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(54) Titre : NOUVEAUX DERIVES D'ARYLE PIPERAZINE PRESENTANT UNE UTILITE MEDICALE
(54) Title: ARYL PIPERAZINE DERIVATIVES FOR THE TREATMENT OF NEUROPSYCHIATRIC DISORDERS

(57) **Abrégé/Abstract:**

This invention provides novel aryl piperazine derivatives having medical utility, in particular as modulators of dopamine and serotonin receptors, preferably the D₃, D₂-like and 5-HT₂ receptor subtypes, and in particular useful for the treatment of neuropsychiatric disorders incl. schizophrenia. Formula (I) an enantiomer thereof or a mixture of its enantiomers, or a pharmaceutically acceptable salt thereof, or an N-oxide thereof.



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(54) Title: ARYL PIPERAZINE DERIVATIVES FOR THE TREATMENT OF NEUROPSYCHIATRIC DISORDERS

(57) Abstract: This invention provides novel aryl piperazine derivatives having medical utility, in particular as modulators of dopamine and serotonin receptors, preferably the D₃, D₂-like and 5-HT₂ receptor subtypes, and in particular useful for the treatment of neuropsychiatric disorders incl. schizophrenia. Formula (I) an enantiomer thereof or a mixture of its enantiomers, or a pharmaceutically acceptable salt thereof, or an N-oxide thereof.

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NOVEL ARYL PIPERAZINE DERIVATIVES WITH MEDICAL UTILITY

TECHNICAL FIELD

5 This invention provides novel aryl piperazine derivatives having medical utility, in particular as modulators of dopamine and serotonin receptors, preferably the D₃, D₂-like and 5-HT₂ receptor subtypes, and in particular useful for the treatment of neuropsychiatric disorders incl. schizophrenia.

10 BACKGROUND ART

Dopamine is involved in several important functions, excitatory and inhibitory, via dopaminergic receptors in the central and peripheral nervous system. Dopamine receptors were originally classified into two main groups: D₁ and D₂. The
15 five currently cloned dopamine receptors fall into these classes. Thus, the D₁-like receptors include D₁ and D₅, while the D₂-like receptors include D₂, D₃ and D₄.

The dopamine receptors, and in particular the D₂-like receptors, are recognised as potential therapeutic targets for various neurological and psychiatric disorders, in particular psychotic disorders, incl. schizophrenia. Other therapeutic
20 indications associated with the dopamine receptors include depression, Parkinson's disease, Huntington's disease, movement disorders such as dystonia, anxiety, restlessness, obsessive-compulsive disorders, mania, geriatric disorders, dementia, sexual dysfunction, musculo-skeletal pain symptoms, e.g. pain associated with fibromyalgia, substance abuse (cocaine abuse and addiction), withdrawal symptoms in
25 drug addicts, and sleep disorders.

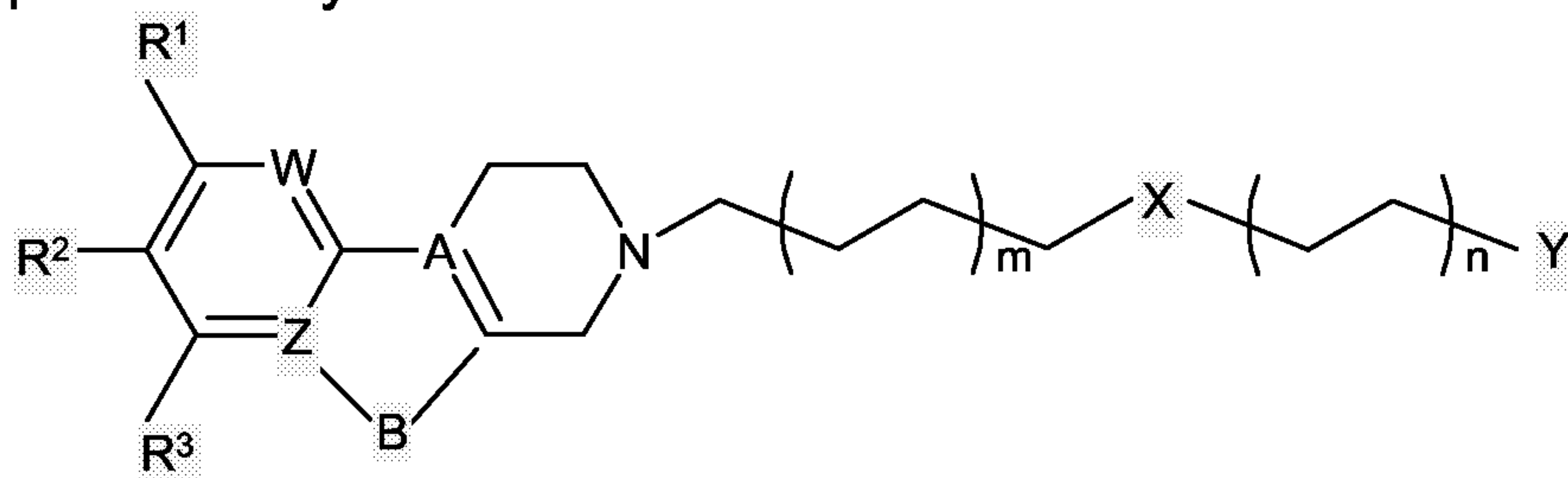
Finally receptor selective ligands find use as diagnostic tools in diagnostic methods, and in particular for *in vivo* receptor imaging (neuroimaging).

Dopamine receptor selective ligands have been described in e.g. WO 2004024878, and by i.a. *Leopoldo et al.* (J. Med. Chem. 2002 **45** 5727-5733), *Campiani et al.* (J. Med. Chem. 2003 **46** 3822-3839) and *Hackling et al.* (J. Med. Chem. 2003 **46**
30 3883-3899).

SUMMARY OF THE INVENTION

35 According to the present invention it has now been found that certain aryl piperazine derivatives show superior activity as modulators of dopamine and serotonin receptors, preferably the D₃, D₂-like and 5-HT₂ receptor subtypes, and thus are particular useful as antipsychotic agents.

Therefore, in its first aspect, the invention provides novel aryl piperazine derivatives represented by Formula I



(I)

an enantiomer thereof or a mixture of its enantiomers, or a pharmaceutically acceptable salt thereof, or an N-oxide thereof, wherein,

R¹, R² and R³, independently of one another, represent hydrogen, alkyl, cycloalkyl, cycloalkyl-alkyl, alkenyl, hydroxy, alkoxy, cycloalkoxy, halo, haloalkyl, haloalkoxy, amino, nitro cyano and/or carboxy;

--- represents an optional double bond; if --- represents a single bond, then

A represents CH or N; if --- represents a double bond, then A represents C;

--B-- may be absent or present: --B-- is absent; and Z represents CH or N; or --B-- is present and represents a methylene bridge (-CH₂-), an ethylene bridge (=CH-), or a bridge -NH-, attached as indicated in the figure; and Z represents C (carbon);

W represents CH, N or CR⁴, wherein R⁴ represents represent hydrogen, alkyl, cycloalkyl, cycloalkyl-alkyl, alkenyl, hydroxy, alkoxy, cycloalkoxy, halo, haloalkyl, haloalkoxy, amino, nitro or cyano;

m and n, independently of each other, is 0, 1 or 2; and

X may be absent or present:

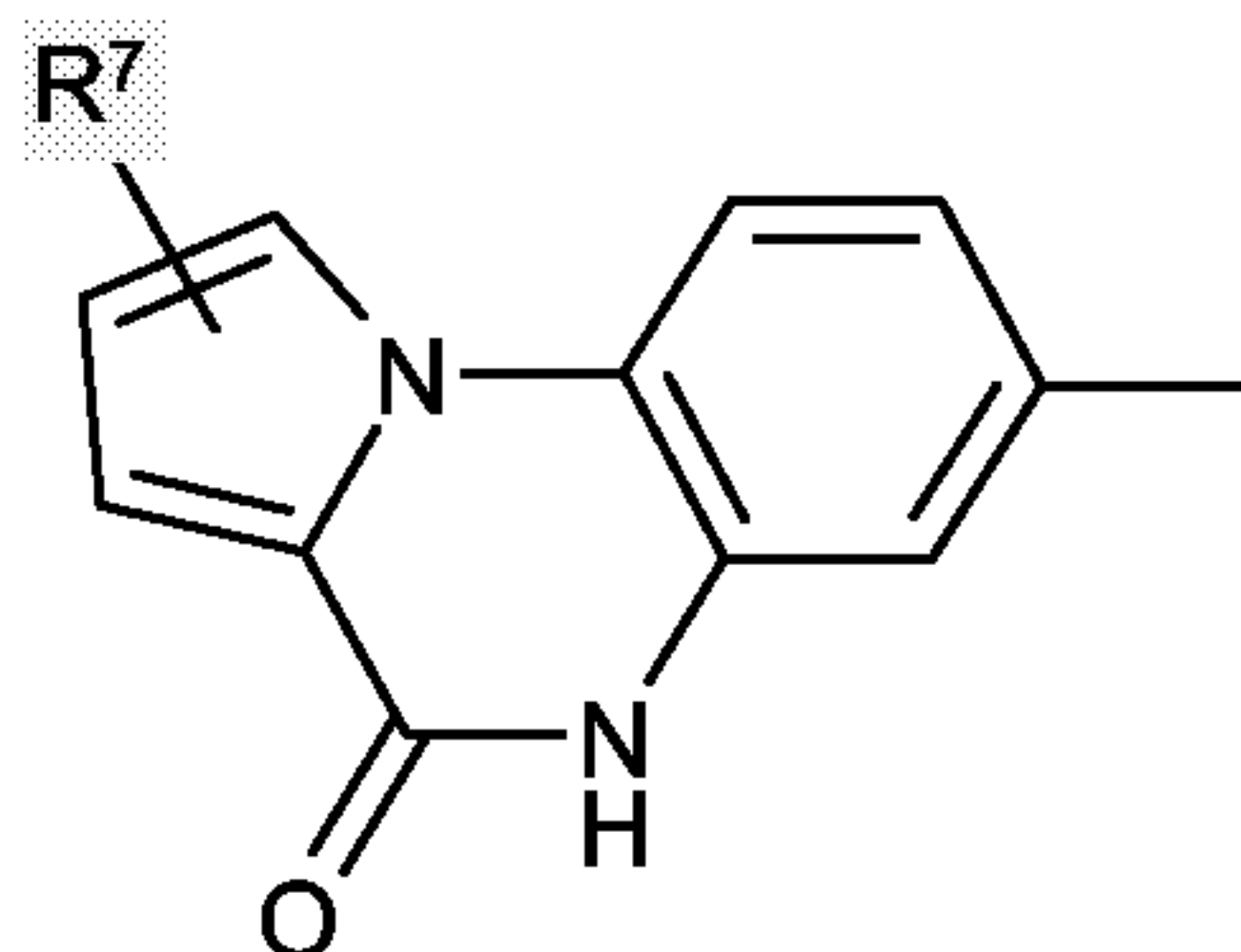
X is present and represents O, S, NR', CO, SO₂, CH₂, CH₂-O, O-CH₂, CH₂-S, S-CH₂, CH₂-NR', CH₂-CO, CH₂-SO₂, NR'-CO, CO-NR', NR'-SO₂, SO₂-NR', CH₂-CH₂, O-CO, CO-O, O-CH=CH, S-CH=CH, NR'-CH=CH, CO-CH=CH, SO₂-CH=CH, CH₂-O-CH=CH, CH₂-S-CH=CH, CH₂-NR'-CH=CH, CH₂-CO-CH=CH, CONHCH₂CH₂ or CH₂-SO₂-CH=CH, wherein R' represents hydrogen or alkyl; and

Y represents phenyl or an aromatic monocyclic or polycyclic heterocyclic group, which phenyl or heterocyclic group may optionally be substituted one or more times with substituents selected from the group consisting of alkyl, cycloalkyl, cycloalkyl-alkyl, alkenyl, hydroxy, alkoxy, cycloalkoxy, halo, haloalkyl, haloalkoxy, amino, nitro and cyano; or

Y represents a hydrogenated heterocyclic group, which hydrogenated heterocyclic group may optionally be substituted one or more times with substituents selected from the group consisting of alkyl, cycloalkyl, cycloalkyl-alkyl, alkenyl, hydroxy, alkoxy, cycloalkoxy, halo, haloalkyl, haloalkoxy, amino, nitro and cyano; or

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Y represents a group of formula III

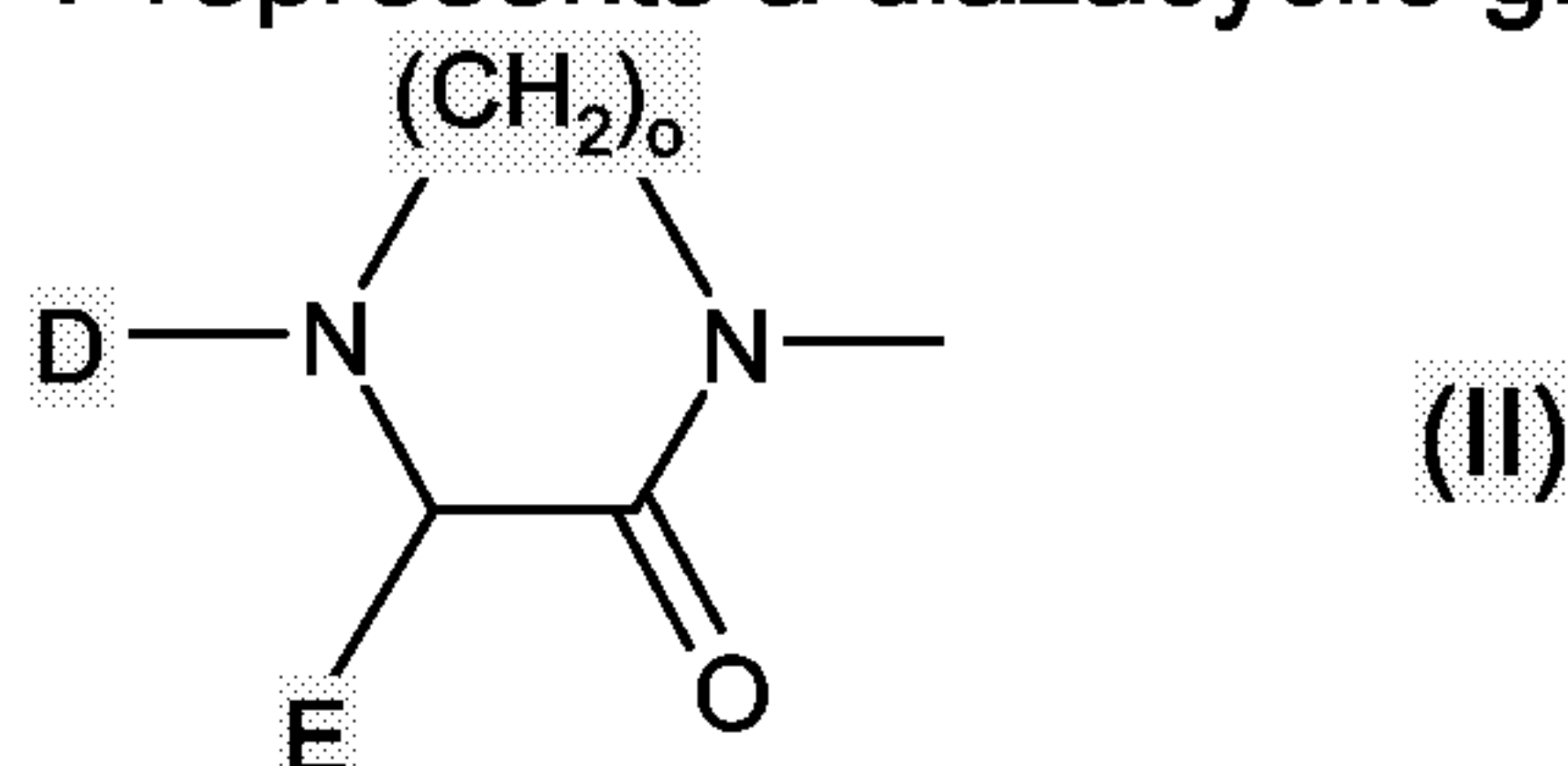


wherein

R^7 represents hydrogen, alkyl, alkoxy, halo or haloalkyl; or

X is absent; and

Y represents a diazacyclic group of Formula II,



wherein,

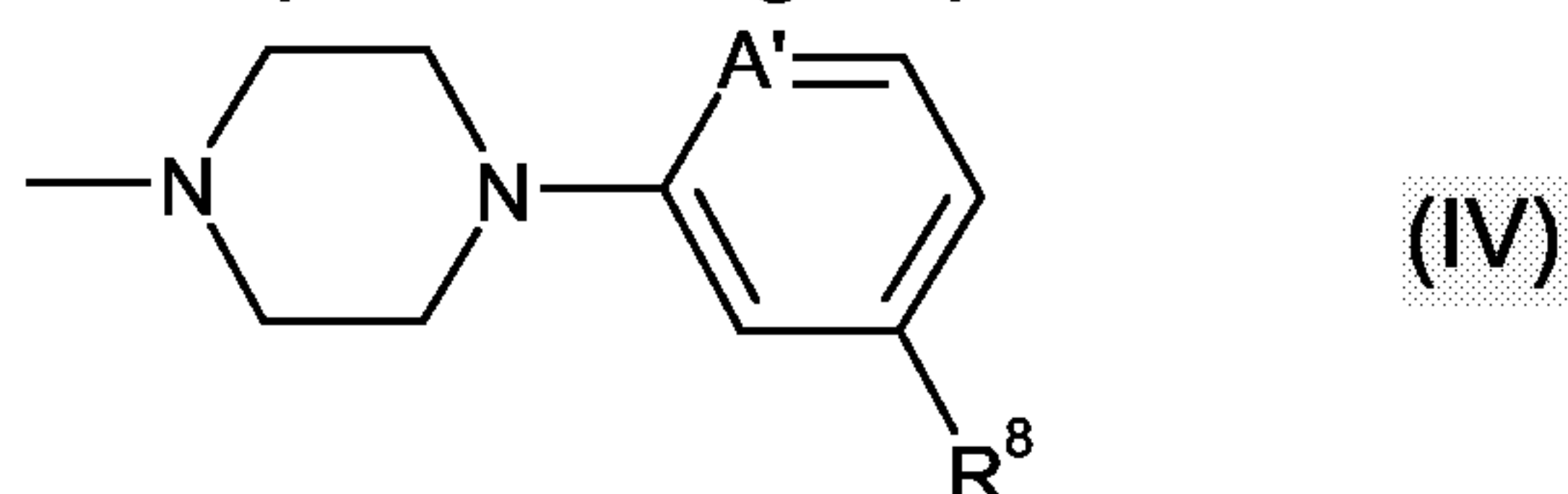
o is 1, 2 or 3;

D represents alkyl, cycloalkyl, cycloalkyl-alkyl, hydroxy, alkoxy, cycloalkoxy, halo, haloalkyl, haloalkoxy, amino, nitro and cyano; and

E represents alkyl, cycloalkyl, cycloalkyl-alkyl, hydroxy, alkoxy, cycloalkoxy, halo, haloalkyl, haloalkoxy, amino, nitro and cyano; or

D and E together with the diazacyclic group form a fused ring system, which fused ring system may optionally be substituted one or more times with substituents selected from the group consisting of alkyl, cycloalkyl, cycloalkyl-alkyl, hydroxy, alkoxy, cycloalkoxy, halo, haloalkyl, haloalkoxy, amino, nitro and cyano;

or Y represents a group of formula IV



wherein A' represents CH or N; and

R^8 represents hydrogen, alkyl, alkoxy, halo or haloalkyl.

In another aspect the invention relates to the use of the aryl piperazine derivative of the invention, or a pharmaceutically acceptable salt thereof, or a prodrug thereof for the manufacture of a pharmaceutical composition.

Viewed from yet another aspect the invention relates to the use of the aryl piperazine derivative of the invention, or a pharmaceutically acceptable salt thereof, or a prodrug thereof, for the manufacture of a pharmaceutical composition for the treatment, prevention or alleviation of a disease or a disorder or a condition of a

mammal, including a human, which disease, disorder or condition is responsive to modulation of the dopamine and serotonin receptors.

In a final aspect the invention provides a method of diagnosis, treatment, prevention or alleviation of a disease or a disorder or a condition of a living animal body, including a human, which disorder, disease or condition is responsive to modulation of the dopamine and serotonin receptors, in particular the D₃, D₂-like and 5-HT₂ receptor subtypes, preferably the dopamine D₃ receptor subtype and/or the D₃/5-HT_{1A} or D₃/5-HT_{2A} receptor subtypes, which method comprises the step of administering to such a living animal body in need thereof, a therapeutically effective amount of the aryl piperazine derivative of the invention, or a pharmaceutically acceptable salt thereof, or a prodrug thereof.

Other objects of the invention will be apparent to the person skilled in the art from the following detailed description and examples.

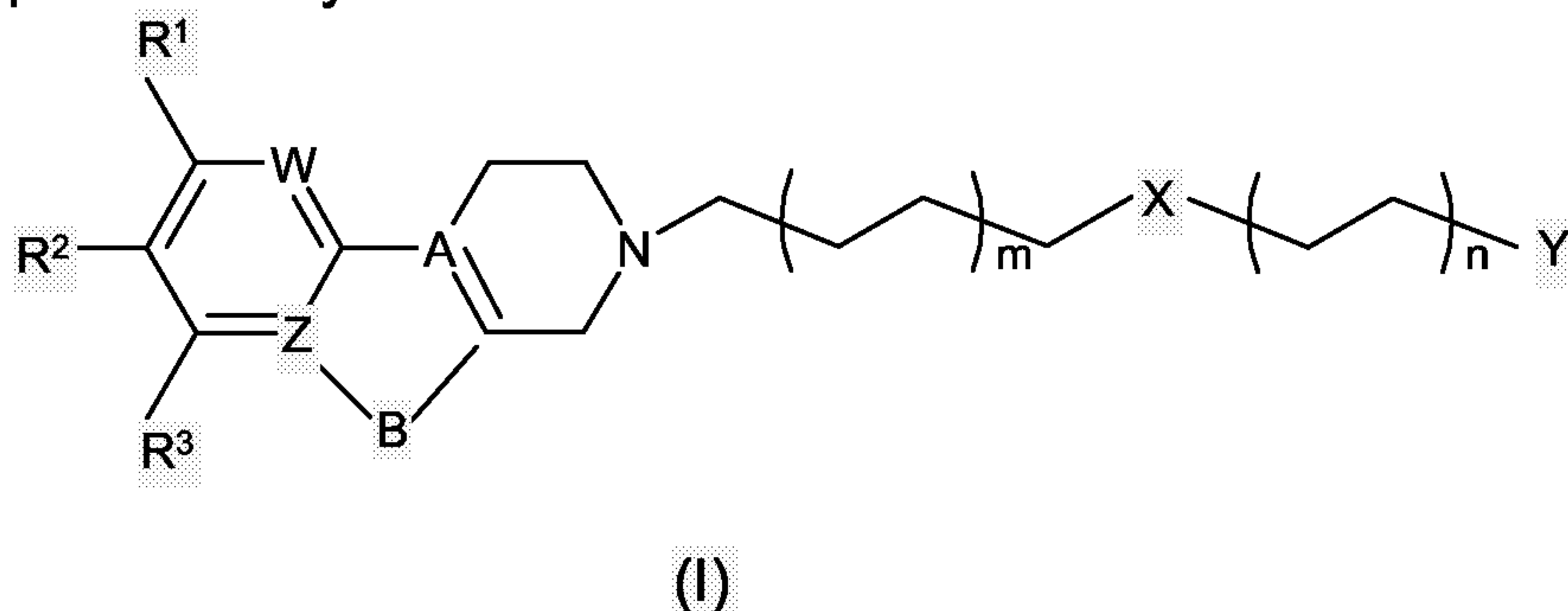
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DETAILED DISCLOSURE OF THE INVENTION

According to the present invention it has now been found that a particular group of aryl piperazine derivatives show a superior biological profile as modulators of dopamine and serotonin receptors.

20

Therefore, in its first aspect, the invention provides novel aryl piperazine derivatives represented by Formula I



an enantiomer thereof or a mixture of its enantiomers, or a pharmaceutically acceptable salt thereof, or an N-oxide thereof, wherein,

25

R¹, R² and R³, independently of one another, represent hydrogen, alkyl, cycloalkyl, cycloalkyl-alkyl, alkenyl, hydroxy, alkoxy, cycloalkoxy, halo, haloalkyl, haloalkoxy, amino, nitro cyano and/or carboxy;

--- represents an optional double bond; if --- represents a single bond, then A represents CH or N; if --- represents a double bond, then A represents C;

30

--B-- may be absent or present: --B-- is absent; and Z represents CH or N; or --B-- is present and represents a methylene bridge (-CH₂-), an ethylene bridge (=CH-), or a bridge -NH-, attached as indicated in the figure; and Z represents C (carbon);

5

W represents CH, N or CR⁴, wherein R⁴ represents represent hydrogen, alkyl, cycloalkyl, cycloalkyl-alkyl, alkenyl, hydroxy, alkoxy, cycloalkoxy, halo, haloalkyl, haloalkoxy, amino, nitro or cyano;

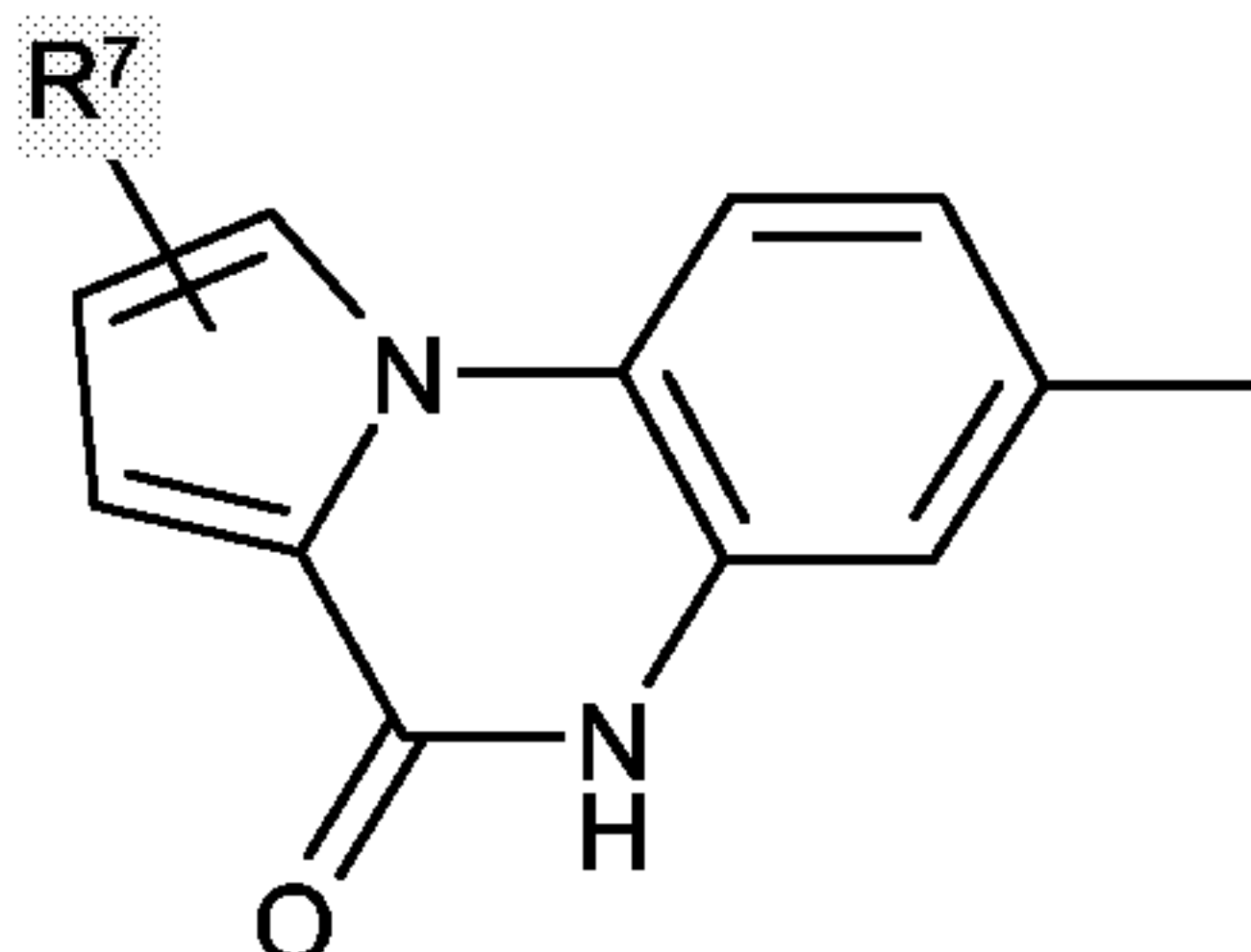
m and n, independently of each other, is 0, 1 or 2; and

5 X may be absent or present:

X is present and represents O, S, NR', CO, SO₂, CH₂, CH₂-O, O-CH₂, CH₂-S, S-CH₂, CH₂-NR', CH₂-CO, CH₂-SO₂, NR'-CO, CO-NR', NR'-SO₂, SO₂-NR', CH₂-CH₂, O-CO, CO-O, O-CH=CH, S-CH=CH, NR'-CH=CH, CO-CH=CH, SO₂-CH=CH, CH₂-O-CH=CH, CH₂-S-CH=CH, CH₂-NR'-CH=CH, CH₂-CO-CH=CH, CONHCH₂CH₂ or
10 CH₂-SO₂-CH=CH, wherein R' represents hydrogen or alkyl; and

Y represents phenyl or an aromatic monocyclic or polycyclic heterocyclic group, which phenyl or heterocyclic group may optionally be substituted one or more times with substituents selected from the group consisting of alkyl, cycloalkyl, cycloalkyl-alkyl, alkenyl, hydroxy, alkoxy, cycloalkoxy, halo, haloalkyl, haloalkoxy, amino, nitro and cyano; or Y represents a hydrogenated heterocyclic group, which
15 hydrogenated heterocyclic group may optionally be substituted one or more times with substituents selected from the group consisting of alkyl, cycloalkyl, cycloalkyl-alkyl, alkenyl, hydroxy, alkoxy, cycloalkoxy, halo, haloalkyl, haloalkoxy, amino, nitro and cyano; or

20 Y represents a group of formula III

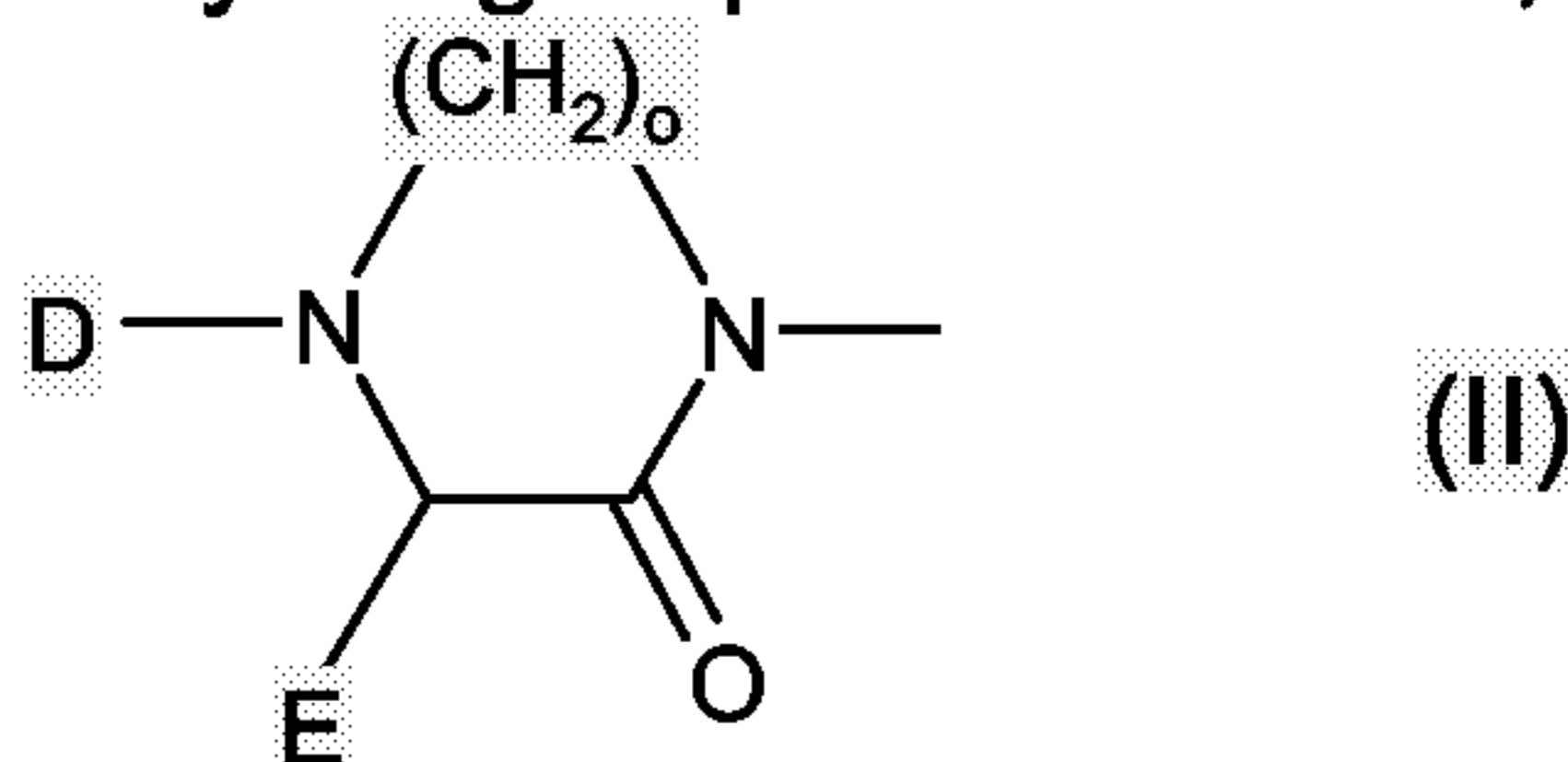


wherein

R⁷ represents hydrogen, alkyl, alkoxy, halo or haloalkyl; or

X is absent; and

25 Y represents a diazacyclic group of Formula II,



wherein,

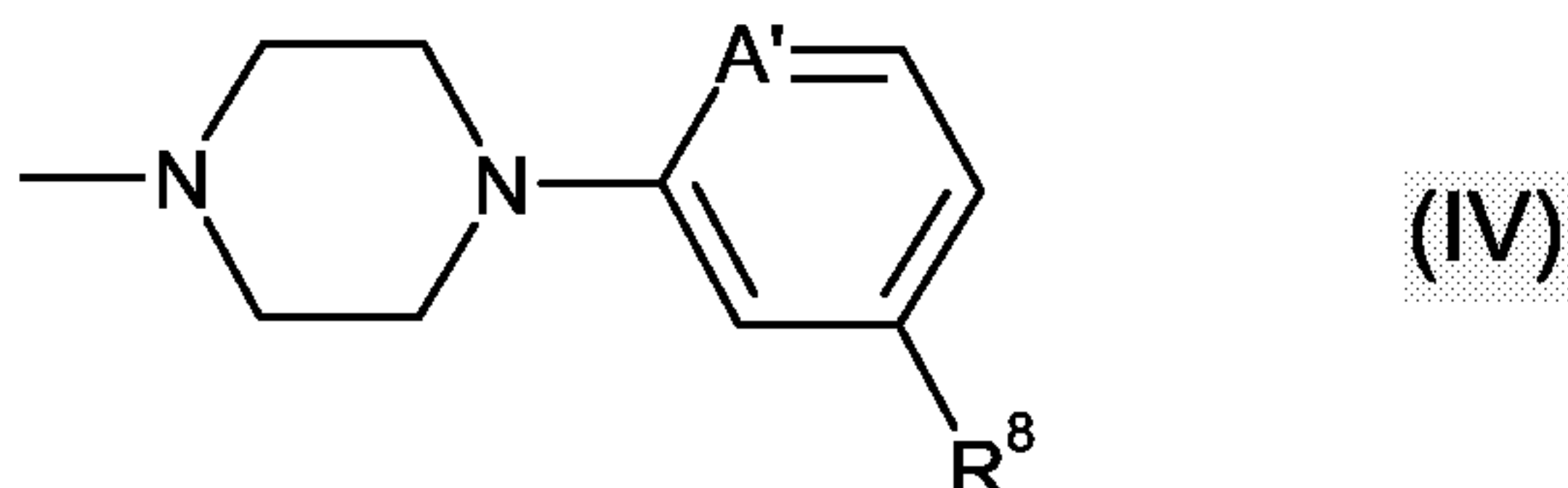
o is 1, 2 or 3;

D represents alkyl, cycloalkyl, cycloalkyl-alkyl, hydroxy, alkoxy, cycloalkoxy, halo, haloalkyl, haloalkoxy, amino, nitro and cyano; and
30

E represents alkyl, cycloalkyl, cycloalkyl-alkyl, hydroxy, alkoxy, cycloalkoxy, halo, haloalkyl, haloalkoxy, amino, nitro and cyano; or

D and E together with the diazacyclic group form a fused ring system, which fused ring system may optionally be substituted one or more times with substituents
5 selected from the group consisting of alkyl, cycloalkyl, cycloalkyl-alkyl, hydroxy, alkoxy, cycloalkoxy, halo, haloalkyl, haloalkoxy, amino, nitro and cyano;

or Y represents a group of formula IV



wherein A' represents CH or N; and

10 R^8 represents hydrogen, alkyl, alkoxy, halo or haloalkyl.

In a more preferred embodiment the aryl piperazine derivative of the invention is a compound of Formula I, wherein

R^1 , R^2 and R^3 , independently of one another, represent hydrogen, alkyl, cycloalkyl, cycloalkyl-alkyl, alkenyl, hydroxy, alkoxy, cycloalkoxy, halo, haloalkyl,
15 haloalkoxy, amino, nitro and/or cyano, carboxy;

---- represents an optional double bond; if ---- represents a single bond, then A represents CH or N; if ---- represents a double bond, then A represents C (carbon);

--B-- may be absent or present: --B-- is absent; and Z represents CH or N; or --B-- is present and represents a methylene bridge (-CH₂-), an ethylene bridge
20 (=CH-), or a bridge -NH-, attached as indicated in the figure; and

Z represents C (carbon);

W represents CH, N or CR⁴, wherein R⁴ represents represent hydrogen, alkyl, cycloalkyl, cycloalkyl-alkyl, alkenyl, hydroxy, alkoxy, cycloalkoxy, halo, haloalkyl, haloalkoxy, amino, nitro or cyano;

25 m and n, independently of each other, is 0, 1 or 2; and

X may be absent or present:

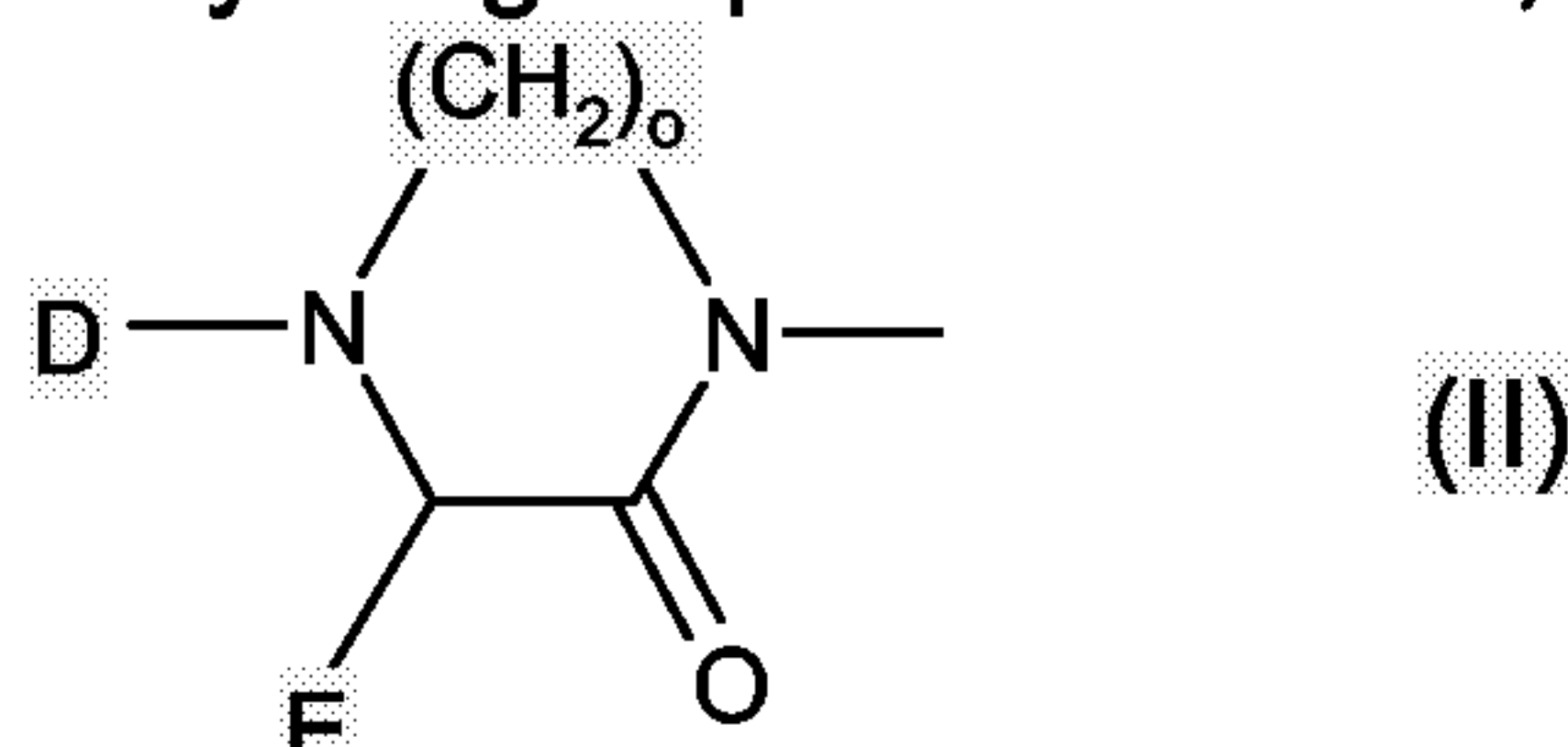
X is present and represents O, S, NR', CO, SO₂, CH₂, CH₂-O, O-CH₂, CH₂-S, S-CH₂, CH₂-NR', CH₂-CO, CH₂-SO₂, NR'-CO, CO-NR', NR'-SO₂, SO₂-NR', CH₂-CH₂, O-CO, CO-O, O-CH=CH, S-CH=CH, NR'-CH=CH, CO-CH=CH, SO₂-CH=CH,
30 CH₂-O-CH=CH, CH₂-S-CH=CH, CH₂-NR'-CH=CH, CH₂-CO-CH=CH, CONHCH₂CH₂ or CH₂-SO₂-CH=CH, wherein R' represents hydrogen or alkyl; and

Y represents phenyl or an aromatic monocyclic or polycyclic heterocyclic group, which phenyl or heterocyclic group may optionally be substituted one or more times with substituents selected from the group consisting of alkyl, cycloalkyl,
35 cycloalkyl-alkyl, alkenyl, hydroxy, alkoxy, cycloalkoxy, halo, haloalkyl, haloalkoxy, amino, nitro and cyano; or

Y represents a hydrogenated heterocyclic group, which hydrogenated heterocyclic group may optionally be substituted one or more times with substituents selected from the group consisting of alkyl, cycloalkyl, cycloalkyl-alkyl, alkenyl, hydroxy, alkoxy, cycloalkoxy, halo, haloalkyl, haloalkoxy, amino, nitro and cyano; or

5 X is absent; and

Y represents a diazacyclic group of Formula II,



wherein,

o is 1, 2 or 3;

10 D represents alkyl, cycloalkyl, cycloalkyl-alkyl, hydroxy, alkoxy, cycloalkoxy, halo, haloalkyl, haloalkoxy, amino, nitro and cyano; and

E represents alkyl, cycloalkyl, cycloalkyl-alkyl, hydroxy, alkoxy, cycloalkoxy, halo, haloalkyl, haloalkoxy, amino, nitro and cyano; or

D and E together with the diazacyclic group form a fused ring system, which
15 fused ring system may optionally be substituted one or more times with substituents selected from the group consisting of alkyl, cycloalkyl, cycloalkyl-alkyl, hydroxy, alkoxy, cycloalkoxy, halo, haloalkyl, haloalkoxy, amino, nitro and cyano.

In another preferred embodiment the aryl piperazine derivative of the invention is a compound of Formula I, wherein --- represents a single bond, and A
20 represents CH or N.

In a more preferred embodiment --- represents a single bond, and A represents N.

In a most preferred embodiment == represents a double bond, and A represents C (carbon).

25 In a third preferred embodiment the aryl piperazine derivative of the invention is a compound of Formula I, wherein W represents CH, N or CR⁴, wherein R⁴ represents represent hydrogen, alkyl, cycloalkyl, cycloalkyl-alkyl, alkenyl, hydroxy, alkoxy, cycloalkoxy, halo, haloalkyl, haloalkoxy, amino, nitro or cyano.

In a more preferred embodiment W represents CR⁴, wherein R⁴ represents
30 represent hydrogen, alkyl, in particular methyl, alkoxy, in particular methoxy or halo, in particular chloro.

In an even more preferred embodiment W represents CR⁴, wherein R⁴ represents represent hydrogen, methyl, ethyl, methoxy, fluoro or chloro.

In a most preferred embodiment W represents CH or N.

In a fourth preferred embodiment the aryl piperazine derivative of the invention is a compound of Formula I, wherein --B-- is absent, and Z represents CH or N.

In a more preferred embodiment --B-- is present and represents a
5 methylene bridge (-CH₂-), an ethylene bridge (=CH-), or a bridge -NH-, attached as indicated in the figure; and Z represents C (carbon).

In an even more preferred embodiment --B-- is present and represents a methylene bridge (-CH₂-), an ethylene bridge (=CH-), or a bridge -NH-, attached as indicated in the figure; and Z represents C (carbon); and W represents CR⁴, wherein
10 R⁴ represents represent hydrogen, alkyl, in particular methyl, alkoxy, in particular methoxy, halo, in particular chloro, haloalkyl, haloalkoxy, amino, nitro or cyano.

In a fourth preferred embodiment the aryl piperazine derivative of the invention is a compound of Formula I, wherein W represents CR⁴, wherein R⁴ represents represent hydrogen, alkyl, in particular methyl, alkoxy, in particular methoxy
15 or halo, in particular chloro.

In a more preferred embodiment W represents CR⁴, wherein R⁴ represents represent hydrogen, methyl, ethyl, methoxy, fluoro or chloro.

In an even more preferred embodiment W represents CR⁴, wherein R⁴ represents represent hydrogen, alkyl or alkoxy [methoxy].

20 In a fifth preferred embodiment the aryl piperazine derivative of the invention is a compound of Formula I, wherein m and n, independently of each other, is 0, 1 or 2.

In a more preferred embodiment m is 1 or 2; and n is 0 or 2.

In an even more preferred embodiment m is 1; and n is 0.

In another preferred embodiment m is 1; and n is 1.

25 In a third preferred embodiment m is 1; and n is 2.

In a still more preferred embodiment m is 2; and n is 0.

In a sixth preferred embodiment the aryl piperazine derivative of the invention is a compound of Formula I, wherein R¹, R² and R³, independently of one another, represent hydrogen, alkyl, in particular methyl, ethyl or propyl, cycloalkyl,
30 cycloalkyl-alkyl, alkenyl, hydroxy, alkoxy, in particular methoxy or ethoxy, cycloalkoxy, halo, in particular fluoro, chloro or bromo, haloalkyl, in particular trifluoromethyl, haloalkoxy, amino, nitro cyano and/or carboxy;

In a more preferred embodiment R¹, R² and R³ represent hydrogen.

In an even more preferred embodiment R¹ represents alkyl, in particular
35 methyl, ethyl or propyl, cycloalkyl, cycloalkyl-alkyl, hydroxy, alkoxy, in particular methoxy or ethoxy, cycloalkoxy, halo, in particular fluoro, chloro or bromo, haloalkyl, in particular trifluoromethyl, haloalkoxy, amino, nitro, cyano or carboxy; and R² and R³ represent hydrogen.

In a still more preferred embodiment R^1 represents alkyl, in particular methyl, ethyl or propyl, cycloalkyl, cycloalkyl-alkyl, hydroxy, alkoxy, in particular methoxy or ethoxy, cycloalkoxy, halo, in particular fluoro, chloro or bromo, haloalkyl, in particular trifluoromethyl, haloalkoxy, amino, nitro or cyano; and R^2 and R^3 represent
5 hydrogen.

In a yet more preferred embodiment R^1 represents alkyl, in particular methyl, ethyl or propyl, cycloalkyl, cycloalkyl-alkyl, hydroxy, alkoxy, in particular methoxy or ethoxy, cycloalkoxy, halo, in particular fluoro, chloro or bromo, haloalkyl, in particular trifluoromethyl, haloalkoxy, amino, nitro or cyano.

10 In a further preferred embodiment R^1 represents alkyl, in particular methyl, ethyl or propyl, alkoxy, in particular methoxy or ethoxy, halo, in particular fluoro, chloro or bromo, haloalkyl, in particular trifluoromethyl, haloalkoxy, amino, nitro or cyano.

In a still further preferred embodiment R^1 represents methyl, ethyl, methoxy, chloro, trifluoromethyl, trifluoromethoxy or cyano.

15

In a still further preferred embodiment R^1 represents methyl, ethyl, methoxy, chloro, trifluoromethyl, trifluoromethoxy, cyano or carboxy.

In another preferred embodiment R^2 represents alkyl, cycloalkyl, cycloalkyl-alkyl, hydroxy, alkoxy, cycloalkoxy, halo, in particular chloro, haloalkyl, haloalkoxy,
20 amino, nitro or cyano; and R^1 and R^3 represent hydrogen.

In a more preferred embodiment R^2 represents alkyl, cycloalkyl, alkoxy, halo, trifluoromethyl, trifluoromethoxy, amino, nitro or cyano.

In an even more preferred embodiment R^2 represents methyl, ethyl, methoxy, chloro, trifluoromethyl, trifluoromethoxy or cyano.

25

In a seventh preferred embodiment the aryl piperazine derivative of the invention is a compound of Formula I, wherein X is present and represents O, S, NR' , CO, SO_2 , CH_2 , CH_2-O , $O-CH_2$, CH_2-S , $S-CH_2$, CH_2-NR' , CH_2-CO , CH_2-SO_2 , $NR'-CO$, $CO-NR'$, CH_2-CH_2 , $O-CO$, $CO-O$, $O-CH=CH$, $S-CH=CH$, $NR'-CH=CH$, $CO-CH=CH$, $SO_2-CH=CH$, $CH_2-O-CH=CH$, $CH_2-S-CH=CH$, $CH_2-NR'-CH=CH$, $CH_2-CO-CH=CH$,
30 $CONHCH_2CH_2$ or $CH_2-SO_2-CH=CH$, wherein R' represents hydrogen or alkyl.

In a more preferred embodiment X represents O, CH_2-O , $O-CH_2$, CH_2-S , $S-CH_2$, CH_2-NR' , CH_2-CO , CH_2-SO_2 , $NR'-CO$, $CO-NR'$, $NR'-SO_2$, SO_2-NR' , $O-CO$, or $CH_2-O-CH=CH$; wherein R' represents hydrogen or alkyl.

In an even more preferred embodiment X represents O, CH_2-O , $O-CH_2$,
35 CH_2-S , $S-CH_2$, CH_2-NR' , CH_2-CO , CH_2-SO_2 , $NR'-CO$, $CO-NR'$, $O-CO$, or $CH_2-O-CH=CH$; wherein R' represents hydrogen or alkyl.

In a still more preferred embodiment X represents O, CH_2-O , $NR'-CO$, $CO-NR'$, $NR'-SO_2$ or $O-CO$; wherein R' represents hydrogen or alkyl.

In a yet more preferred embodiment X represents O, CH₂-O, NR'-CO, CO-NR' or O-CO; wherein R' represents hydrogen or alkyl.

In a most preferred embodiment X represents O, CH₂-O, NH-CO, CO-NH or O-CO.

5 In an eight preferred embodiment the aryl piperazine derivative of the invention is a compound of Formula I, wherein Y represents phenyl or an aromatic monocyclic or polycyclic heterocyclic group, in particular pyridyl, benzo[b]furanyl, indolyl, quinolinyll or isoquinolinyll, which phenyl or heterocyclic group may optionally be substituted one or more times with substituents selected from the group consisting of
10 alkyl, in particular methyl, cycloalkyl, cycloalkyl-alkyl, alkenyl, hydroxy, alkoxy, cycloalkoxy, halo, in particular chloro, haloalkyl, haloalkoxy, amino, nitro and cyano; or Y represents a hydrogenated heterocyclic group, in particular tetrahydroquinolinyll, which hydrogenated heterocyclic group may optionally be substituted one or more times with substituents selected from the group consisting of alkyl, cycloalkyl,
15 cycloalkyl-alkyl, alkenyl, hydroxy, alkoxy, cycloalkoxy, halo, haloalkyl, haloalkoxy, amino, nitro and cyano.

In a more preferred embodiment Y represents phenyl, which phenyl group may optionally be substituted one or more times with substituents selected from the group consisting of alkyl, cycloalkyl, cycloalkyl-alkyl, hydroxy, alkoxy, cycloalkoxy, halo,
20 in particular chloro, haloalkyl, haloalkoxy, amino, nitro and cyano.

In an even more preferred embodiment Y represents phenyl, optionally substituted one or two times with alkyl, alkoxy, chloro, trifluoromethyl and/or trifluoromethoxy.

In a most preferred embodiment Y represents phenyl.

25 In a ninth preferred embodiment the aryl piperazine derivative of the invention is a compound of Formula I, wherein Y represents an aromatic monocyclic heterocyclic group selected from furanyl, thienyl, pyrrolyl, oxazolyl, imidazolyl, pyridyl, pyridazinyl and pyrimidinyl, which aromatic monocyclic heterocyclic group may optionally be substituted one or more times with substituents selected from the group
30 consisting of alkyl, in particular methyl, cycloalkyl, cycloalkyl-alkyl, alkenyl, hydroxy, alkoxy, cycloalkoxy, halo, haloalkyl, haloalkoxy, amino, nitro and cyano.

In a more preferred embodiment Y represents furanyl, thienyl or pyridyl, which aromatic monocyclic heterocyclic group may optionally be substituted one or two times with substituents selected from the group consisting of alkyl, in particular methyl,
35 alkoxy, chloro, trifluoromethyl and trifluoromethoxy.

In a most preferred embodiment Y represents pyridyl, optionally substituted with methyl, ethyl, methoxy, chloro or trifluoromethyl.

In a tenth preferred embodiment the aryl piperazine derivative of the invention is a compound of Formula I, wherein Y represents an aromatic bicyclic heterocyclic group selected from indolyl, isoindolyl, benzo[b]furanyl, benzo[b]thienyl, benzimidazolyl, benzthiazolyl, quinolinyl and isoquinolinyl, which aromatic bicyclic
5 heterocyclic group may optionally be substituted one or two times with substituents selected from the group consisting of alkyl, in particular methyl, cycloalkyl, cycloalkyl-alkyl, hydroxy, alkoxy, cycloalkoxy, halo, in particular chloro, haloalkyl, haloalkoxy, amino, nitro and cyano.

In a more preferred embodiment Y represents indolyl, in particular indol-2-yl
10 or indol-3-yl; benzo[b]furanyl, in particular benzo[b]furan-2-yl or benzo[b]furan-3-yl; benzo[b]thienyl, in particular benzo[b]thien-2-yl or benzo[b]thien-3-yl; quinolinyl in particular quinolin-2-yl, quinolin-3-yl or quinolin-4-yl; or isoquinolinyl, in particular isoquinolin-1-yl, isoquinolin-3-yl, or isoquinolin-4-yl; which aromatic bicyclic heterocyclic group may optionally be substituted one or two times with substituents
15 selected from alkyl, in particular methyl, cycloalkyl, cycloalkyl-alkyl, hydroxy, alkoxy, cycloalkoxy, halo, in particular chloro, haloalkyl, haloalkoxy, amino, nitro and cyano.

In an even more preferred embodiment Y represents indolyl, in particular indol-2-yl or indol-3-yl; benzo[b]furanyl, in particular benzo[b]furan-2-yl or benzo[b]furan-3-yl; quinolinyl, in particular quinolin-2-yl, quinolin-3-yl or quinolin-4-yl; or
20 isoquinolinyl, in particular isoquinolin-1-yl, isoquinolin-3-yl, or isoquinolin-4-yl; which benzo[b]furanyl or isoquinolinyl may optionally be substituted one or two times with substituents selected from alkyl, in particular methyl, hydroxy, alkoxy, chloro, trifluoromethyl, trifluoromethoxy, amino, nitro and cyano.

In a still more preferred embodiment Y represents indol-2-yl, benzo[b]furan-
25 2-yl or isoquinolin-3-yl; which benzo[b]furanyl or isoquinolinyl may optionally be substituted one or two times with substituents selected from alkyl, in particular methyl, hydroxy, alkoxy, chloro, trifluoromethyl, trifluoromethoxy, amino, nitro and cyano.

In a yet more preferred embodiment Y represents indol-2-yl, benzo[b]furan-
2-yl or isoquinolin-3-yl; which benzo[b]furanyl or isoquinolinyl may optionally be
30 substituted with alkyl, in particular methyl, halo, in particular chloro, or trifluoromethyl.

In a further preferred embodiment Y represents indol-2-yl, benzo[b]furan-2-yl or isoquinolin-3-yl; which benzo[b]furanyl or isoquinolinyl may optionally be substituted with methyl, ethyl, fluoro, chloro or trifluoromethyl.

In a most preferred embodiment Y represents indolyl, benzo[b]furanyl, or
35 isoquinolinyl.

In an eleventh preferred embodiment the aryl piperazine derivative of the invention is a compound of Formula I, wherein Y represents a hydrogenated heterocyclic group, in particular tetrahydroquinolinyl, which hydrogenated heterocyclic

group may optionally be substituted one or more times with substituents selected from the group consisting of alkyl, cycloalkyl, cycloalkyl-alkyl, alkenyl, hydroxy, alkoxy, cycloalkoxy, halo, haloalkyl, haloalkoxy, amino, nitro and cyano.

In a more preferred embodiment Y represents tetrahydroquinoliny or
 5 tetrahydroisoquinoliny, which heterocyclic group may optionally be substituted one or two times with substituents selected from the group consisting of alkyl, cycloalkyl, cycloalkyl-alkyl, alkenyl, hydroxy, alkoxy, cycloalkoxy, halo, haloalkyl, haloalkoxy, amino, nitro and cyano.

In a most preferred embodiment Y represents tetrahydroquinoliny or
 10 tetrahydroisoquinoliny.

In another preferred embodiment X represents O, CH₂-O, NH-CO, CO-NH, NR'-SO₂ or CO-O; and Y represents phenyl, methyl-phenyl, pyridyl, indolyl, methyl-indolyl, benzo[b]furanyl, tetrahydroquinoliny, isoquinoliny, or tetrahydroisoquinoliny.

In a more preferred embodiment X represents CH₂-O, NH-CO, CO-NH or
 15 CO-O; and Y represents indolyl, benzo[b]furanyl, tetrahydroquinoliny, isoquinoliny, or tetrahydroisoquinoliny.

In an even more preferred embodiment X represents O, CH₂-O, NH-CO, CO-NH, NR'-SO₂ or CO-O; Y represents phenyl, methyl-phenyl, pyridyl, methyl-pyridyl, indolyl, methyl-indolyl, benzo[b]furanyl, tetrahydroquinoliny, isoquinoliny, or
 20 tetrahydroisoquinoliny; R¹ represents alkyl, cycloalkyl, cycloalkyl-alkyl, hydroxy, alkoxy, cycloalkoxy, halo, haloalkyl, haloalkoxy, amino, nitro or cyano; and R² and R³ represent hydrogen.

In a yet more preferred embodiment X represents CH₂-O, NH-CO, CO-NH or CO-O; Y represents indolyl, benzo[b]furanyl, tetrahydroquinoliny, isoquinoliny, or
 25 tetrahydroisoquinoliny; R¹ represents alkyl, cycloalkyl, cycloalkyl-alkyl, hydroxy, alkoxy, cycloalkoxy, halo, haloalkyl, haloalkoxy, amino, nitro or cyano; and R² and R³ represent hydrogen.

In a most preferred embodiment the aryl piperazine derivative of the invention is

30 *N*-[4-[4-(3-Trifluoromethylphenyl)piperazin-1-yl]butyl]indole-2-carboxamide;

N-[2-(1*H*-Indol-3-yl)ethyl]-3-(4-*m*-tolylpiperazin-1-yl)propanamide;

N-[2-(1*H*-Indol-3-yl)ethyl]-3-[4-(3-methoxyphenyl)piperazin-1-yl]propanamide;

35 Benzo[b]furan-2-carboxylic acid {4-[4-(3-methoxy-phenyl)-piperazin-1-yl]-butyl}-amide;

N-[4-[4-(3-Cyanophenyl)piperazin-1-yl]butyl]benzo[b]furan-2-carboxamide;

Benzo[b]furan-2-carboxylic acid {4-[4-(3-chloro-phenyl)-piperazin-1-yl]-butyl}-amide;

Benzo[b]furan-2-carboxylic acid {4-[4-(3-carboxy-phenyl)-piperazin-1-yl]-butyl}-amide;

N-[4-[4-(*m*-Tolyl)piperazin-1-yl]butyl]benzo[b]furan-2-carboxamide;

Isoquinoline-3-carboxylic acid {4-[4-(3-cyano-phenyl)-piperazin-1-yl]-butyl}-
5 amide;

N-[4-[4-(3-Chlorophenyl)piperazin-1-yl]butyl]isoquinoline-3-carboxamide;

N-[4-[4-(*m*-Tolyl)piperazin-1-yl]butyl]isoquinoline-3-carboxamide;

N-[4-[4-(3-Methoxyphenyl)piperazin-1-yl]butyl]isoquinoline-3-carboxamide;

3-[5-[4-(3-Chlorophenyl)piperazin-1-yl]pentyloxy]isoquinoline;

10 3-{5-[4-(3-Methoxy-phenyl)-piperazin-1-yl]-pentyloxy}-isoquinoline;

3-[5-(4-*m*-Tolylpiperazin-1-yl)pentyloxy]isoquinoline;

3-{5-[4-(3-Cyano-phenyl)-piperazin-1-yl]-pentyloxy}-isoquinoline;

N-[4-(1,2,3,4-Tetrahydro-5-methoxy- β -carbolin-2-yl)butyl]isoquinoline-3-
carboxamide;

15 N-[4-(3,4-Dihydro-6-methoxypyrazino[1,2-*a*]indol-2(1*H*)-yl)butyl]isoquinoline-
3-carboxamide;

N-[4-[4-(Pyridin-2-yl)piperazin-1-yl]butyl]isoquinoline-3-carboxamide;

1,2,3,4-Tetrahydro-quinoline-2-carboxylic acid [4-(4-phenyl-piperazin-1-yl)-
butyl]-amide;

20 (*S*)-(-)-N-[4-[4-(*m*-Tolyl)piperazin-1-yl]butyl]-1,2,3,4-tetrahydroisoquinoline-2-
carboxamide;

(*R*)-(+)-N-[4-[4-(*m*-Tolyl)piperazin-1-yl]butyl]-1,2,3,4-tetrahydroisoquinoline-
2-carboxamide;

1*H*-Indole-2-carboxylic acid {4-[4-(2,4-dichloro-phenyl)-piperazin-1-yl]-butyl}-
25 amide;

5-Chloro-1*H*-indole-2-carboxylic acid {4-[4-(2,4-dichloro-phenyl)-piperazin-1-
yl]-butyl}-amide;

Isoquinoline-3-carboxylic acid {4-[4-(2,3-dichloro-phenyl)-piperazin-1-yl]-
butyl}-amide;

30 3-{4-[4-(2,3-Dichloro-phenyl)-piperazin-1-yl]-butoxy}-isoquinoline;

3-{5-[4-(2,3-Dichloro-phenyl)-piperazin-1-yl]-pentyloxy}-isoquinoline;

4-[4-(2,3-Dichlorophenyl)piperazin-1-yl]butyl 1*H*-indole-2-carboxylate;

N-(4-(4-(Phenylpiperazin-1-yl)butyl)benzo[b]furan-2-carboxamide;

35 Benzo[b]furan-2-carboxylic acid {4-[4-(2,3-dimethyl-phenyl)-piperazin-1-yl]-
butyl}-amide;

N-(4-(4-(3-Methoxyphenyl)piperazin-1-yl)butyl)benzo[b]furan-2-
carboxamide;

N-(4-(4-(6-Methylpyridin-2-yl)piperazin-1-yl)butyl)isoquinoline-3-carboxamide;

N-(4-(4-Phenylpiperazin-1-yl)butyl)isoquinoline-3-carboxamide;

N-(4-(4-(6-Methylpyridin-2-yl)piperazin-1-yl)butyl)benzo[b]furan-2-

5 carboxamide;

N-(4-(4-Phenylpiperazin-1-yl)butyl)quinoline-2-carboxamide;

N-(4-(4-m-Tolylpiperazin-1-yl)butyl)quinoline-2-carboxamide;

N-(4-(4-(3-Methoxyphenyl)piperazin-1-yl)butyl)-1-methyl-1H-indole-2-carboxamide;

10 N-(4-(4-(3-Methoxyphenyl)piperazin-1-yl)butyl)-1H-indole-3-carboxamide;

(S)-1,2,3,4-Tetrahydro-N-(4-(4-phenylpiperazin-1-yl)butyl)quinoline-2-carboxamide;

N-(4-(4-m-Tolylpiperazin-1-yl)butyl)picolinamide;

N-(4-(4-(Quinolin-3-yl)piperazin-1-yl)butyl)isoquinoline-3-carboxamide;

15 N-(4-(4-(3-Methoxyphenyl)piperazin-1-yl)butyl)-6-methylpyridine-2-carboxamide;

N-(4-(4-(3-Methoxyphenyl)piperazin-1-yl)butyl)quinoline-3-carboxamide;

N-(4-(4-(Pyridin-2-yl)piperazin-1-yl)butyl)quinoline-3-carboxamide;

N-(4-(4-Phenylpiperazin-1-yl)butyl)picolinamide;

20 N-(4-(4-(3-Methoxyphenyl)piperazin-1-yl)butyl)picolinamide;

N-(4-(4-(3-Methoxyphenyl)piperazin-1-yl)butyl)benzamide;

N-(4-(4-m-Tolylpiperazin-1-yl)butyl)benzamide;

N-(4-(4-Phenylpiperazin-1-yl)butyl)nicotinamide;

N-(4-(4-(6-Methylpyridin-2-yl)piperazin-1-yl)butyl)benzamide;

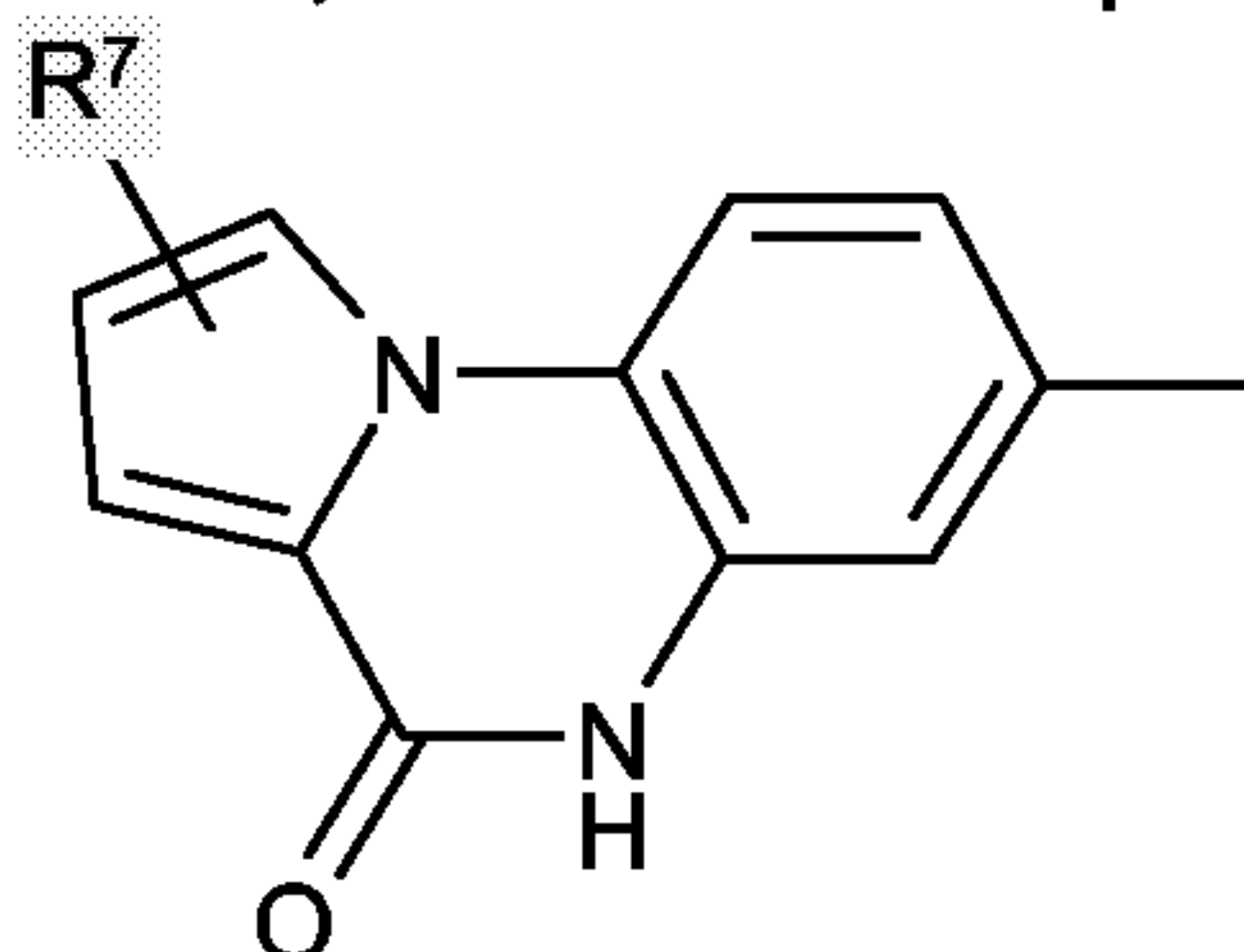
25 N-(4-(4-(6-Methoxypyridin-2-yl)piperazin-1-yl)butyl)benzamide;

N-(4-(4-(6-Methoxypyridin-2-yl)piperazin-1-yl)butyl)picolinamide; or

N-(4-(4-(6-Methylpyridin-2-yl)piperazin-1-yl)butyl)picolinamide;

or a pharmaceutically acceptable salt thereof.

In a twelfth preferred embodiment the aryl piperazine derivative of the invention is a compound of Formula I, wherein Y represents a group of formula III



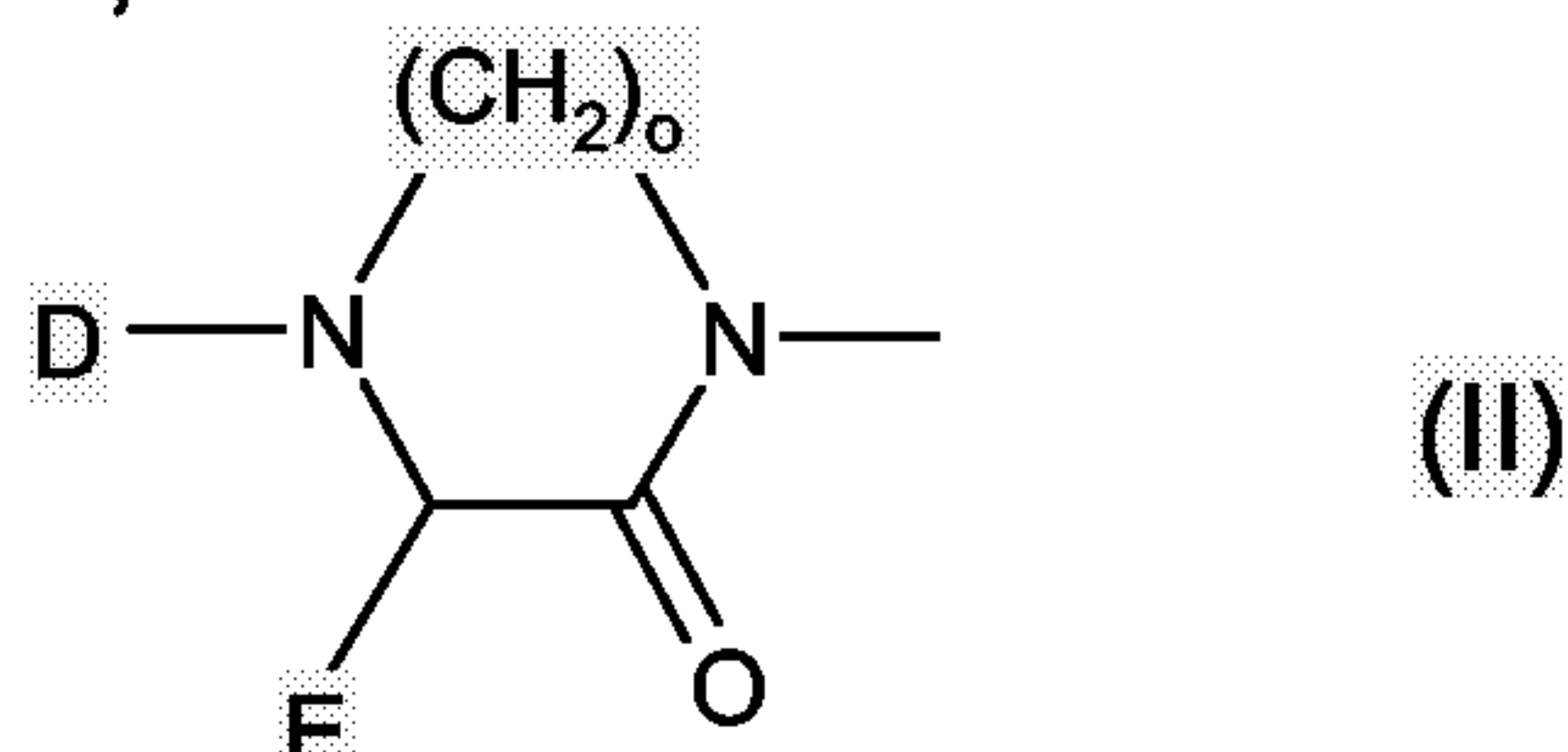
wherein R⁷ represents hydrogen, alkyl, alkoxy, halo or haloalkyl.

In a most preferred embodiment the aryl piperazine derivative of the invention is

7-[4-[4-(2,3-Dichloro-phenyl)-piperazin-1-yl]-butoxy]-pyrrolo[1,2-a]quinoxalin-4(5H)-one; 7-(5-(4-Phenylpiperazin-1-yl)pentyl)pyrrolo[1,2-a]quinoxalin-4(5H)-one;
or

7-(4-(4-Phenylpiperazin-1-yl)butoxy)pyrrolo[1,2-a]quinoxalin-4(5H)-one;
or a pharmaceutically acceptable salt thereof.

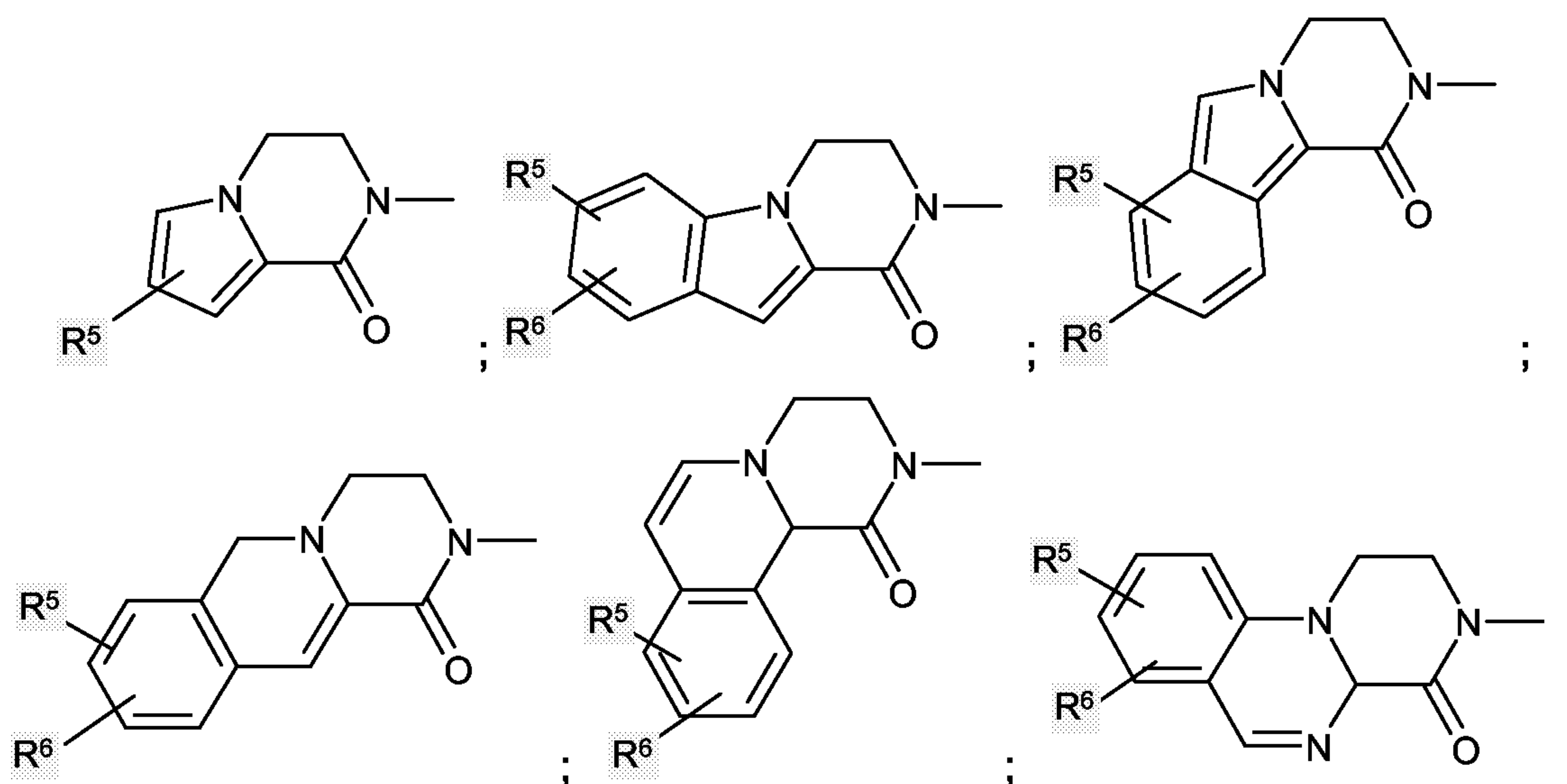
In a thirteenth preferred embodiment the aryl piperazine derivative of the invention is a compound of Formula I, wherein X is absent; and Y represents a diazacyclic group of Formula II,



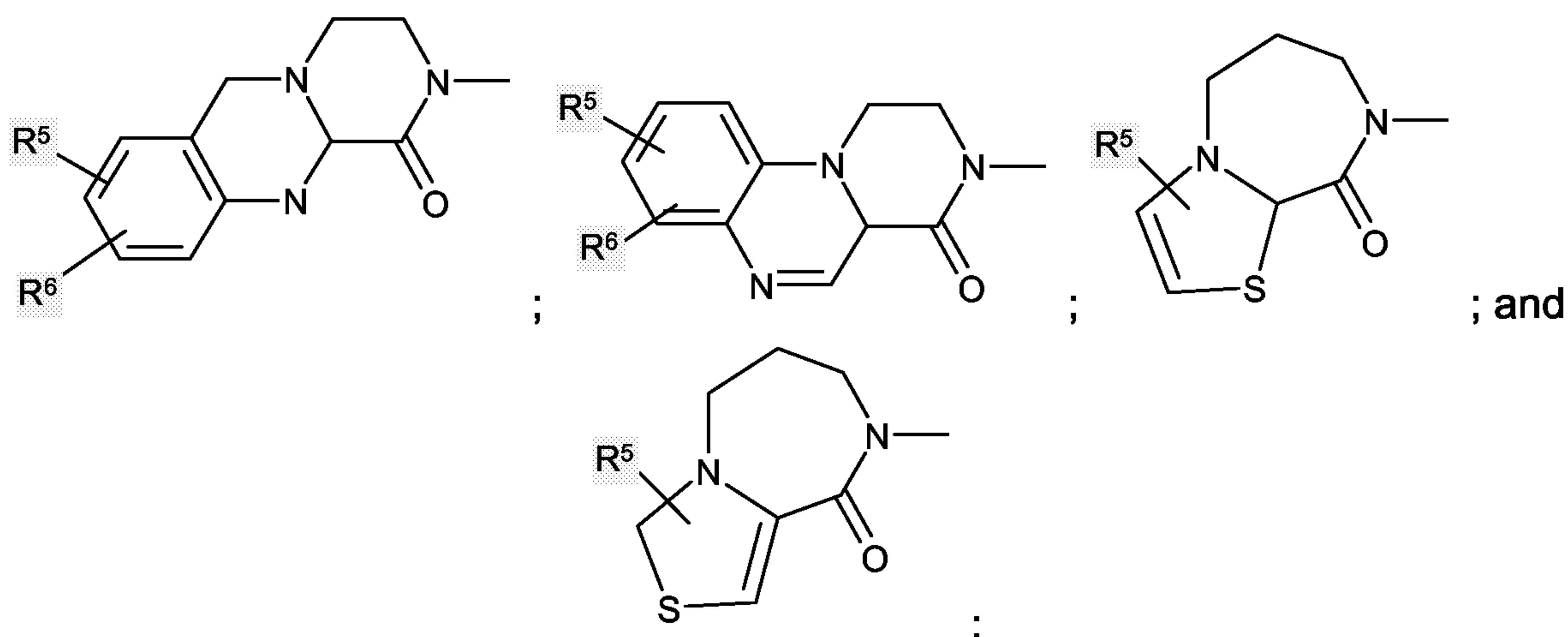
wherein, o is 1, 2 or 3;

D represents alkyl, cycloalkyl, cycloalkyl-alkyl, hydroxy, alkoxy, cycloalkoxy, halo, haloalkyl, haloalkoxy, amino, nitro and cyano; and E represents alkyl, cycloalkyl, cycloalkyl-alkyl, hydroxy, alkoxy, cycloalkoxy, halo, haloalkyl, haloalkoxy, amino, nitro and cyano; or D and E together with the diazacyclic group form a fused ring system, which fused ring system may optionally be substituted one or more times with substituents selected from the group consisting of alkyl, cycloalkyl, cycloalkyl-alkyl, hydroxy, alkoxy, cycloalkoxy, halo, haloalkyl, haloalkoxy, amino, nitro and cyano.

In a more preferred embodiment Y represents a bicyclic heterocyclic group (i.e. fused ring system) selected from the following group:

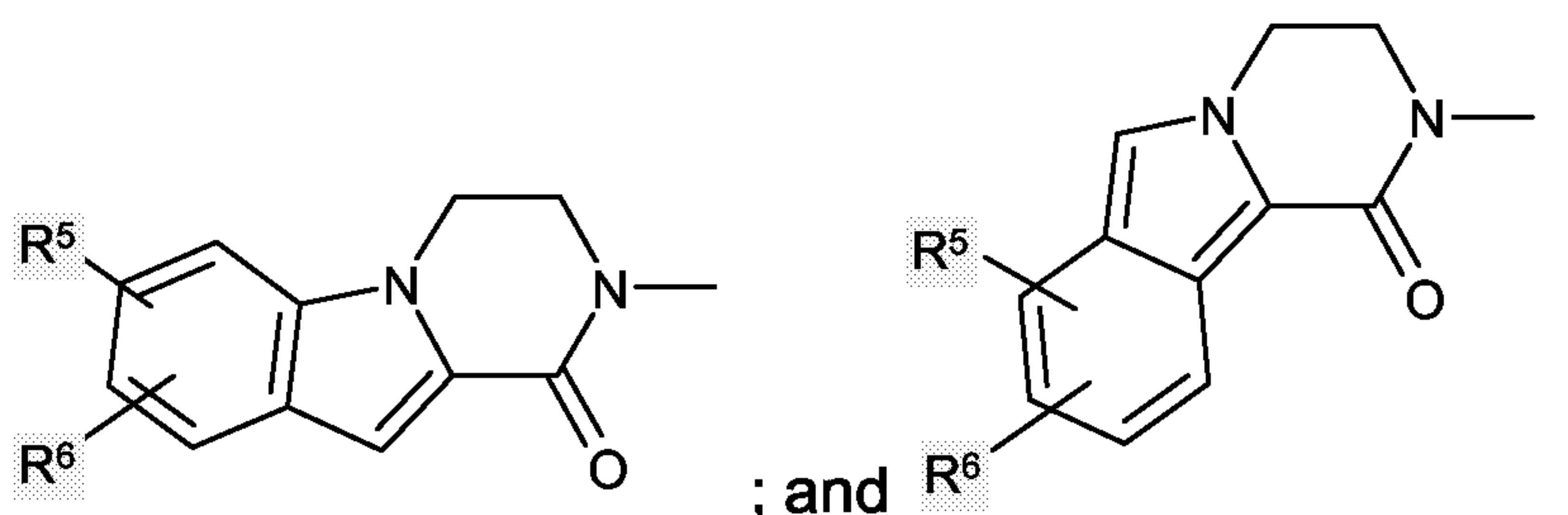


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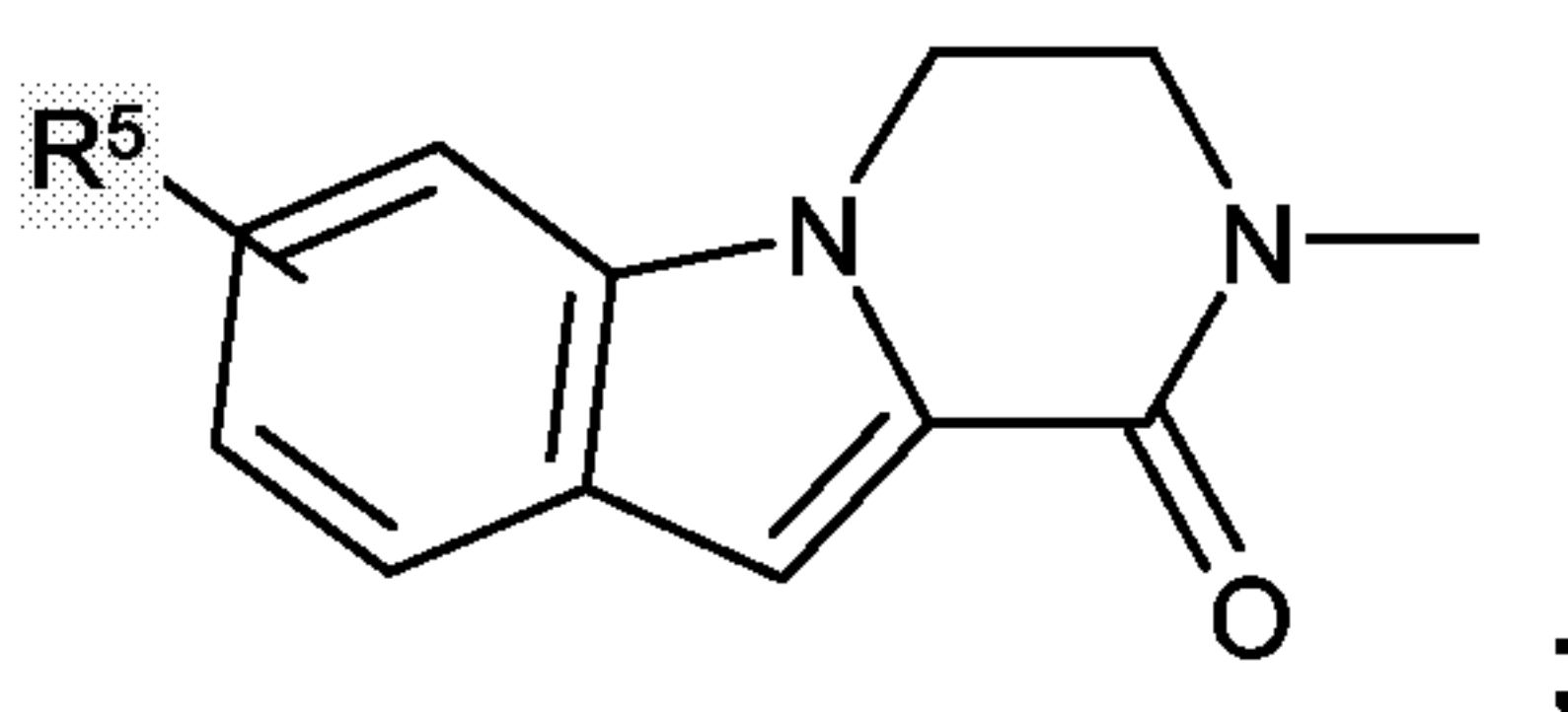
wherein R⁵ and R⁶, independently of each other, represent hydrogen, alkyl, cycloalkyl, cycloalkyl-alkyl, hydroxy, alkoxy, cycloalkoxy, halo, haloalkyl, haloalkoxy, amino, nitro and/or cyano.

In an even more preferred embodiment Y represents a bicyclic heterocyclic group selected from



wherein R⁵ and R⁶, independently of each other, represent hydrogen, alkyl, cycloalkyl, cycloalkyl-alkyl, hydroxy, alkoxy, cycloalkoxy, halo, haloalkyl, haloalkoxy, amino, nitro and/or cyano.

In a yet more preferred embodiment Y represents



wherein R⁵ represents hydrogen, alkyl, halo, trifluoromethyl or trifluoromethoxy.

In a most preferred embodiment the aryl piperazine derivative of the invention is

2-{4-[4-(3-Cyano-phenyl)-piperazin-1-yl]-butyl}-3,4-dihydro-2H-pyrazino[1,2-a]indol-1-one;

2-[4-[4-(3-Chlorophenyl)piperazin-1-yl]butyl]-3,4-dihydropyrazino[1,2-a]indol-1(2H)-one;

2-{4-[4-(3-Methoxy-phenyl)-piperazin-1-yl]-butyl}-3,4-dihydro-2H-pyrazino[1,2-a]indol-1-one;

2-[4-(4-*m*-Tolyl)piperazin-1-yl]butyl]-3,4-dihydropyrazino[1,2-*a*]indol-1(2H)-one;

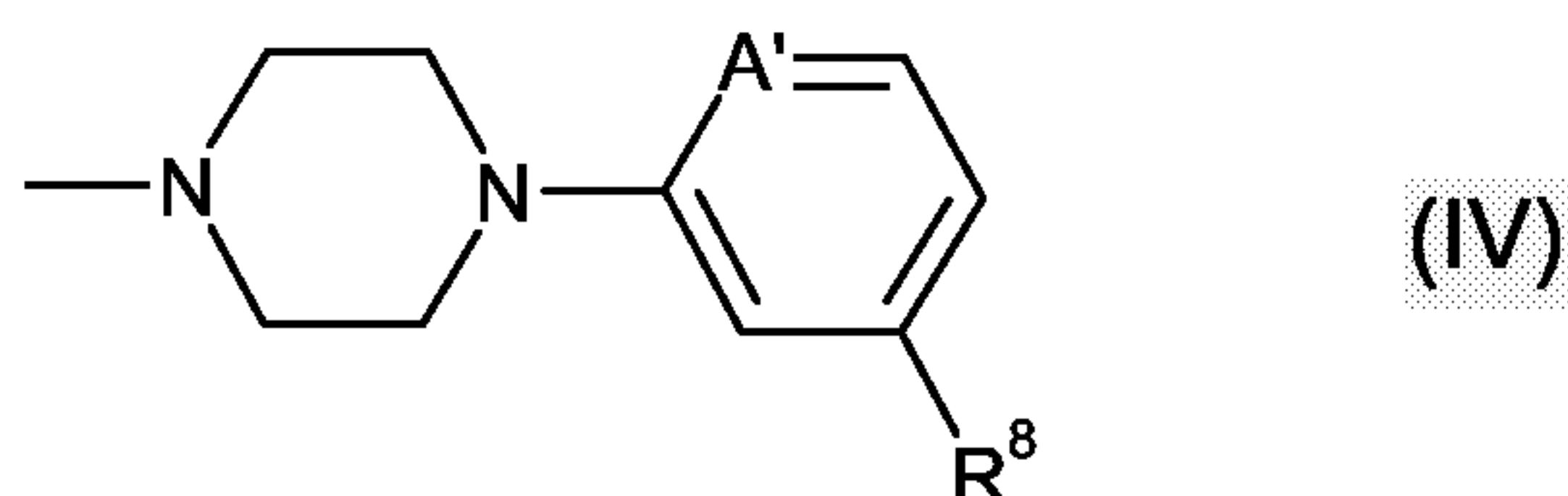
3,4-Dihydro-2-[4-(3,4-dihydro-6-methoxypyrazino[1,2-*a*]indol-2(1H)-yl)butyl]pyrazino[1,2-*a*]indol-1(2H)-one;

5 2-{4-[4-(2-Methoxy-phenyl)-piperazin-1-yl]-butyl}-3,4-dihydro-2H-pyrazino[1,2-*a*]indol-1-one; or

2-{4-[4-(2,3-Dichloro-phenyl)-piperazin-1-yl]-butyl}-3,4-dihydro-2H-pyrazino[1,2-*a*]indol-1-one;

or a pharmaceutically acceptable salt thereof.

10 In a fourteenth preferred embodiment the aryl piperazine derivative of the invention is a compound of Formula I, wherein X is absent; and Y represents a group of formula IV



15 wherein A' represents CH or N; and R⁸ represents hydrogen, alkyl, in particular methyl, alkoxy, in particular methoxy, halo, in particular chloro or haloalkyl.

In a most preferred embodiment the aryl piperazine derivative of the invention is

1,6-Bis(4-(3-chlorophenyl)piperazin-1-yl)hexane;

1,6-Bis(4-(3-methoxyphenyl)piperazin-1-yl)hexane;

20 1,6-Bis(4-phenylpiperazin-1-yl)hexane;

1-(3-Chlorophenyl)-4-(6-(4-(3-methoxyphenyl)piperazin-1-yl)hexyl)piperazine;

1-Phenyl-4-(6-(4-(pyridin-2-yl)piperazin-1-yl)hexyl)piperazine;

1-(6-Methylpyridin-2-yl)-4-(6-(4-*m*-tolylpiperazin-1-yl)hexyl)piperazine;

25 1-(6-Methylpyridin-2-yl)-4-(6-(4-phenylpiperazin-1-yl)hexyl)piperazine;

1-Phenyl-4-(6-(4-*m*-tolylpiperazin-1-yl)hexyl)piperazine;

4-(4-(6-(4-Phenylpiperazin-1-yl)hexyl)piperazin-1-yl)quinoline;

1,6-Bis(4-(pyridin-2-yl)piperazin-1-yl)hexane;

4-(4-(6-(4-*m*-Tolylpiperazin-1-yl)hexyl)piperazin-1-yl)quinoline;

30 1,6-Bis(4-*m*-tolylpiperazin-1-yl)hexane;

1-(Pyridin-2-yl)-4-(6-(4-*m*-tolylpiperazin-1-yl)hexyl)piperazine; or

1-(3-Methoxyphenyl)-4-(6-(4-*m*-tolylpiperazin-1-yl)hexyl)piperazine;

or a pharmaceutically acceptable salt thereof.

Any combination of two or more of the embodiments described herein is
35 considered within the scope of the present invention.

Definition of Substituents

In the context of this invention halo represents fluoro, chloro, bromo or iodo.

In the context of this invention an alkyl group designates a univalent saturated, straight or branched hydrocarbon chain. The hydrocarbon chain preferably contain of from one to eighteen carbon atoms (C_{1-18} -alkyl), more preferred of from one to six carbon atoms (C_{1-6} -alkyl; lower alkyl), including pentyl, isopentyl, neopentyl, tertiary pentyl, hexyl and isohexyl. In a preferred embodiment alkyl represents a C_{1-4} -alkyl group, including butyl, isobutyl, secondary butyl, and tertiary butyl. In another preferred embodiment of this invention alkyl represents a C_{1-3} -alkyl group, which may in particular be methyl, ethyl, propyl or isopropyl.

In the context of this invention a haloalkyl group designates an alkyl group as defined herein, which alkyl group is substituted one or more times with halo. Preferred haloalkyl groups of the invention include trihalomethyl, preferably $-CF_3$.

In the context of this invention an alkoxy group designates an "alkyl-O-" group, wherein alkyl is as defined above. Examples of preferred alkoxy groups of the invention include methoxy and ethoxy.

In the context of this invention a haloalkoxy group designates an alkoxy group as defined herein, which alkoxy group is substituted one or more times with halo. Preferred haloalkoxy groups of the invention include trihalomethoxy, preferably $-OCF_3$.

In the context of this invention a cycloalkyl group designates a cyclic alkyl group, preferably containing of from three to seven carbon atoms (C_{3-7} -cycloalkyl), including cyclopropyl, cyclobutyl, cyclopentyl, cyclohexyl and cycloheptyl.

In the context of this invention a cycloalkyl-alkyl group designates a cycloalkyl group as defined above, which cycloalkyl group is substituted on an alkyl group as also defined above. Examples of preferred cycloalkyl-alkyl groups of the invention include cyclopropylmethyl and cyclopropylethyl.

In the context of this invention a cycloalkoxy group designates a "cycloalkyl-O-" group, wherein cycloalkyl is as defined above. Examples of preferred cycloalkoxy groups of the invention include cyclopropylmethoxy and cyclopropylethoxy.

In the context of this invention an aromatic monocyclic or polycyclic heterocyclic group is a mono- or polycyclic compound, which holds one or more heteroatoms in its ring structure. The term "poly-heterocyclic groups" includes benzo-fused five- and six-membered heterocyclic rings containing one or more heteroatoms. Preferred heteroatoms include nitrogen (N), oxygen (O), and sulphur (S).

Pharmaceutically Acceptable Salts

The aryl piperazine derivatives of the invention may be provided in any form suitable for the intended administration. Suitable forms include pharmaceutically (i.e. physiologically) acceptable salts, and pre- or prodrug forms of the aryl piperazine derivatives of the invention.

Examples of pharmaceutically acceptable salts include, without limitation, the non-toxic inorganic and organic acid salts such as the hydrochloride, the hydrobromide, the nitrate, the perchlorate, the phosphate, the sulphate, the formate, the acetate, the aconate, the ascorbate, the benzenesulphonate, the benzoate, the cinnamate, the citrate, the embonate, the enantate, the fumarate, the glutamate, the glycolate, the lactate, the maleate, the malonate, the mandelate, the methanesulphonate, the naphthalene-2-sulphonate derived, the phthalate, the salicylate, the sorbate, the stearate, the succinate, the tartrate, the toluene-p-sulphonate, and the like. Such salts may be formed by procedures well known and described in the art.

Steric Isomers

Some of the aryl piperazine derivatives of the present invention may exist in (+) and (-) forms as well as in racemic forms ($\pm$). The racemates of these isomers and the individual isomers themselves are within the scope of the present invention.

Racemic forms can be resolved into the optical antipodes by known methods and techniques. One way of separating the diastereomeric salts is by use of an optically active acid, and liberating the optically active amine compound by treatment with a base. Another method for resolving racemates into the optical antipodes is based upon chromatography on an optical active matrix. A stereoselective synthetic approach may be pursued. Racemic compounds of the present invention can thus be resolved into their optical antipodes, e.g., by fractional crystallisation of D- or L- (tartrates, mandelates, or camphorsulphonate) salts for example.

Starting materials and/or intermediate compounds used for producing the chemical compounds of the present invention may also be resolved by the formation of diastereomeric amides by reaction of the aryl piperazine derivative of the present invention with an optically active activated carboxylic acid such as that derived from (+) or (-) phenylalanine, (+) or (-) phenylglycine, (+) or (-) camphanic acid or by the formation of diastereomeric carbamates by reaction of the starting material or intermediate compound for use according to the present invention with an optically active chloroformate or the like.

Additional methods for the resolving the optical isomers are known in the art. Such methods include those described by *Jaques J, Collet A, & Wilen S* in "Enantiomers, Racemates, and Resolutions", John Wiley and Sons, New York (1981).

Optical active compounds can also be prepared from optical active starting materials.

Methods of Preparation

The aryl piperazine derivatives of the invention may be prepared by conventional methods for chemical synthesis, e.g. those described in the working examples.

Generally amides may be prepared by transforming acids or acid chlorides into the corresponding hydroxy amides by a standard procedure. Esters may be obtained by reacting acidic starting materials with 1,4-dihydroxybutane. After substitution of the terminal hydroxy group by a bromine, hydroxyl amides may be treated with the aryl piperazine in the presence of a base to give the desired end product. Compounds based on a ethereal tether may be synthesized starting from the appropriate phenol, which is then condensed with 1,4-dihydroxybutane or 1,5-dihdropentane, followed by transformation into the final products as described above.

Intermediate compounds invention may be resolved by the formation of diastereomeric amides by reaction with an optically active activated carboxylic acid such as that derived from (+) or (-) phenylalanine, (+) or (-) phenylglycine, (+) or (-) camphanic acid or by the formation of diastereomeric carbamates by reaction of the intermediate compound with an optically active chloroformate or the like.

Biological Activity

The aryl piperazine derivatives of the invention were found to possess selectivity for the dopamine and serotonin receptors, in particular the D₃, D₂-like and 5-HT₂ receptor subtypes. Therefore, in a preferred embodiment, the invention relates to use of the aryl piperazine derivatives of the invention for the treatment, prevention or alleviation of a disease or a disorder or a condition of a mammal, including a human, which disease, disorder or condition is responsive to modulation of the dopamine and serotonin receptors, in particular the D₃, D₂-like and 5-HT₂ receptor subtypes, preferably the dopamine D₃ receptor subtype and/or the D₃/5-HT_{1A} or D₃/5-HT_{2A} receptor subtypes.

In a more preferred embodiment the disease, disorder or condition is a neurological or psychiatric disorders, in particular psychotic disorders, incl. schizophrenia, depression, Parkinson's disease, Huntington's disease, movement disorders, in

particular dystonia, anxiety, restlessness, obsessive-compulsive disorders, mania, geriatric disorders, dementia, sexual dysfunction, musculo-skeletal pain symptoms, in particular pain associated with fibromyalgia, sleep disorders, substance abuse or addiction and withdrawal symptoms in drug addicts, cocaine abuse or addiction.

5 In an even more preferred embodiment the disease, disorder or condition is a neurological or psychiatric disorder, in particular a psychotic disorder, preferably schizophrenia.

In another preferred embodiment the disease, disorder or condition contemplated according to the invention is schizophrenia or Parkinson's disease.

10 In yet another preferred embodiment the aryl piperazine derivatives of the invention are used as diagnostic tools in diagnostic methods, and in particular for *in vivo* receptor imaging (neuroimaging).

Pharmaceutical Compositions

15 In another aspect the invention provides novel pharmaceutical compositions comprising a therapeutically effective amount of the aryl piperazine derivative of the invention.

While an aryl piperazine derivative of the invention for use in therapy may be administered in the form of the raw chemical compound, it is preferred to introduce
20 the active ingredient, optionally in the form of a physiologically acceptable salt, in a pharmaceutical composition together with one or more adjuvants, excipients, carriers, buffers, diluents, and/or other customary pharmaceutical auxiliaries.

In a preferred embodiment, the invention provides pharmaceutical compositions comprising the aryl piperazine derivative of the invention, or a
25 pharmaceutically acceptable salt or derivative thereof, together with one or more pharmaceutically acceptable carriers, and, optionally, other therapeutic and/or prophylactic ingredients, known and used in the art. The carrier(s) must be "acceptable" in the sense of being compatible with the other ingredients of the formulation and not harmful to the recipient thereof.

30 The pharmaceutical composition of the invention may be administered by any convenient route, which suits the desired therapy. Preferred routes of administration include oral administration, in particular in tablet, in capsule, in dragé, in powder, or in liquid form, and parenteral administration, in particular cutaneous, subcutaneous, intramuscular, or intravenous injection. The pharmaceutical
35 composition of the invention can be prepared by any person skilled in the art, by use of standard methods and conventional techniques, appropriate to the desired formulation. When desired, compositions adapted to give sustained release of the active ingredient may be employed.

Further details on techniques for formulation and administration may be found in the latest edition of Remington's Pharmaceutical Sciences (Maack Publishing Co., Easton, PA).

The actual dosage depends on the nature and severity of the disease being treated, and is within the discretion of the physician, and may be varied by titration of the dosage to the particular circumstances of this invention to produce the desired therapeutic effect. However, it is presently contemplated that pharmaceutical compositions containing of from about 0.1 to about 500 mg of active ingredient per individual dose, preferably of from about 1 to about 100 mg, most preferred of from about 1 to about 10 mg, are suitable for therapeutic treatments.

The active ingredient may be administered in one or several doses per day. A satisfactory result can, in certain instances, be obtained at a dosage as low as 0.1 $\mu\text{g/kg}$ i.v. and 1 $\mu\text{g/kg}$ p.o. The upper limit of the dosage range is presently considered to be about 10 mg/kg i.v. and 100 mg/kg p.o. Preferred ranges are from about 0.1 $\mu\text{g/kg}$ to about 10 mg/kg/day i.v., and from about 1 $\mu\text{g/kg}$ to about 100 mg/kg/day p.o.

Methods of Therapy

In another aspect the invention provides a method for the diagnosis, treatment, prevention or alleviation of a disease or a disorder or a condition of a living animal body, including a human, which disease, disorder or condition is responsive to modulation of the dopamine and serotonin receptors, and which method comprises administering to such a living animal body, including a human, in need thereof an effective amount of an aryl piperazine derivative of the invention.

In the context of this invention the term "treatment" covers treatment, prevention, prophylaxis or alleviation, and the term "disease" covers illnesses, diseases, disorders and conditions related to the disease in question.

The preferred indications contemplated according to the invention are those stated above.

It is at present contemplated that a suitable dosage of the active pharmaceutical ingredient (API) is within the range of from about 0.1 to about 1000 mg API per day, more preferred of from about 10 to about 500 mg API per day, most preferred of from about 30 to about 100 mg API per day, dependent, however, upon the exact mode of administration, the form in which it is administered, the indication considered, the subject and in particular the body weight of the subject involved, and further the preference and experience of the physician or veterinarian in charge.

EXAMPLES

The invention is further illustrated with reference to the following examples, which are not intended to be in any way limiting to the scope of the invention as claimed.

5

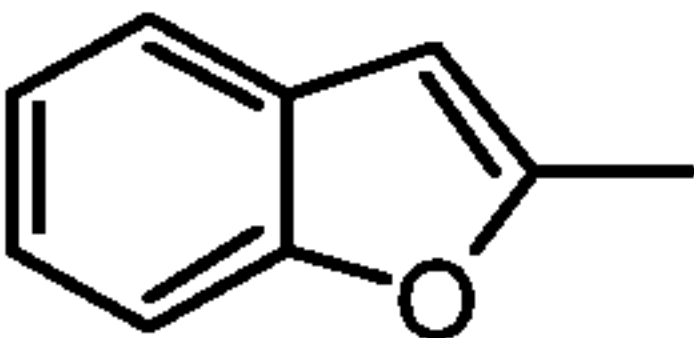
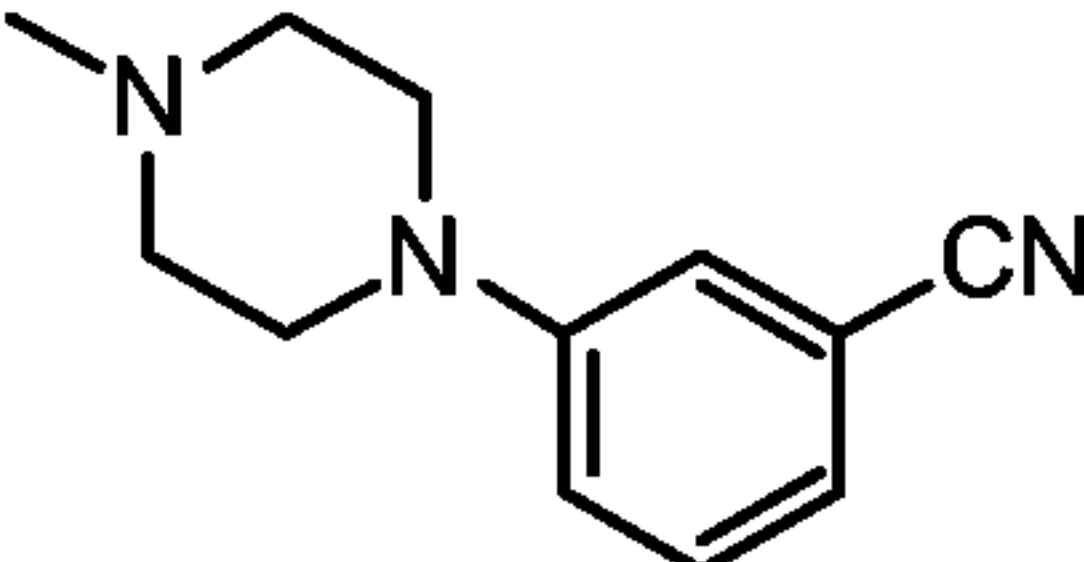
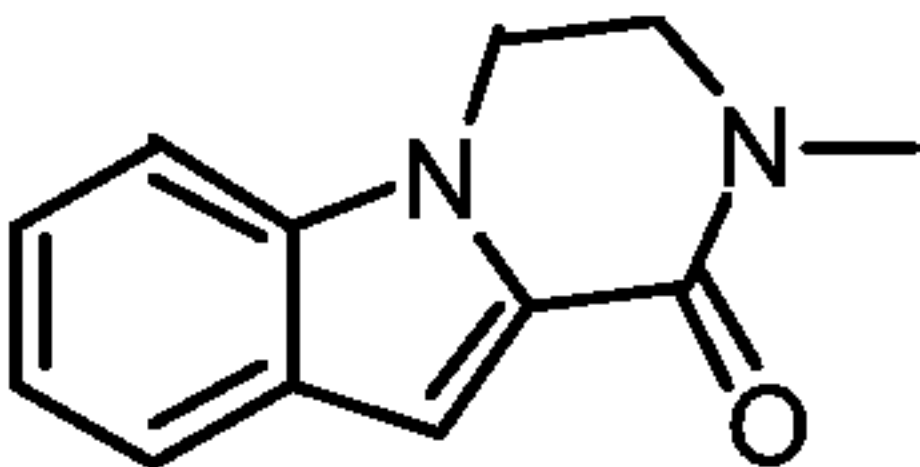
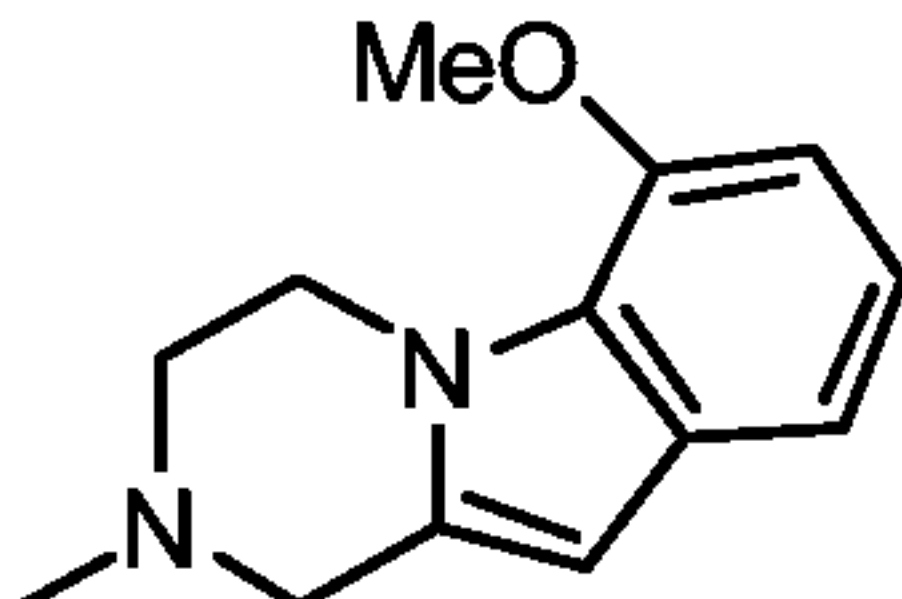
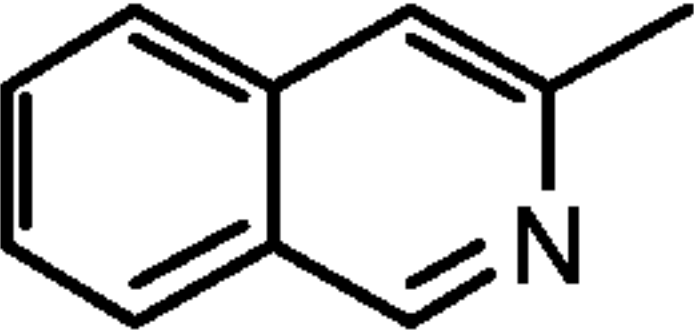
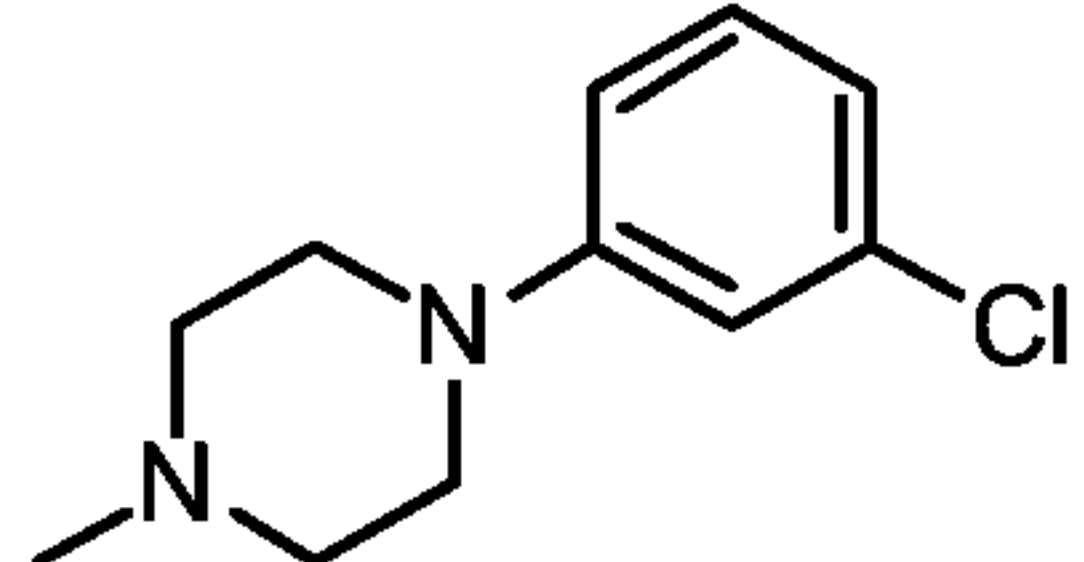
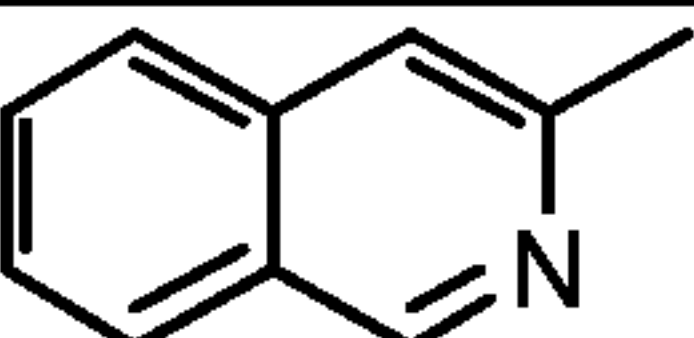
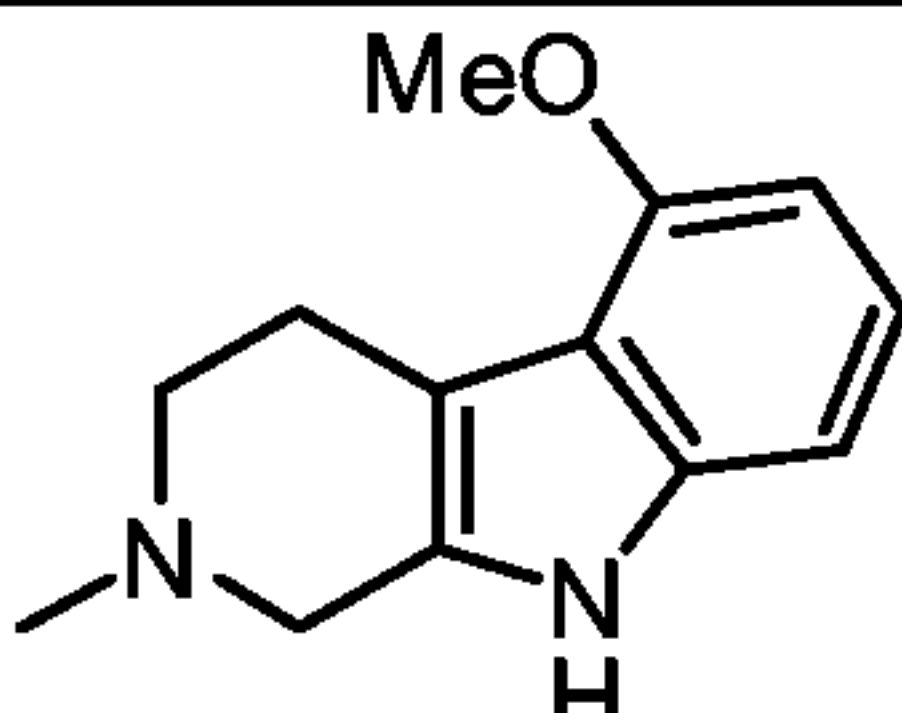
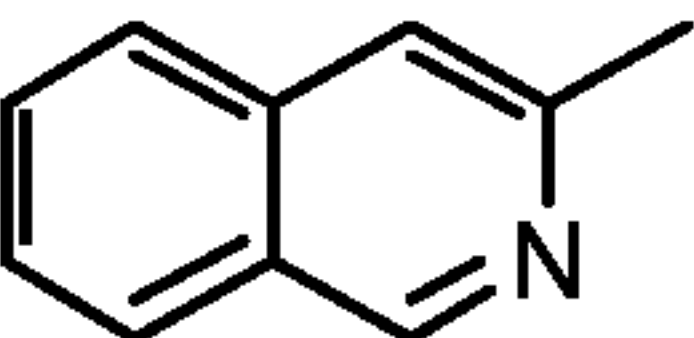
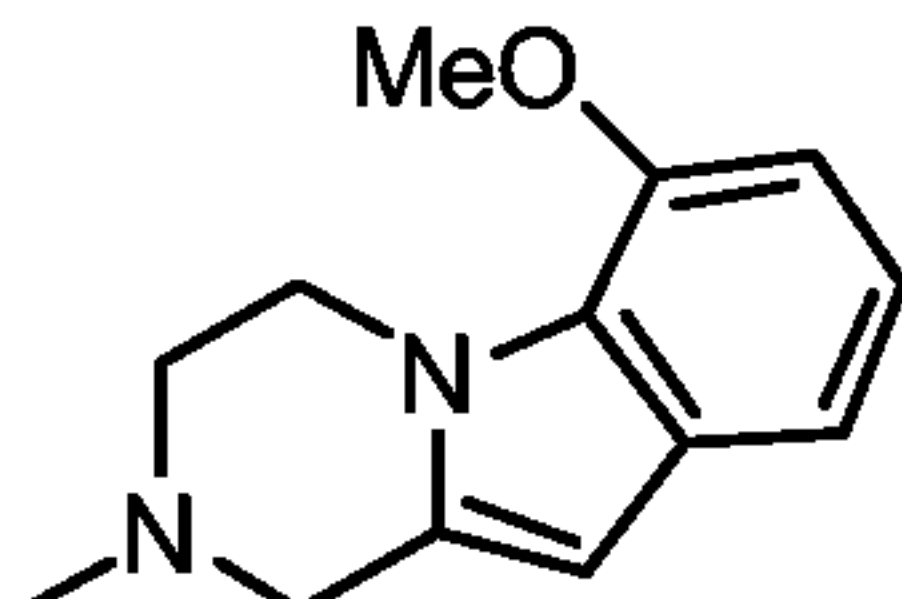
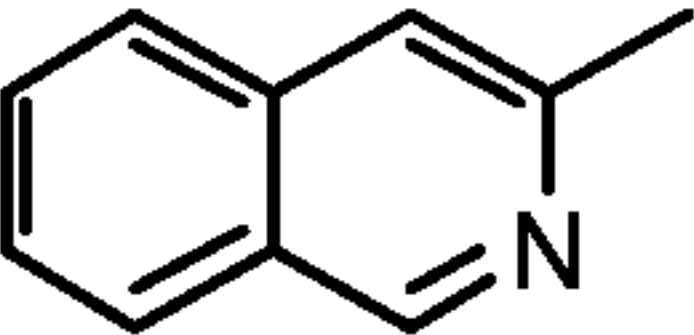
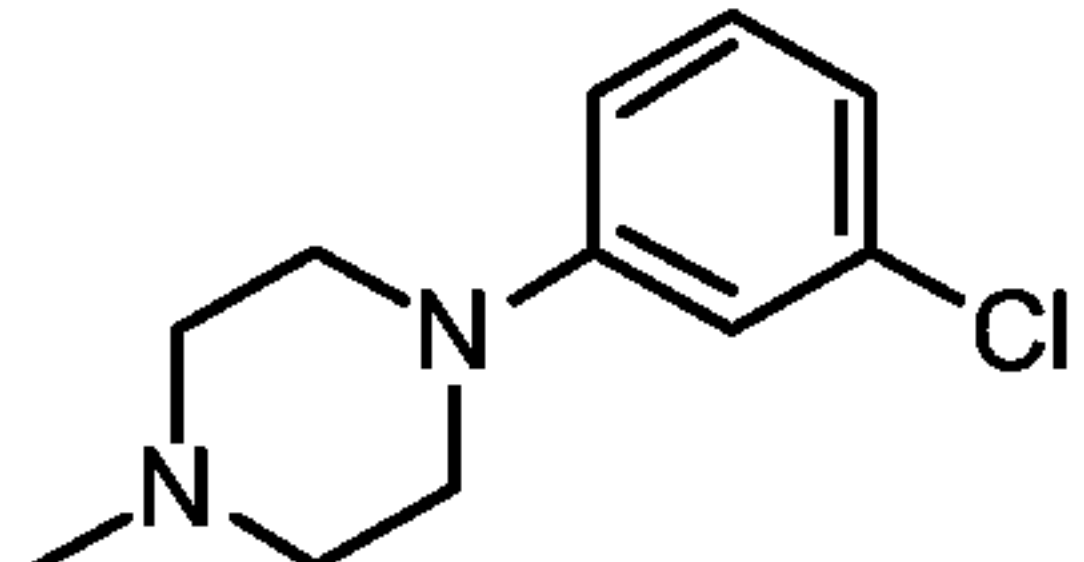
Example 1**Preparatory Example**

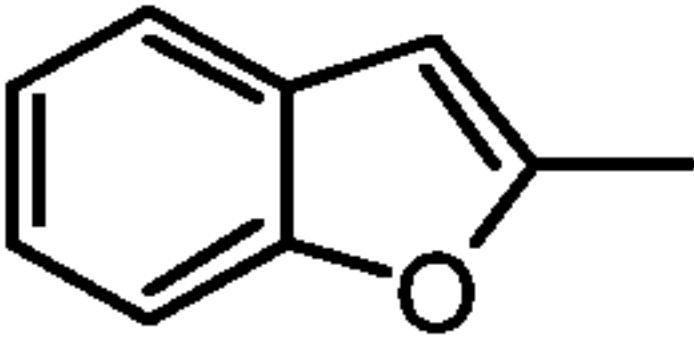
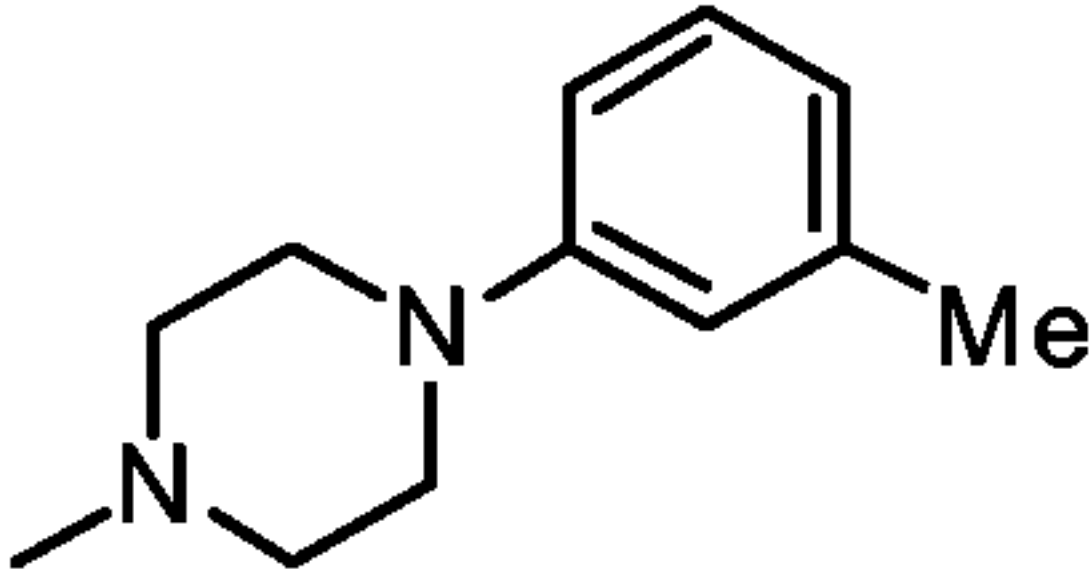
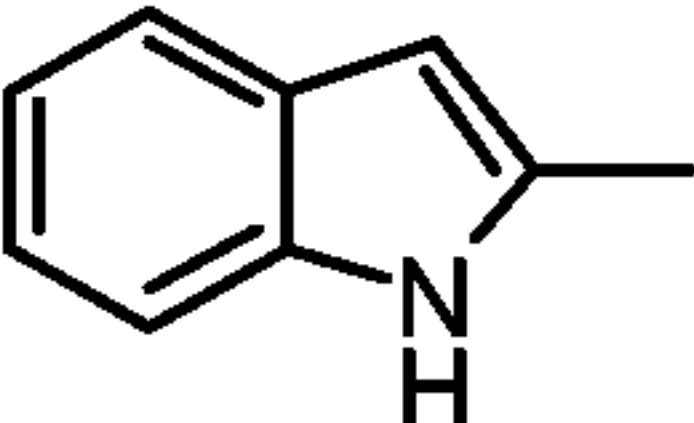
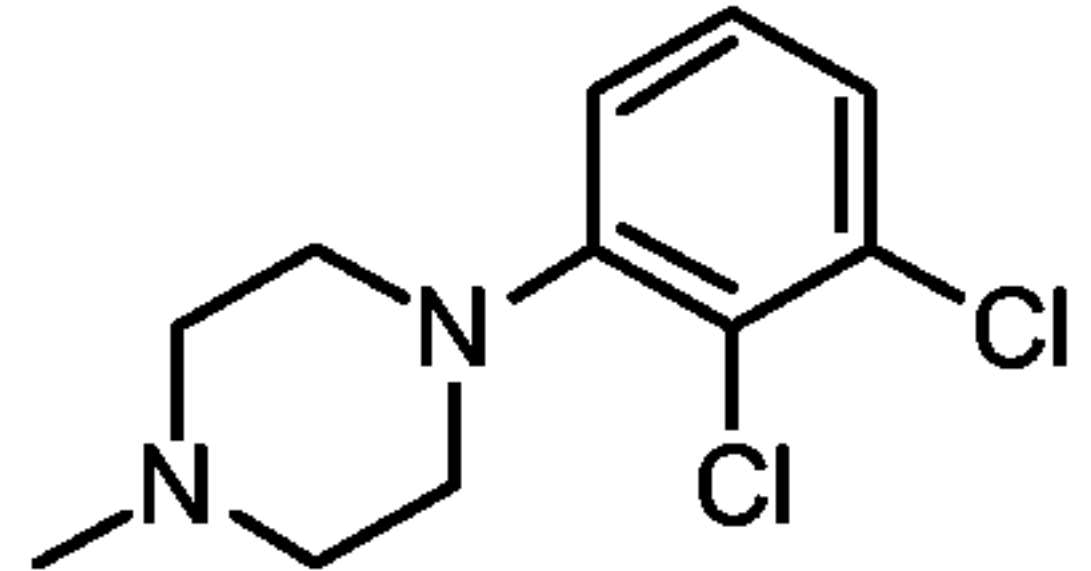
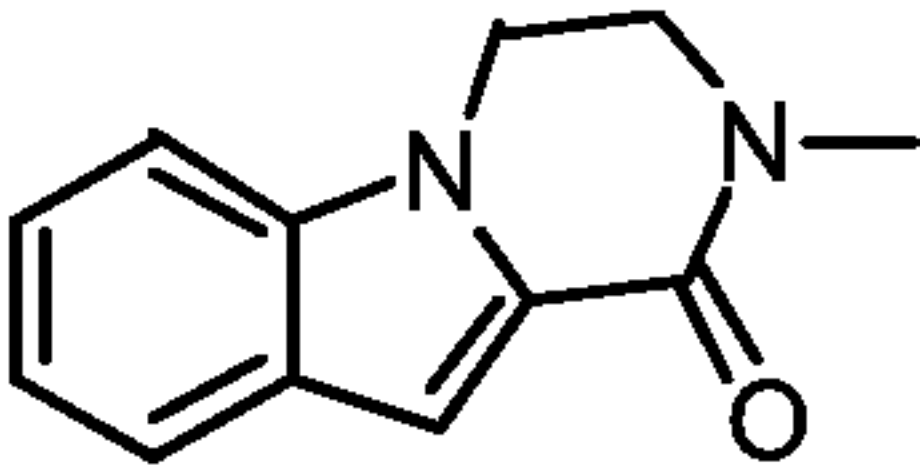
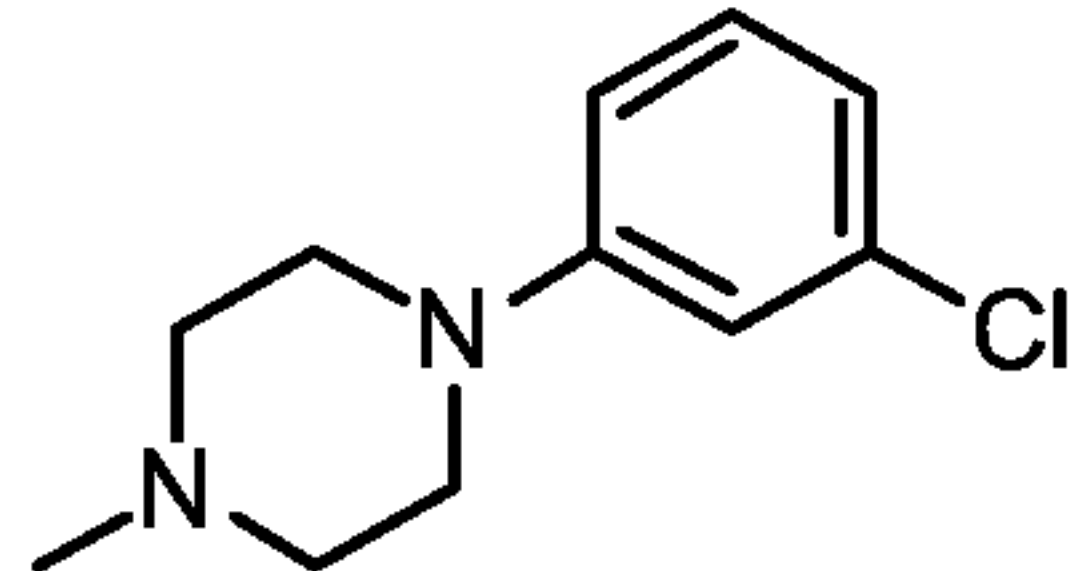
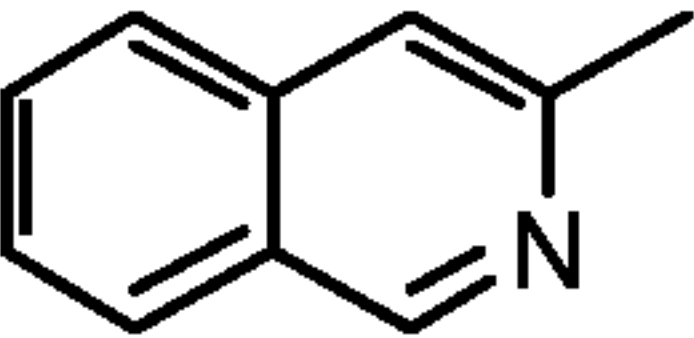
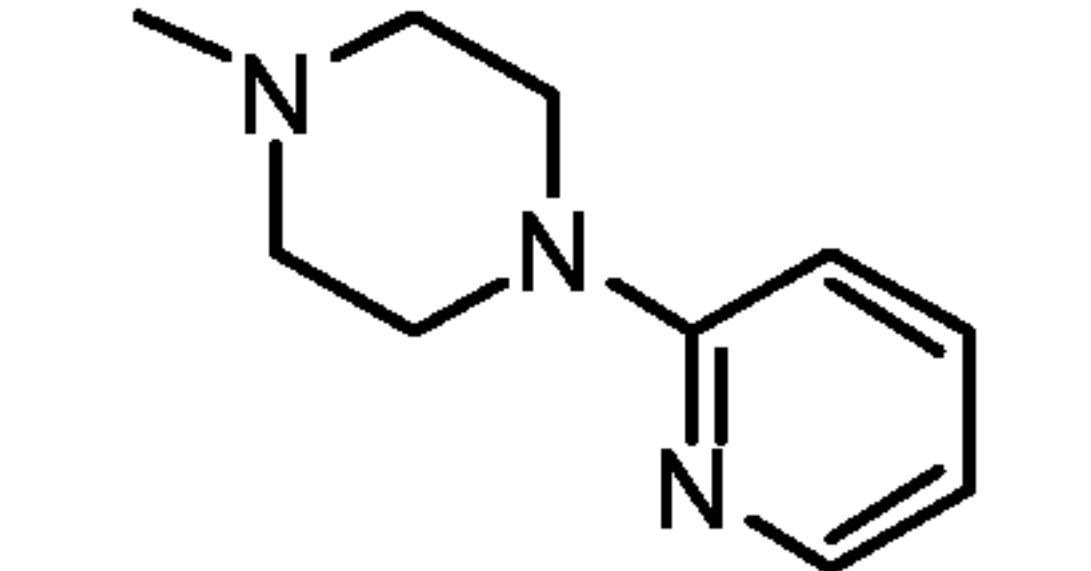
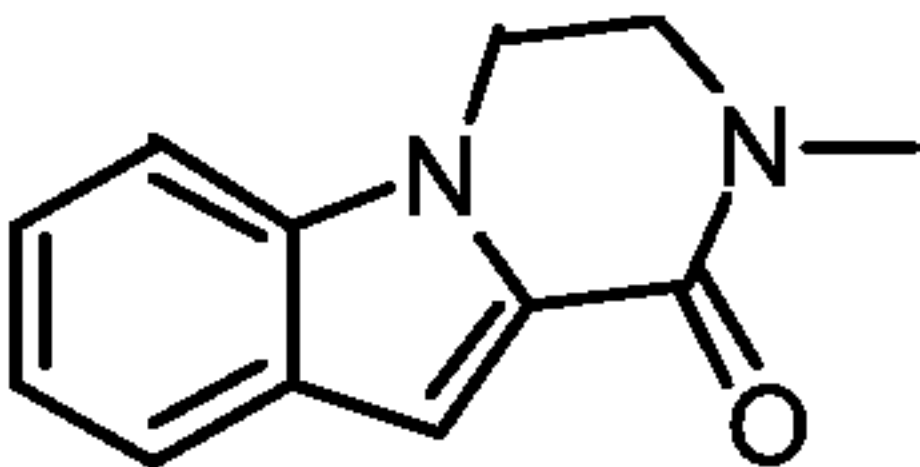
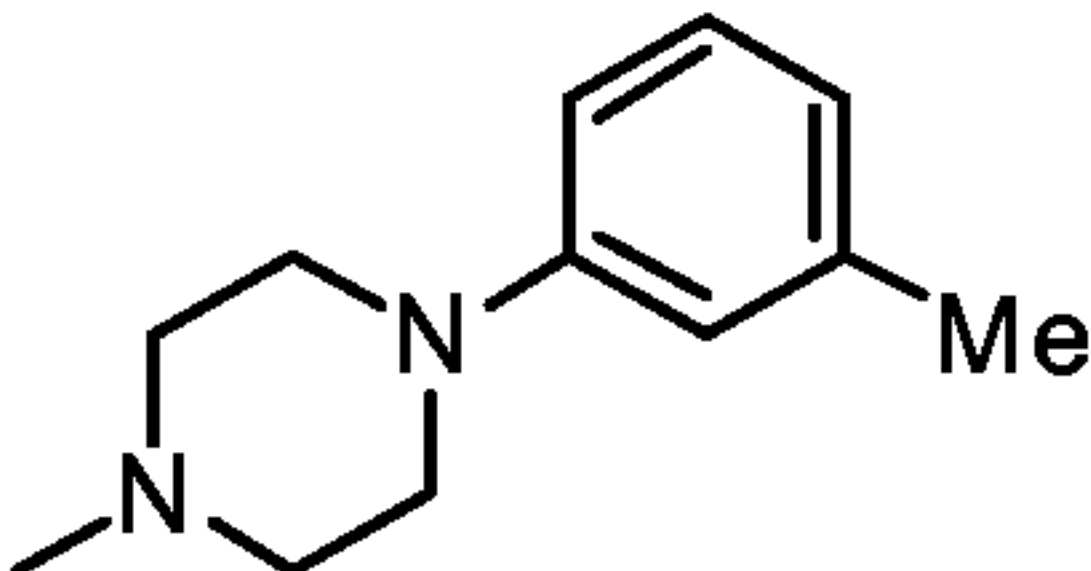
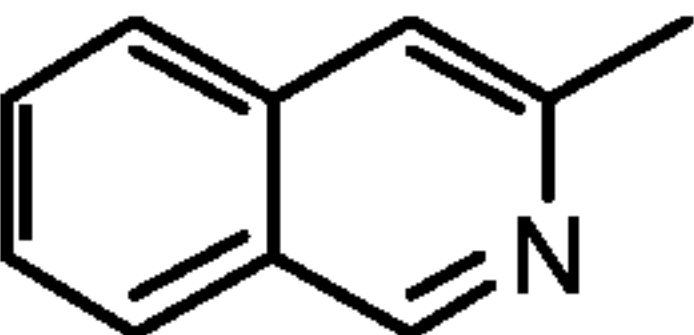
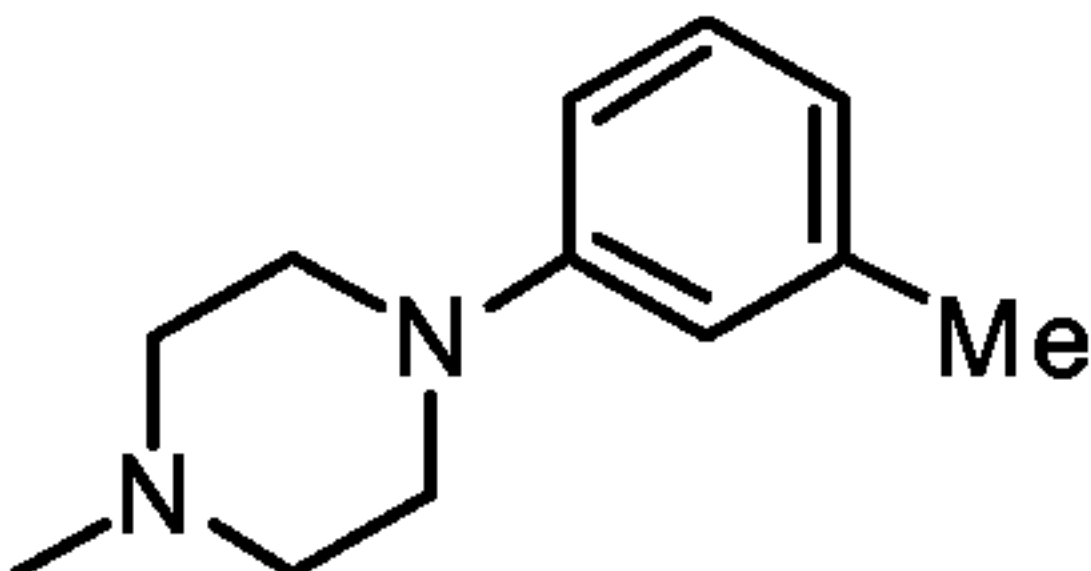
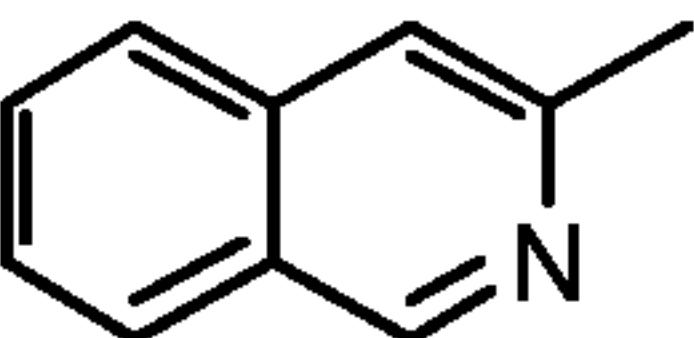
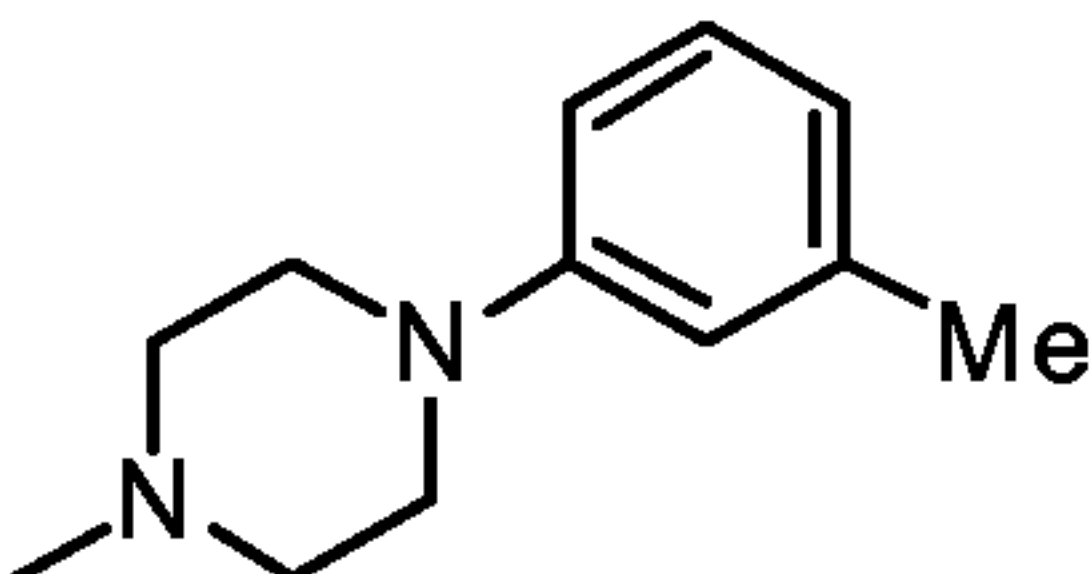
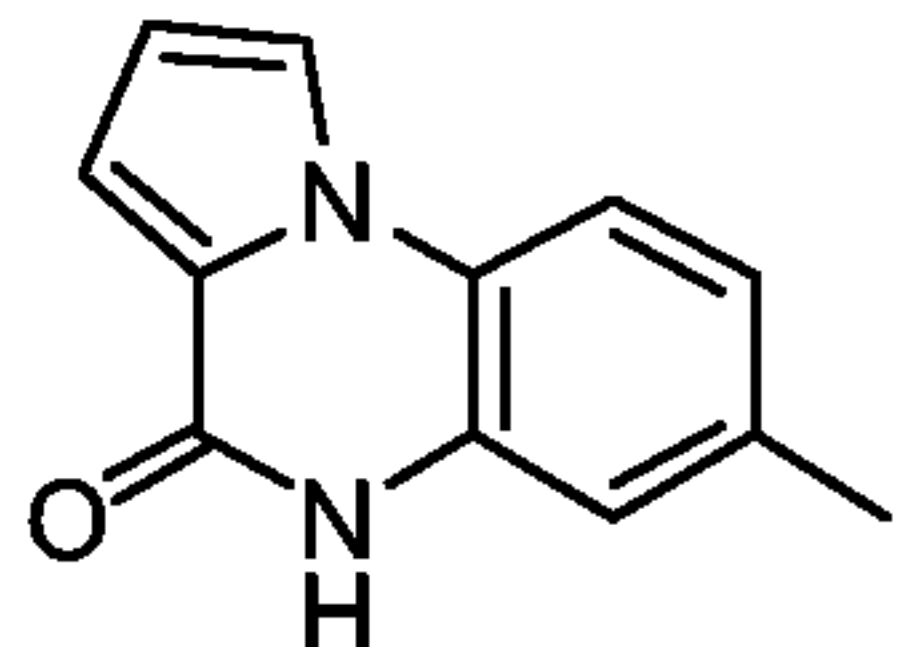
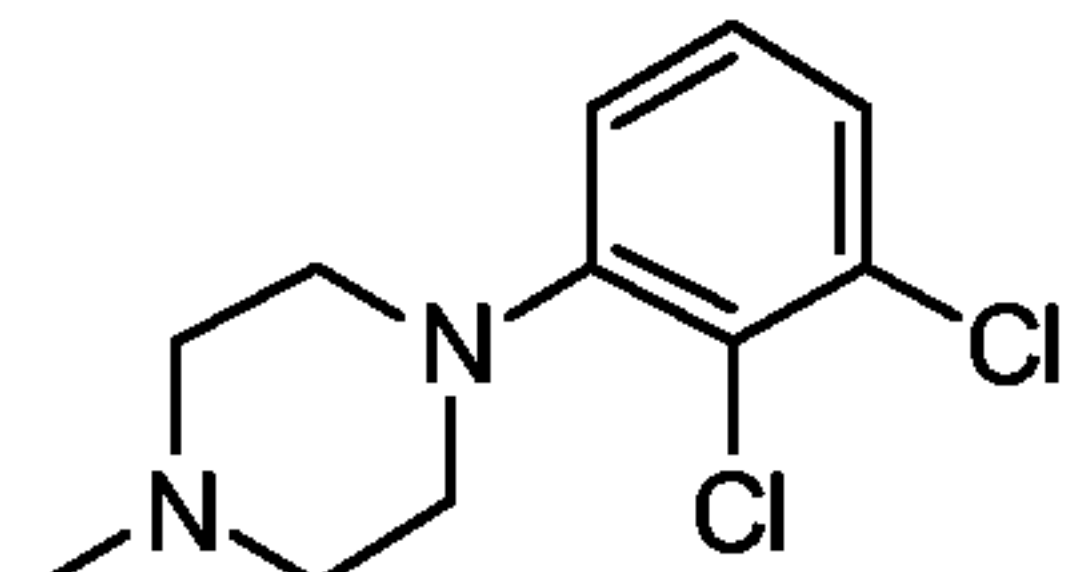
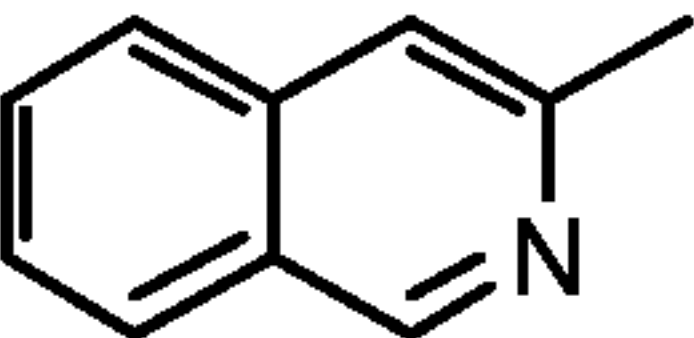
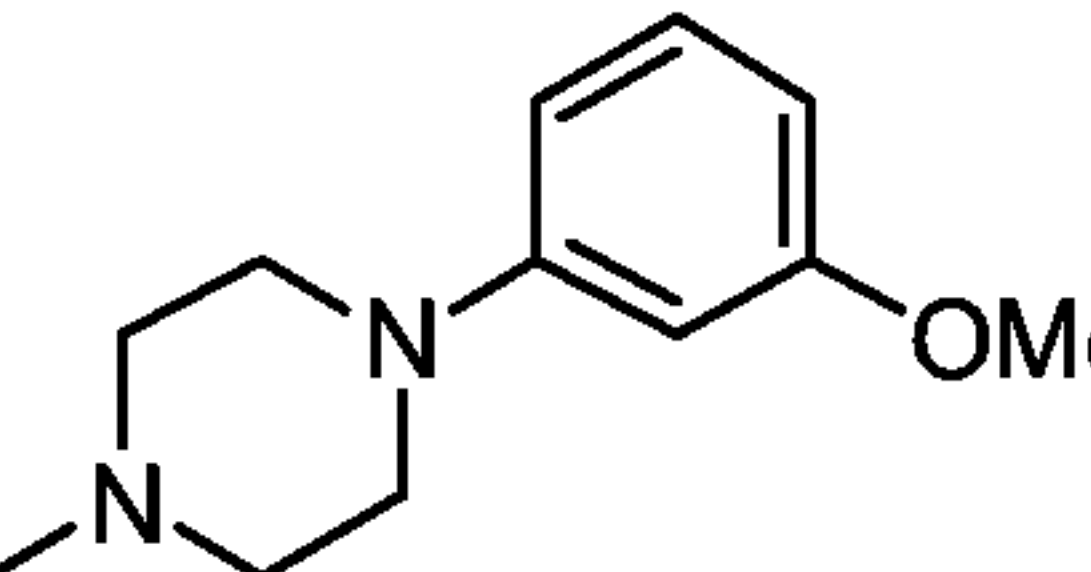
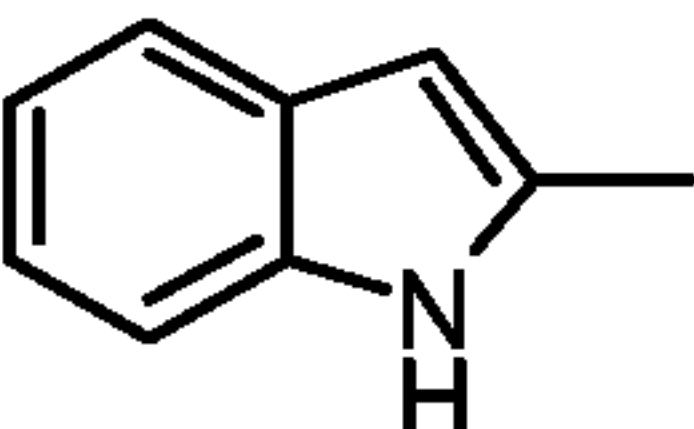
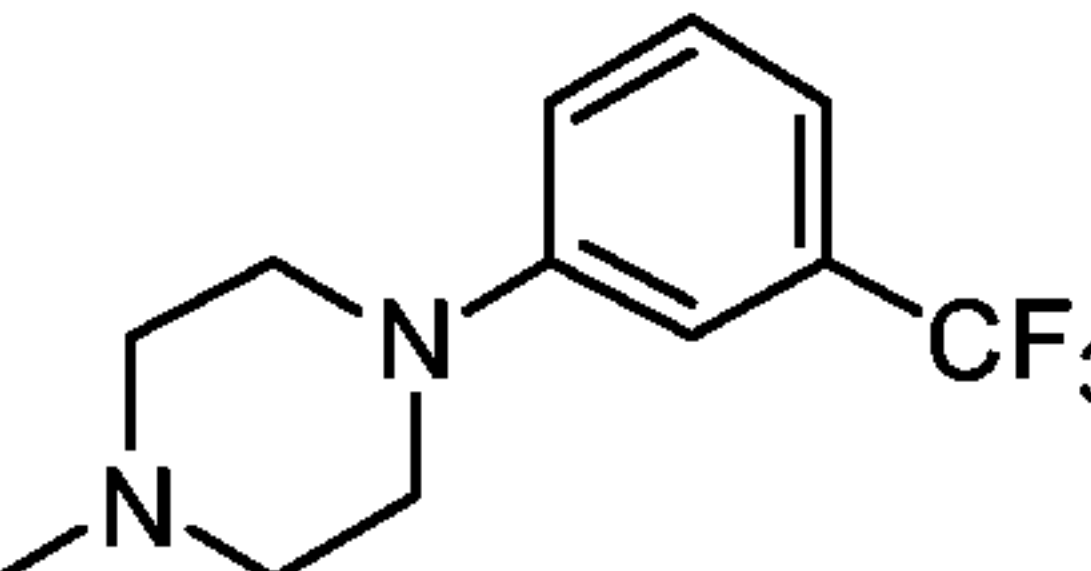
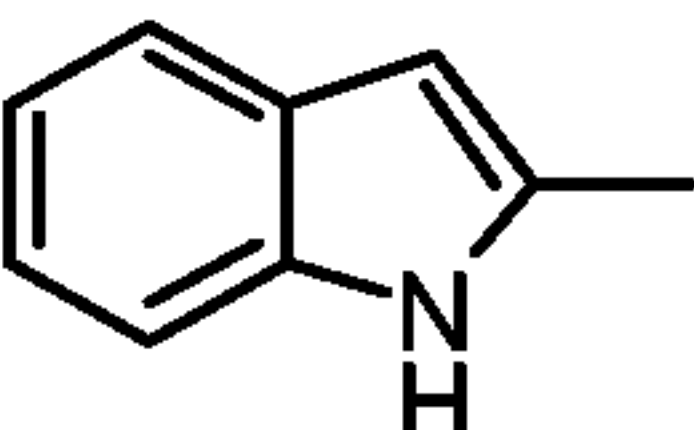
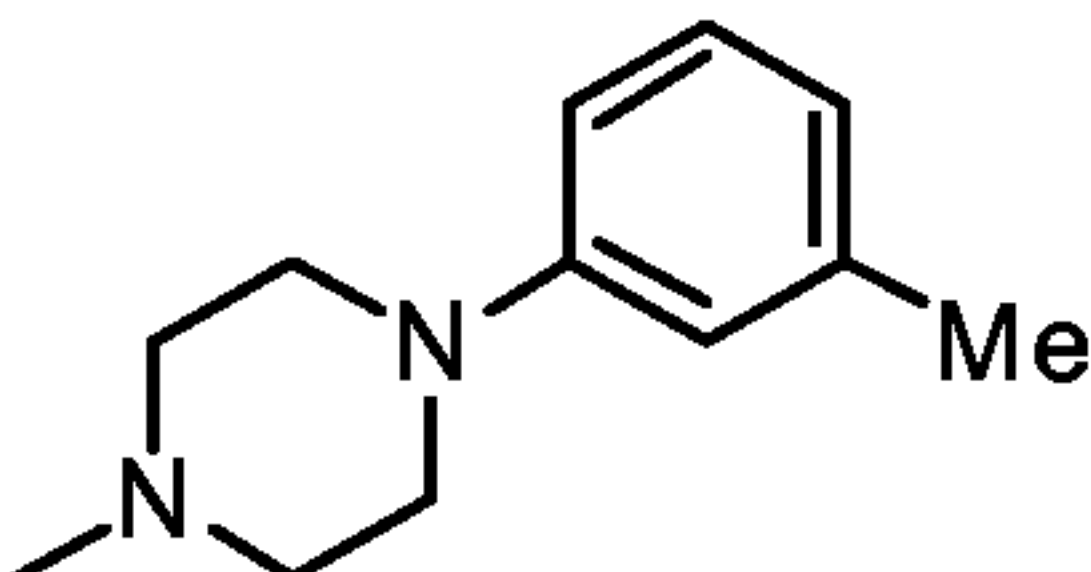
This example describes synthesis of the compounds presented in Table 1. The compounds may be viewed as having the following generic structure:

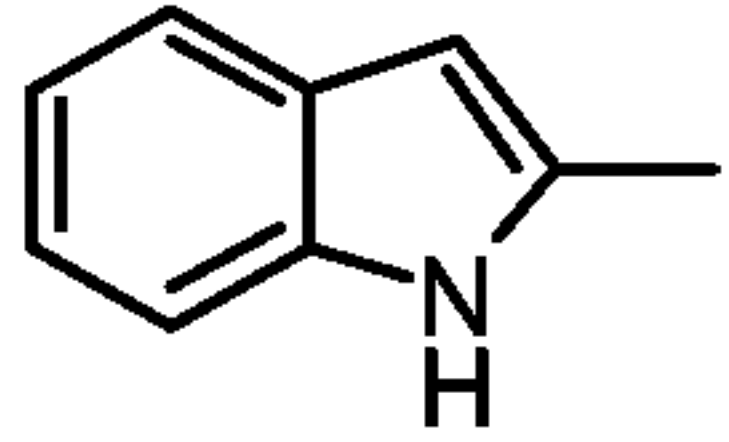
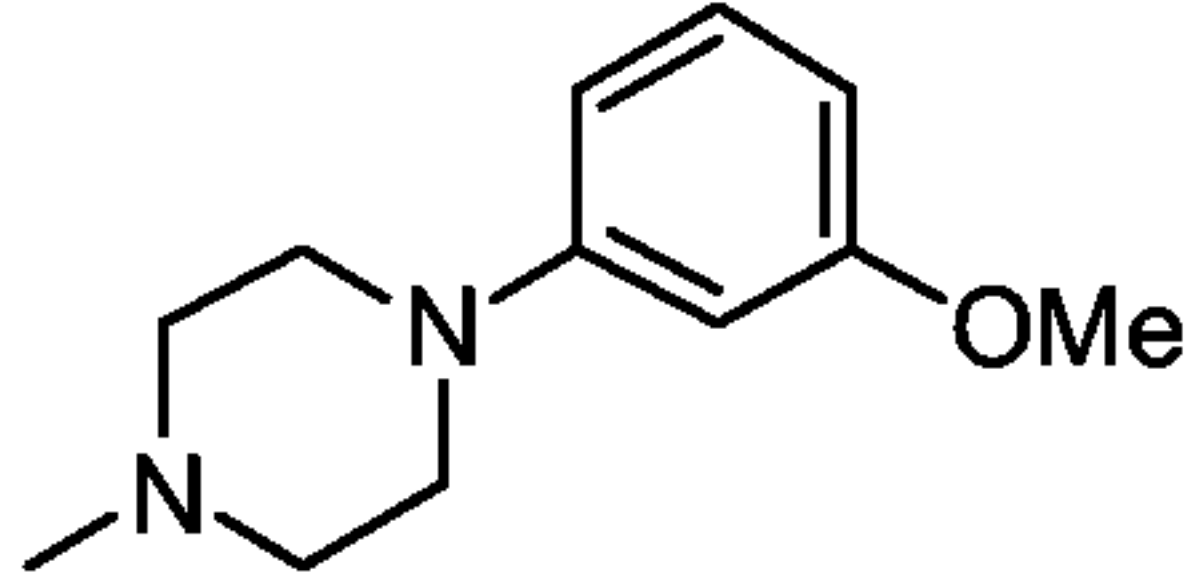
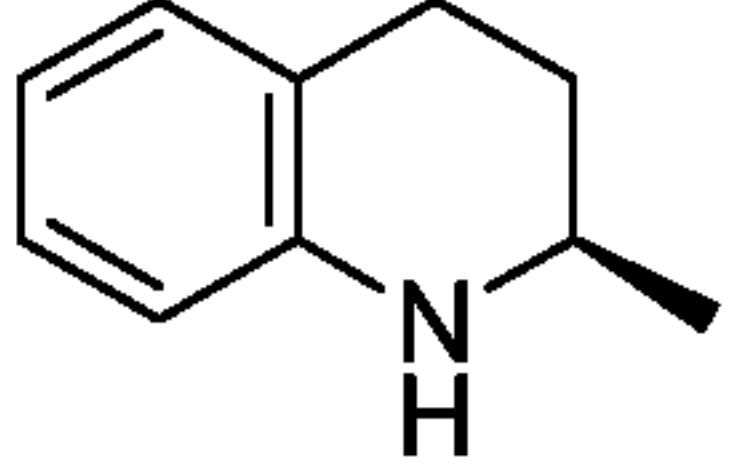
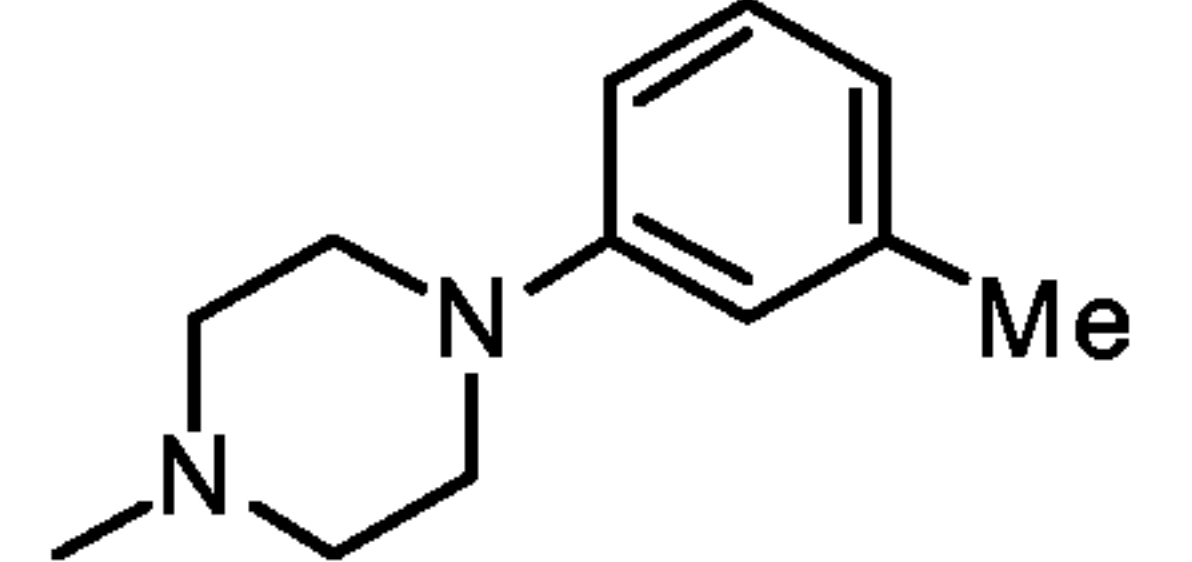
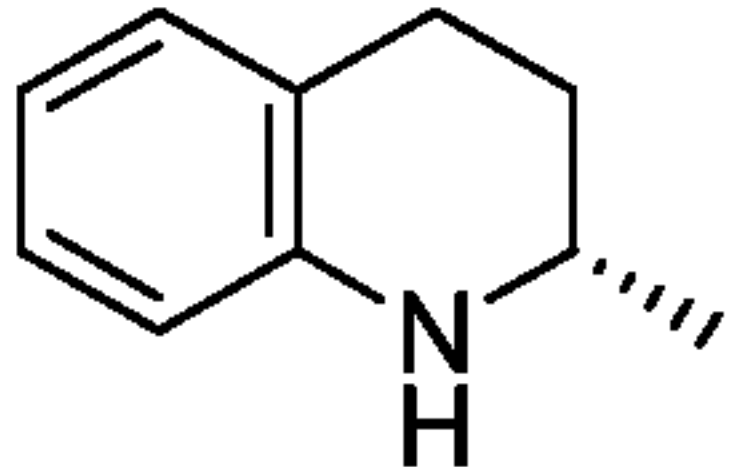
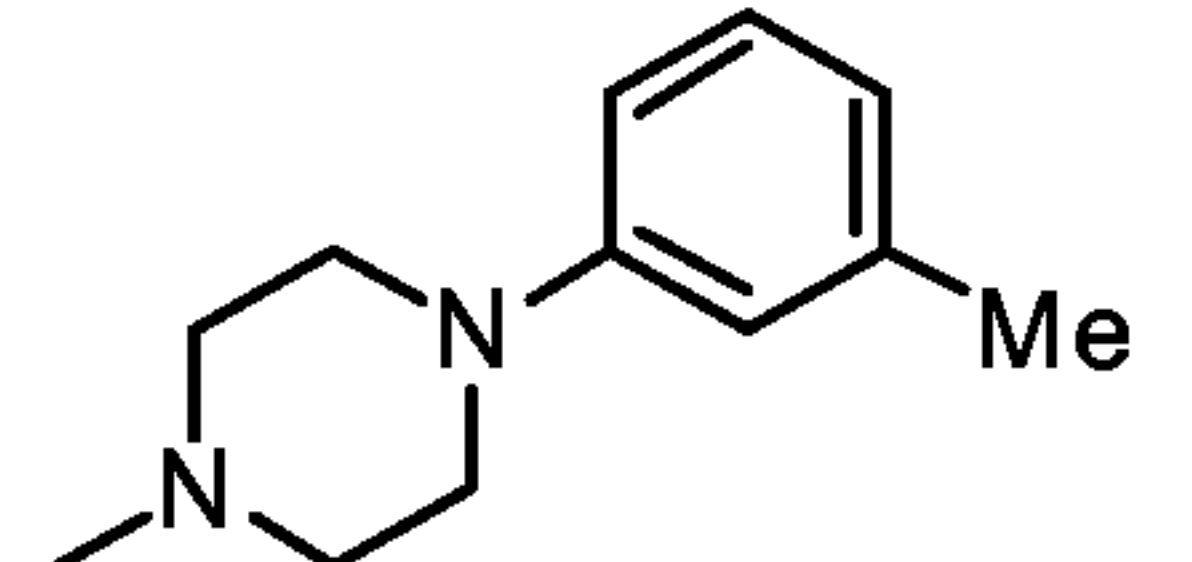
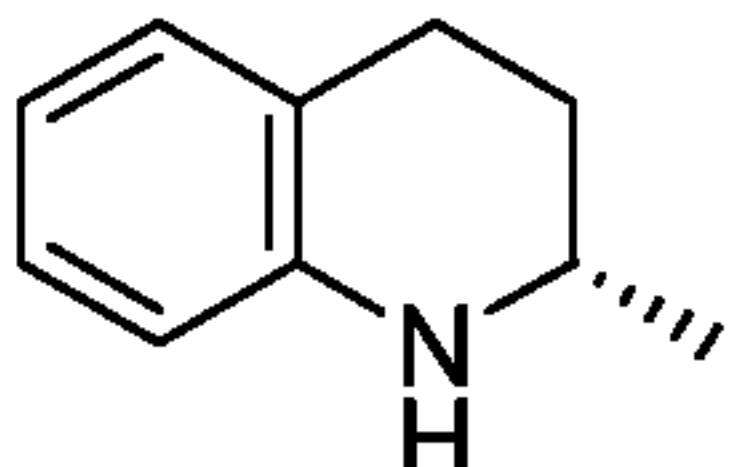
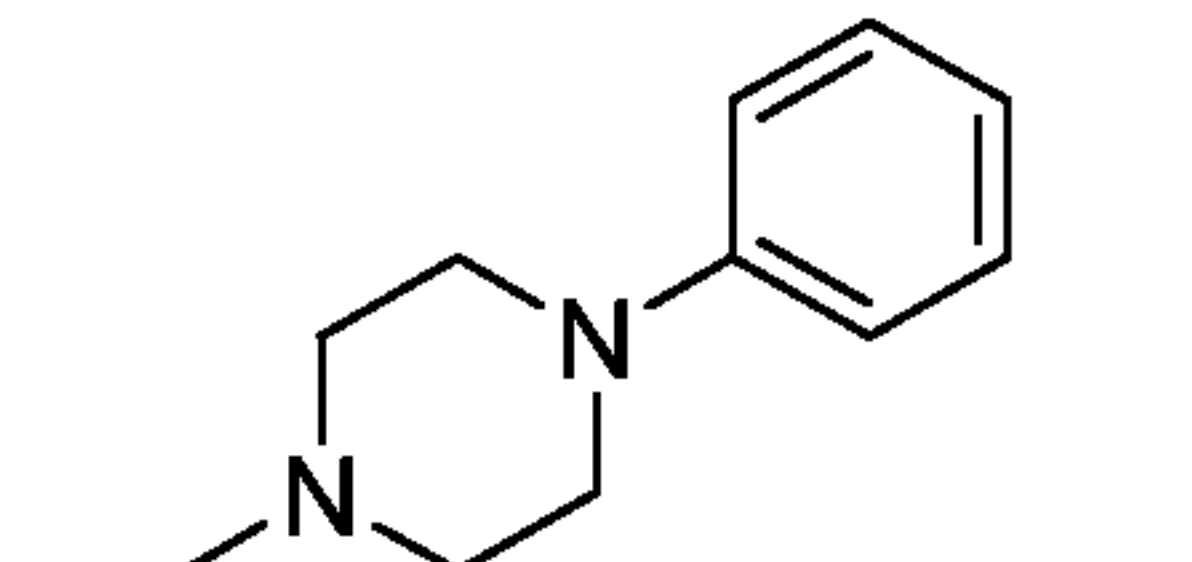
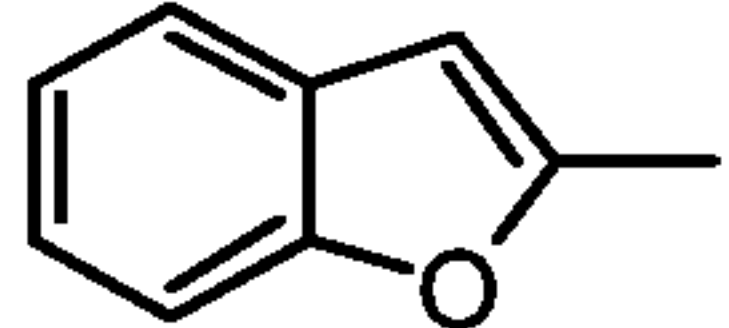
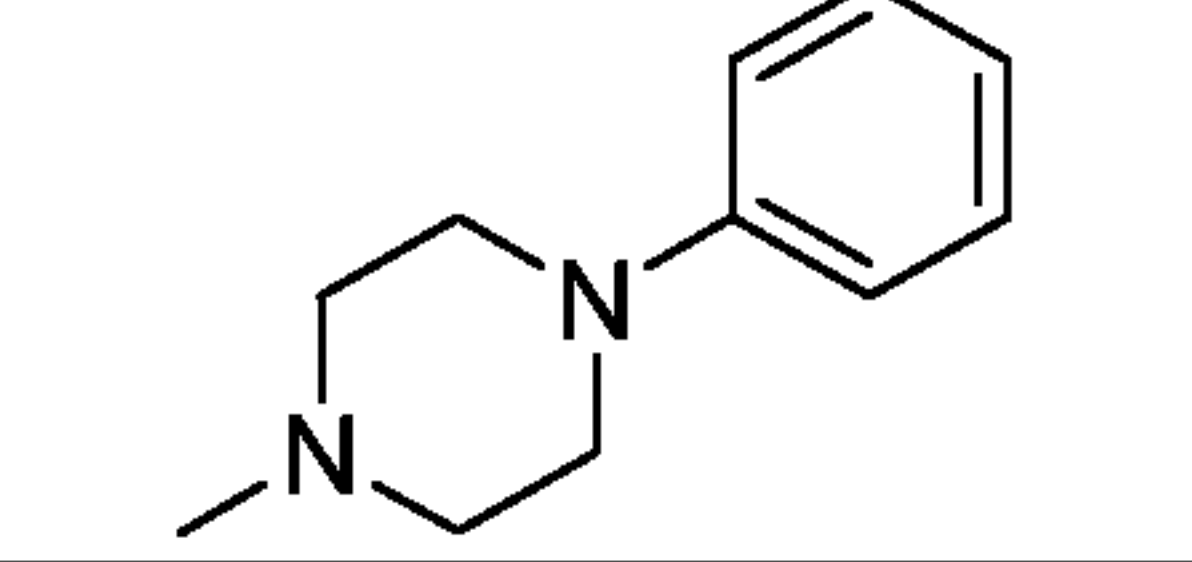
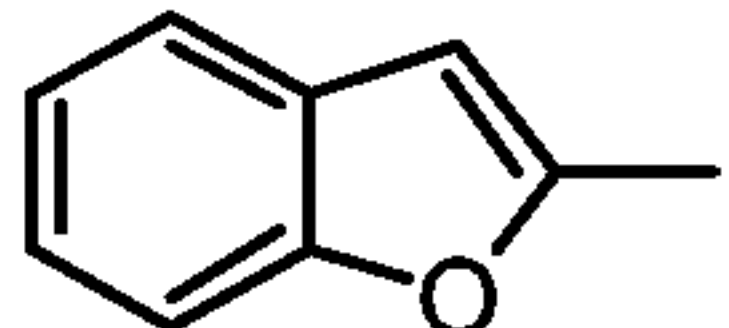
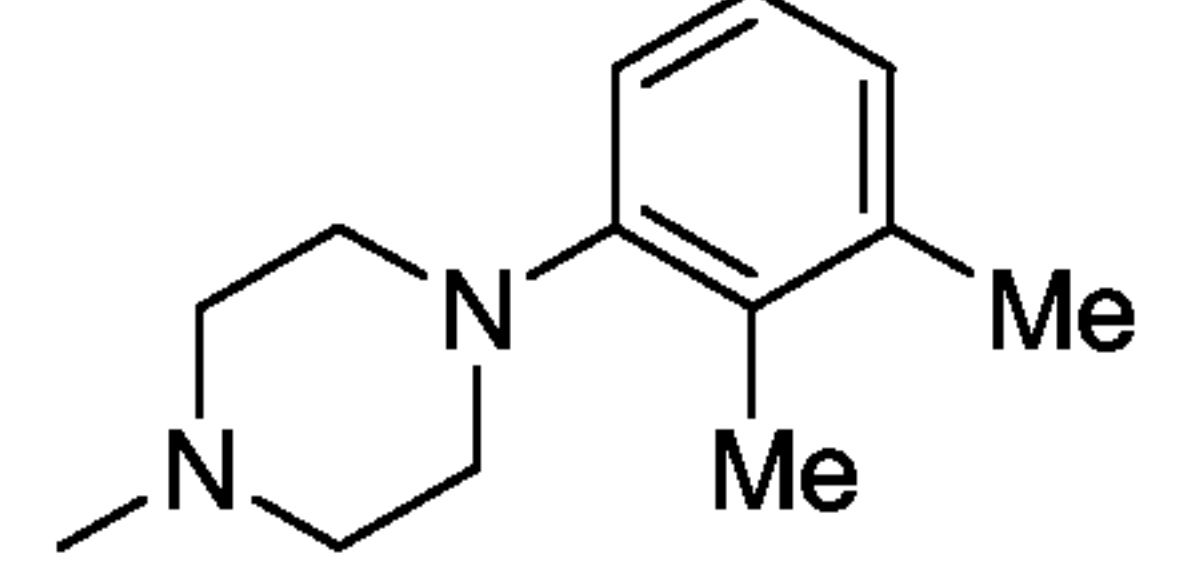
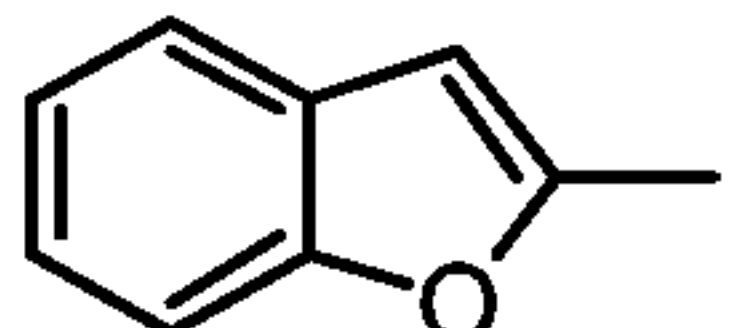
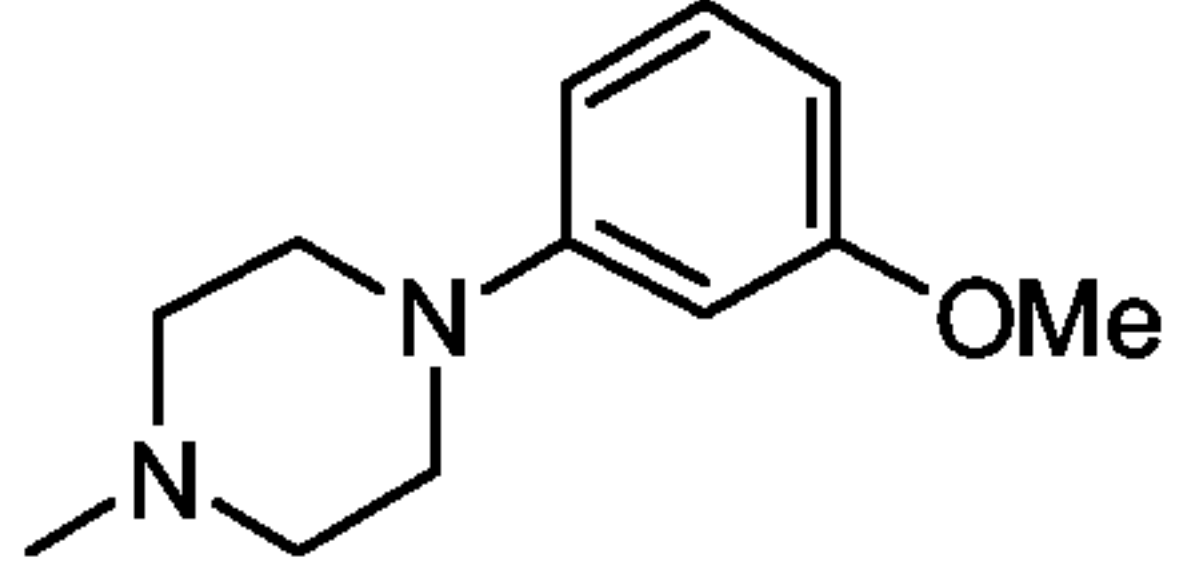
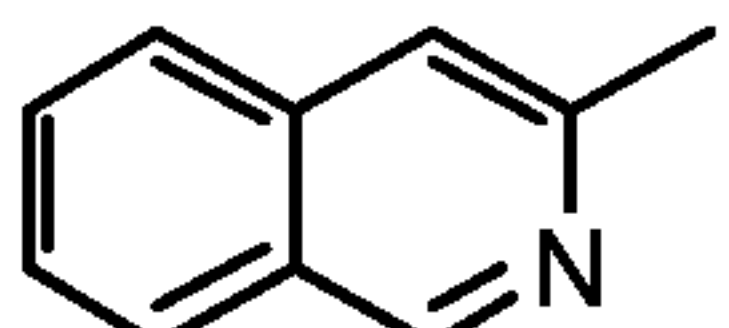
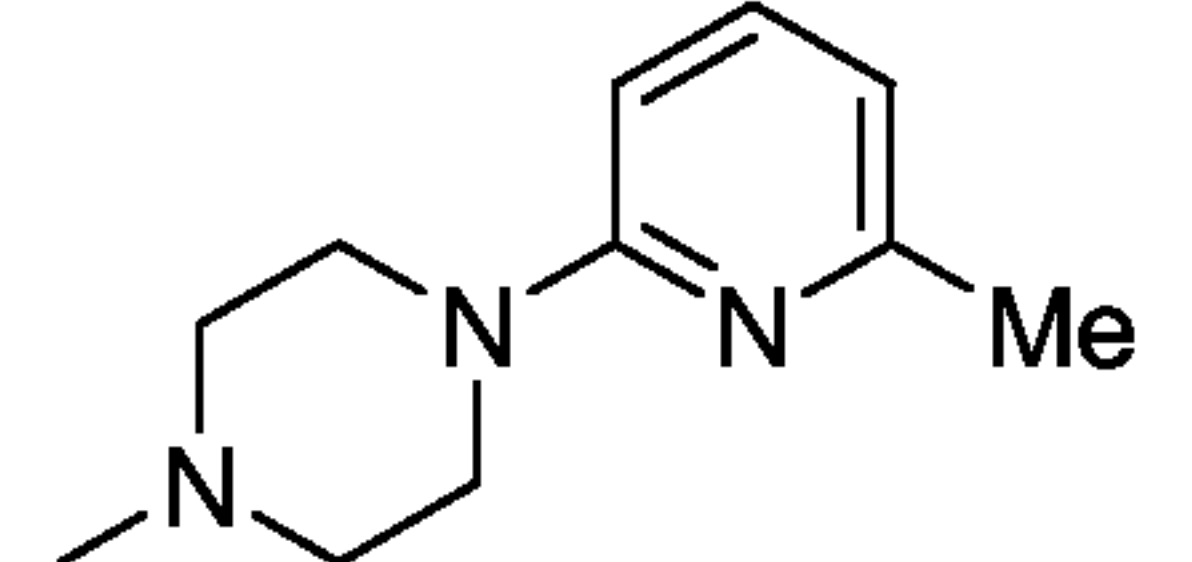
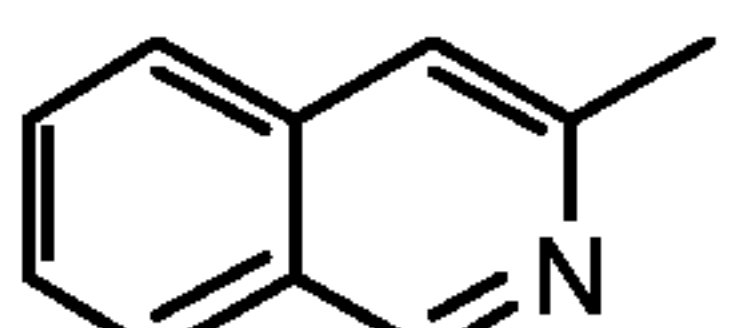
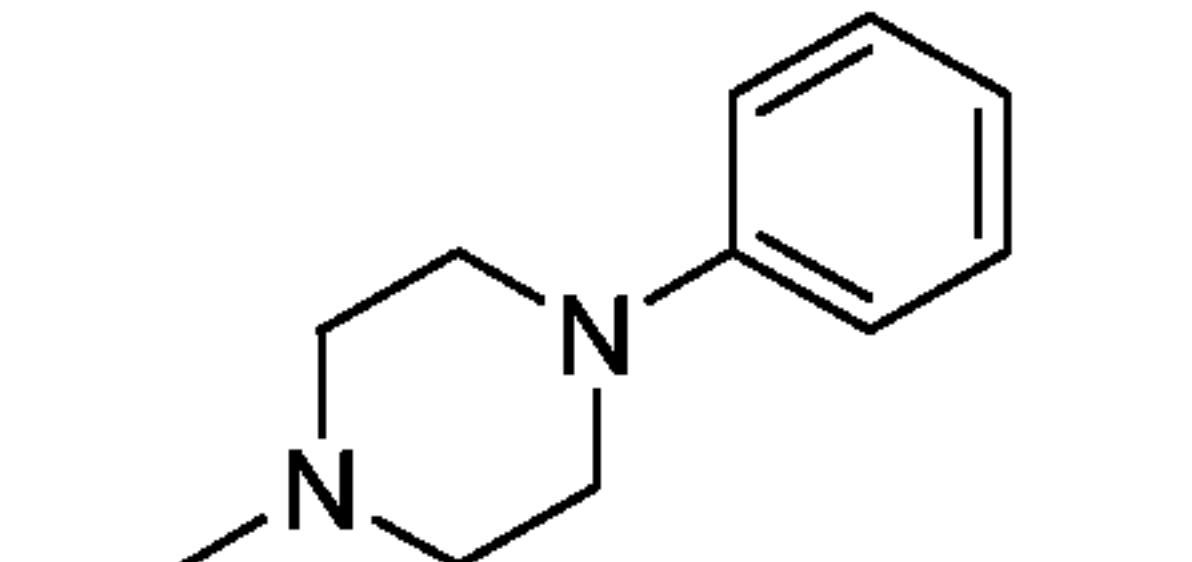
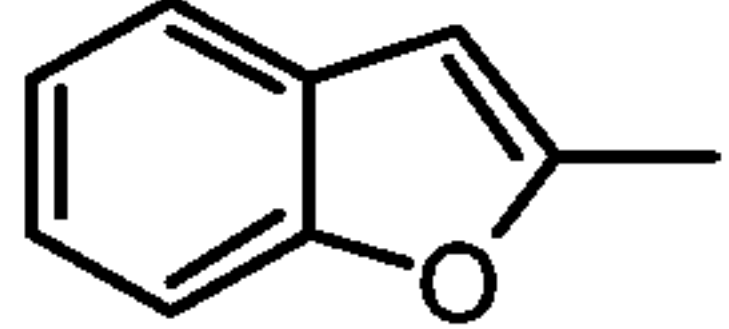
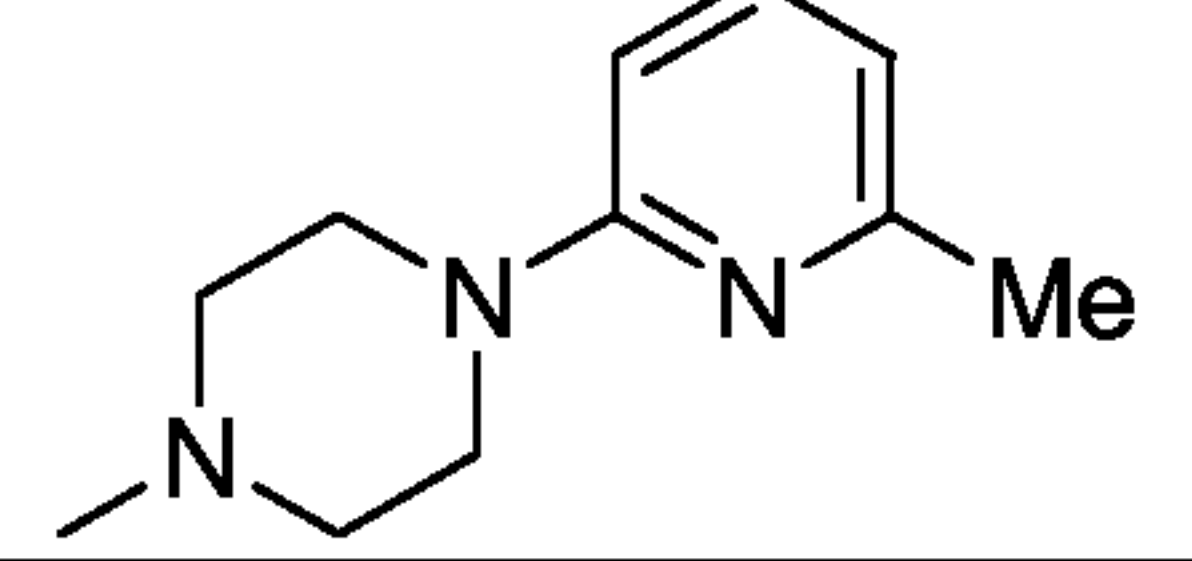
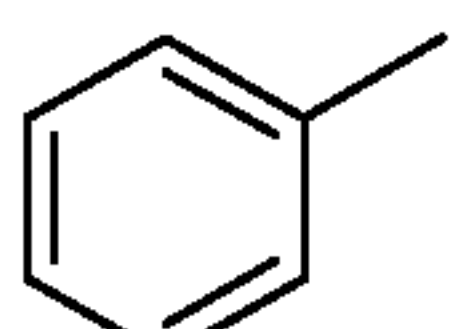
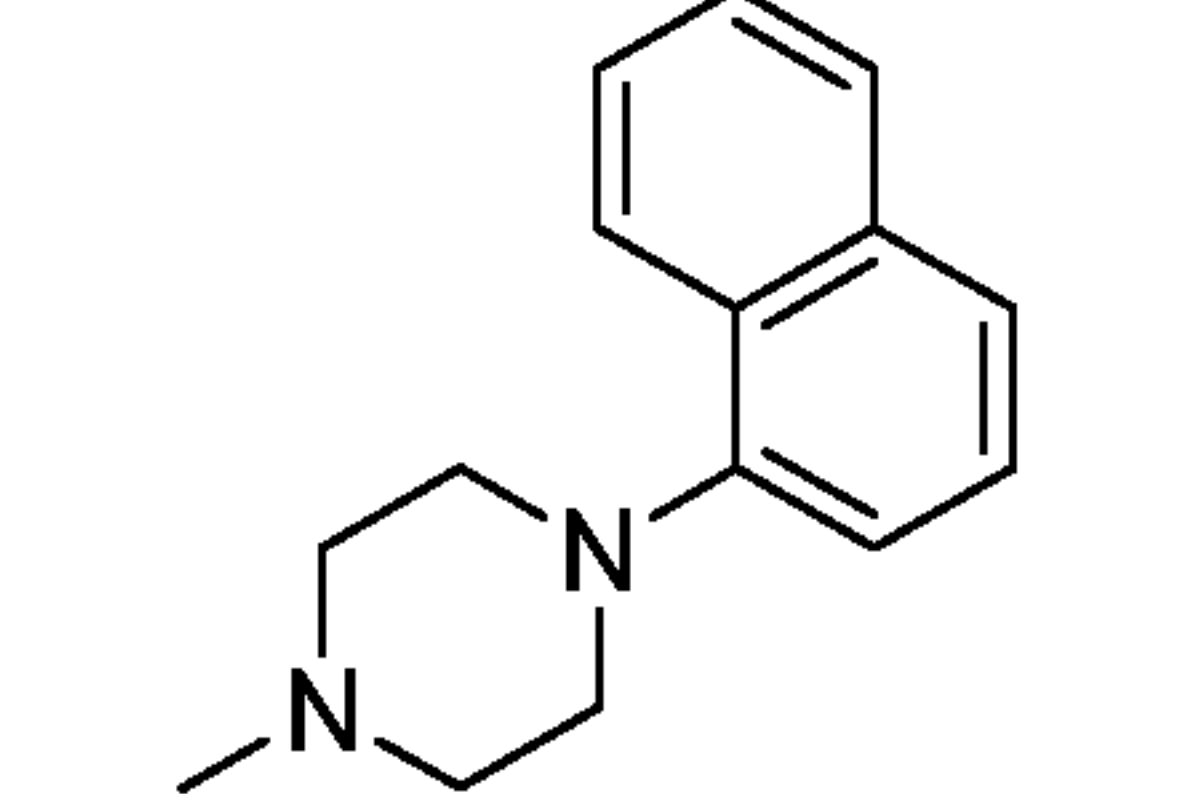
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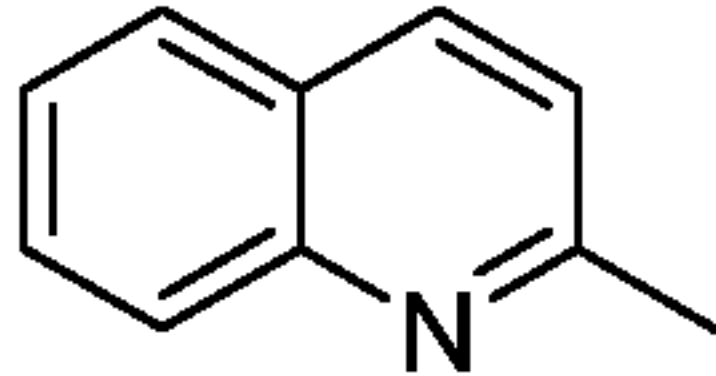
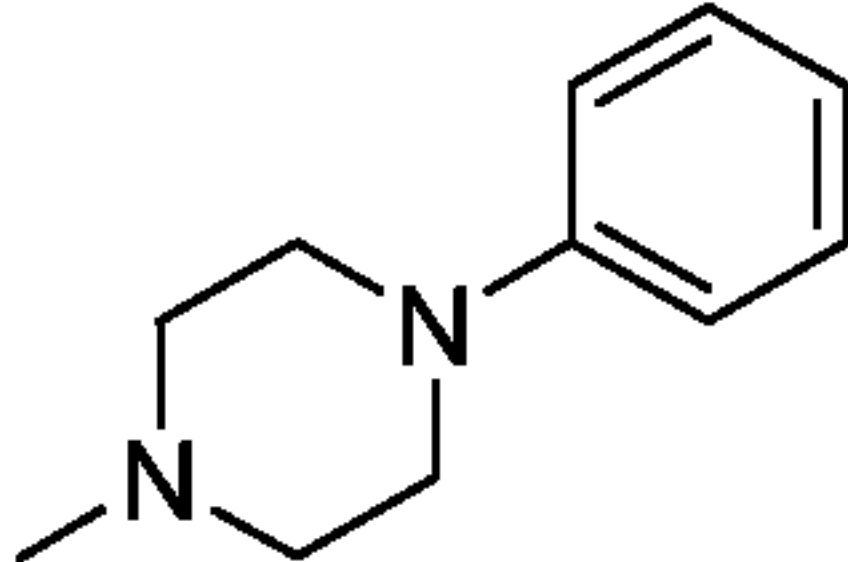
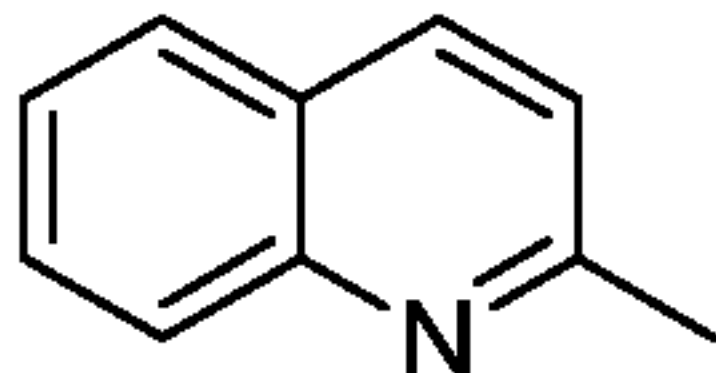
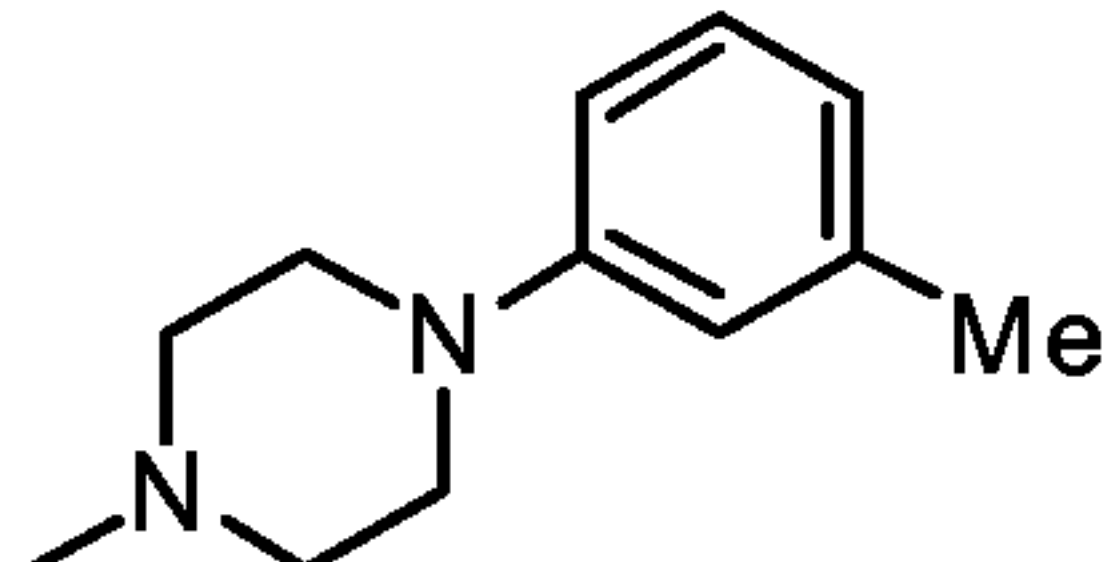
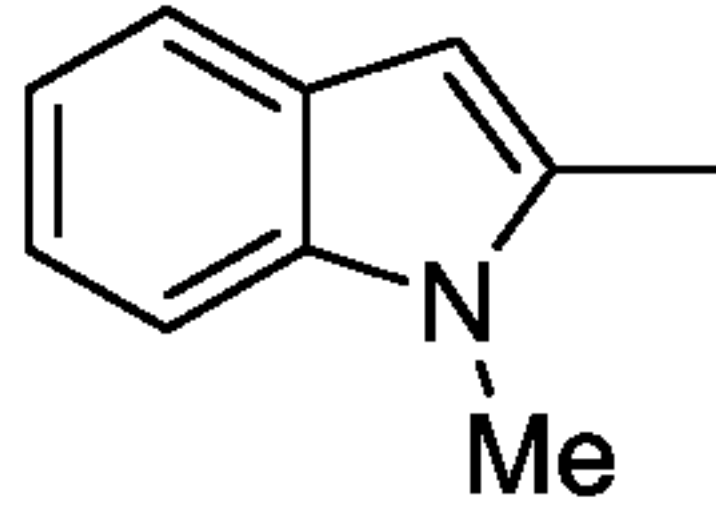
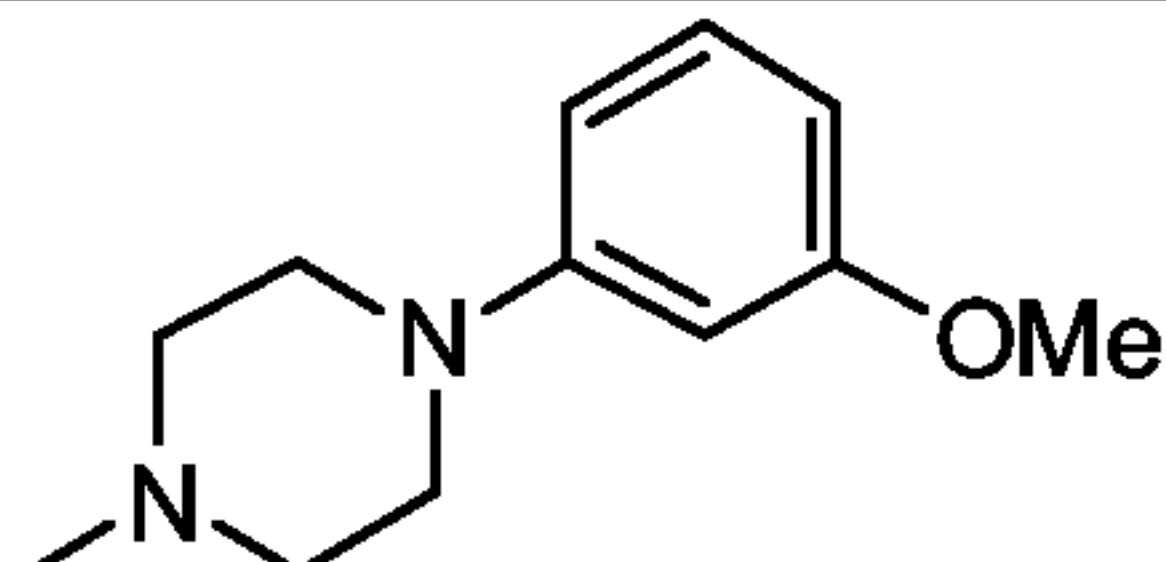
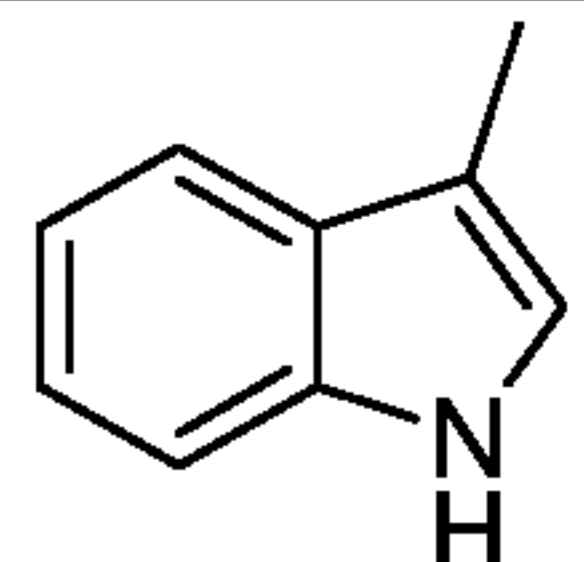
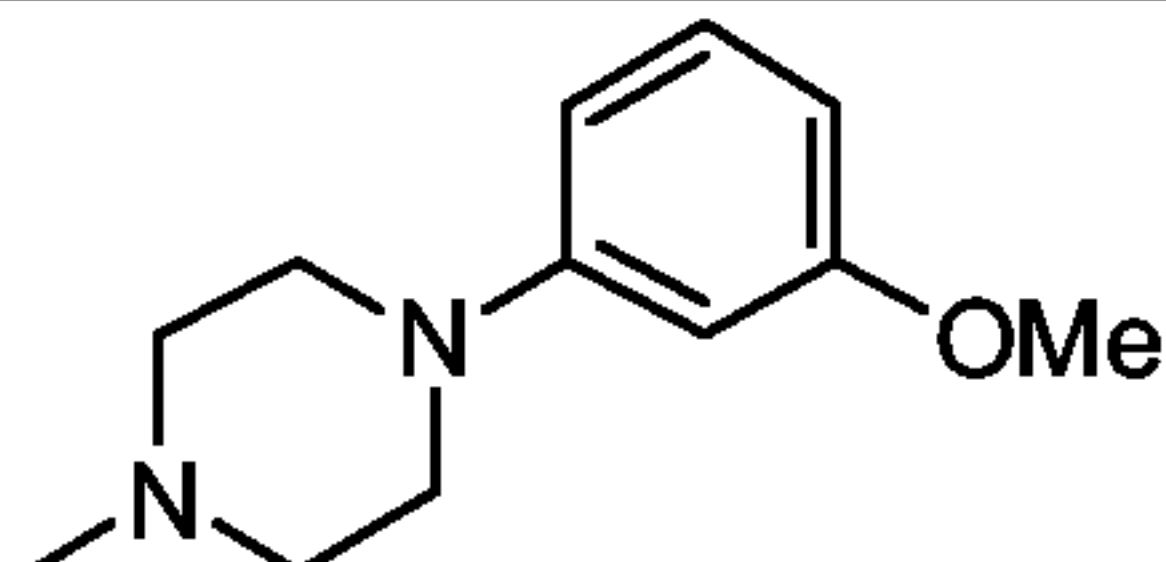
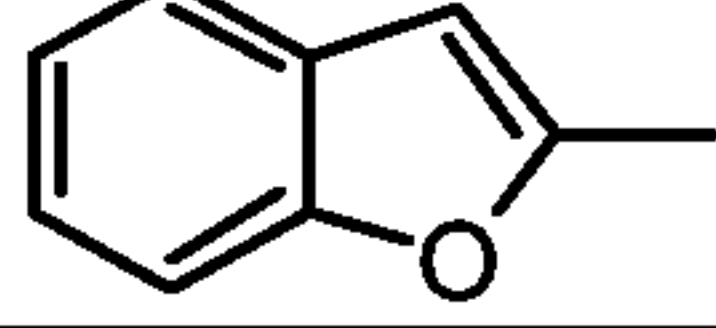
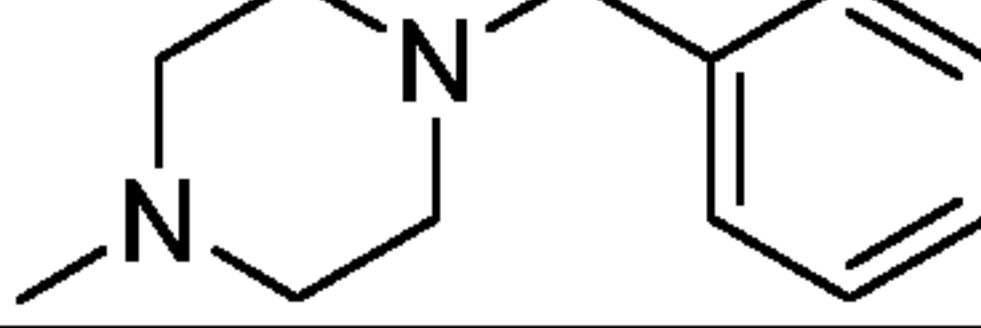
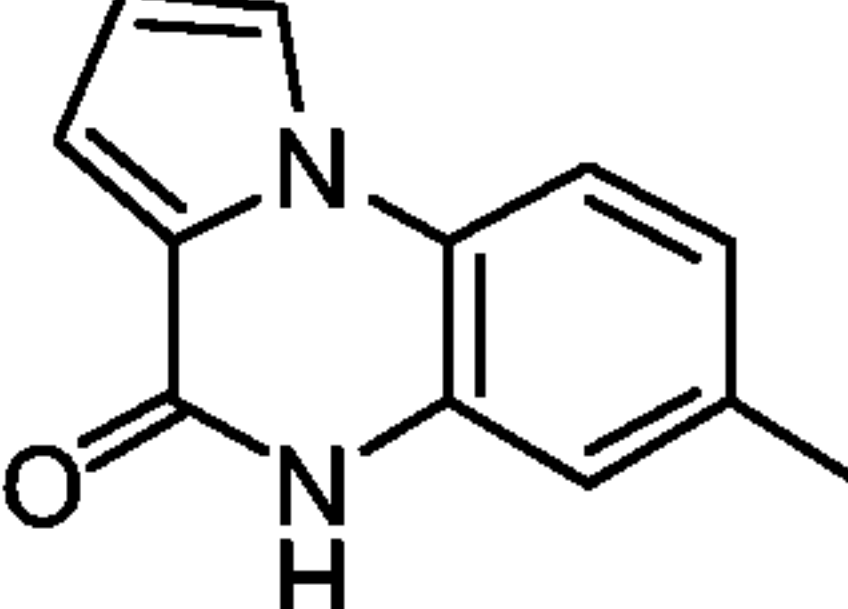
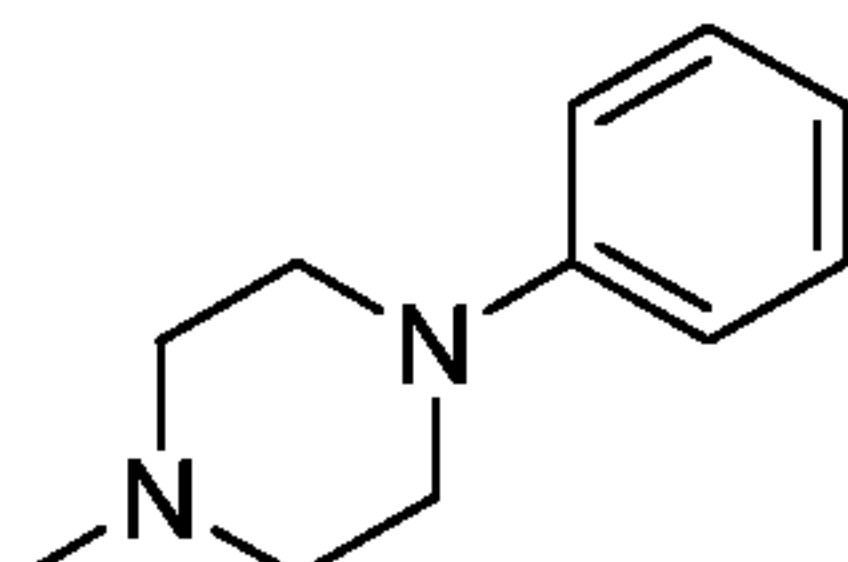
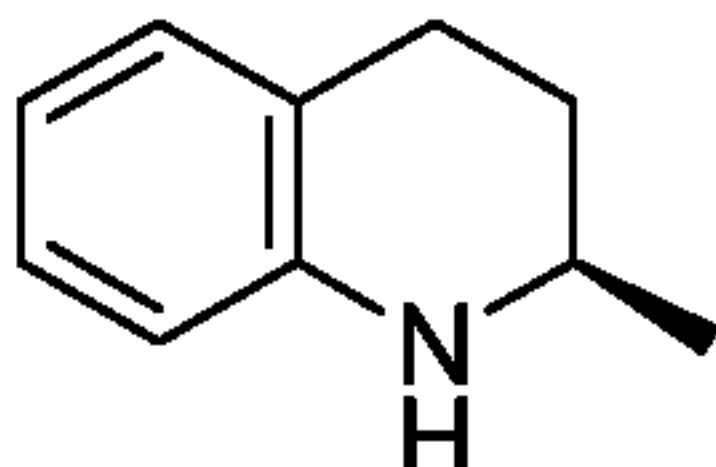
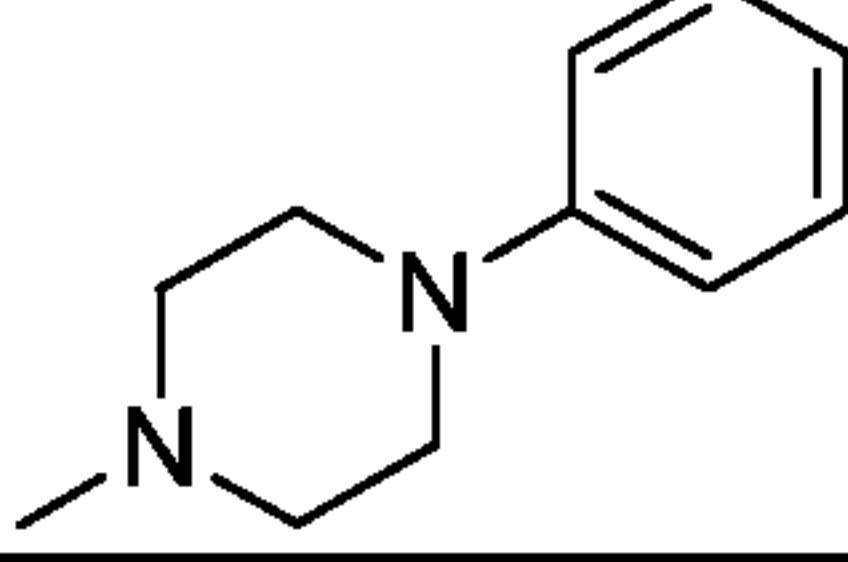
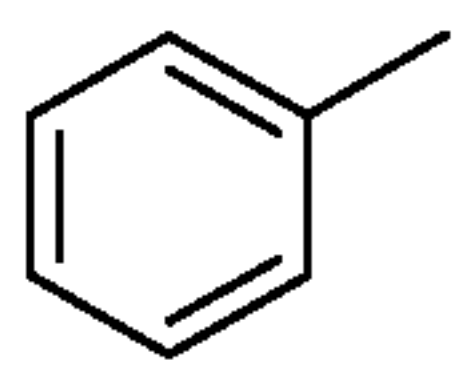
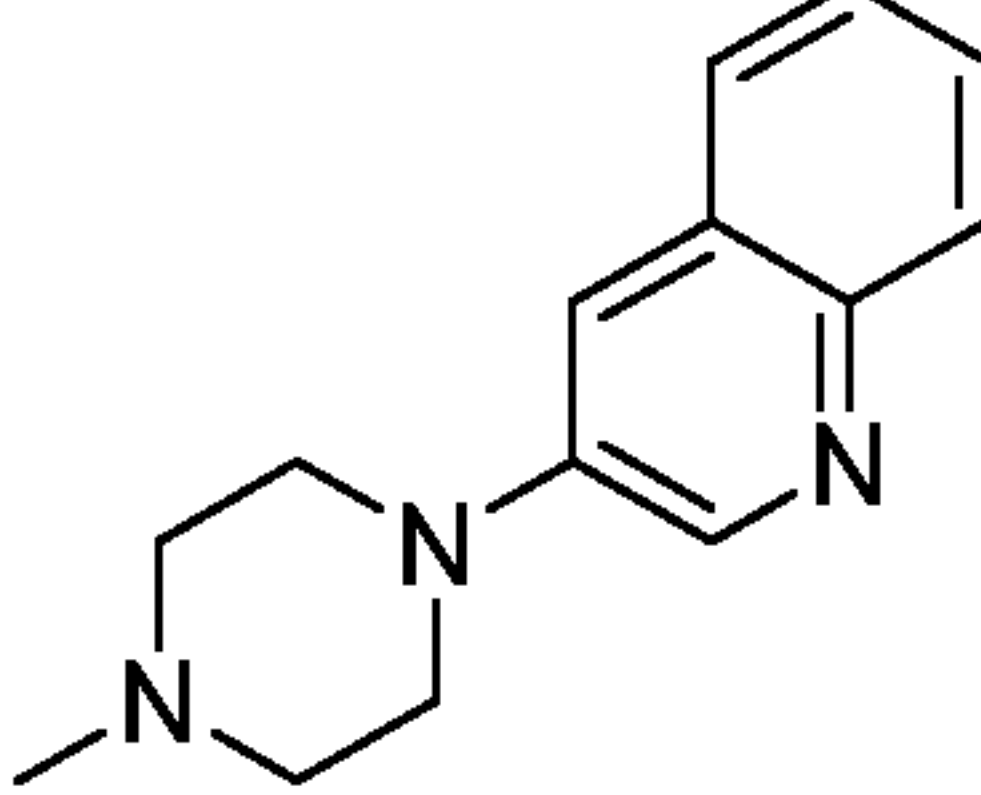
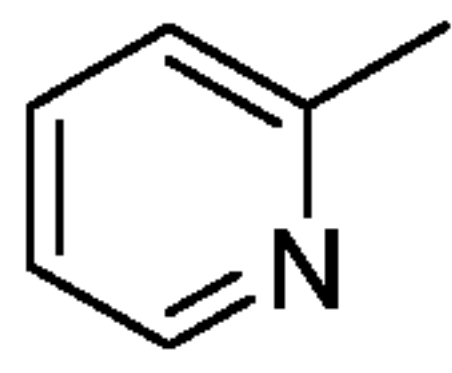
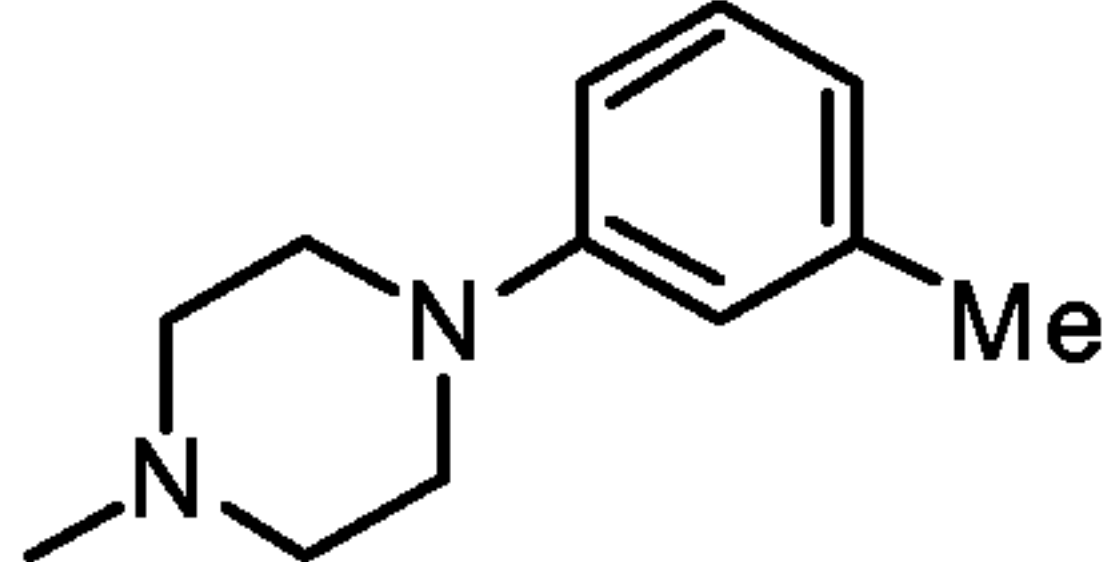
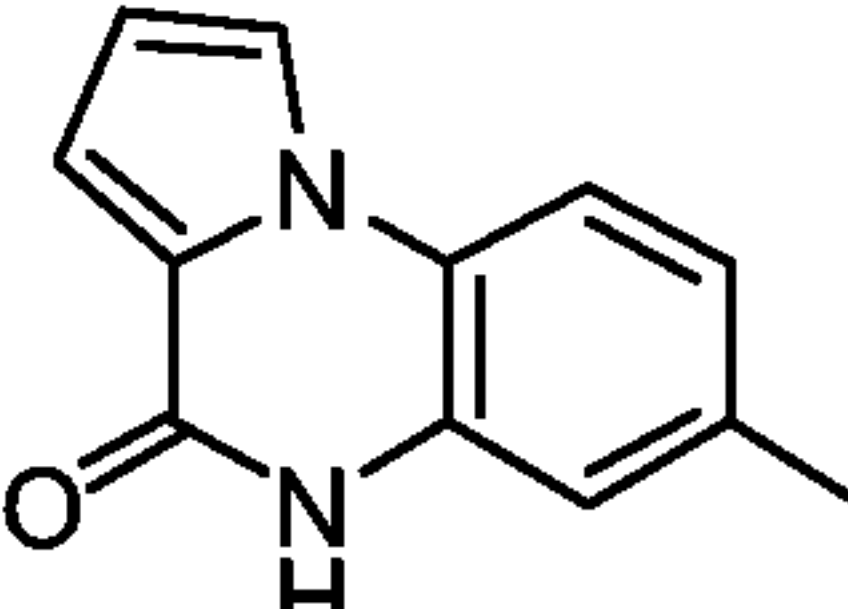
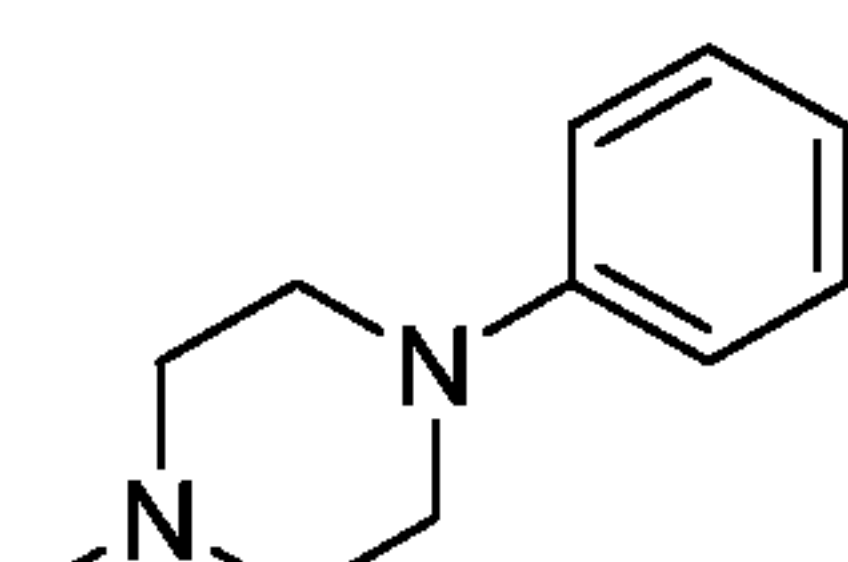
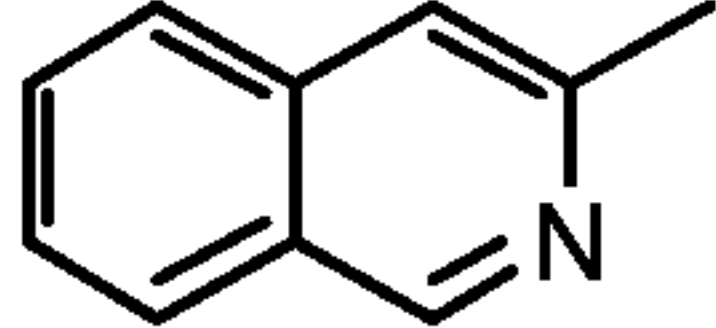
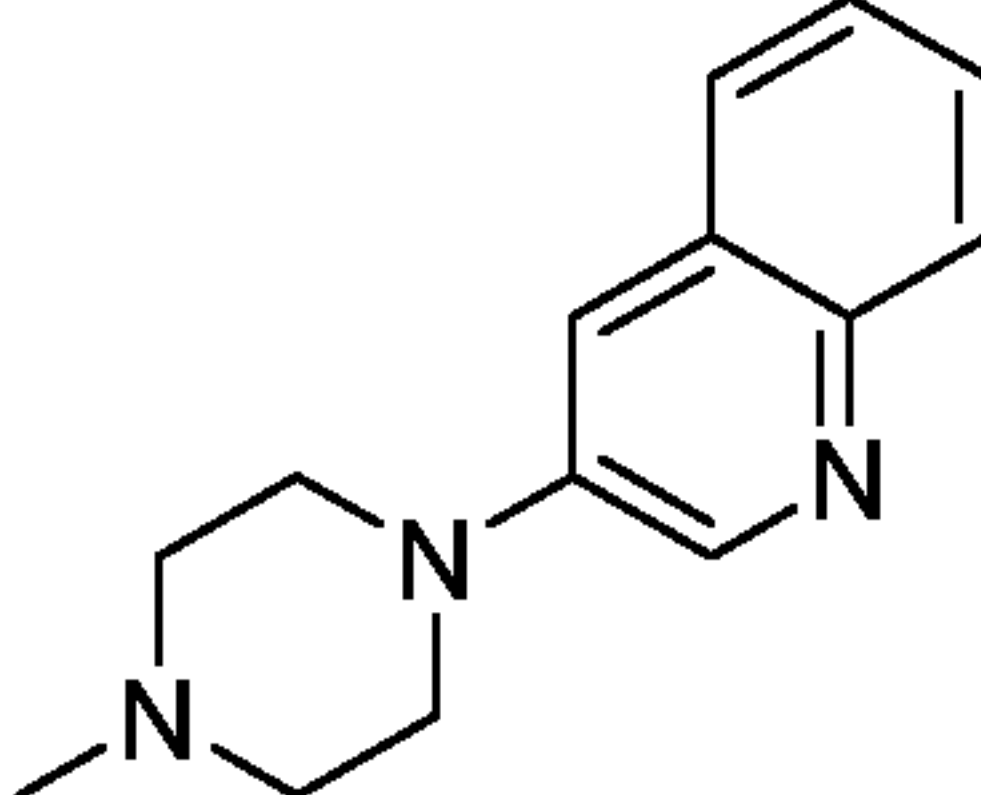
HEAD – LINKER – TAILTable 1Compounds of the invention

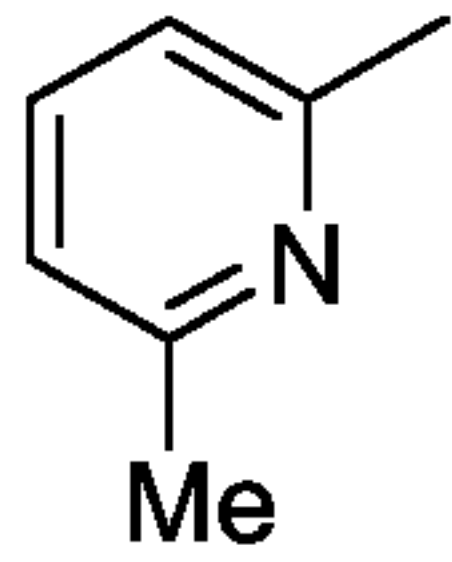
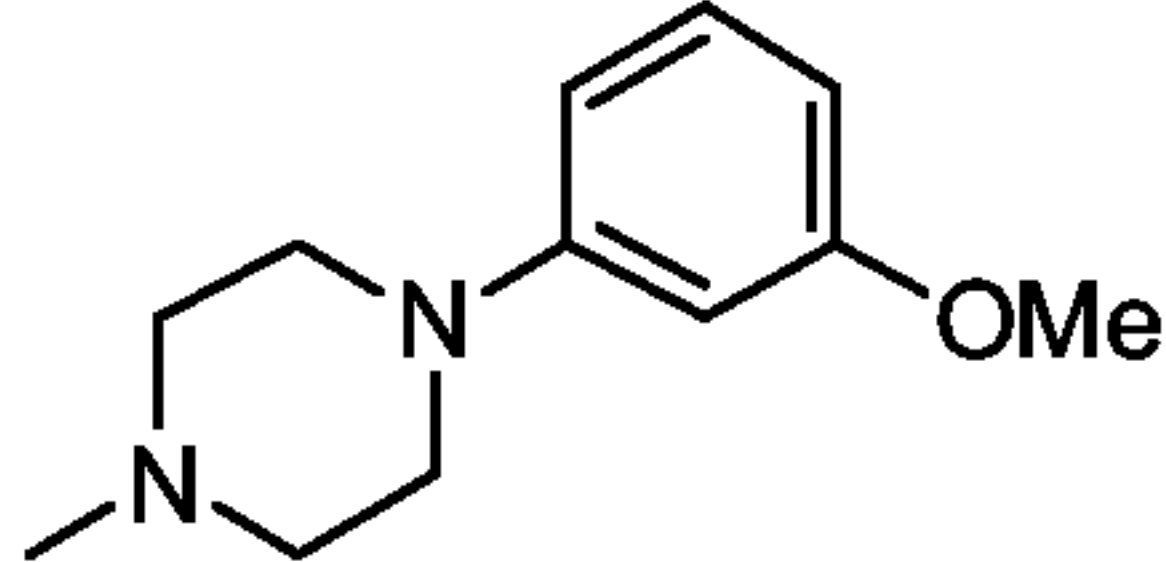
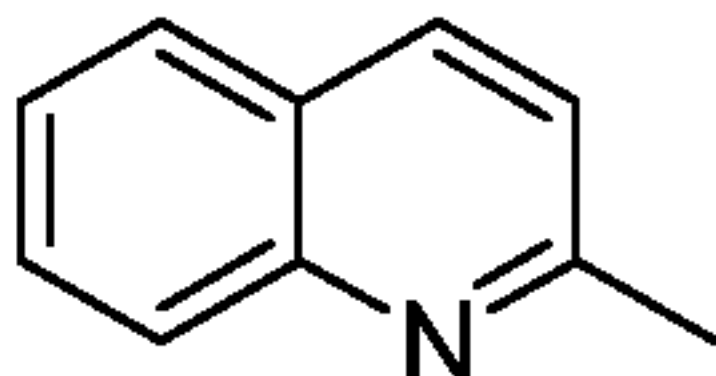
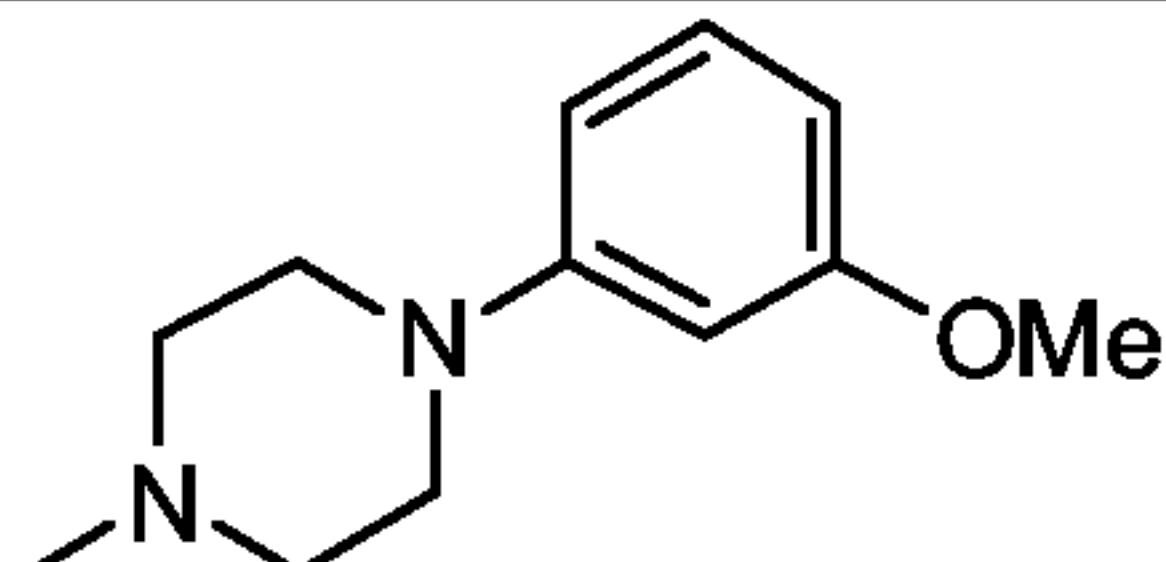
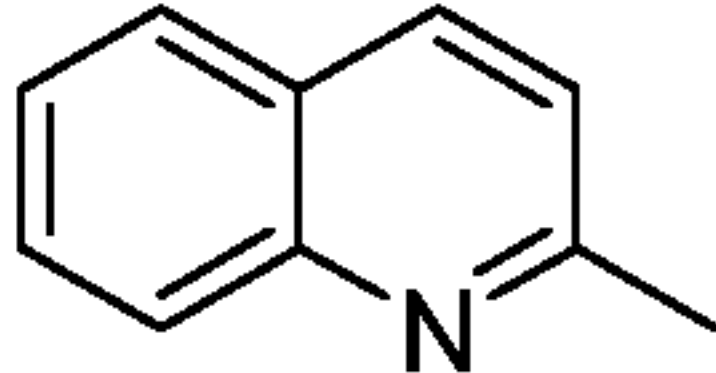
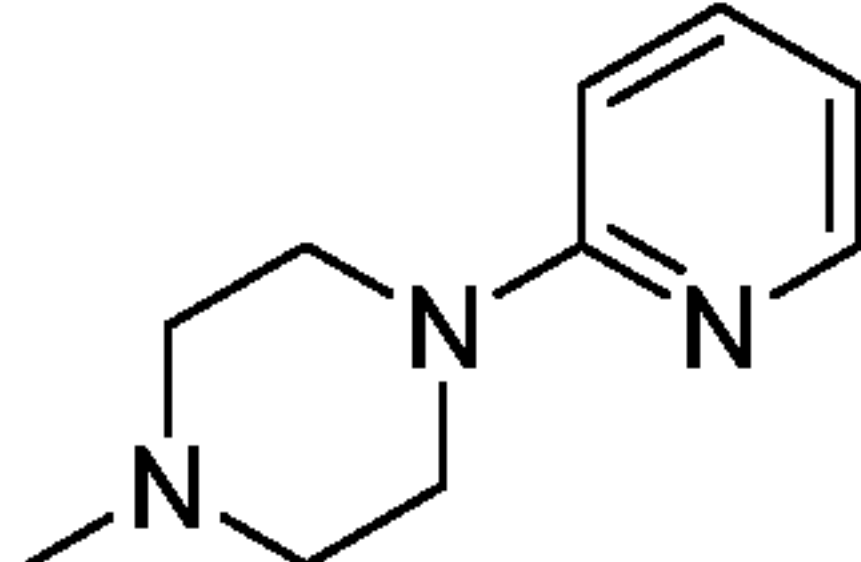
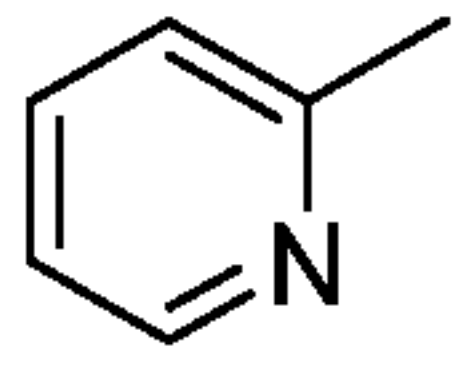
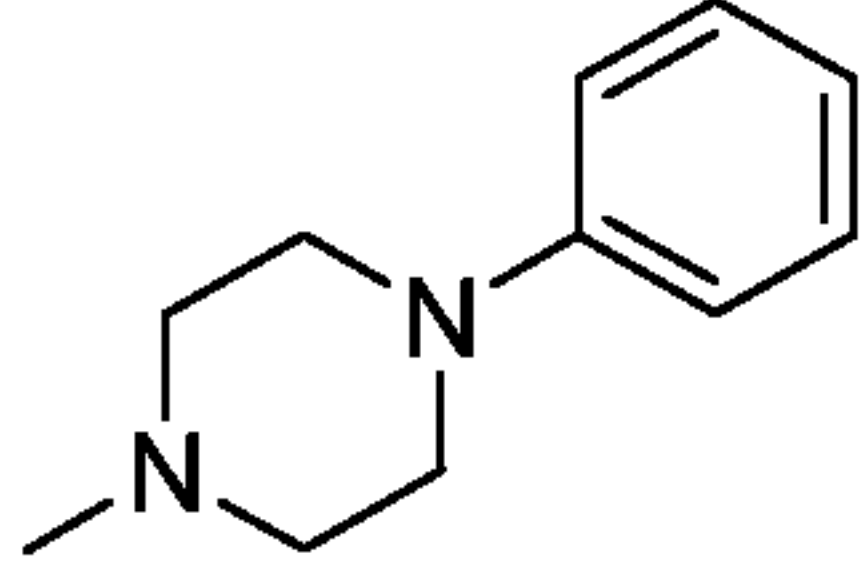
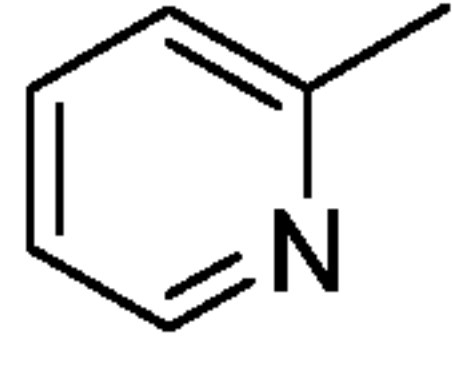
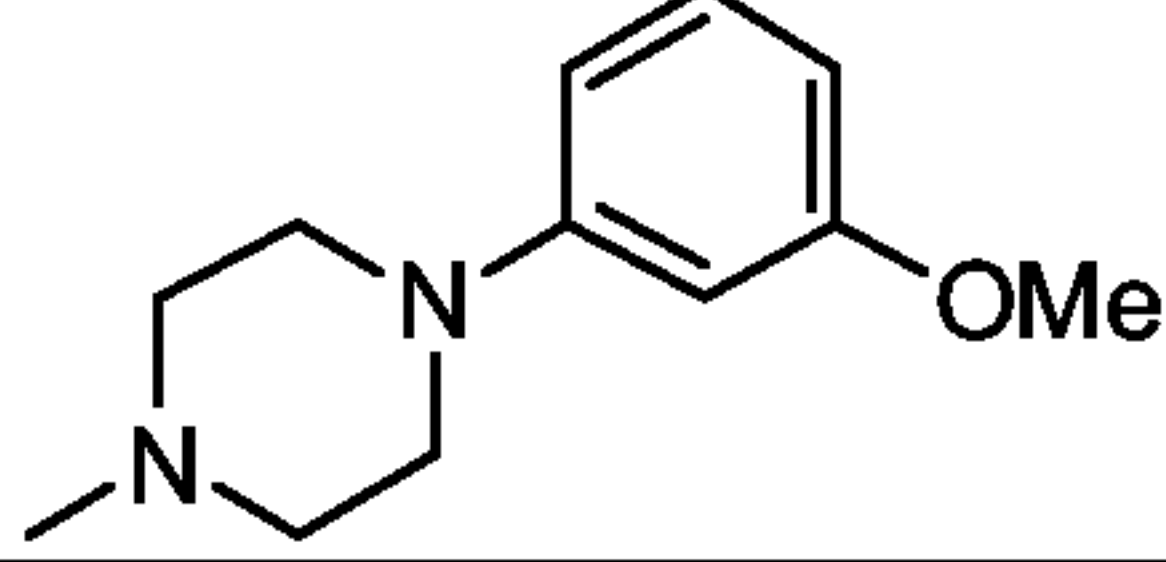
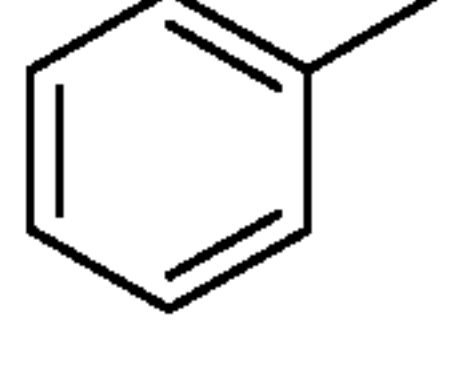
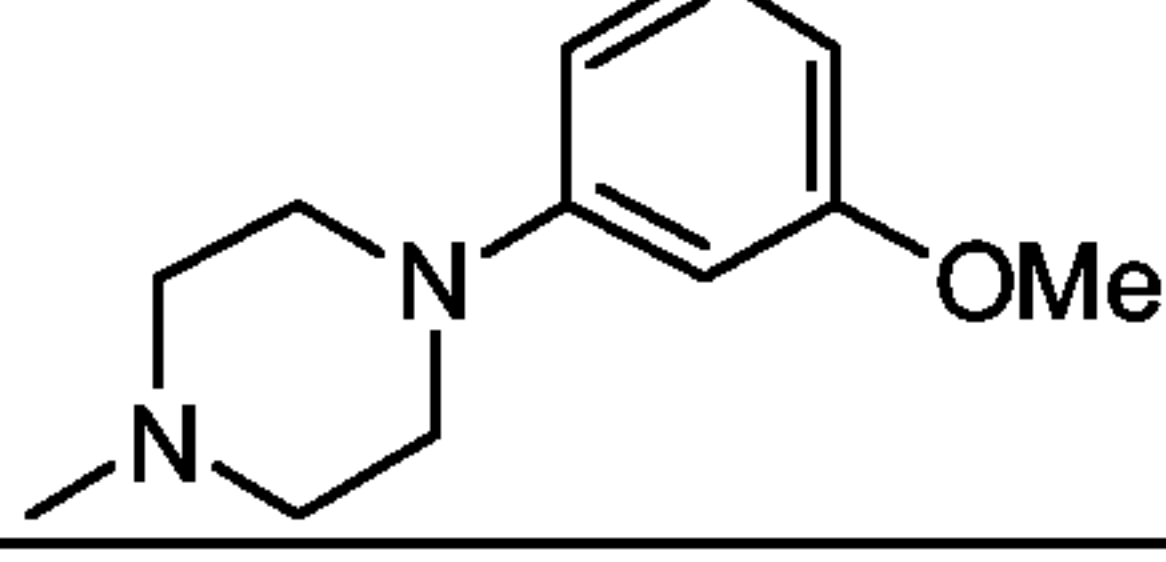
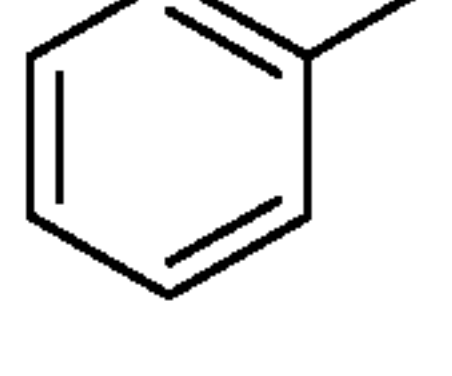
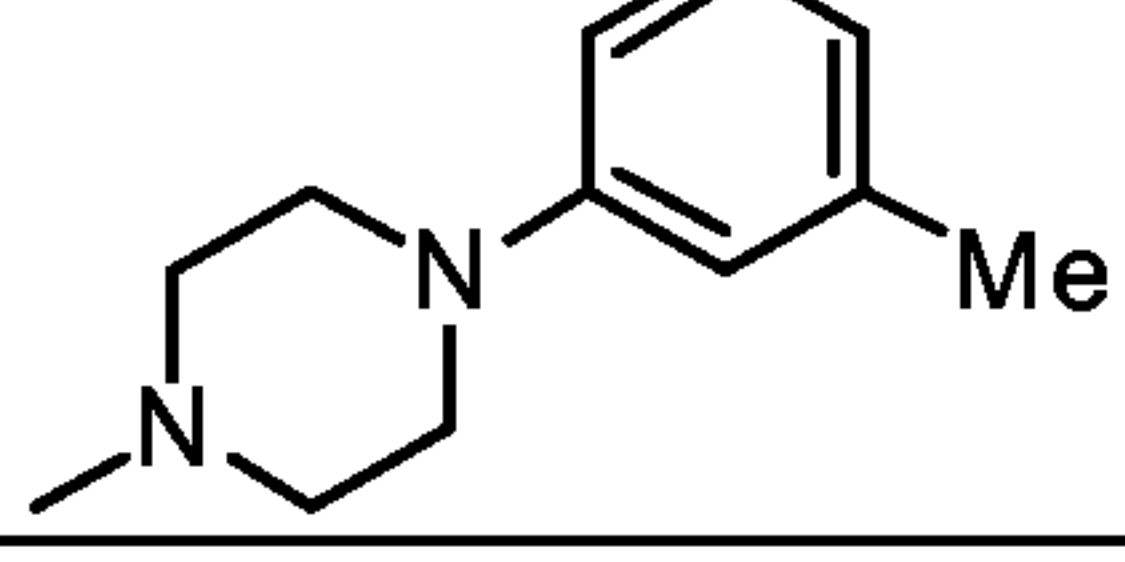
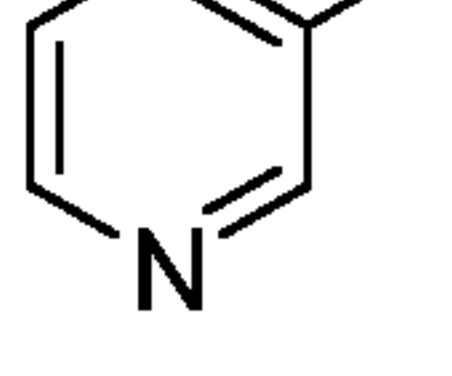
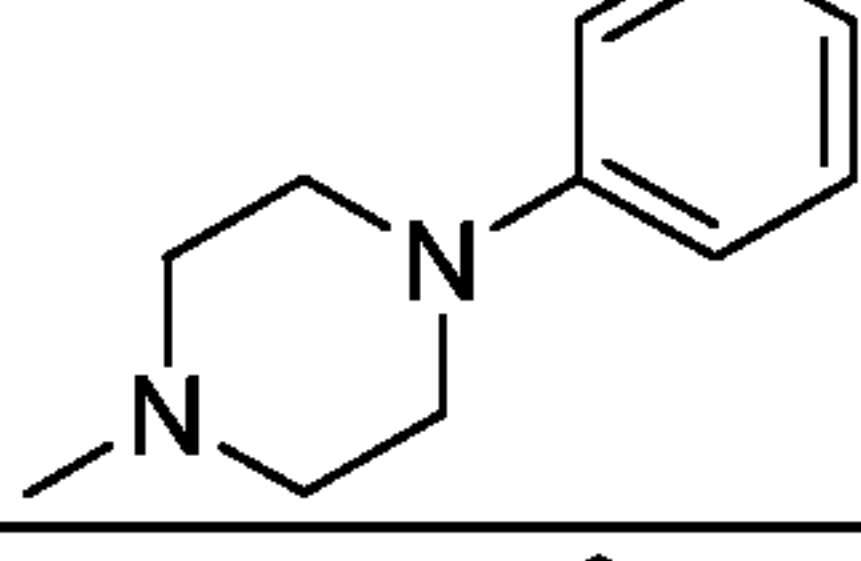
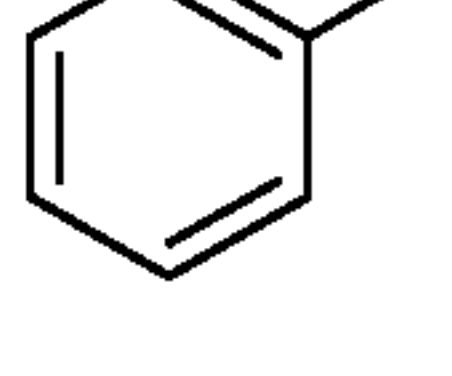
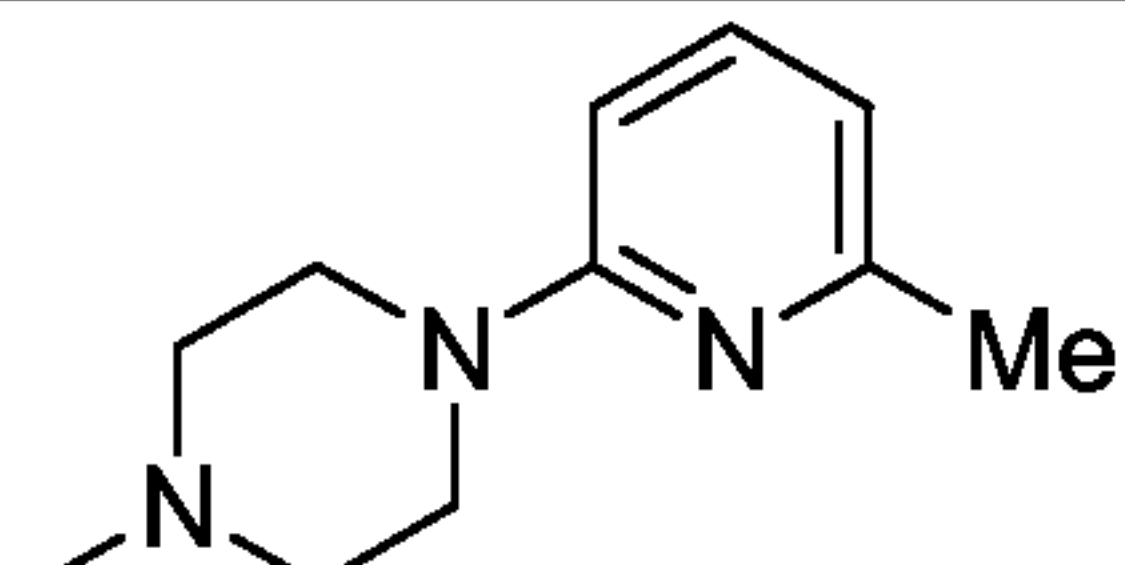
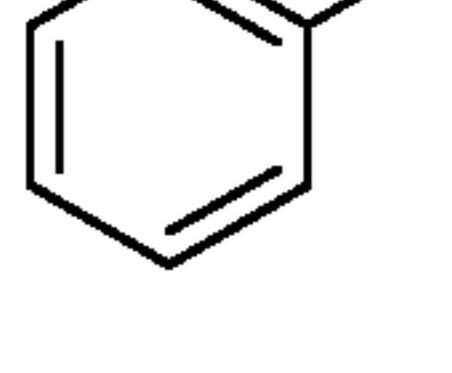
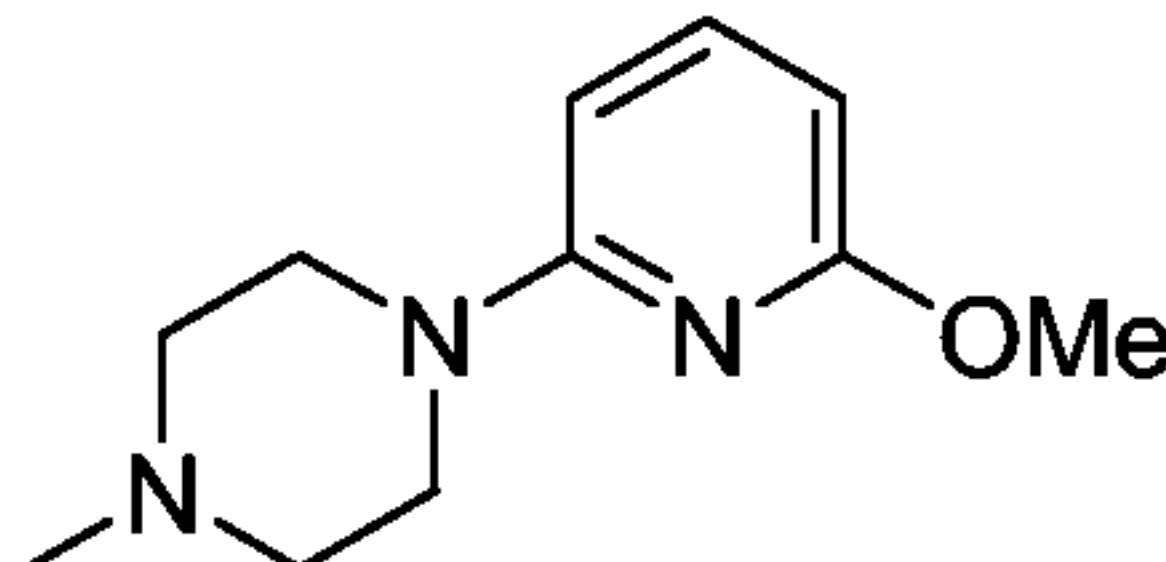
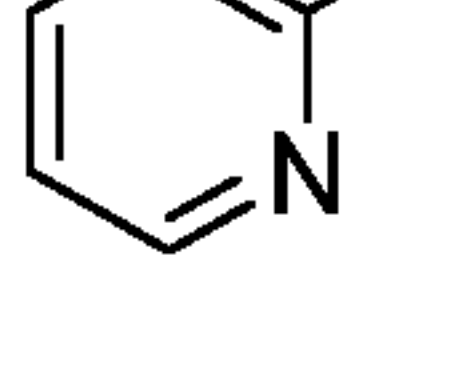
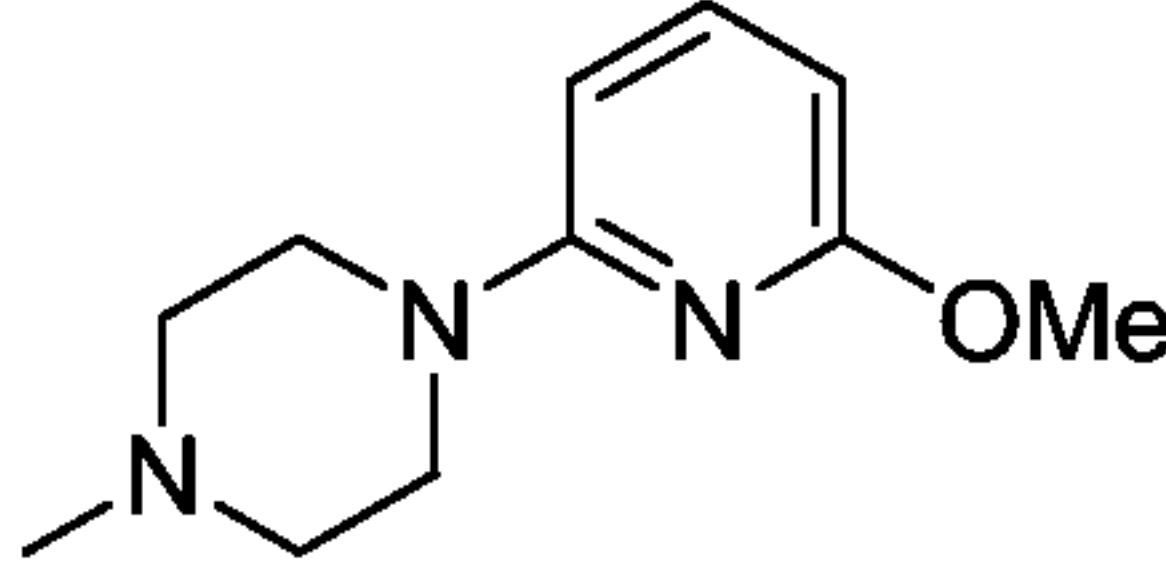
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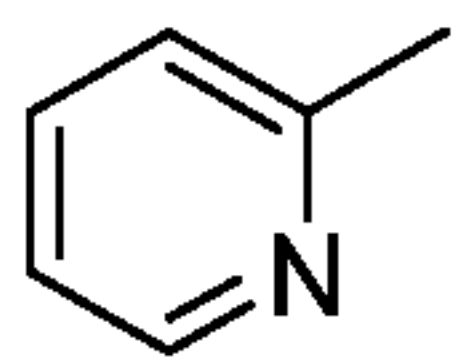
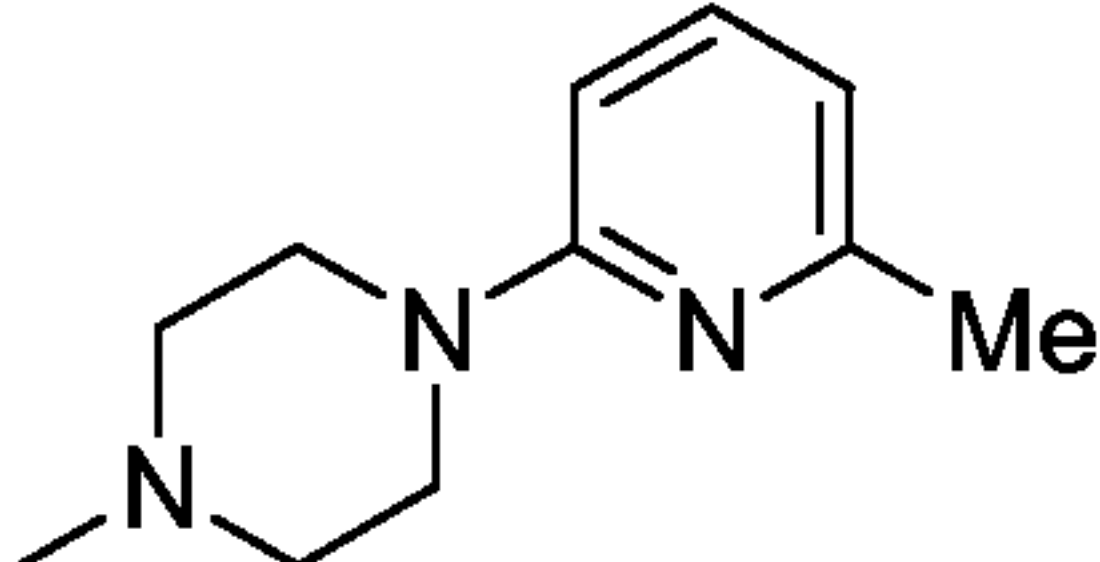
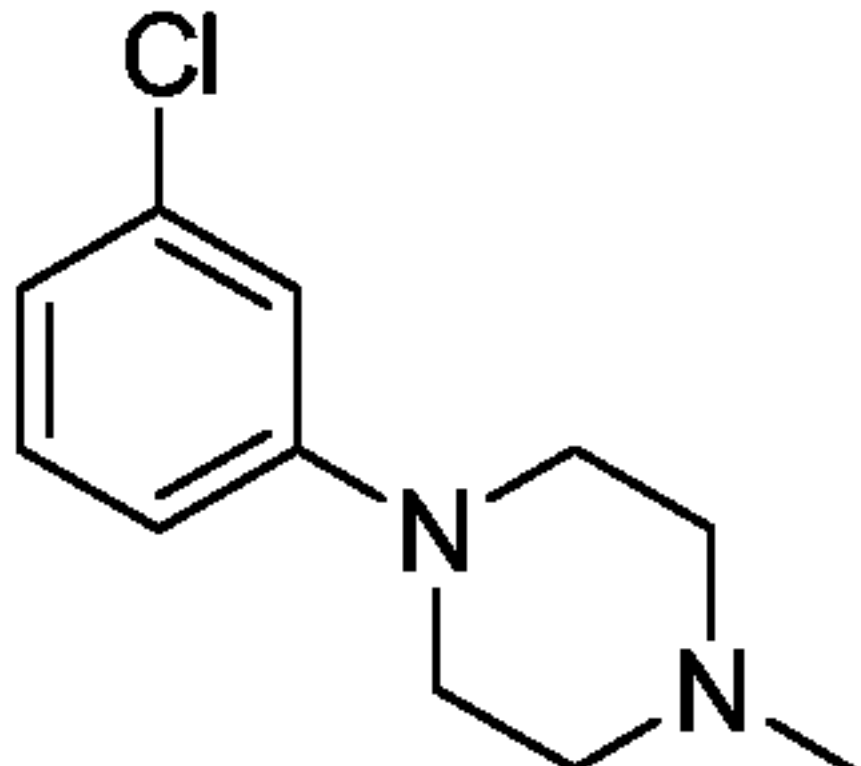
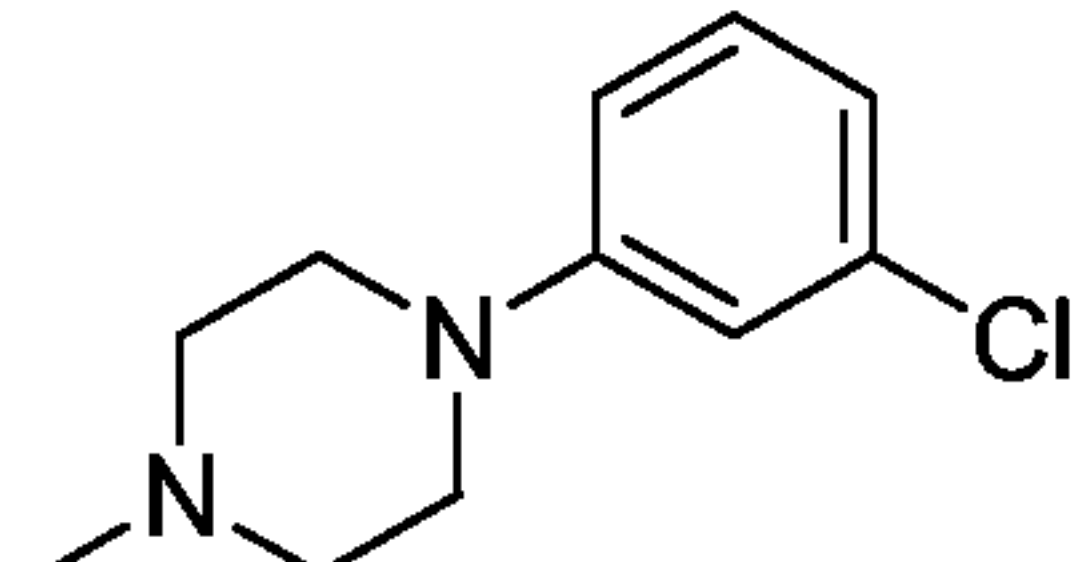
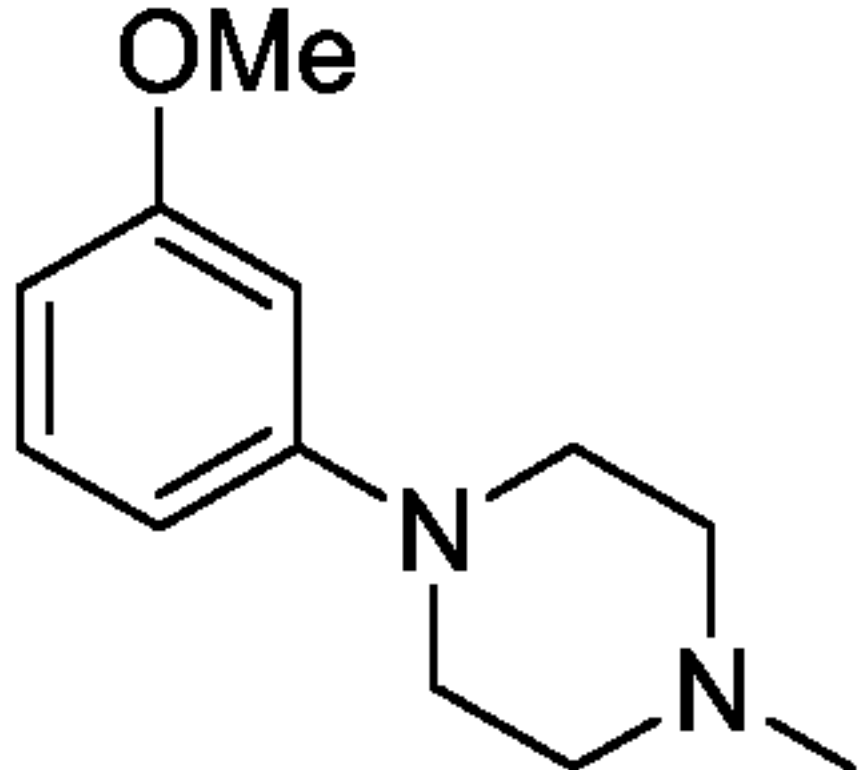
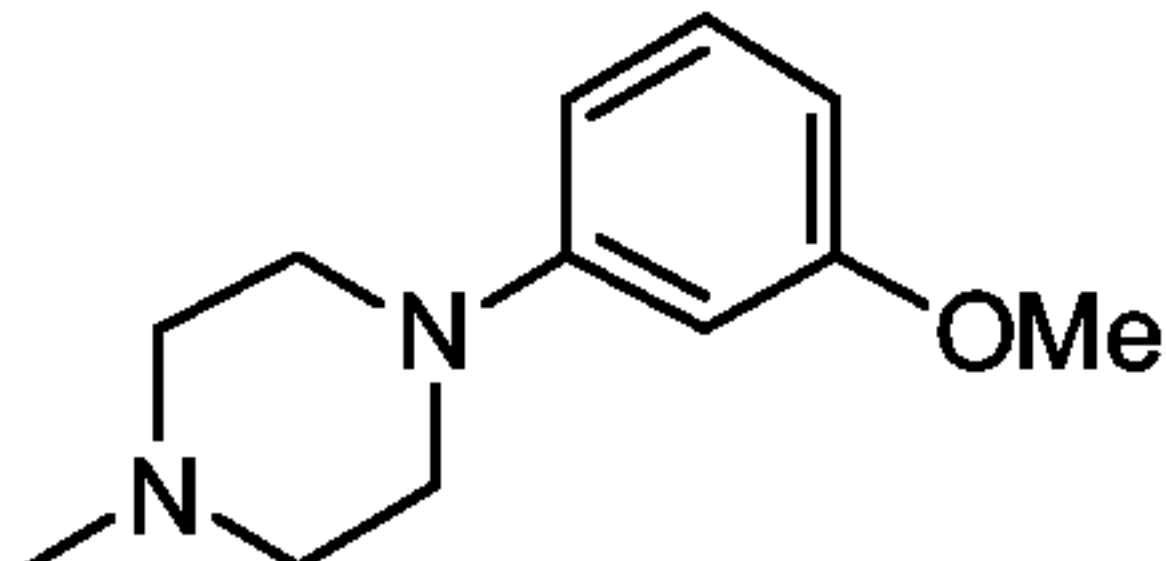
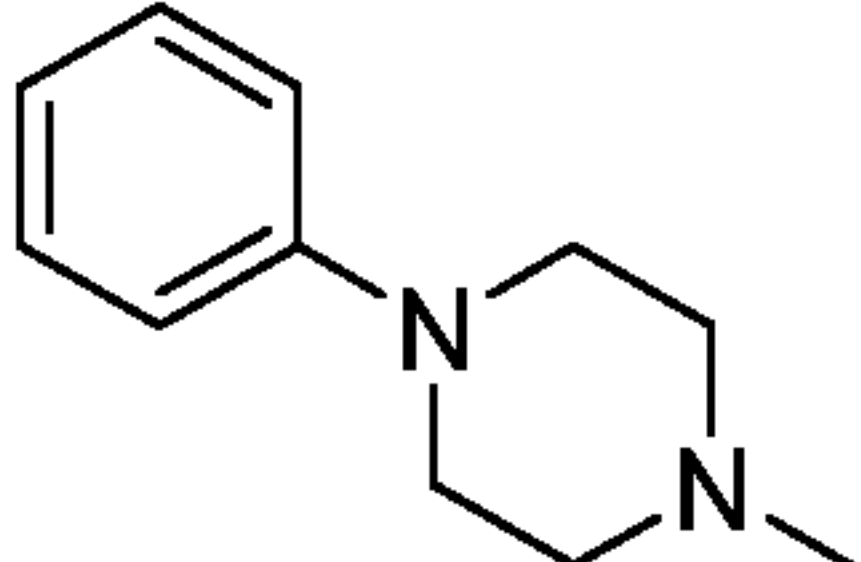
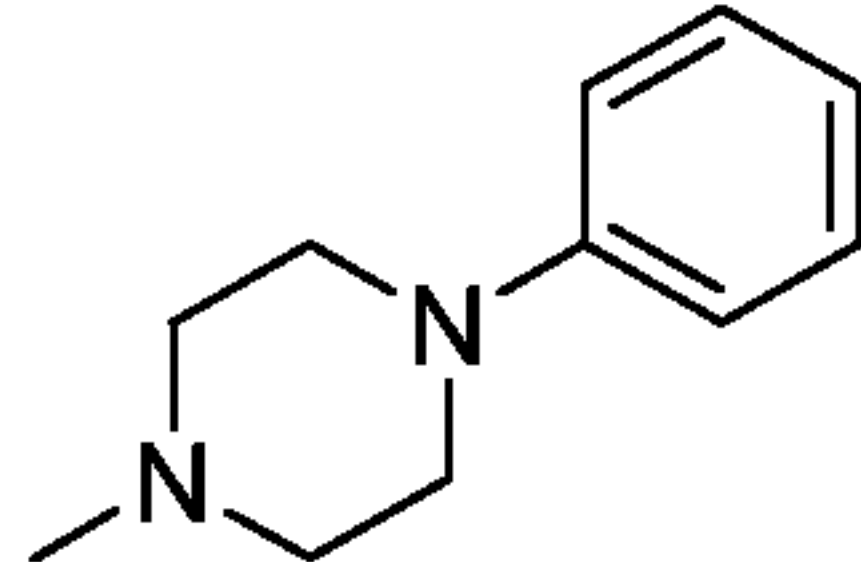
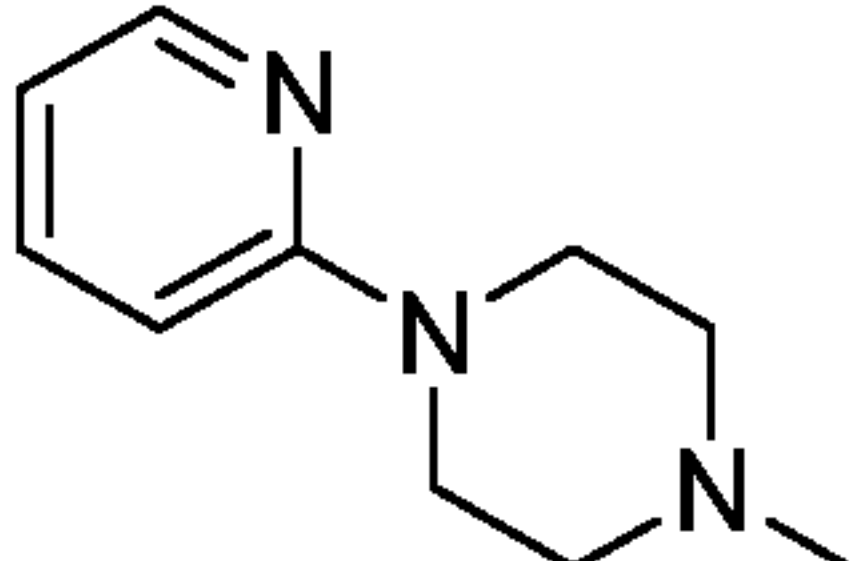
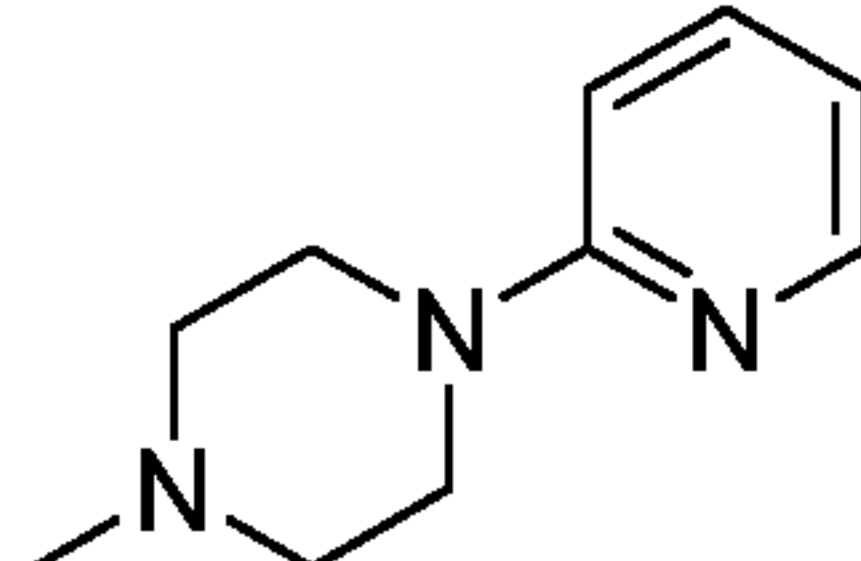
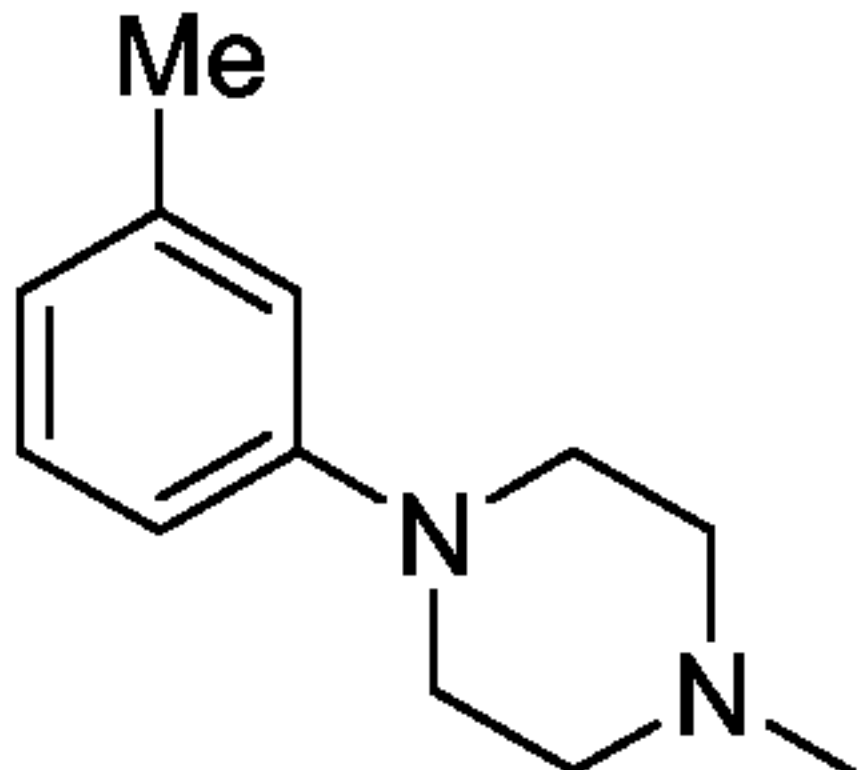
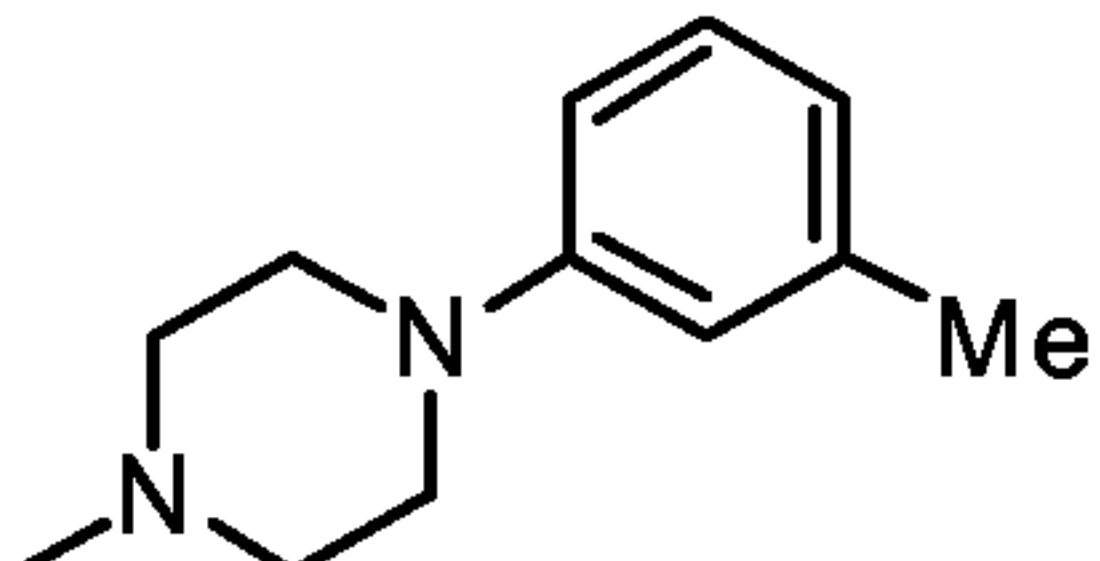
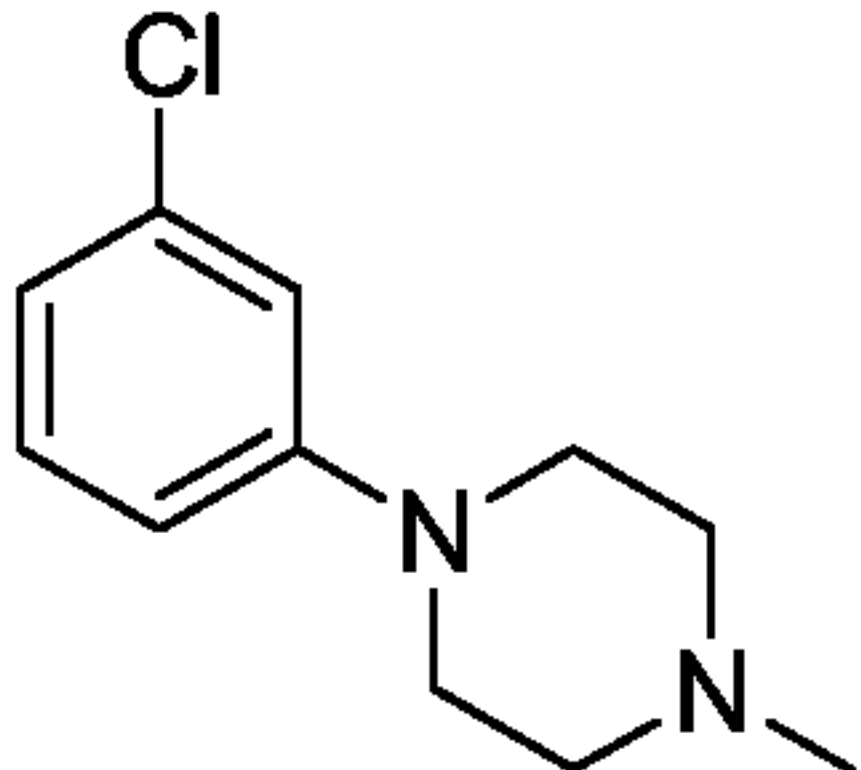
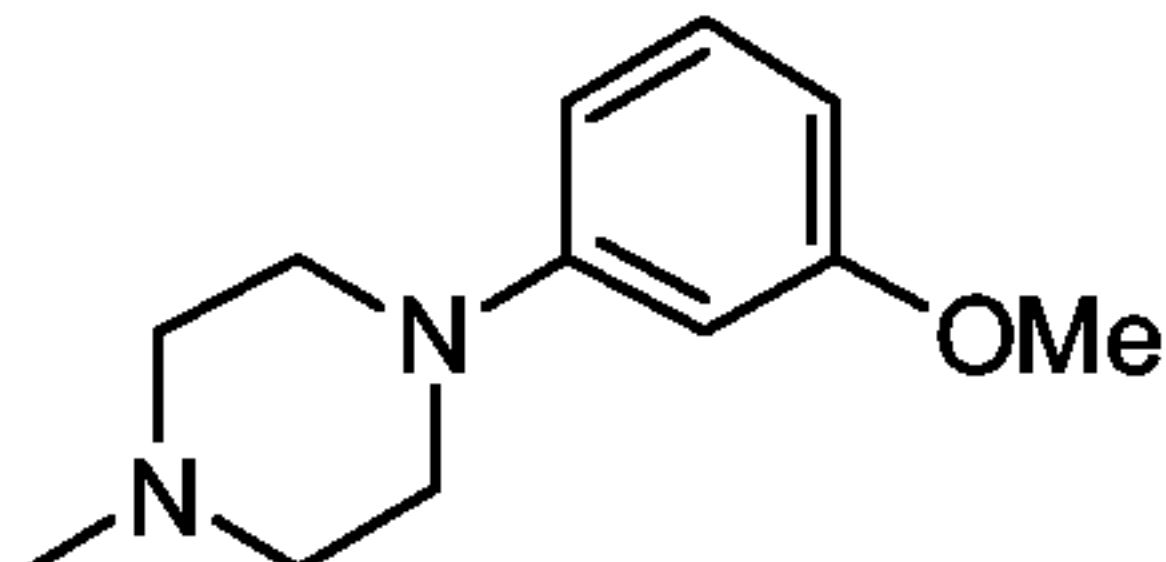
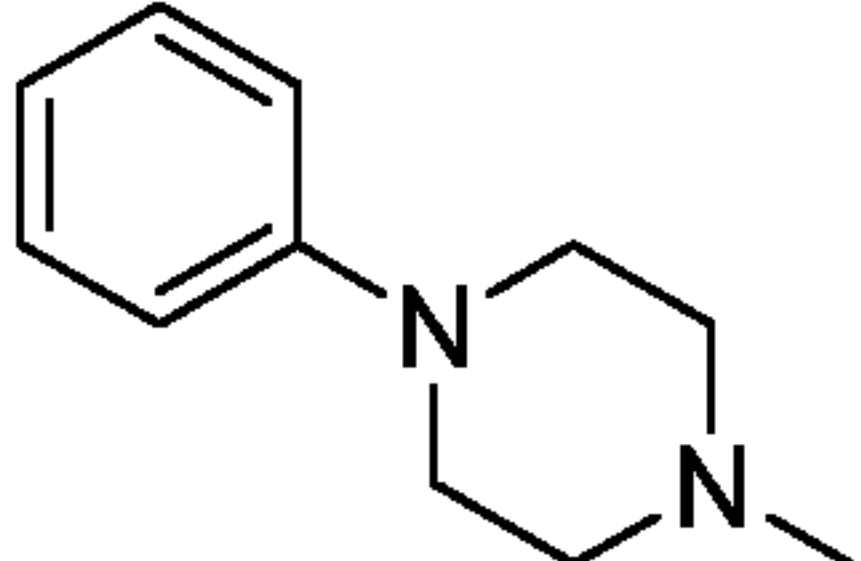
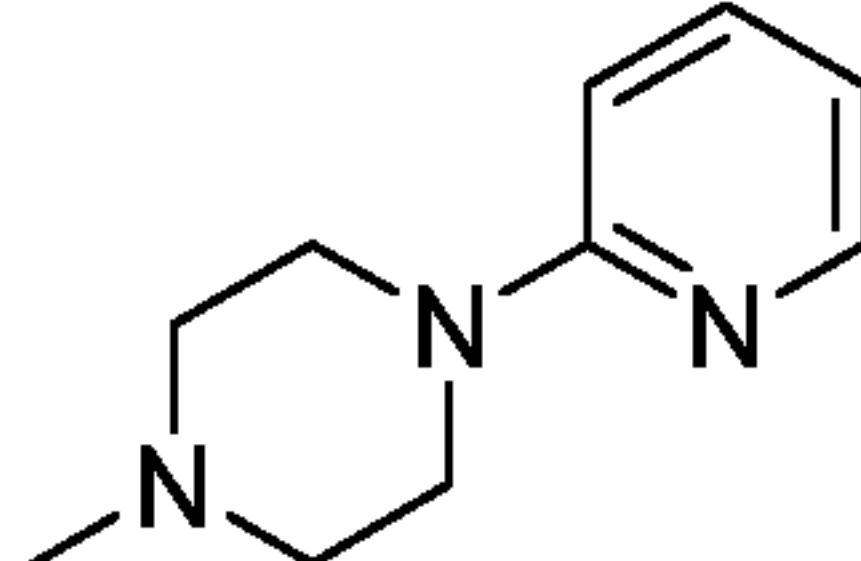
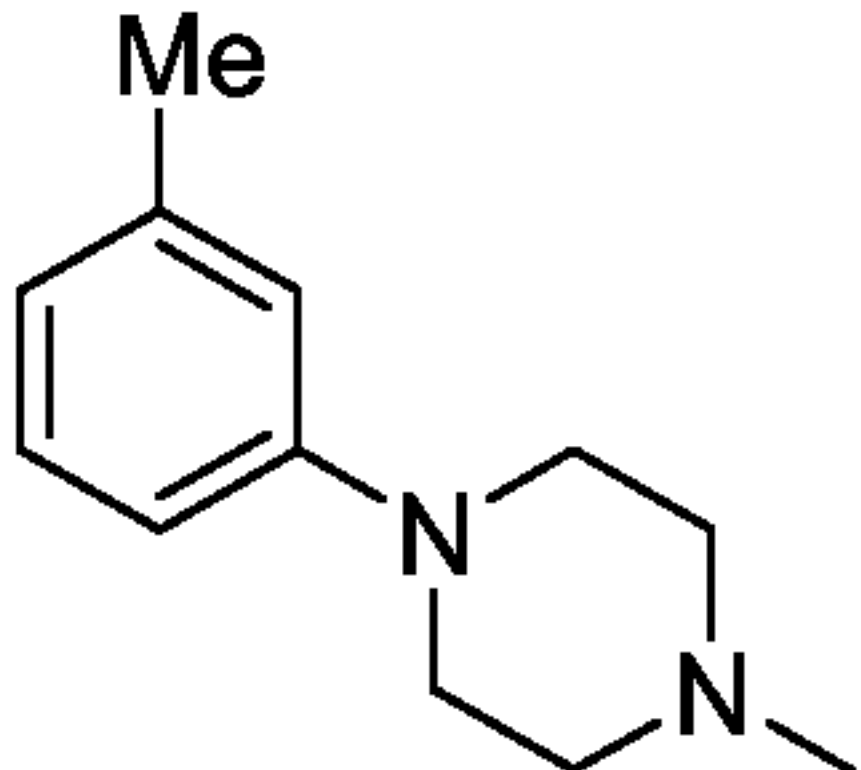
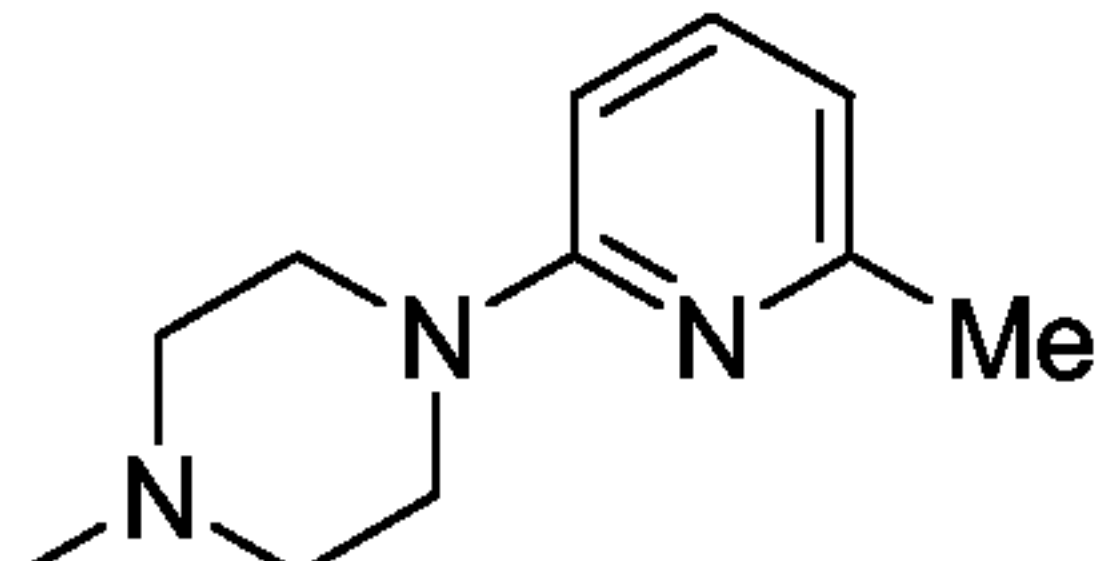
Cp. No.	Head	Linker	Tail
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1-2		-(CH ₂) ₄ -	
1-3		-CONH(CH ₂) ₄ -	
1-4		-CONH(CH ₂) ₄ -	
1-5		-CONH(CH ₂) ₄ -	
1-6		-O(CH ₂) ₅ -	

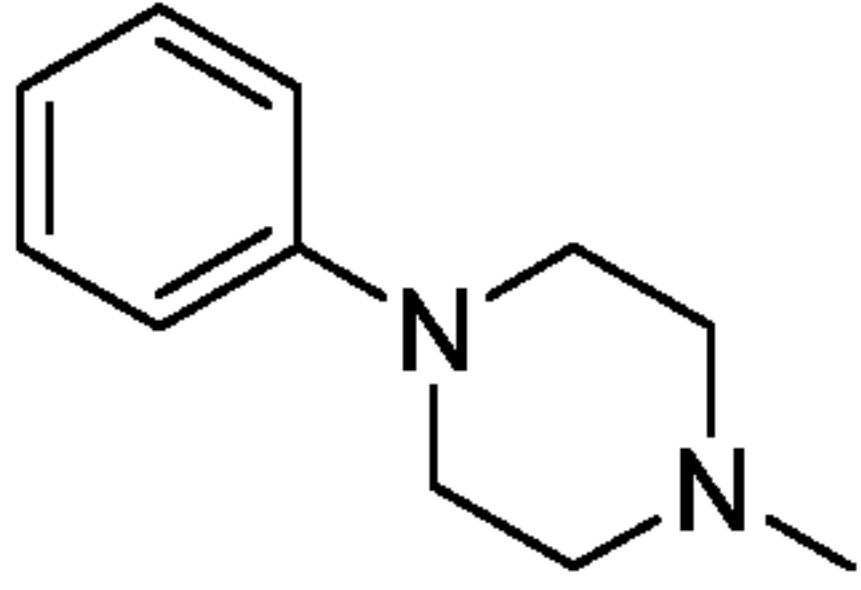
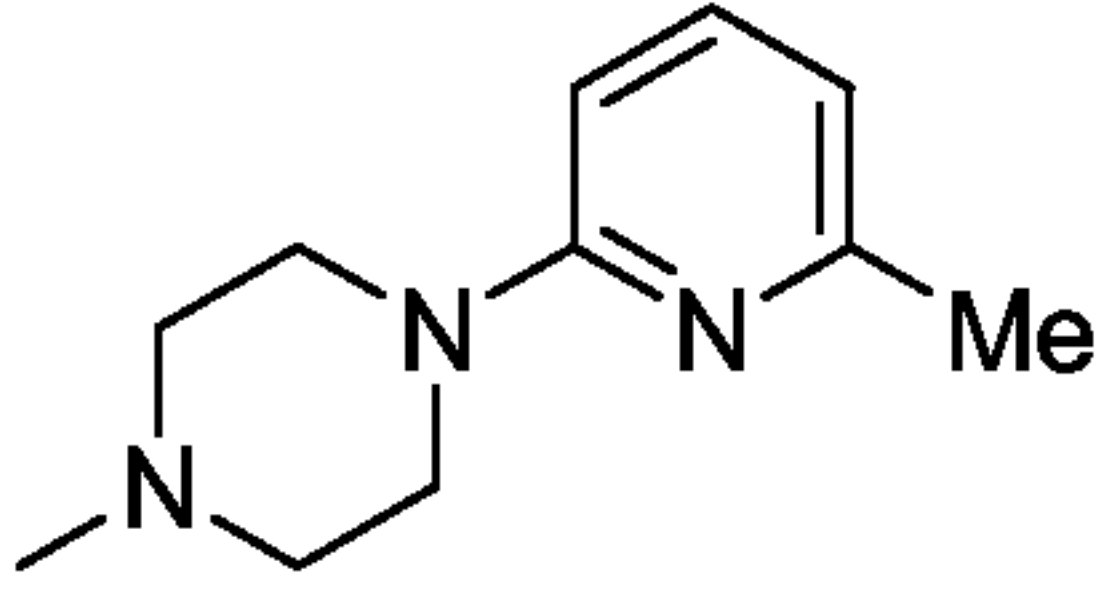
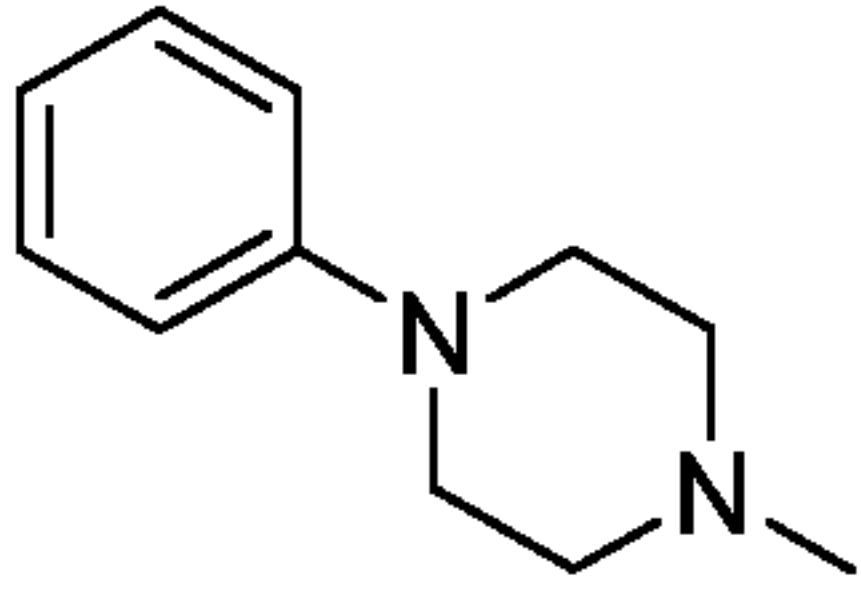
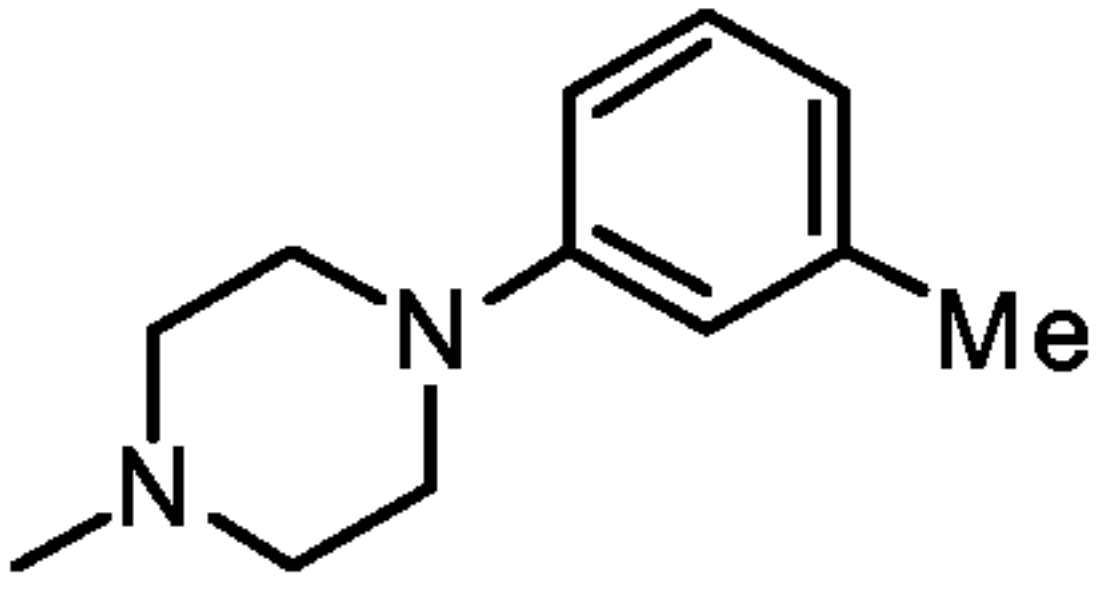
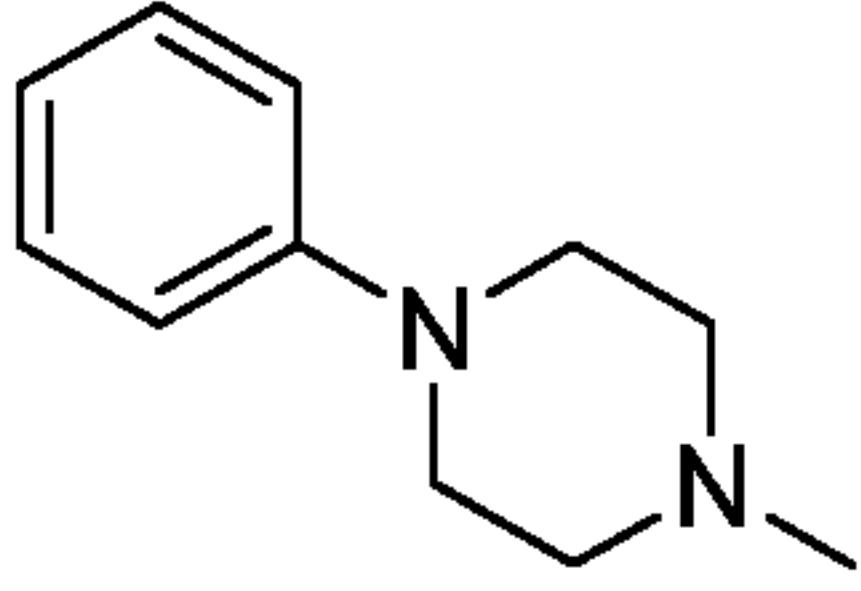
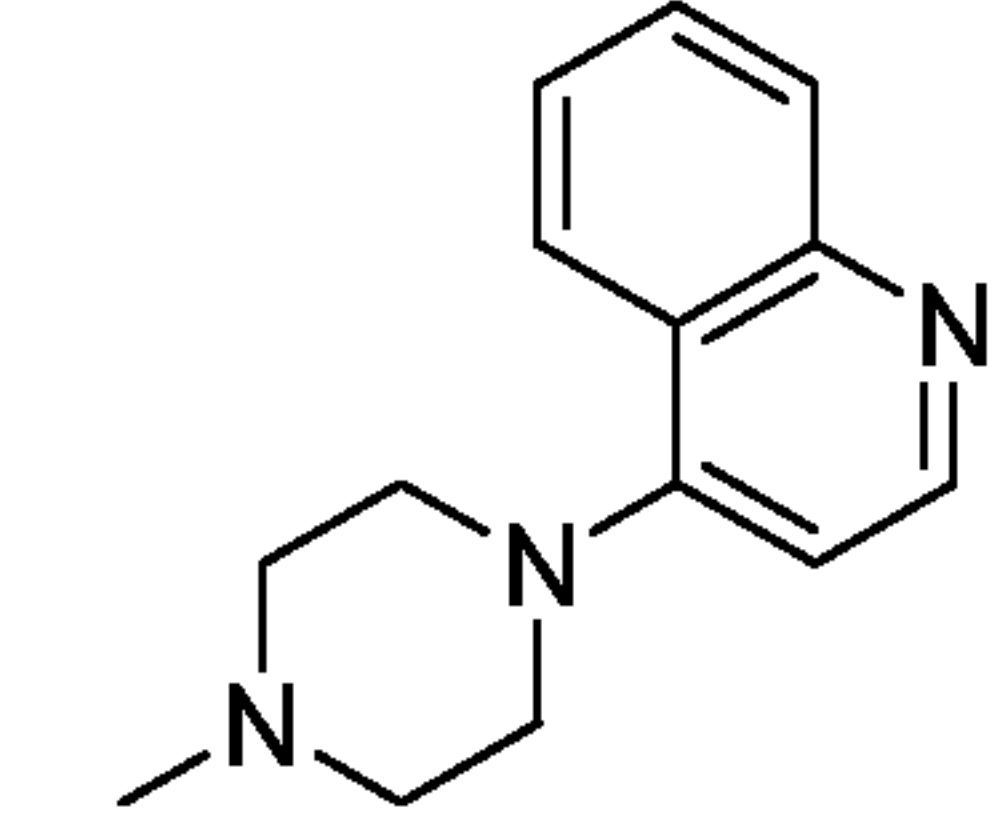
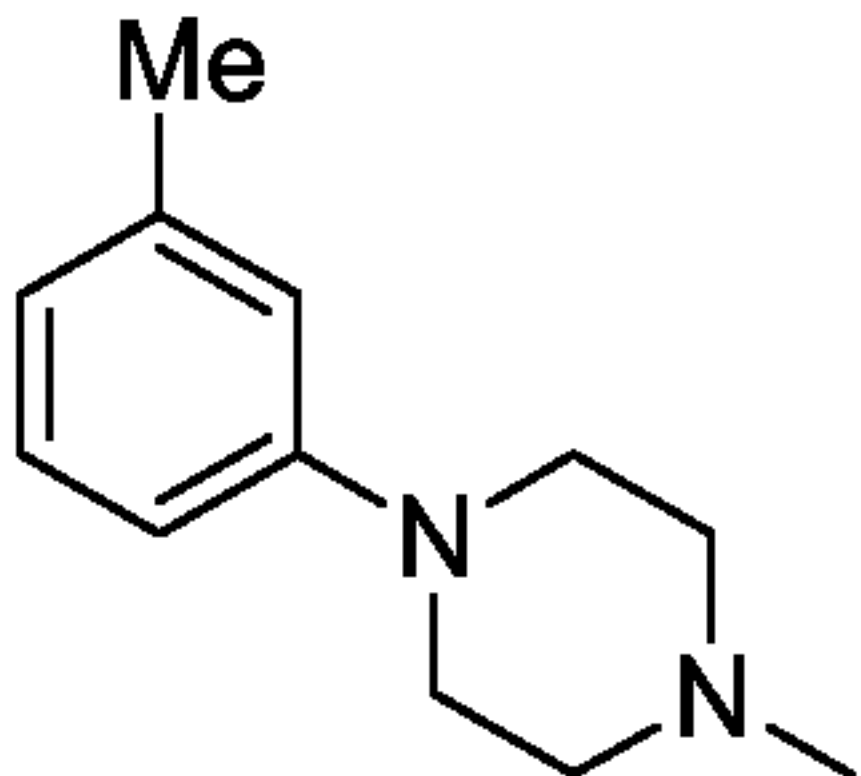
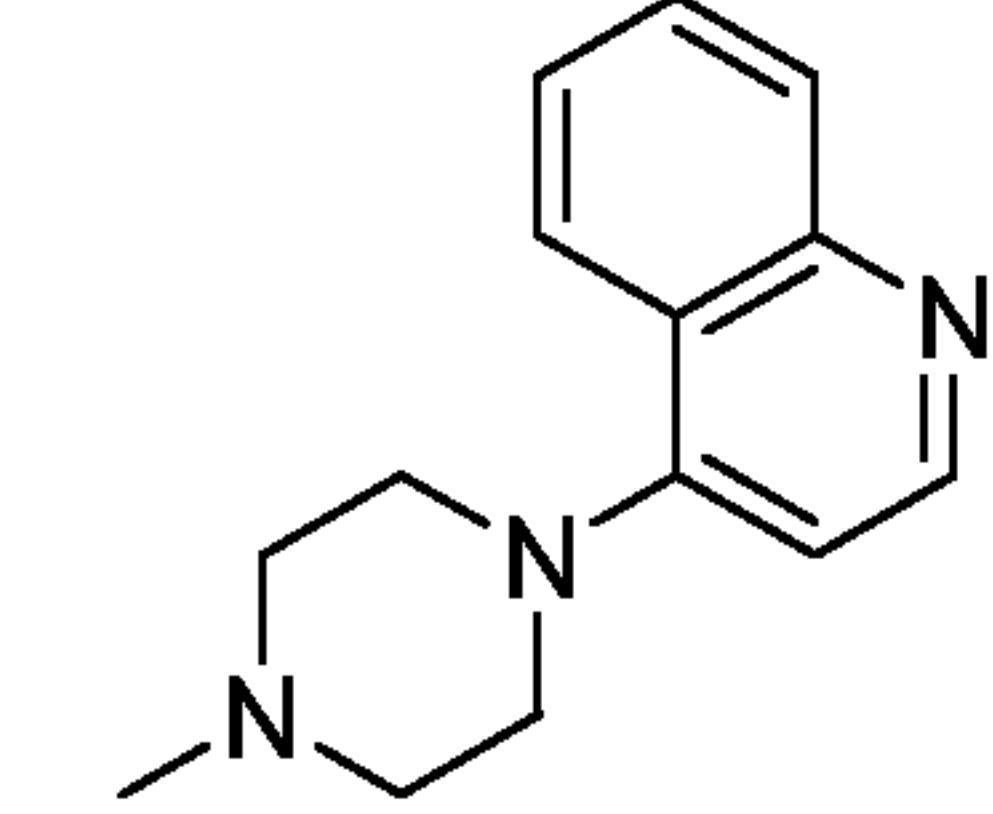
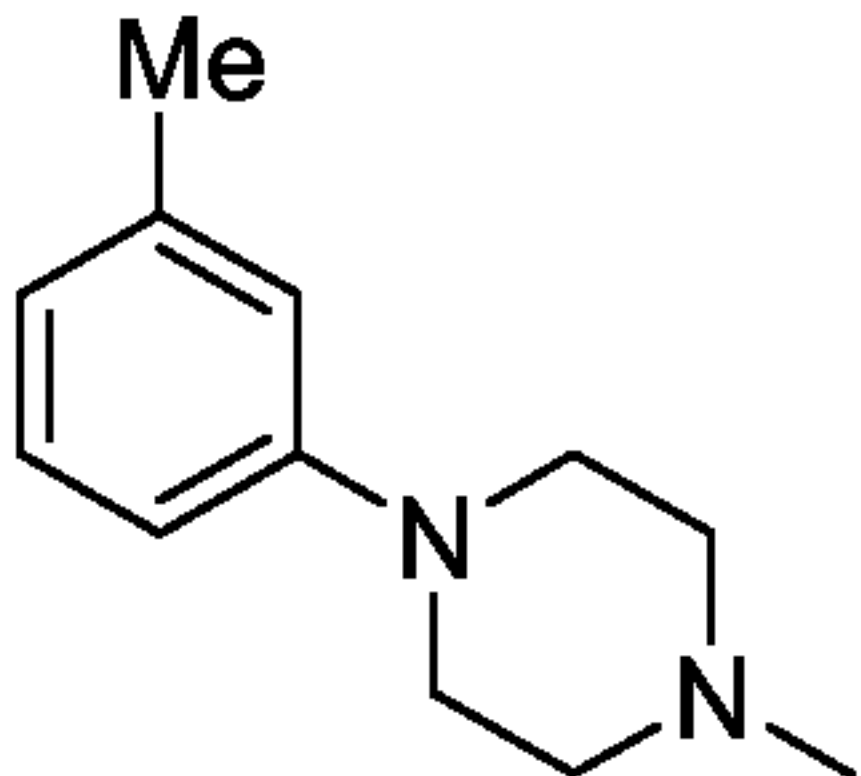
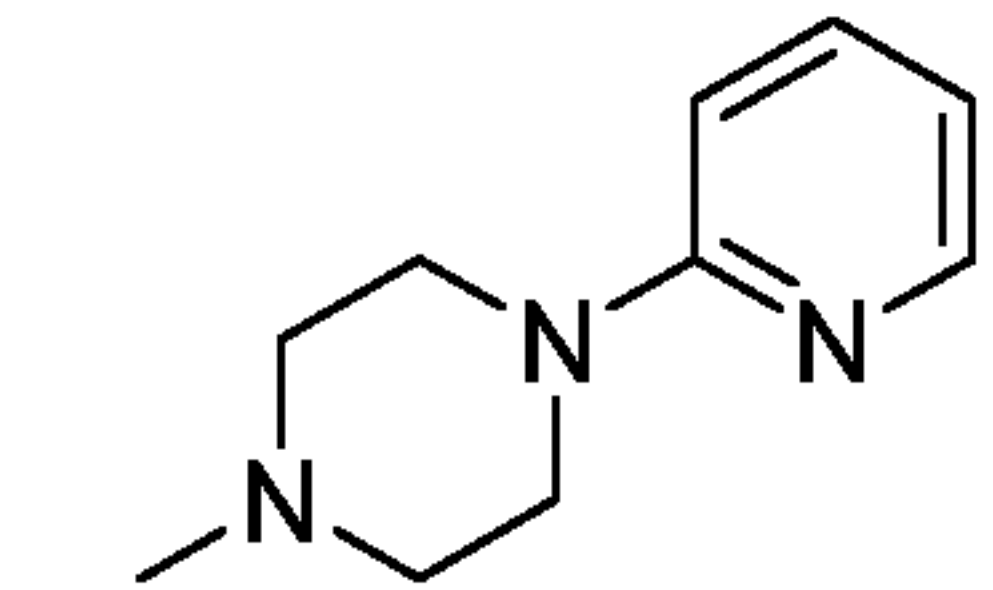
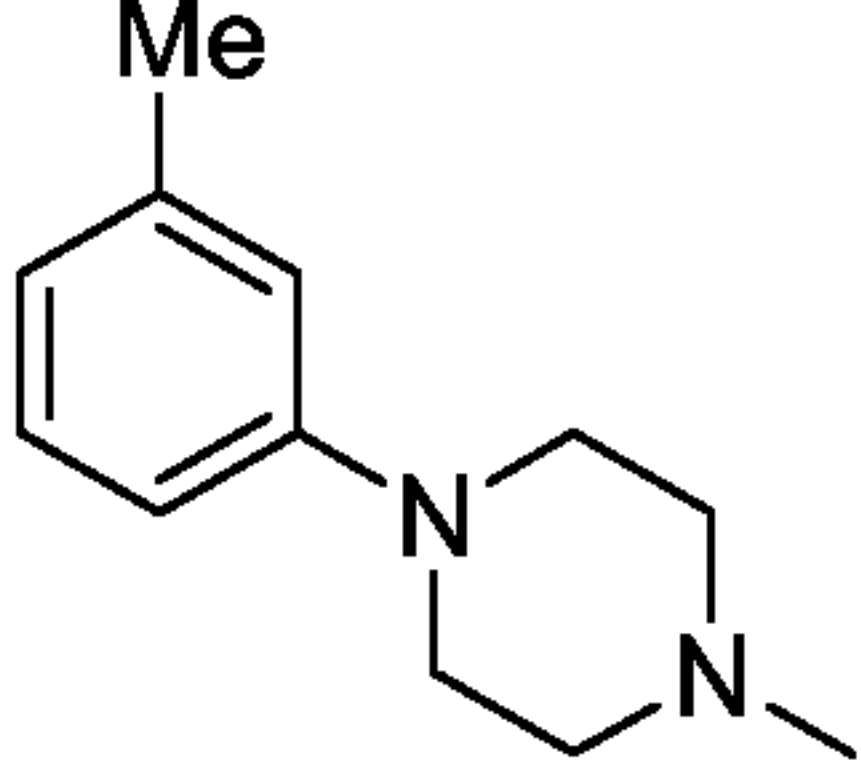
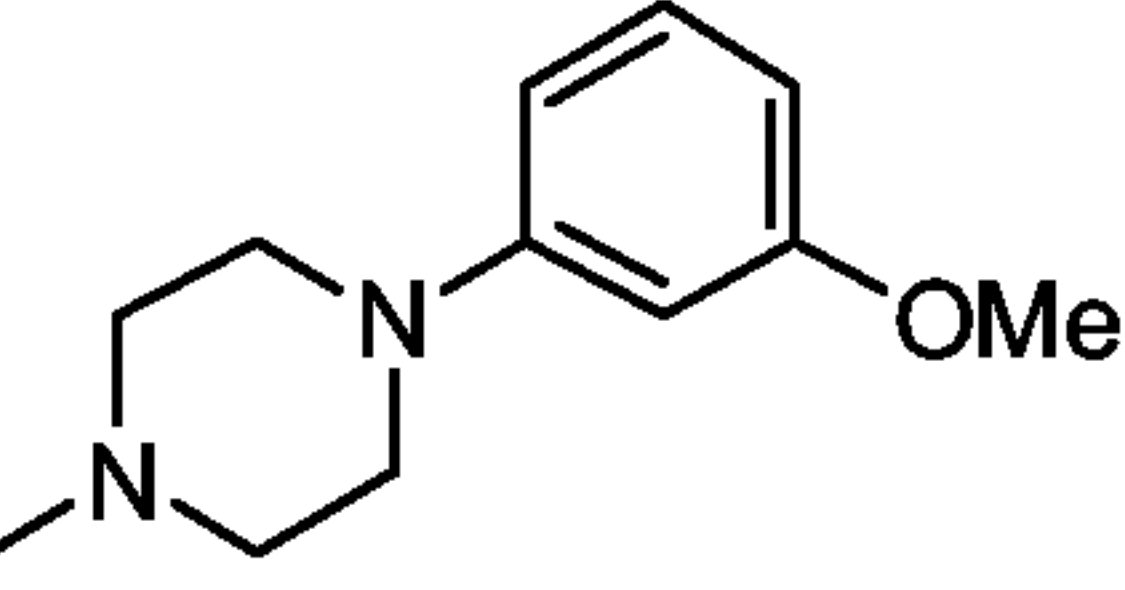
Cp. No.	Head	Linker	Tail
1-7		-CONH(CH ₂) ₄ -	
1-8		-COO(CH ₂) ₄ -	
1-9		-(CH ₂) ₄ -	
1-10		-CONH(CH ₂) ₄ -	
1-11		-(CH ₂) ₄ -	
1-12		-O(CH ₂) ₅ -	
1-13		-CONH(CH ₂) ₄ -	
1-14		-O(CH ₂) ₄ -	
1-15		-CONH(CH ₂) ₄ -	
1-16		-CONH(CH ₂) ₄ -	
1-17		- (CH ₂) ₂ NHCO(CH ₂) ₂ -	

Cp. No.	Head	Linker	Tail
1-18		- (CH ₂) ₂ NHCO(CH ₂) ₂ -	
1-19		-CONH(CH ₂) ₄ -	
1-20		-CONH(CH ₂) ₄ -	
1-21		-CONH(CH ₂) ₄ -	
1-22		-CONH(CH ₂) ₄ -	
1-23		-CONH(CH ₂) ₄ -	
1-24		-CONH(CH ₂) ₄ -	
1-25		-CONH(CH ₂) ₄ -	
1-26		-CONH(CH ₂) ₄ -	
1-27		-CONH(CH ₂) ₄ -	
1-28		-CONH(CH ₂) ₄ -	

Cp. No.	Head	Linker	Tail
1-29		-CONH(CH ₂) ₄ -	
1-30		-CONH(CH ₂) ₄ -	
1-31		-CONH(CH ₂) ₄ -	
1-32		-CONH(CH ₂) ₄ -	
1-33		-CONH(CH ₂) ₄ -	
1-34		-O(CH ₂) ₅ -	
1-35		-CONH(CH ₂) ₄ -	
1-36		-CONH(CH ₂) ₄ -	
1-37		-CONH(CH ₂) ₄ -	
1-38		-O(CH ₂) ₄ -	
1-39		-CONH(CH ₂) ₄ -	

Cp. No.	Head	Linker	Tail
1-40		-CONH(CH ₂) ₄ -	
1-41		-CONH(CH ₂) ₄ -	
1-42		-CONH(CH ₂) ₄ -	
1-43		-CONH(CH ₂) ₄ -	
1-44		-CONH(CH ₂) ₄ -	
1-45		-CONH(CH ₂) ₄ -	
1-46		-CONH(CH ₂) ₄ -	
1-47		-CONH(CH ₂) ₄ -	
1-48		-CONH(CH ₂) ₄ -	
1-49		-CONH(CH ₂) ₄ -	
1-50		-CONH(CH ₂) ₄ -	

Cp. No.	Head	Linker	Tail
1-51		-CONH(CH ₂) ₄ -	
1-52		-(CH ₂) ₆ -	
1-53		-(CH ₂) ₆ -	
1-54		-(CH ₂) ₆ -	
1-55		-(CH ₂) ₆ -	
1-56		-(CH ₂) ₆ -	
1-57		-(CH ₂) ₆ -	
1-58		-(CH ₂) ₆ -	
1-59		-(CH ₂) ₆ -	

Cp. No.	Head	Linker	Tail
1-60		-(CH ₂) ₆ -	
1-61		-(CH ₂) ₆ -	
1-62		-(CH ₂) ₆ -	
1-63		-(CH ₂) ₆ -	
1-64		-(CH ₂) ₆ -	
1-65		-(CH ₂) ₆ -	

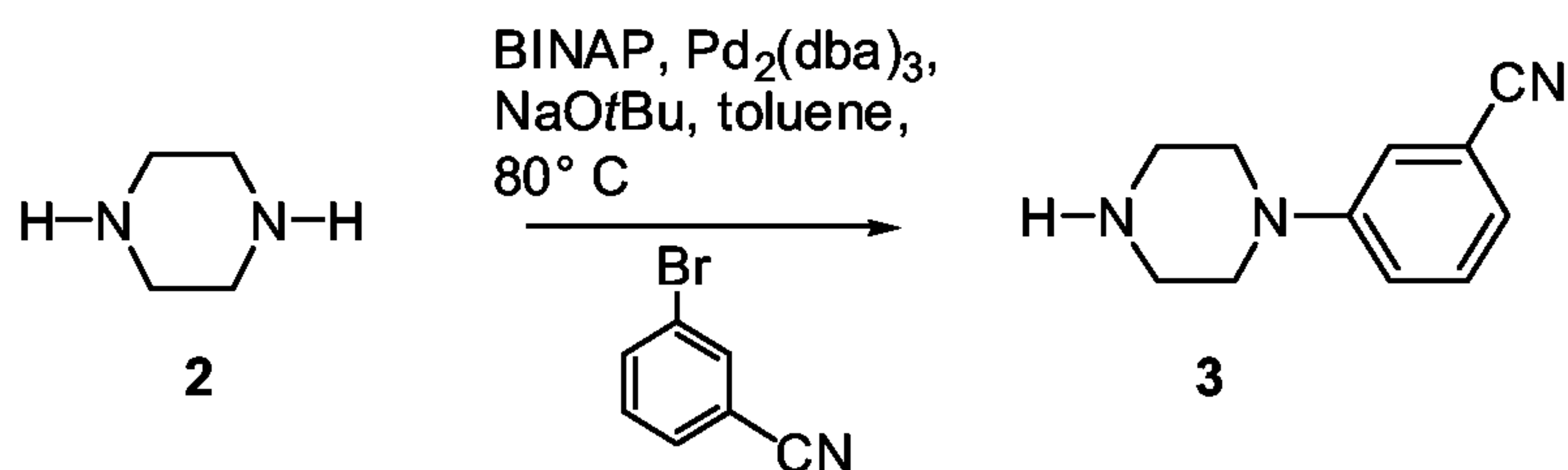
General description of the synthesis

Schemes 1-11 outline the route of synthesis following in this example.

Table 2 specifies the variables indicated in the schemes.

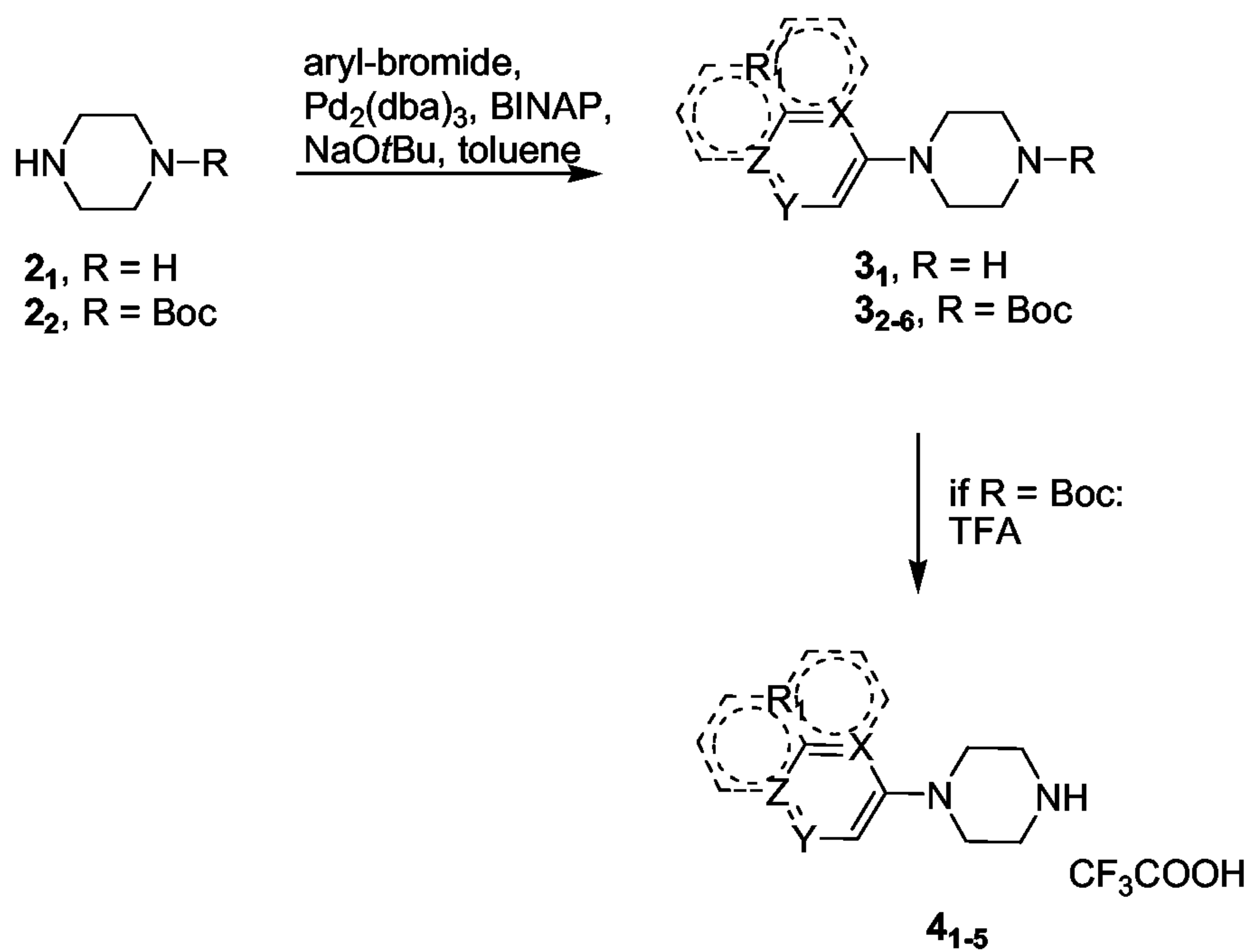
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Scheme 1



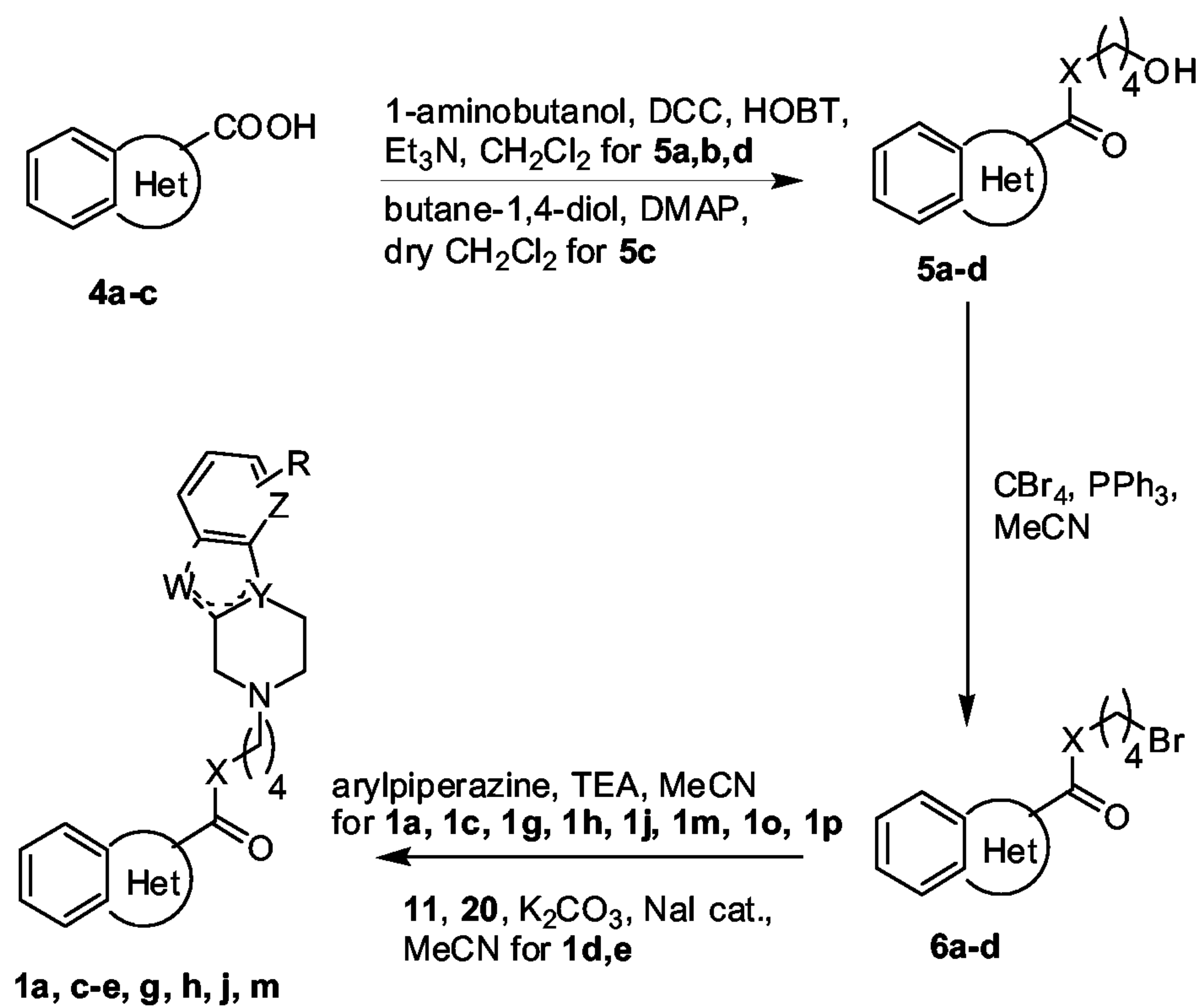
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Scheme 1-2

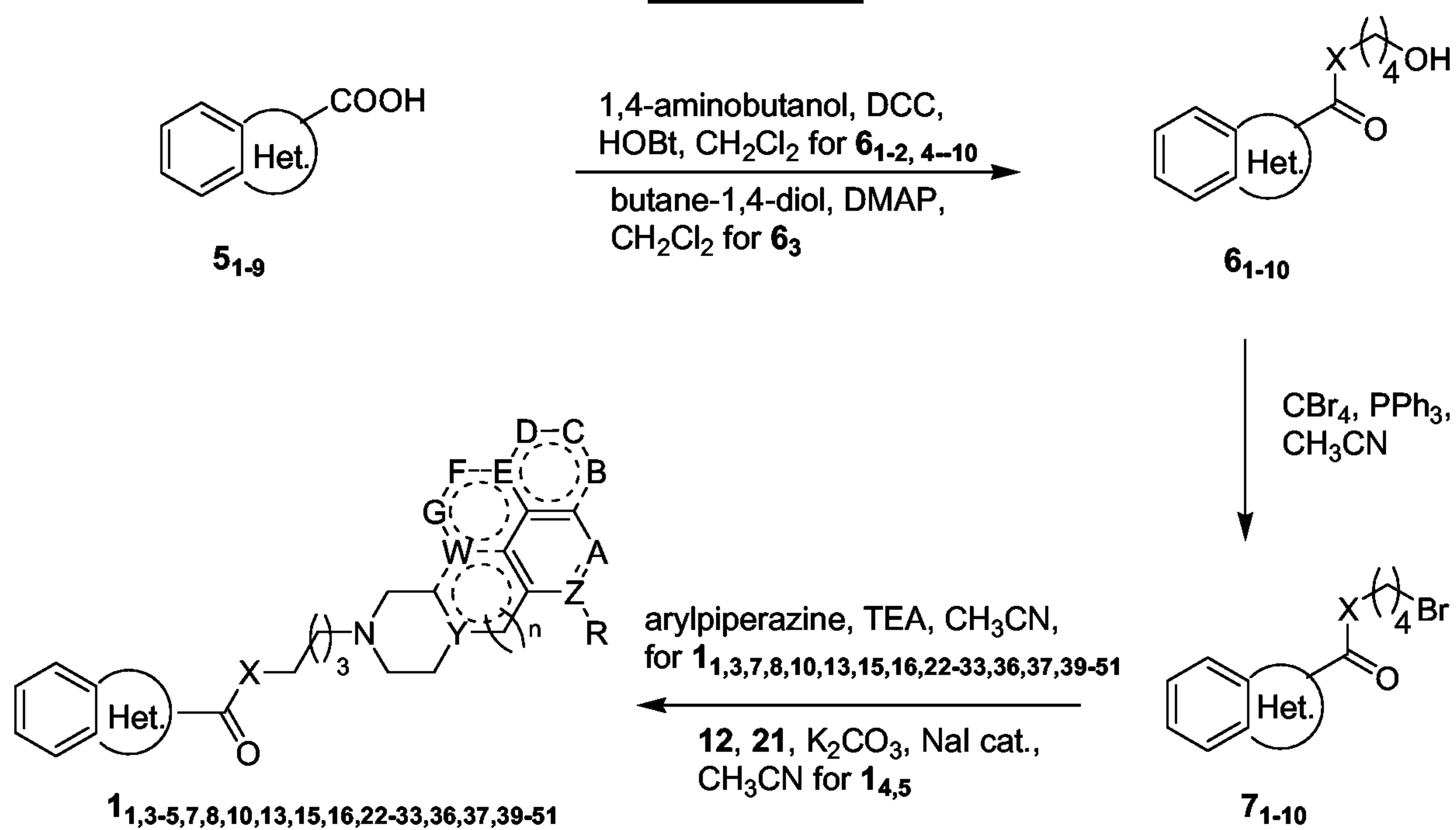


5

Scheme 2



31

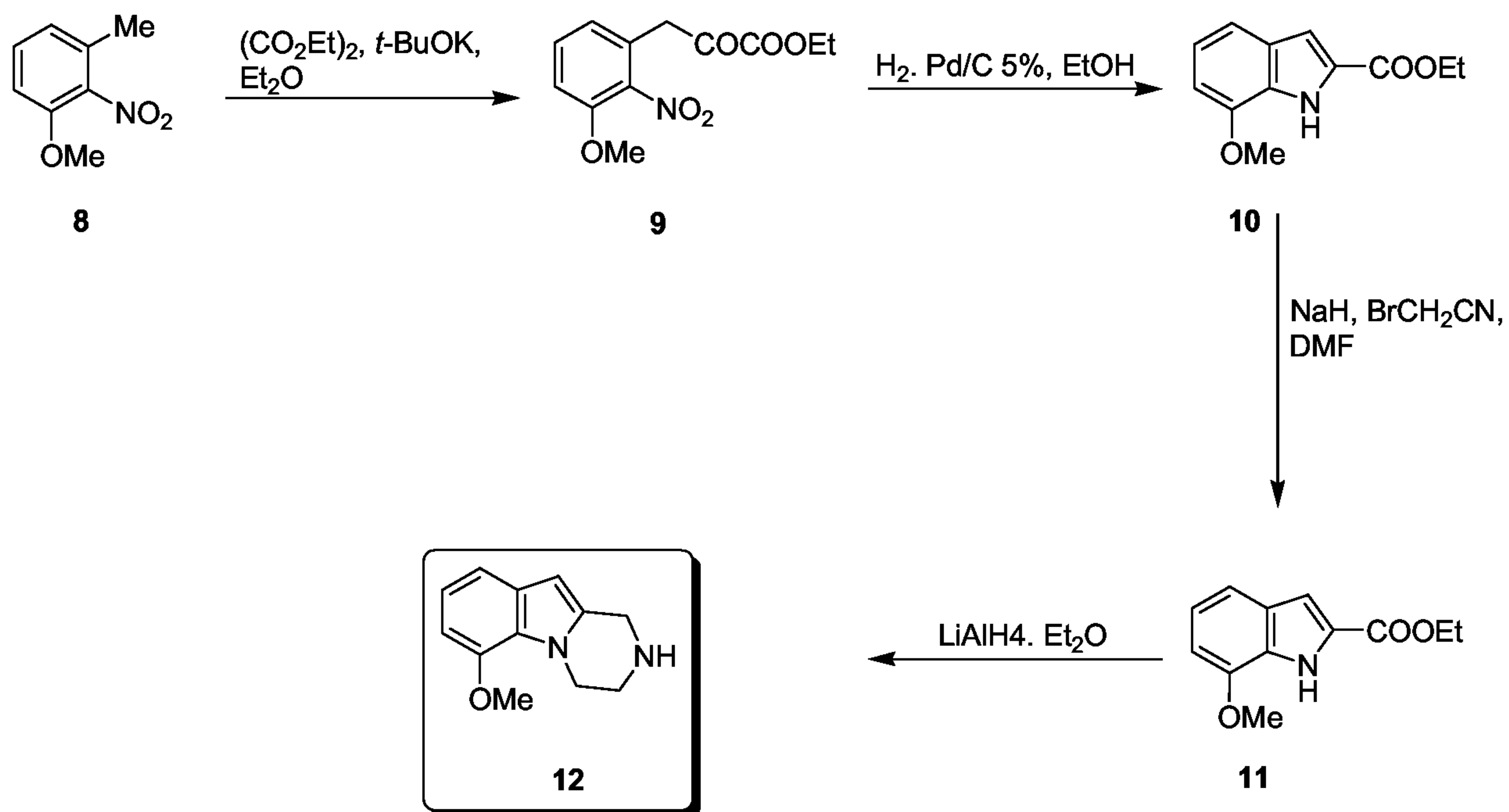
Scheme 2-2**Table 2****5 Specification of variables**

Cp. No.	X	Y	W	Z	R
1-1	NH	N	-	CH	3-CN
1-3	NH	N	-	CH	3-Cl
1-4	NH	C	NH	CH	2-OMe
1-5	NH	N	CH	CH	2-OMe
1-7	NH	N	-	CH	3-Me
1-8	O	N	-	CH	2,3-diCl
1-10	NH	N	-	N	-
1-13	NH	N	-	CH	3-Me
1-15	NH	N	-	CH	3-OMe
1-16	NH	N	-	CH	3-CF ₃
1-22	NH	N	-	CH	CH
1-23	NH	N	Me	CH	CH
1-24	NH	N	-	CH	CH
1-25	NH	N	-	N	CH
1-26	NH	N	-	CH	CH

Cp. No.	X	Y	W	Z	R
1-27	NH	N	-	N	CH
1-28	NH	N	CH	CH	CH
1-29	NH	N	-	CH	CH
1-30	NH	N	-	CH	CH
1-31	NH	N	-	CH	CH
1-32	NH	N	-	CH	CH
1-33	NH	N	-	CH	CH
1-36	NH	N	-	CH	N
1-37	NH	N	-	CH	CH
1-39	NH	N	-	CH	N
1-40	NH	N	-	CH	CH
1-41	NH	N	-	CH	CH
1-42	NH	N	-	N	CH
1-43	NH	N	-	CH	CH
1-44	NH	N	-	CH	CH
1-45	NH	N	-	CH	CH
1-46	NH	N	-	CH	CH
1-47	NH	N	-	N	CH
1-48	NH	N	-	N	CH
1-49	NH	N	-	N	CH
1-50	NH	N	-	CH	CH
1-51	NH	N	-	CH	CH

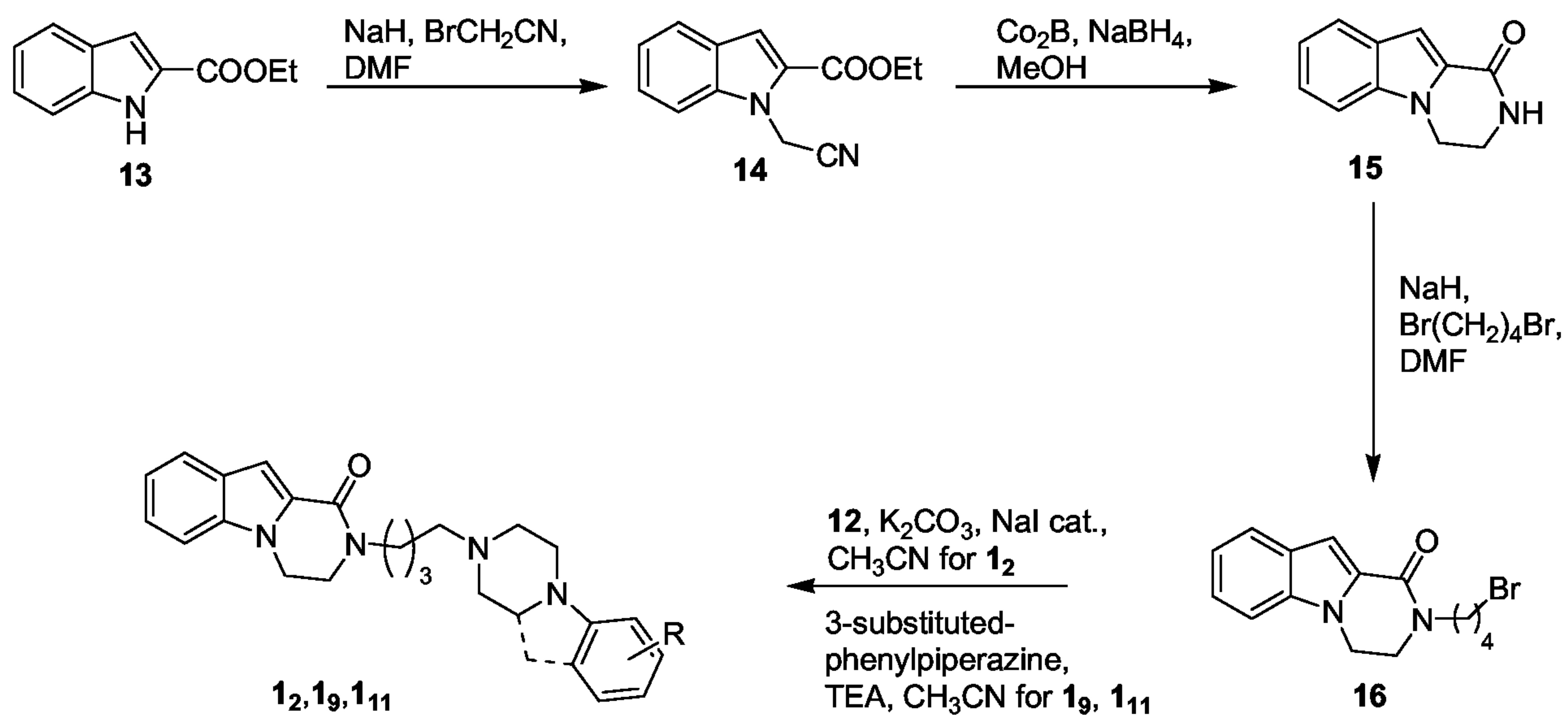
33

Scheme 3



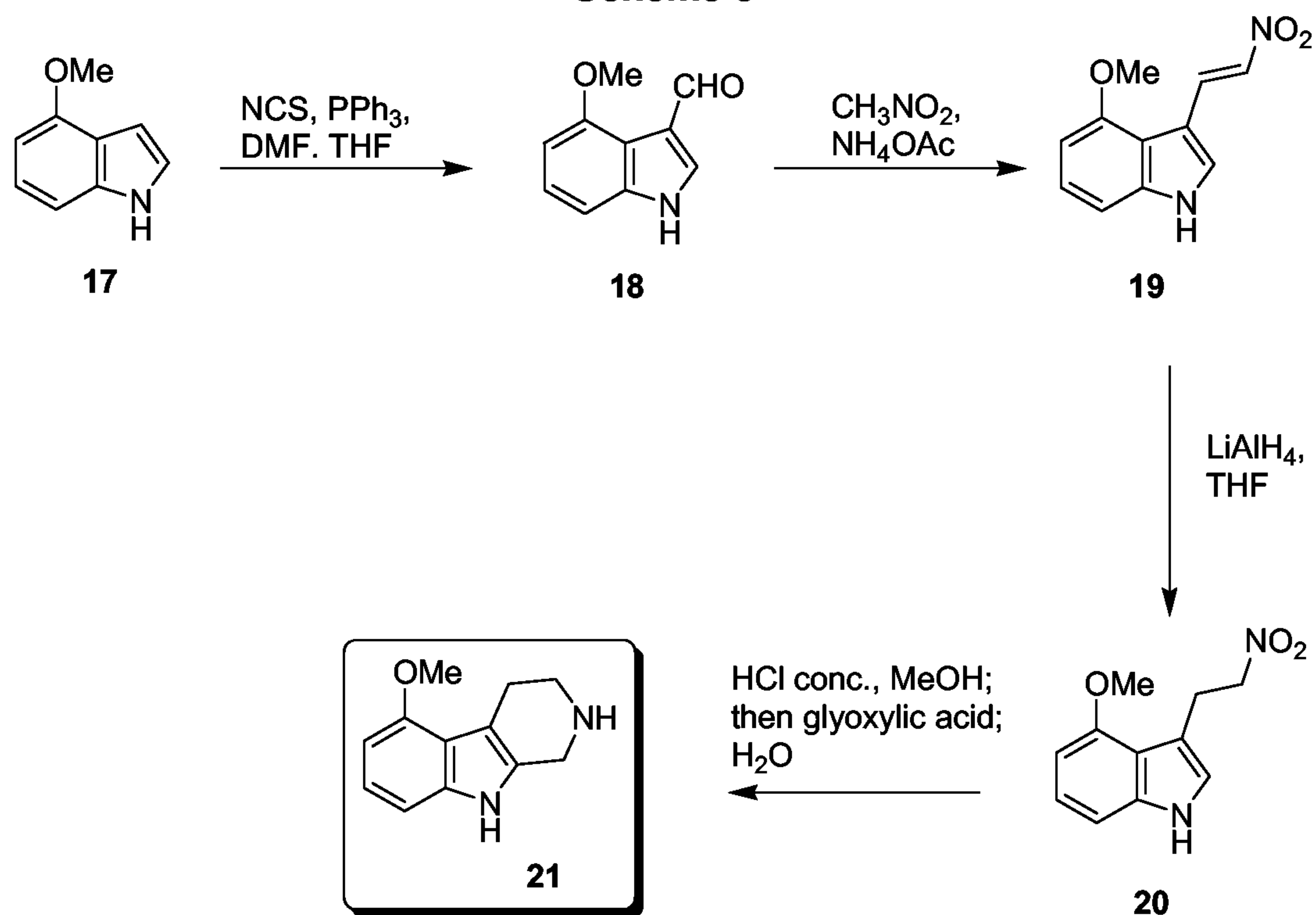
5

Scheme 4

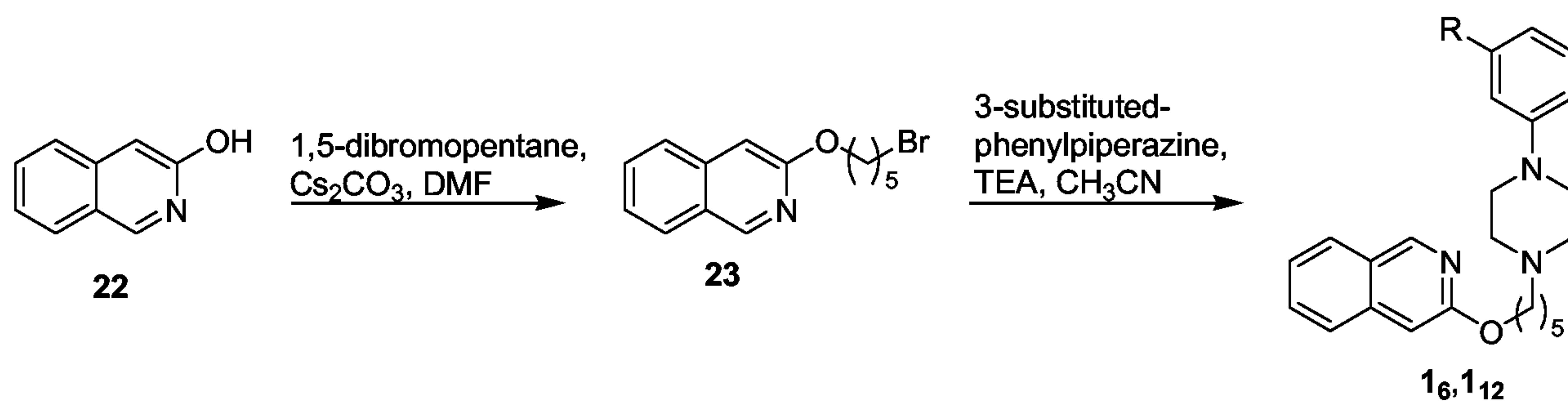


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Scheme 5

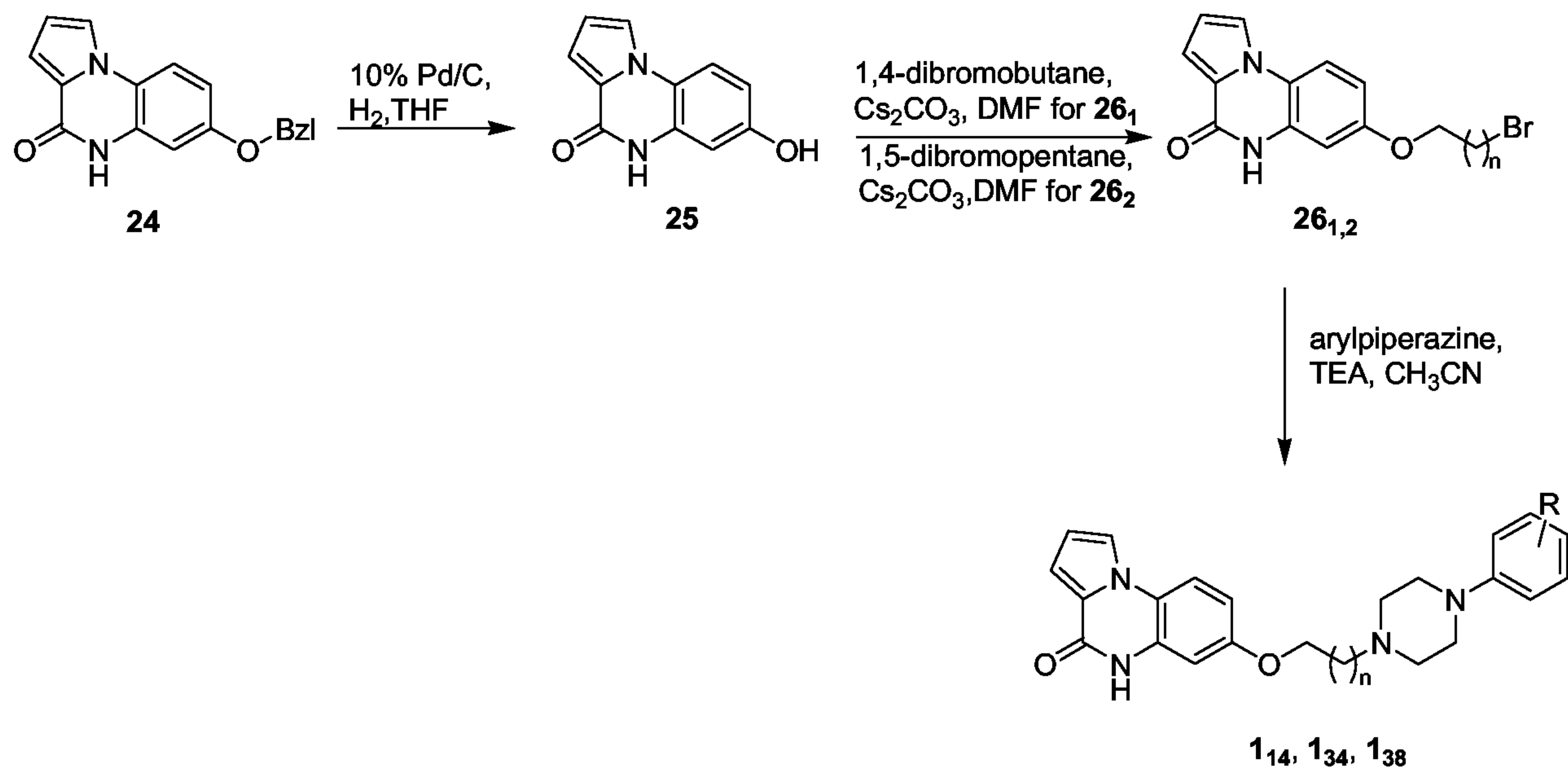


Scheme 6



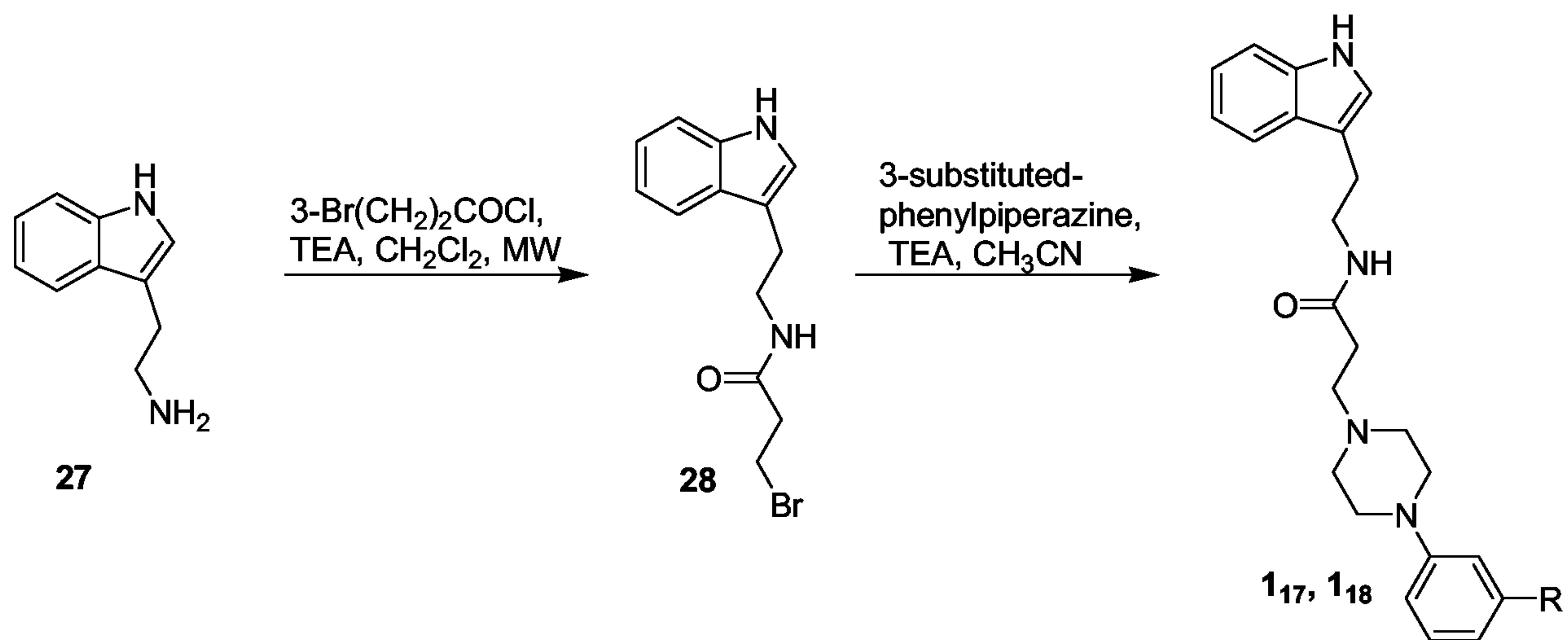
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Scheme 7



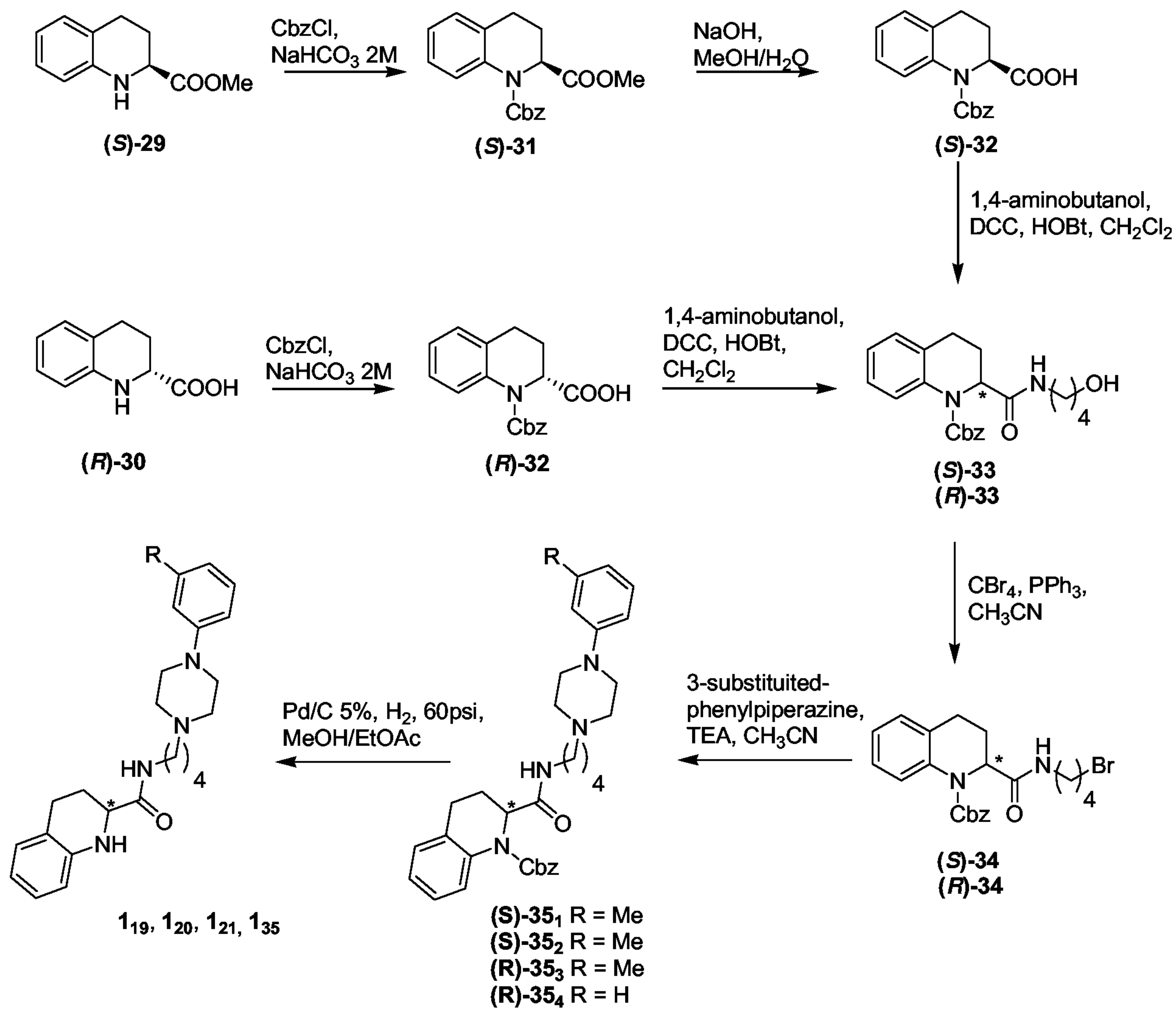
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Scheme 8



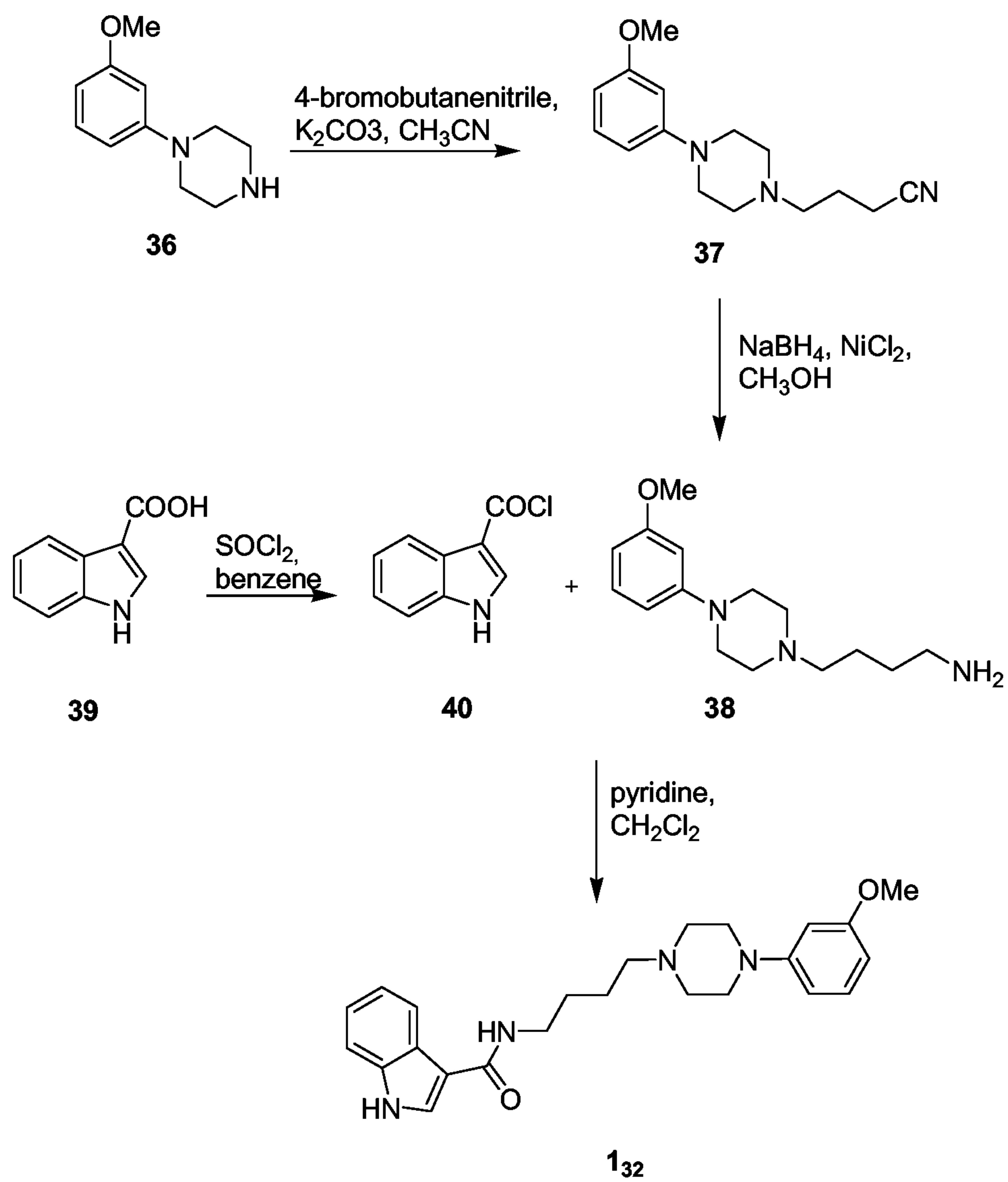
36

Scheme 9



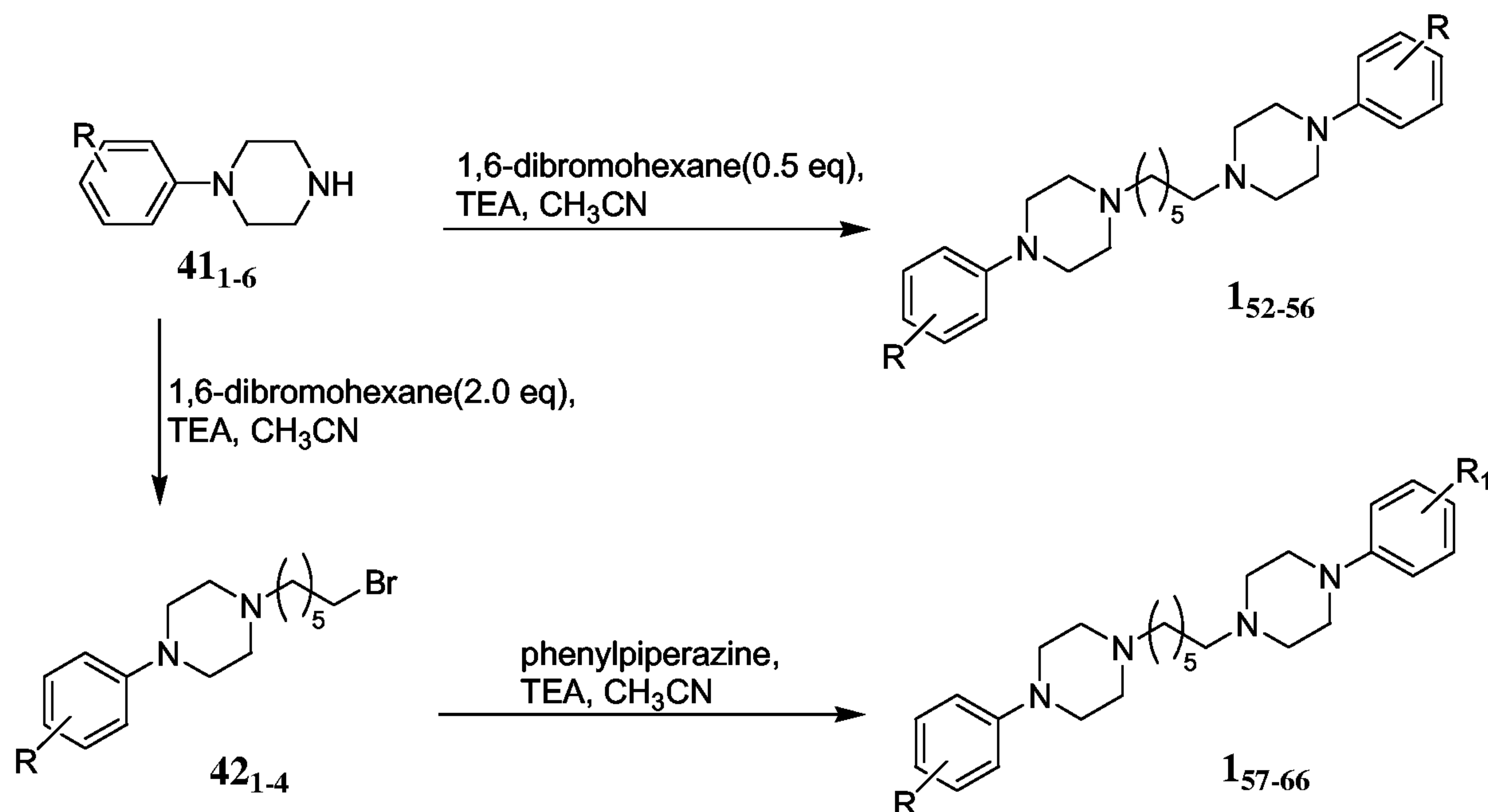
37

Scheme 10



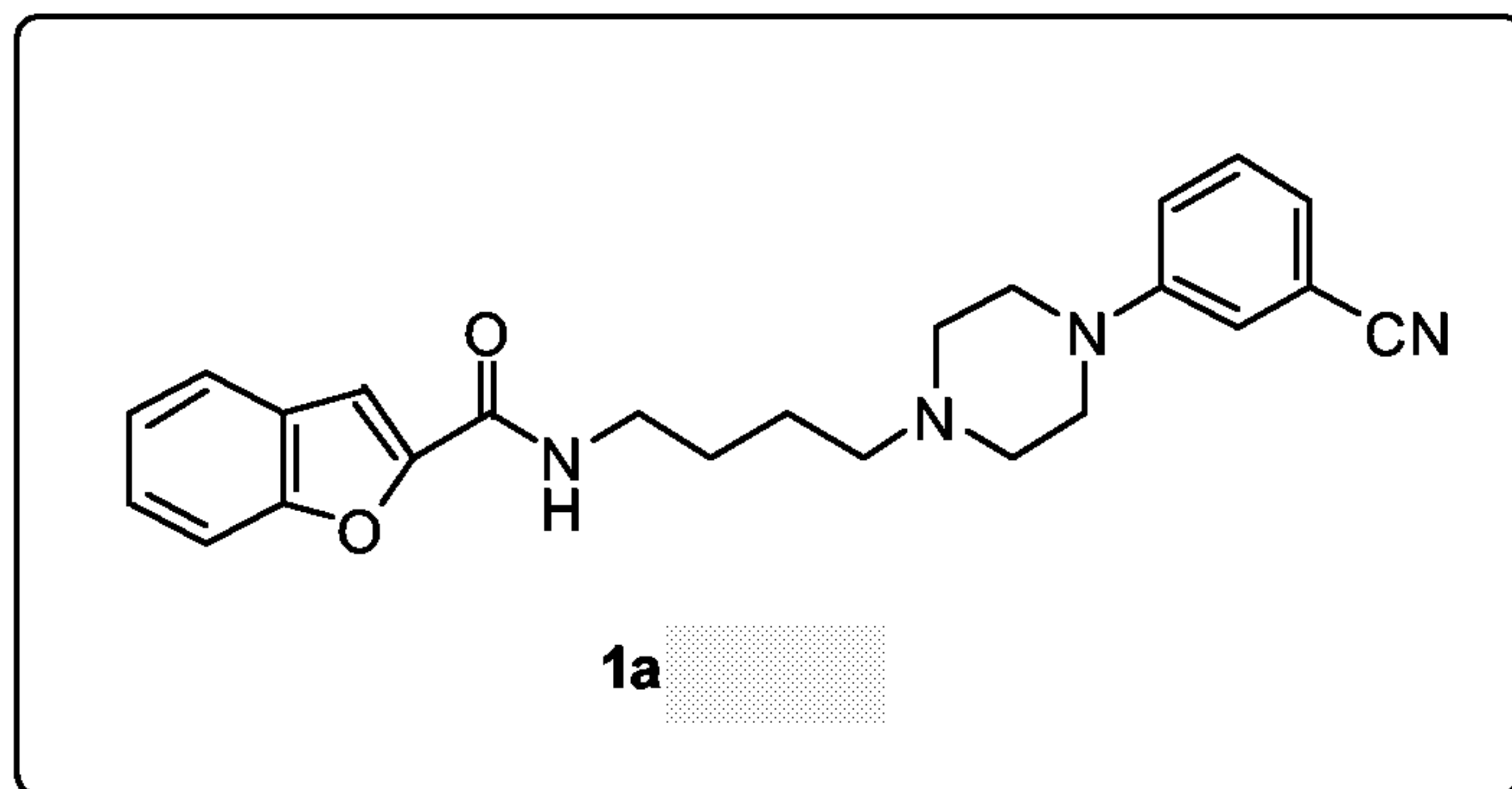
38

Scheme 11



- 5 Melting points were determined using an Electrothermal 8103 apparatus. IR spectra were taken with Perkin-Elmer 398 and FT 1600 spectrophotometers. ¹H NMR spectra were recorded on a Bruker 200 MHz spectrometer with TMS as internal standard; the value of chemical shifts (δ) are given in ppm and coupling constants (J) in Hertz (Hz). All reactions were carried out in an argon atmosphere. GC-MS were
- 10 performed on a Saturn 3 (Varian) or Saturn 2000 (Varian) GC-MS System using a Chrompack DB5 capillary column (30 m x 0.25 mm i. d.; 0.25 μm film thickness). Mass spectra were recorded using a VG 70-250S spectrometer. ESI-MS and APCI-MS spectra were taken by a LCQDeca-ThermoFinnigan spectrometer. Optical rotations were recorded on a Perkin-Elmer Model 343 polarimeter at the sodium D line at 20°C.
- 15 Elemental analyses were done on a Perkin-Elmer 240C elemental analyser and the results were within 0.4% of the theoretical values, unless otherwise noted. Yields refer to purified products and are not optimised. For testing, the claimed compounds were transformed into the corresponding hydrochloride salts by a standard procedure.

***N*-[4-[4-(3-Cyanophenyl)piperazin-1-yl]butyl]benzo[*b*]furan-2-carboxamide (Compound 1-1/1a)**



5 **1-(3-Cyanophenyl)piperazine (3).** A mixture of 3-bromobenzonitrile (0.50 g, 2.74 mmol), piperazine (0.71 g, 8.24 mmol), sodium *tert*-butoxyde (0.37 g, 3.8 mmol), tris(dibenzylideneacetone)dipalladium-(0) (6.27 mg, 0.0068 mmol) and *rac*-2,2'-bis(diphenylphosphino)-1,1'-binaphthyl (BINAP) in dry toluene (8.0 mL) was heated to 80°C under argon. After stirring for 2 h, the mixture was allowed to cool to room
10 temperature, taken up in ethyl ether (30.0 mL), filtered and concentrated. The crude product was then purified by means of flash chromatography (10% methanol in chloroform) to give 0.32 g (63% yield) of **3** as a yellow oil: ¹H NMR (CDCl₃) δ 1.87 (br s, 1H), 3.03 (t, 4H; *J* = 4.4 Hz), 3.17 (t, 4H; *J* = 4.3 Hz), 7.08 (m, 3H), 7.31 (m, 1H); IR (CHCl₃) *v*_{max} 2230 cm⁻¹. Anal. (C₁₁H₁₃N₃) C, H, N.

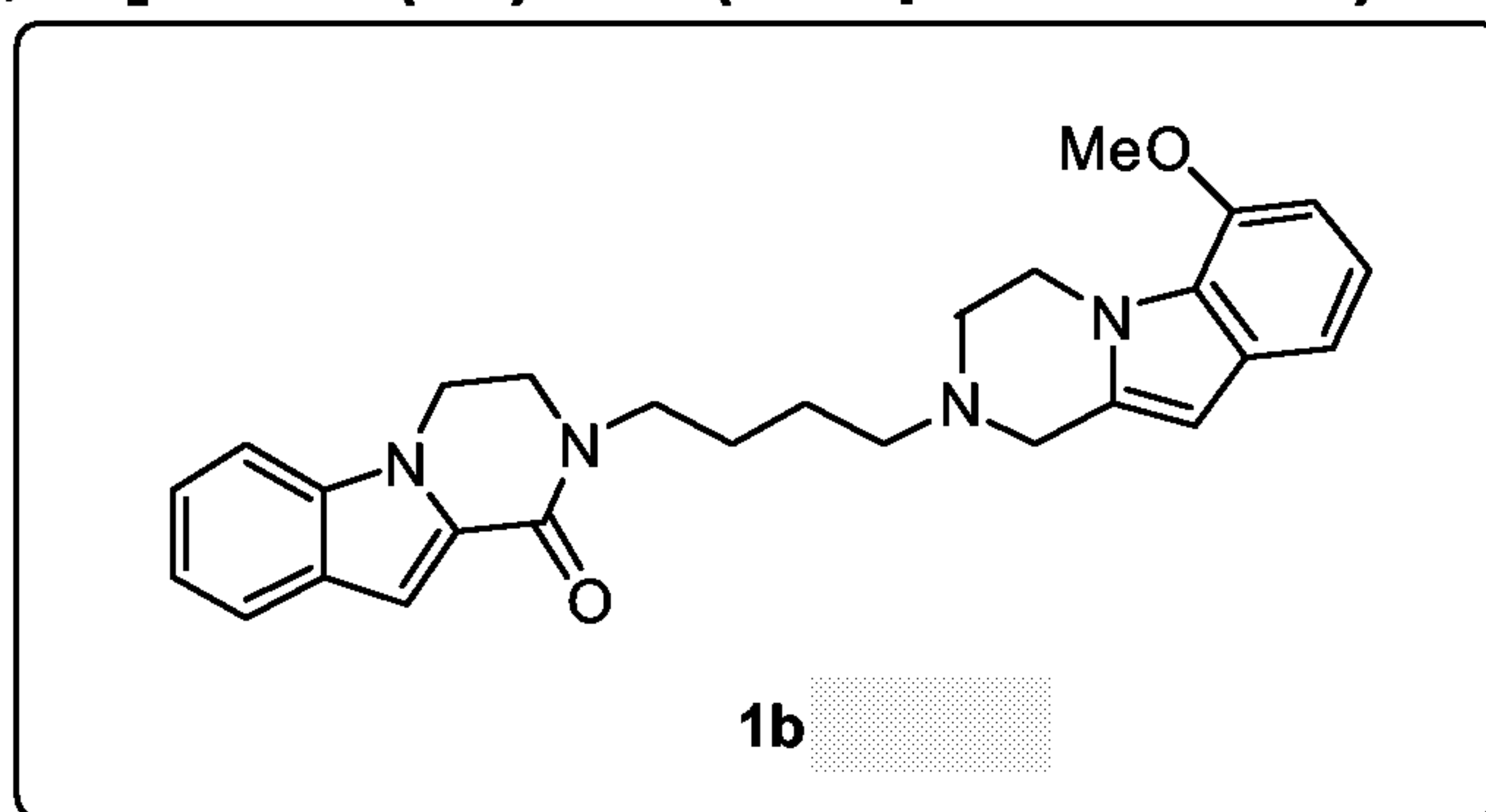
15 ***N*-[4-(1-Hydroxy)butyl]benzo[*b*]furan-2-carboxamide (5a).** To a solution of 2-benzofuranecarboxylic acid **4a** (0.50 g, 3.08 mmol) in dry dichloromethane (10.0 mL), 1-hydroxybenzotriazole hydrate (HOBT) (0.46 g, 3.40 mmol) and 1,3-dicyclohexylcarbodiimide (0.70 g, 3.40 mmol) were added at 0°C under argon; the suspension was warmed to room temperature and stirred for 1 h. Then 4-amino-1-
20 butanol (0.28 mL, 3.08 mmol) was added and the mixture was stirred overnight at room temperature. The resulting suspension was filtered through Celite®, washed with chloroform (3 x 10 mL) and the filtrate evaporated. The crude product was purified by means of flash chromatography (10% methanol in chloroform) to give 0.70 g (97%) of **5a** as a white solid: mp (methanol) 95-96°C; ¹H NMR (CDCl₃) δ 1.67 (m, 4H), 2.14 (br s, 1H), 3.53 (m, 2H), 3.73 (m, 2H), 6.89 (br s, 1H), 7.25-7.48 (m, 4H), 7.63 (d, 1H; *J* = 7.7 Hz). Anal. (C₁₃H₁₅NO₃) C, H, N.

***N*-[4-(1-Bromo)butyl]benzo[*b*]furan-2-carboxamide (6a).** To a vigorous stirred solution of **5a** (0.50 g, 2.14 mmol) in dry acetonitrile (25.0 mL), triphenylphosphine (0.86 g, 3.22 mmol) and carbon tetrabromide (1.06 g, 3.22 mmol)
30 were added at room temperature. After 2 h the mixture was quenched with 15% NaOH and the heterogeneous mixture was extracted with ethyl acetate (EtOAc) (3 x 25 mL). The organic layers were dried and evaporated. The residue was chromatographed

(20% *n*-hexane in ethyl acetate) to afford 0.58 g (91% yield) of **6a** as white solid: mp (EtOAc) 65-66°C; ¹H NMR (CDCl₃) δ 1.67 (m, 4H), 3.37 (m, 4H), 7.36 (m, 4H), 7.63 (d, 1H; *J* = 7.7 Hz); GC-MS *m/z* 297 [M+H]⁺, 216 (100), 202, 188, 174, 161, 145, 118, 89. Anal. (C₁₃H₁₄BrNO₂) C, H, N.

- 5 **N-[4-[4-(3-Cyanophenyl)piperazin-1-yl]butyl]benzo[*b*]furan-2-carboxamide (1-1/1a).** To a stirred solution of **6a** (50.0 mg, 0.17 mmol) in dry acetonitrile (3.0 mL) under argon, 1-(3-cyanophenyl)piperazine **3** (31.7 mg, 0.17 mmol) and triethylamine (38.2 μL, 0.27 mmol) were added; the solution was refluxed overnight under stirring. The solvent was removed under reduced pressure, water was
10 added and the mixture was extracted with dichlorometane (3 x 10 mL). The organic layers were dried and concentrated and the crude product was chromatographed (10% methanol in chloroform) to give 60.0 mg of **1a** (90% yield) as colorless oil. ¹H NMR (CDCl₃) δ 1.72 (m, 4H), 2.46 (t, 2H, *J* = 6.7 Hz), 2.61 (t, 4H, *J* = 4.9 Hz), 3.24 (t, 4, *J* = 5.0 Hz), 3.52 (q, 2H, *J* = 6.1 Hz), 6.89 (br s, 1H), 7.09 (m, 3H), 7.47-7.25 (m, 5H), 7.66
15 (d, 1H, *J* = 7.5); FAB-MS *m/z* 403 [M+H]⁺, 147. Anal. (C₂₄H₂₆N₄O₂) C, H, N.

3,4-Dihydro-2-[4-(3,4-dihydro-6-methoxypyrazino[1,2-*a*]indol-2(1*H*)-yl)butyl]pyrazino[1,2-*a*]indol-1(2*H*)-one (Compound 1-2/1b)



- 20 **Ethyl 3-(3-methoxy-2-nitrophenyl)-2-oxopropanoate (8).** To a suspension of potassium *tert*-butoxyde (2.0 g, 18.0 mmol) in dry diethyl ether (50.0 mL), diethyl oxalate (3.16 mL, 23.3 mmol) was added dropwise at room temperature under and the mixture was stirred for 15 min. Then 3-methoxy-2-nitrotoluene **7** (3.0 g, 18.0 mmol) was added and the mixture was stirred for 30 min. and left 12 h without stirring. The
25 solvent was removed in vacuo and water and solid ammonium chloride were added to the residue. The aqueous mixture was extracted with ethyl acetate (3 x 25 mL) and the collected organic layer were dried over anhydrous sodium sulfate (Na₂SO₄) and the solvent was evaporated. The crude product was chromatographed (30% EtOAc in *n*-hexane) to give 4.2 g of pure **8** as yellow oil 88% yield; ¹H NMR (CDCl₃) δ 1.27 (m, 3H), 2.18 (s, 3H), 3.75 (m, 2H), 4.25 (m, 2H), 6.78 (m, 2H), 7.20 (m, 1H); GC-MS *m/z*
30 267 [M]⁺ 194, 166 (100), 135, 121; ES-MS *m/z* 268 [M+H]⁺. Anal. (C₁₂H₁₃NO₆) C, H, N.

Ethyl 7-methoxy-1*H*-indole-2-carboxylate (9). To a solution of **8** (4.8 g, 18.0 mmol) in absolute ethanol (120.0 mL) previously degassed under N₂, catalytic 5% Pd/C was added and the mixture was allowed under hydrogen atmosphere at room temperature for 24 h. The mixture was filtered over Celite[®] washing with ethanol and the filtrate was evaporated under reduced pressure. The crude product was purified by means of flash chromatography (20% EtOAc in *n*-hexane) to afford **9** as yellow solid (79%): mp 69-72°C; ¹H NMR (CDCl₃) δ 1.42 (t, 3H, *J* = 6.94 Hz), 3.96 (s, 3H), 4.41 (q, 2H, *J* = 7.2 Hz), 6.72 (d, 1H, *J* = 7.5 Hz), 7.07 (t, 1H, *J* = 7.9 Hz), 7.25 (m, 2H), 9.18 (br s, 1H). ESI-MS *m/z* 220 [M+H]⁺, ES-MS/MS of [M+H]⁺ 192, 176, 174 (100), 176, 148.
10 Anal. (C₁₂ H₁₃ NO₃) C, H, N.

Ethyl 1-(cyanomethyl)-7-methoxy-1*H*-indol-2-carboxylate (10). A mixture of sodium hydride (60% dispersion in mineral oil, 509.6 mg, 21.23 mmol) and ethyl 7-methoxyindole-2-carboxylate **9** (3.1 g, 14.15 mmol) in dry *N,N*-dimethylformamide (DMF) (15.0 mL), was stirred at room temperature for 30 min and to this 15 bromoacetonitrile (2.0 mL, 28.3 mmol) in dry DMF (2.0 mL) was added. The reaction mixture was then maintained at 60-65°C for 30 min, and stirred for further 6 h at room temperature, left overnight and decomposed with ice. The separated solid was filtered and purified by means of flash chromatography (33% *n*-hexane in dichloromethane) to give **10** (30% yield) as white solid: mp (ethanol) 99-101°C; ¹H NMR (CDCl₃) δ 1.41 (t, 3H *J* = 7.2 Hz), 3.99 (s, 3H), 4.40 (q, 2H, *J* = 7.1 Hz), 5.96 (s, 2H), 6.80 (d, 1H, *J* = 7.7 Hz), 7.10 (t, 1H, *J* = 7.9 Hz), 7.25 m, 1H), 7.33 (s, 1H). GC-MS *m/z* 258 (100) [M]⁺, 232, 213, 201, 187, 172, 144, 130, 114, 89. Anal. (C₁₄H₁₄N₂O₃) C, H, N.

1,2,3,4-Tetrahydro-6-methoxypyrazino[1,2-*a*]indole (11). A suspension of **10** (0.50 g, 1.93 mmol) in dry diethyl ether (Et₂O) (20.0 mL) was added slowly to a 25 well-stirred slurry of lithiumaluminium hydride (LiAlH₄) (293.4 mg, 7.72 mmol) in dry Et₂O (10.0 mL). The mixture was refluxed for 8 h. The reaction mixture was poured into ice-water bath and 1N NaOH (10.0 mL) was added. The aqueous phase was extracted with EtOAc (3 x 30 mL) and the collected organic layers were dried and evaporated. The crude product was chromatographed (10% methanol in chloroform) to afford **11** as 30 yellow solid (40% yield): mp 120-122°C; ¹H NMR (CDCl₃) δ 7.14 (d, 1H, *J* = 7.8 Hz), 6.97 (t, 1H, *J* = 7.7 Hz), 6.58 (d, 1H, *J* = 7.7 Hz), 6.14 (s, 1H), 4.47 (t, 2H, *J* = 5.8 Hz), 4.17 (s, 2H), 3.90 (s, 3H), 3.26 (t, 2H, *J* = 5.7 Hz); ES-MS *m/z* 405 [2M+H]⁺, 203 (100) [M+H]⁺. Anal. (C₁₂H₁₄N₂O) C, H, N.

Ethyl 1-(cyanomethyl)-1*H*-indol-2-carboxylate (13). A mixture of sodium 35 hydride (60% dispersion in mineral oil, 190.0 mg, 7.94 mmol) and ethyl indole-2-carboxylate **12** (1.0 g, 5.29 mmol) in dry DMF (4.6 mL), was stirred at room temperature for 30 min and to this bromoacetonitrile (0.74 mL, 10.60 mmol) in dry DMF (1.0 mL) was added. The reaction mixture was then maintained at 65°C for 30 min,

and stirred for further 6 h at room temperature, left overnight and decomposed with ice. The separated solid was re-crystallized from ethanol to give **13** (90% yield) as white solid: mp (ethanol) 83-84°C; ¹H NMR (CDCl₃) δ 1.42 (t, 3H; *J* = 7.3 Hz), 4.41 (q, 2H; *J* = 14.2, 7.2 Hz), 5.60 (s, 2H), 7.37 (m, 4H), 7.71 (d, 1H; *J* = 7.9 Hz); GC-MS *m/z* 228
5 [M]⁺ (100), 199, 182, 154, 128, 115, 101, 89, 77. Anal. (C₁₃H₁₂N₂O₂) C, H, N.

1,2,3,4-Tetrahydropyrazino(2*H*)-1-one[1,2-*a*]indole (14). To a warm solution (60°C) of **13** (200.0 mg, 0.87 mmol) in dry methanol (8.0 mL) under argon, freshly prepared cobalt boride (450.0, 3.50 mmol), was added under stirring. Sodium borohydride (166.0 mg, 4.38 mmol) was cautiously added portionwise and the mixture
10 was refluxed for 3 h. The mixture was cooled, and the solvent removed under reduced pressure then water was added and the mixture was extracted with EtOAc (3 x 25 mL). The organic layers were dried, evaporated and the crude product was purified by means of flash chromatography (10% methanol in chloroform) to give **14** (68% yield) as white solid: mp (methanol) 261-265°C (dec.); ¹H NMR (CDCl₃) δ 3.82 (m, 2H), 4.27
15 (m, 2H), 6.65 (br s, 1H), 7.23 (m, 4H), 7.72 (d, 1H; *J* = 8.0 Hz); APCI-MS *m/z* 187 [M+H]⁺; APCI-MS/MS of [M+H]⁺ 159 (100), 144. Anal. (C₁₁H₁₀N₂O) C, H, N.

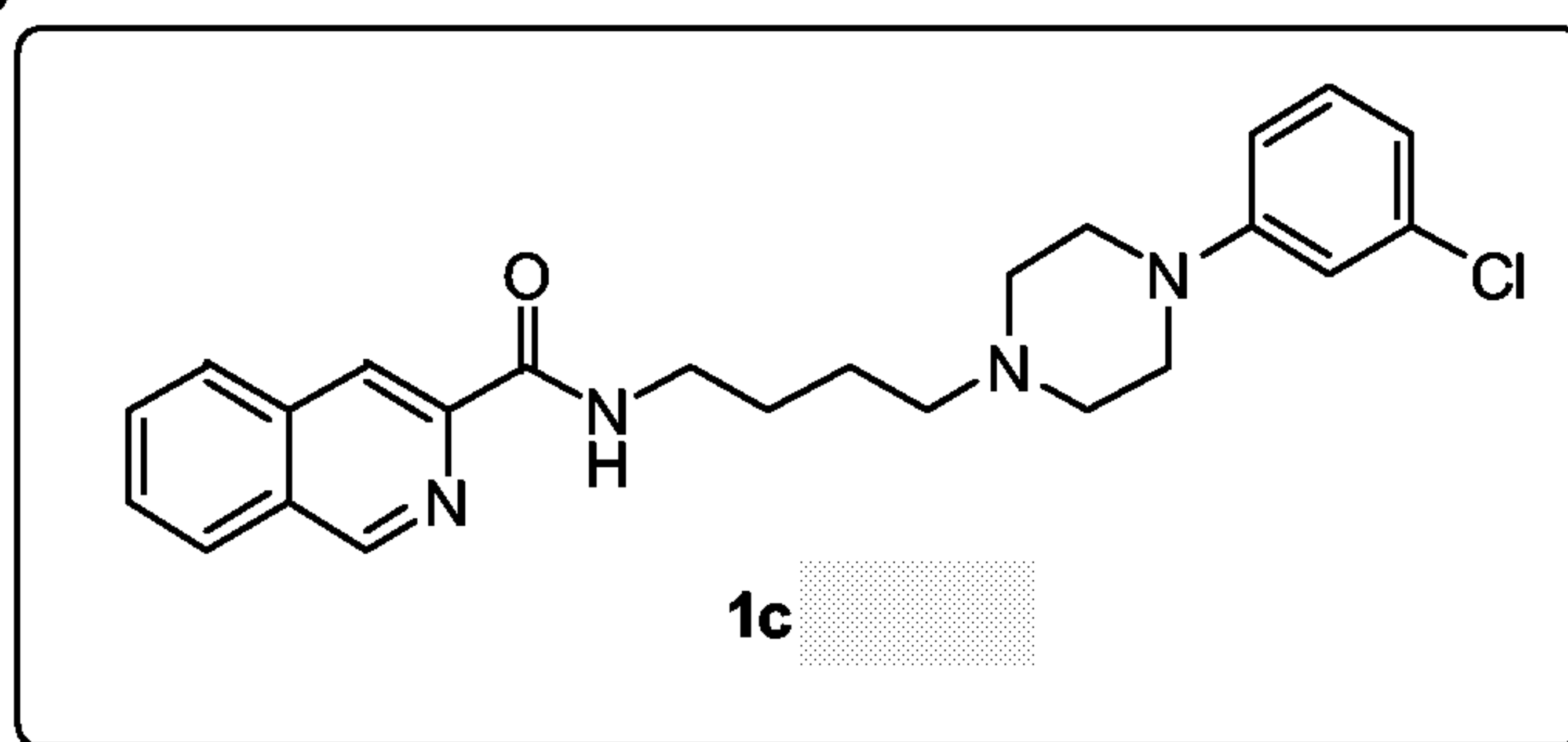
N-[1-(4-Bromo)butyl]-1,2,3,4-tetrahydropyrazino(2*H*)-1-one[1,2-*a*]indole (15). To a suspension of **14** (130.0 mg, 0.69) dry DMF (1.0 mL) sodium hydride, 60% in mineral oil, (20.0 mg, 0.83 mmol) was added. After stirring for 1 h at 60°C under
20 argon, a solution of 1,4-dibromobutane (0.41 mL, 3.47 mmol) in dry DMF (0.50 mL) was added dropwise. The mixture was refluxed under argon at 110°C for 3 h. Then the solvent was evaporated under reduced pressure, and the residue was re-suspended in water and extracted with dichloromethane (3 x 10 mL). The combined organic layers were dried evaporated and the residue was chromatographed (30% EtOAc in *n*-
25 hexane) to give **15** as yellow solid (41% yield): mp (EtOAc) 101-102°C; ¹H NMR (CDCl₃) δ 1.85 (m, 4H), 3.67 (m, 4H), 3.81 (m, 2H), 4.29 (m, 2H), 7.20 (m, 4H), 7.70 (d, 1H; *J* = 8.0 Hz); APCI-MS *m/z* 321 [M+H]⁺, 241, 227, 199 (100), 187, 159, 144, 117. Anal. (C₁₅H₁₇BrN₂O) C, H, N.

3,4-Dihydro-2-[4-(3,4-dihydro-6-methoxypyrazino[1,2-*a*]indol-2(1*H*)-yl)butyl]pyrazino[1,2-*a*]indol-1(2*H*)-one (1b). To a suspension of 1,2,3,4-tetrahydro-6-methoxypyrazino[1,2-*a*]indole **11** (30.0 mg, 0.15 mmol) and K₂CO₃ (71.6 mg, 0.52 mol) in dry acetonitrile (5.0 mL) bromo-derivative **15** (47.7 mg, 0.15 mmol) and a catalytic amount of sodium iodide (NaI) were added and the resulting mixture was heated at reflux for 18 h. Then the mixture was filtered and the filtrate was evaporated
35 to dryness under reduced pressure. The residue was suspended in water (10.0 mL) and extracted with Et₂O (2 x 25 mL). The combined ethereal extract was evaporated under reduced pressure and the crude product was purified by means of flash chromatography (5% methanol in chloroform) affording to **1b** as yellow oil (62% yield);

¹H NMR (CDCl₃) δ 1.69 (m, 4H), 2.58 (t, 2H, *J* = 6.6 Hz), 2.88 (t, 2H, *J* = 5.5 Hz), 3.66 (t, 2H, *J* = 6.7 Hz), 3.77 (m, 4H), 3.88 (s, 3H), 4.24 (t, 2H, *J* = 5.8 Hz), 4.45 (t, 2H, *J* = 5.6 Hz), 6.10 (s, 1H), 6.54 (d, 1H, *J* = 7.6 Hz), 6.93 (t, 1H, *J* = 7.8 Hz), 7.13 (m, 3H), 7.29 (m, 2H), 7.70 (d, 1H, *J* = 7.9 Hz); ES-MS *m/z* 907 [2M+Na]⁺, 884 [2M+H]⁺, 443 (100) [M+H]⁺; ¹³C NMR (CDCl₃) δ 24.3, 25.3, 29.6, 40.2, 45.5, 45.9, 46.1, 51.2, 51.7, 55.3, 57.2, 97.1, 101.8, 106.0, 109.5, 112.9, 120.6, 122.6, 124.3, 125.9, 127.5, 129.4, 130.3, 134.5, 136.3, 147.7, 159.9. Anal. (C₂₇H₃₀N₄O₂) C, H, N.

***N*-[4-[4-(3-Chlorophenyl)piperazin-1-yl]butyl]isoquinoline-3-carboxamide**

10 **(Compound 1-3/1c)**



***N*-[1-(4-Hydroxy)butyl]isoquinolin-3-carboxamide (5b).** The title compound was prepared starting from 3-isoquinolinecarboxylic acid **4b** (100.0 mg, 0.57 mmol) and following the procedure as described to obtain **5a**. The derivative **5b** was obtained as white solid (96% yield): mp (methanol) 126-127°C; ¹H NMR (CDCl₃) δ 1.74 (m, 4H), 3.57 (q, 2H; *J* = 6.3 Hz), 3.73 (t, 2H; *J* = 5.9 Hz), 7.40 (m, 2H), 7.75 (m, 2H), 8.39 (br s, 1H), 8.57 (s, 1H), 9.14 (s, 1H); ES-MS *m/z* 510 [2M+Na]⁺, 267 (100) [M+Na]⁺, 245 [M+H]⁺, ES-MS/MS of [M+H]⁺ 227, 174. Anal. (C₁₄H₁₆N₂O₂) C, H, N.

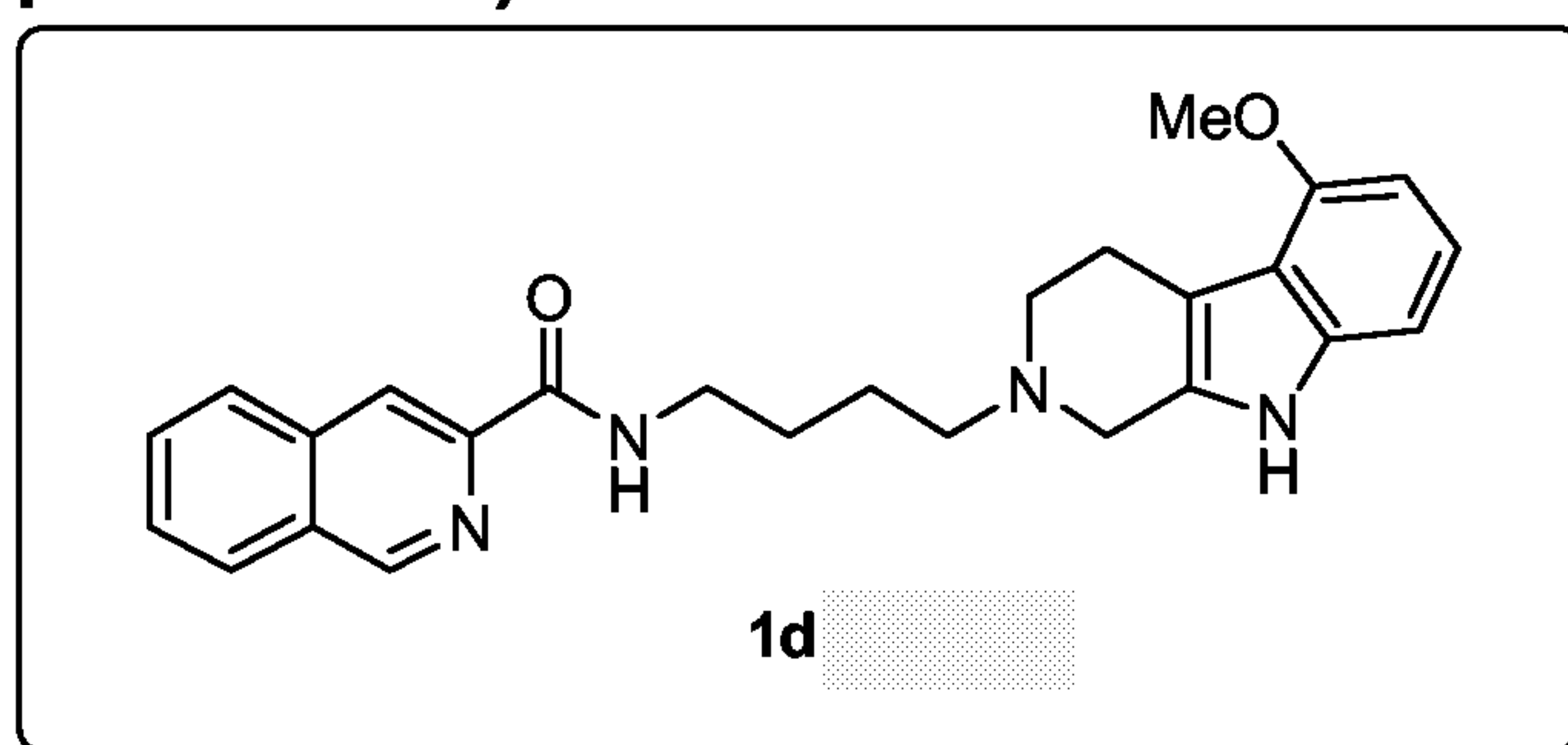
***N*-[1-(4-Bromo)butyl]isoquinolin-3-carboxamide (6b).** To a solution of **5b** (140.0 mg, 0.57 mmol) in dry acetonitrile (10.0 mL) triphenylphosphine (225.0 mg, 0.86 mmol) and carbon tetrabromide (285.0 mg, 0.86 mmol) were added under vigorous stirring at room temperature. After 2 h the mixture was quenched with 15% NaOH and extracted with EtOAc (3 x 10 mL). The organic layers were dried and evaporated. The residue was chromatographed (30% *n*-hexane in EtOAc) to give 130.0 mg of **6b** (75% yield) as yellow solid: mp (EtOAc) 72-73°C; ¹H NMR (CDCl₃) δ 2.06 (m, 4H), 3.48 (m, 4H), 7.66 (m, 2H), 7.93 (m, 2H), 8.36 (br s, 1H), 8.55 (s, 1H), 9.08 (s, 1H); ES-MS *m/z* 329 [M+Na]⁺, 308 (100) [M+Na]⁺. Anal. (C₁₄H₁₅BrN₂O) C, H, N.

***N*-[4-[4-(3-Chlorophenyl)piperazin-1-yl]butyl]isoquinoline-3-carboxamide (1c).** To a stirred solution of **6b** (190.0 mg, 0.62 mmol) in dry acetonitrile (20.0 mL) under argon, 1-(3-chlorophenyl)piperazine hydrochloride (144.0 mg, 0.62 mmol) and triethylamine (141.0 μL, 1.0 mmol) were added; the solution was refluxed overnight under stirring. The solvent was removed under reduced pressure, water was added and the mixture was extracted with dichlorometane (3 x 10 mL). The organic

layers were dried and concentrated and the crude product was chromatographed (10% methanol in chloroform) to give 130.0 mg of **1c** (50% yield) as white solid: mp (methanol) 156-157°C; ¹H NMR (CDCl₃) δ 1.65 (m, 4H), 2.46 (t, 2H, *J* = 6.7 Hz), 2.60 (t, 4H, *J* = 4.9 Hz), 3.21 (t, 4H, *J* = 5.0 Hz), 3.57 (q, 2H, *J* = 6.5 Hz), 6.78 (m, 2H), 6.86 (d, 1H, *J* = 1.6 Hz), 7.14 (t, 1H, *J* = 8.0 Hz), 7.72 (m, 2H), 8.00 (t, 2H, *J* = 8.2 Hz), 8.33 (br s, 1H), 8.61 (s, 1H), 9.14 (s, 1H); ES-MS *m/z* 445 (100) [M+Na]⁺, 423 [M+H]⁺, ES-MS/MS of [M+H]⁺ 251, 227 (100); ¹³C NMR (CDCl₃) δ 24.4, 27.8, 29.8, 39.5, 48.7, 53.1, 58.2, 114.0, 115.9, 119.4, 120.4, 127.8, 128.3, 128.9, 129.8, 130.2, 131.2, 135.1, 136.2, 144.0, 151.2, 152.5, 165.0. Anal. (C₂₄H₂₇ClN₄O) C, H, N.

10

***N*-[4-(1,2,3,4-Tetrahydro-5-methoxy-β-carbolin-2-yl)butyl]isoquinoline-3-carboxamide (Compound 1-4/1d)**



4-Methoxy-1*H*-indole-3-carbaldehyde (17). *N*-Chlorosuccinimide (2.72 g, 20.41 mmol) was added portionwise to a solution of triphenylphosphine (5.35 g, 20.41 mmol) in tetrahydrofuran (100.0 mL) and stirred at room temperature for 30 min. DMF (1.54 mL, 40.8 mmol) was added to the suspension, and the mixture was heated to reflux for 1 h. Then 4-methoxy-1*H*-indole **16** (1.0 g, 6.80 mmol) was added and the mixture was heated to reflux for 1 h. After cooling, tetrahydrofuran was evaporated, water (80.0 mL) added, and the mixture heated to reflux for 1 h and then alkalized with 10% NaOH. After the aqueous phase was extracted with EtOAc (3 x 50 mL) and the collected organic layers were dried and evaporated. The crude product was purified by means of flash chromatography (50% *n*-hexane in EtOAc) to give **17** as orange solid in quantitative yield: mp (EtOAc) 154-156°C; ¹H NMR (CDCl₃) δ 4.00 (s, 3H), 6.72 (m, 1H), 7.07 (d, 1H, *J* = 8.1 Hz), 7.19 (d, 1H, *J* = 8.1 Hz), 7.92 (d, 1H, *J* = 2.9 Hz), 9.05 (br s, 1H), 10.50 (s, 1H); FAB-MS *m/z* 175 (100) [M]⁺, 160, 144, 129, 116, 104, 89, 77. Anal. (C₁₀H₉NO₂) C, H, N.

4-Methoxy-3-(2-nitrovinyl)-1*H*-indole (18). Ammonium acetate (168.0 mg, 2.19 mmol), was added to 4-methoxy-1*H*-indole-3-carbaldehyde **17** (1.20 g, 7.27 mmol) in nitromethane (12.0 mL) and the mixture was stirred vigorously while heating to reflux for 1 h. The resulting solution was concentrated under reduced pressure and the crude product was purified by means of flash chromatography (50% *n*-hexane in EtOAc) to give 0.95 g of **18** as bright-yellow solid (64% yield): mp (EtOAc) 179-181°C

dec.; ^1H NMR ($\text{DMSO-}d_6$) δ 3.95 (s, 3H), 6.73 (d, 1H, $J = 7.3$ Hz), 7.13 (m, 2H), 8.08 (d, 1H, $J = 13.4$ Hz), 8.24 (s, 1H), 8.55 (d, 1H, $J = 13.0$ Hz), 12.20 (br s, 1H). Anal. ($\text{C}_{11}\text{H}_{10}\text{N}_2\text{O}_3$) C, H, N.

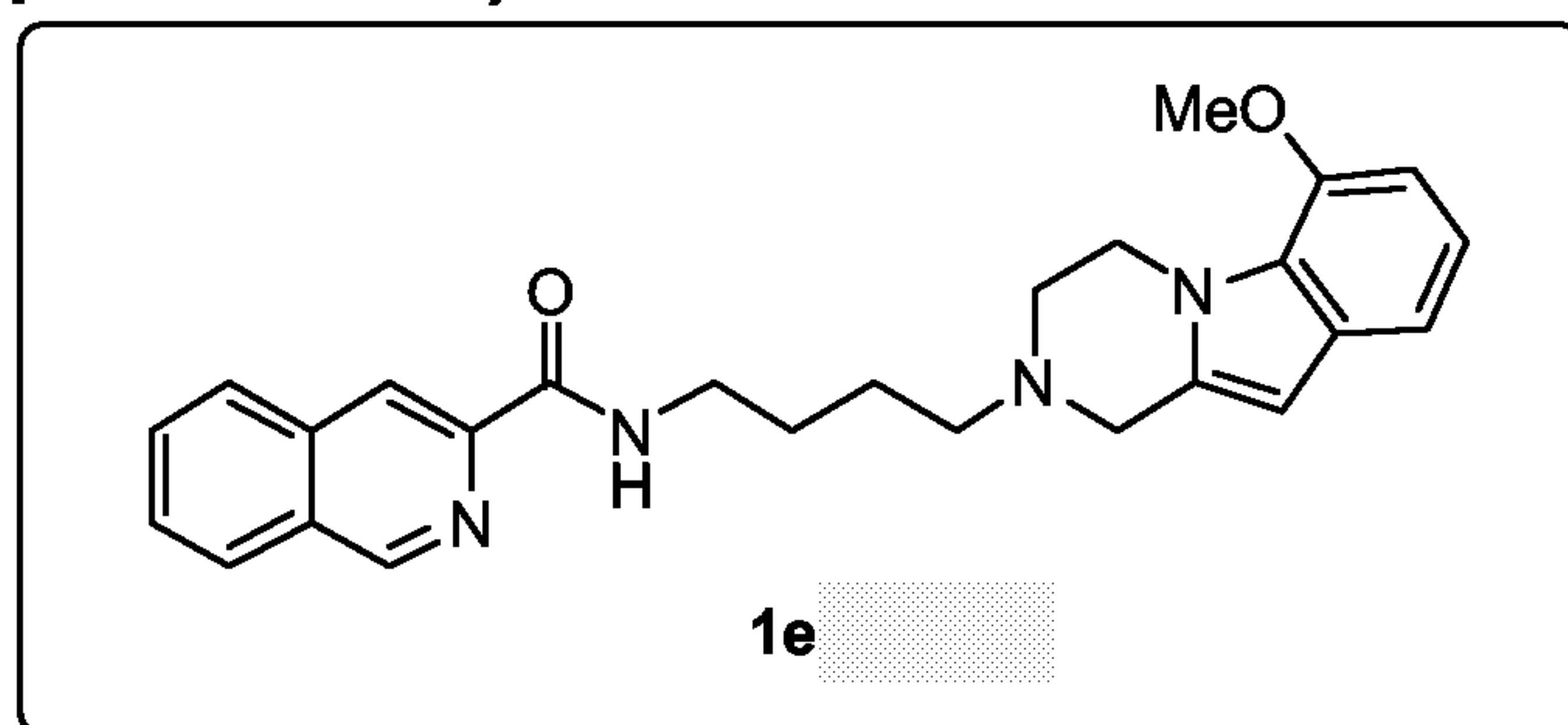
4-Methoxytryptamine (19). A solution of **18** (0.90 g, 4.33 mmol) in dry tetrahydrofuran (40.0 mL) was added dropwise to a suspension of LiAlH_4 (1.73 g, 45.22 mmol) in dry tetrahydrofuran (17.0 mL) and heated under reflux for 1 h with stirring. Excess of LiAlH_4 was quenched by addition of methanol with caution under cooling in an ice bath. Then water and s.s. sodium-potassium tartrate were added and the mixture was extracted with a solution of dichloromethane-methanol (95 : 5 v/v). The organic layers were washed with brine, dried over Na_2SO_4 , and evaporated under reduced pressure. The crude product was purified by means of flash chromatography (CHCl_3 -MeOH- NH_4OH 20 : 5 : 1 v/v) to afford 0.60 g of **19** as white solid (77% yield: mp (methanol) 139-140°C; ^1H NMR (CDCl_3) δ 2.00 (br s, 2H), 3.00 (m, 4H), 3.89 (s, 3H), 6.46 (d, 1H, $J = 7.6$ Hz), 6.80 (s, 1H), 6.92 (d, 1H, $J = 8.1$ Hz), 7.06 (t, 1H, $J = 7.9$ Hz), 8.85 (br s, 1H). Anal. ($\text{C}_{11}\text{H}_{14}\text{N}_2\text{O}$) C, H, N.

1,2,3,4-Tetrahydro-5-methoxy- β -carboline (20). 4-Methoxytryptamine **19** (375.0 mg, 1.97 mmol) was previously transformed in the corresponding hydrochloride salt by standard procedure. To a solution of 4-methoxytryptamine hydrochloride (445.0 mg, 1.97 mmol) in water (50.0 mL) glyoxylic acid monohydrate (181.2 mg, 1.97 mmol) was added and the mixture was stirred at reflux for 1 h. After cooling at room temperature a solution of 20% NaOH was added and the mixture was extracted with EtOAc (3 x 30 mL) and the organic layers were dried and evaporated. The crude product was chromatographed (CHCl_3 -MeOH- NH_4OH 20 : 5 : 0.5 v/v) to give **20** as an amorphous solid (63% yield); ^1H NMR (CDCl_3) δ 1.67 (br s, 2H), 2.96 (m, 2H), 3.13 (m, 2H), 3.88 (s, 3H), 3.98 (s, 2H), 6.47 (d, 1H, $J = 7.6$ Hz), 6.89 (d, 1H, $J = 8.1$ Hz), 7.01 (t, 1H, $J = 7.9$ Hz), 7.75 (br s, 1H). Anal. ($\text{C}_{12}\text{H}_{14}\text{N}_2\text{O}$) C, H, N.

N-[4-(1,2,3,4-Tetrahydro-5-methoxy- β -carbolin-2-yl)butyl]isoquinoline-3-carboxamide (1d). To a suspension of 1,2,3,4-tetrahydro-5-methoxy- β -carboline **20** (94.0 mg, 0.55 mmol) and K_2CO_3 (218.6 mg, 1.57 mol) in dry acetonitrile (10.0 mL) bromo-derivative **6b** (137.0 mg, 0.45 mmol) and a catalytic amount of NaI were added and the resulting mixture was heated at reflux for 18 h. Then the mixture was filtered and the filtrate was evaporated to dryness under reduced pressure. The residue was suspended in water (10.0 mL) and extracted with Et_2O (2 x 25 mL) and dichloromethane (1 x 25 mL). The combined organic layers was evaporated under reduced pressure and the crude product was purified by means of flash chromatography (0.5% methanol in chloroform) affording to **1d** as yellow oil (30% yield); ^1H NMR (CDCl_3) δ 1.74 (m, 4H), 2.64 (m, 2H), 2.82 (m, 2H), 3.03 (m, 2H), 3.57 (m, 4H), 3.86 (s, 3H), 6.44 (d, 1H, $J = 7.5$ Hz), 6.92 (m, 2H), 7.72 (m, 2H), 7.97 (m,

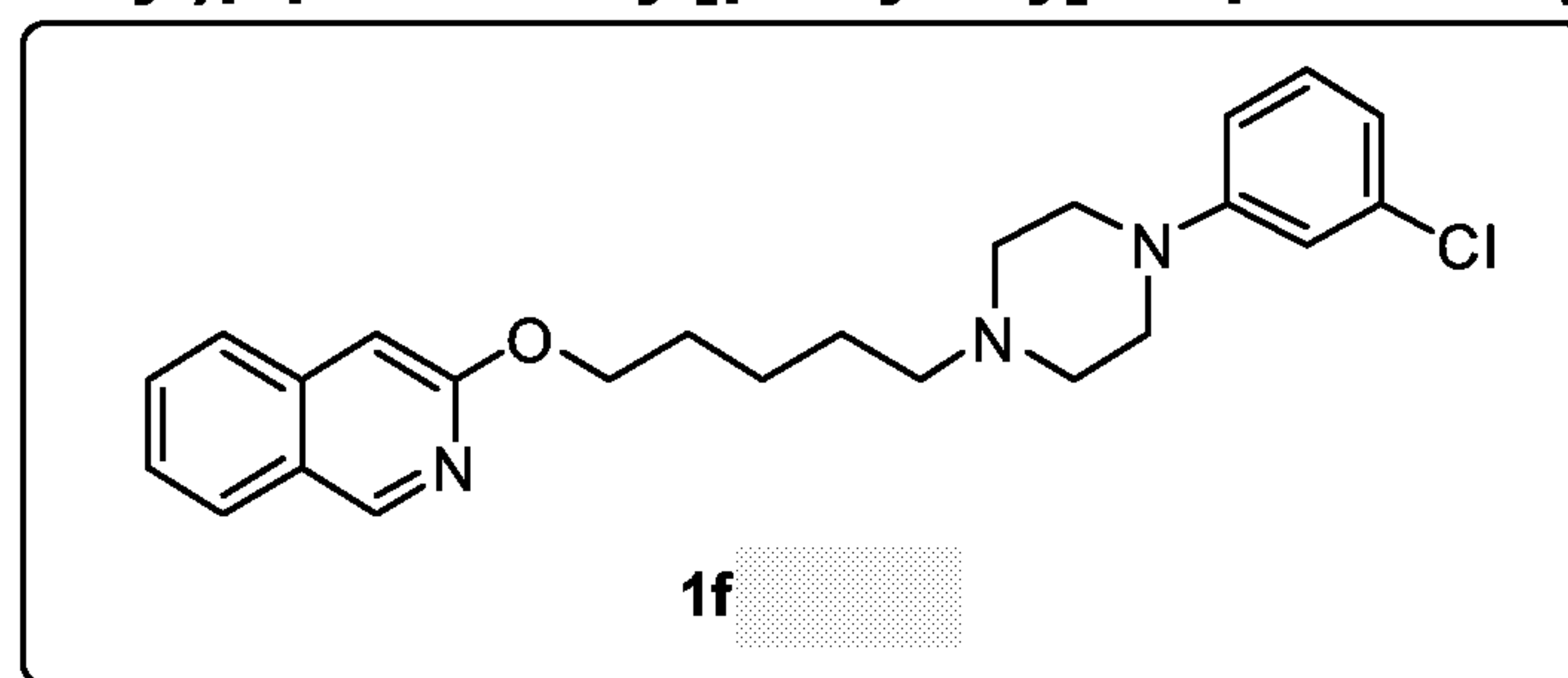
2H), 8.39 (br s, 1H), 8.59 (s, 1H), 9.07 (s, 1H); ES-MS m/z 429 (100) $[M+H]^+$, 256, 227. Anal. ($C_{26}H_{28}N_4O_2$) C, H, N.

***N*-[4-(3,4-Dihydro-6-methoxypyrazino[1,2-*a*]indol-2(1*H*)-yl)butyl]isoquinoline-3-carboxamide (Compound 1-5/1e)**



***N*-[4-(3,4-Dihydro-6-methoxypyrazino[1,2-*a*]indol-2(1*H*)-yl)butyl]isoquinoline-3-carboxamide (1e).** The title compound was prepared using the bromo-derivative **6b** (98.0 mg, 0.32 mmol) and the amino-derivative **11** (0.32 mmol) and following the procedure described to obtain **1b**. The compound **1e** was obtained as colourless oil (55% yield); ^1H NMR ($CDCl_3$) δ 1.75 (m, 4H), 2.60 (m, 2H), 2.89 (t, 2H, $J = 5.5$ Hz), 3.57 (q, 2H, $J = 6.1$ Hz), 3.79 (s, 2H), 3.86 (s, 3H), 4.49 (t, 2H, $J = 5.6$ Hz), 6.12 (s, 1H), 6.53 (d, 1H, $J = 7.6$ Hz), 6.93 (t, 1H, $J = 7.7$ Hz), 7.10 (d, 1H, $J = 7.9$ Hz), 7.70 (m, 2H), 7.97 (m, 2H), 8.39 (br s, 1H), 8.59 (s, 1H), 9.05 (s, 1H); ES-MS m/z 879 $[2M+Na]^+$, 451 $[M+Na]^+$, 429 (100) $[M+H]^+$. Anal. ($C_{26}H_{28}N_4O_2$) C, H, N.

3-[5-[4-(3-Chlorophenyl)piperazin-1-yl]pentyloxy]isoquinoline (Compound 1-6/1f)

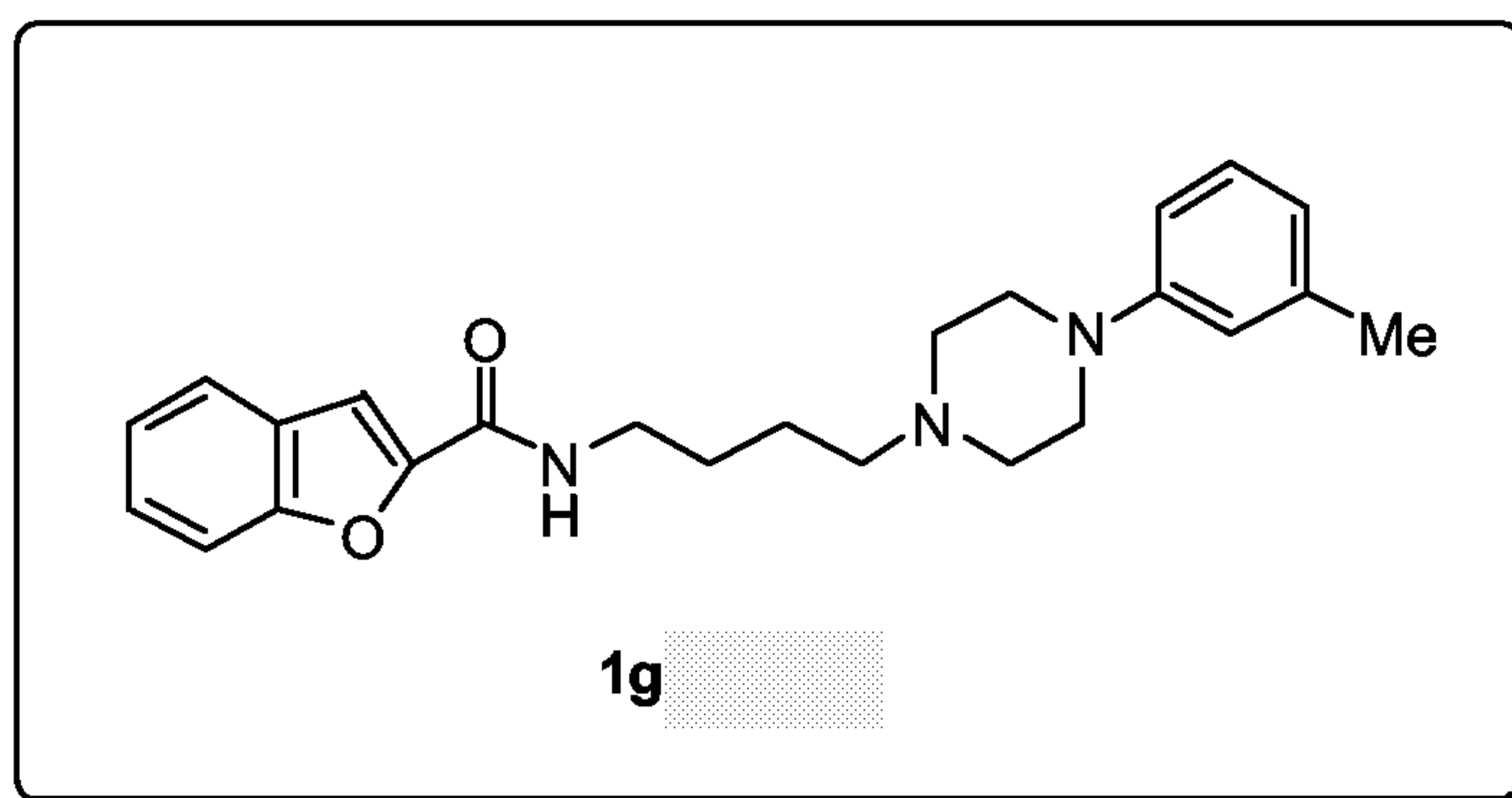


3-(5-Bromopentyloxy)isoquinoline (22). To a solution of isoquinolin-3-ol **21** (200.0 mg, 1.37 mmol) in dry DMF (5.0 mL) 1,5-dibromopentane (204.0 μ L, 1.50 mmol) was added and the mixture was stirred at room temperature for 10 min. Then caesium carbonate (538.0 mg, 1.64 mmol) was added and the mixture was heated at 65°C for 12 h. After cooling at room temperature methyl-*tert*-butyl-ether (MTBE) (20.0 mL) and water (15.0 mL) were added and the mixture was extracted with MTBE (3 x 25 mL). The collected organic layers were dried over Na_2SO_4 , filtered and evaporated. The residue was chromatographed (dichloromethane) to afford 197.0 mg of pure **22** as yellow oil (49% yield). ^1H NMR ($CDCl_3$) δ 1.64 (m, 2H), 1.89 (m, 4H), 3.43 (t, 2H, $J = 6.5$ Hz), 4.34 (t, 2H, $J = 6.3$ Hz), 6.97 (s, 1H), 7.33 (m, 1H), 7.54 (t, 1H, $J = 7.2$ Hz),

7.66 (d, 1H, $J = 8.3$ Hz), 7.85 (d, 1H, $J = 8.2$ Hz), 8.92 (s, 1H); ES-MS m/z 296 (100) $[M+H]^+$, 146. Anal. ($C_{14}H_{16}BrNO$) C, H, N.

3-[5-[4-(3-Chlorophenyl)piperazin-1-yl]pentyloxy]isoquinoline (1f). To a stirred solution of **22** (430.0 mg, 1.46 mmol) in dry acetonitrile (30.0 mL) under argon, 1-(3-chlorophenyl)piperazine hydrochloride (338.7 mg, 1.46 mmol) and triethylamine (329.0 μ L, 2.36 mmol) were added and the solution was refluxed for 4 h under stirring. The solvent was removed under reduced pressure, water was added and the mixture was extracted with dichlorometane (3 x 10 mL). The organic layers were dried and concentrated and the crude product was chromatographed (50% *n*-hexane in EtOAc) to give 320.0 mg of **1f** (78.2% yield) as white solid: mp (EtOAc) 88-89°C; ^1H NMR ($CDCl_3$) δ 1.52-1.76 (m, 4H), 1.88 (q, 2H, $J = 6.6$ Hz), 2.42 (t, 2H, $J = 7.2$ Hz), 2.57 (m, 4H), 3.18 (m, 4H), 4.35 (t, 2H, $J = 6.4$ Hz), 6.73-6.85 (m, 3H), 6.97 (s, 1H), 7.13 (t, 1H, $J = 8.0$ Hz), 7.34 (dd, 1H, $J = 8.3, 6.4$ Hz), 7.54 (dd, 1H, $J = 7.9, 6.4$ Hz), 7.66 (d, 1H, $J = 8.1$ Hz), 7.85 (d, 1H, $J = 8.2$ Hz), 8.93 (s, 1H); ES-MS m/z 410 (100) $[M+H]^+$, 265. Anal. ($C_{24}H_{28}ClN_3O$) C, H, N.

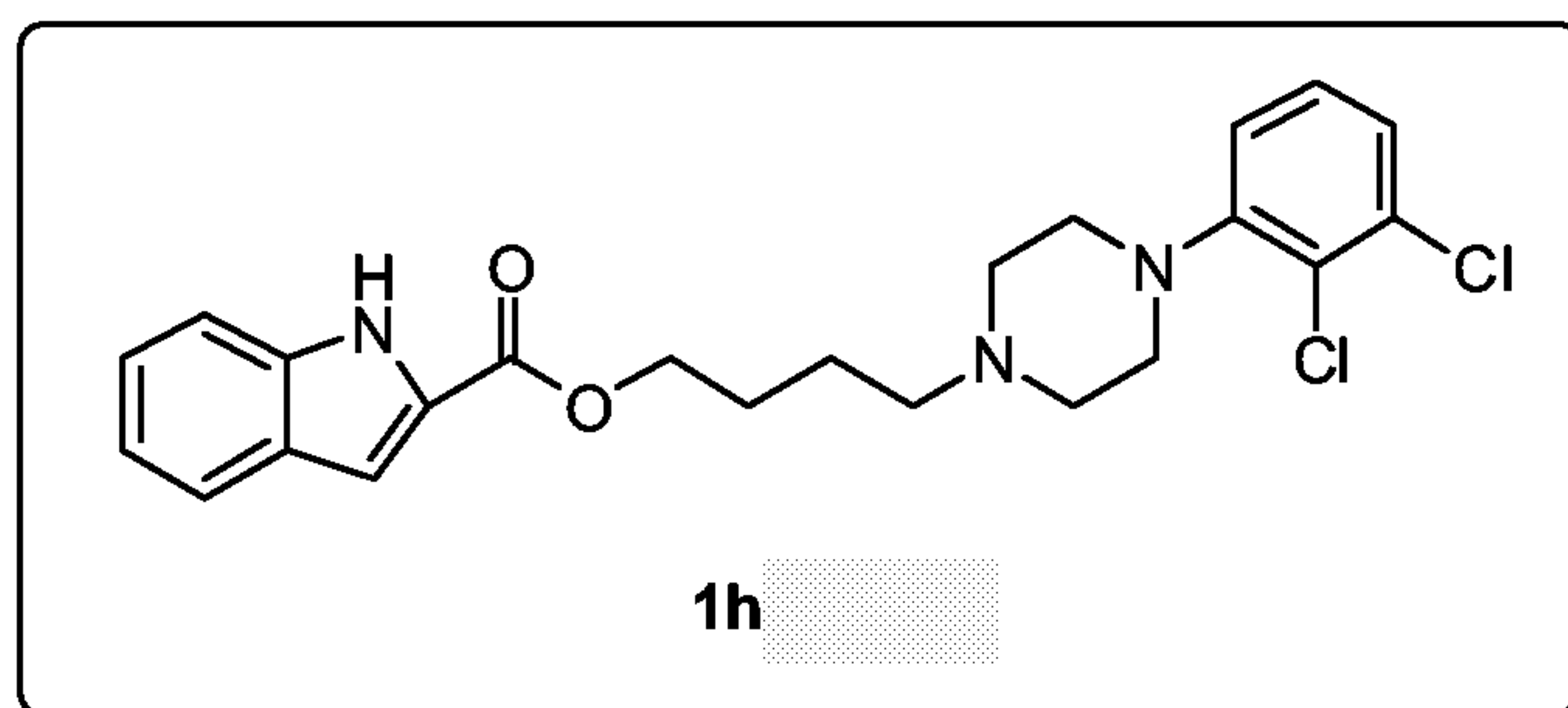
***N*-[4-[4-(*m*-Tolyl)piperazin-1-yl]butyl]benzo[*b*]furan-2-carboxamide (Compound 1-7/1g)**



***N*-[4-[4-(*m*-Tolyl)piperazin-1-yl]butyl]benzo[*b*]furan-2-carboxamide (1g).** To a stirred solution of **6a** (0.62 g, 2.09 mmol) in dry acetonitrile (30.0 mL) under argon, 1-(*m*-tolyl)piperazine dihydrochloride (0.52 g, 2.09 mmol) and triethylamine (0.62 mL, 4.60 mmol) were added and the solution was refluxed overnight under stirring. The solvent was removed under reduced pressure, water was added and the mixture was extracted with dichlorometane (3 x 30 mL). The organic layers were dried and concentrated and the crude product was chromatographed (6% methanol in chloroform) to give 0.42 g of **1g** (52% yield) as white solid: mp 119-120°C; ^1H NMR ($CDCl_3$) δ 1.70 (m, 4H), 2.31 (s, 3H), 2.46 (t, 2H, $J = 6.6$ Hz), 2.62 (t, 4H, $J = 4.9$ Hz), 3.23 (t, 4H, $J = 4.9$ Hz), 3.52 (q, 2H, $J = 6.1$ Hz), 6.70 (m, 3H), 7.00 (br s, 1H), 7.13 (t, 1H, $J = 4.4$ Hz), 7.18-7.48 (m, 4H), 7.66 (d, 1H, $J = 7.7$ Hz); ES-MS m/z 805 (100) $[2M+Na]^+$, 414 $[M+Na]^+$, 392 $[M+H]^+$; ^{13}C NMR ($CDCl_3$) δ 22.0, 24.5, 27.7, 39.4, 49.3,

53.5, 58.1, 110.5, 111.9, 113.4, 117.1, 120.9, 122.9, 123.9, 127.0, 127.9, 129.2, 139.0, 149.2, 151.5, 154.9, 159.1. Anal. (C₂₄H₂₉N₃O₂) C, H, N.

4-[4-(2,3-Dichlorophenyl)piperazin-1-yl]butyl 1*H*-indole-2-carboxylate (Compound 1-8/1h)



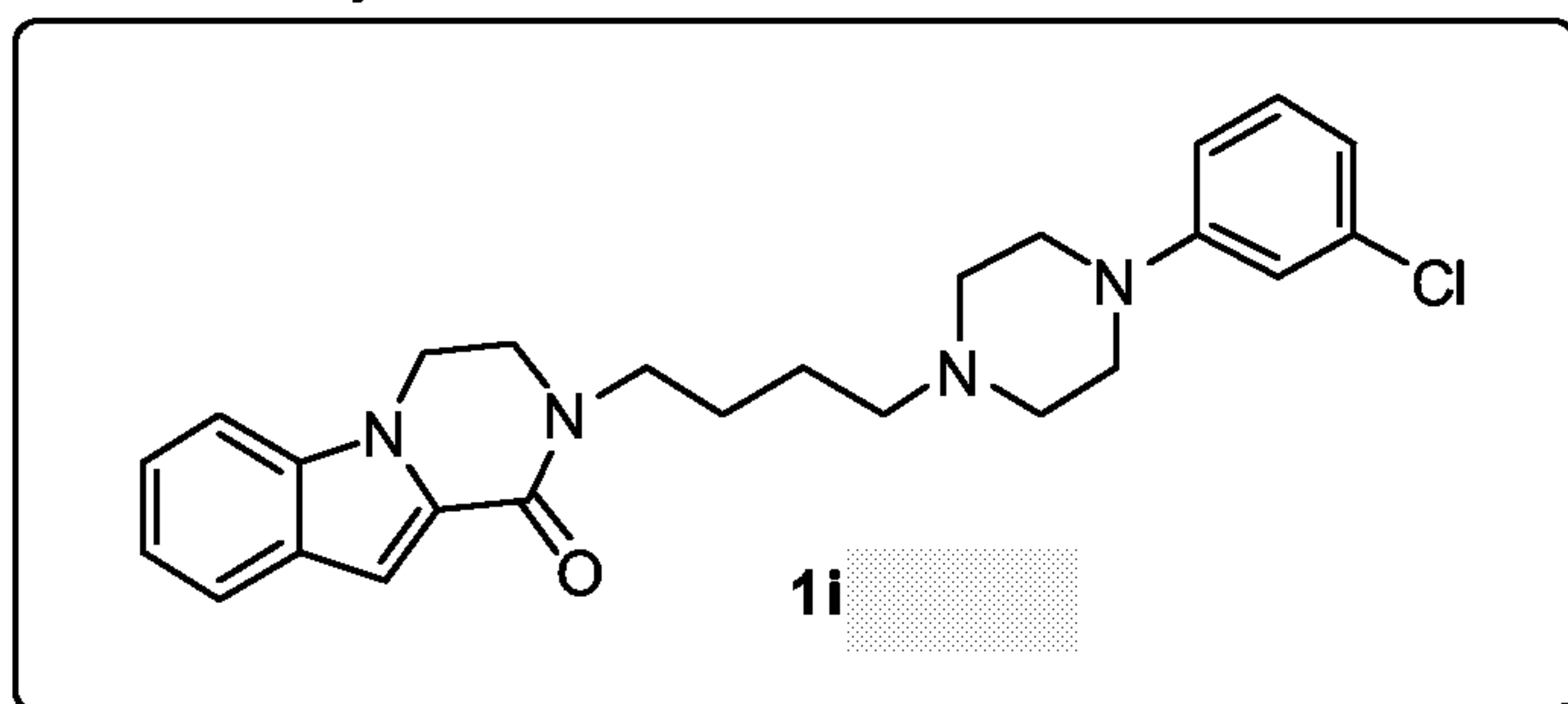
4-Hydroxybutyl 1*H*-indole-2-carboxylate (5c). To a solution of butane-1,4-diol (0.46 mL, 5.21 mmol), dimethylaminopyridine (DMAP) (68.41 mg, 0.56 mmol), and the 1*H*-indole-2-carboxylic acid **4c** (1.0 g, 6.20 mmol) in dry dichloromethane (20.0 mL) at 0°C was added dropwise over 45 min a solution of DCC (1.4 g, 6.76 mmol) in dry dichloromethane (10.0 mL). The resulting suspension was stirred for an additional 1 h at 0°C, the cooling bath was removed, and the mixture was stirred for an additional 12 h. The mixture was filtered through Celite® and evaporated to dryness under reduced pressure. The product was purified by means of flash chromatography (7.5% methanol in chloroform) to give **5c** as white amorphous solid (45% yield). ¹H NMR (CDCl₃) δ 1.81 (m, 4H), 2.08 (br s, 1H), 3.73 (t, 2H, *J* = 6.0 Hz), 4.39 (t, 2H, *J* = 6.2 Hz), 7.14 (t, 1H, *J* = 7.4 Hz), 7.27 (m, 3H), 7.42 (d, 1H, *J* = 8.2 Hz), 7.68 (d, 1H, *J* = 8.0 Hz), 9.39 (br s, 1H); ES-MS *m/z* 232 (100) [*M*-H]⁻ 160, 116. Anal. (C₁₃H₁₅NO₃) C, H, N.

4-Bromobutyl 1*H*-indole-2-carboxylate (6c). The title compound was prepared starting from **5c** (0.45 g, 1.93 mmol) and following the procedure described to obtain **6a**. The compound **6c** was obtained as white solid (91% yield): mp (ethyl acetate) 85-85°C; ¹H NMR (CDCl₃) δ 1.93 (m, 4H), 3.44 (t, 2H, *J* = 6.2 Hz), 4.37 (t, 2H, *J* = 6.0 Hz), 7.15 (t, 1H, *J* = 7.3 Hz), 7.30 (m, 2H), 7.45 (d, 1H, *J* = 8.2 Hz), 7.69 (d, 1H, *J* = 8.0 Hz), 9.81 (br s, 1H). Anal. (C₁₃H₁₄BrNO₂) C, H, N.

4-[4-(2,3-Dichlorophenyl)piperazin-1-yl]butyl 1*H*-indole-2-carboxylate (1h). To a stirred solution of **6c** (220.0 mg, 0.74 mmol) in dry acetonitrile (20.0 mL) under argon, 1-(2,3-dichloro)piperazine hydrochloride (198.0 mg, 0.74 mmol) and triethylamine (167.0 μL, 1.20 mmol) were added and the solution was refluxed overnight under stirring. The solvent was removed under reduced pressure, water was added and the mixture was extracted with dichloromethane (3 x 30 mL). The organic layers were dried and concentrated and the crude product was chromatographed (5% methanol in chloroform) to give **1h** (60% yield) as white solid: mp (methanol) 136-137°C; ¹H NMR (CDCl₃) δ 1.79 (m, 4H), 2.50 (t, 2H, *J* = 6.7 Hz), 2.66 (m, 4H), 3.07 (m,

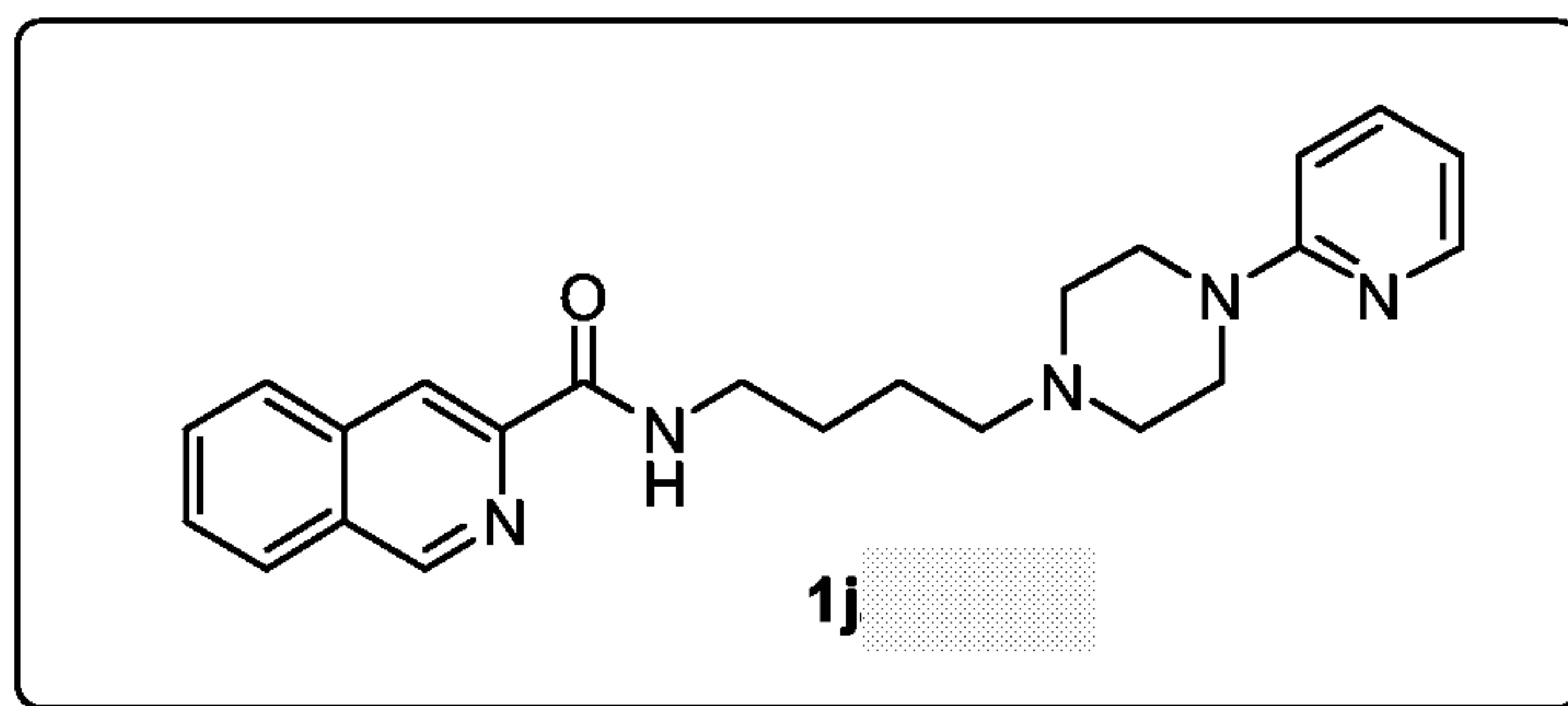
4H), 4.40 (t, 2H, $J = 5.9$ Hz), 6.93 (m, 1H), 7.08-7.35 (m, 5H), 7.43 (d, 1H, $J = 8.1$ Hz), 7.69 (d, 1H, $J = 7.9$ Hz), 9.16 (br s, 1H); ES-MS m/z 468 $[H+Na]^+$, 446 (100) $[M+Na]^+$.
Anal. ($C_{23}H_{25}Cl_2N_3O_2$) C, H, N.

5 **2-[4-[4-(3-Chlorophenyl)piperazin-1-yl]butyl]-3,4-dihydropyrazino[1,2-*a*]indol-1(2*H*)-one (Compound 1-9/1i)**



2-[4-[4-(3-Chlorophenyl)piperazin-1-yl]butyl]-3,4-dihydropyrazino[1,2-*a*]indol-1(2*H*)-one (1i). The title compound was prepared starting from **15** (410.0 mg, 1.28 mmol) and following the procedure described to obtain **1c**. The compound **1i** was
10 obtained as white solid (68% yield): mp (EtOAc) 180-181°C; ^1H NMR ($CDCl_3$) δ 1.64 (m, 4H), 2.43 (t, 2H, $J = 7.1$ Hz), 2.56 (t, 4H, $J = 4.9$ Hz), 3.17 (t, 4H, $J = 4.9$ Hz), 3.62 (t, 2H, $J = 6.8$ Hz), 3.75 (t, 2H, $J = 5.9$ Hz), 4.22 (m, 3H), 6.76 (m, 3H), 6.84 (d, 1H, $J = 2.0$ Hz), 7.14 (m, 2H), 7.30 (m, 2H), 7.69 (d, 1H, $J = 7.9$ Hz); ES-MS m/z 437 $[M+H]^+$;
15 ^{13}C NMR ($CDCl_3$) δ 24.0, 25.5, 40.2, 46.0, 46.2, 48.5, 53.0, 58.0, 106.0, 109.4, 113.7, 115.6, 119.1, 120.6, 122.6, 124.3, 127.5, 129.4, 129.9, 134.9, 136.3, 152.3, 159.8.
Anal. ($C_{25}H_{29}ClN_4O$) C, H, N.

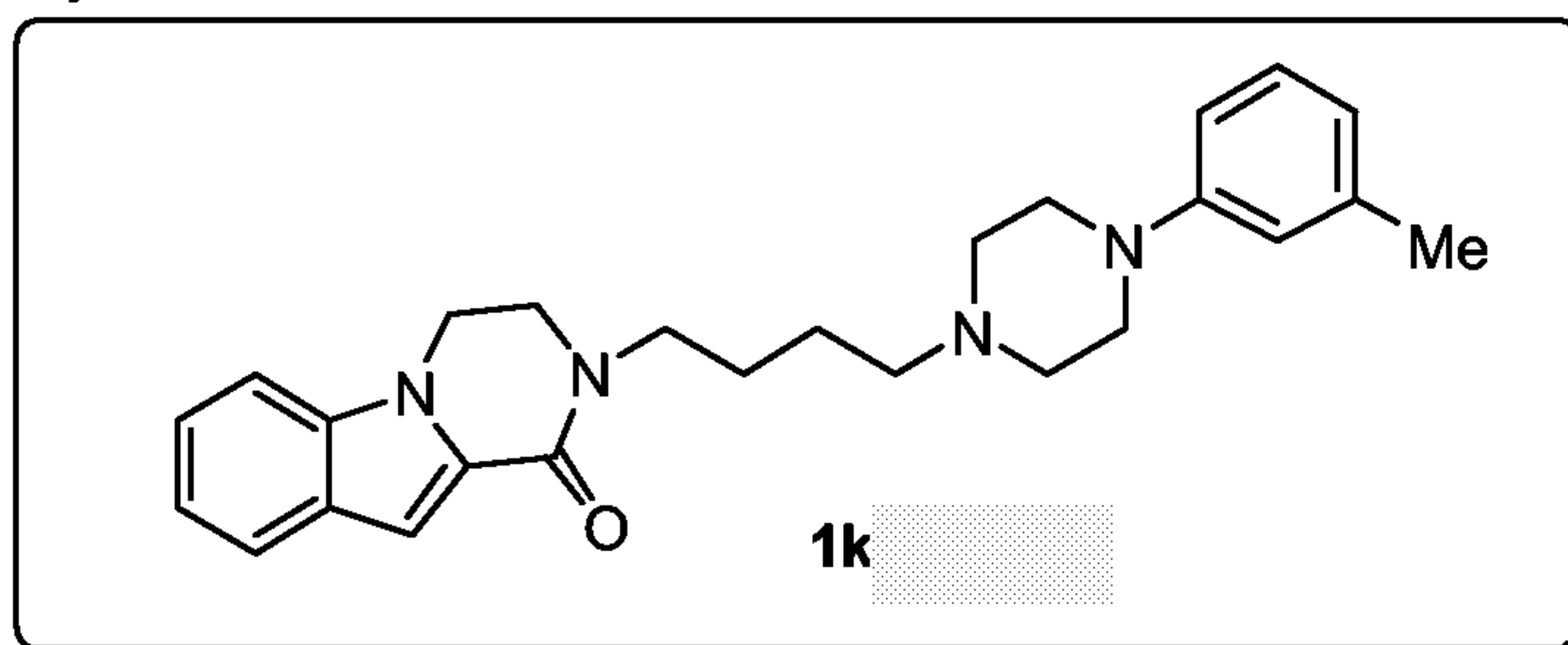
20 **N-[4-[4-(Pyridin-2-yl)piperazin-1-yl]butyl]isoquinoline-3-carboxamide (Compound 1-10/1j)**



N-[4-[4-(Pyridin-2-yl)piperazin-1-yl]butyl]isoquinoline-3-carboxamide (1j). To a stirred solution of **6b** (190.0 mg, 0.62 mmol) in dry acetonitrile (20.0 mL) under argon, 1-(2-pyridin-2-yl)piperazine hydrochloride (101.0 mg, 0.62 mmol) and
25 triethylamine (141.0 μ L, 1.0 mmol) were added and the solution was refluxed overnight under stirring. The solvent was removed and the crude product was chromatographed (10% methanol in chloroform) to give 225.0 mg of **1j** (93.4% yield) as white solid: mp (methanol) 108-109°C; ^1H NMR ($CDCl_3$) δ 1.62 (m, 4H), 2.38 (m, 2H), 2.49 (m, 4H),

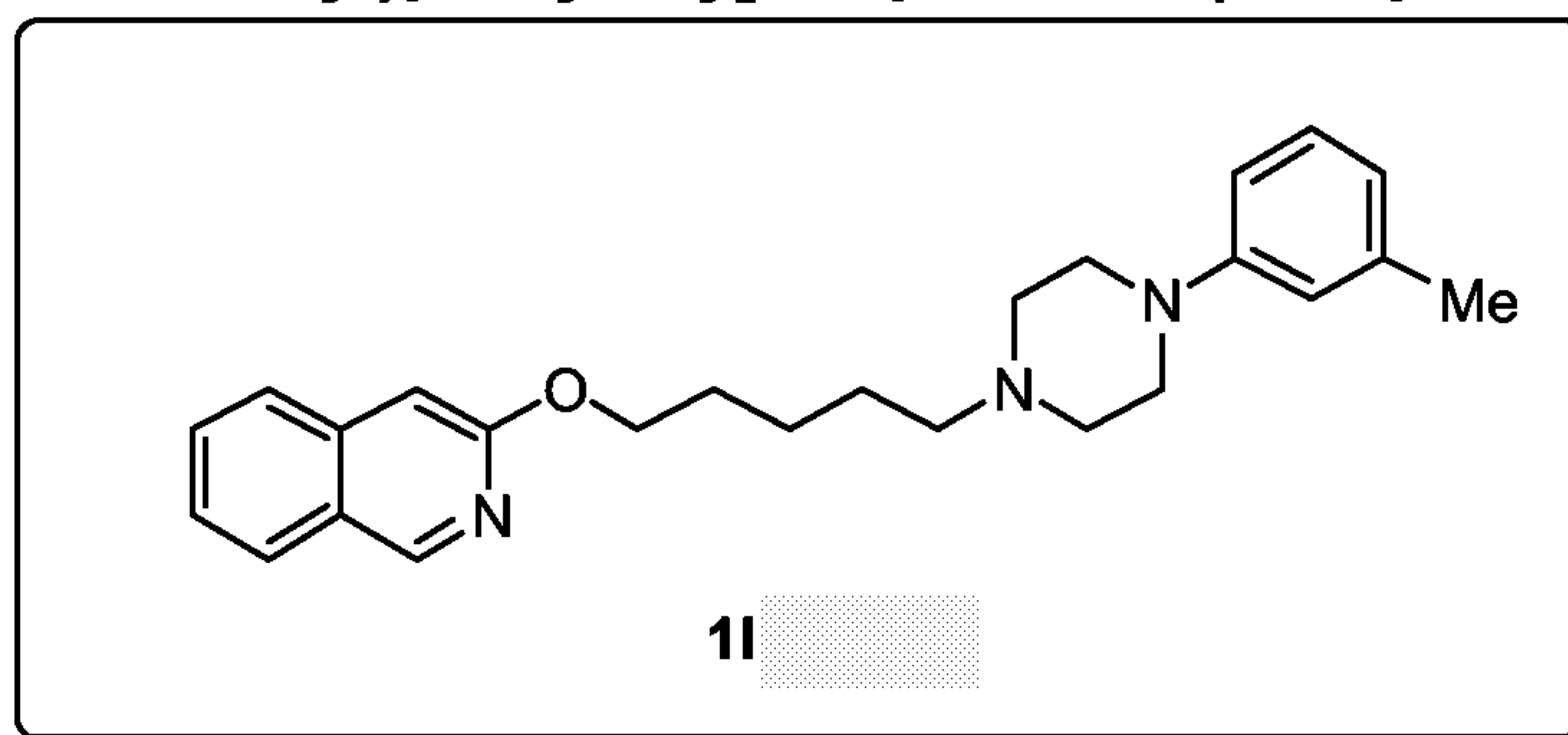
3.52 (m, 6H), 6.54 (m, 2H), 7.40 (m, 1H), 7.65 (m, 2H), 7.91 (t, 2H, $J = 8.6$ Hz), 8.11 (d, 1H, $J = 4.7$ Hz), 8.32 (br s, 1H), 8.54 (s, 1H), 9.06 (s, 1H); ES-MS m/z 412 (100) $[M+Na^+]$, 390 $[M+H^+]$, 242. Anal. ($C_{23}H_{27}N_5O$) C, H, N.

5 **2-[4-(4-*m*-Tolyl)piperazin-1-yl]butyl]-3,4-dihydropyrazino[1,2-*a*]indol-1(2*H*)-one (Compound 1-11/1k)**

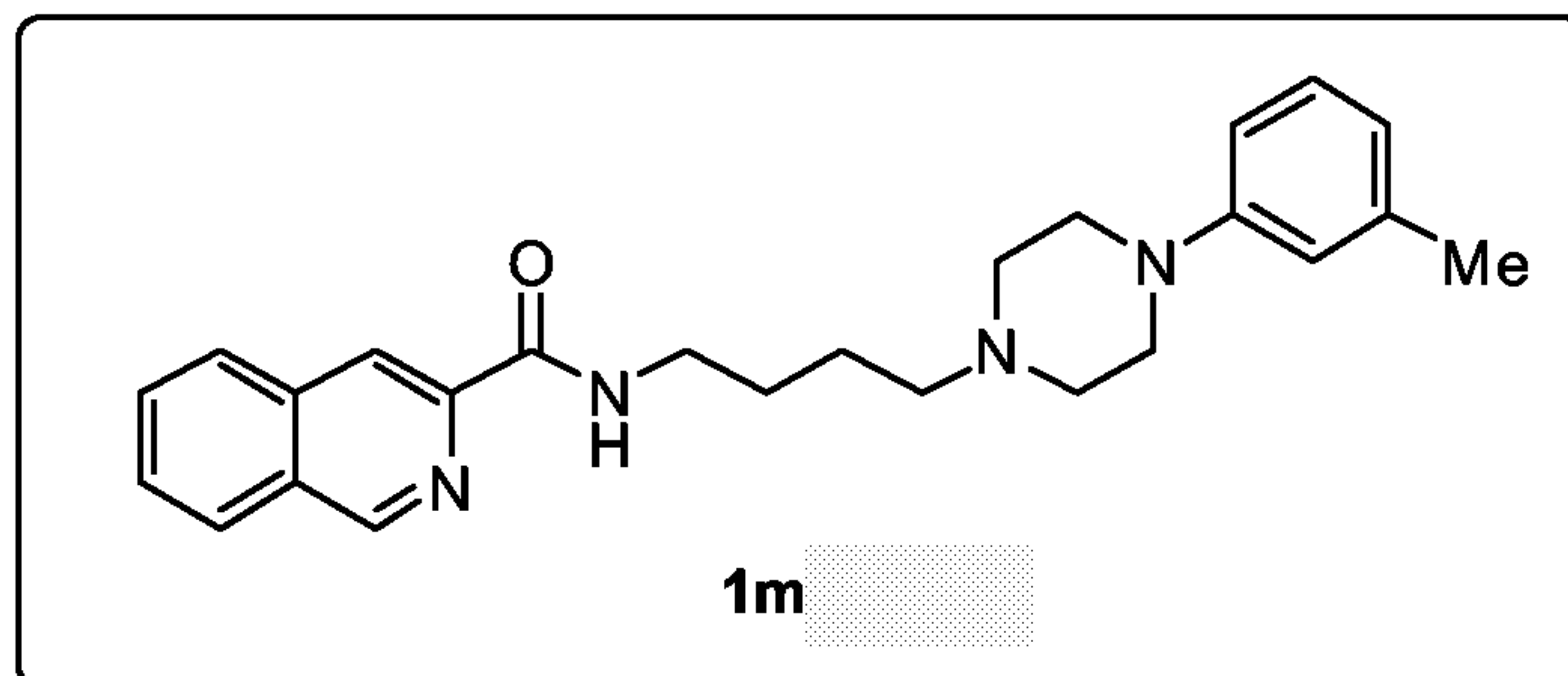


2-[4-(4-*m*-Tolyl)piperazin-1-yl]butyl]-3,4-dihydropyrazino[1,2-*a*]indol-1(2*H*)-one (1k). Starting from **15** (127.0 mg, 0.40 mmol) and 1-(*m*-tolyl)piperazine dihydrochloride (0.40 mmol), the title compound was prepared following the procedure described for **1g**. The product **1k** was obtained as white solid (40.0% yield): mp (methanol) 155-156°C; ^1H NMR ($CDCl_3$) δ 1.68 (m, 4H), 2.36 (s, 3H), 2.49 (m, 2H), 2.60 (t, 4H, $J = 5.0$ Hz), 3.18 (t, 4H, $J = 4.9$ Hz), 3.66 (m, 2H), 3.78 (t, 2H, $J = 3.0$ Hz), 4.25 (m, 2H), 6.70 (m, 4H), 7.14 (m, 2H), 7.31 (m, 2H), 7.70 (d, 1H, $J = 8.2$ Hz); ES-
15 MS m/z 416 $[M+H]^+$. Anal. ($C_{26}H_{32}N_4O$) C, H, N.

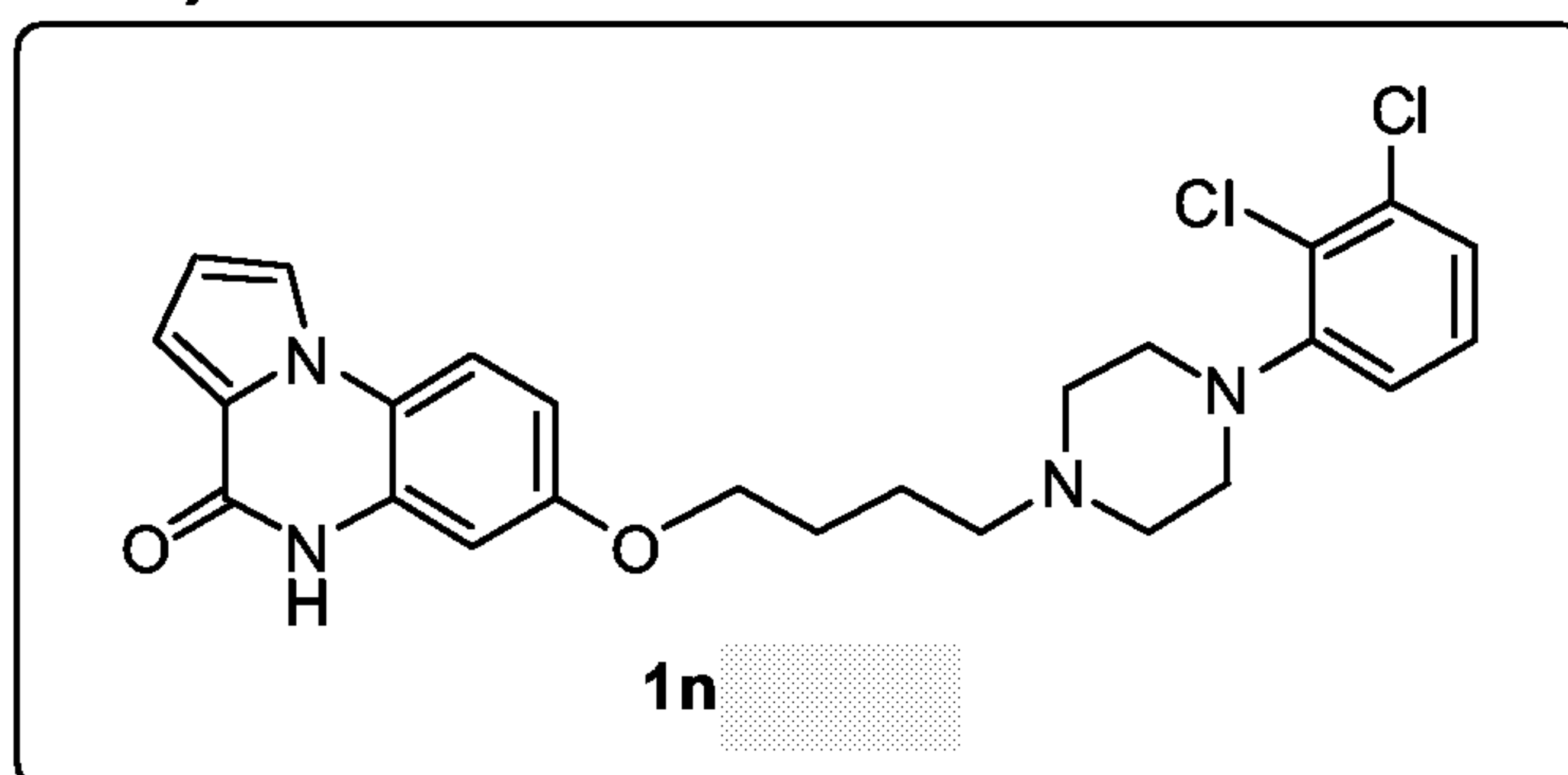
3-[5-(4-*m*-Tolylpiperazin-1-yl)pentyloxy]isoquinoline (Compound 1-12/1l)



3-[5-(4-*m*-Tolylpiperazin-1-yl)pentyloxy]isoquinoline (1l). Starting from
20 **22** (101.0 mg, 0.34 mmol) and 1-(*m*-tolyl)piperazine dihydrochloride (0.34 mmol), the title compound was prepared following the procedure described for **1f**. The product **1l** was obtained as white solid (65.0% yield): mp (methanol) 94-95°C; ^1H NMR ($CDCl_3$) δ 1.72 (m, 4H), 1.92 (m, 2H), 2.30 (s, 3H), 2.42 (t, 2H, $J = 6.8$ Hz), 2.60 (m, 4H), 3.19 (m, 4H), 4.34 (t, 2H, $J = 6.5$ Hz), 6.70 (m, 3H), 6.97 (s, 1H), 7.13 (t, 1H, $J = 8.1$ Hz), 7.55
25 (t, 1H, $J = 7.2$ Hz), 7.67 (d, 1H, $J = 8.1$ Hz), 7.86 (d, 1H, $J = 8.2$ Hz), 8.93 (s, 1H). Anal. ($C_{25}H_{31}N_3O$) C, H, N.

N*-[4-[4-(*m*-Tolyl)piperazin-1-yl]butyl]isoquinoline-3-carboxamide (Compound 1-13/1m)**N*-[4-[4-(*m*-Tolyl)piperazin-1-yl]butyl]isoquinoline-3-carboxamide (1m).**

Starting from **6b** (1.0 g, 3.26 mmol) and 1-(*m*-tolyl)piperazine dihydrochloride (3.26 mmol), the title compound was prepared following the procedure described for **1g**. The product **1m** was obtained as yellowish solid (48.0% yield): mp (methanol) 152-153°C; ¹H NMR (CDCl₃) δ 1.68 (m, 4H), 2.30 (s, 3H), 2.46 (t, 2H, *J* = 6.8 Hz), 2.60 (t, 4H, *J* = 5.0 Hz), 3.20 (t, 4H, *J* = 4.9 Hz), 3.58 (q, 2H, *J* = 6.4 Hz), 6.70 (m, 3H), 7.14 (t, 1H, *J* = 8.1 Hz), 7.72 (m, 2H), 8.00 (t, 2H, *J* = 8.0 Hz), 8.33 (br s, 1H), 8.61 (s, 1H), 9.14 (s, 1H); ES-MS *m/z* 403 [M+H]⁺; ¹³C NMR (DMSO-*d*₆) 21.3, 22.0, 27.1, 39.1, 46.2, 51.1, 55.7, 114.1, 117.5, 121.1, 121.9, 128.7, 129.0, 129.7, 130.2, 133.0, 136.5, 139.0, 143.0, 150.0, 151.7, 164.1, 170.0. Anal. (C₂₅H₃₀N₄O) C, H, N.

7-[4-[4-(2,3-Dichlorophenyl)piperazin-1-yl]butoxy]pyrrolo[1,2-*a*]quinoxalin-4(5*H*)-one (Compound 1-14/1n)

7-Hydroxypyrrolo[1,2-*a*]quinoxalin-4(5*H*)-one (24). A solution of **23** (100.0 mg, 0.35 mmol) in THF (70.0 mL) was hydrogenated at atmospheric pressure over 10% Pd-C (1.62 mg) for 16 h. The catalyst was removed by filtration, the solvent was evaporated, and the residue was purified by means of flash chromatography (15% methanol in chloroform) to afford compound **24** in quantitative yield as an amorphous solid. ¹H NMR (DMSO-*d*₆) δ 6.57 (m, 2H), 6.69 (m, 1H), 6.90 (m, 1H), 7.80 (d, 1H, *J* = 8.8 Hz), 7.98 (s, 1H), 9.62 (s, 1H), 11.03 (s, 1H). Anal. (C₁₁H₈N₂O₂) C, H, N.

7-(4-Bromobutoxy)pyrrolo[1,2-*a*]quinoxalin-4(5*H*)-one (25). To a solution of compound **24** (50.0 mg, 0.25 mmol) in dry DMF (5.0 mL) 1,4-dibromobutane (64.0 μL, 0.29 mmol) was added and the mixture was stirred at room temperature for 10 min.

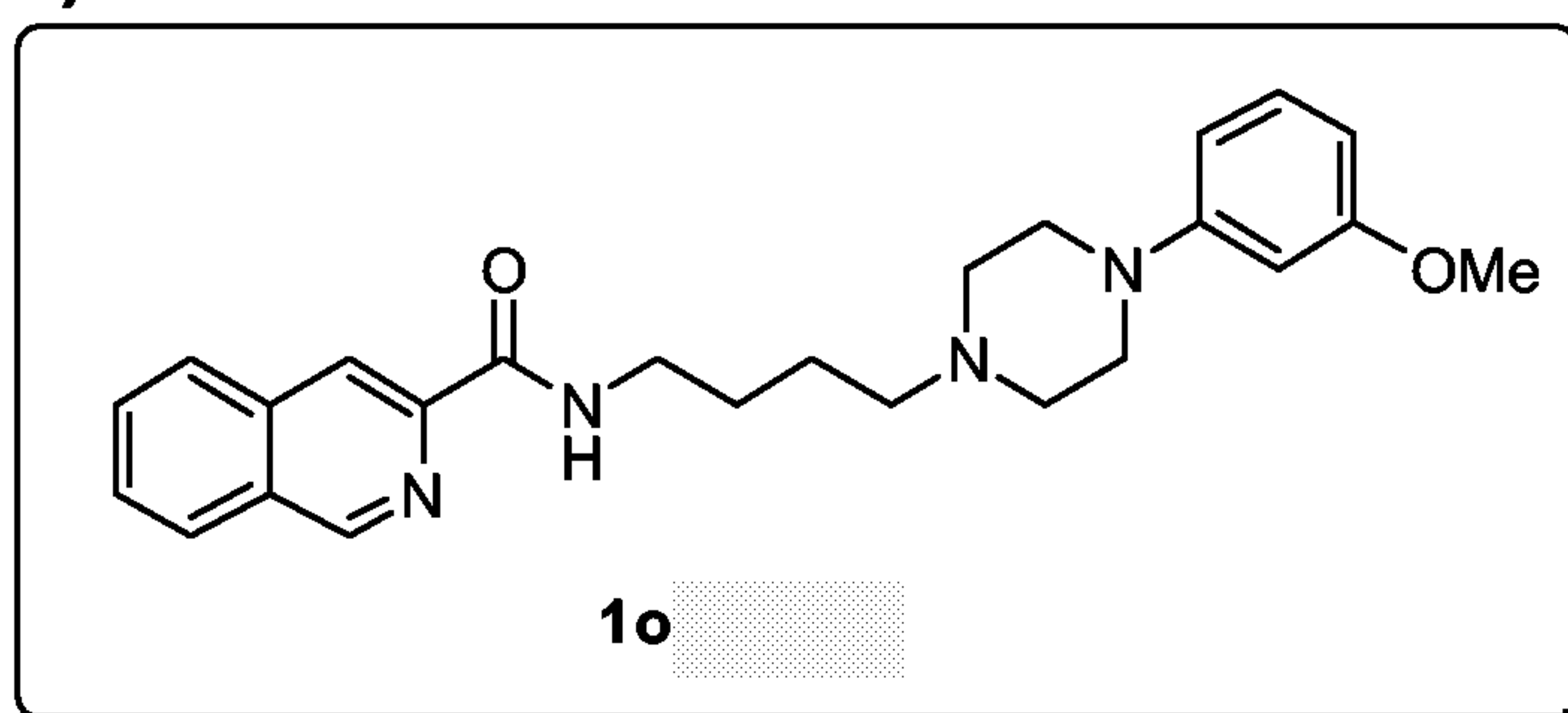
Then caesium carbonate (98.0 mg, 0.30 mmol) was added and the mixture was heated at 65°C for 12 h. After cooling at room temperature methyl-*tert*-butylether (MTBE) (10.0 mL) and water (5.0 mL) were added and the mixture was extracted with MTBE (3 x 25 mL). The collected organic layers were dried over Na₂SO₄, filtered and evaporated.

5 The residue was chromatographed (15% *n*-hexane in EtOAc) to afford pure **25** as yellow oil (22.5% yield). ¹H NMR (CD₃OD) δ 1.64 (m, 2H), 1.96 (m, 4H), 3.52 (m, 2H), 3.99 (m, 2H), 6.62 (m, 1H), 6.77 (m, 2H), 7.10 (d, 1H, *J* = 3.5 Hz), 7.73 (m, 1H), 7.83 (d, 1H, *J* = 1.5 Hz). Anal. (C₁₅H₁₅BrN₂O₂) C, H, N.

7-[4-[4-(2,3-Dichlorophenyl)piperazin-1-yl]butoxy]pyrrolo[1,2-

10 **a]quinoxalin-4(5*H*)-one (1n).** Starting from **25** (100.0 mg, 0.50 mmol) and (2,3-dichloro)phenylpiperazine dihydrochloride (0.50 mmol), the title compound was prepared following the procedure described for **1f**. The product **1n** was obtained as white amorphous solid (81.0% yield). ¹H NMR (DMSO-*d*₆) δ 1.67 (m, 4H), 2.44 (m, 6H), 2.95 (m, 4H), 3.99 (t, 2H, *J* = 5.9 Hz), 6.77 (m, 2H), 6.94 (m, 1H), 7.08 (m, 1H), 7.25
15 (m, 2H), 7.92 (d, 1H, *J* = 8.6 Hz), 8.04 (s, 1H), 11.03 (s, 1H). Anal. (C₂₅H₂₆Cl₂N₄O₂) C, H, N.

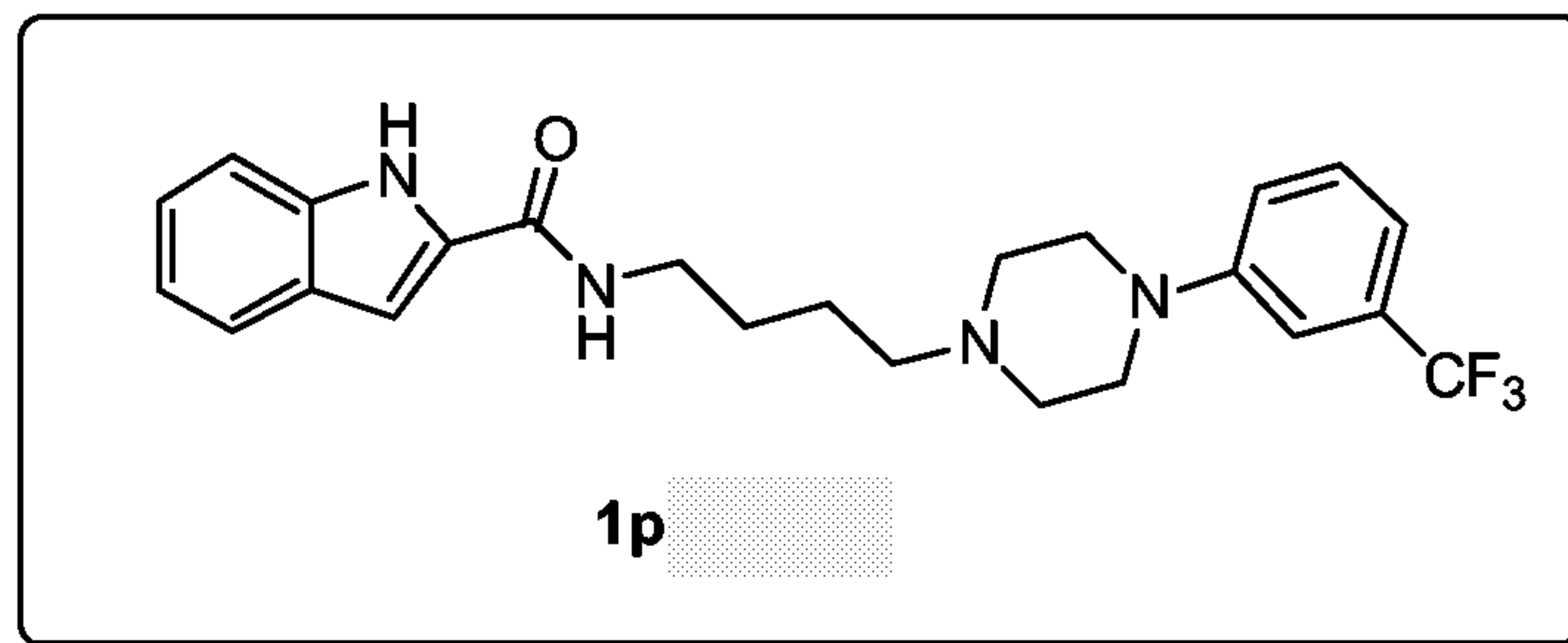
***N*-[4-[4-(3-Methoxyphenyl)piperazin-1-yl]butyl]isoquinoline-3-carboxamide (Compound 1-15/1o)**



***N*-[4-[4-(3-Methoxyphenyl)piperazin-1-yl]butyl]isoquinoline-3-**

20 **carboxamide (1o).** Starting from **6b** (1.0 g, 2.39 mmol) and (3-methoxy)phenylpiperazine (458.9 mg, 2.39 mmol), the title compound was prepared following the procedure described for **1g**. The product **1o** was obtained as a colourless
25 oil (54.0% yield). ¹H NMR (CDCl₃) δ 1.66 (m, 4H), 2.44 (t, 2H, *J* = 6.8 Hz), 2.59 (t, 4H, *J* = 4.9 Hz), 3.19 (t, 4H, *J* = 4.9 Hz), 3.56 (q, 2H, *J* = 6.3 Hz), 3.77 (s, 3H), 6.47 (m, 3H), 7.14 (t, 1H, *J* = 8.1 Hz), 7.73 (m, 2H), 7.99 (t, 2H, *J* = 8.2 Hz), 8.32 (br s, 1H), 8.60 (s, 1H), 9.12 (s, 1H); ES-MS *m/z* 441 [M+Na]⁺, 419 [M+H]⁺. Anal. (C₂₅H₃₀N₄O₂) C, H, N.

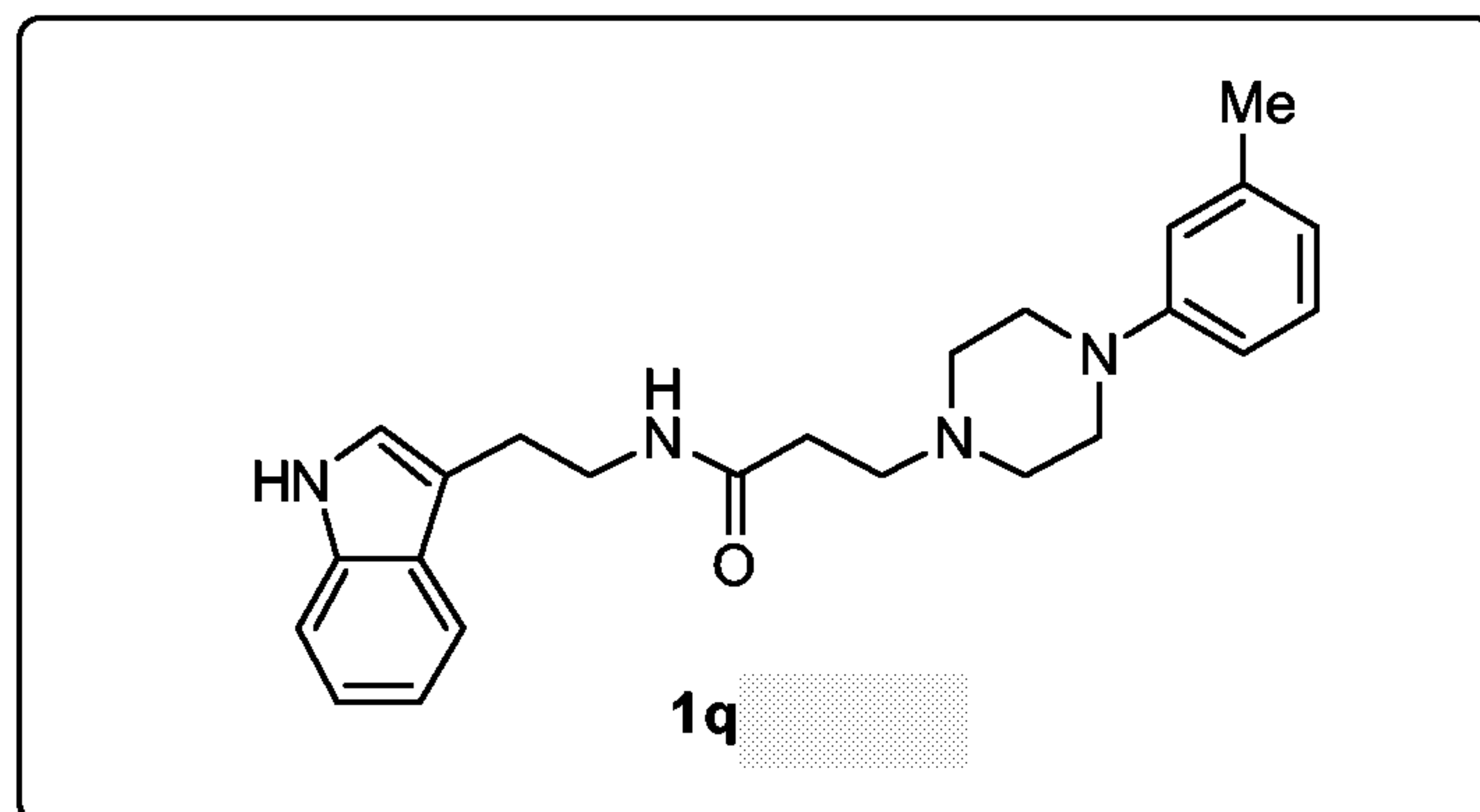
***N*-[4-[4-(3-Trifluoromethylphenyl)piperazin-1-yl]butyl]indole-2-carboxamide (Compound 1-16/1p)**



***N*-[1-(4-Hydroxy)butyl]indole-2-carboxamide (5d).** To a solution of 2-indolecarboxylic acid **4c** (150.0 mg, 0.93 mmol) in dry dichloromethane (20.0 mL), 1-hydroxybenzotriazole hydrate (460.0 mg, 1.03 mmol) and 1,3-dicyclohexylcarbodiimide (210.0 mg, 1.03 mmol) were added at 0°C under argon; the suspension was warmed to room temperature and stirred for 1 h. Then 4-amino-1-butanol (93.6 µL, 1.03 mmol) was added and the mixture was stirred at room temperature for 16 h. The resulting suspension was filtered through Celite, washed with chloroform, and the filtrate evaporated. The crude product was purified by flash chromatography (10% methanol in chloroform) to give of **5d** as colorless as colorless prisms (93% yield): mp (methanol) 108-109°C; ¹H NMR (CDCl₃) δ 1.67 (m, 4H), 3.52 (q, 2H, *J* 11.5, 5.6) 3.72 (t, 2H, *J* 5.8 Hz), 6.65 (br s, 1H), 6.82 (s, 1H), 7.11 (d, 1H, *J* 8.0 Hz), 7.29 (m, 1H), 7.39 (d, 1H, *J* 7.7 Hz), 7.59 (d, 1H, *J* 7.8 Hz), 9.25 (br s, 1H). Anal. (C₁₃H₁₆N₂O₂) C, H, N.

***N*-[1-(4-Bromo)butyl]indole-2-carboxamide (6d).** To a stirred solution of **5d** (170.0 mg, 0.73 mmol) in acetonitrile (25.0 mL), triphenylphosphine (0.86 g, 3.22 mmol) and carbon tetrabromide (1.06 g, 3.22 mmol) were added at room temperature. After 2 h, the mixture was quenched with 15% NaOH and extracted with ethyl acetate. The organic layers were dried and evaporated. The residue was purified by means of flash chromatography (20% *n*-hexane in ethyl acetate) to afford **6b** as a colorless prisms (84% yield): mp (ethyl acetate) 133-134°C; ¹H NMR (CDCl₃) δ 1.96 (m, 4H), 3.56 (m, 4H), 7.28 (m, 5H), 7.60 (d, 1H, *J* 7.6 Hz), 9.80 (br s, 1H). Anal. (C₁₃H₁₅BrN₂O) C, H, N.

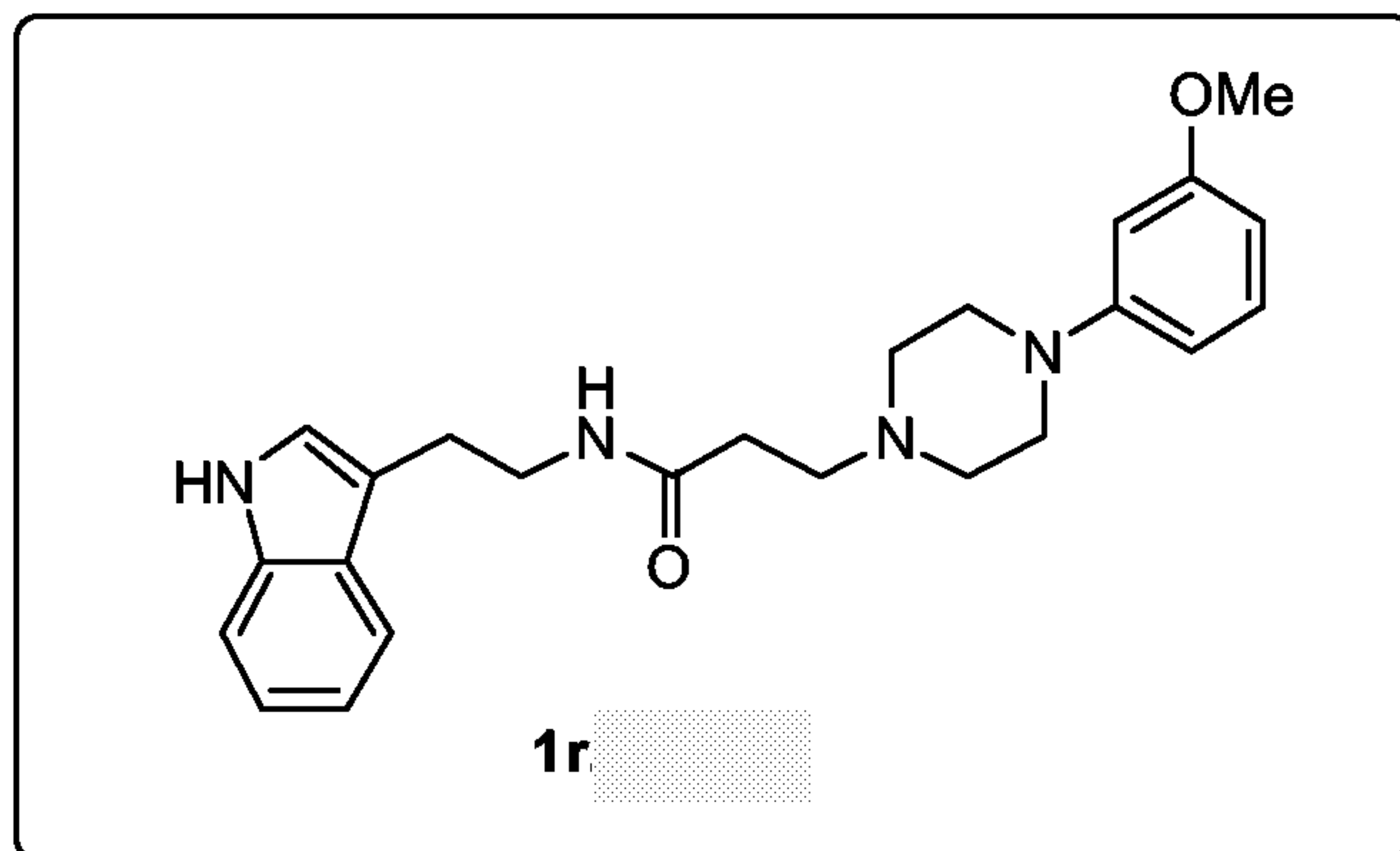
***N*-[4-[4-(3-Trifluoromethylphenyl)piperazin-1-yl]butyl]indole-2-carboxamide (1p).** Starting from **6d** (35.0 mg, 0.12 mmol) and (3-trifluoromethyl)phenylpiperazine (27.3 mg, 0.12 mmol) the title compound was prepared following the procedure described for **1g** and was obtained as a yellow oil (56.0% yield). ¹H NMR (CDCl₃) δ 1.82 (m, 4H), 2.43 (m, 2H), 2.57 (m, 4H), 3.21 (m, 4H), 3.54 (m, 2H), 6.58 (m, 1H), 6.83 (s, 1H), 7.11 (m, 3H), 7.31 (m, 2H), 7.45 (d, 1H, *J* = 8.0 Hz), 7.61 (d, 1H, *J* = 7.9 Hz), 10.08 (br s, 1H); ES-MS *m/z* 445 [M+H]⁺. Anal. (C₂₄H₂₇F₃N₄O) C, H, N.

***N*-[2-(1*H*-Indol-3-yl)ethyl]-3-(4-*m*-tolylpiperazin-1-yl)propanamide (Compound 1-17/1q)**

5 ***N*-[2-(1*H*-Indol-3-yl)ethyl]-3-bromopropanamide (27).** To a solution of tryptamine (1.0 g, 6.24 mmol) in dry dichloromethane (10.0 mL), 3-bromopropanoyl chloride (691.0 μ l, 6.86 mmol) and triethylamine (870.0 μ l, 6.24 mmol) were added and the solution was stirred into a microwave oven for 1 min at 200 W. Then the solvent was evaporated, water was added to the residue and was extracted with EtOAc (3 x 20
10 mL). The crude product was purified by means of flash chromatography (10% methanol in chloroform) to afford **27** as white solid (22.0% yield): mp (EtOAc)= 106-107°C. ^1H NMR (CDCl_3) δ 2.64 (t, 2H, J = 6.4 Hz), 2.98 (t, 2H, J = 6.6 Hz), 3.56 (m, 4H), 5.61 (br s, 1H), 7.06 (m, 1H), 7.18 (m, 2H), 7.36 (d, 1H, J = 7.9 Hz), 7.60 (d, 1H, J = 7.6 Hz), 8.10 (br s, 1H); ES-MS m/z 319 $[\text{M}+\text{Na}]^+$, 295 $[\text{M}+\text{H}]^+$. Anal. Anal.
15 ($\text{C}_{13}\text{H}_{15}\text{BrN}_2\text{O}$) C, H, N.

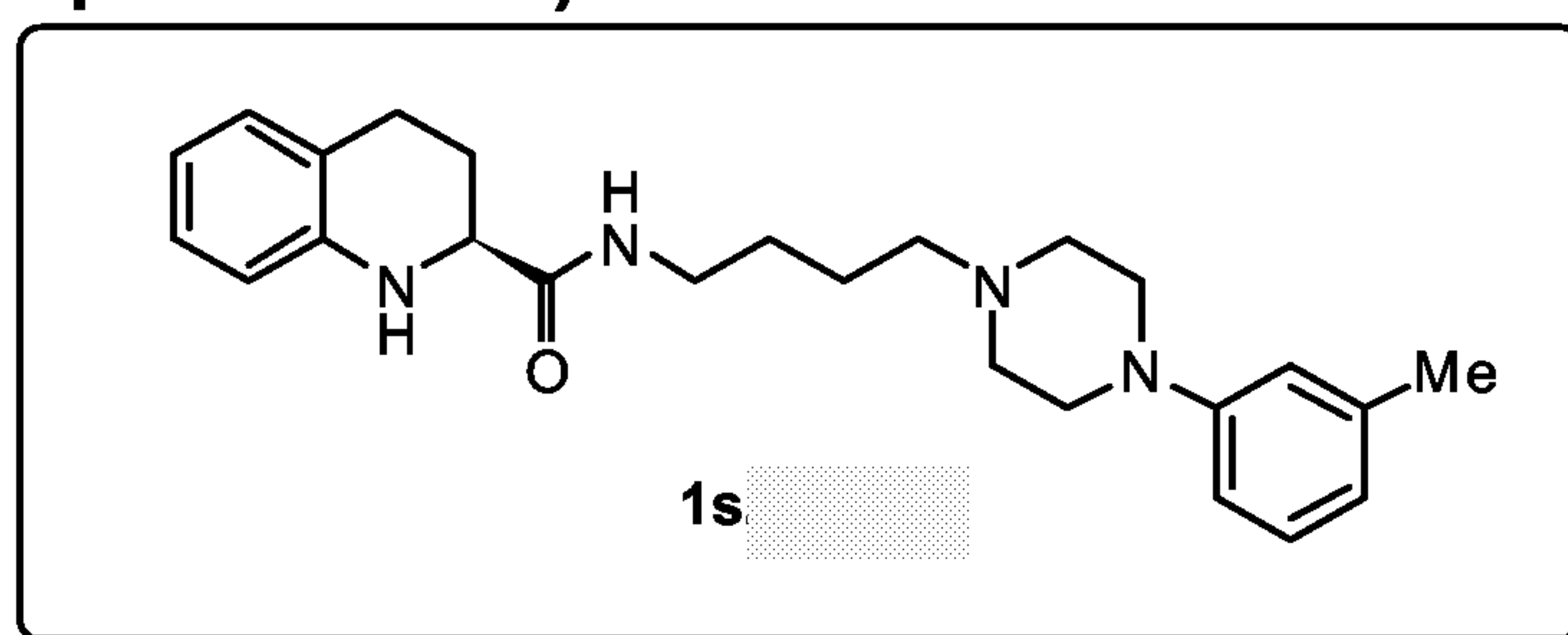
***N*-[2-(1*H*-Indol-3-yl)ethyl]-3-(4-*m*-tolylpiperazin-1-yl)propanamide (1q).** To a stirred solution of **27** (200.0 mg, 0.68 mmol) in dry acetonitrile (20.0 mL) under argon, 1-(*m*-tolyl)piperazine dihydrochloride (0.68 mmol) and triethylamine (141.0 μ L, 1.0 mmol) were added; the solution was refluxed overnight while stirring. The solvent
20 was removed under reduced pressure, water was added and the mixture was extracted with dichloromethane (3 x 10 mL). The organic layers were dried and concentrated and the crude product was chromatographed (10% methanol in chloroform) to give **1q** (50% yield) as white amorphous solid. ^1H NMR (CDCl_3) δ 2.23-2.41 (m, 9H), 2.51 (m, 2H), 2.74 (m, 4H), 2.96 (t, 2H, J = 6.5 Hz), 3.64 (q, 2H, J = 6.3
25 Hz), 6.60 (m, 2H), 6.69 (m, 1H), 6.98-7.28 (m, 5H), 7.58 (m, 1H), 8.09 (br s, 1H), 8.20 (br s, 1H); ES-MS m/z 413 $[\text{M}+\text{Na}]^+$, 391 $[\text{M}+\text{H}]^+$. Anal. ($\text{C}_{24}\text{H}_{30}\text{N}_4\text{O}$) C, H, N.

***N*-[2-(1*H*-Indol-3-yl)ethyl]-3-[4-(3-methoxyphenyl)piperazin-1-yl]propanamide
(Compound 1-18/1r)**



***N*-[2-(1*H*-Indol-3-yl)ethyl]-3-[4-(3-methoxyphenyl)piperazin-1-yl]propanamide (1r).** Starting from **27** (100.0 mg, 0.34 mmol) and (3-methoxy)phenylpiperazine (0.34 mmol) the title compound was prepared following the procedure described for **1q** and was obtained as a white amorphous solid (47.0% yield). ¹H NMR (CDCl₃) δ 2.33 (m, 6H), 2.46 (m, 2H), 2.73 (m, 4H), 2.95 (m, 2H), 3.62 (m, 2H), 3.79 (s, 3H), 6.38 (m, 3H), 6.97 (s, 1H), 7.03-7.27 (m, 4H), 7.57 (d, 1H, *J* = 7.4 Hz), 8.24 (br s, 1H), 8.48 (br s, 1H). Anal. (C₂₄H₃₀N₄O₂) C, H, N.

(*S*)-(-)-*N*-[4-[4-(*m*-Tolyl)piperazin-1-yl]butyl]-1,2,3,4-tetrahydroisoquinoline-2-carboxamide (Compound 1-19/1s)



2-Methyl (*S*)-(-)-1-(benzyloxycarbonyl)-1,2,3,4-tetrahydroquinoline-2-carboxylate ((*S*)-30). To a solution of amino ester (**S**)-**28** (160.0 mg, 0.84 mmol) in aq. NaHCO₃ (2M), benzyl chloroformate (158.2 mg, 0.92 mmol) was added dropwise in 30 min. The mixture was stirred for 1.5 h at room temperature then evaporated. The residue was extracted with EtOAc (3 x 20 mL) and the organic layers were dried and evaporated. The crude product was purified by means of flash chromatography (20% acetone in *n*-hexane) to give compound (**S**)-**30** as colourless oil (80% yield). [α]_D²⁰ = -50.0° (*c* = 0.94, MeOH); ¹H NMR (CDCl₃) δ 1.81 (m, 1H), 2.31-2.43 (m, 1H), 2.43-2.69 (m, 2H), 3.61 (s, 3H), 4.96 (t, 1H, *J* = 7.6 Hz), 5.24 (s, 2H), 6.97-7.08 (m, 2H), 7.16-7.23 (m, 1H), 7.24-7.35 (m, 5H), 7.81 (d, 1H, *J* = 7.4 Hz); ESI-MS *m/z* 325 [*M*⁺], 281, 266, 222, 190, 130, 91. Anal. (C₁₉H₁₉NO₄) C, H, N.

(S)-(-)-1-(Benzyloxycarbonyl)-1,2,3,4-tetrahydroquinoline-2-carboxylic acid [(S)-31]. To a solution of **(S)-30** (218.5 mg, 0.67 mmol) in methanol and water (3:2) NaOH (27.0 mg, 0.67 mmol) was added and the mixture was heated to reflux for 2 h. Then the solvents were evaporated, water was added to the residue and the mixture was acidified with HCl 1N. The aqueous layer was extracted with chloroform (3 x 15 mL) and the collected organic layers were dried and evaporated. The crude product was purified by means of flash chromatography (CHCl₃/ MeOH/ CH₃COOH 9:1:0.1) to afford **(S)-31** as amorphous solid and in quantitative yield. ¹H NMR (CDCl₃) δ 1.81-1.99 (m, 1H), 2.31-2.43 (m, 1H), 2.46-2.69 (m, 2H), 3.61 (s, 3H), 4.96 (t, 1H, *J* = 7.6 Hz), 5.24 (s, 2H), 6.97-7.08 (m, 2H), 7.16-7.23 (m, 1H), 7.24-7.35 (m, 5H), 7.81 (d, 1H, *J* = 7.4 Hz); ESI-MS *m/z* 310 [M]⁺ (100), 266, 202. Anal. (C₁₈H₁₇NO₄) C, H, N. $[\alpha]^{20}_{\text{D}} -50^{\circ}$ (*c* = 0.98, MeOH).

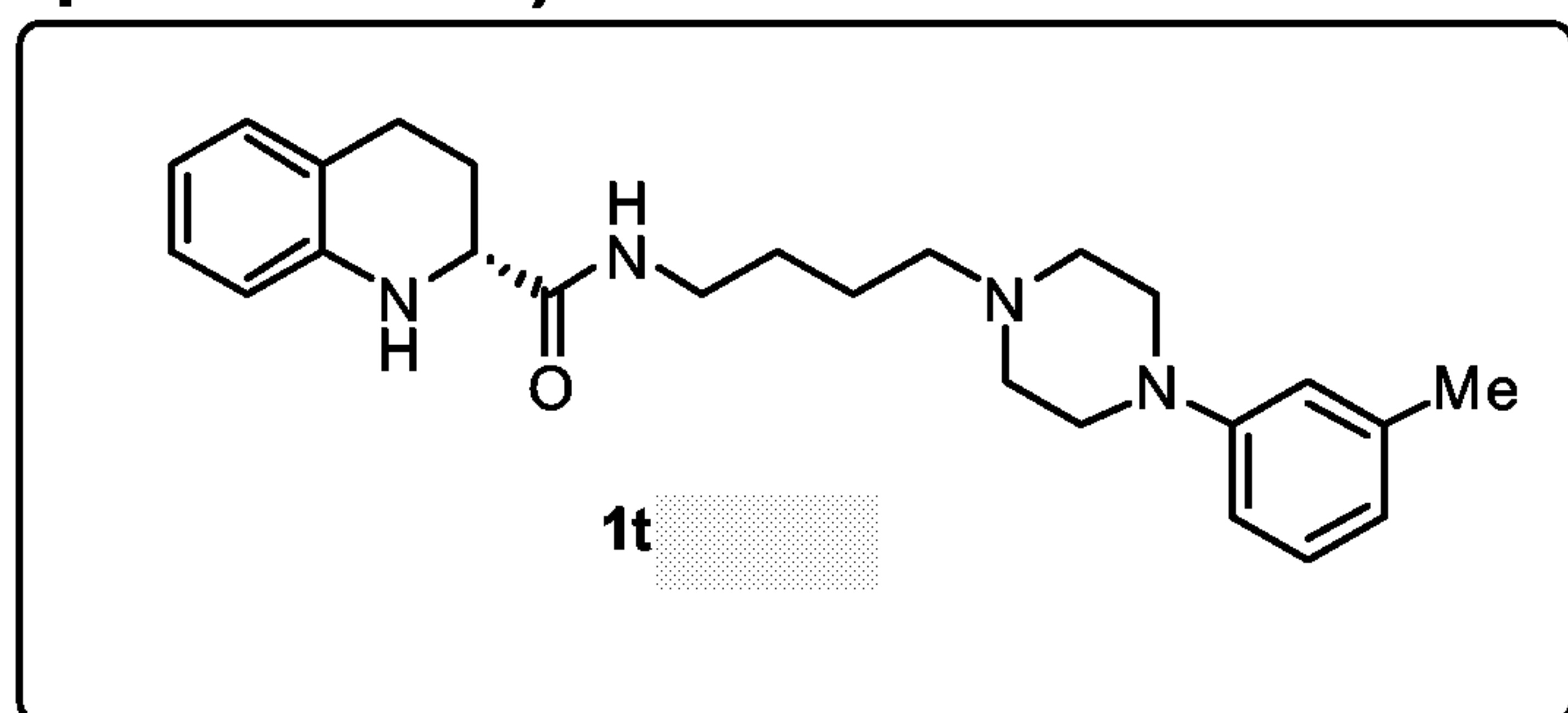
(S)-(-)-N-[4-(1-Hydroxy)butyl]-1-(benzyloxycarbonyl)-1,2,3,4-tetrahydroisoquinoline-2-carboxamide [(S)-32]. To a solution acid **(S)-31** (980.5 mg, 3.15 mmol) in dry dichlorometane (20.0 mL), 1-hydroxybenzotriazole hydrate (HOBT) (920.0 mg, 6.80 mmol) and 1,3-dicyclohexylcarbodiimide (1.40 g, 6.80 mmol) were added at 0 °C under argon; the suspension was warmed to room temperature and stirred for 1 h. Then 4-amino-1-butanol (0.56 mL, 6.16 mmol) was added and the mixture was stirred overnight at room temperature. The resulting suspension was filtered through Celite[®], washed with chloroform (3 x 25 mL) and the filtrate evaporated. The crude product was purified by means of flash chromatography (10% methanol in chloroform) to give **(S)-32** as colourless oil (84% yield). ¹H NMR (CDCl₃) δ 1.17-1.40 (m, 4H), 2.03-2.32 (m, 2H), 2.50-2.74 (m, 2H), 3.11 (m, 2H), 3.36-3.43 (m, 2H), 4.92(t, 1H, *J* = 6.8 Hz), 5.12-5.27 (m, 2H), 6.43 (br s, 1H), 6.96-7.17 (m, 3H), 7.31 (m, 5H), 7.63 (d, 1H, *J* = 8.10 Hz); ESI-MS *m/z* 405 [M + Na]⁺ (100); MS/MS (405) *m/z* 361, 270. $[\alpha]^{20}_{\text{D}} + 41.9^{\circ}$ (*c* = 1.56, CHCl₃). Anal. (C₂₂H₂₆N₂O₄) C, H, N.

(S)-(-)-N-[4-(1-Bromo)butyl]-1-(benzyloxycarbonyl)-1,2,3,4-tetrahydroisoquinoline-2-carboxamide [(S)-33]. To a vigorous stirred solution of **(S)-32** (1.0 g, 2.62 mmol) in dry acetonitrile (50.0 mL), triphenylphosphine (0.86 g, 3.22 mmol) and carbon tetrabromide (1.06 g, 3.22 mmol) were added at room temperature. After 2 h the mixture was quenched with 15% NaOH and the heterogeneous mixture was extracted with ethyl acetate (EtOAc) (3 x 25 mL). The organic layers were dried and evaporated. The residue was chromatographed (20% *n*-hexane in ethyl acetate) to afford 0.58 g (91% yield) of **(S)-33** as yellow oil (33% yield). ¹H NMR (CDCl₃) δ 1.34-1.61 (m, 4H), 2.15-2.26 (m, 2H), 2.57-2.78 (m, 2H), 3.02-3.30 (m, 4H), 5.00 (t, 1H, *J* = 6.70 Hz), 5.14-5.30 (m, 2H), 6.07 (br s, 1H), 6.99-7.21 (m, 3H), 7.33 (m, 5H), 7.61 (d, 1H, *J* = 8.02 Hz); ESI-MS *m/z* 467 [M + Na]⁺. $[\alpha]^{20}_{\text{D}} -50.9^{\circ}$ (*c* = 0.53, CHCl₃). Anal. (C₂₂H₂₅BrN₂O₃) C, H, N.

(S)-(-)-N-[4-[4-(*m*-Tolyl)piperazin-1-yl]butyl]-2-(benzyloxycarbonyl)-1,2,3,4-tetrahydroisoquinoline-2-carboxamide [(S)-34a]. To a stirred solution of **(S)-33** (180.4 mg, 0.40 mmol) in dry acetonitrile (10.0 mL) under argon, 1-(*m*-tolyl)piperazine dihydrochloride (150.9 mg, 0.40 mmol) and triethylamine (62.0 μ L, 0.46 mmol) were added and the solution was refluxed overnight under stirring. The solvent was removed under reduced pressure, water was added and the mixture was extracted with dichlorometane (3 x 30 mL). The organic layers were dried and concentrated and the crude product was chromatographed (6% methanol in chloroform) to give **(S)-34a** as yellow oil (40% yield). ^1H NMR (CDCl_3) δ 1.25-1.37 (m, 4H), 2.15-2.33 (m, 7H), 2.47-2.57 (m, 4H), 2.62-2.79 (m, 2H), 3.12-3.27 (m, 6H), 4.97 (t, 1H, $J = 6.65$ Hz), 5.16-5.31 (m, 2H), 6.12 (br s, 1H), 6.65-6.73 (m, 3H), 7.03-7.24 (m, 3H), 7.34 (m, 5H), 7.64 (d, 1H, $J = 8.10$ Hz). $[\alpha]^{20}_{\text{D}} = -34.3^\circ$ ($c = 1.75$, CHCl_3). Anal. ($\text{C}_{33}\text{H}_{40}\text{N}_4\text{O}_3$) C, H, N.

(S)-(-)-N-[4-[4-(*m*-Tolyl)piperazin-1-yl]butyl]-1,2,3,4-tetrahydroisoquinoline-2-carboxamide (1s). To a solution of **(S)-34a** (50.0 mg, 0.15 mmol) in methanol and EtOAc (1:1) catalytic Pd on carbon 5% was added under argon and the suspension was hydrogenated at 60 psi for 8 h. The mixture was then filtered through Celite® and the filtrate was evaporated. The crude product was chromatographed (10% methanol in chloroform) to afford **1s** as colourless oil (90% yield). ^1H NMR (CDCl_3) δ 1.20-1.58 (m, 4H), 1.86-1.95 (m, 4H), 2.19-1.37 (m, 3H), 2.39-2.46 (m, 2H), 2.57-2.77 (m, 4H), 3.22-3.33 (m, 6H), 3.64-3.84 (m, 1H), 6.63-6.73 (m, 3H), 6.96-7.03 (m, 2H), 7.07-7.18 (m,); ESI-MS m/z 407 $[\text{M}]^+$ (100); MS/MS (407) m/z 300, 276, 258, 248, 231, 189, 177, 161, 132. $[\alpha]^{20}_{\text{D}} = -42.1^\circ$ ($c = 1.26$, MeOH). Anal. ($\text{C}_{25}\text{H}_{34}\text{N}_4\text{O}$) C, H, N.

(R)-(+)-N-[4-[4-(*m*-Tolyl)piperazin-1-yl]butyl]-1,2,3,4-tetrahydroisoquinoline-2-carboxamide (Compound 1-20/1t)



(R)-(+)-1-(Benzyloxycarbonyl)-1,2,3,4-tetrahydroquinoline-2-carboxylic acid [(R)-31]. The title compound was prepared starting from **(R)-29** (1.30 g, 7.34 mmol) and following the procedure described to obtain **(S)-31**. The compound **(R)-29** was obtained as colourless oil (81% yield). ^1H NMR (CDCl_3) δ 1.85-1.99 (m, 1H), 2.35-2.50 (m, 1H), 2.58-2.79 (m, 2H), 4.99 (t, 1H, $J = 7.74$ Hz), 5.19-5.34 (m, 2H), 6.99-7.10

(m, 2H), 7.18-7.25 (m, 1H), 7.32-7.38 (m, 5H), 7.78 (d, 1H, $J = 7.92$ Hz), 9.94 (br s, 1H). $[\alpha]_D^{20} + 44.6^\circ$ ($c = 0.74$, MeOH). Anal. ($C_{18}H_{17}NO_4$) C, H, N

(*R*)-(+)-*N*-[4-(1-Hydroxy)butyl]-1-(benzyloxycarbonyl)-1,2,3,4-

tetrahydroisoquinoline-2-carboxamide [(*R*)-32]. The title compound was prepared

5 starting from (*R*)-31 (418.2 mg, 1.34 mmol) and following the procedure described to obtain (*S*)-32. The compound (*R*)-32 was obtained as colourless oil (72% yield). ^1H NMR ($CDCl_3$) δ 1.21-1.40 (m, 4H), 2.01-2.10 (m, 1H), 2.14-2.28 (m, 1H), 2.56-2.74 (m, 2H), 2.82 (br s, 1H), 3.10-3.13 (m, 2H), 3.40-3.45 (m, 2H), 4.87-4.94 (m, 1H), 5.11-5.26 (m, 2H), 6.51 (br s, 1H), 6.95-7.17 (m, 3H), 7.30 (m, 5H), 7.64 (d, 1H, $J = 8.14$ Hz); ESI-MS m/z 405 $[M + Na]^+$ (100), 267. $[\alpha]_D^{20} + 50^\circ$ ($c = 1.94$, $CHCl_3$). Anal. ($C_{22}H_{26}N_2O_4$) C, H, N.

(*R*)-(+)-*N*-[4-(1-Bromo)butyl]-1-(benzyloxycarbonyl)-1,2,3,4-

tetrahydroisoquinoline-2-carboxamide [(*R*)-33]. The title compound was prepared

15 starting from (*R*)-32 (368.9 mg, 0.97 mmol) and following the procedure described to obtain (*S*)-33. The compound (*R*)-33 was obtained as colourless oil (33% yield). ^1H NMR ($CDCl_3$) δ 1.40-1.64 (m, 4H), 2.20-2.31 (m, 2H), 2.62-2.80 (m, 2H), 3.07-3.28 (m, 4H), 4.99 (t, 1H, $J = 6.67$ Hz), 5.16-5.31 (m, 2H), 6.07 (br s, 1H), 7.04-7.21 (m, 3H), 7.34 (m, 5H), 7.62 (d, 1H, $J = 8.06$ Hz); $[\alpha]_D^{20} + 50.9^\circ$ ($c = 0.15$, $CHCl_3$). Anal. ($C_{22}H_{25}BrN_2O_3$) C, H, N.

(*R*)-(+)-*N*-[4-[4-(*m*-Tolyl)piperazin-1-yl]butyl]-2-(benzyloxycarbonyl)-

1,2,3,4-tetrahydroisoquinoline-2-carboxamide [(*R*)-34a]. The title compound was

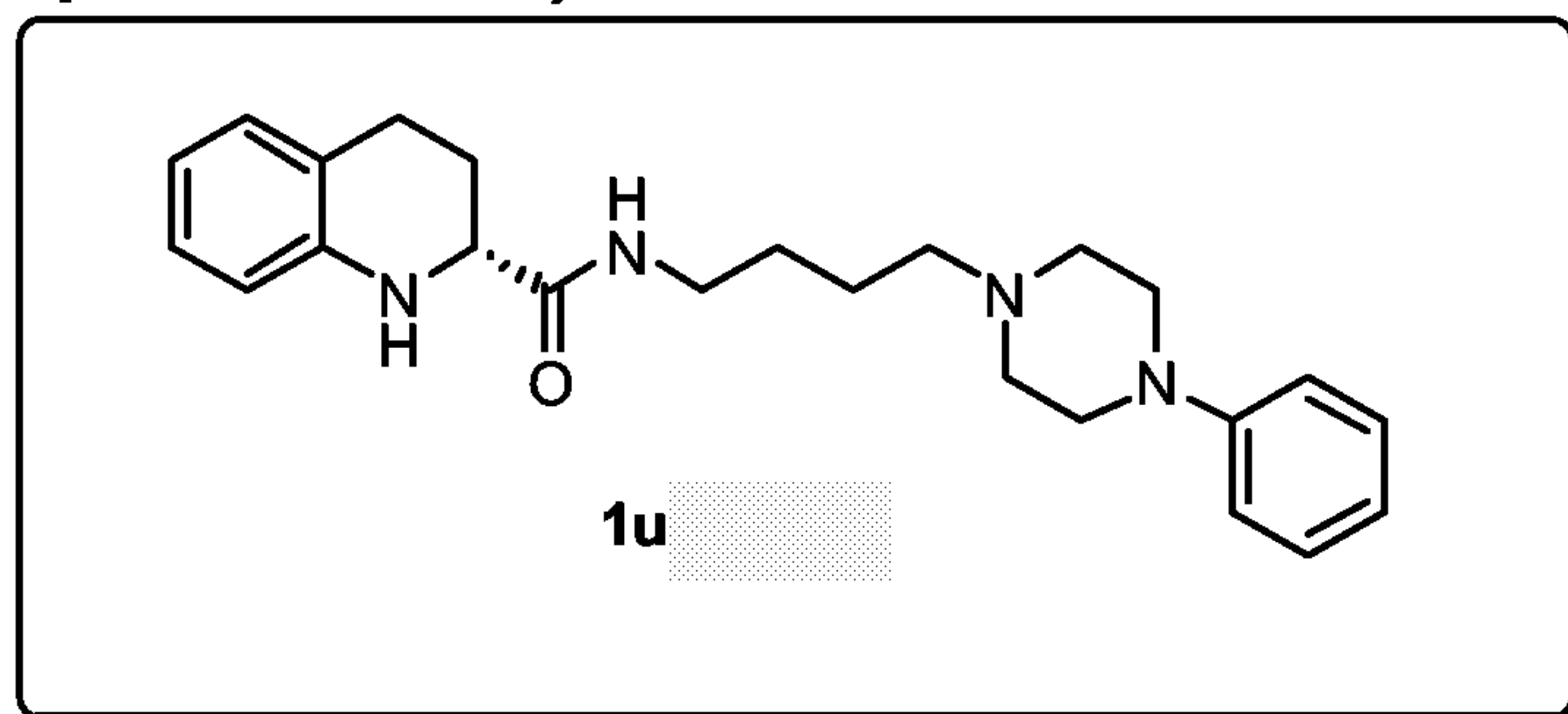
20 prepared starting from (*R*)-33 (70.0 mg, 0.16 mmol) and (*m*-tolyl)piperazine dihydrochloride (39 mg, 0.16 mmol) following the procedure described to obtain (*S*)-34a. The compound (*R*)-34a was obtained as colourless oil (40% yield). ^1H NMR ($CDCl_3$) δ 1.25-1.46 (m, 4H), 2.16-2.28 (m, 4H), 2.31 (s, 3H), 2.48-2.58 (m, 4H), 2.64-2.80 (m, 2H), 3.12-3.25 (m, 6H), 4.95-5.01 (m, 1H), 5.16-5.32 (m, 2H), 6.05 (br s, 1H), 6.66-6.73 (m, 3H), 7.04-7.21 (m, 3H), 7.25 (s, 1H), 7.35 (m, 5H), 7.63 (d, 1H, $J = 8.11$ Hz). $[\alpha]_D^{20} = +34.3^\circ$ ($c = 0.19$, $CHCl_3$). Anal. ($C_{33}H_{40}N_4O_3$) C, H, N.

(*R*)-(+)-*N*-[4-[4-(*m*-Tolyl)piperazin-1-yl]butyl]-1,2,3,4-

30 **tetrahydroisoquinoline-2-carboxamide (1t).** The title compound was prepared

starting from (*R*)-34a (50.0 mg, 0.15 mmol) following the procedure described to obtain 1s. Compound 1t was obtained as colourless oil (85% yield). ^1H NMR ($CDCl_3$) δ 1.20-1.58 (m, 4H), 1.86-1.95 (m, 4H), 2.19-1.37 (m, 3H), 2.39-2.46 (m, 2H), 2.57-2.77 (m, 4H), 3.22-3.33 (m, 6H), 3.64-3.84 (m, 1H), 6.63-6.73 (m, 3H), 6.96-7.03 (m, 2H), 7.07-7.18 (m,); ESI-MS m/z 407 $[M]^+$ (100); MS/MS (407) m/z 300, 276, 258, 248, 231, 189, 177, 161, 132. $[\alpha]_D^{20} = +42.1^\circ$ ($c = 1.26$, MeOH). Anal. ($C_{25}H_{34}N_4O$) C, H, N.

(R)-(+)-N-[4-(4-Phenylpiperazin-1-yl)butyl]-1,2,3,4-tetrahydroisoquinoline-2-carboxamide (Compound 1-21/1u)



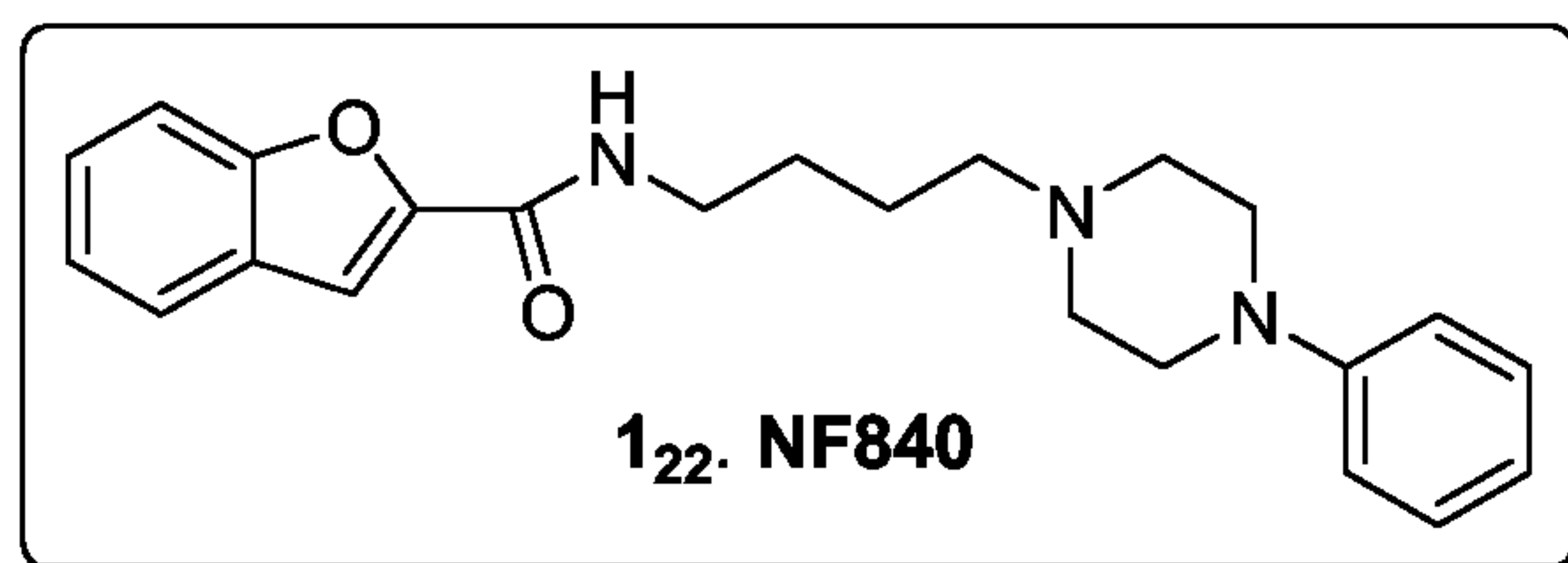
(R)-(+)-N-[4-[4-(3-Chloro)phenylpiperazin-1-yl]butyl]-2-

(benzyloxycarbonyl)-1,2,3,4-tetrahydroisoquinoline-2-carboxamide [(R)-34b]. The title compound was prepared starting from **(R)-33** (140.0 mg, 0.31 mmol) and (3-chloro)phenylpiperazine hydrochloride (73.4 mg, 0.31 mmol) following the procedure described to obtain **(S)-34a**. The compound **(R)-34b** was obtained as colourless oil (40% yield). ¹H NMR (CDCl₃) δ 1.25-1.36 (m, 4H), 2.20-2.45 (m, 4H), 2.48-2.59 (m, 4H), 2.64-2.80 (m, 2H), 3.12-3.21 (m, 6H), 4.98 (t, 1H, *J* = 6.65 Hz), 5.16-5.31 (m, 2H), 6.02 (br s, 1H), 6.74-6.85 (m, 3H), 7.04-7.21 (m, 3H), 7.25 (s, 1H), 7.34 (m, 5H), 7.63 (d, 1H, *J* = 7.97 Hz); ESI-MS *m/z* 584 [M+Na⁺], 561 [M+H⁺] (100), 508. Anal (C₃₂H₃₇N₄O₃) C, H, N. [α]_D²⁰ + 31° (c = 0.19, CHCl₃). Anal. (C₃₂H₃₇ClN₄O₃) C, H, N.

(R)-(+)-N-[4-(4-Phenylpiperazin-1-yl)butyl]-1,2,3,4-

tetrahydroisoquinoline-2-carboxamide (1u). The title compound was prepared starting from **(R)-34b** (50.0 mg, 0.15 mmol) following the procedure described to obtain **1s**. The compound **1u** was obtained as colourless oil (92% yield). ¹H NMR (CDCl₃) δ 1.49-1.53 (m, 4H), 1.79-1.95 (m, 2H), 2.24-2.46 (m, 2H), 2.48-2.61 (m, 5H), 2.65-2.78 (m, 1H), 3.13-3.18 (m, 4H), 3.24-3.33 (m, 2H), 3.93-4.00 (m, 1H), 6.59-6.74 (m, 2H), 6.80-7.06 (m, 5H), 7.20-7.28 (m, 2H). ESI-MS *m/z* 393 [M⁺] (100), 132. Anal (C₂₄H₃₂N₄O) C, H, N. [α]_D²⁰ = +41.66° (c = 0.24, CHCl₃). Anal. (C₂₃H₃₀N₄O) C, H, N.

N-(4-(4-(Phenylpiperazin-1-yl)butyl)benzo[*b*]furan-2-carboxamide (Compound 1-22)



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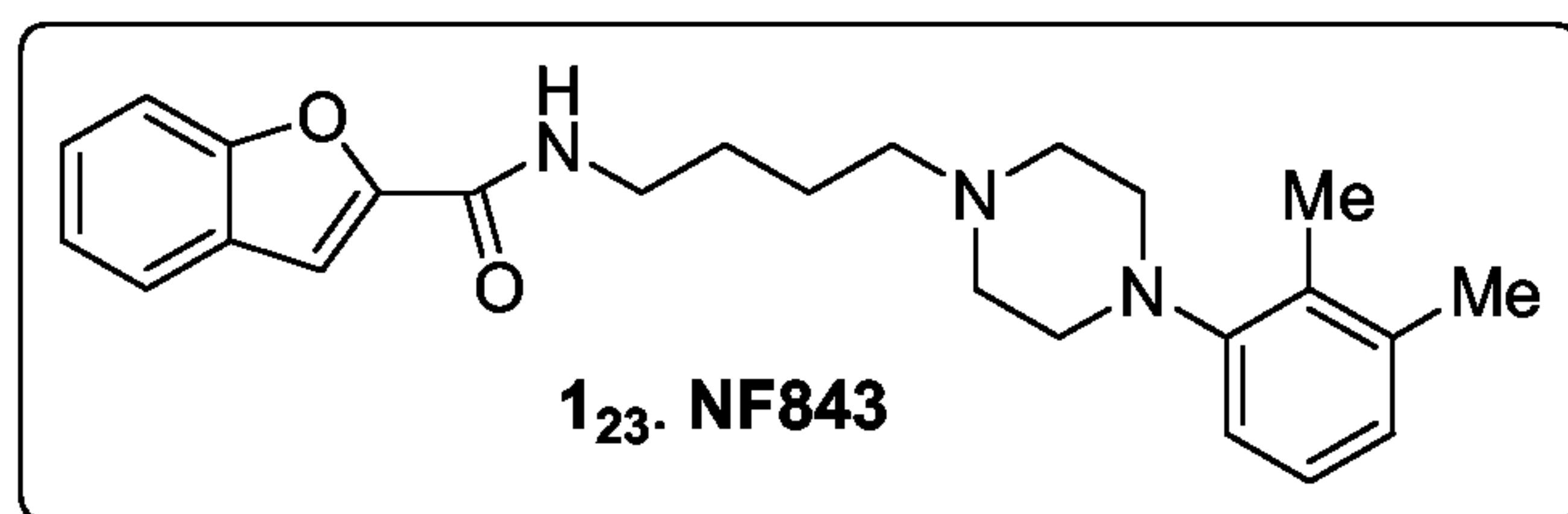
Starting from **7₁** and 1-phenylpiperazine, the title compound was prepared following the procedure described to obtain **1₇**. Compound **1₂₂** was obtained as white solid (70% yield): mp (methanol) 149-150°C; ¹H NMR, 300MHz, (CDCl₃) δ 1.71 (m, 4H), 2.47 (m, 2H), 2.64 (m, 4H), 3.24 (m, 4H), 3.53 (m, 2H), 6.89 (m, 3H), 7.02 (br s,

60

1H), 7.28 (m, 3H), 7.39 (m, 1H), 7.46 (m, 2H), 7.66 (m, 1H). ESI-MS m/z 400 $[M+Na^+]$, 377 $[M+H^+]$ (100). Anal ($C_{23}H_{27}N_3O_2$) C, H, N

***N*-(4-(4-(2,3-Dimethylphenyl)piperazin-1-yl)butyl)benzo[*b*]furan-2-carboxamide**

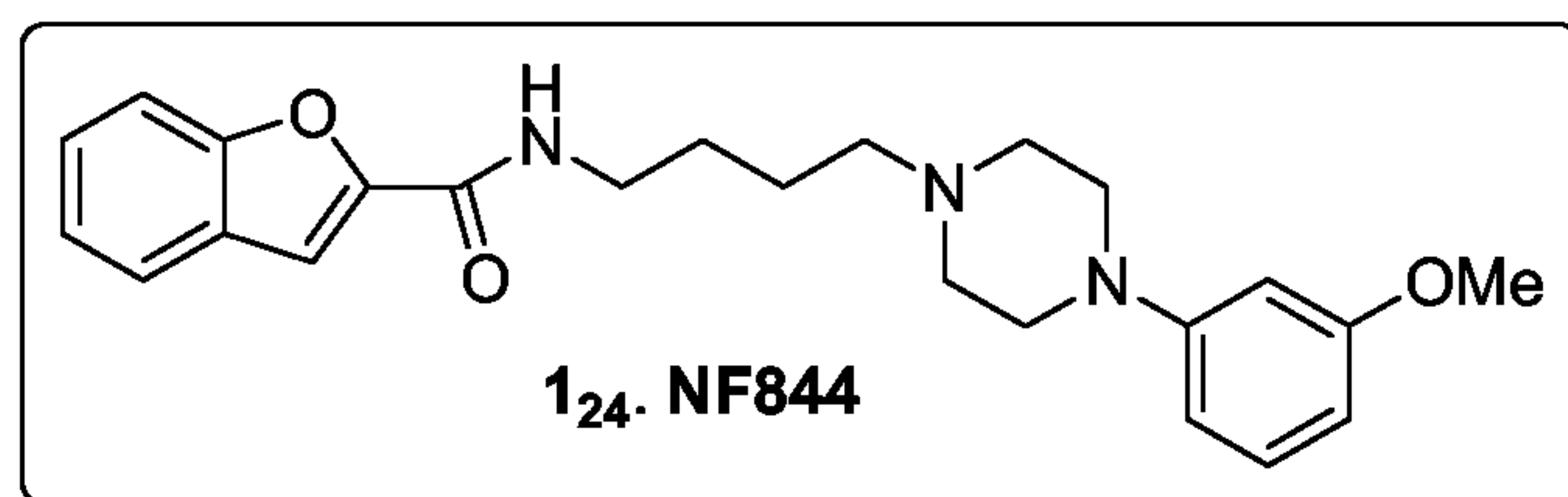
5 (Compound 1-23)



Starting from **7₁** and 4-(2,3-dimethylphenyl)piperazine, the title compound was prepared following the procedure described to obtain **1₇**. Compound **1₂₃** was obtained as white solid (73% yield): mp (methanol) 151-152°C. ¹H NMR, 200MHz, (CDCl₃) δ 1.73 (m, 4H), 2.21 (s, 3H), 2.25 (s, 3H), 2.47 (m, 2H), 2.62 (m, 4H), 2.93 (m, 4H), 3.52 (m, 2H), 6.87 (m, 2H), 7.05 (m, 2H), 7.35 (m, 3H), 7.64 (m, 1H). ESI-MS m/z 428 $[M+Na^+]$, 406 $[M+H^+]$ (100). Anal ($C_{25}H_{31}N_3O_2$) C, H, N.

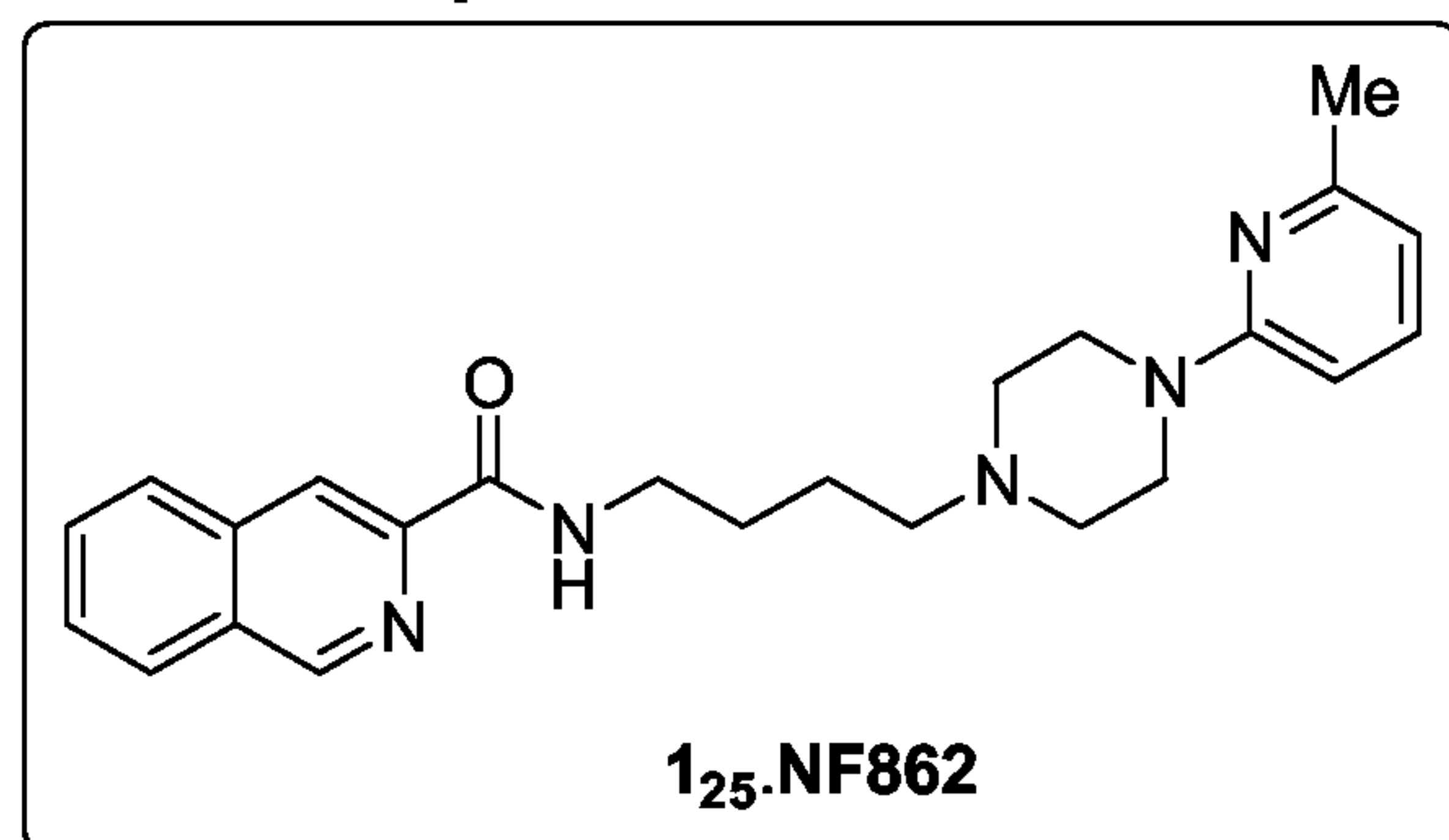
***N*-(4-(4-(3-Methoxyphenyl)piperazin-1-yl)butyl)benzo[*b*]furan-2-carboxamide**

15 (Compound 1-24)



Starting from **7₁** and 4-(3-methoxyphenyl)piperazine, the title compound was prepared following the procedure described to obtain **1₇**. Compound **1₂₄** was obtained as white solid (70% yield): mp (methanol) 104-105°C. ¹H NMR, 200MHz, (CDCl₃) δ 1.62 (m, 4H), 2.40 (m, 2H), 2.56 (m, 4H), 3.19 (m, 4H), 3.49 (m, 2H), 3.74 (s, 3H), 6.44 (m, 3H), 7.25 (m, 5H), 7.61 (m, 1H). ESI-MS m/z 430 $[M+Na^+]$, 408 $[M+H^+]$ (100). Anal ($C_{24}H_{29}N_3O_3$) C, H, N.

Experimental Procedure for Compound 1-25

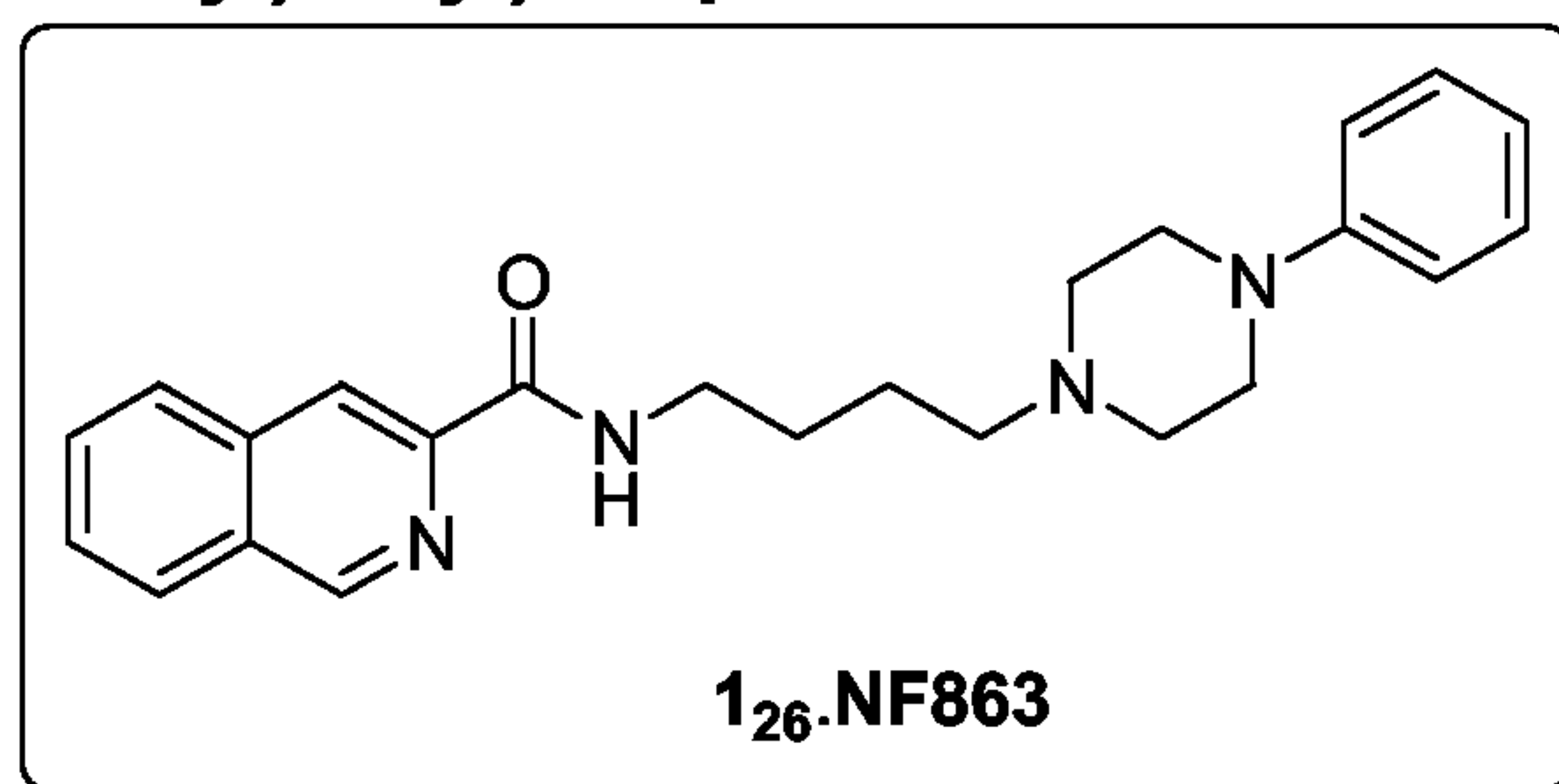


***tert*-Butyl-4-(6-methylpyridin-2-yl)piperazine-1-carboxylate (3₂).** In a sealed tube, 2-bromo-6-methylpyridine (461 mg, 2.68 mmol) Pd₂(dba)₂ (2%), BINAP (4%), and sodium *t*-butoxide (386.4 mg, 4.02 mmol) were added to *N*-Boc-piperazine (500 mg, 2.68 mmol) and the solids were dissolved in dry toluene (5 mL). The mixture
 5 was stirred at 70°C for 90 min., filtered over Celite®, washing with ethylacetate and the organic layer was evaporated under reduced pressure. The crude was purified by flash chromatography (40% ethylacetate in hexane) to give 3₂ as pail yellow solid (95% yield): mp (methanol) 84-85 °C; ¹H NMR, 200MHz, (CDCl₃) δ 1.41 (s, 9H), 2.31 (s, 3H), 3.42 (m, 8H), 6.37 (m, 2H), 7.28 (m, 1H). ESI-MS *m/z* 300 [M+Na⁺], 278 [M+H⁺] (100). Anal
 10 (C₁₅H₂₃N₃O₂) C, H, N.

1-(6-Methylpyridin-2-yl)piperazine trifluoroacetate (4₁). Trifluoroacetic acid (4 mL) was added to 3₂, cooling in ice bath, and the mixture was stirred for 60 min. at room temperature. The crude was concentrated and washed with diethylether till the solid became colorless.

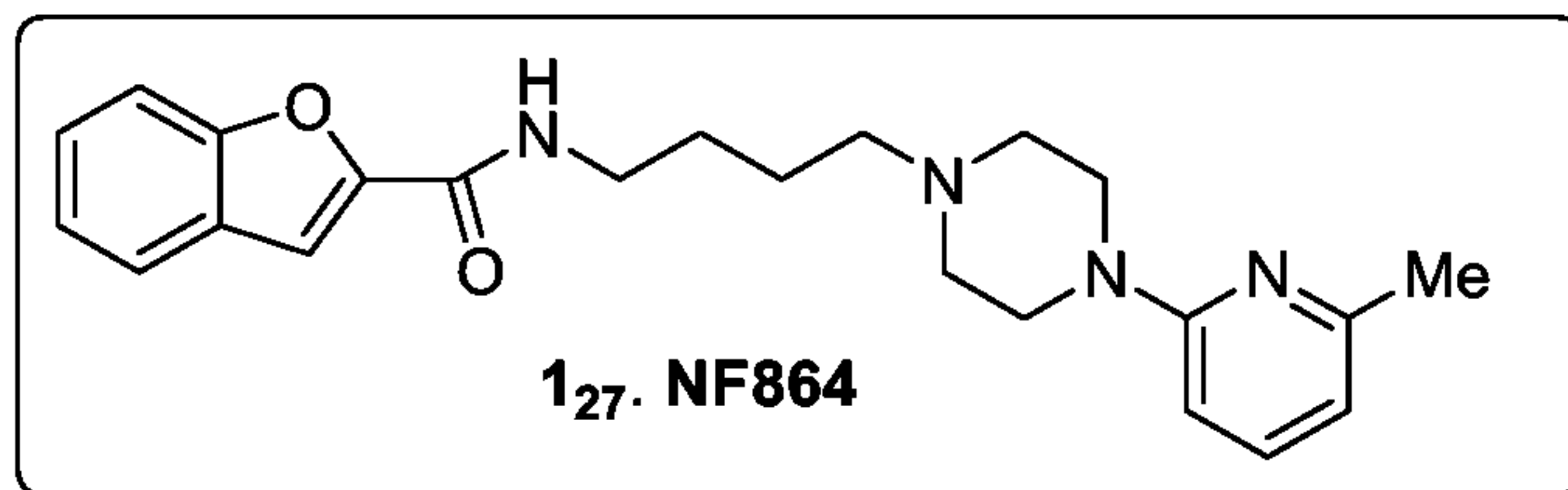
15 ***N*-(4-(4-(6-Methylpyridin-2-yl)piperazin-1-yl)butyl)isoquinoline-3-carboxamide (Compound 1-25).** Starting from 7₂ and 4₁, the title compound was prepared following the procedure described to obtain 1₃. Compound 1₂₅ was obtained as white solid (70% yield): mp (methanol) 124-125°C. ¹H NMR, 200MHz, (CDCl₃) δ 1.71 (m, 4H), 2.38 (s, 3H), 2.47 (m, 2H), 2.56 (m, 4H), 3.55 (m, 6H), 6.44 (m, 2H), 7.30
 20 (m, 1H), 7.72 (m, 2H), 8.00 (m, 2H), 8.33 (br s, 1H), 8.60 (m, 1H), 9.14 (m, 1H). ESI-MS *m/z* 426 [M+Na⁺], 404 [M+H⁺] (100). Anal (C₂₄H₂₉N₅O) C, H, N.

***N*-(4-(4-Phenylpiperazin-1-yl)butyl)isoquinoline-3-carboxamide (Compound 1-26)**



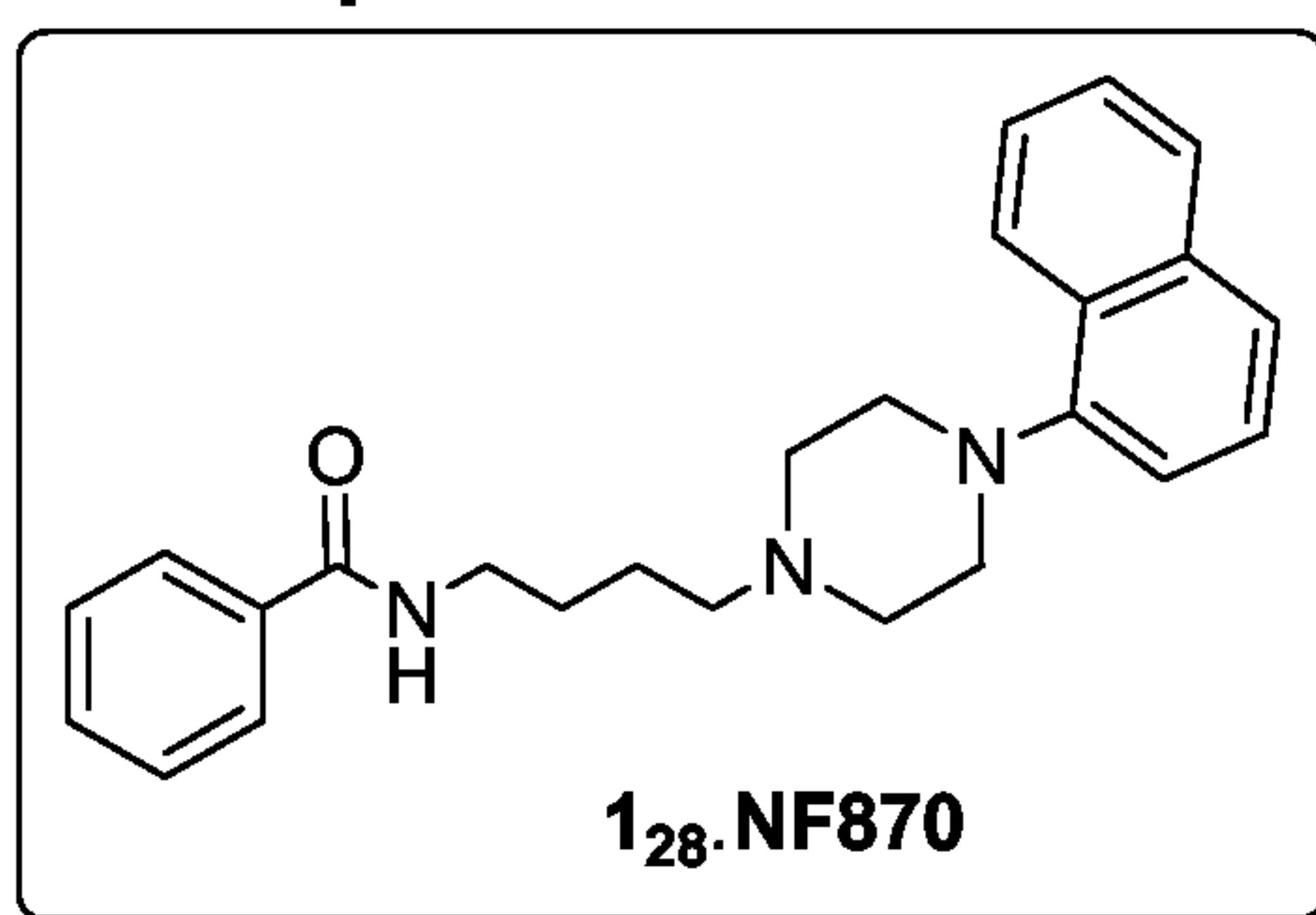
25 Starting from 7₂ and 1-phenylpiperazine, the title compound was prepared following the procedure described to obtain 1₃. Compound 1₂₆ was obtained as white solid (76% yield): mp (methanol) 153-154°C. ¹H NMR, 300MHz, (CDCl₃) δ 1.71 (m, 4H), 2.46 (m, 2H), 2.62 (m, 4H), 3.21 (m, 4H), 3.57 (m, 2H), 6.88 (m, 3H), 7.26 (m, 2H), 7.72 (m, 2H), 8.00 (m, 2H), 8.36 (br s, 1H), 8.61 (m, 1H), 9.14 (m, 1H). ESI-MS
 30 *m/z* 411 [M+Na⁺], 389 [M+H⁺] (100). Anal (C₂₄H₂₈N₄O) C, H, N.

***N*-(4-(4-(6-Methylpyridin-2-yl)piperazin-1-yl)butyl)benzofuran-2-carboxamide
(Compound 1-27)**



Starting from **7₁** and **4₁**, the title compound was prepared following the procedure described to obtain **1₇**. Compound **1₂₇** was obtained as white solid (75% yield): mp (methanol) 107-109°C. ¹H NMR, 200MHz, (CDCl₃) δ 1.70 (m, 4H), 2.39 (s, 3H), 2.45 (m, 2H), 2.58 (m, 4H), 3.54 (m, 6H), 6.45 (m, 2H), 7.02 (br s, 1H), 7.35 (m, 5H), 7.65 (m, 1H). ESI-MS *m/z* 415 [M+Na⁺], 393 [M+H⁺] (100). Anal (C₂₃H₂₈N₄O₂) C, H, N.

Experimental Procedure for Compound 1-28

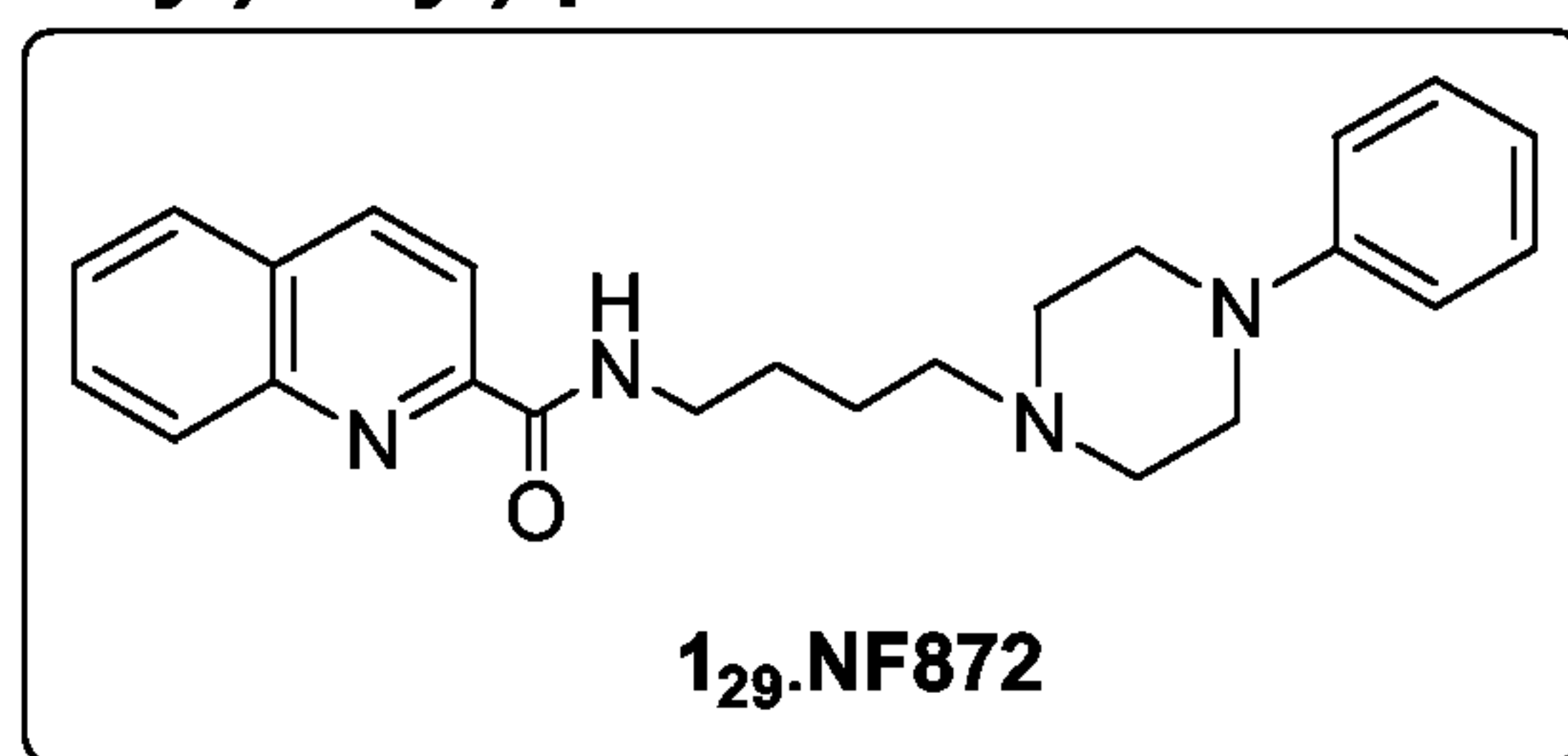


***tert*-Butyl-4-(naphthalen-1-yl)piperazine-1-carboxylate (**3₃**)**. Starting from 1-bromonaphthalene (200 mg, 0.97 mmol) the title compound was prepared following the procedure described to obtain **3₂**: ¹H NMR, 200MHz, (CDCl₃) δ 1.55 (s, 9H), 3.05 (m, 4H), 3.72 (m, 4H), 7.05 (m, 1H), 7.49 (m, 4H), 7.82 (m, 1H), 8.22 (m, 1H). ESI-MS *m/z* 335 [M+Na⁺], 313 [M+H⁺] (100). Anal (C₁₉H₂₄N₂O₂) C, H, N.

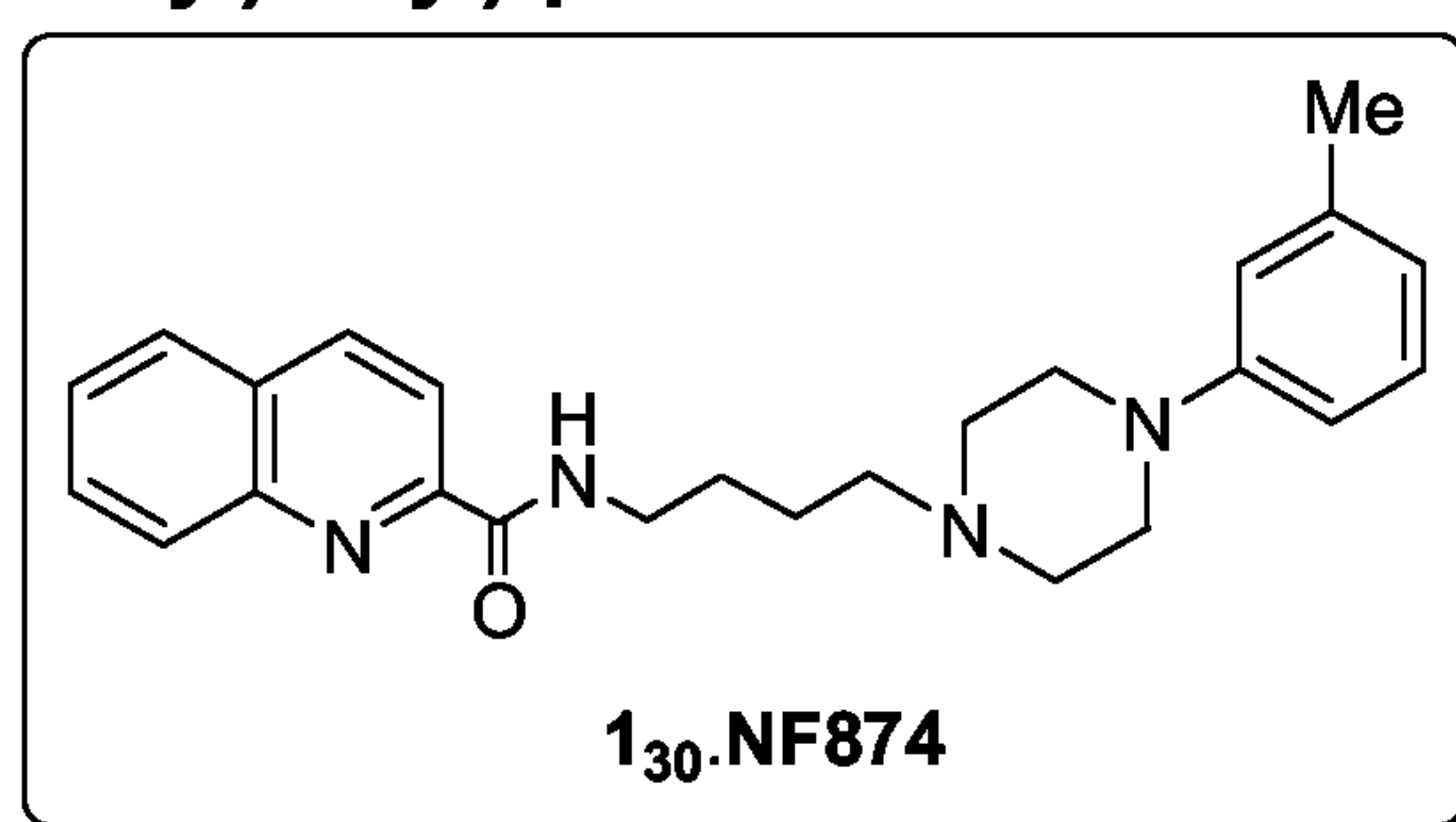
1-(Naphthalen-1-yl)piperazine trifluoroacetate (4₂**)**. Starting from **3₃** the title compound was prepared following the procedure described to obtain **4₁**.

***N*-(4-(4-(Naphthalen-1-yl)piperazin-1-yl)butyl)benzamide (Compound 1-28)**. Starting from **7₅** and **4₂**, the title compound was prepared following the procedure described to obtain **1₃**. Compound **1₂₈** was obtained as yellow oil (70% yield): ¹H NMR, 200MHz, (CDCl₃) δ 1.68 (m, 4H), 2.49 (m, 4H), 2.70 (m, 4H), 3.34 (m, 2H), 7.01 (m, 2H), 7.43 (m, 6H), 7.78 (m, 3H), 8.18 (m, 1H). ESI-MS *m/z* 410 [M+Na⁺], 388 [M+H⁺] (100). Anal (C₂₅H₂₉N₃O) C, H, N.

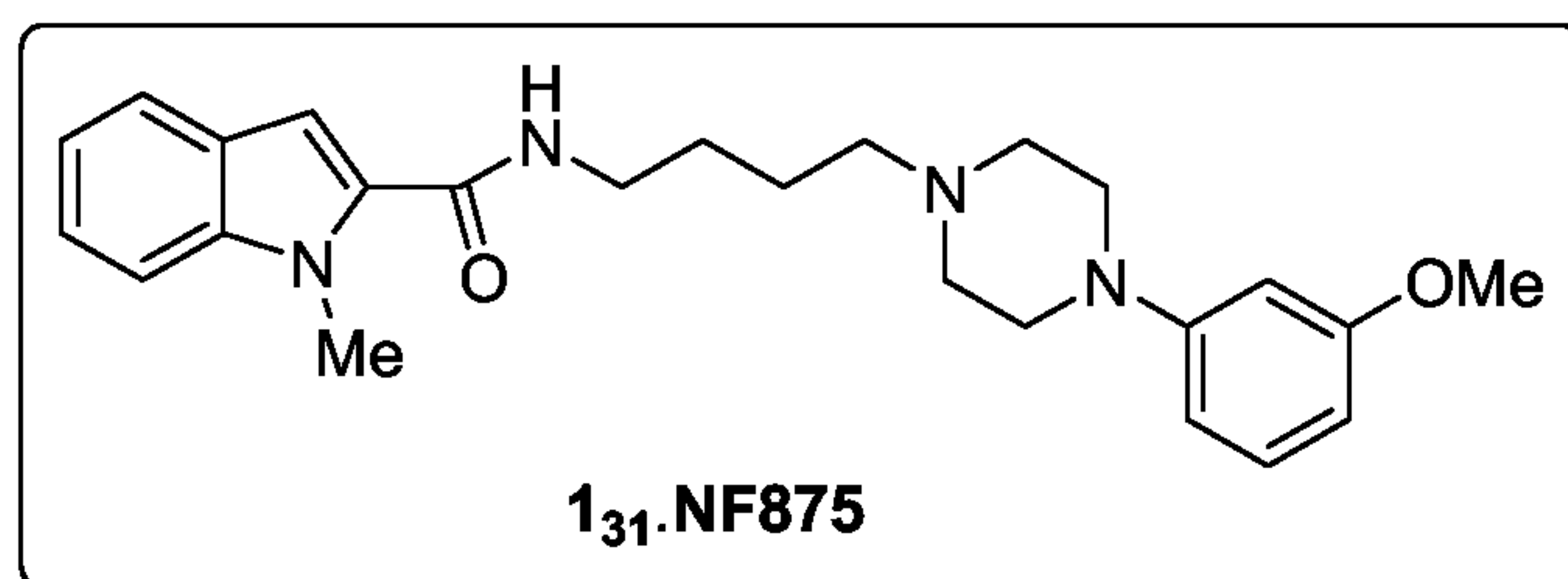
63

***N*-(4-(4-Phenylpiperazin-1-yl)butyl)quinoline-2-carboxamide (Compound 1-29)**

Starting from **7₂** and 1-phenylpiperazine, the title compound was prepared following the procedure described to obtain **1₃**. Compound **1₂₉** was obtained as white solid (70% yield): mp (methanol) 120-121°C. ¹H NMR, 200MHz, (CDCl₃) δ 1.69 (m, 4H), 2.46 (m, 2H), 2.61 (m, 4H), 3.20 (m, 4H), 3.56 (m, 2H), 6.86 (m, 3H), 7.24 (m, 2H), 7.59 (m, 1H), 7.75 (m, 1H), 7.85 (m, 1H), 8.09 (m, 1H), 8.29 (m, 2H). ESI-MS *m/z* 411 [M+Na⁺], 389 [M+H⁺] (100). Anal (C₂₄H₂₈N₄O) C, H, N.

***N*-(4-(4-*m*-Tolylpiperazin-1-yl)butyl)quinoline-2-carboxamide (Compound 1-30)**

Starting from **7₂** and 4-(3-methylphenyl)piperazine, the title compound was prepared following the procedure described to obtain **1₃**. Compound **1₃₀** was obtained as yellow oil: ¹H NMR, 200MHz, (CDCl₃) δ 1.72 (m, 4H), 2.30 (s, 3H), 2.47 (m, 2H), 2.61 (m, 4H), 3.19 (m, 4H), 3.47 (m, 2H), 6.69 (m, 4H), 7.11 (m, 1H), 7.59 (m, 1H), 7.75 (m, 1H), 7.85 (m, 1H), 8.09 (m, 1H), 8.33 (m, 2H). ESI-MS *m/z* 403 [M+H⁺] (100). Anal (C₂₅H₃₀N₄O) C, H, N.

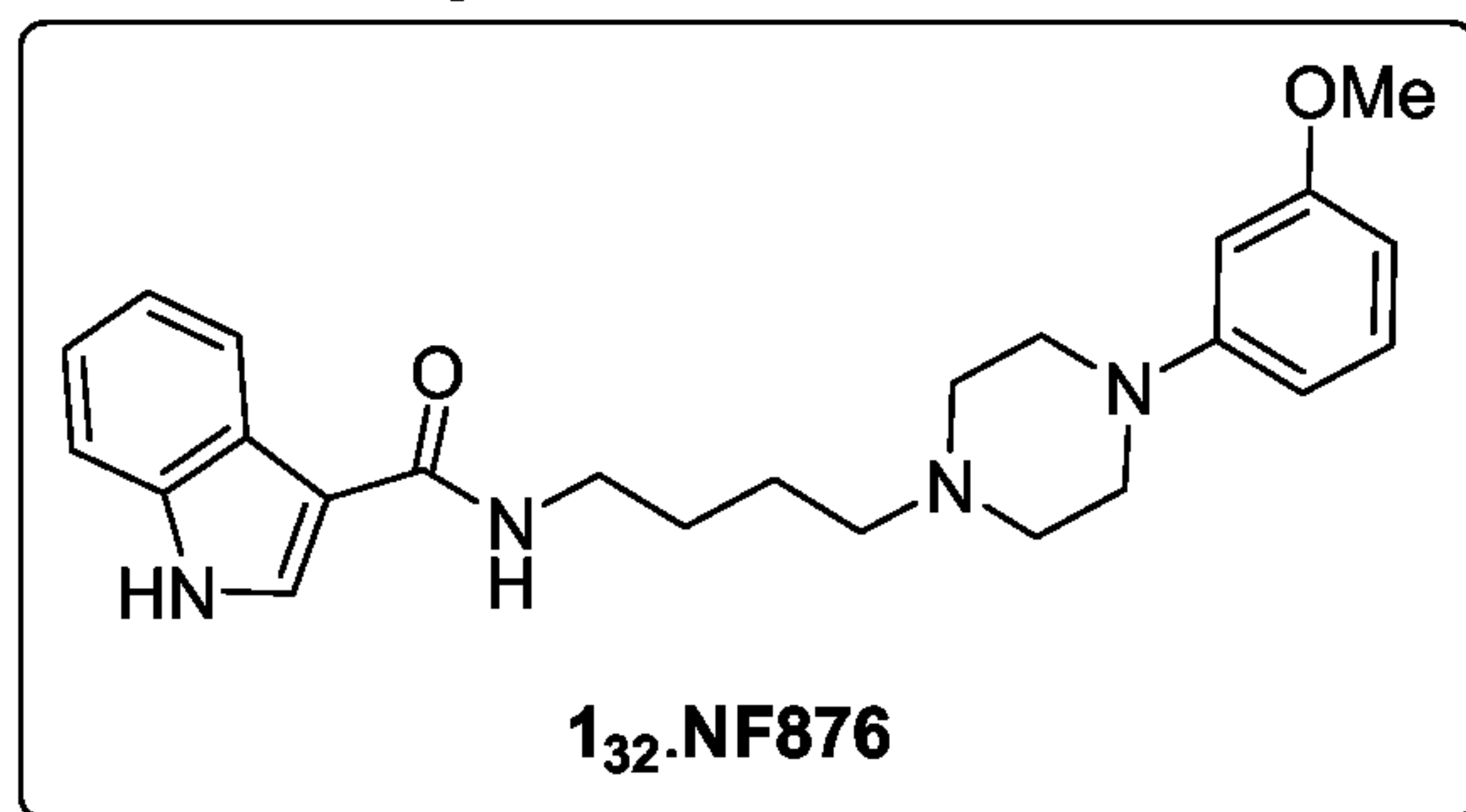
***N*-(4-(4-(3-Methoxyphenyl)piperazin-1-yl)butyl)-1-methyl-1*H*-indole-2-carboxamide (Compound 1-31)**

Starting from **7₇** and 4-(3-methoxyphenyl)piperazine, the title compound was prepared following the procedure described to obtain **1₃**. Compound **1₃₁** was

obtained as white solid (60% yield): mp (methanol) 141-142°C. ¹H NMR, 200MHz, (CDCl₃) δ 1.69 (m, 4H), 2.48 (m, 2H), 2.65 (m, 4H), 3.08 (m, 4H), 3.47 (m, 2H), 3.84 (s, 3H), 4.03 (s, 3H), 6.90 (m, 5H), 7.16(m, 1H), 7.32 (m, 2H), 7.60 (m, 1H). ESI-MS *m/z* 421 [M+H⁺] (100). Anal (C₂₅H₃₂N₄O₂) C, H, N.

5

Experimental Procedure for Compound 1-32



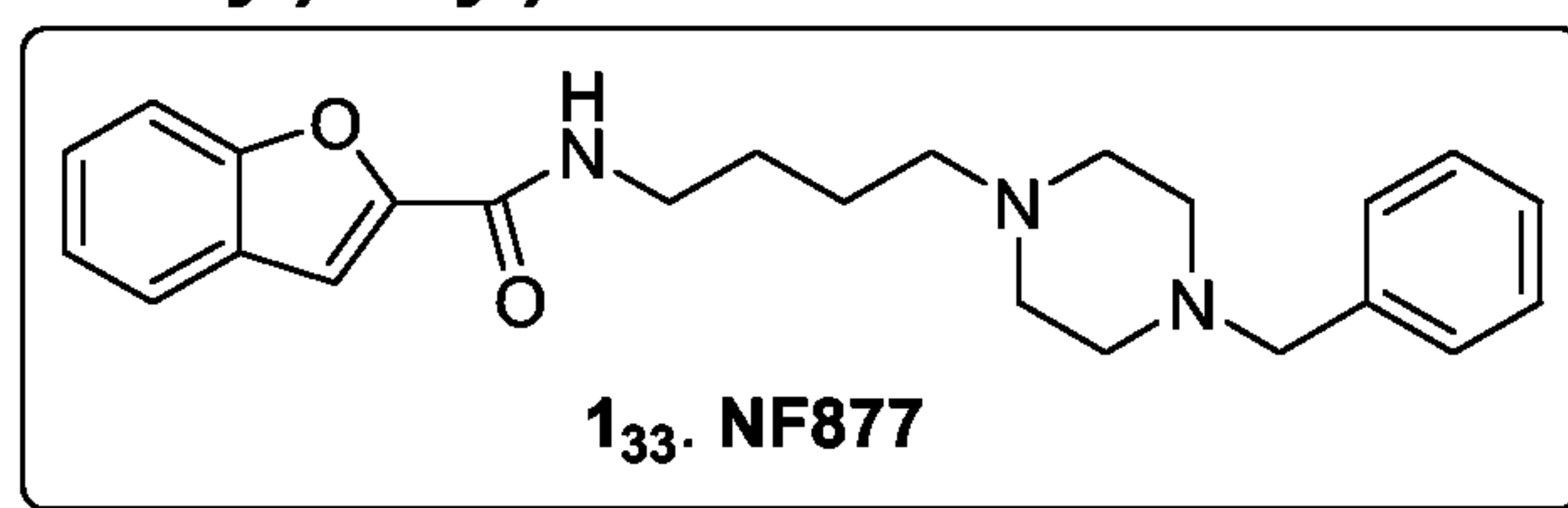
4-(4-(3-Methoxyphenyl)piperazin-1-yl)butanenitrile. (37). To a stirred solution of 1-(3-methoxyphenyl)piperazine (**36**) (100.0 mg, 0.52 mmol) in acetonitrile (10.0 mL), 4-bromobutanenitrile (84.7 mg, 0.57 mmol) and potassium carbonate (107.6 mg, 0.78 mmol) were added at room temperature. The mixture was heated to reflux over night then filtrated and evaporated. The crude product was purified by means of flash chromatography (10% methanol in chloroform) to give 98.0 mg (73% yield) of **37** as a yellow oil: ¹H NMR, 200MHz, (CDCl₃) δ 1.83 (m, 2H), 2.49 (m, 8H), 3.17 (m, 4H), 3.77 (s, 3H), 6.48 (m, 3H), 7.16 (m, 1H). ESI-MS *m/z* 282 [M+H⁺] 260 [M+H⁺] (100). Anal (C₁₅H₂₁N₃O) C, H, N.

4-(4-(3-Methoxyphenyl)piperazin-1-yl)butan-1-amine. (38). To a stirred solution of **37** (300.0 mg, 1.16 mmol) in dry methanol (15.0 mL), at 0°C, nickel(II) chloride hexahydrate (28.0 mg, 0.12 mmol) and sodium borohydride (307.2 mg, 8.12 mmol) were added. The mixture was stirred at room temperature for 90 min, then filtered over Celite[®], washing with methanol, and the filtrate was evaporated under reduced pressure. The residue was extracted with EtOAc (3 x 30 mL), the organic layers were dried and concentrated and the crude product was chromatographed (15% *n*-hexane in EtOAc) to give **38** (60% yield): ¹H NMR, 200MHz, (CDCl₃) δ 1.54 (m, 4H), 2.40 (m, 4H), 2.58 (m, 4H), 3.19 (m, 4H), 3.76 (s, 3H), 6.46 (m, 3H), 7.16 (m, 1H). ESI-MS *m/z* 286 [M+H⁺] 264 [M+H⁺] (100). Anal (C₁₅H₂₅N₃O) C, H, N.

1*H*-Indole-3-carbonylchloride (40). To a solution of 1*H*-indole-3-carboxylic acid (**39**) (100.0 mg, 0.6 mmol) in benzene dry (2.0 mL), thionylchloride (130.0 μL, 1.80 mmol) was added and the mixture was heated to reflux for 120 min. The crude was washed with benzene (2 x 10 mL) and evaporated to give **40** in quantitative yield. ¹H NMR, 200MHz, (CDCl₃) δ 10.85 (br s, 1H), 8.20 (m, 1H), 7.48 (m, 1H), 7.30 (m, 1H), 7.19 (m, 1H), 7.03 (m, 1H). Anal (C₉H₆ClNO) C, H, N.

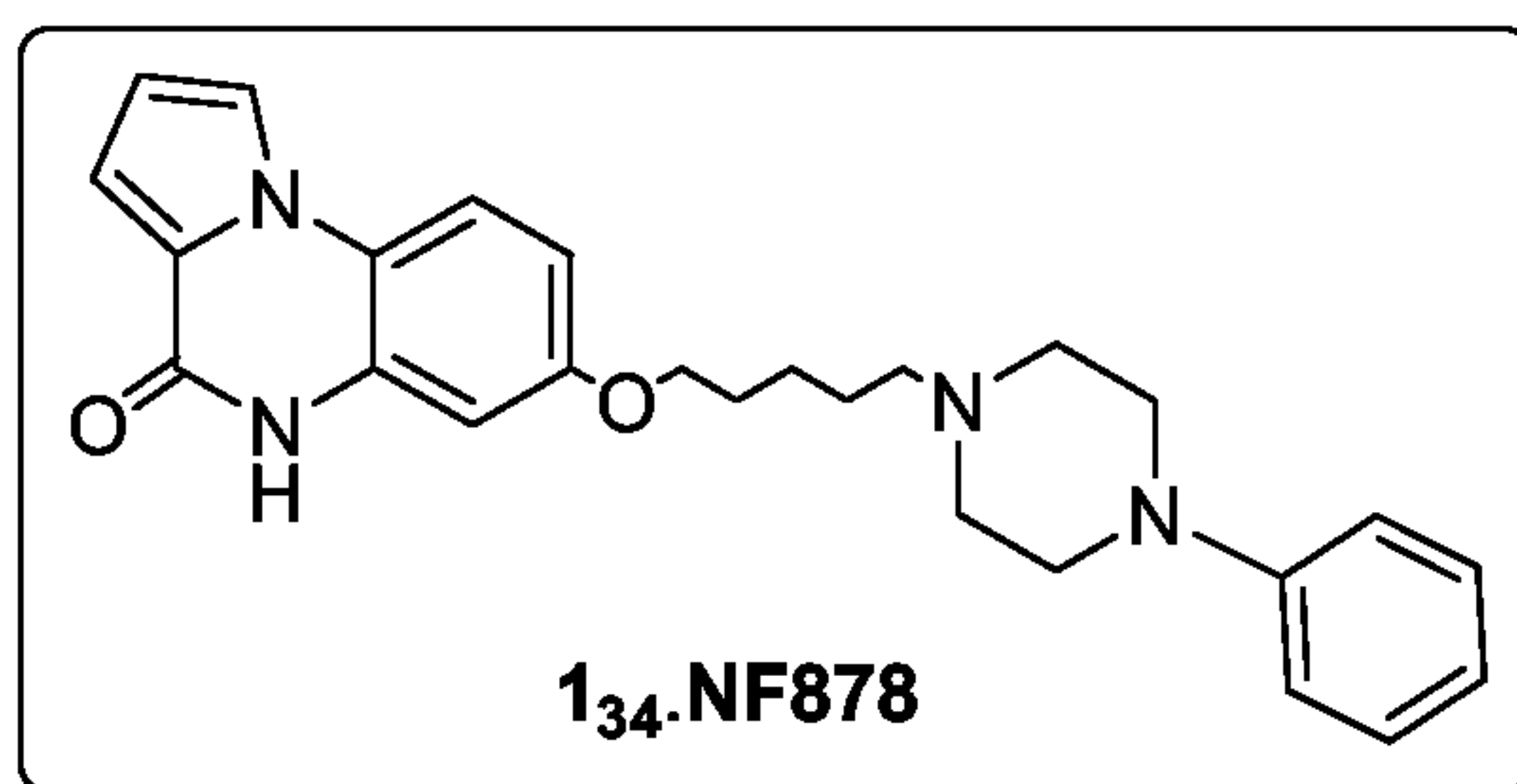
***N*-(4-(4-(3-Methoxyphenyl)piperazin-1-yl)butyl)-1*H*-indole-3-carboxamide (Compound 1-32).** To a stirred solution of **40** (100.0 mg, 0.6 mmol) and **37** (158.0 mg, 0.6 mmol) in dry dichloromethane (15.0 mL), pyridine (145 μ L, 1.8 mmol) was added. The mixture was stirred at room temperature overnight. Sodium bicarbonate saturated solution was added and the mixture, extracted with EtOAc (3 x 15 mL), was dried and evaporated. The crude product was purified by means of flash chromatography (10% methanol in chloroform) to give **1₃₂** (50% yield) as a white solid: mp (methanol) 154-155°C. ¹H NMR, 200MHz, (CDCl₃) δ 1.65 (m, 4H), 2.41 (m, 2H), 2.56(m, 4H), 3.13 (m, 4H), 3.50 (m, 2H), 3.77 (s, 3H), 6.45 (m, 2H), 7.19 (m, 3H), 7.38 (m, 1H), 7.66 (m, 1H), 7.95 (m, 1H), 9.79 (br s, 1H). ESI-MS *m/z* 429 [M+Na⁺], 407 [M+H⁺] (100). Anal (C₂₄H₃₀N₄O₂) C, H, N.

***N*-(4-(4-Benzylpiperazin-1-yl)butyl)benzofuran-2-carboxamide (Compound 1-33)**



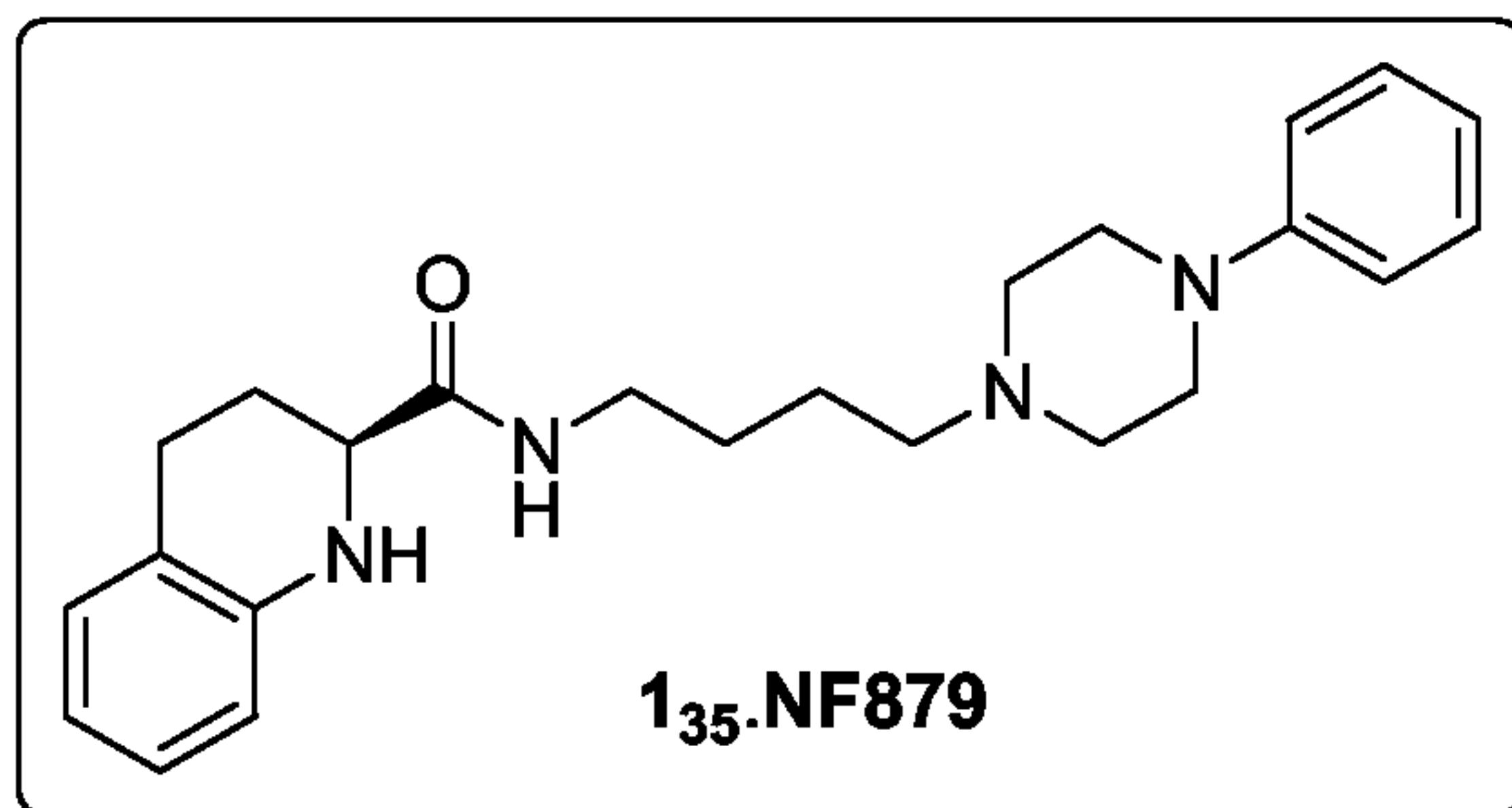
Starting from **7₁** and 1-benzylpiperazine, the title compound was prepared following the procedure described to obtain **1₇**. Compound **1₃₃** was obtained as yellow oil (70% yield): ¹H NMR, 200MHz, (CDCl₃) δ 1.64 (m, 4H), 2.39 (m, 2H), 2.50 (m, 8H), 3.49 (m, 4H), 7.04 (br s, 1H), 7.36 (m, 10H), 7.65 (m, 1H). ESI-MS *m/z* 414 [M+Na⁺], 392 [M+H⁺] (100). Anal (C₂₄H₂₉N₃O₂) C, H, N.

7-(5-(4-Phenylpiperazin-1-yl)pentyloxy)pyrrolo[1,2-*a*]quinoxalin-4(5*H*)-one (Compound 1-34)



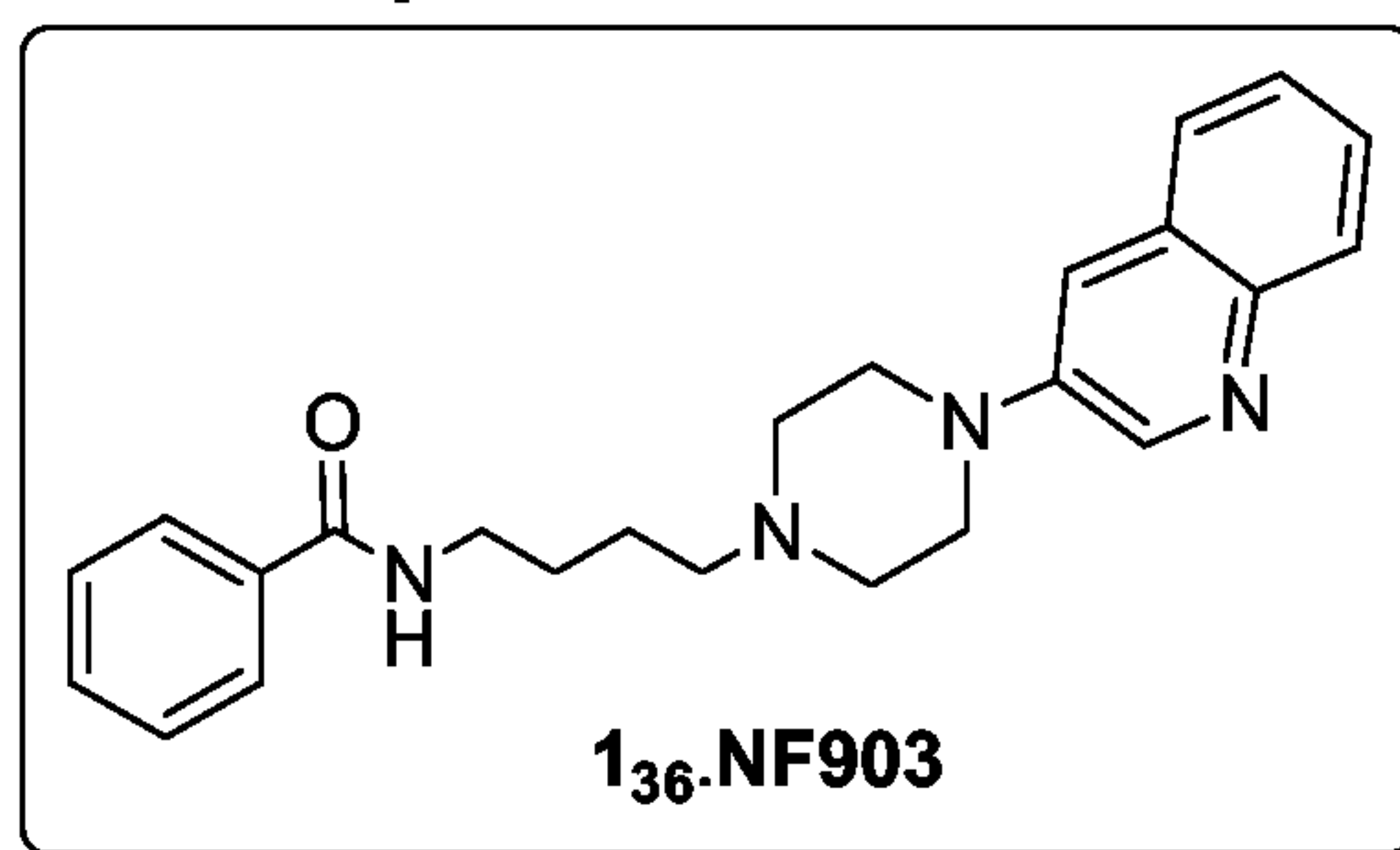
Starting from **26₂** and 1-phenylpiperazine, the title compound was prepared following the procedure described to obtain **1₁₄**. Compound **1₃₄** was obtained as amorphous solid (60% yield). ¹H NMR (CDCl₃) δ 1.56 (m, 4H), 1.86 (m, 2H), 2.45 (m, 2H), 2.64 (m, 4H), 3.22 (m, 4H), 4.03 (m, 2H), 6.66 (m, 1H), 6.79 (m, 3H), 6.91 (m, 2H), 7.25 (m, 3H), 7.56 (m, 2H), 10.19 (br s, 1H). ESI-MS *m/z* 453 [M+Na⁺], 431 [M+H⁺] (100). Anal. (C₂₆H₃₀N₄O₂) C, H, N.

(S)-1,2,3,4-Tetrahydro-N-(4-(4-phenylpiperazin-1-yl)butyl)quinoline-2-carboxamide (Compound 1-35)



Starting from **(S)-34** and 1-phenylpiperazine, the title compound was prepared following the procedure described to obtain **1₂₁**. Compound **1₃₅** was obtained as an oil (70% yield): ¹H NMR (CDCl₃) δ 1.25-1.36 (m, 4H), 2.20-2.45 (m, 4H), 2.48-2.59 (m, 4H), 2.64-2.80 (m, 2H), 3.12-3.21 (m, 6H), 4.98 (t, 1H, *J* = 6.65 Hz), 5.16-5.31 (m, 2H), 6.02 (br s, 1H), 6.74-6.85 (m, 3H), 7.04-7.21 (m, 3H), 7.25 (s, 1H), 7.34 (m, 5H), 7.63 (d, 1H, *J* = 7.97 Hz); ESI-MS *m/z* 584 [M+Na⁺], 561 [M+H⁺] (100). [α]_D²⁰ -31° (c = 0.18, CHCl₃). Anal. (C₂₃H₃₂N₄O) C, H, N.

Experimental Procedure for Compound 1-36

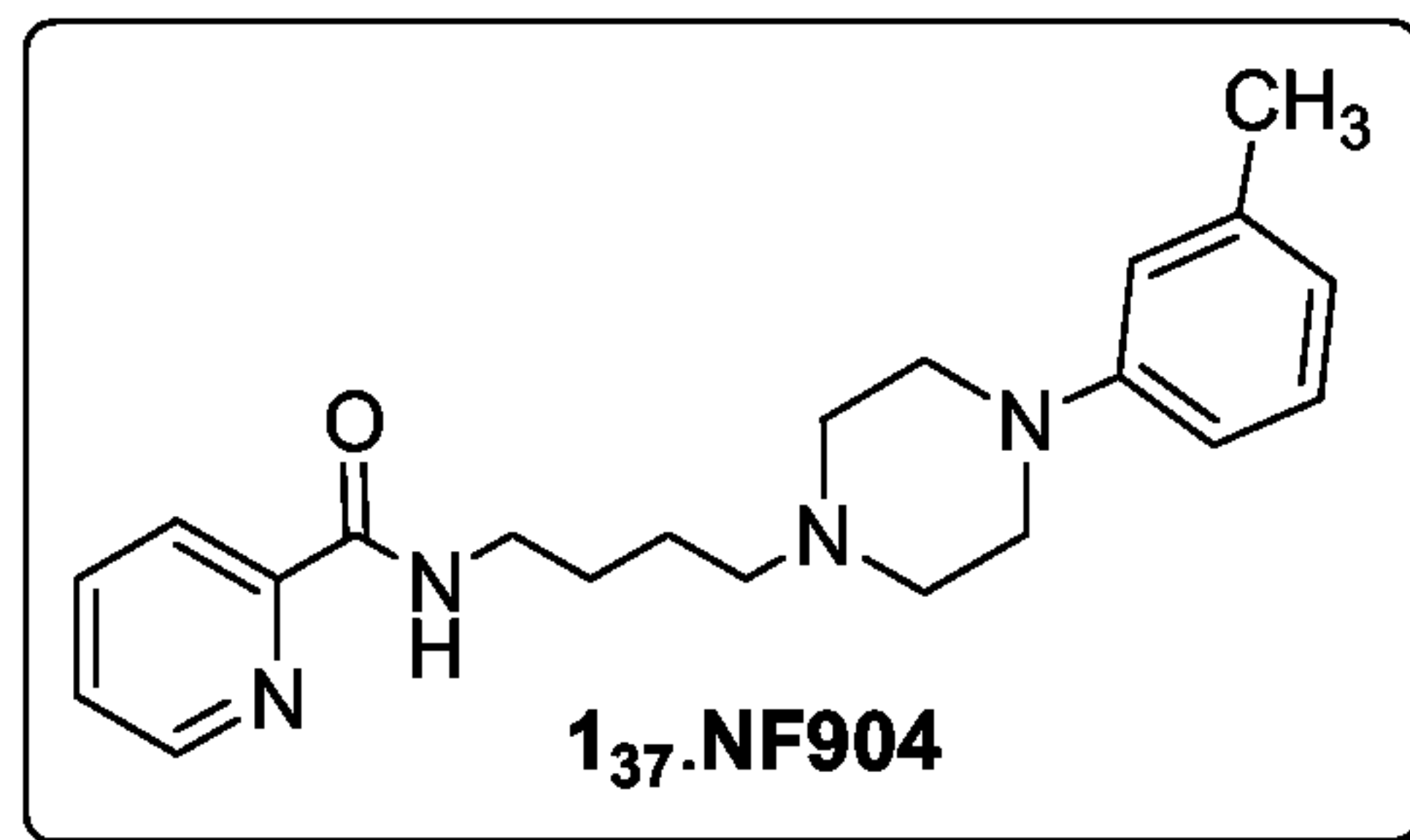


tert-Butyl-4-(quinolin-3-yl)piperazine-1-carboxylate (3₄). Starting from 3-bromoquinoline, the title compound was prepared following the procedure described to obtain **4₁**. Compound **3₄** was obtained as white solid: mp (methanol) 114-115°C. ¹H NMR, 200MHz, (CDCl₃) δ 1.46 (s, 9H), 3.18 (m, 4H), 7.28 (m, 1H), 7.43 (m, 2H), 7.63 (m, 1H), 7.96 (m, 1H), 8.74 (m, 1H). ESI-MS *m/z* 336 [M+Na⁺] (100). Anal. (C₁₈H₂₃N₃O₂) C, H, N.

3-(4-Methylpiperazin-1-yl)quinoline trifluoroacetate (4₃). Starting from **3₄**, the title compound was prepared following the procedure described to obtain **(4₁)**

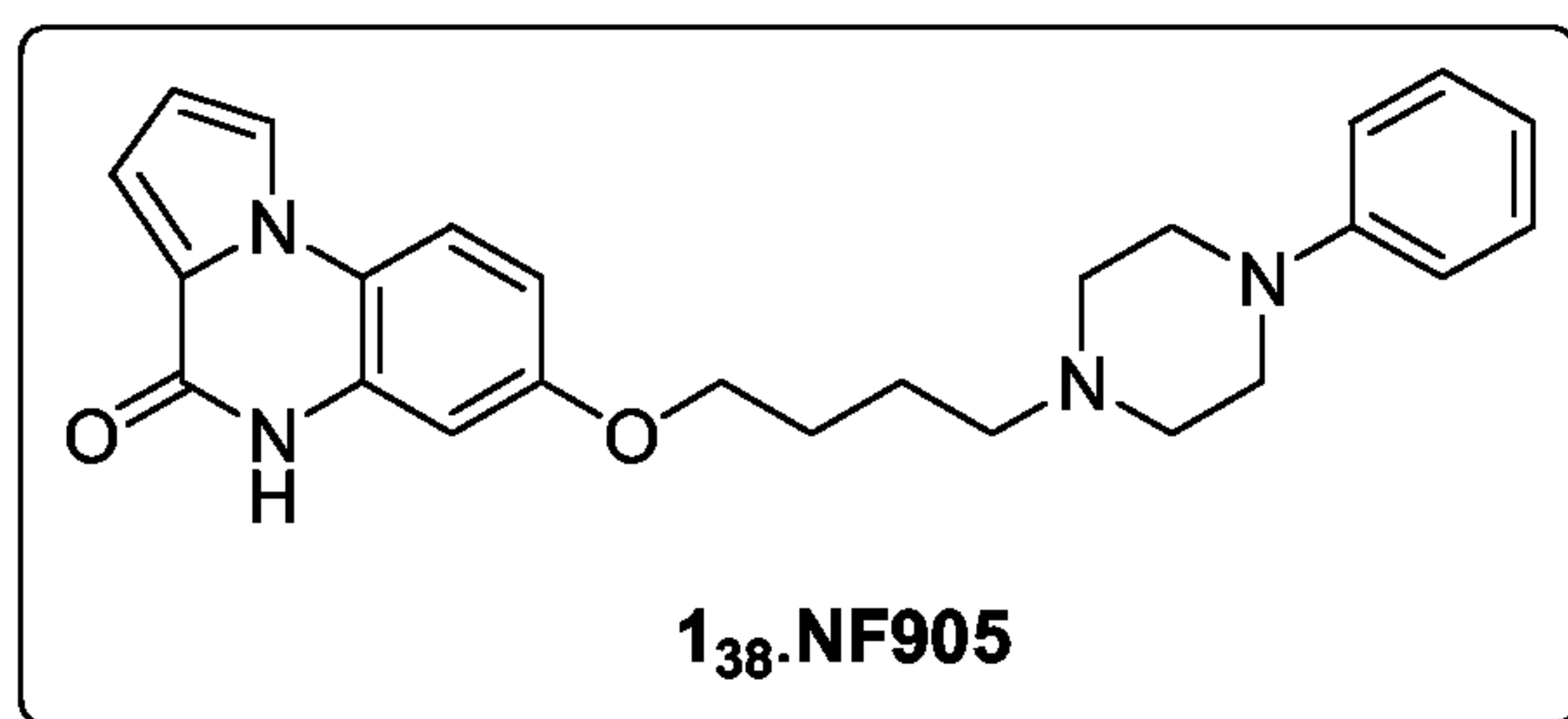
N-(4-(4-(Quinolin-3-yl)piperazin-1-yl)butyl)benzamide (Compound 1-36). Starting from **7₅** and **4₃**, the title compound was prepared following the procedure described to obtain **1₃**. Compound **1₃₆** was obtained as white solid (70% yield): mp (methanol) 124-125°C. ¹H NMR, 200MHz, (CDCl₃) δ 1.68 (m, 4H), 2.45 (m, 2H), 2.65 (m, 4H), 3.27 (m, 4H), 3.53 (m, 2H), 6.63 (br s, 1H), 7.38 (m, 6H), 7.65 (m, 1H), 7.75 (m, 2H), 7.97 (m, 1H), 8.76 (m, 1H). ESI-MS *m/z* 389 [M+H⁺] (100). Anal (C₂₄H₂₈N₄O) C, H, N.

67

***N*-(4-(4-*m*-Tolylpiperazin-1-yl)butyl)picolinamide (Compound 1-37)**

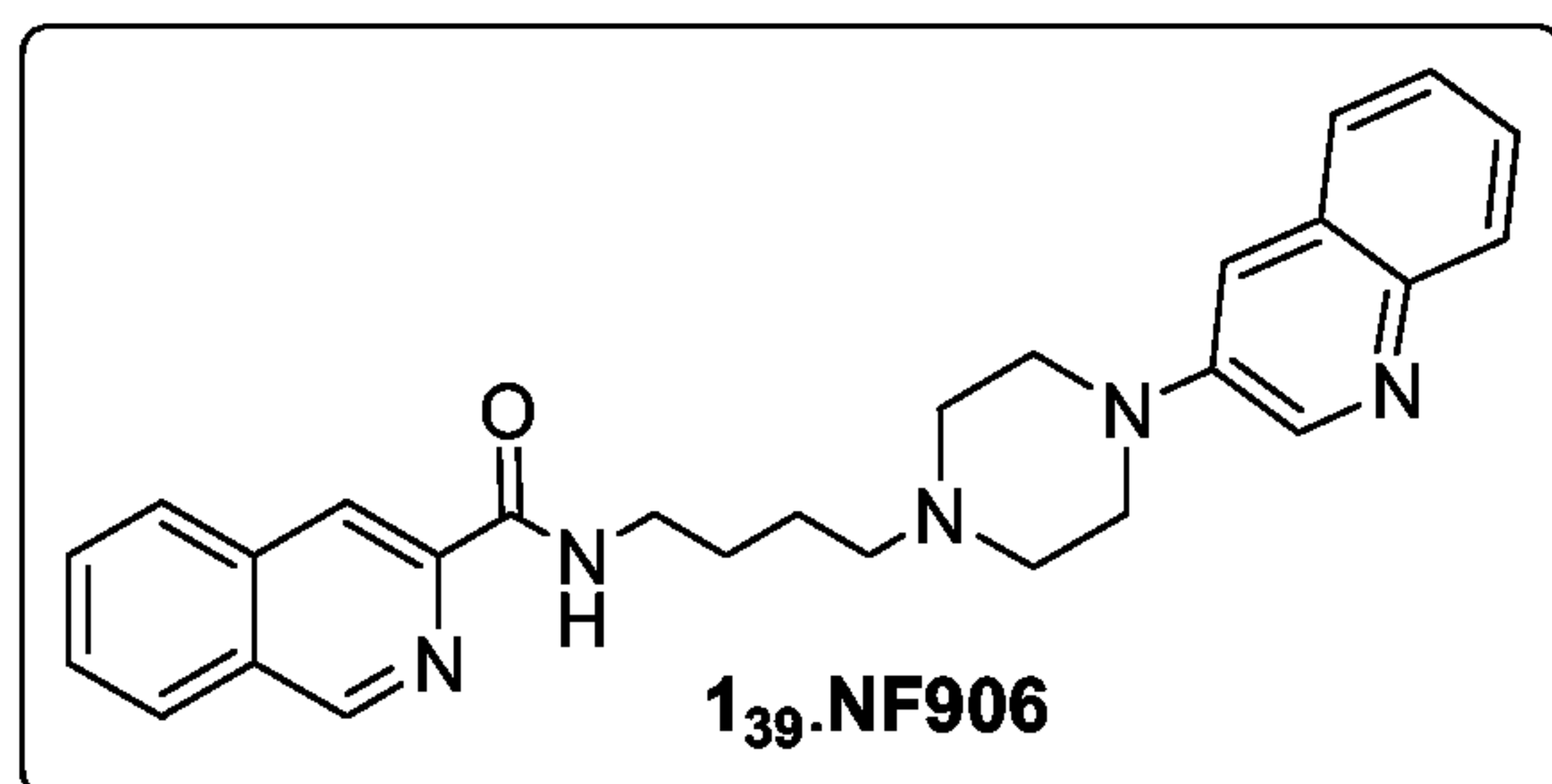
Starting from **7₈** and 4-(3-methylphenyl)piperazine, the title compound was prepared following the procedure described to obtain **1₃**. Compound **1₃₇** was obtained as yellow oil (70% yield): ¹H NMR, 200MHz, (CDCl₃) δ 1.67 (m, 4H), 2.30 (s, 3H), 2.45 (m, 2H), 2.61 (m, 4H), 3.20 (m, 4H), 3.51 (m, 2H), 6.70 (m, 3H), 7.14 (m, 1H), 7.40 (m, 1H), 7.84 (m, 1H), 8.19 (m, 2H), 8.52 (m, 1H). ESI-MS *m/z* 375 [M+Na⁺], 353 [M+H⁺] (100). Anal (C₂₁H₂₈N₄O) C, H, N.

10

7-(4-(4-Phenylpiperazin-1-yl)butoxy)pyrrolo[1,2-*a*]quinoxalin-4(5*H*)-one (Compound 1-38)

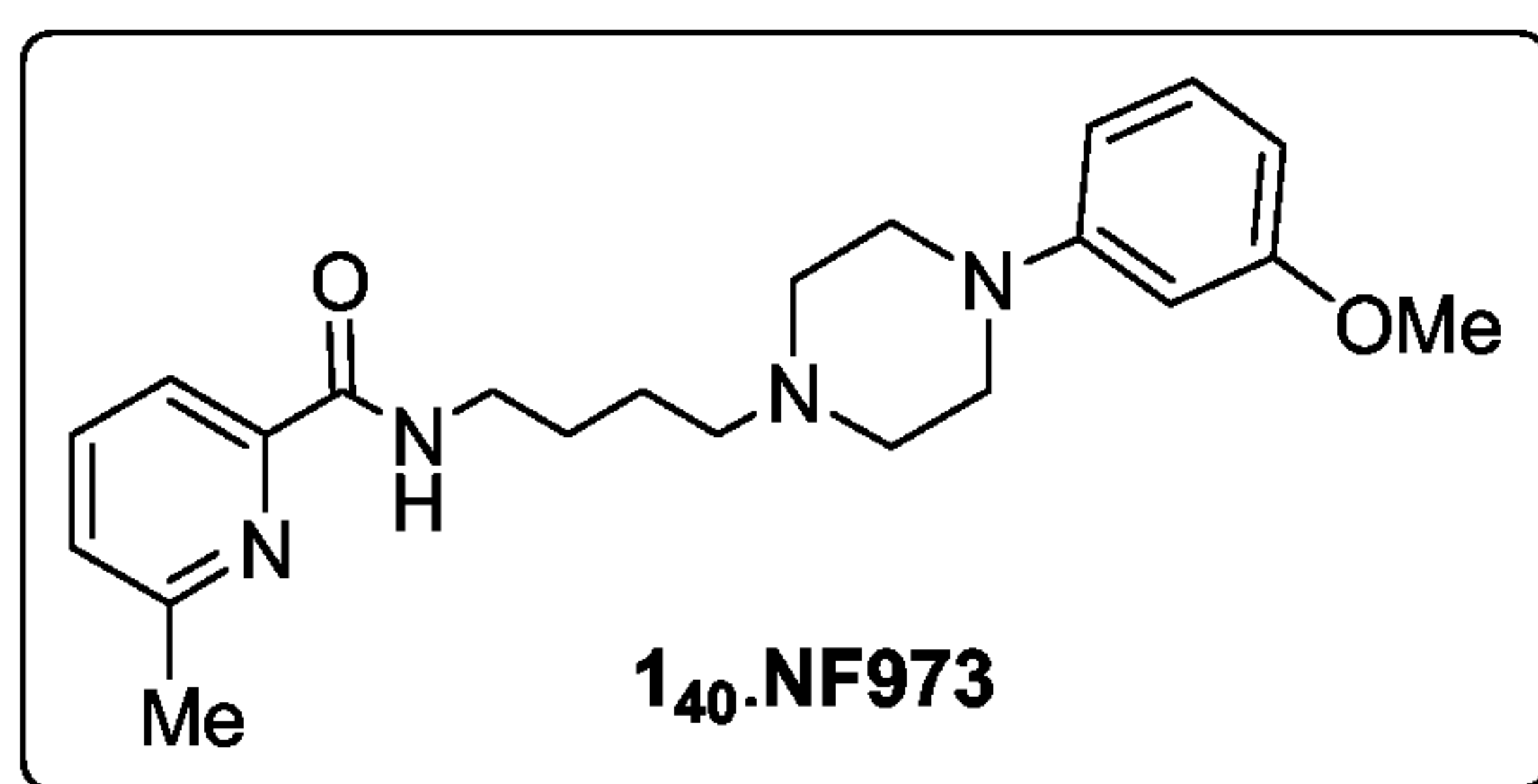
Starting from **26₁** and 1-phenylpiperazine, the title compound was prepared following the procedure described to obtain **1₁₄**. Compound **1₃₈** was obtained as amorphous solid (60% yield). ¹H NMR (CDCl₃) δ 1.81 (m, 4H), 2.49 (m, 2H), 2.65 (m, 4H), 3.21 (m, 4H), 4.06 (m, 2H), 6.66 (m, 1H), 6.74 (m, 3H), 6.89 (m, 2H), 7.23 (m, 3H), 7.56 (m, 2H), 10.27 (br s, 1H). ESI-MS *m/z* 440 [M+Na⁺], 417 [M+H⁺] (100). Anal. (C₂₅H₂₈N₄O₂) C, H, N.

20

***N*-(4-(4-(Quinolin-3-yl)piperazin-1-yl)butyl)isoquinoline-3-carboxamide (Compound 1-39)**

Starting from **7₂** and **4₃**, the title compound was prepared following the procedure described to obtain **1₃**. Compound **1₃₉** was obtained as white solid (70% yield): mp (methanol) 153-154°C. ¹H NMR, 200MHz, (CDCl₃) δ 1.80(m, 4H), 2.37 (m, 2H), 2.67 (m, 4H), 3.32 (m, 4H), 3.75 (m, 2H), 7.30 (m, 1H), 7.45 (m, 2H), 7.67 (m, 4H), 7.93 (m, 2H), 8.33 (br s, 1H), 8.60 (m, 1H), 8.78 (m, 1H), 9.12 (m, 1H). ESI-MS *m/z* 462 [M+Na⁺], 440 [M+H⁺] (100). Anal (C₂₇H₂₉N₅O) C, H, N.

***N*-(4-(4-(3-Methoxyphenyl)piperazin-1-yl)butyl)-6-methylpyridine-2-carboxamide (Compound 1-40)**

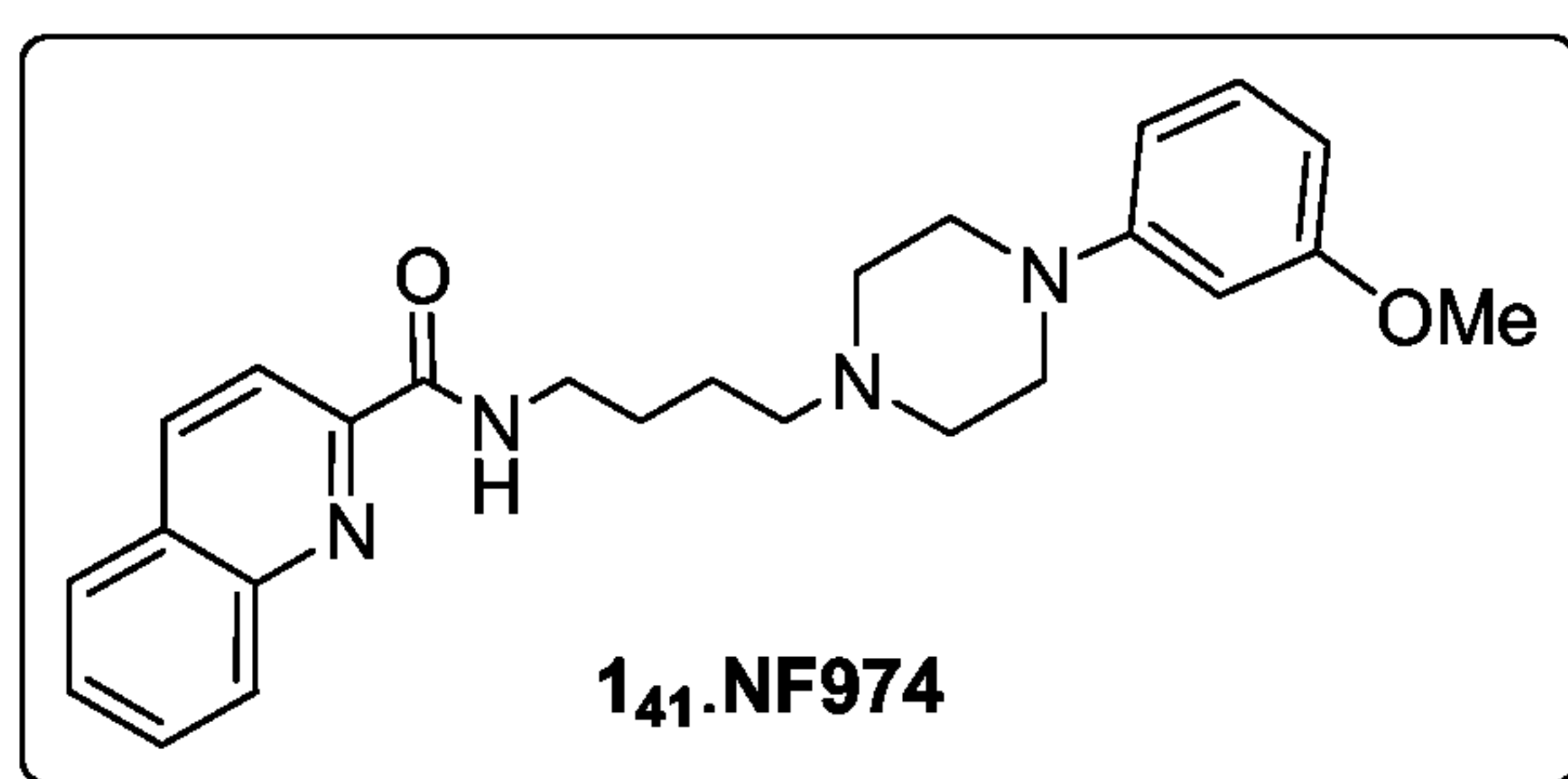


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Starting from **7₉** and 4-(3-methoxyphenyl)piperazine, the title compound was prepared following the procedure described to obtain **1₃**. Compound **1₄₀** was obtained as yellow oil (78% yield): ¹H NMR, 200MHz, (CDCl₃) δ 1.64 (m, 4H), 2.41 (m, 2H), 2.53 (s, 3H), 2.59 (m, 4H), 3.17 (m, 4H), 3.49 (m, 2H), 3.75 (s, 3H), 6.45 (m, 3H), 7.17 (m, 2H), 7.67(m, 1H), 7.97 (m, 1H), 8.14 (br s, 1H). ESI-MS *m/z* 405 [M+Na⁺], 383 [M+H⁺] (100). Anal (C₂₂H₃₀N₄O₂) C, H, N.

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***N*-(4-(4-(3-Methoxyphenyl)piperazin-1-yl)butyl)quinoline-3-carboxamide (Compound 1-41)**

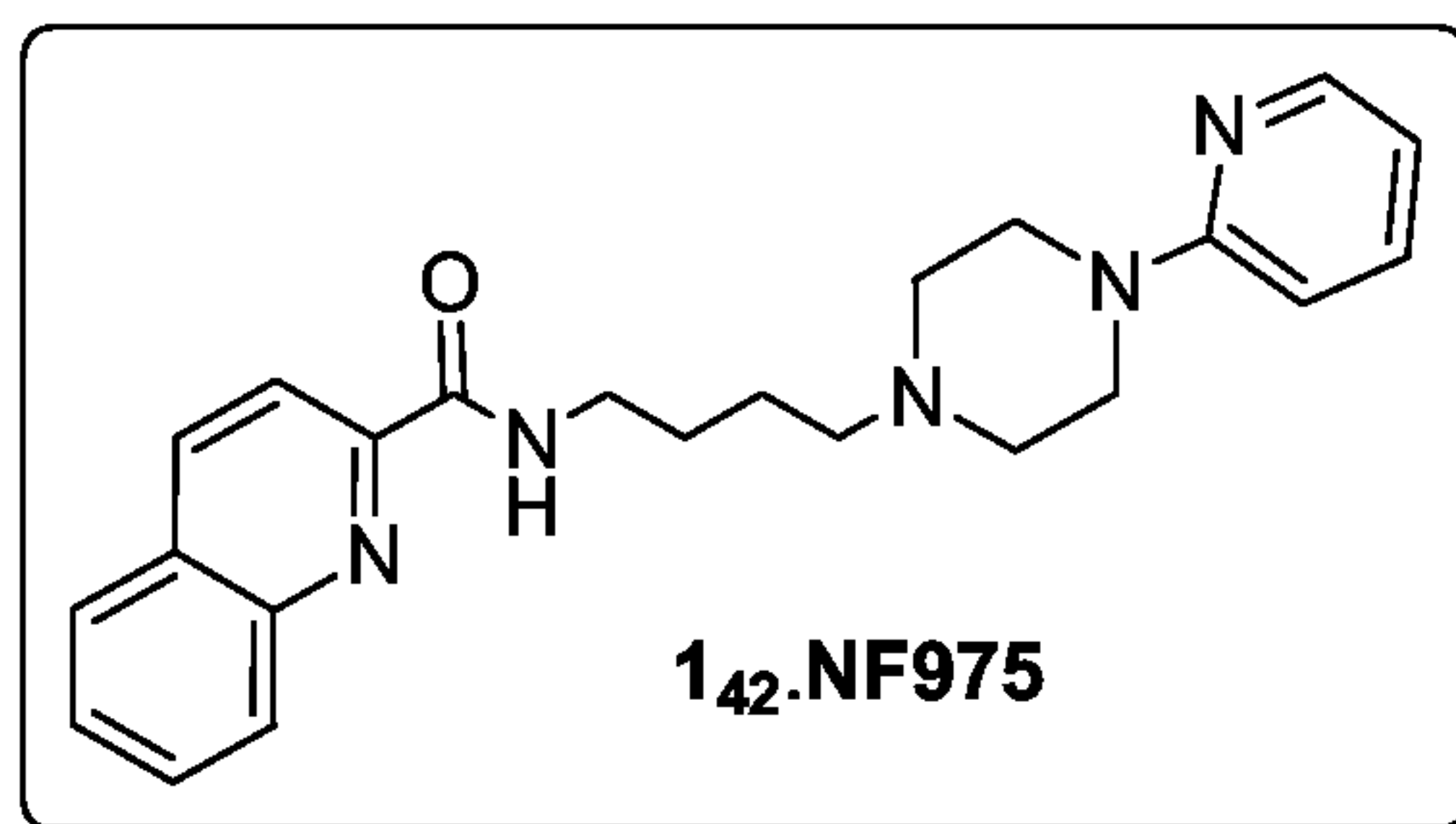


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Starting from **7₆** and 4-(3-methoxyphenyl)piperazine, the title compound was prepared following the procedure described to obtain **1₃**. Compound **1₄₁** was obtained as yellow oil (78% yield): ¹H NMR, 200MHz, (CDCl₃) δ 1.63 (m, 4H), 2.41 (m, 2H), 2.56 (m, 4H), 3.15 (m, 4H), 3.54 (m, 2H), 3.73 (s, 3H), 6.43 (m, 4H), 7.13 (m, 1H), 7.55 (m, 1H), 7.70 (m, 1H), 7.81 (m, 1H), 8.06 (m, 1H), 8.26 (m, 1H), 8.31 (br s, 1H). ESI-MS *m/z* 441 [M+Na⁺], 419 [M+H⁺] (100). Anal (C₂₅H₃₀N₄O₂) C, H, N.

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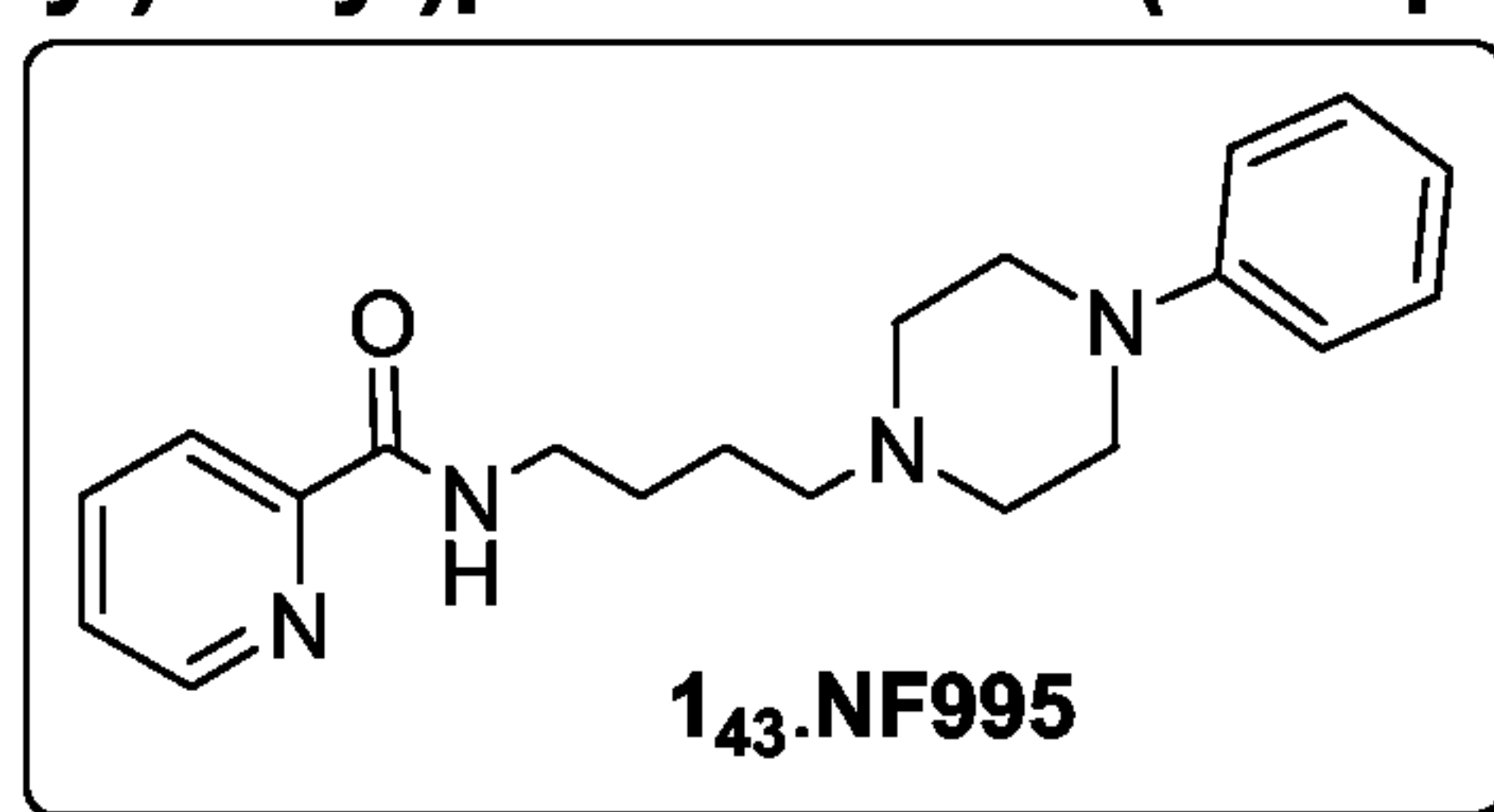
***N*-(4-(4-(Pyridin-2-yl)piperazin-1-yl)butyl)quinoline-3-carboxamide
(Compound 1-42)**



Starting from **7₆** and 1-(pyridin-2-yl)piperazine, the title compound was prepared following the procedure described to obtain **1₃**. Compound **1₄₂** was obtained as yellow oil (70% yield): ¹H NMR, 200MHz, (CDCl₃) δ 1.82 (m, 4H), 2.39 (m, 2H), 2.50 (m, 4H), 3.52 (m, 6H), 6.55 (m, 2H), 7.40 (m, 1H), 7.53 (m, 1H), 7.69 (m, 1H), 7.80 (m, 1H), 8.17 (m, 5H). ESI-MS *m/z* 412 [M+Na⁺], 390 [M+H⁺] (100). Anal (C₂₃H₂₇N₅O) C, H, N.

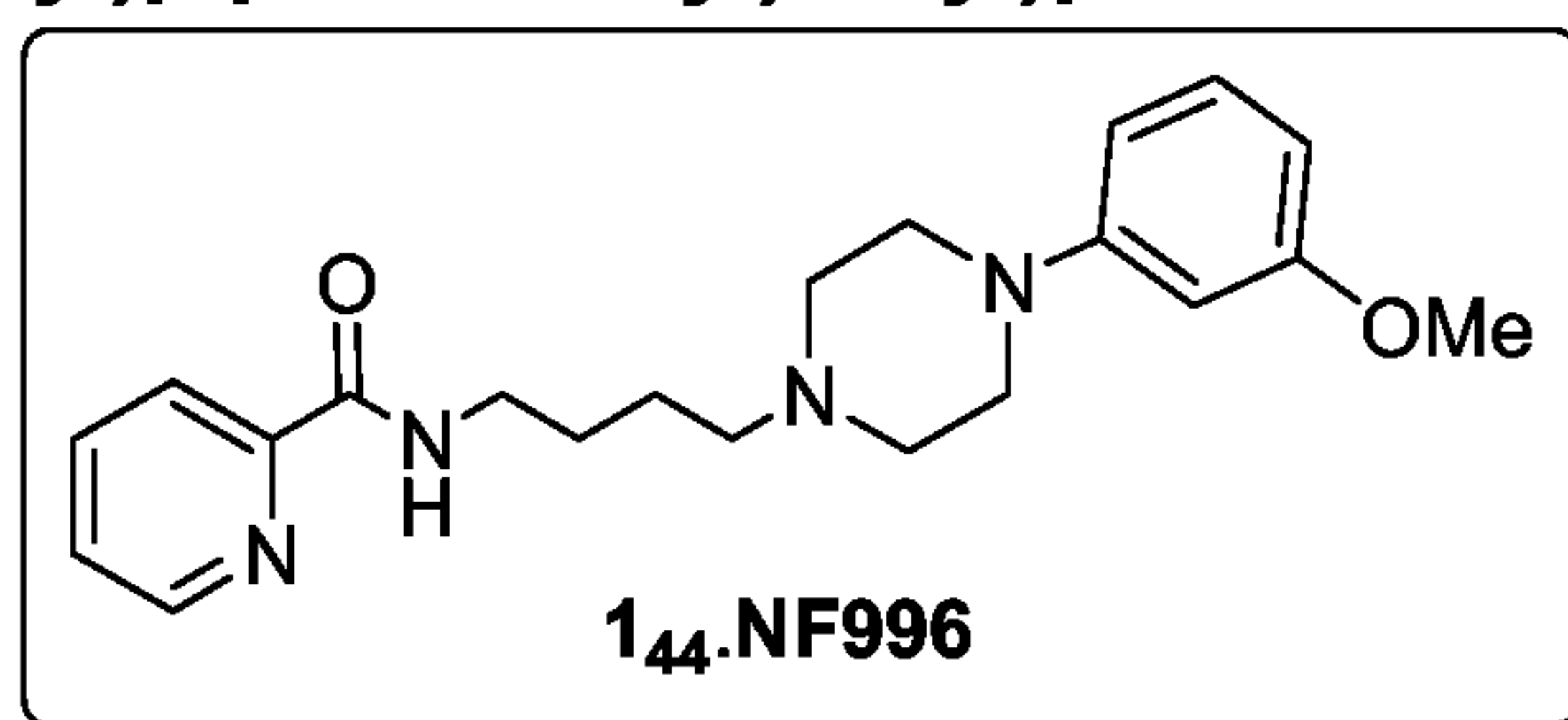
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***N*-(4-(4-Phenylpiperazin-1-yl)butyl)picolinamide (Compound 1-43)**



Starting from **7₈** and 1-phenylpiperazine, the title compound was prepared following the procedure described to obtain **1₃**. Compound **1₄₃** was obtained as yellow oil (82% yield): ¹H NMR, 400MHz, (CDCl₃) δ 1.63 (m, 4H), 2.39 (m, 2H), 2.56 (m, 4H), 3.17 (m, 4H), 3.47 (m, 2H), 6.80 (m, 1H), 6.88 (m, 2H), 7.21 (m, 2H), 7.35 (m, 1H), 7.78 (m, 1H), 8.16 (m, 1H), 8.48 (m, 1H). ESI-MS *m/z* 361 [M+Na⁺], 339 [M+H⁺] (100). Anal (C₂₀H₂₆N₄O) C, H, N.

***N*-(4-(4-(3-Methoxyphenyl)piperazin-1-yl)butyl)picolinamide (Compound 1-44)**

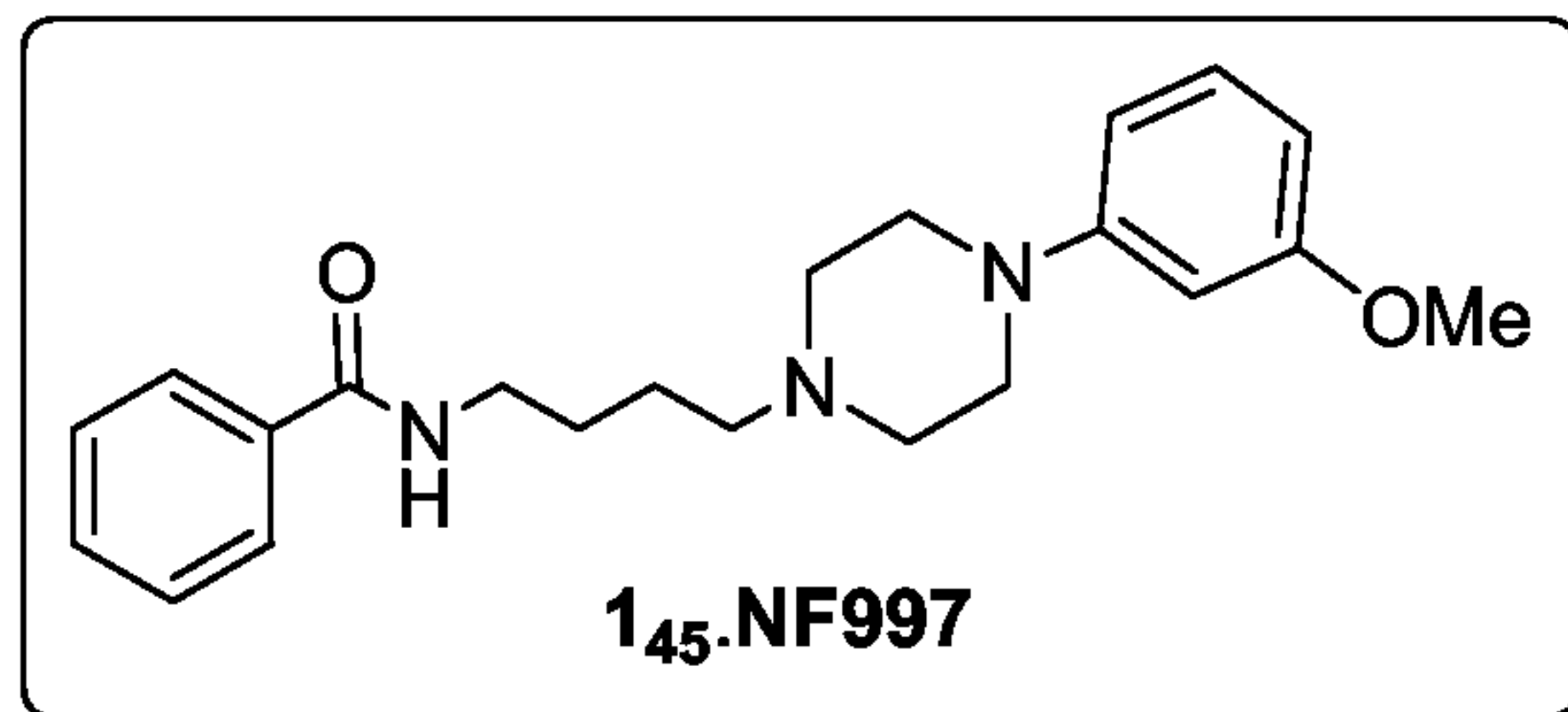


Starting from **7₈** and 4-(3-methoxyphenyl)piperazine, the title compound was prepared following the procedure described to obtain **1₃**. Compound **1₄₄** was obtained as yellow oil (72% yield): ¹H NMR, 400MHz, (CDCl₃) δ 1.57 (m, 4H), 2.33 (m, 2H), 2.49 (m, 4H), 3.11 (m, 4H), 3.43 (m, 2H), 3.68 (s, 3H), 6.32 (m, 2H), 6.38 (m, 1H),

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6.45 (m, 1H), 7.07 (m, 1H), 7.30 (m, 1H), 7.72 (m, 1H), 8.11 (m, 1H), 8.43 (m, 1H). ESI-MS m/z 369 $[M+H^+]$ (100). Anal ($C_{21}H_{28}N_4O_2$) C, H, N.

***N*-(4-(4-(3-Methoxyphenyl)piperazin-1-yl)butyl)benzamide (Compound 1-45)**

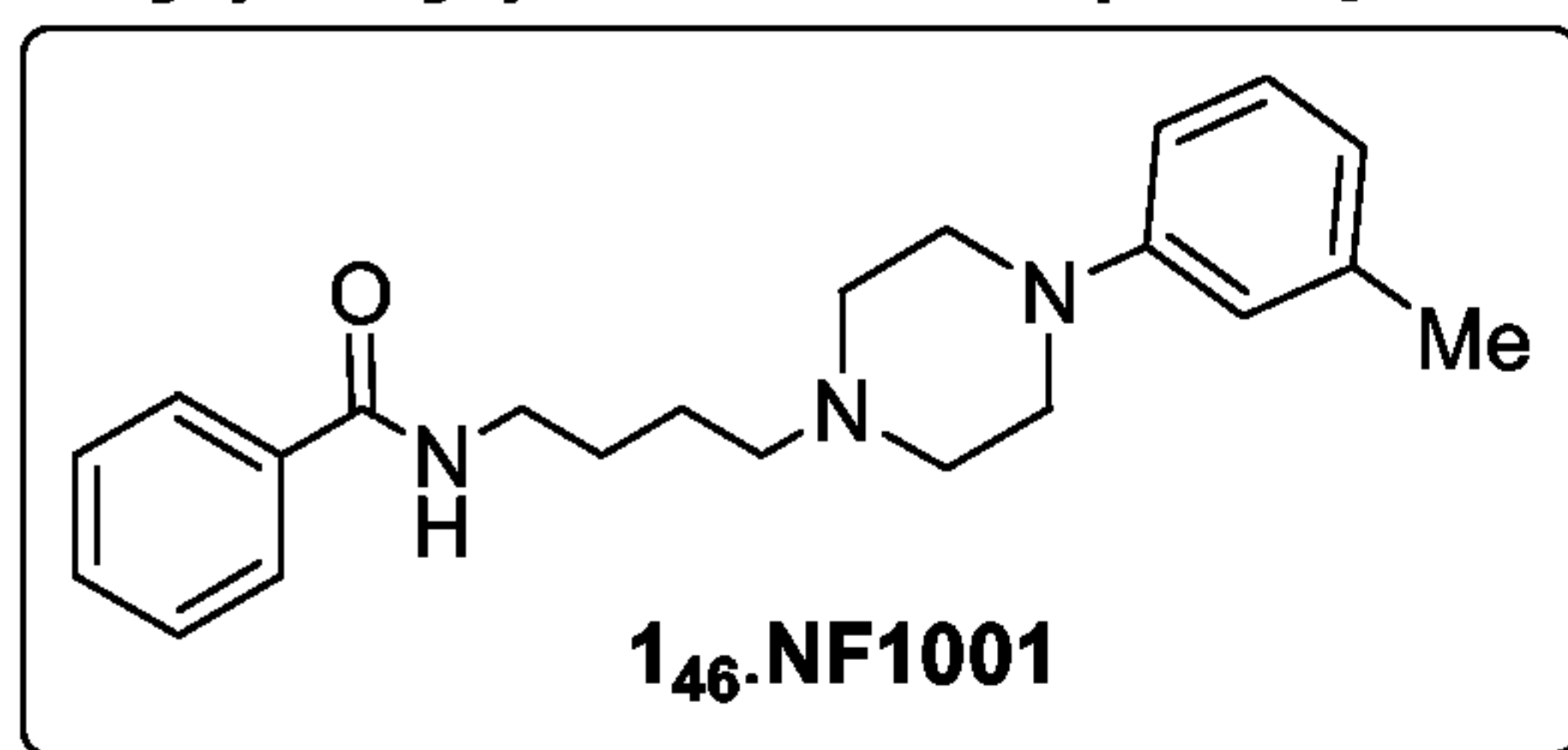


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Starting from **7₅** and 4-(3-methoxyphenyl)piperazine, the title compound was prepared following the procedure described to obtain **1₃**. Compound **1₄₅** was obtained as white solid (79% yield): mp (methanol) 111-112°C.: ^1H NMR, 400MHz, ($CDCl_3$) δ 1.62 (m, 4H), 2.39 (m, 2H), 2.54 (m, 4H), 3.13 (m, 4H), 3.42 (m, 2H), 3.75 (s, 3H), 6.40 (m, 2H), 6.49 (m, 1H), 6.83 (br s, 1H), 7.14 (m, 1H), 7.36 (m, 1H), 7.44 (m, 1H), 7.74 (m, 2H). ESI-MS m/z 390 $[M+Na^+]$, 368 $[M+H^+]$ (100). Anal ($C_{22}H_{29}N_3O_2$) C, H, N.

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***N*-(4-(4-*m*-Tolylpiperazin-1-yl)butyl)benzamide (Compound 1-46)**

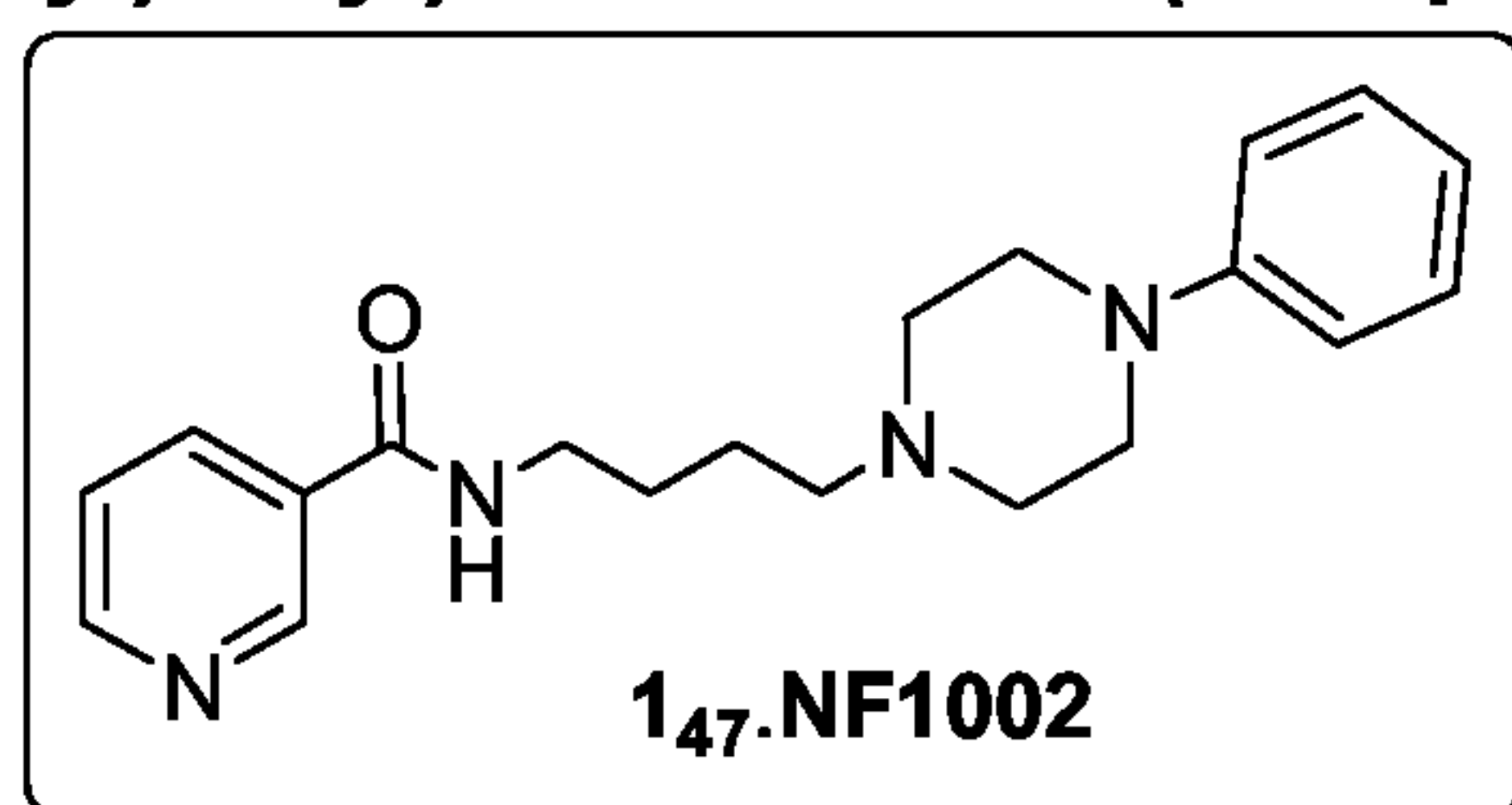


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Starting from **7₅** and 4-(3-methylphenyl)piperazine, the title compound was prepared following the procedure described to obtain **1₃**. Compound **1₄₆** was obtained as white solid (77% yield): mp (methanol) 126-127°C. ^1H NMR, 400MHz, ($CDCl_3$) δ 1.64 (m, 4H), 2.30 (s, 3H), 2.40 (m, 2H), 2.55 (m, 4H), 3.13 (m, 4H), 3.45 (m, 2H), 6.68 (m, 3H), 6.90 (br s, 1H), 7.13 (m, 1H), 7.37 (m, 2H), 7.43 (m, 1H), 7.75 (m, 2H). ESI-MS m/z 374 $[M+Na^+]$, 352 $[M+H^+]$ (100). Anal ($C_{22}H_{29}N_3O$) C, H, N.

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***N*-(4-(4-Phenylpiperazin-1-yl)butyl)nicotinamide (Compound 1-47)**



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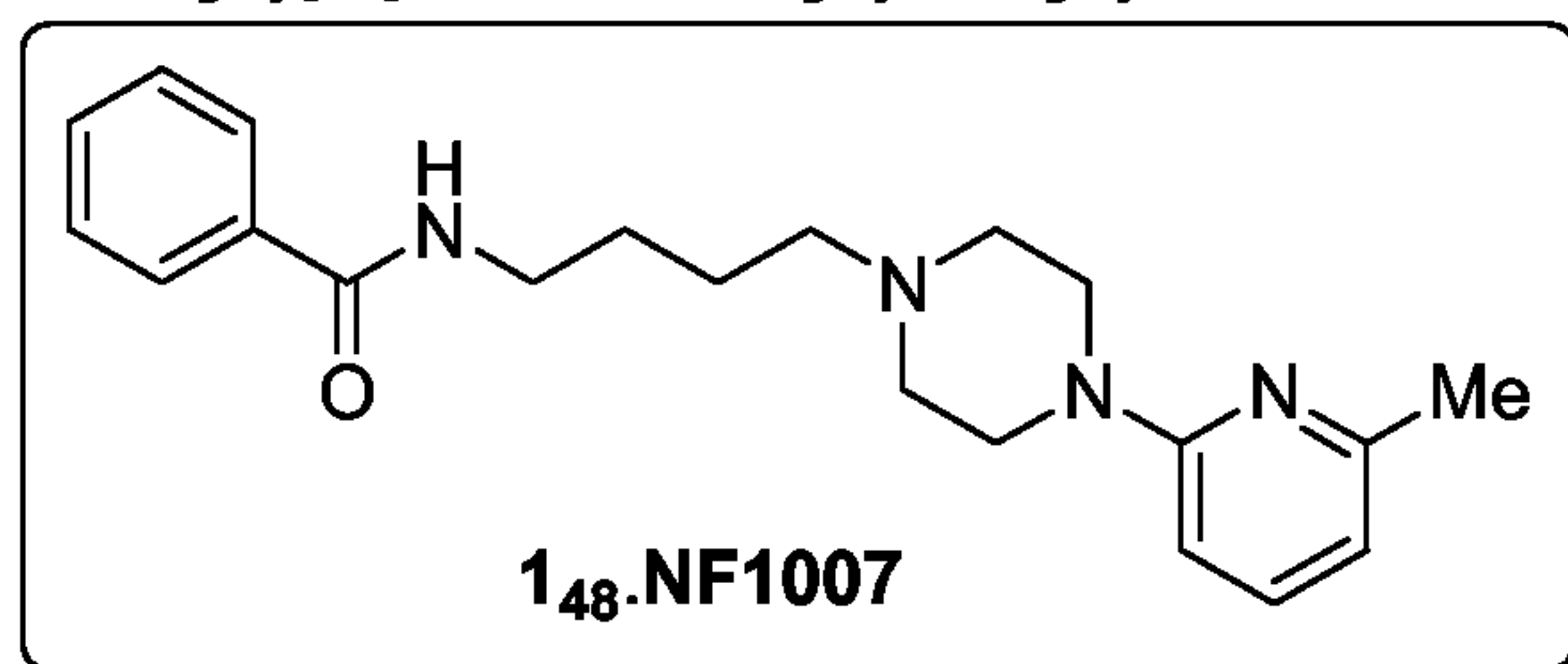
Starting from **7₁₀** and 1-phenylpiperazine, the title compound was prepared following the procedure described to obtain **1₃**. Compound **1₄₇** was obtained as white

71

solid (80% yield): mp (methanol) 119-120°C. ¹H NMR, 400MHz, (CDCl₃) δ 1.65 (m, 4H), 2.42 (m, 2H), 2.56 (m, 4H), 3.12 (m, 4H), 3.46 (m, 2H), 6.84 (m, 3H), 7.11 (br s, 1H), 7.23 (m, 2H), 7.31 (m, 1H), 8.07 (m, 1H), 8.65 (m, 1H), 8.94 (m, 1H). ESI-MS *m/z* 339 [M+H⁺] (100). Anal (C₂₀H₂₆N₄O) C, H, N.

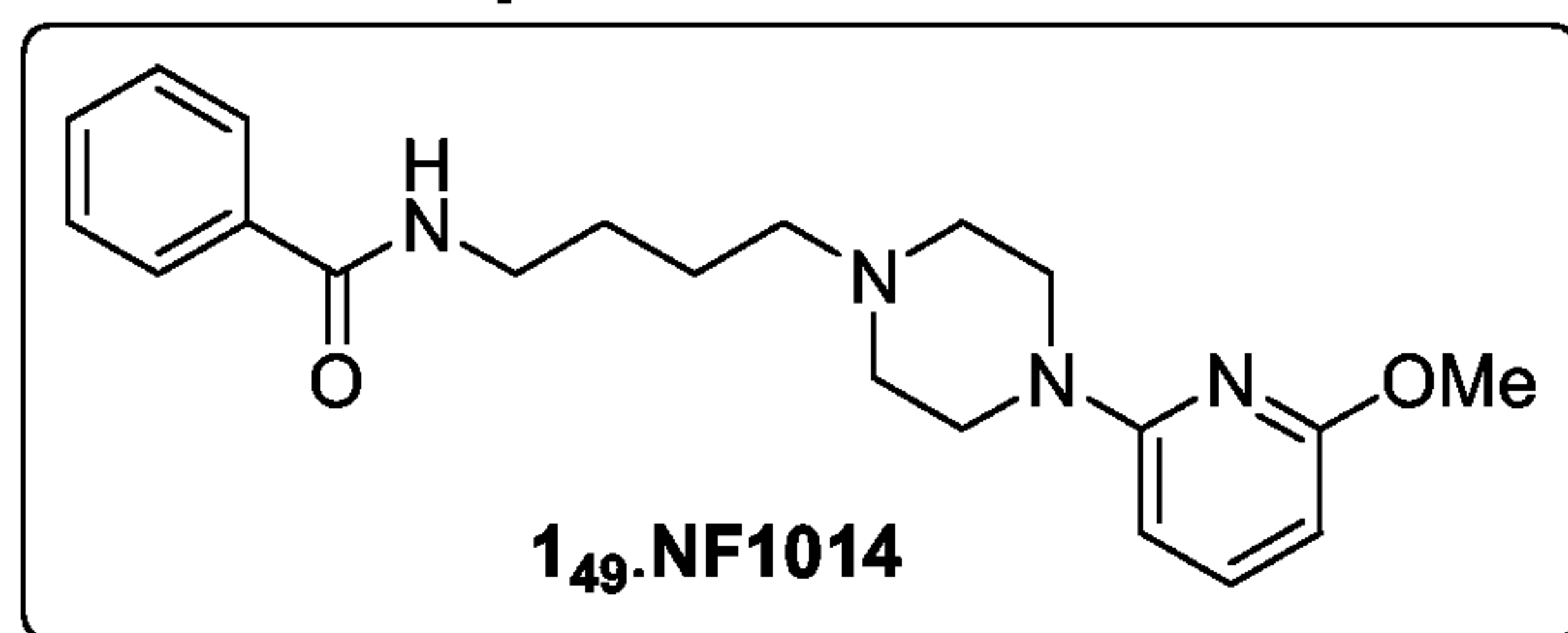
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***N*-(4-(4-(6-Methylpyridin-2-yl)piperazin-1-yl)butyl)benzamide (Compound 1-48)**



Starting from **7₅** and **4₁**, the title compound was prepared following the procedure described to obtain **1₃**. Compound **1₄₈** was obtained as white solid (82% yield): mp (methanol) 102-103°C. ¹H NMR, 200MHz, (CDCl₃) δ 1.59 (m, 4H), 2.34 (m, 5H), 2.46 (m, 4H), 3.46 (m, 6H), 6.39 (m, 2H), 7.07 (br s, 1H), 7.33 (m, 4H), 7.73 (m, 2H). ESI-MS *m/z* 375 [M+Na⁺], 353 [M+H⁺] (100). Anal (C₂₁H₂₈N₄O) C, H, N.

Experimental Procedure for Compound 1-49



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***tert*-Butyl-4-(6-methoxypyridin-2-yl)piperazine-1-carboxylate (**3₅**).**

Starting from 2-bromo-6-methoxypyridine the title compound was prepared following the procedure described to obtain **3₂**: ¹H NMR, 200MHz, (CDCl₃) δ 1.42 (s, 9H), 3.19 (m, 4H), 3.73 (s, 3H), 3.79 (m, 4H), 5.70 (m, 1H), 5.90 (m, 1H), 7.44 (m, 1H), ESI-MS *m/z* 316 [M+Na⁺], 294 [M+H⁺] (100). Anal (C₁₅H₂₃N₃O₃) C, H, N.

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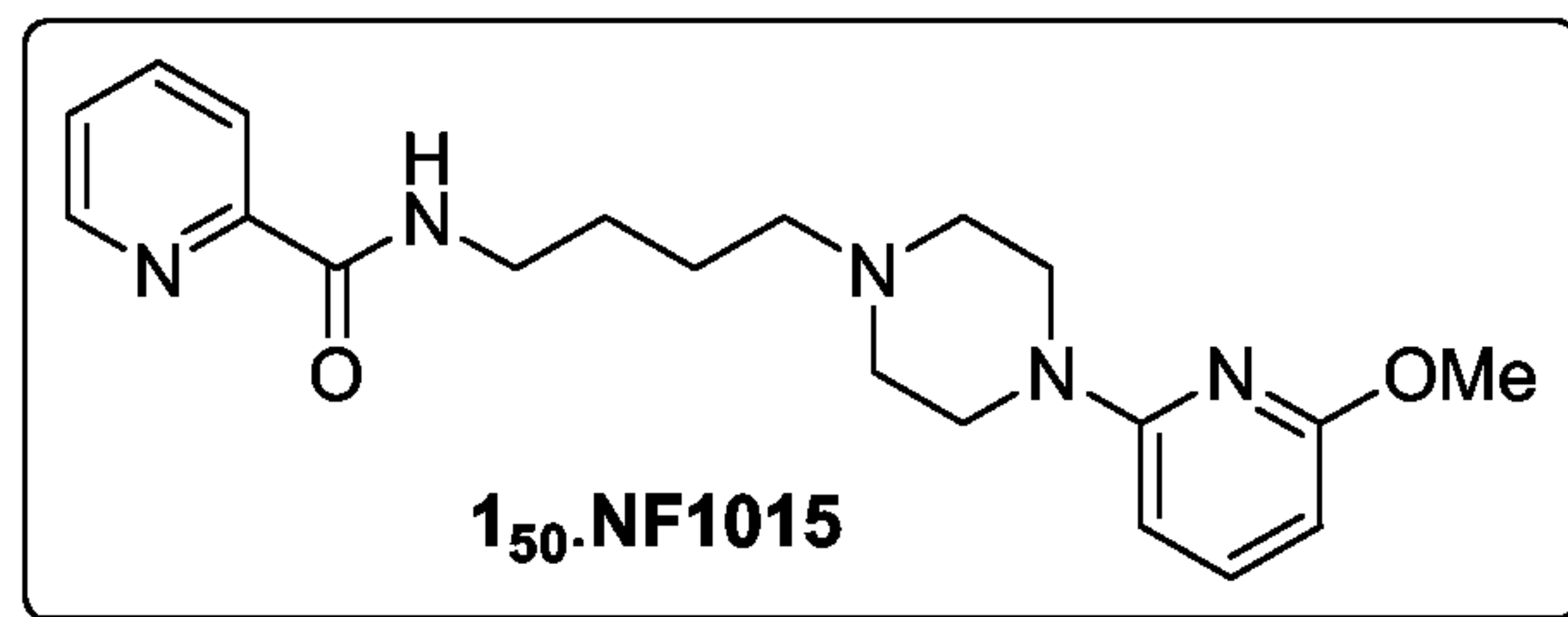
1-(6-Methoxypyridin-2-yl)piperazine (4₄**).** Starting from **3₅**, the title compound was prepared following the procedure described to obtain **4₁**

***N*-(4-(4-(6-Methoxypyridin-2-yl)piperazin-1-yl)butyl)benzamide**

(Compound 1-49). Starting from **7₅** and **4₄**, the title compound was prepared following

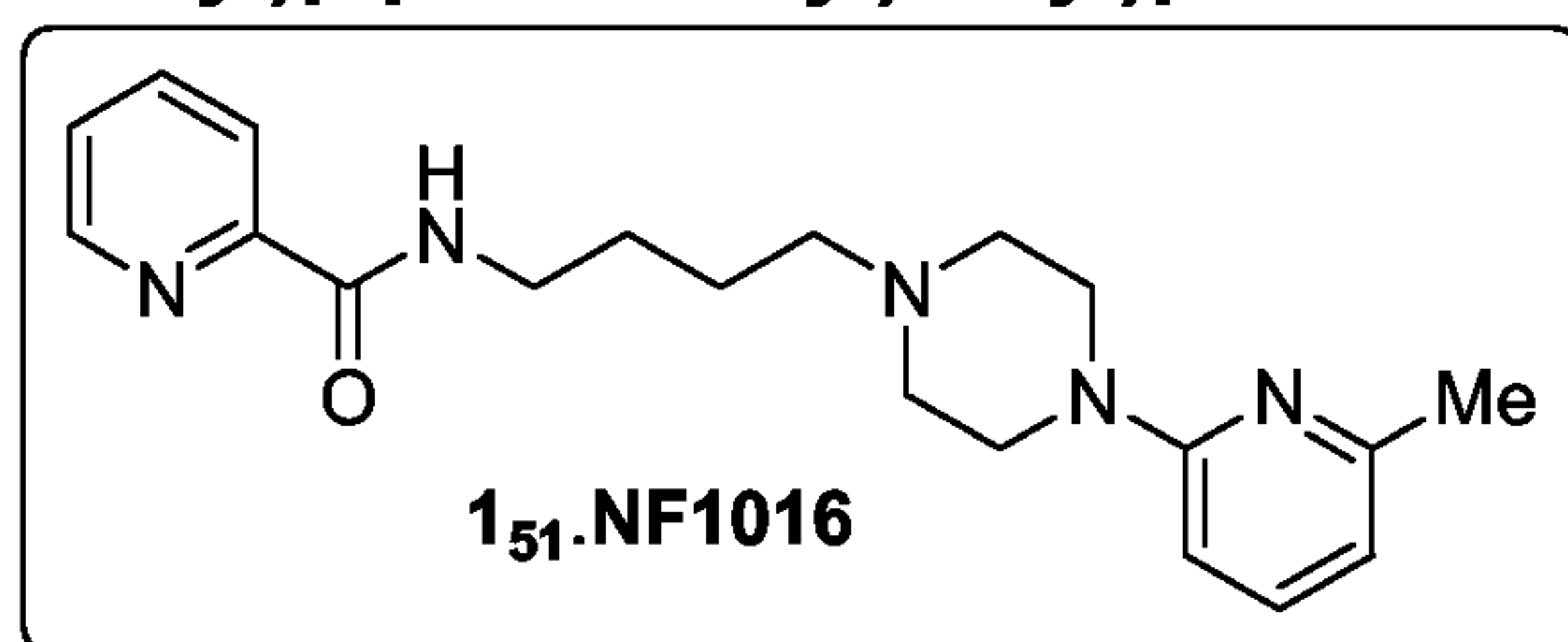
the procedure described to obtain **1₃**. Compound **1₄₉** was obtained as white solid (85% yield): mp (methanol) 120-121°C. ¹H NMR, 200MHz, (CDCl₃) δ 1.61 (m, 4H), 2.37 (m, 2H), 2.47 (m, 4H), 3.43 (m, 6H), 3.81 (s, 3H), 6.06 (m, 2H), 6.85 (br s, 1H), 7.38 (m, 4H), 7.72 (m, 2H). ESI-MS *m/z* 391 [M+Na⁺], 369 [M+H⁺] (100). Anal (C₂₁H₂₈N₄O₂) C, H, N.

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***N*-(4-(4-(6-Methoxypyridin-2-yl)piperazin-1-yl)butyl)picolinamide (Compound 1-50)**

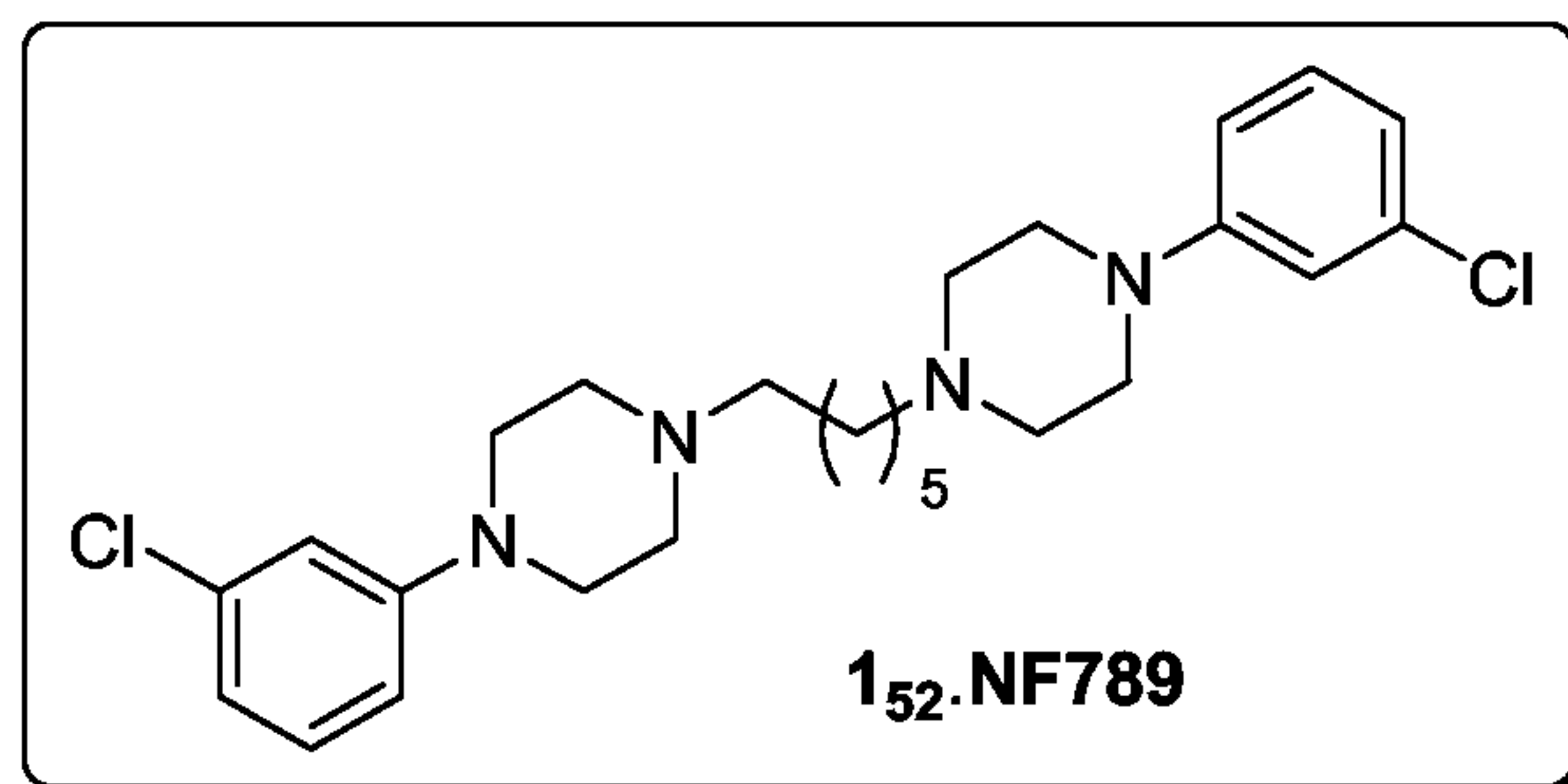
Starting from **7₈** and **4₄**, the title compound was prepared following the procedure described to obtain **1₃**. Compound **1₅₀** was obtained as yellow oil (80% yield): ¹H NMR, 300MHz, (CDCl₃) δ 1.63 (m, 4H), 2.37 (m, 2H), 2.48 (m, 4H), 3.47 (m, 4H), 3.80 (m, 3H), 6.05 (m, 2H), 7.34 (m, 2H), 7.77 (m, 1H), 8.14 (m, 2H), 8.47 (m, 1H). ESI-MS *m/z* 429 [M+Na⁺], 407 [M+H⁺] (100). ESI-MS *m/z* 376 [M+Na⁺], 354 [M+H⁺] (100). Anal (C₂₀H₂₇N₅O₂) C, H, N.

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***N*-(4-(4-(6-Methylpyridin-2-yl)piperazin-1-yl)butyl)picolinamide (Compound 1-51)**

Starting from **7₈** and **4₁**, the title compound was prepared following the procedure described to obtain **1₃**. Compound **1₅₁** was obtained as yellow (90% yield): ¹H NMR, 300MHz, (CDCl₃) δ 1.58 (m, 4H), 2.31 (m, 5H), 2.45 (m, 4H), 3.43 (m, 6H), 6.36 (m, 2H), 7.29 (m, 2H), 7.72 (m, 1H), 8.11 (m, 2H), 8.43 (m, 1H). ESI-MS *m/z* 376 [M+Na⁺], 354 [M+H⁺] (100). Anal (C₂₀H₂₇N₅O) C, H, N.

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Experimental Procedure for Compound 1-52

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1,6-Bis(4-(3-chlorophenyl)piperazin-1-yl)hexane (Compound 1-52). To a solution of 3-chlorophenylpiperazine (**40₆**) (100.0 mg, 0.51 mmol) in acetonitrile dry (15.0 mL), 1,6-dibromohexane (34.72 μL, 0.25 mmol) and TEA (71.1 μL, 0.51 mmol) was added and the mixture was stirred at room temperature overnight. The crude was extracted with dichloromethane (3 x 10 mL), dried and evaporated. The residue was

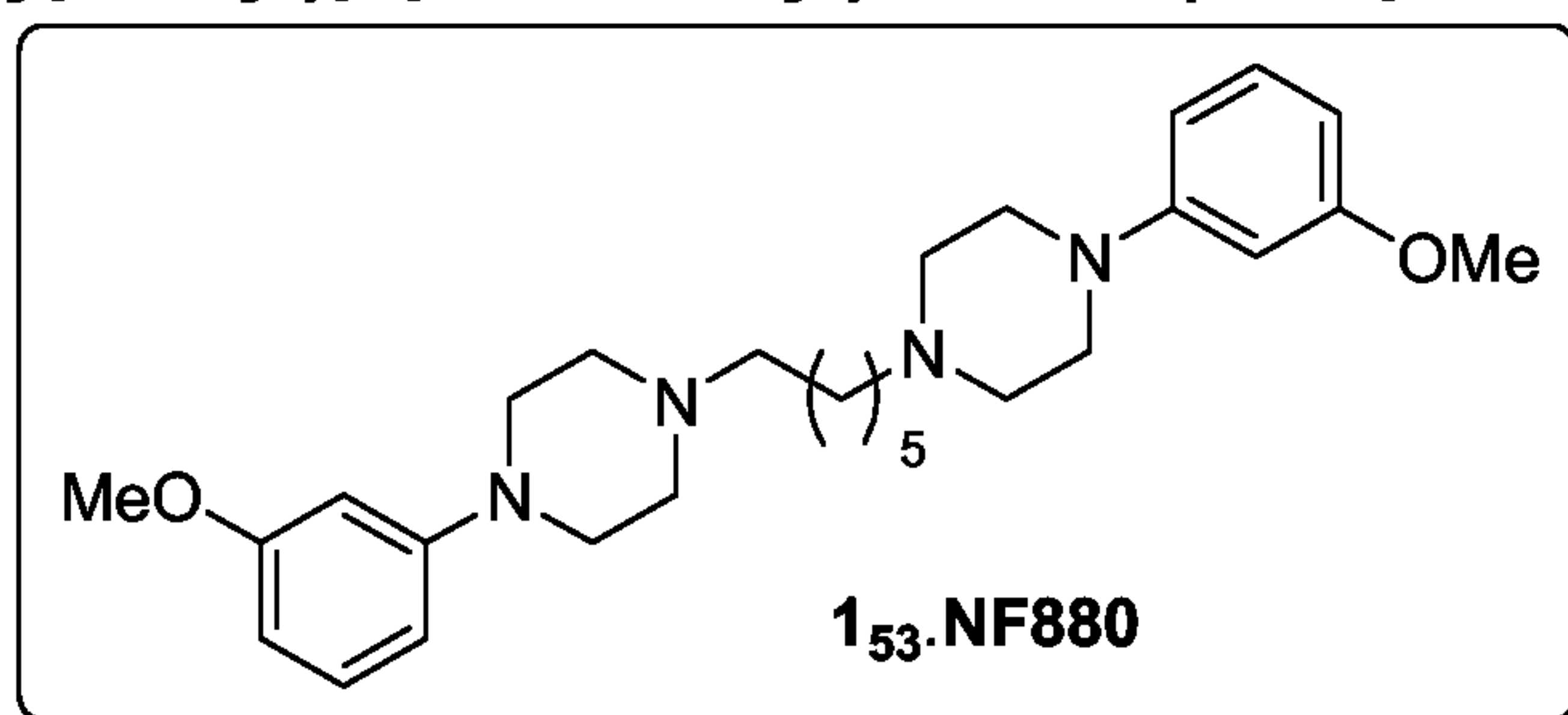
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chromatographed (10% methanol in chloroform) to give **1₅₂** (90% yield) as yellow: ¹H NMR, 200MHz, (CDCl₃) δ 1.37 (m, 4H), 1.52 (m, 4H), 2.37 (m, 4H), 2.57 (m, 8H), 3.20 (m, 8H), 6.77 (m, 4H), 6.86 (m, 2H), 7.14 (m, 2H). ESI-MS *m/z* 475 [M+H⁺] (100). Anal (C₂₆H₃₆Cl₂N₄) C, H, N.

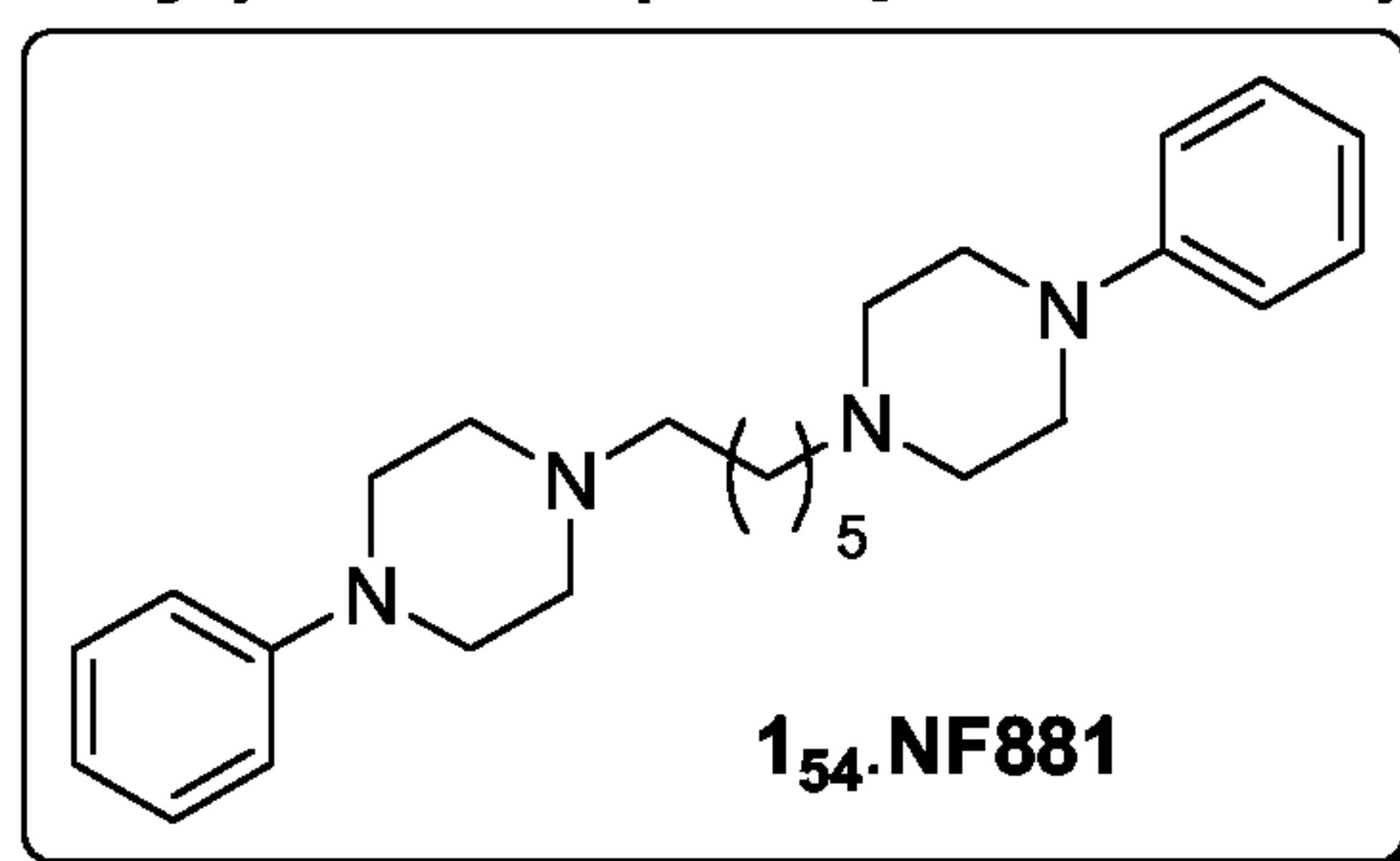
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1,6-Bis(4-(3-methoxyphenyl)piperazin-1-yl)hexane (Compound 1-53)



Starting from 4-(3-methoxyphenyl)piperazine, the title compound was prepared following the procedure described to obtain **1₅₂**. Compound **1₅₃** was obtained as white solid (85% yield): mp (methanol) 109-110°C. ¹H NMR, 200MHz, (CDCl₃) δ 1.36 (m, 4H), 1.54 (m, 4H), 2.38 (m, 4H), 2.58 (m, 8H), 3.20 (m, 8H), 3.77 (m, 8H), 6.44 (m, 6H), 7.15 (m, 2H), ESI-MS *m/z* 467 [M+H⁺] (100). Anal (C₂₈H₄₂N₄O₂) C, H, N.

1,6-Bis(4-phenylpiperazin-1-yl)hexane (Compound 1-54)

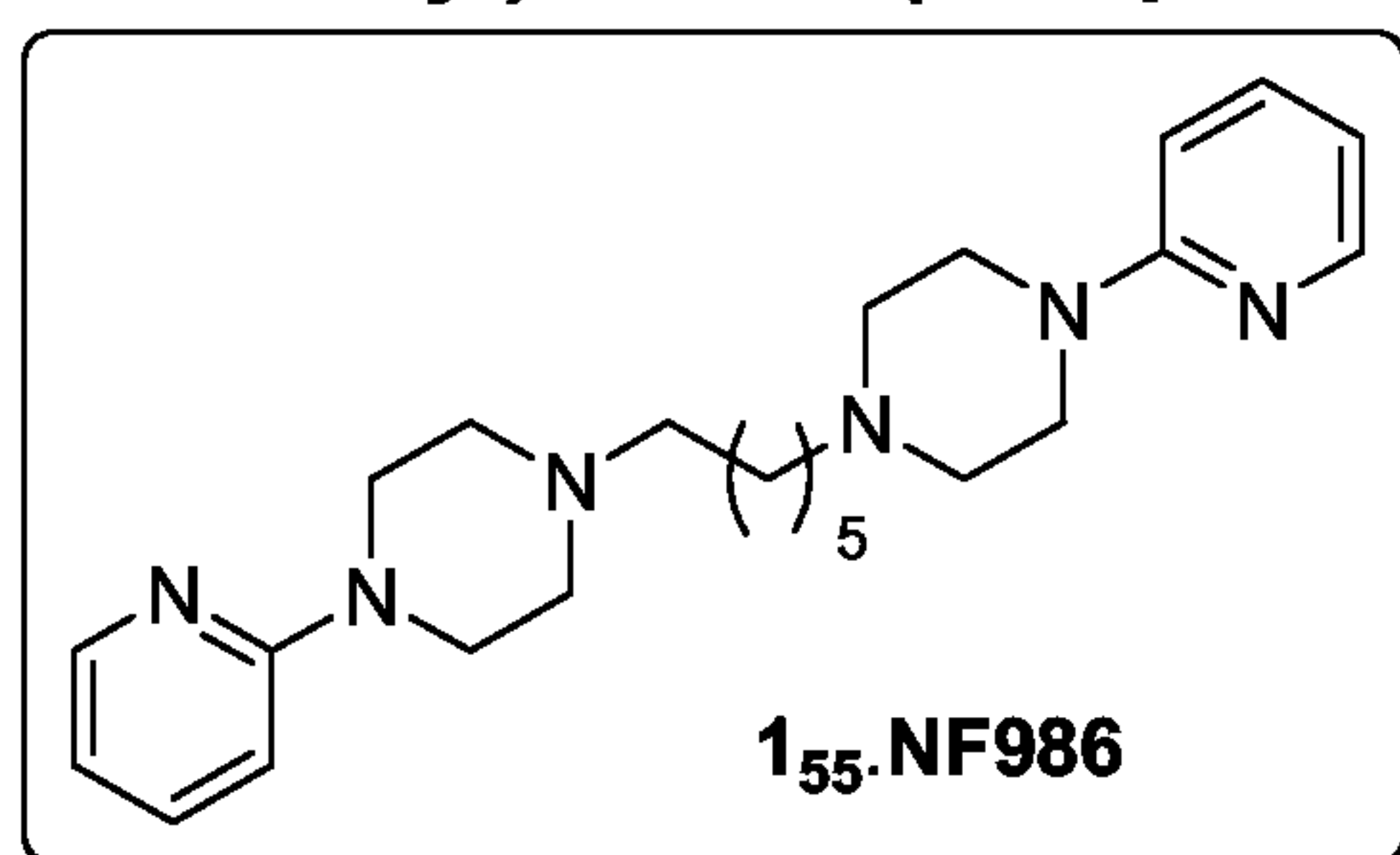


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Starting from 1-phenylpiperazine the title compound was prepared following the procedure described to obtain **1₅₂**. Compound **1₅₄** was obtained as yellow (95% yield): ¹H NMR, 200MHz, (CDCl₃) δ 1.39 (m, 4H), 1.57 (m, 4H), 2.41 (m, 4H), 2.62 (m, 8H), 3.22 (m, 8H), 6.89 (m, 6H), 7.27 (m, 6H). ESI-MS *m/z* 429 [M+Na⁺], 407 [M+H⁺] (100). Anal (C₂₆H₃₈N₄) C, H, N.

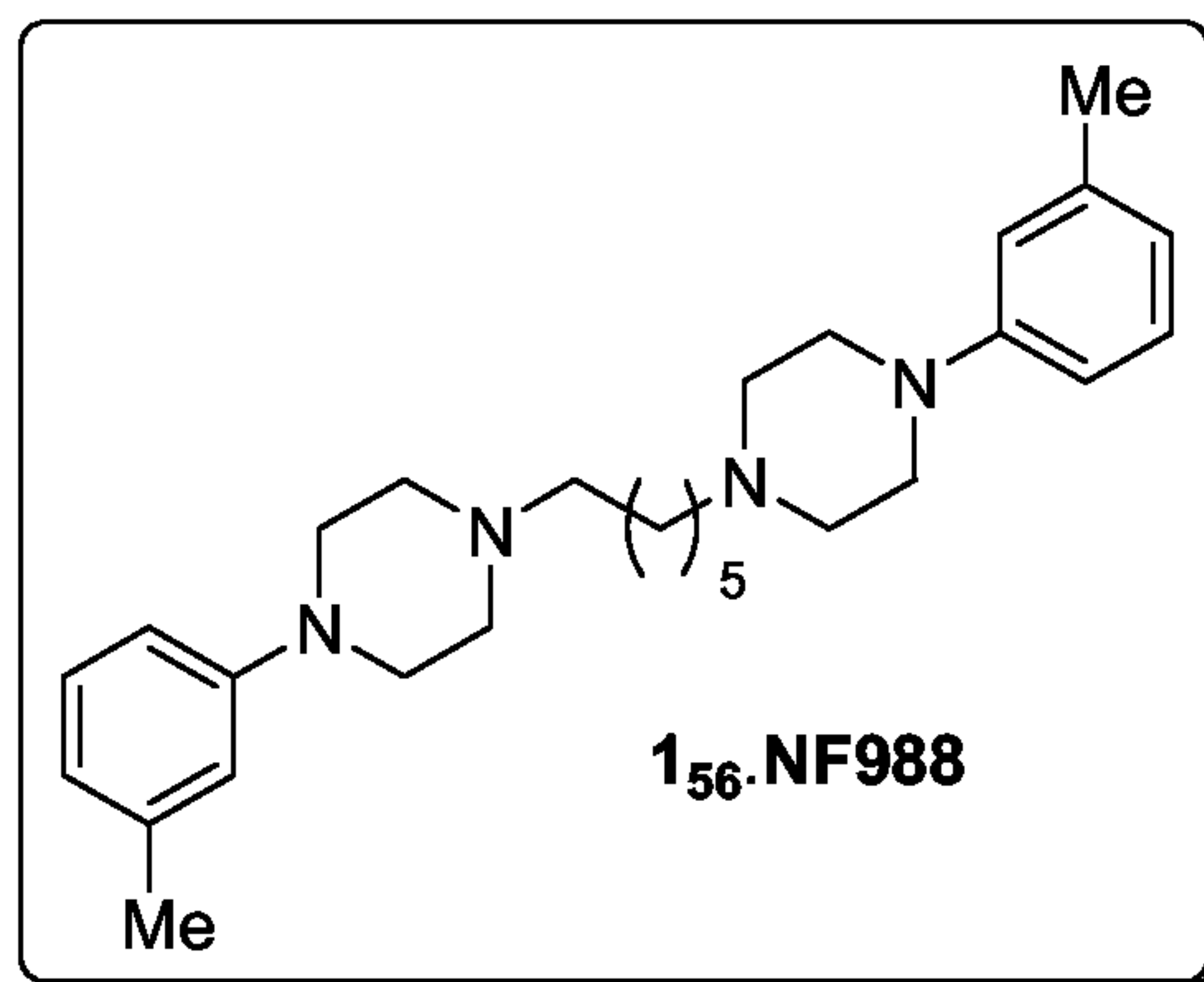
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1,6-Bis(4-(pyridin-2-yl)piperazin-1-yl)hexane (Compound 1-55)



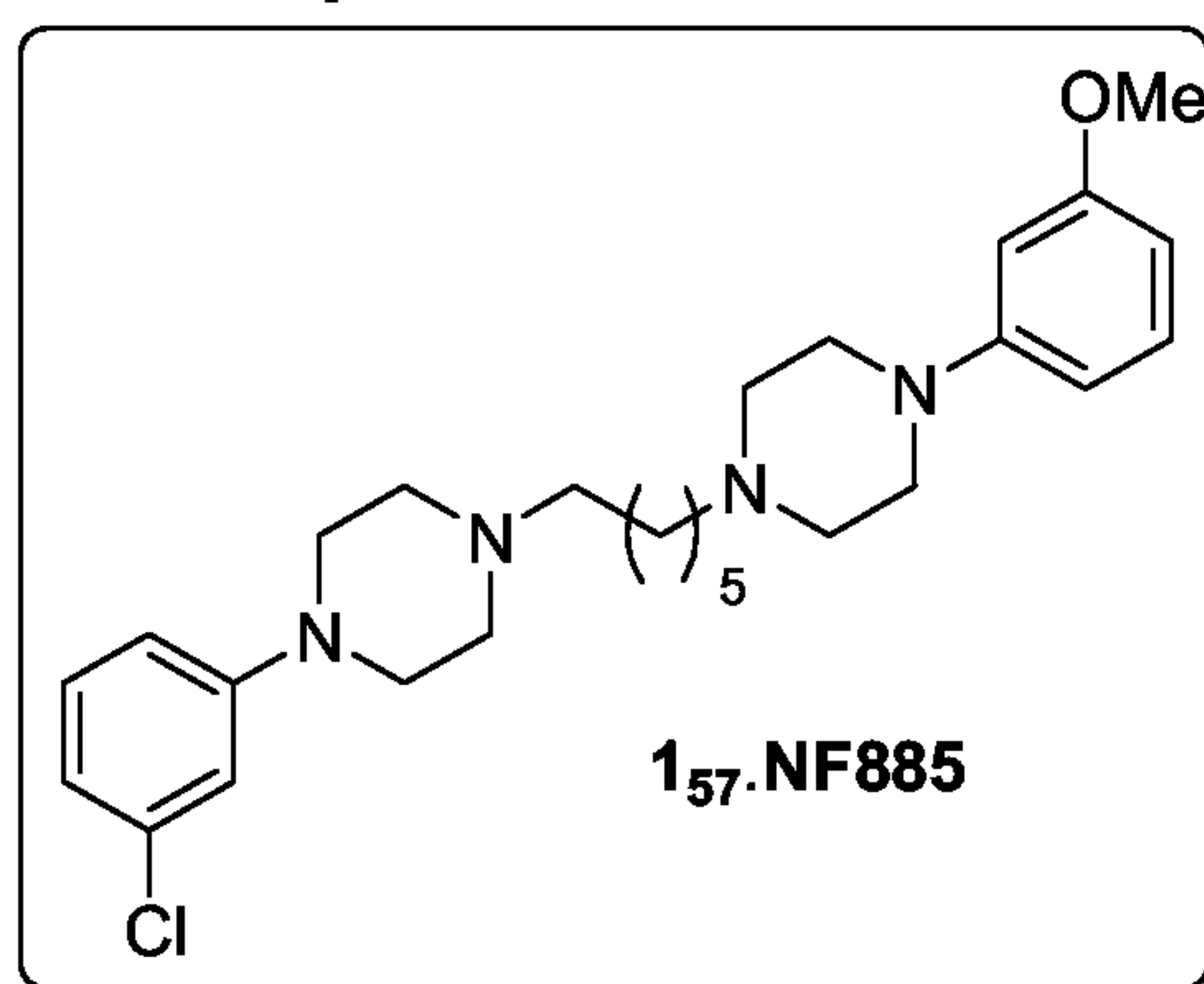
1 Starting from 1-(pyridin-2-yl)piperazine, the title compound was prepared following the procedure described to obtain **1₅₂**. Compound **1₅₅** was obtained as yellow oil: ¹H NMR, 400MHz, (CDCl₃) δ 1.32 (m, 4H), 1.50 (m, 4H), 2.32 (m, 4H), 2.49 (m, 8H), 3.50 (m, 8H), 6.56 (m, 4H), 7.40 (m, 2H), 8.14 (m, 2H). ESI-MS *m/z* 431 [M+Na⁺],
 5 409 [M+H⁺] (100). Anal (C₂₄H₃₆N₆) C, H, N.

1,6-Bis(4-*m*-tolylpiperazin-1-yl)hexane (Compound 1-56)



Starting from 4-(3-methylphenyl)piperazine, the title compound was prepared following the procedure described to obtain **1₅₂**. Compound **1₅₆** was obtained as yellow oil (95% yield): ¹H NMR, 400MHz, (CDCl₃) δ 1.37 (m, 4H), 1.55(m, 4H), 2.31 (s, 6H), 2.39 (m, 4H), 2.60 (m, 4H), 3.20 (m, 4H), 6.71 (m, 6H), 7.14 (m, 2H). ESI-MS *m/z* 435 [M+H⁺] (100). Anal (C₂₈H₄₂N₄) C, H, N.

15 Experimental Procedure for Compound 1-57

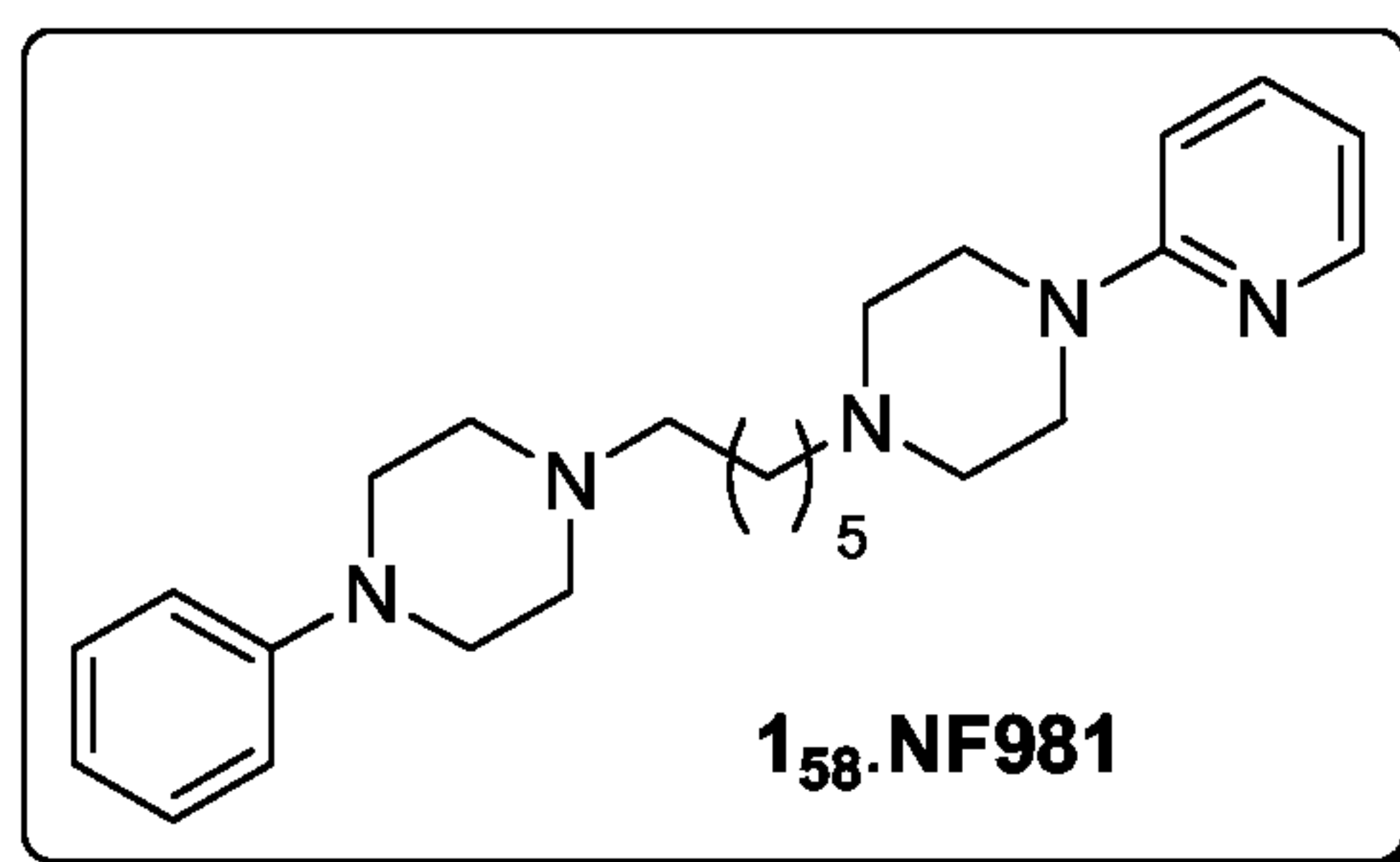


1-(6-Bromohexyl)-4-(3-methoxyphenyl)piperazine (42₁). To a solution of 3-methoxyphenylpiperazine (**41₁**) (200.0 mg, 1.04 mmol) in acetonitrile dry (15.0 mL), 1,6-dibromohexane (212.4 μL, 1.56 mmol) and TEA (145.0 μL, 1.04 mmol) was added
 20 and the mixture was stirred at room temperature overnight. The crude was extracted with dichloromethane (3 x 10 mL), dried and evaporated. The residue was chromatographed (15% *n*-hexane in EtOAc) to give **42₁** (65% yield): ¹H NMR, 300MHz, (CDCl₃) δ 7.12 (m, 1H), 7.02 (m, 1H), 6.76 (m, 1H), 6.60 (m, 1H), 6.47 (m, 1H), 6.39 (m, 1H), 6.27 (m, 1H), 6.15 (m, 1H), 3.73 (m, 3H), 3.44 (m, 4H), 2.59 (m, 4H), 2.36 (m,

4H), 1.39 (m, 4H), 1.29 (m, 4H). ESI-MS m/z 493 $[M+Na^+]$, 471 $[M+H^+]$ (100). Anal ($C_{27}H_{39}ClN_4O$) C, H, N.

1-(3-Chlorophenyl)-4-(6-(4-(3-methoxyphenyl)piperazin-1-yl)hexyl)piperazine (Compound 1-57). To a solution of **42₁** (100.0 mg, 0.52 mmol) in
 5 acetonitrile dry (10.0 mL), 3-chlorophenylpiperazine (101.9 mg, 0.52 mmol) and TEA (72.5 μ L, 0.52 mmol) was added and the mixture was stirred at room temperature overnight. The crude was extracted with dichloromethane (3 x 10 mL), dried and evaporated. The residue was chromatographed (10% methanol in chloroform) to give
 10 **1₅₇** (80% yield) as an yellow oil: ^1H NMR, 300MHz, ($CDCl_3$) δ 1.35 (m, 4H), 1.54 (m, 4H), 2.39 (m, 4H), 2.59 (m, 8H), 3.20 (m, 8H), 3.78 (s, 3H), 6.42 (m, 2H), 6.53 (m, 1H), 6.78 (m, 2H), 6.86 (m, 1H), 7.15 (m, 2H). ESI-MS m/z 493 $[M+Na^+]$, 471 $[M+H^+]$ (100). Anal ($C_{27}H_{39}ClN_4O$) C, H, N.

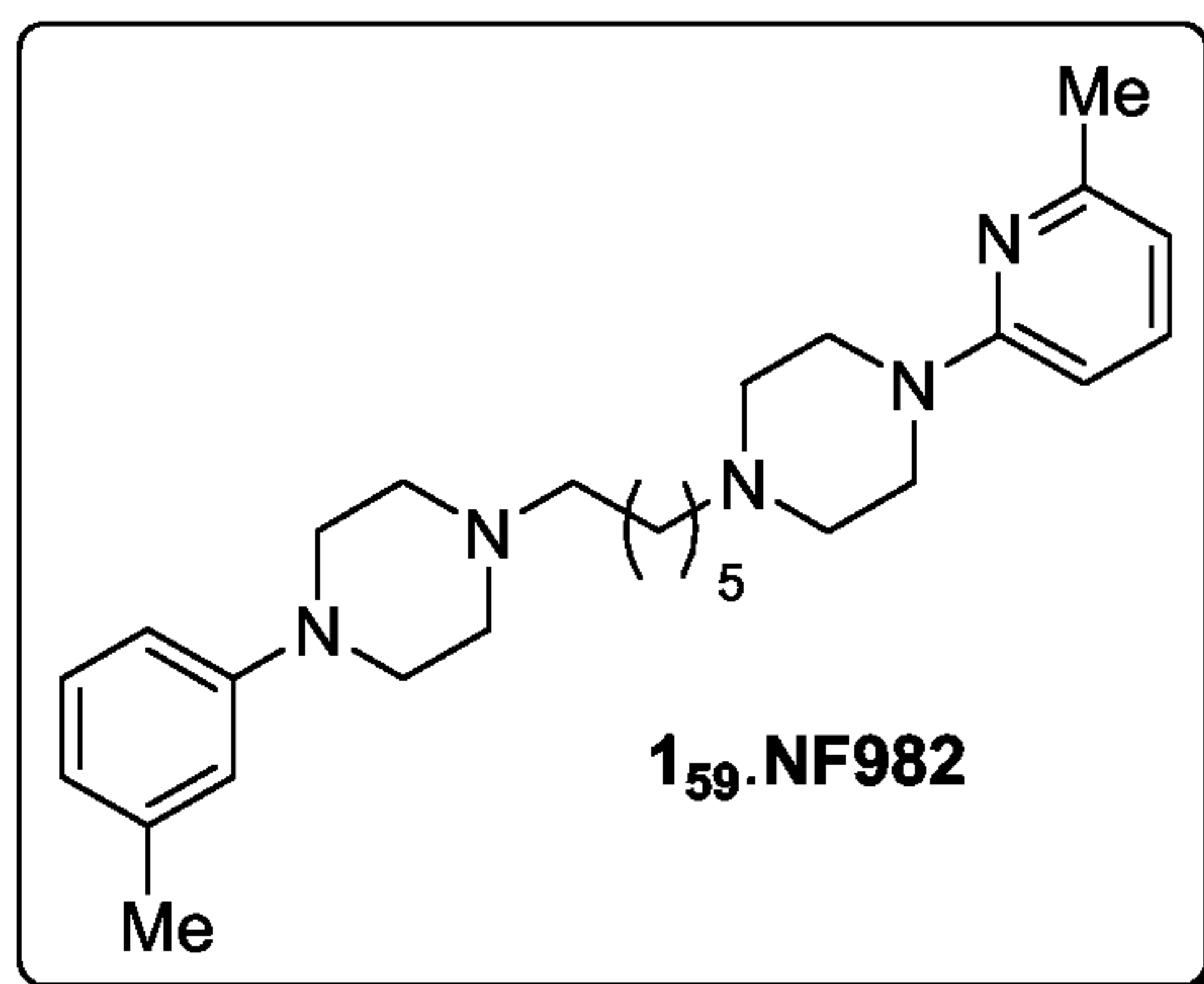
1-Phenyl-4-(6-(4-(pyridin-2-yl)piperazin-1-yl)hexyl)piperazine (Compound 1-58)



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Starting from **42₂** and 1-(pyridin-2-yl)piperazine, the title compound was prepared following the procedure described to obtain **1₅₇**. Compound **1₅₈** was obtained as yellow oil (60% yield): ^1H NMR, 400MHz, ($CDCl_3$) δ 1.39 (m, 4H), 1.58 (m, 4H), 2.43 (m, 4H), 2.64 (m, 8H), 3.24 (m, 8H), 6.88 (m, 1H), 6.96 (m, 4H), 7.28 (m, 4H). ESI-MS
 20 m/z 430 $[M+Na^+]$, 408 $[M+H^+]$ (100). Anal ($C_{25}H_{37}N_5$) C, H, N.

1-(6-Methylpyridin-2-yl)-4-(6-(4-*m*-tolylpiperazin-1-yl)hexyl)piperazine (Compound 1-59)



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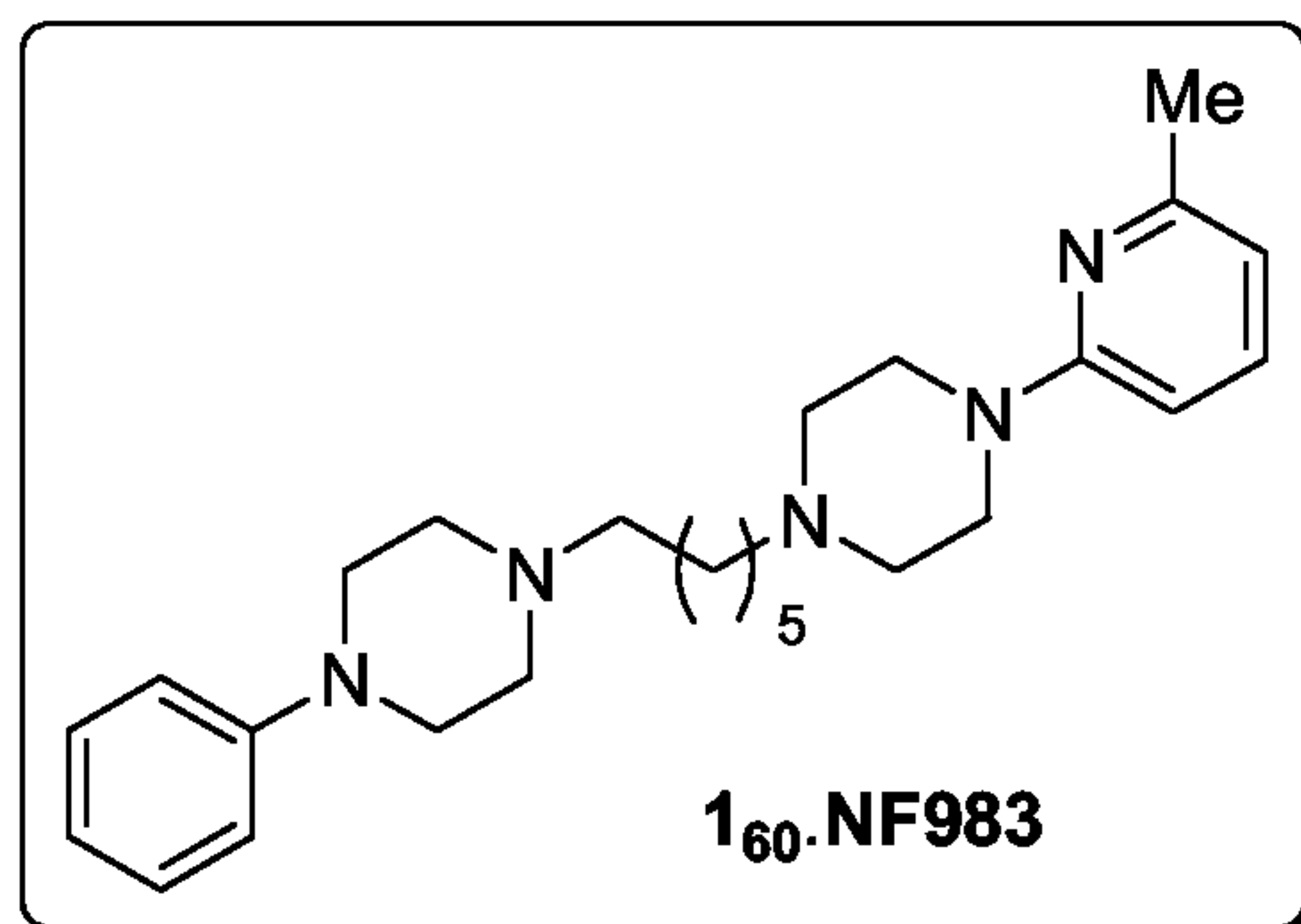
Starting from **42₃** and 1-(6-methylpyridin-2-yl)piperazine, the title compound was prepared following the procedure described to obtain **1₅₇**. Compound **1₅₉** was

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obtained as yellow oil (63% yield): ^1H NMR, 400MHz, (CDCl_3) δ 1.39 (m, 4H), 1.58 (m, 4H), 2.33 (s, 3H), 2.40 (m, 7H), 2.59 (m, 8H), 3.22 (m, 4H), 3.56 (m, 4H), 6.47 (m, 2H), 6.69 (m, 1H), 6.76 (m, 2H), 7.16 (m, 1H), 7.38 (m, 1H). ESI-MS m/z 458 [$\text{M}+\text{Na}^+$], 436 [$\text{M}+\text{H}^+$] (100). Anal ($\text{C}_{27}\text{H}_{41}\text{N}_5$) C, H, N.

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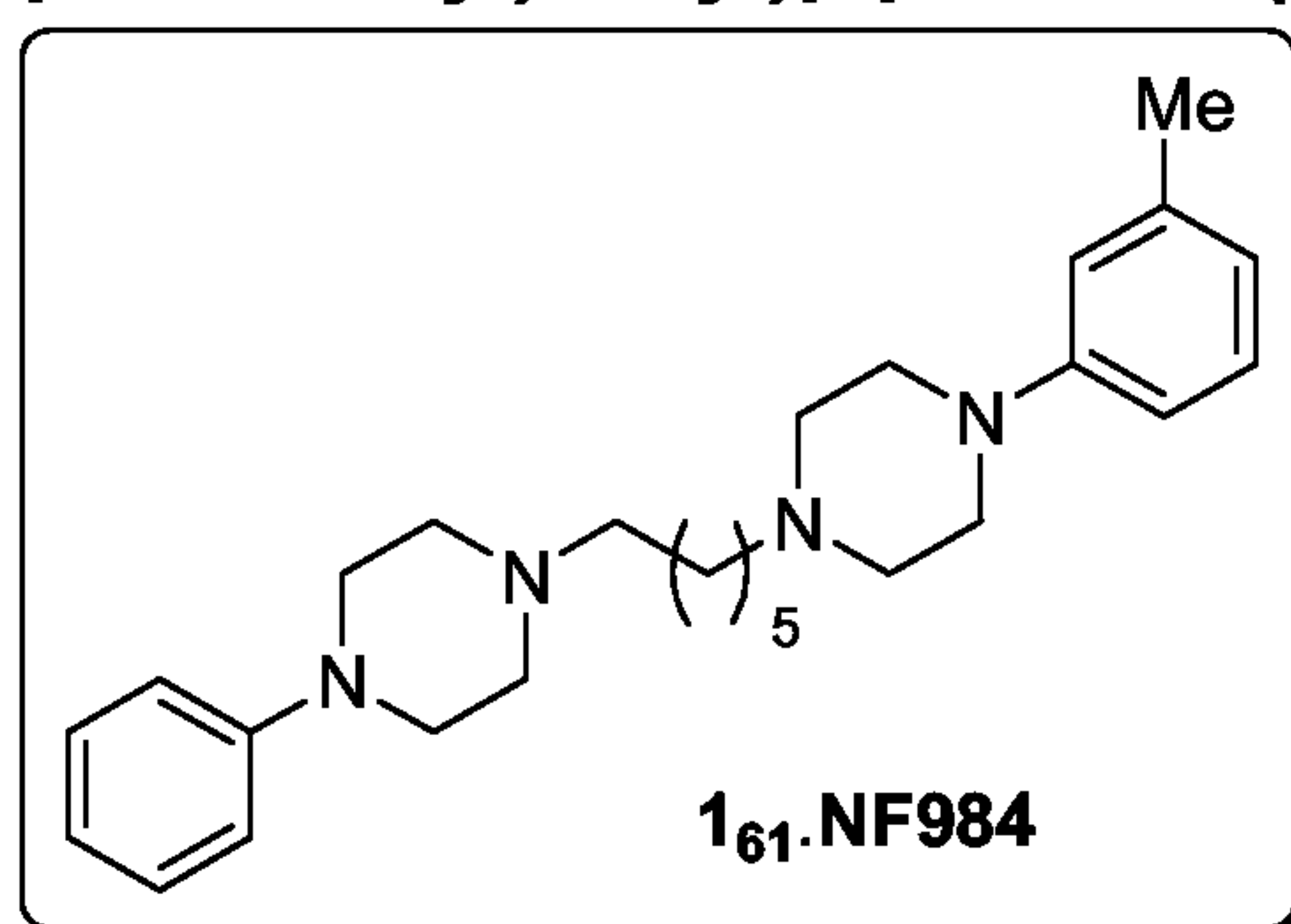
1-(6-Methylpyridin-2-yl)-4-(6-(4-phenylpiperazin-1-yl)hexyl)piperazine (Compound 1-60)



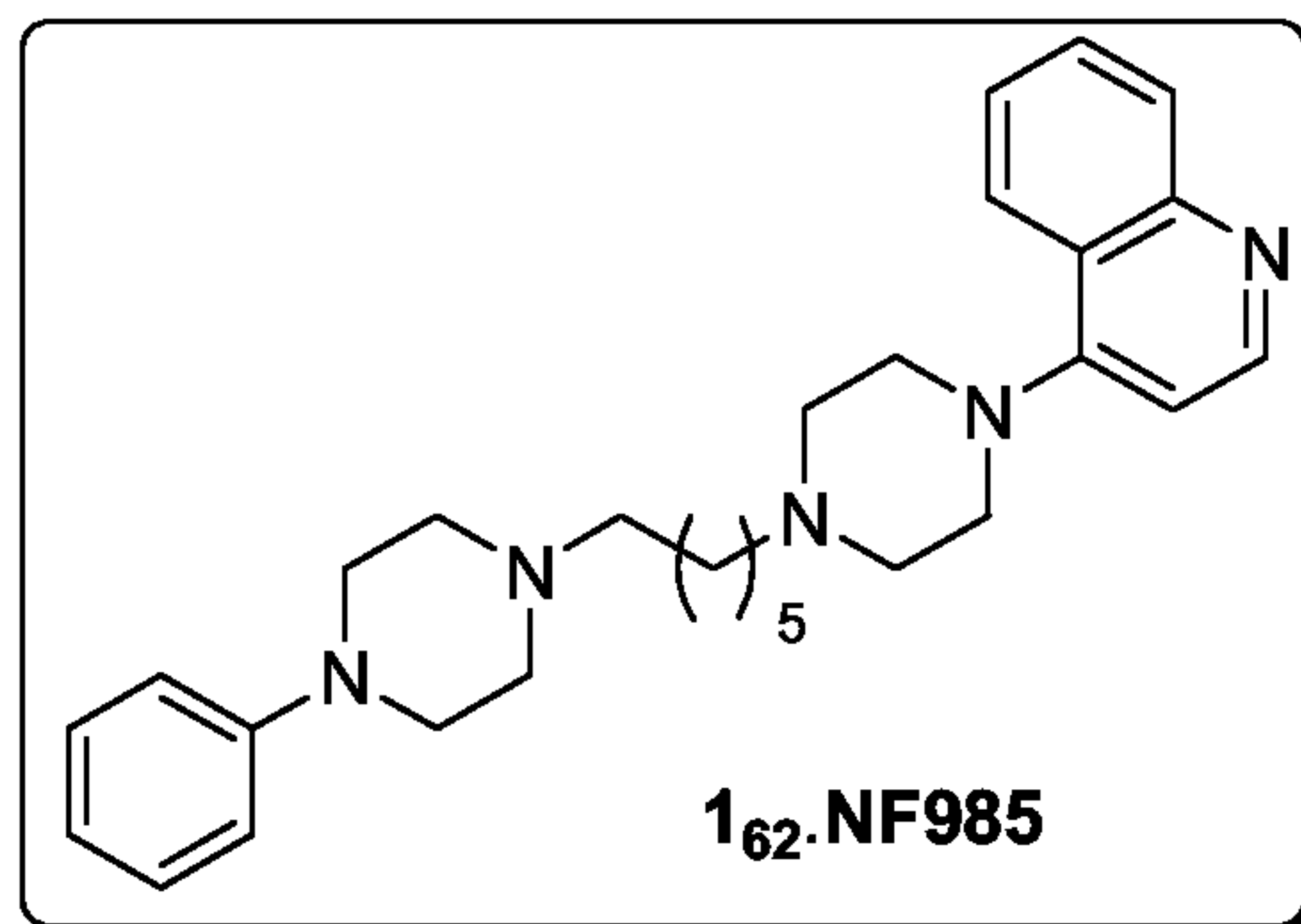
Starting from **42₂** and 1-(6-methylpyridin-2-yl)piperazine, the title compound was prepared following the procedure described to obtain **1₅₇**. Compound **1₆₀** was obtained as yellow oil (60% yield): ^1H NMR, 400MHz, (CDCl_3) δ 1.39 (m, 4H), 1.58 (m, 4H), 2.41 (m, 7H), 3.23 (m, 4H), 3.58 (m, 4H), 6.47 (m, 2H), 6.87 (m, 1H), 6.95 (m, 2H), 7.28 (m, 2H), 7.38 (m, 1H). ESI-MS m/z 422 [$\text{M}+\text{H}^+$] (100). Anal ($\text{C}_{26}\text{H}_{39}\text{N}_5$) C, H, N.

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1-Phenyl-4-(6-(4-*m*-tolylpiperazin-1-yl)hexyl)piperazine (Compound 1-61)



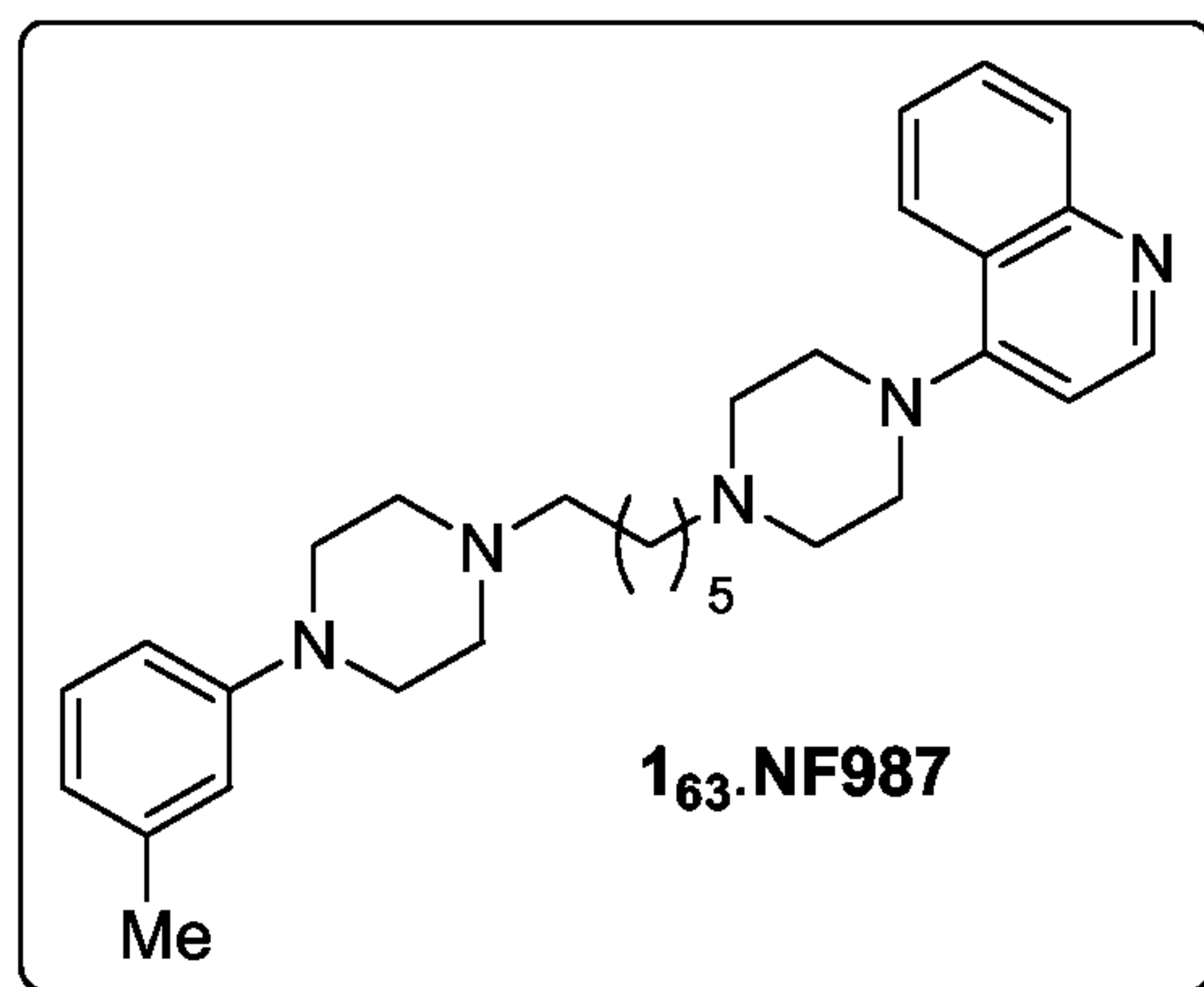
Starting from **42₂** and 4-(3-methylphenyl)piperazine, the title compound was prepared following the procedure described to obtain **1₅₇**. Compound **1₆₁** was obtained as yellow oil (70% yield): ^1H NMR, 400MHz, (CDCl_3) δ 1.39 (m, 4H), 1.57 (m, 4H), 2.34 (s, 3H), 2.42 (m, 4H), 2.63 (m, 8H), 3.23 (m, 8H), 6.73 (m, 1H), 6.78 (m, 2H), 6.88 (m, 1H), 6.96 (m, 2H), 7.18 (m, 1H), 7.29 (m, 2H). ESI-MS m/z 435 [$\text{M}+\text{Na}^+$], 413 [$\text{M}+\text{H}^+$] (100). Anal ($\text{C}_{27}\text{H}_{32}\text{N}_4$) C, H, N.

4-(4-(6-(4-Phenylpiperazin-1-yl)hexyl)piperazin-1-yl)quinoline (Compound 1-62)

tert-Butyl-4-(quinolin-4-yl)piperazine-1-carboxylate (3₆). Starting from 4-bromoquinoline, the title compound was prepared following the procedure described to obtain 3₂. Compound 3₆ was obtained as yellow oil: ¹H NMR, 200MHz, (CDCl₃) δ 1.38 (s, 9H), 2.98 (m, 4H), 3.56 (m, 4H), 6.62 (m, 1H), 7.54 (m, 1H), 7.72 (m, 1H), 7.85 (m, 1H), 7.93 (m, 1H), 8.57 (m, 1H). ESI-MS *m/z* 336 [M+Na⁺], 314 [M+H⁺] (100). Anal (C₁₈H₂₃N₃O₂) C, H, N.

4-(Piperazin-1-yl)quinoline (4₅). Starting from 3₆, the title compound was prepared following the procedure described to obtain 4₁.

4-(4-(6-(4-Phenylpiperazin-1-yl)hexyl)piperazin-1-yl)quinoline (Compound 1-62). Starting from 4₂ and 4₅, the title compound was prepared following the procedure described to obtain 1₅₇. Compound 1₆₂ was obtained as yellow oil (65% yield): ¹H NMR, 400MHz, (CDCl₃) δ 1.40 (m, 4H), 1.65 (m, 8H), 2.46 (m, 4H), 2.68 (m, 8H), 3.26 (m, 8H), 6.90 (m, 4H), 7.27 (m, 2H), 7.49 (m, 1H), 7.66 (m, 1H), 8.28 (m, 2H), 8.74 (m, 1H). ESI-MS *m/z* 480 [M+Na⁺], 458 [M+H⁺] (100). Anal (C₂₉H₃₉N₅) C, H, N.

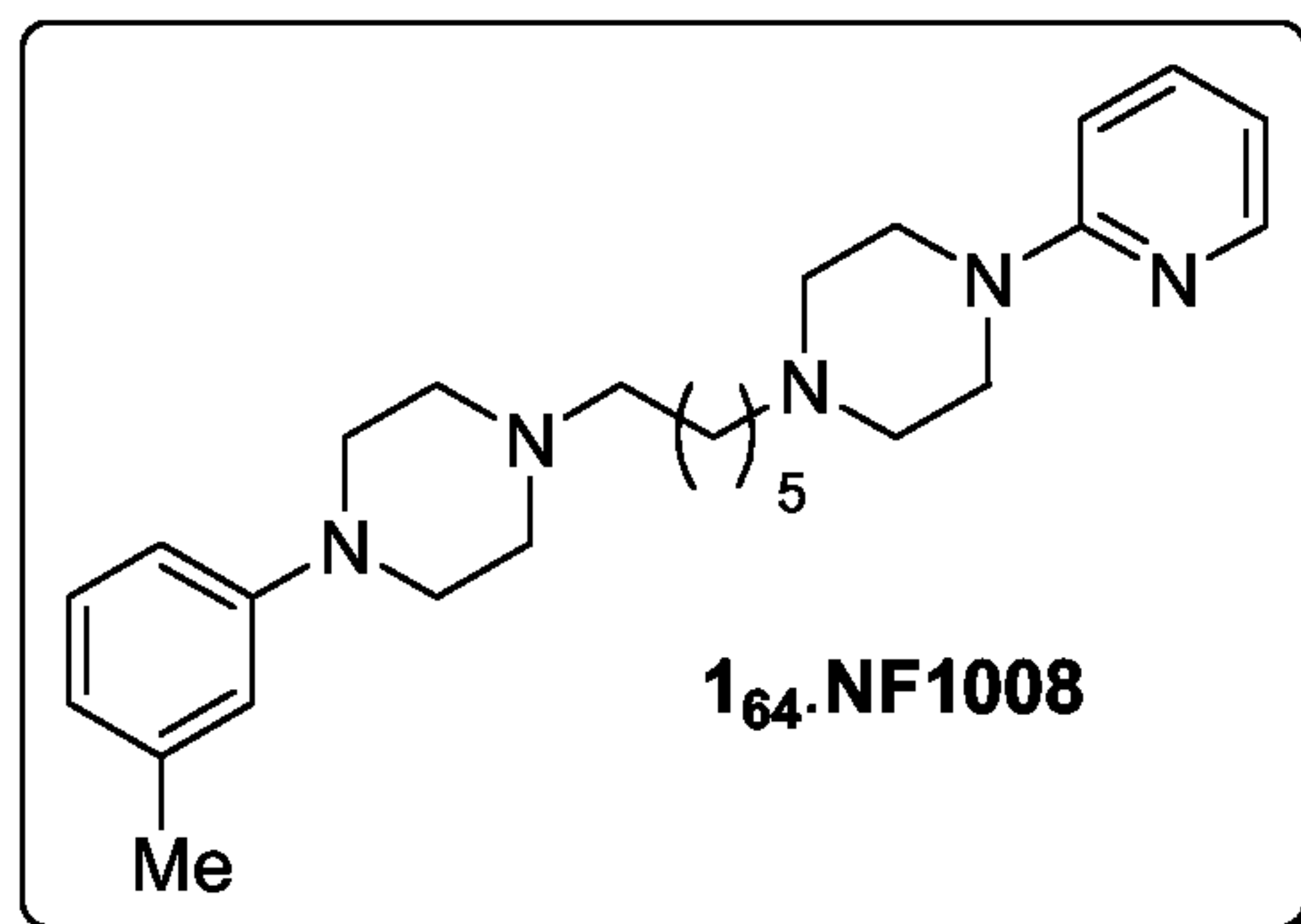
4-(4-(6-(4-*m*-Tolylpiperazin-1-yl)hexyl)piperazin-1-yl)quinoline (Compound 1-63)

Starting from 4₂ and 4₅, the title compound was prepared following the procedure described to obtain 1₅₇. Compound 1₆₃ was obtained as yellow oil (70% yield): ¹H NMR, 400MHz, (CDCl₃) δ 1.33 (m, 4H), 1.59 (m, 4H), 2.32 (s, 3H), 2.47 (m, 4H), 2.63 (m, 4H), 2.72 (m, 4H), 3.23 (m, 8H), 6.72 (m, 3H), 6.85 (m, 1H), 7.15 (m,

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1H), 7.49 (m, 1H), 7.66 (m, 1H), 8.04 (m, 2H), 8.73 (m, 1H). ESI-MS m/z 494 $[M+Na^+]$, 472 $[M+H^+]$ (100). Anal ($C_{30}H_{41}N_5$) C, H, N.

1-(Pyridin-2-yl)-4-(6-(4-*m*-tolylpiperazin-1-yl)hexyl)piperazine (Compound 1-64)

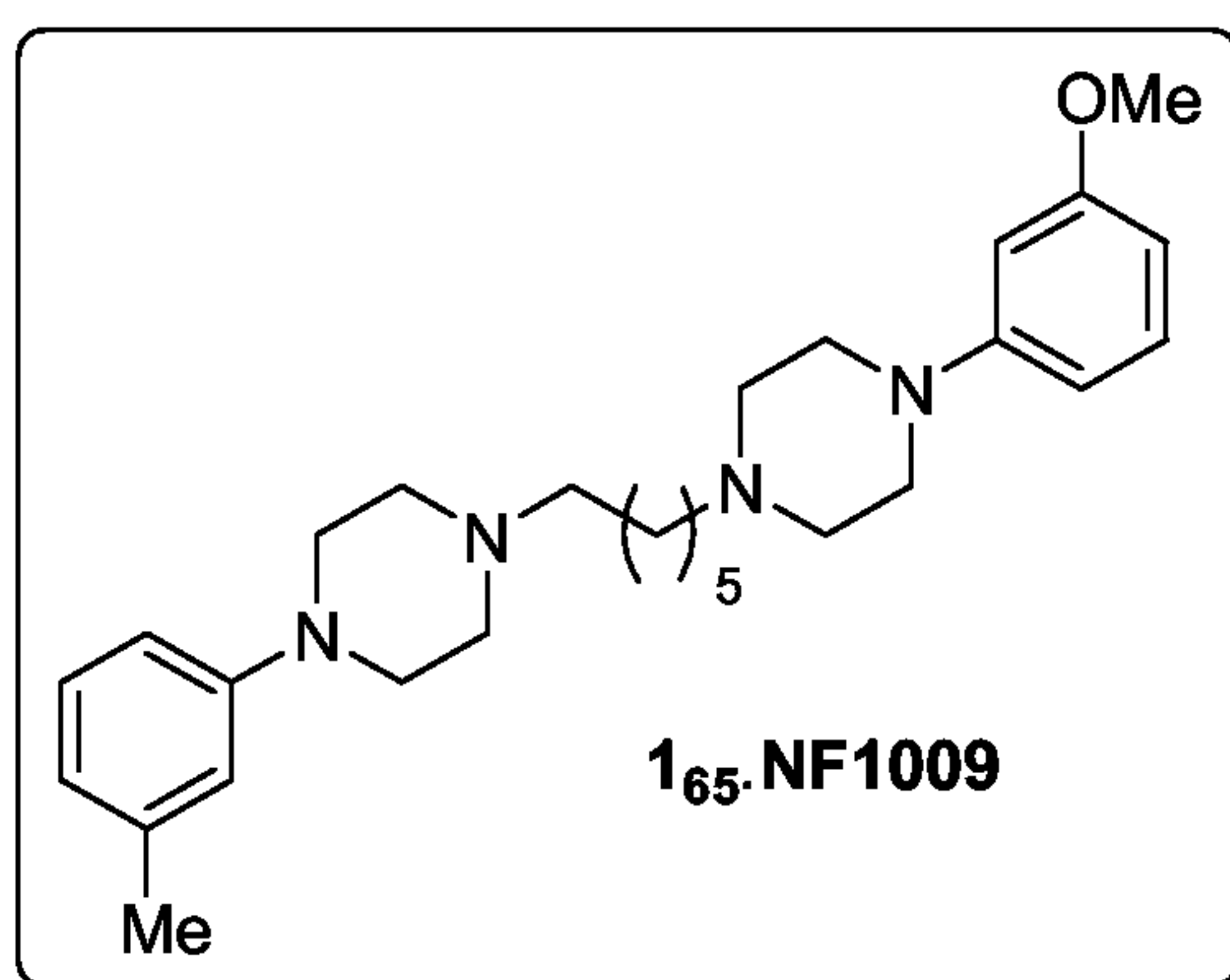


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Starting from **42₃** and 1-(pyridin-2-yl)piperazine the title compound was prepared following the procedure described to obtain **1₅₇**. Compound **1₆₄** was obtained as yellow (68% yield): ^1H NMR, 200MHz, ($CDCl_3$) δ 1.36 (m, 4H), 1.55 (m, 4H), 2.30 (s, 3H), 2.38 (m, 4H), 2.57 (m, 8H), 3.19 (m, 4H), 3.55 (m, 4H), 6.66 (m, 5H), 7.14 (m, 1H), 7.43 (m, 1H), 8.18 (m, 1H). ESI-MS m/z 422 $[M+H^+]$ (100). Anal ($C_{26}H_{39}N_5$) C, H, N.

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1-(3-Methoxyphenyl)-4-(6-(4-*m*-tolylpiperazin-1-yl)hexyl)piperazine (Compound 1-65)



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Starting from **42₃** and 4-(3-methoxyphenyl)piperazine, the title compound was prepared following the procedure described to obtain **1₅₇**. Compound **1₆₅** was obtained as yellow (80% yield): ^1H NMR, 200MHz, ($CDCl_3$) δ 1.37 (m, 4H), 1.55 (m, 4H), 2.31 (s, 3H), 2.39 (m, 4H), 2.60 (m, 8H), 3.20 (m, 8H), 3.78 (s, 3H), 6.43 (m, 2H), 6.53 (m, 2H), 6.71 (m, 2H), 7.15 (m, 2H), ESI-MS m/z 451 $[M+H^+]$ (100). Anal ($C_{28}H_{42}N_4O$) C, H, N.

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Biological Activity

In vitro Binding Studies

This example demonstrates the affinity of the compounds of the invention for the dopamine and serotonin receptor subtypes. These binding assays were carried out according to the procedure of *Campiani et al.*; J. Med. Chem. 2003 **46** 3822-3839.

Male CRL:CD(SD)BR-COBS rats (Charles River, Italy) were killed by decapitation; their brains were rapidly dissected into the various areas (striatum for D₁ and D₂ receptors, olfactory tubercle for D₃ receptors and cortex for 5-HT₂ receptors) and stored at -80°C until assay. Tissues were homogenized in about 50 volumes of ice-cold Tris HCl, 50 mM, pH 7.4 (for D₁, D₂ and 5-HT₂ receptors), or 50 mM Hepes Na, pH 7.5 (for D₃ receptors) using an Ultra-Turrax TP-1810 homogenizer (2x20 s), and centrifuged at 48000 g for 10 minutes (Beckman Avanti J-25 centrifuge). Each pellet was resuspended in the same volume of fresh buffer, incubated at 37°C for 10 minutes, and centrifuged again at 48000 g for 10 minutes. The pellet was then washed once by resuspension in fresh buffer and centrifuged as before. The resulting pellets were resuspended just before the binding assay in the appropriate incubation buffer (50 mM Tris HCl, pH 7.4, containing 10µM pargyline, 0.1% ascorbic acid, 120 mM NaCl, 5mM KCl, 2mM CaCl₂, 1mM MgCl₂ for D₁ and D₂ receptors; 50 mM Hepes Na, pH 7.5, containing 1mM EDTA, 0.005% ascorbic acid, 0.1% albumin, 200nM eliprodil for D₃ receptors and 50 mM Tris HCl, pH 7.7 for 5-HT₂ receptors).

[³H]-SCH 23390 (specific activity, 71.1 Ci/mmol; NEN), a reference substance for determination of binding to D₁ receptors, was assayed in a final incubation volume of 0.5 mL, consisting of 0.25 mL of membrane suspension (2 mg of tissue/sample), 0.25 mL of [³H]ligand (0.4 nM), and 10 µL of displacing agent or solvent. Non-specific binding was obtained in the presence of 10 µM (-)-cis-flupentixol.

[³H]-Spiperone (specific activity, 16.5 Ci/mmol; NEN), a reference substance for determination of binding to D₂ receptors, was assayed in a final incubation volume of 1 mL, consisting of 0.5 mL of membrane suspension (1 mg of tissue/sample), 0.5 mL of [³H]-ligand (0.2 nM), and 20 µL of displacing agent or solvent. Non-specific binding was obtained in the presence of 100 µM (-)-sulpiride.

[³H]-7-OH-DPAT (specific activity, 159 Ci/mmol; Amersham), a reference substance for determination of binding to D₃ receptors, was assayed in a final incubation volume of 1 mL, consisting of 0.5 mL of membrane suspension (10 g of prot./sample of rat cloned dopamine receptor D3 in Sf9 cells (Signal Screen)), 0.5 mL of [³H]-ligand (0.7 nM), and 20 µL of displacing agent or solvent. Non-specific binding was obtained in the presence of 1 µM dopamine.

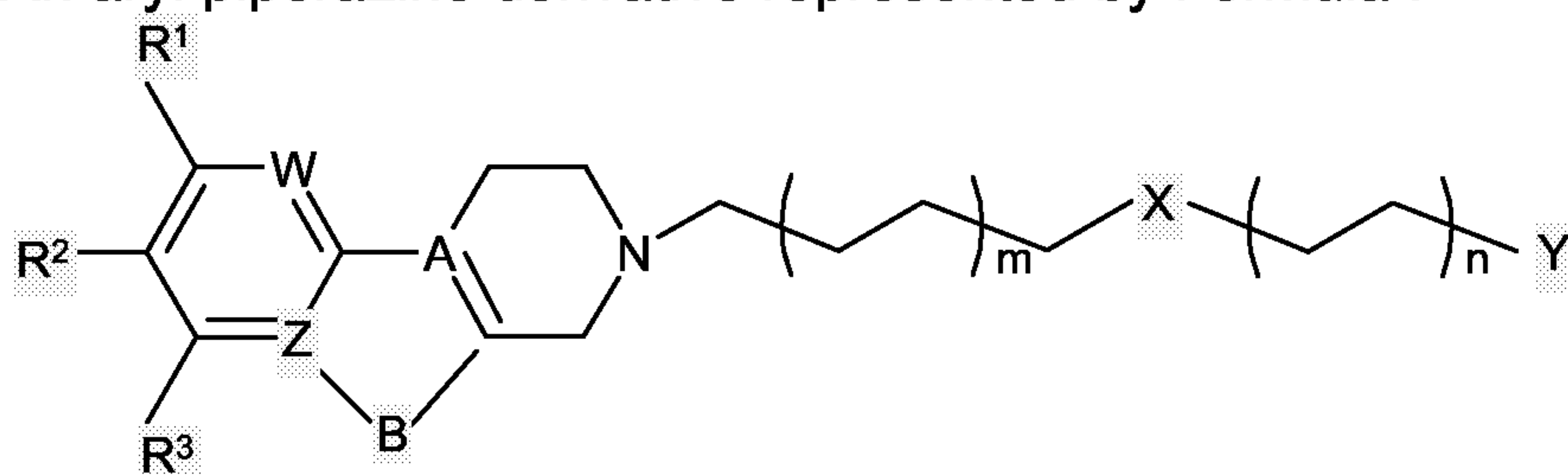
[³H]-Ketanserin (specific activity, 63.3 Ci/mmol; Amersham), a reference substance for determination of binding to 5-HT₂ receptors, was assayed in a final

incubation volume of 1 mL, consisting of 0.5 mL of membrane suspension (5 mg of tissue/sample), 0.5 mL of [^{3} H]-ligand (0.7 nM), and 20 μ L of displacing agent or solvent. Non-specific binding was obtained in the presence of 1 μ M methysergide.

Incubations (15 minutes at 37°C for D₁, D₂ and 5-HT₂ receptors; 60 minutes
5 at 25°C for D₃ receptors) were stopped by rapid filtration under vacuum through GF/B (for D₁, D₂ and 5-HT₂ receptors) or GF/C (for D₃ receptors) filters, which were then washed with 12 mL (4x3 times) of ice-cold buffer (50 mM Tris HCl, pH 7.7) using a Brandel M-48R cell harvester. The radioactivity trapped on the filters was counted in 4
10 mL of Ultima Gold MV (Packard) in a LKB 1214 rack beta liquid scintillation spectrometer with a counting efficiency of 50%.

CLAIMS:

1. An aryl piperazine derivative represented by Formula I



(I)

5 an enantiomer thereof or a mixture of its enantiomers, or a pharmaceutically acceptable salt thereof, or an N-oxide thereof, wherein,

R^1 , R^2 and R^3 , independently of one another, represent hydrogen, alkyl, cycloalkyl, cycloalkyl-alkyl, alkenyl, hydroxy, alkoxy, cycloalkoxy, halo, haloalkyl,
10 haloalkoxy, amino, nitro cyano and/or carboxy;

--- represents an optional double bond;

if --- represents a single bond, then

A represents CH or N;

15 if --- represents a double bond, then

A represents C;

--B-- may be absent or present:

--B-- is absent; and

20 Z represents CH or N; or

--B-- is present and represents a methylene bridge (-CH₂-), an ethylene bridge (=CH-), or a bridge -NH-, attached as indicated in the figure; and

Z represents C (carbon);

25 W represents CH, N or CR⁴, wherein R⁴ represents represent hydrogen, alkyl, cycloalkyl, cycloalkyl-alkyl, alkenyl, hydroxy, alkoxy, cycloalkoxy, halo, haloalkyl, haloalkoxy, amino, nitro or cyano;

m and n, independently of each other, is 0, 1 or 2; and

30

X may be absent or present:

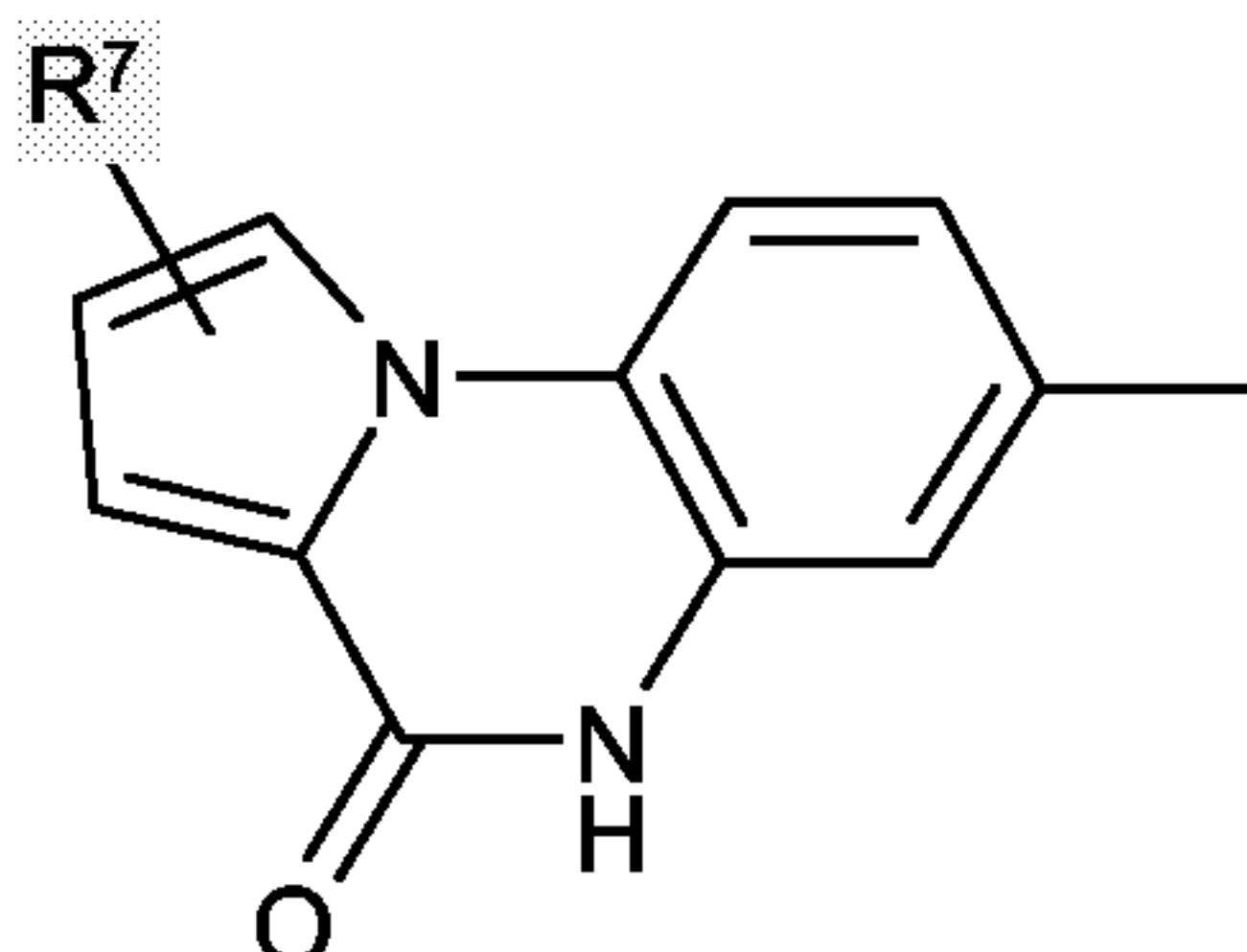
X is present and represents O, S, NR', CO, SO₂, CH₂, CH₂-O, O-CH₂, CH₂-S, S-CH₂, CH₂-NR', CH₂-CO, CH₂-SO₂, NR'-CO, CO-NR', NR'-SO₂, SO₂-NR', CH₂-

CH₂, O-CO, CO-O, O-CH=CH, S-CH=CH, NR'-CH=CH, CO-CH=CH, SO₂-CH=CH, CH₂-O-CH=CH, CH₂-S-CH=CH, CH₂-NR'-CH=CH, CH₂-CO-CH=CH, CONHCH₂CH₂ or CH₂-SO₂-CH=CH, wherein R' represents hydrogen or alkyl; and

Y represents phenyl or an aromatic monocyclic or polycyclic heterocyclic group, which phenyl or heterocyclic group may optionally be substituted one or more times with substituents selected from the group consisting of alkyl, cycloalkyl, cycloalkyl-alkyl, alkenyl, hydroxy, alkoxy, cycloalkoxy, halo, haloalkyl, haloalkoxy, amino, nitro and cyano; or

Y represents a hydrogenated heterocyclic group, which hydrogenated heterocyclic group may optionally be substituted one or more times with substituents selected from the group consisting of alkyl, cycloalkyl, cycloalkyl-alkyl, alkenyl, hydroxy, alkoxy, cycloalkoxy, halo, haloalkyl, haloalkoxy, amino, nitro and cyano; or

Y represents a group of formula III

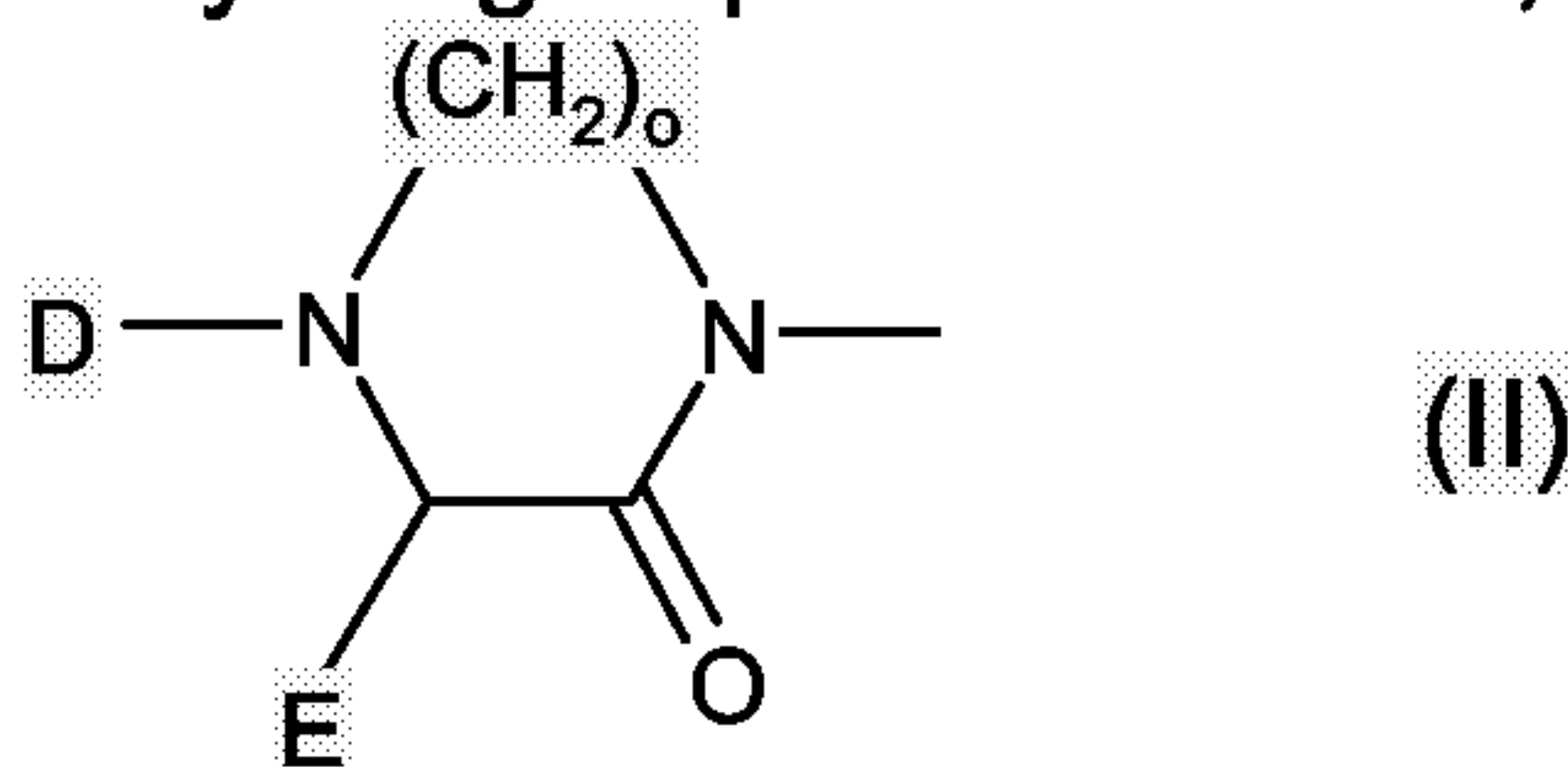


wherein

R⁷ represents hydrogen, alkyl, alkoxy, halo or haloalkyl; or

X is absent; and

Y represents a diazacyclic group of Formula II,



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wherein,

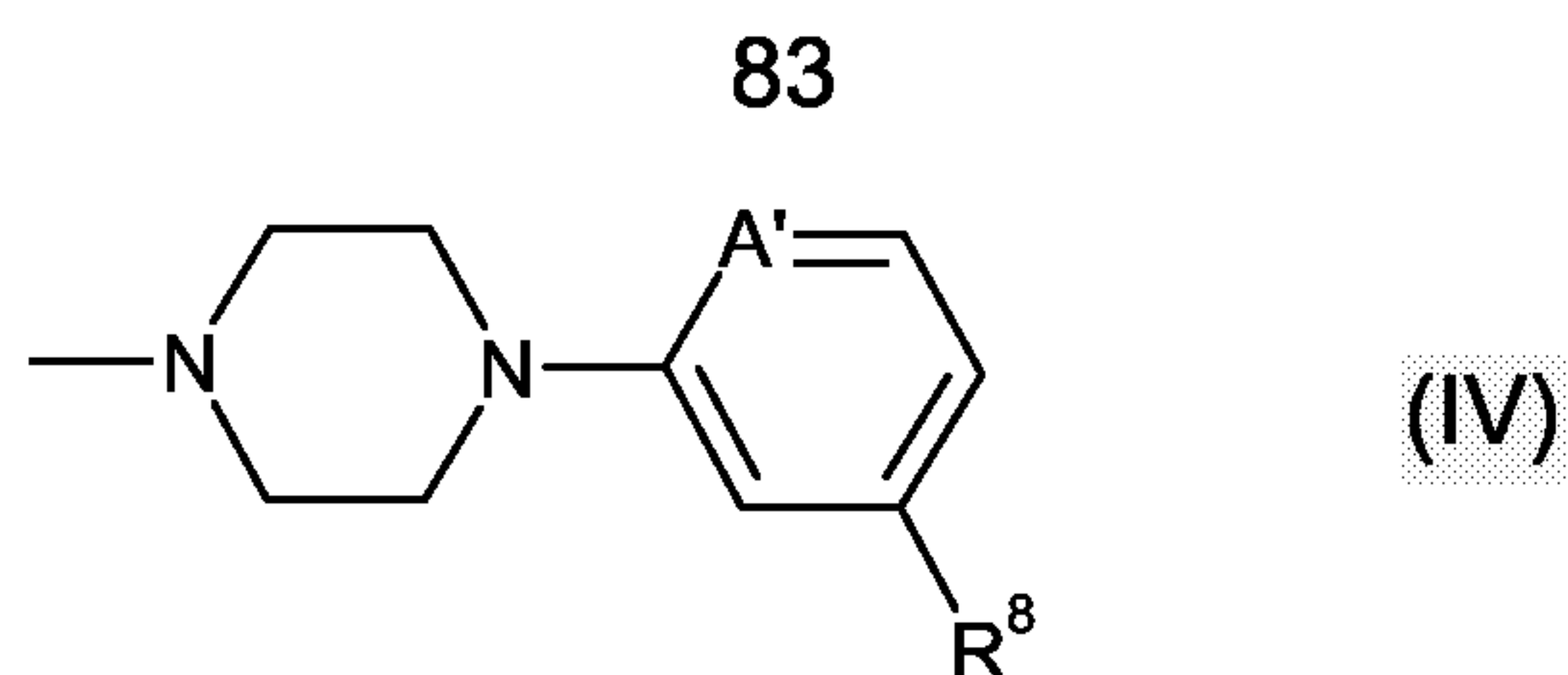
o is 1, 2 or 3;

D represents alkyl, cycloalkyl, cycloalkyl-alkyl, hydroxy, alkoxy, cycloalkoxy, halo, haloalkyl, haloalkoxy, amino, nitro and cyano; and

E represents alkyl, cycloalkyl, cycloalkyl-alkyl, hydroxy, alkoxy, cycloalkoxy, halo, haloalkyl, haloalkoxy, amino, nitro and cyano; or

D and E together with the diazacyclic group form a fused ring system, which fused ring system may optionally be substituted one or more times with substituents selected from the group consisting of alkyl, cycloalkyl, cycloalkyl-alkyl, hydroxy, alkoxy, cycloalkoxy, halo, haloalkyl, haloalkoxy, amino, nitro and cyano;

or Y represents a group of formula IV



wherein A' represents CH or N; and
 R^8 represents hydrogen, alkyl, alkoxy, halo or haloalkyl.

- 5 2. The aryl piperazine derivative of claim 1, wherein
 --- represents a single bond, and
 A represents CH or N.
- 10 3. The aryl piperazine derivative of claim 1, wherein
 == represents a double bond, and
 A represents C (carbon).
- 15 4. The aryl piperazine derivative of any one of claims 1-3, wherein
 W represents CH, N or CR^4 , wherein R^4 represents represent hydrogen,
 alkyl, cycloalkyl, cycloalkyl-alkyl, alkenyl, hydroxy, alkoxy, cycloalkoxy, halo, haloalkyl,
 haloalkoxy, amino, nitro or cyano.
- 20 5. The aryl piperazine derivative of any one of claims 1-4, wherein
 --B-- is absent, and
 Z represents CH or N.
- 25 6. The aryl piperazine derivative of any one of claims 1-5, wherein
 --B-- is present and represents a methylene bridge ($-CH_2-$), an ethylene
 bridge ($=CH-$), or a bridge $-NH-$, attached as indicated in the figure; and
 Z represents C (carbon).
- 30 7. The aryl piperazine derivative of claim 6, wherein
 --B-- is present and represents a methylene bridge ($-CH_2-$), an ethylene
 bridge ($=CH-$), or a bridge $-NH-$, attached as indicated in the figure; and
 Z represents C (carbon); and
 W represents CR^4 , wherein R^4 represents represent hydrogen, alkyl, alkoxy,
 halo, haloalkyl, haloalkoxy, amino, nitro or cyano.
- 35 8. The aryl piperazine derivative of any one of claims 1-7, wherein
 m and n, independently of each other, is 0, 1 or 2.

9. The aryl piperazine derivative of claim 8, wherein
m is 1 or 2; and
n is 0 or 2.

5 10. The aryl piperazine derivative of any one of claims 1-9, wherein
R¹, R² and R³, independently of one another, represent hydrogen, alkyl,
cycloalkyl, cycloalkyl-alkyl, alkenyl, hydroxy, alkoxy, cycloalkoxy, halo, haloalkyl,
haloalkoxy, amino, nitro cyano and/or carboxy;

10 11. The aryl piperazine derivative of claim 10, wherein
R¹ represents alkyl, cycloalkyl, cycloalkyl-alkyl, hydroxy, alkoxy, cycloalkoxy,
halo, haloalkyl, haloalkoxy, amino, nitro, cyano or carboxy; and
R² and R³ represent hydrogen.

15 12. The aryl piperazine derivative of claim 10, wherein
R² represents alkyl, cycloalkyl, cycloalkyl-alkyl, hydroxy, alkoxy, cycloalkoxy,
halo, haloalkyl, haloalkoxy, amino, nitro or cyano; and
R¹ and R³ represent hydrogen.

20 13. The aryl piperazine derivative of any one of claims 1-12, wherein
X is present and represents O, S, NR', CO, SO₂, CH₂, CH₂-O, O-CH₂, CH₂-
S, S-CH₂, CH₂-NR', CH₂-CO, CH₂-SO₂, NR'-CO, CO-NR', CH₂-CH₂, O-CO, CO-O, O-
CH=CH, S-CH=CH, NR'-CH=CH, CO-CH=CH, SO₂-CH=CH, CH₂-O-CH=CH, CH₂-S-
CH=CH, CH₂-NR'-CH=CH, CH₂-CO-CH=CH, CONHCH₂CH₂ or CH₂-SO₂-CH=CH,
25 wherein R' represents hydrogen or alkyl.

14. The aryl piperazine derivative of claim 13, wherein X represents O, CH₂-
O, O-CH₂, CH₂-S, S-CH₂, CH₂-NR', CH₂-CO, CH₂-SO₂, NR'-CO, CO-NR', NR'-SO₂,
SO₂-NR', O-CO, or CH₂-O-CH=CH; wherein R' represents hydrogen or alkyl.

30 15. The aryl piperazine derivative of claim 14, wherein X represents O, CH₂-
O, NR'-CO, CO-NR', NR'-SO₂ or O-CO; wherein R' represents hydrogen or alkyl.

16. The aryl piperazine derivative of any one of claims 13-15, wherein
35 Y represents phenyl or an aromatic monocyclic or polycyclic heterocyclic
group, which phenyl or heterocyclic group may optionally be substituted one or more
times with substituents selected from the group consisting of alkyl, cycloalkyl,

cycloalkyl-alkyl, alkenyl, hydroxy, alkoxy, cycloalkoxy, halo, haloalkyl, haloalkoxy, amino, nitro and cyano; or

Y represents a hydrogenated heterocyclic group, which hydrogenated heterocyclic group may optionally be substituted one or more times with substituents
5 selected from the group consisting of alkyl, cycloalkyl, cycloalkyl-alkyl, alkenyl, hydroxy, alkoxy, cycloalkoxy, halo, haloalkyl, haloalkoxy, amino, nitro and cyano.

17. The aryl piperazine derivative of claim 16, wherein Y represents phenyl, which phenyl group may optionally be substituted one or more times with substituents
10 selected from the group consisting of alkyl, cycloalkyl, cycloalkyl-alkyl, hydroxy, alkoxy, cycloalkoxy, halo, haloalkyl, haloalkoxy, amino, nitro and cyano.

18. The aryl piperazine derivative of any one of claims 13-15, wherein Y represents an aromatic monocyclic heterocyclic group selected from furanyl, thienyl, pyrrolyl, oxazolyl, imidazolyl, pyridyl, pyridazinyl and pyrimidinyl, which aromatic
15 monocyclic heterocyclic group may optionally be substituted one or more times with substituents selected from the group consisting of alkyl, cycloalkyl, cycloalkyl-alkyl, alkenyl, hydroxy, alkoxy, cycloalkoxy, halo, haloalkyl, haloalkoxy, amino, nitro and cyano.

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19. The aryl piperazine derivative of claim 18, wherein Y represents furanyl, thienyl or pyridyl, which aromatic monocyclic heterocyclic group may optionally be substituted one or two times with substituents selected from the group consisting of alkyl, alkoxy, chloro, trifluoromethyl and trifluoromethoxy.

25

20. The aryl piperazine derivative of any one of claims 13-15, wherein Y represents an aromatic bicyclic heterocyclic group selected from indolyl, isoindolyl, benzo[b]furanyl, benzo[b]thienyl, benzimidazolyl, benzthiazolyl, quinolinyl and isoquinolinyl, which aromatic bicyclic heterocyclic group may optionally be substituted
30 one or two times with substituents selected from the group consisting of alkyl, cycloalkyl, cycloalkyl-alkyl, hydroxy, alkoxy, cycloalkoxy, halo, haloalkyl, haloalkoxy, amino, nitro and cyano.

21. The aryl piperazine derivative of claim 20, wherein Y represents indolyl, in particular indol-2-yl or indol-3-yl; benzo[b]furanyl, in particular benzo[b]furan-2-yl or benzo[b]furan-3-yl; benzo[b]thienyl, in particular benzo[b]thien-2-yl or benzo[b]thien-3-yl; quinolinyl in particular quinolin-2-yl, quinolin-3-yl or quinolin-4-yl; or isoquinolinyl, in particular isoquinolin-1-yl, isoquinolin-3-yl, or isoquinolin-4-yl; which aromatic bicyclic
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heterocyclic group may optionally be substituted one or two times with substituents selected from alkyl, cycloalkyl, cycloalkyl-alkyl, hydroxy, alkoxy, cycloalkoxy, halo, haloalkyl, haloalkoxy, amino, nitro and cyano.

5 22. The aryl piperazine derivative of claim 21, wherein Y represents indolyl, in particular indol-2-yl or indol-3-yl; benzo[b]furanyl, in particular benzo[b]furan-2-yl or benzo[b]furan-3-yl; quinolinyl, in particular quinolin-2-yl, quinolin-3-yl or quinolin-4-yl; or isoquinolinyl, in particular isoquinolin-1-yl, isoquinolin-3-yl, or isoquinolin-4-yl; which
10 substituents selected from alkyl, hydroxy, alkoxy, chloro, trifluoromethyl, trifluoromethoxy, amino, nitro and cyano.

 23. The aryl piperazine derivative of claim 22, wherein Y represents indol-2-yl, benzo[b]furan-2-yl or isoquinolin-3-yl; which benzo[b]furanyl or isoquinolinyl may
15 optionally be substituted one or two times with substituents selected from alkyl, hydroxy, alkoxy, chloro, trifluoromethyl, trifluoromethoxy, amino, nitro and cyano.

 24. The aryl piperazine derivative of claim 23, wherein Y represents indolyl, benzo[b]furanyl, or isoquinolinyl.
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 25. The aryl piperazine derivative of any one of claims 13-15, wherein Y represents a hydrogenated heterocyclic group, which hydrogenated heterocyclic group may optionally be substituted one or more times with substituents selected from the group consisting of alkyl, cycloalkyl, cycloalkyl-alkyl, alkenyl, hydroxy, alkoxy, cycloalkoxy, halo, haloalkyl, haloalkoxy, amino, nitro and cyano.
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 26. The aryl piperazine derivative of claim 25, wherein Y represents tetrahydroquinolinyl or tetrahydroisoquinolinyl, which heterocyclic group may optionally be substituted one or two times with substituents selected from the group consisting of
30 alkyl, cycloalkyl, cycloalkyl-alkyl, alkenyl, hydroxy, alkoxy, cycloalkoxy, halo, haloalkyl, haloalkoxy, amino, nitro and cyano.

 27. The aryl piperazine derivative of claim 26, wherein Y represents tetrahydroquinolinyl or tetrahydroisoquinolinyl.
35

 28. The aryl piperazine derivative of claim 13, wherein
X represents O, CH₂-O, NH-CO, CO-NH, NR'-SO₂ or CO-O; and

Y represents phenyl, methyl-phenyl, pyridyl, indolyl, methyl-indolyl, benzo[b]furanyl, tetrahydroquinoliny, isoquinoliny, or tetrahydroisoquinoliny.

29. The aryl piperazine derivative of claim 28, wherein

X represents O, CH₂-O, NH-CO, CO-NH, NR'-SO₂ or CO-O;

Y represents phenyl, methyl-phenyl, pyridyl, methyl-pyridyl, indolyl, methyl-indolyl, benzo[b]furanyl, tetrahydroquinoliny, isoquinoliny, or tetrahydroisoquinoliny;

R¹ represents alkyl, cycloalkyl, cycloalkyl-alkyl, hydroxy, alkoxy, cycloalkoxy, halo, haloalkyl, haloalkoxy, amino, nitro or cyano; and

R² and R³ represent hydrogen.

30. The aryl piperazine derivative of claim 28, which is *N*-[4-[4-(3-Trifluoromethylphenyl)piperazin-1-yl]butyl]indole-2-carboxamide;

N-[2-(1*H*-Indol-3-yl)ethyl]-3-(4-*m*-tolylpiperazin-1-yl)propanamide;

N-[2-(1*H*-Indol-3-yl)ethyl]-3-[4-(3-methoxyphenyl)piperazin-1-yl]propanamide;

Benzo[b]furan-2-carboxylic acid {4-[4-(3-methoxy-phenyl)-piperazin-1-yl]-butyl}-amide;

N-[4-[4-(3-Cyanophenyl)piperazin-1-yl]butyl]benzo[b]furan-2-carboxamide;

Benzo[b]furan-2-carboxylic acid {4-[4-(3-chloro-phenyl)-piperazin-1-yl]-butyl}-amide;

Benzo[b]furan-2-carboxylic acid {4-[4-(3-carboxy-phenyl)-piperazin-1-yl]-butyl}-amide;

N-[4-[4-(*m*-Tolyl)piperazin-1-yl]butyl]benzo[b]furan-2-carboxamide;

Isoquinoline-3-carboxylic acid {4-[4-(3-cyano-phenyl)-piperazin-1-yl]-butyl}-amide;

N-[4-[4-(3-Chlorophenyl)piperazin-1-yl]butyl]isoquinoline-3-carboxamide;

N-[4-[4-(*m*-Tolyl)piperazin-1-yl]butyl]isoquinoline-3-carboxamide;

N-[4-[4-(3-Methoxyphenyl)piperazin-1-yl]butyl]isoquinoline-3-carboxamide;

3-[5-[4-(3-Chlorophenyl)piperazin-1-yl]pentyloxy]isoquinoline;

3-{5-[4-(3-Methoxy-phenyl)-piperazin-1-yl]-pentyloxy}-isoquinoline;

3-[5-(4-*m*-Tolylpiperazin-1-yl)pentyloxy]isoquinoline;

3-{5-[4-(3-Cyano-phenyl)-piperazin-1-yl]-pentyloxy}-isoquinoline;

N-[4-(1,2,3,4-Tetrahydro-5-methoxy-β-carbolin-2-yl)butyl]isoquinoline-3-carboxamide;

N-[4-(3,4-Dihydro-6-methoxypyrazino[1,2-*a*]indol-2(1*H*)-yl)butyl]isoquinoline-3-carboxamide;

N-[4-[4-(Pyridin-2-yl)piperazin-1-yl]butyl]isoquinoline-3-carboxamide;

1,2,3,4-Tetrahydro-quinoline-2-carboxylic acid [4-(4-phenyl-piperazin-1-yl)-butyl]-amide;

(S)-(-)-N-[4-[4-(*m*-Tolyl)piperazin-1-yl]butyl]-1,2,3,4-tetrahydroisoquinoline-2-carboxamide;

5 (R)-(+)-N-[4-[4-(*m*-Tolyl)piperazin-1-yl]butyl]-1,2,3,4-tetrahydroisoquinoline-2-carboxamide;

1H-Indole-2-carboxylic acid {4-[4-(2,4-dichloro-phenyl)-piperazin-1-yl]-butyl}-amide;

5-Chloro-1H-indole-2-carboxylic acid {4-[4-(2,4-dichloro-phenyl)-piperazin-1-yl]-butyl}-amide;

Isoquinoline-3-carboxylic acid {4-[4-(2,3-dichloro-phenyl)-piperazin-1-yl]-butyl}-amide;

3-{4-[4-(2,3-Dichloro-phenyl)-piperazin-1-yl]-butoxy}-isoquinoline;

3-{5-[4-(2,3-Dichloro-phenyl)-piperazin-1-yl]-pentyloxy}-isoquinoline;

15 4-[4-(2,3-Dichlorophenyl)piperazin-1-yl]butyl 1H-indole-2-carboxylate;

N-(4-(4-(Phenylpiperazin-1-yl)butyl)benzo[b]furan-2-carboxamide;

Benzo[b]furan-2-carboxylic acid {4-[4-(2,3-dimethyl-phenyl)-piperazin-1-yl]-butyl}-amide;

20 N-(4-(4-(3-Methoxyphenyl)piperazin-1-yl)butyl)benzo[b]furan-2-carboxamide;

N-(4-(4-(6-Methylpyridin-2-yl)piperazin-1-yl)butyl)isoquinoline-3-carboxamide;

N-(4-(4-Phenylpiperazin-1-yl)butyl)isoquinoline-3-carboxamide;

25 N-(4-(4-(6-Methylpyridin-2-yl)piperazin-1-yl)butyl)benzo[b]furan-2-carboxamide;

N-(4-(4-Phenylpiperazin-1-yl)butyl)quinoline-2-carboxamide;

N-(4-(4-*m*-Tolylpiperazin-1-yl)butyl)quinoline-2-carboxamide;

N-(4-(4-(3-Methoxyphenyl)piperazin-1-yl)butyl)-1-methyl-1H-indole-2-carboxamide;

30 N-(4-(4-(3-Methoxyphenyl)piperazin-1-yl)butyl)-1H-indole-3-carboxamide;
(S)-1,2,3,4-Tetrahydro-N-(4-(4-phenylpiperazin-1-yl)butyl)quinoline-2-carboxamide;

N-(4-(4-*m*-Tolylpiperazin-1-yl)butyl)picolinamide;

N-(4-(4-(Quinolin-3-yl)piperazin-1-yl)butyl)isoquinoline-3-carboxamide;

35 N-(4-(4-(3-Methoxyphenyl)piperazin-1-yl)butyl)-6-methylpyridine-2-carboxamide;

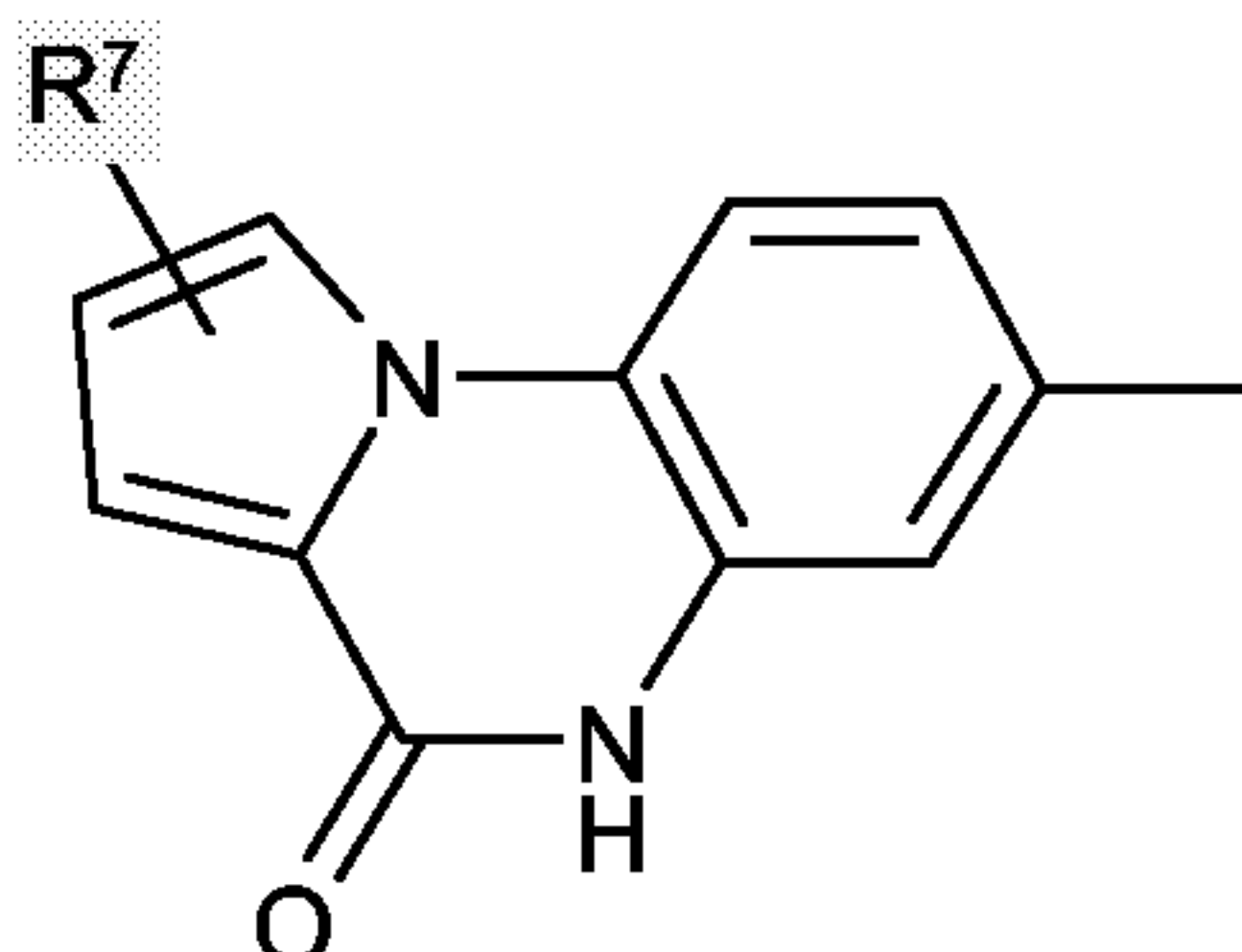
N-(4-(4-(3-Methoxyphenyl)piperazin-1-yl)butyl)quinoline-3-carboxamide;

N-(4-(4-(Pyridin-2-yl)piperazin-1-yl)butyl)quinoline-3-carboxamide;

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N-(4-(4-Phenylpiperazin-1-yl)butyl)picolinamide;
 N-(4-(4-(3-Methoxyphenyl)piperazin-1-yl)butyl)picolinamide;
 N-(4-(4-(3-Methoxyphenyl)piperazin-1-yl)butyl)benzamide;
 N-(4-(4-m-Tolylpiperazin-1-yl)butyl)benzamide;
 5 N-(4-(4-Phenylpiperazin-1-yl)butyl)nicotinamide;
 N-(4-(4-(6-Methylpyridin-2-yl)piperazin-1-yl)butyl)benzamide;
 N-(4-(4-(6-Methoxypyridin-2-yl)piperazin-1-yl)butyl)benzamide;
 N-(4-(4-(6-Methoxypyridin-2-yl)piperazin-1-yl)butyl)picolinamide; or
 N-(4-(4-(6-Methylpyridin-2-yl)piperazin-1-yl)butyl)picolinamide;
 10 or a pharmaceutically acceptable salt thereof.

31. The aryl piperazine derivative of any one of claims 13-15, wherein
 Y represents a group of formula III



15 wherein

R^7 represents hydrogen, alkyl, alkoxy, halo or haloalkyl.

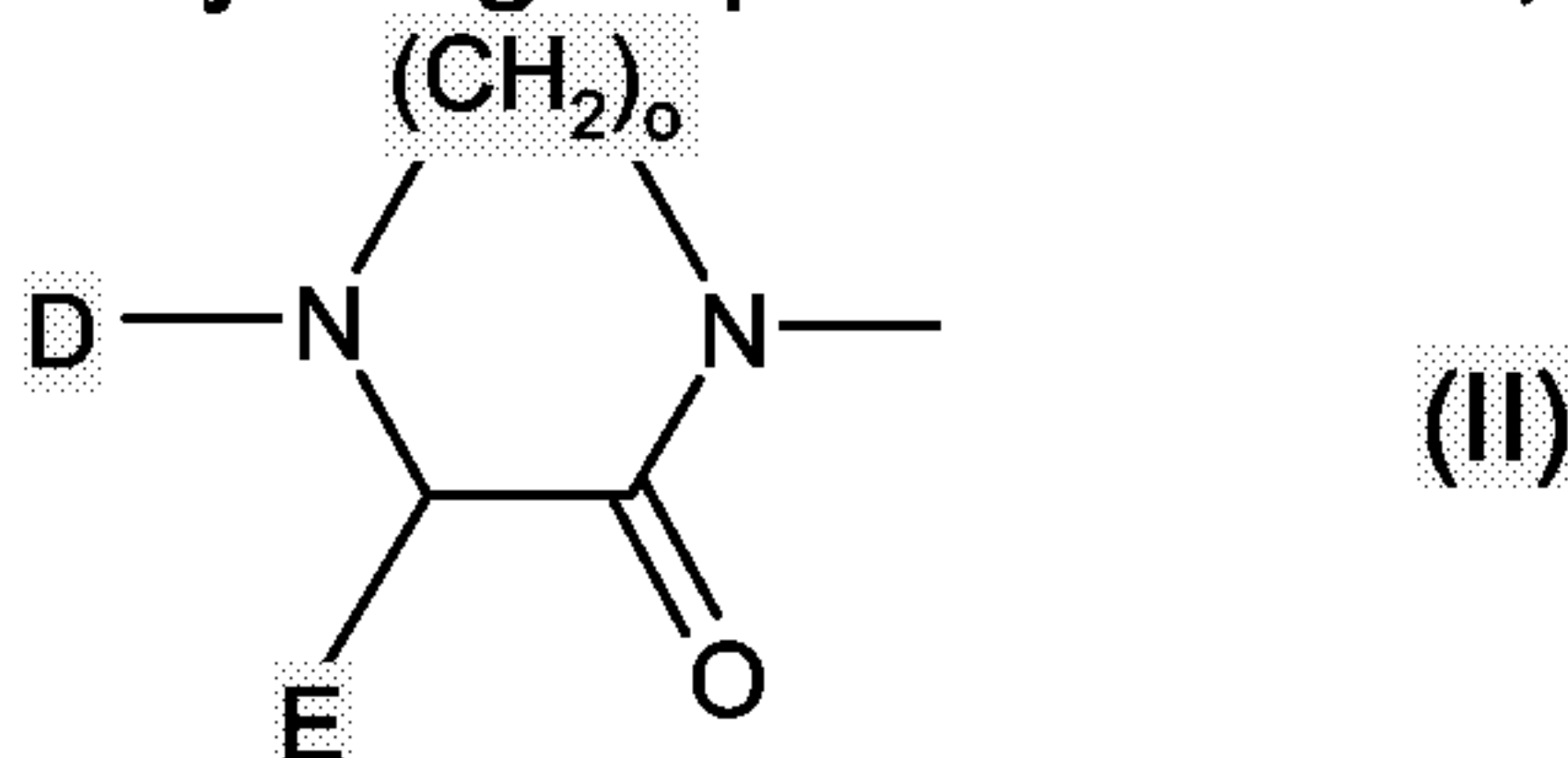
32. The aryl piperazine derivative of claim 31, which is

7-[4-[4-(2,3-Dichloro-phenyl)-piperazin-1-yl]-butoxy]-pyrrolo[1,2-a]quinoxalin-
 20 4(5H)-one; 7-(5-(4-Phenylpiperazin-1-yl)pentyl)pyrrolo[1,2-a]quinoxalin-4(5H)-one;
 or

7-(4-(4-Phenylpiperazin-1-yl)butoxy)pyrrolo[1,2-a]quinoxalin-4(5H)-one;
 or a pharmaceutically acceptable salt thereof.

33. The aryl piperazine derivative of any one of claims 1-12, wherein
 X is absent; and

Y represents a diazacyclic group of Formula II,



wherein,

o is 1, 2 or 3;

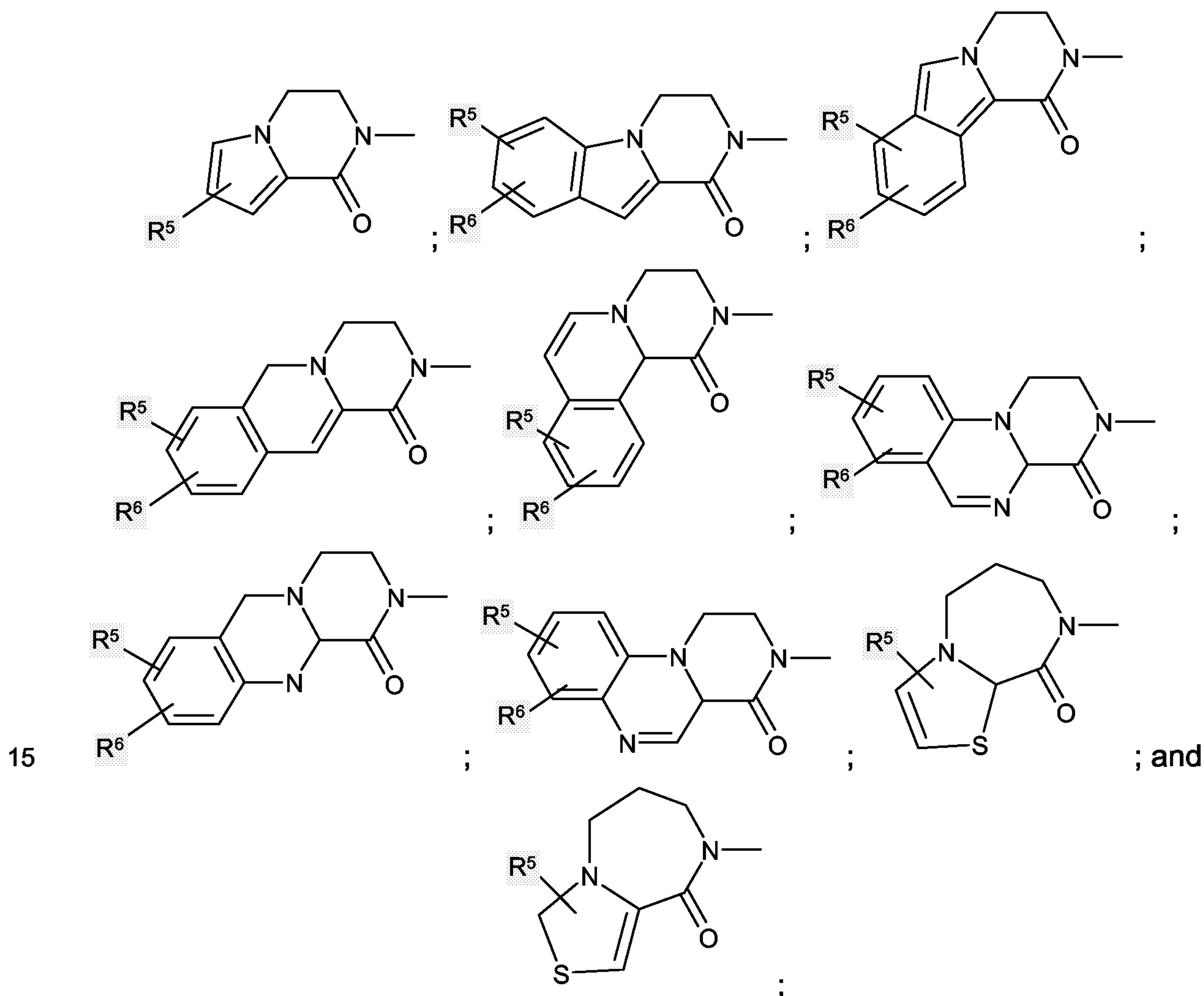
D represents alkyl, cycloalkyl, cycloalkyl-alkyl, hydroxy, alkoxy, cycloalkoxy, halo, haloalkyl, haloalkoxy, amino, nitro and cyano; and

E represents alkyl, cycloalkyl, cycloalkyl-alkyl, hydroxy, alkoxy, cycloalkoxy, halo, haloalkyl, haloalkoxy, amino, nitro and cyano; or

5 D and E together with the diazacyclic group form a fused ring system, which fused ring system may optionally be substituted one or more times with substituents selected from the group consisting of alkyl, cycloalkyl, cycloalkyl-alkyl, hydroxy, alkoxy, cycloalkoxy, halo, haloalkyl, haloalkoxy, amino, nitro and cyano.

10 34. The aryl piperazine derivative of claim 33, wherein

Y represents a bicyclic heterocyclic group (i.e. fused ring system) selected from the following group:

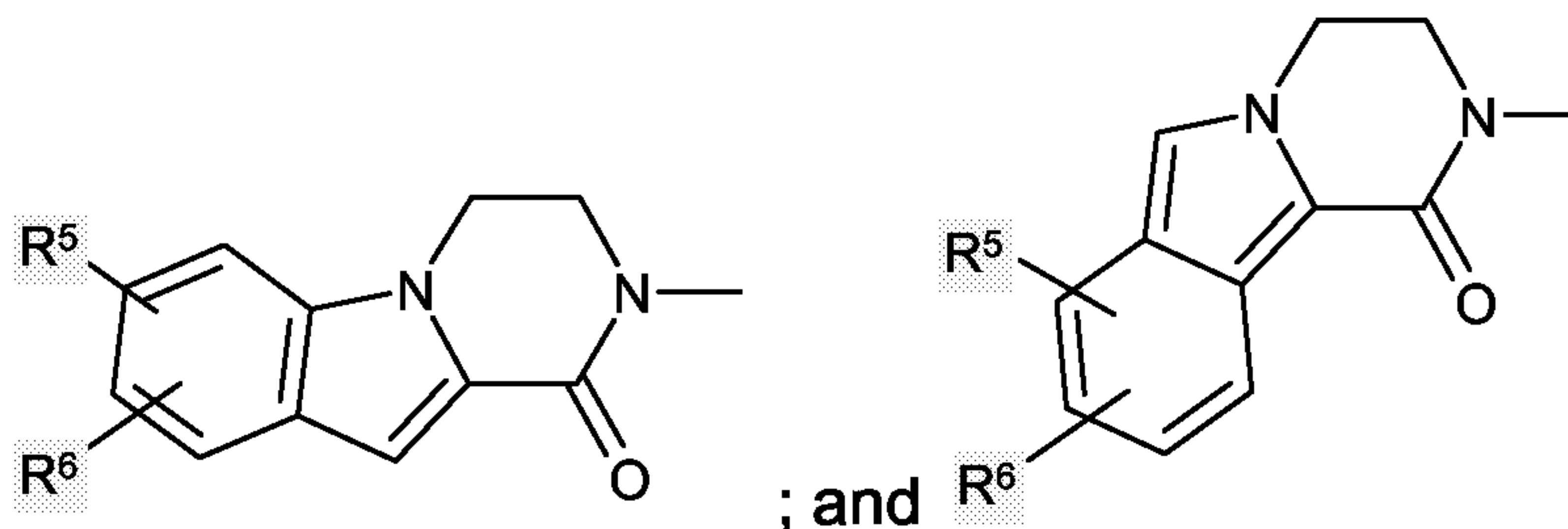


wherein R⁵ and R⁶, independently of each other, represent hydrogen, alkyl, cycloalkyl, cycloalkyl-alkyl, hydroxy, alkoxy, cycloalkoxy, halo, haloalkyl, haloalkoxy, amino, nitro and/or cyano.

35. The aryl piperazine derivative of claim 34, wherein

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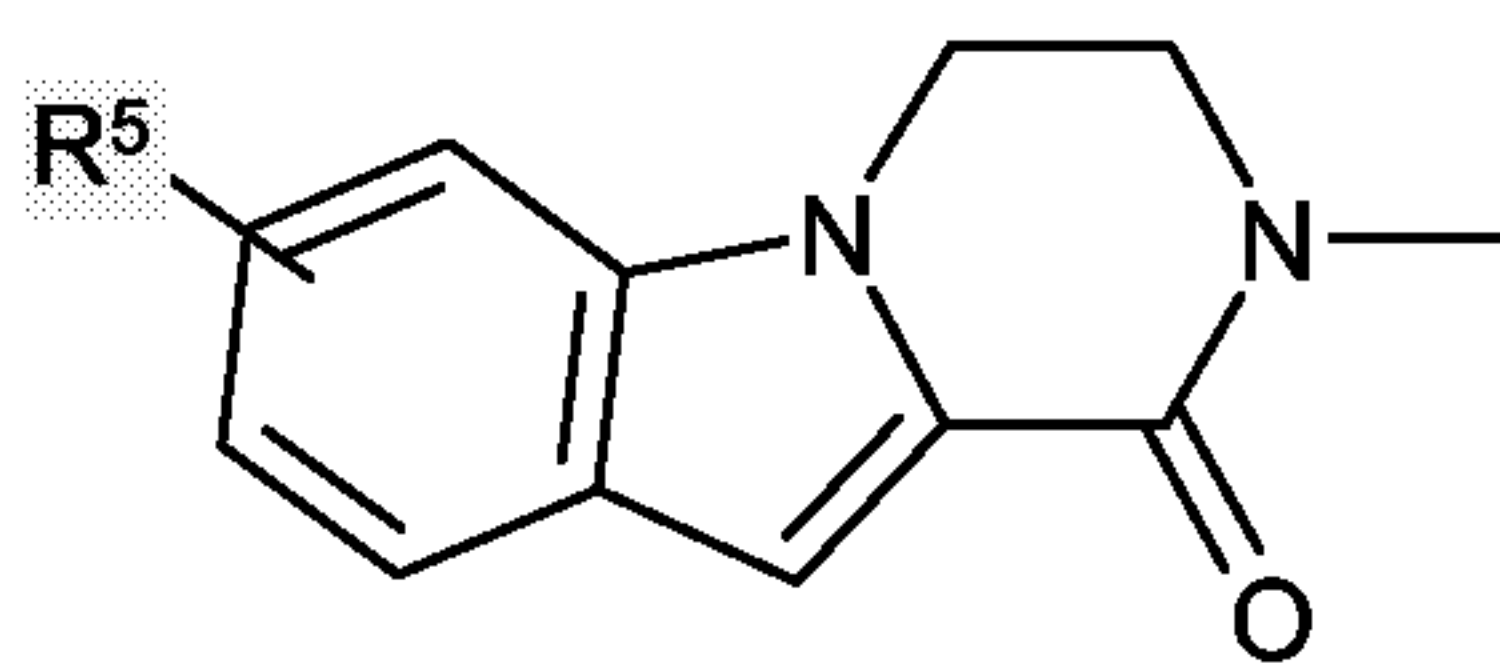
Y represents a bicyclic heterocyclic group selected from



wherein R^5 and R^6 , independently of each other, represent hydrogen, alkyl, cycloalkyl, cycloalkyl-alkyl, hydroxy, alkoxy, cycloalkoxy, halo, haloalkyl, haloalkoxy, amino, nitro and/or cyano.

36. The aryl piperazine derivative of claim 35, wherein

Y represents



; wherein

R^5 represents hydrogen, alkyl, halo, trifluoromethyl or trifluoromethoxy.

37. The aryl piperazine derivative of claim 36, which is

2-{4-[4-(3-Cyano-phenyl)-piperazin-1-yl]-butyl}-3,4-dihydro-2H-pyrazino[1,2-a]indol-1-one;

2-[4-[4-(3-Chlorophenyl)piperazin-1-yl]butyl]-3,4-dihydropyrazino[1,2-a]indol-1(2H)-one;

2-[4-[4-(3-Methoxy-phenyl)-piperazin-1-yl]-butyl]-3,4-dihydro-2H-pyrazino[1,2-a]indol-1-one;

2-[4-(4-*m*-Tolyl)piperazin-1-yl]butyl]-3,4-dihydropyrazino[1,2-a]indol-1(2H)-one;

3,4-Dihydro-2-[4-(3,4-dihydro-6-methoxypyrazino[1,2-a]indol-2(1H)-yl)butyl]pyrazino[1,2-a]indol-1(2H)-one;

2-[4-[4-(2-Methoxy-phenyl)-piperazin-1-yl]-butyl]-3,4-dihydro-2H-pyrazino[1,2-a]indol-1-one; or

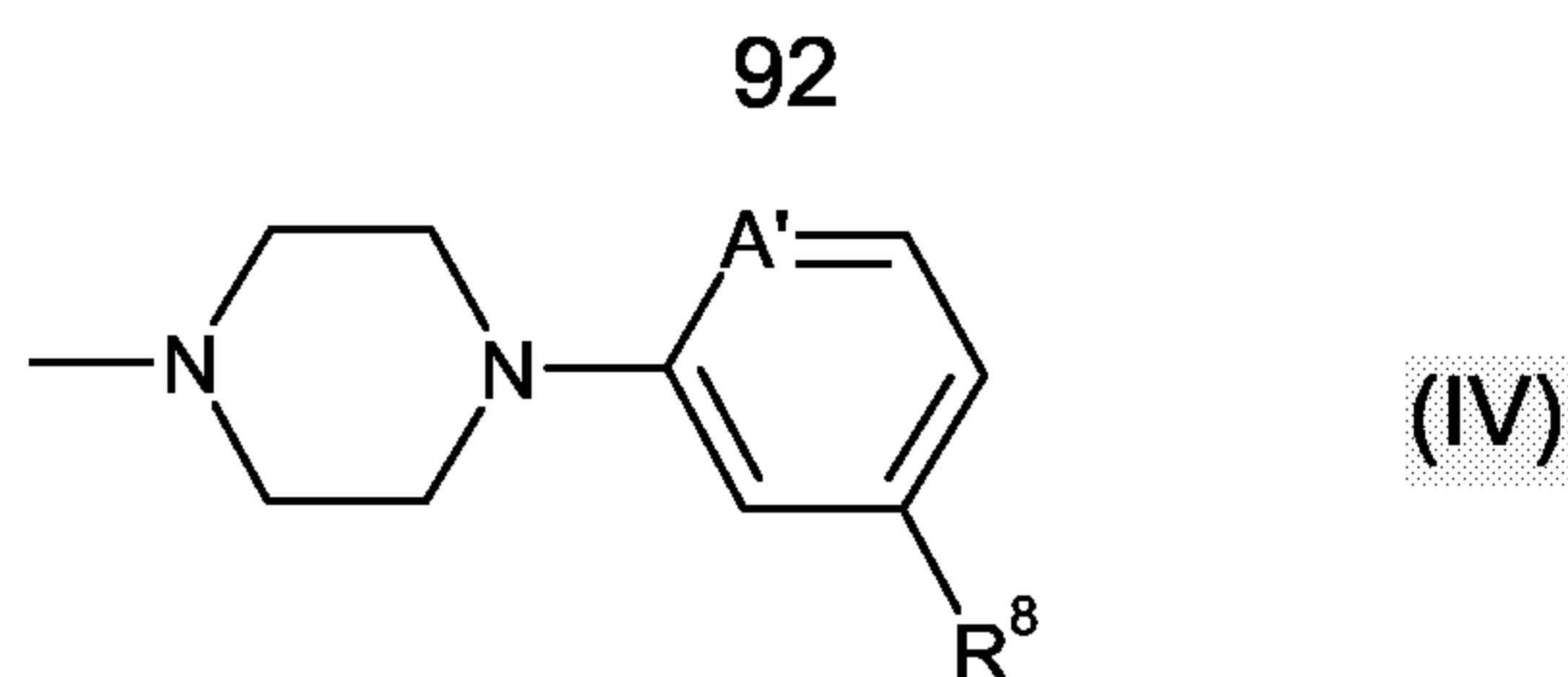
2-[4-[4-(2,3-Dichloro-phenyl)-piperazin-1-yl]-butyl]-3,4-dihydro-2H-pyrazino[1,2-a]indol-1-one;

or a pharmaceutically acceptable salt thereof.

38. The aryl piperazine derivative of any one of claims 1-12, wherein

X is absent; and

Y represents a group of formula IV



wherein A' represents CH or N; and
R⁸ represents hydrogen, alkyl, alkoxy, halo or haloalkyl.

- 5 39. The aryl piperazine derivative of claim 38, which is
1,6-Bis(4-(3-chlorophenyl)piperazin-1-yl)hexane;
1,6-Bis(4-(3-methoxyphenyl)piperazin-1-yl)hexane;
1,6-Bis(4-phenylpiperazin-1-yl)hexane;
1-(3-Chlorophenyl)-4-(6-(4-(3-methoxyphenyl)piperazin-1-yl)hexyl)piperazine;
10 yl)hexyl)piperazine;
1-Phenyl-4-(6-(4-(pyridin-2-yl)piperazin-1-yl)hexyl)piperazine;
1-(6-Methylpyridin-2-yl)-4-(6-(4-m-tolylpiperazin-1-yl)hexyl)piperazine;
1-(6-Methylpyridin-2-yl)-4-(6-(4-phenylpiperazin-1-yl)hexyl)piperazine;
1-Phenyl-4-(6-(4-m-tolylpiperazin-1-yl)hexyl)piperazine;
15 4-(4-(6-(4-Phenylpiperazin-1-yl)hexyl)piperazin-1-yl)quinoline;
1,6-Bis(4-(pyridin-2-yl)piperazin-1-yl)hexane;
4-(4-(6-(4-m-Tolylpiperazin-1-yl)hexyl)piperazin-1-yl)quinoline;
1,6-Bis(4-m-tolylpiperazin-1-yl)hexane;
1-(Pyridin-2-yl)-4-(6-(4-m-tolylpiperazin-1-yl)hexyl)piperazine; or
20 1-(3-Methoxyphenyl)-4-(6-(4-m-tolylpiperazin-1-yl)hexyl)piperazine;
or a pharmaceutically acceptable salt thereof.

40. A pharmaceutical composition comprising a therapeutically effective amount of an aryl piperazine derivative of any one of claims 1-39, or a
25 pharmaceutically-acceptable addition salt thereof, or a prodrug thereof, together with at least one pharmaceutically acceptable carrier or diluent.

41. Use of the aryl piperazine derivative of any one of claims 1-39, or a pharmaceutically acceptable salt thereof, or a prodrug thereof, for the manufacture of a
30 pharmaceutical composition.

42. Use of the aryl piperazine derivative of any one of claims 1-39, or a pharmaceutically acceptable salt thereof, for the manufacture of a pharmaceutical composition for the treatment, prevention or alleviation of a disease or a disorder or a
35 condition of a mammal, including a human, which disease, disorder or condition is responsive to modulation of the dopamine and serotonin receptors.

43. The use according to claim 42, wherein the disease or a disorder or a condition is a neurological or psychiatric disorders, in particular psychotic disorders, schizophrenia, depression, Parkinson's disease, Huntington's disease, movement disorders, dystonia, anxiety, restlessness, obsessive-compulsive disorders, mania, geriatric disorders, dementia, sexual dysfunction, musculo-skeletal pain symptoms, pain associated with fibromyalgia, sleep disorders, substance abuse or addiction and withdrawal symptoms in drug addicts, cocaine abuse or addiction.

10 44. The use according to claim 43, wherein the disease or a disorder or a condition is a neurological or psychiatric disorder, in particular a psychotic disorder, preferably schizophrenia.

15 45. A method of diagnosis, treatment, prevention or alleviation of a disease or a disorder or a condition of a living animal body, including a human, which disorder, disease or condition is responsive to modulation of the dopamine and serotonin receptors, in particular the D₃, D₂-like and 5-HT₂ receptor subtypes, preferably the dopamine D₃ receptor subtype and/or the D₃/5-HT_{1A} or D₃/5-HT_{2A} receptor sybtypes, which method comprises the step of administering to such a living animal body in need
20 thereof, a therapeutically effective amount of an aryl piperazine derivative according to any one of claims 1-39, a pharmaceutically acceptable salt thereof, or a prodrug thereof.