), 3.45 (m, 2H), 3.64 (m, 1H), 4.28 (m, 2H), 6.02 (d, J=9.4 Hz, 1H), 6.1 (t, J=14.6 Hz, 1H), 6.72 (m, 3H), 6.94 (m, 2H), 7.22 (m, 2H), 7.37 (m, 2H), 7.61 (t, J=8.2 Hz, 1H), 8.06 (m, 5H), 8.46 (d, J=6 Hz, 1H), 8.69 (m, 1H), 9.08 (s, 1H), 9.35 (s, 1H).

[00124] 1,2,3,4-Tetrahydro-2-[(S)-N,O-bis(isoquinolinesulfonyl)-N-methyl-tyrosyl]-1,4-pyrazino[1,2-a]indole. Following the general procedure C this product was obtained. m.p. 110-112°C; [α] = -4.5, c=0.58% in CHCl3; 1H-NMR (CDCl3): d 2.53 (m, 1H), 3.02 (s, 3H), 3.12 (m, 1H), 3.59 (m, 5H), 4.57 (dd, J=8.8 and 6 Hz, 1H), 4.86 (d, 8.8 Hz, 1H), 5.12 (m, 1H), 6.28 (d, J=9.0 Hz, 1H), 6.68 (t, J=6.8 Hz, 2H), 6.96 (t, J=6.8 Hz, 2H), 7.24 (m, 3H), 7.39 (q, J=7.2 Hz, 2H), 7.56 (t, J=7.8 Hz, 1H), 8.11 (m, 5H), 8.46 (d, J=6.2 Hz, 1H), 8.77 (t, J=4.2 Hz, 1H), 9.16 (s, 1H), 9.28 (s, 1H).
[00125] 1,2,3,4-Tetrahydro-2-[(S)-N,O-bis(isoquinolinesulfonoyl)-N-methyl-tyrosyl]-8-fluoro-1,4-pyrazino[1,2-a]indole. Following the general procedure C this product was obtained. m.p. 105-107°C; [a] = -37, c=0.58% in CHCl₃; 1H-NMR (CDCl₃): δ 2.53 (m, 1H), 3.02 (s, 3H), 3.24 (m, 1H), 3.69 (m, 5H), 4.64 (dd, J= 9.2 and 6.2 Hz, 1H), 4.88 (d, 8.8 Hz, 1H), 5.12 (m, 1H), 6.28 (d, J=9.0 Hz, 1H), 6.68 (t, J=9.0 Hz, 2H), 6.96 (m, 3H), 7.45 (t, J=7.8 Hz, 1H), 7.58 (t, J=7.8 Hz, 1H), 7.57 (t, J=7.8 Hz, 1H), 8.16 (m, 5H), 8.46 (d, J=6.0 Hz, 1H), 8.64 (d, J=4.2 Hz, 1H), 8.80 (t, J=6.4 Hz, 1H), 9.20 (s, 1H), 9.30 (s, 1H).

[00126] Changes in plasma membrane permeability. ATP-dependent increases in plasma membrane permeability were measured with the extracellular fluorescent tracer ethidium bromide (Molecular Probes, Inc., Eugene, OR). For ethidium bromide uptake cells were incubated in a thermostat-controlled fluorometer cuvette (37°C) for 20 min in the dark at a concentration of 10⁶ cells/ml in the presence of 20 mM ethidium bromide and challenged with 1 mM ATP. Cell suspension was incubated with KN62 or synthesized compounds (25 nM-5000 nM) for 5 min at 37°C before fluorimetric analysis in a stirred cuvette at 37°C. Fluorescence changes were monitored at the wavelength pair 360/580 nm. After several washings to remove the extracellular dye, cells were analyzed with an inverted fluorescence microscope (Olympus IMT-2, Olympus Optical Co. Ltd., Tokyo, Japan). All experiments were repeated three times.

[00127] Ca²⁺ measurements. Changes in Ca²⁺ were measured with the fluorescent indicator fura-2/AM (Molecular Probes, Inc., Eugene, OR) as described previously. Briefly, cells were loaded with 4 mM of fura-2/AM and
incubated in a thermostat-controlled (37°C) and magnetically stirred fluorometer cuvette (model LS50, Perkin-Elmer Ltd., Beaconsfield, UK).

Intracellular Ca²⁺ concentration was determined with the 340/380 excitation ratio at an emission wavelength of 500 nM. All experiments were repeated three times.

[00128] **Cytokine release.** IL-1β release was measured in macrophage monolayers primed for two h with bacterial endotoxin (lipopolysaccharide, LPS) at the concentration of 10 μg/ml, and the stimulated with 3 mM ATP for 30 min. Inhibitors, when used, were added 5 min prior to ATP. Supernatants were centrifuged for 5 min at 900 g to remove floating cells and were assayed for IL-1 content by ELISA (R&D Systems, Minneapolis, MN, USA).

### TABLE I

<table>
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<th>s</th>
<th>P2X₇ Antagonist Activity IC₅₀ (nM)</th>
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<tr>
<td>KN62</td>
<td>51</td>
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<tr>
<td>1-[(S)-N,O-bis-(isoquinolinesulfonyl)-N-methyl-tyrosyl]-4-(4-nitrophenyl)-piperazine</td>
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<td>tyrosyl]-4-(4-fluorophenyl)-piperazine</td>
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<tr>
<td>1-[S]-N,O-bis-(isoquinolinesulfonyl]-N-methyl-tyrosyl]-4-(pyridin-2-yl)-piperazine</td>
<td>170</td>
</tr>
<tr>
<td>1-[S]-N,O-bis-(isoquinolinesulfonyl]-N-methyl-tyrosyl]-4-(pyrimidin-2-yl)-piperazine</td>
<td>79.8</td>
</tr>
<tr>
<td>s</td>
<td>P2X&lt;sub&gt;7&lt;/sub&gt; Antagonist Activity IC&lt;sub&gt;50&lt;/sub&gt; (nM)</td>
</tr>
<tr>
<td>-----------------------------------------------------------------</td>
<td>--------------------------------------------------------</td>
</tr>
<tr>
<td>1-[(S)-N,O-bis-(isoquinolinesulfonyl)-N-methyl-tyrosyl]-4-(4-fluorobenzoyl)-piperazine</td>
<td>380.2</td>
</tr>
<tr>
<td>1-[(S)-N,O-bis-(isoquinolinesulfonyl)-N-methyl-tyrosyl]-4-benzylpiperidine</td>
<td>65.31</td>
</tr>
<tr>
<td>1-[(S)-N,O-bis-(isoquinolinesulfonyl)-N-methyl-tyrosyl]-4-phenethyl-piperazine</td>
<td>599.8</td>
</tr>
<tr>
<td>1-[(S)-N,O-bis-(3-pyridinesulfonyl)-N-methyl-tyrosyl]-4-phenyl-piperazine</td>
<td>955</td>
</tr>
<tr>
<td>1-[(S)-N,O-bis-(3-pyridinesulfonyl)-N-methyl-tyrosyl]-4-(2-methylphenyl)-piperazine</td>
<td>9120</td>
</tr>
<tr>
<td>1-[(S)-N,O-bis-(isoquinolinesulfonyl)tyrosyl]-4-(o-tolyl)-piperazine</td>
<td>28.84</td>
</tr>
<tr>
<td>1-[(S)-N,O-bis-(isoquinolinesulfonyl)-N-methyl-tyrosyl]-4-(2,3-dimethylphenyl)-piperazine</td>
<td>1122</td>
</tr>
</tbody>
</table>
What is claimed is:

[1] A compound of the formula

![Chemical Structure]

wherein R₁ and R₂ are independently hydrogen, C1-C4 alkyl, C1-C4 substituted alkyl, C1-C4 alkoxy, C1-C4 substituted alkoxy, C1-C4 acyl, halogen, cyano, nitro, amino, alkylamino, or dialkylamino;

R₃, R₄, R₅, R₆, R₇, and R₈ are independently CH or nitrogen;

R₉ is hydrogen or methyl;

R₁₀ is C=O or (CH₂)ₙ;

where n is 0, 1, 2, 3, or 4;

R₁₁ and R₁₂ are independently nitrogen or CH;

X₁ and X₂ are independently hydrogen, deuterium, tritium or halogen;

and

X₃ is nitrogen or CH;

[2] The pharmaceutically acceptable salts of the compounds of claim [1].
[3] A compound of claim [1] wherein R1 is methyl substituted at the ortho-
position; R2 is hydrogen; R3 and R8 are each nitrogen; R4, R5, R6, and
R7, are each CH; R9 is methyl; R10 is (CH2)n where n is 0; R11 and R12
are each CH; X1 and X2 are each tritium; and X3 is nitrogen.

[4] The compounds of claim [1] wherein R1 and R2 are independently
hydrogen; R3 and R8 are independently nitrogen; R4, R5, R6, and R7 are
independently CH; and R11, R12, and X3 are independently CH.

[5] The compounds of claim [1] wherein R3 and R8 are independently N
and where R4, R5, R6, and R7 are independently CH.

[6] The compound of claim [1] wherein R3, R5, R6, and R8 are
independently CH, and where R4 and R7 are independently nitrogen.

independently nitrogen and where R5 and R6 are independently CH.

[8] The compound of claim [1] wherein R3, R5, R6, and R8 are
independently nitrogen and where R4 and R7 are independently CH.

[9] The compound of claim [1] wherein R1 is hydrogen, R2 is hydrogen,
and R10 is (CH2)n wherein n is equal to 1.

[10] The compound of claim [1] wherein R1 is hydrogen, R2 is hydrogen,
and R10 is (CH2)n wherein n is equal to 2.

[11] The compound of claim [1] wherein R1 is a fluoro-group in the para-
position and R2 is hydrogen.

[12] The compound of claim [1] wherein R1 is a methyl-group in the para-
position and R2 is hydrogen.

[13] The compound of claim [1] wherein R1 is a nitro-group in the para-
position and R2 is hydrogen.

[14] The compound of claim [1] wherein R1 is a methyl-group in the ortho-
position and R2 is hydrogen.

[16] The compound of claim [1] wherein R₁ is a chloro-group in the ortho-position and R₂ is hydrogen.

[17] The compound of claim [1] wherein R₁ is a chloro-group in the para-position and R₂ is hydrogen.

[18] The compound of claim [1] wherein R₁ is an iodo-group in the para-position and R₂ is hydrogen.

[19] The compound of claim [1] wherein R₁ is a methoxy-group in the para-position and R₂ is hydrogen.

[20] The compound of claim [1] wherein R₁ is a cyano-group in the para-position and R₂ is hydrogen.

[21] The compound of claim [1] wherein R₁ is an acetyl-group in the para-position and R₂ is hydrogen.

[22] The compound of claim [1] wherein R₁ is a methoxy-group in the ortho-position and R₂ is hydrogen.

[23] The compound of claim [1] wherein R₁ is a methyl-group in the ortho-position and R₂ is a methyl-group in the meta-position.

[24] The compound of claim [1] wherein R₁ is a chloro-group in the meta-position and R₂ is hydrogen.

[25] The compound of claim [1] wherein R₁ is a trifluoromethyl-group in the meta-position and R₂ is hydrogen.

[26] The compound of claim [1] wherein R₁ is a chloro-group in the meta-position and R₂ is a chloro-group in the para position.

[27] The compound of claim [1] wherein R₁ and R₂ are independently hydrogen, R₁₁ is nitrogen, and R₁₂ is CH.
[28] The compound of claim [1] wherein $R_1$ and $R_2$ are independently hydrogen and $R_{11}$ and $R_{12}$ are independently nitrogen.

[29] The compound of claim [1] wherein $R_1$ is an amino-group in the para-position and $R_2$ is hydrogen.

[30] A compound of the formula

![Chemical Structure](image)

wherein:

$R_1$ is hydrogen, C1-C4 alkyl, C1-C4 alkoxy, C1-C4 acyl, halogen, cyano, nitro, amino, alkylamino, or dialkylamino; $R_9$ is hydrogen or methyl; and $X_1$ and $X_2$ are independently hydrogen, deuterium, tritium, or halogen.

[31] The pharmaceutically acceptable salts of the compounds of claim [30].

[32] A compound of the formula
wherein:

R₁ and R₂ are independently hydrogen, C1-C4 alkyl, C1-C4 alkoxy, C1-C4 acyl, halogen, cyano, nitro, amino, alkylamino, or dialkylamino;

R₉ is hydrogen or methyl;

X₁ and X₂ are independently hydrogen, deuterium, tritium, or halogen;

and

X₃ is CH or nitrogen.

[33] The pharmaceutically acceptable salts of claim [32].

[34] A compound of the formula
wherein:

R₁ and R₂ are independently hydrogen, C1-C4 alkyl, C1-C4 alkoxy, halogen, cyano, nitro, or amino;

R₃, R₄, R₅, R₆, R₇, and R₈ are independently CH or nitrogen;

n is 0, 1, 2, 3, 4; and

with the proviso that when n is 0 either R₁ or R₂ is not hydrogen.

[35] The salts of the compounds of claim [34] that are pharmaceutically acceptable.

[36] The compounds of claim [34] wherein R₃ and R₈ are independently N and where R₄, R₅, R₆, and R₇ are independently CH₁.

[37] The compounds of claim [34] wherein R₃, R₅, R₆, and R₈ are independently CH₁, and where R₄ and R₇ are independently nitrogen.

[38] The compounds of claim [34] wherein R₃, R₄, R₇, and R₈ are independently nitrogen and where R₅ and R₆ are independently CH.

[39] The compounds of claim [34] wherein R₃, R₅, R₆, and R₈ are independently nitrogen and where R₄ and R₇ are independently CH.

[40] The compounds of claim [34] wherein R₁ is hydrogen, R₂ is hydrogen, and n is equal to 1.

[41] The compounds of claim [34] wherein R₁ is a fluoro-group in the para-position and R₂ is hydrogen.

[42] The compounds of claim [34] wherein R₁ is a methyl-group in the para-position and R₂ is hydrogen.

[43] The compounds of claim [34] wherein R₁ is a nitro-group in the para-position and R₂ is hydrogen.

[44] The compounds of claim [34] wherein R₁ is a methyl-group in the ortho-
position and \( R_2 \) is hydrogen.

[45] The compounds of claim [34] wherein \( R_1 \) is a fluoro-group in the ortho-position and \( R_2 \) is hydrogen.

[46] The compounds of claim [34] wherein \( R_1 \) is a chloro-group in the ortho-position and \( R_2 \) is hydrogen.

[47] The compounds of claim [34] wherein \( R_1 \) is a chloro-group in the meta-position and \( R_2 \) is hydrogen.

[48] The compounds of claim [34] wherein \( R_1 \) is a chloro-group in the meta-position and \( R_2 \) is a chloro-group in the para position.

[49] A method of identifying tumor cells rich in purinergic P2X7 receptors in a mammal, comprising administering to the mammal an amount of a compound of claim [1] sufficient to label the purinergic receptors.

[50] The method of claim [49] wherein the compound is methyl substituted at the ortho-position; \( R_2 \) is hydrogen; \( R_3 \) and \( R_8 \) are each nitrogen; \( R_4, R_5, R_6, \) and \( R_7 \), are each CH; \( R_9 \) is methyl; \( R_{10} \) is \((\text{CH}_2)_n\) where \( n \) is 0; \( R_{11} \) and \( R_{12} \) are each CH; \( X_1 \) and \( X_2 \) are each tritium; and \( X_3 \) is nitrogen.

[51] A method of treating a medical condition in a mammal, comprising the administration to the mammal in need thereof, of an effective amount of a compound of claim [1], [30], [32], or [34].

[52] The method of claim [51] wherein the compound is one of the pharmaceutically acceptable salts of the compounds of claim [1].

[53] The method of claim [51] wherein the compound one of the pharmaceutically acceptable salts of the compounds of claim [30].

[54] The method of claim [51] wherein the compound is one of the pharmaceutically acceptable salts of the compounds of claim [32].

[55] The method of claim [51] wherein the compound is one of the
pharmaceutically acceptable salts of the compounds of claim [34].

[56] The method of claim [51] wherein the mammal is a human.

[57] The method of claim [51] wherein the medical condition is an inflammatory disease.

[58] The method of claim [51] wherein the medical condition is a disease of the immune system.

[59] The method of claim [51] wherein the medical condition is rheumatoid arthritis.

[60] The method of claim [51] wherein the medical condition is tuberculosis.

[61] The method of claim [51] wherein the medical condition is sterility.

[62] The method of claim [51] wherein the medical condition is inflammatory bowel disease.

[63] The method of claim [51] wherein the medical condition is lupus erythematosus.

[64] The method of claim [51] wherein the medical condition is the suppression of the immune response in a patient in need of an organ transplant.

[65] The method of claim [51] wherein the medical condition is cancer in which the tumor cells are rich in P2X7 receptors.

[66] The method of claim [65] further comprising co-administering a cytotoxic agent.

[67] The method of claim [66] wherein the cytotoxic agent is a topoisomerase-II inhibitor.

[68] The method of claim [67] wherein the topoisomerase-II inhibitor is selected from the list consisting of etoposide (VP-16), podophyllotoxin, and teniposide (VM-26).
[69] The method of claim [51] wherein the medical condition is a wound.

[70] The method claim of claim [69] wherein the medical condition is a chronic wound.

[71] A method of inducing apoptosis in neoplastic cells in a patient comprising administering to that patient a compound of claim [1], [30], [32], or [34] in a pharmaceutical carrier.

[72] The method of claim [71] further comprising co-administering a cytotoxic agent.

[73] The method of claim [72] wherein the cytotoxic agent is a topoisomerase-II inhibitor.

[74] The method of claim [73] wherein the topoisomerase-II inhibitor is selected from the list consisting of etoposide (VP-16), podophyllotoxin, and teniposide (VM-26).

[75] A compound selected from the group of tyrosyl piperazine derivatives consisting of:

a. (S)-N-tert-butyloxycarbonyl-N-methyl-tyrosyl]-4-(4-nitrophenyl)-piperazine;

b. 1-[(S)-N-tert-butyloxycarbonyl-N-methyl-tyrosyl]-4-(p-tolyl)-piperazine;

c. 1-[(S)-N-tert-butyloxycarbonyl-N-methyl-tyrosyl]-4-(2-chlorophenyl)-piperazine;

d. 1-[(S)-N-tert-butyloxycarbonyl-N-methyl-tyrosyl]-4-(4-fluorophenyl)-piperazine;

e. 1-[(S)-N-tert-butyloxycarbonyl-N-methyl-tyrosyl]-4-(3,4-dichlorophenyl)-piperazine;

b. 1-[(S)-N-tert-butyloxycarbonyl-N-methyl-tyrosyl]-4-(4-cyanophenyl)-piperazine;
c. 1-[(S)-N-tert-butyloxy carbonyl-N-methyl-tyrosyl]-4-(4-chlorophenyl)-piperazine;

d. 1-[(S)-N-tert-butyloxy carbonyl-N-methyl-tyrosyl]-4-(4-methoxyphenyl)-piperazine;

e. 1-[(S)-N-tert-butyloxy carbonyl-N-methyl-tyrosyl]-4-benzyl-piperazine;

f. 1-[(S)-N-tert-butyloxy carbonyl-N-methyl-tyrosyl]-4-phenethylpiperazine;

g. 1-[(S)-N-tert-butyloxy carbonyl-N-methyl-tyrosyl]-4-(4-iodophenyl)-piperazine;

h. 1-[(S)-N-tert-butyloxy carbonyl-N-methyl-tyrosyl]-4-(4-acetylphenyl)-piperazine;

i. 1-[(S)-N-tert-butyloxy carbonyl-N-methyl-tyrosyl]-4-(4-fluorobenzyl)-piperazine;

j. 1-[(S)-N-tert-butyloxy carbonyl-N-methyl-tyrosyl]-4-(4-fluorobenzoyl)-piperazine;

k. 1-[(S)-N-tert-butyloxy carbonyl-N-methyl-tyrosyl]-4-(4-nitrobenzyl)-piperazine;

l. 1-[(S)-N-tert-butyloxy carbonyl-N-methyl-tyrosyl]-4-(2-fluorophenyl)-piperazine;

m. 1-[(S)-N-tert-butyloxy carbonyl-N-methyl-tyrosyl]-4-(o-toly)-piperazine;

n. 1-[(S)-N-tert-butyloxy carbonyl-N-methyl-tyrosyl]-4-(2-methoxyphenyl)-piperazine;

o. 1-[(S)-N-tert-butyloxy carbonyl-N-methyl-tyrosyl]-4-(3-chlorophenyl)-piperazine;
p. 1-[(S)-N-tert-butyloxycarbonyl-N-methyl-tyrosyl]-4-(3-trifluoromethylphenyl)-piperazine;

q. 1-[(S)-N-tert-butyloxycarbonyl-N-methyl-tyrosyl]-4-(2,3-dimethylphenyl)-piperazine;

r. 1-[(S)-N-tert-butyloxycarbonyl-N-methyl-tyrosyl]-4-(pyridin-2-yl)-piperazine;

s. 1-[(S)-N-tert-butyloxycarbonyl-N-methyl-tyrosyl]-4-(pyrimidin-2-yl)-piperazine;

t. 1-[(S)-N-tert-butyloxycarbonyl-N-methyl-tyrosyl]-4-benzylpiperidine;

u. 1-[(S)-N-tert-butyloxycarbonyl-tyrosyl]-4-(4-fluorophenyl)-piperazine;

v. 1-[(S)-N-tert-butyloxycarbonyl-tyrosyl]-4-(o-toly1)-piperazine;

w. 1-[(S)-N-tert-butyloxycarbonyl-N-methyl-tyrosyl]-4-(4-aminophenyl)-piperazine;

x. 1-[(S)-N-tert-butyloxycarbonyl-N-methyl-tyrosyl]-4-(4-bromo-2-methylphenyl)-piperazine.

[76] A compound selected from the group of tyrosyl piperazine derivatives consisting of:

a. 1-[(S)-O-isoquinolinesulfonyl-N-tert-butyloxycarbonyl-N-methyl-tyrosyl]-4-(4-nitrophenyl)-piperazine;

b. 1-[(S)-O-isoquinolinesulfonyl-N-tert-butyloxycarbonyl-N-methyl-tyrosyl]-4-(p-toly1)-piperazine;

c. 1-[(S)-O-isoquinolinesulfonyl-N-tert-butyloxycarbonyl-N-methyl-tyrosyl]-4-(2-chlorophenyl)-piperazine;

d. 1-[(S)-O-isoquinolinesulfonyl-N-tert-butyloxycarbonyl-N-methyl-
tyrosyl]-4-(4-fluorophenyl)-piperazine];

e. 1-[(S)-O-isoquinolinesulfonfyl-N-tert-butyloxycarbonyl-N-methyl-
tyrosyl]-4-(3,4-dichlorophenyl)-piperazine;

f. 1-[(S)-O-isoquinolinesulfonfyl-N-tert-butyloxycarbonyl-N-methyl-
tyrosyl]-4-(4-cyanophenyl)-piperazine;

g. 1-[(S)-O-isoquinolinesulfonfyl-N-tert-butyloxycarbonyl-N-methyl-
tyrosyl]-4-(4-chlorophenyl)-piperazine;

h. 1-[(S)-O-isoquinolinesulfonfyl-N-tert-butyloxycarbonyl-N-methyl-
tyrosyl]-4-(4-methoxyphenyl)-piperazine;

i. 1-[(S)-O-isoquinolinesulfonfyl-N-tert-butyloxycarbonyl-N-methyl-
tyrosyl]-4-benzylpiperazine;

j. 1-[(S)-O-isoquinolinesulfonfyl-N-tert-butyloxycarbonyl-N-methyl-
tyrosyl]-4-phenethylpiperazine;

k. 1-[(S)-O-isoquinolinesulfonfyl-N-tert-butyloxycarbonyl-N-methyl-
tyrosyl]-4-(4-iodophenyl)-piperazine;

l. 1-[(S)-O-isoquinolinesulfonfyl-N-tert-butyloxycarbonyl-N-methyl-
tyrosyl]-4-(4-acetylphenyl)-piperazine;

m. 1-[(S)-O-isoquinolinesulfonfyl-N-tert-butyloxycarbonyl-N-methyl-
tyrosyl]-4-(4-fluorobenzyl)-piperazine;

n. 1-[(S)-O-isoquinolinesulfonfyl-N-tert-butyloxycarbonyl-N-methyl-
tyrosyl]-4-(4-fluorobenzoyl)-piperazine;

o. 1-[(S)-O-isoquinolinesulfonfyl-N-tert-butyloxycarbonyl-N-methyl-
tyrosyl]-4-(4-nitrobenzyl)-piperazine;

p. 1-[(S)-O-isoquinolinesulfonfyl-N-tert-butyloxycarbonyl-N-methyl-
tyrosyl]-4-(2-fluorophenyl)-piperazine;

q. 1-[(S)-O-isoquinolinesulfonfyl-N-tert-butyloxycarbonyl-N-methyl-
Tyrosyl]-4-(o-tolyl)-piperazine;

\[\text{r.}\quad 1-[(S)-O-\text{isoquinolinesulfonyl}-\text{N-tert-butyloxy carbonyl}-\text{N-methyl-tyrosyl}]-4-(2\text{-methoxyphenyl})-\text{piperazine};\]

\[\text{s.}\quad 1-[(S)-O-\text{isoquinolinesulfonyl}-\text{N-tert-butyloxy carbonyl}-\text{N-methyl-tyrosyl}]-4-(3\text{-chlorophenyl})-\text{piperazine};\]

\[\text{t.}\quad 1-[(S)-O-\text{isoquinolinesulfonyl}-\text{N-tert-butyloxy carbonyl}-\text{N-methyl-tyrosyl}]-4-(3\text{-trifluoromethylphenyl})-\text{piperazine};\]

\[\text{u.}\quad 1-[(S)-O-\text{isoquinolinesulfonyl}-\text{N-tert-butyloxy carbonyl}-\text{N-methyl-tyrosyl}]-4-(2,3\text{-dimethylphenyl})-\text{piperazine};\]

\[\text{v.}\quad 1-[(S)-O-\text{isoquinolinesulfonyl}-\text{N-tert-butyloxy carbonyl}-\text{N-methyl-tyrosyl}]-4-(\text{pyridin-2-yl})-\text{piperazine};\]

\[\text{w.}\quad 1-[(S)-O-\text{isoquinolinesulfonyl}-\text{N-tert-butyloxy carbonyl}-\text{N-methyl-tyrosyl}]-4-(\text{pyrimidin-2-yl})-\text{piperazine};\]

\[\text{x.}\quad 1-[(S)-O-\text{isoquinolinesulfonyl}-\text{N-tert-butyloxy carbonyl}-\text{N-methyl-tyrosyl}]-4-\text{benzyl)piperazine};\]

\[\text{y.}\quad 1-[(S)-O-\text{isoquinolinesulfonyl}-\text{N-tert-butyloxy carbonyl-tyrosyl}]-4-(4\text{-fluorophenyl})-\text{piperidine};\]

\[\text{z.}\quad 1-[(S)-O-\text{isoquinolinesulfonyl}-\text{N-tert-butyloxy carbonyl-tyrosyl}]-4-(o-tolyl)-\text{piperazine};\]

\[\text{aa.}\quad 1-[(S)-O-\text{isoquinolinesulfonyl}-\text{N-tert-butyloxy carbonyl-N-methyl-tyrosyl}]-4-(4\text{-aminophenyl})-\text{piperazine};\]

\[\text{bb.}\quad 1-[(S)-O-(3\text{-pyridinesulfonyl})-\text{N-tert-butyloxy carbonyl-tyrosyl}]-4-(o-tolyl)-\text{piperazine};\]

\[\text{y.}\quad 1-[(S)-O-(3-pyridinesulfonyl)-\text{N-tert-butyloxy carbonyl-N-methyl-tyrosyl}]-4-(\text{phenyl})-\text{piperazine};\]

\[\text{z.}\quad 1-[(S)-O-(3-pyridinesulfonyl)-\text{N-tert-butyloxy carbonyl-tyrosyl}]-4-\]
(2-methylphenyl)-piperazin;

aa. 1-[(S)-O-isoquinolinesulfonyl-N-tert-butyloxycarbonyl-tyrosyl]-4-(4-bromo-2-methylphenyl)-piperazin.

[77] A compound selected from the group of tyrosyl piperazine derivatives consisting of:

a. 1-[(S)-N,O-bis-(isoquinolinesulfonfyl)-N-methyl-tyrosyl]-4-(4-nitrophenyl)-piperazin;

b. 1-[(S)-N,O-bis-(isoquinolinesulfonfyl)-N-methyl-tyrosyl]-4-(p-tolyl)-piperazin;

c. 1-[(S)-N,O-bis-(isoquinolinesulfonfyl)-N-methyl-tyrosyl]-4-(2-chlorophenyl)-piperazin;

d. 1-[(S)-N,O-bis-(isoquinolinesulfonfyl)-N-methyl-tyrosyl]-4-(4-fluorophenyl)-piperazin;

e. 1-[(S)-N,O-bis-(isoquinolinesulfonfyl)-N-methyl-tyrosyl]-4-(3,4-dichloro-phenyl)-piperazin;

f. 1-[(S)-N,O-bis-(isoquinolinesulfonfyl)-N-methyl-tyrosyl]-4-(4-cyanophenyl)-piperazin;

g. 1-[(S)-N,O-bis-(isoquinolinesulfonfyl)-N-methyl-tyrosyl]-4-(4-chlorophenyl)-piperazin;

h. 1-[(S)-N,O-bis-(isoquinolinesulfonfyl)-N-methyl-tyrosyl]-4-(4-methoxy-phenyl)-piperazin;

i. 1-[(S)-N,O-bis-(isoquinolinesulfonfyl)-N-methyl-tyrosyl]-4-benzylpiperazin;

j. 1-[(S)-N,O-bis-(isoquinolinesulfonfyl)-N-methyl-tyrosyl]-4-phenethyl-piperazin;

k. 1-[(S)-N,O-bis-(isoquinolinesulfonfyl)-N-methyl-tyrosyl]-4-(4-
iodophenyl]-piperazine];

l. 1-[(S)-N,O-bis-(isoquinolinesulfonyl)-N-methyl-tyrosyl]-4-(4-acetylyphenyl]-piperazine];

m. 1-[(S)-N,O-bis-(isoquinolinesulfonyl)-N-methyl-tyrosyl]-4-(4-fluorobenzyl]-piperazine];

n. 1-[(S)-N,O-bis-(isoquinolinesulfonyl)-N-methyl-tyrosyl]-4-(4-fluorobenzyloyl]-piperazine];

o. 1-[(S)-N,O-bis-(isoquinolinesulfonyl)-N-methyl-tyrosyl]-4-(4-nitrobenzyl]-piperazine];

p. 1-[(S)-N,O-bis-(isoquinolinesulfonyl)-N-methyl-tyrosyl]-4-(2-fluorophenyl]-piperazine];

q. 1-[(S)-N,O-bis-(isoquinolinesulfonyl)-N-methyl-tyrosyl]-4-o-toly]-piperazine;

r. 1-[(S)-N,O-bis-(isoquinolinesulfonyl)-N-methyl-tyrosyl]-4-(2-methoxy-phenyl]-piperazine;

s. 1-[(S)-N,O-bis-(isoquinolinesulfonyl)-N-methyl-tyrosyl]-4-(3-chlorophenyl]-piperazine;

t. 1-[(S)-N,O-bis-(isoquinolinesulfonyl)-N-methyl-tyrosyl]-4-(3-trifluoromethyl-phenyl]-piperazine;

u. 1-[(S)-N,O-bis-(isoquinolinesulfonyl)-N-methyl-tyrosyl]-4-(2,3-dimethylphenyl]-piperazine;

v. 1-[(S)-N,O-bis-(isoquinolinesulfonyl)-N-methyl-tyrosyl]-4-(pyridin-2-yl]-piperazine;

w. 1-[(S)-N,O-bis-(isoquinolinesulfonyl)-N-methyl-tyrosyl]-4-(pyrimidin-2-yl]-piperazine;

x. 1-[(S)-N,O-bis-(isoquinolinesulfonyl)-N-methyl-tyrosyl]-4-
benzylpiperidine;

y. 1-[(S)-N,O-bis-(isoquinolinesulfonyl)tyrosyl]-4-(4-fluorophenyl)-piperazine;

z. 1-[(S)-N,O-bis-(isoquinolinesulfonyl)tyrosyl]-4-(o-tolyl)-piperazine;

aa. 1-[(S)-N,O-bis-(isoquinolinesulfonyl)-N-methyl-tyrosyl]-4-(4-aminophenyl)-piperazine

bb. 1-[(S)-N,O-bis-(3-pyridinesulfonyl)-N-methyl-tyrosyl]-4-(4-fluorophenyl)-piperazine;

cc. 1-[(S)-N,O-bis-(3-pyridinesulfonyl)-N-methyl-tyrosyl]-4-phenyl-piperazine;

dd. 1-[(S)-N,O-bis-(3-pyridinesulfonyl)-N-methyl-tyrosyl]-4-(2-methylphenyl)-piperazine;

ee. 1-[(S)-N,O-bis-(isoquinolinesulfonyl)-N-methyl-tyrosyl]-4-(4-bromo-2-methyl-phenyl)-piperazine;

ff. 1-[(S)-N,O-bis-(isoquinolinesulfonyl)-N-methyl-tyrosyl]-4-(2-methyl-4-[3H]-phenyl)-piperazine.
Figure 1

\[
\begin{align*}
\text{R1} & \quad \text{R2} \\
\text{R3} & \quad \text{R4} \\
\text{R5} & \quad \text{R6}
\end{align*}
\]

\[
\begin{align*}
\text{R7} & \quad \text{R8} \\
\text{R9} & \quad \text{R10}
\end{align*}
\]
Figure 3

Chemical structures and reaction steps are shown as follows:

1. Reaction a:
   - Initial compound
   - Transformation to target compound

2. Reaction b:
   - Further transformation

3. Reaction c, d:
   - Additional steps
   - Final product

Chemical structures and reaction arrows are depicted to illustrate the process.