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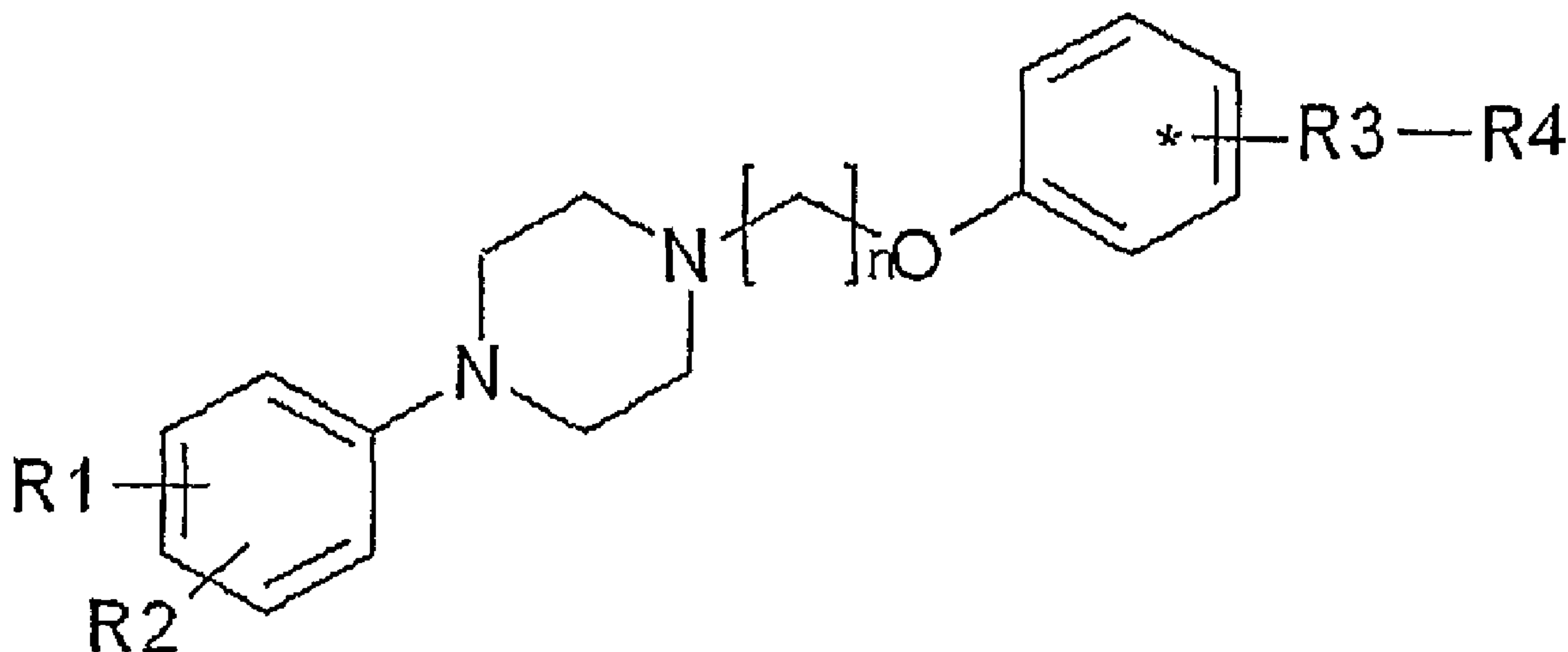
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(72) **Inventeurs/Inventors:**
KIM, YONGGIL, KR;
CHO, NAHMYUNG, KR;
KIM, YUNHEE, KR;
HEO, JOON, KR;
DONG, SEONMIN, KR;
JI, MI KYUNG, KR;
CHA, MAN-YOUNG, KR;
LEE, KIHOO, KR

(73) **Propriétaire/Owner:**

(54) **Titre : COMPOSES DE PHENYL-PIPERAZINE, COMPOSITION PHARMACEUTIQUE LES COMPRENANT, ET UTILISATION ASSOCIEE**

(54) **Title: PHENYL PIPERAZINE COMPOUNDS, PHARMACEUTICAL COMPOSITION INCLUDING THE SAME, AND USE THEREOF**



(I)

(57) **Abrégé/Abstract:**

The present invention relates to novel piperazine derivatives or pharmaceutically acceptable salts thereof, and a pharmaceutical composition for treatment and/or prevention of depression and anxiety including an effective amount of the piperazine compound.



(73) **Propriétaires(suite)/Owners(continued)**:SK BIOPHARMACEUTICALS CO., LTD, KR

(74) **Agent**: NORTON ROSE FULBRIGHT CANADA LLP/S.E.N.C.R.L., S.R.L.

ABSTRACT

The present invention relates to novel piperazine derivatives or pharmaceutically acceptable salts thereof, and a pharmaceutical composition for treatment and/or prevention of depression and anxiety including an effective amount of the piperazine compound.

PHENYL PIPERAZINE COMPOUNDS, PHARMACEUTICAL COMPOSITION INCLUDING THE SAME, AND USE THEREOF

FIELD OF THE INVENTION

5 The present invention relates to novel piperazine derivatives or
pharmaceutically acceptable salts thereof, a process for preparing the same, and in
particular, a high binding for Serotonin 1A(5-hydroxytryptamine; 5-HT1A) receptor, a
pharmaceutical composition for treatment and/or prevention of depression and anxiety
including an effective amount of the piperazine compound, and a method of treating
10 depression, anxiety and other conditions related to 5-HT1A receptor in a mammal.

BACKGROUND OF THE INVENTION

Depression affects approximately 14 million people in the United States and
340 million people worldwide, making it one of the leading causes of disability [Kessler
15 RC. Et al., JAMA, 2003, 289, 3095-3105]. Depression is also associated with high rates
of relapse, recurrence, disability, and death [Hirschfield RM., et al., JAMA, 1997, 277,
333-340; Keller MB., J. Psychopharmacol.1996, 10(suppl 1);41-44].

The role of serotonin in the treatment of depressive and anxiety disorders is
underscored by the therapeutic action of selective 5-HT reuptake inhibitors acting to
20 enhance the degree of activation of various 5-HT receptor subtypes [Blier P. and Ward
M., Biol. Psychiatry, 2003, 53, 193-203]. Selective serotonin reuptake inhibitors(SSRIs)
have had significant success in treating depression and related disorders and have
become among the most prescribed drugs since 1980s. But, the use of SSRIs leads to
the indiscriminate activation of all serotonin receptors and it can be understood as
25 undesirable actions of serotonin in undesirable pathways at undesirable receptor
subtypes [Stahl SM., 2008, Essential Psychopharmacology(3rd ed.), 531]. Although
there are various treatment options for depressive and anxiety disorders, a need still
exists for new drugs with improved tolerability and adequate efficacy.

In contrast to the SSRIs, the 5-HT1A agonist or partial agonist acts directly on
30 postsynaptic serotonin receptors to increase serotonergic neurotransmission. And, the 5-

HT1A partial agonists, Buspirone and Gepirone [Robinson DS., et al., J. Clin. Psychopharmacol., 1990, 10(3), 67S-76S; Bielski RJ., J. Clin. Psychiatry, 2008, 69(4), 571-577], and 5-HT1A agonist, Flexinoxan [Grof P., International Clin. Psychopharmacology, 1993, 8(3), 167-172], have shown efficacy in clinical trials for
 5 the treatment of depression. Moreover, because of their unique pharmacological profile, 5-HT1A agonists possess theoretic advantages in the treatment of major depression relative to other classes of antidepressants. In particular, these drugs are not expected to produce weight gain, sedation, or sexual dysfunctions, which are often encountered with some of the antidepressants introduced in the last 10 years [Blier P. and Ward M., Biol.
 10 Psychiatry, 2003, 53, 193-203].

Many reports have disclosed that phenyl piperazine compounds are effectively used for controlling depression and anxiety.

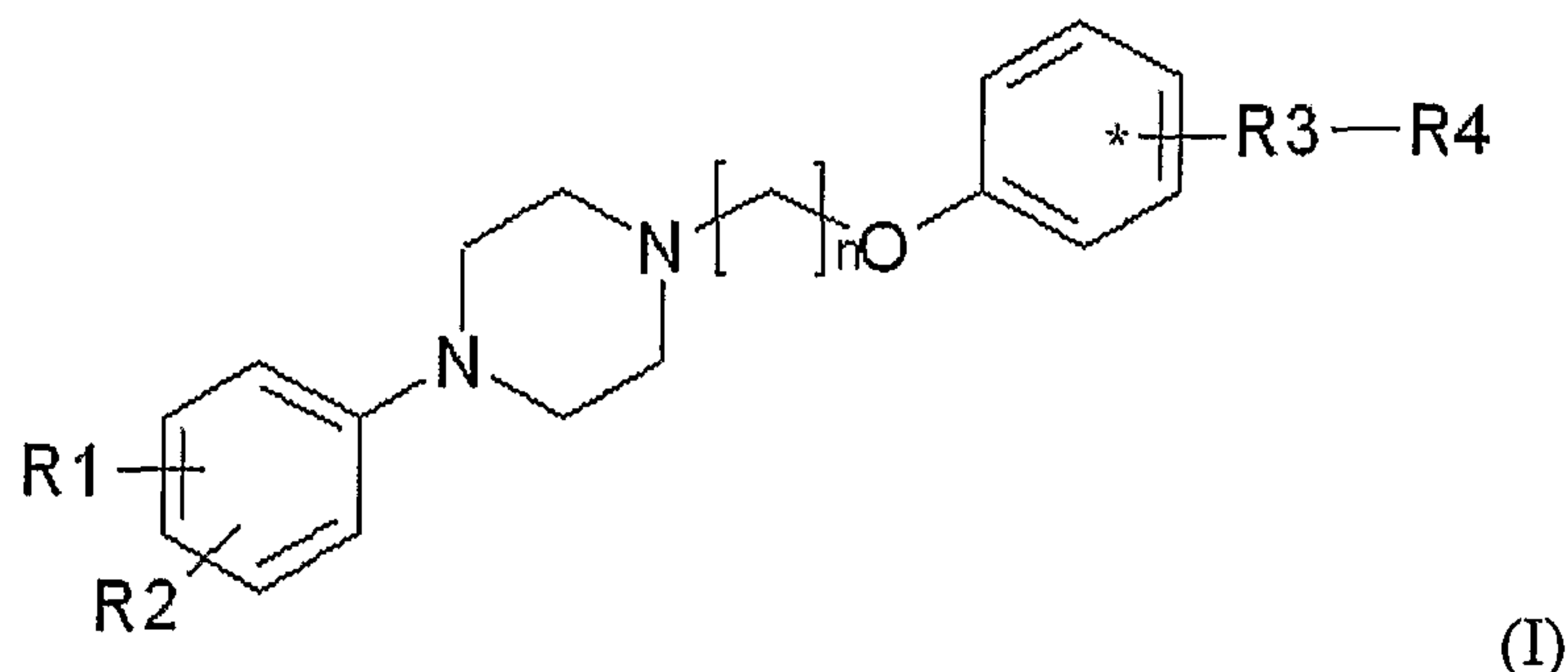
For example, US 5,578,596 discloses that the 2-alkoxy-5,6,7,8-tetrahydroquinoxaline derivatives have a strong affinity for serotonin 1A receptor and
 15 are useful for preventing and treating serotonergic neuron-related disease.

These compounds are found to be very effective as therapeutical medicines for managing depression and anxiety.

Active research and development efforts have continued to be directed to the application of phenyl piperazine compounds for the treatment of depression and anxiety.
 20

SUMMARY OF THE INVENTION

In one aspect, the invention provides a piperazine compound represented by Formula (I) or pharmaceutically acceptable salts thereof:



(I)

wherein

n is an integer from 2 to 6;

R1 and R2 are the same or different and are independently selected from the
5 group consisting of hydrogen, a hydroxyl group, a halogen, nitrogen dioxide, a straight
or branched chain alkyl group with 1 to 4 carbon atoms, and a straight or branched
chain alkoxy group with 1 to 4 carbon atoms;

R3 is a C1-C2 alkylene; and

R4 is selected from the group consisting of:

10 (a) a C2-C6 dialkylamine,

(b) a 5 to 9-membered aromatic amine wherein the ring is independently
substituted with at least of hydrogen, a C1-C6 aliphatic alkyl, a C3 to C10 cyclic alkyl,
a C6-C10 aryl group and a halogen,

(c) a 5 to 9-membered heteroaromatic amine comprising at least a nitrogen
15 atom as a ring constituent wherein the ring is independently substituted with at least one
of hydrogen, a C1-C6 aliphatic alkyl, a C3 to C10 cyclic alkyl, a C6-C10 aryl group and
a halogen,

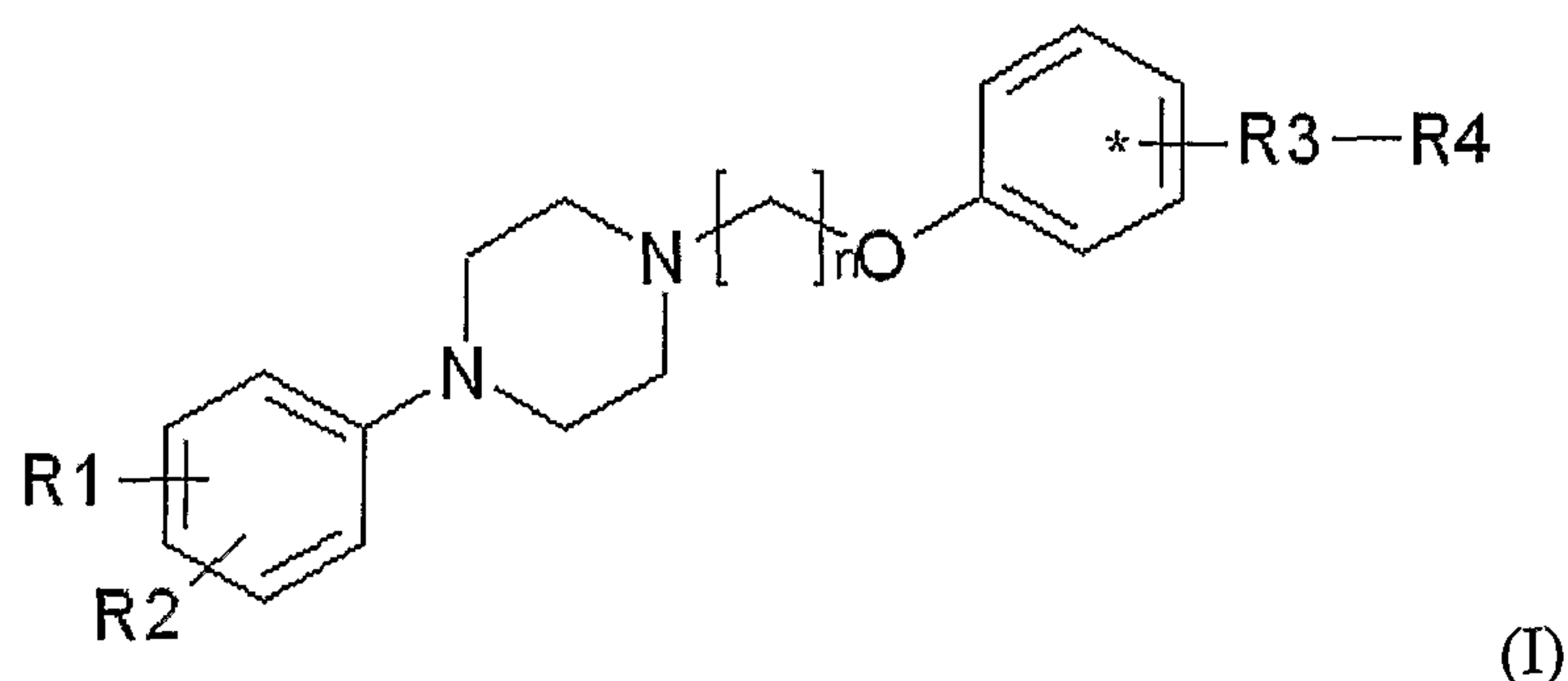
(d) a 5 to 9-membered heterocyclic ring comprising at least a nitrogen atom
wherein the ring is independently substituted with at least one of hydrogen, a C1-C6
20 aliphatic alkyl, a C3 to C10 cyclic alkyl, a C6-C10 aryl group and a halogen, and

(e) a 5 to 9-membered heteroaromatic ring comprising at least a nitrogen atom
wherein the ring is independently substituted with at least one of hydrogen, a C1-C6
aliphatic alkyl, a C3 to C10 cyclic alkyl, a C6-C10 aryl group and a halogen; and

R4 is connected to R3 group through a nitrogen atom therein.

25 In another aspect, the invention provides a pharmaceutical composition
comprising:

(A) an effective amount of a piperazine compound represented by Formula (I):



or pharmaceutically acceptable salts thereof, wherein

n is an integer from 2 to 6;

5 R1 and R2 are the same or different and are independently selected from the group consisting of hydrogen, a hydroxyl group, a halogen, nitrogen dioxide, a straight or branched chain alkyl group with 1 to 4 carbon atoms, and a straight or branched chain alkoxy group with 1 to 4 carbon atoms;

R3 is a C1-C2 alkylene; and

10 R4 is selected from the group consisting of:

(a) a C2-C6 dialkylamine,

(b) a 5 to 9-membered aromatic amine wherein the ring is independently substituted with at least one of hydrogen, a C1-C6 aliphatic alkyl, a C3 to C10 cyclic alkyl, a C6-C10 aryl group and a halogen,

15 (c) a 5 to 9-membered heteroaromatic amine comprising at least a nitrogen atom as a ring constituent wherein the ring is independently substituted with at least one of hydrogen, a C1-C6 aliphatic alkyl, a C3 to C10 cyclic alkyl, a C6-C10 aryl group and a halogen,

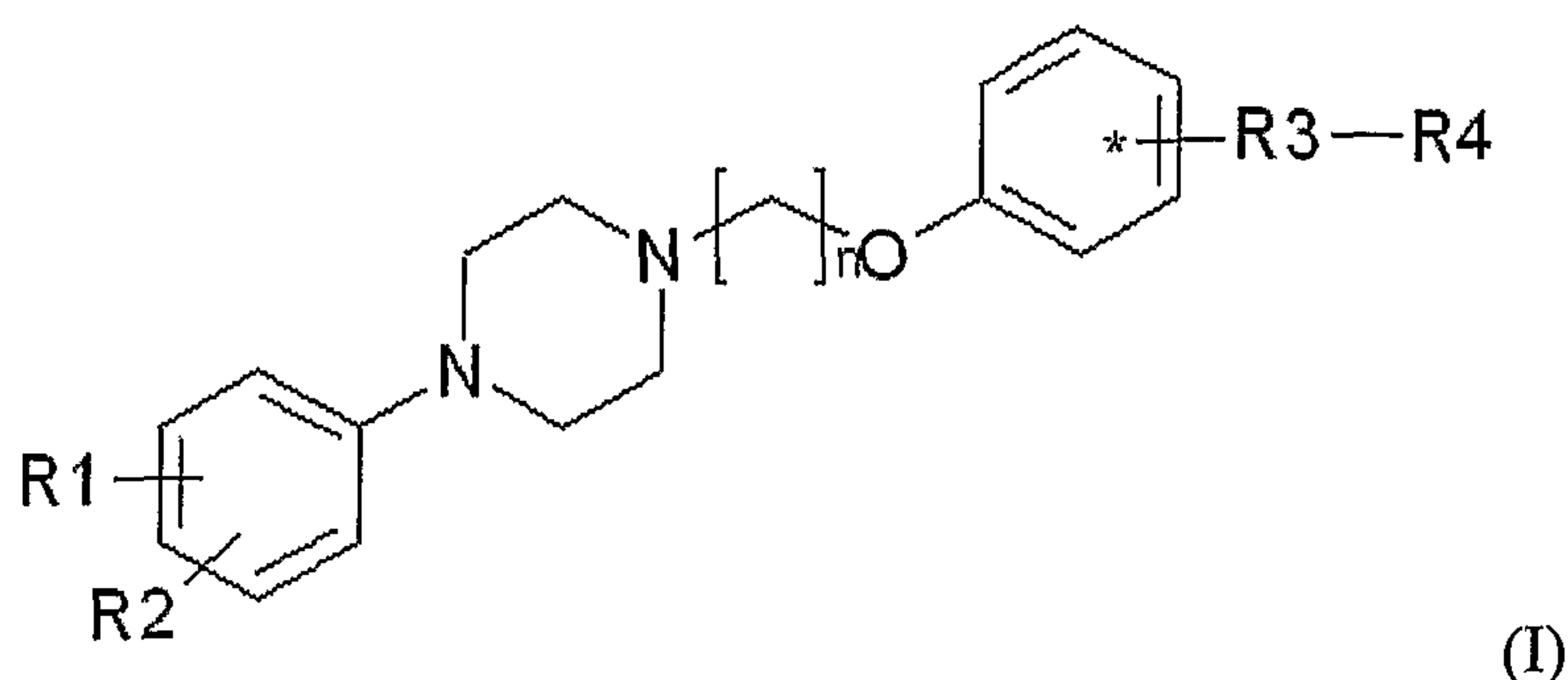
(d) a 5 to 9-membered heterocyclic ring comprising at least a nitrogen atom
20 wherein the ring is independently substituted with at least of hydrogen, a C1-C6 aliphatic alkyl, a C3 to C10 cyclic alkyl, a C6-C10 aryl group and a halogen, and

(e) a 5 to 9-membered heteroaromatic ring comprising at least a nitrogen atom wherein the ring is independently substituted with at least one of hydrogen, a C1-C6 aliphatic alkyl, a C3 to C10 cyclic alkyl, a C6-C10 aryl group and a halogen; and

25 R4 is connected to R3 group through a nitrogen atom therein; and

(B) a pharmaceutically acceptable carrier or excipient.

In yet another aspect, the invention provides a method for treating at least one of depression and anxiety in a mammal comprising administering to a mammal in need thereof an effective amount of a piperazine compound represented by Formula (I):



5

or pharmaceutically acceptable salts thereof, wherein

n is an integer from 2 to 6;

R1 and R2 are the same or different and are independently selected from the group consisting of hydrogen, a hydroxyl group, a halogen, nitrogen dioxide, a straight or branched chain alkyl group with 1 to 4 carbon atoms, and a straight or branched chain alkoxy group with 1 to 4 carbon atoms;

R3 is a C1-C2 alkylene; and

R4 is selected from the group consisting of:

(a) a C2-C6 dialkylamine,

(b) a 5 to 9-membered aromatic amine wherein the ring is independently substituted with at least one of hydrogen, a C1-C6 aliphatic alkyl, a C3 to C10 cyclic alkyl, a C6-C10 aryl group and a halogen,

(c) a 5 to 9-membered heteroaromatic amine comprising at least a nitrogen atom as a ring constituent wherein the ring is independently substituted with at least one of hydrogen, a C1-C6 aliphatic alkyl, a C3 to C10 cyclic alkyl, a C6-C10 aryl group and a halogen,

(d) a 5 to 9-membered heterocyclic ring comprising at least a nitrogen atom wherein the ring is independently substituted with at least one of hydrogen, a C1-C6 aliphatic alkyl, a C3 to C10 cyclic alkyl, a C6-C10 aryl group and a halogen, and

(e) a 5 to 9-membered heteroaromatic ring comprising at least a nitrogen atom wherein the ring is independently substituted with at least one of hydrogen, a C1-C6 aliphatic alkyl, a C3 to C10 cyclic alkyl, a C6-C10 aryl group and a halogen; and

R4 is connected to R3 group through a nitrogen atom therein.

DETAILED DESCRIPTION OF THE INVENTION

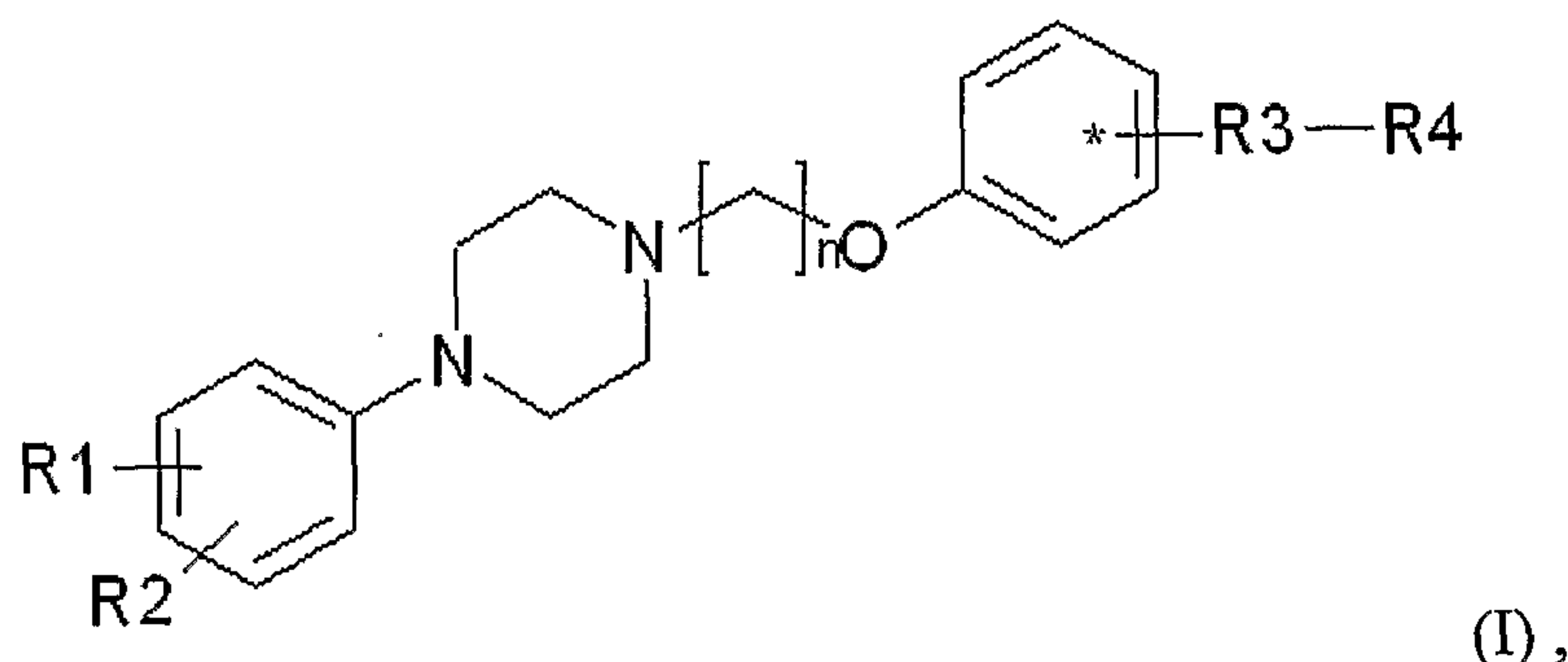
Before any embodiments of the invention are explained in detail, it is to be understood that the invention is not limited in its application to the details of construction and the arrangement of components set forth in the following description. The invention is capable of other embodiments and of being practiced or of being carried out in various ways. Also, it is to be understood that the phraseology and terminology used herein is for the purpose of description and should not be regarded as limiting. The use of “including,” “comprising,” or “having” and variations thereof herein is meant to encompass the items listed thereafter and equivalents thereof as well as additional items.

It also is understood that any numerical range recited herein includes all values from the lower value to the upper value. For example, if a concentration range is stated as 1% to 50%, it is intended that values such as 2% to 40%, 10% to 30%, or 1% to 3%, etc., are expressly enumerated in this specification. These are only examples of what is specifically intended, and all possible combinations of numerical values between and including the lowest value and the highest value enumerated are to be considered to be expressly stated in this application.

Throughout the specification and the appended claims, a given chemical formula or name shall encompass all stereo and optical isomers and racemates thereof as well as mixtures in different proportions of the separate enantiomers, where such isomers and enantiomers exist, as well as pharmaceutically acceptable salts thereof and solvates thereof such as, for instance, hydrates. Isomers may be separated using conventional techniques, e.g. chromatography or fractional crystallization. The enantiomers may be isolated by separation of racemates for example by fractional crystallization, resolution, or HPLC. The diastereomers may be isolated by separation of isomer mixtures for instance by fractional crystallization, HPLC, or flash chromatography. A “heteroaromatic ring” or a “heterocyclic ring” means a ring containing at least one heteroatom. A “heteroatom” means an atom other than carbon

in the ring of a heterocyclic group or a heteroaromatic group. Heteroatoms may be at least one of oxygen, sulfur, and nitrogen atoms. Groups containing more than one heteroatom may contain different heteroatoms.

The piperazine compounds of the invention have Chemical Formula (I) or
5 pharmaceutically acceptable salts thereof.



wherein

n is an integer from 2 to 6;

R1 and R2 are the same or different and are independently selected from the
10 group consisting of hydrogen, a hydroxyl group, a halogen, nitrogen dioxide, a straight or branched chain alkyl group with 1 to 4 carbon atoms, and a straight or branched chain alkoxy group with 1 to 4 carbon atoms;

R3 is a C1-C2 alkylene; and

R4 is selected from the group consisting of:

15 (a) a C2-C6 dialkylamine,

(b) a 5 to 9-membered aromatic amine wherein the ring is independently substituted with at least of hydrogen, a C1-C6 aliphatic alkyl, a C3 to C10 cyclic alkyl, a C6-C10 aryl group and a halogen,

(c) a 5 to 9-membered heteroaromatic amine comprising at least a nitrogen
20 atom as a ring constituent wherein the ring is independently substituted with at least one of hydrogen, a C1-C6 aliphatic alkyl, a C3 to C10 cyclic alkyl, a C6-C10 aryl group and a halogen,

(d) a 5 to 9-membered heterocyclic ring comprising at least a nitrogen atom
25 wherein the ring is independently substituted with at least one of hydrogen, a C1-C6 aliphatic alkyl, a C3 to C10 cyclic alkyl, a C6-C10 aryl group and a halogen, and

(e) a 5 to 9-membered heteroaromatic ring comprising at least a nitrogen atom

wherein the ring is independently substituted with at least one of hydrogen, a C1-C6 aliphatic alkyl, a C3 to C10 cyclic alkyl, a C6-C10 aryl group and a halogen; and

R4 is connected to R3 group through a nitrogen atom therein.

5 In one embodiment, R1 and R2 are independently selected from the group consisting of hydrogen, a hydroxyl group, a halogen, nitrogen dioxide, a straight or branched chain alkyl group with 1 to 4 carbon atoms, and a straight or branched chain alkoxy group with 1 to 4 carbon atoms. For example, the halogen may be F, Cl, Br, or I. The alkyl group may be methyl, ethyl, n-propyl, isopropyl, n-butyl, iso-butyl, sec-butyl,
10 and t-butyl, and particularly may be methyl, ethyl, propyl, isopropyl, and tertiary butyl. Unless otherwise stated or indicated, the term "alkoxy" denotes a group O-alkyl, wherein alkyl is methyl, ethyl, n-propyl, isopropyl, n-butyl, iso-butyl, sec-butyl, or t-butyl.

 Unless otherwise stated or indicated, the term "halogen" shall mean fluorine,
15 chlorine, bromine, or iodine.

 Examples of R4 include, without limitation, dimethyl amine, diethylamine, dipropylamine, methylethyl amine, methylpropyl amine, methylbutyl amine, and ethylpropyl amine.

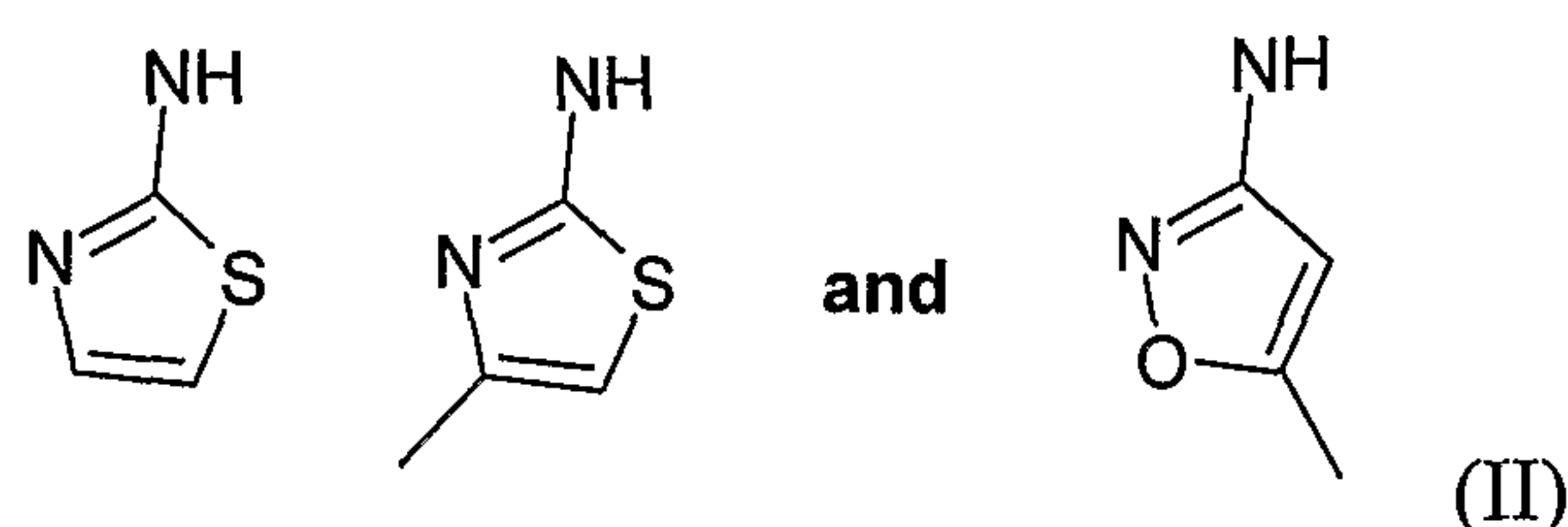
 When R4 is a 5 to 9-membered aromatic amine or a 5 to 9-membered
20 heteroaromatic amine, R4 is connected to R3 through a nitrogen atom in an amino group.

 R4 may be a 5 to 9-membered aromatic amine wherein the ring is independently substituted with at least one of hydrogen, a C1-C6 aliphatic alkyl, a C3 to C10 cyclic alkyl, a C6-C10 aryl group and a halogen. In one embodiment, examples of
25 a 5 to 9-membered aromatic amine in R4 is a 5 or 6-membered aromatic amine substituted with at least one of hydrogen, a C1-C6 alkyl, and a halogen, and particularly, a 6-membered aromatic amine substituted with hydrogen, such as aniline.

 R4 may be a 5 to 9-membered heteroaromatic amine containing at least a nitrogen atom where the ring is independently substituted with at least one of hydrogen,

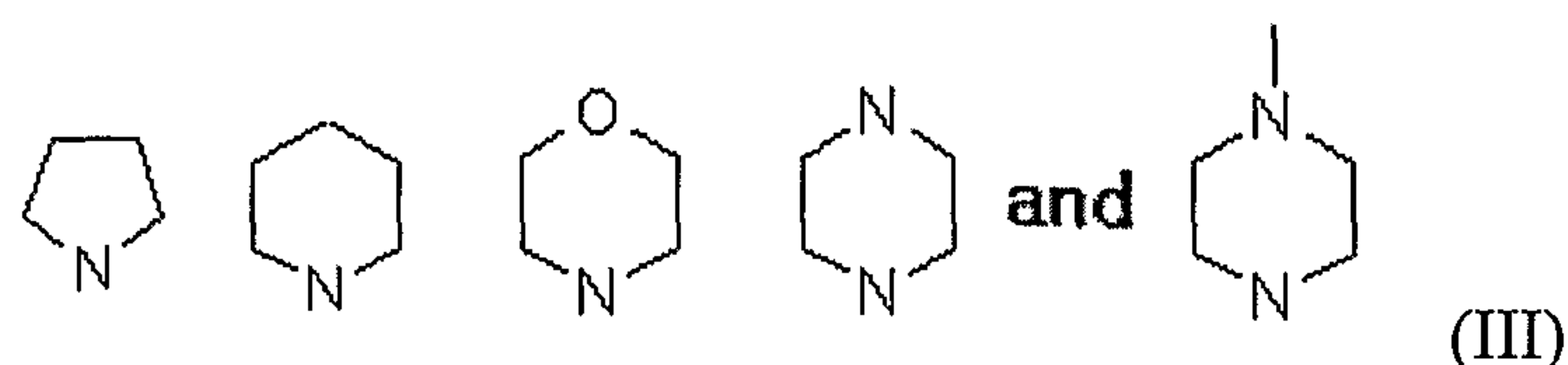
a C1-C6 aliphatic alkyl, a C3 to C10 cyclic alkyl, a C6-C10 aryl group, and a halogen. In one embodiment, examples of a 5 to 9-membered heteroaromatic amine include a 5 or 6-membered heteroaromatic amine substituted with at least one of a C1-C6 alkyl and a halogen, wherein the heteroaromatic amine comprises at least two heteroatoms as ring constituents where a first heteroatom is N and a second heteroatom is independently selected from the group consisting of N, O, and S.

The 5-membered heteroaromatic amine may have a structure (II) selected from the group consisting of:



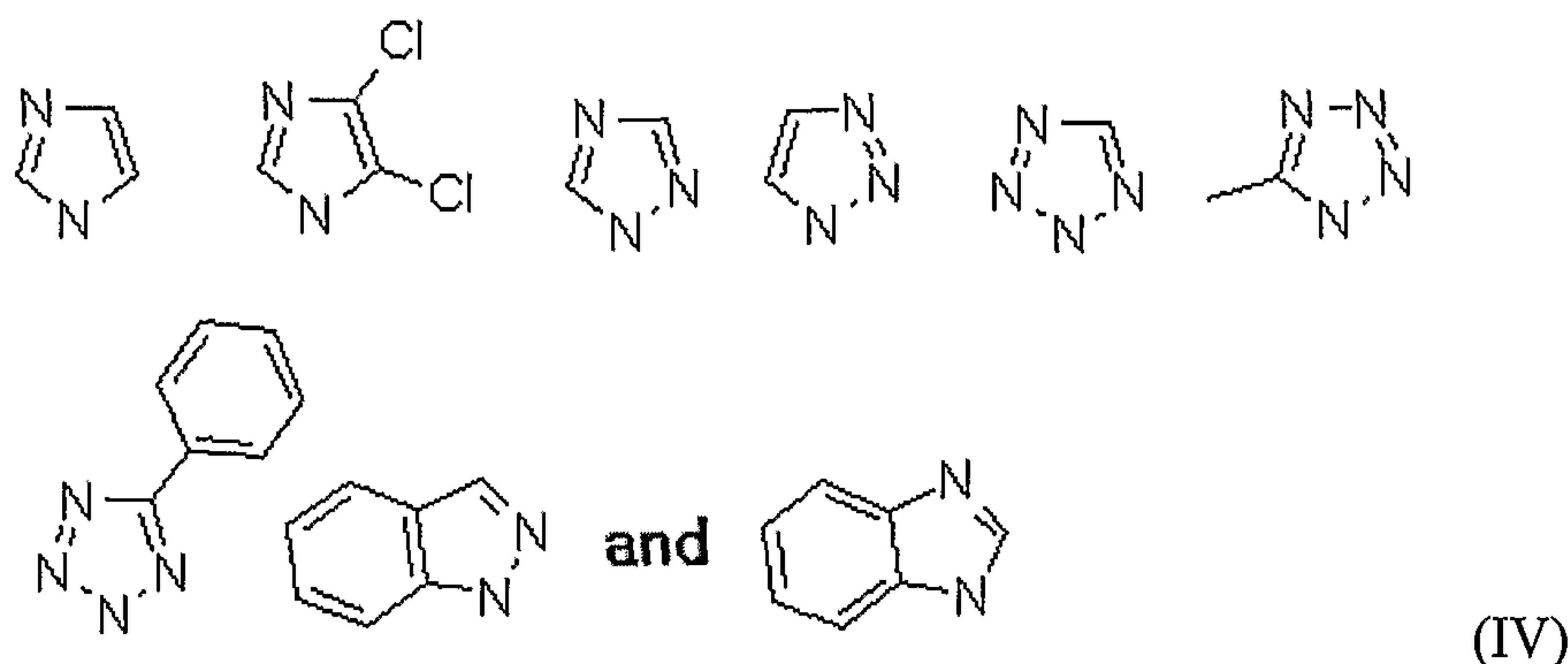
When R4 is a 5 to 9-membered heterocyclic ring or a 5 to 9-membered heteroaromatic ring, R4 may be connected to R3 through a nitrogen atom contained in the ring as a heteroatom of the 5 to 9-membered heterocyclic ring or heteroaromatic ring.

R4 may be a 5 to 9-membered heterocyclic ring containing at least a nitrogen atom where the ring is independently substituted with at least one of hydrogen, a C1-C6 aliphatic alkyl, a C3 to C10 cyclic alkyl, a C6-C10 aryl group, and a halogen. Examples of a 5 to 9-membered heterocyclic ring include, without limitation, a 5 or 6-membered heterocyclic ring having a structure (III) selected from the group consisting of:



R4 may be a 5 to 9-membered heteroaromatic ring containing at least a nitrogen atom where the ring is independently substituted with at least one of hydrogen, a C1-C6 aliphatic alkyl, a C3 to C10 cyclic alkyl, a C6-C10 aryl group, and a halogen. Examples of a heteroaromatic ring include, without limitation, an azole compound such as diazole, triazole, tetraazol, benzotriazole, imidazole, pyrazole, benzimidazole or indazole. The

azole ring may be independently substituted with at least one of hydrogen, a C1-C6 aliphatic alkyl, a C3 to C10 cyclic alkyl, a C6-C10 aryl group, and a halogen. The azole compound may have a structure (IV) selected from the group consisting of:



- 5 Examples of compounds having Chemical Formula (I) include, without limitation, 1-[4-(4-imidazol-1-ylmethyl-phenoxy)-butyl]-4-(2-methoxy-phenyl)-piperazine, 1-(2-methoxy-phenyl)-4-[4-(4-[1,2,4]triazol-1-ylmethyl-phenoxy)-butyl]-piperazine, 1-(2-methoxy-phenyl)-4-[4-(4-tetrazol-1-ylmethyl-phenoxy)-butyl]-piperazine, 1-(2-methoxy-phenyl)-4-[4-(4-tetrazol-2-ylmethyl-phenoxy)-butyl]-piperazine, 1-[4-(3-imidazol-1-ylmethyl-phenoxy)-butyl]-4-(2-methoxy-phenyl)-piperazine- hydrochloride, 1-(2-methoxy-phenyl)-4-[4-(3-[1,2,4]triazol-1-ylmethyl-phenoxy)-butyl]-piperazine hydrochloride, 1-(2-methoxy-phenyl)-4-[4-(3-tetrazol-1-ylmethyl-phenoxy)-butyl]-piperazine hydrochloride, 1-(2-methoxy-phenyl)-4-[4-(3-tetrazol-2-ylmethyl-phenoxy)-butyl]-piperazine hydrochloride, 1-(4-{4-[4-(2-methoxy-phenyl)-piperazin-1-yl]-butoxy}-benzyl)-1H-benzoimidazole, 1-(2-Methoxy-phenyl)-4-{4-[4-(2-methyl-imidazol-1-ylmethyl)-phenoxy]-butyl}-piperazine, 1-(2-methoxy-phenyl)-4-[4-(4-[1,2,3]triazol-2-ylmethyl-phenoxy)-butyl]-piperazine, 1-(2-methoxy-phenyl)-4-[4-(4-[1,2,3]triazol-1-ylmethyl-phenoxy)-butyl]-piperazine, 1-(4-{4-[4-(2-Methoxy-phenyl)-piperazin-1-yl]-butoxy}-benzyl)-1H-indazole, 1-(4-{4-[4-(2-Methoxy-phenyl)-piperazin-1-yl]-butoxy}-benzyl)-1H-benzotriazole, 1-(2-methoxy-phenyl)-4-{4-[4-(5-phenyl-tetrazol-2-ylmethyl)-phenoxy]-butyl}-piperazine, 1-(2-methoxy-phenyl)-4-{4-[4-(5-phenyl-tetrazol-1-ylmethyl)-phenoxy]-butyl}-piperazine, 1-(2-methoxy-phenyl)-4-{4-[4-(5-methyl-tetrazol-2-ylmethyl)-phenoxy]-butyl}-piperazine, 1-(2-methoxy-phenyl)-4-{4-[4-(5-methyl-tetrazol-1-ylmethyl)-phenoxy]-
- 10
- 15
- 20

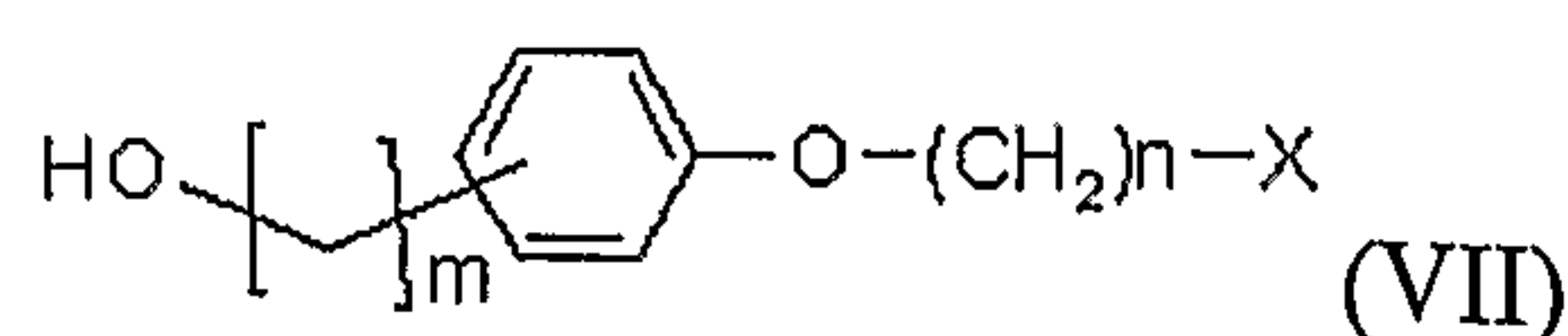
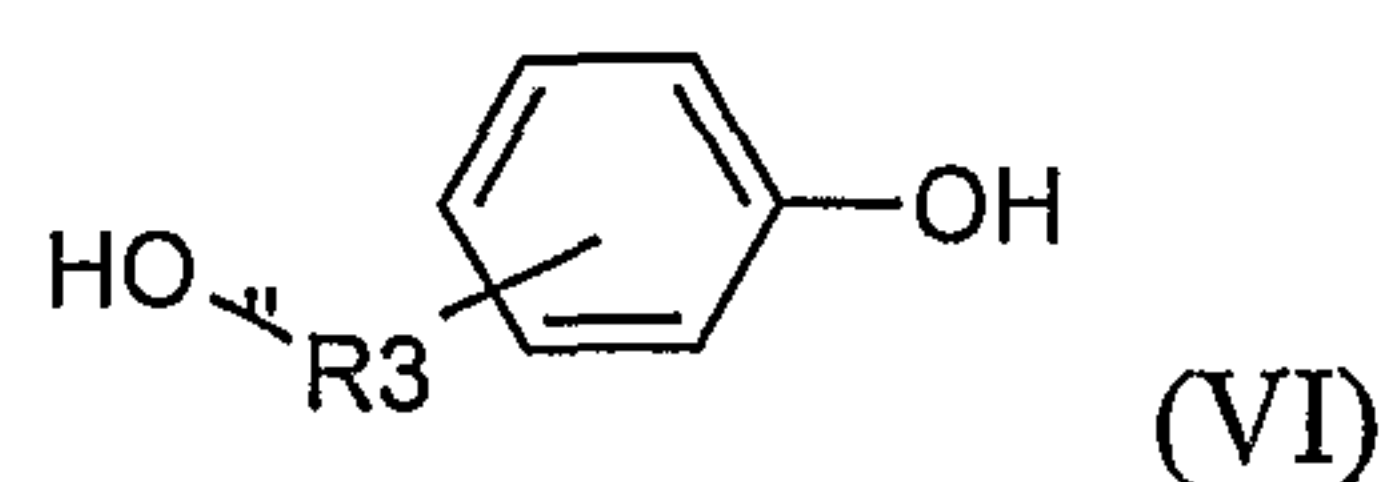
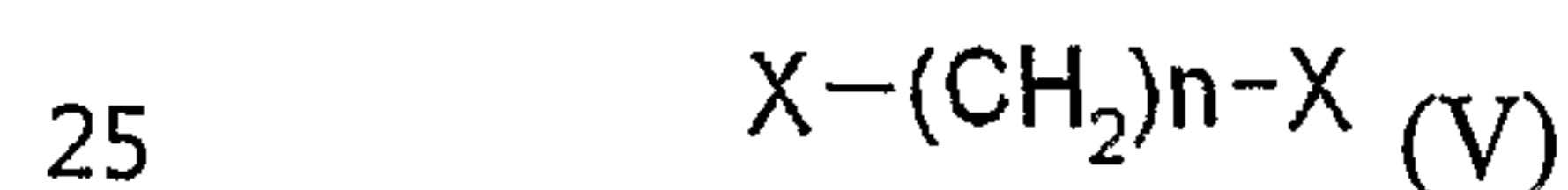
butyl}-piperazine,(4-{4-[4-(2-methoxy-phenyl)-piperazin-1-yl]-butoxy}-benzyl)-
dimethyl-amine di-hydrochloride, 1-(2-methoxy-phenyl)-4-[4-(4-piperidin-1-ylmethyl-
phenoxy)-butyl]-piperazine, (4-{4-[4-(2-methoxy-phenyl)-piperazin-1-yl]-butoxy}-
benzyl)-phenyl-amine, (4-{4-[4-(2-methoxy-phenyl)-piperazin-1-yl]-butoxy}-benzyl)-
5 thiazol-2-yl-amine, 1-(2-chloro-phenyl)-4-[4-(4-[1,2,4]triazol-1-ylmethyl-phenoxy)-
butyl]-piperazine, 1-(2-methoxy-phenyl)-4-[4-(3-[1,2,3]triazol-2-ylmethyl-phenoxy)-
butyl]-piperazine, 1-(2-Methoxy-phenyl)-4-[4-(3-[1,2,3]triazol-1-ylmethyl-phenoxy)-
butyl]-piperazine, 1-(2-Methoxy-phenyl)-4-[4-(3-[1,2,3]triazol-2-ylmethyl-phenoxy)-
butyl]-piperazine, 1-(2-methoxy-phenyl)-4-{4-[3-(5-methyl-tetrazol-1-ylmethyl)-
10 phenoxy]-butyl}-piperazine, (3-{4-[4-(2-methoxy-phenyl)-piperazin-1-yl]-butoxy}-
benzyl)-dimethyl-amine, 4-(3-{4-[4-(2-methoxy-phenyl)-piperazin-1-yl]-butoxy}-
benzyl)-morpholine, 1-{4-[4-(4,5-dichloro-imidazol-1-ylmethyl)-phenoxy]-butyl}-4-(2-
methoxy-phenyl)-piperazine, 1-(2-chloro-phenyl)-4-[4-(4-tetrazol-2-ylmethyl-
phenoxy)-butyl]-piperazine, 4-(4-{4-[4-(2-methoxy-phenyl)-piperazin-1-yl]-butoxy}-
15 benzyl)-morpholine, (4-{4-[4-(2-Chloro-phenyl)-piperazin-1-yl]-butoxy}-benzyl)-
dimethyl-amine, 1-(3-fluoro-phenyl)-4-[4-(4-[1,2,4]triazol-1-ylmethyl-phenoxy)-butyl]-
piperazine, 1-(2-methoxy-phenyl)-4-[4-(4-4-methylpiperazine-1-ylmethyl-phenoxy)-
butyl]-piperazine, , 1-(2,3-dichloro-phenyl)-4-[4-(4-tetrazol-2-ylmethyl-phenoxy)-
butyl]-piperazine, 1-(2,3-Dichloro-phenyl)-4-{4-[4-(5-methyl-tetrazol-1-ylmethyl)-
20 phenoxy]-butyl}-piperazine, 1-(2,3-Dichloro-phenyl)-4-{4-[4-(5-methyl-tetrazol-2-
ylmethyl)-phenoxy]-butyl}-piperazine, (4-{4-[4-(2,3-dichloro-phenyl)-piperazin-1-yl]-
butoxy}-benzyl)-dimethyl-amine, 4-(4-{4-[4-(2,3-Dichloro-phenyl)-piperazin-1-yl]-
butoxy}-benzyl)-morpholine, 1-(2-methoxy-phenyl)-4-[4-(4-4-methylpiperazine-1-
ylmethyl-phenoxy)-butyl]-piperazine, 1-(2-chloro-phenyl)-4-[4-(4-[1,2,3]triazol-1-
25 ylmethyl-phenoxy)-butyl]-piperazine, (4-{4-[4-(2-Methoxy-phenyl)-piperazin-1-yl]-
butoxy}-benzyl)-[1,3,4]thiadiazol-2-yl-amine, 1-(2,3-dichloro-phenyl)-4-[4-(4-
[1,2,3]triazol-1-ylmethyl-phenoxy)-butyl]-piperazine, (4-{4-[4-(2-Methoxy-phenyl)-
piperazin-1-yl]-butoxy}-benzyl)-(5-methyl-isoxazol-3-yl)-amine, (4-{4-[4-(2-methoxy-
phenyl)-piperazin-1-yl]-butoxy}-benzyl)-(5-methyl-isoxazol-3-yl)-amine, 1-{4-[4-(2-
30 imidazol-1-yl-ethyl)-phenoxy]-butyl}-4-(2-methoxy-phenyl)-piperazine, 1-(2-methoxy-
phenyl)-4-{4-[4-(2-[1,2,4]triazol-1-yl-ethyl)-phenoxy]-butyl}-piperazine, 1-(2-
methoxy-phenyl)-4-{4-[4-(2-[1,2,3]triazol-2-yl-ethyl)-phenoxy]-butyl}-piperazine, 1-

(2-methoxy-phenyl)-4-{4-[4-(2-[1,2,3]triazol-1-yl-ethyl)-phenoxy]-butyl}-piperazine,
 1-(2-methoxy-phenyl)-4-{4-[4-(2-tetrazol-2-yl-ethyl)-phenoxy]-butyl}-piperazine, 1-(2-
 methoxy-phenyl)-4-{4-[4-(2-tetrazol-1-yl-ethyl)-phenoxy]-butyl}-piperazine, 1-(2-
 Methoxy-phenyl)-4-(4-{4-[2-(5-methyl-tetrazol-1-yl)-ethyl]-phenoxy}-butyl)-
 5 piperazine, 1-(2-Methoxy-phenyl)-4-(4-{4-[2-(5-methyl-tetrazol-2-yl)-ethyl]-phenoxy}-
 butyl)-piperazine, 2-{4-[4-(4-[1,2,3]-triazol-1-ylmethyl-phenoxy)-butyl]-piperazin-1-
 yl}-benzonitrile, and 1-(2-chloro-phenyl)-4-[4-(4-[1,2,3]triazol-2-ylmethyl-phenoxy)-
 butyl]-piperazine.

A “pharmaceutically acceptable salt”, where such salts are possible, includes
 10 both pharmaceutically acceptable acid and base addition salts. A suitable
 pharmaceutically acceptable salt of a compound of Formula I is, for example, an acid-
 addition salt of a compound of Formula I that is sufficiently basic, for example an acid-
 addition salt with an inorganic or organic acid such as hydrochloric, hydrobromic,
 sulphuric, trifluoroacetic, citric or maleic acid; or, for example, a salt of a compound of
 15 Formula I that is sufficiently acidic, for example an alkali or alkaline earth metal salt
 such as a sodium, calcium, or magnesium salt, or an ammonium salt, or a salt with an
 organic base such as methylamine, dimethylamine, trimethylamine, piperidine,
 morpholine, or tris-(2-hydroxyethyl)amine.

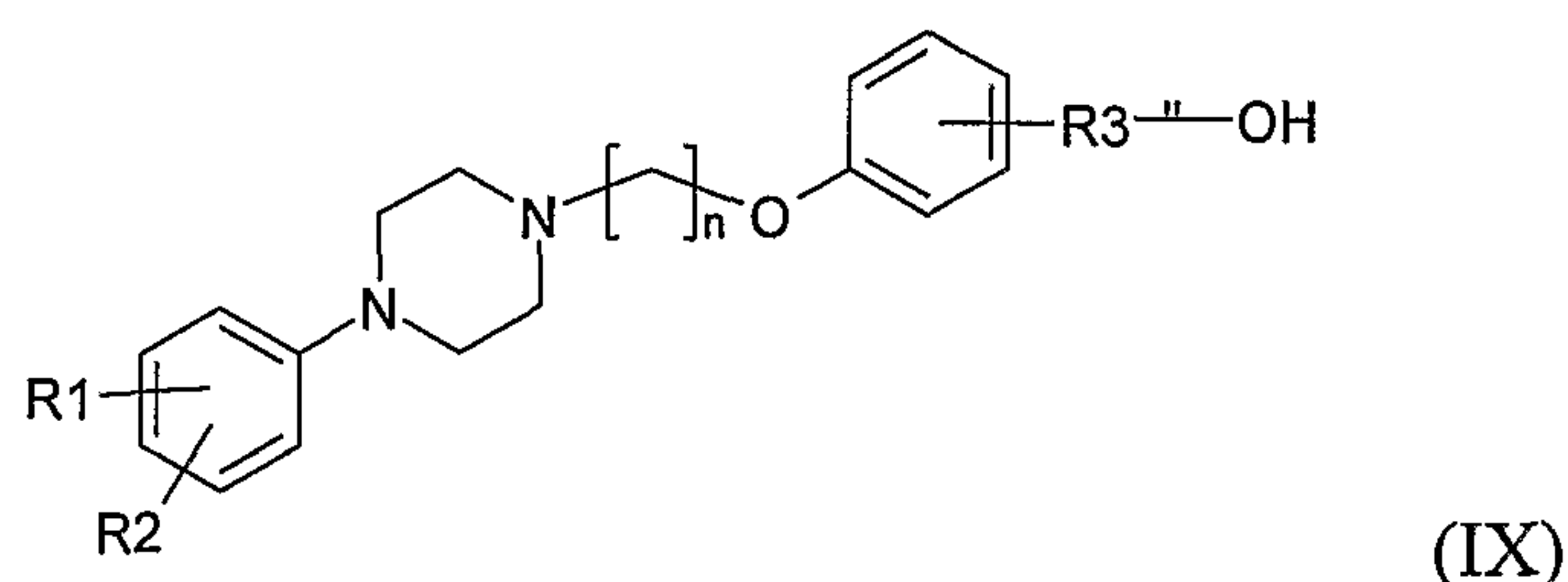
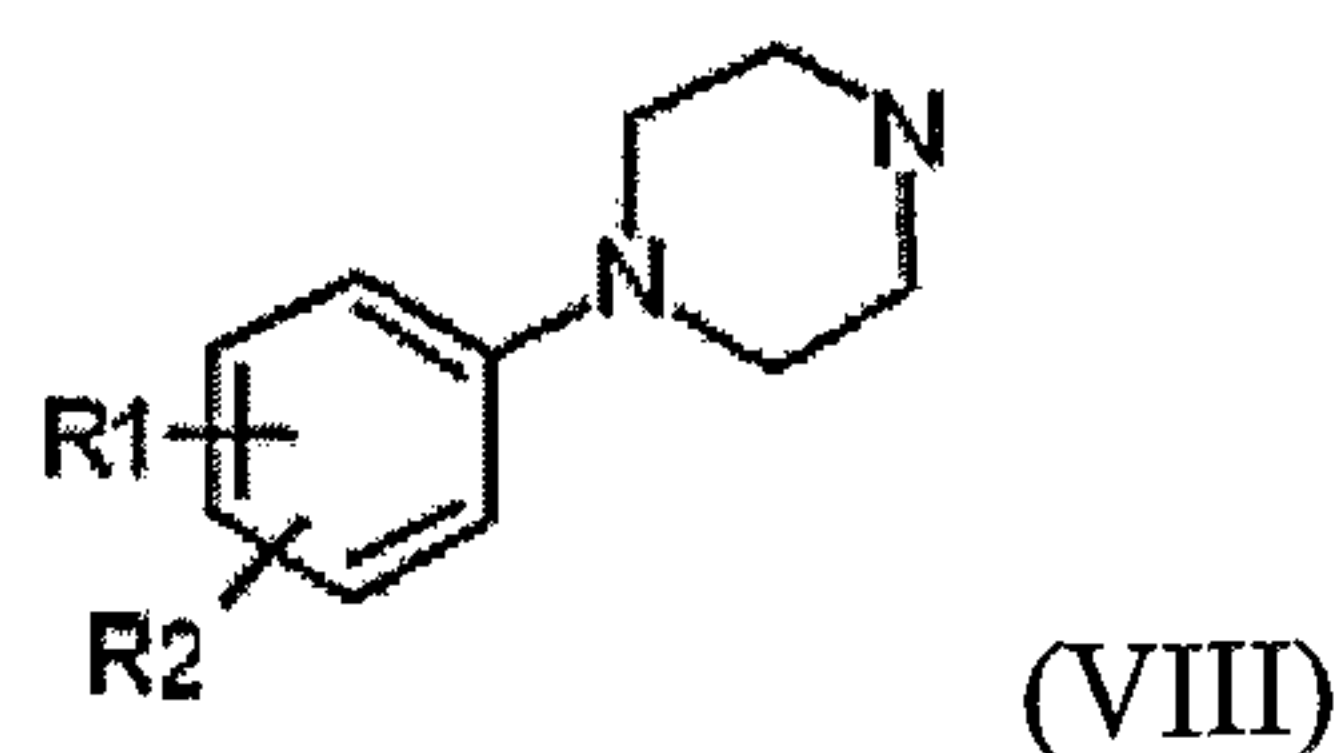
A method for preparing the above piperazine derivative, represented by
 20 chemical Formula (I) will be described below in detail.

First, phenols of Formula (VI) as starting material are reacted with dihalide
 alkanes represented by Formula (V) to synthesize halogenized compounds represented
 by Formula (VII):



wherein n is the same as defined above and X is a halogen such as, without limitation, chloride and bromide.

The halogenized compound represented by Formula (VII) is reacted with phenyl piperazines of Formula (VIII) to obtain the compounds having hydroxy group represented by the Formula (IX):

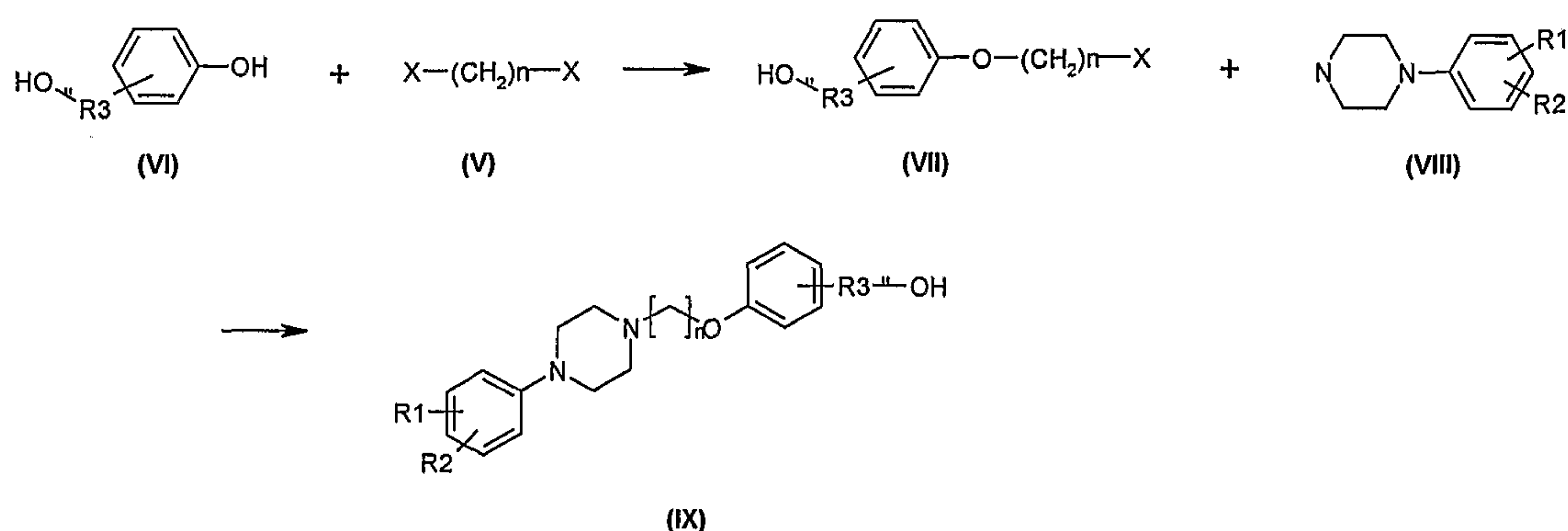


wherein R1, R2, n and R3 are the same as defined above.

This procedure is summarized as set forth in Reaction Scheme (I) below.

10

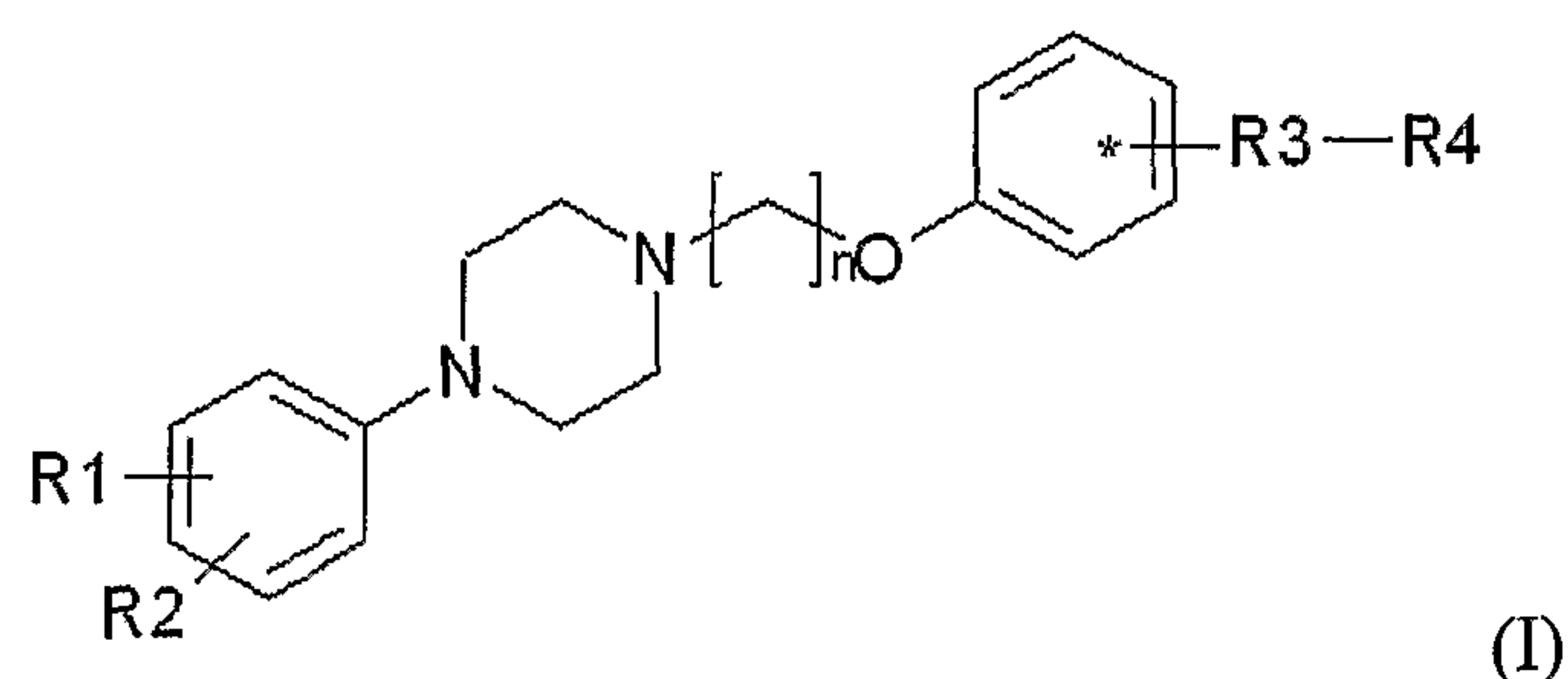
Reaction Scheme I



Details of the reaction conditions described in Reaction Scheme I may be as follows. For the conversion of the phenols (VI) to the halogenized compound (VII), the concentration of the phenols (VI) may be about 0.005 to about 0.1 moles, with a dihalide alkane (V) ranging from about 2.0 to about 3.0 equivalents and an organic or

inorganic base from about 3.0 to about 4.0 equivalents. This reaction may be refluxed. The resulting product may be purified by column chromatography. For the conversion of the halogenized compounds (VII) to the compound having hydroxy group (IX), a mixture of (VII) and substituted phenylpiperazine (VIII) may be refluxed in about 30ml
 5 of acetonitrile for about 6h. For this coupling reaction, an ethereal solvent such as diethyl ether and tetrahydrofuran, a halogenated hydrocarbon solvent such as dichloromethane and chloroform, or a mixture thereof may be used.

Then, the hydroxy compounds having hydroxy group represented by Formula (IX) are reacted with thionyl chloride and then with dialkylamines, aromatic amine,
 10 heteroaromatic amine, heterocyclic ring, or heteroaromatic ring groups to produce the phenyl piperazine compounds represented by Formula (I):



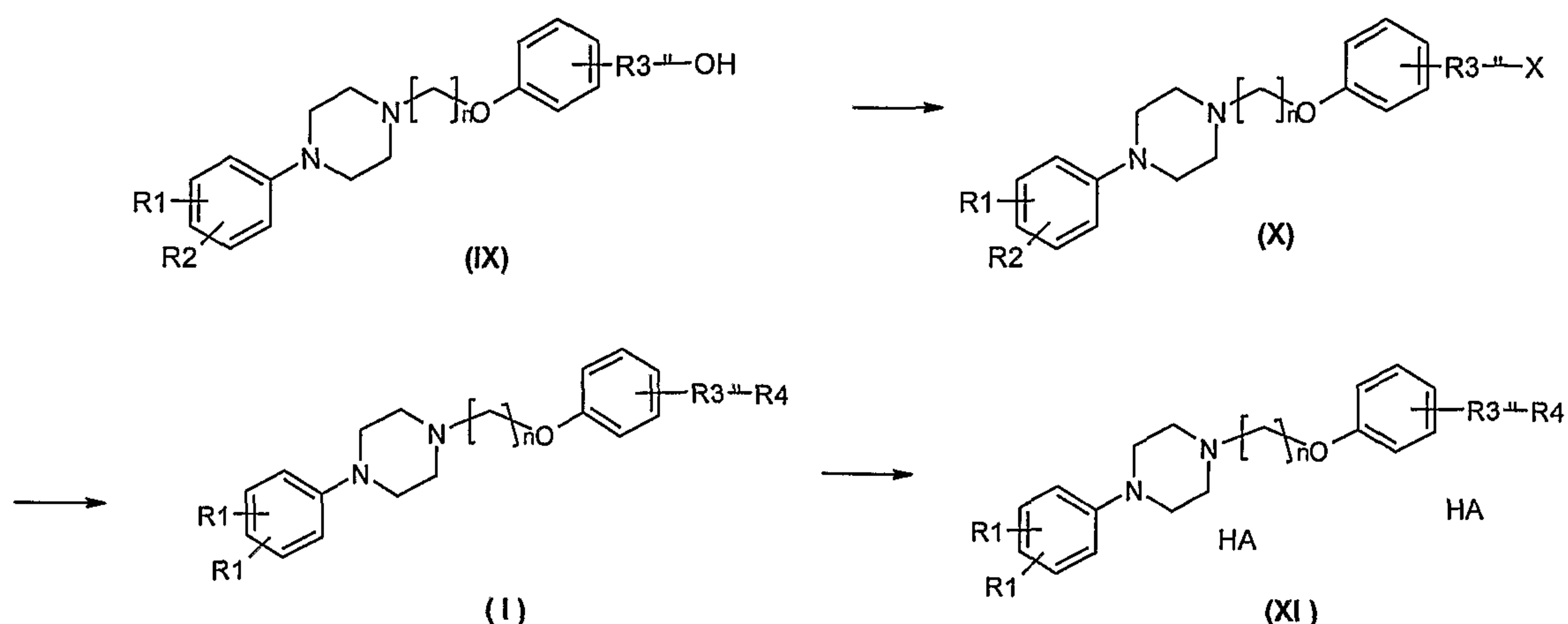
wherein,

R1, R2, R3, R4, and n are as previously defined.

15 The pharmaceutically acceptable salts thereof represented by Formula (XI) as below can be obtained by treating a phenyl piperazine compound of Formula (I) with an anhydrous acid in a solution without further purification.

This procedure is summarized as set forth in Reaction Scheme (II) below.

Reaction Scheme II



Details of the reaction conditions described in Reaction Scheme II are as follows. For the conversion of the compounds having hydroxy group (IX) to the compound (X), the concentration of the compounds having hydroxy group (IX) may be about 0.005 to about 0.1 moles with thionyl chloride ranging from about 1.0 to about 1.5 equivalents. This reaction may be carried out at a temperature of about 0°C. The resulting product may be purified by column chromatography. The resulting compound (X) may be treated with about 2.0 to about 3.0 equivalents of dialkylamines, aromatic amine, heteroaromatic amine, heterocyclic ring, or heteroaromatic ring at a reflux to give the compound of the General Formula (I). For this coupling reaction, tetrahydrofuran, acetonitrile, a halogenated hydrocarbon solvent such as dichloromethane and chloroform, or a mixture thereof may be used.

In Reaction Scheme II, HA represents an acid that is capable of forming a pharmacologically useful salt with the basic nitrogen atom. Specific examples of the anhydrous acid used for the preparation of the compound (XI) include, without limitation, hydrochloric acid, sulfuric acid, phosphoric acid, acetic acid, benzoic acid, citric acid, malonic acid, salicylic acid, malic acid, fumaric acid, oxalic acid, succinic acid, tartaric acid, lactic acid, gluconic acid, ascorbic acid, maleic acid, aspartic acid, benzene sulfonic acid, methane sulfonic acid, ethane sulfonic acid, hydroxymethane sulfonic acid, hydroxyethane sulfonic acid, and the like. For additional acids, one can refer to "Pharmaceutical Salts", J. Pharm. Sci., 1977; 66(1): 1-19. This preparation may be executed in a reaction media that can be exemplified by an ethereal solvent such as tetrahydrofuran, an alcoholic solvent such as methanol, an ester solvent such as ethyl

acetate, a halogenated hydrocarbon solvent, and mixtures thereof. In one embodiment, an ethereal solvent is recommended as an addition solution, including ethyl ether, propyl ether, isopropyl ether, butyl ether, and isobutyl ether. The concentration of the compound (I) may be in the order of about 0.01 to about 5 moles.

5 In another embodiment of the present invention, the present invention provides a pharmaceutical composition including an effective amount of phenyl piperazine compounds represented by Formula (I) for treating at least one of depression and anxiety.

10 In a further embodiment of the present invention, the present invention provides a method of treating at least one of depression and anxiety in a mammal comprising administering to a mammal in need thereof an effective amount of the piperazine compounds represented by Structural Formula (I), alone or in combination with a pharmaceutically acceptable carrier or excipient.

15 The activity of the compounds of the present invention was examined through the Mouse Tail Suspension and Marble Burying Test.

In therapeutic use as agents for depression and anxiety the compounds of the present invention are used, alone or in combination with a pharmaceutically acceptable carrier or excipient.

20 The compounds of the present invention may be administered orally or parentally, neat or in combination with conventional pharmaceutical carriers. Applicable solid carriers can include, without limitation, one or more substances which may also act as flavoring agents, lubricants, solubilizers, suspending agents, fillers, glidants, compression aids, binders, tablet-disintegrating agents, or encapsulating materials. In powders, the carrier may be a finely divided solid that may be in
25 admixture with the finely divided active ingredient. In tablets, the active ingredient may be mixed with a carrier having suitable compression properties in suitable proportions and compacted in the shape and size desired. The powders and tablets may contain up to about 99% of the active ingredient.

Suitable solid carriers include, for example, calcium phosphate, magnesium stearate, talc, sugars, lactose, dextrin, starch, gelatin, cellulose, methyl cellulose, sodium carboxymethyl cellulose, polyvinylpyrrolidone, low melting waxes, and ion exchange resins. Liquid carriers may be used in preparing solutions, suspensions, emulsions, syrups, and elixirs.

The active ingredient of this invention may be dissolved or suspended in a pharmaceutically acceptable liquid carrier such as water, an organic solvent, a mixture of both, or pharmaceutically acceptable oils or fats. The liquid carrier may contain other suitable pharmaceutical additives such as solubilizers, emulsifiers, buffers, preservatives, sweeteners, flavoring agents, suspending agents, thickening agents, colors, viscosity regulators, stabilizers, or osmo-regulators. Suitable examples of liquid carriers for oral and parenteral administration include water (particularly containing additives as above, e.g., cellulose derivatives such as, without limitation, a sodium carboxymethyl cellulose solution), alcohols (including, without limitation, monohydric alcohols and polyhydric alcohols, e.g., glycols) and their derivatives, and oils (e.g., without limitation, fractionated coconut oil and arachis oil).

For parenteral administration the carrier can also be an oily ester such as ethyl oleate and isopropyl myristate. Sterile liquid carriers are used in sterile liquid form compositions for parenteral administration. Liquid pharmaceutical compositions that are sterile solutions or suspensions can be utilized by, for example, intramuscular, intraperitoneal, or subcutaneous injection. Sterile solutions can also be administered intravenously.

Oral administration may be either in liquid or solid composition form. In one embodiment, the pharmaceutical compositions containing the present compounds are in unit dosage form, e.g., as tablets or capsules. In such form, the composition may be sub-divided in unit dosages containing appropriate quantities of the active ingredients. The unit dosage forms can be packaged compositions, for example, packaged powders, vials, ampoules, prefilled syringes or sachets containing liquids. Alternatively, the unit dosage form can be, for example, a capsule or tablet itself, or it can be the appropriate number of any such compositions in package form. The therapeutically effective

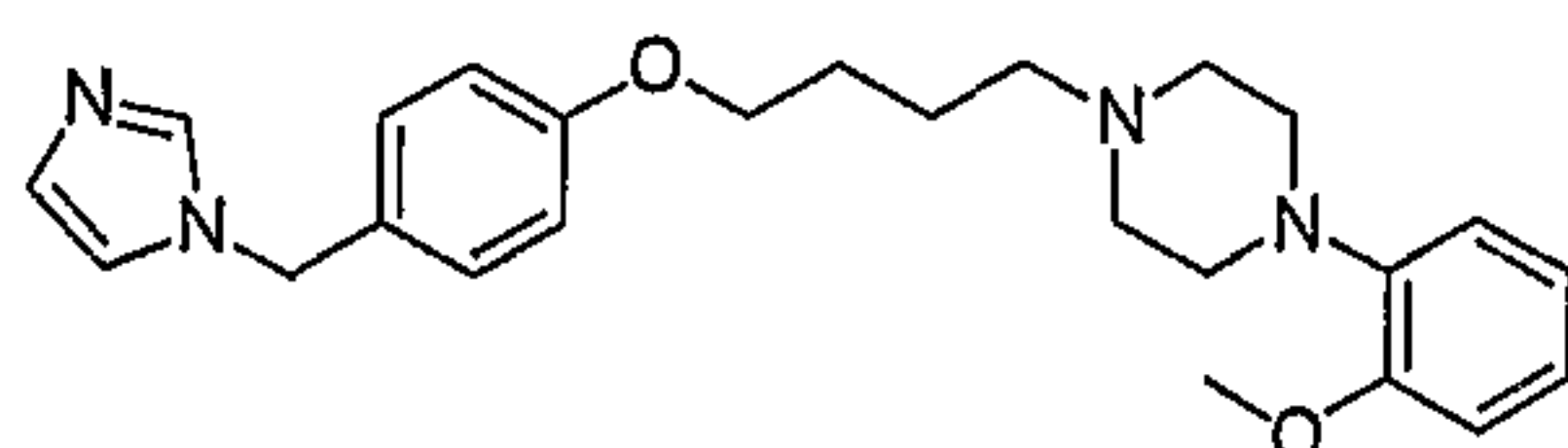
dosage to be used may be varied or adjusted by the physician and generally ranges from about 0.5 mg to about 750 mg, according to the specific condition(s) being treated and the size, age, and response pattern of the patient.

The compounds of the present invention may be administered to patients at a dosage of from about 0.7 to about 7000 mg per day. For example, for a normal human adult with a body weight of approximately 70kg, the administration amount is translated into a daily dose of about 0.01 to about 100 mg per kg of body weight. The specific dosage employed, however, may vary depending upon the requirements of the patient, the severity of the patient's condition, and the activity of the compound. The determination of optimum dosages for a particular situation may be clinically done and is within the skill of the art.

A better understanding of the present invention may be obtained in light of the following examples to illustrate, but are not to be construed to limit, the present invention.

Example 1

1-[4-(4-imidazol-1-ylmethyl-phenoxy)-butyl]-4-(2-methoxy-phenyl)-piperazine.



20

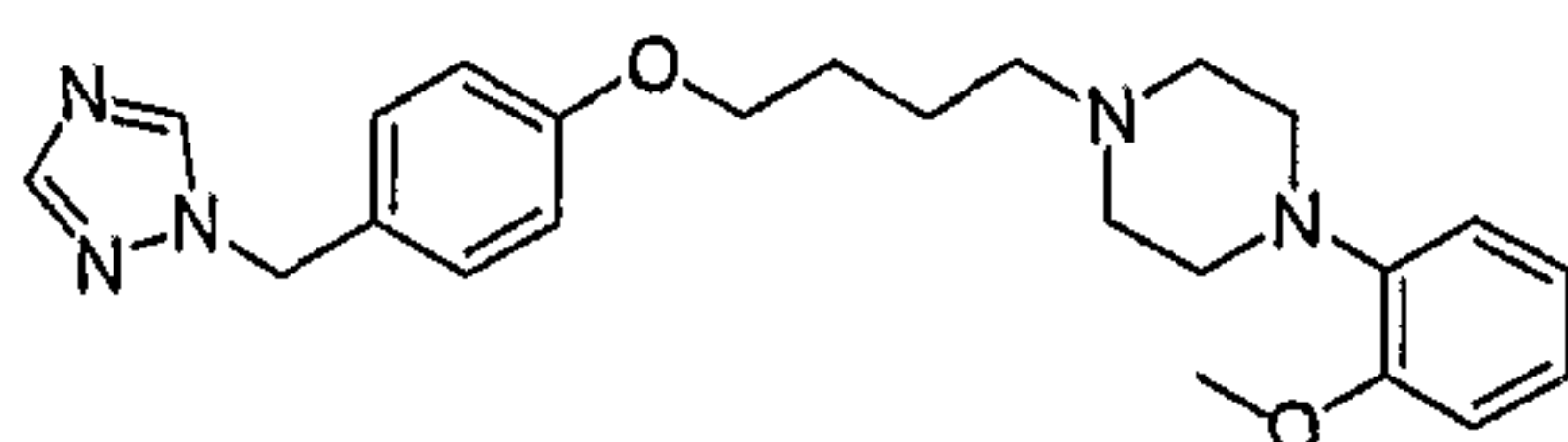
A mixture of 4-hydroxybenzaldehyde (5mmol), 1-bromo-4-chlorobutane (5mmol), and potassium carbonate (15mmol) was refluxed in 100ml of acetone for 6h. This solution was then concentrated on a rotary evaporator and diluted with ethyl acetate. This mixture was then washed with brine, and the resulting organic layer was dried and purified by column chromatography. This was dissolved in methanol (50ml) and was added with sodium borohydride (10mmol) at 25°C. This mixture was stirred at 25°C for 2h. This solution was then concentrated in a rotary evaporator and diluted with methylene chloride, then washed with brine, and the resulting organic layer was dried and concentrated in vacuo. The crude product was dissolved in isopropanol

(50ml) and was added with 1-(2-methoxyphenyl)-piperazine (5mmol), sodium carbonate (15mmol), and potassium iodide (5mmol) at 25 °C, and the reaction mixture was refluxed for 12h. This solution was then concentrated on a rotary evaporator and diluted with methylene chloride, then washed with brine, and the resulting organic layer was dried and purified by column chromatography. This product was dissolved in CHCl₃ (30ml) and was added with pyridine and thionyl chloride (5mmol) at 0 °C, then stirred at room temperature for 16h, and water was added to terminate the reaction. The organic layer was extracted 3 times with dichloromethane, dried, and concentrated in vacuo. The residue was purified by column chromatography. This was dissolved in acetonitrile (30ml) and was added with imidazole (6mmol), potassium carbonate (15mmol), and potassium iodide (5mmol) at 25 °C, and the reaction mixture was refluxed for 12h. This solution was then concentrated in a rotary evaporator and diluted with methylene chloride, then washed with brine, and the resulting organic layer was dried and purified by column chromatography. The resulting 1-[4-(4-imidazole-1-ylmethyl-phenoxy)-butyl]-4-(2-methoxy-phenyl)-piperazine was dissolved in dichloromethane and the solution was treated with a solution of HCl in ethyl ether. The resulting precipitate was filtered to give 1-[4-(4-imidazole-1-ylmethyl-phenoxy)-butyl]-4-(2-methoxy-phenyl)-piperazine hydrochloride.

¹H-NMR (CDCl₃, 200MHz) δ 11.1 (br, 1H), 7.5 (s, 1H), 7.3 (s, 1H), 7.2(m, 2H), 6.9(m, 7H), 5.0(s, 2H), 4.0(t, 2H), 3.8 (s, 3H), 3.2(m, 4H), 2.7(m, 4H), 2.5(t, 2H), 1.8(m, 4H)

Example 2

1-(2-methoxy-phenyl)-4-[4-(4-[1,2,4]triazol-1-ylmethyl-phenoxy)-butyl]-piperazine.



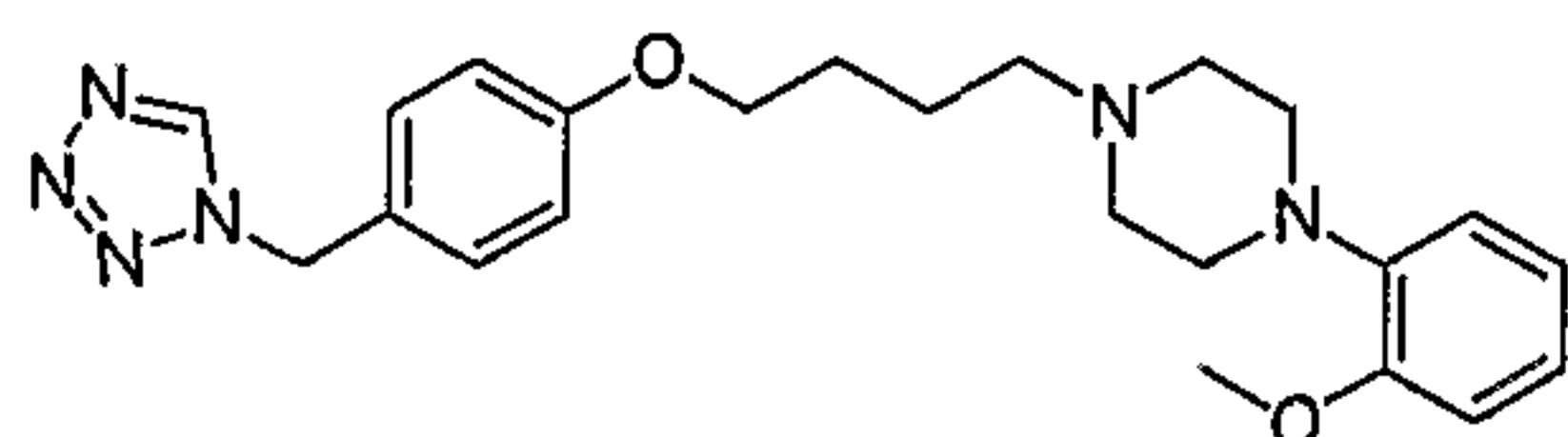
The procedure given in Example 1 was followed using 1H-1,2,4-triazole as reactants, instead of imidazole, to give 1-(2-methoxy-phenyl)-4-[4-(4-[1,2,4]triazole-1-ylmethyl-phenoxy)-butyl]-piperazine.

¹H-NMR (CDCl₃, 200MHz) δ 8.1 (s, 1H), 8.0 (s, 1H), 7.2(m, 2H), 6.9(m, 6H),

5.2(s, 2H), 4.0(t, 2H), 3.8 (s, 3H), 3.2(m, 4H), 2.7(m, 4H), 2.5(t, 2H), 1.8(m, 4H)

Example 3

1-(2-methoxy-phenyl)-4-[4-(4-tetrazol-1-ylmethyl-phenoxy)-butyl]-piperazine.



5

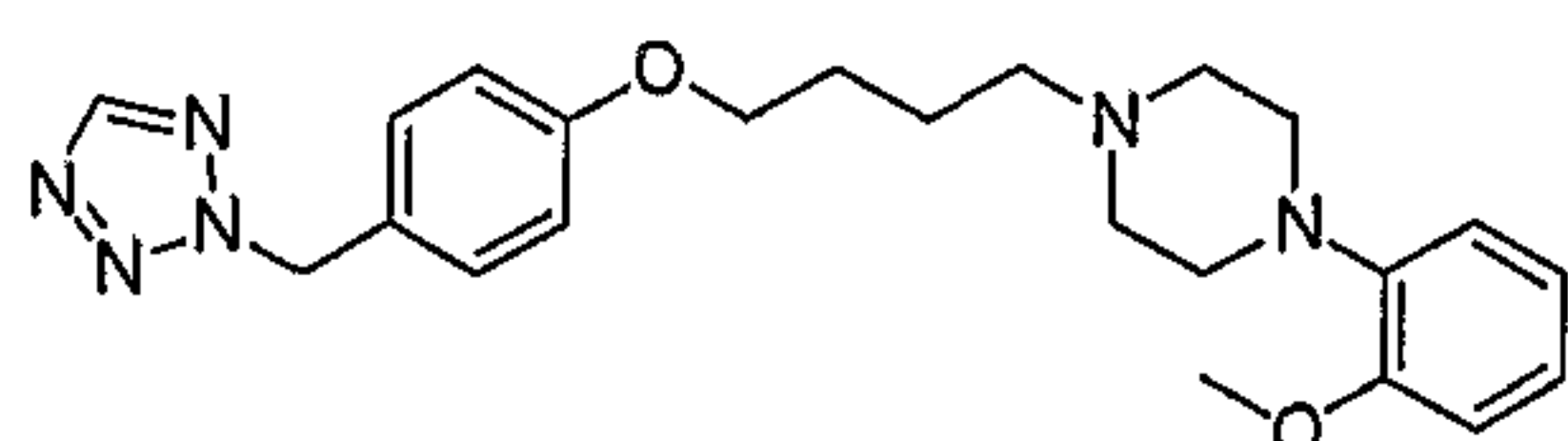
The procedure given in Example 1 was followed using 1H-tetrazole as reactants, instead of imidazole, to give 1-(2-methoxy-phenyl)-4-[4-(4-tetrazol-1-ylmethyl-phenoxy)-butyl]-piperazine.

10 $^1\text{H-NMR}$ (CDCl_3 , 200MHz) δ 8.6(s, 1H), 7.2 (m, 2H), 7.0(m, 6H), 5.6 (s, 2H), 4.0(t, 2H), 3.8(s, 3H)3.2(m, 4H), 2.9(m, 4H), 2.7(t, 2H), 1.9(m, 4H)

Example 4

1-(2-methoxy-phenyl)-4-[4-(4-tetrazol-2-ylmethyl-phenoxy)-butyl]-piperazine.

15

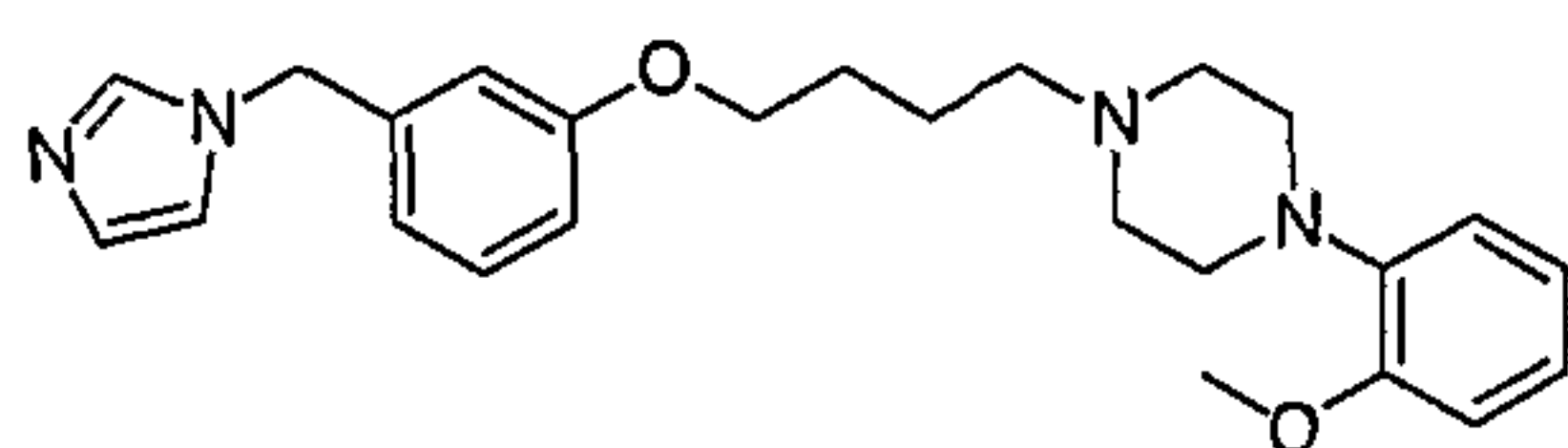


The procedure given in Example 1 was followed using 1H-tetrazole as reactants, instead of imidazole, to give 1-(2-methoxy-phenyl)-4-[4-(4-tetrazol-2-ylmethyl-phenoxy)-butyl]-piperazine.

20 $^1\text{H-NMR}$ (CDCl_3 , 200MHz) δ 8.6(s, 1H), 7.2 (m, 2H), 7.0(m, 6H), 5.8 (s, 2H), 4.0(t, 2H), 3.8(s, 3H)3.2(m, 4H), 2.9(m, 4H), 2.7(t, 2H), 1.9(m, 4H)

Example 5

25 **1-[4-(3-imidazol-1-ylmethyl-phenoxy)-butyl]-4-(2-methoxy-phenyl)-piperazine-hydrochloride.**



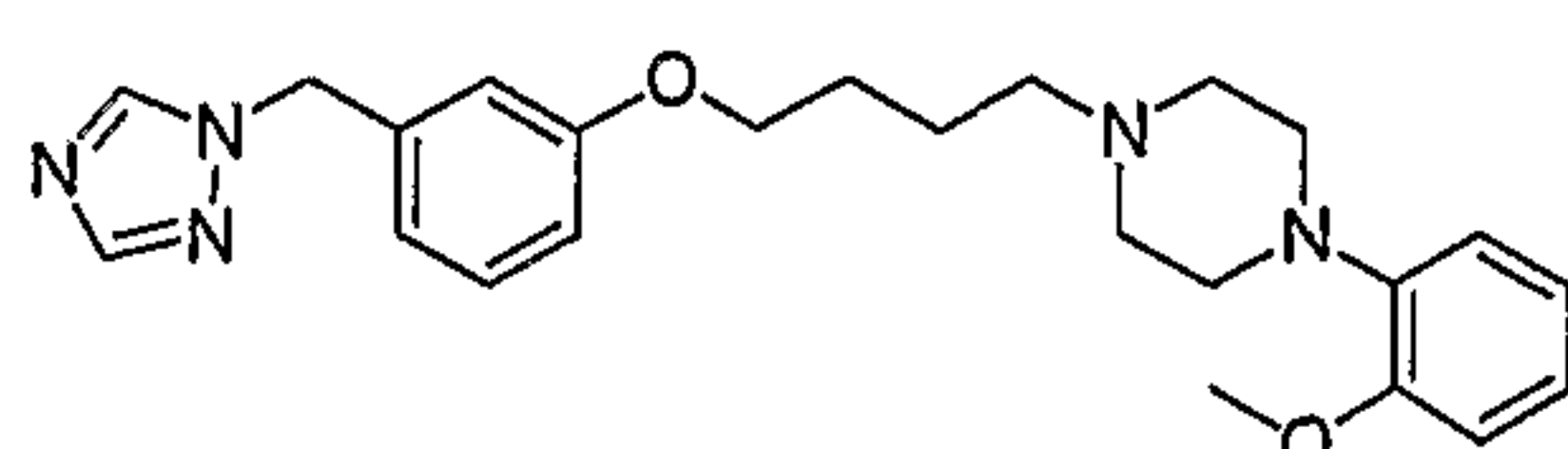
A mixture of 3-hydroxybenzaldehyde (5mmol), 1-bromo-4-chlorobutane (5mmol), and potassium carbonate (15mmol) was refluxed in 100ml of acetone for 6h. This solution was then concentrated in a rotary evaporator and diluted with ethyl acetate, then washed with brine, and the resulting organic layer was dried and purified by column chromatography. This was dissolved in methanol (50ml) and was added with sodium borohydride (10mmol) at 25°C, and was stirred at 25°C for 2h. This solution was then concentrated in a rotary evaporator and diluted with methylene chloride, then washed with brine, and the resulting organic layer was dried and concentrated in vacuo. The crude product was dissolved in isopropanol (50ml) and was added with 1-(2-methoxyphenyl)-piperazine (5mmol), sodium carbonate (15mmol), and potassium iodide (5mmol) at 25°C, and the reaction mixture was refluxed for 12h. This solution was then concentrated in a rotary evaporator and diluted with methylene chloride, then washed with brine, and the resulting organic layer was dried and purified by column chromatography. This product was dissolved in CHCl₃ (30ml) and was added with pyridine and thionyl chloride (5mmol) at 0°C, and then the resulting reaction mixture was stirred at room temperature for 16h, and water was added to terminate the reaction. The organic layer was extracted 3 times with dichloromethane, then dried and concentrated in vacuo, and the residue was purified by column chromatography. This was dissolved in acetonitrile (30ml) and was added with imidazole (6mmol), potassium carbonate (15mmol), and potassium iodide (5mmol) at 25°C, and the reaction mixture was refluxed for 12h. This solution was then concentrated in a rotary evaporator and diluted with methylene chloride, then washed with brine, and the resulting organic layer was dried and purified by column chromatography. The resulting 1-[4-(3-imidazole-1-ylmethyl-phenoxy)-butyl]-4-(2-methoxy-phenyl)-piperazine was dissolved in dichloromethane and the solution was treated with a solution of HCl in ethyl ether. The resulting precipitate was filtered to give 1-[4-(3-imidazol-1-ylmethyl-phenoxy)-butyl]-4-(2-methoxy-phenyl)-piperazine hydrochloride.

¹H-NMR (DMSO, 200MHz) δ 11.6 (br,1H), 9.5 (s,1H), 7.8 (s, 1H), 7.6 (s, 1H),

7.2(m, 2H), 7.0(m, 6H), 5.4(s, 2H), 4.0(t, 2H), 3.8(s, 3H), 3.6-3.2 (m, 10H), 2.0(m, 2H), 1.8(m, 2H)

Example 6

5 **1-(2-methoxy-phenyl)-4-[4-(3-[1,2,4]triazol-1-ylmethyl-phenoxy)-butyl]-piperazine hydrochloride.**



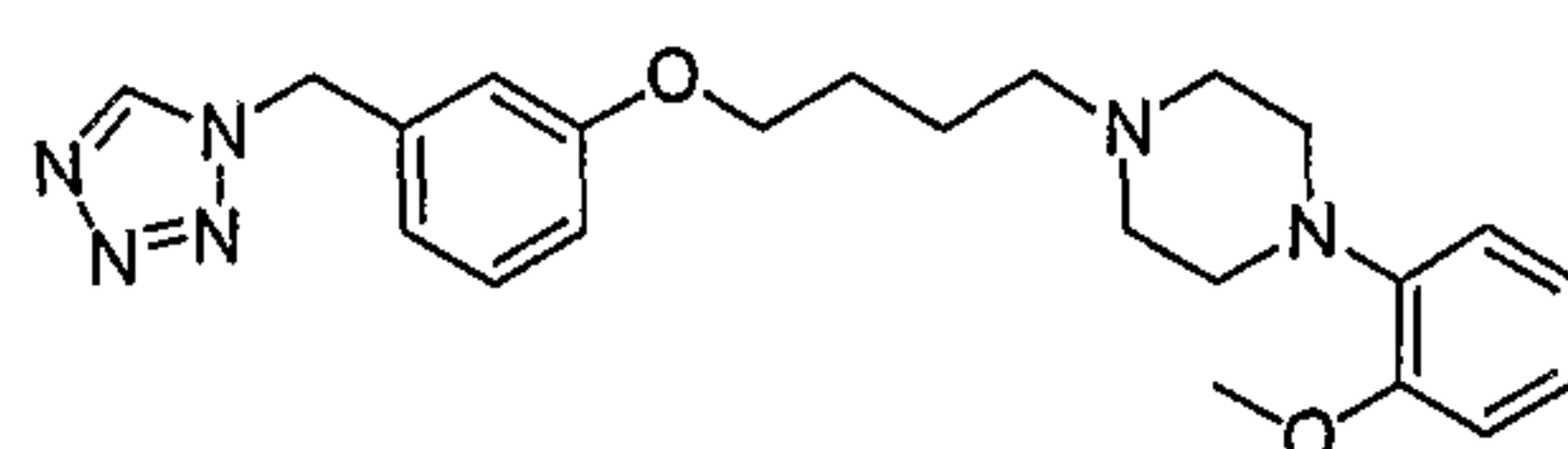
10 The procedure given in Example 5 was followed using 1H-1,2,4-triazole as reactants, instead of imidazole, to give 1-(2-methoxy-phenyl)-4-[4-(3-[1,2,4]triazol-1-ylmethyl-phenoxy)-butyl]-piperazine.

¹H-NMR (DMSO, 200MHz) δ 11.6 (br,1H), 9.5 (s,1H), 8.5(s, 1H), 7.2(m, 2H), 7.0(m, 6H), 5.4(s, 2H), 4.0(t, 2H), 3.8(s, 3H), 3.6-3.2 (m, 10H), 2.0(m, 2H), 1.8(m, 2H)

15

Example 7

1-(2-methoxy-phenyl)-4-[4-(3-tetrazol-1-ylmethyl-phenoxy)-butyl]-piperazine hydrochloride.



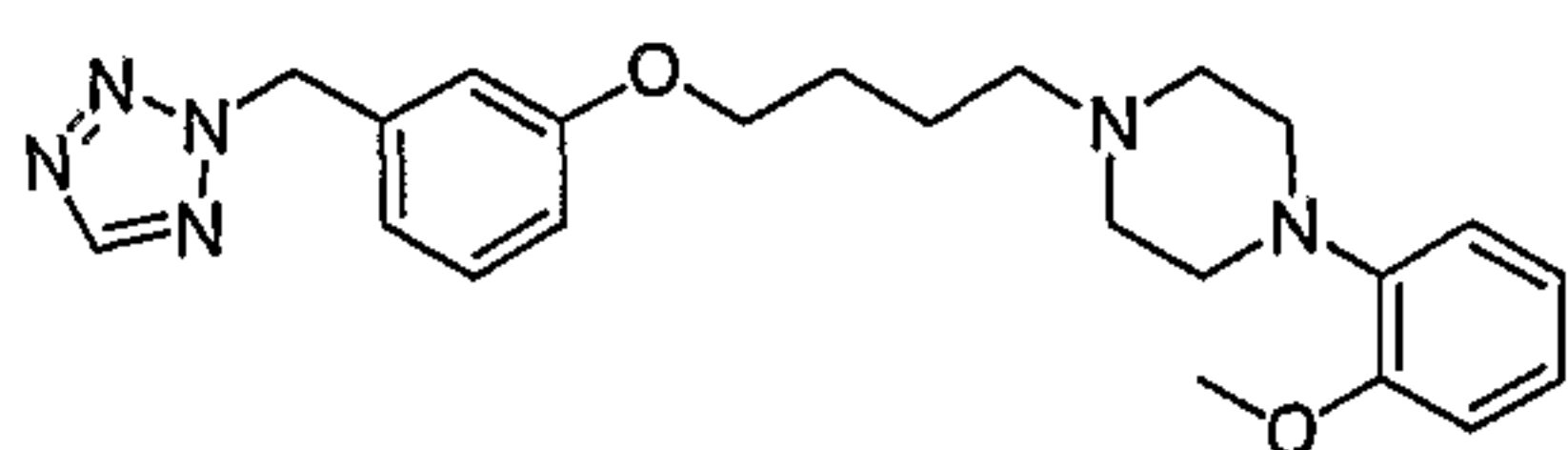
20

The procedure given in Example 5 was followed using 1H-tetrazole as reactants, instead of imidazole, to give 1-(2-methoxy-phenyl)-4-[4-(3-tetrazol-1-ylmethyl-phenoxy)-butyl]-piperazine.

25 ¹H-NMR (DMSO, 200MHz) δ 10.8 (br,1H), 9.6 (s,1H), 7.2(m, 2H), 7.0(m, 6H), 5.4(s, 2H), 4.0(t, 2H), 3.8(s, 3H), 3.6 (m, 4H), 3.2 (m, 6H), 2.0(m, 2H), 1.8(m, 2H)

Example 8

1-(2-methoxy-phenyl)-4-[4-(3-tetrazol-2-ylmethyl-phenoxy)-butyl]-piperazine hydrochloride.



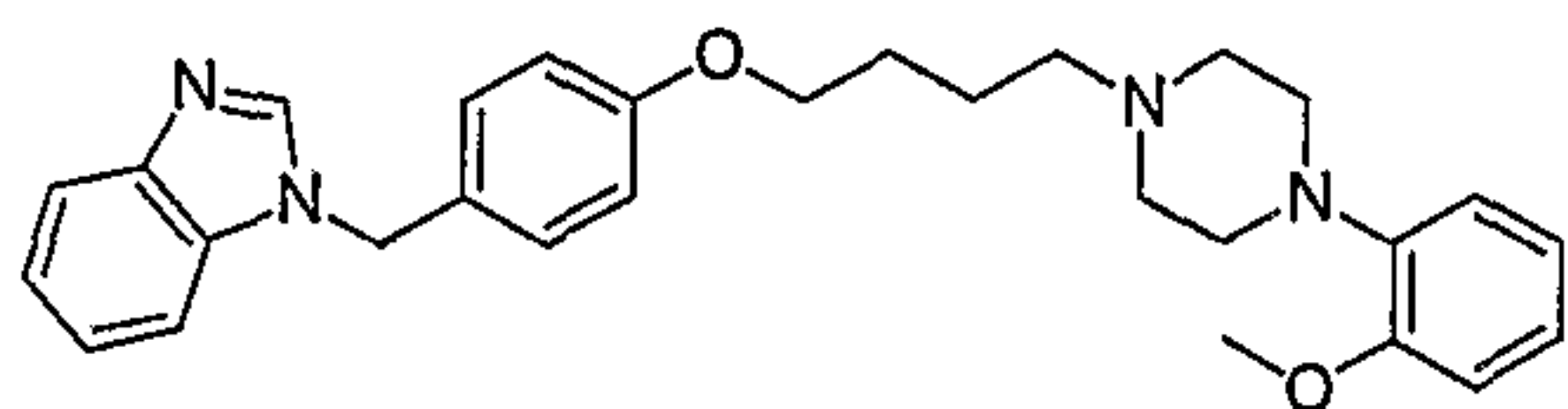
5

The procedure given in Example 5 was followed using 1H-tetrazole as reactants, instead of imidazole, to give 1-(2-methoxy-phenyl)-4-[4-(3-tetrazol-2-ylmethyl-phenoxy)-butyl]-piperazine.

¹H-NMR (DMSO, 200MHz) δ 10.8 (br, 1H), 9.0 (s, 1H), 7.2(m, 2H), 7.0(m, 6H),
10 5.9(s, 2H), 4.0(t, 2H), 3.8(s, 3H), 3.6 (m, 4H), 3.2 (m, 6H), 2.0(m, 2H), 1.8(m, 2H)

Example 9

1-(4-{4-[4-(2-methoxy-phenyl)-piperazin-1-yl]-butoxy}-benzyl)-1H-benzoimidazole.



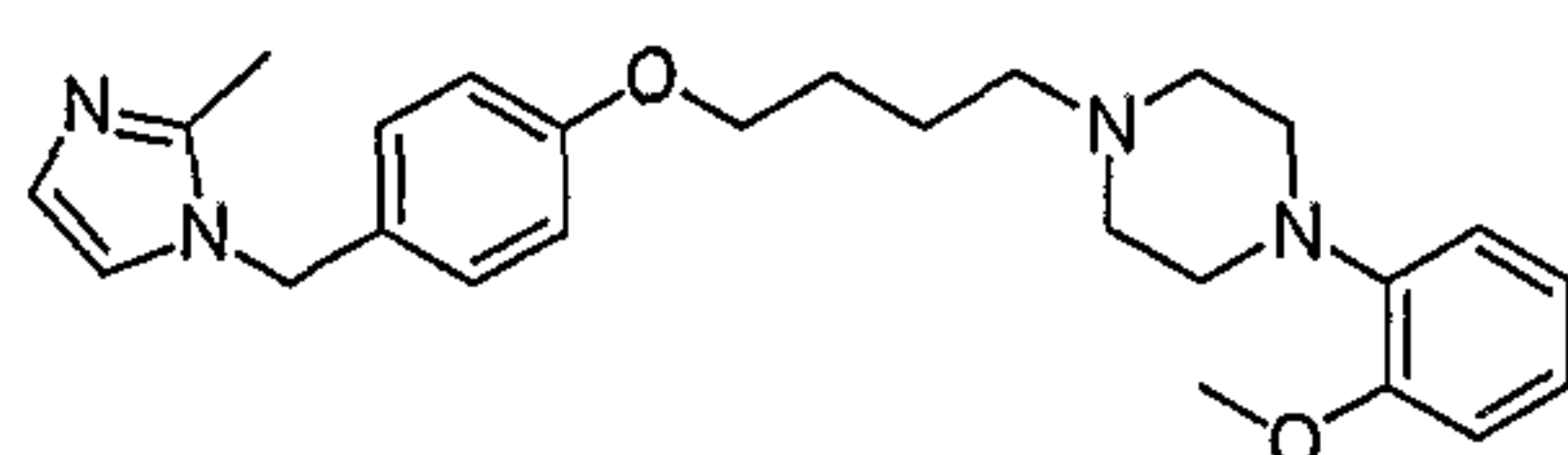
15

The procedure given in Example 1 was followed using 1H-benzoimidazole as reactants, instead of imidazole, to give 1-(4-{4-[4-(2-methoxy-phenyl)-piperazin-1-yl]-butoxy}-benzyl)-1H-benzoimidazole.

¹H-NMR (CDCl₃, 200MHz) δ 8.0 (s, 1H), 7.8 (m, 1H), 7.3 (m, 3H), 7.2(m., 2H),
20 7.0(m, 6H), 5.3 (s, 2H), 4.0 (t, 2H), 3.8(s, 3H), 3.1(m, 4H), 2.7(m, 4H), 2.5(t, 2H),
1.8(m, 4H)

Example 10

25 **1-(2-Methoxy-phenyl)-4-{4-[4-(2-methyl-imidazol-1-ylmethyl)-phenoxy]-butyl}-piperazine.**

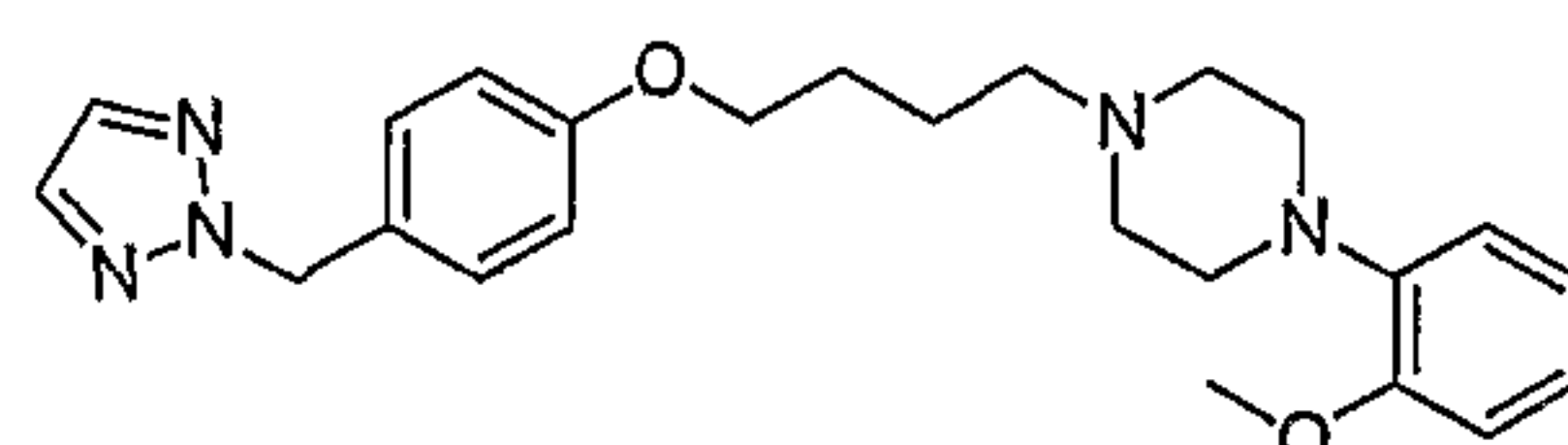


The procedure given in Example 1 was followed using 2-methyl-imidazole as reactants, instead of imidazole, to give 1-(2-Methoxy-phenyl)-4-{4-[4-(2-methyl-
5 imidazol-1-ylmethyl)-phenoxy]-butyl}-piperazine.

$^1\text{H-NMR}$ (CDCl_3 , 200MHz) δ 7.1~6.8 (m, 10H), 5.0 (s, 2H), 4.0(t, 2H), 3.8 (s, 3H), 3.2(m, 4H), 2.7(m, 4H), 2.5(t, 2H), 2.2 (s,3H), 1.8(m, 4H)

Example 11

10 **1-(2-methoxy-phenyl)-4-[4-(4-[1,2,3]triazol-2-ylmethyl-phenoxy)-butyl]-piperazine**

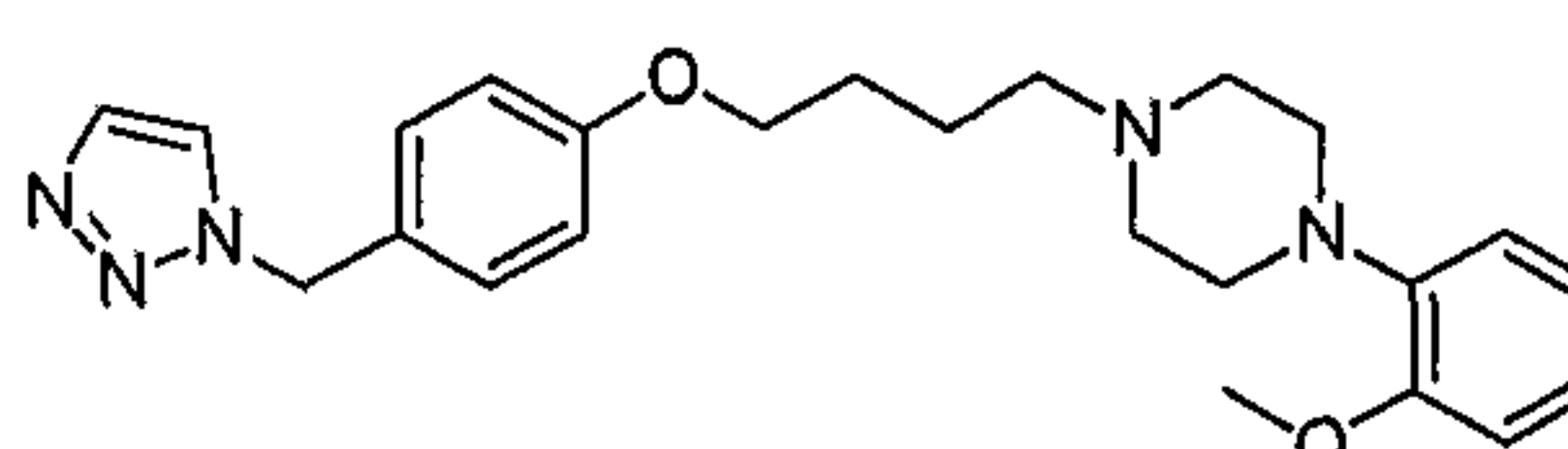


The procedure given in Example 1 was followed using 1H-1,2,3-triazole as reactants, instead of imidazole, to give 1-(2-methoxy-phenyl)-4-[4-(4-[1,2,3]triazole-2-
15 ylmethyl-phenoxy)-butyl]-piperazine.

$^1\text{H-NMR}$ (CDCl_3 , 200MHz) δ 7.6 (s, 2H), 7.2(m, 2H), 6.9(m, 6H), 5.6 (s, 2H), 4.0(t, 2H), 3.8 (s, 3H), 3.2(m, 4H), 2.7(m, 4H), 2.5(t, 2H), 1.8(m, 4H)

Example 12

20 **1-(2-methoxy-phenyl)-4-[4-(4-[1,2,3]triazol-1-ylmethyl-phenoxy)-butyl]-piperazine**

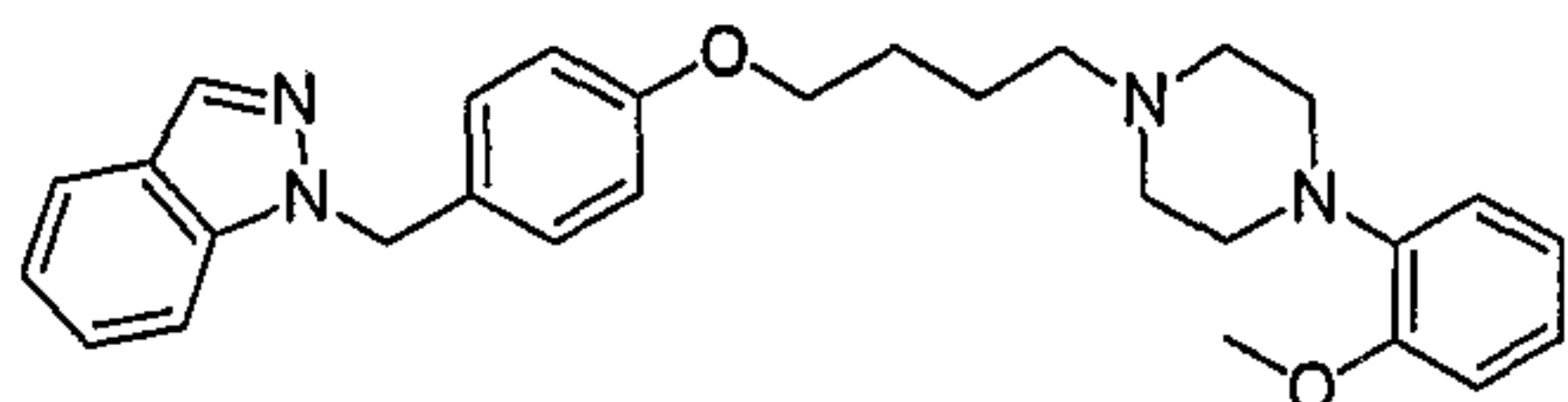


The procedure given in Example 1 was followed using 1H-1,2,3-triazole as reactants, instead of imidazole, to give 1-(2-methoxy-phenyl)-4-[4-(4-[1,2,3]triazole-1-
25 ylmethyl-phenoxy)-butyl]-piperazine.

$^1\text{H-NMR}$ (CDCl_3 , 200MHz) δ 7.7 (s, 1H), 7.4 (s, 1H), 7.2(m, 2H), 6.9(m, 6H), 5.5 (s, 2H), 4.0(t, 2H), 3.8 (s, 3H), 3.2(m, 4H), 2.7(m, 4H), 2.5(t, 2H), 1.8(m, 4H)

Example 13

5 1-(4-{4-[4-(2-Methoxy-phenyl)-piperazin-1-yl]-butoxy}-benzyl)-1H-indazole

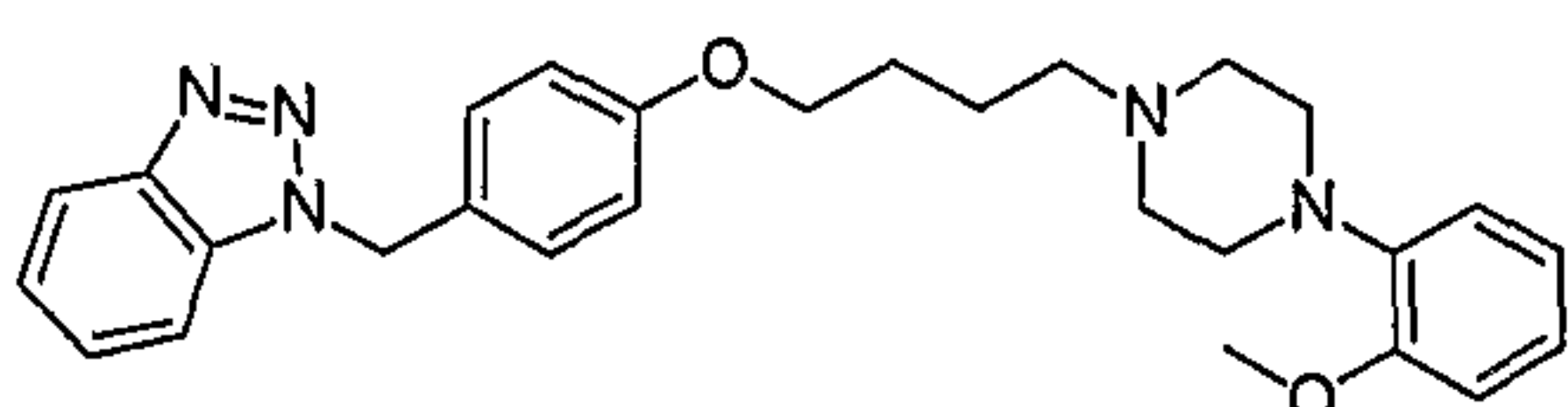


The procedure given in Example 1 was followed using 1H-Indazole as reactants, instead of imidazole, to give 1-(4-{4-[4-(2-methoxy-phenyl)-piperazin-1-yl]-butoxy}-benzyl)-1H-indazole.

$^1\text{H-NMR}$ (CDCl_3 , 200MHz) δ 8.1 (s, 1H), 7.7 (m, 1H), 7.3 (m, 3H), 7.2(m., 2H), 7.0(m, 6H), 5.3 (s, 2H), 4.0 (t, 2H), 3.8(s, 3H), 3.1(m, 4H), 2.7(m, 4H), 2.5(t, 2H), 1.8(m, 4H)

Example 14

1-(4-{4-[4-(2-Methoxy-phenyl)-piperazin-1-yl]-butoxy}-benzyl)-1H-benzotriazole.



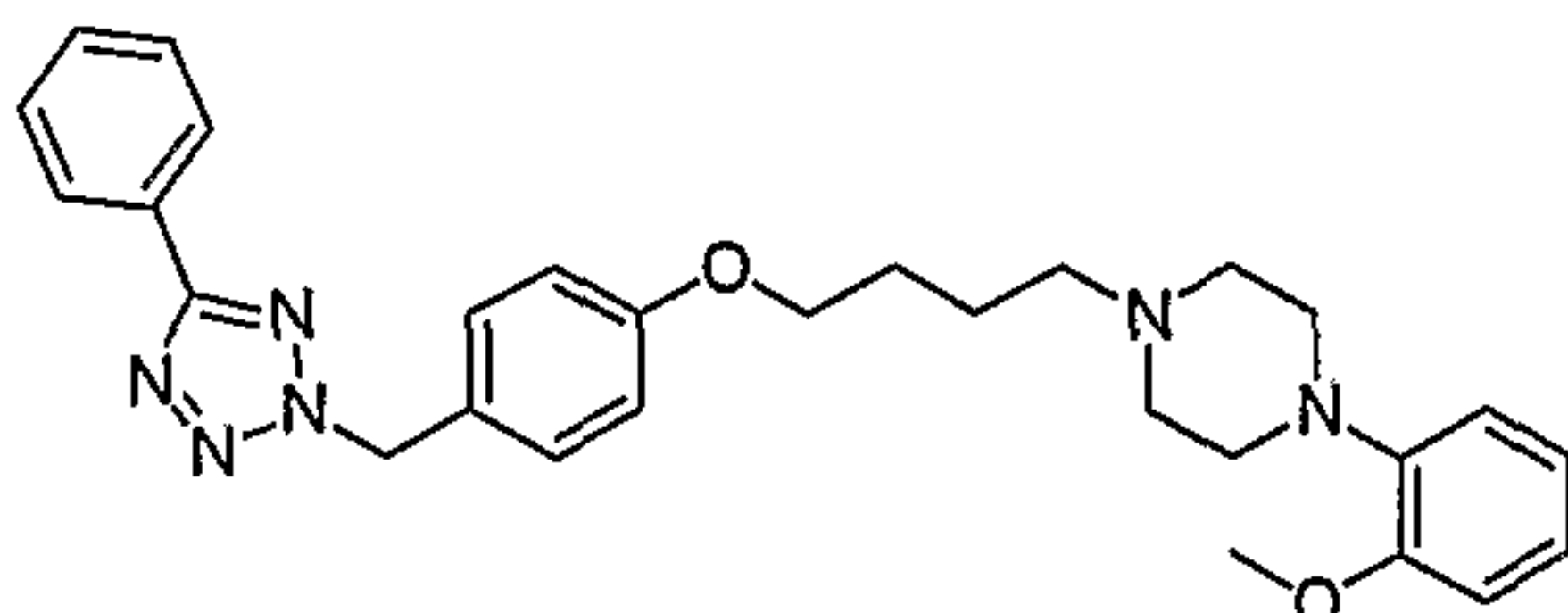
The procedure given in Example 1 was followed using benzotriazole as reactants, instead of imidazole, to give 1-(4-{4-[4-(2-Methoxy-phenyl)-piperazin-1-yl]-butoxy}-benzyl)-1H-benzotriazole.

$^1\text{H-NMR}$ (CDCl_3 , 200MHz) δ 8.1 (m, 1H), 7.4~7.2 (m, 5H), 7.0~6.8 (m, 6H), 5.8 (s, 2H), 4.0 (t, 2H), 3.8(s, 3H), 3.1(m, 4H), 2.7(m, 4H), 2.5(t, 2H), 1.8(m, 4H)

Example 15

1-(2-methoxy-phenyl)-4-{4-[4-(5-phenyl-tetrazol-2-ylmethyl)-phenoxy]-butyl}-

piperazine.



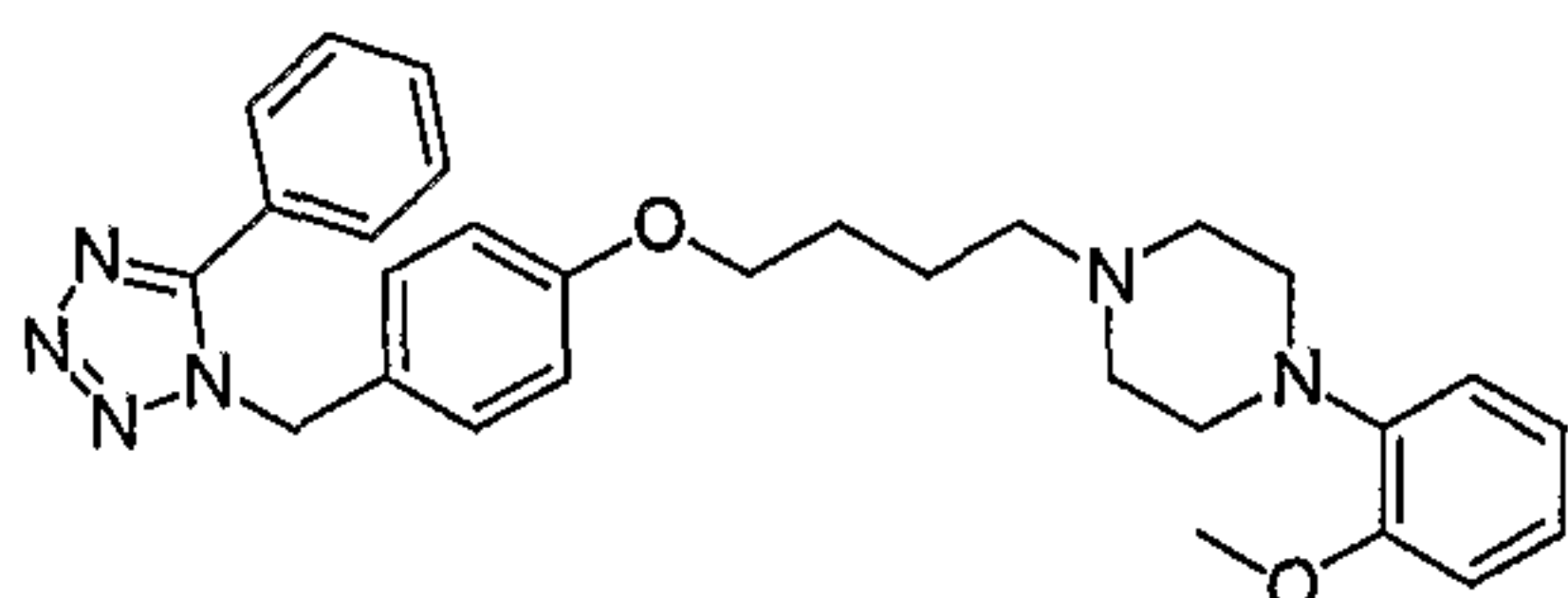
5 The procedure given in Example 1 was followed using 5-phenyl-1H-tetrazole as reactants, instead of imidazole, to give 1-(2-methoxy-phenyl)-4-{4-[4-(5-phenyl-tetrazol-2-ylmethyl)-phenoxy]-butyl}-piperazine.

¹H-NMR (CDCl₃, 200MHz) δ 8.2 (m, 2H), 7.6 (m, 5H), 7.2~7.0(m., 6H), 5.8 (s, 2H), 4.0 (t, 2H), 3.8(s, 3H), 3.1(m, 4H), 2.7(m, 4H), 2.5(t, 2H), 1.8(m, 4H)

10

Example 16

1-(2-methoxy-phenyl)-4-{4-[4-(5-phenyl-tetrazol-1-ylmethyl)-phenoxy]-butyl}-piperazine



15

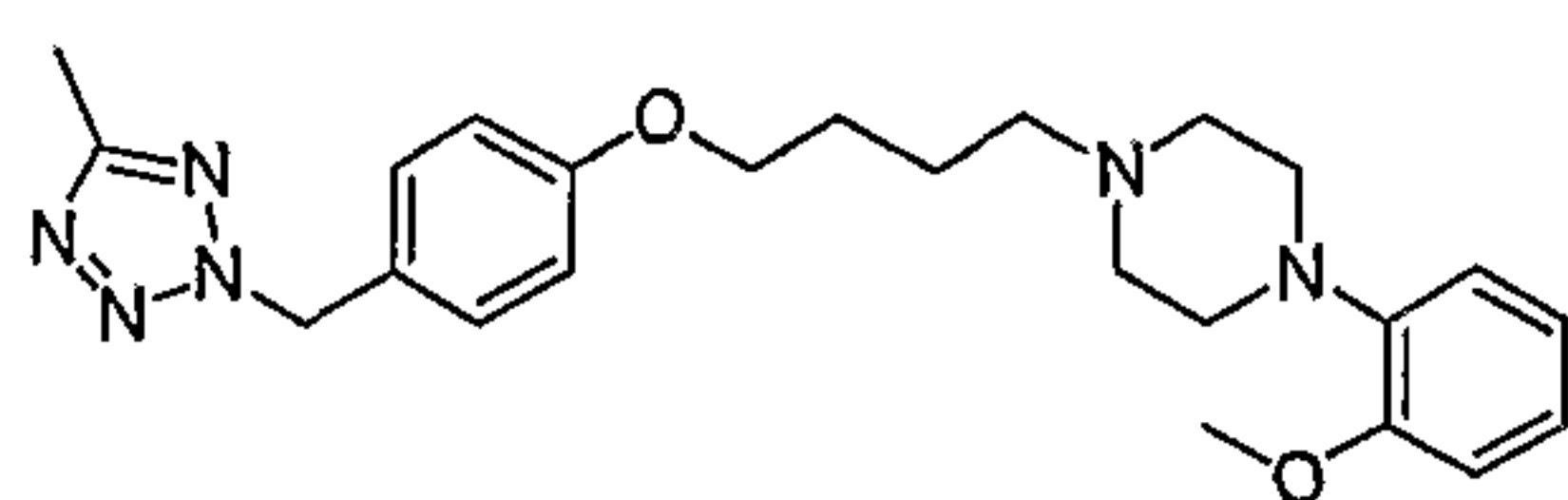
The procedure given in Example 1 was followed using 5-phenyl-1H-tetrazole as reactants, instead of imidazole, to give 1-(2-methoxy-phenyl)-4-{4-[4-(5-phenyl-tetrazol-1-ylmethyl)-phenoxy]-butyl}-piperazine.

20 ¹H-NMR (CDCl₃, 200MHz) δ 7.6 (m, 4H), 7.2(m., 3H), 6.9 (m, 6H), 5.6 (s, 2H), 4.0 (t, 2H), 3.8(s, 3H), 3.1(m, 4H), 2.7(m, 4H), 2.5(t, 2H), 1.8(m, 4H)

Example 17

1-(2-methoxy-phenyl)-4-{4-[4-(5-methyl-tetrazol-2-ylmethyl)-phenoxy]-butyl}-piperazine

25

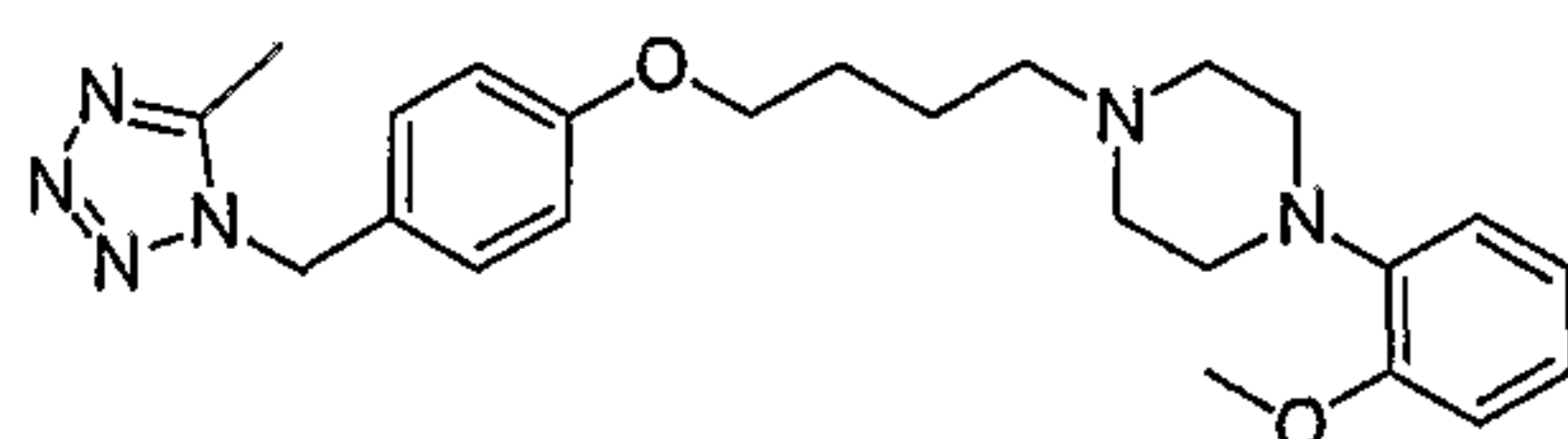


The procedure given in Example 1 was followed using 5-methyl-1H-tetrazole as reactants, instead of imidazole, to give 1-(2-methoxy-phenyl)-4-{4-[4-(5-methyl-tetrazol-2-ylmethyl)-phenoxy]-butyl}-piperazine.

$^1\text{H-NMR}$ (CDCl_3 , 200MHz) δ 7.4(m, 2H), 7.0(m, 6H), 5.6 (s, 2H), 4.0(t, 2H), 3.8(s, 3H), 3.1(m, 4H), 2.7(m, 4H), 2.5(t, 2H), 2.5(s, 3H), 1.8(m, 4H)

Example 18

1-(2-methoxy-phenyl)-4-{4-[4-(5-methyl-tetrazol-1-ylmethyl)-phenoxy]-butyl}-piperazine

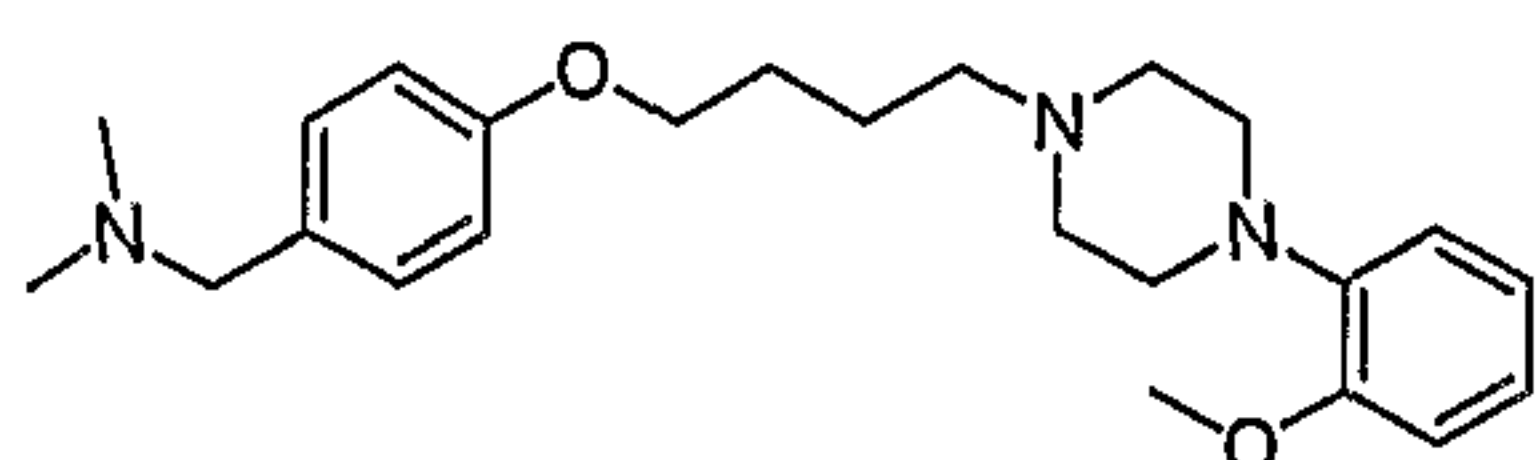


The procedure given in Example 1 was followed using 5-methyl-1H-tetrazole as reactants, instead of imidazole, to give 1-(2-methoxy-phenyl)-4-{4-[4-(5-methyl-tetrazol-1-ylmethyl)-phenoxy]-butyl}-piperazine.

$^1\text{H-NMR}$ (CDCl_3 , 200MHz) δ 7.2 (m, 2H), 7.0(m, 6H), 5.4 (s, 2H), 4.0(t, 2H), 3.8(s, 3H), 3.1(m, 4H), 2.7(m, 4H), 2.5(t, 2H), 2.5(s, 3H), 1.8(m, 4H)

Example 19

(4-{4-[4-(2-methoxy-phenyl)-piperazin-1-yl]-butoxy}-benzyl)-dimethyl-amine dihydrochloride

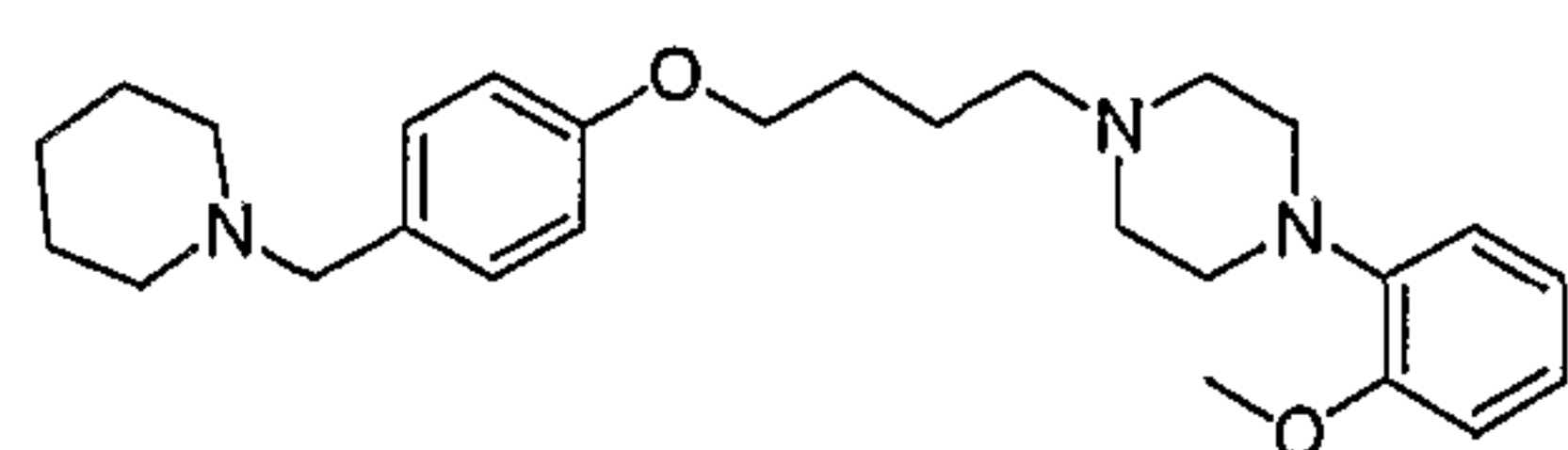


The procedure given in Example 1 was followed using dimethyl amine as reactants, instead of imidazole, to give (4-{4-[4-(2-methoxy-phenyl)-piperazin-1-yl]-butoxy}-benzyl)-dimethyl-amine dihydrochloride.

¹H-NMR (DMSO, 200MHz) δ 11.3 (br,1H), 11.1 (br,1H), 7.5(m, 2H), 7.0(m, 6H), 4.2 (m, 2H), 4.0(t, 2H), 3.8(s, 3H), 3.6 (m, 4H), 3.2 (m, 6H), 2.6(m, 6H), 1.8(m, 4H)

Example 20

1-(2-methoxy-phenyl)-4-[4-(4-piperidin-1-ylmethyl-phenoxy)-butyl]-piperazine

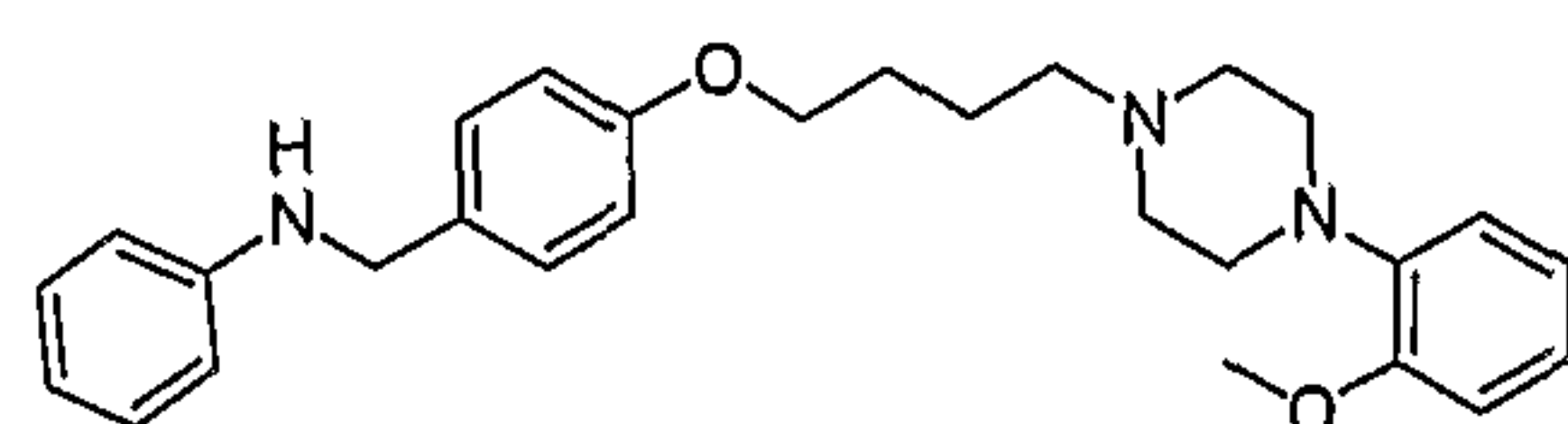


The procedure given in Example 1 was followed using piperidine as reactants, instead of imidazole, to give 1-(2-methoxy-phenyl)-4-[4-(4-piperidin-1-ylmethyl-phenoxy)-butyl]-piperazine.

¹H-NMR (CDCl₃, 200MHz) δ 7.2(m, 2H), 6.9(m, 6H), 4.0(t, 2H), 3.8 (s, 3H), 3.4 (s, 2H), 3.2(m, 4H), 2.7(m, 4H), 2.5(t, 2H), 2.4 (m,4H), 1.8(m, 4H), 1.6(m, 4H), 1.4 (m,2H)

Example 21

(4-{4-[4-(2-methoxy-phenyl)-piperazin-1-yl]-butoxy}-benzyl)-phenyl-amine



The procedure given in Example 1 was followed using aniline as reactants, instead of imidazole, to give (4-{4-[4-(2-methoxy-phenyl)-piperazin-1-yl]-butoxy}-benzyl)-phenyl-amine.

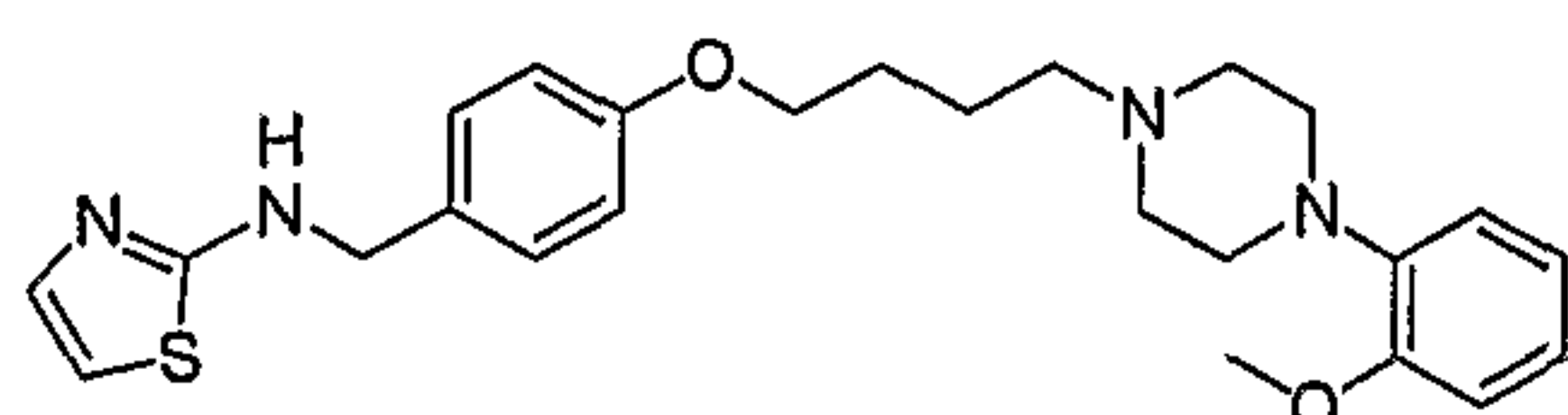
¹H-NMR (CDCl₃, 200MHz) δ 7.2(m, 2H), 7.0(m, 6H), 6.8 (m, 5H), 4.3(s, 2H),

4.0(t, 2H), 3.8 (s, 3H), 3.6 (s, 1H), 3.2(m, 4H), 2.7(m, 4H), 2.5(t, 2H), 1.8(m, 4H)

Example 22 (10663)

(4-{4-[4-(2-methoxy-phenyl)-piperazin-1-yl]-butoxy}-benzyl)-thiazol-2-yl-amine

5

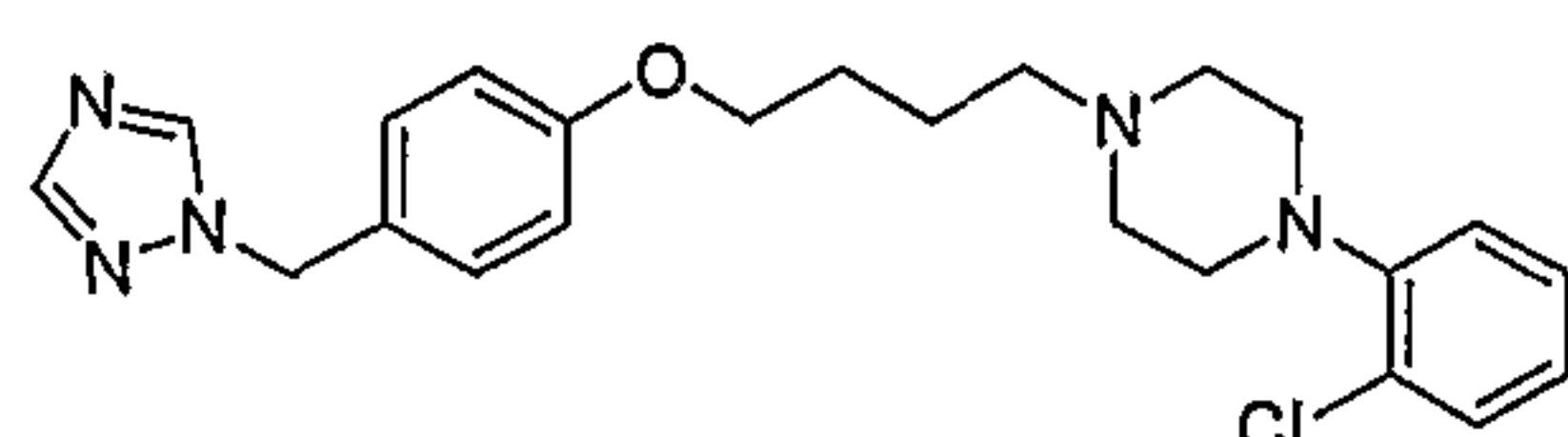


The procedure given in Example 1 was followed using thiazol-2-ylamine as reactants, instead of imidazole, to give (4-{4-[4-(2-methoxy-phenyl)-piperazin-1-yl]-butoxy}-benzyl)-thiazol-2-yl-amine.

¹H-NMR (CDCl₃, 200MHz) δ 7.5 (s, 1H), 7.2(m, 2H), 7.0(m, 6H), 6.6 (s, 1H), 4.3(s, 2H), 4.0(t, 2H), 3.8 (s, 3H), 3.6 (s, 1H), 3.2(m, 4H), 2.7(m, 4H), 2.5(t, 2H), 1.8(m, 4H)

15 Example 23

1-(2-chloro-phenyl)-4-[4-(4-[1,2,4]triazol-1-ylmethyl-phenoxy)-butyl]-piperazine

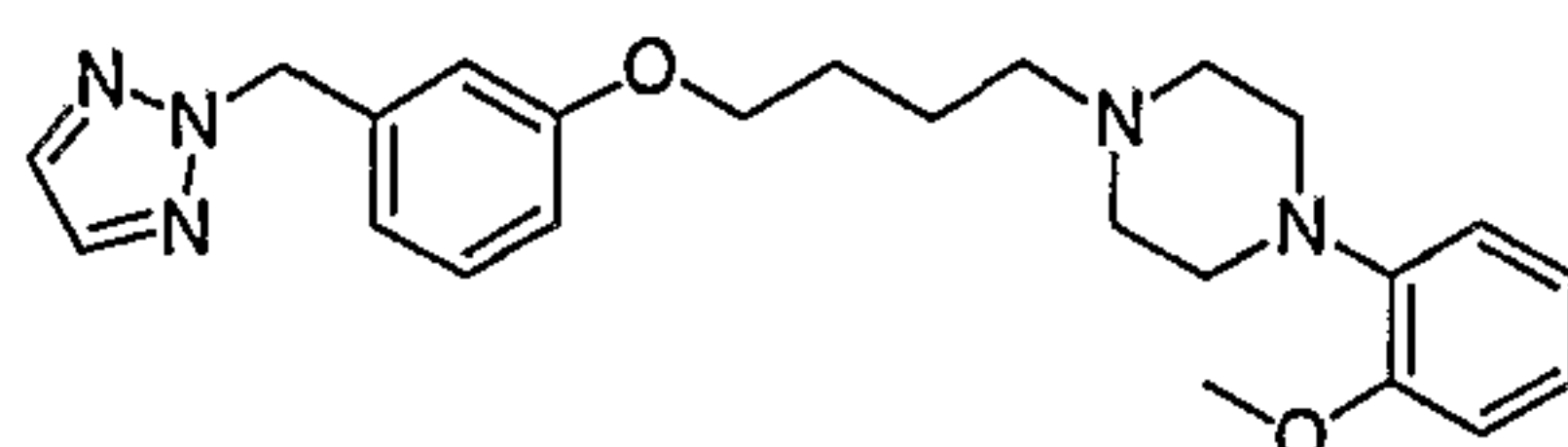


The procedure given in Example 1 was followed using 1-(2-chloro-phenyl)-piperazine and 1H-1,2,4-triazole as reactants, instead of 1-(2-methoxyphenyl)-piperazine and imidazole, to give 1-(2-chloro-phenyl)-4-[4-(4-[1,2,4]triazol-1-ylmethyl-phenoxy)-butyl]-piperazine.

¹H-NMR (CDCl₃, 200MHz) δ 8.1 (s, 1H), 8.0 (s, 1H), 7.2(m, 2H), 6.9(m, 6H), 5.2(s, 2H), 4.0(t, 2H), 3.2(m, 4H), 2.7(m, 4H), 2.5(t, 2H), 1.8(m, 4H)

Example 24

1-(2-methoxy-phenyl)-4-[4-(3-[1,2,3]triazol-2-ylmethyl-phenoxy)-butyl]-piperazine

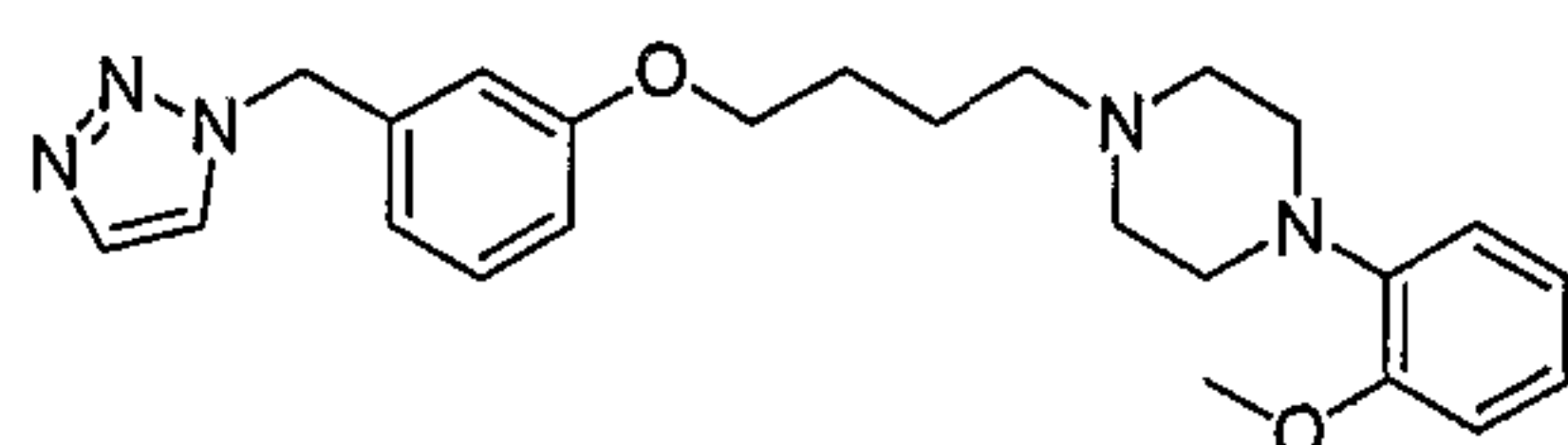


The procedure given in Example 5 was followed using 1H-1,2,3-triazole as
 5 reactants, instead of imidazole, to give 1-(2-methoxy-phenyl)-4-[4-(3-[1,2,3]triazol-2-ylmethyl-phenoxy)-butyl]-piperazine.

¹H-NMR (CDCl₃, 200MHz) δ 7.6 (s, 2H), 7.2(m, 2H), 6.9(m, 6H), 5.4 (s, 2H),
 4.0(t, 2H), 3.8 (s, 3H), 3.2(m, 4H), 2.7(m, 4H), 2.5(t, 2H), 1.8(m, 4H)

10 Example 25

1-(2-Methoxy-phenyl)-4-[4-(3-[1,2,3]triazol-1-ylmethyl-phenoxy)-butyl]-piperazine .

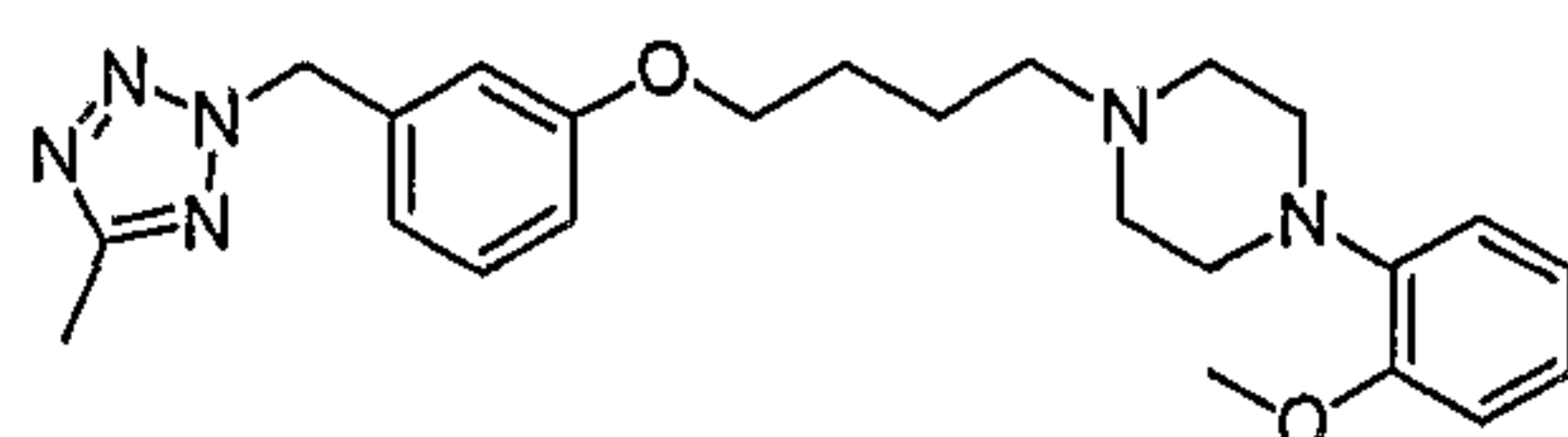


15 The procedure given in Example 5 was followed using 1H-1,2,3-triazole as
 reactants, instead of Imidazole, to give 1-(2-Methoxy-phenyl)-4-[4-(3-[1,2,3]triazol-1-ylmethyl-phenoxy)-butyl]-piperazine.

¹H-NMR (CDCl₃, 200MHz) δ 7.7 (s, 1H), 7.4 (s, 1H), 7.2 (m, 2H), 7.0-6.8 (m,
 6H), 5.5 (s, 2H), 4.0(t, 2H), 3.8(s, 3H), 3.1(m, 4H), 2.7(m, 4H), 2.5(t, 2H), 2.5(s,
 20 3H),1.8(m, 4H)

Example 26

**1-(2-Methoxy-phenyl)-4-{4-[3-(5-methyl-tetrazol-2-ylmethyl)-phenoxy]-butyl}-
 piperazine.**



25

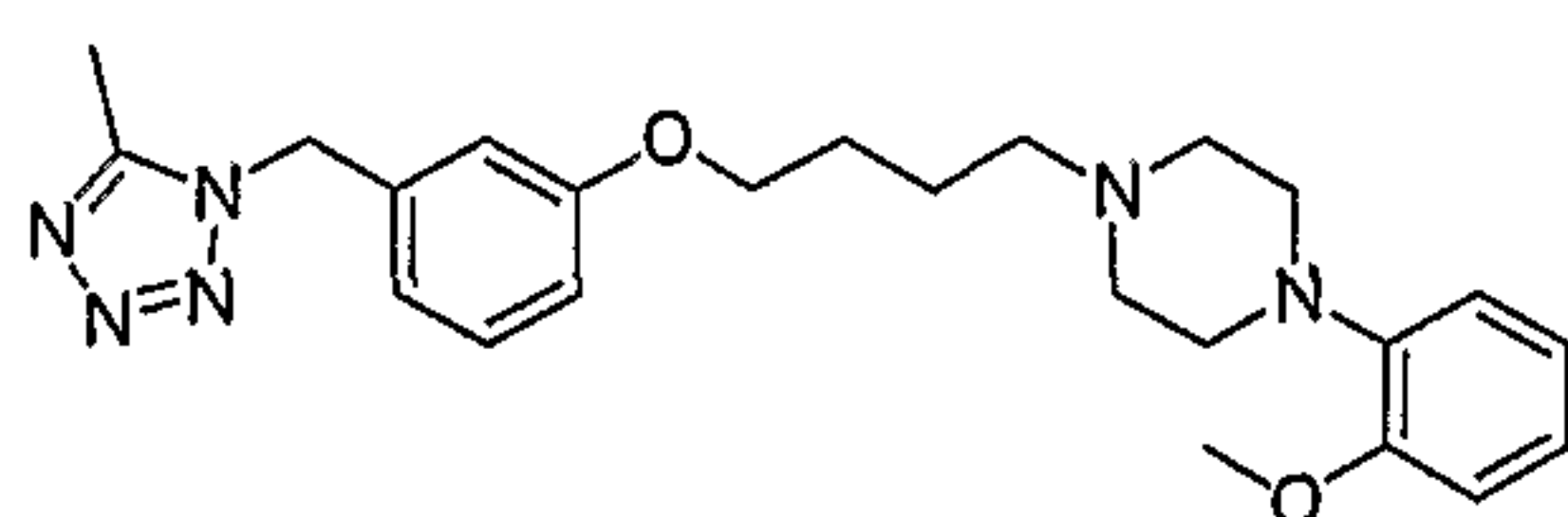
The procedure given in Example 5 was followed using 5-methyl-1H-tetrazole as reactants, instead of imidazole, to give 1-(2-Methoxy-phenyl)-4-{4-[3-(5-methyl-tetrazol-2-ylmethyl)-phenoxy]-butyl}-piperazine.

¹H-NMR (CDCl₃, 200MHz) δ 7.6 (s, 2H), 7.2 (m, 2H), 7.0-6.8 (m, 6H), 5.5 (s, 2H), 4.0(t, 2H), 3.8(s, 3H), 3.1(m, 4H), 2.7(m, 4H), 2.5(t, 2H), 2.5(s, 3H), 1.8(m, 4H)

Example 27

1-(2-methoxy-phenyl)-4-{4-[3-(5-methyl-tetrazol-1-ylmethyl)-phenoxy]-butyl}-piperazine

10



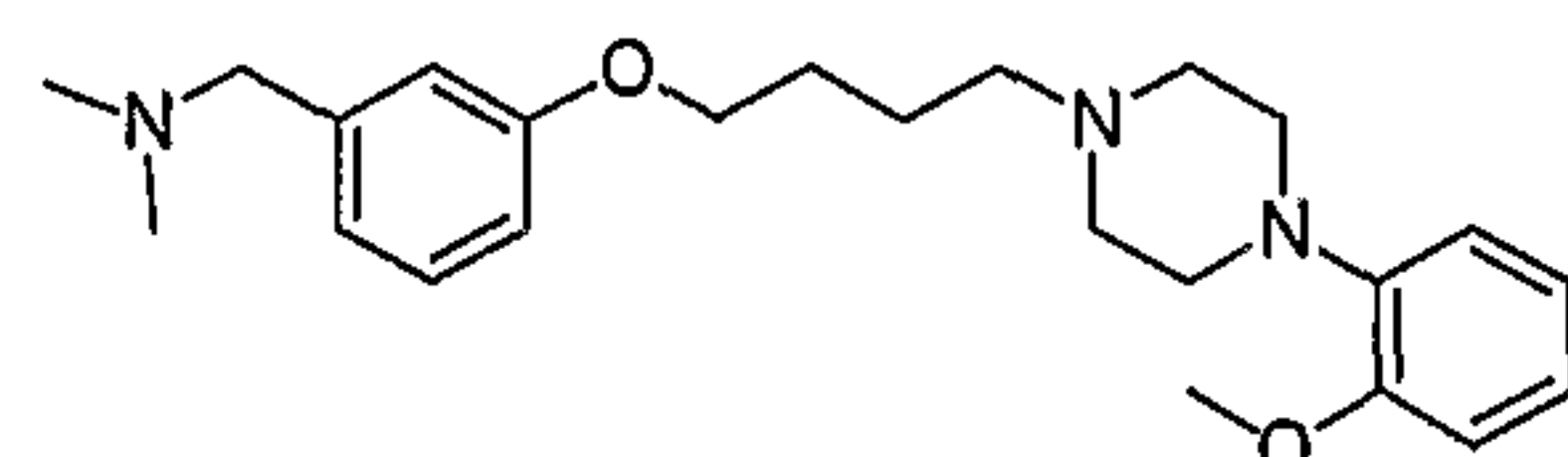
The procedure given in Example 5 was followed using 5-methyl-1H-tetrazole as reactants, instead of imidazole, to give 1-(2-methoxy-phenyl)-4-{4-[3-(5-methyl-tetrazol-1-ylmethyl)-phenoxy]-butyl}-piperazine.

¹H-NMR (CDCl₃, 200MHz) δ 7.2 (m, 2H), 7.0-6.7 (m, 6H), 5.5 (s, 2H), 4.0(t, 2H), 3.8(s, 3H), 3.1(m, 4H), 2.7(m, 4H), 2.5(t, 2H), 2.5(s, 3H), 1.8(m, 4H)

Example 28

(3-{4-[4-(2-methoxy-phenyl)-piperazin-1-yl]-butoxy}-benzyl)-dimethyl-amine

20

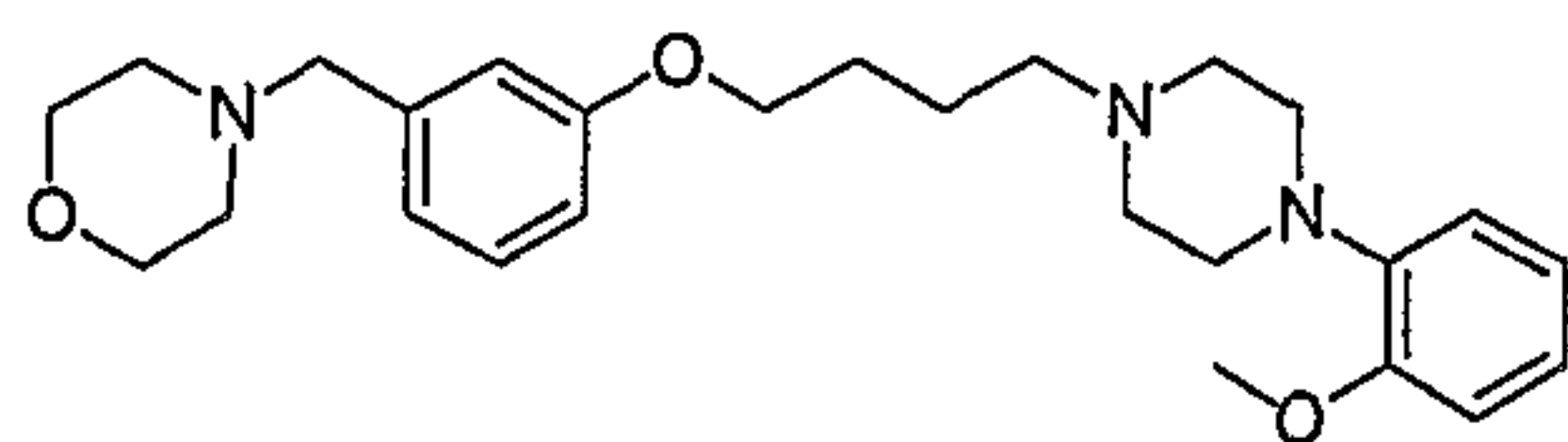


The procedure given in Example 5 was followed using dimethyl amine as reactants, instead of imidazole, to give (3-{4-[4-(2-methoxy-phenyl)-piperazin-1-yl]-butoxy}-benzyl)-dimethyl-amine.

¹H-NMR (CDCl₃, 200MHz) δ 7.3(m, 2H), 6.9(m, 6H), 4.0(t, 2H), 3.9(s, 3H), 3.2(m, 4H), 2.7(m, 4H), 2.6(s, 6H), 2.5(t, 2H), 1.8(m, 4H)

Example 29**4-(3-{4-[4-(2-methoxy-phenyl)-piperazin-1-yl]-butoxy}-benzyl)-morpholine**

5

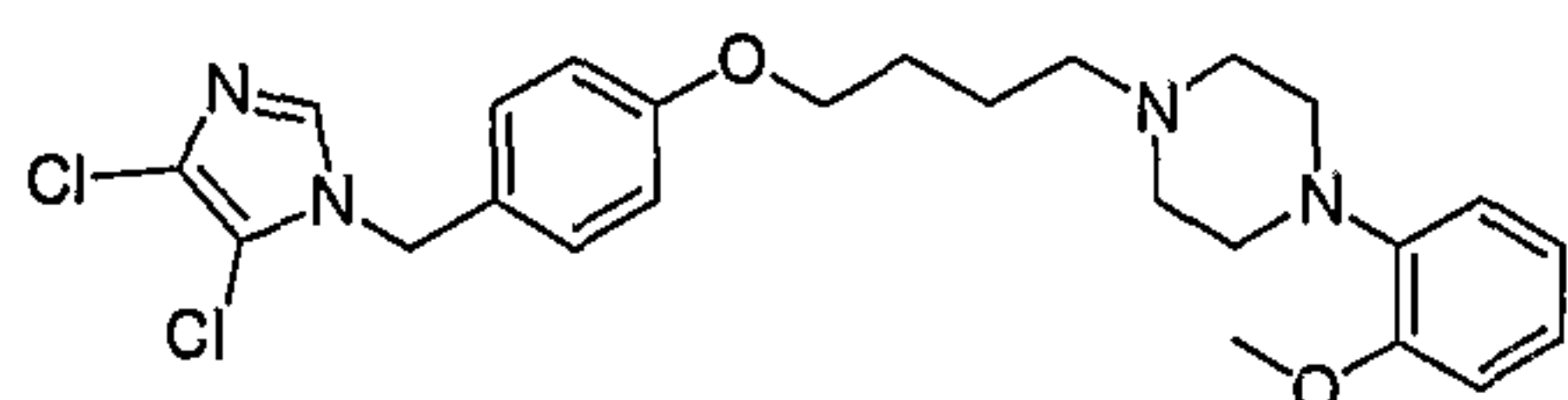


The procedure given in Example 5 was followed using morpholine as reactants, instead of imidazole, to give 4-(3-{4-[4-(2-methoxy-phenyl)-piperazin-1-yl]-butoxy}-benzyl)-morpholine.

10 $^1\text{H-NMR}$ (CDCl_3 , 200MHz) 7.2(m, 2H), 6.9(m, 6H), 4.1(t, 2H), 3.9(s, 3H), 3.7(m, 4H), 3.5 (s, 2H), 3.2(m, 4H), 2.8(m, 4H), 2.6(t, 2H), 2.5 (m, 4H), 1.8(m, 4H)

Example 30**1-{4-[4-(4,5-dichloro-imidazol-1-ylmethyl)-phenoxy]-butyl}-4-(2-methoxy-phenyl)-piperazine**

15

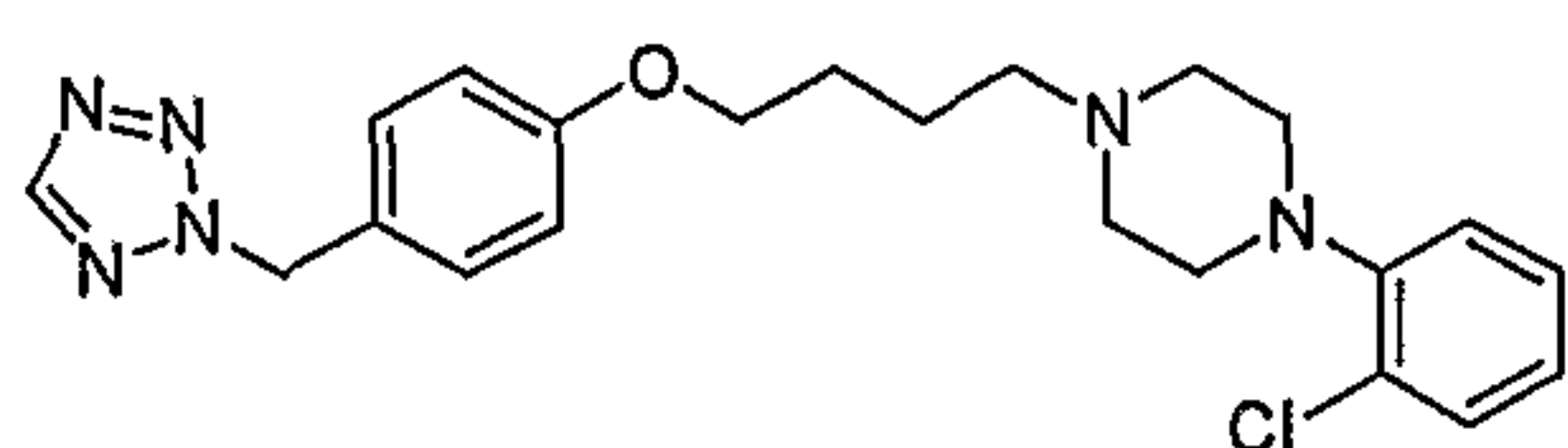


The procedure given in Example 1 was followed using 4,5-dichloro-imidazole as reactants, instead of imidazole, to give 1-{4-[4-(4,5-dichloro-imidazol-1-ylmethyl)-phenoxy]-butyl}-4-(2-methoxy-phenyl)-piperazine.

20 $^1\text{H-NMR}$ (CDCl_3 , 200MHz) δ 7.4 (s, 1H), 7.2(m, 2H), 6.9(m, 6H), 5.0 (s, 2H), 4.0(t, 2H), 3.8 (s, 3H), 3.2(m, 4H), 2.7(m, 4H), 2.5(t, 2H), 1.8(m, 4H)

Example 31**1-(2-chloro-phenyl)-4-[4-(4-tetrazol-2-ylmethyl-phenoxy)-butyl]-piperazine**

25

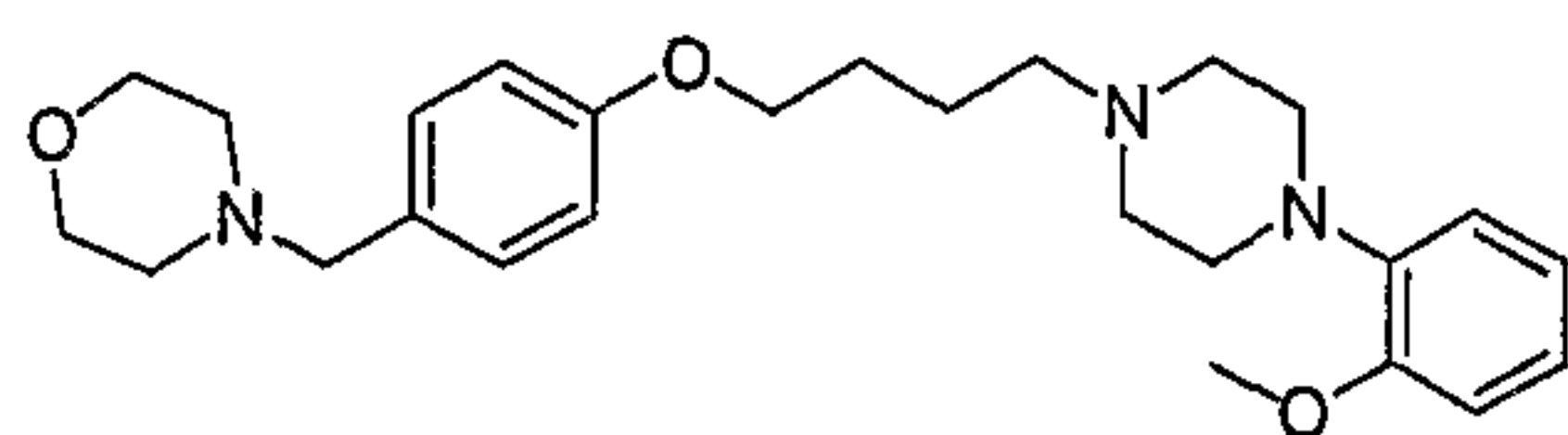


The procedure given in Example 1 was followed using 1-(2-chloro-phenyl)-piperazine and 1H-tetrazole as reactants, instead of 1-(2-methoxyphenyl)-piperazine and imidazole, to give 1-(2-chloro-phenyl)-4-[4-(4-tetrazol-2-ylmethyl-phenoxy)-butyl]-piperazine.

¹H-NMR (CDCl₃, 200MHz) δ 8.5(m, 1H), 7.4(m, 4H), 7.0(m, 2H), 6.8(m, 2H), 5.8 (s, 2H), 4.0(t, 2H), 3.2(m, 4H), 2.9(m, 4H), 2.7(t, 2H), 1.9(m, 4H)

10 Example 32

4-(4-{4-[4-(2-methoxy-phenyl)-piperazin-1-yl]-butoxy}-benzyl)-morpholine



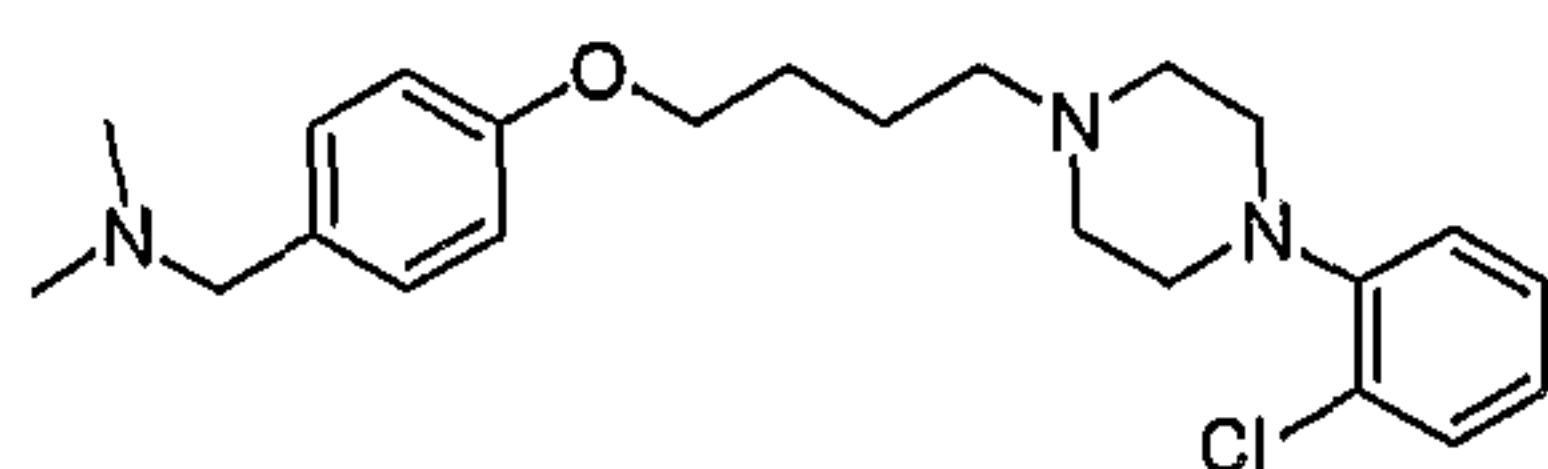
15 The procedure given in Example 1 was followed using morpholine as reactants, instead of imidazole, to give 4-(4-{4-[4-(2-methoxy-phenyl)-piperazin-1-yl]-butoxy}-benzyl)-morpholine.

¹H-NMR (CDCl₃, 200MHz) δ 7.2(m, 2H), 6.9(m, 6H), 4.0(t, 2H), 3.8 (s, 3H), 3.4 (s, 2H), 3.2(m, 4H), 2.7(m, 4H), 2.5(t, 2H), 2.4 (m, 4H), 1.8(m, 4H), 1.6(m, 4H)

20

Example 33

(4-{4-[4-(2-Chloro-phenyl)-piperazin-1-yl]-butoxy}-benzyl)-dimethyl-amine



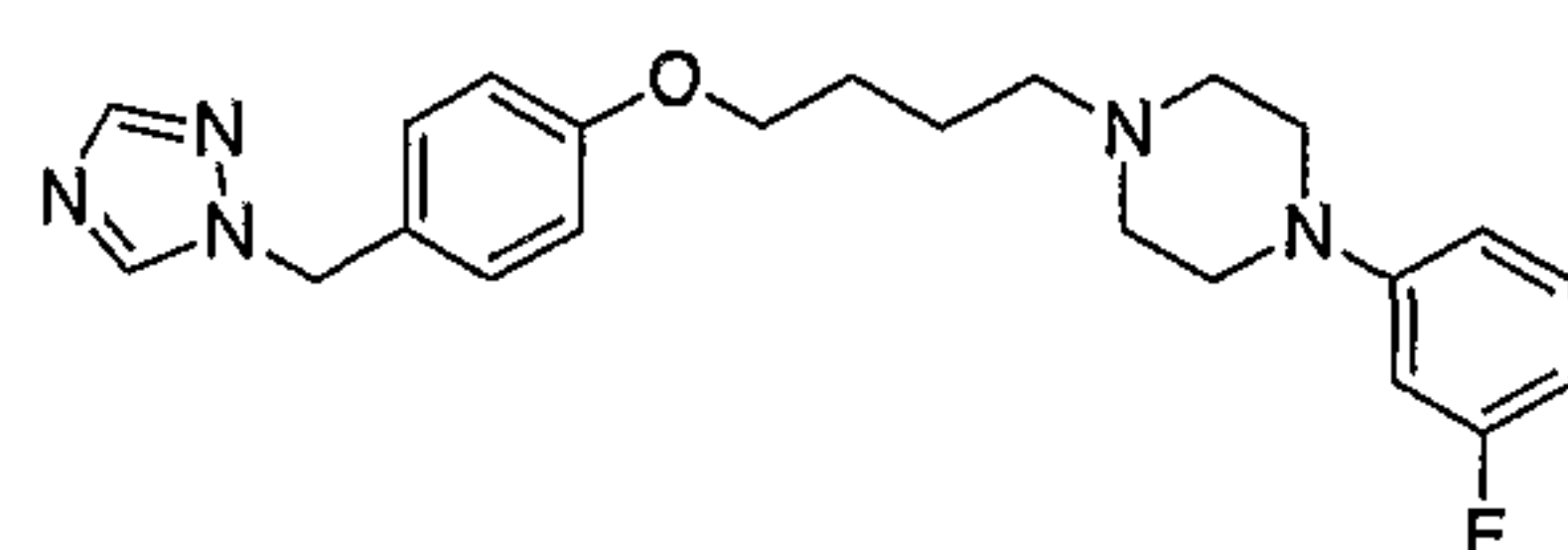
25

The procedure given in Example 1 was followed using 1-(2-chloro-phenyl)-piperazine and dimethylamine, instead of 1-(2-methoxyphenyl)-piperazine and imidazole, to give (4-{4-[4-(2-Chloro-phenyl)-piperazin-1-yl]-butoxy}-benzyl)-dimethyl-amine.

¹H-NMR (CDCl₃, 200MHz) δ 7.3~7.1 (m, 4H), 7.1~6.8 (m, 4H), 4.2 (t, 2H), 3.4(m, 2H), 3.1(m, 4H), 2.7 (m, 4H), 2.5 (m, 2H), 2.4 (s, 6H), 1.8~1.7 (m, 4H)

Example 34

1-(3-fluoro-phenyl)-4-[4-(4-[1,2,4]triazol-1-ylmethyl-phenoxy)-butyl]-piperazine

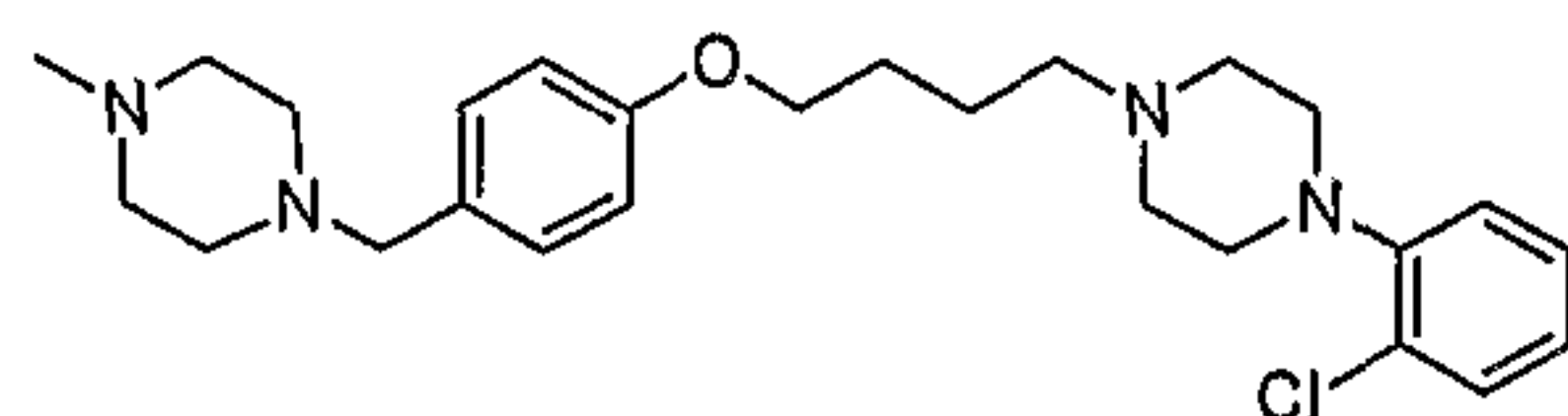


The procedure given in Example 1 was followed using 1-(3-fluoro-phenyl)-piperazine and 1H-1,2,4-triazole as reactants, instead of 1-(2-methoxyphenyl)-piperazine and imidazole, to give 1-(3-fluoro-phenyl)-4-[4-(4-[1,2,4]triazol-1-ylmethyl-phenoxy)-butyl]-piperazine.

¹H-NMR (CDCl₃, 200MHz) δ 7.9 (s, 1H), 7.7 (s, 1H), 7.2(m, 2H), 6.9(m, 6H), 5.5(s, 2H), 4.0(t, 2H), 3.2(m, 4H), 2.8(m, 4H), 2.6(t, 2H), 1.8(m, 4H)

Example 35

1-(2-methoxy-phenyl)-4-[4-(4-methylpiperazine-1-ylmethyl-phenoxy)-butyl]-piperazine

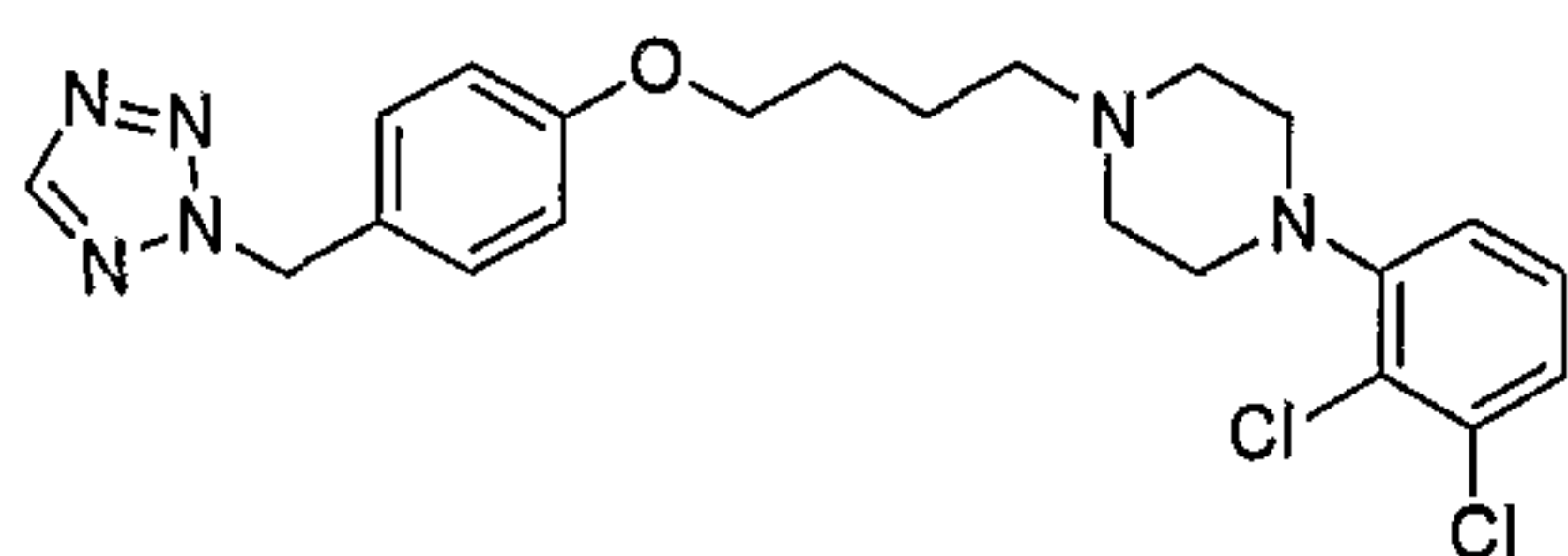


The procedure given in Example 1 was followed using 1-(2-chloro-phenyl)-piperazine and methylpiperazine, instead of instead of 1-(2-methoxyphenyl)-piperazine and imidazole, to give 1-(2-methoxy-phenyl)-4-[4-(4-methylpiperazine-1-ylmethyl-phenoxy)-butyl]-piperazine.

$^1\text{H-NMR}$ (CDCl_3 , 200MHz) δ 7.3~7.1 (m, 4H), 7.1~6.8 (m, 4H), 4.3 (t, 2H), 3.4(m, 2H), 3.1(m, 4H), 2.7 (m, 4H), 2.6 (m, 8H,) 2.5 (m, 2H), 2.3 (s, 3H), 1.8~1.7 (m, 4H)

5 Example 36

1-(2,3-dichloro-phenyl)-4-[4-(4-tetrazol-2-ylmethyl-phenoxy)-butyl]-piperazine



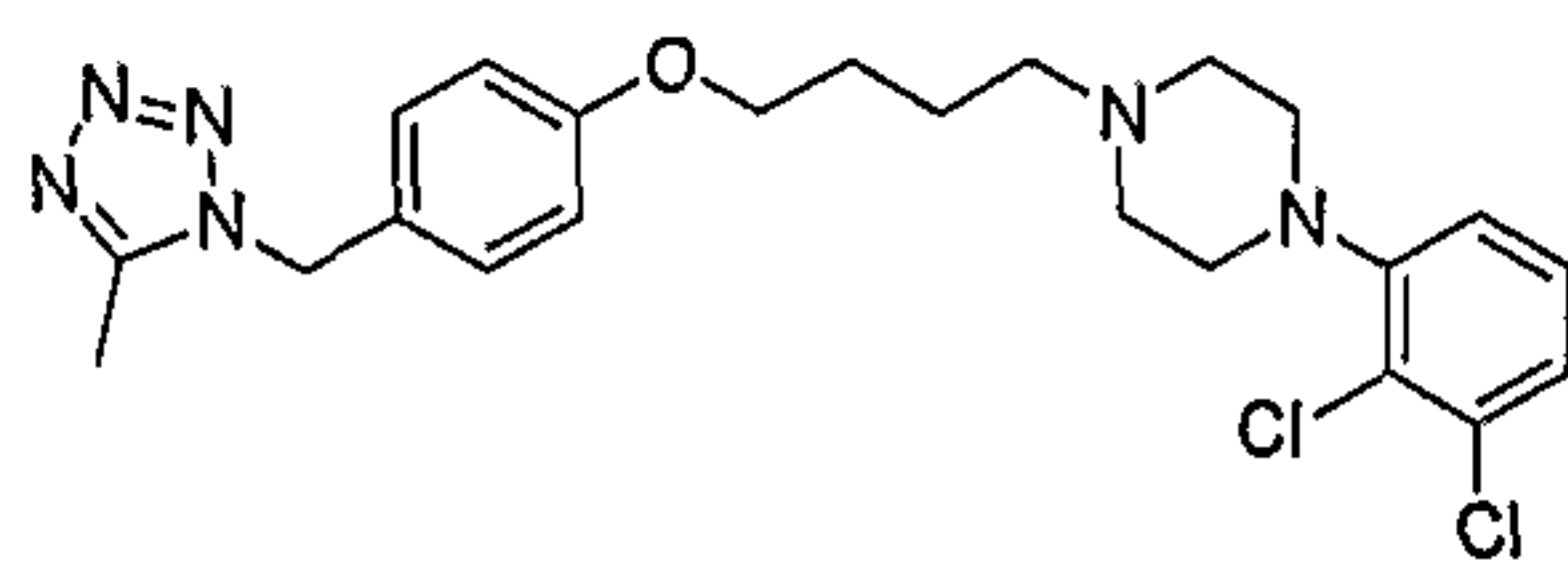
10 The procedure given in Example 1 was followed using 1-(2,3-dichloro-phenyl)-piperazine and 1H-tetrazole as reactants, instead of 1-(2-methoxyphenyl)-piperazine and imidazole, to give 1-(2,3-dichloro-phenyl)-4-[4-(4-tetrazol-2-ylmethyl-phenoxy)-butyl]-piperazine.

15 $^1\text{H-NMR}$ (CDCl_3 , 200MHz) δ 8.5 (m, 1H), 7.4-6.8 (m, 7H), 5.8 (s, 2H), 4.0(t, 2H), 3.2(m, 4H), 2.9(m, 4H), 2.7(t, 2H), 1.9(m, 4H)

Example 37

1-(2,3-Dichloro-phenyl)-4-{4-[4-(5-methyl-tetrazol-1-ylmethyl)-phenoxy]-butyl}-piperazine

20



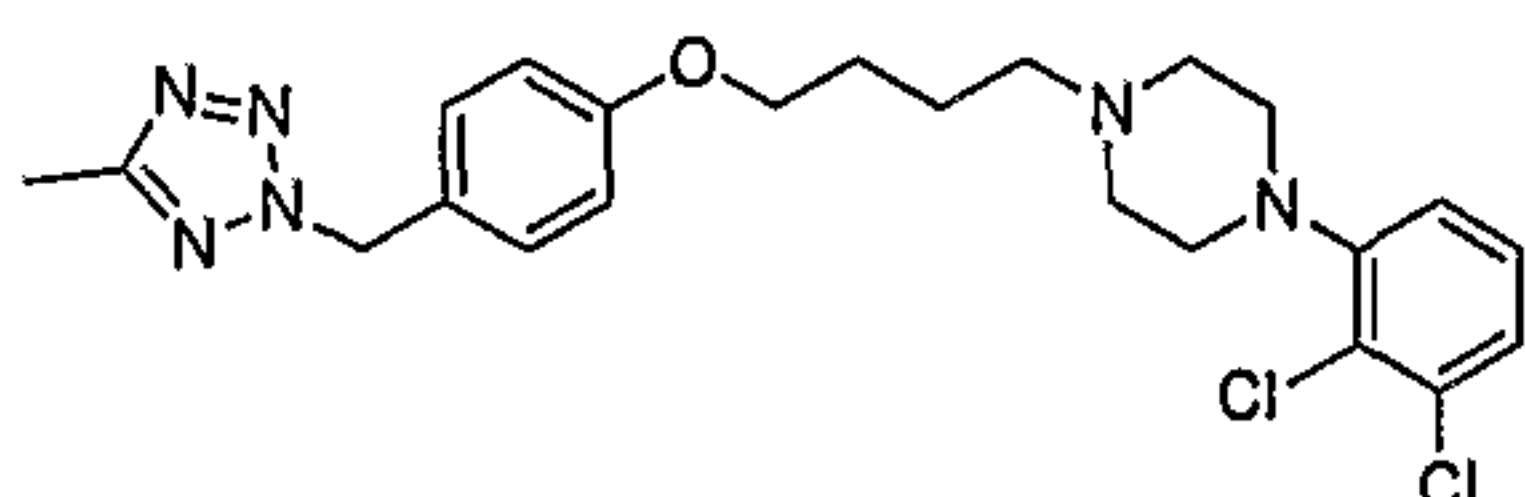
The procedure given in Example 1 was followed using 1-(2,3-dichloro-phenyl)-piperazine and 5-methyl-1H-tetrazole as reactants, instead of 1-(2-methoxyphenyl)-piperazine and imidazole, to give 1-(2,3-Dichloro-phenyl)-4-{4-[4-(5-methyl-tetrazol-1-ylmethyl)-phenoxy]-butyl}-piperazine.

25 $^1\text{H-NMR}$ (CDCl_3 , 200MHz) δ 7.2 (m, 2H), 7.0(m, 5H), 5.4 (s, 2H), 4.0(t, 2H),

3.1(m, 4H), 2.7(m, 4H), 2.5(t, 2H), 2.6(s, 3H), 1.8(m, 4H)

Example 38

1-(2,3-Dichloro-phenyl)-4-{4-[4-(5-methyl-tetrazol-2-ylmethyl)-phenoxy]-butyl}-
5 piperazine



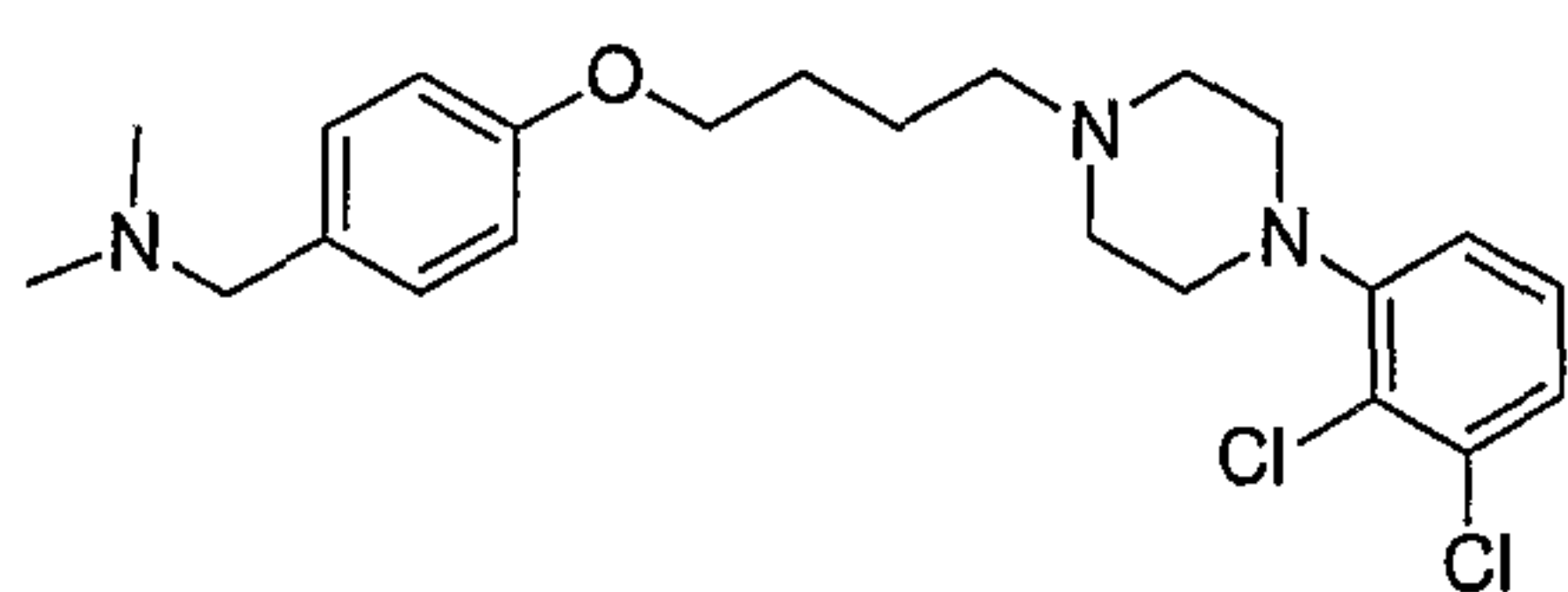
The procedure given in Example 1 was followed using 1-(2,3-dichloro-phenyl)-
10 piperazine and 5-methyl-1H-tetrazole as reactants, instead of 1-(2-methoxyphenyl)-
piperazine and imidazole, to give 1-(2,3-Dichloro-phenyl)-4-{4-[4-(5-methyl-tetrazol-2-
ylmethyl)-phenoxy]-butyl}-piperazine.

¹H-NMR (CDCl₃, 200MHz) δ 7.2~7.0(m, 7H), 5.6 (s, 2H), 4.0(t, 2H), 3.1(m,
4H), 2.7(m, 4H), 2.5(t, 2H), 2.5(s, 3H), 1.8(m, 4H)

15

Example 39

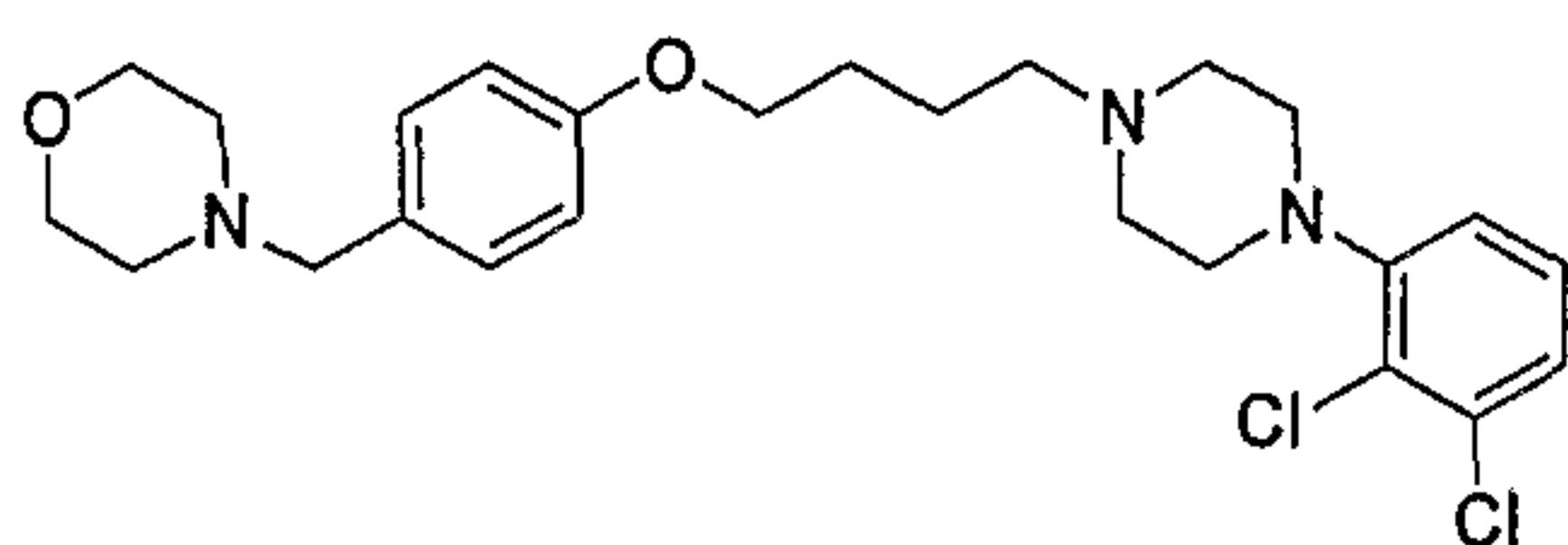
(4-{4-[4-(2,3-dichloro-phenyl)-piperazin-1-yl]-butoxy}-benzyl)-dimethyl-amine



20

The procedure given in Example 1 was followed using 1-(2,3-dichloro-phenyl)-
piperazine and dimethyl amine as reactants, instead of 1-(2-methoxyphenyl)-piperazine
and imidazole, to give (4-{4-[4-(2,3-dichloro-phenyl)-piperazin-1-yl]-butoxy}-benzyl)-
dimethyl-amine.

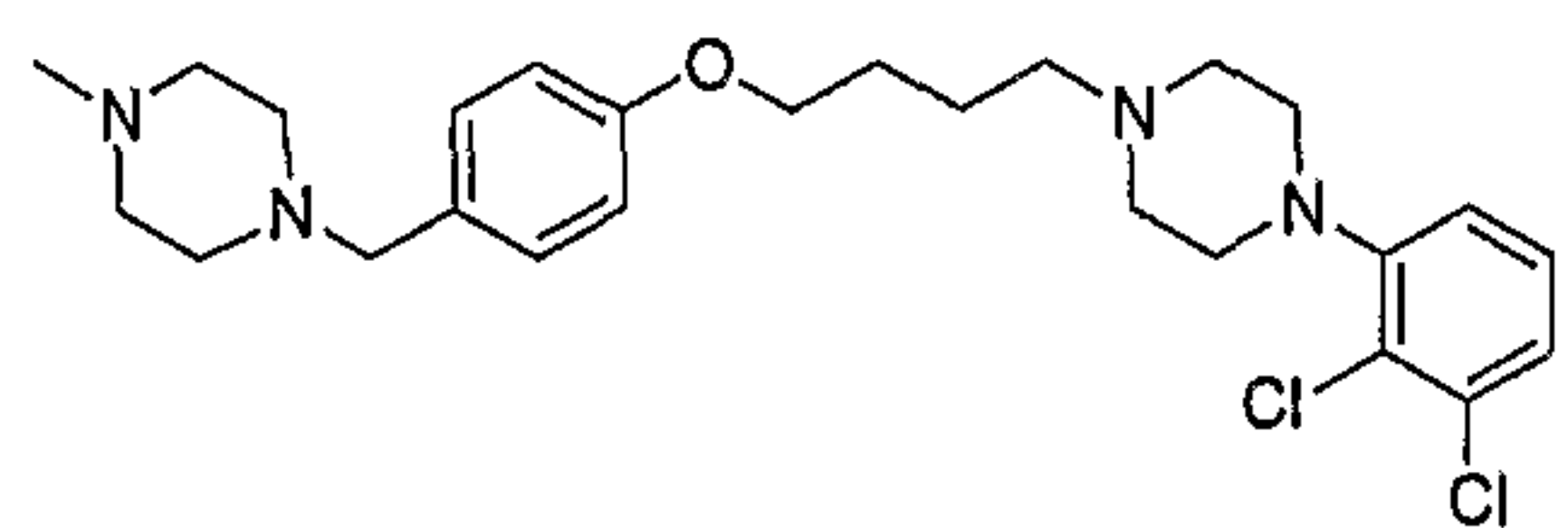
25 ¹H-NMR (DMSO, 200MHz) δ 11.3 (br,1H), 11.1 (br,1H), 7.5(m, 2H), 7.0(m,
5H), 4.2 (m, 2H), 4.0(t, 2H), 3.6 (m, 4H), 3.2 (m, 6H), 2.6(m, 6H), 1.8(m, 4H)

Example 40**4-(4-{4-[4-(2,3-Dichloro-phenyl)-piperazin-1-yl]-butoxy}-benzyl)-morpholine**

5 The procedure given in Example 1 was followed using 1-(2,3-dichloro-phenyl)-piperazine and morpholine, instead of 1-(2-methoxyphenyl)-piperazine and imidazole, to give 4-(4-{4-[4-(2,3-Dichloro-phenyl)-piperazin-1-yl]-butoxy}-benzyl)-morpholine

¹H-NMR (CDCl₃, 200MHz) δ 7.2(m, 2H), 6.9(m, 6H), 4.2(t, 2H), 3.7(m, 4H), 3.5 (s, 2H), 3.2(m, 4H), 2.8(m, 4H), 2.6(t, 2H), 2.5 (m, 4H), 1.8(m, 4H)

10

Example 41**1-(2-methoxy-phenyl)-4-[4-(4-methylpiperazine-1-ylmethyl-phenoxy)-butyl]-piperazine**

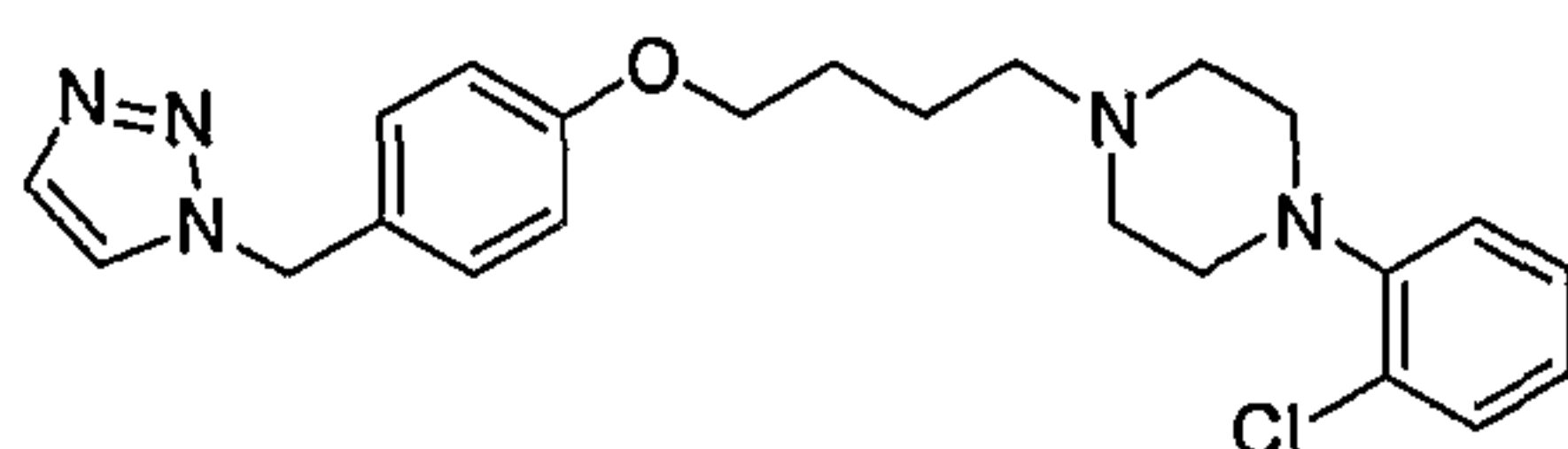
15

The procedure given in Example 1 was followed using 1-(2,3-dichloro-phenyl)-piperazine and methylpiperazine, instead of 1-(2-methoxyphenyl)-piperazine and imidazole to give 1-(2-methoxy-phenyl)-4-[4-(4-methylpiperazine-1-ylmethyl-phenoxy)-butyl]-piperazine.

20 ¹H-NMR (CDCl₃, 200MHz) δ 7.3~6.8 (m, 7H), 4.3 (t, 2H), 3.4(m, 2H), 3.1(m, 4H), 2.7 (m, 4H), 2.6 (m, 8H,) 2.5 (m, 2H), 2.3 (s, 3H), 1.8~1.7 (m, 4H)

Example 42**1-(2-chloro-phenyl)-4-[4-(4-[1,2,3]triazol-1-ylmethyl-phenoxy)-butyl]-piperazine**

25

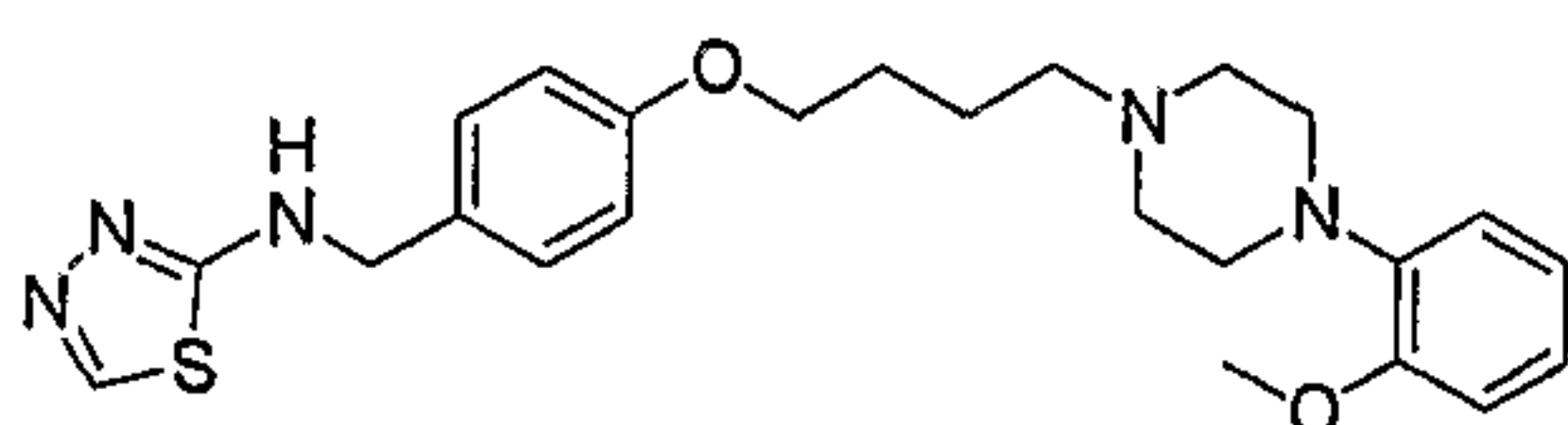


The procedure given in Example 1 was followed using 1-(2-chloro-phenyl)-piperazine and 1H-1,2,3-triazole as reactants, instead of 1-(2-methoxyphenyl)-piperazine and imidazole, to give 1-(2-chloro-phenyl)-4-[4-(4-[1,2,3]triazol-1-ylmethyl-phenoxy)-butyl]-piperazine.

$^1\text{H-NMR}$ (CDCl_3 , 200MHz) δ 7.7 (s, 1H), 7.4 (s, 1H), 7.2(m, 2H), 6.9(m, 6H), 5.5(s, 2H), 4.0(t, 2H), 3.2(m, 4H), 2.7(m, 4H), 2.5(t, 2H), 1.8(m, 4H)

Example 43

(4-{4-[4-(2-Methoxy-phenyl)-piperazin-1-yl]-butoxy}-benzyl)-[1,3,4]thiadiazol-2-yl-amine

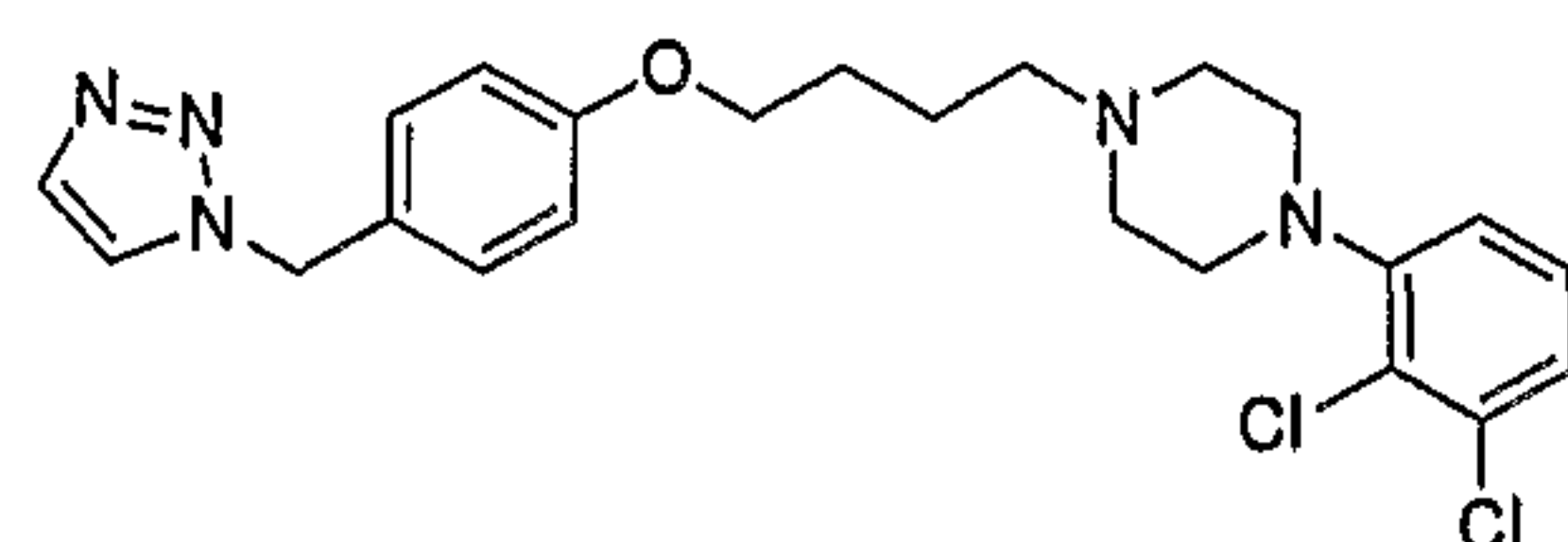


The procedure given in Example 1 was followed using [1,3,4]Thiadiazol-2-ylamine as reactants, instead of imidazole, to give (4-{4-[4-(2-Methoxy-phenyl)-piperazin-1-yl]-butoxy}-benzyl)-[1,3,4]thiadiazol-2-yl-amine.

$^1\text{H-NMR}$ (CDCl_3 , 200MHz) δ 7.2~ 6.8 (m, 9H), 4.3(s, 2H), 4.0(t, 2H), 3.8 (s, 3H), 3.2(m, 4H), 2.7(m, 4H), 2.5(t, 2H), 1.8(m, 4H)

Example 44

1-(2,3-dichloro-phenyl)-4-[4-(4-[1,2,3]triazol-1-ylmethyl-phenoxy)-butyl]-piperazine

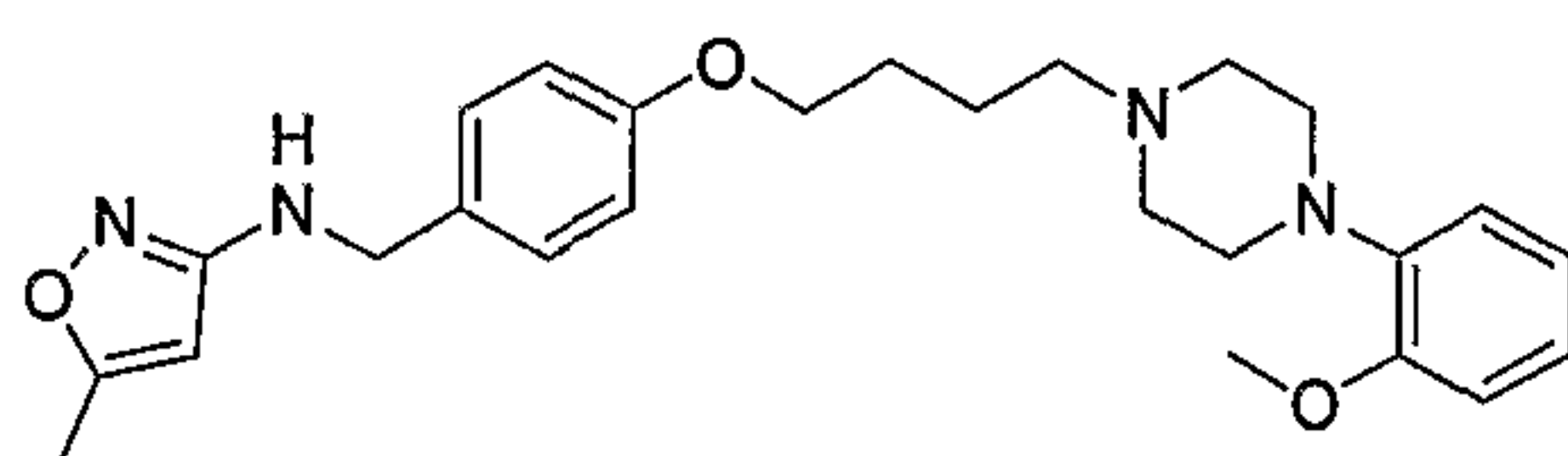


The procedure given in Example 1 was followed using 1-(2,3-dichloro-phenyl)-piperazine and 1H-1,2,3-triazole as reactants, instead of 1-(2-methoxyphenyl)-piperazine and imidazole, to give 1-(2,3-dichloro-phenyl)-4-[4-(4-[1,2,3]triazol-1-ylmethyl-phenoxy)-butyl]-piperazine.

¹H-NMR (CDCl₃, 200MHz) δ 7.7 (s, 1H), 7.4-6.8 (m, 8H), 5.8 (s, 2H), 4.0(t, 2H), 3.2(m, 4H), 2.9(m, 4H), 2.7(t, 2H), 1.9(m, 4H)

Example 45

(4-{4-[4-(2-Methoxy-phenyl)-piperazin-1-yl]-butoxy}-benzyl)-(5-methyl-isoxazol-3-yl)-amine

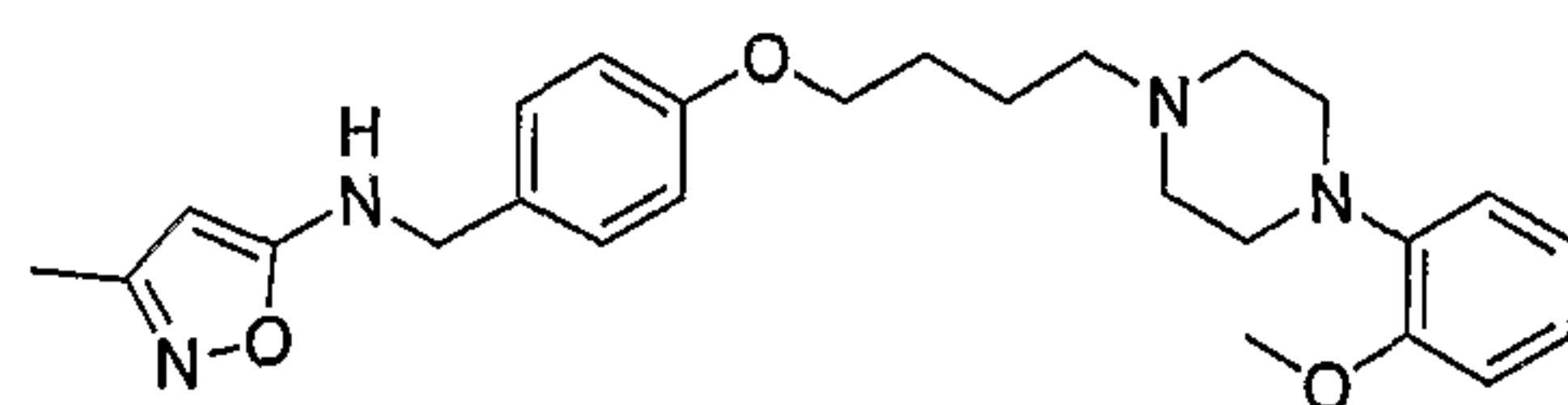


The procedure given in Example 1 was followed using 5-methyl-isoxazol-3-ylamine as reactants, instead of imidazole, to give (4-{4-[4-(2-Methoxy-phenyl)-piperazin-1-yl]-butoxy}-benzyl)-(5-methyl-isoxazol-3-yl)-amine.

¹H-NMR (CDCl₃, 200MHz) δ 7.2~6.8(m, 9H), 4.3(s, 2H), 4.0(t, 2H), 3.8 (s, 3H), 3.6 (s, 1H)3.2(m, 4H), 2.7(m, 4H), 2.5(t, 2H), 2.3 (s, 3H), 1.8(m, 4H)

Example 46

(4-{4-[4-(2-methoxy-phenyl)-piperazin-1-yl]-butoxy}-benzyl)-(3-methyl-isoxazol-5-yl)-amine

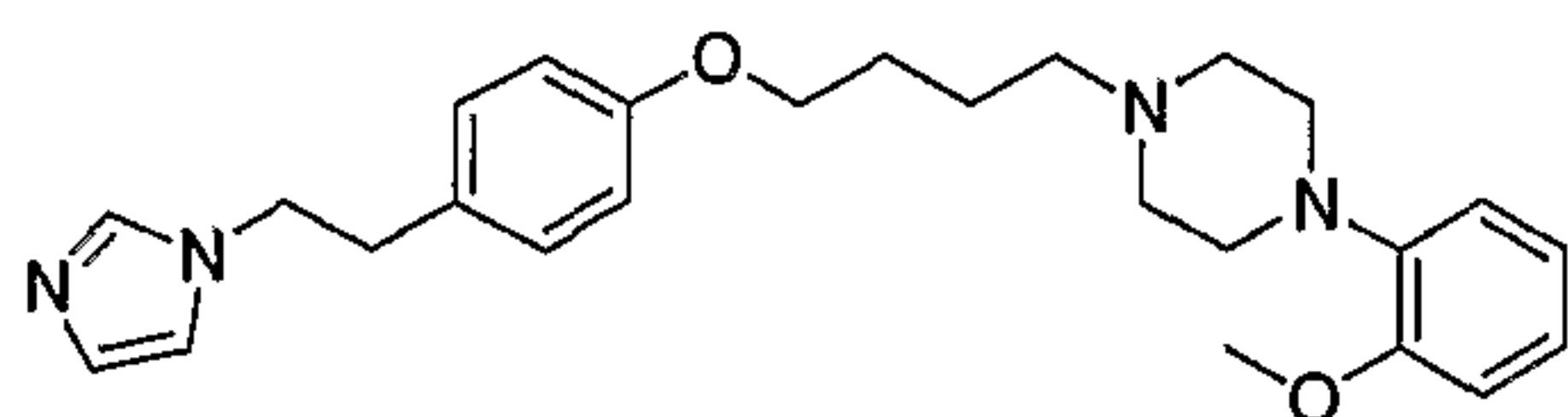


The procedure given in Example 1 was followed using 3-methyl-isoxazol-5-ylamine as reactants, instead of imidazole, to give (4-{4-[4-(2-methoxy-phenyl)-piperazin-1-yl]-butoxy}-benzyl)-(3-methyl-isoxazol-5-yl)-amine.

¹H-NMR (CDCl₃, 200MHz) δ 7.2(m, 2H), 7.0(m, 6H), 6.8 (s, 1H), 4.3(s, 2H), 4.0(t, 2H), 3.8 (s, 3H), 3.6 (s, 1H), 3.2(m, 4H), 2.7(m, 4H), 2.5(t, 2H), 2.3 (s,3H), 1.8(m, 4H)

Example 47**1-{4-[4-(2-imidazol-1-yl-ethyl)-phenoxy]-butyl}-4-(2-methoxy-phenyl)-piperazine**

5

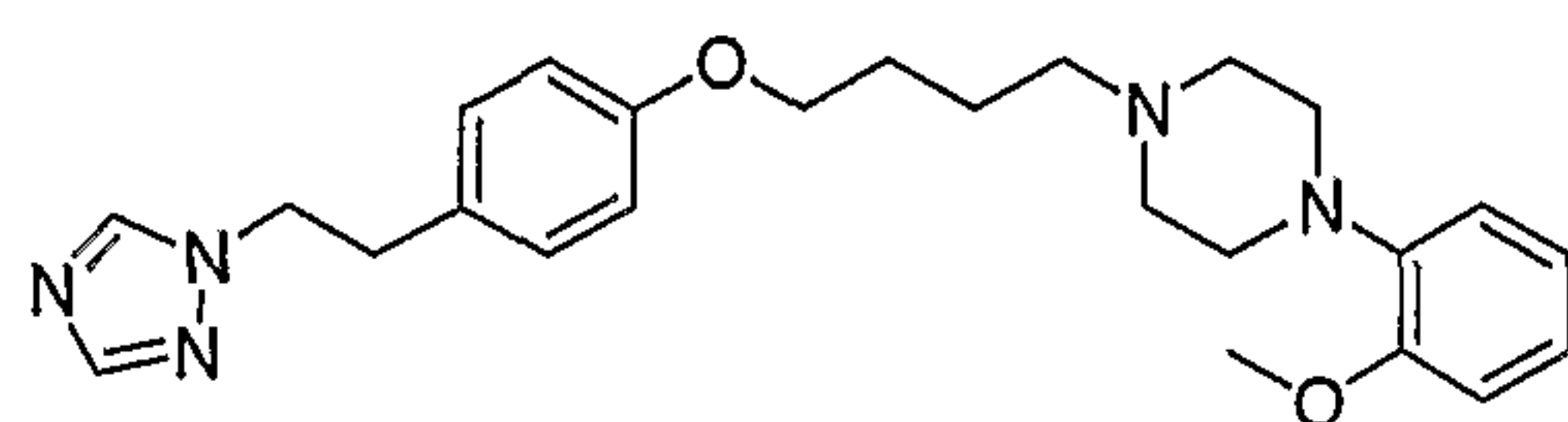


A mixture of 4-hydroxyphenethylalcohol (5mmol), 1-bromo-4-chlorobutane (5mmol), and potassium carbonate (15mmol) was refluxed in 100ml of acetone for 6h. This solution was then concentrated in a rotary evaporator and diluted with ethyl acetate. This mixture was then washed with brine, and the resulting organic layer was dried and purified by column chromatography. The product was dissolved in isopropanol (50ml) and was added with 1-(2-methoxyphenyl)-piperazine (5mmol), sodium carbonate (15mmol), and potassium iodide (5mmol) at 25 °C and the reaction mixture was refluxed for 12h. This solution was then concentrated in a rotary evaporator and diluted with methylene chloride. This mixture was then washed with brine, and the resulting organic layer was dried and purified by column chromatography. The product was dissolved in THF and was added with imidazole (15mmol), triphenylphosphine (15mmol), and diisopropyl azodicarboxylate (15mmol) dropwise at 0 °C and warmed to room temperature. After 2h, the solvent was removed and the residue was washed with brine, and then purified by column chromatography.

¹H-NMR (CDCl₃, 200MHz) δ 7.3 (s, 1H), 7.0(m, 10H), 4.1(t, 2H), 4.0(t, 2H), 3.8 (s, 3H), 3.1(m, 4H), 3.0(m, 2H), 2.7(m, 4H), 2.6(t, 2H), 1.8(m, 4H)

Example 48

1-(2-methoxy-phenyl)-4-{4-[4-(2-[1,2,4]triazol-1-yl-ethyl)-phenoxy]-butyl}-piperazine

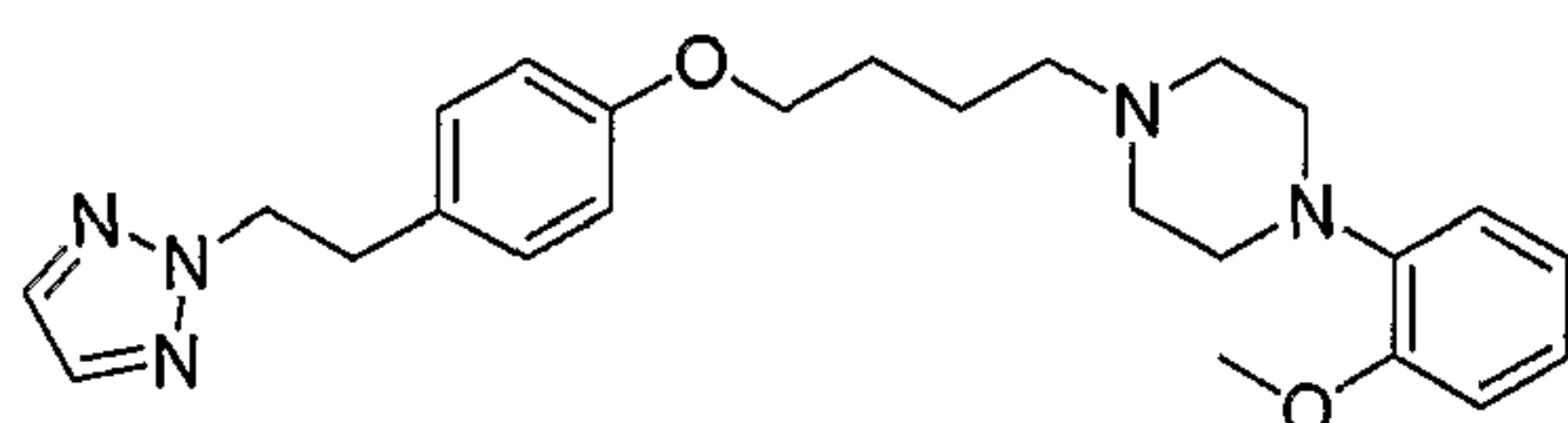


The procedure given in Example 47 was followed using 1H-1,2,4-triazole as a reactant, instead of imidazole, to give 1-(2-methoxy-phenyl)-4-{4-[4-(2-[1,2,4]triazol-1-yl-ethyl)-phenoxy]-butyl}-piperazine.

¹H-NMR (CDCl₃, 200MHz) δ 8.0(s, 1H), 7.8(s, 1H), 7.0(m, 8H), 4.4(t, 2H), 4.0(t, 2H), 3.8 (s, 3H), 3.1(m, 6H), 2.7(m, 4H), 2.5(t, 2H), 1.8(m, 4H)

Example 49

1-(2-methoxy-phenyl)-4-{4-[4-(2-[1,2,3]triazol-2-yl-ethyl)-phenoxy]-butyl}-piperazine

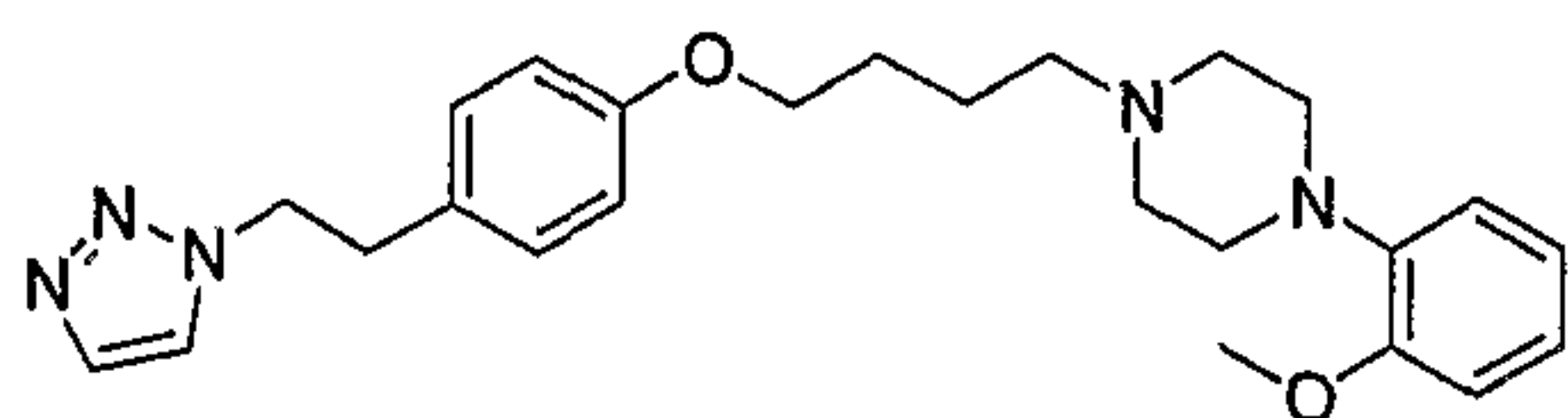


The procedure given in Example 47 was followed using 1H-1,2,3-triazole as a reactant, instead of imidazole, to give 1-(2-methoxy-phenyl)-4-{4-[4-(2-[1,2,3]triazol-2-yl-ethyl)-phenoxy]-butyl}-piperazine.

¹H-NMR (CDCl₃, 200MHz) δ 7.7(s, 2H), 7.0(m, 8H), 4.6(t, 2H), 4.0(t, 2H), 3.8 (s, 3H), 3.1(m, 6H), 2.7(m, 4H), 2.5(t, 2H), 1.8(m, 4H)

Example 50

1-(2-methoxy-phenyl)-4-{4-[4-(2-[1,2,3]triazol-1-yl-ethyl)-phenoxy]-butyl}-piperazine

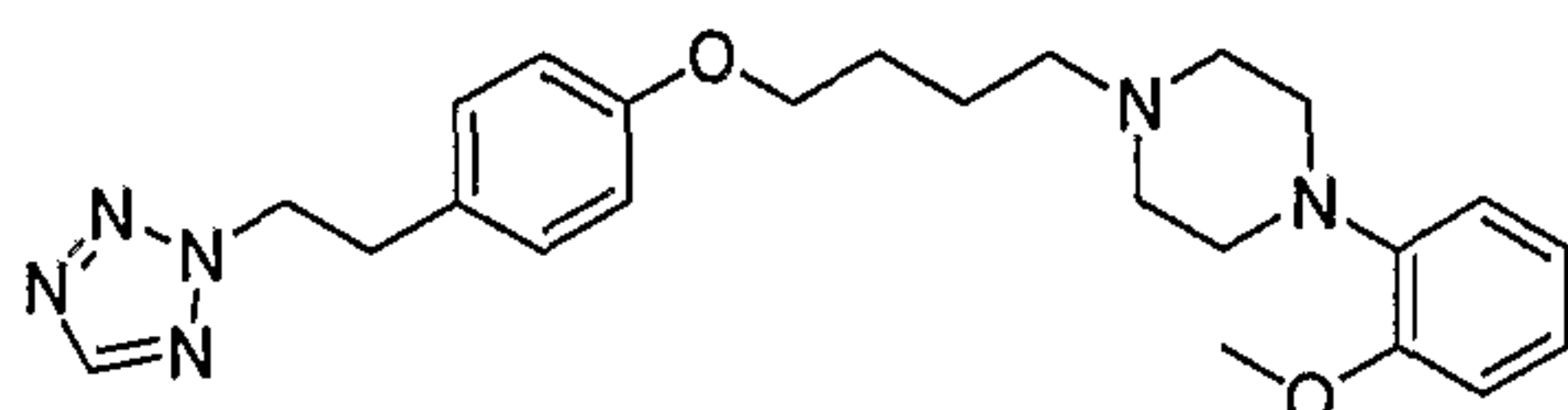


The procedure given in Example 47 was followed using 1H-1,2,3-triazole as a reactant, instead of imidazole, to give 1-(2-methoxy-phenyl)-4-{4-[4-(2-[1,2,3]triazol-1-yl-ethyl)-phenoxy]-butyl}-piperazine.

^1H -NMR (CDCl_3 , 200MHz) δ 7.6(s, 1H), 7.3(s, 1H), 7.0(m, 8H), 4.6(t, 2H), 4.0(t, 2H), 3.8 (s, 3H), 3.1(m, 6H), 2.7(m, 4H), 2.5(t, 2H), 1.8(m, 4H)

Example 51

5 1-(2-methoxy-phenyl)-4-{4-[4-(2-tetrazol-2-yl-ethyl)-phenoxy]-butyl}-piperazine

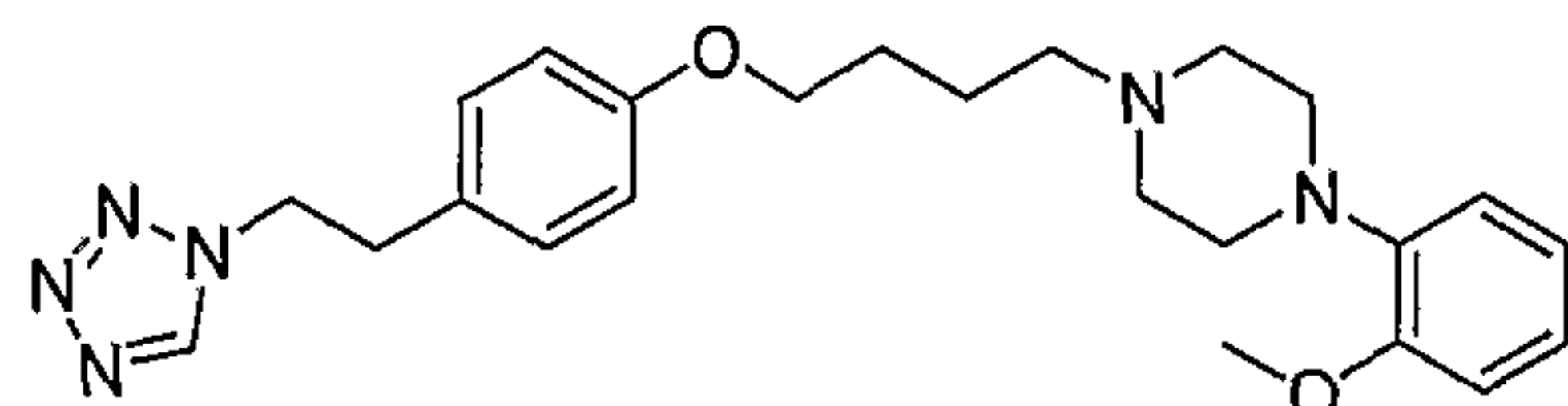


The procedure given in Example 47 was followed using 1H-tetrazole as a reactant, instead of imidazole, to give 1-(2-methoxy-phenyl)-4-{4-[4-(2-tetrazol-2-yl-ethyl)-phenoxy]-butyl}-piperazine.

^1H -NMR (CDCl_3 , 200MHz) δ 8.5(s, 1H), 7.0(m, 8H), 4.9(t, 2H), 4.0(t, 2H), 3.8 (s, 3H), 3.3(t, 2H), 3.1(m, 4H), 2.7(m, 4H), 2.5(t, 2H), 1.8(m, 4H)

Example 52

15 1-(2-methoxy-phenyl)-4-{4-[4-(2-tetrazol-1-yl-ethyl)-phenoxy]-butyl}-piperazine

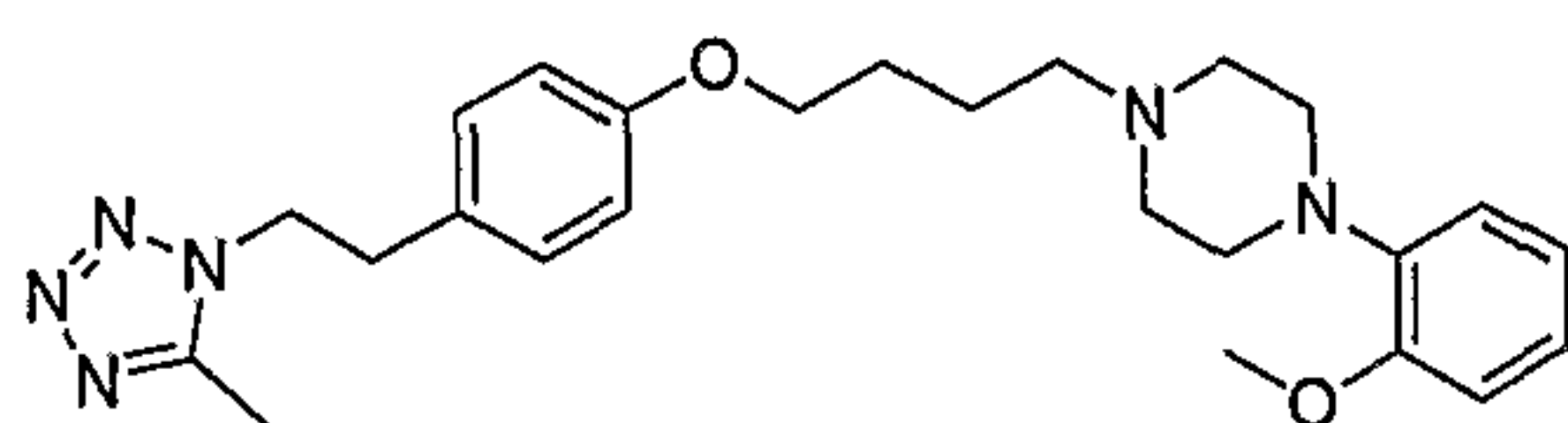


The procedure given in Example 47 was followed using 1H-tetrazole as a reactant, instead of imidazole, to give 1-(2-methoxy-phenyl)-4-{4-[4-(2-tetrazol-1-yl-ethyl)-phenoxy]-butyl}-piperazine.

^1H -NMR (CDCl_3 , 200MHz) δ 8.2(s, 1H), 7.0(m, 8H), 4.7(t, 2H), 4.0(t, 2H), 3.8 (s, 3H), 3.1(m, 6H), 2.7(m, 4H), 2.5(t, 2H), 1.8(m, 4H)

25 Example 53

1-(2-Methoxy-phenyl)-4-(4-{4-[2-(5-methyl-tetrazol-1-yl)-ethyl]-phenoxy}-butyl)-piperazine

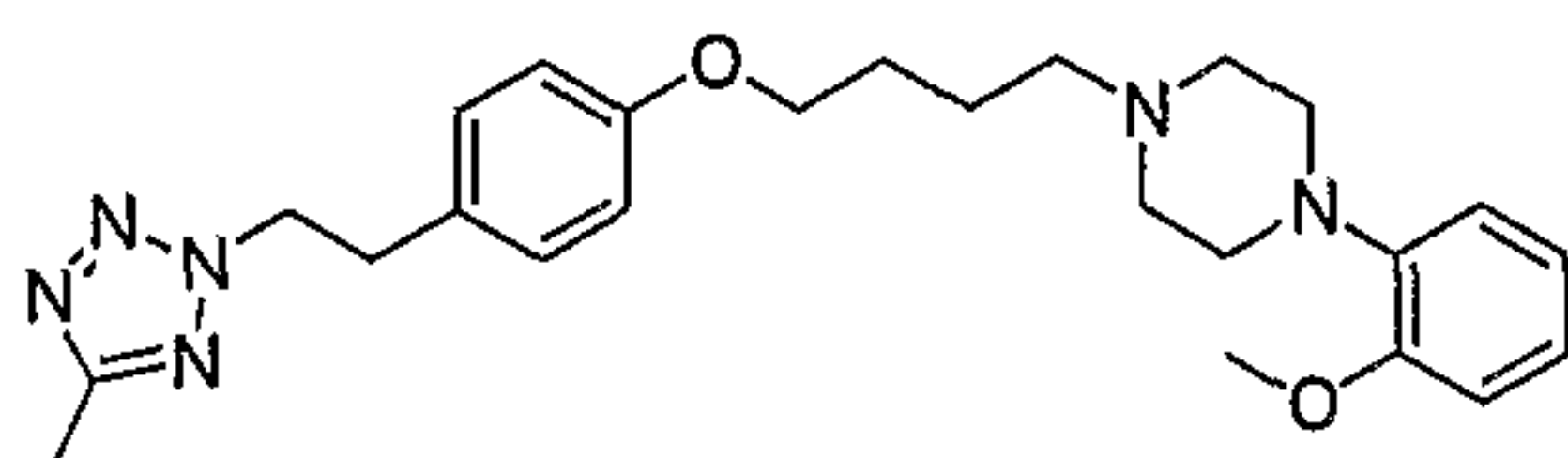


The procedure given in Example 47 was followed using 5-Methyl-tetrazole as a reactant, instead of imidazole, to give 1-(2-Methoxy-phenyl)-4-(4-{4-[2-(5-methyl-tetrazol-1-yl)-ethyl]-phenoxy}-butyl)-piperazine.

¹H-NMR (CDCl₃, 200MHz) δ 7.2~7.0(m, 8H), 5.0 (t, 2H), 4.0(t, 2H), 3.8 (s, 3H), 3.1(m, 6H), 2.7(m, 4H), 2.3~2.5 (m, 5H), 1.8(m, 4H)

Example 54

1-(2-Methoxy-phenyl)-4-(4-{4-[2-(5-methyl-tetrazol-2-yl)-ethyl]-phenoxy}-butyl)-piperazine.

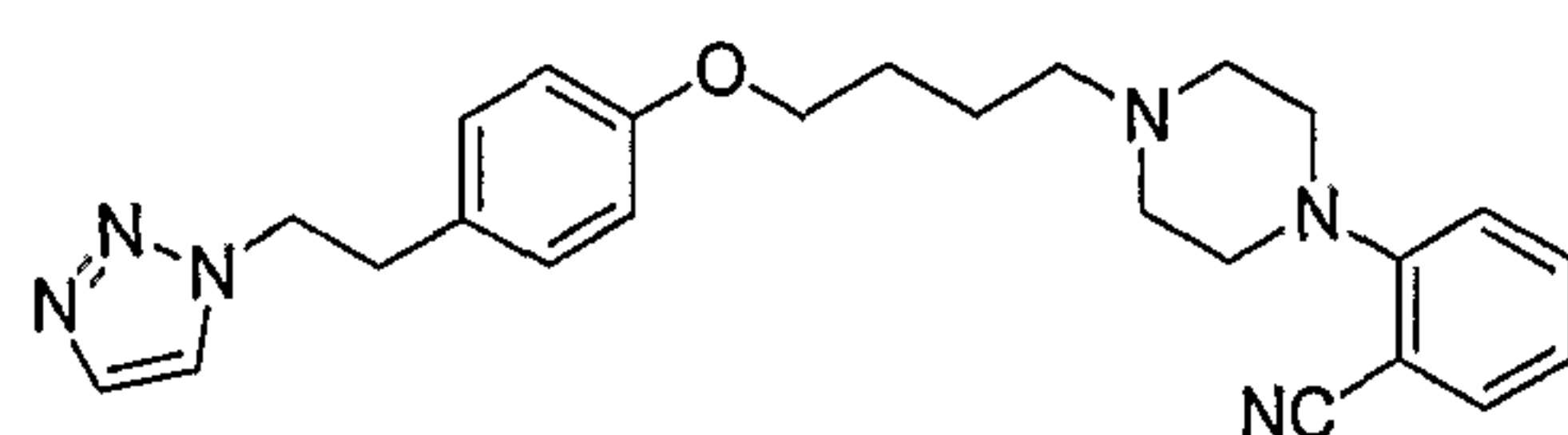


The procedure given in Example 47 was followed using 5-Methyl-tetrazole as a reactant, instead of imidazole, to give 1-(2-Methoxy-phenyl)-4-(4-{4-[2-(5-methyl-tetrazol-2-yl)-ethyl]-phenoxy}-butyl)-piperazine.

¹H-NMR (CDCl₃, 200MHz) δ 7.2~7.0(m, 8H), 5.2 (t, 2H), 4.0(t, 2H), 3.8 (s, 3H), 3.1(m, 6H), 2.7(m, 4H), 2.3~2.5 (m, 5H), 1.8(m, 4H)

Example 55

2-{4-[4-(4-[1,2,3]-triazol-1-ylmethyl-phenoxy)-butyl]-piperazin-1-yl}-benzonitrile

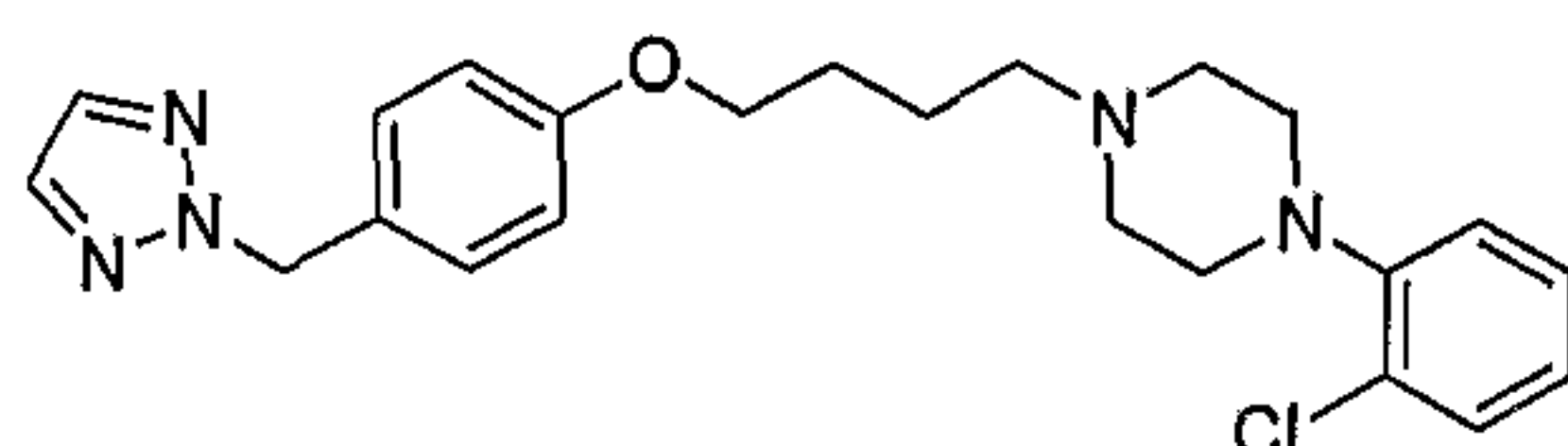


The procedure given in Example 1 was followed using 1-(2-cyano-phenyl)-piperazine and 1H-1,2,3-triazole as reactants, instead of 1-(2-methoxyphenyl)-piperazine and imidazole, to give 2-{4-[4-(4-[1,2,3]-triazol-1-ylmethyl-phenoxy)-butyl]-piperazin-1-yl}-benzonitrile.

$^1\text{H-NMR}$ (CDCl_3 , 200MHz) δ 7.9 (s, 1H), 7.8 (s, 1H), 7.2(m, 2H), 6.9(m, 6H), 5.5(s, 2H), 4.0(t, 2H), 3.2(m, 4H), 2.8(m, 4H), 2.6(t, 2H), 1.8(m, 4H)

Example 56

5 1-(2-chloro-phenyl)-4-[4-(4-[1,2,3]triazol-2-ylmethyl-phenoxy)-butyl]-piperazine



The procedure given in Example 1 was followed using 1-(2-chloro-phenyl)-piperazine and 1H-1,2,3-triazole as reactants, instead of 1-(2-methoxyphenyl)-piperazine and imidazole, to give 1-(2-chloro-phenyl)-4-[4-(4-[1,2,3]triazol-1-ylmethyl-phenoxy)-butyl]-piperazine.

$^1\text{H-NMR}$ (CDCl_3 , 200MHz) δ 7.6 (s, 2H), 7.2(m, 2H), 6.9(m, 6H), 5.6 (s, 2H), 4.0(t, 2H), 3.2(m, 4H), 2.7(m, 4H), 2.5(t, 2H), 1.8(m, 4H)

15 The therapeutic use of the compounds of general structural formula (I) and their pharmaceutically useful salts are demonstrated by the following tests.

Example 57: Serotonin 1A (5-HT1A) receptor inhibition assay

20 The method to test the ability of compounds to inhibit serotonin 1A(5-HT1A) receptors was using Hall. et al., J NeuroChem., 1985, 44, p1685~1696 with modification.

25 The Sprague-Dawley (SD) rats were killed by decapitation and their brains rapidly removed at 4 °C. The cortex tissue were homogenized in 30 volumes of ice-cold 50mM Tris-HCl buffer(pH7.4) using an ultra-turrax T8 and centrifuged at 48,000 g for 20 min. The supernatant was discarded and the pellet washed twice by resuspension in 20 volumes Tris-HCl and centrifugation, homogenized in 20 volumes Tris-HCl, and incubated at 37 °C for 10 min. Membranes were than collected by centrifugation and washed twice before final resuspension in 10 volumes of 50 mM Tris-HCl, pH7.4.

For binding assays, the incubation medium consisted of 162.5ug of tissue homogenate, 0.92nM of [3H]8-OH-DPAT and vehicle or 10uM of 5-HT or 10nM of test compounds per well. 5-HT and test compounds were dissolved in distilled water and incubation medium was 50mM Tris (pH7.4 at room temperature). The assay plates(96well) were incubated for 60 min at 25 °C. The reaction was terminated by rapid filtration using a Tomtec harvester, through GF/C glassfibre filter with 5 times washes of Tris buffer. The radioactivity retained on the filters was counted by scintillation spectroscopy (MicroBeta TriLux, Wallac). The tests were triplicates. Percent inhibition was calculated as below equation.

$$\% \text{ inhibition} = \frac{\text{Total binding} - \text{Compound binding}}{\text{Specific(Total - Nonspecific) binding}}$$

Total binding is the value of vehicle treated group and specific binding is the values that deduct non-specific binding (i.e. the value of non-specific ligand, 5-HT).

The results obtained by testing compounds of the invention are given in the following Table 1.

Table 1

Test Compound	5-HT1a % inhibition, at 10nM
Example 1	83.1
Example 2	80.3
Example 3	77.8
Example 4	75.9
Example 5	50.7
Example 6	50.1
Example 7	78.4
Example 8	81.6
Example 9	52.2
Example 10	71.8
Example 11	61.8
Example 12	60.9

Example 13	50.4
Example 14	51.1
Example 15	23.5
Example 16	62.5
Example 17	56.4
Example 18	69.5
Example 19	59.6
Example 20	68.5
Example 21	38.2
Example 22	53.4
Example 23	17.2
Example 24	51.6
Example 25	45.2
Example 26	47.0
Example 27	40.9
Example 28	13.5
Example 29	45.8
Example 30	38.3
Example 31	30.3
Example 33	53.7
Example 35	73.3
Example 36	28.1
Example 37	24.8
Example 38	29.4
Example 39	52.9
Example 40	45.6
Example 41	82.1
Example 42	36.2
Example 43	95.6
Example 44	17.4
Example 45	73.8
Example 46	64.6
Example 47	70.0
Example 48	48.0
Example 49	45.0
Example 50	51.0

Example 51	47.0
Example 52	62.0
Example 53	46.0
Example 54	71.0
Example 56	24.3

Example 58: Tail Suspension Test in mice (TST)

5 Tail Suspension Test in mice is the well-known animal model to determine antidepressant efficacy of compounds by checking escaping behavior and immobility time of mice. Mice treated with antidepressant drug show escaping behavior continuously comparing with control group.

10 The mice were mainly treated orally with the test compound dissolved in 30% PEG400 or with only 30% PEG400 as control. Tail of mouse is suspended to the rod of TST equipment and end of tail is fixed with sticky tape. Suspended mouse is incubated during 2 min for training and adaptation and after following 2min, observe escaping behavior and check immobility time for 4min. The potent ability of the compounds was determined as percent value of reduction in immobility comparing to control group as
15 100% baseline.

The results obtained by testing compounds of the invention are given in the following Table 2:

Table 2

Test Compound	% reduction at 1mg/kg, po
Example 5	21.2
Example 7	21.1
Example 8	19.6
Example 11	25
Example 12	12.7
Example 18	14.7
Example 19	50.6
Example 33	26.8

Example 39	30.4
Example 40	10.6
Example 41	14.1
Example 48	26.2
Example 49	34.3
Example 50	46.9
Example 51	14.7
Example 52	26.4
Example 54	31.8
Estalopram	47, at 30mg/kg, po
Fluxetine	49. at 30mg/kg, po

This anti-depressant effect, as with other anti-depressant drugs, suggested potentials for treating depression.

5 **Example 59: Anti-Marble Burying Behavior Test in Mice**

Marble burying was developed and validated as a pre-clinical assay of potential anxiolytic activity (Andrews and Broekkamp (1993). Procedures to Identify Anxiolytic or Anxiogenic agents. In Behavioural Neuroscience, ed. A Sahgal, pp. 37-54. IRL Press, Oxford). The marble burying test places a naive mouse into a novel environment containing 25 marbles (arranged on top of a sawdust surface). A reduction in the number of marbles buried by the mouse was hypothesized to be an anxiolytic-like effect.

The results obtained by testing compounds of the invention are given in the following Table 3:

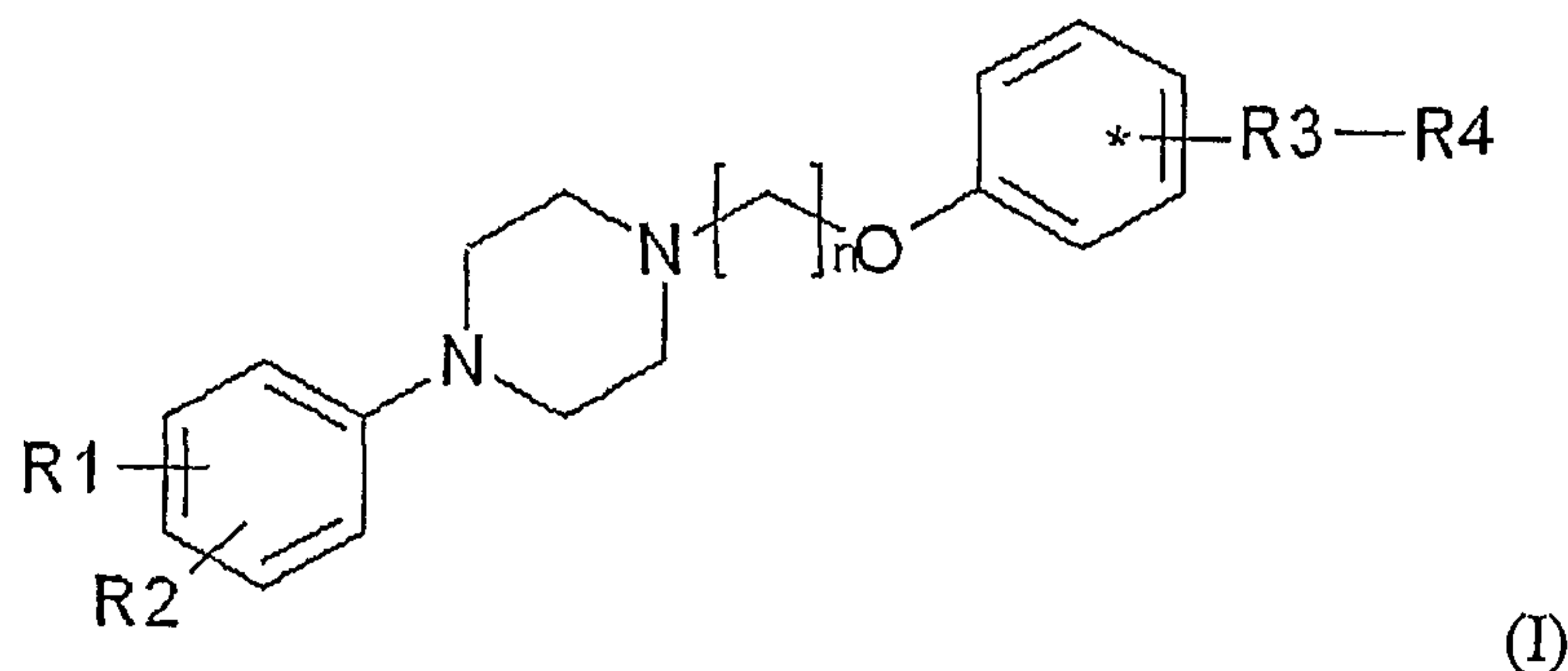
Table 3

Test Compound	% reduction, at 3mg/kg,ip
Example 1	28.7
Example 2	93.3
Example 5	60.3, at 7.5mg/kg, ip
Example 7	61.1, at 7.5mg/kg, ip
Example 11	69.0, at 7.5mg/kg, ip
Example 12	97.3
Example 19	50.8, at 7.5mg/kg, ip
Example 20	27.0, at 7.5mg/kg, ip
Example 21	29.9
Example 24	62.6
Example 28	24.6
Example 32	27.8, at 7.5mg/kg, ip
Example 36	25.3
Example 47	39.3
Example 48	31.3
Example 50	96.8, at 7.5mg/kg, ip
Example 51	44.4, at 7.5mg/kg, ip
Buspirone	56.0, at 20mg/kg, ip

An anti-marble burying effect, as with other anti-anxiety drugs, suggested potentials for treating anxiety.

What we claimed is:

1. A piperazine compound represented by Formula (I):



5

or pharmaceutically acceptable salts thereof, wherein

n is an integer of 2 to 6;

R1 and R2 are the same or different and are independently selected from the group consisting of hydrogen, a hydroxyl group, a halogen, nitrogen dioxide, a straight or branched chain alkyl group with 1 to 4 carbon atoms, and a straight or branched chain alkoxy group with 1 to 4 carbon atoms;

R3 is a C1-C2 alkylene; and

R4 is selected from the group consisting of:

(a) a C2-C6 dialkylamine,

(b) a 5 to 9-membered aromatic amine wherein the ring is independently substituted with at least one of hydrogen, a C1-C6 aliphatic alkyl, a C3 to C10 cyclic alkyl, a C6-C10 aryl group and a halogen,

(c) a 5 to 9-membered heteroaromatic amine comprising at least a nitrogen atom as a ring constituent wherein the ring is independently substituted with at least one of hydrogen, a C1-C6 aliphatic alkyl, a C3 to C10 cyclic alkyl, a C6-C10 aryl group and a halogen,

(d) a 5 to 9-membered heterocyclic ring comprising at least a nitrogen atom as a ring constituent wherein the ring is independently substituted with at least one of hydrogen, a C1-C6 aliphatic alkyl, a C3 to C10 cyclic alkyl, a C6-C10 aryl group and a halogen, and

(e) a 5 to 9-membered heteroaromatic ring comprising at least a nitrogen atom as a ring constituent wherein the ring is independently substituted with at least one

of hydrogen, a C1-C6 aliphatic alkyl, a C3 to C10 cyclic alkyl, a C6-C10 aryl group and a halogen; and

R4 is connected to R3 group through a nitrogen atom therein.

5 2. The piperazine compound of Claim 1, wherein R4 is dimethylamine, or diethylamine.

3. The piperazine compound of Claim 1, wherein R4 is connected to R3 through a nitrogen atom in an amino group of the 5 to 9-membered aromatic amine or
10 heteroaromatic amine.

4. The piperazine compound of Claim 3, wherein R4 is a 5 or 6-membered aromatic amine substituted with at least one of hydrogen, a C1-C6 alkyl, and a halogen.

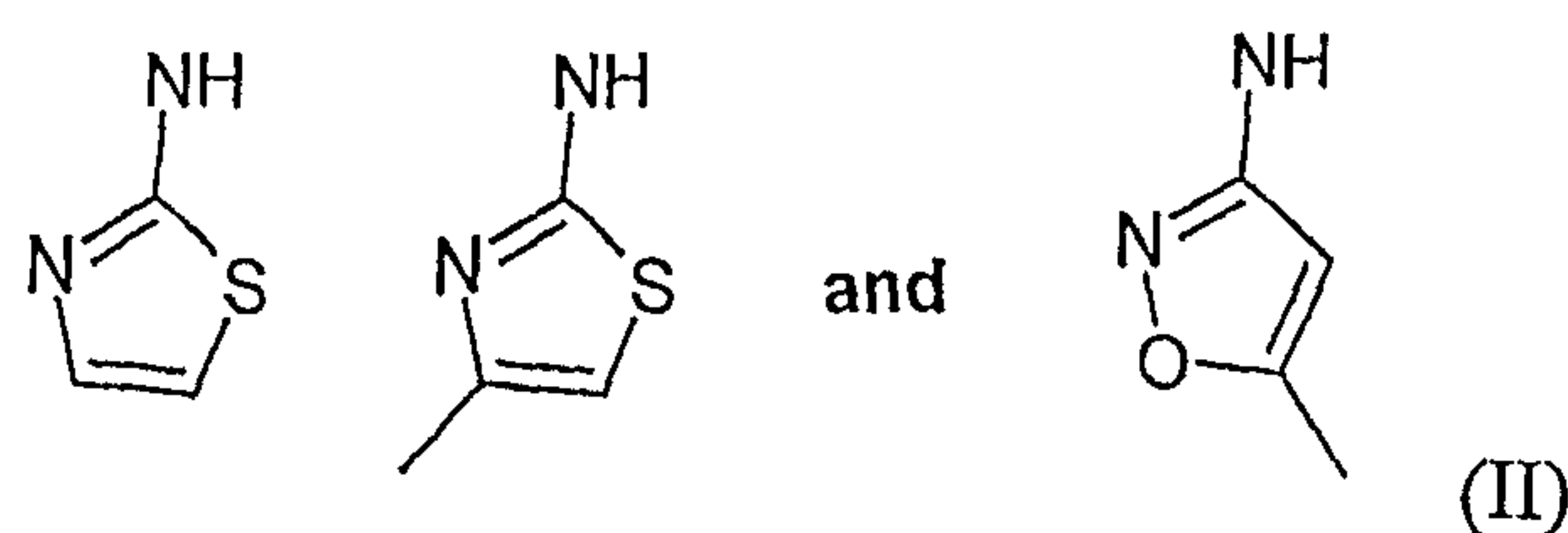
15

5. The piperazine compound of Claim 4, wherein R4 is a 6-membered aromatic amine substituted with hydrogen.

6. The piperazine compound of Claim 3, wherein R4 is a 5 or 6-membered heteroaromatic amine substituted with at least one group selected from the group consisting of a C1-C6 alkyl and a halogen, wherein the heteroaromatic amine comprises at least two heteroatoms as ring constituents where a first heteroatom is N and a second heteroatom is independently selected from the group consisting of N, O, and S.

25

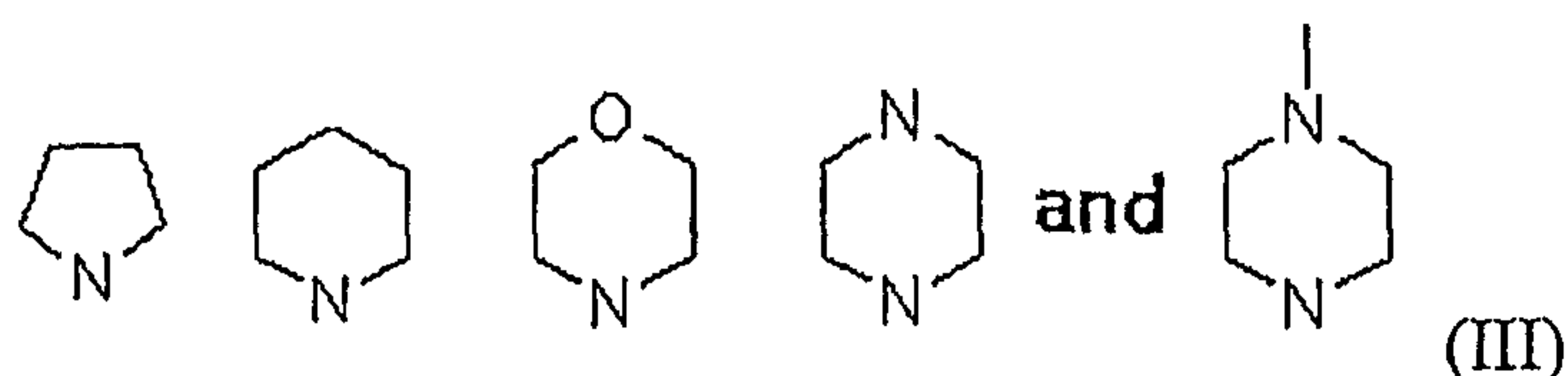
7. The piperazine compound of Claim 6, wherein R4 is a 5-membered heteroaromatic amine having a structure (II) selected from the group consisting of:



8. The piperazine compound of Claim 1, wherein R4 is connected to R3 through a nitrogen atom contained in a ring as a heteroatom of the 5 to 9-membered heterocyclic ring or heteroaromatic ring.

5

9. The piperazine compound of Claim 8, wherein R4 is a 5 or 6-membered heterocyclic ring having a structure (III) selected from the group consisting of:

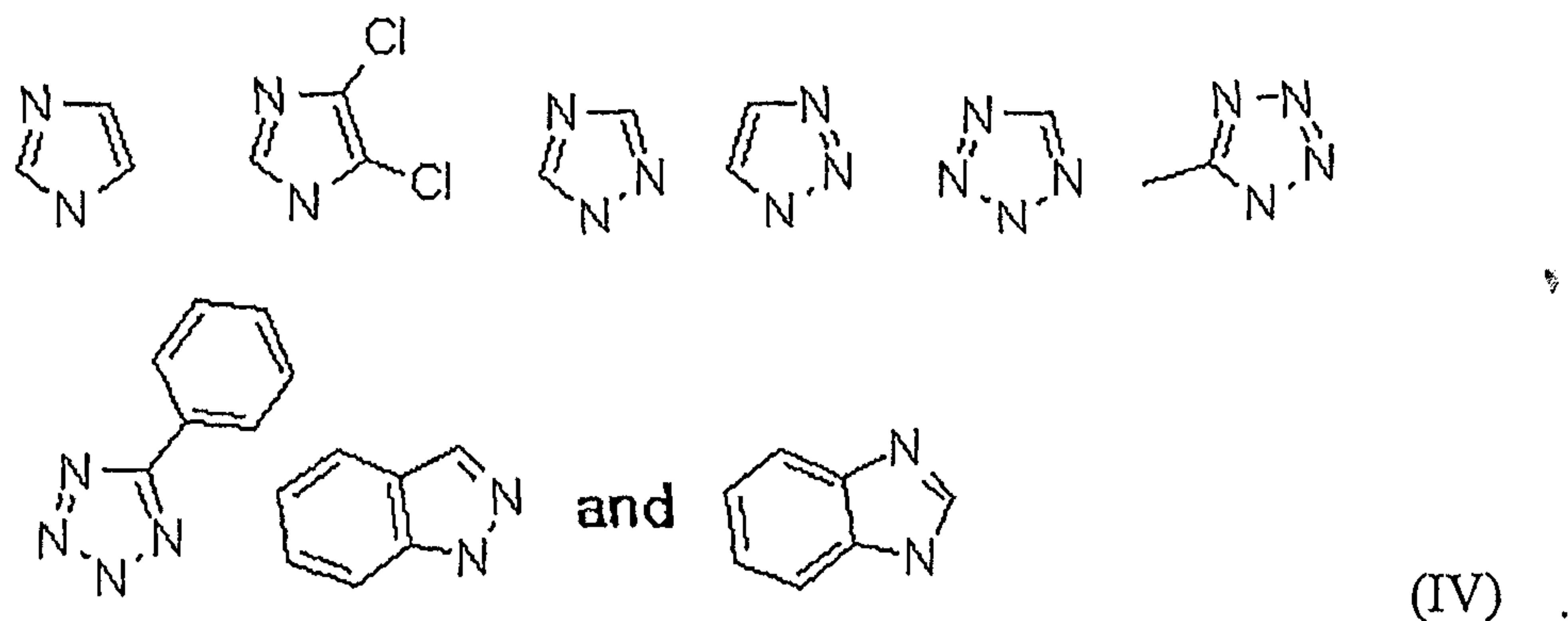


10

10. The piperazine compound of Claim 8, wherein R4 is selected from the group consisting of diazole, triazole, tetraazol, benzotriazole, imidazole, pyrazole, benzimidazole, and indazole.

15

11. The piperazine compound of Claim 10, wherein the azole has a structure (IV) selected from the group consisting:



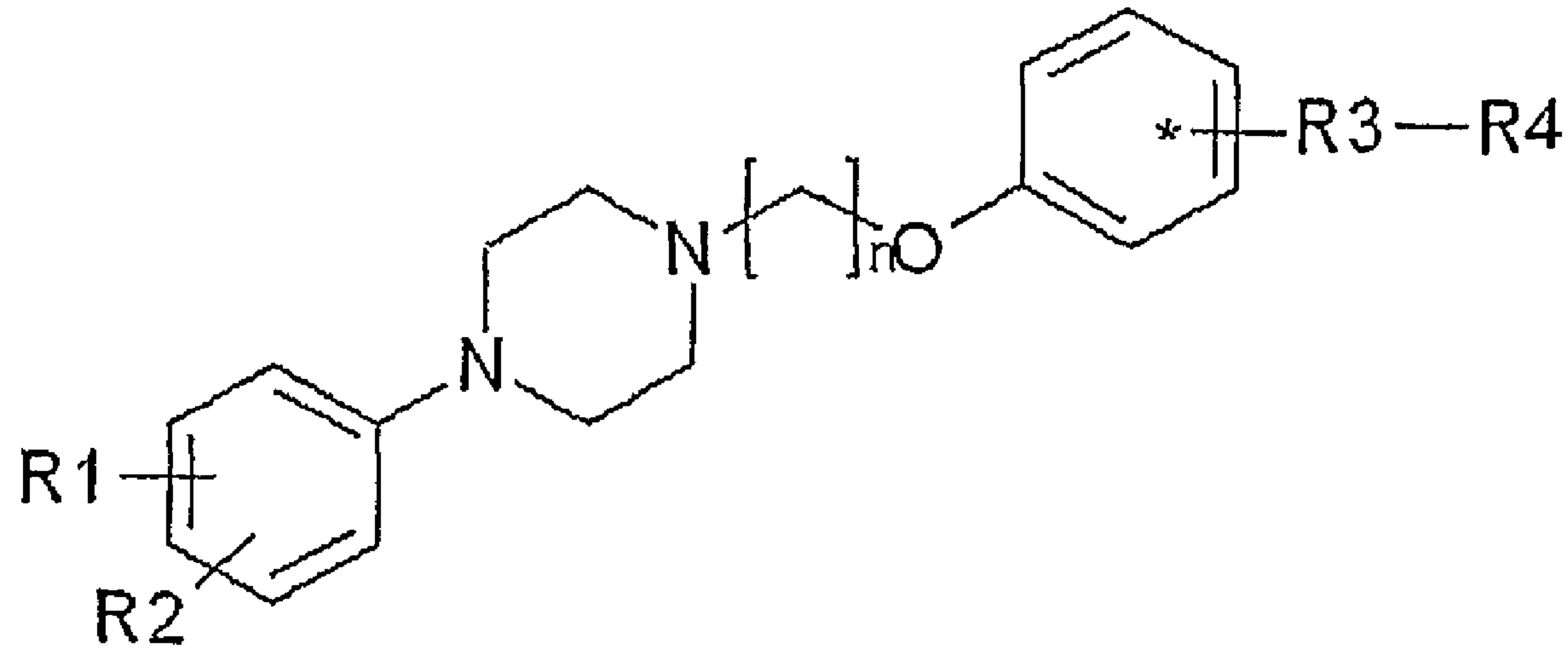
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12. The piperazine compound of Claim 1, wherein R1 and R2 are independently selected from the group consisting of hydrogen, a halogen, a straight or branched chain alkyl group with 1 to 4 carbon atoms, and a straight or branched chain alkoxy group with 1 to 4 carbon atoms.

13. The piperazine compound of Claim 1, wherein said compound is selected from the group consisting of: 1-[4-(4-imidazol-1-ylmethyl-phenoxy)-butyl]-4-(2-methoxy-phenyl)-piperazine, 1-(2-methoxy-phenyl)-4-[4-(4-[1,2,4]triazol-1-ylmethyl-phenoxy)-butyl]-piperazine, 1-(2-methoxy-phenyl)-4-[4-(4-tetrazol-1-ylmethyl-phenoxy)-butyl]-piperazine, 1-(2-methoxy-phenyl)-4-[4-(4-tetrazol-2-ylmethyl-phenoxy)-butyl]-piperazine, 1-[4-(3-imidazol-1-ylmethyl-phenoxy)-butyl]-4-(2-methoxy-phenyl)-piperazine-hydrochloride, 1-(2-methoxy-phenyl)-4-[4-(3-[1,2,4]triazol-1-ylmethyl-phenoxy)-butyl]-piperazine hydrochloride, 1-(2-methoxy-phenyl)-4-[4-(3-tetrazol-1-ylmethyl-phenoxy)-butyl]-piperazine hydrochloride, 1-(2-methoxy-phenyl)-4-[4-(3-tetrazol-2-ylmethyl-phenoxy)-butyl]-piperazine hydrochloride, 1-(4-{4-[4-(2-methoxy-phenyl)-piperazin-1-yl]-butoxy}-benzyl)-1H-benzimidazole, 1-(2-Methoxy-phenyl)-4-{4-[4-(2-methyl-imidazol-1-ylmethyl)-phenoxy]-butyl}-piperazine, 1-(2-methoxy-phenyl)-4-[4-(4-[1,2,3]triazol-2-ylmethyl-phenoxy)-butyl]-piperazine, 1-(2-methoxy-phenyl)-4-[4-(4-[1,2,3]triazol-1-ylmethyl-phenoxy)-butyl]-piperazine, 1-(4-{4-[4-(2-Methoxy-phenyl)-piperazin-1-yl]-butoxy}-benzyl)-1H-indazole, 1-(4-{4-[4-(2-Methoxy-phenyl)-piperazin-1-yl]-butoxy}-benzyl)-1H-benzotriazole, 1-(2-methoxy-phenyl)-4-{4-[4-(5-phenyl-tetrazol-2-ylmethyl)-phenoxy]-butyl}-piperazine, 1-(2-methoxy-phenyl)-4-{4-[4-(5-phenyl-tetrazol-1-ylmethyl)-phenoxy]-butyl}-piperazine, 1-(2-methoxy-phenyl)-4-{4-[4-(5-methyl-tetrazol-2-ylmethyl)-phenoxy]-butyl}-piperazine, 1-(2-methoxy-phenyl)-4-{4-[4-(5-methyl-tetrazol-1-ylmethyl)-phenoxy]-butyl}-piperazine, (4-{4-[4-(2-methoxy-phenyl)-piperazin-1-yl]-butoxy}-benzyl)-dimethyl-amine di-hydrochloride, 1-(2-methoxy-phenyl)-4-[4-(4-piperidin-1-ylmethyl-phenoxy)-butyl]-piperazine, (4-{4-[4-(2-methoxy-phenyl)-piperazin-1-yl]-butoxy}-benzyl)-phenyl-amine, (4-{4-[4-(2-methoxy-phenyl)-piperazin-1-yl]-butoxy}-benzyl)-thiazol-2-yl-amine, 1-(2-chloro-phenyl)-4-[4-(4-[1,2,4]triazol-1-ylmethyl-phenoxy)-butyl]-piperazine, 1-(2-methoxy-phenyl)-4-[4-(3-[1,2,3]triazol-2-ylmethyl-phenoxy)-butyl]-piperazine, 1-(2-Methoxy-phenyl)-4-[4-(3-[1,2,3]triazol-1-ylmethyl-phenoxy)-butyl]-piperazine, 1-(2-Methoxy-phenyl)-4-[4-(3-[1,2,3]triazol-2-ylmethyl-phenoxy)-butyl]-piperazine, 1-(2-methoxy-phenyl)-4-{4-[3-(5-methyl-tetrazol-1-ylmethyl)-phenoxy]-butyl}-piperazine, (3-{4-[4-(2-methoxy-phenyl)-piperazin-1-yl]-butoxy}-benzyl)-dimethyl-amine, 4-(3-{4-[4-(2-methoxy-phenyl)-piperazin-1-yl]-butoxy}-benzyl)-morpholine, 1-{4-[4-(4,5-dichloro-imidazol-1-

ylmethyl)-phenoxy]-butyl}-4-(2-methoxy-phenyl)-piperazine, 1-(2-chloro-phenyl)-4-[4-(4-tetrazol-2-ylmethyl-phenoxy)-butyl]-piperazine, 4-(4-{4-[4-(2-methoxy-phenyl)-piperazin-1-yl]-butoxy}-benzyl)-morpholine, (4-{4-[4-(2-Chloro-phenyl)-piperazin-1-yl]-butoxy}-benzyl)-dimethyl-amine, 1-(3-fluoro-phenyl)-4-[4-(4-[1,2,4]triazol-1-ylmethyl-phenoxy)-butyl]-piperazine, 1-(2-methoxy-phenyl)-4-[4-(4-4-methylpiperazine-1-ylmethyl-phenoxy)-butyl]-piperazine, , 1-(2,3-dichloro-phenyl)-4-[4-(4-tetrazol-2-ylmethyl-phenoxy)-butyl]-piperazine, 1-(2,3-Dichloro-phenyl)-4-{4-[4-(5-methyl-tetrazol-1-ylmethyl)-phenoxy]-butyl}-piperazine, 1-(2,3-Dichloro-phenyl)-4-{4-[4-(5-methyl-tetrazol-2-ylmethyl)-phenoxy]-butyl}-piperazine, (4-{4-[4-(2,3-dichloro-phenyl)-piperazin-1-yl]-butoxy}-benzyl)-dimethyl-amine, 4-(4-{4-[4-(2,3-Dichloro-phenyl)-piperazin-1-yl]-butoxy}-benzyl)-morpholine, 1-(2-methoxy-phenyl)-4-[4-(4-4-methylpiperazine-1-ylmethyl-phenoxy)-butyl]-piperazine, 1-(2-chloro-phenyl)-4-[4-(4-[1,2,3]triazol-1-ylmethyl-phenoxy)-butyl]-piperazine, (4-{4-[4-(2-Methoxy-phenyl)-piperazin-1-yl]-butoxy}-benzyl)-[1,3,4]thiadiazol-2-yl-amine, 1-(2,3-dichloro-phenyl)-4-[4-(4-[1,2,3]triazol-1-ylmethyl-phenoxy)-butyl]-piperazine, (4-{4-[4-(2-Methoxy-phenyl)-piperazin-1-yl]-butoxy}-benzyl)-(5-methyl-isoxazol-3-yl)-amine, (4-{4-[4-(2-methoxy-phenyl)-piperazin-1-yl]-butoxy}-benzyl)-(5-methyl-isoxazol-3-yl)-amine, 1-{4-[4-(2-imidazol-1-yl-ethyl)-phenoxy]-butyl}-4-(2-methoxy-phenyl)-piperazine, 1-(2-methoxy-phenyl)-4-{4-[4-(2-[1,2,4]triazol-1-yl-ethyl)-phenoxy]-butyl}-piperazine, 1-(2-methoxy-phenyl)-4-{4-[4-(2-[1,2,3]triazol-2-yl-ethyl)-phenoxy]-butyl}-piperazine, 1-(2-methoxy-phenyl)-4-{4-[4-(2-[1,2,3]triazol-1-yl-ethyl)-phenoxy]-butyl}-piperazine, 1-(2-methoxy-phenyl)-4-{4-[4-(2-tetrazol-2-yl-ethyl)-phenoxy]-butyl}-piperazine, 1-(2-methoxy-phenyl)-4-{4-[4-(2-tetrazol-1-yl-ethyl)-phenoxy]-butyl}-piperazine, 1-(2-Methoxy-phenyl)-4-(4-{4-[2-(5-methyl-tetrazol-1-yl)-ethyl]-phenoxy}-butyl)-piperazine, 1-(2-Methoxy-phenyl)-4-(4-{4-[2-(5-methyl-tetrazol-2-yl)-ethyl]-phenoxy}-butyl)-piperazine, 2-{4-[4-(4-[1,2,3]-triazol-1-ylmethyl-phenoxy)-butyl]-piperazin-1-yl}-benzonitrile, and 1-(2-chloro-phenyl)-4-[4-(4-[1,2,3]triazol-2-ylmethyl-phenoxy)-butyl]-piperazine.

14. A pharmaceutical composition for treating and preventing depression and anxiety comprising an effective amount of the piperazine compound of any one of Claims 1 to 13, and a pharmaceutically acceptable carrier or excipient.



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